

Profiling the neuroinflammatory response in AD — potential for personalized medicine and therapeutic modulation

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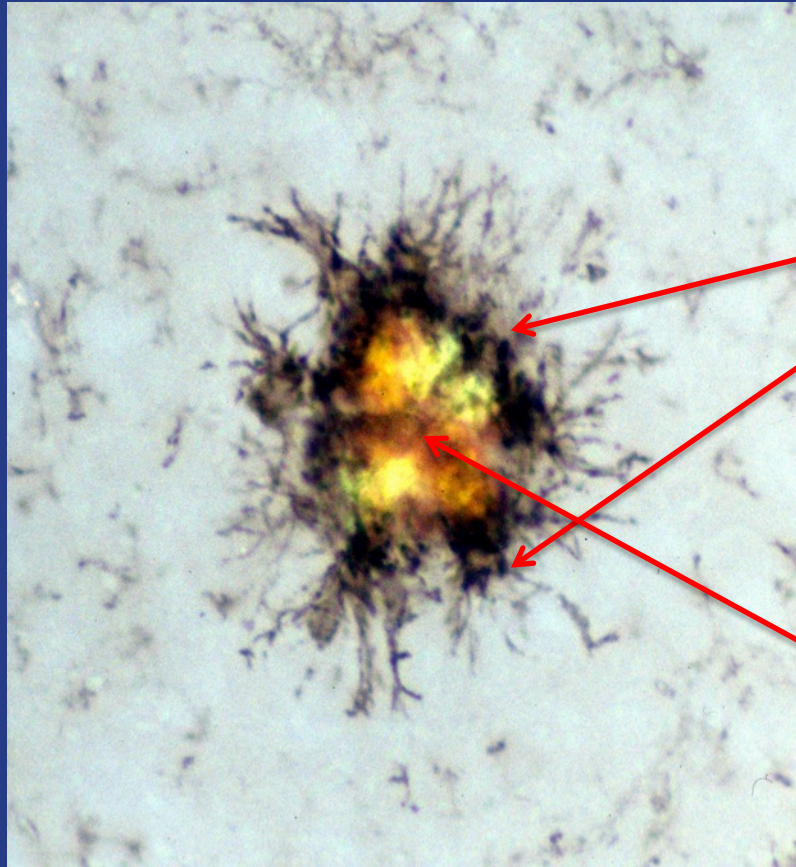
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Microglial cells surround plaques and tangles

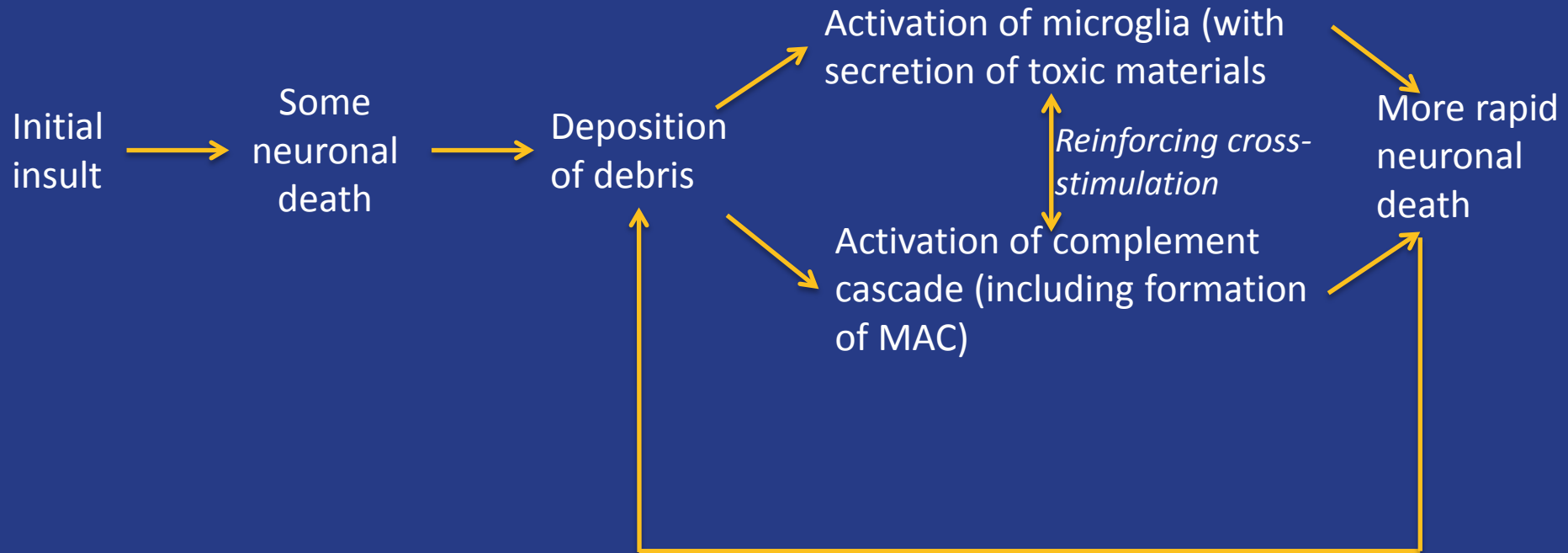


Microglial
cells

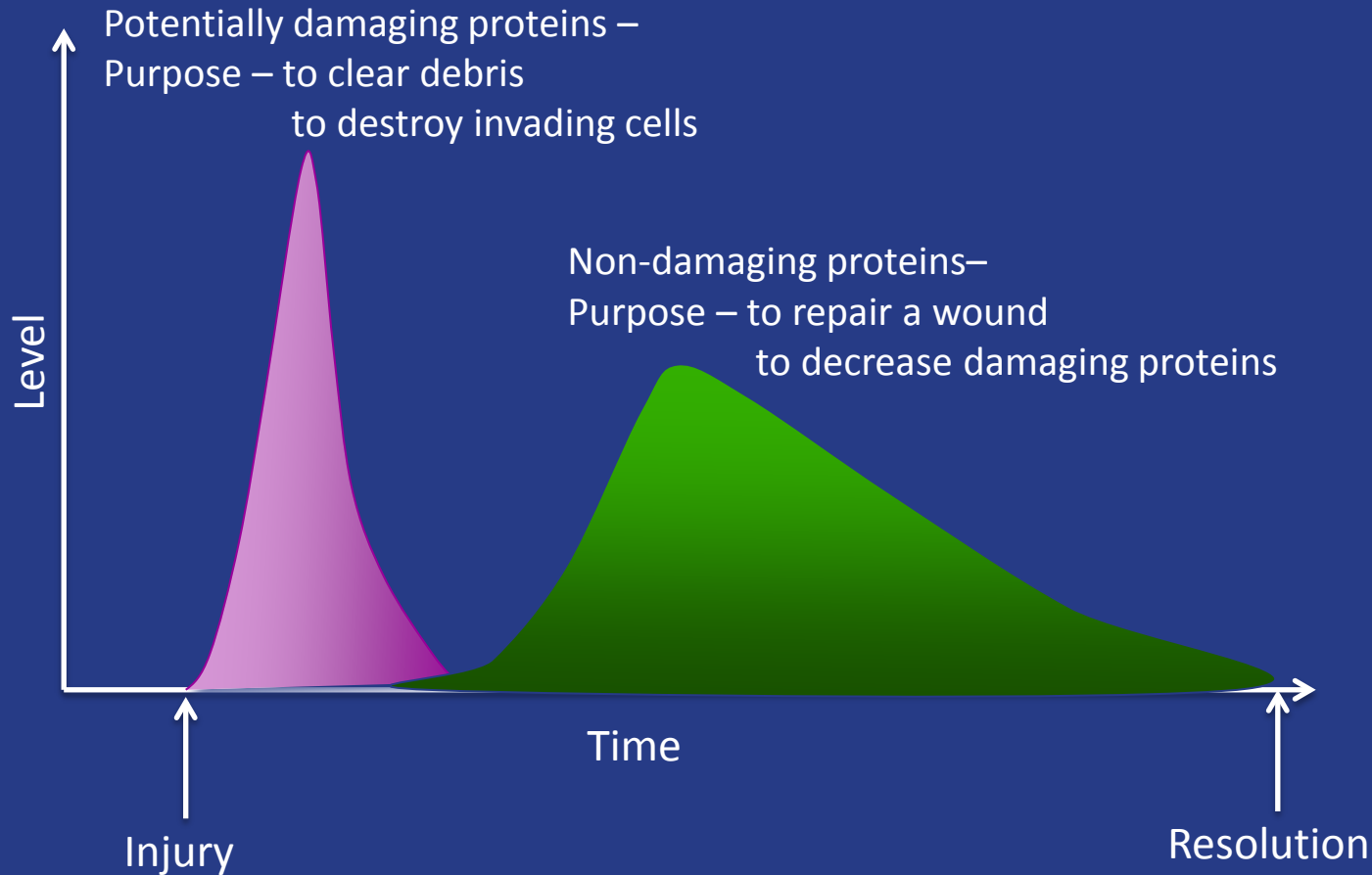
Plaque

The original view of inflammation in AD

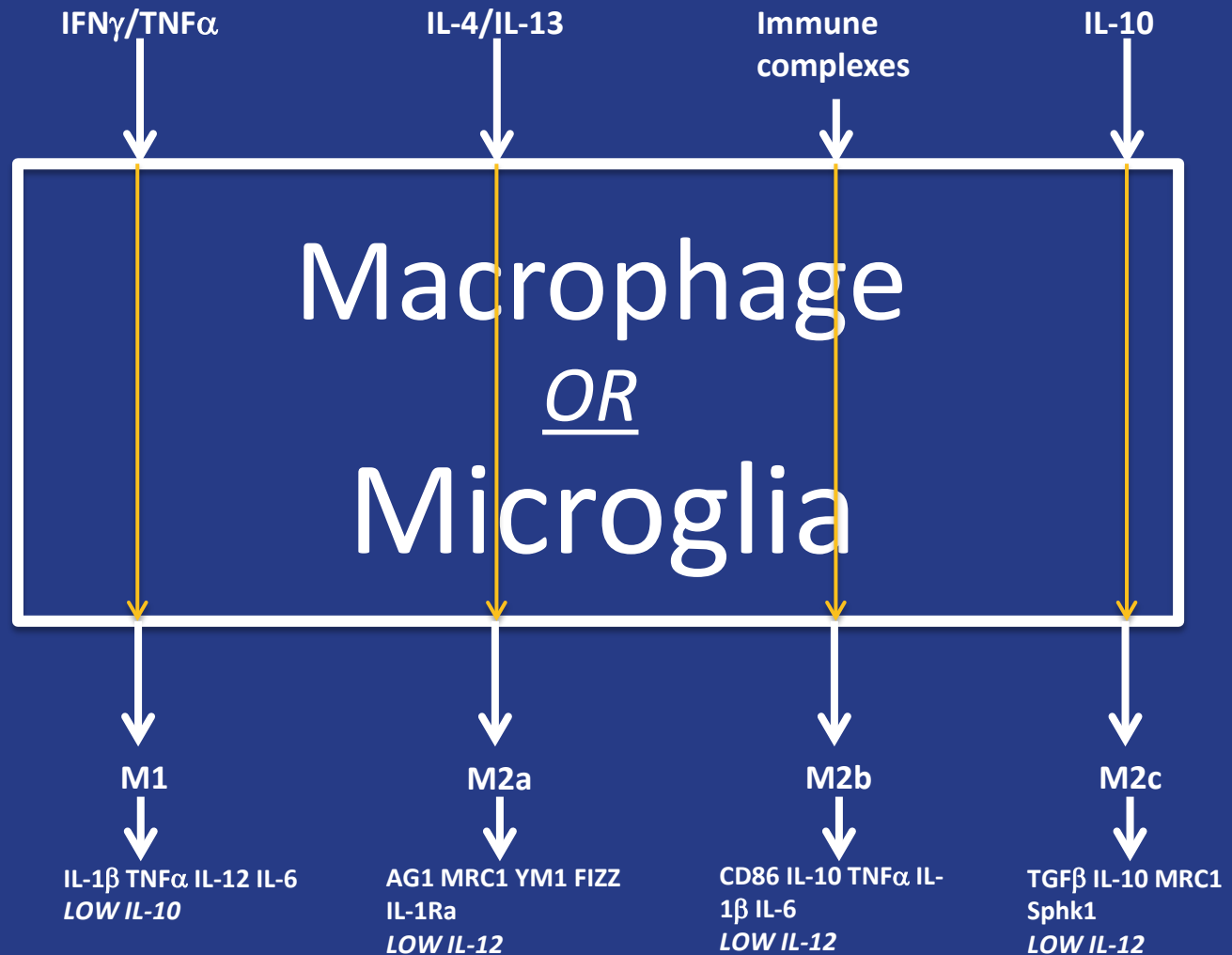
An autotoxic loop



Inflammation has a purpose



We can identify types of neuroinflammation



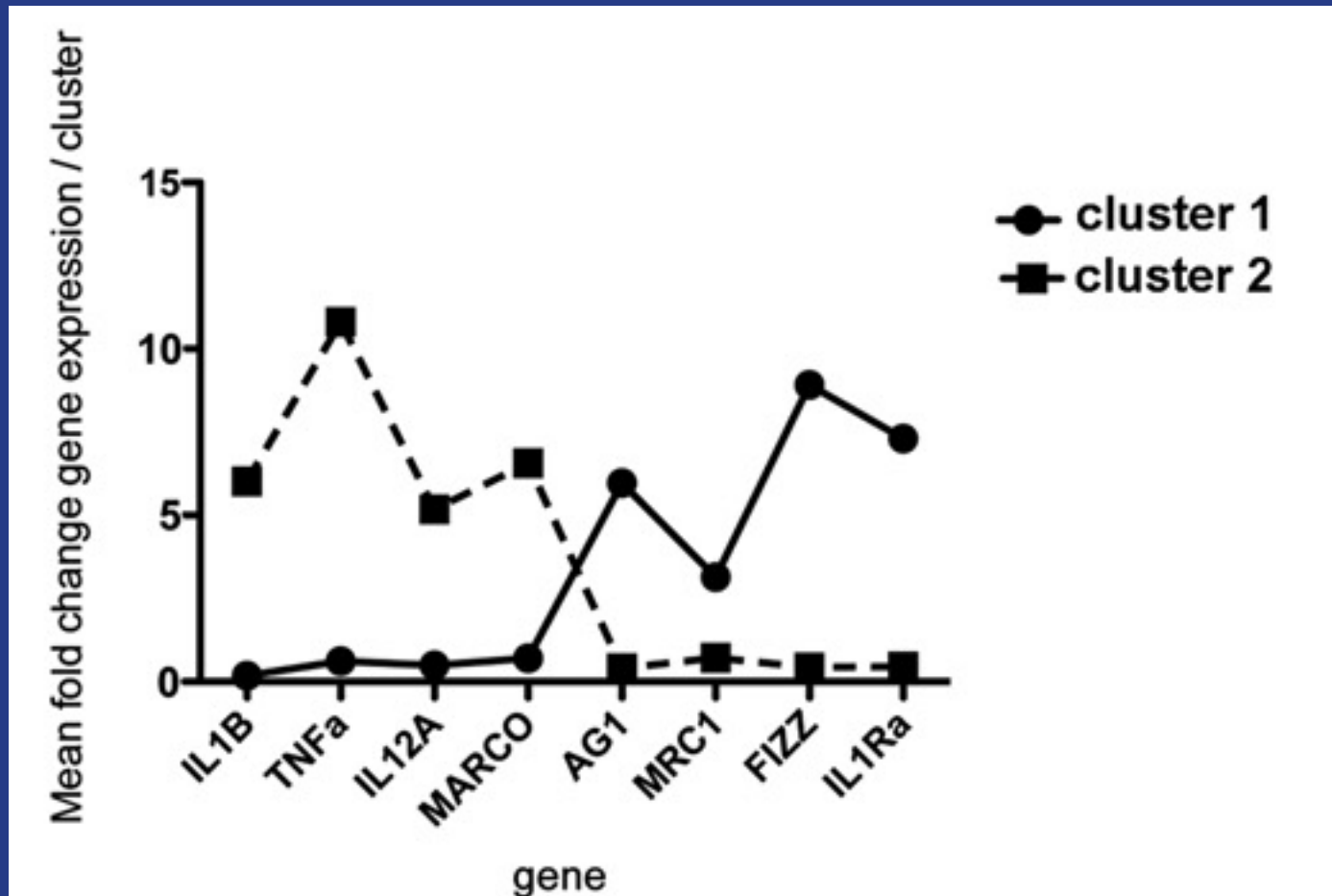
Determining the inflammatory state of the human Alzheimer's disease brain

- Many postmortem tissue have used late-stage AD brain samples.
- **We hypothesized that there may be differences in the neuroinflammatory state as AD progresses.**
- We obtained tissue samples from early AD, late AD and age-matched, non-demented controls.
- Gene expression levels of neuroinflammatory markers measured by qRT-PCR from frozen brain tissue frontal cortex and cerebellum.
- Serum analyzed for predictive markers of the brain neuroinflammatory state.
- Clinical histories of patients examined to determine common non-AD factors that account for differences in the neuroinflammatory states.

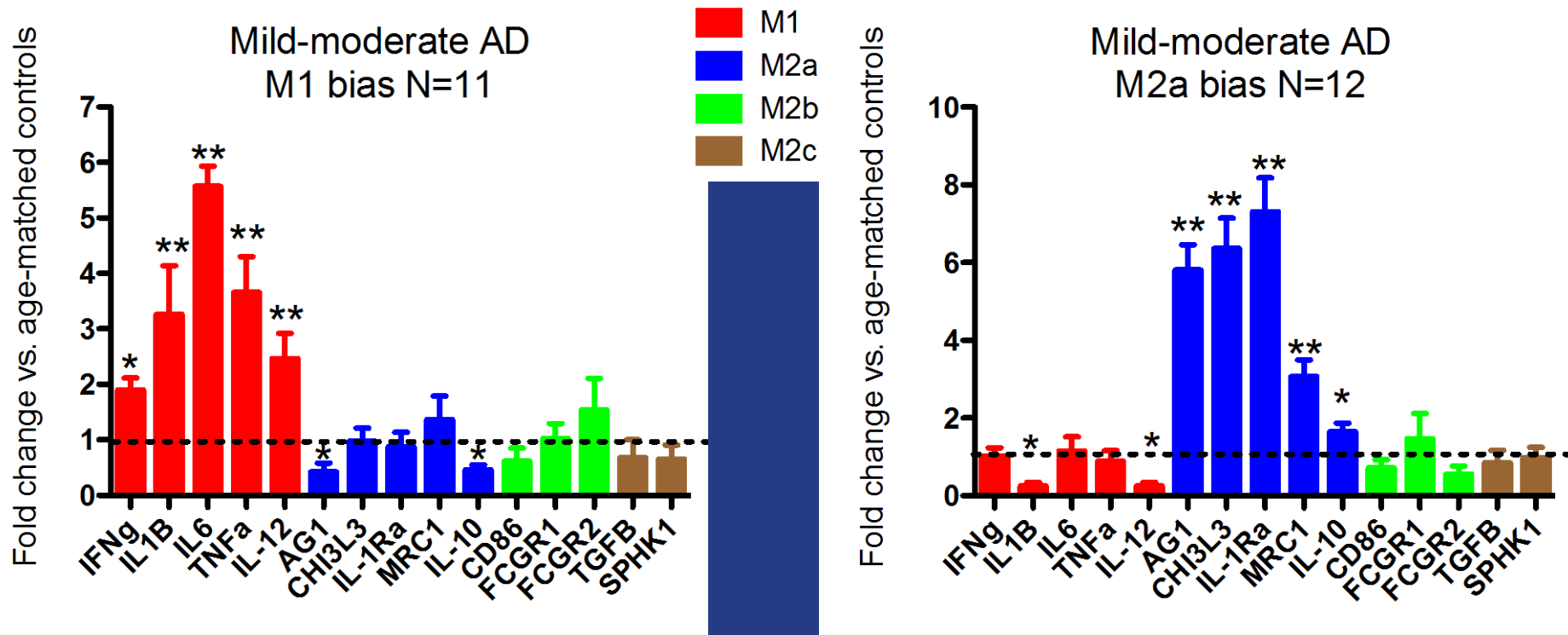
Human AD tissue characteristics

Group	Age range (yr)	MMSE	ApoE4 status	Braak stage	PMI (hr)
Early AD N=23	77-100 (mean = 87.2)	20-24 (mean = 22.6)	-/4 = 12 4/4 = 3	3-5	1.0-6.5 (mean = 3.6)
Late AD N= 16	74-88 (mean 85.6)	0-13 (mean 7.25)	-/4 = 6 4/4 = 4	6	1.75-11.0 (mean =5.4)
Control N=37	77-96 (mean = 84.3)	28-30 (mean = 29.1)	-/4 = 10 4/4 = 3	0-2	1.75-8.0 (mean = 4.2)

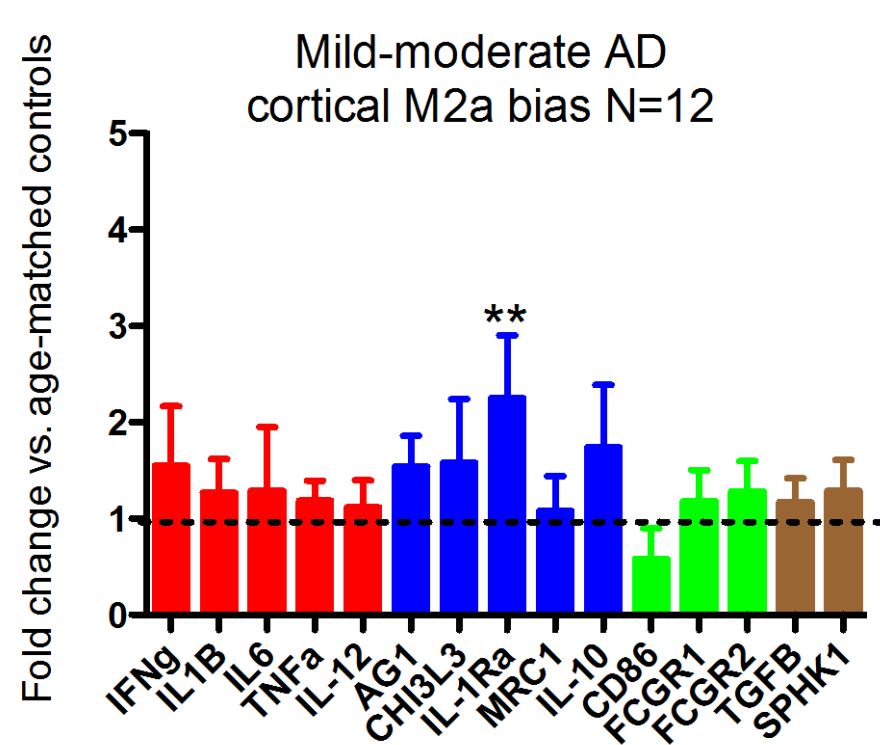
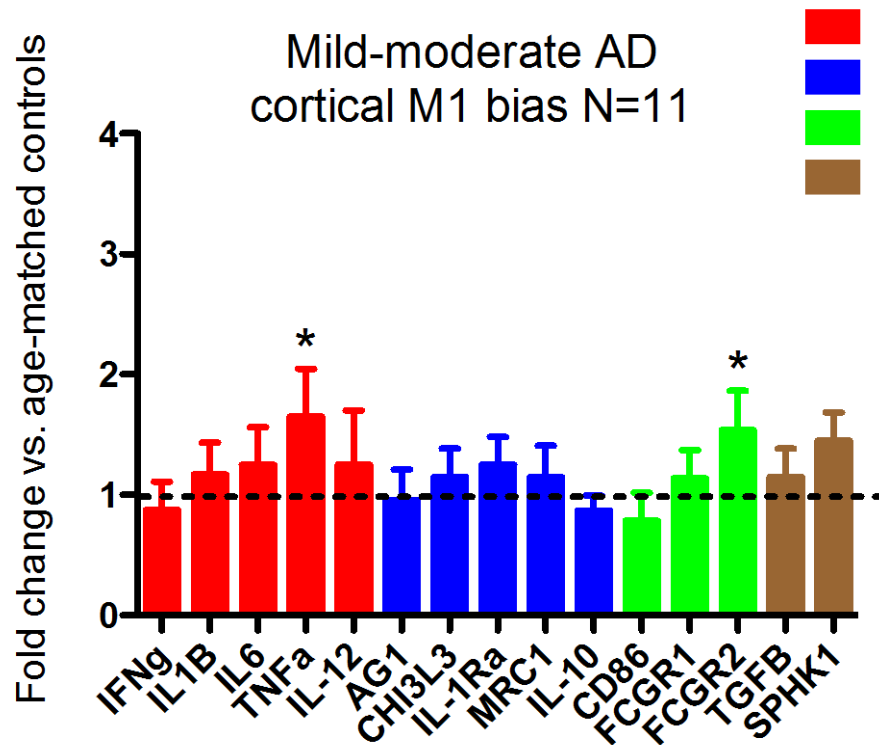
Cluster analysis revealed two distinct populations in the early AD group



Early AD brain is biased to either the M1 or M2a phenotype in the frontal cortex

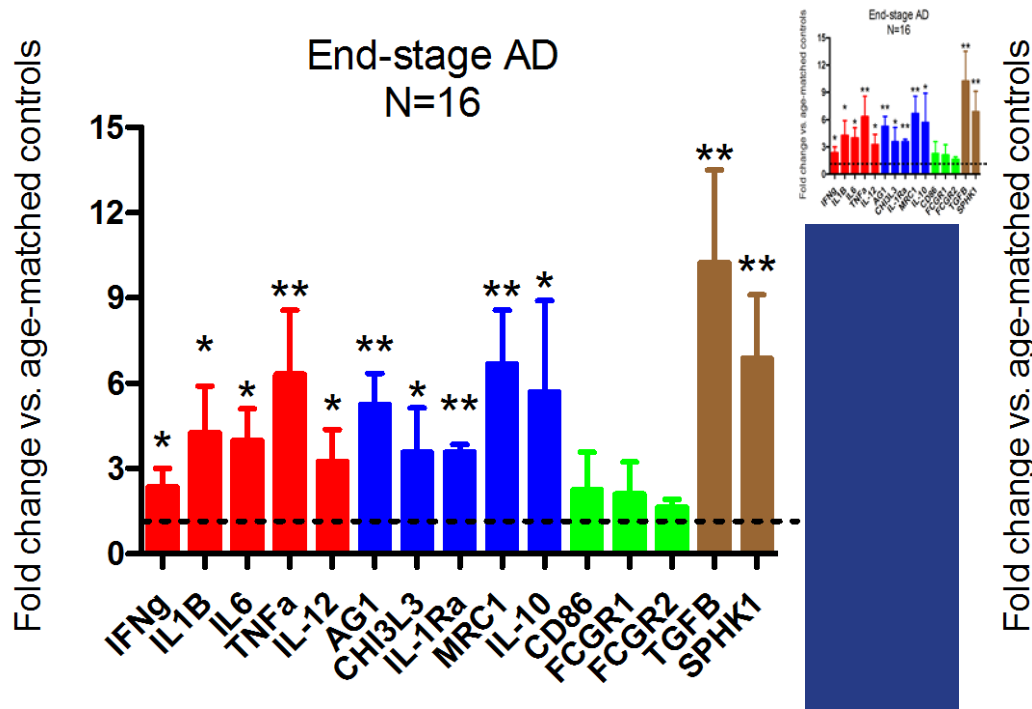


In the cerebellum the inflammatory polarization does not exist

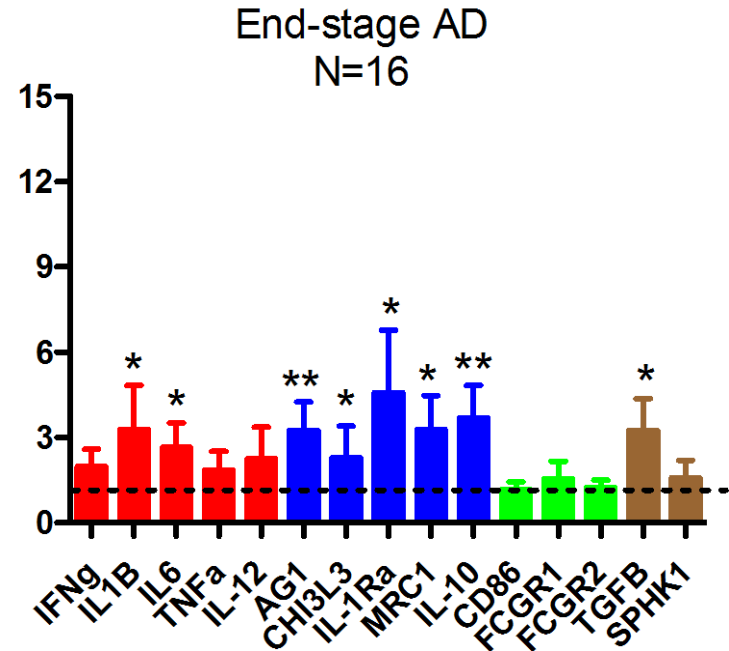


End-stage AD brain does not show the same heterogeneity observed in early stage

Frontal Cortex



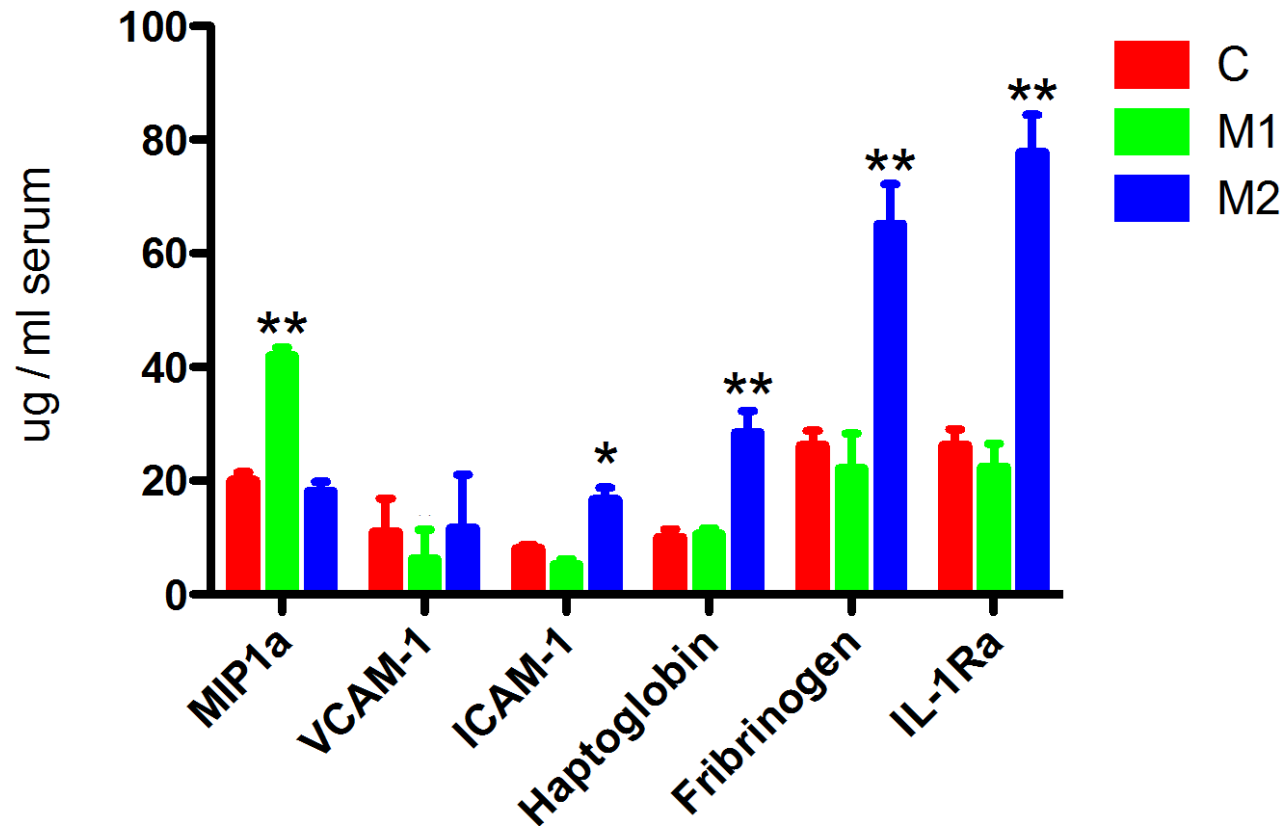
Cerebellum



Next step....

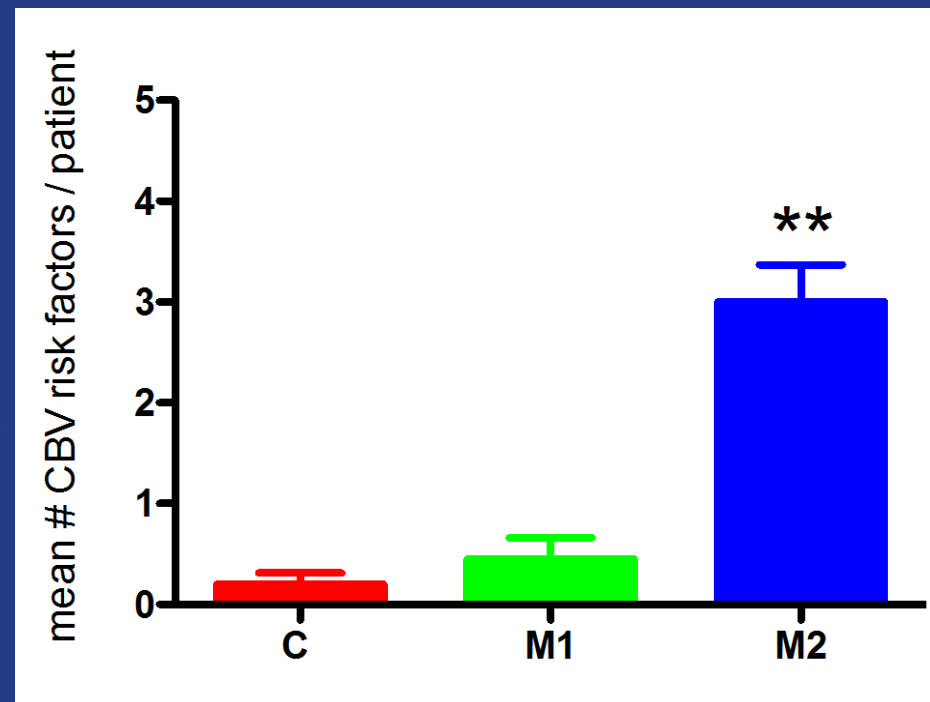
- *Hypothesis: The polarization of the neuroinflammatory state of the early AD brain to either M1 or M2 will significantly influence response to therapy.*
- Serum from our samples were run on the Myriad-RBM human inflammation MAP.
- Our goal was to identify serum biomarkers predictive of the brain neuroinflammatory state.

Serum markers are predictive of brain neuroinflammatory state



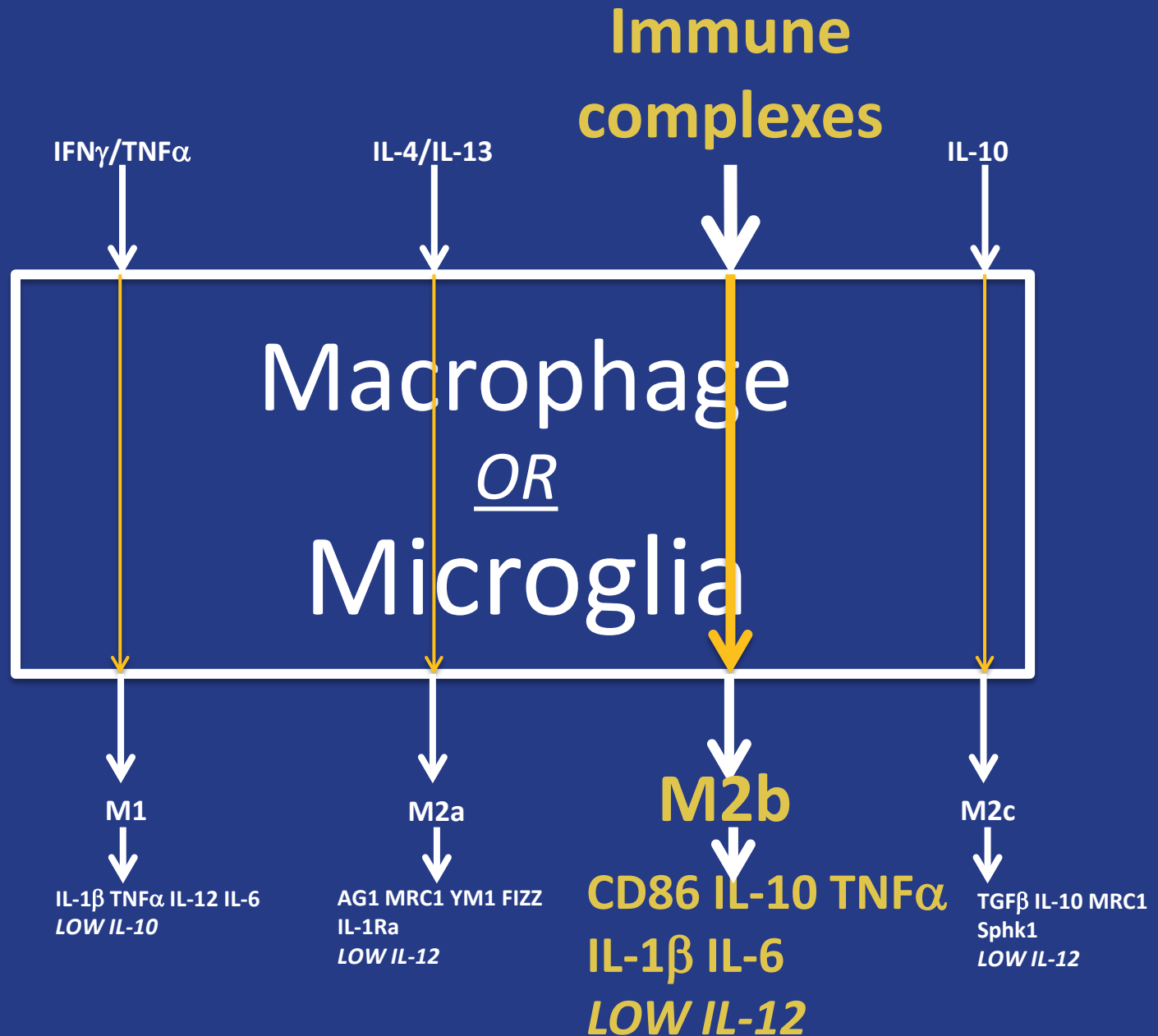
Cerebrovascular disease risk factors are present with an M2 polarization

- We retrieved the following history:
 - Congestive heart failure
 - Angina
 - Hypertension
 - Peripheral vascular disease
 - Atrial fibrillation
 - Coronary artery bypass graft
 - Angioplasty
- We added up the number of risk factors present and analyzed this based on the brain neuroinflammatory profile.
- We found that the M2 phenotype is associated with the increased presence of cerebrovascular disease risk factors.



Can we modulate the inflammatory response and influence AD pathology?

Modulation to M2b



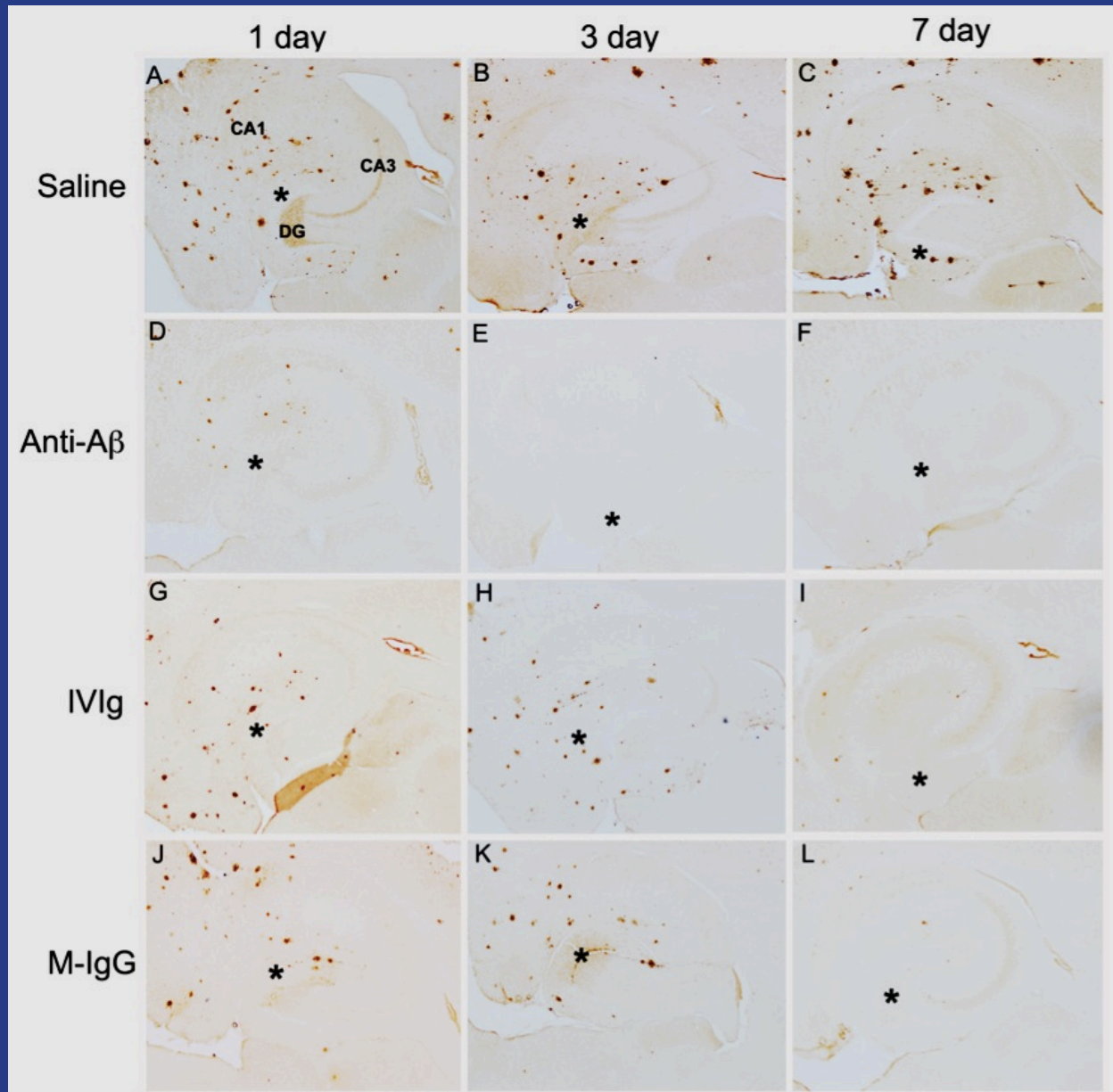
Study design

- 120 seven month old APP/PS1 mice were assigned to one of 4 treatment groups.
 - Saline.
 - Anti-A β antibody (6E10, A β_{3-8} , IgG1)
 - IVIg (composed primarily of IgG1 and IgG2)
 - Mouse IgG (composed primarily of IgG1 and IgG2a).
- Intracranial injections were performed bilaterally in the frontal cortex and hippocampus.
- The right side was dissected for biochemistry and the left was fixed and processed for histology.

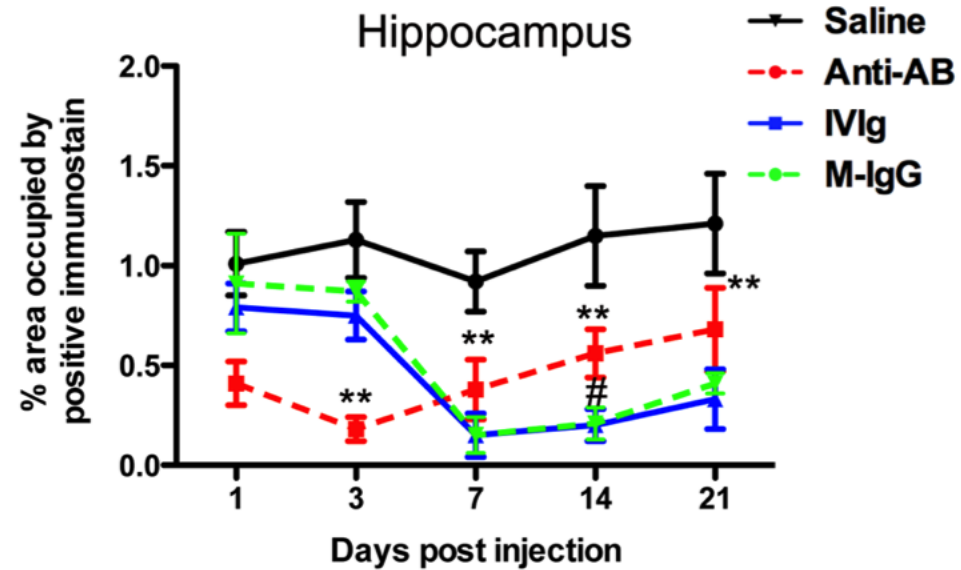
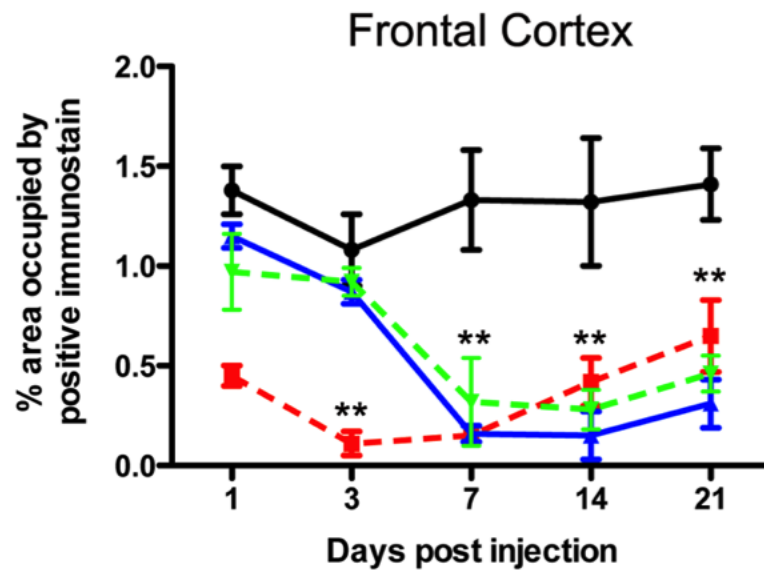
Intracranial
injection



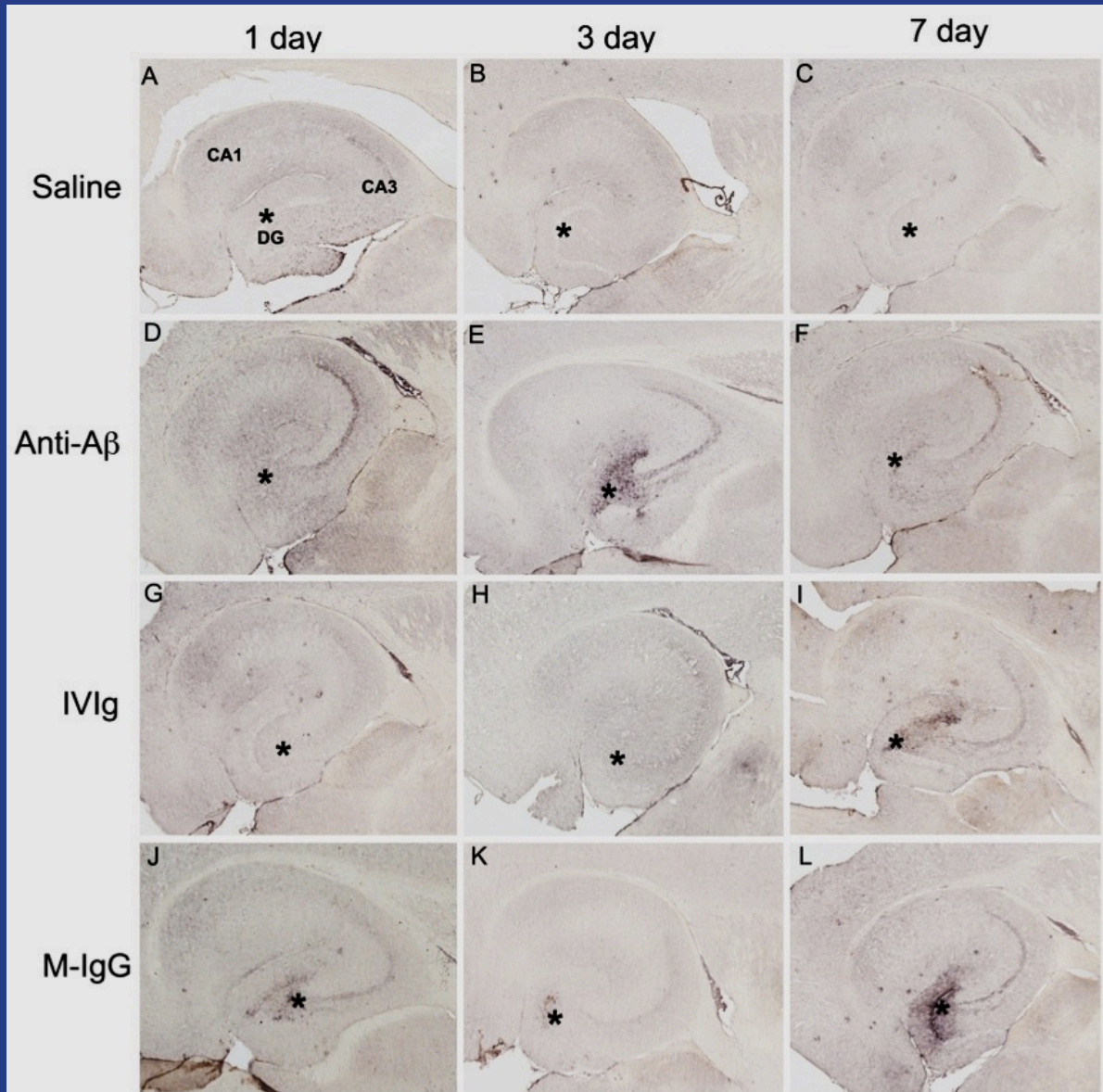
A β is reduced by all treatments but anti-A β antibody shows a more rapid reduction



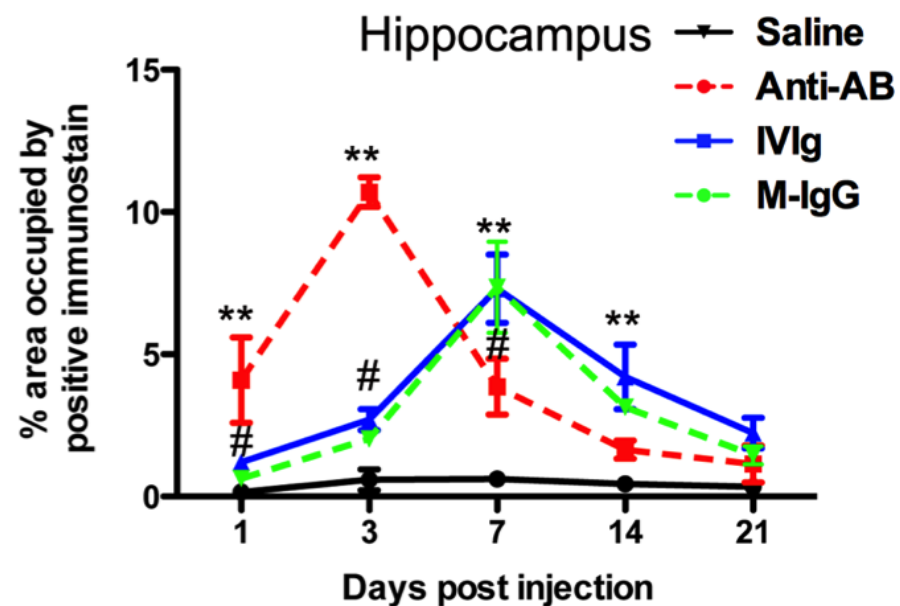
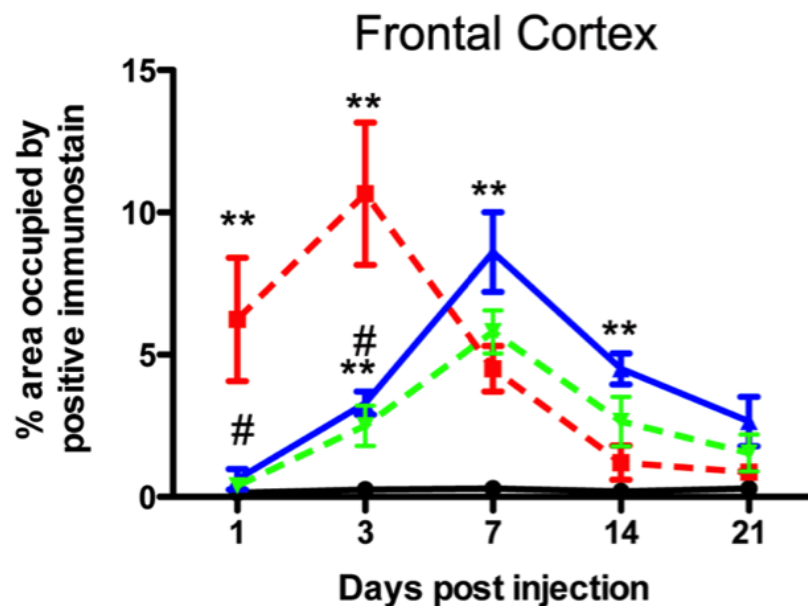
A β is reduced by all treatments but anti-A β antibody shows a more rapid reduction



Microglial activation is induced by all three antibody injections

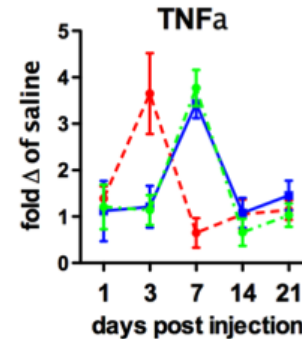
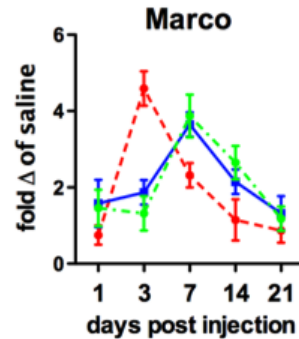
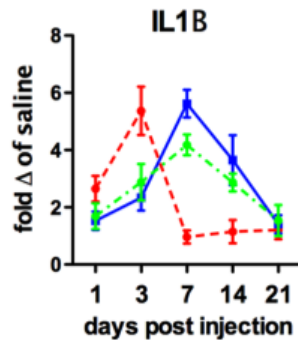


Microglial activation peaks later with IVIg than anti-A β antibody

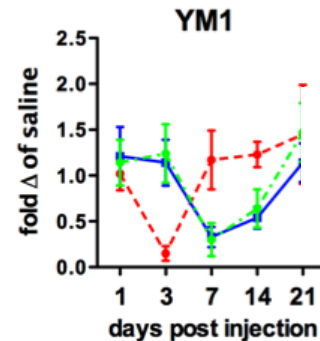
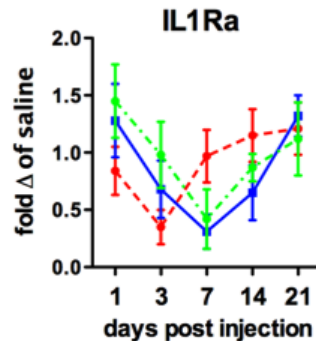
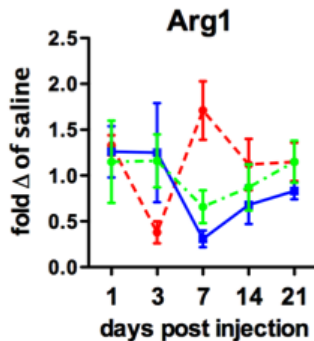


Neuroinflammatory phenotypes are modulated by antibody presence in the brain

A: M1

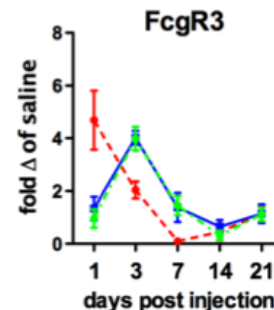
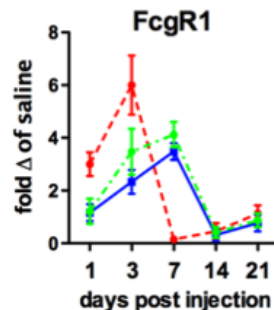
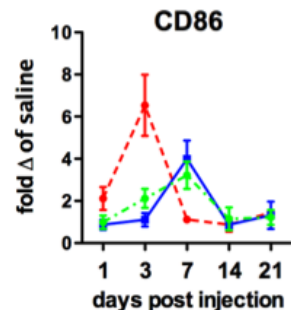


B: M2a



ANTI-AB
IVIg
M-IgG

C: M2b



Summary and conclusions

- Neuroinflammatory profiles can be used to phenotype the inflammatory response in the brain.
- Early AD brain exhibits diverse neuroinflammatory phenotypes that will likely directly influence response to therapeutic interventions.
- M2 inflammatory phenotypes in the brain are associated with elevated cerebrovascular disease risk factors.
- IVIg, when administered intracranially, promotes an M2b phenotype that appears to precede the amyloid reductions.
- We hypothesize that “modulation” of the neuroinflammatory phenotype is a potential therapeutic approach for the treatment of Alzheimer’s disease.

Our working hypotheses

- Neuroinflammatory phenotypes can directly influence Alzheimer's disease pathology onset and progression.
- The co-morbidity of vascular dementia with Alzheimer's disease will require different therapeutic approaches than pure AD alone.

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