Oral Presentations

(8:30am)

MECHANISMS OF TOPICAL ADJUVANT EFFECT ON IMMUNE RESPONSES TO SUBCUTANEOUS ANTIGEN. Hossain M. Najar and Jan P. Dutz. Department of Medicine and CF Research Institute of Children and Women's Health, University of British Columbia, Vancouver, British Columbia, Canada.

We have previously shown that topical Toll like receptor-9 (TLR-9) agonist administration improves immune responses to either topical or subcutaneous protein antigens and enables antigen-specific cytotoxic T cell activation (priming). This provides a simple method to improve vaccine responses. A clear understanding of the mechanism involved is required to optimize this method. The primary target for antigen and adjuvant are thought to be skin dendritic cells (DC). However, it is unclear which DC subset is responsible for the priming of T cells to subcutaneous antigen and how topical TLR-9 agonist affects this DC subset. Newly available anti-langerin (CD207) antibodies allow a clear identification of LC. Fluorescinated ovalbumin (OVA-FITC) provides an antigen than can be followed ex-vivo. We immunized the C57Bl/6 mice with OVA-FITC subcutaneously and applied CPG onto the overlying skin. Analysis of the draining lymph nodes at 24 hrs demonstrated that $CD11c^{high}$, $CD207^{low}$, $CD8^{low}$ DC residing in DLN predominantly acquire the protein antigen. DC activation is noted as soon as 24 hours after topical CPG administration. LC do not acquire the subcutaneous antigen and appear in the lymph node only several days after immunization. Topical CPG induces expression of type -1 interferons in the local skin and muscle as determined by MX staining. In contrast to parenteral CPG administration, no systemic cytokine release is noted following topical CPG administration. These results favor a LC-independent mechanism of local inflammation in the adjuvant activity of topical CPG. A more precise modulation of this inflammation may further improve immune responses.

(8:42am)

DEVELOPING A SAFE NON-REJECTABLE SKIN SUBSTITUTE: DIFFERENTIAL EFFECT OF INDOLEAMINE 2, 3-DIOXYGENASE(IDO) EXPRESSION ON VIABILITY OF HUMAN T-CELLS VERSUS SKIN CELLS. Farshad Forouzandeh[1], Reza B. Jalili[1], Marc Germain[2], Vincent Duronio[2], Aziz Ghahary[1]. 1-Burn and Wound Healing Lab, Department of Surgery, University of British Columbia 2-Department of Medicine, University of British Columbia.

Introduction: Although applying a skin substitute composing of keratinocytes is one of the most effective ways to help patients suffering from skin loss, preparing sheets of autologous keratinocytes has many limitations. Therefore, utilizing an allogeneic and readily available skin substitute would be a logical alternative. IDO catalyzes tryptophan, the least available essential amino acid, to kynurenine. Indeed, we plan to make use of IDO immuno-suppressive properties to improve the acceptance rate of allogenic grafted skin by making a Non-Rejectable Allograft Cultured Skin Substitute (NACSS). As the survival of fibroblasts and keratinocytes is crucial for the efficacy of NACSS, we need to make sure that IDO expression will not disturb the survival of these cells. **Methods:** We have evaluated the cell survival rate and proliferation of our suggestive IDO sensitive (T-

cells) and resistant (fibroblasts and keratinocytes) in IDO induced low tryptophan media. Moreover, we looked at stress related pathways, specifically GCN2 Kinase pathway, in these cells. **Results:** After 4 days of co-culturing IDO expressing fibrobalsts with our different bystander cells, we could see a significant decrease in cell survival and proliferation of human T-cells compared to bystander fibroblasts and keratinocytes which mostly remains alive ($P<0.01$). In addition, we found out convincing evidences that GCN2 kinase activation plays an important role in IDO expression effects. **Significance:** This study supports the idea that preparation of a non-rejectable skin substitute is feasible and safe to be used as wound coverage without compromising skin cells survival. The finding of this study would assist us to promote the rates of graft taking by development and application of a non-rejectable skin substitute in our future studies.

(8:54am)

Prognostic Significance of Nuclear ING4 and p-Akt Expression in Human Cutaneous Melanoma. Jun Li[1], Derek L. Dai[1], Magdalena Martinka[2], and Gang Li[1]. [1]Department of Dermatology and Skin Science, Jack Bell Research Center; [2]Department of Pathology, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, British Columbia, Canada.

The inhibitor of growth family, member 4 (ING4) is a novel member of ING tumor suppressor family. It can physically interact with p300 and p65 (RelA) subunit of NF-κB, and consequently enhance acetylation of p53 and repress transcription of NF-κB-responsive genes. Overexpression of ING4 can diminish colony-forming efficiency, decrease cell population in S phase, and induce p53 dependent apoptosis. Melanoma is the most lethal form of skin cancer, but the underlying mechanisms that regulate the progression of melanoma still remain mostly unknown. Our previous studies showed that ING4 can inhibit melanoma cell migration. This study focused on the correlation of ING4 expression and melanoma progression and prognosis. We established the tissue microarray and evaluated ING4 expression by immunohistochemistry in 50 dysplastic nevi, 101 primary melanomas, and 49 melanoma metastases. We also analyzed the association of ING4 expression with melanoma progression and patient survival. Our data showed that ING4 expression significantly decreased in primary melanoma and metastatic melanoma when compared with dysplastic nevi. Furthermore, we also found that reduced ING4 staining is associated with melanoma thickness, ulceration and patients' age. Moreover, ING4 staining showed significant correlation with both overall and disease-specific 5-year survival of primary melanoma patients. Strikingly, this study also revealed that nuclear ING4 staining is an independent prognostic factor in primary melanomas. Generally, results from this study led to better understanding of the role of ING4 in melanoma progression and offered an important prognostic marker and a potential therapeutical target for melanoma patients.

(9:06)

RESEARCH PROPOSAL: PREVALENCE OF BODY DYSMORPHIC DISORDER IN CANADIAN DERMATOLOGY PATIENTS. Se Mang Wong, MD, Gillian de Gannes, MD, FRCP(C), Harvey Lui, MD, FRCP(C). UBC Department of Dermatology and Skin Science.

Body Dysmorphic Disorder (BDD) is a common, yet under-recognized psychiatric condition. It is categorized in the DSM-IV as a somatoform disorder. These patients are preoccupied with an imagined defect in a body part. Where a slight physical abnormality is present, it causes excessive concern. This leads to clinical distress or significant functional impairment. This preoccupation is exclusive of another psychiatric diagnosis. With the perceived defect, these patients frequently seek out physicians to correct or validate their observations. Therefore, dermatologists and cosmetic surgeons are often consulted. However, literature suggests, due to the underlying psychiatric disorder, these patients are often unsatisfied with therapeutic measures or will shift the preoccupation to changes secondary to the treatment. General population prevalence of BDD is approximately 1%. Rates in college students suggest there may be societal factors that influence BDD development as American students showed higher rates than German students did. Prevalence data in dermatology patients is scarce. American data suggest rates as high as 11.9%. Turkish data in acne patients showed a rate of 8.8%. Since Canadians are exposed to many of the same societal influences as our American counterparts, the prevalence of BDD is expected to be similar. This research protocol proposes to determine the prevalence of BDD in a large Canadian center using the same screening tool from the American study. Furthermore, with a large Chinese population in Greater Vancouver, a translated screening questionnaire will generate data in Chinese-Canadian dermatology patients.

(9:18am)

PREDICTING MELANOMA PATIENTS' SURVIVAL USING A NEW METASTASIS MARKER. Liren Tang[1], Mingwan Su[1], Derek Dai[1], Belinda Campbell[2], Wency Ip[1], Magdalena Martinka[3], Gang Li[1], and Youwen Zhou[1]. [1]Department of Dermatology and Skin Science, Faculty of Medicine, University of British Columbia and Vancouver Coastal Health Research Institute; [2] BC Cancer Agency, and [3] Department of Pathology and Laboratory Medicine, Vancouver General Hospital.

Objectives: Predicting melanoma patients' risk of mortality is difficult at present. The overall goal of our research is to identify useful molecular markers that can help improve risk prognostication. Specifically, we report here the results of a pilot experiment using a newly discovered metastasis marker, alpha-1 antichymotrypsin (ACT), as a prognosticator of melanoma. Methods: Immunohistochemistry was performed on clinically annotated archival melanoma biopsies arranged in tissue microarrays to quantify the expression levels of ACT in each specimen using a four point scoring scale (0+, 1+, 2+ and 3+). The survival was analyzed according to the ACT staining intensity using Kaplan-Meier method for each staining intensity level and log rank test was used to evaluate the statistical significance of any differences observed. Results: In the pilot experiment, 172 specimens of primary melanoma and 79 cases of metastatic melanoma were examined. There is a significant increase of staining intensity of ACT as melanoma progressed from *in situ*, to invasive and metastatic stages. In addition, in thin melanoma, strong expression of ACT results in a 2.5 fold increase of mortality at 5-years compared with weak or no ACT expression. Similarly, in metastatic melanoma, strong expression of ACT is associated with a 4 fold increase of mortality risk at 5-years. Conclusion: For both thin and metastatic melanoma patients, strong expression of ACT protein in tumor biopsies is a strong prognostic factor for increased mortality. Further investigation involving a larger patient population is warranted to fully evaluate the clinical utility of ACT.

(9:30am)

QUANTUM DOTS NANOPARTICLE PENETRATION INTO MOUSE SKIN AND FLUORESCENCE PROPERTY CHANGES. Qingli He, Kevin McElwee, Xiao Han, Harvey Lui, David I. McLean, Haishan Zeng. Laboratory for Advanced Medical Photonics (LAMP). Dept. of Dermatology and Skin Science, UBC, Dept. of Cancer Imaging, BC Cancer Research Centre.

Although very effective on removing black hairs from light colored skin, hair removal laser treatment is ineffective on light colored hairs because of the lacking of photon absorbing melanin in the hair shaft. Exogenous chromophores may be used to enhance the contrast of light energy deposition between therapeutic targets and the surrounding tissue. We explored the use of near infrared absorbing quantum dot (QD) nanoparticles as the exogenous chromophore to target the hair follicles for improving laser hair removal procedures. Using a microspectrophotometer, we investigated the distribution of topically applied core-shell QDs CdSe/ZnS across mouse skin, compared the penetration of two QD solutions of different concentrations, and investigated the fluorescence properties of QDs in tissue. The fluorescence images and spectra revealed that most of the QDs accumulated on the surface or in the stratum corneum, especially near the open hair follicles. This distribution increased in a concentration-dependent manner. Significant amounts of QDs were found in hair follicles. These results suggested that follicular uptake is a penetration pathway for QDs' percutaneous transport into and across the skin barrier. Non-follicular structures did not offer an alternative penetration pathway for QDs, whose transport was clearly obstructed by the stratum corneum. This favors the use of QDs as an exogenous chromophore for improving laser hair removal treatment. As a byproduct, we also found that core-shell QDs exhibited blue shifts on fluorescence emission when located in mouse skin compared to their original solutions. This could have significant implications for bioimaging applications of QDs.

(9:42am)

GENE EXPRESSION PROFILING REVEALS DIFFERENCES BETWEEN DIFFERENT SUBTYPES OF BASAL CELL CARCINOMA. Mei Yu[1], David Zloty[1], Bryce Cowan[1], Laurence Warshawski[1], Nicholas Carr[2], Jerry Shapiro[1], Blanche K Lo[1], Kevin J McElwee[1]. 1- Department of Dermatology and Skin Science, 2- Department of Plastic Surgery, University of British Columbia, Vancouver, Canada.

Basal cell carcinoma (BCC) is the most common malignant neoplasm in humans. It may occur in a variety of morphological presentations with some more aggressive than others. A key goal is to relate a cancer phenotype to a list of defining molecular principles. Here we determined differences in gene expression patterns between different morphological presentations of BCC (8 superficial, 8 nodular, 7 morphea form, versus 8 normal skin epithelium) using microarray analysis (21K cDNA glass arrays). Selected genes were validated using quantitative RT-PCR analysis using an expanded set of 31 BCC samples. Six global gene expression profiles between each respective BCC subtype, and different subtypes compared with normal skin, were distinguished by unpaired T test with greater than 1.5 fold expression. Based on the Gene Ontology (GO) database, we identified

different categories represented in assigned biological processes, molecular functions, and cellular components with different gene expression profiles. Notably, angiogenesis associated genes, oncogenes, and immune response genes were uniquely upregulated, in morpheic BCCs which may reflect the relative aggressiveness of this BCC form. Gene ontology analysis also indicated significant variation in genes associated with MAPK pathways. Our results indicate a relative similarity in gene expression patterns between nodular and superficial BCC subtypes while morphea form BCCs are relatively distinct with gene expression patterns present that were not observed in other BCC subtypes. The data may help us to better understand the complex behavior of BCC subtypes and lead to improved prognostication and tailor-made therapeutic strategies.

(10:10am)

MODELS FOR MUCOSAL AND SKIN WOUND HEALING. Hannu Larjava and Lari Hakkinen. Faculty of Dentistry, University of British Columbia, Vancouver, Canada.

Wound healing problems in skin (non-healing, chronic wounds or over-healing, hypertrophic scars or keloids) impose a significant burden to the health care system. Our laboratory is using a number of different model systems to better understand the molecular processes that are involved in scar formation, development of chronic wounds and aberrant wound healing associated with immunosuppression therapy. As oral wounds generally heal with minimal scar-formation, by comparing scar-free and scar-forming wounds we hope to unravel the mechanisms that cause scarring and develop therapies to reduce scar-formation in the skin. In order to unravel the signaling pathways critical for scar-free healing, we have collected standardized human oral mucosal wounds at various time-points, and analyzed them by using immunocytochemistry, real-time PCR, ELISA and transcriptional profiling. We have also developed a pig model, in which both oral and dermal healing closely mimic human wound healing. This model allows us to directly compare the molecular pathways that result in minimal scarring (oral wounds) and hypertrophic-like scars (dermal wounds) in the same animals over time. Because impaired re-epithelialization plays a role in the development of chronic skin wounds, we have studied how glycogen synthase kinase-3 (GSK-3) regulates the epidermal wound closure by using in vitro and in vivo models. We have also developed a method to culture stem cell-like keratinocytes from transgenic mice and used them to study the role of keratinocyte $\alpha v\beta 6$ integrin in the activation of transforming growth factor-$\beta 1$ (TGF-$\beta 1$). By using transgenic mice lacking or over-expressing $\alpha v\beta 6$ integrin we also investigate molecular mechanisms of formation of chronic wounds and immunocompromised healing in vivo.

(10:22am)

API-2 AND AD-PUMA COMBINATION TREATMENT INHIBITS HUMAN MELANOMA TUMOR GROWTH *IN VIVO*. Alison M. Karst, Derek L. Dai, and Gang Li. Department of Dermatology and Skin Science, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, Canada.

The serine/threonine kinase Akt is overexpressed and/or hyperactivated in many types of cancer, including melanoma. High levels of phosphorylated Akt (p-Akt) have been associated with melanoma progression, invasion, and poor 5-year patient survival. Here

we show that treatment with the Akt/protein kinase B signaling inhibitor-2 (API-2) reduces p-Akt levels in melanoma cells and inhibits their survival and proliferation in a dose- and time-dependent manner. We previously reported that a recombinant adenovirus containing human PUMA cDNA (ad-PUMA) efficiently induces apoptosis of melanoma cells and suppresses the growth of human melanoma xenografts by 40-60% in a SCID mouse model. By combining ad-PUMA and API-2 treatments, we were able to inhibit human melanoma tumor growth by >80% *in vivo*, compared to controls. Our results suggest that a strategy to correct both dysregulated PUMA and p-Akt expression in malignant melanoma may be a promising therapeutic option.

(10:34am)

A MODEL OF UV INDUCED LUPUS. Beleznay, Katie; Ghoreishi, Mehran; Dutz, Jan. Department of Medicine, Division of Dermatology, University of British Columbia

Background: The roles of interferon-α (IFN-α) and ultraviolet B light (UVB) on autoantibody production were examined using a non-obese diabetic (NOD) mouse model. Topical Imiquimod cream, a Toll-like receptor 7 (TLR-7) agonist, created a pro-inflammatory environment through synthesis of IFN-α while UVB induced inflammation and keratinocyte apoptosis. This research has clinical relevance in autoimmune diseases such as systemic lupus erythematosus (SLE) and type 1 diabetes mellitus. **Methods**: 28 mice were split into 4 groups: No treatment, UVB only, UVB + Imiquimod, and Imiquimod only. Sera were sampled bi-weekly and tested for 1) anti-nuclear antibodies (ANA); 2) anti-double stranded DNA (anti-dsDNA) antibodies; 3) anti-desmoglein-3 (anti-dsg-3) antibodies. The study end-point resulted when the mice developed diabetes. **Results**: 1) UVB + Imiquimod showed the greatest rate of seroconversion to ANA followed by Imiquimod alone, then UVB alone, then the no treatment group. 2) Conversely, UVB alone caused the greatest seroconversion to anti-dsDNA antibodies followed by the UVB + Imiquimod group. The Imiquimod and no treatment groups did not show seroconversion. 3) Finally, mice treated cutaneously with Imiquimod cream developed an increased amount of anti-dsg-3 antibodies. **Conclusion**: UVB light and IFN-α accelerate autoantibody production which may be clinically relevant in autoimmune diseases. UVB appears most important for anti-DNA antibody seroconversion. Imiquimod appears most important in ANA and anti-dsg-3 antibody seroconversion.

(10:46am)

NEPHROGENIC FIBROSING DERMOPATHY: A CANADIAN SURVEY. Gillian de Gannes[1], Adeera Levin[2], Tarek Afifi[1], and Richard Crawford[1,3]. Department of Dermatology[1], Division of Nephrology[2], and Department of Pathology[3], St. Paul's Hospital and University of British Columbia, Vancouver, BC, Canada.

Background: Nephrogenic fibrosing dermopathy (NFD) is a recently described fibrosing disorder seen in patients with renal disease. Cutaneous involvement is characterized by the acute onset of symmetric indurated papules and plaques involving the trunk and extremities, with rapidly developing woody fibrosis that often results in limited joint motion. Internal organs may be involved. The histopathologic features of NFD are distinctive. A unique circulating fibrocyte has been implicated in the pathogenesis.

Current treatment options are limited. It is unclear why NFD has been recognized as a clinicopathologic entity only recently. Acute onset, occurrence in the setting of dialysis and geographic clustering suggest an environmental trigger. A registry at Yale University has confirmed over 170 cases from Europe, the Middle East and the US, but a cause has yet to be identified. Despite an estimated 1.9 million Canadians having chronic kidney disease, no cases from Canada have been reported to the registry, raising the possibility that differing practices have allowed patients to avoid the disease. **Objective:** To evaluate the Canadian experience with NFD in patients with renal disease. **Hypothesis**: NFD is not occurring in Canadian patients with renal disease. **Methods:** A survey has been distributed to all Canadian dermatology residents, dermatologists, dermatopathologists, and nephrologists to collect information on physician demographics, awareness of NFD, and clinical and pathologically confirmed cases of NFD. Additional clinical details and a review of histopathologic features will be sought for all potential cases. Results will include descriptive data and an analysis of NFD prevalence in Canada.

(10:58am)

FUNCTIONAL IMPACT OF COLLAGEN TRIPLE HELIX REPEAT CONTAINING PROTEIN 1 IN MELANOMA CELLS. Wency Ip[1], Liren Tang[1, 2], Mingwan Su[1], Jan P. Dutz[1, 3] and Youwen Zhou[1, 3]. [1]Department of Dermatology and Skin Science, and Chieng Genomics Center, Laboratory of Predictive Medicine and Therapeutics, Vancouver Coastal Health Research Institute, and University of British Columbia; [2]Present affiliations: Weilichem Biotechnology, Inc. Burnaby, BC; [3]Skin Oncology Group, BC Cancer Agency.

Collagen Triple Helix Containing 1 (CTHRC1), a protein previously identified in our laboratory to be up-regulated in metastatic melanoma and involved in regulation of cancer cell migration, was investigated in this study to further characterize its role in cancer progression and metastasis. Functional assays for melanoma cell survival, apoptosis, invasion, angiogenesis, and adhesion were performed using melanoma cells with and without CTHRC1 expression. Results showed that CTHRC1 had no effect on angiogenesis, but was able to increase cell survival, decrease apoptosis, and enhance cell attachment to the matrix. In this study, we have shown that CTHRC1 is an important protein in cancer metastasis, and a potential specific target for designing therapeutics for malignant melanoma.

(11:10am)

MULTIPLE DOSES OF TOPICAL TLR-7/8 AGONIST ENHANCE CTL PRIMING TO SUBCUTANEOUSLY ADMINISTERED ANTIGEN IN COMPARISON TO SINGLE DOSES. Brent A. Chang, Hossain M. Najar, and Jan P. Dutz. Child and Family Research Institute and Faculty of Medicine, Department of Dermatology, University of British Columbia, Vancouver, Canada.

Generation of effective Cytotoxic T Lymphocyte (CTL) mediated immune responses remains a hurdle for current vaccine strategies. The skin represents an ideal target for vaccine therapies which can strongly promote CTL priming. In this study, we explore the topical use of a TLR-7/8 agonist (resiquimod, R-848) to enhance CTL priming when

administered along with subcutaneous ovalbumin (OVA) antigen in a murine model. In this study mice were shaved and divided into two groups which were both immunized subcutaneously with OVA antigen. One group was then started on multiple (3) daily doses of TLR-7/8 agonist on the skin at the site of immunization. The other group was given only single doses of TLR-7/8 agonist. Subsequent analysis revealed that mice treated with multiple daily doses had enhanced antigen-specific CTL activity. The spleens of these mice had a significantly higher percent of antigen specific CD8+ T cells in their spleen at 1.12 ± 0.15% (n=11) compared to the spleens of mice treated with single doses at 0.70 ± 0.12% (n=11) with a p value of 0.04. We also show here that topical resiquimod induces antigen specific cytotoxicity in vivo. These results show great promise for implementing a simple, effective, and non-invasive way of enhancing the efficacy of current human vaccines.

(11:22am)

CLINICAL ASSESSMENT OF SKIN CANCERS USING INTEGRATED REAL-TIME RAMAN SPECTROMETER SYSTEM. Jianhua Zhao, Harvey Lui, David I. McLean, Haishan Zeng. The Laboratory for Advanced Medical Photonics (LAMP), Department of Dermatology and Skin Science, University of British Columbia, and Cancer Imaging Department, BC Cancer Research Center, Vancouver, BC, Canada.

Background: Raman spectroscopy is a non-invasive optical technique, which has the capability in determining the molecular structure and conformation of biochemical constitutes at the molecular level. Because the probability of Raman scattering is so low (~10^{-10}) that clinical applications of Raman spectroscopy have been limited either by the weak signal or by the long acquisition time. Recent development of Raman probes reduces the acquisition time, paving the way for Raman in the clinical setting. **Hypothesis**: The morphological and molecular structure, and the biochemical constitutes has been altered in the cancerous (or diseased) skin. **Methods and Patients**: An integrated real-time Raman spectroscopy system for skin disease evaluation has been designed. It combines the novel system design and software implementation. The system design implements full-chip vertical hardware binning and improves the signal-to-noise ratio. The real-time data acquisition and processing include background removal, wavelength calibration, spectral response calibration, intensity calibration, signal saturation rejection, cosmic ray rejection, fluorescence background removal, and data model analysis. In the pilot study, a few patients with BCC, SCC and melanoma were recruited. The study was approved by the clinical research ethics board of the University of British Columbia and Vancouver Coastal Health Research Institute. Base Raman spectra of the skin constitutes, such as cholesterol, collagen, keratin, oleic acid etc., were used in the general least square model analysis. **Results and Conclusion**: The total time for a single measurement and analysis can be reduced to 100 milliseconds. It was found that the (cancerous) skin Raman spectra can be well modeled using the base Raman spectra. In vivo clinical results validate that real-time Raman can be a very promising research and practice technique for skin cancer diagnosis.

(1:30pm)

Obesity, Waist Circumference, Weight Change and the Risk of Psoriasis in Women – A Prospective Study. Hyon Choi. Department of Rheumatology, University of British Columbia.

Psoriasis is a common chronic inflammatory disease of the skin that poses a lifelong burden on those affected. Higher adiposity may increase the risk of psoriasis, but no prospective data are available on this relation. We prospectively examined over a 14-year period (1991-2005) the relations between body mass index (BMI), weight change, waist circumference, hip circumference, waist to hip ratio and incident psoriasis in 78,626 women in the Nurses Health Study II. The primary outcome was incident, self-reported, physician-diagnosed psoriasis. During the 14 years of follow-up, there were 892 self-reported incident cases of psoriasis. There was a graded positive association between body mass index measured at multiple time-points (age 18, baseline, and updated biennially during follow-up) and the risk of incident psoriasis. When we analyzed BMI updated every 2 years, compared to a BMI of 21 to 22.9 kg/m^2, the multivariate RRs of psoriasis were 1.40 (95% CI, 1.13-1.73) for a BMI of 25 to 29.9, 1.48 (95% CI, 1.15-1.91) for BMI of 30 to 34.9 and 2.69 (95% CI, 2.12-3.40) for a BMI 35 or greater (*P* for trend <0.001). When we analyzed BMI at age 18 years, compared to a BMI of 21 to 22.9, the multivariate RR for the top BMI category (≥ 30) was 1.73 (95% CI, 1.24-2.41) and that for a lower BMI category (<21) was 0.76 (95% CI, 0.65-0.90) (*P* for trend <0.001). Weight gain from age 18, higher waist circumference, hip circumference, and waist-to-hip ratio were all associated with a higher risk of incident psoriasis (all P-values for trend <0.001). This large prospective study indicates that increased adiposity and weight gain are strong risk factors for incident psoriasis in women. Weight loss may potentially be an important target for the prevention and management of psoriasis.

(1:42pm)

THE BIOLOGICAL ROLE OF BONE MARROW-DERIVED KERATINOCYTE PRECURSOR CELLS IN WOUND HEALING. Abelardo Medina, MD, FACS; Ruhangiz T. Kilani, PhD; Aziz Ghahary, PhD. BC Professional Fire Fighters' Burn/Wound Healing Research Lab Department of Surgery, University of British Columbia.

The skin is the most extensive organ in the human body and exerts multiple vital functions. Both chronic and extensive acute dermal wounds constitute major health problems. Bone marrow-derived stem cells may be a potential source for the preparation of skin substitutes due to their capacity to be reprogrammed into unexpected peripheral cells. We hypothesize that circulating bone marrow-derived stem cells might contribute to the production of skin substitutes due to their transformation into keratinocyte-like cells. We also hypothesize that these cells might interact with dermal fibroblasts modulating the extracellular matrix (ECM) production and improving the wound healing outcome. We have characterized a peripheral blood mononuclear cell (PBMC) subset that develops keratinocyte-like profile (14-3-3 sigma +ve and keratin 5 +ve staining). They also release factors into conditioned media that promote MMP-1 expression in dermal fibroblasts in a time-dependent manner. The latter finding is due, at least in part, to releasable 14-3-3 sigma protein. Findings from this research project will provide us new insights into the wound healing that would facilitate not only the production of skin substitutes to replace dead tissues in extensively burned patients, but also the better

understanding of the healing process and subsequently the treatment of chronic non-healing wounds (i.e., elderly people, diabetic and immuno-compromised patients) as well as those associated with over-healing wounds (i.e., post-burn hypertrophic scarring). Thus, the identification of a releasable fraction of 14-3-3 sigma in PBMC-derived keratinocyte-like cells discloses new alternatives to control the fibrogenic process associated to tissue injury.

(1:54pm)

The Antimalarial Chloroquine Blocks TLR 9 Mediated DC Maturation And CD8 T Cell Activation In Vivo. YiQun Zhang and Jan Dutz. Department of Medicine and Child & Family Research Institute, University of British Columbia, Vancouver, BC, Canada.

Chloroquine is effective in the treatment of autoimmune diseases such as lupus and arthritis. Here we demonstrate that chloroquine inhibits toll like receptor 9 (TLR 9) mediated dendritic cell (DC) maturation and T cell responses to either soluble antigens (ovalbumin) or auto-antigens (IGRP – an islet-specific auto-antigen). Firstly, two in vitro experimental models showed that TLR9 agonist, CPG, induced CD4 and CD8 T cell activation in response to soluble ovalbumin protein and β-cell antigens respectively. Addition of chloroquine to the culture of bone marrow DC (BMDC) pulsed with soluble or auto-antigens and stimulated with CPG strongly inhibited CD4 and CD8 T cell proliferation and CD25 expression. Furthermore, chloroquine inhibited CPG-induced CD40 upregulation and IL-12 p70 secretion from BMDC. Secondly, injection of diabetes-prone NOD mice with CPG peritoneally induced secretion of IL-12 p70, IL-6, IFN-gamma and MCP-1 and CD8 T cell activation, as manifested by CD69 upregulation on CD8 T cells. Administration of chloroquine decreased both cytokine secretion and CD8 T cell activation induced by CPG but not LPS. Thirdly, treatment of NOD mice with chloroquine delayed diabetes development and down-regulated CD40 expression on DC which suggest that TLR9 signals might contribute to diabetes development. Taken together, these data indicate that one mode of action of chloroquine in the treatment of auto-immune disease is the inhibition of dendritic cell maturation, and consequently T cell activation, by TLR9 ligands.

(2:06pm)

ROLE OF THE TUMOR SUPPRESSOR ING1b IN CELL CYCLE PROGRESSION. Garate, M; Wang, Y. and Li, G. Department of Dermatology and Skin Science, University of British Columbia, Vancouver, Canada.

The tumor suppressor ING1b plays a prominent role in cellular stress events including cell cycle arrest, apoptosis, chromatin remodeling, and DNA repair. Previous reports described that overexpression of ING1b enhances the G_2/M DNA damage checkpoint induced by adriamycin and decreases cell proliferation. It has also been suggested that overexpression of ING1b downregulate cyclin B1. We have previously shown that in melanoma cell lines ultraviolet irradiation induces ING1b expression in time- and dose-dependent manner. Recently, we have shown that events that evoke DNA-damage induce a rapid phosphorylation of ING1b, stabilizing this tumor suppressor and for the first time we identified the Ser126 residue to be phosphorylated. Since ING1b can

potentially control the expression of cyclin B1 to regulate cell proliferation, we hypothesize that ING1b expression is cell cycle restricted and the phosphorylation associated to this tumor suppressor upon DNA-damage induces cell cycle arrest and inhibits cell proliferation in melanoma cells. Working with synchronized cultures we observed that ING1b expression is indeed cell cycle restricted in melanoma cells. The overexpression of wild-type ING1b and a phosphomimetic S126E but not an unphosporylable S126A mutant downregulate cyclin B1, suggesting that ING1b may play a key role in cell cycle regulation. Consistently, ING1b expression inhibited cell proliferation and this effect was dependent of Ser126 phosphorylation. This work will contribute to unveil the molecular mechanism of how tumor suppressors control cell cycle and in particular in the design of better therapies to treat melanoma patients targeting events that define the fate of normal and malignant cells.

(2:18pm)

MELANIN QUANTIFICATION BY *IN VITRO* AND *IN VIVO* ANALYSIS OF NEAR INFRARED FLUORESCENCE: PRELIMINARY OBSERVATIONS. Kalia S., Zhao J., Zeng H., McLean D., and Lui H. University of British Columbia and British Columbia Cancer Agency, Vancouver, British Columbia.

The biological structure, property and function of melanin is of considerable interest in understanding its role in normal and diseased skin. Our objectives are to quantify NIR autofluorescence of melanin (i) in solution or suspension as a function of concentration, and (ii) within normal skin and pathologic lesions. We hypothesize that NIR autofluorescence can be measurably correlated with melanin expression. Synthetic DOPA and *Sepia* melanin were prepared in deionized distilled water and in aqueous NH_4OH solution. Both *in vitro* melanin samples and *in vivo* human skin NIR autofluorescence were measured using a custom rapid Raman spectrometer system under 785nm excitation. Both types of melanin in water and *Sepia* melanin in NH_4OH showed similar fluorescence patterns: (i) the signal intensities were proportional to concentration up to 2.50-5.00 mg/mL, (ii) when melanin concentrations were increased above 5.00 mg/mL fluorescence intensity was decreased. Synthetic DOPA melanin in NH_4OH formed a dark brown uniform solution and demonstrated a similar pattern but the peak fluorescence was almost four times higher. *In vivo* examinations have previously shown fluorescence to be higher when pigment is increased in normal skin. However, in pathological conditions such as heavily pigmented melanoma we have noted that fluorescence is seemingly decreased, which are analogous with our *in vitro* findings. We have shown that NIR autofluorescence of melanin *in vitro* and *in vivo* is directly correlated with melanin content up to a certain concentration, beyond which the fluorescence appears to decrease. These preliminary results show that NIR autofluorescence can be used to some extent to quantify melanin *in vivo*.

(2:30pm)

EFFECT OF TOPICAL CALCIPOTRIOL ON IMMUNITY IN THE SKIN. Bach P., Ghoreishi M. and Dutz J.P. Department of Dermatology, University of British Columbia, Vancouver, BC, Canada.

1,25-dihydroxyvitamin D3 (Vitamin D) promotes the generation of T regulatory cells (Tregs) both *in vitro* and when administered orally or intraperitoneally *in vivo*. Using a method of transcutaneous immunization (TCI), three days of topical application of the Vitamin D analog calcipotriol combined with ovalbumin (OVA) protein and CpG can result in the generation of CD4+CD25+ Tregs capable of mediating transferable OVA-specific tolerance. Here we demonstrate that a single topical calcipotriol pretreatment is sufficient to decrease CTL priming to topical antigen and CpG (54 $\pm$ 17 % decrease in priming of adoptively transferred OT-1 CTLs in the draining lymph nodes, when compared to antigen and CpG alone). Moreover, three days of topical calcipotriol can also diminish CTL priming to subcutaneously injected OVA with topical CpG (log percent OVA-specific CTL amongst CD8+ T cells in peripheral blood: calcipotriol+CpG+OVAsc = 1.08 $\pm$ 0.19 %, compared to placebo+CpG+OVAsc = 0.57 $\pm$ 0.14 %. p = 0.04). Humoral immunity was not affected as evidenced by lack of change in OVA-specific IgG levels. Together these results indicate that topical calcipotriol has a profound effect on immune responses originating in the skin and support the idea of using the skin as an easy and effective vector for clinical immunoregulatory therapy.

(2:42pm)

LASER SPECKLE IMAGING SYSTEM FOR SKIN SURFACE ROUGHNESS ASSESSMENT.

M. Mirski[1], C. Russell[1], J. Shariff[1], L. Tchvialeva[2,3], T.K. Lee[2,3], D.I. McLean[2], H. Lui[2,3], H. Zeng[2,3]. [1]Engineering Physics, Dept. of Physics and Astronomy, UBC. [2]Department of Dermatology and Skin Science, UBC. [3]BC Cancer Research Centre.

The illumination of rough surfaces under coherent laser light results in speckle: random interference patterns that are determined by the surface properties. In clinical dermatology the evaluation of a skin lesion's surface texture by appearance and touch provides important clues about its diagnosis. We hypothesize that the specific relationship between speckle contrast and surface roughness can be quantified and used as a clinical method to evaluate skin lesions. Specifically, the initial focus of our studies will be to use speckle analysis as a means for separating malignant melanoma from seborrheic keratoses, both of which exhibit positive findings according to the conventional ABCD method for skin cancer detection. To implement a working prototype for this device, a portable laser speckle imaging system suitable for clinical *in vivo* measurements has been developed. Two semiconductor diode lasers serve as illumination sources at opposite ends of the visible spectrum. A pair of CCD cameras fitted with orthogonal polarizers (alternately parallel and perpendicular to the source polarization) captures simultaneous images for each source. Imaging at two distinct polarizations differentiates surface-reflected light from light penetrating the skin before reflecting. The optical geometry ensures that each CCD captures only scattered light, avoiding the direct, specularly reflected beam. A command-line interface program acquires, displays, and saves images, with timing electronics triggering the hardware in the correct sequence. Preliminary images show the shorter wavelength source to be more effective. With the completion of an enclosure for the device, this prototype will be ready for use in a clinical setting.

(2:54pm)

SCREENING FOR MELANOMA AND NON-MELANOMA SKIN CANCER WITH ANNUAL CUTANEOUS EXAMINATION: REVIEW OF OUTCOMES & COMPLIANCE. Shannon Humphrey MD, Katie Beleznay BSc, Jason Rivers MD FRCPC. Department of Dermatology and Skin Science, University of British Columbia, British Columbia (BC), Vancouver, Canada.

Justification: Annual cutaneous examination (ACE) is recommended by dermatologists as screening for melanoma and non-melanoma skin cancer in patients with risk factors for these cancers. There is no conclusive evidence to support this practice. **Hypotheses**: 1) Patients targeted for ACE have a higher incidence of skin cancer than patients not targeted for ACE. 2) Patients targeted for ACE have a higher incidence of skin cancer than the general population. 3) Most patients targeted for ACE comply with this recommendation. **Objectives**: 1) To determine if patients targeted for and compliant with ACE develop skin cancer at a greater rate than those not targeted for ACE. 2) To determine if patients targeted for and compliant with ACE develop skin cancer at a greater rate than the general population. 3) To determine what percentage of patients comply with ACE. 4) To explore reasons for non-compliance with ACE. **Methods**: A retrospective review will be completed using charts from a single dermatologist affiliated with Department of Dermatology and Skin Science, UBC. Charts are selected using the BC Medical Services Plan diagnostic codes 172: malignant melanoma of the skin (n=258), and 216: benign neoplasm of the skin (n=3956), over an 8-year period from October 1, 1993-September 30, 2001. The rates of skin cancer will be compared between the compliant ACE group and non-ACE group for the 216 and 172 patients separately, and with the general population of BC. Patients who were non-compliant with ACE will be invited to complete a survey to explore reasons for non-compliance.

(The following three abstracts will be presented at noon rounds. Presentation dates to be determined.)

HEALTH RELATED QUALITY OF LIFE IN PATIENTS WITH ROSACEA. D. Adam, J. Rivers. Department of Dermatology and Skin Science, Skin Care Center – Vancouver General Hospital and University of British Columbia.

Objectives: The goals are to measure the health related quality of life (HRQOL) of patients with rosacea, to compare these values to the HRQOL in other diseases and to determine if there is a relationship between clinical and demographic factors and HRQOL. **Methods:** A prospective observational evaluation of the HRQOL of patients with rosacea recruited from Skin Care Center clinics. Patients completed a Dermatology Life Quality Index (DLQI), Short Form 36 (SF36), and a demographic survey. The severity of patients' rosacea was assessed. **Results:** One hundred surveys were distributed with 40 completed. Data for the first 24 patients are presented with final analysis to follow. Patient assessed disease severity was 4.9/10 ± 2.3. Global physician assessment was 5/10 ±1.7. Pooled severity score was 13.6/30 ± 4.5. Mean DLQI was 3.9/30 ± 2.9. This was similar to acne patients and better than values for psoriasis patients. Mean SF-36 score was 77/100 ±15. Normative scoring for the Physical Component Score (PCS) was 51.61±10 and 47.72±10 for the Mental Component Score (MCS). Compared to the general population the PCS was at the 46th percentile and the MCS at the 33rd. The PCS was slightly lower than healthy controls while the MCS was

comparable to patients with arthritis or cancer. Relationships between clinical and demographic factors and HRQOL will be completed as will inclusion of the final 14 patients in the final analysis. **Preliminary Conclusions:** The HRQOL of patients with rosacea is impaired. The MCS compares to values seen with arthritis and cancer.

MYCOSIS FUNGOIDES IN MANITOBA 1982-2002. Marcie Ulmer MD[1,2], Jack Toole MD[2], Morel Rubinger MD[3,4], Alain Demers PhD[5,6], Zoann Nugent PhD[5], Marni C Wiseman MD[2,3]. [1]Department of Dermatology and Skin Science, University of British Columbia, Vancouver, Canada. [2]Division of Dermatology, University of Manitoba, Winnipeg, Canada. [3]CancerCare Manitoba, Winnipeg, Canada. [4]Division of Medical Oncology and Haematology, University of Manitoba, Winnipeg, Canada. [5]CancerCare Manitoba, Epidemiology and Cancer Registry, Winnipeg, Canada. [6]Department of Community Health Sciences, University of Manitoba, Winnipeg, Canada.

Introduction: Cutaneous T-cell lymphomas are malignant T-cell lymphoproliferative diseases with primary involvement of the skin. Mycosis Fungoides (MF) behaves predominantly as an indolent variant. Literature review reveals a paucity of published data on the epidemiology of MF in Canada and specifically on the MF experience in Manitoba. **Objective**: To examine trends in incidence, mortality and survival of MF in Manitoba. **Methods**: Patients diagnosed with MF between 1982 and 2002 were identified. Annual population estimates derived from Manitoba Health's Population Registry were used for denominators of rates. The 1991 Canadian population was used to age-standardize rates. **Results**: A total of 83 MF cases were identified. Both sexes had a similar mean age at diagnosis. MF was identified more frequently in men and in older individuals. The average age-standardized incidence rate in men (0.43/100,000 men) was higher than in women (0.26/100,000 women). The overall age-standardized mortality rate was 0.17/100,000 men and 0.04/100,000 women, for men and women respectively. The 5-year relative survival rate was 85.8% with lower survival among men compared to women. **Conclusions**: The average age-standardized incidence rate of MF in males and females in Manitoba is low. While the absolute mortality rates are small, men experience 4 times more deaths from the disease than women, and this difference is yet unexplained. It is known that survival is highly stage dependent and detailed analysis of prognostic factors might be informative. This information contributes to the existing literature regarding MF in Canada and provides valuable information for the multi-disciplinary MF Clinic at CancerCare Manitoba, Winnipeg, Manitoba.

SURVEY OF RECENT CANADIAN DERMATOLOGY GRADUATES. Stephanie J. Côté and Richard I. Crawford. University of British Columbia, Vancouver.

Background: Despite workforce shortages, there are relatively few dermatologists trained every year in Canada. A Canadian dermatology workforce survey conducted in 2001 confirmed this reality and provided information about the demographics, workload, and future career plans of dermatologists in this country. An appraisal of dermatology residency training in 2004 provided data to assist dermatology programs with the improvement of their curricula. No prior studies have evaluated how recent dermatology graduates perceive their residency to have prepared them for their careers, nor has any previous study examined the demographics and practice components of this group. **Hypotheses:** 1) Current residency programs provide a broad-based training curriculum; and 2) Components of recent graduates' current practices differ from what they had

perceived during residency that these would subsequently be. **Objectives:** 1) To identify the basic demographics and practice components of recently graduated Canadian dermatology residents; 2) To characterize additional formal and informal training completed after residency; 3) To assess their perceived adequacy of residency training in preparing them for their current endeavors; 4) To provide suggestions for improvement in residency training programs; and 5) To help evaluate whether areas of need are being filled in Canada. **Methods:** Anonymous survey of Canadian dermatology graduates from the classes of 2001-2006.

USE OF BOTULINUM EXOTOXIN A TO PREVENT ABNORMAL SCARRING OF CHEST WALL SURGICAL WOUNDS: A PROSPECTIVE, DOUBLE-BLINDED, PLACEBO-CONTROLLED STUDY. Jennifer A. Baron, MD, Bryce J. Cowan, MD, and David M. Zloty, MD, Department of Dermatology and Skin Science, University of British Columbia, Vancouver, Canada.

Background: Cutaneous wounds of the chest wall can heal poorly, often with the formation of spread, hypertrophic, or keloidal scars. Both intra- and post-operative methods have been employed to address these unsightly and occasionally symptomatic scars. Techniques include adequate undermining and alignment with Langer's lines as well as post-operative scar therapy with intralesional corticosteroids, intralesional 5-fluorouracil, various lasers, topical silicone sheeting, and many others. Few, if any, of these techniques have reproducibly prevented poor scar outcomes in this anatomic location, possibly because they have not eliminated the underlying wound-edge tension effected by dynamic pectoralis movements and/or increased scar myofibroblast activity. Intraoperative use of botulinum exotoxin type A has been shown to prevent widening of facial scars in primates and in humans in small subjective studies. **Methods:** In 29* patients who underwent surgical excision of various malignant and non-malignant lesions of the skin and subcutaneous tissues of the chest, botulinum exotoxin A was employed intra-operatively to temporarily reduce presumed contractile forces within and/or directly underlying the healing wound. One-half of each wound served as an internal control and was injected with sterile saline solution on the day of surgery. Clinical scar evaluations were made using the standardized Vancouver Scar Scale (VSS) and a patient scar self-rating scale at 2-weeks, 8-weeks, and 3-months post-operatively. Histologic outcomes were assessed with incisional biopsies at 3 months post-operatively.
**target n, still enrolling subjects at this time (through April, 15 2007)*