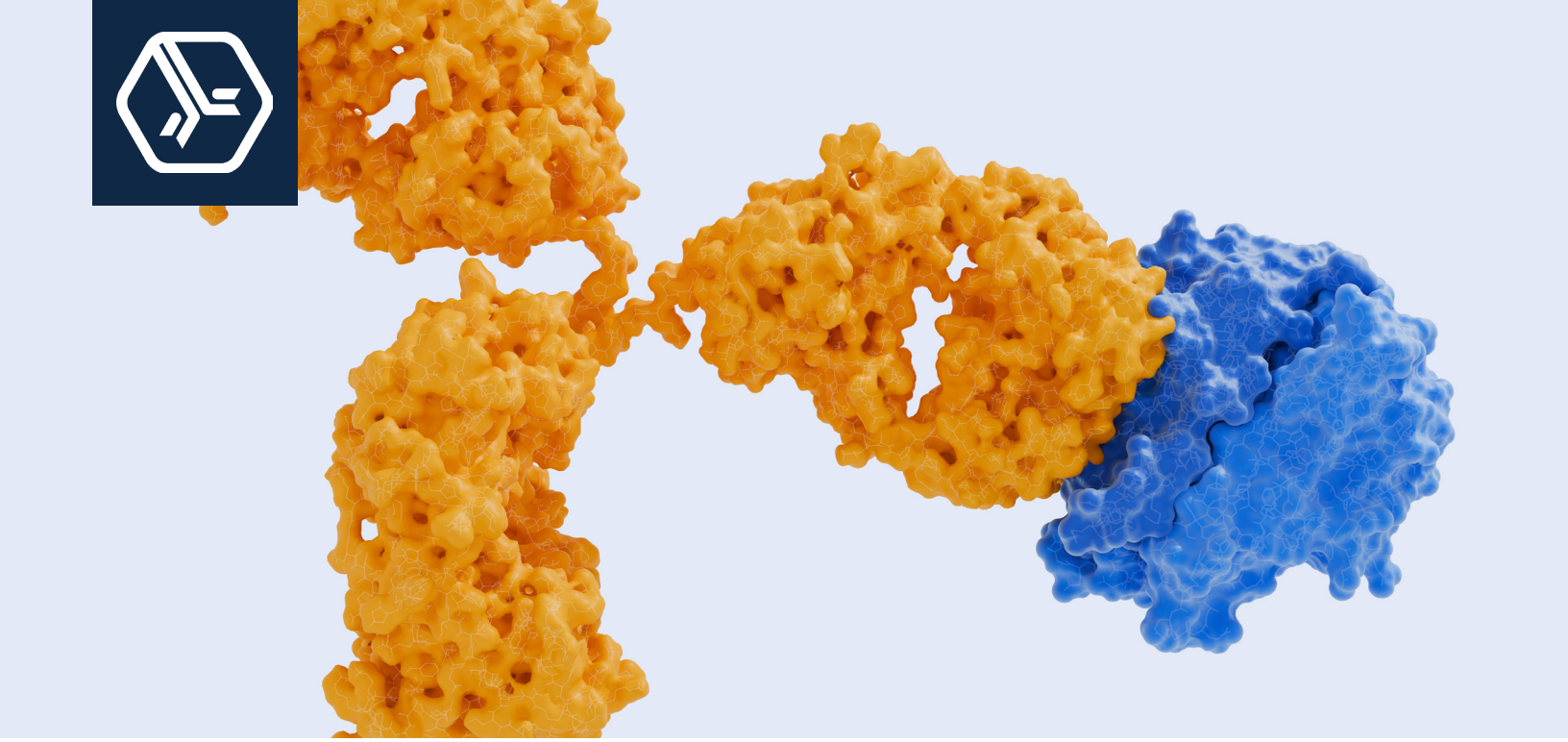

WHITE PAPER
ANTI-CYTOKINE AUTOANTIBODIES

Anti-Cytokine Autoantibodies in Health, Disease, and Treatment

- Explore how anti-cytokine autoantibodies (ACAAs) affect immune regulation in health and drive disease pathogenesis
- Understand the therapeutic potential of anti-cytokine antibodies being investigated in preclinical and clinical studies
- Learn how Sengenics protein microarrays can enhance ACAA research, supporting advancements in immunotherapy and vaccine development

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Introduction

Anti-cytokine autoantibodies (ACAAs) are naturally occurring or elicited antibodies that target cytokines—key proteins that mediate and regulate immune responses (Table 1). While cytokines generally direct and modulate immune activity, ACAAs often inhibit or potentiate these effects, influencing immune regulation in both health and disease. Although less common, ACAAs can also directly drive disease processes. This white paper delves into the role of ACAAs across various disease contexts and explores their potential use in predicting treatment outcomes, classifying disease severity, guiding vaccine development, and other therapeutic applications.

ACAAs in Health

Low levels of ACAAs are relatively common in the general population. A Danish study of nearly 9,000 healthy blood donors found that 86% of participants had at least one detectable ACAA, although the prevalence varied significantly depending on the cytokine target (2). Anti-IL-6 ACAAs were the most frequent, present in 65% of participants, while anti-GM-CSF ACAAs were found in just 10%. Interestingly, the study also found that the cumulative presence of multiple ACAAs correlated with several indicators of immune function, including self-reported health scores and the frequency of antibiotic prescriptions, supporting the belief that ACAAs influence overall immune health and resilience (3).

ACAAs could function as natural regulators, balancing the immune response and reducing the risk of excessive inflammation without compromising the body's ability to fight infections. By neutralizing pro-inflammatory cytokines, they may help prevent harmful immune over-activation like cytokine storms. These storms trigger excessive cytokine production, leading to severe inflammation across multiple organs and systems, which can potentially result in multi-organ failure and death.

ACAAs in Disease

ACAAs were initially discovered in patients with thymoma-associated autoimmune diseases but are now known to be present in healthy individuals and a variety of other conditions (4). These include autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus, and psoriasis; immunodeficiencies; and infectious diseases. In these contexts, ACAAs may play a causative or associative role, potentially contributing to disease by inhibiting cytokines crucial for immune defense. They can also be linked to specific subtypes within disease categories.

For instance, ACAAs can increase susceptibility to **infections** (5). Anti-IFNγ antibodies are strongly associated with disseminated non-tuberculous mycobacterial (NTM) infections. Anti-IL-6 ACAAs have been linked to severe staphylococcal and streptococcal infections while anti-IL-17/IL-22 antibodies are tied to chronic mucosal candidiasis. Anti-GM-CSF antibodies have been implicated in opportunistic infections such as those caused by *Nocardia spp.* and *Cryptococcus spp.*, as they impair macrophage function, which is essential for combating these pathogens. In at least one patient, anti-GM-CSF autoantibodies were detected 10 years prior to developing *Nocardia spp.* infection (6).

GM-CSF also plays a key role in the pathophysiology of **pulmonary alveolar proteinosis** (PAP), which is a lung condition characterized by the buildup of surfactant in the alveoli. The titer of circulating anti-GM-CSF autoantibodies may help predict how well a patient will response to PAP treatment with subcutaneous recombinant human GM-CSF (7).

During the **COVID-19** pandemic, the discovery of anti-IFN-α and IFN-ω ACAAs in some patients offered critical insights into why certain individuals experienced more severe outcomes (8). These antibodies impair the body's antiviral defense by neutralizing key interferons essential for early viral response, thereby

Cytokine-Based Therapies

The crucial role of cytokines in disease is evident through the numerous cytokine-based therapies approved by the U.S. Food and Drug Administration (FDA). To date, at least 39 therapies that mimic or target cytokines or their receptors have been approved for clinical use (Table 1) (1).

Table 1. Cytokine-based therapies approved by the U.S. FDA

Cytokine	Drug Type	Brand Name	Disease Area
G-CSF	Protein	Neupogen, Neulasta	neutropenia
GM-CSF	Protein	Leukine	neutropenia
IFN-α	Protein	Intron A, Roferon-A	chronic hepatitis B, chronic hepatitis C, hairy cell leukemia, Kaposi's sarcoma, malignant melanoma, follicular lymphoma, chronic myelogenous leukemia (CML)
IFN-β	Protein	Avonex, Betaseron, Rebif, Plegridy	multiple sclerosis (MS)
IFN-γ	Protein	Actimmune	chronic granulomatous disease (CGD), severe malignant osteopetrosis
IL-1R	Small molecule	Kineret	rheumatoid arthritis, neonatal-onset multisystem inflammatory disease (NOMID)
IL-2	Protein	Proleukin	metastatic renal cell carcinoma, metastatic melanoma
IL-5	Antibody	Nucala, Cinqair, Fasenra	severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis (EGPA)
IL-6R	Antibody	Actemra, Kevzara	rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, cytokine release syndrome
IL-11	Protein	Neumega	severe thrombocytopenia
IL-12/23 [1]	Antibody	Stelara, Tremfya, Omvoh	psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis
IL-13	Antibody	Adbry	atopic dermatitis
IL-17A	Antibody	Cosentyx, Taltz, Siliq	psoriasis, psoriatic arthritis, ankylosing spondylitis, axial spondyloarthritis (axSpA), hidradenitis suppurativa (HS)
IL-17A/IL-17F [2]	Antibody	Bimzelx	psoriatic arthritis, axSpA, ankylosing spondylitis
IL-23	Antibody	Tremfya, Ilumya, Skyrizi	psoriasis, psoriatic arthritis, Crohn's disease
TNF	Antibody	Remicade, Humira, Cimzia, Simponi	rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriasis, psoriatic arthritis
TNFR	Receptor fusion protein	Enbrel	rheumatoid arthritis, psoriasis, ankylosing spondylitis, juvenile idiopathic arthritis

[1] Drugs target a shared subunit between IL-12 and IL-23.
[2] Drug targets IL-17A and IL-17F separately or as a heterodimer.

increasing susceptibility to severe COVID-19. Interestingly, the frequency of these ACAAs was associated with increased age and male sex in patients with critical COVID-19 ($p = 3x10^{-6}$ and $p = 0.003$, respectively) (9).

Another study found that recovered COVID-19 patients with higher autoantibody titers targeting a subset of cytokines known as chemokines—specifically CCL21, CXCL13, and CXCL16—were less likely to experience long COVID-19 symptoms one year after infection (10). This suggests that certain ACAAs may be linked to the progression and outcome of the disease.

In **systemic lupus erythematosus (SLE)**, disease severity is linked to elevated levels of IFN-α and ACAAs targeting BAFF, a cytokine involved in B-cell activation (5). On the other hand, ACAAs that neutralize IFN-α and TNF have been associated with reduced lupus severity, suggesting that ACAAs may have therapeutic potential in diseases driven by cytokine activity.

Beyond these established associations, emerging research suggests that ACAAs may be more widespread, with implications for conditions like cancer, cardiovascular disease, and neurological disorders.

It is also worth mentioning that ACAAs may also arise as unintended consequences of severe infections or tissue damage, contributing to immune dysregulation. As such, they could serve as early indicators of immune imbalance and dysfunction.

Expanding Role of Anti-Cytokine Antibodies (ACAs) in Disease Treatment and Therapeutics

The therapeutic potential of ACAs is being explored in various disease contexts (Table 1). In **oncology**, ACAs have garnered attention for their possible roles in treating cancer-related cachexia (CRC) and improving the efficacy of monoclonal antibody (mAb) therapies. Among the most promising approaches for treatment of CRC-associated cachexia is a combination of anti-IL-1A antibodies and thalidomide, reducing the inflammatory burden associated with the condition (11).

Additionally, researchers are investigating a new class of therapies called immunocytokines (12-14). Immunocytokines are antibody-cytokine fusion proteins or therapeutic ACAs (such as those listed in Table 1) that are coupled to antibodies targeting cancer-specific or cancer-associated tumor antigens. These are designed to address the challenges posed by the tumor micro-environment in solid tumors, which often suppresses immune activity and diminishes mAb efficacy, yet remains sensitive to pro-inflammatory cytokines.

Traditional cytokine therapies have been limited by off-target toxicity and the short half-life of cytokines when administered alone. Immunocytokines offer a solution by delivering cytokines directly to the tumor site, extending their half-life, and reducing systemic toxicity. These fusion proteins can also bridge local cytotoxic immune cells, such as macrophages and natural killer (NK) cells, with tumor cells, enhancing the immune system's ability to target and destroy cancer cells.

Several immunocytokines are currently in clinical trials (Table 2), demonstrating promise for future cancer treatment strategies by optimizing immune activation at the tumor site without the widespread side effects of systemic cytokine therapy (13,14).

Experimental models suggest that ACAAs may play a protective role in certain **cardiovascular diseases** by modulating inflammatory responses. For instance, anti-IL-17 antibodies have been shown to reduce inflammation in murine models of autoimmune myocarditis, a condition driven by an autoimmune response against cardiac myosin (15). In Kawasaki Disease, a meta-analysis of mAb studies revealed that while anti-TNF did not lower the incidence of coronary artery aneurysms, it did reduce resistance to treatment with intravenous immune globulin (16).

Additionally, romilkimab, a bispecific ACA that neutralizes IL-4 and IL-13, has shown promise in treating patients with systemic sclerosis (17). Tocilizumab (TCZ), an mAb targeting the IL-6R and blocking its interaction with IL-6, is used to treat Takayasu arteritis, giant cell arteritis, and other inflammatory diseases, including Castleman disease, idiopathic juvenile arthritis, and rheumatoid arthritis.

In **neurological disorders**, murine models have demonstrated that ACAs can reduce the severity of experimental autoimmune encephalitis (EAE), which is a model for multiple sclerosis (MS)(18). Additionally, anti-cytokine mAbs targeting IL-1β and IL-6 have shown promise in reducing brain inflammation and preventing blood-brain barrier permeability in fetal ischemia-reperfusion injury ovine models (19). These findings suggest a potential therapeutic role for ACAs in neuroinflammatory and neurodegenerative conditions.

ACAs that target TNF, IL-12, and IL-23 are in clinical use to treat **inflammatory bowel disease** (IBD), such as Crohn's disease and ulcerative colitis (1). These mAbs bind to their respective pro-inflammatory cytokine, inhibiting their function, which helps reduce inflammation and alleviate pain.

Table 2. Clinical trials using immunocytokines

Cytokine	Target Antigen	Name	Cancer Type	Phase
IFN-α2B	CD38	Modakafusp alfa (TAK-573)	multiple myeloma	I, II
IL-2	GD2	Hu14.18-IL-2	neuroblastoma, melanoma, sarcoma, solid childhood tumors	I, II
IL-2	EpCAM	huKS-IL2	SCLC, prostate, ovarian, breast, bladder, kidney, lung, solid tumors	I, II
IL-2	CD20	DI-Leu16-IL2	B cell lymphoma	I, II
IL-2	Tenascin-C	F16-IL2	breast, AML, solid tumors, MCC	II
IL-2 variant	CEA	CEA-IL2v (RG7813)	solid tumors	I
IL-2 variant	FAP	FAP-IL12v	solid tumors, RCC, melanoma, pancreatic, breast, HNC, esophageal, cervical	I, II
IL-2 variant	PD-1	RG6279, IBI363, IAP0971	solid tumors	I
IL-2, IL-12, TNF	EDB	L19-IL2, L19-TNF, BC1-IL-12 (AS1409), L19-IL-12	melanoma, RCC, NSCLC, solid tumors, pancreatic, colorectal, DLBCL, glioblastoma, sarcoma, glioma	I, II, III
IL-2LT, IL-12	Histone/DNA structures	NHS-IL12	NSCLC, solid tumors, pancreatic, urogenital, bladder, NHL, Kaposi sarcoma, melanoma	I, II
IL-15	PD-L1	KD033, SIM0237, IGM-7354	solid tumors	I
IL-21	PD-1	AMG256	solid tumors	I

AML = acute myeloid leukemia, DLBCL = diffuse large B-cell lymphoma, HNC = head and neck cancer, MCC = Merkel cell carcinoma, NSCLC = non-small cell lung cancer, RCC = renal cell carcinoma

Additional conditions treated with FDA-approved mAbs targeting cytokines or cytokine receptors are listed in Table 1.

ACAAs in Disease Prevention

Leveraging ACAAs through anti-cytokine vaccination before disease onset has demonstrated promise in preclinical animal studies. For instance, vaccines targeting IL-17 have been effective in reducing the severity of collagen-induced arthritis (CIA) and EAE (20). Similarly, an anti-IL-6 vaccine protected mice from CIA, while an anti-IL-18 vaccine helped reduce the severity of SLE and prevented renal damage (21). Anti-cytokine vaccination also shows potential in other conditions, including cachexia, antibody-induced arthritis, Leishmaniasis, atherosclerosis, and collagen antibody-induced arthritis (CAIA).

However, clinical trials are needed to evaluate the long-term safety, efficacy, and potential side effects of anti-cytokine vaccination in humans. If successful, these vaccines could provide a new, targeted approach for managing autoimmune diseases and reducing the need for lifelong immunosuppressive therapies.

Measuring ACAAs and ACAs with Precision

Protein microarrays are indispensable in ACAA and ACA research, offering a rapid and cost-effective way to simultaneously screen for the presence of multiple antibody specificities in any indication. They enable researchers to profile ACAAs to understand their role in both protecting against and driving disease, evaluate the specificity of cytokine-based immunotherapies for targeted treatments, and measure immune responses to anti-cytokine vaccines, providing critical insights into vaccine efficacy and immune system regulation.

Further applications of protein microarrays in anti-cytokine therapeutics and disease profiling include:

- Detecting anti-drug antibodies in patients treated with recombinant cytokine therapies
- Identifying ACAAs linked to protection or pathology
- Profiling ACAAs to classify health and disease subtypes, reflecting genetic predispositions and immune history
- Exploring anti-cytokine therapy or vaccination approaches
- Developing protease-activatable, targeted cytokines masked by ACAs
- Enhancing cytokine stabilization
- Engineering bispecific or trispecific antibodies for targeted cytokine delivery to tumors or other tissues

With 90% of antibodies binding to conformational epitopes, Sengenics utilizes its proprietary KREX® technology to preserve the native structure of these crucial protein antigens, ensuring reproducible and precise ACAA and ACA profiling.

Sengenics's comprehensive protein library includes over 2,000 human proteins, such as cytokines, chemokines, cytokine and chemokine receptors, antimicrobial peptides, cytotoxic effectors, and various other immune effectors and modulators (Table 3). Notably, chemokines are a specific subset of cytokines. These antigens were meticulously curated by immunologists for their known or potential antigenicity, relevance in disease, their biological functions, the compartments and tissues where they are highly expressed, and the immune cells that respond within both the innate and adaptive immune systems.

Sengenics offers flexible solutions, with ready-to-use panels and customizable options to suit specific research needs. Custom cytokine panels, incorporating additional antigens relevant to fields like rheumatology, oncology, neurology, and infectious diseases, allow researchers to study both ACAAs and other disease-relevant antibodies across various research areas. Comprehensive support is provided at every stage—from experimental design to advanced bioinformatics analysis—ensuring optimal outcomes for ACAA and ACA measurement and immune profiling.

Conclusion

ACAAs play a dual role, acting as natural immune regulators while also contributing to pathology by impairing critical cytokine functions. Numerous studies highlight their potential as biomarkers for predicting disease severity, progression, and treatment response. Monoclonal ACAs are being explored as therapeutic tools in diseases like cancer, cardiovascular disease, and neurological disorders, offering targeted immune modulation. Continued research into ACAAs and ACAs, especially through precision antibody profiling with Sengenics protein microarrays, holds transformative potential for treating immune-mediated diseases and paving the way for personalized, more precise interventions.

Contact Us

Sengenics develops key solutions for biological research, specializing in the discovery and validation of autoantibody biomarker signatures. For more information on how Sengenics can advance your research, email us at enquiries@sengenics.com or visit our website at sengenics.com.

Table 3. Cytokines, chemokines, and their receptors included in the Sengenics protein library *

Cytokines	Chemokines	Receptors
Activin A (INHBA)	CCL1	Cytokine Receptors
Amphiregulin (AREG)	CCL2	ACVR2A
APRIL (TNFSF13)	CCL3	ACVR2B
G-CSF (CSF3)	CCL7	CSF3R
IFNA2	CCL8	CXCR2
IFNB2	CCL13	IL13RA1
IFNW1	CCL16	IL13RA2
IFNG	CCL17	IL21R
IL1A	CCL19	IL6ST
IL1β	CCL20	
IL3	CCL21	Chemokine Receptors
IL5	CCL22	CCR5
IL6	CCL25	CXCR2
IL7	CCL27	CXCR4
IL8 (CXCL8)	CCL28	CXCR6
IL10	CXCL6	
IL11	CXCL8	
IL12A	CXCL9	
IL12B	CXCL10	
IL13	CXCL11	
IL15	CXCL12	
IL17A	CXCL13	
IL17F	CXCL16	
IL18	CXCL17	
IL19	CX3CL1	
IL20		
IL21		
IL22		
IL23 (IL23A+IL12B)		
IL24		
IL26		
IL27		
IL31		
IL32		
IL34		
IL35		
IL36		
IL37		
IL39 (IL23A+EBI3)		
IL40 (C17orf99)		
M-CSF (CSF2)		
TNF		
TSLP		

* Visit the Sengenics website or contact us for the most up-to-date list of available proteins

Resources

Find out why protein shape matters in antibody binding [White Paper]: https://sengenics.com/wp-content/uploads/2024/04/White-Paper-Antibody-Antigen-Binding-Shape-Matters-vs1pt0.pdf

Watch a 1-minute video to discover why protein shape matters in antibody-antigen binding [Video]: https://www.youtube.com/watch?v=lBEYLlk5Yws

Learn how precision antibody profiling with Sengenics protein microarrays can streamline vaccine development [White Paper]: https://sengenics.com/wp-content/uploads/2024/10/Address-Key-Challenges-in-Vaccine-Development-with-Antibody-Profiling_vs1pt0.pdf

Browse Sengenics protein microarrays, which include custom and ready-to-use panels: https://sengenics.com/services/autoantibody-biomarker-profiling/

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