

Curriculum Vitae for MDRC 2008

A. IDENTIFICATION

Name **Jun-Li Liu**
Office Address Fraser Laboratories for Diabetes Research, Room M3-15, Department of Medicine, McGill University Health Centre, 687 Pine Avenue West, Montreal, QC H3A 1A1, Canada
Telephone (514) 934-1934 Ext 35059
Fax (514) 843-2819
E-mail jun-li.liu@mcgill.ca
Web site <http://www.montreal-diabetes-research-center.org/en/liu/liu.asp>

B. EDUCATION:

Undergraduate 1978-1982 Peking University, China, **Biology, BSc**
Graduate 1 1982-1985 Beijing Medical University, China, **Physiology, MSc**
Thesis Topic *Cysteamine-induced duodenal ulcer in the rat*
Supervisor Dr. Xi-Jin Zhang
Graduate 2 1990-1995 McGill University, Montreal, Canada. **Experimental Medicine, PhD**
Thesis Topic *Regulation of somatostatin gene expression by glucocorticoids*
Supervisor Dr. Yogesh C. Patel
Post-graduate training 1995-2000 National Institutes of Health, Bethesda, MD;
on **Diabetes & Endocrinology**
Research *Tissue-specific IGF-I gene targeting using the Cre/loxP system*
Supervisor Dr. Derek LeRoith
Clinical N/A
Professional Certifications N/A

C. APPOINTMENTS (current and past; indicate department, rank and year)

University Associate Professor (2008.7-); Assistant Professor (2000-2008), Department of Medicine, Division of Endocrinology and Metabolism, McGill University, Montreal, Canada
Member, Division of Experimental Medicine in the Department of Medicine, McGill University, Montreal, Canada; 2000-present
Academic Advisor to graduate students, Division of Experimental Medicine in the Department of Medicine, McGill University, Montreal, Canada; 2005-present
Lecturer, Department of Physiology, Beijing Medical University, China; 1985-1988

Hospital	Medical Scientist, Department of Medicine, McGill University Health Centre, Montreal, Canada; 2000-present Member, the Research Institute of McGill University Health Centre, Montreal, Canada; 2000-present Visiting Professor, Shanghai Clinical Center for Endocrine and Metabolic Diseases, Shanghai, PR China; 2004-2007
Other	Member, Montreal Diabetes Research Centre, Montreal, Canada; 2003-present

D. SPECIAL HONORS, AWARDS, RECOGNITION

- 1993-1995 Studentship award, the Research Institute of Royal Victoria Hospital, McGill University, Montreal, Canada
- 1996-1999 Fellowship award, Medical Research Council of Canada
- 1999-2000 Fellowship award in the NIH Visiting Program, National Institutes of Health, Bethesda, MD
- 1998 Quest Diagnostics New Investigator Award, The Endocrine Society, Annual Meeting in New Orleans, LA
- 1999 Fellows Award for Research Excellence, National Institutes of Health, Bethesda, MD
- 2000-2005 Career Development Award, Juvenile Diabetes Research Foundation International, New York, NY
- 2001 Travel Grant Award, The Endocrine Society, Annual Meeting in Denver, CO
- 2005-2008 John R. & Clara M. Fraser Memorial Award, Faculty of Medicine, McGill University, Montreal, Canada
- 2008-2011 Chercheurs-boursiers-Fondamental, Senior (Research Scholarship at senior level), Fonds de la recherche en santé Québec (FRSQ; Quebec Medical Research Foundation)

E. TEACHING

1. McGill Courses, Post-graduate

Department of Medicine, *Advanced Endocrinology* 516-503B. From winter 2001-present (4 Lectures of 6 hours total)

Department of Medicine, *Seminars in Endocrinology* 516-603B. From winter 2001-present (30 hours p.a.)

McGill Courses, Undergraduate

Departments of Medicine and Physiology, *Physiology and Biochemistry of the Endocrine Systems* 516-401B. From winter 2006 – present (6 Lectures of 6 hour total)

2. Research Trainees Supervised (since 2000)

Graduate students: 6
Post-doctoral fellows: 6
Undergraduate students: 13

3. Invited Lectures, Talks, Presentations

- 1997 Institute of Cell Biology, China Academy of Science, Shanghai, China. Topic: Cre/loxP-mediated tissue-specific gene targeting
- 1999 G. Brush Cancer Research Institute, California Pacific Medical Center, San Francisco, CA. Topic: Liver-specific IGF-I gene targeting
- 1999 Columbia University, Cardiac Physiology Laboratory, New York, NY. Topic: Liver-specific IGF-I gene targeting on somatic growth and development
- 2000 The Lawson Research Institute, Molecular Medicine / Maternal Newborn Health, London, ON, Canada. Title: Conditional targeting of IGF-I gene using a Cre/loxP system
- 2001 Department of Anatomy and Cell Biology & Department of Physiology, McGill University, Montreal, Canada. Insulin-like growth factor I as the Somatomedin and a metabolic regulator: New lessons learnt from knockout models
- 2002 Department of Internal Medicine, Division of Endocrinology, University of Vermont, Burlington, VT. Physiological roles of GH/IGF-I axis in glucose homeostasis from studies of LID and GHR^{-/-} mice
- 2003 The McGill University-Montreal Children's Hospital, Research Institute Seminar, Montreal, Canada. May 5. Title: Liver- and pancreas-specific IGF-I gene knockouts have opposite effects on experimental diabetes
- 2003 Medical Science Club, Marianopolis College, Montreal, Quebec. March 27. Title: Neuroendocrine control of appetite and body weight
- 2004 Scientific Retreat of The JDRF Center for β -Cell Replacement at McGill University and University of Montreal, Montreal, QC. March 17. Title: Pancreatic islet-specific expression of an IGF-I transgene increases islet cell mass in GHR^{-/-} mice
- 2004 Shanghai 2nd Medical University, Division of Endocrinology, Shanghai, China. July 8. Topic: Effects of IGF-I on pancreatic islet cell growth and insulin actions
- 2004 The 1st International Conference of Chinese Physiological Scientists, Beijing, China. July 14-17. Title: Interplay of growth hormone and insulin-like growth factor I in pancreatic islet growth and insulin production

- 2005 Diabetes gene discovery group retreat. McGill University, New Residence Hall. Title: Liver- and pancreatic-specific IGF-I gene deficiency on islet cell growth
- 2005 The 6th Annual Rachmiel Levine Diabetes Symposium: From Cell Biology to Cell Therapy. November 9-12. City of Hope National Medical Center, Universal City, CA. Title: Does IGF-I promotes islet cell growth?
- 2008 New England Biolabs, Ipswich, MA. May 1. Title: The search for islet growth factors, from IGF-I to Reg proteins.

4. **Clinical Teaching** (e.g. tutorial groups, ward rounds):

- 2001- Endocrine Journal Club, Department of Medicine, McGill University Health Centre, Montreal, Canada.
- 2002 Monday resident teaching sessions. March 11, 2002. Title: Re-examination of GH-IGF axis using gene targeting techniques. One hour
- 2003 MUHC combined endocrine rounds, McGill University, Montreal, Canada. February 20. Title: GH/IGF axis in pancreatic islet function and glucose homeostasis: gene targeting in LID, GHR^{-/-}, & MKR mice

F. OTHER CONTRIBUTIONS

(If necessary, use appendices by category and sub-category).

1. Journals

Editorial Boards (Journal name, years)

The Open Physiology Journal, Bentham Science Publishers
(<http://www.bentham.org/>), 2007-present

Journal of Diabetes, Blackwell Publishing, 2008-present

Ad hoc reviews (List journals for last three years):

Diabetes

Regulatory Peptides

Endocrinology

Neuroscience Letters

Amer J Physiol –Endocrinol & Metab

Biochimica et Biophysica Acta (BBA)

Endocrine

Exp Biol Med

Pediatric Endocrinology

Acta Physiologica Sinica

2. Grant Reviews

Panel Member:

Juvenile Diabetes Research Foundation International, 2005

Changjiang Scholars Program, Education Ministry, PR China, 2007

Ad hoc reviews:

Canadian Diabetes Association, Operating grant

Canadian Institutes of Health Research, Metabolism committee

American Diabetes Association, Research program on Type 1 diabetes

3. Administrative Responsibilities

McGill Department of Medicine, Division of Experimental Medicine, **Academic advisor** for graduate students, 2005-present. I am currently responsible for 9 graduate students.

Hospital Member of the Awards Committee for Studentship and Fellowship, The Research Institutes of McGill University Health Centre.

Member of the Health and Safety Committee, The RVH site of McGill University Health Centre. 2008-present

4. Committees (Current and past; list name, your position, years)

Members of graduate student thesis committees (annual meetings), PhD defense committees and thesis examiner for the Departments of Medicine and Pharmacology, McGill University, 2002-

Abstract reviewer, Toronto 2006 Canadian Diabetes Association (CDA)/CSEM Professional Conference and Annual Meetings

Internal preview of CIHR grants, MUHC Research Institutes, February 2008

Award jury, Montreal Diabetes Research Center annual retreat, January 2008

5. Professional and/or Learned Societies

2000-present The Endocrine Society (Bethesda, MD, USA), Member

2000-present American Diabetes Association, Member

2002-present The American Physiological Society, Member

1998-present The International Society for IGF Research, Member

2007-present Canadian Diabetes Association, C&SS member

6. Other Professional and Scientific Contributions

2002 Guest editor for a special issue of the journal on *Conditional gene targeting in mice*. *Endocrine* 2002; 19(3).

2003 Co-chair, the symposium “Application of transgenic/knockout approaches to metabolic regulation”, International Union of Biochemistry and Molecular Biology (IUBMB) Congress, Toronto, ON, Canada.

2004 Chair of symposium on Endocrinology and Metabolism. The 1st International Conference of Chinese Physiological Scientists, Beijing, China.

- 2005- Member of the International Reviewers Panel, Medical Science Monitor, International Scientific Literature, Inc. Albertson, NY.
- 2005 Mentor, on postdoctoral studies, Minority Affairs Committee, The Endocrine Society (USA)
- 2005- The Science Advisory Board, 2111 Wilson Boulevard, Suite 250, Arlington, VA
- 2005- Expert consultant, MEDACorp Consultant Liaison Team, Boston, MA
- 2007- Member, Society of Industry Leaders, consultation for Standard & Poor's Research clients, Vista Research Inc., Sunnyvale, CA
- 2007- CIHR Synapse mentor, Youth and Public Outreach
- 2006- Served as a contact person and/or research host for the Frontiers in Physiology and Undergraduate Summer Research fellowship programs, American Physiological Society

G. RESEARCH

1. Research Activities (Briefly indicate your main areas of research)

Past: MSc Research (1982-1985)

While studying in Beijing Medical University, Department of Physiology, I established cysteamine-induced duodenal ulcer in rats and explored the roles of pancreatic polypeptide, somatostatin, hypothalamic-pituitary-adrenal axis, sulfhydryls and some trace elements in the disease mechanism and/or interventions.

Past: PhD Research (1989-1995)

Under the supervision of Dr. Yogesh C Patel, McGill University, I studied the regulation of somatostatin gene expression at the levels of transcription and mRNA stability. I demonstrated that glucocorticoids exert time- and dose-dependent, significant effects on somatostatin production and steady state mRNA levels in normal tissues and in tumor cells; glucocorticoids stimulated the gene transcription in a protein kinase A-dependent fashion; and glucocorticoids decreased steady state somatostatin-mRNA level and somatostatin secretion in tumor cells, independent of its effect on transcription. Therefore, at low doses, glucocorticoids activate somatostatin gene transcription via a positive interaction with CREB, an effect manifested in peripheral tissues; at high doses, glucocorticoids accelerate somatostatin mRNA degradation, an action occur in neurons and some peripheral tissues.

Past: Postdoctoral Research (1995-2000)

In five years, under the direction of Dr. Derek LeRoith, National Institutes of Health, I accomplished three major studies: (1) Creation of mice with loxP-tagged IGF-I gene via homologous recombination (**IGF-I/loxP mice**). Exon 4 of the IGF-I gene was tagged by two loxP repeats that serve as recognition sites for Cre recombinase. This was the first peptide hormone gene to be tagged, and it enabled Cre-mediated conditional

knockout of the IGF-I gene. As IGF-I is expressed extensively in various tissues and throughout development, international collaborations have been established to specifically knock out IGF-I gene in target tissues including bone, mammary gland, ovary, prostate gland, heart, brain, and pancreatic islets.

(2) **Revised the Somatomedin Hypothesis.** Using the Cre/loxP-induced conditional gene targeting, we demonstrated that lack of IGF-I production from the liver, which accounts for 75% of the circulating level, had no effect on normal growth and development. Therefore, we proposed that growth hormone acts directly on target tissues (rather than through liver IGF-I, as previously proposed) and promotes local (paracrine) production of IGF-I, thereby promoting tissue growth. It represented a breakthrough in 40 years of somatomedin research. As a major research development at the time, this report was highlighted by Steve Bunk on *Scientist* 1999; 13(15); and has been cited 429 times in the literature to date.

(3) Creation of **viable IGF-I-null mice** using the Cre/loxP system. These were generated while studying EIIa-Cre-induced gene recombination in IGF-I/loxP mice. Offspring of mosaic IGF-I gene recombination transmitted a totally deleted IGF-I allele through the germline in 3rd generation inbreeding. Due to differences in the target region and the removal of the neomycin cassette, this model has a 42% postnatal survival rate (compared with 5% reported in conventional knockout), enabling postnatal studies. Using this unique tool, I demonstrated that IGF-I is essential for growth hormone-stimulated postnatal growth, further supporting the revised Somatomedin Hypothesis.

Past: Independent Research

Tissue-specific effects of IGF-I on pancreatic islet growth and insulin production. Using Cre/loxP-mediated conditional gene targeting, I have studied the effects of IGF-I deficiency in the liver (LID) and pancreas (PID) on pancreatic islet growth and insulin production. (1) LID mice exhibit insulin resistance that results in islet cell hyperplasia and hyperinsulinemia. Insulin resistance occurs mostly in skeletal muscles and can be relieved by inhibiting growth hormone secretion. As a compensatory response, islet hyperplasia provided no protection against streptozotocin-induced islet cell damage and diabetes. Our results indicate that liver-produced IGF-I normally enhances insulin sensitivity in part by inhibiting growth hormone release. (2) PID mice exhibit islet enlargement and hypoglycemia; are significantly resistant to streptozotocin-induced type 1 diabetes by preventing islet β -cell apoptosis; and are resistant to high-fat-diet-induced type 2 diabetes by stimulating islet cell growth. Our results suggest that locally produced IGF-I within the pancreas *inhibits* islet cell growth, its deficiency provides a protective environment to the β -cells and a potential in combating diabetes. This surprising result was featured on MDLinx on December 1, 2004.

Acting through its receptor (GHR), GH is essential for somatic growth and development and maintaining metabolic homeostasis. In my 1st report, **GHR gene deficiency (GHR^{-/-})** was shown to cause reduced islet β -cell mass, diminished islet cell replication, and decreased insulin mRNA and serum insulin levels. As the islet changes were proportionally greater than body growth retardation, we concluded that GH signaling is essential for maintaining pancreatic islet size, islet hormone production and

normal insulin sensitivity. Unlike the liver which is mostly unaffected by changes in the IGF-I level, skeletal muscles express high levels of IGF-I receptor (IGF-IR). The net result of a concurrent deficiency in the actions of both GH and IGF-I (in GHR^{-/-} mice), which exert opposite influences on insulin responsiveness, has not been evaluated. We have studied insulin-stimulated early responses in the insulin receptor (IR), IRS-1 and p85 subunit of PI3K. Upon in vivo insulin stimulation, the skeletal muscles of GHR^{-/-} mice exhibit transient delayed responses in IR and IRS-1 phosphorylation, but normal level of p85 association with IRS-1. This is in contrast to normal/elevated insulin responses in hepatocytes and indicates tissue-specific effects. Finally, to study whether the islet cell overgrowth as a result of insulin resistance is dependent on GH signaling, we have studied the response of GHR^{-/-} mice to high-fat diet (HFD)-induced obesity. After 17 weeks on a HFD, GHR^{-/-} mice became more significantly obese than the wild-type and exhibited increased β -cell mass to a slightly higher extent. It demonstrates that GH signaling is not required for compensatory islet growth.

Ghrelin gene expression is age-dependent and influenced by gender and the level of circulating IGF-I. Ghrelin activates GH release and is implicated in growth and metabolic regulation. The regulation of its biosynthesis has not been well studied. We have examined some of the factors that may influence ghrelin gene expression in the stomach. Thus, in C57BL/6 mice, ghrelin mRNA was detectable by Northern blots throughout the age groups studied, but the levels varied markedly over time. Ghrelin mRNA levels were low at embryonic day (E) 18.5 and increased rapidly after birth to 6-fold at postnatal day (P) 14 before peaking to 8-fold at P21. The levels then exhibited a gradual decline at P60 and at 6 months and a drastic decrease as the animals aged to 19 months (only 5%). We further studied sexual dimorphic gene expression, the effect of liver-derived IGF-I deficiency, as well as ghrelin secretion. Our results support a role of ghrelin in growth/metabolism in juvenile and young adult mice of both sexes and in sexually dimorphic regulation of GH secretion in aged mice.

Current research activities

Built on my early success in characterizing the role of IGF-I and GH in islet cell growth, my current research is focused on the effects of novel growth factors in maintaining β -cell mass and/or function with the hope of developing therapeutic interventions against the ever increasing incidence of diabetes mellitus.

Effects of Reg proteins on islet β -cell growth and protection: operating grants supported by CIHR and Canadian Diabetes Association. IGF-I had been known to stimulate islet cell growth in vitro and in transgenic mice. In the past 6 years, we and others have investigated the role of IGF-I and its receptor (IGF-IR) in islet β -cell growth using tissue-specific gene targeting. Surprisingly, our results have shown that IGF-I does not play a positive role in islet β -cell growth. Especially, pancreatic-specific IGF-I deficiency (PID) causes increased β -cell growth and profound protection of islet cells against damage caused by streptozotocin (SID) or high-fat diet. These effects are unlikely to be caused directly by the deficiency of IGF-I, a prominent growth factor. Indeed, a DNA microarray analysis revealed significant and specific up regulation of Reg family

genes, especially Reg2 and Reg3 β , in the pancreas of these PID mice. Additionally, their mRNA levels are drastically elevated in the pancreas of SID mice, while undergoing islet regeneration and recovery from diabetes. Among 7 Reg family proteins, Reg1 and INGAP (Reg3 δ) have been known to stimulate β -cell proliferation or neogenesis, while the others have not been well characterized. Recently, Reg2 has been demonstrated to be expressed predominantly in islet β -cells and to play a dual role of growth factor and β -cell autoantigene; gene knockout studies demonstrated that Reg3 β is a critical for liver regeneration. I propose that Reg family proteins, Reg2 and Reg3 β in particular, normally promote islet β -cell replication, increase in islet cell size, β -cell neogenesis from precursors and/or inhibit β -cell apoptosis, thus maintaining islet cell growth and enable protection against diabetes. Effects of Reg family proteins exhibit clear subtype-specificity and even domain-specific roles in the case of Reg2. Although much is unclear concerning the physiology of Reg2 and Reg3 β , it is vital to establish their effectiveness on islet cell growth and death, before embarking on detailed studies of their regulation or mechanism of action. Toward that goal, I propose (1) to transfect and overexpress Reg2 and Reg3 β cDNAs in vitro, or treat islet cells with recombinant proteins, and study the effects on islet cell replication and apoptosis; (2) to overexpress Reg2 and Reg3 β genes in the pancreatic islets of transgenic mice and, together with the available Reg1 transgenic (Ins-Reg1) mice, characterize the effects on islet cell growth; (3) to investigate and compare the responses of the Reg1, Reg2 and Reg3 β transgenic mice to streptozotocin-induced β -cell damage and diabetes; (4) to study the effects of inactivating the endogenous Reg genes in islet growth and protection.

Reassessing the effects of IGF-I on pancreatic islet cell growth, insulin secretion and hepatic glucose production: a discovery grant supported by NSERC. Changes in pancreatic islet cell mass, insulin secretion and the rates of glucose disposal and production compensate for insulin resistance and prevent onset of type 2 diabetes. IGF-I promotes embryonic development, postnatal growth and maturation of major organ systems and had been reported to stimulate the replication of pancreatic islet cells in vitro. Recently however, both IGF-I and receptor (IGF-IR) gene-targeted experiments indicate that endogenous IGF-I does not promote normal islet cell growth. There are reports that IGF-I inhibits, stimulates or has no effect on glucose-stimulated insulin secretion from the β -cells. IGF-I also has clear insulin-like effects on glucose disposal in skeletal muscles, causing decreased blood glucose level. Very little is known, however, whether IGF-I can act directly to inhibit hepatic glucose production. In the past 6 years, we have studied various IGF-I transgenic and knockout mice, on changes in islet cell function and metabolic regulation. Most recently, we have characterized a robust, general yet islet-enriched IGF-I overexpression in MT-IGF mice, driven by metallothionein promoter. Because of its extreme high level of expression, it provides a unique opportunity for us to reexamine the effects of IGF-I on islet cell growth, insulin secretion and hepatic glucose production. Based on our preliminary findings and the literature, our *working hypothesis* is that IGF-I promotes pancreatic islet cell growth in a glucose-dependent fashion, prevents programmed cell death (thus maintaining normal islet cell mass), and inhibits insulin secretion and hepatic glucose production directly, independent of insulin receptors. In IGF-I overexpressing MT-IGF mice, in order to clarify the emerging controversies in

islet cell growth, insulin secretion and hepatic glucose production and to understand the mechanism why these mice display extreme hypoglycemia and significant resistance to diabetes, I will study (1) The interplay of IGF-I overexpression and high glucose on islet cell growth in vivo and in vitro and on cytokine-induced islet cell death. We will measure changes in β -cell mass in vivo, islet cell replication in vitro, and cytokine-induced cell apoptosis caused by IGF-I overexpression; (2) The Effects of IGF-I overexpression on basal and glucose-stimulated insulin secretion; (3) The Effects of IGF-I overexpression on hepatic glucose production in vivo and in isolated hepatocytes, and on the levels of key enzymes involved in glucose production. As its name reflects accurately, IGF-I has significant growth and metabolic effects. The proposed research will clarify its precise effects on islet cell growth, survival, function (insulin secretion) and its inhibition on glucose production, thereby establishing its role in normal islet growth and physiology. The results will provide a solid basis for us to develop diabetic interventions, based on IGF, by preserving islet integrity, restoring islet cell mass, or suppressing overnight hyperglycemia.

2. Research Grants (For group grants, indicate your share)

Current

4/2007-3/2012 Natural Sciences and Engineering Research Council of Canada, Discovery grant, total \$109,000. Title: The role of IGF-I in pancreatic islet cell growth and glucose homeostasis (341205-07; PI: JL Liu)

7/2007-6/2008 Canadian Diabetes Association, Innovative grant, total \$50,000. Title: Pancreatic islet-specific overexpression of Reg family genes (IG-1-07-2305-JL; PI: JL Liu)

7/2007-6/2011 Canadian Institutes of Health Research, Operating grant. Year 1: \$58,803, Year 2-4: \$100,686 p.a., total \$360,861. Title: Reg proteins on pancreatic islet cell growth and protection (MOP-84389; PI: JL Liu)

01/2008-12/2010 Canadian Institutes of Health Research, operating grant, China-Canada joint health research initiative. \$30,000 p.a., total \$90,000. Title: Reg family proteins on pancreatic islet cell growth (CCI-85675; PI: JL Liu)

10/2008 Échanges FRSQ/NSFC (Chine), Fonds de la recherche en santé Québec \$11,000 “Les effets des protéines Reg sur la croissance et la protection des cellules beta pancréatiques” (PI: JL Liu)

Past (Summarize by indicating source and years; e.g. MRC 19__ - 19__)

4/2000 MUHC Research Institute, Start up fund, \$42,500 total. Title: Tissue-specific knockout of insulin-like growth factor I (PI: JL Liu)

7/2000-6/2005 Juvenile Diabetes Research Foundation International, New York, NY. Career Development Award, \$110,875 USD p.a. (total \$554,375 USD) Title: The role of insulin-like growth factor I in pancreatic islet function and peripheral insulin signaling: Studies using transgenic and cell-specific

knockout mice (PI: JL Liu)

- 4/2002-3/2005 Canadian Institutes of Health Research, Operating grant, \$86,850 p.a. and \$9,207 equipment (total \$279,407). Title: Pancreatic islet-specific over expression of insulin-like growth factor I (PI: JL Liu)
- 4/2002 Canada Foundation for Innovation, On-going new opportunity award, \$252,000 total. Title: Tissue-specific knockout of insulin-like growth factor I (PI: JL Liu)
- 6/2004 McGill University Health Centre, Equipment fund for Beckman rotors, \$37,011 total (PI: JL Liu)
- 7/2005-12/2006: Institutional bridging fund, MUHC Research Institute, McGill University, Montreal, Canada. Amount: \$55,000 total (PI: JL Liu)
- 4/2003-3/2008 Canada Foundation for Innovation, Infrastructure operating fund, \$30,778 total (PI: JL Liu)
- 3/2007 Canadian Institutes of Health Research, Operating grant, \$83,766 total. Title: Reg proteins on pancreatic islet cell growth and protection (NMD-83124; PI: JL Liu)

3. Publications, organize in the following categories:

- a) Articles in peer reviewed journals. DO NOT LIST articles "in preparation". DO include "accepted" or "in press". Place an asterisk (*) next to articles in which the first author is/was your graduate student, post-doctoral fellow or resident.

Published as PI from McGill University (the names of research trainees under my direct supervision are underlined)

1. *K Robertson, Y Lu, B Li, Q Su, PK Lund and **JL Liu**. A general and islet cell-enriched overexpression of IGF-I results in normal islet cell growth, hypoglycemia and significant resistance to experimental diabetes. *Amer J Physiol-Endo Metab* 2008; 294: E928-38*
2. *K Robertson, JJ Kopchick and **JL Liu**. Growth hormone receptor deficiency causes delayed insulin responsiveness in skeletal muscles without affecting compensatory islet cell overgrowth in obese mice. *Amer J Physiol-Endo Metab* 2006; 291: E491-498*
3. *Y Lu, A Ponton, H Okamoto, S Takasawa, PL Herrera, and **JL Liu**. Activation of the Reg family genes by pancreatic-specific IGF-I gene deficiency and after streptozotocin-induced diabetes in mouse pancreas. *Amer J Physiol-Endo Metab* 2006; 291: E50-58*
4. *Z Tang, R Yu, Y Lu, AF Parlow and **JL Liu**. Age-dependent onset of liver-specific IGF-I gene deficiency and its persistence in old age: implications for postnatal growth and insulin resistance in LID mice. *Amer J Physiol-Endo Metab* 2005; 289:

E288-295*

5. *Y Guo, Y Lu, D Houle, K Robertson, Z Tang, JJ Kopchick, YL Liu and **JL Liu**. Pancreatic islet-specific expression of an IGF-I transgene compensates islet cell growth in growth hormone receptor gene deficient mice. *Endocrinology* 2005; 146: 2602–2609*
6. *Y Lu, PL Herrera, Y Guo, D Sun, Z Tang, D LeRoith, and **JL Liu**. Pancreatic specific inactivation of IGF-I gene causes enlarged pancreatic islets and significant resistance to diabetes. *Diabetes* 2004; 53: 3131-3141*
7. **JL Liu**, KT Coschigano, K Robertson, M Lipsett, Y Guo, JJ Kopchick, U Kumar, and YL Liu. Disruption of growth hormone receptor gene causes diminished pancreatic islet size and increased insulin sensitivity in mice. *Am J Physiol-Endo Metab* 2004; 287: E405-413
8. *R Yu, S Yakar, YL Liu, Y Lu, D LeRoith, D Miao, and **JL Liu**. Liver-specific IGF-I gene deficient mice exhibit accelerated diabetes in response to streptozotocin, associated with early onset of insulin resistance. *Mol Cell Endocrinol* 2003; 204: 31-42*
9. *YL Liu, S Yakar, V Otero-Corchon, MJ Low, **JL Liu**. Ghrelin gene expression is age-dependent and influenced by gender and the level of circulating IGF-I. *Mol Cell Endocrinol* 2002; 189: 97-103*
10. Å Tivesten, E Bollano, I Andersson, S Fitzgerald, K Caidahl, K Sjögren, O Skott, **JL Liu**, D LeRoith, R Mobini, OGP Isaksson, JO Jansson, C Ohlsson, G Bergström, J Isgaard. Liver-derived insulin-like growth factor-I is involved in the regulation of blood pressure in mice. *Endocrinology* 2002; 143: 4235-4242
11. S Yakar, CJ Rosen, WG Beamer, CL Ackert-Bicknell, Y Wu, **JL Liu**, GT Ooi, J Setser, J Frystyk, YR Boisclair, and D LeRoith. Circulating levels of IGF-1 directly regulate bone growth and density. *J Clin Invest* 2002; 110: 771-781
12. K Sjögren, M Sheng, S Moverare, **JL Liu**, K Wallenius, J Törnell, O Isaksson, J-O Jansson, S Mohan, C Ohlsson. Effects of liver-derived insulin-like growth factor I on bone metabolism in mice. *J Bone Mineral Res* 2002; 17: 1977-87
13. K Wallenius, K Sjogren, XD Peng, S Park, V Wallenius, **JL Liu**, M Umaerus, H Wennbo, O Isaksson, L Frohman, R Kineman, C Ohlsson, JO Jansson. Liver-derived IGF-I regulates growth hormone secretion at the pituitary level in mice. *Endocrinology* 2001; 142: 4762-4770
14. C Lu, G Schwartzbauer, MA Sperling, SU Devaskar, S Thamocharan, PD Robbins, CF McTiernan, **JL Liu**, J Jiang, SJ Frank, RK Menon. Demonstration of direct effects of growth hormone on neonatal cardiomyocytes. *J Biol Chem* 2001; 276: 22892-22900

Postdoctoral work (at National Institutes of Health)

15. Hellstrom A, Perruzzi C, Ju M, Engstrom E, Hard AL, **Liu JL**, Albertsson-Wikland

- K, Carlsson B, Niklasson A, Sjodell L, LeRoith D, Senger DR, Smith LE. Low IGF-I suppresses VEGF-survival signaling in retinal endothelial cells: Direct correlation with clinical retinopathy of prematurity. *Proc Natl Acad Sci USA* 2001; 98: 5804-5808
16. K Sjögren, K Wallenius, **JL Liu**, M Bohlooly-Y, G Pacini, L Svensson, J Törnell, OGP Isaksson, B Ahrén, JO Jansson and C Ohlsson. Liver-derived IGF-I is of importance for normal carbohydrate and lipid metabolism. *Diabetes* 2001; 50: 1539-1545
 17. S Yakar, **JL Liu**, AM Fernandez, Y Wu, AV Schally, J Frystyk, SD Chernausek, WM Mejia, D LeRoith. Liver-specific *igf-1* gene deletion leads to muscle insulin insensitivity. *Diabetes* 2001; 50: 1110-1118
 18. **JL Liu**, S Yakar, D LeRoith. Mice deficient in liver production of insulin-like growth factor I display sexual dimorphism in growth hormone-stimulated postnatal growth. *Endocrinology* 2000; 141: 4436-41
 19. **JL Liu**, D LeRoith. Insulin-like growth factor-I is essential for post-natal growth in response to growth hormone. *Endocrinology* 1999; 140: 5178-5184
 20. M Karas, T Zaks, **JL Liu**, D LeRoith. T cell receptor-induced activation and apoptosis in human T cells are cell cycle independent. *Mol. Biol. Cell* 1999; 10: 4441-50
 21. K Sjögren, **JL Liu**, S Skrtic, O Vidal, K Blad, V Wallenius, O Isaksson, D LeRoith, J Törnell, JO Jansson, C Ohlsson. Liver-derived insulin-like growth factor I (IGF-I) is the principal source of IGF-I in blood but is not required for postnatal body growth in mice. *Proc. Natl. Acad. Sci. USA* 1999; 96: 7088-7092
 22. S Yakar, **JL Liu**, B Stannard, A Butler, D Accili, B Sauer, D LeRoith. Normal growth and development in the absence of hepatic insulin-like growth factor I. *Proc. Natl. Acad. Sci. USA* 1999; 96: 7324-7329
 23. **JL Liu**, A Grinberg, H Westphal, B Sauer, D Accili, M Karas, D LeRoith. Insulin-like growth factor I affects perinatal lethality and post-natal development in a gene dosage-dependent manner: manipulation using the Cre/loxP system in transgenic mice. *Mol Endocrinol* 1998; 12: 1452-1462
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