Resilience-Associated CD33 Antibody ATLX-1088, A Potent Stimulator of Microglial Phagocytosis

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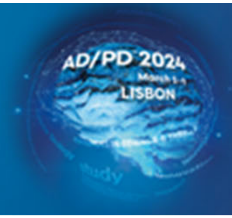
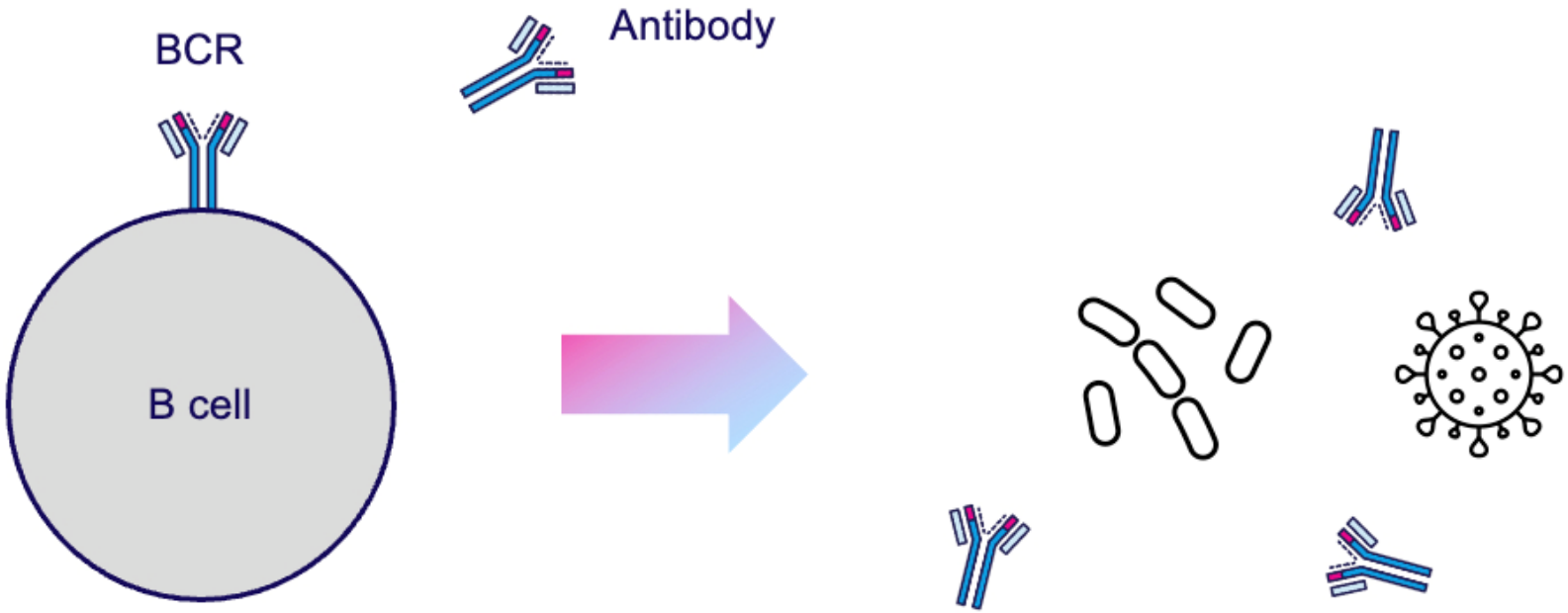


	No, Nothing to disclose
✓	Yes, please specify

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
Alchemab					✓		✓	

Could antibodies be the key to disease resilience?



An individual can produce > ***1e12*** antibody variants to enable protection against foreign pathogens

In some instances, autoantibodies are also produced

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These can be pathogenic

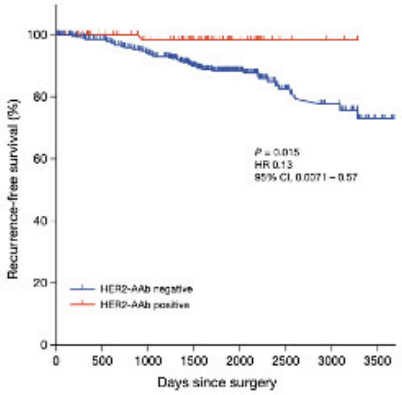
- SLE (Polyclonal autoreactive B cells)
- Myasthenia Gravis (anti-AchR)
- Neurological disease (anti-NMDA)
- Pemphigus (anti-desmosomal proteins)

But *also* protective

Breast Cancer Res Treat (2016) 157:55–63
DOI 10.1007/s10549-016-3801-4

Protective effect of naturally occurring anti-HER2 autoantibodies on breast cancer

Yukiko Tabuchi[1] · Masafumi Shimoda[1] · Naofumi Kagara[1] · Yasuto Naoi[1] · Tomonori Taneі[1] · Atsushi Shimomura[1] · Kenzo Shimazu[1] · Seung Jin Kim[1] · Shinzaburo Noguchi[1]



Drug discovery based on disease resilience

WE IDENTIFY

We identify especially resilient individuals –
and learn how they overcome or resist disease

WE SEQUENCE

We sequence B cells from the resilient individuals and identify antibodies with similar properties

WE DISCOVER

We discover the binding targets of the antibodies, understand their protective properties and subsequently develop therapeutic candidates that replicate the protective effect

IMMUNOLOGY

Decoding the autoantibody reactome

Autoantibodies influence a wide range of conditions beyond autoimmune diseases

By Jillian R. Jaycox[1,2], Yile Dai[1], Aaron M. Ring[2]

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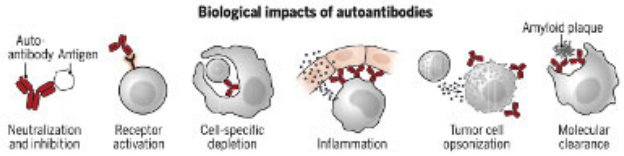

Our anti-CD33 antibody was discovered in individuals with Alzheimer's Disease risk factors

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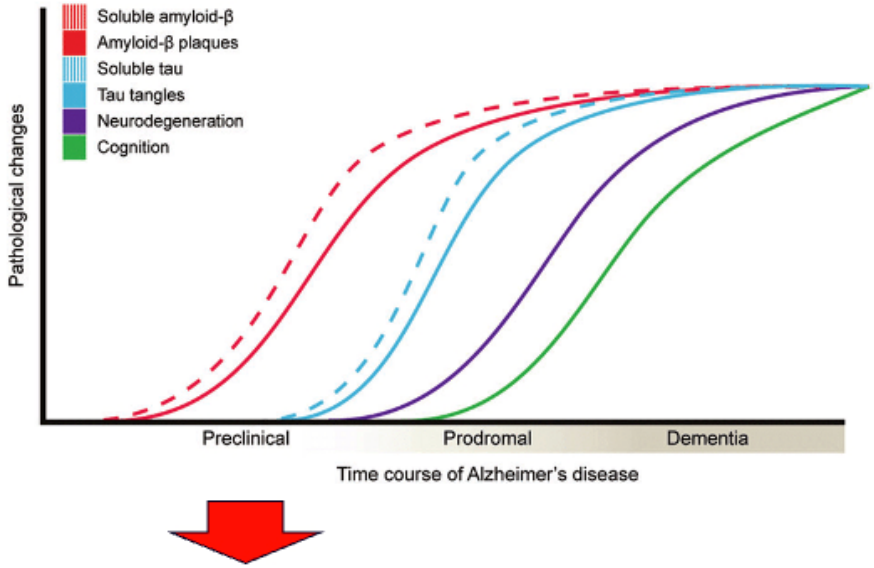
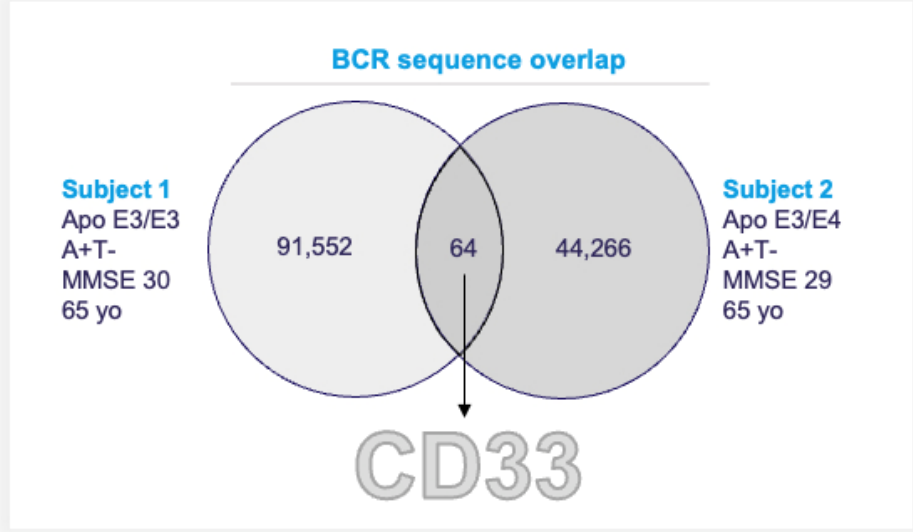
CD33 antibodies were found to be convergent in resilient individuals [$A\beta^{+}$,$pTau^{-}$,$MMSE^{High}$]



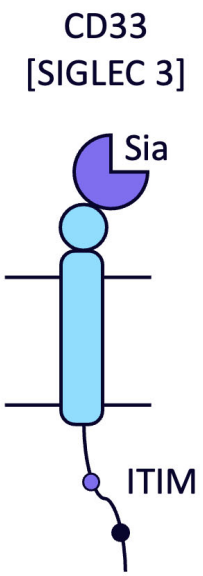


EPAD consortium: preclinical stage, normal pTau
100-plus cohort: advanced age, no MMSE decline

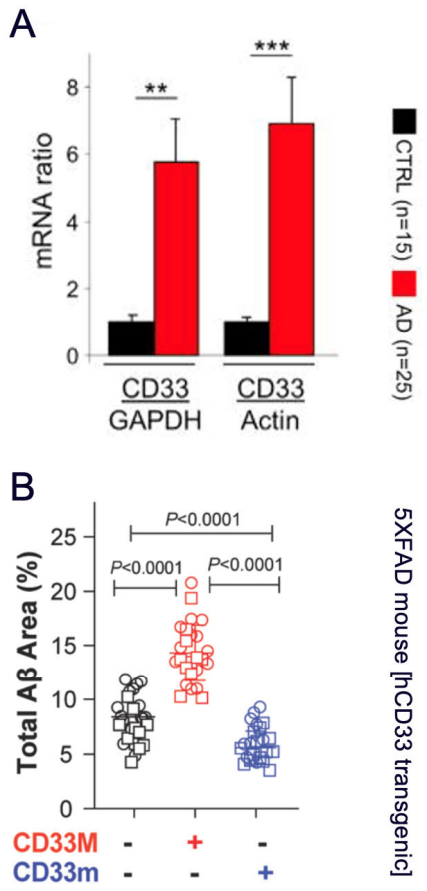
Lead antibody ATLX-1088 discovered in the 100-plus cohort

EPAD: European Prevention of Alzheimer's Dementia

CD33 is an inhibitory receptor which impairs microglial function in AD



- CD33 is an inhibitory receptor on myeloid cells
- CD33 is genetically linked to AD risk
  - rs38658444 [loss of Sia binding domain] : lower AD risk
  - rs2455069 [increased Sia binding] : higher AD risk
- CD33 is overexpressed on microglia in AD brains (A)
- Higher CD33 expression is linked to more advanced cognitive decline
- CD33 signalling *inhibits* microglial function (B)



Sia: Sialoglycan
ITIM: Immunoreceptor tyrosine-based inhibitory motif

Griciuc et al 2013 Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. Neuron. 78(4):631-43
Karch et al 2012 Expression of novel Alz-heimer's disease risk genes in control and Alz-heimer's disease brains. PLoS One 7:e50976.
Eskandari-Sedighi et al 2023 Alzheimer's disease associated isoforms of human CD33 distinctively modulate microglial cell responses in 5xFAD mice. bioRxiv https://doi.org/10.1101/2023.07.04.547548

CD33 inhibitor ATLX-1088 causes a significant increase in phagocytosis in human iPSC microglia

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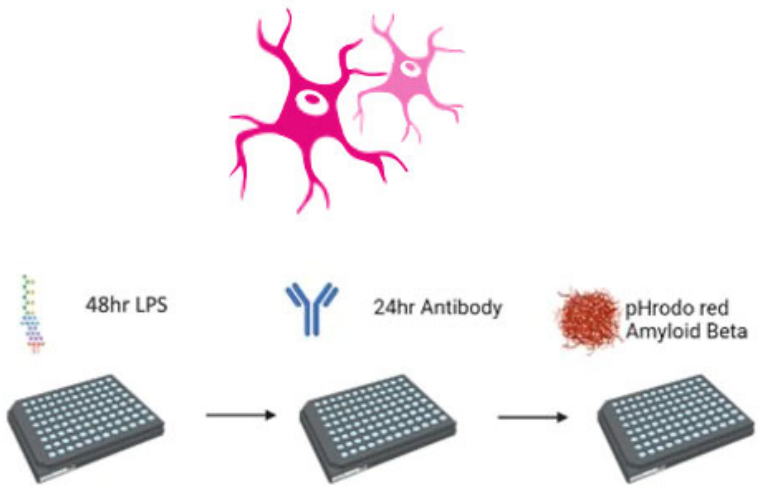
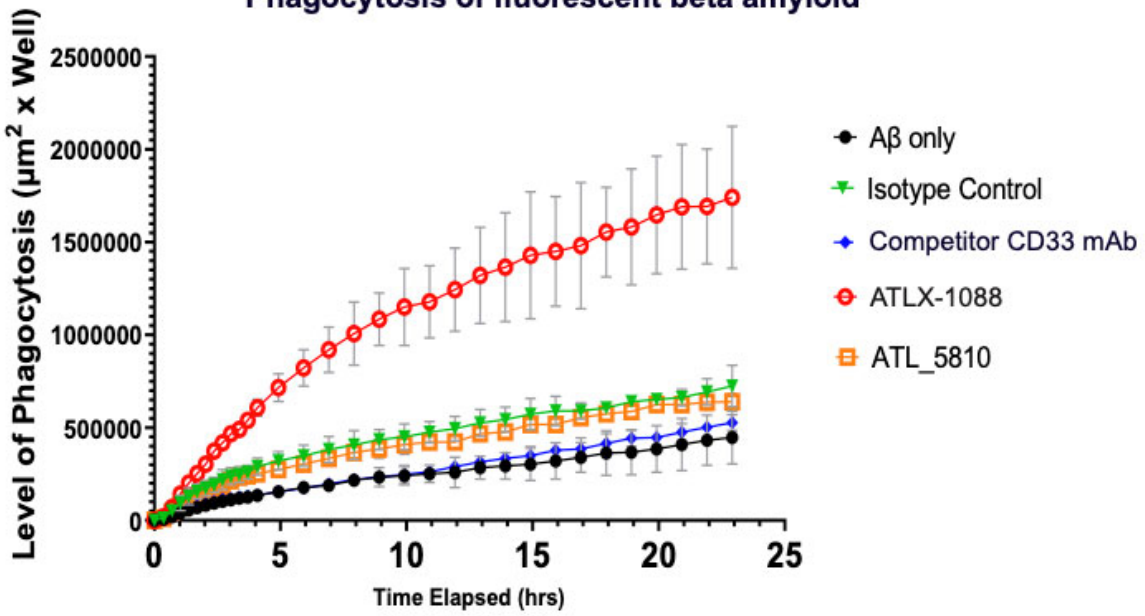
Human iPSC microglia phagocytosis assay



Phagocytosis of fluorescent beta amyloid



Phagocytosis of toxic proteins by microglia is an important function suppressed by CD33 signalling

ATLX-1088 increases phagocytosis of beta amyloid; other CD33 mAbs do not

ATLX-1088 binds at the Sialoglycan epitope and is likely to compete for the ligand binding site

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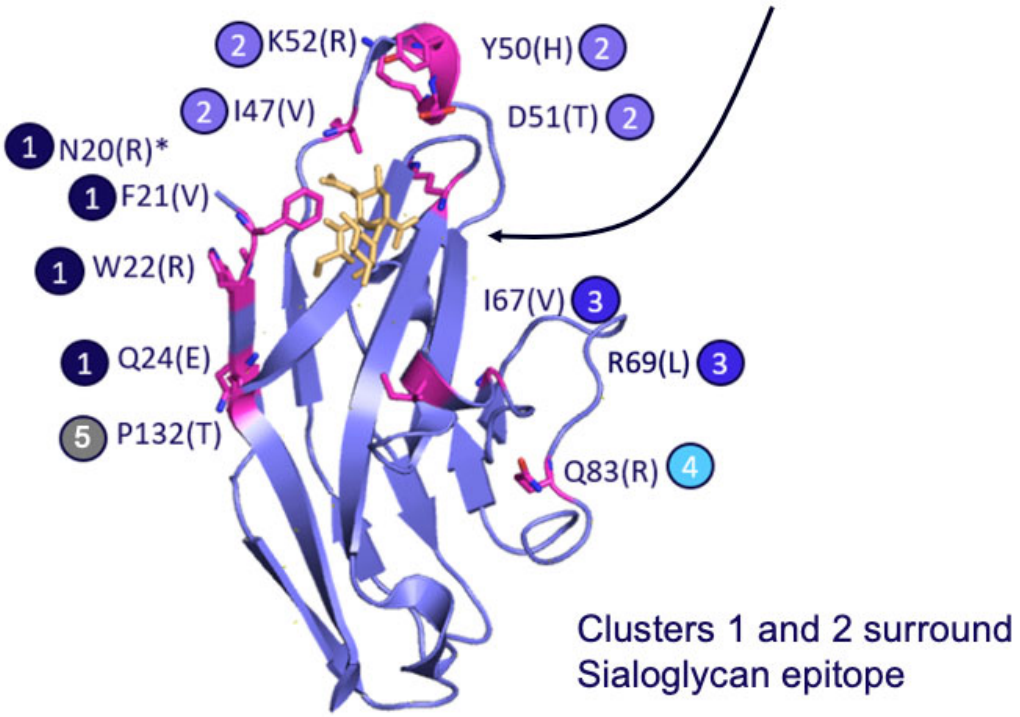
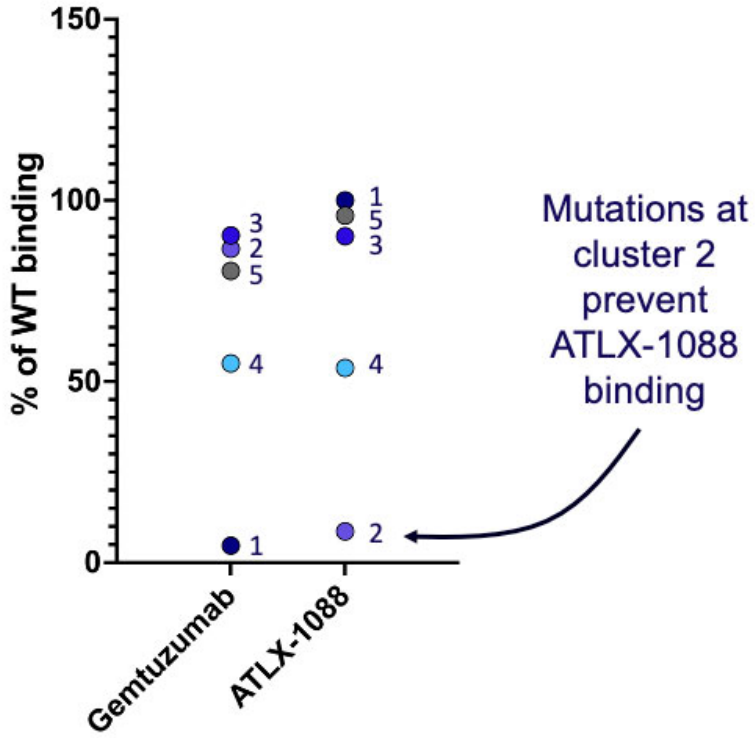
CD33 structure with Sialoglycan ligand (orange)



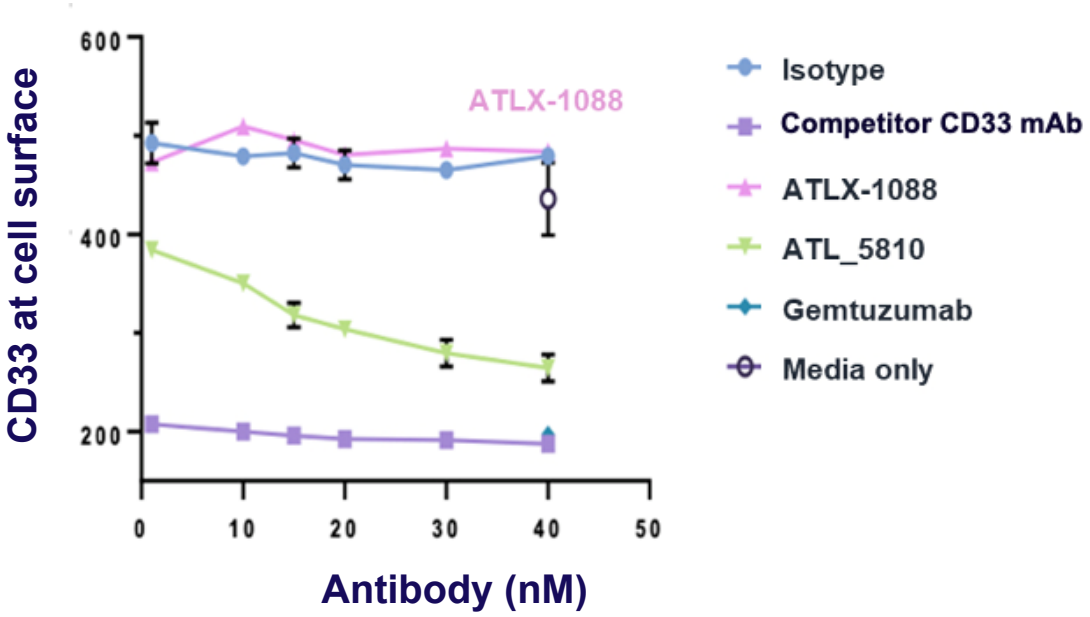
Clusters 1 and 2 surround Sialoglycan epitope

mAbs binding to CD33 mutants

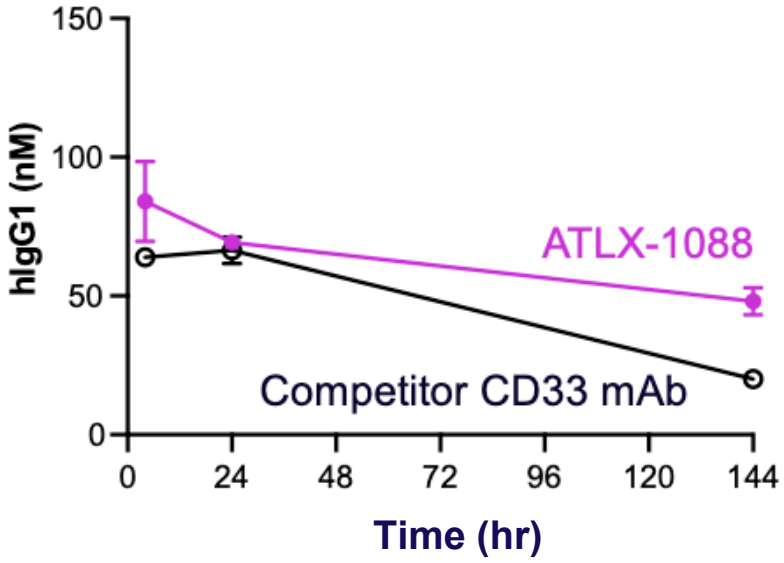


ATLX-1088 is non-internalizing, with improved pharmacokinetics

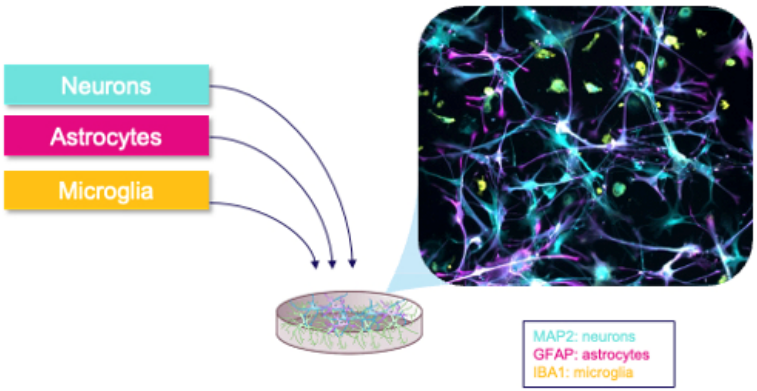
CD33 depletion on human monocytes (5 hrs)



PK in HuCD33 transgenic mice

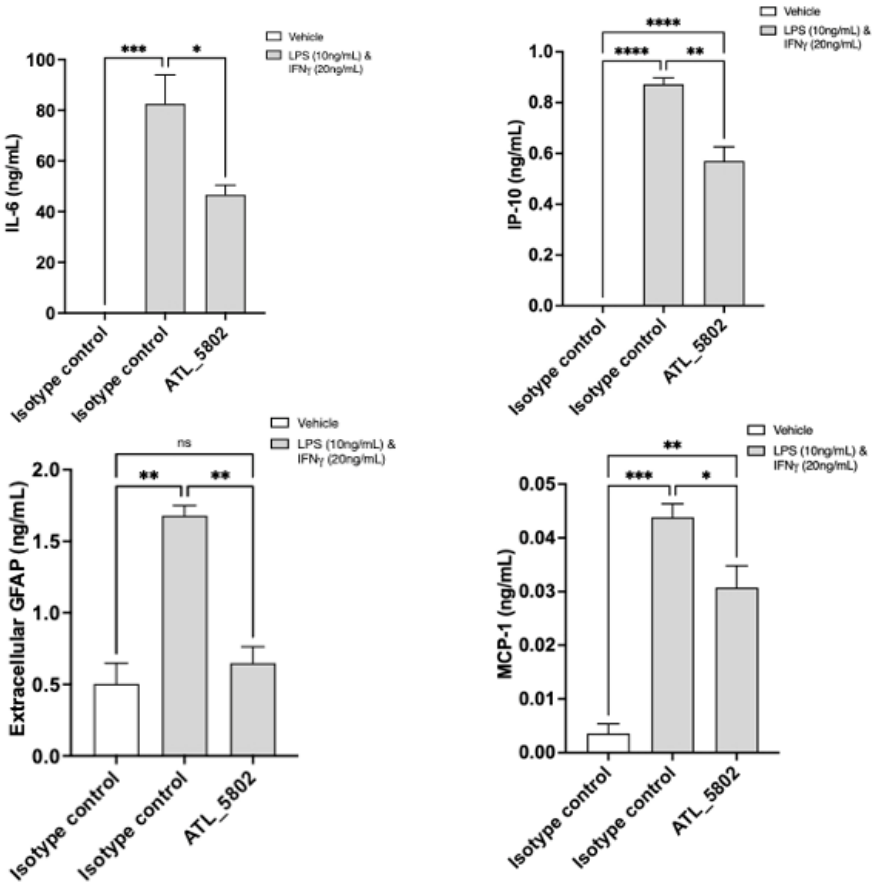


Effects of ATLX-1088 in an iPSC Tri-culture model: Reversal of astrogliosis and inflammation



LPS and IFN-γ increase IL-6, IP-10, extracellular GFAP and MCP-1 in the tri-culture model

ATLX-1088 partially reverses these increases, suggesting a general anti-inflammatory effect



Conclusion: CD33 antagonist ATLX-1088 is an attractive approach for microglial modulation

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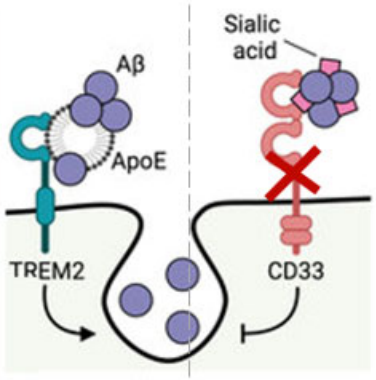
	TREM2 agonists	CD33 antagonist ATLX-1088
genetics	Odds ratio 2.7 for AD risk variant	Odds ratio 0.89 for AD protective variant
microglia	Agonism linked to phagocytosis, proliferation and inflammation	Antagonism linked to phagocytosis and anti-inflammatory effects
format	Unconventional Ab formats with Fc mutations to increase agonism	Conventional Ab format with no Fc effector function
potency	VGL101 drives phagocytosis of Aβ DNL919, AL002 show no activity	ATLX-1088 drives potent phagocytosis of Aβ and anti-inflammatory effects
efficacy	Biomarker changes in Phase I No clinical efficacy data	Evidence for target engagement in vivo, including microglial changes
safety	AL002 ARIA in APOE4 homozygotes DNL919 discontinued due to anemia	No evidence of cytokine release to date, Fc null



Acknowledgements

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- Our Investors
- Our Collaborators
- The Patients