## University of Toronto Spine Program

# SPINEFEST2019

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# SCIENTIFIC ABSTRACTS

| Abstract # | Co-Authors | Title |
|---|---|---|
| 1 | **Allison Clement,** Cari Whyne, Margarete Akens, Phoenix Wilkie, Albert Yee, Michael Hardisty | DIFFERENTIATION BETWEEN OSTEOBLASTIC AND HEALTHY TISSUE IN METASTATICALLY INVOLVED VERTEBRAE USING RADIOMIC FEATURES |
| 2 | **A Desimone**, JM Badhiwala, MG Fehlings | THE ROLE OF APOLIPOPROTEIN E4 IN THE PATHOPHYSIOLOGY AND CLINICAL OUTCOMES OF DEGENERATIVE CERVICAL MYELOPATHY |
| 3 | **A Post**, M Khazaei, MG Fehlings | THE EFFECT OF CONDITIONAL GDNF EXPRESSION IN IPSC-NPCS USING CELL STATE-SPECIFIC PROMOTERS FOLLOWING SPINAL CORD INJURIES. |
| 4 | **Christopher S. Ahuja,** Mohamad Khazaei, Yao Yao, Nayaab Punjani, Sohanthen Udayashankar, Zijian Lou, Vjura Senthilnathan, Inaara Walji, Ali Hasan, William Luong, Alex Post, Gokce Ozdemir, Edward Robinson, Priscilla Chan, Michael G. Fehlings | QL6 PEPTIDE BIOMATERIAL TO ENHANCE HUMAN NEURAL STEM CELL THERAPY FOR TRAUMATIC SPINAL CORD INJURY |
| 5 | **Dallis Ferguson** , William Lo, Daniel Molenhuis, Lothar Lilge, Fynn Schwiegelshohn, Vaughn Betz Cari M. Whyne, Margarete K. Akens | BPD-MA MEDIATED PDT OF SPINAL BONE METASTASES: DETERMINING PDT THRESHOLD VALUES |
| 6 | **Amanda Hope**, Hikmat Sahak, Cari Whyne, Michael Hardisty, and Joel Finkelstein | SURGICAL SIMULATOR FOR SPINAL DECOMPRESSION |
| 7 | **Jonathon Chio**, Jian Wang1, Anna Badner, James Hong, Vithushan Surendran, Michael Fehlings | DRUG REPURPOSING: HIGH DOSE HUMAN IMMUNOGLOBULIN G FOR TREATMENT OF TRAUMATIC CERVICAL SPINAL CORD INJURY |
| 8 | **Jamie RF Wilson**, Jetan H Badhiwala, Fan Jiang, Jefferson R Wilson, Branko Kopjar, Alexander Vaccaro, Michael G Fehlings | THE IMPACT OF OLDER AGE ON FUNCTIONAL RECOVERY AND QUALITY OF LIFE OUTCOMES AFTER SURGICAL DECOMPRESSION FOR DEGENERATIVE CERVICAL MYELOPATHY: RESULTS FROM AN INTERNATIONAL, MULTICENTRE, PROSPECTIVE DATASET OF 757 PATIENTS. |
| 9 | **Jamie Wilson**, F Jiang, JH Badhiwala, CI Shaffrey, LY Carreon, KMC Cheung, BT Dahle, LG Lenke, MG Fehlings | THE EFFECT OF TOBACCO SMOKING ON ADVERSE EVENTS FOLLOWING ADULT COMPLEX DEFORMITY SURGERY: ANALYSIS OF 270 PATIENTS FROM THE PROSPECTIVE, MULTI-CENTER SCOLI-RISK-1 STUDY.a |

| | | |
|---|---|---|
| **10** | **Jamie Wilson**, H Joshi, F Jiang, PH Wu, J Bauer, F Mathieu, EM Massicotte. | DAY SURGERY ANTERIOR CERVICAL DISCECTOMY AND FUSION AT ONE, TWO AND THREE LEVELS IS SAFE AND EFFECTIVE IN A PUBLIC HEALTH SYSTEM; EXPERIENCE FROM 273 PATIENTS AT A SINGLE CANADIAN INSTITUTION. |
| **11** | **Ajay Matta** , M. Zia Karim DVM, MPhil, Hoda Gerami, Alyssa Goldstein, Warren Foltz Marshall Sussman, Peter Jun, Martha Funabashi, Greg Kawchuk, W Mark Erwin | A NOVEL, BIOLOGICAL THERAPEUTIC (NTG-101) FOR THE TREATMENT OF DEGENERATIVE DISC DISEASE |
| **12** | **M.M. Schneider**, L.Tetreault, J. Badhiwala, M.P Zhu, R.K. Idler, J.R. Wilson, M.G. Fehlings | INCIDENCE AND ASSOCIATED FACTORS OF NECK PAIN IN PATIENTS WITH DEGENERATIVE CERVICAL MYELOPATHY: RESULTS FROM THE MULTICENTER INTERNATIONAL PROSPECTIVE AOSPINE STUDIES |
| **13** | **Frank Lyons, Matthew Guttman, Avery Nathens, Jeremie Larouche** | NECK PAIN RESPONSE TO OPERATIVE INTERVENTION IN PATIENTS WITH DEGENERATIVE CERVICAL MYELOPATHY: RESULTS FROM THE MULTICENTER INTERNATIONAL PROSPECTIVE AOSPINE STUDIES |
| **14** | **Mohammad Zavvarian**, James Hong, Mohamad Khazaei, Jian Wang, Michael G. Fehlings. | SYSTEMIC PROTEIN KINASE INHIBITION REDUCES LOCAL INFLAMMATION AFTER CERVICAL SPINAL CORD INJURY |
| **15** | **Omar Khan**; Jetan Badhiwala; Michael Fehlings, | MACHINE LEARNING MODELS SHOW EXCELLENT PERFORMANCE IN PREDICTION OF FUNCTIONAL OUTCOMES AFTER TRAUMATIC SPINAL CORD INJURY |
| **16** | **Omar Khan**; Jetan Badhiwala; Michael Fehlings, | PREDICTION OF WORSE FUNCTIONAL OUTCOMES AFTER DECOMPRESSION SURGERY FOR DEGENERATIVE CERVICAL MYELOPATHY USING MACHINE LEARNING |
| **17** | **Omar Khan**; Jetan Badhiwala; Michael Fehlings, | TREATMENT APPROACHES FOR DEGENERATIVE LUMBAR SPONDYLOLISTHESIS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. |
| **18** | **Kalsi P**, Charalampidis A, Rampersaud R | OUTCOMES FOR MINIMALLY INVASIVE TLIF FOR LOW-GRADE LUMBAR SPONDYLOLISTHESIS: A FIVE-YEAR FOLLOW-UP STUDY |
| **19** | **Paige Smith**, Natalia Ogrodnik, Meaghan O'Reilly | LOW-INTENSITY FOCUSED ULTRASOUND AND MICROBUBBLES CAUSES INCREASED AND LOCALIZED DELIVERY OF TRASTUZUMAB INTO LEPTOMENINGEAL METASTASES SITUATED IN THE SPINAL CORD |
| **20** | **Rui Xu**, Meaghan O'Reilly. | A SPINE-SPECIFIC ULTRASOUND ARRAY FOR NON-INVASIVE SPINAL CORD THERAPY. |
| **21** | **Stecia-Marie Fletcher**, Meaghan O'Reilly | FOCUSED ULTRASOUND + MICROBUBBLE MEDIATED BLOOD-SPINAL CORD BARRIER OPENING (BSCBO) USING SHORT BURST, PHASE KEYING EXPOSURES |
| **22** | **William Luong,** Christopher S. Ahuja, Mohamad Khazaei, and Michael G. Fehlings | GENOME ENGINEERING NEURAL PRECURSOR CELLS FOR CLOSED-LOOP DELIVERY OF CHONDROITINASE ABC |

| | | |
|---|---|---|
| **23** | **Zijian Lou,** Mohamed Khazaei, Christopher S Ahuja, and Michael G Fehlings | TRIPOTENT NEUROGENIC NPCS FOR REPAIR AND REGENERATION OF THE INJURED SPINAL CORD |
| **24** | **Gokce Ozdemir**, Mohamad Khazaei, Michael G Fehlings | THE EFFECT OF SYNAPTIC ACTIVITY ON DIFFERENTIATION AND INTEGRATION OF TRANSPLANTED NEURAL PROGENITOR CELLS AND FUNCTIONAL RECOVERY AFTER SPINAL CORD INJURY |
| **25** | **Jennifer A. Dermott,** Reinhard Zeller, David E. Lebel | COMPARISON OF SURGEON VERSUS PHYSICAL THERAPIST APPLIED SPINAL CASTS FOR THE TREATMENT OF SEVERE EARLY ONSET SCOLIOSIS: RESULTS AND COMPLICATIONS |
| **26** | **Muhammad Ali Akbar**, Allan Martin, Jetan Badhiwala1, Julien Cohen-Adad, David Mikulis, Sukhvinder Kalsi-Ryan, Jefferson Wilson, Michael Fehlings | DIAGNOSTIC VALUE OF MULTIPARAMETRIC QUANTITATIVE MRI IN DEGENERATIVE CERVICAL MYELOPATHY: AN EXPLORATORY ANALYSIS USING TRADITIONAL STATISTICAL AND SUPERVISED MACHINE LEARNING METHODOLOGY |
| **27** | **Mohamad Khazaei**, Hiroaki Nakashima, Christopher S Ahuja, Priscilla Chan, Jian Wang, Balazs Varga, Andras Nagy, Michael G Fehlings | DISTINCTIVE RESPONSE OF NEUROEPITHELIAL STEM CELLS WITH CORTICAL AND SPINAL CORD IDENTITY TO THE NOTCH SIGNALING IN INJURED SPINAL CORD MICROENVIRONMENT |
| **28** | **Carlo Ammendolia**, Pierre Cote, Michael Schneider, Raja Rampersaud, Gillian Hawker | DOES DURATION OF SYMPTOMS AFFECT WALKING OUTCOMES IN PATIENTS RECEIVING NON-SURGICAL CARE FOR LUMBAR SPINAL STENOSIS? |
| **29** | **Mior SA,** Hogg-Johnson S, Ammendolia C. | THE ASSOCIATION BETWEEN PATIENT EXPECTATION AND IMPROVED WALKING DISTANCE IN PATIENTS RECEIVING NON-SURGICAL CARE FOR LUMBAR SPINAL STENOSIS |
| **30** | **Carlo Ammendolia**, Pierre Cote, Michael Schneider, Raja Rampersaud, Gillian Hawker | WHO SHOULD RECEIVE NON-OPERATIVE TREATMENT FOR LUMBAR SPINAL STENOSIS? PREDICTORS OF IMPROVED WALKING DISTANCE USING THE BOOT CAMP PROGRAMS |
| **31** | **Frank Lyons**, Matthew Guttman, Avery Nathens, Jeremie Larouche | SURGICAL MANAGEMENT OF SPINAL FRACTURES IN THE ABSENCE OF NEUROLOGICAL INJURY: DOES TIMING OF SURGERY INFLUENCE PATIENT OUTCOME? A RETROSPECTIVE COHORT STUDY FROM THE AMERICAN COLLEGE OF SURGEONS TRAUMA QUALITY IMPROVEMENT PROGRAM DATABASE. |

# ABSTRACT # 1

**TITLE:** DIFFERENTIATION BETWEEN OSTEOBLASTIC AND HEALTHY TISSUE IN METASTATICALLY INVOLVED VERTEBRAE USING RADIOMIC FEATURES

**AUTHORS AND AFFILIATIONS:** Allison Clement, Cari Whyne, Margarete Akens, Phoenix Wilkie, Albert Yee, Michael Hardisty

Sunnybrook Research Institute, Institute of Biomedical and Biomaterials Engineering, Department of Surgery, Techna Institute, Medical Biophysics, University of Toronto, Canada

**PURPOSE**: Skeletal metastasis affects bone quality, which is visualized in preclinical models as changes in trabecular bone texture on μCT imaging. This investigation aims to develop an automated method to segment spinal osteoblastic metastases in μCT images using radiomic-based features. We hypothesize that radiomics will be sensitive to changes in osteoblastic bone texture and will be useful for automating segmentation.

**METHOD**: Osteoblastic metastases were generated via intracardiac injection of human ZR-75-1 breast cancer cells into an athymic rat model (n=3). Four months post inoculation, ex-vivo μCT images (34μm) were acquired of the third lumbar vertebrae. Trabecular bone was isolated using an atlas and level-set approach. Pyradiomics was used to calculate voxel based radiomic features and osteoblastic lesion isolation was accomplished through thresholding. Segmentation accuracy was evaluated on randomly selected 2D slices (n=6). A Random Forest Classifier was used to combine multiple features. Randomly selected slices were used for training (n=6) and test data (n=3) and compared to manual segmentations via Dice Similarity Coefficients (DSC).

**RESULTS**: Features that best segmented while optimizing computational time were derived from the Neighbouring Gray Tone Difference Matrix (NGTDM). Coarseness yielded the best agreement with manual segmentations (DSC=70±7%) followed by contrast, strength and complexity (DSC=65±13%, 54±28%, and 48±26%, respectively). Combining features using machine learning improved segmentation performance, in training (DSC=99±.2%, n=6) and test data (DSC=74±14%, n=3).

**CONCLUSIONS**:: This pilot study using a radiomic-based approach demonstrates the utility of the NGTDM features combined with machine learning for segmentation of vertebral osteoblastic lesions, with potential for improvement with additional training data.

# ABSTRACT # 2

**TITLE:** THE ROLE OF APOLIPOPROTEIN E4 IN THE PATHOPHYSIOLOGY AND CLINICAL OUTCOMES OF DEGENERATIVE CERVICAL MYELOPATHY

**AUTHORS AND AFFILIATIONS:** A Desimone[1,2], JM Badhiwala[2,3], MG Fehlings[1,2,3,4]

1. Department of Genetics and Development, Krembil Research Institute, University Health Network; 2. Institute of Medical Science, University of Toronto; 3. Department of Surgery, University of Toronto; 4. Faculty of Medicine, University of Toronto

**PURPOSE**: We intend to evaluate the role of apolipoprotein E4 (ApoE4) as a prognostic biomarker of neurological outcomes in patients with degenerative cervical myelopathy (DCM). DCM is the progressive compression of the spinal cord resulting in neurological dysfunction. The standard treatment for DCM is surgical decompression, yet many patients suffer from residual disability, and 7-11% may deteriorate neurologically. ApoE4 is a candidate protein which merits closer study considering its crucial role in Alzheimer's disease and association with poorer outcomes following traumatic brain injury. It is hypothesized that ApoE4 is a marker of poor neurological outcomes following surgical decompression in DCM patients.

**METHOD**: One-hundred DCM patients undergoing surgical intervention will be prospectively enrolled. At time of DCM diagnosis, venous blood samples will be obtained and clinical outcomes assessed by the modified Japanese Orthopaedic Association (mJOA), Nurick grade, Neck Disability Index, and SF-36. Presence of the ApoE2, E3, and E4 alleles will be evaluated by single nucleotide polymorphism genotyping by allele-specific quantitative polymerase chain reaction. At 1-year post-surgery, clinical outcomes will be reassessed.

**PRELIMINARY RESULTS**: We have found ApoE4 to be associated with neurological decline following surgical decompression for DCM. Specifically, in a prospective cohort of 66 patients with DCM, 33% of patients with the ApoE4 allele deteriorated 2 points in the mJOA scale score at 1-year post-surgery, compared to 0% of patients with the ApoE3 allele. With our expanded cohort, we expect to see similar results.

**CONCLUSIONS**: This study represents an important step towards personalized medicine for DCM. Building upon exciting preliminary data that indicates ApoE4 as a potential prognostic biomarker will serve to individualize treatment strategies. This study sits on the translational front, with the potential of

integrating investigation in rodent models of DCM to complement clinical evaluation in human DCM patients.

## ABSTRACT # 3

**TITLE:** THE EFFECT OF CONDITIONAL GDNF EXPRESSION IN IPSC-NPCS USING CELL STATE-SPECIFIC PROMOTERS FOLLOWING SPINAL CORD INJURIES.

**AUTHORS AND AFFILIATIONS**: A Post1,2, M Khazaei1, and MG Fehlings1,2,3,4

Division of Genetics and Development, Krembil Research Institute1; Institute of Medical Science, University of Toronto2; Division of Neurosurgery, University of Toronto3; Faculty of Medicine, University of Toronto4.

**PURPOSE:** Recent findings from our lab show that glial-derived neurotrophic factor (GDNF) expression in neural progenitor cells (NPC) enhances differentiation to neurons; increases synapse formation; and, promotes graft survival following spinal cord transplantation. However, the ramifications of indefinite GDNF expression are unclear. To improve safety, we are genetically modifying NPCs for progenitor state-specific GDNF expression. By limiting GDNF expression to the cell stages where it is most beneficial, we hypothesize that GDNF expression under a progenitor state-specific promoter will enhance neuroregeneration and repair while mitigating deleterious effects.

**METHODS:** $GFP^{+}$hiPSC-NPCs will be genetically modified using a third-generation lentiviral system for neural progenitor-specific expression of GDNF under one of the following stem cell promoters: Nestin, Pax6, DCX, or Sox2. Upon the creation of a stable monoclonal cell line, we will perform *in vitro* characterization of GDNF expressing cells by qPCR, immunocytochemistry and whole-cell patch clamping. To validate the genetically modified $GFP^{+}$hiPSC-NPCs *in* vivo, we will perform cellular spinal transplants of cell-state specific or constitutive GDNF expressing cell lines into our labs established spinal cord injury model of RNU rats (n=8 per group). We will euthanize a rat weekly for 6 weeks to evaluate promoter strength and efficacy.

**RESULTS:** hiPSC-NPC expression of GDNF under a progenitor state-specific promoter minimizes off-target effects and reduces the tumorigenic potential of transplanted cells while enhancing their neuroregenerative capabilities.

**CONCLUSIONS:** An in-depth analysis of conditional GDNF expression under several stem cell state-specific promoters will highlight the safety and ideal level of GDNF expression in NPCs after SCI.

## ABSTRACT # 4

**TITLE:** QL6 PEPTIDE BIOMATERIAL TO ENHANCE HUMAN NEURAL STEM CELL THERAPY FOR TRAUMATIC SPINAL CORD INJURY

**AUTHORS AND AFFILIATIONS:** Christopher S. Ahuja, MD, Mohamad Khazaei, PhD, Yao Yao, Nayaab Punjani, Sohanthen Udayashankar, Zijian Lou, Vjura Senthilnathan, Inaara Walji, Ali Hasan, William Luong, Alex Post, Gokce Ozdemir, Edward Robinson, Priscilla Chan, Michael G. Fehlings, MD, PhD, FRCSC

Department of Genetics and Development, Krembil Research Institute, Toronto Western Hospital, University Health Network, Toronto, Canada, Department of Surgery, University of Toronto, Toronto, Canada, Institute of Medical Science, University of Toronto, Toronto, Canada

**PURPOSE**: Pluripotent cell-derived neural stem cell (NSC) approaches have emerged as a promising therapeutic strategy for regeneration after traumatic spinal cord injury (SCI). Unfortunately, the hostile post-injury microenvironment hinders regeneration. QL6 (Medtronic Inc.) is a novel, pH-neutral, biodegradable peptide capable of self-assembling into an extracellular matrix-like lattice *in vivo*. Early evidence suggests QL6 reduces cavity volume and supports the survival of mouse NSCs after SCI. We hypothesize that this synergistic approach can be extended to support translationally-relevant human induced pluripotent stem cell (hiPS) derived NSCs.

**METHOD**: hiPS-NSCs were passaged into a pseudo-monolayer on QL6. hNSC survival, proliferation, and neurosphere formation was extensively characterized in vitro. qPCR and an EDTA assay were used to determine mechanisms of cell adhesion. This is being further extended by RNA sequencing of hiPS-NSCs on QL6 vs geltrex control. T-cell deficient RNU rats with C6-7 clip-contusion injuries were randomized to: (1) vehicle treatment, (2) hiPS-NSCs, (3) QL6, (4) QL6+hiPS-NSCs, or (5) sham surgery (laminectomy alone). All animals received treadmill rehabilitation.

**RESULTS**: hiPS-NSCs proliferated robustly on QL6 versus geltrex control (Ki67+ 29vs6%; $p<0.01$). EDTA assay suggested that human NSC-QL6 binding is largely $Ca^{2+}$ independent. hNSCs cultured on QL6 downregulated apoptosis markers, upregulated pro-neuronal markers and select Ca-independent cell

adhesion molecules. QL6 also promoted adherent neurosphere formation, the native conformation of NSCs. Blinded analyses of rat sensorimotor data, immunohistochemistry, and RNA sequencing are ongoing.

**CONCLUSIONS**: This work provides proof-of-concept evidence that QL6 self-assembling peptide could support human NSCs when co-engrafted after SCI. This has important implications in developing translational strategies.

## ABSTRACT # 5

**TITLE:** BPD-MA MEDIATED PDT OF SPINAL BONE METASTASES: DETERMINING PDT THRESHOLD VALUES

**AUTHORS AND AFFILIATIONS:** Dallis Ferguson [1], William Lo[2,3,4], Daniel Molenhuis[5], Lothar Lilge[2,5], Fynn Schwiegelshohn[6], Vaughn Betz[6], Cari M. Whyne[1,7], Margarete K. Akens[1,5,8]

1Institute of Biomaterials and Biomedical Engineering, University of Toronto, 2Princess Margaret Hospital, University Health Network, Toronto, Canada, 3Harvard Medical School, Boston, MA 4Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA 5Department of Medical Biophysics, University of Toronto, 6Department of Electrical and Computer Engineering, University of Toronto, 7 Sunnybrook Research Institute, Toronto, 8Techna Institute, University Health Network, Toronto, Canada

**PURPOSE:** Photodynamic therapy (PDT) is an emerging treatment option for vertebral bone metastases as demonstrated in a recently completed successful Phase I clinical trial using BPD-MA as the photosensitizer. Critical to safety and treatment planning is knowledge of the spinal cord photodynamic threshold. This study aims to derive the spinal cord threshold of BPD-MA mediated PDT for a preclinical model of spinal bone metastasis using a Monte Carlo simulation and experimentally derived histological data.

**METHOD:** An osteolytic murine model was developed and a rat was treated using BPD-MA mediated PDT. At the time of necroscopy, the region surrounding the PDT treated vertebrae was harvested and stained with haematoxcyclin and eosin to quantify depth of necrosis.

The 3D simulation geometry was constructed based on a segmented murine atlas and assigned tissue optical properties. The fluence distribution was computed using FullMonte and visualized using ParaView 5.6.0. The photodynamic necrosis threshold for the spinal cord was calculated using $T=2.3\varepsilon CH(rc)$ , where ε is the molar extinction coefficient, C is the tissue concentration of the photosensitizer in the spinal cord, and H(rc) is the fluence at the radius of necrosis.

**RESULTS**: The threshold for the spinal cord was calculated to be T ~$3.5 \times 10^{18}$ photons $cm^{-3}$ for a necrosis depth of ~3.7 mm and a fluence of ~1.5 J $mm^{-2}$.

**CONCLUSIONS:** Knowledge of the photodynamic necrosis threshold for the spinal cord will minimize chances of spinal cord damage following treatment. Ongoing analysis will resolve BPD-MA mediated PDT threshold values for vertebral bone, surrounding muscle and metastatic tissue.

## ABSTRACT # 6

**TITLE:** SURGICAL SIMULATOR FOR SPINAL DECOMPRESSION

**AUTHORS AND AFFILIATIONS:** Amanda Hope[1], Hikmat Sahak[1], Cari Whyne[1,3,4], Michael Hardisty[1,4], and Joel Finkelstein[2,4]

1. Physical Sciences Platform, Sunnybrook Research Institute
2. Division of Orthopaedic Surgery, Centre for Spinal Trauma, Sunnybrook Health Sciences Centre (SHSC)
3. Institute of Biomaterials and Biomedical Engineering, University of Toronto
4. Department of Surgery, University of Toronto

**PURPOSE**: Spinal decompression surgery requires appropriate planning depending on the specific situation. Given the potential for neural complications, there exists significant barriers to residents obtaining adequate spinal decompression experience. The aim of this work was to develop a spinal decompression specific open-source 3D virtual simulator as a teaching tool to improve orthopaedic training.

**METHOD**: A spinal decompression simulator was built using 3D Slicer; an open-source software platform for medical image visualization and processing. The procedural steps include import of patient-specific CT and MR imaging, image registration, bone threshold-based segmentation, soft tissue segmentation, surgical field simulation, and simulation of laminectomy/spinal decompression. Bone and soft tissue resecting tools were developed by customizing embedded 3D segmentation tools. Laminectomy

simulation was enabled through bone and ligament resection at the site of compression. Neural element decompression was simulated by interpolation of the un-deformed anatomy around site of compression.

**RESULTS**: The completed workflow allows patient specific simulations of decompression. The surgical exposure, design of bone and ligament resecting tools, and surgical accuracy was found to adequately encompass important challenges encountered in decompression surgery. Visualization of decompression, tissue resection and positioning can be evaluated after completing the virtual procedure.

**CONCLUSIONS**: This software development project has resulted in a well-characterized accessible tool for simulating spinal surgery that a trainee can review to improve their skills. Future work will integrate and evaluate the simulator within existing orthopaedic resident competency-based curriculum and fellowship training instruction. Best practices for effectively teaching decompression in tight areas of spinal stenosis using virtual simulation will also be investigated.

## ABSTRACT # 7

**TITLE:** DRUG REPURPOSING: HIGH DOSE HUMAN IMMUNOGLOBULIN G FOR TREATMENT OF TRAUMATIC CERVICAL SPINAL CORD INJURY

**AUTHORS AND AFFILIATIONS:** Jonathon Chio[1,2], Jian Wang[1], Anna Badner[3], James Hong[1,2], Vithushan Surendran[1], Michael Fehlings[1,2,4]

1. Department of Genetics and Development, Krembil Research Institute, University Health Network; 2. Institute of Medical Science, University of Toronto, 3. Sue and Bill Gross Stem Cell Research Centre, University of California, Irvine, California, United States 4. Faculty of Medicine, University of Toronto

**PURPOSE**: After spinal cord injury (SCI), neuroinflammation exacerbates damage from the initial physical trauma. Severity of neuroinflammation depends on the integrity of the blood-spinal cord-barrier (BSCB). After SCI, a compromised BSCB enhances neuroinflammation by facilitating immune cell migration to the injured spinal cord. By targeting neuroinflammation, immunosuppressants are used to treat SCI patients. But, as selective components of neuroinflammation are beneficial after SCI, immunomodulation is more effective than general immunosuppression. We have shown that human intravenous Immunoglobulin G (hIgG), which is used in clinic to treat inflammatory disorders, is beneficial after SCI. It is hypothesized that hIgG modulates inflammation through preserving BSCB integrity.

**METHOD**: With a clinically-relevant rat model of SCI, single bolus of hIgG (0.4 or 2g/kg), methylprednisolone (immunosuppressant; 0.03g//kg) or vehicle was administered intravenously at 15 minutes, 1 hour and 4 hours post-SCI. Spinal cord, spleen, and serum were collected at 24 hours and six weeks post-SCI to evaluate hIgG's short and long-term effects.

**RESULTS**: hIgG co-localized with BSCB. At 24 hours post-SCI, relative to hIgG (0.4g/kg) and vehicle, hIgG (2g/kg) was superior in enhancing BSCB integrity. This was associated with reduced spinal cord neuroinflammation. Intriguingly, hIgG (2g/kg) increased serum levels of inflammatory cytokines and directed immune cells to the spleen; changes which were not observed in animals treated with vehicle control or methylprednisolone. Furthermore, short term benefits were maintained when administering hIgG (2g/kg) up to 4 hours post-SCI and enhanced tissue preservation and functional recovery at six weeks post-injury.

**CONCLUSIONS**: At 2g/kg, hIgG is a clinically-relevant biological molecule that reduces SCI neuroinflammation. Importantly, this is achieved without increasing the risk of immune suppression.

## ABSTRACT # 8

**TITLE:** THE IMPACT OF OLDER AGE ON FUNCTIONAL RECOVERY AND QUALITY OF LIFE OUTCOMES AFTER SURGICAL DECOMPRESSION FOR DEGENERATIVE CERVICAL MYELOPATHY: RESULTS FROM AN INTERNATIONAL, MULTICENTRE, PROSPECTIVE DATASET OF 757 PATIENTS.

**AUTHORS AND AFFILIATIONS:** Jamie RF Wilsona, Jetan H Badhiwalaa, Fan Jianga, Jefferson R Wilsonb, Branko Kopjarc, Alexander Vaccarod, Michael G Fehlingsa, on behalf of Investigators from the AO Spine North America and CSM-International Studies.

**PURPOSE**: Surgical decompression has been shown to improve long-term function, disability, and quality of life (QOL) in degenerative cervical myelopathy (DCM); however, the role of surgery, and the effect on functional and QOL outcomes, in elderly patients with DCM is controversial.

**METHOD**: Of 757 patients enrolled in the AOSpine CSM-North America and International studies, 107 were identified as elderly (≥70 years). Functional and quality of life (QOL) outcomes were assessed at 6,

12 and 24 months, with the elderly group compared to the younger adults through unadjusted univariate analyses and multiple linear regression adjusting for age-related variables.

**RESULTS**: The baseline functional assessment in the elderly group was worse compared to the younger group with mJOA (11.0 vs 12.9; $p<0.01$) and Nurick grade (3.80 vs 3.15; $p>0.01$). The change in mJOA scores were similar for both groups at all intervals, but after adjustment, the coefficient for change in the elderly group was worse. The result for Nurick grade was equivalent. With QOL outcomes, the younger cohort demonstrated greater improvement in the SF-36 physical component after surgery, yet both groups had a similar degree of improvement in the SF-36 mental component scores.

**CONCLUSIONS**: In this combined dataset from 2 large prospectively collected multi-centre studies on DCM surgery, the group aged 70 or greater demonstrated significantly worse functional and QOL recovery when compared to the younger cohort after adjusting for the effect of co-morbidites, number of operated levels, surgical approach and baseline mJOA. Elderly patients undergoing surgery for DCM should therefore be counseled appropriately regarding expectations of surgery.

## ABSTRACT # 9

**TITLE:** THE EFFECT OF TOBACCO SMOKING ON ADVERSE EVENTS FOLLOWING ADULT COMPLEX DEFORMITY SURGERY: ANALYSIS OF 270 PATIENTS FROM THE PROSPECTIVE, MULTI-CENTER SCOLI-RISK-1 STUDY.

**AUTHORS AND AFFILIATIONS:** JRF Wilson FRCS(Neurosurgery)[a], F Jiang FRCSC[a], JH Badhiwala MD[a], CI Shaffrey[b], LY Carreon[c], KMC Cheung[d], BT Dahl[e,f], LG Lenke[g], MG Fehlings PhD FRCSC[a], on behalf of the AOSpine International and SRS Scoli-RISK-1 Study Group*

a University of Toronto Spine Program, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, M5T2S8.

b Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia

c Norton Leatherman Spine Center, Louisville, Kentucky

d Department of Orthopaedics and Traumatology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

e Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

f Texas Children's Hospital and Baylor College of Medicine, Houston, Texas

g Department of Orthopedic Surgery, Columbia University, New York, New York

*The AOSpine International and SRS Scoli-RISK-1 Study Group includes Christopher P. Ames, MD; Oheneba Boachie-Adjei, MD; Mark B. Dekutoski, MD; Khaled M. Kebaish, MD; Stephen J. Lewis, MD, MSc, FRCSC; Yukihiro Matsuyama, MD, PhD; Hossein Mehdian, MD; Ferran Pellisé, MD, PhD; Yong Qiu, MD; and Frank J. Schwab, MD

**PURPOSE**: Smoking is a known predictor of medical complications after adult deformity surgery, but the effect on complications, implant failure and other AE has not been adequately described in prospective studies. Our objective was to analyze the impact of smoking on rates of postoperative adverse events (AE) in patients undergoing high-risk adult spine deformity surgery.

**METHOD**: 26 patients with a history of smoking were identified out of the 272 patients enrolled in the SCOLI-RISK-1 study who underwent complex adult spinal deformity surgery at 15 centers, with 2 year follow up. The outcomes and incidence of AE in these patients were compared to the non-smoking cohort (n=244) using univariate analysis, with additional multivariate regression to adjust for the effect of patient demographics, complexity of surgery and other confounders.

**RESULTS**: The number of levels and complexity of surgery in both cohorts were equivalent. In the univariate analysis, the rates of implant failure were almost double (n=7; 26.9%; Odds Ratio 2.28[0.75-6.18]) that observed in the non-smoking group (n=34; 13.9%; p=0.088), but this was not statistically significant. Surgery-related excessive bleeding (>4 liters) was significantly higher in the smoking group (n=5 vs n=9; 19.2% vs 3.7%; OR 6.22[1.48 – 22.75]; p=0.006). Wound infection rates and respiratory complications were similar in both groups. In the multivariate analysis, the smoking group demonstrated a higher (but non-significant) incidence of any AE over 2 years (n=13 vs n=95; 50.0% vs 38.9%; OR 2.12 [0.88-5.09]) (p=0.094).

**CONCLUSIONS**: In this sub-analysis of patients from the SCOLI-RISK-1 study, a history of smoking significantly increased the risk of excessive intra-operative bleeding and non-significantly increased the rate of implant failure or surgery-related AE over 2 years. The authors therefore advocate a smoking cessation program in patients undergoing complex adult spine deformity surgery.

## ABSTRACT # 10

**TITLE:** DAY SURGERY ANTERIOR CERVICAL DISCECTOMY AND FUSION AT ONE, TWO AND THREE LEVELS IS SAFE AND EFFECTIVE IN A PUBLIC HEALTH SYSTEM; EXPERIENCE FROM 273 PATIENTS AT A SINGLE CANADIAN INSTITUTION.

**AUTHORS AND AFFILIATIONS:** JRF Wilson[a], H Joshi[a], F Jiang[a], PH Wu[a], J Bauer, F Mathieu[a], EM Massicotte[a].

[a] University of Toronto Spine Program, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, Canada, M5T2S8.

**PURPOSE**: To compare the complication profile and outcomes of a cohort of patients undergoing day surgery Anterior Cervical Discectomy and Fusion (ACDF) for 1–3 levels, compared to patients undergoing similar procedures with a short stay admission.

**METHOD**: A retrospective review of inpatient records of single surgeon from 2005–2018 was performed at a single Canadian tertiary spine centre. Perioperative and post-operative complication rates, 30-day readmission and patient-reported outcomes (Neck Disability Index [NDI] and SF-36 scores) were compared with univariable and propensity analysis, with multivariate regression used to adjust between groups for age and number of operate levels.

**RESULTS**: 144 patients underwent ACDF with the intention to treat (ITT) as a day surgery procedure, with 129 admitted for short stay (24-hours). The day surgery cohort included 74 single, 51 two and 19 three level patients. The short stay cohort included 54 single, 45 two, 29 three level and 1 four level procedures. 6 patients (4%) with the ITT as day surgery were admitted for overnight stay or longer (range 2–21 days). Intra-operative dural tear was reported in 8 patients (5.8%) in the day surgery group (4 required admission), compared to 4 patients (3.1%) in the short stay group (odds ratio [OR] = 1.81 [0.53-6.2], p=0.5). 1 patient (0.7%) in the day surgery group suffered a permanent post-operative neurological deficit compared to 0 patients in the short stay group (p=1). 3 patients (2.1%) in the day surgery group and 2 patients (1.5%) in the short stay group required readmission within 30 days (OR = 1.36 [95%CI 0.22 – 8.3], p=1). Regression analysis showed no significant differences in the 2-month and 2-year outcomes post-ACDF between groups (p=0.796, 0.315 respectively) after accounting for total number of levels.

**CONCLUSIONS**: Day surgery 1, 2 or 3 level ACDF is safe and effective in the public healthcare setting, with rates of complications and outcome measures comparable to short stay patients.

# ABSTRACT # 11

**TITLE:** A NOVEL, BIOLOGICAL THERAPEUTIC (NTG-101) FOR THE TREATMENT OF DEGENERATIVE DISC DISEASE

**AUTHORS AND AFFILIATIONS:** Ajay Matta PhD, M. Zia Karim DVM, MSc, MPhil (Hons), Hoda Gerami BSc, Alyssa Goldstein DVM, Warren Foltz PhD, Marshall Sussman PhD, Peter Jun MSc, Martha Funabashi PhD, Greg Kawchuk DC, MSC, PhD, W Mark Erwin DC PhD

**PURPOSE**: DDD-related spinal pain is an enormously expensive malady and a major cause of disability worldwide with no effective treatment available that can promote repair. We have developed a novel biological therapeutic based upon the notochordal cell secretome (NTG-101) that includes recombinant human TGFβ1+CTGF. Here we present extensive *in vivo* evidence in two validated pre-clinical animal models of DDD and human IVD NP cells that a single injection of NTG-101 can mitigate the progression of DDD and induce a regenerative effect upon the degenerative IVD.

**METHOD**: We used image-guided needle puncture disc injury to induce DDD in two pre-clinical animal models of DDD (rat and chondrodystrophic [CD] canine) followed by a single injection of NTG-101 and assessment at the endpoint. We assayed our results using histological, immunohistochemical, genomic, protein detection, imaging (radiographs and MRI), and biomechanics assays for NTG-101 vs placebo. We assessed outcomes 10-weeks post injury in rats and 18-weeks post injury in CD canines. Assays consisted of histological and immunohistochemical scoring, expression analysis of extra-cellular matrix (ECM), inflammation, and pain associated genes / proteins using qRT-PCR, and Western blotting analysis. We also used radiographic and MRI techniques and quantitative biomechanical analyses. Additionally, we assayed the effects of this biological therapeutic upon human IVD NP cells *in vitro* using genomic evaluation of pro inflammatory and pain-related genes as well as pro-anabolic extracellular matrix genes.

**RESULTS**: Both animal models showed increased expression of inflammation and pain associated genes and proteins (Cox-2, MMP-13, IL-1β, TNFα, IL-6 and IL-8) using qRT-PCR, immunohistochemistry and Western blotting after needle puncture injury. We also observed increased PGE2 levels in injured, degenerative IVD-NPs (rats and CD canines). However, a single, intra-discal injection of NTG-101 markedly reduced the expression of Cox-2, MMP-13, IL-1β, TNFα, IL-6, and IL-8 in treated IVD-NPs. Furthermore, NTG-101 treated IVD-NPs demonstrated a robust increase in the expression of the vital

ECM proteins, (aggrecan and collagen type 2) and a marker of stemness (Oct4). Radiographic analysis demonstrated retention of normal disc height in NTG-101 treated discs in comparison to placebo injected IVDs. MRI and gross pathological analysis showed that placebo injected discs developed significant DDD whereas NTG-101 injected IVDs appeared healthy. Biomechanical analysis demonstrated that NTG-101 injected discs conferred significantly improved viscoelastic properties in flexion and lateral bending. Human NP cells treated with the biological therapeutic reduced gene expression of COX-2 and MMP-13 and upregulation of aggrecan and collagen 2.

**CONCLUSIONS**: A single injection of NTG-101 into the injured/degenerative IVD in both rat-tail and CD canine IVDs mitigates the progression of DDD and induces a regenerative effect resulting in a healthy IVD NP with near normal cellularity and healthy ECM. CTGF+TGF-β1 used in combination, downregulate pro-inflammatory and pain related genes and upregulate the expression of important extracellular matrix genes indicating that these growth factors in combination have an anti-degenerative/pro-anabolic effect upon human NP cells.

## ABSTRACT # 12

**TITLE:** INCIDENCE AND ASSOCIATED FACTORS OF NECK PAIN IN PATIENTS WITH DEGENERATIVE CERVICAL MYELOPATHY: RESULTS FROM THE MULTICENTER INTERNATIONAL PROSPECTIVE AOSPINE STUDIES

**AUTHORS AND AFFILIATIONS:** M.M. Schneider1, L.Tetreault1,2, J. Badhiwala1,4, M.P Zhu3, R.K. Idler2, J.R. Wilson3, M.G. Fehlings1,4

[1] Toronto Western Hospital, Department of Neurosurgery, Canada

[2] University College Cork, Cork, Ireland

[3] St. Michael's Hospital, Department of Neurosurgery, Canada

[4] University of Toronto, Canada

**PURPOSE**: The objectives of this study are to evaluate the incidence and severity of, and factors associated with, neck pain in patients with DCM.

**METHOD**: From 2005 to 2011, 757 patients with DCM were enrolled in either the AOSpine CSM-North America or CSM-International study at 16 global sites. All patients were extensively assessed before

surgical decompression of the cervical spine. A total of 664 patients had complete neck pain scores and were eligible for inclusion in this study. As part of the NDI questionnaire, patients were asked to rate their neck pain as none, very mild, moderate, fairly severe, very severe or the worst imaginable. Frequencies and percentages were used to summarize the incidence and severity of neck pain. The association of comorbidities, MRI features, previous treatment, gender, smoking status, and body mass index (BMI) with presence of neck pain was evaluated by univariable logistic regression to derive odds ratios and 95% confidence intervals.

**RESULTS**: One hundred thirty-eight (20.8%) patients had no neck pain, whereas 526 (79.2%) reported pain. Of these, 134 patients (20.2%) rated their pain as very mild, 185 (27.9%) as moderate, 130 (19.6%) as fairly severe, 64 (9.6%) as very severe and 13 (2.0%) as the worst imaginable. Functional status (mJOA, p=0.593), number of stenotic levels (p=0.925), age (p=0.376), and duration of symptoms (p=0.31) did not significantly differ in patients with and without pain. Female patients (OR 2.12, CI 1.38-3.26, p=0.0006), BMI $\geq$ 27kg/m$^2$ (OR 1.6, CI 1.08-2.33, p=0.017), rheumatologic (OR 4.84, CI 1.15-20.4, p=0.031) and gastrointestinal (OR 1.93, 1.04-3.57, p=0.036) comorbidities, and age < 57 years (OR 1.75, CI 1.2-2.56, p=0.0038) were associated with presence of neck pain.

**CONCLUSIONS**: Here, we demonstrate a high incidence of neck pain in patients with DCM, and elucidate a possible link between gender, body weight, comorbidity and age with neck pain. Further studies are needed to assess the effect of surgery on pain, and the impact of neck pain on quality of life in this patient population.

## ABSTRACT # 13

**TITLE:** NECK PAIN RESPONSE TO OPERATIVE INTERVENTION IN PATIENTS WITH DEGENERATIVE CERVICAL MYELOPATHY: RESULTS FROM THE MULTICENTER INTERNATIONAL PROSPECTIVE AOSPINE STUDIES

**AUTHORS AND AFFILIATIONS:** M.M. Schneider1, J. Badhiwala1,4, L.Tetreault1,2, M.P Zhu3, R.K. Idler2, J.R. Wilson3, M.G. Fehlings1,4

[1] Toronto Western Hospital, Department of Neurosurgery, Canada

[2] University College Cork, Cork, Ireland

[3] St. Michael's Hospital, Department of Neurosurgery, Canada

[4] University of Toronto, Canada

**PURPOSE**: The objectives of this study are to assess neck pain outcomes at 6, 12 and 24 months following surgery for DCM.

**METHOD**: From 2005 to 2011, 757 patients with DCM were enrolled in either the AOSpine CSM-North America or CSM-International study at 16 global sites. All patients underwent surgical decompression of the cervical spine and were assessed at 6, 12 and 24 months post-operatively. A total of 664 patients had complete pre-operative pain scores and 497 had pain outcomes at 24-month follow-up. As part of the NDI questionnaire, patients were asked to rate their neck pain as none, very mild, moderate, fairly severe, very severe or the worst imaginable. Frequencies and percentages were used to describe pain outcomes at 6, 12 and 24 months following surgery. The association of pre-operative pain severity on improvement in pain was evaluated by univariable logistic regression to derive an odds ratio and 95% confidence interval.

**RESULTS**: Compared to the pre-operative incidence of neck pain (79.2%, n=526), neck pain was less frequent at 6 months (67.1%, n=380), 12 months (60.3%, n=324), and lowest at 24 months (52.1%, n=259). Pain intensity was significantly lower 24-months after surgery (mean NDI 1.83 ±1.32; 0.96 ±1.13; $p<0.0001$). Whereas pre-operatively 130 patients (19.6%) rated their pain as fairly severe, 64 (9.6%) as very severe, and 13 (2.0%) as worst imaginable, at 24 months, only 32 (6.4%) indicated fairly severe, 14 (2.8%) very severe, and 3 patients (0.6%) worst imaginable. Patients who reported more severe neck pain pre-operatively were more likely to have experienced improvement at 24 months (OR 1.8, 95% CI:1.4 to 2.3, $p<0.0001$).

**CONCLUSIONS**: To our knowledge, this is the first multi-center, international study to demonstrating significant improvements in neck pain up to 24 months after surgical decompression for DCM. Further studies are needed that evaluate important predictors of improvement in neck pain.

## ABSTRACT # 14

**TITLE:** SYSTEMIC PROTEIN KINASE INHIBITION REDUCES LOCAL INFLAMMATION AFTER CERVICAL SPINAL CORD INJURY

**AUTHORS AND AFFILIATIONS:** Mohammad Zavvarian[1, 2], James Hong[1, 2], Mohamad Khazaei [1, 2], Jian Wang[1], Michael G. Fehlings[1, 2]

1. Division of Genetics and Development, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada
2. Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

**PURPOSE**: The disruption of blood-spinal cord barrier (BSCB) by the physical trauma is a major challenge in spinal cord injury (SCI), as it results in the infiltration of reactive immune cells that cause further secondary damage to the spinal cord. Therapeutic stabilization of BSCB can potentially attenuate the immune cells migration and improve SCI recovery. The purpose of this study is to examine the effects of systemic protein kinase inhibition on BSCB integrity, and to determine its efficacy as a treatment for SCI. It is hypothesized that midostaurin—a clinically approved protein kinase inhibitor—mitigates the secondary SCI pathogenesis by reducing immune cells migration.

**METHOD**: SCI was induced in female Wistar rats using the clip-compression injury model at C6-7. All subjects were sacrificed at 24-hours post-operation, and the total RNA and protein were extracted from the spinal cord to evaluate the molecular changes.

**RESULTS**: Administration of 25 mg/kg midostaurin reduced the phosphorylated GSK3 and STAT3 at the injury epicenter (1-day post-injury). The transcriptional analysis reveals downregulation of adhesive and migratory genes including JAM2, THY1, and ITGB1. This ultimately leads to the mitigation of pro-inflammatory markers, such as fractalkine, IL-1a, and IL-5 at 1-day post-injury.

**CONCLUSIONS**: This study demonstrates that systemic protein kinase inhibition is an effective strategy for preventing secondary SCI damage, which can have a significant impact on the enhancement of neuroprotective regime applied upon traumatic SCI.

## ABSTRACT # 15

**TITLE:** MACHINE LEARNING MODELS SHOW EXCELLENT PERFORMANCE IN PREDICTION OF FUNCTIONAL OUTCOMES AFTER TRAUMATIC SPINAL CORD INJURY

**AUTHORS AND AFFILIATIONS:** Omar Khan[1]; Jetan Badhiwala, MD[1]; Michael Fehlings, MD, PhD[1]. Affiliations: 1: Division of Neurosurgery, Department of Surgery, and University of Toronto

**PURPOSE**: Traumatic Spinal Cord Injury (SCI) has devastating physical, emotional, and economic consequences for patients, families, and society at large. Given the wide-ranging implications of SCI,

accurate determination of SCI prognosis in multiple functional areas can be enormously beneficial. Here, we developed machine learning (ML) models to predict the improvement of 1119 SCI patients across 14 domains from the functional independence measure 1-year post-injury.

**METHODS**: For each patient, 158 demographic and clinical variables (e.g. age, sex, neurological measures) were collected at initial presentation, while the 14 functional outcomes were collected 1 year after injury. ML algorithms were trained for each outcome using nested cross-validation, and their performances evaluated using out-of-fold testing data. Additionally, the ML model predicting independent bladder function was externally validated against a 1250-patient European SCI dataset.

**RESULTS**: ML models showed excellent discrimination against out-of-fold testing data, with areas under the ROC curves (AUCs) ranging from 0.90-0.93, exceeding the performance of previous regression models. Moreover, the ML model for bladder function exhibited an AUC of 0.90 on external validation. Via predictor importance estimates, our models also provided insight about which phenotypes were associated with the best outcomes. For instance, patients with higher lower extremity motor scores were more likely to walk and climb stairs independently at 1 year, while older patients were less likely to be independent across all functional domains.

**CONCLUSIONS**: Using data from only patient history and physical examination findings, we built ML models with excellent predictive power, providing clinicians a powerful framework for managing SCI.

## ABSTRACT # 16

**TITLE:** PREDICTION OF WORSE FUNCTIONAL OUTCOMES AFTER DECOMPRESSION SURGERY FOR DEGENERATIVE CERVICAL MYELOPATHY USING MACHINE LEARNING

**AUTHORS AND AFFILIATIONS:** Omar Khan[1]; Jetan Badhiwala, MD[1]; Michael Fehlings, MD, PhD[1]. Affiliations: 1: Division of Neurosurgery, Department of Surgery, University of Toronto

**PURPOSE**: Degenerative cervical myelopathy (DCM) is the most common cause of spinal cord dysfunction worldwide. Frequently, DCM patients are managed surgically to prevent functional decline. However, for reasons not fully understood, some of those patients continue to show functional decline despite surgical intervention. Here, we used machine learning (ML) algorithms to determine predictors of worsening functional status after surgery for DCM.

**METHODS**: Data from 757 patients enrolled in two, prospective international AOSpine clinical studies who underwent surgery for DCM were collected. The modified Japanese Orthopedic Association (mJOA) score, a marker of functional status, was obtained before and 1 year after surgery. For each patient, the difference between the mJOA at 1 year and at baseline was computed and dichotomized according to whether the difference was negative (worse functional status) or non-negative (same or better functional status). Multiple ML algorithms were then trained, optimized, and tested to evaluate algorithm performance and determine predictors of worse functional status at 1 year.

**RESULTS**: The highest-performing ML model, a linear support vector machine (SVM), showed good discrimination when evaluated on the testing data, with an AUC of 0.807, a sensitivity of 88%, and a specificity of 72%. Additionally, our model predicted that patients with psychiatric co-morbidities, respiratory co-morbidities, a high BMI, and a high mJOA prior to surgery were more likely to have a worse functional status after 1 year.

**CONCLUSIONS**: ML shows good performance and provides important predictions about which patients are likely to worsen after surgery, helping guide the management of DCM.

## ABSTRACT # 17

**TITLE:** TREATMENT APPROACHES FOR DEGENERATIVE LUMBAR SPONDYLOLISTHESIS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

**AUTHORS AND AFFILIATIONS:** Omar Khan[1]; Jetan Badhiwala, MD[1]; Michael Fehlings, MD, PhD[1]. Affiliations: 1: Division of Neurosurgery, Department of Surgery, University of Toronto

**PURPOSE**: Degenerative Spondylolisthesis (DS) of the lumbar spine is an age-related spine condition defined as slippage of one vertebral body relative to the adjacent vertebral body below. In addition to conservative treatment, there are several surgical options available for treating DS, involving multiple anatomical approaches. We performed a network meta-analysis of randomized controlled trials (RCTs) to determine the most effective management strategies at improving quality-of-life and functional outcomes in lumbar DS.

**METHODS**: Multiple electronic databases were searched, including OVID Medline, Embase, EBSCO, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews, for RCTs comparing treatments for lumbar DS. Our primary outcome measures included the Oswetry Disability Index (ODI) and Short-Form 36 (SF-36) scores.

**RESULTS**: From the database search, we identified 5689 articles, from which 23 RCTs were used for the network meta-analysis. Surgical treatments for DS showed significantly greater improvements in SF-36 scores and ODI ($p < 0.00001$). In addition, among articles comparing decompression alone to decompression and fusion, the complications rates, ODI scores, and SF-36 scores were not significantly different between the groups. The use of different anatomical approaches to decompression and fusion (e.g. lateral interbody fusion vs. transforaminal lumbar interbody fusion) did not result in significantly different ODI or SF-36 scores ($p > 0.05$).

**CONCLUSIONS**: Based on our analysis, surgery for DS results in marked improvement compared to conservative treatments, while there is little difference between the different surgical approaches. More RCTs are needed to determine the optimal surgical approach for DS patients.

## ABSTRACT # 18

**TITLE**: OUTCOMES FOR MINIMALLY INVASIVE TLIF FOR LOW-GRADE LUMBAR SPONDYLOLISTHESIS: A FIVE-YEAR FOLLOW-UP STUDY

**AUTHORS AND AFFILIATIONS:** Kalsi P*, Charalampidis A*, Rampersaud R**

*Spine Fellow, UHN; ** Orthopaedic Spine Staff UNH

**PURPOSE**: The majority of studies have reported short-term benefits and equivalent outcomes at 2-years of minimally invasive lumbar interbody fusion (MIS-IF) compared with open procedures. We assessed patient reported outcomes (PROs) and re-operation rates in patients having MIS-IF at 5-years follow-up.

**METHOD**: Retrospective analysis of prospectively collected data. 5-year follow-up. 174 patients had MIS-IF for low-grade lumbar spondylolisthesis, single surgeon experience. 155 patients had 1-year follow-up and 101 had 5-year follow-up. Re-operation rates and PROs including ODI, VAS Back and Leg pain were analyzed. (Pre-operative, 6 week, 3,6 month & 12 month, 2, 3 & 5 years). ANOVA and Tukey's test used for group comparisons.

**RESULTS**: Mean age 55.5 years (range 16-80). F:M 68:33. 60 degenerative and 41 isthmic types. 30% L5-S1, 33% L4-5, 3% L3-4 and 34% >1 level.

Preoperative ODI (43.9+/-1.7) and 6 weeks (33.6+/-2.6), p=0.48; ODI 3 months (25.9+/-2) & 5 years (19.4+/-1.7), p<0.0005; Leg VAS preoperative (6.3+/-0.32), 6 weeks (2.5+/-0.33), (5 years (2.5+/-0.29), p<0.0005; Back VAS preoperatively (6.4+/-0.29), 6 weeks (2.76+/-0.27), 5 years (2.7+/-0.22), p<0.0005.

At 6-weeks, 3 & 6 months, 1,2,3 and 5-years there was no statistically significant difference in Leg and Back VAS. 15 of the 101 patients had revision surgery within 5 years. 2 - removal of hardware. 3 - revision of screws (2 malposition, 1 screw fracture). 4 - revision decompression for adjacent segment disease (ASD). 4 - revision decompression and fusion for ASD. 1 patient had revision decompression and fusion for infection. 1 patient had revision surgery for deformity.

**CONCLUSIONS**: There was a significant improvement of Back and Leg VAS at 6-weeks post-operatively compared to pre-operatively and this was maintained over 5-years at all time-points. Similarly, significant improvement of ODI at 3 months was maintained at 5 years. Re-operation rates at 5-years comparable to reported data from open surgeries. MIS lumbar fusion techniques provide a durable alternative to open techniques.

## ABSTRACT # 19

**TITLE:** LOW-INTENSITY FOCUSED ULTRASOUND AND MICROBUBBLES CAUSES INCREASED AND LOCALIZED DELIVERY OF TRASTUZUMAB INTO LEPTOMENINGEAL METASTASES SITUATED IN THE SPINAL CORD.

**AUTHORS AND AFFILIATIONS:** Paige Smith*[+], Natalia Ogrodnik[+], Meaghan O'Reilly*[+] (*University of Toronto – Medical Biophysics; [+]Sunnybrook Research Institute – Physical Sciences)

**PURPOSE**: Preclinical studies have shown that focused ultrasound (FUS) can open the blood-spinal cord barrier (BSCB) in small animals, allowing otherwise impenetrable molecules to pass through. The purpose of this study was to investigate if FUS increases the delivery of Trastuzumab to leptomeningeal metastases (LM) situated in the spinal cord.

**METHOD**: Three athymic rats underwent a laminectomy at L4 and a catheter was inserted into the subarachnoid space and directed 2 cm cephalad. 10 days following surgery, HER2+ human breast cancer

cells (MDA-MB 231) suspended in Matrigel were injected via the catheter. Tumors were confirmed via contrast-enhanced T1-weighted MRI at 7T. Tumors were treated using FUS one week following. Gadolinium, Herceptin, and Definity microbubbles were injected intravenously immediately before FUS treatment (580kHz, 10ms bursts @ 1Hz for two minutes). BSCB opening was confirmed using T1-weighted MRI and Evans blue dye was injected intravenously. The rats were transcardially perfused two hours post-treatment. Tissue sections were stained with Hematoxylin and Eosin (H&E) and an anti-human IgG antibody.

**RESULTS**: Tumors were visible five days post-implantation. BSCB opening was achieved in all three rats. No sign of gross tissue damage was visible on the H&E stained slides. Slides stained with the IgG stain showed increased signal at the location of FUS delivery in both normal and tumor tissues.

**CONCLUSIONS**: Immunohistochemistry suggests that the temporary FUS-induced opening of the BSCB facilitates increased delivery of Trastuzumab into LM deposits and the spinal cord parenchyma. This illustrates the potential for non-invasive drug delivery for the treatment of spinal cord diseases.

## ABSTRACT # 20

**TITLE:** A SPINE-SPECIFIC ULTRASOUND ARRAY FOR NON-INVASIVE SPINAL CORD THERAPY.

**AUTHORS AND AFFILIATIONS:** Rui Xu, Meaghan O'Reilly.

University of Toronto, Department of Medical Biophysics. Sunnybrook Research Institute.

**PURPOSE**: To design a clinical scale, spine-specific ultrasound phased array intended to efficiently produce controlled treatment foci within the thoracic spinal cord.

**METHOD**: Numerical simulation was used model sound propagation from a target in the spinal canal, backwards through the vertebral arch to a measurement surface representing a hypothetical transducer, to identify the optimal device footprint. Using a previously validated model, ultrasound propagation at 500 kHz was simulated from virtual sources located within an *ex vivo* human thoracic vertebral canal via paralaminar and translaminar paths. The resultant mean spatial acoustic distributions on the measurement surface and a method analogous to subtractive manufacturing were used to identify optimal locations for a 256 cylindrical element (7.5mm diameter, operating at 500 kHz) array.

**RESULTS**: Backward simulation shows that sound propagation via paralaminar and translaminar paths is spatially distinct at the measurement surface, allowing for the design of a laterally-symmetric 4-component array: two components for paralaminar focusing, two for translaminar focusing. Forward simulation with the array to 300 targets spanning the thoracic spinal cord (1mm spacing) shows the mean targeting error was 1.8 ± 1.9 mm, and the mean 50% pressure contour dimensions were 10.8 ± 2.7 mm (sagittal axis), 4.2 ± 2.7 mm (frontal axis), and 5.9 ± 2.1 mm (vertical axis).

**CONCLUSIONS**: Acoustic simulation was used to design a spine-specific ultrasound array, and used to demonstrate accurate focusing to the thoracic spinal cord; an important step to the clinical translation of non-invasive focused ultrasound spinal cord treatment. Future work will include device prototyping and characterization, followed by *in vivo* testing in a porcine model.

## ABSTRACT # 21

**TITLE:** FOCUSED ULTRASOUND + MICROBUBBLE MEDIATED BLOOD-SPINAL CORD BARRIER OPENING (BSCBO) USING SHORT BURST, PHASE KEYING EXPOSURES

**AUTHORS AND AFFILIATIONS: Stecia-Marie Fletcher[1,2] and Meaghan O'Reilly[1,2]**

[1]Department of Medical Biophysics, University of Toronto. [2]Physical Sciences Platform, Sunnybrook Research Institute.

**PURPOSE**: We previously developed short burst, phase keying(SBPK) focused ultrasound(FUS) to mitigate standing waves in the human vertebral canal for FUS-mediated drug delivery. Here, we test these exposures for BSCBO in rats and correlate acoustic emissions from microbubbles (MBs) with tissue bioeffects.

**METHOD**: SBPK FUS was generated using confocal transducers ($f_0$=514kHz; aperture=5cm; focal length=6cm). A 250kHz acoustic receiver was coaligned with the focus to detect acoustic emissions. Frequency spectra of received signals were calculated using the maximum projection of short time windows and pulse inversion was leveraged to improve detection of transvertebral emissions. In rats (n=7), SBPK FUS+MBs (0.02ml/kg Definity; 10ms pulse trains; 1Hz pulse repetition frequency; 2min duration) was applied to 3 locations/spinal cord at fixed pressures (~0.27-0.47MPa *in situ*, true pressures may vary). 2.5mL/kg Evans blue dye was injected post treatment to locate BSCBO locations after tissue

harvesting. T1-weighted, contrast enhanced MRI and H&E histological staining were used to assess BSCBO and tissue damage.

**RESULTS**:

BSCBO was achieved at 19/21 locations, with mean enhancement 51±45% (15%-182%). These locations were confirmed with Evans blue dye. $f_0/2$ was detected at 12/19 BSCBO locations. At the highest pressures ($f_0/2$ present) histology showed widespread red blood cell extravasation throughout the focus. At the lowest pressures, BSCBO was achieved without RBC extravasation.

**CONCLUSIONS**: SBPK exposures successfully produced BSCBO. $2f_0$ MB emission indicated successful opening, while $f_0/2$ emission indicated widespread bleeding, consistent with existing reports using longer bursts. Future work will demonstrate *in vivo* BSCBO in an animal model of clinically relevant scale.

## ABSTRACT # 22

**TITLE:** GENOME ENGINEERING NEURAL PRECURSOR CELLS FOR CLOSED-LOOP DELIVERY OF CHONDROITINASE ABC

**AUTHORS AND AFFILIATIONS:** William Luong[1,2], Christopher S. Ahuja[1,2,3], Mohamad Khazaei[1] and Michael G. Fehlings[1,2,3]

[1]Division of Genetics and Development, Krembil Research Institute; [2]Institute of Medical Science, University of Toronto; [3]Division of Neurosurgery, Department of Surgery, University of Toronto

**PURPOSE**: Engineered neural precursor cells (NPCs) that deliver chondroitinase ABC in a closed-loop feedback system will degrade excess inhibitory CSPGs that are increased after spinal cord injury.

**METHOD**: Human induced pluripotent stem cell-derived NPCs were exposed to varying levels of CSPGs. RNA was extracted from the cells and analyzed by RNA-sequencing and qRT-PCR to find differentially expressed genes. Candidate genes will be selected based on fold-change in expression between physiological and injury levels of CSPGs. The promoter of the candidate gene will be cloned into a CRISPR/Cas9 plasmid construct with chondroitinase ABC and stably transfected into hiPS-NPCs by

electroporation. The engineered cells will be characterized for their chondroitinase ABC secretion and responsiveness to CSPG.

**RESULTS**: In qRT- PCR experiments, NPCs alter their gene expression in response to CSPG exposure. Further analysis of the RNA will narrow down candidate genes for selection of an optimal closed-loop system promoter.

**CONCLUSIONS**: These transcriptional responses will be used to design a gene circuit in NPCs for delivery of chondroitinase ABC. Ultimately, these findings further the development of combinatorial cell therapy approach to regenerate the spinal cord after chronic injury.

## ABSTRACT # 23

**TITLE:** TRIPOTENT NEUROGENIC NPCS FOR REPAIR AND REGENERATION OF THE INJURED SPINAL CORD

**AUTHORS AND AFFILIATIONS:** Zijian Lou (1,2), Mohamed Khazaei (1), Christopher S Ahuja (1,2), and Michael G Fehlings (1,2,3)

1. Division of Genetics and Development, Krembil Research Institute; 2. Institute of Medical Science, University of Toronto; 3. Division of Neurosurgery, Department of Surgery, University of Toronto.

**PURPOSE**: We are investigating the optimal ratio of neuron, oligodendrocyte, and astrocyte differentiation in transplanted tripotent neural precursor cells (NPCs) for promoting neurobehavioral recovery in SCI. In addition, we will screen for cell surface markers that target synapse formation to specific neuron subsets of the host neural network to enhance effects of NPC transplantation.

**METHOD**: Detailed *in vitro* characterization of the neurogenic neural precursor cell (nNPC) line will be done by immunostaining, qPCR, and RNA sequencing to determine their genetic identity and differentiation profile. Oligodendrocyte biased NPCs (oNPC), nNPCs, and conventional NPCs will be transplanted into RNU rats 2-week post C6-7 compression-contusion injury. The rats will undergo treadmill rehabilitation along with behaviour analysis over 12 weeks. Differentiation and viability of transplanted nNPCs will be analyzed postmortem using neuron tracing, FACS, immunohistochemistry, and patch clamp. In addition, genes involved in targeting synapse formation towards specific neuronal subgroups will be screened for.

**RESULTS**: Preliminary *in vitro* data has shown that nNPCs differentiate in an approximately 40:40:20 ratio of astrocytes, neurons, and oligodendrocytes. qPCR analysis has shown that the nNPCs over-express neuronal markers such as NEUROD1 and ASCL1 and under express astrocyte markers such as GFAP and NF1A when compared to conventional NPCs.

**CONCLUSIONS**: Optimizing the differentiation profile for NPC grafts into the injured spinal cord will allow for sufficient replacement of lost neurons, remyelination of denuded axons, and trophic support, and targeted synaptic formation will allow for an increased proportion of newly differentiated neurons to form synapses with functionally relevant neurons.

## ABSTRACT # 24

**TITLE:** THE EFFECT OF SYNAPTIC ACTIVITY ON DIFFERENTIATION AND INTEGRATION OF TRANSPLANTED NEURAL PROGENITOR CELLS AND FUNCTIONAL RECOVERY AFTER SPINAL CORD INJURY

**AUTHORS AND AFFILIATIONS:** Gokce Ozdemir[1,2], Mohamad Khazaei[1], and Michael G Fehlings[1,2,3,4]

Division of Genetics and Development, Krembil Research Institute[1]; Institute of Medical Science, University of Toronto[2]; Division of Neurosurgery, University of Toronto[3]; Faculty of Medicine, University of Toronto[4].

**PURPOSE**: Using a clinically relevant rat model of C6/C7 level spinal cord injury (SCI), the purpose of this project is investigating the role of synaptic activity on improved forelimb function observed in this model upon transplanting glial derived neurotrophic factor (GDNF)-expressing neural progenitor cells, derived from human induced pluripotent stem cells (hiPSC-NPCs), in the sub-acute phase of a clip-compression injury. We hypothesize that synaptic activity of hiPSC-NPCs is important for their differentiation, integration into local network, and functional recovery; and this effect can be interrogated by blocking neurotransmission with tetanus toxin light chain (TeTxLC).

**METHOD**: $GFP^{+}$GDNF-hiPSC-NPCs will be genetically modified using a *PiggyBac* transposon with a TetON system and a human synaptophysin 1 (hSYN1) promoter for neuron-specific expression of TeTxLC. Upon *in vitro* characterization of TeTxLC expressing cells by immunocytochemistry and whole-cell patch clamping, the *in vivo* effect of synaptic activity will be elucidated by transplanting immunodeficient Rowett Nude (RNU) rats with TetON-hSYN1::TeTxLC NPCs 2 weeks after a C6/7 SCI. During the 8 weeks after transplantation, animals will undergo neurobehavioral tests and motor evoked

potential measurements, followed by sacrifice for *ex vivo* patch clamping, immunohistochemistry, and immune-transmission electron microscopy.

**RESULTS**: It is expected that even though TeTxLC neurons will be able to project appropriately, they will fail to maintain synaptic connections, resulting in reduced number of neurons, integration, and functional recovery.

**CONCLUSIONS**: Differences in NPC-mediated repair due to inhibition of neurotransmission will highlight the role of synaptic activity on functional recovery, independent from other stem cell mediated repair mechanisms such as myelination and trophic support.

## ABSTRACT # 25

**TITLE:** COMPARISON OF SURGEON VERSUS PHYSICAL THERAPIST APPLIED SPINAL CASTS FOR THE TREATMENT OF SEVERE EARLY ONSET SCOLIOSIS: RESULTS AND COMPLICATIONS

**AUTHORS AND AFFILIATIONS:** Jennifer A. Dermott[1], Reinhard Zeller[1], David E. Lebel[1]

[1]Hospital for Sick Children

**PURPOSE**: Spinal casting is used in severe early onset scoliosis to delay the need for surgical intervention. Casts are typically applied by a spine surgeon, however, since July, 2014 spinal casting has been performed at our institution by a PT. There are no studies to date that explore the outcomes of spinal cast treatment when the cast is applied by a non-surgical health care provider.

**METHODS:** Retrospective chart and radiographic review of all 28 scoliosis patients that underwent spinal cast treatment between 2006 and 2016, and have at least 2-year follow-up. Comparative analyses were performed for the amount of correction achieved with the 1st cast, and the complication rates. Casts applied between November 2006 and July 2014 were applied by an orthopaedic surgeon whereas all casts applied after July 2014 were applied by a PT.

**RESULTS:** The spine surgeon cast 15 patients (11 female, 9 idiopathic), average age 4.36±1.6 yrs and mean Cobb angle of 62.5±11.3°. Similarly, the PT cast 14 patients (9 female, 7 idiopathic), average age of 3.7±1.6 yrs (p=0.24) and mean Cobb angle of 64.2±17.2° (p=0.74). In the initial cast the surgeon

obtained 42.4±13.3% correction and the PT 57.4±13% ($p<0.01$). The average number of casts was similar (3.7 vs. 3.3, $p=0.5$).

There were no reported complications for the surgeon group. One patient in the PT group developed SMA which resolved with cast removal. The patient had 5 subsequent casts with no further issue.

With follow-up ranging from 2.4-4.6yrs in the PT group, 1 patient has undergone surgical intervention (4.3 yrs after 1st cast). In the surgeon group, surgery was initiated 1.8-10.3 yrs after 1st cast (n=11).

**CONCLUSION:** Our results support the use of our current model of care pertaining to spinal casting and the use of a non-surgical health care practitioner to achieve comparable outcomes.

## ABSTRACT # 26

**TITLE:** DIAGNOSTIC VALUE OF MULTIPARAMETRIC QUANTITATIVE MRI IN DEGENERATIVE CERVICAL MYELOPATHY: AN EXPLORATORY ANALYSIS USING TRADITIONAL STATISTICAL AND SUPERVISED MACHINE LEARNING METHODOLOGY

**AUTHORS AND AFFILIATIONS:** Muhammad Ali Akbar[1], Allan Martin[1], Jetan Badhiwala[1], Julien Cohen-Adad[2], David Mikulis[1], Sukhvinder Kalsi-Ryan[1], Jefferson Wilson[1], Michael Fehlings[1]

[1] University of Toronto, Toronto, ON, Canada

[2] Polytechnique Montreal, Montreal, QC, Canada

**PURPOSE**: Clinical diagnosis of myelopathy can be challenging as the symptoms and signs are subjective and diagnostic uncertainty is common. Anatomical MRI showing cord compression has poor specificity. MRI techniques that provide measures of demyelination, axonal injury, and atrophy may provide enhanced accuracy for cases with diagnostic uncertainty. DCM is a progressive disease and early detection and treatment can avoid permanent disability. We describe a multiparametric quantitative MRI protocol for microstructural analysis of the spinal cord to determine the precise degree of injury to the spine in the setting of degenerative cervical myelopathy (DCM). We used the metrics derived from the multiparametric MRI of the cervical spine to develop a diagnostic tool, comparing multiple statistical and supervised machine learning approaches for classification between healthy subjects and patients DCM.

**METHOD**: 40 healthy subjects and 57 DCM patients were included in the analysis. All subjects were examined clinically followed by MRI scans in a 3T GE scanner acquiring T2-weighted (T2w) imaging, diffusion tensor imaging (DTI), magnetization transfer (MT), and T2*-weighted (T2*w) imaging covering C1-C7. Image analysis was performed on Spinal Cord Toolbox (SCT) to calculate SC cross-sectional area (CSA), fractional anisotropy (FA), MT ratio (MTR), and T2*w white to grey matter signal intensity ratio (T2*w WM/GM) in the cord and normalized for confounding variables. A multivariate logistic regression model was created and compared to univariate logistic regression for each metric. The following supervised machine learning models were also trained using 10 fold cross validation: 1) Logistic regression with regularization (LRR), 2) linear discriminant analysis (LDA), 3) principle component analysis followed by logistic regression (LR-PCA), 4) Random forests (RF) 5) Support vector machine (SVM) model and 6) Stochastic gradient boosting model (GBM). Estimates of diagnostic accuracy were reported as corrected area under receiver operating characteristic curves (AUC).

**RESULTS**: Multivariate logistic regression (AUC of 90.0%) outperformed the univariate models (AUC=67.5-87.6%). All 6 supervised ML models showed good diagnostic accuracy, with the RF (AUC=91.3%), and SVM (AUC=90.4%) models outperforming LRR (AUC=89.5%), LR-PCA (AUC=89.2%), LDA (AUC=85.7%), GBM (AUC=89.2%).

**CONCLUSIONS**: Multiparametric quantitative MRI has superior utility to individual imaging techniques with respect to diagnosis of DCM. Supervised machine learning algorithms such as support vector machines and random forests can be effectively used for analysis of spinal cord quantitative MRI data providing comparable results to traditional statistical modeling.

## ABSTRACT # 27

**TITLE:** DISTINCTIVE RESPONSE OF NEUROEPITHELIAL STEM CELLS WITH CORTICAL AND SPINAL CORD IDENTITY TO THE NOTCH SIGNALING IN INJURED SPINAL CORD MICROENVIRONMENT

**AUTHORS AND AFFILIATIONS:** Mohamad Khazaei[1], Hiroaki Nakashima[1], Christopher S Ahuja[1,2,3], Priscilla Chan[1,3], Jian Wang[1], Balazs Varga[4], Andras Nagy[4], Michael G Fehlings[1,2,3]

1-Division of Genetics and Development, Krembil Research Institute, University Health Network, Toronto, Ontario, Canada
2-Division of Neurosurgery and Spinal Program, University of Toronto, Toronto Western Hospital, Toronto, Ontario, Canada

3-Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
4-Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada

**PURPOSE**: Transplantation of tripotent neural stem/progenitor cells is a promising therapeutic strategy for traumatic spinal cord injury (SCI), however, the optimal temporal and spatial developmental stage for these cells remains to be determined. In this study, we compared the fate determination of neuroepithelial stem/progenitor cells (NECs) with an anterior cortical identity to NECs patterned to acquire a ventral spinal cord identity in the injured spinal cord microenvironment.

**METHOD**: Human-induced pluripotent stem cell (hiPSC) derived cortical NECs (cNECs) and spinal NECs (spNECs) were generated and transplanted into the T-cell deficient RNU rat models of C6-7 clip-contusion SCIs two weeks after cervical injury. Neurobehavioural assessments were performed during 12 weeks post transplantation. Histology was performed at the endpoint of 14 weeks post-injury to study the graft survival, cell differentiation, extracellular matrix changes, and graft-host connectivity (trans-synaptic tracing).

**RESULTS**: cNECs mainly differentiated into neurons, while spNECs mainly differentiated to myelinating oligodendrocytes. The unique differentiation profiles were mainly due to differential Pax6 expression between the two lines and were affected by activation of Notch signaling in the injured spinal cord microenvironment. cNECs excreted their effect in functional recovery in part through differentiation to neurons, migration towards cavity and making a cellular bridge, while spNECs implemented their effect partially through remyelination. Both lines provided trophic support for tissue preservation and regeneration.

**CONCLUSIONS**: As research continues into strategies to generate neural stem/progenitor cells with different identities, recognizing the optimal differentiation state of cells for transplantation to treat SCI is vital to clinical translation. Overall, our study demonstrates that transplantation of human cNECs and spNECs can exert positive effects through trophic support and cell replacement. Both cNECs and spNECs secret a plethora of different trophic factors.

## ABSTRACT # 28

**TITLE**: DOES DURATION OF SYMPTOMS AFFECT WALKING OUTCOMES IN PATIENTS RECEIVING NON-SURGICAL CARE FOR LUMBAR SPINAL STENOSIS?

**AUTHORS AND AFFILIATIONS:** Carlo Ammendolia, Pierre Cote, Michael Schneider, Raja Rampersaud, Gillian Hawker

**PURPOSE**: Degenerative lumbar spinal stenosis (DLSS) is a common disorder in older adults that can significantly impact walking ability. Previous studies suggest that longer duration of symptoms in DLSS is associated with poorer self-report outcomes. However, it is unknown whether duration of symptoms in DLSS affects objective walking distance. Objectives: to evaluate whether baseline duration of back or leg symptoms can predict short and long term improvements in walking distance in DLSS patients receiving non surgical care.

**METHOD**: Participants: Eligible participants were 50 years or older, symptoms of neurogenic claudication of at least 3-months, walk without assistance for 20 meters and less than 30 minutes, able to perform mild-moderate exercise, and not surgical candidate within 12 months. Design**:** Secondary analysis of data (n=104) from a randomized control trial comparing the effectiveness of two non-surgical interventions in improving walking ability in DLSS. Exposure**:** Duration of back and leg symptoms at baseline were each dichotomized to $\leq$ 12 months or > 12 months. Outcomes**:** The primary outcome, walking distance, was measured using the self-paced walk test (SPWT) at 8 weeks, and 3, 6 and 12 months. Data analysis: We used theory and empirical evidence to identify potential confounders. We first assessed the relationship of confounders to duration of back and leg symptoms. We built two separate models for duration of back and leg symptoms since these two duration variables may be correlated. General linear models were used to assess the relationship between walking distance (at each follow-up separately) and back and legs symptoms, adjusting for baseline walking distance and any covariate that altered the symptom duration coefficient by 10% or more.

**RESULTS**: Back or leg symptom duration had no statistically significant impact on objective walking distance at any follow-up period after adjusting for their baseline walking distance and confounders. There was a large but non-significant increase walking distance of 334.2 metres (95% CI (-42.9, 711.2, p =0.08) at 6 months among patients with back symptom duration of $\leq$ 12 month compared to patients with back symptoms > 12 months after adjusting for comorbid heart disease and the Oswestry Disability Index.

Limitations**:** Masking of participants and clinician not possible. SPWT was underestimated because improvement walking distance beyond 30 minutes was not captured. The small sample size is the most likely reason for the non-significant association.

**CONCLUSION:** Our results suggest that baseline back or leg symptom duration is associated with increased distance walked; but the association is not statistically significant. Future studies will assess other potential baseline factors that can impact walking distance in DLSS patients receiving non-surgical care.

## ABSTRACT # 29

**TITLE**: THE ASSOCIATION BETWEEN PATIENT EXPECTATION AND IMPROVED WALKING DISTANCE IN PATIENTS RECEIVING NON-SURGICAL CARE FOR LUMBAR SPINAL STENOSIS

**AUTHORS AND AFFILIATIONS:** Mior SA, Hogg-Johnson S, Ammendolia C.

**PURPOSE**: Degenerative lumbar spinal stenosis (DLSS) is a common disorder in older adults that can significantly impact walking ability. Patient expectations can impact surgical spine outcomes. It is unknown whether patient expectations are associated with improved outcomes in DLSS patients receiving non-surgical treatment. Objectives: To assess whether patients' baseline expectations of symptom change predict short and long-term improvement in walking ability in DLSS patients receiving non-surgical treatment.

**METHOD**: Secondary analysis of data (n=104) from a randomized control trial comparing the effectiveness of two non-surgical interventions in improving walking ability in lumbar spinal stenosis. Expectations of symptom change was measured at baseline: "Do you think that your spinal stenosis symptoms will get better soon, get better slowly, never get better, don't know, declined." The primary outcome, walking distance, was measured using the self-paced walk test (SPWT) and assessed at 8 weeks, and 3, 6 and 12 months. We used theory and empirical evidence to identify potential confounders/covariates. We first assessed the relationship of confounders/covariates to expectations. General linear models were then used to assess the relationship between walking distance (at each follow-up separately) and expectations, adjusting for baseline walking distance and any covariate that altered the expectations coefficient by 10% or more.

**RESULTS**: Our findings suggest that subjects expecting their spinal stenosis symptoms to get better soon at baseline, have six month walking distance on average 324 metres (95%CI 7.1, 640.9) more than those who don't expect to recover soon, after adjusting for their baseline walking distance, baseline SF36

Physical Function and whether they had comorbid diabetes or not. This finding was similar to that at 12 months but was not significant at 8 weeks and 3 months. Baseline walking distance and SF36 Physical Function were significant predictors of outcome at each follow-up time.

**CONCLUSION**: Our results suggest that baseline expectation is associated with increased distance walked at 6 and 12 months. Despite the chronic nature of DLSS, only self-report physical function confounded the association between expectation and distance walked. Our findings suggest clinicians should consider pre treatment expectations in their management of patients with DLSS.

## ABSTRACT # 30

**TITLE**: WHO SHOULD RECEIVE NON-OPERATIVE TREATMENT FOR LUMBAR SPINAL STENOSIS? PREDICTORS OF IMPROVED WALKING DISTANCE USING THE BOOT CAMP PROGRAMS.

Study Design: Secondary analysis of a randomized controlled trial (RCT)

**AUTHORS AND AFFILIATIONS:** Carlo Ammendolia, Pierre Cote, Michael Schneider, Raja Rampersaud, Gillian Hawker

**PURPOSE:** To determine baseline predictors of at least 30% improvement in walking distance at 12 months among participants randomized to comprehensive non-operative or self-directed Boot Camp treatment programs for lumbar spinal stenosis (LSS).

Summary of Background Data: Walking is the dominant physical impairment among older adults with LSS. Our RCT demonstrated significant short and long-term improvement in mean walking distance at the group level for both comprehensive and self-directed treatment. However, individual baseline characteristics predicting successful improvement in walking distance with non-operative treatment are unknown.

**METHODS:** Secondary analysis of a RCT comparing comprehensive (N=51) or self-directed (N=53) treatment for LSS using intention-to-treat analysis. The primary outcome was the change in walking distance from baseline using the self-paced walk test (SPWT). A 30% improvement in walking distance was deemed clinically important. Using univariate analysis all individual baseline variables with potential

interaction with improved walking distance (p<=0.2) at 12 months were entered into a multivariate model to select significant predictors of improved walking distance.

**RESULTS:** At baseline the mean maximum distance walked was 328.7 metres. At 12 months 81% of comprehensive and 59% of self- directed participants achieved at least 30%improvement in walking distance. Multivariate analysis demonstrated baseline Zurich Claudication Questionnaire Function score (Odds Ratio 3.865, 95% CI: 1.168 to 12.787, and p-value=0.0268), SF-36 Vitality score (Odds Ratio 1.036, 95% CI: 1.004 to 1.069, and p-value=0.0262), Short Physical Performance Battery Total score (Odds Ratio 1.375, 95% CI: 1.011 to 1.868, and p-value=0.0421) and baseline SPWT distance (Odds Ratio 0.998, 95% CI: 0.997 to 1.000, and p-value=0.0182) predicted at least 30% improvement in walking distance at 12 months.

**CONCLUSIONS:** LSS patients with higher baseline functional status, vitality (energy/fatigue) and physical performance as well as a lower baseline walking distance, appear more likely to achieve clinically important long-term improvement in walking distance with non-operative treatment.

## ABSTRACT # 31

**TITLE:** SURGICAL MANAGEMENT OF SPINAL FRACTURES IN THE ABSENCE OF NEUROLOGICAL INJURY: DOES TIMING OF SURGERY INFLUENCE PATIENT OUTCOME? A RETROSPECTIVE COHORT STUDY FROM THE AMERICAN COLLEGE OF SURGEONS TRAUMA QUALITY IMPROVEMENT PROGRAM DATABASE.

**AUTHORS AND AFFILIATIONS:** [1] Frank Lyons, [2] Matthew Guttman, [2,3] Avery Nathens, [4] Jeremie Larouche

[1] Spine/Trauma Clinical Fellowship, University of Toronto, Sunnybrook Health Sciences Centre

[2] Division of General Surgery, University of Toronto, Sunnybrook Health Sciences Centre

[3] Institute of Health Policy, Management, and Evaluation, University of Toronto

[4] Department of Orthopaedic Surgery, University of Toronto, Sunnybrook Health Sciences Centre

**PURPOSE**: To assess the relationship between time to spine surgical fixation and patient outcome in the setting of spinal fracture without neurological injury.

**METHOD**: This was an observational cohort study using the American College of Surgeons Trauma Quality Improvement Program (ACS TQIP) database. Patients with a diagnostic code (ICD or AIS) indicating any degree of spinal cord injury were excluded. A total of 19,310 adult patients admitted to 389 TQIP participating level I and II trauma centres from 2011-2015 with severe injury (Abbreviated Injury Scale [AIS] severity ≥3 in at least one body region) were included. Restricted cubic spline effects were used to model the time to spinal stabilisation in a generalized estimating equation model. This allowed us to assess the association between the time to surgery and outcome while adjusting for other covariates. This association was plotted and inspected for an inflection point that represents a potential threshold after which stabilisation might be associated with a higher rate of adverse events as defined by TQIP.

**RESULTS**: This study demonstrates an inflection point where the lowest rate of major complications occurs among patients who undergo spinal stabilization within the first 21 hours after presentation (regression OR 1.29 [1.14-1.45], propensity score matching RR 1.25 [1.13-1.39]).

**CONCLUSIONS**: Patients with traumatic spinal fractures without SCI in the context of multisystem injury are at high risk for in-hospital complications, which might be mitigated in part by early spinal stabilisation.

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