Listen to a recording of this eBook

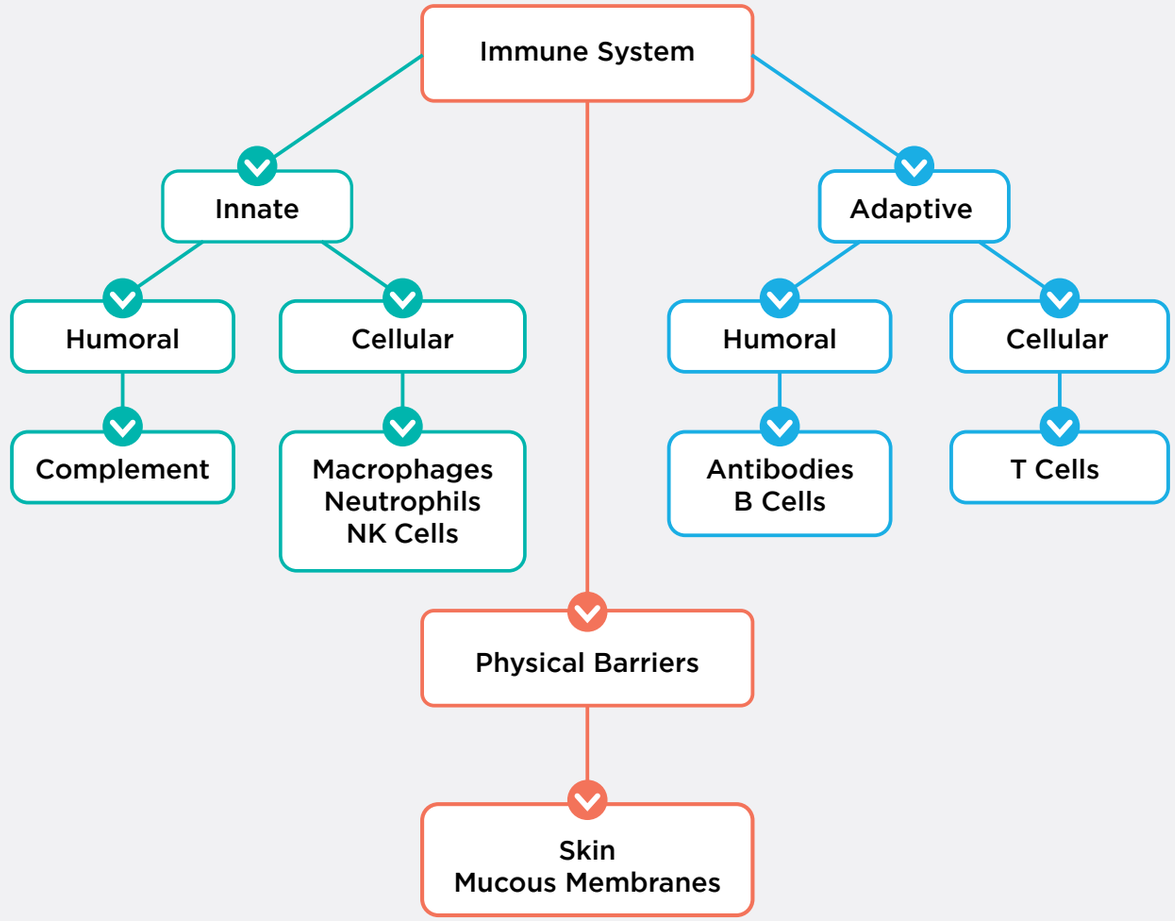
Key Biomarkers of Immunomodulation: Complement Factors and Cytokines

ALTASCIENCES

The Importance of Monitoring Complement Factors and Cytokines

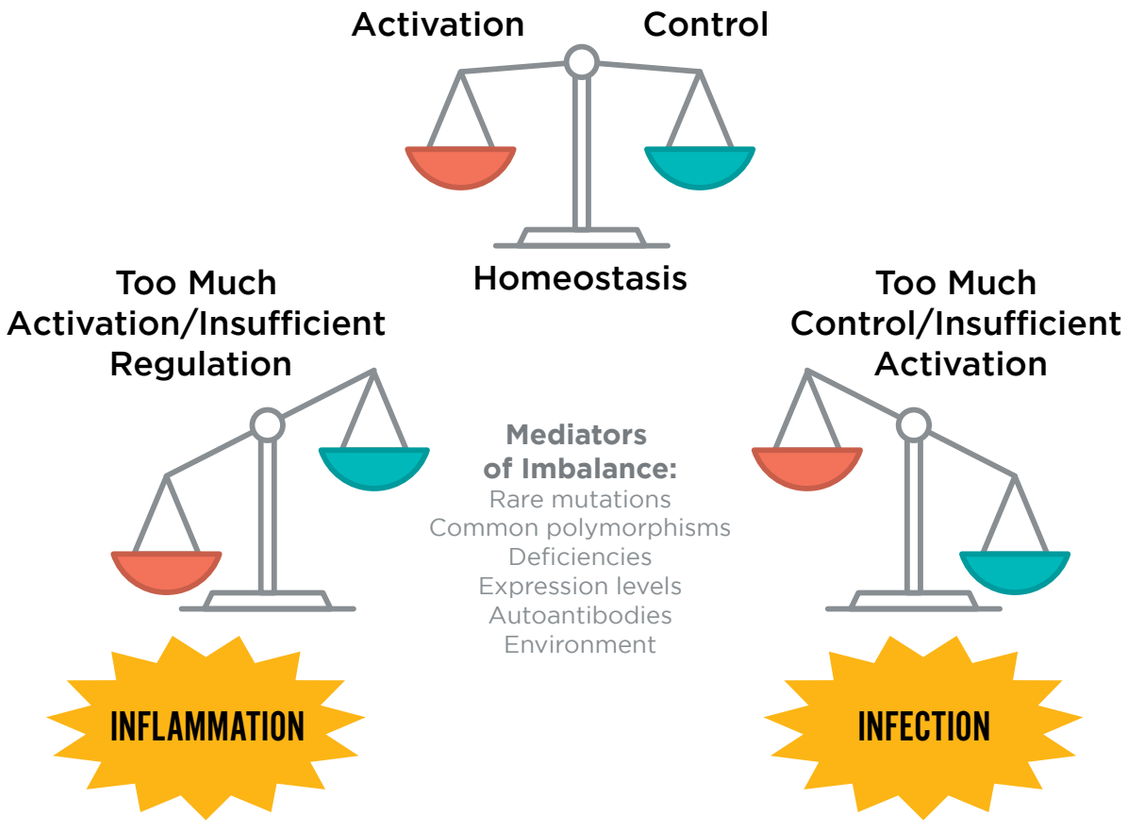
Complement factors and cytokines are small proteins that work within the immune system. Monitoring them has become increasingly important as the movement toward personalized treatments for cancers and genetic diseases has spurred research and development into biologics, vaccines, and small molecules that can have unintended consequences due to their immunomodulatory effects. Regulatory bodies have responded to unanticipated adverse events, like one that occurred during Phase I trials of the monoclonal antibody TGN1412 in 2006 in Great Britain, by enacting stricter rules around testing these kinds of drugs. FDA guidelines recommend assessing the efficacy and toxicity of these novel drugs in a relevant nonclinical species; this may involve the measurement of cytokines and of complement factors. Drugs and vaccines can also be monitored for efficacy when their intended biological effect is to activate T helper (Th) cells that cause a pro-inflammatory (Th1) or anti-inflammatory (Th2) response.

Cytokines and complement factors can activate or inactivate the immune response, which is made up of two different parts: innate and adaptive. The innate immune system is the body's first line of defense against pathogens, whereas adaptive immunity is specific to each foreign challenge. It is activated by exposure to diseases or vaccination, and is composed of the humoral and cellular responses.



ALTASCIENCES

Cytokines can activate the complement system, while complement factors can produce peptides that stimulate innate immune cells to secrete cytokines. Under healthy conditions, these reciprocal functions contribute to keeping the body in homeostasis. However, when cytokines or complement factors are abnormally expressed or triggered, they can lead to a positive feedback loop, resulting in autoimmune disorders and inflammation. Deficiencies can also occur, preventing the body from mounting a sufficient immune response to pathogens and cancers.



Credit: https://link.springer.com/article/10.1007/s00281-017-0655-8

Research into cytokines and the complement system has resulted in the ability to manipulate them to produce therapeutic effects. For instance, cytokines IFN-γ and IL-2 can be used in cancer treatment to promote the activity of immune cells that target tumor cells. Also driving research is a growing awareness of the risks posed by cytokine and complement overexpression, from the implication of chronic inflammation in a wide range of diseases to severe complications from viral illnesses like COVID-19. Complement and cytokine proteins can be used as biomarkers that serve as targets for therapeutic treatment, while convertase inhibitors can interrupt the complement cascade process.

ALTASCIENCES

Measuring cytokines and complement factors to test for inflammation has several advantages and challenges compared with more traditional methods like tissue-sample or organ slide examination by pathologists. While these methods are still being used, cytokine and complement testing can offer supporting information by employing relatively non-invasive techniques. The ability to multiplex cytokine assays is an especially important breakthrough, given the large quantity of information available with a single low-volume sample. Understanding the advantages as well as the challenges is essential to enabling researchers to choose the right method, or combination of methods, for each application.

Pros and Cons of Measuring Cytokines and Complement

ADVANTAGES	CHALLENGES
Accessibility (simple blood draw)	Not a local assessment (tissue-specific)
Serial monitoring (multiple timepoints)	Transient
Quantitative assessment	Species, strain differences
Fast analytical turnaround time	Phenotypic manifestation are not well characterized
Potential for translatability of preclinical data to the clinic	

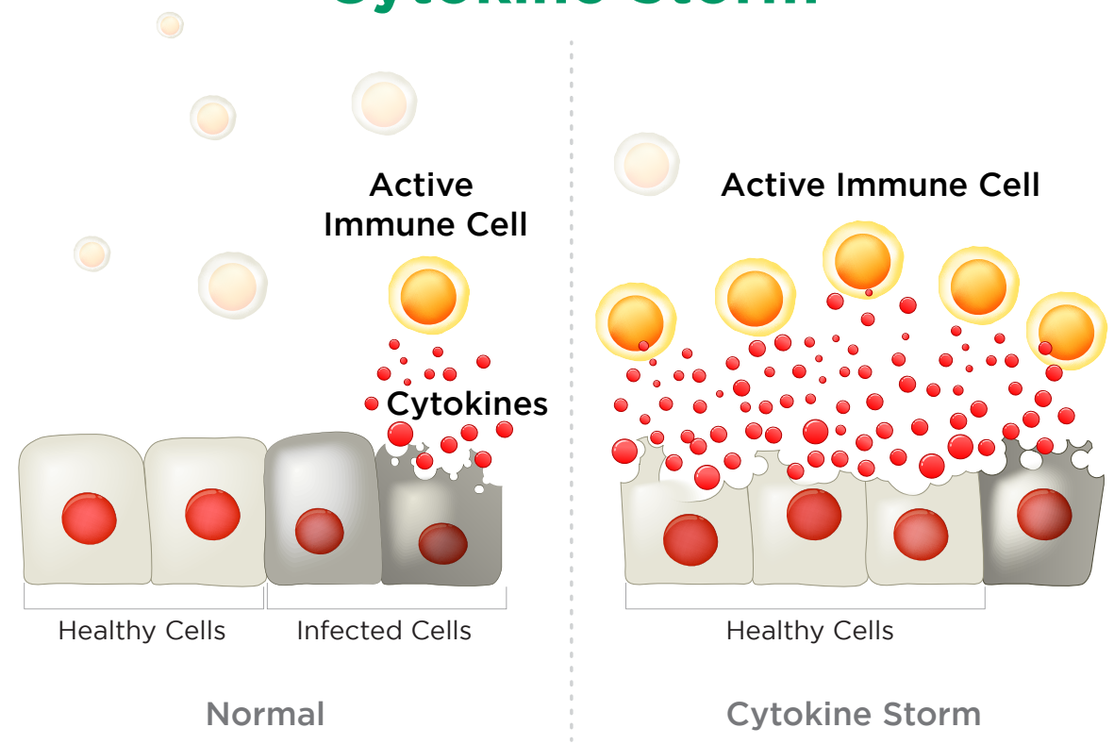
What Is the Complement System?

Complement consists of over 40 serum and membrane-associated proteins, including some that can be serially activated. These can recognize invading microbes based on their specific molecular patterns and structure, and result in the initiation of a powerful proinflammatory process. Complement also works to recognize debris from destruction of the invaders, or from excess immune complexes in the host. It can, however, be too much of a good thing: what is of a great benefit in fighting infection locally, can be detrimental when it happens systemically.

Complement and Novel Drugs

Complement often recognizes novel biological drugs and oligonucleotides as foreign. This can stimulate immune cells to secrete cytokines. The outcome can be cytokine storm with multiple organ failure and even death, highlighting the importance of running careful, reliable bioanalytical tests when investigating these drugs.

Cytokine Storm



Credit: https://www.gettyimages.ca/detail/illustration/cytokine-storm-or-hypercytokinemia-royalty-free-illustration/1281435328?adppopup=true

Major Functions of the Complement System

Complement plays a central role in interacting with cells in the innate and adaptive immune response systems, performing three major functions: opsonization, inflammation, and lysis. The level of activation of each can be measured by specific proteins that are created during the complement cascade process.

FUNCTION	DESCRIPTION	MEASURABLE PROTEINS
Opsonization	• Tags antigens to be cleared	C3b, C4b, C1q
Inflammation	• Recruits macrophages, neutrophils, mast cells, and dendritic cells to clear tagged particles • Releases histamines and cytokines	C3a, C5a
Lysis	• Ruptures the cell wall or membrane • Activates membrane attack complex (MAC) to directly kill pathogen	C5b-9, CH50

Complement System: Three Activation Pathways

The complement system can be activated along any one of three pathways: classical, alternative, and lectin. Proteins created during these processes can be tested by using them as biomarkers.

Classical Pathway:

- Activated by the formation of antigen-antibody complexes and anti-drug antibodies
- Can be tested using assays to measure C4a or C4d protein levels

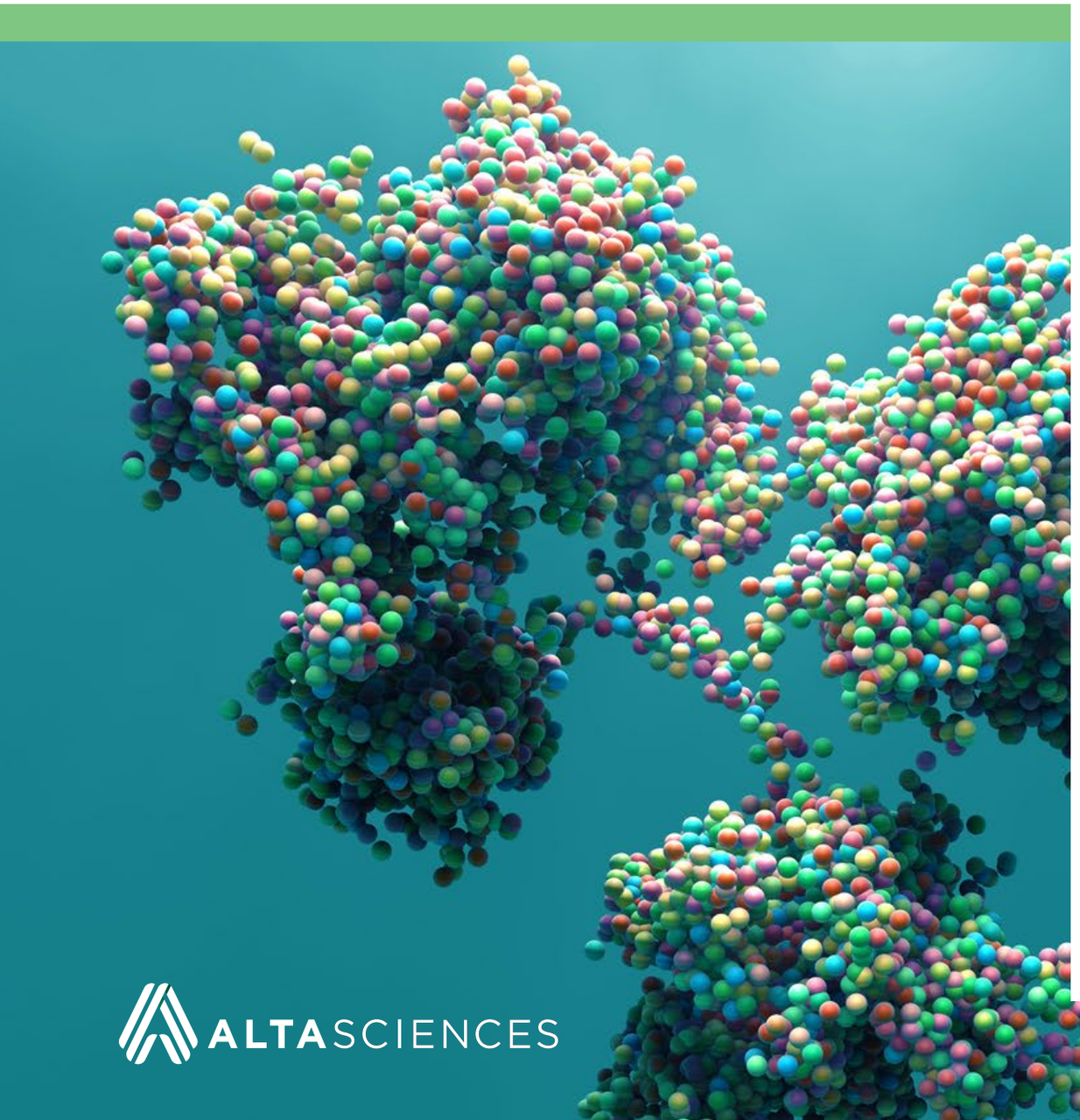
Alternative Pathway:

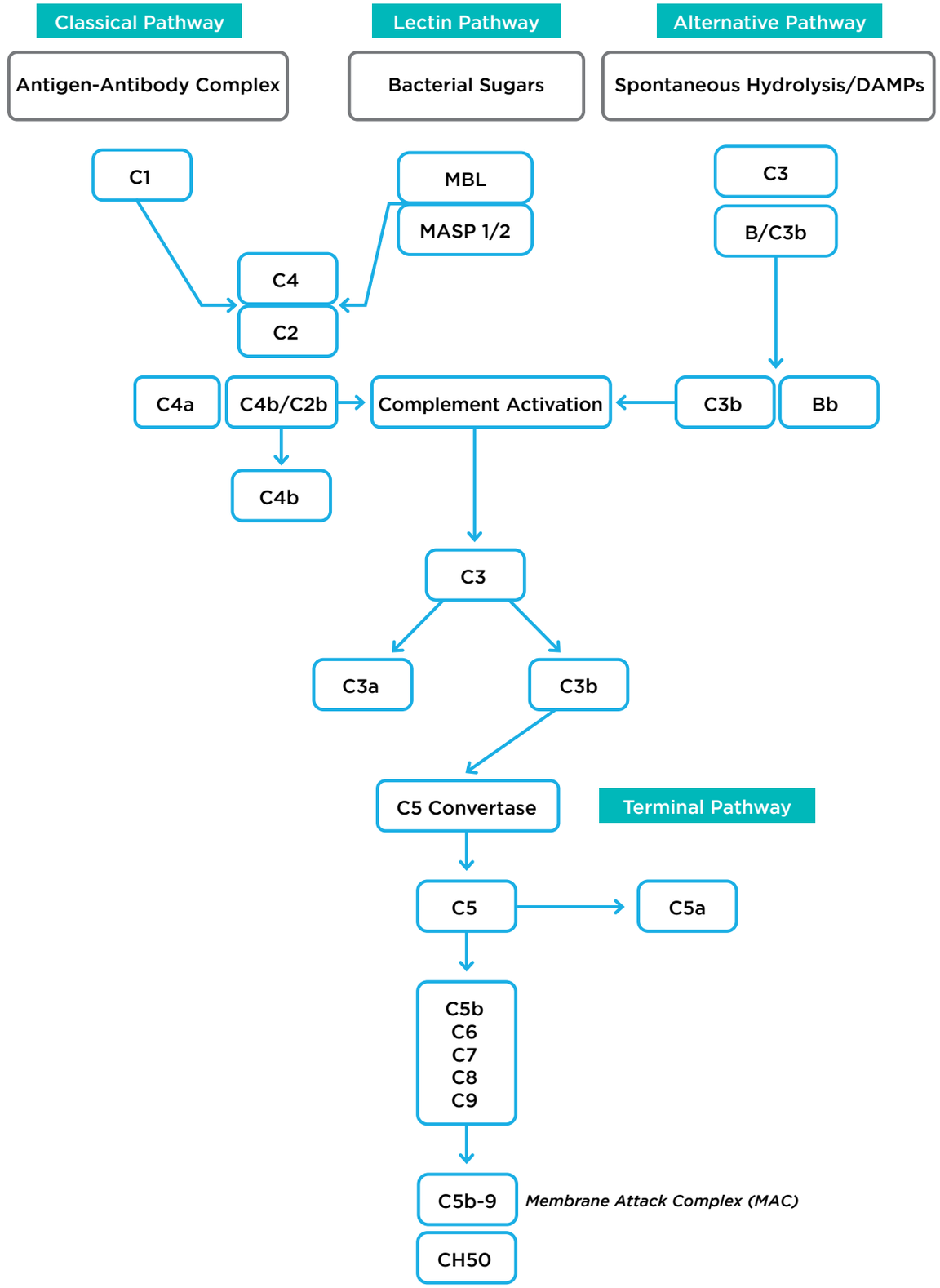
- Always active at a low level to check for lipids found on bacterial surfaces
  - Crucial to test lipid-based drugs for host-cell protein contamination to avoid overactivation
- Can be tested by measuring Bb protein levels

Lectin Pathway:

- Activated by the recognition of pathogens by mannose-binding lectin

At each step of the complement cascade, proteins are broken down into smaller proteins, peptides, and amino acids. The activation process begins with C3 convertase, a serine protease that cleaves C3 into C3a and C3b. Proteins created at each step of the process can be measured using highly sophisticated, state-of-the-art bioanalytical equipment.





ALTASCIENCES

Complement Monitoring Assays in Nonclinical Studies

ASSAY	DESCRIPTION
C3a	• Plays a central role in the activation of complement system – Both classical and alternative complement activation pathways • Low level may indicate susceptibility to bacterial infection
Bb	• The fragment of complement factor B that results from activation of the alternative pathway • Involved in the proliferation of pre-activated B lymphocytes
C4d	• A measure of the classical pathway activation • High levels may indicate rheumatoid arthritis or systemic lupus erythematosus • Its measure also has uses in graft rejection
C5b-9	• Membrane attack complex (MAC) • High level may indicate systemic lupus erythematosus

What Are Cytokines?

Cytokines are chemical messengers made up of proteins, peptides, and glycoproteins. While their function is normally tightly regulated, they can be abnormally expressed under pathological conditions. Cytokine proteins include chemokines, interferons (IFN), tumor necrosis factor (TNF), interleukins, and lymphokines. They play an important role in protecting against cancers and pathogens, like bacteria and viruses, and regulating the immune response, but can become dangerous if overexpressed.

Cytokine testing is used to assess the efficacy of drugs being developed to modulate their expression. It also serves a crucial purpose in safety evaluation, particularly for biological drugs that have the potential to cause serious adverse effects. Given their dual ability to either cause or diminish inflammation, cytokines can serve as valuable biomarkers to diagnose inflammation-related illnesses. For example, in the case of COVID-19, measuring the cytokines IL-6 and TNF-α helps identify cytokine storm, one of the disease's more serious complications. Testing also serves as a tool to measure the therapeutic effects of drugs used to manipulate cytokines. For instance, IFN-γ and IL-2 are used in cancer treatments to promote immune cell activity that fights tumor cells. Drugs that decrease TNF-α levels, used in the treatment of autoimmune disease, can also be tested during development to monitor efficacy.

CYTOKINE	TYPE OF CYTOKINE	FUNCTION
IFN-γ	Interferon/Chemokine	Pathogen recognition/ Anti-viral
IL-6	Interleukin/Chemokine	Pro-inflammatory
TNF-α	Tumor necrosis factor	Pro-inflammatory/ Induces chemokine production in the central nervous system
IL-2	Interleukin/Chemokine	Proliferation of T & B cells
IL-10	Interleukin	Anti-inflammatory/ Regulator of chemokine expression
IL-8	Interleukin/Chemokine	Attracts neutrophils
MCP-1	Monocyte chemoattractant protein/Chemokine	Attracts monocytes

Complement and Cytokine Monitoring

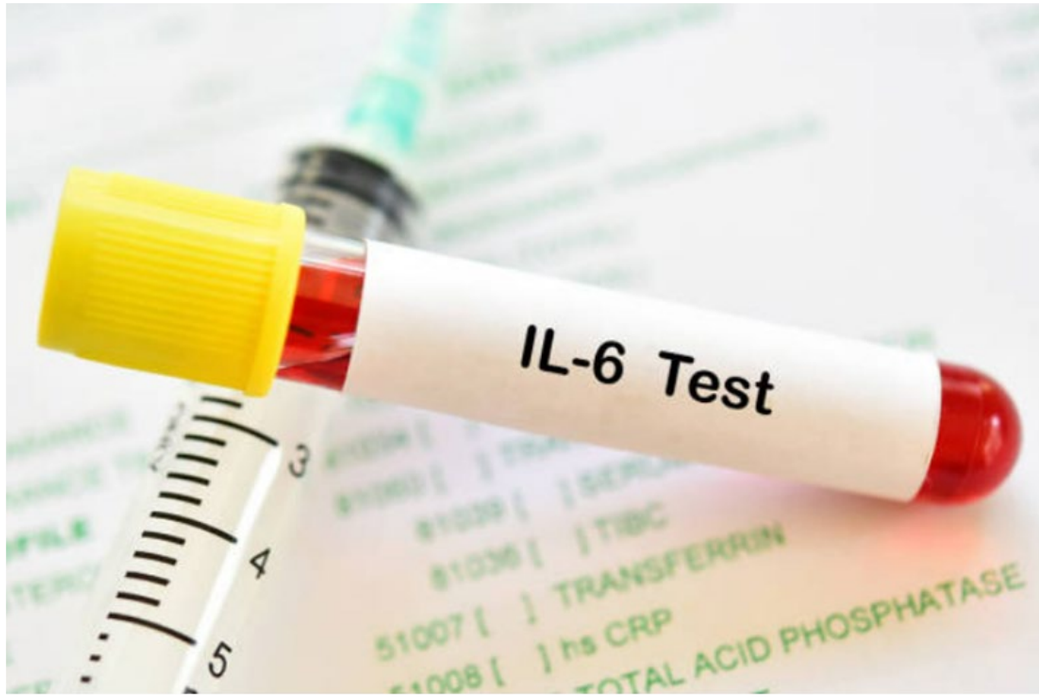
Relying on a simple blood draw, complement and cytokine testing has the advantage of being a non-invasive, low-cost solution. Altasciences will select the appropriate technology combination to meet your needs and help you obtain reliable, quality research data.

- **Flow cytometry** — Flow cytometry is a highly sensitive fluorescent labeling and detection system used to measure biomarkers. Flow cytometry can be conducted in less than two hours, detecting multiple intracellular cytokines simultaneously. It can also distinguish cytokine-secreting cell subgroups based on cellular immune phenotype. No tissue culture is required, and whole blood analysis is possible.

- **ELISA** — Enzyme-linked immunosorbent assay (ELISA) is a commonly used, well-established, inexpensive method for screening a wide variety of cytokines and complement factors.

- **Multiplexed assays** — Multiplexing systems, such as the Luminex and MesoScale platforms, can detect multiple biomarkers simultaneously, significantly reducing the time required for each assay.

In addition to these frequently requested assays, Altasciences is able to provide custom services to develop, optimize, and validate sponsor-specific assays.



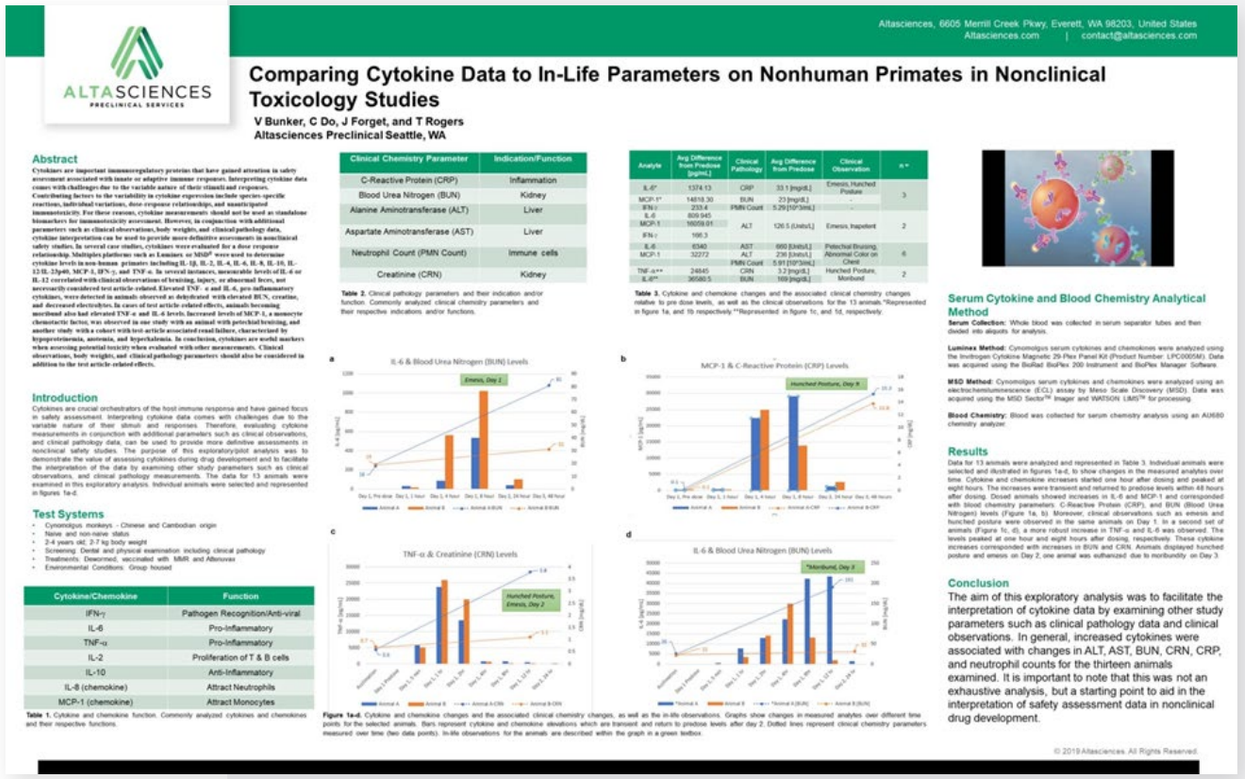
Complement and cytokine tests are frequently used in these therapeutic areas:

- Cancer Research
- Cytokine Storm Monitoring
- Autoimmune Diseases (RA, SLE)
- Inflammation
- Immunomodulation
- Allergy
- Atopic Dermatitis
- Graft Rejection
- Infectious Diseases
- Hemolytic Diseases
- Nephrology
- Osteoporosis
- Cardiology
- Vascular Diseases
- Diabetes
- Hypertension
- Apoptosis Research

Case Study

In nonclinical studies, cytokine data can be correlated to other observations like clinical pathology and clinical data. In the case study below, increased cytokines were associated with changes in ALT, AST, BUN, CRN, CRP, and neutrophil counts for a number of animals examined. More work is needed in that space in order to evaluate the correlation between cytokine levels and various indicators of toxicity, and to determine how cytokine assessment can contribute to evaluating toxicity and immunotoxicity throughout drug development.

CLICK HERE TO VIEW THE CASE STUDY



ALTASCIENCES PRECLINICAL SERVICES

Altasciences, 6605 Merrill Creek Pkwy, Everett, WA 98203, United States
Altasciences.com | contact@altasciences.com

Comparing Cytokine Data to In-Life Parameters on Nonhuman Primates in Nonclinical Toxicology Studies

V Bunker, C Do, J Forget, and T Rogers
Altasciences Preclinical Seattle, WA

Abstract

Cytokines are important immunoregulatory proteins that have gained attention in safety assessment associated with innate or adaptive immune responses. Interpreting cytokine data comes with challenges due to the variable nature of their stimuli and responses. Contributing factors to the variability in cytokine expression include species-specific reactions, individual variations, dose-response relationships, and massive/spotted immunotoxicity. For these reasons, cytokine measurements should not be used as standalone biomarkers for immunotoxicity assessment. However, in conjunction with additional parameters such as clinical observations, body weights, and clinical pathology data, cytokine interpretation can be used to provide more definitive assessments in nonclinical safety studies. In several case studies, cytokines were evaluated for a dose response relationship. Multiplex platforms such as Luminex or MSD® were used to determine cytokine levels in non-human primates including IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12/IL-23p40, MCP-1, IFN-γ, and TNF-α. In several instances, measurable levels of IL-6 or IL-12 correlated with clinical observations of bruising, injury, or abnormal feces, but necessarily considered test article-related. Elevated TNF- α and IL-6, pro-inflammatory cytokines, were detected in animals observed as dehydrated with elevated BUN, creatine, and decreased electrolytes. In cases of test article-related effects, animals becoming moribund also had elevated TNF-α and IL-6 levels. Increased levels of MCP-1, a monocyte chemotactic factor, was observed in one study with an animal with petechial bruising, and another study with a cohort with test-article associated renal failure, characterized by hypoproteinemia, azotemia, and hyperkalemia. In conclusion, cytokines are useful markers when assessing potential toxicity when evaluated with other measurements. Clinical observations, body weights, and clinical pathology parameters should also be considered in addition to the test article related effects.

Introduction

Cytokines are crucial orchestrators of the host immune response and have gained focus in safety assessment. Interpreting cytokine data comes with challenges due to the variable nature of their stimuli and responses. Therefore, evaluating cytokine measurements in conjunction with additional parameters such as clinical observations, and clinical pathology data, can be used to provide more definitive assessments in nonclinical safety studies. The purpose of this exploratory/pilot analysis was to demonstrate the value of assessing cytokines during drug development and to facilitate the interpretation of the data by examining other study parameters such as clinical observations, and clinical pathology measurements. The data for 13 animals were examined in this exploratory analysis. Individual animals were selected and represented in figures 1a-d.

Test Systems

- Cynomolgus monkeys - Chinese and Cambodian origin
- Naive and non-naive status
- 2-4 years old; 2-7 kg body weight
- Screening: Dental and physical examination including clinical pathology
- Treatments: Dexamed, vaccinated with MMR and Attenuvax
- Environmental Conditions: Group housed

Cytokine/Chemokine	Function
IFN-γ	Pathogen Recognition/Anti-viral
IL-6	Pro-Inflammatory
TNF-α	Pro-Inflammatory
IL-2	Proliferation of T & B cells
IL-10	Anti-Inflammatory
IL-8 (chemokine)	Attract Neutrophils
MCP-1 (chemokine)	Attract Monocytes

Table 1. Cytokine and chemokine function. Commonly analyzed cytokines and chemokines and their respective functions.

Clinical Chemistry Parameter	Indication/Function
C-Reactive Protein (CRP)	Inflammation
Blood Urea Nitrogen (BUN)	Kidney
Alanine Aminotransferase (ALT)	Liver
Aspartate Aminotransferase (AST)	Liver
Neutrophil Count (PMN Count)	Immune cells
Creatinine (CRN)	Kidney

Table 2. Clinical pathology parameters and their indication and/or function. Commonly analyzed clinical chemistry parameters and their respective indications and/or functions.

Analyte	Avg Difference from Predose [pg/mL]	Clinical Pathology	Avg Difference from Predose	Clinical Observation	n*
IL-6*	1374.13	CRP	33.1 [mg/dL]	Emesis, Hunched Posture	3
MCP-1*	14818.30	BUN	23 [mg/dL]	-	
IFN-γ	233.4	PMN Count	5.29 [10^3/mL]	-	
IL-6	809.945				
MCP-1	16059.01	ALT	126.5 [Units/L]	Emesis, Inapetent	2
IFN-γ	166.3				
IL-6	6340	AST	660 [Units/L]	Petechial Bruising, Abnormal Color on Chest	6
MCP-1	32272	ALT	230 [Units/L]		
		PMN Count	5.91 [10^3/mL]		
TNF-α**	24645	CRN	3.2 [mg/dL]	Hunched Posture, Moribund	2
IL-6**	36580.5	BUN	109 [mg/dL]		

Table 3. Cytokine and chemokine changes and the associated clinical chemistry changes relative to pre dose levels, as well as the clinical observations for the 13 animals *Represented in figure 1a, and 1b respectively.**Represented in figure 1c, and 1d, respectively.

Figure 1a-d. Cytokine and chemokine changes and the associated clinical chemistry changes, as well as the in-life observations. Graphs show changes in measured analytes over different time points for the selected animals. Bars represent cytokine and chemokine elevations which are transient and return to predose levels after day 2. Dotted lines represent clinical chemistry parameters measured over time (two data points). In-life observations for the animals are described within the graph in a green textbox.

Serum Cytokine and Blood Chemistry Analytical Method

Serum Collection: Whole blood was collected in serum separator tubes and then divided into aliquots for analysis.

Luminex Method: Cynomolgus serum cytokines and chemokines were analyzed using the Invitrogen Cytokine Magnetic 29-Plex Panel Kit (Product Number: LPC0005M). Data was acquired using the BioRad BioPlex 200 Instrument and BioPlex Manager Software.

MSD Method: Cynomolgus serum cytokines and chemokines were analyzed using an electrochemiluminescence (ECL) assay by Meso Scale Discovery (MSD). Data was acquired using the MSD Sector™ Imager and WATSON LIMS™ for processing.

Blood Chemistry: Blood was collected for serum chemistry analysis using an AU680 chemistry analyzer.

Results

Data for 13 animals were analyzed and represented in Table 3. Individual animals were selected and illustrated in figures 1a-d, to show changes in the measured analytes over time. Cytokine and chemokine increases started one hour after dosing and peaked at eight hours. The increases were transient and returned to predose levels within 48 hours after dosing. Dosed animals showed increases in IL-6 and MCP-1 and corresponded with blood chemistry parameters. C-Reactive Protein (CRP), and BUN (Blood Urea Nitrogen) levels (Figure 1a, b). Moreover, clinical observations such as emesis and hunched posture were observed in the same animals on Day 1. In a second set of animals (Figure 1c, d), a more robust increase in TNF-α and IL-6 was observed. The levels peaked at one hour and eight hours after dosing, respectively. These cytokine increases corresponded with increases in BUN and CRN. Animals displayed hunched posture and emesis on Day 2, one animal was euthanized due to moribundity on Day 3.

Conclusion

The aim of this exploratory analysis was to facilitate the interpretation of cytokine data by examining other study parameters such as clinical pathology data and clinical observations. In general, increased cytokines were associated with changes in ALT, AST, BUN, CRN, CRP, and neutrophil counts for the thirteen animals examined. It is important to note that this was not an exhaustive analysis, but a starting point to aid in the interpretation of safety assessment data in nonclinical drug development.

Biomarker Analysis at Altasciences

Altasciences is fully equipped to analyze a comprehensive range of biomarkers to support your nonclinical toxicology programs. Clinical assays may also be available by request.

NHP 10-Plex With MSD U-Plex (validated, serum)

- IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12/IL-23p40, IFN-γ, MCP-1 and TNF-α

NHP Complement Assays With Synergy H1 (validated, plasma)

- Bb ELISA, C3a ELISA

Rat 27-Plex With Luminex (qualified, serum)

- EGF, Eotaxin, Fractalkine, G-CSF, GM-CSF, GRO/KC/CINC-1, IFN-γ, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12(p70), IL-13, IL-17A, IL-18, IP-10, Leptin, LIX, MCP-1, MIP-1α, MIP-2, RANTES, TNF-α, and VEGF

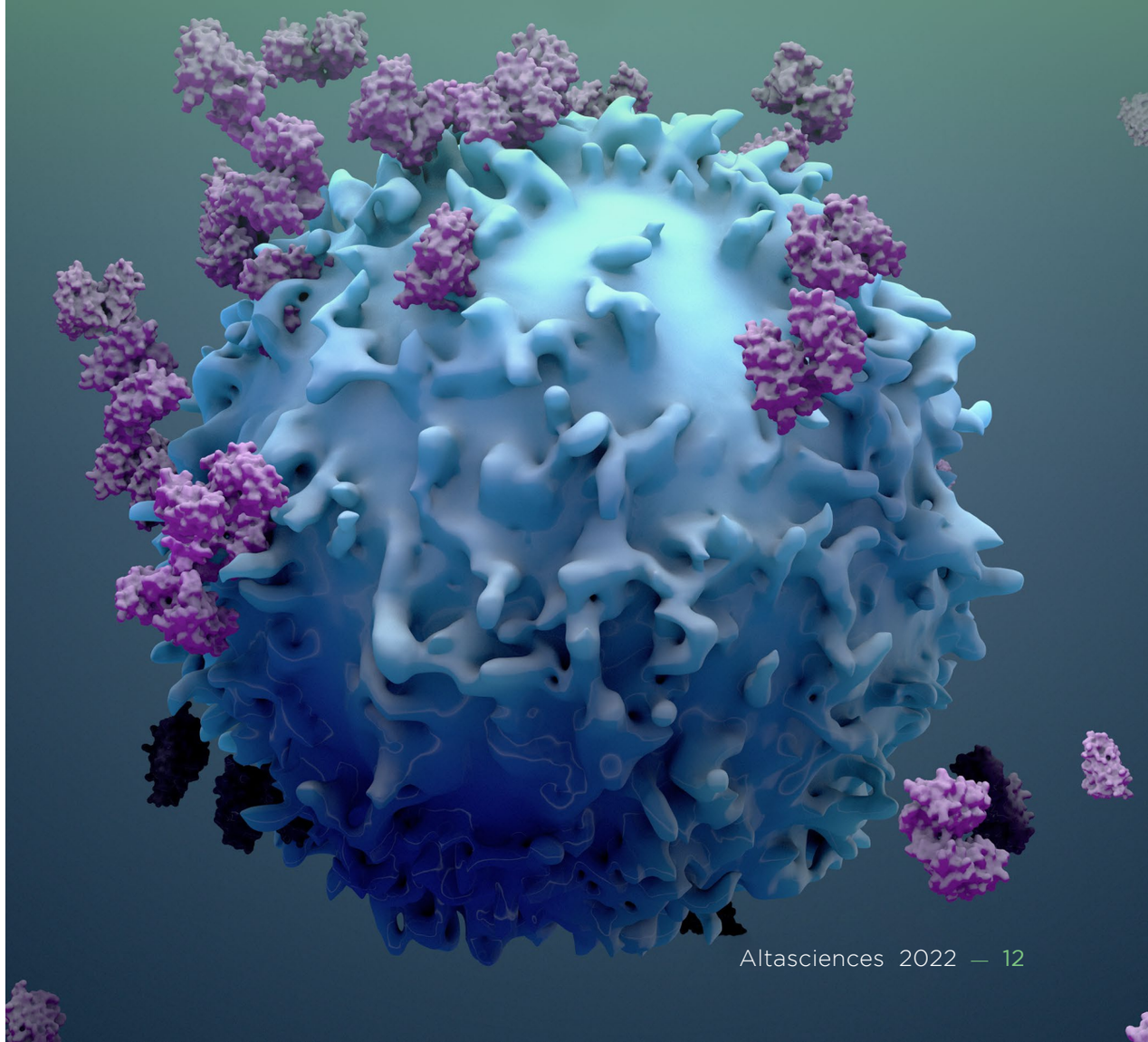
NHP Complement Assays With Synergy 2 (validation to start soon)

- sC5b-9 ELISA, C4d ELISA

ALTASCIENCES

"Assessing cytokines and complement in nonclinical studies can yield valuable information about a drug's potential toxicity and immunotoxicity, in addition to providing insights into its efficacy."

Lynne Le Sauteur, PhD, Vice President, Laboratory Sciences, Altasciences



About Altasciences' Bioanalytical Solutions

Altasciences has been delivering excellence in bioanalytical services for more than 30 years. With over 260 scientists working in our state-of-the-art laboratories and shifts running 24/7, as needed, our laboratory teams are able to process as many as 60,000 samples per month. Our areas of expertise include large molecules, such as proteins, bi-speci ic antibodies, monoclonal antibodies, antibody-drug conjugates, small peptides, as well as small molecules, oligonucleotides, and vaccines.

Every project we take on is managed by a bioanalytical principal investigator who works hand-in-hand with you through every step of the project. Altasciences can support your entire drug development programs end to end, or you can partner with us for just one study — we offer you complete lexibility.

Nonclinical Outline: a 13-Week Single IV Infusion Dose Gene Edit Study in Cynomolgus Monkeys (Non-GLP)

STUDY DESIGN	
Test System	Naïve, cynomolgus monkeys
Number of Animals	21 animals (21♂) plus (2♂) spares (spares removed from study after the first dose on Day 1)
Dosing Period	Single Dose on Day 1
Study Length	91 days
Regulations	Non-GLP

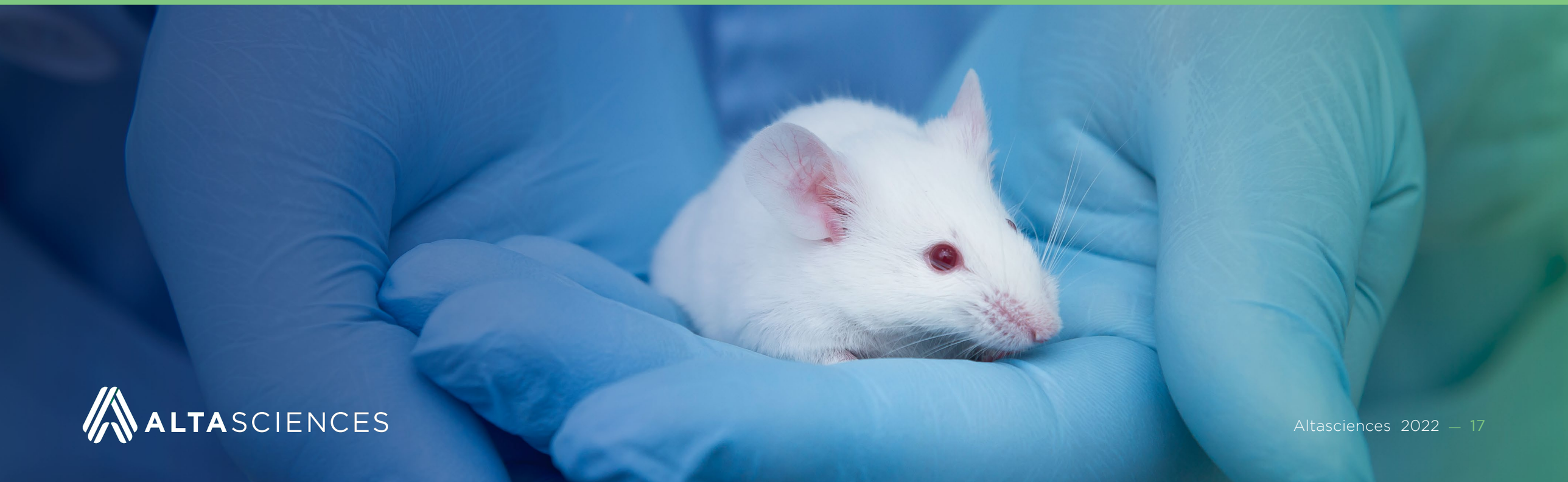
Group	Test Article	Dose Level	Dose Route	Number of Animals
				Males (♂)
1	Vehicule	0	IV infusion 30 min	3[a]
2	XXX	TBD	IV infusion 30 min	3[a]
3	XXX	TBD	IV infusion 30 min	3[a]
4	XXX	TBD	IV infusion 30 min	3[a]
5	XXX	TBD	IV infusion 30 min	3[a]
6	XXX	TBD	IV infusion 30 min	3[a]
7	XXX	TBD	IV infusion 30 min	3[a]

[a] Necropsy, Day 91

STUDY DETAILS		
Procedure	**Timepoints**	**Notes**
Dose Concentration Analysis	Day 1 formulation	
Clinical Observations	• Twice daily mortality checks • Once daily cage-side observation	
Food Consumption	Daily	Appetency check, performed with A.M. clinical observation
Body Weights	Once weekly	
Hematology	• Once during acclimation • Once on Days 2, 4, 7, and 91	Standard panel Clinical pathology reporting
Serum Chemistry	• Once during acclimation • Once on Days 2, 4, 7, and 91	Standard panel Clinical pathology reporting
Blood Draws for PK/ Guide and Message Analysis	• Day 1: Five and 90 minutes, and six, 24 hours post-dose • Once on Days 3, 4, 5, and 7	Processed to plasma and divided into 7 aliquots of 50 µl each
PK Data Evaluation and Reporting	WinNonlin	
Blood Draws for Cytokine Analysis	• Day 1: 90 minutes, then 6- and 24-hours post-dose • Once on Day 7	Processed to serum and divided into 2 equal aliquots. Analysis performed by Altasciences (single batch analysis) via NHP U-Plex panel: IFN-γ, IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p40, MCP-1 and TNF-α.
Blood Collection For Biomarker	• Three times during acclimation • Once on Days 7, 15, 28, 42, 56, 70, 84, and 91	Processed to serum and divided into: • Five aliquots of 100 µL each • 10 aliquots of 25 µL each • Remaining serum will be stored as a 16th aliquot

STUDY DETAILS		
Procedure	**Timepoints**	**Notes**
Liver Biopsy	Day 15	Biopsy samples will be measured post-collection for a minimum of 1.5 cm of total liver biopsy collected per animal. Each biopsy specimen will be flash-frozen, and stored in pre-weighed MB Biomedical bead tubes.
Ecropsy and Tissue Collection	All animals	1. Adrenal 2.Bone marrow (femur) 3. Brain (right frontal) 4. Diaphragm 5. Heart 6. Heart (atria) 7. Heart (ventricles) 8. Kidney (right cortex) 9. Liver (left lateral lobe) 10. Liver (right lateral lobe) 11. Liver (median lobe) 12. Liver (caudate lobe) 13. Liver (remaining) 14. Lung 15. Skeletal muscle (proximal, mid and distal) 16. Spleen 17. Testes Samples transferred to MP Biomedical bead tubes. All samples will be flash frozen in liquid nitrogen.
Bone Marrow Smears	All animals	Bone marrow smear will be prepared for all animals at necropsy; examination of smears.

STUDY DETAILS		
Procedure	**Timepoints**	**Notes**
ORGAN WEIGHTS	All animals	Standard tissue list
HISTOPATHOLOGY	**Paraffin embedding** • All animals: standard tissue list **Slide preparation with H&E stain** • All animals: standard tissue list **Slide reading** • All animals: standard tissue list	
STATISTICAL ANALYSIS		Mean and standard deviation
REPORT	Standard draft and final report	
ARCHIVE		1 year
SEND	N/A	Not required



Sources:

1. The Role of Complement in Inflammatory Diseases From Behind the Scenes into the Spotlight https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1959484/

2. Complement System Part I – Molecular Mechanisms of Activation and Regulation https://www.frontiersin.org/articles/10.3389/fimmu.2015.00262/full

3. Complement System Part II: Role in Immunity https://www.frontiersin.org/articles/10.3389/fimmu.2015.00257/full

4. The Good, the Bad, and the Opportunities of the Complement System in Neurodegenerative Disease https://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-020-02024-8

5. Complement System https://www.immunology.org/public-information/bitesized-immunology/systems-and-processes/complement-system

6. Assessing Host Cell Protein Contamination in Biotechnological Products https://www.europeanpharmaceuticalreview.com/article/90922/assessing-host-cell-protein-contamination-in-biotechnological-products/

7. Host Cell Proteins: Ignore at Your Own Risk https://www.biocompare.com/Editorial-Articles/354656-Host-Cell-Proteins-Ignore-at-Your-Own-Risk/

8. NIH — U.S. National Library of Medicine https://clinicaltrials.gov/

9. Complement System https://www.physio-pedia.com/Complement_System

10. Cytokines and Their Side Effects https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/cytokines.html

11. Cytokine Storm Syndrome in Coronavirus Disease 2019: A Narrative Review https://onlinelibrary.wiley.com/doi/10.1111/joim.13144

12. Developing and Manufacturing Drugs Including Biologics https://www.fda.gov/drugs/coronavirus-covid-19-drugs/developing-and-manufacturing-drugs-including-biologics

13. Guidance for Industry https://www.fda.gov/media/71542/download

14. Bioanalytical Method Validation Guidance for Industry https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf

15. CMC Regulatory Considerations for Oligonucleotide Drug Products: FDA Perspective https://pqri.org/wp-content/uploads/2017/02/3-SapruPQRI-FDA-Conference-Oligo-2017-Presentation.pdf

16. Chronic Inflammation in the Etiology of Disease Across the Life Span https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7147972/

ALTASCIENCES

Altasciences is a forward-thinking, drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to **preclinical** and **clinical pharmacology** studies, including **formulation, manufacturing, and analytical services**. For over 30 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include **preclinical safety testing**, **clinical pharmacology and proof of concept**, **bioanalysis**, **program management**, medical writing, biostatistics, **clinical monitoring**, and data management, all customizable to specific sponsor requirements.

Altasciences helps sponsors get better drugs to the people who need them, faster.

CONTACT US

LEARN MORE