The Complement–Neutrophil Axis in Dialysis and AKI

Factor H Enhancement and CD55 Mimicry

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Invizius Ltd

Overview

Suberites domuncula

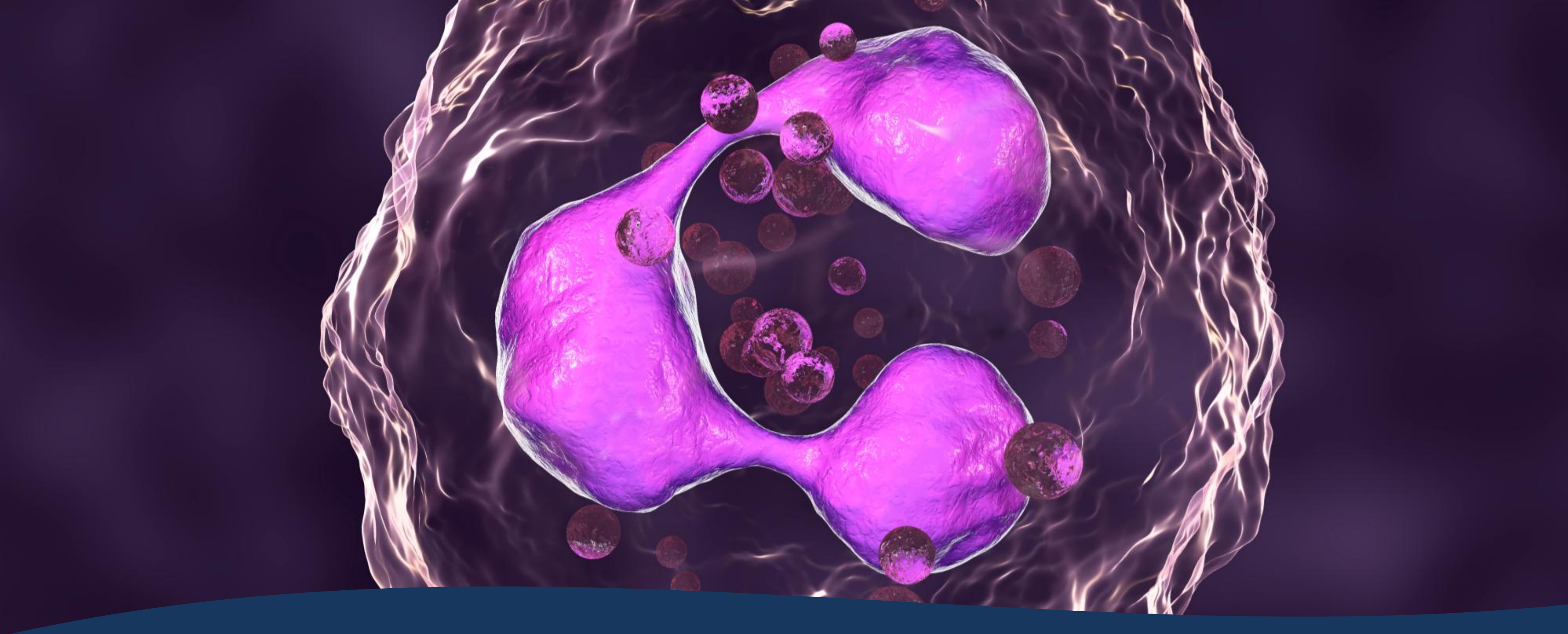
Complement–neutrophil cross-activation drives tissue injury in all dialysis modes from Peritoneal Dialysis to AKI-CRRT.

C5a and C5b-9 activate neutrophils → MPO, NETs, IL-6 release.

Persistent inflammation causes systemic organ damage.

Invizius Platform:

- **H-Guard® – Factor H enhancer (systemic control)**
- **Meso-Guard™ – CD55 mimic (local protection)**
- **We have seen some interesting Neutrophil data emerge from our studies.**

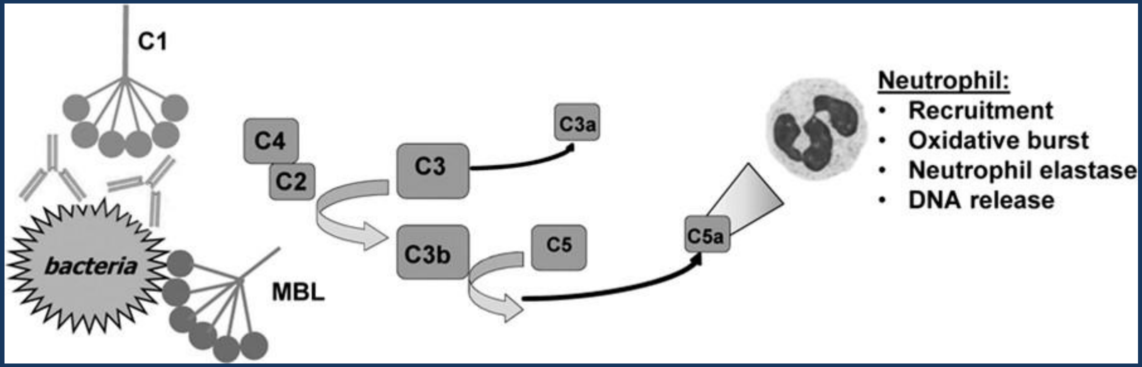


Complement & Neutrophils a 500m year old partnership

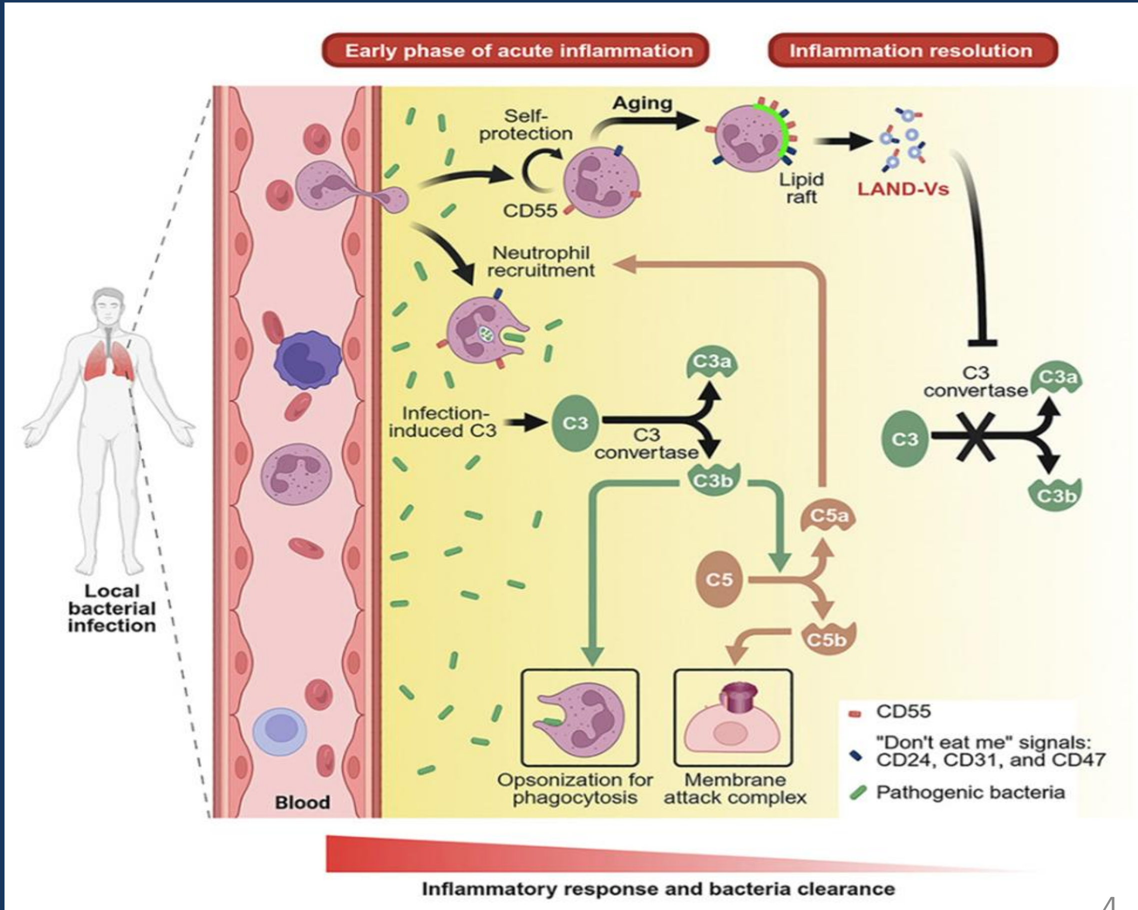
- C3bBb amplification → C5a/C5b-9 → Neutrophil MPO → Tissue damage.
- C5a drives neutrophil activation, oxidative burst, and NET formation.
- Neutrophil oxidants further activate complement – a self-reinforcing cycle.
- **Chronic complement–neutrophil signalling underpins multi-organ inflammation.**

Neutrophils & Complement

Complement Effectors of Inflammation in Cystic Fibrosis Lung Fluid Correlate with Clinical Measures of Disease by Laura A. Sass, Pamela S. Hair et al, published in *PLOS One*, December 2015.



CD55⁺ LAND-Vs originate in ordered lipid raft domains, where CD55 accumulates asymmetrically during neutrophil aging, and are subsequently formed through RhoA-dependent budding.(Hsu, A.Y et al (2025) Cell Vol 188 (6) 1623-1641.)



Senescent “Zombie” Neutrophils

Delayed Apoptosis driven by C5a and other signals(PBUT)

Move from Phagocytic to Pro-Inflammatory

NETosis, MPO & Elastases

Seen in:

Cardiovascular Disease

CKD & HD & PD

IgAN & C3G

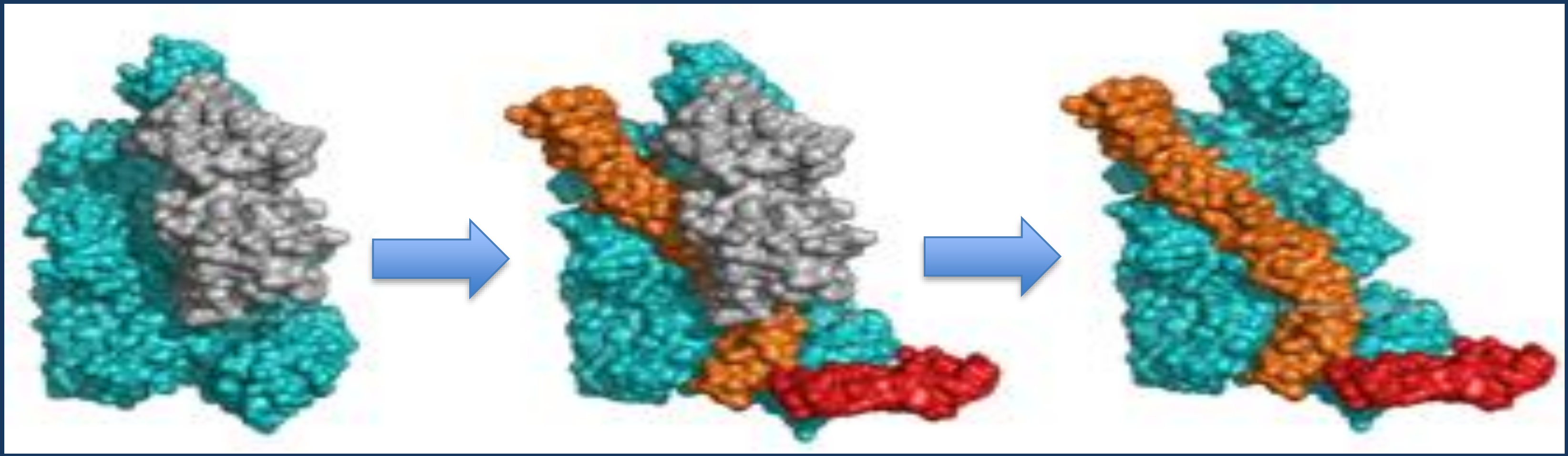
SLE, COPD & Cystic Fibrosis

Alzheimer’s & Parkinsons Disease

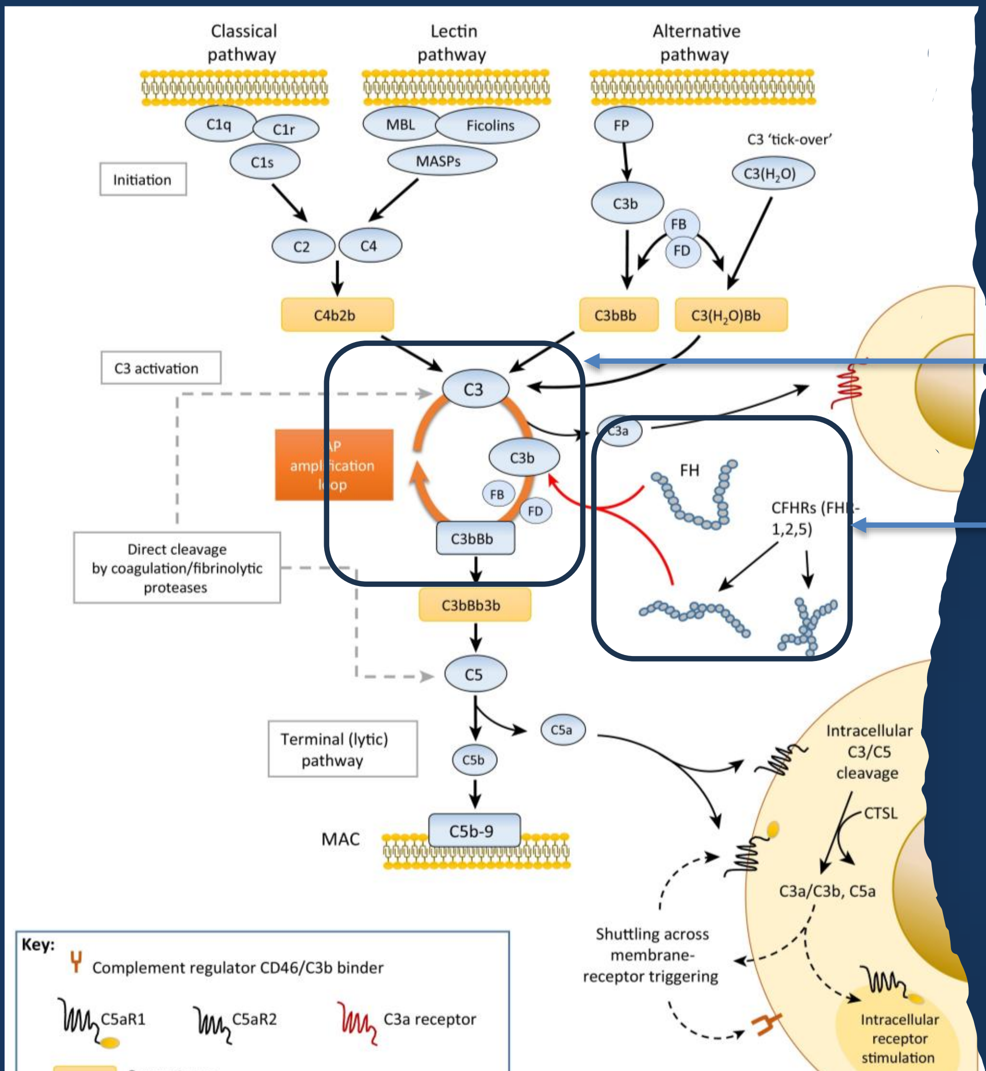
Others…

H-Guard® (Factor H Enhancer)

- Mechanism: Reinforces control of the alternative pathway by stabilizing Factor H regulation.
- Evidence: 40% MPO reduction (dHL-60 cells), ↓ C5b-9 and MPO during dialysis.
- **Outcome: ↓ Complement activation, ↓ Neutrophil MPO/NETs, ↓ IL-6.**
- H-Guard makes Factor H 500% better at displacing Bb from C3b.



Overview of the Complement Activation Cascade



At the heart of the cascade is the **'Ring of Fire'**, an amplification loop that constructs inflammatory proteins

Factor H plays a role in slowing down the cascade. Our breakthrough has been to find a way to **amplify Factor H activity**, giving it a stronger role in restraining the cascade and quelling inflammation

Mastellos, D. C et al Trends in Immunology, June 2017, Vol. 38, No. 6

Dialysis Complement Activation

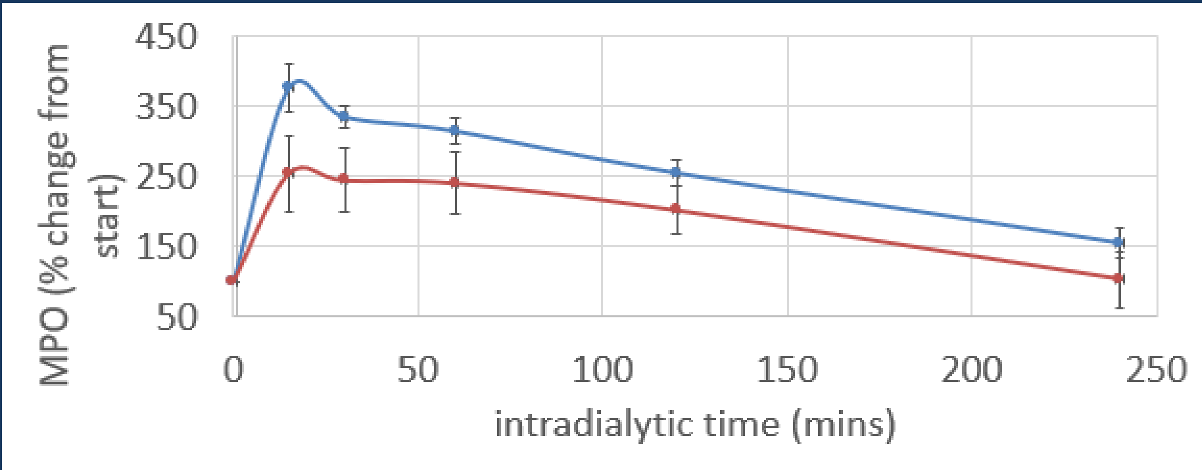
- HD/CRRT membranes activate the alternative pathway (C3b, Factor B, C5b-9).
- Neutrophils adhere, degranulate, release MPO/ROS.
- Compact HD: MPO doubled (5–60 min).
- Lifespan Reduction from 20 years to 5-10 years for 60-year-old
- **Chronic exposure → Systemic inflammation, cardiovascular risk**.

H-Guard Interrupts the “Ring of Fire”

- H-Guard coating ↓ Complement activation on extracorporeal surfaces.
- **↓ C5b-9 and ↓ MPO release (confirmed in Phase2a).**
- ↓ NET formation and endothelial injury.
- Outcome: Reduced systemic inflammation and organ crosstalk injury.

Successful Ph2a Safety Trial indicated a Reduction in Inflammatory Markers

Significant reduction of key inflammatory mediators: C5a, C5b9 and MPO

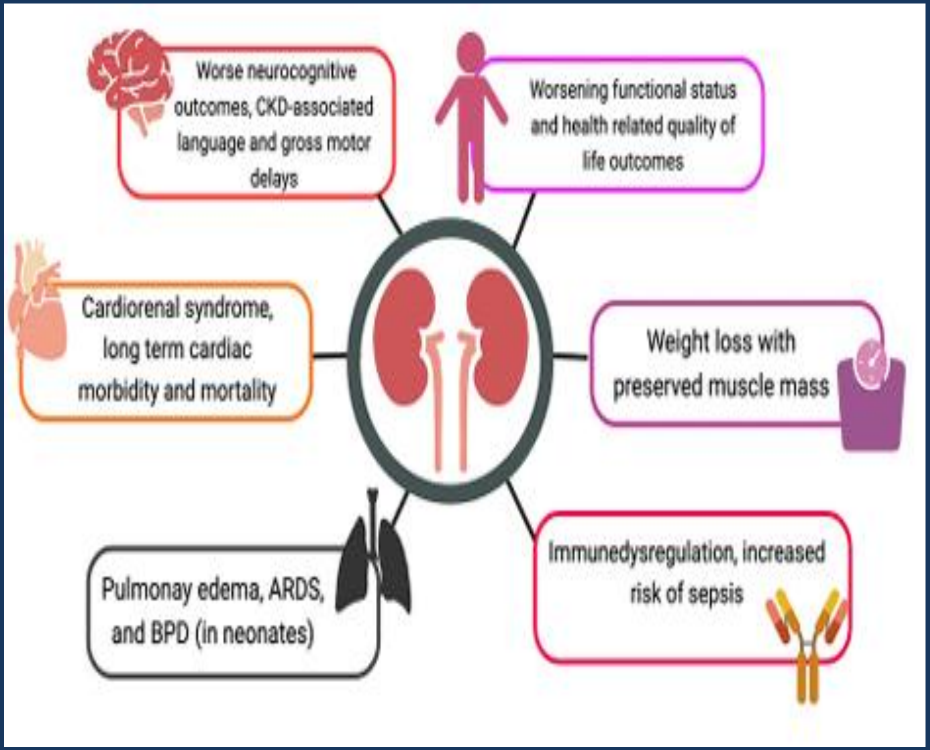


% change MPO from start at 15mins dialysis			
	ave (% change)	+/- SD	T Test: Baseline vs H Guard
baseline	376.521	34.36483	P= 0.008338
H Guard	255.1727	54.14784	

H-Guard in Paediatric AKI-CRRT

Ann & Robert H. Lurie Children's Hospital of Chicago

- Background: 25–40% PICU AKI;
- 35–45% mortality on CRRT.
- Mechanism:
- Factor H enhancement →
- ↓ C5a/C5b-9 →
- **↓ MPO/NETs → ↓ IL-6.**
- Expected Benefits:
- • ↓ Systemic inflammation
- • ↓ Endothelial injury
- • ↓ ICU LOS (−6d)
- • ↑ Survival (+10–15%)
- **Orphan Designation Planned**
- **Adult Phase2b Approved**



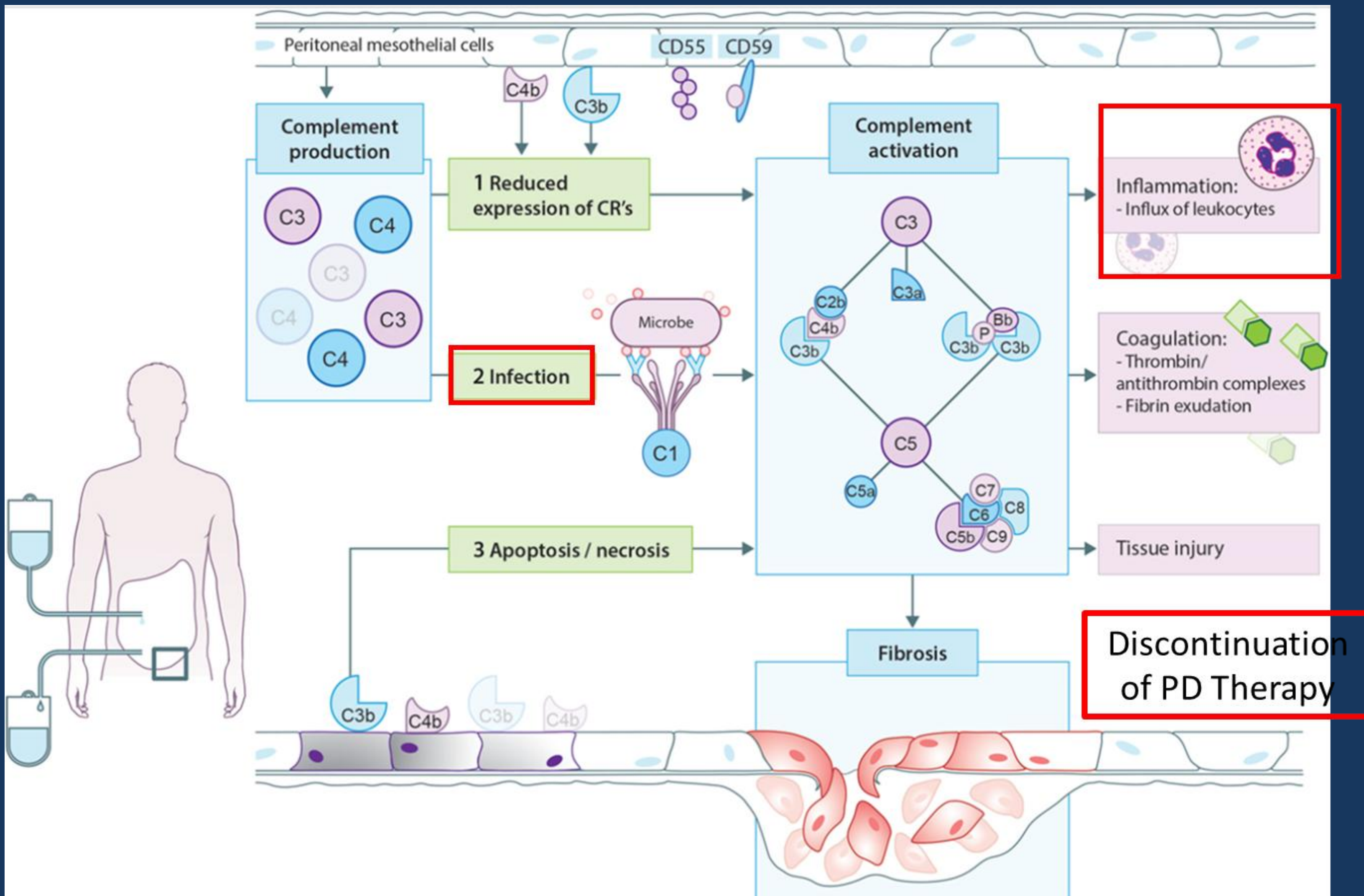
Pande, C.K et al (2022) Frontiers in Pediatrics June Vol 10 Article 893993

In paediatric AKI–CRRT, C5a and neutrophil priming is very high. The neutrophils circulating through extracorporeal tubing shed granules, release MPO, and return to the kidney in a hyperactivated state. That makes the kidney's microvasculature and tubules prime targets when the blood is re-oxygenated and reperfused..

Meso-Guard PD window extension

- Problem: PD failure within 3–5 years from complement- and neutrophil-driven fibrosis.
- Mechanism: CD55 mimic blocks convertases, prevents C5a release → limits MPO/NET-driven fibrosis.
- **Expected Results: Preserved mesothelium, ↓ IL-6/TGF-β, +24-month PD function, ~$500M cost savings.**
- $30Kper patient per year saving

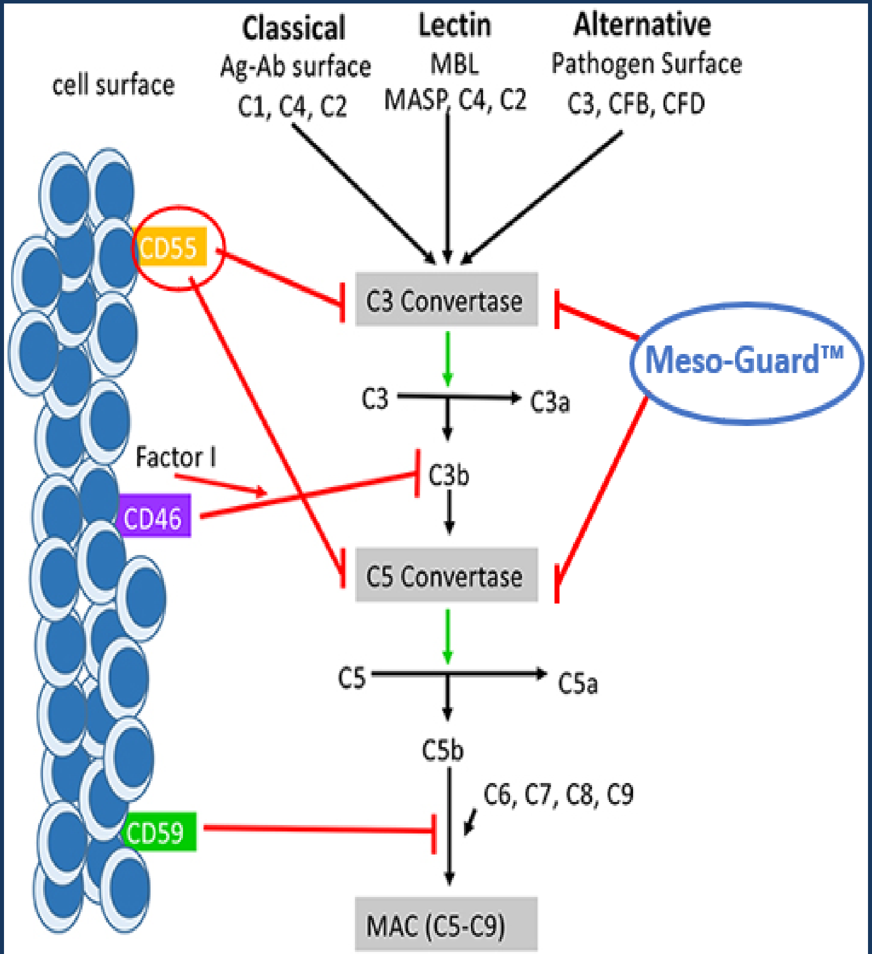
Complement dysregulation in PD failure



Poppelaars, F et al (2018) Clinical Nephrology/Nephrology Dialysis Transplantation

Meso-Guard™ (CD55 Mimic)

- Mechanism: Mimics DAF/CD55, disassembling C3/C5 convertases on peritoneal surfaces.
- Outcomes: ↓ C5a/C5b-9, ↓ **Neutrophil activation, ↓ TGF-β, ↓ IL-6, ↓ MPO.**
- Prevents mesothelial–mesenchymal transition (MMT) → Reduced fibrosis.



Effluent from non-infected PD patients contains a broad range of innate immune mediators, showing that even clinically stable PD fluid is immunologically active.

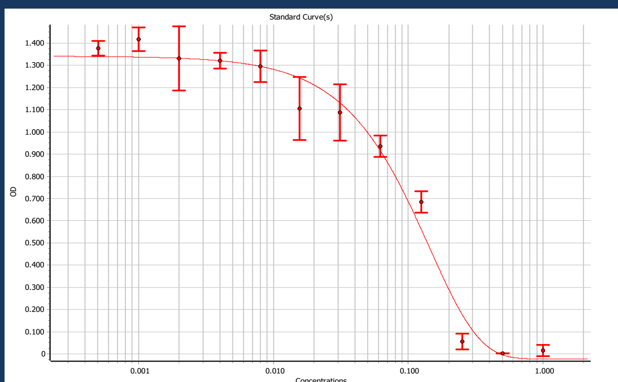
- IL-6 – 984pg/ml (Central pro-inflammatory cytokine)
- IL-8 – 68pg/ml (Neutrophil chemoattractant)
- MCP-1 – 457pg/ml (Monocyte recruitment)
- PDGF- AB-BB – 140pg/ml (Fibrosis and mesothelial repair)
- **IL-6 dominates, reaching levels typical of acute inflammatory states.**

PD effluent from stable patients shows chronic innate immune activation

Meso-Guard™ is a potent inhibitor of all three complement pathways in Human Serum

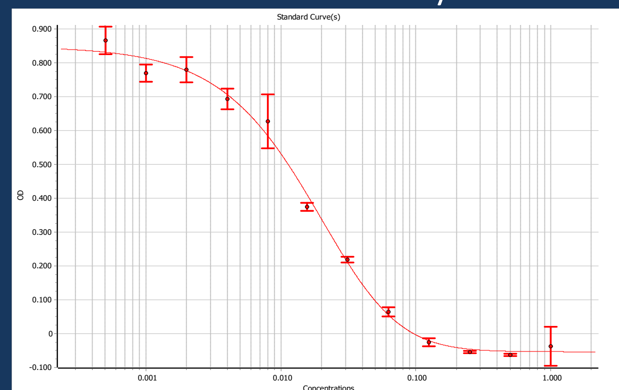
Alternative Pathway

OD450 nm →

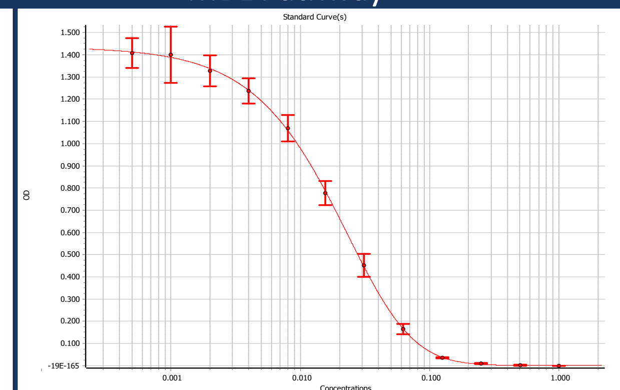


Meso-Guard concentration (µM) →

Classical Pathway



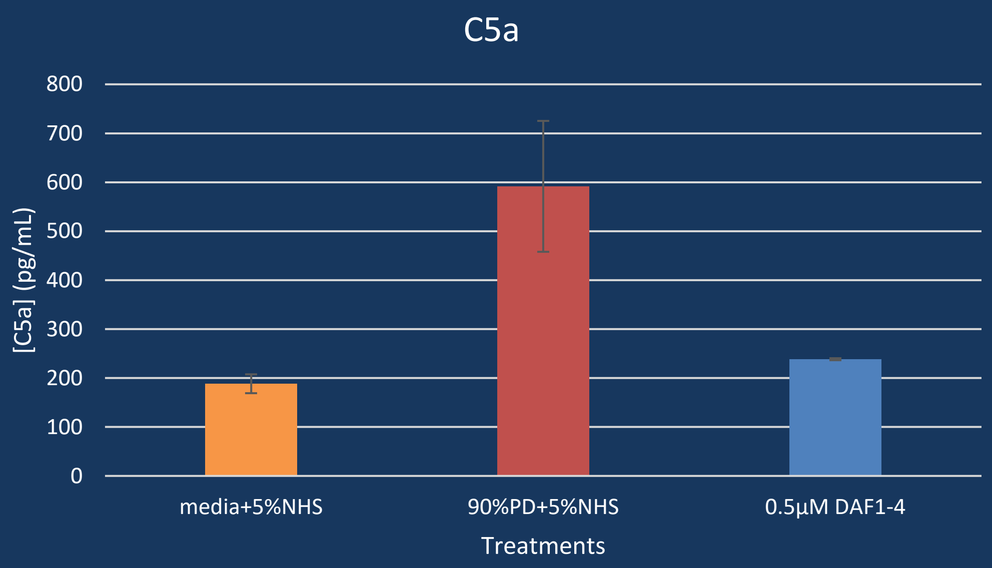
MBL Pathway

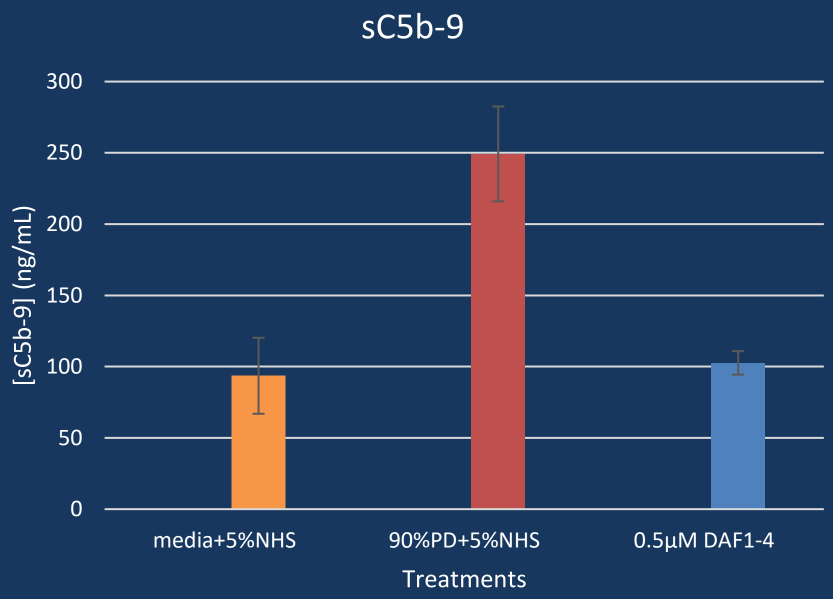


	Alternative	Classical	MBL
Meso-Guard EC50	**105 nM**	**16 nM**	**18 nM**
R^2	0.98	0.99	0.99

Meso-Guard prevents PD Fluid- induced complement activation

- Anaphylatoxin (C5a) and soluble terminal complement component (sC5b-9) are robust readouts of activation of all three complement pathways





NHS = Normal Human Serum

Myeloperoxidase (MPO) Across PD Fluid Types

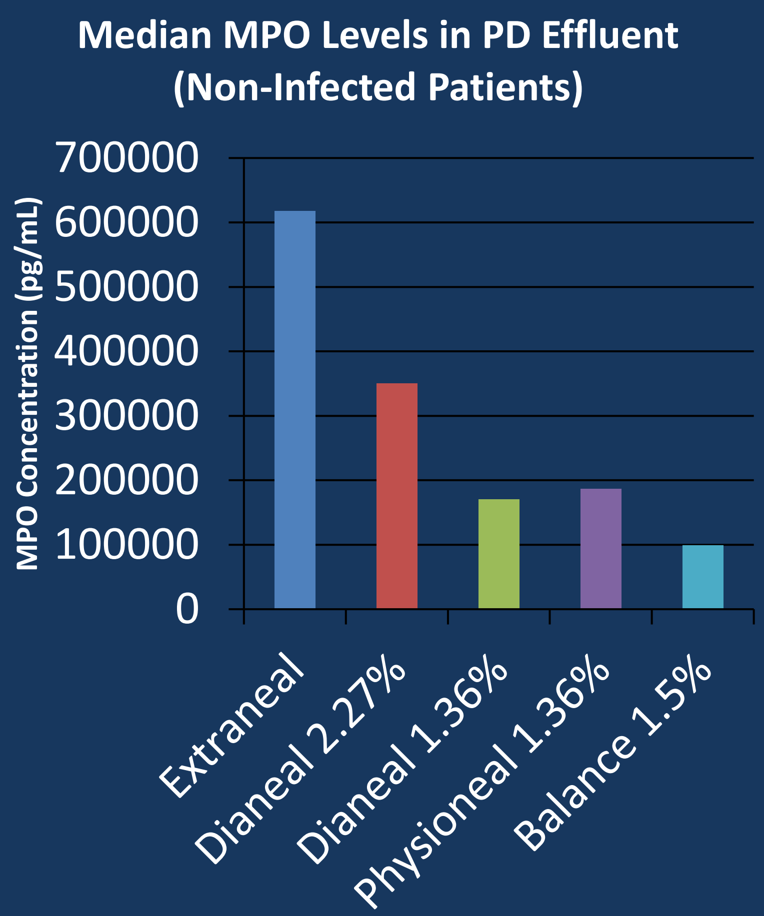
Effluent from PD patients shows wide variation in myeloid biomarkers depending on dialysate.

MPO concentrations are highest in Extraneal (617,739 pg./mL) and lowest in Balance (98,716 pg./mL).

Similar trends for **Elastase** and **NGAL** confirm stronger neutrophil activation with Icodrextrin and glucose-based fluids.

Neutral-pH, bicarbonate-based fluids show the lowest inflammatory marker levels.

Glucose-rich or acidic dialysates amplify oxidative and proteolytic inflammation, while neutral-pH biocompatible solutions reduce these effects.

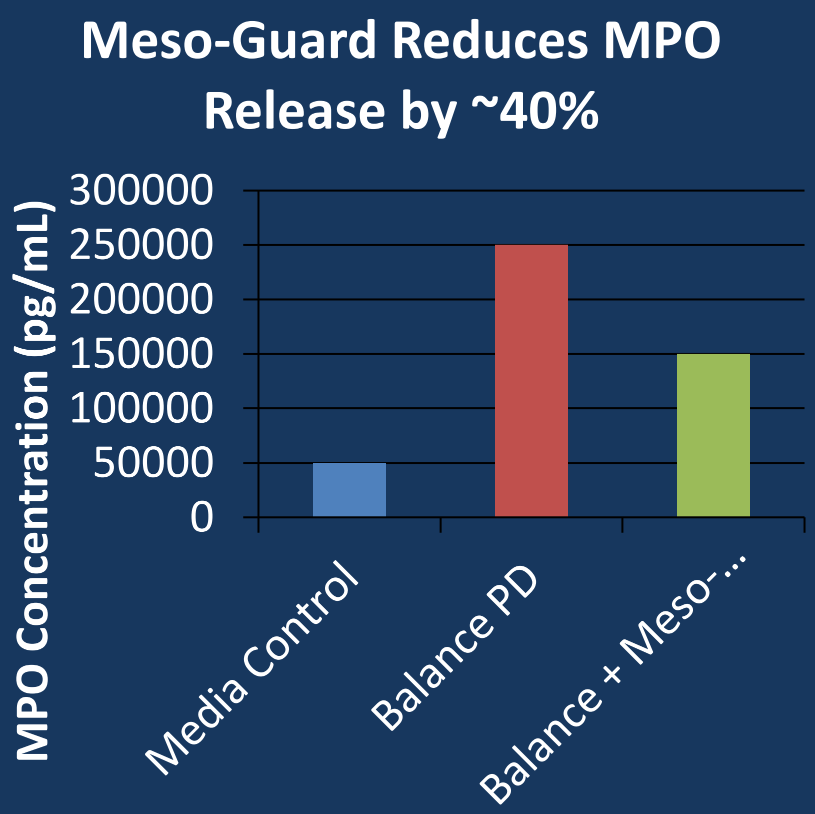


Complement-modulating additives may further protect peritoneal membranes from inflammatory and fibrotic injury.

Meso-Guard Reduces PD Fluid–Induced Activation of Neutrophil-Like Cells (dHL-60)

Neutrophil-like cells were exposed to Balance PD fluid ± 0.5 µM Meso-Guard. Myeloperoxidase (MPO) levels in supernatant were quantified as a marker of oxidative neutrophil activation.

PD fluid exposure caused a 5-fold increase in MPO release vs. media control.



Meso-Guard dampens PD fluid–induced activation of neutrophil-like cells, reducing peritoneal oxidative injury and chronic inflammation risk

Coherence across three complement markers re MMP-2 (Mesothelial to Mesenchymal Transforming enzyme)

Correlations	sC5b-9 vs MMP-2	C3a vs MMP-2	C5a vs MMP-2
Spearman's rank correlation coefficient (r_s)	**0.4895**	**0.6015**	**0.5686**
r^2	0.2396	0.3618	0.3233
P-value	0.03766	0.006217	0.01617
Covariance	15.5	21.0526	16.2059
Sample size (n)	19	20	18

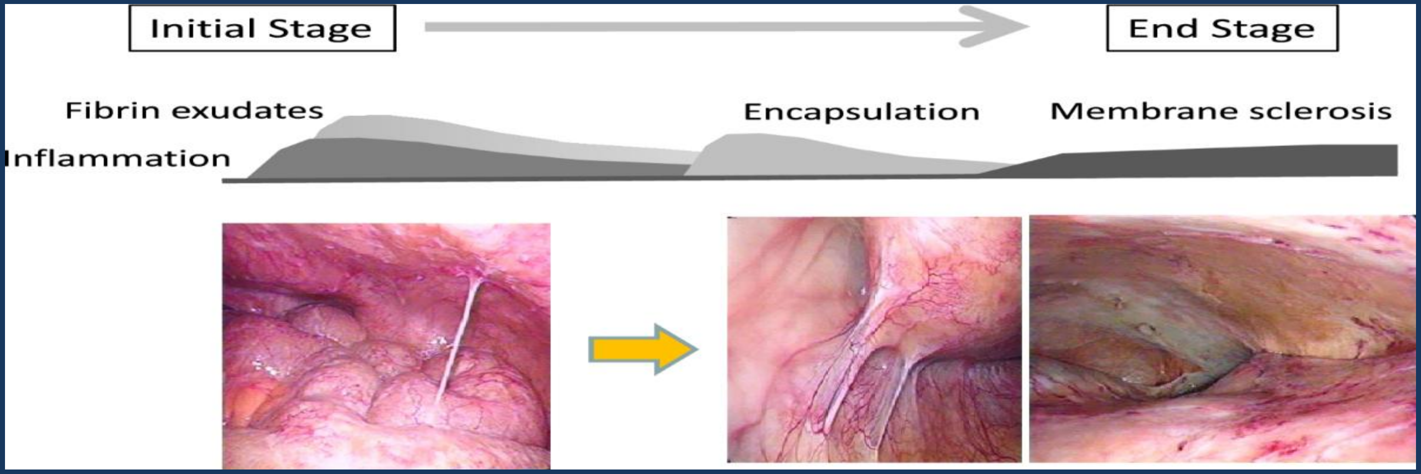
The correlation between complement effectors, sC5b-9, C3a, C5a with MMP-2 levels in the non-infected PD effluent, using the spearman correlation rank coefficient (*r* represents the spearman's rho).

- sC5b-9 ⟷ MMP-2 shows a **moderate, significant positive association**
- C3a ⟷ MMP-2 shows a **stronger, highly significant association** — the tightest of the three.
- C5a ⟷ MMP-2 also shows a **moderate–strong, significant association**.

MMP-2 shapes the inflammatory damage that neutrophils (MMP-9) amplifies

Preventing Encapsulating Peritoneal Sclerosis (EPS)

- **Mechanism of pathology:**
- - PD fluids trigger complement activation → C5a, C5b-9.
- - C5a recruits neutrophils → MPO, NETs → mesothelial damage.
- - IL-6, TGF-β, and VEGF drive MMT and fibrosis → EPS.
- **Meso-Guard™ (CD55 mimic):** Blocks C3/C5 convertases, prevents local complement activation. Preserves mesothelium, prevents MMT.
- **H-Guard® (Factor H enhancer):** Reduces systemic complement amplification and C5a generation. Dampens neutrophil and MPO-mediated inflammation.
- **Expected Benefits:**
- - Prevents progression to EPS &- Extends PD viability.
- - **First disease-modifying prophylaxis for EPS, not symptomatic treatment.**



Future: Neutrophils in Cystic Fibrosis and T1D

Indication	**Pathophysiology**	**Role of C5a–Neutrophil Axis**	**Therapeutic Strategy**
Cystic Fibrosis	Airway neutrophilia & NETs	Drives oxidative mucus plugging	Meso-Guard aerosol CD55 mimic
Type 1 Diabetes	Early β-cell inflammation	MPO/NETs expose autoantigens	Low-dose H-Guard

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- **Complement/Neutrophil control = Inflammation control.**
- H-Guard: Upstream regulation via Factor H enhancement.
- Meso-Guard: Surface defence via CD55 mimicry.
- Potentially protects kidneys, heart, lungs, and brain from neutrophil/MPO-driven damage.
- **Invizius Platform: Unified complement regulation for inflammation and fibrosis prevention.**

I would like to acknowledge and thank:

Prof Claus Schmitt (University of Heidelberg)
Prof Donald Fraser (Cardiff University School of Medicine)
Prof Sandip Mitra (Manchester University)

Thank you for your attention

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