2017 ADC Meeting
Induced Pluripotent Stem Cells

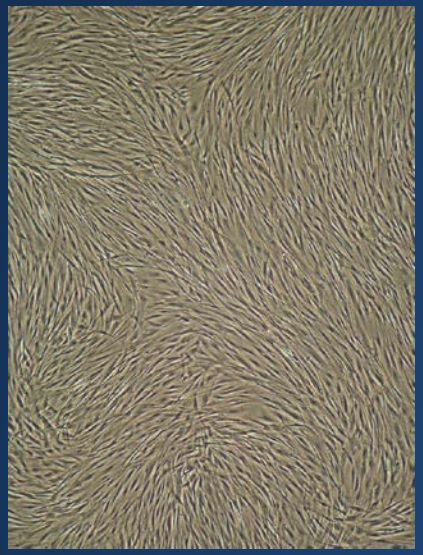
October 14, 2017

Mathew Blurton-Jones, PhD

UC Irvine ADRC iPS cell core leader

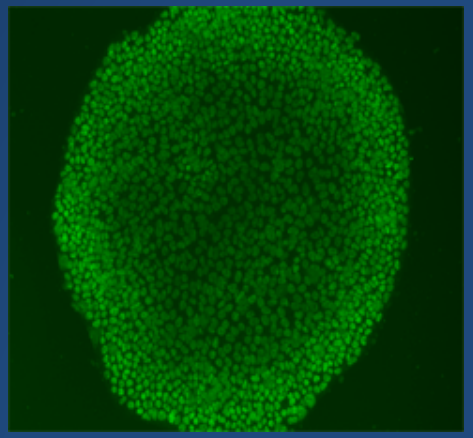
The UCI ADRC iPSC core is tasked with generating and distributing AD, MCI, and Control iPSCs and fibroblasts

ADRC patient fibroblasts

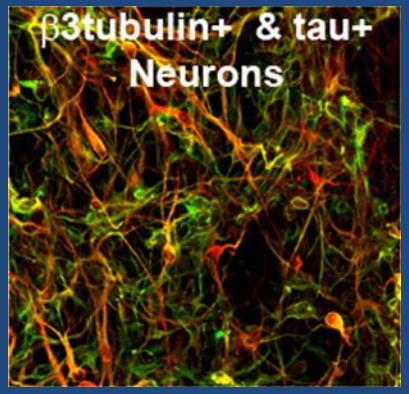


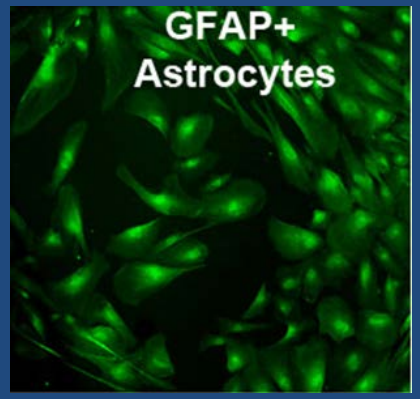
Clinical and Education Cores consent and obtain skin samples

ADRC iPS lines



Late-onset AD is ~79% genetic





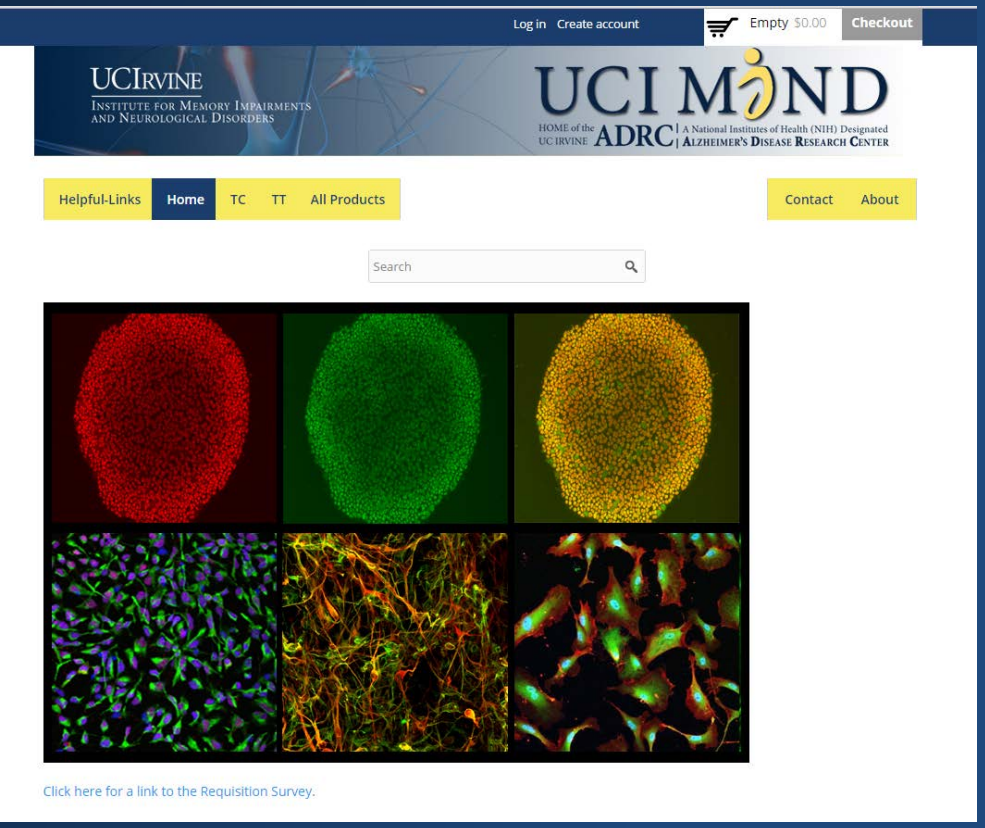
Do genetic differences shift the function or phenotype of AD Patient brain cells?

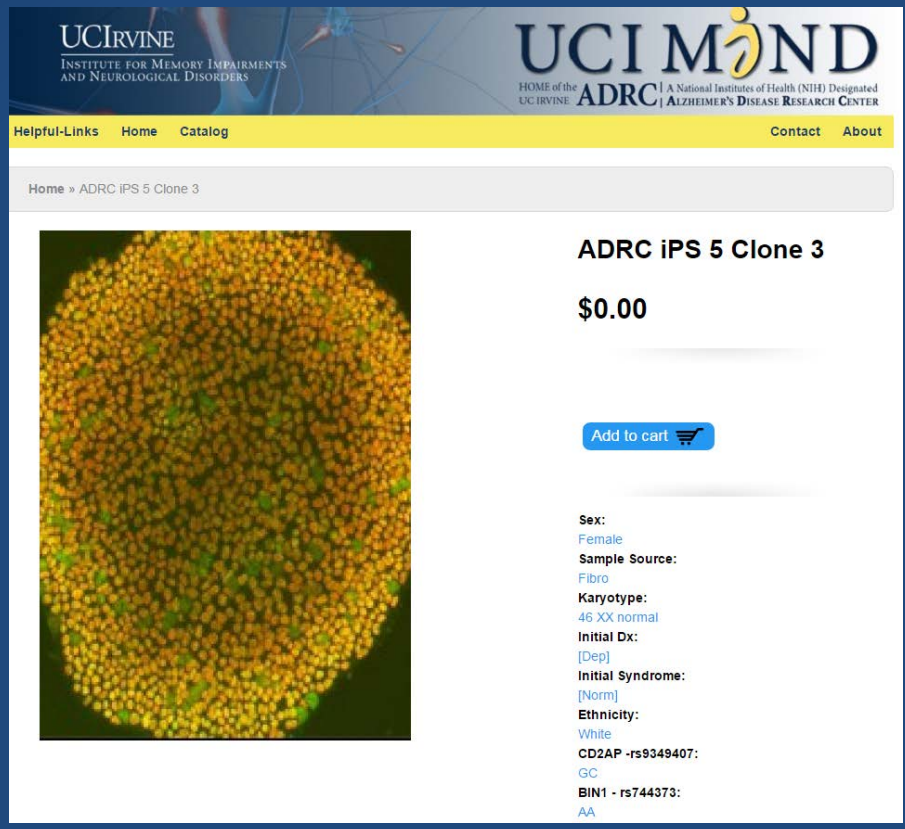
UCI ADRC iPSC core

- 87% consent rate for PBMC reprogramming (84% for fibroblasts).
- Fibroblasts expanded and banked from 117 subjects.
- iPSC lines from 62 subjects made, characterized, and available thus far (3-4 clones/subject, 50 vials/subject banked at P10).
- Letters of support and/or feasibility data provided to 12 non-UCI Researchers and 12 UCI researchers.
- iPSC core website established to help researchers select appropriate lines: https://stemcells.mind.uci.edu/
- Isogenic TREM2 heterozygous and homozygous knockout lines made and gene corrected lines being generated.

In collaboration with the DMSC the iPS core website was established to help researchers choose and request lines.

https://stemcells.mind.uci.edu/





An example of a collaborative research project that used UCI ADRC iPSC lines:

CellPress

Neuron
NeuroResource

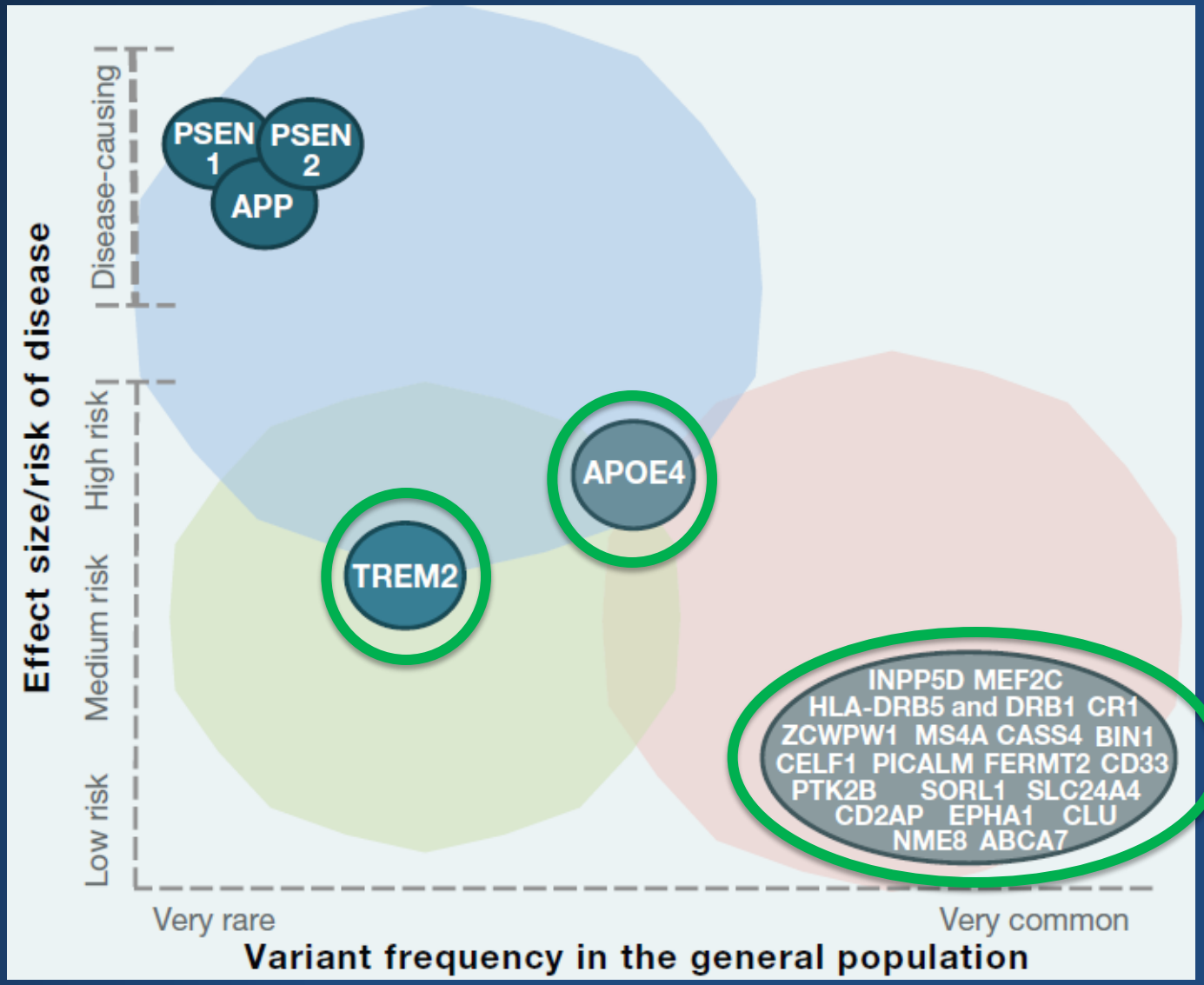
iPSC-Derived Human Microglia-like Cells to Study Neurological Diseases

Edsel M. Abud,[1,2,3] Ricardo N. Ramirez,[4] Eric S. Martinez,[1,2,3] Luke M. Healy,[5] Cecilia H.H. Nguyen,[1,2,3] Sean A. Newman,[2] Andriy V. Yeromin,[6] Vanessa M. Scarfone,[2] Samuel E. Marsh,[2,3] Cristhian Fimbres,[3] Chad A. Caraway,[3] Gianna M. Fote,[1,2,3] Abdullah M. Madany,[11] Anshu Agrawal,[7] Rakez Kayed,[8] Karen H. Gylys,[9] Michael D. Cahalan,[6] Brian J. Cummings,[2,3,10] Jack P. Antel,[5] Ali Mortazavi,[4] Monica J. Carson,[11] Wayne W. Poon,[3,*] and Mathew Blurton-Jones[1,2,3,12,*]

This project used 10 ADRC iPSC lines

Experimental Models: Cell Lines		
Rat Hippocampal neurons	This paper	N/A
Commercial iHPCs (Lot# 021405)	Cellular Dynamics International	Cat# HPC-301-020-001-PT
Human: iPSC line from Fibroblast: Male	UCI ADRC iPSC Core	ADRC 2
Human: iPSC line from Fibroblast: Male	UCI ADRC iPSC Core	ADRC 4
Human: iPSC line from Fibroblast: Female	UCI ADRC iPSC Core	ADRC 5
Human: iPSC line from PBMC: Male	UCI ADRC iPSC Core	ADRC 12
Human: iPSC line from Fibroblast: Male	UCI ADRC iPSC Core	ADRC F14
Human: iPSC line from Fibroblast: Female	UCI ADRC iPSC Core	ADRC 20
Human: iPSC line from PBMC: Female	UCI ADRC iPSC Core	ADRC 22
Human: iPSC line from PBMC: Male	UCI ADRC iPSC Core	ADRC 76
Human: iPSC line from Fibroblast: Male	UCI ADRC iPSC Core	ADRC 85
Human: iPSC line from Fibroblast: Female	UCI ADRC iPSC Core	ADRC 86

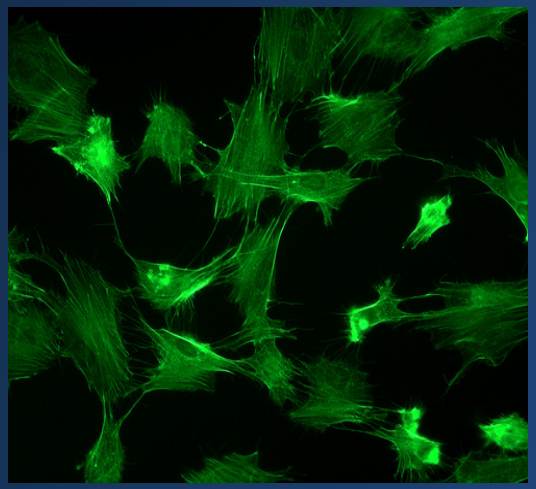
Many AD risk genes are highly expressed in Microglia



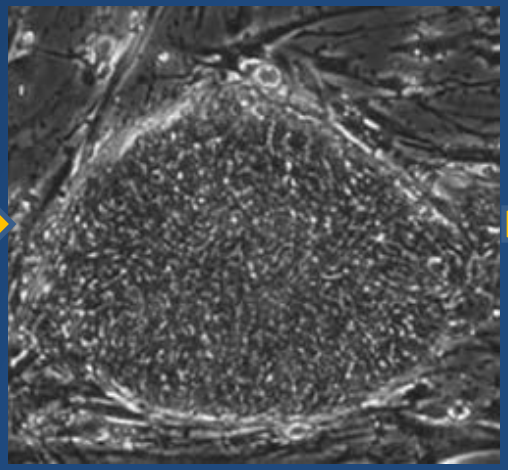
Guerreiro, Brás, and Hardy, Cell 2013

Can human Microglia be generated from induced pluripotent stem cells (iPSC) to study these AD risk genes?

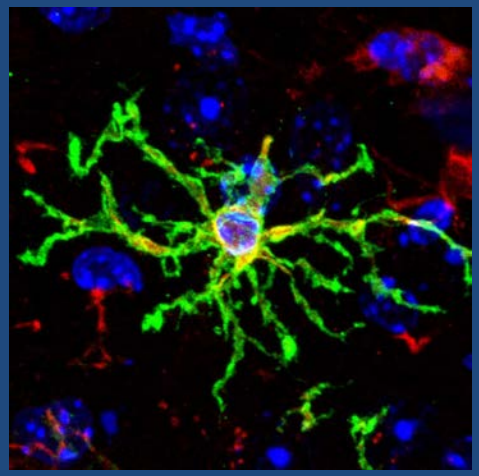
AD Patient Fibroblasts



Human iPS lines

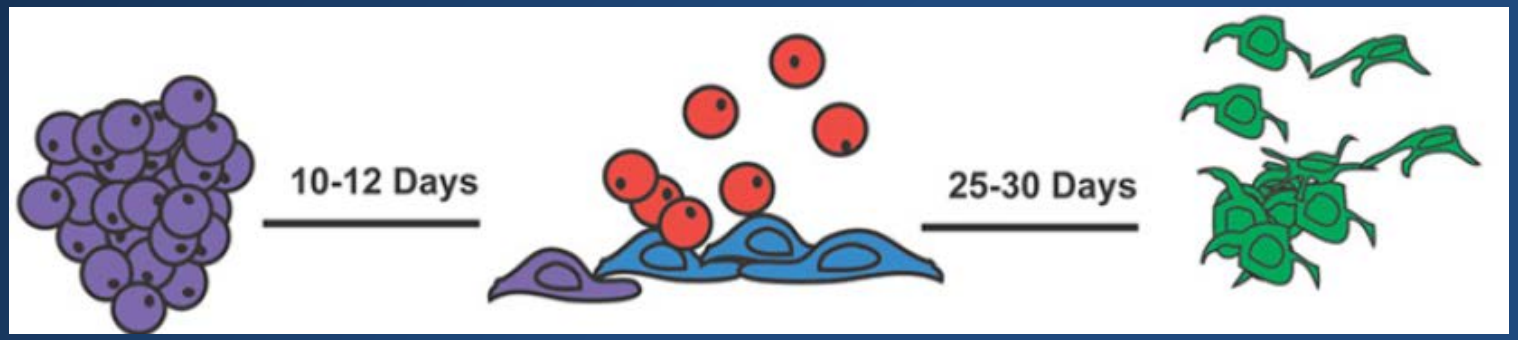


Patient-derived Microglia?

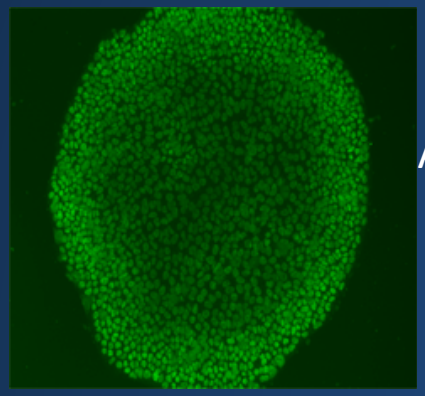


Development of fully-defined microglial differentiation approach

Edsel Abud. PhD



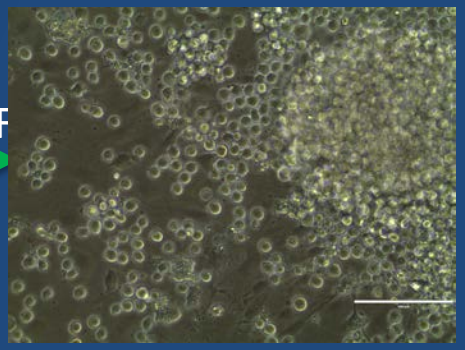
iPS cells



Hypoxia
FGF2, BMP4,
ActivinA, VEGF

TPO, SCF,
Il3,Il6

CD43+ HPCs



Non-adherent dishes
+ IL34,
+ CSF-1,

+ TGFB1
+ CD200
+ CX3CL1

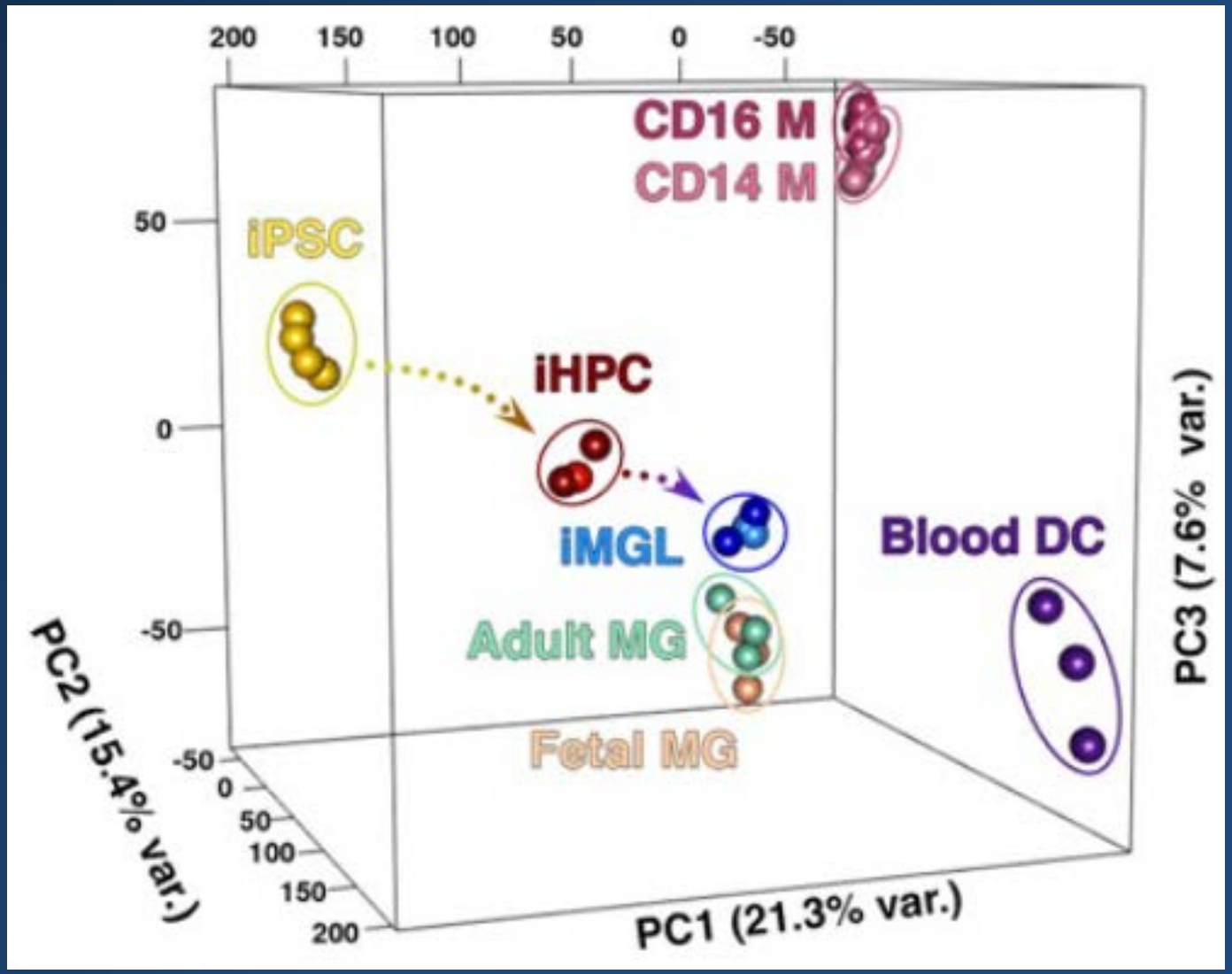
iMGLs

97% P2ry12/Trem2+

1 million iPSCs yields 30-40 million iMGLs

Abud et. al., *Neuron*, 2017

Whole-transcriptome RNA-seq analysis of iMGLs



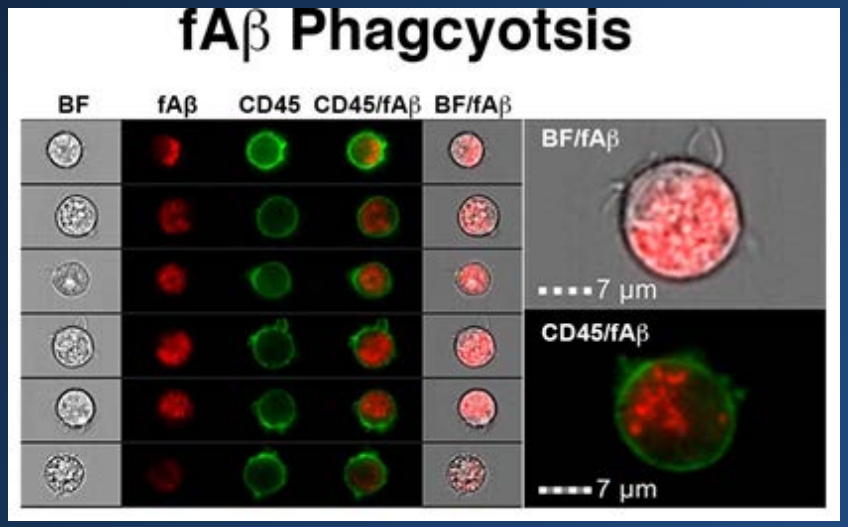
With Ricardo Ramirez and Ali Mortazavi (UCI)
Luke Healy and Jack Antel, (McGill University)

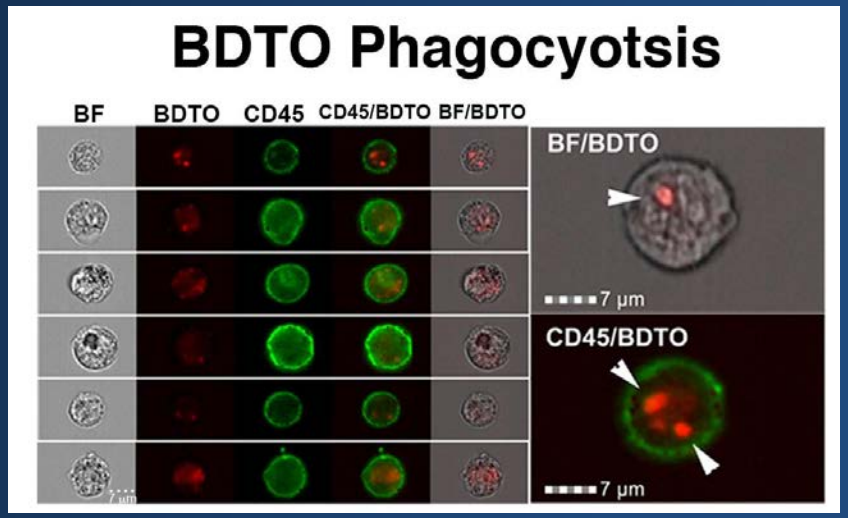
Abud et. al., *Neuron*, 2017

Can iMGLs be used to study microglial function?

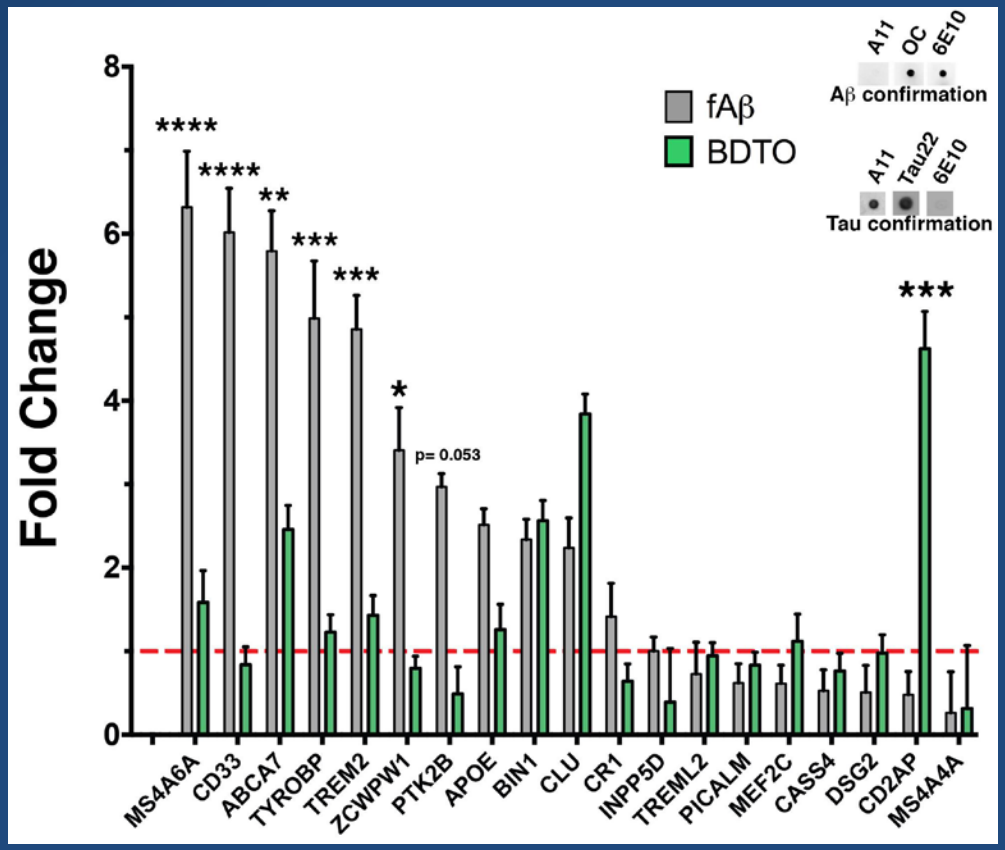
- Directed Migration
- Cytokine production
- **Phagocytosis of CNS substrates**
- **Interactions with neurons/astrocytes/plaques?**

Does Tau or Aβ exposure alter iMGL gene expression?



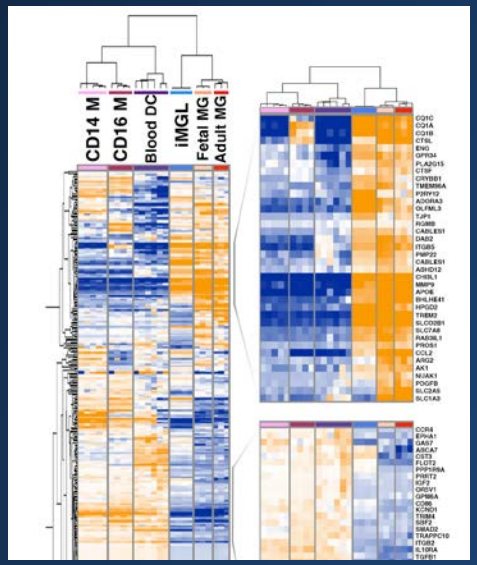


with Rakez Kayed (U Texas)



Abud et. al., *Neuron*, 2017

Now using iMGLs to investigate how TREM2 mutations affect microglial migration, gene expression, phagocytosis, energetics, etc.



iPSC lines

R47H carriers (n=4)

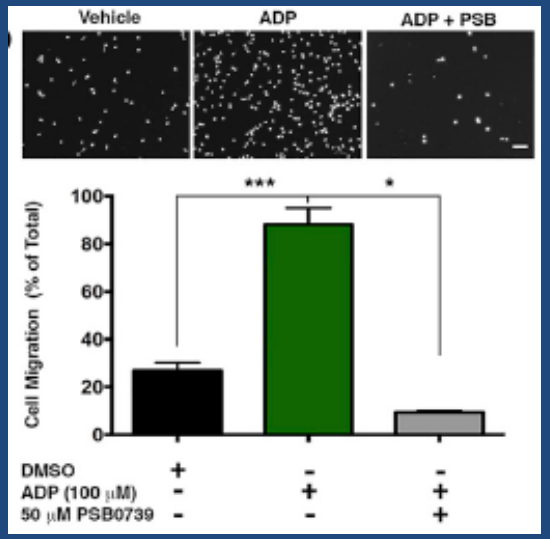
T66M carriers (n=3)

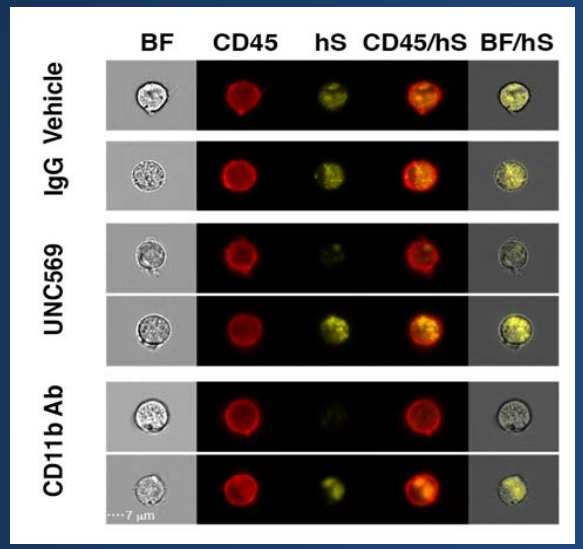
WT controls (n>10)

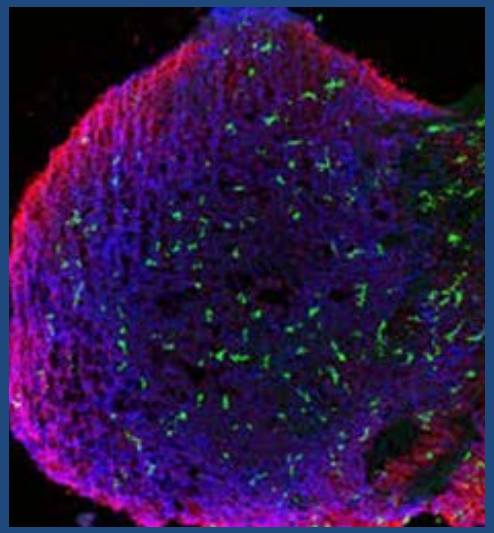
Isogenic TREM2 KO (n=2, so far)

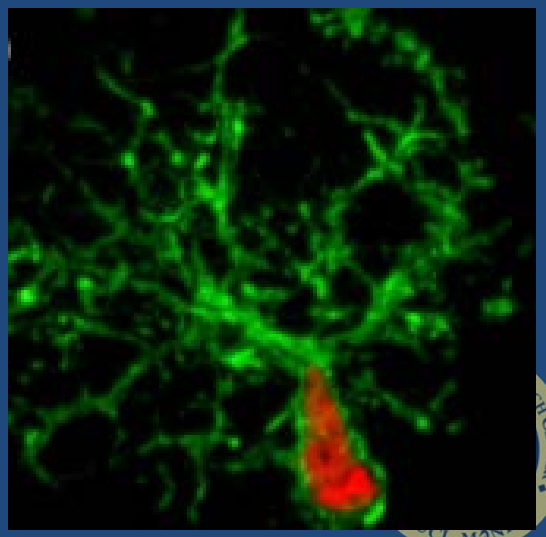
Isogenic TREM2 repaired lines

(screening clones)









How can we increase collaboration and use of ADC iPS cells?

- Further publicizing availability of this resource and similar banks at other ADCs.
- Better linking iPSC lines to the wealth of other clinical and genetic data available (NACC/ADGC) for these subjects to help researchers select appropriate lines for study.
- Given the power of CRISPR isogenic lines, should we shift our focus and resources to produce more.
- Creating a centralized iPS cell repository: NCRAD?

Acknowledgements

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- Ali Mortazavi, PhD

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- Abdullah Madany

McGill University

- Jack Antel, MD
- Luke Healy, PhD

UC Los Angeles

- Karen Gylys, PhD

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- Rakez Kayed, PhD

Univ. College, London

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