EVE DIAGNOSTICS

CYTOKINE, CHEMOKINE AND GROWTH FACTOR 95-PLEX ANALYTE GLOSSARY

GROUP A1 – INNATE / AUTOIMMUNE INFLAMMATION

FGF-2 (Basic fibroblast growth factor)[1] – Growth factor that plays a role in the development and homeostasis of several tissues, notably in the musculoskeletal and cardiovascular systems, and is a pro-angiogenic factor. FGF-2 also has pro-inflammatory functions and its expression is increased in inflammation. FGF-2 may contribute to the pathogenesis of autoimmune conditions (i.e., RA and multiple sclerosis), colitis, orbitopathy in Graves disease, lung and kidney fibrosis, and cancer.

IFNα2[2] – A type I interferon, IFNα2 is expressed following viral infections and the recognition of stress-associated molecular patterns. IFNα2 induces an innate antiviral response preventing viral spread, and contributes to adaptive immune responses, notably type 1 immunity. There is evidence that IFNα2 expression may be detrimental in bacterial, fungal and parasitic infections, which may play a role in secondary bacterial infection following a primary viral infection. Increased expression of IFNα2 has been implicated in the pathogenesis autoimmune diseases like systemic lupus erythematosus and Sjögren's syndrome, and in autoinflammatory interferopathies.

IL-1α[3,4] A potent pro-inflammatory cytokine of the innate immune system and inducer of several components of the acute phase response. IL-1α is constitutively expressed in non-myeloid cells (e.g., keratinocytes, lung and gut epithelial cells) and is released from necrotic cells to initiate inflammation following tissue damage. IL-1 is also an important factor in the proliferation and function of Th17 cells, acting synergistically with **IL-23** to induce the release of **IL-17A**. Increased release of IL-1 has been observed in many pathological conditions, including autoimmune diseases, metabolic syndromes, acute inflammation, chronic inflammation, and invasive cancers. Studies in mouse models suggest that IL-1α, and not IL-1β, may be specifically implicated in inflammatory diseases of the skin, such as hidradenitis suppurativa and pyoderma gangrenosum, and in colitis.

IL-1β[3,4] Similar functions to IL-1α (both are ligands of a common receptor (IL-1R) with identical affinities). Unlike IL-1α, IL-1β is expressed only in myeloid cells and requires proteolytic processing prior to secretion to be activated. Activation is mediated by caspase-1 following the formation of inflammasome complexes upon detection of signals indicating the presence pathogens, inflammation, or physiological stress. IL-1β also supports the production of type 3 cytokines **IL-17A** and **IL-22** in ILC3s.

IL-1RA (IL-1 receptor antagonist)[3] Antagonist of the IL-1 receptor, IL-1RA blocks the effects of **IL-1α** and **IL-1β**. Thought to be an acute phase factor that balances the physiologic effects of IL-1. IL-1RA is often observed to be elevated in cytokine storm, and is likely induced as an negative regulator of IL-1-driven inflammation[5].

IL-2[6] **–** A key factor in Th1, Th2, Treg, and CD8+ T cell proliferation and clonal expansion (but inhibitory of Th17 development), characterized by an initial peak at the onset of the T cell response followed by a rapid decline. Low, baseline levels of IL-2 promote immunomodulatory Treg development and survival, whereas higher levels in response to immune stimulation promote the activation and proliferation of natural killer (NK) cells and CD8+ cytotoxic T cells. IL-2 has context-specific dual roles in either promoting or suppressing autoimmunity[7].

***IL-17A*[8]** – A signature cytokine released by Th17 cells and one of the main drivers of type 3 immune responses, IL-17A contributes to host defense and pathogen clearance of extracellular bacteria and fungi, as well as regulation of the gut microbiota. Dysregulation of Th17 activity is a key driver of autoimmunity, and elevated IL-17A has been recognized as an important contributor to autoimmune disorders including psoriasis, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease. IL-17A blocking agents have been approved or are being investigated for the treatment of psoriasis, rheumatoid arthritis, ankylosing spondylitis, and multiple sclerosis.

> *IL-1, type I interferons such as IFNα2, IL-17A, and FGF-2 are known contributors to autoimmune disorders, and elevated IL-2 promotes active inflammation. IL-17A and FGF-2 have been shown to synergistically promote inflammation in autoimmune arthritis[9]. IL-1, IL-17 and FGF-2 can initiate and potentiate type 3 (Th17-mediated) immunity (a key driver of autoimmunity), while IL-has been shown to be a negative regulator of Th17 activity. Type I IFNs have also been shown to suppress Th17 cells in some contexts[10], although there is evidence that IFNα2 can exacerbate Th17-mediated inflammation in autoimmune diseases[11], such as in systemic lupus erythematosus (SLE) where IFNα2 and IL-17A contribute to a pathogenic signaling axis with BAFF (Group B)[12]. IL-1 is also one of the major drivers of innate inflammatory responses, and IL-1RA is expressed as a negative regulator of IL-1 signaling.*

GROUP A2 – PRO-INFLAMMATORY CYTOKINES / T CELL BIOMARKERS

***Fractalkine (CX3CL1)*[13] –** Drives the recruitment of CX3CR1-expressing immune cells, including monocytes, macrophages, microglia, Th1 cells, CD8+ T cells, NK cells, γδ T cells, and conventional dendritic cells (cDC) to sites of inflammation. Fractalkine signaling contributes to continuing type 1 immune responses, and can also contribute to Th2 responses in asthma and Th17 responses in gut inflammation. The fractalkine-CX3CR1 axis has been implicated in a variety of diseases, such as atherosclerosis, allergic airway disease and asthma, inflammatory bowel disease, and cancer.

***IFNγ*[14] –** The major signature cytokine secreted by Th1 cells, as well as NKs, ILC1s, and antigen-presenting cells like DCs and macrophages, IFNγ is the key factor in orchestrating type 1 adaptive immune responses against intracellular pathogens. IFNγ promotes Th1 cell differentiation, induces M1 polarization in macrophages, drives the expression of anti-microbial and anti-viral factors, and regulates inflammatory responses by inducing several cytokines and chemokines (e.g., **IP-10** and **MIG**). As a key regulator of type 1 immunity, IFNγ dysregulation contributes to autoimmune and other chronic inflammatory conditions driven by Th1 cells.

***IL-4*[15] –** A key cytokine orchestrating type 2 immune responses, IL-4 promotes the differentiation, proliferation and survival of Th2 cells and is also secreted by activated Th2 cells. IL-4 induces Ig isotype switching to IgG1 and IgE in B cells and drives the maturation and activation of DCs. In the context of dysregulated Th2 immunity, IL-4 is thought to be a key factor in the initiation phase of allergic inflammation and related diseases (asthma, atopic dermatitis, etc.). IL-4 (with TGF-β or IL-1β) also drives the differentiation of **IL-9** producing Th9 cells.

***IL-5*[15] –** A signature cytokine secreted by Th2 cells, IL-5 stimulates antibody production in B cells and is an important factor in the differentiation of mature eosinophils from their precursors. As a key factor in Th2-mediated responses, IL-5 contributes to diseases of allergic inflammation such as asthma.

***IL-9*[16,17]** – A pleiotropic cytokine that is highly expressed by Th9 cells, mast cells and type 2 ILCs, and can be expressed by Th17 cells. Depending on the immunological context, IL-9 contributes to the regulation of Th1, Th2, and Th17-mediated immune responses and Treg-mediated immune tolerance, as well as regulating innate immune cells like mast cells, macrophages, ILCs, and dendritic cells. High levels of IL-9 have been associated with allergic diseases (e.g., asthma, allergic rhinitis, food allergies) and

autoinflammatory/autoimmune diseases (e.g., inflammatory bowel disease, multiple sclerosis, lupus nephritis).

***IL-12p40*[18] –** A subunit of the biologically active cytokines **IL-12p70** (heterodimer with IL-12p35, associated with type 1 immune responses) and **IL-23** (heterodimer with IL-23p19, associated with type 3 immune responses). IL-12p40 is highly expressed by macrophages and DCs upon microbial stimulation. When expressed at high levels, IL-12p40 can form homodimers that provide negative feedback to IL-12 and IL-23 signalling by competitively binding to the IL-12 and IL-23 receptors.

***IL-12p70*[19] –** The active form of IL-12. Released mainly by DCs, monocytes, and macrophages upon bacterial- or viral-specific pattern recognition receptor activation, IL-12 is the main driver of Th1 cell differentiation and, when present with **IL-18**, induces **IFNγ** release from Th1 cells. Also promotes the differentiation of ILC1s and the proliferation of peripheral T cells and NK cells. Additionally, IL-12p70 promotes Th17 cell differentiation to the pathogenic GM-CSF and IFNγ-expressing Th1/17 phenotype[20]. IL-12 signaling is implicated in several inflammatory and autoimmune diseases, such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, diabetes mellitus, and Sjögren's syndrome.

***IL-13*[15] –** A signature Th2-released cytokine that is also produced by CD8+ T cells, mast cells, eosinophils DCs, and ILC2s, IL-13 contributes to the type 2 immune response by serving as a co-stimulator that drives B cell maturation, activation and antibody release. IL-13 has been shown to inhibit the production of pro-inflammatory cytokines (**IL-1β, TNFα, IL-12**) by monocytes and may have a protective effect in type 1 inflammation, although both Th1 and Th17 cells have been shown to co-express IL-13 with their signature cytokines in some contexts[21]. IL-13 contributes to allergic inflammatory responses and is thought to drive the effector, rather than the initiation, phase of allergic diseases such as asthma.

***IL-17F*[22]** – An effector cytokine of type 3 immune responses that is released by activated Th17 cells, IL-17F forms homodimers or heterodimers with IL-17A to promote host defense at mucosal barriers. Unlike IL-17A, IL-17F can also be produced by activated monocytes and epithelial cells. Elevated IL-17F (and dysregulated type 3 immunity) has been recognized as a key contributor to autoimmune disorders including psoriasis, rheumatoid arthritis, multiple sclerosis, as well as inflammatory bowel disease.

***IL-22*[23]** – A cytokine released primarily by lymphoid cells, including Th22 cells (thought to be the major source of IL-22 in the peripheral circulation), as well as Th17 cells, type 3 innate lymphoid cells (ILC3s), and NKs. Depending on the tissue and pathological context, IL-22 can either reduce inflammation and drive epithelial repair and regeneration, or it can induce pro-inflammatory mediators and promote type 1 or type 3 inflammation. High plasma levels of IL-22 have been observed in patients with inflammatory bowel disease, rheumatoid arthritis and malignancy.

***MCP-3 (Monocyte chemotactic protein 3; CCL7)*[24]** – Induced in response to pathogen detection and inflammatory cytokine signaling (e.g. **IL-1β, TNFα, IFNγ**), MCP-3 signals via CCR1, CCR2, CCR3, and CCR4 to drive the recruitment of a variety of immune cells, most prominently monocytes, but also eosinophils, basophils, DCs, NK cells, Th2 cells, and neutrophils. MCP-3 signaling impacts the immune response to viral, bacterial, and fungal infections.

***MIP-1α (Macrophage inflammatory protein-1α; CCL3)*[25]** – Recruitment of T cells, B cells, DCs, neutrophils, monocytes, and eosinophils to sites of inflammation via the receptors CCR1, CCR4 and CCR5. MIP-1α is an important factor in CD8+ memory T cell development in the lymph nodes and may promote Th1 polarization (and prevent Th2 polarization) in naïve CD4+ T cells[26]. MIP-1α has also been identified as a primary driver of progressive disease in multiple myeloma.

***TGF-α (Transforming growth factor α)*[27]** – A ligand of the EGF receptor, TGFα drives cell proliferation and stem cell survival, and contributes to developmental processes and tissue homeostasis throughout the body. Several immune cells, including neutrophils, monocytes, and eosinophils, express and release TGF-

α upon degranulation, which may contribute to tissue healing following the inflammatory response. Persistently elevated TGF-α in the context of chronic inflammation may be a driver of fibrosis.

TNFα (Tumour necrosis factor α)[28] – Important pro-inflammatory cytokine that is released following the detection of pathogen and other danger-associated molecular patterns, inflammatory signals, and stress, with a particularly important role in driving the early phase of the inflammatory response. TNFα is also released by Th1 and Th17 cells and has been shown to promote type 1, type 2, and type 3 immune responses, and is co-stimulatory in B cell development. TNFα is a pro-angiogenic factor that contributes to wound healing responses. Dysregulated production of TNFα has been associated with rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA) and cardiovascular disease. TNFα blocking agents have been approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, ulcerative colitis, and Crohn's disease.

TNFβ (Tumour necrosis factor β; Lymphotoxin-α)[29] – Pro-inflammatory cytokine that also contributes to the development of the immune system. TNFβ is released by Th1 cells, CD8+ T cells, NK cells, and macrophages, and contributes to type 1 immune responses. It is also essential in the differentiation of NK cells and plays a role in NK recruitment and function. TNFβ has been implicated in the pathogenesis of rheumatoid arthritis (and may be a key factor in patients that are resistant to TNFα blockade), and cardiovascular disease.

> *The analytes in this group consist of pro-inflammatory cytokines that can initiate and propagate innate inflammation and contribute to adaptive immune responses. The cytokine profile may indicate responses orchestrated by Th1 (IFNγ, IL-12p70, TNFβ; intracellular pathogen infection/autoimmunity), Th2 (IL-4, IL-5, IL-13, IL-9; helminth infection, allergy and/or tissue repair and fibrosis), and/or Th17 cells (IL-17F, IL-22; extracellular pathogen infection/autoimmunity) along with Th9 (IL-9[17]) and Th22 cells (IL-22, IL-13), which may contribute to allergy and autoimmunity. Patterns of mixed T cell cytokine release could indicate a multifaceted immune response with multiple types of inflammation, could reflect the heterogeneity and plasticity observed in T cells in vivo, since "hybrid" cells that co-express the signature cytokines of two different T cell subtypes (e.g., IL-4 with IFNγ, IFNγ with IL-17A, IL-4 with IL-17A, IL-13 expressed by both Th1 and Th17 cells) may be common[21,30,31], or could indicate regulatory mechanisms (e.g. type 2 cytokines released following tissue damage caused by type 1 or type 3 immune responses[32]).*

GROUP A3 – HEMATOPOIETIC GROWTH FACTORS

G-CSF (Granulocyte colony-stimulating factor)[33] **–** Hematopoietic growth factor that is an important driver of neutrophil development and proliferation. Also induces the mobilization of hematopoietic stem and progenitor cells from the bone marrow into circulation.

GM-CSF (Granulocyte-macrophage colony-stimulating factor)[34-36] **–** A pro-inflammatory cytokine that acts as a bridge between T cells and effector leukocytes during inflammation. GM-CSF also acts as a hematopoietic growth factor that drives the replication, differentiation, activation, and survival of a variety of myeloid cells and promotes pathogenic macrophage polarization. Most GM-CSF released during acute inflammation is released by CD4+ T cells (Th1 and Th17) and ILC3s, and contributes mainly to type 1 and type 3 immune responses, but can also play a role in type 2 immune responses in the airway. GM-CSF has been shown to be a major contributor to the pathogenesis of several chronic inflammatory and autoimmune diseases including rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and allergic diseases such as asthma.

IL-3[37] **–** Originally known as multi-CSF, IL-3 drives the differentiation of bone marrow precursors to a wide variety of myeloid cells including monocytes, macrophages, neutrophils, eosinophils, basophils, and mast cells, and stimulates proliferation in hematopoietic stem cells. IL-3 also induces degranulation in mature basophils and mast cells and is an important factor promoting type 1 IFN release from plasmacytoid DCs

(pDCs). IL-3 acts on early hematopoietic precursor cells, and so can serve as a growth factor in the pathogenesis of acute and chronic myelogenous leukemia.

IL-7[38] – An essential factor in the proliferation, survival, and development of T and B cells. Also plays an important role in the development and function of ILC2s and ILC3s. Circulating levels of IL-7 increase in response to lymphopenia, and a deficiency in IL-7 signaling results in severe combined immunodeficiency (SCID).

High levels of the analytes in this group

GROUP B – INNATE INFLAMMATION / CYTOKINE 'STORM'

BAFF (B cell activating factor)[39,40] **–** Member of the TNF family of cytokines that promote B cell survival and proliferation. The BAFF/APRIL system has been implicated as an important contributor to autoimmune diseases, most prominently systemic lupus erythematosus (SLE), and may also play important roles in the development of graft vs. host disease (GVHD) and cancer.

Flt3L (FMS-related tyrosine kinase 3 ligand)[41] – Hematopoietic growth factor that drives hematopoietic stem cells towards a lympho-myeloid fate, is an essential factor in the generation of DCs, and contributes to the proliferation and maintenance of B cells. Additionally, Flt3L synergizes with other hematopoietic growth factors in the development and expansion of myeloid cells (e.g., with **SCF**, **IL-3**, **IL-6**, **GM-CSF**, and **G-CSF**) and promotes the expansion and maintenance of lymphoid progenitors in synergy with **IL-7**. Increases in Flt3L can massively expand migrating and resident DC populations in the periphery, and dysregulation of the Flt3L-Flt signaling axis has been identified as an important contributor to leukemia.

IL-6[42,43] **–** Plays a central role in innate immunity as a key factor driving acute phase protein release from hepatocytes, and in adaptive immunity by stimulating antibody release from B cells and promoting CD4+ T cell differentiation to Th2 (with **IL-4**) and Th17 (with TGF-β) subtypes. IL-6 is thought to be an important contributor to 'cytokine storm' (cytokine release syndrome, CRS) in conditions such as MAS, AOSD, and COVID-19. IL-6 blocking agents have been approved or are being investigated for the treatment of a wide range of autoimmune, acute and chronic inflammatory diseases including rheumatoid arthritis, Castleman's disease, juvenile idiopathic arthritis, cytokine release syndrome (including severe COVID19), among several others[44].

IL-8 (CXCL8)[45] – An important factor in the recruitment and activation of neutrophils, as well as monocytes, eosinophils, and mast cells via CXCR1 and CXCR2. As a CXCR2 ligand, IL-8 is also a pro-angiogenic chemokine that contributes to wound healing responses. Elevated levels of IL-8 are associated with chronic inflammatory conditions like psoriasis, rheumatoid arthritis, COPD, and asthma.

IL-10[46] – A potent anti-inflammatory factor. IL-10 promotes immunomodulatory Treg development, decreases inflammatory cytokine production and prevents the development of T cell-mediated immune responses. Despite its established role as an anti-inflammatory cytokine, IL-10 has been implicated as a potential contributing factor to the 'cytokine storm' in severe COVID-19[47].

IL-15[48] – Promotes adaptive immune responses by driving the proliferation and survival of activated T cells, along with the generation, activation and proliferation of ILC1s and NK cells. IL-15 may play a role in the development of hematological malignancies.

IL-18[3,4] – Produced mainly by macrophages and DCs, IL-18 is a key factor in type 1 immunity. IL-18 acts synergistically with IL-12p70 to stimulate the expression of IFNγ in Th1 cells and ILC1s, sustains Th1 and cytotoxic T cell activation, and is a key component regulating ILC1 and NK cell function. Like IL-1β, IL-18 is activated following inflammasome formation. Some inflammatory and autoimmune diseases are thought to be mediated by dysregulation of IL-18 signaling, such as systemic lupus erythematosus, rheumatoid arthritis, type-1 diabetes, Crohn's disease, psoriasis, and graft versus host disease. IL-18 may also be an

important contributor to 'cytokine storm' in conditions such as macrophage activation syndrome, adult-onset Still's disease, and COVID-19.

IL-27[49] **–** A pleiotropic cytokine with both pro- and anti-inflammatory functions. Contributes to Th1 cell differentiation and expansion at the onset of a type 1 immune response, but also inhibits the release of IL-2 and induces the release of IL-10, which suppress the Th1 response, so IL-27 may contribute to both the initiation and resolution of type 1 inflammatory responses. IL-27 has also been shown to inhibit Th2 and Th17-mediated immune responses and to promote the development of immunomodulatory Treg cells.

MIG (Monokine induced by gamma interferon; CXCL9),
IP-10 (Interferon gamma-induced protein 10; CXCL10),
I-TAC (CXCL11)[50,51] – CXCR3 ligands induced by IFNγ that drive the recruitment of macrophages, dendritic cells, NK cells, and Th1 cells to inflamed, infected, or neoplastic regions, and so are important chemokines that contribute to type 1 immune responses. MIG, IP-10, and I-TAC also contribute to the regulation of apoptosis and cell proliferation, and are angiostatic factors released late in wound healing responses that promote transition to the remodeling phase.

MCP-1 (Monocyte chemotactic protein 1; CCL2)[52] – Chemotaxis of CCR2-expressing immune cells, and regulation of T cells favouring polarization to the Th2 subtype. MCP-1 is also a pro-angiogenic chemokine that contributes to wound healing responses. Elevated MCP-1 is associated with cardiovascular disease, allergic asthma, rheumatoid arthritis, and invasive cancer.

MCP-2 (Monocyte chemotactic protein 2; CCL8)[53] **–** Drives the recruitment of a variety of immune cells, including monocytes, eosinophils, basophils, DCs, NK cells, activated T cells, and neutrophils via CCR1, CCR2, CCR3, and CCR5.

M-CSF (macrophage colony-stimulating factor)[34] **–** Hematopoietic growth factor that drives the replication, differentiation, activation, and survival of a variety of myeloid cells, most prominently macrophages with a possible bias to protective M2 polarization. Both protective and pathogenic roles for M-CSF have been observed in several inflammatory conditions, but it has been implicated in the pathogenesis of conditions including arthritis, pulmonary fibrosis, and atherosclerosis.

MIP-1β (Macrophage inflammatory protein-1β; CCL4)[53] **–** Regulates the trafficking of immune cells, including Th2 cells, B cells, monocytes, eosinophils, DCs, macrophages and NK cells, to sites of inflammation via the receptors CCR1, CCR4 and CCR5.

MIP-3α (Macrophage inflammatory protein-3α; CCL20)[54] **–** Drives the recruitment of immature and mature DCs to sites of epithelial inflammation, and the homing of both T helper cells and DCs to mucosal lymphoid tissue via CCR6.

MIP-3β (Macrophage inflammatory protein-3β; CCL19)[55] **–** Drives the recruitment of CCR7-expressing T-cells to sites of inflammation and potentiates T cell responses. Also regulates the steady-state trafficking of lymphocytes and DCs. MIP-3β is also essential in the TLR-driven maturation of DCs.

> *High levels of the analytes in this group may be associated with innate immune responses – IL-6 plays a central role in innate immunity as a key factor driving acute phase protein release*[42,43]*, IL-18 is a pro-inflammatory alarmin released following inflammasome activation*[3]*, and Flt-3L is an important factor in innate lymphoid cell development*[56]*. High results across this group may indicate severe systemic inflammatory responses such as 'cytokine storm' (cytokine release syndrome; CRS). IL-6, IL-10, IL-18, IL-8, MIG, IP-10, MIP-1ß, MCP-1 have been found to be important soluble mediators of cytokine storm*[5]*. The anti-inflammatory factor IL-10 has been found to be upregulated in cytokine storm, likely representing an insufficient regulatory response.*
>
> *High values across the analytes in this group are frequently observed in conditions associated with CRS, such as macrophage activation syndrome (MAS), adult-onset Still's disease (AOSD), and*

systemic arthritis, as well as lymphoproliferative disorders such as hemophagocytic lymphohistiocytosis (HLH) and lymphocytic leukemia.

GROUP C – CELL DEATH BIOMARKERS

***Perforin*[57] –** Cell death-inducing glycoprotein released mainly by NK cells and CD8+ T cells which forms pores in the membranes of target cells. Perforin deficiency has been associated with hemophagocytic lymphohistiocytosis (HLH), leukemias and lymphomas, infectious diseases, and autoimmune diseases.

***sFas (Soluble Fas)*[58,59] –** Soluble form of the apoptosis-inducing receptor Fas. May protect Fas-expressing cells from FasL-induced apoptosis. High circulating levels of sFas have been observed in SLE patients and may contribute to autoimmunity.

***TRAIL (TNF-related apoptosis-inducing ligand)*[60]** - Apoptosis-inducing member of the TNF superfamily. TRAIL is an important factor in NK-mediated apoptosis and has potent anti-tumour activity by preferentially inducing apoptosis in cancer cells but not in normal cells. TRAIL has also been shown to promote the resolution of inflammation by accelerating apoptosis of neutrophils and has anti-inflammatory effects on T cell function by inhibiting the proliferation of Th1 cells, promoting Treg proliferation, and inducing apoptosis in autoreactive T cells and B cells.

The analytes in this group promote cell death through facilitating (perforin) or directly inducing apoptosis (sFas, TRAIL).

GROUP D1 – LYMPHOCYTE RECRUITMENT/ACTIVATION

***BCA-1 (B cell-attracting chemokine 1; CXCL13)*[61,62] –** Drives the recruitment and promotes the differentiation of B cells and T_{FH} cells (along with small numbers of dendritic cells, NK cells, and macrophage progenitors) via CXCR5, playing a key role in the generation of lymphoid follicles. High levels of BCA-1 are associated with aberrant B cell and/or T_{FH} cell aggregates in several autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, multiple sclerosis, etc.) and the initiation and progression of lymphoproliferative and solid tumour cancers. BCA-1 has also been identified as a predictive marker of lethal COVID-19 cases.

***CCL28 (MEC (Mucosae-associated epithelial chemokine))*[63] –** Drives the trafficking of T and B cells via CCR10, and eosinophils via CCR3. CCL28 is constitutively expressed and regulates the steady-state recruitment of immune cells to tissues, but its expression is increased in response to pro-inflammatory cytokines and bacterial products. Deregulated levels of CCL28 have been associated with salivary gland tumors, Hodgkin's disease, and Sjögren's syndrome.

***Granzyme A, Granzyme B*[64] –** Cell death-inducing serine proteases stored in the granules of NK cells and cytotoxic T cells that contribute to type 1 immune responses. Extracellular granzymes may be secreted by mast cells, neutrophils, and activated macrophages during inflammation and have pro-inflammatory functions. Granzyme A can activate pro IL-1β and may proteolytically activate macrophages to secrete cytokines. Extracellular granzymes A and B also degrade extracellular matrix, which may facilitate immune cells' access to sites of inflammation, or induce anoikis in anchorage-dependent cells.

***I-309 (CCL1)*[65]** – Ligand of the CCR8 receptor that may play a role in the recruitment of T cells and eosinophils to sites of inflammation, and has been shown to play an important role in the trafficking and activation of ILC2 cells to promote type 2 immunity. I-309 has also been shown to drive Treg recruitment[66]. Elevated I-309 levels are associated with allergic diseases such as asthma and with poor prognosis in cancer.

IL-16[67] – A ligand of the CD4 receptor, IL-16 acts as a chemoattractant and activating factor for CD4+ T cells, eosinophils, monocytes and DCs. IL-16 also potentiates IL-2- or IL-15-driven CD4+ T cell proliferation. Elevated secretion of IL-16 has been observed in asthma and inflammatory bowel disease.

IL-23[68] **–** Drives the differentiation of Th17 cells (when present with IL-1) and induces IL-17 release. As a key regulator of the type 3 immune response, dysregulation of IL-23 contributes to autoimmunity, and elevated levels are associated with chronic bowel inflammation, inflammatory joint diseases, psoriasis, and multiple sclerosis. Th17 cells can acquire the ability to secrete IFN-γ/GM-CSF (the highly inflammatory and pathogenic Th17.1 phenotype) following prolonged exposure to elevated levels of IL-23 and IL-1β[69]. IL-23 blocking agents have been approved or are being investigated for the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, and ankylosing spondylitis, and inflammatory bowel disease. IBD patients that do not respond to TNF blockers (indicative of a refractory phenotype) tend to respond well to anti-IL-23 antibody therapy[70].

IL-35[71] **–** A potent anti-inflammatory cytokine secreted by Tregs and Bregs that suppresses T cell proliferation and induces IL-35-secreting Treg cells (iTr35). IL-35 levels have been observed to be inversely correlated with disease severity in several autoimmune (RA, SLE, MS, Sjögren's) and inflammatory diseases (IBD, atherosclerosis), whereas increased IL-35 levels are associated with worse prognosis in some cancers.

Lymphotactin (XCL1)[72] – A key factor in the activation and function of cytotoxic T cells. Produced mainly by CD8+ T cells, lymphotactin drives the recruitment and facilitates the interaction of XCR1-expressing antigen-presenting DCs with CD8+ T cells.

sCD137[73,74] **–** Soluble form of the Th1-polarizing CD137 receptor, which is released by activated T and NK cells and some cancer cells. Soluble CD137 binds to CD137 ligand, preventing the stimulation of CD137-expressing T cells and reducing Th1 development. High levels of sCD137 may be pathogenic in conditions resolved by Th1-mediated immunity such as viral infection and cancer, and protective in conditions characterized by excessive Th1 activity, such as autoimmune diseases.

sFasL (Soluble Fas ligand)[58] **–** Soluble form of the apoptosis-inducing Fas ligand. Promotes apoptosis in Fas-expressing cells (less potently than membrane-bound Fas). High levels of soluble FasL have been observed in patients with lymphocytic leukemia. sFasL may be protective in autoimmune diseases like SLE, and a lower ratio of sFasL/sFas may be indicative of disease severity[75].

TPO (Thrombopoietin)[76] **–** Hormone that is the key driver in the generation of platelets, with deficiencies resulting in thrombocytopenia. TPO also contributes to the survival and expansion of hematopoietic stem cells and acts synergistically with IL-3 and SCF to enhance the development of a variety of immune cells.

> *Elevated levels of the analytes in this group could indicate the recruitment and activation of NK cells, T cells, and B cells. Granzyme A, granzyme B are cytotoxic mediators released by NK cells and CD8+ T cells; sCD137 is an indicator of NK and T cell activity; sFasL is a regulator of cell death and apoptosis, and is shed by NK cells and CD8+ T cells; lymphotactin(CD8+ T cells), CCL28 (NK cells and T cells), I-309 and IL-16 (CD4+ T cells) drive recruitment lymphocytes to sites of inflammation; IL-23 is a pro-inflammatory factor that has context-specific regulatory effects on NK and CD8+ T cell function*[77]*; IL-35 is an immunosuppressive factor that inhibits cytotoxic cell function.*

GROUP D2 – MUCOSAL INFLAMMATION/DAMAGE

Eotaxin-3 (CCL26)[78] **–** Recruitment eosinophils, basophils, mast cells, and activated Th2 cells, to sites of inflammation via CCR3. The eotaxins are major contributors to type 2 (Th2-mediated) immunity, and high levels are associated with allergic diseases such as asthma, atopic dermatitis, and allergic rhinitis, as well as parasite infections and other inflammatory conditions (i.e., eosinophilic esophagitis, gastroenteritis).

***HMGB1 (High mobility group box 1)*[79] –** A chromosomal protein. Extracellular HMGB1, either actively secreted by immune cells or passively released by dying or damaged cells, serves as a danger-associated molecular pattern (DAMP) and functions as an immune adjuvant to potentiate the activation of a wide range of immune cells to maintain long-term inflammatory responses. Elevated serum HMGB1 levels are associated with a wide spectrum of disease states, including sepsis, autoimmune diseases, chronic inflammatory diseases, and cancer.

***IFNβ*[80,81] –** A type I interferon with high affinity to the IFNA receptors, IFNβ induces an antiviral response preventing viral spread, and contributes to the adaptive type 1 (Th1-mediated) immune response following viral infection. Type I interferons are potent suppressors of IL-17 production, and IFNβ is used therapeutically to treat MS.

***IFNω*[82] –** A type I interferon, IFNω induces an antiviral response preventing viral spread, and contributes to the adaptive type 1 (Th1-mediated) immune response following viral infection, along with regulating innate immune functions. Type I interferons are also potent suppressors of IL-17 production.

***IL-11*[83] –** A cytokine of the IL-6 family, IL-11 has been implicated in the pathogenesis of fibrotic diseases and cancer. IL-11 has also been identified to potentially contribute to autoimmune diseases such as rheumatoid arthritis and MS, and inflammatory diseases such as asthma, IBD and psoriasis.

IL-17E/IL-25[22] – An epithelial alarmin released in response to danger signals, IL-17E/IL-25 amplifies type 2 immune responses by promoting the production of **IL-4**, **IL-5**, and **IL-13** by Th2 cells and ILC2s, playing a contributing role to allergic inflammatory diseases such as asthma. It also promotes the pathogenesis of psoriasis, and may have both pro- and anti-inflammatory roles in inflammatory bowel disease. IL-17E has been shown to block Th17 polarization and to generally have a protective role in Th17-driven autoimmune disorders[84].

***IL-20*[85]** – Pro-inflammatory cytokine that may facilitate the communication between leukocytes and epithelial cells, thereby enhancing innate defence mechanisms and tissue repair processes at epithelial surfaces[86]. IL-20 has been implicated in the pathogenesis of autoimmune conditions such as rheumatoid arthritis, psoriasis, and nephritis.

***IL-21*[87]** – Pleiotropic cytokine produced by NK and T cells (most prominently Th17 and Tfh subsets) with broad effects in regulating both innate and adaptive immune responses, IL-21 is an important factor in promoting sustained immunity to chronic infections. IL-21 also contributes to mucosal immunity by supporting B cell class switching to IgA, and may drive differentiation of naïve CD4+ T cells to Th17 cells (with TGF-β) and to Tfh cells (in the absence of TGF-β).

***IL-24*[88] –** Cytokine in the IL-20 family with important roles in wound healing and host defense to infections. Elevated levels of IL-24 have been observed in autoimmune diseases such as psoriasis, and allergic diseases such as asthma and atopic dermatitis.

***IL-28A (IFNλ2)*[89]** – A type III interferon, IL-28A is released in response to viral infection and induces antiviral activity in target cells, and contributes to type 1 immune responses (the IFNλ receptor is restricted mainly to epithelial cells, in contrast to the wide distribution of expression of other IFN subtype receptors). There is evidence that IL-28A may also have protective effects in conditions associated with type 2 and type 3 inflammation[90].

***IL-29(IFNλ1)*[91] –** The most abundant type III interferon, predominantly produced by dendritic cells and macrophages. Induces antiviral activity in target cells, and contributes to type 1 immune responses (the IFNλ receptor is restricted mainly to epithelial cells, in contrast to the wide distribution of expression of other IFN subtype receptors).

***IL-31*[92] –** A pro-inflammatory cytokine released mainly by Th2 cells, macrophages, dendritic cells, and a sub-population of T helper cells that migrate selectively to the skin. IL-31 has been identified as a major

contributor to non-histamine-mediated skin itch, and is prominently implicated in the pathogenesis of atopic dermatitis. IL-31 may also contribute to the pathogenesis of other allergic diseases such as asthma.

IL-33[4,93] – A key cytokine in type 2 immunity, IL-33 induces type 2 cytokine release (IL-4, IL-5, IL-13) in Th2 cells, ILC2s, basophils, mast cells, and macrophages. Also, DCs activated by IL-33 promote Th2 polarization. IL-33 can also contribute to the resolution of inflammation by promoting tissue repair and integrity through the regulation of Tregs. IL-33 release is increased in mucosal tissues following tissue damage due to inflammation or infection and is thought to be a major contributor to allergic diseases such as asthma and atopic dermatitis, as well as chronic inflammatory or fibrotic diseases like ulcerative colitis and COPD.

IL-34[94] **–** An important factor in the development of Langerhans cells and microglia, IL-34 may also play a role in the development and maintenance of macrophage populations (it shares a receptor with M-CSF). IL-34 expression has been found to increase with disease progression in a number of inflammatory, autoimmune and neoplastic diseases.

LIF (Leukemia inhibitory factor)[95] – A pleiotropic cytokine with both pro- and anti-inflammatory functions, depending on the immunological context. LIF is expressed by Tregs and suppresses Th17 differentiation, and so may promote immune tolerance. LIF expression is induced by pro-inflammatory cytokines, and elevated levels of LIF have been observed in rheumatoid arthritis, airway infections, acute respiratory distress, asthma, sepsis, and neural inflammation, although its role is often thought to be anti-inflammatory and protective.

TSLP (Thymic stromal lymphopoietin)[96] – Produced mainly by epithelial tissues in response to inflammatory stimuli, TSLP is a key regulator of type 2 immune responses. TSLP primes DCs to induce Th2 polarization, plays a role in the development of ILC2s, and drives the expression of type 2 cytokines (IL-4, IL-5, IL-13). Elevated levels of TSLP are associated with allergic diseases such as asthma, atopic dermatitis, and eosinophilic esophagitis.

> *Elevated levels of the analytes in this group could indicate a state of tissue injury and mucosal inflammation. IL-17E/IL-25, TSLP and IL-33 are epithelial alarmins that activate type 2 immune responses; IFNβ and IFNω are type 1 interferons and IL-28A and IL-29 are type 3 intererons, which are associated with innate anti-viral responses and mucosal immunity*[97]*; HMGB1 is an alarmin released by damaged cells and can drive interferon expression; IL-34 plays a role in maintaining mucosal resident macrophages; IL-11, IL-20 and IL-21 are important factors in epithelial defence and tissue repair.*

GROUP E – IMMUNE CELL RECRUITMENT

6CKine (CCL21)[98] **–** Drives the recruitment and trafficking of T cells via CCR7. Plays a key role in homing of lymphocytes to lymph nodes and Peyer's patches, and contributes to immune tolerance by regulating the steady state trafficking of DCs from mucosal tissues to lymph nodes.

CTACK (Cutaneous T cell-attracting chemokine; CCL27)[99] **–** Expressed primarily in keratinocytes in the skin, CTACK drives the recruitment and homeostatic trafficking of CCR10-expressing T cells to the skin. Elevated levels of CTACK have been observed in inflammatory conditions of the skin, including diffuse or limited cutaneous systemic sclerosis, atopic dermatitis, and psoriasis vulgaris.

Eotaxin-1 (CCL11), -2 (CCL24)[78] **–** Recruitment of eosinophils, basophils, mast cells, and activatedTh2 cells, to sites of inflammation via CCR3. The eotaxins are major effectors of Th2-mediated inflammation, and high levels are associated with allergic diseases such as asthma, atopic dermatitis, and allergic rhinitis, as well as parasite infections and other inflammatory conditions (i.e., eosinophilic esophagitis, gastroenteritis).

MDC (Macrophage-derived chemokine; CCL22)[100] – Drives the recruitment of CCR4-expressing immune cells, most notably Th2 cells, to sites of inflammation. Higher levels of these chemokines are observed in allergic diseases such as asthma and atopic dermatitis, as well as in some cancers.

MIP-1δ (Macrophage inflammatory protein 1δ; CCL15)[101] **–** Drives the recruitment of immune cells, particularly eosinophils and basophils, via CCR1 and CCR3. MIP-1δ has been implicated in the pathogenesis of asthma, particularly in severe asthma with mixed Th1/Th2-driven inflammation and airway remodeling. MIP-1δ has also been observed to contribute to plaque instability in atherosclerosis, angiogenesis in lung cancer, and elevated levels are observed in patients with advanced sarcoidosis.

MPIF-1 (Myeloid progenitor inhibitory factor-1; CCL23)[102] **–** Drives the recruitment of dendritic cells, resting T cells, and monocytes via CCR1. Also promotes angiogenesis by activating CCR1 on vascular endothelial cells.

RANTES (Regulated on activation, normal T cell expressed and secreted; CCL5)[103] – A chemokine contributing to both type 1 and type 2 immune responses, RANTES drives the recruitment of T cells (both Th1 and Th2), dendritic cells, eosinophils, NK cells, mast cells and basophils via CCR1, CCR3 and CCR5. RANTES is also a pro-angiogenic chemokine that contributes to wound healing responses. Release of RANTES is prominently associated with viral infections, and is also implicated in asthma, atherosclerosis, angiogenesis in cancer, and fibrotic diseases.

SCF (Stem cell factor)[104] – Growth factor that contributes to homeostasis in a wide variety of tissues throughout the body, with a prominent role in the maintenance of early hematopoietic stem cells. SCF primes DCs to induce Th2 or Th17 differentiation and drives the maturation, degranulation, and homing of mast cells, and thus is implicated in the pathogenesis of allergic diseases such as asthma. SCF and its receptor c-Kit can also contribute to the development of several types of cancer.

SDF-1 (Stromal cell-derived factor 1; CXCL12)[105,106] – Ligand of the CXCR4 receptor with important roles in development, including the homing and maintenance of hematopoietic stem cells and the production of immune cells, including B cells, pDCs, and NK cells. May play a role in the onset or progression of cancer, viral infections, inflammatory bowel diseases, rheumatoid arthritis and osteoarthritis, asthma and acute lung injury, amyotrophic lateral sclerosis, and WHIM syndrome.

> *The analytes in this group drive the recruitment, homing and activation of leukocytes and lymphocytes.*

GROUP H – PLATELET ACTIVATION / WOUND HEALING

APRIL (A proliferation inducing ligand)[39,40] **–** Member of the TNF family of cytokines that promote B cell survival and proliferation. The BAFF/APRIL system has been implicated as an important contributor to autoimmune diseases, most prominently systemic lupus erythematosus (SLE), and may also play important roles in the development of graft vs. host disease (GVHD) and cancer.

EGF (Epidermal growth factor)[107] **–** Important growth factor involved in development, homeostasis and wound repair in tissues throughout the body. It is also a major factor that drives the proliferation and survival of several cancers.

ENA-78 (Epithelial neutrophil-activating protein 78; CXCL5)[53] **–** Drives the recruitment of neutrophils, basophils and B cells via CXCR1 and CXCR2. ENA-78 is also a pro-angiogenic chemokine, and so can contribute both to wound healing and to the progression of some cancers.

GCP-2 (Granulocyte chemotactic protein 2; CXCL6)[108] **–** Drive the recruitment and activation of neutrophils via CXCR1 and CXCR2

GROα (CXCL1)[109] – Recruitment of granulocytes (most notably neutrophils), monocytes, and CXCR2-expressing CD8+ T cells and NK cells to sites of inflammation. GROα is a pro-angiogenic chemokine, and so can contribute both to wound healing and to the progression of some cancers.

MCP-4 (Monocyte chemotactic protein 4; CCL13)[110] – Drives the recruitment of eosinophils, basophils, monocytes, macrophages, immature DCs, and T cells via CCR1, CCR2, CCR3, CCR5 and CCR11. Also induces eosinophil degranulation, basophil histamine release, and the release of pro-inflammatory cytokines from epithelial and endothelial cells. There is evidence that MCP-4 contributes to many diseases, most prominently to airway diseases such as asthma and COPD, autoimmune diseases such as rheumatoid arthritis, and skin diseases such as atopic dermatitis.

PDGF AA, AB, BB (Platelet-derived growth factor)[111] – Growth factors comprised of homodimers or heterodimers of two PDGF subunits (A and B). PDGFs play a major role in development, and their release from activated platelets contributes to wound healing. They are important contributors to the development and progression of some cancers, as well as vascular diseases (i.e., atherosclerosis, pulmonary hypertension) and fibrotic diseases.

sCD40L (Soluble CD40 ligand)[112] – Soluble form of the costimulatory molecule in the TNF family that promotes immunoglobulin isotype switching and the development of humoral immune memory in B cells, and primes DCs to activate T cell responses. High sCD40L levels have been observed in several autoimmune diseases.

TARC (Thymus and activation regulated chemokine; CCL17)[100] – Recruitment of CCR4-expressing immune cells, most notably Th2 cells, to sites of inflammation. Higher levels of TARC are observed in allergic diseases such as asthma and atopic dermatitis (TARC has been shown to be upregulated following allergen challenge in atopic subjects), as well as in some cancers.

VEGF-A (Vascular endothelial growth factor)[113] – Growth factor that plays a major role in vasculogenesis and angiogenesis and is essential for vascular homeostasis. Tumour-secreted VEGF contributes to cancer progression by promoting angiogenesis in the tumour microenvironment. VEGF-A also contributes to retinopathy in several blinding eye diseases.

> *High levels of most or all of the analytes in this group could indicate a platelet activation/wound healing response, as all of these factors are stored in and released by platelets and/or take part in angiogenic, tissue remodeling or inflammatory processes during wound healing[114]. High results in this group are often observed in conditions typically associated with vascular injury, angiogenesis and/or thrombocytosis, such as AOSD, Kawasaki disease, juvenile arthritis, FMF, COVID-19 and Crohn's disease, whereas lower results have been observed in conditions associated with thrombocytopenia such as HLH, lymphocytic leukemia, and hematopoietic stem cell transplantation. Levels of the analytes in this group are significantly higher in serum samples than in plasma samples drawn from the same subjects.*

1. Xie Y, Su N, Yang J, et al. FGF/FGFR signaling in health and disease. *Signal Transduct Target Ther*. 09 2020;5(1):181. doi:10.1038/s41392-020-00222-7

2. Paul F, Pellegrini S, Uzé G. IFNA2: The prototypic human alpha interferon. *Gene*. Aug 2015;567(2):132-7. doi:10.1016/j.gene.2015.04.087

3. Kaneko N, Kurata M, Yamamoto T, Morikawa S, Masumoto J. The role of interleukin-1 in general pathology. *Inflamm Regen*. 2019;39:12. doi:10.1186/s41232-019-0101-5

4. Mantovani A, Dinarello CA, Molgora M, Garlanda C. Interleukin-1 and Related Cytokines in the Regulation of Inflammation and Immunity. *Immunity*. Apr 16 2019;50(4):778-795. doi:10.1016/j.immuni.2019.03.012

5. Fajgenbaum DC, June CH. Cytokine Storm. *N Engl J Med*. 12 03 2020;383(23):2255-2273. doi:10.1056/NEJMra2026131

6. Arenas-Ramirez N, Woytschak J, Boyman O. Interleukin-2: Biology, Design and Application. *Trends Immunol*. Dec 2015;36(12):763-777. doi:10.1016/j.it.2015.10.003

7. Sharma R, Fu SM, Ju ST. IL-2: a two-faced master regulator of autoimmunity. *J Autoimmun*. Mar 2011;36(2):91-7. doi:10.1016/j.jaut.2011.01.001

8. Chen K, Kolls JK. Interluekin-17A (IL17A). *Gene*. May 2017;614:8-14. doi:10.1016/j.gene.2017.01.016

9. Shao X, Chen S, Yang D, et al. FGF2 cooperates with IL-17 to promote autoimmune inflammation. *Sci Rep*. 08 01 2017;7(1):7024. doi:10.1038/s41598-017-07597-8

10. Pennell LM, Fish EN. Immunoregulatory effects of interferon-β in suppression of Th17 cells. *J Interferon Cytokine Res*. May 2014;34(5):330-41. doi:10.1089/jir.2013.0088

11. Axtell RC, Raman C, Steinman L. Type I interferons: beneficial in Th1 and detrimental in Th17 autoimmunity. *Clin Rev Allergy Immunol*. Apr 2013;44(2):114-20. doi:10.1007/s12016-011-8296-5

12. López P, Rodríguez-Carrio J, Caminal-Montero L, Mozo L, Suárez A. A pathogenic IFNα, BLyS and IL-17 axis in Systemic Lupus Erythematosus patients. *Sci Rep*. Feb 05 2016;6:20651. doi:10.1038/srep20651

13. Lee M, Lee Y, Song J, Lee J, Chang SY. Tissue-specific Role of CX. *Immune Netw*. Feb 2018;18(1):e5. doi:10.4110/in.2018.18.e5

14. Ivashkiv LB. IFNγ: signalling, epigenetics and roles in immunity, metabolism, disease and cancer immunotherapy. *Nat Rev Immunol*. 09 2018;18(9):545-558. doi:10.1038/s41577-018-0029-z

15. Raphael I, Nalawade S, Eagar TN, Forsthuber TG. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. *Cytokine*. Jul 2015;74(1):5-17. doi:10.1016/j.cyto.2014.09.011

16. Do-Thi VA, Lee JO, Lee H, Kim YS. Crosstalk between the Producers and Immune Targets of IL-9. *Immune Netw*. Dec 2020;20(6):e45. doi:10.4110/in.2020.20.e45

17. Chakraborty S, Kubatzky KF, Mitra DK. An Update on Interleukin-9: From Its Cellular Source and Signal Transduction to Its Role in Immunopathogenesis. *Int J Mol Sci*. Apr 2019;20(9)doi:10.3390/ijms20092113

18. Cooper AM, Khader SA. IL-12p40: an inherently agonistic cytokine. *Trends Immunol*. Jan 2007;28(1):33-8. doi:10.1016/j.it.2006.11.002

19. Ullrich KA, Schulze LL, Paap EM, Müller TM, Neurath MF, Zundler S. Immunology of IL-12: An update on functional activities and implications for disease. *EXCLI J*. 2020;19:1563-1589. doi:10.17179/excli2020-3104

20. Piper C, Pesenacker AM, Bending D, et al. T cell expression of granulocyte-macrophage colony-stimulating factor in juvenile arthritis is contingent upon Th17 plasticity. *Arthritis Rheumatol*. Jul 2014;66(7):1955-60. doi:10.1002/art.38647

21. Gallo E, Katzman S, Villarino AV. IL-13-producing Th1 and Th17 cells characterize adaptive responses to both self and foreign antigens. *Eur J Immunol*. Sep 2012;42(9):2322-8. doi:10.1002/eji.201142227

22. Brevi A, Cogrossi LL, Grazia G, et al. Much More Than IL-17A: Cytokines of the IL-17 Family Between Microbiota and Cancer. *Front Immunol*. 2020;11:565470. doi:10.3389/fimmu.2020.565470

23. Dudakov JA, Hanash AM, van den Brink MR. Interleukin-22: immunobiology and pathology. *Annu Rev Immunol*. 2015;33:747-85. doi:10.1146/annurev-immunol-032414-112123

24. Liu Y, Cai Y, Liu L, Wu Y, Xiong X. Crucial biological functions of CCL7 in cancer. *PeerJ*. 2018;6:e4928. doi:10.7717/peerj.4928

25. Schaller TH, Batich KA, Suryadevara CM, Desai R, Sampson JH. Chemokines as adjuvants for immunotherapy: implications for immune activation with CCL3. *Expert Rev Clin Immunol*. 11 2017;13(11):1049-1060. doi:10.1080/1744666X.2017.1384313

26. Karpus WJ, Kennedy KJ. MIP-1alpha and MCP-1 differentially regulate acute and relapsing autoimmune encephalomyelitis as well as Th1/Th2 lymphocyte differentiation. *J Leukoc Biol*. Nov 1997;62(5):681-7.

27. Singh B, Coffey RJ. From wavy hair to naked proteins: the role of transforming growth factor alpha in health and disease. *Semin Cell Dev Biol*. Apr 2014;28:12-21. doi:10.1016/j.semcdb.2014.03.003

28. Kalliolias GD, Ivashkiv LB. TNF biology, pathogenic mechanisms and emerging therapeutic strategies. *Nat Rev Rheumatol*. Jan 2016;12(1):49-62. doi:10.1038/nrrheum.2015.169

29. Calmon-Hamaty F, Combe B, Hahne M, Morel J. Lymphotoxin α revisited: general features and implications in rheumatoid arthritis. *Arthritis Res Ther*. Jul 2011;13(4):232. doi:10.1186/ar3376

30. Zhu J. T Helper Cell Differentiation, Heterogeneity, and Plasticity. *Cold Spring Harb Perspect Biol*. 10 01 2018;10(10)doi:10.1101/cshperspect.a030338

31. Cosmi L, Maggi L, Santarlasci V, Liotta F, Annunziato F. T helper cells plasticity in inflammation. *Cytometry A*. Jan 2014;85(1):36-42. doi:10.1002/cyto.a.22348

32. Gieseck RL, Wilson MS, Wynn TA. Type 2 immunity in tissue repair and fibrosis. *Nat Rev Immunol*. Jan 2018;18(1):62-76. doi:10.1038/nri.2017.90

33. Bendall LJ, Bradstock KF. G-CSF: From granulopoietic stimulant to bone marrow stem cell mobilizing agent. *Cytokine Growth Factor Rev*. Aug 2014;25(4):355-67. doi:10.1016/j.cytogfr.2014.07.011

34. Hamilton JA. Colony-stimulating factors in inflammation and autoimmunity. *Nat Rev Immunol*. Jul 2008;8(7):533-44. doi:10.1038/nri2356

35. Lee KMC, Achuthan AA, Hamilton JA. GM-CSF: A Promising Target in Inflammation and Autoimmunity. *Immunotargets Ther*. 2020;9:225-240. doi:10.2147/ITT.S262566

36. Shiomi A, Usui T. Pivotal roles of GM-CSF in autoimmunity and inflammation. *Mediators Inflamm*. 2015;2015:568543. doi:10.1155/2015/568543

37. Dougan M, Dranoff G, Dougan SK. GM-CSF, IL-3, and IL-5 Family of Cytokines: Regulators of Inflammation. *Immunity*. 04 2019;50(4):796-811. doi:10.1016/j.immuni.2019.03.022

38. Mackall CL, Fry TJ, Gress RE. Harnessing the biology of IL-7 for therapeutic application. *Nat Rev Immunol*. May 2011;11(5):330-42. doi:10.1038/nri2970

39. Vincent FB, Saulep-Easton D, Figgett WA, Fairfax KA, Mackay F. The BAFF/APRIL system: emerging functions beyond B cell biology and autoimmunity. *Cytokine Growth Factor Rev*. Jun 2013;24(3):203-15. doi:10.1016/j.cytogfr.2013.04.003

40. Nakayamada S, Tanaka Y. BAFF- and APRIL-targeted therapy in systemic autoimmune diseases. *Inflamm Regen*. 2016;36:6. doi:10.1186/s41232-016-0015-4

41. Tsapogas P, Mooney CJ, Brown G, Rolink A. The Cytokine Flt3-Ligand in Normal and Malignant Hematopoiesis. *Int J Mol Sci*. May 24 2017;18(6)doi:10.3390/ijms18061115

42. Kany S, Vollrath JT, Relja B. Cytokines in Inflammatory Disease. *Int J Mol Sci*. Nov 2019;20(23)doi:10.3390/ijms20236008

43. Narazaki M, Kishimoto T. The Two-Faced Cytokine IL-6 in Host Defense and Diseases. *Int J Mol Sci*. Nov 09 2018;19(11)doi:10.3390/ijms19113528

44. Tanaka T, Narazaki M, Kishimoto T. Interleukin (IL-6) Immunotherapy. *Cold Spring Harb Perspect Biol*. Aug 01 2018;10(8)doi:10.1101/cshperspect.a028456

45. Palomino DC, Marti LC. Chemokines and immunity. *Einstein (Sao Paulo)*. 2015 Jul-Sep 2015;13(3):469-73. doi:10.1590/S1679-45082015RB3438

46. Saraiva M, Vieira P, O'Garra A. Biology and therapeutic potential of interleukin-10. *J Exp Med*. 01 2020;217(1)doi:10.1084/jem.20190418

47. Lu L, Zhang H, Dauphars DJ, He YW. A Potential Role of Interleukin 10 in COVID-19 Pathogenesis. *Trends Immunol*. 01 2021;42(1):3-5. doi:10.1016/j.it.2020.10.012

48. Steel JC, Waldmann TA, Morris JC. Interleukin-15 biology and its therapeutic implications in cancer. *Trends Pharmacol Sci*. Jan 2012;33(1):35-41. doi:10.1016/j.tips.2011.09.004

49. Iwasaki Y, Fujio K, Okamura T, Yamamoto K. Interleukin-27 in T cell immunity. *Int J Mol Sci*. Jan 27 2015;16(2):2851-63. doi:10.3390/ijms16022851

50. Liu M, Guo S, Hibbert JM, et al. CXCL10/IP-10 in infectious diseases pathogenesis and potential therapeutic implications. *Cytokine Growth Factor Rev*. Jun 2011;22(3):121-30. doi:10.1016/j.cytogfr.2011.06.001

51. Metzemaekers M, Vanheule V, Janssens R, Struyf S, Proost P. Overview of the Mechanisms that May Contribute to the Non-Redundant Activities of Interferon-Inducible CXC Chemokine Receptor 3 Ligands. *Front Immunol*. 2017;8:1970. doi:10.3389/fimmu.2017.01970

52. Deshmane SL, Kremlev S, Amini S, Sawaya BE. Monocyte chemoattractant protein-1 (MCP-1): an overview. *J Interferon Cytokine Res*. Jun 2009;29(6):313-26. doi:10.1089/jir.2008.0027

53. Hughes CE, Nibbs RJB. A guide to chemokines and their receptors. *FEBS J*. 08 2018;285(16):2944-2971. doi:10.1111/febs.14466

54. Ito T, Carson WF, Cavassani KA, Connett JM, Kunkel SL. CCR6 as a mediator of immunity in the lung and gut. *Exp Cell Res*. Mar 10 2011;317(5):613-9. doi:10.1016/j.yexcr.2010.12.018

55. Gowhari Shabgah A, Al-Obaidi ZMJ, Sulaiman Rahman H, et al. Does CCL19 act as a double-edged sword in cancer development? *Clin Exp Immunol*. Apr 04 2022;207(2):164-175. doi:10.1093/cei/uxab039

56. Watowich SS, Liu YJ. Mechanisms regulating dendritic cell specification and development. *Immunol Rev*. Nov 2010;238(1):76-92. doi:10.1111/j.1600-065X.2010.00949.x

57. Osińska I, Popko K, Demkow U. Perforin: an important player in immune response. *Cent Eur J Immunol*. 2014;39(1):109-15. doi:10.5114/ceji.2014.42135

58. Nagata S. Fas-induced apoptosis, and diseases caused by its abnormality. *Genes Cells*. Oct 1996;1(10):873-9. doi:10.1046/j.1365-2443.1996.d01-214.x

59. Cheng J, Zhou T, Liu C, et al. Protection from Fas-mediated apoptosis by a soluble form of the Fas molecule. *Science*. Mar 25 1994;263(5154):1759-62. doi:10.1126/science.7510905

60. Beyer K, Baukloh AK, Stoyanova A, Kamphues C, Sattler A, Kotsch K. Interactions of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) with the Immune System: Implications for Inflammation and Cancer. *Cancers (Basel)*. Aug 13 2019;11(8)doi:10.3390/cancers11081161

61. Kazanietz MG, Durando M, Cooke M. CXCL13 and Its Receptor CXCR5 in Cancer: Inflammation, Immune Response, and Beyond. *Front Endocrinol (Lausanne)*. 2019;10:471. doi:10.3389/fendo.2019.00471

62. Wang B, Wang M, Ao D, Wei X. CXCL13-CXCR5 axis: Regulation in inflammatory diseases and cancer. *Biochim Biophys Acta Rev Cancer*. Sep 2022;1877(5):188799. doi:10.1016/j.bbcan.2022.188799

63. Mohan T, Deng L, Wang BZ. CCL28 chemokine: An anchoring point bridging innate and adaptive immunity. *Int Immunopharmacol*. Oct 2017;51:165-170. doi:10.1016/j.intimp.2017.08.012

64. Chowdhury D, Lieberman J. Death by a thousand cuts: granzyme pathways of programmed cell death. *Annu Rev Immunol*. 2008;26:389-420. doi:10.1146/annurev.immunol.26.021607.090404

65. Knipfer L, Schulz-Kuhnt A, Kindermann M, et al. A CCL1/CCR8-dependent feed-forward mechanism drives ILC2 functions in type 2-mediated inflammation. *J Exp Med*. 12 2019;216(12):2763-2777. doi:10.1084/jem.20182111

66. Ohue Y, Nishikawa H. Regulatory T (Treg) cells in cancer: Can Treg cells be a new therapeutic target? *Cancer Sci*. Jul 2019;110(7):2080-2089. doi:10.1111/cas.14069

67. Cruikshank WW, Kornfeld H, Center DM. Interleukin-16. *J Leukoc Biol*. Jun 2000;67(6):757-66. doi:10.1002/jlb.67.6.757

68. Duvallet E, Semerano L, Assier E, Falgarone G, Boissier MC. Interleukin-23: a key cytokine in inflammatory diseases. *Ann Med*. Nov 2011;43(7):503-11. doi:10.3109/07853890.2011.577093

69. Mourik BC, Lubberts E, de Steenwinkel JEM, Ottenhoff THM, Leenen PJM. Interactions between Type 1 Interferons and the Th17 Response in Tuberculosis: Lessons Learned from Autoimmune Diseases. *Front Immunol*. 2017;8:294. doi:10.3389/fimmu.2017.00294

70. Atreya R, Neurath MF. IL-23 Blockade in Anti-TNF Refractory IBD: From Mechanisms to Clinical Reality. *J Crohns Colitis*. May 11 2022;16(Supplement_2):ii54-ii63. doi:10.1093/ecco-jcc/jjac007

71. Ye C, Yano H, Workman CJ, Vignali DAA. Interleukin-35: Structure, Function and Its Impact on Immune-Related Diseases. *J Interferon Cytokine Res*. Nov 2021;41(11):391-406. doi:10.1089/jir.2021.0147

72. Matsuo K, Yoshie O, Kitahata K, Kamei M, Hara Y, Nakayama T. Recent Progress in Dendritic Cell-Based Cancer Immunotherapy. *Cancers (Basel)*. May 20 2021;13(10)doi:10.3390/cancers13102495

73. Dharmadhikari B, Wu M, Abdullah NS, et al. CD137 and CD137L signals are main drivers of type 1, cell-mediated immune responses. *Oncoimmunology*. Apr 2016;5(4):e1113367. doi:10.1080/2162402X.2015.1113367

74. Luu K, Shao Z, Schwarz H. The relevance of soluble CD137 in the regulation of immune responses and for immunotherapeutic intervention. *J Leukoc Biol*. May 2020;107(5):731-738. doi:10.1002/JLB.2MR1119-224R

75. Vincent FB, Kandane-Rathnayake R, Koelmeyer R, et al. Associations of serum soluble Fas and Fas ligand (FasL) with outcomes in systemic lupus erythematosus. *Lupus Sci Med*. Jun 2020;7(1)doi:10.1136/lupus-2019-000375

76. Kaushansky K. Thrombopoietin: a tool for understanding thrombopoiesis. *J Thromb Haemost*. Jul 2003;1(7):1587-92. doi:10.1046/j.1538-7836.2003.00273.x

77. Mirlekar B, Pylayeva-Gupta Y. IL-12 Family Cytokines in Cancer and Immunotherapy. *Cancers (Basel)*. Jan 06 2021;13(2)doi:10.3390/cancers13020167

78. Zajkowska M, Mroczko B. From Allergy to Cancer-Clinical Usefulness of Eotaxins. *Cancers (Basel)*. Jan 2021;13(1)doi:10.3390/cancers13010128

79. Kang R, Chen R, Zhang Q, et al. HMGB1 in health and disease. *Mol Aspects Med*. Dec 2014;40:1-116. doi:10.1016/j.mam.2014.05.001

80. Wittling MC, Cahalan SR, Levenson EA, Rabin RL. Shared and Unique Features of Human Interferon-Beta and Interferon-Alpha Subtypes. *Front Immunol*. 2020;11:605673. doi:10.3389/fimmu.2020.605673

81. de Weerd NA, Nguyen T. The interferons and their receptors--distribution and regulation. *Immunol Cell Biol*. May 2012;90(5):483-91. doi:10.1038/icb.2012.9

82. Li SF, Zhao FR, Shao JJ, Xie YL, Chang HY, Zhang YG. Interferon-omega: Current status in clinical applications. *Int Immunopharmacol*. Nov 2017;52:253-260. doi:10.1016/j.intimp.2017.08.028

83. Fung KY, Louis C, Metcalfe RD, et al. Emerging roles for IL-11 in inflammatory diseases. *Cytokine*. Jan 2022;149:155750. doi:10.1016/j.cyto.2021.155750

84. Deng C, Peng N, Tang Y, et al. Roles of IL-25 in Type 2 Inflammation and Autoimmune Pathogenesis. *Front Immunol*. 2021;12:691559. doi:10.3389/fimmu.2021.691559

85. Chen J, Caspi RR, Chong WP. IL-20 receptor cytokines in autoimmune diseases. *J Leukoc Biol*. 11 2018;104(5):953-959. doi:10.1002/JLB.MR1117-471R

86. Rutz S, Wang X, Ouyang W. The IL-20 subfamily of cytokines--from host defence to tissue homeostasis. *Nat Rev Immunol*. Dec 2014;14(12):783-95. doi:10.1038/nri3766

87. Yi JS, Cox MA, Zajac AJ. Interleukin-21: a multifunctional regulator of immunity to infections. *Microbes Infect*. Dec 2010;12(14-15):1111-9. doi:10.1016/j.micinf.2010.08.008

88. Mitamura Y, Nunomura S, Furue M, Izuhara K. IL-24: A new player in the pathogenesis of pro-inflammatory and allergic skin diseases. *Allergol Int*. Jul 2020;69(3):405-411. doi:10.1016/j.alit.2019.12.003

89. Donnelly RP, Kotenko SV. Interferon-lambda: a new addition to an old family. *J Interferon Cytokine Res*. Aug 2010;30(8):555-64. doi:10.1089/jir.2010.0078

90. Koltsida O, Hausding M, Stavropoulos A, et al. IL-28A (IFN-λ2) modulates lung DC function to promote Th1 immune skewing and suppress allergic airway disease. *EMBO Mol Med*. Jun 2011;3(6):348-61. doi:10.1002/emmm.201100142

91. Kelm NE, Zhu Z, Ding VA, et al. The role of IL-29 in immunity and cancer. *Crit Rev Oncol Hematol*. Oct 2016;106:91-8. doi:10.1016/j.critrevonc.2016.08.002

92. Borgia F, Custurone P, Li Pomi F, Cordiano R, Alessandrello C, Gangemi S. IL-31: State of the Art for an Inflammation-Oriented Interleukin. *Int J Mol Sci*. Jun 10 2022;23(12)doi:10.3390/ijms23126507

93. Molofsky AB, Savage AK, Locksley RM. Interleukin-33 in Tissue Homeostasis, Injury, and Inflammation. *Immunity*. Jun 2015;42(6):1005-19. doi:10.1016/j.immuni.2015.06.006

94. Lelios I, Cansever D, Utz SG, Mildenberger W, Stifter SA, Greter M. Emerging roles of IL-34 in health and disease. *J Exp Med*. Mar 02 2020;217(3)doi:10.1084/jem.20190290

95. Gadient RA, Patterson PH. Leukemia inhibitory factor, Interleukin 6, and other cytokines using the GP130 transducing receptor: roles in inflammation and injury. *Stem Cells*. 1999;17(3):127-37. doi:10.1002/stem.170127

96. Tsilingiri K, Fornasa G, Rescigno M. Thymic Stromal Lymphopoietin: To Cut a Long Story Short. *Cell Mol Gastroenterol Hepatol*. Mar 2017;3(2):174-182. doi:10.1016/j.jcmgh.2017.01.005

97. Mangan NE, Fung KY. Type I interferons in regulation of mucosal immunity. *Immunol Cell Biol*. May 2012;90(5):510-9. doi:10.1038/icb.2012.13

98. Förster R, Davalos-Misslitz AC, Rot A. CCR7 and its ligands: balancing immunity and tolerance. *Nat Rev Immunol*. May 2008;8(5):362-71. doi:10.1038/nri2297

99. Xiong N, Fu Y, Hu S, Xia M, Yang J. CCR10 and its ligands in regulation of epithelial immunity and diseases. *Protein Cell*. Aug 2012;3(8):571-80. doi:10.1007/s13238-012-2927-3

100. Solari R, Pease JE. Targeting chemokine receptors in disease--a case study of CCR4. *Eur J Pharmacol*. Sep 2015;763(Pt B):169-77. doi:10.1016/j.ejphar.2015.05.018

101. Shimizu Y, Dobashi K. CC-chemokine CCL15 expression and possible implications for the pathogenesis of IgE-related severe asthma. *Mediators Inflamm*. 2012;2012:475253. doi:10.1155/2012/475253

102. Korbecki J, Kojder K, Simińska D, et al. CC Chemokines in a Tumor: A Review of Pro-Cancer and Anti-Cancer Properties of the Ligands of Receptors CCR1, CCR2, CCR3, and CCR4. *Int J Mol Sci*. Nov 09 2020;21(21)doi:10.3390/ijms21218412

103. Marques RE, Guabiraba R, Russo RC, Teixeira MM. Targeting CCL5 in inflammation. *Expert Opin Ther Targets*. Dec 2013;17(12):1439-60. doi:10.1517/14728222.2013.837886

104. Lennartsson J, Rönnstrand L. Stem cell factor receptor/c-Kit: from basic science to clinical implications. *Physiol Rev*. Oct 2012;92(4):1619-49. doi:10.1152/physrev.00046.2011

105. Nagasawa T. CXCL12/SDF-1 and CXCR4. *Front Immunol*. 2015;6:301. doi:10.3389/fimmu.2015.00301

106. Janssens R, Struyf S, Proost P. Pathological roles of the homeostatic chemokine CXCL12. *Cytokine Growth Factor Rev*. 12 2018;44:51-68. doi:10.1016/j.cytogfr.2018.10.004

107. Chen J, Zeng F, Forrester SJ, Eguchi S, Zhang MZ, Harris RC. Expression and Function of the Epidermal Growth Factor Receptor in Physiology and Disease. *Physiol Rev*. Jul 2016;96(3):1025-1069. doi:10.1152/physrev.00030.2015

108. Rajarathnam K, Schnoor M, Richardson RM, Rajagopal S. How do chemokines navigate neutrophils to the target site: Dissecting the structural mechanisms and signaling pathways. *Cell Signal*. Feb 2019;54:69-80. doi:10.1016/j.cellsig.2018.11.004

109. Amiri KI, Richmond A. Fine tuning the transcriptional regulation of the CXCL1 chemokine. *Prog Nucleic Acid Res Mol Biol*. 2003;74:1-36. doi:10.1016/s0079-6603(03)01009-2

110. Li L, Dai F, Wang L, et al. CCL13 and human diseases. *Front Immunol*. 2023;14:1176639. doi:10.3389/fimmu.2023.1176639

111. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. *Genes Dev*. May 2008;22(10):1276-312. doi:10.1101/gad.1653708

112. Elgueta R, Benson MJ, de Vries VC, Wasiuk A, Guo Y, Noelle RJ. Molecular mechanism and function of CD40/CD40L engagement in the immune system. *Immunol Rev*. May 2009;229(1):152-72. doi:10.1111/j.1600-065X.2009.00782.x

113. Apte RS, Chen DS, Ferrara N. VEGF in Signaling and Disease: Beyond Discovery and Development. *Cell*. 03 2019;176(6):1248-1264. doi:10.1016/j.cell.2019.01.021

114. von Hundelshausen P, Weber C. Platelets as immune cells: bridging inflammation and cardiovascular disease. *Circ Res*. Jan 05 2007;100(1):27-40. doi:10.1161/01.RES.0000252802.25497.b7