DUTCH SOCIETY FOR IMMUNOLOGY (NVVI)

BACK TO OUR ROOTS

VIBRANT IMMUNOLOGY AT A FAMILIAR LOCATION

Abstracts

NVVI SPRING SYMPOSIUM 2025,
MARCH 20 & 21
DE WERELT, LUNTEREN

Thursday March 20, 2025

11.00 Welcome and introduction
Michiel van der Vlist, UMC Utrecht

Session I - Immuno metabolism
Chair: Jeroen den Dunnen

11.15 **Why we get sick: immune-mediated modulation of systemic metabolism in context of disease**
Felix Wensveen, University of Rijeka, Croatia

12.00 **Metabolic roots of immunology**
Jan Van den Bossche, Amsterdam UMC, Location VUmc

12.45 Lunch and sponsor visiting

Session II - Cancer immunology
Chair: Febe van Maldegem

13.45 **Fighting glyco-immuno wars at the tumor microenvironment**
Sandra van Vliet, Amsterdam UMC, Location VUmc

14.30 **Unveiling the determinants of myeloid cell heterogeneity in cancer**
Leila Akkari, NKI, Amsterdam

15.15 Coffee/tea break and sponsor visiting

Session III - Expanding horizons
Chair: Wendy Unger

16.00 **Extracellular Vesicles in the context of immune defense**
Esther Nolte-'t Hoen, Utrecht University

16.45 **Innate immunity in metabolic complications: a translational immunometabolic view**
Rinke Stienstra, Wageningen University

17.30 Drinks
17.30 -18:15 Young NVvI Career Workshop
18:15 Diner

Key note lecture
Chair: Michiel van der Vlist

20.00 **Curiouser and curiouser: regulating the remarkable intracellular dynamics of killer T cells**
Gillian Griffiths, Cambridge Institute for Medical Research, UK

21.00 Drinks (at own account)

Friday March 21, 2025

08.15 Meet the speaker breakfast sessions

Session IV - Infection

Chair: Laia Querol

09.00 **Antibodies & complement against bacterial infections**
Suzan Rooijakkers, UMC Utrecht

09.45 **The impact of the nature of the dying cell on macrophage function: Tell me what you eat and I will tell you who you are**
Lidia Bosurgi, University Medical Center Hamburg-Eppendorf, Germany

10.30 Coffee and sponsor visiting

Session V - B cell responses

Chair: Iosifina Foskolou

11.00 **Manipulation of human B cell memory: vaccination and allergen immunotherapy**
Menno van Zelm, Erasmus MC, Rotterdam

11.45 **Human B cell responses**
Anja ten Brinke, Sanquin Research, Amsterdam

12.30 Lunch and sponsor visiting

Session VI - Multi-omics in immunity

Chair: Gwenny Verstappen

13.30 **Location, Location, Location:**
Spatial analysis of the tumor immune microenvironment
Yvonne Vercoulen, UMC Utrecht

14.15 **Molecular mechanisms underpinning systemic autoimmunity**
Carola Vinuesa, The Francis Crick Institute, UK

15.00 **Closure**
Michiel van der Vlist

Abstracts are available on:

www.nvvi-dsi.nl

or scan QR code:

Why we get sick: On the immunology of sickness metabolism

Felix Wensveen, University of Rijeka, Croatia

When we get sick, we feel miserable. We get a temperature, we feel weak and we just want to lay in bed. We experience this as a pathology. After all, how can feeling bad be good? But in fact, the alterations to our physiological state in response to infection are the result of a carefully regulated set of metabolic changes mediated by the immune system. Its purpose is to generate a metabolic environment in which the body is optimally able to fight infection, while denying pathogens vital nutrients for their replication. Infection-induced metabolic changes, also known as sickness metabolism, depend on tissue-specific interactions between the immune system and organs involved in regulation of systemic homeostasis. Alterations to homeostatic set points leads to altered production and uptake of nutrients in circulation, which modifies the metabolic rate of key organs. This is what we experience as being sick. Surprisingly, whereas we are all familiar with being sick, the underlying mechanisms are only now starting to be understood. In this presentation I will provide some new insights into how the immune system modulates systemic physiology following viral infection and how this benefits the anti-pathogenic response. In addition, I will explain how these mechanisms are chronically activated in obesity and thus contribute to the development of metabolic disease.

Metabolic roots of macrophage activation and inflammation

Jan Van den Bossche, Amsterdam UMC, Location VUmc

Macrophages play a central role in regulating immune responses and inflammation. Their function is tightly controlled by metabolic processes, which are crucial for determining both the nature and intensity of immune activation. During the NVVI spring meeting, I will discuss how macrophage metabolism underpins their inflammatory responses and subsequent disease outcomes, with a specific focus on mitochondrial dysfunction. Mitochondria are critical hubs for cellular energy production, and their dysfunction in macrophages has profound implications for immune regulation. Inflammatory macrophages exhibit altered mitochondrial bioenergetics, which is not only manifested by a reduction in mitochondrial respiration but also by the accumulation of specific "immunometabolites." These immunometabolites, such as succinate, itaconate, and 2-hydroxyglutarate, act as metabolic regulators of inflammation and immune activation, influencing key signaling pathways that drive the inflammatory cascade. The dysfunction of mitochondrial respiration in macrophages impairs their ability to repolarize and resolve inflammation efficiently, which is a hallmark of chronic inflammatory diseases. By targeting the metabolic pathways linked to mitochondrial dysfunction and immunometabolite accumulation, we could open new therapeutic avenues for treating chronic inflammatory conditions. Ultimately, understanding how macrophage metabolism drives inflammation and disease will provide valuable insights into immune-based therapies for inflammatory diseases.

Fighting glyco-immuno wars at the tumor microenvironment

Sandra van Vliet, Amsterdam UMC, Location VUmc

Glycans play a crucial role in shaping adaptive immune responses. The recognition of glycans by glycan-binding receptors, such as the Siglecs and C-type lectins, has illustrated their potent immune modulatory role and has implicated glycans not only in infectious diseases, but also revealed their extraordinary properties in tumor progression. Malignant transformation is frequently accompanied by an increased expression of truncated O-glycans, as well as fucosylated and sialylated structures. The presence of these tumor-associated glycan antigens is generally correlated to metastasis formation and a lower disease-free survival. We study how the "glyco-code" is read by the immune system and how aberrant glycan expression orchestrates immune responses in the tumor microenvironment. Using CRISPR/Cas9 technology we have generated a vast collection of syngeneic glycovariant cell lines that either lack or de novo express certain glycosyltransferases or glycosylation-related enzymes. We have challenged mice with these glycovariants and analyzed both tumor growth as well as the immune landscapes within the tumors. Our work has highlighted that aberrant glycan structures are crucial for the tumor to evade anti-tumor immunity. Strikingly, the induction of immune suppression is not only dependent on the interacting glycan, but also strongly influenced by the tumor type expressing the glycan epitope and the location of the tumor. Together our results emphasize that the impact of tumor-associated glycan structures on cancer immunity has a higher level of complexity than originally thought.

Unveiling the determinants of myeloid cell heterogeneity in cancer

Leila Akkari, NKI, Amsterdam

Tumors growing in metabolically-challenged environments are particularly reliant on cancer cells and immune cell metabolic cross-talk to satisfy their high metabolic needs. However, the intricacies of this metabolic interplay and the consequences on immune cell subsets diversity and function remain largely unexplored. We interrogated the heterogeneity of the tumor microenvironment using multi-omics analyses in preclinical brain and liver cancer mouse models and patient datasets and identified metabolically-rewired tumor-associated macrophage (TAM), myeloid cells and regulatory T cell subpopulations fueling cancer progression and resistance to standard of care and immunotherapies. Our work reveal the dynamic evolution of specific immune cell compartment and resist to therapies, with potential for exploiting these vulnerabilities therapeutically.

Extracellular Vesicles in the context of immune defense

Esther Nolte-'t Hoen, Utrecht University

In the last decade there has been an enormous rise in interest in extracellular vesicles (EVs) as means of intercellular communication. The 50-300 nm sized EVs contain lipids, (membrane-bound) proteins, and nucleic acids. Release and uptake of EVs is a highly conserved means of communication used by cells in many organisms across the three kingdoms of life. EVs can be found in a multitude of body fluids and are studied in in vitro (primary) cell cultures and in vivo models. EVs have been implicated in several diseases, including immune-related disorders, cancer, infection, neurological disorders and cardiovascular diseases. I will start with a short introduction on EVs and explain why these signaling entities are in the limelight of attention of researchers, clinicians and the industry. I will also provide examples of how immune cells use EVs and respond to EVs from various (diseased) tissues.

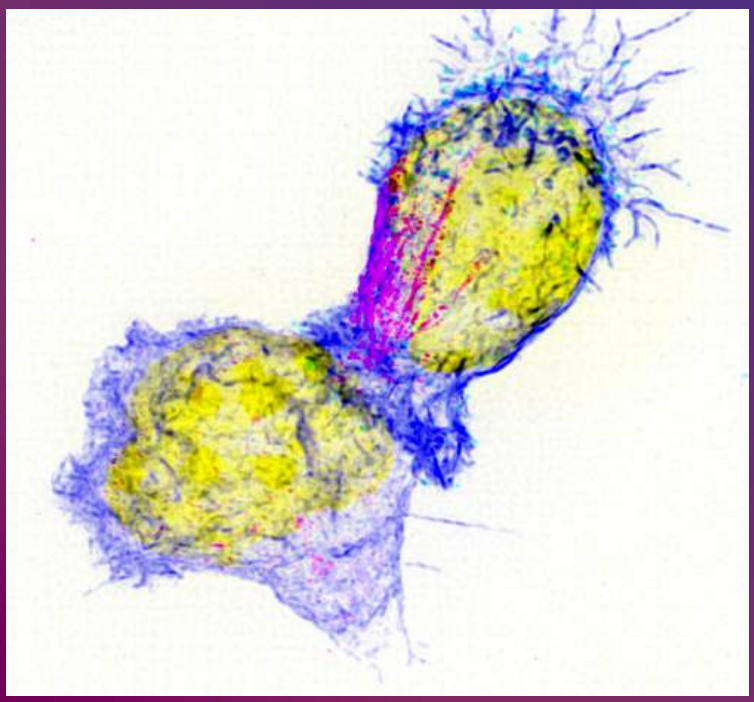
My group investigates the role of EVs in the context of virus- and other microbial infections. I will elaborate on our current work on non-enveloped (naked) RNA viruses, mainly those belonging to the family Picornaviridae. These naked viruses can escape intact cells via enclosure in EVs. Inside these EVs, virions can stay under the radar of the host's immune system. We previously described an important role for the viral non-structural proteins and modulation of specific host kinases in the induction of these EV-enclosed viruses. In contrast to naked viruses, the EV-enclosed viruses can efficiently transmit infection in the presence of neutralizing antibodies. Although these EVs can undermine antiviral defense via the humoral arm of the immune system, our recent work shows that monocytes can take up the virus-induced EVs and react by production of antiviral cytokines.

I will close off with ideas on how two different appearance forms of the same virus (naked and EV-enclosed) interact with our immune defense systems and how this may affect viral clearance/persistence and inflammatory tissue damage.

Curiouser and curiouser: regulating the remarkable intracellular dynamics of killer T cells

Gillian Griffiths, Cambridge Institute for Medical Research, UK

Killer cells of the immune system provide a vital defence against pathogens and cancer. There is increasing interest in understanding how these cells work as recent advances in immunotherapies have successfully harnessed the killing potential of these cells to combat cancers. How best to optimise these treatments and regulate killing is the subject of intense research. However, most research to date has focused on modifying the receptors that recognise targets at the cell surface. In this seminar I will describe what happens underneath the surface of these cells when they encounter their targets and the multiple mechanisms that regulate killer cell function by mechanisms that are both unusual and fascinating, linking rapid membrane changes to changes in transcription, translation and intracellular polarity that are all required for optimal killing.



A killer T cell (right) attacking a cancer target (left)

The impact of the nature of the dying cell on macrophage function: Tell me what you eat and I will tell you who you are

Lidia Bosurgi, University Medical Center Hamburg-Eppendorf, Germany

The clearance of apoptotic cells by phagocytes is crucial for restoring tissue balance after damage. In autoimmune liver diseases such as primary sclerosing cholangitis, cell death is triggered by the accumulation of toxic bile acids within parenchymal cells. However, whether dying cells loaded with bile acids influence the efficiency of phagocytosis in restoring tissue balance remains unexplored.

Our recently generated data demonstrate that apoptotic hepatocytes laden with bile acids in vitro can act as Trojan horses, transporting bile acids into efferocytic macrophages. Consequently, in a murine model of cholangitis, bile acids accumulate in a subpopulation of macrophages exhibiting pro-inflammatory features—contrasting with macrophages that engulf apoptotic parenchymal cells devoid of bile acids.

Overall, this delineates a system in which the contents of phagocytosed dying cells—specifically, bile acid-laden hepatocytes—induce a pro-inflammatory signature in efferocytic macrophages, likely contributing to chronic hepatic inflammation.

Manipulation of human B cell memory: vaccination and allergen immunotherapy

Menno van Zelm, Erasmus MC, Rotterdam

Direct exposure to microorganisms from birth onwards drives immune responses and formation of immunological memory in humans. While extensive immune memory provides immunity against disease on subsequent re-exposure, impaired or dysfunctional immune B-cell memory (Bmem) underlies disorders such as immunodeficiency, autoimmunity and allergy, as well as poor responses to multiple vaccines for infectious diseases. A historical barrier to examine pathogenic Bmem is the detection of rare antigen-specific cells within the total pool.

In my group, we have established a pipeline for production of recombinant proteins that can be used in high-parameter flow cytometry to detect antigen-specific Bmem. We apply this technology in longitudinal studies to provide a deeper understanding into the formation and durability of newly-formed Bmem, as well as their plasticity upon intervention.

We demonstrated that following SARS-CoV-2 infection, Spike RBD and nucleocapsid specific Bmem were robustly formed and durable for >8 months. Novel COVID-19 vaccines were capable of inducing similar Bmem directed against the Spike RBD. Despite differences in serum Ig levels, double-dose mRNA (Pfizer) and adenoviral vector (AstraZeneca) vaccination elicited similar Bmem numbers. While third and fourth dose ancestral mRNA vaccinations boosted the capacity to respond to Omicron subvariants, fourth dose BA.1 and BA.5 bivalent vaccinations elicited higher Bmem numbers that recognized emerging omicron subvariants. Current studies into the fifth dose XBB.1.5 booster are ongoing to identify if such a monovalent vaccine yields superior Bmem formation.

Furthermore, we studied the transcriptional and immunophenotypic diversity of antigen-specific Bmem in patients with allergic disease, as well as the effects of allergen-immunotherapy. We identified that 4 months of immunotherapy for grass pollen allergy resulted in increased CD23, CD29 and IL4Ra on allergen-specific Bmem. Importantly, CD23 and IL4Ra were proposed as markers of a pathogenic type 2 Bmem population in allergy. We found that allergen-specific type 2 Bmem are increased after immunotherapy for grass pollen and for bee venom allergy. However, higher proportions of these type 2 Bmem expressed CD29 and IgG4. This change in phenotype suggests modulation of their pathogenicity by allergen immunotherapy, and that Bmem specificity and functionality can be manipulated through treatment intervention.

Differentiation and regulation of human B cell responses

Anja ten Brinke, Sanquin Research, Amsterdam

Recent advances in multi-parameter flowcytometry analysis together with the opportunity to analyse development of de novo antigen-specific B cells large-scale in humans ex vivo upon SARS-CoV2 infection or vaccination, have strongly advanced our insights in human B cell differentiation dynamics beyond major conventional populations. B cells can either differentiate in an early extrafollicular response or in the follicle in a germinal center response. Our results show that the extrafollicular induced "atypical" CD11c+ B cells (DN2; CD27-CD21+CD11c+), previously linked to autoimmunity and chronic exposure, are early constituents of a normal B cell response (1-3). Furthermore we identified multiple other antigen-specific activated B cell populations (ActB cell; CD71+CD27+CD21-). Within the early IgG+ ActB cell compartment, several distinct clusters were identified of which some interestingly expressed CD11c (2). Hereby raising the question if CD11c+ CD71+ActB cells are germinal center-derived or not?

By studying B cell responses in patients on TNFi therapy, widely used as treatment for different immune-mediated inflammatory diseases, additional insights were obtained. TNFi therapy causes a lower induction and faster waning of antibody responses following vaccination (4). Antigen-specific B cell analysis revealed that TNFi therapy reduced early induction of the class-switched CD11c- ActB cell compartment, coined to be germinal center-derived and long-term memory B cell formation. Conversely, CD11c+ B cells, both DN2 and CD11c+ CD71+ ActB cells were not affected by TNFi therapy (5). All together this suggest that TNFi therapy interferes with germinal center-derived B cell differentiation after antigen encounter, providing us with hints that CD11c+CD71+ActB cells are formed extrafollicular. Currently we are attempting to decipher the relatedness and origin of different B cell populations and define key regulators of early B cell differentiation combining single cell RNA sequencing and BCR sequencing.

To study ways to target unwanted B cell responses in human in vitro B cell culture systems are needed. Therefor we are setting-up different co-culture models in which we for instance integrate a more physiological 3D lymph node environment to study and interfere in T cell dependent - naïve B cell differentiation.

In conclusion, our work delineates the early stages of the antigen-specific B cell response. Detection of ActB cell clusters early after antigen encounter opens avenues for future evaluation of their potential to serve as a proxy for antigen-reactive B cells in autoimmunity or other unwanted B cell responses.

Location, Location, Location: Spatial analysis of the tumor immune microenvironment

Yvonne Vercoulen, UMC Utrecht

Dr. Vercoulen will discuss how the spatial tumor immune landscape could guide therapeutic strategies in cancer treatment, using 2 examples:

i) Immune Checkpoint Inhibition (ICI) remains ineffective in a significant proportion of metastatic melanoma patients. Immune profiling of the melanoma Tumour Microenvironment pre-treatment using high-plex imaging and RNA sequencing revealed that monocyte-derived macrophage (MDM) and T cell recruitment associates with anti-PD1 therapy response and survival. This study provides important clues for future precision combination therapy strategies.

ii) MSI-high (mismatch repair deficient) colon cancer rarely metastasizes. Hence, for most patients, surgery would be an effective treatment and only 1 out of 5 patients would require adjuvant chemotherapy. However, to date biomarkers for prediction of risk for distant metastasis are lacking, leading to overtreatment in ~80% of the cases.
We used high-plex imaging, and uncovered that not the numbers of infiltrating CD8 T cells, but the location of these T cells in the tumor is predictive for metastasis1:
In primary tumors that later metastasized CD8+ T cells resided in the stroma, surrounded by fibroblasts, and showed an inactive phenotype, while in non-metastatic tumors, the T cells localized close to the tumor cells and were more active. T-cell-tumor distance showed high sensitivity and specificity as a biomarker for metastatic risk and is currently validated in a larger cohort for potential clinical application. Moreover, we are developing fibroblast phenotyping strategies to assess the potential role of the stroma in T cell entrapment and function related to metastatic risk.