Pathogenic Mechanisms and Translational Applications of Anti–IFN-γ Autoantibodies

Anti–interferon-γ autoantibodies are major drivers of adult-onset immunodeficiency in Southeast Asia, predisposing affected individuals to severe opportunistic infections, including *Talaromyces marneffei* infection and nontuberculous mycobacterial disease. To define their pathogenic mechanisms, we used single-cell antibody cloning to generate 19 monoclonal anti–IFN-γ autoantibodies and identified three distinct epitope groups on IFN-γ. Although all clones displayed high-affinity binding, with dissociation constants below 10^{-9} M, only a subset potently neutralized IFN-γ–induced STAT1 signaling. Mechanistic analyses revealed that group I antibodies prevent IFN-γ binding to IFN-γR1, whereas group II and group III antibodies disrupt IFN-γR1–IFN-γR2 receptor complex formation after ligand engagement. Notably, group III antibodies also mediated antibody-dependent cellular cytotoxicity, suggesting an additional mechanism by which AIGAs may impair IFN-γ–responsive immunity.

To selectively eliminate pathogenic autoreactive B cells, we developed IFN-γ chimeric autoantibody receptor T cells using an engineered receptor-nonbinding IFN-γ variant as the extracellular bait. These IFN-γ CAAR-T cells specifically recognized patient-derived autoreactive B cells reduced circulating AIGAs in a mouse model, and avoided receptor-mediated off-target effects and Fc-dependent toxicity, providing a potential strategy to restore IFN-γ immunity in affected patients.

In parallel, we are expanding the clinical understanding of AIGAs in tuberculosis. Although AIGAs have rarely been reported in patients with tuberculosis, our recent findings suggest that they are preferentially associated with disseminated and extrapulmonary tuberculosis rather than isolated pulmonary disease. Functional analyses further indicate that AIGAs from tuberculosis patients exhibit weaker neutralizing activity than those from patients with nontuberculous mycobacterial disease.

Together, our work defines the molecular heterogeneity and clinical impact of AIGAs, and establishes a translational framework in which pathogenic autoantibodies can be selectively eliminated or repurposed as therapeutic agents for IFN-γ–driven autoimmune diseases such as vitiligo.

Recognizing and Rethinking AIGA: From Misdiagnosis to Individualized Management

Anti-interferon-γ autoantibody (AIGA) disease is an acquired immunodeficiency predominantly affecting previously healthy adults of Asian descent, yet it remains substantially underrecognized in clinical practice. Affected patients frequently present with disseminated nontuberculous mycobacterial infections, opportunistic fungal diseases, and a broad spectrum of inflammatory manifestations that can closely mimic malignancy, tuberculosis, or primary immunodeficiency — leading to diagnostic delays and misclassification that compromise patient outcomes.

Drawing on a prospective multicenter cohort followed since 2015, this lecture examines the full clinical spectrum of AIGA disease, with particular attention to presentations that challenge conventional diagnostic frameworks. Validated screening approaches, including repurposed diagnostic tools, will be discussed in the context of improving early recognition across specialties.

Beyond diagnosis, emerging evidence suggests that disease trajectory in AIGA is more heterogeneous than previously appreciated. A subset of patients may achieve sustained clinical resolution with antimicrobial therapy alone, without recourse to immunosuppressive agents. This is an observation with important implications for how treatment decisions are individualized. Identifying clinical and biological markers that distinguish patients likely to resolve spontaneously from those requiring escalated intervention remains an active area of investigation.

This lecture aims to reframe AIGA not as a condition with a single treatment pathway, but as a spectrum requiring thoughtful, patient-centered assessment at every stage, from first suspicion to long-term management.

Diverse Epidemiology and Outcomes of AIGA Across Taiwan Based on our National Health Insurance Database

背景

抗丙型干擾素自體抗體（AIGA）引發的後天免疫失調，主要好發於亞裔族群，與特定 HLA 基因型高度相關。患者因體內產生中和性抗體攻擊 IFN-gamma，導致巨噬細胞無法活化，對非結核分枝桿菌（NTM）及沙門氏菌等胞內菌失去防禦力。臨床上 95% 患者呈現播散性感染，且常伴隨帶狀疱疹或馬爾尼菲籃狀菌等併發症。目前僅靠抗生素難以根除，且七成患者面臨反覆感染，形成沉重的醫療負擔。

目的

本研究旨在描述 AIGA 患者的臨床表現與感染菌種分布，分析其門診與住院之醫療費用。同時，探討接受免疫調節治療（如 Rituximab, Daratumumab 等）對改變病程及降低醫療開支的影響。此外，建立一套精準的病例篩選邏輯，以利未來申請全國健保資料庫進行大規模分析。

方法

採回溯性研究，選取 2006 年 1 月 1 日至 2025 年 12 月 31 日於台大醫院就診之個案。研究將定義特定臨床特徵與檢驗組合，從醫整部資料庫篩選病患，並與已知確診名單比對以驗證準確性。收集指標包括：臨床症狀、病原體種類、免疫調節藥物使用紀錄及各項醫療費用數據。

預期結果

預計能勾勒出台灣 AIGA 患者的本土臨床圖像與醫療花費軌跡。預期發現免疫調節治療能有效降低抗體效價並減少復發率，進而顯著降低長期抗微生物藥物與住院帶來的醫療成本。最終將建立有效的健保資料庫識別通則，以申請健保資料分析，為全國性政策評估提供數據支持。

Title: Adult-Onset Immunodeficiency in Japan

Takuro Sakagami
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Adult-onset immunodeficiency (AOID) associated with anti-interferon-γ autoantibodies (AIGA) has emerged as an important cause of disseminated nontuberculous mycobacterial (dNTM) infection, particularly in East and Southeast Asia. However, despite increasing recognition of this condition, its epidemiology, clinical spectrum, and healthcare burden in Japan have remained poorly characterized due to the absence of nationwide surveillance systems and standardized diagnostic frameworks.

Since establishing a diagnostic platform for AIGA detection in 2012, we have conducted nationwide diagnostic support for suspected dNTM cases across Japan. Through multicenter collaboration, more than 100 patients with AIGA-positive AOID have been identified. Nationwide surveillance studies further demonstrated that dNTM disease is distributed broadly throughout Japan and involves multiple clinical specialties, including respiratory medicine, infectious diseases, and rheumatology. Importantly, a substantial proportion of patients with unexplained dNTM infection were found to harbor AIGA, suggesting that AOID remains substantially underrecognized in routine clinical practice. Furthermore, some dNTM patients lacked both known immunodeficiency-associated conditions and detectable AIGA, raising the possibility that other forms of AOID mediated by anti-cytokine autoantibodies, including anti-IL-23 autoantibodies, may also be hidden among clinically unexplained dNTM cases.

To address these unmet needs, we are currently developing a nationwide AOID registry and biospecimen repository through a government-supported research program. These infrastructures are expected to facilitate future investigations into the natural history, diagnostic delay, organ involvement, treatment outcomes, and immunopathogenesis of AOID. In parallel, multicenter clinical data collection is ongoing to establish a foundation for future evidence-based diagnostic and management strategies.

Japan has now entered the registry and guideline era of AOID research. Nevertheless, because AOID is an ultra-rare disease, no single country can fully elucidate its pathogenesis or optimize management strategies alone. International collaboration and harmonization of

diagnostic and clinical frameworks across countries and regions will therefore be essential for future guideline development and therapeutic innovation.

Lecture Abstract

The Oncology Intersection: Thymoma and Autoantibodies

Wei-Li Ma, M.D, National Taiwan University Hospital

Thymic epithelial tumors are rare malignancies that include thymoma, thymic carcinoma and other uncommon subtypes. Higher rates of thymoma have been reported among Asian/Pacific Islander populations than among Caucasians. Beyond its rarity, thymoma is biologically distinct from thymic carcinoma because it more often retains a thymus-like immune microenvironment that may support aberrant thymopoiesis and impair negative selection and regulatory T-cell development, allowing autoreactive immune clones to escape.

This immune dysregulation is reflected by the strong association between thymoma and autoimmune diseases. Myasthenia gravis is the most common manifestation. Other associated disorders include Good's syndrome, neuromyotonia, polymyositis, pure red cell aplasia, systemic lupus erythematosus, autoimmune hepatitis, myocarditis and encephalitis. Many of these paraneoplastic manifestations may be mediated by corresponding autoantibodies. The presence of anti-cytokine autoantibodies further links thymoma to both autoimmunity and immune deficiency. Earlier studies showed that thymoma cells can spontaneously produce anti-IFN-α and anti-IL-12 autoantibodies. Subsequent work linked anti-cytokine autoantibodies in thymic neoplasia to opportunistic infections. More recent data in Good's syndrome demonstrate persistent anti-interferon and other anti-cytokine autoantibodies despite profound B-cell loss and severe hypogammaglobulinemia. Together, these findings support the concept that thymoma is not only a mediastinal malignancy, but also a disease of central tolerance failure with direct implications for autoimmune surveillance and infection risk assessment.

This lecture will review the mechanisms linking thymoma to immune tolerance escape and autoantibody development. It will focus on abnormalities in thymic epithelial cells, negative selection and regulatory T-cell generation that may drive thymoma-associated autoimmunity. Anti-cytokine autoantibodies will be discussed as an emerging bridge between autoimmunity and immune deficiency. We will also share preliminary observations regarding anti-cytokine autoantibodies in patients with thymoma at our hospital.

Therapeutic Cytokine Blockade and Host Defense: Clinical Observations from Allergy and Immunology Practice

The rapid expansion of cytokine-targeted therapies has transformed the management of allergic and inflammatory diseases. Monoclonal antibodies directed against IL-4 receptor α, IL-5, IL-5 receptor, thymic stromal lymphopoietin (TSLP), IgE, and other immune pathways are now widely used for asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps, eosinophilic disorders, and related conditions. These therapies provide a unique opportunity to examine cytokine function directly in humans.

Clinical experience with targeted cytokine blockade has revealed important insights into host defense. Despite the central role of many cytokines in immune regulation, inhibition of type 2 inflammatory pathways has generally been associated with a favorable infectious safety profile. In contrast, disruption of selected cytokine pathways through inborn errors of immunity, anti-cytokine autoantibodies, or therapeutic intervention can result in distinctive patterns of infectious susceptibility, highlighting the differing roles of cytokines in antimicrobial defense and immune homeostasis.

Comparisons among therapeutic cytokine blockade, monogenic immune defects, and anti-cytokine autoantibody syndromes provide a framework for understanding redundancy and specialization within human immune networks. Clinical observations from allergy and immunology practice further illustrate how severe, recurrent, or unusual infections may serve as clues to underlying immune dysregulation and prompt evaluation for inborn errors of immunity or anti-cytokine autoantibodies.

The convergence of biologic therapies, genetic immunodeficiencies, and anti-cytokine autoantibody syndromes offers a powerful model for understanding human cytokine biology and its implications for infectious diseases.

The Odyssey of Anti-Cytokine Autoantibodies

Steven M. Holland, MD — NIH Distinguished Investigator; Scientific Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, USA

Anti-cytokine autoantibodies have emerged over the past two decades as a major mechanism of adult-onset immunodeficiency, phenocopying inborn errors of immunity and explaining severe, unusual, or refractory infections in previously healthy adults. This lecture traces the odyssey of their discovery — from early clinical puzzles to mechanistic definition and targeted therapy.

Neutralizing anti-interferon-γ autoantibodies, first characterized in patients across Southeast Asia with disseminated nontuberculous mycobacterial infection, defined a distinct acquired susceptibility to intramacrophagic pathogens and revealed striking associations with HLA class II alleles. Anti-GM-CSF autoantibodies, initially linked to pulmonary alveolar proteinosis, were subsequently shown to underlie cryptococcal meningitis and severe nocardiosis in otherwise immunocompetent hosts. Anti-type I interferon autoantibodies, long observed in thymoma and autoimmune polyendocrine syndrome type 1, gained renewed urgency with the demonstration that they account for a substantial fraction of life-threatening COVID-19. Most recently, neutralizing anti-interleukin-23 autoantibodies were identified in patients with thymoma and in adults with severe, persistent opportunistic infections, extending the spectrum of interleukin-12/interleukin-23 pathway disruption from genetic lesions to acquired autoimmunity.

Together, these syndromes illustrate a unifying principle: autoimmunity trespassing on antimicrobial immunity. This talk will review the clinical phenotypes, diagnostic approaches, and mechanisms of each major anti-cytokine autoantibody syndrome, discuss B-cell–directed and plasma-cell–directed therapies, and outline the challenges ahead — standardized assays, international guidelines, and screening strategies — as the field moves from discovery toward precision management of these acquired immunodeficiencies.

History and future of Immunotherapy for interferon-gamma autoantibodies: lessons from Southeast Asia.

Ploenchan Chetchotisakd, MD

Professor of Medicine, Senior Researcher, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Anti-interferon-gamma (IFN-γ) autoantibodies (AIGAs) has emerged over the past two decades as a major cause of adult-onset immunodeficiency disease (AOID) in Southeast Asia, particularly among previously healthy individuals presenting with disseminated intracellular pathogens, including nontuberculous mycobacterial, Salmonella, fungal, and varicella-zoster infections. Early recognition of the syndrome in Thailand and neighboring countries transformed understanding of host immunity by identifying neutralizing anti–interferon gamma (IFN-γ) autoantibodies as a distinct acquired immunodeficiency disorder rather than a congenital immune defect. Initial treatment strategies focused primarily on prolonged antimicrobial therapy; however, high relapse rates and persistent autoantibody production highlighted the need for targeted immunomodulatory approaches.

Current immunotherapy approaches can be conceptually divided into induction and maintenance phases. Induction therapy is primarily intended to rapidly reduce autoantibody-producing B cells and plasma cells in patients with severe, relapsing, or refractory disease. Rituximab is an important B-cell–targeted therapy with favorable outcomes in refractory cases. Cyclophosphamide, with or without corticosteroids, is an alternative regimen because of its accessibility and clinical efficacy in reducing disease activity, while bortezomib has shown promise in selected patients through plasma cell depletion, particularly in treatment-resistant disease. Following successful disease control, maintenance therapy with azathioprine has been increasingly utilized to sustain remission, reduce relapse risk, and minimize cumulative exposure to more toxic immunosuppressive agents.

Despite significant advances, major challenges remain regarding the optimal use of immunotherapy in IFN-γ autoantibody disease. Future research should focus on identifying which patients would benefit from immunotherapy at initial presentation rather than after recurrent infections or antimicrobial failure. In addition, prospective studies are urgently needed to define the optimal regimen, dosage, duration, and sequencing of induction and maintenance immunotherapy. Lessons from Southeast Asia continue to provide critical insights into the pathogenesis and management of this unique acquired immunodeficiency syndrome and will guide the development of evidence-based treatment strategies in the future.

Anti-GM-CSF Autoantibodies:
Impact on Human Lung Macrophages and Implications for Treatment

Hélène Salvator, Respiratory diseases dept, FOCH Hospital, FRANCE

GM-CSF is an essential growth factor for the differentiation of monocytes into alveolar macrophages. The acquisition of anti-GM-CSF autoantibodies has been linked to a form of interstitial lung disease, autoimmune alveolar proteinosis, as well as to the development of severe opportunistic infections such as cryptococcal meningitis or disseminated nocardiosis. The biological determinants linking these autoantibodies to the clinical phenotype remain unclear. Neither the concentration of antibodies nor their overall neutralizing potent differentiates these patients' cohorts.

We hypothesize that, within the human pulmonary microenvironment, sensitivity to GM-CSF and therefore the impact of anti-GM-CSF antibodies differ depending on the degree of differentiation of cells in the monocyte-macrophage lineage. Thus, the phenotype will express according to the cell type that is predominantly targeted in the lungs.

We compared the intracellular GM-CSF signaling and assessed the impact of anti GM-CSF antibodies (both commercial monoclonal antibody (mAb) and polyclonal antibodies from patients'sera) in three cell types: circulating monocytes (MOs), monocyte-derived macrophages (MDMs) and human pulmonary macrophages (MPs). MPS were isolated from human lung surgical specimens.

Intracellular GM-CSF signaling, as assessed by intracellular STAT5 phosphorylation, was lower in MPs than in circulating monocytes and monocytes lost their sensitivity to GM-CSF during differentiation into MD. This observation was correlated with lower expression of the alpha and beta chains of the GM-CSF receptor on the surface of MPs. Anti GM-CSF antibodies impacted the MDM differentiation process and altered surfactant catabolism, whereas they did not modify MP function.

Globally, in human lung, GM-CSF sensitivity seems to be dependent on the level of cellular differentiation. Anti GM-CSF antibodies have less impact on fully differentiated cells. The study of antibody specificity based on patient serum samples is currently underway. These

observations could have implications both in terms of a better understanding of the pathophysiology of lung diseases induced by anti-cytokine antibodies, and in terms of treatment, timing of exogenous GM-CSF administration for example.

Precision Therapy for Anticytokine Autoantibody–Mediated Immunodeficiency in Taiwan

Adult-onset immunodeficiency from neutralizing anti–interferon-γ autoantibodies (nAIGAs) is a debilitating, relapsing syndrome with a 5-year mortality of 6–20%. Antimicrobial therapy is itself complex: macrolide-based regimens anchor *Mycobacterium avium* complex treatment, but disease burden for *M. abscessus* often demands years of multidrug combinations with challenging agents such as clofazimine, amikacin, linezolid, or tigecycline. Even with sustained antimicrobial response, recurrence with new opportunistic pathogens — *Talaromyces*, *Burkholderia*, *Cryptococcus*, *Histoplasma, Aspergillus* — is the rule rather than the exception. Patients without durable autoantibody titer reduction report substantially reduced quality of life across SF-36 physical, pain, social, and mental health domains, with attempted suicides and late-onset cancers in a minority.

Broad profiling shows that pure, isolated nAIGAs are rare; concomitant anti-nuclear, anti-thyroid, and anti-phospholipid autoantibodies frame the disease as polyfunctional autoimmunity. At National Taiwan University Hospital, antibiotics alone control disease in under half of patients. Adding rituximab, abatacept or cyclophosphamide raises real-world effectiveness to roughly three-quarters; cyclophosphamide achieves deeper autoantibody suppression at lower costs (no pre-authorization under Taiwan's National Health Insurance) but with longer treatment courses. Rituximab can also be used to treat nAIGA associated IgG4 disease, while abatacept can be used to treat concomitant rheumatoid arthritis. Rituximab failures may reflect immune-privileged IFN-γ–specific antibody-secreting cells: single-cell RNA-seq localized nAIGA-secreting clones to a $CD11c^{+}ZEB2^{+}$ bone-marrow plasma-cell cluster, supporting salvage with anti-CD38 (daratumumab) and anti-BAFF (belimumab); daratumumab has also been valuable during the COVID-19 pandemic to avoid persistent SARS-CoV-2 shedding post rituximab. The role of emerging strategies — antigen-specific hemoadsorption and CAR-T-cell therapy against nAIGA-producing B cells will be discussed, as well as the reported successful use of daratumumab for depleting anti-IL-23 and anti-GM-CSF.

Long-term follow-up over 5–10 years has been reassuring. We routinely administer antiviral prophylaxis before immunomodulation; no severe breakthrough infections, nor profound hypogammaglobulinemia, nor transfusion requirements have been observed at the lower dose intensities used for nAIGA. We have not observed any cases of progressive multifocal leukoencephalopathy (PML). However, this is expected since the reported incidence of PML is extremely rare, estimated to be around 1 case per 25,000 rituximab-plus-prior immunomodulation exposures for non-hematological malignancies. Physicians should embrace nAIGA as a treatable disease in which the decision when — and whether — to initiate immunomodulation remains patient- and situation-dependent.

Managing Autoimmunity: The Adult Rheumatologist's Perspective

Hung-Cheng, Tsai, M.D.

The management of complex autoimmune conditions requires a nuanced understanding of immune dysregulation and its diverse clinical manifestations. From the perspective of an adult rheumatologist, addressing these disorders involves not only the treatment of acute symptoms but also the long-term modulation of the underlying immune response. This presentation provides a high-level overview of the strategic approaches used in the clinical management of autoimmunity, particularly in the context of emerging and multifaceted syndromes.

We will discuss the fundamental principles of diagnosis and the ongoing challenges of selecting appropriate therapeutic interventions in a rapidly evolving landscape. The session will highlight the importance of an individualized approach to patient care, considering the balance between effective immunosuppression and the maintenance of host defense. Furthermore, the role of multidisciplinary collaboration in managing the systemic complications of these conditions will be emphasized.

By sharing insights from rheumatological practice, this talk aims to outline a comprehensive framework for clinicians to navigate the complexities of autoimmune management, with the ultimate goal of optimizing patient stability and long-term health outcomes.

When Lymphoma Is Not Lymphoma: Lessons from Anti–Interferon-γ Autoantibody–Associated Lymphadenopathy

Adult-onset immunodeficiency associated with neutralizing anti–interferon-γ autoantibodies (AIGA) is an emerging clinical entity that frequently presents with lymphadenopathy and can closely mimic malignant lymphoma, particularly nodal T follicular helper cell lymphoma and classic Hodgkin lymphoma, both clinically and pathologically. This diagnostic overlap poses a significant challenge for pathologists and clinicians, with important therapeutic implications.

In this talk, I will present a comprehensive clinicopathological characterization of AIGA-associated lymphadenopathy, highlighting its diverse morphological spectrum, including granulomatous inflammation and lymphoma-like lymphoproliferative patterns, occasionally accompanied by monoclonal T-cell expansion. These findings underscore the risk of misdiagnosis and potential overtreatment. Building on these observations, I will introduce CXCL9 immunohistochemistry and targeted next-generation sequencing as practical diagnostic tools for distinguishing AIGA from lymphoma.

This presentation aims to provide a **tissue-based diagnostic framework** for recognizing infection-related lymphoma mimics and to emphasize the importance of interdisciplinary evaluation in modern hematopathology. By integrating histopathology with clinical and immunological insights, this approach highlights the unique role of pathologists in bridging infectious disease and lymphoma diagnostics.

Clinical Management of AOID- Japanese Experience

Isano Hase
Department of Respiratory Medicine
Southern TOHOKU General Hospital, Japan

Adult-onset immunodeficiency (AOID) is a rare disease that is frequently observed in East Asia. Japan has a relatively small number of AOID cases, around 100, but it has several distinctive characteristics from other countries.

The age of onset of AOID in Japan is higher than in other countries. Most AOID cases present disseminated nontuberculous mycobacterium (dNTM) and rarely have medical histories of tuberculosis or Salmonella infections. Slow-growing mycobacterium is a major causative species, especially *Mycobacterium avium* complex. In addition to the lung and lymph nodes, bones are frequently involved organs. Diagnostic difficulties in imaging, culture, and pathology with nonspecific symptoms, lead to incorrect diagnoses, including malignant diseases. FDG-PET/CT is suggested to be more sensitive than CT in evaluating the distribution of dNTM lesions and disease activity, including treatment response. QuantiFERON is a standard screening test for neutralizing anti-interferon gamma autoantibodies. Long-term treatments are required, since recurrence after cessation of treatment is commonly observed in Japan. The prognosis for cases in Japan is basically good. However, former immunosuppressive therapy or delayed diagnosis can lead to a poor prognosis.

I would like to share the clinical management of AOID in Japan, using the reported 42 cases in the literature and 18 cases from a multicenter retrospective cohort study.

Title:

Bridging the Gap: Unmet Needs in Current Protocols

Abstract

Anti-cytokine autoantibodies have emerged as an important cause of adult-onset immunodeficiency, particularly in Asia, where a substantial number of patients present with severe opportunistic infections such as disseminated nontuberculous mycobacterial disease. Despite increasing recognition of this condition, significant gaps remain in clinical management. Currently, no internationally accepted diagnostic criteria, treatment algorithms, or monitoring strategies have been established.

As a result, clinical practice varies widely across institutions and countries. Patients are often managed with heterogeneous combinations of antimicrobial therapy and immunomodulatory interventions, including rituximab or other immunosuppressive approaches, without clear evidence-based protocols. This variability highlights the urgent need for standardized frameworks to guide diagnosis, treatment, and long-term follow-up.

In this lecture, I will discuss current challenges in the management of anti-cytokine autoantibody–associated diseases, focusing on anti–interferon-γ autoantibody–mediated immunodeficiency as a representative example. I will review emerging clinical data from Asia and other regions, outline key unmet needs in current protocols, and discuss opportunities for harmonizing diagnostic and therapeutic strategies.

Importantly, the development of consensus-based clinical guidelines through international collaboration represents a critical first step toward standardization. Such a framework will facilitate multicenter clinical studies, enable systematic data collection, and accelerate the development of evidence-based treatment strategies. Ultimately, coordinated global efforts will be essential to improve outcomes for patients affected by these rare but increasingly recognized immunological disorders.

Cytokine-based CAAR T Cells as a precision therapy for anti-cytokine autoantibody-driven immunodeficiency

Neutralizing anti-interferon-γ autoantibodies (nAIGAs) impair IFN-γ-mediated immunity and predispose patients to severe opportunistic infections caused by intracellular pathogens, including nontuberculous mycobacteria and Talaromyces marneffei. Current treatment strategies rely largely on prolonged antimicrobial therapy and nonspecific immunosuppression, while therapies capable of selectively eliminating autoreactive B cells remain limited. In this study, we developed a cytokine-based chimeric autoantibody receptor (CAAR) T-cell platform targeting pathogenic anti-cytokine autoantibody–producing B cells. We engineered IFN-γ CAAR T cells using an IFN-γ variant designed to preserve autoantibody recognition while minimizing endogenous IFN-γ receptor signaling, thereby enabling selective recognition of autoreactive B cells through their surface B-cell receptors (BCRs). IFN-γ CAAR T cells efficiently eliminated target cells in vitro and retained therapeutic activity in an NSG xenograft model using Nalm-6 cells expressing patient-derived nAIGA BCRs. Despite partial attenuation by circulating nAIGAs, treatment reduced circulating autoantibody levels and suppressed autoreactive BCR-expressing cells. In addition, no evidence of IFN-γ receptor cross-reactivity or Fc-mediated cytotoxicity was observed. Ex vivo studies further demonstrated effective depletion of autoreactive B cells derived from patients. To broaden the applicability of this strategy, we extended the platform to type I IFN and GM-CSF CAAR T cells, both of which selectively recognized and eliminated cells expressing cognate autoreactive BCRs. Collectively, these findings establish cytokine-based CAAR T cells as a promising precision immunotherapy platform for anti-cytokine autoantibody–mediated diseases and infection-associated immunodeficiency.

Case Sharing 1: Pulmonary Manifestations: Identifying Rare Cases

Anti-cytokine autoantibodies (ACAAs) represent an emerging and underrecognized cause of immunodeficiency and susceptibility to opportunistic infections. Among the diverse clinical manifestations associated with ACAAs, pulmonary involvement poses particular diagnostic challenges due to its heterogeneous presentation and frequent overlap with other infectious, inflammatory, and autoimmune conditions.
This case-sharing session highlights rare pulmonary manifestations observed in patients with confirmed ACAAs, with a focus on anti-interferon-γ (IFN-γ) autoantibodies — a condition increasingly identified across East and Southeast Asia. Affected individuals often present with recurrent or refractory pulmonary infections caused by non-tuberculous mycobacteria (NTM), Talaromyces marneffei, Cryptococcus species, and other opportunistic pathogens, frequently in the absence of conventional immunodeficiency risk factors such as HIV infection or iatrogenic immunosuppression.

Through illustrative cases, we examine atypical radiological findings, diagnostic pitfalls, and the critical clinical clues that prompted ACAA evaluation. Key themes include the importance of considering ACAAs in patients with unexplained recurrent pulmonary infections, the role of high-resolution computed tomography in characterizing lesion patterns, and strategies for confirming the diagnosis through cytokine neutralization assays.

These cases underscore the necessity of raising clinical awareness among pulmonologists, infectious disease specialists, and intensivists. Early recognition of ACAA-associated pulmonary disease enables timely initiation of targeted antimicrobial therapy and consideration of immunomodulatory interventions, ultimately improving patient outcomes. This session aims to foster multidisciplinary dialogue and promote consensus on diagnostic and management approaches for this rare but clinically significant entity.

Cutaneous manifestations are found in approximately **80% of patients** with adult-onset immunodeficiency (AOID), specifically the syndrome caused by anti-interferon-gamma (IFN-γ) autoantibodies which are more common in Asians. These skin findings often serve as early clinical indicators of underlying systemic infections and can be broadly categorized into two groups:

1. Reactive Dermatoses (Most Common) , such as Sweet Syndrome and pustular eruptions simulating generalized pustular psoriasis. Other reactive cutaneous conditions includes **lobular panniculitis** (inflammation of subcutaneous fat) and **leukocytoclastic vasculitis**.

2. Infective dermatoses which occur when pathogens directly infect the skin through inoculation or dissemination due to the impaired cell-mediated immunity.

The treatment of these eruptions requires both the control of the specific opportunistic infections and correction of the underlying anti-IFN-γ autoantibody by either B-cell depleting agents such as r**ituximab and cyclophosphamide. Other agents such as IVIG, anakinra, azathioprine, acitretin, corticosteroid, colchicine, dapsone, NSAIDs and calcitriol have all been used with variable results.**

Title: AIGA with Concomitant Hematological Malignancy - Is Chemotherapy the Curative Answer?

Tai-Chung Huang, MD, PhD, National Taiwan University Hospital

Abstract
Anti-cytokine autoantibodies (ACAs) could be pathogenic immunoglobulins that neutralize cytokines, impairing immune responses and predisposing patients to severe infections and immune dysregulation syndromes. While immunosuppressive agents such as corticosteroids, plasmapheresis, and rituximab have been utilized for ACA-mediated diseases, chemotherapy also emerged as a potential therapeutic option due to its ability to broadly deplete immune effector cells, including autoreactive B cells responsible for autoantibody production. This abstract presents the rationale, clinical experience, and limitations of chemotherapy in the management of ACA-driven autoimmunity. Evidence suggests that cytotoxic chemotherapies can temporarily reduce autoantibody titers and mitigate disease severity in refractory cases. More targeted approaches, such as monoclonal antibodies against B cells or plasma cell inhibitors, might offer a more favorable safety profile. Precision immunotherapies targeting the mechanisms of autoantibody production represent a more promising direction for future treatment paradigm.