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# Artificial intelligence meets the world experts; updates and novel therapies in autoimmunity - The 14th international congress on autoimmunity 2024 (AUTO14), Ljubljana

Naim Mahroum [a,*], Abdulrahman Elsalti [a], Maisam Al Shawaf [a], Mohammad Darkhabani [a], Abdulrahman Alwani [a], Ravend Seida [a], Muhammet Tayfur Ertas [a], Ayse Gulnihan Simsek [a], Mustafa Awad [a], Mona Habra [a], Mohamad Aosama Alrifaai [a], Dimitrios Bogdanos [b], Yehuda Shoenfeld [c,d]

[a] International School of Medicine, Istanbul Medipol University, Istanbul, Turkey
[b] Department of Rheumatology and Clinical Immunology, University Hospital of Larisa, School of Medicine, University of Thessaly, Larissa, Greece
[c] Zabludowicz Center for autoimmune diseases, Sheba Medical Center, Ramat-Gan, Israel
[d] Reichman University, Herzliya, Israel

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ABSTRACT

The bi-annual international congress on autoimmunity is a huge opportunity for the medical community to discuss the latest updates in the field. During the 14th congress 2024 (AUTO14) in Ljubljana, artificial intelligence (AI) occupied special attention due to its recent and ongoing unequivocal role in various medical fields including autoimmunity. For instance, through a challenging debate between world-experts and the most popular AI bot used (ChatGPT), several clinical cases including a case of vasculitis were discussed in the plenary sessions. ChatGPT agreed with the clinical decisions made by the experts nevertheless, the bot added additional aspects related to the specific case. In this regard, ChatGPT emphasized the need for osteoporosis prophylaxis in a patient planned to be treated with systemic steroids for a long time. Furthermore, AUTO14 included the newest updates on most autoimmune disorders, distributed among tens of sessions. Among others, infection and autoimmunity, the sequalae of the pandemic of COVID-19, as well as COVID-19 vaccines were discussed as well. Due to the high numbers of the works presented, and for ensuring that important updates are not missed; we divided our paper into sections. The subtitles throughout the paper correspond to different sessions of the congress, all presenting new updates in the field. A figure aiding in navigating throughout the paper was also provided.

## 1. Introduction

For more than 25 years, the community of autoimmunity has used to meet with its members from all around the world. The meeting, occurring bi-annually, took place this time in Ljubljana, Slovenia, making the 14th international autoimmunity congress (AUTO14), 2024. In fact, in the last couple of years, the world of autoimmunity has drawn the attention of the scientific community worldwide [1]. While autoimmunity is an old and prestigious field of medicine; the role it has played during the pandemic of COVID-19 contributed to an increased interest and recognition. Autoimmunity, the interaction between the host and immune system; and autoimmune diseases, when the concerned interaction produces diseases, is the basis for the implication of autoimmunity in medicine. The manifestations of autoimmune disorders are numerous, ranging from nonspecific general symptoms to more specific and system-directed ones. Of importance, are the triggers of autoimmune diseases. Among others, environmental factors like infections, adjuvants, and chemicals constitute the majority of stimulators [2]. Once autoimmune diseases emerge, the diagnosis is very challenging and therefore, diagnosis of autoimmune diseases is an active field of research. Similarly, as self-directed antibodies "autoantibodies" form the solid base of diagnosis, autoantibody detection challenges the developers of diagnostics for better, faster, safer, and cost-effective methods. COVID-19 is not the only one to accuse of the innovations in

* Corresponding author at: International School of Medicine, Istanbul Medipol University, Kavacık, Göztepe Mah, Atatürk Cd. No:40, 34810 Beykoz, Istanbul, Turkey.
*E-mail address:* naim.mahroum@gmail.com (N. Mahroum).

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1568-9972/© 2024 Elsevier B.V. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

autoimmunity. Artificial intelligence (AI) has revolutionized the world of autoimmunity as well [3]. Accordingly, AI and its famous bot, the ChatGPT, received a special session during the AUTO14. In a very interesting plenary session, ChatGPT was challenged with clinical scenarios given by experts in the field of autoimmunity and rheumatology. Interestingly, the AI bot agreed with the management of the patients made by the specialists, however, it drew attention to additional aspects like the prevention of osteoporosis or vaccination during immunosuppression treatment.

During AUTO14, researchers, experts, and young enthusiasts have come across to present and discuss the latest developments in the field of autoimmunity. Due to the fact sessions of the congress were made of top lectures in autoimmunity, we brought here in our current paper, the pearls of the meeting. Divided into sections concerned with autoimmunity, lectures were grouped under subtitles of the related domains. With around 500 abstracts presented, making it challenging to conclude, hereby we aimed to conclude the main leading points and latest innovations in the field of autoimmunity.

To facilitate the navigation throughout the paper, for its titles and subtitles the reader is referred to Fig. 1.

## 2. Artificial intelligence, data, prediction, monitoring, and prevention in AUTO14

In recent years, AI has taken the world by storm, spreading its roots into every specialty, and the field of autoimmunity is no exception [3]. The topic of large language model (LLM), the ChatGPT, was the focus of discussion throughout AUTO14. During the congress, Darkhabani discussed the possibilities and benefits of using OpenAI's ChatGPT in autoimmunity and research, with the emphasis on its potential use in clinics, in conjugation to physicians, to build differential diagnosis lists based on basic minimal information like patient history, aiding to widen the possible diagnoses. Actually, ChatGPT could also be used to help writing up reports to save valuable time for physicians, such as writing letters to insurance companies or patient reports. The same presenter also discussed the possibility –and controversy—of using ChatGPT in scientific writing and medical research. Despite that, there are various limitations, such as bias, plagiarism, and inaccuracy of citations. Moreover, potential future threats of ChatGPT, such as security risks, data breaches, and malicous attacks were also addressed during the discussion.

The AUTO14 also had a session named as "Hippocrates versus ChatGPT", where after a small introduction about ChatGPT by the cyber intelligence expert Yoad Dvir, leading professors in the autoimmunity field took turns to challenge ChatGPT. The AI was given real autoimmune cases seen by the experts and observed how ChatGPT dealt with the patients, from diagnosis to treatment plans. Surprisingly, ChatGPT agreed with the diagnosis made by the clinicians and provided comprehensive treatment plans in addition to preventive therapy for undiagnosed conditions patients had the risk factors for. For instance, a patient diagnosed with vasculitis and planned to start high dose corticosteroids therapy, ChatGPT recommended on screening and treatment of osteoporosis. The addition of vitamin D and calcium was suggested as well. Furthermore, in another case, vaccinating the patient against common infections such as pneumococcal ones, was highly advised.

ChatGPT was not the only AI tool discussed in AUTO14. For instance, Shapiro demonstrated the possibility of using a machine learning tool PredictAI to detect and identify undiagnosed psoriatic arthritis (PsA) cases early. The tool discussed proved useful in detecting half the undiagnosed PsA cases at a 90 % specificity preventing the usual delay in

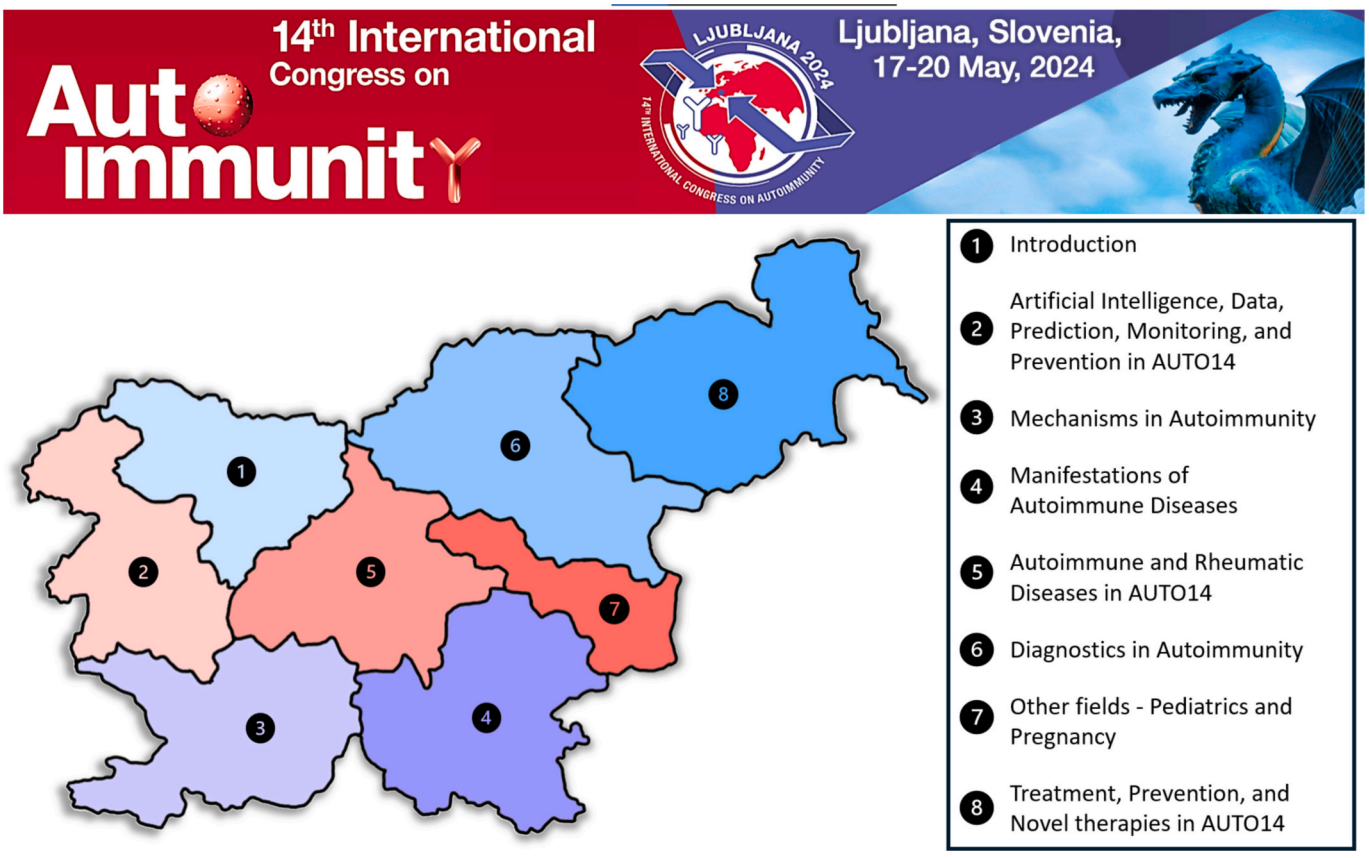


**Fig. 1.** The sections of the article designated as parts of Slovenia. As illustrated, the 8 sections presented refer to the subtilties of the manuscript starting from the introduction and moving forward. Of note, the names of the sections in the manuscript and here in the map are correlated to the names of the sessions of AUTO14. The map aids the reader in navigating throughout the paper.

diagnosis of PsA for up to a year [4]. Furthermore, Arnaud from France gave a compelling presentation about digital health technologies and there application in the field of autoimmunity. The digital tools presented proved especially useful in the field of rare connective tissue diseases (rCTDS), improving patient monitoring, adherence, and outcomes [5].

There is no secret that the current state of AI development is still in its early stages, and heavily depends on human input and training of the AI. Or Degany highlighted this in AUTO14 by suggesting to move away from training AI in the conventional methods, and trying to use AI in a targeted manner for complex autoimmune cases that do not follow traditional evidence-based approaches.

Seunghee Cha from the department of oral and maxillofacial diagnostic sciences in the University of Florida discussed a data-driven study for the stratification of pediatric patients suspected with Sjogren's disease by using machine learning. The study cross-validated machine learning models applied to a pediatric cohort, resulting in the creation of a physician-friendly scoring system assisting physicians in clinical reasoning for long-term monitoring of these patients [6].

In fact, systemic autoimmune connective tissue diseases (CTDs) pose a great challenge for physicians due to their rare nature, robust pathological processes, and heterogeneity of these diseases. During AUTO14, Schneider proposed a solution for this matter – big data analysis can help identify more homogeneous subgroups and clusters, where there should be a standardized easily accessible core data set for all CTDs [7].

Zandman-Goddard gave an update about the use of precision medicine in SLE via integrating molecular and biochemical markers, which can aid in identifying specific personal markers that can assist in choosing the proper medication for the individual SLE patient. Zandman-Goddard concluded that precision medicine enables the physician to use additional tools to identify subsets of lupus patients [8].

It has been long known that severe autoimmune hemolytic anemia (AIHA) is among the contributing factors for mortality of SLE patients. Pons-Estel and colleagues from Argentina aimed to predict the occurrence of severe AIHA by using Cox proportional hazards regressions and logistic regression analyses to examine the association of severe AlHA with mortality. It turns out that male sex and higher disease activity at diagnosis are independent predictors of an early course severe AIHA occurrence [9].

In his talk, Luis Eduardo Andrade discussed the vital part that autoantibodies play in advancing Precision Medicine (PM) for autoimmune diseases. The author explained how certain disease related features can relate to different groups of autoantibodies like anti-SS-A/Ro60 and anti-Sm in SLE. How autoantibodies such as rheumatoid factor (RF), anticyclic citrullinated peptide antibodies (ACPA), and anti-topoisomerase I or Scl-70 give insights into disease heterogeneity as well as therapeutic decision making in RA and SSc were also demonstrated. Andrade emphasized the potential of novel technologies such as AI in integrating autoantibodies with other complementary markers to enhance patient-centered management and fully exploit the benefits of PM in autoimmune diseases [10].

In recent years, autoimmunity and autoantibodies were found to be implicated in atherosclerosis and cardiovascular disease. During AUTO14, Hanna Grasshoff from the University of Lübeck in Germany discussed how CXC-motif-chemokine receptor 3 (CXCR3) autoantibodies are linked with cardiovascular end-organ damage, predicting all-cause death, cardiac morbidity and mortality in conjugation with the acceleration of atherosclerosis [11].

## 3. Mechanisms in autoimmunity

During AUTO14 several sessions including plenary, oral and poster ones, addressed the leading mechanisms of autoimmunity. The discussed ones were arranged as follows:

### 3.1. Infection and autoimmunity

AUTO14 witnessed the signing ceremony of the third edition of the famous book "Infection and autoimmunity" [2]. Edited by Mahroum, Watad, and Shoenfeld, the book focused on the basics of infection as a trigger for, associated with, and accompanying autoimmune diseases. Mahroum presented the concept and history of infectious and autoimmunity with acute rheumatic fever as the historical example of this correlation. The recent pandemic of COVID-19 and its autoimmune related phenomena were presented as well [12,13]. In the same regard, the post-COVID syndrome (PCS), a condition that affects approximately 5 % of patients after a mild-to-moderate SARS-CoV-2 infection was discussed in details during the AUTO14. For example, PCS was found to share similarities with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) [14]. Studies illustrated various potential mechanisms behind PCS and ME/CFS, such as inflammation, autoantibodies, circulatory issues, and viral persistence. Autoimmunity is believed to play a significant role in the pathophysiology of ME/CFS [15]. Specifically, the ß2-adrenergic receptor antibody (ADRB2 AAB) is identified as a key discriminator of PCS, with high levels strongly associated with fatigue and vasomotor symptoms in PCS-ME/CFS patients. Treatments targeting autoantibodies, including B cell depletion and immunoadsorption, have shown promise in managing ME/CFS. Ongoing trials are investigating the efficacy of AAB depletion through immunoadsorption in PCS and ME/CFS, with initial observations suggesting positive outcomes in patients with post-infectious conditions like post-COVID-19 ME/CFS. Similarly, cases of two female patients who developed RA following SARS-CoV-2 infection have been reported. The first patient, aged 79, exhibited arthritis in the shoulder and hand joints, while the second patient, aged 74, had polyarthritis affecting multiple hand joints. Both patients showed elevated inflammatory markers and were treated with medications like corticosteroids and methotrexate, leading to improvement of symptoms. These cases suggest a potential link between SARS-CoV-2 infection and the development of autoimmune conditions such as RA [16,17]. Furthermore, SARS-CoV-2 infection has an important impact on patients with thyroid autoimmunity. SARS-CoV-2 can enter thyroid cells through the ACE2 receptor, leading to various thyroid disorders like subacute thyroiditis, thyrotoxicosis, and non-thyroidal illness syndrome [18]. COVID-19 can trigger autoimmune thyroid diseases like Hashimoto thyroiditis and Graves' disease by interfering with the immune system and inducing autoantibodies. Studies suggested a higher COVID-19 frequency in patients with thyroid autoimmunity, with more severe disease in those with thyroid conditions [19]. Mechanisms like immune system activation and molecular mimicry are believed to induce autoimmunity.

In terms of vaccination, COVID-19 vaccines have led to reported autoimmune adverse events [20]. While a causal link has not been confirmed, similar immune mechanisms reported in post-COVID autoimmune diseases may play a role in vaccine-induced autoimmunity, possibly through molecular mimicry and autoantibody production [21,22]. Besides, cases of new-onset autoimmune diseases following the COVID-19 Sputnik vaccination have been reported. Between March 2021 and December 2022, 28 patients developed autoimmune diseases after receiving the Sputnik vaccine. The observed autoimmune manifestations included neurological, hematological, thrombotic, autoimmune hemolytic anemia, rheumatological, and endocrine disorders. While the Sputnik vaccine is generally considered safe, adverse effects such as thrombosis and Guillain-Barre were notable in this group of patients [23].

Vaccines and autoimmunity were not confined to COVID-vaccines only. Another study presented a case of a healthy 15-year-old girl who developed severe psychiatric and neurological symptoms after receiving the HPV vaccine. She tested positive for various infectious agents and autoantibodies against nervous system antigens, leading to autoimmune encephalitis, pediatric acute-onset neuropsychiatric syndrome, and chronic fatigue syndrome diagnoses. Genetic testing revealed

susceptibilities to autoimmune diseases. In fact, post-vaccination activation of latent infections is noted with HPV, SARS-CoV-2, and influenza vaccines, potentially causing autoimmune and inflammatory conditions in genetically predisposed individuals. Triggers like cellular stress from vaccines, particularly those with aluminum adjuvants like Gardasil, may play a role in activating latent infections [24,25].

During the sessions related to infection and autoimmunity in AUTO14, the development of SARS-CoV-2-specific T cell immunity post-infection or vaccination, discussing cross-reactive T cell immunity and various viral proteins were addressed. Moreover, the characteristics of SARS-CoV-2-specific T cells in different COVID-19 stages, including long-COVID, aiming for personalized therapy, particularly for vulnerable populations like chronic kidney disease patients was also discussed along the immunogenicity of COVID-19 vaccines and the importance of immune monitoring in both immunocompetent and immunocompromised patients [26–28].

Another domain of interest is immune checkpoint inhibitors (ICIs) as they have revolutionized cancer treatment by blocking signals in tumor cells, leading to cell death. Common ICIs include CTLA-4, anti-PD-1 (pembrolizumab, nivolumab), and anti-PD-L1 (atezolizumab, durvalumab, avelumab). However, ICIs can cause immune-related adverse events (irAEs) affecting multiple organ systems differently from typical autoimmune diseases [29]. The impact of ICIs on autoimmune disease patterns, especially during the COVID-19 pandemic, is a topic of interest for understanding epidemiological shifts in autoimmune conditions under ICIs and that was presented by Mahroum [2].

### 3.2. The autoimmune/inflammatory syndrome induced by adjuvants

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was first introduced by Shoenfeld as an autoimmune phenomenon induced by adjuvants in 2011 [30]. ASIA, also known as Shoenfeld's syndrome, encompasses several autoimmune conditions/phenomena induced following the exposure to substances with adjuvant activity [31,32]. However, the spectrum of ASIA syndrome has been proposed to include tattoos, implants, and among other etiologies.

Tervaert discussed the correlation between ASIA and implants. Implants like breast and mesh implants have been linked to ASIA (Shoenfeld's syndrome), yet the precise pathophysiological mechanisms remain unclear, leading to debate within the scientific community about the syndrome's validity, particularly given its overlap with conditions like fibromyalgia and chronic fatigue syndrome [33]. In fact, very recent evidence has shown that there is a causal link between implants and ASIA – in line with Bradford Hill criteria – and significant improvement of symptoms has been observed in patients after implant removal [34]. Yet, many physicians are still very skeptical about this condition. Patients affected by ASIA often report feeling delegitimized and stigmatized, and having difficulty accessing treatment and understanding the nature of their illness. This "epistemic injustice" – lack of recognition of illness experience by healthcare providers – has been demonstrated to foster the formation of online communities where patients share experiences and search for emotional support. In these communities, patients often adopt a biomedical perspective on their condition, which may conflict with that of physicians who do not believe in ASIA. This contributes to the creation of a skeptical "physician effect" which in turn may fuel the hype around this unexplained condition, potentially causing further harm to patients [34].

Szappanos also presented a case report on a 42-year-old female patient with silicone breast implants since 2005 and replacement in 2015. In 2018, she was diagnosed with heart failure accompanied by a left ventricular ejection fraction of 20 %. In 2019, endomyocardial biopsy confirmed lymphocytic myocarditis. Intracapsular rupture of breast implants was discovered via chest CT, prompting surgical removal alongside high-dose steroid treatment, therapeutic plasma exchanges, and intravenous immunoglobulin therapy based on her myocarditis and suspected ASIA syndrome history. After 127 days of intensive therapy, the patient was discharged with improved cardiac function and commenced monthly IVIG therapy.

Tervaert also highlighted the overlap between ASIA caused by breast implants and Sjogren syndrome, with a focus on dry eyes. The discussion compared ASIA due to breast implants, Sjogren syndrome, and healthy individuals, where 80 % of ASIA patients reported dry eyes, with 73 % exhibiting impaired tear production and 31 % showing severe impairment similar to healthy individuals. The results showed that dry eyes experienced in ASIA do not meet the criteria for Sjogren syndrome. Therefore, measuring IgG/IgG subclass levels to differentiate sicca symptoms between ASIA and SS patients could be worthwhile [35]. Additionally, it was also found that patients with ASIA have elevated serum prolactin levels, compared to patients without ASIA [36].

Furthermore, tattoos and autoimmunity in the context of ASIA syndrome was discussed by Tanay. Two cases were presented, concluding that individuals with preexisting psoriasis, pyoderma gangrenosum, susceptible to the isomorphic phenomenon should avoid tattooing. Moreover, individuals with immune suppression and/or silicone implants are at risk of ASIA syndrome induced by tattoos and should avoid it altogether [37]. To further support the notion that tattoos can contribute to autoimmunity, Elsalti provided results of a study consisting of 137 participants with tattoos. The study investigated the difference between two groups, those with tattoos and autoimmune diseases, and those without autoimmune diseases. Interestingly, the color of the tattoos, particularly black one, was significantly related to autoimmune diseases. The composition of substances such as cobalt, mercury, and aluminum, which increases the likelihood that tattoo and autoimmunity could serve as the leading mechanism and requires further analysis. In fact, not only tattoos, but other cosmetics like paraffin oil have also been reported to cause ASIA syndrome, as highlighted by Habra [37].

Vaccination is one of the main strategies to prevent infections, especially in children with immune-mediated diseases, who are frequently immunocompromised by the disease or its treatment. The hazards of vaccination in immunocompromised children was discussed by Toplak [38]. Inborn errors of immunity (IEI) represent a group of more than 450 diseases divided into 10 groups, with different levels of immunosuppression. Severe combined immune deficiencies (SCID) make vaccines ineffective, leaving stem cell transplantation as the only curative approach. Additionally, live attenuated vaccines may cause infection in SCID and are therefore contraindicated. Children with autoimmune rheumatic diseases (ARD) are also immunocompromised hosts, mainly due to the therapy. Recommendations for vaccination of children with ARD have recently changed and decisions should consider safety, immunogenicity, and the risk of infections. Non-live vaccines, including SARS-CoV-2 vaccines, are safe and immunogenic but may have lower effectiveness compared to healthy children. In IEI, live vaccines are not administered. In ARD, MMR boosters can be given, even in patients on methotrexate or biologics which is supported by recent studies of safety and efficacy [39]. VZV vaccination should also be considered, especially in settings of higher infection risks.

### 3.3. Cytokines and autoimmunity

Neuropsychiatric lupus (NPSLE) impacts around half of individuals with SLE, causing cognitive dysfunction, memory decline, as well as feelings of depression and anxiety. Moore et al., implied in a couple of studies that increased levels of the inflammatory cytokine IL-6 in both NPSLE patients and lupus-afflicted mice could initiate neuroinflammation. However, the exact mechanism behind this condition has not yet been adequately elucidated. The study claimed that there is accumulation of inflammatory glial genes resulting from IL-6 compromising effect on the integrity of the blood-CSF barrier within the choroid plexus. Moreover, the elevated environment of IL-6 in SLE is believed to cause NPSLE by impeding the function of BCRP and the ability of choroid plexus to clear potentially harmful metabolites [40,41].

Macrophage migration inhibitory factor (MIF) is a cytokine

implicated in inflammatory and autoimmune diseases. Studies by Cavalli et al. not only demonstrated the receptors interacting with MIF, including CD74, JAB1, CXCR2 and CXCR4, but also established the connection between MIF and autoimmune/inflammatory diseases. However, it was indicated that MIF participates in the regulation of glucocorticoid-mediated immunosuppression and survival signaling pathways. Therefore, MIF-targeted therapies are being developed. If confirmed, such therapies could greatly enhance the treatment of autoimmune and inflammatory diseases [42].

McGonagle and colleagues examined the immunological characteristics of spinal, hip, and knee entheses in order to assess whether there were differences in the ability of peripheral and axial peri-entheseal bone (PEB) to generate IL-23 [43]. It was noticed that the production of IL-23 by spinal and hip PEB was 10–100 times higher compared to knee PEB. The findings suggest that axial PEB, which is central to the pathology of ankylosing spondylitis, produces more IL-23 than peripheral tissue when activated.

Croci displayed the involvement of interleukin 8 (IL-8) in immunological responses, such as the recruitment of immune cells and stimulation of angiogenesis. The effect of Tuftsin-PhosphorylCholine (TPC), a novel anti-inflammatory chemical, on IL-8 expression in endothelial cells and inflamed human artery biopsies from patients with giant cell arteritis (GCA) was also investigated. According to the author, TPC showed a dramatic decrease in IL-8 levels in the cells and biopsies, indicating that it could be used to treat giant-cell arteritis (GCA) and other autoimmune disorders [44].

Maione looked at the anti-inflammatory and immunomodulatory properties of a mango extract (referred to as MIE) in mice with inflammatory bowel disease (IBD), as well as its influence on IBD patients. MIE, which contained primarily mangiferin, was given to mice with induced colitis. The results demonstrated a reduction in colitis severity, modulation of immune cell populations, better gut permeability, and regulation of pro/anti-inflammatory cytokines. MIE therapy also lowered TNF-α and IL-17 levels in IBD patient sera. According to the result, MIE may be effective in reducing immunological abnormalities associated with colitis and systemic inflammation in IBD patients, potentially serving as a nutraceutical or functional food [45].

Alves highlighted the role of glycans in the mechanism of lupus nephritis (LN). Tissue glycomics characterization and mass spectrometry imaging were used to analyze human kidney biopsies, revealing that LN has a unique glycan profile characterized by high quantities of mannose-enriched glycans. These abnormal structures activated γδ T-cells, leading to an autoimmune response driven by IL-17a. Furthermore, metabolic changes in kidney tissue inhibited IL-17a production by γδT-cells, controlling disease progression. The findings pointed to glycans as possible agents for restructuring tissue glyco-metabolism, providing a viable option for targeted therapy in autoimmune disease management and prevention [46].

Celiac disease, (CD) the intestinal damage occurring due to the reaction between gluten and the immune system, and its connection with IL-10 was discussed by Gianfrani. The role of IL-10 regulatory cells in CD progression was studied via collecting samples from children with CD of different stages, including potential-CD, acute-CD, and those on a gluten-free diet. Dendritic cells secreting IL-10 (DC-10) were found to control T-cell responses in CD patients. Regardless of the CD stage, gliadin-specific IFN-$\gamma^+$ T cells were detected in circulation. On the other hand, potential CD patients exhibited high levels of DC-10 and gliadin-specific T cells resulting in increased IFN-γ production by the inhibition of IL-10 [47].

### 3.4. Malignancy in autoimmunity

Autoimmune diseases serve an array of manifestations. Not surprisingly, many such diseases have an increased risk for malignancy, whether due to cytokines, inflammation, dysregulated immune system, or even antibodies [48]. Abdul Razzaque Ahmed with his detailed work showcased the autoantibodies to Laminin-332, a component of basement membrane, and its relation to malignancy. He used Laminin-332 Pemphigoid (LM-332Pg) as a prototype to compare clinical profiles of patients. His preliminary analysis showed that Laminin-332 positivity had high malignancy incidence; therefore, could be used as a biomarker for correlating malignancy incidence. In other words, paraneoplastic autoimmune Laminin-332 syndrome (PALS) [49].

## 4. Manifestations of autoimmune diseases

The self-reactive immune response in autoimmune diseases can lead to chronic inflammation and damage in various organs and systems. Therefore, the manifestations of autoimmune diseases are diverse, reflecting the specific tissues and organs targeted by the immune response. In this section, we will explore the clinical presentations and underlying mechanisms of three significant manifestations: uveitis, myositis, and central nervous system (CNS) disorders seen in autoimmune disorders. Understanding the presented manifestations is crucial for accurate diagnosis, effective treatment, and improving the quality of life for individuals affected by autoimmune diseases.

### 4.1. Uveitis

The uvea is highly vascularized and susceptible to inflammation in autoimmune diseases due to its accessibility to immune cells and antibodies. Despite being an immune-privileged site, specific antigens in the uvea may attract immune responses, potentially through molecular mimicry or antigenic similarity, triggering the immune system to mistakenly attack the uvea, as discussed by Vishnevskia. Common autoimmune conditions associated with uveitis include RA, ankylosing spondylitis, juvenile idiopathic arthritis, SLE, and others. A systematic review of 126 articles describing 29,877 patients with spondyloarthropathies reported 32.7 % as the mean prevalence of uveitis [50]. Additionally, Sampaio-Barros et al. conducted a retrospective study of 350 spondyloarthropathy patients, finding that acute anterior uveitis was significantly associated with juvenile-onset ankylosing spondylitis and lower limb enthesopathies, particularly in patients with the HLA-B*2705 allele [51]. Furthermore, Patt discussed the connection between psoriasis and uveitis. Patt and colleagues conducted a retrospective study to examine the prevalence of uveitis among psoriasis patients. They found that while the overall prevalence was slightly higher in psoriasis patients compared to controls (1.3 % vs. 1.1 %), after adjusting for factors such as psoriasis severity and the presence of spondyloarthritis (SpA)-related conditions; no significant association between psoriasis alone and uveitis was observed. The study suggests that the apparent link between psoriasis and uveitis is primarily attributable to the coexistence of SpA-related conditions, indicating a potential shared pathogenetic mechanism [52].

### 4.2. Myositis

Myositis, an inflammatory muscle disease, presents significant challenges and complexities, especially within the context of autoimmune diseases. This section explores various aspects of myositis as discussed in recent studies and presentations illustrated during AUTO14, providing a comprehensive overview of the latest findings and insights. McGonagle and colleagues investigated the surge in anti-MDA5 positive dermatomyositis (MDA5 + -DM) cases during the COVID-19 pandemic [53]. MDA5, a key receptor for SARS-CoV-2, was linked to new onset myositis in Yorkshire from 2018 to 2022. The study found a significant increase in MDA5+ cases, correlating with regional SARS-CoV-2 positivity rates. Bioinformatic analysis revealed shared immunopathological mechanisms between COVID-19 and autoimmune lung diseases, suggesting that the COVID-19 virus may trigger or exacerbate autoimmune responses leading to myositis. Tocut presented a rare case of statin-induced necrotizing autoimmune myopathy (SINAM) [54]. The

condition, also known as anti-HMGCR myopathy, can occur after statin therapy and is characterized by proximal muscle weakness and elevated CPK levels. The case involved a 74-year-old female who developed severe muscle weakness and elevated muscle enzymes while on statin therapy. The diagnosis was confirmed by the presence of anti-HMGCoA reductase antibodies, and treatment included high-dose steroids and intravenous immunoglobulin (IVIG). Early recognition and treatment of SINAM are crucial for improving patient outcomes. Another aspect to consider in the context of autoimmune diseases like myositis is the relationship between fibromyalgia and nutrition, as reviewed by Adawi. Fibromyalgia (FM), often accompanying myositis, is a chronic pain condition with symptoms such as fatigue, sleep disturbances, and mood disorders. Adawi emphasized that nutritional deficits can worsen FM, while nutritional supplements may alleviate symptoms. Obesity and certain food products can exacerbate FM, whereas diets rich in antioxidants, like vegan and vegetarian diets, might provide non-pharmacological benefits for affected patients [55]. Dietary interventions could play a role in the multidisciplinary treatment of FM, potentially benefiting patients with concurrent autoimmune conditions like myositis, the author concluded.

These studies collectively highlight the diverse manifestations of myositis and the importance of recognizing its potential triggers and underlying mechanisms, particularly in the context of autoimmune diseases and external factors such as viral infections and medications. The ongoing research underscores the need for continued exploration to improve diagnosis, treatment, and management of myositis in affected patients.

### 4.3. Central nervous system involvement

CNS disorders encompass a wide range of neurological conditions, each with distinct pathophysiological mechanisms and clinical manifestations. Recent studies and clinical trials provide new insights into these disorders, particularly focusing on Long-COVID, small fiber neuropathy, cognitive decline, pain modulation, and multiple sclerosis. Milo discussed the evolving role of B cells in the pathogenesis and treatment of multiple sclerosis (MS) [56]. B cells in MS exhibit a pro-inflammatory profile, contributing to the disease through antibody production, antigen presentation, and cytokine release. Recent advances in B cell-targeted therapies, such as rituximab, ocrelizumab, and ublituximab, have shown significant efficacy in reducing disease activity and progression. Additionally, novel therapies targeting Bruton's tyrosine kinase (BTK) and CD40 ligand are under investigation, offering promising new avenues for treating MS. The mechanisms of pain modulation in inflammatory arthritis (IA) through JAK inhibition were presented by Navarini [57]. The study evaluated the effects of upadacitinib, a JAK1 inhibitor, on microglial cells, which are pivotal in chronic inflammation and pain perception. Upadacitinib was found to reduce the expression of BDNF, a key molecule in pain modulation, and decrease neuroinflammatory and pain-related pathways. Martinez-Lavin addressed small fiber neuropathy (SFN) alongside its clinical manifestations and relationship with fibromyalgia [58]. SFN typically presents with spontaneous and evoked pain in the distal extremities, accompanied by autonomic symptoms such as dry eyes, orthostatic complaints, and gastrointestinal dysmotility [59]. The diagnosis is confirmed through skin biopsy or corneal confocal microscopy. Interestingly, more than half of fibromyalgia patients exhibit small nerve fiber pathology, supporting the hypothesis that fibromyalgia is a generalized neuropathic pain syndrome. The study suggests that various stressors can induce neuropathic pain through their impact on dorsal root ganglia.

In terms of CNS and COVID-19, Babel highlighted the severe and persistent neurological symptoms experienced by affected individuals in Long-COVID syndrome [60]. The study examined the role of autoantibodies targeting vasoregulatory and autonomic nervous system receptors. Patients with Long-COVID showed significantly higher levels of autoantibodies, particularly those targeting adrenergic receptor B1 and B2 and the muscarinic acetylcholine receptor M3 and M4. These autoantibodies correlated with the severity of neurological disorders, including psychomotor speed, visual search, attention, and fatigue. The findings suggest that autoimmunity plays a crucial role in the neurological manifestations of Long-COVID. Amedi explored the impact of digital psycho-cognitive training on brain plasticity and neuroinflammation in individuals with subjective cognitive decline (SCD) [61]. The training involved a two-week digital protocol designed to enhance cognitive functions through multisensory navigation tasks. The results indicated a significant reduction in the pro-inflammatory cytokine IL-18 and increased resting-state functional connectivity (rsFC) in brain regions associated with the default mode network (DMN) and salience network (SN). The findings suggest that psycho-cognitive training can positively affect brain plasticity and reduce neuroinflammation, potentially mitigating cognitive decline in aging and degenerative diseases.

## 5. Autoimmune and rheumatic diseases in AUTO14

One of the pearls of AUTO14 is the presentation and discussion of the latest findings in autoimmune and rheumatic diseases. The diseases considered were:

### 5.1. SLE

SLE is considered a classical and common autoimmune disease. The following aspects of SLE were discussed during AUTO14:

- Flares prediction - SLE is characterized by a remitting and relapsing course. Flares, particularly in patients with remission or low disease activity (LDA) result in high damage. Therefore, instruments for prediction and stratification of SLE are of extreme importance. Several methods were used for prediction however limitations such as accuracy, sensitivity, and feasibility to apply were among the drawbacks. Recently, the SLE disease activity score (SLE-DAS) was introduced showing a significant improvement [62]. A study aiming to assess the relationship between immunonutritional status indexes with SLE clinical disease activity, concluded the following: PNI index, albumin, basophil count ELR index and albumin/globulin ratio are adequate and can be used in conjugation with complementary biomarkers to assess SLE clinical activity [63].
- Vitamin D in SLE - Many factors affect the course of SLE like vitamin D. Through its metabolite calcitriol, vitamin D regulates immunomodulation of cells, expressing the vitamin D receptor (VDR), such as dendritic cells, macrophages, and T and B lymphocytes. Therefore, vitamin D deficiency is associated with more severe SLE activity. Moreover, various genes responsible for vitamin D metabolism are associated with different spectrums of clinical activity and disease susceptibility [64].
- Complications - Pulmonary arterial hypertension (PAH) is a severe complication of SLE, however SLE patients with HLA-DQA1*03:02 have a documented risk factor considered a negative prognostic factor. Therefore, SLE patients with these alleles should be regularly followed up for early diagnosis and treatment [65].

### 5.2. Antiphospholipid syndrome (APS)

The first description of APS appeared around 40 years ago, and it has become more popular since then. Nevertheless, APS is still often missed due to the lack of linkage between APS and various manifestations it could have. An example of underreported clinical features of APS are neurological diseases such as stroke and transient ischemic attack which have been described as one of the earliest presentations of the disease.

Memory loss is also considered the most common manifestation of APS. The association between memory disorders and APS was supported by Hughes showing an increase in word finding capabilities from below 20 % to over 80 % after 2–3 weeks of daily administration of low molecular weight heparin [66]. Epilepsy and seizures have been linked to APS as well with a prevalence 8–10 times higher than in the general population, especially in young patients. During AUTO14, the correlation between SARS-CoV-2 and APS was also discussed. In fact, the hypercoagulability states seen in patients with COVID-19, the need for anticoagulant treatment, and the appearance of aPL antibodies in those patents supports the suggested link [13]. Unsurprisingly, the authors called this correlation "two-sides of a coin".

In terms of diagnosis, the diagnosis of APS was based on the Sapporo criteria established in 1999 and revised in 2006. As our understanding of APS increased and due to the limitation of Sapporo criteria, new APS classification criteria, the 2023 ACR/EULAR criteria, was created with the primary objective of reaching the highest possible specificity (99 % versus 86 % of the Sapporo criteria) [67]. The 2023 ACR/EULAR classification criteria included moderate and high levels of aCL/anti-β2GPI positivity applied only to ELISA and not to other automated platforms. Thus, the lack of standardization resulted in a heterogenicity of aPL test results among different detection methods, including ELISA [68]. Importantly, the 2023 ACR/EULAR guidelines have two different diagnostic thresholds: one for classification criteria which is directed toward research purposes such as facilitating patient inclusion in studies and trials; while the other for laboratory diagnostic criteria used in daily clinical practice to diagnose and treat patients [69]. In addition, the 2023 ACR/EULAR includes two components: the first is clinical criteria divided upon six domains: Macrovascular (venous thromboembolism), macrovascular (arterial thromboembolism), microvascular, obstetric, cardiac valve, and hematological manifestations. The second component is the laboratory criteria including: lupus anticoagulant (LAC), IgM/IgG anticardiolipin antibody or IgM/IgG anti-β2-GPI antibody. Antibodies targeting domain one of the β2-GPI acquire the highest diagnostic/prognostic value for APS [70]. However, antibodies targeting domains 4,5 are not thrombogenic in animals and are not associated with APS clinical manifestations.

### 5.3. Rheumatoid arthritis

Rheumatoid arthritis (RA) was long known for joint inflammation and destruction. Currently, the focus is on the systemic inflammatory nature of the disease. During AUTO14, Edwards elaborated on the systems affected by the chronic inflammation of RA, such as cardiovascular diseases and how DMARDs help in reducing the risk. Actually, more research is showing that inflammation affects the brain causing increased risk of dementia, stroke, and depression/anxiety [71]. Moreover, RA as with other autoimmune diseases has female prevalence [72]. However, is the same sex preference applied to the disease course and prognosis? Atzeni explained based on her studies that males with RA were at higher risk of cardiovascular events compared to females with similar disease activity [73]. Unfortunately, females still comprise the vast majority in up to 25 % prevalence of difficult-to-treat (D2T) RA. In the same regard, Slobodin listed multiple factors, such as inflammatory, structural, and psychological, that play a role in the refractoriness of treatment. No single test or study could predict or diagnose D2T RA. Although, having a more severe disease at presentation and insufficient aggressive initial therapy may lead to D2T RA [74].

### 5.4. Vasculitis

The pathogenesis of ANCA associated vasculitis (AAV) highly depends on the host adaptive immune system and this was discussed during the AUTO14 [75]. Inflammation and the innate immune system have a vital role in the executive functions of the adaptive immune system. For instance, neutrophils activation, by many mechanisms like infection, can cause tissue necrosis due to NETosis and can activate the alternative complement pathway. This results in the production of C5a which in turn initiates a positive feedback loop that activates and attracts neutrophils. Activated neutrophils also cause damage to the endothelial cells and thus activating the intrinsic coagulation pathway which subsequently increases thrombotic complications of AAV. Therefore, complement activation, inflammation and coagulation are described as the Bermuda triangle of the innate immune system [76].

Another point in the field of vasculitis is its subtypes with emphasis on CNS vasculitis. The classification of CNS vasculitis is divided into primary (type I and II) and secondary (type III and IV) [77,78]. Type I refers to vasculitis limited to CNS, and type II refers to diseases with systemic vasculitis association. Type III describes CNS vasculitis associated with autoimmune diseases, while type IV refers to CNS vasculitis associated with non-autoimmune systemic diseases such as infections, drugs, and malignancies. The advancement in radiographic imaging including MRI, high resolution contrast enhanced MRI, digital subtraction angiography (DSA), and MRA facilitated the differentiation not only between primary and secondary CNS vasculitis but also with CNS vasculitis and conditions mimicking vasculitis. Mimickers of vasculitis include reversible cerebral vasoconstriction syndrome (RCVS), cerebral angiopathy-Aβ-elated-angiitis (ABRA), intravascular lymphoma, and cerebral amyloid angiopathy-related inflammation (CAA-RI). Treatment of CNS vasculitis is mostly achieved by high dose glucocorticoids and cyclophosphamide [79].

IgA vasculitis is an immune-complex mediated vasculitis characterized by IgA deposition in small vessels [80]. IgA vasculitis is the most reported vasculitis in children, and it is also frequently diagnosed in adults. Interestingly, unlike most other autoimmune diseases, IgA vasculitis in adults tends to affect males more than females. Many factors such as genetics and environmental triggers (medications, infections, and vaccine) have been implicated in the pathogenesis of the disease. In comparison with children, adults tend to have worse acute disease course manifested as necrotic purpura, severe gastrointestinal involvement, and acute kidney injury. Furthermore, the following risk factors are used to predict severity of acute disease: age, gender, extension of skin lesion, smoking status, and laboratory tests (neutrophils to lymphocyte ratio, serum IgA levels). Not only acute disease, adults tend also to have worse long term prognosis and higher mortality rate compared to children due to the progression of chronic kidney disease and associated comorbidities. Treatment of adult IgA vasculitis is challenging, and most patients require systemic immunomodulatory treatment [81].

### 5.5. Autoimmune thyroid diseases

Autoimmune thyroid diseases (AITD) are a commonly seen organ-specific autoimmune disorders. and is the most frequently seen autoimmune disease in poly-autoimmune conditions [82]. This is supported by a study conducted by Antonelli evaluating the prevalence of other autoimmune diseases in 3069 patients with chronic autoimmune thyroiditis (AT) including Hashimoto's thyroiditis, and Graves' thyroiditis, in comparison with two age- and sex- matched control groups. Increased prevalence of the following autoimmune diseases was demonstrated: vitiligo, chronic autoimmune gastritis, polymyalgia rheumatica, RA, celiac disease, Sjögren syndrome, diabetes mellitus, multiple sclerosis, SLE, alopecia, sarcoidosis, psoriatic arthritis, HCV-related cryoglobulinemia, and systemic sclerosis, in the AT group. The results emphasized the need of careful follow up of AT patients for early detection of autoimmune diseases [83,84].

Although Vitamin D deficiency is known to have a role in the etiopathogenesis of many autoimmune diseases, its relationship with AITD is still controversial. A study of Lazurova on Slovak premenopausal women with newly diagnosed AITD found no association between vitamin D deficiency and AITD [85].

### 5.6. Mixed connective tissue disease

Luc Mouthon described how mixed connective tissue disease (MCTD or Sharp disease) is a distinct entity, classified by Kasukawa or Sharp criteria. MCTDs is characterized by the presence of anti-U1RNP antibodies associated with features from other CTD such as SLE, Systemic sclerosis (SSc), or Idiopathic inflammatory myopathies (IIM). Features contain a wide array of signs and symptoms such as Raynaud's phenomenon, interstitial lung disease, and pulmonary hypertension. The results of Mouthon in his cohort of MCTD patients showed that 25 % of patients progressed to differentiated CTD [86]. Furthermore, patients that did not progress were more likely to achieve remission; re-iterating the diagnosis of MCTD as independent. Speaking of the features of CTDs, they are considered the second most common cause for pulmonary arterial hypertension (PAH), identified as the leading cause of mortality in SSc and MCTD. In 2018, the pulmonary hypertension threshold decreased from mean pulmonary artery pressure of $\geq$25 mmHg to >20 mmHg. Mouthon, further viewed CTD-PAH, listing the main cause as SLE and MCTD in Asian countries, while SSc is the leading cause for CTD-PAH in Western countries. Screening for PAH in patients at high risk particularly as early detection improves survival in SSc-related PAH, while immunosuppressants can be beneficial in SLE-PAH and MCTD-PAH [87].

Gerli and colleagues displayed their work on evaluating the healthcare needs and epidemiology of primary Sjogren's Syndrome (pSS) in Italy. The results showed an extremely low prevalence of the disease; however, a higher pharmacological need and cost compared to the general population [88]. Cristian Iperi, along with her colleagues, aimed to check another aspect of pSS. Four groups of patients with different antibody positivity were investigated and compared. Anti-Ro52/TRIM21 antibody showed a great association with the interferon pathway which leads to clinical presentations, mainly. Moreover, anti-Ro52/TRIM21 and anti-Ro60/SSA antibodies synchronous positivity was associated with a greater pSS severity [89].

### 5.7. Polymyalgia rheumatica

A study performed by Perricone investigated the predictive factors of sustained 24-month remission and flares in 137 patients with polymyalgia rheumatica (PMR) [90]. Patients were retrospectively evaluated at a baseline of 1, 3, 6, 12, and 24 months. The study showed that erythrocyte sedimentation rate was lower in patients who achieved full remission compared to patients who did not. Additionally, female patients had lower rates of complete remission. The findings were also related to higher dose of corticosteroids at baseline. Patients who did not achieve complete remission suffered from more and earlier flares than patients who did.

The presentation of Slobodin highlighted the diagnostic challenges in differentiating between PMR and late-onset PMR-like rheumatoid arthritis (RA) [91,92]. Both conditions present with overlapping symptoms, such as elevated CRP and ESR levels. However, RA may show additional signs like synovitis of peripheral joints. The study underscored the need for high suspicion and thorough examination to accurately diagnose late-onset RA, which may initially present with PMR-like symptoms.

## 6. Diagnostics in autoimmunity during the AUTO14

Diagnostic approaches are an ever-changing field in medicine and in autoimmunity, with new approaches and criterions being developed and researched to aid in early detection and treatment.

### 6.1. Criteria

In 2019 the EULAR/ACR SLE classification criteria was found. The criteria have been structured based on ANA positive plus an entry requirement and weighted criteria across 10 domains [93]. In validation cohort studies, a high sensitivity (96 %) and specificity (93 %) was recorded, which took into account different SLE populations. There have been 28 worldwide validation studies with a total population of over 8800 SLE patients and 6463 non-SLE patients. The consistency was observed with ANA positivity at 97 % among SLE patients despite variations in populations including ethnicities, gender, and disease duration. The performance showed that it could be used irrespective of these differences while still having comparable sensitivity like other established criteria, such as SLICC, especially at early stages when many would present without typical clinical findings. In later stages, the EULAR/ACR SLE classification criteria sensitivity increased to numbers greater than that of SLICC. Moreover, a higher criteria count was found to correlate with increased disease burden and damage, termed ominosity, indicating the utility of the criteria beyond classification in assessing disease severity and prognosis.

### 6.2. Autoantibodies

Bizzaro addressed during the AUTO14 the critical issues in autoantibodies testing criteria in autoimmune diseases, highlighting the importance of updating the criteria for autoantibodies in autoimmune diseases. While the criteria often include laboratory tests, the dynamics of test methods may not be in sync with developments in autoimmunology and thereby confound operations within autoimmunology laboratories [94]. Furthermore, immunoassays for autoantibody detection come in a variety of formats which can impact the consistency and comparability of research studies. Recently, a systematic review of the classification criteria for autoimmune rheumatic disease (ARD) underscores that classification systems across ARDs must be periodically reassessed and updated in view of advances in laboratory technology, particularly in autoantibody tests. Finally, the importance of the involvement of laboratory specialists in multi-disciplinary teams was put forth, to ensure that relevant laboratory issues are addressed, and newer tests are used.

### 6.3. Markers

Within the same scope, Infantino proposed the use of calprotectin, a heterodimeric complex formed by two S100 proteins (S100A8/A9), in the diagnosis of autoimmune diseases. Circulating calprotectin (cCLP) serves as a potential prognostic biomarker in ARD, reflecting local or systemic inflammation [95]. High cCLP levels are associated with worse structural outcomes in RA and, to a lesser extent, spondyloarthritis. Furthermore, cCLP predicts disease relapse in SLE, anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV), and severe manifestations of connective tissue diseases. Such findings suggest that the application of cCLP may help in identifying patients who need careful monitoring. Moreover, in other non-rheumatic diseases, studies conducted yielded promising yet conflicting results, indicating that further research is required to study the role of cCLP in disease severity across a range of conditions, including myasthenia gravis, multiple sclerosis, and autoimmune bullous diseases. Olivas also provided study results that correlated cCLP levels with RA and psoriatic arthritis (PsA). This suggests that cCLP may serve as a valuable inflammation biomarker, offering insight into disease severity and aiding in treatment decision-making for RA, PsA, and possibly other autoimmune diseases [96].

The use of epitopes to decrease dependence on invasive biopsies in gluten-related disorders (GRD) was highlighted by Matthias. The main point of the discussion was to compare between two new multiparametric test systems (GRD-POC and GRD-BLOT) in pediatric gluten-related disorders in relation to standard diagnostic techniques. The new assays allowed simultaneous measurement of IgA antibodies against several GRD-related antigens [97]. The highest AUC found among them was tTG IgA, followed by tTG-neo IgA and mTG-neo IgA. Additionally,

correlation with the EMA readout was strongest for tTG-neo IgA. Method agreement between GRD-BLOT and GRD-POC was greater than 93.4 %. The study suggested that such multiparametric antibody analyses have the advantage of saving time and money, which allows for fast commencing of therapy, diagnosis, avoiding unnecessary biopsies, which is a very important but invasive tool in the diagnosis of GRD.

A study form Slovenia was conducted by Zigon and friends focused on small extracellular vehicles (sEVs) in people with APS [98]. The group used modern technologies such as the ExoView® platform and nanoparticle tracking analysis. As a result, a higher total count of sEVs in APS patients was detected. Moreover, despite the absence of acute blood clotting events, endothelial and platelet activation was exhibited in APS patients, and this was explained by the elevated levels of CD62P and ICAM-1 in such patients. This concludes that APS patients have higher amounts of some sEVs associated with cellular activation.

### 6.4. Imaging

Diffuse Idiopathic Skeletal Hyperostosis (DISH) is traditionally seen as a non-inflammatory condition characterized by new bone formation in the axial skeleton. However, Eshed challenged this view, suggesting potential inflammatory components in DISH [99]. Imaging studies reveal similarities with spondyloarthritis, indicating an overlap in inflammatory processes. Genetic factors and increased visceral fat in DISH may promote inflammation and new bone formation, suggesting that the inflammatory nature of DISH needs further exploration. Eshed also addressed the differences of CT versus MRI, later highlighting the importance of radiologic modalities in distinguishing similar diseases. Two similar entities among the rare autoinflammatory bone disorders are chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. In CRMO, MRI came into importance in characterizing the multifocal lesions caused by recurrent non-infectious inflammation in bones. While in SAPHO, spotlight imaging modalities were more of use to identify hyperostosis and osteitis, especially in the sternoclavicular joint. Eshed elaborated on the differentiation between these two syndromes as the therapeutic modalities differ [100].

### 6.5. Others

Traumatic spinal cord injuries (SCI) lack a reliable prognostic tool, as highlighted by Pues. Although the existing neurological scoring systems, like the American Spinal Injury Association impairment scale (AIS), along with imaging techniques, were developed; the SCI course remains difficult to predict. Via the screening of a healthy and SCI spinal cord cDNA, six novel antigens were identified (UH-SCI.104–105–106-108-109-110). After validating antibody reactivity against these antigens in individual plasma samples from SCI patients at different time stamps post-injury compared with controls, some striking patterns were evident. Specifically, antibody reactivity against some antigens decreased immediately after injury, but increased over time to attain levels almost equivalent to those in healthy controls. In addition, SCI patients with an elevated antibody reactivity against specific antigens at later time points had a less severe conversion of the AIS grade. The identified autoantibodies could be used as new biomarkers for prognosis in SCI and might help stratify patients in clinical trials and inform clinical decisions in SCI management, the authors concluded [101].

The usage of infrared spectroscopy in the diagnosis of rheumatic disorders was proposed by Gilburd. Infrared spectroscopy refers to the measurement of the interaction of infrared radiation with matter by absorption, emission, or reflection, and can offer a new way of analyzing blood samples for detecting autoimmune diseases [102]. Using a Bruker Vertex 80 V instrument, blood samples from 34 RA patients, 24 fibromyalgia (FM) patients, and 16 healthy individuals were assessed. Promising results were displayed, as the infrared patterns were different among FM, RA, and healthy individuals, suggesting that IR spectroscopy could revolutionize diagnosis and monitoring of autoimmune disorders.

Mouthon described the diagnosis and treatment of eosinophilic fasciitis (EF), an uncommon disease that is defined by acute onset swelling, induration of the skin, eosinophilia and fascial inflammation [103]. Pinal-Fernandez proposed a diagnostic criteria consisting of major criteria of skin thickening and indurated fascia, and minor criteria of eosinophilia, and proximal muscle weakness. The etiology of EF can be associated with morphea, drug-related or malignancy-related disease. Interestingly, morphea has been reported in 20 % to 40 % of patients with EF. Additionally, there has also been associations with hematologic disorders and solid malignancies such as breast, lung, prostate and others; however, the strength of this association is controversial. Glucocorticoids are the main treatment option for EF. Other therapeutic options have been reported in case series with variable benefit such as thalidomide, etanercept, infliximab and mycophenolate mofetil. There is no consensus on duration of therapy or how to manage relapses. Despite recent advances in the diagnostic criteria and therapeutic options, the literature on EF is predominantly composed of case reports and the management of this disorder remains challenging [104].

Nilsson from SciLifeLab introduced the potential of new biomarkers to test for relapse in vasculitis. High-throughput multiplex technologies, such as protein arrays and proximity extension assays, have been used to screen plasma and serum samples from vasculitis and systemic sclerosis patients. A wide range of proteins including proteolytic fragments, secreted proteins and cell surface-associated proteins were analyzed in a single assay plate. Many potential biomarker candidates were identified and verified in vasculitis (including ANCA-associated and hypersensitivity angiitis) and systemic sclerosis plasma samples. The biomarker candidates are involved in processes related to the pathology of the diseases and intriguingly some were confirmed in plasma samples from patients who experience relapse events. It is believed that biomarkers of relapse could improve diagnosis and subclassification of patients with particular clinical features (e.g. skin and lung fibrosis). The findings demonstrate the contribution of these biomarkers to the monitoring of patients with vasculitis [105].

## 7. Other fields of autoimmunity during AUTO14:

### 7.1. Pediatrics in the AUTO14

The relationship between autoimmunity and pediatrics extends beyond genetic predisposition, including the interplay of maternal antibodies, prenatal environment, and epigenetic factors that influence the development of autoimmune conditions in children. Autoantibodies and proinflammatory cytokines of maternal autoimmune diseases can in some circumstances influence children long-term outcome as highlighted by Tincani opening the pediatric session.

Galli et al. explored the neurodevelopmental profile of 20 children born to mothers with systemic sclerosis, finding that while children typically exhibited normal cognitive and adaptive functions, they experienced an increased vulnerability to psychopathological issues and social fragility. The findings suggested a potential association between maternal autoimmune disease and the susceptibility of offspring to psychological challenges [106]. In addition, Battelino discussed the immune interventions in type 1 diabetes mellitus. In their study, the group investigated the role of extracellular vesicle (EV) miRNAs in the pathogenesis of type 1 diabetes (T1D). By analyzing blood plasma EV miRNA profiles from individuals with T1D, including those with beta-cell destruction and those who received Langerhans islet transplantation, the study identified specific miRNA patterns associated with T1D progression. In vitro experiments demonstrated that these EV miRNAs modulate immune cell activation and cytokine release, potentially through TLR7/8 activation, contributing to autoimmune responses and beta-cell destruction. The findings suggest a novel mechanism for T1D development and highlight the potential of EV miRNAs as therapeutic targets [107]. Furthermore, Avcin discussed the various allergic,

autoimmune and inflammatory complications of inborn errors of immunity. The study examined 247 patients with primary immunodeficiencies (PIDs) in Slovenia, finding that 29 % had non-infectious and non-malignant manifestations. Autoimmune issues were the most common, affecting 22 % of patients, followed by lymphoproliferative/granulomatous conditions (12 %), autoinflammatory (5 %), and allergies (4 %). Patients with immune dysregulation-related PIDs had the highest prevalence of autoimmune manifestations. The findings highlight the importance of screening PID patients for autoimmune and inflammatory phenomena at diagnosis and during follow-up [108].

Belot presented different genes involved in monogenic SLE and highlighted their importance in the development of the disease. Monogenic lupus, a relatively newer concept, involves single gene defects affecting various pathways like efferocytosis, interferonopathies, JAK-STATopathies, rasopathies, and the dysregulation in T and B cells. Identification of this monogenic susceptibility to lupus is essential in early-onset, syndromic, male, or familial cases, guiding targeted therapies based on specific clinical and biological features [109].

In addition, recent therapeutic advances in juvenile idiopathic arthritis (JIA) was presented by Ravelli. The presenter illustrated the evolution of JIA management over the past two decades, emphasizing the shift toward early aggressive interventions and novel biologic medications. The author also demonstrated the randomized controlled trials which examined the efficacy of treatments such as golimumab and tocilizumab in polyarticular JIA, alongside the potential of methotrexate to enhance the effects of intra-articular corticosteroid injections in oligoarthritis. Notably, there is current interest in determining the optimal time to discontinue medications once sustained remission is achieved in JIA [110].

### 7.2. Pregnancy and autoimmunity during AUTO14

One important topic that cannot be neglected when discussing autoimmunity is pregnancy and its related autoimmune disorders. Unsurprisingly, pregnancy and autoimmunity received special attention during the AUTO14 meeting.

The hormonal changes occurring during pregnancy influence the immune system which may lead to the triggering of autoimmunity [111]. One of the discussed topics was recurrent spontaneous abortion (RSA) and pregnancy failure occurring in women with autoimmune diseases [112]. Thyroid dysfunction and Hashimoto's thyroiditis among other autoimmune thyroid diseases have been implicated in complicated pregnancies. Of the argued mechanisms is the direct effect of anti-thyroid antibodies on the placenta. Additionally, anti-thyroid antibodies are capable of interacting with chorionic gonadotropin and chorionic thyrotropin thus altering their function.

Complications during pregnancy in SLE patients have been extensively studied and reported in medical literature [113]. According to a study presented in the AUTO14, polyhydramnios was the most frequent complication encountered in SLE pregnant patients followed by preeclampsia.

Another topic included the effect of pregnancy on the sacroiliac joint (SIJ) in the context of axial spondyloarthritis which was also discussed in the AUTO14. SIJ withstands a lot of stress due to biomechanical changes resulting in pubic instability, inflammation, bone oedema and stress fractures. The nonspecific symptoms occurring due to this condition complicate the diagnosis and thus necessitate the use of imaging techniques. The importance of MRI in evaluating postpartum lesions has been highlighted as well [114].

## 8. Treatment, prevention, and novel therapies in AUTO14

In addition to the aforementioned sessions of the 14th international congress on autoimmunity; therapeutics received their own attention due to the importance of newly introduced treatment agents in autoimmune diseases. The pearls of this sessions are concluded in the following aspects:

### 8.1. Treatment approaches in autoimmune diseases

Throughout AUTO14, the spotlight was directed around novel therapies for autoimmune diseases, especially chimeric antigen receptor (CAR)-T cell therapy. Andrade stressed that the research of cell therapy extends beyond regenerative medicine and cancer, enveloping chronic inflammatory and autoimmune diseases. Mesenchymal stromal cell (MSC) [115] transplantation and CAR-T cell infusion showed positive results in treating these conditions [116]. CAR-T cells, targeting CD19 or BCMA, effectively deplete antibody-secreting cells, including long-lived plasma cells (LLPC), possibly aiding in the treatment of SLE and other autoimmune diseases. However, CAR-T cell therapy may be a cause of the induction of secondary immunodeficiency by affecting protective antibodies. MSCs, derived from various sources, regulate immune responses and have shown great success in animal models of arthritis, lupus nephritis, and autoimmune encephalomyelitis (EAE). In the same regard, Lytton discussed the possibility of using innovative immune therapies in the rare autoimmune blistering disease bullous pemphigoid (BP) and epidermolysis bullosa acquisita (EBA). The author suggested that by using peptide autoantigen-CAR T-cell technology, one can deliver more precise immune modulation than rituximab, where BP180-BP230 peptides have shown greater sensitivity than recombinant autoantigen-based ELISA [117].

Shifting the focus to another interesting topic of discussion in AUTO14, cannabinoids and their effect on the immune system. Cannabis plants have held a significant role in human history for centuries, utilized in cultural rituals and medical applications. While approximately 500 cannabinoids have been identified, medical categorization typically divides cannabinoids into two main categories: tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations [118]. It has been proven that the consumption of cannabinoids has beneficial analgesic and immunomodulatory effects [119], whether through smoking, inhalation, or sublingual administration. According to Amital and friends, cannabis interacts primarily with two cannabinoid receptors in the human body: CB1 receptors, which are distributed mainly in the CNS, and CB2 receptors, which can be found throughout organs and tissues, including lymphoid cells. Hence, the medical community is beginning to hold the view that cannabis may act through these receptors to have immunomodulatory or immune-suppressive effects. Research using animal models of autoimmune disorders (AD) revealed that both synthetic and natural cannabis reduce the inflammatory responses that immune cells trigger [120], which are responsible for AD development and chronicity. Even though just two clinical trials including synthetic cannabinoid-like compounds were conducted, the results supported the possibility of using cannabinoids to treat some ADs.

In a case report presented by Borislava Zhelezarova during AUTO14, a 65 year-old patient was hospitalized in the rheumatology clinic due to the appearance of diffuse petechial rashes on both his legs without a prior infection. The diagnosis of Necrotizing vasculitis was made and after outpatient administration of corticosteroids, intravenous immunoglobulin products (IVIg) were applied for 3 consecutive months. Although IVIg is used off-label in this case, the patient's condition significantly improved, and there was a reverse evolution of the necrotic lesions with the appearance of hyperpigmented spots.

Prevention of disease was also a field of interest and questioning for many during AUTO14. Juvenile idiopathic arthritis (JIA) patients on anti-cytokine treatment (AIT) stand a higher risk of developing a severe varicella zoster (VZV) infection. The best prevention against these illnesses is still vaccination [121]. Although varicella vaccine was typically safe, an immunological response was not always induced. However, it worked in 81 % of patients receiving AIT, successfully avoiding serious illness in all those who received the vaccination. Understanding VZV-specific cellular immunity may provide more insight into the immunogenicity of the vaccine.

### 8.2. Novel therapies in AUTO14

During AUTO14, an abundance of advanced groundbreaking treatment approaches were discussed. For instance, anti-TNF medications are essential for the management of autoimmune illnesses; nevertheless, the emergence of anti-drug antibodies (ADA) may affect their efficacy and frequently require stopping treatment. The results obtained [122] suggest that during anti-TNF medication, B cell activation and ADA production are triggered by the same mechanism. Adalimumab has a greater ADA frequency than ustekinumab, although having comparable immunogenicity potentials. Serum type-I IFN levels are raised in adalimumab-treated patients, especially in those with detectable ADA. Anti-TNF therapy increases plasmacytoid dendritic cells (pDCs) synthesis of type-I IFN, which in turn stimulates B cell activation and the generation of IgG. Mouse models demonstrate faster ADA development with anti-TNF therapy with type-I IFN pathway activation, supporting the findings. Colafrancesco and colleagues presented the effectiveness of anakinra and canakinumab, interleukin-1 inhibitors in treating Still's disease. IL-1 inhibitors were compelling in controlling inflammatory manifestations plus causing clinical recession. Regardless of the age at disease onset or pattern of disease such treatments were efficient [123]. Moreover, recent data showed a low incidence of adverse events and the absence of severe ones, making IL-1 inhibitors a feasible and effective strategy for long-term disease management. Novel therapies for immune-mediated inflammatory disorders (IMIDs) were also discussed during the AUTO14 meeting. IMIDs consist of many inflammatory mediators, with the main ones being interleukin (IL)-17A and IL-17F [124]. By targeting the involved cytokines significant clinical benefits can be achieved. However, there are still concerns with the limited effectiveness and immunogenicity. A new variant called nIL-17TM displays higher pro-inflammatory properties and promotes the recruitment of leukocytes. In comparison to traditional biologics, Ab-IPL-IL-17TM effectively mitigates IL-17-induced effects with fewer off-target effects. Ab-IPL-IL-17TM reduces arthritis symptoms and neutralizes high IL-17 levels in IBD patient blood in preclinical models and patient samples from RA and inflammatory bowel disease (IBD).

Lai and colleagues discussed how immune checkpoint molecules are crucial to manage peripheral tolerance, preventing autoimmune diseases [125]. The team recently discovered a novel immune checkpoint molecule TAPBPL, which improved the mice experimental autoimmune encephalomyelitis EAE and collagen type II-induced arthritis (CIA). The latter was associated with a decrease in Th1/Th17 inflammatory cytokines and an increase in Tregs, while showing a decrease in activated CD4 and CD8 T cells. Moreover, TAPBPL protein decreased the mice generation of autoantibodies and suppressed the proliferation of autoantigen-specific T cells as well as the expression of Th1 and Th17 cytokines. Moreover, in animal models of CIA, alpha-1 antitrypsin (AAT) protein and gene therapy delay and reverse type 1 diabetes and RA. Recent research has demonstrated that AAT gene therapy prolongs life span in spontaneously lupus-prone animal models and avoids the onset of lupus. The study demonstrated that AAT therapy suppresses the generation of inflammatory cytokines by blocking NF-kB signaling pathways alongside decreasing the maturation and activities of dendritic cells (DCs) by blocking intracellular TLR activation [126]. Crucially, in autoimmune illness models, AAT therapy decreased the formation of autoantibodies.

AUTO14 also brought to light the significance of treating autoimmune and inflammatory diseases with P140, also known as Lupuzor. Currently undergoing phase III clinical trials globally for SLE [127], P140 has shown outstanding outcomes. The findings were promising in various animal models, including those mimicking Sjögren's syndrome, chronic inflammatory demyelinating polyneuropathy, IBD, gout, asthma, and periodontitis. The biochemical and cellular analyses explored whether P140 might exhibit a potential effect, similar to that observed in oncology. Such effects could possibly target a cell receptor in a lymphoid structure and affect inflamed organs at a distance by targeting key elements of *endo*-lysosomal autophagy [128], a dysregulated pathway in acute and chronic inflammation models, as Muller stated.

Finally, in a very interesting presentation titled: "A look into the future of targeted medicine", Gellerman discussed the use of photodynamic therapy (PDT) and sonodynamic therapy (SDT), which are capable of killing cancer cells, to kill unwanted cells in the body upon light irradiation by producing "Killing" reactive oxygen species (ROS). PDT was applied for many diseases such as RA, lichen plans, lichen sclerosis, psoriasis, bullous dermatoses and more. SDT proved a more effective therapy than PDT, especially for diseases located deep within the tissues [129].

## 9. Conclusion

The field of autoimmunity is an active domain of research for the scientific community. Therefore, the innovations registered in terms of diagnosis and treatment are of significant importance. The last international meeting on autoimmunity discussed the latest developments in autoimmunity including the role of artificial intelligence in assisting physicians, not replacing them, alongside the recent results of the ongoing research in the field. The post-COVID syndrome and the role of autoimmune mechanisms were illustrated in detail. Understanding autoimmune mechanisms of systemic diseases, infections as triggers, manifestations in vaccination, is of critical meaning when managing patients. Now, it is time for discovering the next innovation for the next meeting.

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No data was used for the research described in the article.

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