Trans-cellular propagation: New therapeutic and diagnostic strategies

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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
- ΔK280: increased
- ΔK280/PP: no beta sheet
- P301L/V337M: strongly increased
Fluorescence Readings from Cell Monolayers

\[ \lambda_{\text{ex}} \quad \lambda_{\text{em}} \]
Propagation of Misfolding

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

FRET
Tau fibrils approach the membrane
Tau fibrils are engulfed by the cell

John Heuser, M.D.  Mei Li, M.D., Ph.D.
Tau uptake by endocytosis
Tau uptake by endocytosis
External Tau Oligomers Induce Intracellular Tau Misfolding

monomer-treated

oligomer-treated
Fibril Induction Measured by FRET

Najla Kfoury, Ph.D.
Coculture: Trans-Cellular Induction of Aggregation

Najla Kfoury, Ph.D.
HJ9.3 Blocks Propagation

Co-culture of ΔK-CFP & ΔK-YFP

Transfer

Intracellular

Najla Kfoury, Ph.D.
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
New Opportunities for Diagnosis and Therapy

Antibodies
Small molecules

Uptake
Release
Conversion
Diamond Lab
Najla Kfoury, Ph.D.
Brandon Holmes
Angela Richmond, Ph.D.
David Sanders
Suzanne Schindler, M.D., Ph.D.
Kiran Yanamandra, Ph.D.
Hilda Mirbaha, M.D.
Ning Wang
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Support
NIH/NINDS, Hope Center, Knight-ADRC, MDA, AHAF, Broad Foundation, Tau Consortium, AstraZeneca
Clinical Diversity of Tauopathy