RESEARCH REPORT

1. Name: Mireillle Bélanger （ID No.: SP054001）

2. Current affiliation: Université de Montréal

3. Research fields and specialties:

Humanities Social Sciences Mathematical and Physical Sciences
Chemistry Engineering Sciences x Biological Sciences
Agricultural Sciences Medical, Dental and Pharmaceutical Sciences
Interdisciplinary and Frontier Sciences

4. Host institution: Tohoku University

5. Host researcher: Prof. Tetsuya Terasaki

6. Description of your current research

Acute liver failure (ALF) may occur following viral infection or as a result of toxic liver injury (eg. acetaminophen toxicity). Irrespective of its etiology, ALF is associated with serious neurological complications including hepatic encephalopathy, a syndrome characterized by altered mental status that may rapidly progress to stupor and coma. Brain edema is a second major complication of ALF since it can lead to intracranial hypertension and brain herniation, a common cause of mortality in ALF.

Most of my research efforts have been aimed at identifying alterations in gene expression in the brain of rats with ALF as well as understanding the consequences of these changes in gene expression. Our results demonstrate that ALF affects the expression of key astrocytic proteins, many of which may be implicated in the apparition of brain edema

However, very little is known about the effects of ammonia on brain endothelial cells (which form the blood-brain barrier (BBB) and are in direct contact with blood-borne ammonia). The present study was undertaken to study the effects of ammonia (ammonium chloride: NH_4Cl) on gene expression and function in cultured BBB cells in order to identify possible alterations in BBB function in hyperammonemia and ALF.

7. Research implementation and results under the program

(As much as possible, describe the contents and results of your research in a manner that is easily understandable to a non-specialist in your field.):

Title of your research plan:

Effects of ammonium chloride on TM-BBB cells

Description of the research activities:

1. Gene expression screening following exposure to NH_4Cl in TM-BBB4 cells

Purpose

Study the effects of exposure to ammonia on TM-BBB cells. To do so, mRNA expression of a series of target genes was screened in a pilot study using real time PCR. A preliminary study was first conducted if needed to confirm the expression of some of the target genes in TM-BBB cells.

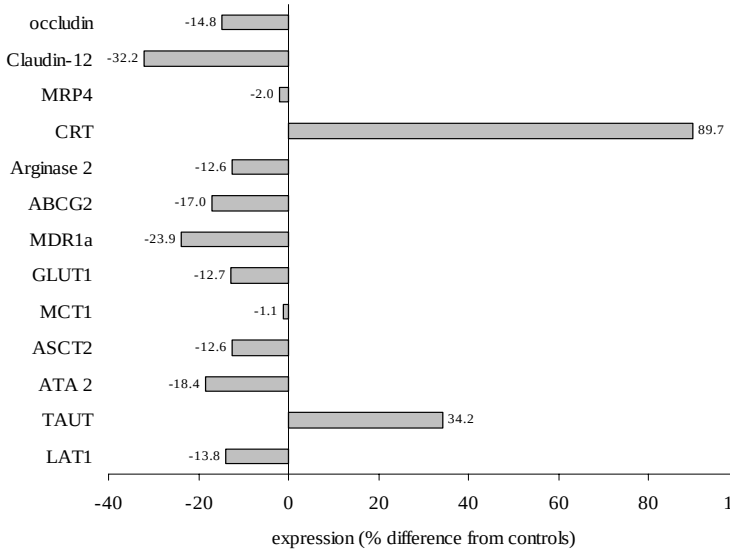

Figure 1. Effects of exposure to 5 mM NH_4Cl for 72 hours on gene expression in TM-BBB4 cells (pilot study). mRNA was measured by real-time PCR (pilot study).

- mRNA expression for most genes was only slightly affected by exposure to ammonia with the exception of:
  - Claudin-12, which was decreased by 32.2 %
  - CRT which was increased by 89.7 %
  - TAUT which was increased by 34.2 %

2. Quantitative Real Time PCR analysis of CRT and TAUT (confirmation of results) (n=5)

- TAUT mRNA levels were significantly increased (2.0-fold) in TM-BBB cells after exposure to 5mM NH_4Cl for 72 hours, confirming the result of the pilot study.
- CRT mRNA levels were significantly increased (1.9-fold) in TM-BBB cells

after exposure to 5mM NH_4Cl for 72 hours which also confirmed the result of the pilot study.

3.4 Uptake study

Purpose: Confirm and characterize the functional consequences of TAUT and CRT up-regulation in TM-BBB cells exposed to ammonia.

- Uptake of both [^{3}H] Taurine and [^{14}C] Creatine into TM-BBB cells were increased following exopusure to ammonia, suggesting that the observed increase in mRNA levels translated into significant gain of function of these two transporters
- Taurine is be implicated in osmoregulation and TAUT up-regulation at the BBB in hyperammonemia may facilitate the efflux of taurine from the brain and contribute to reduce brain swelling.
- Creatine and phosphocreatine are important for rapid buffering of high energy phosphates. Increase expression of CRT at the BBB may be help regulate brain energy metabolism which are altered in hyperammonemia.

RESEARCH REPORT

1. Name: Lulu Bursztyn （ID No.: SP05402）

2. Current affiliation: Queen's University

3. Research fields and specialties:

Humanities Social Sciences Mathematical and Physical Sciences
Chemistry Engineering Sciences Biological Sciences
Agricultural Sciences X Medical, Dental and Pharmaceutical Sciences
Interdisciplinary and Frontier Sciences

4. Host institution: Advanced Telecommunications Research Institute International

5. Host researcher: Dr. Mitsuo Kawato

6. Description of your current research

The goal of my research is to investigate how the brain represents object dynamics and how people learn dynamics of multiple objects. Our ability to skillfully manipulate a wide variety of objects with different dynamic properties – relating forces applied to the object and object motion – suggests that we acquire and store in memory representations or models that capture the dynamics of multiple objects. To study learning of dynamics, previous studies have examined how people adapt to novel force-fields applied through a hand-held manipulandum during reaching movements. Following adaptation, during which initially perturbed hand trajectories return to normal, transfer of learning is tested when the arm is rotated to a new spatial location. The finding that transfer is good when the force-field rotates with the arm but not when the field translates with the hand has been taken as evidence that novel dynamics are encoded in intrinsic coordinates related to the arm. However, an alternate explanation is that people code dynamics in object coordinates and that rotation of the arm is equivalent to rotation of a hand-held object. The first experiment of my project will test this possibility by dissociating, for the first time, object coordinates from intrinsic coordinates.

Subjects will perform a centre-out reaching task in a horizontal plane while grasping a handle, or hand-held object, attached to the robot arm. Unlike previous force-field experiments, the grasped object will have a distinct shape, such as a teardrop, that provides information about its orientation. Subjects will see a visual image of the object (provided by a virtual reality projection system) but will not see their arm. After adapting to a force-field in one location, the arm will be rotated and transfer of learning will be tested. In four different groups of subjects, the field will either be rotated or translated and the grasped object will either be rotated or kept in the same orientation. We

hypothesize that good transfer of learning will be observed only when the force-field and object share the same orientation. For example, we predict good transfer when the field is translated but the object is not rotated with the arm. Confirmation of this hypothesis would be a change to the currently accepted view that dynamics are encoded in intrinsic coordinates and would suggest, instead, that they are linked to manipulated objects and encoded in object coordinates.

Previous studies have shown that people cannot simultaneously learn two opposing force-fields, perturbing the hand in opposite directions, when the fields are experienced in alternation. The second experiment of my project will examine whether opposing force-fields can be learned if the dynamics are linked to separate objects. While grasping a handle attached to the robot arm, subjects will “pick up” (by pressing a switch on the handle), move and drop off (by releasing the switch) virtual balls in a horizontal plane. Balls of two distinct colours will be used and associated with opposing force-fields. Subjects will move the balls in alternation from a common start point to a common drop off point. A control group will make similar movements against alternating force-fields but without the object cues. We hypothesize that subjects will be able to learn the opposing force-fields when these are linked to distinct objects. Confirmation of this hypothesis would provide the first demonstration that opposing force-fields experienced in alternation can be learned and would also provide further evidence that the representation of dynamics in the brain is linked to objects.

7. Research implementation and results under the program

(As much as possible, describe the contents and results of your research in a manner that is easily understandable to a non-specialist in your field.):

Title of your research plan:

Isolation of Internal Model Loading Using fMRI

Description of the research activities:

When learning novel motor tasks, people construct internal models – representations of the dynamics of the object or force-field – that allow successful manipulation of a new object. The acquisition of internal models is frequently tested through a robot manipulandum, where subjects adapt to a force field applied through a handle attached to the robot arm that perturbs the arm during reaching. Subjects readily learn to make straight movements in the presence of the field and show negative after effects of the same magnitude as the initial perturbations if the field is unexpectedly removed. However, once the subject releases the handle, they do not exhibit similar after effects while moving about in the natural environment. Upon re-grasping, adaptation returns with little to no loss. The same results occur

even if the force-field is introduced so gradually that subjects are unaware of its existence. This suggests that the internal model is loaded into the brain at some point between the grasp and the onset of movement and unloaded after the movement. We hypothesized that this loading is triggered by the act of grasping the handle.

Subjects were trained to perform a simple motor task using a 1 degree of freedom manipulandum. They learned to grasp a handle on the robot which allowed them to move a cursor from a start position to a target position on a projected display. After passing a test to demonstrate learning, subjects entered the fMRI scanner and performed 40 repetitions each of 3 randomly interspersed tasks: the learned movement, a similar movement without the handle and squeezing the handle. The two control conditions should theoretically allow isolation of the brain activity related to the loading of the model. Preliminary data collected from 7 subjects shows significant activity in M1, SMA and the cerebellum at the moment of grasping in the trained movement condition. This suggests that model loading may indeed be triggered by grasping.

RESEARCH REPORT

1. Name: Christiana Cheng （ID No.: SP05403）

2. Current affiliation: Department of Biological Sciences, Simon Fraser University, British Columbia, Canada

3. Research fields and specialties:

Humanities Social Sciences Mathematical and Physical Sciences
Chemistry Engineering Sciences xBiological Sciences
Agricultural Sciences Medical, Dental and Pharmaceutical Sciences
Interdisciplinary and Frontier Sciences

4. Host institution: Tokyo University of Marine Science and Technology

5. Host researcher: Dr. Goro Yoshizaki

6. Description of your current research

The vertebrate retina has different spectral types of cone photoreceptors that permit colour vision. The cone photoreceptors of salmonid fishes are arranged in a square mosaic, the unit of which consists of four double cones (whose long axes lie along the sides of the square) with a single central cone in the middle and four single cones located at the corners of the square. Each of these morphological cone types has a predominant visual pigment (opsin) which determines its wavelength of maximum absorbance (λ_{max}), i.e. its spectral phenotype. Double cones are most sensitive to middle wavelength (green) and long wavelength (red) light, while single cones are most sensitive to short wavelength (blue) or ultraviolet (UV) light. It is the combined action of different spectral types of cones that permits colour vision.

My research has shown that the single cones in the retinas of juvenile salmonid fishes transform from UV to blue phenotype by changeover of opsins. All the salmonid fishes that I have examined (pink, chum, coho, chinook salmon, as well as rainbow trout) have single cones that express UV opsin at hatching exclusively. However, as the fish grow, the single cones stop producing UV opsin and start producing blue opsin, thereby changing their spectral absorbance from UV to blue. This changeover in opsins occurs as the animal switches habitats from life in surface waters (where UV light is abundant) to life in deeper waters (where blue light prevails). Thus, the single cone transformation maximizes the sensitivity of the animal to a new photic environment.

The molecular mechanisms that underlie the transformation form the subject of my present PhD research.

7. Research implementation and results under the program

(As much as possible, describe the contents and results of your research in a manner that is easily understandable to a non-specialist in your field.):

Title of your research plan: Regulation of visual pigment expression in the retinal of salmonid fishes

Description of the research activities:

Proposed Research: The distinct temporal expression of UV opsin and blue opsin observed in various salmonid fishes indicates that specific molecular determinants must control the expression pattern of these genes. Expression of proteins (in this case opsins) is often regulated at the transcriptional level through the interaction of transcription factors and the gene's promoter, which is located upstream of the gene. Our collaborative research with Dr. Yoshizaki aims to uncover the regulatory mechanisms guiding the UV to blue opsin changeover in the single cones of salmonid fishes by characterizing the functional promoter region of the opsins. Functional

analysis of cone opsin promoters has not been carried out extensively, especially in salmonids, thus the length of the functional promoter in these fishes is unknown. To determine the minimal functional length, a large piece of DNA sequence lying upstream of the UV and blue opsin gene will be cleaved into various sizes and each fragment will be tested in a reporter-cell transfection assay.

Method: A ~4kilobase (kb) DNA sequence lying upstream of the two opsin genes has been previously isolated by screening the Atlantic salmon genomic DNA library. The upstream sequences were cleaved into fragments of various lengths, which were cloned into a reporter vector to assay their function. If the fragment is part of a functional unit, it will drive the expression of the detectable reporter and the expression level will be proportional to the strength of the upstream sequence. The effectiveness of the fragment was tested in cell transfection assay and in zebrafish embryo for its in vivo relevance.

Results: First trail of cell transfection experiments showed that UV opsin upstream sequence of 3.5kb, 2.5kb, 1.5kb and 0.5kb, and blue opsin upstream sequence of 3.0kb, 2.0kb, 1.0kb and 0.5kb were all able to direct the expression of reporter. Microinjection of reporter constructs containing 3.5kb of the UV opsin upstream sequence and 3.0kb of the blue opsin showed that both promoters were capable to direct expression of reporter in vivo.

Addition experiments will be needed to confirm present results and to examine the relative strength of each promoter fragment.

RESEARCH REPORT

1. Name: Corrie J.B. daCosta （ID No.: SP05404）

2. Current affiliation: University of Ottawa, Canada

3. Research fields and specialties:

Humanities Social Sciences Mathematical and Physical Sciences
Chemistry Engineering Sciences X Biological Sciences
Agricultural Sciences Medical, Dental and Pharmaceutical Sciences
Interdisciplinary and Frontier Sciences

4. Host institution: Kyoto University

5. Host researcher: Dr. Yoshinori Fujiyoshi

6. Description of your current research

All living cells are encapsulated by a plasma membrane which protects them from their surrounding environment. While this barrier is essential for maintaining homeostasis, its presence has necessitated the evolution of complex mechanisms which allow cells to sense and respond to external stimuli. To survive, cells must exchange and transport specific solutes across this barrier in a highly regulated and selective way. In addition, extracellular signals must be transduced into intracellular responses. The molecules responsible for these essential and diverse functions are a class of proteins collectively referred to as “integral membrane proteins”.

Integral membrane proteins traverse the hydrophobic plasma membrane and act as the “gate keepers” of the cell. Because they are the cells main means of communication with the outside world, integral membrane proteins are recognized as important therapeutic targets. In fact, roughly 60% of current pharmaceuticals target integral membrane proteins, therefore a detailed understanding of the structure, function and mechanism of this class of proteins is essential.

My research in Canada focuses on elucidating how the composition of the surrounding membrane modulates membrane protein structure and function. In particular, I am interested in a class of membrane proteins called neurotransmitter receptors, which are responsible for inter-neuronal communication in the brain. The function of these proteins has been shown to be intimately related to their membrane.

7. Research implementation and results under the program

(As much as possible, describe the contents and results of your research in a manner that is easily understandable to a non-specialist in your field.):

Title of your research plan:

Structural Studies of a Bacterial Voltage-Gated Sodium Channel

Description of the research activities:

Neurons, the cells of the central nervous system, communicate with each other through electric signals called “action potentials”. These action potentials are waves of depolarization which result from the flow of salt, or more precisely, ions across the neuronal membrane. The permeability of the neuronal membrane to specific ions, such as sodium and potassium, is tightly regulated by molecular machines called ion channels. Deciphering how these ion channels function is essential for a detailed understanding of the central nervous system.

In 1998 our understanding of ion channels took a momentous leap forward with the elucidation of a bacterial potassium channel structure at atomic resolution. This work, for which Roderick MacKinnon was awarded the 2003 Nobel Prize in Chemistry, highlighted the fact that in order to understand how ion channels work it is necessary to determine their three dimensional structure. While this structure greatly increased our understanding of ion channel function, several important questions remain. In particular, while we know a great deal about potassium selectivity, much less is known about sodium selectivity. How do sodium channels discriminate, with exquisite precision, between sodium and potassium ions, both of which are monovalent cationic spheres?

Another key question involves channel gating (opening and closing). Action potentials arise from coordinated changes in the relative permeability of the neuronal membrane to both sodium and potassium. In the depolarizing phase of an action potential sodium channels must open, while in the repolarizing phase they must close. The driving force for this gating is the electrical potential difference (or voltage) across the neuronal membrane (hence the term “voltage-dependent ion channels”). The fundamental question remains: how are changes in membrane voltage coupled to ion channel gating?

In order to address these questions, Dr. Fujiyoshi’s laboratory is actively trying to solve the atomic resolution structure of a bacterial voltage-dependent sodium channel (called NaChBac). The advantage of using protein derived from a bacterial source is that it can be produced in relatively large quantities, a requirement for structural studies. Dr. Fujiyoshi’s lab also specializes in cryo-electron microscopy, which is a novel technique in which the structure of a membrane protein can be determined while it is still embedded in a membrane. This technique may be particularly suited to proteins like ion channels which often require their surrounding

membrane for structural stability.

My time in Japan has been spent working on refining the NaChBac purification protocol. In particular, I have included lipid throughout the purification procedure since preliminary data suggests that lipids may be essential for NaChBac's structural integrity. Including lipid in the purification procedure is not trivial as the presence of lipid can affect the solubility of the protein. In order to be purified chromatographically, proteins must be soluble. For membrane proteins this means removing them from their insoluble membrane, usually with the use of amphiphilic molecules called detergents. As both the function and structure of many membrane proteins is intimately related to their surrounding membrane this can result in the protein being denatured, rendering it useless for structural analysis.

We have expressed and purified both N- and C-terminally His-tagged NaChBac. This protein has been purified by Ni^{2+} affinity chromatography. The lipid concentration and type, as well as the detergent concentration has been varied in column wash buffers in order to determine which lipid:detergent:protein ratio is optimal for protein solubility and yield. We have also performed two-dimensional crystallization trials on these purified protein samples, which are being monitored by negative staining electron microscopy. We have been able to re-incorporate NaChBac into lipid membranes of a defined composition. This is an important step towards its crystallization and thus structure determination.

8. Please add your comments (if any): Thank you JSPS, and the people of Japan for the opportunity to work with one of your internationally renowned scientists. Thank you Dr. Yoshinori Fujiyoshi for allowing me to be involved in such an exciting project, and thanks to Dr. Tomoya Imai for all the help over the past two months.

9. Advisor's remarks (if any):

I am very happy to have a chance to meet Mr. Corrie J. B. daCosta and collaborate with him on our channel project. Our members (including Dr. Tomoya Imai who is a researcher collaborating with Corrie) said to me they are also happy, because Corrie is very nice scientist and has nice personality. After his visit, our projects were very well advanced by his help. I hope we will be able to keep nice collaboration with Corrie. I would therefore like to thank the JSPS program.

RESEARCH REPORT

1. Name: Dany Dionne （ID No.: SP05405 ）

2. Current affiliation: Mechanical Engineering Department
Concordia University, Montreal, Canada

3. Research fields and specialties:

Humanities Social Sciences Mathematical and Physical Sciences
Chemistry X Engineering Sciences Biological Sciences
Agricultural Sciences Medical, Dental and Pharmaceutical Sciences
Interdisciplinary and Frontier Sciences

4. Host institution: Kyushu Institute of Technology

5. Host researcher: Professor Norikazu Ikoma

6. Description of your current research

Title:

On decentralized task allocation in control of a group of vehicles.

Description:

Dynamic task allocation is an essential requirement for multi-robot systems operating in unknown dynamic environments. It allows robots to change their behavior in response to environmental changes or actions of other robots in order to improve overall system performance. Emergent coordination algorithms for task allocation that use only local sensing and no direct communication between robots are attractive because they are robust and scalable. However, a lack of formal analysis tools makes emergent coordination algorithms difficult to design.

The current research is concerned with the decentralized dynamic task allocation task in a specific application of the type “systems of systems”, that is, the decentralized control of a fleet of unmanned aerial vehicles (a first system) aiming to intercept a fleet of targets (a second system).

7. Research implementation and results under the program

(As much as possible, describe the contents and results of your research in a manner that is easily understandable to a non-specialist in your field.):

Title of your research plan:

Design of particle filters for the tracking of non-cooperative maneuverable targets.

Description of the research activities:

The problem of tracking an object moving in space in general involves nonlinear dynamics, nonlinear measurements, and non-Gaussian uncertainties. In standard solution approaches, the nonlinear dynamics and measurements are approximated by a linear model while the uncertainties are approximated to have a known Gaussian distribution.

The recently developed particle filter algorithms permits to solve the tracking problem using the full nonlinear/non-Gaussian description. However, as a trade-off, particle filters provide only approximate solutions as they solve the problem

numerically rather than analytically.

For the tracking problem of non-cooperative maneuverable targets, the analytical approximations are found to severely degrade the description of the system. The particle filters are then interesting tools in obtaining solutions.

RESEARCH REPORT

1. Name: Chantal Dupasquier (ID No.: SP05406)

2. Current affiliation:

National Centre for Agri-Food Research in Medicine, St. Boniface General Hospital Research Centre, University of Manitoba, Winnipeg, Canada

3. Research fields and specialties:

Humanities Social Sciences Mathematical and Physical Sciences
Chemistry Engineering Sciences **X** Biological Sciences
Agricultural Sciences **X** Medical, Dental and Pharmaceutical Sciences
Interdisciplinary and Frontier Sciences

4. Host institution: Graduate School of Medicine, Chiba University, Chiba, Japan

5. Host researcher: Drs. Y. Saito and H. Bujo

6. Description of your current research

My current research aims at determining the physiological, cellular and molecular mechanisms by which dietary flaxseed reduces the development of atherosclerosis. Atherosclerosis is a common degenerative condition caused by the build up of fatty deposits into plaques in the walls of arteries. Atherosclerosis causes narrowing of blood vessels, limiting blood flow to tissues of the body. Atherosclerosis is the leading cause of ischemic heart disease and stroke. The first event in atherosclerosis is thought to be damage to the lining of arteries caused by oxidized cholesterol or a common infection, thereby activating an immune reaction and inflammation. Protecting against this action, therefore, represents an important therapeutic strategy. Consuming flaxseed, a grain common in the Canadian prairies, is thought to reduce the risk of atherosclerosis by reducing inflammation and circulating cholesterol levels. Flaxseed is the richest plant source of polyunsaturated omega-3 fatty acids, is free of cholesterol, and is an excellent source of fibre and the lignan SDG. Dietary supplementation with omega-3 fatty acids decreases the generation of pro-inflammatory mediators and reduces circulating cholesterol levels. The fiber found in flaxseed can also lower cholesterol levels. The lignan SDG has demonstrated anti-inflammatory activity. My M.Sc. research demonstrates that flaxseed reduces plasma cholesterol levels and reduces the progression of atherosclerosis in hypercholesterolemic rabbits and in low-density lipoprotein (LDL) receptor deficient mice. The mechanisms by which flaxseed is anti-atherogenic remain to be fully elucidated. I will conduct further analyses to clarify the effects of flaxseed on the following parameters thought to be involved in atherogenesis; the effects of flaxseed on lipid, cholesterol, and inflammatory cell infiltration into atherosclerotic plaques, on oxidation

and inflammation, on vascular smooth muscle cell (SMC) migration and proliferation, on the expression of genes, and the effects of flaxseed on different cell types and organs, such as adipose (fat) tissue and the liver. I will require training by experts in these fields to conduct these tests. The information to be obtained should be some of the most comprehensive tissue, cellular and subcellular data regarding the effects of flaxseed on atherosclerotic cardiovascular disease and vascular function in an inflammatory situation.

7. Research implementation and results under the program

(As much as possible, describe the contents and results of your research in a manner that is easily understandable to a non-specialist in your field.):

Title of your research plan:

Functional analyses of adipocytes in obesity-associated co-morbidity

Description of the research activities:

My research goal during the JSPS summer program was to learn the research techniques related to the metabolism of fat tissue. I have learned the techniques related to fat (adipocyte) cell culture and adipocyte metabolism.

Obesity is known to be related to metabolic disorders leading to atherosclerosis, such as diabetes mellitus, hyperlipidemia and hypertension. The distribution of fat accumulation in the body is particularly important with regards to complications from these metabolic disorders. The disturbed function of adipocytes accumulated in the visceral area of the body is a determining factor of obesity-associated co-morbidity. My research goal was to learn the techniques to help elucidate the mechanism by which pathological adipocytes secrete cytokines which contribute to metabolic syndrome.

I have learned the following techniques: 1) The preparation and differentiation of mature adipocytes from mouse adipose tissue (primary adipocyte) and 3T3-L1 preadipocytes. I assessed the accumulation of lipid in the cultured adipocytes using Oil red O stain, which stains lipids red. 2) The extraction of adipose tissue from mice and the preparation of primary adipocytes in culture using a collagenase treatment and size fractionation techniques using nylon filters. 3) The preparation of protein and RNA samples from the size-fractionated adipocytes. 4) The quantification of RNA gene expression in the size-fractionated adipocytes using specific primers with RT-PCR (Reverse Transcription and Polymerase Chain Reaction). 5) The quantification of transcription factor regulation in 3T3-L1 adipocytes. The adipocytes were transfected with the promotion vectors PPARg1 and PPARg2. The expression of C/EBPα and PPARg2 were quantified by luciferase and renilla assays.

I will integrate the knowledge learned during my stay in Japan into my thesis

research project in Canada to help me determine if flaxseed has any effects on adipocytes and obesity. It is known that other fats, namely the polyunsaturated fatty acid conjugated linoleic acid, commonly found in ruminant meats and dairy products, can reduce the accumulation of fat mass and beneficially affect adipocyte metabolism. I will conduct tests in Canada if flaxseed can beneficially affect fat metabolism and obesity.

8. Please add your comments (if any):

I have had a wonderful time enjoying Japanese culture. I have visited Tokyo, Nagoya, Osaka, Kyoto, Kamakura, and Niigata. I have done two home stays, visited many temples, attended a sumo tournament and a music festival, went fishing on the Japan Sea, and had some fantastic Japanese food and drinks. I have made great friends through the JSPS program and with the members of my laboratory. I was treated very well in my laboratory. My coworkers were welcoming, friendly, patient, and generous. I also had the opportunity to attend four research conferences, including the 37th Japan Atherosclerosis Society Annual Meeting in Tokyo. This has been a memorable experience. A big THANK YOU to JSPS, the Canadian Embassy, NSERC, my professors Drs. Saito and Bujo, and the staff and students of Chiba University!

9. Advisor's remarks (if any):

We could have a fruitful time with Chantal Dupasquier for 2 months. In this summer course, we could provide her the knowledge and techniques for research of adipocytes. I hope that Chantal will develop her work in Canada by adding them to her original interests.

In addition to science, we could have a very happy time with Chantal over the inconvenience of English-speaking problem with us. This is totally up to her gentle, friendly and heartful behavior in our labo. I am sure that Chantal could have a lot of funny and valuable experiences with us.

I would like to thank to JSPS for a nice meeting with excellent Chantal.

Thank you, and a good luck in your future, Chantal!

From Hideaki Bujo and all in labo.

RESEARCH REPORT

1. Name: Julie Dutil （ID No.: SP05407）

2. Current affiliation:

University of Montreal, CHUM Reseach Center

3. Research fields and specialties:

Humanities Social Sciences Mathematical and Physical Sciences
Chemistry Engineering Sciences XBiological Sciences
Agricultural Sciences XMedical, Dental and Pharmaceutical Sciences
Interdisciplinary and Frontier Sciences

4. Host institution: Osaka University Hospital, Graduate School of Medicine

5. Host researcher: Dr Tomohiro Katsuya

6. Description of your current research

Hypertension afflicts up to 30% of the North American population and is a leading cause of death as it is associated with an increased risk of cardiovascular diseases. Blood pressure (BP) regulation is a complex trait because it is influenced by a genetic component involving multiple genes, and an environmental component including diet, exercise and stress. Little is known about the genes regulating BP. Study of the genetic basis to human hypertension is limited by the heterogeneity of human populations and by environmental influences. Rat models are tools that facilitate the study of complex traits by providing homologous populations that can be manipulated easily in a controlled environment. We are using the Dalh Salt-sensitive (S) rat, a genetically hypertensive rat model, in combination with the congenic strain approach. This model is unique in Canada. A congenic strain is made by a series of selective breeding in which a region of the S rat is replaced by the homologous region from the normotensive Milan strain (M). If the congenic has a BP lower than that of the S rat, the region replaced contains is involved in the regulation of BP. The congenic strain approach allows to dissect the complex traits into individual regions each contributing to the BP variations. These regions are called quantitative trait loci (QTL). In my PhD work, this model has allowed to narrow down the rat chromosome 2 BP QTL from a region of 80 centiMorgan (cM) to three non-overlapping regions each containing at least one distinct BP QTL: QTL1 (5cM), QTL2 (10cM) and QTL3 (2cM).

7. Research implementation and results under the program

(As much as possible, describe the contents and results of your research in a manner that is easily understandable to a non-specialist in your field.):

Title of your research plan:

Identification of the genetic bases to hypertension: from rats models to human.

Description of the research activities:

Introduction

Once the regions of interest are identified with the help of animal models, their relevance to human hypertension needs to be assessed. The research conducted in Japan was designed to initiate the transition from rat to human by studying genetic variations in human candidate genes located in regions homologous to the rat BP QTL.

The Dahl Salt-sensitive rat is a model of salt sensitive hypertension. Previous studies by Dr Katsuya *et al.* [1] have shown that polymorphisms in genes involved in salt-sensitive hypertension were more frequent in the Japanese population than in the Caucasian population. The abundance of salt-sensitive hypertension predisposing alleles in the Japanese population makes it a suitable population for the evaluation of candidate genes from salt-sensitive rats.

Methods and results

Comparative mapping using the information available on the National Center for Biotechnology Information (NCBI) has allowed to determine that the chromosome 2 regions of interest in the rat are homologous to segments of Chr 13, 3 and 4 in human. Within each synthenic segment, gene order is conserved between rat and human.

From the list of genes present in the human region of interest, candidate genes were selected for further studies. A candidate gene is defined as a gene whose function is known and may be related to cardiovascular system homeostasis. The following genes met those requirements: MME coding for the membrane metallo-endopeptidase, CCNA1 coding for cyclin A1, NBEA coding for neurobeachin A, NPY2R coding for neuropeptide Y receptor 2, and SLC33A1 coding for solute carrier family 33 (acetyl-CoA transporter), member 1.

In these candidate genes, a total of 13 single nucleotide polymorphisms (SNP) were identified and available for genotyping (SNP browser 3.0 from Applied Biosystem). SNPs are variations at a single base pair in the DNA sequence. SNPs resulting in a amino acid change in the protein or SNPs localized to the regulatory regions of the gene were selected.

A population consisting of 597 individuals including severe cases of hypertensive patients (case) and normotensive (controls) was genotyped at each SNP

locus. 10 of the SNPs studied were not polymorphic among the Japanese population. The remaining SNPs showed variations among the Japanese population. Polymorphic SNPs were examined for their statistical association with the blood pressure phenotype. The genotype at hCV29013142 (NPY2Rb) and hCV2835813 (SLC33A1) were not associated with blood pressure variations. AA genotype at hCV1131982 (NPY2Ra) was associated with a higher risk of hypertension than the GG or AG genotype.

Conclusions

We have identified a variation in the regulatory region of NPY2R gene coding for the neuropeptide Y2 receptor. Neuropeptide Y is a neurotransmitter and a potent endothelium-derived angiogenic factor and vascular mitogen. Bearing the AA genotype at this locus is associated with a higher risk of hypertension. For these reasons, NPY2R is a candidate for the genetic determination of blood pressure level.

Perspectives Hypertension is a major risk factor for the onset of lethal cardiovascular diseases. However, detection and control is achieved in only 13% of hypertensive patients. Identification of genes for hypertension is necessary for the development of genetic diagnostic tools, design of new medications and a personalized treatment based on the genetic profile of a given patient, a field known as pharmacogenomics. Prevention and individualized treatment means reduction in cost and optimal efficiency of health delivery system.

Reference

1 Katsuya *et al*. 2003. Salt-Sensitivity of Japanese from the Viewpoint of Gene Polymorphism. *Hypertension Research* 26 : 521-525

8. Please add your comments (if any):

'Domo arigato gozaimasu' to Dr Katsuya and his team for their help and support on the project and for answering my numerous questions about this great country! . Thanks to JSPS , the Canadian Embassy and the Canadian Institutes for Health Research for funding and for working to provide students with such exceptional opportunities.

RESEARCH REPORT

1. Name: Khosro Shahbazi （ID No.: SP05408 ）

2. Current affiliation: University of Toronto

3. Research fields and specialties:

Humanities Social Sciences Mathematical and Physical Sciences
Chemistry X Engineering Sciences Biological Sciences
Agricultural Sciences Medical, Dental and Pharmaceutical Sciences
Interdisciplinary and Frontier Sciences

4. Host institution: Physiological Flow Studies Laboratories, Tohoku University

5. Host researcher: Prof. Takami Yamaguchi

6. Description of your current research

Introduction

Heart valve disease is a life-threatening condition leading to 250,000 valve repairs and/or replacements per year worldwide. Replacement valves are either tissue valves or mechanical heart valves (MHVs). There are about 50 different types of MHVs, which tend to be implanted in younger patients due to their superior durability.

However, MHV recipients suffer from complications related to platelet activation,

so they must undergo life-long anticoagulant therapy which has severe side-effects. Platelet activation occurs as platelets pass through a MHV, where they experience

non-physiological flow patterns characterized by high incidence of flow stagnation and flow separation, high shear stresses and high turbulence. These non-physiological flow

patterns are related to MHV design sub-optimality. Realizing this problem suggests the need to improve current valve designs and/or strive for radical new designs. To this end, the best approach, the fastest and the least expensive one, is to use computer simulations which are based on numerically solving the governing partial differential equations for fluid flow, the Navier-Stokes equations. We choose this approach in this research project.

Objective

Blood flow through a MHV is very complex. It is highly three dimensional,

unsteady, transitional and highly anisotropic and intermittently turbulent.

Previous numerical modeling work of blood flow through MHVs has considered

highly simplified models such as two dimensional turbulence models, which are

inadequate. Therefore, my research objective is to develop a three dimensional unsteady Navier-Stokes solver for direct numerical simulation (DNS) of transition and turbulenc in complex mechnical heart valve geometry

Methodology

Feasibility of DNS of transition and turbulence, in which all active temporal and spatial scales in the flow are resolved, depends upon the availability of

massive computational resources as well as devising a highly efficient numerical scheme for solving the Navier-Stokes equations and the large scale parallel

implementation of this scheme. Based on the state-of-the-art literature and

our own contributions , we have proposed to use high-oder spatial discretization along with a discontinuous Galerkin formulation. The parallel implementation is based on

the Algorithm Oriented Mesh Database (AOMD) of Rensseslaer Polytechnic

Institute, the Portable, Extensible Toolkit for Scientific Computing (PETSC) of US Argonne National Laboratory, and the C++ programming language.

Significance

We will use the developed code as a design tool to execute parametric studies on contemporary valve designs and even new configurations, with the aim of finding optimal designs based on performance criterion of minimal platelet activation. This innovative, interdisciplinary research is based on contributions of computer science, mathematics, bioengineering and biology, and will ultimately improve millions of people's health worldwide.

7. Research implementation and results under the program

(As much as possible, describe the contents and results of your research in a manner that is easily understandable to a non-specialist in your field.):

Title of your research plan:

Verifiction and Performance Improvement of the Unsteady Incompressible Navier-Stokes Solver

Description of the research activities:

I have carried out the following tasks during my stay in Japan.

1. I have compeleted the implementation of the Navier-Stokes solver using high-order discontinuous Galerkin methd.

2. I have verified the accuracy of the developed Navier-Stokes solver using two benchmark tests. In the first test, an analytical solution of the Navier-Stokes on a square domain was confirmed. In the second test, the accuracy of the solver was evauated using the plane channel flow instability at Reynolds number equal 7500. The analytical energy growth rate of the small disturbances have been obtained through the numerical experiments. This test was particularly relavant to the blood flow regimes through mechanical heart valves.

3. Using the parallel computers of my Japanses hosts, I was able to evaluate the performace of the solver and also make some improvements. The CPU and memory usages of the code were measured and confirmed with the expected theoretical bounds. I also improved the CPU time of the solver by a factor of three for a benchmark problem. This improvement is critical for the large scale computation of the blood flow through mechanical heart valves which we will carry out in the near future.

Future Work

As a result of our communication with Prof. Yamaguchi`s research group, we have agreed to continue working together on the project of

simulating blood flow through mechnical heart valves

and assessments of platelet activation and red blood

cell damages. Prof. Yamagochi's group are able to obtain experimental data related to the geometry of the heart, heart valves as well as blood flow condition in the heart. This information is essential for realistic simulation of blood flow through MHVs, which I will be carrying out in the near future.

RESEARCH REPORT

1. Name: Sarah Catherine Shaughnessy （ID No.: SP05409 ）

2. Current affiliation: University of Toronto

3. Research fields and specialties:

Humanities X Social Sciences Mathematical and Physical Sciences
Chemistry Engineering Sciences Biological Sciences
Agricultural Sciences Medical, Dental and Pharmaceutical Sciences
Interdisciplinary and Frontier Sciences

4. Host institution: University of Tokyo

5. Host researcher: Dr. Susumu Yamaguchi

6. Description of your current research

I am involved with several lines of research within the field of cross-cultural psychology including an investigation of changes in self-identity among international students at the University of Toronto and, in collaboration with Dr. Susumu Yamaguchi, an examination of the basis of cultural differences in self-reports of self-esteem. Recently, I have also been investigating the cultural conditioning of perception, an area that has been the subject of renewed interest over the past few years, particularly in relation to East-West contrasts. Much of the research in this area has been premised on the claim that East Asians tend to utilize a more inclusive perceptual set than do Western Europeans (see e.g. Nisbett, Peng, Choi, & Norenzayan, 2001). A number of studies have indicated that East Asians tend to be more holistic, contextual, and relational than Westerners in dealing with perceptual content. In contrast, North Americans have been more likely to selectively attend to focal objects, ignore contextual information, and overlook relational frames as a basis for categorization. The inclusive perceptual style attributed to East Asians has been termed *holistic*, and the focal Western style has been termed *analytic* (Nisbett et al., 2001).

Intriguingly, my own research in this area failed to obtain the results predicted by the analytic/holistic distinction theory. Through the use of a computerized social memory task I investigated how Chinese and Western-European Canadian participants allocated attention to social targets of varying relevance. Ethnographic accounts have suggested that the tendency to partition the social world into differentially relevant layers is more pronounced among Chinese than those of Western European heritage. I therefore expected that relatively unacculturated Chinese Canadians would be more inclined to disregard persons who are largely irrelevant to their situational interests. In fact, although Chinese Canadians were no more likely than their Western-European counterparts to forget information concerning the less relevant targets, they did not demonstrate the type of holistic perception that has been attributed as characteristic of East Asians. Minimally, this suggests that strong claims about East-West differences in this regard require some qualification and refinement.

7. Research implementation and results under the program

Title of your research plan:

Exploring Cultural Differences in Cognition

Description of the research activities:

A complementary strategy for examining the analytic/holistic distinction in relation to culture is to compare groups on the “global precedence” phenomenon.

The global precedence hypothesis posits that the processing of a visual scene proceeds from the global to the local. That is, global aspects of a visual configuration are structured before a more fine-grained analysis occurs. It is most often demonstrated by examining perception of a hierarchical pattern consisting of smaller figures (local elements) that form a larger figure (global element). The effect is reflected in: 1) the tendency for global forms in compound stimuli to be recognized more quickly than local forms, and 2) greater difficulty in identifying local forms in the presence of conflicting global forms than vice versa (Navon, 1977). The global precedence paradigm provides an ideal paradigm for examining cultural differences on the analytic/holistic dimension. Quite simply, cultural groups believed to be more holistic, as defined above, should show greater global precedence than do group believed to be more analytic.

During my time at the University of Tokyo I had opportunity to continue working on this project which has been conducted in collaboration with Dr. Hiroaki Morio and Yuka Ozaki of Dr. Yamaguchi's lab. Two cultural samples were collected for this study; a Japanese sample at the University of Tokyo and a Western-European Canadian sample at the University of Toronto. The experimental procedure required laboratory sessions with individual participants and the primary task was computerized. Participants were presented with global figures (circles and squares) that were composed of local figures (also circles and squares). Global and local were matched on some trials and mismatched (conflicting) on others. The perception task involved 288 trials spread across 6 blocks. On each trial, the participant's only task was to press, as quickly as possible, one of two keys to indicate whether the global or local figure in the display was a circle or a square. Global versus local identification was varied across blocks, allowing for the response time advantage of global consistency for local identification to be compared with that of local consistency for global identification.

Although results from this study supported both global precedence effects, there were no cultural group differences with regard to the phenomenon. In contrast to the logical predictions of the analytic/holistic distinction theory, Japanese participants did not show a greater global precedence effect in comparison to the Canadian participants. The results of this study, however, remain preliminary while a second sample is collected at the University of Toronto due to some methodological problems with the original data collection.

As a JSPS summer program participant, I also had an excellent opportunity to discuss research with the graduate students, and post-doctoral fellows in Dr. Yamaguchi's lab. It was a privilege to attend and participate in their weekly lab meetings during the month of July, and attend a colloquium talk given by cross-cultural psychologist, Dr. Yoshi Kashima from the University of Melbourne

8. Please add your comments (if any): This program has been an excellent opportunity to study Japanese culture in vivo. I'm certain that my experiences of the past few weeks will continue to inform my research in cross-cultural psychology for years to come. I look forward to future collaborations with Dr. Yamaguchi and other members of his lab. Thank you for the opportunity to take part in this outstanding program.

9. Advisor's remarks (if any):

I believe that her stay was productive for both of us. She has excellent ideas and is sensitive to Japanese culture. Although we did not have enough time to finalize the details of our collaboration, I am sure we will start a join project in the near future. I do hope that she will be able to return to Tokyo for our collaboration.

RESEARCH REPORT

1. Name: Winnie N. Ye （ID No.: SP05410）

2. Current affiliation: Carleton University, Ottawa, ON Canada K1S 5B6

3. Research fields and specialties:

Humanities Social Sciences Mathematical and Physical Sciences
Chemistry X Engineering Sciences Biological Sciences
Agricultural Sciences Medical, Dental and Pharmaceutical Sciences
Interdisciplinary and Frontier Sciences

4. Host institution: University of Tokyo

5. Host researcher: Professor Yasuhiko Arakawa

6. Description of your current research

My Ph.D. research involves the design and fabrication of innovative microphotonic devices involving a high index contrast silicon-on-insulator (SOI) material system. Silicon-on-insulator (SOI) is a promising platform for making multifunctional and high-density integrated optic devices. The mature silicon microfabrication technologies have established a firm foundation for making low-cost and compact integrated photonic devices. Furthermore, having a high refractive index contrast between the cladding and the waveguide core facilitates the confinement and guiding of light in structures with micron or submicron dimensions. However, the high index contrast makes the control of waveguide birefringence extremely challenging. In our study, we have shown that stress engineering is an effective tool to modify or eliminate polarization dispersion in SOI waveguide devices, for a wide range of waveguide cross-section shapes and dimensions. Excellent agreement has been achieved between the experimental results and the numerical simulations from the normalized plane strain model we proposed, confirming that the thickness and the stress level of the upper cladding layer are two useful parameters for effective birefringence tuning. We have also successfully demonstrated the elimination of polarization dependent spectral shifts in SOI arrayed waveguide grating (AWG) demultiplexers by applying the stress technique. Novel stress-induced passive waveguide devices have been designed for polarization splitting and filtering. These devices will be fabricated and the performance of these devices will be tested in the near future.

7. Research implementation and results under the program

(As much as possible, describe the contents and results of your research in a manner that is easily understandable to a non-specialist in your field.):

Title of your research plan:

Fabrication Technologies of Nanocavities on Photonic Crystal Slabs

Description of the research activities:

During my eight-week stay at the University of Tokyo, I have participated in the fabrication and characterization of nanocavities formed in air-bridged photonic crystal slabs. Photonic crystals (PCs) are periodic dielectric nanostructures that are designed to affect the light propagation by defining forbidden band gaps. Introducing defects to a band-gap structure changes the performance of the PCs and opens up a wide range of functionalities. During the last decade, PCs have attracted tremendous interests due to their great potential in making compact integrated optical devices. Our PCs consist of a GaAs substrated and a thin GaAs slab with periodic air hole arrays (nanocavities), separated by an 170μm air bridge, as shown on Fig. 1. We first pattern our PC samples using E-Beam lithography, followed by four processing steps for the nanocavities. First of all, the photoresist on the PC sample needs to be developed, then the oxide layer is etched down by using the CF_4 dry-etching. After that, the nanocavities on the GaAs slab are formed by running the Cl_2 dry-etching through the oxide mask. Finally, the sample is dipped into the HF acid to remove the 170μm-thick layer underneath the GaAs slab, creating an air bridge between the slab and the substrate. The processing of the samples requires trials and errors, before obtaining the optimal processing conditions. After the samples are fully processed, measurements on the photoluminescence spectra of the PCs are performed.

(Please see Figure 1.)

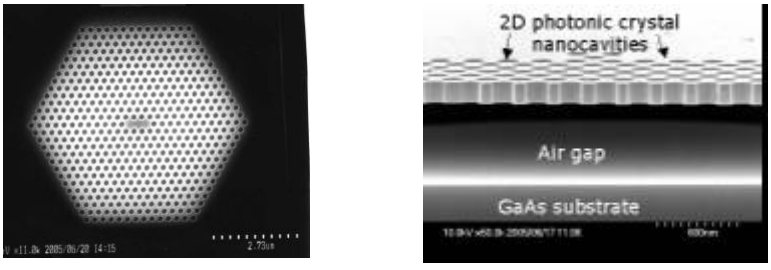

Fig. 1: Top view (left) and side view (right) of our photonic crystals with nanocavities (with the permission from Dr. M. Nomura from University of Tokyo).

8. Please add your comments (if any):

Professor Arakawa is a pioneer in the fields of photonic nanostructure fabrication and semiconductor nanotechnology. It was a privilege to work under the supervision of

Professor Arakawa in his world-class fabrication facility at the University of Tokyo this summer (see picture on the right). I have had a truly amazing experience. I enjoyed working in the multidisciplinary research team with members from Australia, Britain, China, France, Korea, Japan, Switzerland, and US. The two-month summer program not only enhanced my professional knowledge but also my personal development. The experience that I gained from this summer program, and the knowledge I obtained from my research work at the University of Tokyo, more than fulfilled my original goals.

9. Advisor's remarks (if any):

I am happy that Ms. Winnie N. Ye has had various experiences on doing research on a specific topic using experimental facilities at my labs. The success is mainly due to her brightness and wonderful personality. I also greatly appreciate an excellent guidance by a lab's member (Dr. Nomura).

RESEARCH REPORT

1. Name: Frank Xiaofei Gu （ID No.: SP05411 ）

2. Current affiliation: Department of Chemical Engineering, Queen's University, Kingston, ON, Canada

3. Research fields and specialties:

Humanities Social Sciences Mathematical and Physical Sciences
Chemistry X Engineering Sciences Biological Sciences
Agricultural Sciences Medical, Dental and Pharmaceutical Sciences
Interdisciplinary and Frontier Sciences

4. Host institution: Department of Material Engineering, University of Tokyo, Japan.

5. Host researcher: Professor Kazunori Kataoka

6. Description of your current research

My research is on the development of a smart insulin delivery device using nanotechnology for the treatment of type 2 diabetes. Diabetes is characterized by a progressive decline in insulin secretion and results in a greater fluctuation of blood glucose concentration. Currently, there are several types of insulin analogues that are used for controlling the blood glucose concentration via daily multi-injection regimens. However, frequent-injection is painful and can lead to the development of a hypoglycemic coma, due to an overdose of insulin. In other cases, an insufficient amount of injected insulin has led to hyperglycemia and an insufficient therapeutic effect. Therefore, a self-regulated insulin delivery system needs to release insulin when sensing a rise in glucose concentration, and has the ability to automatic shut off of release when blood glucose restores to normal. We developed a glucose sensitive device using polyionic complex (PIC) micelles of insulin and a block copolymer of poly(ethylene glycol)-co-poly-L-Lysine (PEGPLL). The micelles were assembled by the polyionic interaction between the lysine residues on the block copolymer and the cationic amino acids on insulin. The ultimate goal was to provide a tighter control of blood glucose for diabetic patients in order to reduce progression of diabetes and its associated vascular complications.

7. Research implementation and results under the program

(As much as possible, describe the contents and results of your research in a manner that is easily understandable to a non-specialist in your field.):

Title of your research plan:

Glucose-Sensitive Insulin Delivery System using Polyionic Complex Micelles

Description of the research activities:

The objective of my summer research was to design and characterize an insulin delivery device using nanomolecular assembly of insulin and a block copolymer of poly(ethylene glycol)-co-poly-L-Lysine (PEGPLL). The size of the insulin micelles was measured by dynamic light scattering, and the insulin release was characterized by insulin specific enzyme linked immuno sorbent assay. We found that the insulin nanoparticle complex can be formed readily at ambient conditions with a narrow size distribution. The micelles had an average diameter of 110 nanometers. A glucose sensor was added to the micellar core so that the device could modulate the amount of insulin release in response to the fluctuations of blood glucose concentration. It was found that the PIC micelles responded readily to the increase in glucose concentration and released insulin by rapid micellar disintegration. The polyionic complex micelles demonstrated promising potentials as a future insulin delivery vehicle for treating types II diabetes.

8. Please add your comments (if any):

I had a wonderful and a productive summer at Prof. Kataoka's lab. My most sincere thank you to Prof. Kataoka, Drs. Yamasaki, Jang and Yuan, Mr. Kumagai, and Ms. Koyoma for your guidance and your hospitality. Thank you JSPS, Sokendai, and the Canadian Embassy for providing this wonderful research experience. Domo Arigado Gozaimasu.