# Biphasic Dose Response in a Model of Tauopathy Utilizing Cyanine Dyes

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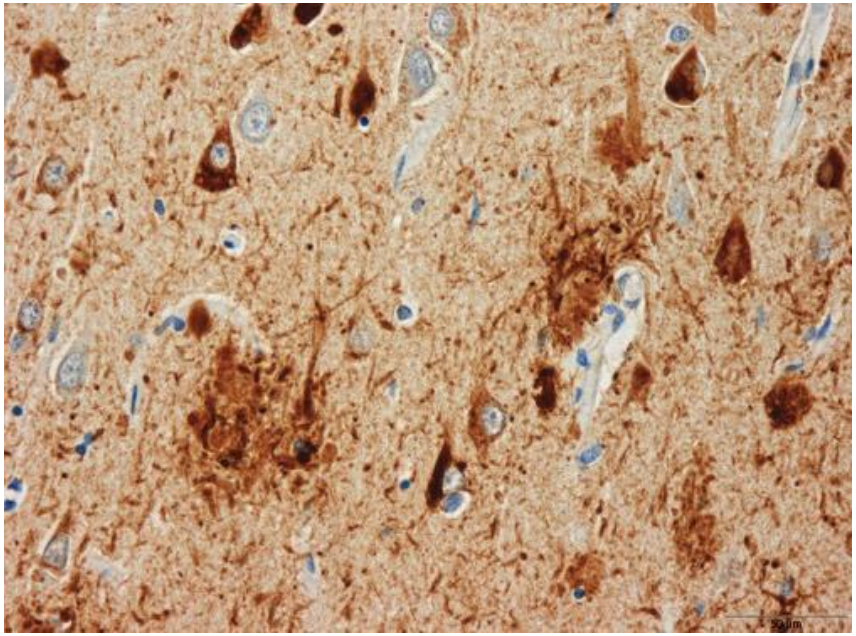
Columbia University Medical Center

Taub Institute for research on Alzheimer's Disease and the aging brain

-Many neurodegenerative diseases involve protein misfolding and polymerization

-Huntington's, Parkinson's, Alzheimer's, Prion diseases

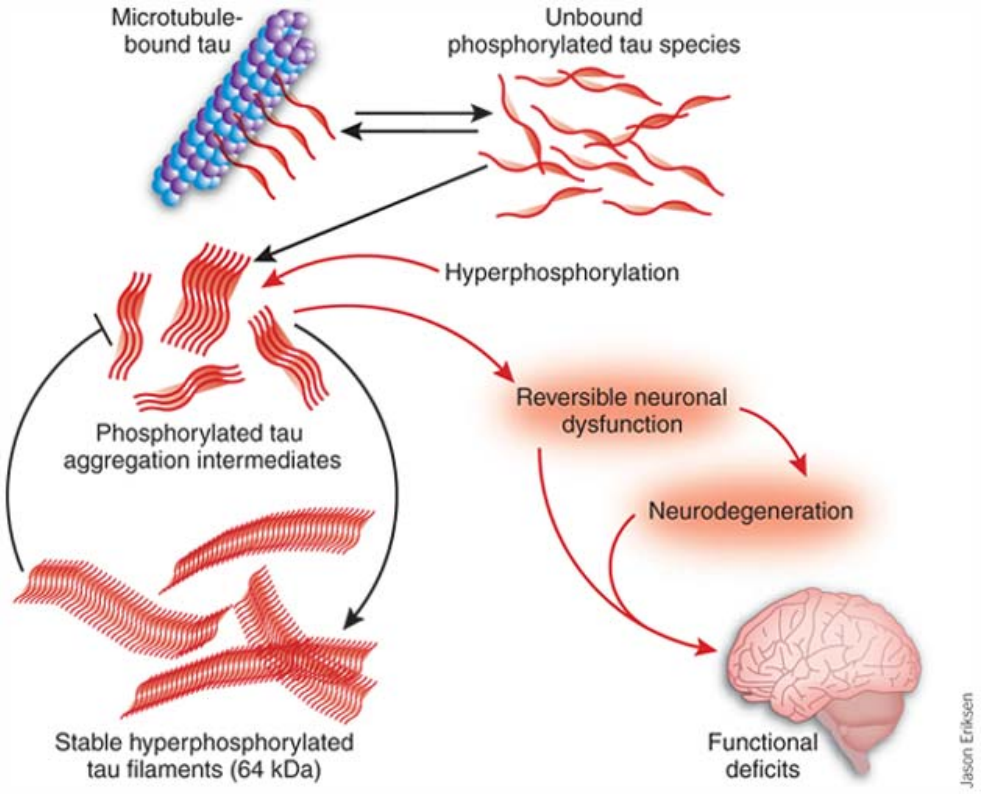
- AD is defined by the presence of amyloid-β plaques and neurofibrillary tangles composed of tau



-Tau pathology correlates with neurona loss and symptom severity

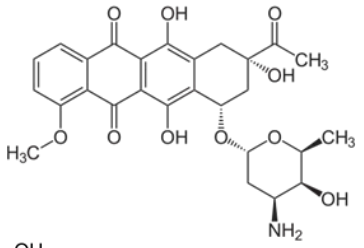
-Misfolded and polymerized tau is found in multiple conditions

-Tau is an attractive target for small molecules

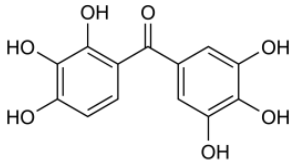


Several classes of molecules affect tau polymerization:

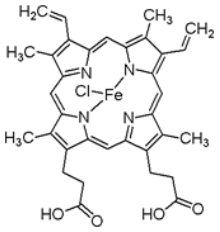
Anthraquinones



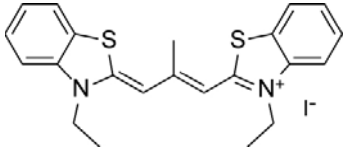
Polyphenols



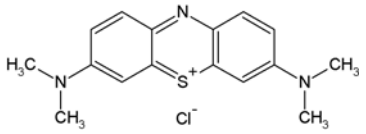
Porphyrins



Cyanine dyes



Phenothiazines



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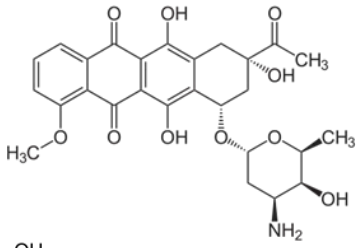

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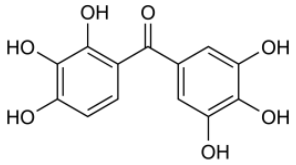

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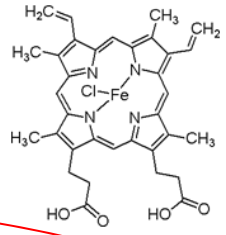

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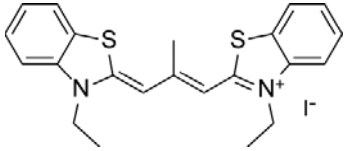

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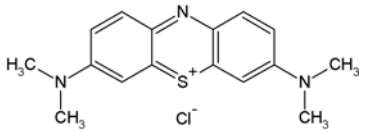

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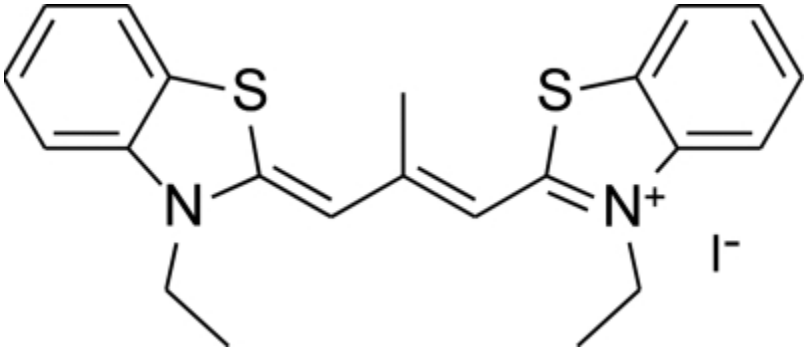
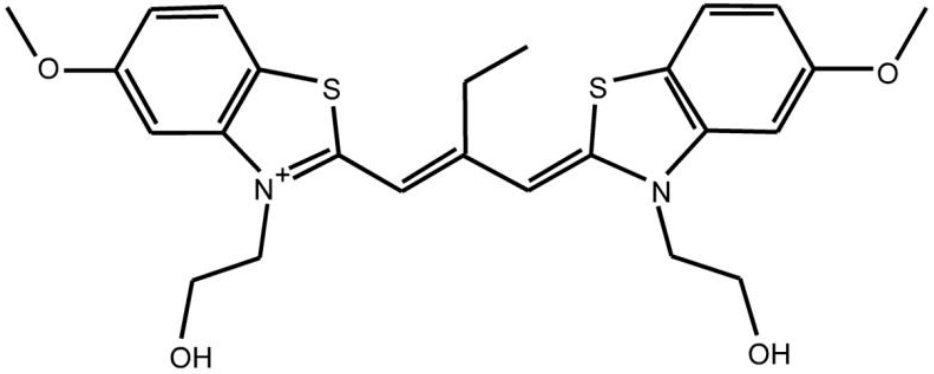
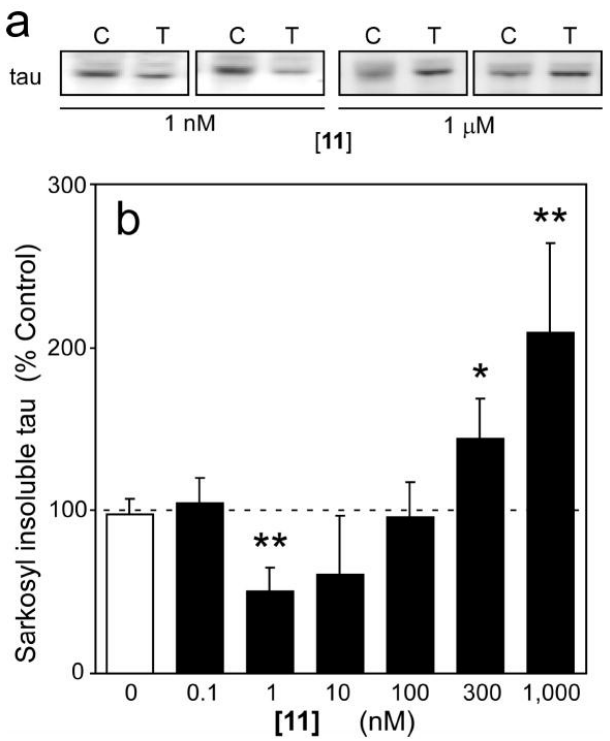


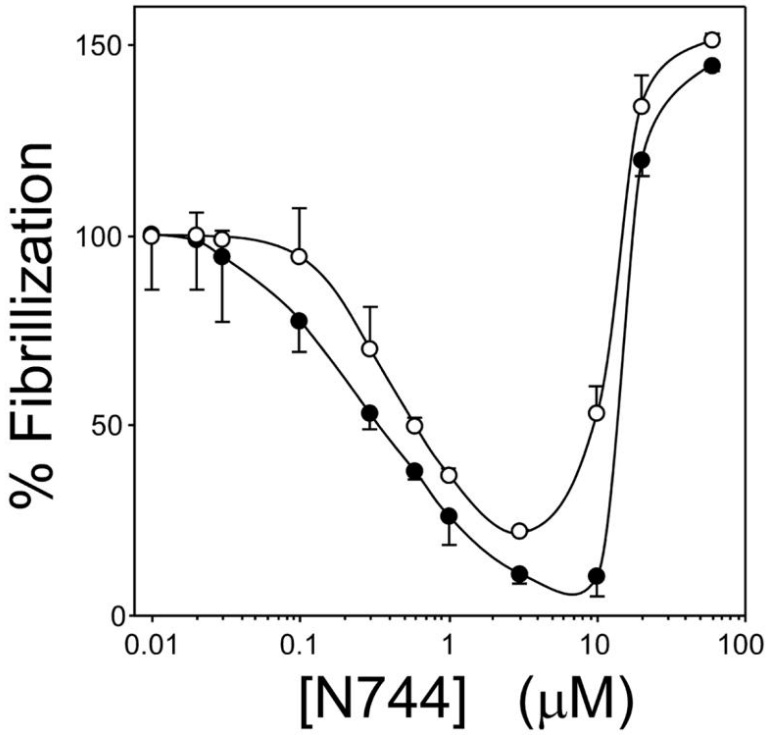

C11

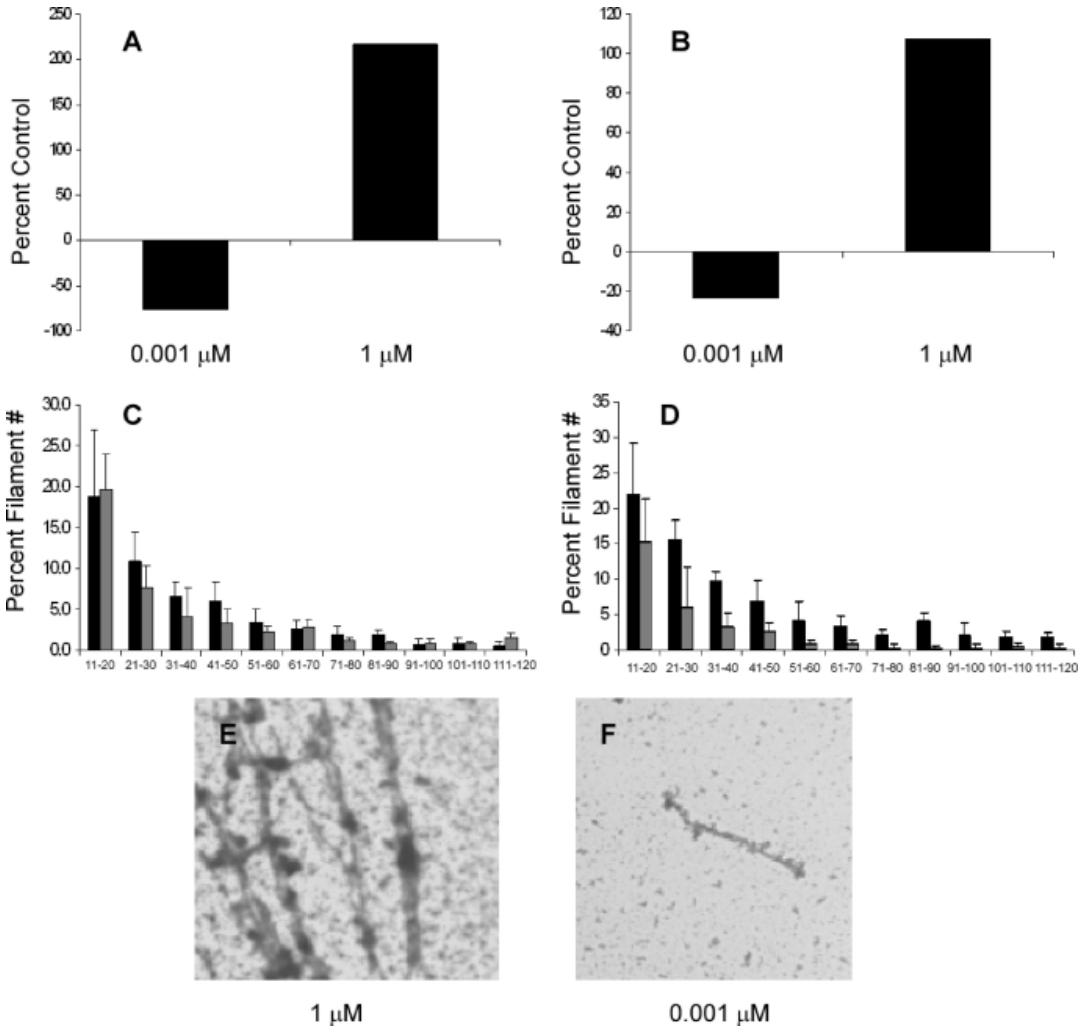



N744

# Cyanine Dyes Display Biphasic Dose Response Curves

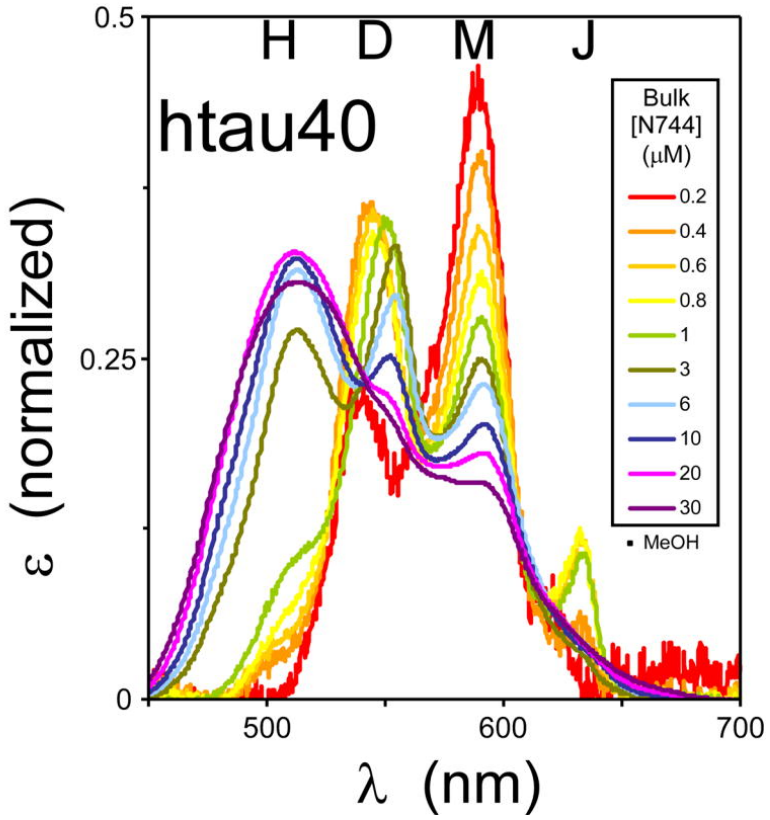



A
Percent Control
250
200
150
100
50
0
-50
-100
0.001 μM
1 μM
B
Percent Control
120
100
80
60
40
20
0
-20
-40
0.001 μM
1 μM
C
Percent Filament #
30.0
25.0
20.0
15.0
10.0
5.0
0.0
11-20
21-30
31-40
41-50
51-60
61-70
71-80
81-90
91-100
101-110
111-120
D
Percent Filament #
35
30
25
20
15
10
5
0
11-20
21-30
31-40
41-50
51-60
61-70
71-80
81-90
91-100
101-110
111-120
E
F
1 μM
0.001 μM

- Dye self-association as potential mechanism

# Dye Activity Correlates with Aggregation State



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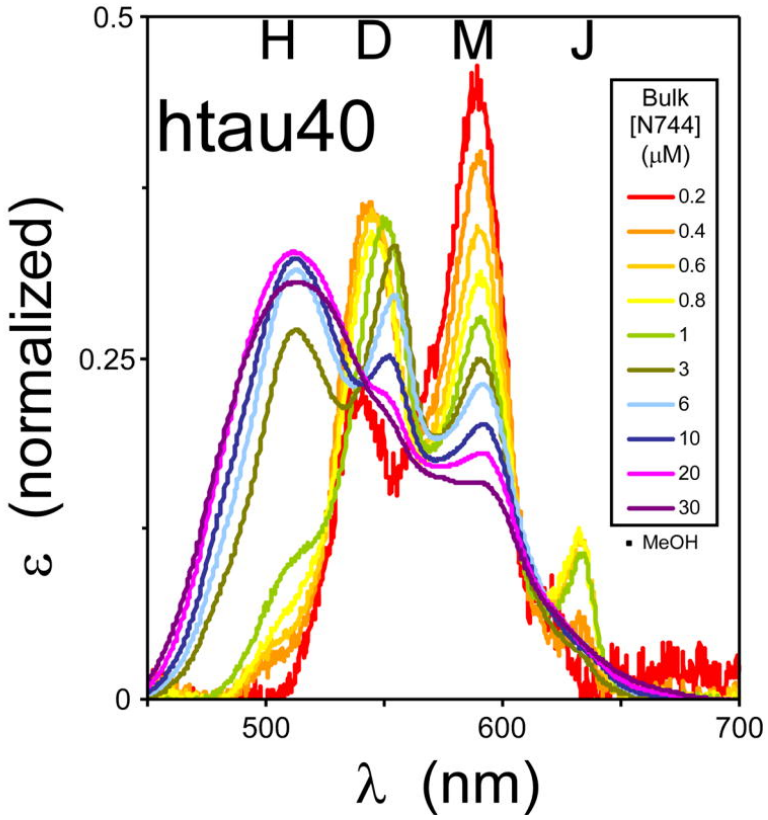
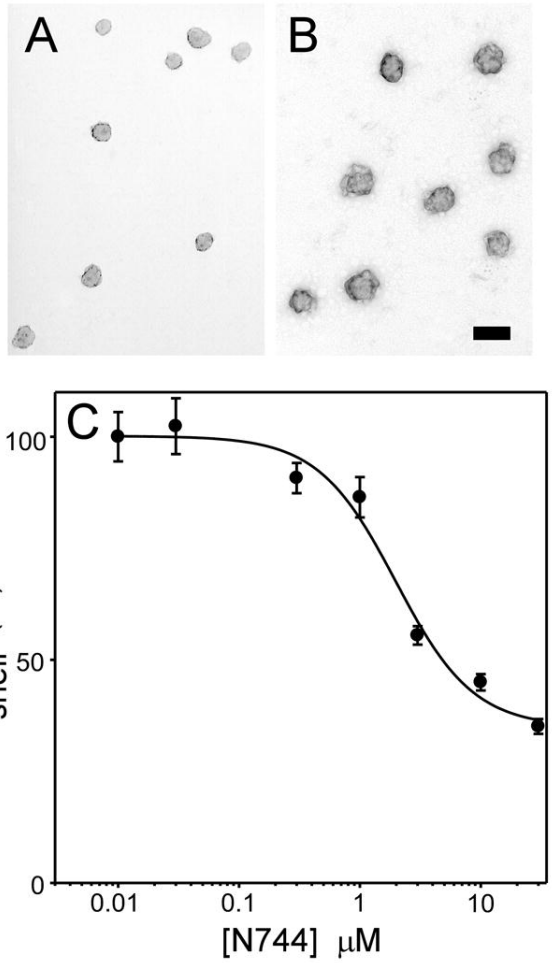
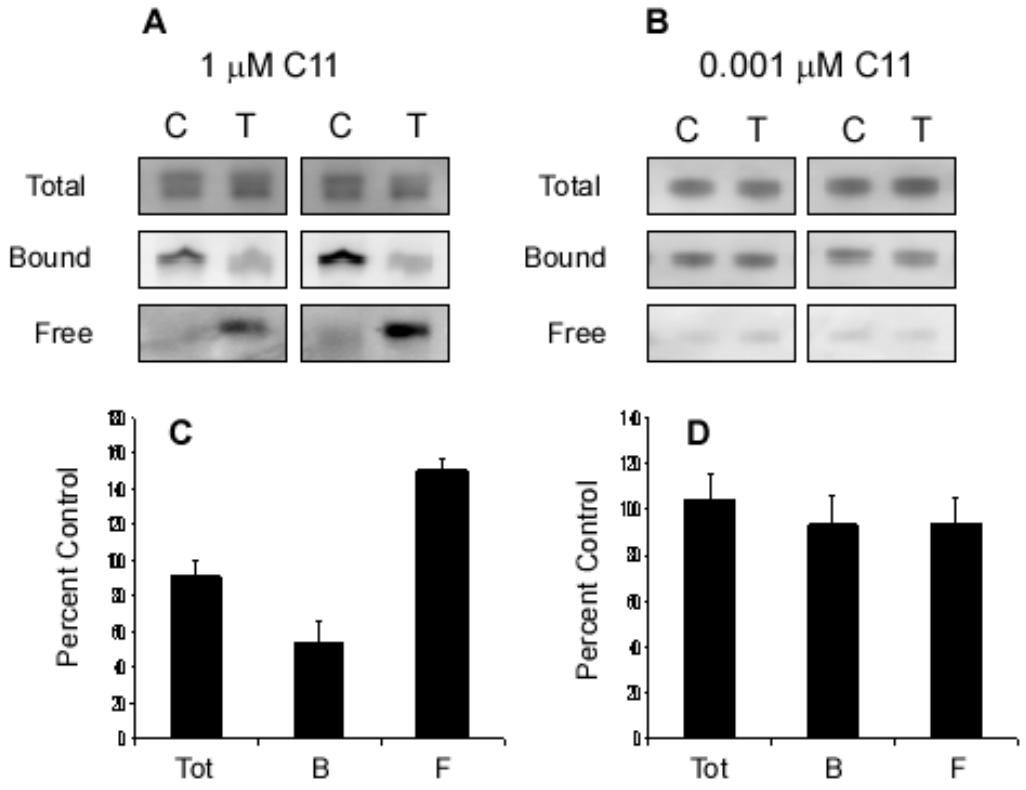
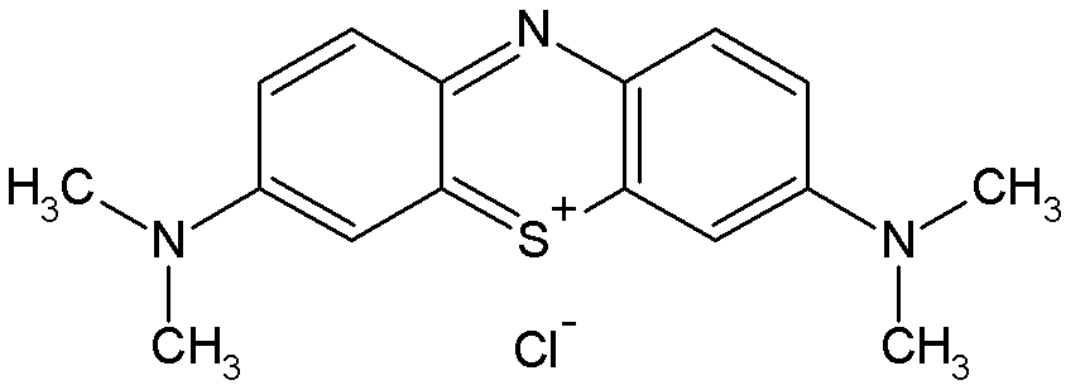


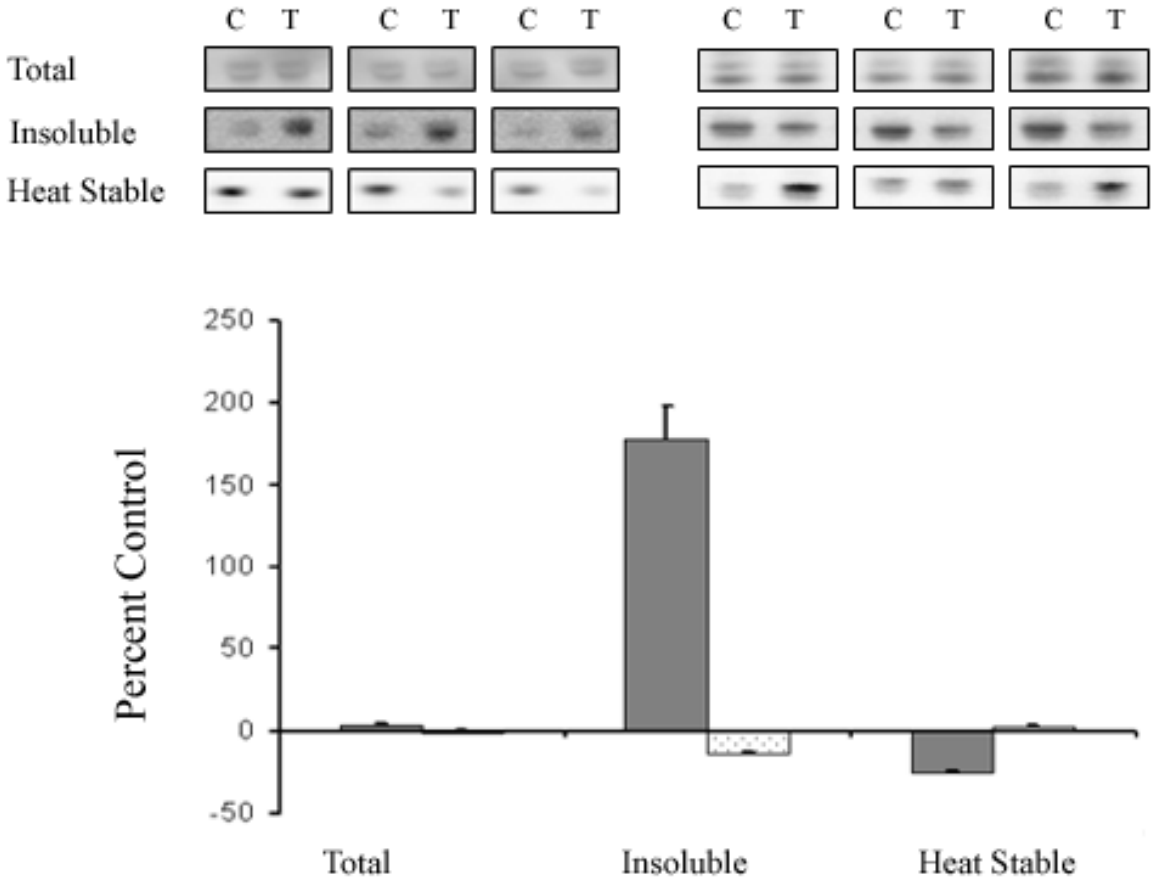
# C11 Disrupts Tau-Microtubule Binding



Phenothiazines




Methylene blue


C T C T C T C T C T C T
Total
Insoluble
Heat Stable
Percent Control
250
200
150
100
50
0
-50
Total
Insoluble
Heat Stable

-Both cyanines and phenothaizines are potent inhibitors of tau polymerization at sub-micromolar doses

-Both also produce biphasic dose response curves with dye concentration determining its effect

-Dye aggregation state represents a potential mechanism for this effect

-Small molecules which modulate polymerization have multiple uses

-Tau and other protein filaments are potential targets for therapeutics

-In disease multiple forms of tau are present
(monomers, oligomers, filaments)
- Modulating polymerization can give information regarding the toxic species

# Acknowledgments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COLUMBIA UNIVERSITY MEDICAL CENTER