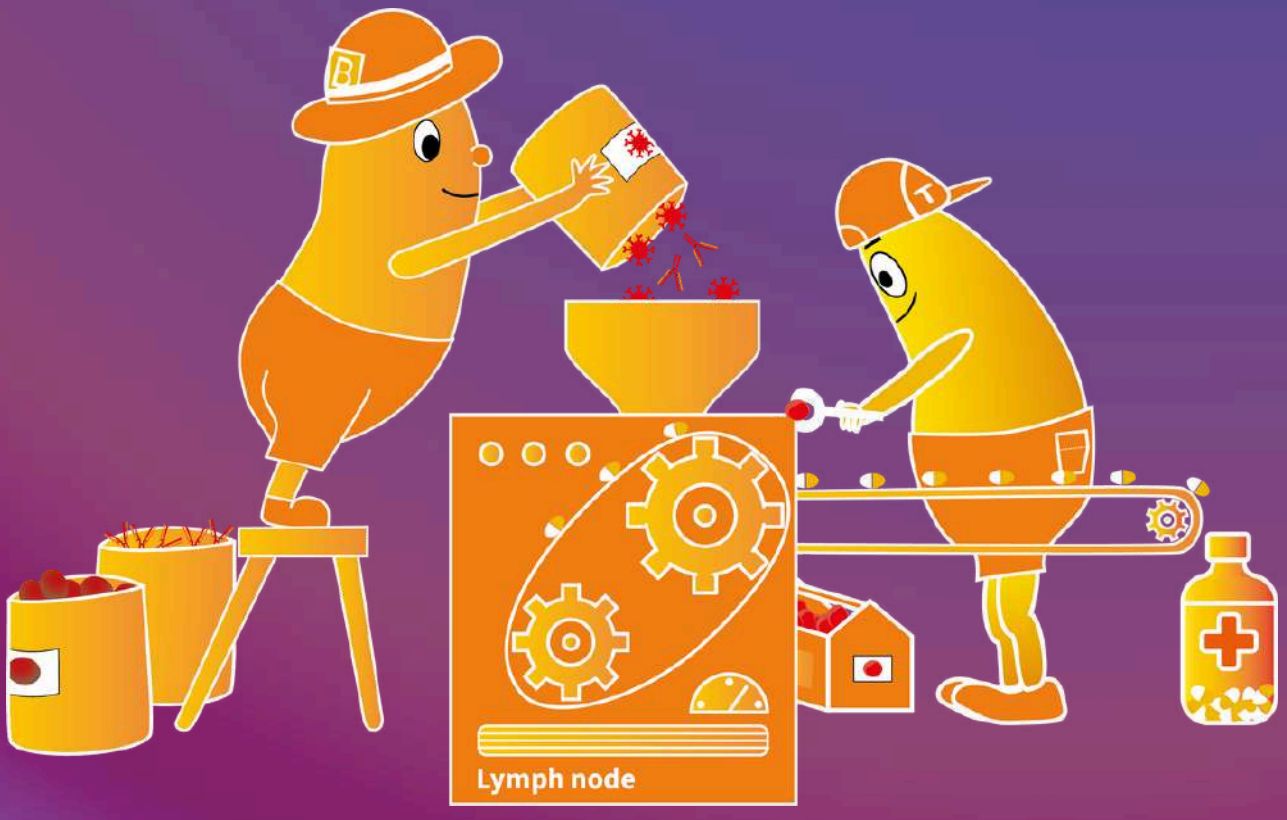
Dutch Society for Immunology (NVvI)

Abstracts

NVVI SPRING SYMPOSIUM 2026,
APRIL 9 & 10

IMMUNITY IN ACTION: MECHANISM TO MEDICINE



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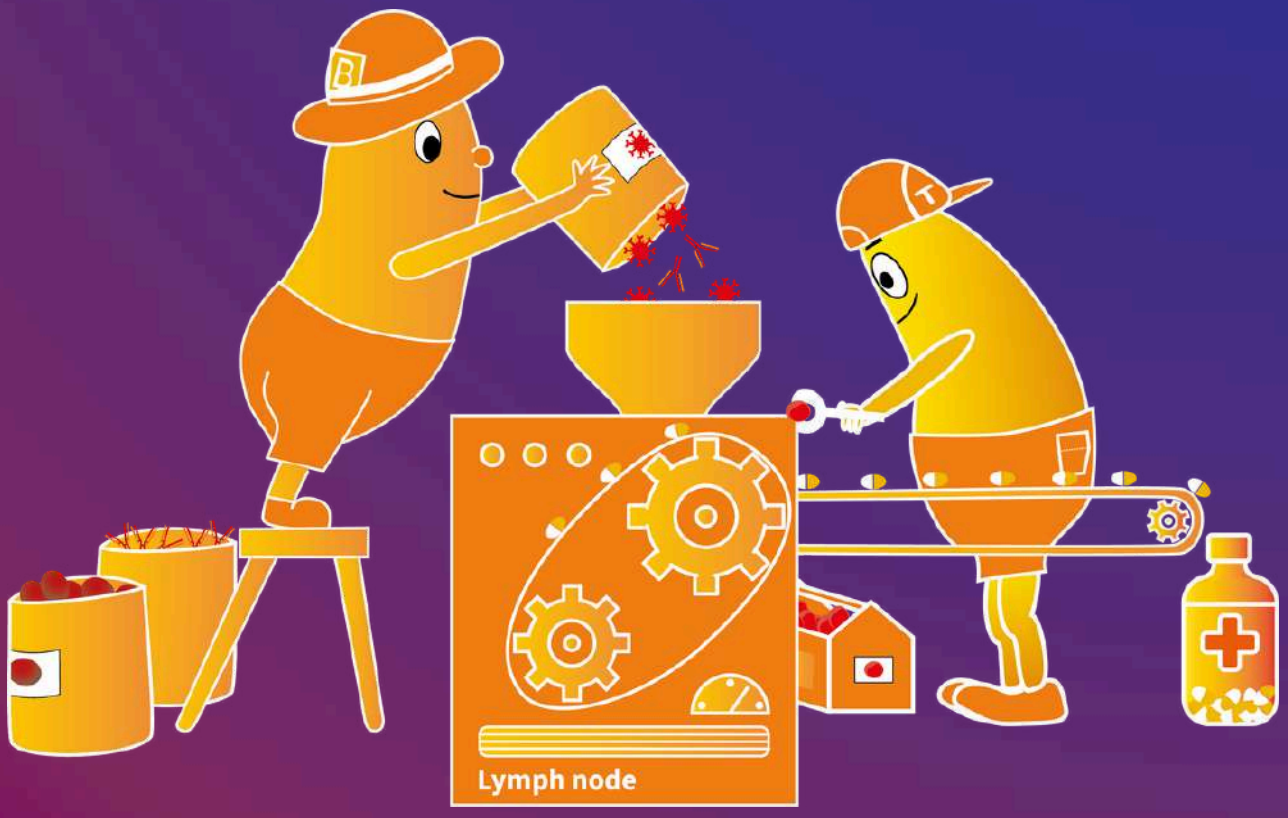

Coping strategies used by regulatory T cells to tolerate self-reactivity

Derk Amsen, Sanquin

Conventional (Tconv) and FoxP3$^+$ regulatory (Treg) CD4$^+$ T cells respond to the same signals: activation of T cell receptor (TCR), costimulatory (f.i. CD28) and cytokine receptors. The molecular and genetic make-up of these cell types is also largely the same. How then can these ostensibly similar cells generate such drastically different signal output from the same signal input: production of cytokines, like IL-2 and IFNg, and expressing immune-stimulatory CD40L by Tconv or a host of immunosuppressive mechanisms by Tregs. Cell type-specific enhancer landscapes and the Treg transcription factor FoxP3 are two well-characterized layers of regulation determining response specificity. Here, we examined a potential third regulatory layer: differential signal processing from surface receptors. This idea is conceptually appealing, given the fundamental differences in TCR usage between these cells. The foreign antigen-specific TCR on Tconv is activated only rarely and transiently (for instance when their cognate antigen is introduced by an infectious organism). Prolonged repetitive TCR stimulation on Tconv in fact causes loss of function ("exhaustion"). In contrast, Treg TCRs are largely autoreactive and therefore "see" their cognate antigen continuously, necessitating adaptations that prevent loss of function from repetitive TCR signaling. Apart from contributing to our fundamental understanding of Treg/Tconv biology, identifying differences in signal transduction between these cells may yield therapeutic opportunities. Kinases are among the best druggable targets and preferential use of kinases by one cell type over the other may allow more subset-selective inhibition, thereby improving net therapeutic effect. Here, we will discuss our studies on processing and perception of input signals in Tregs and Tconv. Our results confirmed that marked differences in signal transduction pathways represent a third regulatory layer determining cell type specific response characteristics and identify cell type-specific vulnerabilities for therapeutic manipulation.

Antibody designs and effector function engineering for tailored outcome

Jan Terje Andersen, University of Oslo and Oslo University Hospital, Norway

Antibody-based biologics are continually expanding the therapeutic landscape, with tailoring of effector functions and plasma half-life emerging as key commercial differentiators. In humans, the average plasma half-life of most IgG antibodies and albumin is approximately three weeks. This characteristic makes IgG the preferred choice for designing antibody formats, while albumin is increasingly utilized as a fusion partner for a variety of therapeutic modalities. Remarkably, the plasma half-life of these distinct proteins is extended by a shared cellular Fc receptor known as FcRn. Moreover, engineering the Fc region to enhance or silence effector functions is crucial for achieving potent and specific modes of action, which must be carefully tailored to the specific context of each case. In this talk, I will discuss how comprehensive insights into the complex structural and cellular mechanisms that govern FcRn functions can facilitate the design of antibody and albumin-based formats with enhanced binding and transport properties. This perspective will further be discussed in light of Fc engineering for specific engagement of Fc receptors and the complement system.

Investigating the impact of Fc gamma receptors on the efficacy of antibody therapy for cancer

Stephen Beers, Centre for Cancer Immunology, University of Southampton, UK

Monoclonal antibodies (mAb) have revolutionised cancer therapy; however, treatment resistance remains common, underscoring the need for new antibodies and improved strategies. Although the number of mAb entering clinical practice continues to increase, genuinely novel targets are limited and often fail during development. A major challenge in advancing antibody therapeutics is the limited understanding of the biological mechanisms that prevent promising candidates from achieving clinical success.

Almost all antibody therapeutics currently used in the clinic are of the IgG class and are therefore able, to varying degrees, to engage immune effector pathways via Fc gamma receptors (FcγR). Classical FcγR include both activating and inhibitory members, which mediate pro inflammatory or suppressive effects, respectively, upon recognition of IgG. Myeloid cells such as macrophages express both receptor types, and their relative expression shifts with cellular activation state. These dynamic changes not only influence the efficacy of distinct mAb classes but can even alter their dominant mechanism of action.

The tumour microenvironment is highly complex, often immunosuppressive, and is now recognised as a critical determinant of therapeutic response to antibodies. Gaining a deeper understanding of the tumour microenvironment in patients, including the influence of host factors such as body composition on its inflammatory state, and modelling these features accurately will be essential for improving drug development and combination strategies.

This discussion will explore how the tumour microenvironment drives an immunosuppressive phenotype in tumour associated macrophages (TAM), promoting preferential expression of inhibitory over activating FcγR. This shift fundamentally alters how different mAb subclasses perform within the tumour setting and can diminish therapeutic effects. Importantly, by understanding these dynamics, it becomes possible to select optimal mAb subclasses or to engineer antibodies and combination approaches that counteract this suppressive environment, thereby enabling enhanced therapeutic responses.

Optimising CAR-T cell sensitivity by engineering extracellular receptor/ligand sizes

Omer Dushek, Sir William Dunn School of Pathology, University of Oxford, UK

Chimeric antigen receptor (CAR)-T cells exhibit low antigen sensitivity, which restricts their therapeutic efficacy and leads to patient relapses when cancer cells downregulate antigen expression. Despite the pressing need to overcome this limitation, the underlying mechanisms remain poorly understood. Here, we demonstrate that enhancing CAR sensitivity to match the sensitivity of the T-cell receptor (TCR) can be achieved by engineering matched extracellular sizes of CAR/antigen and CD2/CD58 complexes. We find that different CAR/antigen sizes, which are generated by different CAR architectures and different target antigens, require a different CD2/CD58 size to optimise sensitivity. This extracellular size-matching improves antigen engagement and co-localisation of CAR/antigen and CD2/CD58 complexes. We also find that size-matching controls co-inhibition of CARs by PD-1/PD-L1. These findings highlight the importance of size-matching for signal integration by surface receptors and offers a new approach to tune CAR-T cell sensitivity by matching or mismatching extracellular sizes.

Innate immune cells in multiple sclerosis: a transcriptomic point of view on microglia

Susanne Kooistra, UMC Groningen

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). Affected tissue areas – lesions – are classified into various types based on location and the degree of demyelination and inflammation. Lesions occur in white matter (pre-active, active, mixed active/inactive, inactive, remyelinated) and grey matter (leukocortical, intracortical, subpial) that differentially correlate to disease course and symptom severity. What factors trigger the development of these lesions and their progression is not yet known and involves both CNS-resident and immune cells.

Microglia have long been recognized as the endogenous innate immune elements in the (CNS) parenchyma. Besides fulfilling local immune-related functions, they provide crosstalk between the CNS and the immune system at large. In the adult CNS, microglia are involved in maintaining brain homeostasis, modulating synaptic transmission and clearance of apoptotic cells. In MS, given their role in neuroinflammation and their ability to phagocytose myelin debris and set the stage for myelin repair, they are thought to play an important role in lesion initiation and development.

To better understand the biological processes underlying lesion progression, we studied the heterogeneity of CNS cells and their (altered) interactions in different MS lesion types with single-nucleus RNA sequencing and spatial transcriptomics of human post-mortem material with a focus on microglia. We further integrated our multiple types of transcriptomics data to infer relevant processes and to localize changes in cell states that might be involved in lesion evolution.

Our integrated transcriptomic data suggest discrete microglia state-transitions across lesion areas, and we propose that these lesion-associated microglia and their affected cellular processes are involved in MS lesion expansion, and as such represent attractive targets to modulate disease progression.

Targeting Fc receptors in cancer and auto immunity: IgG or IgA, the ying and yang of antibody therapy

Jeanette Leusen, UMC Utrecht

Fc receptors (FcRs) play a central role in antibody-based immunotherapy by linking antigen recognition to immune cell effector functions. Therapeutic antibodies engage FcRs through their Fc domains, enabling immune cells to eliminate target cells via mechanisms such as antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and cytokine release. Among antibody isotypes, IgG has historically been the dominant platform for therapeutic development due to its long serum half-life, well-characterized biology, and ability to engage Fcγ receptors (FcγRs) expressed on natural killer (NK) cells, macrophages, and other immune cells. In cancer therapy, IgG antibodies can trigger potent antitumor responses primarily through FcγRIII (CD16)-mediated ADCC and FcγRI-mediated phagocytosis. In autoimmune diseases, IgG-based therapeutics can also be engineered to block pathogenic pathways, neutralize autoantigens, or inhibit immune complex–mediated activation of FcγRs, thereby reducing inflammatory responses.

More recently, IgA antibodies have emerged as an attractive alternative platform for cancer immunotherapy. IgA interacts with FcαRI (CD89), a receptor highly expressed on neutrophils and certain myeloid cells. Because neutrophils are abundant and potent cytotoxic effector cells, IgA antibodies can induce strong tumor cell killing through FcαRI-mediated ADCC and phagocytosis. In several preclinical models, IgA antibodies demonstrate superior recruitment of neutrophils compared with IgG antibodies, leading to enhanced elimination of tumor cells, particularly in solid tumors. Furthermore, IgA-based therapies may reduce certain adverse effects associated with IgG antibodies, depending on the target antigen and tissue distribution.

Together, these findings highlight the importance of FcR biology in therapeutic antibody design. While IgG antibodies remain highly effective for both oncology and autoimmune indications, IgA antibodies represent a promising next-generation platform for cancer therapy by harnessing neutrophil-mediated immunity. Rational engineering of antibody Fc domains to selectively engage activating or inhibitory Fc receptors may further enhance therapeutic efficacy while minimizing immune-related toxicity.
In my presentation, I will show 2 examples based on these recent publications:

1) IgA antibody immunotherapy targeting GD2 is effective in preclinical neuroblastoma models. Stip MC, Evers M, Nederend M, Chan C, Reiding KR, Damen MJ, Heck AJR, Koustoulidou S, Ramakers R, Krijger GC, de Roos R, Souteyrand E, Cornel AM, Dierselhuis MP, Jansen M, de Boer M, Valerius T, van Tetering G, Leusen JHW, Meyer-Wentrup F. J Immunother Cancer. 2023 Jul;11(7):e006948. doi: 10.1136/jitc-2023-006948.PMID: 37479484

2) Preclinical assessment of two FcγRI-specific antibodies that competitively inhibit immune complex-FcγRI binding to suppress autoimmune responses. Holtrop T, Brandsma AM, Feitsma LJ, Krohn S, Moerer P, van den Haak F, Versnel A, Voss L, Passchier EM, Nederend M, Jansen JHM, van Mourik AG, Urbanus RT, van der Woude D, Schutgens REG, Toes REM, Janssen BJC, Lux A, Budding K, Peipp M, Leusen JHW. Nat Commun. 2025 Nov 19;16(1):10068. doi: 10.1038/s41467-025-65133-z.PMID: 41258113

The immune regulating microenvironment of lymph nodes

Reina Mebius, Amsterdam UMC, loc. VUmc

Lymph nodes are strategically positioned within tissue drainage areas, functioning as critical filters for tissue-derived factors, damaged cells, toxins, and infectious organisms. Naïve lymphocytes continuously pass through these lymph nodes, seeking alarm signals that initiate adaptive immune responses.. This way, lymph nodes are the vital site for the initiation and coordination of the immune response that is essential for establishing protective immunity against infectious diseases. It is however also the place where unwanted immune reactivity takes place, ultimately leading to pathology.

Within the lymph node, stromal cells play a pivotal role in guiding immune cell migration, supporting their survival and differentiation, and controlling autoreactive T cells. By creating a specialized microenvironment, stromal cells facilitate the rapid expansion of antigen-specific lymphocytes and provide a niche for memory lymphocytes during the contraction phase of the immune response. The differentiation of stromal cells into distinct subsets, each with unique functions, is crucial for orchestrating immune responses. This differentiation is influenced by the local environment, including immune cells, tissue-derived factors, and the extracellular matrix, as well as by variables such as sex and age.

Consequently, the adaptive immune response originating in secondary lymphoid organs like lymph nodes is shaped by these factors, which can result in either effective immunity or, in certain scenarios, chronic immune-mediated diseases. To better understand how an adequate immune response may transition into pathological outcomes, we are employing human 3D lymph node models to study these processes in detail.

Why you can’t escape theoretical thinking in immunology

Thomas Pradeu, CNRS & the University of Bordeaux, France

In this talk, I argue that theoretical thinking is inescapable in immunology, and I will develop three main points. First, theories have played a crucial role in immunology since its inception at the end of the 19th century, and this remains the case today. Second, theories guide both our thinking and our practice, whether experimental or therapeutic. Third, those who consider that they have no need for theoretical thinking are, in fact, prisoners of tacit theoretical frameworks. These three points will be illustrated through numerous examples. I will then examine some of the key questions in contemporary immunology for which theoretical thinking appears to be particularly warranted.

Dendritic cells against cancer

Gerty Schreibelt, Radboudumc, Nijmegen

Dendritic cell (DC) vaccination was introduced in the 1990s as a strategy to stimulate or enhance antitumor immunity by presenting tumor antigens to the host immune system. Over the past three decades, numerous clinical studies have evaluated diverse DC subsets, manufacturing protocols, and treatment schedules. These studies consistently demonstrate that DC vaccination is safe and capable of inducing antitumor immune responses, yet robust evidence for objective clinical benefit remains limited. Most trials have focused on patients with metastatic disease, whose immune competence may be impaired by an immunosuppressive tumor microenvironment. Harnessing the full therapeutic potential of DC vaccination may therefore require shifting toward preventive or early-stage interventions in individuals with minimal or no tumor burden.

Carriers of germline mutations in DNA mismatch repair (MMR) genes, including individuals with Lynch syndrome and constitutional mismatch repair deficiency (CMMRD), represent a compelling clinical model for such preventive strategies. Despite intensive surveillance, these patients face a markedly elevated lifetime risk of developing multiple malignancies. MMR-deficient tumors accumulate high numbers of insertion–deletion mutations within microsatellite regions. When these mutations occur in coding microsatellites, they generate novel frameshift peptides (FSPs) that function as tumor-specific neoantigens and are attractive targets for immunotherapy.

In a phase I/II study involving three patients with a recent history of colorectal cancer and twenty cancer-free Lynch syndrome carriers, we demonstrated that DC vaccination targeting frameshift neoantigens is safe, well tolerated, and capable of eliciting strong T-cell responses. Notably, preventively vaccinated Lynch syndrome patients who developed T-cell immunity against a TGFβRII-derived FSP remained cancer-free for more than 8–10 years. These findings support the concept that neoantigen-based DC vaccination may offer a viable strategy for cancer prevention in MMR-deficient individuals.

Building on this work, we investigated whether recurrent frameshift mutations in CMMRD-associated tumors give rise to shared FSPs suitable for broader DC vaccine development. Whole-exome and whole-genome sequencing of 44 tumors from 19 CMMRD patients identified multiple recurrent coding microsatellite indels predicted to generate immunogenic FSPs. Using complementary in silico tools, we assessed proteasomal processing and HLA class I binding potential. Functional validation demonstrated that a selection of recurrent FSPs was endogenously processed, presented, and recognized by cytotoxic T cells, and thus represents a promising set of shared targets for both therapeutic and preventive DC-based vaccination in MMR-deficient cancers. A subset of these peptides will be incorporated into an upcoming DC vaccination trial in Lynch syndrome patients.

50 shades of lymphoid structures in cancer

Karina Silina, IPW, D-CHAB, ETH Zurich

Tertiary lymphoid structures (TLS) with active germinal centres are positive prognostic indicators for most solid tumours in both, untreated and immunotherapy-treated setting. Viral infection models have demonstrated that TLS recapitulate the structure and functions of secondary lymphoid organs. Together, these findings have spurred the hypothesis that TLS contribute to tumour immune control by serving as in situ sites for cancer-specific effector cell priming as well as supporting niches for stem-like T cells. However, mechanisms of TLS development, maturation and function in cancer are not well understood. In this talk, I will cover our recent results aimed at answering the above question using spatial omics approaches in treatment-naïve and immunotherapy-treated cohorts of lung cancer and melanoma.

We explored the makeup of organised immune infiltrates in late-stage melanoma and lung cancer patients from the perspective of various clinical parameters, including prediction of response to immunotherapy at baseline. We found that tumour progression and organ site imposed a prominent confounding effect on baseline TLS development, which obscured their predictive associations. We identified a different type of immune niche composed mainly of T cells, while lacking a B cell compartment, and hence not classified as TLS. The formation of such T cell clusters was not confounded by tumour progression or organ site. Niches enriched with TCF1-expressing T cells showed the dominant positive association with survival in immunotherapy-treated melanoma and lung cancer patients, while TLS had no prognostic relevance when adjusted for the T cell infiltrate.

We next analysed a cohort of non-metastatic treatment-naïve lung cancer patients that were enriched with mature germinal centre-containing TLS but showed opposing outcomes (short- and long-term survival). While histologically the TLS appeared equally mature in both survival groups, their transcriptome and proteome showed significantly increased T cell and B cell function in long- compared to short-term survivors. Finally, we found that an immune cell niche composed of PD-L1-high myeloid cells surrounded tumour nests significantly less in TLS-rich short-term survivors. Such niches contained the highest proportion of CD11C+ dendritic cells, plasma cells and proliferating CD8+ T cells in comparison to TLS or scattered stromal areas. Together, our analysis identifies novel organised immune cell niches associated with survival in treatment-naïve and immunotherapy settings and indicates that TLS effects are dependant on the T cell function. This calls for an improved understanding of the functional regulation of TLS in cancer before their induction can be considered as a therapeutic approach.

Autoreactive B cell responses in human autoimmune disease; what makes them different?

Rene Toes, LUMC, Leiden

The Immune system is crucial for protection against infections from viruses and bacteria. However, sometimes it does not function properly and targets own tissues, including bone and joints. This can lead to an autoimmune disease, such as rheumatoid arthritis or systemic sclerosis. Despite significant advancements in the treatment of many of these diseases in recent times, most autoimmune diseases can still not be cured or prevented. Patients often suffer greatly from their chronic illness, significantly impacting the way they can lead their lives.

Break of immunological tolerance is at the basis of the development of autoimmunity and consequently autoimmune diseases. B cell targeted therapies are effective in several autoimmune diseases, revealing a pivotal role of these immune cells in disease pathogenesis. The laboratory aims to understand how B-cell tolerance towards self-antigens is broken. More specifically, the research focusses on understanding how and why the immune system derails and starts attacking the body's own tissues causing the development of autoimmune rheumatic joint diseases. The laboratory thrives to implement the knowledge acquired on the breach of tolerance and the evolution of human auto-reactive B-cell responses into the design of preventive strategies and/or interventions aiming to restore normal immune-homeostasis against autoantigens and ultimately cure of B-cell mediated auto-immune diseases.