

# Interleukin-31: The ‘itchy’ cytokine in inflammation and therapy

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## Abstract

Interleukin-31 has been implicated in the pathophysiology of multiple atopic disorders such as atopic dermatitis (AD), rhinitis and airway hyperreactivity. In AD, IL-31 has been identified as one of the main ‘drivers’ of its cardinal symptom pruritus. Here, we aim to summarize the mechanisms by which IL-31 modulates inflammatory and allergic diseases. TH2 cells play a central role in AD and release high levels of TH2-produced cytokines including IL-31, thereby mediating inflammatory responses, initiating immunoregulatory circuits, and stimulating itch and neuronal outgrowth through activation of the heterodimer receptor IL-31 receptor alpha (IL31RA)/Oncostatin M receptor  $\beta$ . IL31RA expression is found on human and murine dorsal root ganglia neurons, epithelial cells including keratinocytes as well as various innate immune cells. IL-31 is a critical cytokine involved in neuro-immune communication, which opens new avenues for cytokine modulation in neuroinflammatory diseases including AD/pruritus, as validated by recent clinical trials using an anti-IL-31 antibody. Accordingly, inhibition of IL-31 downstream signaling may be a beneficial approach for various inflammatory diseases including prurigo nodularis. For example, whether downstream JAK inhibitors directly block IL-31-mediated-signaling needs to be clarified. Targeting the IL-31/IL31RA/OSMR $\beta$  axis appears to be a promising approach for inflammatory, neuroinflammatory and pruritic disorders in the future.

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## Interleukin-31: The ‘itchy’ cytokine in inflammation and therapy

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**Abbreviations:** AAM, alternatively activated macrophage; AD, atopic dermatitis; AHR, airway hyperreactivity; AE, adverse event; AKT, protein Kinase B; APC, antigen presenting cell; CCL, chemokine (C-C motif) ligand; CD, cluster of differentiation or Crohn's disease; CDC2, cell division cycle protein 2 homolog; CDK6, cell division protein kinase 6; CLA, cutaneous lymphocyte antigen; CNTF, ciliary inhibitory factor; CT-1, cardiotropin-1; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; DC, dendritic cell; DLQI, Dermatology Life Quality Index; DRG, dorsal root ganglion; EASI, Eczema Area Severity Index; EGF, endothelial growth factor; ERK, extracellular signal-regulated kinase; GRO- $\alpha$ , growth-related oncogene- $\alpha$ ? FDA, Food and Drug Administration; gp, glycoprotein; GIT, gastrointestinal tract; HLA-DR, histocompatibility antigen-DR; HDM, house dust mites; IBD, inflammatory bowel disease; IGA, Investigator's Global Assessment; IgG, immunoglobulin G; IL, interleukin; IL31RA, IL-31 receptor-??? JAK, janus kinase; JNK, c-Jun N-terminal kinase; LIF, leukemia inhibitory factor; LOCF, Last Observation Carried Forward; MAPK, Mitogen-activated protein kinase; MI, Multiple Imputation; mTOR, mammalian target of rapamycin; NA, not available; NFAT1, nuclear factor of activated T-cells; NGF, nerve growth factor; NP, nasal polyps; NPN, neuropoietin; NRS, Numeric Rating Scale; OSM, oncostatin M; OSMR $\beta$ ??? oncostatin M receptor beta; PbO, placebo; PCR, polymerase chain reaction; ppNRS, peak pruritus Numerical Rating Scale; PI3K, phosphoinositide 3-kinase; PRR, pattern recognition receptor; Pt, part; p38, p38 mitogen-activated protein kinase; SA, *Staphylococcus aureus*; SEB, staphylococcal enterotoxins; SMAD2/3, mothers against decapentaplegic homolog 2/3; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TARC, thymus- and activation-regulated chemokine; TGF- $\beta$ ?? transforming growth factor beta??T<sub>H</sub>, T helper cell; TLR, toll like receptor; TNF $\alpha$ ??tumor necrosis factor alpha; TRP, transient receptor potential; TRPA1, TRP ankyrin receptor 1; TRPV1, TRP vanilloid receptor 1; TSLP, thymic stromal lymphopoietin; T1/ST2 receptor, Interleukin 1 receptor-like 1; Tc1, type 1 CD8<sup>+</sup> T cells;

Tc2, type 2 CD8<sup>+</sup> T cells; UC, ulcerative colitis; VAS, Visual Analog Scale; VEGF, vascular endothelial growth factor;  $\Delta$ , change.

## Abstract

Interleukin-31 has been implicated in the pathophysiology of multiple atopic disorders such as atopic dermatitis (AD), rhinitis and airway hyperreactivity. In AD, IL-31 has been identified as one of the main ‘drivers’ of its cardinal symptom pruritus. Here, we aim to summarize the mechanisms by which IL-31 modulates inflammatory and allergic diseases. T<sub>H</sub>2 cells play a central role in AD and release high levels of T<sub>H</sub>2-produced cytokines including IL-31, thereby mediating inflammatory responses, initiating immunoregulatory circuits, and stimulating itch and neuronal outgrowth through activation of the heterodimer receptor IL-31 receptor alpha (IL31RA)/Oncostatin M receptor  $\beta$ . IL31RA expression is found on human and murine dorsal root ganglia neurons, epithelial cells including keratinocytes as well as various innate immune cells. IL-31 is a critical cytokine involved in neuro-immune communication, which opens new avenues for cytokine modulation in neuroinflammatory diseases including AD/pruritus, as validated by recent clinical trials using an anti-IL-31 antibody. Accordingly, inhibition of IL-31 downstream signaling may be a beneficial approach for various inflammatory diseases including prurigo nodularis. For example, whether downstream JAK inhibitors directly block IL-31-mediated-signaling needs to be clarified. Targeting the IL-31/IL31RA/OSMR $\beta$  axis appears to be a promising approach for inflammatory, neuroinflammatory and pruritic disorders in the future.

**Key words:** Interleukin-31, Interleukin-31 receptor A, Oncostatin M receptor, atopic dermatitis, neuroinflammation.

## Introduction

### IL-31 structure and function

The first major role of IL-31 was described in an induced mouse model of atopic dermatitis (AD), where it was reported to cause cutaneous inflammation along with pruritus when IL-31 was genetically overexpressed.<sup>1</sup> Ever since this observation, IL-31 and its respective receptor heterodimer IL-31 receptor-A (IL31RA)/Oncostatin M receptor  $\beta$  (OSMR $\beta$ ) have been studied for their role in tissue homeostasis, inflammation, immune defence, neuroimmune circuits and pruritus.

IL-31 belongs to the family of IL-6-derived cytokines. Interleukin-6 family cytokines are commonly clustered based on their pro-inflammatory character and a shared signaling pathway engaging in gp130 receptor subunit activation. The IL-6 cytokine family is often referred to as the gp130/IL-6 family of cytokines. Family members are IL-6, IL-11, IL-21, IL-27, neuropoietin (NPN), ciliary inhibitory factor (CNTF), cardiotropin-1 (CT-1), leukemia inhibitory factor (LIF), oncostatin M (OSM) and IL-31. Apart from IL-31, IL-6 family cytokines signal through a heterodimeric receptor composed of two subunits of which one typically is gp130.<sup>2</sup> IL-31 does not engage with gp130 itself, but rather interacts with a heterodimer complex that is composed of the gp130-like subunit IL31RA and OSMR $\beta$ .<sup>1</sup> This receptor heterodimer is activated with similar affinities by oncostatin M (OSM) and IL-31. The OSMR $\beta$  subunit is widely expressed throughout the various cell types of the mammalian body, while IL31RA subunit expression is predominantly observed in epithelial and neuronal cell types. In humans, IL31RA forms either a long or a short isoform, with the short isoform resuming a non-signaling inhibitory function. In rodents, only the long isoform has been detected.<sup>3</sup> Engagement of OSM or IL-31 with the IL31RA/OSMR $\beta$  heterodimer initiates activation of canonical JAK/STAT, AKT/PI3K and MAPK-JNK/p38 pathways (Figure 1). Of note, at least MAPK activity is not inducible by signaling through the IL31RA alone but needs both receptor subunits to cooperate.<sup>4</sup> Activation of IL-31 signaling pathways leads to the induction of various cellular processes including cell survival, proliferation and differentiation.

The physiological function of IL-31 is still not fully understood. Recently, a major role for IL-31 in humans has been described in various inflammatory disorders, including AD, inflammatory bowel disease (IBD), nasal polyposis (NP) and airway hyperreactivity (AHR).

IL-31 has been identified as a secretory product of T<sub>H</sub>2 cells and immature dendritic cells (iDC),<sup>5</sup> and ac-

tivates IL31RA/OSMR $\beta$  receptor expressing dorsal root ganglia (DRG) neurons and keratinocytes, among others,<sup>3,5-7</sup> linking immune cells to epithelium and the neuronal network in the skin, and probably also gut and airways.<sup>6</sup> Intradermal application of IL-31 indeed leads to sensations of itch, underlying the capacity of IL-31 to activate target neurons.<sup>8</sup> Here, we summarize our current understanding about the pathophysiological role of the IL-31/IL31RA/OSMR $\beta$  axis in skin and mucosa, with an emphasis on neuro-immune communication and its translational importance for the treatment of inflammatory and neuroimmune diseases of skin, gut and airways in the future.

## IL-31 and the immune system

The source of IL-31 and the factors modulating IL-31 expression are still poorly understood. Several studies point to a preferential expression of IL-31 in mice and humans by CD3<sup>+</sup>CD4<sup>+</sup> type 2 T-helper cells (T<sub>H</sub>2).<sup>1,5,9,10</sup> A recent large-scale tissue bank screening approach confirmed almost exclusive expression of IL-31 by CD3<sup>+</sup> CD4<sup>+</sup> immune cells.<sup>11</sup> Stott *et al* . propose that in humans IL-31 expression in CD3<sup>+</sup> CD4<sup>+</sup>T<sub>H</sub>2 cells is under primary control of IL-4 whereas IL-33 stimulation seems to boost IL-31 secretion human T<sub>H</sub>2 cells via a STAT6-dependent regulation of T1/ST2 receptor.<sup>9,11,12</sup> In contrast, TGF- $\beta$  has a rather damping effect on IL-31 secretion via phosphorylation of SMAD2/3 molecules. This effect might explain why fully differentiated T<sub>H</sub>9 cells express only moderate IL-31 levels since differentiation of T<sub>H</sub>9 is initiated by co-stimulation with IL-4 and TGF- $\beta$ . While the IL-4 signal initiates IL-31 expression, the simultaneous TGF- $\beta$  signal dampens IL-31 expression counter-regulating the IL-4 effect. T<sub>H</sub>2 cells, in comparison, are not relying on TGF- $\beta$  as they differentiate from naïve T cells dependent on IL-4 signaling from the microenvironment alone and maintain their phenotype by autocrine IL-4 signaling which in parallel supports IL-31 expression.<sup>9</sup> The transcription of the *Il31* gene in T<sub>H</sub>2 and (probably IL-4 producing) mast cells is under control of calcium-dependent NFAT1 and NFAT2 and a ‘usual suspect’ of cytokine expression regulators, the protein family of suppressor of cytokine signaling (SOCS), was found to have a pivotal role in suppression of ‘uncontrolled’ IL-31 expression (Figure 1).<sup>13,14</sup> However, it remains unclear how secretion of IL-31 is restricted to IL-4-expressing cells (T<sub>H</sub>2 cells in particular) and if IL-31<sup>+</sup> T<sub>H</sub>2 cells could mark a distinct subpopulation within T<sub>H</sub>2 cells. Notably, our knowledge about the communication between IL-31 and IL-13 or TSLP is very poor.

## IL-31 in neuro-immune communication

Multiple mediators including cytokines can induce pruritus (itch) which can develop into being intractable by nature, as seen in skin diseases or systemic disorders such as allergies, metabolic diseases or cancer.<sup>15-17</sup> Peripheral nerve endings in the epidermis and dermis become activated by various endogenous or exogenous trigger factors during inflammation, allergies or systemic diseases.<sup>18,19</sup> After activation of cytokine receptors on sensory nerve endings, like IL31RA, the nerves transmit the itch or pain signal to the central nervous system via the spinal cord and contralateral tractus spinothalamicus.<sup>20,21</sup> Through an axon-reflex mechanism,<sup>22</sup> neighbouring nerve branches become activated and release neuropeptides into the skin thereby inducing neurogenic inflammation, which can be also induced by IL-31.<sup>23,24</sup> For example, IL-31 induced b-type natriuretic peptide (BNP) release from murine DRG neurons and skin cells mediated neuroinflammation by stimulating cytokine, chemokine and endothelin-1 (ET-1) release from keratinocytes.<sup>23,24</sup> Multiple pruritogens, their cognate receptors, channels and interaction networks have been identified.<sup>15,25-27</sup> The capsaicin receptor TRP vanilloid receptor 1 (TRPV1) and mustard oil activated TRP ankyrin receptor 1 (TRPA1) are expressed on DRG neurons and are essential for the correct pruritic signal transmission of diverse pruritogens including IL-31.<sup>6,28-31</sup> Together, these studies point at an essential role of IL-31 for the neuroimmune communication between T<sub>H</sub>2 cells, sensory nerves and keratinocytes, thereby initiating inflammation, epithelial dysregulation and pruritus, all characteristics of atopic dermatitis pathophysiology.

Cytokines have been found to act as pruritic sensitizers or activators, respectively, dependent on the concentration.<sup>32,33</sup> In genetically modified mice, overexpression of only a single cytokine (demonstrated for IL-4, IL-13, IL-18, IL-31 or TSLP) is sufficient to cause pruritic AD-like skin lesions.<sup>25</sup> In humans, our current knowledge points at IL-4 and IL-13 being the major molecular ‘drivers’ of AD.<sup>32,34</sup> However, a transgenic mouse model demonstrated that overexpression of IL-31 is enough to initiate a severe AD-like

phenotype with eczema and itch.<sup>1</sup> In addition, implantation of GABAergic interneurons into the spinal cord of IL-31-overexpressing mice induced healing of skin lesions and alleviated pruritus.<sup>35</sup> In AD patients, elevated expression levels of IL-31 and IL31RA were found in a significant amount of patients, but not all. While some patients showed high levels for IL-31 mRNA and IL31RA mRNA, others showed low levels for both, some low levels for either IL-31 or IL31RA.<sup>6</sup> This result supports the hypothesis about AD being a clinically and molecular heterogenic disease in which patients differ with respect to their expression levels for IL-4, -13 and -31. This, of course, needs to be verified/falsified in the future.

Furthermore, IL31RA expression can be found in human dorsal root ganglia (sensory nerves), skin-infiltrating mononuclear cells and CD11b<sup>+</sup> cells, establishing an important role of IL-31 in human AD as well. Considering that T<sub>H</sub>2 cells represent the main source of IL-31, the IL-31 axis could serve as a strong neuro-immune link between IL-31-expressing T cells and IL31RA-expressing sensory neurons.<sup>5,36</sup> The receptor is predominantly expressed by small-to-medium size human DRG neurons (< 30 µm) co-expressing TRPV1 while large-diameter DRG neurons (< 50 µm) are mainly IL31RA-negative.<sup>36</sup> In mice, both TRPV1 and TRPA1 ion channels are functionally linked to IL31RA since genetically (TRPV1, TRPA1 KO mice) or chemical blocking of TRPV1 can abrogate IL-31-mediated itch.<sup>6</sup>

A study conducting transcriptomics-based analysis in IL-31-activated DRG neurons revealed that IL-31 is further involved in neuronal proliferation, survival and metabolism.<sup>37</sup> Pump-equipped mice receiving a continuous IL-31 stimulus over weeks develop a denser cutaneous neural network than vehicle-treated control mice. The IL-31-mediated increase in cutaneous nerve fibre density is achieved by a STAT3-dependent increase in branching, extension and quantity of small-diameter sensory neurons along with the induction of neuronal survival via PI3K/AKT pathway activation.<sup>37</sup> These findings may partly explain the increased epidermal sensory nerve fibre density in AD patients.<sup>38–42</sup> which probably accounts for the higher ‘skin sensitivity’ in AD patients to minimal stimuli. This is in line with the assumption that neural changes occur in direct response to on-going inflammatory signals in AD. However, a recent study conducted in a mouse model of AD utilizing continuous *in vivo* imaging of peripheral sensory nerves and blood vessels implicates that neural changes might precede immune cell infiltration, vascularization and vascular permeability.<sup>40</sup> The author suggests that ‘allergic stimulation in a chronic eczema model requires neural recruitment and activation early in the process for the initiation and maintenance of the inflammatory cascade’.<sup>40</sup> With early neuronal imprinting established, subsequent recruitment of IL-31<sup>+</sup> T cells to neuronal IL31RA<sup>+</sup> structures and immuno-neuronal communication could then feed into the severity of itch, inflammation, and changes of the epidermal nerve fiber density characteristic for AD.

## IL-31 and its role in mucosal diseases

Multiple studies have established a role for members of the IL-6 family in the regulation of epithelial cell function in lung, skin and gastrointestinal tract (GIT).<sup>43–45</sup> Mucosal epithelial cells express OSMRβ that can be activated by IL-31 and OSM.<sup>5</sup> While the downstream effect of OSM interaction with its cognate receptor is well-described,<sup>46,47</sup> evidence is emerging for a significant role of IL-31 mediating inflammatory processes at mucosal sites. Mucosal sites are protected by an epithelial barrier, which senses incoming pathogens or allergens, and can respond to these by release of “alarmins” including IL-33, a cytokine of the IL-1 family which signals through its cognate T1/ST2 receptor connecting epithelial sites with the immune system by activating eosinophils, mast cells and T<sub>H</sub>2 lymphocytes.<sup>48,49</sup> In particular IL-33-driven activation of T<sub>H</sub>2 lymphocytes results in effective secretion of IL-31 from T cells, which can subsequently activate IL31RA/OSMRβ<sup>+</sup> epithelial cells, neurons and tissue-residing immune cells.

## The IL-31 axis in the skin

The role of the IL-31/IL31RA axis in pruritus and pruritic disorders such as AD is firmly accepted, although precise aspects about the pathophysiological role of IL-31 signaling remain to be elucidated. In humans, IL-31 acts as a pruritogen but evokes a rather late itch response when applied intradermally.<sup>50</sup> In AD patients, serum IL-31 and IL-33 levels are found to be increased when compared to healthy volunteers, nurturing the hypothesis that IL-33 might stimulate the secretion of IL-31 from T<sub>H</sub>2 cells or epithelial cells

*in vivo*.<sup>51</sup> In the skin, IL-31 enforces tissue alterations that are typically seen in AD patients (Figure 2). A recent study associated IL-31 with epidermal thickening as well as impaired skin barrier function and impaired mechanical integrity due to reduced junction plakoglobin (*Jup*) gene expression.<sup>52</sup> In organotypic skin models, IL-31 signaling induced differentiation defects depicted by the deficit in filaggrin expression and a reduction of the lipid envelope.<sup>53</sup> Gene expression analysis confirmed a direct IL-31 dependent regulation of genes involved in skin barrier and identified the IL-1 cytokine network as a downstream effector of IL-31 signaling.<sup>54</sup> Accordingly, anakinra-mediated IL1R blockage was effective to abrogate IL-31-mediated loss of skin differentiation. However, complete inhibition of IL-31 signaling might not be a desirable therapeutic outcome, since low doses of IL-31 are needed for the release of antibacterial peptides from keratinocytes.<sup>54</sup>

*In vitro* data from mouse keratinocytes suggest involvement of IL-31 in immune-cell recruitment, an important process during AD development. IL-31 initiates the release of various immune cell-attracting chemokines such as CCL4, CCL17, CCL22 and CCL25.<sup>1</sup> CCL17 and CCL22, for instance, recruit cutaneous lymphocyte antigen (CLA<sup>+</sup>)-expressing T cells to the epidermis. This immune cell subset is of major interest in AD since CLA<sup>+</sup> T cells are abundant allergen-reactive T cells in the circulation and lesional skin of AD-affected patients.<sup>55</sup> Whether IL-4- and IL-13-producing CLA<sup>+</sup> CD3<sup>+</sup> T cells or specific subtypes express IL-31 is not known but anticipated. However, the epidermis of AD-derived skin expresses elevated levels of IL31RA and forms a 'sensitized' target for IL-31.<sup>10</sup> AD-conditioned' keratinocytes could perpetuate the recruitment of CLA<sup>+</sup>, probably IL-31<sup>+</sup>-T<sub>H</sub>2 cells to the skin via release of chemokines, which in turn further activate keratinocytes via IL-31, thereby completing a positive feedback loop between the skin and immune system communication (Figure 1). That circuit would result in the progression of inflammation, pruritus and impaired skin barrier, thus progression of AD. The critical factor(s) that modulate(s) epidermal IL31RA expression levels in AD *in vivo* is not known yet. However, pro-inflammatory signals such as IFN $\gamma$  or neuropeptides like BNP are candidates, highlighting the importance of functional IL-31 in pro-inflammatory environments.<sup>23,24,56</sup>

Recent observations emphasize the importance of skin-resident memory T cells (CD3<sup>+</sup> CD45RO<sup>+</sup>CLA<sup>+</sup>) for AD onset.<sup>10,57–59</sup> Most of the skin-resident memory T cells are antigen-experienced and expresses the surface histocompatibility antigen-DR (HLA-DR). Challenge of this T cell subset with AD-associated bacterial superantigens such as staphylococcal enterotoxins B (SEB) or house dust mites (HDM)-derived antigens enhances the effector phenotype of the cutaneous T<sub>H</sub>2 pool.<sup>60,61</sup> Such priming and expansion of skin-resident memory T cells by antigens originating from skin-colonizing *Staphylococcal aureus* (SA) and HDM is a common observation in AD patients. Recently, elevated frequencies of HDM-reactive IL-31<sup>+</sup> T cells were observed in the periphery of chronic AD patients associated with decreased T<sub>H</sub>1/T<sub>H</sub>2 and Tc1/Tc2 ratios.<sup>62</sup> This finding indicates that allergen-specific T cells are subject to pre-existing T<sub>H</sub>2-Tc2 and that IL-31 may be involved in T<sub>H</sub>31-Tc31 programming.<sup>62</sup> The capacity of SA-specific T cells to produce and secrete IL-31 has not been tested yet. However, SEB is known to activate multiple T cell subsets, to act nonspecifically, and thereby might be ineffective to expand an IL-31<sup>+</sup> T cell subset.<sup>56,60</sup> A more general stimulation of toll-like receptor (TLR)-2 by bacterial cell wall components or 'atopic' cytokines increased IL31RA- and OSM-expression levels as well as CCL2 release in human keratinocytes, linking IL-31 to skin colonization and innate immunity.<sup>56</sup> Priming of T cells, however, is a complex process, which relies on an intricate interplay between the innate and adaptive immune system. Patrolling phagocytes of the adaptive immune system recognize via TLRs or pattern-recognition receptors (PRRs) invading pathogens or allergens and present them to cells of the adaptive immune system, such as CD4<sup>+</sup> T helper cells. The most effective antigen-presenting cells (APCs) are tissue resident dendritic cells (DCs), which capture the antigen and - depending on the subsequent activation of the respective TLR - activate either effector or regulatory T cells. Like keratinocytes, exposure of primary human CD1c<sup>+</sup> and monocyte-derived dendritic cells to IL-31 results in STAT-1 activation and subsequent IL31RA increase.<sup>63</sup> IL-31-stimulated dendritic cells secrete an extensive number of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF $\alpha$ ), IL-6, IL-8 and chemokines such as CCL2, CCL5 and CCL22, leading to amplified tissue inflammation.<sup>63</sup> DC-derived cytokines induce a massive influx of immune cells including T<sub>H</sub>2 cells and eosinophils. A recent study reports that eosinophils express IL31RA,<sup>64</sup> and that IL-31 functions as a survival signal lowering the rate of apoptosis in these

cells.<sup>65</sup> Thus, IL-31 signaling may offer a survival advantage to AD-associated eosinophils reinforcing the inflammatory cascade. Uncontrolled clonal expansion of effector T cells leads to the recruitment of additional eosinophils and CD68<sup>+</sup> macrophages.<sup>10</sup> Finally, activated DCs participate in the activation of CD4<sup>+</sup> T cells, including T<sub>H</sub>2 cells, by presenting SEB- or HDM-antigen to tissue-resident or infiltrated naïve T-cells.

### Translational importance of IL-31 and clinical trials

The T<sub>H</sub>2 cytokines IL-4 and IL-13 have recently been identified as central mediators of AD, leading to the development of antibodies targeting IL-4 or IL13, or both, for AD treatment.<sup>34,66</sup> In particular, the success of dupilumab, a fully human IgG4 $\alpha$  monoclonal antibody binding to the  $\alpha$ - subunit of the interleukin-4 receptor (IL4R $\alpha$ ), validated an essential role of the T<sub>H</sub>2 (type-2) inflammatory axis in AD. Dupilumab treatment achieved a rapid and robust improvement of skin lesions and pruritus and has been designated as a breakthrough therapy for AD by the US Food and Drug Administration (FDA).<sup>67</sup>

Considering the multifaceted role of IL-31 in T<sub>H</sub>2-driven AD, efforts have been intensified to develop agents that efficiently block also the IL-31/IL31RA axis. Early IL-31/IL31RA inhibition approaches in NC/Nga-inbred mice resulted in the first observation of reduced scratching.<sup>68</sup> Several follow up studies demonstrated that blocking of IL31RA by a neutralizing antibody effectively prevented itch in AD mouse models and AD patients.<sup>69–74</sup> IL-31-dependent pruritic activity has been described in mice, canines, primates and humans despite the low inter-species homology of the cytokine.<sup>75–77</sup>

Michels et al., demonstrated that subcutaneous administration of lokivetmab, a caninized anti-canine monoclonal anti-IL-31 antibody, alleviates itch symptoms in dogs with AD.<sup>77,78</sup> The decrease of itch was stable for over a month and associated with decreased IL-31 serum levels.<sup>78</sup> Similar results have been obtained in cynomolgus monkeys, where an AD-like phenotype was caused by administration of human and cynomolgus IL-31.<sup>75,79</sup> Moreover, blockage of IL-31 signaling using an anti-IL31RA antibody resulted in significant itch reduction.<sup>27714851</sup>

In humans, the first data of a clinical phase I/Ib trial assessing the efficacy of a humanized anti-IL31RA monoclonal antibody (CIM331, nemolizumab) revealed a marked dose-dependent reduction of pruritus after a single subcutaneous dose (Table 1).<sup>72</sup> Nemolizumab inhibited IL-31-mediated cell signaling efficaciously and safely, reduced pruritus to about 50% at week 4, improved sleep efficiency and decreased use of topical hydrocortisone.<sup>72</sup> A follow-up trial concluded the safe use of nemolizumab with no significant adverse event in combination with corticosteroid therapy.<sup>73</sup> In this phase-II clinical trial, nemolizumab (0.1, 0.5, 2 mg/kg) reduced itch by 43.7%, 59.8%, 63.1%, respectively, compared to 20.9% itch reduction with placebo (P<0.01). Changes in the Eczema Area Severity Index (EASI) score were -23.0%, -42.3%, and -40.9% in the nemolizumab groups versus -26.6% in the placebo group. The affected body surface area (BSA) was reduced by 7.5%, 20.0%, and 19.4% in the nemolizumab groups vs. 15.7% in the placebo group. Thus, nemolizumab every 4 weeks significantly improved pruritus in moderate-to-severe AD, was safe and well tolerated. In contrast, the secondary endpoints (EASI, BSA) were not significantly different in treatment and placebo group at 12 weeks with chosen dosages.<sup>80</sup> A phase-IIb clinical trial investigated the effects of nemolizumab (10, 30, and 90 mg) administered every 4 weeks over 24 weeks in adults with uncontrolled moderate-to-severe AD associated with severe pruritus.<sup>80</sup> Concomitant topical corticosteroid treatment was allowed. Here, 30 mg nemolizumab was the most efficacious, markedly improving EASI, Investigator's Global Assessment (IGA), and Peak Pruritus Numerical Rating Scale (ppNRS) vs. placebo group already at week 8, but not week 24, with an overall acceptable safety profile. A phase-III follow-up extension study investigated Japanese adult patients with moderate-to-severe AD and pruritus treated with nemolizumab (60 mg, every 4 weeks) versus placebo over 16 weeks.<sup>74</sup> Here, nemolizumab reduced the median VAS score by 42.8% vs. placebo (21.4%, P<0.001). Mean EASI score, Dermatology Life Quality Index (DLQI) score also improved in nemolizumab group compared to the placebo group. Injection site reaction was the most frequent adverse event. Finally, a recent phase-II, long-term extension study was published in moderate-to-severe atopic dermatitis.<sup>71</sup> Improvement of itch was observed at week 64 with 0.5-mg/kg nemolizumab. No long-term safety concerns were identified. Since AD is a clinically heterogeneous disease it will be important to better understand the subtypes of AD which will profit the most from the current and future therapies targeting IL-4, -13 and -31.

## IL-31 in Mucosal Airway and Intestine

Recently, IL-31 signaling has been detected in mucosal sites of the human lung, nasal sinus and intestine (Figure 3).<sup>81–83</sup> Lung epithelial cells express IL31RA, OSMR $\beta$  and gp130. Although both, OSM and IL-31, engage with equal affinities to IL31RA/OSMR $\beta$  of lung epithelium and activate common signal transduction pathways, each agonist can activate distinct downstream signaling cascades.<sup>81</sup> For instance, OSM activation leads to balanced phosphorylation of STAT3, ERK and STAT5, whereas IL-31 increases STAT3 phosphorylation, while attenuating STAT5 responses and leaving pERK levels unaffected.<sup>81</sup> Neither OSM nor IL-31 initiate the expression of any of the other “classical” IL-6 targets such as STAT1.<sup>81</sup> STAT3 signaling has been linked to both proinflammatory and anti-inflammatory responses and is involved in regenerative processes, such as proliferation and inhibition of apoptosis.<sup>84,85</sup> As to whether IL-31 is implicated in these functional roles within intestinal epithelium via STAT3 activation has yet to be determined.

In the epithelial-like human lung adenocarcinoma cell line (A549), IL-31 induces morphological changes characterized by formation of podosomal extensions and a reduction in cell-cell interactions.<sup>81</sup> Furthermore, IL-31 activation induces cell-cycle arrest and an impaired regulation and expression of cell cycle proteins such as cyclin B1, CDK6 and CDK1 (CDC2), and suppressing proliferation. This indicates a profound role of IL-31 in tissue homeostasis.<sup>81</sup> Of note, the responses of lung epithelial cells to IL-31 activation can vary due to the inducible expression of IL31RA and differences in receptor abundance between donors. For example, the expression of IL31RA is transiently downregulated after engagement of its ligand by downstream signaling effects.<sup>81</sup>

In T<sub>H</sub>2-dominated asthmatic or non-asthmatic airway inflammation changes in IL31RA abundance could be essential, since IL-31 was found to support the progression of the asthmatic phenotype leading to the notion by some that IL-31 might serve as a marker of allergic asthma.<sup>51,86,87</sup> Contrary to findings in the skin, this study suggests that the culprit IL-31 would not be exclusively expressed by T cells but rather stems from unidentified cells in the lung that respond to IL-4. Interestingly, IL-33 is secreted continuously by lung epithelial cells during asthmatic inflammatory reactions as an alarm signal against invading pathogens and allergens<sup>88</sup> but appears to fail to signal in pulmonary T<sub>H</sub>2 cells to up-regulate IL-31 release levels in an allergic situation.<sup>11</sup> Interestingly, asthma was found as one of the dose-dependent side effects in clinical trials with nemolizumab.<sup>80</sup> The asthmatic events have exclusively been observed in patients with a pre-existing asthma, probably due to improved health and increased activity levels that triggered asthma.

In human bronchial epithelial cells and co-cultures with eosinophils, IL-31 alone or in cooperation with T<sub>H</sub>2 cytokines (IL-4 or IL-13) was shown to alter the production of inflammatory cytokines (IL-6, IL-8), chemokines (CCL2) and growth factors (vascular endothelial growth factor (VEGF), endothelial growth factor (EGF)). CCL2, VEGF and EGF are involved in the recruitment of inflammatory cells, and the autocrine remodelling of epithelial cells,<sup>89</sup> indicating an overall pro-inflammatory role for IL-31 in pulmonary inflammation. Subsequent studies, however, describe IL-31 as a regulatory rather than an inflammatory cytokine in the lung, suggesting a dual role for IL-31 in airway function. Perrigoue et al. described ameliorating effects of the IL-31/IL31RA axis in a murine model of pulmonary type 2 inflammation.<sup>90</sup> Mice infected with *S. mansoni* eggs, lodging in the small blood vessels of the lung, develop pulmonary granulomas, due to IL-4/IL-13 signaling, but displayed intensified inflammation of the parenchymal lung tissue when IL31RA was absent.<sup>90</sup> In this model, IL31RA<sup>-/-</sup> mice showed an increased production of type-2 cytokines (IL-4, IL-5, IL-13) upon secondary challenge of isolated lymph node cells with *S. mansoni* egg antigen. Contrary to initial studies in lung inflammation models, these findings suggest a stronger anti-inflammatory function of IL31RA signaling in the parasite-affected lung tissue. However, the increase in cytokine production in IL31RA<sup>-/-</sup> mice leads to an elevated frequency of alternatively activated macrophages (AAMs) resulting in pulmonary tissue remodeling and fibrosis. Naïve CD4<sup>+</sup> T cells from IL31RA<sup>-/-</sup> mice demonstrated an augmented proliferative capacity and elevated T<sub>H</sub>2-cytokine production without differentiation into T<sub>H</sub>2 polarized cells. These findings indicate a regulatory engagement of the IL-31/IL31RA axis with GATA-3 in undifferentiated T cells, resulting in a refined control of cytokine production. However, these effects were absent in fully differentiated effector T<sub>H</sub>2 cells. Thus, IL-31 activation of antigen-presenting cells (e.g. macrophages) appears to restrict



the proliferation of naïve and T<sub>H</sub>2 differentiated cells without impairing their antigen-presenting capacity in lung cells.<sup>90</sup> Therefore, IL-31 may suppress some innate immune cells, thereby regulating activation of the adaptive immune system during airway inflammation.

IL-31 has recently been implicated in the pathogenesis of nasal polyps (NP) of the sinus mucosa.<sup>82</sup> Nasal polyps are similar to AD histologically characterized by an infiltration of lymphocytes, especially T<sub>H</sub>2 cells, and eosinophils, considered now as a type-2 inflammation. The expression of IL-31 is elevated in NPs and IL-31 protein levels correlated with clinical outcome, probably due to the IL-31-amplified T<sub>H</sub>2-skewed inflammation profile.<sup>82</sup>

Expression levels of IL-31 and IL31RA were further found upregulated in the inferior turbinate of patients with allergic rhinitis.<sup>91</sup> IL31RA primarily localized to submucosal glands and stimulation of A549 cells induced expression of the *mucin 5AC* (*MUC5AC*) gene suggesting a role for IL-31 in mucus overproduction during nasal allergic inflammation.<sup>91</sup>

In the intestine, IL-31 imbalance seems to be associated with inflammatory bowel disease (IBD). IBD is a frequent autoimmune disorder of the gastrointestinal tract presenting with mucosal inflammation and ulceration due to an imbalance in effector and regulatory T cells.<sup>92,93</sup> Two major types of IBD have been described, ulcerative colitis (UC) and Crohn's disease (CD). Expression analysis revealed elevated levels of IL-31, IL31RA and OSMR mRNA in inflamed colonic lesions of CD and UC patients which correlated with lesional IL-8 expression.<sup>94</sup> Beyond this descriptive finding, an IL-31-specific impact on cellular mechanisms in CD or UC are still missing. In colorectal HCT116 cells, however, pro-inflammatory cytokines (TNF $\alpha$ , IL-1 $\beta$ ) and bacterial lipopolysaccharide (LPS) induced IL-31, IL31RA, and OSMR $\beta$  mRNA expression, suggesting involvement of the IL-31 axis in intestinal inflammation.<sup>94</sup>

A pro-inflammatory effect of IL-31 has further been revealed in human colonic subepithelial myofibroblasts. IL-31 dependent activation led to *in vitro* production of IL-8 (CXCL8), growth-related oncogene- $\alpha$  (GRO- $\alpha$ ), CXCL1, monocyte chemoattractant protein-3 (MCP-3), CXCL3 (GRO-3), IL-6 and various metalloproteinases.<sup>95</sup> The inflammatory impact of IL-31 *in vivo* on the intestinal epithelial layer has not been shown so far. To elucidate the function of IL-31/IL31RA in chronic intestinal inflammation in humans will necessitate detailed assessments of IL-31-induced signaling traits in disease-promoting cell types, including intestinal epithelial cells, effector/regulatory T cells, nerves and DCs.

Similar to the role of IL-31 signaling in *S. mansoni* -induced airway inflammation, IL-31-/L31RA has been associated with immunological responses in a murine model of parasitic infection.<sup>83</sup> Infection of mice with *Trichuris muris* initiates priming of T<sub>H</sub>2 cells and subsequent production of T<sub>H</sub>2 effector cytokines in the early infection stage and to a conversion of the immune response to a T<sub>H</sub>1-dominated phenotype including IFN $\gamma$ .<sup>83</sup> Perrigoue et al. demonstrated that IL-31 expression increased under inflammatory conditions when IL-4 was present to skew naïve T cells towards a T<sub>H</sub>2 phenotype. Like their results on the role of IL-31/IL31RA in inflamed lung tissue, the group demonstrated an enhanced production of type-2 cytokines in the absence of IL31RA, implying an immuno-regulatory function of IL-31 in the inflamed intestine.<sup>83</sup> Nevertheless, although these observations are consistent in lung and intestine, the results await confirmation by additional studies since observations in the skin reveal a rather pro-inflammatory role of IL-31.

### Concluding remarks and future perspectives

Although the biological function of IL-31 has predominantly been associated with AD and pruritus, it is now clear that IL-31 is more than an 'itchy' cytokine. The importance of IL31RA in AD pathophysiology was demonstrated by early and recent trials validating a marked reduction in itch along with improvement of eczema, in some studies, in AD patients using anti-IL31RA antibody.<sup>72,74,80</sup> The success of these trials in moderate to severe AD suggests that sole blockage of the IL-31 pathway may be sufficient to achieve an acceptable therapeutic outcome in some patients. However, the success of the IL-4R $\alpha$ -inhibiting antibody dupilumab in AD patients demands further evaluation how to stratify the heterogeneous population of AD patients for the best 'personalized' benefit. More large-scale, long-term studies will help to understand benefit of IL-31-axis inhibition on AD onset, progression and resolution, as well as its impact beside pruritus on

inflammation (eczema) and barrier dysregulation. A recent trial of nemolizumab in prurigo nodularis patients suggests the applicability of anti-IL31/IL31RA biologicals as therapeutics of certain pruritic diseases.<sup>96</sup> For example, in cancer-associated itch the IL-31 axis might be recognized as a valid treatment target, considering the growth-promoting capacity of IL-31 signaling in various cell types.<sup>37,52,97</sup> The efficacy of the IL-31-axis inhibition in different types of itch will be important to understand in order to further develop and enhance our therapeutic ‘toolbox’ for the treatment of currently therapy-refractory pruritic diseases.

IL-31 triggers regulatory responses in epithelial cells of all mucosal sites, namely skin, lung and the GI tract. However, while we begin to understand the cutaneous function of IL-31, its effect on intestinal and pulmonary cell populations is less clear. The involvement of IL-31 in inflammatory disorders of the GI tract or lung is at this stage preliminary and far from being understood. IL-31 likely acts in both tissues in a similar fashion as observed in skin, nurturing inflammatory responses of resident cells and cross-communicating as a regulatory signal to receptive T cells, DC subsets and probably nerves. However, to fully understand the IL-31-axis in gut, lung and skin during homeostasis and inflammatory conditions, an array of *in vitro*, *ex vivo* and *in vivo* studies will need to be performed.

Deciphering the precise IL-31-induced mechanisms in organ- and disease models, will probably lead to new therapeutic options for the treatment of skin diseases, as well as atopic disorders (nasal polyposis), or disorders in the lung or gastrointestinal tract. However, as mentioned above, because IL-31 itself has a dual inflammatory effect depending on disease stage, the beneficial role of neutralizing the IL-31 pathway needs to be explored for each disease.

### Conflict of interest statement

AD, MA, FA and JB do not declare any conflict of interest. MS is a consultant for Pfizer, Janssen, Eli-Lilly, Novartis, UCB, Celgene, Galderma, Leo, MenloTx. Sanofi, Regeneron. Grants by Pfizer, Novartis, Leo, Galderma. Speaker for Pfizer, Janssen, Eli-Lilly, Novartis, UCB, Celgene, Galderma, Leo, MenloTx, Sanofi, Regeneron.

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**Table 1: Clinical trial design for completed trials testing nemolizumab efficacy in AD and PN**

	Nemolizumab (CD14152; CIM331; humanized IgG2x?	Nemolizumab (CD14152; CIM331; humanized IgG2x?	Nemolizumab (CD14152; CIM331; humanized IgG2x?	Nemolizumab (CD14152; CIM331; humanized IgG2x?	Nemolizumab (CD14152; CIM331; humanized IgG2x?
<b>Mechanism of biologic</b>	Anti-IL31RA monoclonal antibody blocking IL- 31-dependent receptor activation and downstream signaling	Anti-IL31RA monoclonal antibody blocking IL- 31-dependent receptor activation and downstream signaling	Anti-IL31RA monoclonal antibody blocking IL- 31-dependent receptor activation and downstream signaling	Anti-IL31RA monoclonal antibody blocking IL- 31-dependent receptor activation and downstream signaling	Anti-IL31RA monoclonal antibody blocking IL- 31-dependent receptor activation and downstream signaling
<b>Study design</b>	Randomized, placebo- controlled, double-blind, multi-center	Randomized, placebo- controlled, double-blind, multi-center	Randomized, placebo- controlled, double-blind, multi-center dose ranging	Randomized, placebo- controlled, double-blind, multi-center XCIMA study group	Randomized, placebo- controlled, double-blind, multi-center
<b>Identifier number Publication</b>	JapicCTI- 173740 Kabashima et al., 2020, <sup>74</sup>	NCT03181503 Stander et al., 2020, <sup>96</sup>	NCT03100344 Siverberg et al, 2020, <sup>80</sup>	NCT01986933 Part A: Ruzicka et al 2017, <sup>73</sup> Part B: Kabashima et al., 2018, <sup>71</sup>	NA Nemoto et al 2016, <sup>72</sup>
<b>Phase Recruitment status Duration</b>	3 Completed 16 wk	2 Completed 16 wk	2B Completed 32 wk	2 Completed Part A:12 wk; Part B: 52 wk	1/1b Completed 127 days
<b>Participant ethnicity</b>	Japanese	NA	NA	NA	Japanese, white



	Nemolizumab (CD14152; CIM331; humanized IgG2x?)	Nemolizumab (CD14152; CIM331; humanized IgG2x?)	Nemolizumab (CD14152; CIM331; humanized IgG2x?)	Nemolizumab (CD14152; CIM331; humanized IgG2x?)	Nemolizumab (CD14152; CIM331; humanized IgG2x?)
<b>Dosing</b>	60 mg Q4W, subcutaneous	0.5mg/kg Q4W up to wk 8, subcutaneous	10, 30, 90 mg Q4W up to wk 20, subcutaneous	Pt A: 0.1, 0.5, or 2.0 mg/kg Q4W, or 2.0 mg/kg Q8W, wk 12 Pt B: above, wk 52	0.003, 0.01, 0.03, 0.1, 0.3, 1.0, 3.0 mg/kg, single dose, subcutaneous
<b>Sample size</b>	N = 143 (72 PbO), (204 target size)	N = 70 (34 PbO)	N = 226 (57 PbO)	Pt A: n = 216 (264 target size); Pt B: n = 131 (191 target size)	N = 145 Pt A: n = 56 (14 PbO); Pt B: n = 24 (6 PbO); Pt C: n = 36 (9 PbO)
<b>Key inclu- sion/exclusion criteria</b>	AD with moderate or severe pruritus	Clinical diagnosis of PN [?] 6 months, pruritus	Chronic AD [?] 2 years	Pruritic AD	AD of moderate or greater severity
<b>Primary endpoint</b>	Mean %Δ VAS (range 0-100), wk 16	%Δ pruritus NRS score using LOCF, MI and observed data, wk 4;	%Δ EASI, wk 24	%Δ VAS, wk 12	Assessment of AE

**Figure legends**  
**Figure 1. IL-31 σιγναλινγ ια ιτς ζογνατε IL31PA/OSMRβ ρεζεπτορ η-ετεροδιμερ.** Binding of IL-31 leads to receptor dimerization, cytosolic phosphorylation and subsequent activation of canonical kinase pathways including JAK/STAT, PI3K/AKT and MAPK cascades. Note that OSMRβ specific recruitment of the adapter proteins SHC and SHP-2 facilitates phosphorylation and activation of various MAPK cascade members. Dependent on cell type and cell environment, downstream transcription factor activation subsequently controls the expression of genes involved in inflammation, proliferation and cell survival.  
**Figure 2. Illustration depicting the effects of IL-31 in atopic dermatitis skin.** CLA<sup>+</sup> T<sub>H</sub>2 cells are abundant allergen-reactive T cells in the circulation of AD patients and are recruited to the AD-affected skin through CCL17 and CCL22 signaling. In the skin, CLA<sup>+</sup> T<sub>H</sub>2 cells secrete IL-31, which in turn can activate IL31RA/OSMRβ-expressing cutaneous sensory nerves, innate immune cells including DCs, monocytes and eosinophils (not shown) and keratinocytes of the epidermis. In human AD skin, keratinocytes show elevated levels of IL31RA/OSMRβ expression resulting in stronger receptiveness to IL-31. Cutaneous IL-31 signaling results in peripheral pruritus, (neuro)-inflammation and an impaired barrier function through IL-31-mediated suppression of terminally differentiated genes such as filaggrin and a reduced lipid envelope. Activated keratinocytes secrete various chemo-attractants that trigger an additional recruitment of IL-31-expressing CLA<sup>+</sup>T<sub>H</sub>2 cells to the site of inflammation, nurturing a feedback-in loop of skin inflammation and pruritus. Human and mouse sensory neurons express IL31RA/OSMRβ mostly in neurons that also co-express TRPV1. Sensory nerve endings demonstrate high IL31RA levels in AD skin and IL-31 stimulation leads to enhanced neuronal growth probably causing pruritic hypersensitivity and an elevation of peripheral pruritus. In the central nervous system, IL31RA/OSMRβ immunoreactivity has been shown in the dorsal horn of the spinal cord, indicating that IL-31 signaling is likely involved in central pruritus and sensitization of spinal cord neurons.  
**Figure 3. IL-31 Function in Mucosal Sites.**



