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FlowCytomix™

Multiple Analyte Detection User Guide

Individual Analyte Combinations for Your Particular Application

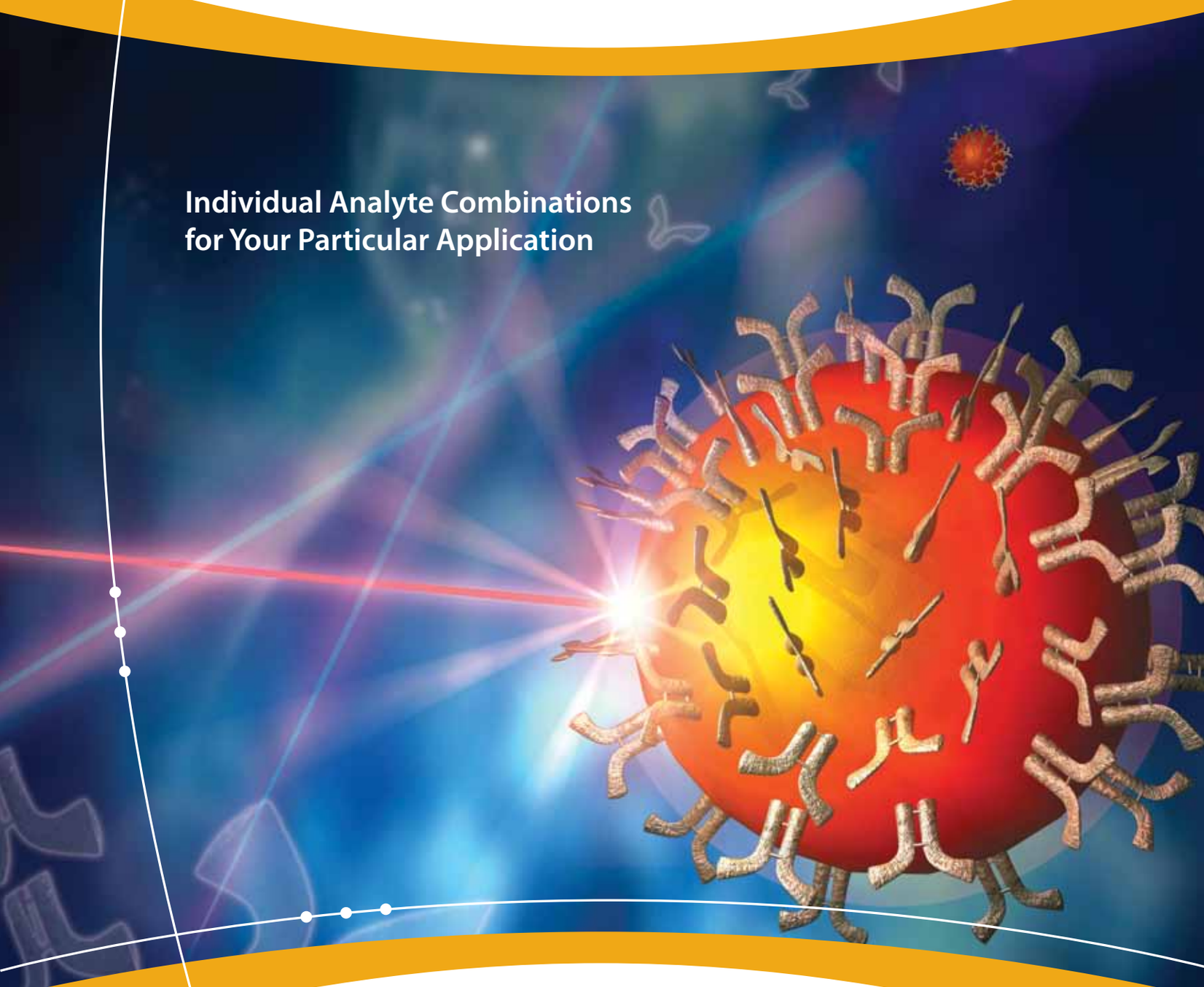

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Table of Contents

1. FlowCytomix™ 1

FlowCytomix™ Multiple Analyte Detection System . . 1
FlowCytomix™ Formats. 3
FlowCytomix™ User Guide. 4

2. FlowCytomix™ Panels 5

Human Airway Inflammation Panel 5
Human Atopic Dermatitis Panel 9
Human Apoptosis Panel 11
Human Bone Biology Panel. 13
Human Cardiovascular Diseases Panel 17
Human Diabetes Mellitus Panel 20
Human Growth and Differentiation Panel 24
Human Immune Regulation Panel. 28
Human Inflammation Panel. 31
Human Multiple Sclerosis Panel 35
Human Obesity Panel. 38
Human Pain Panel 41
Human Preeclampsia Panel 43
Human Rheumatoid Arthritis Panel 45
Human Sepsis / Septic Shock Panel 49
Human Systemic Lupus Erythematosus Panel 53
Human Th17 Panel 56
Human TNF/TNF-R Panel 60
Human Transplantation Panel 63
Human Tumor Biology Panel 67

3. FlowCytomix™ Pro Software 70

4. FlowCytomix™ Complete Product List 73

FlowCytomix™

- FlowCytomix™ Multiple Analyte Detection System
- FlowCytomix™ Formats
- FlowCytomix™ User Guide

QUALITY
DESIGN.
PERFORMANCE.

FlowCytomix™ Multiple Analyte Detection System

Bead-based multiplex immunoassays for the flow cytometer

Multiple analyte detection is an invaluable tool for the comprehensive study of biological systems, as they are comprised of networks of cytokines, chemokines, growth factors and related proteins. The eBioscience FlowCytomix™ Multiple Analyte Detection System, developed by Bender MedSystems, is designed to simultaneously quantify up to 20 protein targets quickly and easily.

Advantages of the FlowCytomix™ Multiple Analyte Detection System

- **Sample friendly** – requires only 25 µL of sample from serum, plasma, or cell culture supernatants.
- **Easy to customize** – choose from a menu of protein targets to create your own assay panels.
- **Flexible protocol** – adaptable for use with 96 well plates or individual tubes.
- **Free software** – no need to spend hundreds of dollars extra for data analysis software.
- **Broad usage** – can be used on most flow cytometers, including single laser instruments.

How FlowCytomix™ Works

The kits contain fluorescent bead sets, each pre-coated with a unique antibody specificity. Within two bead size populations, A and B (4 µm & 5 µm), there are multiple bead subsets, differentiated by varying intensities of an internal fluorescent dye. The dye can be excited by an Argon or He-Ne laser, and emits at 690 nm (the far red spectrum). The combination of the two different bead sizes and different internal dye intensities makes it possible to distinguish up to 20 bead sets in one fluorescent channel. Streptavidin-PE, which binds to the biotin conjugate, emits at 578 nm, allowing the quantification of the analyte.

FlowCytomix™ bead-based assays follow the same principle as a sandwich immunoassay:

Figure 1. Antibody-coated beads are added and incubated with sample.

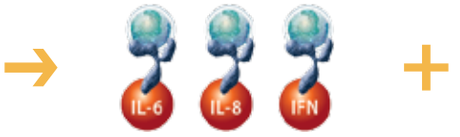


Figure 2. Target analytes in your sample are captured by specific antibodies on each bead set.

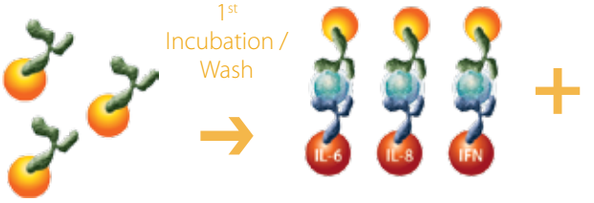


Figure 3. Biotin-conjugated, optimally paired antibodies specific for bound analytes are added.

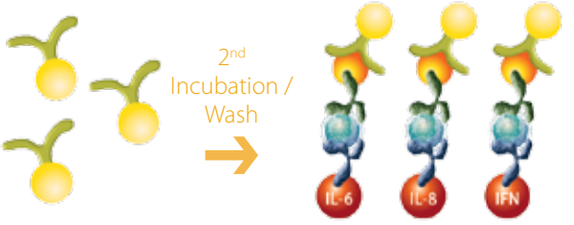


Figure 4. Streptavidin-PE is added for detection of biotin-conjugated antibody.

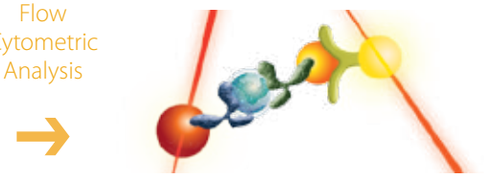


Figure 5. Flow cytometry is used to differentiate bead populations according to bead size and fluorescent signature.

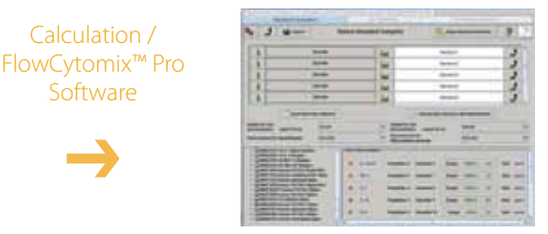


Figure 6. FlowCytomix™ Pro Software conveniently and easily calculates analyte concentrations in the samples.

FlowCytomix™ Formats

Multiplex Kits

Multiplex Kits are designed to focus on a specific group of functionally related proteins and contain all the necessary reagents needed for detection of multiple analyte combinations.

Simplex Kits

Simplex Kits are individual bead sets for detection of one specific analyte, on any flow cytometer. Combine Simplex Kits to create your own customized analyte panels, or use them to extend our predesigned Multiplex Kits for maximum flexibility.

Note: Basic Kits are needed in order to use the Simplex kits.

Basic Kits

Basic Kits contain buffers, plates, streptavidin-PE and set-up beads required to utilize Simplex Kits. Basic Kits are not required if Simplex Kits are combined with Multiplex Kits.

Configuration of the FlowCytomix™ System

Multiplex Kit	=	Simplex Kit	+	Basic Kit
Fluorescent bead sets – each set coated with a unique antibody specificity within a related group		Individual fluorescent bead set - coated with one unique antibody specificity		
Recombinant protein standard panel – proteins corresponding to antibodies provided in the set		Recombinant protein standard		
Biotin-conjugated detection antibodies		Biotin-conjugated detection antibody		
Streptavidin-PE				Streptavidin-PE
96 well filter plate				96 well filter plate
Assay and dilution buffers				Assay and dilution buffers
Set-up beads				Set-up beads

Human Th1/Th2 11plex Ready-to-Use (RTU) FlowCytomix™ Multiplex

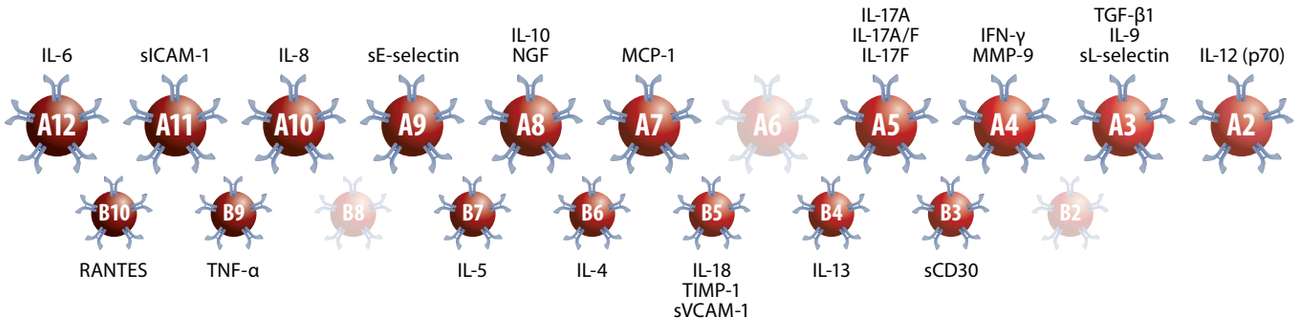
Our most popular human Th1/Th2 cytokine 11plex for the simultaneous detection of multiple analytes is available in a Ready-to-Use format. The designation "RTU" signifies that **all antibody coated bead populations, biotin conjugates, and lyophilized standards are premixed in one vial each.** Simultaneous detection of 11 analytes (IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α and TNF-β) becomes as convenient as to perform one conventional ELISA.

Still, the assay may be combined with additional Simplex Kits. Reduced working steps save about 1 hour hands-on time per kit as compared to conventional format. The human Th1/Th2 11plex Ready-to-Use FlowCytomix™ Multiplex is set-up in 10 minutes.

FlowCytomix™ User Guide

Simplex Kits are individual bead sets for detection of one specific analyte and are designed to be freely combined in order to create individual customized combinations. The panels featured in this guide are designed to help you choose the analytes relevant for your particular research application; a scientific summary explains the role of the respective analytes and lists recent, cutting-edge publications. The illustration at the beginning of each particular research field features the human analytes applicable in this field and the corresponding fluorescent bead populations. The panels include research areas such as Immune Regulation, Inflammation, and Tumor Biology, as well as more specific ones like Atopic Dermatitis, Diabetes and Rheumatoid Arthritis.

Human Airway Inflammation Panel



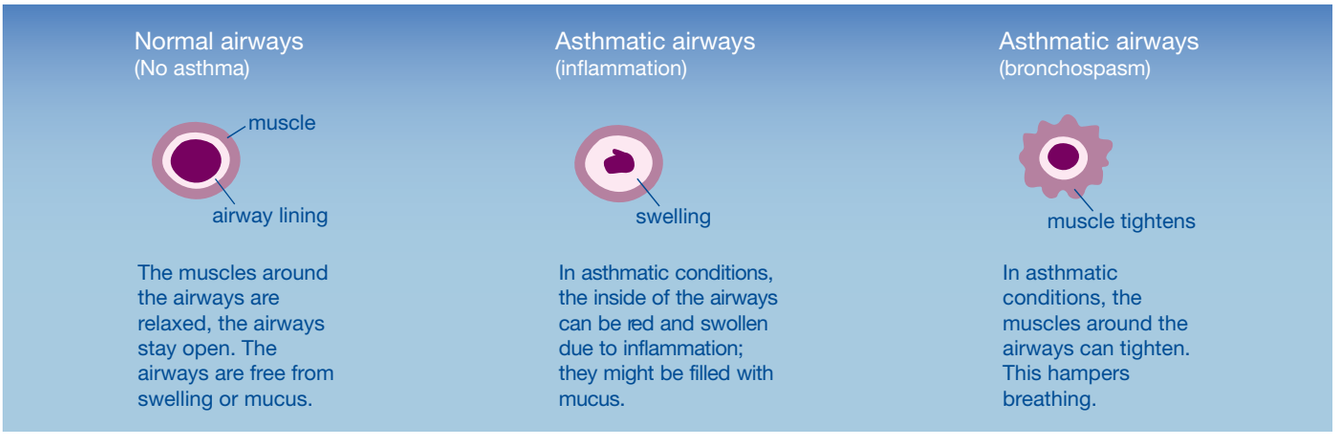
Inflammation, while an important and basic mechanism by which the body reacts to infection, can also promote detrimental conditions such as COPD (chronic obstructive pulmonary disease), sleep apnoea syndromes, and asthma (1), a chronic inflammatory disorder in the lungs with symptoms, including coughing, shortness of breath, tightness in the chest, and wheezing (2) and ranging from mild to life-threatening. In the case of asthma, development of disease results from multiple factors. Predisposing factors, such as allergic reactions to foreign substances, causal factors which may sensitize the airways (e.g. dust mites), and other contributing factors like tobacco smoke or air quality, can have synergistic effects. Other triggers include viral respiratory infections or physical exercise.

Proinflammatory cytokines, **IL-5, IL-6, IL-12, IL-17A, IL-17F** and **IL-18**, as well as the Th2 cytokines **IL-10** and **IL-13**, are present in significantly higher levels in allergic asthma patients. For example, IL-13 is a central mediator of asthma as a modulator of IgE production and IgE-mediated allergic responses. IL-13 shares particular features with **IL-4**, including induction of Th1 cells, and both cytokines can synergize with **TNF-α** or IL-5 in eosinophil activation. IL-17A, a relatively novel proinflammatory cytokine, induces IL-6, **ICAM-1** and GM-CSF expression, as well as T cell proliferation. Expression levels of IL-17F in asthmatic airways may correlate with disease severity and in fact, overexpression of the IL-17F gene in the airways of mice is associated with airway neutrophilia, induction of many cytokines, increased airway hyperreactivity, and mucus hypersecretion (3). In mouse models, it is suggested that IL-18 increases allergic sensitization, serum IgE, Th2 cytokines and airway eosinophilia (4, 5). **IL-8** has been shown to be significantly increased in bronchioalveolar fluid in COPD (6). Asthmatic patients produce large amounts of **IL-9**, released by activated T cells, which contributes to the development of asthma and may correlate with biological parameters of the disease (7). IL-33 broadly enhances allergic inflammation through its effects on hematopoietic cell types. Higher levels of IL-33 are expressed in airway smooth muscle cells in asthmatic patients, and especially in subjects with severe asthma (8, 9).

In concert with cytokine involvement, adhesion molecules also play a key role in the development of inflammatory conditions of the respiratory tract. A study investigating the relationship between air pollution and asthma revealed that serum levels of **sICAM-1** and **sVCAM-1** were dramatically higher in asthmatic children (10). Similar changes in sVCAM-1 and **sE-selectin** were observed in serum samples from patients suffering from severe asthma (11, 12). In mouse models, ICAM-1 and **L-selectin** trigger development of allergic airway inflammation and airway hyper-responsiveness in asthma by mediating leukocyte rolling on inflamed pulmonary endothelium (13). In the case of COPD, patients display increased levels of **TIMP-1**, MMP-1, -8, and **MMP-9**. Specific differences in MMP profiles are observed in association with COPD, asthma and cigarette smokers (18).

Chemokines, small-sized cytokines and key mediators in the recruitment of regulatory and effector leukocytes, are thought to stimulate histamine or leukotriene release from mast cells or basophils, induction of **TGF-β** production by fibroblasts, and enhancement of Th2 polarization. **MCP-1** expression is increased in animal models of allergic asthma or idiopathic pulmonary fibrosis, and moreover, the process of the disease can be attenuated by MCP-1 neutralization

(19). Mononuclear cells isolated from atopic asthma patients produce **RANTES** in response to specific allergen (20) and serum concentrations are significantly increased in asthmatic children (10). Recently there is evidence that neuronal dysfunction contributes to the development of allergic asthma. In particular, neurotrophins, e.g. **NGF** (nerve growth factor), seem to have a major impact on various immune cells involved in the pathogenesis of allergic disease. Immune cells themselves produce neurotrophins, which are significantly upregulated in allergic conditions, leading to bronchial hyperreactivity, a hallmark of asthma, and neurogenic inflammation. In asthma patients, bronchial provocation with allergen leads to an increase in NGF expression and release (15-17).



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Human FlowCytomix™ Airway Inflammation Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Th1/Th2 11plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FF
Th1/Th2 11plex Ready-to-Use	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FFRTU
Th1/Th2/Th9/Th17/ Th22 13plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p70), IL-13, IL-17A, IL-22, TNF-α	BMS817FF
Chemokine 6plex	G-CSF, IL-8, MCP-1, MIG, MIP-1α, MIP-1β	BMS813FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
sE-selectin	A9	1.2 ng/ml	4.0 - 3,000 ng/ml	BMS8205FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-5	B7	1.6 pg/ml	27 - 20,000 pg/ml	BMS8278FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-9	A10	1.5 pg/ml	2.7 - 2,000 pg/ml	BMS82081FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-13	B4	4.5 pg/ml	27 - 20,000 pg/ml	BMS8231FF
IL-17A	A5	2.5 pg/ml	13.7 - 10,000 pg/ml	BMS82017FF
IL-17A/F	A5	16 pg/ml	27 - 20,000 pg/ml	BMS82082FF
IL-17F	A5	8.0 pg/ml	27 - 20,000 pg/ml	BMS82037FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
sL-selectin[1)]	A3	70 pg/ml	137 - 100,000 pg/ml	BMS80206FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MMP-9[1)5)]	A4	95 pg/ml	0.1 - 100 ng/ml	BMS82016FF
NGF	A8	126.75 pg/ml	412 - 300,000 pg/ml	BMS82044FF
RANTES[1)]	B10	25 pg/ml	41 - 30,000 pg/ml	BMS8287FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TIMP-1[1)5)]	B5	28 pg/ml	137 - 100,000 pg/ml	BMS82018FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF

Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Th1/Th2 10plex	GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, TNF-α	BMS820FF
Th1/Th2/Th17/Th22 13plex	IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17A, IL-21, IL-22, IL-27, TNF-α	BMS822FF
Chemokine 6plex	GM-CSF, MCP-1, MCP-3, MIP-1α, MIP-1β, RANTES	BMS821FF

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Further Species (continued)

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-5	A8	4.0 pg/ml	27 - 20,000 pg/ml	BMS8610FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
IL-13	A2	9.3 pg/ml	27 - 20,000 pg/ml	BMS86015FF
IL-17A	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS86001FF
IL-17A/F	B10	1.0 pg/ml	2.7 - 2,000 pg/ml	BMS86026FF
IL-17F	A7	6.0 pg/ml	27 - 20,000 pg/ml	BMS86020FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
IL-33	A3	see www.eBioscience.com		BMS86025FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
RANTES	B4	6.1 pg/ml	27 - 20,000 pg/ml	BMS86009FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokine 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
IL-17A	A10	5.0 pg/ml	7.0 - 5,000 pg/ml	BMS8635FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

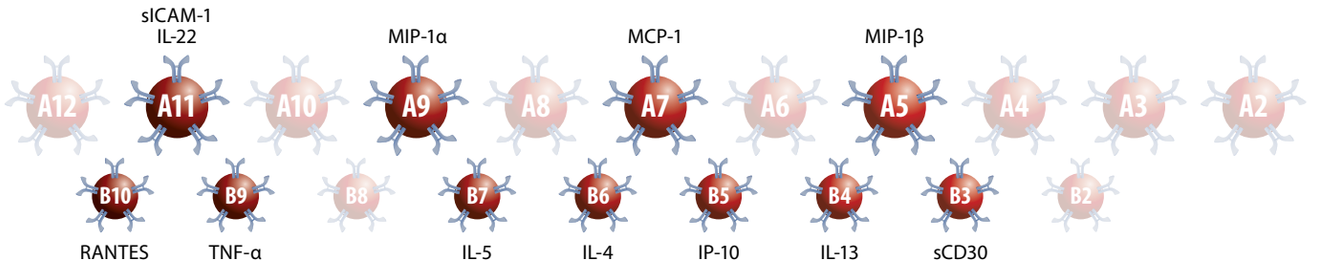
1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.

4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.

5) MMP Simplex Kits cannot be combined with the TIMP-1 Simplex Kit.

New products are launched regularly. **Discover more at www.eBioscience.com.**

Human Atopic Dermatitis Panel



Atopic dermatitis (AD) affects up to 1 in 5 children. While it's less prevalent in adults, a significant number of people do carry the condition into adulthood. Interestingly, an increase in incidence in developed nations, has been noted up to three-fold , over the past decades. AD is characterized as a chronic, inflammatory skin disease, and is often associated with allergic rhinitis and asthma. At the cellular level, AD is characterized by elevated serum IgE levels, with T cells being key modulators. Most T cells in the tissue environs of AD skin produce Th2 cytokines such as **IL-4**, **IL-5** and **IL-13**, which may contribute to pathogenesis. Both T cells and mast cells secrete IL-4 and IL-13, which are capable of inducing an IgG to IgE switch. T cell activation and activation of accessory cell types, which release cytokines and chemokines, further attract inflammatory cells into the affected area(s) of the skin (1, 2).

Distinct **IL-22**-producing CD4+ and CD8+ T cell populations are significantly increased in AD skin. IL-22+ CD8+ T cell frequency often correlates with AD disease severity (6), and serum levels of **RANTES**, **MCP-1**, and **MIP-1β** are also increased in AD patients.

Spontaneous production of RANTES, MCP-1, **MIP-1α** and MIP-1β by PBMCS is augmented in AD patients. Serum RANTES levels correlate with total serum IgE and eosinophil numbers (7). Furthermore, increased **IP-10** levels have been detected in AD plasma. IP-10 is produced by keratinocytes upon IL-18 stimulation. Fibroblasts from AD patients have higher IP-10 expression and are more sensitive to TNF-α stimulation (8, 9). Generally, inflammatory skin disorders like AD and psoriasis are accompanied by elevated **ICAM-1** expression in lesional skin keratinocytes, which might be mediated by a degranulation of mast cells. Mast cells contain **TNF-α**, which is thought to induce ICAM-1 expression (3).

CD30, a TNF receptor superfamily member, is a costimulatory molecule expressed on activated T- and B cells. On T cells, CD30 is a marker of the Th2 phenotype. In atopic children, soluble CD30 was demonstrated to be significantly increased in serum, and these levels correlated with disease severity. Rather than a single cell type expressing the protein, it was found that various cells types will express CD30 in AD skin lesions. For example, CD4+ T cells, CD1a+ Langerhans cells and CD8+ T cells all have been positively stained for CD30, and this is correlated with disease severity (4, 5).

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Human FlowCytomix™ Atopic Dermatitis Panel

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-5	B7	1.6 pg/ml	27 - 20,000 pg/ml	BMS8278FF
IL-13	B4	4.5 pg/ml	27 - 20,000 pg/ml	BMS8231FF
IL-22	A11	43.3 pg/ml	110 - 80,000 pg/ml	BMS82047FF
IP-10	B5	6.0 pg/ml	17 - 12,500 pg/ml	BMS8284FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MIP-1α	A9	1.0 pg/ml	13.7 - 10,000 pg/ml	BMS82029FF
MIP-1β	A5	1.0 pg/ml	4.0 - 3,000 pg/ml	BMS82030FF
RANTES[1)]	B10	25 pg/ml	41 - 30,000 pg/ml	BMS8287FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF

Further Species

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
IP-10	A3	9.8 pg/ml	41 - 30,000 pg/ml	BMS86018FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-5	A8	4.0 pg/ml	27 - 20,000 pg/ml	BMS8610FF
IL-13	A2	9.3 pg/ml	27 - 20,000 pg/ml	BMS86015FF
IL-22	A5	5.5 pg/ml	6.9 - 5,000 pg/ml	BMS86016FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
MIP-1α	A11	1.8 pg/ml	27 - 20,000 pg/ml	BMS86013FF
MIP-1β	B2	14.9 pg/ml	27 - 20,000 pg/ml	BMS86014FF
RANTES	B4	6.1 pg/ml	27 - 20,000 pg/ml	BMS86009FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.

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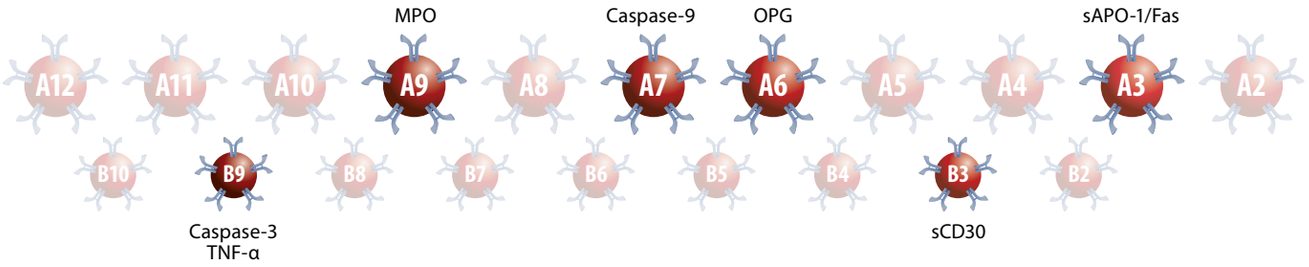
Human Apoptosis Panel



Cell death can occur via several pathways, including apoptosis, necrosis, and other "emerging" pathways which have become the focus of intense research. Classification of these types of cell death involves a defined set of morphological and/or biochemical criteria. Apoptosis is a physiological form of programmed cell death which plays an important role in cellular homeostasis in the immune system, in the selection of T cell repertoire, deletion of self-reactive lymphocytes, and cytotoxic response against target cells. **APO-1/Fas** is an apoptosis-signaling receptor molecule on the surface of various cell types. Soluble APO-1/Fas may neutralize and therefore prevent cells from undergoing Fas Ligand-induced apoptosis, e.g. tumor cells that release soluble APO-1/Fas may escape immunosurveillance (1). Caspases, cysteine proteases and so-called "executioners of apoptosis", include initiator **caspases** (-2, -8, **-9**, -10) which become activated by their homodimerization and release into the cytoplasm. Further down the signaling pathway, effector caspases (-3, -6, -7), cleave other protein substrates within the cell. Apoptosis within many cell types, and in particular in osteoclasts, is regulated by the Bcl-2 family protein Bim. **Caspase-3** promotes the degradation of Bim during osteoclast apoptosis. This caspase-3/Bim axis plays an important role in the regulation of apoptosis as well as activation of osteoclasts (2).

In addition to Fas and TNF-RI, a variety of other cell surface receptors can induce the apoptotic cell signaling cascade. For example, in anaplastic large cell lymphoma cells, **CD30** stimulation leads to growth arrest and apoptosis. In eosinophils, CD30 expression levels correlate with their susceptibility to apoptotic cell death. Levels of soluble CD30 in serum, however, are a marker of acute graft rejection (3-5). TNF-R (60kDa) is expressed on most cell types, and initiates the majority of biological activities induced by TNF-α. Binding of **TNF-α** to TNF-R (60kDa) is a classic model of apoptotic cell death. However, TNF-R (60kDa) activation can also induce anti-apoptotic cell/survival signals (6, 7). TNF-α secretion by activated macrophages, T-cells and NK cells, may be regulated and/or neutralized by its own soluble TNF-α receptors. In neurodegenerative diseases such as MS (multiple sclerosis), Alzheimer´s disease, prion disease, and Parkinson's disease, TNF-α production by activated microglial cells leads to neuronal degeneration due to apoptosis of neuronal tissue and increased inflammation. **MPO** (myeloperoxidase) can act as a key mediator in oxidative stress-mediated apoptosis in myeloid leukemic cells and has been demonstrated to serve as a redox switch that regulates apoptosis in ovarian cancer cells (8, 9). Finally, **OPG** (osteoprotegerin) is a decoy receptor for TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) which can compete with death receptors for ligand binding, although OPG itself does not transduce apoptotic signals (10).

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Human FlowCytomix™ Apoptosis Panel

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sAPO-1/Fas[1)]	A3	10.0 pg/ml	34 - 25,000 pg/ml	BMS80245FF
Caspase-3[6)]	B9	20 pg/ml	82 - 60,000 pg/ml	BMS82012FF
Caspase-9[6)]	A7	0.07 ng/ml	0.2 - 150 ng/ml	BMS82025FF
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
MPO	A9	0.02 ng/ml	0.14 - 100 ng/ml	BMS82038FF
OPG	A6	7.9 pg/ml	27 - 20,000 pg/ml	BMS82021FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF

Further Species

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.

6) The Caspase-3 Simplex Kit may only be combined with the Caspase-9 Simplex Kit and vice versa.

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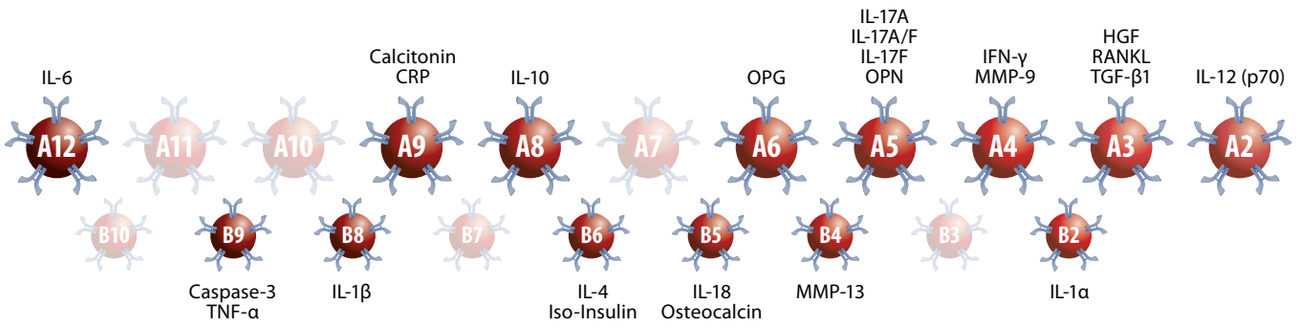
Human Bone Biology Panel



Bone remodeling involves the specific interaction between two specific types of cells. Osteoclasts, named from the Greek words for broken and bone, develop from the hematopoietic mononuclear cells, and can remove bone tissue via resorption. Osteoblasts, also from the Greek words meaning embryonic and bone, originate from mesenchymal stem cells, and as such are involved in formation of new tissue. For these interactions to work well, many types of cytokines and signaling proteins are expressed and are essential in the bone remodeling process. M-CSF and **RANKL** are secreted by bone marrow stromal cells and osteoblasts, and are essential for osteoclastogenesis. RANK, the receptor for RANKL, is expressed on mononuclear osteoclast precursors. **OPG** (osteoprotegerin) is a natural decoy receptor for RANKL and acts as a soluble bone protector. In fact, in OPG knock-out models, mice show greater decreased bone density and volume and develop osteoporosis, bone fractures and vertebral deformities. In contrast, RANKL transgenic mice exhibit marked osteoporosis. Mice with disrupted RANKL are strongly osteopetrotic, and lack any mature osteoclasts. RANKL triggers RANK+ cancer cell migration and growth in bone tissue. RANK was detected in more than 50% of human osteosarcoma specimens examined. RANKL also induces MCP-1 (monocyte chemotactic protein-1) and IL-8, which act in autocrine fashion to upregulate RANKL expression and heighten inflammation and associated pathologies. **IL-1, IL-6, IL-17**, and **TNF-α** also promote RANKL production and thus osteoclastogenesis, whereas **IL-4, IL-10, IL-12, IL-18** and GM-CSF decrease osteoclast differentiation. IFN-β and **IFN-γ** also inhibit osteoclast differentiation and activation.

In association with arthritic pathologies, elevated levels of osteoclastogenesis-promoting cytokines such as IL-1, IL-6, IL-17, TNF-α, and RANKL have also been observed in synovial fluid from arthritic joints. IL-6 may modulate the imbalance between MMPs and TIMPs in rheumatoid arthritis (RA), conditions which lead to joint and cartilage destruction. RANKL and IL-17 are increasingly produced by CD4+ T cells from patients with ankylosing spondylitis.

T cells may also contribute significantly to the pathogenesis of osteoporosis. CD8+ CD57+ T cells are increased in women with osteoporotic fractures. These cells secrete the proinflammatory cytokine TNF-α. Peripheral blood mononuclear cells from postmenopausal women release significantly higher amounts of IL-1, IL-6, and TNF-α (1-6).

Increased serum levels of the acute phase protein **CRP** (C-reactive protein) are associated with low bone mineral density in elderly females. Serum CRP is furthermore elevated in patients with bacterial-, rheumatoid- and crystal induced arthritis. CRP also enhances shedding of IL-6 receptor, which is increased in synovial fluid in RA (7, 8).

OPN (osteopontin), produced by multiple tissue types, is most abundant in bone. It is also expressed by cancer cells and plays a key role in cancer growth, progression and metastasis. OPN results in production of uPA, which is able to activate growth factors such as **HGF** (hepatocyte growth factor), **TGF-β** and basic FGF . TGF-β is the most abundant growth factor in human bone and is critical during embryonic development for promoting migration of cells to sites of skeletogenesis. TGF-β also induces mesenchymal cell differentiation to chondrocytes or osteoblasts, and inhibits the expression of **osteocalcin** (9, 10). Osteocalcin is expressed by osteoblasts, odontoblasts, and some chondrocytes. It can accumulate in the extracellular matrix of bone, or be found in serum, where its levels reflect osteoblast activity and the rate of bone formation (11, 12). *In vitro* and *In vivo* studies demonstrate calcitonin's potent inhibitory effect on osteoclasts. Calcitonin may protect bone during periods

of 'calcium stress', e.g. growth, pregnancy, and lactation. Calcitonin is an approved treatment for osteoporosis (13).

Finally, **caspase-3** influences osteoclast differentiation via regulation of Bim degradation in the course of osteoclast apoptosis. Caspase-3-deficient mice display delayed ossification and decreased bone mineral density (14, 15). The **insulin**-signaling apparatus is involved in bone growth and bone formation (16). Another product of osteoclast cells is **MMP-9** (matrix metalloproteinase-9), which can affect prostate tumor growth in the bone microenvironment of mice. **MMP-13** plays a role in osteolysis associated with breast cancer bone metastasis and MMP-13 mRNA is increased in osteoarthritic subchondral bone osteoblasts (17, 18). IL-33 has recently been shown to promote formation of functional osteoclasts from CD14+ monocytes (19).

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Human FlowCytomix™ Bone Biology Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Th1/Th2 11plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FF
Th1/Th2 11plex Ready-to-Use	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FFRTU
Th1/Th2/Th9/Th17/ Th22 13plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p70), IL-13, IL-17A, IL-22, TNF-α	BMS817FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
Calcitonin	A9	12 pg/ml	14 - 10,000 pg/ml	BMS82067FF
Caspase-3[6)]	B9	20 pg/ml	82 - 60,000 pg/ml	BMS82012FF
CRP[1)]	A9	0.07 ng/ml	0.1 - 70 ng/ml	BMS8288FF
HGF	A3	52 pg/ml	206 - 150,000 pg/ml	BMS82069FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-1α	B2	0.5 pg/ml	1.4 - 1,000 pg/ml	BMS80243FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-17A	A5	2.5 pg/ml	13.7 - 10,000 pg/ml	BMS82017FF
IL-17A/F	A5	16 pg/ml	27 - 20,000 pg/ml	BMS82082FF
IL-17F	A5	8.0 pg/ml	27 - 20,000 pg/ml	BMS82037FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
Iso-Insulin	B6	80 pg/ml	274 - 200,000 pg/ml	BMS82003FF
MMP-9[1)5)]	A4	95 pg/ml	0.1 - 100 ng/ml	BMS82016FF
MMP-13[5)]	B4	0.05 ng/ml	0.17 - 125 ng/ml	BMS82022FF
OPG	A6	7.9 pg/ml	27 - 20,000 pg/ml	BMS82021FF
OPN	A5	432 pg/ml	274 - 200,000 pg/ml	BMS82066FF
Osteocalcin	B5	6.9 pg/ml	27 - 20,000 pg/ml	BMS82020FF
RANKL	A3	16 pg/ml	55 - 40,000 pg/ml	BMS82005FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF

Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Th1/Th2 10plex	GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, TNF-α	BMS820FF
Th1/Th2/Th17/Th22 13plex	IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17A, IL-21, IL-22, IL-27, TNF-α	BMS822FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-1α	A4	15.7 pg/ml	27 - 20,000 pg/ml	BMS8611FF
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF

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Further Species (continued)

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits (cont.)				
IL-17A	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS86001FF
IL-17A/F	B10	1.0 pg/ml	2.7 - 2,000 pg/ml	BMS86026FF
IL-17F	A7	6.0 pg/ml	27 - 20,000 pg/ml	BMS86020FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
IL-33	A3	see www.eBioscience.com		BMS86025FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokine 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-1α	A6	8.5 pg/ml	27 - 20,000 pg/ml	BMS8627FF
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
IL-17A	A10	5.0 pg/ml	7 - 5,000 pg/ml	BMS8635FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.
4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.
5) MMP Simplex Kits cannot be combined with the TIMP-1 Simplex Kit.
6) The Caspase-3 Simplex Kit may only be combined with the Caspase-9 Simplex Kit and vice versa.

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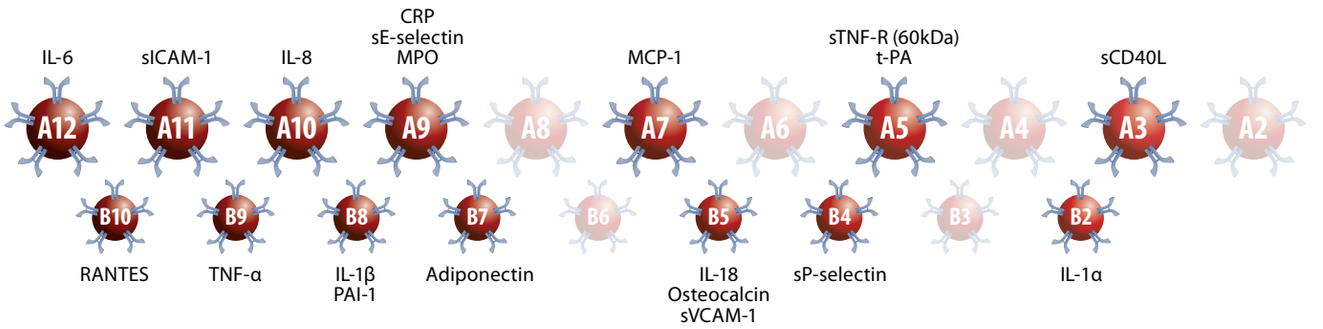
Human Cardiovascular Diseases Panel



Cardiovascular diseases are commonly associated with systemic inflammatory responses, as evidenced by increased expression of the inflammatory proteins **CRP**, **IL-1**, **IL-6**, **IL-18** and **TNF-α**. These proteins may be regarded as diagnostic markers in risk assessment for various cardio-related conditions (1, 2). , for example, is considered a prognostic plasma marker in patients during the acute phase following myocardial infarction (3). CD40, another member of the TNF receptor superfamily, and CD40L expression by activated T helper cells, each play a key role in immune activation, particularly in T cell dependent B cell responses. CD40 and CD40L contribute to the development of atherosclerosis and thrombosis (1-4), and in fact, **CD40L** expression may be a predictor of further risk after coronary syndrome.

Pathological cardiovascular conditions are also associated with increased expression of adhesion molecules, in particular **sICAM-1**, **sVCAM-1** and **sE-selectin** (5). Levels of sICAM-1, sVCAM-1, sE-selectin and **sP-selectin** have been correlated with smoking, as well as high blood pressure and serum cholesterol. sICAM-1 and sE-selectin are closely related to CRP concentrations (6, 7).

Heart disease-related inflammatory processes begin with infiltration of the myocardium by activated monocytes and macrophages and consequent damage of cardiomyocytes. Here an important mediator is **MCP-1**, a chemokine which functions to recruit these effector cells into the affected tissue. MCP-1 is expressed in atherosclerosis, myocardial infarction and congestive heart failure, and is particularly heightened in cases of dilated cardiomyopathy (8, 9). Other inflammatory mediators like IL-6, **IL-8** and MCP-1 induce tissue factor, the main initiator of the extrinsic coagulation cascade. Taken together, the rise in inflammatory markers together with the activation of the coagulation cascade may predict an unfavorable outcome in acute coronary syndromes (10).

Increased **RANTES** serum levels are detectable in coronary artery disease (11). **t-PA** plasma levels may be altered in cardiac transplant recipients. t-PA is described as a factor correlating to the risk of development of cardiovascular disease. Changes of t-PA levels were shown in myocardial infarction. In stroke patients, high t-PA antigen concentrations indicate an activation of the fibrinolytic system or a complex formation with the inhibitors. High t-PA and **PAI-1** levels are therefore considered markers of stroke acute phase (12). PAI-1 is the primary inhibitor of plasminogen activators in plasma, rapidly inactivating both tissue t-PA and u-PA. Increased PAI-1 levels have been shown to be associated with a number of atherosclerotic risk factors, and has been shown to act as a prothrombic factor in both arterial and venous thromboembolic disorders. Furthermore, PAI-1 levels are increased in instances of chronic and acute coronary artery diseases as well as in patients who suffer from restenosis after coronary angioplasty (13-15).

MPO (myeloperoxidase) is an enzyme in the azurophilic granules of neutrophils and in the lysosomes of monocytes. Its major role is to aid in microbial killing, but it has also been demonstrated to affect atherosclerosis, in that MPO deficiency may protect against cardiovascular disease (16). Adipokines, factors secreted by adipocytes, are commonly known to promote pathological cardiovascular conditions. However, **adiponectin** exerts protective effects against in both diabetes and cardiovascular diseases. Adiponectin acts to increase insulin sensitivity and to enhance fatty acid oxidation. Other functions include its ability to suppress monocyte-endothelial interaction, to lower blood pressure, and to moderate adipose tissue growth (17, 18).

Finally, bone-derived osteocalcin regulates insulin secretion and sensitivity in mice, and reduced serum total **osteocalcin** is associated with diabetes in humans. A recent study has shown that reduced serum osteocalcin levels increased waist circumference, glucose and triglyceride levels are associated in aging men. It remains to be seen whether raising osteocalcin can reduce cardiovascular risk (19).

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Human FlowCytomix™ Cardiovascular Diseases Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Adhesion 6plex	sE-selectin, sICAM-1, sICAM-3, sPECAM-1, sP-selectin, sVCAM-1	BMS812FF
Cardiovascular 6plex	sCD40L, IL-6, IL-8, MCP-1, sP-selectin, t-PA	BMS811/2FF
Obesity 9plex	sCD40L, sICAM-1, IL-6, Leptin, MCP-1, MPO, OPG, Resistin, sTNF-R (60kDa)	BMS816/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
Adiponectin[1)]	B7	0.06 ng/ml	0.1 - 50 ng/ml	BMS82032FF
sCD40L	A3	23.4 pg/ml	55 - 40,000 pg/ml	BMS8239/2FF
CRP[1)]	A9	0.07 ng/ml	0.1 - 70 ng/ml	BMS8288FF
sE-selectin	A9	1.2 ng/ml	4.0 - 3,000 ng/ml	BMS8205FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
IL-1α	B2	0.5 pg/ml	1.4 - 1,000 pg/ml	BMS80243FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MPO	A9	0.02 ng/ml	0.14 - 100 ng/ml	BMS82038FF
PAI-1[1)3)]	B8	13.5 pg/ml	137 - 100,000 pg/ml	BMS82033FF
Osteocalcin	B5	6.9 pg/ml	27 - 20,000 pg/ml	BMS82020FF
sP-selectin	B4	1.2 ng/ml	2.8 - 2,000 ng/ml	BMS8219/2FF
RANTES[1)]	B10	25 pg/ml	41 - 30,000 pg/ml	BMS8287FF
TNF-α[2)]	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
sTNF-R (60kDa)[2)]	A5	0.08 ng/ml	0.14 - 100 ng/ml	BMS8203FF
t-PA[3)]	A5	4.8 pg/ml	27 - 20,000 pg/ml	BMS8258FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF

1) *Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.*
2) *The TNF-R (60kDa) Simplex Kit cannot be assayed simultaneously with the TNF-α or the TNF-β Simplex Kit.*
3) *PAI-1 and t-PA Simplex Kits cannot be assayed simultaneously.*

Further Species

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IL-1α	A4	15.7 pg/ml	27 - 20,000 pg/ml	BMS8611FF
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
RANTES	B4	6.1 pg/ml	27 - 20,000 pg/ml	BMS86009FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0- 2,000 pg/ml	BMS8621/3FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

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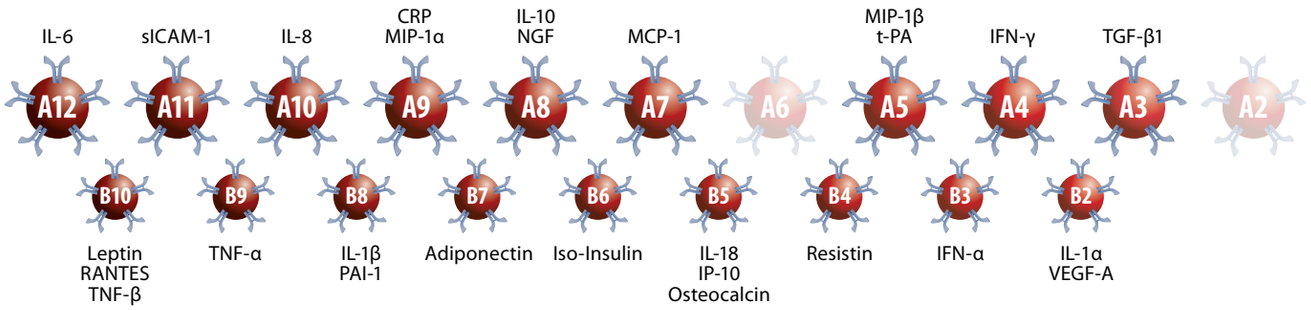
Human Diabetes Mellitus Panel



Diabetes mellitus is comprised of a group of disorders, of multiple origins. Typical symptoms include hyperglycemia, with disturbed carbohydrate, fat, and protein metabolism due to defects in insulin secretion and/or insulin action.

Type 1 diabetes (T1D) is characterized by insulin deficiency due to autoimmune-associated destruction of insulin-producing β-cells in the islets of Langerhans. Symptoms arise when the β-cell mass becomes diminished. β-cells express the receptors for **IL-1β**, **TNF-α** and **IFN-γ**, cytokines which are observed at increased levels in animal models and in humans at the onset of the disease. In isolated rat β-cells, IL-1β is cytotoxic, and its effects are potentiated by TNF-α and IFN-γ (1).

Th1 cytokines IFN-γ and **TNF-β**, as well TNF-α, **IL-6**, **IL-10**, **TGF-β**, and chemokines such as **RANTES** and **MCP-1** were elevated in T1D children (2). A study evaluating T1D risk in first degree relatives of T1D patients demonstrated increased levels of **MIP-1α** and **MIP-1β**, but decreased MCP-1 in the multiple islet autoantibody-positive group (3). Generally, **IP-10**, MCP-1, and **VEGF-A** have been found to be elevated in vitreous, whereas MIP-1β, RANTES, and VEGF-A are increased in serum of diabetic patients (8). In patients with recent onset of T1D, IL-18 can be increased and MCP-1 decreased (4). A study focusing on **NGF** (nerve growth factor) and TGF-β2 levels in T1D showed increased NGF levels in sera of T1D patients compared to healthy controls, but also compared to T2D (type 2 diabetes) patients. In contrast, TGF-β2 levels were decreased in T1D patients compared to the other two groups (5).

In Type 2 Diabetes (T2D), **insulin** may be present, but has decreased effects in target tissues; a condition known as insulin resistance. T2D may also result from a secretory defect of insulin, with or without insulin resistance. In fact, elevated insulin levels can be seen in T2D. The mechanism in this disease may involve the acute phase response and activation of the innate immune system. Clinical conditions such as insulin resistance and central obesity are often associated with T2D. Adipose tissue (AT) contains multiple cell types: adipocytes, nerve cells, stromal-vascular cells, macrophages, endothelial cells, and fibroblasts. Long believed to be a passive tissue, the endocrine capacity of adipose tissue is of recent interest as it contains cells expressing pro-inflammatory mediators. These have been causally linked with insulin resistance. Cytokines expressed by AT are also referred to as "adipokines" and include TNF-α, IL-6, **IL-8**, MCP-1, **CRP**, **PAI-1**, **adiponectin** and others. Elevated concentrations of IL-1β and IL-6 are associated with increased incidence of diabetes. TNF-α is a key adipocyte-expressed cytokine. It is often overexpressed in obesity, can impair insulin sensitivity, and may synergize with other cytokines to accelerate dysfunction and destruction of β-cells. IL-6 affects glucose homeostasis and metabolism by influencing skeletal muscle cells, adipocytes, hepatocytes, pancreatic β-cells, and neuroendocrine cells. It also induces increased plasma concentrations of fibrinogen, PAI-1, and CRP. In combination with other cytokines, IL-6 has been shown to have cytotoxic effects on β-cells.

An interesting cytokine-like hormone is **leptin**, which is primarily a product of adipocytes. It acts on the hypothalamus, inhibits appetite and increases energy consumption. In humans, studies suggest a correlation between leptin and insulin signaling in that insulin can induce mRNA and protein expression by adipocytes. Increased serum leptin levels are found preceding the onset of diabetes in nonobese diabetic mice. Leptin administration seems to raise both inflammatory infiltrates and IFN-γ production in peripheral T cells, accelerating pancreatic β-cell impairment. MCP-1 plays a key role in the recruitment of monocytes into AT by activating resident macrophages to produce those cytokines that attract monocytes and macrophages into

the tissue, amplifying localized inflammation. Adiponectin, an adipose-specific plasma protein, is decreased in parallel with obesity-related insulin resistance and T2D. **Resistin**, another adipocyte-derived hormone, is mainly expressed in white AT, is found in serum, and may play a role in insulin resistance (6). Moreover, T2D is associated with increased concentrations of total **t-PA** and its inhibitor PAI-1(7).

Osteocalcin has been described to be increased in T2D. During pregnancy plasma osteocalcin is significantly higher in women with gestational diabetes mellitus than in healthy women, and may also correlate with insulin secretion parameters (9). Furthermore, a potential role of IL-27 in autoimmune diabetes is suggested in that higher levels of IL-27 have been detected in diabetic NOD mice. Neutralization of IL-27 can delay the onset of diabetic splenocyte-transferred diabetes, while IL-27-treated diabetic splenocytes can promote the onset of the disease (10).

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Human FlowCytomix™ Diabetes Mellitus Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Cardiovascular 6plex	sCD40L, IL-6, IL-8, MCP-1, sP-selectin, t-PA	BMS811/2FF
Obesity 9plex	sCD40L, sICAM-1, IL-6, Leptin, MCP-1, MPO, OPG, Resistin, sTNF-R (60kDa)	BMS816/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
Adiponectin[1)]	B7	0.06 ng/ml	0.1 - 50 ng/ml	BMS82032FF
CRP[1)]	A9	0.07 ng/ml	0.1 - 70 ng/ml	BMS8288FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
IFN-α	B3	8.06 pg/ml	27 - 20,000 pg/ml	BMS8216FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-1α	B2	0.5 pg/ml	1.4 - 1,000 pg/ml	BMS80243FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
IP-10	B5	6.0 pg/ml	17 - 12,500 pg/ml	BMS8284FF
Iso-Insulin	B6	80 pg/ml	274 - 200,000 pg/ml	BMS82003FF
Leptin	B10	0.05 ng/ml	0.3 - 250 ng/ml	BMS82039/2FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MIP-1α	A9	1.0 pg/ml	13.7 - 10,000 pg/ml	BMS82029FF
MIP-1β	A5	1.0 pg/ml	4.0 - 3,000 pg/ml	BMS82030FF
NGF	A8	126.75 pg/ml	412 - 300,000 pg/ml	BMS82044FF
Osteocalcin	B5	6.9 pg/ml	27 - 20,000 pg/ml	BMS82020FF
PAI-1[1)3)]	B8	13.5 pg/ml	137 - 100,000 pg/ml	BMS82033FF
RANTES[1)]	B10	25 pg/ml	41 - 30,000 pg/ml	BMS8287FF
Resistin	B4	1.7 pg/ml	55 - 40,000 pg/ml	BMS82040FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
TNF-β	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS8202FF
t-PA[3)]	A5	4.8 pg/ml	27 - 20,000 pg/ml	BMS8258FF
VEGF-A	B2	7.2 pg/ml	27 - 20,000 pg/ml	BMS80277FF

Further Species

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-1α	A4	15.7 pg/ml	27 - 20,000 pg/ml	BMS8611FF
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
IL-27	B2	31.5 pg/ml	69 - 50,000 pg/ml	BMS86024FF

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Further Species (continued)

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits (cont.)				
IP-10	A3	9.8 pg/ml	41 - 30,000 pg/ml	BMS86018FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
MIP-1α	A11	1.8 pg/ml	27 - 20,000 pg/ml	BMS86013FF
MIP-1β	B2	14.9 pg/ml	27 - 20,000 pg/ml	BMS86014FF
RANTES	B4	6.1 pg/ml	27 - 20,000 pg/ml	BMS86009FF
TGF-β1	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokine 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-1α	A6	8.5 pg/ml	27 - 20,000 pg/ml	BMS8627FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.
3) PAI-1 and t-PA Simplex Kits cannot be assayed simultaneously.
4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.

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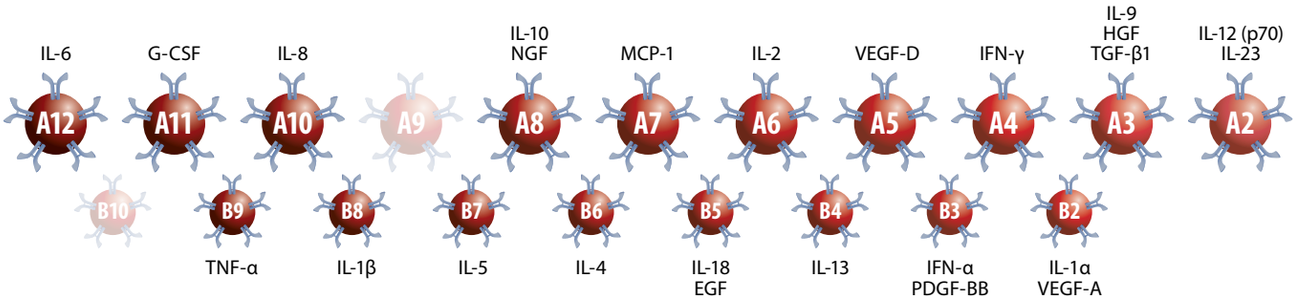
Human Growth and Differentiation Panel



VEGF (vascular endothelial growth factor) is a key factor in the promotion of growth and development of new blood vessels. This function is particularly important during embryonic development, as well as in repair of damaged vessels, and cancer. The direct role of VEGF in these processes is well known, and has been demonstrated by the finding that the loss of a single VEGF allele results in defective vascularization and early embryonic lethality. Unfortunately, VEGF and its overexpression can promote and/or contribute to disease, in particular in the vascularization and thus the potention of solid tumors, which rely on adequate blood supplies to grow. Numerous studies have confirmed VEGF's role as a mediator of pathological angiogenesis. A majority of human tumors express VEGF and increased serum concentrations are often observed (1). Like many cytokines and growth factors, VEGF exists in more than one form, e.g. VEGF-A, -B, -C, and –D. All of these are part of a larger family of platelet-derived growth factors, and all are important mediators of vascular genesis.

VEGF-D induces angiogenesis and lymphangiogenesis. In several types of cancer such as lung cancer, oesophageal carcinoma and primary lymphedema VEGF-D has been shown to be increased in patient serum. **PDGF** (platelet-derived growth factor) is an important mitogen for connective tissue, and also has important roles during embryonal development. Increased levels in serum have been shown in various cancer types, e.g. breast cancer, as well as in other pathologies (2-4). **EGF** (epidermal growth factor) is a strong mitogen for many cell types. Serum levels are decreased in various types of cancer and other conditions such as chronic schizophrenia (5). EGF overexpression is often observed in human carcinomas and epithelial cancers. **HGF** (hepatocyte growth factor), as its name implies, is mainly produced in the liver, and is considered a key molecule for the construction of normal tissue structure during embryogenesis, organogenesis, and organ regeneration. HGF is elevated in serum of liver disease patients, and also in patients with various kinds of cancers (6, 7).

Growth factors, cytokines, hormones, and related proteins all participate in driving cell growth, cell proliferation and differentiation / maturation. While there are a great number and variety of these proteins, each is capable of promoting its own set of biological effects, from specific to broadly overlapping activities. **IL-12** and **IFN-γ**, each produced by dendritic cells, promote the differentiation of Th0 to Th1 cells, **IL-4** on the other hand skews towards Th2. Smeltz and colleagues investigated the role of cytokines in the regulation of IL-18R (IL-18 receptor) α-chain expression, since **IL-18** is known to influence IL-12-mediated IFN-γ production and IL-4 production, and to thereby facilitate Th2 differentiation (8). Activated CD4+ IL-18Rα^{low} T cells released IFN-γ upon stimulation with IL-12 plus IL-18; whereas CD4+ IL-18Rα^{high} responded to IL-18 alone. T cells stimulated with IL-4 downregulated IL-18Rα expression. Furthermore, IL-18 also time-dependently modulates Th1/Th2 cytokine secretion from NKT (natural killer T) cells, as has been shown in the mouse by Uchida *et al* (9).

The differentiation of regulatory T cells is enhanced by **TGF-β**, whereas a combination of TGF-β and **IL-6** promotes the development of Th17 cells, which are characterized by the expression of the transcription factor RORγt (10, 11). **IL-23** is needed for the survival and expansion of Th17 populations, and to some degree for Th17 lineage commitment. In addition, **IL-1** and **TNF-α** enhance Th17 development, whereas IL-4, IFN-γ, **IL-27** and **IL-2** suppress Th17 differentiation (12). IL-2, a T cell growth factor is probably one of the best studied growth factors. Yet even with its longer history, its known functions are still being expanded, with data even in the last few years to demonstrate IL-2's ability to IL-17 production (13). As opposed to the Th17 lineage,

naive CD4+ T cells derived from cord blood are driven to become Tr1 (Treg) cells by endogenous or exogenous **IL-10** in combination with **IFN-α**. Treg cells display the phenotype IL-10+ IFN-γ+ IL-2$^{-/low}$ IL-4- (14). The impact of cytokines on human B cell growth and differentiation has been addressed by Banchereau *et al* (15). If CD40 antigen on B cells is crosslinked, the cells enter a state of sustained proliferation. The addition of IL-4 leads to the generation of long-term normal B cell lines and secretion of IgE after isotype switching. IL-10 on the other hand differentiates these B cells into plasma cells, which are characterized by very high immunoglobulin production, but limited proliferation. IL-10 combined with TGF-β induces IgA production by naive sIgD+ (soluble IgD+), sIgM+ B cells. B cells are further activated by Th cell products, such as **IL-5** and IL-6 (16).

It has been shown in a mouse model that **IL-27** together with SCF (stem cell factor) acts on hematopoietic stem cells and supports their early differentiation *in vitro* and *in vivo*. A similar effect could be shown for human CD34+ cells (17). **IL-15** is crucial for the development, homeostasis, and function of a specific group of immune cells that includes CD8+ T cells, NK cells, and NKT cells. In contrast to other secreted cytokines, IL-15 primarily exists bound to the high affinity IL-15 receptor α (IL-15/IL-15Rα) (18).

IL-3, IL-5 and **NGF** (nerve growth factor) each may act as basophil agonists, as do the chemokines **IL-8** and **MCP-1** (19). **G-CSF** contributes to proliferation, survival, and differentiation of granulocyte precursor cells in the bone marrow. Its cognate receptor G-CSF-R is expressed on the surface of myeloid progenitor cells. Mice lacking G-CSF and G-CSF-R are still capable of producing morphologically mature neutrophils, but at low levels compared to wild type. Therefore G-CSF is thought to play a supportive role in enabling myeloid precursors to differentiate to mature neutrophils (20). M1 macrophages (IL-12^{high}, IL-23^{high}, IL-10^{low}), are known to be induced by IFN-γ either alone, in parallel with microbial components such as LPS, or by cytokines, e.g. TNF-α. IL-4 and **IL-13**. Monocytes are circulating precursors of macrophages, as well as precursors for dendritic cells. It has been shown TNF, but not IL-1, induces the differentiation of monocytes to become dendritic cells, thereby facilitating the induction of adaptive immunity (21).

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Human FlowCytomix™ Growth and Differentiation Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Th1/Th2 11plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FF
Th1/Th2 11plex Ready-to-Use	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FFRTU
Th1/Th2/Th9/Th17/ Th22 13plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p70), IL-13, IL-17A, IL-22, TNF-α	BMS817FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
EGF	B5	22.7 pg/ml	27 - 20,000 pg/ml	BMS82070FF
G-CSF	A11	3.4 pg/ml	34 - 25,000 pg/ml	BMS82001FF
HGF	A3	52 pg/ml	206 - 150,000 pg/ml	BMS82069FF
IFN-α	B3	8.06 pg/ml	27 - 20,000 pg/ml	BMS8216FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-1α	B2	0.5 pg/ml	1.4 - 1,000 pg/ml	BMS80243FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-2	A6	16.4 pg/ml	27 - 20,000 pg/ml	BMS8221FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-5	B7	1.6 pg/ml	27 - 20,000 pg/ml	BMS8278FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-9	A10	1.5 pg/ml	2.7 - 2,000 pg/ml	BMS82081FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-13	B4	4.5 pg/ml	27 - 20,000 pg/ml	BMS8231FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
IL-23	A2	21.9 pg/ml	69 - 50,000 pg/ml	BMS82023FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
NGF	A8	126.75 pg/ml	412 - 300,000 pg/ml	BMS82044FF
PDGF-BB	B3	3.4 pg/ml	21 - 15,000 pg/ml	BMS82071FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
VEGF-A	B2	7.2 pg/ml	27 - 20,000 pg/ml	BMS80277FF
VEGF-D	A5	25.0 pg/ml	55 - 40,000 pg/ml	BMS82076FF

Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Th1/Th2 10plex	GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, TNF-α	BMS820FF
Th1/Th2/Th17/Th22 13plex	IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17A, IL-21, IL-22, IL-27, TNF-α	BMS822FF

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Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-1α	A4	15.7 pg/ml	27 - 20,000 pg/ml	BMS8611FF

Further Species (continued)

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits (cont.)				
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-2	A6	8.8 pg/ml	27 - 20,000 pg/ml	BMS8601FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-5	A8	4.0 pg/ml	27 - 20,000 pg/ml	BMS8610FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
IL-13	A2	9.3 pg/ml	27 - 20,000 pg/ml	BMS86015FF
IL-15/IL-15R	A11	5.0 pg/ml	6.9 - 5,000 pg/ml	BMS86023FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
IL-21	A9	5.0 pg/ml	27 - 20,000 pg/ml	BMS86021FF
IL-23	B5	14.5 pg/ml	55 - 40,000 pg/ml	BMS86017FF
IL-27	B2	31.5 pg/ml	69 - 50,000 pg/ml	BMS86024FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokine 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-1α	A6	8.5 pg/ml	27 - 20,000 pg/ml	BMS8627FF
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.

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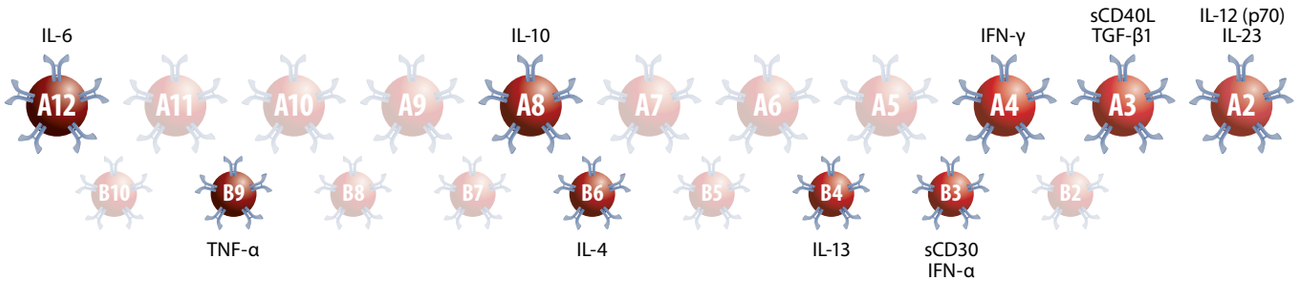
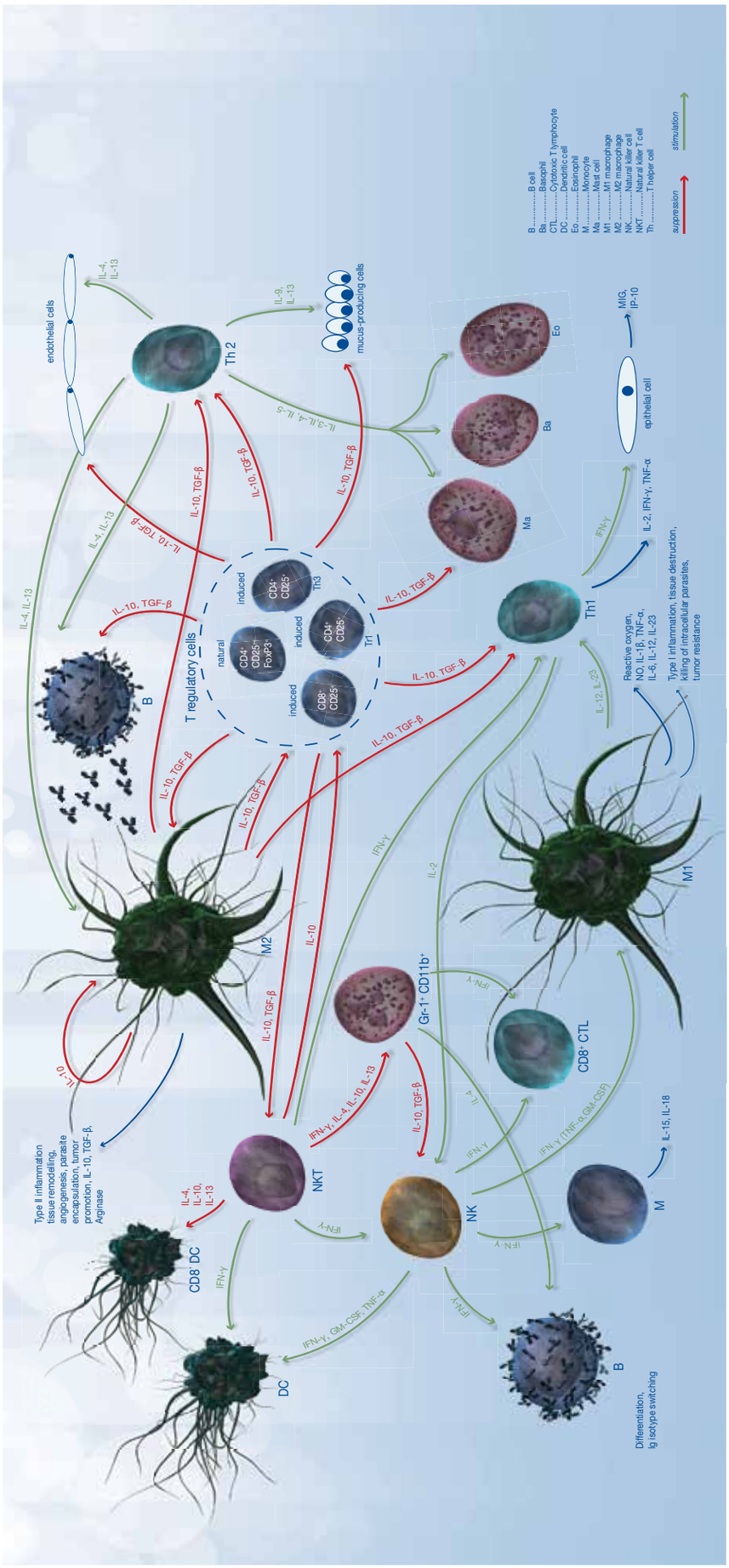
Human Immune Regulation Panel



Maintaining homeostasis within our immune system requires multiple systems that control infection and tumor growth and those that prevent inflammation and autoimmune diseases. There exist subsets of regulatory T cells (Treg cells) that provide a key role in immune regulation. It has been demonstrated that natural/constitutive and inducible/adaptive subsets of regulatory T cells exist, with complimentary and overlapping functions (1). Natural $CD4^+$ $CD25^+$ $FoxP3^+$ T regulatory cells are continuously produced in the thymus and then enter peripheral tissues, where they suppress the activation of other T cells (2). Tr1 (Treg 1) and Th3 (T helper 3) cells on the other hand are generated from naive T cells in the periphery upon encounter of distinct antigen presenting dendritic cells. Tr1 cells utilize multiple suppressor mechanisms, such as the secretion of **IL-10** and **TGF-β** and various surface molecules, such as CTLA-4 (3). Th3 cells however primarily secrete TGF-β and varying amounts of **IL-4** and IL-10 (4). Both natural regulatory T cells and Tr1 cells are able to suppress proliferation of and cytokine production by naïve $CD4^+$ $CD25^-$ T cells or antigen-specific Th1 or Th2 cells *in vitro* (5, 6). Their corresponding *in vivo* functions are a major subject of current investigations. Overall it seems that Tr1 and Th3 cells exert immunosuppression via the release of suppressive cytokines, while natural regulatory T cells depend at least partially on direct cell contact. Furthermore, there is also evidence for immunosuppressive $CD8^+$ regulatory T cells, which secrete either IL-10 or TGF-β (7), which might also exhibit anti-tumor activity. The common Th2 subset of $CD4^+$ T cells might also have regulatory functions, as they secrete IL-4, IL-5, IL-10 and **IL-13**, which mediate several regulatory and effector functions. Th1 cells are known for the production of **IFN-γ**, which e.g. upregulates several chemokines in epithelial cells (7). Additionally NKT (natural killer T) cells have been observed to release regulatory cytokines, such as IL-4, IL-10 and IL-13 (8). IFN-γ leads to an M1 polarization, whereas IL-4/IL-13, TGF-β and glucocorticoids cause the development of M2 macrophages (9). M1 cells have an **IL-12**^{high}, **IL-23**^{high}, IL-10^{low} phenotype and produce inflammatory cytokines, such as IL-1β, **IL-6** and **TNF-α**. They contribute to type I inflammation, tissue destruction and tumor resistance. M2 cells are generally IL-12^{low}, IL-23^{low}, TNF^{low}, IL-10^{high} and promote type II inflammation and tumor development.

IL-27, along with IL-12, IL-23, and IL-35, belongs to the IL-12 family of cytokines, which plays a role in Th cell differentiation. While IL-27 can induce Th1 differentiation, it may also suppress certain immune responses. The absence of IL-27-mediated immunosuppression results in hyperproduction of proinflammatory cytokines, and consequently leads to severe inflammation. Immunosuppressive effects of IL-27 depend on IL-2 suppression, inhibition of Th17 development, and IL-10 induction (10). **IL-21** exerts pleiotropic effects on both innate and adaptive immune responses. It enhances proliferation of lymphoid cells, increases cytotoxicity of CD8+ T cells and NK cells, and differentiation of B cells into plasma cells. In contrast, IL-21 also inhibits antigen presentation of DCs, and has proapoptotic effects on B and NK cells. Furthermore, IL-21 is a regulator of Th17 development (11). NK (natural killer) cell activity has been observed to be upregulated upon exposure to **IL-15** induced by viral infection. IL-15 is required for Th1 cytokine production *in vivo*, NK cell responses, optimal IL-12 and IFN-γ synthesis by DCs (dendritic cells), and malaria-specific antibody responses, all of which contribute to the early control and timely resolution of blood-stage malaria infection. In contrast to other secreted cytokines, IL-15 primarily exists bound to the high affinity IL-15 receptor α (IL-15/IL-15Rα) (12, 13).



Immune Regulation: Natural regulatory T cells, induced regulatory T cells, macrophages, neutrophils, dendritic cells, NK cells, NKT cells and many more act in concert to guide a host's immune system.

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Human FlowCytomix™ Immune Regulation Panel

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
sCD40L	A3	23.4 pg/ml	55 - 40,000 pg/ml	BMS8239/2FF
IFN-α	B3	8.06 pg/ml	27 - 20,000 pg/ml	BMS8216FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-13	B4	4.5 pg/ml	27 - 20,000 pg/ml	BMS8231FF
IL-23	A2	21.9 pg/ml	69 - 50,000 pg/ml	BMS82023FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF

Further Species

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
IL-13	A2	9.3 pg/ml	27 - 20,000 pg/ml	BMS86015FF
IL-15/IL-15R	A11	5.0 pg/ml	6,9 - 5,000 pg/ml	BMS86023FF
IL-21	A9	5.0 pg/ml	27 - 20,000 pg/ml	BMS86021FF
IL-23	B5	14.5 pg/ml	55 - 40,000 pg/ml	BMS86017FF
IL-27	B2	31.5 pg/ml	69 - 50,000 pg/ml	BMS86024FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.

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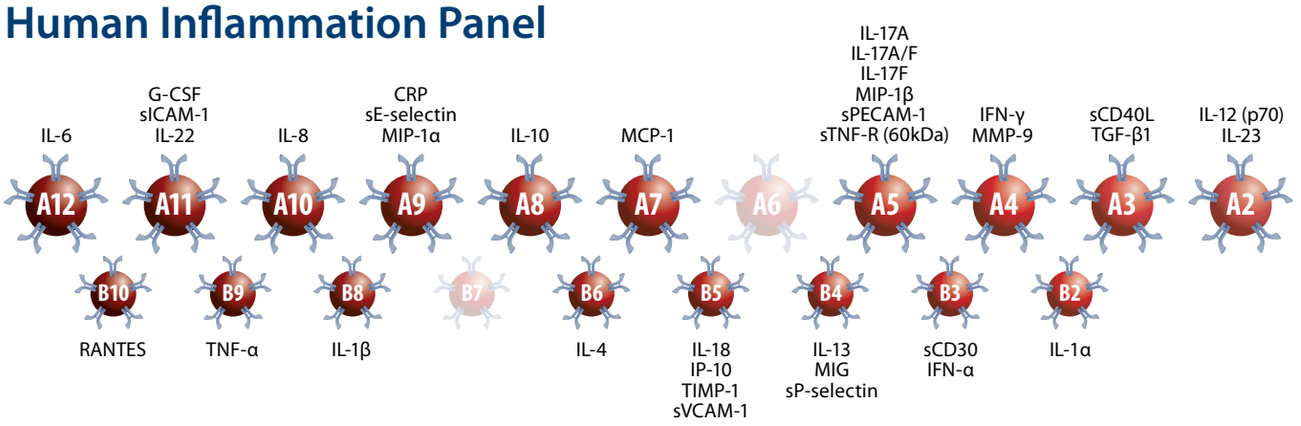
Human Inflammation Panel



Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a protective attempt by an organism to remove injurious stimuli as well as initiate the healing process for the tissue. In a healthy individual, the liver constantly synthesizes a characteristic set of plasma proteins. During an inflammation the rate of synthesis changes, primarily influenced by **IL-1** and **TNF-α**, in combination with corticosteroids. Plasma proteins that increase during the acute phase response are called acute phase proteins. One of them is **CRP**, which might increase up to 1000-fold over its normal level. IL-6 is an early phase mediator of the acute phase. It favors chronic inflammation by stimulation of T and B cells. Most proteins are produced by hepatocytes, some by monocytes, and others by endothelial cells, fibroblasts or adipocytes. The response has two aspects: the local component includes polymorphonuclear, followed by mononuclear, infiltration of the infected tissue. The systemic component comprises the secretion of acute phase reactants, or in other words, plasma proteins whose profiles change during the acute phase response.

Acute inflammation typically resolves within a few days or weeks. Sometimes however, the causal situation continues to exist, leading to chronic inflammation. Examples include the persistence of a low-grade infection, the continuing presence of physical or chemical irritants, or hypersensitivity reactions (for instance accompanying autoimmune disease). Monocytes and macrophages are central to inflammation, as they produce early phase mediators such as TNF-α, IL-1, or **IL-6**. Furthermore, they are phagocytic, and therefore involved in microbial killing, as are neutrophils. Neutrophils have a short life-span and are continuously replaced from the bone marrow. Mast cells and basophils are particularly important for secretion of vasoactive mediators, together with platelets. These cells are at least partially under the control of cytokines. Several chronic inflammatory diseases are associated with increased mast cell numbers as well as upregulation of the TNF-R family member **CD30**, which can induce the synthesis and release of chemokines such as **IL-8**, **MIP-1α**, and **MIP-1β** (1).

Another molecule whose pleiotropic effects include a role in inflammation, is **CD40L** (CD154). CD40/CD40L interactions are important for T cell activation, and CD40L is also expressed by monocytes, macrophages and dendritic cells. On these cell types, CD40L initiates inflammatory responses such as synthesis of IL-1, IL-6 and TNF-α. CD40L on activated platelets binds to CD40 on endothelial cells. The resulting inflammation of the endothelium promotes upregulation of the adhesion molecules **E-selectin**, **VCAM-1** and **ICAM-1**, as well as the chemokines IL-8 and **MCP-1** (2, 3). The combined expression of these adhesion molecules and chemokines is crucial for lymphocyte recruitment into inflamed tissue. Various adhesion molecules and chemokines (MCP-1, MIP-1α, **MIG**) are also expressed in the liver. Inflammation or injury results in the expression of additional adhesion molecules like VCAM-1, **P-selectin** and E-selectin, as well as upregulation of chemokines (4).

IP-10 is a proinflammatory chemokine, induced by type I interferons, which plays a role in the progression of chronic inflammation. IP-10 is implicated in cell recruitment and activation during inflammation and tissue repair (11, 12). In the case of patients with metabolic syndrome, increased plasma concentrations of proinflammatory mediators and adhesion molecules, accompanied by increased plasma concentrations of pro-**MMP-9**, MMP-8, and **TIMP-1**, are observed (13).

Cytokines in Inflammation

Cytokines can be divided in two broad categories: proinflammatory cytokines are mainly secreted by activated macrophages and upregulate inflammation; IL-1, IL-6, **IL-12**, TNF-α, **IFN-α**, -β and **-γ**, **TGF-β** as well as the chemokines IL-8, MIP-1α, MIP-1β, MCP-1, -2, -3, and **RANTES** belong to this group. The overexpression of IL-18 in murine lungs has been demonstrated to cause diseases like pulmonary inflammation, lung fibrosis, and COPD (chronic obstructive pulmonary disease) along with increased levels of IFN-γ, IL-5 and **IL-13** (5). Th17 cells secrete a number of proinflammatory cytokines. Probably the most prominent among them is **IL-17**, which seems to be involved in the development of autoimmunity.

IL-17 exhibits proinflammatory activities similar to innate immune cytokines like IL-1β and TNF-α, among other functions (6, 7). **IL-23** promotes the development of IL-17-producing Th17 cells and thereby favors chronic inflammation, dominated by IL-17, IL-6, IL-8 and TNF-α as well as neutrophils and monocytes (8). IL-23 was also found to have a potential function in the pathogenesis of psoriasis, a chronic autoimmune disease which affects the skin and joints. **IL-22**, which is preferentially produced by Th17 cells, mediates the acanthosis induced by IL-23 in psoriasis patients. IL-23 or IL-6 can directly induce the production of IL-22 from both murine and human naïve T cells (10).

Anti-inflammatory cytokines are primarily T cell-derived; these include **IL-4**, IL-6, **IL-10**, and IL-13. Furthermore, TGF-β also exhibits anti-inflammatory functions by inhibition of IL-1, IL-6, and TNF-α production. Additionally, soluble cytokine receptors also exhibit anti-inflammatory activity; **TNF-R (60kDa)** and TNF-R (80kDa) for example bind to trimeric TNF-a in the circulation, thereby preventing membrane-bound TNF-R-TNF-α signal induction (9).

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Human FlowCytomix™ Inflammation Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Th1/Th2 11plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FF
Th1/Th2 11plex Ready-to-Use	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FFRTU
Th1/Th2/Th9/Th17/ Th22 13plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p70), IL-13, IL-17A, IL-22, TNF-α	BMS817FF
Chemokine 6plex	G-CSF, IL-8, MCP-1, MIG, MIP-1α, MIP-1β	BMS813FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
sCD40L	A3	23.4 pg/ml	55 - 40,000 pg/ml	BMS8239/2FF
CRP[1)]	A9	0.07 ng/ml	0.1 - 70 ng/ml	BMS8288FF
sE-selectin	A9	1.2 ng/ml	4.0 - 3,000 ng/ml	BMS8205FF
G-CSF	A11	3.4 pg/ml	34 - 25,000 pg/ml	BMS82001FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
IFN-α	B3	8.06 pg/ml	27 - 20,000 pg/ml	BMS8216FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-1α	B2	0.5 pg/ml	1.4 - 1,000 pg/ml	BMS80243FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-5	B7	1.6 pg/ml	27 - 20,000 pg/ml	BMS8278FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-13	B4	4.5 pg/ml	27 - 20,000 pg/ml	BMS8231FF
IL-17A	A5	2.5 pg/ml	13.7 - 10,000 pg/ml	BMS82017FF
IL-17A/F	A5	16 pg/ml	27 - 20,000 pg/ml	BMS82082FF
IL-17F	A5	8.0 pg/ml	27 - 20,000 pg/ml	BMS82037FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
IL-22	A11	43.3 pg/ml	110 - 80,000 pg/ml	BMS82047FF
IL-23	A2	21.9 pg/ml	69 - 50,000 pg/ml	BMS82023FF
IP-10	B5	6.0 pg/ml	17 - 12,500 pg/ml	BMS8284FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MIG	B4	0.9 pg/ml	6.9 - 5,000 pg/ml	BMS8285FF
MIP-1α	A9	1.0 pg/ml	13.7 - 10,000 pg/ml	BMS82029FF
MIP-1β	A5	1.0 pg/ml	4.0 - 3,000 pg/ml	BMS82030FF
MMP-9[1)5)]	A4	95 pg/ml	0.1 - 100 ng/ml	BMS82016FF
sPECAM-1	A5	0.8 ng/ml	4.0 - 3,000 ng/ml	BMS8229FF
sP-selectin	B4	1.2 ng/ml	2.8 - 2,000 ng/ml	BMS8219/2FF
RANTES[1)]	B10	25 pg/ml	41 - 30,000 pg/ml	BMS8287FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TIMP-1[1) 5)]	B5	28 pg/ml	137 - 100,000 pg/ml	BMS82018FF
TNF-α[2)]	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
sTNF-R (60kDa)[2)]	A5	0.08 ng/ml	0.14 - 100 ng/ml	BMS8203FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF

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Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Th1/Th2 10plex	GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, TNF-α	BMS820FF
Th1/Th2/Th17/Th22 13plex	IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17A, IL-21, IL-22, IL-27, TNF-α	BMS822FF
Chemokine 6plex	GM-CSF, MCP-1, MCP-3, MIP-1α, MIP-1β, RANTES	BMS821FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-1α	A4	15.7 pg/ml	27 - 20,000 pg/ml	BMS8611FF
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-5	A8	4.0 pg/ml	27 - 20,000 pg/ml	BMS8610FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
IL-13	A2	9.3 pg/ml	27 - 20,000 pg/ml	BMS86015FF
IL-17A	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS86001FF
IL-17A/F	B10	1.0 pg/ml	2.7 - 2,000 pg/ml	BMS86026FF
IL-17F	A7	6.0 pg/ml	27 - 20,000 pg/ml	BMS86020FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
IL-22	A5	5.5 pg/ml	6.9 - 5,000 pg/ml	BMS86016FF
IL-23	B5	14.5 pg/ml	55 - 40,000 pg/ml	BMS86017FF
IP-10	A3	9.8 pg/ml	41 - 30,000 pg/ml	BMS86018FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
MIP-1α	A11	1.8 pg/ml	27 - 20,000 pg/ml	BMS86013FF
MIP-1β	B2	14.9 pg/ml	27 - 20,000 pg/ml	BMS86014FF
RANTES	B4	6.1 pg/ml	27 - 20,000 pg/ml	BMS86009FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokine 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-1α	A6	8.5 pg/ml	27 - 20,000 pg/ml	BMS8627FF
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
IL-17A	A10	5.0 pg/ml	7 - 5,000 pg/ml	BMS8635FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

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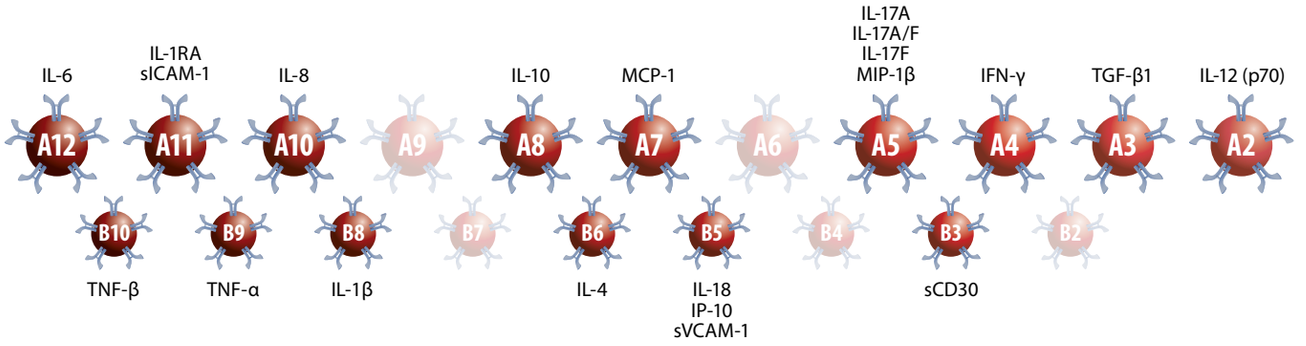
1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.

2) The TNF-R (60kDa) Simplex Kit cannot be assayed simultaneously with the TNF-α or the TNF-β Simplex Kit.

4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.

5) MMP Simplex Kits cannot be combined with the TIMP-1 Simplex Kit.

Human Multiple Sclerosis Panel



The dramatic cytokine imbalance that is seen in **MS (multiple sclerosis)** is characterized by a simultaneous upregulation of proinflammatory cytokines such as **IFN-γ**, **TNF-α**, **TNF-β**, **IL-6** and **IL-12** and immune response-downregulating cytokines like **IL-10** and **TGF-β**. Pro- and anti-inflammatory markers are furthermore produced by astrocytes and microglia, which build a network of cytokines that communicates with the immune system (1). These fluctuations may even vary seasonally in patients, who may possess high IFN-γ levels in winter and an excess of IL-10 with the summer season (2). **IL-17** is frequently found to be expressed in brain tissue of MS patients, specifically released from lymphocytes, astrocytes and oligodendrocytes in active areas of MS lesions. The frequency of IL-17+ T cells was significantly increased in active compared to non-active lesion areas (3). Microglia, a crucial cell type in MS pathogenesis, upregulate IL-6, MIP-2, adhesion molecules and neurotrophic factors upon exposure to IL-17. In response to IL-23 or IL-1β, microglia start expressing IL-17 themselves. Since microglia also produce IL-23 and IL-1β, an autocrine loop mechanism has been suggested (4). **IL-18** is an important MS marker, because it augments Th1 responses by stimulating T and NK cells to secrete IFN-γ. IL-12 is also capable of inducing IFN-γ, but the two markers seem to act independently. IL-18 is elevated both in serum and CSF (cerebrospinal fluid) of MS patients. Increased IL-18 levels are dependent on an interaction with $CD4^+$ T cells via CD40/CD40L. Moreover, IL-18 concentrations correlate with disease duration in secondary progressive MS (5, 6).

IP-10 levels in CSF and serum are markedly increased when inflammation is prominent (7). The expression of the costimulatory molecule **CD30** on a regulatory subpopulation of dendritic cells mediates the resting and activated physiological balance between Th1 and Th2 immune functions, supported by the observation of an impaired regulation when soluble CD30 is increased. Soluble CD30 has been shown to be elevated in serum and CSF of MS patients (8, 9). Adhesion molecules such as ICAM-1 are found in blood and CSF of patients with primary progressive MS; VCAM-1 levels are only increased in blood. Furthermore, the chemokines **IL-8** and **MCP-1** are probably expressed intrathecally, and **MIP-1β** in serum correlated with particular disease parameters (10). Furthermore, **IL-1β** and **IL-1RA** (IL-1 receptor antagonist) are increased in CSF in MS patients, and IL-1β is also increased in serum (11).

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Human FlowCytomix™ Multiple Sclerosis Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Th1/Th2 11plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FF
Th1/Th2 11plex Ready-to-Use	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FFRTU
Th1/Th2/Th9/Th17/ Th22 13plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p70), IL-13, IL-17A, IL-22, TNF-α	BMS817FF
Chemokine 6plex	G-CSF, IL-8, MCP-1, MIG, MIP-1α, MIP-1β	BMS813FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-1RA	A11	96 pg/ml	137 - 100,000 pg/ml	BMS82080FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-17A	A5	2.5 pg/ml	13.7 - 10,000 pg/ml	BMS82017FF
IL-17A/F	A5	16 pg/ml	27 - 20,000 pg/ml	BMS82082FF
IL-17F	A5	8.0 pg/ml	27 - 20,000 pg/ml	BMS82037FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
IP-10	B5	6.0 pg/ml	17 - 12,500 pg/ml	BMS8284FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MIP-1β	A5	1.0 pg/ml	4.0 - 3,000 pg/ml	BMS82030FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
TNF-β	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS8202FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF

Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Th1/Th2 10plex	GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, TNF-α	BMS820FF
Th1/Th2/Th17/Th22 13plex	IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17A, IL-21, IL-22, IL-27, TNF-α	BMS822FF
Chemokine 6plex	GM-CSF, MCP-1, MCP-3, MIP-1α, MIP-1β, RANTES	BMS821FF

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Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF

Further Species (continued)

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits (cont.)				
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
IL-17A	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS86001FF
IL-17A/F	B10	1.0 pg/ml	2.7 - 2,000 pg/ml	BMS86026FF
IL-17F	A7	6.0 pg/ml	27 - 20,000 pg/ml	BMS86020FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
IP-10	A3	9.8 pg/ml	41 - 30,000 pg/ml	BMS86018FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
MIP-1β	B2	14.9 pg/ml	27 - 20,000 pg/ml	BMS86014FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokine 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
IL-17A	A10	5.0 pg/ml	7 - 5,000 pg/ml	BMS8635FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.

4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.

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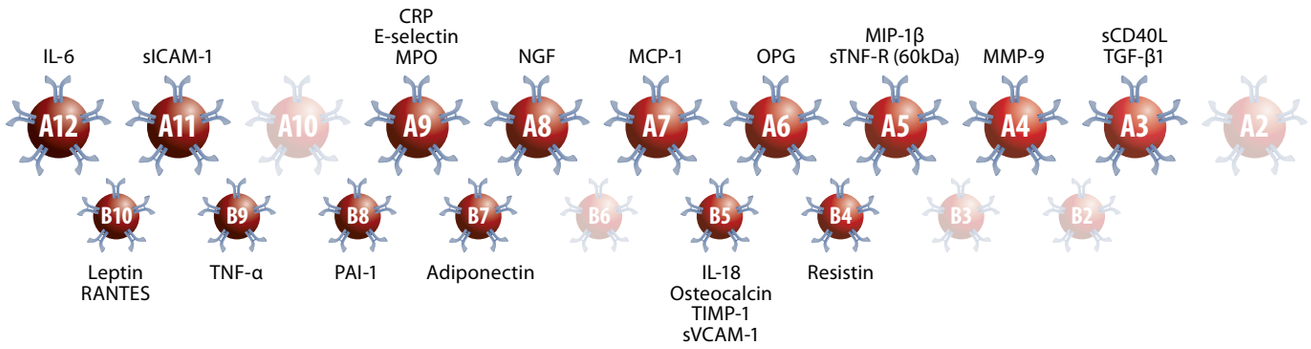
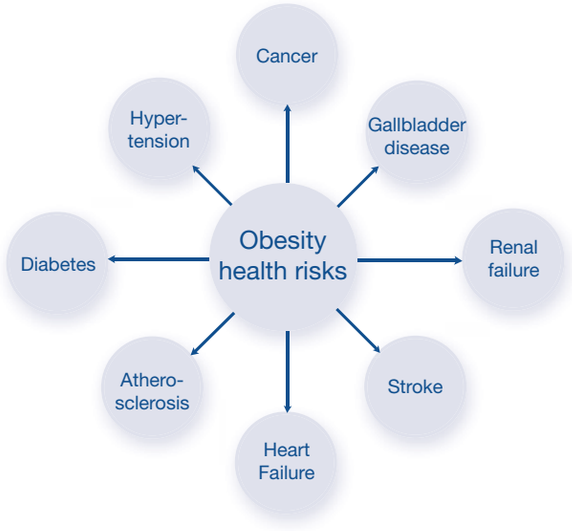
Human Obesity Panel



Obesity is a systemic disease that predisposes affected individuals to a variety of co-morbidities and complications that effect overall health. A variety of common disorders, like hyperglycemia, hyperlipidemia, and hypertension, are common in obese individuals. Simultaneous development of these disorders is collectively called "The Metabolic Syndrome". One of the major challenges of this syndrome is the high prevalence of cardiovascular diseases arising from atherosclerosis (1). Carrying extra body weight and body fat go hand in hand with the development of T2D (type 2 diabetes). Obesity is associated with an increased risk of developing insulin resistance and T2D. In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, proinflammatory cytokines and other factors that are involved in the development of insulin resistance. When insulin resistance is accompanied by dysfunction of pancreatic islet cells (the cells that release insulin), failure to control blood glucose levels results. Abnormalities in cell function are therefore critical in defining the risk and development of T2D (2, 3).



Metabolic syndrome is associated with abdominal obesity, blood lipid disorders, inflammation, insulin resistance or full-blown diabetes, and increased risk of developing cardiovascular diseases arising from atherosclerosis. Humoral factors secreted by adipose tissue contribute to the development of metabolic syndrome and vascular disease. These substances, collectively called adipokines, include **leptin**, **adiponectin**, **resistin**, **TNF-α**, **IL-6**, **PAI-1**, angiotensinogen, **CRP** (C-reactive protein), and others (4). Resistin is a putative adipocyte-derived signaling polypeptide. It is a member of the newly recognized family of cysteine-rich secretory proteins called RELM (resistin-like molecules) or FIIZ (found in the inflammatory zone). It is expressed almost exclusively in white adipose tissue. Some current publications show that when resistin levels are high in the blood, and the heart undergoes a major cardiac event such as a heart attack, it takes much longer to recover. Resistin seems to be linked to the release of a TNF-α, which is associated with inflammation and increased heart cell death. Resistin may eventually be able to be used as a biomarker for diagnosis and treatment during heart attack (3, 5). The adhesion molecule **ICAM-1** is also increased in diabetes, and furthermore, may predict cardiovascular disease in diabetic patients. ICAM-1 induction is associated with an elevated level of triglycerides. Elevated concentrations of soluble ICAM-1, **VCAM-1**, and **E-selectin** have been found in obese, hypertensive, and diabetic children suggesting endothelial activation, and adhesion molecules are associated with early atherosclerosis (6). Leptin is a protein hormone produced predominantly by adipocytes. Data from animal and human studies collectively suggest that leptin plays major roles in the pathophysiology of obesity-related atherogenesis by impacting multiple steps, including vascular inflammation, proliferation, calcification, and elevated oxidative stress (2). Furthermore leptin seems to play a crucial role in CNS (central nervous system) regulation of glucose metabolism, which may relate to the pathogenesis of insulin resistance and T2D associated with

obesity (7). Adiponectin is produced exclusively by mature adipocytes. As is the case with leptin, adiponectin is higher in women than men, but in contrast to leptin, adiponectin is reduced in obesity and increases in response to severe weight loss. Plasma adiponectin levels in humans are quite high, normally ranging from 3 to 30 µg/ml. The expression of adiponectin in adipose tissue is reportedly regulated by several mechanisms via humoral and neuronal pathways. The mechanism underlying the adiponectin reduction in obese subjects remains unclear, but a plausible explanation is that inflammatory cytokines, e.g. TNF-α, cause transcriptional suppression and secretory inhibition of adiponectin. **MCP-1** secretion from adipocytes is stimulated by insulin. Under obese conditions higher MCP-1 levels promote increased invasion of monocytes and macrophages into adipose tissue. While insulin resistance in obesity is associated with decreased serum **OPG** (osteoprotegerin) levels, the marker is significantly increased in sera of diabetes patients. Soluble **CD40L** is another marker increased in obesity, diabetes, and myocardial infarction. **NGF** (nerve growth factor) plasma levels have been shown to be increased in overweight and obese subjects in multiple studies. In morbidly obese patients, however, the marker appears lower, but still elevated compared to normal controls.

Moreover, NGF concentrations are positively related to inflammatory markers in obese conditions (8). **MMP-9** and **TIMP-1** plasma levels have been found to be significantly increased in obese subjects. Serum MMP-9, among other markers, independently predicts early risk of cardiovascular disease or myocardial infarction in patients with metabolic syndrome (9-11). Increased levels of **RANTES**, **MIP-1β**, and TIMP-1 are secreted by adipocytes in culture isolated from obese subjects (12). A study investigating the effect of obesity on the release of **TGF-β1** by human adipose tissue reveals a significant correlation between the body mass index of the fat donors and the subsequent release of TGF-β1 release by subcutaneous adipose tissue. Release of TGF-β1 by adipose tissue is enhanced in the presence of insulin. TGF-β1 is primarily secreted by non-fat cells within human adipose tissue (13).

Osteocalcin is a hormone produced by osteoblasts. It has been shown in athletes that an acute increase in serum osteocalcin blunts the expected increase of serum leptin that should occur with fat mass gain. These results indicate that osteocalcin is a negative regulator of serum leptin in humans. Serum osteocalcin levels are inversely correlated with body mass index, fasting glucose and insulin, triglycerides, and leptin, and positively correlated with adiponectin (14, 15).

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Human FlowCytomix™ Obesity Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Cardiovascular 6plex	sCD40L, IL-6, IL-8, MCP-1, sP-selectin, t-PA	BMS811/2FF
Obesity 9plex	sCD40L, sICAM-1, IL-6, Leptin, MCP-1, MPO, OPG, Resistin, sTNF-R (60kDa)	BMS816/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
Adiponectin[1)]	B7	0.06 ng/ml	0.1 - 50 ng/ml	BMS82032FF
sCD40L	A3	23.4 pg/ml	55 - 40,000 pg/ml	BMS8239/2FF
CRP[1)]	A9	0.07 ng/ml	0.1 - 70 ng/ml	BMS8288FF
sE-selectin	A9	1.2 ng/ml	4.0 - 3,000 ng/ml	BMS8205FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
Leptin	B10	0.05 ng/ml	0.3 - 250 ng/ml	BMS82039/2FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MIP-1β	A5	1.0 pg/ml	4.0 - 3,000 pg/ml	BMS82030FF
MMP-9[1)5)]	A4	95 pg/ml	0.1 - 100 ng/ml	BMS82016FF
MPO	A9	0.02 ng/ml	0.14 - 100 ng/ml	BMS82038FF
NGF	A8	126.75 pg/ml	412 - 300,000 pg/ml	BMS82044FF
OPG	A6	7.9 pg/ml	27 - 20,000 pg/ml	BMS82021FF
Osteocalcin	B5	6.9 pg/ml	27 - 20,000 pg/ml	BMS82020FF
PAI-1[1)]	B8	13.5 pg/ml	137 - 100,000 pg/ml	BMS82033FF
RANTES[1)]	B10	25 pg/ml	41 - 30,000 pg/ml	BMS8287FF
Resistin	B4	1.7 pg/ml	55 - 40,000 pg/ml	BMS82040FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TIMP-1[1)5)]	B5	28 pg/ml	137 - 100,000 pg/ml	BMS82018FF
TNF-α[2)]	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
sTNF-R (60kDa)[2)]	A5	0.08 ng/ml	0.14 - 100 ng/ml	BMS8203FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF

1) *Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.*
2) *The TNF-R (60kDa) Simplex Kit cannot be assayed simultaneously with the TNF-α or the TNF-β Simplex Kit.*
4) *Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.*
5) *MMP Simplex Kits cannot be combined with the TIMP-1 Simplex Kit.*

Further Species

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
MIP-1β	B2	14.9 pg/ml	27 - 20,000 pg/ml	BMS86014FF
RANTES	B4	6.1 pg/ml	27 - 20,000 pg/ml	BMS86009FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

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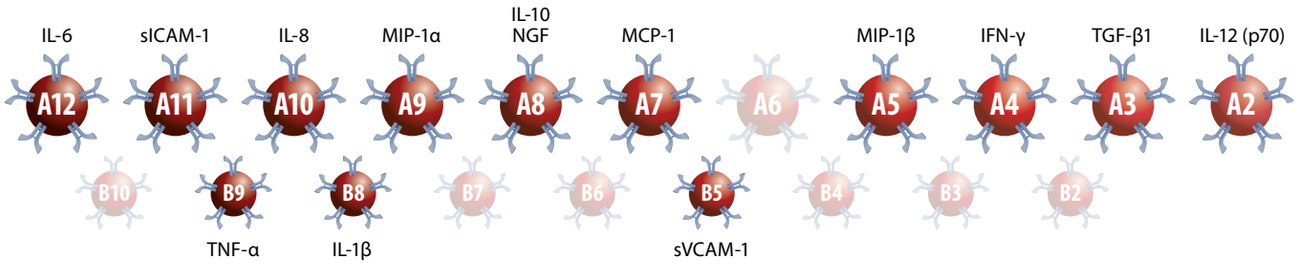
Human Pain Panel



The "unpleasant sensory and emotional experience associated with actual or potential tissue damage", or in other words **pain**, is a major symptom of multiple pathological conditions. Pain is the result of nociception; an activity in the nervous system that results from the stimulation of nociceptors. The phenomenon may manifest as neuropathic pain, which is a result of a primary lesion or dysfunction in the nervous system. Central pain describes when the lesion or dysfunction affects the central nervous system (1). Pain is a hallmark of inflammation, where important pain mediators such as **TNF-α**, **IL-1β** and **NGF** (nerve growth factor), are released. TNF-α and IL-1β are well-known inflammatory cytokines, but there is increasing interest surrounding NGF, a neurotrophic factor supporting the development of neurons in the peripheral nervous system, including almost all nociceptors. All of these proteins are capable of activating, and sensitizing peripheral nociceptive neurons and thereby can contribute to ongoing pain. NGF may exert some of these effects indirectly, via mast cells, sympathetic efferent neurons, and neutrophils. IL-1β and TNF-α upregulate NGF expression; in return, NGF stimulates mast cells to proliferate, degranulate, and release inflammatory mediators including IL-1β, TNF-α and NGF, thereby creating a vicious circle of pain-promoting events (2, 3). **MCP-1** levels are increased in numerous inflammatory conditions, and have been evaluated in this context as well. Data has shown MCP-1 can depolarize sensory neurons isolated from compressed ganglia, via increased activation of a non-selective cation channel and inhibition of voltage-gated potassium channels (4). A correlation can exist between cytokine levels and pain severity. IL-1β, IL-2, **IL-6**, **IFN-γ** and TNF-α are examples for proteins that increase in human plasma with increasing pain intensity (5).

The seminal plasma of patients suffering from chronic prostatitis / chronic pelvic pain syndrome contains significantly increased amounts of IL-1β, IL-6, **IL-10**, **IL-12 (p70)**, IL-2R, **MIP-1α**, **MIP-1β**, TNF-α and **IL-8** (6-8). In a study of 25 different cytokines and chemokines associated with complex regional pain syndrome type 1, numerous cytokines were found to be elevated in blister fluid obtained from involved extremities, including IL-1RA, IL-6, IL-8, TNF-α, IL-12 (p40), MCP-1 and MIP-1β (9).

Finally, adhesion molecules like **ICAM-1** and **VCAM-1** may be considered as markers of endothelial dysfunction in patients with anginal chest pain and normal coronary arteries, also known as syndrome X (10, 11). As pain may be caused by inflammatory processes, it is not unexpected that anti-inflammatory Th2 cytokines, such as IL-4 and IL-10, have been shown to be decreased in multiple studies (12, 13).

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Human FlowCytomix™ Pain Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Chemokine 6plex	G-CSF, IL-8, MCP-1, MIG, MIP-1α, MIP-1β	BMS813FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MIP-1α	A9	1.0 pg/ml	13.7 - 10,000 pg/ml	BMS82029FF
MIP-1β	A5	1.0 pg/ml	4.0 - 3,000 pg/ml	BMS82030FF
NGF	A8	126.75 pg/ml	412 - 300,000 pg/ml	BMS82044FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF

Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Chemokine 6plex	GM-CSF, MCP-1, MCP-3, MIP-1α, MIP-1β, RANTES	BMS821FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
MIP-1α	A11	1.8 pg/ml	27 - 20,000 pg/ml	BMS86013FF
MIP-1β	B2	14.9 pg/ml	27 - 20,000 pg/ml	BMS86014FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

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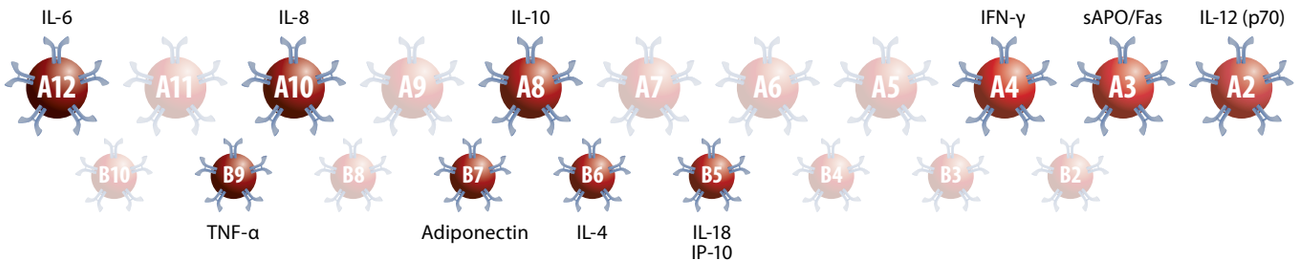
Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.

4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.

Human Preeclampsia Panel



Preeclampsia is a pregnancy-related condition characterized by two primary symptoms: hypertension and proteinuria. If untreated, it can cause maternal and fetal morbidity. Its etiology is not fully defined, and there can be a good deal of variability in measured serum cytokine levels observed between different patients. Parameters such as gestational age at the time of sample drawing, assay sensitivities, and choice of plasma or serum samples for analysis, seems to have a great impact on the results. Although there are seemingly contradictory results, distinct markers are generally reported to be elevated in preeclampsia (1). The inflammatory response in normal pregnancy and preeclampsia originates from the placenta. Many placental products are raised in the circulation of preeclamptic women, as are some types of proinflammatory cytokines, syncytiotrophoblast microparticles, lipid peroxides, and Activin A, a member of the TGF-β superfamily (2). One study comparing preeclamptic versus non-preclamptic women found significantly elevated serum levels of **IFN-γ**, as well as of the IFN-γ-inducing cytokines **IL-12 (p70)**, IL-15, and **IL-18**. IFN-γ promotes the cytotoxic activation of T- and NK cells, activates macrophages and phagocytosis, and induces proinflammatory cytokine expression. Monocytes and macrophages, activated during an enhanced maternal response to placental debris, are not only a source of **IL-6**, **IL-8**, and **TNF-α**, but may also promote increased IL-18 concentrations. In this case, no differences in **IL-10** levels were detected (1, 3), but variability in preeclampsia associated IL-10 levels have been widely reported (4). It has furthermore been implicated, that low IL-10 could possibly contribute to enhanced inflammatory responses towards the trophoblasts elicited by TNF-α and IFN-γ. The resulting infarction of the placenta leads to leakage of increasing amounts of placenta fragments and cytokines in the maternal circulation and enhanced endothelial activation occurring in preeclampsia (5). Patients with preeclampsia have significantly higher serum concentrations of **IP-10** than both normal pregnant women and mothers who have SGA (small for gestational age) neonates (6). **Adiponectin** has recently been reported to be elevated in preeclampsia. Adiponectin is a marker also detectable in normal individuals, but is decreased in various conditions, for example obesity or diabetes. In preeclampsia however, it has been suggested to exert proinflammatory influence on monocytic cells (7).

As often occurs in association with inflammation, certain cell types are triggered to undergo apoptotic processes as a result. Increased apoptosis of the extravillous trophoblast in the placental bed and villous trophoblast have been reported in preeclampsia. Serum from preclamptic women has been shown to reduce trophoblast viability, and that effect seemed to be related to changes in trophoblast sensitivity to **APO-1/Fas**-mediated apoptosis. Elevated serum soluble APO-1/Fas is associated with preeclampsia (8, 9).

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8) *Neale DM et al. Obstet Gynecol 2001;97:530-2.*

Human FlowCytomix™ Preeclampsia Panel

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
Adiponectin[1)]	B7	0.06 ng/ml	0.1 - 50 ng/ml	BMS82032FF
sAPO-1/Fas[1)]	A3	10.0 pg/ml	34 - 25,000 pg/ml	BMS80245FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
IP-10	B5	6.0 pg/ml	17 - 12,500 pg/ml	BMS8284FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF

Further Species

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
IL-15/IL-15R	A11	5.0 pg/ml	6.9 - 5,000 pg/ml	BMS86023FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
IP-10	A3	9.8 pg/ml	41 - 30,000 pg/ml	BMS86018FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.

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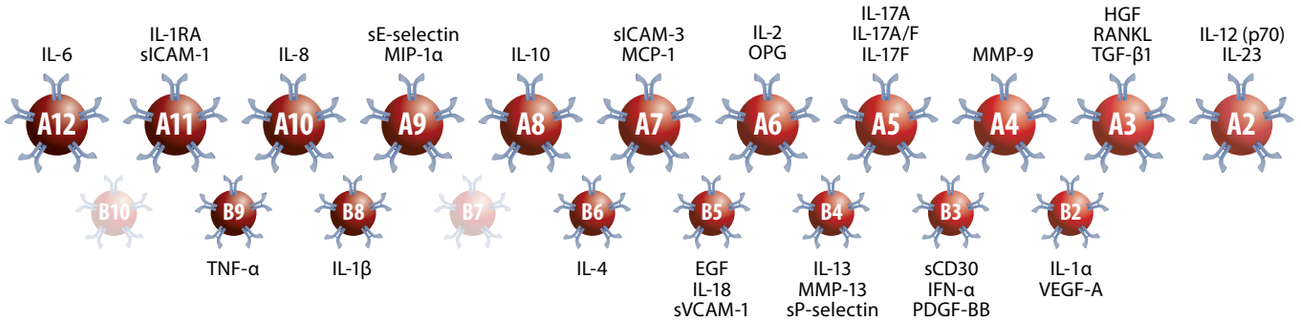
Human Rheumatoid Arthritis Panel



RA (rheumatoid arthritis) is the most common type of inflammatory arthritis. It primarily affects the synovial membrane, cartilage and bone, and as a result can be a major cause of physical disability in patients. The pathology of this disease was originally identified as being caused by auto-antibodies and their formation of immune complexes. T cell-mediated antigen-specific responses, T cell-independent cytokine networks, and aggressive tumor-like behaviour of rheumatoid synovium have also been implicated (1). Numerous cytokines are involved in the pathogenesis of RA; their roles being related to specific processes that promote autoimmunity, chronic inflammation, and joint destruction. After onset of clinical disease, the normally hypocellular synovial membrane becomes hyperplastic and then contains various cells, such as synovial fibroblasts, macrophages, mast cells, CD4+ and CD8+ T cells, NK (natural killer) cells, NKT (natural killer T) cells, B- and plasma cells. The inflamed synovium expands to adjacent cartilage and promotes articular destruction. Cytokines play a major role in each phase of RA pathogenesis, by driving autoimmunity, maintaining chronic inflammatory synovitis, and by promoting the destruction of adjacent joint tissue. Partially, the disease may be driven by systemic cytokines released by inflamed synovium, secondary lymphoid organs, or target tissues. **IL-6**, for instance, causes the production of acute phase proteins by the liver. Several proinflammatory cytokines contribute to altered function of adipocytes, e.g. adipocytokine release (2). IL-33, produced mainly in inflamed joints in RA patients, has been shown to be increased in serum and synovial fluid particularly in high disease activity individuals. IL-33 signaling might also play an important role in joint inflammation of human RA (3).

In addition to cytokines, adhesion molecules can be markers of rheumatoid synovitis. Soluble forms of **ICAM-1**, **ICAM-3**, **E-selectin**, **P-selectin**, **VCAM-1** and **VEGF-A** have been discovered to be increased in patient sera compared to patients presenting with osteoarthritis. Concentrations also correlated with markers of disease activity and serum CRP values (4-6). RA is closely linked to angiogenesis, with key angiogenic mediators such as **EGF** (epidermal growth factor), **HGF** (hepatocyte growth factor), and **PDGF** (platelet-derived growth factor) observed in synovium and tenosynovium of rheumatoid joints (7). MMPs are responsible for the destruction of cartilage in RA patients. **MMP-9** production in human monocytes/macrophages is stimulated by **IL-17**. Concentration and activity levels of **MMP-9** and **-13** are significantly higher in RA serum and synovial fluid than in osteoarthritis (12, 13). Also in RA, there may exist an imbalance between **RANKL**, which is an inducer of osteoclast differentiation and bone-resorbing activity, its receptor RANK and their common modulator, **OPG** (osteoprotegerin). As a result of this dysregulation, RA associated bone loss may follow(2).

The role of T cells and B cells

RA had long been considered a Th1-mediated disorder, driven by cytokines such as IFN-γ and **TNF- α**. More recent data also implicates Th17 cells as crucial effectors. IL-17 expression, a hallmark of Th17 cells, has been detected in rheumatoid synovial membranes. IL-17 activates and triggers cytokine release by neutrophils, monocytes and synovial fibroblasts, just to name a few. Together with TNF, IL-17 may activate dendritic cells in the joint. and a potent role in joint damage has been proposed (2). In established disease, the synovial milieu contains numerous factors, like **IL-1α**, **IL-1β**, **IL-6**, **IL-12**, **IL-18**, **IL-23**, and **TGF-β**, which can drive the differentiation of Th1 and/or Th17 cells. **IL-21**, secreted by CD4+ T cells, enhances local T-cell activation, proliferation and proinflammatory cytokine secretion (14). Cytokine levels in the joint depend on the stage of disease. In early RA, **IL-4** and **IL-13** are elevated, whereas established disease features a lack of IL-4 and low levels of

IL-13. Natural CD4+ CD25++ FoxP3+ regulatory T cells can be found in the synovium of patients with active disease, but their regulatory capacity seems to be impaired (2). Significantly increased levels of soluble **CD30**, a member of the TNF receptor superfamily, has also been reported (8). An important feature of RA is that several regulatory cytokines such as **IL-10**, IL-11, and **IL-1RA** (IL-1 receptor antagonist) are not present in sufficient local concentrations to balance and regulate the dominant proinflammatory milieu. Mice deficient in IL-1RA develop spontaneous erosive arthritis associated with the induction of Th17 cells. By comparison, B cells are the source of those auto-antibodies which form RA-related immune complexes. In addition, these cells release cytokines and chemokines, such as IL-6 or **IL-10**, that further these processes. B cell survival and activation is mainly provided by TNF superfamily members, like APRIL (a proliferation-inducing ligand) a product of mature dendritic cells in synovial membranes, or BAFF (B cell-activation factor belonging to the TNF family) produced by macrophages and synovial fibroblasts. When cultured synovial fibroblasts are exposed to TNF and IFN-γ, they secrete high levels of BAFF (2).

Innate immune effector cells

Since macrophages produce proinflammatory cytokines, they are often the key cytokine producers in RA pathogenesis. TNF for example promotes many key pathological features of RA and its inhibition significantly improves a patient's condition. **IFN-α** and IFN-β are also expressed in RA. Type I IFN responses may possibly discriminate clinically distinct subsets of RA patients (2). Moreover, synovial tissue macrophages are the dominant source of **MCP-1** in RA. In synovial fluid, high MCP-1 levels strongly correlate with increased **IL-8** concentrations, which is chemotactic for neutrophils and lymphocytes (9, 10). High numbers of neutrophils in synovial fluid release TNF, IL-1, IL-18, IL-6, **MIP-1α**, and BAFF (2, 11). Finally, mast cells are also commonly recruited into RA synovial tissue, where they produce various proteases and proinflammatory cytokines (2).

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Human FlowCytomix™ Rheumatoid Arthritis Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Th1/Th2 11plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FF
Th1/Th2 11plex Ready-to-Use	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FFRTU
Th1/Th2/Th9/Th17/ Th22 13plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p70), IL-13, IL-17A, IL-22, TNF-α	BMS817FF
Adhesion 6plex	sE-selectin, sICAM-1, sICAM-3, sPECAM-1, sP-selectin, sVCAM-1	BMS812FF
Chemokine 6plex	G-CSF, IL-8, MCP-1, MIG, MIP-1α, MIP-1β	BMS813FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
EGF	B5	22.7 pg/ml	27 - 20,000 pg/ml	BMS82070FF
sE-selectin	A9	1.2 ng/ml	4.0 - 3,000 ng/ml	BMS8205FF
HGF	A3	52 pg/ml	206 - 150,000 pg/ml	BMS82069FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
sICAM-3	A7	4.8 ng/ml	11 - 8,000 ng/ml	BMS8218FF
IFN-α	B3	8.06 pg/ml	27 - 20,000 pg/ml	BMS8216FF
IL-1α	B2	0.5 pg/ml	1.4 - 1,000 pg/ml	BMS80243FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-1RA	A11	96 pg/ml	137 - 100,000 pg/ml	BMS82080FF
IL-2	A6	16.4 pg/ml	27 - 20,000 pg/ml	BMS8221FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-13	B4	4.5 pg/ml	27 - 20,000 pg/ml	BMS8231FF
IL-17A	A5	2.5 pg/ml	13.7 - 10,000 pg/ml	BMS82017FF
IL-17A/F	A5	16 pg/ml	27.4 - 20,000 pg/ml	BMS82082FF
IL-17F	A5	8.0 pg/ml	27 - 20,000 pg/ml	BMS82037FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
IL-23	A2	21.9 pg/ml	69 - 50,000 pg/ml	BMS82023FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MIP-1α	A9	1.0 pg/ml	13.7 - 10,000 pg/ml	BMS82029FF
MMP-9[1)]	A4	95 pg/ml	0.1 - 100 ng/ml	BMS82016FF
MMP-13	B4	0.05 ng/ml	0.17 - 125 ng/ml	BMS82022FF
OPG	A6	7.9 pg/ml	27 - 20,000 pg/ml	BMS82021FF
PDGF-BB	B3	3.4 pg/ml	21 - 15,000 pg/ml	BMS82071FF
sP-selectin	B4	1.2 ng/ml	2.8 - 2,000 ng/ml	BMS8219/2FF
RANKL	A3	16 pg/ml	55 - 40,000 pg/ml	BMS82005FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF
VEGF-A	B2	7.2 pg/ml	27 - 20,000 pg/ml	BMS80277FF

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Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Th1/Th2 10plex	GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, TNF-α	BMS820FF
Th1/Th2/Th17/Th22 13plex	IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17A, IL-21, IL-22, IL-27, TNF-α	BMS822FF
Chemokine 6plex	GM-CSF, MCP-1, MCP-3, MIP-1α, MIP-1β, RANTES	BMS821FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IL-1α	A4	15.7 pg/ml	27 - 20,000 pg/ml	BMS8611FF
IL-1β	B4	34.3 pg/ml	69 - 50.000 pg/ml	BMS86002FF
IL-2	A6	8.8 pg/ml	27 - 20,000 pg/ml	BMS8601FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
IL-13	A2	9.3 pg/ml	27 - 20,000 pg/ml	BMS86015FF
IL-17A	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS86001FF
IL-17A/F	B10	1.0 pg/ml	2.7 - 2,000 pg/ml	BMS86026FF
IL-17F	A7	6.0 pg/ml	27 - 20,000 pg/ml	BMS86020FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
IL-21	A9	5.0 pg/ml	27 - 20,000 pg/ml	BMS86021FF
IL-23	B5	14.5 pg/ml	55 - 40,000 pg/ml	BMS86017FF
IL-33	A3	see www.eBioscience.com		BMS86025FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
MIP-1α	A11	1.8 pg/ml	27 - 20,000 pg/ml	BMS86013FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokine 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
IL-17A	A10	5.0 pg/ml	7 - 5,000 pg/ml	BMS8635FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

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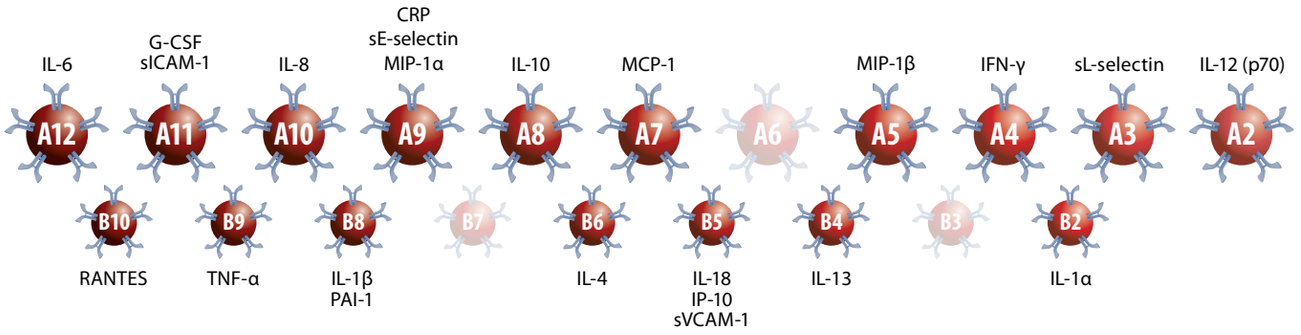
1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.

4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.

Human Sepsis / Septic Shock Panel



Sepsis is a serious medical condition, characterized by a systemic inflammatory state caused by infection. Symptoms of sepsis are often related to the underlying infectious process. When an infection crosses into sepsis, the resulting symptoms are that of SIRS (systemic inflammatory response syndrome): general inflammation, fever, elevated white blood cell count (leukocytosis), and raised heart rate and breathing rate. The immunological response that causes sepsis is a systemic inflammatory response causing widespread activation of inflammation and coagulation pathways. This may progress to dysfunction of the circulatory system and, even under optimal treatment, may result in multiple organ dysfunction syndrome and eventually death. Sepsis conditions are a major cause of death in intensive care units worldwide, with mortality rates that range from 20% for sepsis to 40% for severe sepsis to >60% for septic shock. Three of the major players in inflammation are **IL-1**, **IL-6** and **TNF-α**; cytokines, which are also well-known as markers of sepsis. Osuchowski and coworkers showed in a mouse study that multiple plasma proteins are elevated during murine sepsis. IL-1β, IL-6, TNF and **MCP-1** were among elevated proinflammatory cytokines, whereas TNF soluble receptors and **IL-10** were found to be increased anti-inflammatory markers. Distinct combinations of elevated markers predict mortality within 24 hours (1, 2). However, there are also studies documenting a decrease of IL-1β concentration, e.g. in neonatal sepsis (2, 3). Multiple studies reveal elevated **IL-18** plasma concentrations in sepsis, e.g. in patients with surgical wounds, IL-18 levels rose significantly after 48 hours, and this also correlated with **CRP** (C-reactive protein) levels (4, 5). This is furthermore associated with a poor clinical outcome. Moreover, such significantly high IL-18 plasma concentrations help to discriminate between Gram-positive and Gram-negative related sepsis (6). Since chemokines regulate leukocyte activation and trafficking in inflammatory processes, particular chemokines also influence responses to sepsis. In septic patients elevated levels of **MIP-1α** and **MIP-1β** were observed within 24 hours of sepsis and decreased in parallel with TNF-α and IL-6 (7). Among adhesion molecules, **ICAM-1**, **E-selectin**, and **VCAM-1** are key markers in sepsis. In neonatal sepsis, ICAM-1 levels are increased early on, and levels can be correlated with the clinical severity of the disease (8). A study investigating soluble ICAM-1 and E-selectin in patients revealed that these two markers are raised in nonsurviving patients with severe sepsis compared to patients with infection lacking systemic sepsis. Additionally, E-selectin levels present a potential prognostic tool for the severity, possible course, and outcome of developing sepsis (9, 10). In meningitis, patients show increased concentrations of ICAM-1, E-selectin, VCAM-1 and TNF-α in CSF (cerebrospinal fluid). Higher values in CSF correlate with higher serum levels (11). Soluble L-selectin has been suggested as a predictor of survival in sepsis patients. Those admitted with low sL-selectin are characterized by a high mortality within the subsequent 12-month period (12).

A study conducted with severely burned patients addresses the question whether serum cytokine profiling can be used to identify patients at risk of developing and subsequently dying from sepsis. In serum samples significant elevations of IL-6, **IL-8**, IL-10, GM-CSF, TNF, and **IL-12 (p70)** had been found in patients who succumbed to sepsis the time of hospital admission. Serum IL-6, IL-12p70, and TNF seem to be useful as prognostic markers to identify burn patients who are at high risk of death from sepsis (13). **IP-10** has been shown to be a sensitive early marker of sepsis in preterm infants (14). Decreased levels of **RANTES** predict the development of sepsis-induced disseminated intravascular coagulation in neonates, which enables early sepsis treatment. Low circulating levels are associated with poor outcome (15).

There are, however, distinct patterns of elevated cytokine levels, which discriminate severe sepsis from **septic shock**. It could be shown by evaluating 17 cytokines in 60 patients with a recent diagnosis of severe sepsis that a number of markers are significantly higher in septic shock patients. These include IL-1β, IL-6, IL-8, IL-10, **IL-13**, **IFN-γ**, MCP-1, and TNF-α. Concentrations werefurther associated with severity and evolution of organ dysfunction. Moreover, IL-6, IL-8 and G-CSF concentrations during the first 24 hours were predictive of worsening organ dysfunction to improve on day three. IL-1β, **IL-4**, IL-6, IL-8, MCP-1, and **G-CSF** levels seem to predict early mortality (< 48 hours), whereas IL-8 and MCP-1 had the best accuracy for predicting mortality at 28 days (16). **PAI-1** is considered the main inhibitor of fibrinolysis in sepsis. Levels were found to be significantly higher in septic shock patients compared to severe sepsis (17). In children developing sepsis-induced multiple organ failure and mortality, increased PAI-1 release and systemic activity was observed. Activity levels correlated with elevated IL-6 as well as nitrite and nitrate concentrations. Increased systemic activity was associated with organ failure (18).

It has recently been demonstrated that IL-33 helps shield the body from bacterial sepsis. In a sepsis mouse model it was found that administering IL-33 markedly enhanced the influx of neutrophils into the infectious focus, reducing bacterial counts and increasing survival. Moreover, ST2-deficient mice showed increased sensitivity to sepsis compared to wild-type mice, supporting a crucial role for the IL-33/ST2 axis in bacterial sepsis (19).

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Human FlowCytomix™ Sepsis/Septic Shock Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Th1/Th2 11plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FF
Th1/Th2 11plex Ready-to-Use	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FFRTU
Th1/Th2/Th9/Th17/ Th22 13plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p70), IL-13, IL-17A, IL-22, TNF-α	BMS817FF
Chemokine 6plex	G-CSF, IL-8, MCP-1, MIG, MIP-1α, MIP-1β	BMS813FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
CRP[1)]	A9	0.07 ng/ml	0.1 - 70 ng/ml	BMS8288FF
sE-selectin	A9	1.2 ng/ml	4.0 - 3,000 ng/ml	BMS8205FF
G-CSF	A11	3.4 pg/ml	34 - 25,000 pg/ml	BMS82001FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-1α	B2	0.5 pg/ml	1.4 - 1,000 pg/ml	BMS80243FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-13	B4	4.5 pg/ml	27 - 20,000 pg/ml	BMS8231FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
IP-10	B5	6.0 pg/ml	17 - 12,500 pg/ml	BMS8284FF
sL-selectin[1)]	A3	70 pg/ml	137 - 100,000 pg/ml	BMS80206FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MIP-1α	A9	1.0 pg/ml	13.7 - 10,000 pg/ml	BMS82029FF
MIP-1β	A5	1.0 pg/ml	4.0 - 3,000 pg/ml	BMS82030FF
PAI-1[1)]	B8	13.5 pg/ml	137 - 100,000 pg/ml	BMS82033FF
RANTES[1)]	B10	25 pg/ml	41 - 30,000 pg/ml	BMS8287FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF

Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Th1/Th2 10plex	GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, TNF-α	BMS820FF
Th1/Th2/Th17/Th22 13plex	IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17A, IL-21, IL-22, IL-27, TNF-α	BMS822FF
Chemokine 6plex	GM-CSF, MCP-1, MCP-3, MIP-1α, MIP-1β, RANTES	BMS821FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-1α	A4	15.7 pg/ml	27 - 20,000 pg/ml	BMS8611FF

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Further Species (continued)

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits (cont.)				
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
IL-13	A2	9.3 pg/ml	27 - 20,000 pg/ml	BMS86015FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
IL-33	A3	see www.eBioscience.com		BMS86025FF
IP-10	A3	9.8 pg/ml	41 - 30,000 pg/ml	BMS86018FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
MIP-1α	A11	1.8 pg/ml	27 - 20,000 pg/ml	BMS86013FF
MIP-1β	B2	14.9 pg/ml	27 - 20,000 pg/ml	BMS86014FF
RANTES	B4	6.1 pg/ml	27 - 20,000 pg/ml	BMS86009FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokine 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-1α	A6	8.5 pg/ml	27 - 20,000 pg/ml	BMS8627FF
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.

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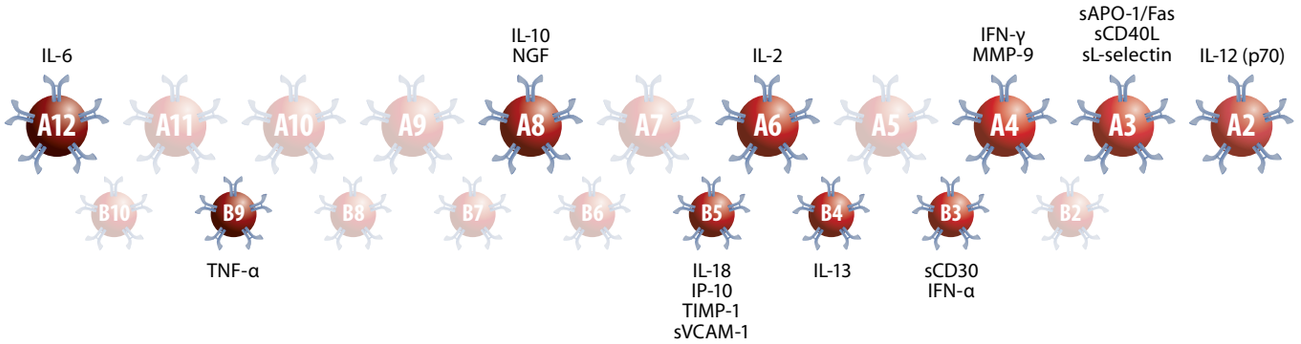
Human Systemic Lupus Erythematosus Panel



SLE (systemic lupus erythematosus) is a multi-system, autoimmune disease associated with significant morbidity and mortality. SLE can affect any part of the body, but most often affects the heart, joints, skin, lungs, blood vessels, liver, kidneys and nervous system. As in other autoimmune diseases, the immune system attacks the body's own cells and tissue, resulting in inflammation and tissue damage. Multiple studies have investigated the expression and role of **CD40L** (CD154) in SLE, as its expression appears to be significantly increased. In both human and mouse model systems, prolonged expression of CD40L is found on lupus T cells, where it may cause excessive B cell activation, and in turn contribute to disease pathogenesis (1, 2). Furthermore, auto-antibodies to CD40L have been detected in significant percentage of SLE patients, which is associated with thrombocytopenia (3). **CD30** is a marker of cells producing Th2 cytokines. Elevated levels of soluble CD30 in SLE sera present a marker for the evaluation of disease activity (4). **IL-10** as a prominent Th2 cytokine has also been shown to play a role in this autoimmune disorder (5). Additionally, **IL-13** has been a focus of SLE research. During active disease, IL-13 levels reach highest concentrations in serum. Nevertheless, in inactive disease IL-13 is still increased compared to healthy controls (6). The elevation of proinflammatory cytokines such as **IL-6**, **IL-12**, **IL-18** and **TNF-α** may trigger the inflammatory process in SLE. All these markers have been found to be increased in SLE patients, and to correlate well with disease activity (7-9). Increased **IFN-α** levels in serum of patients with active SLE has long been known, specifically, intracellular vesicular inclusions in renal endothelial cells of SLE patients are inducible by IFN-α. Studies on human and murine samples suggest a primary role for type 1 IFNs (IFN-α, IFN-β) in systemic autoimmunity (10, 11). Like CD40L and CD30, **NGF** (nerve growth factor) is another SLE marker belonging to the TNF-R superfamily. This neurotrophic factor is present in mast cells, and in T- and B cells. It is reported to influence immune cell development, and is also present in higher concentrations in inflammation and in some autoimmune diseases. In SLE in particular, NGF levels may correlate with disease activity (6, 12). A significant clinical SLE marker found in urine is the adhesion molecule **VCAM-1**. In patients, soluble VCAM-1 is about 7-fold increased compared to normal controls, whereas for soluble ICAM-1 no significant difference could be observed. Urinary VCAM-1 concentrations correlate with overall disease activity and damage scores in SLE (13). Furthermore, concentrations of soluble **L-selectin** have been found to be increased in SLE patients' serum. Levels correlate with genotype and a subgroup of lupus with vasculopathy (14). Additionally, elevated serum **IP-10** levels have been detected in SLE patients, which were significantly higher in the presence of active hematological and mucocutaneous manifestations. PBMCs from these patents exhibit enhanced spontaneous IP-10 production *in vitro*. IP-10 levels are also higher in CSF of lupus patients with central nervous system involvement than in non-CNS lupus patients (15, 16). Symptoms originating from the CNS occur frequently in patients with SLE, and CNS involvement in lupus is associated with increased morbidity and mortality.

MMPs (matrix metalloproteinases) are a group of tissue degrading enzymes that may be involved in ongoing brain destruction. Intrathecal **MMP-9** levels were significantly increased in CNS lupus patients compared with non-CNS SLE patients and healthy control individuals. PBMCs from SLE patients secrete more MMP-9 in culture. Their serum MMP-9 and **TIMP-1** concentrations are, however, decreased, but no relationship was found between serum MMP-9 concentration and the SLE Disease Activity Index (SLEDAI) (17-19).

Moreover, CD95 (**Apo-1/Fas**), a prototypic cell surface receptor for the induction of apoptosis, is found

in its soluble form to be increased in SLE serum. Fas promoter polymorphisms might contribute to individual susceptibility to SLE and influence autoantibody response in patients (20, 21). IL-27 exerts suppressive effects on Th17 cells. This observation has been linked to the development of SLE, in that serum IL-27 levels are decreased in SLE patients. Exogenous administration of IL-27 suppresses some diseases of autoimmune origin, as could be demonstrated in autoimmune diabetes and murine lupus (22, 23).

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Human FlowCytomix™ Systemic Lupus Erythematosus Panel

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sAPO-1/Fas[1)]	A3	10.0 pg/ml	34 - 25,000 pg/ml	BMS80245FF
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
sCD40L	A3	23.4 pg/ml	55 - 40,000 pg/ml	BMS8239/2FF
IFN-α	B3	8.06 pg/ml	27 - 20,000 pg/ml	BMS8216FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-2	A6	16.4 pg/ml	27 - 20,000 pg/ml	BMS8221FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-13	B4	4.5 pg/ml	27 - 20,000 pg/ml	BMS8231FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
IP-10	B5	6.0 pg/ml	17 - 12,500 pg/ml	BMS8284FF
sL-selectin[1)]	A3	70 pg/ml	137 - 100,000 pg/ml	BMS80206FF
MMP-9[1)5)]	A4	95 pg/ml	0.1 - 100 ng/ml	BMS82016FF
NGF	A8	126.75 pg/ml	412 - 300,000 pg/ml	BMS82044FF
TIMP-1[1)5)]	B5	28 pg/ml	137 - 100,000 pg/ml	BMS82018FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF

Further Species

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-2	A6	8.8 pg/ml	27 - 20,000 pg/ml	BMS8601FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
IL-13	A2	9.3 pg/ml	27 - 20,000 pg/ml	BMS86015FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
IL-27	B2	31.5 pg/ml	69 - 50,000 pg/ml	BMS86024FF
IP-10	A3	9.8 pg/ml	41 - 30,000 pg/ml	BMS86018FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.
5) MMP Simplex Kits cannot be combined with the TIMP-1 Simplex Kit.

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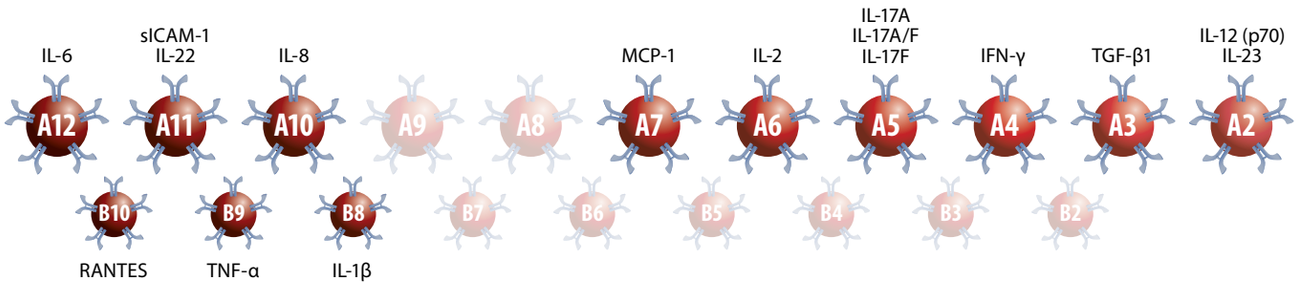
Human Th17 Panel



Th17 cells are very efficient inducers of tissue inflammation and initiators of organ-specific autoimmunity. Furthermore, they play a role in allergy and tumor development.

Murine Th17 cells express a master transcription factor different from Th1 and Th2 cells, an orphan receptor known as retinoic acid-related orphan receptor RORγt. A second orphan receptor, named RORα, has also been found to contribute to the development of murine Th17 cells. Studies in humans showed that Th17 cells express RORC, CCR6, CCR4 and the IL-23R, but also CD161, the equivalent of murine NK1.1. Th17 cells secrete a range of cytokines including **IL-6**, **IL-17A**, **IL-17F**, IL-20, IL-21, **IL-22**, IL-26, **TNF-α**, CCL20, and GM-CSF. Another difference between murine and human Th17 cells was found with regard to their origin. While murine Th17 cells originate from a naive Th cell in the presence of **TGF-β** and IL-6, human Th17 cells exclusively originate in the presence of **IL-1β** and **IL-23** from a small subset of naïve CD4+ Th cells that express CD161, which are present in the umbilical cord blood and newborn thymus. (1, 2).

Th17 differentiation and expansion

TGF-β, together with IL-6, induces Th17 differentiation, while **IL-1β** and TNF-α cytokines can amplify this response. Without the influence of these proinflammatory cytokines, TGF-β promotes the development of CD4+ CD25++ FoxP3+ Tregs from naïve CD4+ T cells. IL-23, primarily secreted by activated dendritic cells (DC), is then required to stabilize and expand the Th17 population (1, 3, 13). The orphan nuclear receptor RORγt directs the differentiation program of the mouse Th17 lineage. IL-21, which is highly expressed by mouse Th17 cells, also potently induces Th17 differentiation and suppresses FoxP3 (4). In contrast to humans, where Th17 cells are suppressed by **IL-12**, the differentiation of mouse Th17 cells is inhibited by **IFN-γ** (1). GM-CSF is known to be a crucial factor in the development of organ-related autoimmune diseases, but the mechanism has not been fully revealed. GM-CSF induces IL-6 responses and generation of pathological Th17, but not Th1 cells. Regarding Th17 cells, high dose antigen is necessary for differentiation by enhancing CD40L expression on DC and IL-6 production. Lack of CD40-CD40L interaction leads to a significantly impaired Th17 induction and to autoimmunity *in vivo*. Thus IL-6 production, a key event for Th17 development, is regulated by GM-CSF, antigen dose, and CD40-CD40L crosstalk (14).

Th17 cytokines

Differentiated Th17 cells produce a number of cytokines, such as IL-6, IL-17A, IL-17F, IL-20, IL-21, IL-22, IL-26, TNF-α, CCL20 and GM-CSF (6). In the mouse, IL-17 itself is a potent upregulator of additional cytokine/chemokine cascades resulting in further expression of IL-6, **IL-8**, PGE-2, **MCP-1** or G-CSF from a variety of cell types. In human cells, IL-17 induces proliferation of T cells, and growth and differentiation of CD34+ human progenitor cells into neutrophils. It has been shown *in vitro* that IL-17 induces GM-CSF (together with TNF-α), as well as inducing IL-6, IL-8, **RANTES** and MCP-1 in conjunction with CD40L (11). IL-22 promotes anti-microbial defense, protects against damage, and re-organizes non-immune tissues. Furthermore, it induces acute phase reactants. Endogenous IL-22 plays a proinflammatory role in CIA in mice (5, 6, 12).

Th17 cells in autoimmunity and host defense

Th17 cells are very efficient inducers of tissue inflammation and crucial initiators of organ-specific autoimmunity. While FoxP3+ Tregs prevent autoimmunity, Th17 cells promote autoimmune tissue inflammation (7). Mice overexpressing TGF-β generate more Th17 cells and show

exacerbated EAE pathology. In the absence of Th17 cells, no autoimmune pathology is observed. Neutralizing anti-IL-17 antibodies improve joint damage in CIA, and IL-17 auto-vaccine experiments showed a protection of mice against EAE, arthritis and myocarditis (8). In humans, IL-17 mRNA has been detected in multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, inflammatory bowel diseases, and in the skin of patients suffering from nickel-induced contact dermatitis or psoriasis (1). Th17 cells also show major involvement in the defense against pathogens. By the production of IL-17, Th17 cells induce the secretion of G-CSF, which leads to the mobilization and new generation of neutrophils, linking innate and adaptive immune mechanisms.

Th17 in tumor microenvironment + Th17/Treg balance

Th17 cells have been observed in the tumor microenvironment. Both Th17 and Tregs are increased in the course of tumor development and exist in highest numbers in advanced tumors, where the Th17 differentiation cytokines IL-6 and TGF-β reach high concentrations. The balance between Th17 and Tregs is maintained by the differential effects of IL-2 on the two distinct T cell lineages. IL-2 is essential for Treg cell generation and effector function. *In vitro*, the number of Th17 is reduced upon IL-2 treatment, whereas **IL-2** neutralization boosts Th17 differentiation. In contrast, Treg numbers increase under the influence of IL-2. These observations have been confirmed *in vivo* using B16 tumor-bearing mice (9, 10).

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Human FlowCytomix™ Th17 Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Th1/Th2 11plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FF
Th1/Th2 11plex Ready-to-Use	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FFRTU
Th1/Th2/Th9/Th17/ Th22 13plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p70), IL-13, IL-17A, IL-22, TNF-α	BMS817FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-2	A6	16.4 pg/ml	27 - 20,000 pg/ml	BMS8221FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-17A	A5	2.5 pg/ml	13.7 - 10,000 pg/ml	BMS82017FF
IL-17A/F	A5	16 pg/ml	27 - 20,000 pg/ml	BMS82082FF
IL-17F	A5	8.0 pg/ml	27 - 20,000 pg/ml	BMS82037FF
IL-22	A11	43.3 pg/ml	110 - 80,000 pg/ml	BMS82047FF
IL-23	A2	21.9 pg/ml	69 - 50,000 pg/ml	BMS82023FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
RANTES[1)]	B10	25 pg/ml	41 - 30,000 pg/ml	BMS8287FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF

Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Th1/Th2 10plex	GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, TNF-α	BMS820FF
Th1/Th2/Th17/Th22 13plex	IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17A, IL-21, IL-22, IL-27, TNF-α	BMS822FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-2	A6	8.8 pg/ml	27 - 20,000 pg/ml	BMS8601FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
IL-17A	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS86001FF
IL-17A/F	B10	1.0 pg/ml	2.7 - 2,000 pg/ml	BMS86026FF
IL-17F	A7	6.0 pg/ml	27 - 20,000 pg/ml	BMS86020FF
IL-21	A9	5.0 pg/ml	27 - 20,000 pg/ml	BMS86021FF
IL-22	A5	5.5 pg/ml	6.9 - 5,000 pg/ml	BMS86016FF
IL-23	B5	14.5 pg/ml	55 - 40,000 pg/ml	BMS86017FF

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Further Species (continued)

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits (cont.)				
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
RANTES	B4	6.1 pg/ml	27 - 20,000 pg/ml	BMS86009FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokine 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-17A	A10	5.0 pg/ml	7 - 5,000 pg/ml	BMS8635FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.

4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.

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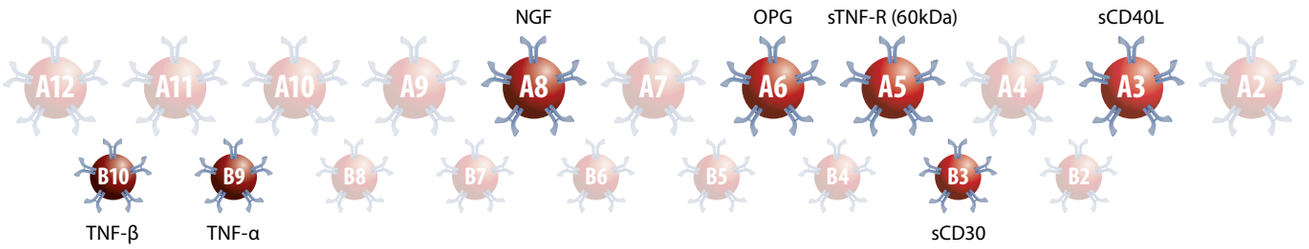
Human TNF/TNF-R Panel



The **tumor necrosis factor (TNF)-related family** of cytokines and receptors are major regulators of cell death and cell survival. These receptor-ligand interactions coordinate differentiation of tissue to defend against intracellular pathogens, as well as regulation and development of lymphoid tissue. Cellular responses are initiated by a corresponding family of specific receptors that includes two distinct TNF receptors (**TNF-R (60kDa)** and TNF-R (80kDa)), CD95 (Apo-1/Fas), CD40, and Lymphotoxin β-receptor (LTβR), among others. CD40 and LTβR are receptors involved in induction NFκB and cell survival (1). The so-called "death receptors", including TNF-R (60kDa), CD95 (Fas), DR4 and DR5, and TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), typically initiate cell death /apoptosis via an extrinsic pathway, i.e. activated by ligand binding, or by an intrinsic pathway, which is mitochondria-dependent.

One of the most studied death receptors is CD95 (Fas), which upon binding by FasL, leads to receptor trimerization and recruitment of specific death-domain containing adaptor proteins. The Fas receptor contains a DD (death domain) in its cytoplasmic region, which interacts with adaptor proteins, FADD (Fas-associated death domain protein), forming a DISC (death receptor-induced signaling complex). Procaspase-8 is proteolytically activated to the enzymatically activated caspase-8, which in turn activates downstream effector caspases. Other death receptors activate caspases in a similar manner: **TNF-α** induces signaling via both TNF-R (60kDa) and TNF-R (80kDa). TNF-R (60kDa) contains a DD and promotes both survival and cell death signals, while TNF-R (80kDa) lacks a cytoplasmic DD and predominantly provides survival signals. TNF-R (60kDa) is indirectly linked to FADD by the DD-containing adaptor protein TRADD (tumor necrosis factor receptor-associated death domain protein) (2,3).

TNF was originally discovered as a serum protein capable of promoting necrosis of transplantable mouse tumors *in vivo* and cytotoxic effects against some transformed cells *in vitro* (3). TNF includes two MHC-encoded cytokines, TNF-α (cachectin) and **TNF-β** (lymphotoxin- α), both of which can mediate a wide variety of biological effects (4,5). TNF-α is a polypeptide cytokine produced by monocytes and macrophages and is a potent modulator of immune responses (5). TNF-α circulates throughout the body responding to stimuli (infectious agents or tissue injury), activating neutrophils, altering the properties of vascular endothelial cells, regulating metabolic activities of other tissues, as well as exhibiting tumoricidal activity by inducing localized blood clotting. TNF-α may play a significant role in the pathogenesis of inflammatory diseases of the joints and other tissues (6,7). As a major inflammatory protein TNF-α is also a well-known marker of sepsis (8, 9). Elevated TNF-α concentrations, along with elevated TNF-R (60kDa) levels, play a crucial role in viral myocarditis (10).

TNF-β is induced in an antigen-specific, MHC-restricted fashion from T cells. TNF-β has several effects on target cells including cell death, growth stimulation, induction of adhesion molecule (ICAM-1) expression (11), and induction of differentiation. The mechanisms of TNF-β effects involve receptor binding and internalization and several sequelae including changes in prostaglandins and chromosome integrity. Studies have demonstrated that both TNF-α and TNF-β are capable of activating neutrophils *in vitro* (12). The release of IL-1 from human endothelial cells is also induced by TNF-α and TNF-β (13).

OPG (osteoprotegerin) is a another member of the TNF receptor family expressed by osteoblasts. OPG has documented effects on the regulation of bone metabolism. It inhibits bone resorption and binds with strong affinity

to its ligand RANKL (receptor activator of nuclear factor kappa B ligand), thereby preventing RANKL from binding its receptor RANK. This system is regulated by calcium-modifying hormones and by humoral factors. OPG also has a role in the regulation of the immune response, specifically related to interactions between T cells and dendritic cells. A number of implications for the OPG/RANKL/RANK system for bone and vascular diseases have been described, as well as its potential link to mechanisms in obesity (14).

CD154 (**CD40L**) is expressed on cells of high proliferative potential of lymphoid and epithelial origins, and exhibits bimodal growth-regulatory properties with distinct physiological effects. The outcome of CD40 ligation in B cells depends on the cells' differentiation stage, e.g. being mitogenic or anti-apoptotic in resting cells, yet growth-inhibitory in activated cells. In low-grade B cell malignancies CD40 engagement contributes to cell survival and resistance to chemotherapy, whereas in high-grade malignancies it causes growth arrest and apoptosis. CD40-mediated apoptosis has been documented in biliary, hepatocyte and carcinoma cells ectopically expressing CD40, where death occurs by autocrine/paracrine induction of death ligands such as TNF-α, FasL, and TRAIL (15). A soluble isoform of CD40L has been shown to exist in the circulation; it exhibits full activity in B cell proliferation and differentiation assays, is able to rescue B cells from apoptosis, and binds soluble CD40 (16, 17).

NGF (nerve growth factor), a neurotrophin and member of the TNF/NGF superfamily, is involved in neuronal growth and survival. Furthermore it greatly influences inflammation, and also repair and remodelling of tissues. It has been associated with these process, as well as with hyperresponsiveness and airway remodelling in asthma (18). Additionally, NGF levels are increased in type 1 diabetes (19) and autoimmune diseases such as systemic lupus erythematosus (20). NGF is a peripheral pain mediator, particularly in inflammatory pain states. Interestingly, NGF-neutralizing molecules are effective analgesic agents in many models of persistent pain (21).

Finally, **CD30,** is a member of the TNF-R superfamily that was originally identifed on the surface of Reed-Sternberg cells and anaplastic large cell lymphomas in Hodgkin's disease patients. Low serum levels of soluble CD30 (sCD30) were found in healthy individuals, whereas increased sCD30 serum concentrations were detected under pathophysiological situations such as systemic lupus erythematosus, rheumatoid arthritis, certain viral infections and adult T cell leukaemia/lymphoma. Pre- or post-transplant levels of sCD30 represent a biomarker for graft rejection associated with an impaired outcome for transplanted patients (22).

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21) *Pezet S et al. Annu Rev Neurosci 2006;29:507-38.*
22) *Schlaf G et al. Histol Histopathol 2007;22:1269-79.*

Human FlowCytomix™ TNF/TNF-R Panel

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
sCD40L	A3	23.4 pg/ml	55 - 40,000 pg/ml	BMS8239/2FF
NGF	A8	126.75 pg/ml	412 - 300,000 pg/ml	BMS82044FF
OPG	A6	7.9 pg/ml	27 - 20,000 pg/ml	BMS82021FF
TNF-α[2)]	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
TNF-β[2)]	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS8202FF
sTNF-R (60kDa)[2)]	A5	0.08 ng/ml	0.14 - 100 ng/ml	BMS8203FF

Further Species

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

2) The TNF-R (60kDa) Simplex Kit cannot be assayed simultaneously with the TNF-α or the TNF-β Simplex Kit.

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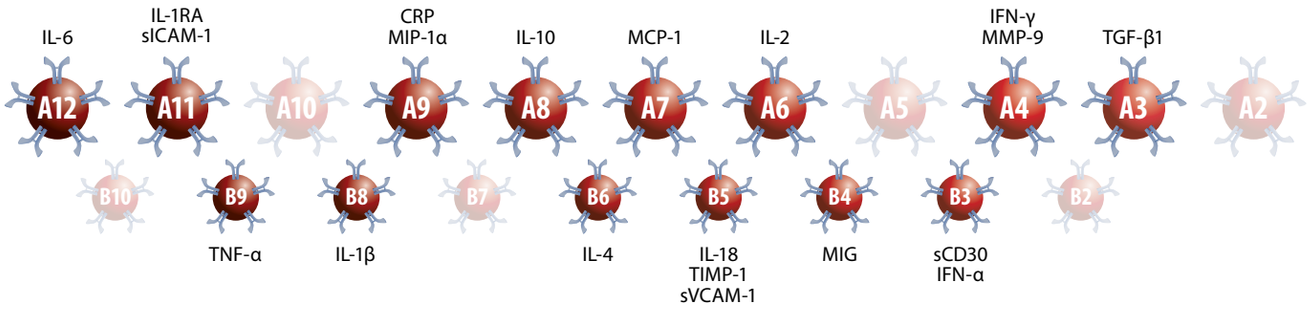
Human Transplantation Panel



Transplantation immunology refers to the extensive biological sequelae associated with therapeutic allograft or xenograft transfer intended to repair tissue damage. Antigen-independent causes of tissue damage (i.e. ischemia, hypothermia, reperfusion injury) are the result of mechanical trauma as well as disruption of the blood supply. In contrast, antigen-dependent causes of tissue damage involve immune-mediated damage and occur after exposure of a recipient to foreign, non-self HLA (histocompatibility antigens). Genes within the MHC (major histocompatibility complex), are highly polymorphic and thus it is highly unlikely that two unrelated persons have the same HLA type. Transplant rejection may be mediated by antibodies, lymphocytes, or both, and is manifested as hyperacute rejection (immediately post-transplant), acute rejection (occuring at any time) or chronic rejection (a slowly developing process causing a progressive decline in graft function). Vascularized organs, especially kidney and heart, are at risk for hyperacute rejection, if the patient has pre-formed donor-specific alloantibodies resulting from previous transplantation, blood transfusion or pregnancy. Hyperacute rejection is mediated by complement activation and the release of various inflammatory mediators, like **TNF-α**, and the initiation of the coagulation and fibrinolytic systems. In renal graft recipients, consistently high serum **CRP** (C-reactive protein) concentrations predict a low chance of allograft survival (1). The major players in acute rejection are lymphocytes which have become alloactivated against transplantation antigens. T cell activation requires TCR (T cell receptor) engagement, which ensures antigen specificity of the immune response. Additional signals, delivered by costimulatory molecules, sustain and integrate TCR signaling resulting in optimal cell proliferation and differentiation. The best characterized costimulatory pathway involves the CD28 receptor expressed on T cells which binds CD80 (B7-1) and CD86 (B7-2) ligands expressed on APC (antigen presenting cells). Additional costimulatory molecules include CD27, CD40L, **CD30**, and integrins that interact with their counterparts on APC, namely CD27L, CD40, CD30L and **ICAM-1**.

In specific types of transplantation systems, different protein expression patterns are observed pre- and post-transplant. For example, before lung transplantation, soluble CD30 indicates a risk of bronchiolitis obliterans syndrome after transplantation (2). Furthermore, the measurement of sCD30 has been proposed to evaluate the risk of acute graft rejection after transplantation (3). Delivery of the first signal (TCR engagement) in the absence of the second signal(s) (costimulation) leads to apoptosis or anergy. Activated lymphocytes infiltrate the graft by means of chemokines and adhesion molecules, like ICAM-1, **VCAM-1**, selectins and integrins. CD4+ and CD8+ lymphocytes induce various effector mechanisms of allograft immunity, like direct cytotoxic effects or delayed type hypersensitivity. The latter involves the recruitment of macrophages and the release of various cytokines like **IFN-γ**, **IL-4**, **IL-10**, and TNF-α. In kidney transplant recipients, serum **TGF-β1** is elevated during the first post-transplantation year (8), followed by chronic rejection and its characteristic fibrosis, tissue ischemia and progressive loss of organ function. This pathology likely involves both humoral and cellular immune mechanisms. Immunosuppressive drugs, like cyclosporine and corticosteroids, are typically administered to control graft rejection. Of these, cyclosporine blocks transcription of **IL-2**, **IL-4**, **IFN-α** and IL-2R and thereby inhibits the production of lymphokines which induce the activation and differentiation of alloreactive T cells. Corticosteroids induce the lysis of certain T cell subsets and block gene transcription in macrophages, especially for **IL-1**, **IL-6** and TNF-α (4). It has been proposed that regulatory T cells can prolong transplant function due to their anti-inflammatory properties. Thus, skewing of responses towards Th17 or Th1 (and not towards regulatory T cells) may cause acute transplant rejection in humans (5).

GVHD (Graft-Versus-Host Disease) is a persisting immune rejection associated with hematopoietic stem cell transplantation. Most recipients of allogeneic HSC experience some degree of acute GVHD after transplantation. GVHD progresses rapidly and is characterized by immunosuppression and tissue injury, which involves various organs such as the liver, skin, and intestinal mucosa. The progressive phases of GVHD are often classified into three main phases (6, 7). In early GVHD, injured host epithelium and endothelium release signals that recruit donor T cells, creating an inflammatory environment. Inflammatory cytokines such as TNF-α and IL-1 are induced. Increased expression of MHC antigens and adhesion molecules leads to enhanced recognition of host MHC and/or minor histocompatibility by mature donor T cells. Subsequently, donor T cells recognize alloantigens, leading to T cell activation and proliferation. Proliferating T cells release IL-2 and IFN-γ, which causes further T cell expansion and induce cytotoxic T cells and NK cells. During acute GVHD, **IL-18** is elevated with major targets including macrophages, NK cells, T cells and B cells. Together these proteins can modulate both Th1 and Th2 responses. Furthermore, additional mononuclear phagocytes are stimulated to secrete TNF-α and IL-1. NK cells are reconstituted quickly after stem cell transplantation, and may secrete IFN-γ, TNF-α and nitric oxide upon stimulation, leading to the tissue injury. LPS leaking through the intestinal mucosa, further stimulates macrophages to release cytokines and nitric oxide together with IFN-γ. In mouse models, several chemokines and their receptors have been shown to play a key role during acute GVHD. In particular, **MIP-1α**, MIP-2, **MIG**, **MCP-1**, MCP-3 and CCR5 mediate T cell infiltration into target tissues. The activated T cells cause further damage due to specific and non-specific mechanisms. TGF-β1 has been found to suppress acute GVHD, but to exacerbate chronic GVHD (9). Parenchymal disease in the allograft lung is associated with interstitial remodeling believed to be mediated by MMPs (matrix metalloproteinases). **MMP-9** and **TIMP-1** are increased in allograft bronchoalveolar lavage (BAL) in the first 2 years post transplantation, which appears to be associated with lung transplantation itself, and not infection or rejection (10). DGF (delayed graft function) increases the risk of acute allograft rejection and may affect long-term graft survival. Finally, soluble **IL-1RA** (IL-1 receptor antagonist) has been found to be reduced in plasma immediately following transplant in DGF (10).

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8) *Kusec V et al. Calcif Tissue Int 2004;75:1-6.*
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Human FlowCytomix™ Transplantation Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Th1/Th2 11plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FF
Th1/Th2 11plex Ready-to-Use	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FFRTU
Th1/Th2/Th9/Th17/ Th22 13plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p70), IL-13, IL-17A, IL-22, TNF-α	BMS817FF
Chemokine 6plex	G-CSF, IL-8, MCP-1, MIG, MIP-1α, MIP-1β	BMS813FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
CRP[1)]	A9	0.07 ng/ml	0.1 - 70 ng/ml	BMS8288FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
IFN-α	B3	8.06 pg/ml	27 - 20,000 pg/ml	BMS8216FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-1RA	A11	96 pg/ml	137 - 100,000 pg/ml	BMS82080FF
IL-2	A6	16.4 pg/ml	27 - 20,000 pg/ml	BMS8221FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MIG	B4	0.9 pg/ml	6.9 - 5,000 pg/ml	BMS8285FF
MIP-1α	A9	1.0 pg/ml	13.7 - 10,000 pg/ml	BMS82029FF
MMP-9[1)5)]	A4	95 pg/ml	0.1 - 100 ng/ml	BMS82016FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TIMP-1[1)5)]	B5	28 pg/ml	137 - 100,000 pg/ml	BMS82018FF
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF

Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Th1/Th2 10plex	GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, TNF-α	BMS820FF
Th1/Th2/Th17/Th22 13plex	IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17A, IL-21, IL-22, IL-27, TNF-α	BMS822FF
Chemokine 6plex	GM-CSF, MCP-1, MCP-3, MIP-1α, MIP-1β, RANTES	BMS821FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-2	A6	8.8 pg/ml	27 - 20,000 pg/ml	BMS8601FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF

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Further Species (continued)

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits (cont.)				
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
MIP-1α	A11	1.8 pg/ml	27 - 20,000 pg/ml	BMS86013FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokine 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.
4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.
5) MMP Simplex Kits cannot be combined with the TIMP-1 Simplex Kit.

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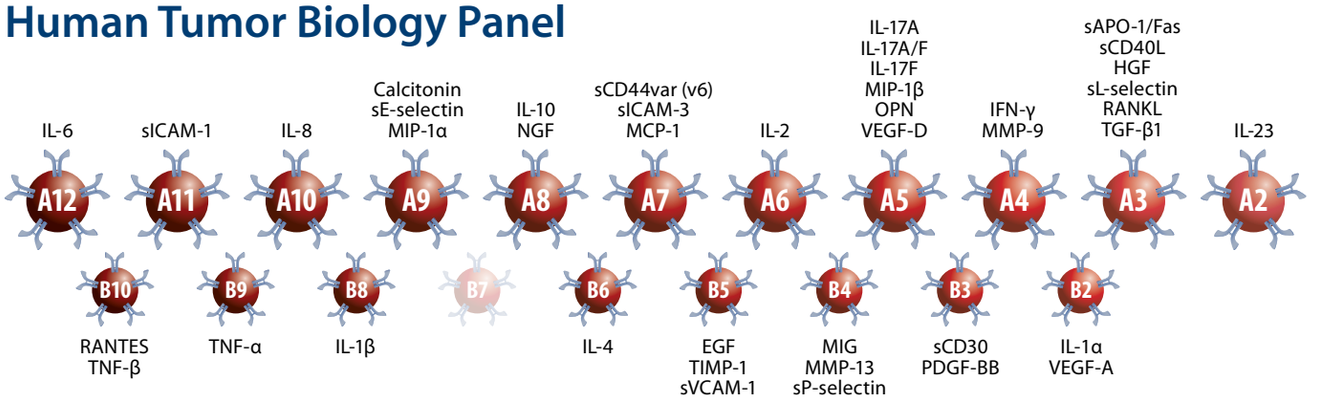
Human Tumor Biology Panel



During carcinoma formation, cancer cells release various **cytokines** and **growth factors** into their surroundings and recruit and reprogram many other types of cells in order to establish a tumor microenvironment. Consequently, the tumor tissues almost always contain a large number of endothelial cells, fibroblasts, and infiltrating inflammatory cells that in turn produce a variety of cytokines which are key factors in modulating the immune response either against or in favor of tumorigenesis in the microenvironment. The interactions between immune and cancer cells involve multiple cascades of cytokines, chemokines, and/or growth factors.

Tumor cell-derived **VEGF** acts on endothelial cells to promote angiogenesis and tumor growth, invasion and metastasis. In addition to vascular effects, VEGF also mobilizes mononucleic cells and probably endothelial progenitor cells from bone marrow, whereas former enhances tumor inflammation, the latter participates in vasculogenesis. VEGF-induced vascular tortuosity and leakiness also provide a structural basis for tumor cell invasion into the circulation system, leading to distal metastasis.

At the tumor site, monocytes differentiate into tumor-associated macrophages (TAM), which are a source of growth factors, proteases, angiogenic mediators, cytokines such as **TNF-α**, **IL-1** and **IL-6**, and chemokines like CCL2 (**MCP-1**), CCL5 (**RANTES**). Some of these cytokines induce further promalignant factors such as matrix metalloproteinases (MMP). In contrast, chemokines like CXCL10 (IP-10) and CXCL9 (MIG) may result in the recruitment of leukocytes that inhibit cancer progression.

Adhesion molecules such as **ICAM-1**, **ICAM-3**, **VCAM-1** and **selectins** are expressed by many different kinds of tumor cells, and are often crucial for the metastatic potential of malignant cells.

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2) *Lichtenberger BM et al. Cell 2010; 140:268.*
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Human FlowCytomix™ Tumor Biology Panel

Product	Analytes	Cat. No.
Human Multiplex Kits		
Th1/Th2 11plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FF
Th1/Th2 11plex Ready-to-Use	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FFRTU
Th1/Th2/Th9/Th17/ Th22 13plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p70), IL-13, IL-17A, IL-22, TNF-α	BMS817FF
Chemokine 6plex	G-CSF, IL-8, MCP-1, MIG, MIP-1α, MIP-1β	BMS813FF
Adhesion 6plex	sE-selectin, sICAM-1, sICAM-3, sPECAM-1, sP-selectin, sVCAM-1	BMS812FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
sAPO-1/Fas[1)]	A3	10.0 pg/ml	34 - 25,000 pg/ml	BMS80245FF
Calcitonin	A9	12 pg/ml	14 - 10,000 pg/ml	BMS82067FF
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
sCD40L	A3	23.4 pg/ml	55 - 40,000 pg/ml	BMS8239/2FF
sCD44var (v6)[1)]	A7	126.0 pg/ml	137 - 100,000 pg/ml	BMS80210FF
EGF	B5	22.7 pg/ml	27 - 20,000 pg/ml	BMS82070FF
sE-selectin	A9	1.2 ng/ml	4.0 - 3,000 ng/ml	BMS8205FF
HGF	A3	52 pg/ml	206 - 150,000 pg/ml	BMS82069FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
sICAM-3	A7	4.8 ng/ml	11 - 8,000 ng/ml	BMS8218FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-1α	B2	0.5 pg/ml	1.4 - 1,000 pg/ml	BMS80243FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-2	A6	16.4 pg/ml	27 - 20,000 pg/ml	BMS8221FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-17A	A5	2.5 pg/ml	13.7 - 10,000 pg/ml	BMS82017FF
IL-17A/F	A5	16 pg/ml	27 - 20,000 pg/ml	BMS82082FF
IL-17F	A5	8.0 pg/ml	27 - 20,000 pg/ml	BMS82037FF
IL-23	A2	21.9 pg/ml	69 - 50,000 pg/ml	BMS82023FF
sL-selectin[1)]	A3	70 pg/ml	137 - 100,000 pg/ml	BMS80206FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MIG	B4	0.9 pg/ml	6.9 - 5,000 pg/ml	BMS8285FF
MIP-1α	A9	1.0 pg/ml	13.7 - 10,000 pg/ml	BMS82029FF
MIP-1β	A5	1.0 pg/ml	4.0 - 3,000 pg/ml	BMS82030FF
MMP-9[1)5)]	A4	95 pg/ml	0.1 - 100 ng/ml	BMS82016FF
MMP-13[1)5)]	B4	0.05 ng/ml	0.17 - 125 ng/ml	BMS82022FF
NGF	A8	126.75 pg/ml	412 - 300,000 pg/ml	BMS82044FF
OPN	A5	432 pg/ml	274 - 200,000 pg/ml	BMS82066FF
PDGF-BB	B3	3.4 pg/ml	21 - 15,000 pg/ml	BMS82071FF
sP-selectin	B4	1.2 ng/ml	2.8 - 2,000 ng/ml	BMS8219/2FF
RANKL	A3	16 pg/ml	55 - 40,000 pg/ml	BMS82005FF
RANTES[1)]	B10	25 pg/ml	41 - 30,000 pg/ml	BMS8287FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TIMP-1[1)5)]	B5	28 pg/ml	137 - 100,000 pg/ml	BMS82018FF

New products are launched regularly. **Discover more at www.eBioscience.com.**

Human FlowCytomix™ Tumor Biology Panel (continued)

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits (cont.)				
TNF-α	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
TNF-β	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS8202FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF
VEGF-A	B2	7.2 pg/ml	27 - 20,000 pg/ml	BMS80277FF
VEGF-D	A5	25.0 pg/ml	55 - 40,000 pg/ml	BMS82076FF

Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Th1/Th2 10plex	GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, TNF-α	BMS820FF
Th1/Th2/Th17/Th22 13plex	IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17A, IL-21, IL-22, IL-27, TNF-α	BMS822FF
Chemokine 6plex	MIP-1α, MCP-3, MIP-1β, GM-CSF, RANTES, MCP-1	BMS821FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-1α	A4	15.7 pg/ml	27 - 20,000 pg/ml	BMS8611FF
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-2	A6	8.8 pg/ml	27 - 20,000 pg/ml	BMS8601FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-17A	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS86001FF
IL-17A/F	B10	1.0 pg/ml	2.7 - 2,000 pg/ml	BMS86026FF
IL-17F	A7	6.0 pg/ml	27 - 20,000 pg/ml	BMS86020FF
IL-21	A9	5.0 pg/ml	27 - 20,000 pg/ml	BMS86021FF
IL-23	B5	14.5 pg/ml	55 - 40,000 pg/ml	BMS86017FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
MIP-1α	A11	1.8 pg/ml	27 - 20,000 pg/ml	BMS86013FF
MIP-1β	B2	14.9 pg/ml	27 - 20,000 pg/ml	BMS86014FF
RANTES	B4	6.1 pg/ml	27 - 20,000 pg/ml	BMS86009FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokine 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-1α	A6	8.5 pg/ml	27 - 20,000 pg/ml	BMS8627FF
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

1) Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.

4) Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.

5) MMP Simplex Kits cannot be combined with the TIMP-1 Simplex Kit.

New products are launched regularly. **Discover more at www.eBioscience.com.**

3 FlowCytomix™ Pro Software

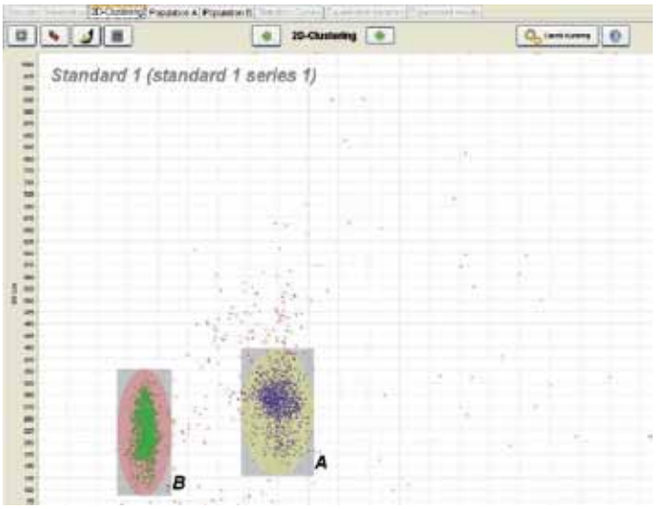
Download
FlowCytomix™ Pro Software
at www.eBioscience.com
Available for PC and Mac computers.

FlowCytomix™ Pro Software is free with your purchase of any FlowCytomix™ kit. This software is an easy-to-use tool to analyze FlowCytomix™ assays in a minimum of time. In addition to the self-explanatory configuration of the software, each step is supported with detailed instructions included in the program, which can be accessed at any step during the experimental evaluation.

- **Flexible** – Analyze your samples in single, duplicate or triplicate.
- **Enhanced performance** – Faster file loading and the ability to save individual settings and plots for improved analysis capabilities.

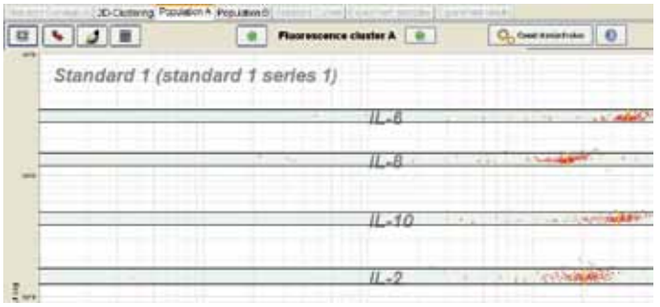
Select Standard Samples

By default, the software uses single data points for determination of the standard curve, but it also allows switching to duplicate or triplicate determination. By clicking the "Browse" button, all standard files are imported.



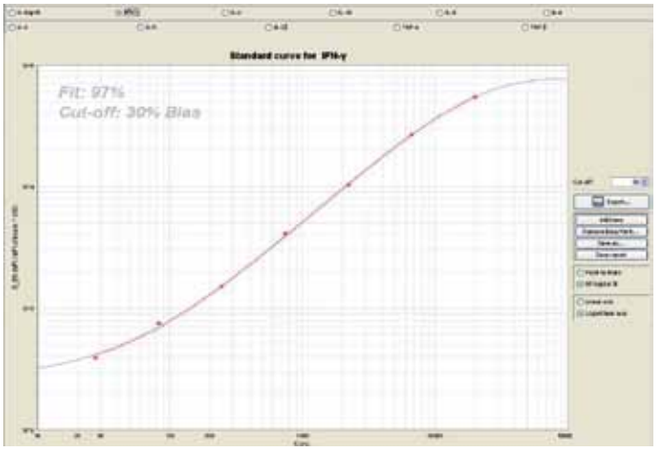
2D-clustering

The program suggests two bead clusters, A representing the large bead population (5 µm) and B representing the smaller beads (4 µm). Still, you can implicate or exclude some data points manually by resizing the colored ellipses.



Fluorescence clusters A and B

The bead clusters A and B contain several bead populations, each of them corresponding to a particular analyte. Two pages, "Fluorescence cluster A" and "Fluorescence cluster B", display the fluorescence intensities of these bead populations. The software will automatically provide gray lines to separate the populations. Again, gates may be readjusted manually.

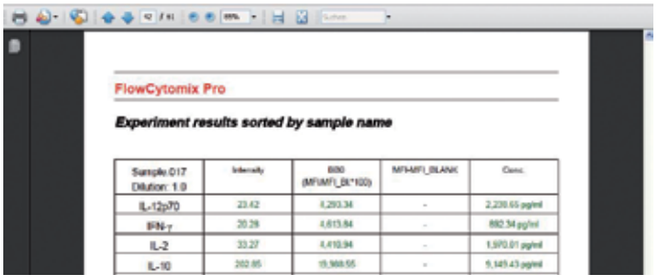


Standard Curves

FlowCytomix™ Pro Software establishes standard curves, which already include all changes implemented by the operator during previous steps. You may evaluate and manually adjust all standard curves for later calculation of analyte concentrations.

Experiment results

Once the standard curves are confirmed the operator is asked to import the sample files, whereupon the software calculates the analyte concentrations and immediately lists the results sorted by sample name as well as by analyte. At this stage, you can still go back a few steps and readjust all gates and standard curves. It is often helpful to click through all analysis steps again, to check if the settings are suitable for each sample file.



Report generation

To obtain final reports of your results, FlowCytomix™ Pro Software offers three options. You can generate a pdf report, or alternatively, choose a csv report, or a csv report giving the raw data in 96 well plate format. In the pdf report, the standard curves will be shown as diagrams as they have been set by the operator, complemented with a table displaying the key data. Sample results will be provided sorted by sample name or by analyte respectively. A result matrix displays comparison data at a glance.

How to Work with Standard Curves

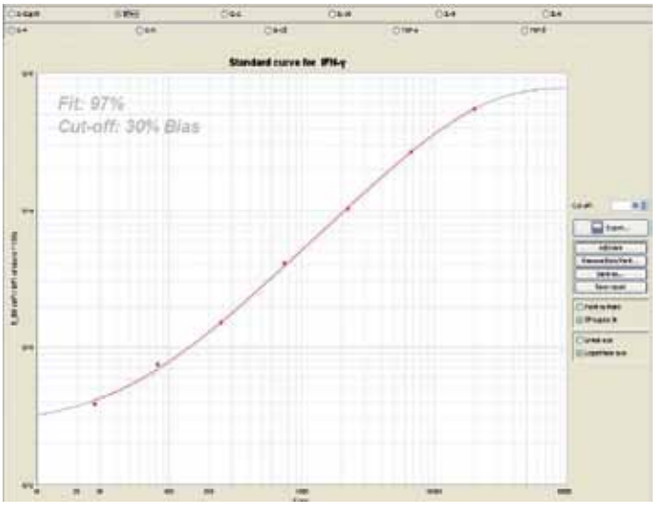


Fig. 1: Example of a reliable standard curve.

FlowCytomix™ Standard Curves

The FlowCytomix™ Pro Software generates standard curves in the 5 parameter logistic fit mode, where the program finds the best curve fit y=d+[(a-d)/(1+(x/c)^b)^g] and provides S-shaped sigmoid curves, representing a special case of sigmoid function. There is a direct relationship between the signal variable (y, mean fluorescence intensity, MFI, blank corrected) and the analyte concentration variable (x, given in pg/ml or ng/ml respectively).

The greater the signal, the higher the concentration of free analyte. The rate of change of signal versus concentration value varies throughout the standard curve concentration range, from steep to shallow. According to the sigmoid curve shape the beginning and end parts often tend to be shallow. Generally, the steeper the curve, the more reliable is its concentration dependence. Within extremely shallow sections of the standard curve, minimal changes of MFI result in large changes of analyte concentrations, whereas in steep sections, a large signal change stands for a small concentration change.

Therefore, results obtained from steep parts of a standard curve are the most reliable. If a standard curve was determined in duplicates, the curve is defined by the mean values of the duplicate determinations of standard 1 (highest concentration) to standard 7 (lowest concentration). A reliable standard curve features low coefficients of variation (CV < 15%) and does not contain any significant outlier (see Figure 1).

Considerations for the interpretation of a standard curve

+ Shape of the standard curve: The curve should be fairly sigmoid.
+ Steepness of the standard curve: The steeper the more reliable.
+ Coefficients of variation (CV): Should be < 15%.
+ Outlier: No standard curve data point should be a significant outlier.

Flaws in the standard curve - What can I do?

If a standard curve is inaccurate, FlowCytomix™ Pro Software offers several possibilities for adjustment. **- Shallow sections in the standard curve** result in an imprecise calculation of sample values (see Figure 2).

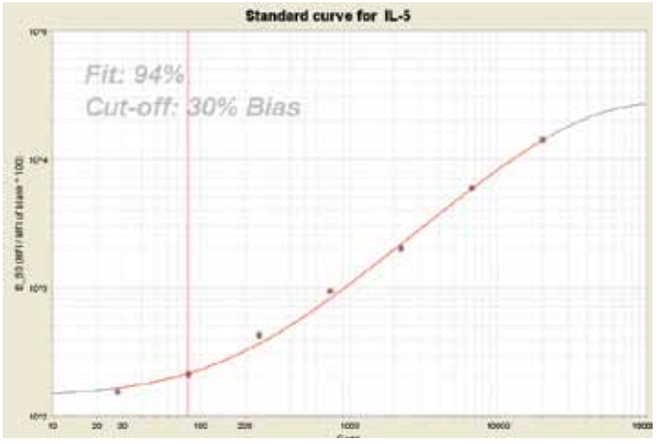


Fig. 2: Standard curves might contain shallow sections, which could lead to imprecise calculation of analyte concentrations. Sections to the left of the red bar may indicate areas of the standard curve with a Bias above the chosen Cut-off. Sample concentrations within these areas will later be marked red in the final report.

Fig. 3: FlowCytomix™ Pro Software offers the possibility to remove single standard data points.

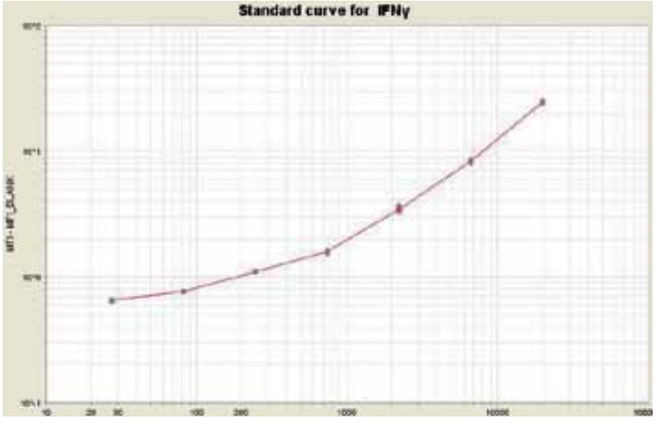


Fig. 4: In FlowCytomix™ Pro Software you can choose the point-to-point mode as an alternative interpolation model.

Small differences in MFI cause major differences in analyte concentrations. Shallow parts in the low concentration range of the standard curve might be improved by removing the highest standard point, standard 1, but only if sample values are expected in the low concentration range (see Figure 3).
- If one data point is definitely a outlier (e.g. fluorescent intensity of a lower standard point is higher than fluorescent intensity of a standard point with higher concentration), the data point has to be excluded. Outlier may distort the whole standard curve and the calculation of results will not be correct.
- Coefficients of variance (CV) of standard curves in FlowCytomix™ assays should be lower than 15%. Sometimes, high CVs might result from inaccurate preparation of the FlowCytomix™ kit. Additionally, CV values tend to increase in the low range of the standard curve. Therefore, it is not recommended to report values extrapolated below the lowest standard point. Analyte concentrations determined lower than standard 7 or higher than standard 1 lie outside the standard range of the assay and cannot be regarded significant. The reason for a standard curve being inapplicable may not always be obvious. It might be useful to change to Point-to-point fit on a logarithmic axis. The program will interpolate between two adjacent data points instead of trying to find the best curve fit (see Figure 4).

In the pdf report of results, several control functions help to judge standard curves. You will find Back calculation concentration and bias, which have been introduced as additional control tools. The program back fits the standard values from the standard curve. The Cut-off represents the highest acceptable Back calculation bias and may be adjusted during the creation of the standard curve. The level, at which the Cut-off should be set, depends on your specific research requirements. Values exceeding the Cut-off appear highlighted in red in the pdf report. Additionally, related areas of the standard curve are left of the red bar (see Figure 2). Furthermore, the average curve fit stated in the diagram provides an additional hint on the quality of the curve.

Technical tips for generating the perfect standard curve

+ *It is highly recommended to determine standard curves in duplicates, because imprecise standard curves can be judged and adjusted more easily. Moreover, CV values further help to estimate the significance of data points. Spin down lyophilized standard protein before opening the vial.*
+ *Add distilled water and wait ten minutes to ensure complete standard reconstitution. For Ready-to-Use format use Assay Buffer for reconstitution.*
+ *Once reconstituted, use standard solutions immediately and do not freeze.*
+ *When preparing the bead mix, vortex vials thoroughly for 5 seconds right before use. Beads are prone to settle at the bottom of the vial, imprecise bead additions change assay sensitivities.*

FlowCytomix™ Complete Product List

Product	Analytes	Cat. No.
Human Multiplex Kits		
Th1/Th2 11plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FF
Th1/Th2 11plex Ready-to-Use	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), TNF-α, TNF-β	BMS810FFRTU
Th1/Th2/Th9/Th17/ Th22 13plex	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p70), IL-13, IL-17A, IL-22, TNF-α	BMS817FF
Chemokine 6plex	G-CSF, IL-8, MCP-1, MIG, MIP-1α, MIP-1β	BMS813FF
Adhesion 6plex	sE-selectin, sICAM-1, sICAM-3, sPECAM-1, sP-selectin, sVCAM-1	BMS812FF
Cardiovascular 6plex	sCD40L, IL-6, IL-8, MCP-1, sP-selectin, t-PA	BMS811/2FF
Obesity 9plex	sCD40L, sICAM-1, IL-6, Leptin, MCP-1, MPO, OPG, Resistin, sTNF-R (60kDa)	BMS816/2FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits				
Adiponectin[1)]	B7	0.06 ng/ml	0.1 - 50 ng/ml	BMS82032FF
sAPO-1/Fas[1)]	A3	10.0 pg/ml	34 - 25,000 pg/ml	BMS80245FF
Calcitonin	A9	12 pg/ml	14 - 10,000 pg/ml	BMS82067FF
Caspase-3[6)]	B9	20 pg/ml	82 - 60,000 pg/ml	BMS82012FF
Caspase-9[6)]	A7	0.07 ng/ml	0.2 - 150 ng/ml	BMS82025FF
sCD30	B3	5.1 pg/ml	0.3 - 250 ng/ml	BMS8240FF
sCD40L	A3	23.4 pg/ml	55 - 40,000 pg/ml	BMS8239/2FF
sCD44var (v6)[1)]	A7	126.0 pg/ml	137 - 100,000 pg/ml	BMS80210FF
CRP[1)]	A9	0.07 ng/ml	0.1 - 70 ng/ml	BMS8288FF
EGF	B5	22.7 pg/ml	27 - 20,000 pg/ml	BMS82070FF
sE-selectin	A9	1.2 ng/ml	4.0 - 3,000 ng/ml	BMS8205FF
G-CSF	A11	3.4 pg/ml	34 - 25,000 pg/ml	BMS82001FF
FGF-2	B4	11 pg/ml	27 - 20,000 pg/ml	BMS82074FF
HGF	A3	52 pg/ml	206 - 150,000 pg/ml	BMS82069FF
sICAM-1	A11	5.3 ng/ml	5.4 - 4,000 ng/ml	BMS80201FF
sICAM-3	A7	4.8 ng/ml	11 - 8,000 ng/ml	BMS8218FF
IFN-α	B3	8.06 pg/ml	27 - 20,000 pg/ml	BMS8216FF
IFN-γ	A4	1.6 pg/ml	27 - 20,000 pg/ml	BMS8228FF
IL-1α	B2	0.5 pg/ml	1.4 - 1,000 pg/ml	BMS80243FF
IL-1β	B8	4.2 pg/ml	27 - 20,000 pg/ml	BMS8224FF
IL-1RA	A11	96 pg/ml	137 - 100,000 pg/ml	BMS82080FF
IL-2	A6	16.4 pg/ml	27 - 20,000 pg/ml	BMS8221FF
IL-4	B6	20.8 pg/ml	27 - 20,000 pg/ml	BMS8225FF
IL-5	B7	1.6 pg/ml	27 - 20,000 pg/ml	BMS8278FF
IL-6	A12	1.2 pg/ml	27 - 20,000 pg/ml	BMS8213FF
IL-8	A10	0.5 pg/ml	13.7 - 10,000 pg/ml	BMS8204FF
IL-9	A10	1.5 pg/ml	2.7 -2,000 pg/ml	BMS82081FF
IL-10	A8	1.9 pg/ml	27 - 20,000 pg/ml	BMS8215FF
IL-12 (p70)	A2	1.5 pg/ml	27 - 20,000 pg/ml	BMS8238FF
IL-13	B4	4.5 pg/ml	27 - 20,000 pg/ml	BMS8231FF

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Human FlowCytomix™ (continued)

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Human Simplex Kits (cont.)				
IL-17A	A5	2.5 pg/ml	13.7 - 10,000 pg/ml	BMS82017FF
IL-17A/F	A5	16 pg/ml	27.4 - 20,000 pg/ml	BMS82082FF
IL-17F	A5	8.0 pg/ml	27 - 20,000 pg/ml	BMS82037FF
IL-18	B5	3.34 pg/ml	27 - 20,000 pg/ml	BMS8267FF
IL-22	A11	43.3 pg/ml	110 - 80,000 pg/ml	BMS82047FF
IL-23	A2	21.9 pg/ml	69 - 50,000 pg/ml	BMS82023FF
IP-10	B5	6.0 pg/ml	17 - 12,500 pg/ml	BMS8284FF
Iso-Insulin	B6	80 pg/ml	274 - 200,000 pg/ml	BMS82003FF
Leptin	B10	0.05 ng/ml	0.3 - 250 ng/ml	BMS82039/2FF
sL-selectin[1)]	A3	70 pg/ml	137 - 100,000 pg/ml	BMS80206FF
MCP-1	A7	2.2 pg/ml	41 - 30,000 pg/ml	BMS8281FF
MIG	B4	0.9 pg/ml	6.9 - 5,000 pg/ml	BMS8285FF
MIP-1α	A9	1.0 pg/ml	13.7 - 10,000 pg/ml	BMS82029FF
MIP-1β	A5	1.0 pg/ml	4.0 - 3,000 pg/ml	BMS82030FF
MMP-9[1)5)]	A4	95 pg/ml	0.1 - 100 ng/ml	BMS82016FF
MMP-13[5)]	B4	0.05 ng/ml	0.17 - 125 ng/ml	BMS82022FF
MPO	A9	0.02 ng/ml	0.14 - 100 ng/ml	BMS82038FF
NGF	A8	126.75 pg/ml	412 - 300,000 pg/ml	BMS82044FF
OPG	A6	7.9 pg/ml	27 - 20,000 pg/ml	BMS82021FF
OPN	A5	432 pg/ml	274 - 200,000 pg/ml	BMS82066FF
Osteocalcin	B5	6.9 pg/ml	27 - 20,000 pg/ml	BMS82020FF
PAI-1[1)3)]	B8	13.5 pg/ml	137 - 100,000 pg/ml	BMS82033FF
PDGF-BB	B3	3.4 pg/ml	21 - 15,000 pg/ml	BMS82071FF
sPECAM-1	A5	0.8 ng/ml	4.0 - 3,000 ng/ml	BMS8229FF
sP-selectin	B4	1.2 ng/ml	2.8 - 2,000 ng/ml	BMS8219/2FF
RANKL	A3	16 pg/ml	55 - 40,000 pg/ml	BMS82005FF
RANTES[1)]	B10	25 pg/ml	41 - 30,000 pg/ml	BMS8287FF
Resistin	B4	1.7 pg/ml	55 - 40,000 pg/ml	BMS82040FF
TGF-β1[4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8249FF
TIMP-1[1)5)]	B5	28 pg/ml	137 - 100,000 pg/ml	BMS82018FF
TNF-α[2)]	B9	3.2 pg/ml	27 - 20,000 pg/ml	BMS8223FF
TNF-β[2)]	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS8202FF
sTNF-R (60kDa)[2)]	A5	0.08 ng/ml	0.14 - 100 ng/ml	BMS8203FF
t-PA[3)]	A5	4.8 pg/ml	27 - 20,000 pg/ml	BMS8258FF
sVCAM-1[1)]	B5	0.9 ng/ml	3.0 - 2,000 ng/ml	BMS8232/2FF
VEGF-A	B2	7.2 pg/ml	27 - 20,000 pg/ml	BMS80277FF
VEGF-D	A5	25.0 pg/ml	55 - 40,000 pg/ml	BMS82076FF

New products are launched regularly. **Discover more at www.eBioscience.com.**

Further Species

Product	Analytes	Cat. No.
Mouse Multiplex Kits		
Th1/Th2 10plex	GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, TNF-α	BMS820FF
Th1/Th2/Th17/Th22 13plex	IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17A, IL-21, IL-22, IL-27, TNF-α	BMS822FF
Chemokine 6plex	GM-CSF, MCP-1, MCP-3, MIP-1α, MIP-1β, RANTES	BMS821FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Mouse Simplex Kits				
CXCL1/KC	A5	3.0 pg/ml	4.8 - 3,500 pg/ml	BMS86019FF
GM-CSF	B8	10.9 pg/ml	27 - 20,000 pg/ml	BMS8612FF
IFN-γ	B6	6.5 pg/ml	27 - 20,000 pg/ml	BMS8606/2FF
IL-1α	A4	15.7 pg/ml	27 - 20,000 pg/ml	BMS8611FF
IL-1β	B4	34.3 pg/ml	69 - 50,000 pg/ml	BMS86002FF
IL-2	A6	8.8 pg/ml	27 - 20,000 pg/ml	BMS8601FF
IL-4	B9	0.7 pg/ml	27 - 20,000 pg/ml	BMS8613FF
IL-5	A8	4.0 pg/ml	27 - 20,000 pg/ml	BMS8610FF
IL-6	A10	2.2 pg/ml	27 - 20,000 pg/ml	BMS8603FF
IL-10	A12	5.4 pg/ml	27 - 20,000 pg/ml	BMS8614/2FF
IL-12 (p70)	B5	8.6 pg/ml	27 - 20,000 pg/ml	BMS86004FF
IL-13	A2	9.3 pg/ml	27 - 20,000 pg/ml	BMS86015FF
IL-15/IL-15R	A11	5.0 pg/ml	6.9 - 5,000 pg/ml	BMS86023FF
IL-17A	B10	2.4 pg/ml	27 - 20,000 pg/ml	BMS86001FF
IL-17A/F	B10	1.0 pg/ml	2.7 - 2,000 pg/ml	BMS86026FF
IL-17F	A7	6.0 pg/ml	27 - 20,000 pg/ml	BMS86020FF
IL-18	B3	116.9 pg/ml	412 - 300,000 pg/ml	BMS8618FF
IL-21	A9	5.0 pg/ml	27 - 20,000 pg/ml	BMS86021FF
IL-22	A5	5.5 pg/ml	6.9 - 5,000 pg/ml	BMS86016FF
IL-23	B5	14.5 pg/ml	55 - 40,000 pg/ml	BMS86017FF
IL-27	B2	31.5 pg/ml	69 - 50,000 pg/ml	BMS86024FF
IL-33	A3	see www.eBioscience.com		BMS86025FF
IP-10	A3	9.8 pg/ml	41 - 30,000 pg/ml	BMS86018FF
MCP-1	A9	42.0 pg/ml	55 - 40,000 pg/ml	BMS86005FF
MCP-3	A7	1.4 pg/ml	27 - 20,000 pg/ml	BMS86006FF
MIP-1α	A11	1.8 pg/ml	27 - 20,000 pg/ml	BMS86013FF
MIP-1β	B2	14.9 pg/ml	27 - 20,000 pg/ml	BMS86014FF
RANTES	B4	6.1 pg/ml	27 - 20,000 pg/ml	BMS86009FF
TGF-β1 [4)]	A3	10.0 pg/ml	13.7 - 10,000 pg/ml	BMS8608FF
TNF-α	B7	2.1 pg/ml	27 - 20,000 pg/ml	BMS8607/2FF

1) *Samples must be prediluted in Assay Buffer before starting the test procedure: In combination with other Simplex Kits it is recommended to evaluate both, an undiluted and a prediluted sample.*
2) *The TNF-R (60kDa) Simplex Kit cannot be assayed simultaneously with the TNF-α or the TNF-β Simplex Kit.*
3) *PAI-1 and t-PA Simplex Kits cannot be assayed simultaneously.*
4) *Samples must be pretreated (acidified) with HCl before starting the test procedure. Thus this Simplex Kit cannot be combined with other Simplex or Multiplex Kits.*
5) *MMP Simplex Kits cannot be combined with the TIMP-1 Simplex Kit.*
6) *The Caspase-3 Simplex Kit may only be combined with the Caspase-9 Simplex Kit and vice versa.*

Product	Analytes	Cat. No.
Rat Multiplex Kits		
Cytokines 6plex	GM-CSF, IFN-γ, IL-1α, IL-4, MCP-1, TNF-α	BMS825/3FF

Analyte	Bead set	Sensitivity	Standard range	Cat. No.
Rat Simplex Kits				
GM-CSF	B9	5.0 pg/ml	27 - 20,000 pg/ml	BMS8633FF
IFN-γ	B8	0.6 pg/ml	3.0 - 2,000 pg/ml	BMS8621/3FF
IL-1α	A6	8.5 pg/ml	27 - 20,000 pg/ml	BMS8627FF
IL-4	B10	0.3 pg/ml	3.0 - 2,000 pg/ml	BMS8628FF
IL-17A	A10	5.0 pg/ml	7 - 5,000 pg/ml	BMS8635FF
MCP-1	A8	0.5 pg/ml	7.0 - 5,000 pg/ml	BMS8631/2FF
TNF-α	A12	4.3 pg/ml	27 - 20,000 pg/ml	BMS8622FF

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