

# VEGF blockage prevents retinal tissue regrowth in retinal vascular disease

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# Financial Disclosure

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All have equity interest in Retinal Solutions LLC

# Summary

VEGF blockage prevents retinal tissue regrowth

Noregen (a modified Norrin protein ) driven

Wnt signaling promotes retinal tissue regrowth

# Clinical Finding

- It has become clear in many human retinal vascular studies treating with anti-VEGF that areas of capillary loss measured at the beginning of the study are the same at the end of the study when anti-VEGF is no longer needed

# Why does that occur ?

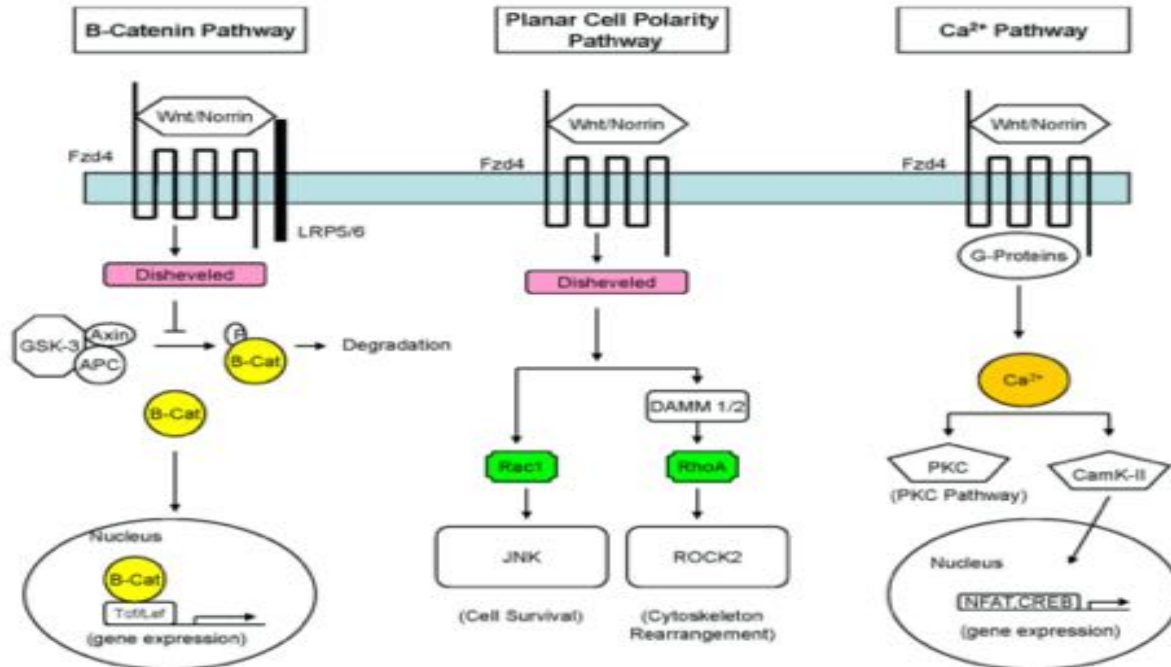
- We think that the hypoxic retina which originally drove the VEGF activation is at the end of the study anoxic due to continuing neuronal death reducing VEGF drive

# Noregen : a modified Norrin Protein

- Norries Disease has taught us much about normal retinal development Norrin driven Wnt signaling stimulates a myriad of proteins which supports retinal development during the first several months of life
- Norries Disease is caused by the absence of the ability to make the Norrin protein which results in
  - 100% bilateral blindness
  - 40% hearing loss
  - 40% CNS alterations

# What are Wnt Pathways

- Signal transduction pathways made of proteins
- Expressed in epithelial and endothelial cells
- 19 Wnts Norrin is a Wnt mimic





# Why the difference ?

- Other Wnt activators can result in hearing and CNS function
- No substitute for Norrin driven Wnt signaling for retinal development

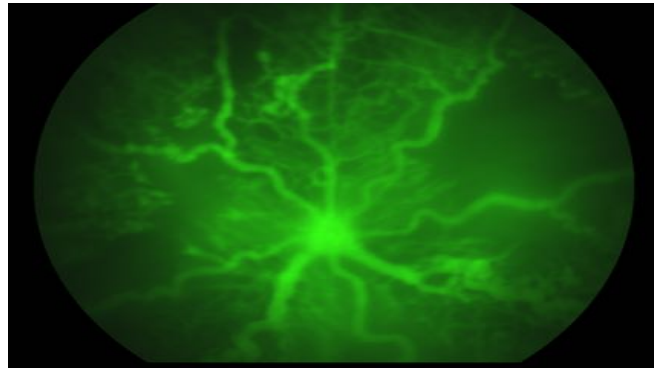
# Norrin protein activity in animal models of retinal vascular disease

- Directly repairs vascular Tight Junction proteins in human retinal endothelial cell tissue culture and animal models
- Block PLVAP pinocytotic vascular leakage
- Blocks neovascularization
- Promotes growth of non-fenestrated retinal capillaries and retinal neurons by altering the microenvironment to activate insitu retinal progenitor cells
- This is the environment which grew healthy retina originally

# *In Vivo* POC: Protects from VEGF insult

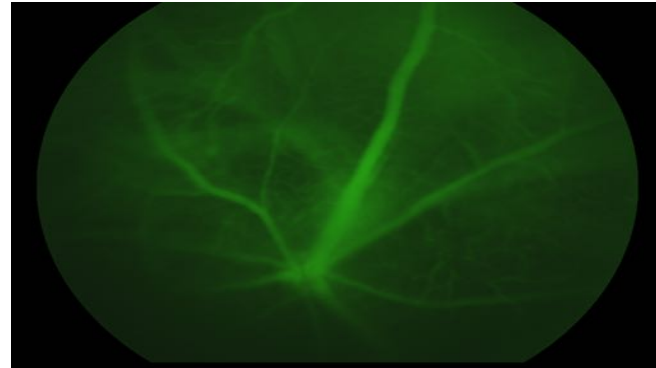
At peak VEGF activity in an oxygen-induced retinopathy murine model, Norrin protein treated eye does not show the leakage and disorganized vascularization of VEGF insult ( Both slides P17)

Peak VEGF effect



- Leakage (fuzzy vessels) from compromised cellular junctions and through-cell transfer (pinocytosis)
- Disorganized pathologic new growth

Norrin protein treated

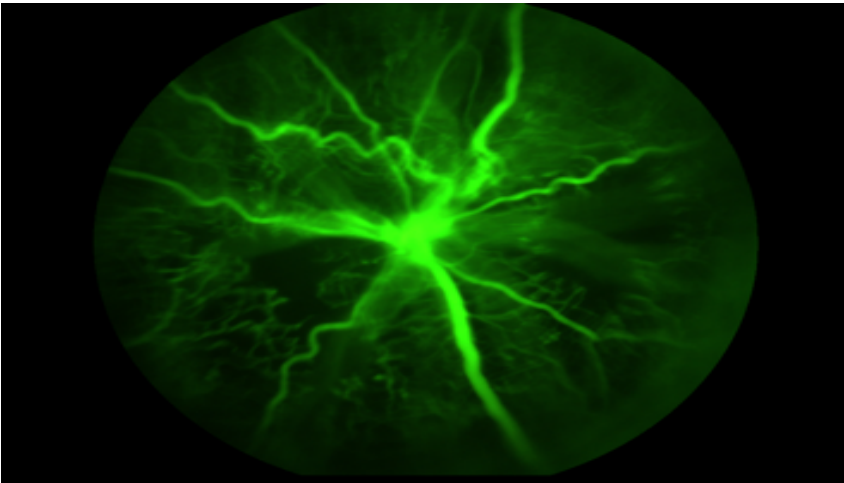


- No evidence of leakage
- Organized vessel growth

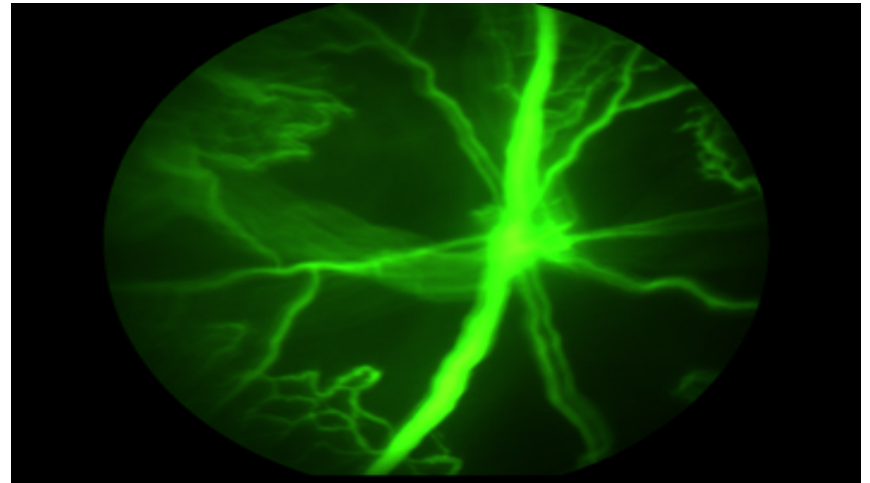
# Aflibercept injection

VEGF blockage does not allow normal  
capillary growth or regrowth as  
demonstrated in human DR studies

**Peak VEGF effect**



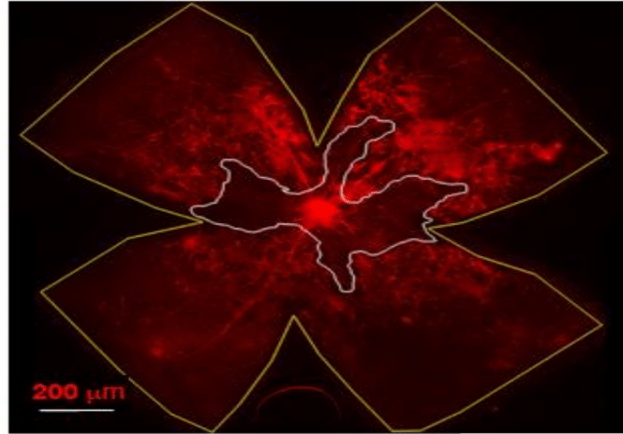
**Aflibercept injection**



**P17**

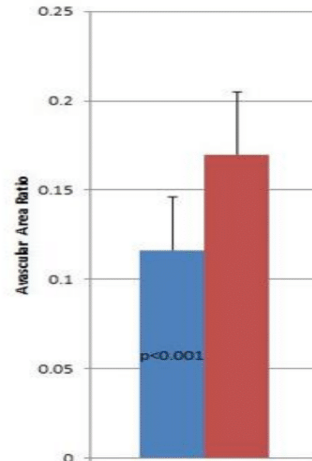
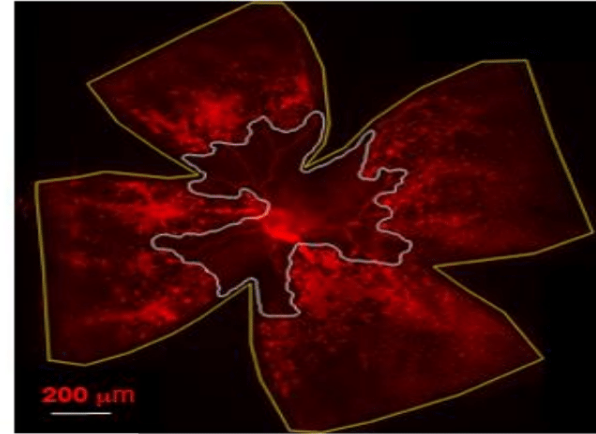
**Right Treated**

Norrin



**Left Untreated**

PBS



$p < 0.001$



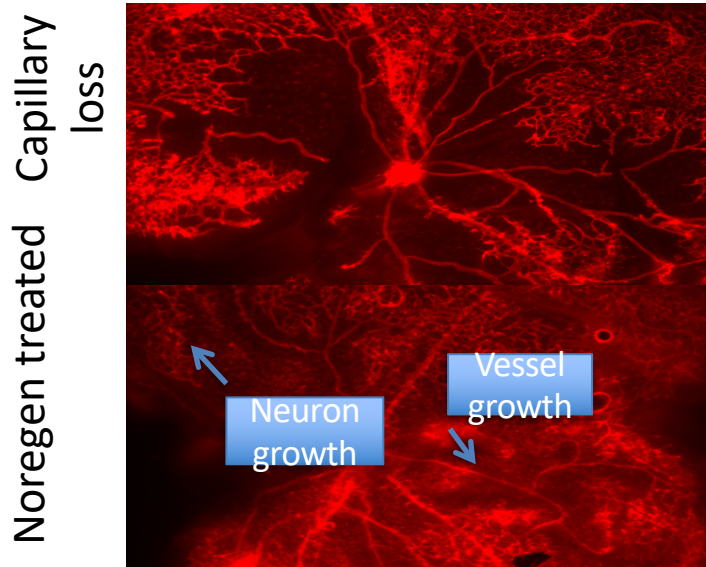
Anti-VEGF blocks  
PATHOLOGIC  
and  
APROPRIATE  
ANGIOGENESIS

Modulated VEGF is needed for healthy retinal  
development

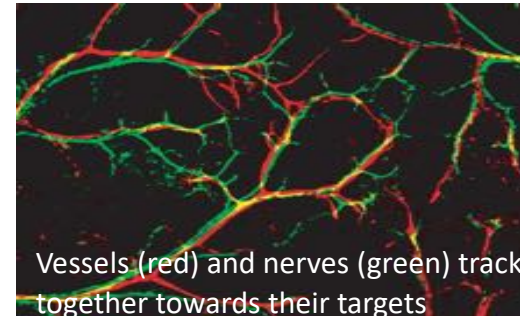
# *In Vivo* POC: Neurovascular Unit

Norrin protein stimulates vascular and neuronal growth in appropriate areas

(oxygen-induced retinopathy model)



Healthy capillary growth  
requires neural pathways to  
guide capillary development



# Progenitor cells have been identified in the Retina

- Mueller cells and amacrine cells
- Ohlmann in murine retina has shown that these progenitor cells respond to stimulation by Norrin to form healthy retinal tissue including the deep capillary plexus



# Conclusion

- Plan to be in clinical trials in 2021 for this insitu Retinal Regenerative Therapeutic