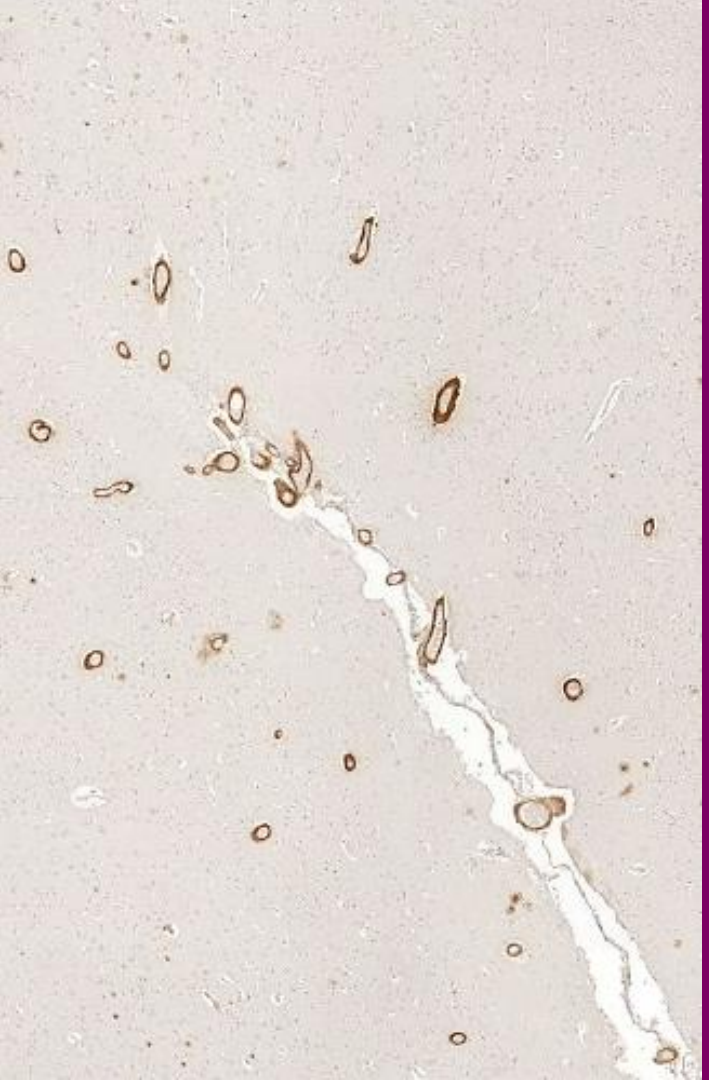

THE PRESENCE OF CIRCULATING HUMAN APOLIPOPROTEIN J REDUCES THE OCCURRENCE OF CEREBRAL MICROBLEEDS IN A TRANSGENIC MOUSE MODEL WITH CEREBRAL AMYLOID ANGIOPATHY

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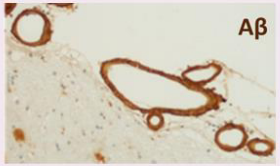
Neurovascular Research Lab
Vall d'Hebron Research Institute, Barcelona (Spain)

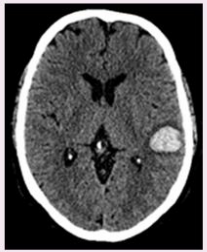
RICORS ICH Symposium2024
8th October 2024

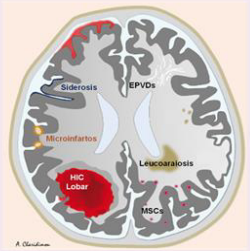
Cerebral amyloid Angiopathy (CAA)



Clinical presentations:

- Lobar intracerebral hemorrhage
- Cognitive impairment





Charidimou et al., Brain2017

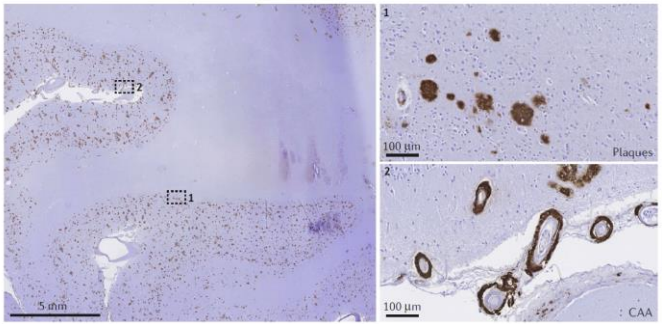
No treatment

Diagnosis- Histopathological confirmation

Nat Rev Neurol. 2020 January ; 16(1): 30–42. doi:10.1038/s41582-019-0281-2.

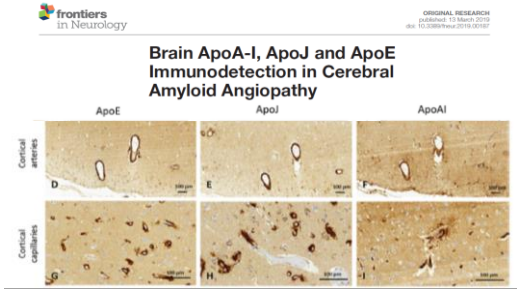
Cerebral amyloid angiopathy and Alzheimer disease — one peptide, two pathways

Steven M. Greenberg[1,*], Brian J. Bacskai[1], Mar Hernandez-Guillamon[2], Jeremy Pruzin[3], Reisa Sperling[3], Susanne J. van Veluw[1]



Apoliportein J (ApoJ) = Clusterin

Apolipoproteins involved in cerebral β-amyloidosis



Camacho et al., Front Neurol 2019

Genetic variants in *CLU* identified as risk factors for AD

Harold et al., 2009; Lambert et al., 2013; Foster et al., 2019

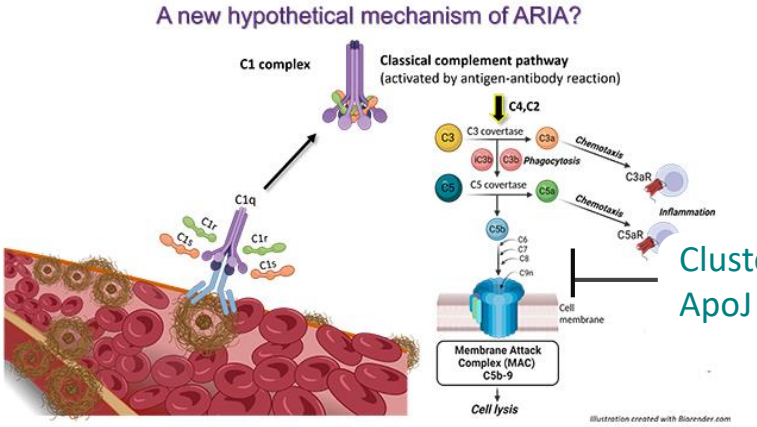
ApoJ: ability to bind **Aβ** and prevent its **fibrilization**

Yerbury et al., 2007; Beeg et al., 2016; Wojtas et al., 2020

The alteration of ApoJ expression impacts on **Aβ deposition** in vivo

Qi et al., 2018; Montoliu-Gaya et al., 2018; Fernandez-de retana et al., 2019; Wojtas et al., 2020; Chen et al., 2021

CAA-AD interactions: AD immunotherapy



Clusterin/ ApoJ

Cynthia Lemere and Maria Tzousi Papavergi - www.alzforum.org

Effect of the increase or circulating levels of ApoJ/clusterin in a AD/CAA Tg model

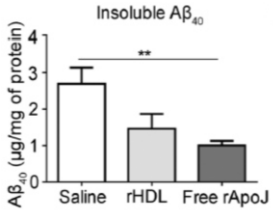
Retana et al. Alzheimer's Research & Therapy (2019) 11:42
https://doi.org/10.1186/s13195-019-0498-8

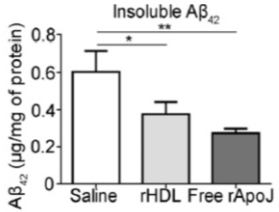
Alzheimer's Research & Therapy

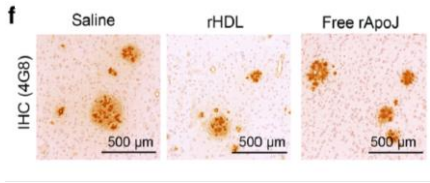
RESEARCH Open Access

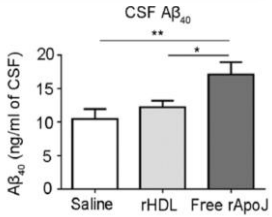
Peripheral administration of human recombinant ApoJ/clusterin modulates brain beta-amyloid levels in APP23 mice

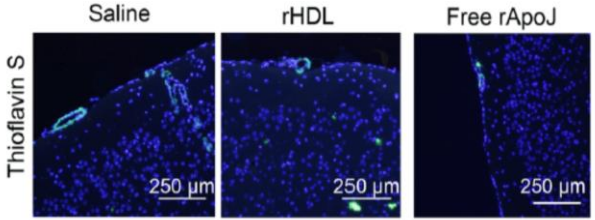
Sofía Fernández de Retana[1], Paula Marazuela[1], Montse Solé[1], Guillem Colell[1], Anna Bonaterra[1], Jose Luis Sánchez-Quesada[2,3], Joan Montaner[1], Daniel Maspoch[4,5], Mary Cano-Sarabia[4,5] and Mar Hernández-Guillamon[1*]

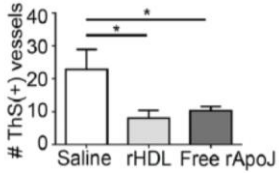


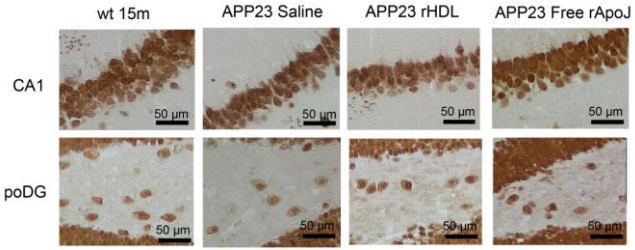


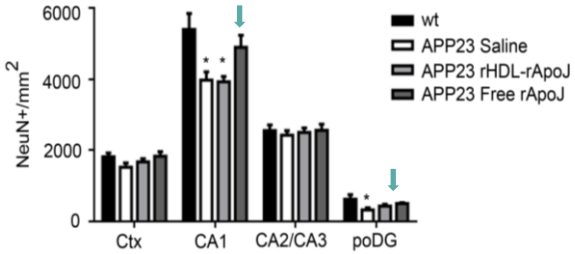








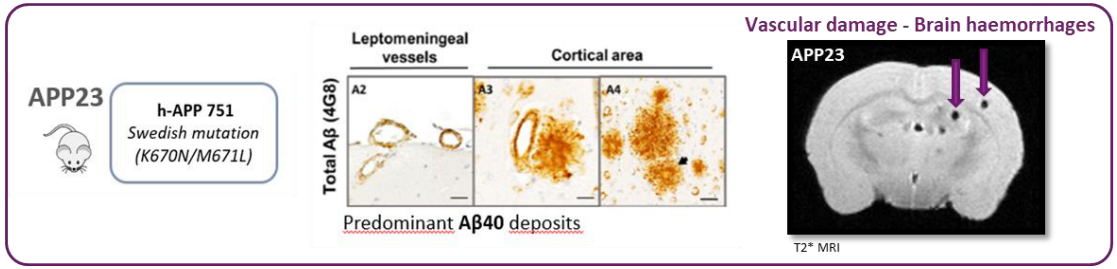


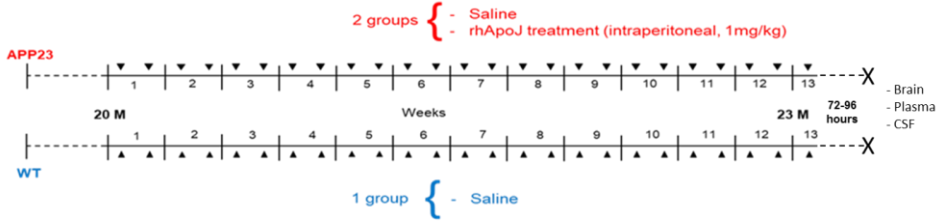


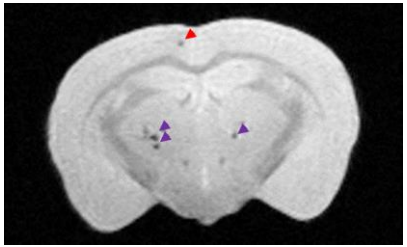
Chronic iv treatment hrApoJ 15 mo APP23:

- ↓ Brain insoluble Aβ40 /Aβ42
- ↓ CAA
- ↑ Aβ40 in CSF
- ↓ Neurodegeneration

Aim: To evaluate the effect of the peripheral increase of human ApoJ/clusterin in terms of cerebral hemorrhagic load in a CAA Tg mouse model



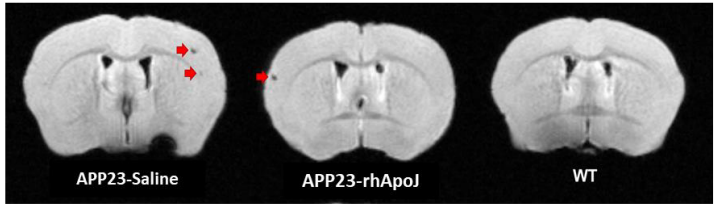


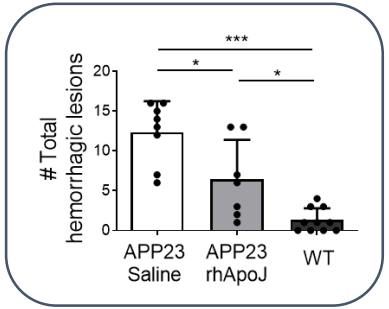


Hypointense signal on T2* were counted as hemorrhages and classified as CMB (50-300 µm diameter) or larger hemorrhages (>300 µm).

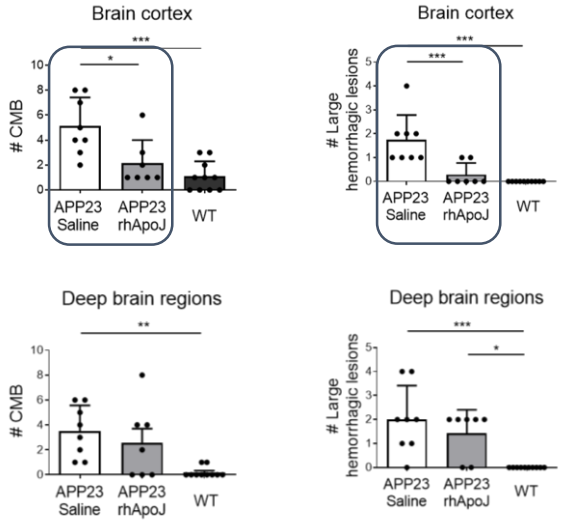
Bonaterra-Pastra et al. Alzheimers Res Ther. 2024

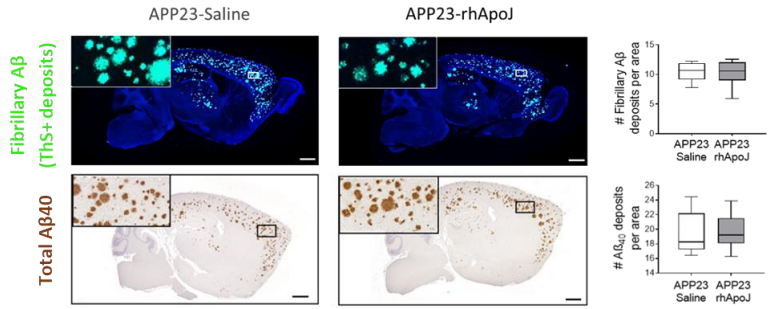
Peripheral increase of human ApoJ/clusterin in an AD/CAA Tg model





rhApoJ-treated mice presented lower number of cortical hemorrhagic lesions than saline-treated APP23 mice.





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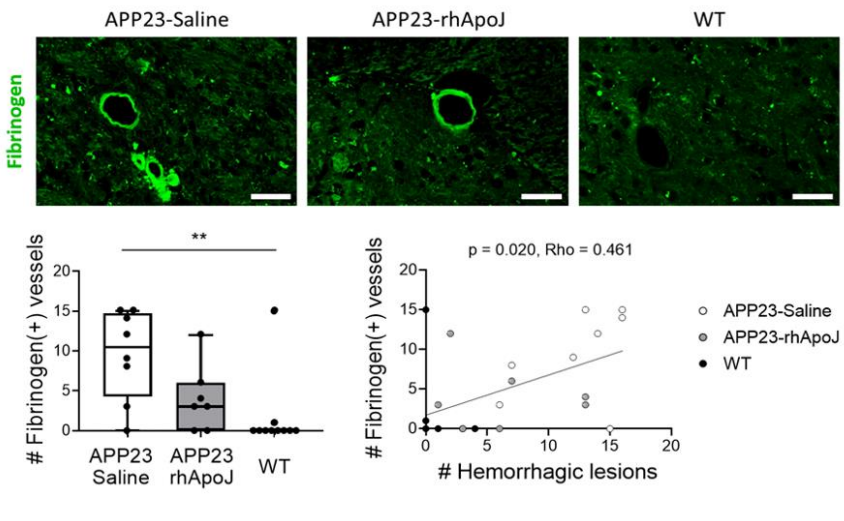
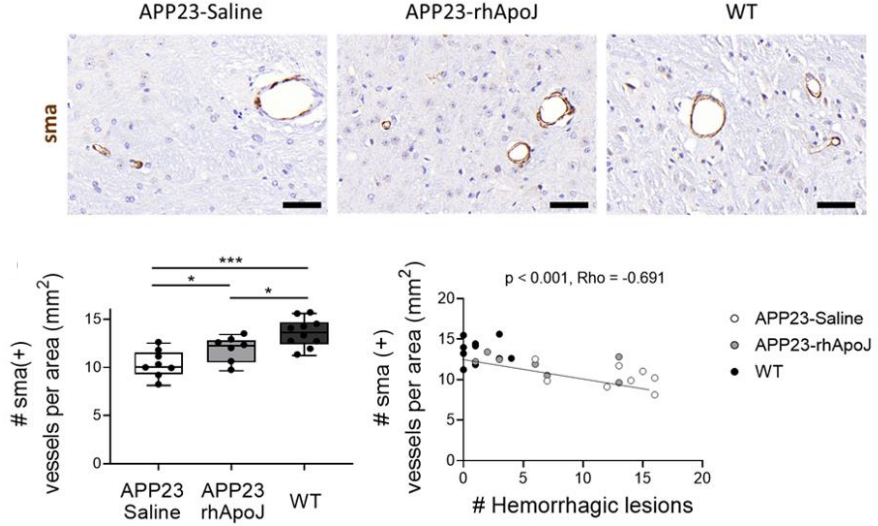
Peripheral increase of human ApoJ/clusterin in an AD/CAA Tg model



APP23 saline-treated mice presented significantly more **fibrinogen-positive vessels** than WT mice



rhApoJ treatment **prevented the loss of sma-positive** brain vessels in APP23 mice

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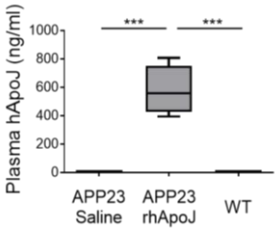
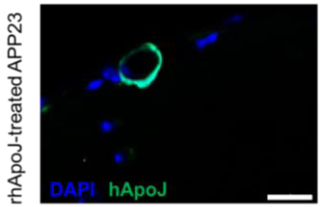
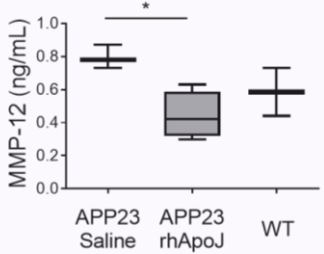
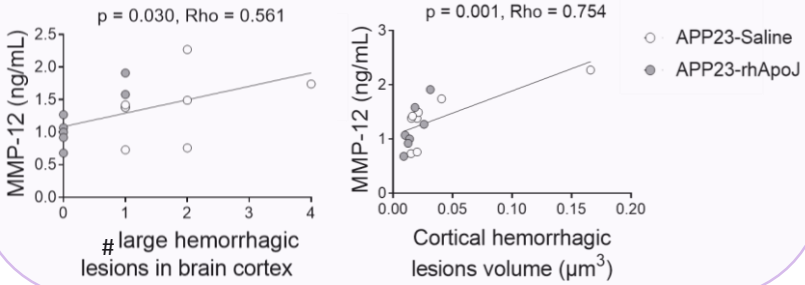




Macrophage elastase (MMP-12)





	Saline – treatment (N = 3)	ApoJ – treatment (N = 4)	WT (N = 3)	p-value
Gro α (pg/mL)	12.14 [11.78 – 16.56]	34.73 * [28.33 – 51.82]	20.21 [18.88 – 21.04]	**0.030**
IL-1 β (pg/mL)	0.11 [0.11 – 12.29]	0.11 [0.11 – 1.20]	5.01 [4.33 – 6.36]	0.145
IL-10 (pg/mL)	1.33 [0.81 – 4.68]	11.02 [4.75 – 27.63]	5.66 [2.97 – 21.37]	0.481
IL-17A (pg/mL)	3.65 [3.30 – 4.89]	4.69 [2.94 – 6.43]	3.34 [3.14 – 10.67]	0.962
MCP-1 (pg/mL)	4.10 [4.10 – 4.10]	5.35 [4.73 – 24.82]	56.63 * [35.42 – 57.72]	**0.035**
MIP-1 α (pg/mL)	0.08 [0.08 – 0.08]	0.38 * [0.30 – 0.86]	0.19 [0.14 – 0.62]	**0.040**
MIP-1 β (pg/mL)	0.60 [0.60 – 0.66]	1.58 [0.95 – 2.14]	1.30 [0.95 – 5.06]	0.719
MIP-2 α (pg/mL)	2.49 ± 1.50	5.07 ± 3.70	4.67 ± 4.65	0.630
MMP-2 (ng/mL)	440.80 [415.85 – 559.60]	434.30 [414.80 – 480.60]	361.60 [359.95 – 375.65]	0.057
MMP-3 (ng/mL)	33.60 [28.45 – 35.25]	43.80 [37.10 – 61.35]	37.10 [31.30 – 192.10]	0.211
MMP-8 (ng/mL)	124.60 [115.85 – 164.90]	144.90 [124.05 – 203.90]	116.70 [111.55 – 220.75]	0.815
proMMP-9 (ng/mL)	12.37 [11.55 – 17.56]	14.21 [11.03 – 26.80]	7.72 [7.62 – 19.43]	0.554
MMP-12 (ng/mL)	0.78 ± 0.07	0.42 ± 0.14 *	0.59 ±0.21	**0.042**

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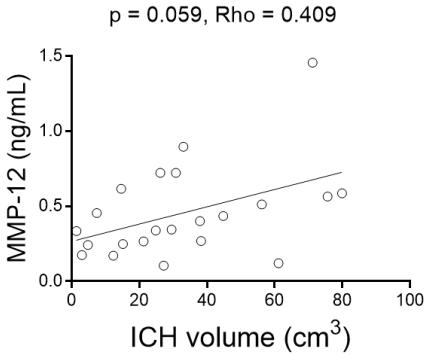
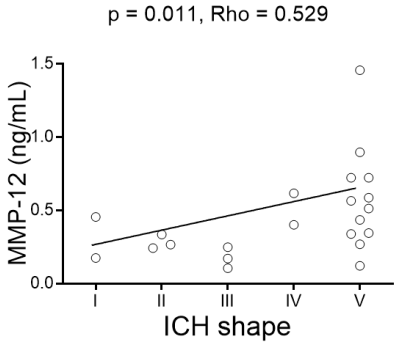
Plasma levels of MMP-12 in humans: Cohort of patients with intracerebral hemorrhage (ICH)

Lobar ICH (N=22)

	Lobar ICH n=22
Sex (female)	13 (59.1%)
Age	82.0 [70.0 — 85.0]
MMP-12 (ng/mL)	0.37 [0.25 — 0.59]
HTA	16 (72.7%)
Atrial fibrillation	2 (9.1%)
Diabetes Mellitus	3 (13.6%)
ICH volume (cm^3)	28.35 [14.65 — 44.78]
Cholesterolemia	7 (31.8%)
ApoE≤2	4 (21.1%)
ApoE≤4	4 (21.1%)
Creatinine (mg/dL)	0.80 [0.72 — 1.07]
Fibrinogen (g/L)	4.13 ± 0.65
Glucose (mg/dL)	113.00 [95.0 — 127.0]
Hemoglobin (g/dL)	13.32 ± 1.94
Anticoagulant treatment	2 (8%)
International Normalized Ratio (INR)	0.99 [0.93 — 1.03]
Platelets (units/nL)	214.73 ± 55.33
Prothrombin time (s)	12.10 [11.20 — 13.30]
Partial thromboplastin time (s)	27.30 [24.50 — 30.70]
White blood cells (units/nL)	8.83 ± 3.25





	B [CI 95%]	p-value
ICH volume	0.006 [0.000 — 0.011]	0.040
Sex	–	–
Age	–	–
Prothrombin time	–	–

	B [CI 95%]	p-value
ICH Shape	0.095 [0.007 — 0.183]	0.036
Sex	–	–
Age	–	–
Prothrombin time	–	–

Plasma MMP-12 levels correlate with ICH volumen and shape in an acute lobar ICH cohort.

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Conclusions

- The presence of circulating **rhApoJ** in APP23 mice **decreased the occurrence of cerebrocortical microbleeds** without reducing insoluble Aβ deposits in the brain.

- Acute rhApoJ treatment significantly **decreased plasma MMP-12 levels**, a protein previously associated with blood-brain barrier disruption and cerebral hemorrhages in rodent models.

- Elevated plasma **MMP-12** levels are associated with increased hemorrhagic volume and irregular shape in a **lobar intracerebral hemorrhage** cohort, indicating the potential relevance of MMP-12 in both ICH and CAA.

- **Treatments aimed at increasing circulating ApoJ levels represent a non-invasive therapeutic approach to avoid hemorrhagic complications associated with CAA.**

Cerebral Amyloidosis Group

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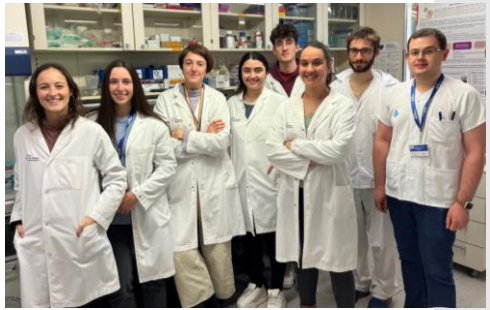
Anas Chaachou



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