

**ANNUAL RESEARCH DAY PROGRAM  
DEPARTMENT OF PATHOLOGY AND LABORATORY  
MEDICINE  
UNIVERSITY OF OTTAWA**

**APRIL 23<sup>rd</sup>, 2008**

**ROOM 2021  
ROGER GUINDON HALL  
HEALTH SCIENCES BUILDING**

- 
- 9:10           **WELCOME**
- 9:15-9:30      **EPITHELIOID MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR (MPNST) ARISING IN THE INFRAORBITAL NERVE.**  
**B Purgina<sup>1</sup> MD,** DH Gravel<sup>1</sup> MD FRCPC, J. Tibbo<sup>2</sup> MD, MW Allen<sup>2</sup> MD FRCPS. Dept of <sup>2</sup>Pathology and Laboratory Medicine and <sup>2</sup>Otolaryngology, The Ottawa Hospital, Ottawa, Ontario.
- 9:30-9:45      **UTILITY FLOW CYTOMETRY IN THE DIAGNOSIS OF HEMATOLYMPHOID DISEASES: THE TOH EXPERIENCE.**  
**D. Salloum<sup>1</sup>,** D. Allan<sup>2</sup>, J. Bormanis<sup>1</sup>, <sup>1</sup>Departments of Pathology and Laboratory Medicine and <sup>2</sup>Clinical Hematology, The Ottawa Hospital, Ottawa, Canada.
- 9:45-10:00    **RENAL EPITHELIOID ANGIOMYOLIPOMA: A STUDY OF SIX CASES ON SOME MORPHOLOGIC FEATURES AIDING THE RECOGNITION OF THE ENTITY AND A META-ANALYSIS ON THE CLINICAL DATA AND PROGNOSIS.**  
**Hamidreza Faraji;** Kien T. Mai; Susan J. Robertson; Eric C. Belanger; Don Wang; E. Celia Marginean. Department of Pathology, University of Ottawa, Ottawa, Ontario, Canada
- 10:00-10:15   **HISTOPATHOGENESIS OF ENDOMETRIUM WITH ASYNCHRONOUS GLANDS IN DYSFUNCTIONAL UTERINE BLEEDING**  
KT Mai<sup>1,2</sup>, **I Teo<sup>2</sup>,** EC Marginean<sup>1,2</sup>, JP Veinot<sup>1,2</sup> and MK Senterman<sup>1,2</sup>. <sup>1</sup>Department of Laboratory Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada; <sup>2</sup>Department of Pathology and Laboratory Medicine, University of Ottawa, Ontario, Canada.

10:15-10:30 **NEUROENDOCRINE DIFFERENTIATION OF OVARIAN GRANULOSA CELL TUMOR.**

**IT Ahmed**, MD, EC Marginean MD, S Islam, M Lamba, M Senterman, MD, KT Mai, MD. Department of Pathology and Laboratory Medicine, The Ottawa Hospital, The University of Ottawa, Ottawa, Ontario K1H 8L6, Canada.

10:30-10:45 **MALE BREAST CARCINOMA AND LOBULE DEVELOPMENT IN MALES: 5 YEAR REVIEW AT TOH.**

**Marinescu, M, MD**, Ahmed IT, MD, Robertson, S.J, MD (Division of Anatomical Pathology, Laboratory Medicine, TOH, and the University of Ottawa, Ottawa, Ontario)

10:45-11:00 **BREAK**

11:00-11:15 **HISTOLOGICAL AND BIOLOGICAL COMPARISON OF CORNEAL EPITHELIUM REMOVAL BY MECHANICAL AND CHEMICAL METHODS.**

**Michel Belliveau, MD**<sup>1,2</sup>, Patrick Gooi, MD<sup>1,2</sup>, Seymour Brownstein, MD<sup>1,2</sup>, W. Bruce Jackson, MD<sup>2</sup>, George Mintsoulis, MD<sup>2</sup>, Subhadra Dravida, MSc<sup>2</sup>, Emma Dare, BSc<sup>2</sup>, Ralf Buhmann, MD PhD<sup>2</sup>, May Griffith, PhD<sup>2</sup>  
<sup>1</sup>Department of Pathology and Laboratory Medicine, University of Ottawa.  
<sup>2</sup>Department of Ophthalmology, University of Ottawa Eye Institute, and The Ottawa Hospital.

11:15-11:30 **ENTEROPATHIC T-CELL LYMPHOMA PRESENTING WITH ACUTE HEPATIC FAILURE.**

**I Teo**<sup>2</sup>, M Lamba<sup>1,2</sup>, B Nguyen<sup>1,2</sup> and BF Burns<sup>1,2</sup>.  
<sup>1</sup>Division of Anatomical Pathology, Department of Pathology and Laboratory Medicine, The Ottawa Hospital; <sup>2</sup>Department of Pathology, University of Ottawa, Ottawa, Ontario, Canada

11:30-11:45 **LOCALICATION OF D2-40 AND PODOPLANIN IN LUNG ADENOCARCINOMA AND MESOTHELIOMA: DIAGNOSTIC UTILITY IN DISCRIMINATING THESE TWO ENTITIES.**

**Itrat T Ahmed, MD**, Cyrille Bicomumpaka, MD, PhD, Mitra Nabavi, MD, Kien T. Mai, MD, Shahidul Islam, MD, PhD. Department of Pathology and Laboratory Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada.

- 11:45-12:00 **SIMULTANEOUS OCCURENCE OF UROTHELIAL CARCINOMA AND PROSTATIC ADENOCARCINOMA IN THE URINARY BLADDER**  
**Mihaela Marinescu**, MD, Hatim Q. AlMaghrabi, MD; Ali Assiri, MD, Eric C. Belanger, MD, FRCPC, Susan J. Robertson, MD, FRCPC, Kien T. Mai, MD, FRCPC  
 Division of Anatomical Pathology, Department of Pathology and Laboratory Medicine, The Ottawa Hospital and University of Ottawa, Ottawa, Ontario, Canada
- 12:00-1:15 **LUNCH AND POSTER VIEWING**  
 (ATRIUM 2<sup>ND</sup> FLOOR, FACULTY OF MEDICINE)
- 1:15-2:15 **GUEST SPEAKER**  
**Dr. Marc Ruel**  
***Update on Cardiac Cell-Based Therapy***  
 Cardiac Surgeon & Cardiac Surgery Research Chair  
 University of Ottawa Heart Institute  
 Associate Professor of Surgery, Cellular & Molecular Medicine, and Epidemiology  
 University of Ottawa
- 2:15-2:30 **CHOLESTEROL RETENTION IN ALZHEIMER'S BRAIN IS RESPONSIBLE FOR HIGH AND SECRETASE ACTIVITIES AND A PRODUCTION.**  
 Huaqi Xiong<sup>a,b</sup>, Debbie Callaghan<sup>a</sup>, Aimee Jones<sup>a</sup>, Douglas G. Walker<sup>c</sup>, Lih-Fen Lue<sup>c</sup>, Thomas G. Beach<sup>c</sup>, Lucia I. Sue<sup>c</sup>, John Woulfe<sup>b</sup>, Huaxi Xu<sup>d</sup>, Danica B. Stanimirovic<sup>a,□□,b</sup>, **Wandong Zhang**<sup>a□□,b</sup>
- 2:30-2:45 **POSSIBLE RELATIONSHIP BETWEEN MULTILOCULAR CYSTIC RCC AND CYSTIC NEPHROMA.**  
**Bibianna M Purgina, MD**, Trevor A Flood MD, Eric C Belanger MD, FRCPC, E. Celia Marginean MD, FRCPC, Kien T. Mai, MD, FRCPC  
 Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, ON, Canada
- 2:45-3:00 **RENAL LYMPHOMA MASQUERADING RENAL CELL CARCINOMA**  
**H. Faraji\***, MD; M. Lamba\*, MD, FRCPC; Bruce F. Burns\*, MD, FRCPC; Brian D.M. Blew<sup>†</sup>, MD, FRCSC.  
 \*Department of Pathology and Laboratory Medicine, University of Ottawa, and the <sup>†</sup>Department of Urology, General hospital, Ottawa, Ontario.

- 3:00-3:15     **BREAK (ATRIUM)**
- 3:15-3:30     **A RARE COMPLICATION OF CONTINUOUS  
AMBULATORY PERITONEAL DIALYSIS**  
**T.A. Flood** and J.P.Veinot. Department of Pathology and  
Laboratory Medicine, University of Ottawa, Ottawa Hospital,  
Ottawa, Ontario.
- 3:30-3:45     **CYTOPATHOLOGICAL STUDY OF UPPER URINARY  
TRACT UROTHELIAL CARCINOMA: IMMUNOSTAINING  
AS A DIAGNOSTIC AID.**  
KT Mai<sup>1,2</sup>, **I Teo**<sup>2</sup>, SJ Robertson<sup>1,2</sup>, EC Marginean<sup>1,2</sup>, S  
Islam<sup>1,2</sup>, EC Belanger<sup>1,2</sup>.  
<sup>1</sup>Division of Anatomical Pathology, Department of  
Laboratory Medicine, The Ottawa Hospital, Ottawa,  
Ontario, Canada; <sup>2</sup>Department of Pathology and  
Laboratory Medicine, University of Ottawa, Ottawa,  
Ontario, Canada
- 3:45-4:00     **PULMONARY ANGIOMYOLIPOMA (AML) IN A  
WOMAN WITH A HISTORY OF RENAL AML.**  
**BM Purgina**<sup>1</sup> MD, TA Flood<sup>1</sup> MD, KT Mai<sup>1</sup> MD FRCPC,  
DH Gravel<sup>1</sup> MD FRCPC, F Matzinger<sup>2</sup> MD FRCPC, H  
Choudary<sup>2</sup> MD FRCPC. <sup>1</sup>Dept Lab Medicine, Div  
Anatomical Pathology and <sup>2</sup>Dept Radiology, The Ottawa  
Hospital, Ottawa, ON, K1H 8M6 Canada
- 4:00           **ANNOUNCEMENT OF PRIZE WINNERS AND CONCLUSION**
- **Nadia Mickhael Award for Best Paper presented by a  
Junior Resident**
  - **2<sup>nd</sup> Best paper by a Junior Resident**
  - **Virbala Acharya Award for Best Presentation by a Senior  
Resident or Fellow**
  - **2<sup>nd</sup> Best paper by a Senior Resident or Fellow**
  - **Best Poster Presentation by a Graduate Student**
  - **Best Poster Presentation by a Resident**
  - **2<sup>nd</sup> Best Poster Presentation by a Resident**
  - **Dr. M. Orizaga Award for Best Teacher**

## POSTERS

### 1. ROLE OF THE 26S PROTEASOME IN THE ACTIVATION OF RETINOIC ACID RESPONSIVE GENES

Aliaa Higazi and Qiao Li

Department of Pathology and Laboratory Medicine, Department of Cellular and Molecular Medicine, Faculty of Medicine, Ottawa University, Ottawa, Ontario, Canada.

### 2. ROLE OF p300 HAT ACTIVITY IN SKELETAL MUSCLE DIFFERENTIATION.

Tanja Francetic and Qiao Li

Department of Pathology and Laboratory Medicine, Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada.

### 3. ROLES OF HISTONE DEACETYLASE INHIBITORS IN p300-MEDIATED CELL CYCLE REGULATION

Feras Al-Ghazawi and Qiao Li

Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada.

### 4. CONCURRENT JAK2(V617F) AND BCR/ABL TRANSLOCATION IN A PATIENT WITH MYELOPROLIFERATIVE NEOPLASM AND NEUROFIBROMATOSIS TYPE 2. A CASE FOR MULTISTEP CARCINOGENESIS.

D. Salloum, J.P. Li, M. Sabloff, D. Scarvelis, R. Padmore.

Departments of Pathology and Laboratory Medicine and Clinical Hematology, The Ottawa Hospital, Ottawa, Canada.

### 5. NEOPLASTIC SPLENIC EXTRAMEDULLARY HEMATOPOIESIS WITH POTENTIAL FOR MALIGNANT TRANSFORMATION.

D Salloum, M Lamba, M Carrier, J Bormanis, L Heubsch,

B.F.Burns. Departments of Pathology and Laboratory Medicine and Hematology, The Ottawa Hospital, Ottawa, Canada.

### 6. ONCOCYTIC PAPILLARY RCC WITH SOLID ARCHITECTURE: AN IMITATOR OF RENAL ONCOCYTOMA.

BM Purgina, MD, TA Flood MD, DM Kohler MD, EC Belanger MD, FRCPC, EC Marginean MD, FRCPC, KT Mai, MD, FRCPC. Dept Path & Lab Med, Univ of Ottawa, Ottawa, ON, CAN.

**7. COMPARISON OF PAIRED PRIMARY AND LIVER METASTATIC COLORECTAL CANCER (CRC) TISSUES FOR EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) PROTEIN EXPRESSION AND THE PRESENCE OF MUTATIONS IN THE EGFR TYROSINE KINASE DOMAIN.**

J.A. Maroun<sup>1</sup>, D.J. Jonker<sup>1</sup>, H.C. Birnboim<sup>1</sup>, T. Asmis<sup>1</sup>, T. Moyana<sup>2</sup>, E.C. Marginean<sup>2</sup>, **I. Teo<sup>2</sup>**, I. Gorn<sup>1</sup>, D. Samson<sup>1</sup>, G. Chiritescu<sup>1</sup>, H. Marginean<sup>1</sup>

<sup>1</sup> The Ottawa Hospital Regional Cancer Centre (TOHRCC),  
Ottawa, Ontario, Canada,

<sup>2</sup> Department of Anatomical Pathology, The Ottawa Hospital,  
Ottawa, Ontario, Canada.

**8. FOLLICULAR DENDRITIC CELL SARCOMA OF THE LYMPH NODE: A RARE ENTITY.**

**Cyrille Bicamumpaka<sup>1</sup>**, M. Lamba<sup>1</sup>, B. F. Burns<sup>1</sup>. <sup>1</sup>Department of Anatomical Pathology, Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada.

**9. HIGH GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA IN THE PROSTATIC CENTRAL ZONE.**

**Cyrille Bicamumpaka, MD, PhD**, Nicholas R. Delatour, MD, Eric C. Belanger, MD, Kien T. Mai, MD. Department of Pathology and Laboratory Medicine, The Ottawa Hospital, and University of Ottawa, Ontario, Canada

**10. CELL DAMAGE FOLLOWING MULTIPLE MYELOMA MANIFESTING AS ACUTE LYMPHOBLASTIC LEUKEMIA AND MYELODYSPLASTIC SYNDROME: A CASE REPORT.**

**F. Alseraye<sup>1</sup>**, J. McGowan-Jordan<sup>2</sup>, H. Atkins<sup>3</sup>, F. AlGahtani<sup>3</sup>, R.F. Padmore.<sup>1</sup>

<sup>1</sup>Division of Hematopathology and Transfusion Medicine, and

<sup>3</sup>Division of Hematology, The Ottawa Hospital, Ottawa, Ontario K1H 8L6 and <sup>2</sup>Department of Cytogenetics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, K1H 8L1.

**11. AN UNUSUAL CASE OF T-CELL PROLYMPHOCYTIC LEUKEMIA IN A PATIENT WITH RHEUMATOID ARTHRITIS**

**Dr. M. Wozniak**, Dr. M. Lamba, Dr. L. Huebsch, Dr. A. Giulivi, Department of Pathology and Laboratory Medicine, The Ottawa Hospital, Ottawa, Ontario, K1H 8L6

**12. DETECTION OF MSRA BY THE BD GENOHM ASSAY (BMA) FROM FLOCKED SWABS TRANSPORTED IN LIQUID AMIES (LA).**

David Goldfarb<sup>3</sup>, Peter Jessamine<sup>1,2</sup>, Angela Bonneau<sup>1</sup>, Karam Ramotar<sup>1,2</sup>, Marc Desjardins<sup>1,2</sup>

The Ottawa Hospital<sup>1</sup>, The Ottawa Hospital Research Institute<sup>2</sup>, Children's Hospital of Eastern Ontario<sup>3</sup>

**13. SELECTION OF HIGH LEVEL TELITHROMYCIN RESISTANCE IN ERYTHROMYCIN RESISTANT GROUP A (GAS) AND GROUP B (GBS) STREPTOCOCCUS.**

Sarah-Beth Harvey<sup>2</sup>, Karam Ramotar<sup>1,2</sup>, Marc Desjardins<sup>1,2</sup>

The Ottawa Hospital<sup>1</sup>, The Ottawa Hospital Research Institute<sup>2</sup>

**14. NEONATAL PLATELET TRANSFUSIONS USING VOLUME REDUCED PLATELETS**

Al Sughair, D. Neurath, B. Olberg, A. Giulivi, Transfusion Medicine, Department of Pathology and Laboratory Medicine, The Ottawa Hospital, Ottawa, ON Canada

**15. REGULATION OF THE FUNCTION OF TRANSCRIPTIONAL COACTIVATOR p300.**

Jihong Chen, Jonathan St-Germain, Sabina Halappanavar and Qiao Li

Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

**16. USE OF WIKI IN UNDERGRADUATE MEDICAL EDUCATION**  
**A. Jalali, M. Mioduszewski, M. Gauthier, L. Varpio**

Department of Pathology and Laboratory Medicine, Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ontario, Canada.

**17. ABC G2 UPREGULATION AND INTERACTION WITH AMYLOID PEPTIDE IN ALZHEIMER'S BRAIN WITH CEREBRAL AMYLOID ANGIOPATHY.**

D. Callaghan<sup>1</sup>, K. Jahangir<sup>2</sup>, A. Jones<sup>1</sup>, I. Rasquinha<sup>1</sup>, D. Walker<sup>3</sup>, L-F.Lue<sup>3</sup>, TG. Beach<sup>3</sup>, L. Sue<sup>3</sup>, W. Zhang<sup>1,2</sup>

<sup>1</sup>Neurobiology Program, Institute for Biological Sciences, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6.

<sup>2</sup>University of Ottawa, Ottawa, Canada. <sup>3</sup>Sun Health Research Institute, Arizona, USA.

*WELCOME*



**EPITHELIOID MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR (MPNST) ARISING IN THE INFRAORBITAL NERVE.**

**B Purgina<sup>1</sup> MD,** DH Gravel<sup>1</sup> MD FRCPC, J. Tibbo<sup>2</sup> MD, MW Allen<sup>2</sup> MD FRCPS. Dept of <sup>2</sup>Pathology and Laboratory Medicine and <sup>2</sup>Otolaryngology, The Ottawa Hospital, Ottawa, Ontario.

**BACKGROUND:** MPNSTs, an uncommon variant of sarcomas, affect the head and neck in less than 10% of cases. The epithelioid variant of MPNST accounts for less than 5% of total MPNSTs. This variant usually affects patients between the 2<sup>nd</sup> and 5<sup>th</sup> decades and has rarely been reported in the head and neck. We present a case of an epithelioid MPNST arising in the infraorbital nerve of an otherwise healthy 34 year old woman. She described a slow growing itchy nodule that arose in the dermis at the dorsal aspect of the right side of her nose. She underwent a complicated surgical excision which included excision of the infraorbital nerve to the base of the skull.

**RESULTS:**The lesion is composed of epithelioid and spindle tumour cells. The epithelioid cells, arranged in nests and cords, demonstrated significant pleomorphism, multinucleation and moderate amounts of eosinophilic and vacuolated cytoplasm. The spindle cells were located deeper to the epithelioid cells, arranged in fascicles, and had wavy nuclei with prominent nucleoli. Foci of necrosis were noted. Mitoses were up to 8 per 10 high power fields and some were atypical. The tumour almost entirely replaces the nerve and demonstrates a plexiform growth pattern. A small amount of residual normal compressed neural tissue was seen in one section located at the periphery immediately below the EMA positive perineural capsule. The tumour was positive for S100, vimentin and GFAP (focally), and was negative for HMB45 and CK.

**DISCUSSION:** A diagnosis of epithelioid malignant peripheral nerve sheath tumour (MPNST) was rendered based on histological features combined with the immunohistochemical profile of the tumour. In order to make the diagnosis of MPNST, one must demonstrate an origin from nerve or nerve sheath or find a focus of conventional malignant schwannoma.

## UTILITY FLOW CYTOMETRY IN THE DIAGNOSIS OF HEMATOLYMPHOID DISEASES: THE TOH EXPERIENCE.

**D. Salloum<sup>1</sup>, D. Allan<sup>2</sup>, J. Bormanis<sup>1</sup>,** <sup>1</sup>Departments of Pathology and Laboratory Medicine and <sup>2</sup>Clinical Hematology, The Ottawa Hospital, Ottawa, Canada.

**Background:** Additional ancillary tests are often requested on blood, marrow, lymph node and fluid samples for diagnostic characterization of hematolymphoid disorders. These tests include flow cytometric immunophenotyping (FC), molecular genetics and cytogenetic techniques. Although FC has emerged as the standard of practice in the diagnosis of disorders such as lymphoma and leukemia, specific limitations can result in reduced sensitivity or specificity that affect its overall utility as a diagnostic tool. We performed a utility analysis of FC during a three month period on all cases performed at our institution to gain a current perspective on the operational characteristics of this important diagnostic modality.

**Methods:** All cases where FC was requested on blood, marrow, lymphoid tissue and other fluids were included during the period of July-September 2007. Samples were classified as “positive” if such and such, “normal” as such and such and “non-diagnostic” for all others. Cases that were cancelled were noted and if an inadequate specimen was received, these were classified separately.

**Results:** A total of 273 cases were performed. A total of 152 FC studies were informative with 113 “positive” cases (41%) and 39 “normal” cases. A total of 61 cases were “non diagnostic” and 39 “cancelled” and in 18 cases “inadequate specimen” was received. The diagnostic yield was highest for peripheral blood studies (76% informative) followed by lymph node (47% informative), bone marrow (43% informative) and tissue (41% informative). The proportion of marrow (BM) cases that were normal (18%) or non-diagnostic (30%) was high in comparison with other sample types.

**Conclusion:** FC offered an informative diagnosis in a large proportion of cases and was useful in terms of diagnosis for peripheral blood samples. Flow cytometry offers informative diagnostic information compared to other diagnostic modes, is readily available (low cancellation rate), and has a rapid turn around time. Also, FC can focus on subpopulations without prior purification and has modest requirements in terms of laboratory facilities and equipment. The high rate of “normal” and “non-diagnostic” bone marrow cases was unexpected as the morphology of these cases are reviewed by a hematopathologist prior FC. Our data provides a baseline for future analysis of pre-test-probability in cases sent for FC which may assist in further refinement of its overall clinical utility.

**RENAL EPITHELIROID ANGIOMYOLIPOMA: A STUDY OF SIX CASES ON SOME MORPHOLOGIC FEATURES AIDING THE RECOGNITION OF THE ENTITY AND A META-ANALYSIS ON THE CLINICAL DATA AND PROGNOSIS.**

**Hamidreza Faraji:** Kien T. Mai; Susan J. Robertson; Eric C. Belanger; Don Wang; E.Celia Marginean. Department of Pathology, University of Ottawa, Ottawa, Ontario, Canada

**Background:** Renal epithelioid angiomyolipoma (EAML) are uncommon and are only reported in case reports or in multi-institutional small series. **Materials and Methods:** We report cases of EAML seen at our institution and perform a meta-analysis using cases retrieved from PubMed. **Results:** There were a total of 6 cases out of 650 renal cell carcinoma (RCC) and oncocytoma from our institution and 62 cases from a literature review. In the 6 cases, there were areas resembling high grade RCC (2 cases), clear cell RCC (1 case), sarcomatoid RCC (1 case) chromophil RCC (1 case), invasive urothelial carcinoma of the renal pelvis (1 case) and renal oncocytoma (2 cases). The tumors cells displayed positive reactivity for melanocytic markers, CD68, CD117 and estrogen/progesterone receptors. In the absence of areas of typical AML, features of EAML aiding in the differential diagnosis with epithelial renal neoplasms are: extreme degree of cytologic atypia, histiocytoid appearance, and presence of melanocytic pigment, solid architecture with the absence of frequent areas of alveolar pattern, papillary or tubular formation and scars. For a total of 67 cases from the meta-analysis and the cases at our institution, the patient ages ranged from 11 to 76 (mean:  $43\pm 17$ ), and the female: male ratio was 3:1. The tumors measured from 1cm to 15 cm. EAML was associated with tuberous sclerosis in 10 out of 60 cases (16%). Follow up ranging from 9 to 84 months (mean  $43\pm 27$ ) showed lymph node involvement in 7 cases (10%), distant metastasis in 11 cases (16%), and both in 2 cases. Venous invasion and local recurrence occurred in additional 2 and 3 cases respectively. **Conclusions:** Renal neoplasms with atypical features of renal epithelial neoplasms should be investigated with immunostaining to rule out the EAML. The tumors were associated with less frequent distant metastasis and patient death than RCC.

## HISTOPATHOGENESIS OF ENDOMETRIUM WITH ASYNCHRONOUS GLANDS IN DYSFUNCTIONAL UTERINE BLEEDING

KT Mai<sup>1,2</sup>, **I Teo**<sup>2</sup>, EC Marginean<sup>1,2</sup>, JP Veinot<sup>1,2</sup> and MK Senterman<sup>1,2</sup>.

<sup>1</sup>Department of Laboratory Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada; <sup>2</sup>Department of Pathology and Laboratory Medicine, University of Ottawa, Ontario, Canada.

**Aims:** In dysfunctional uterine bleeding (DUB), the origin of endometria containing asynchronous glands, i.e., both secretory and proliferative glands, is not well understood. This pattern of endometrial changes is thought to be related to a persistent corpus luteum. It is also thought that endometrial stromal cells (ESC) strongly influence endometrial glands through stromal-epithelial interactions. Prior work at our institution showed that ESC in the functionalis layer of normal secretory endometria is strongly reactive for calretinin and negative for CD34; ESC in the basalis is reactive for CD34. In this study, we compared the calretinin and CD34 profiles in the ESC of endometria with asynchronous glands with that of normal endometria.

**Materials and Methods:** Fifty consecutive endometrial specimens with secretory activity from women with DUB were obtained from the files at our institution and immunohistochemical stains for calretinin and CD34 were performed.

**Results:** Four specimens contained both secretory and proliferative glands with mitoses. Thirty specimens contained secretory and weakly proliferative glands. Sixteen specimens showed the normal immunostaining pattern. The ESC surrounding asynchronous glands often revealed altered staining patterns for calretinin and CD34, but the staining pattern was not predictable, showing any combination of calretinin and CD34 positivity.

**Conclusions:** The continued presence of proliferative-type endometrial glands in the secretory phase may represent delayed or absent conversion from a proliferative to a secretory phenotype under the influence of altered ESC.

## NEURO ENDOCRINE DIFFERENTIATION OF OVARIAN GRANULOSA CELL TUMOR

**IT Ahmed**<sup>1</sup>, EC Marginean<sup>1</sup>, S Islam<sup>1</sup>, M Senterman<sup>1</sup> and KT Mai<sup>1</sup>.

<sup>1</sup>Division of Anatomical Pathology, Department of Laboratory Medicine, Ottawa Hospital and the Department of Pathology and Laboratory Medicine, The University of Ottawa, Ottawa, Ontario, Canada.

**Background:** Emerging data indicates that testicular Leydig cells may be a new member of the diffuse neuroendocrine (NE) system. It has been hypothesized that testicular carcinoid tumor (TCT) represents a neoplasm arising from the testicular Leydig cells. In this study, we investigate the possible NE differentiation of ovarian granulosa cell tumor (OGT) and its possible association with the ovarian carcinoid tumor (OCT).

**Design:** Twenty-four cases of OGT, 2 cases of primary OCT and 10 cases of OCT associated with teratoma (OT) or struma ovarii (SO) and 2 cases representing metastatic OCT from small intestine were retrieved from the Anatomical Pathology files in our institution. Representative sections were submitted for immunostaining for cytokeratin AE1/3, calretinin, inhibin, NSE, synaptophysin, nestin and various neuropeptide hormones.

**Result:** Five out of 24 (20.8%) OGT displayed focal NE differentiation with reactivity for cytokeratin AE1/3 (moderate to strong) and NE markers including neuropeptides. The two primary OCTs, in addition to NE markers showed strong reactivity for calretinin and inhibin in the stromal cells within the interstitial tissue, between the nests of NE tumor cells. For the other OCTs (associated with OT and SO and the metastatic), the inhibin or calretinin reactivity was undetectable.

**Conclusion:** A subset of OGTs expressing reactivity for cytokeratin was often associated with NE differentiation. It is likely that some primary OCT originate from granulosa cells having the potential of NE differentiation.

## MALE BREAST CARCINOMA AND LOBULE DEVELOPMENT IN MALES: 5 YEAR REVIEW AT TOH.

**Marinescu, M, MD**, Ahmed IT, MD, Robertson, S.J, MD (Division of Anatomical Pathology, Laboratory Medicine, TOH, and the University of Ottawa, Ottawa, Ontario)

**Background:** Breast carcinoma in men is rare, with < 1% of breast cancers are found in men<sup>1,5</sup>. Only one large study<sup>3</sup> gives a closer estimate with .009%. Lobular carcinoma of breast in men is even rarer with lobular cancers reported mostly as single case reports. There are a few recent larger series in which pure lobular carcinoma ranges from 0.39% to 3.6%<sup>1,2,3,7</sup>. However, none of the series confirmed this by IHC. It has been stated that lobular carcinoma is rare in men because of the absence of terminal lobules in male breast<sup>1,2,3</sup>. Tavasoli<sup>2</sup> found lobules adjacent to 2/3 male lobular carcinomas but did not report the presence of lobules adjacent to male ductal cancer. There is also no recent data on the presence of lobules in normal adult male breast or in adult male breast from cases of clinical gynecomastia. Thus, the frequency of lobules in male breast is of interest. These questions were addressed in a five year review of male breast surgery specimens.

**Method:** A computer search between January 2003 and February 2008 was done with all cases of male breast cancer and clinical gynecomastia reviewed. Cases were confirmed to be from males and cases with no breast parenchyma were excluded. The presence of lobules was documented microscopically in non-neoplastic breast parenchyma. Also age, sub-type of cancer, stage, grade, and receptor status was recorded. Using a lobular score (0=none, 1= poorly defined, 2= well developed), mean scores in the non-malignant and carcinoma groups were calculated.

**Results:** Of 4853 breast cancers, 16 were from males (.003%). The mean age of 68 ± 12.9 is similar to the literature (61, range 9-94)<sup>1,2,4</sup>. 35% were T1 tumours and 69% were N0, reflecting the Canadian literature on male breast cancer<sup>1</sup> (37% T1, 43% N0). 28.5% were high grade which is close to 33% reported<sup>7</sup>. In our series 2 of the 16 (12.5%) were lobular carcinoma as defined by histology and IHC. Where available, uninvolved adjacent breast showed lobules in 3/12; only one of which was a lobular carcinoma.

Our review of 106 non-malignant breast cases showed 9 without breast parenchyma. In the remaining 97 cases (mean age=36.5 ± 17.8), microscopic review showed 48.5% no lobules, 39.2% poorly defined lobules and 12.4% well developed lobules. There was a significant difference in mean lobular score in the non-malignant and malignant cases (0.64 versus 0.25, t = 2.62, p=.02).

**Conclusion:** Our results for breast carcinoma are similar to those seen in the literature, except for the much higher % of lobular carcinoma; likely explained by the small sample size. In our study the development of lobules was not restricted to the cases with lobular carcinoma and, unexpectedly, the % of lobular formation in non-neoplastic male breast tissue was not rare (well developed lobules in 12.4%). Although this was not a study of normal male breast, unless gynecomastia is itself pre-malignant, this increase of lobules in non-malignant breast does not support the presence of lobules as a risk factor for any type of cancer (let alone lobular carcinoma). The high % of lobule formation in non-malignant breast also does not support the contention that lobular carcinoma is rare in men because of lack of lobular development. Further study is necessary with respect to presence of lobules in truly normal male breast in order to

asses this and to further assess the relationship of altered hormonal milieu and lobule development.

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*BREAK*



## HISTOLOGICAL AND BIOLOGICAL COMPARISON OF CRONEAL EPITHELIUM REMOVAL BY MECHANICAL AND CHEMICAL METHODS

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**Purpose:** Epi-photorefractive keratectomy (Epi-PRK) and alcohol-assisted photorefractive keratectomy (AA-PRK) are forms of excimer laser vision correction in which the corneal epithelium is removed prior to treatment. In AA-PRK, alcohol is used to loosen the epithelium, while in Epi-PRK it is lifted mechanically with an epithelial delaminator. In patients undergoing phototherapeutic keratectomy for recurrent erosion syndrome (PTK-RES), the epithelium is removed mechanically using a microhoe. The cleavage plane of these methods has not been well established and this information may have implications related to clinical outcomes, including post-operative pain and visual recovery. This study characterized the epithelial cleavage plane of these methods using light microscopy. We also investigated the viability and proliferative ability of the corneal epithelium basal cell layer after removal.

**Methods:** Prospective case series on subjects whose corneal epithelium was removed using an epithelial delaminator (n=10), application of 20% alcohol for 20 seconds (n=10), or a microhoe (n=10). Histological studies with PAS were used to characterize the proportion of cleavage at six levels for each epithelial flap. The mean proportion of cleavage at each level was then calculated for each of the three study groups. Basal epithelial cell proliferation was measured by staining with MIB-1 (immunohistochemistry) and PCNA (immunofluorescence) antibodies. Viability testing was performed using SYTO 10 & EthD-2 stains (immunofluorescence). Corneas with no evidence of epithelial disease (n=5), obtained through routine corneal transplant surgery, were used as a control for proliferation and viability testing. The proportion of proliferating/viable cells was determined for each specimen and the mean calculated for each of the four groups.

**Results:** The mean proportion of cleavage at the level of the basement membrane was 39% in Epi-PRK, 5% in AA-PRK, and 65% in PTK-RES cases. The mean proportion of basal cells showing positivity for MIB-1 and PCNA, respectively, was 1.8% and 11.9% in Epi-PRK, 3.2% and 6.3% in AA-PRK, 4.9% and 3.1% in RES cases, and 5.0% and 5.3% in control corneas. In Epi-PRK, PTK-RES, and controls, more than 98% of the basal cells were viable. In AA-PRK, 80% were viable.

**Conclusions:** Our results indicate that the mechanical methods of corneal epithelial removal (Epi-PRK and PTK-RES) have a higher proportion of cleavage at the basement membrane compared to the chemical method (AA-PRK). There is reduced viability of the basal epithelial cells following removal with alcohol. These findings suggest that if the epithelium is to be repositioned onto the corneal surface following treatment with the excimer laser, initial mechanical removal may be superior.

## **ENTEROPATHIC T-CELL LYMPHOMA PRESENTING WITH ACUTE HEPATIC FAILURE.**

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**Introduction:** Enteropathic T-cell lymphoma (ETCL) is a very rare T-cell lymphoma, accounting for less than 5% of gastrointestinal tract lymphomas. ETCL is an aggressive lymphoma, and is frequently associated with celiac disease. While it typically affects the small bowel, ETCL may affect the stomach and colon; additionally, it may spread to liver, spleen, brain, heart and bone marrow. Some research suggests that ETCL derive from activated cytotoxic intraepithelial lymphocytes, which are CD56 and CD8 positive.

**Design:** We describe a case of ETCL presenting with liver failure and diarrhea, without a history of celiac disease. Clinical and pathologic findings are illustrated.

**Results:** Endoscopy revealed multiple aphthous ulcers in the bowel, esophagitis and diffuse gastritis. Liver biopsy revealed extensive sinusoidal infiltration by atypical lymphocytes. Multiple biopsies showed a marked lymphoid infiltrate within the surface epithelium of stomach, small bowel and colon. The biopsies did not show evidence of celiac disease. These lymphoid infiltrates were positive for CD3, CD8, and CD56. Polymerase chain reaction on both liver and gastrointestinal tract biopsies confirms that these infiltrative T-cells are monoclonal, with a g-T cell receptor rearrangement.

**Conclusions:** While unusual, a widely disseminated ETCL may present with an acute hepatitis-like picture.

## LOCALIZATION OF D2-40, PODOPLANIN AND CADHERIN-11 IN LUNG ADENOCARCINOMA AND MESOTHELIOMA: DIAGNOSTIC UTILITY IN DISCRIMINATING THESE TWO ENTITIES.

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**Background:** Podoplanin is a 38 kDa membrane glycoprotein found first to be expressed in lymphatic endothelium, then in reactive mesothelial cells and finally in mesotheliomas. D2-40 is an antibody against an epitope in the molecule of Podoplanin. Cadherin 11 is a transmembrane glycoprotein adhesion molecule which is expressed normally in some of the cells of the body e.g. mesenchymal cells, osteoblasts and helps in maintaining the architecture of the tissue. The aim of this study is to examine the expression and localization profile of podoplanin, D2-40 and Cadherin-11 in mesotheliomas and adenocarcinomas of the lung and to assess their diagnostic utility as tissue biomarkers.

**Design:** Formalin-fixed, paraffin embedded tissues of lung adenocarcinomas (50 cases) and malignant mesotheliomas (26 cases) were obtained from the surgical pathology archives of the Department of Pathology and Laboratory Medicine of the Ottawa Hospital. Hematoxylin and eosin stained sections were reviewed to confirm the diagnosis. Using monoclonal antibodies for Podoplanin, D2-40 and Cadherin-11, Immunohistochemistry was performed. Cases were considered positive if more than 10% of cell showed positive staining. Intensity of reaction was graded as negative, weak, moderate and strong.

### Results:

	Podoplanin					D2-40				
	M	C + M	C	Total Positive	Negative	M	C + M	C	Total Positive	Negative
<b>Adeno</b>	5 (10%)	1 (2%)	5 (10%)	11 (22%)	39 (78%)	5 (10%)	1 (2%)	2 (4%)	8 (16%)	42 (84%)
<b>Meso</b>	14 (54%)	9 (34%)	0%	23 (88%)	3 (12%)	14 (54%)	8 (30%)	1 (4%)	23 (88%)	3 (12%)

  

Cadherin 11					
M	N	NM	NC	Total Positive	Negative
0 (0%)	35 (70%)	1 (2%)	0 (0%)	36 (72%)	14 (28%)
3 (12%)	11 (42%)	3 (12%)	6 (22%)	23 (88%)	3 (12%)

**Conclusion:** Our study shows that membranous localization of Podoplanin, D2-40 and Cadherin-11 are reliable tissue biomarkers of malignant mesothelioma. We conclude that Podoplanin, D2-40 and Cadherin-11 should be used in the work-up panel for distinguishing lung adenocarcinoma from mesothelioma.

## **SIMULTANEOUS OCCURENCE OF UROTHELIAL CARCINOMA AND PROSTATIC ADENOCARCINOMA IN THE URINARY BLADDER**

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**Abstract:** Urothelial carcinoma (UC) and prostatic adenocarcinoma (PAC) share some common carcinogenic factors and the occurrence of one will be associated with the increased incidence of the other. Prostates harboring simultaneous PAC and UC are not uncommon, however urinary bladder with simultaneous UC and PAC has not been described. Secondary involvement of the urinary bladder by PAC can also pose a diagnostic challenge with UC and other urinary bladder tumors. We report three cases of UC occurring simultaneously with PAC. The patients were 75, 80 and 83 years old. They developed lower urinary tract symptoms or hematuria, and were diagnosed with high grade PAC with increased serum PSA. Cystoscopy revealed suspicious lesions with irregularities of the mucosa in the bladder trigone in two cases and two adjacent tumors in the remaining case. Histologically, the biopsies showed collision tumors consisting of high grade PAC and UC. Immunostaining demonstrated the distinct immunophenotypes with PAC displaying P63-, Keratin 903-, PSA+ and UC showing p63+, Keratin 903+, PSA-. In conclusion, awareness of simultaneous occurrences of PAC and UC in the urinary bladder is helpful in avoiding a misdiagnosis in these cases.

*LUNCH AND  
POSTER  
VIEWING*

*(ATRIUM 2<sup>ND</sup> FLOOR, FACULTY OF  
MEDICINE)*

*DR. MARC RUEL*

*GUEST SPEAKER*

*(Update on Cardiac Cell-Based Therapy)*

*Cardiac Surgeon & Cardiac Surgery Research Chair*

*University of Ottawa Heart Institute*

*Associate Professor of Surgery, Cellular & Molecular  
Medicine, and Epidemiology, University of Ottawa*

## CHOLESTEROL RETENTION IN ALZHEIMER'S BRAIN IS RESPONSIBLE FOR HIGH $\beta$ -SECRETASE ACTIVITIES AND A $\beta$ PRODUCTION.

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**Abstract:** Alzheimer's disease (AD) is characterized by overproduction and deposition of A $\beta$ . A $\beta$  peptide is derived from APP cleavage via  $\beta$ - and  $\gamma$ -secretase pathway. Recent evidence has linked altered cholesterol metabolism to AD pathogenesis. In this study, we show that AD brain had significant cholesterol retention and high  $\beta$ - and  $\gamma$ -secretase activities as compared to age-matched non-demented controls (ND). Over one-half of AD patients had an *apoE4* allele but none of the ND.  $\beta$ - and  $\gamma$ -secretase activities were significantly stimulated *in vitro* by 40 and 80  $\mu$ M cholesterol in AD and ND brains, respectively. Both secretase activities in AD brain were more sensitive to cholesterol (40  $\mu$ M) than those of ND (80  $\mu$ M). Filipin-stained cholesterol overlapped with BACE and A $\beta$  in AD brain sections. Cholesterol (10-80  $\mu$ M) added to N2a cultures significantly increased cellular cholesterol,  $\beta$ - and  $\gamma$ -secretase activities and A $\beta$  secretion. Similarly, addition of cholesterol (20-80  $\mu$ M) to cell lysates stimulated both *in vitro* secretase activities. Ergosterol slightly decreased  $\beta$ -secretase activity at 20-80  $\mu$ M, but strongly inhibited  $\gamma$ -secretase activity at 40  $\mu$ M. Cholesterol depletion reduced cellular cholesterol,  $\beta$ -secretase activity and A $\beta$  secretion. Transcription factor profiling shows that several key nuclear receptors involving cholesterol metabolism were significantly altered in AD brain, including decreased LXR- $\alpha$ , PPAR and TR, and increased RXR. Treatment of N2a cells with LXR, RXR or PPAR agonists strongly stimulated cellular cholesterol efflux to HDL and reduced cellular cholesterol and  $\beta$ -/ $\gamma$ -secretase activities. This study provides direct evidence that cholesterol homeostasis is impaired in AD brain and suggests that altered levels or activities of nuclear receptors may contribute to cholesterol retention which likely enhances  $\beta$ - and  $\gamma$ -secretase activities and A $\beta$  production in human brain.

## **POSSIBLE RELATIONSHIP BETWEEN MULTILOCULAR CYSTIC RCC AND CYSTIC NEPHROMA.**

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**Background:** Multilocular cystic renal cell carcinoma (MCRCC) is a distinct subtype of renal cell carcinoma (RCC). Its histogenesis is not well understood. Since MCRCC and cystic nephroma (CN) share the same gross appearance, we will investigate the relationship between MCRCC and CN.

**Materials and Methods:** Ten MCRCC and sixteen CN were retrieved from the files at our institution. All cases were submitted for immunohistochemical studies. Ten alveolar clear cell RCC (CCRCC) measuring less than 20 cm in diameter were used as control.

**Results:** MCRCC and CN were associated with female:male ratios of 1:4 and 14:2 respectively. There was no statistical difference in patient age or tumor size. Focal areas of MCRCC displayed similar characteristics to CN including a progesterone receptor (PR) positive cellular stroma and cuboidal or flat epithelial cells. Immunostaining for CK7 was noted to be positive in both MCRCC and CN. Focal areas of solid CCRCC in the MCRCC displayed weaker or negative reactivity for CK7 and negative reactivity for RCC and CD10. Conversely, the control alveolar CCRCC displayed CK7- CD10+ and RCC+. The stroma within alveolar CCRCC showed very occasional PR+ cells. In addition, two cases of CN displayed focal areas of clear cell change in the epithelial cells lining the cysts.

**Discussion:** Based on the overlapping morphological features and the results of our immunohistochemical analysis, we propose that there is at least a subset of MCRCC that develop from CN. It is possible that CNs arising in male patients are at increased risk of developing into MCRCC due to the fact the CCRC is more common in men.



## **RENAL LYMPHOMA MASQUERADING RENAL CELL CARCINOMA**

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**Background:** Primary renal lymphoma is extremely rare in part due to the absence of normal lymphoid tissue in the kidney. However, secondary lymphomatous involvement of the kidney is more common with incidence ranging from 34% to 62% in several autopsy series. Imaging studies underestimate the incidence of renal involvement, with CT detecting renal disease in only 3-8% of patients with known lymphoma. The final diagnosis is made only histologically.

**Design:** A 68-year-old Caucasian female with anemia, fatigue and a right renal mass, underwent nephrectomy for the presumed diagnosis of renal cell carcinoma. Morphologic examination, immunohistochemistry, and molecular genetic features were performed on the nephrectomy specimen.

**Results:** There was a 4x3 cm solitary lobulated tumor in the upper pole of the right kidney. Slides revealed a diffuse infiltration by large lymphoid cells replacing most of the renal parenchyma. Lymphoid infiltrate extended into the perihilar fibroadipose tissue. The tumor cells showed positive staining for LCA, Vimentin, CD20, CD10, Bcl6 and negative for Bcl2, CD30, Cyclin-d, and CD23. MIB-1 showed nuclear positivity in 70% of the cells. CEA monoclonal and RCC were negative. Immunoglobulin heavy chain gene rearrangement by PCR showed clonal bands in FR1, FR2, and FR3. BCL2-IgH [t (14; 18)] and BCL6-IgH [t (3; 14)] rearrangement were absent. The diagnosis of diffuse large B-cell type was established.

**Discussion:** Malignant lymphoma should be included in the differential diagnosis of renal lesions, especially when there are atypical radiologic features. A core biopsy or FNA with CT guidance may provide a definitive diagnosis. If a hematologic malignancy is confirmed, nephrectomy can be avoided and the patient can be treated with systemic therapy.

*BREAK*

## **A RARE COMPLICATION OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS**

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**Background:** Sclerosing encapsulating peritonitis (SEP) is a rare serious disease process, often associated with continuous ambulatory peritoneal dialysis (CAPD) of greater than 4 years duration. SEP is characterized by a progressive inflammatory process of the peritoneal cavity resulting in the formation of fibrous tissue sheets that cover and constrict the viscera. Mortality can exceed 50% and is frequently related to complications of surgery, bowel obstruction or sepsis.

**Design:** A elderly male developed end-stage renal disease due to systemic lupus erythematosus. He was placed on CAPD but after four years required supplementation with hemodialysis. Medical history included atrial fibrillation, coronary artery disease, peripheral vascular disease, and recurrent episodes of peritonitis while on CAPD. He presented with an enterocutaneous fistula and was taken to the operating room .

**Results:** Intraoperatively a dense fibrotic tissue rind diffusely covered the loops of small bowel. A resected bowel segment was markedly kinked and covered with thick serosal fibrous adhesions. There were areas of mucosal bowel ischemia with ulceration and haemorrhage. Microscopically, the serosal adhesions demonstrated elastosis and calcification. The patient died shortly after the operation.

**Discussion:** The gross and histological findings of the specimen were consistent with SEP. The diagnosis of SEP is challenging due to variable clinical presentation and a lack of specific radiological findings. Consequently, SEP is frequently only confirmed during operative management of complications. A heightened awareness of this entity may lead to earlier recognition and initiation of potentially life-saving interventions.

## CYTOPATHOLOGICAL STUDY OF UPPER URINARY TRACT UROTHELIAL CARCINOMA: IMMUNOSTAINING AS A DIAGNOSTIC AID

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**Objective:** The preoperative diagnosis of low grade urothelial carcinoma (LGUC) of the upper urinary tract (UUT) plays an important role in the management of the disease especially in the context of nephron-sparing treatment possibilities.

**Study design:** Wash or brush ureteral specimens of LGUC of the UUT with histopathological correlation were retrieved at our institution over a period of 7 years, and studied along with seven ureteral specimens from non-neoplastic ureteric lesions, that served as negative control.

**Results:** From a total of 30 specimens from 25 LGUC, 5 samples (4 cases) were negative for tumor cells and 3 samples (3 cases) showed cytologic atypia. The remaining 22 specimens (18 cases) contained tumor cells with characteristic features of urothelial carcinoma. These features included hard and soft criteria. The four hard criteria included: branching stromal cores, dyshesive cell networks, 3-D papillary clusters and atypia in CK20 positive cells. The two soft criteria included: hypercellularity and atypia in CK20 negative cells. All LGUC of the UUT were associated with at least one of the hard criteria or both of the soft criteria.

**Conclusions:** Branching stromal cores, 3-D papillary clusters, dyshesive cell networks, and atypia with positive CK20 immunostaining appear to be specific and characteristic for LGUC of the UUT.

## **PULMONARY ANGIOMYOLIPOMA (AML) IN A WOMAN WITH A HISTORY OF RENAL AML.**

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**Background:** AML is a rare, benign neoplasm of the kidney. It is a member of the PEComa family of tumours, arising from the perivascular epithelioid cell (PEC), and is composed of three elements: adipose tissue, dysplastic blood vessels, and smooth muscle. Diagnosis is confirmed by HMB45 reactivity. Extra-renal AMLs are exceedingly rare, particularly in the thorax. The most common pulmonary lesion associated with AML is pulmonary lymphangioleiomyomatosis (LAM). Several theories exist explaining how extra-renal AMLs and LAMs arise, including migration of PEC cells or more mature elements of AML to distant sites.

**Design:** We present a case of a 64 year old woman who had a left adrenalectomy and left nephrectomy in 1976 for AMLs and a subsequent wedge resection of the right kidney for an AML. She has no other stigmata or family history of Tuberous Sclerosis. In 2007, she was being investigated for multiple smooth round nodules of lipid density identified in all lobes of both lungs on CT scan. A subsequent needle core biopsy of the largest nodule was done.

**Results:** The lesion was composed of adipose tissue, thick-walled, dysplastic blood vessels and spindle cells. Occasional lipoblast-like cells were seen. Immunohistochemical analysis was performed and the lesion was positive for HMB45, focally positive for PR, and ER negative. A diagnosis of pulmonary AML in a patient with a history of renal AML was rendered.

**Discussion:** The natural history of AML is unknown because of few long-term studies. To our best knowledge, this is the third reported case of pulmonary AML arising in a patient with a history of renal AML. Awareness of this presentation is important in order to distinguish pulmonary AML from malignant sarcomas and LAM. Whether this case represents multifocal disease, migration of AML elements or PECs requires further investigation.

*AWARDS TO  
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# *POSTERS*

## **ROLE OF THE 26S PROTEASOME IN THE ACTIVATION OF RETINOIC ACID RESPONSIVE GENES.**

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Retinoic acid (RA) is the most potent derivative of vitamin A which is involved in many cellular processes such as development, differentiation and apoptosis. Clinically, it is often used as a cancer therapeutic and preventive agent against a variety of tumours including those of the skin, cervix, oral cavity and esophagus. The physiological effects of RA is mediated through retinoic acids receptors (RAR- $\alpha$ , RAR- $\beta$  and RAR- $\gamma$ ) and retinoic X receptors (RXR- $\alpha$ , RXR- $\beta$  and RXR- $\gamma$ ) which are transcription factors that require the function of coactivators such as p300 and SRC and corepressors such as N-CoR. Studies where proteasomal activity is inhibited with MG132 or with microinjection of an antibody specific for the S1/Rpn2 subunit of the 19S proteasome showed that proteasomal activity is required for RAR-mediated transactivation. However, the mechanism by which the 26S proteasome affects the activation of the RAR-mediated gene expression is not identified yet. In the present study, we investigated RAR- $\beta$  gene expression which is mediated by RAR- $\alpha$ /RXR- $\alpha$  heterodimer. We found that MG132 treatment inhibited RA-induced expression of the endogenous RAR- $\beta$  gene without affecting the protein levels of both RAR- $\alpha$  and p300. Additionally, the binding between the endogenous RXR- $\alpha$  and p300 was blocked following co-treatment of the cells with MG132 and RA. Also, SRC1 binding to RXR- $\alpha$  is significantly reduced after the addition of MG132 treatment to RA. Together our data suggest that the 26S proteasome contributes to RAR-mediated gene transcription by other mechanisms rather than the proteolytic function of the proteasome. Analyzing the occupancy of RAR- $\beta$  promoter by coactivators, corepressors, RNA polymerase II and general transcription factors will help us to fully understand the molecular basis underlying the role of the 26S proteasome in modulating RAR-mediated gene transcription.



## **ROLE OF P300 HAT ACTIVITY IN SKELETAL MUSCLE DIFFERENTIATION.**

**Tanja Francetic** and Qiao Li

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Differentiation of skeletal muscle is regulated by MyoD family of transcription factors. *MyoD* or *Myf5* expression determines the cell fate by inducing the expression of skeletal muscle specific genes. However, before *MyoD* and *Myf5* are expressed a number of stimulatory and inhibitory factors are integrated to decide whether or not to express *MyoD* or *Myf5*. This is often referred to as “the nodal point” of differentiation. Recently p300 histone acetyltransferase (HAT) activity was added to the list of requirements for *MyoD* and *Myf5* expression. However, the mechanism of this is not yet understood. p300 is a general transcription co-activator and it has histone acetyltransferase activity. It is further involved in skeletal muscle differentiation by interacting with MyoD and transactivating MyoD-dependant transcription as well MyoD activation by acetylation. Here we show a small enhancement of skeletal muscle differentiation with low concentration of retinoic acid. We further strive to answer whether p300 HAT activity is necessary for chromatin remodelling or co-activator complex recruitment at *MyoD* promoter; or alternatively whether p300 HAT activity is necessary for gene expression or the activity of transcription factors regulating *MyoD* expression. Through our research we hope uncover a novel molecular mechanism by which p300 participates in skeletal muscle differentiation.

## **ROLES OF HISTONE DEACETYLASE INHIBITORS IN p300-MEDIATED CELL CYCLE REGULATION**

**Feras Al-Ghazawi** and Qiao Li

Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada.

Histone deacetylase (HDAC) inhibitors recently emerged as a new class of anticancer drugs because they induce selective apoptosis in transformed culture cells and in cancers. However, the molecular mechanisms of the specific anti-cancer effects of these inhibitors have yet to be fully elucidated. p300 is a transcriptional co-activator for many regulatory genes that control cell cycle and displays an intrinsic histone acetylase transferase (HAT) activity. A proposed mechanism for the anti-tumor effects of the HDAC inhibitors is that the accumulation of acetylated histones leads to activation of the transcription of a selected number of genes whose expression causes inhibition of tumors cell growth and apoptosis. In the present study, we examined roles of several HDAC inhibitors, namely, sodium butyrate, valproic acid and trichostatin A on the expression of p300-regulated genes that are involved in cell cycle regulation such as p21, p57, Egr1, E2F1 and Cyclin D. In addition, we assessed the effects of HDAC inhibitors on the protein expression of these genes at different phases of the cell cycle in synchronized cells and after release. Moreover, flow cytometry analysis of cells subjected to these HDAC inhibitor treatments was performed to further confirm synchronization efficiency. Together, our data suggest that HDAC inhibitors up- and down-regulate p300-mediated genes, which indicate different roles of p300 on gene promoters and that p300 regulates genes throughout discrete mechanisms. Preliminary results from our studies on the promoter occupancy by p300 on these genes in control and in response to HDAC inhibitor treatments suggest that gene susceptibility to HDAC inhibitors is may be related to the promoter framework elements. Understanding roles of HDAC inhibitors will allow the design of more effective strategies to optimize the use of the agents in cancer treatment.

**CONCURRENT JAK2(V617F) AND BCR/ABL TRANSLOCATION IN A PATIENT WITH MYELOPROLIFERATIVE NEOPLASM AND NEUROFIBROMATOSIS TYPE 2. A CASE FOR MULTISTEP CARCINOGENESIS.**

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**Preamble:** We report a patient with neurofibromatosis type 2 (NF2), who developed polycythemia vera (PV), followed seven years later by chronic myelogenous leukemia (CML). Both the JAK2(V617F) mutation and the t(9;22) BCR/ABL translocation were documented in this patient.

**Objective:** A case of a 60 year old man is used to discuss a potential multistep pathway for the development of two chronic myeloproliferative neoplasms, PV and CML, in the context of NF2.

**Findings:** Clinical diagnosis of NF2 was based on the presence of multiple neural tumours, occurring over many years. At the age of 47, the patient presented with an elevated haemoglobin, a hematocrit, and a morphology compatible with PV. He was successfully managed with hydroxyurea and phlebotomy, and was hematologically stable for thirteen years. At the age of 60 he presented with an increasing peripheral blood leukocytosis, a neutrophilia and a left-shift. BCR/ABL translocation was identified, typical of chronic myelogenous leukemia. Flow cytometry showed a myeloid phenotype of the blasts, with expression of CD13, CD33, CD34, and terminal deoxynucleotidyl transfers (TdT). JAK2(V617F) analysis using the amplification refractory mutation system (ARMS) revealed a heterozygous state of this mutation.

**Conclusion:** This case presents the development of two chronic myeloproliferative disorders in a patient with a clinical history of NF2. The diagnostic workup and potential interactions of these three aberrations are discussed.

## **NEOPLASTIC SPLENIC EXTRADULARY HEMATOPOIESIS WITH POTENTIAL FOR MALIGNANT TRANSFORMATION.**

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**Preamble:** Extramedullary Hematopoiesis (EMH) refers to the presence of hematopoietic elements outside bone marrow niche. These active marrow elements can be benign or malignant in nature and differ in their underlying etiology, morphology, immunohistochemistry and molecular features.

**Objective:** A case of EMH in a 54 year old patient with myelofibrosis and massive splenomegaly is used to highlight the diagnostic features of neoplastic EMH. These are then compared to the features of benign EMH.

**Findings:** Histologic evaluation demonstrates foci of trilineage EMH with dysplastic megakaryocytes, immature myeloid, and erythroid precursors. Immunohistochemical analysis reveals MPO positive myeloid elements, Factor VIII/CD31 positive megakaryocytic elements and, HgbA positive erythroid elements. CD34, CD117 and TdT were negative. Molecular analysis using PCR demonstrates the presence of JAK2 V617F mutation. The morphology, immunohistochemical and molecular studies confirm neoplastic splenic extramedullary hematopoiesis. The negative staining with CD34, CD117, TdT indicate absence of malignant transformation to leukemia or granulocytic transformation.

**Conclusion:** This case represents a type of neoplastic EMH with dysplastic features. Since this entity has a potential for malignant transformation, immunohistochemistry and molecular testing should be performed, as was done with this case, to avoid under-diagnosis of this entity.

**ONCOCYTIC PAPILLARY RCC WITH SOLID ARCHITECTURE: AN IMITATOR OF RENAL ONCOCYTOMA.**

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**Objectives:** Distinguishing between the variants of renal cell carcinoma (RCC) poses a diagnostic challenge to the pathologist. Papillary renal cell carcinoma (PRCC) can be further sub-classified by the presence of solid features and, recently a new oncocytic variant has been described. In this study we describe a novel oncocytic variant of solid PRCC.

**Methods:** Eleven renal cell neoplasms possessing oncocytic features and solid architecture were examined retrospectively. Immunohistochemical analysis was performed and included CD117, PR, racemase (AMACR), RCC, Vimentin, CD10, and CK7.

**Results:** The eleven neoplasms consisted of circumscribed tumours with solid and diffuse growth patterns. Tubular structures were identified in six of the specimens and occasional papillae in four. Results of immunohistochemical analysis demonstrated six tumours with CD117+/PR+ (features consistent with RO) and five with CD117-/PR- (features consistent with PRCC). The five CD117-/PR- neoplasms also displayed AMACR+, RCC+, VIM+, CD10+, and mainly focal reactivity for CK7. None of the oncocytic renal cell neoplasms had features of eosinophilic CRCC. The five neoplasms exhibiting the immunohistochemical profile of PRCC had sizes ranging from 1 to 6 cm, patient ages ranging from 52 to 67 years, and a male to female ratio of 4:1. Three of the patients in this group developed progression of their disease: one had tumour extension up to the right atrium; two of the patients had metastases, one of them extensive and resulting in death.

**Discussion:** In this study we describe five solid oncocytic neoplasms that share the morphological characteristics of RO but possess the immunohistochemical profile and behaviour of classic PRCC. We propose that these tumours represent a previously undescribed variant of solid PRCC that exhibit oncocytic features. When confronted with an oncocytic renal cell neoplasm, awareness of this solid oncocytic variant of PRCC may prove useful in making the correct diagnosis.

**COMPARISON OF PAIRED PRIMARY AND LIVER METASTATIC (CRC) TISSUES FOR EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) PROTEIN EXPRESSION AND THE PRESENCE OF MUTATIONS IN THE EGFR TYROSINE KINASE DOMAIN.**

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**Abstract (updated):**

**Background:** Previous studies indicate that drugs that target the EGFR signaling pathways can induce objective responses, prolong time to progression and improve survival for CRC patients with EGFR expression in their primary tumour. However EGFR expression in the primary tumour may not predict response in the metastatic location, and little information is available about the correlation of EGFR expression between the primary tumour and the metastatic site. In other tumour sites, the presence of EGFR mutations was associated with efficacy in a subset of patients.

**Objectives:** The goal of this study is to correlate EGFR expression (using immunohistochemistry, IHC) between primary and liver metastatic sites of the tumour and to assess the mutational status in the EGFR kinase domain. We anticipate that high levels of EGFR will be expressed in metastatic lesions when compared to the primary tumor.

**Methods:** This is a retrospective study of all patients at TOHRCC who underwent surgical resection for CRC between 1999 and 2005, for whom paired paraffin-embedded tissue blocks of primary tumour and resected liver metastases were available. Seventy-four paired samples were identified. EGFR immunostaining was performed using the DakoCytomation EGFR pharmDx kit (DAKO) following manufacturer guidelines at the Department of Pathology, Faculty of Medicine, University of Ottawa. Two pathologists independently evaluated EGFR staining. To evaluate EGFR mutations, DNA was extracted and PCR was performed targeting exons 18, 19 and 21 encompassing most of the tyrosine kinase domain. PCR products were sequenced bi-directionally at the Sequencing Facility of the Ottawa Health Research Institute.

**Results:** EGFR was detectable in most primary and metastatic samples. There was moderately strong correlation between positivity in the primary and paired metastasis. Of 56 cases with EGFR-detectable primaries, only 5 (8.9%) had EGFR undetectable in the metastasis. Both of the EGFR-undetectable primaries had corresponding EGFR-undetectable metastasis. There were 2 cases with mutations in the EGFR kinase domain.

**Conclusions:** Based on these results, it is unlikely that clinical correlative studies will find that evaluation of EGFR expression in metastatic samples will be more predictive than EGFR expression from the primary.

**Note:** The data in this poster show the most recent data analysis.

## **FOLLICULAR DENDRITIC CELL SARCOMA OF THE LYMPH NODE: A RARE ENTITY.**

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**Background:** Follicular dendritic cell (FDC) sarcoma is a rare malignant entity which arises from accessory cells of the lymphoid follicles, member of the antigen-presenting system. It is most commonly found in lymph nodes and is associated with Castleman's disease. A definite diagnosis of FDC sarcoma is based on a combination of histology, immunohistochemistry and electron microscopy.

**Design:** We describe a case of a 63 year-old woman who presented with a 5 cm axillary mass, suspicious for malignancy. Mammography and ultrasound of the breasts were unremarkable. A core needle biopsy was done but was inconclusive. An excisional biopsy was performed and a histopathological examination was carried out.

**Results:** The lymph node showed a diffuse effacement of the normal architecture by a neoplastic infiltrate composed of spindle to ovoid cells focally arranged in a storiform pattern. The cells had a plump and eosinophilic cytoplasm with indistinct borders and were associated with interspersed lymphocytes. The mitotic rate was of 2-4 per 10 HPF. MIB1 showed a proliferation fraction of 20%. Immunohistochemistry showed positivity for vimentin, CD21 and CD23. All others immunostains were negative. Electron microscopy showed spindle cells with interdigitating cytoplasmic projections and typical desmosomes.

**Conclusion:** Nodal FDC sarcoma is an extremely rare tumor that is not usually included in the differential diagnosis of a large lymph node. This is of a great prognostic and therapeutic importance as FDC sarcoma behaves as a low grade sarcoma. Therefore, a high degree of suspicion and immunohistochemistry studies are required for a correct diagnosis.

## **HIGH GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA IN THE PROSTATIC CENTRAL ZONE.**

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**Background:** The prostatic central zone (CZ) has a lower rate of prostatic adenocarcinoma (PCA) than the peripheral zone (PZ). High grade PIN is strongly associated with prostatic carcinoma and is accepted as its precursor. However, although the histology of the CZ has been documented, the HGPIN of the CZ has not been studied.

**Design:** We reviewed consecutive 300 prostatectomies for PCA to identify PCA and HGPIN in the CZ. The CZ was conceptually divided into two parts of equal volume by an imaginary horizontal plane - a lower portion (AP, lower 2/3 of the CZ) and basal portion (BP, upper 1/3) and HGPIN was evaluated in each and compared to that of the PZ.

**Results:** There were only 9 cases with CZ PCA. These were associated with 45 foci of HGPIN in the CZ (32 in the AP and 13 in the BP) and 16 foci in the non-CZ (ie PZ and TZ). The remaining 291 cases of non-CZ PCA were associated with 347 foci of HGPIN in the CZ (295 in the AP and 52 in the BP), and 1270 foci in the non-CZ. For CZ PCA cases, HGPIN in the AP often displayed micropapillary and cribriform histologic patterns, darker cytoplasm, and more hyperchromatic nuclei and prominent nucleoli than those seen in the BP and non-CZ. For non-CZ PCA cases, HGPIN in the CZ (both AP and BP), showed papillary, cribriform, tufting, and flat histologic patterns. These foci of HGPIN were smaller in size and displayed less prominent and less frequent nucleoli compared to those in the non-CZ.

**Conclusions:** In contrast to non-CZ HGPIN, CZ HGPIN was rarer and smaller, and showed overall less nuclear atypia. In the cases associated with CZ PCA however, CZ HGPIN had greater nuclear atypia and darker cytoplasm. There was also a gradient of distribution of HGPIN in the CZ, with a much higher prevalence in the AP compared to the BP.



**STEM CELL DAMAGE FOLLOWING MULTIPLE MYELOMA MANIFESTING AS ACUTE LYMPHOBLASTIC LEUKEMIA AND MYELODYSPLASTIC SYNDROME: A CASE REPORT.**

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**Background:** Treatment-related acute lymphoblastic leukemia (tr-ALL) is much less common than treatment-related acute myeloid leukemia (tr-AML). We report a case of multiple myeloma (MM), followed by precursor B-cell acute lymphoblastic leukemia (B-ALL), followed by myelodysplastic syndrome (MDS) with deletion of the long arm of chromosome 20; del(20q).

**Methods:** Flow cytometry immunophenotyping of the ALL was performed using the FC500 (Beckman-Coulter). Classical karyotyping was performed on metaphase spreads using standard G-banding technique on the MM and MDS. Fluorescence in situ hybridization (FISH) using probes for D20S108 and 20q subtelomeric regions (Vysis/Abbott, Inc.) was performed retrospectively on the MM, ALL and MDS samples.

**Results:** Case report. A 57-year old woman, diagnosed with MM, received chemotherapy and radiation therapy followed by autologous peripheral blood stem cell transplant. She had primary non-engraftment, with autologous reconstitution occurring over a year after the high dose melphalan. She went into remission for 7 years. Then she developed B-ALL which was treated, and she went into complete remission. Then she developed MDS (refractory cytopenia with multilineage dysplasia, RCMD). Deletion (20q) was present in the MDS cells, but not in the MM cells. FISH for del(20q) on the ALL cells is currently pending.

**Conclusion:** We hypothesize the occurrence of treatment-related ALL and MDS related to stem cell damage following autologous transplant.

## **AN UNUSUAL CASE OF T-CELL PROLYMPHOCYTIC LEUKEMIA IN A PATIENT WITH RHEUMATOID ARTHRITIS**

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**Background:** Patients with rheumatoid arthritis (RA) are at increased risk of developing lymphoproliferative malignancies, mainly lymphomas of unspecified B or T cell origin. An isolated case of subcutaneous T-cell lymphoma in an RA patient has been reported, and it is recognized that T-cell large granular lymphocytic leukemia (T-LGL) is associated with RA.

**Design:** A 56 year old woman with a history of RA was referred to the Ottawa Hospital Bone Marrow Transplant Program for consideration of an allogeneic transplant for indolent t-cell prolymphocytic leukemia (T-PLL) diagnosed incidentally 26 months previous. Originally asymptomatic, she has since developed splenomegaly, fatigue, and worsening of her lymphocytosis.

**Results:** The patient presented with mild thrombocytopenia and lymphocytosis comprised mainly of prolymphocytes. Flow cytometry showed a cell population expressing pan t-cell markers (CD2, CD3, CD5, CD7, CD25) and co-expression of CD4 and CD8 compatible with T-cell prolymphocytic leukemia. TCR gamma gene rearrangement studies identified a clonal t-cell population. These findings were identical to her original work up in 2005.

**Conclusion:** RA is a disease of chronic lymphocyte stimulation generating t-cell clonal proliferation. Patients with RA are prone to lymphoproliferative malignancies, specifically T-LGL, an indolent clonal T-cell malignancy. T-cell prolymphocytic leukemia is a rare leukemia most often associated with an aggressive clinical course and short survival but an indolent phase of this disease has been documented. To the best of our knowledge, RA has not been associated with T-PLL moreover its unusual indolent form.

**DETECTION OF MRSA BY THE BD GENOHM MRSA ASSAY (BMA) FROM FLOCKED SWABS TRANSPORTED IN LIQUID AMIES (LA)**

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**Background:** MRSA screening by culture requires 48-72 hours compared to 1 hr with the BMA. At the Ottawa Hospital, nasal and rectal swabs are pooled in a selective broth prior to testing. To improve turnaround times (TAT) we evaluated the performance of the BMA using a flocked swab and a LA transport system.

**Method:** Flocked swabs dipped in a 0.5 McFarland suspension of CMRSA-2, CMRSA-7 and CMRSA-10 isolates were placed in the LA and incubated at room temperature (RT) for 1 hr, 2 hr, and overnight. To simulate a rectal swab, CMRSA-2 an inoculated swab was dipped in an MRSA negative stool and incubated in LA at RT for 1hr, 2 hr and overnight. For the simulated nasal swab, nares of a negative volunteer were swabbed prior to dipping in a CMRSA-2 suspension and incubated 1hr, 2hr and overnight at RT. For BMA testing, swabs were vortexed in the LA and a 50ul aliquot was transferred to the sample diluent buffer and processed according to manufacturer's instructions. All runs were performed in triplicate.

**Results:** All inoculated flocked swabs transported in LA including simulated rectal and nasal specimens were detected by BMA. None of the tests were found to be inhibited.

**Conclusion:** Flocked swabs transported in LA have the potential to be used with the BMA for screening of MRSA colonized patients. Pooling of nasal and rectal specimens collected on flocked swabs and transported in LA could be used with the BMA for direct testing instead of using selective broth and thus potentially reducing TAT. Further evaluations are on going to determine the feasibility and performance of the BMA from nasal and rectal specimens collected on flocked swabs and pooled in LA.

## SELECTION OF HIGH LEVEL TELITHROMYCIN RESISTANCE IN ERYTHROMYCIN RESISTANT GROUP A (GAS) AND GROUP B (GBS) STREPTOCOCCUS.

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**Background:** In Eastern Ontario 17% and 8% of GBS and GAS are erythromycin resistant. Constitutive and inducible *erm* mediated resistance was identified in 46% and 54%, respectively, of erythromycin resistant GBS and 64% and 36%, respectively, of GAS. Erythromycin resistance in the remaining isolates was mediated by efflux (*mefA*). Although telithromycin resistance has been reported in erythromycin resistant GAS, this antibiotic still remains an active therapeutic alternative. We determined telithromycin activity in erythromycin resistant GBS and GAS and selected for high-level resistance in isolates with inducible *erm*. **Method:** A total of 55 and 49 genotypically characterized erythromycin resistant GBS and GAS, respectively, were tested against telithromycin by broth microdilution according to CLSI recommendations. Selection of high-level telithromycin resistance in 3 GBS and 2 GAS with inducible *erm* was performed by serial passage on plates containing increasing doubling concentrations of telithromycin. The attenuator and coding region of the *erm* gene and the 6 alleles of domain V of the 23s RNA of each strain was sequenced and compared before and after passage. Induced telithromycin MICs were determined for GBS and GAS with inducible (26 GBS and 7 GAS) and constitutive *erm* (32 GBS and 44 GAS) by adding 4µg or 16µg erythromycin in each well of the microdilution plates. **Results:** Telithromycin MIC<sub>90</sub> for GAS was 64µg/mL (1 isolate with 64µg/mL) and 0.5µg/mL for GBS. Irreversible high level telithromycin resistance (MIC ≥128µg/mL) was selected for in all GAS and GBS within 12 to 14 passages. No mutations were identified in the *erm* or domain V genes for 2 of 3 GBS and both GAS. For one GBS, a single point mutation (Asp to Ser) was identified at base pair 332 of the *erm* gene. Erythromycin induction increased the telithromycin MIC more than 8 fold from 0.5µg/mL to ≥128µg/mL in isolates with either constitutive or inducible *erm*. **Conclusion:** Telithromycin remains an effective alternative to beta-lactams in erythromycin resistant GBS and GAS. Although the mechanism of telithromycin resistance in GBS and GAS remains unclear, repeated exposure to telithromycin could select for high-level resistance. Changes in *erm* methylation efficiency alone or in combination with other mechanisms could potentially lead to selection and dissemination of isolates with high-level resistance.

## **NEONATAL PLATELET TRANSFUSIONS USING VOLUME REDUCED PLATELETS**

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**Introduction:** Modification of platelets for neonatal transfusions varies with institutions. In our large tertiary care institution platelets for neonatal transfusions are volume reduced. Random donor platelets (RDP) are obtained from the Canadian Blood Services (CBS) as needed. For neonates, platelets are volume reduced to a 10 mL prior to transfusions to prevent problems with 1. ABO incompatibility. 2. Plasma volumes.

**Methods:** Collection data from neonates transfused with platelets over past 3 years included neonatal age, diagnosis, indication for platelet transfusion and pre and post transfusion platelet counts.

**Results:** 58 neonates with mean age of 7 days (1-47 days) were transfused with 123 RDPs. Majority of transfused neonates were premature, with gestation age as low as 24 weeks, the birth weight 450 g and platelet counts between 10-55 x 10<sup>9</sup>/L. Thirty one percent (31%) of neonatal thrombocytopenias were associated with infections (bacterial and viral), the remaining with intrauterine growth retardation, neonatal alloimmune thrombocytopenia (NAIT) and exchange transfusion for HDFN. 37 neonates (64%) received only one platelet transfusion each and did not require additional platelet therapy. 18 neonates (31%) received between 2-4 RDP. The post transfusion platelet counts were between 114 to 485 x 10<sup>9</sup>/L. Three (3) very sick neonates, (2 with severe infections and one with NAIT) required several platelet transfusions: 6, 10 and 21. Most neonates, 55/58 retained their post transfusion platelet counts with good hemostasis for 5 days (data not summarized after 5 days). In vivo platelet survival studies were not done due to very tender age of neonates.

**Conclusion:** Volume reduced platelets are efficacious and safe for neonatal transfusions.

1. Concentrated platelets in a small volume. 2. ABO complications due to plasma incompatibility are prevented; 3. Infusion time reduced and 4. Volume infused is decreased.

## **REGULATION OF THE FUNCTION OF TRANSCRIPTIONAL COACTIVATOR P300.**

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Transcriptional coactivator p300 modulates a broad array of gene expression through instigation of chromatin remodeling and integration of promoter occupancy. Mutations in the p300 gene have been found in various epithelial cancers hence, p300 has been classified as a tumor suppressor. However, high levels of p300 are also found in prostate cancer and are correlated with aggressiveness of the cancer. In general, cells are very sensitive to gene dosage of p300, but little is known about how p300 activity *per se* is regulated. We have reported that Akt/protein kinase B plays an important role in maintaining p300 activity (Chen J et al. 2004. Cell. Mol. Life Sci. 61: 1675-1683). We have also established that histone deacetylase inhibitor such as valproic acid induces p300 degradation through the 26S proteasome pathway. In addition, the negative effects of valproic acid on p300 activity are mediated through augmentation of the B56 $\gamma$ 3 regulatory subunit of PP2A (Chen J et al. 2005. Mol. Cell. Biol. 25: 525-532). Our recent study demonstrates that some p300 is distributed to the cytoplasm prior to valproic acid-induced degradation. Inhibition of proteasome activity does not prevent the redistribution of p300, rather sequesters the cytoplasmic p300 into aggresome. Moreover, the formation of p300 aggresome requires functional microtubule networks and correlates with p300 ubiquitination (Chen J et al. 2007. Epigenetics 2: 96-103). Our studies establish, for the first time, that p300 is also a substrate of the cytoplasmic proteasome system, and provides insight on how the 26S proteasome, cellular trafficking and spatial redistribution regulate the availability and the activity of coactivator p300.

## **USE OF WIKI IN UNDERGRADUATE MEDICAL EDUCATION**

**A. Jalali**, M. Mioduszewski, M. Gauthier, L. Varpio

**Introduction** Wiki allows for a multitude of learning benefits including asynchronous web-based access to information, rapid updating of posted information, editing of incomplete information, facilitating web-based discussion, and inter-linking of content pages. However, existing Wiki resources are often inaccurate or incomplete for medical education purposes.

**Aim** The investigators were interested to see if a Wiki created specifically for a medical student population could be an effective supplement to their current medical education curriculum.

**Methods** Using the technical framework offered by Wikispaces.com, the investigators created MedsWiki ([www.medswiki.ca](http://www.medswiki.ca)) with an organizational structure corresponding to the current medical curriculum offered to the undergraduate class. MedsWiki was populated with articles primarily focused on the first year medical student's Development and Homeostasis block, utilizing a combination of students' notes in anatomy, pathology, biochemistry, genetics, pathophysiology, pharmacology, radiology, surgery, and physical exam. Topic-specific templates, research and clinical publication RSS feeds were also incorporated.

**Results** This poster reports on development of the website, populating it with content and statistics data collection. This data was collected through Wikispaces statistics framework. These reflect the number of visitors and the number of edits each visitor did. Our preliminary data suggests that although the students viewed the site occasionally they were reluctant to edit the contents.

**Conclusion** Although Wiki seems like an interesting concept to improve students' interaction with their curriculum, our preliminary data suggest that students appeared to be passive about interacting with this tool.

## **ABCG2 UPREGULATION AND INTERACTION WITH AMYLOID PEPTIDE IN ALZHEIMER'S BRAIN WITH CEREBRAL AMYLOID ANGIOPATHY.**

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**BACKGROUND:** Alzheimer's disease (AD) is characterized by accumulation and deposition of  $\beta$ -amyloid peptides (A $\beta$ ) in brain parenchyma (senile plaques) and cerebral vessels. Deposition of A $\beta$  in cerebral vessels results in cerebral amyloid angiopathy (CAA), vascular insufficiency (chronic mild ischemia), and permeability changes at the blood-brain barrier (BBB). To investigate the expression changes of BBB-related genes, a custom oligo microarray carrying 273 BBB-related genes was used to analyze AD brains with CAA (AD/CAA) vs. age-matched non-demented control brains (ND). The analysis showed that ABCG2 is upregulated in AD/CAA brain. ABCG2 is an efflux pump expressed in human brain endothelial cells (HBEC) and protects the cells and brain from toxic substrate accumulation. Hypoxic environments upregulate ABCG2 expression via hypoxia-inducible factor-1 (HIF-1). HIF-1 also upregulates  $\beta$ -amyloid precursor protein (APP), from which A $\beta$  is derived. Dual upregulation of ABCG2 and A $\beta$  by hypoxia may lead to aberrant A $\beta$  clearance and contribute to A $\beta$  accumulation in the brain.

**OBJECTIVE:** To study ABCG2 expression in AD/CAA brain tissues and in cultured HBEC under hypoxic conditions, and to determine if A $\beta$  interacts with ABCG2 and is a substrate of ABCG2 transport.

**METHODS:** RNA samples were isolated from brain tissues or cultured cells using Trizol reagent. Microarray hybridization and labeling was achieved using pooled RNA samples from several preparations that were indirectly labeled with Cy3 or Cy5. Spot intensity data were obtained using QuantArray and the data was pre-processed using software Normaliser 3.0 developed in house. RNA and protein lysates were harvested for RT-PCR/real-time Q-PCR and Western blot analyses. Co-immunoprecipitation was carried out by incubating pooled human brain lysates with A $\beta$  peptide, anti-A $\beta$  antibody and A/G sepharose beads. The co-capture of ABCG2 by A $\beta$  was determined using Western blot and ABCG2-specific antibodies. Hypoxic conditions were achieved by treating HBEC cells in a hypoxia chamber for 4, 8 or 16h with or without A $\beta$ <sub>1-40</sub> peptides. Drug or A $\beta$  uptake assays were performed using HEK293 cells transiently transfected with cloned ABCG2 and fluorescently labeled A $\beta$  peptide or rhodamine 123.

**RESULTS:** Microarray showed that ABCG2 expression is upregulated in AD/CAA brain. Both Q-PCR and Western blot confirmed the upregulation of ABCG2 in these samples. Co-IP demonstrated that ABCG2 directly binds and interacts with A $\beta$  peptide. ABCG2 was upregulated in HBEC under hypoxic conditions which activate HIF-1 and increase APP and A $\beta$  peptide generation. Both hypoxia and A $\beta$  peptides synergistically stimulated ABCG2 expression in HBEC.



**CONCLUSION:** ABCG2 is upregulated in AD/CAA brain and in HBEC under hypoxic environments where HIF-1 activation is known to increase APP and A $\beta$  peptides. ABCG2 directly binds and interacts with A $\beta$  peptides, which may affect A $\beta$  transport and clearance and drug transport mediated by ABCG2 at the BBB in AD/CAA.

**Acknowledgments:** The authors thank Dr. A. Pratt and Dr. P-O. Couraud for providing primary and immortalized human brain endothelial cells.