Received: 14 March 2021 | Accepted: 18 March 2021

DOI: 10.1111/exd.14338

SUPPLEMENT ARTICLE

Experimental Dermatology WILEY

Target molecules for future hidradenitis suppurativa treatment

Christos C. Zouboulis[1,2] | John W. Frew[3,4] | Evangelos J. Giamarellos-Bourboulis[1,5] | Gregor B.E. Jemec[1,6,7] | Veronique del Marmol[1,8] | Angelo V. Marzano[1,9,10] | Georgios Nikolakis[1,2] | Christopher J. Sayed[11] | Thrasyvoulos Tzellos[1,12] | Kerstin Wolk[1,13] | Errol P. Prens[1,14,15]

[1]European Hidradenitis Suppurativa Foundation e.V., Dessau, Germany

[2]Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane and Faculty of Health Sciences Brandenburg, Dessau, Germany

[3]Department of Dermatology, Liverpool Hospital, Sydney, NSW, Australia

[4]University of New South Wales, Sydney, NSW, Australia

[5]4th Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Athens, Greece

[6]Department of Dermatology, Zealand University Hospital, Roskilde, Denmark

[7]Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[8]Department of Dermatology, Hôpital Erasme, Universite Libre de Bruxelles, Bruxelles, Belgium

[9]Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[10]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

[11]Department of Dermatology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[12]Department of Dermatology, NLSH University Hospital, Bodø, Norway

[13]Department of Dermatology and Institute of Medical Immunology/Psoriasis Research and Treatment Center, Charité-University Medicine, Berlin, Germany

[14]Laboratory for Experimental Immunodermatology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

[15]Department of Dermatology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

Correspondence
Christos C. Zouboulis, Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane, Auenweg 38, 06847 Dessau, Germany.
Email: christos.zouboulis@mhb-fontane.de

Abstract

The registration of the tumour necrosis factor-α inhibitor adalimumab in 2015 was a major step forward in the treatment of hidradenitis suppurativa/acne inversa (HS). However, it soon became evident that the effectiveness of adalimumab in daily practice was highly variable. A significant unmet medical need of HS patients remained, and the search for novel therapeutic targets was intensified. During the 10th European Hidradenitis Suppurativa Foundation (EHSF) e.V. Conference, reknown international HS investigators virtually presented and discussed the published data on these potential target molecules for future HS treatment. This article addresses the most promising molecules currently under investigation from a pathophysiological and clinical point of view. With phase III trials ongoing, the anti- interleukin (IL)-17 biologics bimekizumab and secukinumab are in the most advanced stage of clinical development showing promising results. In addition, targeting IL-1α with bermekimab has shown encouraging results in two clinical trials. Directing treatment at neutrophil recruitment and activation by targeting IL-36 with spesolimab fits well in the pathogenic concept of HS and clinical phase II trial results are pending. In contrast to in situ evidence, Complement 5a (C5a) and C5a receptor blockade have only shown greater

clinical benefit in patients with severe HS. Inhibition of Janus kinase (JAK) 1 signalling in HS showed clinical efficacy only in the highest dosage, highlighting that careful surveillance of the balance between safety and efficacy of JAK inhibition is warranted. Overall, clinical efficacies of all novel treatments reported so far are modest. To guide drug development, more and better-defined translational data on the pathogenesis of this severe and enigmatic inflammatory skin disease are required.

KEYWORDS
biomarkers, hidradenitis suppurativa, treatment targets

1 | INTRODUCTION

The rapidly increasing interest on hidradenitis suppurativa/acne inversa (HS) and the ongoing elucidation of its pathogenesis[1] intensify the search for target molecules of future HS treatment, which still remains though inconclusive. The total of 113 clinical studies currently documented in ClinicalTrials.gov indicates the wide range of ongoing target search.[2] The use of new agents is likely to accelerate our understanding as they present the opportunity to use clinical effectiveness to validate relevant patterns. On the other hand, the urgent need for robust information from preclinical research is undersigned by the last – due to diverse reasons – unsatisfactory efforts to provide therapeutic efficacy in clinical HS studies, such the ones using complement (C)5a receptor and interleukin (IL)-23 as treatment targets. Competent models for preclinical research have already been published, namely three-dimensional skin culture systems,[3,4] differential gene and protein expression studies[5,6] and repurposing analyses.[7,8] Indeed, conducting inclusive, long-term, controlled multi-centre clinical trials investigating different biological agents or drugs with ancillary analyses of transcriptomes based on next-generation sequence studies will leap forward the HS patient journey. These will build the foundations to fully integrate our HS transcriptome knowledge with clinical records, epidemiologic and demographic factors[9,10]

To date, however, many molecules have been identified in histologic samples,[11,12] but the sequence of the pattern and the key initiators are still work in progress. In the meantime, the inhibition of tumour necrosis factor (TNF)-α, IL-1 and IL-17 has been validated in clinical trials as relevant.[1] This article, which summarizes the data of the homonymous scientific symposium, which took place during the 10th European Hidradenitis Suppurativa Foundation (EHSF) e.V. Conference, February 10–12, 2021, provides expert opinions for target molecules for future HS treatment, which is a current hot topic both for HS interested scientists and the industry.

2 | IL-1

Three published clinical trials demonstrate that blocking IL-1α may be a promising strategy for the management of moderate-to-severe HS. Studied drugs were anakinra and bermekimab. Anakinra is the recombinant human antagonist of the receptor of IL-1 and is able to block both IL-1α and IL-1β. It is administered subcutaneously and due to the short half-life it needs to be administered once daily. Bermekimab is a fully humanized monoclonal antibody that selectively inhibits IL-1α. Both drugs have been studied in small patient populations and a synopsis of their efficacy is provided in Table 1. Their administration for 12 weeks led to the achievement of HS clinical response (HiSCR) in 60%–78% of the treated populations;[13-15] drugs were equally effective in patients naïve to anti-TNF treatment and patients refractory to previous anti-TNF treatment with primary or secondary failure. When patients originally allocated to placebo treatment were switched to treatment with bermekimab during the open-label extension period, similar efficacy was found.[16]

One big advantage of the published randomized clinical trials is that they provide evidence of the mechanism of action at the cell levels. Anakinra treatment was accompanied by improved function for the production of IL-22 by circulating peripheral blood mononuclear cells,[13] whereas bermekimab treatment modulated the influence of chemotactic mediators on skin destruction.[14] Patients treated with bermekimab experienced decrease of circulating IL-8, attenuated capacity of the whole blood for IL-8 production, and decrease of the thickness of the dermis infiltrated by the inflammatory procedure of HS. The depth of dermal involvement assessed by ultrasound was not associated with the capacity for the production of human β-defensin-2, as this was the case among placebo-treated patients.[14]

3 | IL-17

The rationale for selecting IL-17 as a target for therapy in HS is based on the central role of IL-17 in the pathophysiology of HS. Schlapbach et al[17] and Wolk et al[18] already in 2011 demonstrated the high expression of IL-23 and IL-17A and the presence of IL-17 producing T cells in lesional skin of HS patients. At the molecular level, a clear IL-17 signature and dysregulation of T-helper type 17 cytokines in HS lesional skin was demonstrated.[19] In addition, patients with HS showed imbalances in the T-helper 17 cell axis that are similar to those in patients with psoriasis.[12,20,21] The pro-inflammatory isoforms IL-17A, IL-17C and IL-17F have been identified in lesions of HS.[22] These compelling findings led to the first open-label and placebo-controlled trials targeting IL-17.[23,24] The results of the

TABLE 1 Synopsis of the efficacy of anakinra and bermekimab for the management of moderate-to-severe hidradenitis suppurativa

References	Design	Groups of treatment (n)	anti-TNF failure (%)	Primary endpoint	Secondary endpoints
13	RCT	Placebo qd sc × 12 wk (*n* = 10)	30%	Disease activity by wk 12: 20% vs 78%	HiSCR by wk 12: 30% vs 78%
		Anakinra qd sc × 12 wk (*n* = 9)	44%		Prolongation of time to first HS flare-up with anakinra
14	RCT	Placebo q2wk IV × 12 wk (*n* = 10)	50%	HiSCR achievement by wk 12: 10% vs 60%	HiSCR by wk 24: 0% vs 40%
		Bermekimab q2wk IV 7.5 mg/kg × 12 wk (*n* = 10)	70%		Improvement in at least two PROs by wk 12: 40% vs 80%
15	ONRT	Bermekimab 400 mg sc qwk (*n* = 42)	57%	HiSCR achievement by wk 12: 63% among anti-TNF previous failures; 61% among anti-TNF naive	

Abbreviations: HiSCR, hidradenitis suppurativa/acne inversa clinical response; IV, intravenous; *n*, number of patients; ONRT, open label trial; PRO, patient reported outcome; q2wk, one every other week; qd, once daily; qwk, once every week; RCT, randomized clinical trial; sc, subcutaneous; wk, week.

phase II placebo-controlled trials have not yet been published, but only presented at EHSF and SHSA meetings. Case reports and case series showed that secukinumab at 300 mg s.c. was able to induce a significant improvement in HS, even in patients who had failed other biologic therapies. In the largest case series by Casseres et al, secukinumab at 300 mg s.c resulted in >70% HiSCR achievement.[24] On the other hand, in a multicentre retrospective study collecting 31 HS patients treated with secukinumab at the same dose, HiSCR was only achieved by 41% of patients at week 28.[25]

The efficacy of brodalumab, a biologic that targets the IL-17 receptor A, was investigated in 10 patients.[26] An impressive 100% of patients achieved HiSCR and 80% achieved an International HS Severity Score System (IHS4) category change[27] at week 12, and also clear improvements were seen in pain, itch, quality of life and depression. No significant events associated with the use of brodalumab were reported up to week 24. The main limitations of both studies were the open-label design, and thus the lack of a placebo arm. Placebo-controlled phase 2 trials with biologics targeting IL-17 have been conducted by Novartis (www.clinicaltrials.gov identifier: NCT02421172) and UCB (www.clinicaltrials.gov identifier: NCT03248531). The Novartis trial used CJM112, an anti-IL-17 antibody which is structurally closely related to secukinumab. At week 16, thirty-two percent (32.3%) achieved a two-point improvement in their baseline HS-Physician Global Assessment (PGA) score versus 12.5% of patients on placebo. The mean inflammatory lesion count decreased 56.1% in the CJM112 group versus 30.2% in the placebo group.

The phase 2 UCB trial was conducted using bimekizumab. Bimekizumab is a humanized IgG1 monoclonal antibody that neutralizes IL-17AA, IL-17AF and IL-17FF. The trial design was unique in that adalimumab was used as an active comparator, and that it was the first clinical trial utilizing the IHS4 as a secondary outcome measure. The HiSCR[50] rate at week 12 was higher in the bimekizumab group (56.9%) compared to placebo (23.7%). Bimekizumab achieved higher HiSCR[75] and HiSCR[90] scores than adalimumab. Both anti-IL-17 biologics are now the only ones in phase III, which means that the anti-IL-17s are the most advanced in clinical development for the treatment of HS. The clinical efficacy so far looks promising, especially for bimekizumab. However, there is long way to go, because in psoriasis anti-IL-17 biologics are now involved in clinical trials with disease modification as goal (Figure 1).

4 | IL-23 AND IL-36

In the absence of a detailed understanding of the complex pathogenesis of HS, new treatments are generally introduced following clinical observations, for example, TNF blockade was introduced following a serendipitous observation in a patient who had both Crohn's disease and HS experienced that both diseases responded to infliximab treatment.[28] It may be speculated that co-morbidities imply the existence of shared aetiology and/or significant pathogenic steps. Psoriasis is a co-morbidity of HS, and the interfollicular epithelium of HS has psoriasis-like traits supporting an association.[29,30] Furthermore, a number of similarities exist in the currently described pathogenic mechanisms of HS and psoriasis, such as the prominent role of Th17 pathways, neutrophils and epidermal thickening. The clinical clustering of diseases, the patchy understanding of the exact disease mechanisms and serendipitous observations lead to the off-label use of psoriasis treatments in HS.

One such treatment opportunity is to attack the IL-23 and IL-36 pathways, as both are pro-inflammatory and affect neutrophil recruitment as well as activation. For psoriasis, there is increasing evidence of a significant role for the IL-23/IL-17 cytokine axis:

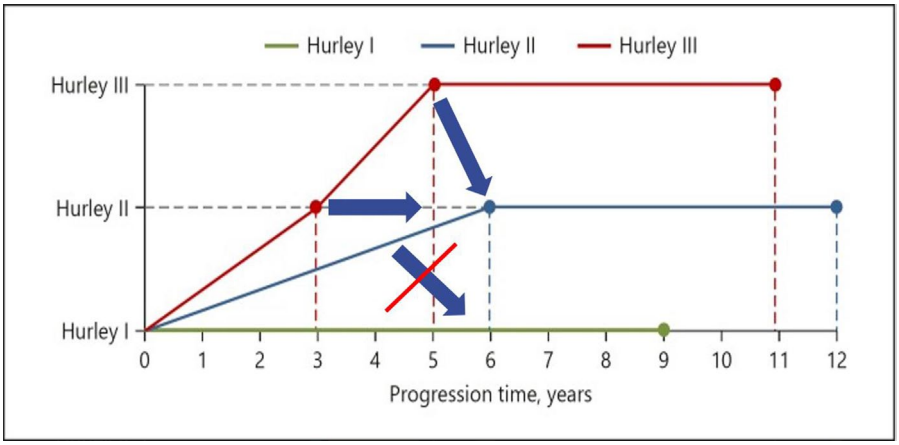

FIGURE 1 Illustration of possible outcomes in hidradenitis suppurativa patients by disease modifying agents

IL-23 secreted by dendritic cells and monocytes/macrophages promotes IL-17–producing T cells. These are, in turn, involved in recruitment and activation of neutrophils. IL-17 pathways also seem affected in HS.[17,19,31] Neutrophil recruitment and activation play a key role in both diseases. In addition, epidermal hyperplasia is induced.

The literature on IL-36 in inflammatory skin disorders is smaller. IL-36 belongs to the IL-1 family and includes three agonists (IL-36α, IL-36β and IL-36γ) and an antagonist (IL-36Ra). It is present in keratinocytes and other epithelia and has been implicated in the pathogenesis of inflammatory bowel disease, psoriasis, acne and HS, where IL-36 cytokines have been linked to inflammation, recruitment of neutrophils and epidermal hyperplasia.[32] IL-36 appears to be elevated in HS lesions supporting its role as an involved IL-1 family member participating in the pathogenesis.[33]

A number of drugs are being developed to target these molecules in other contexts. It is possible that they will prove useful in HS, although experience suggests that dosing will often have to be increased. IL-23 is targeted in different ways, for example by ustekinumab, risankizumab and guselkumab, while IL-36 is currently targeted by spesolimab. Evidence is as yet mostly at the level of cases and case series, but several studies are planned. While waiting for these, two strategies are tempting. Either the waiting time can be spent on a better understanding of the pathogenesis to provide actual translational data to guide development, or the continued collection of larger, unbiased (to include treatment failures) open case series. While both are alluring, the latter approach also provides data that can help to inform the design of the necessary phase 2 studies that are the immediate next step for any of the new molecules.

5 | JANUS KINASES

The Janus kinases (JAK) family is composed of four tyrosine kinases (JAK1, JAK2, JAK3 and TYK2) that have essential roles as signal transducers downstream of activated cytokine receptors.[34] Numerous small molecules target one or more JAK family members. JAK1 and JAK2 are involved in interferon (IFN)-γ signalling, whereas JAK3 is involved in signalling from type I cytokine receptors that use the common gamma chain (γc) including IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21.[34-36] Although the JAK-STAT pathway does not directly suppress IL-17 signalling (thought to be the major pathway contributing to inflammation in HS), it works indirectly through other STAT-dependent cytokines (e.g. IL-23), which directly influence IL-17 levels[36-38] and subsequent cellular activity. There is a plethora of theoretical basis for assessing the role of JAK-STAT blockade in reducing inflammation in HS given associations with not only Th17 cells, but also neutrophil chemotaxis,[38,39] B cell migration and activation,[39] as well as prominent comorbidities such as iron deficiency anaemia[40] given the role of JAKs in haematopoesis.

Janus kinases inhibition has been demonstrated histologically in psoriatic skin to decrease epidermal thickness, number of proliferating epidermal cells (measured by Ki67 staining), number of dermal $CD3^+$ T cells, and number of $CD11c^+$ dendritic cells. It is assumed that similar effects will be seen in the setting of HS although no published data are available to date. It should be noted that given our increasing understanding of the complexity of inflammation in HS, it is likely that the effect of any clinically significant disease improvement in the setting of JAK-STAT blockade will be due to effect upon multiple cell types and inflammatory pathways.[41]

Case reports of the use of tofacitinib in HS have been presented,[42] however, this has been used in combination with other therapeutics, including cyclosporine A. Results from a phase 2 study of JAK1 inhibition[43] demonstrated efficacy above the level of placebo only with the highest dosage, and as expected, the adverse event profile was significantly elevated at this dose.[43] This indicates that further investigation into the balance between safety and efficacy profiles of clinically significant effects of JAK inhibition is warranted. Further results are currently expected from other clinical trials including upadacitinib,[44] topical ruxolitinib[45] and oral tofacitinib in HS patients with Down syndrome.[46]

6 | S100A PROTEINS

The S100 family include 21 members, such as S100A7A (also known as S100A15 or koebnerisin), S100A8/S100A9 (which combine to form calprotectin) and S100A7 (psoriasin), which share significant sequence homology. These proteins, in addition to having antimicrobial activity against gram-negative bacteria, regulate several cellular processes, particularly proliferation, migration and differentiation, and play important roles in a variety of neoplastic and inflammatory immune-mediated disorders.[47] S100A7 is highly increased in psoriasis and atopic dermatitis, displaying a well-established role in the pathogenesis of both conditions.[48] Genes encoding koebnerisin and calprotectin have been demonstrated to be upregulated in HS lesional skin by means of microarray-based gene expression analysis,[5] suggesting a hyperactivation of the innate immunity leading to HS hyperinflammation.[49] S100 antimicrobial peptides also behave as damage-associated molecular pattern (DAMP) molecules triggering the inflammasome activation and contributing to the autoinflammatory signalling in HS.[1]

7 | CXC RECEPTORS

A number of CXC chemokines, such as CXCL1, CXCL3, CXCL5 and IL-8, have been shown to be overexpressed in sporadic HS and its syndromic forms, such as pyoderma gangrenosum, acne and hidradenitis suppurativa (PASH) and pyogenic arthritis and pyoderma gangrenosum, acne and hidradenitis suppurativa (PAPASH).[5,50] CXC ligands and their receptors (CXCR) increase the influx of neutrophils, dendritic cells and memory T and B cells into HS lesions, amplifying the inflammatory network.[5]

Transcriptomic analysis showed a marked increase in the expression of CXCL13, which is dominant driver of memory B cell infiltration into tissues, in HS lesional skin.[51]

8 | IL-1 RECEPTOR-ASSOCIATED KINASES

IL-1 receptor-associated kinases (IRAK) are a family of kinases that sit at the intersection between IL-1 family receptors and Toll-Like Receptor signalling, thus being key effectors of the innate immunity.[52] IRAK1 and IRAK4 activities have been linked with systemic inflammatory immune-mediated conditions and their role in the pathophysiological scenario of HS has been recently suggested.[49] There are two ongoing trials in HS using IRAK degraders, which drive the ubiquitination and destruction of disease-related proteins.[53]

9 | COMPLEMENT 5a (C5a)

The role of the complement in inflammation has been well established in the last 50 years, and its relevance to HS has become increasingly clear in the last decade (Table 2). Complement proteins opsonize and lyse pathogens through formation of the membrane attack complex (MAC), but equally important products of complement activation are the anaphylatoxins C3a, C4a and C5a that further induce the immune response. Cleavage of C5 via the classical, alternative and lectin pathways results in production of the first component of the MAC, C5b, as well as the potent anaphylatoxin C5a.[54] C5a lies at the crossroads linking bacterial response pathways to inflammation as it induces neutrophil chemotaxis and activation, NETosis, macrophage and mast cell degranulation, cutaneous remodelling and production of Th1/17 cytokines such as TNF-α, IL-1, IL-17, IL-23 and IL-8.[41,54-57] Unsurprisingly, C5a and other components of the complement cascade have become therapeutic targets. Eculizumab, a monoclonal antibody that targets and prevents cleavage of C5, was approved by the US Food and Drug Administration in 2007 for the treatment of paroxysmal nocturnal haemoglobinuria. In the last several years, more than a dozen complement antagonists, mostly targeting C5a and its receptor, C5aR, have been evaluated in clinical trials with a major focus on vasculitis, and more recently acutely ill COVID-19 patients.[58] Clinically, HS mimics bacterial skin infections so it is intuitive that the inflammatory mechanisms mediating response to infection are implicated in HS pathogenesis. C5a is highly upregulated in both blood and lesional skin transcriptomes of HS patients,[59] while broad spectrum antibiotics, such as ertapenem, profoundly improve HS temporarily through reduction or alteration of the microbiome population.[60,61]

A phase 2a study of vilobelumab (IFX-1), an intravenous C5a antagonist, for treatment of HS reported HiSCR responses in 10/12 patients after 134 days.[62] A subsequent phase 2b study found HiSCR response rates of 38.7%–51.5% across four dosing regimens at week 16, but it did not achieve superiority compared to the unusually high 47.1% placebo response rate. Only 36 patients were enrolled in the placebo arm, which made it highly susceptible to variability, especially given the relatively high placebo response rates seen in

TABLE 2 Downstream effects of complement Complement C5a signalling

Neutrophils	Chemotaxis, activation, NETosis
Mast cells	Degranulation, histamine release → vasodilation, erythema, oedema
Tissue remodelling	Matrix-metalloproteinases, tissue remodelling, scar
Th1/17 differentiation	Increased TNF-α, IL-1, IL-6, IL-8, IL-17, IL-23, IFNγ
Cutaneous sensitization	Increased Toll-like receptor expression, antimicrobial peptides, C5aR expression
Tumorigenesis	Increased NFκB, angiogenesis, proliferation

most HS trials. Secondary analysis demonstrated dose-related improvement in IHS4 and draining fistula counts, which improved further during the open-label extension.[63] Avacopan, an oral inhibitor of C5aR, recently reported significant improvement in HiSCR responses for Hurley stage III patients treated at 30 mg twice daily (42.6%) compared to placebo (22.4%) at week 16. No improvement was found in patients with Hurley stage II disease or the full treatment population at a dose of 10 or 30 mg twice daily.[64] Both drugs had excellent safety profiles, and further studies of larger populations, aggressive dosing strategies and reliable outcome measurements will be critical to discovering the full potential of C5a/C5aR antagonism in HS.

10 | HORMONES AND METFORMIN

Skin is considered steroidogenic factory, capable to produce most sex steroids de novo from cholesterol and catalyse more or less potent steroids from their precursors, contributing to skin homeostasis.[65,66] Sex hormones were linked with HS: the documented increased prevalence in women, the manifestation of the disease immediately after puberty, its rare postmenopausal occurrence and the effect of pregnancy in disease flares indicate a role of hormones for the pathogenesis of the disease.[1] On the other hand, HS patients demonstrate an increased prevalence of components of the metabolic syndrome,[67] diabetes mellitus type II[68] and showed improvement of disease severity after weight loss.[69] Obesity is known to promote a proinflammatory state, which facilitates the manifestation of inflammatory skin diseases.[70] In contrast, inflammatory skin diseases, such as imiquimod-induced psoriasis-like lesions in mice, can induce reactions in pancreatic beta islet cells mimicking a prediabetic phenotype.[71] In this context, the first-line antidiabetic biguanide metformin appears as a model-drug in HS treatment[72,73], affecting various indirect and direct pathways of inflammation or steroid receptor signalling, both in immune and epithelial cells.[74] Metformin reduces the expression of IL-1β, TNF-α and IL-6 in macrophages direct through inhibition of NFκB activation,[75] increases the Treg/Th17 ratio in mice,[76] interacts with the mechanism of re-epithelization or fibrosis through the TGF-β/SMAD2/3 pathway in fibroblasts and inhibits through the MAPK signalling pathway the keratinocyte proliferation.[77] Moreover, it regulates inflammation and apoptosis through the SIRT1/LKB1/AMPK pathway in bovine retinal capillary endothelial cells and the retina of diabetic mice by inhibiting the reactive oxygen species/PARP signalling.[78] Metformin attenuates the overexpression of the steroidogenic enzyme 11β-hydroxysteroid dehydrogenase-1 caused through cytokine-mediated inflammation.[79] HS was also correlated with dysregulation of adipokines, with leptin and resistin showing an increase and the anti-inflammatory adiponectin showing a decrease in serum of HS patients.[80] Further research with molecules acting on more than one pathophysiologic aspect of the disease might offer the rationale for repurposing of known drugs in order to achieve long-term remission.[7]

11 | PHOSPHODIESTERASE-4

Phosphodiesterase-4 (PDE4) is an intracellular enzyme that hydrolyses intracellular cyclic adenosine monophosphate (cAMP) into non-cyclic AMP. cAMP is a second messenger molecule that is produced from ATP by adenylate cyclase upon cellular stimulation and regulates multiple cellular processes, mainly by the interaction with protein kinase A. The spatially and temporally coordinated degradation of cAMP is essential to ensure the specificity of its action in the cell. Encoded by four different genes (PDE4A, PDE4B, PDE4C and PDE4D), PDE4 exists as at least 25 isotypes and is mainly expressed in immune cells, epithelial cells, myocytes and brain cells.[81,82] The presence of PDE4 in immune cells is of particular interest as this enzyme counteracts cAMP's wide range of anti-inflammatory effects in these cells,[81] making PDE4 an attractive target for inflammatory conditions. In fact, PDE4 inhibition was shown to regulate the inflammatory responses of monocytes/macrophages, dendritic cells, neutrophils and T cells.[81] In activated monocytic cells, for example, PDE4 inhibition leads to reduced production of pro-inflammatory mediators like TNF-α and IL-12 and elevates production of anti-inflammatory mediators like IL-10 and HO-1.[83,84] In line with all that, PDE4 inhibitors have been approved for inflammatory airway disorders (roflumilast, oral application), psoriasis/psoriasis arthritis (apremilast, oral application) and atopic dermatitis (crisaborole, local application). Regarding HS, a phase 2 randomized clinical study with apremilast has recently been published.[85] In this study, patients with moderate disease received either apremilast (n = 15) or placebo (n = 5) for 16 weeks. With 53% of patients fulfiling the HiSCR in the apremilast group compared to 0% in the placebo group, the overall response to apremilast was moderate. The mean values of further parameters including pain and itch were also moderately decreased in the apremilast group compared to baseline, while being mostly increased in the placebo group. Of note, there was a decrease in the overall therapy response over the 16 weeks of treatment;[85] nonetheless, a few study responders showed a sustained therapy response in a 1–2 years follow-up study.[86] While decreasing the cutaneous pro-inflammatory cytokine production is a clearly reasonable approach for HS, the parallel inducing effect of PDE4 inhibitors on IL-10, a cytokine which per se is highly abundant in HS skin, should be viewed critically.[18,87] In a chronic inflammatory setting, IL-10 exerts many beneficial effects on monocytic immune cells, including reduction of pro-inflammatory cytokine production and antigen-presentation and enhancement of phagocytosis of bacteria and apoptotic cells.[88,89] However, at the same time, IL-10 seems to contribute to HS pathogenesis by inhibiting T-cellular IL-22 production, a cytokine known for its epithelial protection and induction of anti-microbial defense.[18]

12 | GRANULOCYTE-COLONY-STIMULATING FACTOR RECEPTOR

The receptor for granulocyte-colony-stimulating factor (G-CSF) is a transmembrane complex composed of two receptor subunits

(G-CSF-R), which is mainly expressed on neutrophils and its precursor cells. Ligand binding induces several signalling events in these cells, including the JAK/STAT, PI3K/AKT and the MAPK pathway.[90,91] Since the G-CSF/G-CSF-R system is known to be central to the biology of neutrophils, it may represent a potential target for the therapy of HS, a disease with signs of neutrophil-driven pathomechanisms.[92] That is also clearly supported by recently published data about HS.[93] This study demonstrates strong expression of both the G-CSF receptor and its ligand in lesional skin of these patients. Here, G-CSF was shown to be mainly derived from dermal fibroblasts, which produce this cytokine particularly in the presence of IL-1β, a cytokine with a crucial role in HS.[94] Keratinocytes also produced G-CSF, with the main stimulus being IL-17, while immune cells did not.[93] Systems biological analyses combined with mechanistic studies into neutrophils revealed that G-CSF/G-CSF-R are the core of a whole pathway active in HS skin. This pathway appears to be triggered and interacting with metabolites from bacteria and damaged host cells (PAMPs, DAMPs),[92] which are abundant in HS skin.[5,49] The pathway (i) ensures the survival of the otherwise short-lived neutrophils in the tissue, (ii) supports the activation of these cells by PAMPs/DAMPs and (iii) primes these cells to produce tissue-degrading proteases,[93] therefore contributing to the disease-typical clinical picture (suppuration/abscesses, progressive tissue damage).[92] Based on these observations, the early therapeutic targeting of G-CSF-R in HS may be very attractive, especially in view of the still far too long time that elapses in European healthcare systems before the correct diagnosis and treatment start for the patients.[95,96] We should not forget, however, that apart from its local role, G-CSF is an important player in the granulopoiesis and neutrophil mobilization from bone marrow,[97] pointing out a potential risk of neutropenia and bacterial infection when blocking G-CSF-R. More information on this is expected from the recently started phase I clinical trial that investigates the safety and pharmacokinetics of a monoclonal antibody (CSL324) against G-CSF-R in patients with HS and palmoplantar pustulosis (total of 40; Clinical trials ID: NCT03972280).

13 | CONCLUSION

The registration of the TNF-α inhibitor adalimumab[98] due to its short- and long-term effectiveness in HS with minor side effects,[99,100] and an additional potential after intensification of treatment in non-responders and patients with loss of response over time[101] opened the doors for new candidates to be compared with adalimumab for even higher effectiveness rates. This article presents the current and future targets aiming to provide information on the therapeutic possibilities and opportunities for HS, the probably most severe and still enigmatic inflammatory skin disease.[1]

ACKNOWLEDGEMENTS

The Department of Dermatology, Zealand University Hospital, Roskilde, Denmark; the Department of Dermatology, Hôpital Erasme, Universite Libre de Bruxelles, Bruxelles, Belgium; the Department of Dermatology, Erasmus University Medical Center Rotterdam, Rotterdam, Netherlands; and the Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane, Dessau, Germany are health care providers of the European Reference Network for Rare and Complex Skin Diseases (ERN Skin – ALLOCATE Skin group).

CONFLICT OF INTEREST

All authors declare that none of the mentioned conflicts of interest had any influence to this manuscript. CCZ has received thematically relevant honoraria from Incyte, Inflarx, Janssen-Cilag, Novartis, Regeneron and UCB as advisor. His departments have received grants from AbbVie, AOTI, Astra Zeneca, Galderma, Inflarx, Naos-Bioderma, Novartis, PPM and UCB for his participation as clinical investigator. JWF was supported in part by a grant (no. UL1 TR001866) from the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) Program. EJG-B has received honoraria from Abbott, Angelini, bioMérieux, InflaRx, MSD and XBiotech; independent educational grants from AbbVie, Abbott, Astellas, AxisShield, bioMérieux, InflaRx, ThermoFisher Brahms, and XBiotech; and funding from the FrameWork 7 program HemoSpec (granted to the National and Kapodistrian University of Athens), the Horizon2020 Marie-Curie Project European Sepsis Academy (granted to the National and Kapodistrian University of Athens), and the Horizon 2020 European Grant ImmunoSep (granted to the Hellenic Institute for the Study of Sepsis). GBEJ has received honoraria from AbbVie, Chemocentryx, Coloplast, Incyte, Inflarx, Kymera Therapeutics, LEO, Novartis and UCB for participation on advisory boards, and grants from Abbvie, Astra-Zeneca, Inflarx, Janssen-Cilag, LEO, Novartis, Regeneron and Sanofi for participation as an investigator, and received speaker honoraria from AbbVie, Boehringer-Ingelheim, Galderma and Novartis. He has also received unrestricted departmental grants from LEO and Novartis. VdM has received honoraria for advisory board participation from BMS, Leo Pharma, Sanofi. CJS has received honoraria as an investigator for AbbVie, Chemocentryx, Incyte, InflaRx, Novartis and UCB; consultancy fees from AbbVie, InflaRx; speaker for AbbVie, Novartis; and consulting fees paid to institution from UCB. TT reports fees from AbbVie, UCB and Sanofi (consultancy, speaker honorarium). KW has received research grants, travel grants, consulting honoraria or lecturer honoraria from AbbVie, Biogen IDEC, Celgene, and Charité Research Organisation. EPP received honoraria from AbbVie, Amgen, Celgene, Galderma, Janssen-Cilag, Novartis and Pfizer for participation as a speaker and serving on advisory boards and investigator-initiated grants (paid to the Erasmus MC) from AbbVie, AstraZeneca, Janssen-Cilag and Pfizer. AVM and GN declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Christos C. Zouboulis wrote a part of the manuscript, read and approved the final manuscript. John W. Frew wrote a part of the manuscript, read and approved the final manuscript. Evangelos J. Giamarellos-Bourboulis wrote a part of the manuscript, read and approved the final manuscript. Gregor B.E. Jemec wrote a part of

the manuscript, read and approved the final manuscript. Veronique del Marmol read and approved the final manuscript. Angelo V. Marzano wrote a part of the manuscript, read and approved the final manuscript. Georgios Nikolakis wrote a part of the manuscript, read and approved the final manuscript. Christopher J. Sayed wrote a part of the manuscript, read and approved the final manuscript. Thrasyvoulos Tzellos read and approved the final manuscript. Kerstin Wolk wrote a part of the manuscript, read and approved the final manuscript. Errol P. Prens wrote a part of the manuscript, read and approved the final manuscript.

REFERENCES

1. Zouboulis CC, Benhadou F, Byrd A, et al. What causes hidradenitis suppurativa? 15 years after. *Exp Dermatol*. 2020;29:1154-1170.
2. https://clinicaltrials.gov/ct2/results?recrs=&cond=Hidradenitis+Suppurativa&term=&cntry=&state=&city=&dist= (website accessed March 4, 2021).
3. Vossen ARJV, Ardon CB, van der Zee HH, Lubberts E, Prens EP. The anti-inflammatory potency of biologics targeting tumour necrosis factor-a, interleukin (IL)-17A, IL-12/23 and CD20 in hidradenitis suppurativa: an ex vivo study. *Br J Dermatol*. 2019;181:314-323.
4. Zouboulis CC. Ex vivo human models of hidradenitis suppurativa / acne inversa for laboratory research and drug screening. *Br J Dermatol*. 2019;181:244-246.
5. Zouboulis CC, Nogueira da Costa A, Makrantonaki E, et al. Alterations in innate immunity and epithelial cell differentiation are the molecular pillars of hidradenitis suppurativa. *J Eur Acad Dermatol Venereol*. 2020;34:846-861.
6. Zouboulis CC, Nogueira da Costa A, Fimmel A, Zouboulis KC. Apocrine glands are bystanders in hidradenitis suppurativa and their involvement is gender-specific. *J Eur Acad Dermatol Venereol*. 2020;34:1555-1563.
7. Zouboulis CC, Nogueira da Costa A. Drug repurposing through drug-gene interaction profiles for hidradenitis suppurativa/acne inversa treatment. *J Eur Acad Dermatol Venereol*. 2021;35:e251-e254.
8. Zouboulis CC, Readhead B, Dudley JT. An additional drug repurposing study for hidradenitis suppurativa/acne inversa. *Br J Dermatol*. 2021;184:748-750.
9. Byrd AS, Dina Y, Okoh UJ, et al. Specimen collection for translational studies in hidradenitis suppurativa. *Sci Rep*. 2019;9:12207.
10. Tricarico P, Boniotto M, Genovese G, Zouboulis CC, Marzano AV, Crovella S. Skin-OMICS: an integrated approach to unravel hidradenitis suppurativa etiopathogenesis. *Front Immunol*. 2019;10:892.
11. Frew JM, Hawkes JE, Sullivan-Whalen M, Gilleaudeau P, Krueger JG. Inter-rater reliability of phenotypes and exploratory genotype-phenotype analysis in inherited hidradenitis suppurativa. *Br J Dermatol*. 2019;181:566-571.
12. Jenei A, Dajnoki Z, Medgyesi B, et al. Apocrine gland-rich skin has a non-inflammatory IL-17 related immune milieu, which turns to inflammatory IL-17 mediated disease in hidradenitis suppurativa. *J Invest Dermatol*. 2019;139:964-968.
13. Tzanetakou V, Kanni T, Giatrakou S, et al. Safety and efficacy of anakinra in severe hidradenitis suppurativa: a randomized controlled trial. *JAMA Dermatol*. 2016;152:52-59.
14. Kanni T, Argyropoulou M, Spyridopoulos T, et al. MABp1 targeting IL-1α for moderate to severe hidradenitis suppurativa not eligible for adalimumab: a randomized study. *J Invest Dermatol*. 2018;138:795-801.
15. Gottlieb A, Natsis NE, Kerdel F, et al. A phase II open-label study of bermekimab in patients with hidradenitis suppurativa shows resolution of inflammatory lesions and pain. *J Invest Dermatol*. 2020;140(8):1538-1545.
16. Kanni T, Argyropoulou M, Dinarello CA, Simard J, Giamarellos-Bourboulis EJ. MABp1 targeting interleukin-1α in hidradenitis supurativa ineligible for adalimumab treatment: results of the open-label extension period. *Clin Exp Dermatol*. 2021;46:162-163.
17. Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol*. 2011;65:790-798.
18. Wolk K, Warszawska K, Hoeflich C, et al. Deficiency of IL-22 contributes to a chronic inflammatory disease: pathogenetic mechanisms in acne inversa. *J Immunol*. 2011;186:1228-1239.
19. Kelly G, Hughes R, McGarry T, et al. Dysregulated cytokine expression in lesional and nonlesional skin in hidradenitis suppurativa. *Br J Dermatol*. 2015;173:1431-1439.
20. Moran B, Sweeney CM, Hughes R, et al. Hidradenitis suppurativa is characterized by dysregulation of the Th17: Treg cell axis, which is corrected by anti-TNF therapy. *J Invest Dermatol*. 2017;137:2389-2395.
21. Fletcher JM, Moran B, Petrasca A, Smith CM. IL-17 in inflammatory skin diseases psoriasis and hidradenitis suppurativa. *Clin Exp Immunol*. 2020;201:121-134.
22. Navrazhina K, Frew JW, Krueger JG. Interleukin 17C is elevated in lesional tissue of hidradenitis suppurativa. *Br J Dermatol*. 2020;182:1045-1047.
23. Thorlacius L, Theut Riis P, Jemec GBE. Severe hidradenitis suppurativa responding to treatment with secukinumab: a case report. *Br J Dermatol*. 2018;179:182-185.
24. Casseres RG, Prussick L, Zancanaro P, et al. Secukinumab in the treatment of moderate to severe hidradenitis suppurativa: results of an open-label trial. *J Am Acad Dermatol*. 2020;82:1524-1526.
25. Frew JW, Navrazhina K, Grand D, et al. The effect of subcutaneous brodalumab on clinical disease activity in hidradenitis suppurativa: an open-label cohort study. *J Am Acad Dermatol*. 2020;83:1341-1348.
26. Ribero S, Ramondetta A, Fabbrocini G, et al. Effectiveness of secukinumab in the treatment of moderate-severe hidradenitis suppurativa: results from an Italian multicentric retrospective study in a real-life setting. *J Eur Acad Dermatol Venereol*. 2021. https://doi.org/10.1111/jdv.17178
27. Zouboulis CC, Tzellos T, Kyrgidis A, et al. Development and validation of IHS4, a novel dynamic scoring system to assess hidradenitis suppurativa/acne inversa severity. *Br J Dermatol*. 2017;177:1401-1409.
28. Martínez F, Nos P, Benlloch S, Ponce J. Hidradenitis suppurativa and Crohn's disease: response to treatment with infliximab. *Inflamm Bowel Dis*. 2001;7:323-326.
29. von Laffert M, Helmbold P, Wohlrab J, Fiedler E, Stadie V, Marsch WC. Hidradenitis suppurativa (acne inversa): early inflammatory events at terminal follicles and at interfollicular epidermis. *Exp Dermatol*. 2010;19:533-537.
30. Kjaersgaard Andersen R, Saunte SK, Jemec GBE, Saunte DM. Psoriasis as a comorbidity of hidradenitis suppurativa. *Int J Dermatol*. 2020;59:216-220.
31. Aggarwal S, Ghilardi N, Xie MH, de Sauvage FJ, Gurney AL. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. *J Biol Chem*. 2003;278:1910-1914.
32. Towne JE, Sims JE. IL-36 in psoriasis. *Curr Opin Pharmacol*. 2012;12:486-490.
33. Di Caprio R, Balato A, Caiazzo G, et al. IL-36 cytokines are increased in acne and hidradenitis suppurativa. *Arch Dermatol Res*. 2017;309:673-678.
34. Babon JJ, Lucet IS, Murphy JM, Nicola NA, Varghese LN. The molecular regulation of Janus kinase (JAK) activation. *Biochem J*. 2014;462:1-13.
35. Zhou YJ, Magnuson KS, Cheng TP, et al. Hierarchy of protein tyrosine kinases in interleukin-2 (IL-2) signaling: activation of syk

depends on Jak3; however, neither Syk nor Lck is required for IL-2-mediated STAT activation. *Mol Cell Biol*. 2000;20:4371-4380.
36. Damsky W, King BA. JAK inhibitors in dermatology: the promise of a new drug class. *J Am Acad Dermatol*. 2017;76:736-744.
37. Works MG, Yin F, Yin CC, et al. Inhibition of TYK2 and JAK1 ameliorates imiquimod-induced psoriasis-like dermatitis by inhibiting IL-22 and the IL-23/IL-17 axis. *J Immunol*. 2014;193:3278-3287.
38. Navrazhina K, Frew JW, Gilleaudeau P, Sullivan-Whalen M, Garcet S, Krueger JG. Epithelialized tunnels are a source of inflamamtion in hidradenitis suppurativa. *J Allerg Clin Immunol*. 2021. https://doi.org/10.1016/j.jaci.2020.12.651
39. Byrd AS, Carmona-Rivera C, O'Neil LJ, et al. Neutrophil extracellular traps, B cells, and type I interferons contribute to immune dysregulation in hidradenitis suppurativa. *Sci Transl Med*. 2019;11(508):eaav5908.
40. Ponikowska M, Matusiak L, Kasztura M, Jankowska EA, Szepietowski JC. Deranged iron status evidenced by iron deficiency characterises patients with hidradenitis suppurativa. *Dermatology*. 2020;236:52-58.
41. Frew JW, Marzano AV, Wolk K, et al. A systematic review of promoting therapeutic targets in hidradenitis suppurativa: a critical evaluation of mechanistic and clinical relevance. *J Invest Dermatol*. 2021;141:316-324.
42. Savage K, Santillian MR, Flood KS, Charrow A, Porter ML, Kimball AB. Tofacitinib shows benefit in conjunction with other therapies in recalcitrant hidradenitis suppurativa. *JAAD Case Rep*. 2020;6:99-102.
43. A placebo-controlled study of the safety of INCB054707 in participants with hidradenitis suppurativa (NCT03607487). ClinicalTrials.gov Website. Accessed July 31, 2020.
44. A study of oral upadacitinib tablet compared to placebo in adult participants with moderate to severe hidradenitis suppurativa to assess change in disease symptoms (NCT04430855). ClinicalTrials.gov (website accessed July 31, 2020).
45. Topical ruxolitinib 1.5% for HS (NCT04414514). ClinicalTrials.gov (website accessed July 31, 2020).
46. Tofacitinib for immune skin conditions in Down syndrome (NCT04246372). ClinicalTrials.gov (website accessed July 31, 2020).
47. Bresnick AR. S100 proteins as therapeutic targets. *Biophys Rev*. 2018;10:1617-1629.
48. Wolf R, Mirmohammadsadegh A, Walz M, et al. Molecular cloning and characterization of alternatively spliced mRNA isoforms from psoriatic skin encoding a novel member of the S100 family. *FASEB J*. 2003;17:1969-1971.
49. Wolk K, Join-Lambert O, Sabat R. Aetiology and pathogenesis of hidradenitis suppurativa. *Br J Dermatol*. 2020;183:999-1010.
50. Marzano AV, Damiani G, Ceccherini I, Berti E, Gattorno M, Cugno M. Autoinflammation in pyoderma gangrenosum and its syndromic form (pyoderma gangrenosum, acne and suppurative hidradenitis). *Br J Dermatol*. 2017;176:1588-1598.
51. Lowe MM, Naik HB, Clancy S, et al. Immunopathogenesis of hidradenitis suppurativa and response to anti-TNF-α therapy. *JCI Insight*. 2020;5:e139932.
52. Gay NJ, Gangloff M, O'Neill LA. What the myddosome structure tells us about the initiation of innate immunity. *Trends Immunol*. 2011;32:104-109.
53. Mullard A. IRAK4 degrader to take on innate immunity. *Nat Biotechnol*. 2020;38:1221-1223.
54. Guo RF, Ward PA. Role of C5a in inflammatory responses. *Annu Rev Immunol*. 2005;23:821-852.
55. Frew JW. Complement, hidradenitis suppurativa and pathogen-driven positive selection. *Br J Dermatol*. 2019;180:685-686.
56. Ghias MH, Hyde MJ, Tomalin LE, et al. Role of the complement pathway in inflammatory skin diseases: a focus on hidradenitis suppurativa. *J Invest Dermatol*. 2020;140(3):531-536.
57. Grand D, Navrazhina K, Frew JW. Integrating complement into the molecular pathogenesis of hidradenitis suppurativa. *Exp Dermatol*. 2020;29:86-92.
58. Ort M, Dingemanse J, van den Anker J, Kaufmann P. Treatment of rare inflammatory kidney diseases: drugs targeting the terminal complement pathway. *Front Immunol*. 2020;11:599417.
59. Hoffman LK, Tomalin LE, Schultz G, et al. Integrating the skin and blood transcriptomes and serum proteome in hidradenitis suppurativa reveals complement dysregulation and a plasma cell signature. *PLoS One*. 2018;13:e0203672.
60. Braunberger TL, Nartker NT, Nicholson CL, et al. Ertapenem - a potent treatment for clinical and quality of life improvement in patients with hidradenitis suppurativa. *Int J Dermatol*. 2018;57:1088-1093.
61. Join-Lambert O, Coignard-Biehler H, Jais JP, et al. Efficacy of ertapenem in severe hidradenitis suppurativa: a pilot study in a cohort of 30 consecutive patients. *J Antimicrob Chemother*. 2016;71:513-520.
62. Giamarellos-Bourboulis EJ, Argyropoulou M, Kanni T, et al. Clinical efficacy of complement C5a inhibition by IFX-1 in hidradenitis suppurativa: an open-label single-arm trial in patients not eligible for adalimumab. *Br J Dermatol*. 2020;183:176-178.
63. Giamarellos-Bourboulis EJ, Prens EP, Habel M, et al. Complement split product C5a is elevated in moderate and severe hidradenitis suppurativa: clinical improvement by targeted therapy coming from the SHINE study. *Exp Dermatol*. 2021.https://doi.org/10.1111/exd.14342
64. Global Newswire. ChemoCentryx Announces Positive Topline Results of Phase II AURORA Clinical Trial of Avacopan in the Treatment of Hidradenitis Suppurativa (HS), 2020.
65. Nikolakis G, Stratakis CA, Kanaki T, Slominski A, Zouboulis CC. Skin steroidogenesis in health and disease. *Rev Endocr Metab Disord*. 2017;17:247-258.
66. Slominski A, Zbytek B, Nikolakis G, et al. Steroidogenesis in the skin: implications for local immune functions. *J Steroid Biochem Mol Biol*. 2013;137:107-123.
67. Sabat R, Chanwangpong A, Schneider-Burrus S, et al. Increased prevalence of metabolic syndrome in patients with acne inversa. *PLoS One*. 2012;7:e31810.
68. Phan K, Charlton O, Smith SD. Hidradenitis suppurativa and diabetes mellitus: updated systematic review and adjusted meta-analysis. *Clin Exp Dermatol*. 2019;44:e126-e132.
69. Kromann CB, Ibler KS, Kristiansen VB, Jemec GBE. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. *Acta Derm Venereol*. 2014;94:553-557.
70. Vilanova I, Hernández JL, Mata C, et al. Insulin resistance in hidradenitis suppurativa: a case–control study. *J Eur Acad Dermatology Venereol*. 2018;32:820-824.
71. Evans EA, Sayers SR, Kodji X, et al. Psoriatic skin inflammation induces a pre-diabetic phenotype via the endocrine actions of skin secretome. *Mol Metab*. 2020;41:101047.
72. Verdolini R, Clayton N, Smith A, Alwash N, Mannello B. Metformin for the treatment of hidradenitis suppurativa: a little help along the way. *J Eur Acad Dermatol Venereol*. 2013;27:1101–1108.
73. Jennings L, Hambly R, Hughes R, Moriarty B, Kirby B. Metformin use in hidradenitis suppurativa. *J Dermatolog Treat*. 2020;31:261–263.
74. Nikolakis G, Kyrgidis A, Zouboulis CC. Is there a role for antiandrogen therapy for hidradenitis suppurativa? A systematic review of published data. *Am J Clin Dermatol*. 2019;20:503-513.
75. Zhou Z, Tang Y, Jin X, et al. Metformin inhibits advanced glycation end products-induced inflammatory response in murine macrophages partly through AMPK activation and RAGE/NF B pathway suppression. *J Diabetes Res*. 2016;2016:4847812.
76. Ursini F, Russo E, Pellino G, et al. Metformin and autoimmunity: a "new deal" of an old drug. *Front Immunol*. 2018;9:1236.
77. Li W, Ma W, Zhong H, Liu W, Sun Q. Metformin inhibits proliferation of human keratinocytes through a mechanism associated

with activation of the MAPK signaling pathway. *Exp Ther Med*. 2014;7:389-392.
78. Zheng Z, Chen H, Li J, et al. Sirtuin 1-mediated cellular metabolic memory of high glucose via the LKB1/AMPK/ROS pathway and therapeutic effects of metformin. *Diabetes*. 2012;61:217-228.
79. Esteves CL, Kelly V, Breton A, et al. Proinflammatory cytokine induction of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in human adipocytes is mediated by MEK, C/EBPβ, and NF-κB/RelA. *J Clin Endocrinol Metab*. 2014;99:E160-E168.
80. González-López MA, Vilanova I, Ocejo-Viñals G, et al. Circulating levels of adiponectin, leptin, resistin and visfatin in non-diabetics patients with hidradenitis suppurativa. *Arch Dermatol Res*. 2020;312:595-600.
81. Li H, Zuo J, Tang W. Phosphodiesterase-4 inhibitors for the treatment of inflammatory diseases. *Front Pharmacol*. 2018;9:1048.
82. Baillie GS. Compartmentalized signalling: spatial regulation of cAMP by the action of compartmentalized phosphodiesterases. *FEBS J*. 2009;276:1790-1799.
83. Seldon PM, Barnes PJ, Giembycz MA. Interleukin-10 does not mediate the inhibitory effect of PDE-4 inhibitors and other cAMP-elevating drugs on lipopolysaccharide-induced tumors necrosis factor-alpha generation from human peripheral blood monocytes. *Cell Biochem Biophys*. 1998;29:179-201.
84. Kwak HJ, Song JS, No ZS, Song JH, Yang SD, Cheon HG. The inhibitory effects of roflumilast on lipopolysaccharide-induced nitric oxide production in RAW264.7 cells are mediated by heme oxygenase-1 and its product carbon monoxide. *Inflamm Res*. 2005;54:508-513.
85. Vossen ARJV, van Doorn MBA, van der Zee HH, Prens EP. Apremilast for moderate hidradenitis suppurativa: results of a randomized controlled trial. *J Am Acad Dermatol*. 2019;80:80-88.
86. Aarts P, Vossen ARJV, van der Zee HH, Prens EP, van Straalen KR. Long-term treatment with apremilast in hidradenitis suppurativa: 2-year follow-up of initial responders. *J Am Acad Dermatol*. 2020:https://doi.org/10.1016/j.jaad.2020.08.113
87. Sabat R, Grütz G, Warszawska K, et al. Biology of interleukin-10. *Cytokine Growth Factor Rev*. 2010;21:331-344.
88. Wolk K, Döcke W, von Baehr V, Volk H, Sabat R. Comparison of monocyte functions after LPS- or IL-10-induced reorientation: importance in clinical immunoparalysis. *Pathobiology*. 1999;67:253-256.
89. Lingnau M, Höflich C, Volk HD, Sabat R, Döcke WD. Interleukin-10 enhances the CD14-dependent phagocytosis of bacteria and apoptotic cells by human monocytes. *Hum Immunol*. 2007;68:730-738.
90. Fukunaga R, Seto Y, Mizushima S, Nagata S. Three different mRNAs encoding human granulocyte colony-stimulating factor receptor. *Proc Natl Acad Sci USA*. 1990;87:8702-8706.
91. Dwivedi P, Greis KD. Granulocyte colony-stimulating factor receptor signaling in severe congenital neutropenia, chronic neutrophilic leukemia, and related malignancies. *Exp Hematol*. 2017;46:9-20.
92. Sabat R, Jemec GBE, Matusiak Ł, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. *Nat Rev Dis Primers*. 2020;6:18.
93. Wolk K, Brembach TC, Šimaitė D, et al. Activity and components of the granulocyte colony-stimulating factor pathway in hidradenitis suppurativa. *Br J Dermatol*. 2021:https://doi.org/10.1111/bjd.19795
94. Witte-Händel E, Wolk K, Tsaousi A, et al. The IL-1 pathway is hyperactive in hidradenitis suppurativa and contributes to skin infiltration and destruction. *J Invest Dermatol*. 2019;139:1294-1305.
95. Saunte DM, Boer J, Stratigos A, et al. Diagnostic delay in hidradenitis suppurativa is a global problem. *Br J Dermatol*. 2015;173:1546-1549.
96. Kokolakis G, Wolk K, Schneider-Burrus S, et al. Delayed diagnosis of hidradenitis suppurativa and its effect on patients and healthcare system. *Dermatology*. 2020;236:421-430.
97. Bendall LJ, Bradstock KF. G-CSF: from granulopoietic stimulant to bone marrow stem cell mobilizing agent. *Cytokine Growth Factor Rev*. 2014;25:355-367.
98. Zouboulis CC. Adalimumab for the treatment of hidradenitis suppurativa/acne inversa. *Expert Rev Clin Immunol*. 2016;12:1015-1026.
99. Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab treatment of hidradenitis suppurativa. *N Engl J Med*. 2016;375:422-434.
100. Zouboulis CC, Okun MM, Prens EP, et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extention study. *J Am Acad Dermatol*. 2019;80:60-69.
101. Zouboulis CC, Hansen H, Caposiena Caro RD, et al. Adalimumab dose intensification in recalcitrant hidradenitis suppurativa/acne inversa. *Dermatology*. 2020;236:25-30.

How to cite this article: Zouboulis CC, Frew JW, Giamarellos-Bourboulis EJ, et al. Target molecules for future hidradenitis suppurativa treatment. *Exp Dermatol*. 2021;30(Suppl. 1):8–17. https://doi.org/10.1111/exd.14338