ABSTRACTS OF THE JOINT INTERNATIONAL SYMPOSIA "VITAMIN D IN PREVENTION AND THERAPY" AND "BIOLOGIC EFFECTS OF LIGHT"

5-7 June, 2019

Schlossberg Hotel, Homburg/Saar, Germany

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Supported by:

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Oral presentations (OP)

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OP No. 6
VITAMIN D_3 HYDROXYLASES FROM BACILLUS MEGATERIUM: CHARACTERIZATION, 3D STRUCTURES AND ENGENEERING

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Background/Aim: Besides mammalian cytochrome P450, also bacterial ones were shown to be able to catalyse the 25- and 1-hydroxylation of vitamin D_3 and produce its active form, calcitriol. This is of biotechnological importance, since the corresponding bacterial P450s can easier be applied as biocatalysts, for industrial production, compared to mammalian ones. *Materials and Methods/Results:* Herein, we report the identification as well as functional and structural characterization of two novel P450s, CYP109E1 and CYP109A2, from Bacillus megaterium DSM319, that can hydroxylate vitamin D_3. CYP109E1 converts vitamin D_3 into several products, including 24(S)-hydroxyvitamin D_3, 25-hydroxyvitamin D_3 and 24S,25-dihydroxyvitamin D_3 as major products, as determined by NMR analysis. Using docking calculations and site-directed mutagenesis, we were able to generate CYP109E1 mutants with higher regio-selectivity towards 25-hydroxylation than the wild type form. In addition, we showed that vitamin D_3 is converted by CYP109A2 with high regio-selectivity, producing mainly 25-hydroxyvitamin D_3 (90% of total products). The crystal structure of substrate-free CYP109A2 was determined at 2.7 Å resolution, displaying an open conformation. High-resolution X-ray structures were also solved of a steroid-free form of CYP109E1 and of complexes with testosterone and corticosterone. *Conclusion:* The 3D structures provide an excellent tool to produce mutants of these enzymes with improved activities and changed selectivities of hydroxylation.

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OP No. 20
INTERFERON ALPHA MAY MEDIATE VITAMIN D ENHANCEMENT OF MONOCLONAL ANTIBODIES IN LYMPHOMA TREATMENT

Jörg Thomas Bittenbring[1,2], Frank Neumann[1,2], Stephan Stilgenbauer[1,2], Dominic Kaddu-Mulindwa[1,2], Moritz Bewarder[1,2], Andreas Keller[3] and Konstantinos Christofyllakis[1,2]

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Background/Aim: Vitamin D deficiency negatively affects overall survival of patients with diffuse large B-cell lymphoma on rituximab chemotherapy (1). Rituximab-mediated NK cell-cytotoxicity may be improved by optimal vitamin D levels. This is suggested by the fact that *in vitro*, the Burkitt lymphoma cell line (Daudi) is more effectively killed by NK cells coated with anti-CD20 antibodies when vitamin D levels are optimal. New-generation anti-CD20s are more effective. *Materials and Methods:* The mechanism of vitamin D action is not yet resolved, therefore we performed transcriptome analysis on resting NK cells after substitution for clarification. PBMCs from eight volunteers were collected and after isolation of NK cells total RNA a microarray analysis was performed by Affymetrix Gene-Chip 2.0™. A total of 7,705 genes were analyzed due to their involvement in the NK cell-cytotoxicity (Gene Ontology). Additionally, 48,145 genes were used in an exploratory analysis for potentially involved pathways. Findings of the screening phase were confirmed by rt-PCR. *Results/Conclusion:* 5 IFN-α subtypes (α2, -α4, -α6, -α7, -α10 and κ) were highly up-regulated and can possibly explain the improved ADCC by correction of vitamin D deficiency. The effect of vitamin D on IFN-α regulation has not been reported to date.

1 Bittenbring JT, Neumann F, Altmann B, Achenbach M, Reichrath J, Ziepert M, Geisel J, Regitz E, Held G and Pfreundschuh M: Vitamin D deficiency impairs rituximab-mediated cellular cytotoxicity and outcome of patients with diffuse large B-cell lymphoma treated with but not without rituximab. J Clin Oncol *32(29)*: 3242-3248, 2014. PMID: 25135997. DOI: 10.1200/JCO.2013.53.4537

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OP No. 34
PHOTOCARCINOGENESIS OF NON-MELANOMA SKIN CANCER: AN UPDATE

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Non-melanoma skin cancers including basal and squamous cell carcinomas, represent the most common cancers in humans. Extensive and chronic UV exposure especially before puberty, as well as DNA repair deficiencies or immunosuppression constitute the most important risk

factors. Fundamental differences in the molecular biology of the two different entities have been unveiled. Besides well-established alterations in basal and squamous cell carcinomas further recurrently mutated genes have been uncovered using modern technologies such as next generation sequencing. The elevated average burden of mutations in non-melanoma skin cancers compared to other solid tumors makes the distinction of driver mutations from passenger mutation challenging. The hedgehog pathway is a well established driving force in basal cell carcinomas, that is activated in about 90% of tumors and hence provides a promising target for small-molecule inhibitors. Frequently mutated genes in squamous cell carcinomas include *TP53, NOTCH* and TGF-beta receptor genes (*TGFBR1* and *TGFBR2*). Surgical excision of early-stage tumors remains the gold-standard therapy for non-melanoma skin cancers. The increasing knowledge of the molecular biology of the different tumor entities will foster the development of further targeted therapeutic approaches to treat advanced and metastatic carcinomas. The use of immune checkpoint inhibitors also provides new and innovative treatment options.

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OP No. 23
VITAMIN D AND COLORECTAL CANCER: CURRENT EVIDENCE AND DESIGN OF A RANDOMIZED TRIAL

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Background/Aim: Previous meta-analyses have shown lower survival of colorectal cancer (CRC) patients with low blood 25-hydroxyvitamin D (25(OH)D) concentrations (1). Recently, several much larger studies reported on the association between 25(OH)D levels and CRC prognosis (2). *Materials and Methods:* We conducted an updated meta-analysis including 11 original studies with an overall number of 7,718 CRC patients (3). *Results/Conclusion:* The dose-response meta-analysis showed a strong inverse relationship between 25(OH)D concentration and mortality, with pooled hazard ratios (95% confidence intervals) comparing lowest versus highest categories of 1.47 (1.18-1.82) and 1.49 (1.28-1.75) for overall and CRC-specific survival, respectively. Cancer patients, including CRC patients often suffer from fatigue which may strongly compromize their quality of life. Recent evidence suggests that vitamin D deficiency, which is common among CRC patients, may be a major risk factor for fatigue and that vitamin D supplementation may help alleviate or overcome fatigue. We designed a randomized trial with the primary aim to assess the impact of personalized, targeted vitamin D supplementation initiated several weeks after initial treatment of CRC on reducing fatigue of CRC patients. The design of the trial which is supported by the World Cancer Research Fund and which will start in summer 2019 will be presented.

1 Maalmi H, Ordóñez-Mena JM, Schöttker B and Brenner H: Serum 25-hydroxyvitamin D levels and survival in colorectal and breast cancer patients: Systematic review and meta-analysis of prospective cohort studies. Eur J Cancer *50*: 1510-1521, 2014. PMID: 24582912. DOI: 10.1016/j.ejca.2014.02.006

2 Maalmi H, Walter V, Jansen L, Chang-Claude J, Owen RW, Ulrich A, Schöttker B, Hoffmeister M and Brenner H: Relationship of very low serum 25-hydroxyvitamin D_3 levels with long-term survival in a large cohort of colorectal cancer patients from Germany. Eur J Epidemiol *32*: 961-971, 2017. PMID: 28884317. DOI: 10.1007/s10654-017-0298-z

3 Maalmi H, Walter V, Jansen L, Boakye D, Schöttker B, Hoffmeister M and Brenner H: Association between blood 25-hydroxyvitamin D levels and survival in colorectal cancer patients: an updated systematic review and meta-analysis. Nutrients *10*: 896, 2018. PMID: 30011816. DOI: 10.3390/nu10070896

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OP No. 2
NUTRITIONAL EPIGENOMICS OF VITAMIN D

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Background/Aim: Next-generation sequencing methods of epigenetics opened the field of epigenomics describing epigenetics on a whole genome view. The field of nutritional epigenomics describes numerous connections between diet-derived metabolites and the accessibility of chromatin. Vitamin D_3 is a micronutrient that has a direct effect on the epigenome *via* 1α,25-dihydroxyvitamin D_3, its biologically most active metabolite, and vitamin D receptor, a transcription factor and member of nuclear receptor superfamily. *Materials and Methods/Results:* We demonstrated that vitamin D receptor (VDR) responds to 1α,25-dihydroxyvitamin D_3 *via* the genome-wide binding to thousands of genomic regions. The interaction with the pioneer transcription factors PU.1 and CEPBA, changes the pattern of histone markers and increases chromatin accessibility, *i.e.*, vitamin D has a significant effect on the human epigenome. In peripheral blood mononuclear cells, obtained in a vitamin D intervention study (VitDbol, NCT02063334) before and after a vitamin D_3 bolus (2000 μg), *i.e.*, in a human *in vivo* settings, we observed similar epigenome-wide effects. In general, epigenome changes in

result of cellular perturbations create a memory, which is termed "trained immunity", when monocytes/macrophages encounter microbes. Vitamin D modulates these epigenetic training events. Some of the epigenome-wide effects of vitamin D translated into changes of the transcriptome, *i.e.*, hundreds of genes are either up- order down-regulated regarding their expression. *Conclusion:* The expression pattern of vitamin D target genes differed significantly between individuals and the average expression change can serve as a marker for vitamin D responsiveness. Different aspects of nutritional epigenomics of vitamin D with a focus on immune responses will be presented.

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OP No. 37
UV AND VITAMIN D IMPACTS ON SKIN CANCER: RESULTS FROM MOUSE EXPERIMENTS

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Solar UV is known to cause skin cancer but also generate vitamin D. Evidently, these adverse and beneficial effects need to weight against each other, even in the restricted context of skin cancer. To this end, we should combine epidemiology with (animal) experiments. Excessive exposure to solar UV radiation is clearly related to skin cancer, but the UV etiology differs between skin cancer types. Squamous cell carcinomas (SCC) are most commonly associated with high level chronic exposure, as in people with outdoor professions, where cutaneous melanomas (CM) tend to show a slightly reduced risk. CM show an increased risk with intermittent peak exposures, in particular with episodes of severe sunburns. The risk of basal cell carcinomas (BCC) is generally higher in people with outdoor jobs but with increasing incidence, the UV etiology of BCC has shifted toward that of melanomas – *i.e.* common in people with office jobs. SCC can be produced by (chronic) exposure of wild-type mice. BCC and CM can be promoted by UV exposure in transgenic mice primed to develop these cancers. Interestingly, epidemiology indicated anticancer effects from solar UV exposure and related vitamin D, and various mouse experiments demonstrated the biological plausibility. Anticancer effects from vitamin D were also confirmed for the 3 types of skin cancer in mouse models. As UV's anticancer effect appears to be not solely mediated by vitamin D, the hunt is on for this 'non-vitamin D' route and it poses the question whether this has also a bearing on skin cancers. Besides unpractical, it would appear unhealthy to shun solar UV exposure, paradoxally, possibly even where skin cancer is concerned.

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OP No. 27
MOLECULAR PATHOLOGY AND CLINICAL MANAGEMENT OF XERODERMA PIGMENTOSUM

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Xeroderma pigmentosum (XP) is a rare autosomal recessive genetic disorder with a worldwide prevalence of 1 in 1,000,000. Patients with this DNA repair-defect syndrome accumulate UV-induced DNA damage due to defective nucleotide excision repair (NER) or defective translesional synthesis by polymerase η. The NER is a sequential mechanism for detecting and repairing lesions in the DNA, such as UV photoproducts cyclobutane pyrimidine dimers (CPD) and 6-pyrimidine-4-pyrimidone dimers (6-4 PP). NER can be subdivided into global genome repair (GGR) and transcription-coupled repair (TCR). As a consequence of defective NER, XP patients develop basal and squamous cell carcinomas as well as melanomas demonstrating the tumor-driving effect of UV-induced DNA damage. Molecular genetic tests can be used to reveal the underlying genetic defect and assign XP complementation groups. Currently, XP can be divided into seven different complementation groups: XP-A to XP-G as well as a variant form with a mutation in the translational polymerase η gene (PolH), also called XP variant (XPV). The complementation groups correspond to the underlying gene defect. Regarding treatment of XP, no curative therapy is available. Thus, an early diagnosis is essential so that systematic sun protection can be ensured. Although no curative therapy exists, new treatment options, topical and systemic, have become available and contribute to the treatment and prophylaxis of skin cancer and neurological degeneration.

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OP No. 29
AFAMELANOTIDE: A PROMOSING DRUG FOR THE TREATMENT OF ERYTHROPOIETIC PROTOPORPYHRIA AND BEYOND

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Erythropoietic protoporphyria (EPP; OMIM177000) results from a major dysfunction of ferrochelatase, the final enzyme

along the heme biosynthetic pathway. Following exposure to visible light, symptoms of acute photosensitivity may occur, including itching, stinging, burning and pain; later followed by reddening and edema. The disease can be misdiagnosed or not diagnosed at all for a considerable time, even for years. Hence, the timespan between the first manifestation of clinical signs and the establishment of the precise diagnosis is usually long, leading to a severe impairment in quality of life. In the past, treatment of EPP consisted primarily of prophylactic measures that were highly unsatisfying. Recently, however, treatment with afamelanotide, an α-melanocyte-stimulating hormone analogue, was shown to enable affected individuals to stay considerably longer in the sun light. Most importantly, this therapy was associated with a markedly reduced pain and an enhanced quality of life.

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OP No. 3
VITAMIN D RECEPTOR POLYMORPHISMS AND CANCER RISK: A SYSTEMATIC REVIEW

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Background/Aim: Increasing scientific evidence supports the association between vitamin D and cancer risk. Vitamin D receptor polymorphisms (VDR) seem to have a role in the mediation of biological action of Vitamin D. The relevance of VDR gene restriction fragment length polymorphisms for various types of cancer has been investigated by several studies but no conclusive results have been obtained. *Materials and Methods:* We have carried out a systematic review of the literature to investigate the role of the most studied VDR polymorphisms (Fok1, Bsm1, Taq1, Apa1, and Cdx2) and factors influencing between-study heterogeneity. Up to December 2018, we identified 177 independent studies with data to calculate risk estimate for breast, prostate, colorectal, skin (melanoma and non-melanoma skin cancer), lung, ovarian, kidney, bladder, gallbladder, esophageal, thyroid, head and neck, liver, and oral squamous cell carcinoma, non-Hodgkin's lymphoma, multiple myeloma, sarcoma, pancreas, sarcoma. *Results:* We found significant associations with prostate (Fok1, Bsm1, Taq1, Apa1, Cdx2), breast (Fok1, Bsm1, Apa1, CdX2), colorectal (Fok1, Bsm1, Taq1, Apa1) and skin cancer (Fok1, Bsm1, Taq1). *Conclusion:* Inconsistent data have been reported for many cancer sites and ethnicity is a key factor for heterogeneity.

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OP No. 39
VITAMIN D STATUS AND CANCER: RESULTS FROM ECOLOGICAL STUDIES, OBSERVATIONAL STUDIES AND CLINICAL TRIAS

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The UVB-vitamin D-cancer hypothesis is now 39 years old, based on the seminal paper by the brothers Cedric and Frank Garland published in 1980 based on a map of colon cancer mortality rates in the United States. Single-country geographical ecological studies have provided strong evidence that mortality rates are inversely correlated with indices of solar UVB doses for many types of cancer. A few ecological studies also found the same for cancer incidence. A study of cancer incidence with respect to occupation in Nordic countries found inverse correlations between an index of solar UVB exposure and 14 types of cancer for men and three for women. Prospective observational studies have found inverse correlations between serum 25-hydroxyvitamin D [25(OH)D] and incidence of a few types of cancer. However, for breast cancer, case-control studies provide the strongest inverse correlations due to the fact that breast cancer can develop very rapidly. The recently completed VITamin D and OmegA-3 TriaL (VITAL) enrolled 25,000 participants and gave half of them 2000 IU/d vitamin D_3. For those with BMI <25 kg/m^2, there was a significant 24% reduction in all-cancer incidence. For black participants, there was an almost significant 23% reduction in all-cancer incidence. For all participants, there was significant 25% reduction in all-cancer mortality rate. The results would have been stronger if participants were given, say, 4,000 IU/d vitamin D_3. Recently it has been noted that most vitamin D clinical trials have been designed based on guidelines for pharmaceutical drugs, not nutrients. The two assumptions of drug trials are that the trial is the only source of the agent and that there is a linear dose-response relationship. Needless to say, neither of these assumptions is valid for vitamin D trials. What is now being proposed is that vitamin D trials be based on 25(OH)D concentrations, starting with an understanding of the 25(OH)D concentration-health outcome relationship, measure 25(OH)D at baseline and try to enroll participants with low concentrations, use sufficient vitamin D_3 doses to raise concentrations to where large changes in risk are expected, measure achieved 25(OH)D during the trial, and evaluate outcomes with respect to achieved 25(OH)D. Grassrootshealth.net has pioneered this approach, finding

significant inverse correlations between 25(OH)D for all- and breast-cancer incidence.

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OP No. 26
SHORT TELOMERES, A COMMON RISK FACTOR OF ALL CAUSE AND CARDIOVASCULAR MORTALITY IN VITAMIN B- AND D-DEFICIENT SUBJECTS

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Background/Aim: Aging is characterized by a progressive decline of organ functions leading to increased risk of age-associated diseases and death. Telomere dysfunction and genomic instability appear to be of critical importance for aging at a cellular level. Vitamin B and D deficiencies have been proposed as potential factors that promote telomere dysfunction through their regulatory role in cell differentiation and proliferation, DNA synthesis, apoptosis, one-carbon metabolism, and the elimination of cytotoxic homocysteine. The present study aimed to explore if leucocyte telomere length and the plasma concentrations of vitamins B and D are linked to mortality. Moreover, we investigated if telomere length is linked to vitamin B and D status. *Materials and Methods:* In the prospective Ludwigshafen Risk and Cardiovascular Health (LURIC) Study we have investigated the predictive role of relative telomere length in blood leucocytes (RTL), vitamin B6, B12 and 25-hydroxy vitamin D (25-OHD) for mortality in cardiovascular patients. The Ludwigshafen Risk and Cardiovascular Health (LURIC) study is a cohort study of subjects referred for coronary angiography between 1997 and 2000. Mortality was tracked for a median of 7.7 years. Potential relationships between RTL, vitamins and indices of inflammation were also explored. *Results:* RTL correlated negatively with age (r=–0.09; $p<0.001$). Patients in quartiles 2-4 of RTL had a lower hazard ratio for all-cause mortality (HR=0.822; 95%CI=0.712-0.915; $p=0.008$) and CVD-mortality (HR=0.836; 95%CI=0.722-0.969; $p=0.017$) when compared to those in the 1st quartile. Low plasma concentrations of vitamin B6, B12 and 25-hydroxy vitamin D were also associated with a markedly increased all-cause and cardiovascular disease mortality. Compared to individuals with the lowest plasma vitamin concentrations, those with optimal levels had a risk reduction between 25 and 75%. HCY, a functional marker of vitamin B6, B9 and B12 status, was also a strong predictor of mortality in the LURIC cohort. HCY and vitamin B6 correlated with age-corrected RTL (r=–0.086, $p<0.001$; r=0.04, $p=0.031$, respectively), IL-6 (r=0.148, $p<0.001$; r=–0.249, $p<0.001$, respectively) and hs-CRP (r=0.101, $p<0.001$; r=–0.320, $p<0.001$, respectively). Moreover, subjects with the longest telomeres had a significantly higher concentration of vitamin B6, but lower concentrations of HCY, IL-6 and hs-CRP. Multiple regression analyses identified HCY as an independent negative predictor of age-corrected RTL.B12 was associated with all-cause mortality, RTL and hsCRP in a non-linear fashion. In the lowest and highest quartiles of B12 mortality was higher than in the mid-range. Amongst subjects with low (1st quartile) and high (4th quartile) B12, those with the longest telomeres had a 40 and 60%, respectively, lower mortality-rate than those with the shortest telomeres. *Conclusion:* Short telomeres and low plasma concentrations of B6, B12 and 25-OHD predict all-cause and cardiovascular mortality. Accelerated telomere shortening seems to be a common mechanism that promotes mortality in vitamin-deficient individuals. Our results also point towards HCY, oxidative stress and systemic inflammation as causative factors that drive telomere shortening in B-vitamin deficient subjects.

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OP No. 1
IMPORTANCE OF VITAMIN D FOR HEALTH FROM BIRTH UNTIL DEATH: A GLOBAL PERSPECTIVE

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Vitamin D has become one of the most recognized nutrients, as being critically important for bone health as well as reducing risk for many chronic illnesses. During pregnancy vitamin D is important in fetal development and reduces the risk for preeclampsia, cesarean section and premature births. In utero vitamin D deficiency increases risk for dental caries and wheezing disorders in infants. Vitamin D deficiency during childhood increases risk for autoimmune diseases and cardiovascular disease later in life. Vitamin D deficiency has been linked with an increased risk for deadly cancers,

autoimmune diseases, neurocognitive disorders, cardiovascular disease, infectious diseases and type 2 diabetes. However there continues to be controversy about the non-skeletal health benefits of vitamin D. The recent VITAL study reported that healthy adults who took 2,000 IUs vitamin D_3/day for 5 years did not reduce risk for cancer or cardiovascular disease. Most of the participants had blood levels of 25-hydroxyvitamin D that were considered to be sufficient or insufficient; baseline was 29.8 ng/mL (male 29.7, female 32 ng/mL). Therefore, giving 2,000 IUs of vitamin D a day to adults who were already vitamin D sufficient would not be expected to have a significant response. However, there was a 25% statistically significant reduction in cancer mortality for those who took 2,000 IUs vitamin D_3/day and there was no evidence of toxicity. Recent evidence suggests that vitamin D itself may have an important role to play in stabilizing endothelial membranes, thereby reducing risk for autoimmune diseases and cardiovascular disease.

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OP No. 17

GENOMIC AND METABOLIC ASPECTS OF VITAMIN D

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Background/Aim: It is well documented that vitamin D plays an essential role in calcium and bone metabolism. There is less acceptance of the role of vitamin D for health benefits not related to calcium metabolism. *Materials and Methods:* Healthy adults were given either 600, 4,000 or 10,000 IUs vitamin D_3/day for 6 months. Blood and urine were collected at various times. Gene expression analysis was performed on peripheral mononuclear cells at baseline and at 6 months.Serum 25-hydroxyvitamin D, calcium and parathyroid hormone were evaluated. Urine and serum were evaluated for metabolomic profiles. *Results:* There was a dose-dependent effect of vitamin D supplementation on serum 25-hydroxyvitamin D, parathyroid hormone and gene expression. More than 2,000 genes were up and down regulated in the adults who received 10,000 IUs daily for 6 months. Serum calcium levels remained normal for all study subjects and no untoward toxicity was observed.The metabolomic profiles were related to the genomic expression analysis.There were significant inter-individual effects on gene expression and metabolomic profile in response to the same dose in those receiving 600, 4000 and 10,000 IU/d, despite similar changes in 25(OH)D concentrations. *Conclusion:* These results may help explain the variability observed in clinical trials regarding vitamin D's non-calcemic health benefits.

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OP No. 41

CAN YOU HAVE YOUR CAKE AND EAT IT TOO: HEALTH BENEFITS OF ULTRAVIOLET RADIATION AND VISIBLE LIGHT

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During exposure to sunlight all of the sun's energy is absorbed into the skin and some passes deep into the body. There is strong epidemiological evidence that exposure to sunlight has a multitude of health benefits including reducing risk for infectious diseases, autoimmune diseases including type 1 diabetes and multiple sclerosis, cardiovascular disease and neurocognitive dysfunction including depression. Ultraviolet B (UVB) radiation with wavelengths of 290-315 nm are absorbed by 7-dehydrocholesterol resulting in the formation of previtamin D_3. Once formed it quickly isomerizes by a membrane enhancing process to form vitamin D_3. UVB and ultraviolet A (321-400 nm) radiation that is absorbed in the skin also serve as signal transducers to enhance a variety of genomic and non-genomic biological responses. These include, among a multitude of other photobiochemicals, the production of beta endorphin and nitric oxide. Both UVB and UVA radiation are also absorbed by DNA and proteins that can cause cross linking and other alterations that have negative consequences in the skin. In response to these cutaneous insults a variety of mechanisms are induced to help repair and prevent further alterations and damage to UVB- and UVA-sensitive macromolecules. Visible radiation penetrates deep into the body. Blue and red light can influence collagen synthesis in the dermis, enhance wound healing and visible light may help regulate cellular circadian rhythms. The development of the LEDs that can be tuned to various wavelengths offers the opportunity to develop photopharmacology as a novel approach for treating and preventing acute and chronic illnesses.

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OP No. 7

RECENT DEVELOPMENTS TOWARDS THE SYNTHESIS OF VITAMIN D METABOLITES

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Due to latest advancements in the development of LC-MS/MS based assays and their applications in clinical

chemistry, low abundant vitamin D metabolites can by now be detected at low concentration in high selectivity and specificity. Consequently, there is a growing need for their synthesis as stable isotopes to be used as calibration and reference standards. Although Palladium (0) catalyzed coupling reactions are already well established in vitamin D synthesis, little is known with regards to application of cobalt complexes for this purpose. In fact, the so-called Pausen-Khand reaction can be applied for the synthesis of a wide range of stable isotopes of vitamin D metabolites that are hardly accessible by other known methods. Applications, scope and limitations of this new promising methodology are discussed.

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OP No. 24
VITAMIN D IN PRECLINICAL MODELS OF FATTY LIVER DISEASE

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Simple steatosis in non-alcoholic fatty liver disease (NAFLD) progresses to Non-alcoholic steatohepatitis (NASH) when excessive fat accumulation is accompanied by ballooning, inflammation, and progressive hepatocyte injury. Due to the increasing incidence of NAFLD/NASH worldwide and the lack of effective drugs, current treatment options are restricted to lifestyle interventions including dietary and physical activity modifications. In this regard, vitamin D has received a widespread attention in recent years, since vitamin D deficiency has been fequently reported in patients with NAFLD and NASH. In line with its diverse physiological roles, pre-clinical animal models and patient cohorts have demonstrated anti-inflammatory, anti-fibrotic and anti-proliferative effects of vitamin D on liver injury. Several animal models of NASH have confirmed the association of vitamin D deficiency and NALFD/NASH severity in humans and revealed benefits of vitamin D supplementation to the diet. Decreased serum aminotransferase activities, reduced hepatic triglyceride levels and suppression of TGFβ1 and α-SMA have been induced in NASH rodent models by vitamin D supplementation. Similarly, phototherapy was successful in reducing hepatic inflammation and fibrosis in CDAA (choline-deficient, amino acid-defined, iron-supplemented diet) diet induced-NASH rodent models as well as in obesity-related NASH (Zucker *fa/fa* rats). Another animal study performed in Sprague-Dawley rats on a high-fat "Western" diet also displayed immunomodulatory actions of vitamin D during NASH progression on lobular inflammation and NAFLD activity scores together with altered levels of resistin, IL-6 and TNF-α in the liver. A high-fat, vitamin D-deficient diet in BALB/c inbred mice impaired the enterohepatic circulation of bile acids through inhibition of the apical sodium-dependent bile acid transporter, and vitamin D supplementation reversed these effects, leading to induction of the transporter and reduction of hepatic inflammation. We demonstrated that *Abcb4* knock-out mice on low vitamin D-diet develop more advanced fibrosis and elevated hepatic collagen contents. Feeding these mice a diet high in vitamin D increased serum vitamin D concentrations, and simultaneously lowered liver enzyme activities, altered expression levels of profibrogenic genes and ameliorated, in part, liver injury. Further studies in preclinical models suggest that not only vitamin D, but also related factors involved in vitamin D metabolism are associated with NAFLD/NASH. For instance, the nuclear vitamin D receptor (VDR) was markedly induced in two mouse models of NAFLD but decreased in NASH. Similarly, proteomics analysis of mice fed a methionine- and choline-deficient diet (MCD) revealed that vitamin D binding protein was among the most differentially expressed proteins. Interestingly, a genome-wide association study in 928 humans has also detected an association between pathogenesis of NAFLD and a SNP in this gene. Liver steatosis in 241 patients with chronic liver diseases was associated with low serum 25(OH)D concentrations but not with other common vitamin D pathway gene variants (*GC, DHCR7, CYP2R1, VDR*). Currently, it remains difficult to non-invasively differentiate between the wide spectrum of disease stages in NAFLD/NASH patients. This, together with the slow nature of disease progression, hamper prospective studies investigating effects of vitamin D in clinical studies. Thus, pre-clinical models of NASH provide critical guidance to define the role and therapeutic potential of vitamin D and downstream mechanisms in the pathogenesis of fatty liver disease.

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OP No. 40
WOMEN WITH GREATER SUN EXPOSURE HABITS SEEM TO LIVE LONGER. ARE THESE RESULTS IN CONTRAST TO OTHER RESEARCH?

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Background: There has been shown decreasing risk of incidental venous thromboembolism, type 2 diabetes mellitus (T2DM), endometrial cancer and all-cause mortality with increasing sun-exposure habits. *Materials and Methods:* We aimed to assess if these results are in contrast with prior research and reviewed results from the large (n=29518) prospective Melanoma in Southern Sweden (MISS) cohort.

Results and Conclusion: Low sun exposure habits were mainly related to increasing risk of cardiovascular disease (CVD) and nonCVD/noncancer disease, while the risk of death due to cancer was only moderately affected. This resulted in increasing prevalence of death due to cancer. If women live longer by not dying in CVD and nonCVD/noncancer disease they will have more time to be diagnosed with a cancer. We observed an increased incidence of skin cancer with increasing sun exposure. However, the all-cause mortality prognosis improves with increasing sun exposure habits. The proportion of death among those with both non-melanoma skin cancer and malignant melanoma decreased with increasing sun exposure habits. Non-smokers with low sun exposure habits are at similar risk of all-cause death as smokers with the greatest sun exposure. We interpret this finding that low sun exposure was a risk factor for all-cause death in the same magnitude as smoking. Thus, it seems that avoidance of sun exposure is the fourth large life style factor affecting our health together with smoking, obesity, and inactivity. We will compare our results and relate them to other research regarding sun exposure; prognosis of cancer, skin cancer, all-cause mortality, sunbed use and finally of use of sunscreens.

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OP No. 21

VITAMIN D IN HEAD AND NECK CANCER

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Background/Aim: Low Vitamin D serum levels are highly frequent in cancer patients and a prognostic relevance was shown for several cancer entities. Furthermore, it is known from several studies that vitamin D can stimulate antitumoral activity of the immune system. For head and neck squamous cell carcinomas (HNSCC), however, valid epidemiological data are rare and there are no functional studies on a putative connection between vitamin D and the patients' immune system. *Materials and Methods:* In our study, we analyzed 25-OH vitamin D serum levels in 231 HNSCC patients and 232 healthy individuals and correlated vitamin D serum levels with patient survival and clinical data. Intra- and peritumoral immune cell infiltration was evaluated in a subset of HNSCC patients using immunohistochemistry. NK-cells were isolated from 11 HNSCC patients before and after substitution with vitamin D and tested for their cytotoxic activity directed against head and neck cancer cells. *Results:* When comparing HNSCC patients with healthy controls, vitamin D serum levels were significantly lower in HNSCC patients and low vitamin D levels were associated with a positive lymph node and a negative HPV status. Additionally, low vitamin D levels were a significant predictor of shorter overall survival. In our immunohistochemical analyzes, HNSCC patients with low vitamin D serum levels showed significantly lower intra- and peritumoral immune cell infiltrates. In 11 HNSCC patients treated with vitamin D for three months, NK cells developed a significant rise in cytotoxic activity directed against HNSCC cells. *Conclusion:* Taken together, we showed that vitamin D deficiency is highly frequent in head and neck cancer patients and predicts poor overall survival. Vitamin D substitution has a potential to stimulate antitumorigenic immune responses, thus improving the patients' prognosis in the context of a multimodal therapy.

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OP No. 30

PHOTOTOXIC AND PHOTOALLERGIC SKIN REACTIONS: AN UPDATE ON CLINICAL MANAGEMENT

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Upon interaction of UV-irradiation with cutaneous photosensitizers photosensitive cutaneous reactions might occur. The term "photosensitizers" comprises both synthetic and naturally-occurring substances, which can provoke phototoxic or photoallergic skin reactions. The action spectrum of such photosensitizers is commonly within in the UVA-range. Phototoxic reactions develop within hours after incubation and are similar to dermatitis solaris. In contrast, photoallergic reactions are type IV hypersensitivity reactions, and resemble eczema. They usually evolve within days and are less common than phototoxic reactions. Diagnosis is based on a careful anamnesis, clinical examination and if nessecary phototesting for minimal phototoxicity dose as well as histopathological examinations. For the latter, a variant of the conventional epicutaneous test, the so-called photopatch test, was developed. In case of a supposed false negative photopatch test result, photoprick-, photoscratch- or an illuminated intracutaneous test might be used. However, if a metabolite of a test substance is the actual photosensitizer, a systemic photoprovocation might be required. Sometimes, it might be difficult to distinguish phototoxic reactions from photoallergic skin reactions clinically. In these cases, typical reaction patterns observed in large-scale studies can be helpful in differentiating such cutaneous photosensitivity reactions. Treatment options include withdrawal of the eliciting agent and avoidance of sunlight *via* UV-protective clothing and broadband sunscreens, especially with UVA filters.

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OP No. 11
PIGMENT GENES NOT SKIN PIGMENTATION AFFECT UVB-INDUCED VITAMIN D

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Background/Aim: Low serum 25-hydroxyvitamin D (25(OH)D) levels in dark-skinned persons is generally believed to be caused by skin pigmentation. *Materials and Methods:* The influence of measured skin pigmentation on UVB-induced 25(OH)D increase was investigated together with 13 genetic (pigment SNPs) and 9 demographic parameters. Forty subjects represent a wide range in skin pigmentation were selected. Participants underwent full-body exposure with identical UVB doses for nine weeks during which serum 25(OH)D were measured weekly. Performed during the winter in Denmark this study was not influenced by latitude, season, sun and clothing habits because ambient UVB is negligible and has no effect on 25(OH)D synthesis. *Results:* The study revealed a considerable variation in 25(OH)D increases (range: 2.9 to 139 nmol/L). Both constitutive and facultative skin pigmentation separately influenced UVB induced linear 25(OH)D increase. However, this influence was lost in the presence of separate significant pigment SNPs. Sex, height, age and seven SNPs located in the ASIP, MTAP, MIR196A29 and Solute Carrier Family genes explained 77.4% of the observed 25(OH)D variation based on a combined linear model. *Conclusion:* This study found that pigment genes supersede actual measured skin pigmentation, but confirmed the influence of sex, age and height on UVB-induced 25(OH)D increase, suggesting the need for a broader focus in the search for causal parameters for low 25(OH)D levels.

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OP No. 38
SKIN CANCER RISK RELATED TO LIFETIME UVR DOSE AND SKIN PHOTOTYPE

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Background/Aim: Ultraviolet radiation (UVR) is the greatest risk factor for human skin cancer (SC) and causes solar lentigines (SL). The study aim was to investigate the association between lifetime UVR dose, skin phototype and SC risk through their common relationship to SL. Patients and Methods: This study investigated the association between UVR dose and SL (part I), and the relation between SL and SC (part II). By combining both study parts, SC risk related to UVR dose was estimated. Part I was based on longitudinal data (1999-2012) from 38 healthy participants wearing personal UVR dosimeters (total 16,897 days) from which the estimated individual lifetime UVR dose was related to facial SL. Part (II) was based on a validated cross-sectional dataset of 2,898 participants including 149 with a SC diagnosis; 116 had been diagnosed with basal/squamous cell carcinomas, 36 with cutaneous malignant melanoma, and three with both. Their facial SLs were assessed, and skin phototype [pigment protection factor (PPF)] were objectively measured. *Results:* In part I, a borderline significantly positive association (power function) was found between SL and lifetime UVR dose but for men only (p=0.060). In part II, SL (p<0.001) and PPF (p=0.001) were significantly associated with SC. Combining parts I and II, we found an increase in SC risk of 1.23 by doubling the average lifetime UVR dose and SC risk was 34.9 times higher with a PPF of 1 (very fair skin) than with a PPF of 9 (dark Mediterranean skin). *Conclusion:* It is possible to estimate SC risk from lifetime UVR dose and skin phototype; skin phototype is of greater relative importance than lifetime UVR dose.

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OP No. 15
GUIDANCE FOR PREVENTION AND TREATMENT OF VITAMIN D DEFICIENCY WITH FOOD FORTIFICATION AND SUPPLEMENTATION

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Vitamin D deficiency contributes to musculoskeletal diseases such as rickets and osteomalacia, and probably also to other skeletal and extra-skeletal diseases. While there are still many open questions regarding the role of vitamin D in various health outcomes, it has been clearly documented that significant parts of the general populations worldwide fail to meet officially recommended dietary reference intakes for vitamin D. This calls for action from a public health perspective, including promotion of a healthier lifestyle with moderate sunlight exposure and optimal nutrition, but will also require approaches such as systematic vitamin D food fortification and vitamin D supplementation. Large randomized controlled trials such as the VITAL study underlined the high safety margin for vitamin D, thus paving the way for introducing and improving systematic approaches for increasing vitamin D supply to the general population. Public health authorities are now responsible for

filling the gap between actual vitamin D status and vitamin D requirements.

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OP No. 43
SOLARIUM USE AND RISK OF MALIGNANT MELANOMA: MANY OPEN QUESTIONS, NOT THE TIME TO CLOSE THE DEBATE

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There is an ongoing debate whether moderate solarium use may increase melanoma risk. However, some recent publications claim that a causal relationship between solarium use and melanoma risk has now been convincingly demonstrated and demand the debate be closed. This presentation summarizes our present knowledge on this topic and concludes that a causal relationship between moderate sunbed use and melanoma risk has not been proven. Proof of such a causal relationship could be provided by randomized controlled trials, but these are lacking. The results of cohort and case–control studies published to date demonstrate weak associations but do not prove causality. Moreover, the overall quality of observational studies on this topic and the resulting evidence levels are low due to severe limitations which lead to bias. In the majority of published studies, many of the confounding factors, including sun exposure, sunburn and skin type, have not been adequately and systematically recorded and adjusted for. We recently performed a meta-analysis (1) that included two cohort and 29 case–control studies. Summary risk estimates suggested a weak association [odds ratio 1.19, 95% confidence interval=1.04-1.35, p=0.009) for 'ever use' of a sunbed with melanoma risk. However, sensitivity analysis failed to demonstrate an association for studies from Europe, studies with a low risk of bias, and studies performed after 1990. Moreover, overall study quality, resulting levels of evidence (3a–) and grades of recommendation (D) were low because of severe limitations including confounding and lack of interventional studies. It must be emphasized that the same risk estimates (*e.g.* odds ratios) as given in published meta-analyses could well be obtained in the following scenario, moderate sunbed use has no effect on melanoma risk, but an 'unhealthy lifestyle' (*e.g.* extensive sunbathing) resulted in an inflated odds ratio of 1.2 in association with sunbed use (it has been reported that 'sun worshippers' more frequently go to tanning salons). Moreover, the criteria defined by Hill in 1965 for plausibility in a biological system (2) are, for many reasons not fulfilled, for the inference that moderate solarium use per se may increase melanoma risk, including the obvious difficulties of confounding factors. It should be noted that a large body of evidence from epidemiological and animal studies demonstrates no increase in melanoma risk following chronic (moderate) UV exposure. Many studies indicate that sub-erythemal chronic exposure to the sun may even be protective and that outdoor workers may have a reduced risk of melanoma. In summary, we conclude that, at present, there is no convincing evidence that moderate/responsible solarium use increases melanoma risk. There remain many open questions and the debate has certainly not closed.

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2 Hill AB: The Environment and Disease: Association or Causation? Proc R Soc Med *58*: 295-300, 1965. PMID: 14283879.

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OP No. 4
RECENT ADVANCES IN THE DEVELOPMENT OF SELECTIVE VDR MODULATORS

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The nuclear vitamin D receptor (VDR) bound to its natural ligand, calcitriol, is a key regulator of calcium and phosphate homeostasis, as well as bone metabolism. In addition to its central role in calcium homeostasis, calcitriol has antiproliferative and anti-inflammatory activities and reduces the severity of the symptoms in preclinical models of autoimmune diseases (*e.g.* inflammatory bowel diseases, lupus, type-1 diabetes) and various types of cancer (*e.g.* prostate and breast cancer). However, the doses required to induce robust therapeutic effects lead to hypercalcemia and mineralization of various tissues that limit calcitriol clinical use. Therefore, research efforts aim to develop selective VDR modulators with limiting calcemic effects. New VDR analogs devoid of hypercalcemic activity and the potential structural mechanism underlying the binding properties of these dissociating ligands, as well as their pharmacological and therapeutical potential, will be described.

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OP No. 10
NEW VITAMIN D METABOLITES IN THE SKIN

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It has been assumed that vitamin D_3 is activated solely through sequential hydroxylation at C25 and C1α to produce $1,25(OH)_2D_3$ [$D_3 \rightarrow 25(OH)D_3 \rightarrow 1,25(OH)_2D_3$], which regulates phenotypic activities through interaction with the vitamin D receptor (VDR) acting as the transcriptional regulator. This dogma has been challenged by our recent discoveries of alternative pathways initiated by the action of cytochrome P450 family 11 subfamily A member 1 (CYP11A1) on the side chain of vitamin D_3 and D_2 firstly to produce $20(OH)D_2/D_3$, which is further hydroxylated by CYP11A1, CYP27A1, CYP24A1, CYP3A4 and finally by CYP27B1 to produce a large number of hydroxy-vitamin D derivatives. In addition, CYP11A1 acts on lumisterol and 7-dehydrocholesterol to produce several hydroxy derivatives with full side chain or short side chain after its cleavage by CYP11A1 and further modifications by steroidogenic enzymes. In the skin, ultraviolet B exposure of 7-dehydrocholesterol and 7-dehydropregnenolone metabolites can generate a large number of secosteroidal products. Novel vitamin D hydroxy derivatives and classic $1,25(OH)_2D_3$ interact not only with the VDR, but also with retinoic acid orphan receptors (ROR)α and RORβ, acting as reverse agonists, and most surprisingly with aryl hydrocarbon receptor. These interactions are dependent on the number of hydroxyl groups in the side chain, and are modulated by the addition of OH to C1α. Importantly $20(OH)D_2/D_3$ and $20,23(OH)_2D_3$ are non-calcemic, while $1,2(OH)_2D_3$ show reduced calcemic activity in comparison to $1,25(OH)_2D_3$. Novel secosteroids have demonstrated biological potency in a number of cell types that is dependent on their chemical structures, and they can act on skin cells as antiproliferative, pro-differentiation and anti-inflammatory or photoprotective agents. In conclusion, we believe that these studies provide an explanation for the pleiotropic and sometimes contradictory phenotypic effects of vitamin D, which are secondary to the action of different vitamin D products acting selectively on alternative nuclear receptors. Finally, lumisterol is biologically active after its enzymatic modification.

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OP No. 22
VITAMIN D AND MELANOMA

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Melanoma affects large segments of the Caucasian population with high incidence, and mortality rate, the highest amongst all types of skin cancer. The ultraviolet B (UVB) spectrum of solar radiation, while being cancerogenic and implicated in the etiology of cutaneous melanoma, is necessary for the production of vitamin D_3 in the skin, a mechanism which provides the majority of its supply to the body. Vitamin D_3 is activated through sequential hydroxylation at C25 and C1 to produce $1,25(OH)_2D_3$ in the canonical pathway, and through the action of the cytochrome P450 family 11 subfamily A member 1 (CYP11A1) in non-canonical pathways. Clinical and clinicopathological observations have shown that low levels of 25(OH)D are associated with histologically thicker melanomas, advanced stages of the disease and reduced survival of patients. Moreover, single nucleotide polymorphism of the genes for vitamin D receptor and of vitamin D-binding protein showed some association with melanomagenesis or disease outcome. Importantly, there is a reduction of expression of vitamin D receptor and cytochrome P450 family 27 subfamily B member 1 (CYP27B1) during melanoma progression, and low levels of these markers correlate with shorter overall and disease-free survival. These are consistent with documented anti-melanoma effects of active forms of vitamin D in experimental models. In addition, an inverse correlation has been found between the levels of expression of retinoic acid orphan receptors (ROR)α and RORβ, which are newly discovered targets of vitamin D, and melanoma progression and disease outcome. In conclusion, defects in vitamin D activation and signaling, and the activities of the corresponding receptors can affect melanoma progression and the natural history of the disease. Thus, optimal vitamin D status and signaling might attenuate malignant behavior of melanoma.

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OP No. 33
ON THE REGULATION OF THE BRAIN AND ENDOCRINE SYSTEMS BY ULTRAVIOLET RADIATION: SPECIAL FOCUS ON THE HPA AXIS

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Ultraviolet radiation (UVR), which includes UVB (λ=280-320 nm) and UVA (λ=320-400 nm) which reach the surface of the Earth, represents a major skin stressor in humans. UVR is not only an etiological factor for different skin pathologies, including but not limited to premature skin aging, solar keratosis, skin cancer and local pathological immune responses, but can also have systemic effects. These effects are secondary to the UVR action on the cutaneous neuro-endocrine system defined by its wavelength and an interaction with local chromophores, predominantly in the case of UVB. A cutaneous neuro-endocrine system not only senses and counteracts the UVR stressor to maintain skin homeostasis, but also communicates with the nervous, endocrine and immune systems to affect body homeostasis. A classic example of such communication is that through vitamin D, produced through photochemical transformation of 7-dehydrocholesterol, which after enzymatic activation not only regulates skin functions, including photoprotection, but also has important systemic effects. Other cutaneous factors affected by UVR are cytokines, corticotropin-releasing factor, urocortin, proopiomelanocortin (POMC) peptides, enkephalins and other hormones that can act on the site to regulate the local hypothalamic-pituitary-adrenal (HPA) axis or be released into systemic circulation to have systemic immune and endocrine effects. In conclusion, these factors can activate the central HPA, or have opioidogenic and immunosuppressive effects. In addition, neural and humoral signals induced by UVR in the skin can lead to the activation of the paraventricular and arcuate nuclei. Furthermore, changes in spleen activities after exposure of the skin to UVB can be very rapid, implicating the brain in these effects. Therefore, our future goal is to define the most optimal schedules for UVR therapy of autoimmune disorders, addiction and obesity.

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OP No. 28
UVB IRRADIATION AND VITAMIN D IN CHRONIC KIDNEY DISEASE

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Background/Aim: The hormonally active metabolite 1,25-dihydroxyvitamin D [1,25$(OH)_2D_3$] is physiologically produced in the kidneys. Patients with chronic kidney disease are often vitamin D-deficient. The skin has not only the capacity to produce vitamin D_3 but also the enzymatic machinery to convert it to 1,25$(OH)_2D_3$. Patients and Methods: Two groups of hemodialysis patients were exposed to whole-body or partial-body suberythemal UVB radiation three times a week for 14 weeks. Serum levels of vitamin D were determined. *Results:* In patients who received partial-body irradiation (anterior of legs only), 25$(OH)D_3$ increased from 127 to 174 nmol/l and 1,25$(OH)_2D_3$ from 25 to 47.5 pmol/l. After whole-body UVB irradiation, there was a statistically significant increase in circulating levels of vitamin D_3 from 6 to 25 nmol/l, 25$(OH)D_3$ from 109 to 214 nmol/l, and 1,25$(OH)_2D_3$ from 50 to 86 pmol/l. Moreover, after whole-body irradiation, the physical capacity (W/kg bodyweight) increased by 5% and maximum oxygen consumption by 12%; the maximum heart rate decreased by 30% and maximum systolic blood pressure by 7%. After 3.5 months observation, in those treated with whole-body UVB irradiation, the trabecular bone density decreased by only 3.5% compared to an 11% decline in the non-irradiated control group. Skin biopsies (of three patients) showed gene expression of vitamin D receptor (VDR) 1 alpha-hydroxylase and 25-hydroxylase. *Conclusion:* Whole-body and partial-body exposure to suberythemal UVB radiation was effective in improving serum levels of all vitamin D forms, and in having a positive influence on bone mineral density, physical capacity and cardiac health.

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OP No. 42
APPLICABILITY OF CRITERIA FOR CAUSALITY TO SUNBED USE AND MELANOMA

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In 2009, the International Agency for Research on Cancer, an agency of the World Health Organization, classified ultraviolet-emitting tanning devices as 'carcinogenic to humans' (1). In 2016, the European Commission's Scientific

Committee on Health, Environmental and Emerging Risks (SCHEER) published its "Opinion on Biological effects of ultraviolet radiation relevant to health with particular reference to sunbeds for cosmetic purpose" (2). This document recognized that using sunbeds: (i) "Causes cutaneous melanoma and squamous cell carcinoma at all ages" especially when first exposure occurs in youth; (ii) "increases the risk of basal cell carcinoma and ocular melanoma"; and (iii) is not justifiable for inducing vitamin D production because its benefits are "outweighed by the adverse effects" and "alternative sources of vitamin D are readily available". The purpose of this review was to apply Hill's epidemiological criteria for causality and respond to scepticism on the impact of sunbed use on melanoma risk in light of the most recently published evidence. We reviewed recent studies on age at first sunbed exposure and melanoma risk, also considering the effect at different body sites and the development of additional primary melanomas. The new evidence on the strength, dose response, and temporality of the association supports the application of the criteria for causality to the relationship between sunbed use and melanoma.

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OP No. 31

PHOTOTHERAPY WITH ULTRAVIOLET LIGHT IN DERMATOLOGY: UPDATE AND OUTLOOK

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Ultraviolet (UV) light exerts both deleterious and beneficial effects on human skin. The former includes the elicitation of a broad range of UV-induced or UV-aggravated skin diseases, photoaging and photocarcinogenesis, and the latter the therapeutic use of UV light (phototherapy) to improve or clear inflammatory skin conditions and the formation of vitamin D in the skin. Phototherapy is often used as an umbrella term and encompasses different modalities such as UVB [nowadays mostly considered as narrow-band UVB (310-315 nm)] and UVA phototherapy (in particular, UVA1, 340-400 nm), and photochemotherapy (administration of psoralens and subsequent irradiation with UVA, also termed PUVA). Phototherapies can be used for a wide range of dermatological disorders due to their pleiotropic effects on various constituents of human skin. UV and PUVA down-regulate inflammatory processes and are therefore beneficial in the treatment of numerous inflammatory skin diseases, *e.g.* psoriasis, eczema and lichen planus. They also potently stimulate melanocyte proliferation, migration and activity which contributes to their therapeutic effect in vitiligo. Finally, UVA and PUVA improve sclerosing skin disorders by inducing matrix metalloproteinase expression in human dermal fibroblasts. Phototherapies have a rapid onset of action, high therapeutic efficacy and a favorable benefit/risk ratio at moderate treatment costs. The major long-term risk of phototherapies is their potential to promote skin cancer, in particular, non-melanoma skin cancer. Phototherapies are challenged by an ever-increasing number of high-priced and widely promoted medications such as biological agents and new small molecules that compete for the same indications. The choice of treatment ultimately depends on carefully weighing up efficacy and safety against individual factors such as the patient's general health status and treatment preference and, last but not least, treatment-related costs incurred by the health system.

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OP No. 16

THE CASE FOR PALEOLITHIC 25-HYDROXYVITAMIN D LEVELS AS BEING OPTIMAL FOR MODERN-DAY HUMANS

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The biology of humans is best suited for life in the tropics. Fitness of a species to an environment is achieved through natural selection. The environmental stress of diminished ultraviolet (UV) light for northward-migrating humans forced biological compromises to permit fitness in the evolutionary sense, *i.e.* to maximize the number of viable births. The most obvious adaptation was whiter skin to allow enough UVB penetration to generate vitamin D, and hence to prevent rickets and cephalo-pelvic disproportion. Modern levels of vitamin D nutrition [serum 25(OH)D] achieve the minimum to prevent rickets. That may not suffice for all its health benefits. Normal paleolithic 25(OH)D levels exceeded 100 nmol/l, as do all

25(OH)D levels measured in healthy primates. These levels are double what is 'normal' for modern Europeans. Bone biology changed for north-migrating adults in order to stiffen bone of the pelvis, but it increased the risk of osteoporosis. Clinical trials of vitamin D in elderly people in regard to osteoporosis show fracture prevention with 800 IU/day. However, clinical trials of primary prevention of disease events have been equivocal. Therapeutic trials that used doses of vitamin D of at least 4,000 IU/day produced 25(OH)D>100 nmol/l, and those showed benefit for patients with prostate cancer and multiple sclerosis. Epidemiological trends consistently show that the highest quartile of serum 25(OH)D (>75 nmol/l) relates to the lowest disease risk and best health outcomes, as do the findings on higher sun exposure and health. Optimal serum 25(OH)D should exceed 75 nmol/I (30 ng/mI). In order for the level to exceed 75 nmol/I in everyone, an average 25(OH)D would be about 100 nmol/l – a value similar to those of paleolithic populations.

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OP No. 12

IS PRACTICAL EXPOSURE TO UV RADIATION A VIABLE SOURCE OF VITAMIN D, OR A REASON TO TAKE A SUPPLEMENT?

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Exposure to solar UV radiation has long been linked with public health issues, most prominently with sunburn and skin cancer (risk), while more recently, the association with vitamin D synthesis (established benefit) has gained increasing support. The ability to balance UV benefit and risk depends on location (climate), skin type and behavior, the latter determined by culture, employment and personal choice. Alternatively, vitamin D can be acquired by ingestion where sun exposure is insufficient to meet vitamin D needs. Previous work has shown how the risk/benefit balance for UV exposure can be achieved in the U.K. (and similar) climate (1, 2). That is, vitamin D needs can be met without risk of sunburn. Although exposure times are short, at least for a white-skinned population, there is a requirement to expose sufficient unprotected skin in the warmest months of the year (more than simply hands and face). Thus, while our solution to acquiring vitamin D needs through sun exposure sounds simple, we ask whether it is pragmatic with modern lifestyles, working practices and multicultural population. Analysis of a series of longitudinal observation studies provides a picture of how closely different sectors of the population by age (12-15 years, 20-60 years, ≥65 years) and ethnicity (White Caucasian, South Asian) meet our exposure guidelines, and how that affects their seasonal vitamin D status. Modern diets are generally low in vitamin D, and there is little food fortification in northern Europe. Therefore, supplementation becomes the most efficient way to provide vitamin D through ingestion. We show how UV climatology can be used to inform the public about the potential need for vitamin D supplementation across the U.K.

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OP No. 5

THE CALCIUM-SELECTIVE CATION CHANNEL TRPV6: LEARNING FROM BATS

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Transient receptor potential cation channel subfamily V6 (TRPV6) is a calcium-selective ion channel which is expressed in humans in a restricted number of tissues including exocrine pancreas, salivary and lacrimal gland and in placenta (1). In placenta, TRPV6 is involved in calcium transport and mutations of the human TRPV6 gene underlie forms of transient neonatal hyperparathyroidism (2, 3). Overall, in healthy human tissue, *TRPV6* transcript expression and TRPV6 protein abundance is very low, whereas in some human malignancies derived from prostate, mammary, ovarian as well as endometrial tissues, *TRPV6* transcripts are highly expressed and may represent a marker for disease progression (1) or even a target to combat disease progression. We compared the TRPV6 transcription/translation in humans and bats and came up with a new strategy for the treatment of TRPV6-positive malignancies.

1 Fecher-Trost C, Weissgerber P and Wissenbach U: TRPV6 Channels. In: Handbook of Experimental Pharmacology. Nilius B and Flockerzi V (eds.). Berlin, Springer *222*: 359-384, 2014.

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neonatal hyperparathyroidism. J Endoc Soc *3*: 602-606, 2019. PMID: 30820485. DOI: 10.1210/js.2018-00374

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OP No. 13

HOW TO IMPROVE PHOTOPROTECTION WITHOUT COMPROMISING VITAMIN D FORMATION

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Photoprotection is recommended to avoid sunburn and skin cancer. Several approaches can be used - alone or in combination. These are: Stay out of the midday sun, seek shade, and use photoprotection with clothes, hat, sunglasses, or sunscreen. Sunscreen use is the most popular protective method but is associated with pitfalls. To function properly, sunscreen must be distributed evenly all over the body and in sufficient amounts (about 35 g). In practice, too little is used, often about one-third to one-fourth of the amount used when determining the sun protection factor (SPF). Several studies have shown that this will reduce the actual SPF exponentially, which means to very low levels. Another problem is that sunscreens are not evenly distributed by the users and 20% of the body area is left unprotected after one application. Yet another concern is that many people do not apply sunscreen before exposing themselves to the sun but wait until they have already spent some time in the sun unprotected. "Use a handful of sunscreen" has been introduced as a rule-of-thumb and may increase the amount used somewhat, but this advice does not solve the issue of unprotected skin areas. We have introduced the following advice: Apply sunscreen twice before exposure to the sun. This reduces the uncovered body area to 9% and increases the amount of sunscreen used to the advisable level, except for the skin on the back and on the back of the legs. Laboratory investigations have shown that the thicker the sunscreen layer, the less vitamin D is formed, not taking into account the real-life uneven thickness of the layer and uncovered skin areas. Even with optimal sunscreen coverage (2 mg/cm^2) on a sunny vacation in Tenerife, the vitamin D level is still adequately increased. Levels of vitamin D obtainable in parts of the world with lower average UV radiation are elaborated on.

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OP No. 32

EFFECTIVE PHOTODYNAMIC THERAPY OF ACTINIC KERATOSES WITHOUT PAIN AND WITH MINIMAL INFLAMMATION

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When photodynamic therapy (PDT) of actinic keratosis with 5-aminolevulinic acid (ALA) or its ester methyl aminolevulinate (MAL) was introduced into the clinic, it was associated with severe pain during pretreatment with curettage of the skin, especially during illumination. After treatment, severe skin inflammation was expected as PDT efficacy was dependent on the phototoxic reaction due to activation of protoporphyrin IX (PpIX) by red light. Conventional PDT allows PpIX to accumulate to high levels before illumination with high-intensity red light. Speculation arose as to whether continuous activation of PpIX during its formation, thereby preventing its accumulation, might be an alternative. If so, pain associated with the treatment might possibly be avoided. Continuous activation can be performed using artificial light sources with specific spectra or daylight with continuous spectrum in visible light. PpIX has several absorption peaks in the visible light spectral range that can absorb light and activate it. We have performed several studies demonstrating that, without compromising efficacy, continuous activation of PpIX is practically painless when started 30 min after MAL application at the time when PpIX begins to form. As daylight is a practical and cheap light source and can be used at home, it also prevents crowded clinics. Large studies from Europe and Australia have confirmed the efficacy of daylight PDT, that it is painless, and that inflammation associated with the treatment is reduced.

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OP No. 25

VITAMIN D AND CARDIOVASCULAR DISEASE

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In the clinical setting, high daily or bolus doses of vitamin D are often administered without clear indication, solely based on vitamin D testing, *i.e.* quantification of circulating 25-hydroxyvitamin D [25(OH)D]. This updated narrative review summarizes the evidence of the effect of vitamin D on cardiovascular disease (CVD). Meta-analyses

of randomized controlled trials (RCTs) have demonstrated that biochemical CVD risk markers, such as lipid parameters and inflammation markers as well as clinical surrogate parameters of CVD risk, such as blood pressure and arterial stiffness, are largely unaffected by vitamin D supplementation. Similar results have been obtained regarding CVD events and mortality from earlier meta-analyses of RCTs and from recent large RCTs with CVD outcomes as the primary endpoint, even in subgroups with circulating 25(OH)D concentrations <50 nmol/l. Likewise, Mendelian randomization studies have indicated that genetically lowering the 25(OH)D concentration does not increase CVD risk, whereas the effect of vitamin D receptor polymorphisms on CVD risk is unclear at present. Some studies do not exclude the possibility of adverse vitamin D effects, such as elevated plasma calcium concentration and an increased CVD risk at a serum 25(OH)D concentration >125 nmol/l. Based on the present data and a conservative benefit–risk management approach, vitamin D doses beyond the nutritionally recommended amounts of 600 to 800 IE daily currently cannot be advised.

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OP No. 14

VITAMIN D INTAKE, BODY WEIGHT AND VITAMIN D STATUS: AN UPDATE

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It is well-known that the increment in circulating 25-hydroxyvitamin D [25(OH)D] following vitamin D supplementation is influenced by body weight. However, compared with normal-weight adults, body weight or body composition is altered in several groups of individuals, such as children and adolescents, pregnant women, obese people, and patients with chronic kidney disease. For these groups, little is known about the effect of vitamin D dose per kilogram of body weight on incremental 25(OH)D. To close the gap in present knowledge, a systematic review of randomized, controlled intervention trials on vitamin D was therefore performed and results are presented. Data are shown as weighted mean differences. Summary estimates of increments in circulating 25(OH)D are illustrated for each group separately. Moreover, calculated daily vitamin D doses for achieving a target 25(OH)D level of 50 and 75 nmol/l in vitamin D-deficient individuals [*i.e.* those with 25(OH)D<30 nmol/l] are presented. The nutritional, clinical, and toxicological relevance of the findings is discussed.

Posters (P)

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P No. 1

ASSOCIATION OF VITAMIN D RECEPTOR GENE POLYMORPHISMS WITH MELANOMA RISK: A META-ANALYSIS AND SYSTEMATIC REVIEW

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Background: Increasing evidence indicates a relevance of the vitamin D endocrine system for pathogenesis of malignant melanoma. Aim: A systematic review and meta-analysis were performed to investigate the association between vitamin D receptor gene polymorphisms and melanoma risk. *Materials and Methods:* A comprehensive literature search of Medline and ISI Web of Science was conducted. A total of 14 studies were included in the meta-analysis. The comparison included seven polymorphisms of vitamin D receptor gene: rs2228570 (*Fok*I), rs731236 (*Taq*I), rs1544410 (*Bsm*I), rs4516035 (A-1012G), rs11568820 (*Cdx*2), rs7975232 (*Apa*I) and rs739837 (*Bg*lI). In the statistical analysis, odds ratios and 95% confidence intervals were calculated for the dominant and recessive models and the results were illustrated in Forest plots. Publication bias was tested using funnel plots and the Egger test. *Results:* Our meta-analysis showed a significant risk reduction of 15% in malignant melanoma incidence associated with the rarer B allele in the dominant model for rs1544410 (*Bsm*I) (*Bb + BB vs. bb*). The dominant model (*Ff + ff vs. FF*) of the rs2228570 (*Fok*I) polymorphism showed that carriers of the rarer f allele were 22% more likely to develop malignant melanoma. For the rs7975232 (ApaI) polymorphism, a 20% higher risk of melanoma was found for carriers of the rarer a allele (*Aa + aa vs. AA*). The results of the meta-analysis revealed no significant association for the other polymorphisms which were investigated. *Conclusion:* The FokI, ApaI and BsmI variants may influence susceptibility to developing melanoma. There is an increased risk of developing malignant melanoma for carriers of the rarer f allele of rs2228570 (*Fok*I) and the rarer a allele of rs7975232 (*Apa*I) polymorphism. In contrast, the less common B allele of the rs1544410 (*Bsm*I) polymorphism has a protective effect and thus a lower disease risk.

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P No. 2
VITAMIN D STATUS AND ALOPECIA AREATA – A META-ANALYSIS

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Background: Recent laboratory and clinical investigations indicate an important role of the vitamin D status in the human immune system in health and disease. Only limited data are available for the impact of the vitamin D status on alopecia areata, a widespread autoimmune disease of the hair follicle that is characterized by a multifactorial and only partly understood pathogenesis. Aim: To perform a meta-analysis to investigate the impact of the vitamin D status on alopecia areata in humans. *Materials and Methods:* A literature search was performed on PubMed, Google Scholar, Cochrane Library, and Web of Science, and analysis was performed using Stats Direct 3.0.150. The quality of all studies identified was assessed using a modified Newcastle-Ottawa Scale (NOS). The meta-analysis in patients with alopecia areata (cases) and controls was performed in three separate parts: (i) the difference in serum 25-hydroxyvitamin D values, (ii) the incidence of serum 25-hydroxyvitamin D values <20 ng/ml, and (iii) the incidence of serum 25-hydroxyvitamin D values <30 ng/ml. *Results:* No interventional or cohort studies were identified and a total of 15 case–control studies were included. The analysis of serum 25-hydroxyvitamin D values (11 studies, 916 cases) revealed a mean difference of 10.09 ng/ml [95% confidence intervaI (CI)=6.87-13.31 ng/mI, $p<0.0001$]. The analysis of vitamin D status showed a concentration <20 ng/ml (six studies, 744 cases) had an odds ratio of 7.66 (95%CI=1.91, 30.73, $p=0.0041$), while a vitamin D status <30 ng/ml (six studies, 471 cases) had an odds ratio of 2.69 (95%CI=0.51-14.29, $p=0.2446$). *Conclusion:* Serum 25-hydroxyvitamin D concentration was markedly reduced in patients with alopecia areata as compared with controls. However, because of limitations of the studies included, including the lack of interventional studies and difficulties in adjusting for confounding factors, our results do not allow any conclusions to be drawn on a causal relationship between vitamin D status and alopecia areata risk. In order to answer question whether the serum 25-hydroxyvitamin D concentration has an impact on risk of alopecia areata or on the clinical outcome of this disease, large-scale prospective interventional studies in particular are still required.

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P No. 3
CROSS-TALK OF VITAMIN D AND P53 SIGNALING PATHWAYS IN A CELL CULTURE MODEL FOR ANALYSIS OF NON-MELANOMA SKIN CANCER

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Background/Aim: Photo-protective effects of vitamin D compounds have been shown, *e.g.* a reduced number of pyrimidine dimers following ultraviolet B irradiation of $1,25(OH)_2D_3$-treated skin cells as compared to untreated cells. Recently, we identified cross-talk between vitamin D and p53 signaling pathways, whose functional significance we now further characterized in a cell culture model designed to investigate the photo-carcinogenesis of non-melanoma skin cancer. *Materials and Methods:* Firstly, RNA and protein expression of members of these two tumor-suppressor pathways were characterized in cultured primary normal human epidermal keratinocytes (NHEKs; functionally intact p53 protein), spontaneously immortalized HaCaT keratinocytes (mutated p53 protein), and in a cutaneous squamous carcinoma cell line (SCL-1; lack of p53 protein), with and without UVB and $1,25(OH)_2D_3$ treatment. *Results:* Interestingly, using quantitative real-time-polymerase chain reaction, Ct values for TA*p53*, δN*p63* and jagged 1 (*JAG1*) following UVB irradiation of $1,25(OH)_2D_3$-treated NHEKs decreased as compared to untreated NHEKs. On the protein level, treatment of keratinocytes with increasing doses of UVB resulted in a decrease of δNp63 protein, which was delayed in NHEKs as compared to HaCaT cells. Both treatment with $1,25(OH)_2D_3$ and with UVB modulated the expression profile of microRNAs. Additionally, the amount of UVB-induced thymine dimers was reduced in $1,25(OH)_2D_3$-treated as compared with untreated cells, with slight differences between NHEKs, HaCaT, and SCL-1 cells. *Conclusion:* Results of this pilot study underline the functional significance of p53 and vitamin D signaling pathways for photo-carcinogenesis of non-melanoma skin cancer.

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P No. 4
SERUM CONCENTRATION OF VITAMIN D METABOLITES FOLLOWING NARROW-BAND UVB PHOTOTHERAPY: A PROSPECTIVE PILOT STUDY ON HEALTHY VOLUNTEERS

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Background: The skin represents a key tissue for the human body's vitamin D endocrine system, being both the site of UVB-induced vitamin D production (approximately 90% of requirement for vitamin D has to be synthesized in the skin through the action of UVB radiation) and a target tissue for biologically active vitamin D metabolites. While it is accepted that vitamin D deficiency, defined as low serum concentrations of 25(OH)D, represents a major health issue, little is known about the production and physiological relevance of other vitamin D metabolites present in skin, including $24,25(OH)_2D_3$, $20(OH)D_3$ and 3-epi-25-OH-VitD_3. *Materials and Methods:* In this prospective pilot study, we investigated the effect of narrow-band UVB (UVBnb, 311 nm) phototherapy (five times/week for 2 weeks) on serum concentrations of $25(OH)D_3$, $24,25(OH)_2D_3$, $1,25(OH)_2D_3$, $1,25\text{-}(OH)_2D_2$, $20(OH)D_3$ and 3-epi-$25(OH)D_3$ in healthy volunteers. *Results:* Two weeks of UVBnb treatment resulted in an increase of serum $25(OH)D_3$ concentration that was associated with marked changes in the serum concentration of other vitamin D metabolites, as well as with other parameters (including blood pressure) analyzed. In conclusion, we were able to characterize a 'fingerprint' of vitamin D metabolites in the serum following UVBnb phototherapy in healthy volunteers.

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P No. 5

VITAMIN D ENDOCRINE SYSTEM, SKIN PIGMENTATION AND EVOLUTION: ASSOCIATION OF VITAMIN D STATUS WITH SINGLE NUCLEOTIDE POLYMORPHISMS OF GENES INVOLVED IN SKIN PIGMENTATION

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Background/Aim: Skin type and other Individual factors that influence an individual's serum 25(OH)D concentration have been identified, but little is known about genetic determinants of their vitamin D status. We analyzed whether single nucleotide polymorphisms of genes (SNPs) involved in skin pigmentation are associated with serum 25(OH)D levels. *Materials and Methods:* Serum 25(OH)D and SNPs (n=960) of genes involved in skin pigmentation were examined in a large cohort (blood samples, participants of the LURIC study, n=2,970). *Results:* A total of 46 SNPs were associated ($p<0.05$) with relatively lower or higher serum 25(OH)D level as compared to the complete cohort (median: 15.5 ng/ml). After correction for multiple comparisons (false discover rate, FDR), one SNP in the exocyst complex (*EXOC*) gene was found to be significantly associated with vitamin D status, reaching a Δ25(OH)D value of >5.00 ng/ml. Eleven SNPs located in genes encoding for endothelin 1 (*EDN1*) (n=3), tyrosinase (TYR) (n=4), tyrosinase-related protein 1 (*TYRP1*) (n=1), protein kinase cathelicidin antimicrobial peptide-activated catalytic subunit gamma (*PRKACG*) (n=1), and microophthalmia-associated transcription factor (*MITF*) (n=2) were also significantly associated with vitamin D status after FDR correction, but did not reach a Δ25(OH)D value of >5.00 ng/ml. *Conclusion:* Variants of genes involved in skin pigmentation are associated with vitamin D status in the Caucasian population.

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P No. 6

RANDOMIZED CONTROLLED PILOT STUDY ON THE EFFECTIVENESS OF AND TOLERANCE TO MILD WHOLE-BODY HYPERTHERMIA FOR PATIENTS WITH IRRITABLE BOWEL SYNDROME

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Background: Mild whole-body hyperthermia (WBH) is widely used in particular for the treatment of musculoskeletal disorders, with there being little experience in internal diseases. Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract. The current diagnostic standard uses Rom-III criteria. In this study, mild WBH, achieved using water-filtered infrared-A (wIRA) irradiation, was evaluated in patients

with IBS. *Materials and Methods:* This was a randomized controlled pilot study in a waiting group design. Effectiveness of and tolerance to WBH were to be examined for patients with Rom-III criteria for moderate to severe IBS. Twenty-four patients (both sexes, aged 18 to 65 years) were to be randomized and to received six ambulatory wIRA irradiation treatments with mild to moderate temperature guidance (core body temperature >38.0°C) offered at weekly intervals. The main outcome parameter was the Irritable Bowel Syndrome-Severity Scoring System (IBS-SSS) score and secondary outcome a modified Nepean Dyspepsia Index (NDI), both measured at baseline (V0) and 1 week after the last therapy (V1), respectively, at week 6 of waiting, and at 3 months after V1 (V2). Patients of the waiting group were offered the same treatment after V1. *Results:* A total of 52 patients were screened. Twenty-four (21 females and three males) were randomized: 11 for treatment, and 13 for the waiting group. Eighteen patients (nine in each group) completed the trial as per protocol. Six patients discontinued the trial (two in the treatment group: heat intolerance in one, and non-compliance in another; four in the waiting group: non-compliance in one, acute illness not related to gastrointestinal tract in two, start of pregnancy in one). At V0 and V1, the mean IBS-SSS sum scores for the treatment group were 293 (range=181-382) and 163 (range=122-208), respectively (p=0.004 non-parametric Wilcoxon signed-rank test). The waiting group had mean IBS-SSS score of 293 (range=182-330) and 310 (range=178-430), respectively (p=0.374). Pain intensity, flatulence, and quality of life showed the greatest improvements. At V2, the treatment group showed a slight rebound to 263. Improvement in symptomatology between V0 and V1 was also shown by a modified NDI. Nine out of 13 patients of the waiting group voluntarily started treatment after V1. At V2, they also presented an improved mean IBS-SSS score of 234. *Conclusion:* In this pilot study on a new indication for WBH and with only six mild to moderate treatments, significant and clinically relevant acute improvements in IBS symptoms were observed with no effect for waiting. Better sustainability might be achieved by longer series or repetition of treatments.

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P No. 7
IMPACT OF VITAMIN D AND ITS ANALOGUES ON ALZHEIMER'S DISEASE

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Received April 24, 2019
Revised May 22, 2019
Accepted May 23, 2019

Background/Aim: Alzheimer's disease (AD) is the most common neurodegenerative disease. One of its major pathological hallmarks is an increased extracellular plaque load in the brain, mainly consisting of Amyloid beta (Aβ), a small hydrophobic peptide derived by sequential cleavage of the Amyloid Precursor Protein (APP). Several epidemiological studies suggest a tight link between a hypovitaminosis of the secosteroid vitamin D and AD. Besides a decreased vitamin D level in AD patients, the vitamin D metabolism, especially in the brain under pathological conditions like AD, remains unknown. Here we investigate the impact of vitamin D and analogues on the pathological mechanisms involved in AD and how vitamin D metabolism is changed under a pathological situation like AD. *Materials and Methods:* To elucidate whether vitamin D affects the molecular mechanisms leading to AD, we systematically investigated the effect of vitamin D_3 and its clinically used analogues and also vitamin D_2 analogues on APP processing in neuroblastoma cells under supraphysiological conditions. Results were confirmed *in vivo* in a mild hypovitaminosis mouse model. An AD dependent altered vitamin D metabolism focusing especially on the vitamin D receptor (VDR) was investigated in two independent cohorts of human *post mortem* brain (n>100). *Results:* All vitamin D_2 and D_3 analogues were able to decrease Aβ production and to increase Aβ degradation in neuroblastoma cell lines. In line, in vitamin D deficient mouse brain Aβ was increased accordingly. Breaking down the underlying mechanisms, we found that this effect is mediated especially by the β-secretase BACE 1 and the Aβ-degrading enzymes IDE or NEP. Moreover, the expression of several genes involved in pathways associated with AD is altered. Analyzing the vitamin D metabolism in AD revealed that both the vitamin D receptor (VDR) and the vitamin D metabolizing enzymes were increased in AD. A significant correlation of the VDR with the Braak stages was observed. *Conclusion:* Vitamin D metabolism plays a crucial role in AD. In mouse model and cell culture, vitamin D and their analogues were able to modulate Aβ homeostasis suggesting a mechanistical causative impact of vitamin D on AD relevant pathways.

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