Proceedings of EIMN's 1st European Immunometabolism Conference

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Meeting Report

Immunometabolism

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Proceedings of EIMN's 1st European Immunometabolism Conference

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Abstract

The 1st European Immunometabolism Conference was organized by the European Immunometabolism Network (EIMN) in Køge near Copenhagen, Denmark from June 26 to June 28, 2024. This conference and network aims to serve as a platform for presenting and discussing the latest and most significant advances in European immunometabolism research. Our vision includes promoting collaboration, training, networking opportunities, and diversity in science, especially for early career and upcoming scientists. Here, we summarize the immunometabolism-related work that was presented during the meeting by members of the network, selected early career researchers, session speakers, and keynote speakers. Additionally, we provide an overview of the discussion points from the round table session and conclude with future aims and planned initiatives of the EIMN.

Keywords: immunometabolism, European Immunometabolism Network, innate immunity, adaptive immunity, cancer, cardiometabolic diseases, technologies, infections

Abbreviation: EIMN: European Immunometabolism Network

1. Birth of the network and organization of the conference

The European Immunometabolism Network (EIMN) (www.immunometnet.eu) was initiated by Bart Everts (Leiden University Medical Center, Netherlands) and Jan Van den Bossche (Amsterdam UMC, Netherlands) as an extension of the Dutch ImmunoMetNet initiative (www.immunometnet.com). In March 2023, a group of prominent and emerging leaders in immunometabolism from across Europe convened to form this network. Tasks were allocated during the initial meeting, leading to rapid progress. Thomas Weichhart, Luciana Berod, and Bart Everts applied for the group to become an EFIS-IL study group, resulting in the approval of the ImmunoMetEurope study group in June 2023.

The conference organizing committee, consisting of Daniel Ketelhuth, Claus Desler, Thekla Cordes, Mauro Corrado, and Rafael J. Argüello, explored various options for hosting the first conference. The Danish members, Daniel Ketelhuth and Claus Desler, proposed seeking support from the Novo Nordisk Foundation (NNF). An application was submitted to the NNF's "Conferences, Symposia, and Workshops" call in October 2023, and by December, the organizers received a grant confirmation. The conference was subsequently announced on LinkedIn and X (formerly Twitter, @immunometeurope) as the "1st European Immunometabolism Conference: Metabolism Meets Immunology" to be held in Køge, Denmark, in June 2024.

The organizing committee prepared the conference website and outlined the conference format, emphasizing the participation of PhD students and postdocs. The NNF grant and host venue cost estimations led to a registration fee of €100 for students and postdocs, with a slightly higher fee for group leaders/professionals. This fee included participation, accommodation, and meals. Support from the European Federation of Immunological Societies and the European Journal of Immunology (EFIS-EJI) allowed 23 early career scientists to receive travel grants, achieving the goal of primarily young scientist attendance.

Pre-registrations opened in February 2024, and by the deadline, over 180 individuals expressed their interest. The organizing committee reviewed scientific abstracts and expanded participation to over 150 attendees by arranging shared accommodation for PhD students and postdocs. Approximately 170 participants were invited from 22 countries, with 18 young career scientists selected for oral presentations and 85 abstracts chosen for poster presentations (Figure 1).

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Daniel F. J. Ketelhuth and Claus Desler are chairs of 1st European Immunometabolism Conference.

Daniel F. J. Ketelhuth, Claus Desler, Thekla Cordes, Mauro Corrrado, and Rafael J. Argüello are organizers of 1st European Immunometabolism Conference.

Bart Everts and Jan Van den Bossche initiated the European Immunometabolism Network (EIMN).

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Figure 1. Picture of the European Immunometabolism Network taken during the 1st European Immunometabolism conference on June 27, 2024, in Køge near Copenhagen, Denmark.

2. Session I – metabolic regulation of innate immunity

Bart Everts (Leiden University Medical Center, Netherlands) kicked off the scientific program of the conference with a presentation on the role of *O*-GlcNAcylation, a nutrient-sensitive post-translational modification that is still understudied in immune cells, in shaping the functional properties of dendritic cells (DCs). He showed that the *O*-GlcNAcylation machinery was selectively increased in DCs priming T helper 2 responses and that specifically T_H2 priming by DCs relies on *O*-GlcNAcylation both in vitro and in vivo, thereby identifying *O*-GlcNAcylation as a potential novel target to shape type 2 immunity.

Thomas Weichhart (Medical University of Vienna, Austria) introduced the concept of a commensal metabolism of macrophages supporting other tissue cells by providing metabolic help. He presented recent data that macrophages, via an mechanistic target of rapamycin complex 1 (mTORC1)-Arginase1-dependent pathway, secrete the polyamines spermine and spermidine, which are being taken up by colon epithelial cells promoting their proliferation and metabolism [1]. He reported novel findings on the global metabolic secretome of bone marrow-derived macrophages and how distinct metabolites promoted the growth and proliferation on mouse colon organoids thereby generalizing the commensal metabolism concept.

David Sancho (Centro Nacional de Investigaciones Cardiovasculares, Spain) shared unpublished results on how conventional type 1 DCs (cDC1s) show a different oxygen consumption than cDC2s upon stimulation. To investigate the relevance of the mitochondrial electron transport chain (ETC) in DC immunogenicity, they generated mice with impaired ETC complex III function in DCs. ETC complex III impairment attenuated poised or adjuvant-triggered cDC1 activation, migration, and capability to prime T cells for anti-cancer immunity, while it had a mild effect on cDC2s. Mechanistically, the loss of complex III in cDC1s led to a deregulated redox and metabolite balance causing DNA hypermethylation of PU.1-binding regions. This diminished early stimulus-induced gene expression linked to the immunogenic responsiveness of cDC1s. Their findings show how ETC differentially regulates the immunogenic function of cDC subsets.

Young researchers selected for short talks in this session discussed (i) the role of transferrin receptor 2 in the modulation of the metabolic changes in response to IFNγ in macrophages (Maria G. Ledesma-Colunga; Dresden University of Technology, Germany), (ii) neutrophil aging in the immunometabolic response to high-fat diet (Anna Parolini; Università degli Studi di Milano, Spain), and (iii) Ubc13 in mitochondrial regulation and innate immunity (Melanie Grusdat; University of Luxembourg).

3. Session II – metabolic regulation of adaptive immunity

Linda Sinclair (University of Dundee, Scotland) talked enthusiastically about nutrient (amino acid) requirements for T cells and the importance nutrient availability has on the regulated proteomic remodeling that occurs after T cell activation [2]. She focused on a yet-to-be-published story about T follicular helper cells and their requirement for sustained amino acid transport via amino acid transporter SLC7A5 for the maintenance of a functional humoral response.

Mauro Corrado (University of Cologne, Germany) presented his work on the role of cardiolipin, the flagship inner mitochondrial membrane lipid, in dictating the mitochondrial dependency of T cells during different phases of an immune response. Moreover, he presented the immune phenotype of a mouse model of cardiolipin synthesis deficiency in T cells describing the systemic- and tissue-specific consequences of a metabolic deficiency in the T cell compartment.

Luciana Berod (University Medical Center Mainz, Germany) summarized her past work on the fatty acid metabolism of T cells [3] and introduced her new work linking fatty acid metabolism with post-translational modifications. She showed how modulation of fatty acid metabolism affects protein acetylation and histone modifications influencing T cell fate.

The afternoon session of early career presentations showcased Yu-San Kao (Johannes Gutenberg-University Mainz, Germany) who spoke about targeting ACC1 in T cells and how this ameliorates psoriatic skin inflammation. Megan Teh (University of Oxford, United Kingdom) presented work from her PhD on the metabolic perturbations of CD8 T cells on iron restriction, in particular highlighting aspartate. Finally, Simon Hirschberger (Ludwig-Maximilian-University, Germany) wrapped up the afternoon talks with his presentation on the impact of major surgery driving cytotoxic T cell immunometabolic paralysis through stress-induced mitochondrial hyperfusion.

4. Session III – immunometabolism in cancer

Anna Schurich (King's College London, United Kingdom) introduced the work of her PhD student Katie Flaherty on the metabolic regulation of differentially co-stimulated chimeric antigen receptor T cells. Building on her previous findings [4],

she presented a new method for assessing T cell responses in an ischemic gradient, designed to better mimic the solid tumor microenvironment as found in vivo. The work of her group demonstrates the distinct impact of co-stimulation on directing chimeric antigen receptor T cell nutrient uptake.

Massimiliano Mazzone (VIB-KU Leuven, Belgium) presented the work of his PhD student Samantha Pretto on metabolic fitness of CD8⁺ T cells in pancreatic cancer. Starting from a two-step approach consisting in the next-generation sequencing and single-cell transcriptomic analysis of a pool of T cells transduced with an in-house sgRNA-based metabolic library, the lab has identified ELOVL1 (the enzyme involved in the elongation of very long chain fatty acid) as a metabolic vulnerability within the tumor microenvironment. The study has shown that ELOVL1 inhibition promotes proliferation and effector functions in CD8⁺ T cells, while reinforcing the memory phenotype. In patients, ELOVL1 low CD8⁺ T cells offer an indication of better disease outcome and response to immune checkpoint blockade.

Invited session speaker Per Thor Straten from the nearby University of Copenhagen (Denmark) presented earlier and new work on how high-intensity exercise modulates anti-tumor immunity.

This exciting session was concluded by three early career researchers. Sofie Hedlund Møller (Ludwig Institute of Cancer Research/Université de Lausanne, Switzerland) presented her work on the IFN-mediated effector program of tumor-specific CD8⁺ T cells in the tumor-draining lymph node. Karen Slattery (Trinity College Dublin, Ireland) talked about dysregulated lipid metabolism as a key driver of immunosuppression in ovarian cancer and Paulina Garcia-Gonzalez (Centre d'Immunologie de Marseille-Luminy, France) presented novel data on metabolic plasticity and epigenetic dynamics in acute myeloid leukemia, providing insights into therapeutic resistance and immune modulation.

5. Session IV – new technologies and translational approaches

David Finlay (Trinity College Dublin, Ireland) presented a novel approach of measuring nutrient uptake in single cells by using clickable probes instead of fluorescently tagged, avoiding altered specificity of labeled nutrients. He started by introducing the recently published glutamine uptake assay with single cell resolution (QUAS-R) technique, employing methionine analogs L-homopropargylglycine and L-azidohomoalanine for measuring glutamine uptake via Slc1a5 [2]. Next, he expanded this idea to measuring fatty acid uptake and presented the first data using a clickable analog of oleic acid as well as natural plant-based sterculic acid. Finally, he introduced a combinational approach, allowing measuring the uptake of multiple nutrients at the same time.

Jan Van den Bossche (Amsterdam UMC, Netherlands) introduced his talk by summarizing how he entered the field of immunometabolism research when he discovered how suppression of mitochondrial metabolism by nitric oxide in inflammatory macrophages blocks future responses to IL-4 stimulation [5]. Next, he used his group's work on 2-hydroxyglutarate [6] and immunometabolic profiling of human white blood cells as examples of how and why future immunometabolism research should take into account timing, spatial distribution, in vivo regulation, and the translation to the human setting in which cellular metabolic pathways are influenced by systemic metabolism and environmental factors including lifestyle.

Rafael José Argüello (Center of Immunology of Marseille-Luminy, France) concluded the new technologies session by unveiling the patented SCENITH™ method, which uses protein synthesis as a metric to profile energy metabolism [7]. Since the publication of this paper in December 2020, co-authored with Alexis Combes, now a principal investigator (PI) at UCSF, Argüello has spearheaded a collaborative network to explore metabolism in human samples. His presentation underscored the necessity for the immunometabolism community to push the boundaries of technology further. He introduced Rosario Lavignolle, a PhD student, to discuss Epic-SCENITH – an innovative expansion of SCENITH into epigenetics. This method probes the interactions between functional metabolic dependencies and epigenetic chromatin modifications in rare human cell populations, ex vivo. Argüello emphasized that embracing single-cell multi-omics, integrating epigenetic, transcriptomic, metabolomic, and spatial data, is crucial for advancing our understanding of metabolic regulation in immunity.

Before the lunch break, three early career researchers presented their work on generating metabolically superior T cells by genetically enabling them to digest trehalose as a novel cancer immunotherapy (Yarden Engel, The Hebrew University of Jerusalem, Israel). Birte Dowerg (University of Braunschweig, Germany) talked about the quantification of mitochondrial metabolism and fluxes in anchorage-independent cultures during viral infections, and Kristine Bertheussen (Leiden University, Netherlands) presented a novel Click-based approach to faithfully quantify oleic acid uptake at the single-cell level.

6. Session V – immunometabolism in cardiometabolic diseases

Soraya Taleb (Paris Cardiovascular Research Center PARCC, Inserm, France) discussed how intestinal indoleamine 2,3-dioxygenase 1 activity is influenced by a high-fat diet and fiber deficiency and how this affects the development of atherosclerosis [8]. Taleb's work also highlighted the importance of the other tryptophan catabolic pathways (indoles and serotonin) in gut inflammation and atherosclerosis. With her group, they showed that reducing intestinal serotonin synthesis lowered vascular inflammation and emphasized the indole/AhR pathway's ability to prevent atherosclerosis.

Giuseppe Danilo Norata (Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy) discussed the crosstalk between systemic and immune cell lipid metabolism with a focus on adaptive immune response. Several players, known to play a role in lipoprotein metabolism, were shown to modulate cellular immune function [9]. This is the case for apolipoprotein E, which regulates cholesterol availability in the DC membrane and therefore modulates MHC-II clustering and T cell activation. Similarly, the low-density lipoprotein receptor (LDL-R) receptor plays a key role in CD8 T cell activation by delivering LDL-cholesterol in the lysosome, a mechanism crucial for mTORC1 complex clustering on the lysosomal membrane and CD8 T cell immunometabolic reprogramming. Finally, also SREBP1c plays a key role in modulating T regulatory cells' suppressive function.

Kate Lykke Lambertsen from the University of Southern Denmark was an invited local speaker who presented how systemic low-grade chronic inflammation affected stroke outcome, focusing on the role of soluble tumor necrosis factor (TNF) versus transmembrane TNF in obesity and cerebrovascular disease. Three early career researchers presented their work on immunometabolism in cardiometabolic diseases. Gareth Purvis

(University of Oxford, United Kingdom) presented his work on how exposure to elevated cholesterol resulted in a non-reversible epigenetic and metabolic shift in macrophages and the association with increased residual inflammatory risk. Jakob Hansen (University of Southern Denmark, Denmark) talked about insights into the role of NPC2 in vascular inflammation and atherosclerosis. Aitor Jarit Cabanillas (CNIC, Spanish National Centre for Cardiovascular Diseases, Spain) showed how calcineurin/nuclear factor of activated T-cells (NFAT) signaling contributes to beta-glucan-induced trained immunity by shaping the epigenomic landscape.

7. Session VI – immunometabolism in infections

Thekla Cordes (University of Braunschweig, Germany) started the last day of the conference with a talk on the signaling roles of mitochondrial metabolites influencing inflammation. She presented novel findings about the immunometabolite itaconate and the regulation of succinate dehydrogenase influencing mitochondrial metabolism [10]. The group's work further highlights the fate of itaconate by applying mass spectrometry and tracing approaches. The findings demonstrate how the dynamic regulation of itaconate metabolism might be beneficial in diseases associated with low oxygen availability.

Dirk Brenner (Luxembourg Institute of Health and University of Luxembourg, Luxembourg) discussed the metabolic differences among various T helper cell subsets and their functional implications. He presented novel insights into the regulation of reactive oxygen species (ROS) in T_H17 cells within the gut, particularly in the context of gastrointestinal infections. The accumulation of mitochondrial ROS was shown to disrupt mitochondrial gene expression and oxidative phosphorylation (OXPHOS), leading to a decrease in cellular adenosine triphosphate (ATP) concentration. These mitochondrial impairments were linked to inefficient activation of the cytosolic phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway, which interfered with the translation of IL-22. IL-22 is essential for maintaining intestinal barrier integrity and ensuring mouse survival during bacterial gastrointestinal infections thus exposing a novel metabolic pathway that is crucial for anti-bacterial mucosal immunity.

Maxim Nosenko (Trinity College Dublin, Ireland) introduced the first results from MSCA Postdoctoral Fellowship project TANK_Sepsis, which is focused on targeting amino acid uptake in natural killer (NK) cells during bacterial infections and sepsis. He presented functional and metabolic characterization of NK cells from the peritoneal cavity of mice upon challenge with lipopolysaccharide (LPS), suggesting two waves of NK response. He also shared preliminary results characterizing the phenotype of murine NK cells upon infection with either *Escherichia coli* or *Staphylococcus aureus* pathogens.

This "Immunometabolism in infections session" was concluded by three early career researchers. Fran Prenen (Rega Institute for Medical Research, Belgium) talked about how janus kinase (JAK)/signal transducer and activator of transcription (STAT) inhibition restores disease tolerance in malaria-infected glucocorticoid receptor knockout mice by preventing lethal hypoglycemia. Lucy Jackson-Jones presented the work of Sheila Macharia (Lancaster University, United Kingdom) on differential responses and metabolism in the pleural cavity and peritoneal macrophages regulated by IgM. Graham Heieis (Leiden University Medical Center, Netherlands) presented his novel data on how O-GlcNAcylation acts as a metabolic break to maintain macrophage residency.

8. Keynote lectures, posters, and round table session

Next to the regular scientific sessions, three keystone lecturers were invited and the evenings were concluded with two very interactive poster sessions in which a total of 85 posters were presented.

Christoph Hess (University of Cambridge, Cambridge, United Kingdom) gave the first keynote lecture on Wednesday and summarized a recent study in which his group revealed nicotinamide adenine dinucleotide (NAD) synthesis induced by Epstein–Barr virus as a metabolic Achilles' heel of virus-induced B cell transformation that can be targeted to modulate Epstein–Barr virus -related diseases [11]. The other two keynote lectures were provided by Inge Marie Svane (University of Copenhagen, Denmark) on Thursday on how to make T cells metabolically fitter to fight cancer and by Elina Zuniga (University of California San Diego, USA) on Friday who talked about multi-system responses and omics approaches to infection [12].

The round table panel debate, chaired by Claus Desler and Thekla Cordes, included experts Kristine Williams (Novo Nordisk Fonden, Denmark), Patrick Schaefer (Cell Metabolism), Alfredo Gimenez-Cassina (Nature Metabolism), Ditte Boilesen (Loma Therapeutics, Denmark), and Joachim Stoltenberg Granhøj (CCIT, Herlev Hospital, Denmark). Key discussion topics included diversity in the field, future potential and challenges of immunometabolism, and the interconnectedness of clinical research, basic science, and industry perspectives. The panel emphasized the importance of interdisciplinary collaboration and diversity for scientific innovation and excellence.

The debate was particularly valuable for students and early career scientists, providing them with a comprehensive view on the diverse career paths. The insights on diversity and interdisciplinary collaboration shared by the esteemed panelists will undoubtedly contribute to the ongoing progress and innovation in immunometabolism.

9. Concluding remarks and future initiatives of EIMN

Before the closing remarks from the organizing committee, the best three oral and poster presentations prizes were awarded to Megan Teh, University of Oxford; Karen Slattery, Trinity College Dublin; Fran Prenen, KU Leuven; Rosario Lavignolle-Heguy, Aix Marseille Université; Fabrizia Bonacina, University of Milan; Alina Brosque, Tel Aviv University. Moving forward, EIMN aims to grow and solidify its base in Europe, supporting initiatives that promote collaboration, training, and networking, especially for young scientists. EIMN aspires to transform itself into a society and plans to hold its next conference in Luxembourg in 2026. Meanwhile, everybody who is interested in immunometabolism or interested in contributing to the initiatives of EIMN can join by signing up for upcoming newsletters via a link that will be published on the www.immunometnet.eu website and that is communicated with all visitors of the 1st EIMN conference.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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