# EMERGING THERAPIES in RHEUMATOLOGY

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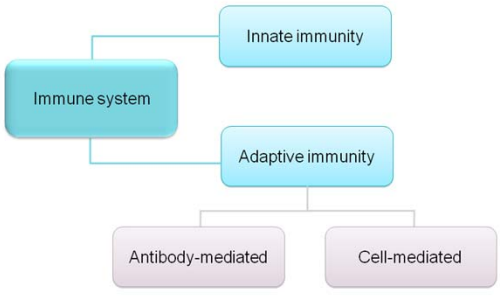
## ADDENDUM 1

IMMUNOLOGY

## Organization of the Immune Response




Kumar V, et al. Diseases of the immune system. In: *Robbins and Cotran Pathologic Basis of Disease*. 8th ed. Philadelphia, PA: Saunders Elsevier; 2009:1-15(epub).

2

## Innate and Adaptive Immunity

| Innate | Adaptive |
|---|---|
| Nonspecific | Specific |
| Present at all times | Develops in response to infection |
| Immediate but general protection | Protection against specific pathogens |
| Activates adaptive immune response | Leverages components of the innate response |
| Does not improve with repeated exposure to a pathogen | Memory develops, which may provide lifelong immunity to re-infection with the same pathogen |

Murphy K, et al. Basic concepts in immunology; Innate immunity. In: *Janeway's Immunobiology*. 7th ed. New York, NY: Garland; 2008:1-38, 39-108.

3

## Key Components of Innate Immunity

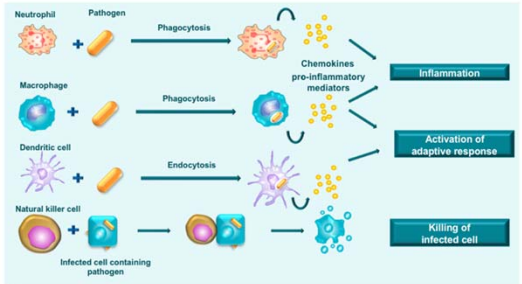
| Components | | Function |
|---|---|---|
| Cells | Macrophage | • Phagocytosis<br>• Activation of bactericidal activity<br>• Antigen presentation |
| | Dendritic cell | • Antigen uptake in the periphery<br>• Antigen presentation |
| | Neutrophil | • Phagocytosis<br>• Activation of bactericidal activity |
| | Other phagocytes (eg, eosinophils, basophils, mast cells) | • Killing of antibody-coated parasites<br>• Release of histamine granules<br>• Unknown |
| | Natural killer cells | • Releases lytic granules to kill some virus-infected cells |
| Soluble proteins | Complement | • Soluble proteins that form a complex to destroy microorganisms |
| | Cytokines | • Proteins secreted by cells that affect the behavior of nearby cells bearing appropriate receptors |

Murphy K, et al. Basic concepts in immunology; Innate immunity. In: *Janeway's Immunobiology*. 7th ed. New York, NY: Garland; 2008:1-38, 39-108.

4

## Innate Immunity

- Innate immunity, the first line of defense, consists of non-specific, rapidly occurring responses that are mediated by phagocytic and natural killer cells as well as soluble molecules.




Murphy K, et al. Basic concepts in immunology; Innate immunity. In: *Janeway's Immunobiology*. 7th ed. New York, NY: Garland; 2008:1-38, 39-108.

5

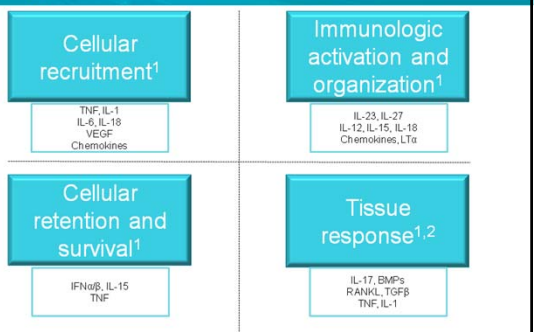
## Key Components of Adaptive Immunity

| | Components | Function |
|---|---|---|
| Cells | T lymphocytes | • Activate macrophages<br>• Help B cells produce antibodies<br>• Kill cells infected with viruses or other intracellular pathogens |
| | B lymphocytes | • Produce antibodies in response to antigens |
| Soluble proteins | Antibodies | • Bind to antigens to neutralize them or facilitate destruction of microorganisms |
| | Cytokines | • Proteins secreted by cells that affect the behavior of nearby cells bearing appropriate receptors |

Murphy K, et al. Basic concepts in immunology, Innate immunity. In: *Janeway's Immunobiology*. 7th ed. New York, NY: Garland; 2008:1-38, 39-108.

6

## Cytokines Are Implicated in Each Phase of RA Pathogenesis




BMPs=bone morphogenetic proteins; IFN=interferon; IL=interleukin; LT=lymphotoxin; RA=rheumatoid arthritis; RANKL=receptor activator of nuclear factor Kappa B ligand; TGF=transforming growth factor; TNF=tumor necrosis factor; VEGF=vascular endothelial growth factor.
1. McInnes IB, Liew FY. *Nat Clin Pract Rheumatol*. 2005;1:31-39; 2. Schett G, et al. *Arthritis Rheum*. 2008;58:2936-2948.

4

Addendum 2:

BIOMARKERS in RHEUMATOLOGY

# Vectra™ DA Intended Use

- Vectra DA was validated in adults diagnosed with rheumatoid arthritis
- Test results are intended to
  - Aid in the assessment of disease activity in RA patients
  - Help inform patient management decisions when used in conjunction with standard clinical assessment
- This test is not intended or validated to diagnose RA

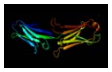
68

## Vectra™ DA Biomarkers: Categories and Primary Role

| Primary Role | Biomarker Category | Biomarker |
|---|---|---|
| Cellular influx and tissue expansion | Adhesion Molecules | VCAM-1 |
| | Growth Factors | EGF<br>VEGF-A |
| Local inflammation and destruction | Cytokine-related Proteins | IL-6<br>TNF-RI |
| Cartilage degradation and joint damage | Matrix Metalloproteinases | MMP-1<br>MMP-3 |
| Stromal activity & regulation (fibroblasts, chondrocytes, vascular cells) | Skeletal-related Proteins | YKL-40 |
| Systemic Inflammatory Response | Hormones | Leptin<br>Resistin |
| | Acute Phase Proteins | SAA<br>CRP |

69

# Adhesion Molecules



- VCAM-1 (Vascular Cellular Adhesion Molecule 1)
  - Expressed by endothelial and synovial cells
  - May contribute to cellular recruitment to and retention within synovial tissue
  - May contribute to cartilage invasion and destruction by fibroblasts
  - Vectra DA measures the soluble form of VCAM-1

van Dinther-Janssen et al. *J Immunol.* 1991;147(12):4207-10. Tokuhira et al. *Arthritis Rheum.* 2000;43(5):1122-33. Seemayer et al. *Am J Pathol.* 2003;162(5):1549-57. Koch et al. *Lab Invest.* 1991;64(3):313-20.

70

## Cytokine-related Proteins

- IL-6 (Interleukin 6)
  - Inflammatory cytokine produced by many cells including leukocytes, fibroblasts, and skeletal cells
  - Associated with both innate and adaptive immunity
  - Promotes MMP production and cartilage degradation
  - Promotes osteoclast activation and bone erosion
  - Stimulates acute phase reaction (CRP, SAA production)

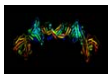
- TNF-RI (Tumor Necrosis Factor Receptor, Type I)
  - Receptor for TNF-alpha
  - Expressed on membrane of various cells
  - TNF-RI–mediated signaling contributes to multiple effects of TNF-α, including induction of cell death
  - Vectra™ DA measures the soluble form which binds and neutralizes TNF-alpha

Hirano et al. *Int Rev Immunol.* 1998;16(3-4):249-84. Smolen & Maini. *Arthritis Res Ther.* 2006;8 Suppl 2:S5. Dayer et al. *Rheumatology (Oxford).* 2010;49(1):15-24. Chen & Goeddel. *Science.* 2002;296(5573):1634-5. Taylor et al. *Nat Rev Rheumatol.* 2009;5(10):578-82.



## Growth Factors

- EGF (Epidermal Growth Factor)
  - Secreted by macrophages, fibroblasts, and endothelial cells in RA joint tissue
  - Associated with proliferation and differentiation of fibroblasts, chondrocytes, and endothelial cells and can induce production of inflammatory mediators and proteinases in these cells
  - May modulate the acute phase response



- VEGF-A (Vascular Endothelial Growth Factor A)
  - Expressed by fibroblasts, macrophages, other synovial cells
  - Potent angiogenic growth factor, vascular permeability factor
  - Promotes inflammation, fluid accumulation, and bone erosion

Afuwape et al. *Histol Histopathol.* 2002;17(3):961-72. Koch et al. *J Immunol.* 1994;152(8):4149-56. Niida et al. *J Exp Med.* 1999 ;190(2):293-8. Xu et al. *Ann Rheum Dis.* 2000;59(10):822-7. Hiraoka et al. *Biochem Int.* 1992;27(6):1083-91. Huh et al. *J Biol Chem.* 2003;278(11):9691-7. Wang et al. *Hepatology.* 1999;30(3):682-97.



## Matrix Metalloproteinases

- MMP-1 (Matrix Metalloproteinase 1 or Collagenase 1)
  - Collagen-degrading enzyme
  - Contributes to cartilage degradation in RA
  - Contributes to leukocyte invasion and angiogenesis in the synovial tissue

- MMP-3 (Matrix Metalloproteinase 3 or Stromelysin 3)
  - Degrades glycosaminoglycan components of cartilage
  - Activates MMP-1

Burrage. *Front Biosci.* 2006;11:529-43. Sorsa. *Semin Arthritis Rheum.* 1992;22(1):44-53. Flannery. *J Biol Chem.* 1992;267:1008-1014. Suzuki K. *Biochemistry.* 1990;29:10261-10270. Okada. *Ann Rheum Dis.* 1989;48(8):645-53.

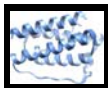
## Skeletal-related Proteins

- YKL-40 (Human Cartilage Glycoprotein 39)
  - Secreted primarily by differentiated macrophages, fibroblasts and chondrocytes
  - May promote chondrocyte and fibroblast proliferation
  - May inhibit cartilage destruction (inhibits MMP production for example)

Hakala et al. *J Biol Chem*.1993;268:25803-10. Kirkpatrick et al. *Exp Cell Res*.1997;237(1):46-54. De Ceuninck et al. *Biochem Biophys Res Commun*. 2001;285: 926-31. Ling et al. *Biochem J*. 2004;380(Pt 3):651-9. Kotzin et al. *Proc Natl Acad Sci U S A*. 2000;97(1):291-6.

74

## Hormones



- Leptin
  - Secreted by adipose tissue, synovial tissue, and bone
  - Associated with obesity and appetite suppression
  - Promotes inflammatory activities of leukocytes
  - Regulates bone remodeling

- Resistin
  - Secreted by adipose tissue, synovial tissue, and bone
  - Associated with obesity and diabetes
  - Promotes inflammatory activities of leukocytes
  - Regulates bone remodeling

Zhang et al. *Nature*.1994;372(6505):425-32. Reseland et al. *J Bone Miner Res*. 2001;16(8):1426-33. Halaas et al. *Science*. 1995;269:543-546. Holloway et al. *J Bone Miner Res*. 2002 ;17(2):200-9. Yadav et al. *Cell*. 2009 ;138(5):976-89. Steppan . *Nature*. 2001;409 (6818): 307–12. Thommesen et al., *J Cell Biochem*. 2006;99(3):824-34. Bokarewa et al. *J Immunol*. 2005;174: 5789-5795..Oshima et al. *Biochem Biophys Res Commun*. 2005 ;331(2):520-6.

75

## Acute Phase Proteins

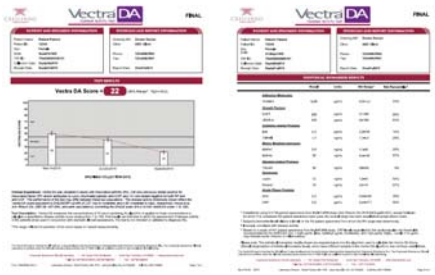
- SAA (Serum Amyloid A)
  - Major acute-phase protein secreted by the liver in response to inflammation
  - Associated with cardiovascular risk
  - May also be produced by synovial fibroblasts and chondrocytes, and may induce proinflammatory activation of fibroblasts, macrophages, and T cells

- CRP (C-Reactive Protein)
  - Major acute-phase protein secreted by the liver in response to inflammation
  - Associated with cardiovascular risk
  - Associated with risk of structural damage

Weinhold & Ruther. *Biochemical J*. 1997;327:425-429. Zhang. *Biochemical J*. 1995;310:143-148. Macintyre et al. *Ann New York Acad Sci*. 1982;389:76-87. van der Meer et al. *Atherosclerosis*. 2006;189(2):464-469. Benigni et al. *Blood*. 1996;87(5):1851-1854. Zhang et al. *J Immunol*. 2005;174 (12):8125–34. Kisilevsky. *Ped Pathol Mol Med*. 2002;21(3):291-305. Kumon et al. *J Rheumatol*. 1999;26:785. O'Hara et al. *Arthritis Res*. 2002;2:142.

76

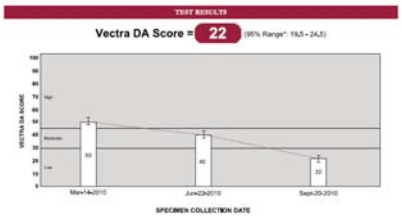
## The Vectra™ DA Report Contains the Vectra DA Score and Supporting Information on the 12 Biomarkers



- Vectra DA is validated for use in adults diagnosed with RA.
- Vectra DA is intended to be used in conjunction with standard clinical practice for the assessment of disease activity in RA patients. It is not intended or validated to diagnose RA

77

## The Vectra™ DA Report Highlights the Current Vectra DA Score and Tracks Changes Over Time




- The 6 most recent Vectra DA scores are reported to allow tracking of trends and changes
- The 95% range is a measure of the analytical precision of the test, developed by running the same sample through the test process multiple times
- Please note: Lines shown between reported Vectra DA scores are for illustrative purposes only and do not represent actual test scores.

78

## ADDENDUM 3

## POTENTIAL Adverse Events of BIOLOGIC Therapy

## Serious Infections

**Reported infections include:**

- **Active tuberculosis (TB), including reactivation of latent TB. Patients frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before SIMPONI® use and during therapy. Treatment for latent infection should be initiated prior to SIMPONI® use**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness**
- **Bacterial, viral, and other infections due to opportunistic pathogens**

80

## Serious Infections

**The risks and benefits of treatment with SIMPONI® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Do not start SIMPONI® in patients with clinically important active infections, including localized infections. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with SIMPONI®, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.**

Other serious infections observed in patients treated with SIMPONI® included sepsis, pneumonia, cellulitis, abscess, and hepatitis B infection.

81

## Malignancies

**Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers of which SIMPONI® is a member.** Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies usually associated with immunosuppression and malignancies not usually observed in children or adolescents. Malignancies occurred after a median of 30 months after the first dose of therapy. Most of the patients were receiving concomitant immunosuppressants.

82

## Malignancies

In the controlled portions of clinical trials of all TNF-blocking agents including SIMPONI®, more cases of lymphoma have been observed among patients receiving TNF-blocking treatment compared with control patients. In clinical trials, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI® group compared with an incidence of 0 (95% CI: 0, 0.96) in the placebo group. In clinical trials, the incidence of malignancies other than lymphoma was not increased with exposure to SIMPONI® and was similar to what would be expected in the general population. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use. The risks and benefits of TNF-blocker therapy should be considered prior to initiating therapy in patients with a known malignancy or who develop a malignancy.

83

## Hepatitis B Reactivation

The use of TNF-blocking agents including SIMPONI® has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers. In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants.

Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating SIMPONI®. Exercise caution when prescribing SIMPONI® for patients identified as carriers of HBV and closely monitor for active HBV infection during and following termination of therapy with SIMPONI®. Discontinue SIMPONI® in patients who develop HBV reactivation, and initiate antiviral therapy with appropriate supportive treatment. Exercise caution when considering resumption of SIMPONI®, and monitor patients closely.

84

## Heart Failure

Cases of worsening congestive heart failure (CHF) and new-onset CHF have been reported. Exercise caution and monitor patients with heart failure. Discontinue SIMPONI® if new or worsening symptoms of heart failure appear.

85

## Demyelinating Disorders

TNF-blocking agents, of which SIMPONI® is a member, have been associated with cases of new-onset or exacerbation of demyelinating disorders, including multiple sclerosis (MS) and Guillain-Barré syndrome. In SIMPONI® clinical trials, cases of MS and peripheral demyelinating polyneuropathy were reported. Exercise caution in considering the use of SIMPONI® in patients with these disorders. Consider discontinuation if these disorders develop.

86

## Hematologic Cytopenias

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving SIMPONI® in clinical trials. Additionally, aplastic anemia has been reported in patients receiving TNF-blocking agents, of which SIMPONI® is a member. Exercise caution when using SIMPONI® in patients who have or had significant cytopenias.

87

## Use With Other Drugs

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections, therefore the use of SIMPONI® in combination with these products is not recommended. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. People receiving SIMPONI® can receive vaccinations, except for live vaccines.

88

## Adverse Reactions

The most serious adverse reactions were serious infections and malignancies.

Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 trials through Week 16, occurring in 7% and 6% of patients treated with SIMPONI® as compared with 6% and 5% of patients in the control group, respectively. The rate of injection-site reactions was 6% with patients treated with SIMPONI® compared with 2% of patients in the control group.

89