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The Complement System in Health and Disease

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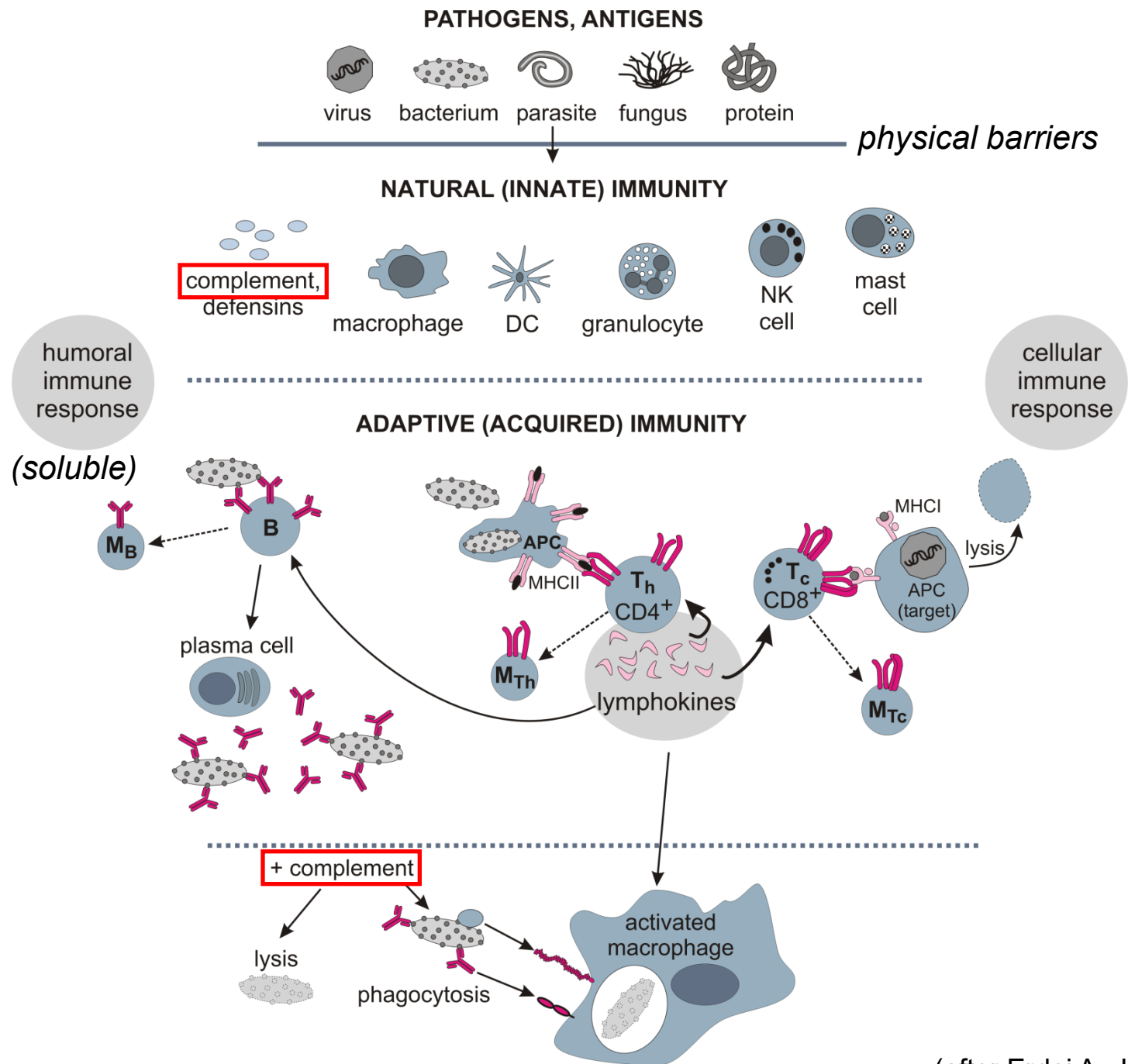
KERC Forum, Brussels, July 1-3, 2025



Complement Research Group at ELTE

- 1997 MSc Diploma, Biology/Immunology, ELTE (Eötvös Loránd University, Budapest)
- 2002 Ph.D. – Immunology (ELTE, Budapest)
- 2002-2005 postdoc, Leibniz Institute HKI, Jena, Germany (group of Prof. P. Zipfel)
- 2006-2012 junior group leader, Leibniz Institute HKI, Jena, Germany
- 2012-2017 head of MTA-ELTE „Lendület“ Complement Research Group at ELTE
- 2017-2020 associate professor, Dept. Immunology, ELTE, Budapest, Hungary
- 2020- full professor, head of Dept. Immunology and director of Bolyai College





(after Erdei A., Immunology)

Complement functions

Innate immunity

- opsonization
- lysis of microbes
- chemotaxis
- inflammation
- cell activation
(PMN, Mf, DC, ...)

Adaptive immunity

- B cell activation
- elimination of self-reactive B cells
- promotion of T cell responses

Other processes

- immune complex clearance
- removal of apoptotic and necrotic cells
- synaptic pruning
- vascularization
- wound healing
- placenta development
- ...

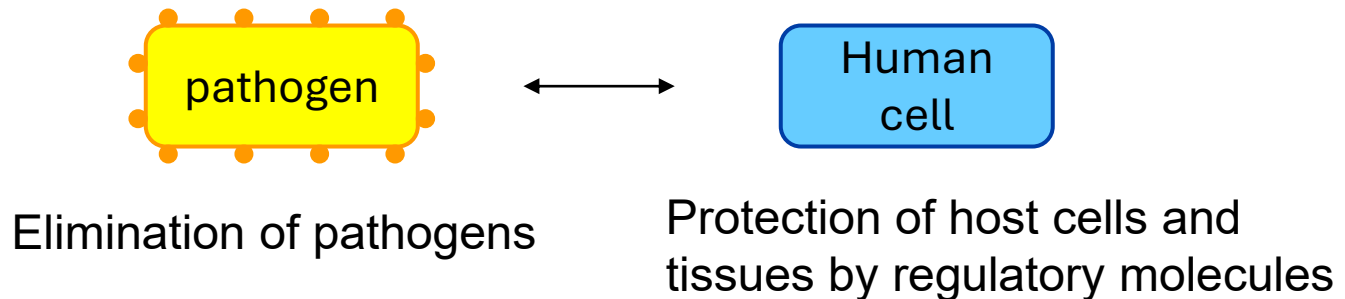


- **systemic – local – intracellular**
- **canonical – non-canonical functions**

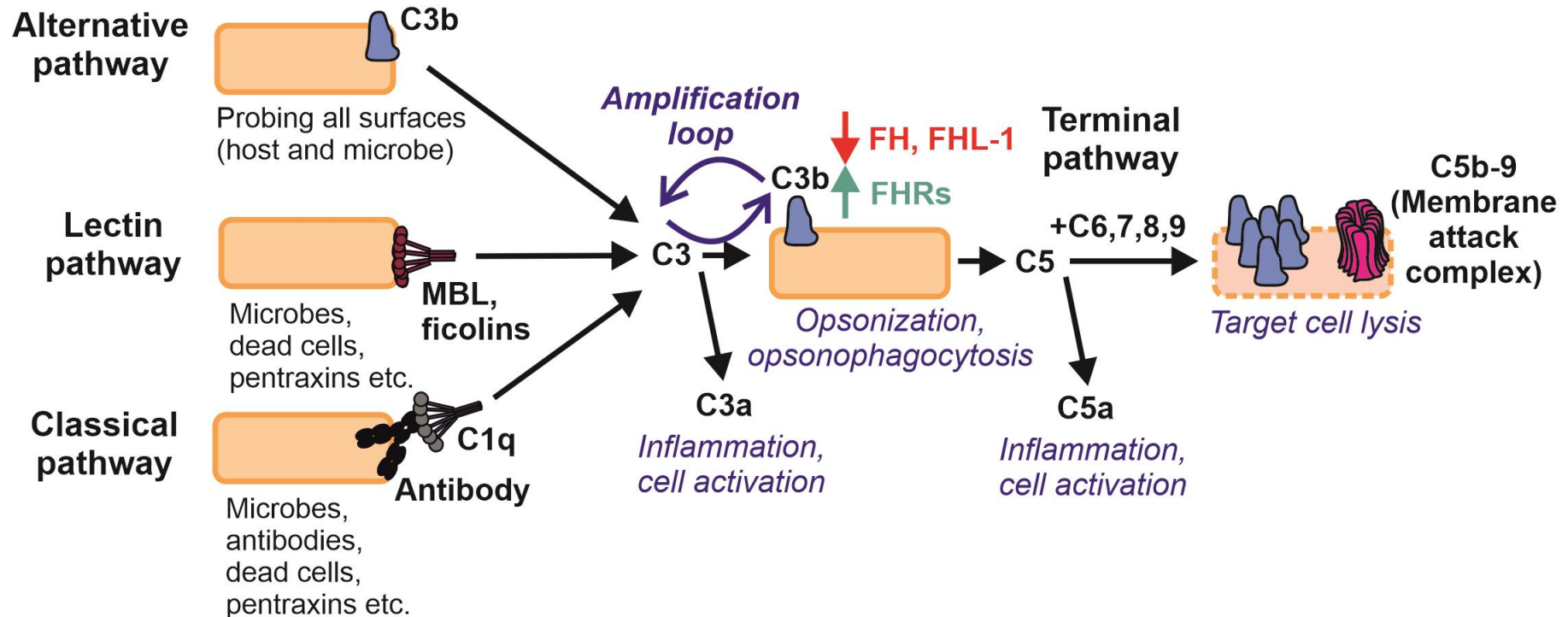
Complement in self / non-self discrimination

Strategy 1: recognize and attack (dangerous) non-self
- adaptive immunity

Strategy 2: attack everything – but protect (healthy) self
- complement alternative pathway



The role of factor H in complement regulation

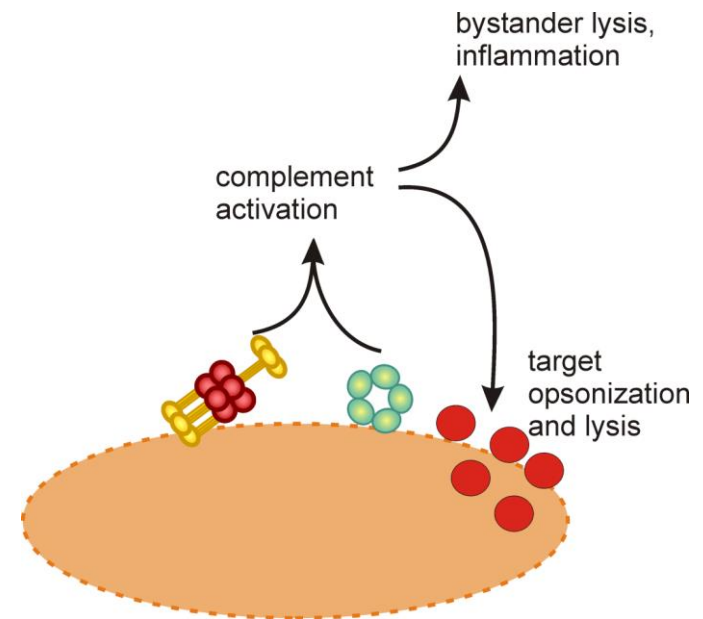
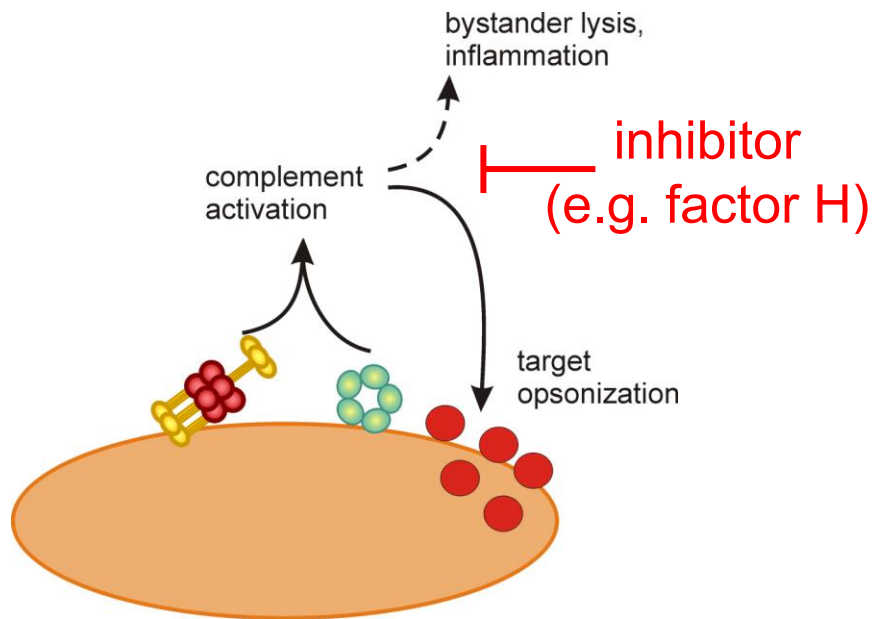


FH: factor H
FHL-1: factor H-like 1
FHR: factor H-related

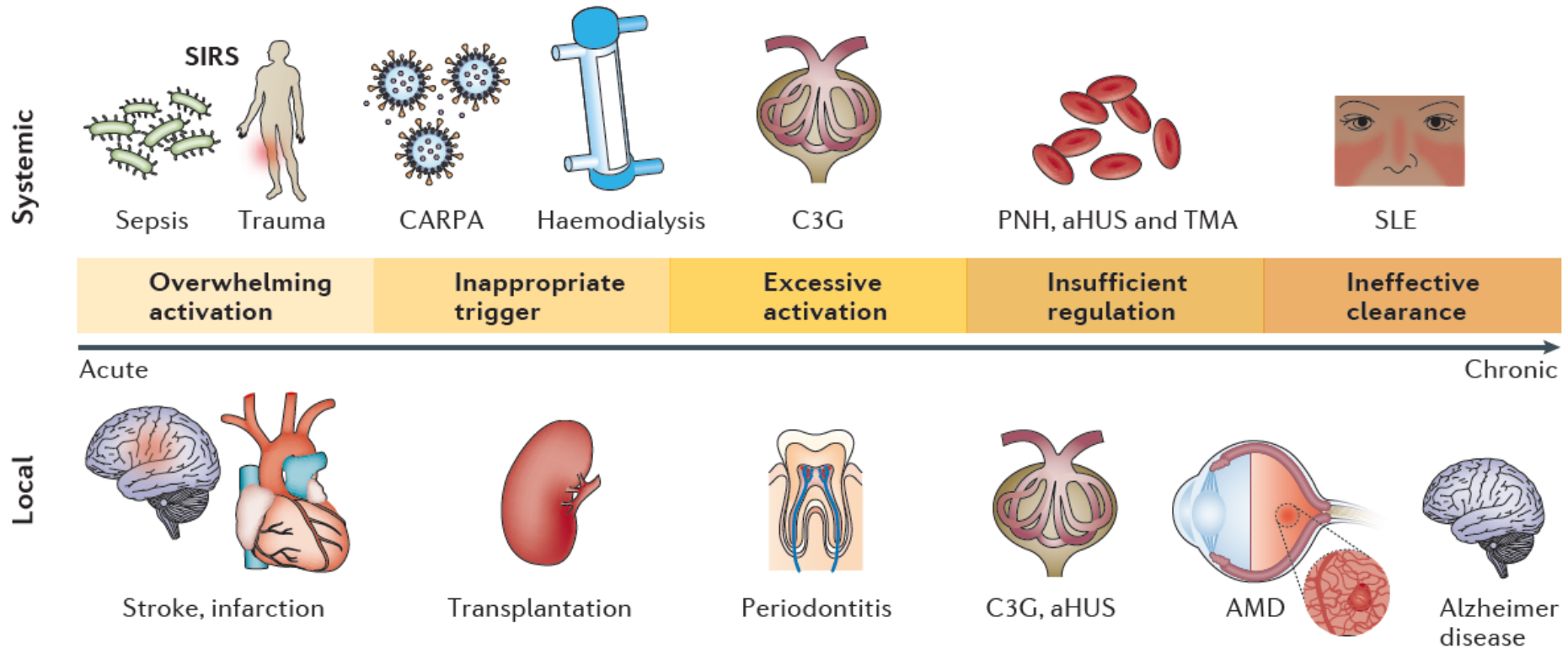
Józsi and Uzonyi, J Allergy Clinical Immunology (2025)

Balance of complement activation / inhibition

- targeted and restricted complement activation (safe opsonization)
- cooperation of pattern recognition molecules and opsonic molecules
- host tissue damage, inflammation, autoimmunity



Complement and diseases



aHUS: atypical haemolytic uraemic syndrome

AMD: age-related macular degeneration

C3G: C3 glomerulopathy

CARPA: complement activation-related pseudo allergy

PNH: paroxysmal nocturnal haemoglobinuria

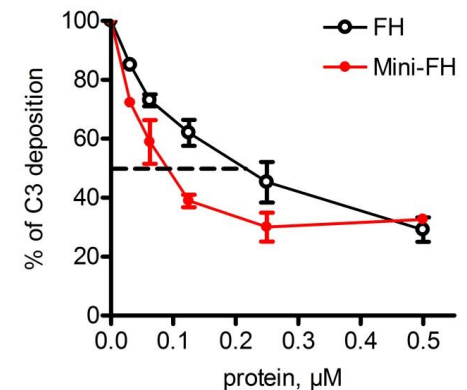
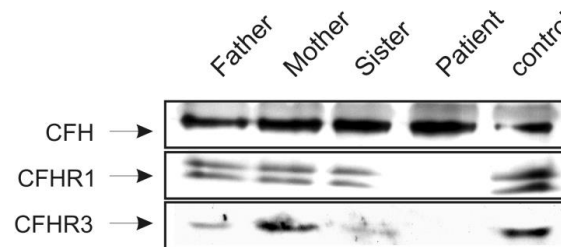
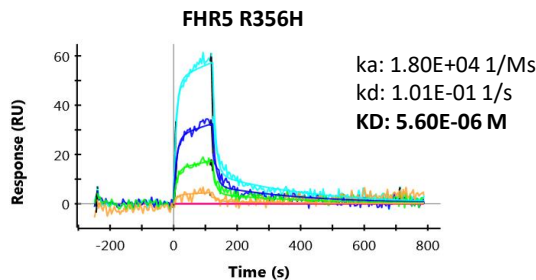
SIRS: systemic inflammatory response syndrome

SLE: systemic lupus erythematosus

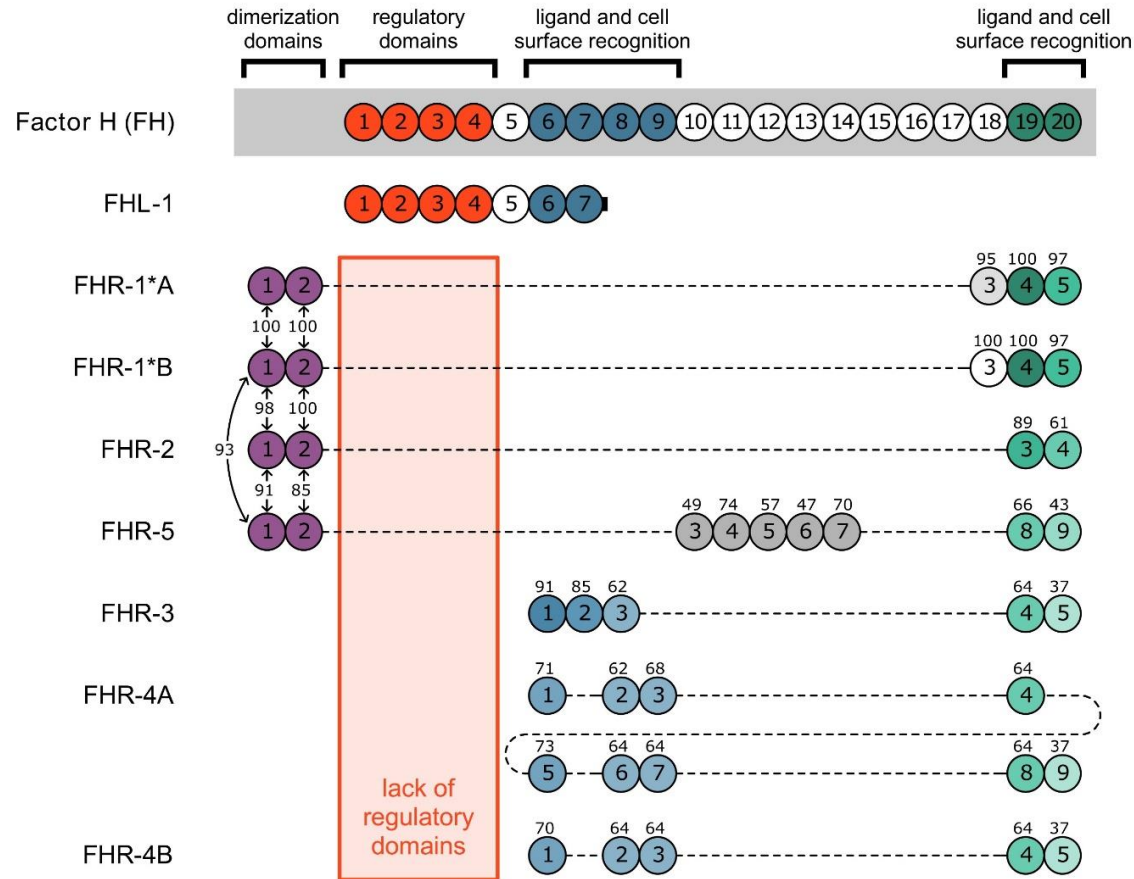
TMA: thrombotic microangiopathy

Research field and interests

- The complement system / innate immunity
- Canonical and non-canonical roles of factor H family proteins
- Soluble pattern recognition molecules
- Anti-complement autoantibodies
- Complement-mediated diseases
- Complement diagnostics and therapy



The factor H gene and protein family

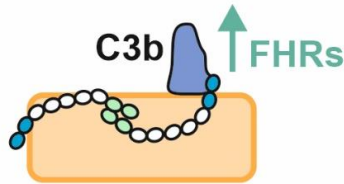


- Kidney diseases
- Age-related macular degeneration
- Infections
- Neuroinflammatory/degenerative diseases
- Cancers
- etc.

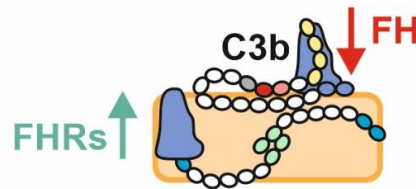
What are their physiological and pathological roles ?

Emerging role of the FHRs as competitive inhibitors of factor H

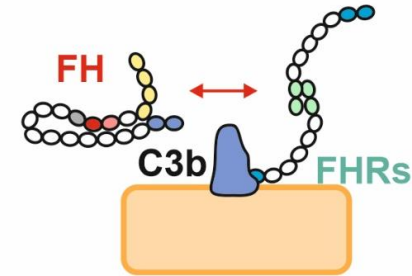
Role of the FHR proteins



Complement activation by FHRs via recruiting C3b



Collaboration of FH and FHRs for optimal opsonization

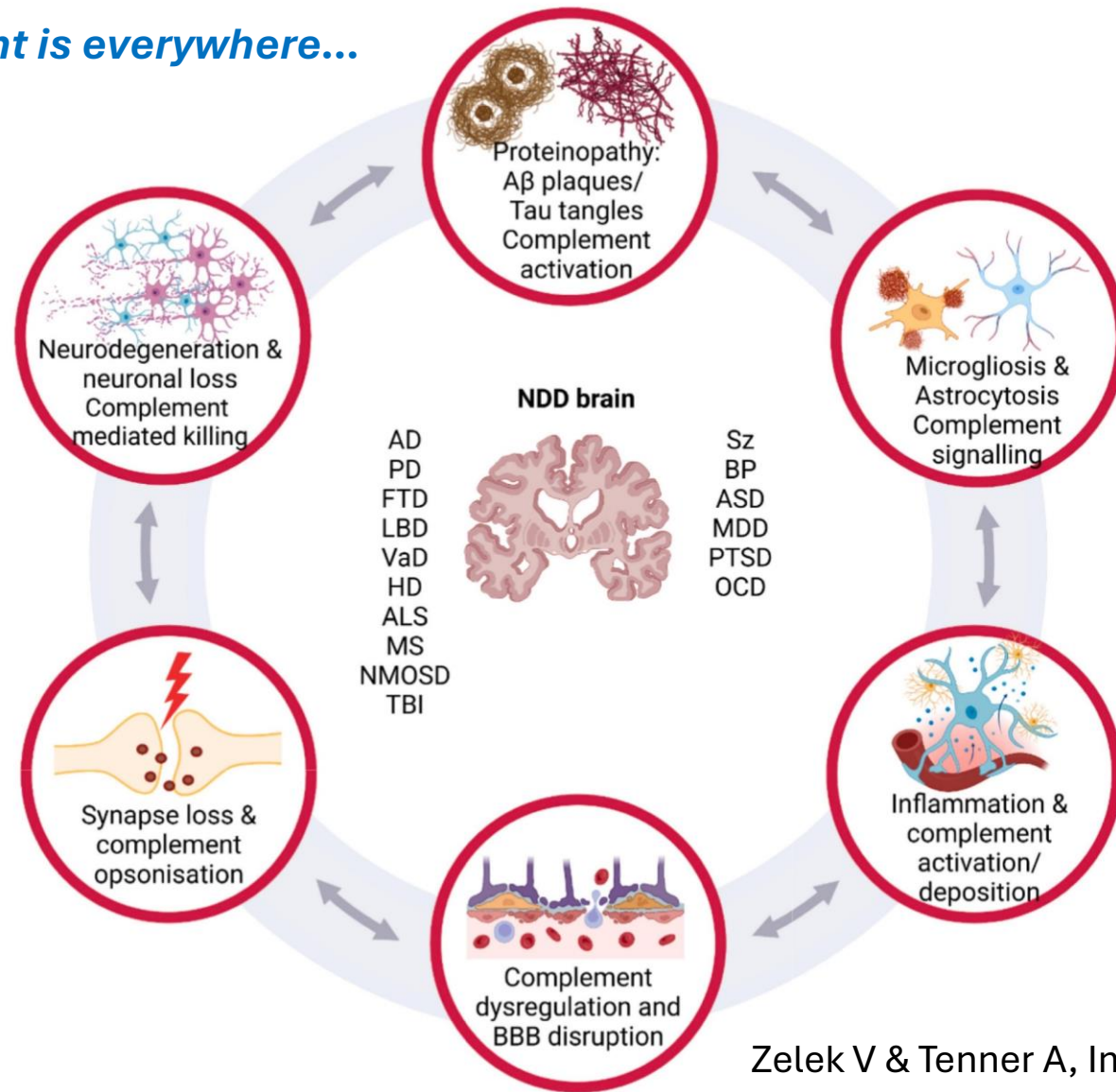


Complement deregulation by FHRs via competition with FH

Józsi and Uzonyi, J Allergy Clinical Immunology (2025)

- Genetic studies indicate their role in complement-mediated diseases
- Conserved domains are those mediating important ligand interactions of factor H and binding to microbes
- They emerge as soluble pattern recognition molecules that promote opsonization locally
- Role in fine-tuning of complement activation/regulation

Complement is everywhere...

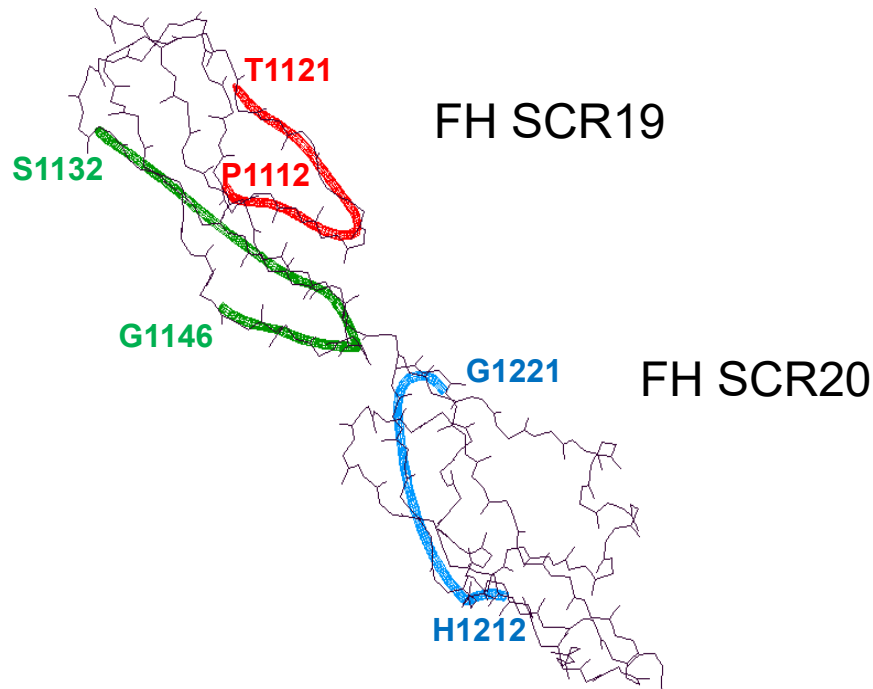


Zelek V & Tenner A, Immunobiology 2025

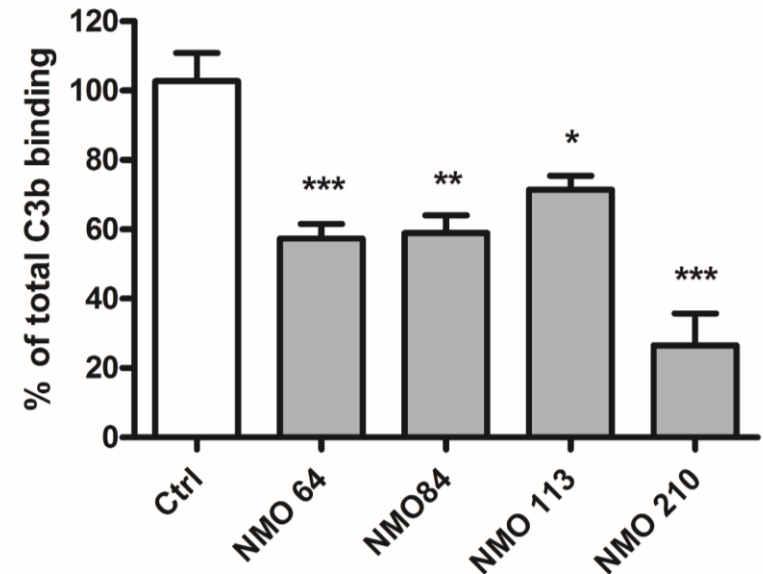


FH-autoantibodies in NMOSD

- bind to the C terminus of FH (peptide array)



- inhibit FH interaction with C3b



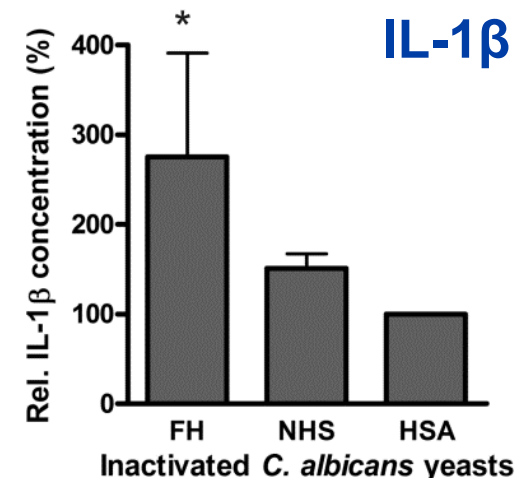
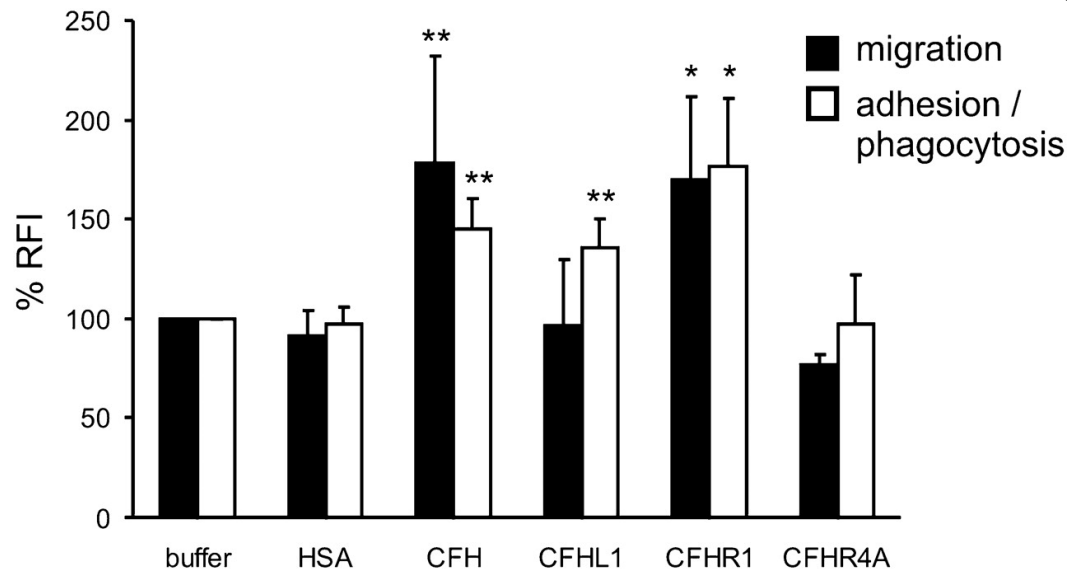
NMOSD: Neuromyelitis optica spectrum disorder

Uzonyi, ..., Józsi, Frontiers in Immunology 2021

FH binding to microbes and host cells

FH acquisition by microbes – not only complement evasion

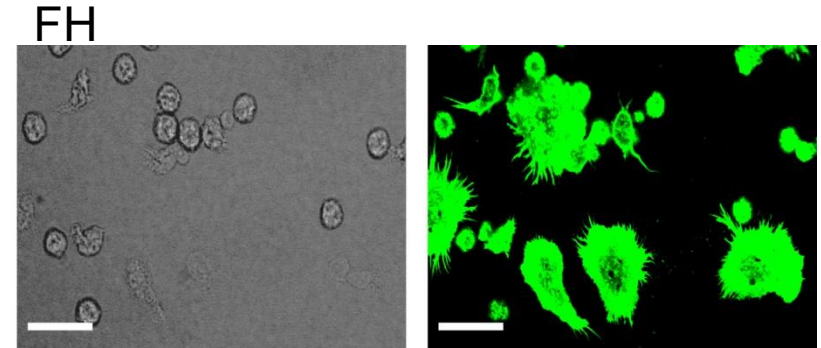
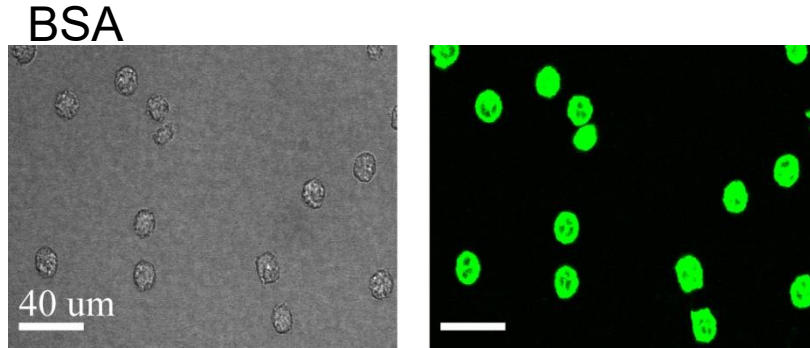
- *Leptospira* spp. – cooperation with A. Barbosa, L. Isaac (São Paulo)
- *Candida albicans* – modulating interaction with neutrophils and macrophages



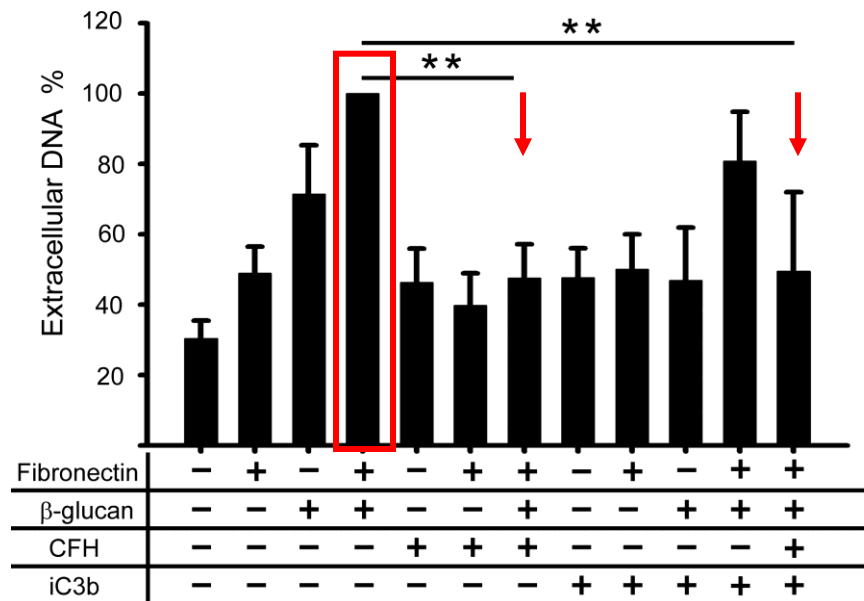
Losse, ..., Józsi, J. Immunol. (2010) 184:912-21.

Svoboda, ..., Józsi, Immunol. Lett. (2015) 168:13.

FH modulates neutrophil activation

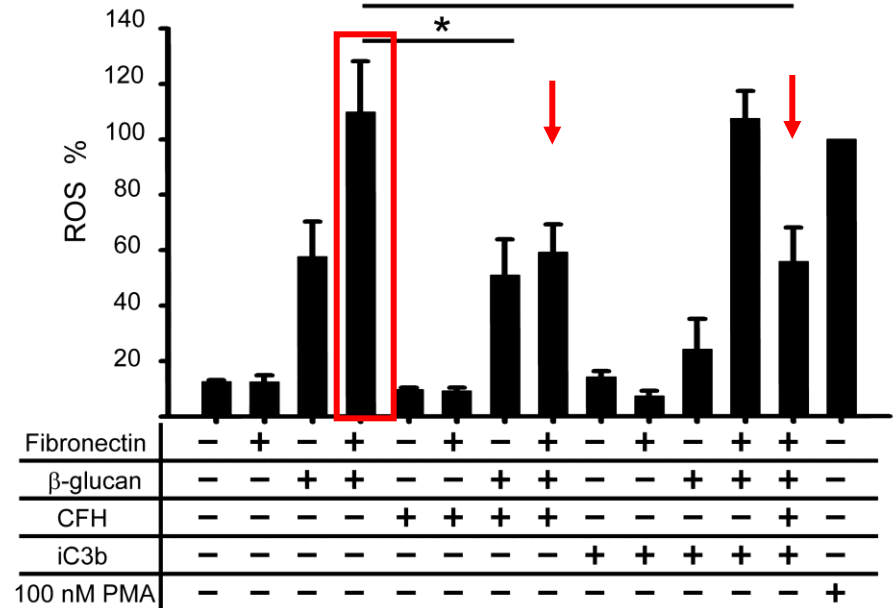


Neutrophil extracellular traps



100% = Fn + β-glu induced NET level

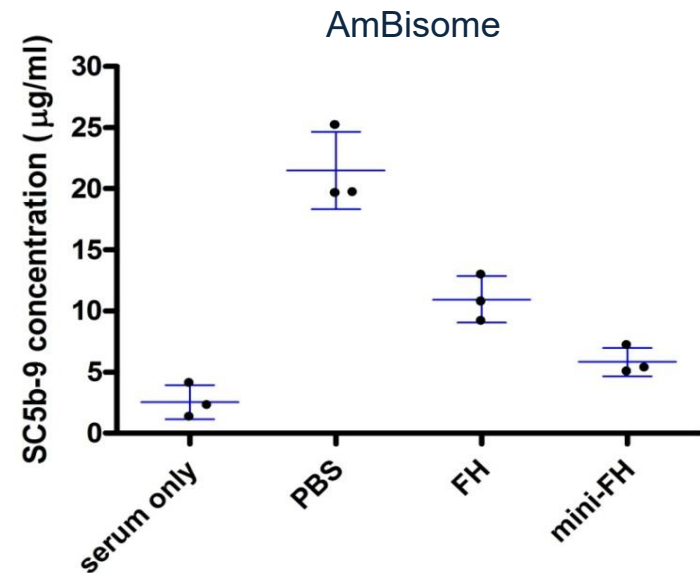
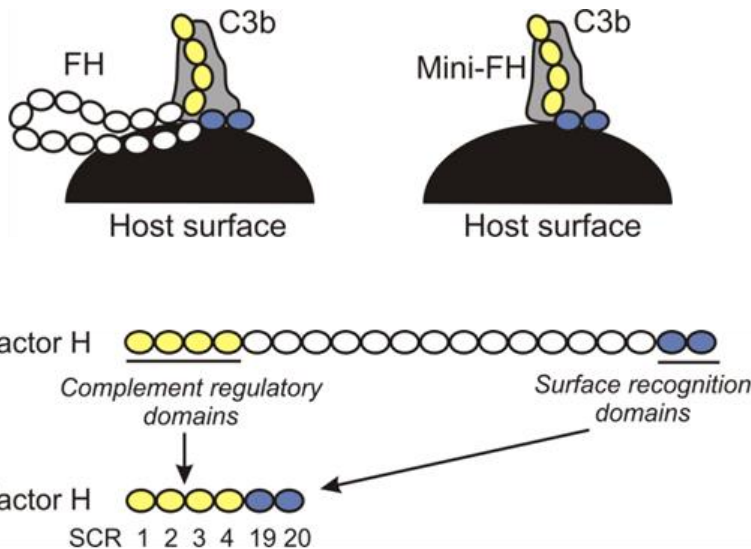
ROS



100% = 100 nM PMA-induced ROS level

"Mini-factor H" – an artificial complement inhibitor

(Mini)-Factor H inhibits liposomal and micellar drug-induced complement activation (CARPA)



Hebecker, ..., Józsi, J Immunol. (2013) 191:912-921.

Mészáros, ..., Józsi, Nanomedicine, 2016, 12: 1023-1031.

→ Also modulates IL-6 and IL-10 release – potential benefits against cytokine storm?

Kozma, ..., Józsi, Szebeni, Front. Immunol. 2021

Towards understanding the role of FH&FHRs

Quantification and functional characterization

- Serum levels, ligands, functions, novel assays – H2020 (FETOPEN) collaborative project
(www.scifimed.eu)



Role in kidney diseases

- Complement regulation on extracellular matrix
- Regulation of complement convertases



Role in inflammatory and infectious diseases



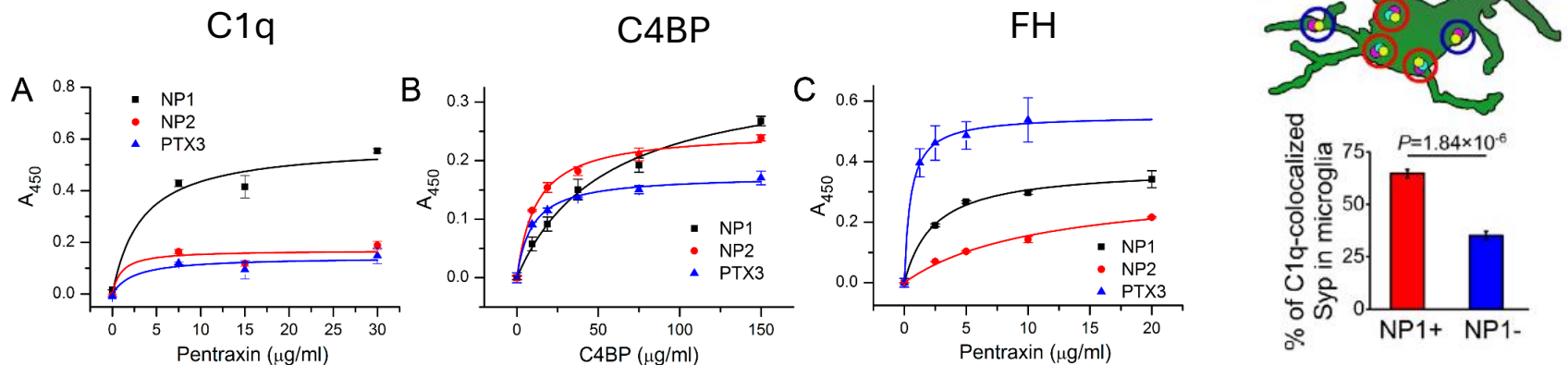
Biomarkers and therapeutic targets

- Autoantibodies
- Mini-FH and Co.
- Complement-mAbs with Biosystems Immunolab Zrt.



Topics / fields to be explored further

- Complement in neuroinflammation and neurodegenerative diseases
- Complement – (neuro)pentraxin cross-talk
- Factor H family proteins in infectious diseases
- Factor H family proteins in cancer
- Engineered inhibitors and complement (auto)antibodies in therapy – inhibition or activation of complement



Acknowledgements

ELTE Dept. Immunology Complement Research Group

Bencze, Dániel
Hammad, Hani Hashim
Dr. Kövesdi, Dorottya
Matola, Alexandra
Sajgó, Martina
Dr. E. Schneider, Andrea
Dr. Szakács, Dávid
Dr. Uzonyi, Barbara

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Dr. Szabó, Zsóka

Collaborations:

Gábor Pál, József Kardos,
Péter Gál, József Dobó, Andrea Kocsis,
János Szebeni, Zoltán Prohászka
János Nacsa (Budapest)
József Lázár, László Takács (Debrecen)

Anna M. Blom (Malmö)

Lourdes Isaac, Angela Barbosa (São Paulo)

Santiago Rodríguez de Córdoba, Agustín
Tortajada (Madrid)

SciFiMed partners:

Diana Pauly (Marburg), Elena Goicoechea
de Jorge (Madrid), Richard Pouw
(Amsterdam), Erik Toonen (Uden), ...

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Thank you for your attention!

