Welcome

Welcome to **Developmental & Perinatal Biology 2016**. This is the **20th Annual Exchange** in developmental and perinatal biology between The University of Toronto and The Karolinska Institute. The research course has been developed to provide a broad based interdisciplinary training for graduate students, research fellows, clinical fellows and residents in the area of developmental biology from both basic science and clinical perspectives. The workshop combines a lecture/seminar program with an active research component. The course is also offered as a component of a Graduate course (PSL1080H) at the University of Toronto and as a Graduate course at the Karolinska Institute.

In 2015, the course was held at the Karolinska Institute in Sweden from August 17-21, organized by Dr. Ola Hermanson with assistance from Aileen Gracias for the social program. It was attended by 5 Faculty and 16 Trainees from the University of Toronto. From the attendance and success in previous years, it has been clear that there is great interest in this type of summer course. This year we have experienced similar enthusiasm, with 4 Faculty and 16 Trainees attending from Sweden along with 19 Trainees from The University of Toronto. In addition, a large number of Faculty from across the University of Toronto will contribute to the course.

The organization of this type of course requires a considerable input of energy. Therefore, we would like to take this opportunity to thank those on the organizing committee for helping to put the exciting course program together, and to Dr. Ola Hermanson for co-ordinating the Swedish side of the exchange. We would also like to thank Bev Bessey, Victoria De Luca, Jenny Katsoulakos, Eva Eng, Ursula Nosi and Andrea Constantinof who have provided invaluable organizational support. Finally, we would like to express our gratitude to our sponsors, many of whom have provided continuous support over the last 20 years, and who have made **Developmental & Perinatal Biology 2016** possible.

Please accept our warmest welcome to what we hope will be an exciting academic and social experience.

Dr. S. G. Matthews
Professor
Physiology, Ob/Gyn & Medicine
University of Toronto

Local Organizing Committee:

Stephen Matthews (Chair)
Bev Bessey
Andrea Constantinof
Brian Cox
Victoria De Luca
Robert Jankov
Evelyn Lambe
Steve Lye
Ursula Nosi

Co-Sponsors:

Hospital for Sick Children, Research Institute
Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital
Department of Obstetrics & Gynaecology, University of Toronto
Fraser Mustard Institute for Human Development, University of Toronto
Department of Physiology, University of Toronto
Faculty of Medicine, University of Toronto
Medicine by Design, University of Toronto
Heart and Stroke/Richard Lewar Centre of Excellence in Cardiovascular Research

Location:

Registration: **22nd August** – Room 2172, Medical Sciences Building, University of Toronto

Lectures: **22nd – 26th August** – Room 2172, Medical Sciences Building, University of Toronto

Practical Workshops: CReATe Fertility Centre; Medical Sciences Building, University of Toronto; OB/GYN - Mount Sinai Hospital; Hospital for Sick Children Research Institute; NICU at Mount Sinai Hospital

Social Activities: 22nd August - Distillery District Tour / Dinner
23rd August - Opening Reception – The Faculty Club, University of Toronto
24th August - Dundas Square / Jack Astors / Shopping
25th August - Casa Loma
26th August - Friday Night at the Royal Ontario Museum
27th August - Day Trip to Niagara Falls

FACULTY:

University of Toronto:

	Department	Location
Dr. Zulfiqar Bhutta	Nutritional Sciences	Hospital for Sick Children
Dr. Kerry Bowman	Family & Community Medicine	University of Toronto
Dr. Amy Caudy	Molecular Genetics	University of Toronto
Dr. Brian Cox	Physiology	University of Toronto
Dr. Paul Delgado Olguin	Molecular Genetics	Hospital for Sick Children
Dr. Yenge Diambomba	Paediatrics	Mount Sinai Hospital
Dr. Paul Frankland	Physiology	Hospital for Sick Children
Dr. Karen Gordon	Otolaryngology	Hospital for Sick Children
Dr. Robert Jankov	Paediatrics & Physiology	Hospital for Sick Children
Dr. Kyoung-Han Kim	PDF – Dr. Hui's Lab	Hospital for Sick Children
Dr. Thomas Kislinger	Medical Biophysics	MaRS Centre, TMDT
Dr. Evelyn Lambe	Physiology	University of Toronto
Dr. Clifford Librach	Obstetrics & Gynecology	CReATe Fertility Centre
Dr. Stephen Lye	Ob/Gyn & Physiology	Lunenfeld-Tanenbaum Research Inst.
Ms. Paula Mackie		CReATe Fertility Centre
Dr. Stephen Matthews	Physiology	University of Toronto
Dr. Patrick McGowan	Biological Sciences	University of Toronto at Scarborough
Dr. Patrick McNamara	Paediatrics & Physiology	Hospital for Sick Children
Dr. Jennifer Mitchell	Cell & Systems Biology	University of Toronto
Dr. Gaspard Montandon	Medicine & Physiology	University of Toronto
Dr. Cristina Nostro	Physiology	University of Toronto
Dr. Monique Rennie	Clinical Trials Manager	MolecuLight Inc.
Dr. Janet Rossant	Molecular Genetics & Ob/Gyn	Hospital for Sick Children
Dr. Greg Ryan	Obstetrics & Gynecology	Mount Sinai Hospital
Dr. Amy Wong	PDF – Dr. Rossant's Lab	Hospital for Sick Children
Dr. Behzad Yeganeh	PDF – Dr. Post's Lab	Hospital for Sick Children

Karolinska Hospital/Institute:

Professor Klas Blomgren	Women's and Children's Health
Professor Ola Hermanson	Neuroscience
Professor Fredrik Lanner	Clinical Science, Intervention and Technology
Professor Urban Lendahl	Cell and Molecular Biology
Dr. Sophie Petropoulos	PDF

Other:

Dr. Shane Norris	Paediatrics	University of Witswatersrand
Dr. Matthew Ratsep	PDF – Dr. Anne Croy's Lab	Queen's University
Dr. Deborah Sloboda	Biochemistry & Biomedical Sciences	McMaster University

Monday, 22nd August

8:30   Registration   Room 2172, Medical Sciences Building
                                                          University of Toronto

8:45   Welcome/Introduction   **Dr. Stephen Matthews**
                                                          International Exchange Program for Developmental and
                                                          Perinatal Biology, University of Toronto

Stem Cells, Embryonic Development and Disease
(Medical Sciences Building, Room **2172**)
Co-ordinator: Dr. Janet Rossant

9:00   ***Stem cells and early development***

Dr. Janet Rossant

9:40   ***Stem cells and modeling human disease***

Dr. Amy Wong

10:20 Coffee

10:40 ***Stem cells and tissue repair***

Dr. Cristina Nostro

11:20 ***Notch signaling in development and disease***

Dr. Urban Lendahl

Trainee Presentations (Orals 1-4)

12:00 ***Using patient-derived iPS cells to in vitro model familiar neuroblastoma***
                                                                                      Ana Marin Navarro[1]

12:15 ***Gradient system for rat testicular organoid formation***
                                                                                      João Pedro Alves Lopes[2]

12:30 ***Stem cell derived hepatocyte transplantation for the correction of liver disease***
                                                                                      Mihaela Zabulica[3]

12:45 ***Using vascularized devices in stem cell therapy for type 1 diabetes***
                                                                                      Yasaman Aghazadeh[4]

13:00 Lunch - MSB Cafeteria

14:00-15:30 ***Research Workshops:***   1) Methods and Tools to Assess Embryo Quality in the
                                                                      IVF Clinic
                                                                  2) CRISPR Genome Editing; Scientific Advances,
                                                                      Potential Therapies and Ethical Concerns

18:00   **Distillery District Tour / Dinner**

Tuesday, 23rd August

Placenta and Birth
(Medical Sciences Building, Room **2172**)
Co-ordinator: Dr. Brian Cox

9:00   *Human preimplantation development*

Dr. Fredrik Lanner

9:40   *Uteroplacental vascular remodeling and hemodynamic implications in normoxic and hypoxic mouse pregnancies*

Dr. Monique Rennie

10:20 Coffee

10:40 *Extracellular vesicular small RNA in human reproductive fluids: regulators of fertility?*

Ms. Paula Mackie

11:20 *Understanding life course trajectories to non-communicable disease*

Dr. Shane Norris

Trainee Presentations (Orals 5-8)

12:00 *Lopinavir- a HIV protease inhibitor impairs the remodelling of uterine spiral arteries*
Smriti Kala[5]

12:15 *Quantifying placental function in terms of oxygen transport using MRI*
Brahmdeep Saini[6]

12:30 *Delineating naïve & primed stem cells from the endogenous preimplantation embryo*
John Paul Schell[7]

12:45 *Transient and dynamically regulate trophoblast subpopulations present in the early human placenta*

Frances Wong[8]

13:00 Lunch - MSB Cafeteria

14:00-15:30   *Research Workshops:*   1) Fetal Therapy Education
                                        2) Mass Spectrometry Based Metabolomics

19:00   **Opening Reception – The Faculty Club, University of Toronto (41 Willcocks Street)**

Wednesday, 24th August

Cardiopulmonary Physiology
(Medical Sciences Building, Room **2172**)
Co-ordinators: Dr. Robert Jankov/Dr. Behzad Yeganeh

9:00   *Embryonic programming of cardiac disease by maternal obesity*
<div align="right">Dr. Paul Delgado Olguin</div>

9:40   *Iroquois homeodomain transcription factors in heart development and function*
<div align="right">Dr. Kyoung-Han Kim</div>

Coffee

10:40   *Development of the respiratory control system and opioid drugs*
<div align="right">Dr. Gaspard Montandon</div>

11:20   *An essential role for autophagy in lung development*
<div align="right">Dr. Behzad Yeganeh</div>

12:00   *GROUP PHOTO*
   (**please assemble outside on steps of MSB facing King's College Circle**)

12:15   **Lunch and Poster Session** – McLeod Auditorium Lobby

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20TH ANNIVERSARY SPECIAL LECTURE

<div align="right">(Medical Sciences Building, Room 2172)</div>

13:30 *"Global child health and development: Challenges and opportunities"*
<div align="right">Dr. Zulfiqar Bhutta</div>

15:00   **Dundas Square / Jack Astors / Shopping**

Neurodevelopment
(Medical Sciences Building, Room **2172**)
Co-ordinator: Dr. Evelyn Lambe

9:00   ***Hippocampal neurogenesis regulates forgetting during adulthood and infancy***
<div align="right">Dr. Paul Frankland</div>

9:40   ***Steering fetal neural stem cell state and fate: new tricks for old dogmas***
<div align="right">Dr. 0la Hermanson</div>

Coffee

10:40   ***Functional consequences of asymmetric hearing in development: evidence from children who use cochlear implants***
<div align="right">Dr. Karen Gordon</div>

11:20   ***Integrating placental growth factor and preeclampsia in development of brain structure and function***
<div align="right">Dr. Matthew Ratsep</div>

Trainee Presentations (Orals 9-11)

12:00   ***The road towards 3D bioprinting with recombinant spider silk protein for neural stem cell constructs***
<div align="right">Jakub Lewicki[9]</div>

12:15   ***Cerebral oxygen delivery, brain growth and white matter maturation are reduced in congenital heart disease fetuses***
<div align="right">Jessie Mei Lim[10]</div>

12:30   ***Modified-protein diet intervention to reduce risk of gestation in chronic kidney disease***
<div align="right">Sara Mahdavi[11]</div>

13:00 Lunch - MSB Cafeteria

14:00-15:30 ***Research Workshops***:   1) Application of Mass Spectrometry Based Proteomics to Pathology and Cell Biology
2) NICU Visit at Mount Sinai Hospital

16:00   **Casa Loma** (for trainees)

Friday, 22nd August

Developmental Origins of Health and Disease
(Medical Sciences Building, Room **2172**)
Co-ordinator: Dr. Stephen Matthews

9:00   *Why the first 2000 days of life really matter*

Dr. Stephen Matthews

9:40   *Early life nutritional impacts on long term metabolism and obesity*

Dr. Deborah Sloboda

10:20 Coffee

10:40 *Epigenetics, neurodevelopment and life-long health*

Dr. Patrick McGowan

11:20 *Injury and repair in the juvenile brain*

Dr. Klas Blomgren

Trainee Presentations (Orals 12-15)

12:00 *Fetal exposure to a higher than normal level of estradiol is associated with adverse pregnancy outcomes in HIV-positive women on combination antiretroviral therapy*

Kayode Balogun[12]

12:15 *Acute but not delayed caffeine administration offers neuroprotection in a mouse model of neonatal hypoxic ischemic brain injury*

Elena Di Martino [13]

12:30 *Cocaine exposure prior to pregnancy alters the psychomotor response to cocaine and transcriptional regulation of the dopamine D1 receptor in adult male offspring*

Aya Sasaki[14]

12:45 *Simvastatin prevents and reverses chronic pulmonary hypertension in newborn rats via pleiotropic inhibition of RhoA signaling*

Mathew Wong[15]

13:00 Lunch - MSB Cafeteria

14:00-15:30   *Research Workshops:*   1) Physiology of the Pulmonary Circulation
                                                      2) Epigenetics

16:00   Friday Night at the Royal Ontario Museum

Practical Workshops:

MONDAY, AUGUST 22nd   *Time:* **2:00 – 3:30 pm**

Title: **Methods and Tools to Assess Embryo Quality in the IVF clinic**
Organizer: **Dr. Clifford Librach**

Location: **CReATe Fertility Centre, 790 Bay Street, 11th Floor, Suite 1100 (Boardroom)**

Leaders: **Dr. Clifford Librach,** Medical and Scientific Director, CReATe Fertility Centre
                  Dr. Svetlana Madjunkova, Director of PGS/PGD, CReATe Fertility Centre
                  Dr. Hanna Balakier, Director of Embryology
                  Dr. Ran Antes, Technologist – PGS
                  Dr. Andree Gauthier-Fisher, Research Scientist - Director of Stem Cell Research
                                          at CReATe Fertility Centre
                  Parshvi Vyas, MSc candidate

NOTE: Maximum of 12 attendees.
Within this workshop, attendees will be introduced to assisted reproductive technologies, focusing on *in vitro* fertilization (IVF) and cutting-edge methods that are currently available and applied at CReATe for the selection of IVF embryos with the greatest chance of successful implantation. Recent advances and ongoing research in pre-implantation genetic screening and diagnosis (PGS/PGD) and non-invasive embryo competency assessments will be presented. Participants will have the opportunity to tour the fertility clinic and laboratories and to interact one-on-one with experts in the field of human embryology.

Title: **CRISPR Genome editing; scientific advances, potential therapies and ethical concerns**

Leaders: **Jennifer Mitchell**, PhD, Molecular Biologist, Cell & Systems Biology,
                  University of Toronto
                  Kerry Bowman, PhD, Clinical Ethicist, Mount Sinai Hospital

Location: **Medical Sciences Building, University of Toronto**
                  1 King's College Circle, Rm 3227

CRISPR genome editing is a revolutionary approach that in the past three years has changed the way we do research in fields as diverse as bacteriology to treatments for HIV infection. The transformational nature of this technique is not that it was a completely new idea, as scientists have been editing genomes for several years, but the relative ease with which the experiments can be conducted. What used to take months in the lab and could fail completely now takes days and has incredibly high success rates. We will explain how this new technology works and highlight recent applications. We will also raise and discuss ethical questions about the application of this technology to the human genome. This workshop is aimed at those not currently using CRISPR but with an interest in applying it in the future.

Title: **<u>Fetal Therapy Education</u>**

Leader: **Dr. Greg Ryan**

Location: **Mount Sinai Hospital, 700 University Avenue, 8th Floor, Room 8-932**
                (OPG Building – corner of University and College)

Fetal Therapy (the active treatment of a fetus in-utero) is one of the youngest and more rapidly developing disciplines in clinical medicine. The Fetal Therapy program at the University of Toronto is one of the larger units in North America. In this workshop, we will briefly review the history and evolution of in-utero fetal therapy.   The principles which guide the use of fetal therapy at the University of Toronto will then be explored and the applications of these principles to clinical practice will be reviewed.   Both medical management (for example maternal medication for fetal cardiac dysrhythmia) and surgical management (for example, fetal transfusion, shunting, etc.) will be examined, using video clips from the procedures. Specific conditions to be discussed include fetal anemia, lower urinary tract obstruction, complicated monochorionic twin pregnancies, congenital diaphragmatic hernia and congenital heart disease. Finally, potential future developments will be considered – including new technologies for education and treatment, etc.

Title: **<u>Mass spectrometry based metabolomics</u>**

Leader: **Dr. Amy Caudy**

Location: **Medical Sciences Building, University of Toronto**
                1 King's College Circle, Rm 3227

The next time you enjoy a meal, take a moment to marvel how your body can digest such a vast array of foods. With the availability of the complete genome sequences of organisms from yeast to humans, we now know the full catalogue of genes for each. However, such lists only hint at how organisms process nutrients. Each cell in our bodies must take in nutrients to maintain itself. If so directed by environmental cues, our cells alter their metabolism in order to produce the building blocks necessary to divide. Now, new tools for chemical analysis permit the study of the metabolome, the chemical intermediates of cellular metabolism. This workshop will consist of a lecture with real-world data plenty of time for discussion describing current methods for metabolomic analysis.

Title: **Application of mass spectrometry based proteomics to pathology and cell biology**

Leader: **Dr. Thomas Kislinger**

Location: **Medical Sciences Building, University of Toronto**
               1 King's College Circle, Rm 3227

Within this workshop attendees will be introduced to the basics of mass spectrometry-based proteomics and its application to clinical proteomics. The first part of the workshop will cover basic aspects of a modern proteomics pipeline and will focus on liquid chromatography coupled to mass spectrometry. Topics such as recent advances in liquid chromatography, protein identification and quantification will be covered. The second part of the workshop will focus on current applications, such as discovery and verification of serum-based biomarkers and identification and functional analyses of novel cell-surface proteins.

Title: **NICU Visit at Mount Sinai Hospital**

Organizer: **Dr. Yenge Diambomba**

Location**:**   **Mount Sinai Hospital, 600 University Avenue, 17th Floor, Room 17-206**
               (Please use University Ave. Elevators)

Mount Sinai Hospital operates one of the busiest perinatal services in Canada with more than 6,800 deliveries annually, many of which are high-risk. Participants will receive a tour of the Neonatal Intensive Care Unit (NICU) at Mount Sinai, and will hear about and discuss common perinatal issues and clinical and ethical dilemmas faced on a regular basis by neonatal clinicians.

Title: **Physiology of the Pulmonary Circulation**

Leader: **Dr. Patrick McNamara**
                Dr. Regan Giesinger

Location: **Hospital for Sick Children, McMaster Building**
                1st Floor LAS Physiology Room
                (Meet in front of building at southeast corner of Elm and Elizabeth Streets)

Participants will be provided with theoretical and technical insights into cardiovascular physiology through the demonstration of ultrasound-based assessments of pulmonary haemodynamics and cardiac function in small rodents. Two-dimensional echocardiography and Doppler ultrasound will be performed on normal and pulmonary hypertensive neonatal rats to familiarize participants with the measurements used to assess pulmonary vascular resistance and right-ventricular function. Differences in findings between the normal and pulmonary hypertensive state will be highlighted.

Title: **Epigenetics**

Leader: Dr. Sophie Petropoulos

Location: **Medical Sciences Building, University of Toronto**
                1 King's College Circle, Rm 3227

This workshop will introduce the field of epigenetics, with focus on DNA methylation. Common techniques used to assess both targeted genes of interest and global DNA methylation will be introduced, described, and compared. Techniques include: LUminometric methylation assay (LUMA), methylated DNA immunoprecipitation (MeDIP), chromatin Immunoprecipitation (ChIP), bisulfite sequencing, pyrosequencing and single-cell genome-wide bisulfite sequencing. In addition, a brief introduction to computational approaches used to analyze genome-wide epigenetic data will be described. Finally the workshop will describe the implications of altered DNA methylation with regards to disease/disorder development and highlight potential therapeutic targets.

Research Workshop Assignments:

MONDAY

Methods and Tools to Assess Embryo Quality in the IVF Clinic

Canadian
Sara Mahdavi
Frances Wong
Judy Seesahai
Mathew Wong
Ursula Nosi
Smriti Kala
Margaret Elizabeth Eng

Swedish
Eleni Gelali
Jakub Lewicki
Elias Uhlin
Lynnea Myers

CRISPR Genome Editing; Scientific Advances, Potential Therapies and Ethical Concerns

Canadian
Yasaman Aghazadeh
Brahmdeep Saini
Aya Sasaki
Jaap Mulder

Swedish
Ana Marin Navarro
Mtakai Ngara
Robin Pronk
Yixin Wang
Mihaela Zabulica
Magdalena Kurek
Elena Di Martino
Abdul Kadir Mukarram

TUESDAY

Fetal Therapy Education

Canadian
Judy Seesahai
Sara Mahdavi
Cristina Ferreira
Jessie Mei Lim
Jaap Mulder
Maria Sqapi
Mathew Wong
Ursula Nosi
Alexandros Mouratidis
Frances Wong

Swedish
Iuliia Savchuk
Eleni Gelali
John Paul Schell
Lynnea Myers
Magdalena Kurek

Mass Spectrometry Based Metabolomics

Canadian
Kayode Balogun
Margaret Elizabeth Eng
YiQing Lü
Virlana Shchuka

Swedish
Mihaela Zabulica
Abdul Kadir Mukarram
João Pedro Alves Lopes

THURSDAY

Application of Mass Spectrometry Based Proteomics to Pathology and Cell Biology

Canadian
Yasaman Aghazadeh
YiQing Lü
Mathew Wong
Alexandros Mouratidis
Smriti Kala
Maria Sqapi
Ursula Nosi

Swedish
João Pedro Alves Lopes
Robin Pronk
Mtakai Ngara
John Paul Schell
Mihaela Zabulica
Elena Di Martino
Jakub Lewicki
Ana Marin Navarro

NICU Visit at Mount Sinai Hospital

Canadian
Margaret Elizabeth Eng
Cristina Ferreira
Virlana Shchuka
Frances Wong
Jessie Mei Lim
Sara Mahdavi
Aya Sasaki
Kayode Balogun
Brahmdeep Saini

Swedish
Iuliia Savchuk
Lynnea Myers
Yixin Wang
Elias Uhlin

FRIDAY

Physiology of the Pulmonary Circulation

Canadian
Cristina Ferreira
Jessie Mei Lim
Judy Seesahai
Smriti Kala
Brahmdeep Saini

Swedish
Iuliia Savchuk
Yixin Wang

Epigenetics

Canadian
YiQing Lü
Alexandros Mouratidis
Aya Sasaki
Jaap Mulder
Kayode Balogun
Yasaman Aghazadeh
Virlana Shchuka
Maria Sqapi

Swedish
Magdalena Kurek
Abdul Kadir Mukarram
John Paul Schell
João Pedro Alves Lopes
Ana Marin Navarro
Mtakai Ngara
Elias Uhlin
Elena Di Martino
Eleni Gelali
Jakub Lewicki
Robin Pronk

ABSTRACTS

- Orals -

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Alves-Lopes, J.P., Söder, O. and Stukenborg, J-B.
> **GRADIENT SYSTEM FOR RAT TESTICULAR ORGANOID FORMATION**

O3

Zabulica, M., Kannisto, K., Jakobsson, T., Vosough, M. and Strom, S.
> **STEM CELL DERIVED HEPATOCYTE TRANSPLANTATION FOR THE CORRECTION OF LIVER DISEASE**

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Aghazadeh, Y., Nunes Vasconcelos, S.S. and Nostro, M.C.
> **USING VASCULARIZED DEVICES IN STEM CELL THERAPY FOR TYPE 1 DIABETES**

O5

Kala, S., Dunk, C.E. and Serghides, L.
> **LOPINAVIR- A HIV PROTEASE INHIBITOR IMPAIRS THE REMODELLING OF UTERINE SPIRAL ARTERIES**

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> **QUANTIFYING PLACENTAL FUNCTION IN TERMS OF OXYGEN TRANSPORT USING MRI**

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> **DELINEATING NAÏVE AND PRIMED STEM CELLS FROM THE ENDOGENOUS PREIMPLANTATION EMBRYO**

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Lewicki, J., Rising, A. and Hermanson, O.
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FETAL EXPOSURE TO A HIGHER THAN NORMAL LEVEL OF ESTRADIOL IS ASSOCIATED WITH ADVERSE PREGNANCY OUTCOMES IN HIV-POSITIVE WOMEN ON COMBINATION ANTIRETROVIRAL THERAPY

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Sasaki, A., Constantinof, A., Pan, P., Kupferschmidt, D.A., McGowan, P.O. and Erb, S.

COCAINE EXPOSURE PRIOR TO PREGNANCY ALTERS THE PSYCHOMOTOR RESPONSE TO COCAINE AND TRANSCRIPTIONAL REGULATION OF THE DOPAMINE D1 RECEPTOR IN ADULT MALE OFFSPRING

O15

Wong, M.J., Kantores, C., Ivanovska, J., Jain, A. and Jankov, R.

SIMVASTATIN PREVENTS AND REVERSES CHRONIC PULMONARY HYPERTENSION IN NEWBORN RATS VIA PLEIOTROPIC INHIBITION OF RHOA SIGNALING

USING PATIENT-DERIVED IPS CELLS TO IN VITRO MODEL FAMILIAR NEUROBLASTOMA

Navarro, A.M.[1,3], Hackland, J.[2], Falk, A.[3] and Wilhelm, M.

[1]Department of Microbiology, Tumor and Cell biology, Karolinska Institute
[2]Biomedical Science Department, University of Sheffield
[3]Department of Neuroscience, Karolinska Institute

Neuroblastoma (NB) is a rare embryonic neuronal cancer that can spontaneously regress, however, children diagnosed with NB after 1 year of age often have extensive or metastatic disease resulting in a poor prognosis. NB develops mainly in the peripheral nervous system, specifically in the adrenal ganglia or in a paraspinal location in the abdomen or chest. Neural crest (NC) cells that give raise to the sympathoadrenal lineage have been hypothesized to be the origin of this cancer. Various genetic aberrations have been identified in NB, importantly, point mutations in anaplastic lymphoma tyrosine kinase (ALK) have been found exclusively in NB. In order to study the contribution of ALK mutations in NB initiation, we have successfully reprogrammed fibroblasts from NB patients carrying a germline mutation in ALK (R1275Q) into iPS cells. More important, we have derived NC cells from iPS control and NB cells. We have been able to sort for p75 bright cell population with an efficiency up to 90%. Moreover, p75 sorted cells were expressing relevant NC markers such as NC specifiers SOX9, SOX10, TFAP2A and FOXD3 but also the Neural tube marker, PAX3. In order to examine the tumorigenic potential of those NC cells carrying out the ALK mutation we have orthotopically injected them into the adrenal gland of nude mice. Tumor growth from patient-derived cell injections will be monitored and compared to control. In that manner, we believe we will be able to develop a robust human in vitro model that can be used for further study of NB initiation and progression.

GRADIENT SYSTEM FOR RAT TESTICULAR ORGANOID FORMATION

Alves-Lopes, J.P., Söder, O. and Stukenborg, J-B.

Department of Women´s and Children´s Health, Pediatric Endocrinology Unit,Karolinska Institutet and University Hospital, SE-17176 Stockholm, Sweden

An efficient *in vitro* model that simulates the testicular microenvironment and germ cell niche formation has been attempted over the last decades; however an effective system was not produced so far. Such model, if available, could be used to study testicular function and spermatogenesis under controlled *in vitro* conditions. Recently, we developed a novel multilayer three-dimensional model to create an in/ outcome gradient of factors which allows rat single cell reorganization into testicular organoids. Our model, the Three-Layer Gradient System, permits the generation of testicular organoids with functional blood-testis barrier and germ cell establishment exclusively *in vitro*. These functional features upgrade the conventional models used before turning this model unique for formation of testicular-like organs *in vitro*. Thus, we demonstrated our Three-Layer Gradient System to be a robust and efficient model to study testicular biology *in vitro* with applications in drug discovery and toxicology as well as germ cell differentiation for potentially future clinical use. Moreover, we have recently applied Three-Layer Gradient System to study human fetal gonadal tissue. So far, *de novo* reorganization of these fetal cells into structures observed *in vivo* was also achieved, giving us the opportunity to study human gonadal organogenesis and development *in vitro*.

STEM CELL DERIVED HEPATOCYTE TRANSPLANTATION FOR THE CORRECTION OF LIVER DISEASE

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Introduction: Urea cycle is a liver-based pathway for the excretion of excess nitrogen. Mutations in any of the genes compromising the cycle cause inborn errors of ammonia detoxification. Urea cycle disorders can lead to encephalopathy, coma and death. The most common urea cycle disorder is Ornithine Transcarbamylase Deficiency (OTCD).

The only definitive therapies for OTCD patients are orthotopic liver transplantation and cell-based therapy. However, the shortage of available liver organ- and cell-donors increases the need to investigate new potential sources of hepatocytes. Presumably, a potential source of hepatocytes could be induced pluripotent stem cells (iPSC). In addition, thanks to technological developments in gene engineering based n CRISPR/Cas9 technology, personalized therapy of liver disease is now theoretically possible.

Aim: The aim of this study is to attempt to correct the genetic defect in cells taken from OTCD patients through gene editing technology, and to examine the phenotype of the corrected cells *in vitro*, as well as *in vivo*.

Methods: Fibroblasts from two OTCD patients were isolated and reprogrammed using the Yamanaka factors. Mutations causing the disease were identified *via* next generation sequencing, and corrected through CRISPR/Cas9 technology.

Preliminary experiments for hepatic differentiation were performed based on protocols developed in our lab. mRNA levels were examined and compared with the respective ones in adult and fetal hepatocytes from 52 individuals. Finally, triply mutant FRGN mice were used as mouse model of liver humanization.

Preliminary results: Seventeen iPSC lines were generated from two OTCD deficient patients and characterized based on pluripotency markers. Pathogenic mutations affecting the natural splice sites were identified in each patient. CRISPR/Cas9 technology was applied to correct the disease-causing mutation with 10% estimated efficiency.

iPSC-hepatocytes were generated and the mRNA levels were compared with the respective ones in fetal and adult hepatocytes revealing a phenotype closer to fetal primary hepatocytes than adult ones. Finally, OTC -proficient and –deficient primary human hepatocytes were transplanted into FRGN mice achieving levels of liver humanization up to 95%.

USING VASCULARIZED DEVICES IN STEM CELL THERAPY FOR TYPE 1 DIABETES

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Type 1 diabetes (T1D) is a chronic disease characterized by hyperglycemia due to the destruction of insulin (INS)-producing pancreatic β cells in the islets of Langerhans. Recently, efficient protocols that direct the differentiation of human embryonic stem cells (hESC) to pancreatic progenitors (PPs) have been established and hold a high potential for use as therapy for T1D. Transplantation of PPs into immunocompromized diabetic mice, restores normoglycemia within 5-8 months. This long time interval suggests that the adult microenvironment fails to provide optimal developmental cues or support to induce prompt β-cell development and/or maturation. Multiple studies have shown that: 1) the development of a vasculature is essential for pancreatic development and expansion; 2) if tissues are larger than 100-200 µm in diameter, they require vascular networks for survival; 3) proper vessel density is essential for optimal glucose sensing and consequent release of adequate INS levels and 4) inefficient vascularization speed and yield from host may directly affect β-cell development and/or PP survival.

Hypothesis: Pre-vascularization of hESC-derived PPs or β-like cells using ready-made microvessels (MVs) can promote higher efficiency and shorter interval period for β-cell functionality and islet development.
Preliminary results: We tested in vivo islet formation from PPs +/- adipose-derived MVs. Our initial data indicate that the recipients of PPs + MVs reach normoglycemia in immunocompromized mice 5 weeks post transplantation and showed normoglycemia after glucose tolerance test. Removal of the devices containing PP + MV leads to recurrence of diabetes.

Our data suggest that pre-vascularization of PPs shortens the diabetes recovery period from 5 months to 5 weeks in mice. We will compare the efficacy of these cells to in vitro differentiated INS-producing (INS+) cells at restoring normoglycemia in diabetic mice. The effect of co-culturing INS+ cells with MV prior to transplantation will also be tested.

LOPINAVIR- A HIV PROTEASE INHIBITOR IMPAIRS THE REMODELLING OF UTERINE SPIRAL ARTERIES

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Protease Inhibitor (PI)-based combination antiretroviral therapy has been associated with adverse pregnancy outcomes such as pre-term delivery and small for gestational age births in HIV-positive women. Previous work in our lab has demonstrated that PIs contribute to these adverse events by altering placental angiogenesis or formation of blood vessels in the fetal part of the placenta. To probe further into the factors that could contribute to PI-induced altered placental angiogenesis, we investigated the effect of PIs on the decidua, which forms the maternal part of the placenta and is crucial for optimum placentation. During pregnancy decidual spiral arteries undergo remodelling into highly dilated vessels to adequately supply blood to the placenta and fetus. Loss of vascular smooth muscle cells and endothelial cells occurs, and arteries are relined by placental-derived extravillous trophoblasts (EVTs). To investigate the effect of PIs on EVT invasion and spiral artery remodelling, first trimester placental-decidual explants were co-cultured in the presence and absence of PIs, followed by immunohistochemical analyses of the co-cultures. Our data show that treatment with lopinavir (a PI commonly used in pregnancy), impairs spiral artery remodelling, as the blood vessels exhibit an undisrupted endothelial lining and an organized smooth muscular sheath, as well as inadequate EVT invasion. We are currently investigating the underlying molecular mechanism by comparing the function of decidual leukocytes in the PI-treated versus untreated group. Overall, our data indicate that PIs, specifically lopinavir, impair remodelling of the uterine spiral arteries, which could lead to sub-optimal placentation and contribute to poor birth outcomes.

QUANTIFYING PLACENTAL FUNCTION IN TERMS OF OXYGEN TRANSPORT USING MRI

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Objectives: To investigate the use of MRI to assess placental function in terms of placental-fetal oxygen (O_2) transport in utero.

Methods: Eight women with normal pregnancies were scanned using a 1.5T Siemens MRI system at an average gestation of 35.5 ± 2.1 weeks. To measure placental-fetal O_2 transport, blood flow (Q) and oxygen content (C) were measured in blood vessels supplying (uterine arteries and fetal descending aorta) and draining (uterine, ovarian and umbilical veins) the placenta. Phase contrast MRI was used to measure Q. Vascular blood T1 and T2 MRI relaxometry were used to measure oxygen saturation and hematocrit to derive C. The oxygen delivery (Do_2) and return (Ro_2) were calculated as C*Q. Oxygen consumption (Vo_2) was calculated using the arterio-venous difference in C of blood supplied to and drained from an organ and multiplying it by Q. All oxygen transport measures were indexed to fetal weight, which was calculated from the 3D MRI acquisition of the uterus.

Results: The mean maternal-Do_2 was 76.5 ± 23.5 ml/min/kg. The mean fetal-Do_2 and -Vo_2 was 24.9 ± 5.9 and 8.0 ± 2.0 ml/min/kg, respectively. The mean placental-Vo_2 was 4.1 ± 1.2 ml/min/kg, which accounted for $33.9 \pm 7.2\%$ of the total placental-fetal-Vo_2 and a mean placental-to fetal-Vo_2 ratio of 0.53 ± 0.17.

Conclusions: Animal studies have shown that under acute hypoxia, placental-Vo_2 is maintained at the cost of fetal-Vo_2, however, under chronic hypoxia, placental-Vo_2 decreased more than the fetal-Vo_2[1,2]. Thus, the placental- to fetal- Vo_2 ratio may be a sensitive marker for assessing placental function in pathologies affecting placental hemodynamics.

1. Gu et al: J Physiol. 1985   2. Owens et al: J Dev Physiol. 1987a

DELINEATING NAÏVE AND PRIMED STEM CELLS FROM THE ENDOGENOUS PREIMPLANTATION EMBRYO

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Naïve Human embryonic stem cells (hESCs) have been justified as a more relevant representation of preimplantation pluripotency than conventional primed hESCs, which correspond to a further mature epithelialized postimplantation stem cell state. While it is recognized that naïve hPSCs transcriptionally cluster closer with endogenous epiblast than conventional primed lines, it has been unclear how strictly these stem cell states parallel embryonic development. Emerging single-cell human embryo data has created a resource for identification of embryonic lineages, refining the gene expression profile of native endogenous pluripotency and better specifying a transcriptional outline for naïve stem cells to recapitulate in vitro. Here we perform single-cell RNA-Seq on primed and naïve stem cells, utilizing two relevant and reproducible naïve culture methods (5iAF and t2iGoY), which we then compare and contrast with our previously reported E3-E7 single cell RNA-Seq human embryo data. By identifying when key pluripotency factors are expressed during preimplantation development we determined an embryonic pseudo-time that can be used to better arbitrate the spectrum of pluripotency between different stem cell states and culture conditions. Based on unbiased clustering as well as clustering enriched for relative expression of pluripotency, we aim to observe how these representative naïve stem cells developmentally relate to endogenous epiblast.

TRANSIENT AND DYNAMICALLY REGULATE TROPHOBLAST SUBPOPULATIONS PRESENT IN THE EARLY HUMAN PLACENTA

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The vascular exchange region of the human placenta, called the villus, facilitates nutrient and gas exchange between maternal and fetal circulations. Placental vascular defects lead to pathologies in up to 10% of all pregnancies, resulting in predisposition to lifelong chronic disease in both the mother and child. We propose our limited knowledge of human villi development is preventing advances in technologies to counter pregnancy complications. As most developmental processes involve transitory populations of cells that drive and organize developing cellular networks, I hypothesize a cellular analysis of the human placenta will identify transitory cell populations which direct villus development. Trophoblast enriched fractions of single cells were enzymatically isolated from human chorionic villi at week 6 and 10 of gestation. Cells were analyzed in duplicate by a high throughput flow cytometry assay for 370 CD antigens. Markers of transient cell subpopulations were selected as those strongly expressed at week 6 and decreased by week 10. Candidate markers and cell populations were confirmed thorough immunohistochemistry of placental sections and gene expression analysis. Using the most stringent filtering criteria, we confidently identified 21 developmentally regulated populations in both replicates of the screen. We selected EpCAM (CD326) and CDCP1 (CD318) for further validation because both markers consistently show decreasing expression and are known to label subpopulations of early mouse trophoblast cells. Immunohistochemistry and flow cytometry analysis confirmed EpCAM and CDCP1 transiently label trophoblasts but interestingly, EpCAM and CDCP1 are expressed by mutually exclusive sub-populations as EpCAM+ cells are predominatly clustered in the base of the proximal column with CDCP1 expressed by discrete cells in the distal column. Genome wide gene expression suggests EpCAM may contribute to cytotrophoblast cells while CDCP1 develop into extravillous trophoblasts. My work has developed strong evidence for heterogeneity among early trophoblast cells and supports the existence of transient subpopulations.

THE ROAD TOWARDS 3D BIOPRINTING WITH RECOMBINANT SPIDER SILK PROTEIN FOR NEURAL STEM CELL CONSTRUCTS

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Tissue engineering of stem cells holds a great promise for regenerative medicine and drug discovery in studying and treating many disorders including neurodegenerative diseases. To produce biologically relevant models of organs it will be essential to establish techniques of manufacturing tissues and/or organs *in vitro* for later basic research or transplantation. Since stem cells characteristics can be strongly influenced by 3D culture conditions complicated 3D architecture of biological structures should be recreated in fabricated constructs. This will require appropriate technology and materials. Here we suggest three-dimensional (3D) bioprinting as a method of material deposition in controlled and precise fashion to manufacture 3D scaffolds for human neuroepithelial-like stem (NES) cells culture. This method has a potential to create complicated spatial microenvironments for NES culture recreating *in vivo*-like architecture. However first essential step on the road towards bioprinting NES 3D constructs is to find appropriate biomaterial. Synthetic hydrogels usually do not provide any biological cues for cell attachment and survival, resulting in high cell death. On the other hand, natural hydrogels often lack good printability or are highly variable, resulting in poor reproducibility. Thus, we suggested application of recombinant spider silk protein as a material for creating scaffolds. Here we demonstrate biocompatibility study of vitronectin-modified recombinant spider silk (v-spider silk). NES cells were cultured on petri dishes coated with v-spider silk and control plates treated with standard coating (poly-l-ornithine and laminin). Cells viability, attachment and proliferation were studied, showing that v-spider silk is sufficient to support cell growth and survival without additional animal-derived components in the coating. Unique molecular structure of v-spider silk mimics ability of natural spider silk to respond to low pH resulting in rapid crosslinking of the recombinant protein. Therefore we propose application of vitronectin-modified spider silk in manufacturing scaffolds for NES cells to create three-dimensional models of neural tissue.

CEREBRAL OXYGEN DELIVERY, BRAIN GROWTH AND WHITE MATTER MATURATION ARE REDUCED IN CONGENITAL HEART DISEASE FETUSES

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Objectives: To investigate the relationship between fetal hemodynamics and brain growth and maturation in congenital heart disease (CHD) fetuses using magnetic resonance imaging (MRI).

Methods: Fetal and newborn brain MRI was performed at 37 ± 1 and 40 ± 1.5 weeks respectively on a 1.5T scanner. Fetal hemodynamics were assessed using our previously published technique, consisting of blood flow measures and T2 based oximetry. We measured fetal combined ventricular output (CVO), umbilical vein (UV) flow, oxygen content (estimated hematocrit), oxygen delivery (DO2) and consumption (VO2). Using superior vena cava flow (QSVC) as a surrogate for cerebral blood flow, we measured cerebral DO2, VO2 (CDO2 & CVO2) and oxygen extraction fraction (OEF) using QSVC and the oxygen saturation (SaO2) difference in the ascending aorta and SVC. All brain volumes (BV) were calculated by segmenting a 3D brain acquisition. Newborn white matter microstructure (WMM) was examined using a diffusion tensor imaging (DTI) sequence with 12 manually placed regions of interest.

Results: 46 normal and 40 CHD fetuses were scanned, of which 35 normal and 34 CHD had newborn DTI. Gestational age and body weight was not different between groups. CHD fetal CDO2 was significantly lower due to lower QUV, UVSaO2, and poor streaming. Despite a larger fraction of DO2 directed to the fetal brain, this was associated with smaller newborn BV. CDO2 and CVO2 indexed to BV were not different between groups. However, when indexed to fetal weight, we found significant correlations between CDO2 and CVO2 and neonatal BV (both $p=0.04$, $r^2=0.05$). The lack of brain growth shown in CHD newborns was associated with abnormal WMM on DTI, but DTI was not significantly correlated with any fetal hemodynamic parameters.

Conclusions: Our results are in keeping with a hemodynamic driver of impaired fetal brain growth typical of CHD.

MODIFIED-PROTEIN DIET INTERVENTION TO REDUCE RISK OF GESTATION IN CHRONIC KIDNEY DISEASE

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Pregnant women with chronic kidney disease (CKD-P) are at risk of adverse outcomes including maternal mortality, decreased maternal kidney function, increased maternal hypertensive disorders, reduced fetal-gestation-period (FGP) size-for-gestational-age (SGA), and infant malformations due to side effects of maternal therapies. Successful dietary manipulation can ameliorate many complications of CKD. Low-protein diets have been safely administered and shown to reduce the accumulation of metabolic products while attenuating progressive loss of kidney function in CKD populations. Pregnancy is a state of negative nitrogen balance, however and recommending low-protein diets to CKD-P may be contraindicated. Vegetable proteins have been shown to induce renal changes comparable to those obtained by reducing the total amount of protein in the diet and prevent the vasodilatory and proteinuric effects of meat. These effects appear to be mediated by hormonal changes involving glucagon secretion and renal prostaglandin production. Protein-modified diet (PMD), rather than protein-restricted diets, may be more advantageous in the treatment of CKD-P. This pilot study will test efficacy, safety and feasibility of PMD in CKD-P. Primary objectives will be impacts of PMD on proteinuria, glomerular filtration rate and blood pressure that are collected monthly as per clinical standard measures (office-blood pressure, 24-hour-urine and fasting-serum collection). Secondary objectives will be to compare FGP and SGA between the controls an intervention group, assessed at clinic visits. Study design will be an open-label-intervention trial, comparing volunteers recruited from the CKD-Gestation clinic at Sunnybrook hospital to follow PMD, versus standard care. The prescribed diet will be an adaptation of a moderate-protein vegetarian diet used in other studies. Intervention diet will be personalized replacing high-protein animal sources with legumes, nuts and whole grains, with a goal protein intake of 0.86-1.0 g/kg per day. The control group will be receiving usual care. An experienced dietitian will monitor diet assessment, prescription and compliance at clinic visits monthly.

FETAL EXPOSURE TO A HIGHER THAN NORMAL LEVEL OF ESTRADIOL IS ASSOCIATED WITH ADVERSE PREGNANCY OUTCOMES IN HIV-POSITIVE WOMEN ON COMBINATION ANTIRETROVIRAL THERAPY

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Background: Combination antiretroviral therapy (cART) has been successfully used to prevent the vertical transmission of the human immunodeficiency virus (HIV). HIV+ women on cART have been shown to have a higher risk for adverse birth outcomes such as preterm delivery (PTD) and small-for-gestational-age (SGA) births; however, the underlying mechanisms are unknown. The roles of sex steroids in the establishment and maintenance of pregnancy have been well documented. We hypothesized that cART contributes to adverse pregnancy events by altering the biosynthesis and/or metabolism of sex steroids.

Methods: We assessed the levels of estradiol (E2), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG), adrenocorticotropic hormone (ACTH) and cortisol in the maternal and cord blood of 86 HIV+ women exposed to cART and 54 matched HIV- pregnant women recruited at 4 different sites in Ontario.

Results: We observed a higher number of low birth weight 25% (14) and SGA 25% (14) babies , and higher PTD 18% (10) in the HIV+ women compared to the HIV- women. We also observed a significantly higher concentrations of E2 in the maternal ($P<0.0001$) and cord blood ($P = 0.003$) of the HIV+ women which correlated negatively with birth weight percentile ($P = 0.004$; $r = -0.43$). SHBG was significantly elevated in the plasma of the HIV+ women, and the levels of the bioavailable estradiol measured as a ratio of E2/SHBG was higher in the maternal ($P = 0.02$) and cord blood ($P = 0.03$) of the HIV+ women. We found a positive correlation ($P < 0.0001$; $r = 0.06$) between the concentrations of cord E2 and DHEAS, and the levels of cortisol and ACTH were the same in both groups

Conclusion: Our data suggest that the use of cART during pregnancy may lead to fetal exposure to a higher than normal concentration of E2 which could contribute to adverse birth outcomes.

ACUTE BUT NOT DELAYED CAFFEINE ADMINISTRATION OFFERS NEUROPROTECTION IN A MOUSE MODEL OF NEONATAL HYPOXIC ISCHEMIC BRAIN INJURY

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Hypoxic ischemic (HI) brain injury remains an important cause of neonatal brain damage with potentially life long sequeale. Caffeine, which is a competitive inhibitor of adenosine receptors, is commonly used as treatment for apnea in prematurity. In addition, caffeine treatment is associated with decreased incidences of cerebral palsy and cognitive delay in children born preterm. In this study we investigated the effects of caffeine in a neonatal HI murine model.

Wild type C57BL/6 mice were subjected to HI by unilateral ligation of the common carotid artery at postnatal day (pnd) 10 and then exposed to 10% oxygen for 60 min. A single dose of 5mg/kg caffeine or phosphate buffered saline (PBS) was administered i.p. directly after or 6, 12 or 24 hours after HI. Open field and rotarod behavioral tests were performed at pnd 24 and the mice were subsequently sacrificed. Infarction size was calculated by loss of MAP-2 staining. Immune response was studied by flow cytometry of brain infiltrating cells at 24h, 72h and 2 weeks after the acute caffeine administration (0h).

An atrophy reduction of 44% (p<0.05) was shown in the group that received an acute administration of caffeine compared to the PBS one, no protection was shown in later treatments. In the open field test, lower locomotor activity was seen in the 0h caffeine group than the PBS one, indicating enhanced learning. No significant difference was shown in the later treatments. A significant reduction of CD8$^+$/CD69 positive cells was detected in the caffeine treated group at 24h but not at 72h and two weeks after the lesion.

Our data indicates that a single dose of caffeine is a possible neuroprotective treatment after neonatal HI without serious immunological side effects or discernible immunological long-term consequences if administered soon after HI. Later treatment does not show any beneficial effect in mice.

COCAINE EXPOSURE PRIOR TO PREGNANCY ALTERS THE PSYCHOMOTOR RESPONSE TO COCAINE AND TRANSCRIPTIONAL REGULATION OF THE DOPAMINE D1 RECEPTOR IN ADULT MALE OFFSPRING

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There is evidence that maternal experience prior to pregnancy can play an important role in behavioral, physiological, and genetic programming of offspring. Likewise, exposure to cocaine in utero can result in marked changes in central nervous system function of offspring. In this study, we examined whether exposure of rat dams to cocaine prior to pregnancy subsequently alters indices of behavior, physiology, and gene expression in offspring. Multiple outcome measures were examined in adult male offspring: (1) behavioral expression of cocaine-induced psychomotor activation; (2) levels of corticosterone in response to immobilization stress; and (3) expression of multiple genes, including dopamine receptor D1 (DRD1) and D2 (DRD2), glucocorticoid receptor (GR), and corticotropin-releasing factor (CRF), in functionally relevant brain regions. Adult Sprague-Dawley females were exposed to cocaine (15-30 mg/kg, i.p.) or saline for 10 days, and were then mated to drug naïve males of the same strain. Separate groups of adult male offspring were tested for their acute psychomotor response to cocaine (0, 15, 30 mg/kg, i.p.), corticosterone responsivity to 20 min of immobilization stress, and expression of multiple genes using quantitative PCR. Offspring of dams exposed to cocaine prior to conception exhibited increased psychomotor sensitivity to cocaine, and upregulated gene expression of DRD1 in the medial prefrontal cortex (mPFC). Neither stress-induced corticosterone levels nor gene expression of GR or CRF genes were altered. These data suggest that cocaine exposure before pregnancy can serve to enhance psychomotor sensitivity to cocaine in offspring, possibly via alterations in dopamine function that include upregulation of the DRD1.

SIMVASTATIN PREVENTS AND REVERSES CHRONIC PULMONARY HYPERTENSION IN NEWBORN RATS VIA PLEIOTROPIC INHIBITION OF RHOA SIGNALING

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Chronic neonatal pulmonary hypertension (PHT) frequently results in early death. Rho-kinase (ROCK) inhibitors have been shown to prevent and reverse chronic PHT in neonatal rats, but at the cost of severe systemic side effects, including systemic hypotension and growth restriction. Simvastatin has pleiotropic inhibitory effects on isoprenoid intermediates that may limit activity of RhoA, which signals upstream of ROCK. We examined the preventive and rescue effects of Simvastatin on chronic hypoxia-mediated chronic PHT. Newborn rats were continuously exposed to normoxia (room air) or moderate normobaric hypoxia (13% O_2) from postnatal day 1 and received Simvastatin (2 mg/kg/day i.p.) from postnatal days 1-14 (prevention protocol) or from days 14-21 (rescue protocol). Chronic hypoxia increased RhoA and ROCK activity in lung tissue. Simvastatin reduced lung content of farnesyl pyrophosphate and decreased RhoA/ROCK signaling in the hypoxia-exposed lung. Preventive or rescue treatment of chronic hypoxia-exposed animals with Simvastatin decreased pulmonary vascular resistance, right ventricular hypertrophy, and pulmonary arterial remodeling. Preventive Simvastatin treatment improved weight gain, did not lower systemic blood pressure, and did not cause apparent toxic effects on skeletal muscle, liver or brain. Our findings indicate that Simvastatin limits RhoA/ROCK activity in the chronic hypoxia-exposed lung, thus preventing or ameliorating hemodynamic and structural markers of chronic PHT, without causing adverse effects.

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P-glycoprotein (P-gp; encoded by *Abcb1*) and breast cancer resistance protein (BCRP; encoded by *Abcg2*) expressed by brain endothelial cells (BEC) efflux an array of drugs, hormones and toxins at the blood-brain barrier (BBB). Our lab has characterized the development expression of P-gp, which is dramatically increased in late gestation, coincident with the endogenous cortisol surge. In cases of preterm birth, synthetic glucocorticoids are administered to mimic the cortisol surge and mature the fetal lungs. The long-term impact of this treatment on BBB transport is unexplored. Our lab has shown P-gp function is increased by corticosteroids in cells derived from gestation day (GD) 50 and 65 and post-natal day (PND) 14 guinea pigs. Most recently, we discovered increased hypothalamic P-gp expression in young guinea pigs 55 days after exposure to sGC *in utero*. Another study concluded that juvenile traumatic brain injury results in suppression of P-gp for up to 6 months. Together, these findings suggest that early exposures can lead to long-term changes (or 'programming') of MDR at the BBB. We therefore hypothesize that maternal sGC treatment increases P-gp and BCRP expression and function at the juvenile and adult BBB, resulting in reduced drug penetration into the brain. We will use a guinea pig model as the species has similar neurodevelopmental profile as humans, and give birth to neuroanatomically mature offspring. Levels of *Abcb1* and *Abcg2* mRNA and P-gp and BCRP protein will be measured by qRT-PCR and Western blot, respectively. BECs will also be derived from microvessels and maintained in primary culture to assess of P-gp and BCRP function, by fluorescent functional assays and by a cytotoxicity bioassay using a toxic P-gp substrate colchicine. This project will advance understanding of how fetal exposures can lead to long-term changes in brain protection and drug sensitivity. These findings will have clinical ramifications, particularly in the neonatal brain where neurotoxicity of P-gp substrates has been reported. Prenatal programming of P-gp at the BBB may also form a link to neurodegenerative diseases such as Alzheimer's disease.

ULTRASOUND ASSESSMENT OF GASTRIC EMPTYING IN PRETERM NEONATES

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Background: Feeding intolerance is the most common clinical problem in preterm infants and associated with parenteral nutrition-related morbidity and prolonged hospital stay. Delayed gastric emptying post-feed is the most frequent clinical sign observed in neonates with feeding intolerance. In part, the delayed gastric emptying may be of developmental origin and related to a prescribed intake volume that exceeds the infant's gastric emptying rate. Yet, limited data are available on the preterm infant's gastric clearance rates to serve as a clinical guide in this respect.
Objectives: To noninvasively measure the gastric content emptying rates of preterm infants (25-36 weeks gestation) during the first week of life.
Methods: Using a published and reliable ultrasound approach, we measured the gastric volume immediately prior, 30 and 60 min after the infant's prescribed breast milk feed volume and calculated the stomach emptying rate, as the difference between the prior value and the other 2-time points.
Results: 65 neonates were studied. As shown in Figure A, the gastric emptying rate was gestational- and postnatal-age dependent. The emptying rate was not uniform over the 60 min. Infants <28 weeks showed an emptying rate increase between 30-60 min, as compared with the first 30 min. In contrast, neonates with gestational age> 29 weeks exhibited a faster emptying rate in the first, as compared with the second 30 min post-feed period (Figure B).
Impact: Knowing the gestational- and postnatal age-dependent gastric emptying rates allows for the use of feed volumes and frequency to allow adequate milk clearance from the stomach.
Conclusion: In preterm infants, gastric emptying rates are developmentally- and postnatally-regulated and not uniform during the first hour post feed. The noninvasive use of ultrasound allows for the bedside gastric measurement of gastric emptying rates and individual adjustment of the infant's enteral feed volume and frequency.

X CHROMOSOME FOLDING AND TOPOLOGY DURING EARLY EMBRYONIC DEVELOPMENT

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In human cells, two meters of DNA sequence are compressed into a nucleus half a million times smaller. It is well established that chromatin is spatially organized in a non-random manner and this is believed to have profound consequences on how genetic information is read. Deciphering how this amazing structural organization is achieved and how DNA functions can ensue in the environment of a cell's nucleus represent central questions for contemporary biology. In the present project, we are focusing on the X chromosome and wish to illuminate its internal architecture during the first few days of life, which are marked by drastic global changes to chromatin organization on multiple levels, from its epigenetic modifications to higher-order structure. To this end, we are developing a high-throughput, high-definition DNA FISH method (hiFISH) that utilizes a combinatorial fluorescence labeling approach, where the identity of a locus is encoded in the combination of fluorophores used to label each locus-specific FISH probe. HiFISH will allow us to visualize and unambiguously identify more than 60 discrete locations along a chromosome. By connecting individual FISH signals according to their position along the genome sequence we will be able to reconstruct the 3D geometry of X chromosome and create a database of the possible shapes it can adopt. At the same time we will be able to monitor how its configuration, spatial localization and volume change across individual cells of the same stage, as well as amongst cells of different developmental stages and possibly catch a glimpse of the global chromatin reconfiguration that is hypothesized to occur during the human pre-implantation development. Finally, probing X chromosomes and monitoring their compaction in female embryos will likely provide us with new insights into the route of X chromosome inactivation.

A XENO- AND FEEDER-FREE, CHEMICALLY DEFINED CULTURE SYSTEM FOR THE DERIVATION OF INTEGRATION-FREE KLINEFELTER SYNDROME IPSCS

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Recently, human recombinant Laminin-521 (LN521) was shown to support the growth of human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) from single cell suspension as monolayer culture under xeno-free (XF) and chemically defined conditions. Combining this approach with a non-integrating reprograming system clinical-grad patient specific iPSCs could be derived.

Human dermal fibroblasts from three healthy and three Klinefelter syndrome donors were transfected with episomal plasmids (pCXLE-hOCT3/4-shp53, pCXLE-hSK and pCXLE-hUL), plated in single cell suspension on Laminin-521 in NutriStem medium and characterized for their pluripotency and reprogramming efficiency. KS iPSCs were derived at a reprograming efficiency of 0.52%, showed a patient specific 47,XXY karyotype, expressed pluripotency genes (NANOG, POU5F1, SOX2, SSEA4) at similar levels as the hESC line (HS980) which was also confirmed at protein level. Furthermore the KS iPSC lines were able to form all three germ layers in vitro as well as in vivo and showed expression of XCL and staining for H3K27me3.

Here, we describe for the first time a highly efficient reprograming method for clinically safe iPSCs of KS patients with non-integrating episomal plasmids in a feeder-free, XF and chemically defined culture system.

FUNCTIONAL CHARACTERIZATION OF PHYSIOLOGICAL REGULATORS OF P53 AND P53 GAIN-OF-FUNCTION MUTANTS

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p53 is the most commonly inactivated tumour suppressor in all cancer. Nearly half of all alterations in p53 are missense mutations clustered in six "hotspots", resulting in the expression of full-length point-mutated p53 proteins that not only lose its wild type activity, but also gained novel oncogenic functions (p53 GOF). Patients with p53 GOF mutations often respond poorly to current therapy and have poor prognosis. Compared to those lacking p53 expression (p53$^{-/-}$), tumours expressing p53 GOF are more invasive, metastatic, and proliferative, and they have increased genome instability and chemoresistance. Differing from wild-type p53 protein, which is normally maintained at low level, p53 GOF found in tumours are hyper-stabilized, thereby actively promoting cancer. Indeed, lowering the expression of p53 GOF reduces growth and metastasis, and triggers tumour regression. All of these suggest tumours harbouring p53 GOF have effectively become addicted to p53 GOF; therefore, understanding the interaction and regulatory network of p53 GOF enables the design of effective strategies for treating many cancers. To identify these physiological regulators of p53 GOF, we shall use unbiased functional genomics and proteomics screens in reporter mice and validate in human cell culture. We shall first identify genes that stabilize p53 GOF and regulate its network by rapid direct *in vivo* screens in reporter mice, using genome-wide lentiviral CRISPR-sgRNA libraries delivered via our established *in utero* ultrasound-guided gene targeting technology. We shall then map the *in vivo* interactome of p53 GOF using proximity-dependent biotin identification (BioID) followed by mass spectrometry. Finally, we shall functionally characterize hits overlapped in p53 GOF interactome and regulatory network that are also druggable, and determine the underlying molecular mechanisms to further explore. Taken together, exploiting vulnerabilities specific to p53 GOF tumours, our findings will offer true progress towards improved therapeutic strategy that may benefit a substantial subset of patients.

METHIONINE-MEDIATED PROTECTION OF SYNTHETIC GLUCOCORTICOID-INDUCED FETAL PROGRAMMING

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Women at risk for preterm delivery receive treatment with synthetic glucocorticoids (sGC) in order to promote the maturation of fetal organs and reduce infant mortality associated with prematurity. However, sGC treatment also alters fetal brain development, and has been shown to modify behaviour and neuroendocrine function in children. We have previously demonstrated in guinea pigs that maternal sGC treatment profoundly modifies gene expression in the fetal hippocampus, and this is associated with reduced DNA methylation in gene promoters. Previous studies have shown that methyl-donor (e.g. methionine) composition of the maternal diet can influence DNA methylation. Increasing maternal intake of methyl-donor compounds influences the methionine cycle, a series of reactions involving the transfer of methyl groups that is vital to the process of DNA methylation, and promotes increased methylation. We hypothesize that sGC will result in DNA hypomethylation in the hippocampus through changes in the expression of key methionine cycle enzymes, and that maternal methionine supplementation will alleviate this hypomethylation and subsequent changes in patterns of gene expression. At gestational day (GD) 30, pregnant guinea pigs will be provided with methionine-enriched drinking water (0.4g/L) or untreated water. On GD 40|41 and 50|51, mothers will be subcutaneously injected with either sGC (betamethasone; 1mg/kg) or saline (vehicle). Liquid chromatography-mass spectrometry will determine the levels of key methionine cycle metabolites (e.g. methionine, homocysteine) in fetal hippocampi and fetal and maternal plasma. qRT-PCR will quantify mRNA levels of key methionine cycle genes (e.g. *Mat, Dnmt*). Transcriptional data will drive epigenetic analysis by pyrosequencing in order to determine the methylation status of genes of interest. This research is clinically relevant as 10% of births worldwide are preterm. This will be the first study to demonstrate protection against adverse effects of prenatal sGC treatment, an important step towards minimizing the life-long neuroendocrine outcomes of this life-saving therapy.

SYSTEMATIC DATA COLLECTION AND DESCRIPTION FOR GENOME ANNOTATION

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Ever decreasing costs for sequencing allow genomes of many species to be acquired. Genome annotation, the identification and characterisation of the genomic elements present in these genomes, still remains as the most challenging task. Even for the best characterised genome, the human genome, this challenge is exemplified by recent large annotation efforts such as ENCODE, FANTOM and Roadmap Epigenomics. Genome annotation projects for model systems are also ongoing through large consortia such as modENCODE and FANTOM.

The systematic collection and description of transcriptomics and epigenomics data is an essential requirement for genome annotation and the above-mentioned consortia relied heavily on manual collection and curation of sequencing data. Here, we propose a strategy to gather sequencing data and detailed data description in a systematic manner. We are using a holistic top-down approach that considers the overall employed experimental design and puts the individual genomics datasets into that context. We have implemented this strategy into a web-based system and employed it to collect and annotate sequencing data for the zebrafish genome through the DANIO-CODE project in collaboration with the ZFIN community.

ROLE OF STROMAL CELL TGFB SIGNALLING IN RENAL VASCULAR FORMATION

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Congenital anomalies of the kidney and urinary tract (CAKUT) is the major cause of childhood renal failure. Defining underlying pathogenic mechanisms is a crucial step toward the development of therapeutic interventions. Mammalian kidney development is dependent on complex reciprocal interactions among ureteric, nephrogenic, and stromal precursor cell populations. CAKUT is characterized by abnormal development of nephrons and adjacent microvascular structures, essential for renal physiological functions. While the ureteric and nephrogenic lineages have been studied extensively, *Foxd1*-positive renal stromal cells, an embryonic cell population that surrounds the nephrogenic elements, have only recently gained attention as an essential contributor to renal development. Stromal cells give rise to the renal capsule and are progenitors of multiple renal cell lineages, including mesangial, renin, smooth muscle and (a subset of) endothelial cells. Targeted deletion of *Foxd1* or removal of *Foxd1*+-stromal cells in mice causes CAKUT characterized by pertubations in nephrogenesis and ureteric branching as well as the renal microvasculature. Yet, the cellular and molecular mechanisms underlying these defects are poorly defined.

We demonstrated that Hedgehog (HH)-GLI signalling plays a critical role in formation of *Foxd1*-positive stroma and a full complement of nephrons. Analysis of gene expression in stromal cells with loss of HH signalling identified TGFb2 as a candidate mediator of the deleterious effects on renal capsule formation and nephrogenesis. Since Tgfβ-receptor II is expressed in endothelial cells, we hypothesize that impaired Tgfβ-signalling affects normal renal microvasculature development. Our initial aim will be to characterize vascular development in mice with stromal cell specific disruption of TgfβRII using immunohistochemistry, gene and protein expression analyses and imaging of vascular patterning. The second aim will be to define the underlying mechanisms.

EXAMINING MINOR PHYSICAL ANOMALIES IN AUTISM SPECTRUM DISORDERS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Objective: The objective of this presentation is to describe findings from clinical dysmorphology exams of a cohort of twins recruited in the Roots of Autism (ASD) and Attention Deficit and Hyperactivity Disorder (ADHD) Study in Sweden (RATSS) in order to identify minor physical anomalies in children and young adults with ASD and ADHD.

Methods: Clinical dysmorphology exams were conducted on 120 children and young adults with ASD, ADHD, or typical development (who were also monozygotic or dizygotic twins) to identify the presence of minor physical anomalies. Two clinical geneticists utilized a standardized checklist covering all major body systems to identify minor physical anomalies. Descriptive statistics were performed to summarize the findings from the exams.

Results: The clinical exams revealed the presence of more physical anomalies in participants with ASD (median=9) and ADHD (median=7) compared to those without a diagnosis of ASD or ADHD (median=6 for both diagnoses). The most common physical anomalies in participants with ASD (n=29) and ADHD (n=34) included hypermobility (n=11 for both diagnoses), high palate (n=10 for ASD), flat feet (n=9 for ASD), sandal gap (n=9 for ASD), underweight (n=10 for ADHD), overweight (n=8 for ADHD), and straight eyebrows (n=8 for ADHD).

Conclusions: Minor physical anomalies were present in children and young adults with ASD and ADHD in greater amounts compared to those without either disorder. Examination of minor physical anomalies in children and young adults with ASD and ADHD may serve as a tool to identify individuals with subtypes of each disorder and/or individuals who may benefit from further testing (i.e., genetic testing).

TRANSCRIPTOMIC ANALYSES OF *P. FALCIPARUM* INTRA-ERYTHROCYTIC DEVELOPMENT AT CELLULAR LEVEL

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Plasmodium falciparum (Apicomplexa) uses complex strategies for survival, transmission and immune system evasion and is still a leading cause of human death. Important parasitic phenotypes, e.g. drug-induced quiescent cells, cell sequestration and sexual commitment, occur at low frequencies within parasitic populations and have therefore been hard to molecularly profile. Here, we have explored the potential of single-cell RNA-sequencing to profile individual and groups of malaria infected red blood cells (miRBCs) at different stages of the intra-erythrocytic life cycle. Analyses of parasite gene expression in single miRBCs identified known life cycle markers but also revealed considerable heterogeneity within miRBC picked at the same time point after culture synchronization. The miRBCs grouped into eight subpopulations by their expression of gene signatures important for its intra-erythrocytic life cycle. Importantly, we identified three miRBCs that had initiated sexual commitment and they specifically expressed a unique signature of genes that included many novel genes not previously associated with sexual commitments. This study highlights the exciting potential in using single-cell RNA-sequencing to profile rare and pathologically important sub-groups of parasites.

ESTABLISHING WHOLE BRAIN ORGANOIDS TO STUDY HUMAN BRAIN DEVELOPMENT AND DISEASE

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With the realization of the complexity of human brain development and neurodevelopmental disorders, the need for more comprehensive *in vitro* models increased. Differentiation protocols are mainly focused on generating pure populations of specific neurons and glia to reduce noise during analysis. This is an excellent approach for addressing molecular questions and to some extent cell-cell interactions. However, despite best efforts, the environment in which these cells are grown is sub-optimal and discards a major influencing factor, the stem cell niche. We use patient specific induced pluripotent stem cells (iPSCs) to generate whole brain organoids as a model to study stem cell function in relation to their niche. So far we are able to generate organoids containing regions of specific cortical identity. In these structures actively dividing radial glia are apparent, showing the functionality of the stem cell niche. This model yields us the opportunity to, more comprehensively, study brain development in health and disease.

RESVERATROL DISRUPTS STEROIDOGENESIS IN HUMAN FETAL ADRENALS

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The phytoestrogen resveratrol found in grapes and other plants has attracted considerable interest due to its proposed ability to extend lifespan, attenuate the development of metabolic syndrome in obese subjects and protect against cardiovascular disease. Self-medication with high pharmacological doses of this polyphenol with aim to improve metabolic parameters and health cannot be excluded in some sensitive health-focusing populations of humans. Prenatal voluntary exposure with resveratrol of pregnant women may negatively influence development of hormonal homeostasis and stress responsiveness in human fetuses.

The aim of the present project was to explore the potential of resveratrol to affect human fetal adrenal steroidogenesis and mitochondrial function at the end of the first trimester (gestational week 9-12). We observed that resveratrol significantly suppressed production of DHEA and androstenedione but elevated the release of progesterone and 17OH-progesterone by primary cultures of ACTH stimulated human fetal adrenocortical cells. These alterations in steroidogenesis were associated with down-regulation of CYP17A1 expression. No significant effects of resveratrol on cell proliferation and mitochondrial function were found.

Together our findings indicate that resveratrol has a potential to disrupt steroidogenesis in human fetal adrenals at the end of the first trimester. Since this is a critical period for the formation of many steroid-dependent organs, our data warn from self-medication with resveratrol especially during pregnancy.

AN ANALYSIS OF THE FACTORS THAT CONTRIBUTE TO FETAL ACIDOSIS IN ELECTIVE CAESAREAN SECTIONS

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Study Protocol

Background:

Blood from the umbilical artery is a reflection of the state of the fetus. If this is severe (pH <7.00) there may be a significant event that has occurred in utero that may warrant close neonatal monitoring. Severe acidosis may be associated with both short term and long term complications. Babies with a significant acidosis at birth many have difficulties in transition and so require resuscitaion or even admission to the Nonatal Intensive Care Unit. When there is evidence of fetal or maternal distress the presence of signficant acidosis can often be anticipated. In elective Caesaren sections at term there are usually no obvious factors that will predispose the fetus to stress and by extension acidosis yet there are babies born with this problem.

Methods:

We intend to retrospectively determine if there are potential identifiable factors that can predict the risk of an infant to significant acidosis. We may be therefore able to develop an algorithm for optimal management of these babies. Data will be collected from existing electronic and paper medical records. We will use a case control method matching 3 neonates for every case. We will calculate the incidence of fetal acidosis in elective caesarean sections and identify any risk factors that may be associated with the development of this in order to predict neonates that may be prone to developing significant acidosis. We will also identify the number of neonates that required intervention and so determine if this is significant and should a protocol be in place to monitor such infants once risk factors are identified.

UNCOVERING THE REGULATORY LANDSCAPE OF LABORING MYOMETRIUM

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With over 10% of worldwide births resulting from preterm labor (PTL) and a 25% rise in late preterm births since 1990, PTL continues to pose a significant clinical problem. To develop appropriate treatment methods, an extensive knowledge of molecular mechanisms regulating normal pregnancy progression and the onset of term labor (TL) needs to be acquired. In studies addressing the question of how uterine muscle contractile activity is controlled at the level of transcription, considerable attention has been paid to uncovering the transcription factors (TFs) and DNA motifs involved in regulating the promoters of some contraction-associated genes. However, gene regulation mechanisms often go beyond promoter activity to include distal regulatory elements (DREs), such as enhancers. Located as far as 1 Mb away from their target gene promoters, enhancers often activate their target genes in a tissue-specific way. Enhancers typically consist of open chromatin and are enriched in select histone modifications, most prominently acetylation of lysine residue 27 on histone protein 3 (H3K27ac). In this study, we sought to identify enhancers that regulate the expression of gestation-associated and TL onset-associated genes. We targeted hyper-acetylated genomic regions using a chromatin immunoprecipitation (ChIP) protocol we established specifically for myometrial tissue. We hypothesize that the loci of genes highly expressed in the myometrium throughout gestation and during TL possess enhancers that regulate these genes in a myometrial tissue-specific way.

OUTCOMES OF PLACENTAL DERIVED SEROTONIN FROM HIGHLY SEASONAL PREGNANT WOMEN

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Neurodevelopmental disorders have a major impact at a personal, familial and societal level, yet our ability to prevent them remains highly limited. Preclinical studies have demonstrated that during pregnancy, serotonin derived from maternal tryptophan at the placenta is an important signal for establishing fetal brain circuitry. Abnormal serotonin signaling during critical periods of brain development represents a major risk factor for various neurodevelopmental disorders. One plausible risk factor is changes in mood and appetite in women during fall and winter seasons. Individuals that are highly seasonal experience low mood, increase in carbohydrate consumption, weight gain and hypersomnia. Thus, pregnancies spanning fall and winter can be vulnerable to these lifestyle changes. Interestingly, numerous population studies have found an excess of births in spring associated with schizophrenia, especially in Northern countries. No studies to date have examined how the placental serotonin system in highly seasonal women differs from healthy pregnant women unaffected by winter. Also, no studies to date have examined whether seasonal changes in mood, weight and energy level influence maternal circulating tryptophan levels during pregnancy. We will study pregnant women taking part in the Ontario Birth Study**,** a large longitudinal pregnancy cohort being recruited at Mount Sinai Hospital. We hypothesize that, 1) Maternal tryptophan levels during pregnancy spanning fall and winter will be reduced and 2) placentas from highly seasonal women will undergo compensatory processes to maximize fetal serotonin when maternal precursor availability is sub-optimal for spring births. Levels of maternal plasma tryptophan levels will be measured at different time points in pregnancy utilizing mass spectrometry. Placental tissue collected at birth will be analyzed for measures of placental serotonin synthesis using reverse transcriptase q-PCR and western blot. This study will generate novel data on placental serotonin metabolism of fundamental importance to understanding early brain development and neurodevelopmental disorders.

CLINICALLY RELEVANT CULTURE CONDITIONS FOR HUMAN IPS CELLS AND NES CELLS IN PURSUIT OF CLINICAL APPLICATIONS

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The rapidly developing field of stem cell research is evolving beyond its infancy and the first clinical trials involving induced pluripotent stem cells (iPSC) signal the dawn of regenerative medicine. At the Falk lab, we are capable of deriving iPSC from patient fibroblasts and further differentiate these into neuroepithelial stem (NES) cells and mature neurons with potential use in regenerative medicine. However, the culture conditions and differentiation protocols used today are reliant on medias and factors that are not chemically defined nor Xeno-free. This represents a major hurdle to applications in regenerative medicine since these subprime conditions can result in batch to batch variations and immunogenic properties of the cells. The possible tumorigenic potential of the cells possesses another barrier, where footprint free reprograming and better differentiation protocols are called for. In order to optimize the use of these cells for future therapeutical applications these obstacles need to be overcome.

LYMPHATIC ENDOTHELIAL CELL EXPRESSION OF PLATELET-DERIVED GROWTH FACTOR B IS REQUIRED FOR MURAL CELL RECRUITMENT TO COLLECTING VESSELS

Wang, Y.[1], Jin, Y.[1], Andaloussi-Mäe, M.[2], Burmakin, M.[1], Betsholtz, C.[2], Mäkinen, T.[2] and Jakobsson, L.[1]

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The lymphatic vasculature is a vital part of our immune defence and regulates homeostasis by draining liquid from tissue, via its blind-ended capillaries and collecting vessels, back to the blood circulation. Unlike the blood vasculature, lymphatic capillaries lack mural cell coverage, whereas the larger collecting vessels are covered by smooth muscle cells (SMCs). Human genetic diseases illustrate the importance of this spatially restricted mural cell coverage for lymphatic function, but the underlying regulatory mechanisms of SMC recruitment have not been clarified. Here we demonstrate that platelet-derived growth factor B (PDGFB) is selectively expressed by lymphatic endothelial cells (LECs) of the collecting vessels but not by capillary LECs. Furthermore, neonatal LEC-specific deletion of *Pdgfb* causes a near complete loss of smooth muscle cell (SMC) recruitment to collecting vessels of the mouse ear. As a consequence collecting vessels are enlarged whereas capillaries are normal. In addition, mice lacking the heparan sulfate binding domain within PDGFB, show reduced mural cell coverage, indicating the importance of locally restricted PDGFB on this process. The genetic mouse model of lymphatic mural cell deficiency will be instrumental in further studies on the importance these cells in lymphatic development and function.

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Developmental and Perinatal Biology 2016

Course Evaluation

Please complete, remove and return the evaluation. This is **important** because it will help us in the design of future courses. Thank you.

Trainee from: (please tick) Karolinska Institute _____   University of Toronto _____

Lecture Course: (please circle one)

1)   Stem Cells, Embryonic Development and Disease:

Overall	could be improved	1	2	3	4	5	excellent
a) **Dr. J. Rossant**		1	2	3	4	5	
b) **Dr. A. Wong**		1	2	3	4	5	
c) **Dr. C. Nostro**		1	2	3	4	5	
d) **Dr. U. Lendahl**		1	2	3	4	5	

2)   Placenta & Birth:

Overall	could be improved	1	2	3	4	5	excellent
a) **Dr. F. Lanner**		1	2	3	4	5	
b) **Dr. M. Rennie**		1	2	3	4	5	
c) **Ms. P. Mackie**		1	2	3	4	5	
d) **Dr. S. Norris**		1	2	3	4	5	

3)   Cardiopulmonary Physiology:

Overall	could be improved	1	2	3	4	5	excellent
a) **Dr. P. Delgado Olguin**		1	2	3	4	5	
b) **Dr. K-H. Kim**		1	2	3	4	5	
c) **Dr. G. Montandon**		1	2	3	4	5	
d) **Dr. B. Yeganeh**		1	2	3	4	5	

4)   *Neurodevelopment:*

Overall	*could be improved*	1	2	3	4	5	*excellent*
a) Dr. P. Frankland		1	2	3	4	5	
b) Dr. O. Hermanson		1	2	3	4	5	
c) Dr. K. Gordon		1	2	3	4	5	
d) Dr. M. Ratsep		1	2	3	4	5	

5)   *Developmental Origins of Health and Disease:*

Overall	*could be improved*	1	2	3	4	5	*excellent*
a) Dr. S. Matthews		1	2	3	4	5	
b) Dr. D. Sloboda		1	2	3	4	5	
c) Dr. P. McGowan		1	2	3	4	5	
d) Dr. K. Blomgren		1	2	3	4	5	

Please outline how you feel the lecture course could be improved:

_____

_____

_____

Practical Courses:

Please indicate which 3 practical courses you attended and evaluate each below:

1. Methods and Tools to Assess Embryo Quality in the IVF Clinic _____

2. CRISPR Genome Editing; Scientific Advances, Potential
   Therapies and Ethical Concerns _____

3. Fetal Therapy Education _____

4. Mass Spectrometry Based Metabolomics _____

5. Application of Mass Spectrometry Based Proteomics to
   Pathology and Cell Biology _____

6. NICU Visit at Mount Sinai Hospital _____

7. Physiology of the Pulmonary Circulation _____

8. Epigenetics _____

1st Course (Methods and Tools to Assess Embryo Quality in the IVF Clinic)

Course Content:
could be improved   1   2   3   4   5   *excellent*

Course Organization:
    1   2   3   4   5

2nd Course (CRISPR Genome Editing; Scientific Advances, Potential Therapies and Ethical Concerns)

Course Content:
could be improved   1   2   3   4   5   *excellent*

Course Organization:
    1   2   3   4   5

3rd Course (Fetal Therapy Education)

Course Content:
could be improved   1   2   3   4   5   *excellent*

Course Organization:
    1   2   3   4   5

4th Course (Mass Spectrometry Based Metabolomics)

Course Content:
    could be improved   1   2   3   4   5   *excellent*

Course Organization:
    1   2   3   4   5

5th Course (Application of Mass Spectrometry Based Proteomics to Pathology and Cell Biology)

Course Content:
    could be improved   1   2   3   4   5   *excellent*

Course Organization:
    1   2   3   4   5

6th Course (NICU Visit at Mount Sinai Hospital)

Course Content:
    could be improved   1   2   3   4   5   *excellent*

Course Organization:
    1   2   3   4   5

7th Course (Physiology of the Pulmonary Circulation)

Course Content:
    could be improved   1   2   3   4   5   *excellent*

Course Organization:
    1   2   3   4   5

8th Course (Epigenetics)

Course Content:
    could be improved   1   2   3   4   5   *excellent*

Course Organization:
    1   2   3   4   5

How could the practical courses be improved:

_____

_____

Social Program:

could be improved   1   2   3   4   5   *excellent*

Could the social program/accommodations be improved:

_____

_____

_____

Overall Course:

could be improved   1   2   3   4   5   *excellent*

How do you think the course could be improved next year:

_____

_____

_____

Thank You