A Novel Anti-Fibrin Antibody to Treat Neurodegenerative Ocular Diseases

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Abstract

Purpose Vascular dysfunction causing leakage of plasma proteins like fibrinogen, deposition of fibrin and subsequent activation of innate Immune cells is a central mechanism underlying neurodegenerative ocular diseases, including diabetic retinopathy (DR), diabetic macular edema (DME) and age-related macular degeneration (AMD). Conversion of the blood coagulation protein fibrinogen to fibrin by thrombin exposes the inflammatory P2 epitope, which is cryptic on soluble fibrinogen. This inflammatory epitope is a ligand for CD11b/CD11c (complement receptor CR3 and CR4) which are found on microglia and macrophages. Recruitment of these cells can result in chronic inflammation. We developed a first-in-class humanized anti-fibrin inflammatory epitope antibody, THN3391, to treat toxic inflammation in neurodegenerative disease and tested it in animal models of ocular diseases.

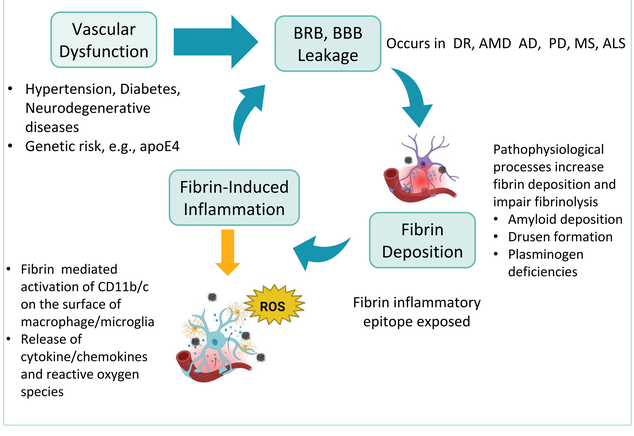
Methods We evaluated THN391 in a rat laser-induced choroidal neovascularization (LCNV) model that is used to assess wet AMD. Rats were lasered on Day 0 and injected with THN391, isotype control, or VEGF antagonists (VO-CRO, Nashville, TN). Lesion permeability was assessed by non-invasive quantitative fluorescein angiography (qFA). The extent of CNV was measured post-mortem using image analysis of isolectin-B4-stained choroidal flat-mounts. We also evaluated THN393 (mouse chimeric THN391) in a murine STZ model of DR. Diabetes was induced with daily STZ injections, Weekly IP injections were given to 3 groups: 1) nondiabetic, isotype control, 2) diabetic, isotype control and 3) diabetic.

Results: THN391 shows efficacy in the LCNV model, reducing both CNV area and the permeability of the laser-induced neovascular lesions, measured non-invasively by qFA. qFA was performed longitudinally at 7-, 14- and 28-days post-laser. On Day 7 and Day 14, THN391 and control VEGF antagonists (aflibercept and bevacizumab) significantly reduced lesion permeability. Lesions show recovery on their own by Day 28. In the STZ model, chimeric mouse THN391 (THN393) results were directionally similar as measured by qFA although did not reach statistical significance.

Conclusion: Our results support further clinical development of THN391 to treat neurodegenerative ocular diseases. The role of macrophages may contribute to the resistance and/or loss of efficacy of the VEGF antagonists in retinal diseases. THN391 alone, or in combination with VEGF antagonists, has the potential to treat these diseases and overcome a key resistance mechanism.

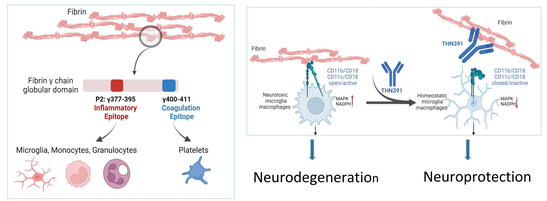
Fibrin is a Nidus of Innate Immune Cell-Mediated Inflammation

- **Loss of vascular integrity results in deposition of fibrin**
- **Fibrin inflammatory epitope triggers immune cell-mediated inflammation**
- **This is a driving mechanism for neurological, ocular & systemic diseases**



Therini is developing THN391, a first-in-class therapeutic antibody targeting the fibrin inflammatory epitope responsible for driving neuroInflammation

THN391 blocks neuroInflammation but has no Impact on hemostasis

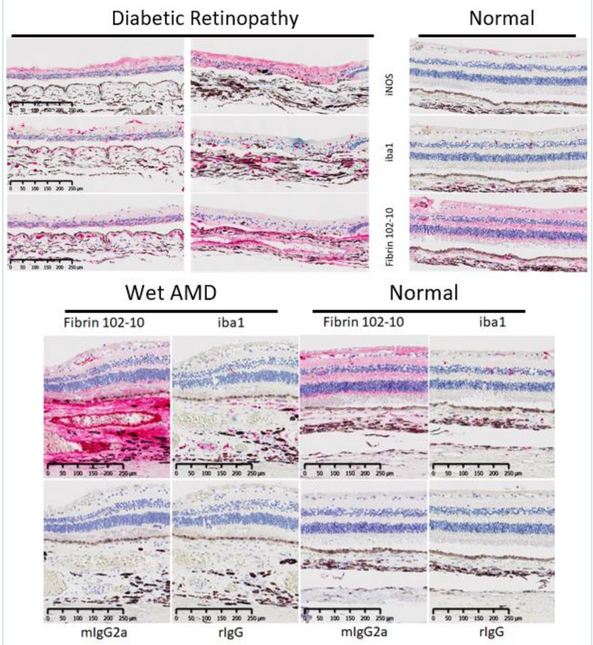


- Inflammatory epitope is cryptic on soluble fibrinogen
- Inflammatory epitope is physically and functionally separated from coagulation site
- Thrombin cleavage → Fibrin → Inflammatory epitope
  - Ligand for CD11b/c → Activates innate immune cells
- Humanized IgG1 w/o effector function
  - Antagonist
  - Minimal risk to hemostasis
- < 1 nM affinity for inflammatory epitope
- >1 uM affinity for fibrinogen
- Blocks innate immune activation
- No impact on coagulation

Kantor, Akassoglou, Stavenhagen (2023). *J Prev Alzheimers Dis*

DR and wet AMD tissues display high levels of fibrin deposition and associated increase in activation of innate immune cells

- Increased microglia/macrophage activation (iba1/iNOS) staining
- Fibrin deposition in the choroid of diabetic retinopathy and AMD



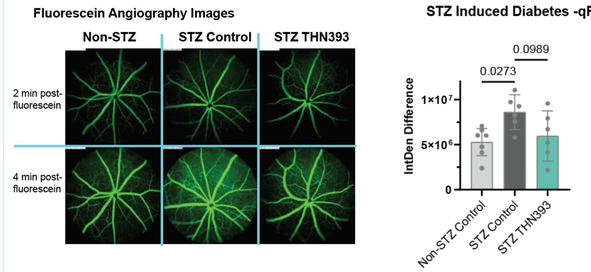
Whole eyes (minus cornea) were obtained from Eversight
Red detection for named markers
Hematoxylin counterstain for nuclei (blue)
Brown color is endogenous melanin

Kimberly Thomas, Therini Bio

THN391/313 binds to the rodent fibrin inflammatory epitope

Species	Fibrin P2 Epitope Sequence	EC50 (nM)
Human	YSMKKTTMKIIPFNRLTIG	0.21 ± 0.14
Rabbit	YSMKETTMKIIPFNRLSIG	0.16 ± 0.13
Rat/Mouse	YSMKKTTMKIIPLNRLSIG	0.14 ± 0.12

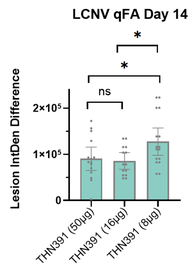
THN393 is effective in the mouse STZ model of diabetic retinopathy



Results shown are individual eyes, mean ± 95% CI.
One-way ANOVA, Dunnett multiple comparisons to the isotype control.

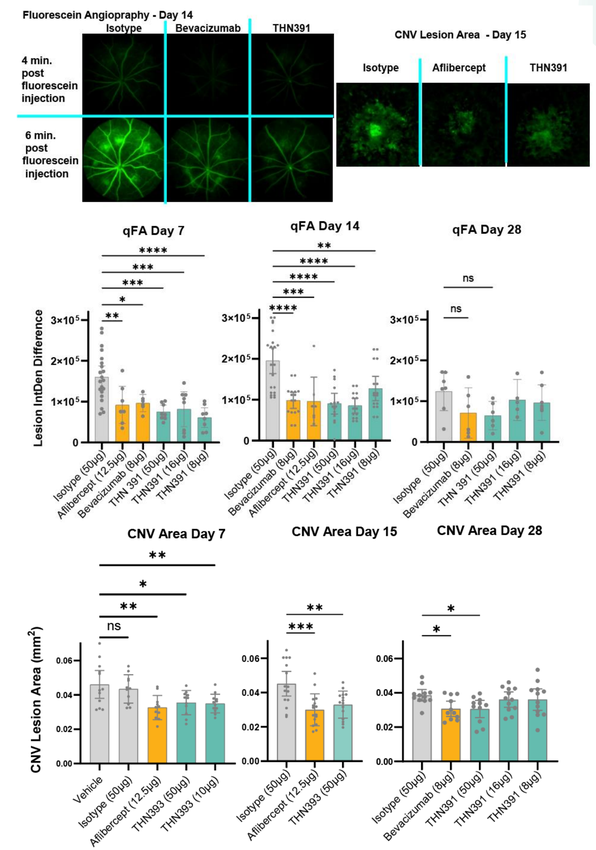
Dose-dependent effect in rat LCNV model informs human dosing

Species	Vitreous Vol (mL)	High Dose (µg/eye)	Low Dose (µg/eye)
Rat	0.02	50	16
Human	4	10,000	3,200



Results shown are individual eyes, mean ± 95% CI
Unpaired t-test.

THN391 is effective in the rat LCNV model of wet AMD



Results shown are individual eyes, mean ± 95% CI.
One-way ANOVA, Dunnett multiple comparisons to the isotype control..

Conclusions

- We are developing THN391, a first-in-class therapeutic monoclonal antibody targeting the fibrin inflammatory epitope responsible for driving neuroinflammation.
- THN391 is currently in a Phase 1 trial to assess safety, tolerability and pharmacokinetics in healthy subjects following intravenous injection of single or multiple ascending doses. THN391 has been safe and well-tolerated to date.
- We demonstrated the effectiveness of intravitreal THN391 in the rat LCNV model of wet age-related macular edema (AMD) and the mouse STZ model of diabetic retinopathy.
- We are planning a Phase 1b/2a study of intravitreal THN391 in diabetic macular edema (DME).
- The dose titration in the rat LCNV model informs on effective doses for human retinal diseases.
- Macrophage-induced inflammation may contribute to the resistance and/or loss of efficacy of the VEGF antagonists in retinal diseases. THN391 alone, or in combination with VEGF antagonists has the potential to improve treatment outcomes.

Acknowledgements

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