

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

Tine Van Bergen

EURETINA · 9-12 September 2021

Financial disclosure: Employee at Oxurion NV

O X U R I O N®

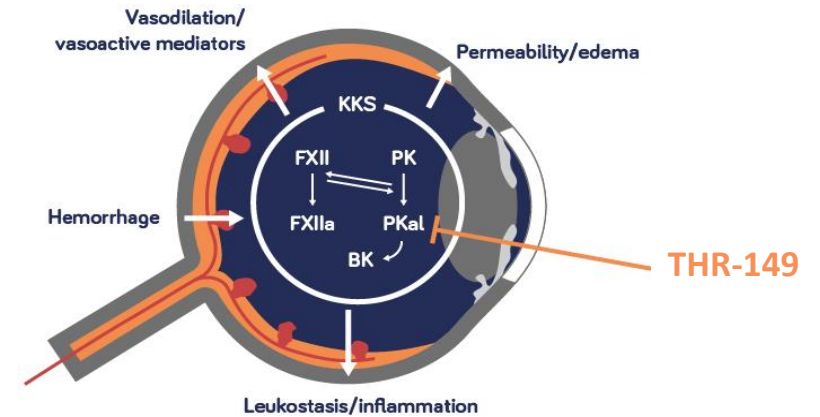
ADVANCING SCIENCE.®
ENHANCING VISION.



Introduction

THR-149: highly potent, selective and stable peptide targeting Plasma Kallikrein

- Elevated plasma kallikrein (PKal) is a known pathogenic factor in DME where it drives VEGF-independent retinal inflammatory processes and vasopermeability
- THR-149 is a novel potent and highly specific bicyclic peptide inhibitor of PKal:
 - High potency: sub-nanomolar K_i values against human PKal
 - Developed by Oxurion in partnership with Bicycle Therapeutics
 - Repeated administration reduced vascular leakage (FITC-BSA) and retinal thickness in a diabetic rat STZ model (Van Bergen T et al. IOVS 2021 - accepted)



Teufel et al. *J Med Chem* 2018;61(7):2823-2836

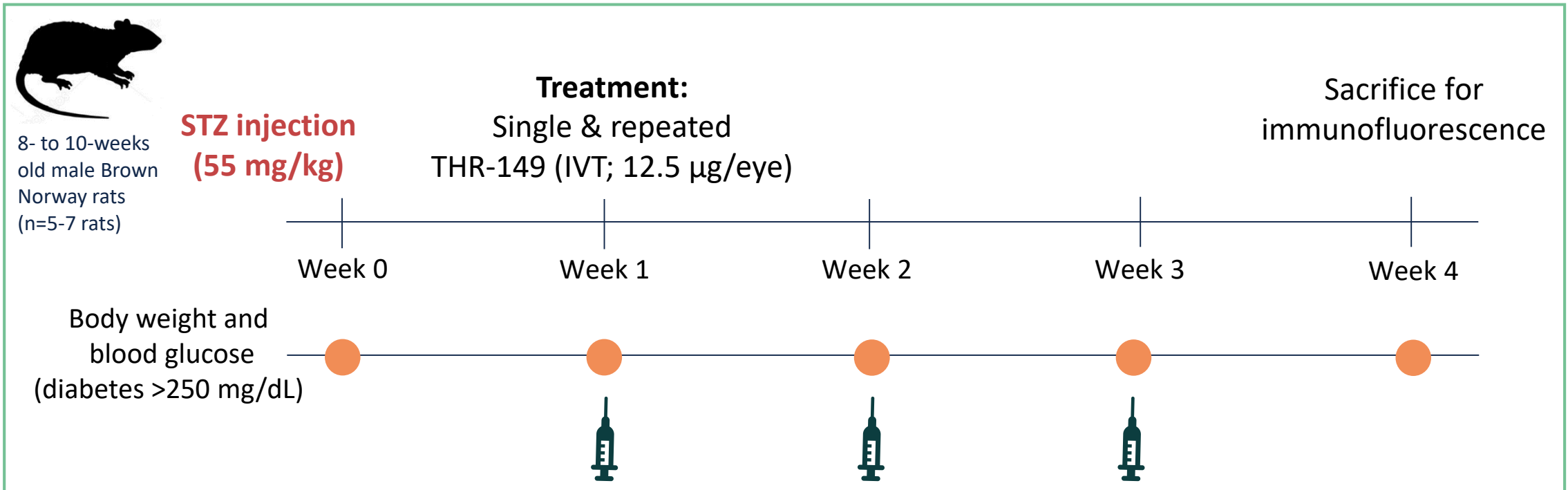
Abbreviation(s): BK, bradykinin; DME, diabetic macular edema; FXII, factor XII; FITC-BSA: fluorescein isothiocyanate labelled bovine serum albumin; KKS, kinin kallikrein system; PK, PreKallikrein; PKal, plasma kallikrein; STZ, streptozotocin; VEGF, vascular endothelial growth factor; STZ, streptozotocin; VEGF, vascular endothelial growth factor

Objective and methods

Objective

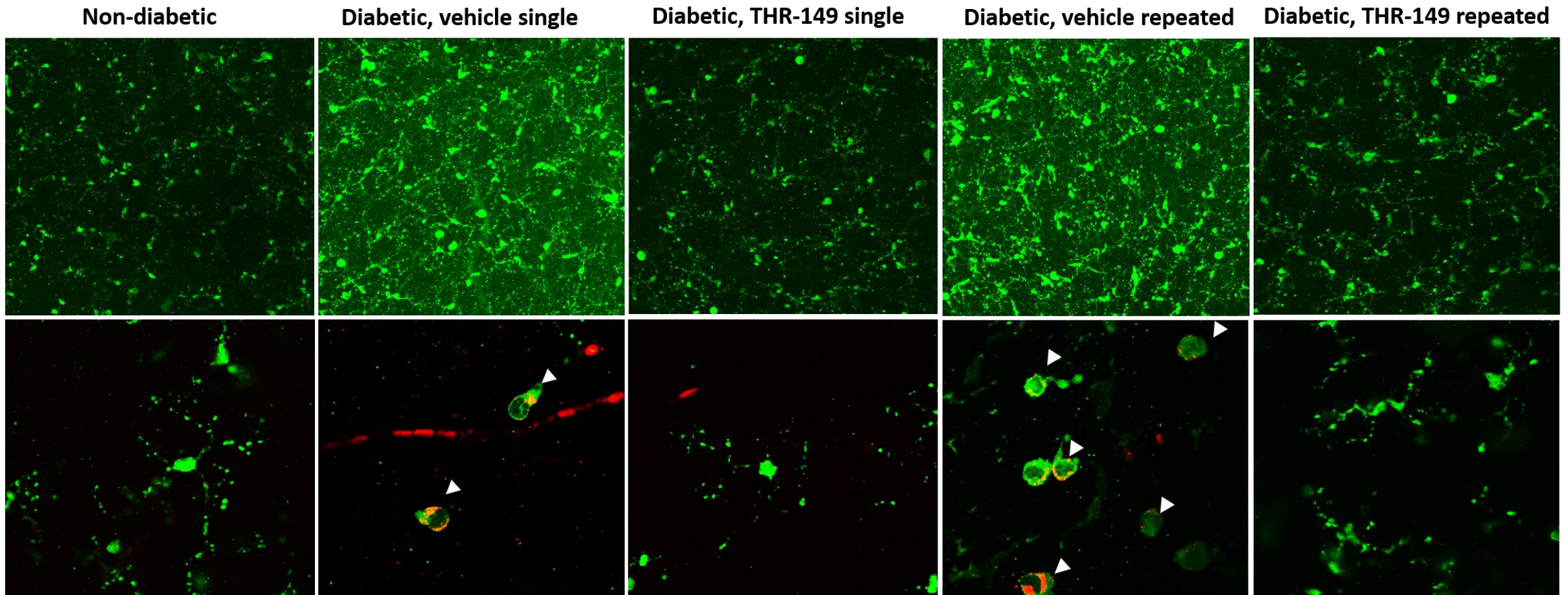
To determine the potential of THR-149 to prevent key pathologies associated with diabetic macular edema, especially in relation to elements of the neurovascular unit, in the streptozotocin (STZ)-induced diabetic rat model.

Methods



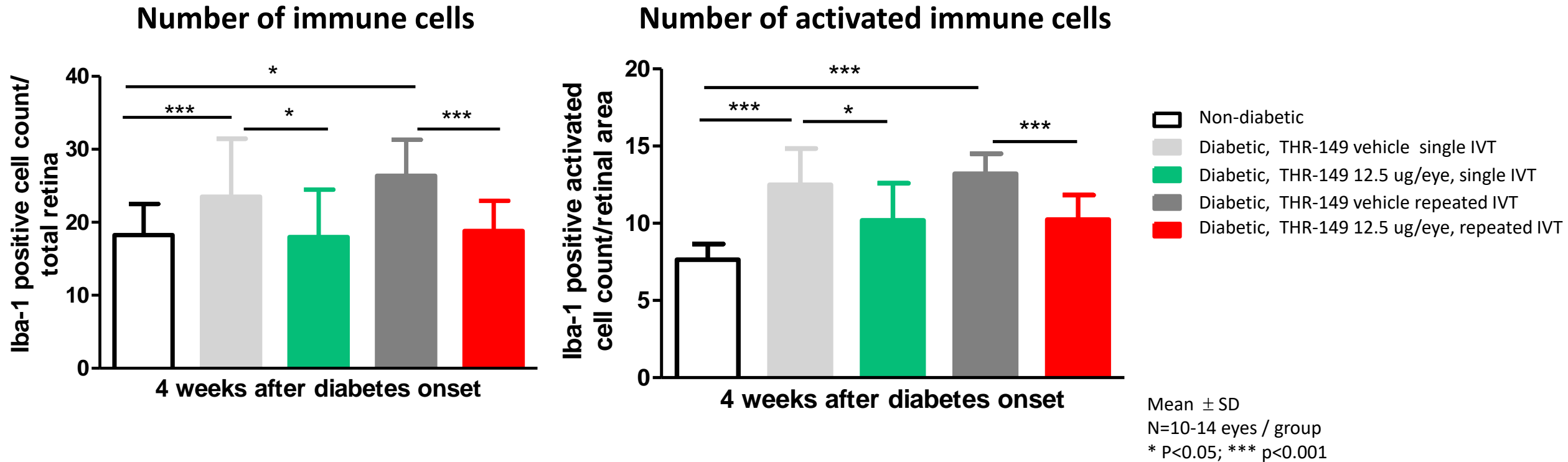
Statistical analysis: one-way ANOVA between control and treatment with Bonferroni's multiple comparisons post hoc test.

Single and repeated IVT administration THR-149 inhibits the number of total and activated immune cells in the STZ diabetic rat



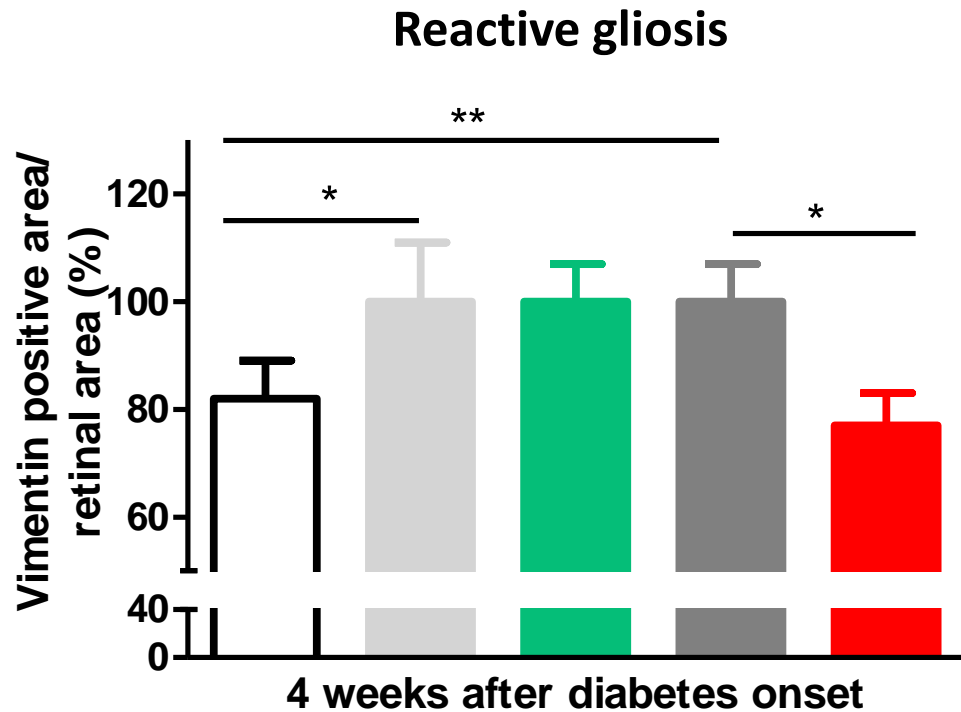
Iba1 (green) and CD68 (red) staining – confocal images – retinal wholemounts

Single and repeated IVT administration THR-149 inhibits the number of total and activated immune cells in the STZ diabetic rat



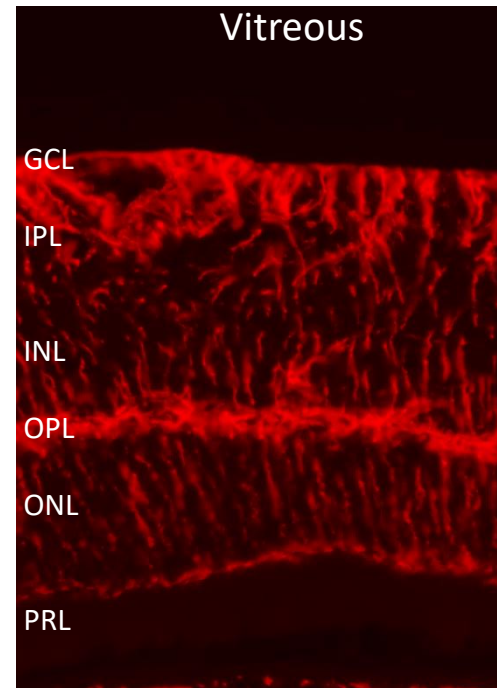
Iba1 staining – fluorescent microscopy analysis (retinal sections)

Repeated IVT administration of THR-149 reduces diabetes-induced reactive gliosis in the STZ diabetic rat

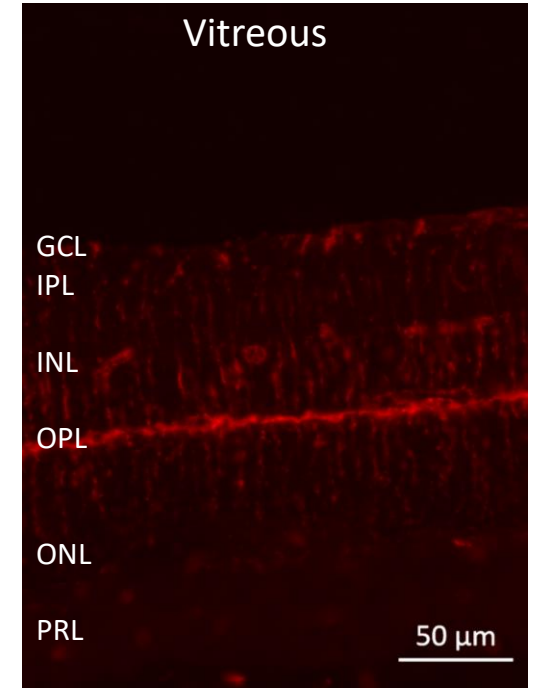


Mean \pm SD
 N=10-14 eyes / group
 * P<0.05; ** p<0.01

- Non-diabetic
- Diabetic, THR-149 vehicle single IVT
- Diabetic, THR-149 12.5 ug/eye, single IVT
- Diabetic, THR-149 vehicle repeated IVT
- Diabetic, THR-149 12.5 ug/eye, repeated IVT



Vehicle - repeated



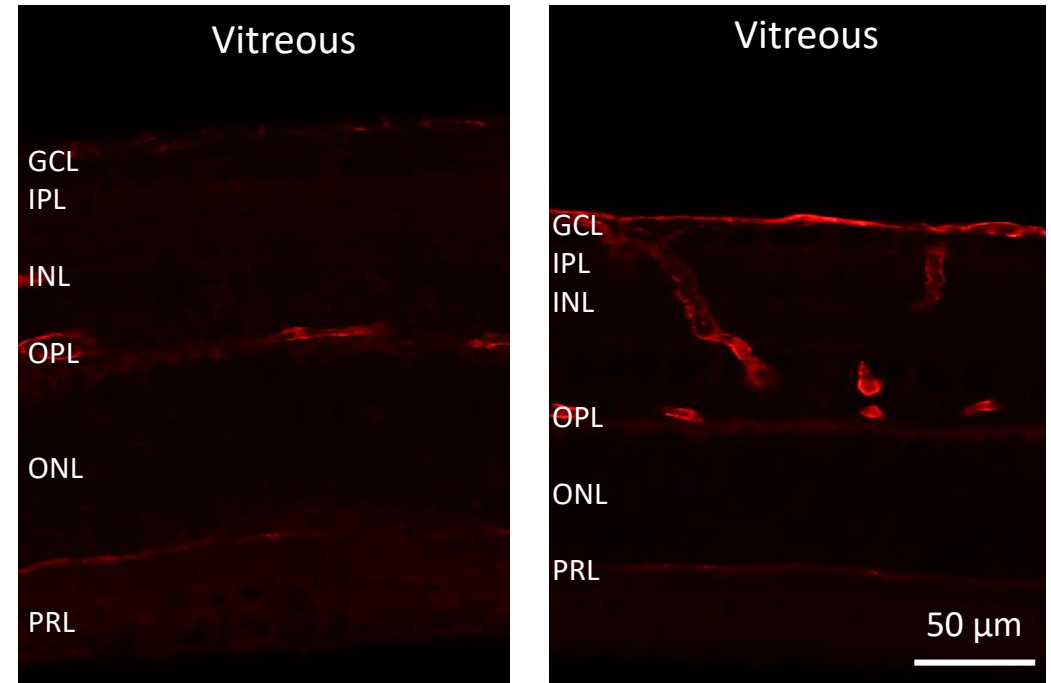
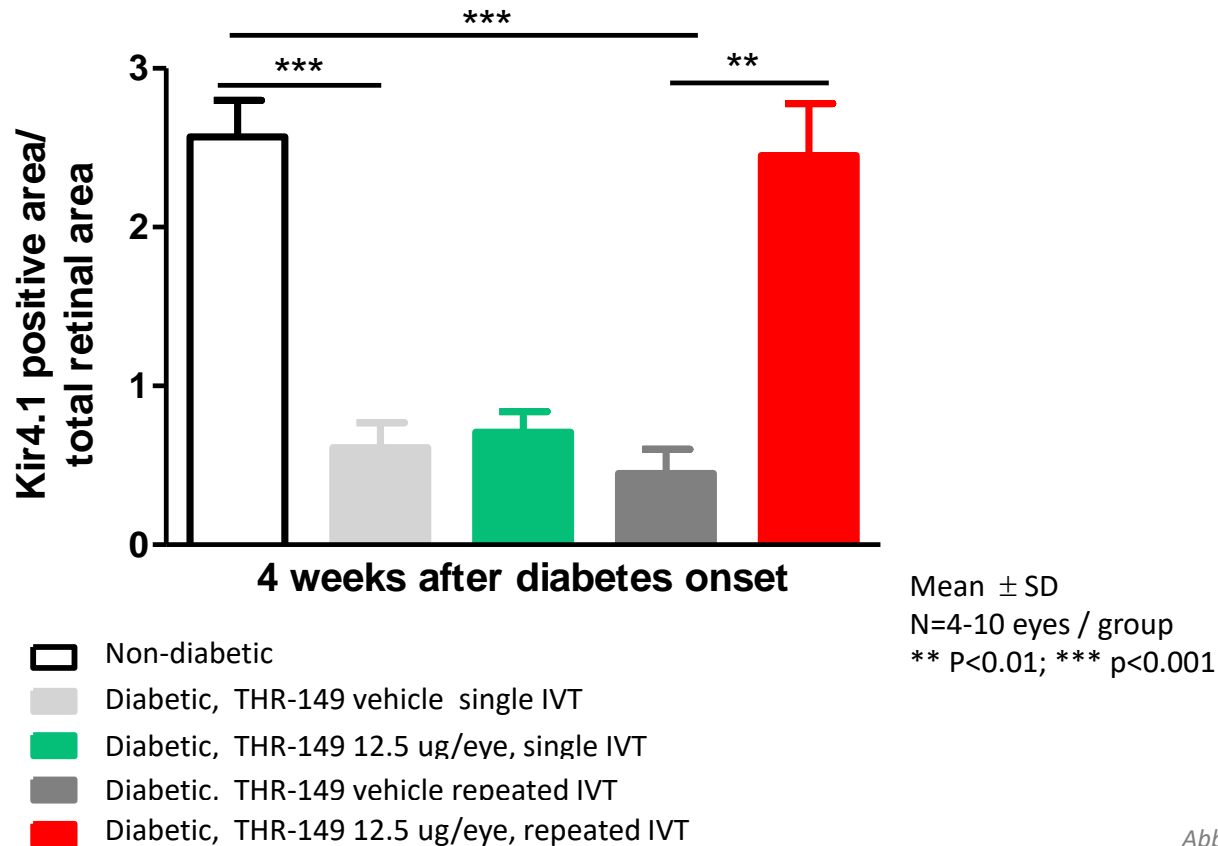
THR-149 - repeated

Vimentin staining fluorescent microscopy analysis (retinal sections)

Abbreviation(s): GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; IVT, intra-vitreous; OPL, outer plexiform layer; ONL, outer nuclear layer; PRL, photoreceptor layer; STZ, streptozotocin

Repeated IVT administration of THR-149 prevents diabetes-induced loss of Kir4.1 potassium channels in the STZ diabetic rat

Kir4.1 potassium channels



Vehicle - repeated

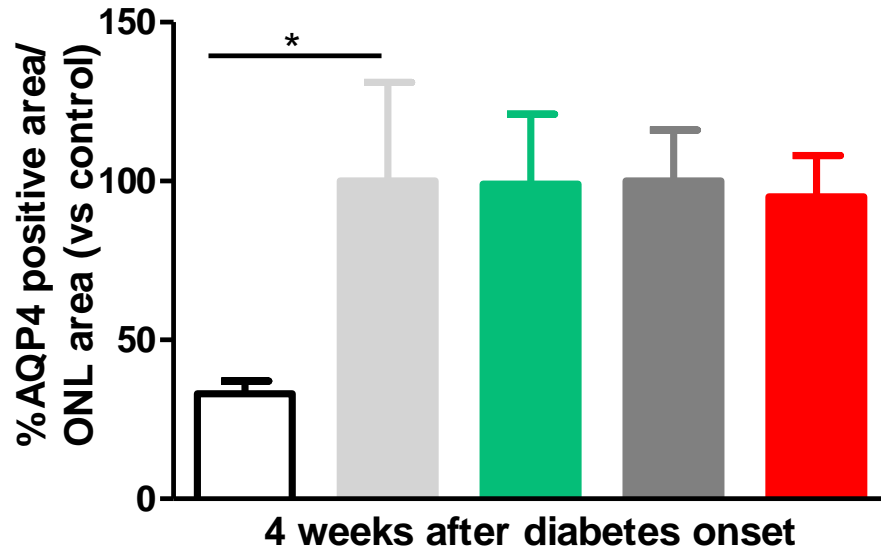
THR-149 - repeated

Kir4.1 staining fluorescent microscopy analysis (retinal sections)

Abbreviation(s): GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; IVT, intravitreal; Kir4.1, inwardly rectifying potassium; OPL, outer plexiform layer; ONL, outer nuclear layer; PRL, photoreceptor layer; STZ, streptozotocin

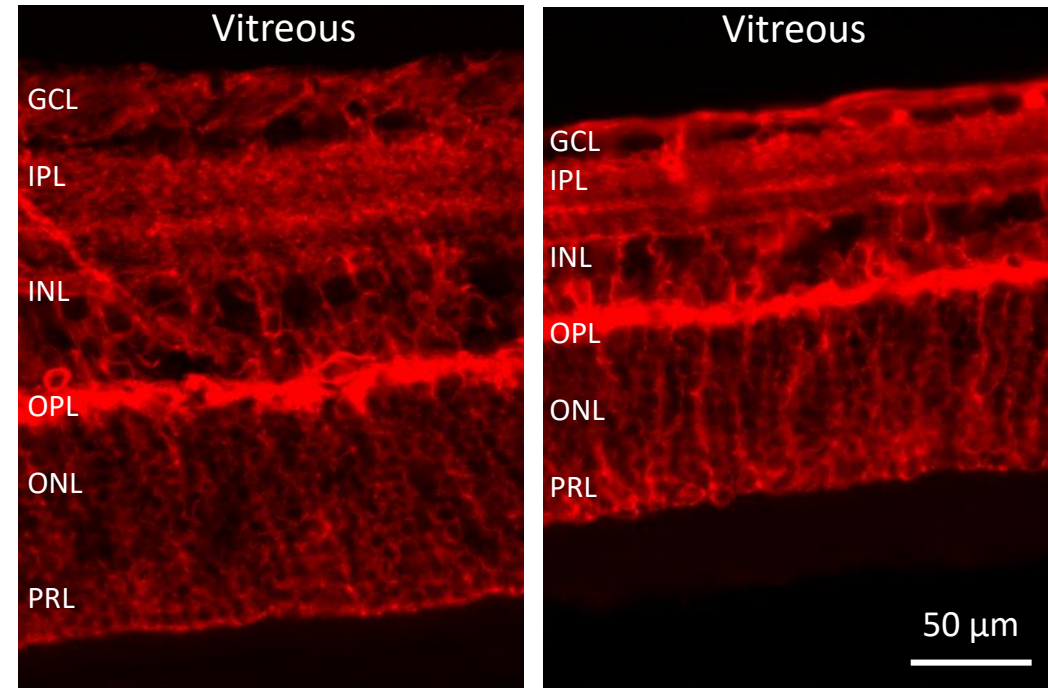
Repeated IVT administration of THR-149 does not prevent diabetes-induced increase of AQP4 water channels in the STZ diabetic rat

AQP4 water channels



Mean \pm SD
N=4-10 eyes / group
* P<0.05; ** p<0.01

- Non-diabetic
- Diabetic, THR-149 vehicle single IVT
- Diabetic, THR-149 12.5 ug/eye, single IVT
- Diabetic, THR-149 vehicle repeated IVT
- Diabetic, THR-149 12.5 ug/eye, repeated IVT



Vehicle - repeated

THR-149 - repeated

AQP4 staining fluorescent microscopy analysis (retinal sections)

Abbreviation(s): AQP4, aquaporin 4; 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; STZ, streptozotocin

Conclusion

These data demonstrate that repeated administration of THR-149, a novel bicyclic peptide inhibitor of PKA, reduces several DME-related key pathologies, such as activation of retinal microglia/macrophages and Müller cells in the diabetic rat retina and restores the decreased expression and mislocalization of Kir4.1-positive potassium channels in the diabetic retina. These observations indicate that modulation of the PKA-pathway using THR-149 has clinical potential to treat patients with DME and that potentially repeated IVT injections are needed to achieve a more complete therapeutic effect in elements of the neurovascular unit.

Acknowledgements

Oxurion

Astrid De Vriese, Valerie Vanheukelom, Lies Roussel, Huberte Moreau, Isabelle Etienne, Tjing-Tjing Hu, Jean HM Feyen, Alan Stitt

University of Leuven

Lies De Groef, Lieve Moons

Queen's University of Belfast

Karis Little

Contact

tine.vanbergen@oxurion.com