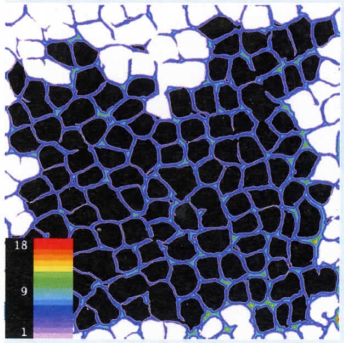
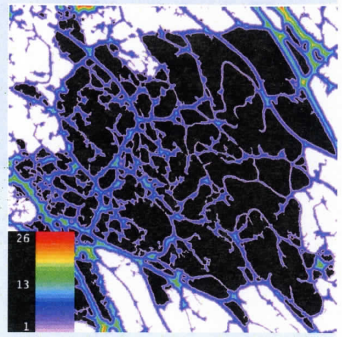
VESGEN Mapping of Bioactive Protection against Intestinal Inflammation: Application to Human Spaceflight and ISS Experiments. PA Parsons-Wingerter[1], X Chen[2], CP Kelly[2], HC Reinecker[3], [1]NASA-GRC Research & Technology, [2] Division of Gastroenterology, Beth Israel Deaconess Medical Center, [3]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School.

Challenges to successful space exploration and colonization include adverse physiological reactions to microgravity and space radiation factors. Constant remodeling of the microvasculature is critical for tissue preservation, wound healing, and recovery after ischemia. Regulation of the vascular system in the intestine is particularly important to enable nutrient absorption while maintaining barrier function and mucosal defense against microbiota. Although tremendous progress has been made in understanding the molecular circuits regulating neovascularization, our knowledge of the adaptations of the vascular system to environmental challenges in the intestine remains incomplete. This is in part because of the lack of methods to observe and quantify the complex processes associated with vascular responses *in vivo.* Developed by GRC as a mature beta version, pre-release research software, VESsel GENeration Analysis (VESGEN) maps and quantifies the fractal-based complexity of vascular branching for novel insights into the cytokine, transgenic and therapeutic regulation of angiogenesis, lymphangiogenesis and microvascular remodeling. Here we demonstrate that VESGEN can be used to characterize the dynamic vascular responses to acute intestinal inflammation and mucosal recovery from *in vivo* confocal microscopic 3D image series. We induced transient intestinal inflammation in mice by DSS treatment and investigated whether the ability of the probiotic yeast *Saccharomyces boulardii* (*Sb*) to protect against intestinal inflammation was due to regulation of vascular remodeling. A primary characteristic of inflammation is excessive neovascularization (angiogenesis) resulting in fragile vessels prone to bleeding. Morphological parameters for triplicate specimens revealed that *Sb* treatment greatly reduced the inflammatory response of vascular networks by an average of 78%. This resulted from *Sb* inhibition of vascular endothelial growth factor receptor signaling, a major angiogenesis signaling pathway. It needs to be determined whether probiotic yeast represents a promising approach to GI protection in space. GRC performed only the VESGEN post-testing analysis.

NASA GRC IR&D04-54/2010 TTP Fund (PPW); NIH DK-068181/DK-043351/AI-093588 (HCR), DK-033506 (HCR/CPK).





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Successful, Long-Term Human Space Exploration
Prophylaxis against GI Inflammation &
Other Microvascular Risk Factors

Microvascular Remodeling and Angiogenesis

Fundamental to healthy physiology, disease progression and successful prophylactic/therapeutic strategies on Earth and in Space

Dynamic Microvascular Remodeling in GI Tract

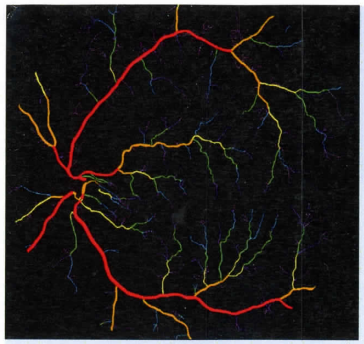
- Permeability enables nutrient absorption
- Yet must provide barrier protection & mucosal defense against microbiota

Analysis Methods Lacking for Remodeling Microvasculature

VESsel GENeration Analysis (VESGEN) Software

- Innovative research discovery tool for informative mapping and quantification of vascular remodeling throughout the body
- Retina as window to the body
- Leaf venation remodeling in ISS-utilized *Arabidopsis thaliana*

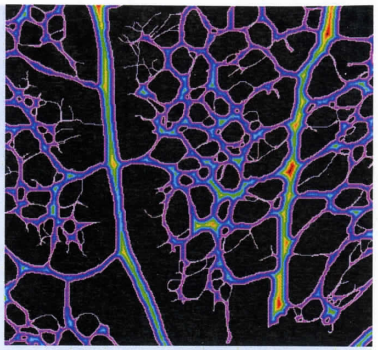
VESGEN Patent Pending



Human Retina

VESGEN

Mapping and Quantification of Branching Vascular Pattern



Mouse Retina

Vascular Trees

Human Retina

Avian CAM, Yolksac and Mouse/Avian Coronary Vessels

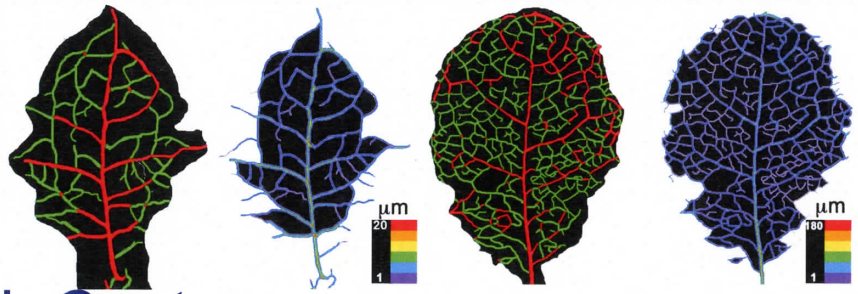
Vascular Networks

Mouse Intestinal Inflammation, CAM Lymphatic Vessels

Vascular Tree-Network Composites

Mouse Postnatal Retina, Early Embryonic Coronary Vessels

Leaf Venation Patterns in *Arabidopsis thaliana*



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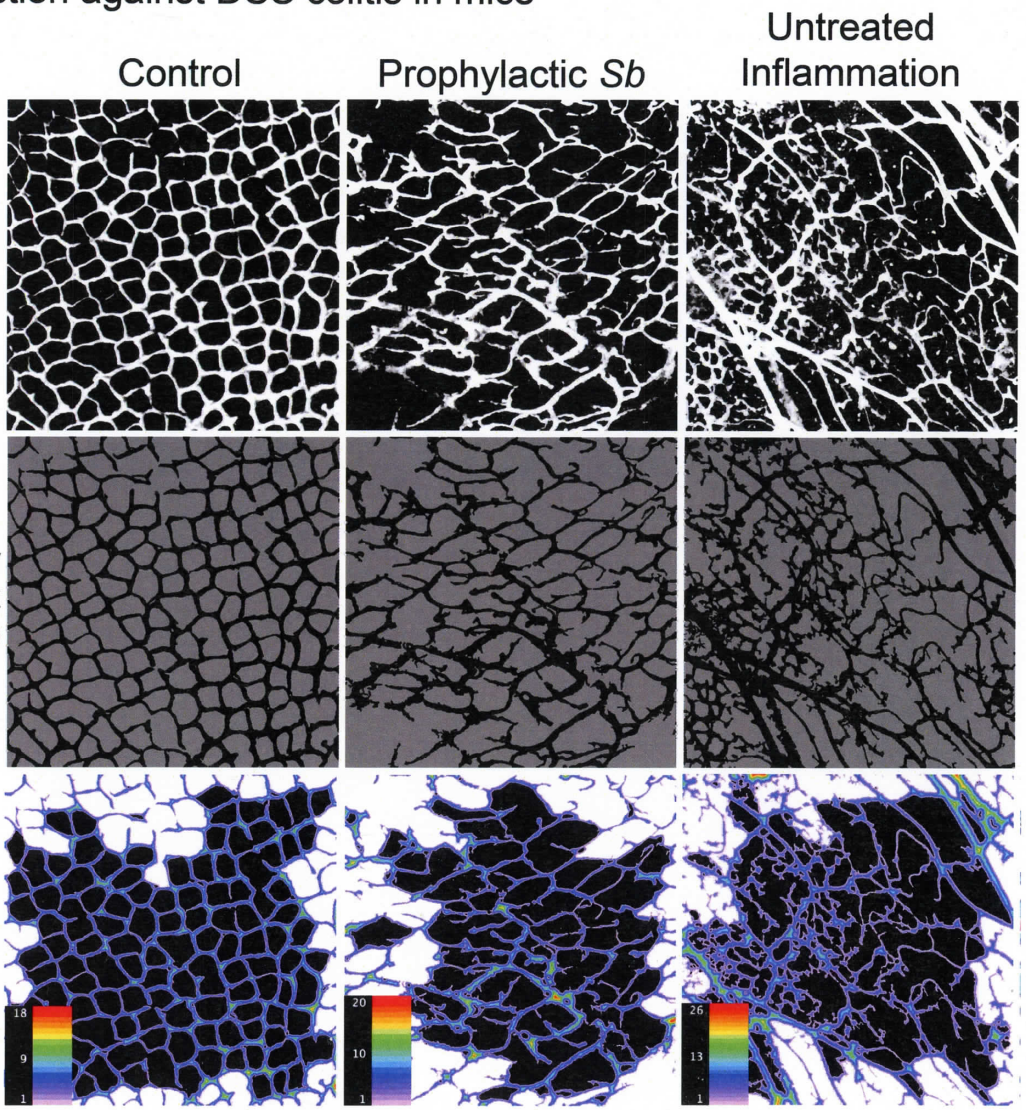
Methods for Experimental Model of GI Inflammation by VESGEN Vascular Analysis

Oral administration of probiotic yeast *Saccharomyces boulardii* (*Sb*) for protection against DSS colitis in mice



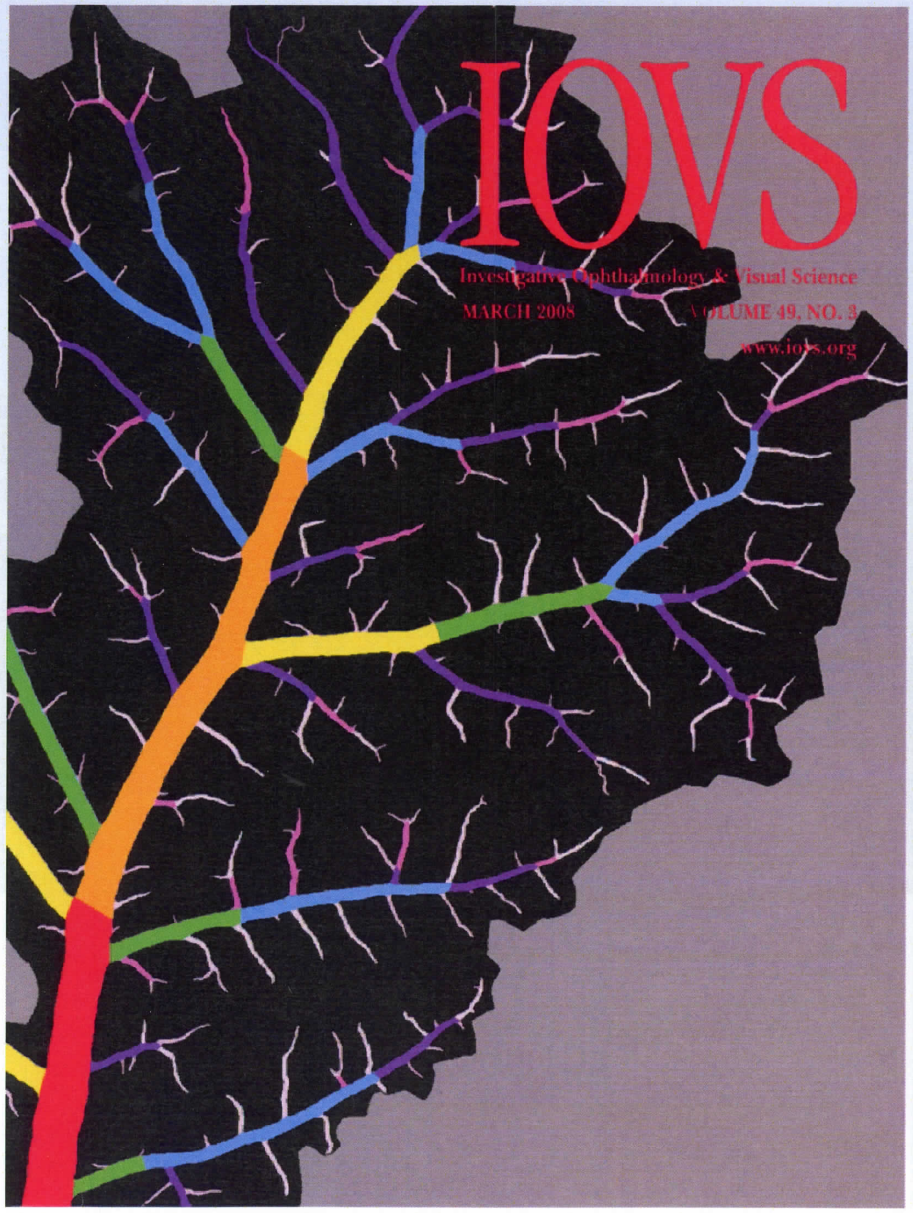
Chen X, Yang G, Song JH, Xu H, Li D, Yang X, Zeng H, Parsons-Wingerter P, Reinecker HC & Kelly CP, in progress
VESGEN Patent Pending

Complex System Results for GI Vascular Networks by VESGEN:

Probiotic *Sb* Restores Normal Vascular Architecture by 78%

Vascular Parameter	*Control*	*Probiotic Sb*	*Inflammation*	PARAMETER CONCLUSION
Vessel Diameter (μ)	16.4 ± 0.5	17.4 ± 1.4	17.6 ± 0.7	***SIMPLE Parameter*** not different
Vascular Area Fraction	0.272 ± 0.020	0.293 ± 0.040	0.409 ± 0.072	***COMPLEX Parameter*** significantly different
Branch Points	326 ± 32	452 ± 25	981 ± 259	***COMPLEX*** significantly different
End Points	134 ± 5	266 ± 41	548 ± 101	***COMPLEX*** significantly different
Avascular Spaces	100 ± 14	104 ± 8	240 ± 79	***COMPLEX*** significantly different

Triplicate mean ± std dev



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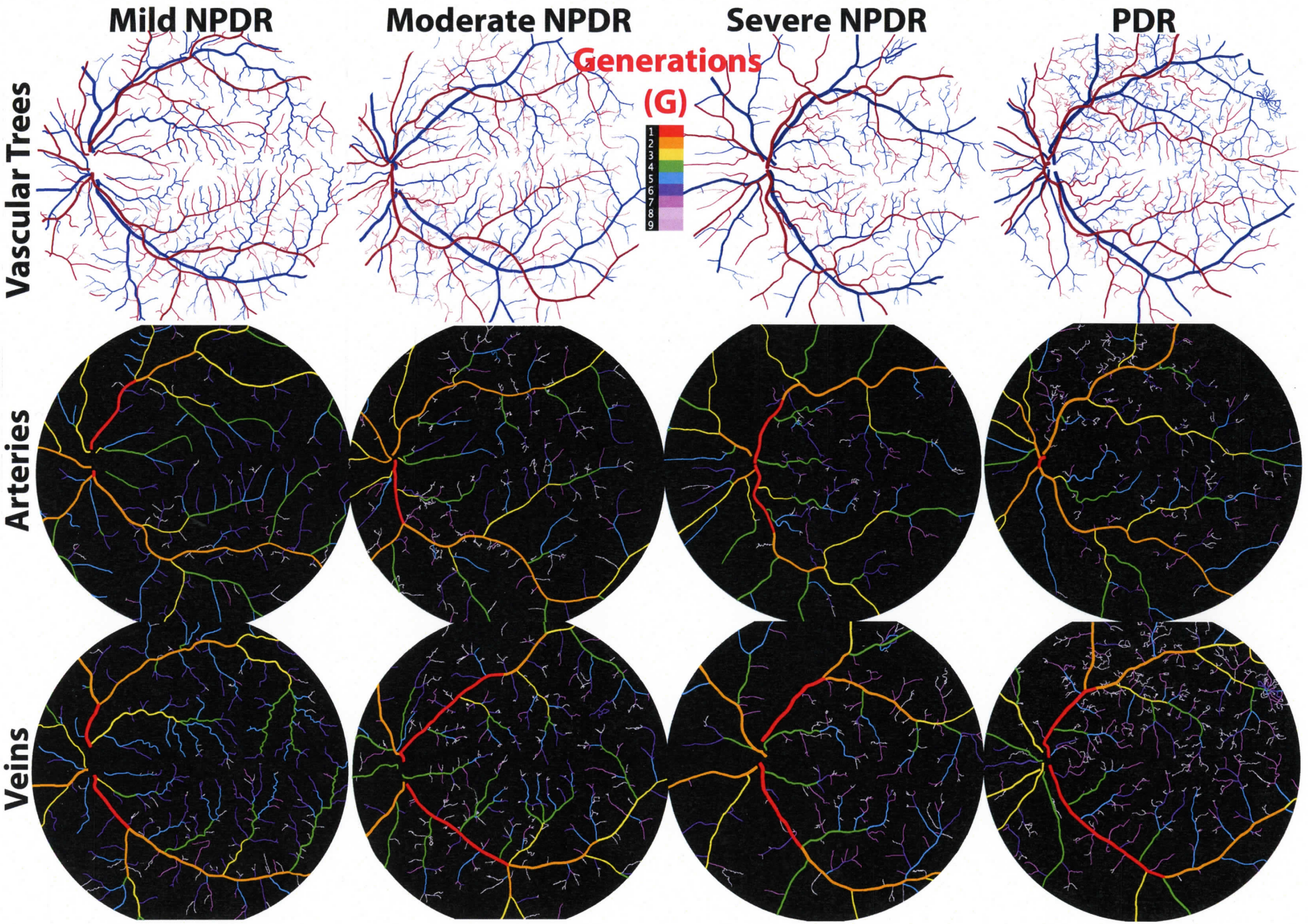
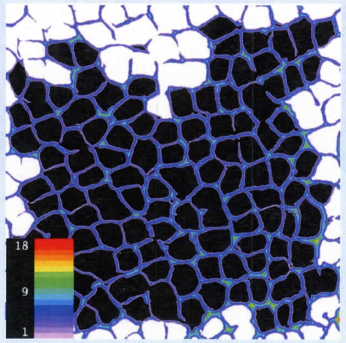
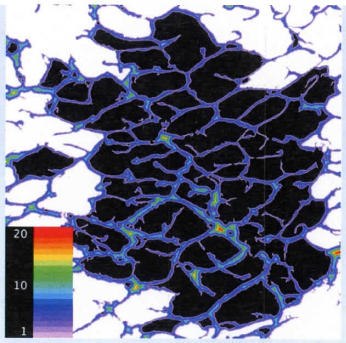
NASA

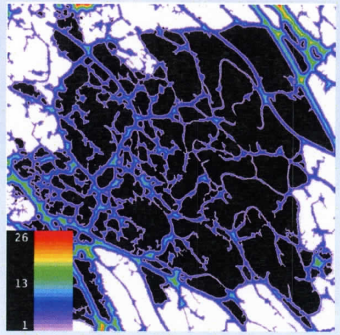
Mapping of Progressive Blinding Human Retinopathy by VESGEN



P Parsons-Wingerter, K Radhakrishnan, M B Vickerman, P K Kaiser, *IOVS* 51(1):498-507 (2010); in progress to IAA







Conclusions

- By VESGEN mapping and quantification, probiotic yeast protected against GI vascular inflammation by 78% *in vivo*

- Probiotic yeast offers a promising approach to GI protection in space, perhaps against radiation and generalized inflammation as well as infectious disease

- Innovative VESGEN application to GI inflammation – building on previously published work for vascular tissues including human and rodent retina; avian CAM, avian and rodent coronary vessels and remodeling leaf venation patterns in *Arabidopsis thaliana*

Acknowledgements

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