Abstract Book

First World Conference on Ichthyosis

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Contacts: H. Traupe, Münster, Email: traupeh@mednet.uni-muenster.de
B. Willis, Münster, Email: brigitte.willis@ukmuenster.de
Barbara Kleinow, Email: abcr.kleinow@t-online.de
Geske Wehr, Email: diewehrs@t-online.de

Location:

Lecture Hall
Department of Dermatology
University Hospital
Von Esmarch-Str. 58
48149 Münster
Germany

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Abstract for the
First World Conference on Ichthyosis

Section: Ichthyoses and the cornified envelope

Author(s):	Karen M. Boeshans and Bijan **Ahvazi** From the X-ray Crystallography Facility/Office of Science and Technology, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892-8024;
Title:	Lamellar Ichthyosis: Mutational Insights from a Transglutaminase 1 Model
	The skin stratum corneum is an effective barrier for maintaining the internal milieu against the external environment. Malformation of the cell envelope (CE) at the cell periphery resulting from mutations of the transglutaminase 1 (TGase 1) gene is the cause of some cases of lamellar ichthyosis (LI). TGase 1 is an enzyme that cross-links proteins within the CE of mature keratinocytes. It is not yet clear how these mutations cause LI. A PubMed survey shows 34 TGase 1 missense mutation sites involved in LI. Not all of these mutations, however, result in loss of in vitro cross-linking ability. We suggest that some mutations cause a defect in binding to other proteins and/or to the correct anchoring of the enzyme to the cytoplasmic side of the plasma membrane. We have identified putative RGD and LVD motifs in TGase 1, which we propose serve to bind TGase 1 to a family of cell-adhesion molecules. Hypothesis: Mutations in TGase 1 may cause LI by either a direct or indirect loss of in vivo protein cross-linking activity. Indirect loss of cross-linking activity may be due to aberrant TGase 1/protein interactions, and/or to the prevention of correct binding of the enzyme to the plasma membrane.

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Section: Ichthyoses and the cornified envelope

Author(s):	K. **Aufenvenne,** T. Walker, V. Oji, H.C. Hennies, N. Seller, P. Bruckner, H. Traupe
Title:	Towards functional understanding of bathing suit ichthyosis
	Bathing suit ichthyosis (BSI) is described as striking and unique clinical subtype of transglutaminase-1 deficient lamellar ichthyosis (LI type 1) with large dark-grey or brownish scales restricted to the bathing suit areas. Recently, in a group of ten individuals of independent families we identified new mutations in the *TGM1* gene which differ from those which can be found in patients with generalized lamellar ichthyosis. Previous clinical analysis, atomic modelling and immunohistochemical studies suggest a temperature depending activity of the identified *TGM1* mutations in BSI patients. To further elucidate the molecular basis of this unusual phenotype we performed in situ mutagenesis studies and expressed eleven mutations in HEK 293 cells. Eight were only identified in BSI patients, three had previously been found in patients with generalized lamellar ichthyosis due to transglutaminase-1 deficiency. Wildtype TGase-1 served as a control. To analyse TGase-1 activity we performed a fluorimetric assay at different temperatures ranging from 21°C to 45°C. The presented data show that the recombinant proteins including BSI-mutations were less active than the wildtype protein and show a shift in temperature-optimum from 37°C/39°C to 31°C/33°C. We suggest that TGase-1 proteins including BSI-mutations in comparison to the wildtype TGase-1 show less thermal stability. By use of circulardicroism (CD)-spectroscopy with four selected mutations and the wildtype TGase-1 protein we want to elucidate the mechanism of temperature sensitivity. These investigations are currently in process.

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Section: Experimental therapies

Author(s):	J. **Chen**, D. Roop, Denver
Title:	Oligonucleotide therapy for keratin disorders
	A number of genodermatoses are caused by keratin gene mutations. Epidermolytic hyperkeratosis (EHK), also known as bullous congenital ichthyosiform erythroderma (BCIE), is a dominant form of ichthyosis caused by point mutations in keratin 1 or keratin 10. Using a "knock-in" approach, our laboratory successfully generated an inducible mouse model for EHK, which accurately mimicked this disease at both the genetic and clinical levels. This mouse model has not only provided insights into the mechanisms that cause various clinical presentations of this disease, it also serves as *in vivo* preclinical model to test novel therapeutic approaches for this disorder. Among several potential therapeutic strategies, selective suppression of expression of mutant keratins with RNAi has the advantages of high specificity, efficiency and potential trans-epidermal delivery capability. siRNA oligonucleotides were able to inhibit the expression level of mutant K10 transcripts in cell lines. Using a lentiviral system, we successfully delivered EHK-specific siRNA to primary keratinocytes. We are currently assessing whether infected keratinocytes isolated from EHK mice, which constitutively express the mutant K10-specific siRNA, will suppress the EHK phenotype when grafted onto nude mice.

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Section: Recent advances in gene mapping and in lipid genes

Author(s):	Judith **Fischer**, Paris
Title:	Mapping genes for (nonbullous) autosomal recessive congenital ichthyosis ARCI: What we know today
	Ichthyoses are severe congenital chronic skin diseases. Around 40 different forms of ichthyoses have been described to date, including autosomal dominant, autosomal recessive (ARCI) and X-linked forms. ARCI are clinical and genetically heterogeneous génodermatoses which can be classified in two groups: non-syndromic or primary ichthyoses; and syndromic ichthyoses which are associated with extracutaneous features. In non-syndromic recessive ichthyoses several localizations have been reported: LI1 (MIM 242300) on chromosome 14q11 (Russel et al, 1994); LI2 (MIM 601277) on chromosome 2q33-35 (Parmentier et al, 1996); LI3 (MIM 604777) on chromosome 19p12-q12 (Fischer et al, 2000); nonlamellar, nonerythrodermic congenital ichthyosis NNCI (MIM 604781) on chromosome 19p13.1-p13.2 (Virolainen et al 2000); LI5 (MIM 606545) also known as NCIE1 (MIM 242100) on chromosome 17p13 (Krebsova et al 2001) and on chromosome 5q33 (Lefèvre et al 2004). Six genes of these loci have been identified to date: transglutaminase 1 (*TGM1*) for LI1 (Huber et al, 1995; Russel et al, 1995) two lipoxygenases (*ALOXE3* and *ALOX12B*) for LI5/NCIE1 (Jobard et al, 2002) on chromosome 17 (MIM 606545), *ABCA12* for LI3 and the more severe harlequin ichthyosis (Lefèvre et al, 2003; Kelsell et al 2005, Akiyama M), *ichthyin* (Lefèvre et al 2004) on chromosome 5, and Cyp4F22 (Lefèvre et al, 2006) for LI3.

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Section: Molecular advances in epidermal differentiation

Author(s):	Karl-Heinz **Grzeschik,** Dorothea Bornholdt, Frank Oeffner, Arne König, María del Carmen Boente, Herbert Enders, Barbara Fritz, Michael Hertl, Ute Grasshoff, Katja Höfling, Vinzenz Oji, Mauro Paradisi, Christian Schuchardt, Zsuzsanna Szalai, Gianluca Tadini, Heiko Traupe, Rudolf Happle
Title:	Deficiency of PORCN, a regulator of Wnt signaling, causes focal dermal hypoplasia
	Focal dermal hypoplasia (FDH, Goltz syndrome, MIM 305600) is an X-linked dominant, male-lethal, multisystem birth defect affecting tissues of ectodermal and mesodermal origin. The phenotype is characterized by widespread lesions of dermal hypoplasia or even aplasia that may give rise to herniation of the underlying fatty tissue. These erythematous, hyperpigmented or yellowish skin changes tend to be arranged along the lines of Blaschko, suggesting mosaicism. Another major diagnostic sign noted on X-rays is longitudinal striation of the long bones, likewise hinting to functional mosaicism. Associated features include patchy or linear areas of hairlessness, periorificial papillomas, hypoplasia or aplasia of bones resulting in asymmetric appearance of the face and the body, syndactyly, coloboma, and microphthalmia or unilateral anophthalmia. In addition, hypodontia or oligodontia, hypoplasia of the enamel, hearing loss, myelomeningocele, bifid ureter, horseshoe kidney, omphalocele or papillomatosis of the larynx may be found. Using a stepwise, generally applicable approach employing i) genetic mapping of FDH in rare familial cases, ii) comparative genome hybridization on custom made high resolution arrays (HR-CGH) to search sporadic cases for small deletions in candidate chromosome areas associated with this Mendelian trait, iii) point mutation analysis in genes highlighted by overlapping deletions, we identify *PORCN*, located in Xp11.23, as the gene mutated in FDH. Focusing CGH by independent methods such as genetic mapping eliminates ambiguities which might arise from the wealth of copy number variants in the human genome unrelated to the phenotype under study. Contiguous gene deletions or stop mutations affecting *PORCN* result in loss of function of this putative O-acyltransferase, crucial for cellular export of WNT signaling proteins. Hence, FDH is a human developmental disease caused by a defect in WNT signal production. The defect is detectable at cellular level. Extreme skewing of X-inactivation or postzygotic mosaicism reduces the deleterious effect of mutations in female patients. Due to the severity of the PORCN-defect in cells with active mutant X-chromosome, effects of missing nehgbouring genes in contiguous deletions are covered by epistasis.

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Section: Molecular advances in epidermal differentiation

Author(s):	Eve Toulza, Nicolas Mattiuzzo, Marie-Florence Galliano, Nathalie Jonca, Carole Dossat, Daniel Jacob, Antoine de Daruvar, Patrick Wincker, Guy Serre and Marina **Guerrin**
Title:	Granular keratinocyte transcriptome : identification and characterisation of new differentiation markers
	A large-scale analysis of the transcriptome of human granular keratinocytes purified from healthy epidermis is expected to contribute to the identification of genes important for barrier function. Purified granular keratinocytes obtained by iterative incubations of pieces of human epidermis with trypsin were used to generate mini-cDNA libraries using the ORESTES method. 22,585 expressed sequence tags (ESTs) were produced that matched 3,387 genes. The relative expression of 73 of them in the basal and granular layers was analysed by quantitative RT-PCR. Among these, 35 were identified as new, highly specific markers of granular keratinocytes. This work led to the characterization of the *DMKN* and *A2ML1* genes. We also identified a gene encoding a new protease as well as protease inhibitors. Moreover, we identified *LIPK*, *LIPM* and *LIPN*, three new lipase genes potentially encoding secreted products. These data increase the present knowledge of genes responsible for the formation of the skin barrier that might constitute new candidates for genodermatoses of unknown origin.

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Section: Proteases and keratinization disorders

Author(s):	Jean-Pierre **Hachem**
Title:	Importance of serine proteases for epidermal differentiation
	Disruption of the permeability barrier stimulates a repair response that leads to the restoration of barrier function. In addition to other family types of proteases, the stratum conreum (SC) contains a multitude of serine proteases (SP;), their inhibitors and cells of the stratum granulosum (SG) express the protease activated receptor (PAR2). Thus SC/SG could crosstalk through the activation of PAR2 enabling serine protease (SP) signaling within the viable layers of the epidermis. We addressed the role of SP/PAR2 signaling in both hairless and PAR2 knockout (ko) mice. We found that PAR2 activation/inhibition (i.e. ko animals and SP inhibitors treated mice) regulates epidermal barrier recovery and lamellar body secretion . Yet, the acute removal of the SC by tape stripping (TS), which increases SP/PAR2 activation, induces a rapid wave of cornification necessary for the formation of the newly lost corneocytes. Inhibition or absence of PAR2 delays the cornification phenomenon occurring after TS as assessed by TUNEL staining and caspase 14 activation. Therefore SP signaling through PAR2 plays a key role in acute barrier response to stress by the rapid delivery lamellar bodies to the SC and production of new corneocytes ensuring the integrity of the mortar and brick.

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Section: Recent advances in gene mapping and in lipid genes

Author(s):	Rudolf **Happle**, Marburg (Germany)
Title:	The CHILD syndrome revisited: the clinical perspective
	The acronym CHILD stands for Congenital Hypoplasia with Ichthyosiform nevus and Limb defects. A hallmark of this X-linked dominant, male-lethal phenotype is the CHILD nevus that shows several peculiar features. Ipsilateral extracutaneous involvement may affect the bones, lung, kidney, heart and brain. During the first months of life, x-rays may show epiphyseal stippling ("chondrodysplasia punctata"). - The inflammatory lesions of CHILD nevus may wax and wane and are covered with waxy, yellowish scales. The nevus either exclusively or predominantly involves one side of the body and shows two different patterns of distribution. In more severe cases there is a striking lateralization diffusely affecting one side of the body with a strict midline demarcation. This unique pattern of lyonization may tell us something about human embryogenesis. On the other hand, lesions may follow Blaschko's lines. Often both patterns are present and intermingled. Another clinical peculiarity of CHILD nevus is a marked affinity to the body folds (ptychotropism). Histopathological changes are reminiscent of psoriasis, but a distinguishing feature is the presence of foamy, lipid-laden histiocytes in the dermal papillae ("verruciform xanthoma"). On EM examination vesicular structures are noted in the horny layer. – In cases of CHILD syndrome, historical misdiagnoses include ILVEN, "epidermal nevus syndrome of Solomon", X-linked dominant chondrodysplasia punctata, psoriasis, or "verruciform xanthoma". Conversely, CHILD syndrome has erroneously been diagnosed in a case of unilateral Conradi-Hünermann-Happle syndrome. - Today, molecular analysis has clarified the following points: i) On rare occasions, female carriers may be found to be clinically healthy, which can be explained by extreme lyonization; ii) by way of exception, a bilateral, almost symmetrical involvement may be observed; iii) many affected women may show minimal involvement in the form of one dystrophic fingernail or a small inflammatory lesion measuring 3 cm only. In fact, numerous so-called sporadic occurrences can today be shown to represent familial cases, when a DNA analysis is performed in the allegedly "unaffected" mother.

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Section: Keratinization disorders and keratins

Author(s):	**Hausser**, Ingrid, Dermatology Department, University Clinic Heidelberg, Germany
Title:	Ultrastrastructure of keratin disorders: What do they have in common?
	All epithelial cells are equipped with a cell-type specific cytoskeleton network of intermediate filaments composed of the large group of keratins. In epidermal keratinocytes they are organized in thick bundles. The dynamic cytoskeleton scaffolding process during differentiation is supported by cell adhesion structures and modification as phosphory-lation. Directly gene-dependent ultrastructural markers of mostly domi-nant epidermal disorders related to main filament-forming keratins reveal a breakdown of the obviously indispensable scaffold that maintains cell and tissue integrity and provides mechanical strength to epithelia and especially epidermis. Examples are rupture or non-assembly of basal keratins (in epidermolysis bullosa simplex); pathognomonic aggregations and clumping of tonofilaments in basal layer (epidermoly-sis bullosa Dowling-Meara) or suprabasal layers (epidermolytic hyperkeratosis); unusual tubular tonofilament conformation (special type of palmoplantar keratoderma); pronounced cytolysis (ichthyosis bullosa Siemens); perinuclear shell formation of variable density (ichthyosis hystrix Curth-Macklin and congenital reticular ichthyosiform erythroderma). Monilethrix is the only hair shaft defect related to mutation in keratins identified so far. The consequences of disturbances in the highly differentiation-specific keratin cytoskeleton are tissue fragility and/or keratinization disorders with compensational hyperkeratosis.

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Section: Workshop on clinical diversity and diagnostic standardization

Author(s):	**Hausser**, Ingrid, Dermatology Department, University Clinic Heidelberg, Germany
Title:	Ultrastructural characterization of lamellar ichthyosis: a tool for diagnostic standardization
	Based on their peculiar and often highly specific ultrastructural features various types of keratinization disorders can be delineated as distinct nosological entities. Lamellar ichthyosis or ichthyosis congenita comprise a heterogeneous group of nonbullous conditions with congenital and generalized onset of scaling and hyperkeratosis. By systematic investigation of ultrastructural aberrations it was evident that heterogeneity is even larger than expected from the clinical features and light microscopic histopathology alone. Four subgroups of autosomal recessive lamellar ichthyosis display specific ultrastructural markers which in part already elucidated pathomechanistic pathways, for example malformation of the cornified cell envelope and disturbance of intercellular lipids in the stratum corneum. EM-type I is characterized by numerous lipid droplets within the lamellae of the hyperkeratotic horny layer; EM-type II by groups of polygonal clefts within the horny lamellae, representing remnants of cholesterol clefts; EM-type III by irregular vacuolic, vesicular and membraneous structures within the granular layer, potentially representing aberrant lamellar bodies; EM-type IV by lentiform swollen areas within the horny lamellae and perinuclearly with the granular layer containing masses of curved membranes. Substantial number of cases as well as rare cases of autosomal-domimant lamellar ichthyosis, however, show morphologically unspecific disturbance of cornification.

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Section: Recent advances in gene mapping and in lipid genes

Author(s):	**Hennies** HC, Eckl KM, Alef T, Kurtenbach J, Torres S, Nätebus M, Preil ML, Küster W, Traupe H, Haußer I, Metze D, Lestringant GG, Krieg P
Title:	Functional understanding of mutations in autosomal recessive congenital ichthyosis (ARCI)
	Ichthyosis is both clinically and genetically a highly heterogeneous phenotype. We have been following various approaches to investigate the genetic heterogeneity and to molecularly characterize the pathways involved. This has included two major approaches: the identification of further genes involved in disorders of keratiniziation and the characterization of the cellular mechanisms leading to the phenotype of ichthyosis caused by mutations in epidermal lipoxygenases. For the identification of new genes, we have concentrated on a syndromic form of ichthyosis also including follicular atrophoderma and hypotrichosis, which has been analysed in two consanguineous families by genome-wide homozygosity mapping. In order to further characterize the pathophysiology of ARCI, we have analysed the role of the epidermal lipoxygenase pathway. Mutations in *ALOX12B* and *ALOXE3* were expressed after site-directed mutagenesis, and mutant enzymes analysed in vitro. We have established 3D organotypic skin models (i.e., epidermis equivalents) to study the suprabasal layers including the stratum corneum. The analysis of the mutation spectrum in ARCI deals with the question of genotype/phenotype correlation in close collaboration with the clinical projects of the network for ichthyoses and related keratinization disorders. These approaches will further contribute to the understanding of epidermal differentiation and give us the chance for novel approaches into therapy.

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Section: Proteases and keratinisation disorders

Author(s):	Akemi **Ishida-Yamamoto**
Title:	Distinct intracellular transport of different epidermal lamellar body molecules
	Epidermal lamellar bodies (LBs) transport and secrete various molecules, including lipids, proteases, protease inhibitors and structural proteins. LBs begin to appear in the upper spinous layer of the epidermis and are most prominent in the granular cell layer. LBs collect at the apical surface of the upper granular cells, fuse with the cell membrane, and extrude their contents into the extracellular space. In my talk, I would like to review what we know about the transportation of LB-molecules and its relevance to ichthyosis. It is generally believed that LBs originate from the trans-Golgi network (TGN). Our previous studies have shown that each LB-molecule is synthesized sequentially and transported in distinct granules within tubulovesicular structures. Presently, very little is known regarding the post-Golgi trafficking routes of LBs. A member of the small GTPase Rab protein family Rab11 is found at high levels in recycling endosomes and is expressed in the epidermis. We have recently found that Rab11 is associated with the TGN and tubolovesicular structures carrying various LB-related molecules. This suggests that Rab11 plays a role in LB trafficking from the TGN to the plasma membrane. It also suggests that there is a close relationship between LBs and recycling endosomes. LB-related ichthyosis has been discovered recently. Abnormalities in LB cargoes result in severe skin diseases such as, Netherton syndrome and the *ichq* phenotype in mice. These are caused by decreased activities of LEKTI and cystatin M/E, respectively. Abnormal transportation and/or secretion of LBs cause ichthyosis seen in CEDNIK syndrome and in ARC syndrome.

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Section: Ichthyoses and the cornified envelope

Author(s):	W K **Jacyk**
Title:	Bathing Suit Ichthyosis, the South African experience
	Bathing suit Icthyosis(BSI) is a unique clinical variant of autosomal recessive congenital ichthyosis(ARCI), first described in South Africa in the 70's. Recently a group of 13 patients with this condition has been reported from Pretoria, South Africa. This particular form of ARCI has also been found in individuals of European and Morrocan descent. Herein the clinical and histopathological findings in 19 South African patients with BSI are presented. Genetic studies performed in the meantime in 8 South African cases included in this presentation disclosed a homozygous missense mutation, pR315L in transglutaminase 1. This particular mutation has not been found in the series of 10 patients with BSI recently reported by Oji et al.

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Section: Recent advances in gene mapping and in lipid genes

Author(s):	**König** A, Achatz B, Leveleki L, Bornholdt D, Happle R, Grzeschik K.-H.
Title:	Functional understanding of NSDHL mutations
	CHILD syndrome (Congenital Hemidysplasia with Ichthyosiform nevus and Limb Defects) is caused by mutations in the *NSDHL* gene at Xq28 (NADPH steroid dehydrogenase-like protein) encoding a 3-beta-hydroxysteroid dehydrogenase. This enzyme is involved in the post-squalene cholesterol biosynthesis, and in order to elucidate its pathogenetic role in CHILD syndrome the mutational spectrum has been analyzed in more than 30 affected patients. In addition, we performed complementation studies in yeast defective for ERG 26, homologous to NSDHL, using the human wild type or mutated enzyme. Thirdly, subcellular localization of human wild type NSDHL and mutants was investigated in localisation studies using transient transfection of COS-7-cells with GFP-*hNSDHL*-constructs. Results: Mutational analyses have revealed a broad spectrum of point mutations (nonsense and missense mutations) as well as deletions. So far, no genotype-phenotype correlation can be observed, i.e. point mutations at various regions of the gene are as fatal as large or complete deletions of the gene. Interestingly, missense mutations detected in CHILD patients do not affect domains required for enzyme function. However, complementation studies in yeast suggest dominant negative action of hNSDHL missense mutations, whereas the human wild type enzyme can complement the ERG 26 defect. On the subcellular level, wild type hNSDHL localizes on the endoplasmic reticulum and around lipid droplets known to be involved in cellular vesicle transport. Several missense mutations are shown to loose this capacity. Conclusion: Maldistribution of NSDHL may impair the vesicular transport or cholesterol biosynthesis even if the catalytic domains are not affected. Both phenomena could affect the sonic hedgehog-signaling pathway. This adds to the pathogenetic concept because i) epidermal differentiation is disturbed, as demonstrated by abnormal lipid vesicles in affected skin of CHILD patients and ii) defective hedgehog signalling during embryogenesis is likely to cause differential left-right involvement and limb and organ dysplasia.

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Section: Recent advances in gene mapping and lipid genes

Author(s):	Nikolas Epp[1], Silvia de Juanes[1], Gerhard Fürstenberger[1], Karsten Müller[1], Silvia de Juanes[1], Michael Leitges[2], Ingrid Hausser[3], Florian Thieme[4], Gerhard Liebisch[4], Gerd Schmitz[4], Hans –Jürgen Stark[5] and Peter **Krieg**[1] [1] Division of Genome Modifications and Carcinogenesis, German Cancer Research Center, D-69120 Heidelberg, Germany; [2]The Biotechnology Centre of Oslo, University of Oslo; N-0317 Oslo, Norway; [3]Dermatological Department, University Clinic, D-69115 Heidelberg, Germany; [4]Institute of Clinical Chemistry, University of Regensburg, D-93042 Regensburg, Germany; [5]Division of Genetics of Skin Carcinogenesis, German Cancer Research Center, D-69120 Heidelberg, Germany
Title:	12R-Lipoxygenase Deficiency impairs Skin Barrier Function
	12R-lipoxygenase (12R-LOX) and the epidermal LOX-3 (eLOX-3) are members of the epidermal subfamily of mammalian LOX and are preferentially expressed in human and mouse skin. Both enzymes are part of a novel eicosanoid pathway involved in terminal differentiation in skin. This view is supported by recent studies showing that inactivating mutations in 12R-LOX and eLOX-3 are linked to the development of autosomal recessive congenital ichthyosis (ARCI) a skin disease associated with hyperkeratosis and impaired barrier function. To analyse the impact of 12R-LOX in the establishment of the epidermal barrier and to investigate its physiological role we generated a 12R-LOX-deficient mouse model by using the Cre/LoxP system. Targeted inactivation of 12R-LOX in mice results in early neonatal death which is due to a severely impaired inwards and outwards permeability barrier function. Loss of barrier function occurs without alterations in proliferation and stratified organization of the keratinoyctes but is associated with ultrastructural anomalies in the upper granular layer suggesting perturbance of the assembly/extrusion of lamellar bodies. Cornified envelopes (CE) from skin of 12R-LOX-deficient mice show increased fragility. In addition, lipid analyses revealed an aberrant composition of CE bound lipids in 12R-LOX$^{-/-}$ mice, which are essential for normal barrier function. Furthermore, processing of profilaggrin to filaggrin is impaired indicating that both lipid metabolism as well as protein processing is affected by 12R-LOX deficiency. While neonatal 12R-LOX$^{-/-}$ mouse skin did not display an obvious clinical phenotype, transplanted 12R-LOX$^{-/-}$ mouse skin resembled that seen in ichthyosis, with epidermal hyperproliferation, acanthosis, hypergranulosis and marked hyperkeratosis. The data document a crucial role of 12R-LOX in the establishment of the epidermal barrier function. Moreover, 12R-LOX knockout mice may be a useful model for ARCI forms associated with an impaired LOX metabolism.

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Section: Workshop on clinical diversity and diagnostic standardization

Author(s):	D. **Metze**, Münster
Title:	Histopathology of ichthyoses: Clues for diagnostic standardization
	Ichthyoses are a heterogeneous group of genetic diseases that present with a generalized and permanent scaling with or without erythroderma. The histologic diagnosis of ichthyotic skin disorders is a problem since valid criteria have not been established so far. In a large series of ichthyotic skin disorders we could define major histologic patterns that reliably contribute to the diagnose. In addition, new histochemical and immunohistochemical tools substitute time consuming genetic investigations.

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Section: Workshop on clinical diversity and diagnostic standardization

Author(s):	V. **Oji** and H. Traupe, Münster
Title:	**How to classify ichthyosis in the future?**
	Ichthyoses form a heterogeneous group of genetically determined cornification disorders characterized by generalized scaling of the skin. Common types such as ichthyosis vulgaris and X-linked recessive ichthyosis manifest after birth. In contrast, rare congenital ichthyoses (CI) are diseases, which at birth typically present collodion membrane or ichthyosiform erythroderma. Syndromic ichthyoses exhibit a variety of associated non-cutaneous symptoms. Much progress on defining the molecular causes of ichthyoses has been made during the last 10 years. This success was recently highlighted by ichthyosis vulgaris, which really became - so to say - a “filaggrin-ichthyosis”, or in Harlequin ichthyosis, which is caused by nonsense mutations in *ABCA12*, yet certain missense mutation in this gene also underlie “lamellar ichthyosis type 2”. Interesting new molecular findings also concern the subgroup of congenital bullous types of ichthyoses” or “epidermolytic hyperkeratoses”. In the literature, e. g. in the OMIM database, some examples of an ichthyosis classification – in line with the “up-to-date” molecular findings – can be found. However, we are lacking a uniform consensus for a classification, which is useful from the clinical point of view and an easy nomenclature for the geneticist, e. g. it should be possible to include new disorders/gene entries into this classification in the future, yet respecting the mode of inheritance as well as the genotype/phenotype correlation. Distinct morphological signs such as “lamellar scaling” versus “ichthyosiform erythroderma” still provide important criteria for the clinician. We would like to propose a modified clinical and molecular ichthyosis classification, which should be discussed during the meeting, and then together would like to propose a consensus nomenclature, that can be used by the community. As a starting point for discussion we provide the following table, which first differentiates between “non-congenital” and “congenital” ichthyosis.

ICHTHYOSIS					
NON-CONGENITAL		**CONGENITAL**			
ISOLATED types	**SYNDROMES**	**ISOLATED types**			**SYNDROMES**
		AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSIS			
Ichthyosis vulgaris (IV)	Refsum syndrome (RS)	*ABCA12*	**ARCI 1a**	Harlequin ichthyosis (HI)	Dorfman Chanarin syndrome (DCS)
			ARCI 1b	erythrodermic lamellar ichthyosis (ELI)	
X-linked recessive ichthyosis (XRI)	multiple sulfatase deficiency (MSD)	*TGM1*	**ARCI 2a**	generalized lamellar ichthyosis (GLI)	Gaucher syndrome type 2 (GD2)
			ARCI 2b	bathing suit ichthyosis (BSI)	Netherton syndrome (NTS)
			ARCI 2c	self-healing collodion baby (SHBC)	Sjoegren Larsson syndrome (SLS)
		ALOXE3	**ARCI 3a**	congenital ichthyosiform erythroderma (CIE)	Trichothiodystrophy (TTD)
		ALOX12	**ARCI 3b**		Conradi-Hünermann-Happle syndrome (CDPX2)
		FLJ39501	**ARCI 4**	? (congenital ichthyosis with fine/focal scaling)	CHILD syndrome
		ichthyin	**ARCI 5**	congenital ichthyosiform erythroderma (CIE)	IFAP syndrome
		9q33-34	**ARCI 6**	ichthyosis prematurity disease (IPD)	
		BULLOUS ICHTHYOSIS = EHK			
		KRT1	**EHK 1a**	bullous ichthyosis with PPK	
			EHK 1b	ichthyosis hystrix Curth Macklin	
		KRT10	**EHK 2a**	bullous ichthyosis without PPK	
			EHK 2b	annular epidermolytic ichthyosis	
		KRT2A	**EHK *3***	ichthyosis bullosa of Siemens (IBS)	
		AUTOSOMAL DOMINANT LAMELLAR ICHTHYOSIS			
		LOR	**ADLI 1**	Loricrin keratoderma	
		?	**ADLI 2**	ADLI with PPK	

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Section: Recent advances in gene mapping and in lipid genes

Author(s):	Thomas A, **O'Toole** EA, Kelsell DP
Title:	In vitro models of harlequin ichthyosis
	Harlequin ichthyosis (HI) is the most severe form of autosomal recessive congenital ichthyosis. Using SNP chip technology and subsequent sequencing, we have previously shown that mutations in the ABCA12 [(ATP)-binding cassette transporter] gene underlie HI and to date over 50 patients analysed have mutations in this gene. Additionally complex mutations, such as a heterozygous whole exon deletion and a multiple exon duplication, have been identified via CGH oligo array and validated by multiplex PCR. The presence of these complex mutations shows the need for thorough investigation when considering pre-natal testing for HI. Our studies also show that there are ethnic-specific mutations in individuals of Pakistani, White British and Balkan origin. In order to elucidate the role of ABCA12 in epidermis, siRNA mediated knockdown was performed in keratinocytes. These cells were used to create 3D organotypic co-culture skin models that mirror many of the phenotypic changes observed in HI patient skin including abnormal lipid content and thickened epidermis. Evidence suggests ABCA12 is involved with lipid transport (Glucosylceramides) in the lamellar granule network of the skin. Additionally, our results from immunostaining experiments on HI skin and the organotypic skin model show that the programme of epidermal differentiation is severely impaired compared to control skin. Markers of late epidermal differentiation such as Keratin 2e, involucrin and transglutaminase appear in the lower and often basal layers of the skin suggesting loss of ABCA12 triggers early terminal differentiation but without the signals to form the cornified envelope. These data suggest the abnormal skin barrier function related to abnormal lamellar granule formation and subsequent abnormal lipid transport seen in HI skin may, in part, be due to the dysregulated keratinocyte differentiation programme driven by absent ABCA12.

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Section: Ichthyoses and the cornified envelope

Author(s):	Mats **Paulsson**, Susan John, Lars Thiebach and Neil Smyth
Title:	Transglutaminase-3 deficient mice: a subtle skin phenotype
	A major biological function of transglutaminases is the covalent crosslinking of epidermal proteins to form and maintain the skin barrier. Seven transglutaminases are present and active in different layers of the skin. To address their *in vivo* function we generated mice lacking TG3. Such mice show a hair phenotype, but have after birth no obvious defect in the skin barrier function. At embryonal day 17.5 we detected a delayed barrier formation in the knock out mice, which had recovered at day 18.5. The TG3 deficient mice showed alterations in hair formation. The fur and whiskers had a curled appearance and show ultrastructural irregularities. The structural hair proteins show an increased solubility, reflecting an altered crosslinking of hair structural proteins.

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Section: Therapy of ichthyosis: a challenge in daily practice

Author(s):	**Preil** ML, Bad Salzschlirf
Title:	Management of Ichthyosis: The TOMESA experience
	The principles of the Ichthyose therapy are: bathing, mechanical scale removal and local therapy with creams. The TOMESA clinic is experienced in 10 years of highly individualized therapy management of patients with Ichthyoses and related keratinization disorders. We offer a therapy plan with steam bath, bathing in death sea salt, medical bathes with sodium bicarbonate, rice, corn and wheat starch for soaking. Afterwards mechanical scale removal with different tissues like micro fibre, special silk from china or morocco, pumice or volcano stones. Lubricating topical treatment, individual chosen and optimized with and keratolytic ingredients like urea pura, polyethylene glycol, lactate, glycerine etc are used. Additional special treatment of the scalp and the face by experienced team is offered. Ichthyoses: There's a lot, you can do!

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Section: Workshop on clinical diversity and diagnostic standardization

Author(s):	JCC Ho, HC Hennies, YC Chen, C Lee, SH Tan, YC Giam, I Hausser, KS Harve, H Traupe, M **Raghunath**
Title:	Congenital Ichthyosis in South East Asia
	We present the first study of South East Asian patients (four patients, one Indian and two Malay families) with lamellar ichthyosis. All 4 presented as collodion baby at birth, and had cornea-threatening ectropion that required systemic retinoid treatment from the first year of life. All showed palmoplantar keratoderma and generalized plate-like ichthyosiform scaling with minimal erythema, with one patient showing a milder phenotype with scaling confined to forehead, sides of the trunk, flexures and wrists. Typical ultrastructural features included cholesterol clefts within horny layer in one patient (EM-type II), numerous lipid droplets (two siblings, EM-type I) and, in the mildest case, membranous structures and abnormal vesicular complexes in keratinocytes (EM-type III). We identified six novel TGM1 mutations in all our LI patients (Gly278Glu and Ser358Gly), (homoz. Glu285Lys, plus homoz. *4T>C), and, in the mildest case (Thr131 Ala and intronic 1646-8A>G). Our findings indicate that also in patients of Indian and Malay descent TGM1 mutations are responsible for LI. This correlated well with the absence or reduction of TGase1 activity in the granular layer. In the mildest case, the effects of the intronic putative splice defect is unknown yet, while the Thr131Ala mutation lies in the N-terminal β-barrel region of the enzyme. In contrast, the other three patients harbour mutations that affect the catalytic site of the enzyme. In this regard, Gly287Arg was described earlier to stall enzyme activity completely. We therefore assume that our novel mutation Gly278Glu has a similar effect. It therefore seems that patients harbouring mutations that directly affect the catalytic site of transglutaminase 1 have a more severe phenotype in comparison to cases where more peripheral locations on the enzyme are affected. The successful identification of TGM1 mutations in patients will improve genetic counselling in families at risk for LI including prenatal diagnosis for future pregnancies and prepare the ground for gene and enzyme substitution therapies. Singapore is a microcosm of South-East Asia, with her population comprised largely of descendants from Malaysia, the Indonesian archipelago, south India as well as the southern provinces of China. The Chinese constitute the majority (76%), followed by the Malays (13%) and Indians (8%). However, Chinese patients were notably absent from our cohort. A plausible explanation for this could be the accepted practice of intermarriage among the Malay and Indian communities.

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Section: Ichthyoses and the cornified envelope

Author(s):	Matthias **Schmuth**, Mary Williams, Peter Elias
Title:	How do abnormalities in corneocyte constituents cause barrier abnormalities?
	Barrier abnormalities in the disorders of cornification can result from defects in multiple different tissue and cell components. Because the permeability barrier resides in the extracellular lipid-enriched domains of the stratum corneum, it was anticipated that disorders of lipid metabolism would perturb the lamellar membrane structures of the extracellular domains and would result in a defective barrier. Unanticipated was the finding that inherited disorders of corneocyte proteins also exhibit, to varying degrees, an impaired permeability barrier. In some instances, the pathogenetic sequence from the gene defect to disease expression is quite straightforward. In others, a more complex sequence is operative. We have examined the correlation between genetic defect, morphological, biochemical, and functional parameters in four corneocyte disorders, lamellar ichthyosis (LI), loricrin keratoderma (LK), ichthyosis vulgaris (IV), and epidermolytic hyperkeratosis (EHK). In both LI and LK, a defective cornified envelope results in impaired scaffold function, leading to fragmented and foreshortened lamellar membrane, but compensatory cross-linking of alternate cornified envelope precursors (which cannot occur in LI) ameliorates the clinical consequences of loricrin mutations in LK. The relationship between the defective corneocyte envelope and the extracellular avenue of increased transepidermal water loss in LI and LK indicates the corneocyte as a scaffold necessary for the supramolecular organization of the extracellular matrix. In IV, it is still unresolved if decreased corneocyte cohesion and increased stratum corneum pH are responsible for the defective organization of extracellular lamellar membrane structures. In contrast, in EHK abnormal keratins impair lamellar body exocytosis, again provoking a barrier abnormality via a defect in the extracellular matrix. Thus, in each of these disorders, the defective intracellular proteins produce the permeability barrier abnormality by divergent mechanisms.

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Section: Recent advances in gene mapping and in lipid genes

Author(s):	Hiroshi **Shimizu**, Hokkaido University Graduate School of Medicne, Sapporo, Japan
Title:	What can we learn from harlequin ichthyosis?
	We showed serious defects in the epidermal keratinocyte lipid transporter ABCA12 are known to result in a deficient skin lipid barrier, leading to harlequin ichthyosis (HI) (Akiyama et al, J Clin Invest 2005). These finding allowed us to provide early DAN based prenatal diagnosis of HI (Akiyama et al, J Invest Dermatol, 2007). Transplanted keratinocytes from patients with HI reconstitute HI skin lesions in immunodeficient mice. ABCA12 is highly expressed in fetal skin and suggest that ABCA12 may play an essential role under both the wet and dry conditions, including the dramatic turning point from a wet environment of the amniotic fluid to a dry environment after birth (Yamanaka et al, Am J Pathol 2007).

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Section: Keratinization disorders and keratins

Author(s):	Jenny Lugassy[1,2], John A McGrath[3], Peter Itin[4], Akemi Ishida-Yamamoto[5], Kristen Holland[6], Susan Huson[7], John DiGiovanna[8], Dani Bercovich[9]; Dan Geiger[10]; Julian Verbov[11], Helen R. Murphy[12], Jouni Uitto[13], Reuven Bergman[1,2], Gabriele Richard[14], Eli **Sprecher**[1,2,15] [1]Department of Dermatology and Laboratory of Molecular Dermatology, Rambam Health Care Campus, Haifa, Israel; [2]Faculty of Medicine, [10]Faculty of Computer Sciences, [15]Rappaport Institute for Research in the Medical Sciences, Technion – Israel Institute of Technology, Haifa, Israel; [3]St John's Institute of Dermatology, The Guy's, King's College and St Thomas' School of Medicine, London, UK; [4]Department of Dermatology, University of Basel, Switzerland; [5]Department of Dermatology, Asahikawa Medical College, Asahikawa, Japan; [6]Department of Dermatology, Medical College of Wisconsin, Milwaukee, WI, USA; [7] Unit of Medical Genetics, St Mary's Hospital, Manchester, UK; [8]Department of Dermatology, Brown University, Providence, RI, USA; [9]Migal - Galilee Technology Center, Kiryat-Shmona, Israel; [11]Department of Paediatric Dermatology and [12]Department of Clinical Genetics, Royal Liverpool Children's Hospital, Liverpool, UK;[13]Department of Dermatology, Thomas Jefferson University, Philadelphia, PA, USA;[14]GeneDx, Gaithersburg, MD, USA
Title:	KRT14 haploinsufficiency results in increased susceptibility of keratinocytes to TNF-α-induced apoptosis and causes Naegeli-Franceschetti-Jadassohn Syndrome
	Naegeli-Franceschetti-Jadassohn syndrome (NFJS) is a rare autosomal dominant disorder characterized by complete absence of dermatoglyphics, reticulate hyperpigmentation of the skin, palmoplantar keratoderma, abnormal sweating, and other subtle developmental anomalies of the teeth, hair, and skin. NFJS was previously shown to map to 17q11.2-q21. In 6 affected families, we identified a total of 4 different heterozygous nonsense or frameshift mutations (Q7X, 17delG, 26delC, C18X) affecting the nonhelical head (E1/V1) domain of KRT14. Using a modified quantitative fluorescent PCR-RFLP assay, we found that mutant cDNA levels were markedly decreased relative to mutant gDNA in patients carrying the C18X, 29delC and Q7X mutations. This indicates that NFJS-causing mutations induce significant mRNA decay. Since increased apoptotic activity was observed in the epidermal basal cell layer in NFJS patients and because previous data suggested that type I keratins may confer resistance to TNF-α-induced apoptosis in epithelial tissues, we assessed the effect of down-regulation of *KRT14* expression on apoptotic activity in keratinocytes. Using a HaCat cell-based assay, we found that decreased *KRT14* expression is associated with increased susceptibility to TNF-α-induced apoptosis. This phenomenon was not observed when cells were cultured in the presence of doxycycline, a known negative regulator of TNF-α-dependant pro-apoptotic signalling. Collectively, our results indicate that NFJS results from haploinsufficiency for keratin 14 and suggest that increased susceptibility of keratinocytes to pro-apoptotic signals may be involved in the pathogenesis of this ectodermal dysplasia syndrome.

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Section: Proteases and keratinization disorders

Author(s):	Alain **Taïeb** and Fanny Morice Centre National de Référence pour les Maladies Rares de la Peau, Service de Dermatologie et Dermatologie Pédiatrique, CHU de Bordeaux, France e-mail : alain.taieb@chu-bordeaux.fr
Title:	Insights into pathophysiology of ichthyosis using TTD as a model
	Trichothiodystrophy (TTD) is a congenital hair dysplasia with autosomal recessive transmission. Cross banding pattern under polarized light plus trichoschisis and a low sulfur content are the mandatory features which define the disorder, which is associated with variable and heterogeneous neuroectodermal symptoms. Photosensitive forms with abnormal DNA repair (group I) are caused by mutations in genes encoding subunits of the transcription factor TFIIH. 10% of non photosensitive patients have *TTDN1* mutations (group II). Group III is composed of non photosensitive non *TTDN1* mutated patients. The aim of this work was to define clinical features of TTD according to their genetic status and to try to etablish genotype-phenotype correlations. We studied 10 patients from our unit and reviewed 68 cases reported in literature. Clinical data have been related to molecular data. Frequency of congenital ichtyosis is significantly higher in group I. Osteosclerosis and hypogonadism are found in both groups without significant difference. Around 2% of collodion babies have TTD. Our data indicate a strong genotype–phenotype correlation between congenital ichthyosis and group I TTD with DNA repair defects. Mutations in TFIIH sub-units XP-D or B might be responsible for a transcription defect leading to abnormal expression in genes involved in epidermal differentiation. For example it has been shown that the γ isotype of nuclear retinoic acid receptors (RARγ) is phosphorylated by TFIIH and that this phosphorylation controls receptor association or dissociation with a coregulator. This could explain the particular dermatological features seen in « photosensitive » cases of TTD. The specific role of *TTDN1* is unknown. It could also be involved in transcription. We suggest a new clinico-genetic classification of TTD which may help clinicians who are confused by the current acronyms used (IBIDS, PIBIDS…). Understanding the TTD ichthyotic phenotype could lead to physiopathological and therapeutic advances in skin physiology and management of other types of ichthyoses.

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Section: Experimental therapies

Author(s):	H. **Traupe**, K. Aufenvenne, Münster
Title:	Enzyme replacement therapy of lamellar ichthyosis: the current state
	Enzyme replacement therapy has greatly benefited genetic skin diseases such as Fabry disease and holds great promise for transglutaminase-1 (TGase-1) deficient lamellar ichthyosis (LI) and other genetic types of nonsyndromic ARCI. The current therapeutic situation for LI is deplorable. We want to change this by developing an enzyme replacement therapy – in other words a "biological". Several options for administering such a biological are conceivable, e.g. direct injection or application with the help of a cream. We actually favour the approach of administering a cream containing the active enzyme. So far, we have cloned two different TGase-1 constructs – one full length form and a shorter construct which lacks the N-terminal 93 AS of the membrane anchor. Both constructs include a C-terminal His-tag for purification of the recombinant proteins expressed in HighFive cells using the Baculovirus Expression System. To analyze the activity of the recombinant TGases we established a fluorimetric activity assay showing that they have specific activity. Application of TGase-1 protein on cryostat sections of LI skin showed a restoration of the TGase-1 activity, but of course the enzyme is not specifically directed to the cell membrane of cells in the stratum granulosum. Therefore we want to develop a lipid based formulation to pack the enzyme into liposomes in the next step. Thus the next immediate aim is to achieve cellular uptake of both liposome and TGase-1 into the keratinocytes of LI patients in cell cultures.

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Section: Therapy of ichthyosis: a challenge in daily practice

Author(s):	Anders **Vahlquist**, MD,PhD, Uppsala University, Sweden
Title:	Therapy of ichthyosis – general principles and substances
	In congenital ichthyosis there may be an abnormal quality or quantity of scale produced, abnormal thickness of stratum corneum or abnormal keratinocyte kinetics, often associated with skin inflammation. Pruritus, skin fragility, ectropion and anhidrosis are frequently associated with the rare types of ichthyosis. All these symptoms need therapy. Three important mechanisms are involved in the action of most agents used in the topical treatment of ichthyosis: hydration, lubrication, and keratolysis. The latter effect can also be achieved with systemic retinoids. For ichthyosis with increased tendency for skin infections, antimicrobials are another group of widely used agents. Considering that ichthyosis patients are potential mega-user of topical therapy with an estimated life-time consumption of about 1 ton cream per capita, surprisingly few controlled trials of various treatments have been performed. Moreover nearly all therapeutic principles were established long before the recent expansion in knowledge concerning the etiology and pathophysiology of ichthyosis. This calls for new ideas and intensified efforts to develop future ichthyosis therapies.

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Section: Therapy of ichthyosis: a challenge in daily practice

Author(s):	A. **Vahlquist**[1], S. Blockhuys[2] [1]Uppsala University Hospital, SWE, on behalf of the LILI investigators group; [2]Barrier Therapeutics nv, BEL
Title:	Oral liarozole in lamellar ichthyosis (LILI): a multinational, double-blind, placebo-controlled trial evaluating safety and efficacy of 75 mg/day and 150 mg/day for 12 weeks
	Liarozole (LIA) is an imidazole inhibiting several mammalian CYP450 isozymes and, as such, acts as Retinoic Acid Metabolism Blocking Agent (RAMBA). LIA has previously been shown an effective and safe treatment for psoriasis and congenital ichthyosis at doses up to 150 mg b.i.d.. In this 12-week double-blind trial 64 patients with moderate to severe lamellar ichthyosis [Investigator's global assessment (IGA) 3 or 4 on 5-point Likert scale] received p.o. either once daily placebo (PLAC) (N=9), LIA 75 mg (N=27) or LIA 150 mg (N=28); emollients could be continued. Patients returned every 4 wks until 4 wks posttreatment. Clinical parameters were IGA, Overall Scaling Score, erythema and pruritus. At baseline (V2), V3, V5 and V6 subjects completed QOLs (SF36 and DLQI); safety tests included blood- and urineparameters, pre- and posttreatment ECG, and ophthalmological exams. Primary endpoint was the proportion of patients that were responders, defined as a 2-point decrease in IGA at week 12. One PLAC patient (11%) was marked as responder, whilst 11/27 (41%) on LIA 75 mg and 14/28 (50%) LIA 150 mg were responders (150 mg vs PLAC: p=0.0557). In both LIA groups IGA and Scaling changes from baseline were significanly better ($p<0.05$) than PLAC at wks 8 and 12. There were no safety issues in any group. One patient stopped treatment (150 mg/day) after 5 days due to a rash. Other AEs were mostly mild to moderate in severity.

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Section: Therapy of ichthyosis: a challenge in daily practice

Author(s):	A.M. **van Steensel**, Maastricht
Title:	Our experience with RAMBAs in treatment of congenital ichthyosis
	Synthetic vitamin A derivatives, retinoids, have long been the mainstay of treatment for several disorders of keratinization, notably the ichthyoses and severe acne. Some forms of psoriasis also respond well. However, retinoids have dose-limiting side effects and can be highly teratogenic, limiting their use in women of childbearing age. Children can also experience long-term side effects. Thus, retinoids have significant disadvantages that preclude their use by a large number of patients who would in principle benefit from them. The recent development of compounds that block the catabolism of endogenous vitamin A, called Retinoic Acid Metabolism Blocking Agents or RAMBAs, offers new possibilities. I will discuss how retinoids work, how they are metabolized and how RAMBAs influence this process. I will also review the presently available data from clinical trials with RAMBAs.

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Section: Workshop on clinical diversity and diagnostic standardization

Author(s):	Hendrik **Verst**, Michael Spitzer, Frank Ückert
Title:	Database and Web System of the NIRK Registry
	The NIRK System is an important tool for a better transfer of knowledge between basic research, application-oriented research, clinical centres, outpatient physicians, hospitals and patient's own institutions. The system offers a central, web based, patient administration, connected with the structured patient data collection of standardised forms (like the general data, medical evidence, material and intermediate anamnesis) and digital pictures. An important factor is the generic data protection concept: The concept implementation splits the clinical database into two parts. The patient-list and the therapy database which are separated logically and physically. A complex identification process enables the physician to search for a patient and to receive the needed information as before, but better secured. The personal data and the therapy data will only be visually merged on the client of the physician. The concept already is approved by all data protection officers of the German federal states. The actual usage statistic as of August 07 presents 580 patients and 16 physicians with one daily access by physicians on average. The most important next steps are the completion of the implementation of genealogical trees, the automatization of image uploads and the further improvement of the internal search engine.

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Section: Ichthyoses and the cornified envelope

Author(s):	**Weidinger** S
Title:	Genetics of epithelial barrier integrity in atopic diseases
	Atopic eczema (AE) is one of the most common inflammatory skin disorders and affects up to 20% of children and up to 10% of adults in developed countries. It is firmly established that AE is under strong genetic control. One of its characteristic features is an impaired epidermal barrier function. A region on chromosome 1q21 which contains the epidermal differentiation complex (EDC) has been linked to AE. Recently, two loss-of-function mutations (R501X and 2282del4) within the EDC gene filaggrin (*FLG*) causing ichthyosis vulgaris, one of the most common inherited skin disorders of keratinisation, have been identified. Subsequently a variety of case-control and transmission studies firmly established an association between each of the two prevalent *FLG* null alleles and AE. Thus, reduction or loss of *FLG* expression leads to a disturbed barrier formation, which manifests as varying degrees of dry skin, ichthyosis, and/or eczema. In addition, it might allow an increased passage of antigens, allergens, and chemicals through the epidermis and thereby facilitate allergic sensitization, what might explain additional associations observed for asthma, sensitization and increased IgE levels in the context of AE. In the meantime additional less common *FLG* mutations associated with AE also in non-European populations have been reported. The results on *FLG* mutations provide strong evidence for the hypothesis that a genetically-determined primary disruption of the epidermal skin barrier is a key-event in the pathogenesis of AE and a considerable risk factor for the development of subsequent sensitizations and respiratory diseases.

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Section: European and international perspective

Author(s):	Ingrid **Zwoch**
Title:	Orphan Diseases and the European Union – what patients and scientists may expect
	The contribution will focus on the Seventh European Framework Programme for Research and Technological Development, its objectives, structure and budget. The area of rare diseases within Theme 1 of the Specific Programme Cooperation of the European Union will be presented as well as participation possibilities for the funding schemes available.

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