INTERPOLATION FLAPS IN THE OUTPATIENT MOHS SURGERY SETTING: PATIENT COMFORT AND SATISFACTION STUDY, AN UPDATED SERIES OF 39 PATIENTS

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To date, no studies have evaluated pain, anxiety, and satisfaction in patients undergoing staged interpolation flaps (SIFs) under local anesthesia in the outpatient setting. SIFs performed under local anesthesia by dermatologic surgeons have lower or equal complication rates compared to specialties in which SIFs are typically performed under general anesthesia. The objective of this prospective, single-institution cohort study was to assess pain, anxiety and satisfaction in patients undergoing SIFs performed by Mohs surgeons. Thirty-nine patients requiring SIFs were included in the study. Pain, anxiety, and satisfaction scores were recorded using 100-point validated Visual Analog Scales (VAS). Twenty-eight patients (72%) had postoperative defects $> 4 \text{cm}^2$. Sixteen patients (41%) had full thickness defects requiring cartilage grafts and repair of the nasal mucosa. On the day of surgery (D0), mean pain (28 ± 25) and mean anxiety (41 ± 29) levels were mild (VAS<35). Mean pain and anxiety peaked at post-operative day 1 and were considered mild-tomoderate (VAS<65). Post-operative days 2-7 showed a gradual and consistent decrease in pain and anxiety back to minimal levels. Patient satisfaction was high on the day of surgery and the day of division. Mean satisfaction levels were not statistically different between D0 (94±14) and the day of flap division (96±7), (ANOVA,p=0.46), indicating that postoperative care and changes in facial appearance due to the presence of the flap pedicle before division did not alter patient's satisfaction. This analysis of patient-reported outcomes concludes that SIFs performed by Mohs surgeons under local anesthesia in the outpatient setting are well-tolerated with high patient satisfaction.

Category: Phase I/II clinical trials

COMPUTER-AIDED DRUG DISCOVERY OF SMALL MOLECULE INHIBATORS TARGETING THE TOX PROTEIN IN SKIN CANCER

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Skin cancer is the most common type of cancer, with over 80,000 cases diagnosed in Canada each year, more than 5,000 of which are melanoma, the mostly deadly form. We have recently identified Thymocyte selection-associated high mobility group box protein (TOX) as a drug target in skin cancer. There are currently no small molecules to directly inhibit TOX. We aim to address this unmet opportunity of developing anti-TOX therapeutics by utilizing a computer-aided drug discovery platform as previously established. The available NMR structure from the PDB database (ID: 2CO9) provides a protein model for the DNA-binding HMG box domain of TOX, suitable for virtual screening of millions of small molecules targeting its protein-DNA interface. To investigate the druggability of TOX, we have performed a pilot in silico screening of 200,000 small molecules using molecular docking software Glide and identified 'hot spots' for drug-binding on the HMG box domain. We then performed a full-scale virtual screening of 7.6 million drug-like small molecules that are available from the latest ZINC15 database using our established computational protocols. A total of 127 top candidate compounds have been selected for experimental validation. Preliminary experimental results have identified several potential small molecules that can inhibit the TOX protein.

Category: Early experiments with well-defined objectives/hypotheses

EVALUATION OF A TELEMEDICNE SERVICE FOR RURAL AND REMOTE BRITISH COLUMBIA

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We are developing a model of dermatology telemedicine service for rural and remote areas. This is a two-year project in collaboration with the referring rural physicians in the Northern Interior, along with the local First Nations groups and their respective health authorities (Northern and First Nations Health Authority). In regard to the evaluation of the model, we have partnered with the UBC Centre for Clinical Epidemiology and Evaluation. We intend to measure clinical effectiveness of this service compared to existing service in comparable areas. The practical question is what to measure. Obvious assays are waiting time, satisfaction with the service (as has been done for the store-and-forward service, ConsultDerm), and frequency of follow-up for the presenting problem. We will use standard measurements, such as the Dermatology Quality of Life Index, EQ-5D, and the static Global Physician Assessment, as are used in clinical trials. More difficult measurements are total cost of the service, including patient travel, time off-work, and accommodation. We will present our preliminary model of these measurements integrated into primary care practice work-flow in the test area.

Category: Early experiments with well-defined objectives/hypotheses

GRANZYME B INCREASES ATOPIC DERMATITIS SEVERITY BY IMPAIRING BARRIER FUNCTION THROUGH FILAGGRIN AND EPIDERMAL JUNCTIONAL PROTEIN CLEAVAGE

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Granzyme B (GzmB) is a serine protease minimally expressed in normal skin but drastically elevated in numerous autoimmune and/or chronic inflammatory skin diseases. While often regarded as a pro-apoptotic protease, GzmB retains its activity and accumulates in the extracellular milieu during dysregulated inflammation. Within the extracellular milieu, GzmB can cleave extracellular matrix proteins, cell adhesion proteins and key proteins within the basement membrane zone/dermal-epidermal junction. We hypothesized GzmB contributes to the onset and progression of atopic dermatitis (AD). In the present study, GzmB was abundant in human AD lesions compared to healthy skin. A causative role for GzmB was assessed in a murine model of AD, comparing GzmB-/- and wild-type (WT) mice. Significant reductions in inflammation, epidermal thickness and overall lesion incidence and severity, were observed in GzmB-/- compared to WT mice. Topical administration of a GzmB inhibitor to WT mice also reduced AD severity compared to vehicle-treated controls. Cultured keratinocyte monolayers exposed to GzmB exhibited a dose-dependent impairment of barrier function that was associated with reduced E-cadherin, desmoglein-1 and desmogelin-3. In vitro, GzmB effectively cleaved filaggrin, E-cadherin, desmoglein-1 and -3. Epidermal levels of filaggrin (stratum corneum), E-cadherin, desmoglein-1 and -3, and dermal decorin levels were all decreased in WT AD-affected mice compared to controls, while GzmB-/- and GzmB inhibitor-treated AD-affected mice displayed significantly greater levels of the aforementioned proteins. In summary, GzmB-mediated proteolytic activity contributes to reduced cell adhesion, impaired barrier function and inflammation and represents a valid therapeutic target for the treatment of AD.

Category 3: Applied/functional experiments (animal models of disease and in vivo studies, etc)

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ME-PPD HAIR DYE SENSITIVITY IN PPD SENSITIVE PATIENTS

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The Contact Dermatitis Clinic database has records for patients seen from 2008-2018 (with a clinic closure between 2015-2016). Over 2800 patients were patched tested to the American Contact Dermatitis Society (ACDS) 80 allergen screening series. 79% of patients were females and 21% were males. There was a 7% positive patch test result to *p*-Phenylenediamine (PPD), a common sensitizer in hair dye products in this population, which is similar to a US study which found a 6.8% positive patch test result to PPD. PPD was named the 2006 "Allergen of the Year" by ACDS. The mainstay of treatment is allergen avoidance and symptomatic treatment. There is a newer derivative of PPD, known as 2-methyoxymethyl-p-Phenylenediamine (Me-PPD), also found in permanent hair dye. Two studies to date have shown ~70% of patients with a previous positive patch test to PPD tolerated Me-PPD. This proposal aims to test the hypothesis that 70% of PPD sensitivity patients will tolerate the PPD derivative, Me-PPD, in a modified patch test protocol (allergy alert test) which involves application of the test ingredient for 45 minutes. The diverse population in Vancouver, BC provides a unique cohort of patients for this type of research.

MXA PROTEIN AND PLASMACYTOID DENDRITIC CELLS IN CUTANEOUS LESIONS OF KIKUCHI FUJIMOTO DISEASE

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Abstract

Kikuchi-Fujimoto disease (KFD), is a benign and self-limited systemic condition. Skin involvement is seen in 40% of patients and is nonspecific. Diagnosis is mainly based on constellation of clinical findings and suggestive pathological changes in the lymph node; histiocytic necrotizing lymphadenitis. The etiology of KFD is still unknown; however, viral and/or autoimmune pathogenesis have been suggested. There is close association of KFD with autoimmune disorders, systemic lupus erythematosus being the most reported. As type 1 interferons (IFN) have been implicated in the pathogenesis of systemic lupus erythematosus, we proposed that type 1 IFN may promote localized inflammation in cutaneous lesions of KFD.

Our objective was to investigate the expression of the type 1 IFN-inducible protein myxovirus A (MxA) and the presence of plasmacytoid dendritic cells (pDC) in lesions of KFD, lesional skin of two patients with KFD was examined by immunohistochemistry for the presence of the type 1 IFN-inducible protein, MxA, and the pDC markers, CD123, and was compared with control skin tissue. Myxovirus A (MxA) was expressed in the dermis in KFD biopsies. Plasma DCs were abundant around vessels in the dermis. We further analyzed the nuclear debri found in the dermis, and found positive staining for DAPI-elastase-MPO; which indicated possible neutrophil remnants. We demonstrate the expression of type 1 IFN-related protein MxA and plasmacytoid DCs in lesional biopsies of cutaneous KFD. These findings suggest a potential role for type 1 interferons in the pathogenesis of KFD and further the possible role of neutrophils in the pathogenesis of KFD.

Category: Early experiment with well-defined objectives/ hypotheses

SKIN CONFIDENT: A SKIN HEALTH AND ACNE EDUCATIONAL PROGRAM THAT IMPROVES ACNE QUALITY OF LIFE MEASURES IN ADOLESCENTS

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Acne is a ubiquitous problem facing adolescents with known negative psychological consequences. There is an unmet community need to provide high quality, unbiased, and effective education to youth on acne and skin health. We sought to determine if a short duration didactic presentation on skin health and acne (the intervention) could improve acne related quality of life (QoL) measures in adolescents.

This was a prospective longitudinal cohort with surveys conducted before and 4 weeks post-intervention in two independent settings (high school and community). The intervention was delivered to five high school classrooms (57 respondents for each survey, 55.3% response rate). Five Girl Guides of Canada Pathfinders groups participated in the community setting (23 respondents, 47.9% response rate). The intervention consisted of a 45-minute standardized slide-based presentation on skin health, acne, self-esteem, and evidence-based skin care. The survey included the Acne-QoL scale which measures 4 domains (self-perception, social roles, emotional roles, and acne symptoms), self-reported global acne severity (GAS), and skin care practices. Four weeks after participation in the skin confident program, there was a statistically significant decrease in summed Acne-QoL scores signalling an overall improvement. Analyzing the Acne-QoL subdomains showed a statistically significant improvement in self-perception, emotional and acne symptoms post intervention. Self-reported GAS improved in high school students.

This initiative improved acne related QoL and GAS ratings. We will be training educators to deliver this program within their own classrooms as a sustainable way to incorporate accurate information on skin health and acne into the Canadian high school curriculum.

Category: Applied/functional experiments

SPATIALLY SELETIVE PHOTOTHERMOLYSIS GUIDED BY REFLECTANCE CONFOCAL MICROSCOPY FOR PRECISE TREATMENT OF CORNEAL NEOVASCULARIZATION

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Laser treatment of hyper- or neo-angiogenesis is currently based on conventional selective photothermolysis in which abnormal blood vessels can be thermally damaged by choosing a wavelength and pulse duration that is appropriate to the therapeutic target. However, because this technique primarily relies on the differential absorption between the targeted chromophore and its surrounding tissue, it may not be sufficiently selective at the microscopic level for treatments involving the eye. For precise microscopic treatment, a spatially selective photothermolysis method has been developed by our group using a mice skin model and femtosecond laser-based two-photon absorption under guidance monitoring with reflectance confocal microscopy (RCM). Since two-photon absorption occurs only at the focal point of the treatment device, the vascular target can be treated precisely while minimizing the collateral damage to surrounding tissue. We hypothesize that our RCM imaging-guided two-photon absorption based photothermolysis system could be used for selectively closing abnormal blood vessels in mice cornea. In a pilot study, six C57BL/6J mice will be used to determine the appropriate laser doses for twophoton laser therapy. Afterwards, thirty mice will be treated with the optimized laser doses. Three types of blood vessels (capillary, artery, and vein) will be treated with 830 nm femtosecond laser irradiation. A multimodality imaging system with two-photon fluorescence imaging, second harmonic generation imaging, and RCM imaging will be used to select the treatment target and monitor the treatment process before, during and after the femtosecond laser treatment. Through this pilot study, we will gain valuable experience for planning a formal study with corneal neovascularization mouse models.

Category: Pilot/exploratory experiments (for study design, hypotheses creation, etc)

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CENTRALIZED REFERRAL SYSTEM FOR SKIN NEOPLASMS: OPTIMIZING ACCESS TO MELANOMA CONSULTATION AT A CANADIAN CENTRE

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Introduction: A Canadian centre in Victoria, BC established a centralized referral system, the Cutaneous Surgery Clinic (CSC), to track and triage skin neoplasm referrals to plastic surgeons for consultation and treatment in July 2016.

Purpose: This project is a quality improvement initiative, using a centralized referral system to quantify the volume of referrals for surgical excision of skin neoplasms, and optimize wait-times for consultation and treatment at a single Canadian centre.

Methods: Referrals to a group of plastic surgeons for the surgical treatment of skin neoplasms were directed through a centralized referral system (the CSC) between July 2016 and December 2018. Referrals were triaged using the diagnosis provided by the referring physician. Referrals were distributed to the first available surgeon based on individual surgeon wait-times, and adjusted accordingly over time.

CSC administrative databases were used to identify all British Columbia patients referred to CSC for surgical treatment of skin lesions between 2016 and 2018. The date of referral and date of consultation were extracted and used to quantify the wait times for pigmented/dysplastic lesions and melanoma using the original referring diagnosis.

Results: In total, 7573 patients were referred for initial consultation between 2016-2018 including 469 pigmented/dysplastic lesions, and 677 melanomas. Median wait time was 11 days [interquartile range (IQR) 7-18] for melanoma and 34 days for dysplastic lesions (IQR 20-64).

Conclusions: The establishment of a centralized referral system has enabled a group of plastic surgeons to provide consistent urgent triage for melanoma and dysplastic lesions at one Canadian centre.

Category: Pilot/exploratory experiments (for study design, hypotheses creation, etc)

BIOPSY METHODS FOR LENTIGO MALIGNA AND LENTIGO MALIGNA MELANOMA- A RETROSPECTIVE ANALYS

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Lentigo maligna (LM) and lentigo maligna melanoma (LMM) represent melanoma in situ and invasive melanoma, respectively, arising within sun-damaged skin. As these melanomas are frequently large and on cosmetically-sensitive areas, biopsy by complete excision, the generally recommended method of sampling melanocytic lesions, is typically not possible. Prior studies have shown that up to 40% of incisional biopsies (i.e. partial sampling) of LM/LMM may miss areas of more severe pathology, and in up to 20% of cases, an invasive melanoma may be missed. Further, since other more benign processes are often present within the same lesion as LM/LMM, the presence of such entities does not exclude the possibility of LM/LMM. To study the current practice and diagnostic accuracy of various biopsy methods for LM/LMM, a retrospective analysis of all cases of LM/LMM from Vancouver General Hospital will be undertaken using an extract from the Sunset surgical pathology database between January 1, 2010 to January 1, 2012. These reference cases will be compared to prior and subsequent biopsies/excisions performed on the same lesion in terms of diagnosis, presence/absence of concurrent lesions and tumor features (i.e. depth, presence/absence of perineural invasion/mitoses). Biopsy methods will be inferred by gross pathology specimen description and classified as punch, shave/saucerization or ellipse. Demographic data from each patient and the clinical size of the lesions at time of the biopsy/biopsies will analyzed. It is hoped that the results of this study will help inform evidence-based best practice for biopsy methods when LM and LMM are being considered.

MAPPING DERMATOLOGY ACCESS IN BRITISH COLUMBIA

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As with most jurisdictions in Canada, access to specialist services in BC for patients in rural and remote areas is limited by geography among other financial barriers. The so-called "Geographic Information System" (GIS) technology allows integration of data from various sources into a map that presents more abstract results such as "access". Other examples of the utility of GIS are to demonstrate migration patterns, analyzing changing ecology, and analysing the impact of various industries. The most famous historical and possible first example is a map of Napoleon's attack and retreat from Moscow as devised by a French engineer to show number of soldiers, date, location, and temperature. We are working to create such a map using information from data we have collected, which categories include: number of dermatology consults as a function of location of patient and provider, community population, distance to nearest dermatologist by road, average gross income by community, road conditions, and number of days required for ground transportation. The goal is to create a tool that can be used for planning future access to dermatology.

PHOTOGRAPHY GUIDELINES FOR TELEDERMATOLOGY CONSULTATION

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Telemedicine is a rapidly growing field in dermatology. Its role in dermatology is especially important in geographic areas where physically accessing a dermatologist is hampered by significantly long commute times or distances. Despite a growing body of evidence demonstrating the reliable diagnostic capacity of teledermatology consultations, this efficacy is inherently reliant on both the quality of the history as well as the quality of the photograph.

This project focuses on creating a set of guidelines and instructions for taking high quality and clinically useful photographs utilizing smartphones for the purpose of teledermatology consultations. Our target audience will be rural physicians in Northern British Columbia.

This guidelines will discuss several key parameters of interest, including direct/tangential lighting, optimizing the distance from the cutaneous lesion, focus, the use of digital/optical zoom, background selection and optimization, stabilization techniques, and teledermoscopy.

After formal completion, this project will be brought to participating physicians in Northern British Columbia for daily use.

RETENTION RATES AMONG PATIENTS UNDERGOING MULTIMODAL FACIAL REJUVENATION TREATMENT VERSUS A SINGLE MODAL TREATMENT IN COSMETIC DERMATOLOGY PRACTICES

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Purpose

Facial aging is a multifactorial process. Accordingly, expert opinion has largely been unanimous that multimodal treatment leads to superior results since it better addresses the various factors leading to the appearance of aging. However, there are a lack of studies exploring patient satisfaction in the context of multimodality treatment approaches. Our goal is to explore patient satisfaction with regards to facial rejuvenation in the context of multimodal treatment as compared to solitary modalities.

Design

A retrospective, multi-center (United States, Canada, Germany) study was performed. Cases were retrieved from July 2015 to June 2016. The study compared patients who had undergone monotherapy (neuromodulator alone), combined multimodal treatment (neuromodulator, filler, energy-based therapy on the same day) and sequential multimodal treatment (neuromodulator, filler, energy-based therapy over a one-year period). Retention rate was used as a surrogate marker of patient satisfaction.

Summary

A total of 566 patients were included in the three groups (monotherapy (351), sequential multimodal treatment (93), and combined multimodal treatment (122)). Patient retention was significantly higher in the combined multimodal treatment group as compared to the monotherapy and sequential multimodal treatment groups (p<0.0001). Subgroup analysis revealed a similar significant difference at the sites in the United States and Germany.

Conclusion

Based on retention rates, patients are most satisfied with their cosmetic outcomes when multiple modalities are used to target the multiple aspects of facial aging during one encounter. This data further solidifies the importance of multimodal therapy for both the provider and the patient.

Category: Early Experiments with well-defined objectives/hypotheses

DEEP TRANSFER LEARNING FOR SKIN CANCER AUTO-DETECTION

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Background and Objective: Dermoscopy, which provides non-invasive *in vivo* visualization of skin details at high resolution is the most common clinical aidused by dermatologists for melanoma diagnosis. However, dermoscopy requires both a specialized device and training. In contrast, routine clinical images taken from everyday cameras are easier to acquire, but the ABCD features from clinical images are less sensitive than dermoscopic features for melanoma assessment. To solve this problem, we propose a new framework which is based on the deep transfer learning technique. We aim to differentiate melanoma from benign melanocytic nevi by utilizing gold-standard dermoscopy images to feed a deep learning model which is sufficiently robust to apply to clinical images.

Proposed Methods: We assume that for both dermoscopy and clinical images, the object of interest (i.e. suspect skin lesion) is within the foreground. We further assume that for the same diseases under these two modalities may have similar high level characteristics and label space; however, their specific pixels are different in distribution due to noise, resolution and many other "low-level" differences.

The key idea in deep transfer learning is to find the space correlation between the source (dermoscopy images) and target (clinical images) domains, i.e. samples do not fit the common space will be removed. We will adjust and fine-tune the domain separation networks (DSN) proposed by Bousmalis, and apply these networks to the public images listed in the DermWeb, Dermofit Library (clinical images), and HAM10000 (dermoscopy images).

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SEVERE CUTANEOUS ADVERSE REACTIONS CAUSED BY ANTIBIOTICS

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Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS) and its more lethal variant, Toxic Epidermal Necrolysis (TEN), are one of the most serious, potentially disabling or life-threatening adverse events, characterized by widespread skin and mucous membrane detachment. Although rare, SCARs contribute disproportionally to mortality and impose an intolerable burden on the healthcare system in Canada. It has been well documented that most of SCARs are triggered by drug exposure. In this study, we retrospectively reviewed our current Canadian Pharmacogenomics Network for Drug Safety (CPNDS) database and found that antibiotics were the most common culprits to cause cutaneous adverse drug reactions (cADRs), ranging from common rash to serious systemic reactions (i.e. SCARs). A total of 3,828 (59.3%) participants in our database were prescribed at least one antibiotic, and over 90% of them were related to β-lactams (e.g. penicillins and cephalosporins) or sulfonamides (e.g. sulfamethoxazole) use. Of these, a total of 904 patients occurred antibiotic-related cADRs, including 30 severe cases met the criteria of the SCAR definition. Our next step is to identify clinical biomarkers and genetic variants associated with antibiotic-induced SCARs through a genome-wide array with comprehensive coverage in the targeted genic regions. Given the widespread use of antibiotics, understanding the pathogenesis of antibiotic-associated severe cutaneous adverse reactions and developing interventions to prevent its onset are critical public health concerns. This study will provide evidence-based strategies for patient-oriented healthcare before antibiotics administration to improve drug safety and reduce the risk of antibioticinduced cADRs.

SYSTEMATIC REVIEW OF THE EFFICACY OF LASER AND LIGHT THERAPY FOR THE TREATMENT OF NEVUS OF OTA, NEVUS OF HORI AND BECKER'S NEVUS

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Background: Disorders of cutaneous hyperpigmentation are common and, because of their visibility, can cause significant psychosocial distress for affected patients, leading to low self-esteem and decreased productivity. As such, effective treatments are needed.

Objective: The aim of our study was to conduct a systematic review of the literature on the efficacy of laser and light therapies for nevus of Ota, nevus of Hori and Becker's nevus. **Methods:** Original publications of randomized controlled clinical trials (RCTs) and controlled clinical trials were identified through searches in MEDLINE (Ovid) and the Cochrane Central Register of Controlled Trials (CENTRAL).

Results: We identified 1 relevant controlled trial for nevus of Ota involving 44 patients, 1 relevant RCT and 1 controlled trial for nevus of Hori involving a total of 23 patients, and 2 relevant RCTs for Becker's nevus involving a total of 33 patients, which met our inclusion criteria. In these studies, several laser and light therapies including QS Nd:YAG laser, QS alexandrite laser, QS ruby laser, CO2 laser, and Er:YAG laser were compared against each other and against topical options for the treatment of nevus of Ota, nevus of Hori and Becker's nevus.

Conclusions: Using combination laser therapy (CO2 laser + QS Ruby or QS 532 nm Nd:YAG + QS 1064 nm Nd:YAG) for treatment of nevus of Hori, and using Er:YAG laser therapy for the treatment of Becker's nevus was found to have superior efficacy and a good side effect profile in comparison to other laser modalities and topical options.

Category: Early Experiments with well-defined objectives/hypotheses