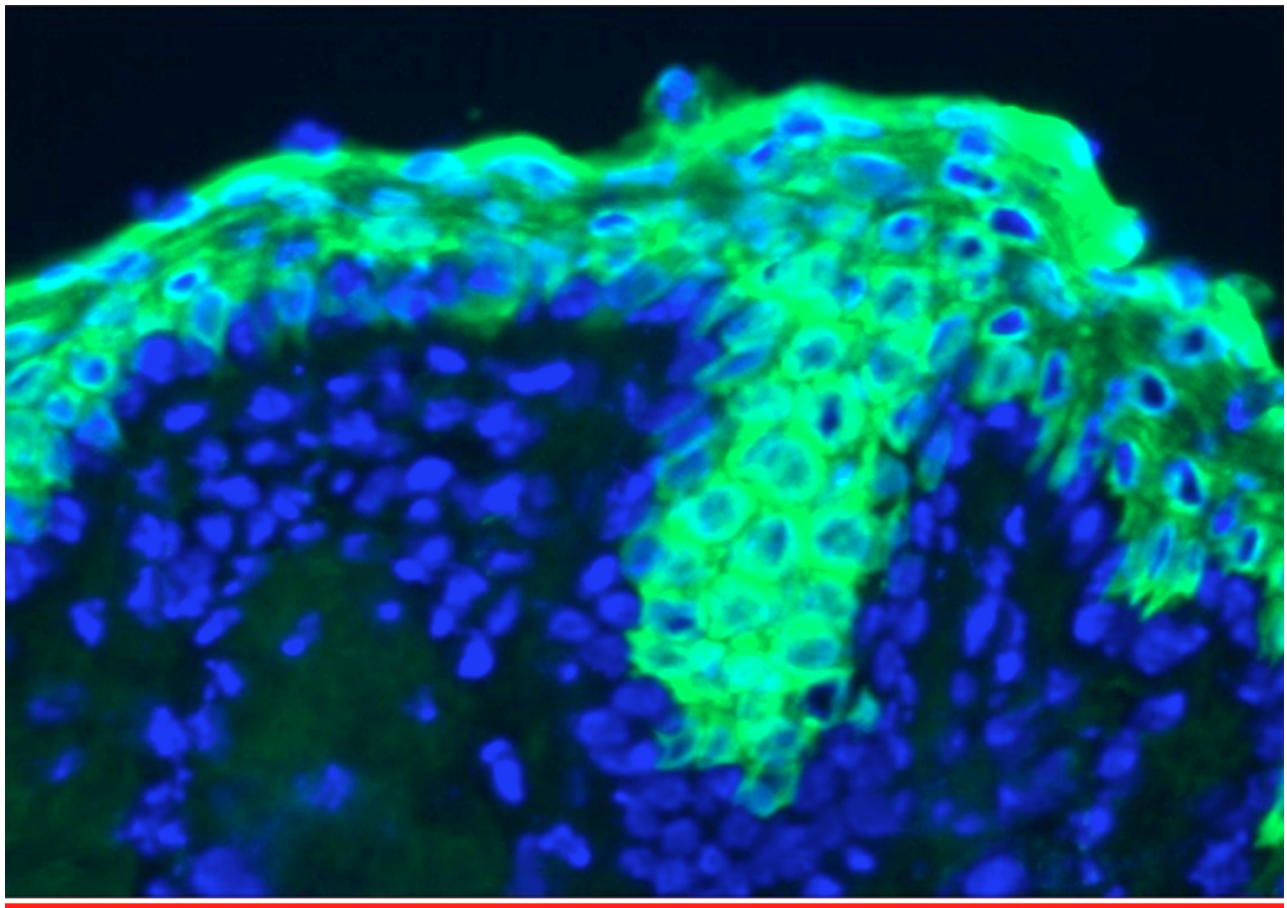
2ieme Symposium Annuel du Regroupement de Recherche sur la Peau

SKIN RESEARCH GROUP
2nd ANNUAL SYMPOSIUM



RESEARCH REPAIR RESTORE REGENERATE

Mai 31, 2015
Théatre de poche, Desjardins Building
Université Laval
Québec, QC

ABSTRACTS BOOKLET

WWW.Skinresearchgroup.org

Dear Skin Research Group Symposium participants,

It is our pleasure to welcome you all to the 2nd Annual Skin Research Group Symposium in beautiful Quebec City. We are delighted to have the participation of two experts in the field as keynote speakers and 15 other bright and enthusiastic skin researchers as speakers. The symposium addresses current hot topics in the field of skin research. We hope you will find the conference scientifically stimulating and take home new research ideas and establish new collaborations. Enjoy the meeting and the beautiful Quebec City and all of its festivities.

Anie Philip, PhD
Professor
McGill University

Stéphane Roy, PhD
Professeur titulaire
Université de Montréal

Symposium Co-Chairs

Chers participants,

Il nous fait plaisir de vous souhaiter la bienvenue au 2ieme Symposium annuel du regroupement de recherche sur la peau dans la belle ville de Québec. Nous sommes ravis d'avoir la participation de deux experts du domaine de recherche en tant que conférenciers et 15 autres jeunes chercheurs brillants et enthousiastes. Le symposium aborde des sujets d'actualité dans le domaine de la recherche sur la peau. Nous espérons que vous trouverez la conférence stimulante et source de nouvelles idées de recherche ainsi qu'une opportunité pour établir de nouvelles collaborations. Nous vous souhaitons un bon symposium et n'oublier pas de profiter de la belle ville de Québec et toutes ses activités.

Anie Philip, PhD	***Stéphane Roy, PhD***
Professor	*Professeur titulaire*
McGill University	*Université de Montréal*

Symposium Co-Chairs

Organizing Committee

Chair

Anie Philip, PhD

Professor

Dept. of Surgery and Medicine

McGill University

Co-Chair

Stéphane Roy, PhD

Professeur titulaire

Faculté de Médecine Dentaire

Université de Montréal

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Full professor, Department of surgery,

Faculty of Medicine, Université Laval

LOEX

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Associate Professor

Faculty of Dentistry

McGill University

Mohit Kapoor, PhD

Associate Professor

Head, Cartilage Biology Research, Arthritis Program,

Toronto Western Research Institute

Dieter P. Reinhardt, PhD

Professor

Faculty of Medicine and Faculty of Dentistry

McGill University

Kenneth Finnson, PhD

Research Associate

Department of Surgery

McGill University

We thank our……..

Judges

Dr. Kenneth Finnson

Dr. Christopher M. Overall

Dr. Boris Hinz

Dr. Francois Berthod

Dr. Véronique J. Moulin

&

Volunteers

Fadi Sader

Jean Francois Denis

Chae Syng Lee

Heena Kumra

Mohammadjavad Paydar

Liqin Xu

Shufeng Zhou

Priyanka Sehgal

Yoon Chi

Mays Merjaneh

Manon Salvetti

Yannick Leclerc

EVENT PROGRAM

Sunday, May 31, 2015

Théâtre de poche

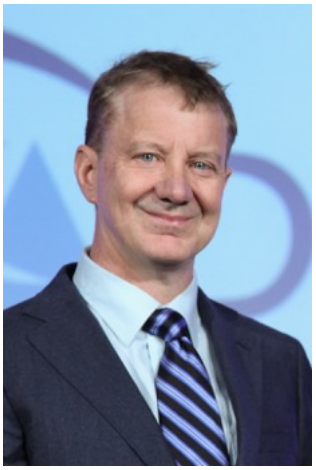
Local 2113 Pavillon M. –Pollack

Desjardins Building, Université Laval

Quebec City, QC

8:00 - 8:30	Registration
8:30 - 8:45	Welcome remarks ***Anie Philip,*** *McGill University, Montreal, QC* ***Stéphane Roy,*** *Université de Montréal, Montréal, QC*
8:45 - 9:15	"Quantitative Proteomics and Systems Biology Analysis of Proteolytic Networks in Skin in vivo" ***Christopher M. Overall,*** *UBC Centre for Blood Research, University of British Columbia, Vancouver, BC*
Session I *Moderators: Stéphane Roy & Jean-François Denis*	
9:15 - 9:25	"Fibrillin-1 interaction with cells regulates microRNAs" ***Dieter P. Reinhardt***, *McGill University, Montreal, QC*
9:25 - 9:35	"The Dual Leucine zipper bearing Kinase induces microtubule reorganisation to cell periphery: a process required for proper keratinocyte differentiation" ***Carolyne Simard-Bisson***, *CMDGT/LOEX, Quebec City, QC*
9:35 - 9:45	"CD109-Deficient Mice Display Impaired Hair Growth and Abnormal Dermal Appendages" ***Liqin Xu***, *McGill University, Montreal, QC*
9:45 - 9:50	"In vitro glycation of an endothelialized and innervated tissue-engineered skin to screen anti-AGE molecules" ***Francois Berthod,*** *Centre LOEX de l'Université Laval, Quebec City, QC*
9:50 - 9:55	"Glycosylation of fibulin-4 regulates tropoelastin interaction and assembly" ***Chae Syng Lee,*** *McGill University, Montreal, QC*
9:55 - 10:00	"Characterization of epithelial to mesenchymal transitions during axolotl limb regeneration" ***Fadi Sader,*** *Université de Montréal, Montréal, QC*
10:00 - 10:05	"Targeting TGF-beta signaling to prevent metastasis in skin squamous cell carcinoma" ***Shufeng Zhou,*** *McGill University, Montreal, QC*

10:05 - 10:10	"Inexpensive production of near-native engineered dermis" ***Stéphane Chabaud,*** *CMDGT/LOEX, Quebec City, QC*
10:10 - 10:15	"Synergistic effects of cellular and plasma fibronectin in tissue organization in vivo" ***Heena Kumra, McGill University, Montreal, QC***
10:15 - 10:30	**COFFEE BREAK**
10:30 - 11:00	"THE STIFFNESS AND STRAIN OF SKIN" ***Boris Hinz,*** *University of Toronto, Toronto, ON*
Session II *Moderators: Dieter P. Reinhardt & Kenneth Finnson*	
11:00 - 11:10	"CD109 as a regulator of squamous carcinoma cell migration and invasion" ***Priyanka Sehgal,*** *McGill University, Montreal, QC*
11:10 - 11:20	"Smad2 is required for axolotl limb regeneration" ***Jean-François Denis,*** *Université de Montréal, Montréal, QC*
11:20 - 11:30	"Early detection of structural abnormalities and cytoplasmic accumulation of TDP-43 in tissue-engineered skins derived from ALS patients" ***Bastien Pare,*** *LOEX/ Université Laval, Quebec City, QC*
11:30 - 11:35	"Endoglin haploinsufficiency is associated with decreased fibrotic parameters during bleomycin-induced skin fibrosis" ***Yoon Chi,*** *McGill University, Montreal, QC*
11:35 - 11:40	"Immunohistochemistry studies of lipoxygenases in human epidermis" ***Bernard Fruteau-de-Laclos,*** *LOEX/ Université Laval, Quebec City, QC*
11:40 - 11:45	"Clinical trial protocol: Self-Assembled Skin Substitute for the Autologous Treatment of Severe Burn Wounds in Acute Stage of Burn Trauma" ***Danielle Larouche,*** *LOEX/ Université Laval, Quebec City, QC*
11:45-12:45	Workshop session – SR4G of Tomorrow
12:45-1:00	**Concluding remarks and Awards Presentation** ***Anie Philip,*** *McGill University, Montreal, QC* ***Stéphane Roy,*** *Université de Montréal, Montréal, QC*



Keynote Speaker

Dr. Christopher M. Overall
UBC Centre for Blood Research
University of British Columbia

Dr. Overall is a Professor and Canada Research Chair in Protease Proteomics and Systems Biology, U.B.C. Vancouver. He completed his Ph.D. at the University of Toronto; and post-doctoral work with Dr. Michael Smith, Nobel Laureate. In 1997/1998 was a Visiting Senior Scientist at British Biotech, Oxford and in 2004/2008 a Visiting Senior Scientist at Novartis, Basel, and is now Honorary Professor, Albert-Ludwigs Universität Freiburg. Dr. Overall was 2002 CIHR Scientist of the Year, the UBC Killam Senior Researcher Award 2005, and the Chair of the 2003 Matrix Metalloproteinase and the 2010 Protease Gordon Research Conferences. With over 12,626 citations for his 210 papers and with an *h factor* of 62 and 22 Nature Review, Nature Journal, Cell Journal, Science and Science Signaling papers he is a leader in the field, which was recently recognized by the International Society of Proteolysis with the 2011 Lifetime Achievement Award; by the Matrix Biology Society of Australia and New Zealand with the 2012 Barry Preston Award; and in 2014 by the Tony Pawson Canadian National Proteomics Network Award for Outstanding Contribution and Leadership to the Canadian Proteomics Community. He is also an elected member of HUPO council, the Chromosome Centric Human Proteome Project (C-HPP) Executive Committee and is an Associate Editor of the Journal of Proteomics Research.

Abstract

Quantitative Proteomics and Systems Biology Analysis of Proteolytic Networks in Skin in vivo

Christopher M. Overall

UBC Centre for Blood Research, University of British Columbia, 2350 Health Sciences Mall, Vancouver, B.C. V6T 1Z3 Canada. chris.overall@ubc.ca http://www.clip.ubc.ca.

In contrast to the traditional dim view of matrix metalloproteinases (MMPs) being dowdy matrix degraders, we show MMPs are protective in inflammation. We explored the roles of the immune-modulatory MMP2 and macrophage MMP12 by quantifying global proteome, protein N-termini (the N-terminome) and the altered abundance of proteases and inhibitors in skin inflammation. Cleavage and inactivation of the C1 inhibitor by MMP2 increased complement activation and bradykinin generation by plasma kallikrein, leading to increased vessel permeability during inflammation and hence influx of acute response proteins. The Mmp2 knock out mice had reduced vessel permeability, reduced acute response proteins and complement activation through pathways controlled by C1 inhibitor. In exploring the role of macrophage MMP12, we found that Mmp12-/- mice display earlier and dramatic severe arthritis vs. wild-type mice characterized by massive neutrophil infiltrations. Overall, MMP12 dampens inflammation by concerted cleavages in multiple inflammation regulatory pathways. MMP12 facilitates macrophage invasion, but inactivates all CXCR2 chemokines responsible for neutrophil recruitment. This terminates neutrophil infiltration so accounting for the masses of neutrophils and the joint destruction in Mmp12-/- arthritis. MMP12 also promotes coagulation and squashes complement activity at multiple levels. Such examples exemplify the general renaissance MMPs are enjoying from matrix remodellers to key cell regulators of extracellular homeostasis. By developing degradomics strategies to explore the roles of proteases in vivo many new substrates and hence functions in diverse processes have been revealed in regulating inflammation and immunity.

Keynote Speaker

Dr. Boris Hinz
Laboratory of Tissue Repair and Regeneration
Matrix Dynamics Group, Faculty of Dentistry
University of Toronto

Boris Hinz is Professor in the Matrix Dynamics Group, Faculty of Dentistry, University of Toronto, Canada. He is cross appointed with the Faculty of Medicine, Department of Surgery and the Institute of Biomaterials and Biomedical Engineering at the University of Toronto. Dr. Hinz holds a PhD degree in Cell Biology and Theoretical Biology from the University of Bonn, Germany, obtained in 1998. From 1999 to 2002, he was postdoctoral fellow of Dr. Giulio Gabbiani, Department of Experimental Pathology, Centre Medical Universitaire, University of Geneva, Switzerland. Dr. Hinz then moved on to lead a research group at the Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland, joining the worlds of Cell Biology, Biophysics, and Bioengineering. He was nominated Maître d'enseignement et de recherche (Assistant Professor level) in 2006 and moved to Toronto in 2009. He is Past President and board member of the European Tissue Repair Society, Secretary and inaugural board member of the Canadian Connective Tissue Society, board member of the Wound Healing Society, the International Dupuytren Society and the Canadian Dupuytren Society, Associate Editor of the Journal Wound Repair and Regeneration, and Associate Member of the Faculty of 1000.

Dr. Hinz aims in understanding the role of contractile myofibroblasts in physiological tissue repair and in causing pathological tissue fibrosis. The findings of his lab are published in peer-reviewed journals, including Nat. Med., Curr. Biol., J. Cell Biol., Stem Cells, Stem Cell Reports, J. Clin. Invest., Nature Immunol., EMBO J., Mol. Biol. Cell, Cardiovascular Res., J. Cell Sci., Biomaterials, Biophys. J., Am. J. Pathol., PLoS One, and the J. Invest. Dermatol., receiving over 7,500 citations by May 2015 with an h-factor of 35. He published 81 peer reviewed articles, 13 book chapters, and more than 300 congress abstracts. His research lead to the creation of two startup companies specialized on anti-fibrotic coatings for silicone implants and novel “soft” cell culture devices. Dr. Hinz’ research is currently funded by grants from the Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada (NSERC), Canada Foundation for Innovation (CFI), Ontario Research Foundation, and the European Union’s Transnational Program for Projects on Rare Diseases.

Abstract

THE STIFFNESS AND STRAIN OF SKIN

Boris Hinz, PhD

Laboratory of Tissue Repair and Regeneration, Matrix Dynamics Group, Faculty of Dentistry, University of Toronto, Toronto, ON M5S 3E2, Canada

Tissues lose their integrity upon injury. To rapidly restore mechanical stability, a variety of different cell types are activated to acquire a reparative phenotype - the myofibroblast. Hallmarks of the myofibroblast are secretion of extracellular matrix (ECM), development of adhesion structures with the ECM, and formation of actomyosin contractile stress fibers. Rapid repair comes at the cost of tissue contracture due to the inability of the myofibroblast to regenerate tissue. When contracture and ECM remodeling become progressive and manifest as organ fibrosis, stiff scar tissue obstructs and ultimately destroys organ function.

One consequence of ECM stiffening is the mechanical activation of the pro-fibrotic growth factor TGF-β1 from stores in the ECM. Our research established a mechanical pulling mechanism of TGF-β1 activation, requiring integrins, cell contraction, and binding of the latent TGF-β1 binding protein-1 (LTBP-1) to the ECM. I will present data showing that the organization level of LTBP-1 controls the availability of TGF-β1 for mechanical activation by pre-straining the latent complex, analogous to loading a mechanical spring. With the aim to establish elastic culture substrates that reproduce the variable softness of normal dermis, we determined the Young's elastic modulus E of human dermis at the cell perception level using atomic force microscopy. The E of dermis ranges from 0.1-10 kPa, varies depending on body area and dermal layer, and tends to increase with age. Human dermal fibroblasts cultured on 'skin-soft' E (5 kPa) silicone culture substrates exhibit an activation profile that is comparable to that of human dermis in contrast to other tested culture conditions (plastic or 3D collagen). Overall, providing biomimetic mechanical conditions of skin generates fibroblasts that are more suitable to investigate physiologically relevant cell processes than fibroblasts spontaneously activated by stiff conventional culture surfaces.

ORAL PRESENTATION
ABSTRACTS

Fibrillin-1 interaction with cells regulates microRNAs

Karina Zeyer[1], Heena Kumra[1], Amani Hassan[1], Dieter P. Reinhardt[1, 2]

[1]Faculty of Medicine and [2]Faculty of Dentistry, McGill University, Montreal, Canada

Background and Aim: Fibrillins are the major components of microfibrils in the extracellular matrix of elastic and non-elastic tissues. They are multi-domain proteins, containing mainly calcium-binding epidermal growth factor-like domains and 8-cysteine/TB domains. Fibrillin-1 contains one evolutionarily conserved Arg-Gly-Asp (RGD) sequence in its fourth TB domain which is required to mediate cell-matrix interactions by binding to cell-surface integrins. Mutations in this domain lead to heritable disorders, including stiff skin syndrome. This study aims to determine the cell signaling function of the fibrillin-1 RGD sequence.

Experimental Procedures: Two recombinant fibrillin-1 fragments were produced, one wild-type RGD-containing fragment and one fragment containing a mutant RGA sequence. The different characteristics of interactions between human skin fibroblasts (HSFs) and the two fragments were analyzed by light and fluorescence microscopy. To determine the differential regulation of signaling pathways, microarray analysis of microRNA (miRNA) as well as mRNA expression was conducted. MiRNAs play a key role in the regulation of gene expression by targeting mRNAs. The expression levels were compared after 24 hours of interaction between HSFs and the two fragments. Real-time quantitative PCR was used to validate the microarray results for a selection of miRNAs and mRNAs, as well as to perform a time course analysis of the differential expression of the selected miRNAs. Interactions between miRNAs and mRNAs were predicted by bioinformatics analysis and predicted interactions were validated in vitro using the mirTrap system. Cell culture studies using miRNA mimics or inhibitors were applied to study the functional effects of miRNA overexpression or inhibition in vitro.

Results: After 24 hours, HSFs attached differently to plates coated with the wild-type fragment in comparison to the RGA-containing fragment. The interaction of HSFs with the RGD sequence of fibrillin 1 showed proliferative potential in immunofluorescence assays. Surprisingly, the microarray displayed differential expression of many miRNAs and mRNAs after 24 h of interaction between HSFs and the two fragments. Differential miRNA expression occurred after only 2 hours of interaction. Pathway analysis indicated that the differentially expressed miRNAs act together in regulating cell adhesion, migration and growth factors, all of which are relevant for extracellular matrix biology and pathology. Overexpression of certain miRNAs in human skin fibroblasts has significant effects on the actin cytoskeleton as well as the activity of focal adhesion kinase, a downstream mediator of integrin signaling. miR-612, miR-1208 and miRNA-3185 are three of the most interesting candidates because they are significantly downregulated upon integrin ligation and regulate not only known growth factors controlled by fibrillin-1 (TGF-β2/BMP2), but also Wnt, fibroblast growth factor and Notch pathways, all potentially important players in extracellular matrix biology and skin pathology. A variety of those growth factors were shown to be targets of miR-612, miR-1208 and miR-3185 in vitro.

The Dual Leucine zipper bearing Kinase induces microtubule reorganisation to cell periphery: a process required for proper keratinocyte differentiation.

Carolyne Simard-Bisson[1], Julie Bidoggia[1], Danielle Larouche[1], Richard Blouin[2], Lucie Germain[1].

[1]Centre de recherche en organogénèse expérimentale de l'Université Laval / LOEX, Centre de recherche FRQS du CHU de Québec, Québec, Qc, G1J 1Z4 Canada, and Département de Chirurgie, Faculté de Médecine, Université Laval, Québec, Qc, G1V 0A6, Canada.

[2] Département de biologie, Université de Sherbrooke, Sherbrooke, QC, J1K 2R1, Canada.

Dual Leucine zipper bearing Kinase (DLK) is a Mitogen Activated Triple Kinase strongly expressed in the granular layer of skin epidermis. Previous studies reported that DLK surexpression in keratinocytes in culture induces differentiation related processes such as decrease of cell proliferation, increased filaggrin expression and enhanced corneocyte formation. However, mechanisms involved in DLK induced keratinocyte differentiation remain to be elucidated. To get more insight about those mechanisms, tissue-engineered skin (TES) were exposed to lentiviral vectors containing shRNA sequence in order to reduce DLK expression (shDLK TES). DLK reduction was confirmed using immunohistochemical staining. As expected, epidermal differentiation was impaired in shDLK TES. Indeed, less keratohyalin granules, a reduced cornified layer and decreased filaggrin and transglutaminase 1 expression were observed. Interestingly, increased intercellular spaces were noted in in shDLK TES keratinocytes suggesting cell junctions defects. Ultrastructural analyses confirmed that desmosomes and tight junctions were altered in shDLK TES. Since DLK was also reported as a kinase promoting microtubule stabilization, microtubule dynamics were studied in keratinocytes in culture following DLK surexpression using adenoviral vectors or in shDLK TES. We found that DLK was able and required for proper microtubule distribution to cell periphery in keratinocytes during differentiation process. To assess the importance of microtubule redistribution, microtubule in TES were disrupted using nocodazole. Interestingly, nocodazole treated TES and shDLK TES shared similar features showing that microtubules are important effectors in DLK induced differentiation. This study confirms a role for microtubules and for DLK in the keratinocyte differentiation process and provide more information about the mechanisms involved in DLK induced differentiation. Support: FQRS, Réseau Thécell, IRSC.

CD109-Deficient Mice Display Impaired Hair Growth and Abnormal Dermal Appendages

Liqin Xu, Kenneth Finnson, Mirko Gilardino, and Anie Philip

Background: Fibrotic disorders such as hypertrophic scarring and systemic sclerosis are debilitating pathologies with limited treatment options. They are characterized by over-abundant deposition of extracellular matrix (ECM) components such as collagen, resulting in skin thickening and loss of elasticity. Transforming growth factor-beta (TGF-β) is a multifunctional protein that plays a critical role in the maintenance of skin homeostasis, and its aberrant signaling has been implicated in the pathogenesis of fibrotic skin diseases. Thus, targeting this pathway represents a promising strategy for the prevention and treatment those disorders. Our group has identified CD109 as a TGF-β co-receptor that antagonizes TGF-β signaling action and inhibits ECM production in vitro. Here, we investigate the role of endogenous CD109 in vivo using CD109 knockout (CD109-/-), heterozygote (CD109+/-) and wild-type (CD109+/+) littermates.

Objective: To analyze the structural and functional features of the skin in CD109-/- mice when compared to their CD109+/- and CD109+/+ littermates.

Methods: Skin samples are harvested at different time points from CD109+/+ mice and their CD109+/- and CD109-/- littermates and evaluated using imaging techniques and histological and biochemical analyses. Genotype was confirmed using PCR and Western blot.

Results: CD109-/- mice exhibit cyclical and varying degrees of hair growth impairment, in contrast to their CD109+/+ littermates' dense, shiny hair. The heterozygote displayed a hair growth phenotype that is somewhat between those of the knockout and the wild type. The specific skin abnormalities in the knockout mice included disorganized direction of hair growth, short fine whiskers, as well as patchy alopecia as a result of impaired hair eruption through the epidermis. Preliminary Masson's trichrome staining results suggest that knockout mice skin display denser collagen content and disorganization under basal and bleomycin-induced conditions, when compared to wild-type littermates.

Conclusion: Our results demonstrate that CD109 is involved in the normal development of skin and dermal appendages in mice. A better understanding of the mechanisms by which CD109 regulates TGF-β signaling pathways and ECM deposition in the skin may lead to strategies for targeting CD109 to block excessive TGF-β action and thus skin fibrosis. Agents that halt or reverse progression of pathological skin fibrosis will result in significant savings in health care costs

In vitro glycation of an endothelialized and innervated tissue-engineered skin to screen anti-AGE molecules

Sébastien Cadau[1], Sabrina Leoty-Okombi[2], Sabine Pain[2], Nicolas Bechetoille[2], Valérie André-Frei[2], François Berthod[1]

[1]Centre LOEX de l'Université Laval, Centre de recherche du CHU de Québec, 1401, 18e rue, Québec (Québec) G1J 1Z4, Canada, and Département de Chirurgie, Faculté de Médecine, Université Laval, Québec (Québec), Canada

[2]BASF Beauty Care Solutions, 32 rue Saint Jean de Dieu, 69007, Lyon, France.

Glycation is one of the major processes responsible for skin aging through induction of the detrimental formation of advanced glycation end-products (AGEs). We developed an innovative tissue-engineered skin combining both a capillary-like and a nerve networks and designed a protocol to induce continuous AGEs formation by a treatment with glyoxal. We determined the optimal concentration of glyoxal to induce AGEs expression identified by carboxymethyl-lysin expression while keeping their toxic effects low. We showed that our tissue-engineered skin cultured for 44 days and treated with 200 µM glyoxal for 31 days displayed high carboxymethyl-lysine expression, which induced a progressively increased alteration of its capillary and nerve networks between 28 to 44 days. Moreover, it produced an epidermal differentiation defect evidenced by the lack of loricrin and filaggrin expression in the epidermis. These effects were almost completely prevented by addition of aminoguanidine 1.5 mM, an anti-glycation compound, and only slightly decreased by alagebrium 500 µM, an AGE-breaker molecule.

This tissue-engineered skin model is the first one to combine a capillary and nerve network and to enable a continuous glycation over a long-term culture period. It is a unique tool to investigate the effects of glycation on skin and to screen new molecules that could prevent AGEs formation. It migth be a useful model to investigate ulcer formation in the context of diabetes.

Glycosylation of fibulin-4 regulates tropoelastin interaction and assembly

Chae Syng Lee[1], Jelena Djokic[1], Dieter P. Reinhardt[1, 2]

[1]Faculty of Medicine and

[2]Faculty of Dentistry, McGill University, Montreal, Quebec

The fibulin family is a group of eight extracellular glycoproteins, characterized by variable numbers of calcium-binding epidermal growth factor (cbEGF) domains followed by a fibulin-type module at the C-terminus. Fibulin-4 is expressed in various elastic tissues, including skin and blood vessels, and are known be important in elastogenesis. It is of great interest as mutations lead to skin and cardiovascular disease in humans. Its absence results in perinatal death in the corresponding knockout mouse model. Human fibulin-4 contains two N-linked glycans of unknown function, at position 592 and 1180.

When recombinantly-expressed fibulin-4 was enzymatically deglycosylated, it exhibited enhanced binding to tropoelastin, the soluble form of elastin, as compared to the fully-glycosylated fibulin-4. Hence, we hypothesized that fibulin-4 glycosylation plays a critical role in elastogenesis. To test this, we generated mutants of fibulin-4 lacking N-glycosylation site(s) at position 592, 1180, and both. The mutant constructs were transfected into HEK293 to ensure proper post-translational modifications. All glycosylation mutants were secreted in significantly lower amounts compared to the wild-type, and showed enhanced activation of the unfolded protein response pathway, indicating that folding in ER was stalled. This demonstrates that fibulin-4 N-linked glycosylation is important for proper secretion into the extracellular matrix. To identify a suitable cell culture model for elastogenesis, various cell lines were surveyed by immunofluorescent staining of relevant elastogenic proteins. Pulmonary aortic smooth muscle cells (PAC1) showed expression of fibronectin, fibrillin-1, and tropoelastin. The fibulin-4 wild-type and the glycosylation mutants were transfected in PAC1 cells to study their consequences on elastogenesis. We found that overexpression of fibulin-4 enhanced tropoelastin secretion from these cells. All glycosylation mutants enhanced the assembly of tropoelastin into extracellular fibers significantly more than the wild-type. The data suggest that fibulin-4 interaction with tropoelastin is regulated by the presence of N-linked glycans, possibly within the secretory pathway as a chaperone function. The data further indicate that the N-linked fibulin-4 glycans inhibit extracellular elastogenesis.

Characterization of epithelial to mesenchymal transitions during axolotl limb regeneration

Fadi Sader[1] and Stéphane Roy [1,2]

1- Dept. of Biochemistry & 2- Dept. of Stomatology, Université de Montréal, Montreal, Quebec, H3T 1J4, Canada

The axolotl (Ambystoma mexicanum) is a vertebrate with remarkable regeneration capacities. It can perfectly regenerate parts of it body following different kinds of amputations. Our lab is interested in understanding the biological processes enabling axolotl regeneration. Discovering the regulation of the signalling pathway leading to regeneration would greatly help the development of therapies for many health problems. Limb regeneration is studied for its ease and low incidence of adverse effects on the animal's health. Regeneration in axolotls can be described as a bi-phasic process in which the first phase has some similarities with mammalian wound healing and the second phase similarities with development. The multifunctional cytokine TGF-β is known to be involved in mammal wound healing. Published results from our lab showed that TGF-β1 is essential for limb regeneration. Treatment with a specific inhibitor of TGF-B, the SB-431542, blocks regeneration. Following these results we wanted to assess functional analysis and characterize TGF-β target genes during regeneration. During the first 2 hours of the process, keratinocytes close to the amputation site migrate to close the wound. We hypothesized that epithelial to mesenchymal transitions (EMT) are necessary for epithelial cell migration to occur during wound closure. TGF-β is known to be a major regulator of the EMT process via Smad (canonical) and non-Smad (non-canonical) signalling. We therefore decided to look at gene expression of EMT markers. Results show a very early up regulation of markers such a Snail, Twist and ZEB. We also see no regulation of epithelial marker E-cadherin. These results suggest an EMT process during the first hours following amputation. Since we believe TGF-β is partially responsible for the process, we will assess expression of markers following treatments of SB-431542, SiS3 (Smad signalling inhibition) and p38 inhibitor SB-203580 (TGF-β non-Smad signalling).

Targeting TGF-beta signaling to prevent metastasis in skin squamous cell carcinoma

[1]Shufeng Zhou, [1]Anie Philip

[1]Division of Plastic Surgery, Department of experimental Surgery, McGill University, Montreal

Background: Skin cancer is the most common malignancy in Canada: it represents 1/3 of all new cancer cases each year and 1 in 7 Canadians will develop some form of skin cancer during their lifetime. Emerging evidence suggest that a sub-population of cancer cells with stem cell-like properties known as cancer stem cells, may be responsible for tumor formation and metastasis in squamous cell carcinoma (SCC). Transforming growth factor-β (TGF-β) is a tumor suppressor in early stages of cancer, but switch to a tumor promoter in advanced carcinomas via induction of epithelial-to-mesenchymal transition and enhancing cancer cells to acquire stem cell-like properties. Our group has identified CD109 as a TGF-β co-receptor that negatively regulates TGF-β signaling. Evidence indicates that in SCC, CD109-positive tumors tend to be well differentiated (low grade), while the CD109-negative tumors are likely to be poorly differentiated (high-grade). Recent results from our laboratory show that CD109 not only hinder TGF−β-induced EMT in SSC but also inhibit TGF-β induced migration and invasion of SCC. However, the significance of aberrant CD109 expression in SCC tumors and the potential of CD109 to regulate SCC progression and metastasis have not been yet explored. The aim of this study is to examine the potential of CD109 as a critical regulator of cancer stem cells and metastasis in SCC, and (ii) the possibility of using CD109 protein as therapeutic target to inhibit SCC cancer progression and metastasis.

Methodology: In this study, we analyzed the effect of CD109 in SCC in vitro using SCC (A431) cells that stably overexpress either CD109 or its empty vector, by determining cell proliferation (cell counting), and apoptosis (flow cytometry propidium iodide labeling, Annexin V). The cancer stem cell population was analyzed by a tumor spheroid formation assay. TGF-β-induced EMT was analyzed by determining the expression of EMT markers by western blot.

Results: We found that CD109 over-expression significantly inhibits TGF-β-induced EMT and spheroid formation in in A431 SSC cells when compared to its empty vector controls, indicating CD109 decrease cancer stem cell population of SCC. Targeting CD109 might provide a new therapeutic strategy for the treatment of SCC

Inexpensive production of near-native engineered dermis.

Stéphane Chabaud, Ph.D. [1]***, Alexandre Rousseau, M.Sc.*** [1]***, Thomas-Louis Marcoux, B.Sc*** [1]***, Stéphane Bolduc, M.D.*** [1, 2]

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The self-assembly approach is an efficient method for the production of engineered physiological and pathological tissues. If it avoids the use of exogenous materials, it remains expensive and requires dexterity, which are features incompatible with large-scale production. We propose a modification to this technique to make easier the production of mesenchymal compartment, to reduce the cost and to improve the histological quality of the self-assembled tissues. The stroma produced by this novel approach allowed epithelial cell differentiation, resulting in an epithelium that shared several features with native tissues (pseudostratification, barrier function, well organized ZO-1 positive junctions). The incorporation of endothelial cells in the reconstructed mesenchyme formed a three-dimensional capillary-like network (PECAM-1 and van Willebrandt factor positive, surrounded by alpha-smooth muscle actin and NG-2 positive cells), which could limit self-contraction of the resulting tissue (-47%). With this new technique, which is relatively inexpensive (reduction of 87.5 % of the cost) and easy to use in a research laboratory set-up (reduction of 65.9 % of incubator space needed and of 75.1 % of labor time), near-native stromas can now be produced with minimal handling time.

Synergistic effects of cellular and plasma fibronectin in tissue organization in vivo

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BACKGROUND: Fibronectin (FN) is an abundant and ubiquitously expressed protein present in plasma and in the extracellular matrix (ECM) of various connective tissues. Soluble plasma FN (pFN) is synthesized by liver hepatocytes, whereas cellular FN (cFN) is secreted and assembled by various mesenchymal cells including fibroblasts and smooth muscle cells. FN plays a crucial role in development, demonstrated by the early embryonic lethality (E8.5) of the FN null mouse. Evidence from cell culture systems exists demonstrating that FN is a "master organizer and stabilizer" for the assembly of various connective tissue proteins including fibrillin-1, collagen I and III and latent TGF-β binding protein-1 (LTBP-1). While the experimental in vitro evidence supports the concept of FN as a master organizer, it is not clear whether it has a similar role in tissue organization in vivo, and what the specific contributions are of the two FN isoforms.

HYPOTHESIS: In this project we hypothesize that cellular and plasma FN play synergistic roles in tissue organization.

RESULTS: To test this hypothesis, the Cre-lox recombination technology was used to generate a smooth muscle-specific and tamoxifen-inducible cFN knockout (KO) mouse model to target blood vessels and lungs. To study the role of pFN in these organs, a liver-specific FN KO mouse model, in which pFN becomes deleted postnatally at P3 was generated. In addition, we have also produced a double KO (dKO) mouse model of cFN and pFN. In preliminary analyses of aorta and lungs from the inducible cFN KO mouse, a reduced and disorganized smooth muscle layer was observed in the bronchioles of experimental mice as compared to the controls. The aortic wall of the experimental mice was also disorganized, featuring numerous breaks and forks in the elastic lamellae. In addition, there was reduced and loose deposition of collagen in both tissues. pFN infiltration was observed in these tissues indicating that pFN can partially replace the function of cFN. In preliminary analyses, the pFN KOs did not have any obvious histological phenotypes. However, the tamoxifen injected dKO mice die postnatally between P6 – P15, indicating a severe phenotype when both FN isoforms are absent. This study indicates a synergistic effect of cFN and pFN in tissue organization of blood vessels and lungs.

CD109 as a regulator of squamous carcinoma cell migration and invasion.

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Introduction: Transforming growth factor β (TGF-β) is a multifunctional growth factor that suppresses tumor formation by inhibiting cell growth and inducing apoptosis. Paradoxically, TGF-β exerts cancer promoting effects in advanced carcinomas by inducing EMT (Epithelial to Mesenchymal Transition), which promotes tumor cell dissemination and metastasis. Thus, blocking TGF-β induced EMT represents a promising strategy for preventing cancer progression. Our group has recently reported the identification of CD109 as a TGF-β co-receptor and potent antagonist of TGF-β signaling and responses such as migration and invasion in human epithelial cells in vitro and in vivo. Moreover, it has been reported that CD109 expression is up-regulated in well-differentiated squamous cell carcinomas (SCC), as compared to normal epithelia, but becomes down-regulated in poorly differentiated carcinomas, suggesting that CD109 may play an important role during Squamous cell carcinoma progression.

Objective: To determine the role of CD109 in TGF-β induced EMT, migration and invasion in Squamous cell carcinoma.

Methods: CD109 was overexpressed or knocked down in A431 squamous carcinoma cells and were used to determine the effect of CD109 on TGF-β induced EMT, migration and invasion. For EMT, Fibronectin and Slug expression levels were assessed by western blot analysis. For migration assay, cells were plated and confluent cells were treated with or without TGF-β and scratch wound healing assay was performed. For invasion assay, Matrigel invasion chambers were used. In addition, the expression of matrix metalloprotease 2 (MMP2) was determined by qPCR.

Results: Our results show that CD109 overexpression resulted in decreased TGF-β induced EMT, migration and invasion and MMP2 expression in SCC A431 cells. Conversely, knock-down of CD109 increased TGF-β induced EMT, migration and invasion and MMP2 expression in A431 cells.

Conclusion: Taken together, our findings suggest that CD109 is an important regulator of TGF-β-induced EMT, migration and invasion in squamous carcinoma cells, and that changes in CD109 expression levels may be important event leading to cancer progression.

Smad2 is required for axolotl limb regeneration

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The skin is our largest organ with the primary role of protecting us against assaults from the outside world. Unfortunately, skin wound healing in mammal is imperfect. Amongst vertebrates, axolotls (Ambystoma mexicanum) have the unique ability to perfectly heal skin wounds (1) and regenerate many parts of their body following injury or amputation (2). Blocking TGF-β signaling with a pharmacological antagonist (SB-431542) inhibits the regeneration process, but specific functions of intracellular effectors Smad2 and Smad3 remain unknown. We hypothesised that cellular migration and proliferation is linked to activation of Smad2 via phosphorylation by TGF-β type I receptor.

We took advantage of 2 specific drugs targeting the TGF-β - Smad signaling pathway. SB-431542 targets the TGF- β type I receptor, blocking phosphorylation of both Smad2 and Smad3 while SiS3 specifically targets Smad3 (3). Treatment of amputated limbs with SB-431542 does not prevent closure of the wound but the blastema does not form. Similar treatment with SiS3 has no effect on the regeneration process. Western blotting results indicate that Smad2 and Smad3 are differentially regulated during the regenerative process. Maximal phosphorylation of Smad2 occurs within the first 48h which coincides with cellular migration, before blastema formation whereas phosphorylation of Smad3 occurs much earlier (3h post-amputation). In addition, phosphorylation of Smad2 is blocked in SB-431542 treated limbs while phosphorylation of Smad3 is reduced (50%). On the contrary, phosphorylation of Smad2 is not affected by SiS3 while phosphorylation of Smad3 is reduced by 50%, indicating that cellular migration and proliferation leading to blastema formation is linked to activation of Smad2. RT-PCR analysis also show that TGF-β target genes MMP2 and MMP9 expression is downregulated in SB-431542 treated regenerating limbs while MMP13 and MMP14 do not seem to be affected.

In conclusion, fine tuning of signaling pathways is essential for proper regeneration to take place. In the context of regeneration, TGF-β signaling via Smad2 is essential in axolotl.

1. Lévesque M, Villiard É, & Roy S (2010) Skin wound healing in axolotls: a scarless process. Journal of Experimental Zoology Part B: Molecular and Developmental Evolution 314B(8): 684-697.

2. Lévesque M, et al. (2007) Transforming Growth Factor: b Signaling Is Essential for Limb Regeneration in Axolotls. PLoS ONE 2(11): e1227.

3. Jinnin M, Ihn H, & Tamaki K (2006) Characterization of SIS3, a novel specific inhibitor of Smad3, and its effect on transforming growth factor-beta1-induced extracellular matrix expression. Mol Pharmacol 69(2): 597-607.

Early detection of structural abnormalities and cytoplasmic accumulation of TDP-43 in tissue-engineered skins derived from ALS patients

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Amyotrophic lateral sclerosis (ALS) is a fatal adult-onset disease characterized by the selective degeneration of motor neurons (MNs) in the central nervous system (CNS). Current diagnosis of ALS is based on clinical assessment of related symptoms which appear late in the disease course after degeneration of a significant number of MNs. As a result, the identification and development of disease-modifying therapies is difficult. Novel strategies for early diagnosis of ALS, to monitor disease progression and to assess response to existing and future treatments, are urgently needed.

Due to the common embryonic origin of both skin and neural tissues, many neurological disorders, including ALS, are accompanied by skin changes that often precede the apparition of neurological symptoms. We have developed a unique tissue-engineered skin model (TES) derived from symptomatic, sporadic and familial ALS patients as well as pre-symptomatic FALS patients carrying a known pathological DNA mutation. TES were generated from isolated keratinocytes and fibroblasts and analyzed using different biochemical, immunohistological and molecular methods. Our ALS-TES presents a number of striking structural and molecular features, uniquely seen in patients-derived TES, including extracellular matrix (ECM) disorganization and cytoplasmic TDP-43 inclusions, a pathological signature found in the majority of ALS cases in the affected regions of the CNS.

Consequently, our ALS-TES could represent a renewable source of human tissue to better understand the physiopathological mechanisms underlying ALS, facilitate the identification of disease biomarkers for early diagnosis and disease monitoring, as well as provide a unique tool for the development of drug screening assays.

ENDOGLIN HAPLOINSUFFICIENCY IS ASSOCIATED WITH DECREASED FIBROTIC PARAMETERS DURING BLEOMYCIN-INDUCED SKIN FIBROSIS.

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Introduction: Tissue fibrosis is characterized by an over-accumulation of extracellular matrix (ECM) components, mainly collagen and fibronectin. Transforming growth factor-beta (TGF-β) is known to promote ECM protein synthesis and its dysregulation has been implicated in skin fibrosis. Previous studies have shown that endoglin, a TGF-β co-receptor, regulates TGF-β signaling jn vitro in skin cells. However, the question as to whether endoglin is a pro-fibrotic or anti-fibrotic factor in skin fibrosis in vivo, remains unknown. The purpose of the study was to examine the role of endoglin in skin fibrosis in vivo using a bleomycin-induced mouse model of skin fibrosis.

Methods: Endoglin-heterozygous mice (HET) expressing only one allele of endoglin and their wild-type (WT) littermate mice were injected with bleomycin (to induce fibrosis) or PBS (control) every other day for 28 days (Endoglin null mice are embryonic lethal). Fibrotic skin tissues were harvested from the injection sites for histology or were snap-frozen for biochemical analysis. Dermal thickness and collagen deposition were determined using Hematoxylin and Eosin, Masson's Trichrome, and picrosirius red staining. Collagen expression was determined by Western blot analysis.

Results: Endoglin HET mice showed a marked decrease in dermal thickness and better collagen organization compared to WT mice ($p<0.005$), after bleomycin injection. In addition, trichrome and picosirius red staining data demonstrate that bleomycin-treated Endoglin HET mice exhibit increased collagen content and cross-linking, when compared to bleomycin-treated WT mice (n=6 each).

Conclusion: Our results demonstrate that endoglin haploinsufficiency leads to a reduction in dermal thickness and better collagen architecture in skin during bleomycin-induced skin fibrosis. Altogether, this suggests that endoglin plays a pro-fibrotic role in the skin. Further studies to determine whether endoglin represents a potential molecular target for therapeutic intervention in skin fibrosis are warranted.

Immunohistochemistry studies of lipoxygenases in human epidermis

Bernard Fruteau-de-Laclos, Lorraine Andrée Parent, Jadson Moreira-Pereira, Lucie Germain, Véronique J. Moulin.

Centre de recherche d'Organogénèse Expérimentale de l'Université Laval/LOEX, Centre de Recherche FRQS du Centre Hospitalier Universitaire de Québec, Faculté de Médecine, Université Laval, Québec, QC, Canada.

Lipoxygenases are oxygenases targeting unsaturated essential fatty acids, that play a pivotal role in the barrier properties of the epidermis. Presence of four different lipoxygenases has been described in the whole epidermis: Alox12, Alox12B, Alox15B and Aloxe3. The epidermal function of Alox12 and Alox15B remains unknown whereas mutations in Alox12B and Aloxe3 genes were found responsible for nonbullous congenital ichthyosiform erythroderma. According to the hypothesis prevailing since then, those 2 enzymes play a cooperative role in the formation of the linkage between the protein and lipid components of stratum corneum. Our project's aim is the localization of the 4 lipoxygenases in normal human epidermis. We hypothesized that Alox12B and Aloxe3 expression was restricted to the most mature layers of the epidermis, their mutations only inducing anomalies in these layers. Five-µm slides were obtained with a cryostat-microtome from normal skin (lipectomy or reduction mammoplasty samples). Commercial antibodies for immunohistochemistry were carefully chosen taking into account the numerous homology regions shared by the 4 epidermis lipoxygenases. The examination of several human skin samples showed expression of the 4 lipoxygenases, Alox12B and Aloxe3 included, throughout the epidermis layers. However, localization of each enzyme is specific into cells: cytoplasmic for Alox12B, membrane for Alox15B and membrane then cytoplasmic for Alox12. A nuclear labelling was found with the anti-Aloxe3 antibody, but that may be attributed to a cross reaction with nuclear proteins sharing homology regions with the Aloxe3 epitope. Those studies will be extended to reconstructed human epidermis; the ultimate goal being the creation of an in vitro model for nonbullous congenital ichthyosiform erythroderma.

Clinical trial protocol: Self-Assembled Skin Substitute for the Autologous Treatment of Severe Burn Wounds in Acute Stage of Burn Trauma

Danielle Larouche, Ph.D., Maria Margarita Becerra Perez, Inf., Louise Duranceau, M.D., FRCS (C), Isabelle Perreault M.D., FRCS (C), Amélie Dumas, M.D., FRCS (C), Patricia Bortoluzzi, M.D., FRCS (C), Louise Caouette-Laberge, M.D., FRCS (C), Lucie Germain, Ph.D., Véronique Moulin, Ph.D., François A. Auger, M.D., FRCP (C)

Burns over large surface area continue to be one of the most difficult medical problem. The standard treatment for large burns requires excision of split-thickness autograft (AG) and application to wounds. However, this practice is associated with some morbidity at the harvesting site. The LOEX self-assembled skin substitute (SASS) is produced by tissue engineering. SASS is composed of both a dermis and an epidermis, and is fully autologous. As AG, SASS can be used for the permanent closure of full-thickness skin injuries. Indeed, SASS were used to treat 15 severely burned patients under the Health Canada's special access program. The present protocol was designed to evaluate whether the graft take of SASS is equivalent to those of AG, with a non-inferiority margin of 10%. The study was plan with a one-tailed design, a statistical power of 90% and an alpha error of 5%. Thus, 17 patients suffering from deep second degree burns or third degree burns over 50% total body surface area will be recruited. At the time of surgery, a site of about 100 cm2 will be selected and divided in two parts "A and B". The type of graft (AG or SASS) for the site A or B will be randomly determined in advance to avoid bias site selection by the surgeon. SASS not used for the site A/B will be transplanted to other locations as needed. Percentage of graft take at site A vs site B, and at other SASS-treated sites will be evaluated twice during the first month. Furthermore, scars evaluation will be performed using Vancouver scar scale and Cutometer (mechanical properties), Mexameter (color) and Dermascan (thickness) devices at 3, 6, 12, 24 and 36 months post-grafting. Incidence of adverse events will be monitored during the follow up. The protocol was authorized by Health Canada and recruitment is underway.

EVENT LOCATION

Théâtre de poche

Local 2113

Pavillon M. –Pollack

Desjardins Building,

Université Laval

Quebec City, QC

Pavillon A. Desjardins 2nd floor
Conference Friday and Saturday
❶Amphitheatre Hydro Quebec
❷Grand Salon
❸ Elevators to the Cercle on 4th floor (gala dinner)

UNIVERSITÉ LAVAL
Bureau des événements campus

Nom de l'activité : SCTC

Date : Dimanche 31 mai 2015
Arrivée : 8 h 30
Début : 9 h
Fin : 13 h

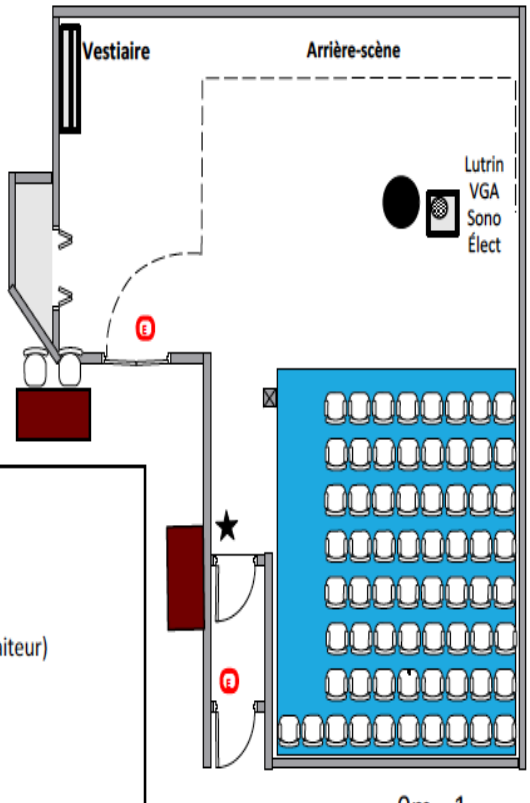
Client : Véronique Moulin

Traiteur : Sodexo

Version : IF 25/05/2015

Théâtre de poche

Local 2113 Pavillon M.-Pollack



Banque d'objets

5 chaises

Table 30"x 60"

Micro Micro

Légende

Entrée / Sortie

Rideaux

Sortie d'urgence

Dimension

Hauteur: 4 m
Largeur scène: 6,71 m
Profondeur scène: 4,27 m
Nombre de places: 65

Notes

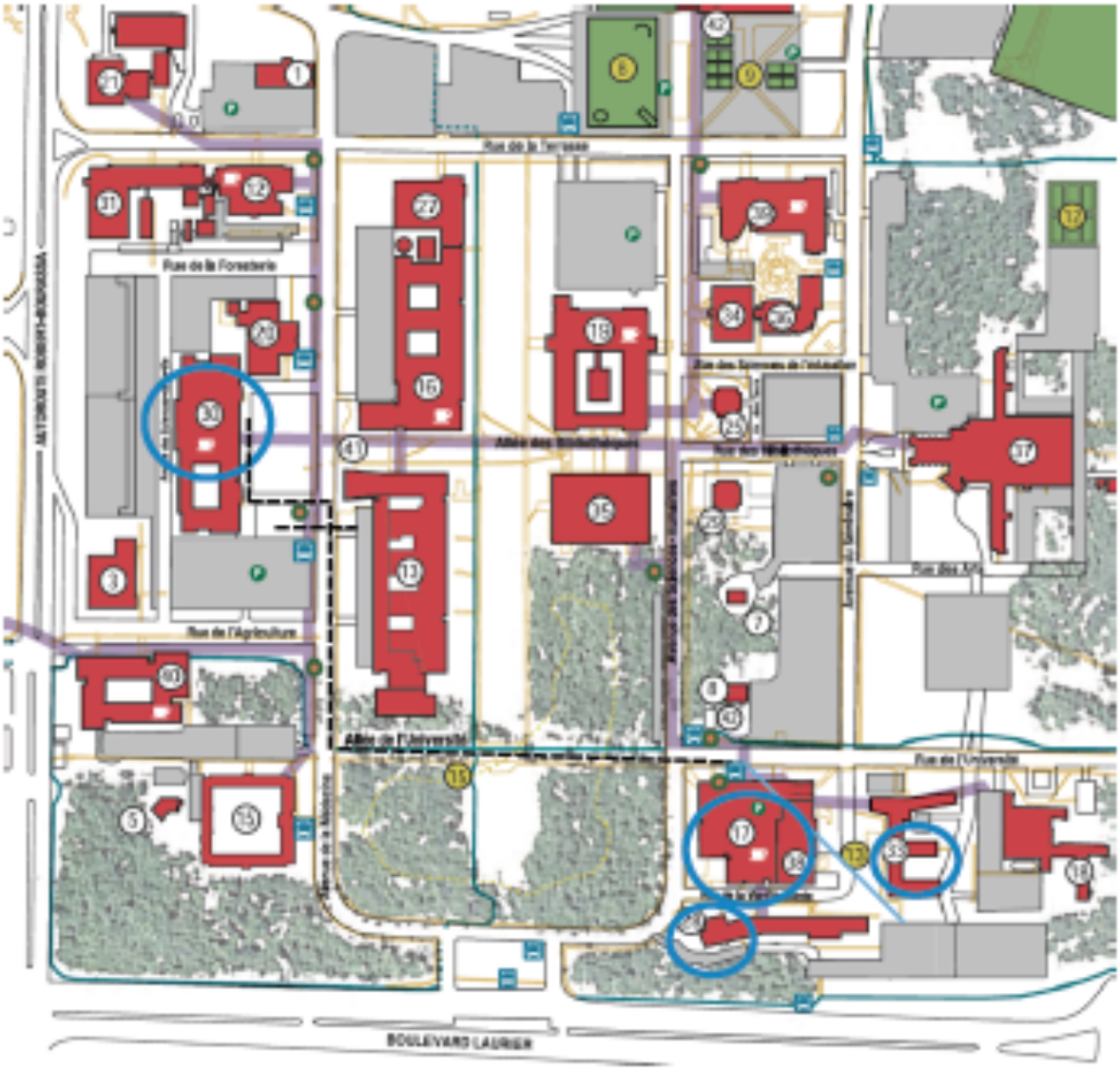
Projecteur / Écran (10 $)
Lutrin-micro
1 table stanging bar nappée
1 table traiteur (nappée par le traiteur)
1 table d'accueil nappée

Échelle

0m 1 3 5 7 9

0pi 5 10 15 20 25 30

Map of the Campus of Université Laval



17: Pavillon Alphonse-Desjardins (the bus stop RTC No 1561 is right in front of it)

30: Pavillon Ferdinand-Vandry

28, 33: Buildings of Residence at University Laval (for accommodations booked through the CCTC 2015 website)

Paid parking is available on the visitor parking lots (follow the indications) 3,75$ per hour for a daily maximum of 17,25$ (weekdays only)

Foot-path between the buildings -----

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