Invited Speaker Presentations

Wednesday, June 13, 2007

Workshop 1
Pattern Hair Loss (PHL) Pre Conference

WS-1-A
Etiology of Pattern Hair Loss
Speaker: Andrew Messenger
Department of Dermatology, Royal Hallamshire Hospital, Sheffield, United Kingdom

Pattern hair loss (PHL) is due to a progressive decline in the activity of scalp hair follicles. The pathology may be regarded as a final common pathway to which a number of factors contribute. Male PHL is genetically determined and androgen-dependent. The prevalence and severity increase with age suggesting that aging mechanisms are also involved in the etiology, and there is some evidence that the same pathology can occur independently of androgens (senile alopecia). Androgens are involved in the etiology of female PHL in some women, but this has been more difficult to prove and it is possible that non-androgenic mechanisms play a more prominent role than in men. Current thinking is that the predisposition to PHL in both sexes is polygenic. Three independent studies have linked male PHL to variant regions in the androgen receptor (AR) gene. However, this alone does not explain the paternal influence on PHL as the AR gene is located on the X chromosome and is inherited from the mother. Advances in our understanding of the molecular control of hair growth are also leading to progress in the pathobiology of PHL, and integrating these findings with genetic information will form a challenge for the future.

WS-1-B
Clinical Presentation, Workup FPHL
Speaker: Elise Olsen
Duke University, Durham, NC, USA

[Abstract/summary not available at the time of printing]

WS-1-C
Management of Male Pattern Hair Loss
Speaker: Dominique van Neste
Skinterface, Tournai, Belgium

Listen, look and touch are the three key actions that characterize the first encounter with a patient complaining about hair loss. In the case of male pattern hair loss (MPHL). The next steps will aim to provide the best possible information about MPHL as a chronic progressive regression phenomenon. This includes fluctuations of its natural course, the methods for its measurement and finally the treatment options. During the lecture, we will present recent information on the practical use of non-invasive methods including global and analytical imaging methods.

Measurement of the continuum of hair restoration is still in its infancy. Who thinks about scalp hair follicles in terms of pharmacodynamic responses? Which functional characteristics in a particular target are of prognostic significance or indicators of potential for therapeutic response? What are the minimal changes of a given parameter that are clinically significant in a before – after evaluation e.g. a drug or a surgical procedure? Are the pharmacodynamic responses correlated with clinically relevant endpoints like : do the patients perceive decreased hair loss? are they satisfied in case of measurable regrowth? is a single variable or a cluster of parameters a valid surrogate for patient global satisfaction?

WS-1-D
Pathology of Pattern Hair Loss
Speaker: Wilma Bergfeld
The Cleveland Clinic Foundation, Cleveland, OH, USA

The histopathology findings correlate to the degree of patterned hair loss variation. The most characteristic finding is a progressive miniaturization of the terminal hair follicles with reduction in follicular size and normal density. Later there is loss of follicular density. There may be histological evidence of a telogen effluvium. With progression, there are increase in vellus hair follicles which results in a terminal: vellus ratio of 2;1 in contrast to normal ratio of 7:1. With miniaturization, there is a diminished size of the dermal papillae, a 30-50% reduction from normal. With progression, there is a decrease in anagen follicles and increase in telogen follicles, a reversal of the anagen telogen ratio. Other features include emptied widen follicular fibrosis tracts Elastic tissue highlights the Araro-Perkins body, a clusters of elastin, at the site of previous dermal papilla within the fibrous tract which identifies previous follicular cycles.

A shorten anagen growth cycle increases the miniaturized telogen follicles. In patterned alopecia, 83% anagen and 17% with telogen follicles as compared to normal scalp 93.5% anagen and 6.5% telogen.

In oily scalps, there is an increase the size of sebaceous glands and frequently secondary seborrheic dermatitis. Chronic lymphocytic folliculitis and or emptied inflamed fibrosis tracts, are observed in 75% with a 5% diffuse follicular and interfollicular fibrosis.

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WS-1-E
Pattern Hair Loss – Medical Therapy
Speaker: Jerry Shapiro, MD
University of British Columbia, Vancouver, BC, Canada

Patients with scalp hair loss seek medical attention for a many different reasons. Some patients are upset psychologically and want treatment. Others worry that their hair loss is a sign of an internal problem and simply want reassurance. As dermatologists, specialists in hair diseases, it behooves us to educate patients on the nature, course and available treatment options for a specific hair loss condition. The most common problems encountered are pattern hair loss, telogen effluvium, alopecia areata and cicatricial alopecias. Practical algorithmic approaches for management will be presented.

Male pattern hair loss (MPHL): Topical minoxidil solution and oral finasteride are the only treatments for MPHL that have been approved by FDA. Use is indicated in males over age 18 with mild to moderate MPHL. Well-controlled studies have proven efficacy. Stabilization, or increased scalp coverage is seen with either agent by 3-6 months of treatment and is evident by 1 year. Early intervention enhances outcome. In responders, treatment must be continued indefinitely to maintain benefit. Stopping treatment results in a return to pre-treatment status by 6 months with minoxidil and by 12 months with finasteride.

Female pattern hair loss (FPHL): Two percent topical minoxidil is the only FDA-approved medication for treatment of FPHL. Use is indicated in women over age 18 with mild to moderate hair loss (Ludwig stage I or II). Results may be less impressive in those with underlying hyperandrogenism.

WS-1-F
Surgical Management of Pattern Hair Loss
Speaker: Ken Washenik, MD, PhD
Bosley Medical Group, Beverly Hills, CA, USA

[Abstract/summary not available at the time of printing]

WS-1-G
In Search Of Therapies For Pattern Hair Loss: Defining The Challenges And Searching For Solutions
Speaker: Satoshi Itami
Osaka University, Osaka, Japan

[Abstract/summary not available at the time of printing]

Workshop 2
Cicatricial Alopecia Pre Conference

WS-2-A
Classification and Clinical Presentation
Speaker: Ralph Trüeb, MD
University Hospital of Zurich, Zurich, Switzerland

The cicatricial alopecias often are both a diagnostic and therapeutic challenge to the practitioner. They encompass a diverse group of disorders characterized by irreversible hair loss due to permanent destruction of the hair follicle. Where there is no obvious physical/chemical injury or acute infectious etiology, clinical differential diagnosis is often difficult. Moreover the cause of many of these disorders remains largely unknown. The loss of follicular orifices in an area of alopecia points to a permanent loss of hair. In all of these cases a scalp biopsy is indicated. Primary and secondary scarring alopecia are differentiated: While the former is due to preferential destruction of the follicle, the latter results from events outside the follicle, which eventually impinge upon and eradicate the follicle. These include infiltrative processes such as granulomatous inflammation or neoplastic disease. In the group of primary scarring alopecia, well-defined chronic-inflammatory diseases of the scalp partly amenable to specific therapies (e.g. lichen planopilaris, lupus erythematosus, folliculitis decalvans, dissecting folliculitis) are differentiated microscopically on the basis of the type of inflammatory cell that predominates (lymphocytic, neutrophilic, or mixed) and the pattern of inflammation. Although clinicopathologic features allow for accurate diagnosis in many cases, diagnostic certainty is sometimes elusive and therapeutic limits reflect the boundaries of our present understanding. Especially management of the less well classified diseases and of end-stage disease (pseudopelade) remains problematic.

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WS-2-B
Histopathology of Cicatricial Alopecia
Speaker: David A. Whiting, MD
Baylor Hair Research and Treatment Center, Dallas, TX, USA

The most common primary cicatricial alopecias are lichen planopilaris, central centrifugal cicatricial alopecia, folliculitis decalvans, discoid lupus erythematosus and nonspecific cicatricial alopecia (including pseudopelade).

The end-stage scarring from all these conditions results from the destruction and fibrosis of hair follicles, perhaps leading to polytrichia, and is frequently nonspecific on histopathologic examination. Microscopic examination of 4mm punch biopsies from early stage disease in active spreading areas of hair loss may show diagnostic changes which support a definitive diagnosis:

Lichen Planopilaris: A lichenoid interface dermatitis is common at the dermoepidermal junction of follicular infundibulum and isthmus. Peri-infundibular hypergranulosis may be seen. Sebaceous epithelium is lost in early lesions. A perifollicular lymphohistiocytic infiltrate with cytoid bodies may be present, but perieccrine infiltrates and epidermal and dermal mucin are absent. Concentric, lamellar fibrosis ensues, with pigment incontinence.

Central centrifugal cicatricial alopecia: Lymphocytic infiltrates occur around blood vessels, lower infundibulum and upper isthmus. Sebaceous epithelium is lost early on. Premature desquamation of the inner root sheath may occur. Progressive thinning of the external root sheath may cause follicular distention, rupture, hair granulomas and dense fibrosis.

Folliculitis decalvans: Acneiform dilatation may result in follicular rupture and abscess formation. The inflammation is initially neutrophilic, but is later lymphohistiocytic with plasma cells and foreign body giant cells. The process is primarily peri-infundibular, but may extend to involve the entire follicle, resulting in perifollicular fibrosis.

Discoid lupus erythematosus: A vacuolar interface dermatitis may involve surface and infundibular epidermis. Lymphocytic inflammation is prominent around hair follicles, eccrine glands between follicles and superficial and deep blood vessels. Moderate dermal mucin is present. Concentric lamellar fibrosis and pigment incontinence occur. A positive immunofluorescent LE band is present in 70% of cases.

Nonspecific cicatricial alopecia: Late stage changes from many causes include a flattened epidermis, scattered, sparse, perivascular lymphocytic infiltrates and dense fibrosis, often involving whole follicular units. A specific diagnosis is often not possible, let alone treatment.

Conclusion: Scalp biopsies are mandatory when the slightest sign of follicular destruction is found in the patient.

WS-2-C
Etiology of Cicatricial Alopecia: Background and Hypotheses to Test
Speaker: Kurt Stenn, MD
Aderans Research Institute, Philadelphia, PA, USA

The commonly recognized features of the primary cicatrical alopecias is clinically, loss of hair shafts and follicular markings and histologically, paucity to absence of sebaceous glands, presence of extrafollicular hair shafts, foreign body inflammatory reactions and follicular track fibrosis. Whatever pathogenesis one might consider must account for these widely recognized cardinal changes. Clearly, to have a hair shaft outside of the outer root sheath in the surrounding perifollicular stroma implies that a follicular implosion or explosion has occurred. In either case, a breach resulted in the outer root sheath, locally or focally, releasing the hair shaft into the dermis and inducing a foreign body reaction; the latter repairing with a focal scar. The result of this process is ablation of the whole hair follicle.

While the focus of our study must be on the elements causing follicular implosion or explosion, the lethal injury is suffered here by the mesenchyme. It is axiomatic in reparative systems that epithelium repairs and regenerates itself readily (as long as its framework is retained) while mesenchymal tissues repair with scar – a tissue with a very different function from the native supportive stroma. This principle would appear to be applicable to the hair follicle as well considering the powerful role the mesenchyme plays in inducing and supporting hair growth from various epithelial platforms. By this argument the vulnerable target in the pathway to a given cicatricial alopecia would be the mesenchyme.

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Two pathogenetic hypotheses have been put forth to explain the earliest injury in these disorders. The first proposes malfunction of the hair follicle stem cell compartment and the second proposes malfunction of the sebaceous gland and egress of the shaft. In the discussion these two hypotheses will be placed in perspective.

WS-2-D
CD200 Attenuates Hair Follicle-specific Inflammation in Mice
Speaker: Michael Rosenblum
Medical College of Wisconsin, Milwaukee, WI, USA
Authors: Michael D. Rosenblum[1,2], Robert L. Truitt[1], Jeffrey E. Woodliff[1], Edit B. Olasz[2], and Kim B. Yancey[3].

[1]Department of Pediatrics, [2]Department of Dermatology, Medical College of Wisconsin, Milwaukee, WI
[3]Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX

Immunosuppressive molecules expressed on tissue-resident cells have the potential to regulate tissue-specific inflammation and autoimmunity. CD200 is a cell surface glycoprotein that transmits an immunosuppressive signal by ligating its receptor, CD200R. We have elucidated the expression of CD200 and CD200R in murine skin and examined the role of CD200-CD200R signaling in maintaining cutaneous immune homeostasis. CD200 was expressed on Langerhans cells (LCs) and on a subset of keratinocytes (KCs). CD200 expressing KCs preferentially localized to the outer root sheath of hair follicles (HF). CD200R was expressed on approximately one-third of freshly isolated LCs. LCs from $CD200^{-/-}$ mice showed a heightened state of activation. CD200 expression had a dramatic effect on protecting HFs from inflammation and autoimmune attack. Grafts of syngeneic gender-matched skin from $CD200^{-/-}$ donors showed persistent perifollicular inflammation with heightened T cell-recruitment and, ultimately, complete destruction of HFs, a phenotype resembling human cicatricial alopecia. Hair follicle destruction could be induced in a $CD200^{-/-}$ host by adoptive transfer of T cells from a mouse previously grafted with $CD200^{-/-}$ skin. Our results suggest that the CD200-CD200R signaling pathway plays a role in establishing and maintaining immune homeostasis in the skin. This pathway may be especially important in attenuating HF-associated inflammation and/or autoimmunity.

WS-2-E
PPAR Gamma Deletion in Stem Cells of the Hair Follicle Causes Scarring Alopecia
Speaker: Pratima Karnik
University Hospital Case Medical Center and Case Western Reserve, Cleveland, OH, USA
P. Karnik, Z. Tekeste, M. Smith, A. Gilliam, T. S. McCormick, K.D. Cooper and P. Mirmirani

Dermatology, University Hospital Case Medical Center and Case Western Reserve University, Cleveland, OH

Primary cicatricial or scarring alopecias (CA) are a group of inflammatory disorders of unknown pathogenesis characterized by permanent destruction of the hair follicle. Current treatment options are ineffective because the molecular basis for CA is not understood. Here we report that the lymphocytic CA, Lichen planopilaris is characterized by progressive loss of peroxisomes, abnormal lipid accumulation and infiltration of inflammatory cells and destruction of the pilosebaceous unit. Microarray analysis of LPP and normal biopsies identified decreased expression of genes required for lipid metabolism and peroxisome biogenesis. The expression of PPARγ, a transcription factor that regulates these processes, was significantly decreased in LPP. Specific agonists of PPARγ but not other PPAR subtypes were effective in inducing peroxisomal and lipid-metabolic gene expression in human keratinocytes. Finally, targeted deletion of PPARγ in the follicular stem cells in mice caused a skin and hair phenotype closely resembling scarring alopecia. These studies suggest that PPARγ is essential for healthy pilosebaceous units and loss of this function underlies the pathogenesis of LPP. We propose that PPARγ targeted therapy represents a new strategy in the treatment of these disorders.

**Note: this presentation is also shown as a Poster Presentation as P-265*

WS-2-F
CCCA Update
Speaker: Elise Olsen, MD
Duke University, Durham, NC, USA

[To view this abstract, go to P-133]

WS-2-G
Secrets of Cicatricial Alopecias Revealed by Mouse Models
Speaker: John P. Sundberg, DVM, PhD
The Jackson Laboratory, Bar Harbor, ME, USA

Cicatricial (scarring) alopecias represent a diverse group of diseases in humans in which the end result is a follicular scar with permanent hairloss. Since human clinical cases, when

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first seen by a physician, are in active or end stages of the disease, it is impossible to investigate the fundamental pathophysiology leading to these disfiguring entities. Not surprisingly, inbred mice with single or multiple genetic mutations develop similar, if not identical lesions. For those single gene mutation models with multiple allelic variants on different inbred backgrounds it is now possible to define variations in disease due to background modifier genes as well as different mutations within the gene itself. In addition to being able to define the specific genes responsible for cicatricial alopecias, which has already been done in many cases with mice, it is possible to study mice from normality to end stage disease to both document progression and define the molecular networks underlying the disease mechanisms involved. Studies with the asebia mutant mice pioneered the field and led to the hypothesis that sebaceous glands are critical in some but not all forms of cicatricial alopecia. We have a group of mutant mice with various defects of sebaceous glands and pilosebaceous units which provide new tools to dissect which anatomical defects are actually critical in the pathogenesis of cicatricial alopecias. An overview of many of these models will be presented. Most of these mouse models are readily available from one or more repositories for investigation and as preclinical models for screening new therapeutic approaches to cicatricial alopecias and defining the pathogenesis of these diseases.

WS-2-H
Cicatricial Alopecia: A Practical Diagnosis and Therapeutic Approach
Speaker: Pascal Reygagne
Centre Sabouraud, Hôpital Saint Louis, PARIS

Scarring alopecia is an irreversible process with a permanent destruction of the follicle. Scarring alopecia may be primary or secondary, but our topic will be only primary cicatricial alopecia, specially lymphocytic. The diagnosis is clinical and histological and we present an overview of the clinical and the histological assessment of cicatricial alopecias.

Clinically, cicatricial alopecia can be pustular or non pustular, and nowadays the classification is based on the predominant cellular infiltrate, but there is a correlation between the clinical and histological aspect.

NON PUSTULAR (lymphocytic)
- lichen planopilaris
- discoid lupus erythematosus
- pseudopelade
- follicular degeneration syndrome
- AGA with scarring evolution
- alopecia mucinosa

PUSTULAR (neutrophilic)
- folliculitis decalvans
- tufted folliculitis
- dissecting folliculitis
- acne necrotica
- keloid folliculitis
- tinea capitis

Treatments are difficult, and most of them are not approved or unauthorised. Non-pustular cicatricial alopecias are treated with corticotherapy, hydroxychoroquine, and immunomodulating agents. Pustular alopecias are treated with antibiotics, and isotretinoïne for dissecting folliculitis.

Lichen planopilaris (LPP) is, in our experience, the most frequent etiology of scarring lymphocitic alopecia. Treatment is difficult and disappointing. Topical ultra potent corticotherapy is our first line therapy. In the last years we proved that antimalarial drugs, thalidomide and acitretine a'nt effective to arrest progression of lichen planopilaris: we treated without success 12 patients with hydroxychloroquine. After this first open trial we tried thalidomide on 4 other patients without any more success but with side-effect. And it was the same no result with acitretine: 8 cases without any success. When the disease is very active the best treatment is oral corticotherapy, but relapse is frequent.

A short course of oral cyclosporine has been reported successful in treating 3 patients. We present 13 patients with refractory LPP treated for 3 to 7 months with cyclosporine and followed at least 6 months after stopping the treatment. They were aged from 31 to 59 years with a diagnosis of LPP from 1 to 19 years. Previous treatment included topical and intralesional corticosteroids, hydroxychloroquine (n=6), chloroquine (n=1), topical tacrolimus (n=2) and oral corticotherapy (n=6). At the beginning of the study, the dosage of cyclosporine was 3mg/kg/Day, increased monthly in case of non-response. Treatment was stopped after 2 months without symptoms. In a few patients we measured hair density on a selected target and performed global standardized photography. We obtained complete clinical resolution of the disease activity at doses ranging from 250mg to 400mg, and treatment duration of 4 to 8 months. A complete clinical response was achieved in 8 patients (8/13=53%) and a partial response in 2 (2/13=23%). Three patients failed to respond. Six months after stopping cyclosporine 4 patients remained symptom free and 6 had relapsed at 3, 3, 4, 4, 5, 6 months. Hair count was available before and after treatment for 10 patients with stabilisation (n=5), increase (n=3) or decrease (n=2). The two patients with a decrease were clinically rated failure or partial response. Side effects were

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minor: these included transient elevations of serum creatinine (n=4), distal paresthesia (4), and hypertrichosis (2).

On the basis of this experience, cyclosporine can be an option to treat refractory LPP, optimal efficient dosage is between 4 and 5 mg/kg/day, optimal course is 4 to 6 months, and success rate is 77% (10/13); relapse rate 6 months after stopping the course is 60%. A study versus systemic oral corticotherapy is necessary.

Chronic cutaneous lupus erythematosus (CCLE) is less frequent than LPP. Cutaneous lesions are frequent, especially on the face. Our first line therapy is hydroxychloroquine and topical corticotherapy. Second line therapy is oral corticotherapy or intralesional injections of triamcinolone acetonide. This treatment is injected every 3 or 4 weeks for 3 months and then every 6 to 8 weeks. Third line therapy is thalidomide or dapsone or mycophenolate mofetil.

Folliculitis decalvans is, in our experience, the most frequent aetiology of scarring neutrophilic alopecia. Our first line therapy is doxycycline alone, 100mg twice a day for one months, then 100mg for 6 months more. Minocycline can be more effective but serious side effects are more frequent especially in black patients. Our second line therapy is the association of rifampicine 300mg twice a day with clindamycine or fusidic acid or ciprofloxacine for 10 weeks. Zinc gluconate with fusidic acid can be an option.

Dissecting folliculitis is less frequent. Isotretinoin is the best treatment. We use 0,5mg/kg to 0,75mg daily for 6 to 9 months. An antistaphylococcic antibiotherapy may avoid a flare-up during the first month of isotretinoin. In case of relapse a second cure is possible and maintenance therapy with a low dosage for many months may be necessary.

In conclusion, treatment of cicatricial alopecia is difficult. A clinical and photographic assessment is important, but the progression of the disease is slow and insidiously and an hair count assessment on a selected area is the better criterion to be sure of the stabilisation and the remission of the disease.

WS-2-I
Cicatricial Alopecia: The Future
Speaker: Rodney D. Sinclair, MBBS, MD, FACD
St. Vincent's Hospital Melbourne, University of Melbourne, SA, Australia

Currently, the cicatricial alopecias include a poorly understood group of hair disorders linked by the common final pathway of permanent hair follicle loss and replacement by fibrous tissue in involved areas. There are no pathognomonic diagnostic tests for the primary cicatricial alopecias. There is no clear understanding of the natural history and in particular whether the primary cicatricial alopecias ever 'burn out'. There is no tool useful for monitoring therapeutic response in multifocal disease on the scalp. There is no treatment known to arrest progression, and severely affected patients lack sufficient donor hair population for transplantation.

In the absence of published randomized controlled clinical trials to guide therapy and no clear investigational protocol for the conduct of such trials, and no clear end-points as when to ultimately cease therapy, I perceive no clear role for medical therapy.

As hair follicle neogenesis is likely to result in new hairs subject to the same fate as the one's they replace, the best possible future outcome that I can envisage is hair cloning with implantation on demand of immunologically distinct hairs (or hair follicle stem cells) that are spared from the inflammatory attack.

Failing that, coloured hair sprays for limited disease and wigs for extensive disease are likely to dominate the foreseeable future. Hair transplantation for secondary cicatricial alopecias and non-progressive primary disease will continue to have a role.

Workshop 3
Alopecia Areata Pre Conference

Supported by an unrestricted educational grant from the National Alopecia Areata Foundation

WS-3-A
Genetics
Speaker: Angela Christiano, PhD
Columbia University, New York, NY, USA

Alopecia areata (AA) is a genetically determined, immune-mediated disorder of the hair follicle with a lifetime risk of approximately 2%, making it one of the most common autoimmune diseases. It is defined by a spectrum of severity that ranges from patchy localized hair loss on the scalp to the complete absence of hair everywhere on the body. In an effort to define the genetic basis of AA, we performed a genomewide search for linkage in 20 families with AA. Our analysis revealed evidence of at least four susceptibility loci on chromosomes 6, 10, 16 and 18, by use of several different statistical approaches. Fine-mapping analysis with additional families yielded a maximum multipoint LOD score of 3.93 on chromosome 18, a two-point affected sib pair (ASP) LOD score of 3.11 on chromosome 16, several ASP LOD scores >2.00 on chromosome 6q, and an HRR LOD of 2.00 on chromosome 6p in the region of the MHC

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locus. Our findings confirm previous studies of association of the MHC locus with human AA, as well as the C3H-HeJ mouse model for AA. The major loci on chromosomes 16 and 18 coincide with loci for psoriasis reported elsewhere and the locus on chromosome 18 corresponds to a region that shows linkage to hereditary hypotrichosis simplex. Our results suggest that these regions may harbor gene(s) involved in a number of different skin and hair disorders.

WS-3-B
Mechanisms of Alopecia Areata
Speaker: Kevin J. McElwee, MD
Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

The last ten years have seen a concerted effort to investigate the nature of alopecia areata (AA). Significant inroads have been made, but our understanding of AA remains limited. Thus far, most evidence is consistent with an autoimmune mechanism of disease development. The transfer of immune cells in disease models has demonstrated that hair loss is primarily mediated by leukocytes. However, without knowledge of the primary target antigen epitopes involved in disease initiation the putative autoimmune nature of AA remains unproven. It is generally accepted that AA probably involves a genetic susceptibility to autoimmunity and AA, but onset of actual hair loss is most likely precipitated by the interaction of genes with the environment. For some, genetics may be the greater influence on AA development while for others the environment may provide a stronger input. Several environmental factors have been suggested to influence the course of AA (such as stress, hormonal fluctuations, and infectious agents), but evidence of their true significance in disease initiation is lacking. The nature of the actual disease promoting mechanism(s) for AA onset and leukocyte targeting of hair follicles remains unknown, but several hypotheses have been suggested. Possible mechanisms involve a failure of the hair follicle's reputed immune privilege, inappropriate presentation of hair follicle antigens to the immune system during catagen regression, failure of central or peripheral immune regulation, non-specific activation of autoreactive lymphocyte clones, or antigen epitope mimicry by pathogens. Overall, fundamental questions concerning the mechanisms of AA development remain to be answered.

WS-3-C
Histopathology of Alopecia Areata
Speaker: David A. Whiting, MD
Baylor Hair Research and Treatment Center, Dallas, TS, USA

The microscopic findings in alopecia areata reflect the duration of the current episode. The characteristic, peribulbar, lymphocytic infiltrate is seen in the acute phase of a developing patch. Initially it surrounds terminal anagen hair bulbs in the lower dermis and causes anagen arrest; in recurrent attacks when most hairs are miniaturized, it may only be found around vellus-like bulbs in the upper dermis. After 3 or 4 weeks the subacute phase supervenes and is signified by the increased numbers of catagen and telogen hairs resulting from the anagen arrest, with decreasing lymphocytes. After 1-2 months the chronic phase ensues, characterized by a marked decrease in terminal hairs and a reciprocal increase in vellus hairs. Recovery is indicated by increasing numbers of terminal anagen hairs, decreasing vellus hairs and the disappearance of inflammation.

Always try and take a biopsy from the spreading edge of the most recent area of hair loss. Diagnostic difficulties arise when biopsies are taken in later stages of an attack, or in the nondescript diffuse form of the disease labeled alopecia areata incognita. High percentages of telogen and/or miniaturized hairs should arouse suspicions , and vellus hair bulbs with surrounding lymphocytes should be sought.

WS-3-D
Clinical Features
Speaker: Maria Hordinsky, MD
University of Minnesota, Minneapolis, MN, USA

CLINICAL FEATURES

Patterns

Alopecia areata may present in one of several distinct patterns:

1. Round or oval patches of hair loss
2. Loss of all terminal scalp hair (alopecia totalis)
3. Loss of all scalp and body hair (alopecia universalis)
4. Ophiasis (bandlike) pattern of hair loss
5. Reticular variant of patchy alopecia areata
6. Diffuse scalp alopecia areata
7. Perinevoid alopecia areata (rare)

Hair Fibers

1. Explanation mark hairs
2. Fibers in anagen arrest

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Pigmentation

1. Hair pigmentation is frequently affected
2. Disease prefers attacking pigmented hairs, sparing unpigmented or white fibers

Differential Diagnosis

1. Tinea capitis
2. Traction alopecia
3. Loose anagen syndrome
4. Aplasia cutis
5. Pseudopelade
6. Other

Nails

1. Frequency of nail abnormalities ranges from 10-66%
2. May precede, follow or occur concurrently with hair loss activity
3. Nail pitting is most commonly seen
4. Other findings include:
   a. Longitudinal ridging
   b. Koilonychia
   c. Brittle nails
   d. Onycholysis
   e. Onychomadesis
   f. Periungual erythema
   g. Other

Sweat Glands

Number and function have been reported to be normal or decreased.

Disease Associations

1. Atopy (allergic rhinitis, asthma, and atopic dermatitis) – up to 40% in some studies while the prevalence of atopic diseases in the population is estimated to be 20%.
2. Thyroid disease
3. Autoimmune diseases
4. Patients seropositive for the human immunodeficiency virus.
5. Type 1 diabetes mellitus
   Interestingly, there is reportedly more diabetes present in the relatives of patients with alopecia areata but not in patients themselves, suggesting that the predisposition of alopecia areata may be protective against the development of diabetes.
6. Down syndrome and Turner syndrome.
7. Autoimmune Polyglandular Syndrome (APS-1), chronic hypoparathyroidism-mucocutaneous candidiasis-autoimmune adrenal insufficiency) – up to 30 percent of affected patients may express alopecia areata.
8. Unusual associations:
   - Testicular atrophy or dysfunction
   - Ophthalmologic changes such as iris color change, pigment hyperplasia of the choroid and retinal epithelium

WS-3-E
Alopecia Areata – Topical Immunotherapy
Speaker: Jerry Shapiro, MD
University of British Columbia, Vancouver, BC, Canada

There are no FDA-approved treatments for alopecia areata (AA). Corticosteroids, contact immunotherapy, topical minoxidil, and psoralen combined with UVA irradiation (PUVA) comprise the more commonly used modalities. None are curative nor reliably effective. Recommendation for use of any one therapeutic agent is hampered by the lack of long-term, randomized, double-blind, placebo-controlled studies of sufficient power and duration to determine efficacy unequivocally. This is further compounded by the failure of many studies to control for rates of spontaneous remission or to stratify patients according to type of disease, among other prognostic factors. Because most patients resolve within 1 year without any intervention, half-head/half-lesion studies are essential to establishing treatment effect. Precise definition of "response", often omitted, aids in interpretation of results. Despite this complexity, there are a number of treatments that do appear to work in some patients with AA. Topical immunotherapy has been shown to be effective in almost 70% of non-totalis patients. Seventeen percent of totalis patients respond to therapy. Half however relapse overtime and no longer respond to therapy. Side effects include dyspigmentation, eczematous dermatitis and lymphadenopathy.

WS-3-F
Biologics, Calcineurin Inhibitors and What's Ahead in Alopecia Areata
Speaker: Vera Price, MD
University of California San Francisco, San Francisco, CA, USA

Alopecia areata (AA) is a T cell-mediated autoimmune disease in which anagen hair bulbs are targeted by CD4+ and CD+8 lymphocytes. The initiation phase of AA is mediated by type 1 cytokines including interferon-gamma, interleukin-2, and tumor necrosis factor-alpha, all of which are expressed in lesional AA skin. The immunologic basis of alopecia areata is similar, though not identical, to that of psoriasis. Knowledge of the immunologic basis of psoriasis has resulted in creation of genetically engineered biologic agents that target the key pathogenic steps, primarily those mediated by T cells and the inflammatory cascade. These

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agents include those that decrease the number of activated T-cells (alefacept), those that block T-cell activation, binding, and trafficking to the dermis and epidermis (efalizumab), and those that specifically bind tumor necrosis factor-alpha (etanercept and infliximab). Biologic therapies target specific cell surface receptors, and their potential advantage is that their greater specificity provides better safety profiles. These four biologic agents have been approved by the US FDA for the treatment of psoriasis. Because previous clinical experience has suggested that treatments effective in psoriasis may also be effective in AA, biologics have been used in alopecia areata. This report includes the use of efalizumab in the first randomized, double-blind, placebo-controlled study in patients with AA. It also highlights the importance of controlled studies to assess efficacy of treatments in AA. So far, the use of biologics in alopecia areata has not shown efficacy. In fact, during the course of treatment with anti-TNF agents, patients have developed alopecia areata. The experience with biologics, calcineurin inhibitors, and future directions in alopecia areata, are the subject of this report.

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Alefacept is a fusion protein that blocks T-cell activation. Efalizumab is a humanized monoclonal antibody that binds to CD11a, a component of LFA-1 that binds to ICAM-1 on antigen presenting cells. Etanercept is a human fusion protein and infliximab is a chimeric (mouse/human) antibody and both inhibit the inflammatory cytokine TNF-alpha. Hyperproduced interferon-gamma has been postulated as a key mediator of autoimmune disease.[4] It is expressed in lesional AA skin, and interferon-gamma knockout mice are resistant to the development of AA.5 A small, open, pilot trial of anti-interferon-gamma antibodies in patients with active AA has shown promise as an early intervention for this disease.

Keywords: alefacept, efalizumab, etanercept, and infliximab

Workshop 4
Hirsutism Pre Conference

WS-4-A
Aetiology of Hirsutism
Speaker: Valerie A. Randall, PhD
University of Bradford, Bradford, United Kingdom

Hirsutism, or male pattern hair distribution in women, causes psychological distress. This is because the main role of the additional hair developed during, and after, puberty focuses on social and sexual communication. Pubic and axillary hair signals adulthood in both sexes, while beard, chest and other body hair identify the sexually mature male. Therefore, hirsutism may make a woman think she is turning into a man.

Most patients with hirsutism present with terminal (readily visible, pigmented) hair on the moustache and chin areas; this is often accompanied by hair on the chest, abdomen and thighs. The amount of increased hair that is unacceptable varies with cultural/ethnic background. Hirsutism may be associated with other signs related to androgens including acne or androgenetic alopecia or with acanthosis nigricans (dark patches of skin).

Androgens are the normal stimulant for adult human hair growth patterns and are strongly implicated in female hirsutism. Hirsutism can be caused by endocrinological changes including increased androgen production by the adrenals or ovaries and is often associated with Polycystic Ovarian Syndrome. Sudden, dramatic onset requires urgent endocrine investigation as it may indicate an androgen-secreting adrenal or ovarian tumour. Although raised circulating androgen levels or low sex hormone binding globulin levels are common, some hirsute women do not show obvious causes i.e. are idiopathic. This is likely to involve an increased sensitivity to normal androgens within the hair follicles themselves. Greater understanding of how androgens act within the hair follicle should lead to better treatments for hirsutism.

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WS-4-B
Presentation and Evaluation of Hirsutism
Speaker: Ulrike Blume-Peytavi, MD
Clinical Research Center for Hair and Skin Physiology – CRC, Charité – Universitätsmedizin Berlin, Berlin, Germany

For many women excessive facial hair growth may have devastating consequences with impact on self image, loose of self confidence, loose of their femininity, hindering them in social contacts. It is a condition which can occur from puberty to adulthood, in menopause and even later. Profound exploration of the patient's history has to be performed, when there is any evidence of gynaecological problems the patient should be referred to an endocrine gynaecologist.

Androgen excess may have profound effects on the skin, soma and psyche of patients presenting clinical signs of peripheral hyperandrogenism. It is one of the most common disorders affecting 10% of adult women before the menopause. Most of these women are suffering from acne, alopecia, seborrhoea, hirsutism, menstrual disturbances, anovulation, insulin resistance and obesity. Virilisation is unusual except in patients with ovary or adrenal cancer. More than 90% of hyperandrogenism is due to *polycystic ovary syndrome (PCOS)* and idiopathic hirsutism. Less frequently suprarenal and ovarian malignant tumors, or drug induced hyperandrogenism can be observed. The latter is mainly due to uptake of anabolic steroids, testosterone, and contraception with long-acting progestogene, long-term corticosteroid or cyclosporine therapy

Polycystic ovary syndrome (PCOS) is a complex phenotypic spectrum of primarily hyperandrogenic signs and symptoms. Common dermatologic manifestations of PCOS include hirsutism, acne, acanthosis nigricans, and androgenic alopecia. Hirsute women often have increased activity of 5α-reductase, the enzyme that converts the androgen testosterone to its active metabolite, in hair follicles. Likewise, androgens affect the formation of acne by increasing sebum production from sebaceous glands in the skin.

Androgen metabolism occurs within the pilosebaceous unit, as recently demonstrated by the presence of local differences in the amounts of aromatase, 5α-reductase as well as the androgen receptor (AR). These steroid metabolising enzymes convert weak to more potent androgens, underscoring that the skin is an endocrine target tissue for androgen hormone action, similar to ovaries, testes, and adrenal glands.

Today, peripheral signs of hyperandrogenemia demand an extensive work up of the underlying cause and often present a challenge to the dermatologists in achieving successful management.

WS-4-C
Hirsutism in Children
Speaker: Danielle Marcoux, MD
CHU Sainte-Justine, University of Montreal, Quebec, Canada.

In prepubertal children, hirsutism will manifest with terminal hair over androgen-dependant areas, usually pubis, axilla, labia majoris or base of the penis. When more severe, and in older children, terminal hair will be present over other androgen – dependant areas, such as the upper lip, chin, jaws, neck, internal thighs, buttocks etc.

Idiopathic hirsutism is the most frequent cause, and is usually familial and ethnic. In prepubertal children, hirsutism with precocious puberty is the most frequent pathological cause and may manifest with isolated adrenarche and pubarche with pubic and axillary hair, body odor and acne. Polycystic ovary syndrome and its variant, hyperthecosis , with or without insulin resistance, may first manifest itself in childhood with hirsutism as an early manifestation. As in adults, serious tumoral or non-tumoral virilizing disorders are extremely rare, account for less than 1% of the etiologies, and may present with cliteromegaly or penile enlargement as well as hirsutism and acne.

Important and sensitive signs of precocious puberty are acceleration of the growth curve pattern with tall stature, advanced bone age and signs of hyperandrogenism.

WS-4-D
Treatment of the Hirsute Patient
Speaker: Wilma Bergfeld
The Cleveland Clinic Foundation, Cleveland, OH, USA

Hirsutism can be seen in females and males. In females it represents unwanted terminal hair in a male distribution while in males it manifests as excessive male body and facial hair. Hirsutism in both sexes has a genetic basis and is related to 1) excess in circulating androgens (organ hormonal abnormalities or over production) or 2) target organ excess (peripheral androgen metabolism) of androgens with in the hair follicle and sebaceous gland. There are multiple potential defects of androgen production, transport, metabolism, and clearance. The majority of patients have a genetic basis for their hirsutism unless a tumor, endocrine cancer or androgenic drugs are identified as the inducer. The first step in treatment is to evaluate the etiology of the hirsutism. Once the androgen defect is identified then a targeted therapy can be employed.

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Targeted therapies include hormonal suppressive therapies, androgen agonists, androgen receptor antagonist, 5 alpha reductase inhibitors, insulin sensitizing agents, weight reduction, and surgery. Topical therapies include enzyme inhibitors of hair growth, physical and chemical removal of hair. These therapies will be discussed. Commonly combined and prolonged therapies are required.

WS-4-E
Lasers and the Future
Speaker: R. Rox Anderson, MD
Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA, USA

"Permanent hair reduction" by laser or intense pulsed light treatments is safe and very effective for hirsute women with dark coarse hair, with some important exceptions. Significant problems include lack of response of white hair, lack of knowledge about combination with medical treatment and infrequently, paradoxical apparently permanent hair stimulation. Stimulation tends to occur in women of Mediterranean and near eastern descent, with a phenotype of fine dark facial hair and an ill-defined frontal hairline. Safe treatment of dark skin with longer wavelength, longer pulse duration devices, with skin cooling and appropriate fluence will be discussed. Repeated photothermal damage of hair follicles at relatively low laser fluence induces a catagen-like state that can be used for hair growth control. In the US, FDA recently cleared a laser hair removal device for home use. Photodynamic therapy with topical aminolevulinic acid (ALA-PDT) and high fluence red light has been shown to inactivate anagen hair follicles and sebaceous glands, but has not been developed as a treatment for hirsutism. ALA-PDT may be superior to laser treatment by targeting both acne and hair, regardless of hair color. Advanced laser microscopy of skin, e.g. by optical coherence tomography, can clearly image whole hair follicles *in vivo*. Potentially, imaging will allow better assessment of response to experimental or routine therapy, and might also be combined with a laser microbeam scanner to provide "robotic" treatment of hirsutism.

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Session 1
Stem Cells

S-1-A
Cancer-Initiating Cells: From Leukemia to Solid Tumors
Speaker: John E. Dick, PhD
University Health Network and University of Toronto, Toronto, ON, Canada

Two fundamental problems in cancer research are identification of the normal cell within which cancer initiates and identification of the cell type capable of sustaining the growth of the neoplastic clone. There is overwhelming evidence that virtually all cancers are clonal and represent the progeny of a single cell. What is less clear for most cancers is which cells within the tumor clone possess tumor initiating or "cancer stem cell" (CSC) properties and are capable of maintaining tumor growth. In the last decade there has been progress to identify the CSC of some hematologic and solid cancers. If CSC lie at the heart of cancer, then the biological properties of CSC provide a foundation for the development of more effective therapies. Studies of human acute myeloid leukemia are the most advanced and this session will review the current state of knowledge of leukemic stem cells. A major finding was that LSCs are not functionally homogeneous but, like the normal hematopoietic stem cell (HSC) compartment, comprised of distinct hierarchically arranged LSC classes. In addition, studies will be described on the development of robust experimental models whereby normal human stem and/or progenitor cells can be transformed into full-blown leukemic cells. This approach provides a significant step forward to understand the mechanisms involved in human leukemogenesis and the rules for converting normal hematopoietic cells into leukemic cells. Finally, recent work on the identification of the CSC in colon cancer will be discussed.

S-1-B
Hair Follicle Stem Cells – Epithelial
Speaker: George Cotsarelis, MD
University of Pennsylvania, Philadelphia, PA, USA

Over 15 years ago, we proposed that quiescent keratinocytes in the hair follicle bulge were epithelial stem cells important for hair follicle cycling, epidermal renewal, wound healing and carcinogenesis. Since that time, we identified cytokeratin 15 (K15) expression as a marker for these cells and developed several transgenic mouse models using the K15 promoter to further study the bulge cells. Using K15-EGFP mice, we isolated bulge cells and demonstrated that they possessed an epithelial stem cell phenotype of quiescence, high proliferative

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potential and multipotency. We also characterized the cells at the molecular level using microarrays and identified approximately 150 differentially expressed genes in these cells. Through genetic lineage analysis using an inducible K15-CrePR;R26R bigenic mouse, we showed that bulge cells generate all of the epithelial lineages within the lower anagen hair follicle. However, ablation of bulge cells using K15-thymidine kinase mice resulted in permanent hair loss but survival of the epidermis. Over a prolonged period, bulge cells did not contribute to epidermal homeostasis, but in response to wounding bulge cell progeny rapidly moved into the wound area to assist in reepithelialization. Bulge derived cells did not persist in the epidermis indicating that epidermal stem cells and hair follicle stem cells are distinct populations each with self renewing capabilities.

Session 2
Mesenchymal Stem Cells

S-2-A
Skin-derived Precursors (SKPs) and Induction of Hair Follicle Morphogenesis
Speaker: Freda Miller
Hospital For Sick Children, University of Toronto, Toronto, ON, Canada

We have previously isolated and characterized a population of neural crest-related precursors from rodent and human dermis termed SKPs for skin-derived precursors. SKPs can differentiate into a number of neural crest-derived cell types including myelinating Schwann cells, bone and cartilage. This talk will focus upon our recent work asking about the endogenous role of SKPs within the dermis. We demonstrate that SKPs, when transplanted into adult skin will reconstitute the dermal components of skin, but not the epidermal. Moreover, SKPs can induce de novo morphogenesis of hair follicles, where they comprise both the dermal papilla and dermal sheath. Thus, SKPs may represent a dermal stem cell that maintains both inductive and differentiation potential throughout adult life.

S-2-B
Manipulating Gene Expression in the Dermal Papilla of the Mouse *in vivo*
Speaker: Bruce A. Morgan
CBRC, Charleston, MA, USA
Authors: David Ensehell-Seijffers and B.A.Morgan

The remarkable progress in hair biology in recent years has been fueled in part by the ability to manipulate gene expression in the stem cells and other keratinocytes of the follicle in vivo and to exploit this ability to purify these populations for in vitro analysis. However, the behavior of these keratinocytes during follicle morphogenesis and cycling is dependent on interactions with the dermal papilla, a mesenchymal component of the follicle. The abilities of dermal papilla to drive de novo follicle formation and to direct morphogenesis of the cycling follicle make these cells an attractive target for either cell based or pharmacologic approaches to augmenting or restoring hair growth. Despite this fact, DP cells remain poorly understood when compared to the keratinocyte constituents of the follicle. To facilitate research on this population ,we have developed mouse strains that express cre recombinase specifically in the dermal papilla of the hair follicle, These allow the manipulation of gene expression in the DP of existing hair follicles. The use of these mice to study gene activity and other aspects of DP cell behavior will be discussed.

S-2-C
Mesenchymal-Epithelial Interactions Needed for Tissue Engineering of Hair Follicles
Speaker: Colin Jahoda
University of Durham, Durham, United Kingdom

[Abstract/summary not available at time of printing]

Session 3
Tissue Engineering

S-3
Tissue Engineering of Hair Follicles
Speaker: Kurt Stenn, MD
Aderans Research Institute, Philadelphia, PA, USA

Session 4A
Hair Surgery

S-4A-a
Update on Concepts and Techniques in Hair Transplantation 2007
Speaker: Walter Unger
University of Toronto, John Hopkins Medical School, Toronto, ON, Canada

Objectives: The objective of the presentation will be to not only present current concepts and techniques in hair restoration surgery for men and women, but also to briefly describe the pros and cons of some of the more controversial and sometimes vigorously promoted aspects of the procedure. The latter includes follicular unit extraction (FUE), "megasessions" of more than 2500 FU/session and "dense packing" of FU (over 35 FU/cm^2). The appropriate

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stage/age at which one can reasonably undergo hair transplanting will also be discussed.

Approach: Techniques and results will be clarified through the use of a large number of photographs. Controversies will be dealt with on the basis of tabulated results of studies that have been done to date.

Results: Current techniques in hair restoration surgery are varied, but each can result in excellent cosmetic results. Long-term consequences of megasessions and dense packing make their use less desirable in younger individuals in whom the long-term prognosis is less certain. FUE rather than conventional harvesting of graft material is appropriate only in a relatively small subset of individuals.

Conclusion: Hair restoration surgery continues to evolve with hair survival and results improving almost yearly. Long-term consequences of the results of recent innovations have yet to be determined and therefore their cautious utilization in properly selected individuals is advocated.

S-4A-b
Evidence Based Hair Restoration
Speaker: Andreas M. Finner, MD
Otto-von-Guericke-University Magdeburg, Hair Clinic, Magdeburg, Germany

In spite of recent advancements in technique and aesthetic results, the evidence based on randomized controlled trials (RCT) is limited in hair transplantation (HT). This is partly due to general problems when assessing hair growth, but there are also unique problems when conducting trials in HT.

However, it is imperative to increase the level of evidence in HT. Potential factors that initially need to be investigated include 1) the dynamics of graft hair growth after the procedure, 2) the extent of shock loss and 3) the survival rate of grafts. Concomitantly, efficacy of various techniques and perioperative management can be investigated.

The International Society of Hair Restoration Surgery has formed a task force for evidence based medicine (EBM) to create guidelines for HT studies, increase motivation for surgeons and patients, define important research topics and promote multi-center trials. The members of this task force include both hair researchers and surgeons.

As a first step, we will initiate one large multi-center RCT to evaluate graft survival under standardized conditions. In future studies, hair thickness may become a representative parameter. There are some initial data indicating that the effect of HT does not only result from adding hairs. Pre-existing vellus and miniaturized hair may merely be partially replaced by thicker terminal hairs of higher quality.

Hair research centers could be very helpful in these efforts with their expertise and by providing control groups in HT trials. In return, evidence based hair restoration will certainly stimulate and enrich the field of hair research.

S-4A-c
Racial Differences in Hair Transplantation
Speaker: Valerie Callendar
Howard University College of Medicine, Washington, DC, USA

Due to the changing demographics in the United States, people of color will represent almost 50% of the population by 2050. Therefore, more patients of color will be presenting to the physician seeking medical and surgical treatment for their hair loss. Hair transplant surgery is a common cosmetic procedure used to correct hair loss in men and women of all races and ethnicities. However, there are racial differences and therapeutic challenges which much be addressed when performing hair transplant surgery in patients of color and a clear understanding of these differences allows a greater success in this population of patients. Although there are no major biochemical differences among black, Caucasian, and Asian hair types, there are apparent differences in the hair morphology and hair densities among racial groups. In most cases, the hair structure of black hair is tightly coiled and the hair follicle curved, which can be challenging to the surgeon in donor harvesting and graft preparation. Furthermore, indications, contraindications, surgical instrumentation, preoperative and postoperative counseling will vary as well. In addition, there is an increase risk of hypertrophic scarring and keloid formation in patients of African descent. Finally, in patients with central centrifugal cicatricial alopecia, an inflammatory form of scarring alopecia, there are special considerations that must be addressed when performing hair transplantation. These include alterations in the hair grooming practices, aggressive medical therapy, a test session with biopsy to confirm the absence of inflammation prior to the surgical procedure and a decrease survival rate of transplanted grafts.

Invited Speaker Presentations

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S-4A-d
Hair Restoration Surgery in Unusual Cases: Cicatricial Alopecia, Congenital Alopecia and Other Alopecias
Speaker: Nilofer P. Farjo
Farjo Medical Center, Manchester, United Kingdom

The vast majority of hair restoration procedures are performed for androgenetic alopecia. Transplanting into areas where there is alopecia due to an inflammatory disease process is considered to be contraindicated. However, there are certain cases where the disease process has 'burnt out' when it may be appropriate to transplant after first ascertaining that the disease has not progressed for a minimum time period and biopsy is negative for inflammation. In these situations the clinical course can be relapsing and remitting so we can never be sure that the disease will not reactivate in future. The patient may, however, be grateful for a temporary cosmetic improvement. Congenital aplasias are also situations in which transplantation may be considered if donor hair is adequate.

I will present a number of cases where the decision to transplant was taken after biopsy and clinical evidence pointed to a quiescence of the disease process. Our criteria for transplantation is: 1. No clinically event disease progression for 5 years 2. Biopsy negative 3. Sufficient donor hair for adequate coverage 4. patient understands that the disease may recur and there may be decreased hair survival. 5. Evaluation of the possible development of or progression of concurrent androgenetic alopecia. In some cases where the nature of the scarring indicates the possibility of poor growth test grafting procedure was employed.

Two techniques were employed in the surgical treatment of the patients: scalp reduction and follicular unit grafting. Cases selected included diagnoses such as lichen planus, ulerythema pyrogenes, triangular alopecia. Surgical results are presented with the minimum follow up period of 6 months. Some long term results are available. In selected cases surgical restoration of hair in conditions generally considered to be contraindicated can be performed.

Session 4B
Pathology: Animal and Human Pathology

S-4B
Histopathology of Selected Mouse Models for Human Hair Diseases
Speakers: David Whiting, MD[1], Magdalena Martinka, MD[2], and John P. Sundberg, DVM, PhD[3]
[1]Dallas Associated Dermatologists, Dallas, Texas; [2]Dept. Pathology, University of British Columbia, Vancouver, BC; [3]The Jackson Laboratory, Bar Harbor, Maine, U.S.A.

While there are obviously big differences in size, hair type and quantity, color, and shape of mice and their hair follicles and fibers when compared to humans, the fundamental anatomy, biology, genetics, and diseases are remarkably similar. Repositories around the world make mouse models readily available for investigators to study many diseases. While not all of the human hair diseases have a known genetic basis, many do and homologous models exist. Drs. Whiting and Martinka will present a series of interesting clinical cases from their respective practices and Dr. Sundberg will attempt to match these, where possible, with similar or identical mouse models. Glass slides and microscopes will be provided in advance as well as after the session. Discussions will focus on gross and histologic features of the hair follicle diseases with a brief summary of the genetics and underlying pathophysiology, if known.

Session 4C – Congenital Hair Loss/ Ectodermal Dysplasia

S-4C
Review of Ectodermal Dysplasias
Speaker: Angela Christiano, PhD
Columbia University, New York, NY, USA

[Abstract/summary not available at time of printing]

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Session 5
Morphogenesis / Follicular Cycling

S-5-A
Ebling Lecturer: Wnt and Notch Signaling Pathways in Development and Cancer of the Gut
Speaker: Hans Clevers
Hubrecht Laboratory, Utrecht, The Netherlands

Mutations in the Wnt pathway components APC, beta-catenin and conductin all induce sustained complex formation of the co-activator beta-catenin with TCF transcription factors. The resulting transactivation of TCF target genes represents the primary transforming event in colorectal cancer (CRC). Yet, the consequence of the presence of mutationally activated beta-catenin/TCF in fully transformed CRC cells is unknown. We have constructed CRC cell lines carrying inducible dominant-negative TCF constructs. Inhibition of beta-catenin/TCF resulted in a rapid G1 arrest. DNA array analysis revealed the downregulation of a small set of transcripts. These genes were expressed in polyps, but also, physiologically, in the crypt progenitor compartments of the colon. Beta-catenin/TCF thus imposes a crypt progenitor phenotype on CRC cells. Moreover, inhibition of beta-catenin/TCF activity restores the differentiation program, despite the presence of multiple other mutations in CRC.

TCF target gene expression is always restricted to the crypt, but target genes can be sub-classified based on expression patterns within the crypt. We have tentatively identified at least three target genes which are expressed uniquely in the crypt stem cells.

The Wnt cascade is not the only signaling pathway controlling cell fate along the crypt-villus axis. Upon blocking the Notch pathway genetically, we observe a massive conversion of proliferative crypt cells into post-mitotic goblet cells. A similar phenotype was obtained by blocking the Notch cascade using a gamma-secretase inhibitor. The inhibitor also induced goblet cell differentiation in intestinal adenomas. Our data imply that gamma-secretase inhibitors, developed for Alzheimer disease, may be of therapeutic benefit in colorectal cancer.

S-5-B
New Insights into Telogen
Speaker: Cheng Ming Chuong, MD, PhD
University of Southern California, Los Angeles, CA, USA

In a population, hair follicles can go through regenerative cycle autonomously, simultaneously, or by coupling to generate waves, resulting in complex living hair cycle domains. Here we show each domain consists of initiation sites, propagating wave, and boundaries. Boundaries form because waves hit follicles which are refractory. Using hair plucking, we can define refractory and competent telogen follicles. Molecularly, refractoriness is characterized by expression of Bmp pathway members intra- and inter-follicularly. A BMP reporter mouse sums up oscillating BMP activities in vivo. KRT14-NOG mice shows minimal refractory telogen and simplified transverse wave dynamics. Mutated skin flap transplanted to a normal host exhibits non-autonomous interactions and partial rescue of refractory telogen. A mathematical model based on cellular automata is developed to simulate the behavior of regenerative waves. This novel systematic approach shows sequential re-entry of hair regeneration depends on the stochastic equilibrium among follicle stem cells, intra-follicle micro-environment, and inter-follicle macro-environment.

S-5-C
Wnt Signaling in the Control of Hair Follicle Development
Speaker: Sarah E. Millar, PhD
University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Wnt/β-catenin signaling is required for embryonic hair follicle induction, and K14 promoter-driven expression of stabilized β-catenin causes ectopic hair follicle formation postnatally, suggesting a key role for this pathway in determining hair follicle fate. However the consequences of forced activation of β-catenin signaling in embryonic mammalian skin are not clear. To address this question we mutated endogenous β-catenin to a dominant active form in embryonic surface ectoderm. Hair follicle placode induction was markedly accelerated in mutant embryos, but the placodes failed to invaginate. Wnt reporter gene activation was widespread in E14.5 mutant skin, unlike its normal pattern in developing placodes. Analysis at E17.5 revealed a global failure of epidermal differentiation in the mutant, indicated by lack of expression of the suprabasal and terminal differentiation markers K10, involucrin and loricrin. Instead, the surface epithelium broadly expressed the hair shaft cortex marker AE13. Consistent with global adoption of hair follicle fate, the molecular regulators of hair follicle development *Bmp2*, *Shh* and *Edar* were expressed broadly in mutant epithelium, and the follicular dermal condensate markers *Bmp4* and alkaline phosphatase were expressed throughout the upper dermis. Hair follicle outer and inner root sheath markers were not expressed, indicating specific adoption of hair shaft cortex fate by mutant epithelial cells. These data demonstrate that Wnt/β-catenin signaling is a master regulator of cell fate

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in embryonic surface ectoderm, suppressing squamous differentiation and activating hair follicle initiation and cortex-like differentiation. In addition, both formation of a patterned array of hair follicle placodes and hair germ invagination require controlled downregulation of β-catenin signaling.

Session 6
Follicular Growth Controls

S-6-A
Controlling Hair Follicle Morphogenesis Through Polyubiquitination
Speaker: Anthony E. Oro, MD, PhD
Stanford University, Stanford, CA, USA
Authors: Anthony E. Oro and Erik Huntzicker, Program in Epithelial Biology, Stanford University School of Medicine

Hair follicle development and maintenance require precise reciprocal signaling interactions between the epithelium and underlying dermis. Several key developmental signaling pathways including Wnt, Shh, BMP, and NFkB/Edar are indispensable for this process and when aberrantly activated, can lead to skin and appendage neoplasms. Recent data point to protein polyubiquitination as playing a central role in regulating the timing, duration and location of signaling. Here we focus on how polyubiquitination regulates one of the signaling pathways, Shh, and demonstrate two distinct destruction pathways are required to regulate the Gli activators and a distinct pathway to regulate Gli3 repressor. We find that at least one of the destruction complexes that regulates Gli stability is shared with both the Wnt and NFkB pathway, arguing that polyubiquitination may be a critical global mechanism for controlling the duration and intensity of the hair cycle.

S-6-B
Hedgehog Functions in the Pilosebaceous Unit
Speaker: Andrzej Dlugosz, MD
University of Michigan, Ann Arbor, MI, USA
Authors: Andrzej Dlugosz, Hong Sheng, and Mark Hutchin – University of Michigan Department of Dermatology, Ann Arbor, MI, USA

The discovery of loss-of-function *PTCH* mutations in Nevoid Basal Cell Carcinoma Syndrome provided the first evidence linking the Hedgehog (Hh) signaling pathway to basal cell carcinoma (BCC) development. PTCH, a receptor for secreted Hh ligands, normally represses the Hh pathway by inhibiting the activity of a key signaling effector called SMO. Consequently, loss of PTCH function in BCCs leads to sustained activation of Hh signaling, which plays a central role in the development and maintenance of these tumors. During hair follicle morphogenesis, precisely regulated expression of Hh ligand, which antagonizes the inhibitory effects of PTCH on SMO, leads to spatially and temporally constrained Hh signaling that is required for proliferation of hair follicle epithelium. To explore the possible functions of Hh signaling in the postnatal hair cycle, we have generated transgenic mice with either epithelium-specific inhibition, or activation, of the Hh pathway. Inhibition of Hh signaling blocks proliferation of hair follicle epithelium during spontaneous and depilation-induced anagen, pointing to an important role for Hh signaling in postnatal growth of the hair follicle. On the other hand, sustained, low-level activation of Hh signaling in the follicle outer root sheath leads to a striking impairment in apoptotic regression of this cellular compartment, coupled with its sustained proliferation, during catagen. These data underscore the importance of Hh signaling in driving proliferation of follicle epithelium during anagen, and suggest that shut-down of Hh signaling is required for programmed regression of follicle epithelium during catagen.

Session 7A – Non-Invasive and Invasive Hair Techniques for Quantifying and Visualizing Hair Growth

S-7A-a
Hair Metrix Update
Speaker: Doug Canfield
Canfield Imaging Systems, Fairfield, NJ, USA

[Abstract/summary not available at time of printing]

S-7A-b
GCP-Validation of TrichoScan
Speaker: Rolf Hoffman, MD
Freiburg University, Freiburg, Germany

TrichoScan was validated by the comparative assessment of TrichoScan analysis versus conventional manual visual hair count evaluation. Two validation studies have been performed. The first was conducted in house by the manufacturer, Tricholog GmbH, Freiburg, Germany, and the second under GCP-rules conducted externally by Bioskin GmbH, Hamburg, Germany; a licensed CRO. Digital dermatoscopic images for TrichoScan software analysis were taken from 10 subjects with androgenetic alopecia, with a tattoo location mark present in the measurement area. The measurement area on the vertex of the scalp was shaved on day 1 of the study and 48-hours later the hair was dyed black. All images were analysed by TrichoScan and by three evaluators who manually counted

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hair parameters in every image three times. All images were analysed randomly in a result-blinded fashion. In total, 27,245 hairs were analyzed by hand in the in house validation study and more than 300,000 in the GCP-validation protocol by Bioskin (study 251109BS) The Pearson correlation coefficient revealed a very good correlation of TrichoScan and visual hair counts. Both the in house and the GCP-conforming study.

	Tricholog	Bioskin
Count	0.933	0.966
Count Term.	0.981	0.956
Cumulative Thickness	0.980	0.982
Cumulative Thickness Term	0.964	0.943
Cumulative Hair Length		0.977

In addition, data variability has been calculated for TrichoScan and manual evaluation.

	Tricholog		Bioskin	
	Manual	TrichoScan	Manual	TrichoScan
Count	6.01 %	0 %	5.34 %	0 %
Count Term.	2.84 %	0 %	9.44 %	0 %
Cum. Thickness [mm]	7.57 %	0 %	6.76 %	0 %
Cum. Thickness Term [mm]	9.27 %	0 %	11.31 %	0 %
Thickness [µm]	12.55 %	0 %	5.53 %	0 %
Thickness Term. [µm]	10.05 %	0 %	3.40 %	0 %
Cum. Hair Length [mm]			6.04 %	0 %

The margin of error and consequent data variability from manually evaluated images would necessitate a larger study sample size to overcome the effect of the variability in collected data on the statistical significance of the results. As results are highly reproducible with TrichoScan, the smaller margin of operator error and the consistency in the collected data allow statistically significant results to be obtained from studies with a smaller sample size which is pivotal in clinical trials.

Conflict of interest: The author is the inventor and distributor of TrichoScan

S-7A-c
Dermoscopy of Hair (video)
Speaker: Antonella Tosti, MD
University of Bologna, Bologna, Italy

Videodermoscopy is useful for close examination of the scalp of the follicular ostia and the hair shafts. Magnification ranges from 20x to 80x.

- *Scalp scaling and dandruff:* dermoscopy permits to distinguish psoriasis and sebopsoriais from seborrheic dermatitis. In psoriasis and sebopsoriasis dermoscopy shows tightly coiled capillary loops which correspond to the tortuous capillaries in the dermal papilla.
- *Patchy alopecia:* alopecia areata can be distinguished from other causes of patchy alopecia though dermoscopy, which shows numerous monomorphous round or polycyclic yellow dots that may centrally have a vellus or intermediate hair These dots disappear with hair regrowth. The yellow dot pattern is also observed in alopecia areata incognita and represent in our hands the only non-invasive method to diagnose this condition.
- *Androgenetic alopecia:* more than 20% variability in the hair shaft diameter is typical of androgenetic alopecia and diagnostic in the early phases. The presence of hair diameter diversity permits of distinguish early androgenetic alopecia from chronic telogen effluvium. Peripilar signs, which appears as brown halos around the follicular ostia are a sign of perifollicular inflammation which is often associated with androgenetic alopecia.
- *Inherited and acquired hair shaft disorders:* the hair shaft abnormalities are easily recognized in vivo at high magnification.
- *Scarring alopecia:* in lichen plano-pilaris and discoid lupus erythematosus, dermoscopy shows scalp atrophy due to loss of follicular ostia and keratotyc plugs around the remaining hairs. In folliculitis decalvans tufted folliculitis are often evident.
- *Nits:* dermoscopy permits to distinguish empty from viable nits.

Session 7C
Stress and Hair

S-7C
Overview
Speaker: Ralf Paus, MD
University of Lübeck, Lübeck, Germany

[Abstract/summary not available at time of printing]

Invited Speaker Presentations

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Session 8
Hair Pigmentation

S-8-A
Hair Pigmentation
Speaker: Greg Barsh
Stanford University, Stanford, CA, USA

[Abstract/summary not available at time of printing]

S-8-B
Mechanisms of Melanocyte Stem Cell Maintenance and Hair Graying
Speaker: Emi K. Nishimura, MD, PhD
Kanazawa University Cancer Research Institute, Kanazawa, Ishikawa, Japan

Hair graying is the most obvious sign of aging in man, yet its mechanism is largely unknown. Qualitative and quantitative changes in stem/progenitor cells have been implicated in physiological aging. Melanocytes may be unique in that the oxidative chemistry of melanin biosynthesis can be cytotoxic. This led to the suggestion that differentiated, pigmented melanocytes (rather than their unpigmented progenitors) are specifically targeted in hair graying. The recent discovery of unpigmented melanocyte stem cells (Nishimura EK et al. Nature 2002), distinctly located within the hair follicle, creates an opportunity to determine whether the process of hair graying arises specifically from changes in differentiated melanocytes or the stem-cell compartment which provides them. Here we utilize melanocyte-tagged transgenic mice and aging human hair follicles to demonstrate that hair graying is caused by defective self-maintenance of melanocyte stem-cells. This process is accelerated dramatically with *Bcl2*-deficiency, which causes selective apoptosis of melanocyte stem-cells within the niche at their entry into the dormant state, but not of differentiated melanocytes. Furthermore, physiologic aging of melanocyte stem-cells was associated with ectopic pigmentation or differentiation within the niche, a process accelerated by mutation of the melanocyte master transcriptional regulator *Mitf*. Our recent studies provide more insights into the mechanisms of stem cell dormancy and roles of the niche microenvironment for stem cell maintenance.

Session 9
Chemotherapy-Induced Hair Loss

S-9
Molecular Mechanisms of Chemotherapy-Induced Hair Loss: Global Changes in Expression of Apoptotic and Non-Apoptotic Genes During the Response of Human Hair Follicles to Doxorubicin
Speaker: Vladimir Botchkarev, MD, PhD
Boston University School of Medicine, Boston, MA, USA

Authors: T.Y. Sharova[1], A.A. Sharov[1], R. Atoyan[1], A.N. Mardaryev[2], V.A. Botchkarev[1,2]
Laboratory of Skin Development, Regeneration and Carcinogenesis,

[1]Dept Dermatology, Boston University School of Medicine, Boston, MA, USA,
[2]Medical Biosciences, School of Life Sciences, University of Bradford, UK

Chemotherapy induces DNA damage in rapidly proliferating hair follicle keratinocytes followed by initiation of apoptosis via recruitment of the p53-dependent and independent pathways. To analyze mechanisms involved in initiation of the hair follicle response to chemotherapy, late anagen hair follicles isolated from scalp of healthy individuals were cultured ex vivo with doxorubicin (30 min) and were harvested three hours after treatment. Hair matrix keratinocytes were obtained from the control and doxorubicin-treated hair follicles using laser capture microdissection system (Arcturus), and global microarray analysis was performed using Agilent Whole Human Genome Array. Microarray data validated by the real-time PCR revealed that about 1300 genes show 2-fold and higher differences in expression in doxorubicin-treated hair follicles compared to the control. Vast majority of these genes encoded molecules that are involved in cell adhesion/extracellular matrix remodeling, cytoskeleton/motility, cell signaling/transcription and cell metabolism.

Interestingly, doxorubicin-treated hair follicles showed strong increase in the expression of genes encoding keratin-associated proteins, while expression of the hair keratin genes decreased compared to control. Among the genes involved in apoptosis/cell cycle regulation, substantial changes in expression were seen in those involved in p53/Fas-dependent cell death (P53AIP1, FAS, CFLAR), TNF signaling (TNFSF10), as well as in genes encoding cyclin-dependent kinase inhibitors (p21, p57). Thus, these data suggest that the response of hair follicle keratinocytes to chemotherapy is more complex than previously appreciated and include involvement of a large number of genes

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whose functions are not directly associated with apoptosis. These data also suggest that p53/Fas and TNF signaling are involved in the initiation of the hair follicle response to chemotherapy and that pharmacological modulation of these pathways may be important for prevention of chemotherapy-induced hair loss.

Session 12
Hair Treatments: What's on the Horizon

S-12-A
Laser Hair Treatments
Speaker: R. Rox Anderson, MD
Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA, USA

Hair removal with selective photothermolysis by targeting follicular melanin, is very popular and clinically useful. Three near infrared laser systems and various xenon flashlamps are used in clinical practice, delivered in combination with skin cooling. The "contest" between follicular and epidermal melanin is such that dark skin is best treated with longer wavelength, longer pulses at lower fluence. While dark coarse hair can generally be permanently removed or reduced regardless of skin type, it is challenging to remove fine and/or light-colored hair. Repeated low-fluence laser treatments can painlessly remove pigmented hair; FDA recently cleared the first laser for home use. What other new laser treatments related to hair follicles will emerge? Optically-stimulated hair growth may occur by at least 3 different mechanisms. Paradoxical stimulation of facial hair by lasers or flashlamps intended for hair removal is seen infrequently in women. Hypertrichosis also occurs after repeated porphyrin-photosensitized exposures, e.g. in porphyria. Topical aminolevulinic acid photosensitizes the entire human hair follicle except arrector pili muscles (root sheath layers, bulge, matrix, papilla and sebaceous gland). Already used widely for acne therapy, photodynamic therapy deserves more study for its effects on human hair follicles. Low-level red and near infrared light may conceivably stimulate hair growth through activation of cytochrome C oxidase, mitochondrial signaling or other pathways. Despite some clinical evidence, optical stimulation of hair growth has not yet been carefully studied. Potentially, light could also be used to affect other changes in hair such as pigmentation, color or curliness.

S-12-B
Nanoparticle-based Targeting of Skin Antigen-Presenting Cells via Hair Follicles
Speaker: Annika Vogt
Clinical Research Center for Hair and Skin Physiology, Berlin, Germany
Authors: Annika Vogt[1], Brice Mahe[2], Wolfram Sterry[1], Behazine Combadiere[2], Ulrike Blume-Peytavi[1]

[1]Clinical Research Center for Hair and Skin Physiology, Department of Dermatology and Allergy, Charite – Universitaetsmedizin Berlin, Berlin, Germany;
[2]Laboratoire d'Immunologie Cellulaire et Tissulaire, Hôpital Pitié Salpêtrière, INSERM U543, Paris, France

Drug delivery systems, which target active compounds to the hair follicle, may result in a better penetration and a higher efficiency of hair and skin therapy. Recent studies performed by our group suggest, that nanoparticles in the size range of 40 nm may be used to transcutaneously deliver active vaccine compounds, via the hair follicle, into cutaneous antigen-specific cells. To further investigate the applicability of transcutaneously applied nanoparticles as vaccine carriers, we investigated the penetration and the migratory profile of 40 nm nanoparticles through the skin and to secondary lymphoïd organs of C57BL6 mice using in vivo confocal microscopy. We found that 40 nm nanoparticles penetrated deeply into open hair follicles of tape-stripped murine skin. Within 24 hrs diffusion into the perifollicular tissue occurred, and, concomitantly, nanoparticle-positive cells could be identified in proximal draining lymph nodes, mesenteric lymph nodes and the spleen. Transcutaneous application of immunogenic compounds such as DNA plasmids encoding for ovalbumin (OVA) or OVA itself induced proliferation of OVA-specific CD8 T cells. Similarly, transcutaneously applied human influenza vaccine elicited antigen-specific T cells assessed by IFNγ ELISPOT. Our results further strengthen our concept transcutaneous targeting of cutaneous antigen-presenting cells. Further studies using functional particle-bound antigens will help to validate this route of immunisation.

S-12-C
Role of Hair Follicles of Transcutaneous Drug Delivery
Speaker: Nina Otberg
University of British Columbia, Vancouver, BC, Canada
Authors: Nina Otberg, Alexa Teichmann, Heike Richter, Sabine Schanzer, Wolfram Sterry, Juergen Lademann, University of British Columbia, Vancouver, BC, Canada

The skin with its appendages is the largest organ of the human body. It is our shield against the environment and is necessary for the maintenance of homeostasis. Hypotheses

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concerning the penetration of substances into the skin have assumed diffusion through the lipid domains of the outermost layer of the skin, the stratum corneum. It was believed that hair follicles play a subordinate role in percutaneous penetration processes, although it was presumed that they represent a weakness in the shield. In the past, the investigation of follicular penetration addressed mostly methodical and technical problems. We present different in vivo and in vitro methods for the measurement of the follicular reservoir function and for the determination of transfollicular absorption. We show that hair follicles can form a relevant reservoir for topically applied substances and can act as shunt routes through the skin.

Session 13A
Shape of Hair/Hair Shaft Abnormalities

S-13A-a
Genes in Distinct Types of Murine Hair Follicles: Involvement of BMP Signaling in the Controlling of Hair Thickness and Shape
Speaker: Vladimir Botchkarev, MD, PhD
Boston University School of Medicine, Boston, MA, USA
Authors: A.A. Sharov[1], T.Y. Sharova[1], A.N. Mardaryev[2], R. Atoyan[1], and V.A. Botchkarev[1,2]

Laboratory of Skin Development, Regeneration and Carcinogenesis, [1]Department of Dermatology, Boston University School of Medicine, [2]Medical Biosciences, School of Life Sciences, University of Bradford

Skin morphogenesis results in the development of the hair follicles (HFs) that generate hairs, whose phenotype (length, thickness, shape and color) varies substantially between distinct anatomical sites of the mammalian body. In murine dorsal skin, HFs are grouped into four principal types (guard, awl, auchene and zig-zag) each characterized by distinct size of the hair bulb and phenotype of the hairs generated. By using laser capture microdissection and global microarray analyses, we show that hair matrix cells of different hair follicle types are characterized by distinct expression profiles of adhesion/extracellular matrix molecules, cytoskeleton/cell motility markers, molecules involved in the control of cell differentiation, metabolism, signaling and transcription. We also show that bone morphogenetic protein (BMP) signaling is involved in the regulation of hair follicle size and hair shape. Transgenic (TG) mice overexpressing the BMP antagonist noggin (promoter: K5) are characterized by the replacement of zig-zag and auchen hairs by awl-like hairs and by marked increase in size of anagen hair follicles (HFs), compared to the age-matched wild-type (WT) controls. Markedly enlarged anagen HFs of TG mice show increased proliferation in the matrix and increased number of hair cortex and medulla cells compared to wild-type HFs associated with a strong decrease in expression of cyclin-dependent kinase inhibitor $p27^{KIP1}$ and increased expression of selected cyclins in TG versus WT mice. These data suggest that BMP signaling plays an important role in controlling hair shaft thickness and shape via modulating cell proliferation and expression of cell-cycle associated genes in hair matrix keratinocytes.

S-13A-b
Characterization of Human Hair Shape: From Hair Bulb to Hair Fiber
Speaker: Bruno Bernard, PhD
L'OREAL Recherche, Clichy, France.
Authors: S. Thibaut, S. Malgouries and B. A. Bernard, L'OREAL Recherche, Clichy, France.

Objective: We investigated curly hair morphology and the formation of the hair shaft.

Approach: A comparative study was carried out on a set of human hair whose shapes ranged from straight to tightly curly. Immunohistology and in vitro culture were used to study the specific features of curly hair bulbs. Hair macrofibril organization was investigated by transmission electron microscopy experiments.

Results: We observed that the curly hair bulb exhibited a retro-curvature. When these follicles were micro-dissected and in vitro cultured, the curvature was maintained in the newly formed hair shaft. At the cellular level, the direct comparison of straight hair and curly hair highlighted an intrinsic asymmetry of the proliferative compartment that clearly extended above the Auber line on the convex side of the curvature. This phenomenon led to a delayed differentiation of the inner root sheath and the outer root sheath. The hair cortex itself was elliptical and asymmetric. hHa8 keratin was accumulated in the concave side of the curvature, whereas in straight hair, positive cortical cells were homogeneously distributed around a circular fiber. This asymmetric arrangement of intermediate filaments in the precortex area of curly hairs could possibly reflect some ortho- versus paracortex segregation. In addition, alpha-smooth muscle actin tension marker was synthesized at the very beginning of ORS differentiation, underlining a mechanical stress in the curvature.

Conclusion: The curly shape of the hair seemed to be a consequence of the asymmetric differentiation of the hair bulb in addition to specific signals from the outer root sheath.

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Session 13B
Nutrition and Hair Growth

S-13B-a
Nutrition and Hair Growth
Speaker: Ralph M. Trüeb, MD
University Hospital of Zurich, Zurich, Switzerland

The quantity and quality of hair growth are closely associated with the nutritional state of an individual. Normal supply, uptake, and transport of proteins, calories, trace elements, and vitamins are of fundamental importance in tissues with a high biosynthetic activity such as the hair follicle. It appears that on a typical Western diet, the hair follicle should have no problem in producing an appropriate hair shaft. Nevertheless, in instances of protein and calorie malnutrition, deficiency of essential amino acids, of trace elements, and of vitamins, hair growth and pigmentation may be impaired. The nutritional defect may be environmental or due to a hereditary defect in absorption or metabolism. Response to substitution therapy is usually good. Since an important commercial interest lies in the nutritional value of various vitamin and amino acid supplements, a question that arises is whether increasing the content of an already adequate diet with specific amino acids, vitamins and/or trace elements may further promote hair growth, particularly in the aging hair follicle, where a physiological deficit is hypothesized.

S-13B-b
Supplements, Iron and Hair Growth
Speaker: Wilma Bergfeld
The Cleveland Clinic Foundation, Cleveland, OH, USA

Iron deficiency is the world's most common nutritional deficiency. In young women the most common cause is excessive menses and diet while in young men the most common is diet. In the pre-menopausal and menopausal women the most common cause is menorrhagia.

Hemoglobin concentration is screen for iron deficiency while ferritin is identifies iron storage deficiency. Elevated ferritin can be attributed to infectious, inflammatory, neoplastic conditions or from excessive iron replacement. Additional laboratory test can include erythrocyte zinc protoporphyrin concentration, transferring concentration, serum iron concentration and transferring saturation. If the cause of iron deficient is not attributed to diet or excessive menstruation, other causes should be investigated.

Several published studies suggest that suggest a relationship between iron deficiency and hair loss. Hair loss secondary to iron storage deficiency and, iron deficiency has been observed telogen effluvium, diffuse pattern hair loss, and alopecia areata. In these disorders, an identification of low hemoglobulin and ferritin, and treatment resulted in clinical improvement. Therapy consists of iron supplements; iron containing foods and treatment of the underlying cause. Laboratory monitoring is initially recommended every 8 weeks. In vegetarians, vega vegetarians or in patients with chronic menorrhagia, chronic iron supplement is necessary. The Institute of Medicine recommends: the upper limit of iron intake for men and pregnant and non pregnant women of 18 years of age of older is 45 mg/day. The major side effect is iron overload which can result in tissue damage and fibrosis and exacerbation of hereditary hemochromatosis .

S-13B-c
Female Pattern Hair Loss and Iron – My View
Speaker: Hugh Rushton
School of Pharmacy & Biomedical Sciences, Portsmouth, United Kingdom

The unit area trichogram was developed in late 70's. With the new ability to identify the three fundamental hair variables involved in hair loss, and the emerging understanding of the role of anti-androgens in hair biology; it seemed only a matter of time before we could help women with non-scarring hair loss. So what has happened over the last 30 years?

The fundamental variables have not changed nor has the ability to evaluate them. However, we now have to deal with lag phases, exogen release, nutritional influences, and non-responders to therapies once thought to be the answer to treating female pattern hair loss. In addition, we now deal with patients presenting with new syndromes:- IRIOTI (I Read It On The Internet), SAS (Seen All Specialists), TAT (Tried All Treatments) and SIR (Select Information Retention). Further, recent concern about hormone replacement therapy (HRT) and hormonal manipulation in premenopausal women has not helped.

Female pattern hair loss presenting at any age is neither serious nor life threatening but for those who suffer it can adversely affect their quality of life. The desire to find treatment modalities has been painfully slow and recent pressures on the medical and pharmaceutical professions, together with the restrictions on cosmetic companies to develop effective 'cosmo-pharmaceuticals,' has not helped. So where does this leave us for the future?

Perhaps it is time for me to retire!