

# #3538580

# A Novel TIE2 Activating Monoclonal Antibody Ameliorates The Lesion of Choroidal Neovascularization in Monkey and Mouse

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## Background

### TIE2 (TEK Receptor Tyrosine Kinase 2)

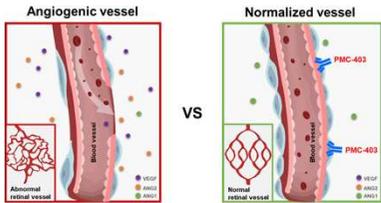
- TIE2 is a cell-surface receptor mainly expressed in endothelial cells and it regulates angiogenesis by binding to angiopoietins (Ang).
- ANG1 is known to promote blood vessel maturation and stabilization while ANG2 acts as a vessel destabilizer.

### Neovascular Age-Related Macular Degeneration

- Similar to VEGF, ANG2 is up-regulated by hypoxia and the ocular level of ANG2 is elevated in the eyes of nAMD patients.
- VEGF neutralizing molecules were approved to treat neovascular ocular diseases but there still is a great need to develop therapeutic agents to treat the patients who do not respond well to anti-VEGF drugs.

### PMC-403

- We are developing a TIE2 activating antibody that mimics the function of ANG1. Here, we are presenting the results from evaluating the efficacy of PMC-403 in animal CNV models.



## Methods

### In vitro study

- Western blot assay: The protein expression was analyzed in HUVECs

### In vivo CNV study

- Experimental CNV was induced by laser photocoagulation in C57BL/6 mice and in rhesus monkeys. The animals received IVT administration of aflibercept or PMC-403 and the dose dependent responses were measured in multiple assays:

- FFA, OCT and ERG were evaluated.
- The number of leakage spots, the percent changes of leakage area, and the maximum retinal thickness of laser-burned spots were evaluated.
- In the monkey CNV model, the level of mRNA expression of 10 genes related to angiogenesis and inflammation was measured.

## Results

Similar to ANG1, PMC-403 activates the vessel stabilizing TIE2 signaling pathway in concentration-dependent manner

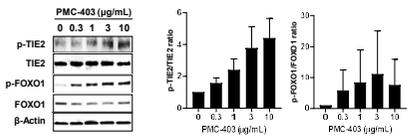


Figure 1. The protein expression levels of TIE2 and FOXO1 phosphorylation in HUVECs

### PMC-403 reduces the leakage of retinal vessels in CNV mouse model

- Model: Laser-induced choroidal neovascularization (CNV)
- Animal: C57BL/6 mice (n=10 mice/group)
- Dosing regimen: Single intravitreal injection (Isotype antibody: Human IgG1, 40 µg)  
 Single intravitreal injection (TIE2 antibody: PMC-403, 20 & 40 µg)  
 Single intravitreal injection (VEGF antibody: Aflibercept, 20 µg)

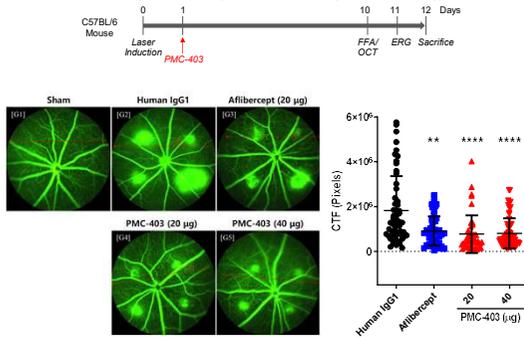


Figure 2. Fluorescein leakage from CNV lesions at 10 days after CNV induction and dosing.

### PMC-403 reduces the thickness of retinal vessels in CNV mouse model

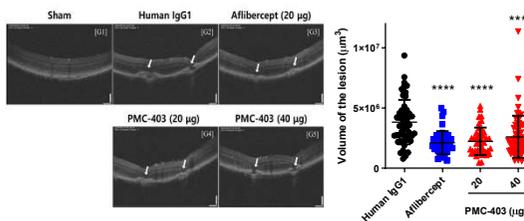


Figure 3. CNV thickness was assessed on cross-sectional images of CNV obtained through OCT

### PMC-403 increases B-wave amplitude in CNV mouse model

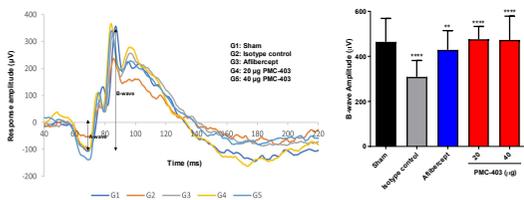


Figure 4. The scotopic ERG response was measured at the light intensity of 0.9 log cds/m<sup>2</sup>

### PMC-403 inhibits retinal leakage in laser-induced CNV monkey model

- Model: Laser-induced choroidal neovascularization (CNV)
- Animal: Rhesus monkey (n=2-3 monkeys/group)
- Dosing regimen: Single intravitreal injection (Isotype antibody: Human IgG1, 2 mg/eye)  
 Single intravitreal injection (TIE2 antibody: PMC-403, 2 mg/eye)  
 Single intravitreal injection (VEGF antibody: Aflibercept, 2 mg/eye)

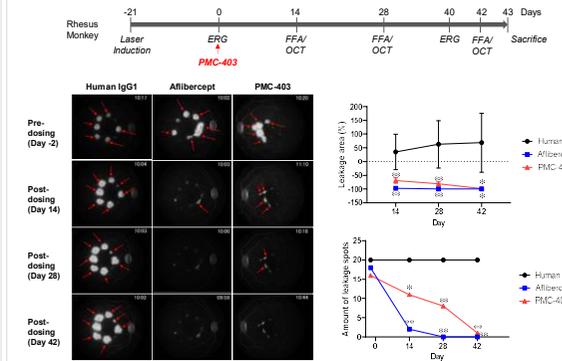


Figure 5. Fluorescein leakage area and spots from CNV lesions in monkey eyes was assessed through FFA

### PMC-403 reduces the thickness of retinal blood vessels in CNV monkey model

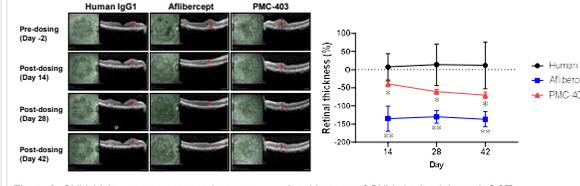


Figure 6. CNV thickness was assessed on cross-sectional images of CNV obtained through OCT

### PMC-403 induces better responses in B-wave and OPs measurement than aflibercept

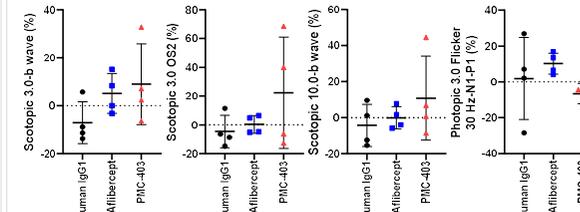


Figure 7. The scotopic ERG response was measured at the light intensity of 0.9 log cds/m<sup>2</sup>

### PMC-403 decreases the level of angiogenesis regulator genes such as ANG2, VEGF, PlGF, and PDGF

#### ❖ Vascular growth factor

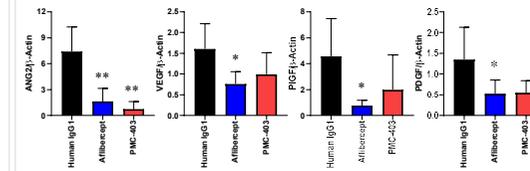


Figure 8. The mRNA expression levels were measured using a real time-PCR at 43 days after drug treatment. n=4 per group

### PMC-403 reduced the level of Cox-2 mRNA and thus, suggests the role of PMC-403 in mitigating inflammation

#### ❖ Inflammatory cytokine and chemokine

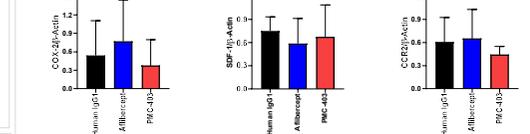


Figure 9. The mRNA expression levels were measured using a real time-PCR at 43 days after drug treatment. n=4 per group

### PMC-403 dramatically increases the mRNA expression ratio of PDGFR-β/CD31

#### ❖ Vessel normalization

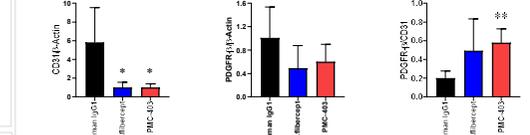


Figure 10. The mRNA expression levels were measured using a real time-PCR at 43 days after drug treatment. n=4 per group

## Conclusion

- PMC-403 normalizes leaky blood vessels, leading to the improvement of sensitivity of optic neurons in animal CNV models.
- The physiological effects of PMC-403 accompanied with the decreased expression of angiogenic and inflammation factors as well as elevated pericytes recruitment.
- These data strongly support the notion that PMC-403 stabilizes leaky retinal and choroidal blood vessels and it can be developed as an effective therapeutic agent to treat a wide variety of retinal and choroidal vascular disorders.

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