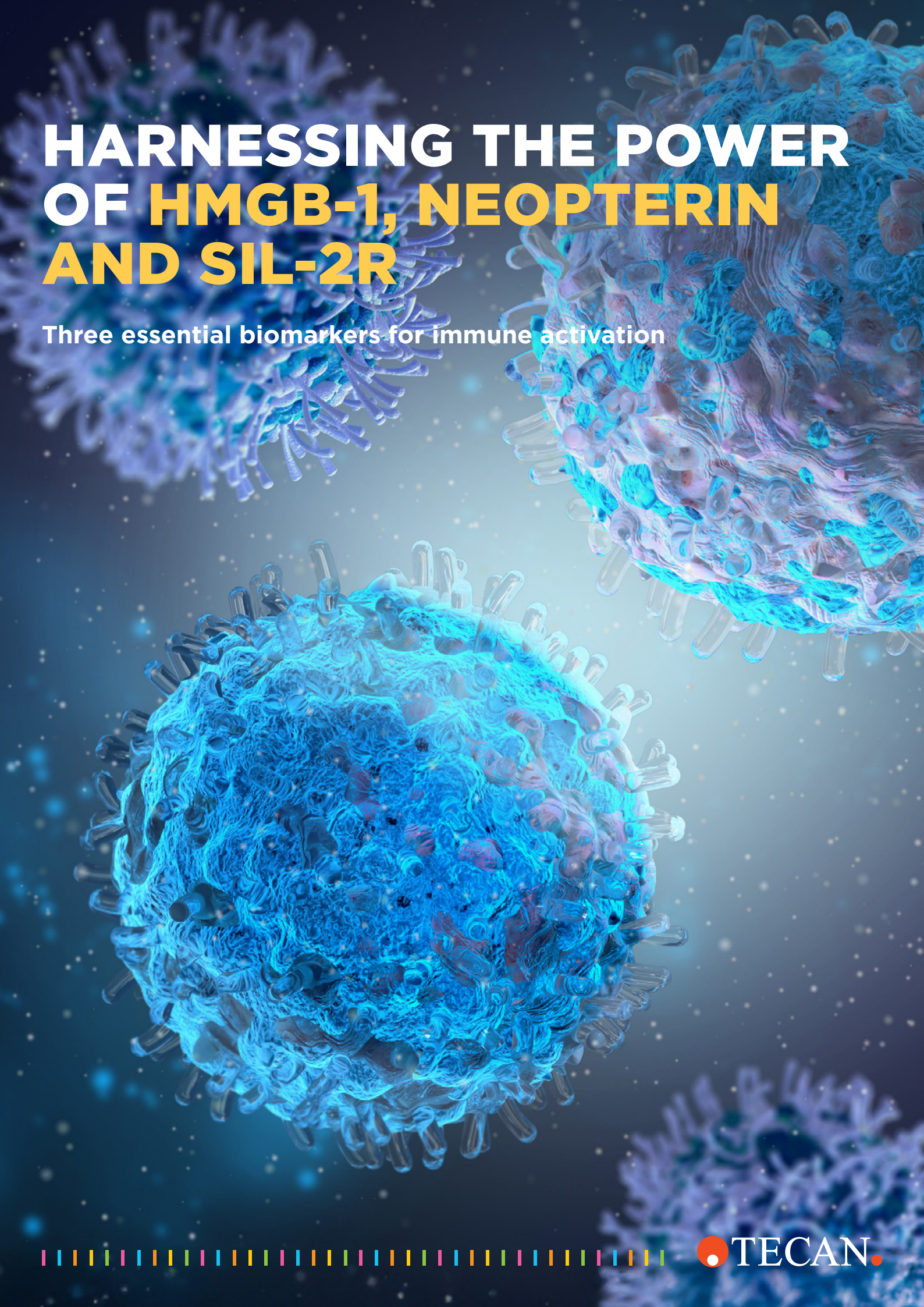
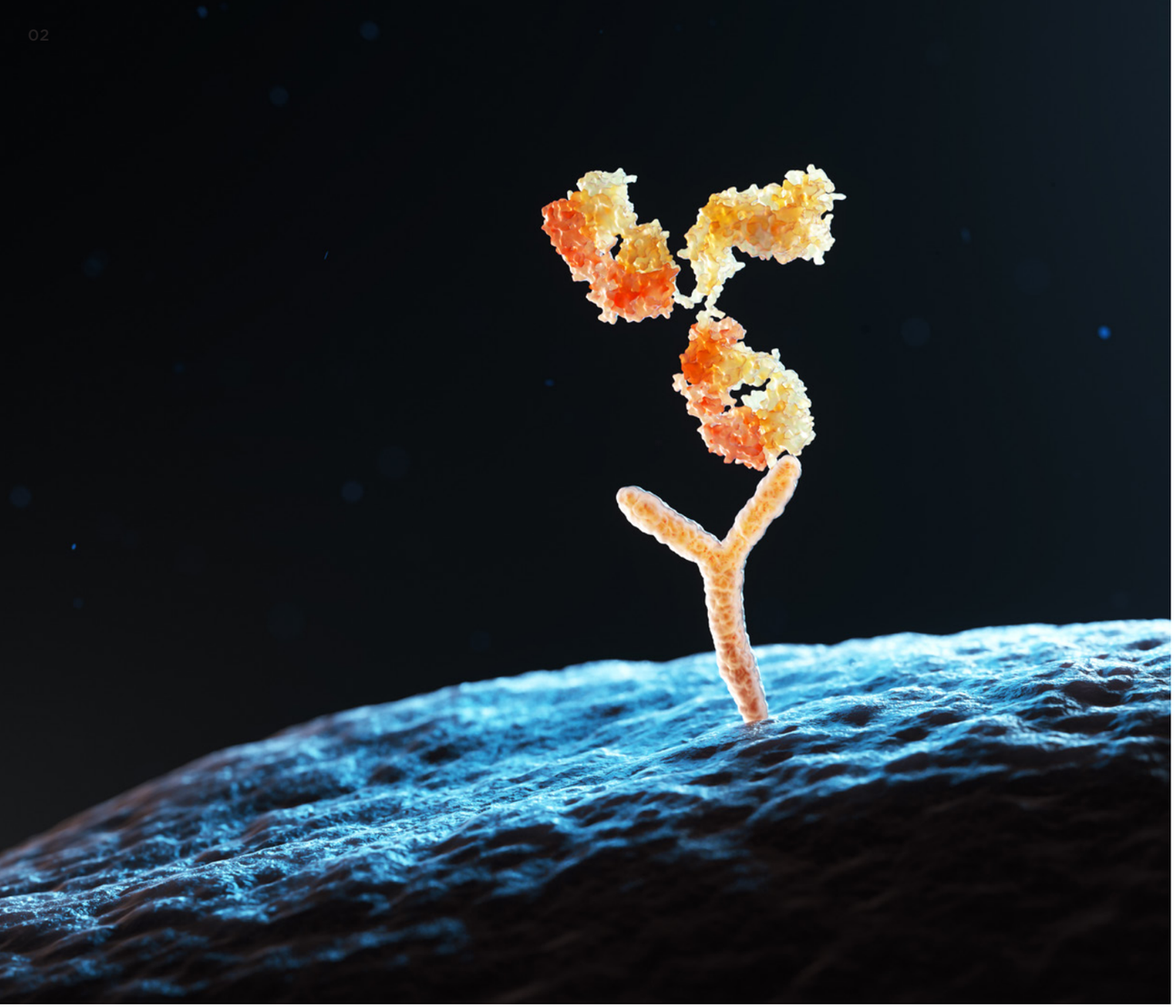


HARNESSING THE POWER OF HMGB-1, NEOPTERIN AND SIL-2R

Three essential biomarkers for immune activation

TECAN



HARNESSING THE POWER OF HMGB-1, NEOPTERIN AND SIL-2R: THREE ESSENTIAL BIOMARKERS FOR IMMUNE ACTIVATION

The immune response is a coordinated process that involves a complex set of molecules and interrelated signaling pathways. The activation of these pathways results in the successful eradication of diseased cells and pathogens in individuals with healthy immune systems. In other cases, the immune system may be over-activated and result in autoimmune disease. Three key molecules that have been proven to play an essential role in this regulation and modulation of the immune response include High Mobility Group Box 1 (HMGB-1), neopterin (Np), and soluble Interleukin-2 receptor (sIL-2R).[1-15]

What are the similarities and differences between these three musketeers of the immune system? When should we be measuring them, and how? They certainly have similarities in their functions, across a broad spectrum of immune-related conditions. All three are useful biomarkers for immune activation, and their roles can be summarized as follows (see also Fig. 1).

Inflammatory Mediators

HMGB-1 is a potent inflammatory mediator released by activated immune cells, acting as a late mediator of inflammation.[1] Neopterin is a byproduct of the GTP-metabolic pathway and is produced by activated macrophages/monocytes, acting as a marker of cellular immune activation, and sIL-2R, also released during immune activation, is considered a marker of T-cell activation and inflammation.[2,3]

Biomarkers of Disease Activity

Elevated levels of HMGB-1, neopterin, and sIL-2R are observed in various inflammatory and autoimmune disorders, making them potential biomarkers for disease activity and severity.[4-6]

Prognostic Indicators

High concentrations of all three molecules have been associated with adverse outcomes and disease progression in conditions such as sepsis, cancer, and autoimmune diseases.[7-9]

Immune Regulation

HMGB-1 can act as a chemoattractant for immune cells and promote their activation and migration.[10] Neopterin has been shown to modulate oxidative stress and apoptosis, as its contribution to immune regulation.[11] Finally, sIL-2R is involved in regulating T-cell proliferation and activation, playing a role in immune homeostasis.[12]

Therapeutic Targets

Strategies targeting HMGB-1, neopterin, and sIL-2R are all being explored as potential therapeutic approaches for various inflammatory and autoimmune disorders such as cancer, rheumatoid arthritis and multiple sclerosis.[13-15]

Does this mean we need to measure all three of these markers, all the time, or will one of them suffice? This will depend on the individual disease state that is being investigated. As a rule of thumb, all three molecules are proven markers for immune activation, so the researcher or clinician could start by correlating the disease they are studying, diagnosing, or treating, with the research that has been done in that area.

The second consideration is that if tests are being carried out in the clinic, as opposed to in the research environment, the ‘tiebreaker’ will be that the clinician needs to use a test that is IVD-compliant, as opposed to RUO (research use only). To enable us to choose the biomarker(s) to monitor the disease state, let us first look briefly at the research that has been done on each of them, before moving on to consider how we might measure them.

1. **Inflammatory Mediators**
   HMGB-1: potent inflammatory mediator
   Neopterin: marker of cellular immune activation
   sIL-2R: marker of T-cell activation and inflammation

2. **Biomarkers of Disease**
   Elevated levels observed in inflammatory and autoimmune disorders

3. **Prognostic Indicators**
   Adverse outcomes and disease progression in sepsis, cancer, and autoimmune disease

4. **Immune Regulation**
   HMGB-1: chemoattractant in immune cell activation and migration
   Neopterin: modulator of oxidative stress and apoptosis
   sIL-2R: regulator in T-cell proliferation and activation

5. **Therapeutic Targets**
   Potential therapeutic targets in diseases such as cancer, rheumatoid arthritis and multiple sclerosis

Figure 1: High Mobility Group Box 1 (HMGB-1), neopterin (Np), and soluble Interleukin-2 receptor (sIL-2R): three key molecules that play an essential role in regulation and modulation of the immune response.

HMGB-1

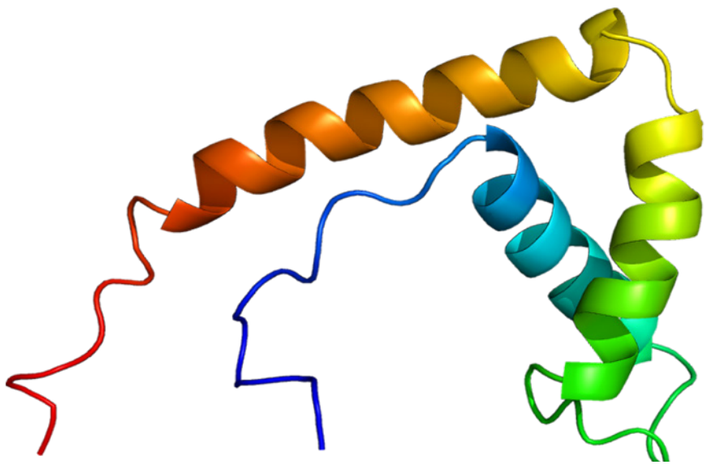
Human HMGB-1 is essential in the cell's stress response, playing a major role in many infectious diseases, as well as ischemia, immune disorders, neurodegenerative diseases, and cancer.[16] It has gained significant interest in recent years due to its role as a potential biomarker for measuring inflammation and immune system dysregulation. A more in-depth explanation of its mechanism of action can be found in the Tecan Blog series, as applied to its role in COVID-19 infection.

HMGB-1 is a non-histone nuclear protein that can be released from cells during cellular stress, injury, or inflammation.[17] Once released into the extracellular environment, it acts as a 'danger-associated molecular pattern' (DAMP) and can trigger inflammatory responses by binding to pattern recognition receptors (PRRs) on immune cells.[18]

Elevated levels of HMGB-1 have been specifically observed in rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis, and inflammatory bowel disease (IBD), which are all considered to be auto-immune diseases.[19] In rheumatoid arthritis, HMGB-1 levels in synovial fluid and serum correlate with disease activity and severity, making it a potential biomarker for disease progression and treatment response.[20] In SLE, HMGB-1 levels are elevated in both serum and urine, and its levels correlate with disease activity, organ damage, and the presence of specific autoantibodies.[21]

HMGB-1 has also been explored as a biomarker for sepsis, a life-threatening condition characterized by an overwhelming immune response to infection.[22] Elevated HMGB-1 levels have also been associated with the development and progression of various cancers, including breast, lung, and colorectal cancers, potentially due to its role in promoting inflammation and tumor growth.[23]

Key advantages of using HMGB-1 as a biomarker include its stability in biological fluids and its direct involvement in the inflammatory and immune responses underlying so many diseases. However, until now it has been difficult to establish standardized methods for measuring HMGB-1 levels and to validate its clinical utility as a diagnostic and prognostic biomarker across different diseases. We shall return to this later, as there are now ELISA tests available that allow us to standardize HMGB-1 assays, and thus enable the comparison of results between labs globally.



HMGB-1

- 'Danger' signal when released from cells
- Triggers inflammation
- Activates immune cells
- Promotes cytokine production

Use: monitoring of the immune response in disease

Figure 2: HMGB-1 plays a key role in the body's response to injury and infection.

Neopterin

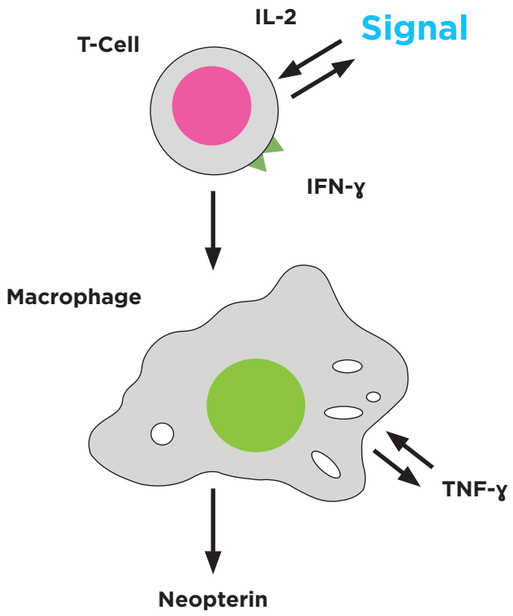
Neopterin (Np) is a compound produced by macrophages and dendritic cells upon stimulation by interferon-gamma (IFN-γ), a cytokine released by activated T-cells and natural killer cells during cellular immune responses.[24,25] Np, with the systematic name 2-amino-4-hydroxy-6-(D-erythro-1′,2′,3′-trihydroxypropyl)-pteridine, belongs to the class of pteridines.[26] This particular Np was first isolated in 1963 from bee larvae, worker bees, and royal jelly.[27-29] Later, in 1967, Np was isolated in human urine by Sakurai and Goto for the first time.[30] It has since been extensively studied in wide-spectrum inflammatory diseases, including viral, bacterial, and parasite infections, cardiovascular diseases, autoimmune diseases, and malignant tumors.[31-37]

Neopterin levels in body fluids, such as serum, urine, and cerebrospinal fluid (CSF), are elevated during various inflammatory and immune-mediated conditions.[38] High Np levels are observed in viral infections, including HIV, hepatitis B and C, and cytomegalovirus, reflecting the activation of the cellular immune response against these pathogens.[26]

In autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus (SLE), and multiple sclerosis, neopterin levels correlate with disease activity and severity, making it a potential biomarker for monitoring disease progression and treatment response.[39] Neopterin levels are also increased in certain malignancies, such as leukemia, lymphoma, and solid tumors, possibly due to the activation of immune cells by tumor antigens.[40]

In allograft recipients, elevated neopterin levels may indicate acute rejection episodes or post-transplant infections, contributing to the monitoring of transplant outcomes.[41] Neopterin has also been studied as a biomarker for cardiovascular diseases, where it is associated with an increased risk of adverse events and may reflect the underlying inflammatory processes contributing to atherosclerosis.[42]

As with HMGB-1, the advantages of using neopterin as a biomarker include its stability in biological fluids, its direct link to cellular immune activation, and the availability of well-established analytical methods for its measurement. An easy and reliable go-to option for measuring neopterin is again ELISA, which is a sensitive, robust, and accurate solution for the quantification of neopterin, even in complex samples like serum, plasma, and urine.



Neopterin:

- Indicator of cellular immune system activation and oxidative stress
- Elevated during inflammatory and immune-mediated conditions e.g. rheumatoid arthritis, organ rejection

Use: early marker for immune reaction, present before antibody response

Figure 3: Neopterin is an early marker for immune activation.

sIL-2 receptor

Like HMGB-1 and neopterin, interleukin-2 (IL-2) is a key signaling molecule in the human immune system. IL-2 is a cytokine, one of a group of small, secreted proteins released by cells that have a specific effect on the interactions and communication between cells, helping regulate the body's natural response to infection, so that it can discriminate between foreign ('non-self') and 'self'.[43]

IL-2 mediates its effects by binding to IL-2 receptors, which are expressed by lymphocytes. The major sources of IL-2 are activated CD4+ T cells and activated CD8+ T cells.[43] On T-cell activation, the soluble form of the interleukin-2 receptor (sIL-2R) is secreted, or 'shed', so that higher than background concentrations of sIL-2R are found in patients suffering from many conditions associated with an ongoing immune response (see Fig. 4).[43]

The quantification of soluble interleukin-2 receptor (sIL-2R) in serum or plasma in adults is used by clinicians to assess immune function *in vivo*, to investigate and manage a broad range of diseases.

Elevated levels of sIL-2R are observed in autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and multiple sclerosis, where it correlates with disease activity and severity.[44,45] In SLE, higher sIL-2R levels also correlate with organ involvement, and the presence of specific autoantibodies.[46]

In rheumatoid arthritis, sIL-2R levels in serum and synovial fluid are associated with joint inflammation and erosion, making it a useful biomarker for monitoring both disease progression and response to treatment.[47] sIL-2R has even been studied as a biomarker for transplant rejection, as its levels increase during acute rejection episodes in various organ transplants, including kidney, liver, and heart.[48]

There is a direct correlation between sIL-2R level and certain hematological malignancies, such as hairy cell leukemia and adult T-cell leukemia/lymphoma, reflecting the proliferation of malignant T-cells.[49] Other immune-mediated diseases associated with increased levels of sIL-2R include sarcoidosis, biliary cirrhosis, chronic immune activation in common variable immunodeficiency (CVID) and hemophagocytic lymphohistiocytosis (HLH).[50-54]

Finally, in infectious diseases, sIL-2R levels may be elevated due to T-cell activation in response to pathogens, such as HIV, cytomegalovirus, and tuberculosis.[55]

Advantages of using sIL-2R as a biomarker include its stability in biological fluids and its direct association with T-cell activation, a central process in many immune-mediated disorders. The relative stability of sIL-2R levels throughout adult life, and the minimal gender-related differences also help make sIL-2R an attractive biomarker.[56,57] However, sIL-2R levels can be influenced by various factors, such as age, renal function, and concomitant medications, which should be considered when interpreting its levels.[58]

Soluble IL-2 receptor levels are generally measured using enzyme-linked immunosorbent assay (ELISA), or chemiluminescent immunoassay (CLIA). Commercially available assays should be calibrated against the international reference standard NIBSC 97/600.

Population	Concentration	Level	Reference
Non-diseased individuals			
Adults >18 yrs	Median: 339 [282.5–440.7] U/mL	Low	Halacli, B., et al. (2016). Journal of critical care, 35, 185–190.
Adults (21-55 yrs)	Mean: 410 (SD: 186) U/mL	Low	Mariotti, S., et al. (1992) Clinical endocrinology, 37(5), 415–422
Adults, n=20 (age 29.5 ± 1.8 yrs), men and women	Mean: 209 (SD: 25) U/mL	Low	Manoussakis, M. N., et al. (1992) Lupus, 1(2), 105–109.
Adults, n=70 (age 37–63 yrs), men and women	Median: 1,028 pg/mL (Range: 263-2210)	Low	Schimmelpennink, M. C., et al. (2020) Expert review of respiratory medicine, 14(7), 749–756.
Diseased individuals			
Sepsis: HLH, n=10, adults	Median: 2,259.9 [971.8-8,180.8] U/mL	High	Halacli, B., et al. (2016). Journal of critical care, 35, 185–190.
Graves' Disease, n=61 men and women	Mean: 1,610 (SD: 962) U/mL	High	Mariotti, S., et al. (1992) Clinical endocrinology, 37(5), 415–422
Systemic Lupus Erythematosus, n=25, men and women	Mean: 682 (SD:115) U/mL	High	Manoussakis, M. N., et al. (1992) Lupus, 1(2), 105–109.
Rheumatoid Arthritis, n=41, men and women	Mean: 734 (SD: 101) U/mL	High	Manoussakis, M. N., et al. (1992) Lupus, 1(2), 105–109.
Sarcoidosis; n=104, men and women	Median: 5,534 pg/mL (Range: 1,351-55,000 pg/mL)	High	Schimmelpennink, M. C., et al. (2020) Expert review of respiratory medicine, 14(7), 749–756.
Löfgren Syndrome (acute form of sarcoidosis), n=17, men and women	Median: 5,682 pg/mL (Range: 560-36,000 pg/mL)	High	Schimmelpennink, M. C., et al. (2020) Expert review of respiratory medicine, 14(7), 749–756.

sIL-2R:

- Marker of T-cell activation
- Helps distinguish self from non-self
- Associated with infection, autoimmune diseases and inflammatory conditions

Use: measurable surrogate for T-cell activation *in vivo* as part of disease prognosis and management.

Figure 4: Soluble IL-2R is a reliable marker for the presence of an ongoing immune response.
For detail and further data, see Tecan article Soluble interleukin-2 receptor in sickness and in health

How do we measure these 'three musketeers' of the immune activation pathway?

We have now established that all three of these immunological markers, HMGB-1, neopterin, and sIL-2R indicate an ongoing immune response and that they could all theoretically be used to monitor a huge range of immune-mediated diseases: in effect, they can all be considered as universal or generic markers for immune activation. The researcher or clinician will then have to make a considered choice regarding which one(s) would be the most appropriate to the disease being studied, diagnosed or treated, according to the empirical evidence that is available in the literature and the commercially available tests.

All three markers can be reliably measured using immunoassays, usually ELISA, and the Tecan Blog articles describe the close correlation of ELISA assays with other available techniques, such as HPLC, RIA or mass spectrometry-related methods. Therefore, as ELISA is by far the simplest method to implement, let us now look at the tests that are available and consider how we might be able to scale and automate these ELISA tests for the most reproducible results, thus enabling their global standardization.

Choosing and implementing ELISAs for immunology biomarkers

There are manifold ELISA tests available for all three of our immune activation biomarkers (HMGB-1, neopterin, and sIL-2R), as can be seen by a simple search of the internet. However, most of them are for research use only (RUO), so even if their utility is proven in terms of research and basic empirical evidence as a marker for a specific disease, their long-term use cannot be assured in the clinical space, which requires the use of IVD-compliant tests. Secondly, most tests are designed to be implemented manually, where ideally, they would be easily automatable and scalable for maximum reproducibility and for inter-lab comparisons.

These are just a couple of the key criteria for using ELISA for measuring immune activation. A more complete checklist might include:

- Ready-to-use assay reagents – no dilution necessary
- Ready-to-use standard-curve reagents – no stock dilution needed
- Kit ready-calibrated against standard preparations and other methods
- Internal kit controls provided
- Easily automatable

Tecan ELISA kits can be run either manually, for initial testing, and validation in the case of IVD-compliant kits for clinical needs, or they can be automated, according to the precise needs of your lab in terms of standardization and throughput goals. Automation scripts are readily available and are so-called ‘open system’, so that they can be easily adapted to your automation platform, and Tecan can also work directly with you to implement this.

Several white papers and articles are available for further study, depending on whether you would like to learn more about the science behind these tests, or whether you are more interested in implementing ELISA in your lab, with or without automation (see Immunology Biomarker Resource list, page 9). For more information on ordering ELISA tests and ongoing promotions, visit your country's website.

Tecan's open approach to IVDR and automation is paving the way for global standardization and automation of ELISA as the primary method for measuring immunology markers in clinical settings, opening up new possibilities for their use in future research as we continue to exploit their huge potential in diagnosing, treating and monitoring disease.

» Discover Tecan’s wide range of products for immunology testing

TECAN RESOURCES FOR IMMUNE SYSTEM ACTIVATION MARKERS*

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HMGB-1

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https://www.tecan.com/tecan-journal/a-voyage-of-discovery-exploring-the-role-of-hmgb1-in-trauma-pathology

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S-IL2R

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