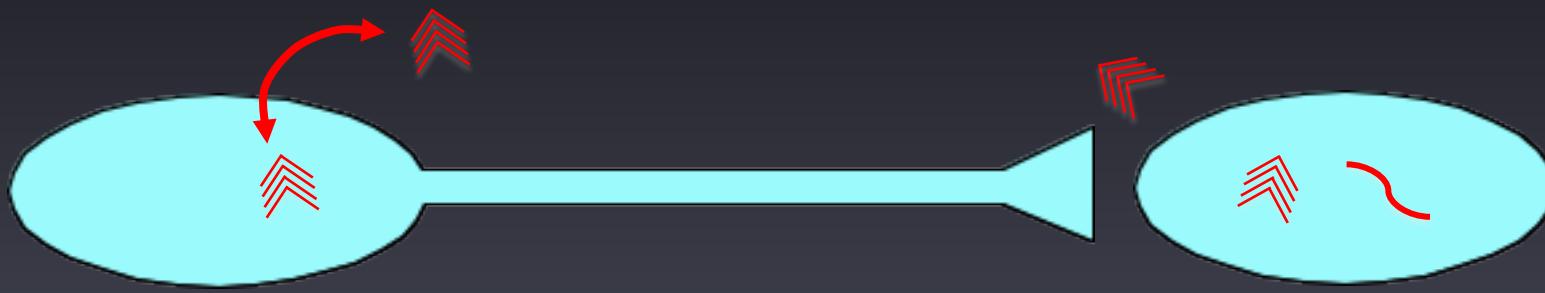


# Trans-cellular propagation: New therapeutic and diagnostic strategies

Marc Diamond, M.D.  
Department of Neurology  
Washington University in St. Louis

ADC Director's Meeting  
April 21, 2012

# New Opportunities for Therapy



Diagnosis: detection of seeds

Therapy: blocking propagation

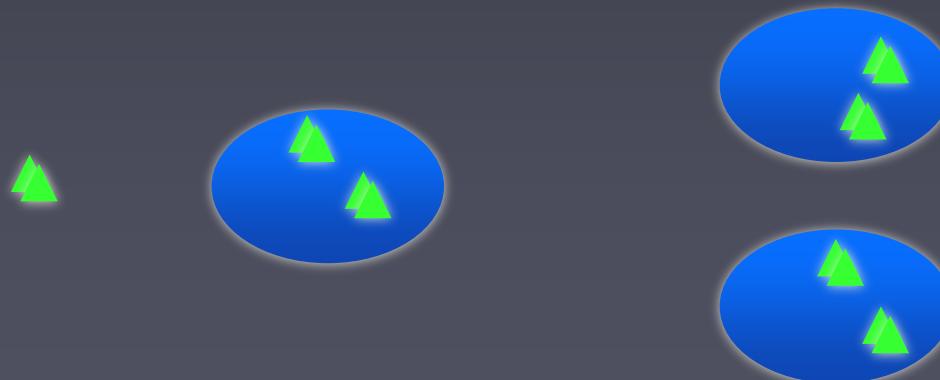
# Modeling Propagation

Aggregates gain cell entry

Conversion of endogenous protein

Trans-cellular movement

Propagation of aggregation

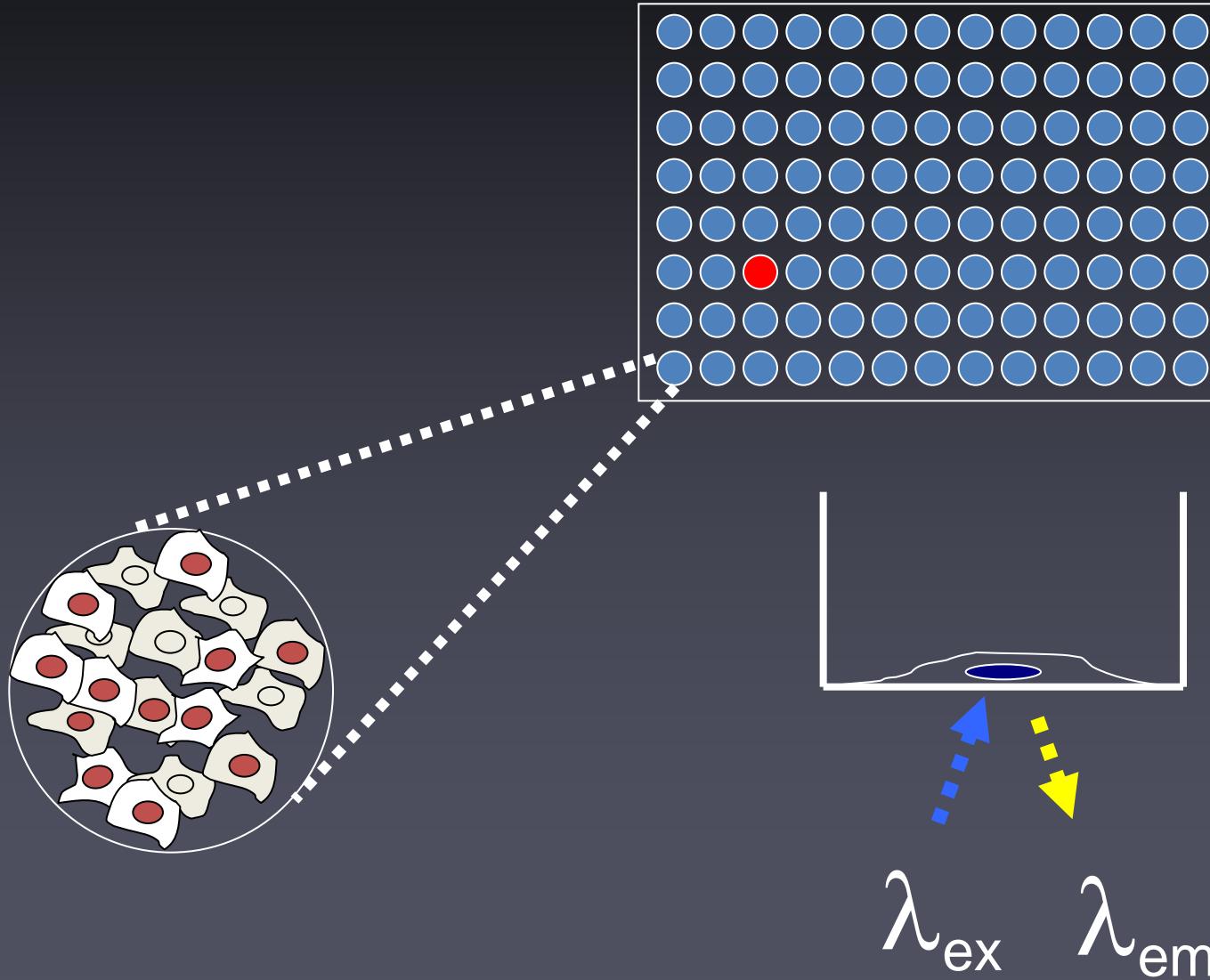


# Monitoring Tau Aggregation

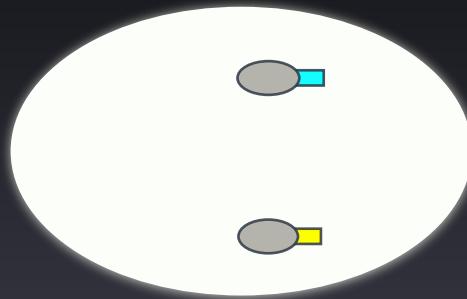


wild-type  
 $\Delta K280$ : increased  
 $\Delta K280/PP$ : no beta sheet  
P301L/V337M: strongly increased

# Fluorescence Readings from Cell Monolayers

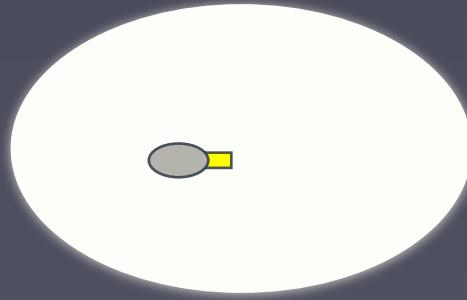
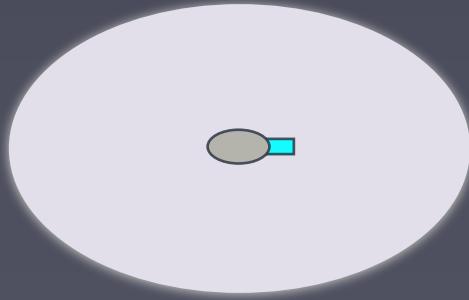


# Propagation of Misfolding



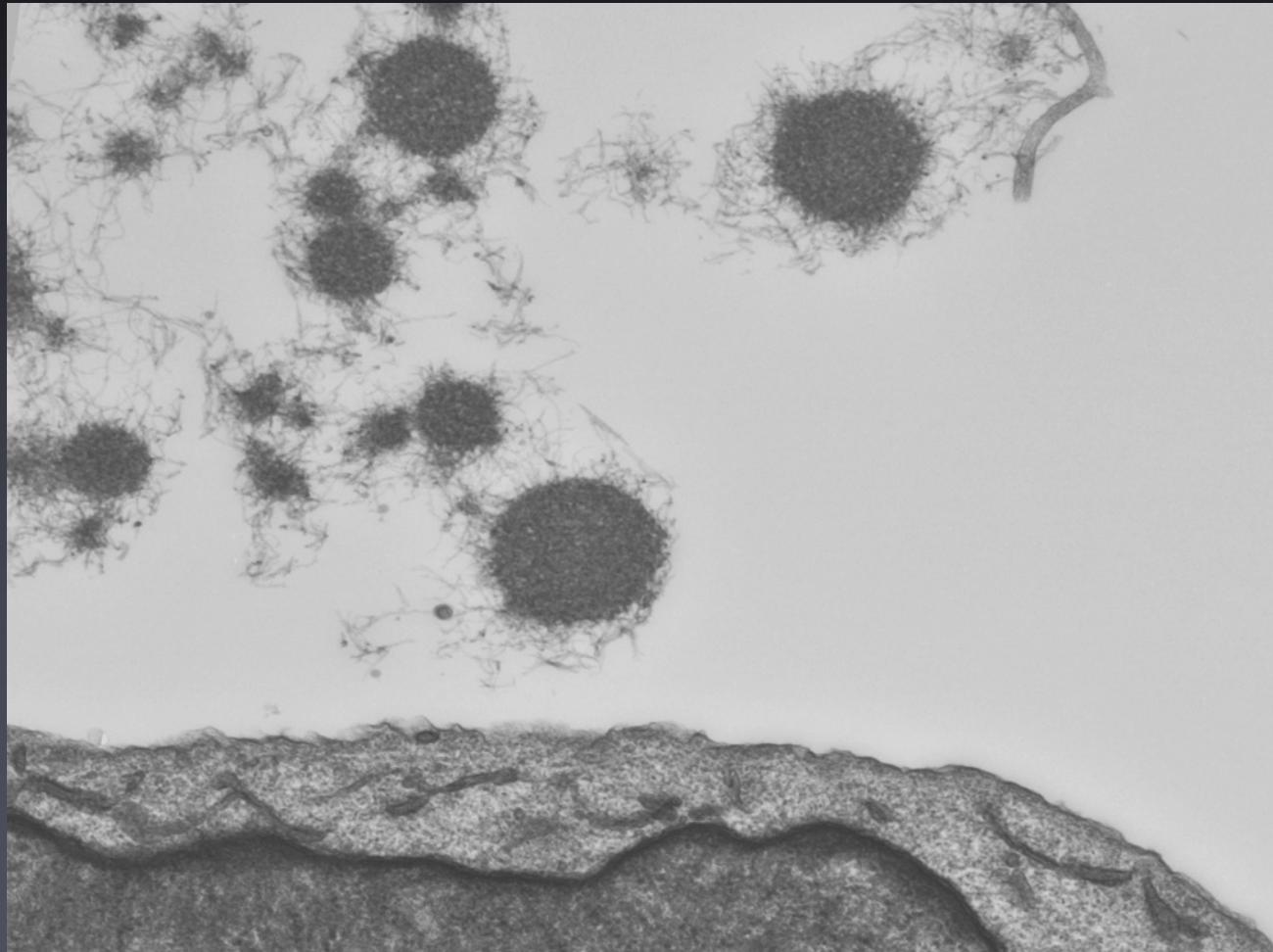
FRET

Trans-cellular Movement  
Induction of Aggregation  
FRET Signal Read on FPR

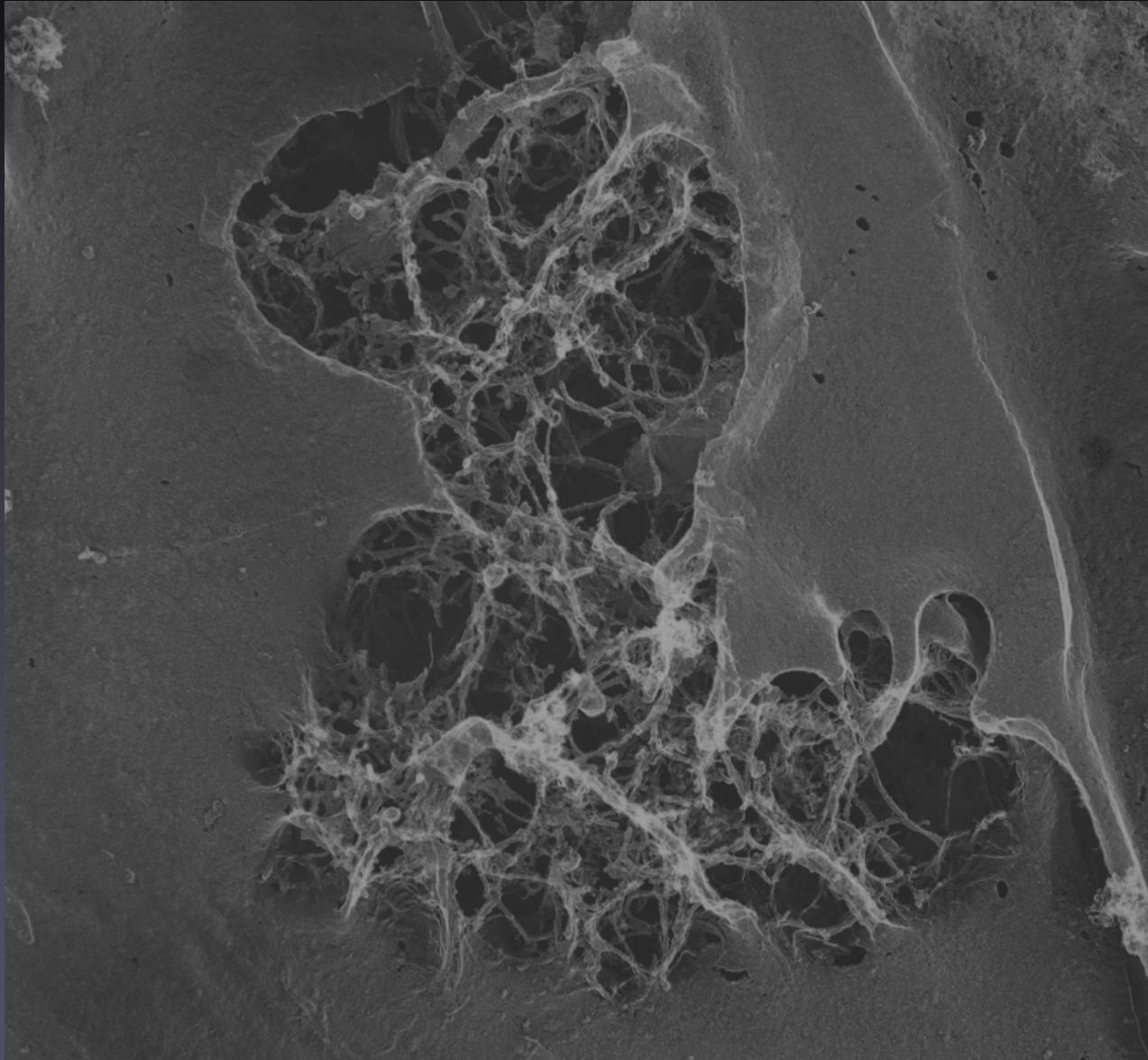


FRET

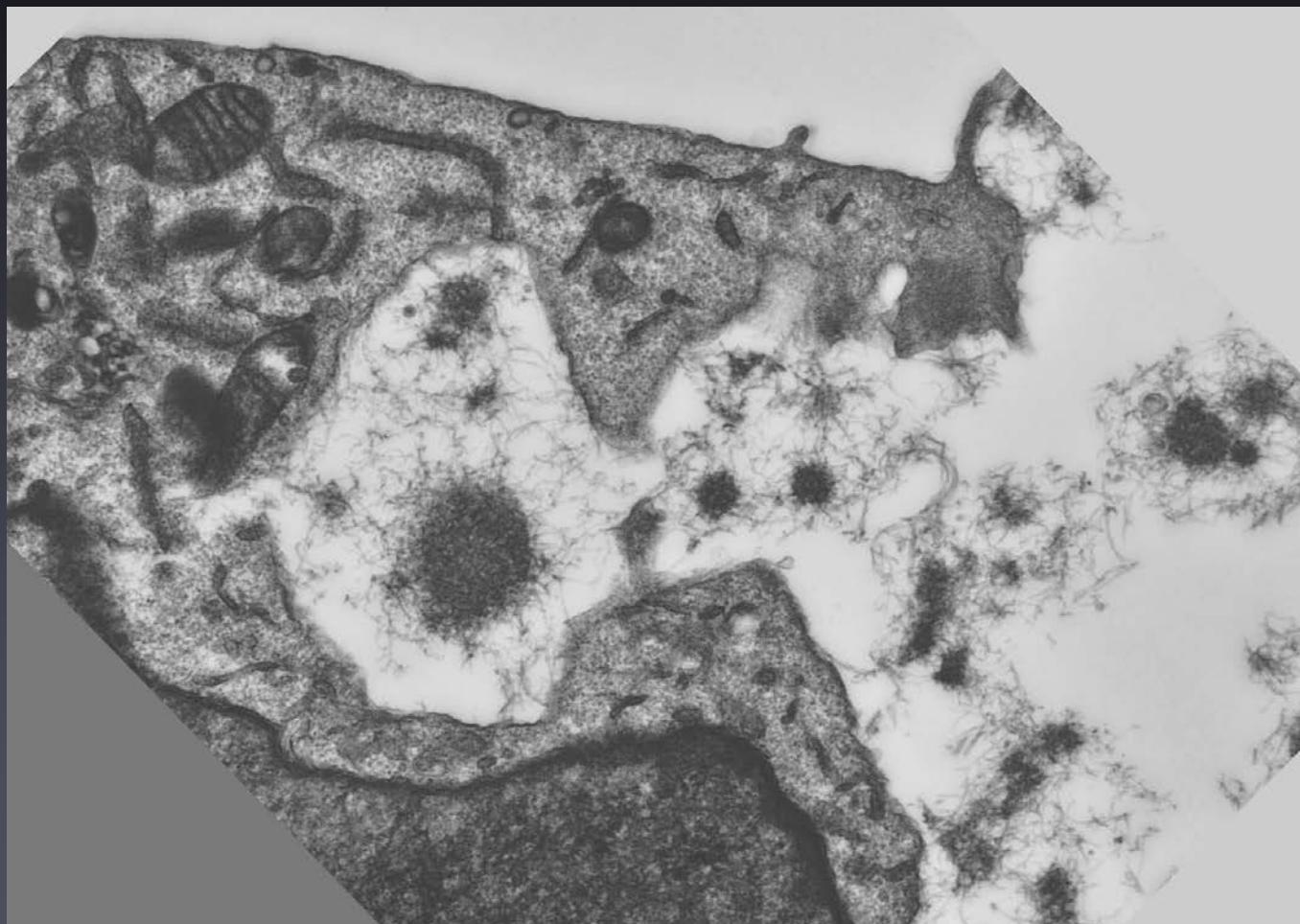
# Tau fibrils approach the membrane



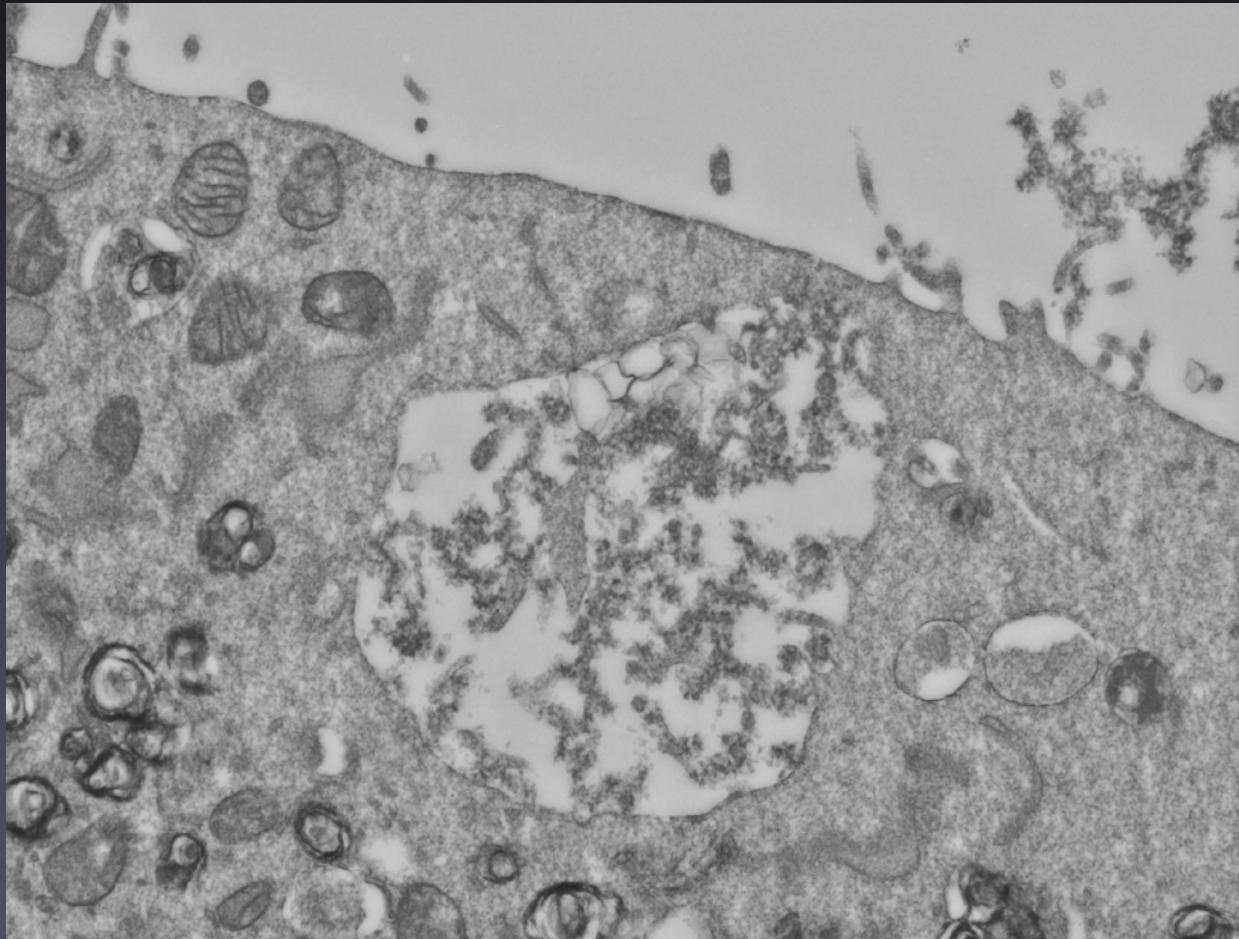
# Tau fibrils are engulfed by the cell



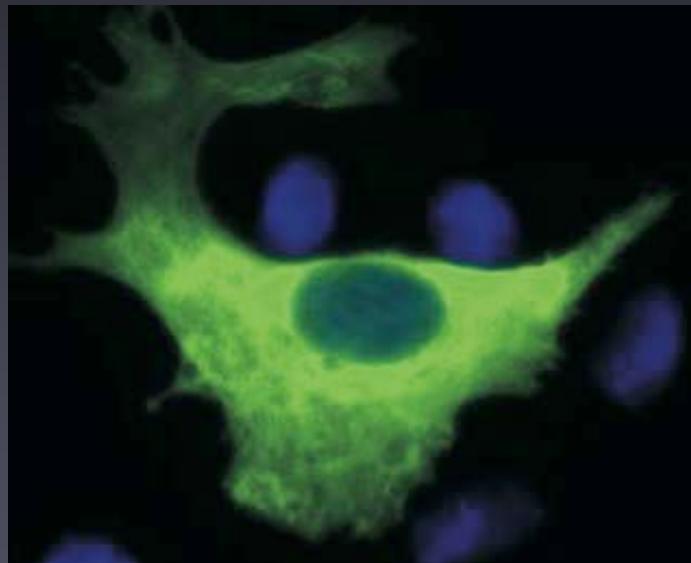
# Tau uptake by endocytosis



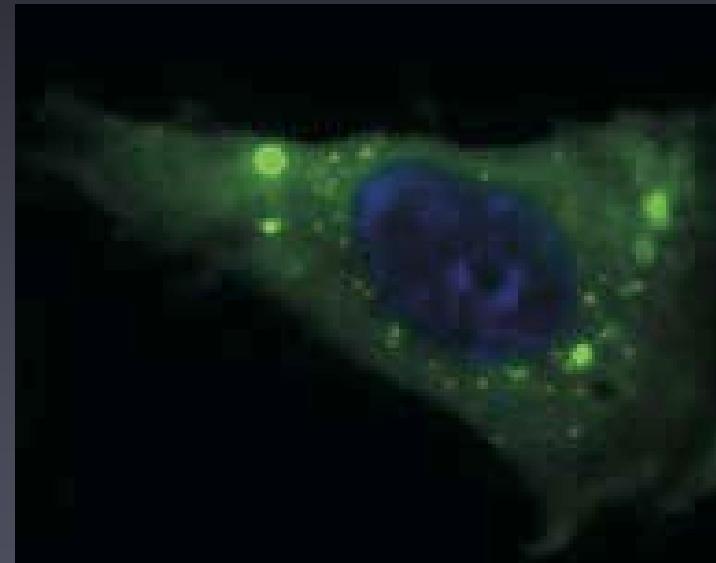
# Tau uptake by endocytosis



# External Tau Oligomers Induce Intracellular Tau Misfolding

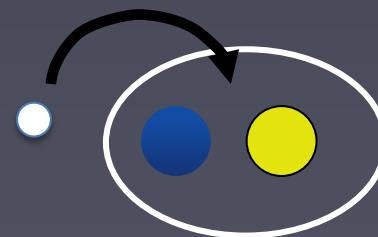
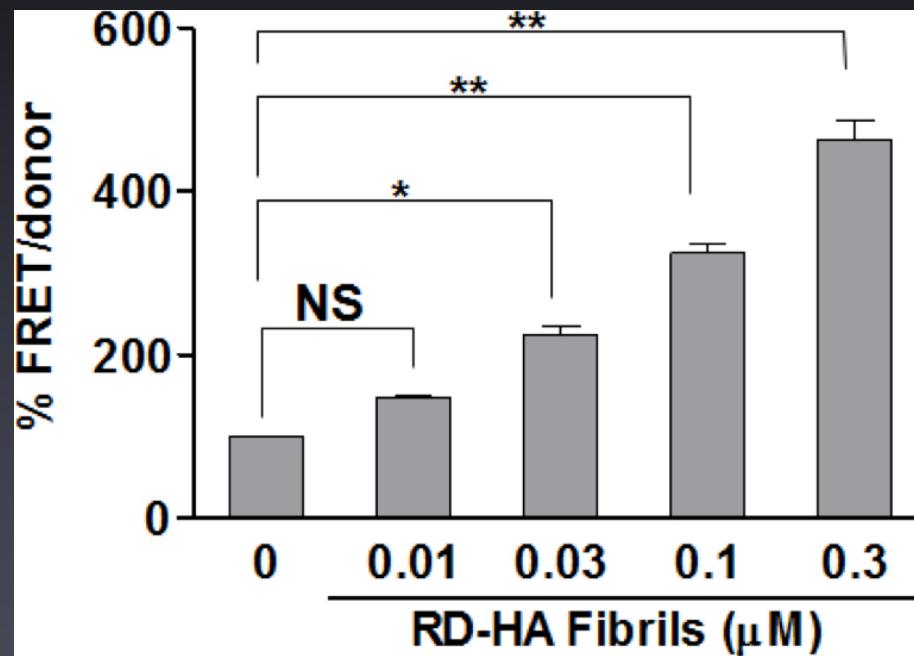


monomer-treated

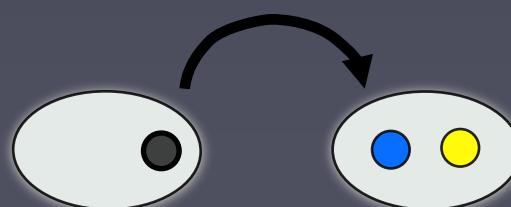
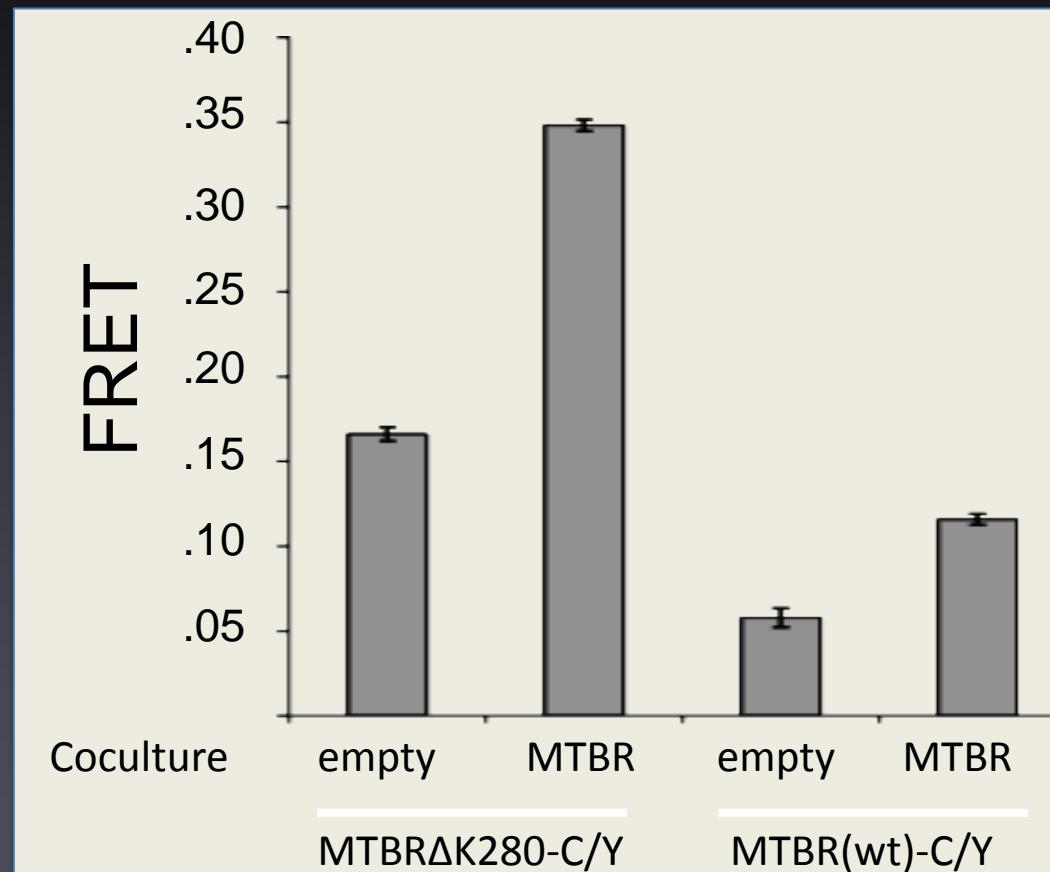


oligomer-treated

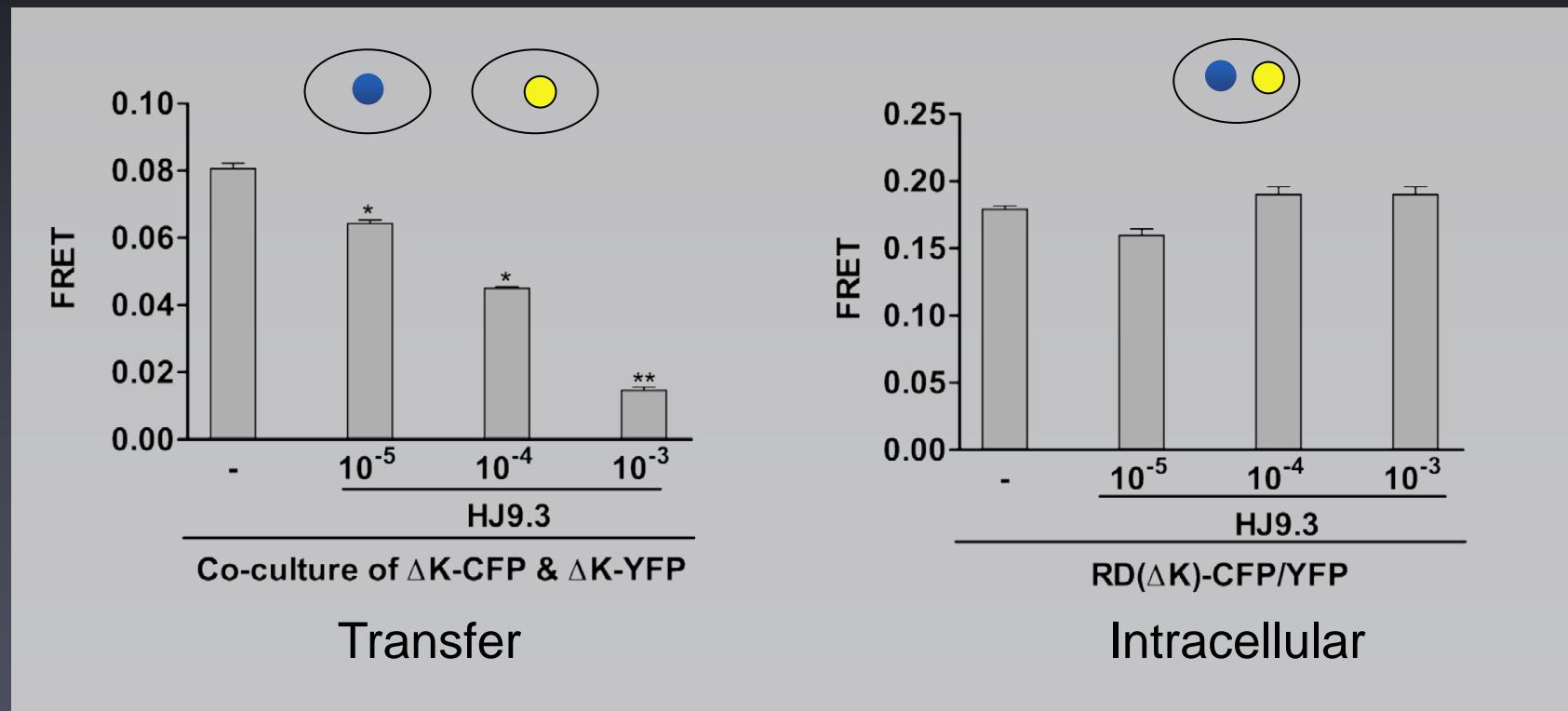
# Fibril Induction Measured by FRET



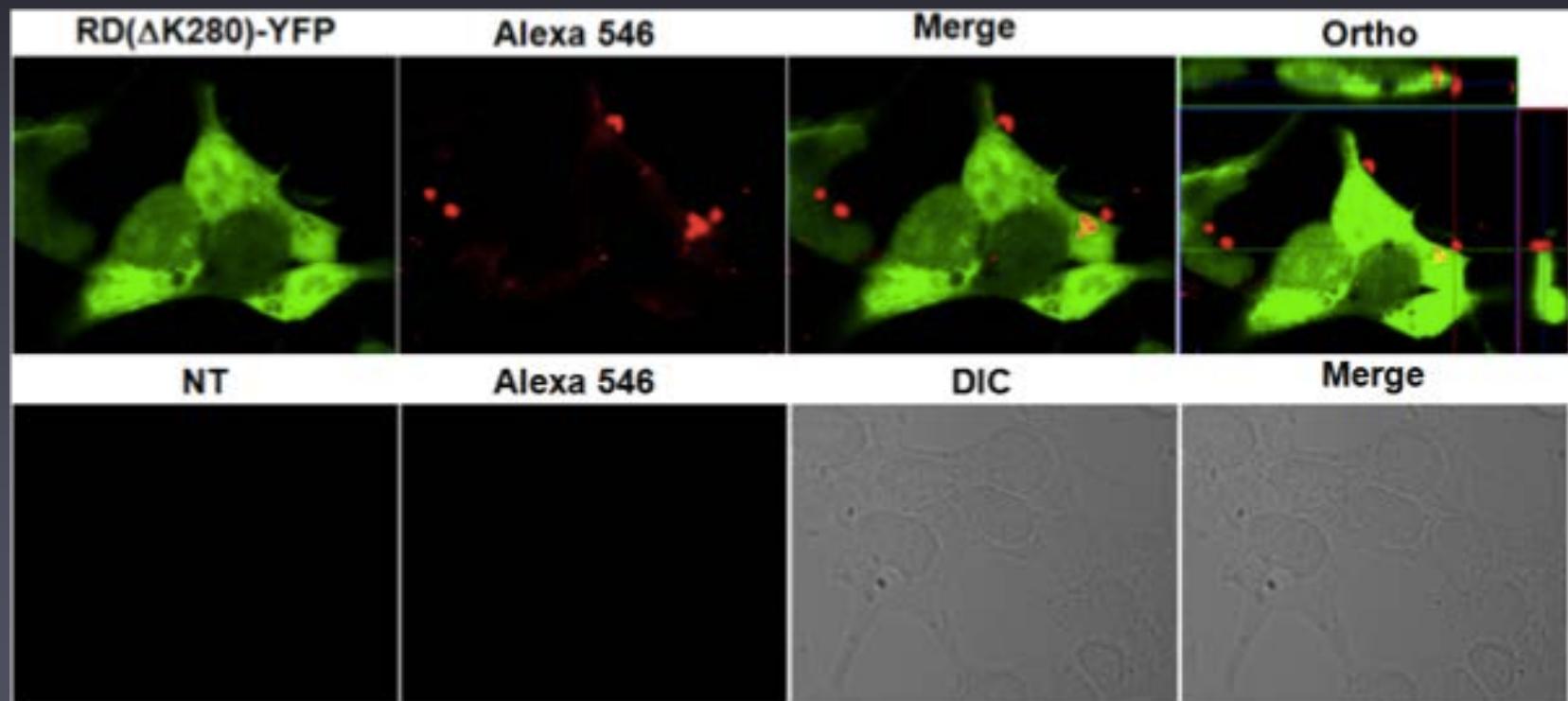
# Coculture: Trans-Cellular Induction of Aggregation



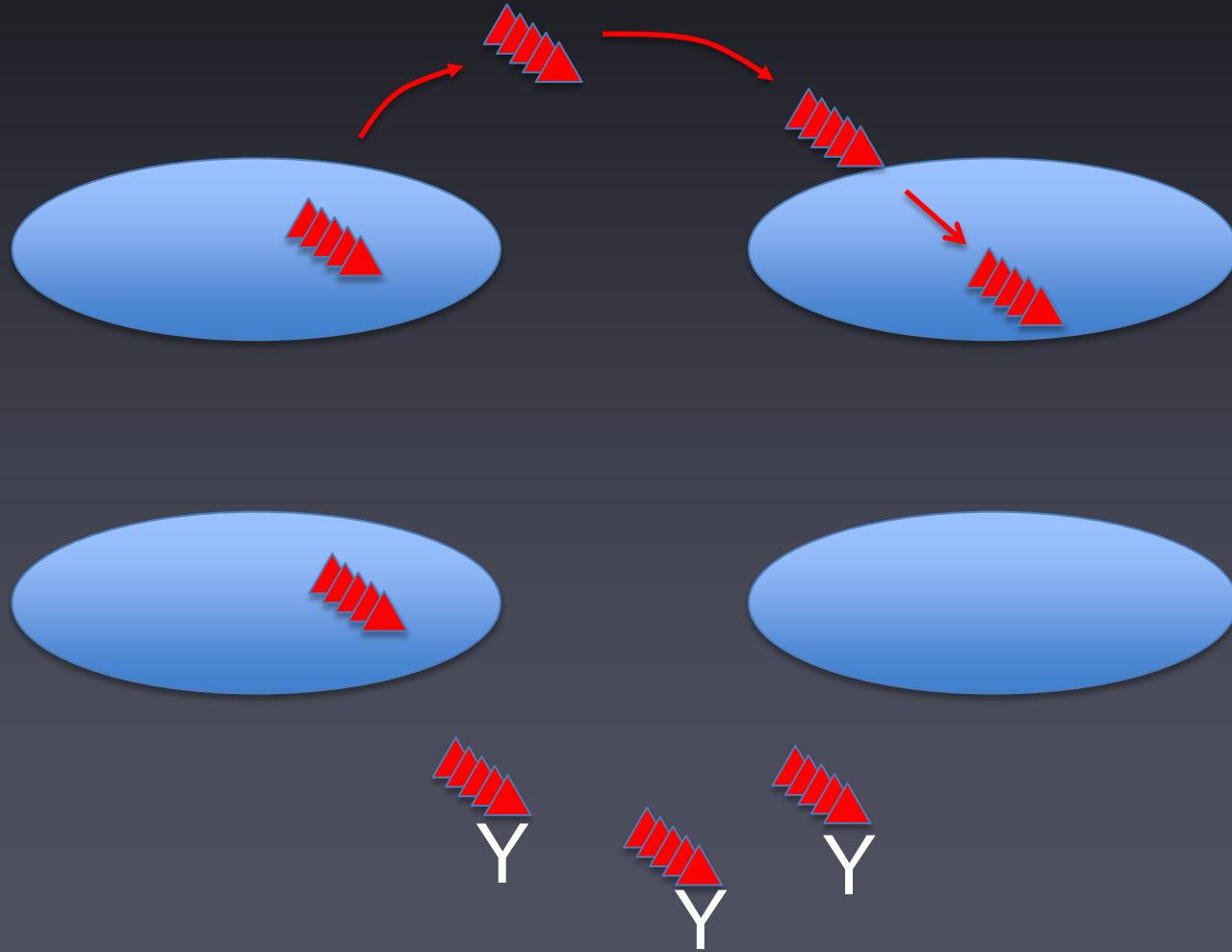
# HJ9.3 Blocks Propagation



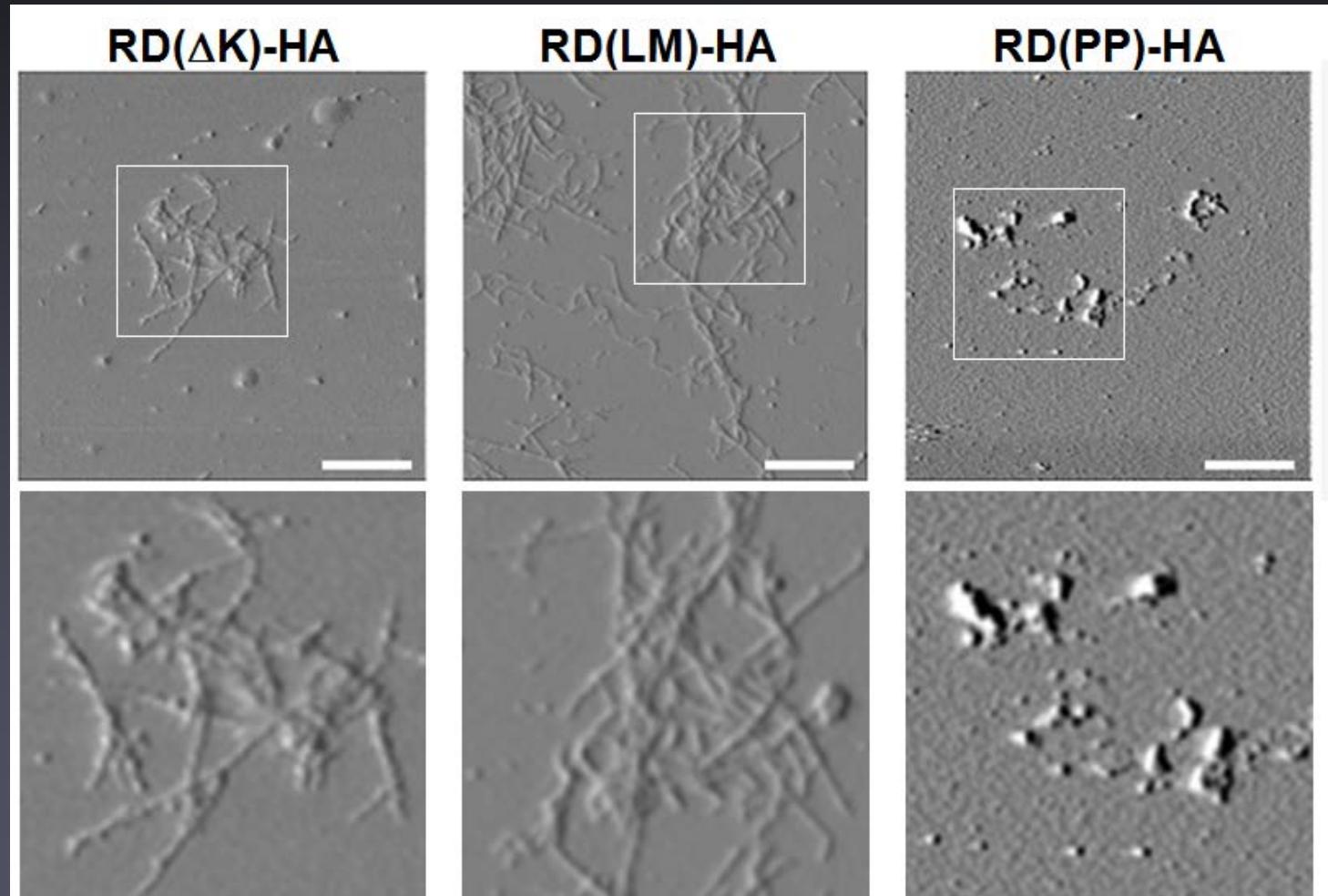
# HJ9.3 Traps Fibrils Outside the Cell



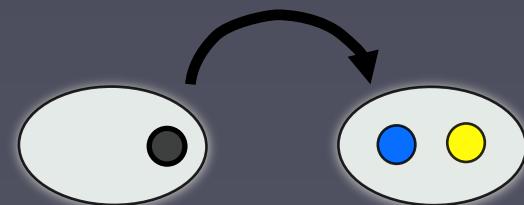
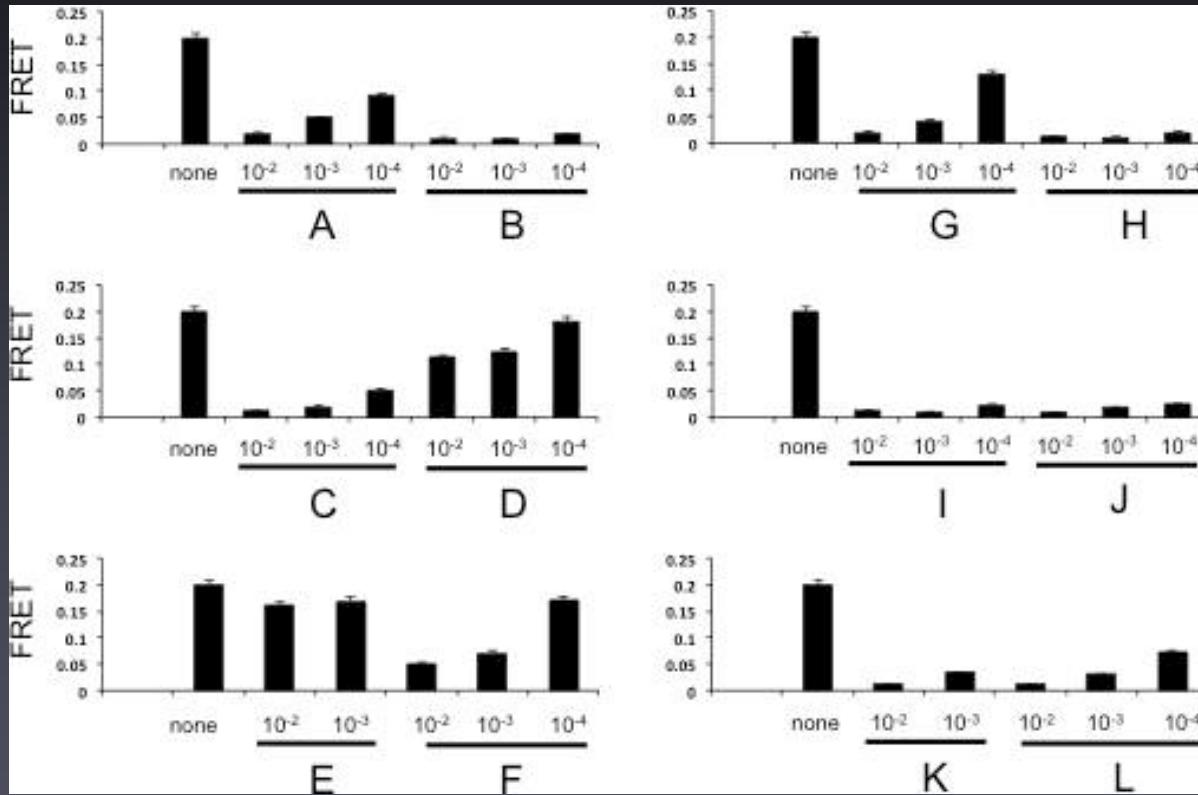
# Aggregate flux in and out of cells



# Tau Antibodies Trap Fibrils from Conditioned Medium



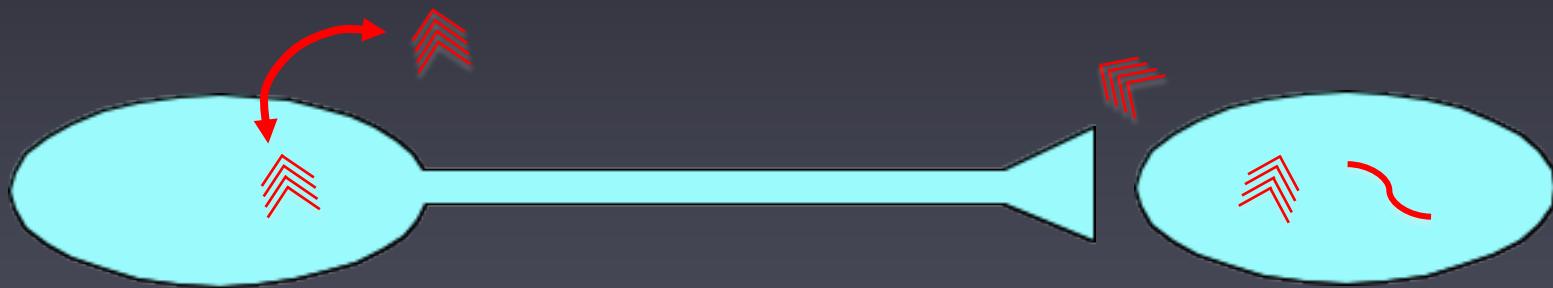
# Anti-Tau Monoclonal Antibodies Block Propagation



Najla Kfoury, Ph.D.  
Hong Jiang, Ph.D.

# New Opportunities for Diagnosis and Therapy

Antibodies  
Small molecules



Uptake  
Release  
Conversion

## Diamond Lab

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# One Tau Pathology, Multiple Diseases

