**ABSTRACTS**

**LB1565**
Primary cutaneous aspergillosis in a patient with CARD9 deficiency
X Wang, Y Zhang and R Li
Peking University First Hospital, Beijing, China
Aspergillus fumigatus is a saprophytic mold, commonly acting as a pathogen in immunocompetent hosts, and primary cutaneous involvement is even less. Herein, we report a patient of primary cutaneous aspergillosis harboring CARD9 mutations. The 45-year-old patient presented with a 37-year history of skin lesions on the left arm, the lesion was a soy-sized rash on his left eyelid at the age of 8, which slowly enlarged and progressed during the past 3 years. Physical examination revealed erythematous plaques with clear border on his face and nose. Direct microscopic examination showed slender, septate, branched hyphae. A biopsy specimen revealed mixed inflammatory infiltrations with septate hyphae noted in multinuclear giant cells. From tissue cultures, Aspergillus fumigatus was isolated and identified. The patient denied any immunosuppressive conditions, and results of routine laboratory examinations were generally normal. A CT scan excluded pulmonary aspergillosis. Therefore, the diagnosis of primary cutaneous aspergillosis was made on the basis of the above findings. The patient responds well to oral itraconazole and is still under treatment. To study the reason for the prolonged infection and identify the genetic background in this seemingly immunocompetent patient, we sequenced the CARD9 gene. The patient was carrier of a heterozygous missense mutation in the CARD9 gene that showed the patient harbored a homozygous frame shift mutation in exon 6 (c.819_820insG, p.D274fsX60), leading to premature termination codons. His son was asymptomatic and heterozygous carrier of the same mutation. CARD9, mainly expressed in myeloid cells, is a key adaptor in the downstream signaling of several C-type lectin receptors, and mediates anti-fungal immunity by forming a complex with BCL10 and MAL1. This is, to our knowledge, the first report that linked cutaneous aspergillosis to CARD9 mutations. This work enriches both the phototypic spectrum of CARD9 deficiencies and the genetic background of primary cutaneous aspergillosis.

**LB1567**
Ablation of macrophages from hypodermal adventitia disrupts the collagen network resulting in hyperelastic skin
B Vision1, T Dobre1, M Kelly1, T Kobayashi2, D Kim3, C Yan1, Y Hu1, M Kelley1 and K Nagata4
1 Galderma R&D, Biot, France, 2 Nestlé Skin Health, Biot, France, 3 Nestlé and Carros, France and 4 Laboratory of Cochlear Development, NIDCD, NIH, Bethesda, MD and 3 National Institutes of Health, Rockville, MD
Skin is a complex multi-layered organ in which structure and cellular composition of each layer reflect its functional specialization. Both immune and stromal cells in superficial layers of the skin, epidermis and dermis, have been extensively studied. However, deeper layers of the skin - the hypodermis - remain largely unexplored. We used single-cell RNA-sequencing (scRNA-seq) to establish comparative maps of the cellular landscape of hypodermis and dermis. Ablation of myeloid subsets in Cre2-KO mice and colony stimulating factor 1 (Csf1r) op/op mice resulted in prominent changes in extracellular matrix (ECM)-associated genes in hydromidal fibroblasts at the single cell level. Using our scRNA-seq data we identified fibroblasts and endothelial cells as major sources of Csf1r and dermis and hypodermis. Further analysis found that a Tie2-Cre driver line would enable layer-specific deletion of Csf1 in the hypodermal adventitia. In the Tie2-Cre x Csf1-floxed mice, the collagen network of the hypodermal adventitia was disrupted, leading to a hyperelastic phenotype. Notably, Tie2-Cre x Csf1-floxed mice exhibited skin hyperelasticity. Immunofluorescence microscopy revealed altered type I, III, and V collagen networks and special stains and transmission electron microscopy further revealed that large collagen fibers were insufficiently formed in Tie2-Cre x Csf1-floxed mouse adventitia. Altogether, our data show that steady-state hypodermal macrophages regulate the integrity of the ECM. Loss of macrophages resulted in altered collagen networks in the hypodermal adventitia that manifested as skin hyperelasticity, a feature observed in genetic connective tissue disorders or aging skin.

**LB1568**
Investigation of inflammatory response mediators in ex vivo skin culture
H Zhou1, R Slominski1, P Dave2, W Wright1, I Seymour1, M Bell1, D Spandau1 and M Turner1
1 Department of Dermatology, Indiana University School of Medicine, Indianapolis, IN, 2 Indiana University-Purdue University Indiana, Indianapolis, IN, 3 Indiana University-Purdue University Indiana, Indianapolis, IN, 4 University of Illinois College of Medicine, Indianapolis, IN, 5 Indiana University School of Medicine, Indianapolis, IN, 6 Departments of Dermatology and Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN and 7 Departments of Dermatology and Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, IN
Ex vivo skin culture is used as a proxy for understanding cutaneous biology. A potential confounding factor of this method is culture-induced expression of cytokines and chemokines. These studies were designed to investigate mechanism(s) of skin culture-induced cytokine and chemokine expression. Time course studies of ex vivo-cultured mouse tail skin samples were performed, and transcript for Il1a, Il6, Tnf, Ccl2 and Cxcl1 were measured by quantitative PCR. Compared to freshly isolated skin, Il6, Ccl2 and Cxcl1 were significantly increased within 4 hours of culture; in contrast, Il1a, Tnf and Tgfp increased later (e.g., 24 hours) with a small molecular weight of protein in cell culture supernatant. IL-1RI in culture-induced cytokine and chemokine expression; however experiments with skin from TLR3 knockout mice and separate experiments with an Kras cocktail added to cultures did not support this conclusion. In addition, TLR5 blockade with inhibitory oligonucleotides 2088 or IFN-18 did not affect transcript levels. To investigate a role for other TLRs and IL-1 family signaling, studies were performed with skin from Myd88 deficient mice. Relative to wild type, Il1a, Il6, Ccl2 and Cxcl1 were reduced in Myd88 deficient skin. Hereby, we hypothesized that other cytokine and chemokine transcripts examined increased during culture. These data demonstrate TLR3 and TLR9 are dispensable and that Myd88-dependent signaling amplifies but does not initiate culture-induced cytokine and chemokine expression in mouse skin.

**LB1569**
Non-clinical and human pharmacology of the potent and selective topical RARγ agonist triflareotide
J Aubert1, B Bertino1, S Blanchet-Rethore1, A Cabran1, D Deret1, A Dubréo1, A Luzz1, C Mouret1, J Pascual1, J Pelisson1, T Portal4, M Rivier1, P Rosso3, E Thoreau5, E Vial1 and JJ Turner7
1 Galderma R&D, Biot, Provence-Alpes-Cote d’Azur, France and 7 Dermatology, University of Zurich, Zurich, Switzerland, 2 Department of Dermatology, University Hospital Bern, Bern, Switzerland, 3 Department of Dermatology, University Hospital Zurich, Zurich, Switzerland, 4 University Hospital University (USZ), Zurich, Switzerland, 5 Dermatology, USZ, Zurich, Switzerland and 6 Galderma SA, Lausanne, Switzerland
Retinoids have a dominant role in topical acne therapy and to date, only RARα agonists are approved. First- and third-generation retinoids even though efficacious in acne, lack full selectivity for dual agonists have reached the market. Given the tissue distribution of RAR isoforms, it was hypothesized that developing RARγ-selective agonists could yield a new generation of topical acne treatments that would increase safety margins while maintaining the robust efficacy of previous drugs. Structure-based design of Trifarotene, a potent and selective RARγ agonist for the treatment of acne
E Thoreau1, J Aralossse1, C Boix-peter1, S Chambon1, L Chantatal1, S Davier2, L Dumas1, G Ducu1, A Felet1, G Ouvry3, J Pascau1, C Raffin1, N Rodewille1, C Soulet1, S Tabet1, S Talano1 and P Tortel1
1 Nestlé Skin Health, Biot, France, 2 Galderma R&D, Biot, France, 3 Nestlé Skin Health, New York, NY, 4 Nestlé Skin Health, Galderma R&D, Biot, France, 5 Virbac, Carros, France and 6 Galderma SA, Lausanne, Switzerland
Structure-based design of Trifarotene, a potent and selective RAR agonist for the treatment of acne
E Thoreau1, J Aralossse1, C Boix-peter1, S Chambon1, L Chantatal1, S Davier2, L Dumas1, G Ducu1, A Felet1, G Ouvry3, J Pascau1, C Raffin1, N Rodewille1, C Soulet1, S Tabet1, S Talano1 and P Tortel1
1 Nestlé Skin Health, Biot, France, 2 Galderma R&D, Biot, France, 3 Nestlé Skin Health, Galderma R&D, Biot, France, 5 Virbac, Carros, France and 6 Galderma SA, Lausanne, Switzerland
Trifarotene, a selective RARγ agonist, is the latest addition to the RAR antagonist drug class. In addition to its anti-inflammatory and anti-metabolic properties, Trifarotene has activity on sebaceous glands and skin immune cells, therefore it has the potential to address acne-related skin disorders and inflammatory skin diseases. Acne is a multifactorial condition with multiple components, including sebaceous gland hyperplasia, hyperkeratinization and inflammation, along with a dysregulated innate immune response. Trifarotene was designed as a potent agonist of RARγ, a nuclear hormone receptor that regulates gene expression in skin, and is therefore a potential therapeutic target for acne. Trifarotene was shown to be efficacious and safe in clinical trials, with a favorable safety profile in acne and ichthyotic disorders.