POSTER #1

PROGNOSTIC SIGNIFICANCE OF NUCLEAR SOX4 EXPRESSION IN CUTANEOUS MELANOMA AND ITS ROLE IN CELL MIGRATION

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Sry-related high-mobility group (Sox) family of genes are involved in various physiological processes including embryonic development and differentiation. Deregulated expression of Sox4 has been reported in several human cancers; nevertheless the expression and possible function of Sox4 in human melanoma progression is yet to be identified. We examined the expression of Sox4 protein in different stages of melanocytic lesions and its role in melanoma cell proliferation and migration. Using tissue microarray and immunohistochemistry, we evaluated Sox4 protein expression in 43 dysplastic nevi, 89 primary melanomas, and 48 metastatic melanomas. We observed a marked reduction in nuclear Sox4 expression in malignant melanomas compared with dysplastic nevi ($p < 0.05$) and Primary melanomas ($p < 0.01$). Moreover, the reduced Sox4 expression was significantly correlated with a poorer disease-specific 5-year survival of patients ($P = 0.039$). Multivariate Cox regression analysis revealed that reduced nuclear Sox4 expression is an independent prognostic factor to predict patient outcome ($p = 0.049$). We also knocked down the expression of Sox4 in MMRU human melanoma cell line and analyzed the migratory capability of the cells as well as their proliferation rate. Sox4 knockdown augmented the migration ability, but did not affect the proliferation rate of melanoma cells. Our results suggest that Sox4 may inhibit melanoma cell migration and metastasis and could be used as a novel prognostic marker and a potential therapeutic target for human melanoma.

POSTER #2

PROGNOSTIC SIGNIFICANCE OF BRMS1 EXPRESSION IN HUMAN MELANOMA

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BRMS1 (Breast Cancer Metastasis Suppressor) has been reported to suppress metastasis without significantly affecting tumorigenicity in breast cancer and ovarian cancer. To investigate the role of BRMS1 in human melanoma progression and prognosis, we used tissue microarray (TMA) to examine BRMS1 expression by immunohistochemistry in

melanocytic lesions at different stages. Our data showed that BRMS1 expression is significantly decreased in metastatic melanoma compared with primary melanoma or dysplastic nevi ($P = 0.021$ and 0.001, respectively, χ^2 test). There is no significant difference for the expression of BRMS1 between dysplastic nevi and primary melanoma ($P = 0.057$, χ^2 test). Reduced BRMS1 staining is significantly correlated with AJCC stages ($P = 0.011$, χ^2 test), but not associated with tumor thickness, tumor ulceration and other clinicopathological parameters. Furthermore, BRMS1 expression is significantly correlated with disease-specific 5-year survival of melanoma patients ($P = 0.007$, log-rank test). Multivariate Cox regression analysis also revealed that BRMS1 staining is an independent prognostic factor for melanoma patients (relative risk = 0.51; confidence interval = 0.29 to 0.91; $P = 0.022$). Moreover, our in vitro studies showed that BRMS1 inhibited the growth and tube formation of endothelial cells by suppressing IL-6 expression. In addition, our in vivo studies confirmed that BRMS1 inhibited blood vessel formation by matrigel plug assay. Taken together, BRMS1 expression is decreased in metastatic melanomas and it inhibits angiogenesis in melanoma. BRMS1 may be used as an important prognostic marker and potential therapeutic target for melanoma.

POSTER #3

USING NAIL CORTISOL TO MEASURE ACCUMULATED STRESS HORMONES IN MALE AND FEMALE STUDENTS

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Background: Abnormalities in both cortisol and dehydroepiandrosterone (DHEA) have been reported in psychiatric disorders. Analysis of blood, saliva and urine cortisol provides an index of hormone levels over a short time period. In contrast, stress hormone levels, deposited in hair fiber as it forms, can be used to analyse long term stress levels. However, individuals may be reluctant to provide hair samples for analysis due to social or religious reasons. Further, study of newborns may not be possible as there can be a time delay between birth and significant hair growth. Fingernails incorporate endogenous hormones that passively diffuse to the nail matrix from capillaries during nail keratinization. This study piloted the measurement of cortisol and DHEA levels in fingernails as a potential measure of their accumulated secretion of steroid hormones over a prolonged time period. Method and Results: 33 university students (18-24 years) provided fingernail samples on two occasions over a school semester. The visits were scheduled so nail cortisol and DHEA levels were collected from periods when students might be under different levels of stress. During the putatively stressful (examination) period, the nail samples showed a significant increase

in the cortisol: DHEA ratio (p=0.001). Conclusions: This pilot study showed that nails can be used to measure cortisol and DHEA, a measure which may reflect environmental stress. More work is required to further validate this technique. Clinical Significance and KT: Pilot study where analysing stress hormones in nails may enable long term monitoring of individuals when hair samples are unavailable.

POSTER #4

CUTANEOUS SECONDARY OXALOSIS

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Secondary hyperoxaluria, also known as secondary oxalosis, occurs when the kidney cannot adequately excrete calcium oxalate, resulting in its deposition in extra-renal tissue, including the skin. The causes of secondary hyperoxaluria include primary hyperoxaluria, ingestion of certain substances, and diseases that modify excretion of calcium oxalate, such as chronic renal failure and malabsorption due to intestinal bypass surgery. Clinically, cutaneous oxalosis is varied in morphology and depends on the site of calcium oxalate deposition. Intravascular deposition causes vascular insufficiency and results in livedo reticularis, acrocyanosis, Raynaud's phenomenon, peripheral gangrene, ulcers and necrosis. Extravascular deposition results in miliary deposits, and both dermal and subcutaneous nodules. Under the microscope, calcium oxalate appears as von Kossa stain positive, birefringent crystals in the blood vessel walls, reticular dermis, and subcutaneous fat. Treatment consists of therapy targeted towards the underlying secondary oxalosis and the ulcer itself. Thus, reducing levels of calcium and general, conservative wound care measures are the mainstays of treatment. A 30-year review of available pathology reports from the Vancouver General Hospital revealed 18 cases of secondary hyperoxaluria. Two cases of cutaneous oxalosis were found. Both patients were morbidly obese adults who had similar underlying conditions that included hemodialysis-dependent renal failure and intestinal bypass surgery for weight loss with subsequent malabsorption. They both presented with persistent leg ulcerations that were refractory to conservative treatment. The diagnosis of cutaneous secondary oxalosis should be considered in those who have cutaneous signs of vascular insufficiency and co-existing renal failure or previous intestinal bypass surgery.

POSTER #5

SAYING "NO" TO CHRONIC WOUNDS: A CLINICAL TRIAL ON THE REDUCTION OF BACTERIA (INCLUDING MRSA) IN MRSA POSITIVE WOUNDS

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Chronic wounds colonised with bacteria, especially if the colonising organisms are organized into a biofilm are known to heal at a slower rate. Over the years the use of antibiotics in the treatment of such wounds contributed to the emergence of resistant organisms such as methicillin resistant *Staphylococcus aureus (*MRSA). Nitric oxide (NO) has been shown to be bactericidal towards various organisms. Previous *in vitro* and *in vivo* animal models have shown antibacterial effects of direct application of 200 ppm gaseous nitric oxide (gNO) on common bacterial strains contributing to wound infections, as well as significant biofilm reduction and promotion of wound healing in a single human subject. The purpose of this study was to investigate the effect of topically applied gNO on bacterial burden reduction, in chronic wounds. gNO at 10,000 ppm was be applied topically to colonized wounds for 30 minutes for 3 consecutive days. Efficacy was evaluated by measuring the number of subjects in whom a minimum of 3-Log reduction of total bacteria, including MRSA, has been confirmed through comparison of punch biopsy cultures of their wounds from day 1 and day 3 of the trial. 1% topical gNO has shown to have bactericidal activity in chronic wounds, however the extent of bacterial kill did not correlate with animal studies. There were no reportable toxicities and NO was found to be safe in human subjects. In summary, although 1% topical gNO did not lead to complete resolution of chronic wounds it contributed to marked clinical improvement.

POSTER #6

LOSS OF INTEGRIN αVβ6 CAUSES ENHANCED KERATINOCYTE PROLIFERATION AND RETARDED HAIR FOLLICLE REGRESSION IN VIVO

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Integrin αvβ6 is an epithelial-specific receptor that binds and activates latent transforming growth factor-β1 (TGF-β1). TGF-β1 has been implicated as an endogenous inducer of hair follicle regression during hair cycling. We found that β6 integrin knock-out (β6-/-) mice exhibited an accelerated wound repair and increased number of proliferating hair follicle keratinocytes compared to wild-type (WT) controls in a

compromised wound healing model. This was associated with a reduced level of TGF-β1 activation. Therefore, we hypothesized that αvβ6 integrin-mediated TGF-β1 signaling regulates hair regeneration and hair follicle involution process. A standardized mouse model of depilation-induced hair cycling was established in WT and β6-/- mice. The expression and distribution of αvβ6 integrin, keratinocyte proliferation, TGF-β1 expression and activation were studied during hair cycle stages using immunohistochemistry and western blotting. Integrin αvβ6 was strongly upregulated during hair regeneration and its expression was hair cycle stage dependent. The β6-/- mice presented with accelerated hair regeneration and a significant delay of hair regression compared to WT controls. β6-/- follicles contain higher numbers of proliferating keratinocytes than WT follicles at an identical stage. In addition, β6-/- follicles displayed reduced levels of TGF-β1 and phospho-Smad2 during early anagen and the onset of catagen development compared to WT controls. Deletion of αvβ6 integrin caused enhanced keratinocyte proliferation and delayed hair follicle regression in vivo, which is associated with reduced TGF-β1 expression and activation in β6-/- follicles. Clinical Significance and KT: Suppressing αvβ6 integrin expression may provide a useful therapeutic tool for human hair growth disorders. Study category: (3) Applied/functional experiments.

POSTER #7

DEFICIENCY IN NUCLEOTIDE EXCISION REPAIR (NER) FAMILY GENE ACTIVITY IS ASSOCIATED WITH NON-PIGMENTED HAIR FIBER GROWTH

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The regulation of melanogenesis and the growth and pigmentation of hair fibers are affected by numerous intrinsic factors including general metabolism and nutritional status, hair-cycle dependent changes, body location, racial and gender differences, hormone-responsiveness, genetic defects and age-associated changes. The hair follicle bulb (HB) is the only site of pigment production for the hair shaft and melanogenically active melanocytes are located in the upper hair matrix (UH). We conducted a microarray study to discover gene expression patterns unique to non- pigmented hair follicles (HF) that may be implicated in the lack of melanogenesis in gray hair. Pigmented and non-pigmented HFs (n=10-20 per group) collected from the same individuals (n=6) were micro-dissected and transected into the lower one third and hair bulb and upper, non-bulbar, hair matrix and sheaths including the bulge region. Microarray data was verified with qPCR and immunohistochemistry. In comparison to pigmented UH and HBs, several nucleotide excision repair (NER) family genes exhibited statistically significantly lower expression both in non- pigmented UH and

non-pigmented HB. These genes were identified as *ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, *ERCC6*, *XPA*, *NTPBP*, *HCNP*, *DDB2* and *POLH*. Immunohistochemistry showed consistent results. Our results suggest that losing NER gene function may be consistent with melanocyte DNA damage accumulation and a lack of melanin production in gray hair. These results offer a new insight into the molecular changes in non-pigmented HF and may also provide information on melanogenesis. Clinical Significance and KT: Further research may improve understanding of gray hair and methods to treat it.

POSTER #8

THE USE OF NOVEL HOLLOW MICRONEEDLES FOR TRANSCUTANEOUS DELIVERY OF VACCINES TO THE SKIN

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The skin is our first line of defense against external pathogens as it provides a physical barrier to the environment. It is also the home to dendritic cells and other specialized antigen-presenting cells (APCs), which play important roles in our second line of defense when the physical barrier is breached. These antigen-presenting cells are responsible for presenting foreign antigens to, and activating T cells. Manipulation of APCs to modulate immune responses to immunization has been a focus in vaccinology. Due to high frequencies of APCs present in the skin, our laboratory is interested in using the skin as a site for immunization. We have shown that topical application of CpG oligodeoxynucleotides (ODN) as adjuvants is superior to subcutaneous application for inducing an immune response to the model antigen OVA. However, mechanical and/or chemical disruption of the stratum corneum barrier is needed for the large CpG ODN molecule to penetrate through the skin for topical application. Here, we propose to use hollow microneedles to directly by-pass the stratum corneum and deliver these molecules into either the epidermal or the dermal layers of the skin. Currently, experiments are being designed to detect the efficacy of microneedle administration using fluorescent latex beads and dyes. As the length of the microneedles does not reach the depth of sensory nerves under the skin, administration using these microneedles will be painless. Our long term goal is to develop these microneedles for the delivery of antigen and/or adjuvant into the skin for effective and painless vaccination.

POSTER #9

OVER EXPRESSION OF SEZARY SPECIFIC GENES IN MYCOSIS FUNGOIDES SKIN BIOPSIES

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Background and Objectives: Mycosis fungoides (MF) and its leukemic variant, Sezary syndrome (SS), are the most common cutaneous T cell lymphomas (CTCL), with their diagnosis remaining a major challenge in clinical practice due to the lack of specific and sensitive markers. Our previous study revealed a number of Sezary cell specific genes (SSGs) by high-density DNA microarray analyses. The purpose of this study is to evaluate if these SSGs are also found in earlier staged MF skin lesions. Materials and Methods: Skin biopsies were obtained from patients with cutaneous MF (N=15), benign inflammatory dermatosis such as psoriasis and chronic dermatitis (N=15) and healthy volunteers (N=21). The mRNA was used for quantitative reverse transcriptase coupled polymerase chain reaction (RT-PCR) on the 6 most significant SSGs (SSG1 to SSG6). Results: The only two of the 6 SSGs were upregulated in cutaneous MF samples. One of them (SSG1) was up in 13 of the 15 samples where as SSG2 was upregulated in 2 of the 15 samples. Only 1 sample showed no upregulation of either one of these two SSGs. In contrast, none of the benign inflammatory dermatosis or normal skin biopsies showed up-regulation of these two genes. Conclusions: Only a small proportion of SSGs were present early in the cutaneous MF skin biopsies. Further, SSG1 may serve as a potentially useful marker for early diagnosis of MF.

POSTER #10

BASAL CELL CARCINOMAS EXPRESS FUNCTIONAL INDOLEAMINE 2,3-DIOXYGENASE (IDO) WHICH MAY CONFER IMMUNOPROTECTION

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Basal cell carcinoma (BCC) is the most common malignancy in humans worldwide. BCCs can derive from hair follicle (HF) bulge keratinocytes; which may exhibit immune

privilege (IP) and express immunoregulatory enzymes, such as indoleamine 2,3-dioxygenase (IDO). IDO suppresses T lymphocyte proliferation via tryptophan catabolism in the kynurenine pathway. We hypothesized that BCCs may also have putative IP and IDO might be involved. In this study, real-time RT-PCR identified significant upregulation of *IDO-1* and *IDO-2* (12.5- and 19.1-fold change respectively) in human nodular BCCs (n=10) as compared to non-lesional skin epithelium tissues (n=10). Dual label immunohistochemistry revealed co-localization of IDO and keratin 17 (K17), a BCC keratinocyte marker, in human BCC tissues (n=5). Western blot detected IDO (42kDa) and a 30kDa IDO-like protein in BCC tissues (n = 6). Kynurenine assay of primary human BCC cell cultures under CXCL11 treatment, which is required for BCC tumor cell growth, showed increased L-kynurenine production in the conditioned medium. In conclusion, the upregulated expression of *IDO-1* and *IDO-2*, the co-expression of the peptide with K17, as well as the IDO-mediated L-kynurenine production in human BCC cell cultures, provide further evidence of functional IDO synthesis by BCCs during their growth. Clinical significance and KT: our research may suggest that treatment to suppress IDO may induce a local collapse of IP in BCC tumors, which in turn may be a novel strategy for BCC treatment and regression.

POSTER #11

MULTIPLE BIOMARKERS AND OUTCOMES IN HUMAN MELANOMA: A CLINICOPATHOLOGIC STUDY OF 150 CASES

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Background: Melanoma is the most lethal form of skin cancer. Previously we investigated the expression of 11 biomarkers in nevi and melanoma. Here, we compared the expression of each biomarker between different stages of melanoma and determined the best combination of biomarkers for melanoma early diagnosis and prognosis. Methods and Findings: We combined the expression of 11 biomarkers (Akt, Bim, BRG1, BRMS1, CTHRC1, ING4, NQO1, NFkB-p50, PUMA, SNF5, and Sox4) in 32 dysplastic nevi, 73 primary melanomas, and 45 metastatic melanomas and analyzed the expression variation of each biomarker between different stages of melanoma. The expression of BRG1, ING4 and PUMA were significantly changed in AJCC I of primary melanoma compared with dysplastic nevi ($P < 0.05$). The 3-marker index score showed more significant difference between dysplastic nevi and AJCC I melanoma ($P < 0.0001$). Six biomarkers (Bim, BRMS1, ING4, NQO1, PUMA, and Sox4) showed significantly decreased expression in AJCC III and IV stages of melanoma compared with AJCC I and II stages ($P < 0.05$), while 6-marker index score exhibited higher variations between AJCC I-II and AJCC III-IV stages than any individual one. In addition, the 6-marker

index score led to better prediction of patients' survival. Furthermore, Cox multivariate regression analysis showed that this 6-marker index score is an independent prognostic indicator in human melanoma. Conclusions: Combination of BRG1, ING4 and PUMA can be applied to early diagnosis, while Bim, BRMS1, ING4, NQO1, PUMA, and Sox4 6-marker system can deliver more accurate prognosis for melanoma patients.

POSTER #12

A SUPPRESSIVE ROLE OF INHIBITOR OF GROWTH 3 (ING3) IN MELANOMA CELL MIGRATION

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The novel tumor suppressor ING3 plays crucial roles in the regulation of gene transcription, cell cycle progression and apoptosis. Our previous studies demonstrated that the nuclear ING3 was remarkably reduced in malignant melanomas, and that was correlated with the progression from dysplastic nevi to metastatic melanoma and also correlated with a poorer disease-specific survival of patients with primary melanoma. However, the underlying mechanisms regarding the role of ING3 in the progression of melanoma remains unknown. Here we showed that knockdown of ING3 using siRNA significantly enhanced MMAN cell migration, while overexpression of ING3 led to inhibition in MMRU cell migration. Analysis of gene encoding ING3 using cDNAs generated from 10 melanoma cell lines indicated multiple mutations in Sk-110 cell line, however, only the 652T/A mutation resulted in an alteration in amino acid (218 serine/threonine) of ING3 protein. So far, our results suggest that ING3 may play a suppressive role in melanoma cell migration, and ING3 mutation may also play a role in melanoma tumorigenesis. For the future plan, we will identify the molecular mechanism involved in the suppressive role of ING3 in melanoma cell migration, and determine the role of ING3 in angiogenesis in vitro and in vivo and the mechanism involved.

POSTER #13

RAMAN MICROSPECTROSCOPY SYSTEM AND ITS BIOMEDICAL APPLICATION

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Raman microspectroscopy is one tool that could provide useful insights on the pathophysiologic processes within biological tissue. As compared to conventional Raman spectroscopy, the microscopic technique can give more precise spatial information as to where the molecular changes may have occurred, due to the relatively small excitation spot that is used. The other advantage of Raman microspectroscopy for *in vitro* studies is that it requires minimal sample preparation. Nevertheless background autofluorescence from the optical system and glass specimen slides interfere with spectral acquisition. We have designed a novel method for building an economical and versatile Raman microspectroscopy system. The conventional normal illumination is replaced by an oblique illumination at 45 degrees and the glass slide is coated with gold. These modifications substantially reduce unwanted background signals arising from the slides and within the optical system. With this special excitation configuration, Raman scattering events have been enhanced in the sample and the background autofluorescence of the system has been successfully avoided during the measurement. Its sensitivity and resolution depend on the diameter of optical fiber used in the system. Raman spectra from the major layers of normal skin (stratum corneum, epidermis, dermis, and subcutaneous fat) have been obtained. Near IR fluorescence imaging is also incorporated into this system, which is acquired by a computer controlled CCD camera. Clinical Significance and KT. This device should be useful for determining the biophysical basis for *in vivo* cutaneous Raman spectroscopy and *in vivo* near IR autofluorescence, two tandem techniques which are currently under systematic investigation by our group for skin cancer detection and evaluation.

POSTER #14

CONFOCAL RAMAN SPECTROSCOPY OF CULTURED CELL MODEL REVEALS SPECTRAL BIOMARKERS

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Raman spectroscopy (RS) measures molecular vibrations and provides data-rich, fingerprint-type signatures for collagen, blood, lipids, proteins, and nucleic acids. We have developed a non-invasive integrated system that combines confocal microscopy techniques with RS to analyze skin micro-structures *in vivo* at different depths. The purpose of this pilot study is to evaluate the potential of this confocal RS system for biochemical analysis of cultured cells. The confocal RS system consisted of a single mode-stabilized diode laser (785 nm, 100mw) for excitation, confocal optics and a

Raman spectrometer. Cultured HaCaT cells were prepared on fused silica coverslips using Cytospin and analyzed under confocal RS system. Confocal images of cell morphology could be clearly obtained. Peaks at 1450, 1308/1339, 1065, 1003, 936, 855, 622/644 cm^{-1} were assigned to various nucleic acids and amino acids. The intracellular spectral variability was low and the intensity of Raman spectrum was positively correlated to spectral acquisition time. Clinical Significance and KT: The findings of consistent spectral signatures of HaCaT cells from this pilot experiment encourage us to further utilize confocal Raman spectroscopy as a label-free tool for biochemical analysis and detection of cancer cells and stem cells in the skin.

POSTER #15

AN ASSESSMENT OF UNDERGRADUATE DERMATOLOGY PERFORMANCE AT THE UNIVERSITY OF BRITISH COLUMBIA

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The Faculty of Medicine at the University of British Columbia has a four-year long medical undergraduate program. Students are geographically distributed among three sites, the University of British Columbia, University of Victoria, and University of Northern BC. Dermatology is taught in second and third year. The second year, pre-clinical dermatology curriculum includes one week of problem-based learning, lectures, clinical skills sessions, and dermatopathology seminars. The third-year clinical curriculum consists of one week of outpatient clinics, teaching-hospital based consults, lectures, and small-group teaching sessions. This format is replicated at all three sites in a similar fashion to ensure consistency and standardization. The research proposal explores the following questions: 1) What is the 10-year trend in student results for a standardized assignment in clinical dermatology clerkship? 2) How do the questions in the assignment map to the expected objectives of the clerkship? 3) How do standardized assessment scores in pre-clinical dermatology correlate with standardized assessment scores in clinical dermatology clerkship? 4) How do scores in dermatology compare among geographically distributed sites of the same medical school? Ethical approval will be sought to obtain access to student marks and these will analyzed to answer the above questions. The results of this research will yield valuable information on the quality of pre-clinical teaching, student assessments, and clinical instruction at each of the three sites. Based on these pending results, the curriculum and examinations may need to be modified.

POSTER #16

INVESTIGATION ON THE EFFECTS OF HPA HORMONES IN THE ONSET AND PROGRESSION OF ALOPECIA AREATA

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Stress and stress hormones may play an important role in the onset and persistence of alopecia areata (AA). In previous studies, skin graft induced AA mice had a marked increase in hypothalamic–pituitary–adrenal (HPA) tone and activity centrally and peripherally. This suggested mice with AA had significantly increased levels of stress. In the current study, we will investigate hormone response within the central and local HPA axis before AA onset and during AA development. AA-grafted (n=18) and sham-grafted (n=18) C3H/HeJ mice will be examined at 2, 4, 6, 8, 10 and 12 weeks after surgery. Plasma corticosterone (CORT) will be determined by RIA and gene expression in brains, lymph nodes, and skin will be measured by quantitative RT-PCR for HPA hormones, receptors and cytokines (IFN-γ, IL-1, IL-17, etc). In experiment 2, adrenalectomy (ADX) will be performed in normal female C3H/HeJ mice (n=36). Sham operated age-matched animals (n=12) will be used as controls. CORT replacement at low or high basal levels will be performed using CORT pellets implanted subcutaneously. Skin grafting with AA affected skin will be carried out 2 weeks after ADX surgery. Onset frequency and severity (percentage extent) of AA will be recorded and we will correlate clinical data with CORT levels in individual animals. HPA hormones and cytokines will also be measured as in experiment 1. Clinical significance and KT: Our project will elucidate the role of stress hormones in the pathogenesis of AA especially the importance of CORT in the onset and severity of AA.

POSTER #17

IMMUNE PRIVILEGE IN HAIR FOLLICLES

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The hair follicle from below the bulge region to the bulb likely has immune privilege (IP) during the anagen growth phase including; reduced MHC Class I expression, decreased presence of antigen presenting cells, and no lymphatic system. My proposed project is to investigate hair follicle IP. Quantitative RT-PCR (qPCR) on microdissected human hair follicle bulbs and shafts in our laboratory revealed that immunosuppressive agents TGF-

β2, αMSH, and MIF are significantly upregulated in the hair shaft portion (fold change 7.99, 4.26, 2.49 respectively). The complement regulator CD59 was significantly downregulated in both the bulb (0.18) and shaft (0.28). Cell surface markers CD80 (0.19), CD86 (0.24), Fas (0.38), and Fas ligand (0.01) were all significantly downregulated in the bulb consistent with immunoregulation and putative IP. The next step will be to conduct qPCR on several more IP associated genes. These will include genes such as MICA, CD200, β-2-microglobulin, and several HLA genes. Subsequently, I will conduct immunohistology on human hair follicles to determine gene product expression distribution. Later, I plan to do qPCR on dermal sheath cells and dermal sheath cup (DSC) cells to look for gene expression differences. Also, I plan to culture DSC cells and implant them into genetically incompatible mice to determine the functional impact of IP associated gene product expression. Our goal is to elucidate the functional mechanism of IP in hair. Clinical significance and KT: If this mechanism is discovered, it may have implications for inflammatory hair loss diseases and beyond the hair follicle, in tissue transplantation.

POSTER #18

TOPICAL SODIUM THIOSULFATE: AN EFFECTIVE TREATMENT FOR CHRONIC LEG ULCERS COMPLICATED BY DYSTROPHIC CALCIFICATION

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Introduction: Dystrophic calcification is a rare complication of leg ulcers, which can lead to significant patient morbidity, pain, and ultimately, poor wound healing. Spontaneous resolution is rare and multiple therapies are usually attempted with minimal efficacy. Methods: We describe a case of an 83 year-old female with two chronic non-healing venous leg ulcers complicated by dystrophic calcification with improved wound healing treated with topical sodium thiosulfate 10% over a five-month period. Dermatologic exam revealed two large ulcers with poor granulation tissue, significant biofilm and calcium deposits within the base. Radiographic studies revealed prominent subcutaneous calcification. Patient consent was obtained to publish clinical photographs for this case report. Initial management included wound debridement, Mepilex® absorbent dressings, and Duke boot compression therapy with minimal improvement. A literature review revealed potential clinical efficacy with topical sodium thiosulfate in a published case report of leg ulcers with dystrophic calcification. We, therefore, initiated biweekly topical sodium thiosulfate 10% solution, 10-20 drops at the base of the ulcer and dressed with a moisture-retention dressing. Concurrent therapy with Mepilex® foam and Duke boot compression resulted in significant clinical improvement over a five-month period. Topical sodium thiosulfate was well-tolerated with no adverse effects reported by the patient. Conclusion: Chronic wounds complicated by dystrophic

calcification are rare and are potentially recalcitrant to conventional therapies resulting in significant patient morbidity. Topical sodium thiosulfate led to calcium dissolution, resulting in improved wound healing in our patient with no reported adverse effects. Topical sodium thiosulfate treatment of dystrophic calcification in wounds warrants further study.

POSTER #19

ESTABLISHMENT OF AN *IN VITRO* SKIN FIBROTIC MODEL USING SILICA GEL BEADS

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Fibrosis is a pathological process that includes scar formation due to an imbalance in extracellular matrix production and degradation as a response to tissue damage. Although a number of animal fibrotic models have been developed and employed to demonstrate the efficacy of compounds which may inhibit or reduce fibrosis, a majority of these compounds have yet to produce clinically comparable results to those found in the animal model. The reason for the difference is that these models lack a distinction between compounds interfering with inflammatory and early antifibrotic response. Therefore, a suitable, quantitative *in vitro* model which lacks inflammation is absolutely needed for the screening of antifibrotic agents. In this study, we reported that silica gel, a compound that is known to cause silicosis in mineral workers, could be used as a simple, fibrotic model *in vitro*. In this model, we found that silica induces skin fibroblasts to aggregate and form a nodule-like structure surrounding the particle in either 2D or 3D culture system. Further analysis revealed that silica could induce collagen and fibronectin expression, while down-regulate metalloproteinase-1 and -3 (MMP-1 and MMP-3) expression in skin fibroblasts. Two compounds including 5-fluorouracil which is used for hypertrophic scar treatment in clinic, and interleukin-1β which is known as an inducer of MMPs, were tested in this model and revealed some antifibrotic activity through either inhibiting fibroblast proliferation or inducing MMPs expression. Thus, the silica gel model may provide a suitable, convenient, and reliable *in vitro* fibrotic model for therapeutic invention in fibrotic diseases.

POSTER #20

KERATINOCYTE REGULATION OF AMINOPEPTIDASE N/CD13 EXPRESSION IN FIBROBLASTS

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Introduction: Following the inflammatory phase of wound healing, cellular interactions become dominated by the interplay of keratinocytes with fibroblasts, which greatly impacts the molecular constitution of the extracellular matrix (ECM). In this study, we examined the influence of keratinocyte co-culturing and keratinocyte-releasable factor stratifin on the expression and catalytic activity of aminopeptidase N (APN)/CD13. Methods: Dermal fibroblasts were co-cultured with primary human keratinocytes or incubated with various concentrations of purified recombinant stratifin protein, and the expression and catalytic activity of APN/CD13 in fibroblasts was detected by Western blot analysis and *in vitro* aminopeptidase activity assay, respectively. Results: When co-cultured with proliferating keratinocytes, fibroblasts were stimulated to synthesize APN/CD13, and the stimulation was more prominent by differentiated keratinocytes. Further, the expression and enzymatic activity of APN/CD13 was induced by stratifin, an MMP1-stimulating factor released by keratinocytes. Clinical Significance and Knowledge Translation: Studies using immune cells and endothelial cells have shown that APN/CD13 participates in cell adhesion and migration, differentiation, proliferation and apoptosis, chemotaxis, and angiogenesis, many of which may also impact the wound healing process when applied in the context of the skin. The present study shows keratinocytes regulate the fibroblast expression of APN/CD13, suggesting that APN/CD13 may function as signal regulator in delivering keratinocyte-mediated ECM modulation by fibroblasts. Understanding the regulation of APN/CD13 will help us to learn more about epidermal-mesenchymal interactions and find therapies for ECM-related skin diseases.

POSTER #21

CUL1 EXPRESSION IS INCREASED IN EARLY STAGES OF HUMAN MELANOMA

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As the largest family of ubiquitin–protein E3 ligases, the SCF (Skp1/Cullin/Rbx1/F-box protein) complexes ubiquitinate a broad range of proteins involved in cell cycle progression, signal transduction and transcription. Cullin1 (Cul1) serves as a rigid

scaffold in SCF complex for Rbx1, Skp1 and F-box protein subunits assembly and aberrant expression of Cul1 is involved in dysfunction of SCF E3 ligases. To investigate the role of Cul1 in the development of melanoma, we examined the expression of Cul1 in melanocytic lesions at different stages and analyzed the correlation between Cul1 expression and clinicopathologic parameters by tissue microarray and immunohistochemistry. The result showed that Cul1 expression was significant increased in primary and metastatic melanoma compared with dysplastic nevi, while there was no significant difference of Cul1 expression between primary and metastatic melanoma, which suggested that Cul1 plays an important role in the initiation stage of melanoma development. We found knockdown of Cul1 inhibited melanoma cell growth and overexpression of Cul1 promoted melanoma cell growth through regulating cyclin dependent kinase (CDK) inhibitor p27 expression. Knockdown of Cul1 abrogated Skp2-induced p27 degradation in melanoma cells. These results suggested that Cul1 is involved in cell cycle regulation of melanoma cells via Cul1-dependent ubiquitination and degradation of the p27 by SCF^{Skp2} complex. In conclusion, our data indicate that Cul1 may serve as a potential marker for human melanoma initiation and early diagnosis.

POSTER #22

EMU OIL HAS AN EFFECT ON GROWTH RATES OF KERATINOCYTES *IN VITRO*

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Emu oil is oil derived from the fat of an emu – a large, flightless bird native to Australia. Traditionally, native aborigines of Australia have used emu oil as an ointment for the treatment of burns, scrapes, and to accelerate wound healing. Although no studies thus far show an effect on humans, previous studies on mice suggest that emu oil, when applied topically, may have anti-inflammatory properties and may promote wound healing. We further invested the effects of emu oil on immortalized human keratinocytes (HaCaT cells) *in vitro* by culturing the cells in media with trace amounts of the oil at 37°C. At two different emu oil concentrations of 0.5% and 1.0%, HaCaT cells appeared to have a significantly shorter average cell population doubling time (1.18X shorter) than those grown without oil. In addition, HaCaT cells cultured in other oils also showed shorter doubling times to varying degrees. Ostrich oil (1.25X shorter) and rhea oil (1.14X shorter) – oils from similar large, flightless birds – yielded similar results while tea tree oil and olive oil showed no significant decrease or an increase (3.08X longer) in cell population doubling time, respectively. This preliminary investigation suggests that emu oil may promote wound healing in humans by accelerating the growth rate of keratinocytes by an unknown mechanism. Combined with potential anti-inflammatory

properties, emu oil may serve as a useful component in bandages and ointments for the treatment of skin wounds.

POSTER #23

BULLOUS PEMPHIGOID ASSOCIATED WITH ACQUIRED HEMOPHILIA A: A CASE REPORT

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Acquired hemophilia is a rare autoimmune disease with an annual incidence of one per million. It has a mortality rate of up to 20%. It is caused by the development of autoantibodies against factor VIII. In approximately 50% of cases, no apparent underlying disease is identified. About half of the reported cases are associated with pregnancy, malignancies, adverse drug reactions, and autoimmune diseases. Autoimmune diseases are the most frequently associated with acquired hemophilia including rheumatoid arthritis, systemic lupus eryhtematosus, cryoglobulinaemia, pemphigus vulgaris and bullous pemphigoid. There are only few reports on the association with bullous pemphigoid. We report a 73-year-old male who presented with cutaneous blistering, upper gastrointestinal bleeding, and hemoptysis. Skin biopsy showed changes consistent with bullous pemphigoid. He was found to have prolonged Partial thromboplastin time, low factor VIII level, and high factor VIII inhibitor level. He was treated with multiple immunosuppressive medications including prednisone, cyclophosphamide, and rituximab, in addition to intravenous immunoglobulin. We also reviewed the literature on this rare association.

POSTER #24

A NOVEL METHOD FOR DETECTION AND CLASSIFICATION OF PIGMENT NETWORK IN DERMOSCOPIC IMAGES

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Analyzing pigment network (PN), a mesh of brown lines appearing in a skin lesion, is an important step in diagnosing skin cancer. The objective of this study is to develop a computerized method to detect, classify and visualize PN in dermoscopic images of skin lesions. Based on the fact that PNs are brown lines surrounded by light-brown holes, our

approach has two complementary steps: a hole detector and a net extractor. First we perform a preprocessing step of image enhancement and edge detection. The resultant binary edge image is converted to a graph, and holes are extracted by finding cyclic subgraphs corresponding to skin texture structures. We filter these cyclic subgraphs to remove other round structures such as globules, dots, and oil bubbles, based on their size and color A Laplacian of Gaussian filter captures the sharp changes of color in pigmentation and extracts the initial approximation of the network. Using the extracted holes and nets, a feature vector is then created which will further delineate the network and classify it into 2 classes of Typical and Atypical. Testing our method over a set of 500 images from a dermoscopic atlas showed a 94.3% accuracy on the 2-classes: Absent PN, or Present PN (Typical or Atypical), using solely the characteristics of the holes. Currently, we are improving the accuracy by incorporating the characteristics of network lines. Clinical Significance and KT: Applied experiments. Our fully automated pigment network analyzer could be used in a computer-aided diagnostic system for skin cancer.

POSTER #25

INTEGRIN-LINKED KINASE (ILK) PROMOTES MELANOMA ANGIOGENESIS BY ACTIVATING IL-6 SIGNALING PATHWAY

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Integrin-linked kinase (ILK) is a highly conserved serine-threonine protein kinase involved in cell-ECM interactions, cytoskeletal organization, and cell signaling. Overexpression of ILK in epithelial cells leads to anchorage-independent growth with increased cell cycle progression. Previously, we have shown that ILK upregulation strongly correlates with melanoma progression, invasion and inversely correlates with 5-year survival of melanoma patients. However, the molecular mechanism by which ILK enhances melanoma angiogenesis is currently unknown. In the present study, we found that pro-angiogenic molecule interleukin-6 (IL-6) is the downstream transcriptional target of ILK in melanoma cells. ILK overexpression increased IL-6 whereas silencing of ILK suppressed IL-6 expression both transcriptionally and translationally. By electromobility shift assays, we found that ILK enhanced the binding of transcription factor (NF-κB) to IL-6 promoter and this binding was reduced in ILK knockdown cells. Furthermore, Conditioned media (CM) from ILK- overexpressing cells enhanced the tube forming ability of HUVEC cells *in vitro*. This tube formation by HUVEC cells was IL-6 dependent as CM from IL6-siRNA treated ILK-overexpressing melanoma cells inhibited the tube formation of HUVEC cells. In order to delineate the mechanism by which ILK-upregulated IL-6 can enhance the growth of endothelial cells, further analysis of the downstream targets of IL-6 signaling showed an increase in activity and nuclear

translocation of STAT3 in ILK-overexpressing cells. As STAT3 binds to VEGF promoter, we found that VEGF levels were elevated in ILK-overexpressing cells and declined in ILK knockdown cells, suggesting that ILK may regulate VEGF expression through IL-6 pathway by upregulating and activating STAT3.

POSTER #26

FABRICATION OF DURABLE SILICONE SKIN PHANTOMS FOR LASER SPECKLE TECHNOLOGY

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When skin is illuminated by a low coherent laser, the laser speckle pattern retrieved contains information on surface roughness and intrinsic optical properties. Laser speckle technology could be useful for skin roughness evaluation and skin lesion differentiation. A suitable skin phantom with controllable surface roughness and intrinsic optical properties is thus needed for the calibration of the speckle device. Objective: Our study aim is to construct durable skin phantoms with known surface roughness, absorption and scattering coefficients. Methods: Silica microspheres, controlling the scattering of the phantom, were added to silicone resin and dispersed in resin-hexane mix using ultrasonic bath. The catalyst was added after hexane evaporation and air bubbles were removed using a vacuum. The microsphere-resin-catalyst mix was then cured on a metal standard base with various roughness values. Pigmented powder was added during the process to control the absorption of the phantom. Results: We successfully created silicone skin phantoms with embedded silica microspheres at desired concentrations and standard surface roughness values. Using confocal microscopy we obtained images of the phantoms and confirmed that the silica microspheres within are randomly and well distributed. We are currently testing the physical properties of the phantoms. Clinical Significance and Knowledge Translation: This process of skin phantom fabrication produces phantoms that simulate the tissue properties desirable in laser speckle measurements, and potentially other imaging techniques. This would provide a potential new method for quality control in the technology currently used for tissue imaging, and help model the performance of newly developed optical equipment.

POSTER #27

DEVELOPMENT OF ALOPECIA AREATA MAY BE ASSOCIATED WITH HEART DISEASE

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Alopecia areata (AA) is a non-scarring, inflammatory hair loss disease that is believed to involve an autoimmune mechanism. In other chronic autoimmune skin conditions, such as psoriasis, there is evidence that affected individuals have an increased risk of coronary heart disease and heart failure. We investigated the potential for a relationship between AA and heart disease using tissues from the C3H/HeJ mouse model. We observed that the heart sizes/wet weights in 18 month old C3H/HeJ skin graft induced AA mice (n=10) were statistically significantly greater than age and sex matched normal littermates (n=11). We conducted quantitative PCR (qPCR) analysis of AA mouse heart and skin tissues for selected genes involved in apoptosis and inflammation. We observed IL18, IL18 receptor-1 (IL18r1) and IL18 binding protein (IL18bp) increased significantly by 4.6, 2.8 and 5.2 fold respectively in the heart (2.4, 3.1 and 5.2 in skin) compared to controls. It has been shown by others that IL18 levels, in both circulation and resident myocardial tissues are increased in patients with heart diseases. Experimentally, administration of IL18 increases heart mass and wall thickness which leads to cardiac dysfunction. Based on our observations, the development of AA may be associated with an increased risk of heart disease. Clinical Significance and KT: Study suggests heart disease monitoring may be required in AA patients and preventative heart disease treatment considered.

POSTER #28

TWO UNUSUAL CASES OF ALOPECIA MUCINOSA

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Background: Alopecia mucinosa (AM) or follicular mucinosis (FM) are used many times interchangeably to describe the accumulation of mucin in the follicular epithelium. FM may be preferable when the presence of mucin is not associated with alopecia. The NAHRS classified AM among the primary lymphocytic scarring alopecias. AM has been described in correlation with a variety of malignancies and benign conditions. While benign AM are more common in childhood, most cases of AM are encountered in

adults where an association with a lymphoproliferative disorder (LYPD) occurs in 30% of patients.
Methods: We report on two unusual cases of follicular mucinosis. Case #1 - a 14 y/o healthy teenager, with a seven year history of a bald spot on her scalp that had re-grown hair and reformed repeatedly. A biopsy confirmed the diagnosis of trichotillomania in addition to the presence of mucin in the follicles. Case #2- A 58 y/o woman giving a six year history of hair loss involving the hair line in a pattern typical of frontal fibrosing alopecia. Two biopsies confirmed the diagnosis of FM with a follicular non-atypical, non-lichenoid lymphoid infiltrate, which was polyclonal by PCR.
Conclusions: 1) FM may represent a secondary change in trichotillomania; 2) FM can be a mimicker of frontal fibrosing alopecia; 3) Long term f/u of adult onset FM is mandatory to exclude development into a LYPD; 4) Routine stains for mucin are important in scalp biopsies.

POSTER #29

EFFECT OF FINASTERIDE ON FEMALE PATTERN HAIR LOSS
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Objective: There is limited data regarding treating female pattern hair loss with finasteride. The objective of this project is to evaluate the efficacy of finasteride in treating female pattern hair loss using self-assessment questions, global photographs and Folliscope. Methods: Twenty-two patients with female pattern hair loss, aged 29-67, took finasteride 2.5mg per day for 9 to 12 months. The hair condition is evaluated by investigators and the patient herself. A new computer software-assisted phototrichogram (Folliscope, LeadM corporation, Seoul, Korea) is available to assess hair density and caliber. The hair caliber and hair density were recorded at baseline and the end of treatment course. The hair coverage is defined by hair caliber times hair density.
Results: There is a trend of increasing hair coverage in more than half of the patients evaluated using Folliscope and global photographs.
Conclusions: Our result showed that finasteride is effective in maintaining hair coverage. Folliscope appears to be a useful tool in evaluating treatment result for hair diseases.
Clinical Significance and KT: The findings of the study encourage dermatologists to try finasteride in patients with female pattern hair loss.

POSTER #30

JUXTATUMORAL PLASMA CELLS AS A HISTOLOGIC CLUE TO SQUAMOUS CELL CARCINOMA IN MOHS MICROGRAPHIC SURGERY

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Most cutaneous tumors have variable densities of mononuclear cell infiltrates in the surrounding stroma. Small nests or single cells of invasive squamous cell carcinoma are sometimes obscured by this dense mononuclear cell infiltrate and can make margin interpretation difficult on frozen section histopathology. Before the advent of immunohistochemistry, pathologists relied more heavily upon inflammation and the predominance of certain inflammatory cells as a clue to presence of tumor. Some of these studies have shown that a high density of plasma cells are associated with invasive squamous cell carcinoma. In an effort to examine if this has any relevance in Mohs micrographic surgery, all cases of primary invasive squamous cell carcinoma were prospectively studied in a 4 month period. We included cases of invasive squamous cell carcinoma with a significant mononuclear cell infiltrate, a prominent population of plasma cells and no discernable tumor on initial sections. We identified 5 cases where initial sections had no histological evidence of tumor and deeper tissue levels showed invasive squamous cell carcinoma in the vicinity of the plasma cell aggregates. These cases demonstrate that plasma cell aggregates may act as a surrogate marker for nearby invasive squamous cell carcinoma. In cases of suspected invasive squamous cell carcinoma, finding a significant amount of plasma cells within the infiltrate can be helpful in deciding whether a tumor may warrant an additional Mohs layer or at least a deeper level on the current block to ensure an adequate margin of resection.