Meso-Guard™ for Peritoneal Dialysis

Dr Magnus Nicolson
Invizius Ltd

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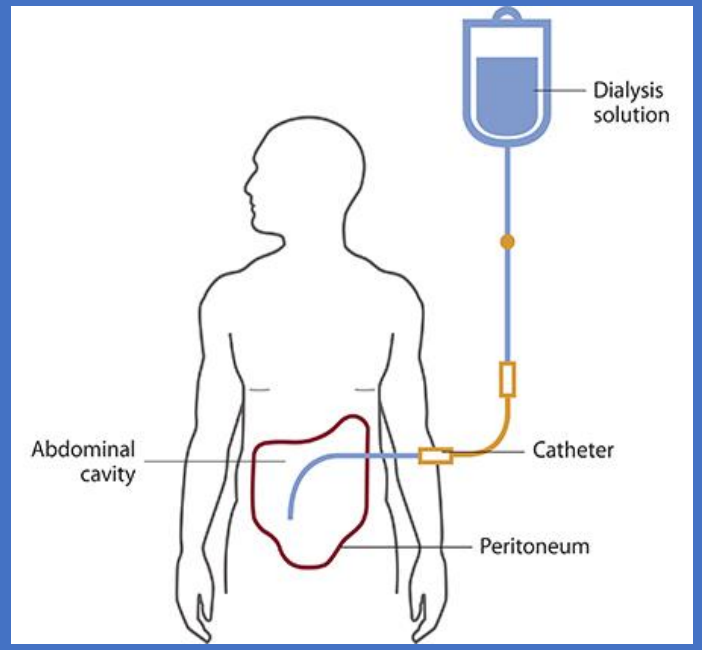
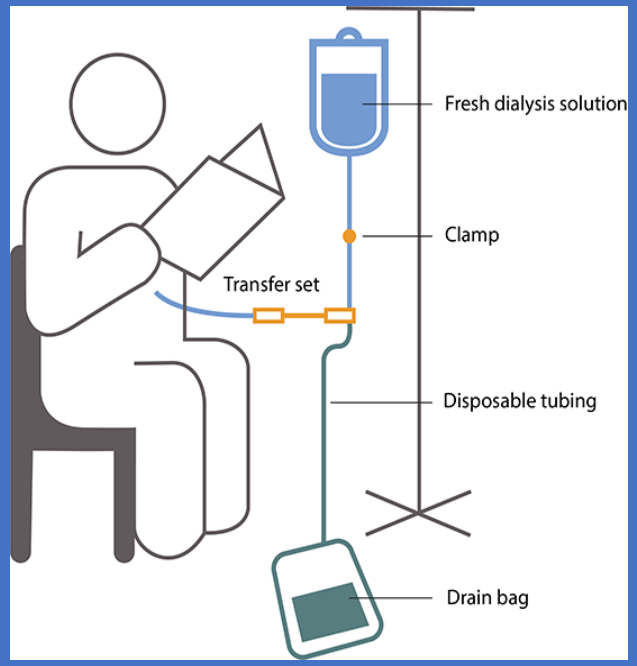
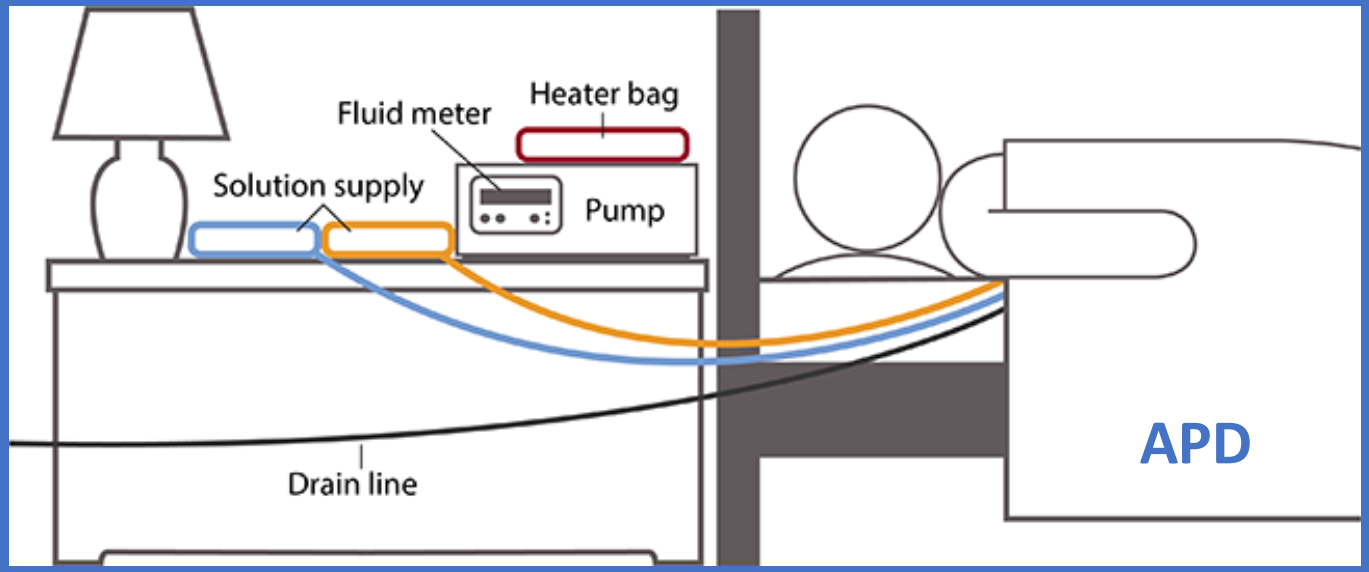
Peritoneal Dialysis (PD)

- PD uses the lining of the abdomen – **the peritoneum** - to physically filter waste products from the blood.
- The peritoneal cavity is filled with PD solution (sugar, salt, water). Waste products and fluid are drawn across the membrane into the peritoneal cavity
- After a prescribed “dwell time”, the cavity is emptied then refilled with fresh PD fluid. This process is called an “exchange”.
- There are two main types of PD:
  - **Continuous Ambulatory Peritoneal Dialysis (CAPD)**
  - **Automated Peritoneal Dialysis (APD)**







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PD is currently not sustainable as a long-term treatment and patients must transfer to HD within about 5 years

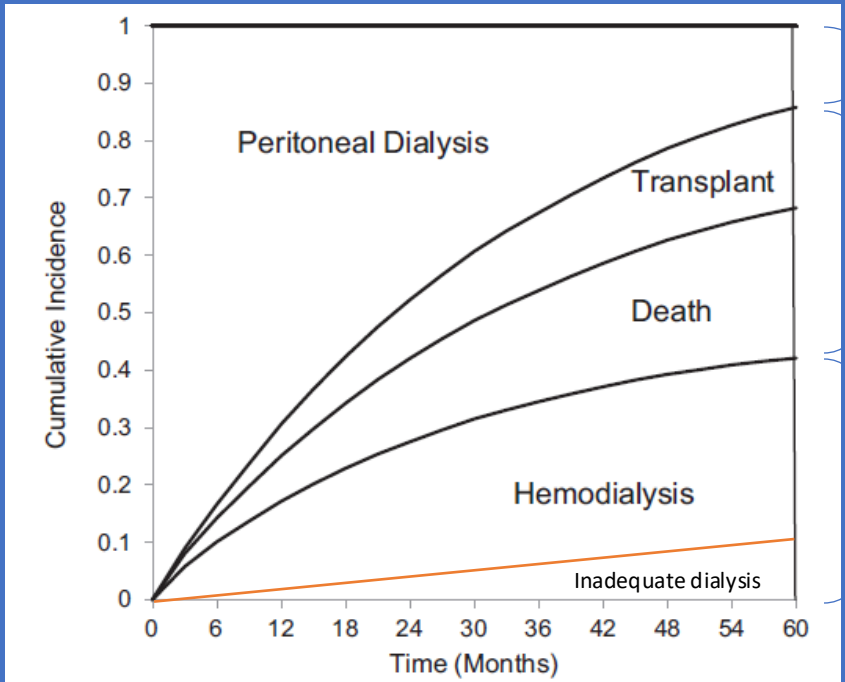


Figure 2. Hemodialysis transfer, kidney transplantation, and death over time for all incident peritoneal dialysis patients. The prevalence of each outcome is shown as the vertical height of the appropriate area at each time point on the horizontal axis.

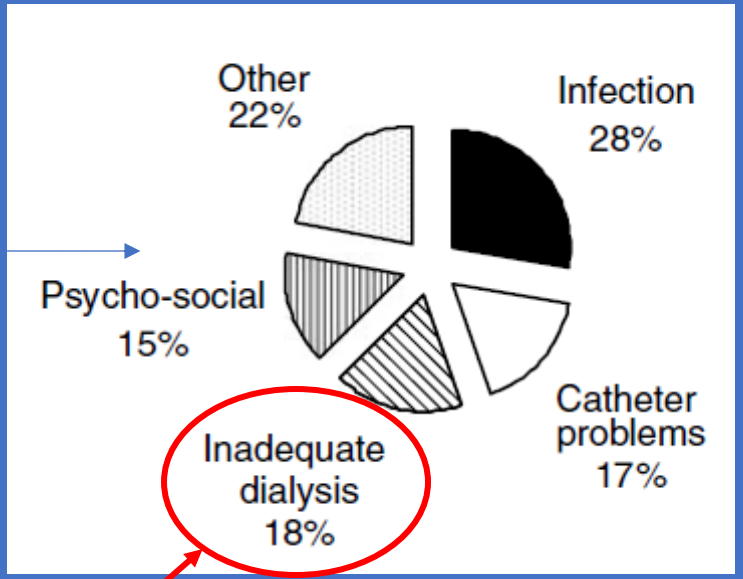
Am J Kidney Dis. 74(5): 620-628. Published online July 10, 2019

After 5 years ~15% of patients remain on PD

After 5 years ~45% of patients have died or had a transplant

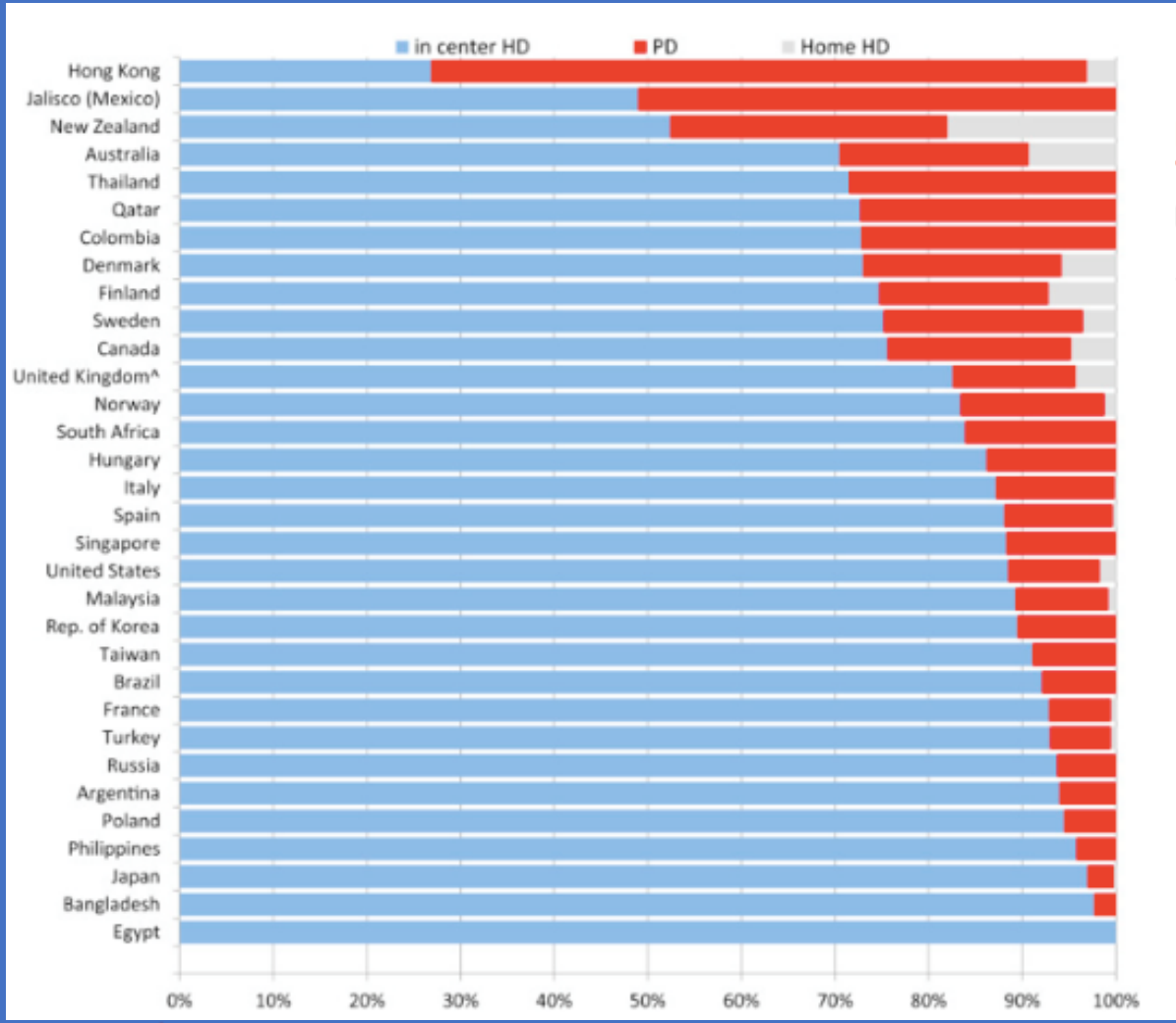
After 5 years, ~40% of patients have transferred to HD

Causes of drop out from PD to HD (Mujais et al Kidney International (2006) 70, S21–S26)



Fibrosis is found in 50 to 80% of patients within one or two years of PD (Zhou Q et al, Preventing peritoneal membrane fibrosis in peritoneal dialysis patients. Kidney Int (2016) 90(3):515–24. 10.1016)

PD is routinely used but HD is the dominant mode of dialysis



- Worldwide, HD is used for 85-90% of dialysis patients
- PD is routinely used but penetration varies considerably by country/region
  - EU ~10%
  - US ~10%
  - Japan ~3%
  - China ~14%

Source: GlobalData

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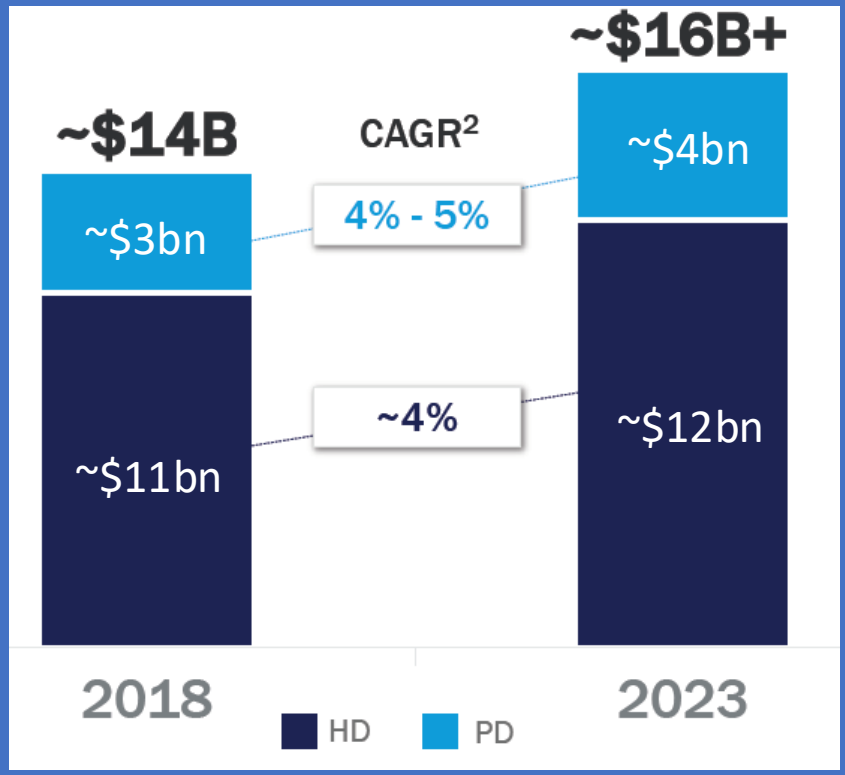
PD is a smaller but more profitable market for dialysis product manufacturers

- Worldwide PD products market serves 350k patients & is worth **~$3.5bn pa**
  - Market is expected to track growth of End Stage Renal Disease (ESRD) patients
- Europe & US PD product market:
  - 150k patients, worth ~**$2.5bn** pa
  - PD gross margins are slightly lower than typical pharmaceutical margins
  - HD gross margins are much lower in the bottom range for medical devices

Patients with chronic kidney failure	**3,706,000**	**100%**
Of which patients with transplants	726,000	20%
Of which dialysis patients	**2,980,000**	**80%**
Hemodialysis (HD)	2,632,000	71%
Peritoneal dialysis (PD)	348,000	9%



- **A significant bottom line loss occurs for PD manufacturers when patients drop out**
- **Like Icodrextrin, Meso-Guard™ can prove to be a strong market share tool**

Sources: GlobalData, Invizius research

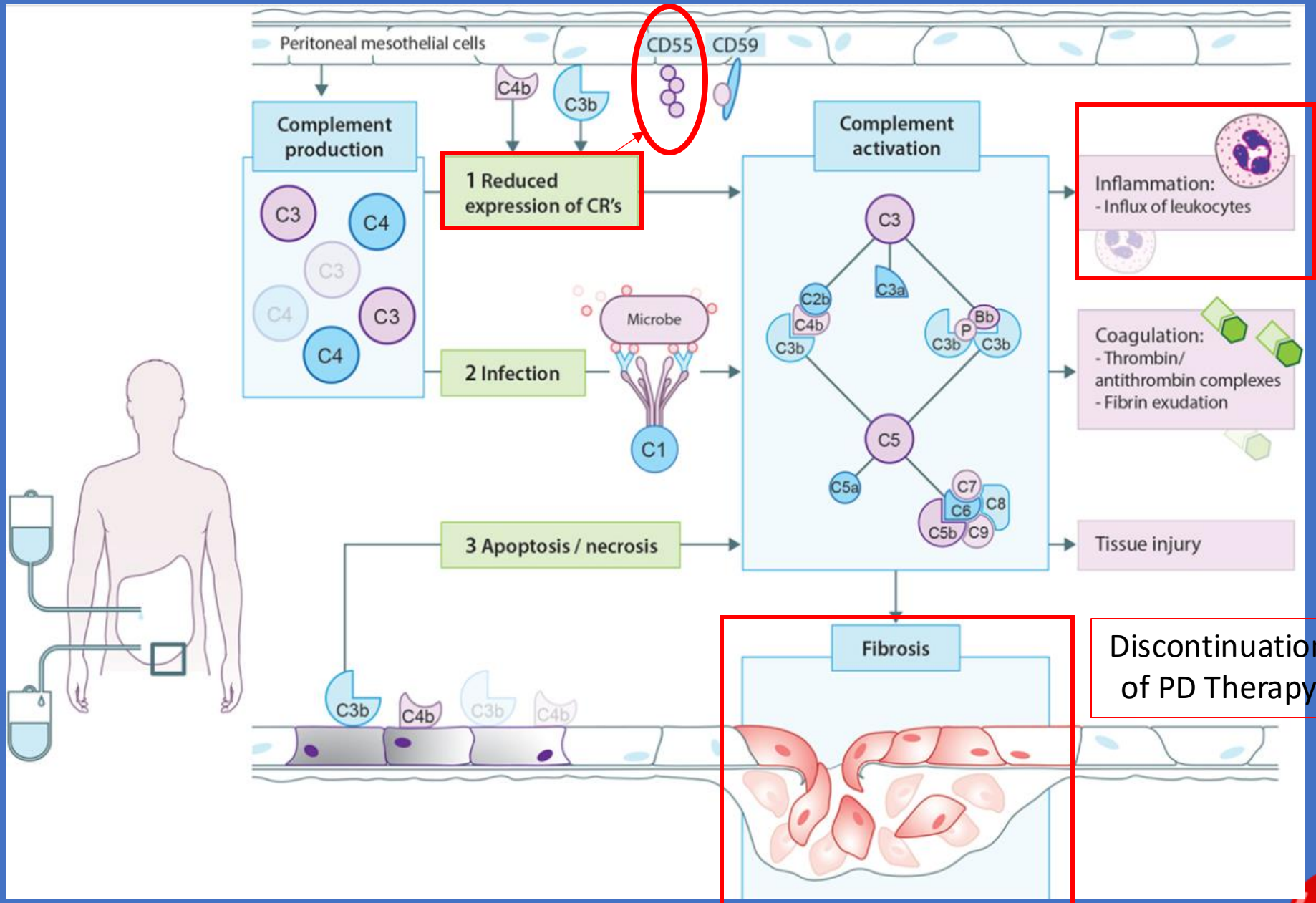
Sources: Fresenius, Baxter

Complement dysregulation is an under-appreciated factor in PD treatment

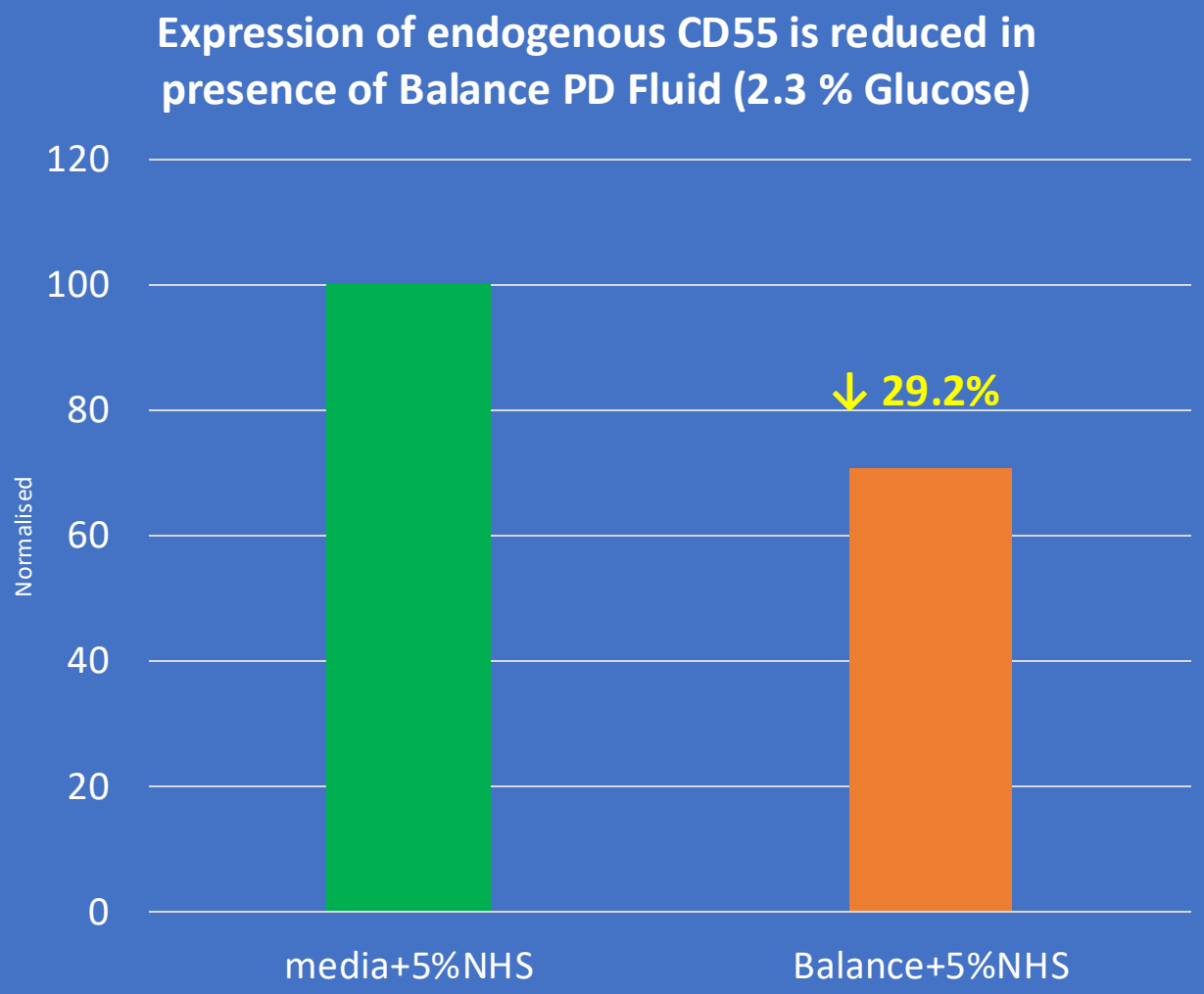
Peritoneal Mesothelial cells produce complement proteins when exposed to PD fluids and peritonitis episodes exacerbate complement activation.

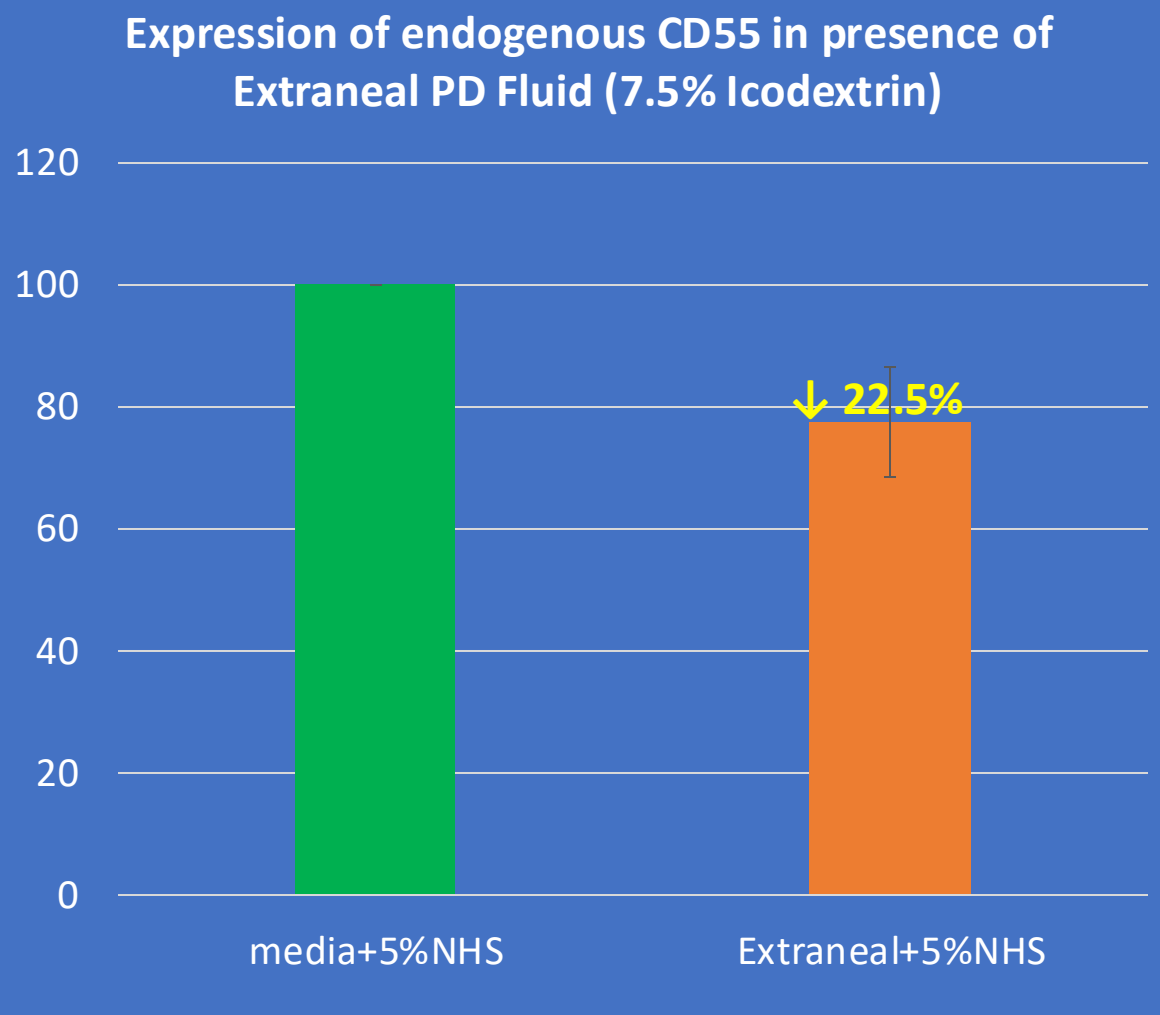
-The PD Fluid induced complement activation is further amplified due to a loss of complement regulator (CR's) expression e.g. CD55

-Uncontrolled complement activation leads to a chronic inflammatory environment leading to tissue damage, Fibrosis, loss of ultrafiltration capacity and eventual discontinuation of PD

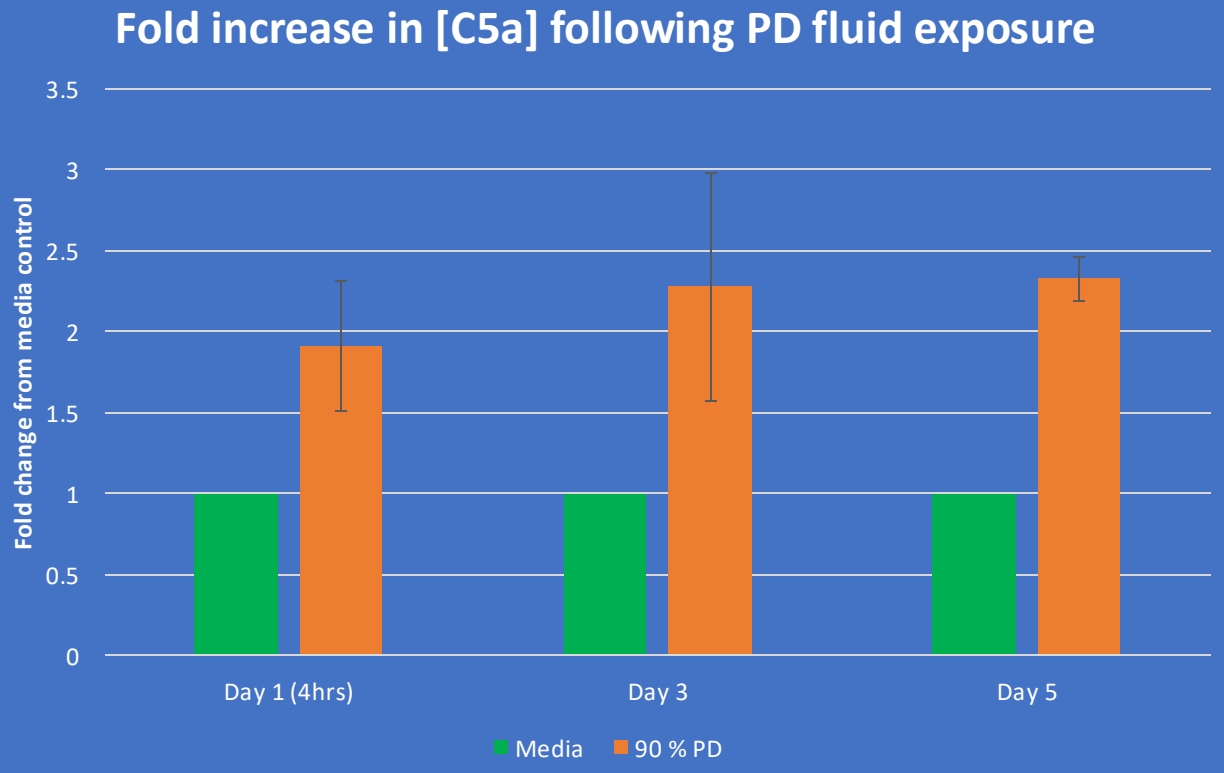


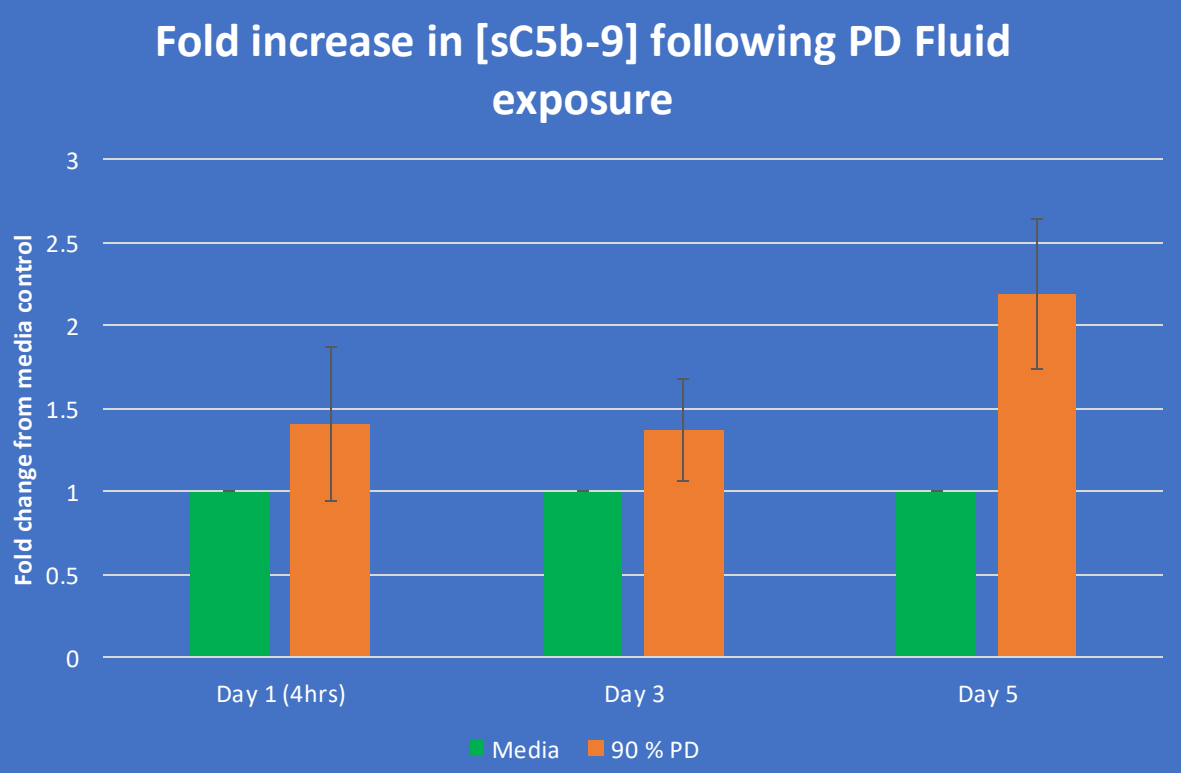
Endogenous complement regulator CD55 is reduced on mesothelial (MET5A) cells following PD Fluid exposure





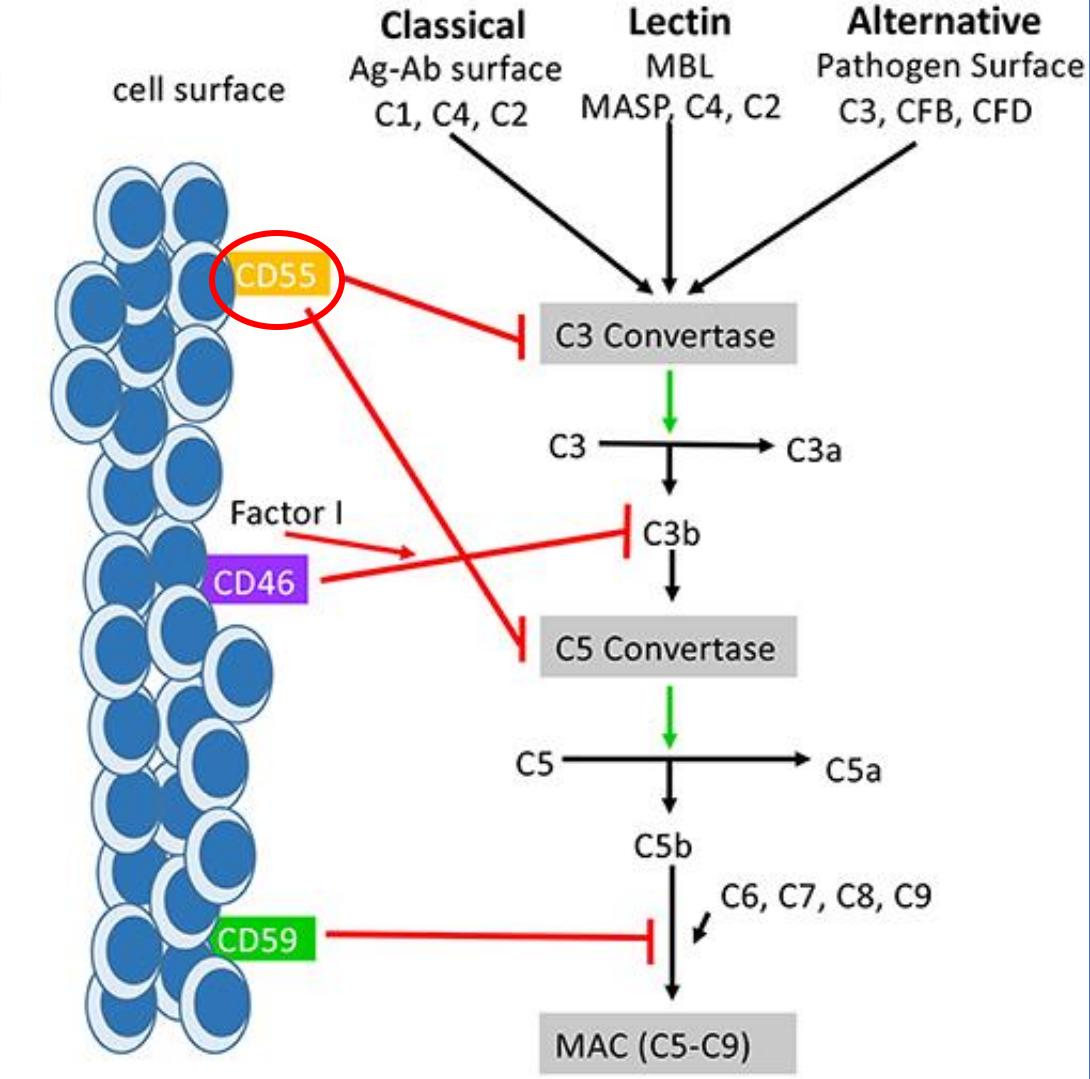
There is consistent increase in complement activation caused by Glucose and non-glucose based PD Fluids





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

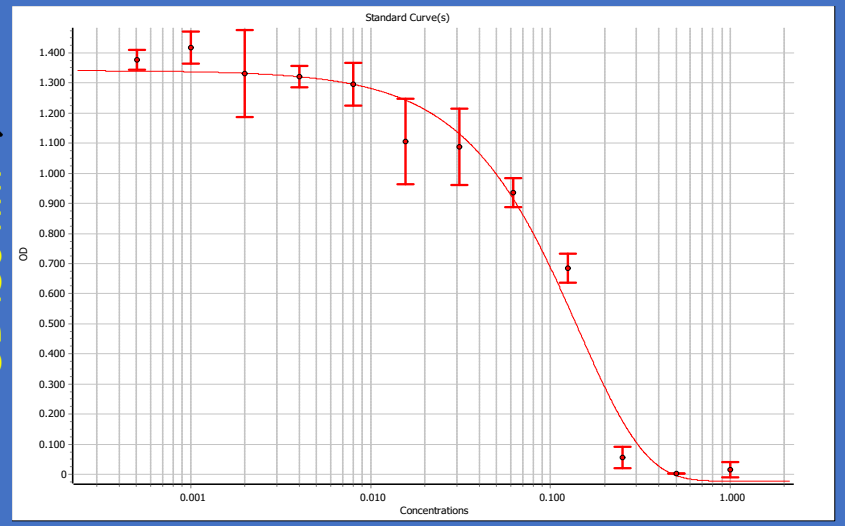
Meso-Guard™ mechanism of action



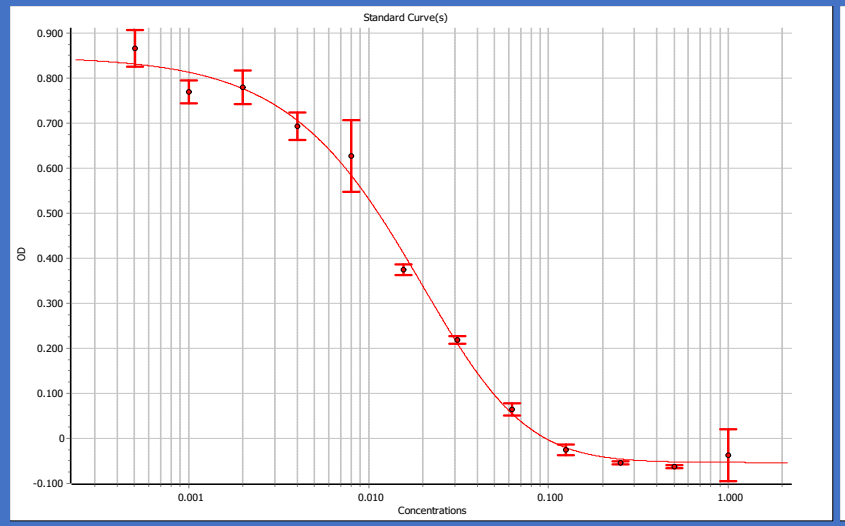
- Complement activation is incredibly fast and dangerous and so needs to be controlled.
- Decay Acceleration Factor (DAF/CD55) is a key controller of the speed of the Complement cascade reaction.
- CD55 protects cells from activation of autologous complement on their surfaces by accelerating the decay of the classical and alternative C3 and C5 convertases, the central amplification enzymes of the cascade.
- Our lead molecule Meso-Guard™ **mimics** the effect of naturally occurring DAF/CD55 and acts to **negatively modulate the complement cascade**

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

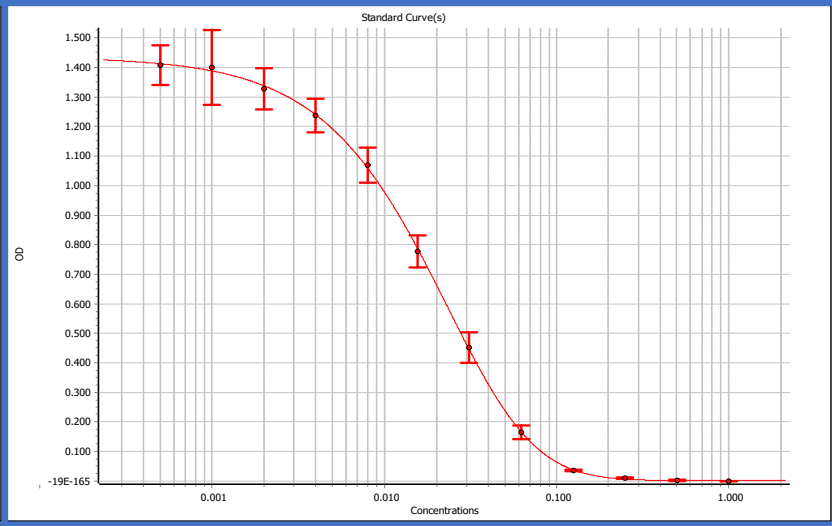
Alternative Pathway



Classical Pathway



MBL Pathway

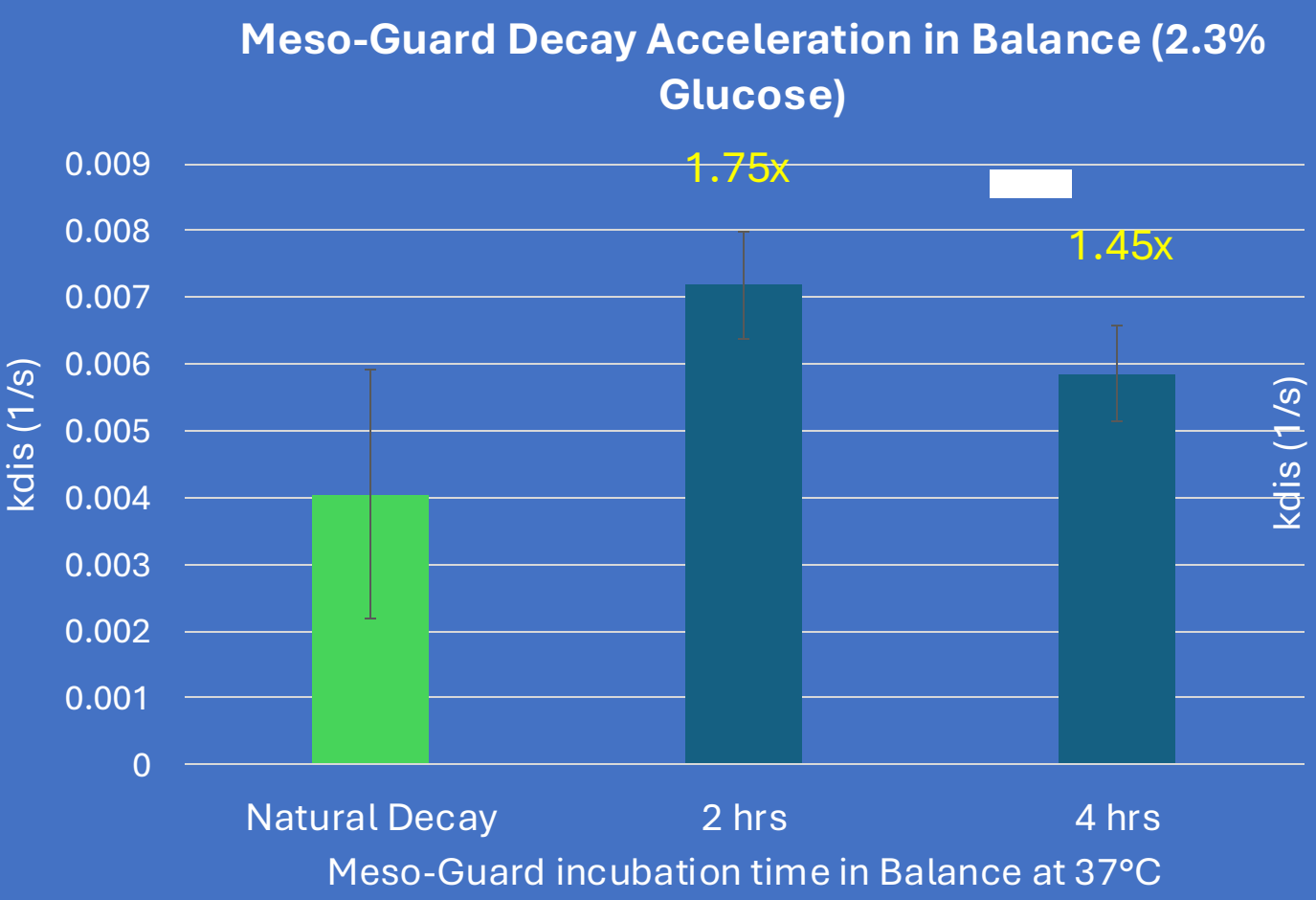


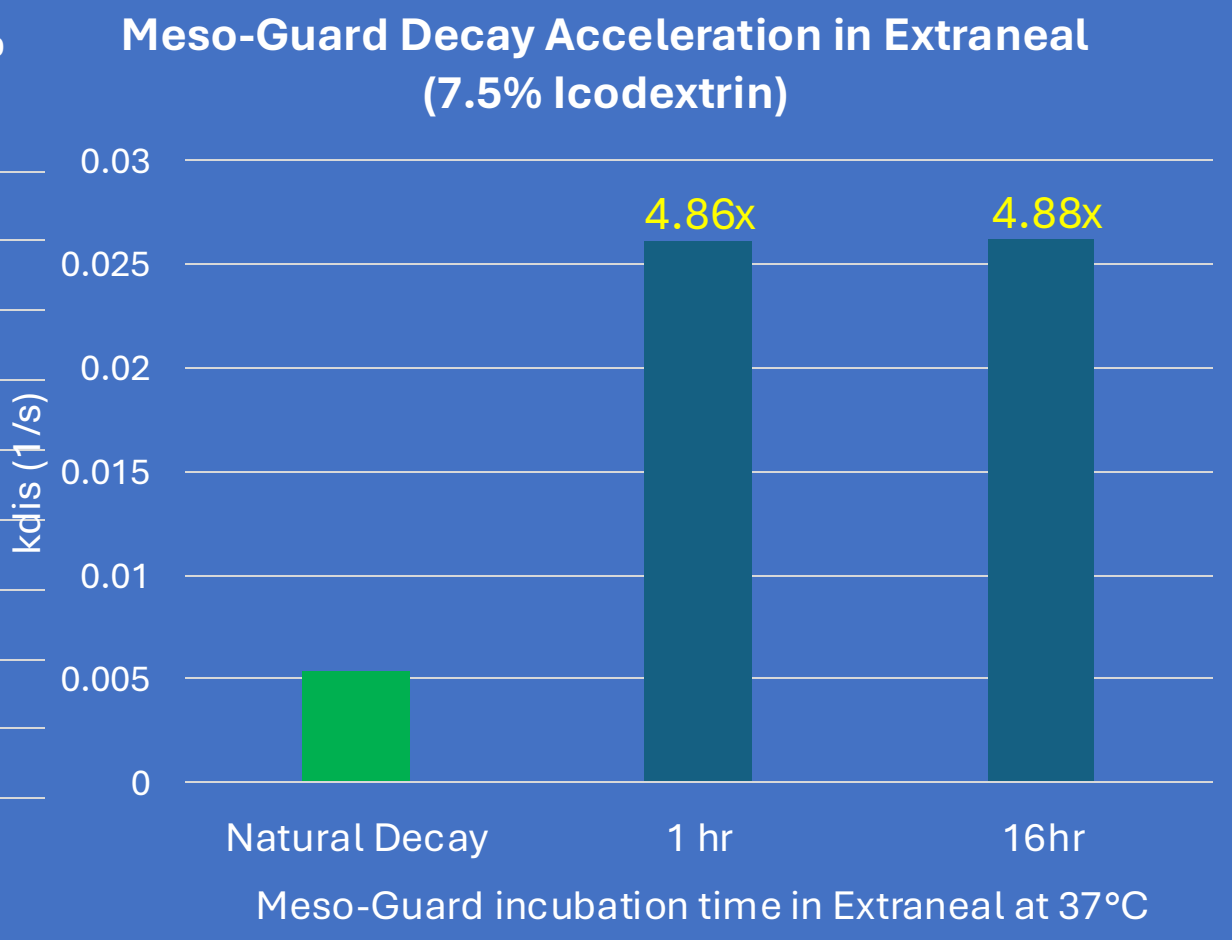
OD450 nm →

Meso-Guard concentration (µM) →

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

Meso-Guard™ Decay Acceleration of C3 Convertase in PD Fluids



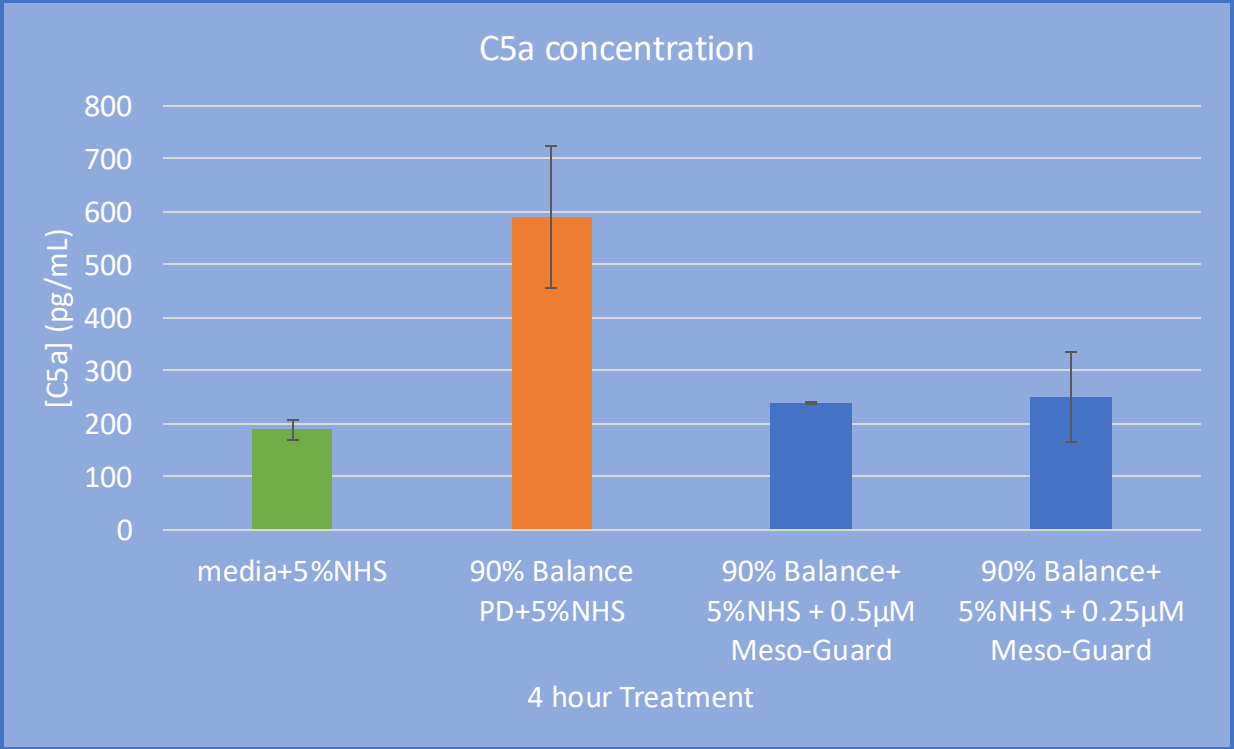


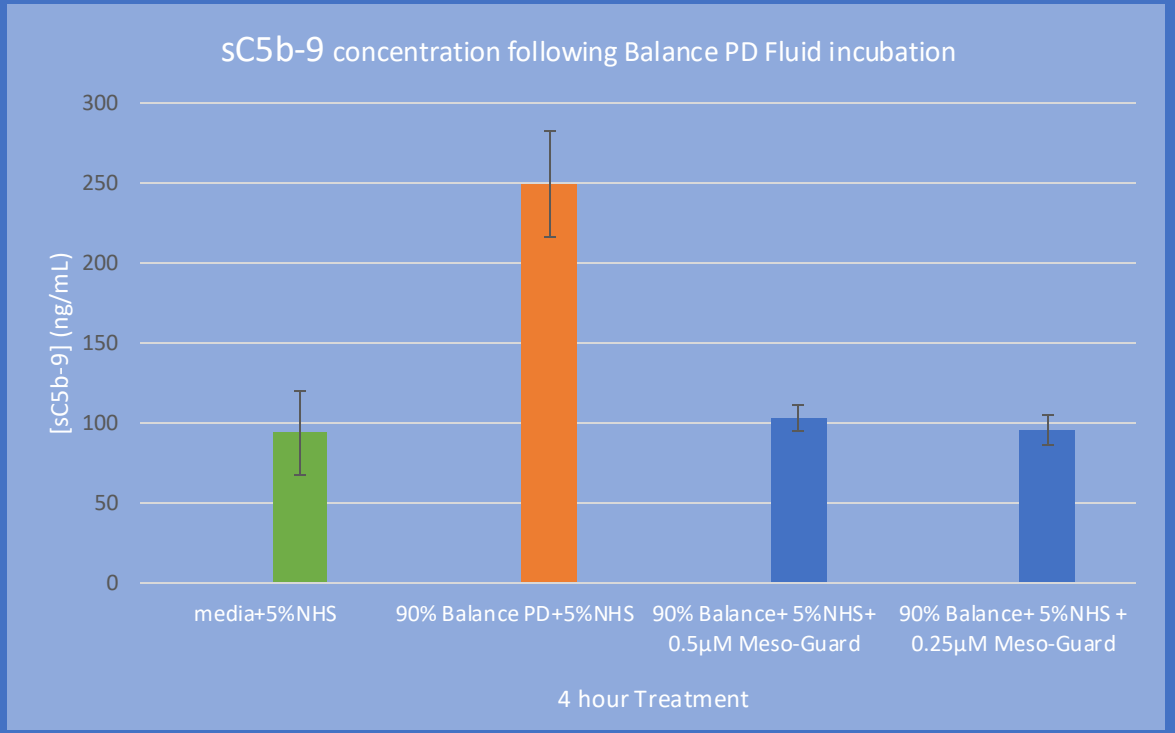
Meso-Guard is active and stable across the recommended dwell times for Glucose and non-glucose based PD Fluids

Meso-Guard potently reduces PD Fluid- induced complement activation

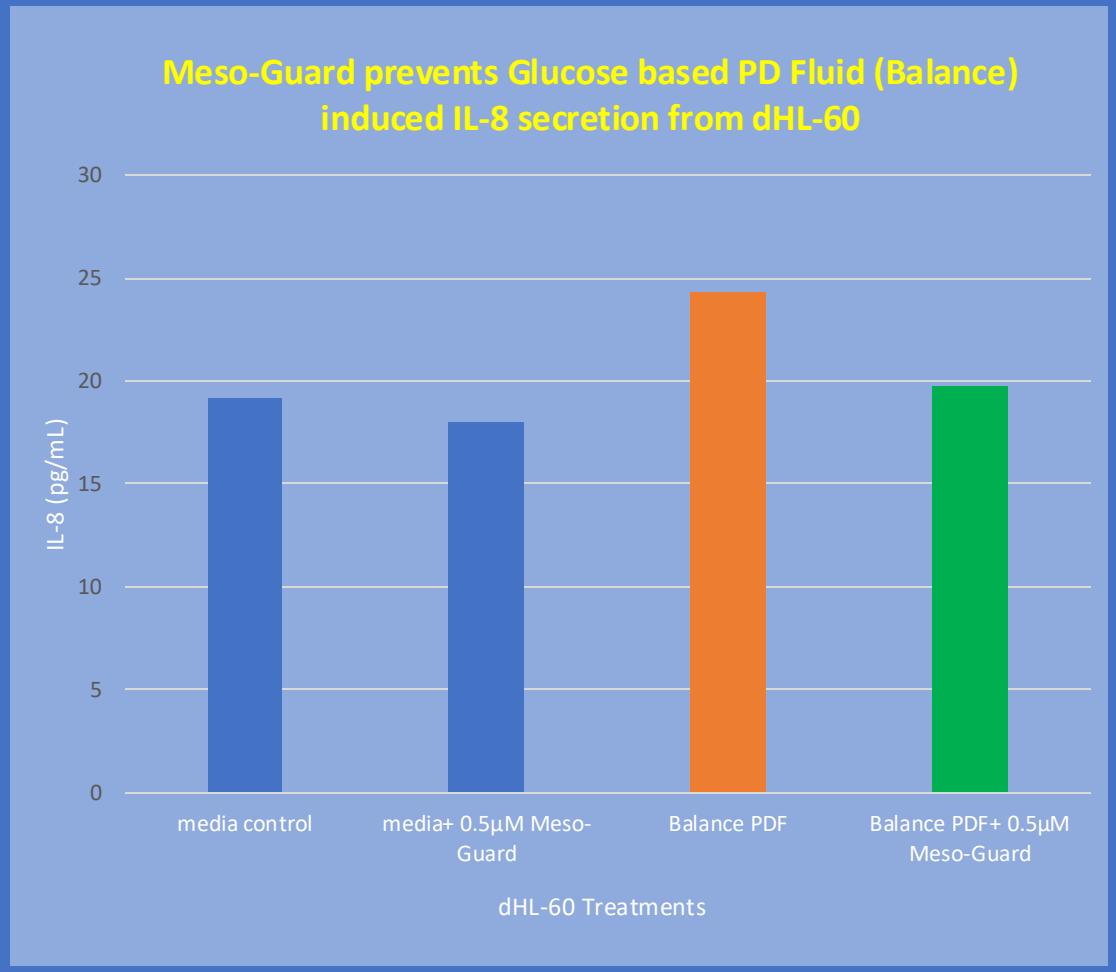
Anaphylatoxin (C5a) and soluble terminal complement component (sC5b-9) are robust readouts of activation of all three complement pathways

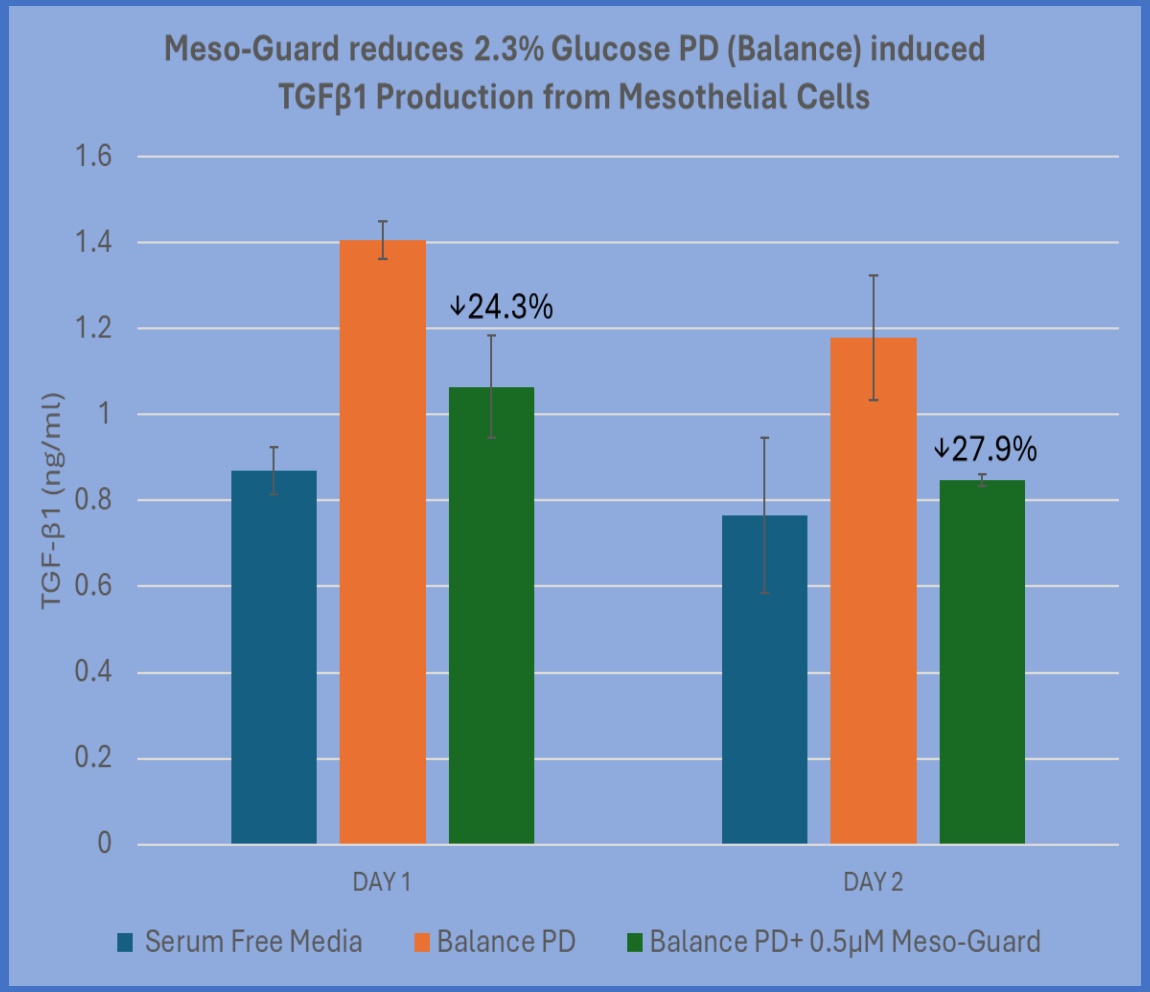
Addition of Meso-Guard to the PD Fluid prevents the PD Fluid induced complement activation





PD Fluid exposure stimulates IL-8 &TGFβ production from Mesothelial cells (Met5A).



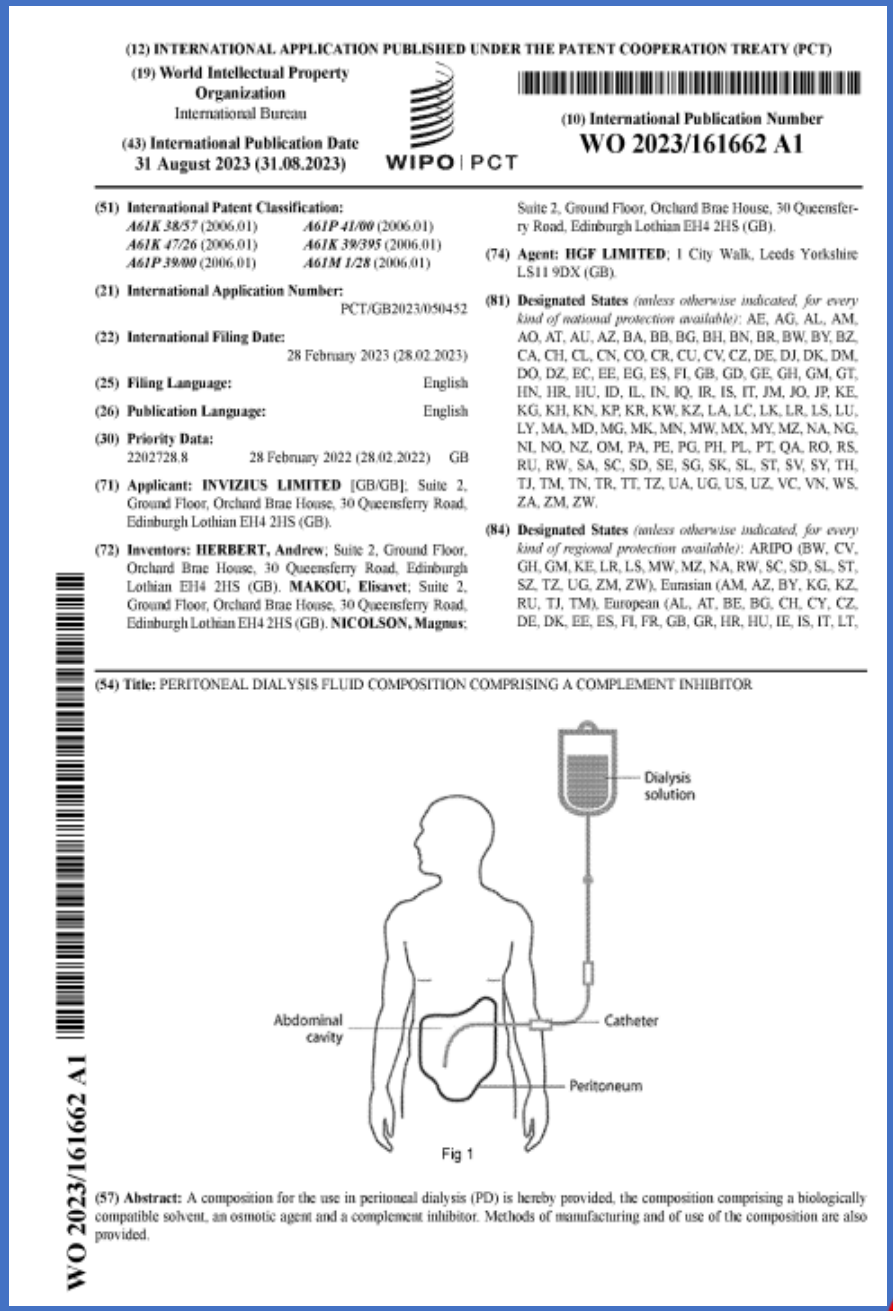


Meso-Guard™ Patent Position

Meso-Guard™ has a strong patent position which restricts others entering the PD field with any other complement inhibitors.

"The complement inhibitor may be a small molecule, a peptide, a macrocyclic peptide, a monoclonal antibody, another recombinant protein, a native protein, an oligonucleotide, a hexaBody, an affibody, a minibody, a nanobody, a Fab, or equivalent antibody derivative, a biologic or an aptamer configured to bind to and inhibit a component of any complement pathway. The complement inhibitor may be a monoclonal antibody, another recombinant protein or an aptamer configured to bind to and activate or enhance one of the natural complement regulators. The complement inhibitor may be unmodified or modified for example with polyethylene glycol, proline-alanine/serine-rich sequences or lipids."

taken from WO 2023/161662 A1



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(71) Applicant: **INVIZIUS LIMITED** [GB/GB]; Suite 2, Ground Floor, Orchard Brae House, 30 Queensferry Road, Edinburgh Lothian EH4 2HS (GB).

(72) Inventors: **HERBERT, Andrew**; Suite 2, Ground Floor, Orchard Brae House, 30 Queensferry Road, Edinburgh Lothian EH4 2HS (GB). **MAKOU, Elisavet**; Suite 2, Ground Floor, Orchard Brae House, 30 Queensferry Road, Edinburgh Lothian EH4 2HS (GB). **NICOLSON, Magnus**; Suite 2, Ground Floor, Orchard Brae House, 30 Queensferry Road, Edinburgh Lothian EH4 2HS (GB).

(74) Agent: **HGF LIMITED**; 1 City Walk, Leeds Yorkshire LS11 9DX (GB).

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(54) Title: PERITONEAL DIALYSIS FLUID COMPOSITION COMPRISING A COMPLEMENT INHIBITOR

Fig 1

(57) Abstract: A composition for the use in peritoneal dialysis (PD) is hereby provided, the composition comprising a biologically compatible solvent, an osmotic agent and a complement inhibitor. Methods of manufacturing and of use of the composition are also provided.

WO 2023/161662 A1