

Targeting plasma kallikrein with a novel bicyclic peptide inhibitor (THR-149) reduces retinal thickening in a diabetic rat model

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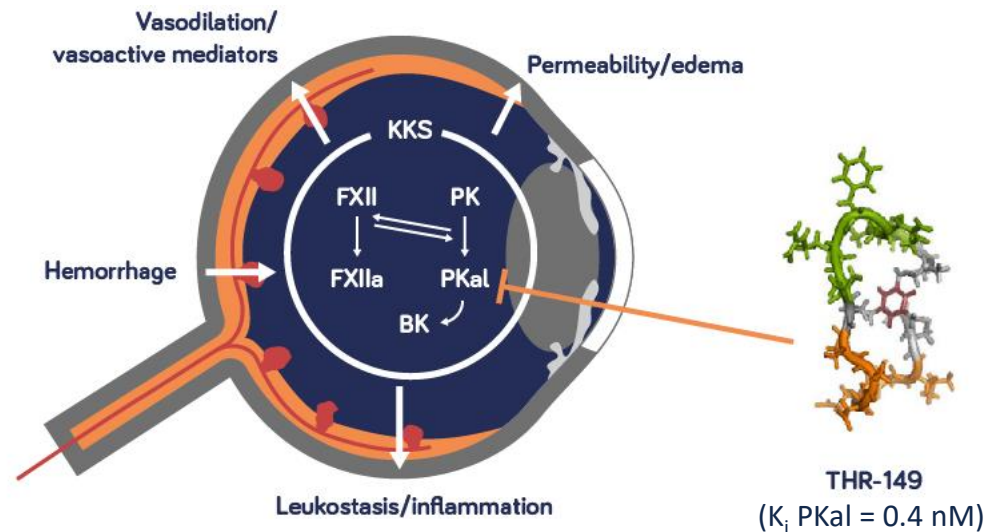
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THR-149: Highly potent plasma kallikrein inhibitor for DME

Highly potent, selective and stable peptide targeting Plasma Kallikrein



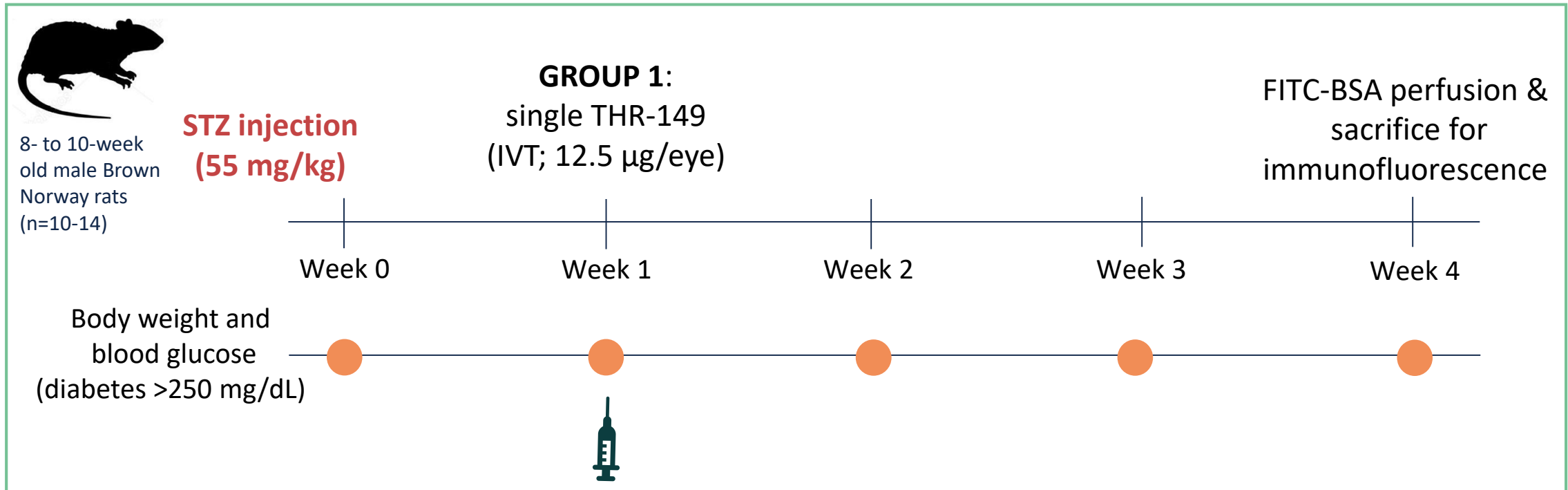
- Plasma Kallikrein is a clinically well validated target for edema, inflammation, and the prevention of microhemorrhages
 - PKal and bradykinins are elevated in diabetic eyes
 - Bradykinins cause retinal edema
 - PKal inhibition lowers bradykinins and reduces edema in the retina
- THR-149 was developed in partnership with Bicycle Therapeutics

Objective and methods

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To investigate the effect of plasma kallikrein (PKal) inhibition, using THR-149, on retinal thickening in the streptozotocin (STZ)-induced diabetic rat model.

Methods



Statistical analysis: one-way ANOVA between control and treatment with Bonferroni's multiple comparisons post hoc test.

Data presentation: data are shown as mean \pm SEM * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Anti-VEGF (IP; 2 mg/kg; 3x/week, week 1 until week 3) was included as positive control.

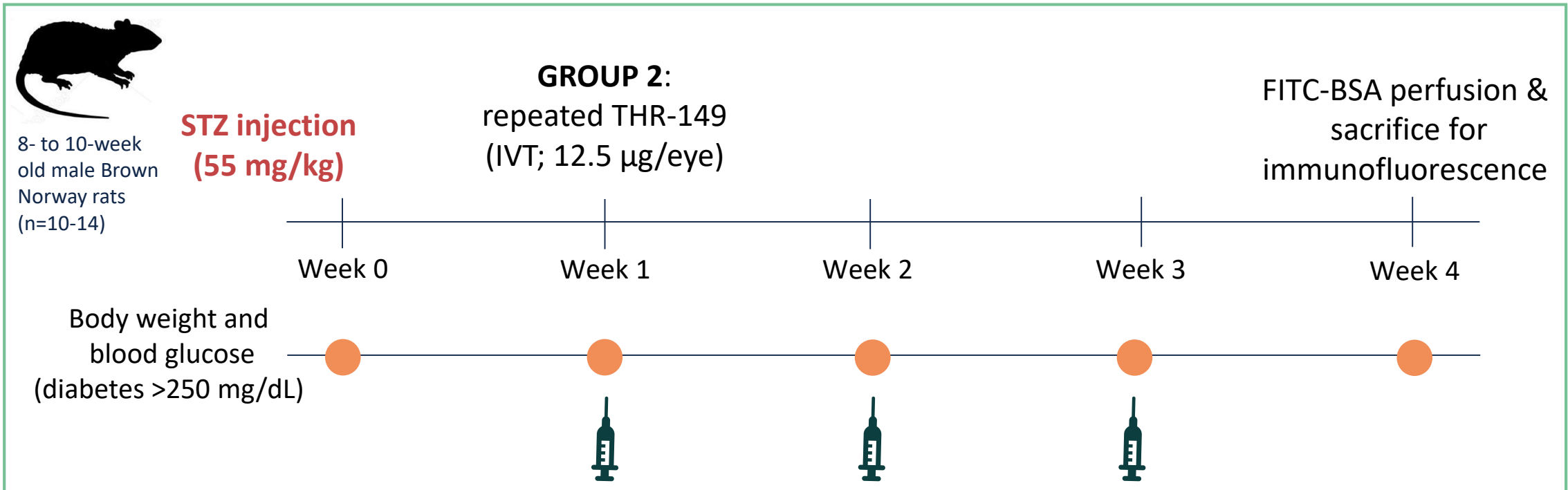
IVT: intravitreal; IP: intraperitoneal; FITC-BSA: fluorescein isothiocyanate labelled bovine serum albumin

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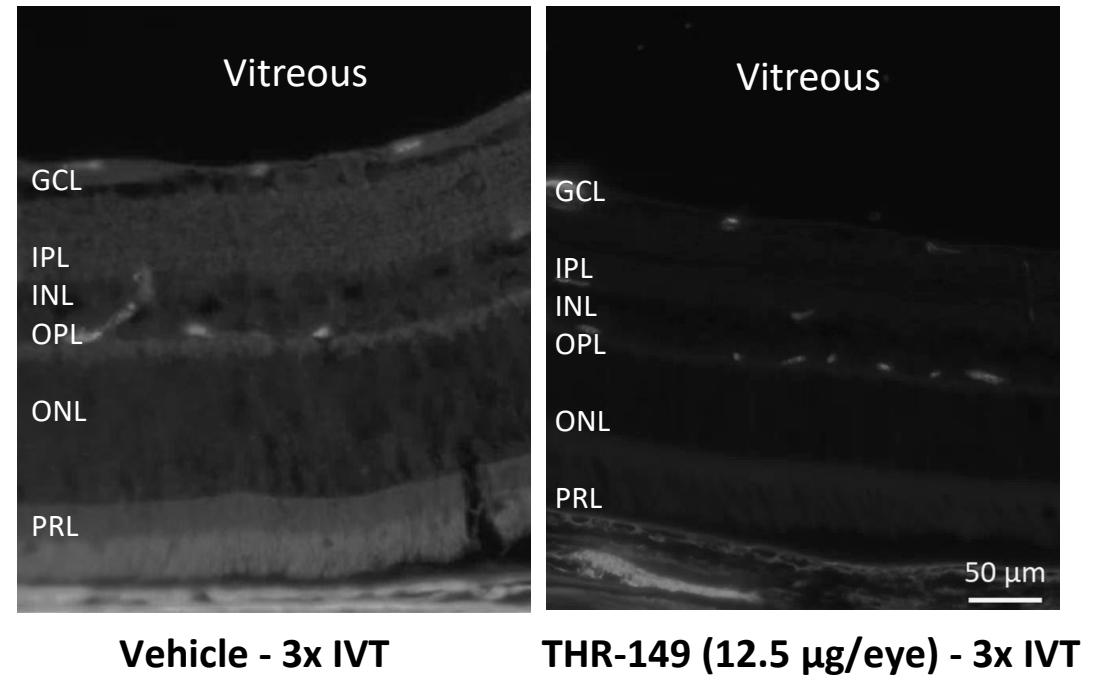
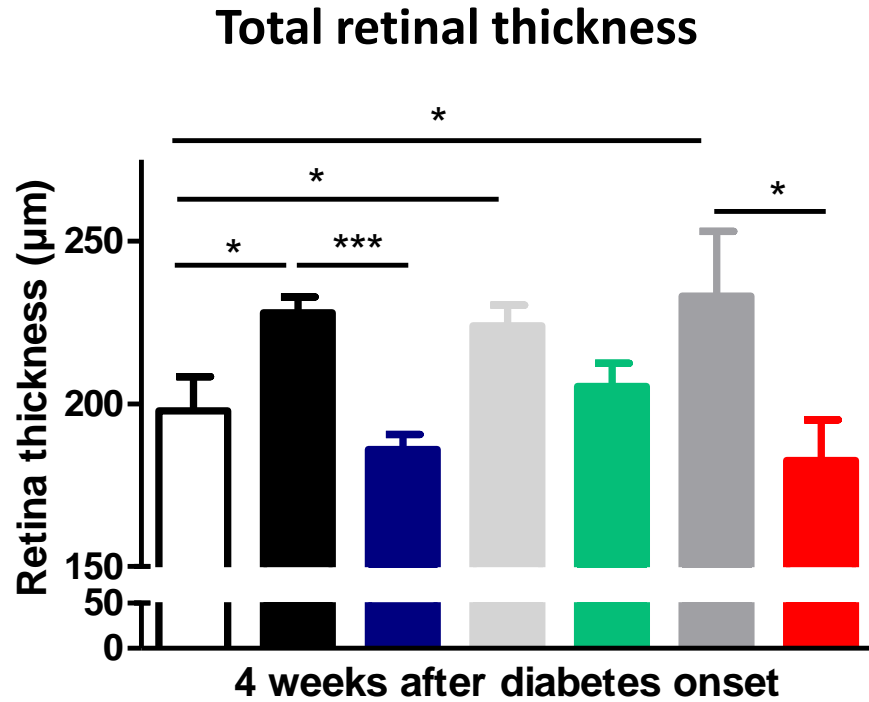
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Repeated IVT administration of THR-149 reduces diabetes-induced total retinal thickening



- Non-diabetic
- Diabetic, buffer VEGF-Trap
- Diabetic, VEGF-Trap
- Diabetic, buffer of THR-149 (1x IVT)
- Diabetic, THR-149 (1x IVT)
- Diabetic, buffer of THR-149 (3x IVT)
- Diabetic, THR-149 (3x IVT)

Analysis: 4 weeks after diabetes onset:

Histological sections to assess retinal thickness

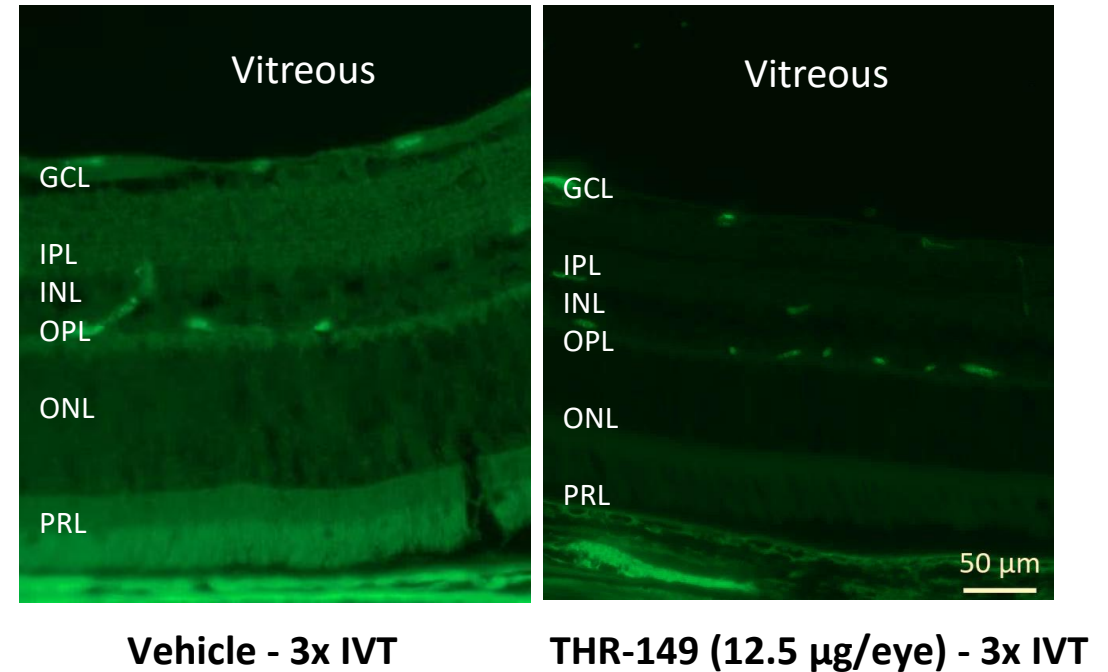
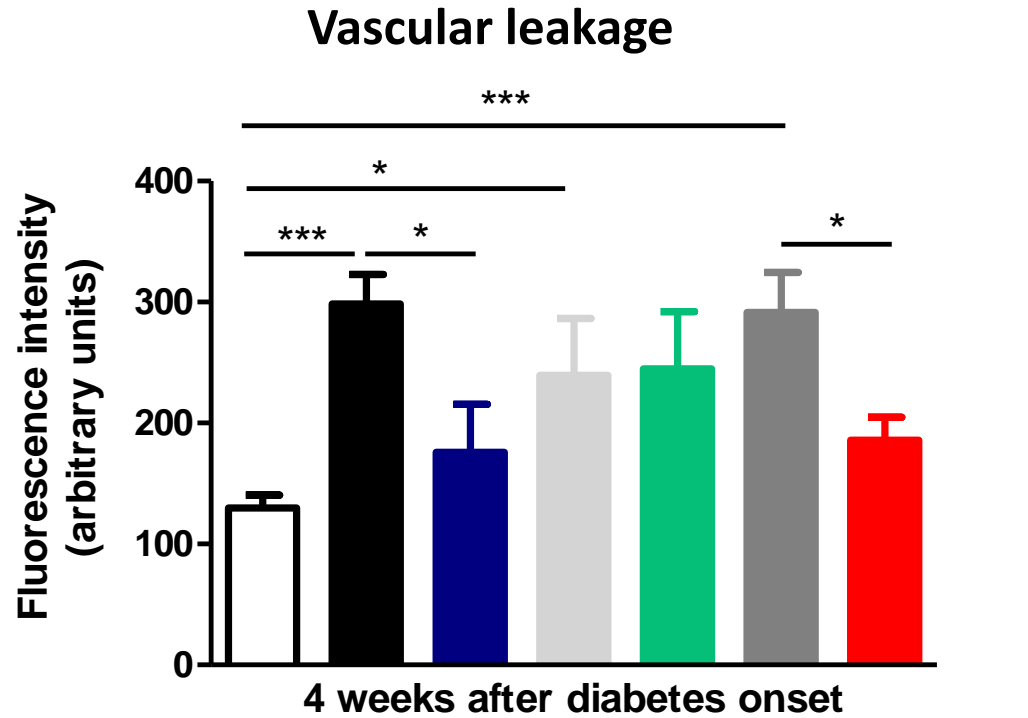
GCL: ganglion cell layer, IPL: inner plexiform layer, INL: inner nuclear layer, IVT: intravitreal, OPL: outer plexiform layer; ONL: outer nuclear layer; PRL: photoreceptor layer

Repeated IVT administration of THR-149 results in reduction of diabetes-induced thickening of specific retinal layers

Retinal layer	Increase in Retinal Thickness (µm)	Diabetes • Reduction in Retinal Thickness (µm) Inhibitor vs. proper vehicle		
	Non-diabetes vs. Diabetes	VEGF-Trap 2.0 mg/kg, 3x IP	THR-149 12.5 µg/eye, 1x IVT	THR-149 12.5 µg/eye, 3x IVT
GCL	1.70 ± 1.07	2.27 ± 0.85	1.12 ± 1.05	2.33 ± 0.56
IPL	19.66 ± 2.54**	11.80 ± 2.56*	8.72 ± 3.01	24.83 ± 2.49***
INL	7.00 ± 2.25**	6.98 ± 1.90*	2.91 ± 1.75	8.73 ± 1.89**
OPL	3.36 ± 0.55	1.50 ± 0.75	0.37 ± 0.64	4.70 ± 0.67
ONL	26.03 ± 1.78***	22.60 ± 1.61**	9.99 ± 3.12 (p=0.06)	26.13 ± 1.05***
PRL	12.65 ± 2.29**	12.79 ± 2.17*	- 0.33 ± 3.39	18.78 ± 1.93***

Mean ± SEM * p<0.05, ** p<0.01, *** p<0.001

Repeated IVT administration of THR-149 reduces diabetes-induced vascular leakage

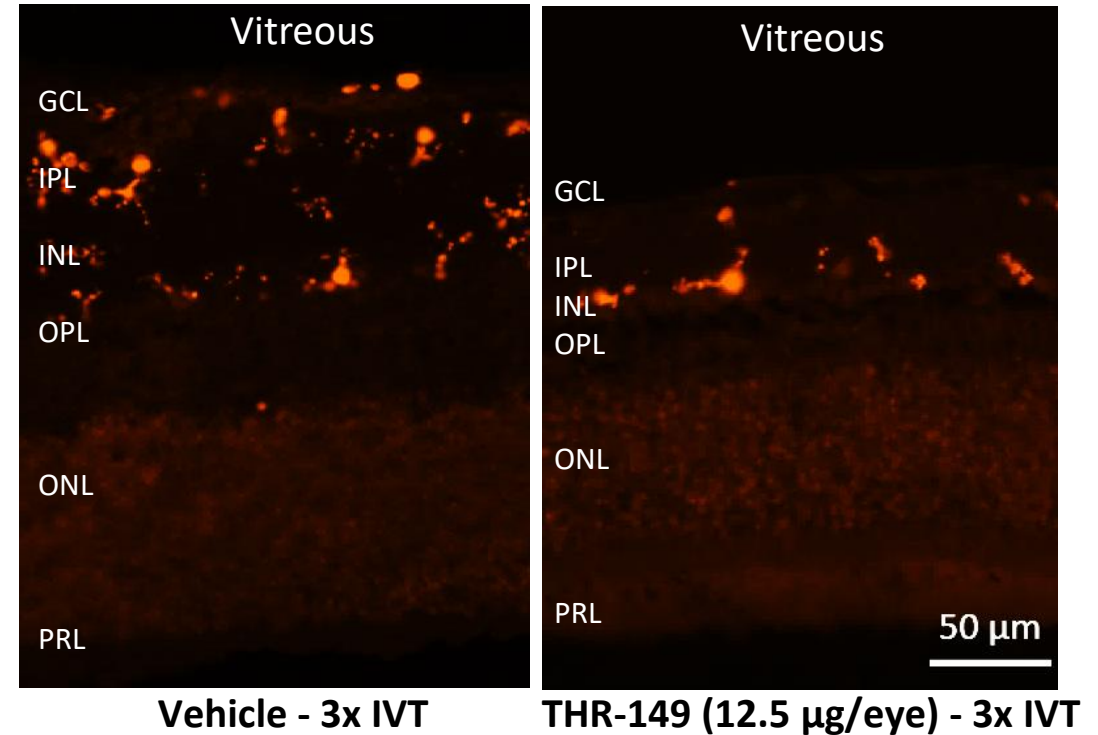
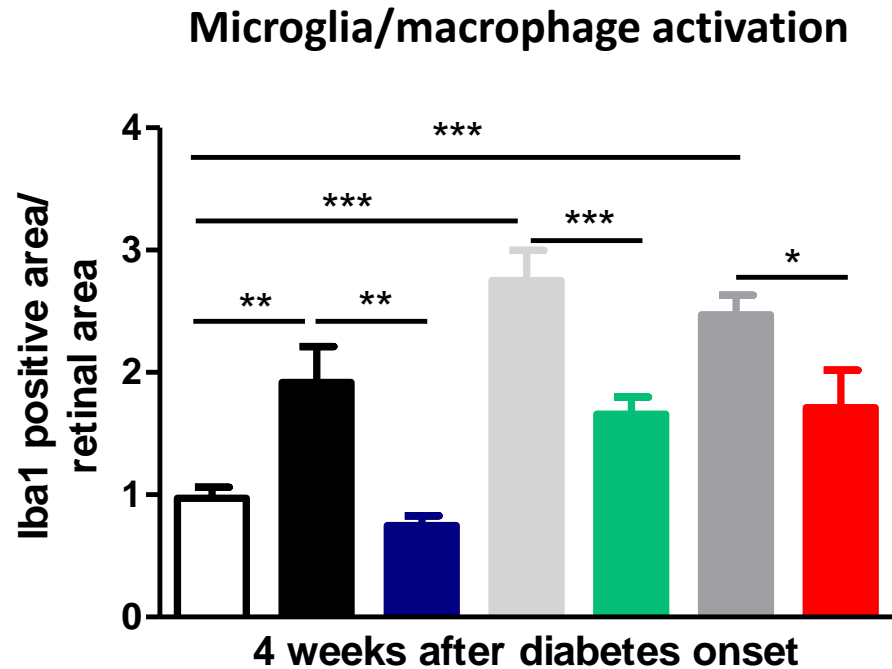


Analysis: 4 weeks after diabetes onset:
FITC-BSA to assess retinal vascular leakage

- Non-diabetic
- Diabetic, buffer VEGF-Trap
- Diabetic, VEGF-Trap
- Diabetic, buffer of THR-149 (1x IVT)
- Diabetic, THR-149 (1x IVT)
- Diabetic, buffer of THR-149 (3x IVT)
- Diabetic, THR-149 (3x IVT)

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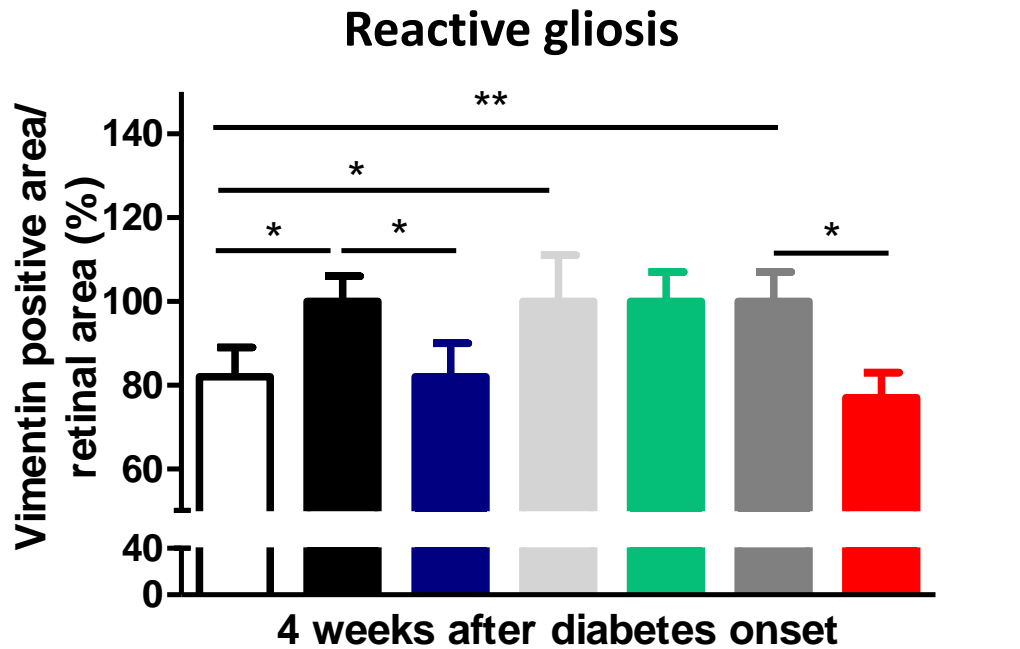
Repeated and single IVT administration of THR-149 reduces diabetes-induced microglia/macrophage activation



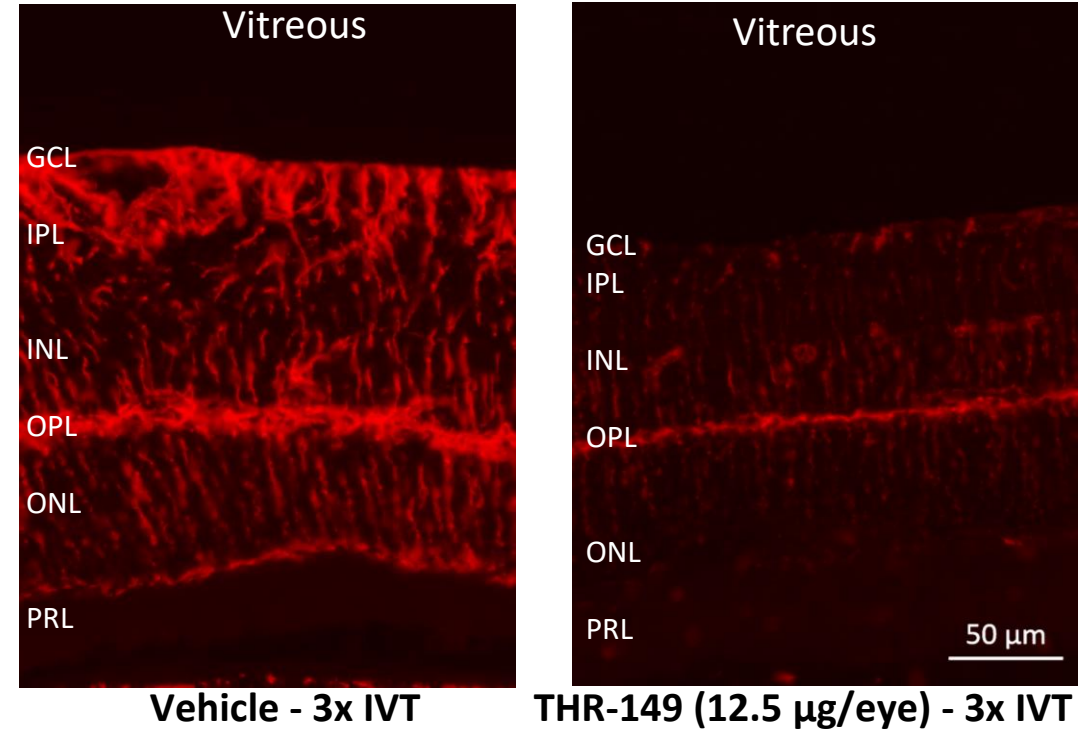
Analysis: 4 weeks after diabetes onset:
Iba1 to assess microglia/macrophage activation

- Non-diabetic
- Diabetic, buffer VEGF-Trap
- Diabetic, VEGF-Trap
- Diabetic, buffer of THR-149 (1x IVT)
- Diabetic, THR-149 (1x IVT)
- Diabetic, buffer of THR-149 (3x IVT)
- Diabetic, THR-149 (3x IVT)

Repeated IVT administration of THR-149 reduces diabetes-induced reactive gliosis



- Non-diabetic
- Diabetic, buffer VEGF-Trap
- Diabetic, VEGF-Trap
- Diabetic, buffer of THR-149 (1x IVT)
- Diabetic, THR-149 (1x IVT)
- Diabetic, buffer of THR-149 (3x IVT)
- Diabetic, THR-149 (3x IVT)

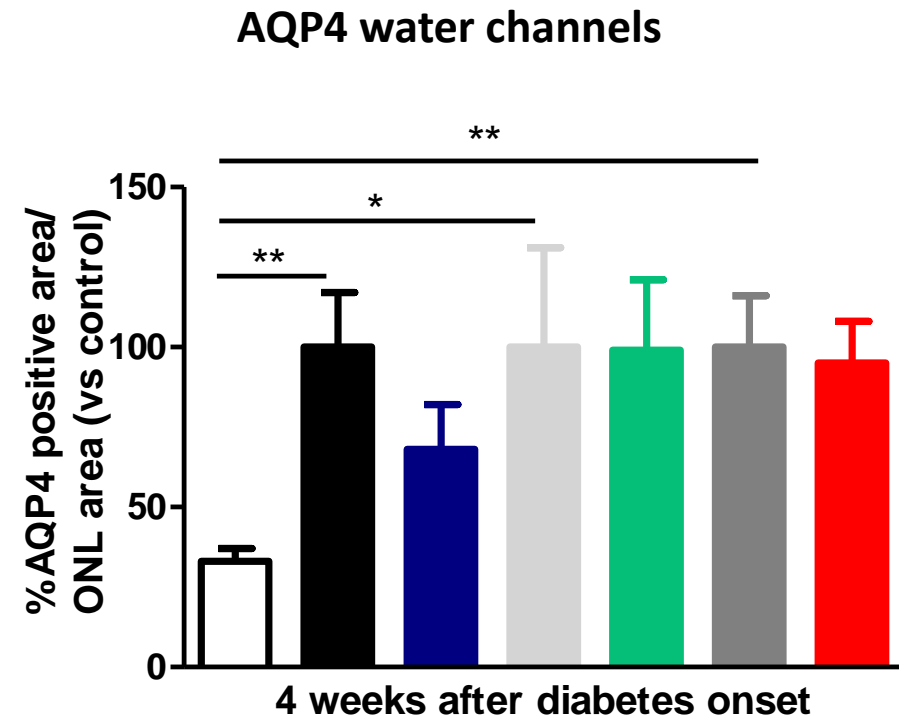
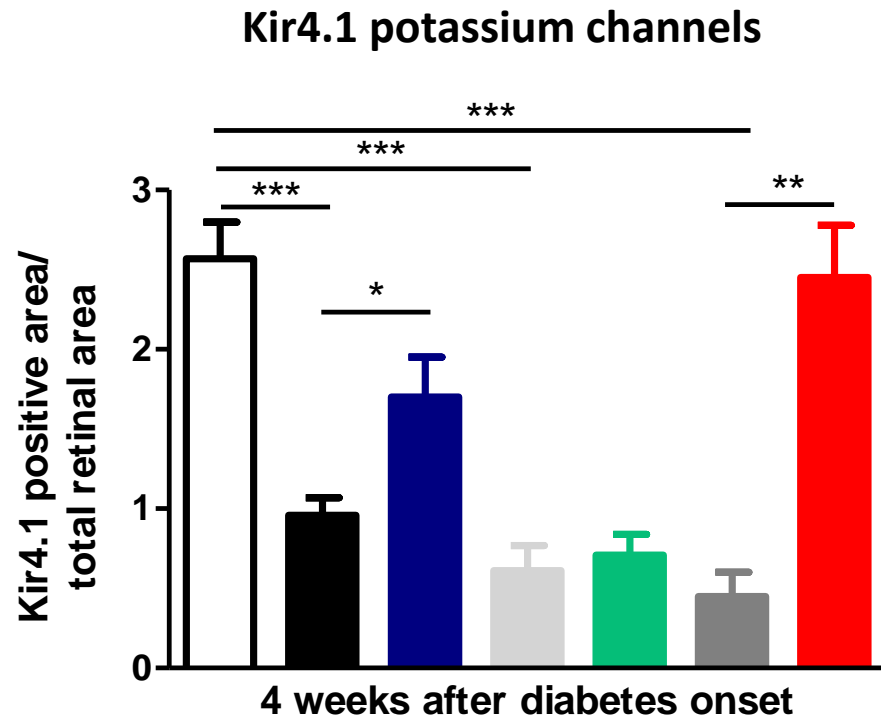


Analysis: 4 weeks after diabetes onset:

Vimentin staining to assess gliosis (= activation astrocytes & Müller glia)

GCL: ganglion cell layer, IPL: inner plexiform layer, INL: inner nuclear layer, IVT: intravitreal, OPL: outer plexiform layer; ONL: outer nuclear layer; PRL: photoreceptor layer

Repeated IVT administration of THR-149 prevents diabetes-induced loss of Kir4.1 potassium channels, but not of AQP4 water channels



- Non-diabetic
- Diabetic, buffer VEGF-Trap
- Diabetic, VEGF-Trap
- Diabetic, buffer of THR-149 (1x IVT)
- Diabetic, THR-149 (1x IVT)
- Diabetic, buffer of THR-149 (3x IVT)
- Diabetic, THR-149 (3x IVT)

Conclusion

Repeated administration of THR-149, a novel bicyclic peptide, significantly reduced retinal thickening in the diabetic rat STZ model, compared to vehicle-treated eyes, associated with reduced gliosis and increased levels of Kir4.1-positive potassium channels. These positive results further strengthen the perspective to use THR-149 as a treatment option for DME and demonstrate that repeated IVT injections are probably needed to induce its complete therapeutic effect.

For more information :
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