VEGF blockage prevents retinal tissue regrowth in retinal vascular disease

Michael Trese MD
Co-Authors

• Kimberly Drenser MD PhD
• Antonio Capone jr MD
• Kenneth Mitton PhD
• Wendy Dailey MS
Financial Disclosure

Antonio Capone Jr MD
Kimberly Drenser MD PhD
Wendy Dailey MS
Michael Trese MD
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 in situ 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
Norrin PBS

Right Treated

Left Untreated

P17

p<0.001
Anti-VEGF blocks PATHOLOGIC and APROPRIATE ANGIOGENASIS

Modulated VEGF is needed for healthy retinal development
In Vivo POC: Neurovascular Unit

Norрин protein stimulates vascular and neuronal growth in appropriate areas (oxygen-induced retinopathy model)

Healthy capillary growth requires neural pathways to guide capillary development

Norrin treated

Capillary loss

Vessels (red) and nerves (green) track together towards their targets

Vessel growth

Neuron growth
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