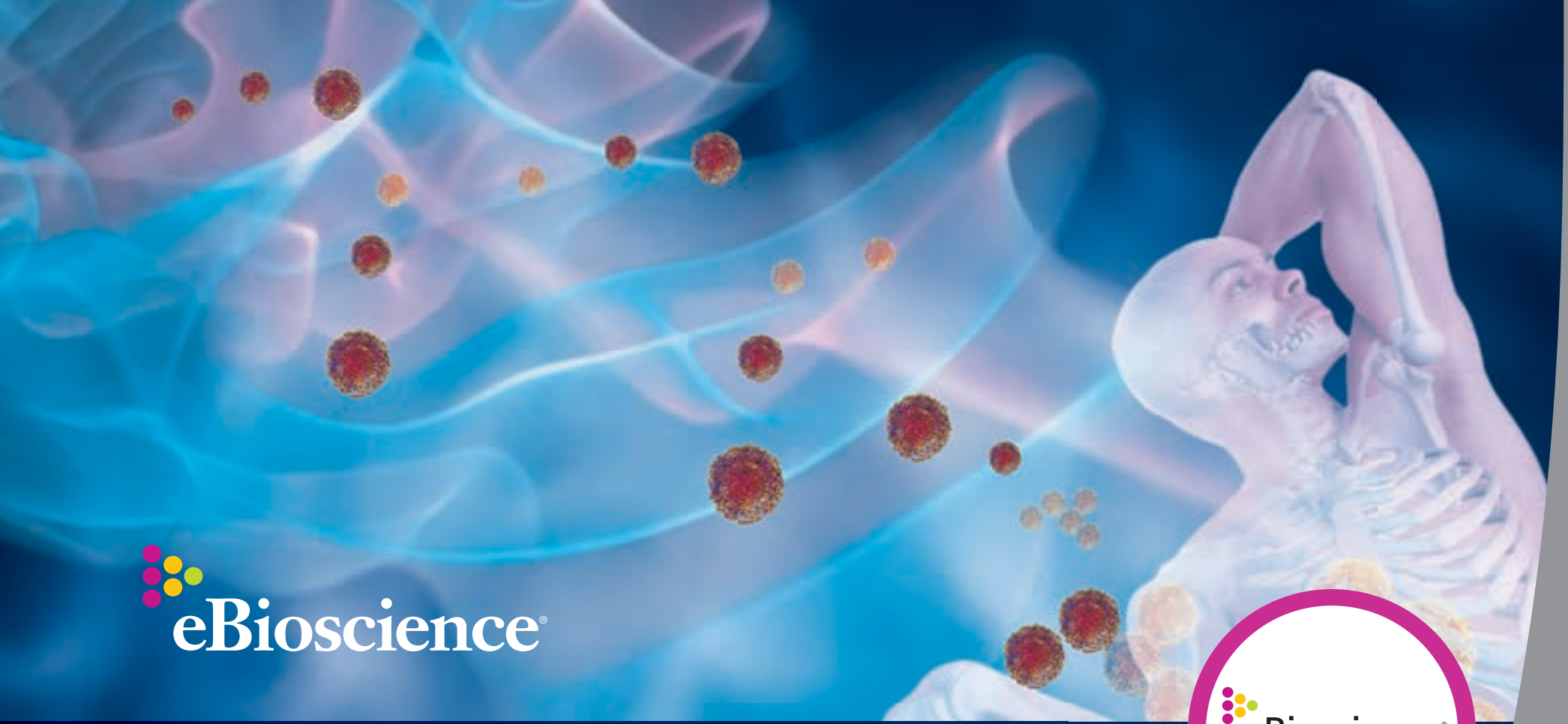

eBioscience®

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Cytokine Atlas

First Edition

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Cytokines

eBioscience, an Affymetrix company, is committed to developing and manufacturing high-quality, innovative reagents in an ISO certified facility. As a provider of more than 11,000 products, we empower our customers worldwide to obtain exceptional results by using reagents that offer a new standard of excellence in quality, innovation and value.

One key area of product focus is cytokines, which are a large group of small signaling molecules that function extensively in cellular communication. Cytokines are most often associated with immune modulating molecules such as interleukins, chemokines, and interferons, but can also include other molecules. The use of cytokines as biomarkers has been adopted due to their proven benefits as a means to understanding disease and therapies. Cytokines have expanded into specialized, disease relevant panels for a more accurate assessment of various diseases that include cardiovascular disease, asthma, inflammation, cancer, diabetes and rheumatoid arthritis. The Cytokine Atlas was developed as a resource guide to give a greater understanding of the various cytokines and their roles in diseases.

Abbreviations:

APC	Antigen Presenting Cell
CCL	C-C motif chemokine
CCR	C-C chemokine receptor
CD	Cluster of Differentiation
DC	Dendritic Cell
CMP	Common Myloid Progenitor cell
CVD	Cardiovascular Disease
CXCR	C-X-C chemokine receptor
CXCL	C-X-C motif chemokine ligand
EAE	Experimental Autoimmune Encephalomyelitis
FGF	Fibroblast Growth Factor
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
iPSC	Induced Pluripotent Stem Cell
LPS	Lipopolysaccharide
MCP	Monocyte Chemoattractant Protein
MIP	Macrophage Inflammatory Protein
MS	Multiple Sclerosis
NK	Natural Killer cell
NKT	Natural Killer T cell
PMN	Polymorphonuclear leukocyte
RA	Rheumatoid Arthritis
T_{FH}	T Follicular Helper Cell
TGF	Transforming Growth Factor
T_H1	T Helper 1 Cell
T_H2	T Helper 2 Cell
T_H9	T Helper 9 Cell
T_H17	T Helper 17 Cell
T_H22	T Helper 22 Cell
T_{Reg}	Regulatory T Cell

T Cell Illustration Legend:

➤ ➤ ➤	Differentiation
—⊣	Negative regulation
⟵	Signal / Activation
❯❯❯	Secretion
(h)	Human
(m)	Mouse

Analyte Listing Key:

Purified	Functional-Grade purified and non-conjugated antibodies
Violet Laser	Antibodies conjugated to eFluor® 450
Blue Laser	Antibodies conjugated to either FITC, Alexa Fluor® 488, PE, PE-Cy5, PerCP-eFluor® 710, PerCP-Cy5.5, PE-Cy5.5, PE-Cy7
Red Laser	Antibodies conjugated to either APC, Alexa Fluor® 647, eFluor® 660, Alexa Fluor® 700, APC-eFluor® 780
Proteins	Functional-Grade recombinant proteins and standard recombinant proteins
Coat-It-Yourself	Complete ELISA assay kits, but require the plates be coated by the end user with supplied reagents
Pre-Coated	ELISAs that are ready to use. Includes traditional, high sensitivity, and Instant ELISA®
Multiplex	FlowCytomix™ multiplex assays for the simultaneous analysis of up to 20 analytes from a single 25 µL sample on a flow cytometer

Disease Symbols:

Diseases that are associated with the various cell types described in the Cytokine Atlas.


Cardiovascular Disease

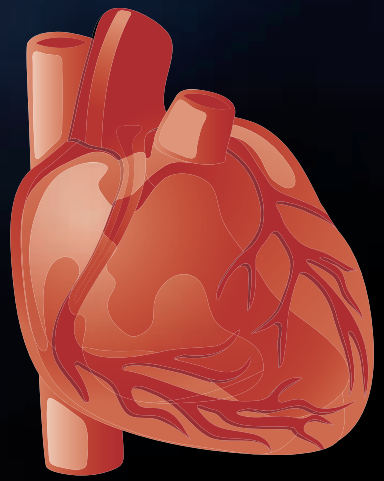

Cancer and Malignancy


Asthma/Airway Inflammation


Inflammation Disease


Rheumatoid Arthritis

Table of Contents



Cardiovascular Cytokine Profile:

CCL2 (MCP-1)	IL-2
CCL3 (MIP-1α)	IL-5
CCL4 (MIP-1β)	IL-6
CRP	IL-8
CSF	IL-8 (CXCL8)
CXCL16	IL-10
Erythropoietin	IL-15
FGF	IL-18
Fractalkine (CX3CL1)	M-CSF
G-CSF	PDGF
GM-CSF	RANTES (CCL5)
IFNγ	TNFα
IL-1	VEGF

Cardiovascular Disease (CVD)

Local and systemic inflammation is a common pathophysiological mechanisms for various cardiovascular diseases (CVD), for which cytokines have become important biomarkers. Numerous pro- and anti-inflammatory cytokines are used to help stage and diagnose various cardiovascular diseases. The pro-inflammatory cytokines IL-1β, IL-6, IL-8, IL-15, IL-18, CCL2 (MCP-1), and TNFα are released in atherosclerotic plaques where they aggravate plaque instability by inhibiting extracellular matrix synthesis and promoting smooth muscle cell apoptosis.[96] This cytokine release also produces many other effects. For instance, oxidized lipoproteins can induce smooth muscle cells and endothelial cells (EC) to produce the chemokine MCP-1 (CCL2), which acts as a chemotactic factor for monocytes and T cells. These T cells are then induced to release the chemotactic factor IL-8 (CXCL8) that, in turn, induces the migration and proliferation of ECs and smooth muscle cells.[96] As such, one therapeutic strategy for treating CVD aims to disrupt the accumulation of monocytes and macrophages by MCP-1 to vulnerable plaques. Unstable plaques are also characterized by infiltrating T_H1 cells that produce IFNγ, IL-2, IL-6, and TNFα.[96] Like atherosclerotic plaques, there appears to be a correlation between congestive heart failure and increased levels of IL-6 and TNFα, which are detected consistently in patients with angina and myocardial infarction.[96] Other chemokines implicated in atherogenesis are fractalkine (CX3CL1), RANTES (CCL5), IL-8 (CXCL8), and CXCL16.[12]

Differential cytokine profiles have also been observed in other areas of cardiovascular disease. Elevated levels of C-Reactive Protein (CRP), IL-6, IL-8, sICAM, MCP-1 (CCL2), and MMP-9 have been used as markers to predict potential rapid progression of coronary heart disease.[80] Elevated circulating levels of both IL-1β and TNFα, as well as decreased IL-10 production, are correlated with increased risk of cardiovascular disease and death.[99] Conversely, elevated serum IL-10 levels are associated with a more favorable prognosis in patients with acute coronary syndromes.[64] This and other data clearly demonstrate the important roles that cytokines and inflammation play in determining the prognosis and outcome of cardiovascular diseases.

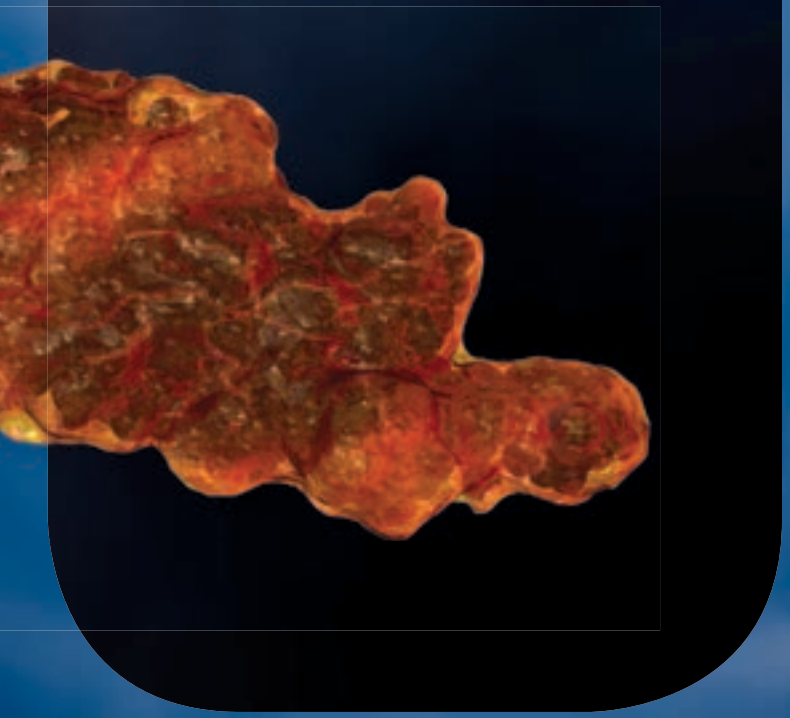
Asthma Cytokine Profile:

- Eotaxin
- GM-CSF
- IFNγ
- IL-4
- IL-5
- IL-8
- IL-10
- IL-12
- IL-13
- IL-17A
- IL-17F
- IL-18
- TNFα

Asthma/Airway Inflammation

Asthma is a disorder characterized physiologically by airway hyper-responsiveness caused by tightening of the muscles surrounding the airways and swelling in the lining of airway passages. These characteristics result in a multitude of symptoms that can range from mild to life-threatening, including chest tightness, coughing, shortness of breath, and wheezing. Asthma is also characterized by chronic inflammation of the respiratory tract due to allergen-specific IgE production, eosinophil infiltration, T cell recruitment to the airways, and alterations in the balance between T_H1 and T_H2 responses.[28] Allergic asthma patients undergoing an asthmatic attack exhibit significantly higher levels of pro-inflammatory cytokines and chemokines, including Eotaxin, GM-CSF, IFNγ, IL-4, IL-5, IL-8, IL-10, IL-12, IL-13, IL-17A, IL-17F, IL-18, and TNFα. Although, IL-4, IL-5, IL-13, and GM-CSF mediate differentiation of T_H2 sub-populations and B cell proliferation, IL-13 is the central mediator of the asthmatic response since it modulates IgE production. These cytokines also help attract and mediate eosinophil and mast cell function, leading to mucosal hypersecretion, epithelial shedding, and bronchial muscle contraction.[105] In addition to T_H1 and T_H2 cells, T_H17 cells are also elevated during asthma, which results in increased secretion of IL-8, TNFα, and GM-CSF.[28] T_{Reg} cells are also implicated in asthma. They function to produce the immunosuppressive IL-10, that can be impaired in some asthmatic patients.[28] Interestingly, recent studies have found no significant differences in peripheral blood cytokine profiles between asthmatic patients (not undergoing an asthmatic attack) and healthy individuals.[28] Finally, asthmatic cytokine profiles change as patients age since levels of Eotaxin, IL-4, IL-5, IL-10, IL-12, and TNFα differ between adult and pediatric asthma patients.[104]

Cancer and Malignancy



Cancer Cytokine Profile:

- Eotaxin
- GM-CSF
- IFNγ
- IL-4
- IL-5
- IL-8
- IL-10
- IL-12
- IL-13
- IL-17A
- IL-17F
- IL-18
- TNFα

Cytokines are integral to many different aspects of cancer, including development/advancement, treatment, and prognosis. Furthermore, cytokines have been established as major mediators of anti-tumor immunity.[97] For example, IFNγ facilitates this anti-tumor activity by promoting antigen presenting cell (APC)-mediated expansion of cytotoxic T cells and activating macrophages to release molecules such as superoxide. Additionally, IL-2 stimulates the proliferation of primed cytotoxic T cells. Furthermore, IL-5 attracts eosinophils that produce cytotoxic proteins that disrupt cell membranes and induce cell death.[97] IL-17 also plays a role in suppressing tumor growth and activity by promoting the expression of MCP-1 and MIP-3α that recruit leukocytes and APCs to the tumor to inhibit its growth.[60]

Cytokines can also influence the effectiveness of cancer treatments. Elevated cytokine levels have been associated with reducing the anti-cancer activity of various treatments. For instance, increased pro-inflammatory cytokine levels can lead to NFkB activation in cancer cells, thus providing a mechanism for these cells to evade apoptosis.[108] Cytokines have also been demonstrated to exacerbate the toxic effects of chemotherapy and affect drug metabolism. Many chemotherapeutic drugs are metabolized in the liver by the CYP enzyme cytochrome P450 and other coenzymes. However, increased levels of pro-inflammatory cytokines, along with CRP, can increase the toxic effects of these drugs by decreasing CYP enzyme activity.[108] Organ toxicity is also affected by higher than normal cytokine levels. For example, cisplatin causes kidney damage (nephrotoxicity) by increasing TNFα levels and bleomycin increases pulmonary toxicity by inducing the production of pro-inflammatory cytokines such as TGFβ1, IL-1, IL-6, and TNFα.[108]

Cytokine profile levels have been used to predict cancer prognosis as differential cytokine expression profiles have been correlated with disease progression. The switch from T_H1 to T_H2 cytokine expression has been associated with potential tumor metastasis and recurrence.[108] Moreover, as the most commonly deregulated cytokine, IL-6 is often used as a prognostic marker for various cancers, with abnormally elevated levels associated with a poor prognosis.[108]

Arthritis Cytokine Profile:

IL-1β	IL-15
IL-1RA	IL-17
IL-6	IL-18
IL-7	IL-23
IL-10	MIP-3α
IL-11	TGFβ
IL-12	TNFα

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by joint inflammation, the production of a wide assortment of cytokines, and ultimately joint destruction. The imbalance between pro-inflammatory and anti-inflammatory cytokines favors induction of RA. By promoting autoimmunity, maintaining chronic inflammatory synovitis, and promoting the destruction of adjacent joint tissue, cytokines have been implicated in each phase of the pathogenesis of this disease.[83] For instance, IL-6 directly regulates the release of acute-phase proteins from hepatocytes and Kupffer cells. Meanwhile, TNFα is often targeted as a common treatment for RA.[83]

Early studies associated RA primarily with T_H1 cytokines. Therefore, RA was considered a disorder driven by a population of T cells that produce inflammatory cytokines and chemokines such as IFNγ, LTβ, and TNF.[83] However, more recently, T_H17 cells have emerged as a key driver of inflammation and, therefore, rheumatoid arthritis. IL-17 is detectable in the rheumatoid synovium and joints of mice suffering from RA. Additionally, IL-17-deficient mice exhibit decreased disease severity, while those with higher IL-17 levels display exacerbated disease. Furthermore, patients with RA have been shown to respond to treatment with anti-IL-17 monoclonal antibodies.[38, 83]

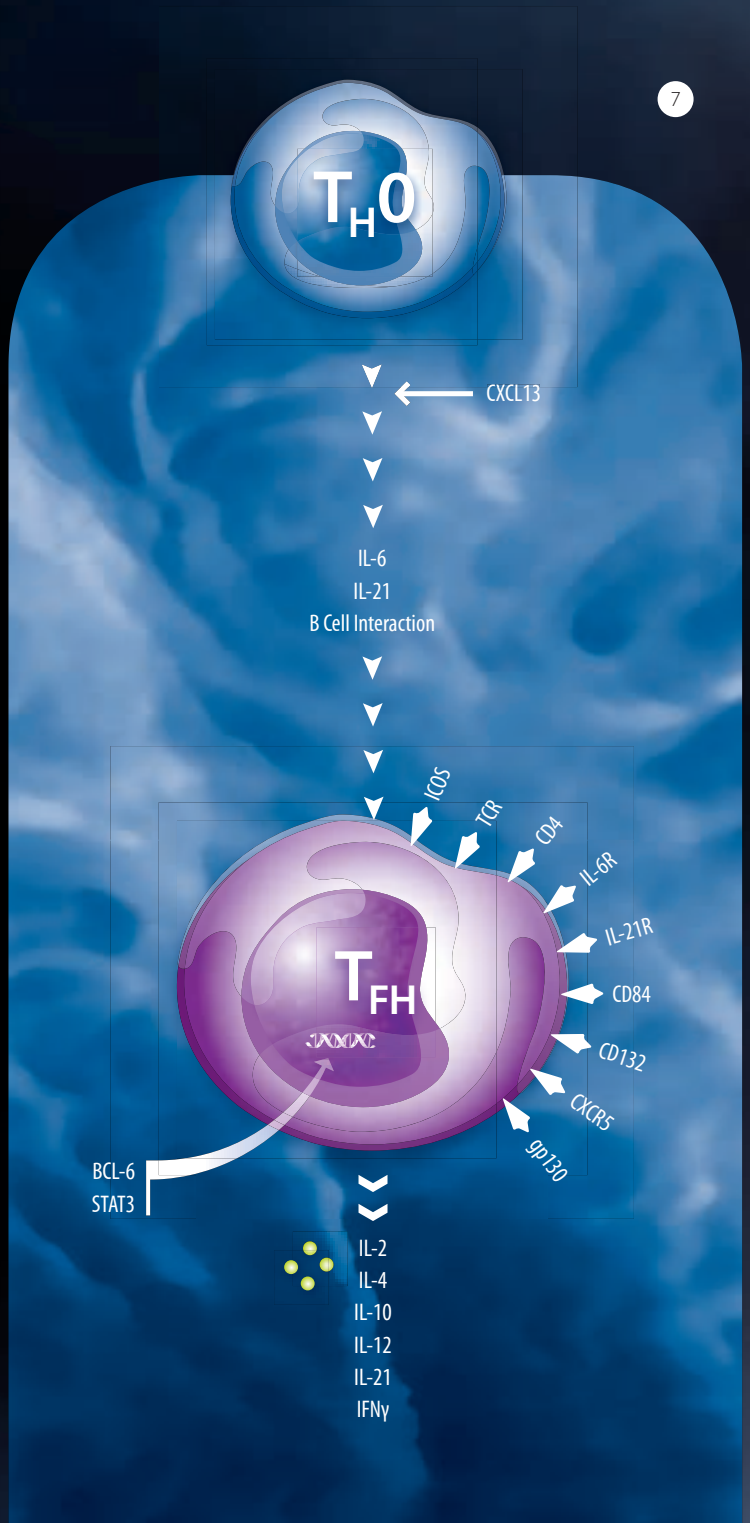
An important feature of rheumatoid arthritis synovitis is the relatively reduced expression of several inhibitory cytokines that creates an imbalance between pro-inflammatory and the anti-inflammatory cytokines in the joints. IL-1RA, IL-10, and IL-11 are detected in this tissue, but not at sufficient concentrations to counterbalance the activity of pro-inflammatory cytokines. Additionally, IL-2 and IL-4 are absent, thereby impairing T_{Reg} cell development in favor of T_H1 and T_H17 cell differentiation. As this autoimmune disease demonstrates, cytokine expression must be carefully regulated in order to maintain an appropriately functioning immune response.

T Follicular Helper Cells

T_{FH}

T follicular helper (T_{FH}) cells are a regulatory class of specialized effector T helper cells that are essential in the development of antigen-specific effector and memory B cell responses. T_{FH} cells are found enriched within the edges of the B cell zones of secondary lymphoid organs such as the lymph nodes, spleen, and Peyer's patches. These cells regulate humoral immunity, particularly germinal center reactions, and play a role in the development of long-term antibody responses. Upon antigen-specific stimulation, T_{FH} cells migrate to the follicular regions of secondary lymphoid tissues, where they form stable contacts with antigen-primed B cells and release IL-4, IL-10, IFNγ, and IL-21 to stimulate mature B cells into forming germinal centers and undergoing antibody class-switching.

T_{FH} cells are defined phenotypically by the high expression of CXCR5 (CD185, CXCL13 receptor), Bcl-6, and IL-21 along with low CCR7 (CD197) expression. Activated $CXCR5^{hi}CCR7^{lo}$ T cells migrate to the B cell follicles in response to high levels of CXCL13 that is secreted by follicular stromal cells. Nevertheless, T_{FH} cells require IL-6, IL-21, and B cell interaction for complete development. A key transcription factor involved in this differentiation is Bcl-6, which regulates the changes in CXCR5 and CCR7 expression required for T cell migration to the follicle. Moreover, unlike the other regulators that induce gene expression, Bcl-6 promotes T_{FH} cell development by repressing Blimp-1, RORγt, T-bet, and GATA3, as well as several miRNAs. Interestingly, Bcl-6 also plays a critical role in germinal center B cell differentiation. Because they mediate antigen-specific B cell immunity, T_{FH} cells have been linked to diseases such as angioimmunoblastic T cell lymphoma, as well as autoimmune disorders including systemic lupus erythematosus and Sjogren's syndrome.



Master Regulator of Differentiation

- Bcl-6

Differentiation Profile

IL-6
- Essential for inducing T_{FH} cell differentiation

IL-21
- Essential for inducing T_{FH} cell differentiation
- Acts as an autocrine growth factor to maintain T_{FH} cell survival

CXCL13
- Critical for recruiting activated CD4+ T cells to the follicles of secondary lymphoid tissues

B cell
- Interaction with B cells within the follicle is required for complete T_{FH} cell development

Cell Marker Profile

- Bcl-6
- CD4
- CD25 (IL-2Ra)
- CD57 (h)
- CD69
- CD84
- CD95
- CD125 (IL-5R)
- CD126 (IL-6R)
- CD132
- CD134 (OX40)
- CD153 (CD30L)
- CD154 (CD40L)
- CD185 (CXCR5) ^{high}
- CD197 (CCR7) ^{low}
- CD200
- CD254 (OX40L)
- CD272 (BTLA)
- CD278 (ICOS)
- CD279 (PD-1)
- Fyn
- IL-21R
- SAP
- TCR

Secreted Cytokine Profile

IL-21
- Mediates B cell proliferation and class switching within germinal centers
- Acts as an autocrine growth factor to induce T_{FH} cell differentiation and maintain their survival

IL-10
- Augments B cell proliferation and maintenance

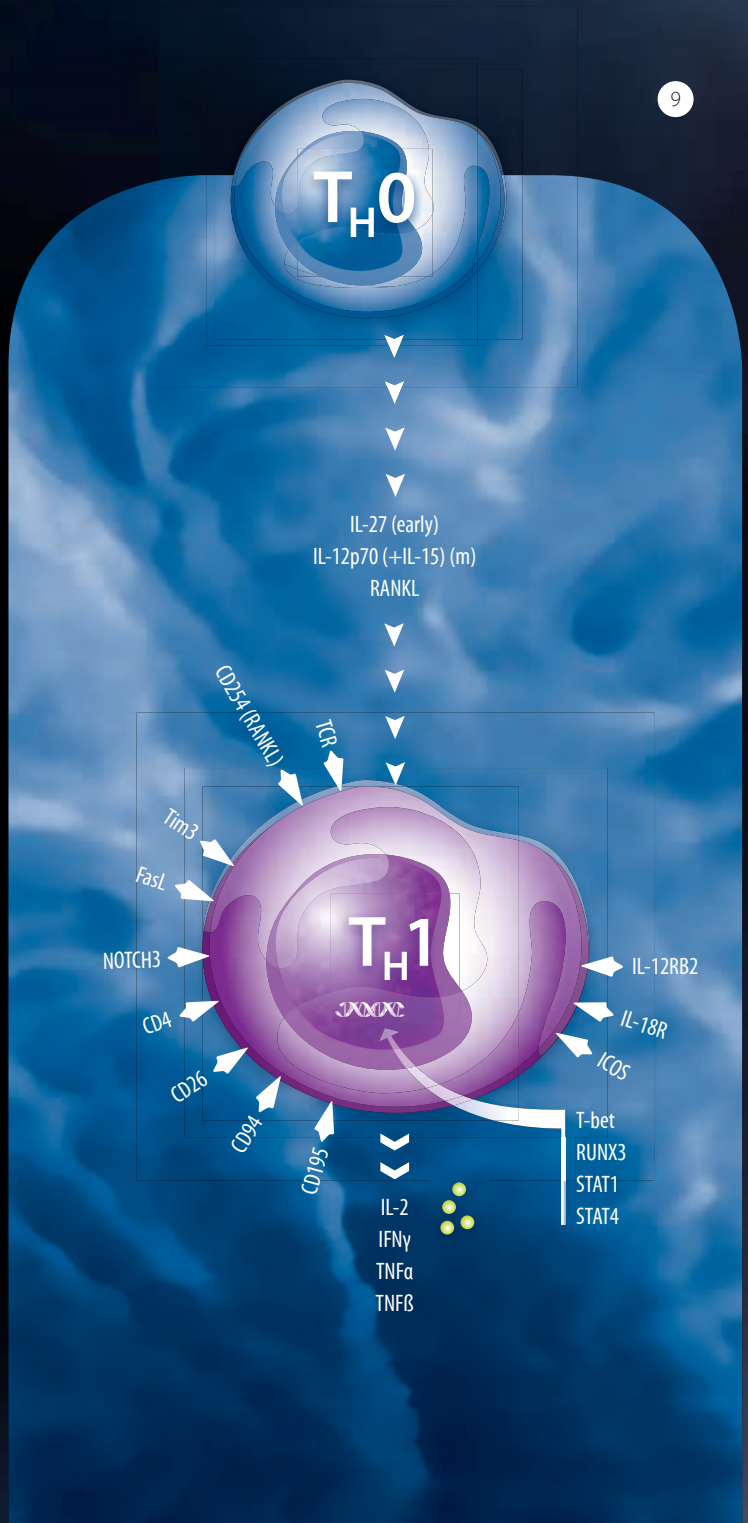
IL-12
- Regulates CXCR5 and ICOS expression on T_{FH} cells
- Assists in B cell function and antibody expression

IL-4
- Required for optimal immunoglobulin somatic hypermutation and affinity maturation
- Contributes to germinal center B cell survival and maintenance
- Highly expressed by T_{FH} cells following helminth infection

T Helper 1 Cells

T_H1

T_H1 lymphocytes are critical in the cellular immune response and they play an important role in host defense systems for intracellular microbial agents and viruses. T_H1 cell promoting factors include IFNγ, IL-12 (p70), and the activation of the transcription factors STAT1 and STAT4. The expression of the Interleukin-12 receptor β2-chain (IL-12Rβ2) is required for T_H1 cellular differentiation since it allows for the responsiveness to IL-12 on the T_H1 cells. IL-12R activation increases IFNγ expression through STAT1 signals to induce the T_H1 master regulator T-bet. This further increases IFNγ expression while suppressing IL-4. T_H1 cells are the primary source for the inflammatory cytokines IFNγ, IL-2, and TNFβ (LTα). T_H1 cytokines stimulate macrophages, lymphocytes, and PMNs in the destruction of bacterial pathogens. These cytokines also help foster the development of cytotoxic lymphocytes (CTL & NK cells) that are responsible for the cell-mediated immune response against viruses and tumor cells. Due to the central role of T_H1 cells in immune system, over activation or misdirected activation also makes them key players in T_H1-dominant autoimmune diseases such as multiple sclerosis, type-1 diabetes, rheumatoid arthritis, and delayed-type hypersensitivity responses.



Master Regulator of Differentiation

T-bet

Differentiation Profile

IL-2
- Expressed by activated T cells, but not by resting T cells
- Mediate proliferation of activated T cells

IL-12
- Produced by activated macrophages
- Promotes survival and growth of T_H1 cells
- Sustains sufficient number of memory/effector T_H1 cells
- Inhibits the formation of T_H2 cells

IL-18
- Produced by monocytes, macrophages, dendritic cells, keratinocytes, and epithelial cells
- Critical inducer of IFNγ
- Functions as a key growth and differentiation factor

IL-27
- Produced by activated monocytes, macrophages, and dendritic cells
- Synergizes with IL-12 to cause the production of IFNγ by naïve T_H cells
- Increases proliferation of cells without affecting memory T-cells

IFNγ
- Autocrine factor in the establishment of T_H1 cells
- Enhanced by the action of IL-12

Cell Marker Profile

CD4
CD94
CD119 (IFNγ R1)
CD183 (CXCR3)
CD186 (CXCR6)
CD191 (CCR1)
CD195 (CCR5)
CD212 (IL-12Rβ1&2)
CD254 (RANKL)
CD278 (ICOS)
IL-18R
MRP1
NOTCH3
TCR
TIM3

Secreted Cytokine Profile

IL-2
- Stimulates growth, differentiation, and survival of antigen-selected cytotoxic T cells
- Necessary for T cell memory, T-cell development, and self / non-self recognition

IL-10
- Auto-regulator of T_H1 cell activation

IFNγ
- Activates macrophages and inhibits T_H2 lymphocyte proliferation
- Stimulates B cells to produce receptors that enhance the attachment of microbes to phagocytes

TNFα
- A general, potent, and pleiotropic immune activator and regulator of immune cell function

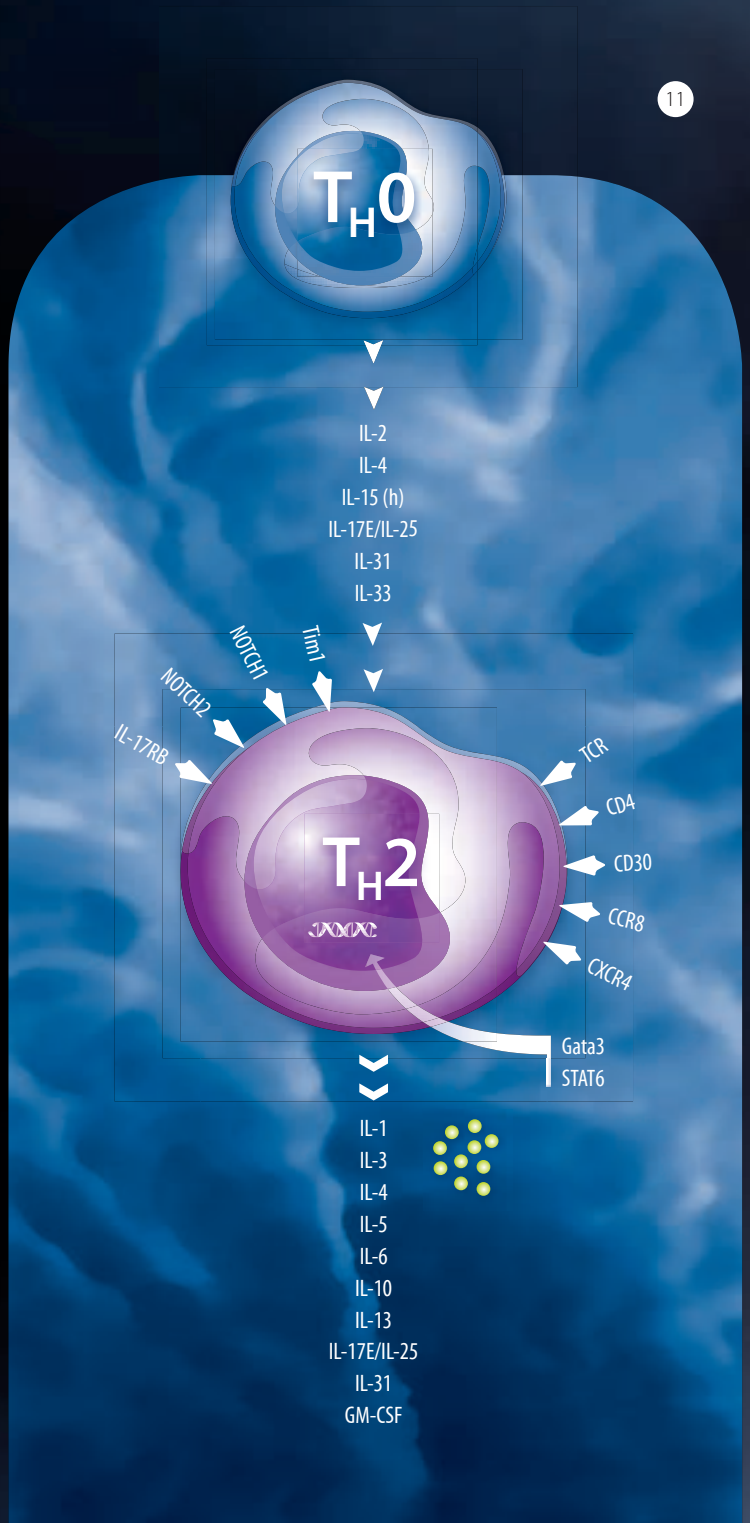
TNFβ/LTα
- Activates neutrophils to enhance their microbial killing activity during phagocytosis

T Helper 2 Cells

T_H2

T_H2 cells mediate the activation and maintenance of the humoral, or antibody-mediated, immune response against extracellular parasites, bacteria, allergens, and toxins. T_H2 cells mediate these functions by producing various cytokines such as IL-4, IL-5, IL-6, IL-9, IL-13, and IL-17E (IL-25) that are responsible for strong antibody production, eosinophil activation, and inhibition of several macrophage functions, thus providing phagocyte-independent protective responses. These cytokines also counteract the T_H1 responses that allow for the T_H2 responsiveness to IL-4. IL-4 signals through STAT6 to upregulate GATA3 expression, the master regulator of T_H2 cell differentiation. Repression of this activity results in the development failure of IL-4 producing cells. IL-4 also suppresses T_H1 and T_H17 cell responses through the upregulation of transcriptional repressor(s) of IFNγ and IL-17 production. However, the IL-4/STAT6 pathway is not completely essential for T_H2 cell differentiation as T_H2 cell differentiation can also occur through other cytokines such as TSLP, IL-17E (IL-25), and IL-33. Regardless, GATA3 expression and STAT5 activation, most commonly through IL-2 for T_H2 cells, is completely essential for T_H2 cellular differentiation.

Functionally, T_H2 cytokines have effects on many cell types in the body as the cytokine receptors are widely expressed on numerous cell types. T_H2 cells stimulate and recruit specialized subsets of immune cells, such as eosinophils and basophils, to the site of infection or in response to allergens or toxin leading to tissue eosinophilia and mast cell hyperplasia. They induce mucus production, goblet cell metaplasia, and airway hyper-responsiveness. T_H2 cells also control the regulation of B cell class-switching to IgE. Because of their influence on the production of antibodies and allergic responses, over activation of T_H2 cells appears to be responsible for the exacerbation of allergies (Type-1, immediate hypersensitivity reactions), autoimmune reactions such as chronic graft-versus-host disease, progressive systemic sclerosis, and systemic lupus erythematosus. Additionally, T_H2 cells are also known to be responsible for the development of asthma and other allergic inflammatory diseases. Interestingly, T_H2 cells also produce the growth factor amphiregulin and IL-24 which have anti-tumor effects.



Master Regulator of Differentiation

GATA3

Differentiation Profile

IL-2
- Expressed by activated T cells
- Mediates their proliferation and clonal expansion

IL-4
- Required for T_H2 priming and maturation
- An autocrine of T_H2 cells during their maturation
- High concentrations can block the generation of T_H1 cells from naïve T cells

IL-6
- Released by APCs
- Initiates maturation of T_H2 cells from T_H0 in conjunction with IL-4
- High concentration can block the generation of T_H1 cells in a similar fashion to IL-4

IL-17E (IL-25)
- Induces cytokine expression
- Helps maintain T_H2 function
- Plays a critical role in the formation of T_H2 memory

IL-31
- Expressed by activated CD4+ cells
- Associated with enhanced IL-4 and IL-13 expression by T_H2

IL-33
- Necessary for T_H2 cytokine production

Cell Marker Profile

CD4
CD30
CD119 (IFNγR1)
CD184 (CXCR4)
CD185 (CXCR5)
CD193 (CCR3)
CD194 (CCR4)
CD197 (CCR7)
CD278 (ICOS)
CD294 (CRTh2)
CDw198 (CCR8)
IL-17RB
IL-33Rα (ST2)
NOTCH1
NOTCH2
TCR
TIM1

Maturation blocked by:

- IFNγ and TNFβ (LTα)

Secreted Cytokine Profile

Amphiregulin
- An EGF family member growth factor with anti-tumor effects

IL-3
- Assists in the recruitment and maintenance of basophils into lymphoid tissues in response to infection

IL-4
- Inhibits the proliferation and differentiation of T_H1 cells
- Stimulates B cell proliferation and maturation into plasma cells
- Regulates the class switching of antibodies
- Increases IgE production

IL-5
- Attracts and activates eosinophils

IL-6
- Critical role in B cell maturation into IgG secreting cells
- Plays a significant role in inflammation and autoimmunity

IL-10
- Inhibits secretion of various cytokines by T_H1 cells, macrophages, and dendritic cells

IL-13
- Stimulates B-cell production of IgE
- Attracts basophils and mediates the release of granules
- Triggers mast cells to release granules

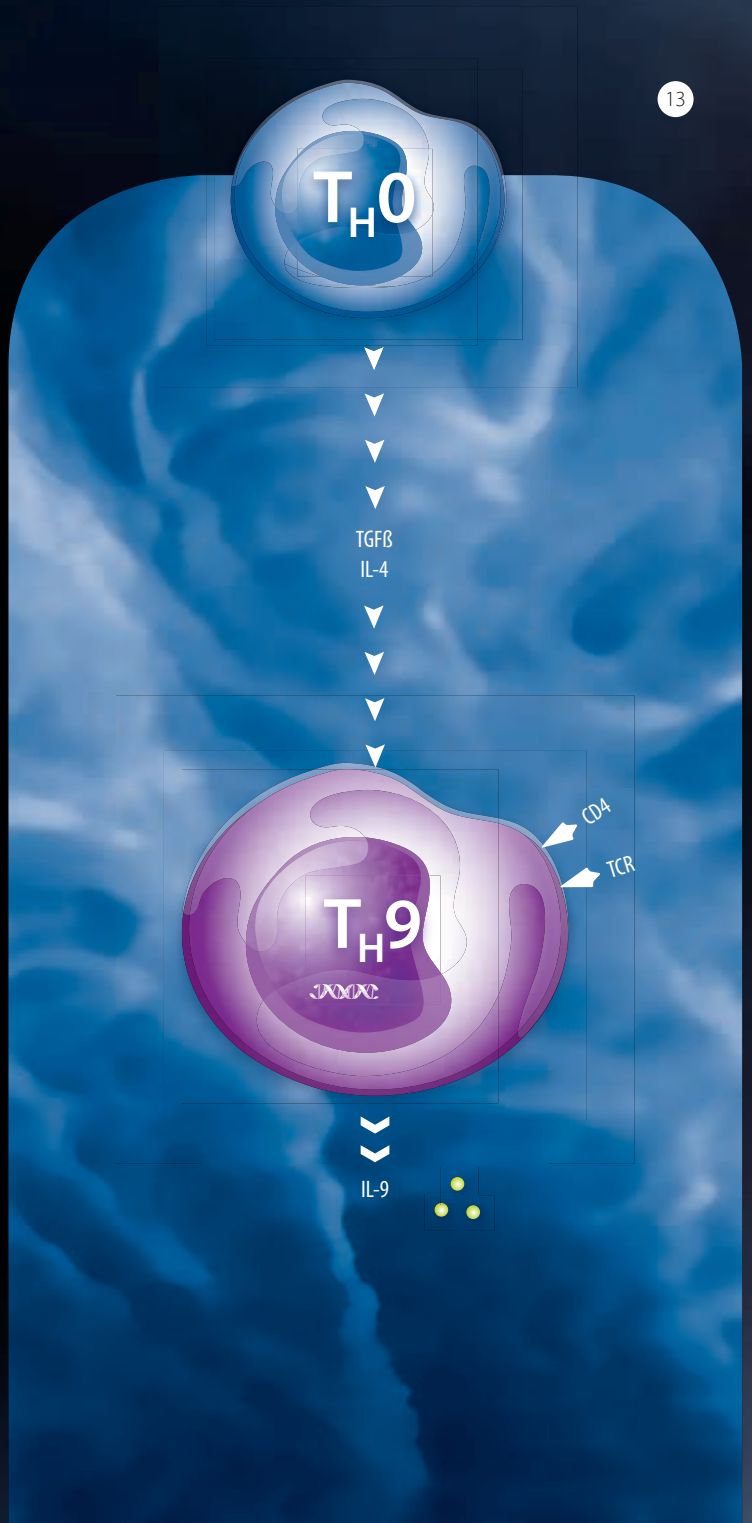
IL-17E (IL-25)
- Co-mediates production IL-4, IL-5 and IL-13

IL-31
- Implicated in inflammatory responses in the skin
- Recruitment of PMNs, monocytes, and T cells to the sites of infection

T Helper 9 Cells

T_H9

T_H9 cells are a novel subset of T_H cells that develop independently of T_H1, T_H2, T_H17, and T_{Reg} cells. T_H9 cells are characterized by the secretion of IL-9. However, in contrast to murine T_H9 cells, IL-10 is not expressed by human T_H9 cells. Naïve CD4+ T cells can be differentiated into T_H9 cells with the combination of TGFβ and IL-4. In this differentiation model, IL-4 suppresses TGFβ-induced Foxp3 expression, while IL-4 mediates the upregulation of GATA3. While the cytokines IL-1β, IL-6, IL-10, IL-21, IFNα, and IFNβ enhance IL-9 expression of cultured T_H9 cells, IFNγ and IL-27 inhibit its production in human T_H9 cells; making it possible that T_H1 response may suppress T_H9 cell differentiation. T_H9 cells do not express many of the other T_H cell associated cytokines such as IFNγ (T_H1), IL-4, IL-5, and IL-13 (T_H2), or IL-17 (T_H17), nor do they express the master regulators of the other T_H cell types T-bet (T_H1), RORγt (T_H17), or Foxp3 (T_{Reg}), with the exception of GATA3 (T_H2). It is believed that GATA3 may be required for IL-9 production as its expression remains under T_H9 polarized conditions. It appears that T_H9 cells are involved in intestinal responses to parasitic worms and may play a role in inflammatory diseases of the gut. T_H9 cells are also known to be capable of inducing tissue inflammation in colitis models, experimental autoimmune encephalomyelitis (EAE), and play a role in allergic asthma.



Master Regulator of Differentiation

Candidate: PU.1 and IRF4

Differentiation Profile

TGFβ

- Essential to the reprogramming of T_H0 cells into mature T_H9 cells

IL-4

- Blocks the generation of TGFβ-induced $Foxp3^+$ T_{Reg} cells and induces T_H9 cell formation

Enhance IL-9 expression of cultured T_H9 cells:

- IL-1β, IL-6, IL-10, IL-21, IFNα, and IFNβ

Inhibit IL-9 production in human T_H9 cells

- IFNγ and IL-27

Cell Marker Profile

CD3

CD4

Foxp3(-)

RORγt(-)

TCR

T-bet(-)

Secreted Cytokine Profile

IL-9

- Involved in immunity to intestinal worms and allergic reactions

IL-10

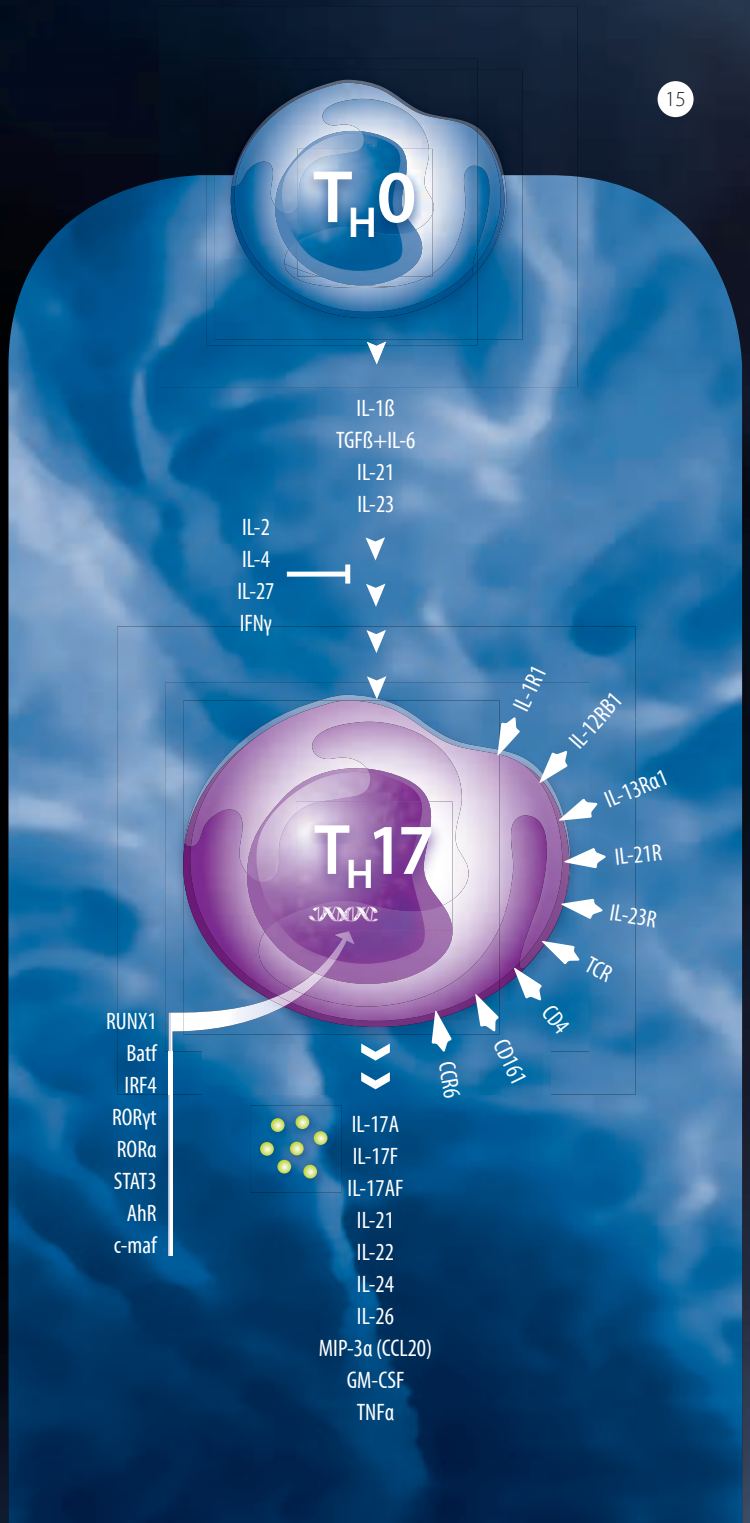
- Inhibits secretion of cytokines and IFNγ by T_H1 cells, and IL-12 from macrophages and dendritic cells
- In humans, suppresses proliferation and cytokine production in all T cells and macrophages while continuing to stimulate plasma cells
- In the presence of T_H9 cells, IL-10 expression can be pro-inflammatory and is associated with allergic inflammation

T Helper 17 Cells

T_H17

T_H17 cells are a subset of activated CD4+ T cells that are responsive to IL-1R1 and IL-23R signaling. They are regulated by the IL-6/STAT3/RORγt lineage control and produce the cytokines IL-17A, IL-17F, IL-17AF, IL-21, IL-22, IL-26 (human), GM-CSF, MIP-3α, and TNFα. T_H17 cells act as a bridge between adaptive and innate immunity where they promote neutrophil activation, immunity to pathogens, and inflammation. Through the study of IL-23, it was discovered that an alternate T_H cell subset promotes chronic inflammation and tissue damage. T_H17 cells were classified as an additional effector CD4+ T cell subset based on their independence from the transcription factors GATA3 and T-bet and the cytokines IFNγ and IL-4, used to define T_H1 and T_H2, respectively. While T_H17 cell differentiation is driven by TGFβ and IL-6 *in vivo*, it has been shown that IL-1β and IL-23 are also necessary *in vivo*, for T_H17 development. T_H17 differentiation is driven and regulated by the lineage-defining transcription factors AHR, BATF, IκBζ, IRF4, c-Maf, RORα, RORγt, and STAT3. STAT3 is critical for T_H17 differentiation and directly regulates the locus encoding IL-17 and is necessary for the expression of many transcription factors involved in T_H17 differentiation. Beyond that, IL-23 is required for T_H17 expansion and stabilization. Cytokines such as IFNγ, IL-27 and IL-4 are known to inhibit T_H17 differentiation. The pathogenic potential of T_H17 cells are restrained by the co-production of IL-10. When the T_H17 cells express T-bet, and cease IL-10 production, they attain stronger pathogenic function.

Functionally, T_H17 cells play a key role in host defense against extracellular microbes such as bacteria and fungi and play a significant role in autoimmune disease and its inflammatory response. T_H17 cells are localized primarily in tissues that separate the host from the environment, principally the skin and mucosa. Through their activation and subsequent cytokine production, they trigger pro-inflammatory signaling that promotes neutrophil mobilization and the expression of antimicrobial peptides such as Reg3γ. Because of their role in inflammation, T_H17 cells are implicated in a broad array of inflammatory and autoimmune responses, and appear to play critical roles in autoimmune diseases such as rheumatoid arthritis, the inflammatory bowel diseases, asthma, multiple sclerosis, psoriasis and many others.



Master Regulator of Differentiation

RORγt

Differentiation Profile

INDUCING:

TGFβ1

- Essential factor needed for T_H0 to T_H17 development in concert with IL-6 and IL-23

IL-1β

- Involved in early T_H17 differentiation
- Upregulates RORγt and IRF4
- Helps maintain T_H17 cytokine profile post-polarization

IL-6

- Essential in the activation of IL-17 specific transcription factor RORγt and IL-21 expression that then activates the expression of IL-17A, IL-17F, and IL-23R on T_H17 cells

IL-21

IL-23

- Decreases the ability of de-differentiation and plasticity in T_H17 cells
- Induces expression of the characteristic T_H17 cytokines
- Essential for the survival and expansion

INHIBITING:

- IFNγ
- IL-2
- IL-4
- IL-27

Cell Marker Profile

CD4
CD27
CD62L
CD127 (IL-7R)
CD161
CD184 (CXCR4)
CD194 (CCR4)
CD196 (CCR6)
CD197 (CCR7)
CD212b1 (IL-12Rβ1)
CD213a1 (IL-13Rα1)
CD278 (ICOS)
IL-1R1
IL-21R
IL-23R

Secreted Cytokine Profile

IL-17A

- Regulates local tissue inflammation through coordinated expression of pro-inflammatory and neutrophil-mobilizing cytokines and chemokines
- Secreted as a homodimer and heterodimer

IL-17F

- Involved in neutrophil recruitment and immunity to extracellular pathogens
- Secreted as a homodimer and heterodimer

IL-17AF heterodimer

- Overlaps in function with IL-17A and IL-17F homodimers

IL-21

- Upregulated early in differentiation by IL-6
- Enhances T_H17 maintenance by upregulating IL-23R
- Helps promotes/sustain T_H17 lineage commitment

IL-22

- Induces anti-microbial peptide and pro-inflammatory cytokine expression on keratinocytes and other non-hematopoietic cells

IL-26

- Enhances T_H17 pro-inflammatory response on epithelial cells

GM-CSF

- Critical for the pro-inflammatory functions of T_H17 cells
- Promotes M1 macrophage differentiation

MIP-3α

- The ligand for CCR6; blocking delays the onset of arthritis

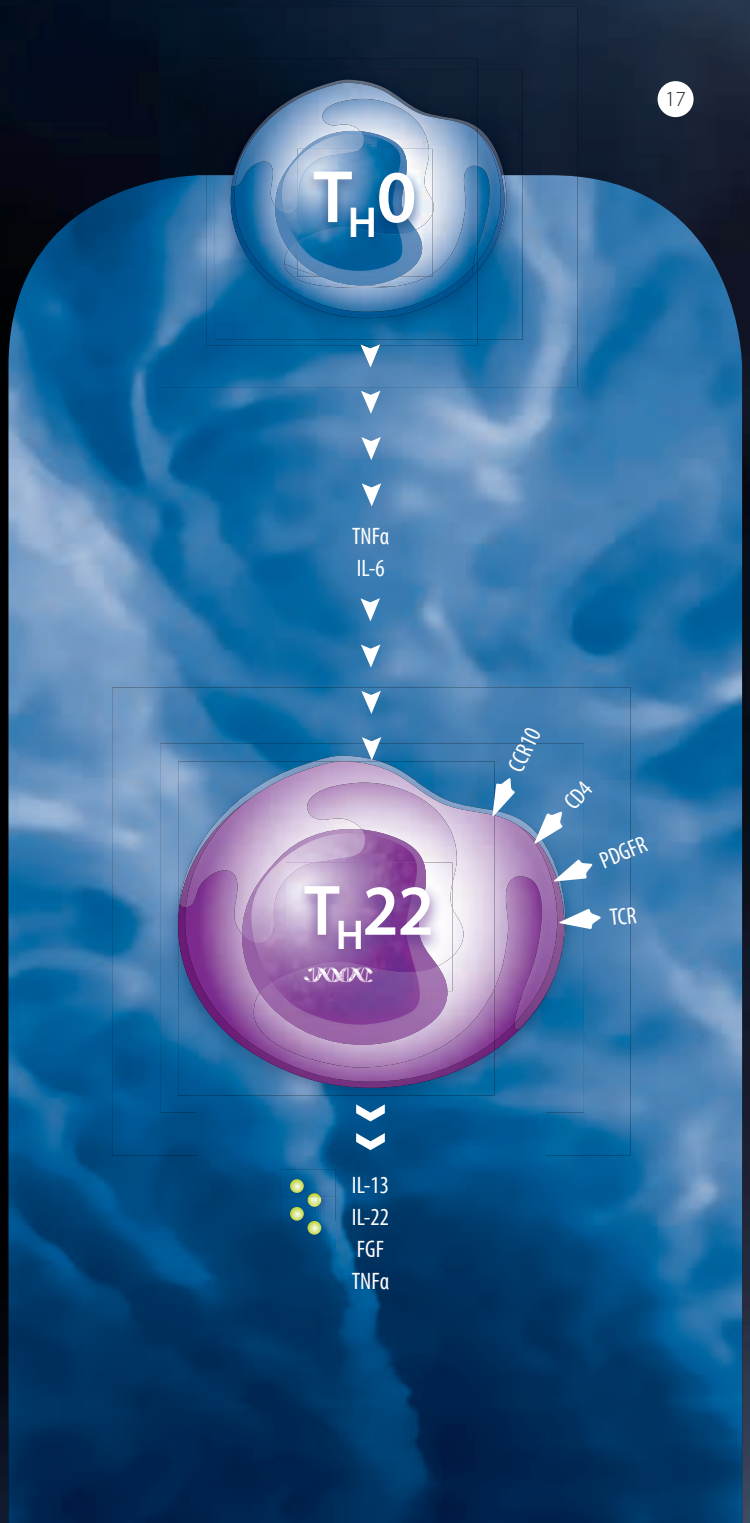
TNFα

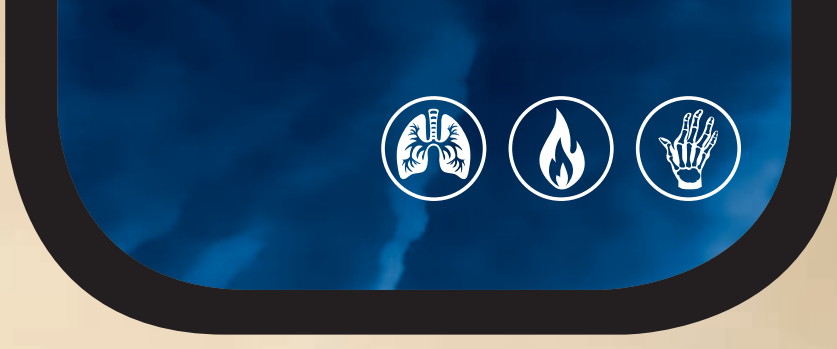
- Pleiotropic immune activator and regulator thought to enhance T_H17 pathology

T Helper 22 Cells

T_H22

T_H22 cells are a CD4+ cell subset dedicated to the production of IL-22, an IL-10 family member. Maturation of T_H22 cells requires TNFα and IL-6. High numbers of T_H22 cells have been found in the epidermis of inflammatory skin disorders and they are believed to be important at other barrier interfaces. T_H22 cells are characterized by the expression of IL-22, IL-13, and other factors including fibroblast growth factor (FGF) isoforms involved in tissue remodeling, but not IFNγ, IL-4, or IL-17.[50, 51] T_H22 cells also express the chemokine receptors CCR4, CCR6, and CCR10. CCR4 and CCR10 expression drives T_H22 cells to migrate to the skin.[50, 51] The expression of IL-22 allows T_H22 cells to act on non-hematopoietic cells including keratinocytes, myofibroblasts, and epithelial cells where the T_H22 cells appear to provide a protective role in regulating wound repair and healing in the skin, gut and lungs.[50, 51] T_H22 cells may also play a pathogenic role in many inflammatory diseases such as asthma, atopic dermatitis, psoriasis, rheumatoid arthritis, scleroderma, Crohn's disease and uveitis.





Master Regulator of Differentiation

Unknown

Differentiation Profile

IL-6

- Necessary for the maintenance of T_H22 cells *in vitro*

TNFα

- Necessary for induction and maintenance of T_H22 cells *in vitro*
- Associated with both pro and anti-inflammatory activities of T cells including T_H22 cells

Cell Marker Profile

AHR (aryl hydrocarbon receptor)
BNC2
CCR10
CD3
CD4
CD8(-)
CD56(-)
CD194 (CCR4)
CD196 (CCR6)
FGFR
FOXO4
IL-23R
PDGFR (CD140)
TCR

Secreted Cytokine Profile

CCL15

- A chemotactic for PMNs, monocytes and lymphocytes
- Binds CCR1 and CCR3 receptors
- Functions to potentiate T_H2/T_H22 cells at the site of infection or inflammation

CCL17

- Binds and induces chemotaxis in T cells via the CCR4 receptor
- Functions to recruit and maintain T_H2/T_H22 cells at the site of infection or inflammation

FGF Family

- Associated with epidermal repair and remodeling as well as wound healing, development, proliferation, angiogenesis and cell maintenance
- Strong mitogens with pluripotent effects on many cell types

IL-22

- Induces innate immune responses and expression of chemokines and anti-bacterial substances by epithelial cells of the gut and lung

TNFα

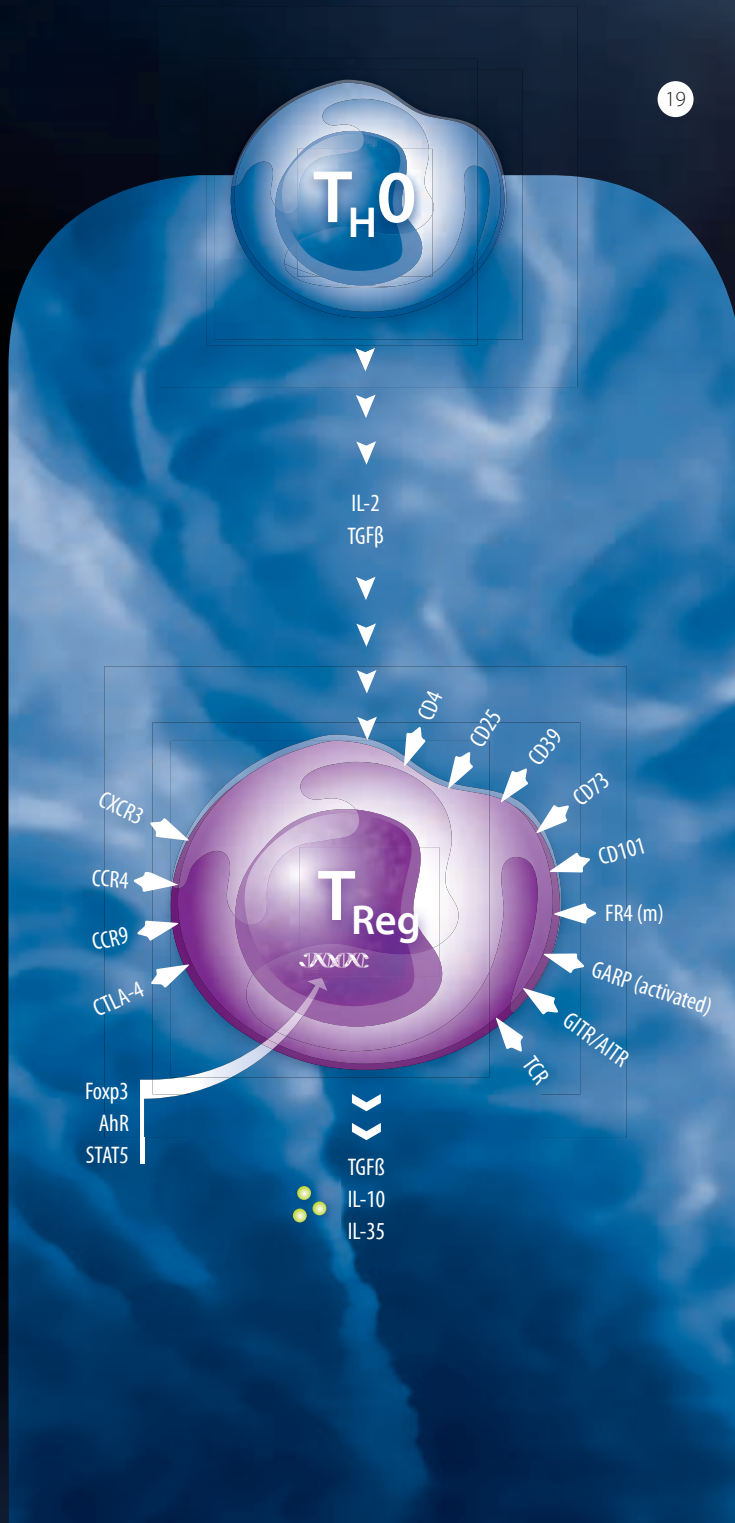
- Potent, pleiotropic immune activator and regulator of immune cell function

Regulatory T Cells

T_{Reg}

Regulatory T (T_{Reg}) cells are specialized $CD4^+$ T cells that function to maintain self-tolerance and immune homeostasis by suppressing the activation, proliferation, and effector functions of various immune cells. Historically, T_{Reg} cells were broadly classified as either natural (i.e., derived in the thymus) or induced (i.e., derived in the periphery). However, because $CD4^+Foxp3^+$ T cells are not homogeneous in their gene expression, phenotype, or suppressive mechanism, it is likely that more than two types of T_{Reg} cells exist. Thymically-derived $CD4^+CD25^+Foxp3^+$ T_{Reg} cells are a relatively homogeneous population until they migrate out into the periphery, where a subpopulation of these cells can develop phenotypic characteristics similar to conventional memory and effector T cells. This phenotypic change enables their subsequent migration to lymphoid and non-lymphoid tissues to maintain proper immune homeostasis. In the periphery, T_{Reg} cells may develop from conventional T cells (i.e., those that exited the thymus as $CD4^+CD25^-Foxp3^-$). Depending on the experimental model system studied, not all induced T_{Reg} cells express Foxp3 or CD25. Reports also demonstrate that, unlike thymically-derived T_{Reg} cells, induced T_{Reg} cells do not express high levels of Helios. Contrary to conventional T cells, T_{Reg} cells express both GARP and LAP/TGFβ transiently on their cell surface upon TCR activation. Additional T_{Reg} subsets can be defined based on the expression of chemokine receptors and adhesion molecules.

There is increasing evidence that T_{Reg} cells mediate their suppressive function through a variety of different mechanisms, suggesting that there is functional specialization depending on the type of immune response and where it is localized. One mechanism involves the secretion of IL-10, which serves to directly or indirectly inhibit effector T cell responses. T_{Reg} cells also secrete IL-35 and TGFβ to induce conventional CD4+ T cells to differentiate into T_{Reg} cells, thereby skewing the ratio of T_{Reg} to T helper cells during an immune response. Equally as important, cell surface molecules such as CTLA-4 also participate in T_{Reg} cell-mediated suppression. CTLA-4 inhibits dendritic cell (DC)-mediated T cell stimulation by binding to CD80 and CD86, which leads to downregulation of these co-stimulatory molecules on the DC and induction of indoleamine 2,3-dioxygenase (IDO), an enzyme that depletes



tryptophan from the microenvironment. Interestingly, there is emerging evidence that T_{Reg} cells use master regulators typically associated with specific T helper subsets to also regulate the immune responses customarily performed by those subsets. Thus, understanding the mechanisms by which T_{Reg} cells exert their suppressive function has broad implications for drug development strategies aimed at treating cancer, diabetes, and other autoimmune diseases.

Master Regulator of Differentiation

Foxp3

Differentiation Profile

IL-2

- Support the development of T_{Reg} in the thymus and maintain peripheral homeostasis by signaling through CD122 (IL-2Rβ)

TGFβ

- Induces Foxp3 expression. Necessary for conversion of T_H0 cells to T_{Reg} in the presence of antigen stimulation of the appropriate level

Cell Marker Profile

CD4
CD25
CD39
CD73
CD45RO
CD121a (IL-1R1)
CD121b (IL-1R2)
CD127 ^{low}
CD134 (OX40)
CD137 (4-1BB)
CD152 (CTLA-4)
CD357 (GITR/AITR)
Foxp3
FR4 (m)
GARP (activated)
Helios
LAP/TGFβ (activated)
TIGIT

Secreted Cytokine Profile

IL-10

- Inhibits cytokine production by T cells, macrophages and dendritic cells
- Suppresses $T_H1/2$ cell proliferation via inhibition of IL-2
- Down regulates MHC class II on monocytes, impairing antigen presentation for proper activation of T cells

IL-35

- Enhances T_{Reg} proliferation and IL-10 expression, while suppressing the development of T_H17 and T_H1 activated T cells

TGFβ

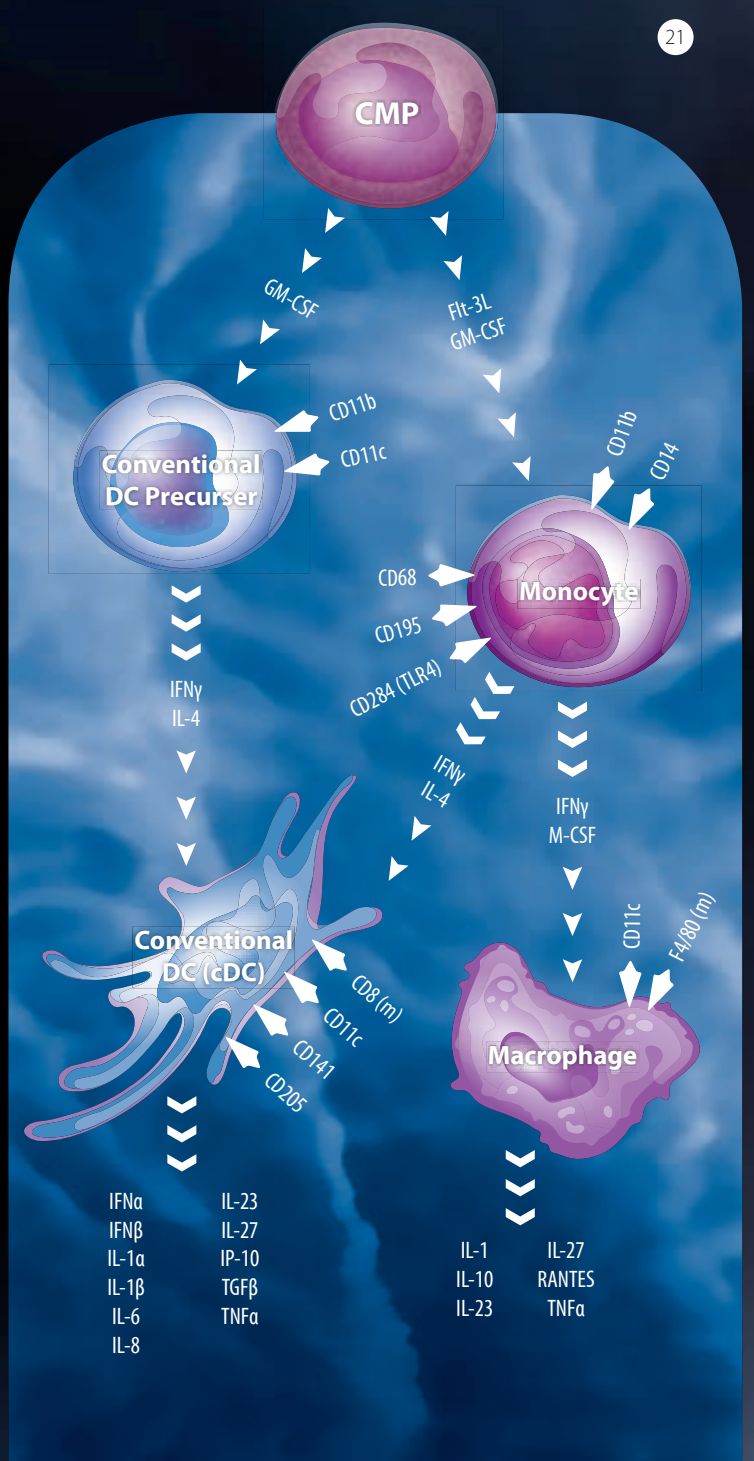
- Inhibits IL-1- and IL-2-dependent T cell proliferation
- Inhibits activation of both T helper and cytotoxic T cells
- Inhibits the secretion of IFNγ, TNFα and other interleukins
- Downregulates the expression of cytokine receptors on activated T cells
- Inhibits the proliferation of macrophages and monocytes and limits their production of reactive oxygen and nitrogen species

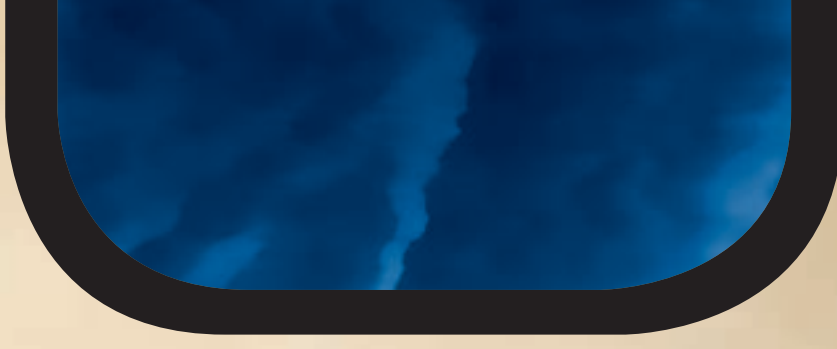
Monocytes, Macrophages, and Dendritic Cells

Monocytes, macrophages, and dendritic cells (DCs) are innate immune cells that arise from myeloid precursors that act as professional phagocytes. Macrophages and DCs are also termed antigen presenting cells (APCs) because of their ability to process and present protein derived antigens in the context of major histocompatibility complex (MHC) molecules. Mainly formed in the bone marrow, these cells circulate in the blood and can migrate into tissue. The migration of monocytes into tissue causes cell differentiation into tissue resident macrophages such as brain microglia, bone osteoclasts, epidermal Langerhans cells, and liver kupffer cells.

Macrophages are a heterogeneous population comprised of M1 or classically activated pro-inflammatory cells, M2 or alternatively activated anti-inflammatory, and various tissue specific macrophages. The cytokines released by macrophages play a major role in the recruitment and activation of cytolytic cells to become effector cells that help destroy infected or cancerous cells.

Dendritic cells (DCs) include myeloid derived DCs and lymphoid derived plasmocytoid dendritic cells (pDC). In general, dendritic cells coordinate the context of antigen presentation to ensure the generation of an appropriate immune response. Like macrophages, DCs are a very heterogeneous cell type. In mice, both CD8+ and CD8- DCs have been described with distinct functions. Although this discrimination of CD8+ and CD8- DCs is not found in humans, it has recently been proposed that CD141+ cells represent the functional equivalent of CD8+ DCs in humans. In addition to their role in activating naïve T cells, DCs are thought to play a critical role in guiding the differentiation of regulatory T cells as well as the development of T cell tolerance. The critical role that dendritic cells play in shaping the functional T cell response to antigenic stimulation makes them attractive targets for immune-modulating therapies for Graft-versus-host disease (GVHD), autoimmune disease, and anti-cancer therapies.





Master Regulator of Differentiation

Candidates: PU.1 & miR-424

Macrophage

Differentiation Profile

- FLT3L
- GM-CSF
- M-CSF

Cell Marker Profile

- CD11b
- CD14 (mono)
- CD16
- CD32
- CD68
- CD85a (ILT5)
- CD163
- CD169
- CD195 (CCR5)
- CD204
- CD206
- CD282 (TLR2)
- CD284 (TLR4)
- CD286 (TLR6)
- CD354 (Trem-1)
- Clec Family
- F4/80 (m)
- HLA-DR

Secreted Cytokine Profile

- CXCL9
- CXCL10
- CXCL11
- G-CSF
- GM-CSF
- IFNβ
- IL-1α
- IL-1β
- IL-6
- IL-8
- IL-10
- IL-12p40 & p70
- IL-18
- IL-23
- IL-27 (IL-27 EBI3 & IL-27 p28)
- M-CSF
- MIP-2α (CXCL2)
- RANTES (CCL5)
- TNFα

Dendritic

Differentiation Profile

- GM-CSF
- IFNγ
- IL-4

Cell Marker Profile

- CD1a
- CD8 (m)
- CD11c
- CD80
- CD83
- CD85 family (ILTs)
- CD86
- CD141 (h)
- CD169
- CD172
- CD184 (CXCR4)
- CD197 (CCR7)
- CD205
- CD206
- CD207
- CD209
- CD215 (IL-15R)
- CD282 (TLR2)
- CD284 (TLR4)
- CD286 (TLR6)
- Clec Family (ex: 9a, 12a)
- CCR7

Secreted Cytokine Profile

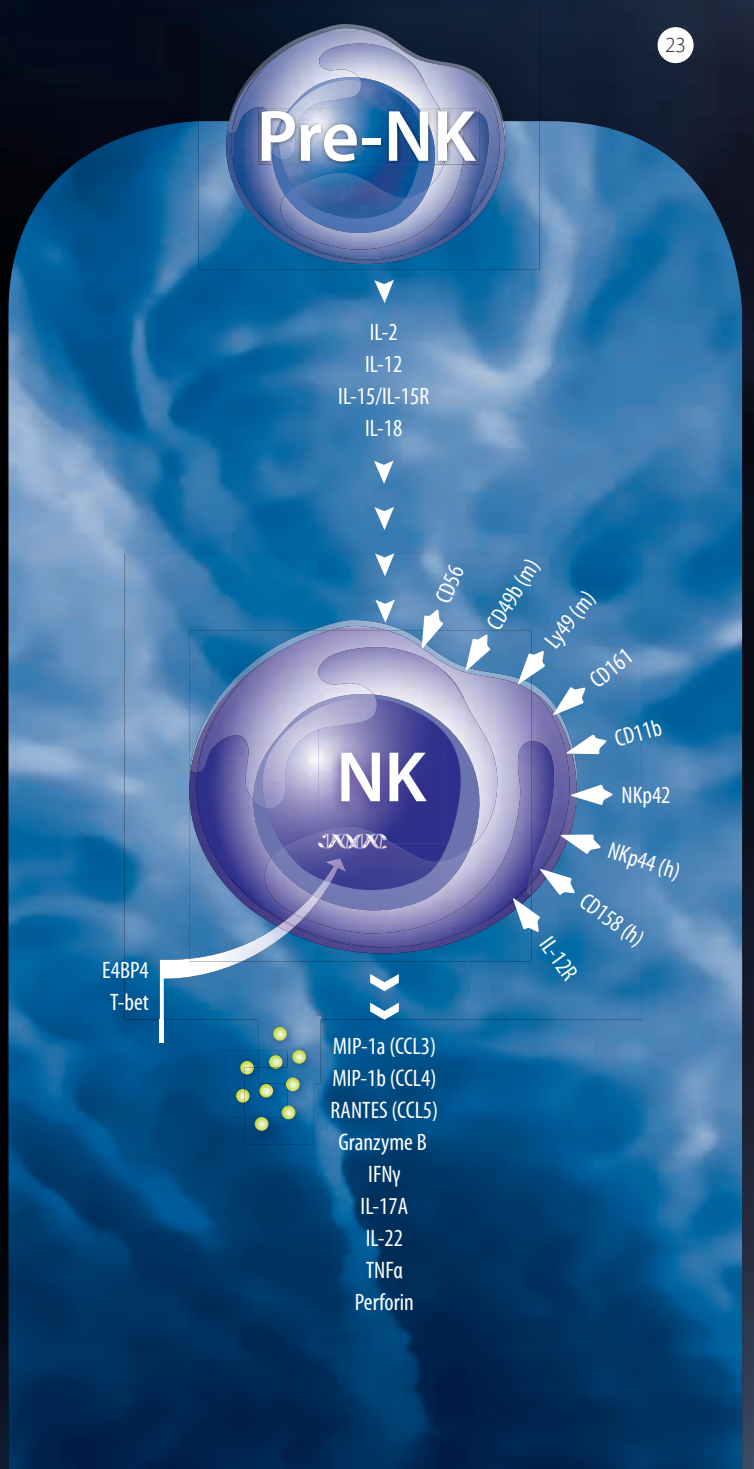
- GM-CSF
- IFNα
- IFNβ
- IL-1α
- IL-1β
- IL-6
- IL-8
- IL-10
- IL-12
- IL-15
- IL-18
- IL-23
- IL-27
- IP-10
- M-CSF
- RANTES (CCL5)
- TGFβ
- TNFα

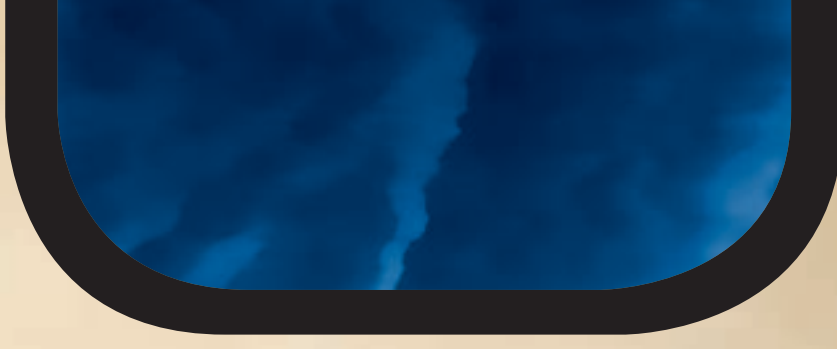
Natural Killer Cells

Natural killer (NK) cells are lymphoid cells poised and ready to assist in the destruction of virally infected cells and tumor cells from the body. Unlike most lymphoid cells, NK cells are part of the innate immune system and mediate their effect in an antigen independent manner that in general does not give rise to immunological memory or protective immunity. NK cells become activated upon stimulation by the cytokines IL-2, IL-15, IL-15RA in complex with IL-15, IL-18 and IL-12 to produce a large variety of cytokines and chemokines that includes IFNγ, TNFα, IL-17 and IL-22 to name a few. Similar to cytolytic CD8+ T cells, NK cells contain a variety of proteins that mediate the destruction of target cells by inducing a program of apoptotic cell death. NK cells are characterized by the presence of cytoplasmic granules that contain proteins such as perforin and granzymes. Perforin creates holes in the target cell membrane and the granzymes move into the target cell to initiate the apoptotic process via the induction of caspases. Granzyme B is the most characterized, but others such as A through M, are also active in initiating the apoptotic process.

NK cells, although derived from the same lineage as T and B cells, do not express an antigen specific receptor such as a T cell receptor or a B cell receptor. However, to recognize their targets, NK cells are equipped with a battery of receptors that bind to specific components present at the surface of bacterias, virally-infected cells, stressed cells, or cancer cells. NK cells are characterized by the expression of CD56 (both high and low levels) and the KIR family receptors in humans and CD49b and Ly49 family members in mice. The repertoire of receptors can be activating or inhibiting thereby allowing a unique and strictly controlled response by the NK cell.

NK cells have been shown to play a beneficial role in suppressing graft-versus-host disease (GVHD) in animal models. In autoimmune disease, NK cells can have a dual role of disease-promoting and disease-controlling. Additionally, the role can change depending on the stage of the disease. Multiple sclerosis and systemic lupus erythematosus (SLE) studies indicate NK cells play a disease-controlling role.





Master Regulator of Differentiation

E4BP4

Stimulants to Mature/Activate

IL-2
- Augments NK cell activity and boosts its cytolytic activity by activating various kinase pathways

IL-12
- Induced activation, stimulates cytotoxicity, and production of IFNγ and TNF

IL-15R/IL-15
- Involved in proliferation, accumulation, and survival

IL-18
- Upregulates NK cell cytotoxicity

Cell Marker Profile

CD16
CD25 (w/activation)
CD49b (m)
CD56 (h)
CD94
CD158 family (KIR)(h)
CD160
CD161
CD181 (CXCR1)
CD183 (CXCR3)
CD184 (CXCR4)
CD186 (CXCR6)
CD192 (activated)
CD195 (CCR5)
CD197 (CCR7)
CD212 (IL-12R)
CD244
CD314 (NKG2D)
CX3CR1
Eomes
KLRG1
Ly49 Family (m)
NK1.1
NKG2A
NKp30 (human and only certain breed of mice)
NKp42
NKp44 (h)
NKp46
T-bet

Secreted Cytokine Profile

Granzyme B (as well as A - M)
- Induces target cell death by apoptosis

IFNγ
- Inhibits proliferation of Th2 cells and enhances proliferation of activated B cells

IL-17A
- Regulates local tissue inflammation

IL-22
- Regulates the production of acute phase proteins

MIP-1α (CCL3)
- Plays in recruitment of leukocytes, particularyly CD8+ T cells, to stimulate strong antigen specific responses

MIP-1β (CCL4)
- Plays in recruitment of leukocytes, particularyly CD4+ T cells, to promote antibody response

Perforin
- Creates holes in target cell membrane

RANTES (CCL5)
- Initates leukocyte recruitment and is involved in proliferation and activation of certain cell types

TNFα
- Involved in regulation of cell survival and pro-inflammatory properties

Cytokine Target Listing

TARGET ANALYTE	SPECIES	ANTIBODIES				PROTEINS	IMMUNOASSAYS		
		PURIFIED	VIOLET LASER	BLUE LASER	RED LASER		COAT-IT-YOURSELF	PRE-COAT	MULTIPLEX
Activin A (INHBA, Inhibin beta A) Activin A is a member of the TGFβ superfamily of proteins. Activins are dimeric proteins formed by the association of two of the four existing β subunits, βA, βB, βC, and βE. These subunits are shared with the inhibin proteins, which are heterodimers of one β and one α chain. Activin A is a homodimer of two 13 kDa βA subunits, which can also associate with βB or βC to form Activin AB or AC, respectively. Activin A is expressed by various cell types and exhibits pleiotropic effects including the regulation of metabolism, homeostasis, cell proliferation and differentiation, apoptosis, and tissue healing. Activin A has been recently reported to work in synergy with TGFβ to promote the induction of antigen specific iT_{Reg} cells leading to inhibition of T_H1 and T_H2-mediated responses.	Human					•			
APRIL (CD256, TNFSF13, Tumor necrosis factor ligand superfamily member 1) APRIL (A Proliferation-Inducing Ligand) is a member of the tumor necrosis factor family and is closely related to BAFF, both of which activate their receptors and transmit survival and growth signals to B cells. In its membrane bound form, APRIL is a homotrimeric type II transmembrane protein. It is proteolytically processed to produce a soluble cytokine. In their soluble forms, both APRIL and BAFF bind to the receptors BCMA and TACI, respectively. APRIL appears to have direct connections to various diseases that include cancer and arthritis with higher levels of APRIL expression seen in various tumors and APRIL-transfected cells showing an increased rate of tumor growth. Concerning arthritis, local production of APRIL is found in the arthritic joints of patients with inflammatory arthritis.	Human							•	
B18R (Vaccinia Virus-Encoded Neutralizing Type I Interferon Receptor; Type I IFN inhibitor) B18R is a virally-encoded protein that acts as a decoy receptor for Type I Interferons (IFNα, IFNβ, IFNε, κ, τ, Δ, ζ, ώ, ν), thereby allowing viral replication by inhibiting IFNα1 and IFNα2 responses. B18R was recently identified to enable increased cell viability during RNA transfection protocols designed to convert human somatic donor cells into iPSCs via direct delivery of synthetic mRNAs for OCT4, SOX2, KLF4 and MYC (OSKM) and Lin28 with the aim to enable highly efficient reprogramming of somatic cells to pluripotency. This allows for re-directed differentiation toward a desired lineage while removing the risk of genomic integration and insertional mutagenesis inherent to DNA-bases methodologies and eliminates the need for virus-based approaches. iPSCs represent a widely available, non-controversial and practically infinite source of pluripotent cells.	All Species					•			
BAFF (CD257, BLyS, Tumor necrosis factor ligand superfamily member 13B) BAFF (B cell activating factor belonging to the TNF family) is a TNF family member. BAFF/BLyS is a B lymphocyte stimulatory molecule that induces B cell proliferation and immunoglobulin secretion. Like APRIL, it is heterotrimeric transmembrane protein that is proteolytically processed to produce a soluble cytokine. BAFF contains a cytoplasmic domain, transmembrane domain and extracellular domain that is cleaved to produce the soluble form detectable in serum. Both BAFF and APRIL bind to the receptors BCMA and TACI, while only BAFF binds to the BAFF Receptor (BAFFR). Both BAFF and APRIL are upregulated by type I interferons, IFNγ, IL-10, G-CSF, and certain TLRs. BAFF functions as a key regulator of B-cell homeostasis and increased levels of BAFF in human sera have been found in primary biliary cirrhosis, autoimmune diabetes, rheumatic diseases, and Sjogren's syndrome.	Human	•		•		•		•	
BMP-2 (Bone morphogenetic protein 2) BMP-2 (Bone Morphogenic Protein 2) is one of fifteen BMP family members that belong to the TGFβ superfamily of growth factors. The BMPs were first identified as the active factors in demineralized bone matrix, with transcripts later being discovered in many other types of tissue. BMPs are synthesized as large precursor molecules and that get cleaved allow them to and subsequently homo- or hetero-dimerize and exhibit functional activity. BMP responsiveness appears to be limited to multipotent and immature cells. The BMPs are essential for osteogenesis and organogenesis during embryonic development, and also play a role in fracture and wound healing in adults.	Human					•			
BDNF (Brain-derived neurotrophic factor) BDNF is a member of the neurotrophin family. BDNF is synthesized as pre-proBDNF, followed by cleavage to proBDNF. Although further processing generates the mature, 14 kDa protein, proBDNF is biologically active and is secreted from synaptic vesicles along with the mature form. BDNF is widely expressed in the central nervous system where it acts in an autocrine and paracrine manner on several classes of neurons. BDNF signaling occurs mainly through the receptor tyrosine kinase TrkB, although binding to the lower-affinity receptor p75NTR has also been demonstrated. Functionally, BDNF promotes neuronal survival and differentiation, it is involved in axonal growth and dendritic growth and morphology, and it is known to be a major regulator of synaptic transmission and plasticity at adult synapses in many regions of the CNS. Additionally, BDNF has been shown to play a critical role in memory formation and synaptic regulation.	Human					•			

CTGF (Connective Tissue Growth Factor, CCN2) CTGF is a member of the CCN family. CTGF is a secreted protein produced by umbilical veins and vascular endothelial cells. CTGF possesses an Insulin-like Growth Factor (IGF)-binding domain, a thrombospondin type 1 domain, and a cysteine knot region. CTGF plays important roles in the proliferation and differentiation of chondrocytes, induces angiogenesis, and promotes cell adhesion in fibroblasts, endothelial, and epithelial cells.	Human					•			
CXCL13 (BLC, BCA-1) CXCL13, or BLC (B-lymphocyte chemoattractant, mouse equivalent of human B cell-attracting chemokine-1), is a 12 kDa an ELR-CXC chemokine. CXCL13 is the ligand for CXCR5. As such, CXCL13 is a chemoattractant for primary B-cells and T follicular helper cells (T_{FH}). It is thought that the increased CXCL13 provides selection signals to both germinal center B cells and T_{FH} cells (see T_{FH} cells in the T_{FH} section). Concomitant with decreased CCR7 expression that is greatly reduced in T_{FH} cells, there is loss of responsiveness to the chemokines CCL19 and CCL21. This further helps enhance the migration of T_{FH} cells toward the CXCL13-rich areas increasing the probability of antigen-specific contact between the specific T_H cells and the antigen primed B cells. This allows for T_{FH} cells homing to regions rich in CXCL13 such as follicular regions and remove the promotion the extrafollicular placement due to CCL19 and CCL21-rich areas in the lymphoid tissue. CXCL13 may also be a good diagnostic biomarker for prostate cancer and its advancement, but futher studies are need to further prove/disprove this correlation.	Mouse	•							
EGF (Epidermal Growth Factor) EGF stimulates the growth and differentiation of many cells types and plays a role in the development and regeneration of various tissues by binding to the receptor tyrosine kinase EGFR that results in receptor dimerization, autophosphorylation, and subsequent signaling cascade down many pathways that include the MAPK and AKT pathways. EGF, like many other members of its family, is synthesized as type I transmembrane protein of 130 kDa with an N-terminal extension called the EGF module, a short juxtamembrane stalk, a hydrophobic transmembrane domain, and a cytoplasmic tail. As a result of proteolytic cleavage, the soluble EGF is released into the extracellular space. Once released, it stimulates the proliferation of epidermal and epithelial cells such as fibroblasts and kidney epithelial cells, endothelial cells, as well as embryonic cells. Blocking the release of EGF receptor ligands inhibits growth and migration in several EGF receptor-dependent cell lines and greatly retards wound re-epithelialization due to impaired keratinocyte migration. Overexpression of one or more receptors and/or ligands is a feature of the majority of human carcinomas and epithelial cancers.	Human					•		•	•
	Mouse					•			
Eotaxin (CCL11, C-C motif chemokine 11) Eotaxin-1 is a member of the CC-family of chemokine. It is expressed in multiple tissue and cell types including smooth muscle cells, chondrocytes, eosinophils, fibroblasts, endothelial cells, and epithelial cells where it plays a fundamental role in the development of allergic responses. Eotaxin-1 is most often induced by various inflammatory cytokines such as IL-1, TNFα and IFNγ and binds to the chemokine receptor CCR3. Eotaxin-1 is also believed to be important to many diseases as it has a role in numerous eosinophil-associated gastrointestinals disorders as food allergy, parasitic infections, allergic colitis and inflammatory bowel disease has been described.	Mouse	•					•	•	
Erythropoietin (EPO) EPO is the prime physiological regulator of red blood cell production. EPO is a hormone produced by cells in the kidney that are sensitive to low blood oxygen levels and functions as a cytokine to promote the formation of red blood cells in the bone marrow by binding to the Epo receptor (EpoR) on erythroid progenitors in bone marrow. This binding elicits proliferation, maturation, and differentiation of red blood cells; thereby increase the oxygen-carrying capacity of the blood. Measurement of serum immunoreactive EPO suggests that overproduction of EPO can be an adaptive response to conditions producing tissue hypoxia, such as smoking chronic obstructive pulmonary disease, renal hypoxia or cyanotic heart disease. Elevated levels of EPO can be detected in polycythemia, a disorder in which there is an excess of red blood cells as well as in patients suffering from various neoplastic diseases, such as renal carcinomas and benign renal tumors, liver carcinomas and hepatomas, and cerebellar hemangioblastomas. Conversely, lower than normal levels of EPO are observed in chronic renal failure and in various forms of anemias. As such, the measurement of EPO in the blood is useful in the study of bone marrow disorders and kidney disease.	Human					•		•	

TARGET ANALYTE	SPECIES	ANTIBODIES				PROTEINS	IMMUNOASSAYS		
		PURIFIED	VIOLET LASER	BLUE LASER	RED LASER		COAT-IT-YOURSELF	PRE-COAT	MULTIPLEX
FGF-1 (FGF acidic, acidic Fibroblast Growth Factor) FGF-1 is a member of a highly conserved family of heparin-binding proteins. Members of the FGF family share four common tyrosine kinase receptors, FGFR 1-4, and require the binding of a second surface protein, the ubiquitously expressed heparin sulfate proteoglycans, in order to fully activate these receptors. FGF acidic and FGF basic share similar biological functions and expression of both has been detected in several cell types, including fibroblasts, macrophages, endothelial cells, epithelial cells, and neurons. Both are unique from other members of the family in their lack of a signal sequence peptide necessary for the secretory pathway, indicating that secretion occurs via an alternate route. The secreted form of FGF-1 is a homodimer that is cleaved into its active form following release from the cell. FGF family members affect the proliferation, differentiation, mobility, and survival of several cell types, including fibroblasts, osteoblasts, smooth muscle cells, and neuroblasts. They are particularly important in embryonic development as triggers of neurogenesis, angiogenesis, and neovascularization. Both FGF acidic and FGF basic remain active during adulthood and play a role in bone formation and tissue repair. FGF family members are also implicated in many types of cancer and may contribute to tumor vascularization.	Human					•			
	Mouse					•			
FGF-2 (basic FGF, basic Fibroblast Growth Factor) FGF-2 is a member of the FGF family of growth factors that exists in several isoforms, and although they are equally active, only the 18 kDa form is secreted while the 23 kDa form localizes to the nucleus. FGF-2 is a ligand for four common tyrosine kinase receptors, FGFR 1-4, and require the binding of a second surface protein, the ubiquitously expressed heparin sulfate proteoglycan, in order to fully activate these receptors. FGF family members affect the proliferation, differentiation, mobility, and survival of several cell types, including fibroblasts, osteoblasts, smooth muscle cells, and neuroblasts. FGF-2 expression has been detected in several cell types, including fibroblasts, macrophages, endothelial cells, epithelial cells, and neurons. FGF-2 is particularly important in embryonic development as triggers of neurogenesis, angiogenesis, and neovascularization and has most recently been studied for its ability to maintain the proliferation of embryonic stem cell cultures in an undifferentiated state. Some members of the family, including FGF-2, remain active during adulthood and play a role in bone formation and tissue repair. FGF family members are also implicated in many types of cancer and may contribute to tumor vascularization.	Human					•			•
	Mouse					•			
FGF-8 (FGF-8b, Fibroblast Growth Factor 8) FGF-8 is a member of the highly conserved fibroblast growth factor family of heparin-binding proteins that affect the proliferation, differentiation, mobility, and survival of several cell types, including fibroblasts, osteoblasts, smooth muscle cells, and neuroblasts. Like FGF-2, it binds to FGFR 1-4 and requires the binding of heparin sulfate proteoglycan to fully activate these receptors. FGF-8 exists in eight isoforms designated a-h, although only a, b, e, and f are present in humans. FGF-8 is active mainly during embryonic development and functions to promote skeletal growth and limb bud formation. Expression in adults is limited to tissues involved in spermatogenesis and oogenesis as well as some cancers. It is the first member of the family to have been identified in breast cancer and is believed to contribute to its progression in an autocrine manner.	Human					•			
Flt3 Ligand (FLT3L, Flk2 Ligand, Fms-related tyrosine kinase 3 ligand) Flt3 Ligand is a growth factor that regulates proliferation of early hematopoietic cells. Flt3 Ligand binds to cells expressing the tyrosine kinase receptor Flt3. By itself, Flt3 Ligand does not stimulate proliferation of early hematopoietic cells. Instead, it synergizes with other colony-stimulating factors (CSFs) and interleukins to induce growth and differentiation. Unlike CSFs, however, Flt3 Ligand exerts no activity on mast cells. Multiple isoforms of Flt3 Ligand have been identified. The predominant biologically active form is anchored to the cell surface as the extracellular domain of a transmembrane protein. The membrane-bound isoform can be proteolytically cleaved to generate a biologically active soluble version. Human and mouse Flt3 Ligand show cross-species activity.	Human					•			
	Mouse					•			
Fractalkine (CX3CL1, neurotactin, C-X3-C motif chemokine 1) Fractalkine is a membrane-bound CX3C chemokine. The mature protein is part of a 397-amino acid precursor consisting of a chemokine domain (76 amino acids), a mucin stalk of 241 residues, a putative transmembrane domain (18 amino acids), and an cytoplasmic tail of 37 amino acids. Within the chemokine domain the first two cysteine residues are separated by 3 amino acids. Fractalkine mRNA is found at high concentrations in the brain, and also in kidney, lung and heart. Fractalkine is chemotactic for monocytes and other leukocytes including NK cells and may play a role in brain inflammation.	Human	•							
	Mouse	•							

G-CSF (Granulocyte Colony-Stimulating Factor, CSF3) G-CSF is a member of the IL-6 cytokine family. G-CSF is produced by activated monocytes, macrophages, endothelial cells, fibroblasts, astrocytes, and osteoblasts in response to infection and inflammatory mediators such as IL-1β, IL-17, TNFα, and LPS, as well as various transformed cells such as carcinoma cells and myeloblastic leukemia cells. G-CSF has been shown to have specific effects on the proliferation, differentiation, and activation of hematopoietic cells. G-CSF binding activates the JAK/STAT signaling pathway that results in the activation and mobilization of granulocytic precursors from the bone marrow and supports the proliferation, activation, and differentiation of neutrophils in the blood. Clinically, the use of G-CSF has been approved for several therapeutical applications including the treatment of neonatal infections, therapy of acute myocardial infarction, therapy in chronic autoimmune neutropenia, treatment of acute myeloid leukemias, Sweet's syndrome, and AIDS. G-CSF has further been shown to be a marker protein for different carcinomas such as bladder cancer. (34, 75)	Human	•		•		•		•	•
	Mouse	•			•	•			
GDNF (Glial Cell Derived Neurotrophic Factor) GDNF a member of the TGFß superfamily, is a neurotrophic factor that promotes the survival of various neuronal populations in both the central and peripheral nervous systems during their development. Neuronal subpopulations affected by GDNF include motor neurons, midbrain dopaminergic neurons and Purkinje cells. Due to GDNF conservation, human and mouse GDNF show cross-species activity.	Human					•			
GITR Ligand (GITRL, TNFSF18, Tumor necrosis factor ligand superfamily member 18) GITRL is a type II transmembrane protein of the TNF superfamily and is expressed by endothelial cells and peripheral blood monocytes. GITRL binds to GITR/AITR, belonging to the Glucocorticoid-Induced TNFR family gene, also known as TNFRSF18. In naïve mice, GITR is expressed predominantly by CD4+CD25+ T regulatory cells (T_{Reg}) and by CD25+ CD4+ CD8- thymocytes. Stimulation with GITRL abrogates T_{Reg} cell-mediated suppression. The removal of GITR-expressing T_{Reg} cells or the administration of GITR antibody (DTA-1) resulted in organ specific autoimmune disease. Interaction of GITR, expressed by CD4+CD25+ T_{Reg} cells, with GITRL is important for cross-talk between T lymphocytes and endothelial cells.	Mouse	•		•					
GM-CSF (Granulocyte-Macrophage colony stimulating factor, GMCSF, Colony-stimulating factor, CSF2) GM-CSF is a differentially glycosylated growth factor produced by a wide variety of tissue types, including fibroblasts, endothelial cells, T cells, macrophages, mesothelial cells, epithelial cells and various tumor types. The biological effects of GM-CSF are mediated through its binding to cell surface receptors that widely expressed on hematopoietic cells, as well as some non-hematopoietic cells such as endothelial cells. GM-CSF stimulates proliferation, activation, and differentiation of macrophages, granulocytes, neutrophils, eosinophils, and monocytes. In most of these tissues, inflammatory mediators, such as IL-1, IL-6,TNFa, or endotoxin, are inducers of GM-CSF gene expression. Monitoring of GM-CSF levels may be porgnostic in human prostate cancer, poorly healing wounds, thyroid carcinoma, severe mucositis, fungal infections, AIDS, bone marrow transplantation, renal cell carcinoma, prostate cancer, acute lymphoblastic leukemia pulmonary inflammation, hematological malignancies, infection, lung cancer. (8, 19, 34, 75)	Human	•		•	•	•	•	•	
	Mouse	•		•		•	•	•	•
	Rat						•	•	•
Granzyme A (GZMA) Granzymes are exogenous serine proteinases released from cytoplasmic granules of cytotoxic lymphocytes (CTLs) and NK cells. The name "granzymes" is derived from: granules + enzymes. Upon binding of the CTL to a target cell, the contents of the granules are released in the intercellular space where perforin perforates the target cell membrane by forming transmembrane pores. Through these pores, granzymes enter the cytosol of the target cell to intiate the apoptotic pathway. Not all granzymes enter the target cell as some are present in the peripheral blood and other biological fluids. Though detectable amounts of granzymes have been found to circulate in healthy volunteers, increased levels serve as biomarkers for many diseases including patients with systemic viral infections such as EBV, HIV, CMV, hepatitis A and Dengue fever. Additionally, lymphomas and carcinomas show a high percentage of Granzyme B positive CTLs in glands of patients suffering from Hodgkin's disease which correlates with a poor prognosis. In rheumatoid arthritis, soluble Granzyme A and B levels are increased in synovial fluid; significantly higher than levels in patients with osteoarthritis. In transplantation, Granzymes are likely involved in the acute rejection of kidney-transplants, as infiltrating lymphocytes in the rejected kidney strongly express granzymes.	Human							•	
Granzyme B (GZMB) Granzymes are exogenous serine proteinases released from cytoplasmic granules of cytotoxic lymphocytes (CTLs) and NK cells. The name "granzymes" is derived from: granules + enzymes. Upon binding of the CTL to a target cell, the contents of the granules are released in the intercellular space where perforin perforates the target cell membrane by forming transmembrane pores. Through these pores, granzymes enter the cytosol of the target cell to intiate the apoptotic pathway. Granzyme B has been called CTLA-1 (cytotoxic T lymphocyte-associated serine esterase 1) based on identification of mRNA in various cytotoxic T cells, but not observed in non-cytotoxic lymphoid cells. Granzyme B is crucial for the rapid induction of target cell death by apoptosis, induced by interaction with cytotoxic T cells. Granzyme B activates the intracellular cascade of caspases finally resulting in the killing of the target cells.	Human			•				•	
	Mouse	•	•	•	•		•	•	

TARGET ANALYTE	SPECIES	ANTIBODIES				PROTEINS	IMMUNOASSAYS		
		PURIFIED	VIOLET LASER	BLUE LASER	RED LASER		COAT-IT-YOURSELF	PRE-COAT	MULTIPLEX
GROα (CXCL1, Growth-regulated alpha protein) GROα is a pro-inflammatory CXC chemokine first identified by its constitutive overexpression in some tumors. It is closely related to GROβ (CXCL2) and GROγ (CXCL3) with which it shares 90% and 86% sequence homology, respectively. These proteins, along with IL-8 (CXCL8), are critical for neutrophil mobilization and degranulation, as well as vascular permeabilization and angiogenesis. GROα is secreted by monocytes, epithelial cells, and fibroblasts in response to pro-inflammatory stimuli such as LPS, IL-1β, and TNFα. Signaling occurs through the GPCR CXCR2, which is shared with both GROβ and GROγ. Overexpression of GROα has been observed in many malignant tumors, where it contributes to tumor vascularization and metastasis.	Human					•			
	Mouse								•
HGF (Hepatocyte Growth Factor, scatter factor) HGF is a paracrine multifunctional growth factor. HGF is produced in the liver as well as human platelets, kidney, serum, placenta, lung and spleen. HGF is a mesenchymally derived heparin-binding glycoprotein that is secreted as a single-chainbiologically inert precursor. HGF is coverted to its biologically active pro-HGF form via proteolytic cleavage in response to various signals such as tissue damage. In its active form, HGF binds to and activates the receptor tyrosine kinase c-Met (HGFR) that is expressed in normal epithelium of almost every tissue as well as other cell types that include melanocytes, endothelial cells, microglial cells, neurons, hematopoietic cells, and a variety of tumor cell lines. Once bound, HGF acts as a mitogen, a motogen, and a morphogen as well as a potent anti-inflammatory agent that is involved in the inflammatory response by intercepting NFκB signaling and subsequently disrupting the expression of NFκB-dependent proinflammatory mediators. HGF is also a potent stimulator of angiogenesis and cancer metastasis through its interaction with c-Met to stimulate chemotaxis and growth of malignant cells. HGF is elevated in serum of liver disease patients, and also in patients with various kinds of cancers.	Human					•		•	•
	Mouse					•			
IFNα1/2 (Interferon-alpha1/2) IFNα is a type I interferon that is a pleiotropic agent that functions in anti-viral, anti-proliferative, and immunomodulatory activities. Type I IFNs inhibit growth-promoting cytokines, induce apoptosis, and inhibit cell proliferation. As such IFNα has a known role as an anti-neoplastic agent in the treatment of several cancers. In humans, the IFNα family comprises more than 20 genes and pseudogenes giving rise to 15 different functional gene products. IFNα is produced by monocytes, macrophages, lymphoblastoid cells, fibroblasts, and a number of different cell types following induction by viruses, nucleic acids, glucocorticoid hormones, and small molecules. IFNα binds to its receptor (IFNAR1/IFNAR2) on various cell types to trigger various pathways including JAK/STAT, p38, PKC, and IRS/PI3K. IFNα sensitizes T cells to IL-2 induced proliferation, enhances the cytotoxicity of γδ T cells, and promotion of NK cell cytotoxic activity against leukemic cells. IFNα is used as a biomarker for various immunotherapeutic approaches such as acute phase of a viral infection, juvenile polyarthritis, rheumatoid arthritis, lupus, ancylosing spondylitis, polychondritis, psoriatic arthritis, polymyalgia rheumatic, and scleroderma.	Human	•		•		•			•
	Mouse					•	•	•	•
IFNα4 (Interferon-alpha 4, IFNA4)	Mouse					•			
IFNβ (Interferon-beta , IFNB) IFNβ is classified as a type I IFN which is a group of structurally and functionally related proteins demonstrating anti-viral, anti-parasitic, and anti-proliferative activities. IFNβ is synthesized and secreted by fibroblasts and many other cell types in response to pathogens. IFNβ binds to type I interferon receptors and induces the upregulation of IRF-7 and activation of Rnase L that cleaves both viral and cellular single stranded mRNA, thereby limiting viral replication and dissemination.	Human	•							
IFNγ (Interferon-gamma, IFNG) IFNγ (Type II interferon) is a homodimeric glycoprotein that is produced by activated T, B and NK cells. IFNγ is produced during infection by cytotoxic T cells (CD8+) and by T_H1 cells where it preferentially inhibits the proliferation of T_H2, resulting in the preferential proliferation of T_H1 cells. IFNγ functions as an anti-viral and anti-parasitic agent and also acts in synergy with other cytokines, such as TNFα to inhibit the proliferation of normal and transformed cells. IFNγ induces immunomodulatory effects on a wide range of cell types that includes being a potent activator of mononuclear phagocytes, augmentation of endocytosis and phagocytosis by monocytes, and activation of macrophages to kill tumor cells. Additionally, it enhances the proliferation of activated B cells and can act synergistically with IL-2 to increase immunoglobulin light-chain synthesis. Finally, IFNγ activates neutrophils, NK cells and vascular endothelial cells. The role of IFNγ as a disease marker has been demonstrated for a number of different pathological situations including infections, autoimmune diseases, transplant rejection, allergy, and diabetes. (21, 22, 43)	Human	•	•	•	•	•	•	•	•
	Mouse	•	•	•	•	•	•	•	•
	Rat	•				•	•	•	•
	Monkey	•							
	Pig						•	•	

IFNλ (IL-28 and IL-29). See IL-28 and IL-29									
IFNω (IFN omega) IFNω is a major component of human leukocyte IFN with a contribution to its total antiviral activity estimated to be in the range of 10 -15 %, though the IFNω gene is not expressed in unstimulated cells. Viral infection results in expression of the gene, followed by its binding to the cell membrane receptor type I. IFNω anti-viral activity has been observed in various systems. Furthermore, IFNω has also been shown in correlation in human carcinoma cell lines. Immunomodulatory effects can as well be ascribed to IFNω. The physiological role of IFNω is currently not known. It is thought that the therapeutically administeration of IFNω may cause measurable serum concentrations in the corresponding patients and that the monitoring of these IFNω serum levels provides an important tool in therapy.	Human	•				•	•	•	
IGF-1 (Insulin-like Growth Factor I) IGF-1 is a member of the insulin-like growth factor family with potent mitogenic and metabolic effects. IGF-1 is produced in many cell types, but mainly in the liver and is secreted into the blood, where it circulates bound to one of six IGF-binding proteins (IGFBPs). Of these proteins, IGFBP-3 is present at the highest level in adults, and is responsible for carrying IGF-1 to target tissues and prolonging its half-life in circulation. In contrast, IGFBP-1 is the most important negative regulator of IGF-1. IGF-1 helps regulate metabolism of glucose, fatty acids, cartilage and bone, as well as growth hormone activity. This protein also plays important roles in Alzheimer's disease and tumor pathogenesis. IGF-1 and IGF-2 share 70% sequence identity.	Human					•			
	Mouse					•			
IL-1 (Interleukin-1) IL-1 is a pleiotropic T_H2 cytokine involved in inflammatory reactions and in immune responses. As its name denotes, IL-1 was the first interleukin described. IL-1 now represents both a gene/protein as well as a family of 11 cytokines that play important roles in innate and adaptive immune responses. The IL-1 family of cytokines includes IL-1α, IL-1β, IL-1Ra, IL-18, IL-33, and the less understood IL-1F5 - IL-1F10 (IL-36α, β, γ, δ and IL-37). IL-1 is a potent analyte of the innate immune system that is expressed by various immune cells such as T and B cells, neutrophils, mast cells, macrophages, monocytes, dendritic cells, and various other cell types such as adult T cell leukemias, fibroblasts, epithelial or endothelial cells, astrocytes, and dying cells. Both IL-1α and IL-1β both signal through the same receptor complex and have identical biological activities in solution. They differ in that IL-1β is produced by monocytes and macrophages and is secreted and circulates systemically, whereas IL-1α generally acts locally as it is associated with the plasma membrane of the producing cell. IL-1 is required for the differentiation and the subsequent maintenance of T_H17 cells from naive T cells. IL-1 and IL-18 enhance the secretion of IL-3, IL-5, IL-6, IL-13, and TNF by mast cells, but only in the presence of IgE or IL-3. On dendritic cells, it increases cytokine production and upregulation of MHC and co-stimulatory molecules. On macrophages, IL-1 increases cytokine production and phagocytosis. On neutrophils, IL-1 acts to increase survival, adhesion, and oxidative burst and protease release, and on basophils, IL-1 increases cytokine and histamine production. On mast cells, IL-1 aids in the maturation, cytokine production, survival, and adhesion and degranulation. IL-1α and IL-1β are important biomarkers. Normal serum has low levels of IL-1β, but elevated levels have been reported in a number of infectious disease conditions and in noninfectious inflammatory conditions such as Crohn's disease. In addition to elevated serum levels, IL-1 has been found in synovial fluids of patients with rheumatoid arthritis and in cerebrospinal fluid after neurological inflammation or insult. At the other end of the spectrum, low levels of IL-1 have been found in malnutrition and advanced neoplasia suggesting perhaps a complex immunological and physiological regulatory role for this cytokine. (8, 56, 65)									
IL-1α (Interleukin-1 alpha ,IL1F1, Hematopoietin-1) IL-1α is a pro-inflammatory cytokine that affects T-helper cells causing the induction of IL-2 secretion and the expression of IL-2 receptors, as well as causing B cells to promote cell proliferation and immunoglobulin synthesis. IL-1α is present in various biological fluids and the monitoring its levels is a valuable biomarker. Elevated serum or blood levels of IL-1α have been found in of several carcinomas such as head and neck cancer, pancreatic cancer and thyroid cancer, in experimental acute pyelonephritis, in acute viral hepatitis and in septic shock. Both elevations in serum levels and joint fluids (synovial fluids) are detected in rheumatoid arthritis. Increased plasma and CSF levels are found in patients with schizophrenia. Significantly elevated concentrations in gingival cervical fluid in subjects with peridantitis are detected. Urinary levels of IL-1α correspond to disease and therapy response in bladder cancer. (56)	Human	•		•		•		•	•
	Mouse	•		•		•	•	•	•
	Rat						•	•	•
IL-1β (Interleukin-1 beta, IL1F2, Catabolin) IL-1β is a pro-inflammatory cytokine expressed by monocytes, macrophages, and dendritic cells. It is synthesized in response to inflammatory stimuli as an inactive pro-form that accumulates in the cytosol. Cleavage of pro-IL-1β into the active protein requires the activation of inflammasomes, which are multi-protein complexes that respond to pathogens, stress conditions, and other danger signals. IL-1β signals through two receptors, IL-1RI and IL-1RII, both of which are shared with IL-1α. These cytokines play important roles in innate host defense by triggering the production of other pro-inflammatory cytokines in target cells and initiating acute-phase responses. Their activity can be moderated by IL-1 Receptor Antagonist (IL-1RA), a protein produced by many cell types that blocks receptor binding through competitive inhibition. Elevated levels of IL-1β have been associated with multiple inflammatory related disorders including type 2 diabetes, cardiovascular disease, rheumatoid arthritis, gout, and several rare auto-inflammatory diseases. (56)	Human	•		•		•	•	•	•
	Mouse	•		•	•	•	•	•	•
	Rat	•				•	•	•	
	Monkey							•	

TARGET ANALYTE	SPECIES	ANTIBODIES				PROTEINS	IMMUNOASSAYS		
		PURIFIED	VIOLET LASER	BLUE LASER	RED LASER		COAT-IT-YOURSELF	PRE-COAT	MULTIPLEX
IL-2 (Interleukin-2) IL-2 is a T_H1 cytokine that plays a central role in the activation and proliferation of lymphocytes that have been primed by antigens. IL-2 is pivotal for the expansion of most T cells, NK cells, and B cells during various phases of their response. IL-2 is made during T cell activation and fuels the growth of activated T cells. Apart from its most important role to mediate antigen-specific T lymphocyte proliferation, IL-2 also modulates the expression of IFNγ and MHC antigens, stimulates proliferation and differentiation of activated B cells, augments NK cell activity, and inhibits granulocyte-macrophage colony formation. IL-2 signals though various signaling pathways that include the activation of JAK/STAT5, the RAS/MAPK, and the PI3 Kinase pathways. These activations make IL-2 a known potent T cell growth factor, inducer of lymphokine-activated killer activity, boosts the cytolytic activity of NK cells, augmentation of Ig production, and an essential factor for the development of T_{Reg} cells. Even though IL-2 is a T_H1 cytokine, it is a critical regulator of T_H2 in a STAT5-dependent manner and an inhibitor T_H17 differentiation/ development. IL-2 is an important serum biomarker in several pathological situations such as cancer, infectious diseases, transplant rejection, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus and type I diabetes.(20, 22, 92, 100)	Human	•		•	•		•	•	•
	Mouse	•	•	•	•	•	•	•	•
	Rat					•	•	•	
	Monkey						•	•	
IL-3 (Interleukin-3, Mast cell growth factor, MCGF) IL-3 is produced by activated T cells, mast cells and eosinophils. IL-3 is a hematopoietic growth factor that stimulates colony formation of erythroid, megakaryocyte, neutrophil, eosinophil, basophil, mast cell and monocytic lineages. Most of these functions are enhanced or dependent on co-stimulation with other cytokines. Human and mouse IL-3 share only 29% sequence identity at the amino acid level and its bioactivity of IL-3 is highly species specific as human IL-3 does not appear to have activity on mouse cells.	Human					•			
	Mouse					•			
IL-4 (Interleukin-4, B-cell stimulatory factor 1) IL-4 is a T_H2 anti-inflammatory cytokine that is secreted by activated T_H2 and NKT cells, and to a lesser extent by T_H1 and mast cells. IL-4 exerts numerous effects on various hematopoietic cell types by biding to either type I or Type II IL-4R (the latter of which IL-13 also binds to and as such is also referred to as IL-13R). IL-4, by the means of STAT6 and GATA3, promotes T_H2 cell differentiation that produces IL-4, IL-5, and IL-13. In B cells, IL-4 promotes proliferation and differentiation, promotes immunological class switching to IgE and IgG1 isotypes (in conjunction with other signals such as CD40), and upregulates MHC class II and CD23 expression. In T and B lymphocytes, mast cells, and endothelial cells, IL-4 promotes survival, growth, and differentiation. In macrophages, IL-4 can inhibit the production of TNF, IL-1, and IL-6. With its relevance to disease, IL-4 is an immune-stimulating molecule. As such it is one of the more recent targets being studied for new asthma treatments. (62)	Human	•		•	•	•	•	•	•
	Mouse	•		•	•	•	•	•	•
	Rat				•	•	•	•	•
IL-5 (Interleukin-5, B-cell differentiation factor I, T-cell replacing factor) IL-5 is a T_H2 cytokine that acts as a hematopoietic growth factor that promotes proliferation, activation, and differentiation of eosinophils from bone marrow stem cells. In the human, IL-5 also supports generation of cytotoxic T cells, whereas in mice, IL-5 acts on B cells to induce IL-2R (CD25) expression on activated B cells, proliferation and secretion of IgM and IgA from endotoxin activated B cells.	Human	•		•		•	•	•	•
	Mouse	•		•		•	•	•	•
IL-6 (Interleukin-6, B-cell hybridoma growth factor, Hybridoma growth factor) IL-6 pleiotropic T_H2 cytokine produced by a variety of cell types that include monocytes, fibroblasts, and endothelial cells. Upon stimulation, IL-6 is secreted by many additional cell types including macrophages, T cells, B cells, mast cells, glial cells, eosinophils, keratinocytes, and granulocytes. IL-6 influences antigen-specific immune responses, inflammatory responses, it is a major mediator of the acute phase reaction and hematopoiesis, and plays a central role in host defense mechanisms. Furthermore, IL-6 is involved in B-cell differentiation, the induction of acute phase proteins in liver cells, growth promotion of myeloma/plasmacytoma/hybridoma cells, induction of IL-2 and IL-2R (CD25) expression, proliferation and differentiation of T cells, inhibition of cell growth of certain myeloid leukemic cell lines, and induction of their differentiation to macrophages. The level of IL-6 has proven to be a very important biomarker. This includes proliferative diseases where elevated plasma levels of IL-6 are observed in patients with multiple myeloma, other B-cell dyscrasias, Lennert's T lymphoma, Castleman's disease, renal cell carcinoma, and various other solid tumors. It is also an important biomarker in monitoring inflammatory responses were IL-6 is involved in the induction of acute phase proteins and induction of fever. Elevated serum levels of IL-6 are also found in patients with inflammatory arthritis and traumatic arthritis. (21, 45, 65, 73, 86, 101)	Human	•		•	•	•	•	•	•
	Mouse	•		•		•	•	•	•
	Rat					•		•	
	Monkey							•	

IL-7 (Interleukin-7, LP-1) IL-7 is an important cytokine that is required for human T cell development and for maintaining and restoring homeostasis of mature T cells. IL-7 is also involved in the proliferation of precursor B lymphocytes. IL-7 is produced mostly by non-hematopoietic stromal cells, rather than leukocytes such as T cells, B cells and NK cells. IL-7 signals through the heterodimeric IL-7 receptor composed of IL-7Rα (CD127) and the common γ chain (CD132) that is expressed by most resting T cells and is downregulated following T cell activation. IL-7 signaling through IL-7R activates the PI3K and JAK/STAT pathways to mediate anti-apoptotic and co-stimulatory proliferative signals. IL-7R activation also results in the downregulation of p27Kip1 and modulation of members of the Bcl-2 family. IL-7 is further responsible for the upregulation of the production of pro-inflammatory cytokines and the stimulation of the tumoricidal activity of monocytes/macrophages. Use of recombinant human IL-7 has be used in clinical trials for diseases such as melanoma, kidney cancer, HIV, HBV, HCV, stem cell transplantation, and pediatric solid tumors. (17)	Human					•		•	
	Mouse					•			
IL-8 (Interleukin-8, CXCL8, NAP-1, MONAP, ANF, MDNCF, NAF) IL-8 is a member of the CXC chemokine family and is a major mediator of inflammatory response. IL-8 is induced by activators such as LPS, IL-1, and TNF to be produced/secrete from a variety of cell types that include monocytes, lymphocytes, granulocytes, fibroblasts, endothelial, and epithelial cells. IL-8 binds primarily to two GPCRs, CXCR1 and CXCR2, on neutrophils, monocytes, endothelial cells, astrocytes, and microglia. IL-8 functions as a strong chemoattractant and an angiogenic factor. Besides its chemotactic influence, IL-8 also triggers the secretion of superoxide anions and lysosomal enzymes in neutrophils. In basophils, IL-8 stimulates the histamine liberation. IL-8 selectively stimulates the ability of neutrophils and T-lymphocytes to invade injured or inflamed tissue. Other findings suggest that endothelial-derived IL-8 may function to attenuate inflammatory events at the interface between vessel wall and blood. IL-8 is also associated with a number diseases including rheumatoid arthritis, psoriasis, asthma, bladder cancer, blood incompatibility, contact dermatitis, graft rejection, inflammatory bowel disease, myocardial infarction, sepsis, and others. (74)	Human	•	•	•	•	•	•	•	•
	Monkey						•		
IL-9 (Interleukin-9, T-cell growth factor P40) IL-9 is a proinflammatory cytokine that was identified by its proliferative effects on T cell populations. IL-9 was historically believed to be involved in type 2 immune responses, however, recent evidence suggests IL-9 may be secreted by other T helper lineages such as T_{Reg} and T_H17 in addition to a new category called T_H9. This T_H9 lineage can either be derived from T_H2 cells with TGFβ or differentiated directly from naïve CD4+ T cells with TGFβ and IL-4. IL-9 is a member of the common cytokine receptor gamma chain-dependent family of cytokines that also includes IL-2, IL-4, IL-7, IL-15 and IL-21. IL-9 binds to a heterodimeric receptor composed of the γ chain portion (CD132) of the IL-2 receptor and the IL-9R chain. Once bound, it activates the JAK/STAT signaling pathways. Its pleiotropic effects on T_H2 lymphocytes, B lymphocytes, mast cells, eosinophils, IgE production, and gut and airway epithelial cells have implicated IL-9 in asthma and other allergy-related disorders. The existence of an IL-9- mediated autocrine loop has been suggested for some malignancies such as Hodgkin's disease and large cell anaplastic lymphoma for Hodgkin's cell lines. IL-9 is expressed by Reed-Sternberg cells and Hodgkin lymphoma cells and some large aplastic lymphoma cells, while non-Hodgkin lymphomas and peripheral T-cell lymphomas do not express it. (37)	Human			•	•	•	•	•	•
	Mouse	•				•	•		
IL-10 (Interleuin-10, Cytokine synthesis inhibitory factor) IL-10 is an anti-inflammatory T_H2 cytokine that has a critical role in limiting the immune response to pathogens to prevent host damage. Though IL-10 is associated with T_H2 response, it appears to be more relevant to T_{Reg} cell responses. IL-10 is known to be expressed by many adaptive immune cells including T_H2, T_H17, T_{Reg}, and B cells, as well as innate immune cells including dendritic cells (DC), macrophages, mast cells, natural killer (NK) cells, eosinophils, and neutrophils. As IL-10 in produced in several T helper populations, it is proposed that it provides a feedback loop to limit the effector functions of macrophages and DCs on T cells. Once expressed, IL-10 signals through the IL-10 receptor (IL-10R) to activate STAT3. As IL-10 is a strong inhibitor of inflammation, it has become a viable biomarker for various diseases and conditions as well as a therapeutic molecule for certain conditions. In addition to elevated levels in parasitic infection, high expression levels of IL-10 are also found in retroviral infections inducing immunodeficiency. The immunosuppressive properties of IL-10 suggest a possible clinical use of IL-10 in suppressing rejections of grafts after organ transplantations. (52, 73, 84)	Human	•	•	•	•	•	•	•	•
	Mouse	•		•	•	•	•	•	•
	Rat						•	•	
	Monkey							•	
IL-11 (Interleukin-11, Adipogenesis inhibitory factor (AGIF)) IL-11 is a member of the IL-6 family of cytokines. It is a pleiotropic cytokine that has been shown to have broad effects on many cell types. IL-11 is produced by various cell types that include epithelial, endothelial, keratinocytes, stromal, neuronal, bone marrow stromal cells, fibroblasts, osteoclasts, and other stromal cells. IL-11 signals through a heterodimeric receptor consisting of a gp130 subunit, shared by several other cytokines, and an IL-11Rα subunit unique to IL-11. IL-11 exhibits pleiotropic effects on various cell types as it acts synergistically with other growth factors such as IL-3, SCF, and IL-4 to promote the development of cells from several hematopoetic lineages and also plays a role in the regulation of osteoclast differentiation and maturation. IL-11 also protects against cell death and inhibit inflammation at sites of tissue injury and has been implicated in T_H2-mediated sensitization and inflammation in asthma.	Human					•			
	Mouse					•			

TARGET ANALYTE	SPECIES	ANTIBODIES				PROTEINS	IMMUNOASSAYS		
		PURIFIED	VIOLET LASER	BLUE LASER	RED LASER		COAT-IT-YOURSELF	PRE-COAT	MULTIPLEX
IL-12 (Interleukin-12) IL-12, with STAT4 and T-bet, promotes differentiation into T_H1 cells that produce IFNγ. The Interleukin-12 (IL-12) family of cytokines, which includes IL-12, IL-23, IL-27, and IL-35, are important mediators of inflammatory disease. Each member is a heterodimeric complex composed of two subunits whose expression is regulated independently. The founding member, IL-12 (also known as IL-12p70), consists of the heterodimer of p35 and p40. Moreover, studies have demonstrated that homodimers and monomers of the p40 subunit also exist (known as IL-12p40) and may act as antagonists of IL-12 function. IL-23 is composed of the heterodimer p40 and p19, which is homologous to p35. IL-27 is a heterodimeric cytokine consisting of Epstein-Barr virus-induced gene 3 (EBI3) and p28, which are related to p40 and p35, respectively. The most recently identified member of this family, IL-35, is composed of p35 and EBI3. As inducers of IFNγ production, IL-12, IL-23, and IL-27 play critical roles in regulating the inflammatory response. Moreover, each is involved in mediating T cell-dependent immunity. For example, IL-12 and IL-27 are involved in T helper 1 (T_H1) differentiation, while IL-23 is critical for T_H17 survival and expansion. (5, 43, 65, 69, 77, 95, 102)									
IL-12 p70 (cytotoxic lymphocyte maturation factor (CLMF) or Natural Killer Cell Stimulatory Factor (NKSF)) IL-12 is a pleiotropic cytokine produced mainly by monocytes, macrophages, and dendritic cells in response to bacterial products such as lipopolysaccharide (LPS), intracellular pathogens, or upon interaction with activated T cells. Biologically active IL-12 is a disulfide-linked heterodimeric 70-kDa cytokine composed of a 35-kDa (p35) and a 40-kDa (p40) subunits. p35, a member of the IL-6 superfamily, is secreted in response to IFNγ and agonists of TLR3, 4, or 7. However, p35 expression has been shown to be inhibited by T_H2 cytokines and expressed at much lower levels than p40. Expression of p40 is regulated independently of p35. Moreover, p40 has been shown to be secreted as either a monomer or homodimer. Although each subunit alone does not possess IL-12 bioactivity, the p40 homodimer can bind to the IL-12 receptor and act as an antagonist to IL-12 p70. IL-12 binds to the receptor complex composed of IL-12Rβ1 and IL-12Rβ2, the latter of which is the signaling component of the receptor. This results in the induction of IFNγ production, cell proliferation, and cytotoxicity mediated by natural killer cells and T cells. Furthermore, studies have established that IL-12 is essential for the differentiation, proliferation, and maintenance of T_H1-responses that lead to IFNγ and IL-2 production. In turn, these cytokines promote T cell responses and macrophage activation. In disease, IL-12 has been shown to play a critical role in the pathogenesis of a variety of diseases including aberrant IL-12 expression in bacterial and viral infections, obstructive jaundice, and septic shock. Additionally, IL-12 has been associated with various autoimmune and inflammatory conditions.(5, 69, 77, 95, 102)	Human					•	•	•	•
	Mouse					•	•	•	•
	Monkey						•	•	
IL-12 p35 (Interleukin-12 subunit alpha, IL12A, NKSF1) p35 is a component of two of the four members of the IL-12 family of cytokines that include IL-12p70 and IL-35. p35 was first identified as a subunit of the IL-12 cytokine that is also known as IL-12p70. The secretion of p35 is induced by IFNγ and agonists of TLR3, 4, or 7, but is inhibited by the T_H2 cytokines. Functionally, IL-12 is essential for the differentiation and maintenance of T_H1 cells. Recently, p35 was also found to dimerize with EBI3 (Epstein-Barr Virus-Induced Gene 3) to form IL-35. The functions of this cytokine are still being elucidated. p35 belongs to the IL-6 superfamily. (5, 69, 77, 95, 102)	Human	•			•				
	Mouse	•			•				
IL-12 p40 (Interleukin-12 subunit beta, IL-12B) p40 dimers with both p35 and p19 to make IL-12p70 and IL-23, respectively. p40 is also believed to be secreted independently as a monomer or homodimer expressed in much higher quantities than p35. The p40 and p35 subunits by themselves have no IL-12 bioactivity, though the p40 homodimer has been shown to bind the IL-12 receptor and to be an antagonist of IL-12 p70. Free p40 is typically secreted in vast excess of IL-12 p70 by cells co-expressing both the p35 and p40 subunits. (95)	Human	•	•	•	•		•	•	
	Mouse	•		•	•		•	•	
IL-13 (Interleukin-13, NC3) IL-13 is a pleiotropic T_H2 cytokine expressed by activated T helper cells, CD8+ T cells, and NK cells. IL-13 functions to suppress macrophage cytotoxic activity, upregulation of IL-1RA expression, and suppression of inflammatory cytokine expression. IL-13 binds to the receptor complex IL-13R composed of IL-4Rα and IL-13Rα1, that it shares with IL-4, on various cell types that include mononuclear phagocytes and large granular lymphocytes B cells. IL-13 induces CD23 expression on B cells, promotes B cell proliferation in combination with anti-Ig or CD40 antibodies, and stimulates secretion IgE, and IgG4. IL-13 has also been shown to prolong survival of human monocytes and increases surface expression of MHC class II and members of the integrin superfamily, like CD11b, CD11c, CD18, CD29 and CD49e, and induces IFNγ production by NK cells. IL-13 also inhibits the production of a series of cytokines that include IL-1, IL-6, IL-8, and TNFα by activated human monocytes. As a biomarker, the measurement of IL-13 in body fluids may thus provide further information about the pathophysiology of atopic diseases and is known to play a central role in the pathogenesis of asthma. (15, 62, 91)	Human	•		•		•	•	•	•
	Mouse	•		•	•	•	•	•	•

IL-15 (Interleukin-15) IL-15 is a pro-inflammatory cytokine that plays a role in the activation of neutrophils, dendritic cells, and macrophages, and is essential for the proliferation and differentiation of NK cells and CD8 T-cells. The receptor for IL-15 is a high affinity heterotrimeric receptor composed of IL-15Rα and 2 the β and γ subunits of IL-2R (CD25). IL-15 signals via the JAK/STAT pathways. Despite the expression of IL-15 mRNA in many cell types, secreted mouse IL-15 protein is rarely detectable in biological samples. Recent research suggests that mouse IL-15 is retained inside the cell and is only secreted in complex with its unique receptor, IL-15Rα. Human IL-15 mRNA is found in a wide variety of cell types that includes PBMC, placenta, skeletal muscle, kidney, lung, liver, and heart, though it is produced most abundantly by epithelial cells and monocytes. Functionally, IL-15 shares many biological properties with IL-2 that includes the stimulation of CTLL proliferation, in vitro generation of alloantigen-specific cytotoxic T cells and non-antigen specific lymphokine activated killer (LAK) cells, and upregulate the expression of IL-17RA by CD8+ T cells. (13)	Human	•				•	•		
	Mouse	•				•	•		
	Mouse IL-15/IL-15R					•	•	•	•
IL-16 (Interleukin-16, Lymphocyte chemoattractant factor (LCF)) IL-16 is a cytokine that induces CD4+ T cell chemotaxis and activates monocytes, mast cells, dendritic cells, and eosinophils. IL-16 is produced by T lymphocytes, mast cells, dendritic cells, eosinophils, epithelial cells, and fibroblasts as a native pro-IL-16 that is cleaved by caspase-3 to produce a protein where the C- and N-termini function as a cytokine and cell cycle regulator, respectively. The cleaved monomers can associate to form a homotetramer that possess high cytokine activity. This cytokine also induces the expression of IL-2R (CD25) and MHC class II molecules on CD4+ T cells, indicating a role in immune-mediated and autoimmune diseases. IL-16 interacts directly with CD4 and has potential therapeutic use in treating HIV infection.	Human					•			
	Mouse					•			
IL-17 (Interleukin-17) Interleukin-17 (IL-17) is a family of 6 closely related cytokines that includes IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F that function in immune response as either homodimers or heterodimers with other family members. Cell type and tissue expression patterns differ greatly between the family members, but there is significant overlap in receptor binding patterns between IL-17 family members. Overall, IL-17 functions in host defense against extracellular bacterial and fungal infections and contributes to the pathogenesis of various autoimmune inflammatory diseases. The unusual structure of both the IL-17 cytokines and their receptors presented a new paradigm in cytokine biology. IL-17A, the prototypic family member, is the most widely studied member of the family and is most similar to IL-17F, the second most studied family member. IL-17A, IL-17E, and IL-17F are important pro-inflammatory cytokines, while much less is known about IL-17B, IL-17C, and IL-17D and their functions remain poorly understood. IL-17A appears to be more involved in autoimmunity than IL-17F, while the *in vivo* role of IL-17AF is still largely unknown. However, with the recent availability of new research reagents such as monoclonal antibodies, ELISAs, multiplex assays, and recombinant proteins for the IL-17AF specific heterodimer, advances in the knowledge of its roles and functions should increase. (1, 3, 14, 22, 40, 43, 65)									
IL-17A (Interleukin-17A, CTLA-8, IL-17) Interleukin-17A (IL-17A) is the prototypic member of the IL-17 family of cytokines. IL-17A plays a critical role in host defense and inflammation. IL-17A expression is most often associated with the T helper 17 (TH17) subset of CD4+ T cells, but has also been observed in CD8+ T cells, neutrophils, and γδ T cells upon stimulation with IL-1 and IL-23. IL-17A is most similarly related to IL-17F with which it shares 50% sequence homology. Both IL-17A and IL-17F exist as either biologically active homodimers (IL-17AA and IL-17FF) or biologically active heterodimers (IL-17AF). All three protein complexes are currently believed to signal through the same receptor complex (IL-17R) composed of the subunits IL-17RA and IL-17RC (IL-17RL), though they appear to have different biological functions. One of the principle IL-17 functions appears to be the regulation of local tissue inflammation via the coordinated expression of various cytokines and chemokines that include IL-1, IL-6, IL-8, GM-CSF, G-CSF, TNF, CXCL1, MCP-1, MIP-2, MCP-3, and MIP-3α. Upon ligand/receptor interaction, IL-17A induces these inflammatory cytokine production in epithelial cells, endothelial cells, and fibroblasts through the NFκB and MAPK family pathways that results in the activation of many of the AP-1 proteins. IL-17 has become an important target for drug discovery for the treatment of various forms of autoimmunity and inflammatory diseases such as asthma, rheumatoid arthritis, multiple sclerosis, psoriasis, transplant rejection, and inflammatory bowel disease (IBD). (1, 3, 14, 22, 40, 43, 65)	Human	•	•	•	•	•	•	•	•
	Mouse	•	•	•	•	•	•	•	•
	Rat		•	•	•	•	•	•	•
IL-17A/F IL-17A and IL-17F are well-characterized homodimeric cytokines secreted by T helper 17 (T_H17) cells, γδ T cells, and several subsets of innate lymphoid cells. Somewhat less appreciated is that IL-17A and IL-17F subunits can also form the heterodimer IL-17AF. Together, these three dimers signal through the IL-17RA/IL-17RC receptor complex to mediate immune responses at mucosal interfaces and are found at lesion sites in inflammatory bowel disease, asthma, atopic dermatitis and rheumatoid arthritis. IL-17AF functions are believed to be similar to both IL-17A and IL-17F with autoimmunity pathology and neutrophil recruitment and immunity to extracellular pathogens. Please review IL-17A and IL-17F for additional information. (1, 3, 14, 22, 40, 43, 65)	Human		•	•		•	•	•	•
	Mouse					•	•	•	•

TARGET ANALYTE	SPECIES	ANTIBODIES				PROTEINS	IMMUNOASSAYS		
		PURIFIED	VIOLET LASER	BLUE LASER	RED LASER		COAT-IT-YOURSELF	PRE-COAT	MULTIPLEX
IL-17B (Interleukin-17B) IL-17B remains poorly characterized and little is known about it. What is known is that IL-17B is expressed in a variety of tissues that include gastrointestinal cells and has particularly high expression in the spinal cord. Once expressed, IL-17B binds to the IL-17RB receptor. Unlike the other IL-17 family members, which are disulfide-linked dimers, IL-17B is a non-covalently linked dimer. Mouse and human IL-17B are highly homologous, exhibiting an 88% amino acid sequence identity between them. Amongst the IL-17 family, mouse IL-17B is most closely related to mouse IL-17D. Reports have linked IL-17B with TNFα production and the exacerbation of inflammatory arthritis. (14, 40, 43, 65)	Mouse					•			
IL-17C (Interleukin-17C, Cytokine CX2) IL-17C remains poorly characterized, but it is believed that IL-17C binds to the receptor IL-17RE and results in the activation of NFκB. IL-17C has also been reported to stimulate the release of TNFα and IL-1 β from certain cell lines. (14, 40, 43, 65)	Human					•			
	Mouse					•			
IL-17E (IL-25) (Interleukin 17E, Interleukin-25) IL-17E (IL-25) was identified as an IL-17 family member based on its sequence homology, though it was originally believed to be a T_H2 cytokine based on the detection of mRNA transcripts in polarized T_H2 cells. Its expression was later observed in epithelial cells, eosinophils, and mast cells. IL-17E is now known to be produced by mucosal epithelial cells as well as many immune cell types that include T_H2, mast cells, macrophages, eosinophils, and NKT cells. Once secreted, IL-17E is known to bind to the receptors IL-17RA and IL-17RB (IL-25R) and activate the NFκB pathway where it is involved as a T_H2 cell-promoting cytokine. IL-17E is believed to both induce T_H2 cell differentiation and responses with the upregulation of such T_H2 cytokines as IL-4, IL-5, and IL-13. IL-17E also suppresses T_H17 cell responses and development by the induction of IL-13 in dendritic cells or by inhibiting IL-23 production in macrophages. Administration of IL-17E also promotes symptoms of allergic asthma, such as eosinophil infiltration, airway hyper-reactivity, and high circulating levels of IgE. (14, 40, 43, 65)	Mouse					•	•		
IL-17F (Interleukin-17F) IL-17F, which is closely related to IL-17A, is known to be expressed by T helper 17 (T_H17) cells, CD8+ cells, γδT cells, NK cells, NKT cells, and LTi cells. Like IL-17A, IL-17F has been shown to form biologically active homodimers (IL-17FF) and heterodimers (IL-17AF). IL-17AA, IL-17FF, and IL-17AF are currently believed to signal through the same receptor complex (IL-17R) composed of the subunits IL-17RA and IL-17RC (IL-17RL), though they appear to have different biological functions. It has been suggested that differential expression patterns of the IL-17R subunits could provide a tissue specific signaling mechanism for IL-17A and IL-17F. Accordingly, the signal elicited upon binding by either IL-17A or IL-17F is remarkably different. The functions of IL-17F are believed to be in neutrophil recruitment and immunity to extracellular pathogens. IL-17F treatment of airway epithelium, vein endothelial cells, and fibroblasts has been reported to induce expression of IL-6, IL-8, GROα, ENA-78, TGFβ, MCP-1, G-CSF, GM-CSF, and ICAM-1. (1, 3, 14, 22, 40, 43, 65)	Human	•		•	•	•	•	•	•
	Mouse	•		•	•	•	•	•	•
	Rat					•			
IL-18 (Interleukin-18, IL1F4, IGIF) IL-18, an IL-1 family member, is a T_H1-promoting cytokine. IL-18 is expressed by macrophages, dendritic cells, and ketatinocytes (epithelial cells). IL-18 binds to IL-18R on T_H1 cells in response to IL-12 stimulation that results in the recruitment and its heterdimerization with IL-18RAP. This activates both the NFκB and MAPK pathways. The activity of IL-18 is held in control by IL-18BP, a soluble IL-18 binding protein found in 20-fold excess of IL-18 in non-inflammatory conditions. IL-18 is known to have various activities that include the induction of IL-4 and IL-13 basophils when combined with IL-3. IL-18 also works on dendritic cells to increase cytokine production and upregulation of MHC and co-stimulatory molecules. On macrophages, IL-18 enables the increased cytokine production and phagocytosis. In neutrophils, IL-18 helps to increase survival, adhesion, and oxidative burst and protease release. In basophils, IL-18 increases cytokine and histamine production. As a biomaker, high levels of IL-18 are found in both the blood and inflamed joints of rheumatoid arthritis patients. (56, 64)	Human						•	•	•
	Mouse							•	•
	Pig	•						•	

IL-19 (Interleukin-19) IL-19 belongs to the IL-10 family, which includes IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, and several virus-encoded cytokines (e.g, Y134R). Similar to IL-22, but unlike IL-10 which exists as a homodimer, IL-19 was found to be a monomer, based on protein crystal structure analysis. IL-19 gene transciption has been detected in resting monocytes and at a lower level in B cells. This is up-regulated in monocytes stimulated with LPS or GM-CSF. Priming monocytes with IL-4 or IL-13 (but not with IFNγ) significantly increases the level of IL-19 mRNA induced by subsequent LPS treatment. IL-19 signals through a receptor complex that is also utilized by IL-20 and IL-24. The complex is composed of two chains, CRF2-8 (or IL-20R1) and CRF2-11 (or IL-20R2), belonging to the class II cytokine receptor family. Receptors from this family also form heterodimeric complexes for type I and type II interferons and for other IL-10-related cytokines. Binding of IL-19 to the receptor complex results in STAT3 phosphorylation. IL-19 induces IL-6 and TNFα production in monocytes. It also induces cell apoptosis and reactive oxygen species production by monocytes. *In vitro,* IL-19 induces IL-4, IL-5, IL-10, and IL-13 production by activated T cells, and might play an important role in the pathogenesis of asthma. (2)	Human					•			
	Mouse	•				•	•		
IL-20 (Interleukin-20) IL-20 is a member of the IL-10 cytokine family that is expressed by monocytes, dendritic cells, and keratinocytes. IL-20 activates STAT3 by activating either of two heterodimeric receptor complexes. One of these consists of IL-20Rβ and IL-20Rα that can be activated by IL-19 and IL-24 as well as IL-20. The other, a complex of IL-20Rβ and IL-22Rα that is activated by only IL-20 and IL-24. IL-20 ligand binding induces the production of proinflammatory cytokines such as IL-1β, IL-6, and TNFα in monocytes and has been implicated in inflammatory conditions such as atherosclerosis, rheumatoid arthritis, and psoriasis. IL-20 also induces the proliferation of hematopoietic progenitor cells and keratinocytes.	Human					•			
IL-21 (Interleukin-21) IL-21 is a memember of the type-I cytokine family and is an immunomodulatory cytokine produced mainly by NKT, T_H17 and T_{FH} cells. Structurally, IL-21 shows homology to IL-2, IL-4, and IL-15 proteins. In T_{FH} cells, IL-21 expression leads to autocrine signaling through the IL-21 receptor (IL-21R) and JAK/STAT3, which leads to additional transcriptional activation by Bcl6. As with IFNγ for T_H1 and IL-4 for T_H2 cells, IL-21 is critical for T_{FH} cell development and effector function. This cytokine plays a role in T cell-dependent B cell differentiation into plasma cells and memory cells and stimulation of IgG production and induction of apoptotic signaling in naive B cells. In T_H17 cells, IL-21 expression and autocrine feedback through STAT3, IRF4 and RORγt lead to upregulation of the IL-23R, thereby preparing T_H17 cells for maturation and maintenance by the inflammatory cytokine IL-23. While upregulating IRF4 and RORγt, IL-21 also mediates the down-regulation of Foxp3. High levels of IL-21 are present in chemically induced colitis models. IL-21-deficient mice are protected from developing colitis upon chemical treatment by their inability to upregulate T_H17-associated molecules. (22, 43, 81, 86, 87, 89, 93)	Human	•		•	•	•	•	•	
	Mouse	•		•	•	•	•	•	•
	Rat	•							
IL-22 (Interleukin-22,TIF, IL-10-related T cell-derived inducible factor) IL-22 is a cytokine that regulates the production of acute phase proteins of the immunological response. IL-22 is produced by T_H1, T_H17, and NK cells acting primarily on epithelial cells and is involved in inflammatory responses. On binding to its receptor (IL-22R1), which is associated to the interleukin-10 receptor 2 (IL-10R2), IL-22 promotes activation of multiple signals including the STAT1, STAT3, ERK, p38, and JNK pathways. IL-22BP, a soluble receptor, that able to bind to IL-22 as an antagonist is thought to provide systemic regulation of IL-22 activity. Interestingly, neither resting nor activated immune cells express IL-22 receptor, nor does it have any effect on these cells *in vitro* and *in vivo*. IL-22 is believed to act more on skin cells and cells of the digestive and respiratory systems. IL-22 serves as a protective molecule to counteract the destructive nature of the immune response to limit tissue damage and acts as a T cell mediator that directly promotes the innate, nonspecific immunity of tissues. (16, 43, 49)	Human	•	•	•	•	•	•	•	•
	Mouse	•		•	•	•	•	•	•
IL-23 (Interleukin-23) IL-23 is a member of the IL-12 family of cytokines. IL-23 is secreted by activated dendritic cells and activated macrophages, and functions in innate and adaptive immunity to regulate T_H17 function and proliferation. It is an important signal mediator of T_H17 differentiation and is thought to contribute to the functional deviation of T_H17 cells. Additionally, IL-23 induces CD8+ memory T cells to proliferate and produce IL-17. As such, IL-23 has been described as a key cytokine controlling inflammation in peripheral tissues. Structurally, IL-23 is a heterodimeric cytokine composed of the p40, shared with IL-12, and p19, a subunit that belongs to the IL-6 superfamily of cytokines. IL-23 interacts with a heterodimeric receptor composed of IL-12Rβ1 and IL-23R that binds to JAK/STATs. Despite activating similar signaling pathways to IL-12, IL-23 binding can lead to weaker activation, especially with STAT4. Expression of IL-23R is linked to the development of Crohn's disease in humans. (8, 21, 22, 43, 65, 69, 73, 95)	Human					•	•	•	•
	Mouse					•	•	•	•
IL-23 p19 (Interleukin-23 subunit alpha, IL23A, Interleukin-23 subunit p19) p19 belongs to the IL-6 superfamily. p19 heterodimerizes with both p40 and p28 to create IL-23 and IL-27, respectively. It is also thought to possibly create a homodimers with itself. It is secreted by activated dendritic cells and found in polarized T_H1 cells and activated macrophages. (65, 69, 95)	Human	•		•		•			
	Mouse	•				•			

TARGET ANALYTE	SPECIES	ANTIBODIES				PROTEINS	IMMUNOASSAYS		
		PURIFIED	VIOLET LASER	BLUE LASER	RED LASER		COAT-IT-YOURSELF	PRE-COAT	MULTIPLEX
IL-23 p40 (Interleukin-12 subunit beta, IL12B) p40 forms dimers with both p35 and p19 to constitue IL-12p70 and IL-23, respectively. p40 is also believed to be secreted independently as a monomer or homodimer expressed in much higher quantities than p35. The p40 and p35 subunits by themselves have no IL-12 bioactivity, though the p40 homodimer has been shown to bind the IL-12 receptor and to be an antagonist of IL-12 p70. Free p40 is typically secreted in vast excess of IL-12 p70 by cells co-expressing both the p35 and p40 subunits. (69, 95)	Human	•	•	•		•	•	•	•
	Mouse	•		•		•	•	•	•
IL-24 (Interleukin-24) IL-24 belongs to the IL-10 family of cytokines. IL-24 is secreted by T cells, monocytes, and macrophages. IL-24 signals through two heterodimeric receptors, IL-20R1/IL-20R2 and IL-22R1/IL-20R2 where it is believed to activate the JAK/STAT pathways. IL-24 has anti-proliferative properties on melanoma cells and may contribute to terminal cell differentiation. IL-24 is also believed to be involved in psoriasis and cancer.									
IL-25 (IL-17E) See IL-17E									
IL-26 (Interleukin-26) IL-26 is a member of the IL-10 family first identified in T cells transformed with HSV (Herpesvirus saimiri). Its gene is expressed almost exclusively in T cells and is overexpressed upon virus transformation. IL-26 has been grouped as a T_H17 cytokine as its expression has been found with cells expressing RORγt. Although not much is known about its biological functions, IL-26 is believed to be pro-inflammatory and targets epithelial cells. Its receptor is made up of the subunits IL-20R1 and IL-10R2 whose activation initiates STAT1 and STAT3 activation. Currently, no mouse counterpart to IL-26 has been identified.	Human					•			
IL-27 (Interleukin-27 (p28/EBI3)) IL-27 is a member of the IL-12 family of cytokines. IL-27 is a heterodimer composed of the Epstein-Barr virus induced gene 3 (EBI3) subunit and p28 (also known as IL-30). EBI3 is a 34-kDa glycoprotein is homologous to the p40 subunit of IL-12 and IL-23. The p28 subunit of IL-27 is similar to p35, and has been shown to function independently of EBI3. Studies demonstrate that IL-27 binds the receptor subunit WSX-1/TCCR (also known as IL-27Ra) that associates with gp130, a common chain utilized by IL-6 family cytokines. IL-27 binding to the IL-27R that is expressed most abundantly on activated T cells and NK cells with lower expression on B cells and naïve T-cells. This leads to the phosphorylation and activation of the JAK/STAT pathway, with STAT1 and STAT3 as the predominant factors mediating the effects of IL-27. In addition to its role in mediating pro- and anti-inflammatory effects, IL-27 promotes CD4+ T cell differentiation to the T_H1 lineage by inducing expression of the transcription factor T-bet and up regulating IL-12Rβ2. In doing so, IL-27 suppresses T_H2 and T_H17 differentiation and proliferation. IL-27 is produced by activated dendritic cells and macrophages in response to Toll-like receptor ligands and pro-inflammatory cytokines. (5, 31, 92, 95)	Human					•	•	•	•
	Mouse					•	•	•	•
IL-27 p28 (Interleukin-27 subunit alpha, IL27A) p28 belongs to the IL-6 superfamily. It is known to have both pro- and anti-inflammatory properties. It is known to help regulate T helper cell development, suppress T cell proliferation, and stimulate T cell activity. It is not known to secret without co-expression of EBI3. (31, 95)	Human				•				
	Mouse	•		•					
IL-27 EBI3 (Interleukin-27 subunit beta, IL27B) EBI3 is a component of two of the four members of the IL-12 family. EBI3 was first found to heterodimerize with p28 (IL-30) to form IL-27 that is secreted by antigen-presenting cells in response to pro-inflammatory stimuli. IL-27 has been shown to have both pro-inflammatory and anti-inflammatory effects. It influences the commitment of CD4+ T-cells toward the T_H1 lineage by inducing the expression of the T-bet transcription factor and the upregulation of IL-12R beta 2. Its anti-inflammatory functions include the suppression of T_H2 and T_H17 proliferation and differentiation. Just as with p35 above, EBI3 was also found to dimerize with another IL-12 family member to form IL-35. (31, 95)	Human			•					
	Mouse	•							

IL-28 & IL-29 /IFNλ (IFN lambda, IL-29, IL-28A, IL-28B) IFNλ is a novel family of interferons that help mediate the induction of anti-viral protection in a wide variety of cells. The three IFNλ family members λ1, λ2, and λ3, also known as IL-29, IL-28A, and IL-28B, respectively, mediate their anti-viral protection through a class II cytokine receptor complex distinct from that of type I IFNs. It is comprised of two essential receptor proteins, CRF2-12/IFN-λR1, which is unique to IFNλ, and CFR2-4/IL-10R2, which is shared with IL-10R, IL-22R, and IL-26R. IFN-λR1 is not expressed by monocytes, but is up-regulated during GM-CSF/IL-4 induced differentiation of DCs from human monocytes, yielding iDCs that are fully responsive to IFNλ. IFNλs activate the same pathways as type I interferons that drives the expression of a common set of IFN-stimulated genes. Functionally, IFNλ has recently been reported to prime dendritic cells to induce proliferation of Foxp3-bearing regulatory T cells. IFNλ-matured DCs express high levels of class I and II MHC gene products, but low levels of co-stimulatory molecules are able to specifically induce IL-2-dependent proliferation of CD4+CD25+Foxp3+ T cell population with contact dependent suppressive activity on T cells.									
IL-28 (IFNλ, Interleukin-28A/B) IL-28A and IL-28B, along with IL-29 (also known as IFN-λ2, IFN-λ3, and IFN-λ1, respectively) are type III Interferons that belong to the IFNλ family; a novel family of cytokines within the IL-10 superfamily. IFNλ mediate their anti-viral protection through a class II cytokine receptor complex distinct from that of type I IFNs that is comprised of two essential receptor proteins, CRF2-12/IFN-λR1, which is unique to IFNλ, and CFR2-4/IL-10R2 that is shared with IL-10, IL-22, and IL-26 receptors. Whereas the two chains of the type I IFN receptor (IFN-AR1 and IFN-AR2) and IL-10R2 are ubiquitously expressed, IFNλR1 expression is limited and cell-type dependent. They signal through the JAK/STAT pathway in a similar manner as the type I IFNs (IFNα/β) and activates many of the same genes despite low sequence homology between the cytokines and receptors in the two families. Both IFN families display antiviral activity through the induction of antiviral protein production in target cells and the upregulation of MHC class I expression. These proteins also exhibit antiproliferative and antitumor effects, making them a possible alternative to IFNα cancer therapies. Unlike the type I IFNs, which are able to stimulate most cells, response to IFNλ stimulation appears to be limited to dendritic and some tumor cells due to the limited expression of IFNλR1.	Human					•			
	Mouse	•				•	•	•	
IL-29 (Interleukin-29, IFNλ1) IL-29 is a protein of the helical cytokine family and is a type III interferon sharing many functions with the type I family of interferons. IL-29 does not bind the IFNα/β receptor, but rather signals through a receptor composed of the IL-28R1 and IL-10R2 subunits that is expressed on most non-hematopoietic cells. Generation of native IL-29 is achieved by monocytes and dendritic cells in response to viral infection and stimulation with toll-like receptor ligands. IL-29 plays an important role in host defenses against microbes and its gene is highly upregulated in cells infected with viruses. IL-29 has significant antiviral activity and immunoregulatory properties and appears to inhibit T helper-2 (T_H2) responses regarding inhibition of IL-13 production, compared with IL-4 or IL-5. The antiviral activities of IL-29 include the upregulation of MHC Class I expression on the cell surface and the expression of PKR.	Human					•	•	•	
IL-31 (Interleukin-31) IL-31 is a member of the gp130/IL-6 family of cytokines that is produced predominantly, but not exclusively, by activated T_H2 cells. IL-31 binds to the heterodimeric receptor complex composed of IL-31RA (GPL) and oncostatin M receptor (OSMR). This receptor complex is expressed constitutively on keratinocytes and epithelial cells and can be upregulated on monocytes by IFNγ or LPS. IL-31 signaling activates the JAK/STAT, PI3 kinase/AKT, and MAP kinase pathways. Due to the ubiquitous expression of its receptor complex, IL-31 has numerous physiological roles including regulation of hematopoiesis and immune response. IL-31 is associated with the promotion of allergic and chronic inflammatory conditions such as dermatitis, pruritus, airway hyper-sensititvity and inflammatory bowel disease.	Human					•		•	
	Mouse					•			
IL-32 (natural killer (NK) cell transcript 4, Tumor necrosis factor alpha-inducing factor (TAIF)) IL-32 is a pro-inflammatory cytokine. There are 6 known splice variants of IL-32 (α, β, γ, δ, ε, and ζ), but the functional differences between the variants nor the receptor(s) are known. IL-32 is produced by T cells, IL-12 activated NK cells, monocytes, IFNγ-activated epithelial cells, and keratinocytes. Functionally, IL-32 is known to activate the NFκB, p38 MAPK, and AP-1 signaling pathways. It is involved in the generation of IL-1β, IL-6, IL-8, IL-10, MIP-2, and TNFα. IL-32 is an interesting cytokine in that it is known to be expressed in both the cytosol and the nucleas of the cell. Functionally, IL-32 is also just as interesting. IL-32 was recently shown to be involved in cisplatin-induced apoptotic cell death of HeLa cells and IL-32γ has recently been shown to inhibit tumor growth (colon and melanoma), but IL-32 was also shown to stimulate cell growth in certain pancreatic cancers. As a biomarker, IL-32 has been used for cancer patients with their responsiveness to IL-2 based immunotherapy. IL-32 is believed to be involved in diseases such as arthritis, psoriasis, ulcerative colitis, and Crohn's disease. (7, 23)									

TARGET ANALYTE	SPECIES	ANTIBODIES					IMMUNOASSAYS		
		PURIFIED	VIOLET LASER	BLUE LASER	RED LASER	PROTEINS	COAT-IT-YOURSELF	PRE-COAT	MULTIPLEX
IL-33 (Interleukin-33, IL-1F11) IL-33 is an IL-1 family member. It is a pro-inflammatory T_H2 polarizing cytokine that enhances T_H2 cell responses. IL-33 is not typically expressed by hematopoietic cells, but rather by fibroblasts, epithelial cells, and endothelial cells. In the absence of pro-inflammatory stimuli, IL-33 localizes to the nucleus, where in its uncleaved form, interacts with H2A and H2B. Mystery surrounds how IL-33 is secreted from cells and whether it is the cleaved or full-length protein that is active in vivo. The activating protein of IL-33 is still up for debate, though it is believed to be calpain that cleaves it to its mature form. IL-33 binds to ST2, an IL-1R family member receptor that is expressed on T_H2, but not T_H1 cells. Upon ligand binding, ST2 heterodimerizes with IL-1RAP that results in the activation of the NFκB and MAPK pathways. The activation of NFκB in mast cells results in mast cell degranulation and production of IL-1β, IL-3, IL-6, TNF, CXCL2, CCL2, CCL3, PGD2, and LTB4. IL-33 also acts directly on eosinophils to enhance their survival and adhesive properties, as well as their production of IL-8 and superoxide. In mast and T cells, the IL-33 activation of the MAPK pathways and induces the production of IL-5, IL-13, CCL5, CCL17, and CCL24. IL-33 is associated with infections, asthma, anaphylaxis, atherosclerosis, Alzheimer's disease, pain, and arthritis, ulcerative colitis, and Crohn's disease. (10, 11, 55)	Human					•		•	
	Mouse					•	•	•	
IL-34 (Interleukin-34) IL-34 has a wide gene expression profile across many organs and tissue types that include liver, kidney, brain, lung, heart, spleen, and thymus. IL-34 was recently been identified as the ligand for M-CSFR in both humans and mice where it binds to M-CSFR with higher affinity than M-CSF. Additionally, like G-CSF, IL-34 is also a ligand for the receptor tyrosine kinase Fms. IL-34 has shown to support survival of human peripheral blood monocytes and promote the formation of macrophage colonies in human bone marrow cell cultures. (46)									
IL-35 (Interleukin-35 (p35/EBI3)) Interleukine-35 (IL-35), a member of the IL-12 family of cytokines, is a heterodimer composed of the p35 and EBI3 subunits that are shared with the other IL-12 family members IL-12 and IL-27, respectively. p35, which is related to IL-6 and G-CSF, is secreted in response to IFNγ and agonists of TLR3, 4, or 7. In contrast, expression of this subunit is inhibited by T_H2 cytokines. EBI3, first identified in B cells following Epstein-Barr virus infection, is homologous to the p40 subunit of IL-12 and IL-23. Studies also indicate that EBI3 exists independently of other subunits and as a heterodimer with p28 (IL-30) to form IL-27. The exact mechanism underlying the formation and production of IL-35 remains under investigation. Functionally, the biology of IL-35 is not well understood. Though studies suggest that IL-35 is produced by regulatory T cells (T_{Reg}) and functions to suppress inflammation. IL-35 may mediate this effect by influencing the proliferation and function of effector T cells. (26)	Human						•		
IL-35 p35 (Interleukin-12 subunit alpha, IL12A, NKSF1) p35 is a component of two of the four members of the IL-12 family of cytokines that include IL-12p70 and IL-35. p35 was first identified as a subunit of the IL-12 cytokine that is also known as IL-12p70. The secretion of p35 is induced by IFN gamma and agonists of TLR3, 4, or 7, but is inhibited by the T_H2 cytokines. Functionally, IL-12 is essential for the differentiation and maintenance of T_H1 cells. Recently, p35 was also found to dimerize with EBI3 (Epstein-Barr Virus-Induced Gene 3) to form IL-35. The functions of this cytokine are still being elucidated. p35 belongs to the IL-6 superfamily.									
IL-35 EBI3 (Interleukin-27 subunit beta, IL27B) EBI3 is a component of two of the four members of the IL-12 family. EBI3 was first found to heterodimerize with p28 (IL-30) to form IL-27, which is secreted by antigen-presenting cells in response to pro-inflammatory stimuli. IL-27 has been shown to have both pro-inflammatory and anti-inflammatory effects. It influences the commitment of CD4+ T-cells toward the T_H1 lineage by inducing the expression of the T-bet transcription factor and the upregulation of IL-12R beta 2. Its anti-inflammatory functions include the suppression of T_H2 and T_H17 proliferation and differentiation. Just as with p35 above, EBI3 was also found to dimerize with another IL-12 family member to form IL-35.									
IL-36 (Interleukin-36, IL-36Ra (IL-1F5), IL-36α (IL-1F6), IL-36β (IL-1F8), and IL-36γ (IL-1F9)) IL-36 is a member of the IL-1 family of cytokines. There are at least 4 known isoforms of IL-36 that include IL-36Ra (IL-1F5), IL-36α (IL-1F6), IL-36β (IL-1F8), and IL-36γ (IL-1F9). They are expressed by macrophages and epithelial cells, and stongly expressed by monocytes. Upon activation, they like the other IL-1 family members (IL-1, IL-18, and IL-33) lead to the activation of the NFκB and MAPK pathways. All of IL-36 isoforms interact with the same IL-1RL2 receptor, but in different ways. IL-36Ra (IL-1F5), an analog of IL-1Ra, is an antagonist that binds to and blocks IL-1RL2 by preventing the other cytokines to bind and the subsequent recruitment of IL-1RAP. The activity of 1F6, 1F8, and 1F9 are regulated by the receptor agonist IL-1F5. The protease(s) responsible for the activation of the IL-36 isoforms still remains elusive, but its discovery will give insight into their regulation as the removal of their N-terminal amino acids increases their specific activity. (36)									

IL-37 (Interleukin-37, IL1F7, IL1RP1) IL-37 is an IL-1 family member. It is the only IL-1 family member with no known mouse orthologue. IL-37 appears to be the most biologically relevant because of its wider expression pattern and abundance compared to the other spliced forms. IL-37 is believed to bind to SIGGR. IL-37 activation is still poorly understood, but it is believed to act as a negative regulator inside the cell where it interacts with SMAD3 that is activated downstream of TGFβ activity. (29, 56)									
IL-38 (IL-1F10) Though little is currently known about IL-38 (IL-1F10), IL-38 has been shown to be expressed in proliferating B cells in tonsil germinal centers and basal epithelium of skin and IL-38 binds to soluble IL-1 receptor Type I.									
IP-10 (CXCL10, C-X-C motif chemokine 10, 10 kDa interferon gamma-induced protein) IP-10 is a member of the CXC subfamily of chemokines expressed by monocytes. IP-10 plays a pivotal role in the immune system development. IP-10 is induced in monocytes, fibroblasts, and endothelial cells by IFNγ. IP-10 is also known to be induced by LPS, IL-1β, TNFα, IL-12, and viral infection. Its pleiotropic functions include the stimulation of monocytes, natural killer, and T-cell migration, as well as the regulation of T-cell and bone marrow progenitor maturation. IP-10 is also involved in the modulation of adhesion molecule expression and inhibition of angiogenesis. IP-10 is also a chemoattractant for CXCR3+ T cells, which play an important role in T_H1-type inflammatory diseases, as well as several endocrine-related autoimmune diseases such as Hashimoto's thyroiditis.	Human					•		•	•
	Mouse					•	•	•	•
LAP (Pro-TGF beta 1, LAP/TGF beta 1, Latency Associated Peptide) TGFβ protein is synthesized as a precursor that contains LAP at the N-terminus and mature TGFβ at the C-terminus. The presence of LAP inhibits the biological activity of TGFβ to allow it to be secreted in a latent/inactive form. LAP must be dissociated from TGFβ or be conformationally altered in order for TGFβ to be active. Processing and cleavage of the precursor protein between amino acids 278 and 279 results in the formation of LAP dimers and TGFβ dimers that then non-covalently associate with each other to form the small latent TGFβ complex. LAP is secreted and can be found in the extracellular matrix. Many different cells produce TGFβ and it mediates effects on the proliferation, differentiation and function of many cell types. In addition, LAP can also be expressed on platelets and activated regulatory T cells. It is believed that this surface-expressed LAP is due to the binding of LAP to GARP (LRRC32), which is a transmembrane protein that is also found at high levels on platelets and activated regulatory T cells. Additionally, it is thought that the detection of LAP in serum is a surrogate for determining the amount of TGFβ without having to process the sample with acid. (9, 32)	Human	•		•			•	•	•
	Mouse			•					
LIF (Leukemia Inhibitory Factor) LIF belongs to the IL-6 receptor family. It binds to a heterodimeric membrane receptor made up of a LIF-specific subunit, gp190 or LIFR, and the subunit gp130, which is shared with the other members of the IL-6 family. LIF expression has been observed in various tissues including thymus, lung, and neuronal tissue. LIF can be up-regulated by pro-inflammatory cytokines such as TNFα and IL-17, and elevated levels of LIF have been found in cases of rheumatoid arthritis, neural injury, systemic inflammation, and tuberculosis. LIF has been shown to inhibit the differentiation of T_H17 cells in EAE mice and that of human T_H17 cells derived from MS subjects. This is believed to occur through LIF exerting an opposing effect on the IL-6-induced STAT3 phosphorylation that is required for T_H17 cell differentiation. LIF is most known in its ability to inhibit the differentiation of embryonic stem cells in mice and contribute to stem cell self-renewal. Inhibition of stem cell differentiation by LIF appears to be mouse-specific.	Human	•				•		•	
	Mouse					•			
M-CSF (Macrophage Colony Stimulating Factor, Monocyte Colony Stimulating Factor, CSF-1, MCSF) M-CSF is a survival factor essential for the proliferation and development of monocytes, macrophages, and osteoclast progenitor cells. M-CSF is present as several bioactive isoforms that differ in potency and stability. The full-length protein is synthesized as a membrane-spanning protein that can be expressed on the cell surface or further cleaved and modified in the secretory vesicle. M-CSF binds to the receptor tyrosine kinase c-Fms (CSF-1R or CD115) induces dimerization and autophosphorylation of the receptor followed by internalization and degradation of the complex. M-CSF is the primary cytokine for the mononuclear phagocyte lineage such as monocytes, macrophages, and osteoclasts. M-CSF regulates their development and effector functions. M-CSF also induces VEGF secretion by macrophages, thereby mediating mobilization of endothelial progenitor cells and neovascularization. (46)	Human					•			
	Mouse					•			
MCP-1 (CCL2, Monocyte Chemotactic Protein 1, C-C motif chemokine 2) MCP-1 is a member of the ß (CC) subfamily of chemokines. MCP-1 is mainly expressed by macrophages in response to a wide range of cytokines that include IL-1β, IL-6, and TNFα, but can also be produced by a variety of other cells and tissues, such as fibroblasts, endothelial cells, or certain tumor cells. MCP-1 functions as a chemoattractant protein for monocytes, T lymphocytes, and NK cells where it helps to regulate their adhesion molecule and cytokine expression patterns. MCP-1 has also been shown to activate monocytes to be cytostatic for some human tumor cell lines and attracting, activating, and inducing basophils to release histamine. Elevated levels of MCP-1 have also been found in connection with inflammation, Alzheimer's disease (AD), myocardial ischemia, and viral infections.	Human	•		•	•	•	•	•	•
	Mouse	•		•			•	•	•
	Rat	•		•				•	•

TARGET ANALYTE	SPECIES	ANTIBODIES					IMMUNOASSAYS		
		PURIFIED	VIOLET LASER	BLUE LASER	RED LASER	PROTEINS	COAT-IT-YOURSELF	PRE-COAT	MULTIPLEX
MCP-3 (CCL7, Monocyte Chemoattractant Protein 3, C-C motif chemokine 7) MCP-3 belongs to the CC-family of chemokines and is one of the most pluripotent chemokine that activates all types of leukocytes acting as a ligand for at least four different chemokine receptors. The natural protein is heterogeneous due to post-translational modifications glycosylation and NH2-terminal processing. In addition to it chemoattractant properties, MCP-3 may also affect HIV-1 infection via inhibiting the binding of HIV envelope to CCR5, the co-receptor to HIV. Like for MCP-1, MCP-3 has also been implicated in Multiple Sclerosis, allergic reactions and viral infections. Furthermore the presence of MCP-3 has been described in several lung diseases, pathologies of the gastro-intestinal system and vernal keratoconjunctivitis.	Human					•			
	Mouse							•	•
MCP-5 (CCL12, C-C motif chemokine 12, Monocyte Chemoattractant Protein 5) MCP-5 is a CC chemokine family member. Constitutive expression of MCP-5 has been detected predominantly in lymph nodes, and its expression is markedly induced in macrophages. Functionally, MCP-5 acts as a strong chemoattractant for monocytes and macrophages where it is involved in allergic inflammation and the host response to pathogens. MCP-5 is only weakly active on eosinophils and inactive on neutrophils though. Once expressed, MCP-5 induces a calcium flux in peripheral blood mononuclear cells.	Mouse							•	
MIG (CXCL9, monokine induced by IFNγ, Chemokine (C-X-C motif) ligand 9) MIG belongs to the CXC subfamily of chemokines. Induced by IFNγ and secreted mostly by macrophages, CXCL9 functions to recruit leukocytes to sites of infection and inflammation by its biding to a receptor that is selectively expressed in activated T-lymphocytes and therefore is a critical mediator of T-lymphocyte migration in T-cell dependent immune responses. Like IP-10, MIG binds to the chemokine receptor CXCR3 in T_H1 immune reactions and exhibits inhibitory functions in neovascularization. Additionally, MIG is an inhibitor for hematopoietic progenitor cells and shows anti-tumor effects. Furthermore, there are indications that MIG plays an important role in mediating cell recruitment and activation necessary for inflammation and the repair of tissue damage (e.g. in liver diseases).	Human							•	•
	Mouse			•	•				
MIP-1α (CCL3, Macrophage Inflammatory Protein 1-alpha, C-C motif chemokine 3) MIP-1α, along with the closely related MIP-1β (CCL4), is a member of the CC-subfamily of chemokines. These proteins play critical roles in the recruitment of leukocytes to the site of inflammation and signal through CCR1, CCR4, and CCR5. MIP-1α and MIP-1β are involved in the response to cellular and humoral immune response. MIP-1α stimulates strong antigen specific responses, while MIP-1β promotes antibody responses. While both CCL3 and CCL4 are both chemoattractant for monocytes, macrophages, and dendritic cells, they differ in their responses with T cells. While MIP-1α preferentially attracts CD8+ T cells, CD4+ T cells are more responsive to MIP-1β. In addition to its chemotactic and co-activator functions, MIP-1α also induces inflammatory cytokine secretion, mast cell degranulation, and NK cell activation. MIP-1 protein expression levels have been shown to be important regarding numerous diseases such as multiple myeloma, asthmatic disorders, EAE, HIV, and sepsis.	Human					•		•	•
	Mouse	•				•			•
MIP-1β (CCL4, C-C motif chemokine 4, Macrophage Inflammatory Protein 1-beta) MIP-1β is a member of the CC-subfamily of chemokines and is most closely related to MIP-1α (CCL3). These proteins play critical roles in the recruitment of leukocytes to the site of inflammation and signal through CCR1, CCR4, and CCR5. MIP-1α and MIP-1β are involved in response to their affects on cellular and humoral immune response. MIP-1α stimulates strong antigen specific responses, while MIP-1β promotes antibody responses. While both CCL3 and CCL4 are both chemoattractant for monocytes, macrophages, and dendritic cells, they differ in there responses with T cells. While MIP-1α preferentially attracts CD8+ T cells, CD4+ T cells are more responsive to MIP-1β. MIP-1 protein expression levels has been shown to be important regarding numerous diseases such as multiple myeloma, asthmatic disorders, EAE, HIV, and sepsis.	Human					•		•	•
	Mouse								•
MIP-3α (CCL20, C-C motif chemokine 20, Macrophage Inflammatory Protein 3 alpha) MIP-3α is a cytokine belonging to the CC chemokine family. MIP-3α is strongly upregulated by inflammatory signals such as TNF and IFNγ and downregulated by the anti-inflammatory cytokine IL-10 in various cell types and tissues such as lyphocytes, lymph node, and the liver. MIP-3α acts as a chemoattractant for lymphocytes and elicits its functions on its target cell by binding to the chemokine receptor CCR6.	Mouse					•			

RANTES (CCL5, Regulated upon Activation Normal T cell Expressed and Secreted,C-C motif chemokine 5) RANTES belongs to the CC-family of chemokines, and along with other family members, plays an important role in the immune response by initiating the recruitment of leukocytes to the site of inflammation by acting as a chemoattractant for T cells, eosinophils, monocytes, and dendritic cells. The activity of the chemokine RANTES however is not restricted merely to chemotaxis. RANTES is also known to be involved in the proliferation and activation of certain immune cell types. RANTES has further been shown to play a role in HIV replication and elevated expression of RANTES has been shown in early pregnancy, suggesting a role in preparing the uterus for blastocyst implantation. RANTES is also involved in the progression and metastasis of some forms of cancer, and constitutive expression has been demonstrated in some malignant tumors.	Human				•	•		•	•
	Mouse	•				•		•	•
SDF-1α (CXCL12 alpha, Stromal cell-derived factor 1, pre-B-cell growth-stimulating factor, PBSF) SDF-1α is a 70-amino acid CXC chemokine originally cloned from a bone marrow stromal cell line. Targeted deletion of the SDF-1 gene resulted in defects of B-cell lymphopoiesis and bone marrow myelopoiesis. SDF-1 has been shown to be chemotactic for lymphocytes. In addition, SDF-1 was recently reported to be a ligand for CXCR4 (LESTR/fusin), a co-receptor for HIV-1 entry into T cells. SDF-1 binding to CXCR4 inhibits HIV-1 entry.	Mouse, Rat	•							
SDF-1β (CXCL12β, stromal cell-derived factor-beta, and pre-B-cell growth-stimulating factor) SDF-1β is a 74-amino acid CXC chemokine originally cloned from a bone marrow stromal cell line. Targeted deletion of SDF-1β gene resulted in defects of B-cell lymphopoiesis and bone marrow myelopoiesis in mice. SDF-1β has been shown to be chemotactic for lymphocytes. In addition, CXCL12 was recently reported to be a ligand for CXCR4 (LESTR/fusin), a co-receptor for HIV-1 entry into T cells. SDF-1β binding to CXCR4 inhibits HIV-1 entry.	Mouse, Rat	•							
Sonic Hedgehog (SHH) Sonic Hedgehog is a highly conserved protein that plays an important role in embryonic development. It is expressed in neural tissue, the gut, and areas of limb development and promotes differentiation and growth in a tissue-specific manner. SHH is synthesized as a 45-kDa precursor protein that is cleaved to generate the active 19-kDa N-terminus. SHH interacts with the Patched and Smoothened transmembrane receptors, leading to the activation of GLI family transcription factors. Disruption of any part of this pathway during embryogenesis is associated with birth defects ranging from mild to severe. In adults, abnormal activation of the SHH pathway has been implicated in several forms of cancer.	Human					•			
	Mouse					•			
Stem Cell Factor (SCF, Kit ligand, KITLG, MGF) Stem Cell Factor (SCF) is a hematopoietic growth factor that binds to the receptor tyrosine kinase c-KIT (CD117) that exerts its activity in the early stages of hematopoiesis. That stimulates the proliferation of myeloid, erythroid, and lymphoid progenitors in bone marrow cultures. SCF also works synergistically with other growth factors to generate mature, functional blood cells.	Human					•			
	Mouse					•			
TGFβ1 (Transforming Growth Factor beta-1) TGFβ is a pleiotropic immunoregulatory cytokine that controls immune responses. TGFβ1 is highly expressed in platelets and also produced by macrophages, lymphocytes, endothelial cells, chondrocytes, and leukemic cells. TGFβ is produced in a pro-form (pro-TGFβ) and is intracellularly cleaved by furin into latent TGFβ. Latent TGFβ is a non-covalently associated complex consisting of Latency-Associated Peptide (LAP) that is the N-terminal portion of pro-TGFβ and the mature TGFβ that is made of the C-terminus of pro-TGFβ. TGFβ is secreted as an inactive (latent) form in a complex with two proteins; LAP (Latency Activated Peptide) and LTBP (Latent TFGβ Binding Protein). Disassociation from this complex is required for its activation that occurs through various means that include low pH, reactive oxygen species, proteases, and several integrins. In this latent form, TGFβ cannot bind the TGFβ receptor and requires activation to become biologically active. In its active form, TGFβ binds to a heterodimeric receptor serine/threonine kinase complex that is comprised of TGFβR1 and TGFβRII. The binding of TGFβ to its receptor results in the phosphorylation/activation of the transcription factors SMAD2/3 that leads to their binding to SMAD4 and subsequent translocation to the nucleus. TGFβ activities include the inhibition of cell growth in epithelial cells, endothelial cells, fibroblasts, neurons, NK cells, T cells, and other hematopoietic cell types. TGFβ1 also downregulates the activities of activated macrophages and blocks the anti-tumor activity of IL-2 – bearing lymphokine-activated killer (LAK) cells. TGFβ1 has also been found to have a critical role in the development of T_{Reg} cells and act as a co-stimulatory factor for expression of Foxp3. These TGFβ1-induced regulatory T cells have been termed iT_{Reg}. Additionally, TGFβ1 and IL-6 together, can induce differentiation of mouse naive T cells into T_H17 cells. (9, 21, 22, 32, 35, 58, 65, 73, 81, 82, 86, 91)	Human	•				•	•	•	•
	Mouse					•	•	•	•
	Rat							•	
TGFβ2 (Transforming Growth Factor beta-2, TGFB2) TGFβ2 is a member of a superfamily of disulfide-linked homodimeric proteins secreted as latent proteins and stored at the cell surface and extracellular matrix. The bioactive TGFβ2 is released from a latent complex by proteolytic processing and conformation changes. TGFβ2 regulates cell proliferation, growth, differentiation and motility as well as synthesis and deposition of the extracellular matrix. TGFβs is also involved in embryogenesis, tissue remodeling and wound healing. Functionally, human TGFβ2 can stimulate mouse cells.	Human					•		•	

TARGET ANALYTE	SPECIES	ANTIBODIES				PROTEINS	IMMUNOASSAYS		
		PURIFIED	VIOLET LASER	BLUE LASER	RED LASER		COAT-IT-YOURSELF	PRE-COAT	MULTIPLEX
TGFβ3 (Transforming Growth Factor beta-3, TGFB3) TGFβ3 is the third member of the transforming growth factor family of cytokines, which also includes TGFβ1 and -β2. These cytokines are secreted in precursor form consisting of a bioactive C-terminal domain attached to an N-terminal domain known as latency associated protein (LAP). Cleavage of LAP results in the mature protein, which functions as a disulfide-linked homodimer. As with all members of the family, TGFβ3 is highly conserved across species, with mouse and human TGFβ3 demonstrating 100% sequence homology and cross-species activity. TGFβ3 is involved in embryogenesis and cell differentiation.	Human					•			
TNFα (Tumor Necrosis Factor alpha) TNFα is a pleiotropic cytokine that plays key roles in innate and adaptive immunity. TNFα is widely implicated in numerous immune responses and regulations, though TNFα is most often associated with regulation of cell survival and pro-inflammatory properties. TNFα is known to induce cellular proliferation/differentiation, tumorigenesis, apoptotic or necrotic cell death (including certain tumor cell lines), immunoregulatory activities, lipid metabolism, coagulation and endothelial function. Its pro-inflammatory properties lead to the recruitment and activation of inflammatory cells to the site of injury where it is known to induce various cytokines that include IL-1, IL-6, IL-8, MCP-1, and RANTES. TNFα is primarily expressed by macrophages and monocytes, but is also expressed by neutrophils, NK-cells, mast-cells, endothelial cells, activated lymphocytes, and various tissue-specific cell types including certain cancers. TNFα is expressed as membrane-bound homotrimer protein that is cleaved by ADAM17 that allows for its release into the blood stream. TNFα binds to two distinctly different type I transmembrane glycoprotein receptors, TNFR1 and TNFR2, that bind to the soluble and membrane-bound forms of TNFα with different affinities. TNFα is associated with numerous diseases due to its role in inflammation and autoimmunity that include rheumatoid arthritis (RA), inflammatory bowel disease (IBS), psoriasis, and multiple sclerosis (MS). Developments of TNFα neutralizing treatments have severely help treat many of these diseases. (67)	Human	•	•	•	•	•	•	•	•
	Mouse	•	•	•	•	•	•	•	•
	Rat	•		•		•	•	•	•
	Monkey						•	•	
TNFβ (Tumor Necrosis Factor beta, Lymphotoxin alpha, LTA) TNFβ is a T_H1 cytokine that can either for a homotrimer or heterodimerize with LTB. In its homotrimer form, TNFβ binds to various receptors that include TNFR1, TNFBR, and TNFRSF14. In its hetrodimeric form with LTB, TNFβ binds to LTBR (TNFRSF3). TNFβ is produced by activated lymphocytes where it is induced in an antigen-specific MHC restricted fashion from class I and class II restricted T cells as well as by lymphoid tissues during viral infections. TNFβ has several effects on target cells that includes killing, proliferation, differentiation and induction of adhesion molecule (ICAM-1) expression. TNFβ participates in tumor immunity, and it has been reported to inhibit carcinogenesis as well as growth of some tumors in vivo.	Human	•		•	•	•	•	•	•
VEGF-A (Vascular Endothelial Growth Factor A) VEGF-A is a growth factor and the central mediator that promotes angiogenesis. VEGFA is active in angiogenesis, vascularization, and endothelial cell growth/survival. It stimulates the secretion and activation of extracellular matrix degrading enzymes. VEGF helps maintain immature vascularization and induces various anti-apoptotic proteins such as Bcl-2 and A1 that help promote cell survival. VEGF also induces angiogenic effects on endothelial cells by binding to the receptor tyrosine kinases VEGFR1/FLT1 and VEGFR2/KDR where it activates various signaling pathways that include Ras/ERK, p38, FAK, PLCγ, and PI3K/AKT. Additionally, VEGF has a potent roll in neovascularization of tumors. Various tumor cell types express VEGF which helps maintains it viability and vascularization. VEGFA consists of various isoforms that include VEGF121 that is acidic and is freely secreted. VEGF145 and VEGF165 that binds to Neuropilin-1 , and VEGF189 is cell associated after secretion and released as a soluble form by heparin or plasmin. (63)	Human					•		•	•
	Mouse					•		•	
VEGF-C (Vascular Endothelial Growth Factor C) VEGF-C has been shown to exhibit angiogenic and lymphangiogenic actions. The VEGF family of growth factors and receptors is involved in the development and growth of the vascular endothelial system. Two of its family members, VEGF-C and VEGF-D, regulate the lymphatic endothelial cells via their receptor VEGFR3, thus acting as mitogens for these cells. VEGF-C expression is associated with hematological malignancies. Like VEGF it acts as survival factor on leukemia. Together with the expression of their receptors, VEGF and VEGF-C result in the generation of autocrine loops that may support cancer cell survival and proliferation. Further VEGF-C expression has been shown in gastrointestinal tract malignancies where it correlates with lymphatic invasion, lymphnode metastasis and reduced survival.	Human							•	
	Rat							•	

VEGF-D (Vascular Endothelial Growth Factor D) VEGF-D is a secreted glycoprotein belonging to the platelet-derived growth factor (PDGF)/ VEGF family that induces angiogenesis and lymphangiogenesis. It is secreted from the cell as a homodimer of the full-length form that can be proteolytically processed to remove the propeptides. VEGF-D is an activating ligand for VEGF-R2/KDR and VEGF-R3/FLT-4, but does not bind to VEGF-R1. VEGF-R2 and VEGF-R3 are localized on vascular and lymphatic endothelial cells and signal for angiogenesis and lymphangiogenesis. VEGF-D is highly expressed in the lung and expression in embryonic lung is upregulated prior to birth. Activation of the VEGF-C/VEGF-D/VEGF-R3 axis increases motility and invasiveness of neoplastic cells, promotes development of metastases in several types of tumors such as lung cancer, breast cancers, cancers of the neck, prostate and large intestine. Generally, VEGF-D is expressed in a large variety of different tumor types like gastric and breast carcinoma, B cell lymphomas, lung adenocarcinoma, non-small cell lung carcinoma, and others. In several types of cancer such as lung cancer, oesophageal carcinoma, and primary lymphedema soluble VEGF-D has been shown to be increased in patient serum.	Human								•

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