Novel Therapeutics that Down Regulate the Complement Cascade on both sides of the Blood Brain Barrier

Dr Magnus Nicolson
Invizius Ltd

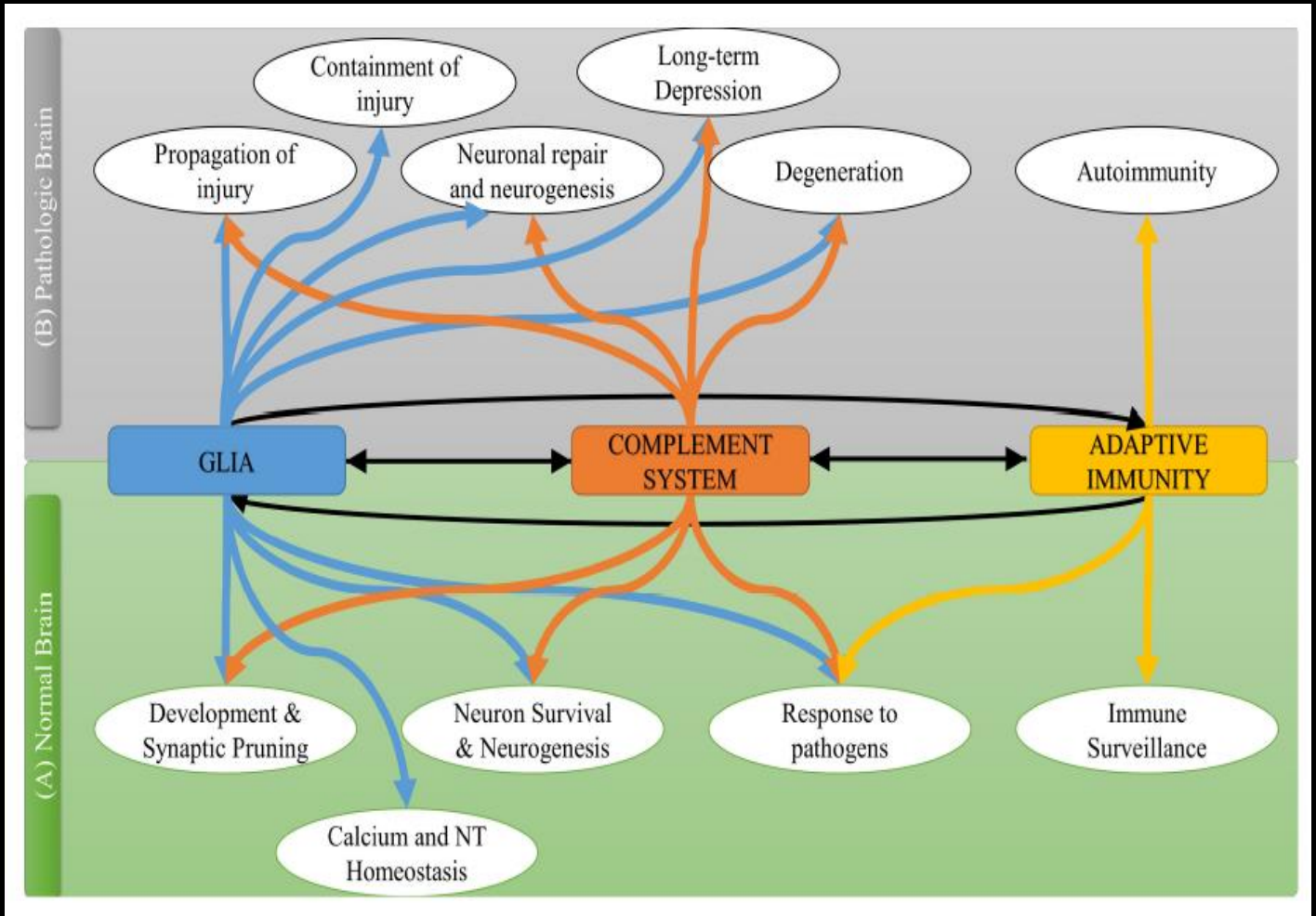
INVIZIUS

The Yin and Yang of Complement in the Normal Brain and Damaged Brain

From: Alawieh A, Elvington A and Tomlinson S (2015)

Complement in the homeostatic and ischemic brain.

Front. Immunol. 6:417. doi: 10.3389/fimmu.2015.00417



Dr Magnus Nicolson
Invizius Ltd

Complement is activated following Traumatic Brain Injury

From: Alawieh A, Elvington A and Tomlinson S (2015)

Complement in the homeostatic and ischemic brain.

Front. Immunol. 6:417. doi: 10.3389/fimmu.2015.00417

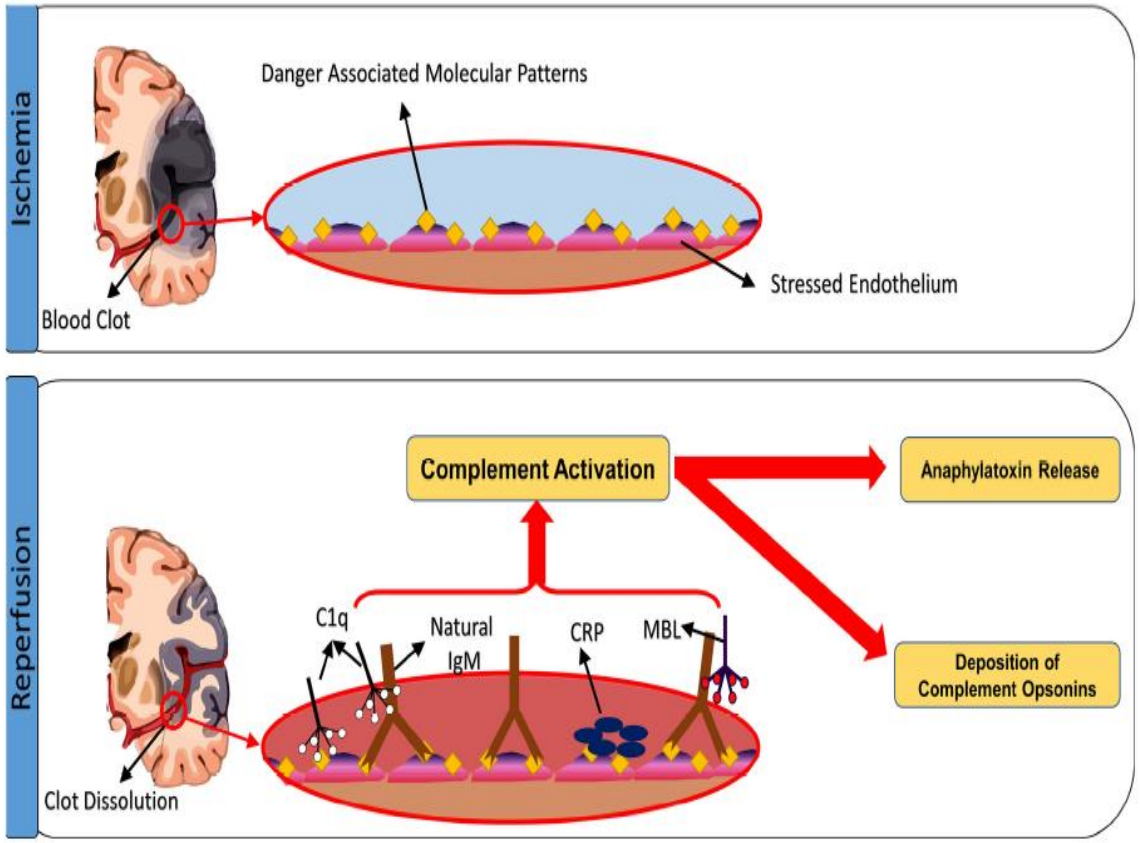
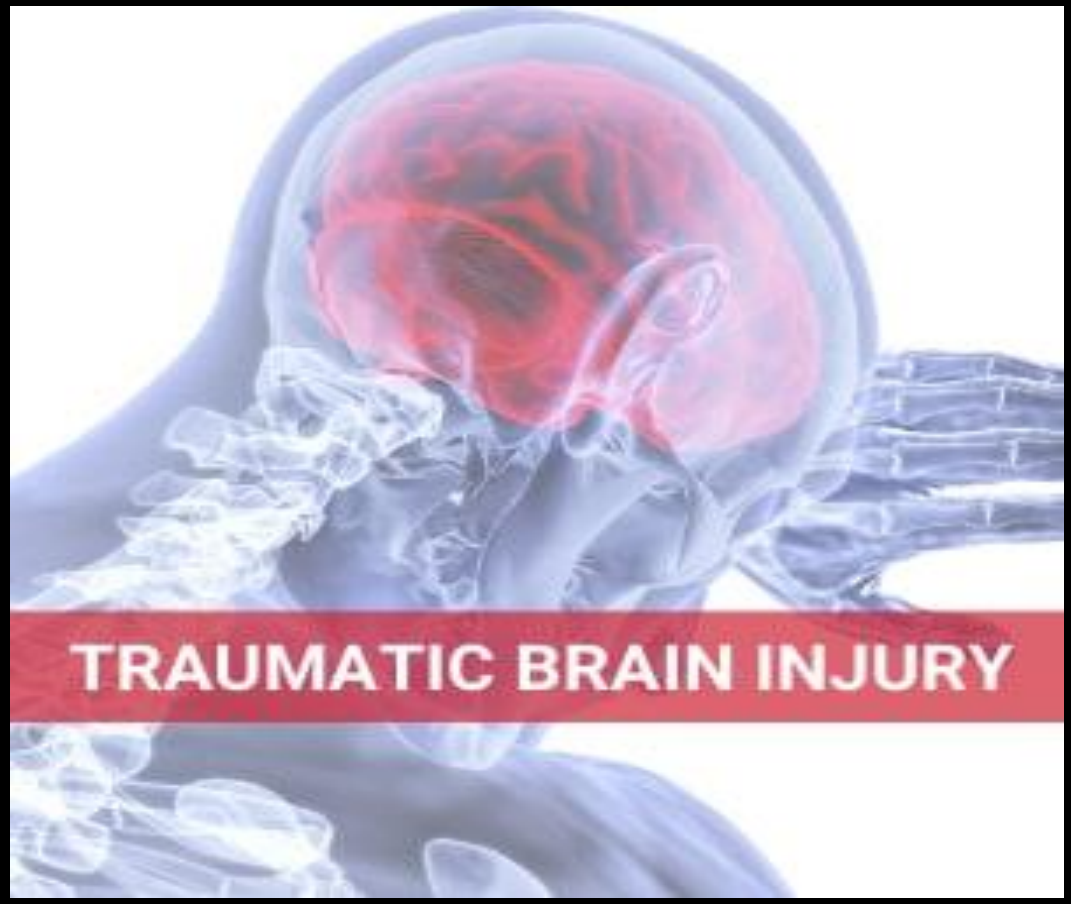


FIGURE 3 | Triggers of complement activation after cerebral ischemia-reperfusion injury. Ischemic insult induces expression of neoepitopes or danger-associated molecular patterns (DAMPs) on the surface of stressed endothelial cells. The exposed DAMPs are recognized by circulating natural self-reactive antibodies, principally IgM, which triggers complement activation. Although IgM binds C1q, it appears to be the binding of MBL and activation of the lectin pathway that drives ischemia and reperfusion injury in the organs systems examined, including the brain. Complement can be also activated through direct binding of C1q to apoptotic cells, as well as through C-reactive protein-induced complement activation.

Dr Magnus Nicolson
Invizius Ltd

Numerous Studies Implicate Complement Activation as Detrimental in TBI

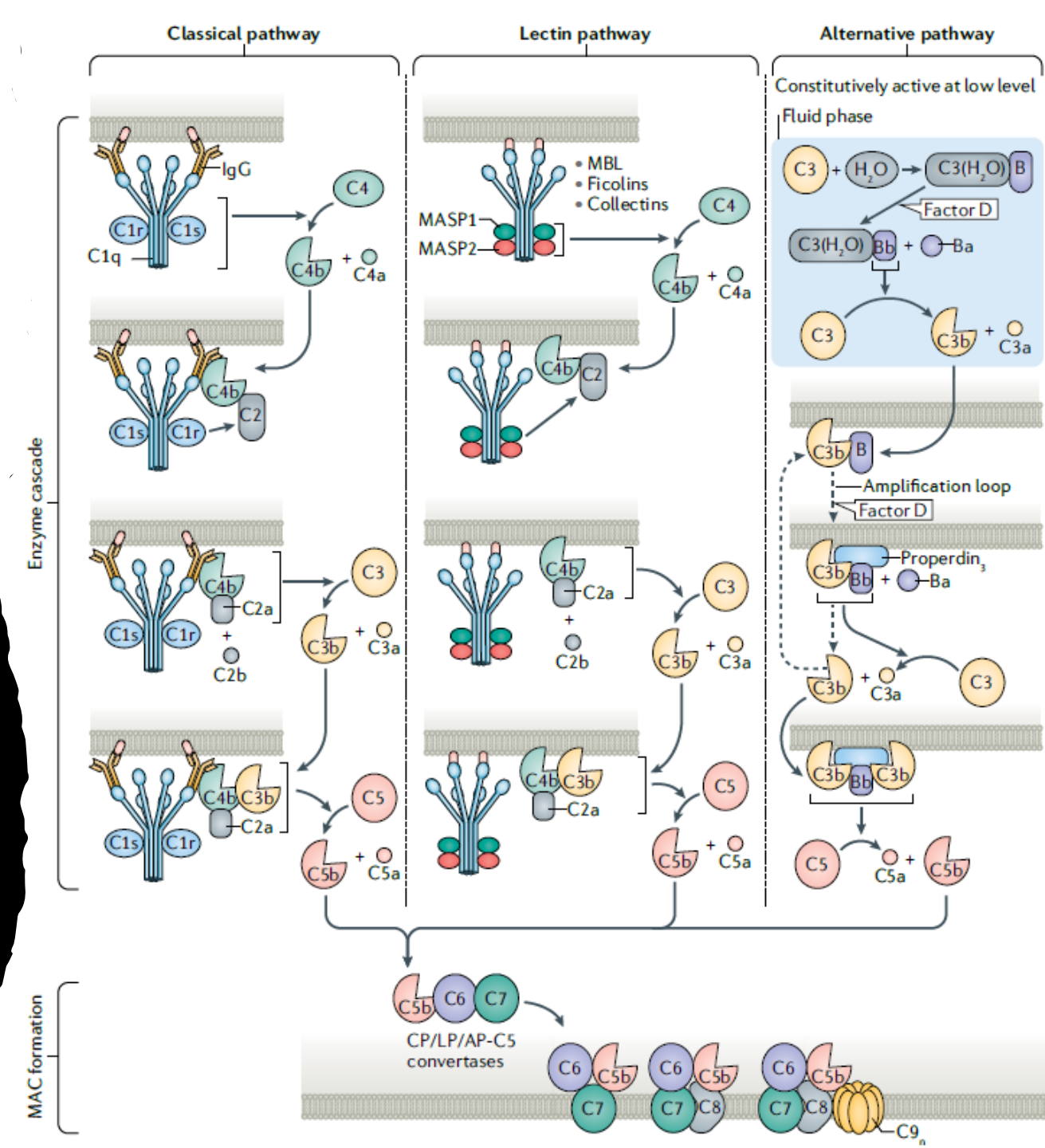
- In TBI patients, high levels of C4, C3, and C5b9 have been found in serum and upregulation of factor B, C3, and C5b9 was detected in the CSF of severe TBI patients.
- Increased immunoreactivity was found in resected contused tissue for C1q, C3b, C3d, and C5b9 within/on neurons located in the penumbra area.
- Intracerebral deposition of MBL, ficolin-2 and 3,and MASP-2 and 3 was found after TBI within the vasculature and in the injured perivascular tissue.
- High levels of complement proteins were strongly associated with lower GCS scores and independently predict mortality or unfavorable clinical outcomes in TBI.



Dr Magnus Nicolson
Invizius Ltd

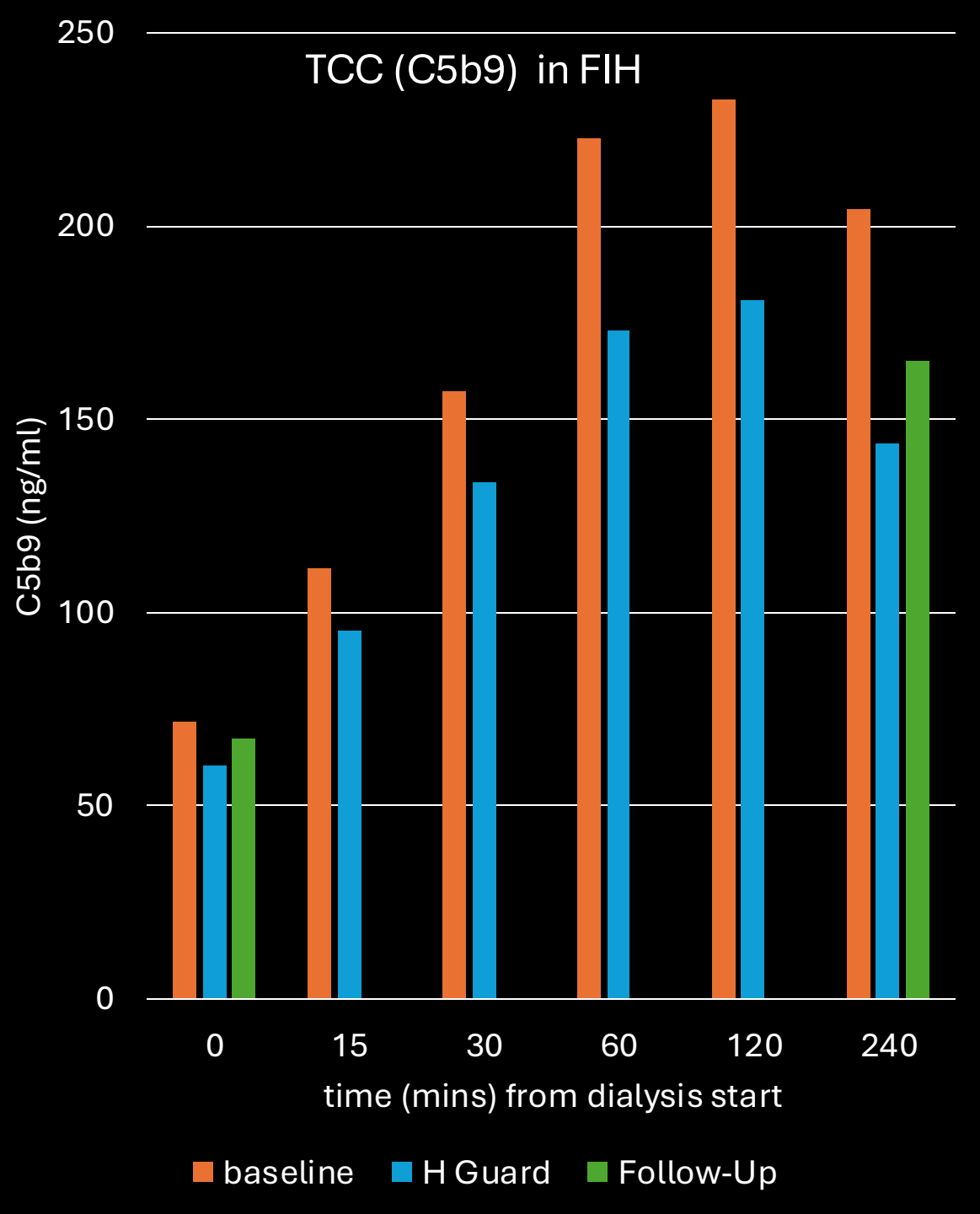
INVIZIUS

Invizius Therapeutics Target the Convertases at the Centre of the Complement Cascade

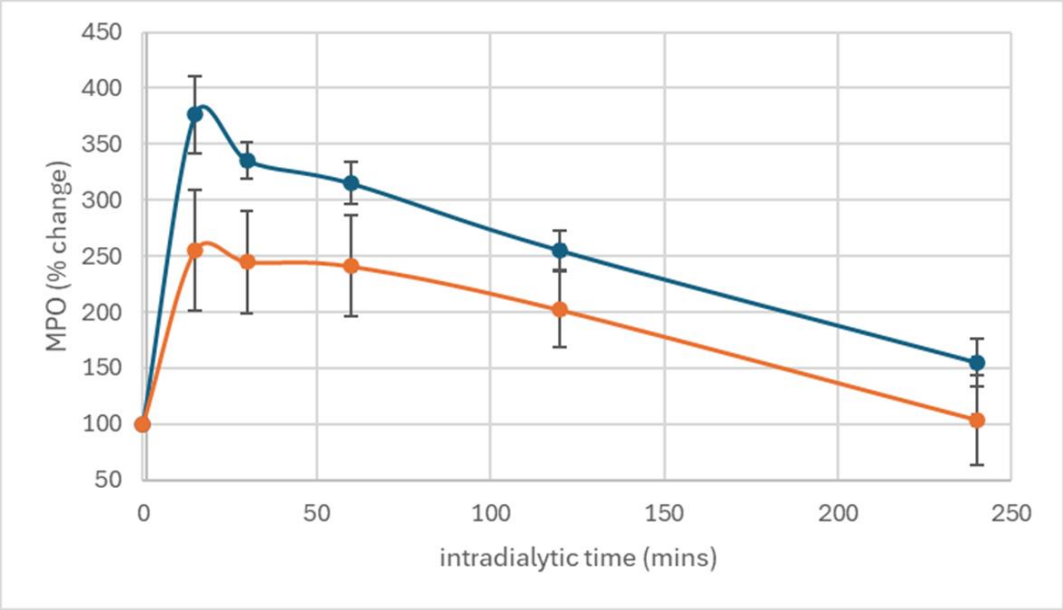


H-Guard® Inhibits Complement in Phase 2a Study

- H-Guard was used to coat dialysis filters and ex vivo and in First in Human study reduced complement activation (as measured by Terminal Complement Complex (C5b9))
- FIH compared a baseline dialysis without H Guard to an H Guard coated filter dialysis.
- A follow-up dialysis session without H Guard suggested a systemic effect



Ph2a – Reduction in Neutrophil Activation (MPO)

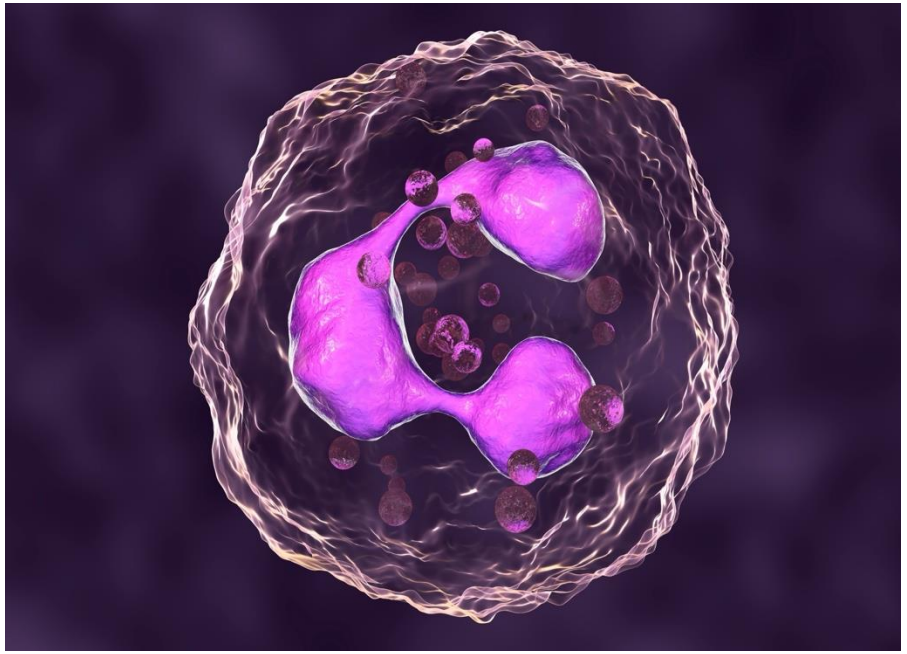


Without H-Guard: higher MPO (more inflammation)

With H-Guard: lower MPO (less inflammation)

H-Guard consistently lowers MPO (Neutrophil Activation) at 15mins with a p= 0.00834

"Myeloperoxidase enzyme (MPO), a well-recognised proinflammatory biomarker released during oxidative stress, is strongly linked with cardiovascular disease, and may provide a pathogenic link between Inflammation and CV disease, both commonly observed in haemodialysis patients." Prof. Sandip Mitra (Manchester Royal Infirmary)

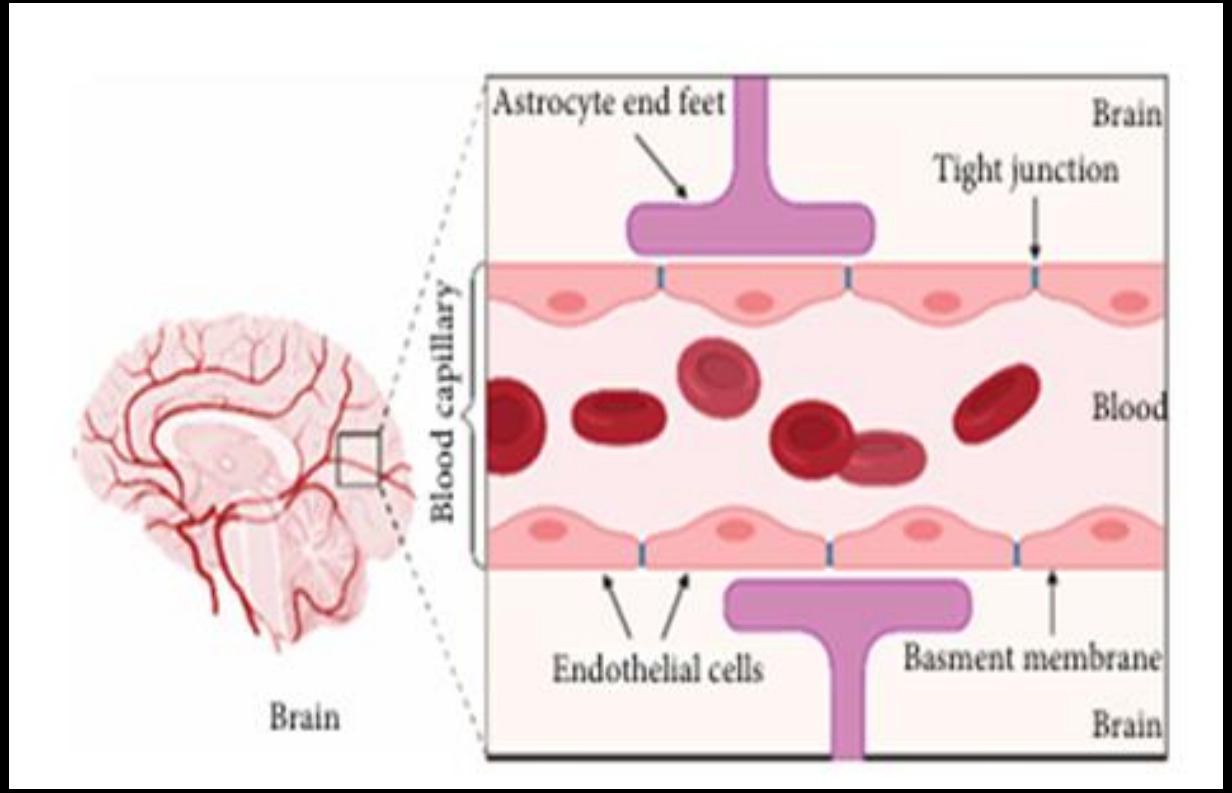


"Thank you for this very interesting finding. It corroborates the fact that MPO and C activation are linked, also a good point is that H-Guard as a mitigating effect. In this perspective, that reinforces the potential of H-Guard for improving AKI3D outcomes." Prof. Bernard Canaud (former Chief Medical Officer Fresenius Medical Care)

Dr Magnus Nicolson
Invizius Ltd

Blood Brain Barrier (BBB)

- The human brain has 644 kilometers of blood vessels that provide oxygen, energy, metabolites, and nutrients to brain cells while also removing carbon dioxide as well as other metabolic wastes from the circulatory system .
- The brain requires 20% of the body's glucose and oxygen, while accounting for just 2% of total body mass, and can quickly increase blood supply and oxygen transfer to its active areas, a mechanism that is known as neurovascular coupling .
- This control is aided by barrier layers at the main interfaces between blood and neural tissue called blood-brain barrier (BBB).
- The BBB is a dynamic, semipermeable, and extremely selective system in the cerebral micro-vessels of most vertebrates.
- It separates the bloodstream from the brain's extra cellular fluid .
- It plays a vital role in regulating the transport of necessary substances for brain function

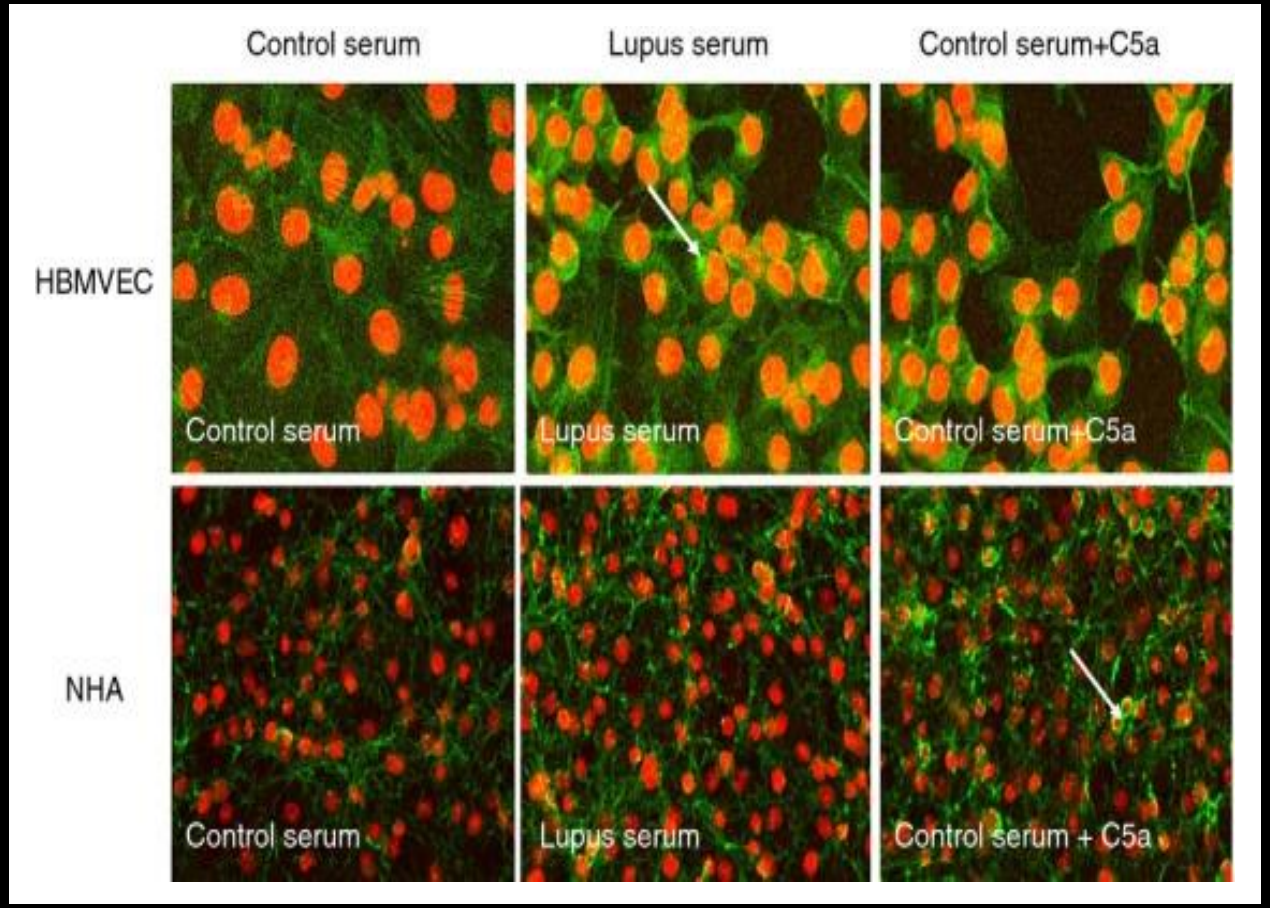


Dr Magnus Nicolson
Invizius Ltd

C5a Regulates BBB Permeability

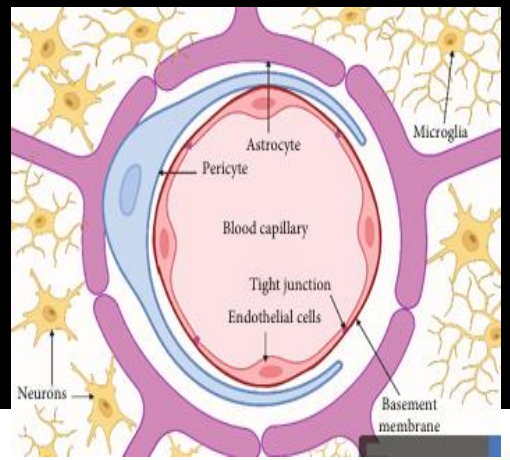
C5a reduces stress fibre formation in human brain microvascular endothelial cells (HBMVECs) and normal human astrocytes (NHAs). Monolayers of HBMVECs and NHA cells were treated with 5% control serum (left), lupus serum (centre) or C5a (right) for 3 hr. Typical patterns of FITC-phalloidin staining indicating actin rearrangement are seen in cells treated with lupus serum compared with cells treated with control serum. Treatment of cells with C5a resulted in actin rearrangement and increased intercellular gaps, similar to that observed with lupus serum. Representative images from three independent experiments are shown. Nuclei were stained with DAPI.

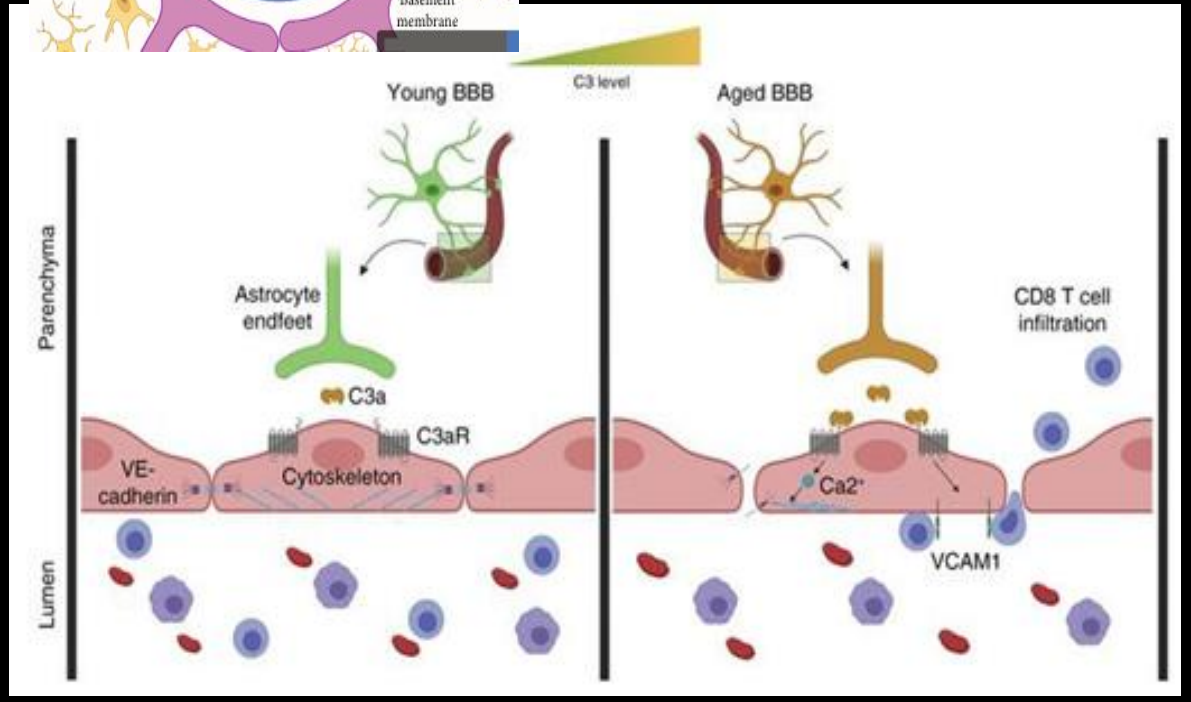
Mahajan ,S .D et al Immunology, (2015)146, 130–143



Dr Magnus Nicolson
Invizius Ltd

C3a and BBB Inflammation





"In conclusion, our work identifies a potentially novel complement regulatory axis at the BBB through endothelial C3aR. It implicates a critical role for a C3aR-dependent endothelial inflammatory transition, which results in increased VCAM1 expression in the aged brain. Our data suggest that blocking complement-mediated effects can have a substantial impact on improving vascular health, rescuing BBB permeability, and decreasing neuroinflammation in aging and neurodegeneration. Since the complement pathway is upregulated in both acute inflammatory conditions, such as stroke and traumatic brain injury, and in neurodegenerative diseases, inparticular Alzheimer disease, of which age is the greatest risk factor, our findings have direct implications for the pathogenesis and therapeutic targeting of these age-related diseases of the brain."
J Clin Invest. 2021;131(1):e140966.

Dr Magnus Nicolson
Invizius Ltd

MPO and Neuroinflammation

- Oxidative stress and inflammation are two critical pathological processes of cerebral ischemia-reperfusion injury.
- Myeloperoxidase (MPO) is a critical inflammatory enzyme and therapeutic target triggering both oxidative stress and neuroinflammation in the pathological process of cerebral ischemia-reperfusion injury.
- MPO is presented in infiltrated neutrophils, activated microglial cells, neurons, and astrocytes in the ischemic brain.
- Activation of MPO can catalyse the reaction of chloride and H2O2 to produce HOCl.
- MPO also mediates oxidative stress by promoting the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), modulating the polarization and inflammation-related signalling pathways in microglia and neutrophils.
- MPO can be a therapeutic target for attenuating oxidative damage and neuroinflammation in ischemic stroke.

Dr Magnus Nicolson
Invizius Ltd

Conclusion

- H-Guard® has the potential to reduce Plasma Side C5a,C3a and MPO mediated BBB damage caused by ischaemic injury or inflammatory injury.

  - SLE & Autoimmune Complement Activation
  - TBI & STROKE
  - Delerium via Extracorporeal Complement Activation (CRRT/ECMO/CPB)

- Meso-Guard™ has the potential of reducing Brain Side endogenous complement activation by delivery across the BBB.

  - In vivo and “Neuro-chip” delivery evaluation models available.
  - Require CDA before disclosing further information.

Dr Magnus Nicolson
Invizius Ltd