19th Annual scientific meeting of the Nederlandse Vereniging voor Experimentele Dermatologie 1 and 2 February 2018

Programme

At the 19th annual scientific meeting of the NVED the ongoing scientific research in dermatology in the Netherlands will be presented.

Programme summary

Thursday 1 February 2018

09.30	-	10.15	Registration and welcome with coffee/tea
10.15	-	10.25	Opening by the chair of the NVED
10.25	-	11.55	Session I: Dermato-Oncology
11.55	-	13.00	Lunch
13.00	-	14.00	Guest Lecture by Prof. dr. Esther de Jong (*AMC*)
14.00	-	15.00	Session II: Immunology & Infection I
15.00	-	16.30	Poster and networking session I (with coffee/tea)
16.30	-	18.00	Session III: Clinical Studies
18.00	-	20.00	Drinks and Dinner
20.00	-	20.30	20th general assembly of the NVED

Friday 2 February 2018

09.00	-	10.15	Session IV: Gene mutation & Function
10.15	-	10.45	Guest Lecture by Prof. dr. Elke de Jong (*RUMC*)
10.45	-	11.30	Poster and networking session II (with coffee/tea)
11.30	-	12:30	Session V: Immunology & Infection II
12:30	-	13.30	Lunch
13.30	-	14.00	Guest Lecture by Prof. dr. Rosalie Luiten (*AMC*)
14.00	-	15.00	Session VI: Skin Biology
15.00	-	15.15	Awards for best presentation and poster, selection breaking news
15.15			Closure

Full programme

THURSDAY 1 FEBRUARY 2018

09.30 - 10.15 **Registration and welcome with coffee/tea**

10.15 - 10.25 **Opening by the chair of the NVED**

10.25 - 11.55 **Session I: Dermato-Oncology**

Session chairs: Remco van Doorn, Klara Mosterd

1.	Nicolas Bastidas *LUMC*	Whole-Genome Sequencing reveals recurrent DNA structural alterations in Primary Cutaneous CD8+ Aggressive Epidermotropic Cytotoxic T-Cell Lymphoma.
2.	Lieke van Delft *MUMC*	Treatment failures after non-invasive therapy for superficial basal cell carcinoma: is there a shift towards a more aggressive histological subtype?
3.	Catarina Salgado *LUMC*	The distribution of DNA hydroxyl- methylation in naevus and melanoma.
4.	Maud Jansen *MUMC*	Topical ingenol mebutate versus 5% 5-fluorouracil versus 5% imiquimod versus photodynamic therapy in the treatment of actinic keratosis: a multi-centre randomized efficacy study.
5.	Darryl Tio *VU/AMC*	Long term efficacy of lentigo maligna treated with 5% imiquimod.
6.	Eline Noels *ErasmusMC*	Management of Actinic Keratosis in Primary and Secondary care in the Netherlands: a mixed methods analysis.

11.55 - 13.00 **Lunch**

13.00 - 14.00 **Guest Lecture by Prof. dr. Esther de Jong (*AMC*): Functional specialization of human skin dendritic cells**

14.00 - 15.00 **Session II: Immunology & Infection I**
Session chairs: Errol Prens, Joost Schalkwijk

7.	Lin Shang *VUMC/ACTA*	Beneficial influence of microcosm biofilm on reconstructed human gingiva.
8.	Danique vd Krieken *RUMC*	The role of gram-positive anaerobe cocci in the human skin microbiome.
9.	Aniek Lamberts *UMCG*	Rituximab in recalcitrant pemphigoid diseases: poor response in IgA dominant cases.
10.	Jorre Mertens *UMCU*	CCL18 as biomarker of disease activity in Localized Scleroderma and Eosinophilic Fasciitis.

15.00 - 16.30 **Poster and networking session I (with coffee and tea)**

P1.	Inge Bronckers *RUMC*	Nail involvement as a predictor for disease severity in pediatric psoriasis: follow-up data from the Dutch ChildCAPTURE registry.
P2.	Wietske Kievit *RUMC*	Starting biologic treatment sequences for plaque psoriasis with ustekinumab or adalimumab is the most cost-effective: a cost utility analysis based on 10 years of Dutch real-world evidence from BioCAPTURE.
P3.	Rutger Melchers *LUMC*	Recommendations for the optimal radiation dose in patients with primary cutaneous anaplastic large cell lymphoma: A report of the Dutch Cutaneous Lymphoma Group.
P4.	Erik de Bakker *VUMC/ACTA*	Low Skin Irritation Threshold in patch test may be a prognostic tool for Hypertrophic Scar Formation.
P5.	Marisol Otero *RUMC*	Beliefs about medicines in psoriasis patients treated with methotrexate or biologics: a cross-sectional survey study.
P6.	Lieneke Ariens *UMCU*	Conjunctivitis Occurring in Atopic Dermatitis Patients Treated with Dupilumab - Clinical Characteristics and Treatment.
P7.	Suzanne van Santen *LUMC*	Folliculotropic mycosis fungoides presenting with a solitary lesion: clinicopathological features and long-term follow-up data in a series of nine cases.
P8.	Denny Siem *LUMC*	Dermoscopy use in the Netherlands.
P9.	Floor Garritsen *UMCU*	Use of oral immunosuppressive drugs in the treatment of atopic dermatitis in the Netherlands.
P10.	Selma Mekic *ErasmusMC*	Healthy diet is associated with less facial wrinkles in women, in a large Dutch population based cohort.
P11.	Angelique Rondags *UMCG*	High reported prevalence of Hidradenitis Suppurativa in Axial Spondyloarthritis patients and high self-reported clinical Axial and Peripheral Spondyloarthritis Features in Hidradenitis Suppurativa patients: two cross sectional studies (HiSpA-1 and HiSpA-2 studies).
P12.	Juul van den Reek *RUMC*	The journey of adult psoriasis patients towards biologics: past and present. Results from the BioCAPTURE Registry.
P13.	Mahdi Saghari *CHDR*	Novel imaging techniques to characterize and assess delayed-type hypersensitivity (DTH) in healthy volunteers.
P14.	Tessa van der Kolk *CHDR*	Characterization of a human skin challenge model of imiquimod-induced skin inflammation.
P15.	Lieke van Vugt *RUMC*	HLA-C*06:02 as a predictor for ustekinumab treatment success in psoriasis patients: a systematic review and meta-analysis.
P16.	Jill de Wit *ErasmusMC*	The prevalence of antibody responses against Staphylococcus aureus antigens in patients with atopic dermatitis: a systematic review and meta-analysis.
P17.	Gijs Rikken *RUMC*	Activation of the aryl hydrocarbon receptor by leflunomide: a novel therapeutic mechanism of action in the treatment of inflammatory skin diseases.
P18.	Jos Smits *RUMC*	The human cutaneous microbiome composition changes after coal tar treatment of both healthy and atopic dermatitis skin.

16.30 - 18.00 **Session III: Clinical Studies**
Session chairs: Loes Hollestein, Juul van den Reek

11.	Floor Garritsen *UMCU*	Improving outcome of azathioprine treatment in chronic eczema by allopurinol co-prescription.
12.	Mark Blankestijn *UMCU*	Diagnosis and characterization of walnut allergy: a tough nut to crack.
13.	Sven van Egmond *ErasmusMC*	Factors influencing current practices and suggested strategies to de-adopt low value follow-up care after basal cell carcinoma: a qualitative study.
14.	Thomas Buters *CHDR*	Omiganan demonstrates pharmacodynamics and clinical activity in patients with mild to moderate atopic dermatitis in a phase 2 proof-of-concept trial.
15.	Tessa Kouwenhoven *RUMC*	Psoriatic dermatitis: an overlap condition of psoriasis and atopic dermatitis in children.
16.	Martijn Doomen ErasmusMC	A clinimetric assessment of a mobile 3D depth sensor on wound surface area measurement.

18.00 - 20.00 **Drinks and Dinner**

20.00 - 20.30 **20th general assembly of the NVED**

20.30 **Social gathering**

FRIDAY 2 FEBRUARY 2018

09.00 - 10.15 **Session IV: Gene mutation & Function**
Session chairs: Ellen van den Bogaard, Marieke Bolling

17.	Frank van Leersum *MUCM*	Improving diagnostic yield for filaggrin; hidden mutations in the Dutch population.
18.	Martijn Sanders *ErasmusMC*	The genetics of seborrheic dermatitis: a candidate gene approach and pilot genome-wide association study.
19.	Jieqiong Qu *RUMC*	EEC syndrome p63 mutations affect epidermal cell identity through rewiring the enhancer landscape.
20.	Eduardo Soares *RUMC*	Dissecting human epidermal commitment in healthy and diseased hiPSC models by single-cell RNA-seq.
21.	Marieke Reinders *MUMC*	Genetic mosaicism in basal cell naevus syndrome.

10.15 - 10.45 **Guest Lecture by Prof. dr. Elke de Jong (*RUMC*): The circle around psoriasis**

10.45 - 11.30 **Poster and networking session II, including posterwalk and presentation of selected posters in conference room (with coffee and tea)**

11.30 - 12.30 **Session V: Immunology & Infection II**
Session chairs: Marcel Teunissen, Marcel Jonkman

22.	Sander Spiekstra *VUMC/ACTA*	Titanium salts tested in reconstructed human skin with integrated Langerhans cells show an irritant rather than sensitizing potential.
23.	Niels de Graaf *VUMC/ACTA*	Improved lymphocyte proliferation in vitro test (LTT) for nickel using CFSE and autologous serum.
24.	Joan Totté *ErasmusMC*	Skin microbiota sampling in atopicdermatitis: to swab or scrub?
25.	Maryam Soltanipoor *AMC*	Examination of irritant-specific effects on the skin barrier requires a multiparameteric approach.

12.30 - 13.30 **Lunch**

13.30 - 14.00 **Guest Lecture by Prof. dr. Rosalie Luiten (*AMC*): Vitiligo and melanoma: yin yang in pigment cell research**

14.00 - 15.00 **Session VI: Skin Biology**
Session chairs: Sue Gibbs, Abdoel El Ghalbzouri

26.	Arnout Mieremet *LUMC*	A reduced external oxygen level improves epidermal barrier formation in human skin equivalents.
27.	Gijs Rikken *RUMC*	Novel AHR ligands for the treatment of atopic dermatitis.
28.	Rajiv Raktoe *LUMC*	Modulation of TGF-β signalling and the effect on (myo)fibroblast differentiation status in hypertrophic scars.
29.	Jos Smits *RUMC*	Aryl hydrocarbon receptor activation upregulates a battery of antimicrobial genes.

15.00 - 15.15 **Awards for best presentation and poster; selection breaking news**

15.15 **Closure**

Meeting Location:
Congress hotel 'De Werelt'
Westhofflaan 2
6741 KH Lunteren
Tel: 0318-484641

Fotograaf: Ineke Schipstra.

Accreditation:
The NVDV has awarded 11 points for full participation in this scientific meeting last year; accreditation for 2018 is applied for.

Programme committee:
Nelleke Gruis (*LUMC*), Michel van Geel (*MUMC*), Patrick Zeeuwen (*RUMC*), Lenie van den Broek (*VUMC*), Gilles Diercks (*UMCG*), Loes Hollestein (*ErasmusMC*), Marcel Bekkenk (*AMC*), Jorien van der Schaft (*UMCU*)

Jury for presentation prize:
Frank de Gruijl (*LUMC*), Hendri Pas (*UMCG*), Ewout Baerveldt (*ErasmusMC*)

Jury for poster prize:
Mijke Visser (*LUMC*), Loes Hollestein (*ErasmusMC*), Patrick Jansen (*RUMC*)

NVED board:
DirkJan Hijnen (chair, *ErasmusMC*, representative in NVDV), Phyllis Spuls (*AMC*) Marieke Seyger (secretary, *RUMC*), Marjon Pasmooij (Treasurer, *UMCG*), Kees Tensen (representative in Federa, *LUMC*)

1. WHOLE-GENOME SEQUENCING REVEALS RECURRENT DNA STRUCTURAL ALTERATIONS IN PRIMARY CUTANEOUS CD8+ AGGRESSIVE EPIDERMOTROPIC CYTOTOXIC T-CELL LYMPHOMA

A.N. Bastidas Torres[1], D. Cats[2], D. Fanoni[3], J. Gliozzo[3], L. Corti[3], M. Vermeer[1], R. Willemze[1], E. Berti[3], C. Tensen[1]
[1]Department of Dermatology, Leiden University Medical Center, Leiden, [2]Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, [3]Department of Dermatology, School of Medicine, University of Milan, Milan, Italy

Background: Primary Cutaneous CD8+ Aggressive Epidermotropic Cytotoxic T-Cell Lymphoma (CD8+ AECTCL) is a rare and aggressive cutaneous T cell lymphoma (CTCL) caused by malignant skin-homing T cells. Although, a variety of clinicopathological features of CD8+ AECTCL have been defined, the genetic basis of the disease is unknown.
Objective: This study aimed at characterizing structural genomic alterations (translocations, copy number alterations (CNAs), etc.) in CD8+ AECTCL by employing Whole Genome Sequencing (WGS).
Methods: Genomic DNA from 13 AECTCL biopsies was subjected to pair-end whole genome sequencing (WGS) on the Illumina HiSeq X-Ten platform. Raw data were processed using an in-house customized pipeline which included quality control assessment, read alignment, CNA detection and structural variant (SV) calling. Finally, processed data was manually curated.
Results: The analysis of the WGS data reveals that gain of 7q11.22 and 17q21.31, and deletion of 1p36.32, 1p36.11, 9p21.3 and 13p14.11 are the most recurrent CNAs in CD8+ AECTCL. We observed numerous inter- and intrachromosomal translocations in all tumor samples, including chromothripsis-like events in chromosomes 1, 4, 6, 10 and 13. Notably, we identified recurrent rearrangements in JAK2 (3/13 samples) and MYC (2/13 samples).
Conclusion: Our high resolution analysis shows that numerical alterations in narrow areas of chromosomes 1, 9, 7, 13 and 17, as well as, translocations in JAK2 and MYC might underlie the pathogenesis of CD8+ AECTCL.

2. TREATMENT FAILURES AFTER NON-INVASIVE THERAPY FOR SUPERFICIAL BASAL CELL CARCINOMA: IS THERE A SHIFT TOWARDS A MORE AGGRESSIVE HISTOLOGICAL SUBTYPE?

L.C.J. van Delft[1,2], P.J. Nelemans[3], M.H.E. Jansen[1,2], A.H.M.M. Arits [1,2,4], M.H. Roozeboom[1,2], M.A. Hamid[5], K. Mosterd[1,2], N.W.J. Kelleners-Smeets[1,2]
[1]Department of Dermatology, Maastricht University Medical Center, Maastricht, [2]GROW Research Institute for Oncology and Developmental Biology, Maastricht University, [3]Department of Epidemiology, Maastricht University, Maastricht, [4]Department of Dermatology, Catharina Hospital Eindhoven, [5]Department of Pathology, Maastricht University Medical Center, Maastricht

Background: There have been concerns that recurrences after non-invasive therapy for superficial basal cell carcinoma (sBCC) transform into a more aggressive histological subtype.
Objective: To evaluate the proportion of patients with an sBCC that develop a treatment failure with a more aggressive histological subtype (nodular or infiltrative) after non-invasive therapy.
Methods: An observational study was performed with data from a single blind, non-inferiority, randomized controlled trial (March 2008 - August 2010). Patients with primary sBCC were treated with imiquimod, 5-fluorouracil or photodynamic therapy (PDT). We evaluated the histological subtype of treatment failure BCCs after five years follow-up. The proportions of more aggressive subtype BCCs were compared between treatment groups and between residual BCC (3 months post-treatment) and recurrenct BCC (later during follow-up).
Results: In 166 patients with a treatment failure, a more aggressive subtype was found in 38.5% (64/166). Assessment per therapy revealed more aggressive residual BCC in 54.8% (17/31) after PDT treatment, in 66.7% (16/24) after 5-fluorouracil, and in 26.3% (5/19) after imiquimod treatment. For recurrent tumors, proportions with a more aggressive subtype were significantly smaller.
Conclusion: Treatment failures after non-invasively treated sBCCs of a more aggressive subtype are more frequently observed 3 months post-treatment. It seems likely that these tumors were underdiagnosed before treatment due to a sampling error of punch biopsies. Residual BCCs following treatment with imiquimod are significantly less often of a more aggressive subtype than following other topical treatments. These results indicate that part of the nodular or infiltrative BCCs may respond to imiquimod.

3. THE DISTRIBUTION OF DNA HYDROXYMETHYLATION IN NAEVUS AND MELANOMA

C. Salgado[1], J. Oosting[2], B. Janssen[3], N. Gruis[1], M. Visser[1], R. van Doorn[1]
[1]Department of Dermatology, Leiden University Medical Center, [2]Department of Pathology, Leiden University Medical Center, [3]GenomeScan, Leiden

Background: Cancer genomes are characterized by global hypomethylation and promoter CpG island hypermethylation. Methylcytosine (5-mC) can be actively demethylated by TET enzymes, a process that involves the oxidation to hydroxymethylcytosine (5-hmC). It has been demonstrated that 5-hmC levels are lower in melanoma than in naevus, and that 5-hmC loss in melanoma is associated with poor prognosis.
Objective: Our aim is to obtain insight into the genomic distribution of DNA hydroxymethylation in the naevus and in melanoma.
Methods: DNA hydroxymethylation and methylation patterns in 8 naevus, 8 non-metastatic melanoma and 8 metastatic primary melanoma tumor samples were analyzed using oxidative bisulphite conversion using beadchips interrogating approximately 850.000 cytosines.
Results: From an unsupervised analysis the 5-hmC patterns of naevus samples can be separated from those of melanoma samples. Only 2% of the interrogated cytosines was hydromethylated in naevus samples. In melanoma there is a pronounced loss of 5-hmC with 0.54% of cytosines showing this covalent modification. The 5-hmC levels were lower in

melanoma across all chromosomes, in promoters, gene bodies, intergenic regions, and in CpG islands, shores and shelves. Differences in 5-hmC between metastatic and non-metastatic melanoma samples were not significant. Interestingly, differentially hydroxymethylated regions included regulatory regions of several tumour suppressor genes.
Conclusion: DNA hydroxymethylation is a rare covalent modification in the naevus and melanoma genome. Gene-centric analysis demonstrates global, but not entirely random depletion of 5-hmC in melanoma. Melanoma samples show lower levels of 5-hmC in regulatory regions of certain tumour suppressor genes, which may contribute to melanoma progression.

4. TOPICAL INGENOL MEBUTATE VERSUS 5% 5-FLUOROURACIL VERSUS 5% IMIQUIMOD VERSUS PHOTODYNAMIC THERAPY IN THE TREATMENT OF ACTINIC KERATOSIS: A MULTI-CENTRE RANDOMIZED EFFICACY STUDY

M.H.E. Jansen[1,2]*, J.P.H.M. Kessels[1-3]*, P.J. Nelemans[4], A.H.M.M. Arits[1,2,5], H.P. van Pelt[6], P.J.F. Quaedvlieg[3], B.A. Essers[7], P.M. Steijlen[1,2,5], N.W.J. Kelleners-Smeets[1,2], K. Mosterd[1,2]
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*These authors contributed equally

Background: In current actinic keratosis (AK) guidelines there are no clear recommendations about which treatment is preferred.
Objective: To evaluate the effectiveness of 5-fluorouracil, imiquimod, photodynamic therapy (PDT) and ingenol mebutate (IM) in patients with multiple AK.
Methods: In this single-blind, randomised controlled multicentre trial, we enrolled patients with clinical diagnosis of ≥5 AK lesions in the head and neck area, involving one continuous area of 25-100 cm2 in four hospitals in the Netherlands. Patients were randomly assigned to receive treatment with 5-fluorouracil (twice daily during four weeks), 5% imiquimod (three days/week for four weeks), methylaminolevulinate (MAL-)PDT (one session), or 0·015% IM (three consecutive days). The primary outcome is the proportion of patients with ≥75% reduction of the number of AK counted at baseline, 12-months post-treatment, according to the intention-to-treat analysis. Here we report the treatment success 3 months post-treatment.
Results: 624 patients were recruited between November 2014 and March 2017 and randomised: 155 to receive 5-fluorouracil, 156 to receive imiquimod, 156 to receive MAL-PDT, and 157 to receive IM. The proportion of patients with treatment success 3-months post-treatment and the relative risk per treatment will be presented.
Conclusion: Our study showed that after 3-months follow-up 5% 5-fluorouracil cream is superior to IM gel in the treatment of patients with multiple grade I-III AK in the head,- and neck area.

5. LONG TERM EFFICACY OF LENTIGO MALIGNA TREATED WITH 5% IMIQUIMOD

D. Tio[1], C.H.G Ruijter[2], C. van Montfrans[3], M.W Bekkenk[2]
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Background: Lentigo maligna (LM) is a precursor lesion of lentigo maligna melanoma (LMM). It is treated to prevent progression. The gold standard of treatment is excision with a 5 mm margin. An alternative option is topical imiquimod (IMQ).
Objective: This study was intended to evaluate the long term efficacy of LM treated with IMQ.
Methods: All LM patients treated with IMQ between 2004-2017, in the Vrije Universiteit medical centre were included. Patients applied IMQ once daily for 12 weeks. Electronic files were retrospectively evaluated.
Results: We identified 57 patients, a mean age of 76 years (53-96 years), and a mean follow-up of 32 months (1-137 months). Of 57 patients treated, 45 (79%) showed a complete clinical response, 6 (11%) a partial response and 3 (5%) no response, 3 (5%) stopped prematurely. A biopsy was taken post-treatment in 42 of 57 patients. Of these biopsies, 38 of 42 were clear. During follow-up recurrence occurred in 7 of 57 patients (12%). All 7 of the patients with recurrence had biopsies in which no LM was found. A single patient developed LMM after 51 months of follow-up with previously no clinical signs of pigmentation and a biopsy post-treatment that showed no LM.
Conclusion: Our study shows that 79% of LM patients treated with IMQ show complete clinical clearance at an average follow-up of 39 months (1-137 months) with a recurrence rate of 12%. IMQ is a treatment alternative for patients who do not qualify for, or do not wish to undergo surgical treatment.

6. MANAGEMENT OF ACTINIC KERATOSIS IN PRIMARY AND SECONDARY CARE IN THE NETHERLANDS: A MIXED METHODS ANALYSIS

E.C. Noels[1], L.M. Hollestein[1,2], M. Lugtenberg[3], B. van Nistelrooij[4], P. Bindels[5], J. van der Lei[6], T. Nijsten[1], M. Wakkee[1]
[1]Department of Dermatology, Erasmus Medical Center Cancer Institute, Rotterdam, [2]Department Research, Netherlands Comprehensive Cancer Center (IKNL), Utrecht, [3]Department of Public Health, Erasmus University Medical Center Rotterdam, Rotterdam, [4]Zorginstituut Nederland, Diemen, [5]Department of General Practice, Erasmus Medical Center, Rotterdam [6]Observational Health Data Sciences and Informatics (OHDSI), Erasmus University Medical Center, Rotterdam

Background: The high prevalence of actinic keratoses (AK) and its potential to progress into squamous cell carcinoma (SCC) requires optimization of healthcare resources.
Objective: To describe the healthcare pathways of AK patients in primary and secondary care in the Netherlands in order to identify areas of improvement.
Methods: A multiple database study design was used to extract information concerning diagnosis, treatment, and follow-up of patients with AK in the Netherlands. The following data sources were included; AK data from a population-based cohort study (Rotterdam Study) linked to general practitioner (GP) records, routine GP records (Integrated Primary Care Information [IPCI]) of patients with an AK diagnosis in primary care, and national claims data to extract secondary care data (DBC information system [DIS]).
Results: Of the people diagnosed with >10 AK during a skin screening visit in the Rotterdam Study, 50% (136/270) had no recording for AK in their routine GP file. Cryotherapy and topical field therapies were the most commonly applied treatments; 74% and 7% by GPs (253/341; 23/341 resp.), and 56% and 26% by dermatologists (203/364; 95/364 resp.). GPs usually did not plan follow-up visits (24%, 46/189), whereas dermatologists plan follow-up visits in more than half of AK patients. after five years of follow up 26% (9,860/38,049) of AK patients in DIS had developed skin cancer.
Conclusion: Limited awareness, risk differentiation, and follow-up visits potentially lead to under treatment in primary care. In secondary care, the numbers of follow-up visits are high potentially leading to overtreatment.

7. BENEFICIAL INFLUENCE OF MICROCOSM BIOFILM ON RECONSTRUCTED HUMAN GINGIVA

L. Shang[1], D. Deng[1], J.K. Buskermolen[2], M.M. Janus1, B.Ph. Krom[1], S. Roffel[2], T. Waaijman[3], C. van Loveren[1], W. Crielaard[1], S. Gibbs[2,3]
Departments of [1]Preventive Dentistry, and [2]Oral Cell Biology, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and VU University Amsterdam, Amsterdam, [3]Department of Dermatology, VU University Medical Centre, Amsterdam

Background: Oral mucosa actively recognizes and responds to microbes. Microbial exposure can modulate a broad diversity of protective responses which are beneficial to the host. However, conventional in vitro models cannot provide sufficient evidence as they lack some representative native features. Therefore, organotypic models were developed to represent the complexity closely to the in vivo situation.
Objective: To investigate the influence of multi-species microcosm biofilm on reconstructed human gingiva (RHG) during a seven day co-culture period.
Methods: The following parameters were compared between microcosm-exposed and unexposed RHGs (Day 1, 2, 4 or 7). Epithelium thickness, cellular proliferation (PCNA, Ki-67) and antimicrobial peptide Elafin were investigated by immunohistochemical staining. The secretion of cytokines was assessed by ELISA. The presence and viability of microcosm was detected by FISH staining and viable bacterial cell counts.
Results: In the microcosm-exposed RHG, a epithelium which more closely represented native tissue was developed. The epithelium was thickened, and highly proliferative as shown by PCNA and Ki-67. Elafin was strongly expressed in upper epithelium where host-microbe interactions begin. While unexposed RHG remained thin, readily senesced and expressed low Elafin. Increased secretion of IL-6, CXCL1, CXCL8, CCL20 was observed in microcosm-exposed RHGs. Although FISH showed the presence of microcosm, a rapid decrease of viable microbes was revealed by counting.
Conclusion: We showed that the exposure to microcosm beneficially stimulates the RHG to become more representative of healthy native gingiva and contributes to regulating its inflammatory and antimicrobial properties, thus increasing the resistance of gingiva to potential pathogens.

8. THE ROLE OF GRAM-POSITIVE ANAEROBE COCCI IN THE HUMAN SKIN MICROBIOME

D.A. van der Krieken[1], G. Rikken[1], I.M.J.J. van Vlijmen-Willems[1], B. van Cranenbroek[2], M. Eilander[1], E.H. van den Bogaard[1], J. Schalkwijk[1], P.L.J.M. Zeeuwen[1]
[1]Department of Dermatology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, [2]Department of Medical Immunology, Radboud University Medical Center, Nijmegen

Background: Individuals with ichthyosis vulgaris (IV) have a loss-of-function mutation in their filaggrin gene. We have recently reported that the absence of this structural skin protein affects the composition of the microbiota present on the skin; FLG-deficient patients have a lower abundancy of gram-positive anaerobic cocci (GPAC).
Objective: As FLG mutations also predispose to develop atopic dermatitis (AD), we are interested in the role of these GPAC in the human skin microbiome and the possible association of the absence of these bacteria with AD.
Methods: The direct influence of GPAC (Finegoldia magna, Anaerococcus prevotii, and Peptoniphilus asaccharolyticus) on the growth of the AD-associated skin pathogen Staphylococcus aureus was assessed in vitro. Furthermore, the interaction of GPAC with peripheral blood mononuclear cells (PBMC) (proliferation and cytokine production) and human primary keratinocytes (gene/ protein expression) was determined.
Results: GPAC did not influence the growth, virulence or biofilm formation of S.aureus strains. F.magna, the most abundant GPAC on skin, did have a pronounced effect on PBMC cytokine production compared to other skin commensals or S.aureus strains. Besides, GPAC and the culture supernatant of PBMC treated with F.magna induced a high and fast expression of antimicrobial proteins in keratinocytes. These results were verified in a human epidermal equivalent.
Conclusion: We suggest that F.magna, in case of skin barrier disruption, can act as an 'alarm signal' and induce a rapid immune response. Thereby, the early production of antimicrobial proteins by keratinocytes, induced by GPAC, could protect against the colonization of pathogens like the AD-associated S.aureus.

9. RITUXIMAB IN RECALCITRANT PEMPHIGOID DISEASES: POOR RESPONSE IN IGA DOMINANT CASES

A. Lamberts[1], H.I. Euverman[1], J.B. Terra[1], M.F. Jonkman[1], B. Horváth[1]
[1]*Department of Dermatology, University Medical Center Groningen, University of Groningen, Groningen*

Background: Rituximab (RTX) is a monoclonal antibody that targets CD20, a transmembrane protein expressed on B cells, causing B cell depletion. RTX has shown great efficacy in pemphigus patients. Data regarding the effectiveness of RTX in pemphigoid diseases are limited.
Objective: To determine the effectiveness and safety of RTX in pemphigoid diseases.
Methods: The medical records of 28 pemphigoid patients treated with RTX were retrospectively reviewed. Response was measured by disease control (DC), partial remission (PR), complete remission (CR) and by relapse rates, which were all defined according to international consensus. Safety was measured by reported adverse events and deaths.
Results: Patients with bullous pemphigoid (BP; n=8), mucous membrane pemphigoid (MMP; n=14), epidermolysis bullosa acquisita (EBA; n=5) and linear IgA disease (LAD; n=1) were included. Treatment with 500mg RTX (n=6) or 1000mg RTX (n=22) was administered on day 0 and 14. DC was achieved in 67.9%, PR in 57.1%, and CR in 21.4% cases. During follow-up 66.7% patients relapsed. No significant difference in response between pemphigoid subtypes was found. Interestingly, IgA dominant cases achieved less DC (20% vs. 81.3%; p=,007), PR (20% vs. 62.5%; p=,149) and CR (0% vs. 18.8%; p =,549) compared to IgG dominant cases. Five grade 3/4 adverse events and 3 deaths were reported. One death was possibly related to RTX.
Conclusion: RTX can be effective in recalcitrant pemphigoid diseases, however not in IgA dominant cases. Cautiousness is warranted in patients with concomitant use of high dose immunosuppressive drugs causing high risk of infection.

10. CCL18 AS BIOMARKER OF DISEASE ACTIVITY IN LOCALIZED SCLERODERMA AND EOSINOPHILIC FASCIITIS

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Background: Localized Scleroderma (LoS) encompasses a group of sclerotic skin conditions.
Objective: In this study, we investigate potential biomarkers for disease activity in LoS.
Methods: Serum was collected from patients affected by LoS or Eosinophilic Fasciitis (EF) and used to determine serum cytokine concentrations. Addditionally, ficoll-separated Peripheral Blood Mononuclear Cells (PBMCs) were isolated and 3 skin biopsies were taken from: the inflammatory border (I) and sclerotic centre (II) of affected skin and from unaffected skin (III). Skin biopsies and isolated PBMCs were used to investigate gene expression.
Results: Serum concentrations of 41 cytokines were investigated in 54 LoS, 20 EF patients, and 22 healthy controls (HC). CCL18 was identified as most promising analyte: CCL18 was significantly increased in EF (median 23.432 pg/ml, [IQR]: 8.599-33.758 pg/ml) and LoS (18.284 pg/ml [7571-27.188 pg/ml]), compared to HC (7.158 pg/ml [2.772-14.069 pg/ml, P-values <0.0001 and 0.0013 versus EF and LoS, respectively]. Additionally, CCL18 concentrations correlated to the modified Localized Scleroderma Skin Severity Index (mLoSSI) (rs=.460, P<0.0001). CCL18 was not expressed in PBMCs. In LoS skin (N=15), CCL18 gene expression was increased in the inflammatory border compared to healthy control skin (Median FC=4.06, P .012), but not in the sclerotic centre of affected tissue.
Conclusion: CCL18 serum concentration is increased in LoS and EF and is associated with clinical scores for disease activity. In addition, CCL18 gene expression is increased in the inflammatory border of skin lesions, but not in circulating immune cells, suggesting both conditions result from skin-directed immune dysregulation rather than systemic immune dysregulation.

11. IMPROVING OUTCOME OF AZATHIOPRINE TREATMENT IN CHRONIC ECZEMA BY ALLOPURINOL CO-PRESCRIPTION

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Background: Azathioprine (AZA) is frequently used in atopic dermatitis (AD). However, high discontinuation rates due to side effects and/or inefficacy are reported. Studies in inflammatory bowel disease led to strategies to reduce toxicity risk and optimize efficacy by adding allopurinol. This co-prescription shifts the AZA metabolism towards 6-thioguanine nucleotide (6-TGN) production, resulting in reduction of hepatotoxicity and increase of clinical effect.
Objective: To investigate the effect of allopurinol co-prescription in patients with AD and/or chronic hand/foot eczema treated with AZA on metabolite levels (6-TGN and methylated 6-methylmercaptopurine [6-MMP]), side effects and clinical efficacy.
Methods: AZA metabolite levels were measured in adult patients with AD and/or chronic hand/foot eczema, during AZA monotherapy and after co-prescription of allopurinol. Clinical effectiveness (Investigator Global Assessment) and side effects were analyzed.
Results: Fifteen patients were enrolled. Reasons for allopurinol co-prescription were inefficacy during AZA monotherapy, side effects or skewed metabolism. After allopurinol addition, 6-MMP levels decreased and 6-TGN levels increased in all

patients. Prior to allopurinol addition, four patients (26.7%) were classified as responder, compared to seven patients (46.7%) after allopurinol co-prescription (p=0.013).
Conclusion: Co-prescription of allopurinol may optimize AZA treatment outcome in chronic eczema by increasing 6-TGN and decreasing 6-MMP levels.

12. DIAGNOSIS AND CHARACTERIZATION OF WALNUT ALLERGY: A TOUGH NUT TO CRACK

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Background: Little is known on the value of diagnostic tests and eliciting doses (EDs) for symptoms in walnut allergy.
Objective: Assess the value of skin prick test and specific IgE (sIgE) tests to walnut extract and components Jug r 1-4 and establish population EDs for walnut allergy.
Methods: In a prospective diagnostic study, adults with a suspected walnut allergy based on history were included, tested and challenged using a double-blind placebo-controlled food challenge.
Results: Fifty-seven subjects were challenged and walnut allergy was confirmed in 33 subjects (58%). Sensitization to Jug r 1 (2S albumin) was most prevalent in the allergic group (55%), while Jug r 2 and 4 were only recognized by a small subset but with a high positive predictive value (90%). Discriminative ability of Jug r 1 sensitization was similar to sensitization to walnut extract in SPT of sIgE testing (AUC 0.75-0.79). Objective symptoms occurred in 20 of the positive challenges (61%). The cumulative EDs in the distribution models ranged from 3.1 to 4.1 mg for the ED05 and from 10.6 to 14.6 mg walnut protein for the ED10.
Conclusion: sIgE to Jug r 1 had the highest discriminative ability of the walnut components, but did not have additional value compared to sIgE to walnut extract or SPT with commercial walnut extract. Population EDs for walnut are slightly higher compared to those for hazelnut allergy, indicating that ED values for hazelnut could be used as a conservative temporary placeholder when implementing risk management strategies for other tree nuts.

13. FACTORS INFLUENCING CURRENT PRACTICES AND SUGGESTED STRATEGIES TO DE-ADOPT LOW VALUE FOLLOW-UP CARE AFTER BASAL CELL CARCINOMA: A QUALITATIVE STUDY

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Background: Providing follow-up care to low-risk basal cell carcinoma (BCC) patients can be considered as low-value care, as evidence is lacking that this translates into improved patient outcomes. Despite Dutch guidelines recommending against it, dermatologists seem to provide more follow-up care than recommended.
Objective: To identify factors influencing current BCC follow-up care and suggested strategies to de-adopt the lower-value follow-up care among dermatologists. As the general practitioner (GP) will be the first contact for the patient after de-adopting the follow-up care, views of GPs are also explored.
Methods: A qualitative study of 40 semi-structured interviews with dermatologists and GPs was conducted. The interviews focused on current practice, influencing factors, and suggested strategies using a predefined topic list. Interviews were audio-taped and transcribed verbatim. Two researchers performed thematic content analysis using the program Atlas.ti.
Results: Factors influencing current follow-up practices among dermatologists included a lack of trust in GPs to adequately identify suspected lesions, complying with patients' preferences and financial incentives for performing follow-up visits. Suggested strategies by dermatologists to de-adopt the low-value care were to provide skin cancer education and training to GPs and to educate patients about the non-effectiveness of follow-up visits. GPs reported a need for improved collaboration and communication between dermatologists and GPs in addition to skin cancer education and training.
Conclusion: Several factors appear to contribute to current low-value follow up practices after BCC. In order to de-adopt the lower-value care it seems useful to target interventions to dermatologists, GPs as well as patients.

14. OMIGANAN DEMONSTRATES PHARMACODYNAMIC AND CLINICAL ACTIVITY IN PATIENTS WITH MILD TO MODERATE ATOPIC DERMATITIS IN A PHASE 2 PROOF-OF-CONCEPT TRIAL

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Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease with a high medical need. Omiganan is an indolicidin analogue with antimicrobial and immunomodulatory properties that could be beneficial to patients with AD.
Objectives: The primary endpoint was to explore the pharmacodynamics and efficacy. Other endpoints included safety, tolerability, and the exploration of the cutaneous microbiota as biomarker.
Methods: We conducted a randomized, double-blind, placebo-controlled phase 2 study involving thirty-six (36) patients with mild to moderate AD with at least an atopic dermatitis lesion (target lesion) at one of the antecubital forearms. They were randomly assigned to topical omiganan 1%, topical omiganan 2.5% or vehicle gel QD for 28 consecutive days. All thirty-six (36) subjects completed the study with good tolerability at the administration site. Baseline characteristics were comparable.
Results: A reduction in the objective SCORAD of the target lesion was observed in both active treatments vs. vehicle, that

was significant for the highest concentration of omiganan (2.5%) compared to vehicle (p = 0.0404). Similar effects were observed in itch in the first half of the day. A shift from lesional to non-lesional microbiota predominantly for reduction in staphylococcus genus was observed in both active treatment groups, but not in the vehicle group.
Conclusion: Topical administration of omiganan QD for up to 28 days is well tolerated. Pharmacological activity of the compound was observed in the oSCORAD, itch and the skin microbiota. This study supports further exploration of the skin microbiota as new biomarker for clinical trials in AD.

15. PSORIATIC DERMATITIS: AN OVERLAP CONDITION OF PSORIASIS AND ATOPIC DERMATITIS IN CHILDREN

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Background: In majority of children, psoriasis is a clinical diagnosis. However, at least 5% presents with a so-called overlap condition with clinical features of both psoriasis and atopic dermatitis (AD), previously described as psoriatic dermatitis (PD). Characteristics of PD and clinical differences from psoriasis are relatively unknown.
Objective: To determine patient and clinical characteristics of children with PD and to compare this population with a pediatric psoriasis cohort.
Methods: Children referred to our pediatric psoriasis outpatient clinic with features of both AD and psoriasis during their first consultation, were included. PD subjects were compared to our ChildCAPTURE cohort, a prospective observational registry of children with psoriasis.
Results: PD was present in 41 subjects (34% boys). Patients with PD were younger than those diagnosed with pediatric psoriasis (9.2±0.7 vs 11.0±0.6 years;p=.000). Koebnerization was less frequently seen in PD(2% vs 34%;p=.000). 44% had atopic disease in the immediate family compared to 10% of the pediatric psoriasis population(p=0.000) whereas 23% of PD subjects had first-degree family members with psoriasis versus 48% of the pediatric psoriasis cohort (p=0.016). Clinical examination revealed lower BSA scores (mean BSA 2.9±0.7 vs 7.4±1.1;p=.002) and less scalp involvement (51% vs 90%;p=.000) in PD subjects. There were no significant differences in presence and intensity of itch.
Conclusion: PD subjects were younger, reported atopic disease in their family more frequently and less koebnerization than pediatric psoriasis patients. Clinical assessment showed lower severity scores as well as less scalp involvement. In contrast to itch, these factors may contribute to distinguish PD from psoriasis in daily clinical practice.

16. A CLINIMETRIC ASSESSMENT OF A MOBILE 3D DEPTH SENSOR ON WOUND SURFACE AREA MEASUREMENT

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Background: Adequate wound management requires objective, valid, reliable wound measurement in order to accurately characterize wound healing and evaluate the intended treatment intervention. While high-end 3D techniques are the most reliable on the market, they remain cumbersome, expensive, and time-consuming. Therefore, low-end 3D techniques might prove more feasible for routine clinical use.
Objective: a clinimetric assessment of a mobile 3D depth sensor on wound surface area measurement.
Methods: Validity was tested by scanning three stickers with a true value of 8,01cm², 16,32cm² and 41,03cm² on respectively the lateral malleolus, forearm and shoulder in order to mimic increasing wound size and body curvature. Reliability was tested scanning fifty wounds in a multi-observer setting using the Occipital™ Structure Sensor, a low-end 3D depth sensor, attached to an iPad Air 2. Wound borders were assigned manually by using the iPad touchscreen and surface area calculation was performed instantly by using the 3DUniversum™ Healthcare application.
Results: Validity of all three stickers showed a Coefficient of Variation (CV) of 1.3%, 0.9% and 0.4% for respectively lateral malleolus, forearm and shoulder measurements. Reliability analysis showed an Intraclass Correlation Coefficient (ICC) of 0.99 with a CV of 2.8%. Limits of agreement (LoA) were calculated at 0 ± 0.10 x mean surface area.
Conclusion: Low-end 3D depth sensors are valid and reliable for wound surface area measurement. The LoA surpasses its high-end counterpart and thus provides more reliable 3D measurements. Further innovation will lead to standard implementation of depth sensors within mobile devices and provide more feasible use of 3D techniques within general wound care.

17. IMPROVING DIAGNOSTIC YIELD FOR FILAGGRIN; HIDDEN MUTATIONS IN THE DUTCH POPULATION

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Background: Molecular diagnostics with conventional Sanger sequencing for ichthyosis vulgaris (IV) has been hampered by the notoriously difficult to analyse filaggrin (FLG) gene, caused by its homologous and polymorphic repeated units. By implementation of single molecule molecular inversion probes (smMIPs) and next generation sequencing (NGS), an alternative screening strategy for analysis of the entire coding region of the FLG gene becomes feasible.

Objective: Genetic analysis of the whole gene instead of screening for only population-specific mutations, would improve diagnostic yield by scrutinizing also for rare family-specific mutations or specific mutations in ethnicities not previously studied.
Methods: The smMIP-NGS strategy is easy to implement, affordable and since exclusion of NGS-duplicate-reads is possible, mutation-percentages can be related and assigned to polymorphic duplicated filaggrin-repeat-unit 8 and 10.
Results: In a cohort of previously screened Dutch patients (N=70) for only the population-specific mutations, retrospectively the whole FLG gene was analysed. Since all known mutations result in premature protein termination, focus of attention was on identifying nonsense and small insertion or deletion mutations. In several (8/70) of the screened patients additional novel truncating mutations were identified, elucidating their previously unexplained (more severe) clinical presentations.
Conclusion: This study emphasises the need for screening the entire FLG gene for mutations, to improve the diagnostic yield in IV and identify hidden variants in the homologous repeated units of the gene. Herein, the smMIP-NGS method proves to be a reliable straightforward strategy to boost clinical diagnostics for IV and opens possibilities to facilitate patient stratification in large cohort studies.

18. THE GENETICS OF SEBORRHEIC DERMATITIS: A CANDIDATE GENE APPROACH AND PILOT GENOME-WIDE ASSOCIATION STUDY

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Background: Seborrheic dermatitis is a chronic inflammatory skin disease with a complex etiology. Genes have been implicated in the susceptibility for other skin inflammatory diseases (e.g. psoriasis), but whether there is genetic susceptibility to develop seborrheic dermatitis is unknown.
Objective: We conducted a candidate gene approach study (CGA) to investigate whether genetic variants previously associated with atopic dermatitis or psoriasis are also associated with an increased risk of seborrheic dermatitis. In addition, we carried out the first genome-wide association study (GWAS) to identify novel genetic variants associated with seborrheic dermatitis.
Methods: Participants of the Rotterdam Study with available genotype data underwent a skin examination by a trained physician to assess whether the participant had seborrheic dermatitis. DNA extraction from whole blood, genotyping, imputation and quality control were carried out following standard protocols.
Results: In total, 609 of the 4,050 participants were diagnosed with seborrheic dermatitis. In the CGA, significant associations between the LCE3 and MICB genes and seborrheic dermatitis were found, although these were not significant after multiple testing correction. Further, we found two significant SNPs in the GWAS: rs58331610 (p-value: 1.75x10-8) that mapped to the MAST4 gene and rs16944244 (p-value: 2.10x10-8) that mapped to an intergenic region between genes PIRT and SHISA. These genes have not been implicated in other skin conditions.
Conclusion: No robust evidence was found for a shared genetic background between seborrheic dermatitis and psoriasis or atopic dermatitis. Two novel hits for seborrheic dermatitis were identified in a pilot GWAS that need to be further validated.

19. EEC SYNDROME P63 MUTATIONS AFFECT EPIDERMAL CELL IDENTITY THROUGH REWIRING THE ENHANCER LANDSCAPE

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Background: Transcription factor p63 is a key regulator of epidermal keratinocyte proliferation and differentiation. Here we characterized the transcriptome and epigenome from Ectrodactyly Ectodermal Dysplasia Cleft Lip/Palate (EEC) syndrome patients carrying heterozygous mutations in the p63 DNA-binding domain.
Methods: Using an established in vitro differentiation model of epidermal keratinocytes, we characterized keratinocytes derived from EEC patients (R204W, R279H and R304W, p63 mutants), as compared to non-EEC individuals (controls). RNA-seq and epigenomic analyses including p63 and RUNX1 ChIP-Seq as well as histone marks H3K27ac, H3K4me3, and H3K27me3 ChIP-Seq, were performed to investigate the underlying mechanism.
Results: The transcriptome of mutant keratinocytes deviates from the normal epidermal cell identity. Epigenomic analyses showed that deregulated gene expression in mutant keratinocytes is caused by an altered distribution of enhancers contributed by the loss of p63 binding and by the unexpected gain of ectopic enhancers. The mutant-specific enhancers are frequently bound by deregulated transcription factors such as RUNX1. Analysis of RUNX1 in mutant keratinocytes confirmed the aberrant recruitment of RUNX1 to the mutant-specific enhancers, and reversing RUNX1 overexpression partially rescued deregulated gene expression.
Conclusion: Our data suggest an intriguing model that a combination of 'dominant negative' and 'gain-of-function' effects of p63 mutations on the enhancer landscape contributes to gene deregulation and phenotypes of EEC syndrome.

20. DISSECTING HUMAN EPIDERMAL COMMITMENT IN HEALTHY AND DISEASED HIPSC MODELS BY SINGLE-CELL RNA-SEQ

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Background: The transcription factor p63 is essential for normal epidermal development. In humans, heterozygous mutations in the DNA binding domain of p63 causes ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome (EEC).
Objective: In order to understand how p63 mutations can lead to developmental defects we established an efficient feeder-free protocol to derive keratinocytes (iKeratinocytes) from human induced pluripotent stem cells (hiPSCs).
Methods: Here we use single-cell RNA-seq to dissect epidermal commitment of normal and p63 mutant hiPSCs at different stages.
Results: We show that control hiPSCs can fully commit into the epidermal fate. At the molecular level, the transcriptional state of normal iKeratinocytes partially resembles the transcriptional state of human primary keratinocytes. Functionally, control iKeratinocytes are able to stratify, similarly to primary keratinocytes. In contrast, hiPSCs cell lines carrying two EEC mutations (R204W and R304W) do not fully commit into the epidermal fate. Instead, we observed increased cell death and delayed maturation of the epidermal commitment, in a heterogeneous manner. The presence of different competing transcriptional programs is being tested at the moment by deconstructing heterogeneity of this particular system.
Conclusions: Taken together, our data show that normal human epidermal commitment can be fully recapitulated in vitro and highlight that proper p63 regulation is essential during epidermal commitment.

21. GENETIC MOSAICISM IN BASAL CELL NAEVUS SYNDROME

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Background: Basal cell naevus syndrome (BCNS) is an autosomal dominant disorder most commonly caused by a germline mutation in the PTCH1 gene and typically characterized by multiple basal cell carcinomas (BCCs), maxillary keratocysts and cerebral calcifications. About 85% of patients have a positive PTCH1 mutation analysis on blood. Mutations in other participants of the hedgehog pathway, like PTCH2 and SUFU, as well as genetic mosaicism has been described in BCNS.
Objective: To unravel the underlying genetics in patients with clinical suspicion of BCNS and negative PTCH1 Sanger mutation analysis on blood.
Methods: We used quantitative techniques like Restriction Fragment Length Polymorphism (RFLP) and Droplet Digital PCR (ddPCR) to detect low-grade PTCH1 mosaicism in blood. Analysis with Molecular Inversion Probes and Next Generation Sequencing was performed on different BCCs of an individual patient to identify a shared PTCH1 mutation.
Results: Low-grade PTCH1 postzygotic mosaicism was detected with RFLP and ddPCR in a patient with a clinical diagnosis of BCNS. In another patient with multiple BCCs on one side of the body we found a shared PTCH1 mutation in different BCCs. This finding was indicative for type 1 segmental mosaicism.
Conclusion: BCNS can be caused by genetic mosaicism. Segmental distribution of BCCs may be present but not always visible. Mosaic BCNS can be diagnosed by using more sensitive techniques for mutation analysis or by comparing the genetic profiles of different BCCs from the same patient. Finding the underlying genetic cause is important to provide personalized medicine and adequate genetic counseling.

22. TITANIUM SALTS TESTED IN RECONSTRUCTED HUMAN SKIN WITH INTEGRATED LANGERHANS CELLS SHOW AN IRRITANT RATHER THAN SEN.SITIZING POTENTIAL

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Background: Titanium is extensively used in dentistry and medicine (e.g. orthopedic surgery and cardiology) even though clinical experience does indicate a relevant number of adverse reactions. It is currently unknown whether titanium ions leaching from medical device implants have sensitizing potential or are irritant / cytotoxic.
Objective: To determine, with the aid of reconstructed human skin with integrated Mutz-3 derived Langerhans Cells (RHS-LC) whether titanium salts representing leached ions from medical devices are labelled in the in vitro model as sensitizer or irritant.
Methods: MUTZ-LC were labelled with CFSE. RHS-LC consisting of reconstructed epidermis containing primary differentiated keratinocytes and CFSE+CD1a+ MUTZ-LC on a primary fibroblast-populated dermis were topically exposed to sub-toxic concentrations of the titanium salts ([CH3CH(O-)CO2NH4]2Ti(OH)2) for 24 hour. MUTZ-LC migration and plasticity was determined.
Results: Topical exposure of the Titanium salt resulted in CFSE+CD1a+LC migration out of the epidermis and into the dermis. Neutralizing antibody to CXCL12 failed to block the accumulation of CFSE+Lang+ MUTZ-LC in the dermis indicating that titanium was not a sensitizer. In contrast anti-CCL5 totally blocked migration of CFSE+Lang+ MUTZ-LC indicating that titanium is an irritant. In line with this finding, submerged

monocultures of MUTZ-LC failed to increase maturation biomarkers CD83, CD86, IL-8 when exposed to non-cytotoxic titanium salts further indicating that titanium is not a sensitizer.
Conclusion: RHS-LC scored titanium salts as irritants rather than sensitizers indicating that titanium implant related complaints could be due to localized cytotoxicity arising from leachables rather than a titanium metal allergy.

23. IMPROVED LYMPHOCYTE PROLIFERATION IN VITRO TEST (LTT) FOR NICKEL USING CFSE AND AUTOLOGOUS SERUM

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Background: The gold standard for the diagnosis of allergic hypersensitivity is skin testing. However, this has only been validated for epidermal antigen contact. For several metals, patch testing gives unreliable results. The current alternative to metal allergy patch-testing is the in vitro lymphocyte proliferation test (LTT) using tritiated thymidine (3H).
This method is promising but requires handling of radioactive material and has a low predictive value.
Objective: to develop a radioactive free LTT by using carboxyfluorescein succinimidyl ester (CFSE) and to evaluate the influence of human pooled serum (HPS) versus autologous serum, on the sensitivity of the LTT to nickel ($NiSO_4$).
Methods: Peripheral blood mononuclear cells of nickel allergic patients and healthy controls were collected, labeled with CFSE and cultured for 7 days in medium containing 10% HPS or 10% autologous serum in the absence or presence of $NiSO_4$. The stimulation index (SI) was calculated as the ratio of the percentage of CFSElow/neg CD3+CD4+ T lymphocytes upon nickel stimulation to the percentage of CFSElow/neg CD3+CD4+ T lymphocytes without antigen. These results were compared with patch-test results.
Results: Using patch-test as a diagnostic reference, a 100% correlation between both positive and negative patch-test groups (threshold: SI=3) was found. Using HPS there was only a 16% correlation in the positive patch test group.
Conclusion: The results demonstrate that the use of carboxyfluorescein succinimidyl ester as tracer for allergen-specific T-cell proliferation in LTT offers a good alternative to radioactive H3. Moreover, autologous serum is the preferred serum when compared to HPS.

24. SKIN MICROBIOTA SAMPLING IN ATOPIC DERMATITIS: TO SWAB OR SCRUB?

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Background: Collecting high quality samples for skin microbial analysis is challenging due to the low number of micro-organisms on the skin. Studies comparing different available techniques for skin sampling are scarce.
Objective: This study compares the detection of total bacterial DNA, Staphylococcus (S.) aureus DNA, microbial diversity and fungi by two different methods, namely dry flocked swabbing and scrubbing.
Methods: As part of an ongoing study in atopic dermatitis, we collected 39 swab and 39 scrub samples from 16 patients. S. aureus specific and total bacterial DNA were measured with quantitative (Q)-PCR. To identify bacteria and fungi we sequenced the 16S rRNA gene and the fungal internal transcribed spacer region 1.
Results: Q-PCR showed a higher absolute amount of total bacterial DNA in the scrubs ($p<0.001$). Sequencing of 16S rRNA identified 323 and 318 different genera in the swabs scrubs, respectively. The majority was identified equally well with the two techniques and biodiversity was not significantly different. Interestingly, we found fungal DNA more often in the scrubs than in the swabs (36% versus 9%).
Conclusion: Scrubs result in a higher collection of bacterial and especially fungal DNA. Therefore, they are preferable for studying low-biomass skin areas or fungi.

25. EXAMINATION OF IRRITANT-SPECIFIC EFFECTS ON THE SKIN BARRIER REQUIRES A MULTIPARAMETERIC APPROACH

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Background: Skin barrier damage is central in irritant contact dermatitis. However, mechanisms underlying skin barrier impairment depend on the intrinsic properties of the irritant. Recently, natural moisturizing factors (NMF) and corneocyte surface topography have been suggested as biomarkers for skin irritation.
Objective: To determine changes in functional, morphological and biochemical parameters caused by common skin irritants.
Methods: Eight healthy volunteers were exposed to n-propanol (60% aq.), SLS (0.5% aq), sodium hydroxide (0.15% aq), acetic acid (2,0%) and occlusion for 30 minutes during four consecutive days. Erythema, transepidermal water loss (TEWL), skin capacitance, Dermal Texture Index (DTI) and natural moisturizing factor (NMF) were measured at baseline, 24 and 96 hours after starting exposure.
Results: Changes in investigated parameters varied between

irritants. The most pronounced effect on erythema and TEWL was caused by SLS and NaOH. While n-propanol caused only slight changes in TEWL and erythema, it showed a high effect on skin hydration, NMF and DTI. NMF was the only parameter which was significantly altered by all investigated irritants.
Conclusion: Skin barrier impairment and inflammatory response are irritant-specific, emphasizing the need for a multiparametric approach when studying skin irritation. The levels of NMF seem to be the most sensitive parameter in detecting skin barrier alterations. SLS, NaOH and n-propanol, caused remarkable changes in corneocyte topography, which were inversely associated with the NMF levels and skin hydration.

26. A REDUCED EXTERNAL OXYGEN LEVEL IMPROVES EPIDERMAL BARRIER FORMATION IN HUMAN SKIN EQUIVALENTS

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Background: One of the major limitations of human skin equivalents (HSEs) is the higher permeability for compounds, when compared to native human skin (NHS). Alterations in the lipid matrix composition of the stratum corneum (SC) highly contribute to this occurrence. These differences could be induced by deviations in external conditions between the in vivo and in vitro situation. One of these differences is the oxygen level, sensed by the hypoxia-inducible factor (HIF) signalling pathway.
Objective: Our aim is to study how oxygen levels affect fibroblast and keratinocyte behaviour and whether it influences barrier formation in HSEs.
Methods: Fibroblast monocultures, keratinocyte (high/low calcium) monocultures and HSEs were developed at 20% and 3% oxygen level. Gene expression analyses were performed to study HIF target gene expression. Immunohistochemical analyses were performed to obtain insights on epidermal morphogenesis. The SC ceramide composition was studied with liquid chromatography coupled to mass spectroscopy.
Results: Monocultures of fibroblasts and keratinocytes in low oxygen have an equal morphology but a reduced proliferation and an altered expression of VEGFA, PDK1 and GLUT1. In HSEs, reduction of oxygen level also induced altered expression of these HIF target genes, decreased thickness of the viable epidermis but no alterations in epidermal morphogenesis. At reduced oxygen level, HSEs exhibit an improved ceramide subclass profile.
Conclusion: Our results indicate that external oxygen levels play an important role during skin reconstruction. The barrier formation in HSEs is enhanced at lower oxygen level, mimicking the NHS to a higher extent.

27. NOVEL AHR LIGANDS FOR THE TREATMENT OF ATOPIC DERMATITIS

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Background: The aryl hydrocarbon receptor (AHR) plays an important role in epidermal differentiation and mediates anti-inflammatory responses. Targeting the AHR, as seen in coal tar treatment, might therefore alleviate the symptoms of chronic inflammatory skin diseases like atopic dermatitis (AD). SGA compounds are synthesized indazole derivatives known to act as selective (AHR) modulators or partial AHR agonists.
Objective: We hypothesize that SGAs affect epidermal differentiation and may have therapeutic effects in inflammatory skin diseases.
Methods: We studied the effect of four AHR modulators namely SGA360, 360f, 315 and 388 on primary human keratinocyte monolayer cultures and 3D skin models for normal and AD skin. Morphological analysis, qPCR and immunohistochemistry were used to study the gene and protein expression levels. Furthermore, the proliferation rate of keratinocytes, CYP1A1 enzyme activity, cell toxicity and mutagenicity of the compounds were analysed.
Results: SGA360f, SGA315 and most strongly SGA388 induced CYP1A1 and epidermal differentiation gene and protein expression and displayed anti-inflammatory effects in Th2-stimulated primary human keratinocytes. SGA360 did not induce CYP1A1 expression nor epidermal differentiation, but did attenuate the Th2-mediated keratinocyte hyperproliferation. No cell toxicity and mutagenicity were observed and CYP1A1 activity was significantly lower compared to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a very potent AHR agonist.
Discussion: Our study indicates that partial AHR agonists induce epidermal differentiation and downregulate the expression of inflammatory genes similar to full AHR agonists, whilst avoiding excessive CYP1A1 activity which is correlated to genotoxicity and DNA mutations. The SGAs studied herein may therefore be novel candidates for topical treatment of AD.

28. MODULATION OF TGF-β SIGNALLING AND THE EFFECT ON (MYO)FIBROBLAST DIFFERENTIATION STATUS IN HYPERTROPHIC SCARS

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Background: In burn patients wound healing is often accompanied by hypertrophic scar (HTS) development, resulting in both functional and aesthetic problems. HTS's are characterized by myofibroblasts abundance. The differentiation route of fibroblasts towards myofibroblasts is predominantly regulated

by TGF-β signalling. However, the exact mechanisms underlying these transformation are not clear. It has been proposed that papillary fibroblasts, opposed to reticular fibroblasts, exhibit anti-fibrotic properties. The question is whether one could use these properties which could improve healing in burn wounds.
Objective: The aim of this study is to investigate whether modulation of TGF-β signalling by exon skipping (ES) could shift the differentiation status of myofibroblasts in HTS monolayers towards papillary-like features.
Methods: HTS biopsies were used to set up fibroblast monocultures, HTS ex vivo models, Fibroblast-derived matrix (FDM) models and Full-thickness Models (FTM). In order to induce ES, AON's targeting ALK5 were supplemented to fibroblast monocultures and FDM models. Ex vivo models were injected. Analysis of papillary and reticular markers and TGF-β signalling downstream targets was performed by qPCR, western blot and immunohistochemistry.
Results: Our data demonstrate that 1) ES of ALK5 is able to downregulate the gene expression of myofibroblast and reticular fibroblast biomarkers and upregulate papillary biomarkers. 2) On macroscopic level morphology of HTS-derived fibroblasts shifted towards a spindle shape-like phenotype, hence papillary fibroblasts.
Conclusion: ES is able to shift the differentiation state of myofibroblasts towards a papillary-like state. With respect to burn wounds and HTS development, ES could open a new therapeutic window towards scarless wound healing.

29. ARYL HYDROCARBON RECEPTOR ACTIVATION UPREGULATES A BATTERY OF ANTIMICROBIAL GENES.

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Background: The Aryl Hydrocarbon Receptor (AHR) is a multifaceted transcription factor involved in xenobiotic metabolism, immune cell development, and epidermal differentiation. AHR is activated by aryl hydrocarbons, of which TCDD is well-known. Coal tar (CT) is an activator of AHR and is used in the clinic as a treatment for atopic dermatitis.
Objective: To better understand AHR activation and downstream effects, we studied ligand-mediated DNA binding by AHR, its target gene transcription, and overall differentially expressed genes in treated keratinocytes.
Methods: TCDD and CT treated human primary keratinocytes were analyzed using RNA-sequencing and ChIP-sequencing to study genome wide effects of AHR activation by both AHR ligands.
Results: TCDD and CT show early (after 2 hours) upregulation of genes involved in detoxification pathways. Also, we found an upregulation of important genes encoding terminal differentiation proteins (IVL, FLG), antimicrobial proteins (e.g. PI3, SLPI, S100A8), and tight junction proteins (CLDN4, OCLN), approximately 24 hours after AHR activation by CT and TCDD.
Conclusion: The genomic binding of the AHR indicates that the canonical cellular responses after CT and TCDD exposure steer primarily towards activation of xenobiotic metabolism pathways. The transcriptional analysis shows additionally differentially regulated genes coding for differentiation proteins, antimicrobial proteins, and tight junction proteins. These may influence the interaction between host and microbes and could have important implications for the skin microbiome composition in coal tar treated AD patients.

P1. NAIL INVOLVEMENT AS A PREDICTOR FOR DISEASE SEVERITY IN PEDIATRIC PSORIASIS: FOLLOW-UP DATA FROM THE DUTCH CHILDCAPTURE REGISTRY

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Background: Psoriasis develops during childhood in almost one-third of the cases. Little is known about the relation between nail psoriasis and psoriasis severity in children, and no longitudinal assessment of psoriasis severity in children and adults with nail psoriasis is currently available.
Objective: To describe epidemiological and disease characteristics of children with nail psoriasis, and to assess the relation between nail involvement and psoriasis severity cross-sectionally and longitudinally.
Methods: Data were obtained from the child-CAPTURE registry, a daily clinical practice cohort of children with psoriasis. Patient characteristics, presence of nail psoriasis, and psoriasis severity scores were collected. Cross-sectional analyses were performed at baseline visit. Longitudinal data until two year follow-up were analyzed by linear mixed models.
Results: Nail psoriasis was present in 19.0% of patients at baseline, occurred more frequently in boys than girls ($p=0.015$) and was cross-sectionally associated with higher Psoriasis Area and Severity Index (PASI) ($p=0.004$), Body Surface Area (BSA) ($p=0.030$) and Physician Global Assessment (PGA) ($p=0.028$). Longitudinal analysis demonstrated higher PASI ($p<0.001$) and PGA ($p<0.001$) during two year follow-up in patients with nail vs without nail involvement at baseline.
Conclusion: The presence of nail psoriasis in children is associated with a more severe disease course during two year follow-up. These findings suggest nail psoriasis to be a potential clinical predictor for disease severity in pediatric psoriasis.

P2. STARTING BIOLOGIC TREATMENT SEQUENCES FOR PLAQUE PSORIASIS WITH USTEKINUMAB OR ADALIMUMAB IS THE MOST COST-EFFECTIVE: A COST UTILITY ANALYSIS BASED ON 10 YEARS OF DUTCH REAL-WORLD EVIDENCE FROM BIOCAPTURE

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Background: Switching of biologics is common, but it is unclear which biologic is most effective to initiate a sequence of biologics. Comparative evidence on (cost)effectiveness of different biologics is limited
Objective: We aimed to evaluate the cost-effectiveness of different biologic treatment sequences for psoriasis based on real-world evidence.
Methods: A sequence model was developed to evaluate the 10 year treatment costs and the total quality-adjusted life years (QALYs of different consecutive lines of biologic treatments based on the three most commonly prescribed biologics: adalimumab, etanercept and ustekinumab (for example adalimumab-etanercept-ustekinumab versus etanercept-ustekinumab-adalimumab). The model was populated with data from the BioCAPTURE registry and scientific literature.
Results: Sequences starting with etanercept would be the most expensive, with 10 year costs from € 147,499 to € 148,442, and also the least effective with an average 7.79 QALYs.
A sequence starting with ustekinumab followed by adalimumab would be the least expensive with 10 year costs of € 141,962, while the health effect is estimated to be 8.02 QALYs.
A sequence starting with adalimumab followed by ustekinumab was marginally more effective with 8.03 QALYs but also slightly more expensive with 10 year costs of € 143,661. When interpreting these results, it should be taken into account that credible intervals were partly overlapping.
Conclusion: The order in which biologics are used influences the cost-effectiveness of treatment both in terms of costs and health effects. Initiation of a biologic treatment sequence for psoriasis may best be done with adalimumab or ustekinumab; etanercept seems less optimal from a health-economic perspective.

P3. RECOMMENDATIONS FOR THE OPTIMAL RADIATION DOSE IN PATIENTS WITH PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA: A REPORT OF THE DUTCH CUTANEOUS LYMPHOMA GROUP

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Objective: To determine the optimal radiation dose for treatment of primary cutaneous anaplastic large cell lymphoma (C-ALCL).
Methods: Patients with C-ALCL, who had been treated with radiotherapy (RT) between 1984 and 2016, were retrieved from the Dutch registry of cutaneous lymphomas. Distinction was made between patients with solitary or localized (n=63), multifocal skin lesions (n=6), and patients with a skin relapse (n=22). Radiation doses, treatment response and follow-up were evaluated. Radiation doses were categorized in low-dose (≤20 Gy), intermediate dose (21-39 Gy) and high-dose (≥40 Gy).
Results: 61/63 (97%) patients presenting with solitary or localized skin lesions showed a complete response (CR). There were no differences in CR between low-dose (16/17), intermediate dose (15/15) and high-dose RT (30/31). After a median follow-up of 46 months, 30/63 (48%) patients had a relapse. Six out of 6 (100%) patients initially presenting with multifocal skin lesions showed a CR (3/3 low-dose, 2/2 intermediate dose, 1/1 high-dose). After a median follow-up of 27 months, 3 of 6 patients had a relapse. Treatment of 33 skin relapses in 22 patients showed no differences in CR between low-dose (18/19), intermediate dose (6/6) and high-dose radiotherapy (8/8). Treatment of multifocal and recurrent lesions with a dose of 8 Gy (2x4 Gy) resulted in CR of 17/18 lesions.
Conclusion: A radiation dose of 20 Gy (8x2.5 Gy) is effective in patients with solitary or localized skin lesions. For patients with multifocal skin lesions and patients with a skin relapse, 8 Gy (2x4 Gy) may be sufficient.

P4. LOW SKIN IRRITATION THRESHOLD IN PATCH TEST MAY BE A PROGNOSTIC TOOL FOR HYPERTROPHIC SCAR FORMATION

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Background: Hypertrophic scar (HS) development following surgery is extremely hard to predict. It is known that some cytokines released early in HS formation are also released during skin irritation. Also it is known that the SLS irritation threshold scored from a patch test differs between individuals. The irritation threshold(IT) may therefore be a distinguishing factor between patients developing normal scar(NS) and HS.
Objective: To examine an association between IT and HS formation and to determine the possible role of SLS patch testing as a tool to predict HS formation.
Methods: 31 patients (NS = 15; HS = 16) were included who had previously undergone reduction mammoplasties. Four days after applying the SLS patch test, the score was read by an experienced dermatologist and with a DermaSpectrometer®. Trans-epidermal waterloss (TEWL) was determined.

Results: Visual scoring of the SLS patch test showed significant more redness in the HS patient group compared to the NS patient group both with 1% and 2% SLS (p=0.017, p=0.013). It could be predicted with 66.7% accuracy whether a patient developed NT or HS scar since HS has a lower IT. Dermatospectrometry and TEWL measurements showed no significant differences between the studied groups.
Conclusion: SLS patch testing, carried out under the supervision of an experienced dermatologist, can be used as a prognostic tool to predict the formation of HS and will allow both surgeons and patients to make a better informed decision about (esthetic) surgery procedures. It will also allow for earlier preventative treatment of HS formation.

P5. BELIEFS ABOUT MEDICINES IN PSORIASIS PATIENTS TREATED WITH METHOTREXATE OR BIOLOGICS: A CROSS-SECTIONAL SURVEY STUDY

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Background: Methotrexate (MTX) and biologics are frequently used treatments to control moderate-to-severe psoriasis. Understanding patient's beliefs about these treatments may help recognize patients' attitude towards these therapies.
Objectives: To get insight in the beliefs about medicines in patients with psoriasis treated with MTX or biologics, and in factors affecting these beliefs.
Methods: This study was a cross-sectional survey using the Beliefs About Medicines Questionnaire Specific (BMQ-Specific). BMQ-specific scores (Necessity and Concerns scales) and the Necessity-Concerns differential (NCD) were calculated. Multivariable regression analysis was used to assess which factors were associated with these scores.
Results: One hundred patients treated with MTX and 100 treated with biologics were included. Patients treated with biologics scored higher than patients treated with MTX on the Necessity scale (mean 18 ± 4.4 vs 15.3 ± 4.6, respectively). The scores in the Concern scale were lower than the Necessity scale for both treatment groups (MTX: 12.3 ± 4.1; biologics: 11.7 ± 3.5). The NCD resulted in a positive score for both treatment groups (MTX: 2.98 ± 5.9; biologics: 6.3 ± 5.6). Factors that influenced the Necessity scale were: the PASI score in both groups and treatment duration in the MTX group. No factors were associated with Concerns scale. Factors influencing the NCD were: higher PASI in the MTX group and having psoriatic arthritis in the biologic group.
Conclusion: These results indicate that patient acknowledge that the medication protect them from becoming worse. To a lesser extent patients worry about the long term effects of medication.

P6. CONJUNCTIVITIS OCCURRING IN ATOPIC DERMATITIS PATIENTS TREATED WITH DUPILUMAB - CLINICAL CHARACTERISTICS AND TREATMENT

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Background: Dupilumab is an antibody directed against the IL-4 receptor which blocks the signaling pathway of IL-4 and IL-13. Dupilumab has been recently approved by the US Food and Drug Administration and the European Commission for the treatment of adult patient with moderate-to-severe atopic dermatitis. During clinical trials, conjunctivitis adverse events were reported more often in dupilumab treated patients compared to placebo.
Objective: In this case-series study, we aimed to describe clinical characteristics and treatment options for this clinically relevant complication of dupilumab-treated atopic dermatitis.
Methods: Patients treated with dupilumab during clinical trials for moderate-severe atopic dermatitis with conjunctivitis as adverse event were described in this case-series study. Patients were assessed by a specialized ophthalmologist to describe clinical ophthalmological features. Clinical characteristics were reported and treatment recommendations were given based on our personal experience.
Results: A total of 13 dupilumab-treated patients developing conjunctivitis as adverse event during clinical trials were included. The prominent feature in these patients was the predominant involvement of the conjunctiva, and especially a hyperemia of the limbus. Two treatment options were particularly successful including fluorometholone 0.1% eye drops leading to clinically significant improvement in all five treated patients and tacrolimus 0.03% eye ointment which improved signs and symptoms in all 4 treated patients.
Conclusion: Clinically characteristic inflammation of the anterior conjunctiva and hyperemia of the limbus was observed during dupilumab treatment, which can be treated successfully with fluorometholone 0.1% eye drops or tacrolimus 0.03% eye ointment.

P7. FOLLICULOTROPIC MYCOSIS FUNGOIDES PRESENTING WITH A SOLITARY LESION: CLINICOPATHOLOGICAL FEATURES AND LONG-TERM FOLLOW-UP DATA IN A SERIES OF NINE CASES

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Background: Folliculotropic mycosis fungoides (FMF) is a distinct variant of mycosis fungoides, which in rare cases may present with a solitary lesion. Reported cases describe an excellent prognosis, but follow-up was generally short.

Objective: Clinicopathologic characteristics, long-term follow up data of nine patients with solitary FMF are presented and differential diagnosis is discussed.
Methods: From a cohort of 203 patients with FMF, nine cases with solitary FMF were selected. Clinical data and histological sections obtained at diagnosis and during follow-up were reviewed.
Results: Skin lesions, in all patients located on the head, went into complete remission after treatment with radiotherapy (six cases) or topical steroids (one case) or regressed spontaneously (two cases). After a median follow-up of 89 months (range 51-203 months), five patients were still in complete remission, two patients had developed multiple skin relapses, while two patients had progressed to extracutaneous and fatal disease. Histologically, all patients showed marked folliculotropism, associated with syringotropism (four cases) and/or follicular mucinosis (five cases). Large cell transformation was observed at presentation (two cases) and during follow-up (three cases).
Conclusion: Long-term follow-up data indicate that patients with solitary FMF do not always have an indolent clinical course and therefore require long-term follow-up. (200)

P8. DERMOSCOPY USE IN THE NETHERLANDS

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Background: Dermoscopy is a well-established tool for the diagnosis of many skin diseases and the early detection of skin cancers. Data about the use of dermoscopy in everyday practice of Dutch dermatologists is lacking.
Objective: To identify factors that influence the use of dermoscopy in daily dermatology practice.
Methods: As a part of a pan-European study all registered dermatologists in the Netherlands were asked to fill in an online survey regarding personal characteristics and questions about dermoscopy training and their attitude towards dermoscopy.
Results: Valid answers were collected for 213 respondents, of which 99% reported to use dermoscopy. Of those, dermoscopy training during residency was reported by 41%, the majority used dermoscopy daily. Nonpolarized immersion contact dermoscopy and the ABCD rule were used most often. Dermoscopy was considered useful for melanocytic and pigmented lesions, especially for the early diagnosis of melanoma, but less useful for inflammatory diagnoses. Sixty-eight percent reported that dermoscopy increased the numbers of melanomas they detected, 66% answered that it decreased unnecessary biopsies of benign lesions. About 27% reported that dermoscopy wrongfully classified cases of melanoma as benign lesions. High use of dermoscopy for different types of skin diseases was reported by 24% and was associated with dermoscopy training during residency, the use of polarized light and pattern analysis.
Conclusion: In contrast to other European countries all Dutch dermatologist have access to dermoscopy equipment and training is integrated into the residency program. Improving dermoscopy training and offering courses to dermatologists could further enhance the benefit of dermoscopy.

P9. USE OF ORAL IMMUNOSUPPRESSIVE DRUGS IN THE TREATMENT OF ATOPIC DERMATITIS IN THE NETHERLANDS

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Background: Data on the percentage of patients with really difficult to treat atopic dermatitis (AD) are scarce. From socio-economic perspective it is important to have more insight in these numbers, as new very effective, but expensive, treatment options will be available in the near future. Estimating the number of AD patients using oral immunosuppressive drugs can give an impression of the percentage of difficult to treat patients in the total AD population.
Objective: To give an overview of the use of oral immunosuppressive drugs in patients with AD in the Netherlands
Methods: Prescription data of oral immunosuppressive drugs in the Netherlands were extracted from a pharmaceutical database containing data of 557 million prescriptions and 7.2 million patients. An algorithm, based on the WHO Anatomical Therapeutic Chemical (ATC) codes, was used to identify patients with AD. The prescription of oral immunosuppressive drugs between January 1st 2012 and January 1st 2017 was evaluated.
Results: 943 AD patients (1.4%) used cyclosporine A, methotrexate, azathioprine or mycophenolic acid. Methotrexate was most commonly used, followed by azathioprine and cyclosporine A. A switch in medication was rarely seen. In the evaluation period a decrease in the prescription of cyclosporine A was seen, together with an increase of the prescription of methotrexate. In 31% of the patients who stopped treatment, the discontinuation took place within the first months of treatment.
Conclusion: Of the AD patients, 1.4% used oral immunosuppressive drugs. Methotrexate was the most commonly used systemic drug in the Netherlands for the treatment of AD.

P10. HEALTHY DIET IS ASSOCIATED WITH LESS FACIAL WRINKLES IN WOMEN, IN A LARGE DUTCH POPULATION BASED COHORT

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Background: Lifestyle factors such as smoking and tanning are known wrinkle aggravators. However, the effects of different dietary patterns on facial wrinkling are unclear. Also, men and women tend to have different risk factors for skin wrinkling.
Objective: Our aim was to investigate the association between diet and facial wrinkling in a large sample of men and women.
Methods: We investigated the association between facial wrinkles and diet in a large population based cohort of 2,753 elderly participants (41% male, age range:51-97 years) of the Rotterdam Study. Wrinkles were digitally quantified from facial photographs and presented as percentage wrinkle area. Dietary intake was assessed using the Food Frequency Questionnaire. Adherence to the Dutch Healthy Diet Index (DHDI) was calculated. With principal component analysis we extracted relevant food patterns in men and women separately. All food patterns and the DHDI, were analyzed for association with wrinkle severity using multivariable linear regression.
Results: When adhering to the Dutch guidelines for a healthy dietary pattern, we observed significantly less wrinkles among women (-4.19% per 10 points increase in DHDI; 95%CI: -7.30,-1.08) but not men. In women, the 'unhealthy pattern' was associated with more facial wrinkles (+3.32 %Δ; 95%CI:0.06,6.68) and the 'fruit pattern' with less wrinkles (-3.20%Δ; 95%CI:-6.24,-0.05).
Conclusion: Dietary habits influence facial wrinkling in women but not in men. Global disease prevention strategies might emphasize less facial wrinkling in women as an additional gain when adhering to a healthy diet.

P11. HIGH REPORTED PREVALENCE OF HIDRADENITIS SUPPURATIVA IN AXIAL SPONDYLOARTHRITIS PATIENTS AND HIGH SELF-REPORTED CLINICAL AXIAL AND PERIPHERAL SPONDYLOARTHRITIS FEATURES IN HIDRADENITIS SUPPURATIVA PATIENTS: TWO CROSS SECTIONAL STUDIES (HISPA-1 AND HISPA-2 STUDIES)

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† HiSpA-2 study

Background: Spondyloarthritis (SpA), a group of inter-related, chronic, auto-inflammatory rheumatic conditions, was reported to be more prevalent in hidradenitis suppurativa (HS) patients than in the general population (2.3-28.2% versus ~1%). On the other hand, the prevalence of HS in SpA patients is not exactly known. Identification of HS symptoms in SpA patients or typical clinical SpA features in HS patients can be challenging for the treating physician while early diagnosis is crucial for disease management and outcome in both SpA and HS.
Objectives: HiSpA-1: To determine the prevalence of HS in patients with axial SpA.
HiSpA-2: To investigate the prevalence of self-reported SpA features in HS-patients and to explore how many are already diagnosed with a SpA condition.
Methods: HiSpA-1: Patients from the Groningen Leeuwarden axial SpA cohort filled out a questionnaire based on validated diagnostic HS questions. Self-reported HS symptoms were verified by checking dermatology medical records or verification by phone by an HS expert physician.
HiSpA-2: HS patients from two Dutch HS referral centers filled out a self-screening questionnaire focusing on clinical axial and peripheral SpA features, based on the Assessment in SpondyloArthritis international Society (ASAS) definitions.
Results: HiSpA-1: Included axial SpA-patients (449/592, 75.6%) had a mean age of 50±13 years, 63% was male, mean symptom duration was 23±13 years, and 78% was HLA-B27 positive. HS diagnosis could be confirmed in 41 patients, resulting in an estimated prevalence of 9.1%.
HiSpA-2: Included HS-patients (620/1313, 47.2%) had a mean age of 43.4±3.9 years, 70.2% were female, mean BMI was 28.0±5.8 kg/m^2, and 83.5% were ex- or current smokers. Overall, 67.1% (416/620) patients reported ≥1 of the four ASAS entry classification criteria for SpA, i.e. chronic back pain starting before the age of 45, peripheral arthritis, enthesitis (of the Achilles tendon) or dactylitis, and 10 (1.6%) patients were already diagnosed with a SpA condition.
Conclusions: HS in our axial SpA cohort is more prevalent compared to the general population (9.1% versus ~1%) and self-reported clinical SpA features seem very common in our HS patients, although a SpA diagnosis was only reported by a few.

P12. THE JOURNEY OF ADULT PSORIASIS PATIENTS TOWARDS BIOLOGICS: PAST AND PRESENT. RESULTS FROM THE BIOCAPTURE REGISTRY

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Background: A considerable disease period often precedes initiation of a biologic in psoriasis patients. Little is known about this important period in patients' lives, but insight herein can reveal opportunities for physicians and decision makers.
Objective: (1) Describe patient and treatment characteristics until the start of biologic treatment in patients with severe

psoriasis, (2) assess shifts in early (2005-2009) versus established (2010-2015) biologics prescription periods, (3) assess changes in hospital/day care admissions before vs. after starting biologics.
Methods: Explorative, retrospective descriptive study on the treatment characteristics of the period until first biologic in patients included in the BioCAPTURE registry.
Results: Median TUS (time until conventional systemic) was 11.0 years; median TUB (time until biologic) was 18.9 years for patients treated from 2005-2015. Most patients received 3 different conventional antipsoriatic systemic therapies.
We noticed a small trend towards a shorter journey (TUB) with only 2 conventional systemic agents instead of 3 before initiating a biologic in later years (2010-2015 vs. 2005-2009). We also noticed a significant decrease of admissions comparing two years before, versus two first years after starting biologic treatment (17.7 versus 8.6 admissions/100 follow-up years, p<0.001). Cyclosporine, dithranol, retinoids and PUVA therapy lost popularity in time.
Conclusion: The 'journey' of psoriasis patients towards a biologic is long, with many different treatments. Shifts towards fewer conventional drugs before biologic initiation and a clear decrease of hospital/day care admissions before vs. after a biologic are seen. Improvement of this journey may decrease negative influences on patients' lives and reduce societal impact.

P13. NOVEL IMAGING TECHNIQUES TO CHARACTERIZE AND ASSESS DELAYED-TYPE HYPERSENSITIVITY (DTH) IN HEALTHY VOLUNTEERS

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Background: Challenge models enabling direct pharmacodynamic assessment are necessary for development of immunomodulatory drugs. Keyhole limpet hemocyanin (KLH) is commonly used for studying T-cell dependent immune response.
Objective: The aim of the study was i) to characterize the adaptive immune response after KLH immunization by measuring anti-KLH immunoglobulin (Ig) M and IgG titers and ii) to assess the skin response after intradermally administered KLH.
Methods: A randomized, double-blind, placebo-controlled study was conducted in 15 healthy male volunteers. KLH (0.1 mg) or placebo was administered in 4:1 ratio on day 0 to the left deltoid muscle. Anti-KLH IgM and IgG titers were measured weekly for 28 days. After 21 days, KLH (0.001 mg) was administered intradermally to the ventral left forearm. A type IV DTH assessment was performed pre-dosing and 48h post-dosing and included perfusion by laser speckle contrast imaging (LSCI), 2D and 3D photography analysis, erythema by colorimetry, and visual erythema grading.
Results: The treatments were well-tolerated, without AEs considered treatment related. Anti-KLH IgG and IgM titers were significantly increased in KLH compared to placebo (p<0.0001 and p=0.0014, respectively). Three-dimensional photography showed significantly increased a* (p=0.0054) and average redness values (p=0.0132) when comparing KLH with placebo. Basal flow and flare with LSCI displayed significantly increased results in KLH compared to placebo (p=0.0236 and p=0.0038 respectively).
Conclusion: The administration of KLH was well tolerated and induced a quantifiable adaptive immune response. Some techniques of the study, i.e. multispectral imaging, LSCI, show potential to serve as novel objective, well-quantifiable assessments to study pharmacodynamic effects of immonumodulators.

P14. CHARACTERIZATION OF A HUMAN SKIN CHALLENGE MODEL OF IMIQUIMOD-INDUCED SKIN INFLAMMATION

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Background: Imiquimod (IMQ) is a known TLR 7/8 agonist that causes psoriasis like skin inflammation in mouse models.
Objective: To develop and refine a temporary human skin inflammation model with IMQ for application in clinical drug development.
Methods: A randomized, open-label, vehicle-controlled, parallel-cohort, dose ranging study was conducted in sixteen (16) healthy male subjects. IMQ (5 mg, 100mg Aldara®) was administered once daily for 3 consecutive days under occlusion by a 12 mm Finn Chamber to the upper back. Subjects were randomized 1:1 to receive tape stripping (TS) of the skin or not prior to the first dose administration. Erythema and perfusion measurements were performed daily. Furthermore skin biopsies were collected for mRNA expression, histology and immunohistochemistry.
Results: All 16 subjects completed the study with good tolerability at the administration site. IMQ application to TS skin induced significant (p<0.0001), dose-dependent hyper perfused erythematous lesions. Histologically these lesions showed acanthosis and infiltrates consisting of CD4+ T-cells, CD8+ T-cells, CD11c+ dendritic cells and HLA-DR macrophages. mRNA expression of CXCL10, hBD-2, ICAM-1 and MX-A was significantly (p<0.01) induced relative to housekeeping gene ABL in this cohort. The maximum effect was at 48h. Effects were fully reversible. Although effects of IMQ were observed without TS, this was much less apparent.
Conclusion: This study validates the human IMQ skin inflammation challenge model, with TS of the skin prior to the first dose administration and 48h of application. Future interaction studies will enable proof pharmacology of novel compounds targeting the innate immune system.

P15. HLA-C*06:02 AS A PREDICTOR FOR USTEKINUMAB TREATMENT SUCCESS IN PSORIASIS PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Located in the PSORS1 genetic locus, the HLA-C*06:02 allele confers the strongest risk for development of plaque psoriasis. Additionally, HLA-C*06:02 has been suggested as a predictor for ustekinumab response, and might be useful in personalized treatment of psoriasis patients eligible for biological therapy.
Objective: To investigate the association between HLA-C*06:02 and the response to ustekinumab in patients with plaque psoriasis, using a meta-analysis of current literature.
Methods: A systematic literature search was conducted using four databases. HLA-C*06:02 genotyping and PASI75 response data during ustekinumab treatment were collected from relevant studies and pooled into a random-effects meta-analysis. In case of duplicate publication of study data, only one of the duplicate studies was included in the meta-analysis. Heterogeneity was assessed by using forest plots, κ2-tests and I2-statistics.
Results: For the meta-analysis of PASI75 response rates at three months' treatment, six studies were included. Random-effects analysis demonstrated a risk ratio of 1.41 (95%CI: 1.25-1.59, P<0.00001) for achieving PASI75 after three months, in favor of HLA-C*06:02 positive patients. For the analyses of treatment response at six months, five studies were included. Meta-analysis showed a risk ratio of 1.33 (95%CI: 1.13-1.57, P=0.0006) in favor of HLA-C*06:02 positive patients achieving PASI75 after six months of treatments. There was substantial study heterogeneity.
Conclusion: HLA-C*06:02 positive psoriasis patients have a higher probability of achieving PASI75 with ustekinumab treatment compared to HLA-C*06:02 negative patients. However, the relative 'risk' is modest, and there is no a clear rationale for using HLA-C*06:02 genotyping in clinical decision making.

P16. THE PREVALENCE OF ANTIBODY RESPONSES AGAINST STAPHYLOCOCCUS AUREUS ANTIGENS IN PATIENTS WITH ATOPIC DERMATITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Staphylococcus (S.) aureus plays a role in the pathogenesis of atopic dermatitis (AD), possibly via the expression of various virulence antigens. An altered antibody response towards these antigens might contribute to inflammation. Current literature reports varying prevalences of antibodies directed against S. aureus antigens.
Objective: To provide an overview of prevalences and odds of antibody responses against S. aureus antigens in AD patients.
Methods: A systematic literature search was conducted. We selected all original observational and experimental studies assessing anti-staphylococcal antibodies in serum of AD patients. Prevalences and odds ratios (ORs) of immunoglobulin (Ig) E, IgG, IgM, IgA against S. aureus in AD patients versus healthy controls were pooled using the random-effects model. We calculated I2 statistics to assess heterogeneity and rated study quality using the Newcastle-Ottawa Scale.
Results: Twenty-six articles (2369 patients) were included of which 10 controlled studies. Study quality was fair to poor. AD patients had higher prevalences of IgE against staphylococcal enterotoxin (SE) A (OR 8.37, 95% CI 2.93-23.92) and SEB (OR 9.34, 95% CI 3.54-24.93) compared to controls. Prevalences of anti-staphylococcal IgE were 33% for SEA, 35% for SEB and 16% for toxic shock syndrome toxin (TSST)-1. However, study heterogeneity and imprecision should be taken in consideration when interpreting the results. Data on IgG, IgM and IgA as well as other antigens were limited.
Conclusion: AD patients more often show an IgE antibody response directed against S. aureus superantigens compared to healthy controls, supporting a role for S. aureus in the AD pathogenesis.

P17. ACTIVATION OF THE ARYL HYDROCARBON RECEPTOR BY LEFLUNOMIDE: A NOVEL THERAPEUTIC MECHANISM OF ACTION IN THE TREATMENT OF INFLAMMATORY SKIN DISEASES

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Background: Leflunomide, a FDA approved drug for the treatment of rheumatoid arthritis, shows therapeutic efficacy in case reports of atopic dermatitis (AD) and psoriasis patients. Leflunomide has recently been described to have aryl hydrocarbon receptor (AHR) agonist activity. The AHR plays an important role in epidermal differentiation and mediates anti-inflammatory responses.
Objective: Targeting the AHR by leflunomide might affect the epidermal differentiation and alleviate symptoms of chronic inflammatory skin diseases like AD.
Methods: We studied the effect of Leflunomide on HEPG2-CYP1A1 reporter cells (AHR activity screen) followed by primary human keratinocyte monolayer cultures and 3D skin models for normal and AD skin. Morphological analysis, qPCR and immunohistochemistry were used to study the gene and protein expression levels. Furthermore, the proliferation rate of keratinocytes, CYP1A1 enzyme activity and cell toxicity were analysed.
Results: Leflunomide, at a concentration of 10 μM, induced CYP1A1 and epidermal differentiation gene and protein expression while strongly downregulating keratinocyte proliferation. Overall, leflunomide successfully counteracted

the pro-inflammatory effects of Th2 cytokine stimulation in human primary keratinocyte cultures. Cell toxicity was only observed at a concentration of 100 µM and leflunomide caused no significant CYP1A1 enzyme activity.
Conclusion: A recent study demonstrated that leflunomide can be delivered effectively when topically applied in an experimental model of rheumatoid arthritis. Adverse events of leflunomide treatment were significantly reduced by topical application versus systemic treatment. The therapeutic effects of leflunomide in our 3D AD skin model suggests that leflunomide may be a novel candidate for topical treatment of AD.

P18.THE HUMAN CUTANEOUS MICROBIOME COMPOSITION CHANGES AFTER COAL TAR TREATMENT OF BOTH HEALTHY AND ATOPIC DERMATITIS SKIN

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Background: Bacterial components of the skin microbiome are known to contribute to atopic dermatitis (AD) pathogenesis in humans. Most notably, Staphylococcus aureus colonization and infection has been shown to correlate to disease severity and response to treatment. Coal tar (CT) treatment is highly effective in AD patients, and we recently found CT to influence host defense mechanisms by induction of antimicrobial proteins in keratinocytes. We therefore postulate that skin microbiome changes after CT treatment may aid in its therapeutic effect.
Objective: Study the effect of coal tar treatment on the skin microbiome.
Methods: We used 16S rRNA marker gene sequencing to identify bacterial taxa that are present on the inner elbow of ten healthy individuals and eight AD patients, before, during, and after CT (or vehicle) treatment.
Results: We observed a near absence of Staphylococcae on healthy individuals and increased abundance of Staphylococcae in lesional AD skin microbiomes. During CT treatment in AD, Staphylococcus decreased in comparison to vehicle control, albeit that Staphylococcus also decreased during vehicle control, but to a lesser extent.
Conclusion: Our study indicates that CT treatment affects the skin microbiome by altering the microbial composition of AD skin, shifting it towards that observed in healthy individuals. This indicates a hitherto undiscovered aspect of the mode of action of CT treatment. We propose that CT provides a long term therapeutic effect on AD skin by shaping the skin microbiome and host-microbe interaction leading to a milieu that is less prone to inflammation.