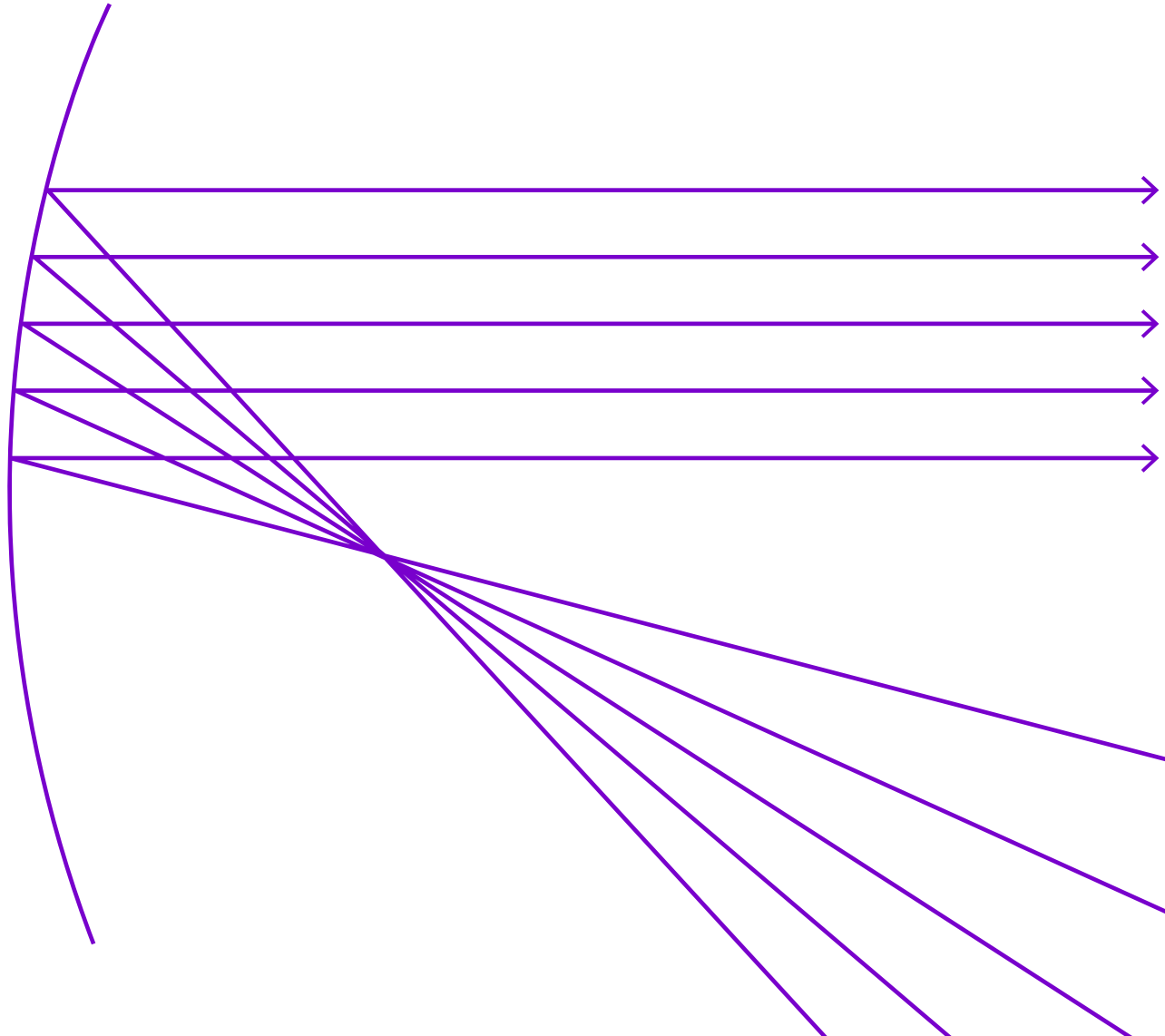
OPTICA
Advancing Optics and Photonics Worldwide
Formerly OSA

Therapeutic Laser Applications Technical Group

Non-Damaging Retinal Laser Therapy: Mechanisms and Applications



Daniel Palanker, Stanford University
20 October 2021

Technical Group Executive Committee

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About Our Technical Group

Our technical group focuses on the use of lasers in surgery or in other treatments of disease Our mission is to connect the 900+ members of our community through technical events, webinars, networking events, and social media.

Our past activities have included:

- Special talk at 2021 OSA Biophotonics Congress on Listening to the Sound of Light to Guide Surgeries by Muyinatu Bell, Johns Hopkins University
- Special talk at Frontiers in Optics 2020 on volumetric imaging of the eye and brain by optical coherence tomography by Bernhard Baumann, Medical University of Vienna
- Best Poster Presentation Award at 2020 OSA Biophotonics Congress, in collaboration with several other TGs from Biomedical Optics Division
- 6 previous webinars available for on-demand viewing at www.optica.org/TGwebinars

Connect With Our Technical Group

Join our online community to stay up to date on our group's activities. You also can share your ideas for technical group events or let us know if you're interested in presenting your research.

Ways to connect with us:

- Our website at www.optica.org/BA
- On LinkedIn at www.linkedin.com/groups/8302285/
- On Facebook at www.facebook.com/groups/opticatherapeuticlaserapplications
- Email us at elina.vitol@gmail.com or TGactivities@optica.org

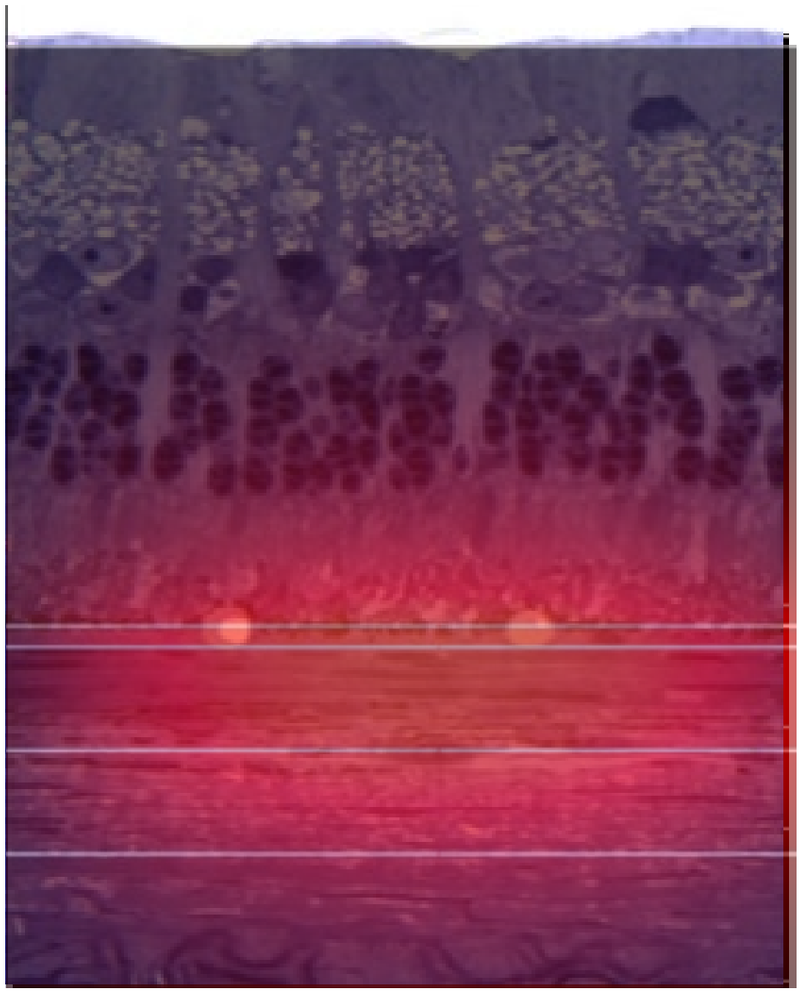
Today’s Speakers

Daniel Palanker

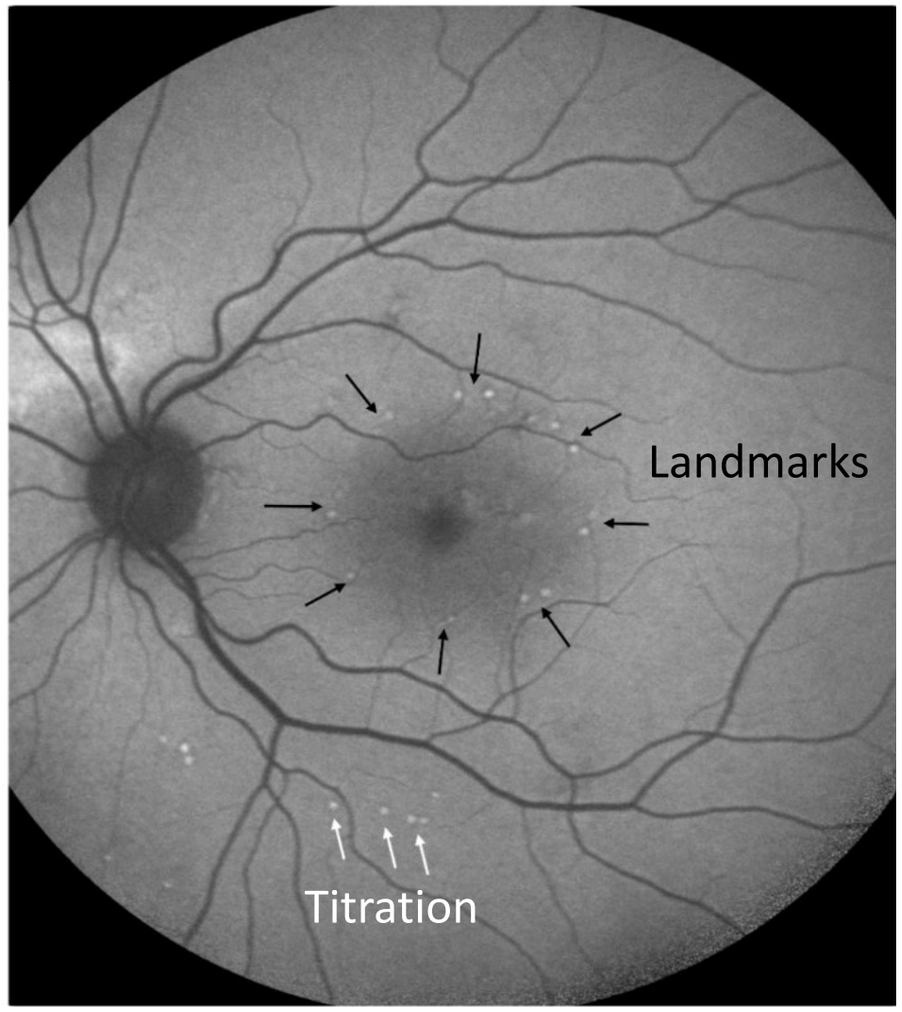
Stanford University

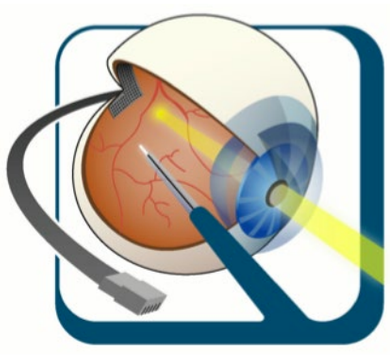
Daniel Palanker is a Professor of Ophthalmology and, by courtesy, of Electrical Engineering at Stanford University. He received MSc in Physics in 1984 from the State University of Armenia in Yerevan, and PhD in Applied Physics in 1994 from the Hebrew University of Jerusalem, Israel. Dr. Palanker studies interactions of electric field with biological cells and tissues, and develops optical and electronic technologies for diagnostic, therapeutic, surgical and prosthetic applications, primarily in ophthalmology.

Non-Damaging Retinal Laser Therapy of the Macula: Mechanisms and Applications



Daniel Palanker





Department of Ophthalmology and
Hansen Experimental Physics Laboratory
Stanford University

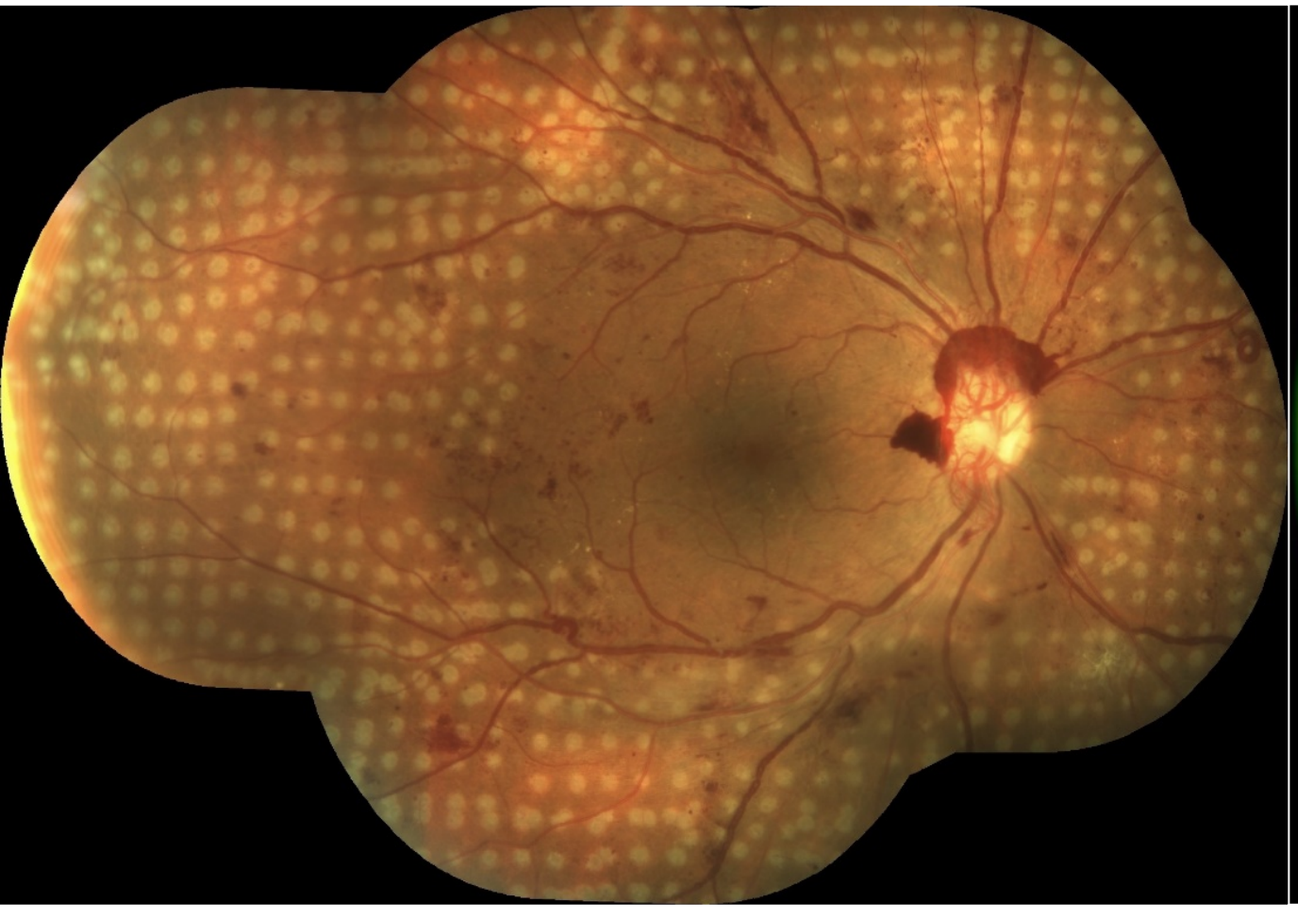
Financial Disclosure

Inventor of the patents and consultant to:

Topcon Medical Laser Systems *
Abbot Medical Optics
Medtronic
Avalanche Biotechnologies
Oculeve (now Allergan)
DigiSight
Pixium Vision

Retinal Photocoagulation

PanRetinal Photocoagulation



Macular Grid

<u>Proliferative Diabetic Retinopathy:</u>

Balancing supply and demand:

- Hypoxic retina cannot sustain full retinal metabolic demand. It secretes VEGF cytokines leading to neovascularization.
- Extensive destruction of photoreceptors in peripheral retina reduces oxygen demand, suppressing VEGF signaling and thus prevents angiogenesis.

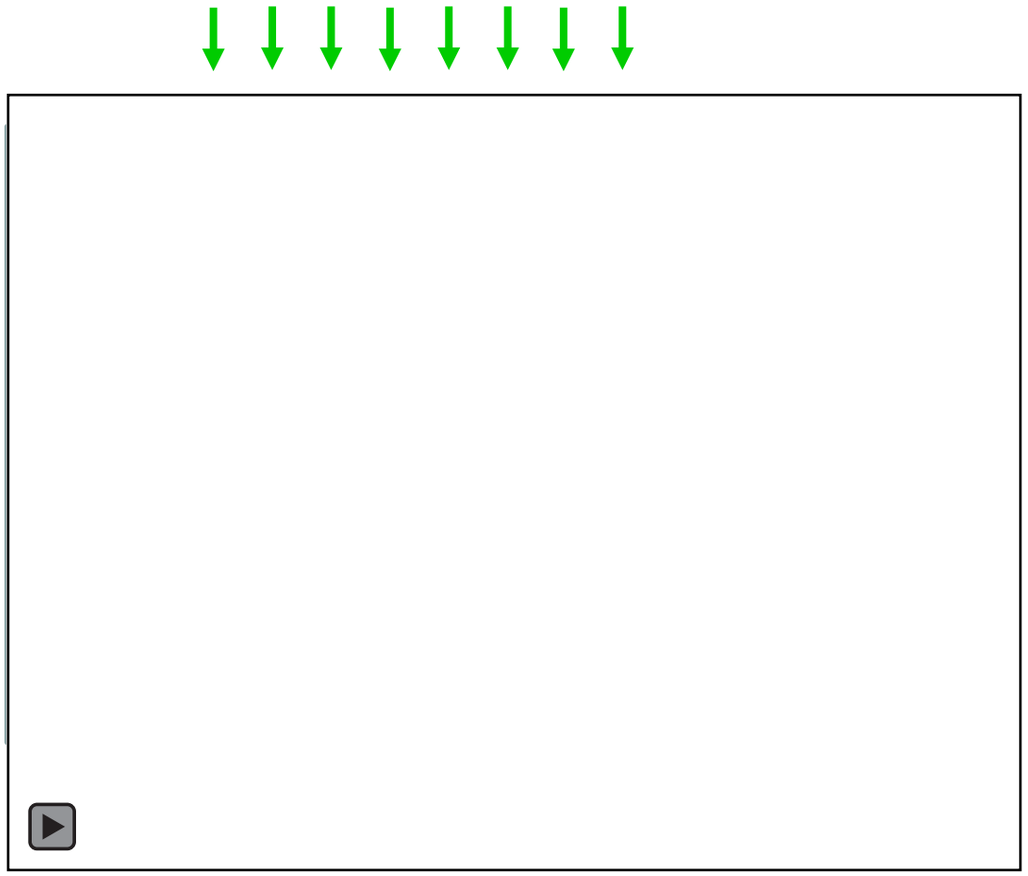
<u>Macular Edema:</u>

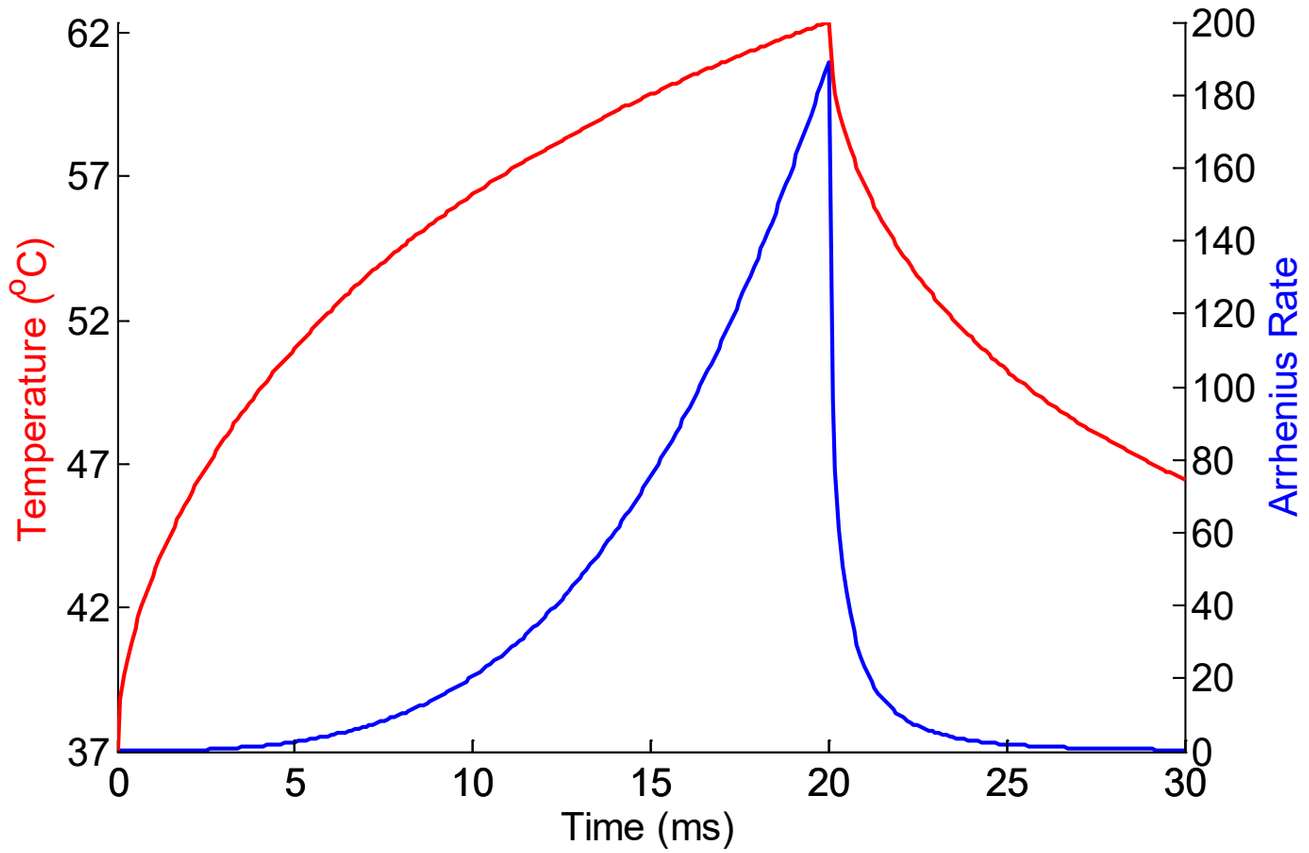
Macular grid reduces edema via <u>unknown mechanism</u>.

<u>Hypothesis</u>: Cells surviving the thermal stress activate repair pathways which help restoring normal function.

Quantifying Thermal Damage in Tissue

1. Calculating temperature in space and time using computational model.





2. Decrease in protein concentration due to thermal denaturation (Arrhenius equation):

$$\frac{dD}{dt} \propto -D \cdot \exp\left(-\frac{E^*}{R \cdot T}\right)$$

$$\Omega(\tau) = -ln\left(\frac{D(\tau)}{D_0}\right) = A\int_0^{\tau} exp\left(-\frac{E^*}{R \cdot T(t)}\right) dt$$

3. Normalizing Arrhenius integral Ω by the threshold of lethal damage,
   i.e. cells are dead when $\Omega > 1$.

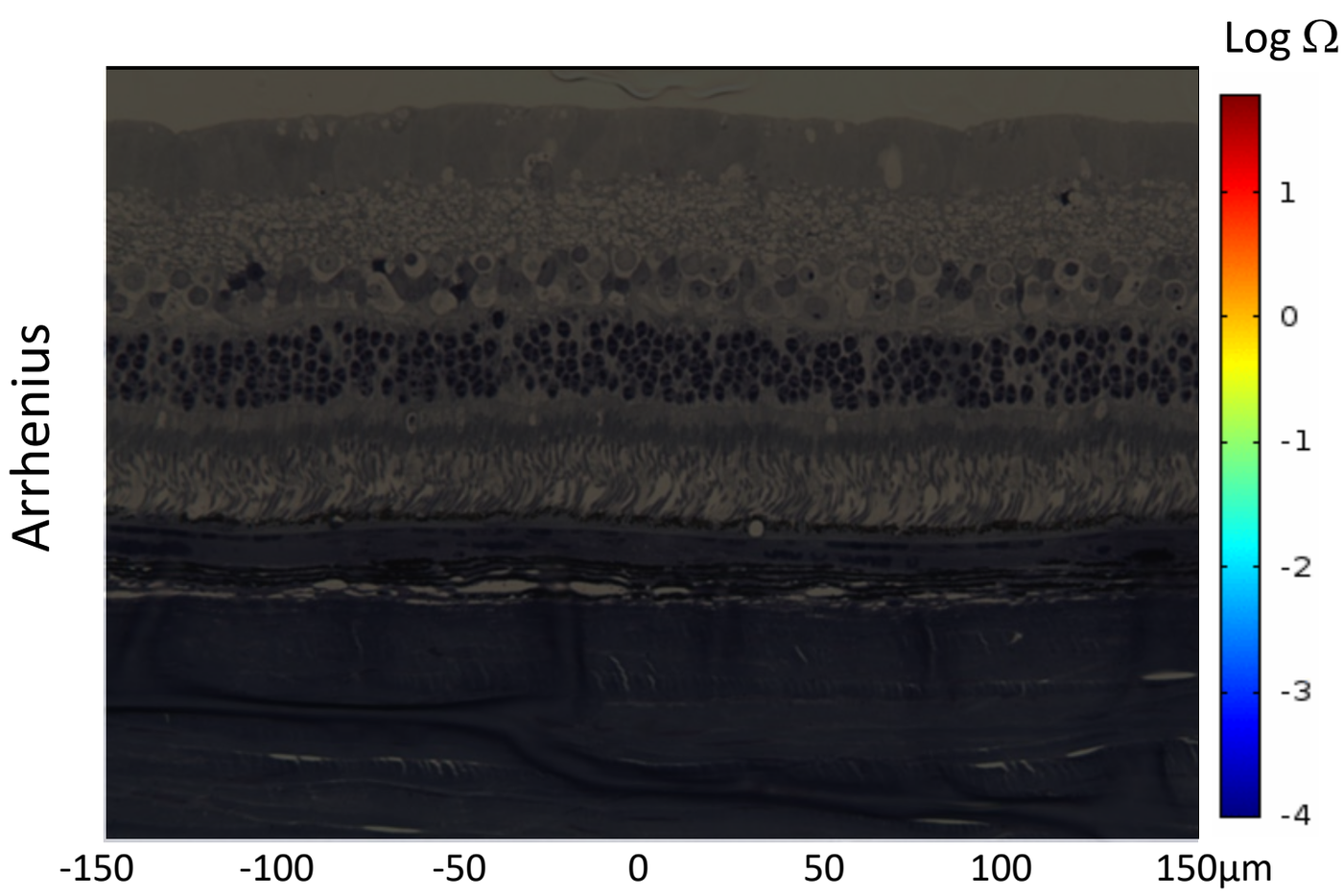
C. Sramek et.al. *J. Biomedical Optics* (2009)

Arrhenius Integral

λ=577nm, d=134μm,
t=20ms, P=50 mW

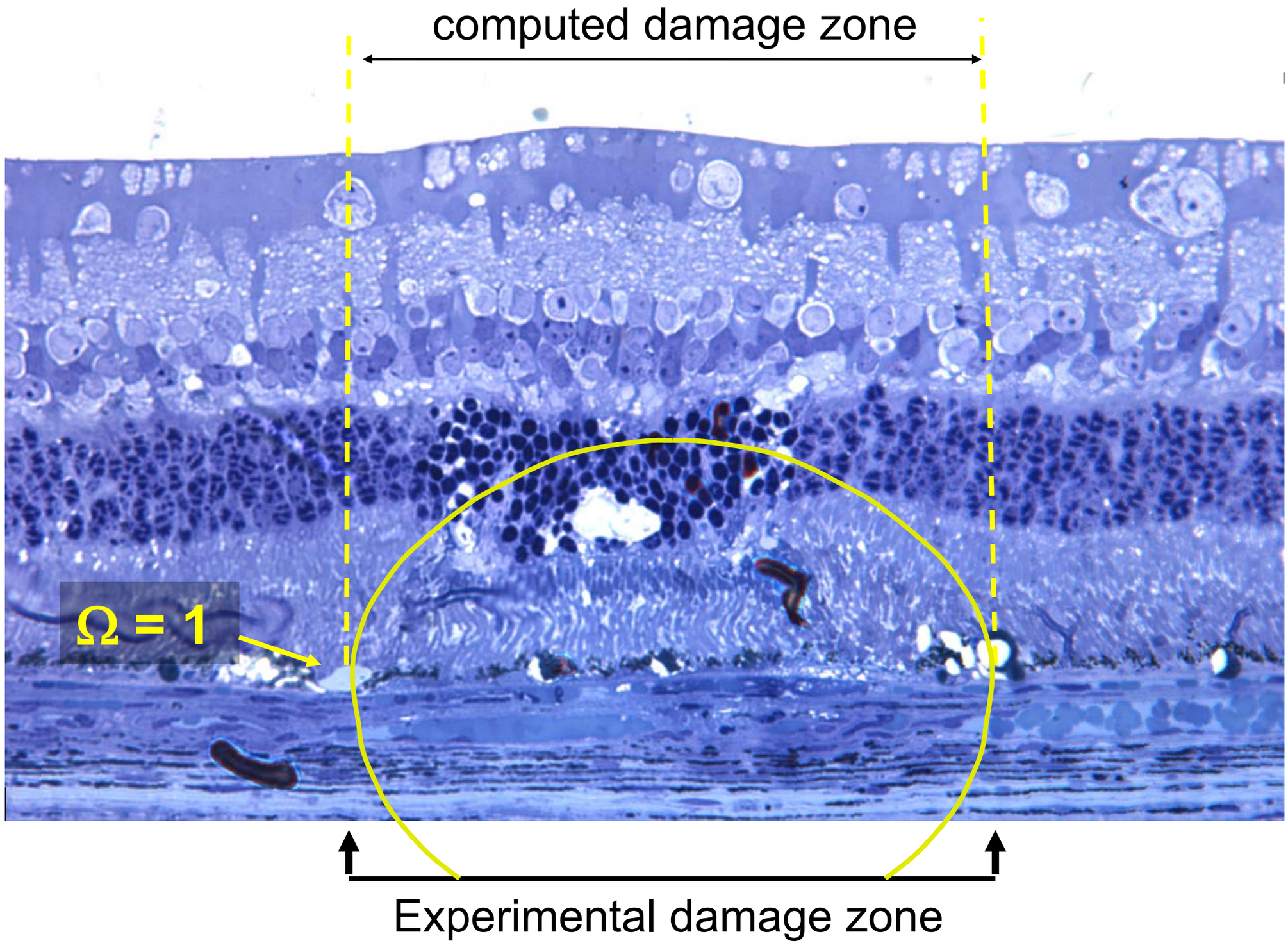
Ω=1

Ω=0.1



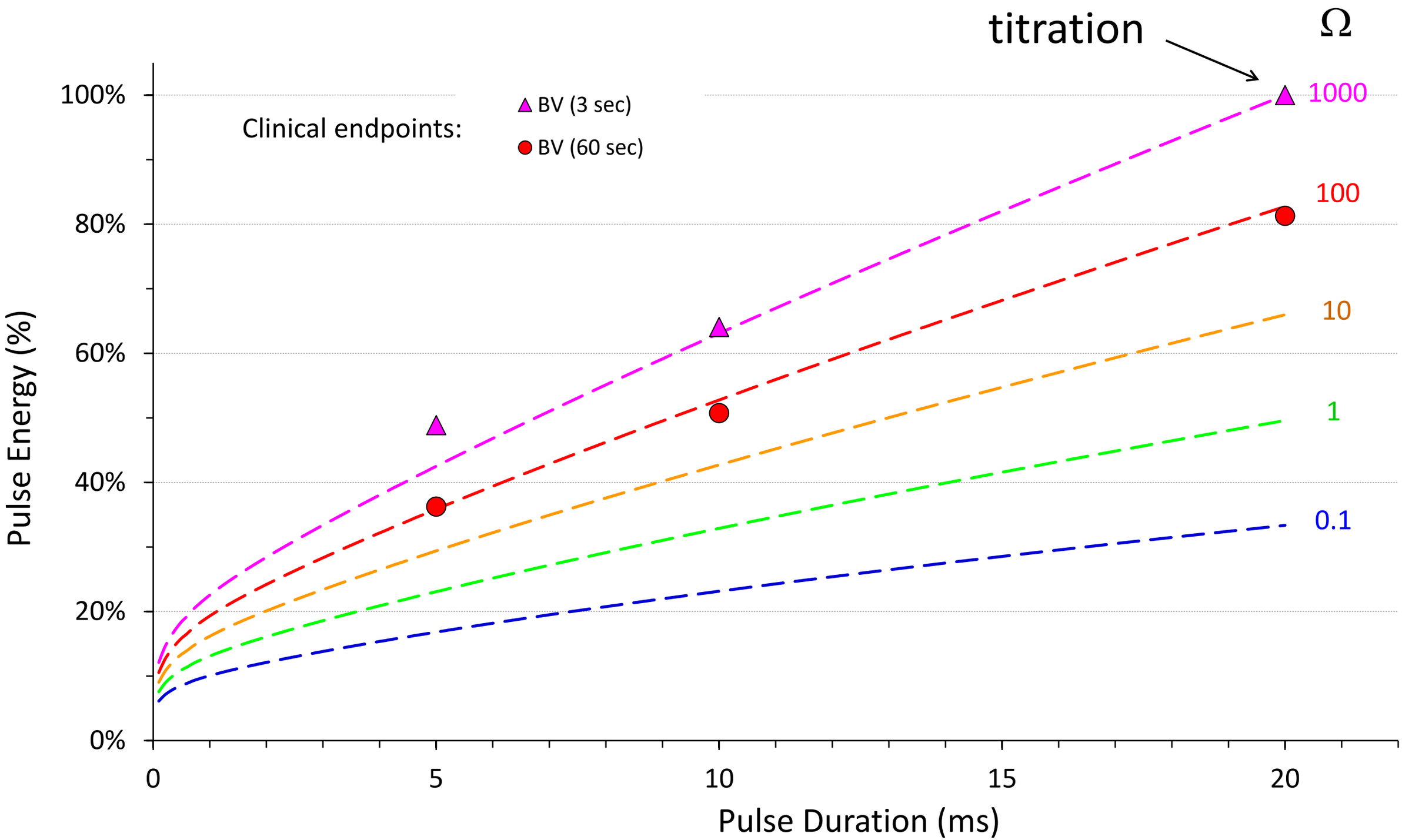
Cellular damage zone

10ms, 150mW



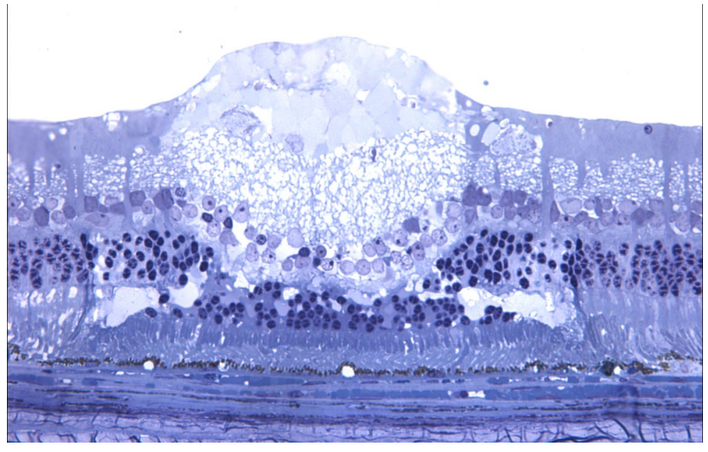
C. Sramek et.al. *J. Biomedical Optics*, 14(3), 034007 (2009)

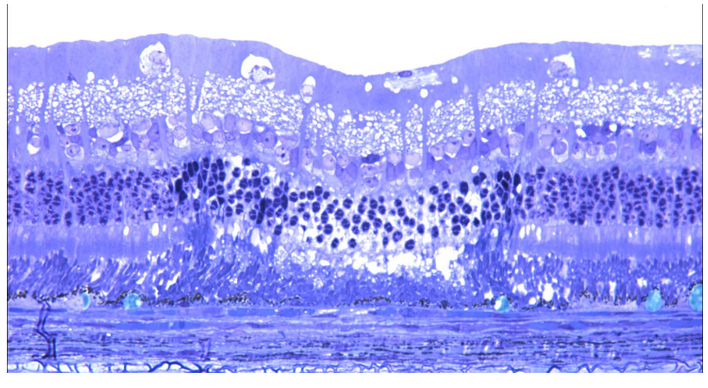
EndPoint Management Algorithm:
Laser Settings for Desired Clinical Outcome



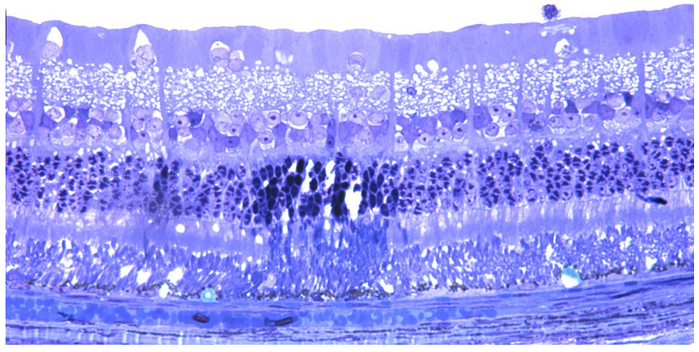
Clinical Endpoints

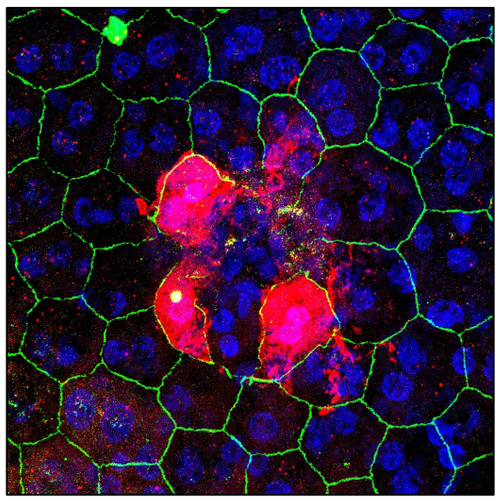
- Ophthalmoscopically visible
  - Moderate
  - Light
  - Barely visible

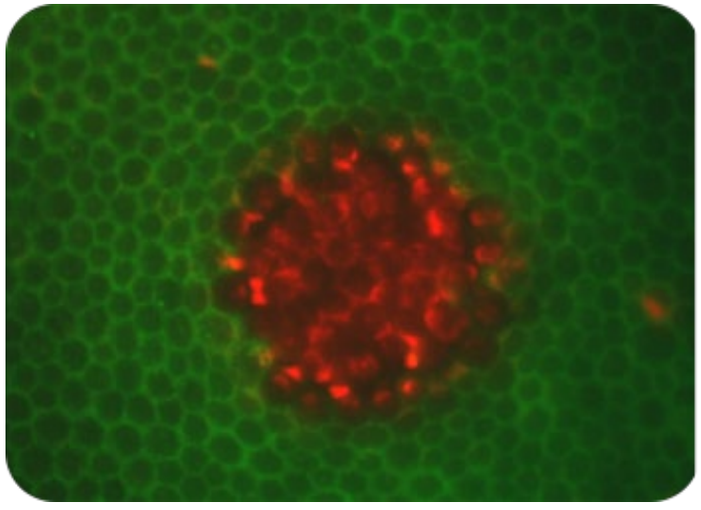




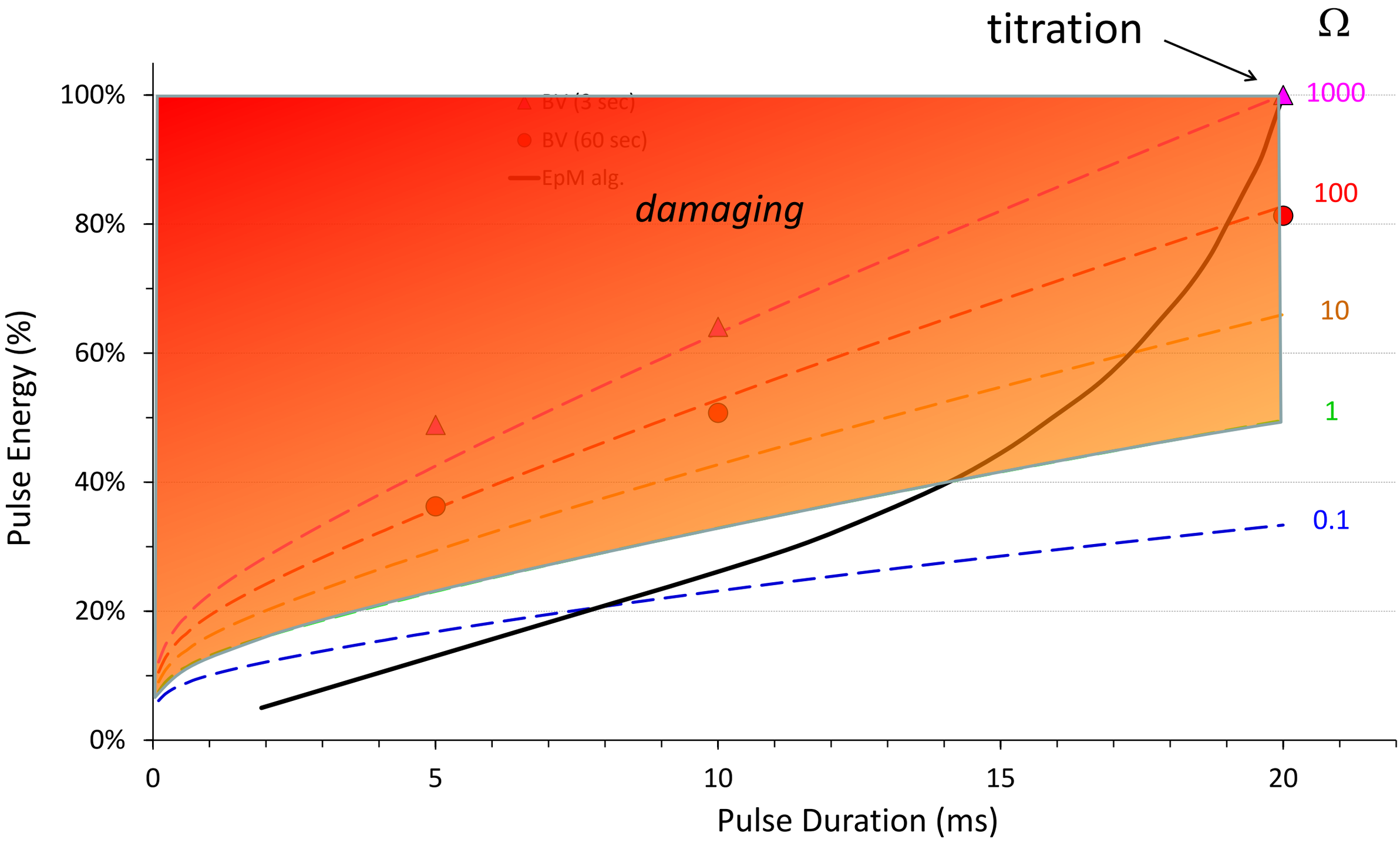
- Ophthalmoscopically invisible
  - OCT (very light PR damage)
  - FA (RPE damage)
  - Non-damaging
  - Sub-therapeutic





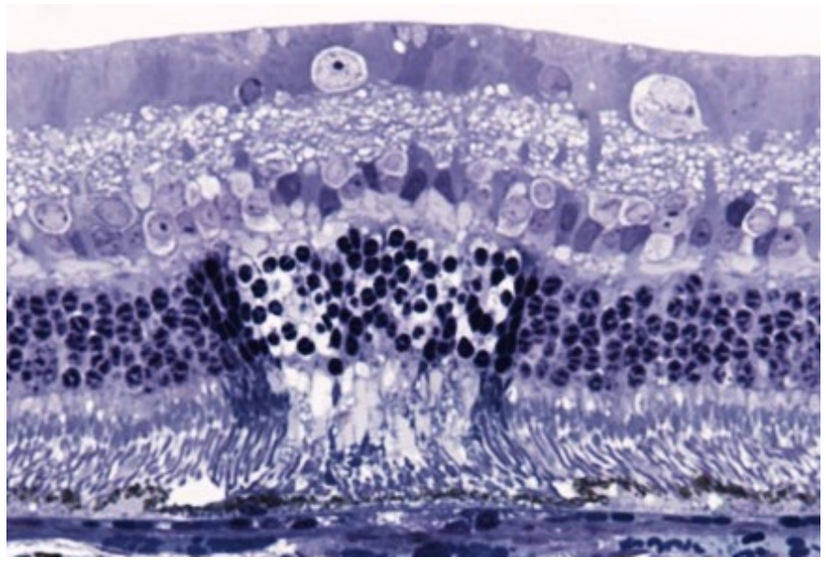


EndPoint Management Algorithm:
Laser Settings for Desired Clinical Outcome

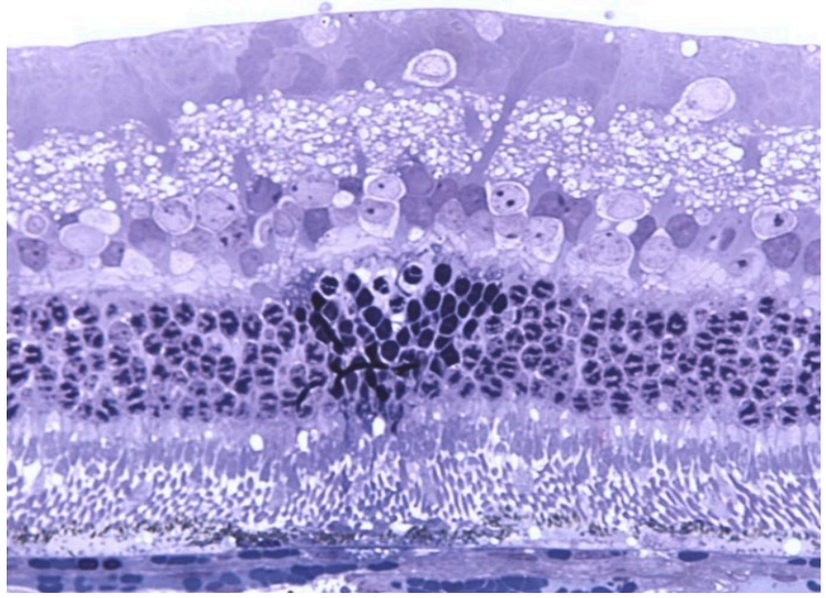


Retinal Damage on EpM scale

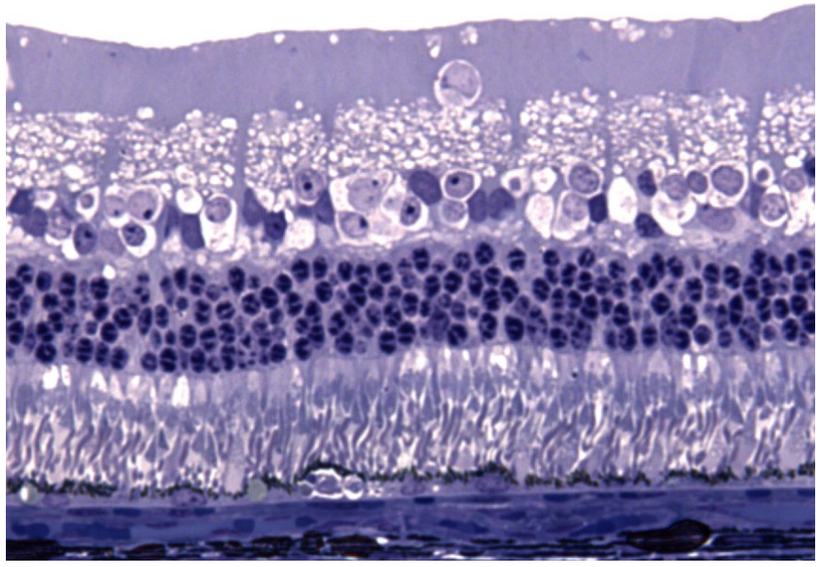
100%



50%

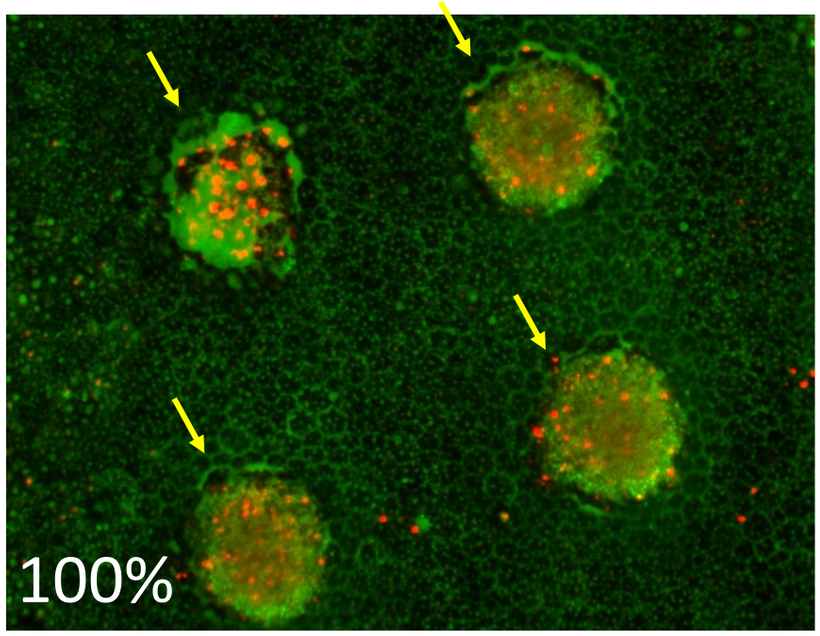


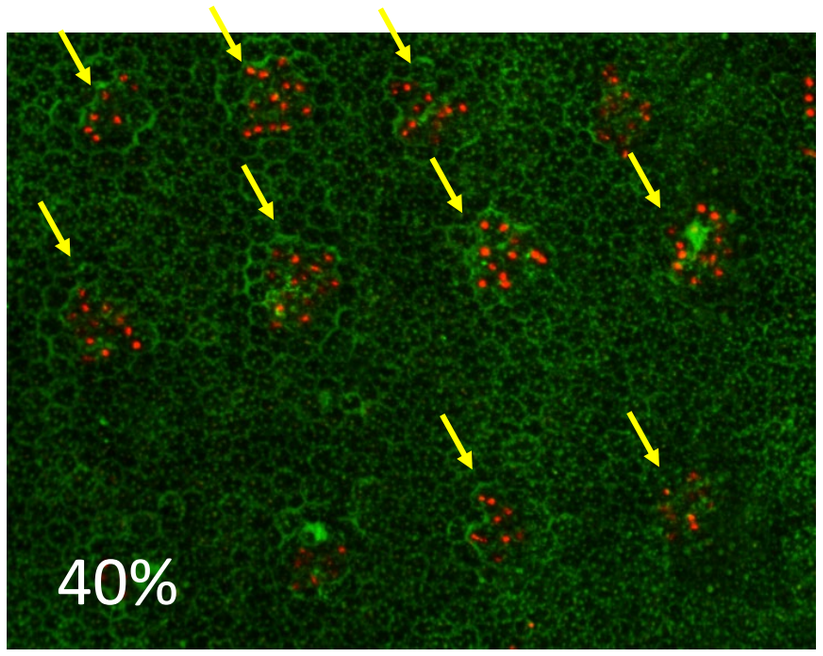
30%

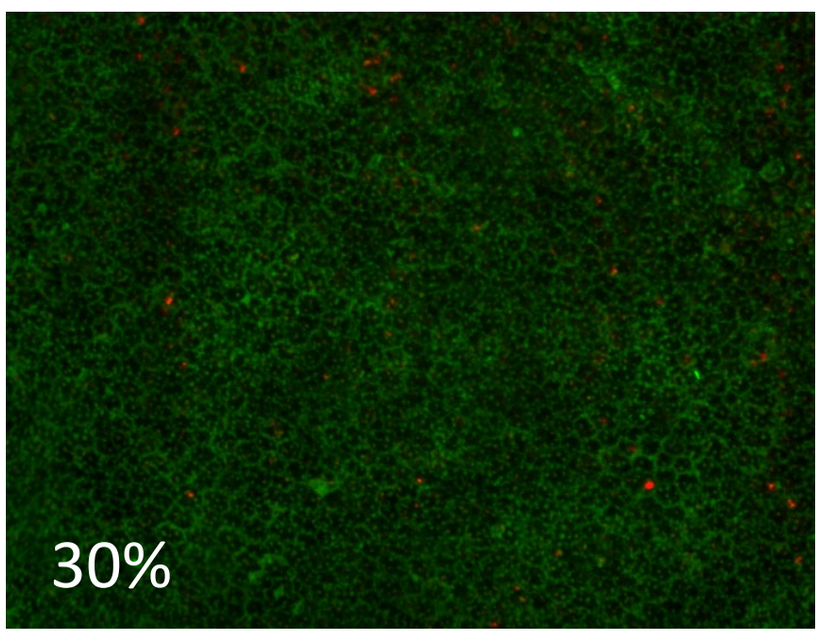


200 μm,1 hour

Live – dead staining of RPE







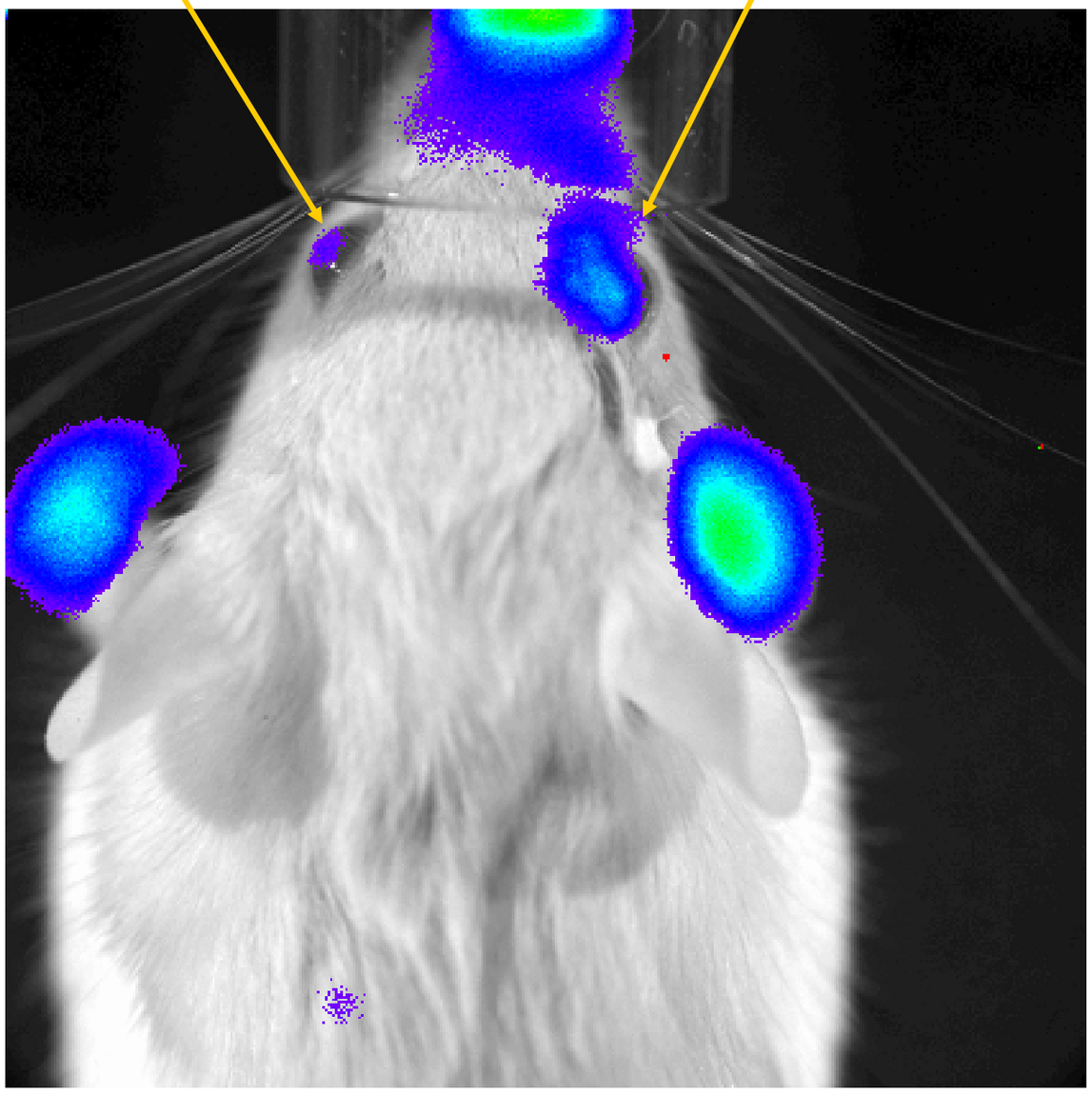
No structural damage

Lavinsky D et al., Retina 2013

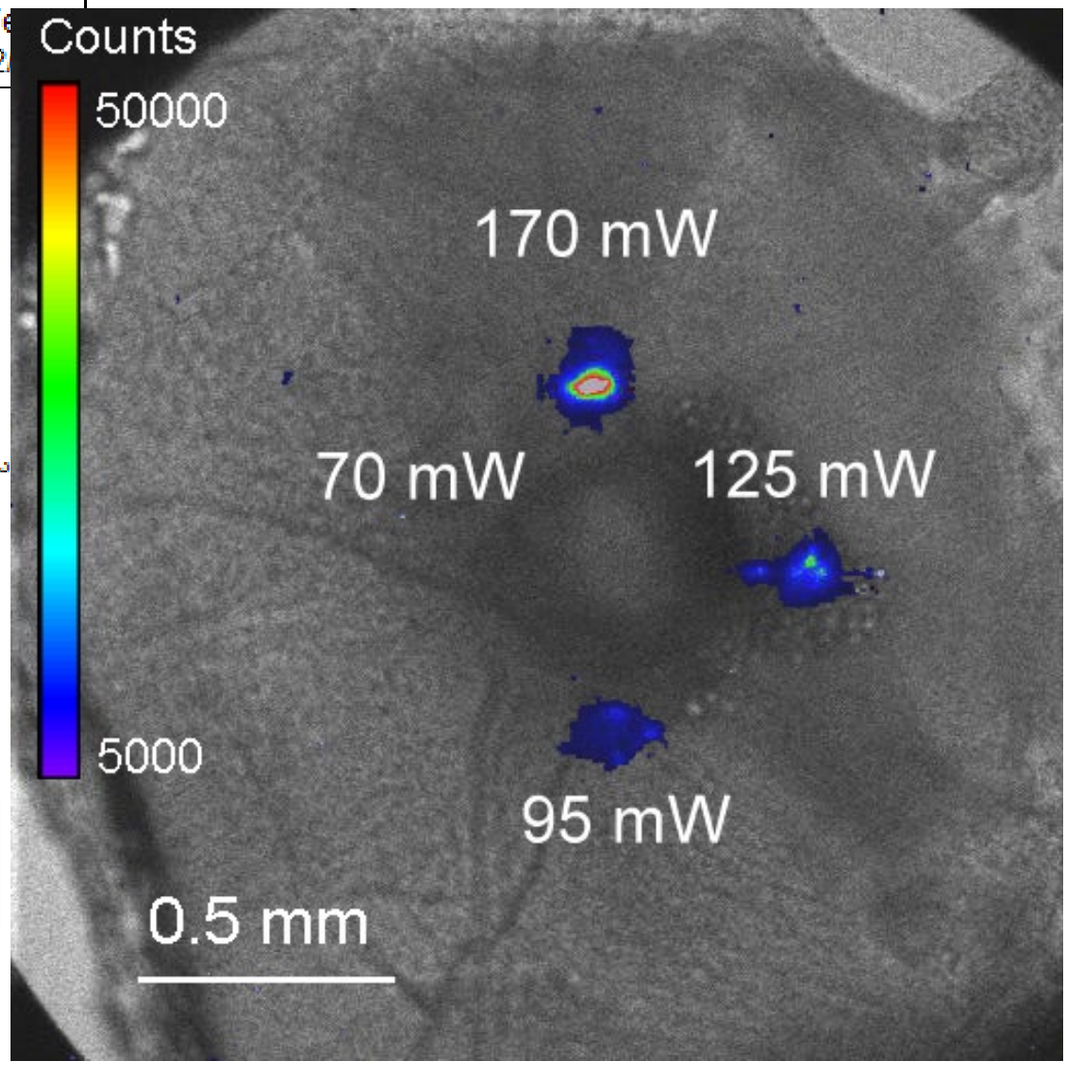
Heat Shock Protein Expression:
bioluminescence of HSP-70

Control eye

Treated eye



Flat-mount posterior pole

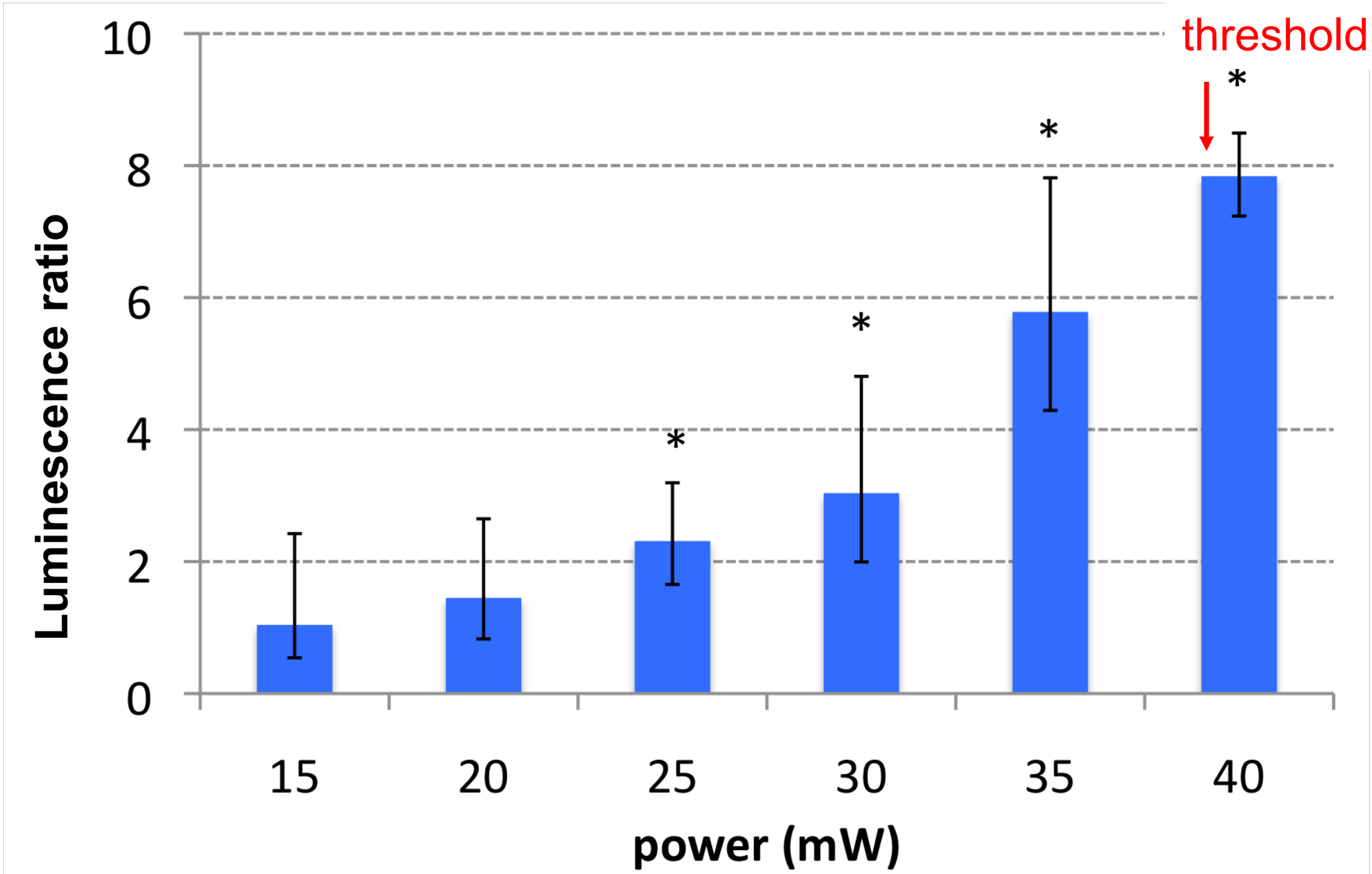


Click # MM20080131172135
Thu, Jan 31, 2008 17:22:06
Em filter=Open
Bin:HR (4), FOV4, f1, 4m
Camera: IVIS 23302, Spectral Instruments Inc.

Series: Nd:Yag
Experiment: Mouse 1
Label: 7 Hours, 2
Comment:
Analysis Comment:

IOVS 52(3):1780-7 (2011)

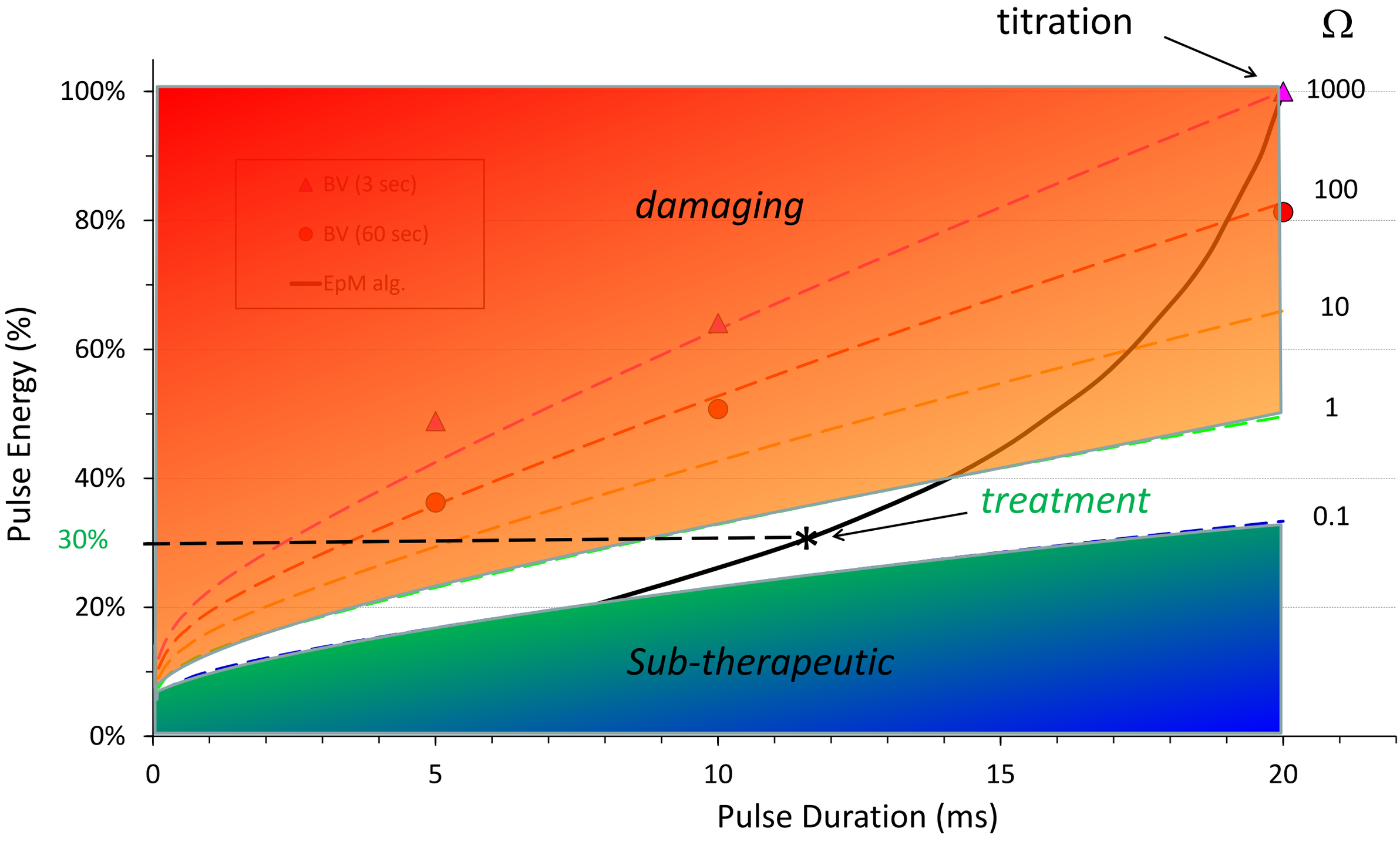
Expression of Heat Shock Protein HSP70: treated/control



$\Omega = 0.1$ $\Omega = 1$

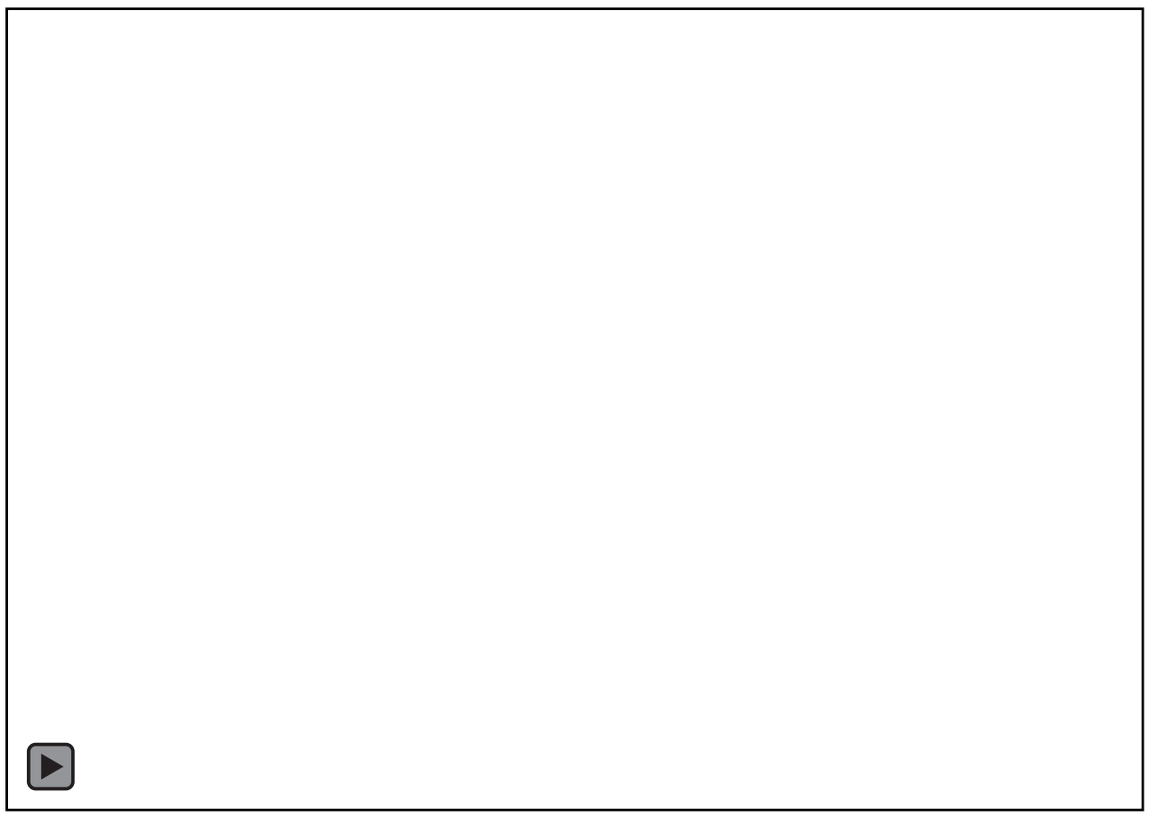
IOVS 52(3):1780-7 (2011)

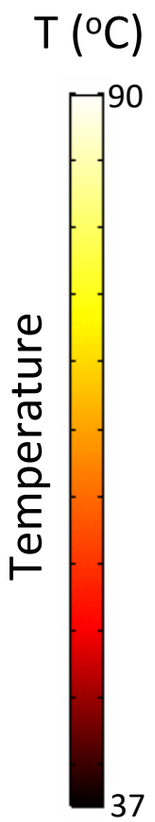
EndPoint Management Algorithm:
Laser Settings for Desired Clinical Outcome

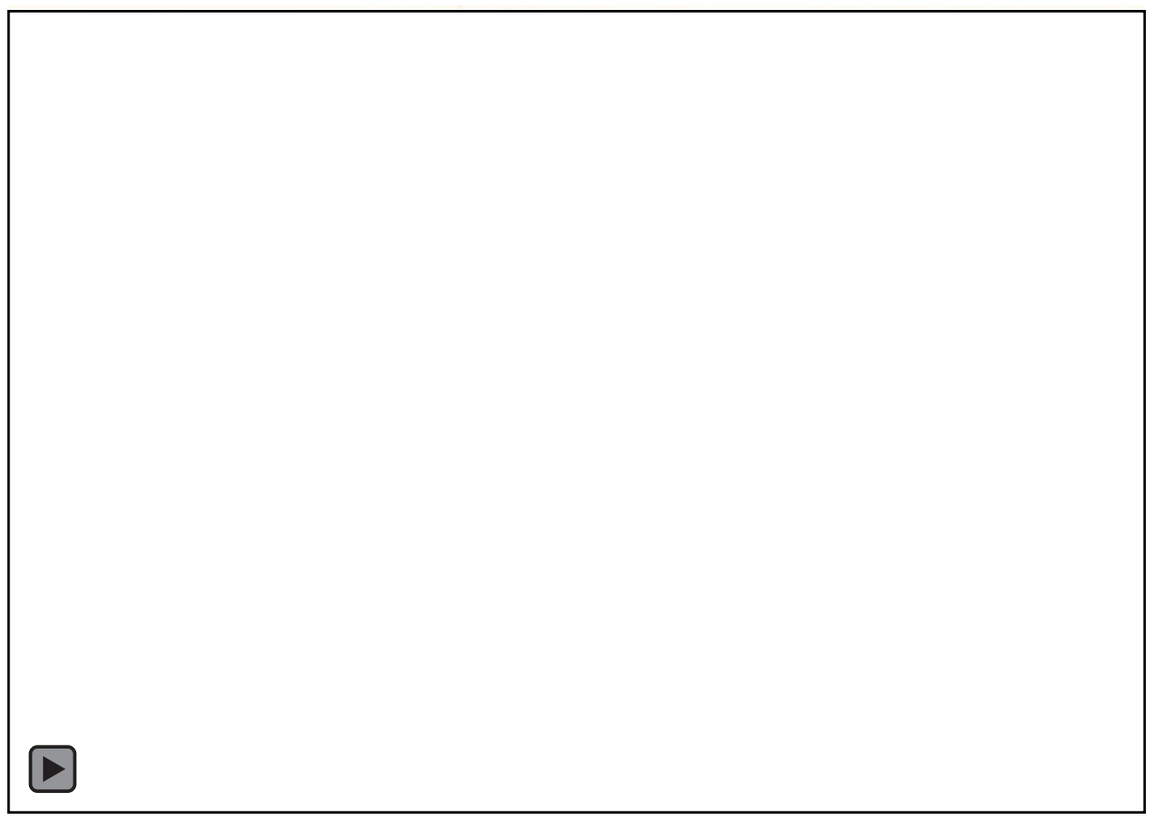


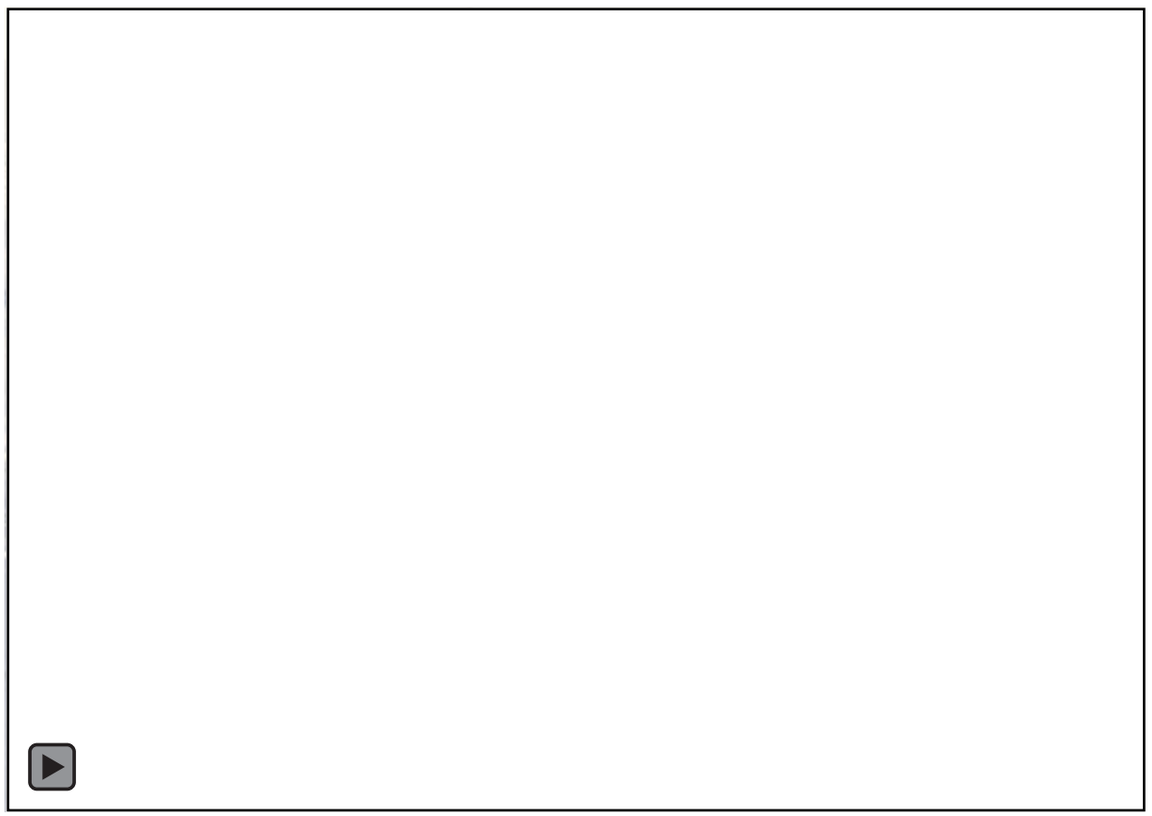
Titration (100%: 74.2 mW, 20 ms)

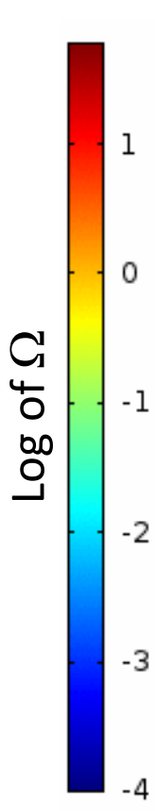
NRT treatment (30%: 37 mW, 11.4 ms)









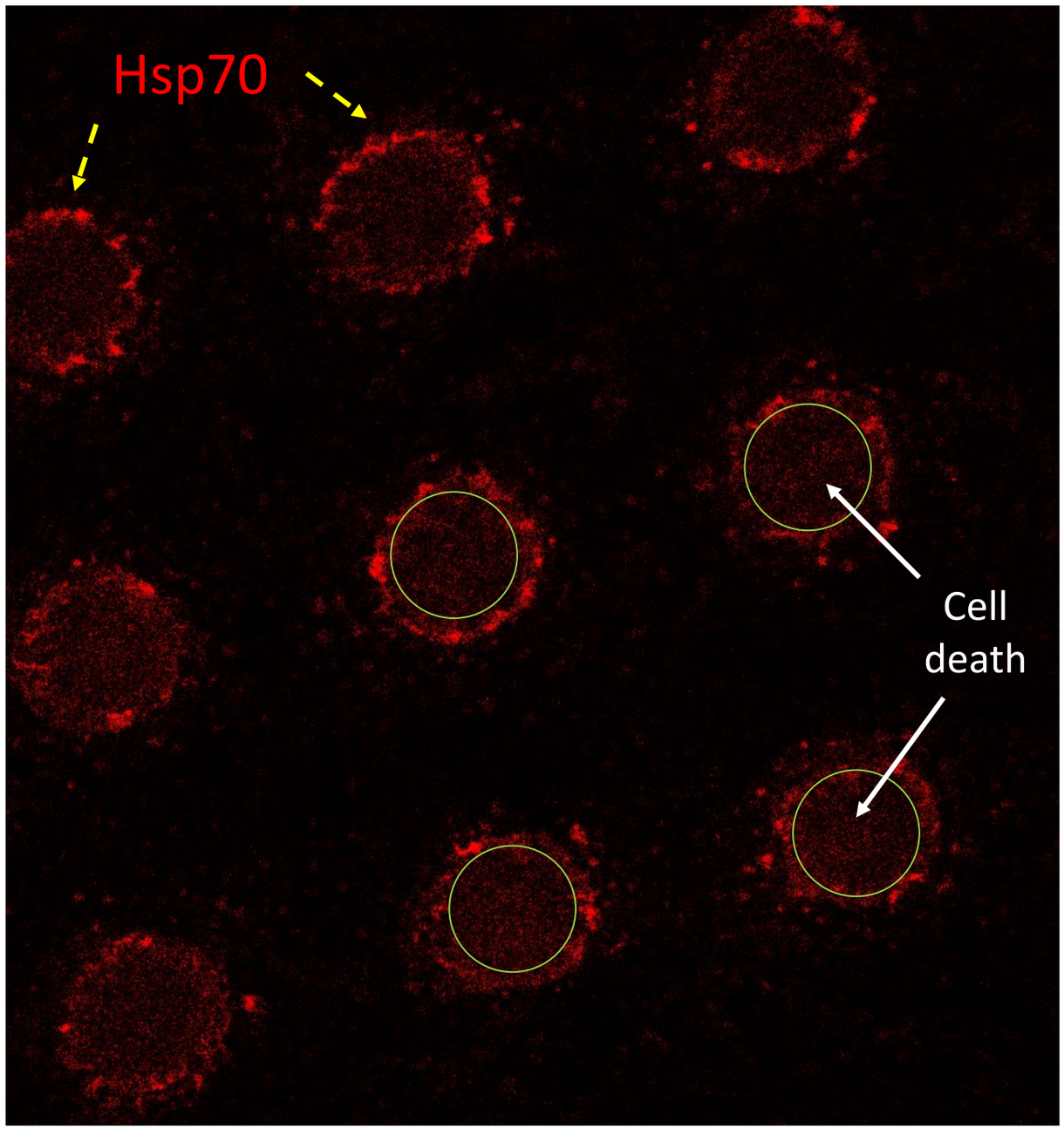


Time course: 40 ms

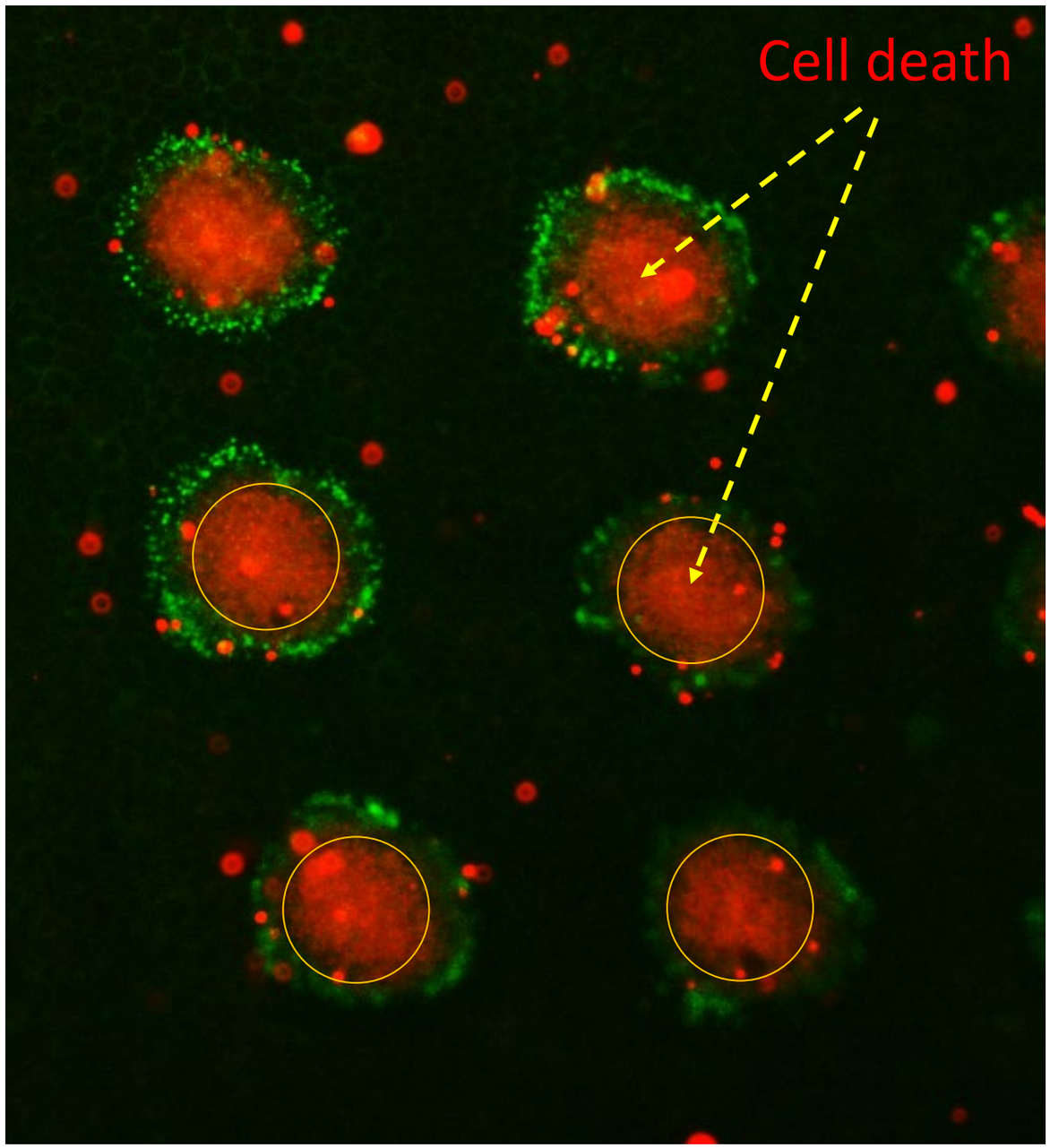
Barely-Visible Burns (100%)

RPE, 7 hours post-laser

HSP 70



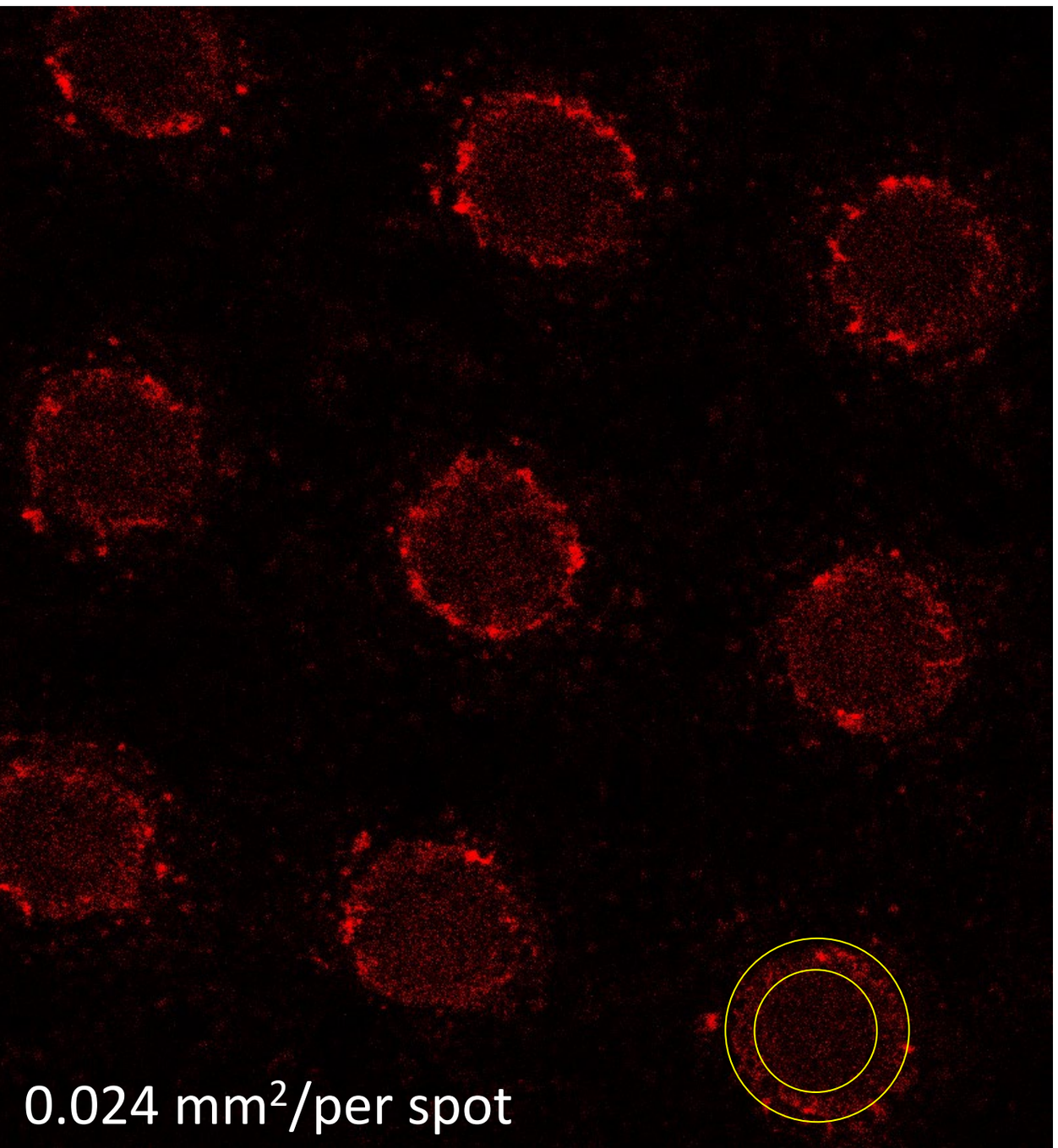
Live-dead staining



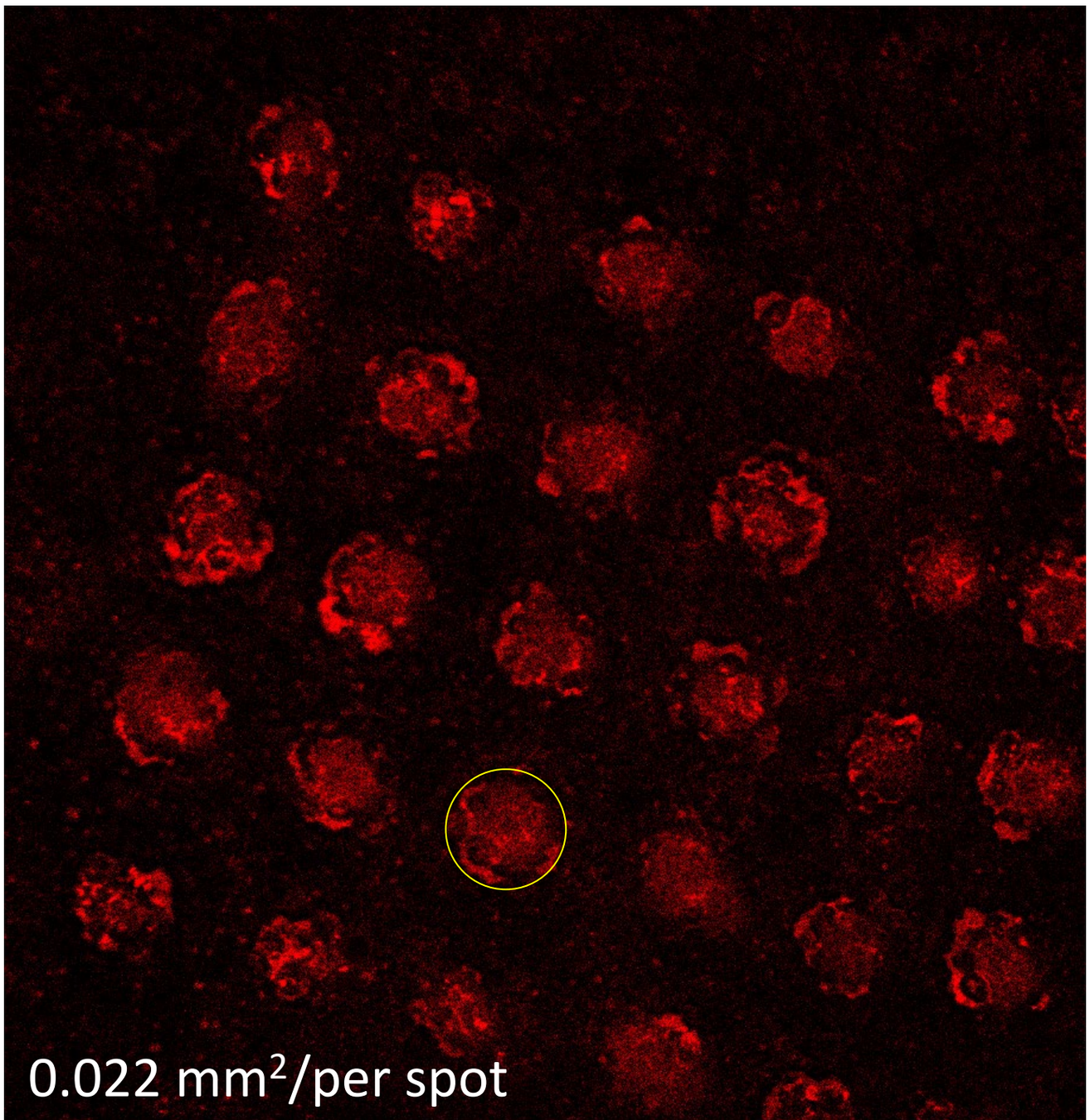
Heat-shock Protein Expression

HSP 70, 7 hours post-laser

100%



30%

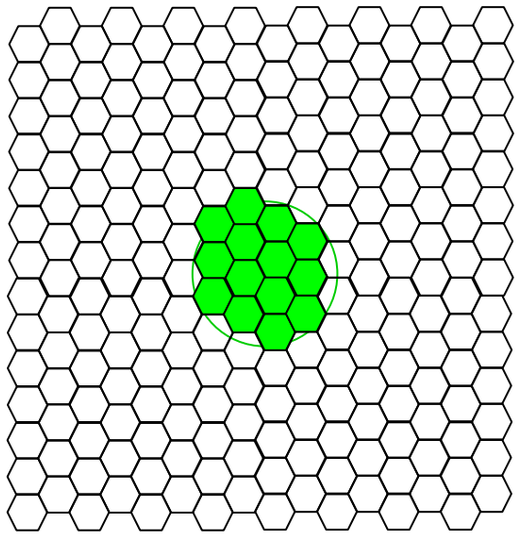


Areas of HSP expression and tissue damage

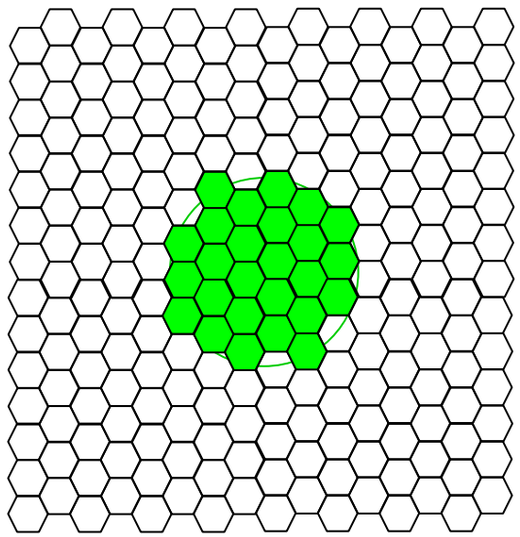
HSP for $\Omega > 0.1$

Damage for $\Omega > 1$

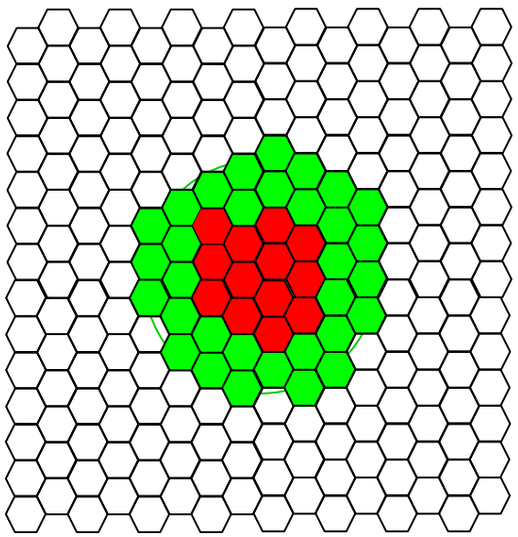
25%



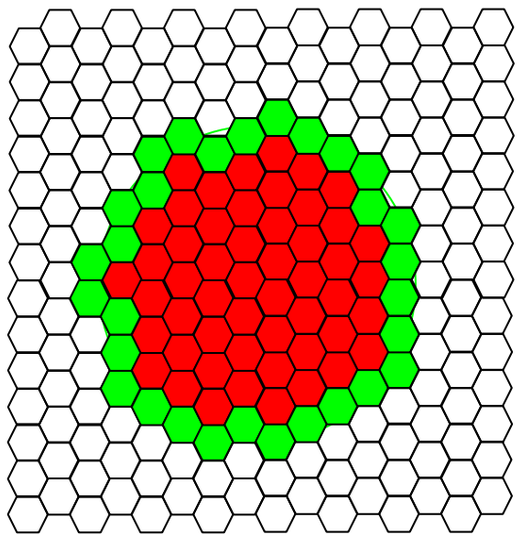
30%



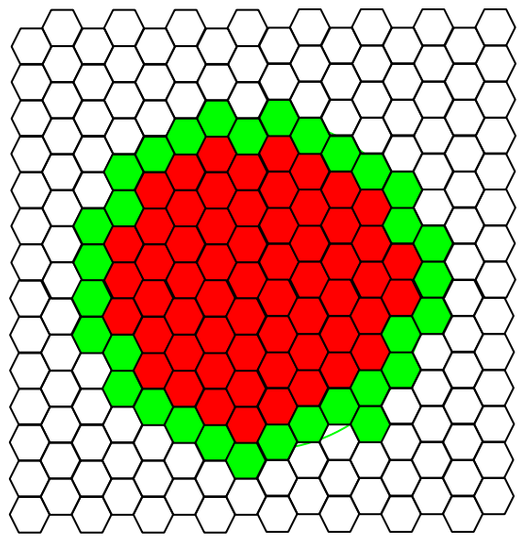
40%



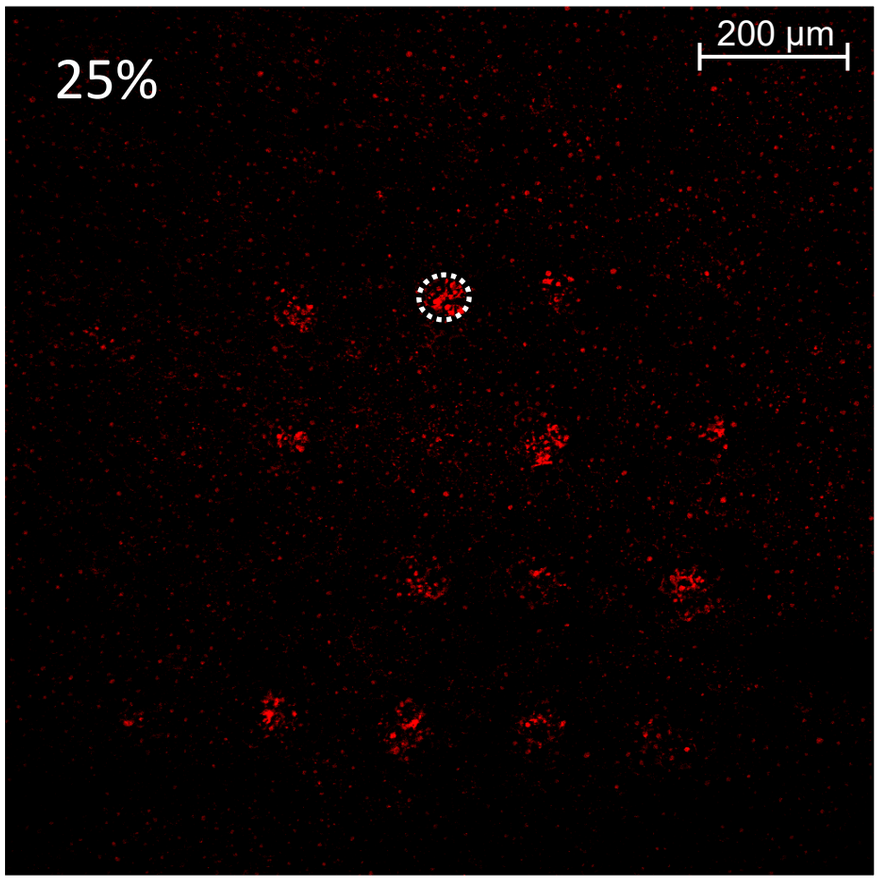
100%

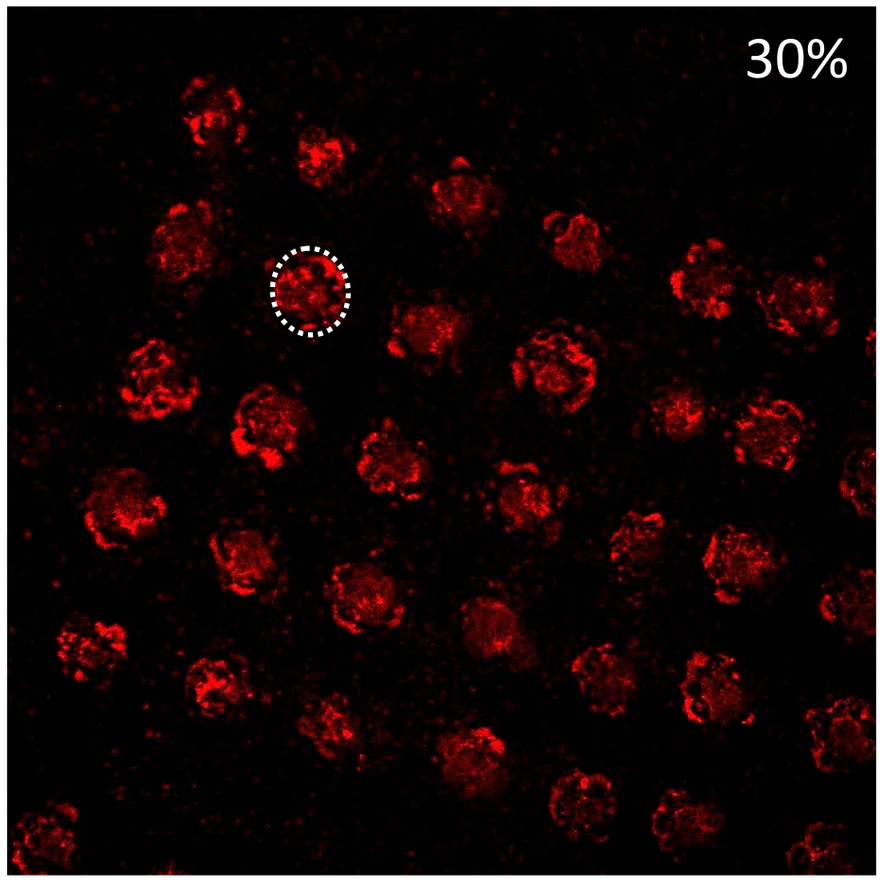


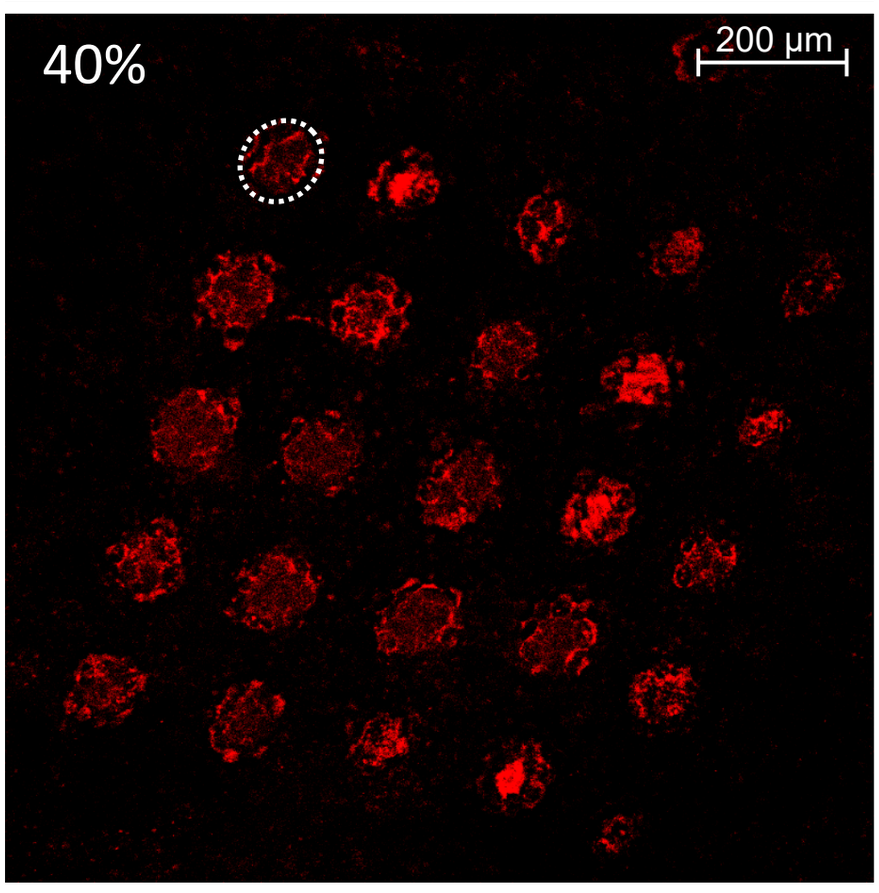
114%

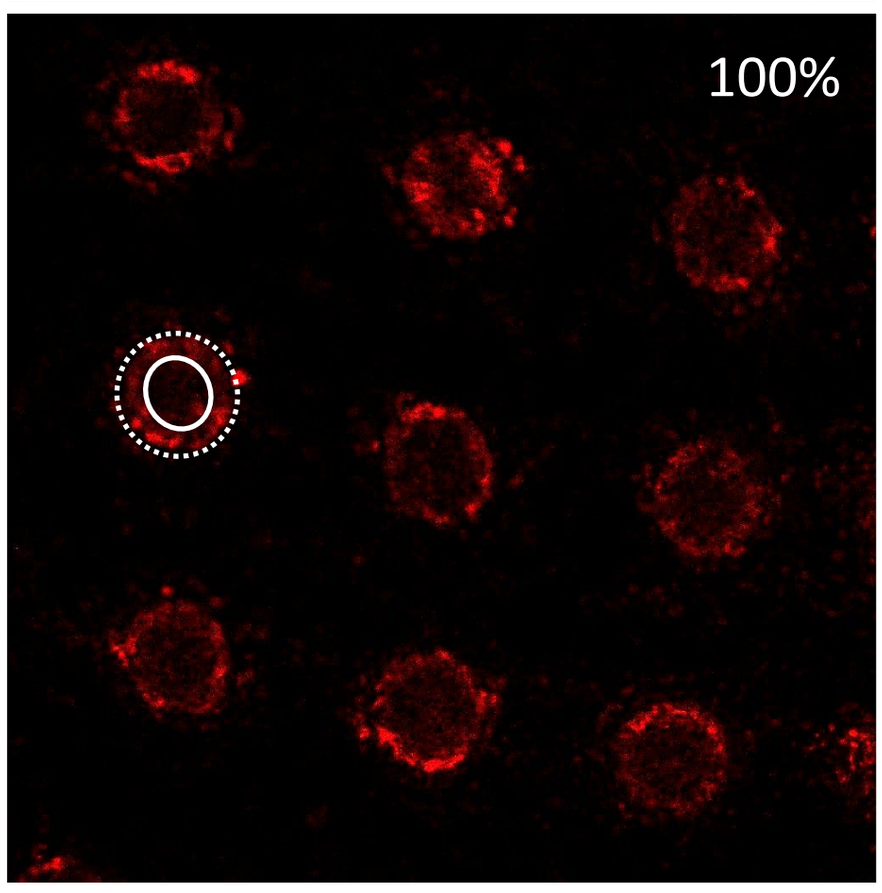


HSP activated area on RPE

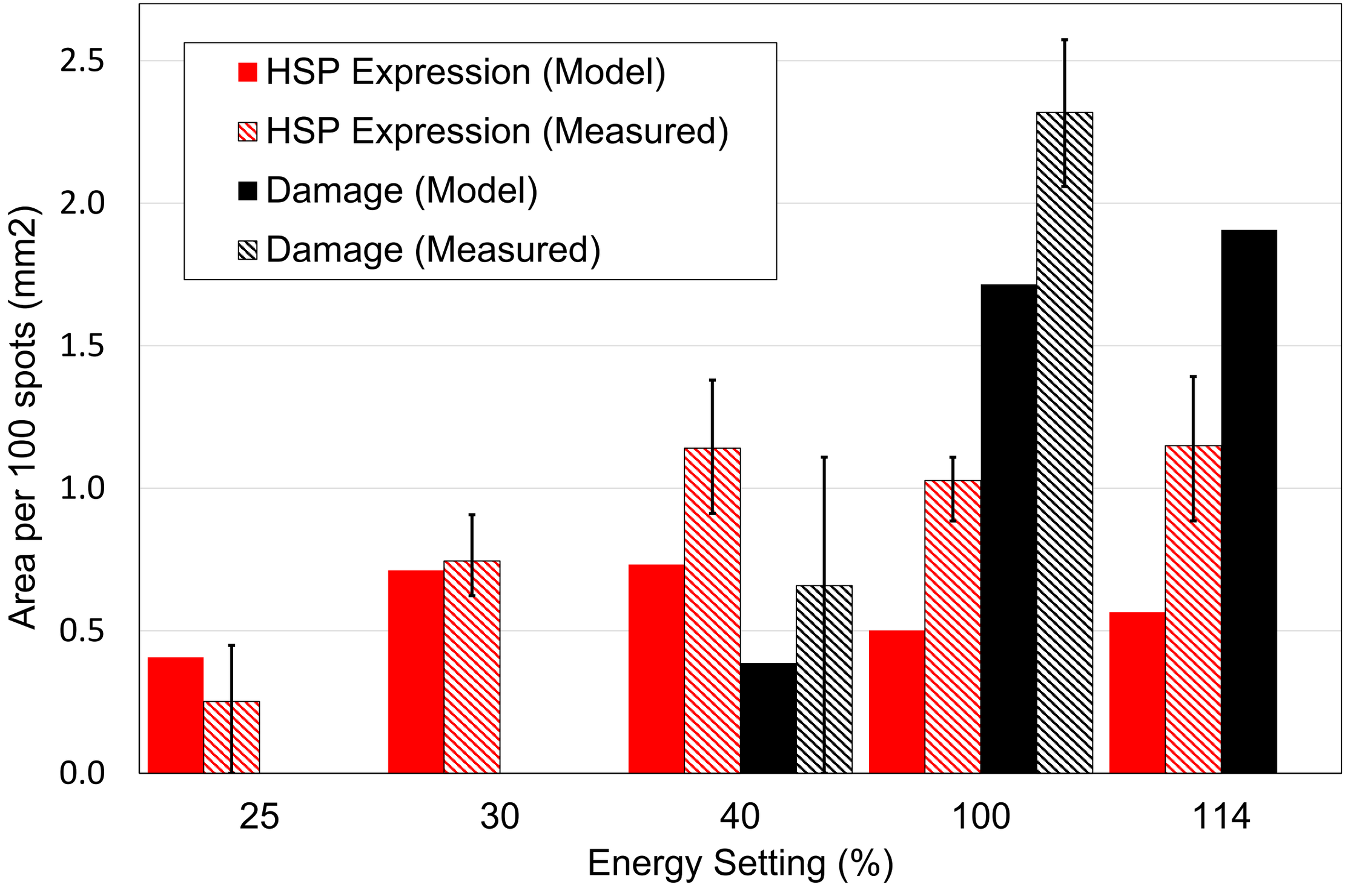








Areas of HSP expression and tissue damage

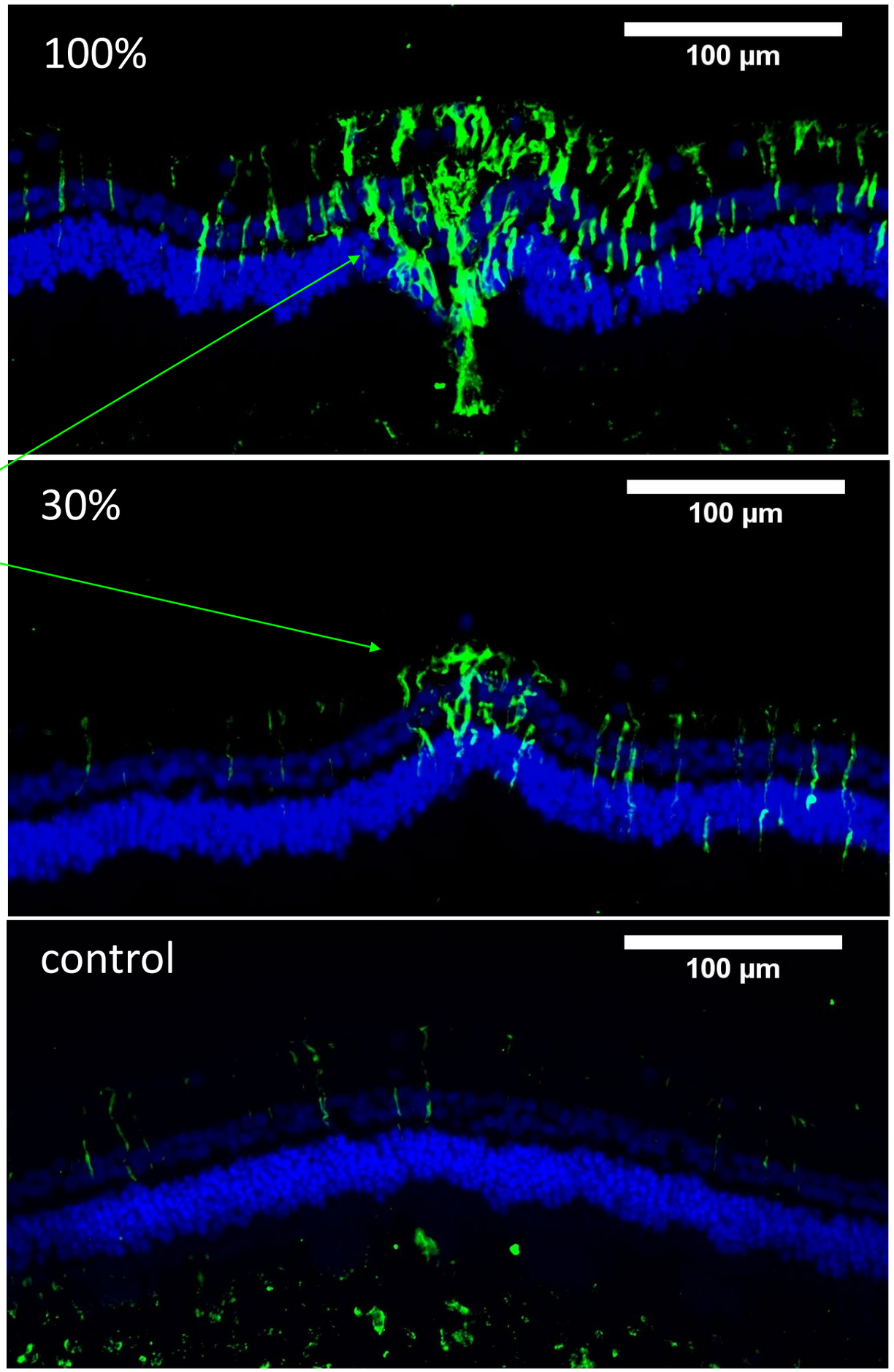


GFAP expression at 1 month

GFAP: Glial fibrillary acidic protein

Activated Muller cells

Control



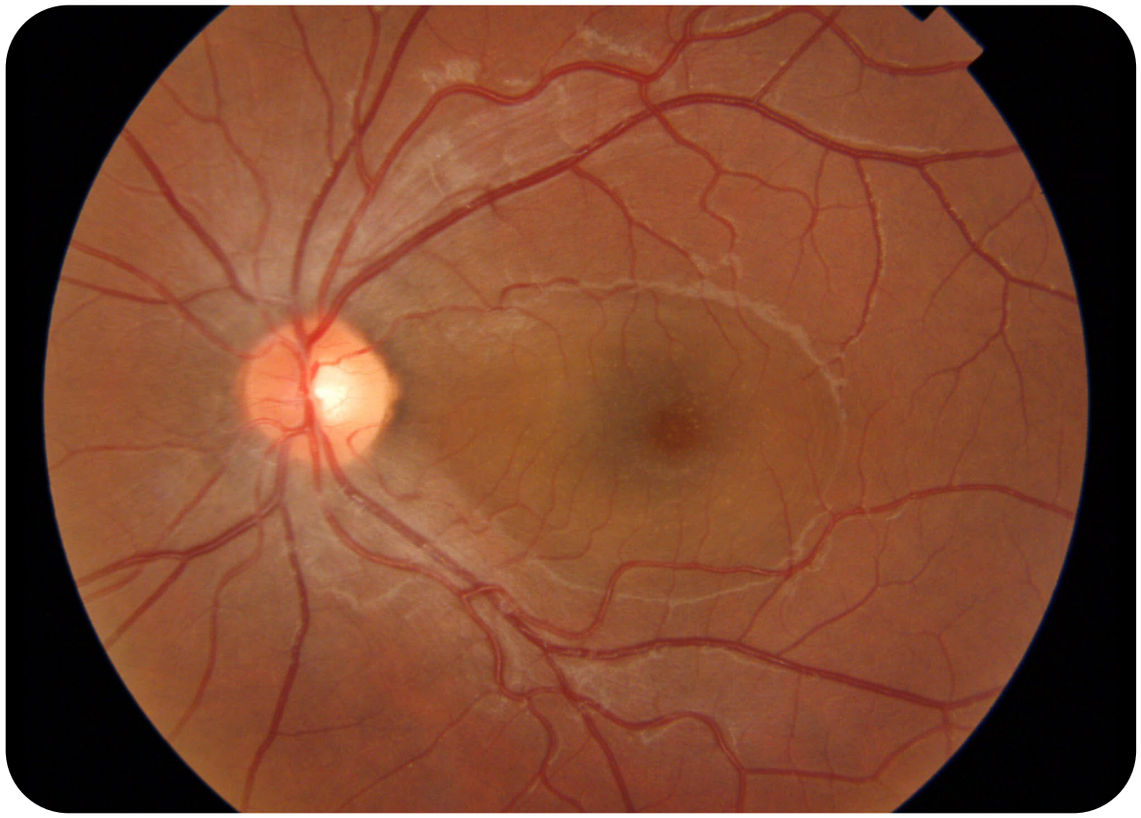
Endpoint Management GUI

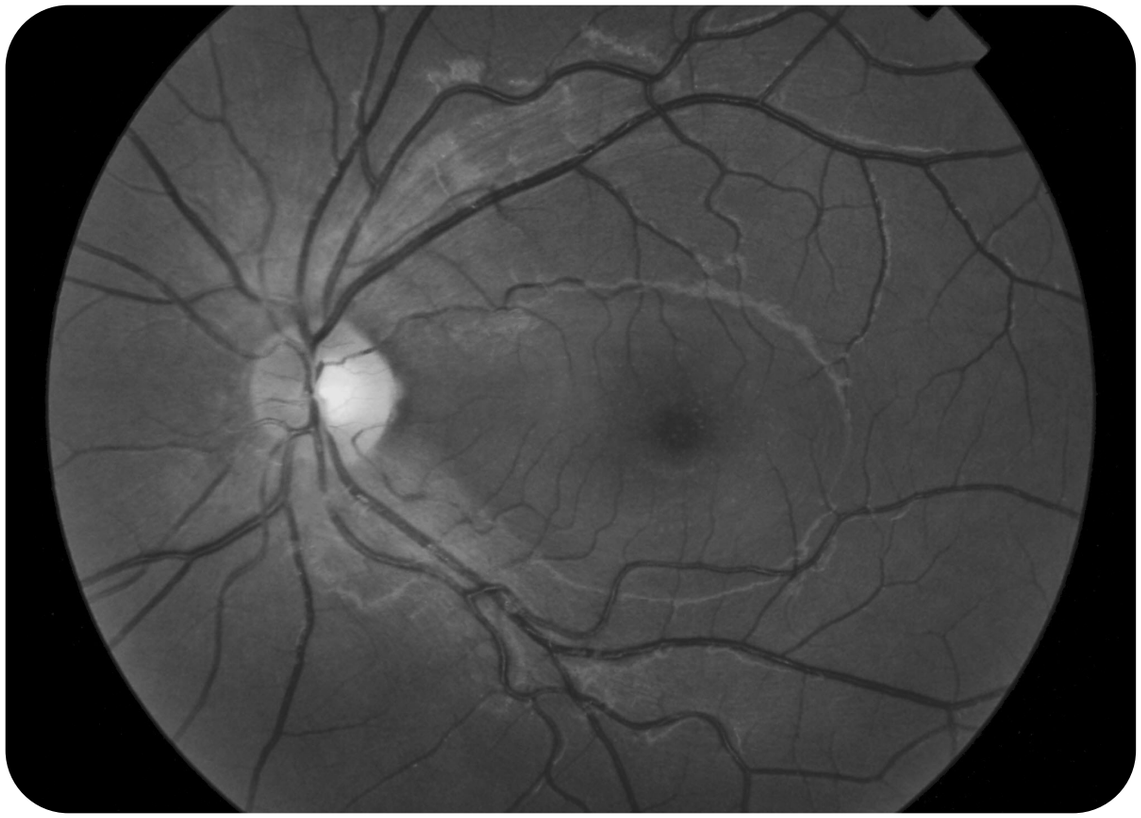
PASCAL | SYNTHESIS™

EpM endpoint MANAGEMENT

1. Titrate power to barely visible burn;
2. Turn energy to 30%;
3. Treat.

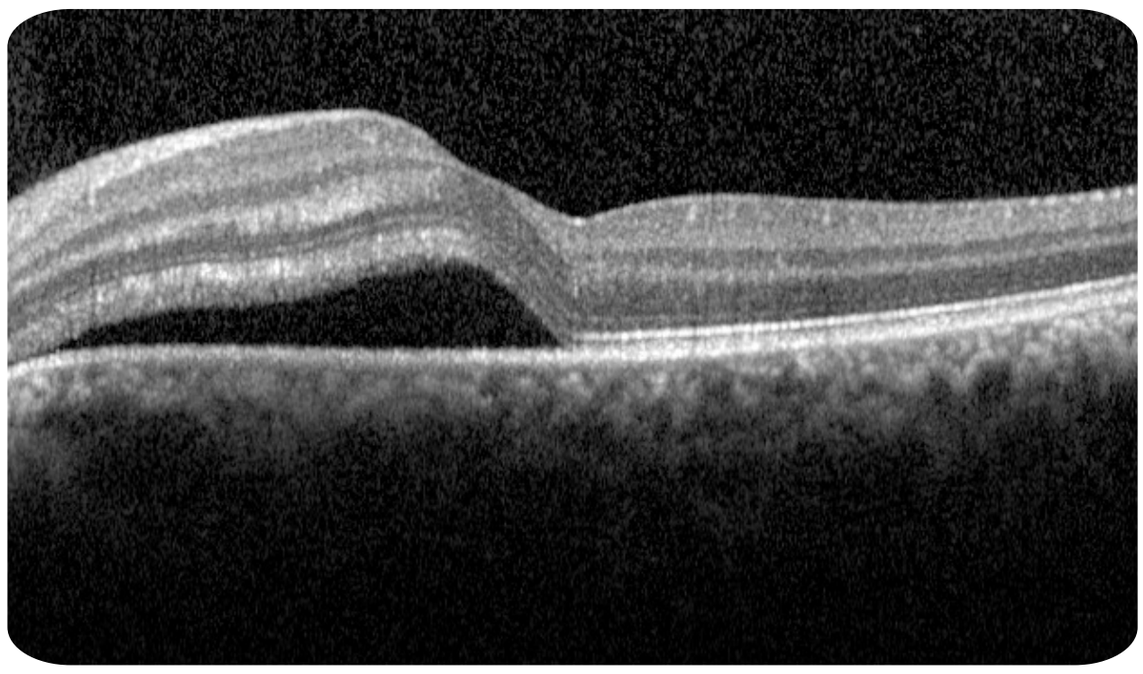
Central Serous ChorioRetinopathy



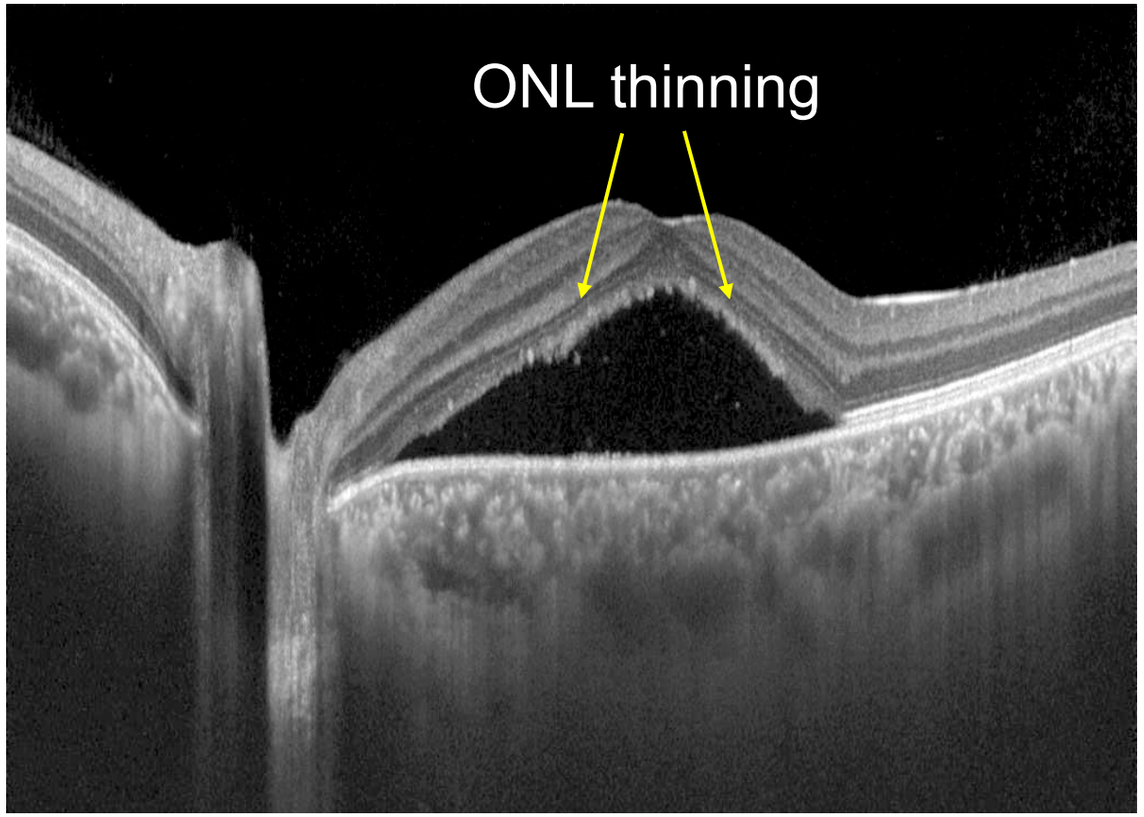


27 years old, military pilot
VA: 20/20 OD, 20/25 OS for 1 month

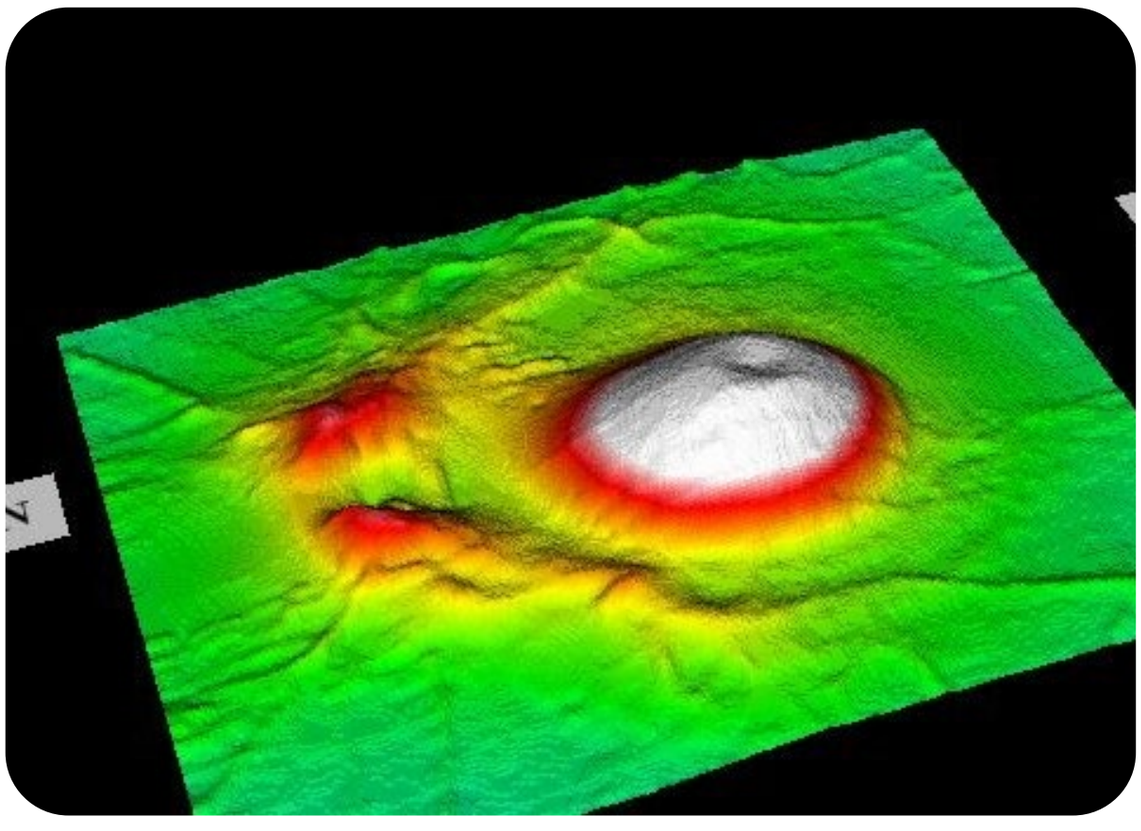
Patient denied the use of steroids or other medications, and decided to wait for spontaneous resolution.



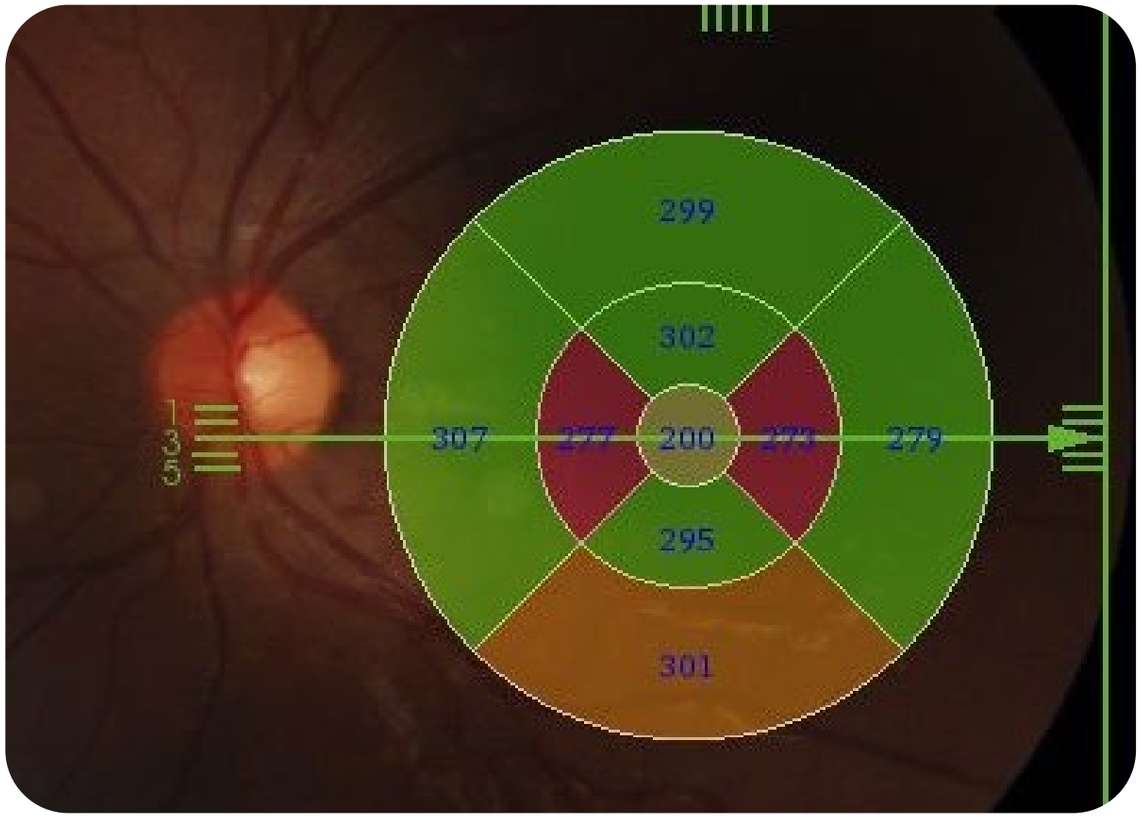
Central Serous ChorioRetinopathy

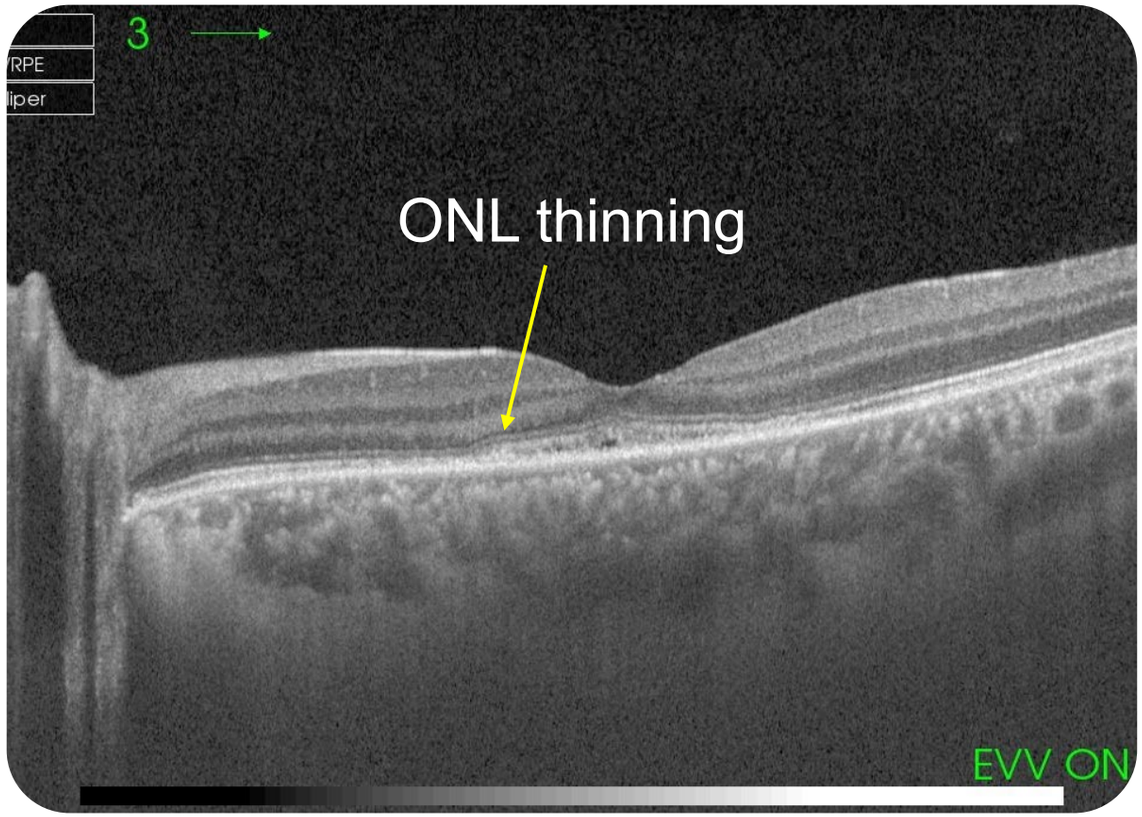


Returned after 3 months
VA 20/30

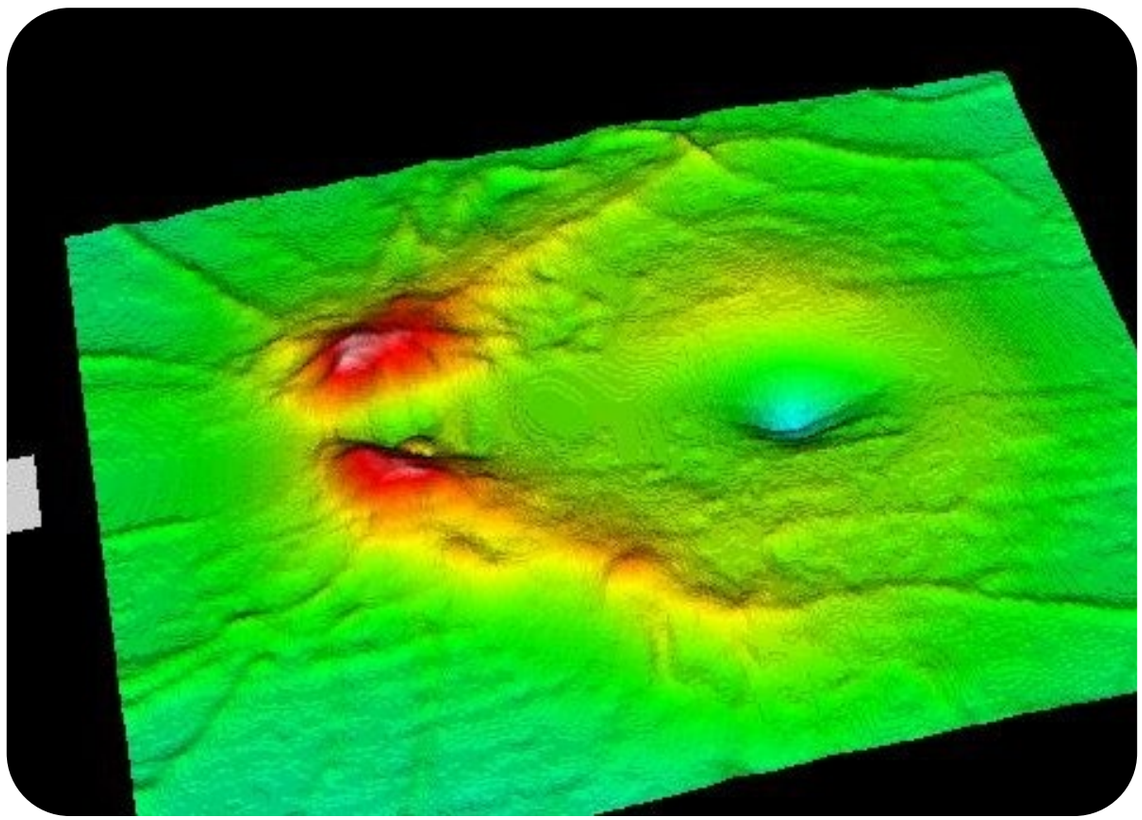


Central Serous ChorioRetinopathy





3 months after NRT:
VA 20/15



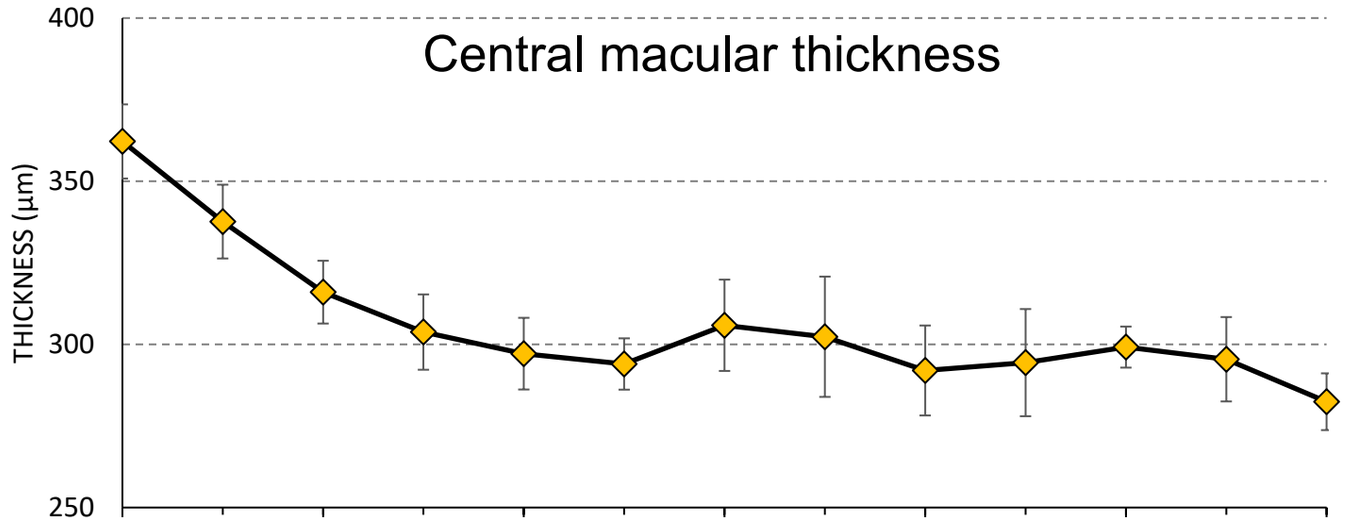
Central Serous ChorioRetinopathy

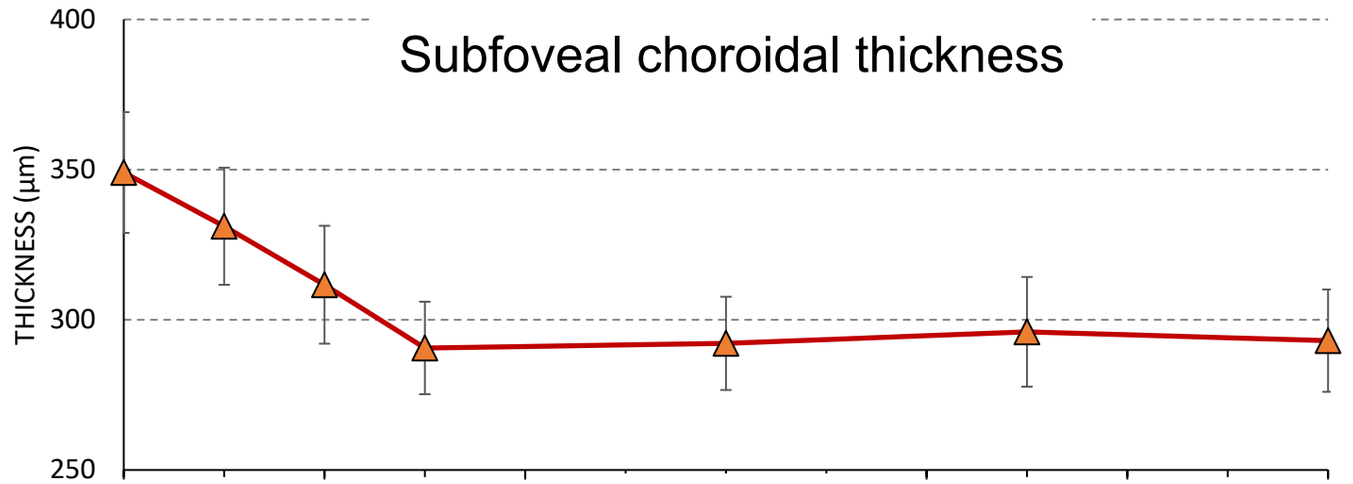
21 eyes, 20 patients

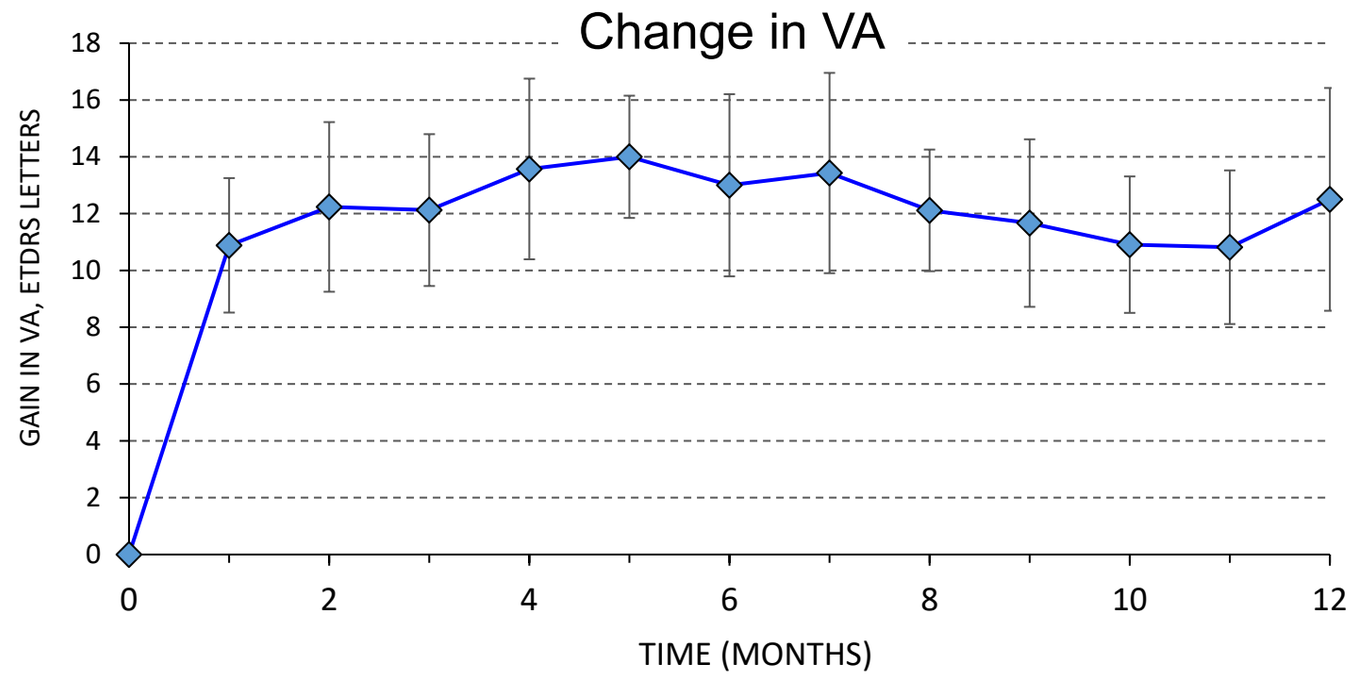
Minimum duration prior to treatment: 4 months.
Average duration prior to treatment: 11+/-4 months.

Treat-ments	1	2	3	4	Average
	16%	58%	16%	10%	**2.2**

Fluid Reso-lution	complete	partial	Non-responder
	81% (17/21)	19% (4/21)	0

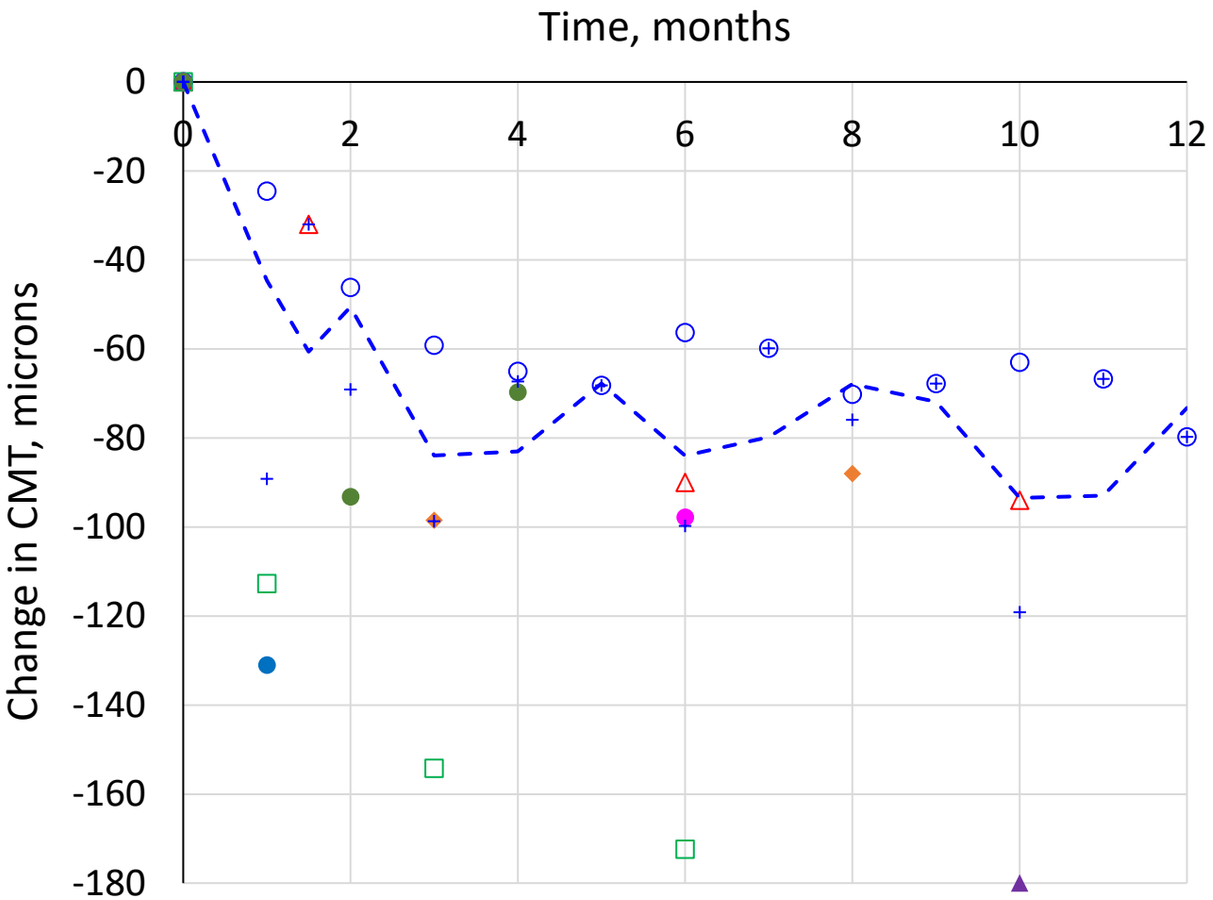






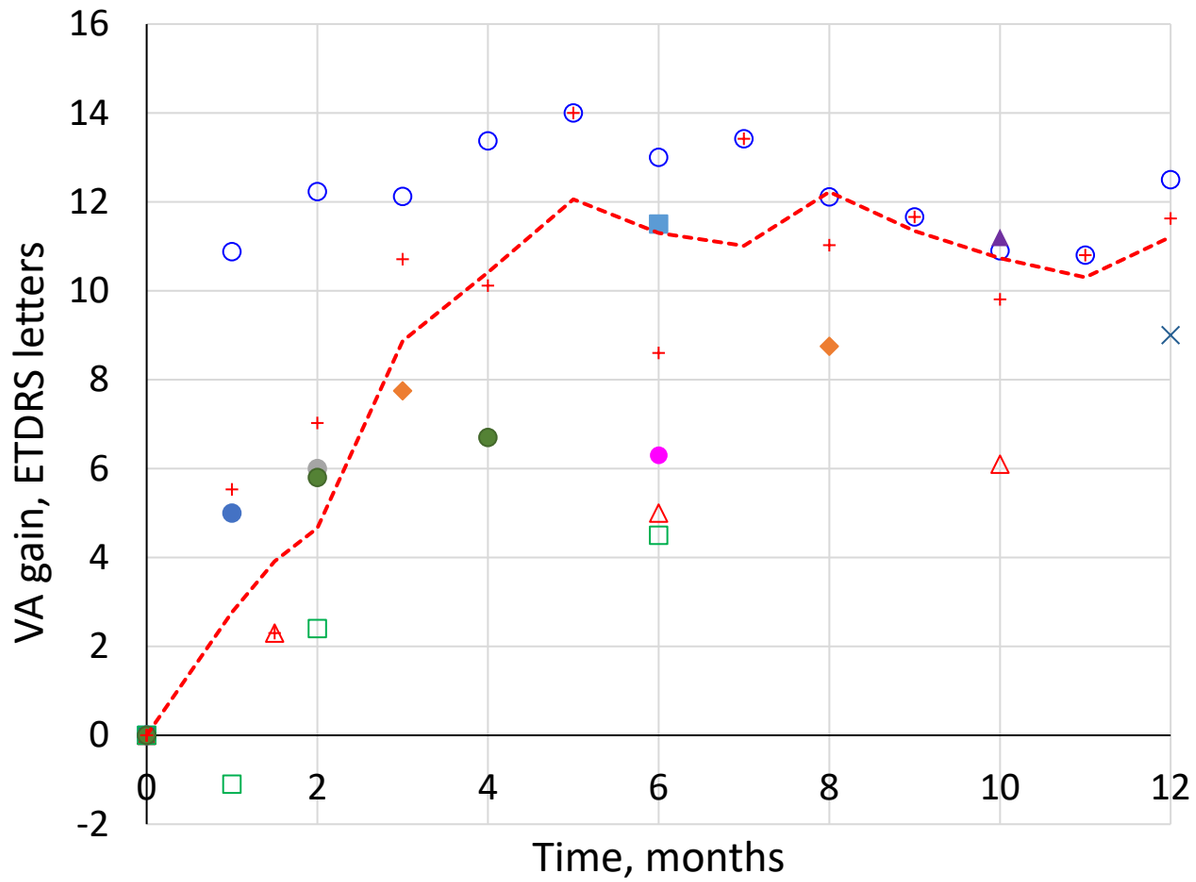
Non-damaging retinal laser therapy for CSCR: overview of clinical studies

Change in Central Macula Thickness



Kim (2015)
Lanzetta (2008)
Koss (2011)
Malik (2015)
W. Average
Lavinsky (2015)
Chen (2008)
Roisman (2011)
Kretz (2015)
2 per. Mov. Avg. (W. Average)

Change in Visual Acuity



Behnia (2013)
Yadav (2015)
Lanzetta (2008)
Ricci (2008)
Roisman (2011)
Malik (2015)
W. Average
Kim (2015)
Lavinsky (2015)
Chen (2008)
Koss (2011)
Gupta (2009)
Kretz (2015)
2 per. Mov. Avg. (W. Average)

Diabetic Macular Edema

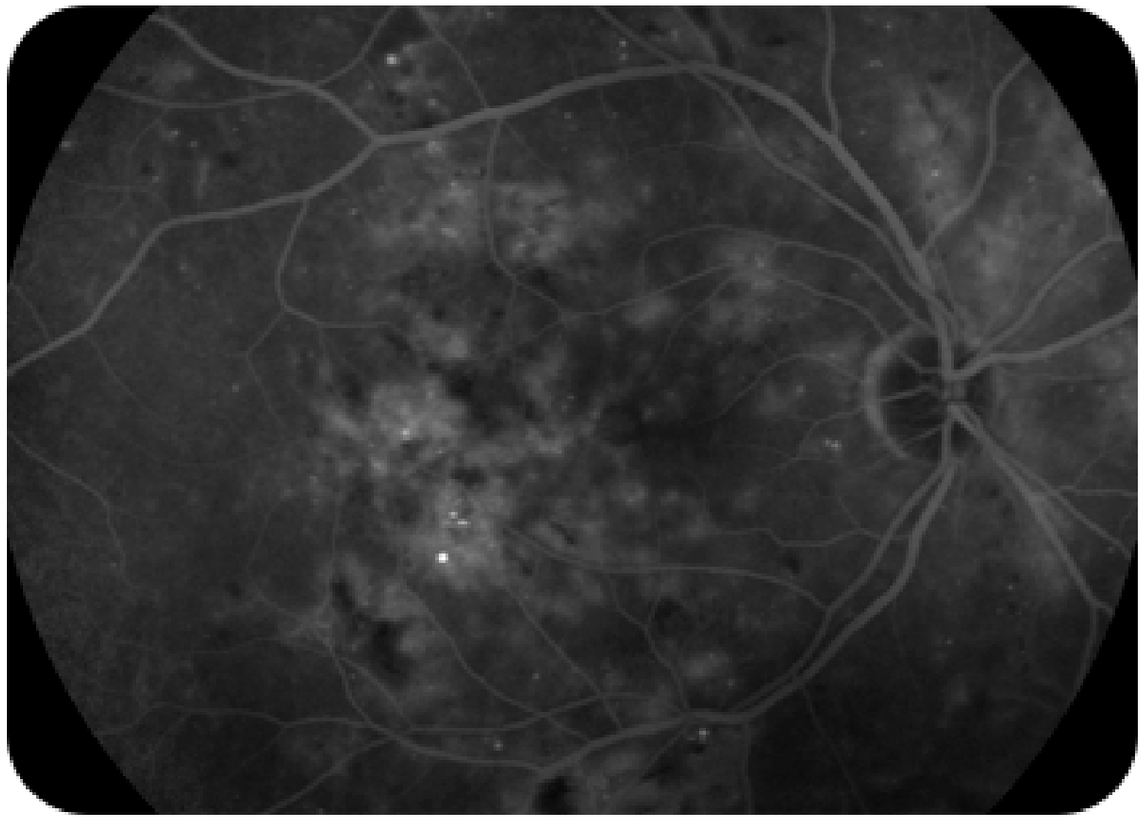
20 patients treated to date.

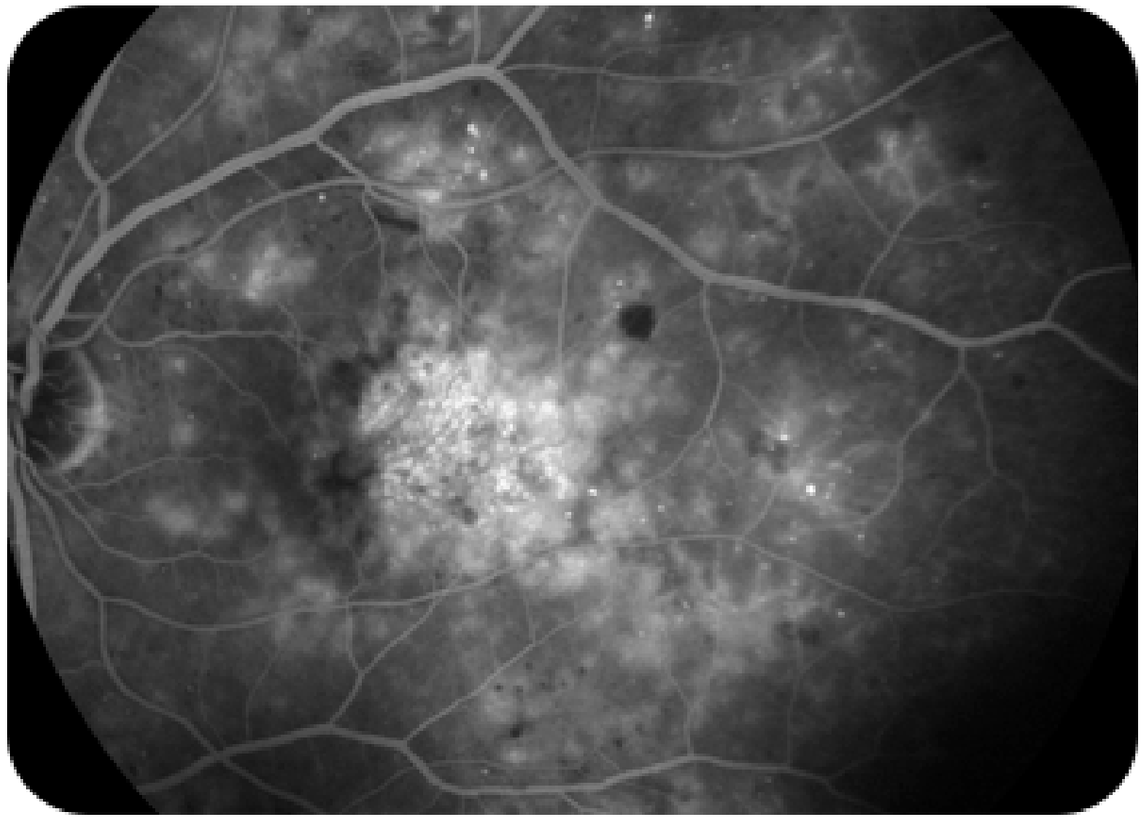
17 Lucentis + laser at 2 weeks.

3 Laser alone

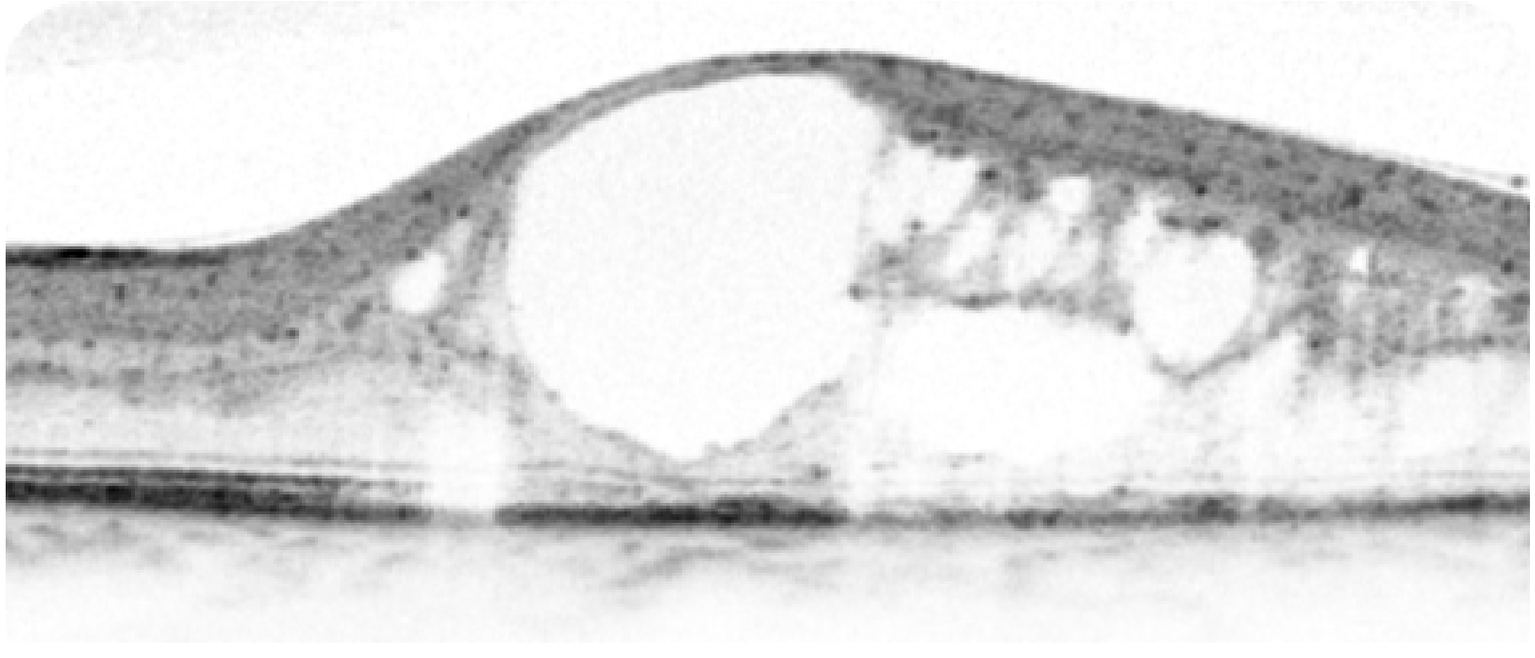
Retreat at 3 months if did not respond.

Retreat as needed if recurred (4-9 months)



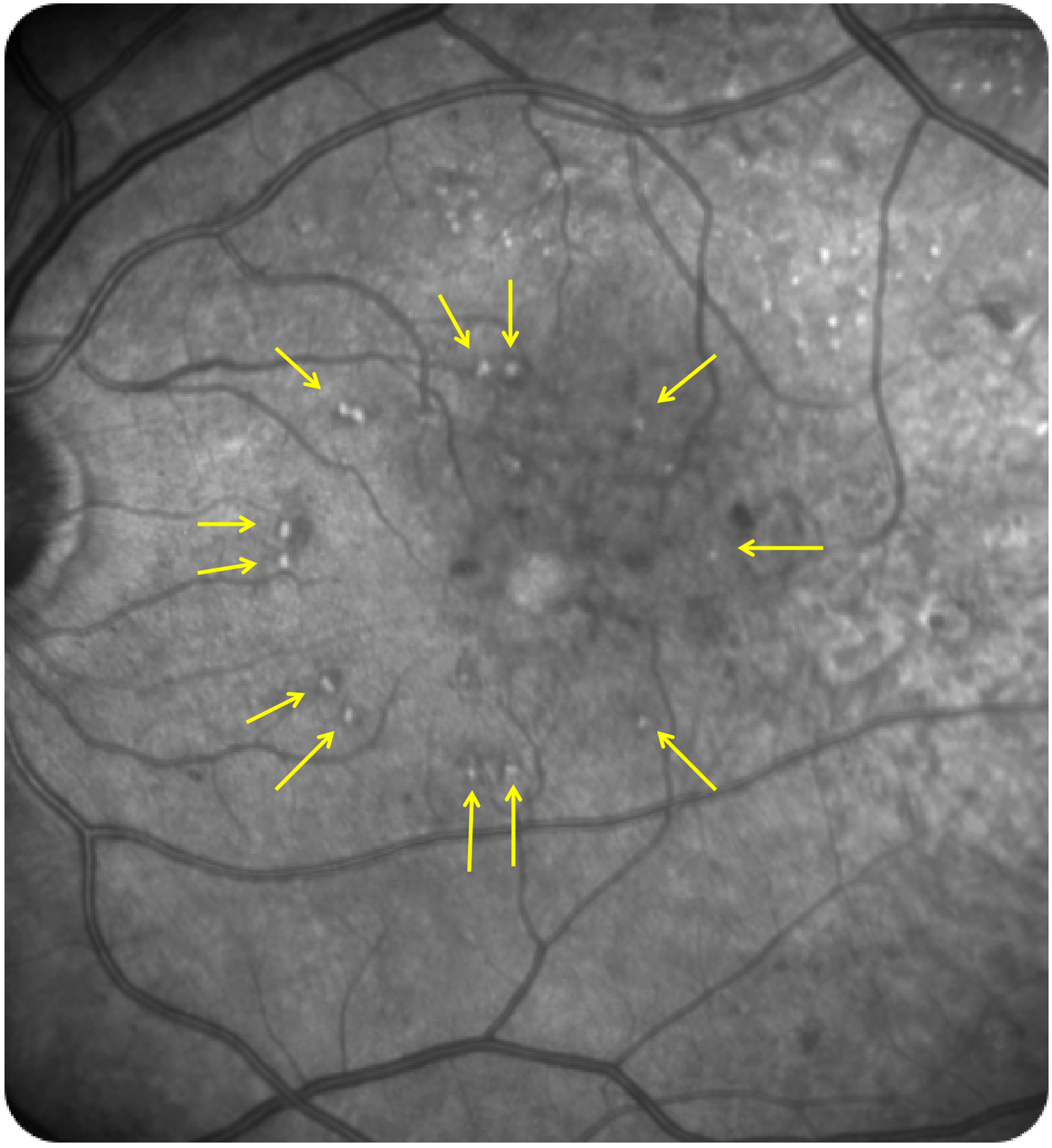


- Visual acuity 20/80
- Severe nonproliferative diabetic retinopathy with macular edema



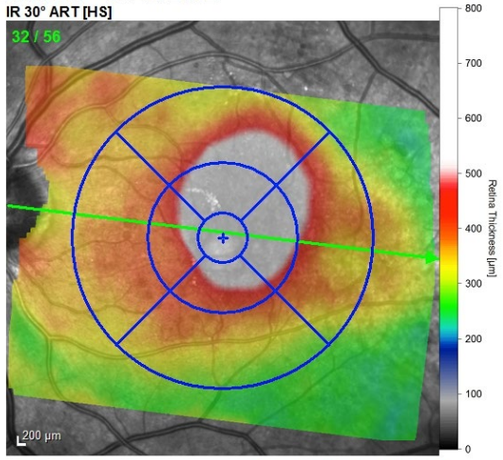
Endpoint Management

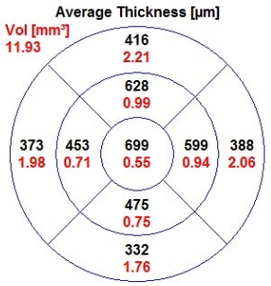
- 200µm spot size
- Area Centralis lens
- 110mW titration for 100%
- 30% treatment
- 0.25 spot distance
- Landmarks ON
- 768 spots



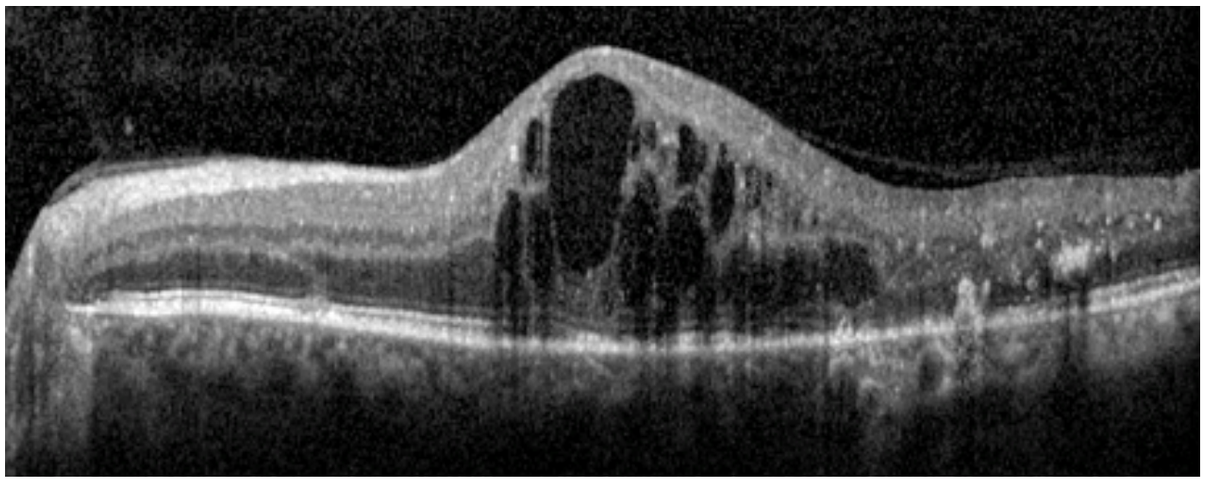
Diabetic Macular Edema

Baseline - 06/12/2012





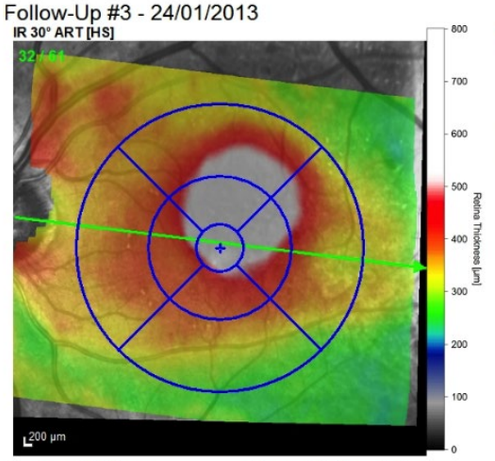
Center: 743 µm Central Min: 591 µm Central Max: 746 µm

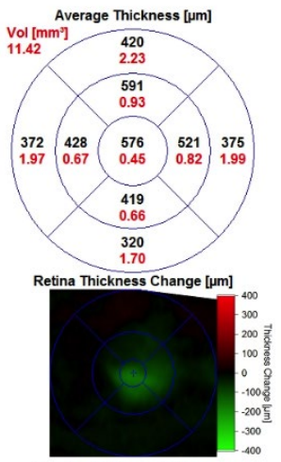


acute

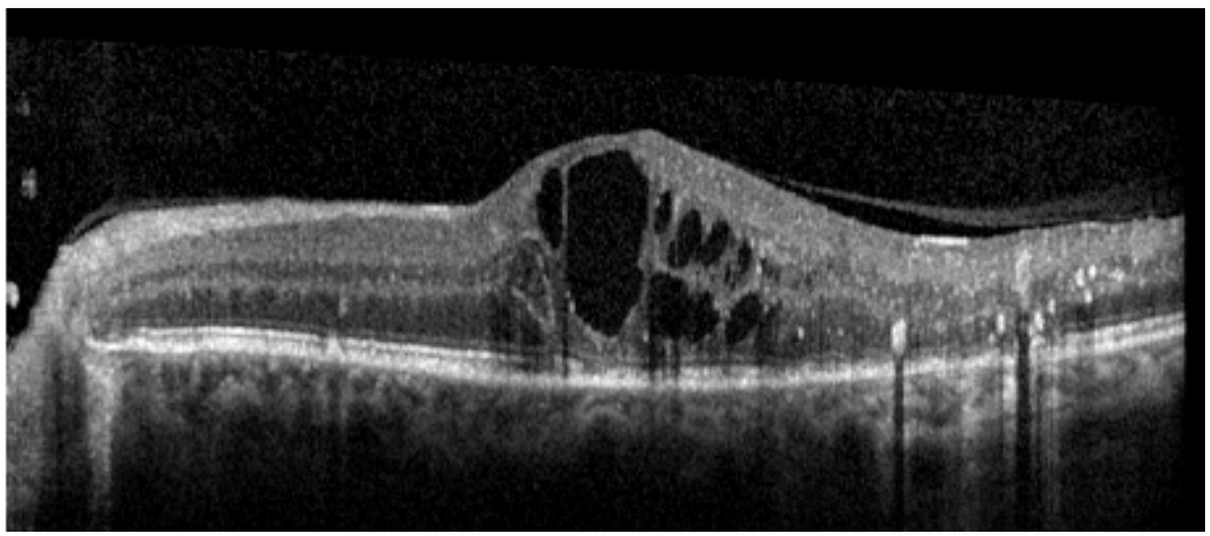
20/80

Follow-Up #3 - 24/01/2013





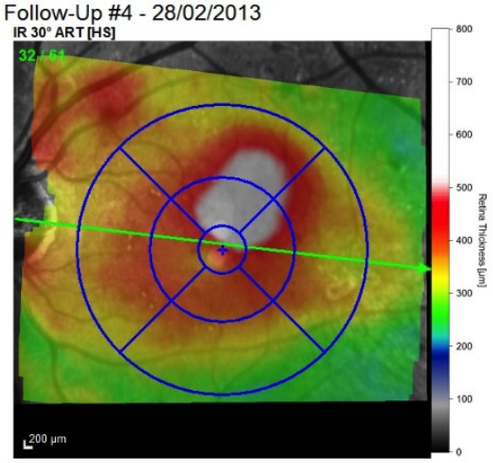
Center: 588 µm Central Min: 460 µm Central Max: 657 µm

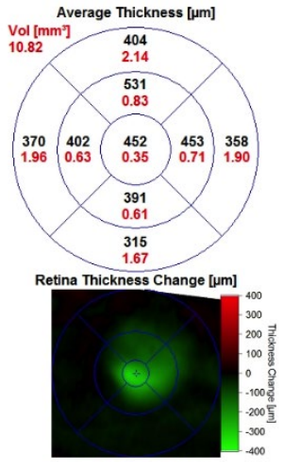


1 month

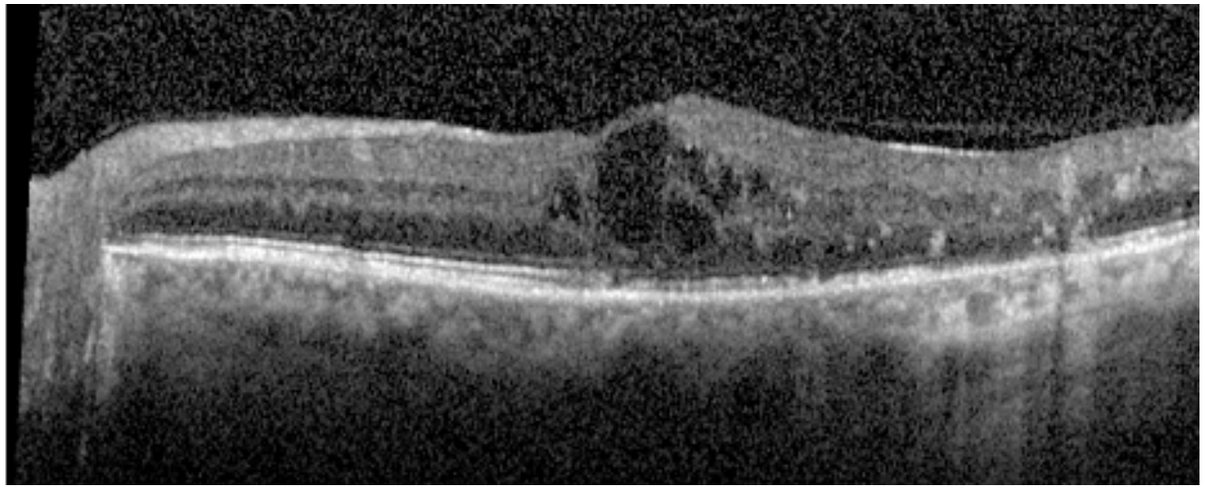
20/60

Follow-Up #4 - 28/02/2013





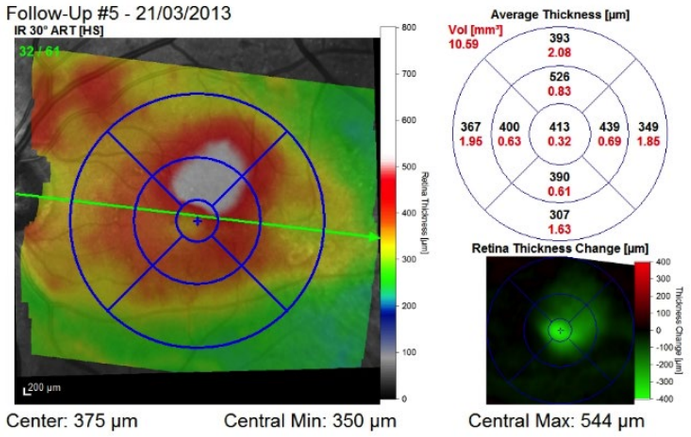
Center: 455 µm Central Min: 360 µm Central Max: 575 µm

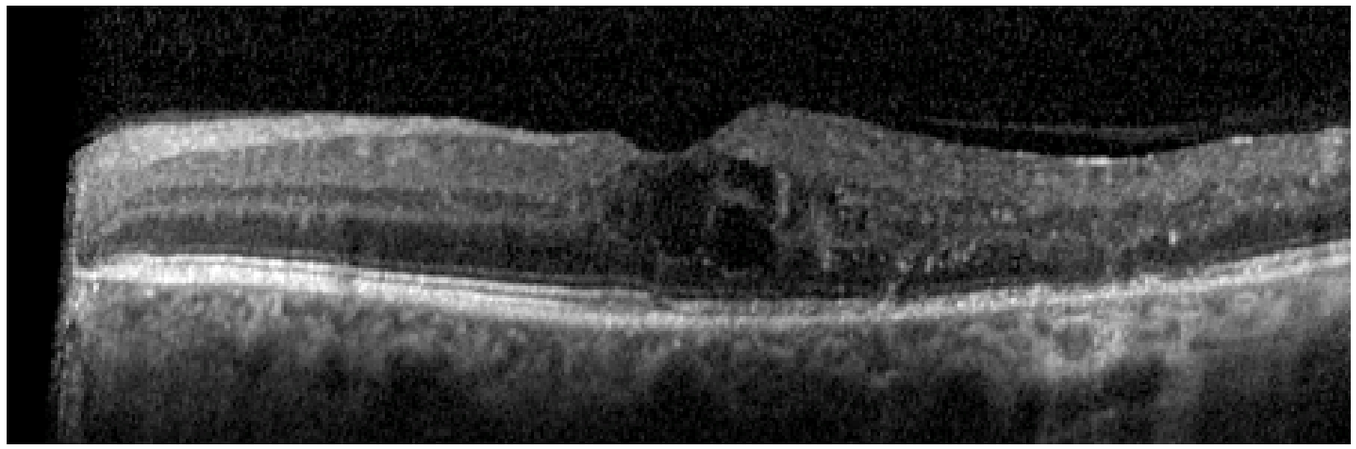


2 months

20/60

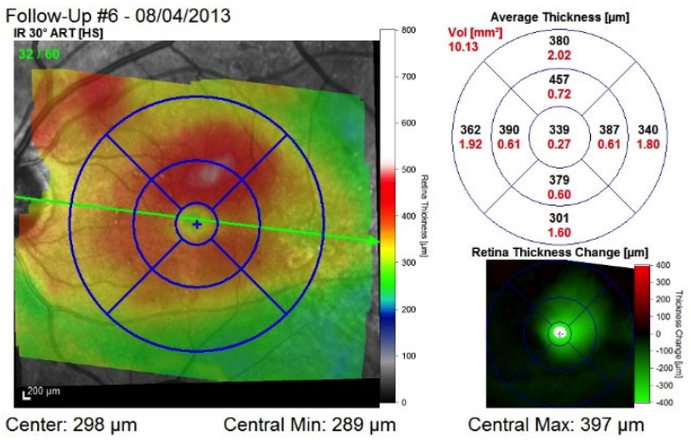
Diabetic Macular Edema

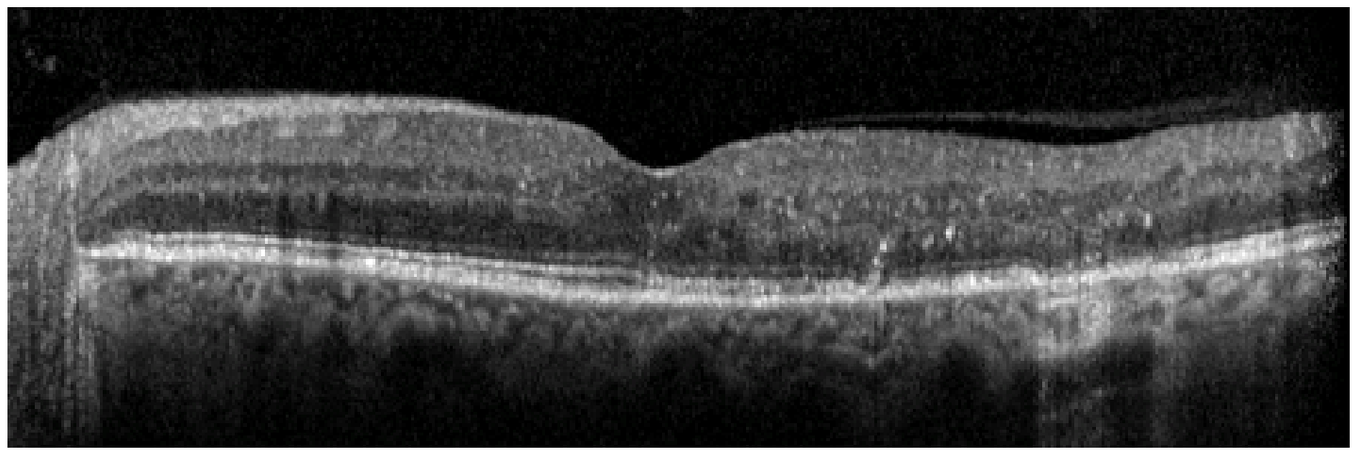




3 months

20/25





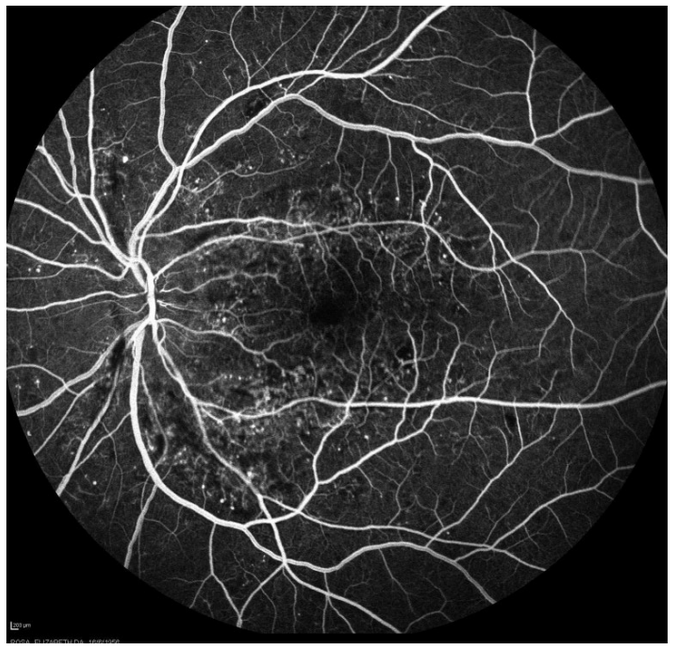
4 months

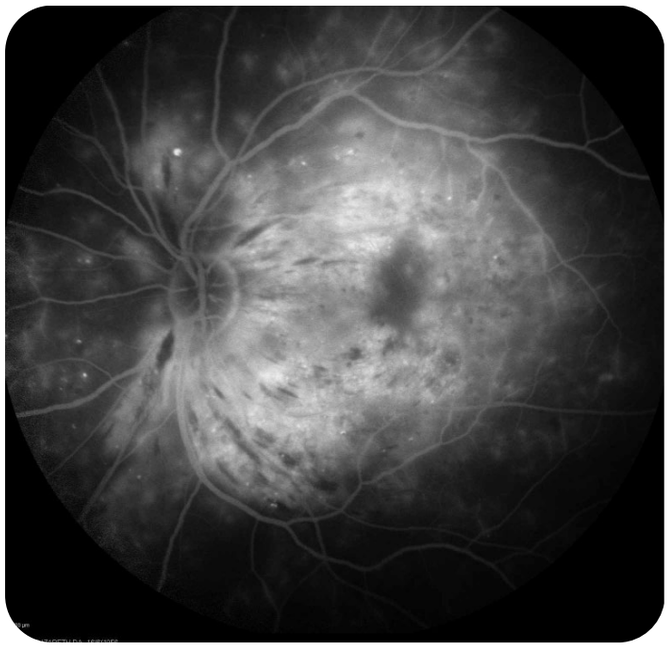
20/25

Δ Central Macular Thickness = 699-397=302 µm

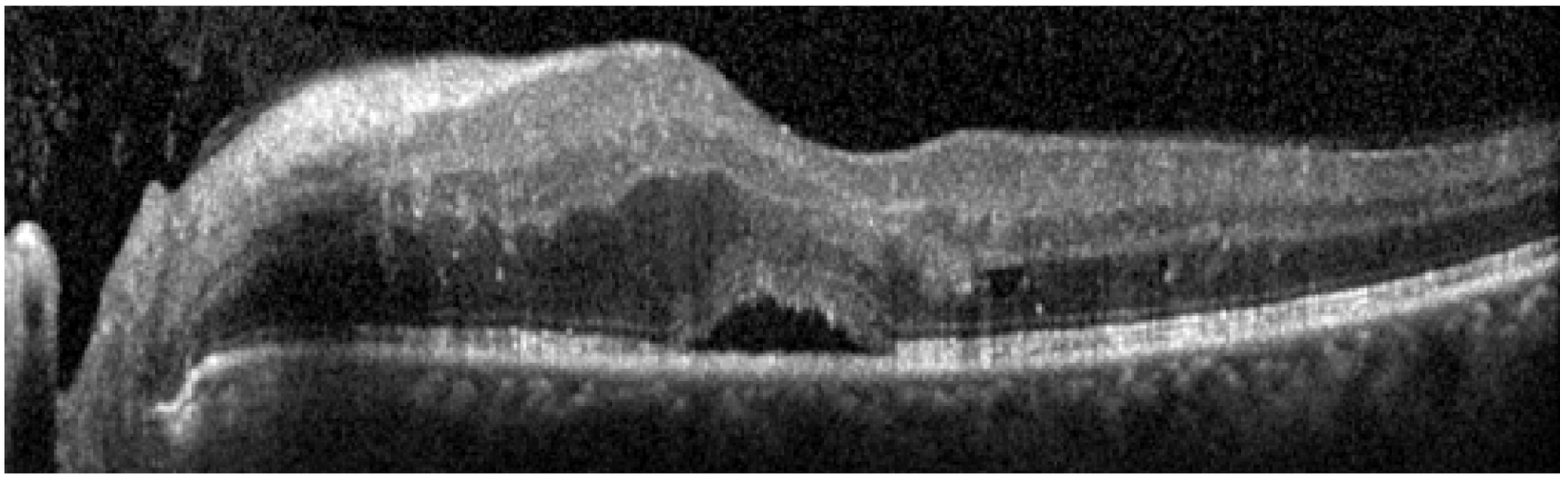
Δ VA: from 20/80 to 20/25

Diabetic Macular Edema

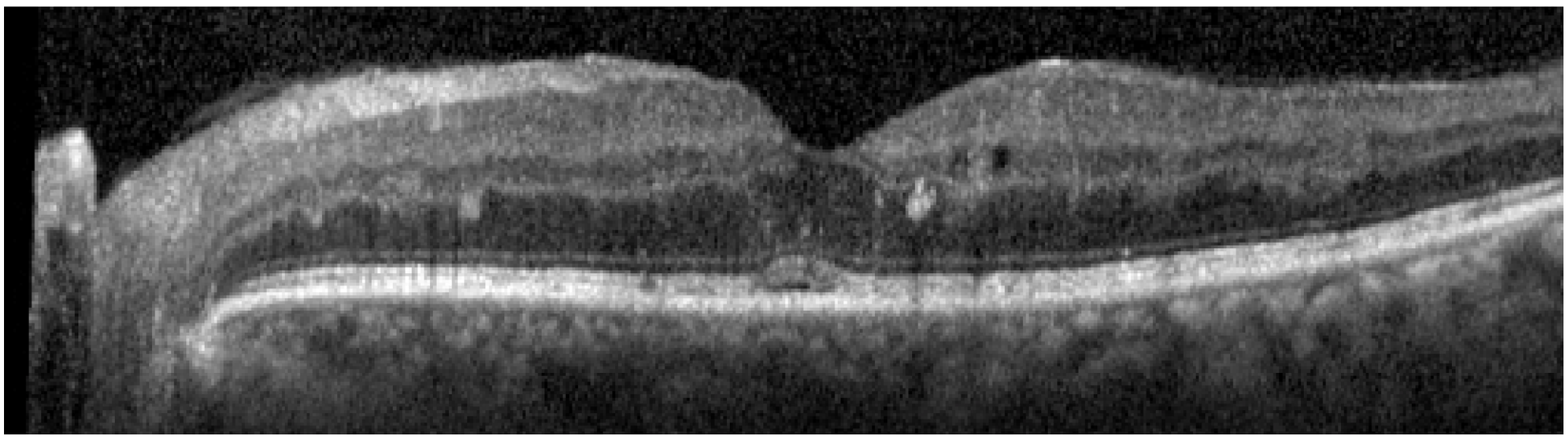




47 years old,
female
Type 2 diabetes
for 12 years
Diffuse DME
BCVA **20/80** OU



EpM,
120mW (100%),
30%, 200µm
0.25 D spacing
693 spots



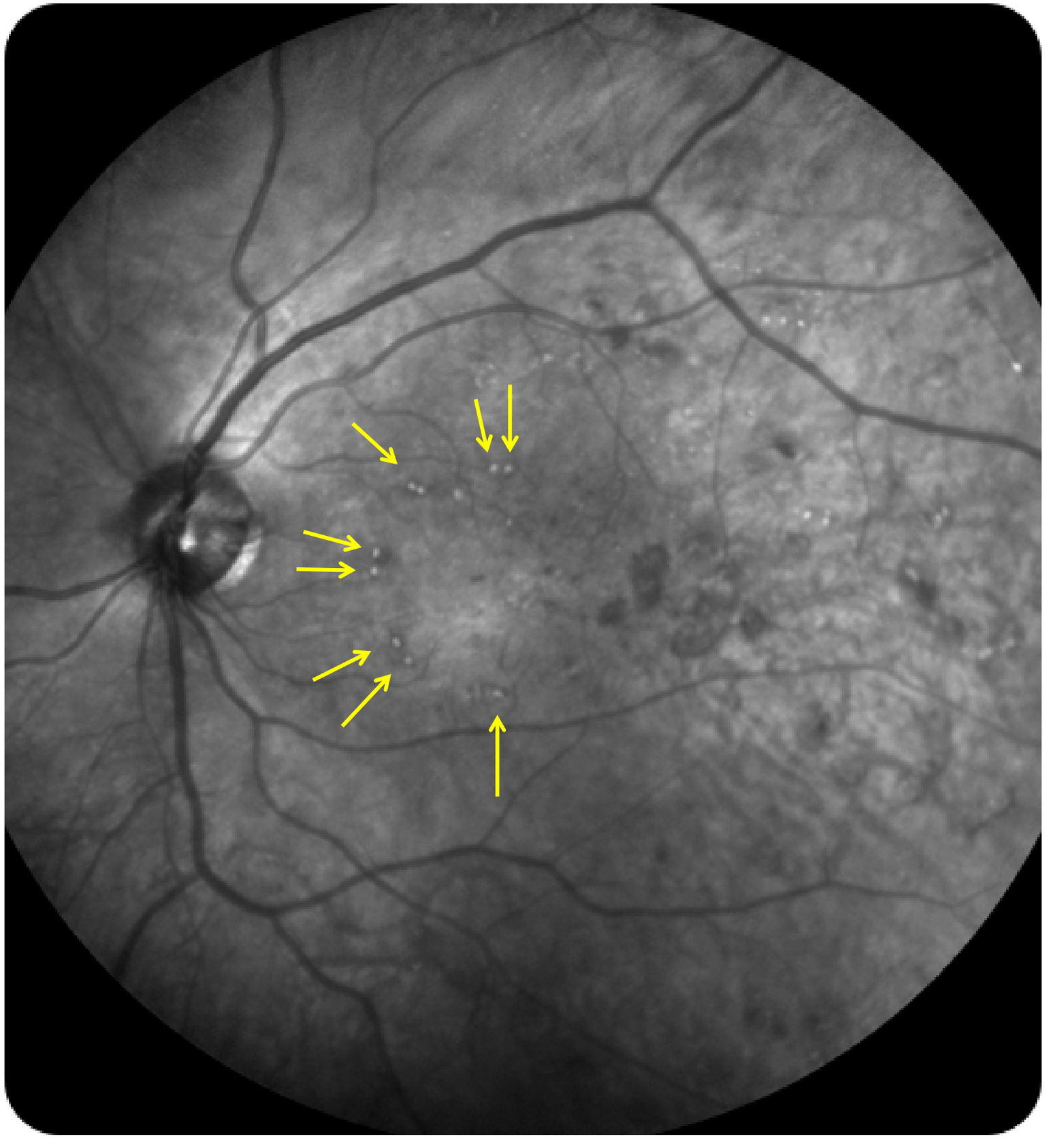
After 6 months
VA **20/25**
No Anti-VEGF
injections

At 4 months

No visible laser burn marks !

At 4 months

Landmarks visible
in infrared

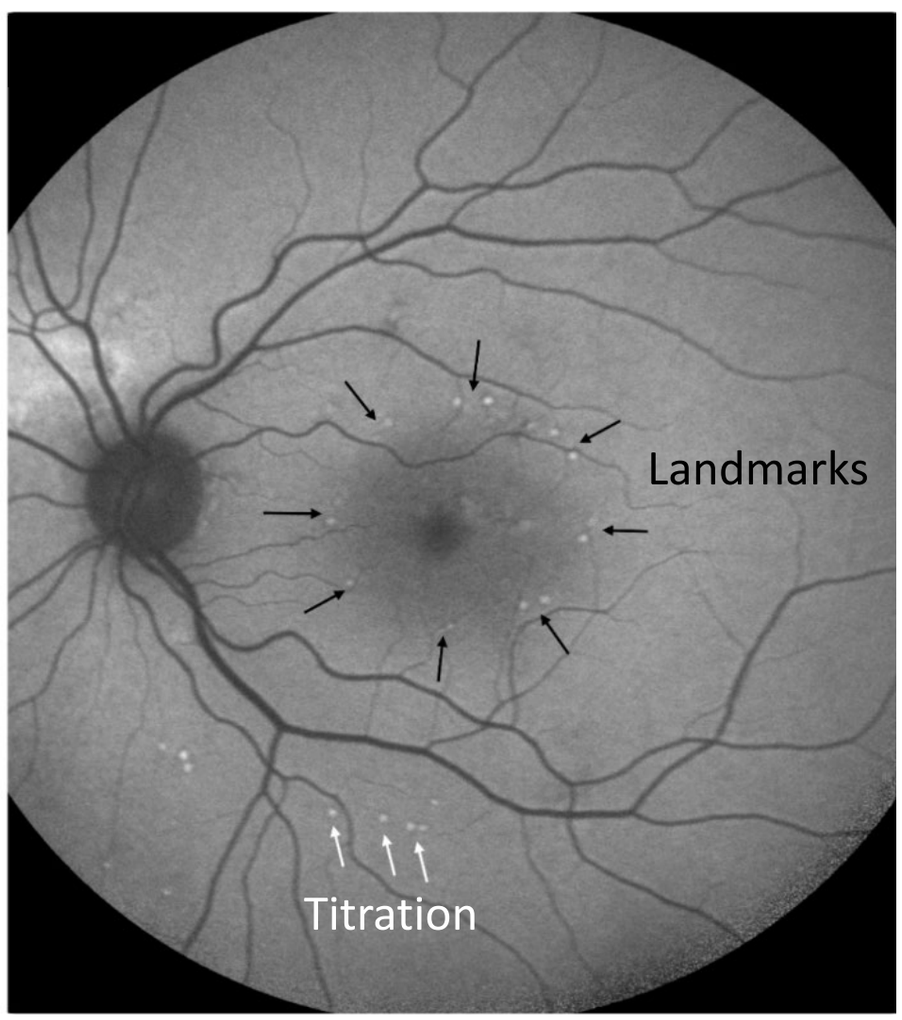


Conclusions

- NRT activates endogenous tissue repair mechanisms.
- Cells surviving the hyperthermia express HSP around the conventional visible burns, as well inside the non-damaging spots, with energies ranging from 25% to 35% on EpM scale.
- Such a narrow window of the HSP expression below damage threshold necessitates careful titration in every patient.
- Lack of tissue damage allows:
  - ✓ High spot density - essential for clinical efficacy.
  - ✓ Periodic retreatments – essential for chronic diseases.
  - ✓ Treatment through the fovea.
- Nearly confluent coverage helps boosting clinical efficacy.
  - 0.25 D spacing corresponds to 50% coverage of the area.
  - 0 spacing corresponds to 79% of the area.
  - ➢ Unlike 9% coverage in conventional macular grid.
- With pulse duration below 15ms, a large number of exposures (400-600) can be rapidly applied using scanner.

Conclusions

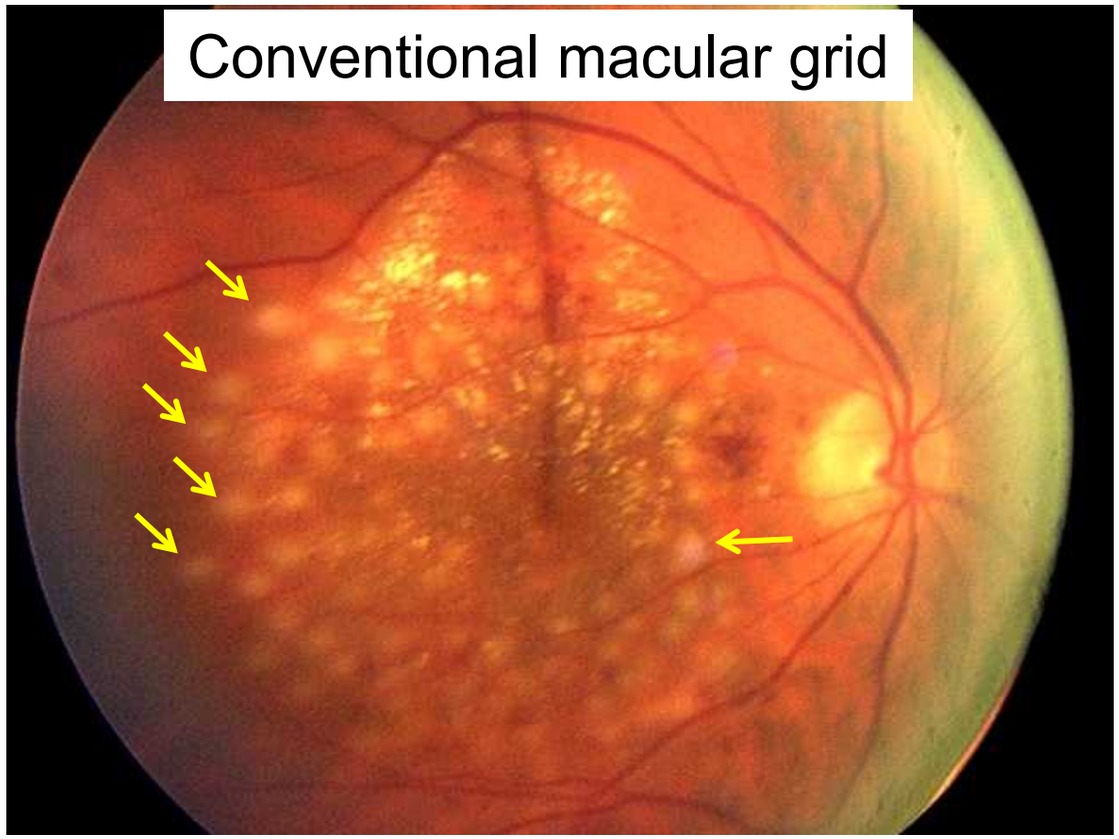
- Proper dosimetry of the laser is no less important than that of drugs
- We developed a protocol for NRT in the macula:
  - Titration (λ = 532, 577 nm)
  - 30% EpM
  - 200μm spot diameter, 0-0.25 D spot spacing, macular ring + 4x4 patterns outside.
- Prospective, randomized, controlled clinical trials of NRT are in progress:
  - DME: to reduce the number of injections, or completely replace them with NRT
  - CSCR, MacTel, AMD (prophylaxis)



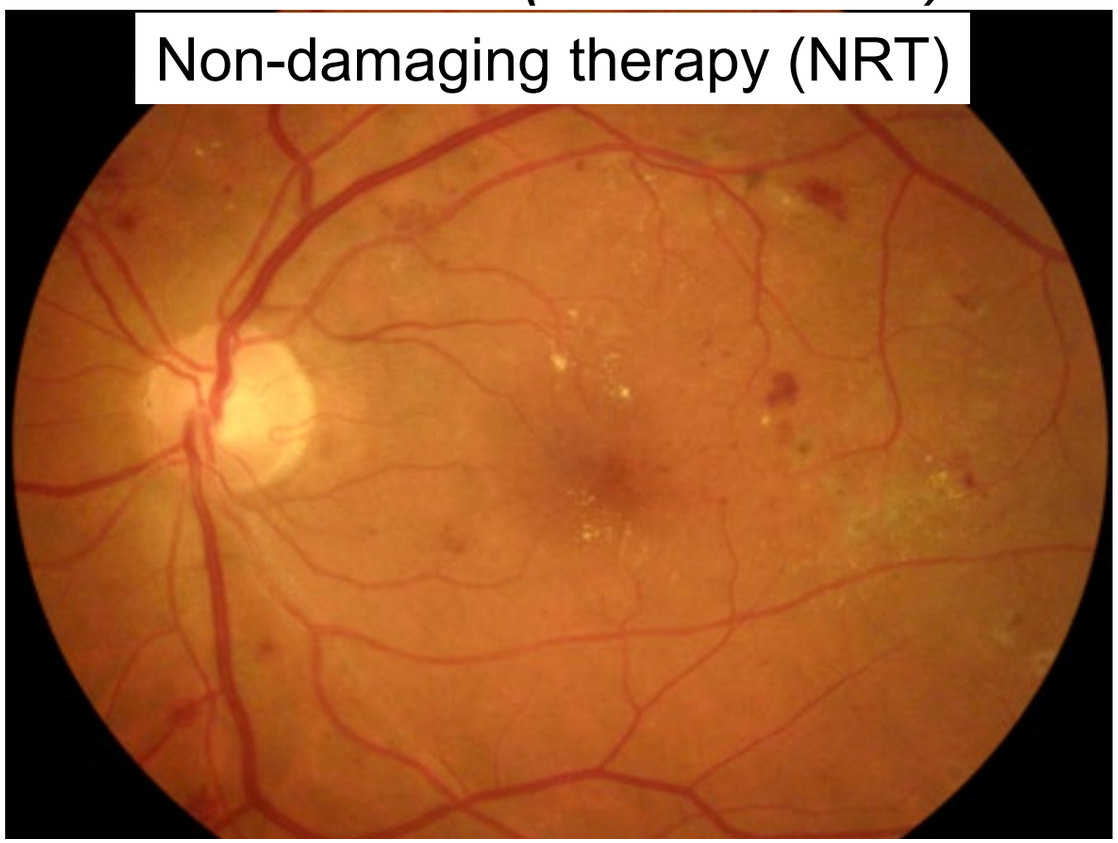
The right dose differentiates a poison and a remedy

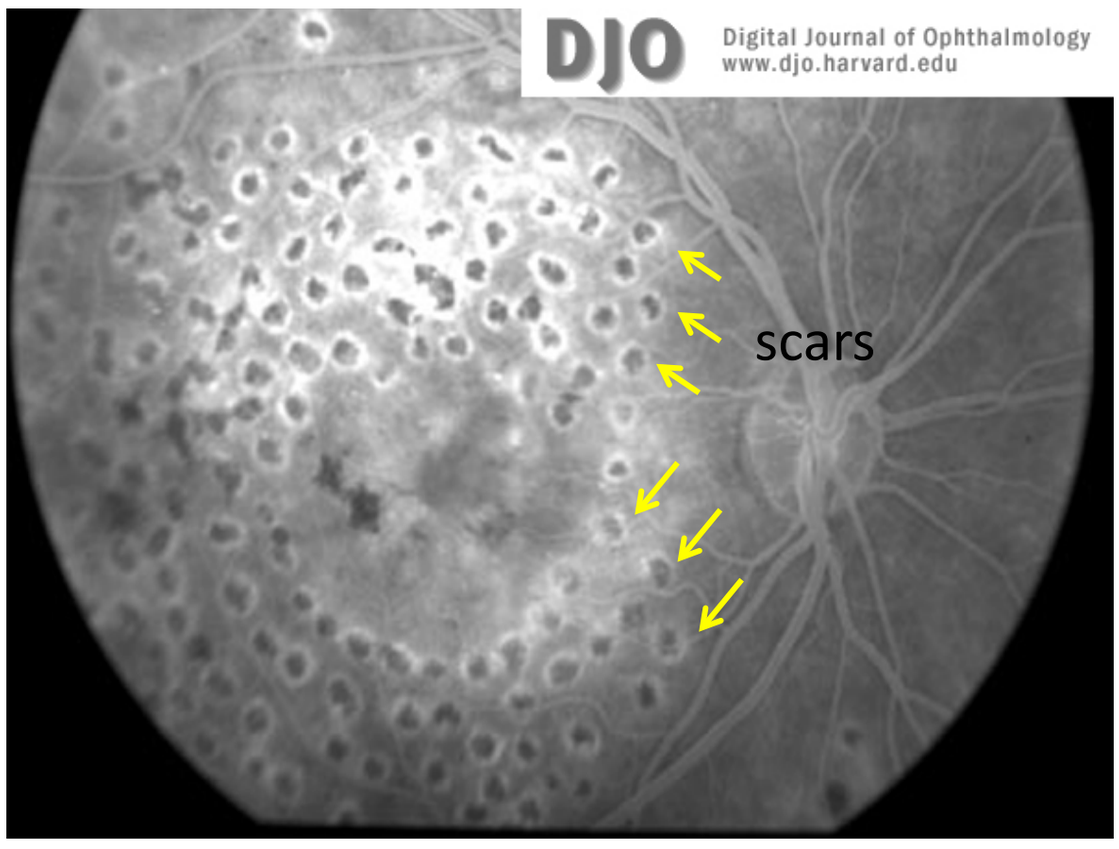
Paracelsus (1493-1541)

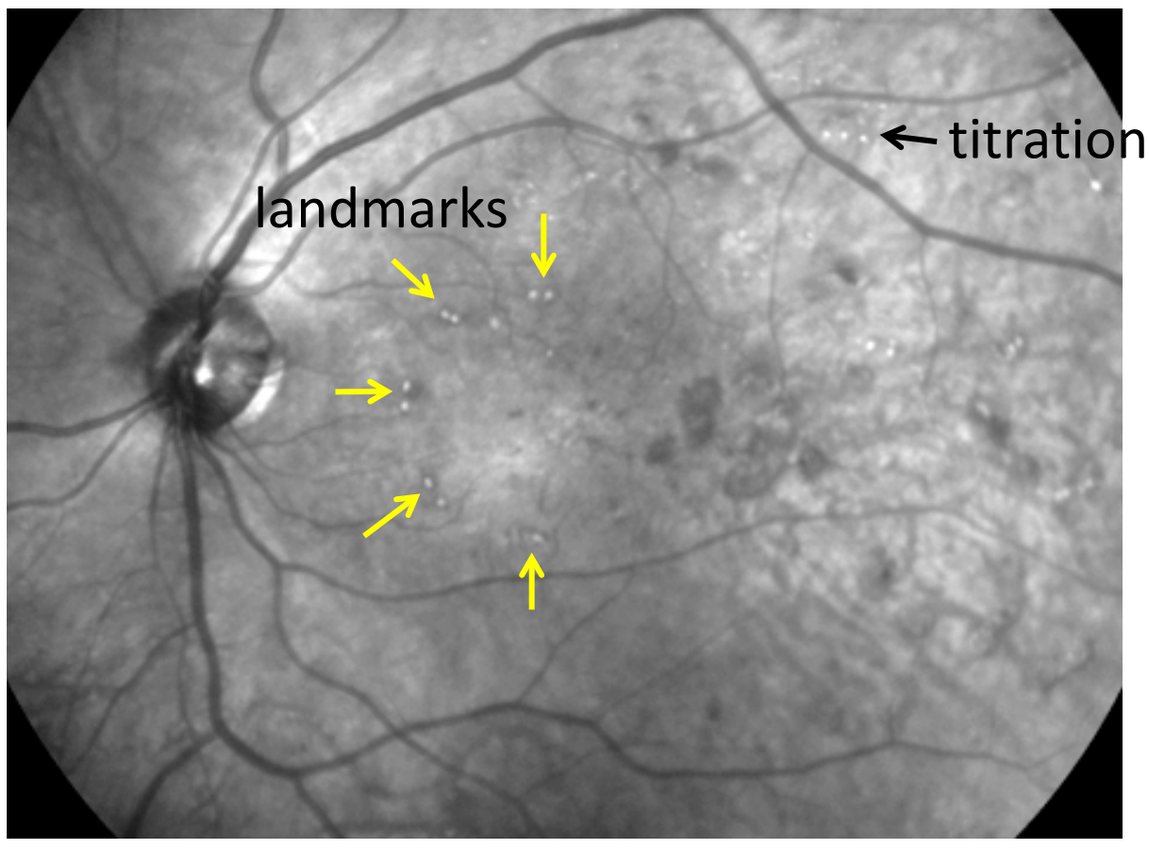
Conventional macular grid



Non-damaging therapy (NRT)







Acknowledgements

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- Roopa Dalal,
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Dr. Daeyoung Lee (visiting scholar, Seoul, Korea)

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