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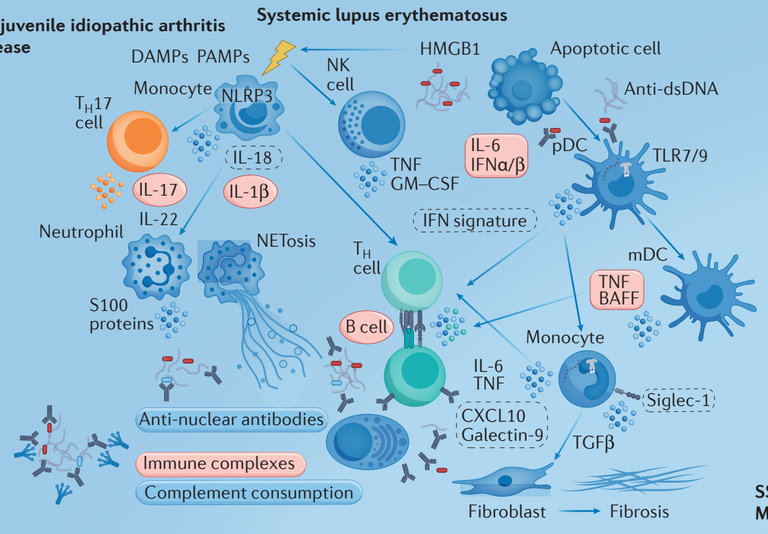
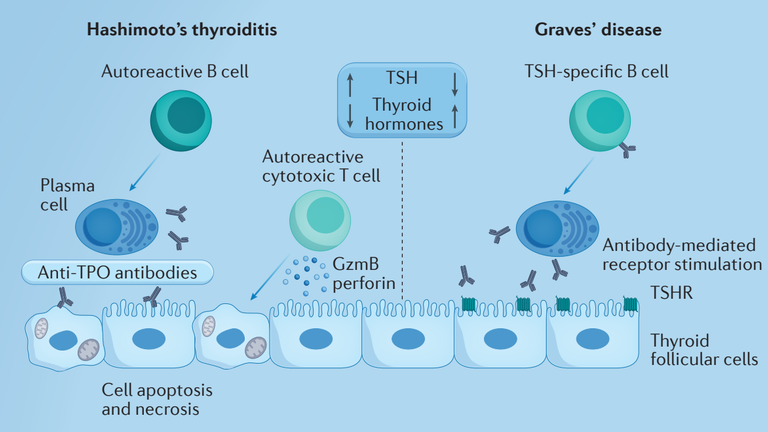
# Immune monitoring and treatment in immune-mediated inflammatory diseases

Femke van Wijk, Marjolein de Bruin, Helen Leavis, Stefan Nierkens

PRECISION for medicine

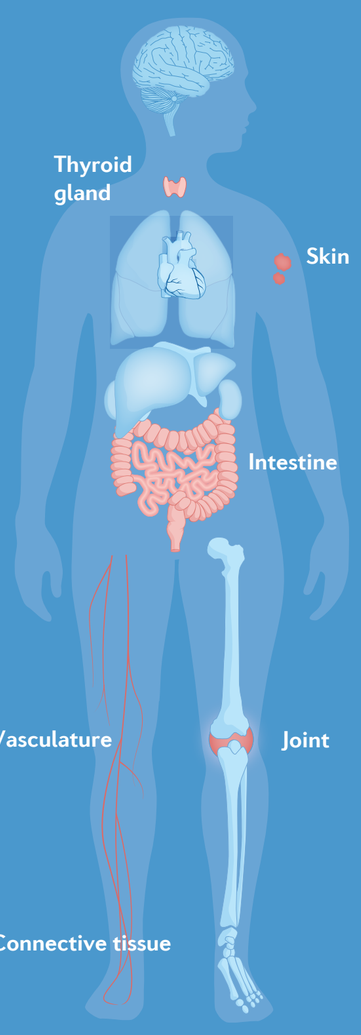
Immune-mediated inflammatory diseases (IMIDs) result from a combination of genetic and often unknown environmental factors that trigger dysregulation of innate and adaptive immunity, leading to episodes of inflammation and organ-specific injuries. These diseases can involve reaction to self-tissue by self-directed antibodies, cells or soluble mediators. Dysregulated responses towards the microbiome and allergens can also have a role. Disease specificity is partly determined by target tissue processes, but most IMIDs are heterogeneous with overlapping clinical characteristics and biological pathways. Targeting specific immune pathways or cytokines with biological drugs has greatly improved the clinical management and mechanistic understanding of IMIDs. Many assays are available for the immune monitoring of patients and new 'omic' technologies are rapidly evolving. These assays and technologies are commonly used in clinical trial settings and scientific research, but the implementation of immune monitoring in routine diagnostics is currently limited. A better molecular classification and follow-up of patients may improve disease prognosis and individualized targeted therapy strategies.

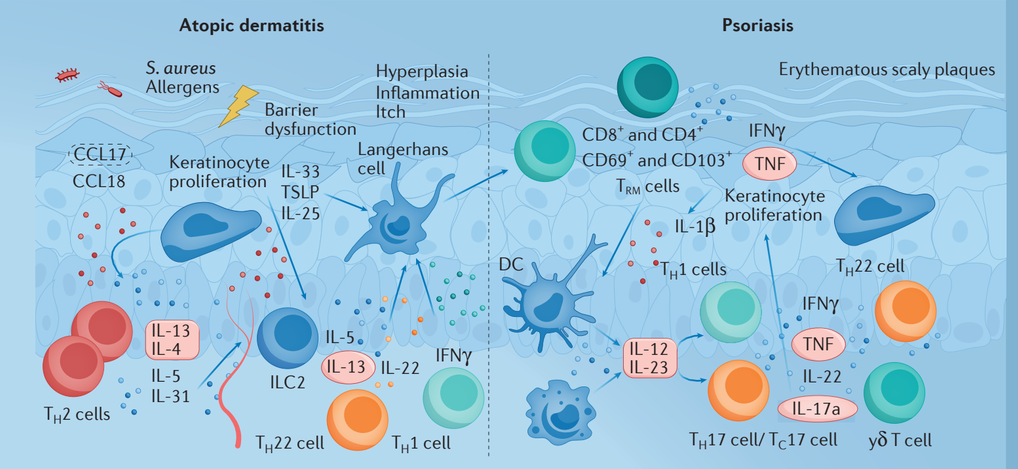


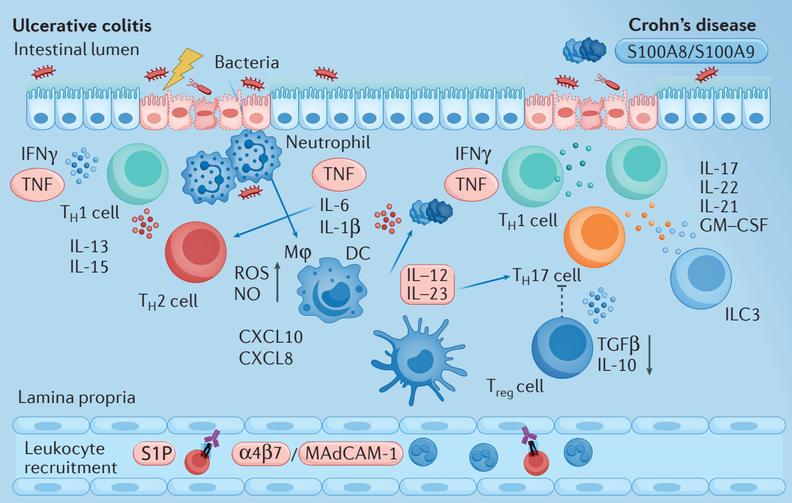



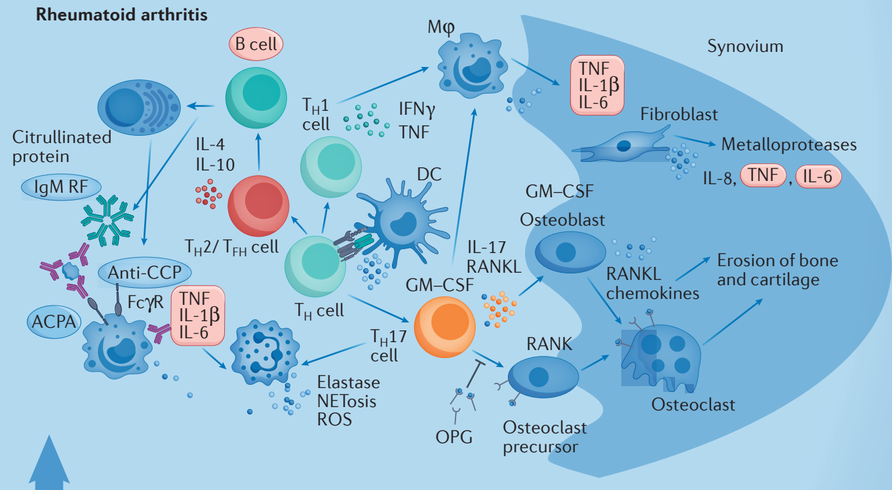

## Organ-specific versus systemic autoimmunity

Destructive autoimmune disease limited to a specific organ, such as the thyroid gland, is characterized by autoantibodies that either cause damage in that organ or affect their function. Diagnosis is based on the presence or absence of specific antibodies or hormone levels. Systemic lupus erythematosus (SLE) is a prototype systemic autoimmune disease that is characterized by the production of anti-nuclear autoantibodies, immune complex deposition, and heterogeneous clinical manifestations that affect multiple organs. Other systemic connective tissue autoimmune diseases share several features and pathways with SLE. Emerging therapies include strategies to inhibit B cells, anti-IFN antibodies and JAK inhibitors.



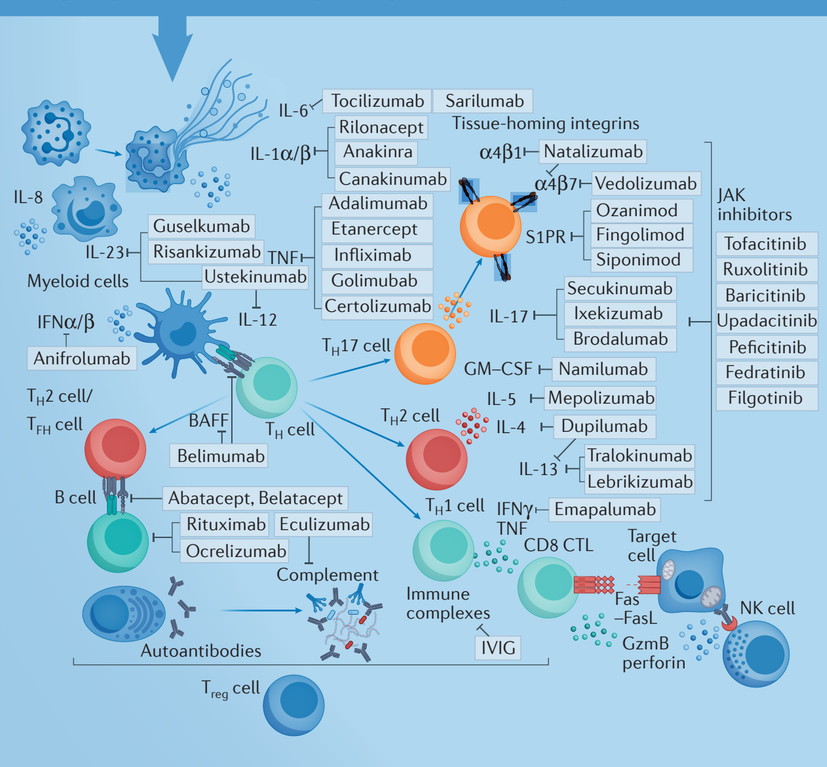




## Therapies and their targets

Targeting specific immune pathways or cytokines with biological drugs has improved the clinical management of IMIDs. In addition, JAK inhibitors inhibit one or more of the Janus kinase family of enzymes (JAK1, JAK2, JAK3 or TYK2) and interfere with JAK–STAT signalling induced by the binding of cytokines and haematopoietic growth factor receptors on various immune cells.



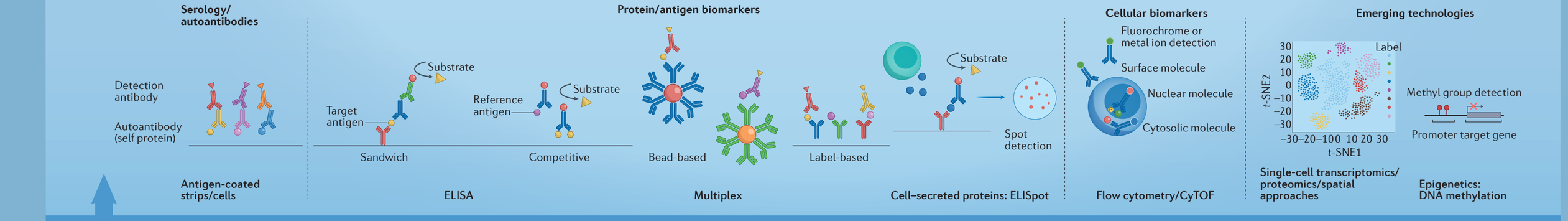

**In diagnostic guidelines**

**Diagnostic expert centres, not in guidelines**

**Target for registered therapy**

## Chronic tissue inflammation

Chronic inflammation can affect multiple organs. Psoriasis and atopic dermatitis are common T cell-mediated inflammatory diseases of the skin. Patients with atopic dermatitis often have allergic or atopy features and a disturbed skin microbial composition. The inflammatory bowel diseases Crohn's disease and ulcerative colitis result from an aberrant immune response to enteric microbiota in genetically susceptible individuals. Pro-inflammatory pathways that are driven by IL-23 and TNF, decreased immune regulatory mechanisms and defective barrier function of the intestinal epithelium contribute to the immune dysregulation. These diseases are highly heterogeneous in presentation, disease course and responses to therapy. Rheumatoid arthritis is a systemic autoimmune disease characterized by joint infiltration of immune cells, synovium hyperplasia and superfluous secretion of pro-inflammatory cytokines, which lead to cartilage degradation and bone erosion. Various autoantibodies are associated with rheumatoid arthritis, including ACPA and RF, and are used in disease diagnosis and prognosis. Depending on the specific disease, blockade of cytokines, JAK inhibitors, or other immunosuppressive approaches can be used.




## Immune monitoring assays and technologies

Various technological platforms are used to measure IMID-related biomarkers, allowing clinicians to determine disease status and supporting precision treatment. These include assays to detect antibody and protein/antigen biomarkers, some of which can be multiplexed. To monitor the activation of immune cells or exclude specific immune deficiencies, cytometry using fluorescently labelled antibodies (flow cytometry) or antibodies conjugated to heavy ions (CyTOF) can identify particular cell subsets. The use of flow cytometry is limited to diagnostics for specific diseases, but monitoring of cell subsets is commonly used in clinical trials and post-marketing drug surveillance studies. (Single-cell) 'omic' approaches for proteome, transcriptome, methylome or epigenome profiling are rapidly emerging, but are not yet the standard of care for the diagnosis or follow-up of IMIDs.

Precision for Medicine is a global, precision-medicine, contract research organization that specializes in the development of biomarker-driven therapeutic agents, with leadership in developing advanced approaches such as Epiontis ID for monitoring the status of the immune system.

Epiontis ID provides precise cell counts by measuring epigenetic markers that indicate specific cell types. This method, performed on DNA by quantitative PCR, is highly reproducible and is flexible in the type of sample accepted, reducing the need for special sample care during transport and storage. Commonly analysed samples include fresh, frozen or paper-spotted blood as well as solid tissues.

With the ability to create a customized panel from among more than 30 pre-validated cell type assays, Precision's Epiontis ID is an ideal service to support the clinical development of autoimmune and immuno-oncology therapeutic agents, in which understanding the status of the immune system is of key importance.

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## Abbreviations

ACPA, anti-citrullinated protein/peptide antibody; anti-CCP, anti-cyclic citrullinated peptide; CyTOF, cytometry by time of flight; DAMPs, damage-associated molecular patterns; DC, dendritic cell; ELISA, enzyme-linked immunosorbent assay; GM–CSF, granulocyte–macrophage colony-stimulating factor; GzmB, granzyme B; HMGB1, High mobility group box 1 protein; IFN, interferon; IL, interleukin; IVIG, intravenous immune globulin; MCTD, mixed connective tissue disease; Mφ, macrophage; NETosis, formation of neutrophil extracellular traps; mDC, myeloid dendritic cell; NK cell, natural killer cell; OPG, osteoprotegerin; PAMPs, pathogen-associated molecular patterns; pDC, plasmacytoid dendritic cell; RF, rheumatoid factor; ROS, reactive oxygen species; S1PR, Sphingosine-1-phosphate receptor; SSc, systemic sclerosis; $T_C17$ cell, IL-17-producing CD8 T cell; $T_{FH}$, follicular T helper cell; $T_H$ cell, T helper cell; TLR, Toll-like receptor; TPO, thyroid peroxidase; $T_{RM}$ cell, resident memory T cell; TSH(R), thyroid stimulating hormone (receptor); TSLP, thymic stromal lymphopoietin.

## Affiliations

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## Competing interests statement

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