(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 August 2009 (20.08.2009)

PCT

(10) International Publication Number
WO 2009/101199 A2

(51) International Patent Classification:
A61K 31/726 (2006.01)

(21) International Application Number:
PCT/EP2009/051749

(22) International Filing Date:
16 February 2009 (16.02.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

08101654.5	15 February 2008 (15.02.2008)	EP
08154022.1	3 April 2008 (03.04.2008)	EP
61/123,294	7 April 2008 (07.04.2008)	US
08164431.2	16 September 2008 (16.09.2008)	EP
08168765.9	10 November 2008 (10.11.2008)	EP

(71) Applicant and
(72) Inventor: **MELNIK, Bodo** [DE/DE]; Eickhoffstr. 20, 33330 Gütersloh (DE).

(74) Agent: **SCHREIBER, Christoph**; Patent Attorneys von Kreisler Selting Werner (224), P.O. Box 10 22 41, 50462 Cologne (DE).

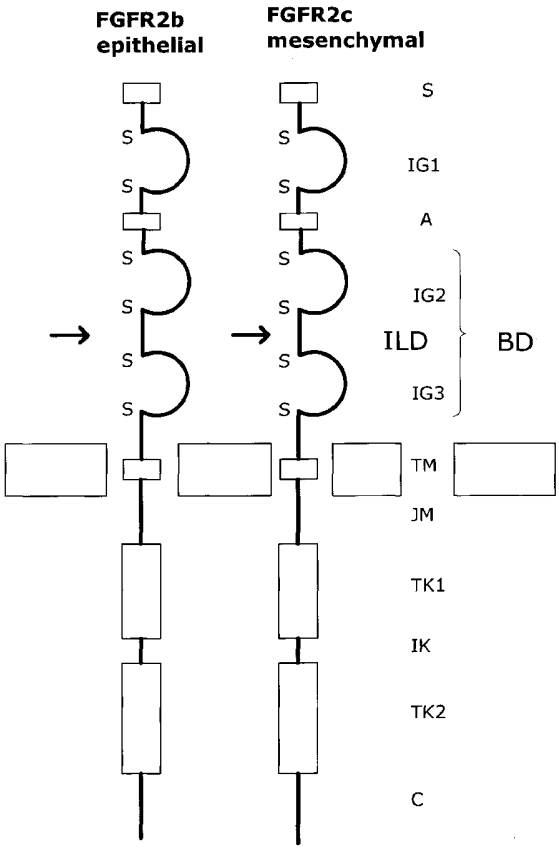
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG,

[Continued on next page]

(54) Title: TREATMENT OF ACNE VULGARIS; ROSACEA AND RHINOPHYM

(57) Abstract: A composition for the treatment of acne vulgaris, rosacea and/or rhinophym comprising at least one inhibitor of the FGFR2 signal pathway and/or IGFR1 signal pathway.

Fig.1



WO 2009/101199 A2

SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

Treatment of acne vulgaris, rosacea and rhinophym

The present invention relates to a composition for the treatment of acne vulgaris, rosacea, and/or rhinophym.

Acne is a chronic inflammatory disease of the pilosebaceous unit, mostly affecting the sebaceous follicles. Major contributors of acne pathogenesis are abnormal follicular differentiation with increased cornification, enhanced sebaceous gland activity with hyperseborrhea, bacterial hypercolonization, inflammation as wells as immunological host reactions. Sebaceous glands function continuously in excreting sebum to the skin surface with an average sebaceous cell transition time of 14 days.[1-3] Androgens play an essential role for the stimulation of the size of sebocytes and sebum production as well as keratinocyte proliferation in the ductus seboglandularis and the acroinfundibulum.[4/5] Exogeneous androgen excess or hyperandrogenism are associated with increased sebum production and the development of severe acne.[6/7] Acne-prone skin exhibits a higher androgen receptor density and higher 5α-reductase type-I activity than not involved skin.[8/9] Anti-androgens reduce the synthesis of sebaceous lipids and improve acne, whereas androgen-insensitive subjects who lack functional androgen receptors do not produce sebum and do not develop acne.[10/11]

Rosacea is an inflammatory skin disease appearing in areas with high density of sebaceous glands. The primary clinical features of rosacea include flushing, inflammatory papules, pustules, and teleangiectases. In rosacea mesenchymal tissue has an increased tendency of proliferation: sebaceous glands with sebaceous hyperplasia, connective tissue with fibrosis and formation of rhinophyma, and increased angiogenesis with formation of multiple teleangiectases. Disturbed homeostasis of vascular and fibroblast growth factors have been implicated in the pathogenesis of rosacea.[11a, 11b, 11c]

Although there are numbers of therapeutics for these diseases which are commonly clinically associated there is still a need for additional ways of treating these diseases.

Surprisingly it has now been understood that these diseases and especially acne can be positively influenced by inhibiting the FGFR2 signal pathway. In a

further embodiment, it has now been understood that these diseases and especially acne can be positively influenced by inhibiting the IGF-1 signal pathway.

1. Fibroblast Growth Factor Receptor-2

The FGFRs comprise a family of related but individually distinct tyrosine kinase receptors. At least 22 distinct FGFs mediate a variety of cellular responses during embryonic development and tissue homeostasis in the adult organism. FGFRs have a similar protein structure, with three immunoglobulin-like domains (D1-D3) in the extracellular region, a single membrane spanning segment, and a cytoplasmic tyrosine kinase domain (Figure 1). Four FGFRs designated FGFR1 to FGFR4 have been identified.[13] FGFRs bind in clusters to heparan sulfate proteoglycans, enabling the ligands to cross-link the receptors. Formation of receptor dimers or oligomers rearrange their cytosolic tails and induce autophosphorylation of the tyrosine residues of tyrosine kinase thereby activating the receptor and initiating the FGF-mediated signaling cascade. An important feature of the FGFR family is that a variety of FGFR isoforms are generated by alternative splicing of FGFR transcripts.[13] Two splice variants of FGFR2 encoded on chromosome 10q26 are designated FGFR2b and FGFR2c. The exclusively in epithelial cells expressed FGFR2b binds FGF7 (KGF) and FGF10, but not FGF2.[14] FGFR2b is expressed mainly in the suprabasal spinous layer of epidermis and plays a crucial role in controlling epithelial proliferation and differentiation.[15] The mesenchymally expressed isoform FGFR2c binds FGF2, FGF4, FGF6, FGF9, FGF17 and FGF18, but not FGF7 and FGF10.[14] Both, the D2- and D3-immunoglobulin-like domains of FGFR2b contribute to the exceptional specificity between FGF10 and FGFR2b.[16] Thus, the lineage-specific expression of the FGFR2b and FGFR2c isoforms enables interaction between epithelial and mesenchymal layers during development in response to different FGFs.[13]

The epithelial isoform FGFR2b is essential for embryogenesis.[17] FGFR2b is expressed throughout the epidermis, hair follicles and sebaceous glands.[18] FGFR2b-null mice die at birth. Reciprocal intercellular signaling between

epithelium and mesenchyme is a fundamental process in the induction and patterning of many organs. FGFs participate in this process instructing cells to proliferate, survive, migrate or differentiate.[18] Germline knockout of the IIIb-exon of the FGFR2 gene results in mice that die at birth from multiple developmental defects, identifying FGFR2b as a critical mediator of organogenesis.[19/20] Similar results were obtained by over expressing a soluble dominant-negative version of FGFR2b.[21] Studies in which FGF10 was knocked out showed that FGF10 is the key ligand for FGFR2b during development.[22/23]

Recently, FGFR2b has been shown to be important for postnatal skin development and hair follicle morphogenesis.[24] Mouse models have been used to study FGFR2b signaling in adult skin. Mice expressing a membrane-bound, dominant-negative FGFR2b, lacking tyrosine kinase activity displayed epidermal atrophy, hair follicle abnormalities, dermal hyperthickening with severely delayed re-epithelialization of excisional wounds.[25] Using Cre-Lox transgenics to delete FGFR2b in cells expressing keratin 5, it has been demonstrated that mice lacking epidermal FGFR2b survive into adulthood but displayed striking abnormalities in hair and sebaceous gland development.[17] Moreover, first evidence of the role of FGFR2b in sebaceous gland development was provided revealing that continued presence of FGFR2b in the skin is a necessary prerequisite for the long-term survival of sebocytes.[17]

Most glands, including the prostate and seminal vesicles undergo branching morphogenesis during development. The importance of FGFR2 in branching morphogenesis has been presented in the mouse seminal vesicle shape (svs) mutation causing branching morphogenesis defects in the prostate and seminal vesicles.[26] The svs-mutation is caused by an insertion of 491 base pairs in the 10th intron of FGFR2 resulting in a loss-of-function of FGFR2 due to changes of the pattern of FGFR2 alternative splicing. Partial loss of FGFR2b causes the svs-phenotype and was associated with down-regulation by several branching morphogenesis regulators including Shh, Ptch1, Gli1, and Gli2.[26] This mouse model underlines the importance of the regular expression FGFR2b for adequate branching morphogenesis of androgen-dependent seminal

vesicles and prostate glands. Using conditional null FGFR2 mice embryos, a requirement for FGFR2 tyrosine kinase for prostatic branching morphogenesis, growth and acquisition of strict androgen dependency for adult tissue homeostasis could be demonstrated.[27]

FGFR2b-signal transduction is mediated by three major pathways, the MAPK/ERK-cascade involved in cell proliferation, the phosphoinositide-3-kinase (PI3K)/Akt pathway regulating lipogensis and the phospholipase C-γ/protein kinase C pathway. FGF7 has been shown to induce lipogenic genes through a PI3K and JNK/SREBP-1 pathway in H292 lung epithelial carcinoma cells. Activation of PI3K-signalling induces sebaceous lipogensesis and increased the expression of the key lipogenic enzyme fatty acid synthase.

ANDROGEN- DEPENDENCE OF FGF-FGFR2-SIGNALING

In the human, both the sebaceous gland and the prostate are androgen-dependent glands. However, the interaction between androgen stimuli and FGF-FGFR-signaling is much further investigated in the prostate because of its importance for the pathogenesis and treatment of prostatic cancer. Comparable to the sebaceous gland, androgens are both essential and sufficient for prostate development, where they stimulate ductal outgrowths, branching morphogenesis, cellular differentiation, and secretory function.[29/30] The evidence for the absolute necessity of androgen comes from the observation of prostatic absence in mice or humans with complete dysfunctional androgen receptors.[31] Corresponding to the situation in the sebaceous gland, it is known that androgen-insensitive subjects who lack functional androgen receptors do not produce sebum and do not develop acne.[10/11] Classic tissue recombinant experiments in the prostate showed the preferred expression of androgen receptors in the mesenchyme. Epithelial androgen receptors are not responsible for prostatic morphogenesis.[32] Androgens regulate the expression of several prostatic morphoregulatory genes including up-regulation of FGF10 expression and FGF10-signaling in the developing prostate.[33] Besides the significant up-regulation of FGF10-expression, androgens increased FGFR2b in the ventral rat prostate, thereby

increasing epithelial cell responsiveness to this secreted mesenchymal morphogen.[33] Sonic hedgehog (Shh), which is an epithelial secreted morphogen essential for prostate development, increased after testosterone stimulation.[33] In the rat prostate, androgens regulate the expression of epithelial morphoregulatory genes of the gland, where FGF10 has been shown to be the proximate regulator of steroid action. Androgens stimulate FGF10- and FGFR2b-expression and epithelial Shh and Hoxb13 expression through an FGF10-dependent pathway.[33]

Androgens have been shown to stimulate FGF2 expression as well. In cultured human prostatic stromal cells dihydrotestosterone stimulated the expression of FGF2.[34] In prostate carcinoma cells androgen receptor expression induces FGF2 production and FGF2 release.[35] FGF2 is also involved in testicular function.[36] In summary, androgen-dependent organs like the prostate and testis induce morphoregulatory and proliferative responses by androgen-dependent up-regulation of FGF-FGFR2-signaling.

INTERACTIONS BETWEEN FGFR2b and p63

Evidence accumulates that the androgen-dependent FGF-FGFR2-signaling mechanisms are also operative in the sebaceous gland. The development and function of human sebaceous glands is critically dependent on the presence of androgens. The transcription factor p63 is essential for skin appendage development and induces the preferential production of the epithelial isoform FGFR2b.[37] p63 regulates gene expression also at the post-transcriptional level and gives a plausible explanation for the lack of FGFR2b transcripts in p63 -/- ectoderm. A link between p63 and FGFR2b is further supported by the similar knockout phenotypes implying that the loss of FGFR2b is likely to have a fundamental impact on the p63 -/- phenotype.[19/20/24/38] Intriguingly, the observed limb defects of p63-mutants and FGFR2b-mutants are highly similar.[19/20/39/40] p63 is essential for regenerative proliferation in limb, craniofacial and epithelial development. Epidermal proliferation is grossly impaired in FGFR2b loss-of-function mutants causing a severely hypoplastic epidermis. Most important with respect to the pathogenesis of acne is the fact

that FGFR2b is the major regulator of skin appendage development. FGFR2b loss-of-function mutants have reduced numbers of hair follicles. Tooth development is arrested at the bud stage and of the five pairs of mammary placodes, only one pair is formed, which however regresses later.[19/24/38] These data from animal experiments clearly show the important role and interaction of p63 and FGFR2b-signaling in organ and skin appendage development and homeostasis.

INTERACTIONS BETWEEN FGFR2b AND SONIC HEDGEHOG

From studies in mice it has been concluded that Shh is a downstream target of FGF10/FGFR2b signaling and that mesenchymally derived FGF10 regulates the epithelial expression of Shh.[41] These results underline the role for FGFR2b-signaling in mammalian palate development and emphasize that coordinated mesenchymal-epithelial interactions are essential during the initial stages of palate development and require a functioning FGFR2-Shh-signaling network.[41]

Shh-signaling is also of great importance for the regulation of sebaceous gland development.[42] Interactions between β-catenin and hedgehog signaling is involved in stem cell lineage determination into lineages of the hair follicle, interfollicular epidermis and sebaceous glands. The homeostatic function of the hedgehog family is important for branching morphogenesis and limb formation.[43] Within the epidermis Shh promotes proliferation of progenitors of hair lineages, whereas Indian hedgehog (Ihh) stimulates proliferation of sebocyte precursors.[44] Cholesterol is necessary for maturation and function of the Shh protein, which is esterified to cholesterol and palmitic acid for normal trafficking to sterol-sensing domains like Patch and membrane lipid rafts. Point mutations of the Shh downstream transcription factor Gli 3 result in Greig cephalopolysyndactyly syndrome with craniofacial abnormalities and post-axial and pre-axial polydactyly as well as syndactyly of hands and feet, clearly pointing to common phenotypic features observed in Apert syndrome.[45] This phenotypical overlap between Apert syndrome and Greig syndrome implies that defects within the FGFR2-Shh-Gli signaling pathway can result in similar developmental defects.

Studies using transgenic mice revealed that inhibition of the Shh-pathway suppressed sebaceous gland development, whereas Shh-pathway activation led to a striking increase both in size and number of sebaceous glands.[42] Shh is produced and secreted by developing hair follicle keratinocytes and activates signaling both in the follicular epithelium and mesenchyme.[46/47] Shh acts on target cells by inhibiting the function of its receptor Patch (Ptch), which normally represses the signal transducer Smoothened (Smo).[48] Gli proteins mediate transcriptional responses to hedgehog family members.[49/50] When Shh-mutant skin was allowed to mature on immunodeficient hosts it exhibited a selective deficiency of sebaceous glands.[51/52] Stimulation of the Shh-pathway in Smo-expressing transgenic mice resulted in increased expression of the sebocyte markers Scd3 and melanocortin-5 receptor (MC5R).[53] MC5R is an important marker of human sebocyte differentiation.[53] In human sebocytes MC5R was only detectable at the onset of differentiation and in fully differentiated cells displaying prominent lipid granules.[53] The functional link between MCR5 and sebogenesis has been shown in MC5R-deficient mice in which lack of MC5R resulted in down-regulation of sebaceous lipids.[54] The importance of centrally produced α-MSH in the regulation of sebaceous lipids has been demonstrated.[55/56] Ablation of the neurointermediate lobe of the pituitary, the source of circulating α-MSH, decreased sebaceous lipid production. Furthermore, in hypophysectomized and castrated rats the reduction of sebaceous lipids was fully restored by concomitant α-MSH and testosterone administration.[56] Using a primary human sebocyte culture system it has been reported that α-MSH can stimulate sebocyte differentiation, sebaceous lipid production and expression of MC5R.[57/58]

In summary, evidence is provided demonstrating that α-MSH signaling via MC5R act on a common pathway with androgen-dependent expression of MC5R by induction of the signaling cascade via androgen → FGF7/FGF10 → FGFR2b → Shh → Gli → MC5R-expression. MC5R is a crucial target gene of Shh-signaling. Moreover, the Shh-pathway is likely to play a role in postnatal

function of sebaceous glands.[42] Intriguingly, retinoids which are known to inhibit sebocyte differentiation have been shown to reduce Gli transcriptional activity in cultured keratinocytes.[59-61] This could lead to retinoid-induced downregulation of MC5R expression and lipogenesis.

In human keratinocytes epidermal growth factor receptor (EGFR) signaling has recently been presented as an important modulator of Shh-Gli target gene expression.[62] EGFR signaling is essential for Gli-induced cell cycle progression in human keratinocytes and modulates Gli-target gene profiles which play an important role in hair follicle outer root sheeth specification and hair growth.[62] Recent reports provided evidence that the biological effect of hedgehog/Gli signaling can be triggered by EGFs and FGFs.[63-67] hedgehog/Gli signaling requires the activation of PI3K/Act and Mek/Erk activation.[68/69]

From this context it becomes apparent that androgen-dependent mesenchymally expressed FGF7 and FGF10 signal via epithelially expressed FGFR2b resulting in downstream up-regulation of Shh and Gli leading to final expression of MC5R for terminal sebocyte differentiation and lipogenesis. In analogy to the androgen-dependent prostate gland, the androgen-dependent sebaceous gland might be as much dependent on mesenchymal stimulation of its surrounding stromal cells, a fact neglected in studies with isolated sebocyte cell lines. The role of mesenchymal cells on sebaceous gland development and function has been recently appreciated by some investigators.[42/70/71]

CROSS-TALK BETWEEN FGFR2, EGFR, p63 AND LIPOGENESIS

Recent evidence points to an important role of ΔNp63α expression by activation of EGFR.[72] ΔNp63α is a target of the phosphoinositide-3-kinase (PI3K) pathway downstream of EGFR. Inhibition of EGFR signaling results in a decrease of ΔNp63α expression.[72] Both, the EGFR and the FGFR2, have a common signaling cascade leading to activation of PI3K, which explains the severe acne in Apert syndrome with a FGFR2 gain-of-function mutation with increased FGFR2 downstream signaling.[28] For the sebocyte, which is a specialized epithelial cell, it might be necessary, that p63 induces the FGFR2b-isoform, predominantly activating epithelial cells.[73] That ΔNp63 enhances the

expression of FGFR2b has also been shown in mice thymic epithelial cells.[74] Thus, there is a close interaction between FGFR2b, EGFR activation and p63 expression.

The human sebaceous gland is a most active site in lipid biosynthesis. The major lipid classes of human sebum, as it leaves the sebaceous gland, are triglycerides, squalene, wax esters, cholesterol and cholesterol esters. Triglyceride biosynthesis affords the synthesis of free fatty acids. There are three major mechanisms utilized for the synthesis of fatty acids: *de novo*-synthesis, microsomal elongation and the mitochondrial process. The *de novo*-mechanism involves two enzymes, the acetyl-CoA-carboxylase and the fatty acid synthase.[75] Since the major component fatty acid in human sebum is palmitic acid, it can be deduced that *de novo*-fatty acid synthesis by the enzyme fatty acid synthase is the major mechanism for sebaceous gland lipogenesis.[75] Thus, regulation of fatty acid synthase gene expression is intimately involved in sebum production. It fits well together, that the master transcription factor ΔNp63 induces fatty acid synthase (FASN) mRNA levels, while ΔNp63-silencing produces a decrease of FASN expression.[76] Furthermore, a correlation between ΔNp63α and FASN expression in cellular proliferation could be observed.[76] These interactions shed a new light on FGFR2b-EGFR-p63-mediated regulation of FASN-dependent sebaceous lipogenesis.

The androgen-dependent mesenchymally-secreted FGF7 and FGF10 signals activate the epithelial FGFR2b on sebocytes thereby up-regulating EGFR, the convergent point of many co-stimulatory hormones signaling through G-protein-coupled receptors.[77] Comparison of EGFR and FGFR downstream signaling pathways show, that for the most part, a similar repertoire of signaling proteins are recruited and activated by the two tyrosine kinase receptors.[78] A cooperative interaction between FGFR2b- and EGFR-signaling in the pilosebaceous follicle has to be expected in mesenchymal-epithelial interactions for sebaceous gland development and homeostasis in the adult tissue.

From animal studies on the role of FGFR2b in skin appendage development and homeostasis as well as androgen-dependent prostate development it can be concluded that the FGF7/FGF10-FGFR2-signaling pathway is androgen-regulated and plays an important role in sebaceous gland development and homeostasis. Different from Apert syndrome, where FGF2 appears to be the major ligand for FGFR2, under physiological conditions FGF7 and FGF10 are supposed to mediate mesenchymally-derived signals to the infundibular epithelium and sebaceous glands. The epithelial splice variant FGFR2b is expressed in sebaceous glands. Experiments in mice showed that mesenchymally-derived FGF10 signal to its epithelial receptor FGFR2b resulting in downstream expression of Shh.[41] In transgenic mice, Shh is a crucial stimulator of MC5R in sebaceous gland, an important marker of the sebocyte differentiation mediating sebaceous lipogenesis.[42/53]

Supposed that androgen-dependent FGFR2b-signaling mechanisms are operative in the human sebaceous gland, the following signaling pathways are predictable: 1. With the onset of puberty increased plasma androgen levels stimulate the surrounding stroma of the sebaceous gland and its infundibum by inducing the expression of FGF7 and FGF10. 2. In a paracrine fashion, FGF7 and FGF10 bind to its epithelial receptor FGFR2b on sebocytes and follicular duct keratinocytes. 3. FGFR2b activation leads to downstream expression of various target genes including the expression interleukin-1α and Shh. 4. Shh-Ptch-Smo-Gli-signaling induces terminal differentiation of sebocytes, up-regulation of MC5R and MC5R-dependent lipogenesis. 5. Androgen-mediated up-regulation of EGFR augments the primary FGF-FGFR2b-effect by the increasing G-protein-coupled receptor-mediated EGFR-transactivation. Most known hormonal stimulators of sebaceous glands like α-MSH signal through G-protein coupled-receptors which all have the ability to cluster around EGFRs and use them for EGFR-transactivation thereby augmenting of proliferative signals. 6. Androgens play an important role for keratinocyte proliferation in the ductus seboglandularis and the acroinfundibulum. This proliferative response of the kerationcytes could be linked to FGFR2b and EGFR-signaling

as well. FGF7-binding to FGFR2b has been shown to induce TGFα and EGFR-upregulation in cultured keratinocytes.[79] Activated FGFR2b and EGFR work in cooperative fashion, using overlapping downstream signaling cascades.[78] FGFR2b-mediated upregulation of interleukin-1α appears to be involved in hyperproliferation of infundibular keratinocytes and comedo formation. Androgen-induced overstimulation of the FGF-FGFR2b-IL-1α-pathway might induce hyperproliferation of infundibular keratinocytes in acne vulgaris. Follicular proliferation of infundibular keratinocytes could be blocked by addition of interleukin-1 receptor antagonist.[12] Another possibility to suppress IL-1α-induced comedogensis is to increase the expression of interleukin-1α antagonist. This is possible by inhibiting dipeptidyl peptidase IV and aminopeptidase N, which suppressed proliferation, enhanced terminal differentiation and slightly decreased total neutral lipid production in SZ95 sebocytes and HaCaT keratinocytes.[80] The inhibition of these ectopeptidases resulted in a significant upregulation of the anti-inflammatory and differentiation-restoring cytokine interleukin-1 receptor antagonist.[80]

The stroma of sebaceous glands is of critical importance for proper FGF-mediated signaling, a physiological requirement easily overlooked when acne research is performed only with isolated sebocyte cell lines. FGFR2b-signaling is cross-linked to the Shh-Gli-pathway and EGFR-dependent signaling events associated with signaling through G-protein-coupled receptors. Obviously, mesenchymal FGF-signaling has a high priority in the receptor network operative in the sebaceous gland and plays an essential role in skin appendage development. Accumulating evidence allows the conclusion, that acne vulgaris is related to an overstimulation of FGF-mediated cell communication of the sebaceous follicle. Clinical observation, animal experiments, and developmental biology support the concept of an exaggerated androgen-dependent mesenchymal-epithelial interaction as a cause of increased proliferation of infundibular keratinocytes and sebaceous cells in acne vulgaris.

2. Insulin like growth factor

IGF1 is a polypeptide hormone of 7.5 kD that plays a key role in the somatotropic axis. It is secreted by a number of tissues in response to a number of stimuli, among which is the one induced by somatotropin, of which IGF1 is the main biological mediator. IGF1 participates in regulation of the cell cycle, inhibiting the processes of apoptosis and stimulating cell proliferation. IGF1 has been described as a potential tumoral promoter. IGF1 downstream signaling shares common signaling cascades with other tyrosine kinase receptors like insulin receptor, epidermal growth factor receptor and fibroblast growth factor receptors.

It is known for a long time that insulin and insulin-like growth factor-1 (IGF1) stimulate sebaceous gland lipogenesis. IGF1 induced SCREBP-1 expression and lipogenesis in SEB-1 sebocytes via activation of the PI3K/Akt pathway. Chemical inhibition of the PI3K completely blocked the IGF1-mediated increase in lipogensis of SEB-1 sebocytes.

The FGFR2b-signalling pathway, IGF1- and insulin signal transduction merge downstream of the activation of the corresponding tyrosine kinase receptor with the activation of MAPK-pathway, PI3K/Akt-pathway and PLCγ/PKC pathway. Thus, the androgen-dependent mesenchymal-epithelial FGFR2-signalling pathway of the pilosebaceous follicle is amplified by insulin and IGF1 merging with overlapping intracellular signal processing pathways.

Association between increased levels of IGF1 in common adenocarcinomas

Several studies have shown a link between serum concentrations of IGF1 and IGF-binding protein 3 (IGFBP3) with increased risk of breast, prostate, colorectal, and lung cancer. High membranous IGF1R staining was observed in 87.5% of breast carcinomas, 100% ovarian carcinomas, 100% endometrial carcinomas, 71.1% of gastric carcinomas, 57.1% pancreatic carcinomas, 90% colon adenocarcinomas, 84.6% lung carcinomas, 54.5% prostatic adenocarinomas, and 100% transitional cell carcinomas of the bladder. Some studies have suggested that IGF1 pathway is related to premenopausal breast

density, one of the strongest known breast cancer risk factors believed to represent epithelial and stromal proliferation. Common genetic variation in IGF1 is strongly associated with percentage mammographic density. A higher risk for cervical ovarian and endometrial cancer is related to high IGF1 levels in post- and premenopausal women. IGF1 appears to play a role in the prostate development and carcinogenesis. Plasma IGF1 levels and inherited variation in IGF1 has been implicated to be a risk factor in prostate carcinoma.

In one embodiment, the present invention provides a composition for the treatment of acne vulgaris, rosacea, and/or rhinophym comprising at least one inhibitor of the FGFR2 signal pathway.

In a preferred embodiment, the inhibitor is a glycosaminoglycan, especially 2-O-hepran sulfate or 2-N-hepran sulfate. Suitable tissue levels are 120 nM or more. A suitable glycosaminoglycan can be prepared according to Chen J et al. (2005) Enzymatic redesigning of biologically active heparan sulfate. J Biol Chem 280: 42817-42825.

In a further embodiment, the inhibitor is directed against FGFR2 and is selected from the group of si-RNA, PD173074, 4-Phenoxyl-6-carboxyl-2-(1H)-quinolinone, a synthetic FGFR2b peptide antagonist, Antisense FRS2alpha (fibroblast growth factor receptor substrate 2alpha), dithranol, FGFR2b antisense oligonucleotides and FGFR2cb antisense oligonucleotides.

PD173074 is a substance developed by Pfizer: N-[2-[[4-(Diethylamino)butyl-6-(3,5-dimethoxyphenyl)-pyrido[2,3-d)pyrimidin-7-yl]-N´-(1,1-dimethylethyl)urea. A suitable concentration is 25 to 100 nM.

4-Phenoxyl-6-carboxyl-2-(1H)-quinolinone is described in Hackett J et al. (2007) Development of keratinocyte growth factor receptor tyrosine kinase inhibitors for the treatment of cancer. Anticancer Research 27: 3801-3806. A suitable concentration starts at 20 µM.

A synthetic FGFR2b peptide antagonist is described in Bottaro DP et al. (1993) A keratinocyte growth factor receptor-derived peptide antagonist identifies part of the ligand binding site. J Biol Chem 268: 9180-9183.

Antisense FRS2alpha (fibroblast growth factor receptor substrate 2alpha) is described in Zhang Y et al. (2008) Role of epithelial cell fibroblast growth factor receptor substrate 2 alpha in prostate development, regeneration and tumorigenesis. Development 135: 775-784.Dithranol (Cignolin) is able to down-regulate the FGFR2b receptor. A suitable concentration is 0.001 to 0.1% by weight in a topical application; see also Nagy N et al. (2006) The expression of keratinocyte growth factor receptor (FGFR2-IIIb) correlates with the high proliferative rate of HaCaT keratinocytes. Exp Dermatology 15: 596-605.

In a further embodiment, the inhibitor is a MAP-kinase inhibitor, for example PD 98059, U0126 or PD 184352. Neomycin and neomycin sulfate as well as paromomycin, streptomycin, gentamicin, tobramycin, netilmicin, amikacin and related aminoglycoside derivatives are also suitable, especially for topical treatment.

PD 98059 is 2-(2-Amino-3-methoxyphenyl)-4H-1-benzypyran-4-on. A suitable concentration is 50 µM or more.

U0126 is 1,4-Diamino-2,3-dicyano-1,4-bis(2-aminophenylthio)butadiene. A suitable concentration starts at 25 µM. Inhibition of MAP-kinase reduces the amount of interleukin 1α.

In a further embodiment, the inhibitor is an inhibitor of p38MAPK, for example SB203580, SB202190 or BIRB8796. SB202190 is 4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)-1H-imidazol.

In a further embodiment, the inhibitor is an inhibitor of protein kinase C. Suitable compounds are calphostin C, myristolyated, Ro 31-8220, GF109203X, Gö 6976, K252a, Ro 31-7549, Gö 6983, Chelerythrine chloride, (-)-Balanol, UCN-01, CGP41251, CGP54345, CGP53506, Aprinocarsen, CGP53506, Ly333531, Ly379196, Ly317615. Calphostin C is effective in a concentration range of 0.5 to 2 µM. Myristolyated is a peptide having the sequence Myr-RFARKGALRQKNV. A suitable concentration range is 8 to 100 µM.

In a preferred embodiment, a combination of the inhibitors of FGFR2, MAPK, p38MAPK and PKC is used.

In a further embodiment, the inhibitor inhibits Sonic Hedgehog (Shh). Suitable inhibitors are Sonic Hedgehog antisense oligonucleotides, Patched antisense oligonucleotides and Gli antisense oligonucleotides.

In a further embodiment, the inhibitor inhibits Smoothened (Smo). Possible compounds are for example cyclopamine, GANT 61 (NSC 136476), GANT 58 (NSC 75503). Cyclopamine is 11-Deoxojervine. A suitable concentration for a topical application is 5 to 25 µM. For GANT 61 and GANT 58, suitable concentrations are about 10 to 15 µM in the tissue.

Any of the inhibitors can be used in combination.

In a preferred embodiment, any of the inhibitors is combined with an inhibitor of dipeptidylpeptidase IV and/or an inhibitor of aminopeptidase N. Suitable compounds are especially Lys[Z(NO_2)]-thiazolidid, Lys[Z(NO_2)]-pyrrolidid, Actinonin, Bestatin, Diprotin A, Ile-Pro-Ile, Sitagliptin, Vildagliptin, Saxagliptin.

Another possibility treating acne and the acne-related diseases is the oral administration of HMG-CoA reductase inhibitors, for example simvastatin (a preferred dosis is 20 mg/day or more) and artorvastatin (a preferred dosis is 80 mg/day or more orally) and related statins. The effects of statins is derived from down-regulation of interleukin-1 tissue expression.[81]

In another formulation for the treatment of acne and rosacea dobesilate (dihydroxy-2,5 benzenesulphonate) reaching tissue concentrations of 10-100 µM can be used as an oral agent.[82]

A further embodiment of the invention is a composition for the treatment of acne vulgaris, rosacea and/or rhinophym comprising at least one inhibitor of the IGF-1 signal pathway.

A suitable inhibitor is selected from the group consisting of anti-IGF-1 receptor antibody or a IGF1 receptor tyrosine kinase inhibitor.

Preferred compounds are selected from αIR3, SCFV/FC, SCF/FV, EM/164, A-12, Bispecific, 19D12, H7C10, CP751-871, KM1468, NVP-AEW541-A, BMS-536924, BMS-554417, Cyclolignan, TAE226, NVP-AEW54, NVPADW742, PQ401, NVP-TAE226, AQIP, PQIP, PPP, decapeptide analogs.

Details can be derived from the following table:

NVP-AEW54	pyrrolo[2,3-d] pyrimidine derivative (Novartis Pharma, Basle)
	selective IGF1R kinase inhibitor
	Concentration range: 0,3-6,8 microM
	Reference:
	Garcia-Echeverriá C et al. (2004) In vivo antitumor activity of NVP-AEW541- A novel, potent, and selective inhibitor of the IGF-IR kinase.
	Cancer Cell 5: 231-239
NVP-ADW742	pyrrolo[2,3-d] pyrimidine derivative (Novartis Pharma, Basle)
	selective IGF1R kinase inhibitor
	concentration range 0.1-0.4 microM
	Reference:
	Warshamana-Greene GS et al. (2004) The insulin-like growth factor-I (IGF-I) receptor kinase inhibitor NVP-ADW742, in combination with STI571, delineates a spectrum of dependence of small cell lung cancer on IGF-I and stem cell factor signalling. Mol Cancer Ther 3: 527-535
NVP-TAE226	dual tyrosine kinase inhibitor of focal adhesion kinase and IGF1R
	Concentration range: 1-10 microM
	Reference:
	Liu T-J et al. (2007) Inhibition of both focal adhesion kinase and insulin-like growth factor-I receptor kinase suppresses glioma proliferation in vitro and in vivo. Mol Cancer Ther 6 : 1357-1367
BMS-554417	2-(4-substituted-2oxo-1,2-dihydropyridin-3-yl)-benzimidazole derivative (Bristol Myers Squibb)
	Dual insulin-like growth factor-I/insulin receptor inhibitor
	Concentration range: 120nM->8.5 microM
	Reference :
	Haluska P et al. (2006) In vitro and in vivo antitumor effects of the dual insulin-like growth factor-I/insulin receptor inhibitor, BMS-554417. Cancer Res 66: 362-371
BMS-536924	1*H*-(benzimidazol-2-yl)-1*H*-pyridin-2-one (Bristol Myers Squibb)
	IGF1R kinase inhibitor
	Concentration range: 0.14-3.63 microM
	Reference:
	Wittman MD et al. (2007) Novel 1*H*-(benzimidazol-2-yl)-1*H*-pyridin-2-one inhibitors of insulin-like growth factor I (IGF-1R) kinase. Bioorganic & Medicinal Chemistry Letters 17: 974-977

AQIP	quinolinyl-derived imidazol[1,5alpha] pyrazine IGF-IR inhibitor
	(OSI Pharmaceuticals Melville NY, USA)
	concentration range 0.086-10 microM
	Reference:
	Mulvihill MJ et al. (2008) Novel 2-phenylqinolin-7-yl-derived imidazol[1,5α]pyrazines as potent insulin-like growth factor-I receptor (IGF-IR) inhibitors. Bioorganic & Medicinal Chemistry 16: 1359-1375
PQIP	cis-3-[3-(4-methyl-piperazin-I-yl)-cyclobutyl]-1-(2-phenyl-quinolin-7yl)-imidazol[1,5α]pyrazin-8-ylamine
	(OSI Pharmaceuticals Melville NY, USA)
	selective IGF1R inhibitor
	concentration range 19nM
	Reference:
	Ji Q-S et al. (2007) A novel, potent and selective insulin-like growth factor-I receptor kinase inhibitor blocks insulin-like growth factor-I receptor signalling in vitro and inhibits insulin-like growth factor-I receptor-dependent tumor growth in vivo. Mol Cancer ther 6: 2158-2167
PPP	picropodophyllin, a cyclolignan (Karolinska Institute)
	selective IGF1R inhibitor
	concentration range: 1-2.5 microM
	Reference:
	Girnita A et al. (2006) The insulin-like growth factor-I receptor inhibitor picropodophyllin causes tumor regression and attenuates mechanisms involved in invasion of uveal melanoma cells. Clin Cancer Res 12: 1383-1391
PQ401	diaryl urea compounds (Telik Corp. Palo Alto Ca. USA)
	selective IGF1R inhibitors
	concentration range: 1-12 microM
	Reference :
	Gable KL et al (2006) Diarylureas are small-molecule inhibitors of insulin-like growth factor I receptor signaling and breast cancer cell growth. Mol Cancer Ther 5: 1079-1086
Decapeptide analog	stable D-peptide analog of IGF-1, D-amino acid peptide JB3 (C-S-K-A-P-K-L-P-A-A-Y-C)
	Concentration range 0.1-10 mg/ml
	Reference :
	Hayry P et al. (1995) Stable D-peptide analog of insulin-like growth factor-I inhibits smooth muscle muscle cell proliferation after corticoid ballooning injury in the rat. FASEB J 9: 1336-1344

A further embodiment of the invention is the use of Biguanides and/or insulin sensitizers for the preparation of a medicament for the treatment of acne, vulgaris, rosacea and/or rhinophym.

A preferred substance is Metformin. Suitable amounts are about 500 to 2000 mg per day.

A further embodiment of the invention is the use of Metformin for the prevention of adenocarcinomas, especially prostate carcinomas and mamma carcinomas, and/or the prevention of atherosclerosis, cardiovascular diseases, neurodegenerative diseases, especially dementia and Alzheimer's disease.

A further embodiment is a composition for the treatment of acne vulgaris, rosacea, and/or rhinophym comprising at least one inhibitor of the IGF-1 signal pathway and at least one inhibitor of the FGFR2 signal pathway.

This composition may comprise the two or more components as a mixture or in two or more separate application forms packed together.

Taking into account, that IGF-1 is involved in the mentioned diseases, uptake of IGF-1 should be reduced or avoided.

Therefore, a further embodiment of the invention is bovine milk or a product from bovine milk having a reduced content of hormones, especially hormones selected from progesterone and growth factors, like insulin-like growth factor-1 (IGF1) and 2 (IGF2), fibroblast growth factors-1 (FGF1) and 2 (FGF2).

Milk from pregnant cows, the external source of gestational steroids

Economies of scale and market efficiencies of westernized countries are the driving force of the dairy industry. With the help of veterinary medicine high-yield milk production is derived from 75% to 90% from pregnant cows. Under physiological conditions, progesterone production finishes at the end of pregnancy and later milk production starts. With "modern" techniques of veterinary medicine, it is possible to gain high-yield milk production during pregnancy. Thus, permanent progesterone-secreting cows are the motor of the industrialized milk machinery. A heifer produces no milk until she is post-partum with her first calf. After feeding the calf for about four weeks, she enters the milking line. Just after her first heat about 6 weeks post-partum the cow is bred and milking continues during the complete 10-months pregnancy until the cow is allowed to "dry" a few weeks before delivery. "Freshening", the

generation of a new fresh milk supply post-partum, results from this cycle. After about 5 pregnancies the milk- and progesterone-synthesizing cow is sold for butchering providing meat and fat enriched in gestational hormones. This practice results in milk that contains placenta-derived progesterone but also dihydrotestosterone precursors including 5α-pregnanedione and 5α-androstanedione. The comparison of progesterone levels of cow plasma, skim milk and whole milk using radioimmunoassay, solid-phase enzyme immunoassay or direct enzyme immunoassay between 24 lactating dairy cows who have high progesterone levels (those in diestrus or pregnant) and low concentrations (those in estrus or anestrus) showed a 8.1 to 40.5fold increase of progesterone in plasma, a 3.3 to 20.5fold in crease of progesterone in skim milk, and a 7.0 to 49fold increase of progesterone in whole milk. These data demonstrate that the technique of milk production by pregnant cows results in an extreme, severalfold progesterone contamination of cow milk and cow plasma. As progesterone is a lipophilic steroid, it is preferentially distributed in the fatty tissues. Fat samples from pregnant cows contain more than 10fold increased levels of the hormone (239-336 µg/kg) versus low levels in fat of heifers (16.7-37.9 µg/kg). Fat progesterone levels of steers (2.62-2.96 µg/ml) are negligible compared to those of heifers and pregnant cows. Data on the progesterone levels of milk and dairy product clearly show the increase of progesterone content with the percentage of fat. The extreme increase of progesterone in cow plasma reflects increased progesterone levels of fat and cow meat which also enters the food chain. This might perfectly explain the association between consumption of red meat and colorectal cancer.

The progesterone-GH-IGF-1 axis in canine mammary tumours

The GH/IGF-1 axis is implicated in the development of human breast cancer. GH is synthesized in the anterior prituitary gland and released in a pulsatile manner. In the dog, the GH pulsatile release is altered or absent when autocrine production of GH occurs by the mammary gland. Autocrine GH production has been related with the exogeneous administration of synthetic progestagens. GH expression has been detected in positive progesterone receptor mammary gland cells. In addition, the GH receptor has been

identified in different benign and malignant mammary tumor cell types, indicating that the conditions for progestin-induced autocrine/paracrine action of GH in canine mammary tumours are present. The systemic effects of GH are mediated mostly by IGF1, which is a proliferative growth factor implicated in breast tumorigenesis. IGF1 plays a role in the development of normal mammary gland, acting as a mediator for GH actions. In human breast cancer, IGF1 is expressed by stromal and neoplastic epithelial cell, suggesting an important role in mammary tumorigenesis. From studies with canine mammary tumours provided evidence that progesterone increases autocrine GH production which might directly stimulate local or systemic IGF1 secretion. The IGF1 effect might be influenced by local levels of 17β-estradiol. The study exhibited two endocrine synergies: (1) between progesterone and GH and (2) between 17β-estradiol and IGF1.These results point to the important role of progesterone stimulating the development and maintenance of mammary tumours in an autocrine/paracrine manner.

Progestin in hormone replacement therapy increases the risk of breast cancer

It is conceivable that like in the human mammary gland and other epithelial cells progesterone or synthetic progestin induces autocrine GH production and local and systemic IGF1 expression resulting in the stimulation of the sebaceous follicle. Indeed, the most frequent adverse events reported in clinical trials that were related to progestin-releasing implants were headaches and acne. Moreover, recent evidence has indicated that there is an increased risk of breast cancer in women that consume a combined regimen of estrogen and progestin for hormone replacement therapy, as compared with those that take estrogen alone or a placebo. It is well known that angiogensis is essential for tumour growth, expansion and metastasis. Vascular endothelial growth factor (VEGF) is one of the most potent angiogenic growth factors and its effects on the proliferation, survival, and permeability of endothelial cells have been extensively studied. Progesterone as well as the synthetic progestin medroxyprogesterone acetate which is extensively used for hormone replacement therapy, regulate VEGF in a subset of breast cancer cells. Recent

evidence has been provided that the PI3K pathway and functional SP-1 predominantly control progestin-dependent VEGF induction response to both the natural hormone progesterone and synthetic ligands in breast cancer cells.

Milk from pregnant cows, the external source of growth hormones

As milk supplies progesterone of the lipid phase and the growth factors in the proteinaceous phase milk exerts a two-hit attack of the human organism. Absorbed IGF1 exerts direct effects on cell growth and survival, whereas ingested progesterone indirectly induces the GH/IGF-1 axis maintaining and potentiating the deleterious effects of cow milk.

Exogeneous and systemically derived IGF1 augment the input of acneigenic signals, clinically appearing as aggravation of acne by consumption of milk-born IGF1 and the association of acne with condition exhibiting elevated IGF1 serum levels like puberty, hyperglycemic diet, acromegaly, and polycystic ovary syndrome.

Epidemiologic observations point to the role of Western diet in the development or aggravation of acne. Cordain et al. studied 1200 Kitavan islanders of Papua New Guinea and 115 Aché hunter-gatherers of Paraguay who do not consume dairy products and have low glycemic diets. No case of acne has been detected in these two non-westernized populations. Diets rich in carbohydrates with a high glycemic index are associated with hyperglycemia, reactive hyperinsulinemia and increased formation of IGF1. IGF1 is a potent mitogen for virtually all body tissues. Raised levels of insulin and IGF1 induce seborrhea and follicular hyperkeratosis. Diets with a low glycemic load decrease serum IGF1 levels and significantly improved acne during a 12-week diet. Direct injections of recombinant IGF1 in humans elicited androgenesis and acne. Diets rich in low-glycemic load foods reduced serum testosterone and fasting glucose levels while improving insulin metabolism.

It is important to note that cow milk contains active IGF1 as well as FGF1 and FGF2. In bovine cheese whey FGF1 and FGF2 and in bovine colostrum FGF2-like growth factor have been identified. Cows treated with bovine somatrotopin

to improve milk yield showed increased levels of IGF-1 in the milk. Human and bovine IGF1 share the same amino acid sequences. The IGF1 concentration in cow milk is in the range of 22 to 26 ng/ml. Milk contains IGF-binding proteins as well as FGF-binding proteins. Several milk proteins including IGF-binding proteins protect IGF1 from digestion in the gut. Milk-borne IGF1 can be absorbed after oral intake. Experiments demonstrate that a significant increase of serum levels of IGF1 could be detected after 1.5 h of consumption of 1 l of cow milk or whey. This confirms that cow milk provides a potent source of biologically active growth factors for systemic uptake by humans. A higher amount of milk consumption was related to an overall increase in total body length of 3 cm in boys.

During puberty, the period of maximum activity of acne, serum androgens and IGF1 levels are increased and the course of acne is more closely related to IGF1 than to androgens. During this period of life, the pilosebaceous follicle is maximally stimulated by androgens and IGF1. Westernized diets containing milk-born IGF1 and FGFs and systemically induced IGF1 by hyperglycemic diets will result in further over-stimulation of the already strongly stimulated pilosebaceous follicle resulting in the manifestation of acne.

Milk-born FGF1 and FGF2 will stimulate mesenchymal cells of the sebaceous follicle and prostate to synthesize FGF7 and FGF10. FGF7 and FGF10 stimulate epithelial FGFR2b of follicular keratinocytes, sebocytes and prostate epithelial cells which activate downstream MAPK/ERK-, PLCγ/PKC-, and PI3K/Akt-pathways amplifying the growth stimulatory signals, lipogenesis and hyperkeratinization. Intriguingly, it has been shown that IGF1/insulin signaling activates androgen signaling through direct interactions of Foxo1 with androgen receptor. Normally, Foxo1 reduces androgen-induced androgen receptor target gene expressions and suppresses the in vitro growth of prostate cancer cells. However, in response to IGF1 or insulin Foxo1 becomes phosphorylated and inactivated by the PI3K/Akt kinase. The IGF1/insulin-mediated inactivation of Foxo1 explains the increased androgen responsiveness of acne leading to increased proliferation of sebaceous glands

and follicular keratinocytes. 13-cis-retinoic acid is rapidly isomerized to all-trans-retinoic acid (ATRA) in SZ95 sebocytes. Binding of ATRA to cellular retinoid acid binding protein-2 (CRABP-2) targets ATRA to the retinoid receptor (RAR) thereby inhibiting proliferation and promoting sebocyte apoptosis. A most plausible explanation of the sebum-suppressive effect of ATRA its effect on the availability of free IGF1. In human dermal papilla cells, ATRA induced a fivefold increase of IGFBP-3, which has been shown to inhibit the activity of IGFs in a variety of systems. IGFBP-3 forms a complex with IGF1 to reduce the concentration of free IGF1 important for maintaining of hair anagen growth phase.

In this respect, milk-derived growth factors have to be regarded as amplifiers of follicular growth signalling. IGF1 is a mitogenic polypeptide that stimulates growth, differentiation and metabolism in a variety of cell types. Milk-derived growth factors are potent serum supplements for the growth of fibroblasts and epithelial cells. Industrial whey contains the bulk of the growth factor activity and promotes growth of mesodermal-derived cell cultures. This fits well to the observation that skim milk had higher acne-promoting activity than whole milk. Strong trophic effects of IGF1 and FGF in human milk on cultured human fetal small intestinal cells show the mitogenic activity of milk in humans. A fraction of bovine whey exhibited high mitotic activity which stimulated wound repair. Cow milk, whey and skim milk and high-glycemic diet-derived IGF1 have direct co-stimulatory effects on androgen-receptor dependent target genes and downstream FGFR2-signalling cascades as well as indirect effect on the FGFR2-signalling by androgen-induction and increased expression of FGF7 and FGF10. Thereby, diet-born IGF1 induces three modes of FGFR2 signal amplification, up-regulating androgen receptor transactivation, promoting the signal input layer of androgen-dependent epithelial cells (IGF1→androgen→FGF7/FGF10) and enhancing IGF1 signal tension (IGF1→IGFR→MAPK/PI3K/PKC) all resulting in a synergistic amplification of growth factor signaling. Thus, diet-induced over-stimulation of FGFR2b-signal transduction explains the development or aggravation of acne in adolescence and the stimulation of prostate epithelial cells in the adult.

The concept of androgen/IGF1-FGF/FGFR2-mediated acneigenesis raises the question whether life-long dietary overstimulation of the androgen-dependent prostatic FGFR2-signalling with IGF1 induces prostate hyperplasia leading to prostate cancer. Epidemiological studies have shown elevated levels of circulating IGF1 to be associated with increased risk of prostate cancer IGF1. Inherited variations in the IGF1 gene have been associated with an increased risk of prostate cancer and seem to influence circulating levels of IGF1. Individuals with IGF1 polymorphisms leading to increased levels of free IGF1 serum might exhibit an increased susceptibility for the development of acne and IGF1-dependent cancers. Severe and prolonged acne in adulthood could reflect these genetic IGF1 variations. High-membranous IGF1-R staining was observed in carcinomas of the breast (87.5%), ovaries (100%), endometrium (100%), stomach (71.1%), pancreas (57.1%), colon (90%), prostate (54.5%), and bladder (100%). The increased incidence of prostate cancer in men with severe acne which afforded prolonged tetracycline treatment points in this direction. Persistent acne in adulthood might be a risk-indicator for the early detection of patients prone to develop IGF1-mediated carcinomas. Continuous milk consumption and hyperglycemic diet induced IGF1-mediated PI3K activation inducing the lipogenic phenotype in cancer pathogenesis. In this respect, long-term uptake of milk and hyperglycemic diets have to be regarded as cancerogenic food. Individuals with increased FGFR2 and PI3K signaling should avoid dairy products and hyperglycemic diets and should strictly control their body weight.

Furthermore, it has found that also Casein from cow milk increases IGF-1 levels. One possible explanation is, that casein comprises sequences of IGF-1 which are released during digestion.

This can be prevented by treating the milk with enzymes to destroy the ability to increase IGF-1 serum levels.

Suitable enzymes can be derived for example from yeast, like yeast used for the production of kefir. A person skilled in the art can test different enzymes

and conditions to treat milk, apply the treated milk to test persons and analyze IGF-1 levels, thereby identifying suitable treatment conditions.

A further embodiment of the invention is a genetically modified cow producing a modified casein which has a reduced effect on IGF-1 levels.

A further embodiment of the invention is the use of milk with modified casein for alimentation and/or the prevention of acne, allergies, adenocarcinomas, especially prostate carcinomas and mamma carcinomas, and/or the prevention of atherosclerosis, cardiovascular diseases, neurodegenerative diseases, especially dementia and Alzheimer's disease.

Acne is not only an androgen-mediated disease of puberty. Prolonged and persistent acne has to be critically regarded as an indicator disease of over-stimulated growth factor signaling bearing the potential of cancer promotion.

'Reduced' means a reduction of 50% of activity of the hormone compared to untreated milk.

The IGF-1 content of the milk or milk product of the invention is preferably in the range of 0 to 5 µg/ml.

The progesterone content of the milk or milk product of the invention is preferably in the range of 0 to 2 µg/ml.

The content of hormones of milk or milk products may be reduced by biophysical methods, for example immuno precipitation or affinity chromatography or by specific enzymatic treatment.

A further embodiment of the invention is therefore a method for reducing the content of hormones in milk or a milk product by biophysically or enzymatically removing/destroying the hormone.

Figure 1 shows the structure of FGFR2 receptors.

Figure 2 shows Signal transduction of insulin, IGF-1, and IGF-2. IGF=insulin-like growth factor; IR= insulin receptor; IGFR=IGF-receptor; MAPK=mitogen activated protein kinase; PI3K=phosphoinositide-3-kinase.

Figure 3 shows Mesenchymal-epithelial interaction between IGF-1- and FGF7/10-mediated signal transduction in the pilosebaceous follicle. FGF= fibroblast growth factor; FGFR=FGF-receptor; T=testosterone; A=androstenedione; DHEA=dehydroepiandrosterone; GH=growth hormone; IGF=insulin-like growth factor; IGF1R=IGF-1-receptor; PCOS=polycystic ovary syndrome; MAPK=mitogen-activated protein kinase; PI3K=phosphoinositide-3 kinase; PLCγ=phospholipase Cγ; MMPs=matrix metalloproteinases; SREBP-1=sterol response element-binding protein-1; IL-1α =interleukin-1α.

REFERENCES

1. Kligman AM, Shelly WB (1958) An investigation into the biology of the sebaceous gland. J Invest Dermatol 30: 99-125
2. Plewig G (1974) Acne vulgaris: proliferative cells in sebaceous glands. Br J Dermatol 90: 623-630
3. Downing DT, Strauss JS (1982) On the mechanism of sebaceous secretion. Arch Dermatol Res 272: 343-349
4. Pochi PE, Strauss JS (1969) Sebaceous gland response in man to the administration of testosterone, delta-4-androstnendione, and dehydroisoandrosterone. J Invest Dermatol 52: 32-36
5. Thiboutot D, Knaggs H, Gilliland K, Lin G (1998) Activity of 5-alpha-reductase and 17-beta-hydroxysteroid dehydrogenase in the infrainfundibulum of subjects with and without acne vulgaris. Dermatology 196: 38-42
6. Marynick SP, Chakmakjian ZH, McCaffree DL, Herndon JH Jr (1983) Androgen excess in cystic acne. N Engl J Med 308: 981-986
7. Melnik B, Jansen T, Grabbe S (2007) Abuse of anabolic-androgenic steroids and bodybuilding acne: an underestimated health problem. J Dtsch Dermatol Ges 5: 110-117
8. Schmidt JB, Spona J, Huber J (1986) Androgen receptor in hirsutism and acne. Gynecol Obstet Invest 22: 206-211
9. Thiboutot D, Harris G, Iles V, et al. (1995) Activity of the type 1 alpha-reductase exhibits regional differences in isolated sebaceous glands and whole skin. J Invest Dermatol 105: 209-214
10. Zouboulis CC (2003) Treatment of acne with antiandrogens – an evidence-based review. J Dtsch Dermatol Ges 1: 535-546
11. Imperato-McGinley J, Gautier T, Cai LQ et al. (1993) The androgen control of sebum production. Studies of subjects with dihydrotestosterone deficiency and complete androgen insensitivity. J Clin Endocrinol Metab 76:524-528

11a. Aroni K, Tsagroni E, Kavantzas N et al. (2007) A study of the pathogenesis of rosacea: how angiogenesis and mast cells participate in a complex multifactorial process. Arch Dermatol Res. Dec 11 [Epub ahead of print].

11b. Cuevas P, Sanchez I, Lozano RM, Gimenez.Gallego G (2005) Dobesilate is an angiogenesis inhibitor. Eur J Med Res 10: 369-372

11c. Cuevas P, Arrazola JM (2005) Therapeutic response of rosacea to dobesilate. 10: 454-456

11d. Otberg N, Finner AM, Shpiro J (2007) Androgenetic alopecia. Endocrinol Metab Clin North Am 36: 379-398

11e. Wa B, Jiang H, Utting OB et al. (2006) Influence of interleukin-1α on androgen receptor expression and cytokine secretion by cultured human dermal papilla cells. Exp Dermatol 15: 784-793

11f. Kawano M, Komi-Kuramochi A, Asada M et al. (2005) Comprehensive analysis of FGF and FGFR expression in skin: FGF18 is highly expressed in hair follicles and capable of inducing anagen from teleogen stage hair follicles. J Invest Dermatol 124: 877-885

11g. Kwack MH, Sung YK, Chung EJ et al (2008) Dihydrotestosterone-inducible dickkopf1 from balding dermal papilla cells causes apoptosis in follicular keratinocytes. J Invest Dermatol 128: 262-269

12. Guy R, Green MR, Kealey T (1996) Modeling acne in vitro. J Invest Dermatol 106: 176-182
13. Eswarakumar VP, Lax I, Schlessinger J (2005) Cellular signaling by fibroblast growth factor receptors. Cytokine Growth Factor Rev 16: 139-149
14. Orr-Urtreger A, Bedfort MT, Burakova T et al. (1993) Developmental localization of the splicing alternatives of fibroblast growth factor receptor-2 (FGFR2). Dev Biol 158: 475-486
15. De Giorgi V, Sestini S, Massi D et al. (2007) Keratinocyte growth factor receptors. Dermatol Clin 25: 477-485
16. Yeh BK, Igarashi M, Eliseenkova AV et al. (2003) Structural basis by which alternative splicing confers specificity in fibroblast growth factor receptors. Proc Nat Acad Sci USA 100: 2266-2271
17. Grose R, Fantl V, Werner S et al. (2007) The role of fibroblast growth factor receptor 2b in skin homeostasis and cancer development. EMBO J 26: 1268-127835.
18. Danilenko DM, Ring BD, Yanagihara D et al. (1995) Keratinocyte growth factor is an important endogeneous mediator of hair follicle growth development, and differentiation. Normaization of the nu/nu follicular differentiation defect and amelioration of chemotherapy-induced alopecia. Am J Pathol 147: 145-154
19. De Moerlooze L, Spencer-Dene B, Revest J et al. (2000) An important role for the IIIb isoform of fibroblast growth factor receptor 2 (FGFR2) in mesenchymal-epithelial signalling during mouse organogenesis. Development 127: 483-492
20. Revest JM, Spencer-Dene B, Kerr K et al. (2001) Fibroblast growth factor receptor 2-IIIb acts upstream of Shh and Fgf4 and is required for limb bud maintenance but not for the induction of Fgf8, Fgf10, Msx1, Bmp4. Dev Biol 231: 47-62
21. Celli G, LaRochelle WJ, Mackem S et al. (1998) Soluble dominant-negative receptor uncovers essential roles for fibroblast growths factors in multi-organ induction and patterning. EMBO J 17: 1642-1655
22. Min H, Danilenko DM, Scully SA et al. (1998) Fgf-10 is required for both limb and lung development and exhibits striking functional similarity to Drosophila branchless. Genes Dev 12: 3156-3161
23. Sekine K, Ohuchi H, Fujiwara M et al. (1999) Fgf10 is essential for limb and lung formation. Nat Genet 21: 138-141
24. Petiot A, Conti FJ, Grose R et al. (2003) A crucial role for Fgfr2-IIIb signalling in epidermal development and hair follicle patterning. Development 130:5493-5501
25. Werner S, Smola H, Liao X et al. (1994) The function of KGF in morphogenesis of epithelium and reepithelialization of wounds. Science 266: 819-822
26. Kuslak SL, Thielen JL, Marker PC (2007) The mouse seminal vesicle shape mutation is allelic with Fgfr2. Development 134: 557-565
27. Lin Y, Liu G, Zhang Y et al. (2007) Fibroblast growth factor receptor 2 tyrosine kinase is required for prostatic morphogenesis and the acquisition of strict androgen dependency for adult tissue homeostasis. Development 134: 723-734
28. Ibrahimi OA, Eliseekova AV, Plotnikov AN et al. (2001) Structural basis for fibroblast growth factor receptor 2 activation in Apert syndrome. Proc Nat Acad Sci USA 98: 7182-7187

29. George FW, Peterson KG (1988) 5α-Dihydrotestosterone formation is necessary for embryogenesis of the rat prostate. Endocrinology 122: 1159-1164
30. Siiteri PK, Wilson JD (1974) Testosterone formation and metabolism during male sexual differentiation in the human embryo. J Clin Endocrinal Metab 38:113-125
31. Marker PC, Donjacour AA, Dahiya R et al. (2003) Hormonal, cellular, and molecular control of prostatic development. Dev Biol 253: 165-174
32. Cunha GR, Donjacour AA, Cooke PS et al. (1987) The endocrinology and developmental biology of the prostate. Endo Rev 8: 338-363
33. Pu Y, Huang L, Birch L, Prins GS (2007) Androgen regulation of prostate morphoregulatory gene expression: Fgf10-dependent and –independent pathways. Endocrinology 148: 1697-1706
34. Tang W, Zheng SB, Zhang JH (2002) Effects of androgen and estrogen on the expression of basic fibroblast growth factor, transforming growth factor and smoothelins. Di Yi Jun Yi Da Xue Xue Bao 22: 13-16
35. Rosini P, Bonaccorsi L, Baldi E et al. (2002) Androgen receptor expression induces FGF2, FGF-binding protein production, and FGF2 release in prostate carcinoma cells: role of FGF2 in growth, survival, and androgen receptor down-regulation. The Prostate 53: 310-321
36. Gonzalez-Herrera IG, Prado-Lourenco L, Pileur F et al. (2006) Testosterone regulates FGF-2 expression during testis maturation by an IRES-dependent translational mechanism. FASEB J 10.1096/fj.04-3314fje
37. Mikkola ML (2007) p63 in skin appendage development. Cell Cycle 6: 285-290
38. Mailleux AA, Spencer-Dene B, Dillon C et al. (2002) Role of FGF10/FGFR2b signaling during mammary gland development in the mouse embryo. Development 130: 5493-5501
39. Mills AA, Zheng BH, Wang XJ et al. (1999) p63 is a p53 homologue required for limb and epidermal morphogenesis. Nature 398: 708-713
40. Yang A, Schweitzer R, Sun DQ et al. (1999) p63 is essential for regenerative proliferation in limb, craniofacial and epidermal development. Nature 398: 714-718
41. Rice R, Spencer-Dene B, Connor EC et al. (2004) Disruption of Fgf10/Fgfr2b-coordinated epithelial-mesenchymal interactions causes cleft palate. J Clin Invest 113: 1692-1700
42. Allen M, Grachtchouk M, Sheng H et al. (2003) Hedgehog signaling regulates sebaceous gland development. Am J Pathol163: 2173-2178
43. Riobo NA, Manning DR (2007) Pathway of signal transduction employed by vertebrate hedgehogs. Biochem J 403: 369-379
44. Niemann C, Unden AB, Lyle S et al. (2003) Indian hedgehog and β-catenin signaling: role in the sebaceous lineage of normal and neoplastic mammalian epidermis. Proc Natl Acad Sci USA 100: 11837-11880
45. Kalff-Suske M, Wild A, Topp J (1999) Point mutations throughout the Gli3 gene cause Greig cephalopolysyndactyly syndrome. Hum Mol Genet 8: 1769-1777
46. Bitgood MJ, McMahon AP (1995) Hedgehog and Bmp genes are coexpressed at many diverse sites of cell-cell interaction in the mouse embryo. Dev Biol 172: 126-138
47. Iseki S, Araga A, Ohuchi H et al. (1996) Sonic hedgehog is expressed in epithelial cells during development of whisker, hair, and tooth. Biochem Biophys Res Commun 218: 688-693
48. Kalderon D (2000) Transducing the hedgehog signal. Cell 103: 371-374

49. Matise MP, Joyner AL (1999) Gli genes in development of cancer. Oncogene 18: 7852-7859
50. Ruiz I, Altaba B, Sanchez P, Dahmane N (2002) Gli and hedgehog in cancer: tumors, embryos and stem cells. Nat Rev Caner 2: 361-372
51. St Jacques B, Dassule HR, Karavanova I et al (1998) Sonic hedgehog signaling is essential for hair development. Curr Biol 8: 1058-1068
52. Chiang C, Swan RZ, Grachtchouk M et al. (1999) Essential role for sonic hedgehog during hair follicle morphogenesis. Dev Biol 205: 1-9
53. Zhang L, Li W-H, Anthonavage M, Eisinger M (2006) Melanocortin-5 receptor: a marker of human sebocyte differentiation. Peptides 27: 413-420
54. Chen W, Kelly MA, Opitz-Araya X et al. (1997) Exocrine gland dysfuction in MC5R-deficient mice: evidence for coordinated regulation of exocrine gland function by melanocortin peptides. Cell 91: 789-798
55. Thody AJ, Shuster S (1975) Control of sebaceous gland function in the rat by alpha-melanocyte-stimulating hormone. J Endocrinol 64: 503-510
56. Thody AJ, Cooper MF, Bowden PE et al. (1976) Effect of alpha-melanocyte-stimulating hormone and testosterone on cutaneous and modified sebaceous glands in the rat. J Endocrinol 71: 279-288
57. Böhm M, Luger TA, Tobin DJ, García-Borrón JC (2006) Melanocortin receptor ligands: new horizons for skin biology and clinical dermatology. J Invest Dermatol 126: 1966-1975
58. Zhang L, Anthonavage M, Huang Q, et al. (2003) Proopiomelanocortin peptides and sebogenesis. Ann NY Acad Sci 994: 154-161
59. Deplewski D, Rosenfield RL (2000) Role of hormones in pilosebaceous unit development. Endocr Rev 21: 363-392
60. Nelson AM, Gilliland KL, Cong Z, Thiboutot DM (2006) 13-cis retinoic acid induces apoptosis and cell cycle arrest in human SEB-1 sebocytes. J Invest Dermatol 126: 2178-2189
61. Goyette P, Allan D, Peschard P et al. (2000) Regulation of Gli activity by all-trans retinoic acid in mouse keratinocytes. Cancer Res 60: 5386-5389
62. Kasper M, Schnidar H, Neill GW et al. (2006) Selective modulation of Hedgehog/GLI target gene expression by epidermal growth factor signaling in human kerationcytes. Mol Cell Biol 26: 6283-6299
63. Bigelow RL, Jen EY, Delehedde M et al. (2005) Sonic hedgehog induces epidermal growth factor dependent matrix infiltration in HaCaT keratinocytes. J Invest Dermatol 124: 457-465
64. Kessaris N, Jamen F, Rubin L, Richardson WD (2004) Cooperation between sonic hedgehog and fibroblast growth factor/MAPK signalling pathways in neocortical precursors. Development 131: 1289-1298
65. Lupo G, Liu Y, Qiu R et al. (2005) Dorsoventral patterning of the Xenopus eye: a collaboration of retinoid, hedgehog, and FGF receptor signaling. Development 132: 1737-1748
66. Palma V, Lim DA, Dahmane N et al. (2005) Sonic hedgehog controls stem cell behavior in the postnatal and adult brain. Development 132: 335-344
67. Palma V, Ruiz I Altaba A (2004) Hedgehog-GLI signaling regulates the behavior of cells with stem cell properties in the developing neocortex. Development 131: 337-345
68. Riobo NA, Haines GM, Emerson CP (2006) Protein kinase C-delta and mitogen-activated protein/extracellular signal-regulated kinase-1 control GLI activation in hedgehog signaling. Cancer Res 66: 839845

69. Riobo NA, Lu K, Ai X et al. (2006) Phosphoinositide 3-kinase and Akt are essential for sonic hedgehog signaling. Proc Nat Acad Sci USA 103: 4505-4510
70. Kartasova T, Scandurro AB, Denning MF et al. (1995) Factors mediating the interactions between epidermal and dermal cells in skin grafts that might be important for hair follicle development. J Invest Dermatol 104: 21S-22S
71. Prouty SM Lawrence L, Stenn KS (1997) Fibroblast-dependent induction of a murine skin lesion similar to human nevus sebaceous of Jadassohn. Lab Invest 76: 179-189
72. Barbieri CE, Barton CE, Pietenpol JA (2003) ΔNp63α expression is regulated by the phosphoinositide 3-kinase pathway. J Biol Chem 278: 51408-51414120.
73. Miki T, Bottaro DP, Fleming TP et al. (1992) Determination of ligand-binding specificity by alternative splicing: two distinct growth factor receptors encoded by a single gene. Proc Natl Acad Sci USA 89: 246-250
74. Candi E, Rufini A, Terrinoni A et al. (2007) ΔNp63 regulates thymic development through enhanced expression of FgfR2 and Jag2. Proc Natl Acad Sci USA 104: 11999-12004
75. Wheatley VR (1986) Biochemical aspects of sebum formation. In: The Physiology and Pathophysiology of the Skin. The Sebaceous Gland. Vol 9, chapt 91, Academic Press London pp 2873-2898
76. D`Erchia AM, Tullo A, Lefkimmiatis K et al. (2006) The fatty acid synthase gene is a conserved p53 family target from worm to human. Cell Cycle 5: 750-758
77. Daub H, Weisss FU, Wallasch C, Ullrich A (1996) Role of transactivation of EGF receptor in signaling by G protein-coupled receptors. Nature 379: 557-560
78. Schlessinger J (2004) Common and distinct elements in cellular signaling via EGF and FGF receptors. Science 306: 1506-1507
79. Dlugosz AA, Cheng C, Denning MF et al. (1994) Keratinocyte growth factor receptor ligands induce transforming growth factor α expression and activate epidermal growth factor receptor signaling pathway in cultured epidermal keratinocytes. Cell Growth & Differentiation 5: 1283-1292
80. Thielitz A, Reinhold D, Vetter R et al. (2007) Inhibitors of dipeptidyl peptidase IV and aminopeptidase N target major pathogenic steps in acne initiation. J Invest Dermatol 127: 1042-1051
81. Zouboulis CC, Eady A, Philpott M et al. (2005) What is the pathogenesis of acne? Exp Dermatol 14: 143-152
82. Wæhre T, Yndestad A, Smith C et al. (2004) Increased expression of interleukin-1 in coronary artery disease with downregulatory effects of HMG-CoA reductase inhibitors. Circulation 109: 1966-1972 133. Cuevas P. Díaz-González D, Giménez-Gallego G, Dujovny M (2005) Dihydroxy-2,5 benzenesulphonate (dobesilate) elicits growth arrest and apoptosis in gliome cells. Neurol Res 27: 797-800

Claims

1. A composition for the treatment of acne vulgaris, rosacea and rhinophym comprising at least one inhibitor of the FGFR2 signal pathway.

2. The composition of claim 1 wherein the inhibitor is a glycosaminoglycan, especially 2-O-hepran sulfate or 2-N-hepran sulfate.

3. The composition of claim 1, wherein the inhibitor is selected from si-RNA, PD173074, 4-Phenoxyl-6-carboxyl-2-(1H)-quinolinone, a synthetic FGFR2b peptide antagonist, antisense FRS2alpha (fibroblast growth factor receptor substrate 2alpha), dithranol, FGFR2b antisense oligonucleotides and FGFR2cb antisense oligonucleotides.

4. The composition of claim 1, wherein the inhibitor is a MAP-kinase inhibitor.

5. The composition of claim 4, wherein the inhibitor is PD 98059, U0126, PD 184352, neomycin, neomycin sulfate, paromomycin, streptomycin, gentamicin, tobramycin, netilmicin, amikacin and related aminoglycoside derivatives and/or dobesilate (dihydroxy-2,5 benzenesulphonate).

6. The composition of claim 4, wherein the inhibitor is an inhibitor of p38MAP-kinase, especially SB203580, SB202190 or BIRB8796.

7. The composition of claim 1, wherein the inhibitor is an inhibitor of protein kinase C.

8. The composition of claim 7, wherein the inhibitor is selected from calphostin C, myristolyated, Ro 31-8220, GF109203X, Gö 6976, K252a, Ro 31-7549, Gö 6983, Chelerythrine chloride, (-)-Balanol, UCN-01, CGP41251, CGP54345, CGP53506, Aprinocarsen, CGP53506, Ly333531, Ly379196, Ly317615.

9. The composition of claim 1 wherein the inhibitor inhibits Sonic Hedgehog (Shh).

10. The composition of claim 9, wherein the inhibitor is selected from Sonic Hedgehog antisense oligonucleotides, Patched antisense oligonucleotides and Gli antisense oligonucleotides.

11. The composition of claim 1 wherein the inhibitor inhibits Smoothened (Smo).

12. The composition of claim 11, wherein the inhibitor is selected from cyclopalmine, GANT 61 (NSC 136476), GANT 58 (NSC 75503).

13. The composition of claim 1, where the inhibitor is TGF-ß1 or TGF-ß2.

14. The composition of claim 1 or 13, further comprising an inhibitor of dipeptidylpeptidase IV and/or an inhibitor of aminopeptidase N.

15. The composition of claim 14, wherein the inhibitor is selected from Lys[Z(NO_2)]-thiazolidid, Lys[Z(NO_2)]-pyrrolidid, Actinonin, Bestatin, Diprotin A, Ile-Pro-Ile, Sitagliptin, Vildagliptin, Saxagliptin.

16. A composition for the treatment of acne vulgaris, rosacea and/or rhinophym comprising at least one inhibitor of the IGF-1 signal pathway.

17. The composition of claim 16 wherein the inhibitor is an anti-IGF-1 receptor antibody or an IGF1 receptor tyrosine kinase inhibitor.

18. The composition of claim 16, wherein the composition is selected from αIR3, SCFV/FC, SCF/FV, EM/164, A-12, Bispecific, 19D12, H7C10, CP751-871, KM1468, NVP-AEW541-A, BMS-536924, BMS-554417, Cyclolignan, TAE226, NVP-AEW541, NVPADW742, PQ401, NVP-TAE226, AQIP, PQIP, PPP, decapeptide analogs.

19. A bovine milk or a product from bovine milk having a reduced content of hormones, especially hormones selected from progesterone and growth factors, like insulin-like growth factor-1 (IGF1) and 2 (IGF2), fibroblast

growth factors-1 (FGF1) and 2 (FGF2) and/or having a modified casein which has a reduced influence on IGF-1 levels.

20. A method for reducing the content of hormones in milk or a milk product by biophysically or enzymatically removing/destroying the hormones.

21. A bovine animal having a genetic modification to produce milk with a reduced content of hormones and/or a modified casein showing reduced IGF-1 serum levels.

22. Use of Biguanides and/or insulin sensitizers for the preparation of a medicament for the treatment of acne, vulgaris, rosacea and/or rhinophym, especially Metformin.

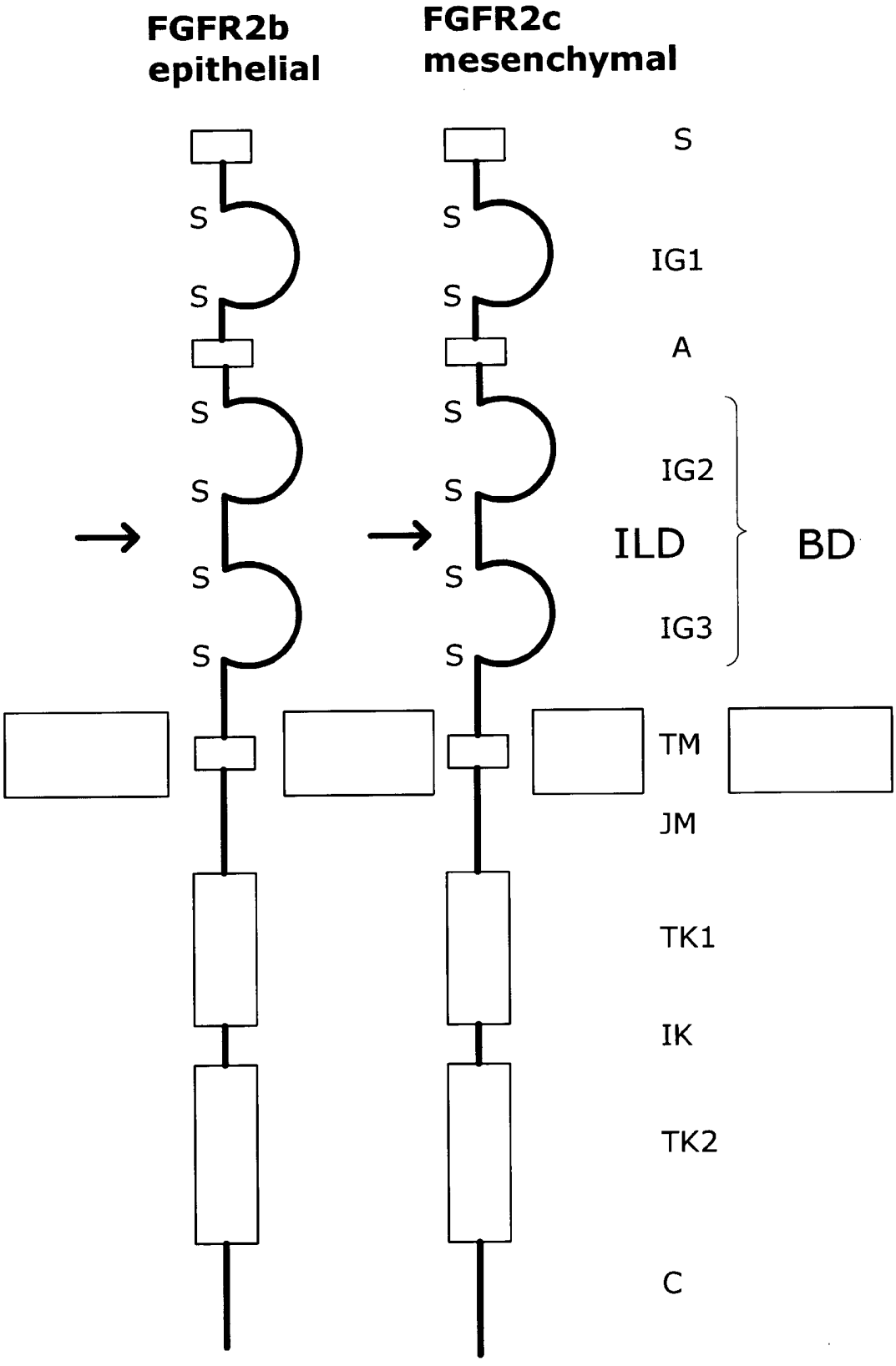
23. Use of Metformin for the prevention of adenocarcinomas, especially prostate carcinomas and mamma carcinomas, and/or the prevention of atherosclerosis, cardiovascular diseases, neurodegenerative diseases, especially dementia and Alzheimer's disease.

24. A method for treating milk to reduce IGF-1 increase by casein comprising the step of

- treating milk with a proteolytic enzyme or enzyme preparation.

25. A composition for the treatment of acne vulgaris, rosacea, and/or rhinophym comprising at least one inhibitor of the IGF-1 signal pathway and at least one inhibitor of the FGFR2 signal pathway.

Fig.1


FGFR2b
epithelial
FGFR2c
mesenchymal
S
IG1
A
IG2
ILD
BD
IG3
TM
JM
TK1
IK
TK2
C

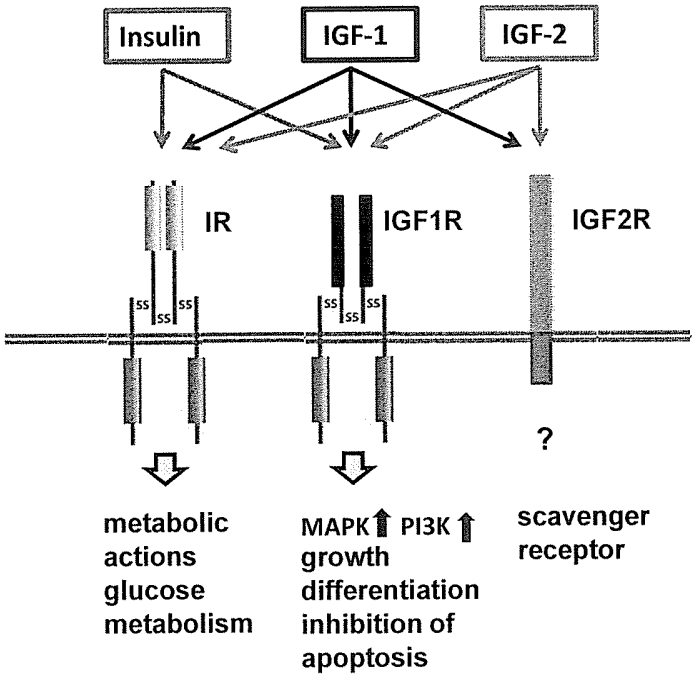

Insulin
IGF-1
IGF-2
IR
IGF1R
IGF2R
ss
?
metabolic actions glucose metabolism
MAPK PI3K
growth differentiation inhibition of apoptosis
scavenger receptor

Figure 2

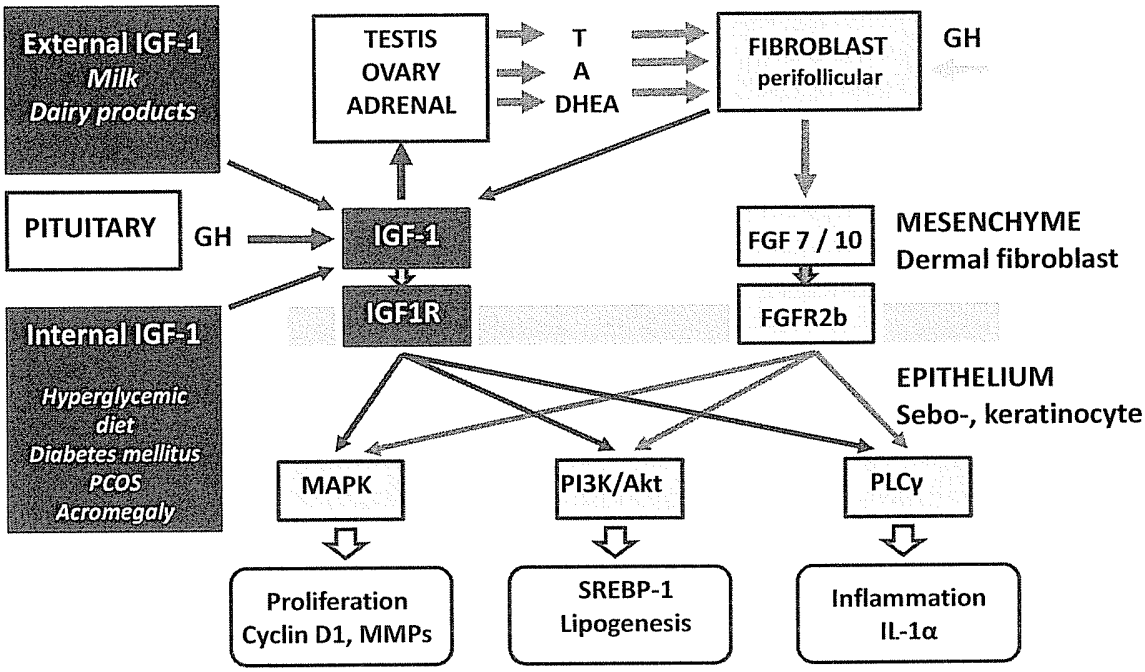

External IGF-1
Milk
Dairy products
TESTIS
OVARY
ADRENAL
T
A
DHEA
FIBROBLAST
perifollicular
GH
PITUITARY
GH
IGF-1
FGF 7 / 10
MESENCHYME
Dermal fibroblast
IGF1R
FGFR2b
Internal IGF-1
Hyperglycemic diet
Diabetes mellitus
PCOS
Acromegaly
EPITHELIUM
Sebo-, keratinocyte
MAPK
PI3K/Akt
PLCγ
Proliferation
Cyclin D1, MMPs
SREBP-1
Lipogenesis
Inflammation
IL-1α

Figure 3