Latest Discoveries in Alzheimer's Disease

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Center for Continuing Medical Education

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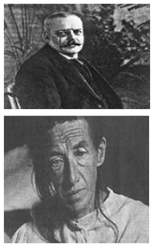
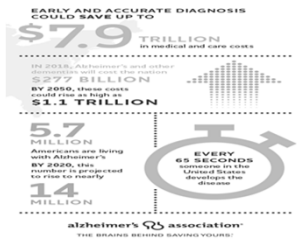
Wexner Medical Center

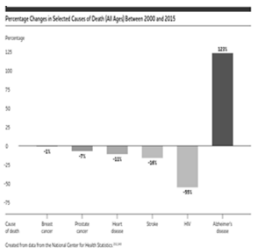
Alzheimer Disease: A Global Epidemic





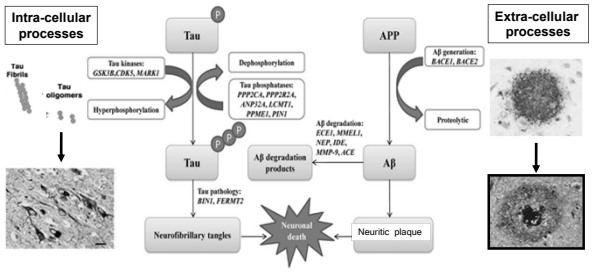
The Alzheimer's Association 2018 Report

Alzheimer Disease: Major Cause of Mortality



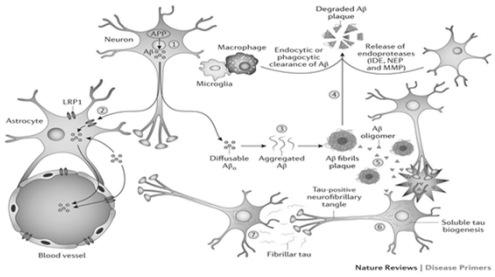
The Alzheimer's Association 2018 Report

Amyloid and Tau Cascades in Alzheimer Disease



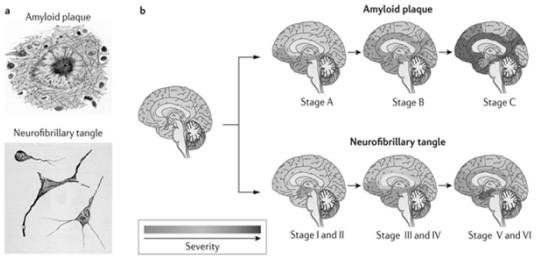
Xiao et al, Front. Aging Neurosci., 06 November 2020 with permission (Open Access) | https://doi.org/10.3389/fnagi.2020.584801

Other Disease Mechanisms and Pathways



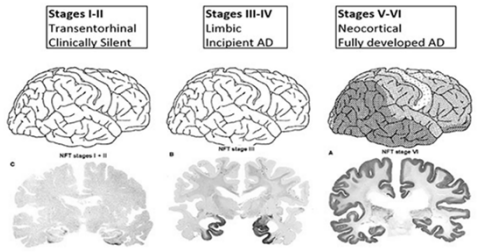
Masters, C. L. *et al.* (2015) Alzheimer's disease *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.56 with permission

The pathological evolution of Alzheimer's disease



Masters, C. L. *et al.* (2015) Alzheimer's disease *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.56 with permission

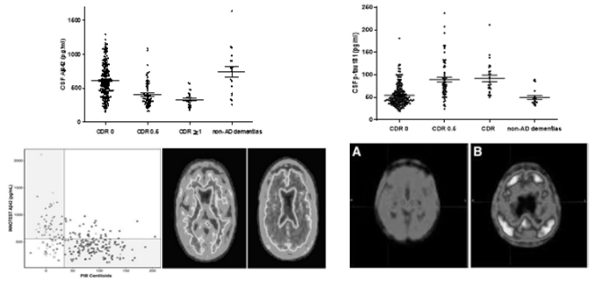
Stages of Neurodegeneration



Braak and Braak 1991

Vies, Saskia M. van der. "Protein kinases orchestrate early pathological events in Alzheimer ' s disease." (2016).

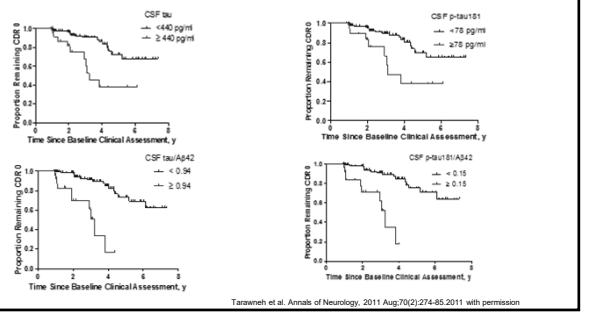
AD Biomarker Profile: High CSF tau and p-tau181 and low CSF Aβ42



Leuzy et al. Brain. 2016 Sep; 139(9): 2540–2553 (with permission-Open Access)

Tarawneh et al. Annals of Neurology, 2011 Aug;70(2):274-85.2011 with permission

CSF tau/Aβ42 and p-tau181/Aβ42 detect preclinical AD

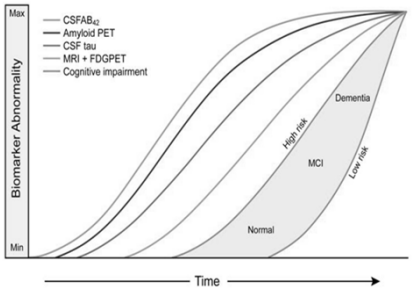


Tarawneh et al. Annals of Neurology. 2011 Aug;70(2):274-85.2011 with permission

I. UPDATED RESEARCH FRAMEWORK FOR AD

TOWARDS BIOMARKER-BASED DEFINITIONS OF AD

Theoretical Model of Disease Progression



Jack et al. Update on hypothetical models of Alzheimer's disease Biomarkers Lancet Neurol. 2013 Feb; 12(2): 207–216.2014 with permission

Biomarkers: Central Concept in the Updated Research Framework of AD: AT(N)

ELSEVIER Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

AT(N) biomarker grouping

A: Aggregated Aβ or associated pathologic state
- CSF $Aβ_{42}$, or $Aβ_{42}/Aβ_{40}$ ratio
- Amyloid PET

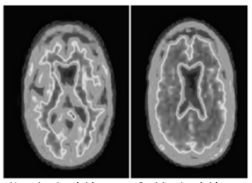
T: Aggregated tau (neurofibrillary tangles) or associated pathologic state
- CSF phosphorylated tau
- Tau PET

(N): Neurodegeneration or neuronal injury
- Anatomic MRI
- FDG PET
- CSF total tau

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

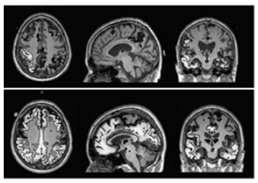
NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease, Alzheimer's & Dementia, 2018. 14 (4): 535-562, https://doi.org/10.1016/j.jalz.2018.02.018 with permission .

The ATN Framework for Alzheimer Disease
Diagnosis and Characterization



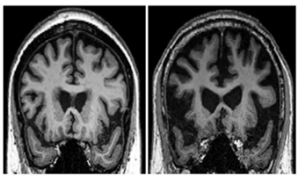
Negative Amyloid scan Positive Amyloid scan

Amyloid "A"



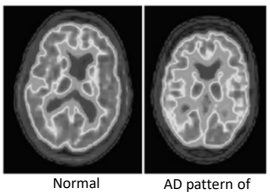
Tau "T"

Imaging Biomarkers of Neurodegeneration "N"



No atrophy Atrophy

Volumetric MRI



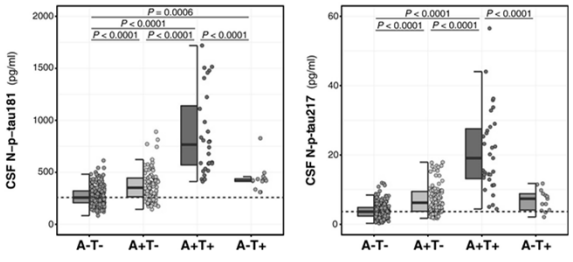
Normal metabolism AD pattern of hypometabolism

FDG-PET

Advances in AD Diagnosis:

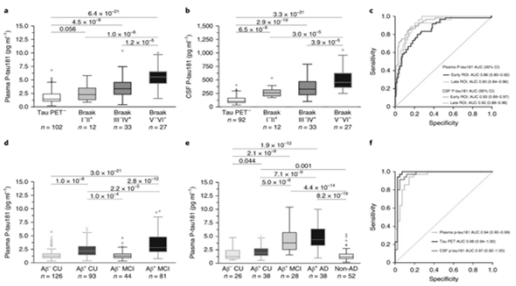
Blood Biomarkers and Emerging Markers of Other Pathologies

CSF p-tau217 outperforms CSF p-tau181



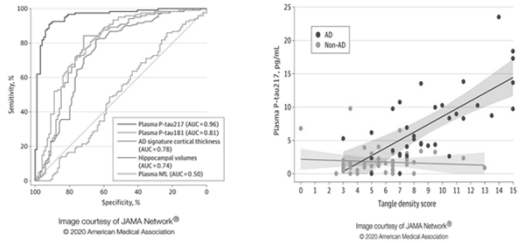
Suarez-Calvet, et al. EMBO Mol Med (2020) 12: 12: e12921 with permission

Plasma p-tau181: New AD-Specific Blood Marker



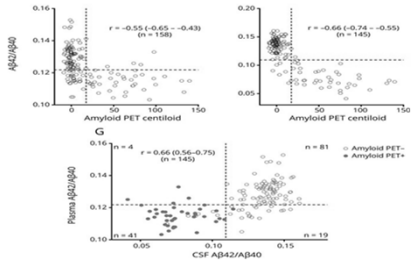
Janelidze et al. Nat Med **26,** 379–386 (2020). https://doi.org/10.1038/s41591-020-0755-1 with permission

Plasma p-tau217: Great Promise as Most Sensitive and Specific Blood Test for AD



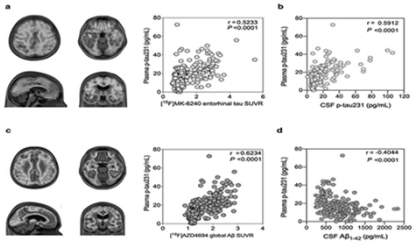
Palmqvist et al. *JAMA*. 2020;324(8):772–781. doi:10.1001/jama.2020.12134 with permission

Plasma Markers Can Detect Brain Amyloid



Schinder SE,et al . *Neurology*. 2019;93(17):e1647-e1659 (with permission)

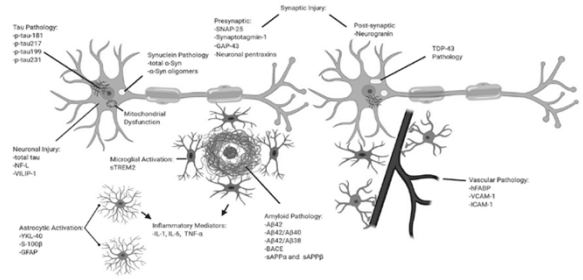
P-tau231 May Precede Amyloid in AD Brains



Ashton et al. Acta Neuropathol **141,** 709–724 (2021). https://doi.org/10.1007/s00401-021-02275-6 with permission (Open Access)

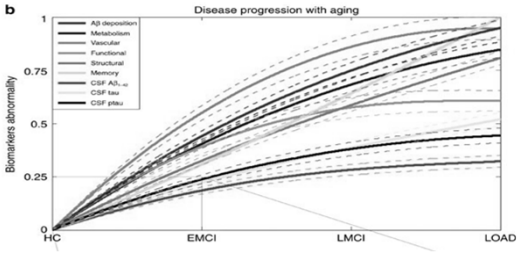
Understanding the Clinicopathological and Molecular Heterogeneity of AD

Biomarkers of AD Pathologies: Beyond Amyloid and Tau



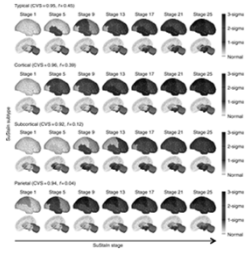
Tarawneh, R. Biomarker Insights, 2020 (with permission)

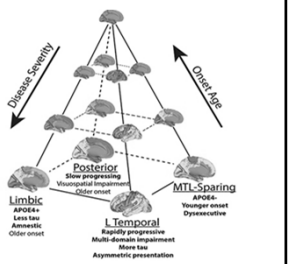
New Biomarkers And Big Data Analytics: Data-Driven Disease Models



Iturria-Medina et al. *Nat Commun* **7,** 11934 (2016) with permission (Open Access)

AI Algorithms Identify 4 AD Subtypes





Young et al. Nat Commun **9,** 4273 (2018) with permission (Open Access) Vogel et al. Nat Med. 2021 May;27(5):871-881 with permission

Update on Investigational AD Therapies

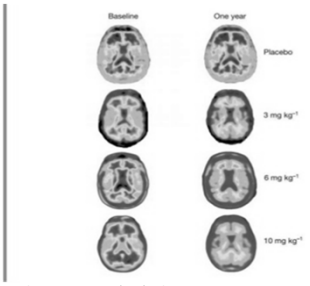
Anti-amyloid immunotherapies: Effectively Remove Amyloid And May Slow Down Disease Progression

Results

Amyloid Plaque Reduction with Aducanumab

Amyloid PET Images at Baseline and at Week 54

- Actually shown to penetrate the brain and decrease Aβ in patients with AD in a time- and dose-dependent manner
- Mean PET SUVR composite score at baseline was 1.44
- After 54 wks of treatment, this decreased significantly ($P < 0.001$) in the 3, 6, and 10 mg/kg dose groups
- Change in placebo group was minimal



Sevigny, J., Chiao, P., Bussière, T. *et al. Nature* **537,** 50–56 (2016) with permission

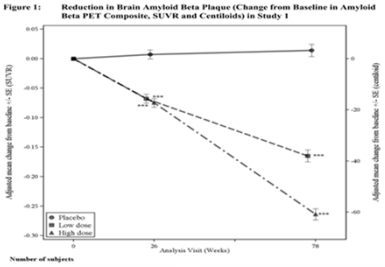
NEWS: Aducanumab FDA-Approved June 7, 2021 As First Disease-Modifying Treatments for AD

- Aducanumab is an amyloid beta-directed antibody indicated for the treatment of early symptomatic Alzheimer's disease.
- This targets soluble and insoluble (aggregated) Aβ peptides
- This indication was just recently approved under accelerated approval based on reduction in amyloid beta plaques observed in treated patients.
- Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.
- Both Phase 3 clinical trials includes patients with:
  - Clinical Dementia Rating (CDR) score of 0.5 (equivalent to MCI)
  - MMSE 24-30
  - RBANS (Repeatable Battery for Assessment of Neuropsychological Status) delayed memory index of ≤ 85

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf

Aducanumab reduces amyloid burden

Figure 1: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 1



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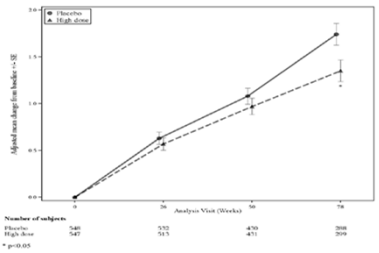
Clinical Endpoints

Figure 2: Line Plot of Primary Efficacy Endpoint (Change From Baseline in CDR Sum of Boxes) in Study 1



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Clinical Endpoints-Continued

Clinical Endpoint at Week 78	ADUHELM High dose (N=547)	Placebo (N=548)
CDR-SB		
Mean baseline	2.51	2.47
Change from baseline	1.35	1.74
Difference from placebo (%)	-0.39 (-22%) p=0.0120	
MMSE		
Mean baseline	26.3	26.4
Change from baseline	-2.7	-3.3
Difference from placebo (%)	0.6 (-18%) p=0.0493	
ADAS-Cog 13		
Mean baseline	22.246	21.867
Change from baseline	3.763	5.162
Difference from placebo (%)	-1.400 (-27%) p=0.0097	
ADCS-ADL-MCI		
Mean baseline	42.5	42.6
Change from baseline	-2.5	-4.3
Difference from placebo (%)	1.7 (-40%) p=0.0006	
NPI-10[1]		
Mean baseline	4.5	4.3
Change from baseline	0.2	1.5
Difference from placebo (%)	-1.3 (-87%) p=0.0215	

[1]P-value was not statistically controlled for multiple comparisons.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf

Biomarker End-points

Biomarker Endpoint at Week 78[1]	ADUHELM High dose	Placebo
Amyloid Beta PET Composite SUVR	N=170	N=159
Mean baseline	1.383	1.375
Change from baseline	-0.264	0.014
Difference from placebo	-0.278, p<0.0001	
Amyloid Beta PET Centiloid	N=170	N=159
Mean baseline	85.3	83.5
Change from baseline (%)	-60.8 (-71%)	3.4
Difference from placebo	-64.2, p<0.0001	
CSF p-Tau (pg/mL)	N=17	N=28
Mean baseline	100.11	72.55
Change from baseline	-22.93	-0.49
Difference from placebo	-22.44, p=0.0005	
CSF t-Tau (pg/mL)	N=17	N=28
Mean baseline	686.65	484.00
Change from baseline	-112.44	-0.39
Difference from placebo	-112.05, p=0.0088	

[1]P-values were not statistically controlled for multiple comparisons.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf

Aducanumab –in the clinic

- Is administered as an intravenous (IV) infusion over approximately one hour every four weeks and at least 21 days apart.
- Patients with mild cognitive impairment due to Alzheimer disease
- Evidence of Amyloid on Amyloid-PET scans
- Brain MRI within a year prior to starting the infusion as a baseline
- Safety has not been assessed in patients who have pre-treatment localized superficial siderosis, 10 or more brain microhemorrhages, and/or with a brain hemorrhage greater than 1 cm within one year of treatment initiation

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf

ARIA-E and ARIA-H

- ARIA-E or ARIA-H were observed in 41% of treatment compared to 10% of placebo groups
- ARIA-E was observed in 35% of treated patients compared to 3% of placebo
- ARIA-E was more common in APOE4 carriers (42%) vs APOE4 noncarriers (20%)
- Most ARIAs occurred within the first 8 doses but can occur any time
- ARIAS were mild in 30%, moderate in 58% and severe in 13%
- Resolution occurred in 68% of ARIA-E patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection
- 10% of patients on the full dose had more than one episode of ARIA
- Besides ARIA, angioedema and hypersensitivity have been reported

Amyloid Related Imaging Abnormalities (ARIAs)

Table 2: ARIA MRI Classification Criteria

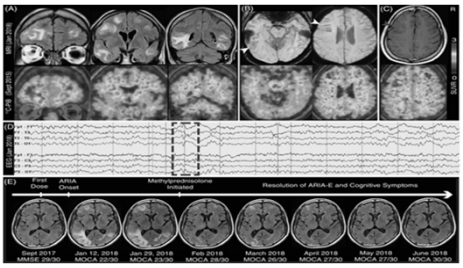
ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location < 5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate sites of involvement may be noted.
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 focal areas of superficial siderosis

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf

ARIA Follow-up

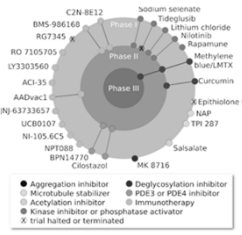
- Enhanced clinical vigilance for ARIA is recommended during the first 8 doses
- Clinical evaluation of symptomatic patients with suspected ARIA should include a brain MRI
- Brain MRIs should be obtained routinely prior to the 7th infusion (first dose of 10 mg/kg) and 12th infusion (sixth dose of 10 mg/kg) to evaluate for the presence of asymptomatic ARIA.
- For patients with radiographic ARIA, enhanced clinical vigilance is recommended including possible need for additional MRIS
- For ARIA-E or mild/moderate ARIA-H, treatment may continue with caution. If dosing is temporarily suspended, dosing may resume at that same dose and titration schedule.
- In Studies 1 and 2, temporary dose suspension was required for radiographically moderate or severe ARIA-E and radiographically moderate ARIA-H.
- In Studies 1 and 2, permanent discontinuation of dosing was required for radiographically severe ARIA-H.

ARIA-Case Report Outlining Suggested Treatment



VandeVrede, L, et al *Alzheimer's Dement*. 2020; 12:e12101. https://doi.org/10.1002/dad2.12101

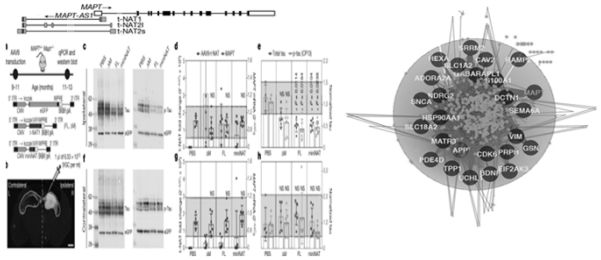
Anti-Tau Trials



Semorinemab	Roche/AC Immune	Pan-tau mAb; N-terminal epitope	Phase II; failed in first phase II, more results due in 2021.
ABBV-8E12	AbbVie/C2N Diagnostics	mAb; N-terminal epitope	Phase II; results due in 2021. Failed in PSP.
Gosuranemab	Biogen/Bristol Myers Squibb	mAb; N-terminal epitope	Phase II; results due in 2021. Failed in PSP.
Zagotenemab	Eli Lilly	mAb; conformational epitope includes N-terminal site	Phase II; results due in 2021.
JNJ-63733657	Johnson & Johnson	Pathogenic tau mAb, targeting mid-region epitope	Phase II; started in 2020.
IONIS-MAPTRx	Biogen/Ionis	Antisense	Phase I/II; results due in 2021.
ACI-35	Johnson & Johnson/AC Immune	Vaccine	Phase I/II
AADvac1	AXON Neuroscience	Vaccine	Phase I
ACI-3024	Eli Lilly /AC Immune	Small-molecule aggregation inhibitor	Phase I
BIIB076	Biogen	mAb	Phase I
E2814	Eisai	mAb	Phase I
Lu AF87908	H. Lundbeck	mAb	Phase I

Current clinical trials *targeting* tau (Adapted from Congdon and Sirgudsson, 2018)

MIR-NATs: Noncoding RNAs That Regulate Tau Translation In Vivo

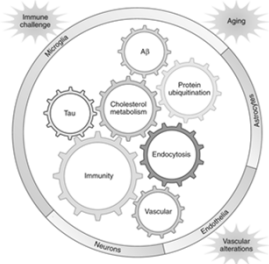


Simone, *et al. Nature* **594,** 117–123 (2021). https://doi.org/10.1038/s41586-021-03556-6 with permission

Unraveling New Disease Mechanisms

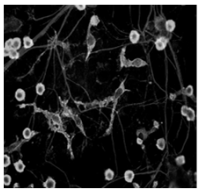
Beyond Protein Aggregation:
Immune Mechanisms and Vascular Disturbances are Key Players

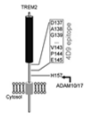
Immune Dysregulation as a Central Mechanism in AD

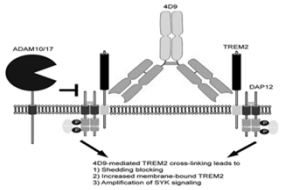


Sims, R., Hill, M. & Williams, J. The multiplex model of the genetics of Alzheimer's disease. *Nat Neurosci* **23,** 311–322 (2020). with permission

Targeting Inflammation in AD; Anti-TREM2 Antibodies







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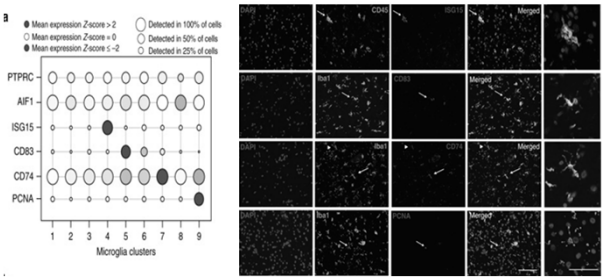
Schelpckow et al. EMBO Mol Med

RNA-seq identifies different microglial subtypes in AD



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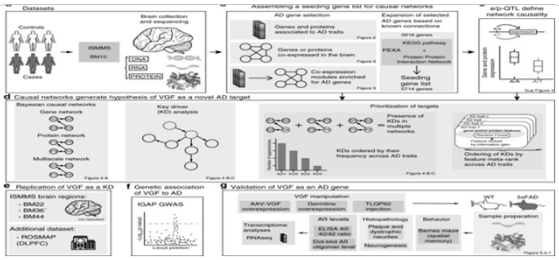
Novel Therapeutic Targets

Big Data Analytics at Forefront of AD Drug Discovery

VGF Gene As A Key Regulator of AD



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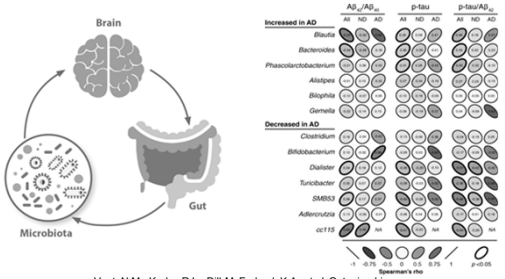
AD and the Gut Microbiome



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