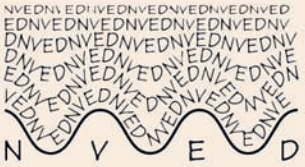

20th Annual scientific meeting of the Nederlandse Vereniging voor Experimentele Dermatologie 31 January and 1 February 2019

Programme

At the 20th annual scientific meeting of the NVED the ongoing scientific research in dermatology in the Netherlands will be presented.

Programme summary

Thursday 31 January 2019

09.30	-	10.15	Registration and welcome with coffee/tea
10.15	-	10.25	Opening by the chair of the NVED
10.25	-	11.50	Session I: Gene Mutation and Function
11.50	-	12.50	Lunch
12.50	-	13.30	Guest Lecture by **Prof. dr. Mihai Netea** (RUMC)
13.30	-	14.45	Session II: Clinical Studies
14.45	-	15.45	Poster and networking session I (with coffee/tea)
15.45	-	17:15	Session III: Immunology & Infection I
17.15	-	20.00	Drinks and Dinner
20.00	-	20.45	21th general assembly of the NVED
20:45	-	01.00	**20th Annual Meeting NVED Anniversary Party**

Friday 1 February 2019

09.00	-	10.00	Session IV: Dermato-Oncology and Epidemiology
10.00	-	11.00	Poster and networking session II (with coffee/tea)
11.00	-	11.40	Guest Lecture by **Prof. dr. Carien Niessen** (CECAD, Cologne)
11.40	-	12:50	Lunch
12.50	-	13.50	Session V: Skin Biology & Skin Physiology and Structure
13.50	-	14.30	Guest Lecture by **Prof. dr. Joost Schalkwijk** (RUMC)
14.30	-	14.40	Break (stretch your legs)
14.40	-	15.55	Session VI: Immunology and Infection
15.55	-	16.15	Awards; Announcement of Breaking News NVDV, Farewell

Full programme

THURSDAY 31 JANUARY 2019

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

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

10.25 - 11.50 **Session I: Gene Mutation and function**
Session chairs: Walbert Bakker (AMC), Marieke Bolling (UMCG)

1.	Frank van Leersum *MUMC*	The challenge of diagnosing genetic mosaicism in dermatology – (applying next generation sequencing techniques).
2.	Eirini Christodoulou *LUMC*	Identification and validation of NEK11 as a novel high penetrance melanoma susceptibility gene.
3.	Hanna Niehues *RUMC*	STAT1 gain-of-function compromises skin host defense in the context of interferon-γ signaling.
4.	Daniela Andrei *UMCG*	A novel desmosomal protein involved in woolly hair, palmoplantar keratoderma, mild skin fragility, and potentially cardiomyopathy.
5.	Mathilde Vermeer *UMCG*	Mechanical strain compromises desmosomal integrity in desmoplakin insufficient cardiac and cutaneous cells.
6.	Marieke Bolling *UMCG*	30 years Epidermolysis Bullosa research in Groningen.

11.50 - 12:50 **Lunch**

12.50 - 13.30 **Guest Lecture by Prof. dr. Mihai Netea (*RUMC*): "Variation and adaptation in the human immune system"**

13.30 - 14.45 **Session II: Clinical studies**

Session chairs: Juul van den Reek (RUMC), Nicole Kukutsch (LUMC)

7.	Linde de Wijs *Erasmus MC*	Dupilumab in combination with systemic immunosuppressive agents: daily practice data.
8.	Minke van Mierlo *Erasmus MC*	The influence of treatment in alpine and moderate maritime climate on the composition of the skin microbiome in patients with difficult to treat atopic dermatitis.
9.	Rutger Melchers *LUMC*	Frequency of associated haematologic malignancies in lymphomatoid papulosis: a preliminary report of 501 patients from the Dutch Cutaneous Lymphoma Group.
10.	Mahdi Saghari *CHDR Leiden*	Novel assessment methods to explore and characterize wound healing after skin punch biopsies in healthy volunteers.
11.	Sanne Uitentuis *VU/AMC*	The ultraviolet light camera, a promising measurement instrument for lesion assessment in vitiligo.

14.45 - 15.45 **Poster and networking session I (with coffee and tea)**

P1.	Elisabetta Michielon *VUmc/ACTA*	Development of an in vitro generated human melanoma model as a research plat form for therapeutic testing.
P2.	Tessa Kouwenhoven *RUMC*	Use of systemic treatment in patients with chronic pruritus: a survey among dermatologists in the Netherlands.
P3.	Lieke van Delft *MUMC*	Single versus multiple level prospective sectioning for the subtyping of basal-cell carcinoma.
P4.	Sander Spiekstra *VUmc/ACTA*	Comparison of the skin sensitization potential of tattoo inks using interleukin-18 as a biomarker in a reconstructed human skin model.
P5.	Yuki Nakagawa *LUMC*	Cell adhesion molecule 1 (CADM1) can be a biomarker for leukemic cells in progressive or refractory Sézary syndrome.
P6.	Yannick Elshot *VU/AMC*	Diagnostic accuracy of handheld reflectance confocal microscopy in the presurgical mapping of lentigo maligna (melanoma): a retrospective pilot study.
P7.	Marcella Willemsen *VU/AMC*	In situ visualization of tissue-resident memory T cells to identify the prognostic relevance in human melanoma development.
P8.	Suzanne van Santen *LUMC*	Levels of IL-31 in different variants of cutaneous T cell lymphomas.
P9.	Lotte Spekhorst *UMCU*	Determinants of omalizumab drug survival in a long-term daily practice cohort of patients with Chronic Urticaria.
P10.	Mariëlle Vermeulen *VU/AMC*	TREatment of ATopic eczema (TREAT) Registry Taskforce: consensus on how and when to measure the core dataset for atopic eczema treatment research registries.
P11.	Melanie Rijsbergen *CHDR Leiden*	A randomized controlled proof-of-pharmacology trial of omiganan in patients with external genital warts.
P12.	Melanie Rijsbergen *CHDR Leiden*	Stereophotogrammetric 3D photography as a method for the clinical visualization and quantification of HPV-induced skin lesions.
P13.	Jart Oosterhaven *UMCG*	Validation of the Dutch Quality Of Life in Hand Eczema Questionnaire (QOLHEQ).
P14.	Joost Meijer *UMCG*	Prevalence of pruritus and pemphigoid in nursing home residents (SSENIOR): a cross-sectional study of an under-recognized disease.
P15.	Finola Bruins *RUMC*	A greater improvement of quality of life in children and young adults with psoriasis is reached with higher PASI responses and systemic treatments.
P16.	Aniek Lamberts *UMCG*	Nonbullous pemphigoid: insights in clinical and diagnostic findings, treatment responses and prognosis.
P17.	Jade Logger *RUMC*	Anatomical site variation of water content in human skin measured by the Epsilon: a pilot study.
P18.	Sanne Uitentuis *VU/AMC*	Treatment and survival of Merkel cell carcinoma since 1993: a population-based cohort study in the Netherlands.
P19.	Sanne Uitentuis *VU/AMC*	Merkel cell carcinoma, the impact of clinical excision margins and Mohs micrographic surgery on recurrence and survival: a systematic review.

P20.	Jill de Wit *Erasmus MC*	Skin disorders are prominent features in primary immunodeficiency diseases: a systematic overview of current data.
P21.	Mariëlle Vermeulen *VU/AMC*	The steps towards evidence based Option Grids for Psoriasis and Atopic Eczema.
P22.	Gayle van der Kraaij *VU/AMC*	Optimizing adalimumab treatment in psoriasis with concomitant methotrexate: OPTIMAP study.
P23.	Bram Doron van Rhijn *UMCU*	Disease and treatment characteristics in pemphigus and pemphigoid patients in a ten-year academic daily practice cohort.
P24.	Selma Atalay *RUMC*	Results of the first randomized controlled trial on tight controlled dose reduction of biologicals compared with usual care in psoriasis patients: the CONDOR study.
P25.	Darryl Tio *VU/AMC*	Prevalence of Cancer Testis Antigens on Lentigo Maligna and Lentigo Maligna Melanoma.
P26.	Cynthia van Amerongen *UMCG*	New positive patch test reactions on D7 - the additional value of the D7 patch test reading.
P27.	Mary-Ann el Sharouni *UMCU*	Clinicopathological gender differences in melanoma: need for tailored management and prevention strategies.
P28.	Lisette Prens *UMCG*	Surgical outcomes of major surgery (STEEP) and the impact of major surgery on quality of life, activity impairment and sexual health in hidradenitis suppurativa patients: a prospective single centre study.
P29.	Lisette Prens *UMCG*	The refined Hurley classification for hidradenitis suppurativa: an accurate and reliable instrument for physicians and patient self-assessment.
P30.	Marloes van Muijen *RUMC*	Demographic and clinical factors associated with psoriatic arthritis in psoriasis patients treated with biologics.
P31.	Hanan Rashid *UMCG*	Daily practice study of rituximab in pemphigus: a retrospective study of 65 patients.
P32.	Lara van der Schoot *RUMC*	Treatment satisfaction with biologics for psoriasis: is there a difference between men and women?
P33.	Daan Dittmar *UMCG*	Contact sensitization to hydroperoxides of limonene and linalool; results of consecutive patch testing and clinical relevance.
P34.	Angelique Voorberg *UMCG*	Dupilumab in atopic hand eczema patients – an observational study.
P35.	Eline Noels *Erasmus MC*	Rising reimbursed costs of benign and (pre) malignant skin tumors due to increasing incidence and introduction of pharmaceuticals in the Netherlands, 2007-2016.
P36.	Wouter ten Voorde *LUMC*	Multimodal imaging of intradermal drug injection using hollow microneedles.
P37.	Sven van Egmond *Erasmus MC*	Insight into the management of actinic keratosis: a qualitative interview study among general practitioners and dermatologists.
P38.	Thomas Buters *CHDR Leiden*	Development of an LPS skin challenge model.
P39.	Thomas Buters *CHDR Leiden*	Omiganan, a topical antimicrobial peptide, normalizes dysbiosis but does not improve atopic dermatitis clinically in a phase II randomized controlled trial.
P40.	Lisa Pagan *CHDR Leiden*	Omiganan enhances the inflammatory response induced by imiquimod in a human skin challenge model.
P41.	Nicholas Schräder *UMCG*	Combined THC and CBD to treat pain in epidermolysis bullosa: a report of three cases.
P42.	Yéssica Rodriguez Rosales *RUMC*	Neutrophil subset examination reveals different phenotype and impaired function in psoriasis.
P43.	Vamsi Yenamandra *UMCG*	Three decades of Epidermolysis Bullosa care in the Netherlands: Epidemiology, Diagnosis, Management and Translational Research experience from an European Expertise Center.

15.45 - 17.15 **Session III: Immunology & Infection**
Session chairs: Marjolein de Bruin-Weller (UMCU), Rosalie Luiten (AMC)

12.	Christine Ardon *Erasmus MC*	The anti-inflammatory potency of biologics targeting TNF-α, IL-17A, IL-12/23 and CD20 in hidradenitis suppurativa: an ex vivo study.
13.	Xiaofei Xu *Erasmus MC*	IL-10 regulates skin thickness and scaling in imiquimod-induced psoriasis-like skin inflammation in mice.
14.	Thomas Ederveen *RUMC*	Cutaneous Staphylococcus profiling at species level in atopic dermatitis by Single Locus Sequence Typing (SLST) marker design and oligotyping for high-resolution sequencing-based microbial profiling.
15.	Paulo Urbano *RUMC*	A Semi-Unsupervised Multivariate Algorithm for Profiling and Mining High-dimensional Flow Cytometry Data in psoriatic patients.
16.	M. Alizadeh Aghdam *UMCU*	FceRI-bearing leukocytes in response to omalizumab treatment in chronic spontaneous urticaria.
17.	Judith Thijs *UMCU*	A combination of serum biomarkers TARC, IL-22, and sIL-2R accurately predicts disease severity in atopic dermatitis patients treated with cyclosporin A or dupilumab.

17.15 - 20.00 **Drinks and Dinner**

20.00 - 20.45 **21th general assembly of the NVED**

20.45 - 01.00 **20 Years NVED Anniversary Party**

FRIDAY 1 FEBRUARY 2019

09.00 - 10.00 **Session IV: Dermato-Oncology and Epidemiology**
Session chairs: Elsemieke Plasmeijer (Erasmus MC), Remco van Doorn (LUMC)

18.	Safa Najidh *LUMC*	Standardized flow cytometry (EuroFlow) demonstrates different functional related phenotypes to Sézary syndrome cells.
19.	Wim Zoutman *LUMC*	Overexpression of self-tolerance protein PD-1 is epigenetically regulated in Sézary syndrome.
20.	Walbert Bakker *VU/AMC*	IFNg and hypoxia co-stimulate PDL1 expression in melanoma cells, independent of HIF1.
21.	Chen Hu *Erasmus MC*	Associations of early life environmental exposures and genetic risk factors with eczema phenotypes. The Generation R study.

10.00 - 11.00 **Poster and networking session II, including poster walk, and presentation of selected posters (with coffee and tea)**

11.00 - 11.40 **Guest Lecture by Prof. dr. Carien Niessen (CECAD, Cologne): "Adhesion and signaling information, maintenance and breaking of the barrier"**

11.40 - 12.50 **Lunch**

12.50 - 13.50 **Session V: Skin Biology and Skin Physiology, and Structure**
Session chairs: Abdoel el Ghalbzouri (LUMC) en Siamaque Kazem (VUmc)

22.	Rajiv Raktoe *LUMC*	The effect of ALK5 inhibition on different fibroblast populations in hypertrophic scars.
23.	Gijs Rikken *RUMC*	IL-4 and IL-13 discovered as direct keratinocyte mitogens – implications for epidermal hyperproliferation in psoriasis and atopic dermatitis.
24.	Klaziena Politiek *UMCG*	Decreased expression of keratin 9 and 14 in hyperkeratotic palmar hand eczema.
25.	Irit Vahav *VUmc/ACTA*	Incorporation of hair follicles into reconstructed human skin.

13.50 - 14.30 **Guest Lecture by Prof. dr. Joost Schalkwijk (*RUMC*): "Terminal Differentiation"**

14.30 - 14.40 **Break (stretch your legs)**

14.40 - 15.55 **Session VI: Immunology and Infection**
Session chairs: Abdoel el Ghalbzouri (LUMC) en Siamaque Kazem (VUmc)

26.	Lieneke Ariens *UMCU*	First experience of dupilumab in atopic dermatitis patients treated in daily practice: 16-week evaluation of clinical effectiveness and serum biomarkers.
27.	Daphne Bakker *UMCU*	Goblet cell scarcity and conjunctival inflammation during treatment with dupilumab in patients with atopic dermatitis.
28.	Tiago Matos *VU/AMC*	Human central memory T cells generate superior numbers of resident memory T cells in skin.
29.	Niels de Graaf *VU/AMC*	In vitro lymphocyte proliferation test (LPT) for nickel using CFSE and autologous serum.
30.	Lin Shang *VUmc/ACTA*	Toll-like receptor signaling in oral mucosa exposed to commensal and pathogenic biofilms in vitro.

15.55 - 16.00 **Awards for best presentation and poster; selection breaking news**

16.00 **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 2019 is applied for.

Programme committee:

Nelleke Gruis (*LUMC*), Michel van Geel (*MUMC*), Patrick Zeeuwen (*RUMC*), Siamaque Kazem (*VUmc*), Gilles Diercks (*UMCG*), Loes Hollestein (*Erasmus MC*), Walbert Bakker (*AMC*), Jorien van der Schaft (*UMCU*)

Jury for presentation prize:

Nelleke Gruis (*LUMC*), Gilles Diercks (*UMCG*), Loes Hollestein (*Erasmus MC*)

Jury for poster prize:

Antoni Gostynski (*MUMC*), Tiago Matos (*VU/AMC*), Jos Smits (*RUMC*)

NVED board:

DirkJan Hijnen (chair, *Erasmus MC*), Marcel Bekkenk (secretary, *VUmc/AMC*), Marjon Pasmooij (Treasurer, *UMCG*), Kees Tensen (representative in Federa, *LUMC*), Sue Gibbs (representative in NVDV 'commissie nascholing', *VUmc/ACTA*)

1. THE CHALLENGE OF DIAGNOSING GENETIC MOSAICISM IN DERMATOLOGY – (APPLYING NEXT GENERATION SEQUENCING TECHNIQUES)

F.S. van Leersum[1], T.E.J. Theunissen[1], R. Janssen[1], M.M.B. Seyger[3], P.M. Steijlen[1], M. van Geel[1,2]
Departments of [1]Dermatology and [2]Clinical Genetics, MUMC, Maastricht, [3]Department of Dermatology, Radboudumc, Nijmegen

Background: Genetic skin diseases can show mosaic presentations caused by postzygotic mutations. This provides difficulties in recognizing the clinical features as well as impeding diagnostic analysis. Low grade mosaicism may escape detection with current methods. To improve success-rates, more sensitive Next Generation Sequencing (NGS) techniques should be implemented in diagnostics.
Objective: Using NGS as a tool for detecting and quantifying low percentage DNA mutations in patients to identify mosaicism and obtain or confirm a diagnosis.
Methods: Whole Exome Sequencing (WES) is used in two patients with unknown diagnosis with suspected mosaicism. Sequence read depths in WES are intermediate (~100x) and may fail to reach the mutation detection threshold. In two cases with symptoms of overgrowth, a targeted gene panel was used with small-molecule molecular inversion probes (smMIPs). This strategy achieves high sequence coverage (>1000x), enabling mosaic detection with great sensitivity.
Results: Through WES, patients with a mosaic clinical presentation were diagnosed. One patient presents with a blaschkoid skin manifestation caused by recessive mosaicism, a new type of postzygotic genetic mosaicism. With smMIP-NGS low mutation percentages were detected in affected tissue of overgrowth patients, not found with previously used techniques. The diagnosis was confirmed and the mutation accurately quantified.
Conclusion: NGS techniques will aid in successful diagnostic work-up of genetic skin disorders. Combined with growing knowledge of genetic mosaicism this will increase diagnostic yield in patients. Genetic mosaicism versus its inherited counterpart can express different or sometimes indistinguishable clinical features. Even low grade postzygotic mosaicism can result in significant phenotypes.

2. IDENTIFICATION AND VALIDATION OF NEK11 AS A NOVEL HIGH PENETRANCE MELANOMA SUSCEPTIBILITY GENE

E. Christodoulou[1], M Visser[1], A.F.A.S Teunisse[2], M. Versluis[3], P.A. van der Velden[3], A.G. Jochemsen[2], N. Hayward[4], R. van Doorn[1], N.A. Gruis[1]
Department of [1]Dermatology, [2]Cell and Molecular Biology and [3]Ophthalmology, LUMC, Leiden, [4]Oncogenomics Laboratory, QIMR Berghofer Medical Research Institute, Brisbane City, Australia

Background: Of all cutaneous melanoma patients, 10% report a family history. Mutations in CDKN2A and other genes are known to cause familial melanoma; however, the genetic basis for over half of families remains unknown.
Objective: Herein, we aimed to identify and validate novel high penetrance genes for familial melanoma.
Methods: Whole Exome Sequencing (WES) analysis was applied to identify novel melanoma susceptibility genes. We characterized the causality of a candidate variant firstly by performing Sanger Sequencing and Digital PCR analyses in patient-derived tissues and secondly by functional in-vitro studies in U2OS and FM6 cells.
Results: WES on a Dutch melanoma family revealed a germline nonsense mutation p.R374X in NEK11; an essential component of G2/M arrest. Co-segregation of this mutation was determined in five affected relatives, confirming the WES results. We showed loss-of-heterozygosity in melanoma tissue as well as presence of NEK11-R374X allele in lymphocyte-RNA of a carrier; collectively suggesting NEK11 p.R374X as an inactivating, loss of function (LOF) mutation. We then proceeded with expressing and determining nuclear-localization patterns of NEK11 WT and p.R374X in U2OS cells. A significantly 5-fold lower protein level of NEK11-R374X was observed when compared to wild-type in U2OS cells ($p<0.0005$). This diminished protein expression was confirmed by cycloheximide (CHX) treatments in FM6 cutaneous melanoma cells whereby we determined NEK11 R374X protein half-life at one hour after CHX treatment.
Conclusion: Collectively, we uncover NEK11 p.R374X as a LOF mutation leading to protein instability and suggesting NEK11 as a potential causal gene for familial melanoma.

3. STAT1 GAIN-OF-FUNCTION COMPROMISES SKIN HOST DEFENSE IN THE CONTEXT OF INTERFERON-γ SIGNALING

H. Niehues[1], B. Rösler[2], D.A. van der Krieken[1], I.M.J.J. van Vlijmen-Willems[1], D. Rodijk-Olthuis[1], M. Peppelman[1], J. Schalkwijk[1], E.H.J. van den Bogaard[1], P.L.J.M. Zeeuwen[1], F.L. van de Veerdonk[2]
Department of [1]Dermatology, Radboud Institute for Molecular Life Sciences and [2]Internal Medicine, Radboud Center for Infectious Diseases (RCI), Radboudumc, Nijmegen

Background: Defective mucosal and skin host defense mechanisms are the hallmarks of the primary immunodeficiency chronic mucocutaneous candidiasis (CMC). We previously reported that heterozygous mutations in the signal transducer and activator of transcription 1 (STAT1) gene are responsible for autosomal dominant CMC. Moreover, we demonstrated that gain-of-function (GOF) mutations of STAT1 lead to its hyperphosphorylation and subsequent impairment of Th17 responses, finally resulting in a severe mucocutaneous Candida albicans infection.
Objective: Although CMC manifests itself at the level of epithelia (skin and oral mucosa), research has so far been limited to the study of immune cells. Using genetically defined epidermal cells, either wild type or carrying STAT1 GOF mutations, we investigated their response to proinflammatory cytokines, with respect to skin barrier and host defense gene expression.
Methods: We generated 3D epidermal equivalents from keratinocytes of healthy controls and CMC patients (STAT1 GOF), and stimulated these with IL-17, IL-22 or IFNγ. The cellular responses were evaluated by immunohistochemistry.

Results: We generated 3D epidermal equivalents from keratinocytes of healthy controls and CMC patients (STAT1 GOF), and stimulated these with IL-17, IL-22 or IFNγ. The cellular responses were evaluated by immunohistochemistry.
Conclusion: This study demonstrates that epithelia of patients with a STAT1 GOF mutation have a functional defect that becomes apparent when immune cell-derived IFNγ is present. This results in structural abnormality of the epidermis and compromises the innate anti-Candida activity of the tissue.

4. A NOVEL DESMOSOMAL PROTEIN INVOLVED IN WOOLLY HAIR, PALMOPLANTAR KERATODERMA, MILD SKIN FRAGILITY, AND POTENTIALLY CARDIOMYOPATHY

D. Andrei[1], M. Vermeer[2], M. Nijenhuis[1], H.H. Pas[1], M.F. Jonkman[1], P. van der Meer[2], M.C. Bolling[1]
Departments of [1]Dermatology and [2]Cardiology, UMCG, Groningen

Background: Desmosomes are cell-membrane structures involved in connecting adjacent cells in stress-bearing tissues like skin and heart. Mutations in desmosomal genes can lead to woolly hair, palmoplantar keratoderma (PPK), skin fragility and/or cardiomyopathy. Here we describe a novel gene, gene A which is potentially involved in a cardiocutaneous syndrome. Two children with a homozygous splice site mutation in gene A (discovered by whole exome sequencing) exhibit woolly hair, PPK, and a mild skin fragility. No evident cardiac features have been observed as yet.
Objective: To investigate the position and function of novel protein A in skin and heart.
Methods: Immunofluorescence-microscopy (IF), RNA and protein analyses of patient and control keratinocytes and cardiomyocytes was performed
Results: IF of control skin and heart showed protein A at the cell-cell border, co-localizing with desmosomal proteins. The splice-site mutation caused alternative splicing with subsequent nonsense-mediated RNA decay and markedly reduced expression of protein in patient cells. Patient keratinocytes showed loss of keratinocyte cell-cell contact, loss of desmosomes and other desmosomal proteins, mimicking the skin fragility in the patients.
Conclusion: Protein A is a novel desmosomal protein expressed in skin and heart. It is involved in maintaining proper cell-cell contact in the epidermis. Mutations affecting this protein cause woolly hair, skin fragility, and PPK, typical for mutations in desmosomal proteins. Protein A is clearly expressed in cardiac desmosomes as well, however its exact function is yet unknown and under investigation. This is ultimately relevant for the children carrying these mutations.

5. MECHANICAL STRAIN COMPROMISES DESMOSOMAL INTEGRITY IN DESMOPLAKIN INSUFFICIENT CARDIAC AND CUTANEOUS CELLS

M. Vermeer[1], D. Andrei[2], M.C. Bolling[2], P. van der Meer[1]
Department of [1]Cardiology and [2]Dermatology, UMCG, Groningen

Background: Desmosomes are cell connecting membrane bound structures that provide resilience against tissue strain. Desmoplakin(DP), an essential constituent of the desmosome, links intermediate filaments to the desmosomal plaque. Patients with mutations in genes encoding for desmosomal constituents are prone to develop arrhythmogenic cardiomyopathy, woolly hair, palmoplantar keratoderma(PPK) and skin fragility. Studies suggest that exercise accelerates cardiac disease progression and cutaneous stress worsens PPK, but direct evidence remains elusive.
Objective: We used mechanical strain as a proxy for exercise or cutaneous stress, to elucidate whether a reduced desmosomal integrity can be provoked in patient-derived cells.
Methods: RNA, protein, immunofluorescence and electron microscopic analysis on ex vivo heart and skin explants and in vitro primary keratinocytes and induced pluripotent stem cell derived cardiomyocytes (iPSC-CMs) was performed.
Results: We describe a family with a novel (c.6687delA) and a previously reported (c.273+5G>A) DSP mutation. Compound heterozygosity segregated with cardiomyopathy leading to heart transplantation, early death, PPK and woolly hair, whereas heterozygosity caused a milder cardiomyopathy and PPK. Primary keratinocytes revealed patients to have lower DP levels, larger more differentiated cells and widened desmosomal intercellular spaces, at baseline or provoked by strain. iPSC-CMs of patients revealed low DP levels and disturbed Wnt-signaling. Upon strain, only patient cells failed to translocate desmosomal proteins to the cell-cell junctions, that resulted in a pronounced difference in desmosomal intercellular spaces compared to control.
Conclusion: These findings support the concept that exercise or stress may accelerate cardiac disease progression or worsening of PPK, respectively.

7. DUPILUMAB IN COMBINATION WITH SYSTEMIC IMMUNOSUPPRESSIVE AGENTS: DAILY PRACTICE DATA

L.E.M. de Wijs, T.E.C. Nijsten, L.M. Hollestein, D.J. Hijnen
Department of Dermatology, Erasmus MC, Rotterdam

Background: Dupilumab is the first biologic treatment for moderate-to-severe atopic dermatitis (AD) which has shown efficacy in clinical trials. Currently, there is no real-world data on dupilumab in combination with other systemic immunosuppressants.
Objective: To evaluate dupilumab treatment with or without other systemic immunosuppressants in daily practice in patients with AD.
Methods: In this observational cohort study we prospectively followed all adult patients with AD treated with dupilumab in the department of Dermatology of the Erasmus University Medical Center. Subcutaneous dupilumab 300mg injections were administered every 2 weeks. Systemic immunosuppressive agents were allowed as co-therapy (off-label). Outcome measures were the Eczema Area and Severity Index (EASI; 0-72) and Patient-Oriented Eczema Measure (POEM; 0-28) at baseline and 16 weeks after start of dupilumab.
Results: In total, 60 patients were enrolled of which 87% (n=52) used systemic immunosuppressants at baseline and 63% (n=33/52) continued use of systemic immunosuppressants

during treatment in tapering dose. The median baseline EASI score was 12.6 (IQR 7.3-23.6) and the median difference between baseline and week 16 was 7.6 (IQR 3.4-13.4). The median POEM was 20 (IQR 16.8-24.0) at baseline with a median difference between baseline and week 16 of 10.5 (IQR 6.5-14.5). Five patients discontinued dupilumab treatment: one due to side-effects and four due to lack of clinical response. Conjunctivitis was reported in 38% of the patients. There was no clinically significant change in laboratory parameters.
Conclusion: Dupilumab treatment in daily practice, often combined with systemic immunosuppressants, shows a clinically relevant improvement with no apparent safety concerns.

8. THE INFLUENCE OF TREATMENT IN ALPINE AND MODERATE MARITIME CLIMATE ON THE COMPOSITION OF THE SKIN MICROBIOME IN PATIENTS WITH DIFFICULT TO TREAT ATOPIC DERMATITIS

M.M.F. van Mierlo[1], J.E.E. Totté[1], K.B. Fieten[2,3], T.J. van den Broek[4], F.H.J. Schuren[4], L.M. Pardo[1], S.G.M.A Pasmans[1]
[1]Department of (Pediatric) Dermatology, Sophia Children's Hospital, Erasmus MC, Rotterdam, [2]Merem Dutch Asthma Center Davos, Switzerland, [3]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zürich, Davos, Switzerland, [4]Microbiology and Systems Biology, TNO, Zeist

Background: Multidisciplinary treatment in alpine climate is known for its positive effect on disease severity in children with atopic dermatitis (AD) and can lead to a different immune response compared to moderate maritime climate. However, the effect on the composition of the skin microbiome in AD is unknown.
Objective: To determine the effect of treatment in maritime and alpine climate on the microbiome for lesional and non-lesional skin in children with difficult to treat AD.
Methods: This study is part of the DAVOS trial, a pragmatic randomized controlled trial including children with difficult to treat AD. Eighty-four patients were randomized to a 6 week personalized integrative multidisciplinary treatment in either alpine climate or moderate maritime climate. Before and directly after treatment swabs were collected from lesional and non-lesional skin and analyzed using 16S-rRNA sequencing. Additional quantitative (q)PCR for Staphylococcus (S.) aureus and S. epidermidis was performed. Disease severity was assessed with SA-EASI.
Results: We found a significant larger decrease in disease severity after 6 weeks of treatment in alpine climate compared to moderate maritime climate. This was accompanied by a significant change in the overall microbial composition on lesional skin, driven by the Staphylococcus genus. Using qPCR we found a significant larger reduction in S. aureus load on lesional skin following alpine climate treatment.
Conclusion: Clinically successful treatment of AD patients in alpine climate leads to a significant change in composition of the microbiome on lesional skin. This was mainly caused by a reduction in the Staphylococcus genus.

9. FREQUENCY OF ASSOCIATED HAEMATOLOGIC MALIGNANCIES IN LYMPHOMATOID PAPULOSIS: A PRELIMINARY REPORT OF 501 PATIENTS FROM THE DUTCH CUTANEOUS LYMPHOMA GROUP

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Background: Recent studies reported that lymphomatoid papulosis (LyP) is associated with other haematological malignancies (HM) in up to 50% of patients. If correct, this would have major consequences for the management of LyP.
Objective: We investigated the frequency of associated HM in patients with LyP in a nationwide study in the Netherlands.
Methods: This multicenter study included 501 patients with LyP, included in the database of the Dutch Cutaneous Lymphoma Group (DCLG) between 1985 and 2018. The presence of an associated HM was evaluated by reviewing DCLG follow-up forms, medical records and pathology reports.
Results: After a median follow-up of 70 months, an associated HM was observed in 78 of 501 patients (15.6%). These included mycosis fungoides (n=31), (cutaneous)-anaplastic large cell lymphoma (n=30), and other types of HM (n=17). These associated HM had been diagnosed before or concurrent (n=43), or after (n=35) the diagnosis LyP had been made. A percentage of 16.7% associated HM was found in a subgroup analysis of patients included before 2005, with a median follow-up of 136 months. Twenty patients developed systemic lymphoma during follow-up: 12 patients with ALCL and 8 patients with another type of HM.
Conclusion: In contrast to the high percentages of associated HM reported by recent studies, in the present study associated HM were found in only 16% of 501 LyP patients. An explanation for these discrepant results is currently lacking, but referral bias or differences in criteria to make a diagnosis MF or C-ALC may play a role.

10. NOVEL ASSESSMENT METHODS TO EXPLORE AND CHARACTERIZE WOUND HEALING AFTER SKIN PUNCH BIOPSIES IN HEALTHY VOLUNTEERS.

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Background: Novel models need to be developed for drug development in wound healing. These models should be feasible

in execution, but also include novel biomarkers and endpoints to objectively monitor treatment effects of interventions. The gold standard, i.e. histological analysis of skin biopsies, is invasive and may induce considerable side effects. Therefore, a study in healthy volunteers was conducted to explore novel assessment methods for wound healing characterization.
Objectives: 1) To evaluate imaging modalities in wound healing assessment, and 2) to compare various non-invasive skin assessment modalities.
Methods: A single-arm, observational study to characterize wound healing after three millimeter skin punch biopsies was performed in eighteen healthy volunteers. Wounds healed without secondary intervention and wound healing was assessed over 70 days using 3D imaging, transepidermal water loss (TEWL), and multispectral imaging. Endpoints were summarized (mean, standard deviation of the mean) by time.
Results: Stereo-photogrammetric analysis showed a decrease of the wound surface after biopsy (7.93mm2, 1.23mm2) up to day 28 when no wounds were present. TEWL baseline values (13.6g/m2h, 4.3g/m2h) increased after biopsy (62.4g/m2h, 8.0g/m2h) followed by a decrease, reaching steady state at day 70 (13.6g/m2h, 5.1g/m2h). Multispectral imaging showed an increase in skin redness from baseline (0.9AU, 0.2AU) to day 2 (2.8AU, 0.3AU), reaching steady state at day 21 (2.2AU, 0.3AU).
Conclusion: Three millimeter skin punch biopsies are a suitable, minimally invasive method to study wound healing in healthy volunteers. All performed pharmacodynamic analyses showed promising results in wound healing evaluation and can be used in future trials.

11. THE ULTRAVIOLET LIGHT CAMERA, A PROMISING MEASUREMENT INSTRUMENT FOR LESION ASSESSMENT IN VITILIGO

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Background: For vitiligo follow-up and research often photographs with the use of UV-light are made. The low intensity of UV-lamps can make photographs lack resolution and/or focus. A UV-camera, which passes UV-light and filters other light might improve picture quality and ameliorate the assessment of lesions in vitiligo.
Objective: To assess picture quality and the validity and reliability of a UV-camera for lesion assessment in vitiligo.
Methods: Pictures of patients with vitiligo were made with a UV-camera, a classic camera and lesions were drawn on graph paper and transparent sheets. Picture quality was assessed by vitiligo experts and medical interns. The intraclass correlation coefficients (ICCs) of the lesion size determined with the use of the UV-camera and the other techniques were hypothesised to be above 0.6. The ICCs between UV-photographs taken by the same physician and between two different physicians were also hypothesized to be above 0.6.
Results: A total of 31 lesions of 17 patients were included. Picture quality was assessed as good or very good for 100% of the UV-camera, versus 26% for the classic camera. ICCs of the UV camera and the classic camera, drawing the lesions on graph paper and transparent sheets were respectively 0.984, 0.983 and 0.988. The ICC's of the intra-rater and inter-rater were 0.999 and 0.998 respectively.
Conclusion: The results of this study suggest that the use of a UV-camera for the assessment of vitiligo lesions improves picture quality and is valid and reliable.

12. THE ANTI-INFLAMMATORY POTENCY OF BIOLOGICS TARGETING TNF-α, IL-17A, IL-12/23 AND CD20 IN HIDRADENITIS SUPPURATIVA: AN EX VIVO STUDY

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Background: Biologics targeting inflammatory mediators are able to clinically improve hidradenitis suppurativa (HS). However, their clinical efficacy shows great inter-patient variability in daily practice.
Objective: To investigate the anti-inflammatory potency of currently available biologics for the treatment of HS in an ex vivo skin culture system using lesional HS biopsies.
Methods: Lesional skin samples of ten HS patients and normal skin of five healthy controls were cultured ex vivo and exposed to prednisolone or biologics targeting TNF-α, IL-17A, IL-12p40/IL-23, or CD20, respectively adalimumab, infliximab, secukinumab, ustekinumab and rituximab. Real-Time quantitative PCR and cytokine bead arrays were used to measure the inhibitory effect of the biologics on cytokines and antimicrobial peptides (AMPs).
Results: The relative mRNA expression of all tested cytokines and AMPs was significantly downregulated by all anti-inflammatory agents ($p<0.0001$). The release of the pro-inflammatory cytokines TNF-α, IFN-γ, IL-1ß, IL-6, IL-17A was significantly inhibited by adalimumab, infliximab, ustekinumab, prednisolone (all $p<0.0001$) and rituximab ($p=0.0071$), but not by secukinumab ($p=0.0663$). In addition, adalimumab, infliximab and prednisolone reduced the levels of a broader mix of individual cytokines than secukinumab, ustekinumab and rituximab.
Conclusion: This ex vivo study suggests that TNF-α inhibitors and prednisolone are the most powerful inhibitors of pro-inflammatory cytokines and AMPs in HS lesional skin, which is in accordance with our clinical experience in patients with HS.

13. IL-10 REGULATES SKIN THICKNESS AND SCALING IN IMIQUIMOD-INDUCED PSORIASIS-LIKE SKIN INFLAMMATION IN MICE

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Background: Psoriasis is an autoimmune skin disease affecting around 0.6 to 3% of the whole population. Previously, we

established a psoriasis-like skin inflammation model in mice using topical application of imiquimod (IMQ). This model successfully re-captures critical features of acute psoriasis. Previous data suggested up-regulation of IL-10 during this model, but its role was not clear.
Objective: To investigate the role of IL-10 in IMQ-induced psoriasis-like skin inflammation.
Methods: Psoriasis-like skin inflammation was induced by topical application of Aldara. Mice were i.p. injected with anti-IL-10 or isotype control antibody. Skin inflammation was scored using a modified PASI score system. Inflammation and skin thickness were scored histologically. Gene expression and immune cells were analyzed using qPCR and flow cytometry, respectively.
Results: At day 10, both skin thickness and scaling were significantly higher after neutralizing IL-10 compared to isotype control. At days 5 and 10, H&E staining confirmed epidermal thickness was more prominent in anti-IL-10 group compared to isotype control, with more profound differences at day 10. Ki-67 staining showed more proliferation at the epidermal basal layer after neutralizing IL-10. Significantly more infiltration of neutrophils were found in skin at Day 10. In early phase (day5), IL-23/IL-17 pathway cytokines were more significantly up-regulated, while at late stage (day10), a significant upregulation were found in IL-19 and IL-24 expressions.
Conclusion: Our data suggest that IL-10 regulates skin thickness and scaling during psoriasis-like skin inflammation through dampening of the IL-23/IL-17 axis in early phase and reducing IL-19 and IL-24 expression at late stage.

14. CUTANEOUS STAPHYLOCOCCUS PROFILING AT SPECIES LEVEL IN ATOPIC DERMATITIS BY SINGLE LOCUS SEQUENCE TYPING (SLST) MARKER DESIGN AND OLIGOTYPING FOR HIGH-RESOLUTION SEQUENCING-BASED MICROBIAL PROFILING

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Background: Single Locus Sequence Typing (SLST) marker gene sequencing has recently been described for down-to strain level identification of specific bacteria within a microbiota, such as on human skin. SLST fills the gap between cheap but coarse-grained 16S, and expensive but higher resolution shotgun metagenomics.
Objective: To build a workflow for finding suitable genome regions for SLST PCR primers, including a methodology for application of SLST and analysis of SLST sequencing data.
Methods: On a human cohort of healthy volunteers, and patients with atopic dermatitis (AD) lesions, we applied and validated the SLST method for high-resolution sequencing-based Staphylococcus profiling on skin. Skin microbiota samples were taken from the inner elbow, and 16S and SLST marker gene amplicons were mixed and sequenced by Illumina.
Results: We identified a suitable SLST candidate in the 30S ribosomal protein S11 gene of Staphylococcus. This target was successfully validated, and allowed for 77.2% of Staphylococcus reads to be assigned to species-level or lower, in comparison to 5.9% for 16S. By SLST, we mainly identified taxa of S. aureus and S. capitis, which were significantly increased in AD, in comparison to taxa of S. epidermidis and a cluster of S. haemolyticus / hominis, which were associated with healthy skin.
Conclusion: We present TaxPhlAn, a new method that allows identification of bacteria down-to the strain level in complex environments. We demonstrated that for the cutaneous Staphylococcus genus, our SLST method enables profiling of its members at (sub)species level, and shows higher resolution than current 16S-based sequencing techniques.

15. A SEMI-UNSUPERVISED MULTIVARIATE ALGORITHM FOR PROFILING AND MINING HIGH-DIMENSIONAL FLOW CYTOMETRY DATA IN PSORIATIC PATIENTS

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Background: Flow cytometry has great potential for immune profiling of psoriasis. The current definition of diseases is mostly based on clinical manifestations but not on complex cellular and molecular interactions underlying disease pathology. Flow cytometry might provide disease associated immune profiles that support diseases stratification, efficient therapy selection and therapy monitoring.
Objective: Primary objective is to generate immune profiles in psoriasis patients based on peripheral blood immune cell subtypes using high dimensional flow cytometry combined with a semi-unsupervised multivariate algorithm tool.
Methods: Freshly drawn whole blood from healthy controls and psoriatic patients were collected, stained with five distinct 10-color flow cytometry panels that enable to characterize T-cell, B-cell, monocyte and NK-cell subsets as well as the T-helper cell profile, T-cell division status an in-depth regulatory T-cell composition. After measuring the samples by flow cytometry, the data was manually analyzed resulting in approximately 300 different immune cell subsets per individual. Next, we performed an unsupervised multivariate analysis and data mining by hierarchical clustering on principal component analysis (HCPC).
Results: Principal component analysis clearly demonstrated that psoriatic patients and healthy controls reveal differential clustering. Importantly the multivariate algorithm was capable to stratify the psoriatic patient cohort in four different clusters that each can be identified by different immune cell subtypes among which CD4+ regulatory T-cells and various T-helper cell subsets.
Conclusion: Our semi-unsupervised algorithm successfully enabled profiling and mining of high-dimensional flow

cytometry data obtained from psoriasis patients. The profiles might be applied for new stratification and personalized treatment strategies.

16. FCERI-BEARING LEUKOCYTES IN RESPONSE TO OMALIZUMAB TREATMENT IN CHRONIC SPONTANEOUS URTICARIA

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Background: The exact pathogenesis of chronic spontaneous urticaria (CSU) and the mechanism of action of omalizumab in CSU remains unclear.
Objective: In this study we assessed the responsiveness and FcεRI expression on various subsets of leukocytes in patients with CSU prior to and during treatment with omalizumab.
Methods: In this monocenter prospective cohort study 30 CSU patients were treated with 6 administrations of 300 mg omalizumab every four weeks followed by a follow-up period of 12 weeks. The portion of basophils, monocytes, dendritic cells (DC) at several time points in blood samples were analyzed. FcεRI expression was measured at the same time points, as well as FcεRI- and C5a-induced basophil degranulation. Results were related to the urticaria activity score (UAS7) after omalizumab treatment.
Results: We demonstrated a prominent reduction of FcεRI on basophils and plasmacytoid dendritic cells during omalizumab treatment, persisting after three months of discontinuation of treatment. Baseline level and treatment response of FcεRI expression was not related to clinical response after omalizumab. Omalizumab treatment led to an increased percentage of basophils in blood. Anti-IgE induced basophil degranulation increased during treatment while a simultaneous decrease in C5a mediated degranulation was demonstrated indicating a differential effect on basophil responsiveness. Baseline levels of degranulation was not different in omalizumab responders versus non-responders, however non-responders showed a stronger increase.
Conclusions: Level of FcεRI expression, Anti-IgE and C5a induced degranulation and basophil number change significantly due to omalizumab treatment in patients with urticaria. None of the markers at baseline could predict therapy efficiency.

17. A COMBINATION OF SERUM BIOMARKERS TARC, IL-22, AND SIL-2R ACCURATELY PREDICTS DISEASE SEVERITY IN ATOPIC DERMATITIS PATIENTS TREATED WITH CYCLOSPORIN A OR DUPILUMAB

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Background: Serum biomarkers offer an objective outcome measure for disease severity in atopic dermatitis (AD). A combination of serum biomarkers TARC, IL-22 and sIL-2R as a signature (predicted EASI) offers an objective measurement tool for disease severity in AD patients treated with topical steroids.
Objective: To validate the predicted EASI (p-EASI) in AD patients treated with Cyclosporin A (CsA) and dupilumab.
Methods: In a retrospective study, 26 AD patients (median age 39, InterQuartileRange (IQR) 23-52, 20 male) treated with CsA (approximately 4-5mg/kg/day) were included. In a prospective study 25 AD patients (median age 44, IQR 19-79, 15 male) treated with Dupilumab 600mg were included. Disease severity was assessed by EASI and serum was collected before start of treatment, after 3 weeks of CsA treatment and after 4,8,12 and 16 weeks of dupilumab treatment. Serum biomarkers TARC, IL-22, and sIL-2R were measured by luminex.
Results: EASI and p-EASI scores highly correlated in CsA ($r=0.71$, $p<0.0001$) and dupilumab treated patients ($r=0.65$, $p<0.0001$). The difference between median EASI and p-EASI before treatment was 0.9 (IQR-6.6–7.4) in CsA, and -3.0 (IQR-11.3–0.4) in dupilumab treated patients. After CsA treatment the median difference was -0.2 (IQR-3.4–2.3) and after 16 weeks of dupilumab treatment -0.8 (IQR-4.7–-0.2). Decrease in TARC preceded decrease in EASI scores in dupilumab treated patients.
Conclusion: A combination of serum biomarkers TARC, IL-22, and sIL-2R accurately predicts disease severity in AD patients treated with topical steroids, cyclosporin A, or dupilumab. Additionally, serum TARC levels may be used to predict treatment effect of dupilumab.

18. STANDARDIZED FLOW CYTOMETRY (EUROFLOW) DEMONSTRATES DIFFERENT FUNCTIONAL RELATED PHENOTYPES TO SÉZARY SYNDROME CELLS

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Background: Sézary syndrome (Sz) is an aggressive type of Cutaneous T-cell Lymphoma. Sézary cells (SCs) are generally considered as CD4+ central memory (TCM) cells of T-helper (Th)2-type subset. However, these cells remain incompletely characterized and discriminatory monitoring tools are lacking for their identification.
Objective: Therefore, our goal was to identify the immunophenotypic profiles of SCs and to investigate their expression of characteristic maturation and T-helper subset markers to increase our general understanding of the disease.
Methods: We applied fully standardized flow cytometric protocols as developed by EuroFlow Consortium on blood samples from 9 Sz patients using 27 immunophenotypic markers included in three antibody panels. Consecutively, SCs were identified (using CD3, CD4), characterized (CD26,CD2,CD7, and CD28) and classified according to maturation (CD45RA, CD27, and CD62L) and differentiation (CXCR3, CCR4, CCR6, and CCR10) subsets.

Results: CD3dim/bright, CD26-/dim, and CD2-/dim were the most commonly observed immunophenotypic aberrancies, followed by CD7-/dim and CD28+/bright. We observed that SCs were of Naïve-like, TCM, and Peripheral Memory origin and mostly shared overexpression of chemokine receptor (CCR) 4 which is preferentially expressed on Th2 differentiated CD4+ T cells. Nevertheless, in the majority of samples (7 out of 9) SCs showed co-expression of additional chemokine receptors, mostly resembling Th17 (CCR4+CCR6+) and Th22 (CCR4+CCR6+CCR10+) T-helper subsets. Interestingly, we observed overlapping but sometimes diverse phenotypic profiles within one patient, showing intra-patient dynamics in SC differentiation.
Conclusion: Here, we demonstrated distinct phenotypic profiles in Sz reflecting SC heterogeneity which is suggestive of a more inter- and intratumor heterogeneous nature of the disease than previously appreciated.

19. OVEREXPRESSION OF SELF-TOLERANCE PROTEIN PD-1 IS EPIGENETICALLY REGULATED IN SÉZARY SYNDROME

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Background: Sézary syndrome (SS) is an aggressive type of cutaneous T-cell lymphoma. Recently, we discovered that the methylome of SS is highly disturbed, resulting in global hypomethylation and gene-specific promoter hypermethylation. Previously, we identified a novel panel of highly sensitive and specific diagnostic DNA methylation biomarkers using genome-wide methylation array data in combination with a stringent analysis. Other studies suggested that several mainstream SS biomarkers (CD26, CD7, PLS3) are regulated by DNA methylation.
Objective: In this study we explored the same methylation array data, albeit with lower stringency, to reveal and/or confirm possible epigenetic regulation of 15 established SS markers.
Methods: We collected peripheral blood from 40 SS patients, 15 benign erythroderma patients and 10 healthy controls. Initially, a representative part of samples was analysed for aberrant methylation using Infinium 450K beadchips. For independent confirmation, methylation specific melting curve analysis was used. Epigenetic regulation was investigated by qPCR, flow cytometry and immunohistochemical staining.
Results: Aberrant methylation patterns were discovered for SS markers CD26, CD7, PLS3 (hypermethylated) and PD-1 (hypomethylated). The strongest correlation between aberrant methylation and epigenetic regulation was observed for PD-1. This protein was consistently expressed in patients of which hypomethylation of corresponding gene promoter was demonstrated.
Conclusion: We discovered that upregulation of self-tolerance protein, PD-1, is highly correlated with hypomethylation of corresponding gene promoter in SS. Administration of anti-PD-1 drugs like Nivolumab might be a helpful treatment option for SS. In addition, use of demethylation agents should be evaluated considering possible reexpression of immune checkpoint molecules like PD-1.

20. IFNG AND HYPOXIA CO-STIMULATE PDL1 EXPRESSION IN MELANOMA CELLS, INDEPENDENT OF HIF1

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Background: The immune system can protect against cancer initiation and progression. However, cancer cells have developed mechanisms to escape immune surveillance. One mechanism is the upregulation of the immune inhibitory molecule programmed death ligand 1 (PDL1) on their cell surface, which binds programmed cell death protein 1 (PD1) on activated immune cells to inactivate these cells. PD1/PDL1 targeting therapies (e.g. nivolumab) have been established for the treatment of melanoma. Yet, not all PDL1 positive tumors respond to aPD1-therapy, while PDL1-negative tumors sometimes do. Therefore a better understanding of the role of PDL1 expression and function in the tumor microenvironment (TME) is needed. Interferon-gamma (IFNg), a cytokine secreted by activated T (and other) immune cells, is a key transcriptional inducer of PDL1. Notably, recent studies report that hypoxia via HIF factors can also induce PDL1 expression in cancer cells.
Objective: In this study we aim to explore the regulation of PDL1 by hypoxia (HIF1) alone, and in combination with IFNg, as both factors are present in the TME.
Methods: We used a panel of human and murine melanoma cell lines to evaluate PDL1 mRNA (qPCR) and protein (flow cytometry) expression in response to hypoxia, IFNg, the HIF1 stabilizing compound DFO, or a combination thereof.
Results & Conclusions: Our observations reveal that hypoxia alone does not induce mRNA or protein PDL1 expression, but does significantly enhance IFNg stimulation of PDL1 mRNA expression in some cell lines. Intriguingly, lentiviral knockdown of HIF1a did not rescue hypoxic enhancement of IFNg-induced PDL1 expression.

21. ASSOCIATIONS OF EARLY LIFE ENVIRONMENTAL EXPOSURES AND GENETIC RISK FACTORS WITH ECZEMA PHENOTYPES. THE GENERATION R STUDY

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Background: Childhood eczema is variable in onset and persistence.
Objective: To identify eczema phenotypes during childhood, and their associations with early life environmental and genetic factors.

Methods: In this study among 5,297 children of a multi-ethnic population-based prospective cohort study, phenotypes based on parental-reported physician-diagnosed eczema from age 6 months until 10 years were identified using latent class growth analysis. Information on environmental factors was obtained by postal questionnaires. Four filaggrin mutations were genotyped and a risk score was calculated based on 30 genetic variants. Weighted adjusted multinomial models were used for association analyses.
Results: We identified five eczema phenotypes: never (76%), early (8%), mid- (6%) and late transient (8%), and persistent eczema (2%). Nulliparity, parental history of eczema, allergy or asthma, late onset and persistent wheezing were associated with increased risks of early transient and persistent eczema (odds ratio (95% confidence interval): range 1.37 (1.07,1.74) and 3.38(1.95, 5.85)), male sex with early transient eczema (1.49 (1.18,1.89) and Non-European with late transient (1.35 (1.03,1.78)) and persistent eczema (1.76 (1.10, 2.82)). Maternal education, breastfeeding, day care attendance and pet exposure were not associated with any eczema phenotype. Children with a filaggrin mutation or additional risk alleles had increased risks of early and late transient and persistent eczema (range 1.07 (1.02,1.12) and 2.21 (1.39, 3.50)). Most effect estimates did not materially change when adjusted for environmental and genetic factors.
Conclusion: Five eczema phenotypes were identified in a multi-ethnic pediatric population with limited differences in risk profiles, except for sex and ethnicity.

22. THE EFFECT OF ALK5 INHIBITION ON DIFFERENT FIBROBLAST POPULATIONS IN HYPERTROPHIC SCARS

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Background: Hypertrophic scars (HTS) are characterized by an overabundance of myofibroblasts, which contributes to excessive production of extracellular matrix, and severe contraction of HTS's. Furthermore, high expression of parallel aligned collagen bundles increases stiffness of the scar. TGF-β signalling plays a key role in the differentiation and activity of myofibroblasts. Previous studies have shown that inhibition of TGF-β receptor I (TGFβRI) in fibrotic diseases such as Dupuytren's disease, results in a significant reduction of the fibrotic load. Furthermore, investigating the effect of TGFβRI inhibition on the different fibroblast subpopulations in HTS is needed. It has been proposed that papillary fibroblasts, as opposed to reticular fibroblasts, exhibit anti-fibrotic properties.
Objective: To investigate the effect of exon skipping of ALK5 (TGFβRI) on different fibroblast populations in HTS.
Methods: HTS-derived fibroblasts were used to set up monocultures, contraction models and fibroblast-derived matrix (FDM) models. In order to induce exon skipping, antisense oligonucleotides (AON's) targeting ALK5 were supplemented to the culture medium of the models. Pharmacological ALK5 inhibition was performed using SB431542.
Results: Our data demonstrate that ALK5 inhibition has a differential effect on fibroblast subtypes in HTS. In addition, ALK5 inhibition showed to reduce contraction of collagen lattices. Furthermore, multi-photon imaging and nanoindentation showed that ALK5 inhibition affects collagen rearrangement and stiffness of FDM's.
Conclusion: Fibroblasts that show papillary-like features gain pre-eminence when influenced by exon skipping of ALK5. Furthermore, exon skipping affects collagen rearrangement and stiffness in FDM's. Altogether, this could open a therapeutic window for the treatment of HTS.

23. IL-4 AND IL-13 DISCOVERED AS DIRECT KERATINOCYTE MITOGENS – IMPLICATIONS FOR EPIDERMAL HYPERPROLIFERATION IN PSORIASIS AND ATOPIC DERMATITIS

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Background: Atopic dermatitis (AD) and psoriasis are multifactorial inflammatory skin diseases characterized by accelerated keratinocyte proliferation, called hyperproliferation, leading to epidermal acanthosis (hyperplasia) and excessive skin scaling. Several factors such as cytokines, chemokines and other soluble factors, derived from keratinocytes or immune cells, have been proposed as inducers of proliferation (mitogens). However, clear evidence pinpointing to specific keratinocyte mitogens is yet lacking, and therefore the mechanism of hyperproliferation in AD and psoriasis is still under debate.
Objective: We aimed to investigate the potential of diverse candidate factors for directly inducing keratinocyte hyperproliferation in vitro.
Methods: Three-dimensional (3D) human epidermal equivalents (HEEs) were stimulated with soluble factors in a dose range and proliferation was analyzed by morphology (measurement of epidermal thickness) and immunohistochemistry (Ki67, 5-ethynyl-2'-deoxyuridine (EdU) labeling). Moreover, morphological features like apoptosis, spongiosis, and epidermal differentiation were analyzed.
Results: We found that T-helper 2 (Th2) cytokines interleukin-4 (IL-4) and interleukin-13 (IL-13) directly increase keratinocyte proliferation in our organotypic HEE model, as witnessed by increased expression of Ki67 and high incorporation rates of EdU. Blocking of the IL-4 receptor signaling cascade with Dupilumab reversed these affects and normalized epidermal proliferation.
Conclusion: We here show that IL-4 and IL-13 are epidermal mitogens directly inducing keratinocyte proliferation in vitro. Both cytokines are well described important regulators in AD and have also been shown to be elevated in psoriasis. Therefore, our study implicates an important role and potential therapeutic target for IL-4 and IL-13 in chronic hyperproliferative disorders like psoriasis and atopic dermatitis.

24. DECREASED EXPRESSION OF KERATIN 9 AND 14 IN HYPERKERATOTIC PALMAR HAND ECZEMA

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Background: Hyperkeratotic palmar hand eczema (HHE) is a clinical subtype of eczema with typically sharply bordered hyperkeratosis on the palms. The pathophysiology of HHE is largely unknown. Objective: To investigate the expression of keratins, epidermal barrier proteins and adhesion molecules in lesional and non-lesional HHE skin compared to palmar skin of healthy controls.
Methods: Palmar skin biopsies (lesional and non-lesional skin) were obtained from seven HHE patients and two healthy controls. Immunofluorescence (IF) staining for keratin (K) 1, 2e, 6, 9, 10, 14, 16, 17, desmoglein-1, desmoglein-3, plakophilin-1, plakoglobin, desmoplakin, filaggrin, loricrin, involucrin and corneodesmosin was performed on all samples. The staining pattern and intensity were examined by two independent observers (K.P and H.H.P).
Results: Periodic acid–Schiff (PAS) stainings of lesional skin confirmed the diagnosis HHE. IF stainings showed a significant reduction or absence of K9 and K14 in lesional skin. There was a significant up-regulation of K6, K16, and K17 in lesional skin compared to non-lesional and healthy skin. Moreover, desmoglein-3 showed a panepidermal pattern in lesional skin (only basal expression in control). Other keratins, epidermal barrier proteins and adhesion molecules did not show significant differences between lesional, non-lesional and healthy skin.
Conclusion: Preliminary results demonstrated a remarkable reduction/absence of K9 and K14 in lesional skin of patients with HHE which might contribute to the underlying pathogenesis of HHE. Additional immunofluorescence data on other palmoplantar differentiation diseases like psoriasis and hereditary keratodermas to compare, as well as genetic analysis (RNA, DNA) could help in elucidate the pathogenesis of HHE.

25. INCORPORATION OF HAIR FOLLICLES INTO RECONSTRUCTED HUMAN SKIN

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Background: The hair follicle plays a critical role in thermal regulation, physical protection, dispersion of sweat and sebum, sensory and tactile functions and social interactions. Although human skin models have shown to be a promising tool for in vitro studies with the potential to replace animal testing, there is no model that includes the hair follicle. Skin models that closely represent human skin physiology and incorporate the hair follicle are required for basic research, modeling skin disease and in vitro drug testing.
Objective: To determine whether neopapillae spheroids, mimicking follicular papillae, can be incorporated into reconstructed human skin and to determine whether they have hair follicle-inductive potential in vitro.
Methods: Dermal papilla cells were isolated from human hair follicles, expanded and used to reconstruct self-aggregated neopapillae spheroids. Neopapillae were incorporated into a bilayered skin substitute (reconstructed epidermis on a fibroblast-populated hydrogel) and cultured air-exposed to promote epidermal stratification.
Results: Notably, neopapillae within the collagen hydrogel stimulated epidermal downgrowth resulting in engulfment of the neopapillae sphere within 10 days of air-exposed culture. Our results indicate, that epidermal invagination might be a response to a local chemotactic gradient generated by underlying neopapillae, demonstrating the native behavioural characteristics of epidermal-dermal interactions in the initial stages of hair follicle morphogenesis.
Conclusions: Reconstructed human skin containing neopapillae with hair follicle-inductive properties can be constructed in vitro thus providing a promising new tool for investigating human hair follicle formation and related hair diseases in vitro.

26. FIRST EXPERIENCE OF DUPILUMAB IN ATOPIC DERMATITIS PATIENTS TREATED IN DAILY PRACTICE: 16-WEEK EVALUATION OF CLINICAL EFFECTIVENESS AND SERUM BIOMARKERS

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Introduction: Dupilumab has shown promising results in phase III trials and has recently been approved for the treatment of moderate to severe atopic dermatitis (AD) in adults. At this moment, daily practice data on dupilumab treatment are lacking.
Objective: To study the effect of 16 weeks treatment with dupilumab on clinical efficacy, serum biomarkers (and peripheral blood T-cell skewing) in adult patients with moderate-severe AD in daily practice.
Methods: Data were extracted from the Bioday registry. 16-weeks clinical effectiveness of dupilumab was expressed as number of patients achieving EASI-50, EASI-75) as well as patient reported outcomes measures (POEM, DLQI, NRS-itch). 29 biomarkers representing different disease pathways were measured in 35 patients treated with dupilumab without concomitant use of oral immunosuppressive drugs at 5 different time points (baseline, 4 weeks, 8 weeks, 12 weeks and 16 weeks).

Results: In total, 105 patients treated with dupilumab in daily practice were included. At week 16, the mean percent change in EASI score was 72%. The EASI-50 and EASI-75 were achieved by 87(85%) and 59(58%) patients after 16 weeks of treatment. The most reported side effect were conjunctivitis in 39(37%) and eosinophilia in 67(65%) patients. Dupilumab significantly decreased type 2 and severity serum biomarkers including, CCL17(TARC), CCL18(PARC), periostin and IL-22.
Conclusion: Treatment with dupilumab improved disease severity and significantly suppressed Th2 and severity related serum biomarkers in patients with very difficult-to-treat AD in a daily practice setting.

27. GOBLET CELL SCARCITY AND CONJUNCTIVAL INFLAMMATION DURING TREATMENT WITH DUPILUMAB IN PATIENTS WITH ATOPIC DERMATITIS

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Background: Dupilumab, a human monoclonal antibody targeting the interleukin-4 receptor alpha subunit and thereby inhibiting the signals of interleukin-4 and interleukin-13 has shown very promising efficacy results in the treatment of moderate to severe atopic dermatitis (AD). However, relatively high rates of conjunctivitis have been reported during dupilumab treatment. The pathomechanism underlying the development of conjunctivitis during dupilumab treatment has not yet been clarified.
Objective: To describe the clinical and histopathological characteristics of conjunctivitis during dupilumab treatment in AD patients.
Methods: In this case series AD patients developing an ophthalmologist-confirmed conjunctivitis during dupilumab treatment were included for further analysis. In all patients complete standardized ophthalmological examination and a diagnostic conjunctival biopsy was performed. Immunohistochemical analysis of conjunctival biopsies was performed by an experienced ophthalmological pathologist.
Results: A total of six patients were included. The severity of dupilumab-related conjunctivitis ranged from mild to severe. Conjunctival biopsies revealed scarcity of intraepithelial goblet cells accompanied by a T-cell (especially CD4+) and eosinophilic infiltrate in the conjunctival stroma.
Conclusion: Our findings indicate that dupilumab-related conjunctivitis is marked by goblet cell scarcity in the conjunctival epithelium accompanied by a T-cell and eosinophilic infiltrate. More insight in the functional T cell profile and activation status of eosinophils is necessary to further clarify the underlying pathomechanism of conjunctivitis during dupilumab treatment in AD patients.

28. HUMAN CENTRAL MEMORY T CELLS GENERATE SUPERIOR NUMBERS OF RESIDENT MEMORY T CELLS IN SKIN

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Background: Resident memory T cells (TRM) are critical in defending peripheral tissues but the precursor cells that give rise to TRM have not been yet studied.
Objective: We studied the ability of three circulating human memory T cell subsets (Central memory T cells (TCM, CCR7+/CD62L+), effector memory T cells (TEM, CCR7-/CD62L-) and migratory memory T cells (TMM, CCR7+/CD62L-) to generate TRM in vitro and in vivo in human-engrafted-mice.
Methods: For in vitro studies, flow-sorted human memory T cell subsets were stimulated and cultured for one week on human keratinocytes and cells were immunostained for the TRM markers CD69 and CD103. To evaluate the ability of human T cell subsets to give rise to TRM in vivo, we utilized a human-engrafted-mouse-model in which NSG mice are grafted with neonatal human foreskin, a tissue that lacks T cells, and infused i.v. with allogeneic T cells.
Results: TEM had the highest rate of conversion to both CD69+ and CD103+ expressing T cells in vitro and TCM had the lowest conversion frequency, with an intermediate frequency for TMM. In vivo, TEM also had the higher conversion rate to TRM in skin. However, TCM persisted longer in the circulation, repopulated the other T cell subsets (TMM and TEM) and accumulated within the skin in higher numbers, giving rise to significantly higher numbers of TRM.
Conclusion: Our studies suggest that TCM can provide long lasting immunity in both the circulating and tissue compartments, making them an ideal candidate for adoptive immunotherapy for cancers and infections.

29. IN VITRO LYMPHOCYTE PROLIFERATION TEST (LPT) FOR NICKEL USING CFSE AND AUTOLOGOUS SERUM

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Background: The gold standard for the diagnosis of allergic hypersensitivity is patch testing (PT). However, PT has only been validated for epidermal antigen contact and several metals give unreliable results. The alternative is the lymphocyte proliferation test (LPT) using tritiated thymidine, which is promising but requires radioactive material and is still being

optimized. Flow cytometric evaluation of lymphocyte proliferation by carboxyfluorescein succinimidyl ester (CFSE) overcomes the above limitations but optimal conditions are not known.
Objective: Investigate the diagnostic potential of flow cytometric evaluation by CFSE for nickel (Ni) hypersensitivity using various test protocols.
Methods: Peripheral blood mononuclear cells (PBMCs) of Ni allergic patients and healthy controls were collected, labeled with CFSE and cultured for 7 days with serum (heat inactivated (HI) human pooled serum (HPS)/autologous serum (HI)/autologous serum) in the absence or presence of $NiSO_4$ and skewing cytokines. The stimulation index (SI) was calculated. The results were evaluated against the patients history of nickel allergy combined with the PT.
Results: The mean proliferation response and SI of CD4+cells in Ni allergic patients was significantly higher using autologous serum compared to HPS-HI or autologous serum-HI. The use of autologous serum without skewing resulted in the best diagnostic values. Addition of Th-2 skewing improved the diagnostic values in HPS supplemented tests.
Conclusion: Flow cytometric LPT by CFSE dilution is a promising method for detecting Ni sensitization. The test protocol using autologous serum without skewing resulted in the best diagnostic values and should be further evaluated for the in-vitro diagnosis of metal allergies.

30. TOLL-LIKE RECEPTOR SIGNALING IN ORAL MUCOSA EXPOSED TO COMMENSAL AND PATHOGENIC BIOFILMS IN VITRO

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Background: Toll-like receptors (TLRs) play important roles in maintaining host-microbe homeostasis in the oral cavity. Although pathogens are classically known for triggering inflammation via TLRs, emerging evidence suggests that many commensal bacteria can also exploit the TLR pathway to the hosts benefit. However, how TLRs react to these oral microbial communities, rather than to single bacterial species has not yet been studied.
Objective: To investigate the influence of multi-species commensal and pathogenic biofilm on TLR signaling in a reconstructed human gingiva model.
Methods: RHG (reconstructed gingiva epithelium on a fibroblast populated hydrogel) were topically exposed to three different multi-species biofilms (commensal, gingivitis and cariogenic) for a 24-hours. Hereafter, RHGs were processed for (immune)histochemical staining (HE, Ki-67); RNA and protein were isolated for a TLR transcript array and western blotting analysis; and the presence of biofilm was detected by FISH (Fluorescence in situ hybridization) staining.
Results: FISH showed the presence of biofilm bacteria rRNA on the surface of RHG. RHG viability was not effected by biofilm exposure. The commensal biofilm activated TLR signaling more than gingivitis or cariogenic biofilms. Key genes involved in MyD88 dependent and independent TLR downstream pathways were more up-regulated by the commensal biofilm than pathogenic biofilms. The biofilms differentially induced TLR protein expression.
Conclusion: Commensal and pathogenic biofilms affect TLR expression and the downstream signaling differently. Furthermore, the strong response of RHG to multi-species commensal biofilm indicates that TLR signaling pathways may be exploited for maintaining oral host-microbe homeostasis.

P1. DEVELOPMENT OF AN IN VITRO GENERATED HUMAN MELANOMA MODEL AS A RESEARCH PLATFORM FOR THERAPEUTIC TESTING

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Background: Validation of novel therapies against cancers, such as melanoma, requires models that reflect the human physiology and immune response. However, the current use of humanized animal models is associated with high costs and low prediction of success in clinical trials, while 2D cultures do not accurately reflect the complex tumor microenvironment. There is thus a need for improved in vitro melanoma models to facilitate development of therapies.
Objective: To establish a robust in vitro melanoma model to investigate tumor formation and progression overtime.
Methods: Melanoma skin equivalents (MSEs) were constructed by co-seeding melanoma cells and keratinocytes onto a fibroblast-populated dermal equivalent followed by culture in air-lifted conditions for up to 6 weeks. (Immuno)histochemical staining was used to identify tumor cells and culture supernatants were used to detect cytokines (ELISA).
Results: Tumor nests developed overtime at the epidermal-dermal junction, and spread towards the dermis, disrupting the basement membrane. These features resemble the initial stages of invasive melanoma in humans. Moreover, cytokines IL-10, CXCL-10, and M-CSF were found to be upregulated in MSEs compared to the healthy controls, illustrating the complex balance between pro- and anti-inflammatory cytokines in melanoma.
Conclusion: Melanoma progression could be followed for up to 6 weeks, demonstrating that the developed MSE model can be used for research on tumor development, melanoma and skin cell interaction, and immune cell infiltration. In the future, the described model will also provide an in vitro tool for preclinical testing of novel therapeutics and brings us one step closer towards personalized medicine.

P2. USE OF SYSTEMIC TREATMENT IN PATIENTS WITH CHRONIC PRURITUS: A SURVEY AMONG DERMATOLOGISTS IN THE NETHERLANDS

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Background: Treatment of chronic pruritus can be a challenge for clinicians. Several systemic treatments have been suggested to reduce itch, such as gabapentinoids and antidepressants. Data on the use of these treatments in daily practice is scarce.
Objective: To assess systemic treatment management of patients with chronic pruritus among Dutch dermatologists and dermatology residents.
Methods: An online survey was sent to all dermatologists and dermatology residents in the Netherlands between July 2017 and April 2018.
Results: The response rate was 193 of 715 (27.0%). Over half of those surveyed (52.6%) prescribed oral antidepressants in patients with chronic pruritus; of which amitriptyline was prescribed most frequently (81.2%), followed by doxepin (29.7%), mirtazapine (12.9%) and paroxetine (11.9%). Approximately 40% prescribed gabapentinoids, of which the majority prescribed gabapentin (85.1%). Other systemic treatments used were oral immunosuppressants, such as methotrexate or cyclosporine A, and opioid antagonists, such as naltrexone. Reasons not to prescribe systemic treatment included a lack of knowledge and experience, risk of side effects considered more important than beneficial effects, and lack of available evidence on efficacy of treatments. In all, only one quarter of respondents felt comfortable prescribing gabapentinoids (24.4%) or antidepressants (23.8%).
Conclusion: Overall, 61.7% of physicians prescribed gabapentinoids or antidepressants in patients with chronic pruritus. Even though evidence is scarce, amitriptyline was prescribed most often by the physicians surveyed, followed by gabapentin, doxepin and mirtazapine. As only a minority of respondents felt comfortable prescribing these drugs, more education on effective and safe dosing is needed.

P3. SINGLE VERSUS MULTIPLE LEVEL PROSPECTIVE SECTIONING FOR THE SUBTYPING OF BASAL-CELL CARCINOMA

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Background: A 3-mm diagnostic skin punch biopsy represents a small part of a lesion, additionally, only a part of this biopsy material is evaluated. Histological subtyping of basal-cell carcinoma (BCC) on a punch biopsy can thus lead to misclassification. Consensus on the optimal approach to process punch biopsies is lacking, though accurate subtyping is important for appropriate treatment.
Objective: The aim of this study is to investigate if evaluating four sectioned levels of a punch biopsy instead of one or two leads to more accurate subtyping.
Methods: In a retrospective study we evaluated 87 punch biopsies of histologically confirmed primary BCCs. The concordance rate of the histological subtype based on four versus one or two levels was assessed (superficial versus non-superficial, nodular versus infiltrative subtype). The combination of four levels was regarded the reference.
Result: The proportion of misclassified BCCs in one level compared to assessment on four levels was 16.5% (14/85, 95%CI: 9.3-26.1%). In four levels, we found 20 infiltrative BCCs; 35.0% (95%CI: 15.4-59.2%) was misclassified in one level. The false-negative rate for missing 'more aggressive' subtypes on two versus four levels was 6.9-12.1% (4-7/58).
Conclusion: One out of six BCCs was misclassified if the subtype was based on one level of a punch biopsy compared to four levels. If two levels were evaluated, cases of misclassification decreased drastically. In order to maximize correct subtyping and plan appropriate treatment, we advise to evaluate at least two, but preferably more levels of a punch biopsy to determine the BCC subtype.

P4. COMPARISON OF THE SKIN SENSITIZATION POTENTIAL OF TATTOO INKS USING INTERLEUKIN-18 AS A BIOMARKER IN A RECONSTRUCTED HUMAN SKIN MODEL

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Background: During the last decade, the number of people with 1 or more tattoos has increased noticeably within the European population. Despite this, limited safety information is available for tattoo inks.
Objective: To test the skin sensitization potential of 5 tattoo inks in vitro by using reconstructed human skin (RHS) and the contact sensitization biomarker interleukin (IL)-18.
Methods: Two red and 3 black tattoo inks, 1 additive (Hamamelis virginiana extract) and 1 irritant control (lactic acid) were tested. The culture medium of RHS (reconstructed epidermis on a fibroblast-populated collagen hydrogel) was supplemented with test substances in a dose-dependent manner for 24 hours, after which cytotoxicity (histology; thiazolyl blue tetrazolium bromide assay) and skin sensitization potential (IL-18 secretion; enzyme-linked immunosorbent assay) were assessed.
Results: All but 1 ink showed cytotoxicity. Notably, 1 red ink and 1 black ink were able to cause an inflammatory response, indicated by substantial release of IL-18, suggesting that these inks may be contact sensitizers.
Conclusions: The in vitro RHS model showed that 4 tattoo inks were cytotoxic and 2 were able to cause an inflammatory IL-18

response, indicating that an individual may develop allergic contact dermatitis when exposed to these tattoo inks, as they contain contact sensitizers.

P5. CELL ADHESION MOLECULE 1 (CADM1) CAN BE A BIOMARKER FOR LEUKEMIC CELLS IN PROGRESSIVE OR REFRACTORY SÉZARY SYNDROME

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Background: Adult T-cellleukemia/lymphoma (ATLL) cells express cell adhesion molecule 1 (CADM1). Recent reports showed CADM1 is also expressed in the skin of early mycosis fungoides (MF) Objective. We studied the expression levels of CADM1 and its splicing variants in Sézary syndrome (SS), and compared the results with those in MF, and other cutaneous T-cell lymphoma (CTCL) Soluble CADM1 was measured in the patients' sera.
Methods: With flow cytometry and/or immunostaining, CADM1+ cells were examined in leukemic cells of SS and infiltrating cells in the cutaneous lesions of MF/SS and anaplastic large cell lymphoma (ALCL). Soluble CADM1 in the sera were measured by ELISA, and the splicing variants of CADM1 were determined by reverse transcriptase-polymerase chain reaction and sequencing. We also checked splicing variants of 27 caucasian SS patients.
Results: CADM1+ cells were significantly increased in 7 of 10 patients with SS, ranging from 7.9% to 74.5% of the CD3+CD4+ fractions (median; 33.7%)(cut off value;6.5%). Higher CADM1 expression was related with poor prognosis. Both CADM1 and CCR4 were highly expressed by the skin infiltrates of SS, but the CADM1+ cells did not always co-express CCR4. Serum levels of soluble form of CADM1 were increased in ATLL, but not significantly increased in SS.CADM1 mRNA expressed by SS/MF cells contained a few splicing variants.
Conclusion: Cellular CADM1 expression can be a diagnostic marker for aggressive/refractory SS.

P6. DIAGNOSTIC ACCURACY OF HANDHELD REFLECTANCE CONFOCAL MICROSCOPY IN THE PRESURGICAL MAPPING OF LENTIGO MALIGNA (MELANOMA): A RETROSPECTIVE PILOT STUDY

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Background: Lentigo maligna (melanoma) typically occur on chronic solar damaged skin in the head and neck. The surgical treatment remains problematic due to subclinical disease often extending beyond the guideline recommended margins.
Objective: In this pilot study, we evaluate our experiences with the surgical management of LM/LMM by HH-RCM-assisted wide-local excision.
Methods: Consecutive histopathological confirmed LM/LMM in the head and neck between December 2015 and July 2017 were eligible for inclusion. All RCM imaging/analysis was performed by a single investigator (Y.E.). Prior to HH-RCM examination the surgical margin was dermatoscopically identified. Adhesive rings were applied bordering the margin and placed overlapping until the entire circumference of the lesion was enclosed. In the presence of positive criteria the margin was redrawn, and the process repeated until the entire lesion was mapped.
Results: 26 patients (20 LM & 6 LMM) were included in this study. In 2 patients RCM-evaluation resulted in a change of management. The remaining 24 lesions were excised, of which 2 were upstaged to LMM. Negative margins were achieved in 83.3%. In 54.2.8% HH-RCM showed subclinical LM beyond the proposed surgical margin. The overall accuracy of subclinical disease detection was 83.3%, with a sensitivity of 82% and a specificity of 85%. After a mean follow-up of 13.8 months 1 patient had a confirmed recurrence.
Conclusion: HH-RCM seems to be well suited to assist in the (surgical) management of LM/LMM. A prospective study with a larger sample size is needed to confirm our findings.

P7. IN SITU VISUALIZATION OF TISSUE-RESIDENT MEMORY T CELLS TO IDENTIFY THE PROGNOSTIC RELEVANCE IN HUMAN MELANOMA DEVELOPMENT

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Background: Tissue-resident memory T (TRM) cells permanently reside in epithelial barrier tissues and function as alarming sensors, cytotoxic killers and provide a long-term local memory that can spread widely within the tissue when re-infected with the same antigen. Recently, CD103+ tumor-resident CD8+ T cells were strongly correlated with improved survival in immunotherapy naïve stage III melanoma patients and expanded during anti-PD-1 therapy. Also, expression of the retention integrin CD49a was shown to mark functional tumor-resident CD8+ T cells and to correlate with survival of melanoma patients. Lastly, mouse models of melanoma have recently shown that tumor-specific TRM cells can protect against highly aggressive melanoma.
Objective: The role of skin TRM cells in melanoma development remains unknown and might be relevant, for there are numerous neoplastic lesions in the skin that rarely become overt cancers. This research, therefore, aimed to identify the prognostic relevance of TRM cells in human melanomagenesis.
Methods: Healthy skin, chronically sun-exposed skin, lentigo maligna, primary lentigo maligna melanoma, naevocellulares

nevi, (superficially spreading and nodular) primary melanoma, and (cutaneous) metastatic melanoma (all n=7) were analyzed by immunohistochemistry for the presence of TRM cells. The prognostic significance of CD103 and CD49a expression on TRM cells was also investigated.
Conclusion: Results of this study will reveal whether TRM cells can serve as a prognostic marker for disease progression.

P8. LEVELS OF IL-31 IN DIFFERENT VARIANTS OF CUTANEOUS T CELL LYMPHOMAS

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Background: Recent studies suggested a role for IL-31 in the pathogenesis of pruritus and disease severity in patients with cutaneous T cell lymphomas (CTCL). However, discrepant results were reported for IL-31 serum levels and correlation with disease severity and/or pruritus intensity. In addition, most studies did not distinguish between different subtypes of CTCL.
Objective: We investigated IL-31 serum levels in different subtypes of CTCL, including Sézary syndrome (often intensely pruritic), Folliculotropic Mycosis Fungoides (FMF) (often pruritic) and classic Mycosis Fungoides (typically not pruritic).
Methods: From 54 CTCL patients a total of 68 serum samples were analyzed with a high sensitivity V-PLEX immunoassay (Mesoscale) for IL-31. Thirty-five patients had advanced stage disease (≥ stage IIB). A visual analog scale score (VAS score) for pruritus was available in 29 CTCL patients (7 SS, 9 FMF and 13 classic MF) and in all other cases information on complaints of pruritus was available from medical records.
Results: In 11/54 (20%) CTCL patients serum levels of IL-31 were detected (mean 0.48pg/mL, range 0.20-1.39pg/mL) including 6/17 (35%) SS patients (mean 0.57pg/mL) and 5/21 (24%) FMF patients (mean 0.33 pg/mL). All 11 patients with detectable levels of IL-31 reported complaints of pruritus and 9/11 patients presented with advanced stage disease (≥IIB). Serum levels of IL-31 did not correlate with VAS pruritus scores.
Conclusion: Low levels of serum IL-31 were detected in SS and FMF patients but could not be found in patients with classic MF.

P9. DETERMINANTS OF OMALIZUMAB DRUG SURVIVAL IN A LONG-TERM DAILY PRACTICE COHORT OF PATIENTS WITH CHRONIC URTICARIA

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Background: Omalizumab has demonstrated high efficacy for treatment of Chronic Urticaria (CU) in trials. Long-term data and especially drug survival studies of omalizumab in patients with CU in daily practice are lacking.
Objective: The aim of this study was to evaluate drug survival of omalizumab in a daily practice CU cohort and to identify determinants of drug survival in the overall population, differentiated by reason of discontinuation.
Methods: Data were extracted from a prospective daily practice cohort (February 2012–February 2018) of patients diagnosed with CU and treated with omalizumab in the University Medical Centre Utrecht. Drug survival was analysed by Kaplan–Meier survival curves. Determinants of drug survival were analysed using univariate and multivariate Cox regression analysis.
Results: The study comprised 142 patients (71% female, mean age 42 year) with a maximum treatment duration of 4.7 years (209 active treatment years). The overall drug survival rates for omalizumab were 77%, 61% and 55% after 1, 2 and 3 years, respectively and were mostly determined by well-controlled disease activity. A limited number of patients discontinued treatment due to ineffectiveness and/or side effects. Chronic inducible urticaria (CindU) component was associated with longer overall drug survival and longer drug survival related to well-controlled disease activity.
Conclusions: We presented the longest reported analysis of omalizumab drug survival and for the first time identified CindU as an independent determinant for longer drug survival related to discontinuation due to well-controlled disease activity.

P10. TREATMENT OF ATOPIC ECZEMA (TREAT) REGISTRY TASKFORCE: CONSENSUS ON HOW AND WHEN TO MEASURE THE CORE DATASET FOR ATOPIC ECZEMA TREATMENT RESEARCH REGISTRIES

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Background: Comparative, real-life and long-term evidence on the effectiveness and safety of photo- and systemic therapy in moderate-to-severe atopic eczema (AE) is limited. Such data must come from well-designed prospective patient registries. Standardisation of data collection is needed for direct comparisons and data pooling.
Objective: To complement the previously developed TREatment of ATopic eczema (TREAT) Registry Taskforce 'what to measure' core dataset by gathering consensus on how and when the previously defined domain items should be measured.
Methods: Proposals for the measurement instruments were based on the recommendations of the Harmonising Outcome Measures for Eczema (HOME) initiative, the existing AE database of TREATgermany, expert opinions and systematic reviews of the literature. The proposals were discussed at multiple face-to-face consensus meetings, one teleconference and via email. The frequency of follow-up visits were determined by an expert survey.
Results: A total of 16 experts from 7 countries participated in the 'how to measure' consensus process and multiple external experts were consulted. Consensus was reached for all domain items on how they should be measured by assigning measurement instruments. A follow-up frequency of initially 4 weeks after commencing treatment, then every 3 months while on treatment and every 6 months while off treatment was defined.
Conclusion: This core dataset for national AE research registries will aid the comparability and pooling of data across centers and country borders and enable international collaboration to assess the long-term effectiveness and safety of photo- and systemic therapy used in patients with AE.

P11. A RANDOMIZED CONTROLLED PROOF-OF-PHARMACOLOGY TRIAL OF OMIGANAN IN PATIENTS WITH EXTERNAL GENITAL WARTS

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Background: Current therapies often fail as treatment for external genital warts causing a high medical need for safe and effective novel treatments. The cationic, antimicrobial peptide omiganan is an indolicidin analogue with immunomodulatory and anti-viral properties as observed in vitro.
Objective: We performed a randomized, vehicle-controlled phase 2a trial to explore the efficacy of the potential new drug omiganan 2.5% for patients with external genital warts.
Methods: Twenty-four (24) patients aged 18 years and older diagnosed with at least 3 external genital warts were randomized to a 12 week treatment period with omiganan 2.5% or placebo (ratio active:placebo= 2:1) and a 12 weeks follow-up.
Results: Omiganan treatment was well tolerated and there were no clinical significant changes in safety parameters and no treatment-related discontinuations. We observed a 29.3% wart clearance in the omiganan group compared to 15.3% in the vehicle group (p-value=0.3918). Furthermore, omiganan treatment decreased the height and volume of the warts compared to vehicle (p=0.0543 and p=0.0655, respectively). The HPV load was statistically significant reduced after 12 weeks treatment with omiganan 2.5% compared to placebo (p= 0.0201).
Conclusions: Omiganan 2.5% is safe to be administered to patients with external genital warts and reduces the HPV load in genital warts after 12 weeks treatment. Omiganan is therefore a potential new therapy for genital warts and further research with b.i.d. application, longer duration and/or combination therapies should be performed.

P12. STEREOPHOTOGRAMMETRIC 3D PHOTOGRAPHY AS A METHOD FOR THE CLINICAL VISUALIZATION AND QUANTIFICATION OF HPV-INDUCED SKIN LESIONS

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Background: Quantification of HPV-induced skin lesions is essential for the clinical evaluation of the course of disease and the response to treatment. However, clinical assessments do not provide complete insight into 3D lesions and its inter-rater variability is often poor.
Objective: The aim of this study was to validate a stereophotogrammetric 3D camera system for the quantification of HPV-induced lesions.
Methods: The camera system was validated for accuracy, precision and inter-operator and inter-rater variability. Subsequently, 3D photographs were quantified and compared to caliper measurements for clinical validation by Bland-Altman modelling, based on data from 80 patients with cutaneous warts (CW), 24 with anogenital warts (AGW) patients and 12 with vulvar high-grade squamous intraepithelial lesions (HSIL) with a total lesion count of 220 CW, 74 AGW and 31 vulvar HSIL.
Results: Technical validation showed excellent accuracy (coefficients of variation (CV)$\leq$0.68%) and reproducibility (CVs$\leq$2%), a good to excellent agreement between operators (CVs$\leq$8.7%) and a good to excellent agreement between different raters for all lesion types (ICCs$\geq$0.86). When comparing 3D with caliper measurements, excellent biases were found for long diameter of AGW (5%), good biases for short diameter of AGW (10%) and height of CW (8%) and acceptable biases were found for the diameter of CW (11%) and vulvar HSIL (short diameter 14%, long diameter 16%). An unfavorable difference between these methods (bias 25%) was found for the assessment of height of AGWs.
Conclusion: Stereophotogrammetric 3D imaging is an objective and reliable method for the clinical visualization and quantification of HPV-induced skin lesions.

P13. VALIDATION OF THE DUTCH QUALITY OF LIFE IN HAND ECZEMA QUESTIONNAIRE (QOLHEQ)

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Background: An instrument measuring disease-specific health-related quality of life (HRQoL) is lacking for Dutch patients.
Objective: To validate measurement properties of the Dutch Quality Of Life in Hand Eczema Questionnaire (QOLHEQ).
Methods: A validation study covering validity, scale structure, reproducibility and responsiveness was performed according to published guidelines. Patients were asked to complete the QOLHEQ, along with skin-specific and general HRQoL instruments at three timepoints (baseline, 1-3 days and 1-3 months). Clinical scores were taken using the Photographic guide for severity of hand eczema and the Hand Eczema Severity Index (HECSI). Methods like item response theory and classical test theory will be applied, along with confirmatory factor analysis, a priori defined hypotheses testing, and assessment of measurement error and agreement.
Results: Data collection is close to finishing and processing of data will be performed during November and December 2018. At that time it will be assessed which measurement properties will be presented together.
Conclusion: Data on single-score validity and reproducibility of the QOLHEQ will certainly be presented together. Most likely along with data on scale structure.

P14. PREVALENCE OF PRURITUS AND PEMPHIGOID IN NURSING HOME RESIDENTS (SSENIOR): A CROSS-SECTIONAL STUDY OF AN UNDER-RECOGNIZED DISEASE

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Background: Pruritus, or itch, is the most common and burdensome skin complaint in elderly people, and may be caused by bullous pemphigoid. However, pemphigoid can be easily missed when it presents as pruritus without skin blistering. The disease is associated with ageing and neurodegenerative diseases, such as dementia.
Objective: We evaluated the prevalence of pruritus and pemphigoid in a high-risk population of nursing home residents.
Methods: We performed a cross-sectional study among nursing home residents aged 65 years or older with and without cognitive impairment. Pruritus was assessed with a pruritus numeric rating scale, skin examination for scratch marks, and information from nursing staff. Diagnosis of pemphigoid was confirmed with various immunoserological laboratory tests.
Results: Between July 2016 and December 2017, 125 consecutive participants were enrolled. They had a mean age of 84.1 years. Fifty-nine subjects (47%) had complaints or signs of pruritus, often of chronic duration (6 weeks or longer, 81%). Of these subjects with a history of pruritus, seven (12%) had pemphigoid, yielding an overall prevalence of 6%. Four subjects had newly diagnosed nonbullous pemphigoid, and three subjects had known bullous pemphigoid.
Conclusion: Pruritus and pemphigoid were highly prevalent amongst nursing home residents. Unrecognized nonbullous pemphigoid as underlying cause of pruritus appeared to be more common than bullous pemphigoid in this high-risk population. Therefore, awareness is needed for this newly identified cause of pruritus, and serological screening for pemphigoid is recommended for the diagnostic work-up of chronic pruritus in elderly people in nursing homes.

P15. A GREATER IMPROVEMENT OF QUALITY OF LIFE IN CHILDREN AND YOUNG ADULTS WITH PSORIASIS IS REACHED WITH HIGHER PASI RESPONSES AND SYSTEMIC TREATMENTS

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Background: It is well known that treatment of psoriasis improves quality of life (QoL). However, the relationship between a higher Psoriasis Area and Severity Index (PASI) response, treatment and more improvement of QoL is hardly studied. Especially in children and young adults in which substantial QoL impairments were found, the question rises whether a higher PASI response and/or a certain type of treatment will result in higher improvement in QoL.
Objective: To assess the real world relationship between A) PASI response and QoL and B) type of treatment and QoL in children and young adults with psoriasis.
Methods: Data were obtained from the child-CAPTURE registry, a daily clinical practice cohort of children with psoriasis. PASI response was categorized into 4 groups: 0-<50; 50-<75; 75-<90; and ≥90. The QoL was measured with the Children's Dermatology Life Quality Index(CDLQI) or Dermatology Life Quality Index(DLQI). Four types of treatment were assessed: topical, dithranol, conventional systemic, and biologic therapy. Analysis was performed with a linear mixed model.
Results: Analysis of 500 treatment episodes demonstrated that a higher relative PASI response resulted in a greater improvement of QoL, with statistical significant differences between PASI response groups 0-<50 and 50-<75 for both CDLQI and DLQI, and between PASI response groups 75-<90 and ≥90 for CDLQI. Systemic treatment (conventional and biologic) achieved a greater CDLQI respectively DLQI improvement compared to topical/dithranol treatment.
Conclusion: Higher PASI response and systemic treatments result in greater improvement of the QoL in children and young adults with psoriasis in daily clinical practice.

P16. NONBULLOUS PEMPHIGOID: INSIGHTS IN CLINICAL AND DIAGNOSTIC FINDINGS, TREATMENT RESPONSES AND PROGNOSIS

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Background: Nonbullous pemphigoid is an under-recognized nonbullous disease variant of the cutaneous autoimmune bullous disease pemphigoid. Several disease aspects have not been studied previously.
Objective: To describe the characteristics of nonbullous pemphigoid.
Methods: This is a retrospective chart review study of patients diagnosed with nonbullous pemphigoid, visiting the dermatology department of the University Medical Center Groningen in the Netherlands.
Results: Sixty-nine patients were included. Skin examination most often showed pruritic papules/nodules (n=25; 37%) or pruritus without primary skin lesions (n=15; 22%). Histopathological findings were nonspecific, with only one case showing a classic subepidermal split. During follow-up blisters formed in 17%, which was associated with positive indirect immunofluorescence results (p=0.014), and anti-BP180 autoantibodies demonstrated by immunoblot (p=0.032). Methotrexate was most successful in achieving remission (41%). The 1-year, 2-year and 3-year mortality rates were 14%, 34%, and 46%, with an 8.6 fold increased risk of mortality in the overall population. Limitations: The retrospective study design.
Conclusion: Histopathology is not useful for diagnosis of nonbullous pemphigoid. High mortality rates in nonbullous pemphigoid do not predict a better prognosis than in bullous pemphigoid.

P17. ANATOMICAL SITE VARIATION OF WATER CONTENT IN HUMAN SKIN MEASURED BY THE EPSILON: A PILOT STUDY

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Background: To assess stratum corneum (SC) hydration state, skin capacitance can be measured with a corneometer. Single sensor corneometers show significant differences in water content between various skin locations. Recently, a multi-sensor corneometer was introduced; the Epsilon. With this new device, no studies are performed yet investigating anatomical site variation of water content.
Objective: This pilot study aimed to investigate the anatomical site variation of water content of the SC on the body with the Epsilon. Secondly, values of the Epsilon were compared to values measured by conventional single sensor corneometers.
Methods: The hydration status of SC was measured in 15 healthy Caucasian volunteers with the Epsilon at five body sites (cheek, lower forearm, mid-calf, lower back and abdomen). Transepidermal water loss (TEWL) was measured with the Aquaflux to get more insight into the condition of the skin barrier. A literature search was performed to compare Epsilon values with conventional corneometers.
Results: The tested anatomical locations showed significant differences in water content (P<0.001) with large inter-individual variations; highest values were found in the cheek (11.64ε) and lowest values in the mid-calf (4.43ε). No correlation between water content and TEWL was found. In general, Epsilon values were lower compared to values of conventional corneometers, with a similar trend.
Conclusion: This pilot study with limited number of measurements showed significant variations in water content at different skin locations measured by the Epsilon. Moreover, the Epsilon measured consistent lower values compared to single sensor corneometers. Further validation of the device is recommended.

P18. TREATMENT AND SURVIVAL OF MERKEL CELL CARCINOMA SINCE 1993: A POPULATION-BASED COHORT STUDY IN THE NETHERLANDS

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Background: Merkel cell carcinoma (MCC) is a rare skin-cancer with a relatively high mortality. MCC is known for its potential rapid growth and its propensity to metastasise.
Objective: To describe the incidence, treatment and survival of MCC in a population-based setting.
Methods: All MCC's diagnosed in the Netherlands between 1993 and 2016 were selected from s Cancer Registry. Patient and tumour characteristics, therapy and vital status were obtained. Cox' proportional hazards were computed and relative survival analyses were performed.
Results: Our cohort included 1977 patients with MCC. Incidence increased from 0.17/100,000 personyears in 1993 to 0.59/100,000 in 2016. The mean age at diagnosis was 75.5. Most MCC's (59.8%), were treated with surgery alone. Relative five-year survival was low (63.0%) and did not improve. Mortality was higher among males (HR: 1.24, 95%CI: 1.11-1.39), higher age (HR 1.07, 95%CI: 1.06-1.07) and nodal (HR1.26, 95%CI: 1.08-1.48) and distant spread of disease (HR2.44, 95%CI: 1.99-2.99).
Conclusion: This study shows a continuously increasing incidence rate of MCC in the Netherlands. Survival after MCC diagnosis remained low. Our results emphasise the need for improvement of therapy.

P19. MERKEL CELL CARCINOMA, THE IMPACT OF CLINICAL EXCISION MARGINS AND MOHS MICROGRAPHIC SURGERY ON RECURRENCE AND SURVIVAL: A SYSTEMATIC REVIEW

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Background: Merkel cell carcinoma (MCC) is a rare but potentially lethal skin cancer, with surgery as a primary treatment. The relation of the wide local excision (WLE) margin with recurrence and survival is unclear. Another surgical option for MCC is Mohs surgery. It is unclear if the local recurrence rate differs between Mohs surgery and WLE.
Objective: The objective of this study is to determine if recurrence and survival of MCC differs for different surgical excision margins and Mohs surgery by systematically assessing the available literature.
Methods: We searched the databases MEDLINE, EMBASE and CENTRAL. Two reviewers selected studies that defined excision margins and either recurrence or survival. When possible, cases were extracted from case series and used for analyses. Other studies were narratively reviewed.
Results: We found 879 eligible studies, of which 8 cohort studies and 17 case series. None of the cohort studies showed significant differences in recurrence and/or survival with respect to excision margins or Mohs surgery. We collected 147 cases from the case series. A logistic regression analysis for recurrence and a Cox regression analysis for survival showed no significant difference between excision margins or Mohs surgery.
Conclusion: In this systematic review, we could not determine differences in recurrence and/or survival rates for MCC between different clinical excision margins and Mohs surgery. There is currently no clear evidence that for Merkel Cell Carcinoma (MCC) the width of the clinical excision margin or the use of Mohs surgery affects the chances of recurrence and/or survival.

P20. SKIN DISORDERS ARE PROMINENT FEATURES IN PRIMARY IMMUNODEFICIENCY DISEASES: A SYSTEMATIC OVERVIEW OF CURRENT DATA

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Background: Primary immunodeficiency diseases (PIDs) are characterized by an increased risk of infections, autoimmunity, autoinflammation, malignancy and allergic disorders. Skin disorders are also common clinical features in PIDs and may be among the presenting manifestations. Recognition of specific PID-associated skin conditions in combination with other clinical features as described in the currently used warning signs could raise suspicion of an underlying PID.
Objective: We aimed to provide a systematically obtained overview of skin disorders and their prevalence in PIDs. Secondary, the prevalence of Staphylococcus (S.) aureus-associated skin disorders and atopy were reviewed, as these are the most prominent skin features in PIDs.
Methods: A systematic search was performed in Embase, Medline, Web of Science, Cochrane and Google Scholar (up to May 9th 2018). All original observational and experimental human studies that address the presence of skin disorders in PIDs were selected. We rated study quality using the Institute of Health Economics Quality Appraisal Checklist for Case Series Studies.
Results: Sixty-seven articles (5030 patients) were included. Study quality ranged from 18.2-88.5%. A broad spectrum of skin disorders was reported in 30 PIDs, mostly in single studies with a low number of included patients. An overview of associated PIDs per skin disorder was generated. Data on S. aureus-associated skin disorders and atopy in PIDs were limited.
Conclusion: Skin disorders are prominent features in PIDs. Through clustering of PIDs per skin disorder, we provide a support tool to use in clinical practice that should raise awareness of PIDs based on presenting skin manifestations.

P21. THE STEPS TOWARDS EVIDENCE BASED OPTION GRIDS FOR PSORIASIS AND ATOPIC ECZEMA

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Background: In Shared Decision Making (SDM) patients and physicians share the best available evidence and patients are encouraged to make informed decisions. Decision aids support this process. One type of decision aids are Option Grids: one-page overviews of possible treatment options, based on patients most important questions.
Objective: The objective of this study was to develop Option Grids for psoriasis and atopic dermatitis (AD) and to provide a framework for others to develop Option Grids.
Methods: We established two working groups, one for each disease, consisting of dermatologists, patients and researchers. In an online survey we asked patients to rate and rank questions about their treatment on importance. The working groups then selected the most important questions and formulated answers based on national and international guidelines, SmPC texts and relevant literature. Input was provided by members of the Dutch National Society for Dermatology and Venereology, patient societies and the pharmaceutical industry. The answers were adjusted if considered necessary according to the working groups. The language was adapted to B1 level according to the Common European Framework of Reference for Languages.
Results: Three option grids were developed, one for biologicals and apremilast in psoriasis, one for topical, photo- or systemic therapy and one for systemic therapy in AD.
Conclusion: We created three evidence based Options Grids.

With this article we aim to inspire and help other researchers to develop Option Grids in the future. More Option Grids for psoriasis will follow, as well as implementation and validation of these Option Grids.

P22. OPTIMIZING ADALIMUMAB TREATMENT IN PSORIASIS WITH CONCOMITANT METHOTREXATE: OPTIMAP STUDY

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Background: Adalimumab is a tumour necrosis factor alpha inhibitor that has shown to be effective in the treatment of psoriasis. However, not all patients have a good clinical response or the initial response declines over time, leading to a short drug survival. One of the factors that could explain this observation is the formation of antidrug antibodies, with a varying incidence of 6-45% reported in clinical studies. Literature from rheumatology shows that adding low-dose methotrexate to adalimumab treatment can reduce antibody formation and therefore increase drug survival.
Objective: Our primary objective is to assess the one-year drug survival in adalimumab monotherapy versus combination therapy with methotrexate in patients with psoriasis. Secondary objectives are to assess the effectivity, safety and quality of life after one year.
Methods: We designed a multicentre, assessor blinded, randomized controlled trial to compare adalimumab monotherapy with combination therapy with methotrexate (10mg/week) in patients with moderate to severe psoriasis. We followed up the patients every 12 weeks for a total duration of 3 years, assessing efficacy (PASI score), quality of life (DLQI, Skindex-29), adverse events, laboratory safety parameters, anti-drug-antibodies and throughlevels at regular visits.
Results: We will present the preliminary results of the drug survival at one year. Furthermore, we will present data on efficacy, quality of life and safety parameters after one year of follow up.
Conclusion: We will present our preliminary conclusions based on this one-year dataset.

P23. DISEASE AND TREATMENT CHARACTERISTICS IN PEMPHIGUS AND PEMPHIGOID PATIENTS IN A TEN-YEAR ACADEMIC DAILY PRACTICE COHORT

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Background: Data on disease and treatment characteristics in pemphigus and pemphigoid are scarce.
Objective: To describe these characteristics from an academic daily practice cohort.
Methods: Using SAS software, we built a retrospective cohort of patients currently visiting our center and diagnosed with pemphigus, pemphigoid, or a subtype between July 2008 and July 2018. We evaluated disease and treatment characteristics, and reasons for discontinuation of treatment.
Results: We identified 45 patients, of which 8 had a form of pemphigus (63% female) and 37 a form of pemphigoid (54% female), with a median follow-up of 8.3 (range 1.2-33.5) and 2.2 (0.2-34) years, respectively. On average, diagnostic delay was 6 (1-172) months, and patients had been admitted once for about 15 days (2-129). All pemphigus patients were treated with systemic therapies and reached disease control, whereas 33 (89%) pemphigoid patients were treated systemically and 31 (84%) ever reached control. Few patients ever reached disease remission (30 vs 25%, resp.). Currently, 1 pemphigus patient (13%) has active disease, vs. 12 pemphigoid patients (32%). Patients used 2 systemic therapies on average (range 0-7), frequently in combination (67%). Pemphigus patients were most frequently treated with prednisone (88%), azathioprine (75%), and tetracycline/nicotinamide (25%). In pemphigoid patients, prednisone (70%), azathioprine (51%), and dapsone (24%) were used mostly. Reasons for discontinuation of treatment were adverse effects (n=23), ineffectiveness (n=23), and disease control/remission (n=24).
Conclusion: Our study confirms the recalcitrant character of pemphigus and pemphigoid diseases and demonstrates the need for long-term treatment with a combination of several systemic therapies.

P24. RESULTS OF THE FIRST RANDOMIZED CONTROLLED TRIAL ON TIGHT CONTROLLED DOSE REDUCTION OF BIOLOGICALS COMPARED WITH USUAL CARE IN PSORIASIS PATIENTS: THE CONDOR STUDY

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Introduction & Objectives: We investigated whether dose tapering of biologicals in stable psoriasis patients was non-inferior (NI) to usual care.
Materials & Methods: We designed a multicenter, pragmatic, randomized, non-inferiority trial. Patients using etanercept, adalimumab or ustekinumab and stable low disease activity (PASI>5 and DLQI>5) were randomized to dose-reduction or usual care. For dose-reduction, treatment intervals were

prolonged stepwise with a factor 1.5 and 2 consecutively. PASI and DLQI were 3-monthly recorded. In case of disease flare (PASI>5 and/or DLQI>5), treatment was adjusted to the previous dose. Primary outcome was non-inferiority (margin 0.5) of PASI at 12 months. Secondary outcomes were PASI-course, DLQI, safety, disease flares and cost-effectiveness.
Results: One hundred-twenty patients were randomized. Mean PASI at month 12 was 3.4±1.8 (SD) in the dose-reduction group, and 2.2±1.7 in the usual care group. Mean corrected difference between PASI at month 12 was 1.1 [CI 95% 0.574;1.722]. This indicates inferiority of dose-reduction compared to usual care. However median PASI and DLQI remained below 5 in both groups. There was no significant difference regarding persistent flares between dose-reduction and usual care (n=5 (9%) and n=3 (5%), resp., p=0.5). Thirty-six patients (68%) still used a low dose after 12 months. No severe adverse events related to the intervention were reported. Cost-effectiveness is currently analyzed.
Conclusions: This study showed that dose-reduction of the investigated biologicals in psoriasis patients was inferior tot usual care with the chosen non-inferiority margin. However, no safety issues were seen nor clinically relevant changes in median PASI and DLQI.

P25. PREVALENCE OF CANCER TESTIS ANTIGENS ON LENTIGO MALIGNA AND LENTIGO MALIGNA MELANOMA

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Background: The Cancer Testis Antigens (CTA) family is a group of genes which is involved in promotion of growth and inhibition of apoptosis. They are exclusively expressed on healthy germ line testis cells and various malignancies.
A systematic review (SR) was performed on the prevalence of CTA's in malignant melanoma that showed frequent expression of MAGE-A1/A3/A6, NY-ESO, PRAME and SSX. Most CTA's are found at a higher expression rate in metastatic tumours, compared to primary tumours Lentigo maligna (LM) and lentigo maligna melanoma (LMM) is a subgroup of melanoma in which the prevalence of CTAs is relatively unknown.
Objective: To evaluate the prevalence of CTAs on LM and LMM.
Methods: A selection of CTAs (MAGE-A3, MAGE-A1, MAGE-A6, NY-ESO-1, PRAME and SSX) was made to evaluate on LM based on the expression rates of CTAs on malignant melanoma. Histology slides of LM (n=8), LMM (n=6), sun exposed skin (n=7) and not sun exposed normal skin (n=7) were selected. Testis tissue was used as a positive control. These slides were stained with the different CTAs and independently scored by two reviewers. If there was no consensus on the score, a dermatopathologist was consulted.
Results: We did not find any positive staining in all four included groups, the positive control showed strong staining.
Conclusion: Lentigo maligna and LMM do not seem to express CTAs. We found no positivity of MAGE-A1, MAGE-A6, NY-ESO-1, PRAME or SSX, although these CTAs are often expressed in malignant melanoma tissue.

P26. NEW POSITIVE PATCH TEST REACTIONS ON D7 - THE ADDITIONAL VALUE OF THE D7 PATCH TEST READING

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Background: Patch test readings are usually performed between D2 and D4. An additional D7 reading can be of great value to identify possible new positive reactions.
Objective: To investigate the added value of the D7 patch test reading for individual allergens and to identify patient characteristics and allergen groups associated with new positive reactions on D7. Methods: A database study was performed on patients who were patch tested between January 2008 and July 2018 to the European baseline series (TRUE Test panels 1 and 2 supplemented with investigator-loaded allergens). Patch test readings were performed on D3 and D7. Positive reactions were categorized into positive on D3 or new positive on D7. Patients were subcategorized in only D3 positive reactions or only D7 positive reactions. Univariable regression analysis was performed to investigate possible associations between patient characteristics and allergen groups on new positive patch test reactions on D7.
Results: Of 3494 positive patch test reactions in 1669 patients, 603 (17.3%) reactions in 192 (11.5%) patients were new positive on D7. Distribution in sex, atopic-, and occupational dermatitis were comparable in patients showing a positive reaction on D3 and patients with a new positive D7 reaction. In the univariable regression analysis, significantly more D7 positive reactions were seen for topicals (OR=2.63, 95%CI; 1.95 – 3.54) and corticosteroids (OR=1.98, 95%CI; 1.15 – 3.39).
Conclusion: A D7 reading to identify new positive patch test reactions is of added value, especially for topicals and corticosteroids. Patient characteristics were not associated with new positive D7 reactions.

P27. CLINICOPATHOLOGICAL GENDER DIFFERENCES IN MELANOMA: NEED FOR TAILORED MANAGEMENT AND PREVENTION STRATEGIES

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Background: In Europe, one of the highest melanoma incidence rates is found in the Netherlands. In our country females are more prone to develop melanoma as compared to males, however survival data are worse for men.
Objective: To identify epidemiological clinicopathological gender-related differences that may improve preventive measures and to identify specific subgroups of melanoma patients who are at higher risk of developing and dying from melanoma.
Methods: Clinicopathological data from the Dutch Nationwide

Network and Registry of Histopathology and Cytopathology (PALGA) were retrieved from patients with primary, cutaneous melanoma in the Netherlands between 2000 and 2014. Follow-up data were retrieved from s Cancer Registry. Gender-related differences were assessed.
Results: A total of 54.645 patients were included (43.7% men). In 2000, 41.7% was male, as compared to 47.3% in 2014 ($p<0.001$). Likewise, in 2000 51.5% of the deceased cohort were men and 60.1% in 2014 ($p<0.001$). Men had significantly thicker melanomas (median Breslow-thickness 1.00mm (IQR 0.60-2.00) vs 0.82mm (IQR 0.50-1.50) for females). Head-and-neck area and trunk were the most prominent localisations for nodular melanomas in men. When stratified for age, older patients more often had thick, nodular, ulcerated and head-and-neck melanomas. Relative excess rate for dying was 0.67 (95% CI 0.61-0.73) for females.
Conclusion: There are evident clinicopathological gender differences in melanoma patients. Furthermore, independent of these differences, survival is worse for males. These findings can provide the basis of tailored management and prevention strategies on population level, but also in daily practice.

P28. SURGICAL OUTCOMES OF MAJOR SURGERY (STEEP) AND THE IMPACT OF MAJOR SURGERY ON QUALITY OF LIFE, ACTIVITY IMPAIRMENT AND SEXUAL HEALTH IN HIDRADENITIS SUPPURATIVA PATIENTS: A PROSPECTIVE SINGLE CENTRE STUDY

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Background: Hidradenitis suppurativa (HS) is a chronic debilitating skin disease, frequently located in the groin and anogenital area, leading to a substantial impact on quality of life and sexual health in HS patients. Skin-tissue-sparing excision with electrosurgical peeling (STEEP) is novel procedure with low recurrence rates and high patient satisfaction in retrospective series. However, there aren't any prospective studies done yet to investigate the impact of any major surgery on specific aspects of the quality of life.
Objectives: To assess surgical outcomes and the effect from the STEEP procedure on the general quality of life, sexual health and activity impairment of HS patients.
Materials and methods: A single centre prospective survey study was conducted among 40 patients undergoing STEEP surgery. Beside the objective parameters (time to wound closure and surface of the wound) patients' reported outcomes were reported.
Results: Thirty-nine patients with a total of 175 responses were included. Time to wound closure was significantly related to surface of the wound, a higher Hurley stage and current treatment with biologics. For patient reported outcomes, DLQI and ASEX scores did not significantly improve during the study period of six month. However, activity and overall work impairment showed considerable improvement after STEEP surgery.
Conclusion: Time to wound closure is significantly influenced by wound surface, Hurley stage and treatment with biologics. STEEP surgery improved the overall work and activity impairment.

P29. THE REFINED HURLEY CLASSIFICATION FOR HIDRADENITIS SUPPURATIVA: AN ACCURATE AND RELIABLE INSTRUMENT FOR PHYSICIANS AND PATIENT SELF-ASSESSMENT

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Background: The original Hurley classification is insufficient to characterise the heterogeneous skin disease hidradenitis suppurativa (HS). Therefore, it was refined into a seven-stage classification.
Objectives: 1. Investigate the correlation between the three severity grades of Hurley I and II and patient-reported quality of life (DLQI) and physician-assessed severity (IHS4). 2. Determine the inter- and intra-observer reliability of the refined Hurley classification. 3. Investigate the reliability of a patient self-assessment questionnaire, for deriving the correct refined Hurley stage.
Methods: 1. HS patients from two observational cohorts were included. DLQI and IHS4 scores were compared between the refined Hurley stages. 2. Physicians scored HS patients in a real-life setting or through a digital survey with standardised photographs of HS patients. 3. HS patients filled out the symptom self-assessment questionnaire. Based on the questionnaire and the physician's dermatologic examination, the refined Hurley stage was determined and compared.
Results: 1. There was a significant positive correlation of DLQI and IHS4 with increasing refined Hurley sub-stages (DLQI: $rs=0.259$ and $rs=0.185$; IHS4 $rs=0.603$ and $rs=0.532$). 2. Real-life assessment showed moderate to high inter-observer reliability (Krippendorf's $\alpha=0.678$ (95% CI 0.318-0.949) and 0.920 (95% CI 0.776-1.00)). The digital assessment demonstrated high inter- and intra-observer reliability ($\alpha=0.809$ (95% CI 0.785-0.832) and mean $\alpha=0.830$ (range 0.711 to 0.967)).
3. A substantial inter-rater agreement and reliability was found (78.7% and $\alpha=0.737$ (95% CI 0.622–0.852)).
Conclusion: The refined Hurley classification accurately correlates with HS severity and shows an overall high reliability. The patient self-assessment questionnaire is an accurate instrument for deriving the refined Hurley stage.

P30. DEMOGRAPHIC AND CLINICAL FACTORS ASSOCIATED WITH PSORIATIC ARTHRITIS IN PSORIASIS PATIENTS TREATED WITH BIOLOGICS

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Background: Previously reported risk factors for the development of psoriatic arthritis (PsA) in psoriasis patients might not

be discriminative enough to identify patients at risk in a population on biologic therapy.
Objective: To get insight in the prevalence of socio-demographic and clinical characteristics of psoriasis patients with or without PsA using biologics, and to identify factors associated with a diagnosis of PsA in this population.
Methods: Data were extracted from a prospective registry of psoriasis patients treated with biologics (BioCAPTURE registry). In univariate analysis, data on socio-demographic and clinical characteristics such as intoxications, psoriasis phenotypes and topographic locations were compared between psoriasis patients with and without PsA. A multivariate logistic regression analysis was performed with variables that showed a p-value ≤0.20 in univariate analysis. A Kaplan-Meier survival curve was plotted to visualize the probability of receiving a diagnosis of PsA over time.
Results: In a multivariate analysis, female gender and a family history of psoriasis were significantly associated with a higher probability for the onset of PsA. Inverse psoriasis and the use of alcohol were associated with a lower risk of PsA. The presence of a particular psoriatic phenotype was not associated with a diagnosis of PsA, neither was psoriasis of the nails or scalp.
Conclusion: Different factors were associated with a diagnosis of PsA in psoriasis patients. However, in contrast to literature, scalp and nail psoriasis may not be suitable to predict the risk of developing PsA in a population of psoriasis patients on biologic therapy.

P31. DAILY PRACTICE STUDY OF RITUXIMAB IN PEMPHIGUS: A RETROSPECTIVE STUDY OF 65 PATIENTS

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Background: Pemphigus is an autoimmune blistering disease mainly treated with long-term doses of systemic corticosteroids associated with significant adverse effects. Recent studies showed high effectiveness of rituximab (RTX), an anti-CD20 antibody, in pemphigus.
Objective: to assess the effectiveness of RTX in pemphigus.
Methods: the medical records of 65 pemphigus patients treated with RTX were reviewed retrospectively. Early and late endpoints, defined according to international consensus, were disease control (DC), complete and partial remission (PR/CR) and relapses. Safety was measured by reported adverse events.
Results: a total of 65 patients were treated with RTX. All patients achieved disease control. Complete remission was achieved in 76,9% and partial remission in 13,8% of the cases. During follow-up, 54,2% patients relapsed. No significant difference in remission rate and time to disease control was seen between RTX naïve and to non-naïve patients. Also no significant difference was seen in remission rate and time to disease control in early (<12 months) versus late (>12 months) admission of RTX. Patients who received RTX at month 6 and 12 showed significantly less relapses compared to patients who didn't receive this (n=12; 43% vs n=24; 71%; p=0,028). Patients with pemphigus foliaceus achieved faster complete remission than pemphigus vulgaris (n=39; mean 48 vs n=11; mean 79 p=0,040). Seven severe adverse events were reported, none life threatening.
Conclusion: RTX is a safe and effective treatment for pemphigus regardless of time administered in disease course and previously received gifts. Additional RTX in month 6 and 12 is recommended to prevent relapses.

P32. TREATMENT SATISFACTION WITH BIOLOGICS FOR PSORIASIS: IS THERE A DIFFERENCE BETWEEN MEN AND WOMEN?

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Background: Female sex has been reported as a predictor for treatment discontinuation with biological therapies. As treatment satisfaction corresponds with adherence, it can be hypothesized that female patients are less adherent compared to male patients as a result of lower treatment satisfaction.
Objective: To identify possible differences in satisfaction with biological treatment between male and female patients in the first year of treatment, using the Treatment Satisfaction Questionnaire for Medication (TSQM version II).
Methods: Data of psoriasis patients treated with biologics were obtained from the prospective, multicentre, daily-practice BioCAPTURE registry. Cross-sectional analyses of patient characteristics were performed at baseline. Longitudinal TSQM data were analyzed by linear mixed models, stratified for each TSQM domain (effectiveness, side-effects, convenience, global satisfaction). Relevant patient characteristics were incorporated as possible confounding factors.
Results: In total, 315 patients were included, with 396 treatment episodes (137 adalimumab, 90 etanercept, 137 ustekinumab, 24 secukinumab, 8 infliximab). Almost sixty percent of the patients were male. Baseline PASI was significantly higher in male patients (p=0.01). Longitudinal analysis demonstrated lower TSQM scores for 'side-effects' (p=0.05) and 'global satisfaction' (p=0.01) in female patients compared to male patients over one year of treatment.
Conclusion: This study provides a prospective, longitudinal analysis of TSQM for biologics in men and women with psoriasis. Female patients were less satisfied with their biological treatment regarding side-effects and global satisfaction. This might be a reason for more discontinuation of biological treatment among female patients.

P33. CONTACT SENSITIZATION TO HYDROPEROXIDES OF LIMONENE AND LINALOOL; RESULTS OF CONSECUTIVE PATCH TESTING AND CLINICAL RELEVANCE

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Background: Limonene and linalool are fragrance terpenes

which, following air exposure and subsequent oxidation, form hydroperoxides that are potent sensitizers.
Objectives: To investigate the prevalence of contact allergy to both hydroperoxides, to report clinical relevance, and to investigate patients demographics.
Methods: A total of 821 patients (35.6% male, mean age 42.4 years ±17.8) were consecutively patch tested with our departmental baseline series and our fragrance series, including hydroperoxides of limonene 0.3% pet. and hydroperoxides of linalool 1.0% pet. The clinical relevance was assessed for all positive reactions. Uni- and multi variable regression analyses were performed to assess risk factors for being allergic to either hydroperoxides.
Results: Positive patch test reactions to hydroperoxides of limonene and to hydroperoxides of linalool were observed in 77 patients (9.4%, 95% confidence interval [CI]; 7.4%-11.4%) and in 96 patients (11.7%, 95%CI; 9.5%-13.9%), respectively. Of all positive patch test reactions to hydroperoxides of limonene and linalool, 40.3% and 46.3%, respectively, were of probable to certain clinical relevance. Patients allergic to either or both hydroperoxides were significantly more female (OR 1.91, 95%CI; 1.25-2.91), aged 40 and over (OR 1.86, 95%CI; 1.26-2.75), and had less atopic dermatitis (OR 0.64, 95%CI; 0.44-0.93) compared to all other patients.
Conclusion: Compared to previous studies, a high number of positive reactions to both hydroperoxides were observed, of which the majority were clinically relevant. The high percentage of doubtful and low percentage of irritant reactions observed to both hydroperoxides might indicate a higher patch test concentration is needed to improve diagnostic performance.

P34. DUPILUMAB IN ATOPIC HAND ECZEMA PATIENTS – AN OBSERVATIONAL STUDY

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Background: Systemic treatment options for chronic hand eczema are limited. Dupilumab is used in atopic dermatitis (AD) but is not licensed for (isolated) hand eczema.
Objective: To determine the response of atopic hand eczema (AHE) to dupilumab.
Methods: Observational prospective study. Adult patients with AHE were treated for AD with dupilumab subcutaneously in a 600mg loading dose, followed by 300mg every two weeks. Primary outcome was response to treatment after 16 weeks, defined as improvement of ≥ 2 steps on the Photographic guide for severity, compared to baseline. Secondary outcomes were hand eczema severity measured with the Hand Eczema Severity Index (HECSI) and the difference of The Quality Of Life in Hand Eczema Questionnaire (QOLHEQ) score.
Results: Thirty patients were included (23 males, 7 females; mean age 46 years). Ten patients (33%) were classified as responder on the Photographic guide after 16 weeks of treatment. There was no difference in response between chronic fissured and recurrent vesicular morphological subtypes. Mean HECSI-score improved in 29 patients (97%) with -76.9%. Mean HECSI-score was already significantly decreased after 4 weeks compared to baseline ($P < .001$). The results of the difference in QOLHEQ score will be available at the NVED 2019 meeting.
Conclusion: This study shows a positive response of AHE to dupilumab. This poses the question whether a response will also be seen in isolated hand eczema.

P35. RISING REIMBURSED COSTS OF BENIGN AND (PRE) MALIGNANT SKIN TUMORS DUE TO INCREASING INCIDENCE AND INTRODUCTION OF PHARMACEUTICALS IN THE NETHERLANDS, 2007-2016

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Background: Skin cancer is the most common type of cancer and incidence is rising. In order to manage the associated direct medical costs, their assessment is vital.
Objective: To describe trends of reimbursed drug and hospital costs of benign and (pre)malignant skin tumors over the past decade. Design – Nationwide hospital and drug reimbursement data.
Results: In 2014, malignant skin tumors positioned fifth place of most costly cancers in the Netherlands (breast, lung, and colon cancer, and leukemias being more costly). The total costs for benign and (pre)malignant skin tumors increased from €279 million for 384.390 patients (2007) to €460 million for 574.309 patients (2016). Drug costs increased from €1.6 to €122.1 million (2007-2016). Dermatologists treat 85% of all patients with low mean costs (2016:€380), whereas medical oncologists treat a fraction (0.5%) at higher mean cost (2016:€6,390). Limitation – Primary care data were not available.
Conclusion: – Skin cancer is the fifth most costly cancer in the Netherlands and is strongly affected by rising incidence and introduction of expensive drugs. Effective skin cancer prevention strategies, efficient use of health care resources and controlling of drug costs are essential for maintaining a sustainable health care system.

P36. MULTIMODAL IMAGING OF INTRADERMAL DRUG INJECTION USING HOLLOW MICRONEEDLES

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Background: Intradermal injection of drugs using hollow microneedles might be less painful than regular subcutaneous injection. Biological drugs which are frequently administered to children, such as adalimumab, might be candidates for this method of administration.
Objectives: 1) To determine the feasibility of intradermal injection of 40 mg adalimumab in 0.4 mL into ex vivo human skin using the MicronJet600. 2) To explore the usability of various imaging methods in the evaluation of intradermal drug injections.
Methods: Defatted ex vivo human skin from bariatric surgery was injected with saline with infrared dye or adalimumab. Injections were done with the MicronJet600 (NanoPass) and a previously validated hollow microneedle system. Measurements included infrared imaging for volume quantification, 3D photography for bleb size, laser speckle contrast imaging for validation (absence of perfusion), optical coherence tomography for epidermal thickness, multispectral imaging for skin colour, and thermography for skin temperature. Microneedles were inspected for damage using bright field microscopy.
Results: The MicronJet600 could be used for intradermal injections of saline and adalimumab up to and including a volume of 0.4 mL. Bleb size was highly variable and distribution in the skin was more widespread than the bleb. Single use did not damage the microneedles.
Conclusion: The MicronJet600 can be used for injection of a volume of 0.4 mL adalimumab into ex vivo human skin. Intradermal injection can be visualized using various imaging modalities. The injected drug might spread further in the skin than the actual bleb.

P37. INSIGHT INTO THE MANAGEMENT OF ACTINIC KERATOSIS: A QUALITATIVE INTERVIEW STUDY AMONG GENERAL PRACTITIONERS AND DERMATOLOGISTS

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Background: The current management of patients with actinic keratosis (AK) seems to vary within and between primary and secondary care, although an in-depth understanding of healthcare providers' management of AK is currently lacking.
Objective: To gain insight into the management of AK by exploring underlying motives of current practices among general practitioners (GPs) and dermatologists in the Netherlands.
Methods: Twenty-two GPs and 18 dermatologists were interviewed, focussing on the underlying motives regarding AK management. A predefined topic list was used. All interviews were audio-taped, transcribed verbatim, and analysed by two researchers.
Results: GPs reported to limitedly conduct proactive cutaneous photodamage evaluation due to perceived lack of value, to vary in their way of diagnosing AK, to mainly apply cryotherapy or refer to secondary care due to lack of experience, to apply varying and mostly patient-driven follow-up care and have a high need for a guideline due to a lack of knowledge on AK management. Dermatologists indicated to pursue proactive photodamage evaluations although time limitations sometimes restrict this, to provide guideline-driven AK care with patient preferences also largely influencing both treatment choices and follow-up regimens and a need for improving skin cancer management in primary care.
Conclusions: For AK care to become more standardized and uniform in primary care, implementation of guidelines and (continuing) education are needed to address the commonly reported barriers of lack of value, experience and knowledge among GPs. In secondary care, linking tools for shared decision making with guidelines for more straightforward AK care may prove useful.

P38. DEVELOPMENT OF AN LPS SKIN CHALLENGE MODEL

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Background: Intravenous lipopolysaccharide (LPS) administration to humans is a widely used, safe and well-tolerated model to study TLR4-driven inflammation. A local LPS challenge, in the skin, would offer the advantage of repeated testing within one subject, in a compartment relevant for dermatological investigational drugs.
Objective: The aim of this study was to develop a transient skin inflammation model. Method. A saline-controlled interventional study was conducted to characterize inflammatory response upon intradermal LPS injection in 18 healthy male volunteers. All received two or four intradermal injections of 10ng LPS, purified from Escherichia Coli: 113: H10K, into the volar aspect of the forearm. The inflammatory response was monitored until 48 hours after administration. Laser speckle contrast imaging, colorimetry and thermography were used to quantify perfusion, erythema, and temperature respectively. The cellular response was analyzed in blister exudates.
Results: All 18 subjects completed the study with good tolerability at the injection side. Erythema and perfusion peaked at 10 hours after administration. Additionally, neutrophil and monocyte influx was observed in blister exudate of LPS injection sites. Mean neutrophil influx peaked at 3h with a 200x increase compared to baseline. Mean monocyte influx peaked at 10h with a 70x increase compared to baseline. Neutrophil and monocyte influx were almost completely normalized at 48h. In the saline injected control sites no influx of immune cells was seen at any time point.
Conclusion: An intradermal LPS injection results in transient skin inflammation. This model could be used in proof-of-pharmacology studies evaluating compounds that modulate dermal pathophysiological processes.

P39. OMIGANAN, A TOPICAL ANTIMICROBIAL PEPTIDE, NORMALIZES DYSBIOSIS BUT DOES NOT IMPROVE ATOPIC DERMATITIS CLINICALLY IN A PHASE II RANDOMIZED CONTROLLED TRIAL

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Background: in a previous phase II trial in 36 patients with mild to moderate AD, omiganan an indolicidin analogue with antimicrobial and immunomodulatory properties significantly reduced target lesion oSCORAD and morning itch, and improved target lesion dysbiosis by reducing Staphylococcus and increasing diversity.
Objective: to explore clinical efficacy and pharmacodynamics of omiganan with an optimized dose regimen in a larger patient population.
Methods: in total 80 patients with mild to moderate AD were enrolled in this single-center, phase II randomized, double-blind, placebo-controlled trial. Patients were randomized 1:1:1:1 to omiganan 1%, omiganan 1.75%, omiganan 2.5% or vehicle gel. The study drug was applied to all AD lesions once daily for 28 consecutive days. Efficacy was evaluated by EASI, oSCORAD and IGA. One AD lesion was assigned as 'target lesion' for various pharmacodynamic assessments.
Results: A reduction of target lesions S. aureus was observed in all active treatment groups in the culture, while an increase was apparent in the vehicle group. This reduction was statistically significant for omiganan 2.5% treatment compared to vehicle (p=0.0249). All active treatments normalized the microbiome by reducing Staphylococcus and increasing diversity. No substantial improvement of AD was observed compared to vehicle.
Conclusions: Recovery of the target lesion dysbiosis by a reduction of S. aureus in culture and Staphylococcus genus in the microbiome was observed in all active treatment groups, while this did not lead to clinical improvement of the lesions. This finding weakens the suggested major role of the microbiome in the pathogenesis of AD.

P40. OMIGANAN ENHANCES THE INFLAMMATORY RESPONSE INDUCED BY IMIQUIMOD IN A HUMAN SKIN CHALLENGE MODEL

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Background: Omiganan (OMI), an immunomodulatory indolicidin analogue, and the TLR 7/8 agonist imiquimod (IMQ) have demonstrated synergistic enhancement of inflammation in vitro.
Objective: We aimed to translate in vitro data to a human model for proof-of-concept, and to explore the potential of add-on treatment for HPV-induced skin diseases (e.g. cutaneous warts, vulvar HSIL, CIN and external genital warts).
Methods: Sixteen (16) healthy male and female volunteers received topical IMQ, OMI or IMQ+OMI in different sequential orders under occlusion for up to 4 days on tape stripped skin of the back. Skin inflammation was clinically assessed by erythema (erythema index, colorimetry, erythema grading scale) and perfusion (laser speckle contract imaging) measurements. Skin punch biopsies for were taken for histopathological analysis of inflammation (mRNA, histology and immunohistochemistry).
Results: All 16 subjects completed the study. Treatments were well tolerated. Skin inflammation was significantly more apparent in erythema and perfusion ($p<0.05$) when the skin was primed with IMQ for 48 hours, followed by 48 hours of OMI, compared to IMQ or OMI alone. Additionally, IFN-γ, IL-10, IL-6, MX1 and MXA mRNA expressions were all higher with this treatment regimen, representing an immune enhancement consistent with the clinical outcomes. Histologically, more infiltration was seen in combined treatment compared to IMQ alone, and IHC staining showed specifically CD4, CD8 and CD14 to be more apparent.
Conclusion: OMI enhances IMQ-induced skin inflammation. Combination therapy in HPV-induced skin diseases might lead to higher efficacy and lower recurrence rates compared to IMQ alone, and should therefore be investigated.

P41. COMBINED THC AND CBD TO TREAT PAIN IN EPIDERMOLYSIS BULLOSA: A REPORT OF THREE CASES

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Background: Epidermolysis bullosa (EB) is a genetic blistering disorder characterized by intense pain related to disease pathology and care-based interventions. Opioid-based therapies underpin pain-care in EB however are unable to provide adequate analgesia in a significant proportion of patients. Cannabinoid-based medicines (CBMs) have been increasingly studied for pain conditions of various aetiologies and pose as a novel dimension for pain-care in EB.
Objective: The aim of this study was to report patient anecdotes and perceived outcomes regarding the use of CBMs in the EB clinic.
Methods: Patient clinical stories were extracted retrospectively from the hospital electronic patient database (EPD) and formulated into individual cases.
Results: We present three cases of EB who were prescribed pharmaceutical-grade sublingually administered CBMs comprising tetrahydrocannabinol (THC) and cannabidiol (CBD). All three patients reported improved pain scores, reduced pruritus and reduction in overall analgesic drug intake.
Conclusion: CBMs may offer additional value to clinical symptomatic therapies for EB.

P42. NEUTROPHIL SUBSET EXAMINATION REVEALS DIFFERENT PHENOTYPE AND IMPAIRED FUNCTION IN PSORIASIS

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Background: Neutrophils represent the first line of defense during infection and injury. For a long time, they have been considered as a homogeneous cell population with only microbicidal function. Recently this paradigm has been challenged and evidence from pathological conditions revealed heterogeneity and plasticity in these cells. Immunoregulatory phenotypes of neutrophils have been characterized in different pathologies such as cancer, autoimmune diseases, and systemic inflammation. Most of these neutrophil subsets show differential expression of surface markers and reveal cross-talk with adaptive immune cells.
Objective: The aim of the present work was to determine the heterogeneity of the neutrophil population in psoriasis and evaluate their function.
Methods: Surface marker expression of neutrophils from 20 psoriasis patients and 20 healthy controls (HC) was evaluated by flow cytometry. Manual gating and unsupervised analysis tools were used to distinguish neutrophil subsets. Whole blood was stimulated in order to evaluate the production of reactive oxygen species by flow cytometry.
Results: Neutrophil subpopulations in whole blood were identified by differential expression of CD10, confirmed by the unsupervised analysis. The subsets found, revealed different maturation stages, as established by nuclei morphology examination. These neutrophil subsets were increased in psoriasis and showed impaired ROS production compared to HC neutrophils.
Conclusions: The heterogeneity of neutrophils in psoriasis reveals an increase in CD10- cells that have different maturation status, show lower activation and impaired ROS production upon stimulation.

P43. THREE DECADES OF EPIDERMOLYSIS BULLOSA CARE IN THE NETHERLANDS: EPIDEMIOLOGY, DIAGNOSIS, MANAGEMENT AND TRANSLATIONAL RESEARCH EXPERIENCE FROM AN EUROPEAN EXPERTISE CENTER

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Background: Epidermolysis bullosa (EB) is a rare and incurable genetic skin fragility disease. Significant scientific advances are made towards finding a cure that are being translated to therapeutic trials. To ensure valid and representative trial outcomes, recognition of well-characterized EB cohorts is essential.
Objective: We aim to summarize a 30-year experience of our center to document a well-characterized cohort and provide a model of care for developing centers.
Methods: In this cross-sectional study, all Dutch EB patients registered at our hospital between 1988-2017 are included. A complete diagnosis was established based on clinical, histological and molecular analysis. Epidemiological estimates have been calculated based on accurate genetic diagnosis.
Results: Overall, 297 Dutch EB families (458 patients) were identified with a prevalence rate of 22.9 per million population. An average of 8 EB patients were born and 7 old EB patients were identified every year with an incidence rate of 43.5 per million live births. A high case fatality rate was noted in the junctional EB spectrum. EB simplex, junctional EB and dystrophic EB were diagnosed in 36%, 19% and 29% respectively with mutations in 17 genes. A specialized multi-disciplinary care is required by 18.3% patients apart from regular management.
Conclusion: Our well-characterised cohort provides accurate epidemiological data of EB in the Netherlands that is useful for the design and execution of upcoming trials. The Dutch model of EB care is efficient in delivering near optimal management to its patient group and can serve as an example to other developing expertise centers.