Therini Bio

Translation Studies and Clinical Development of THN391, a Novel Anti-Fibrin Antibody for the Treatment of Dementia

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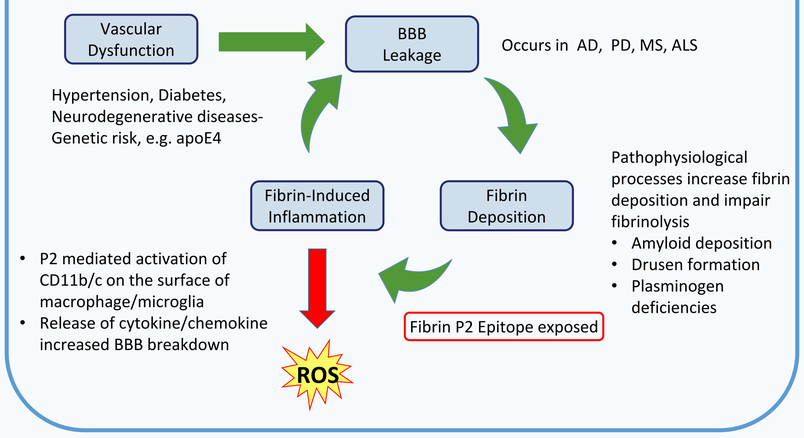
Abstract

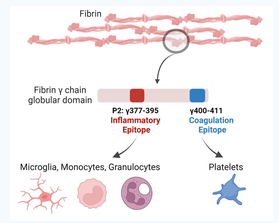
Vascular dysfunction, deposition of blood-derived fibrin and subsequent activation of innate immunity are central to many neurodegenerative diseases, including multiple sclerosis (MS), Alzheimer's disease (AD) and diabetic retinopathy (DR). Conversion of the blood coagulation protein fibrinogen to fibrin by thrombin exposes a cryptic epitope Fibγ377–395, termed P2, which can bind CD11b/CD18 and CD11c/CD18 on microglia, macrophages and dendritic cells and trigger an inflammatory response. The P2 inflammatory epitope is spatially and compositionally distinct from the coagulation epitope. Here, we present the development and preclinical efficacy of a first-in-class anti-fibrin P2 antibody for the treatment of inflammatory neurodegenerative disease. THN391 is a humanized and affinity matured therapeutic antibody. It has a 100-fold greater affinity for fibrin P2 and improved developability properties compared to its parent MAb, 5B8. THN391 is effective in experimental autoimmune encephalomyelitis (EAE) mouse models of MS. Treatment showed significant and consistent improvements in demyelination, inflammatory foci, and clinical disability scores. THN391 is effective in rodent models of ophthalmic disease. It significantly reduced disease in rat models of Diabetic retinopathy and macular degeneration. Treatment is as effective as VEGF antagonists in reducing laser-induced neovascular lesions, as measured by quantitative fluorescein angiography. THN391 does not bind fibrinogen and does not interfere with coagulation *ex vivo* in activated partial thromboplastin time and thromboelastography assessments. We have completed IND enabling studies and have initiated a phase1 trial in healthy subjects. Interim data shows THN391 to be safe and well tolerated with a half-life of ~50 days. We are planning a phase 1B study with appropriate biomarkers to support THN391 target engagement in Dementia and extend our understanding of the role of fibrin-mediated neuro inflammation in vascular diseases.

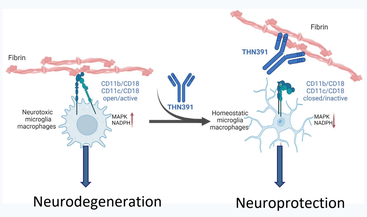
Loss of Vascular Integrity Results in Deposition of Toxic Fibrin (P2 epitope) Triggering An Innate Immune Cell-Mediated Inflammation Disease-Driving Mechanism for Neurological, Ocular & Systemic Diseases



Therini is Developing THN391, A First-In-Class Therapeutic Antibody Targeting the Fibrin P2 Epitope Responsible for Driving NeuroInflammation

Lead Development Candidate (THN391) Blocks NeuroInflammation but has no Impact on Hemostasis

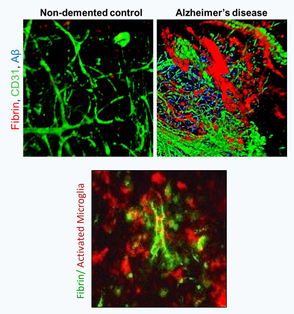




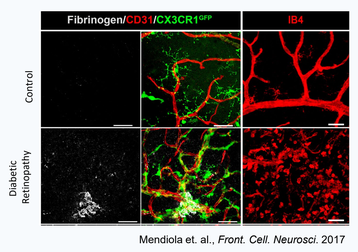
- Soluble fibrinogen is >3mg/ml in blood
- P2 epitope is "cryptic" on soluble fibrinogen
- P2 is physically and functionally separated from coagulation site
- Thrombin cleavage → Fibrin → P2 epitope
  - Ligand for CD11b/c → Activates innate immune cells
- Humanized IgG1 w/o effector function
  - Antagonist
  - Minimal risk to hemostasis
- Sub-nanomolar affinity for P2
- >1uM affinity for fibrinogen
- Blocks innate immune activation
- No impact on coagulation

Fibrin Deposition Drives Chronic Innate Immune Activation In Brain and Retinal Diseases

Fibrin is Associated with Amyloid Beta and Activated Microglia in the Brain in Neurodegenerative Diseases



Fibrin Deposition Leads to Microglial Activation in Retinal Diseases Hallmarked by Loss of Vascular Integrity



Mendiola et. al., *Front. Cell. Neurosci.* 2017

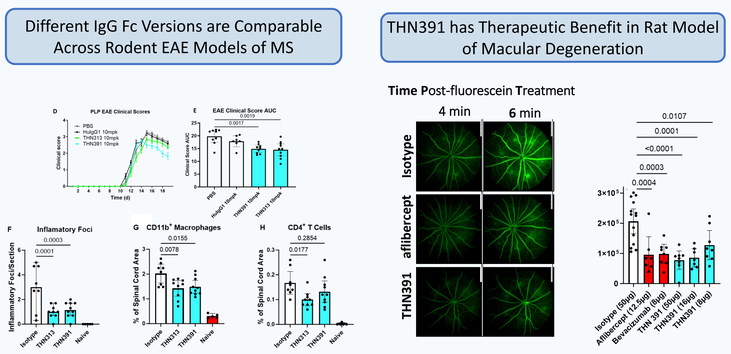
THN391 Is Best-In-Class Therapy For Treatment of Vascular Pathophysiology Leading to Alzheimer's Disease

THN391 Nonclinical Development Activities

- ✓ **Safe and Well Tolerated >100 mg/kg NOAEL**
- ✓ **Expected half-life in Humans > 1 month**
- ✓ GLP Tissue Cross Reactivity (Hu, NHP, Rat)
- ✓ Disposed drug substance and drug product to **support early clinical studies in dementia**
- ✓ Ongoing Study
  6 mo. **GLP Chronic Tox in NHP**

THN391 Blocks Disease Progression In Preclinical Models of Neurodegeneration and Maintains a Clean Safety Profile In In Vitro Models of Coagulation

Different IgG Fc Versions are Comparable Across Rodent EAE Models of MS

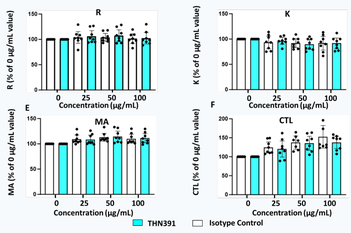


THN391 has Therapeutic Benefit in Rat Model of Macular Degeneration

Lead Development Candidate (THN391) harbors mutations in the IgG constant region that significantly limit antibody effector function to reduce risk of hemostasis

THN391 Shows No Interference in Blood Coagulation TEG/ROTEM Currently Performed as a Bedside Assay During our Phase 1 in Healthy Subjects

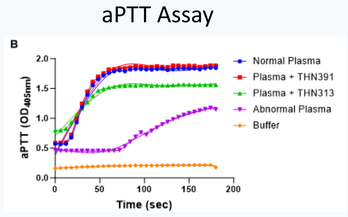
Thromboelastography (TEG) Assay



Human blood from 8-10 independent donors

- R: Time to initial fibrin deposition. Analogous to clot time
- K: Time until clot strength reaches a fixed value of 20 mm Kinetic Rate measurement
- MA: Maximum amplitude. Highly dependent on platelet content
- CLT: Clot Lysis Time. indicative of fibrin breakdown until no resistance is observed

aPTT Assay



- aPTT characterizes the rate and extent of fibrin polymerization
- All experiments performed using human plasma
- THN391/313 do not interfere with fibrin polymerization

THN391 Phase1 Study Interim Data Shows That it is Safe and Well Tolerated and Has A Remarkably Long Half-Life In Healthy Subjects

Study Initiated Q2 2023

SAD
5 NHV Cohorts *n* = 8 per cohort (6:2)
Sentinel Dosing in Cohort 1
Outcome Measures: safety/tolerability/PK/immunogenicity/*ex vivo* PD
Hematological assessments

MAD
4 NHV Cohorts *n* = 8 per cohort (6:2)
Cohorts 1-3: Q2W schedule
Cohort 4: Q4W schedule
Outcome Measures: safety/tolerability/PK/immunogenicity/*ex vivo* PD
Hematological assessments

Biologically-Enriched Dementia Cohort
Single Cohort *n* = 12
Open label, dosing schedule based on SAD/MAD data
Mild to moderate dementia patients; APOe4 homozygous carriers with high CSF fibrinogen
Outcome measures: safety, change from baseline in CSF biomarkers and EEG:ERP

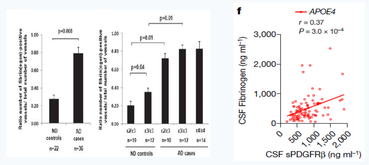
Completed: 0.3, 1.0 & 3.0 mg/kg
Ongoing: 10 mg/kg

Ongoing: 3 mg/kg; 2x weekly

- PK Supportive of monthly or less frequent dosing
- **No serious adverse events observed to date**
- **No infusion reactions/hypersensitivity events**
- **Clean hematologic profile**
- **Well tolerated to date**

Next Steps: Planning Biomarker Study

ApoE4 and CSF Fibrinogen Patient Enrichment Strategy



- Fibrinogen (300kD) levels in CSF have been used as a marker for loss of BBB integrity
- Paired CSF/Serum measurements of Fib, Alb and IgG to determine contribution of blood derived proteins to CSF

Phase 1B Clinical Development Plan*

Strategic Planning:

CONDUCT:

In collaboration w/ large pharma with AD experience, leveraging expertise & AD trial experience and relationships (e.g., CRO's, sites, contracts)

DESIGN:

- Population:
  - Enriched patient population of mild to moderate AD, inclusion criteria based on MMSE, plasma pTau and sMRI
  - 48 patients; 2:1 randomization
- DURATION: 6 mo. treatment duration, up to 6 mo. follow-up
- TRIAL BIOMARKERS: Amyloid(Aβ40, Aβ42) and tau; Neurodegeneration(t-tau, p-tau, Nfl, VILIP-1); Primary response markers - Microglial (sTREM2, sCSF1R, IL1RN, SPP1 (osteopontin); Astrocyte (YKL-40, GFAP, S100B); *Cytokine/ chemokine* Panels

*** Currently seeking additional investment to support trial**

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