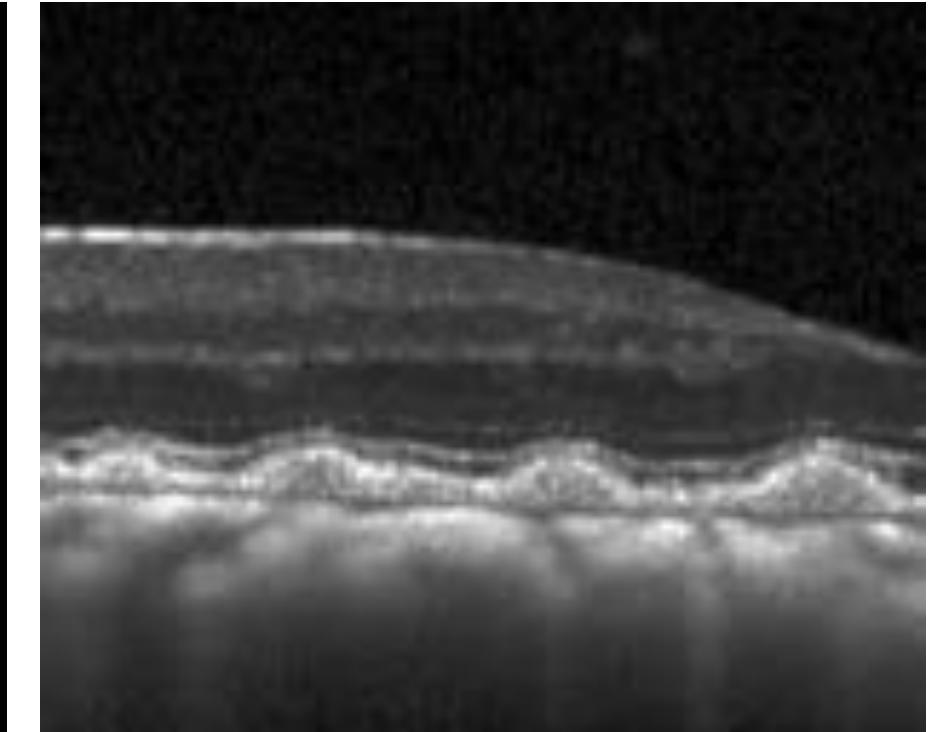
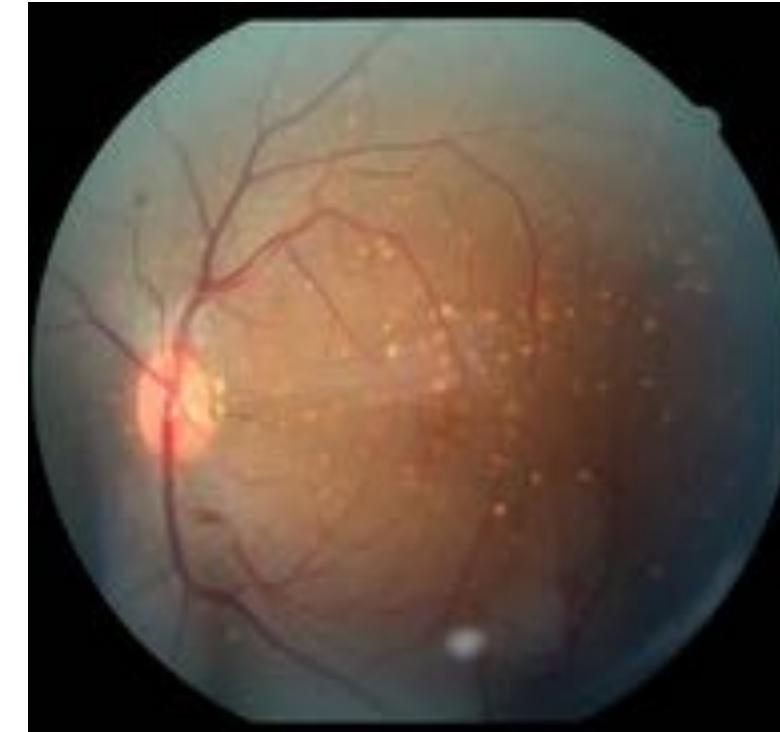


Soft Drusen in Rhesus Macaques

A Translational Model for Early AMD

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UCDAVIS
CALIFORNIA NATIONAL
PRIMATE RESEARCH CENTER



Retina Society 2020
Virtual Meeting
September 21st, 2020



Disclosures

Allergan (C)

Alimera (C)

Carl Zeiss Meditec (C)

Clearside Biomedical (R)

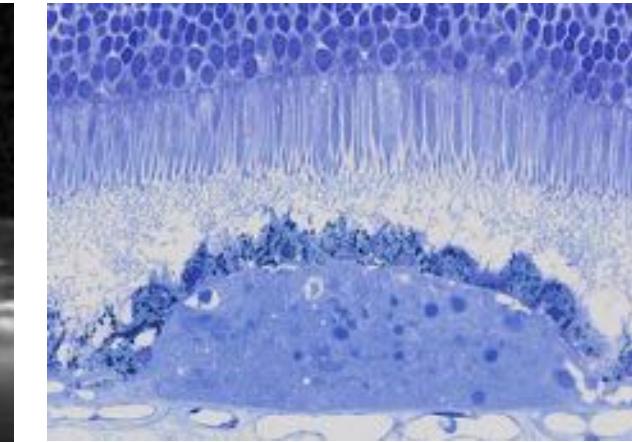
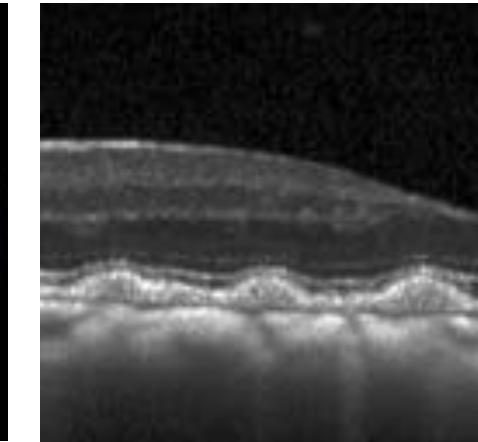
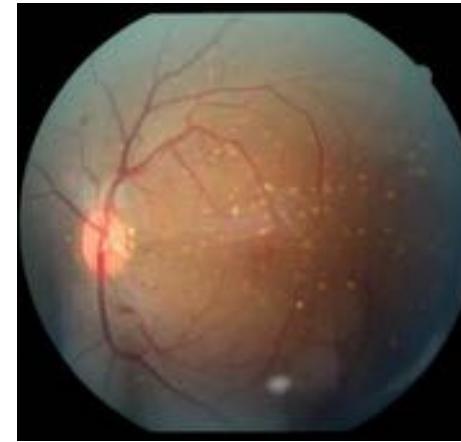
Genentech (R,C)

Iridex (R, C)

Verily (C)



Summary

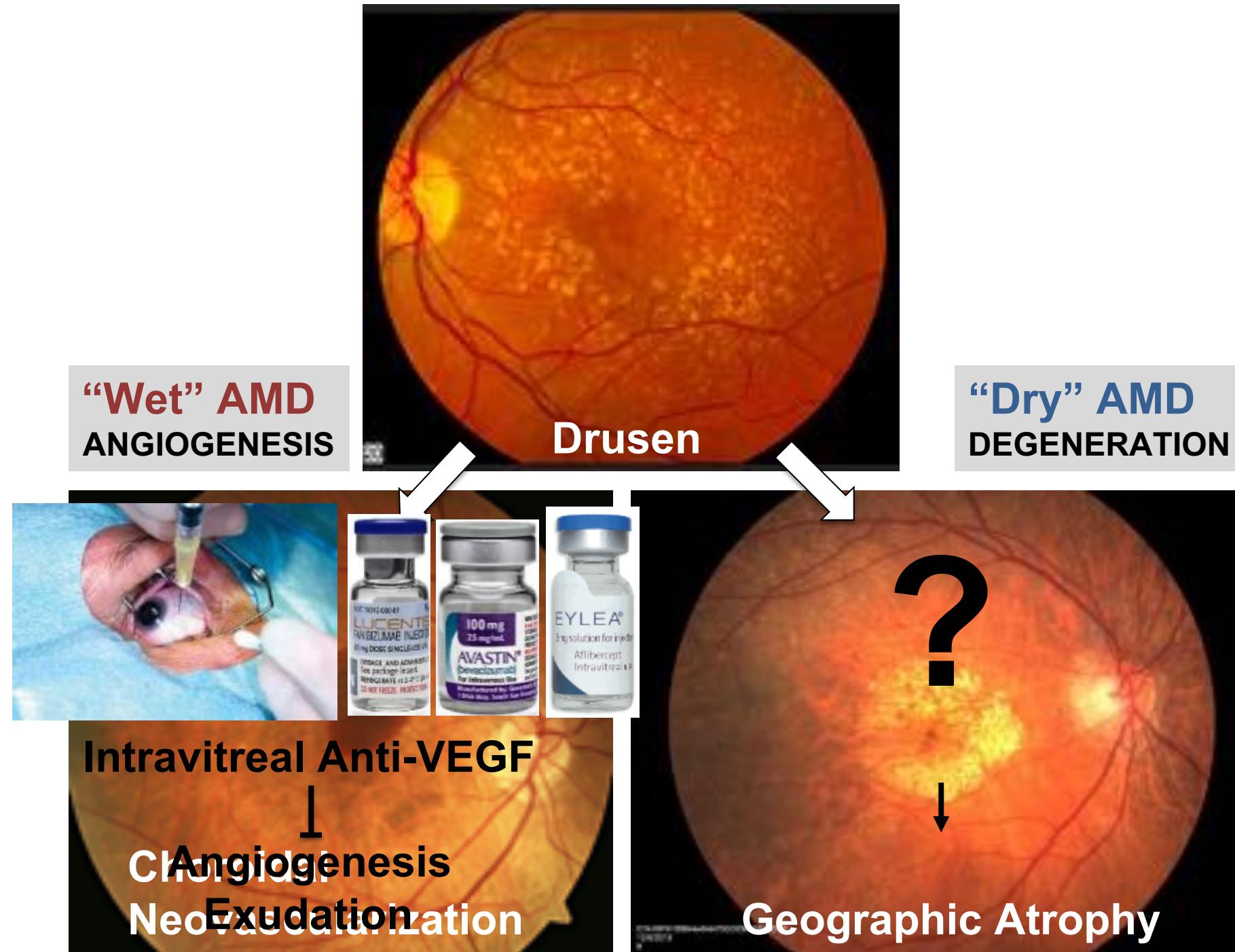


- Primates are the only mammals to possess a macula, and are the premier animal model to study dry AMD
- Rhesus macaques develop soft drusen with age, and share genetic risk alleles with human AMD
- Macaque drusen exhibit dynamic remodeling with time, with imaging/histological features resembling human drusen
- Macaques with drusen do not progress to CNV or GA, but efforts are underway to simulate these features

Treatments are only available for wet AMD



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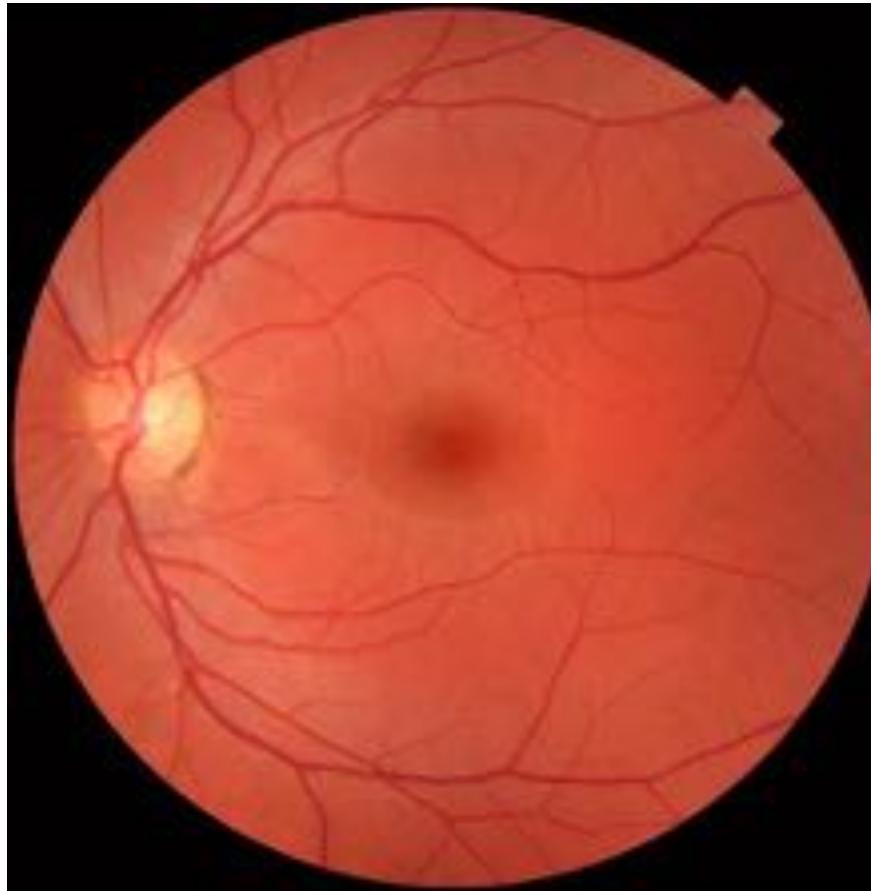


Mice do not have a macula

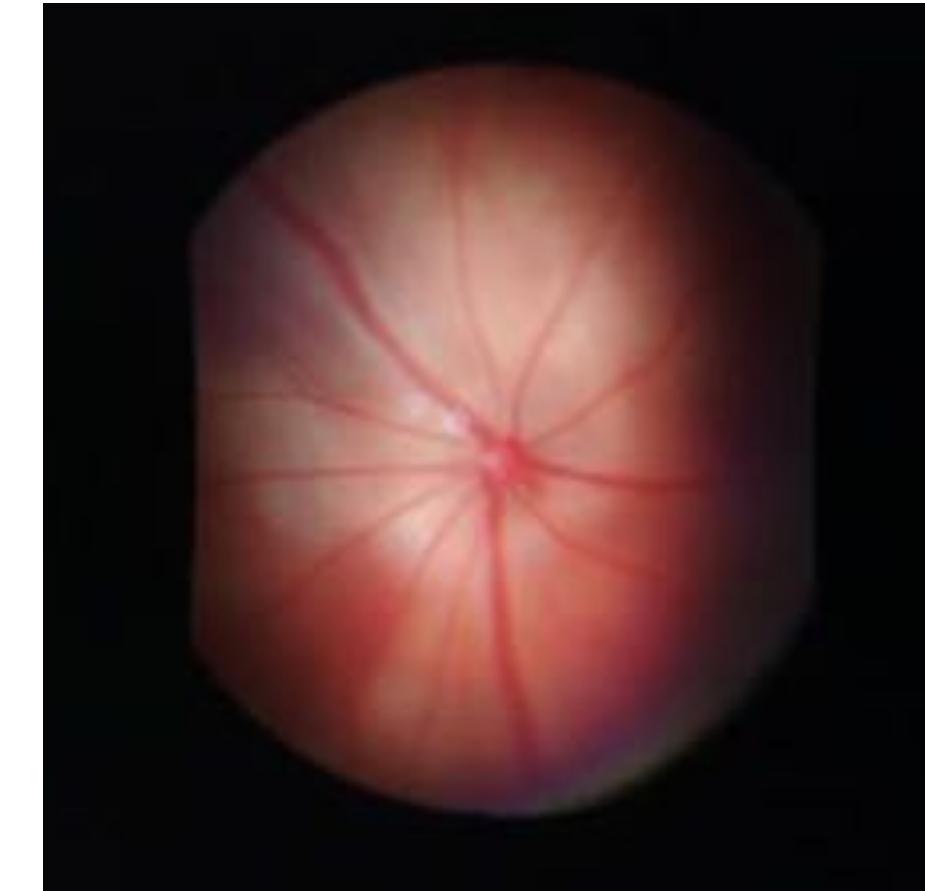


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Human



Mouse



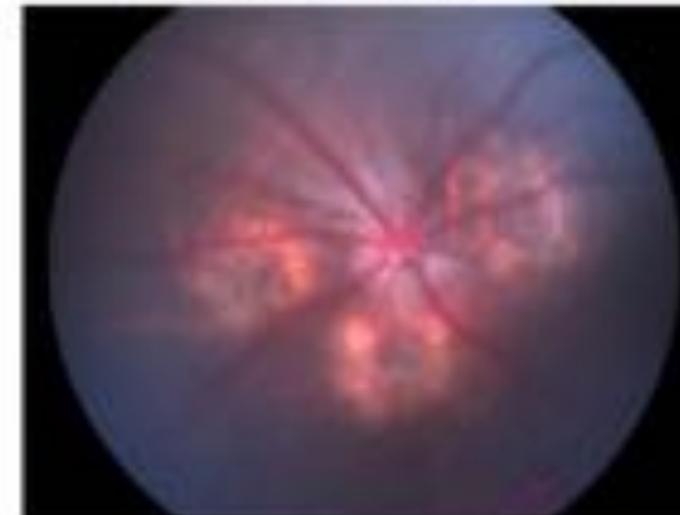
Laser CNV as a model for neovascular AMD



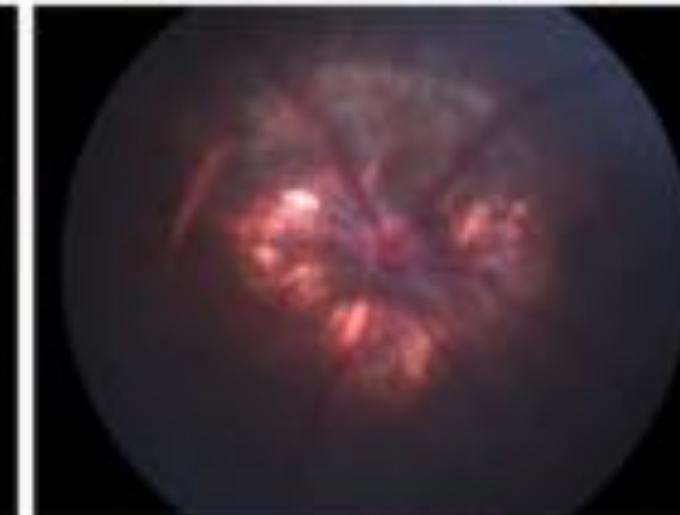
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EYE CENTER

Day 22
color photo

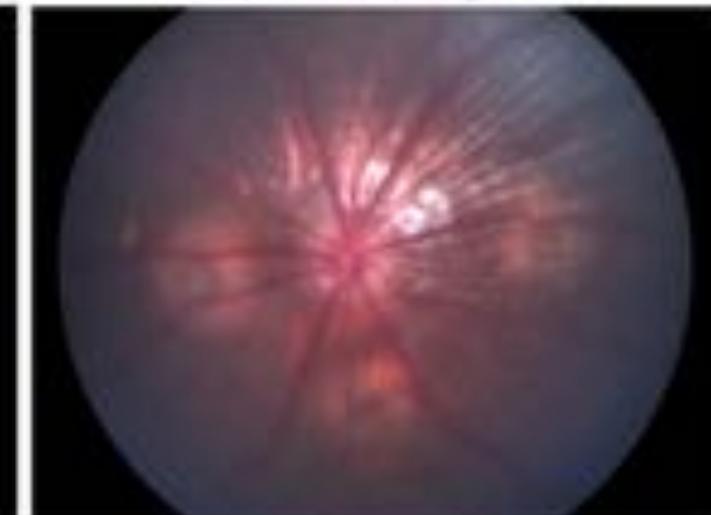
0.9% NaCl



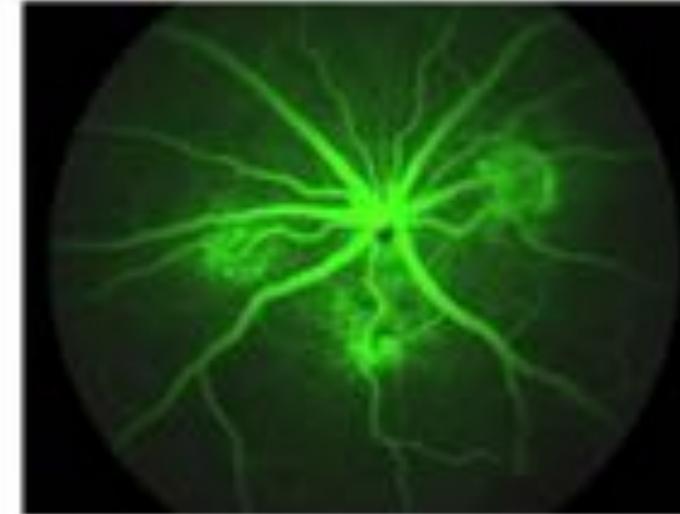
Anti-rat-VEGF Ab



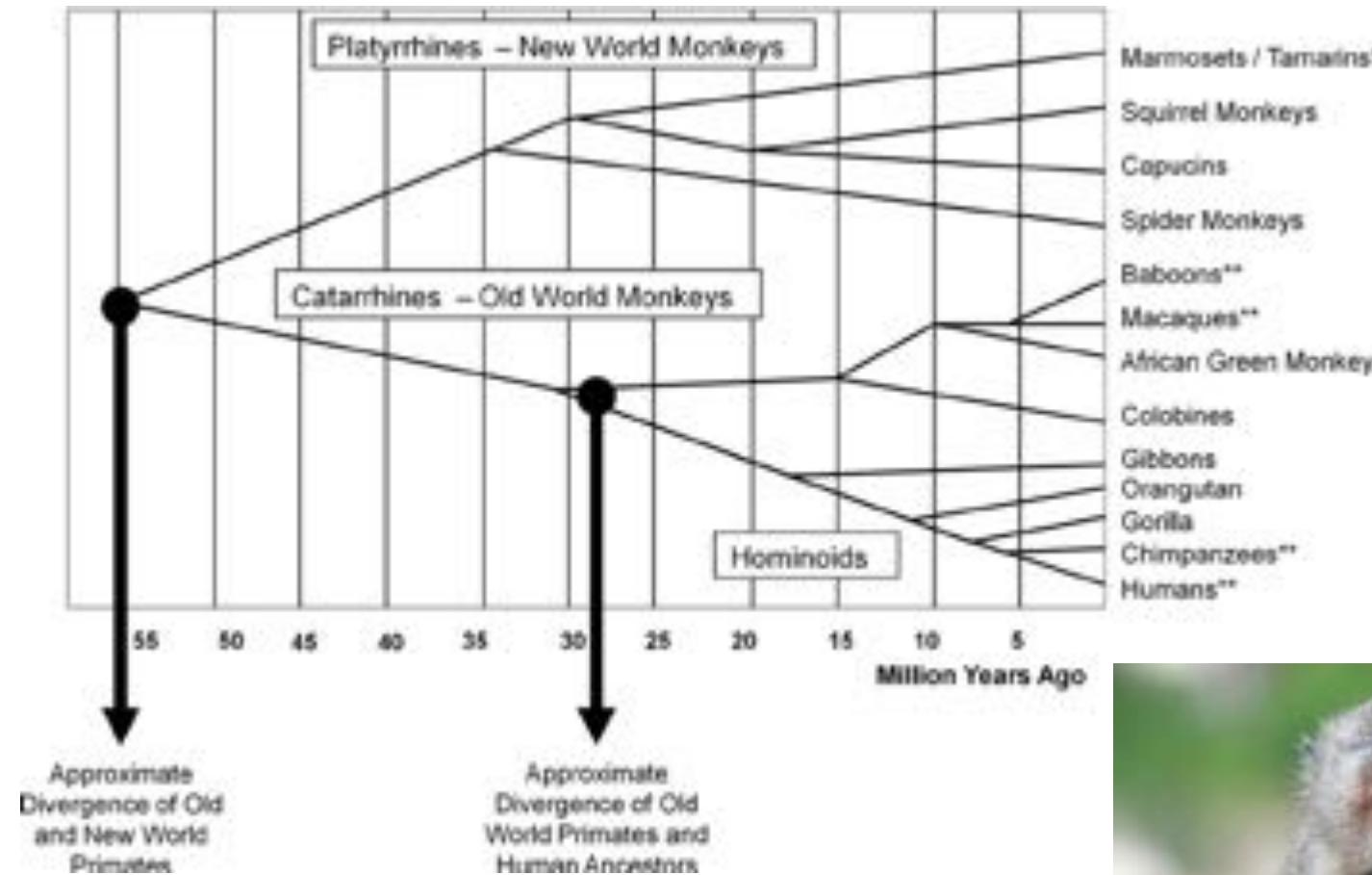
Aflibercept



Day 22
Fluorescein
Angiogram



Nonhuman primates have a macula



Rhesus Macaques
Macaca mulatta



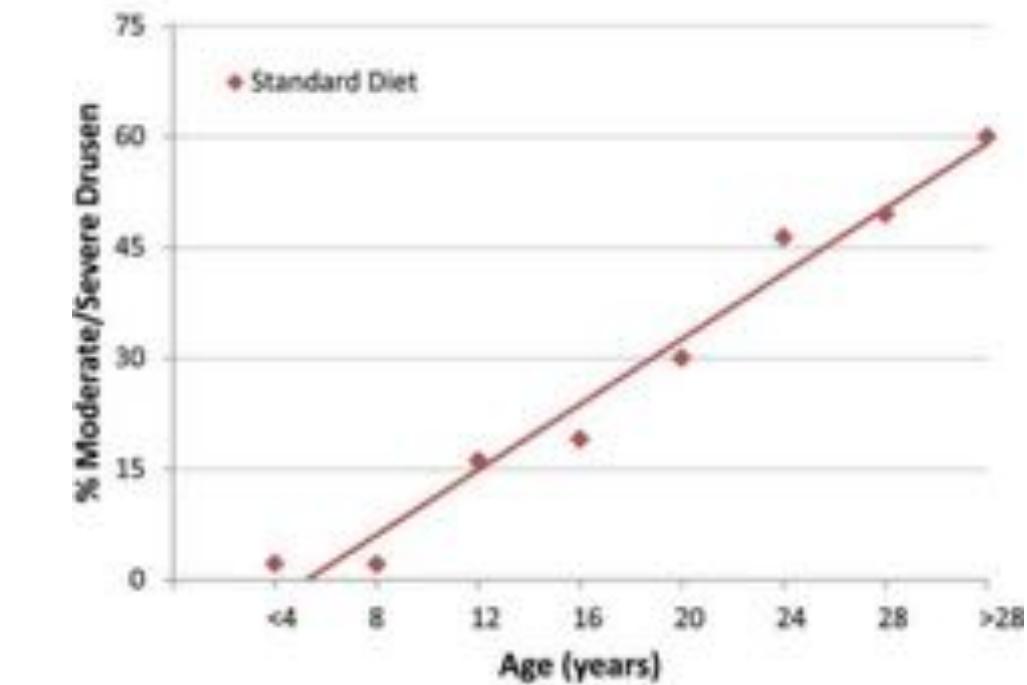
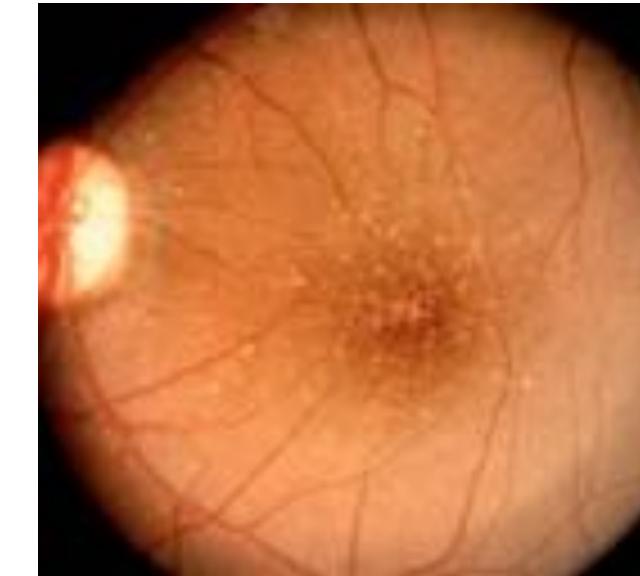
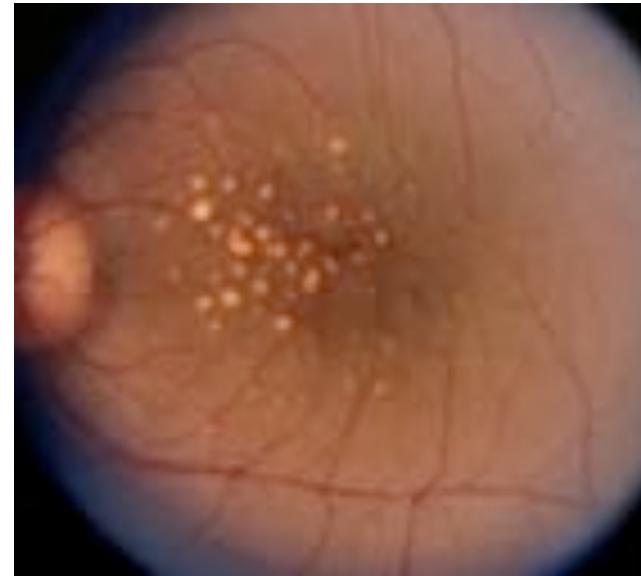
Cynomolgus Macaques
Macaca fascicularis



Japanese Macaques
Macaca fuscata

Nonhuman primates are the only animals to have a macula similar to humans

Nonhuman primates develop drusen

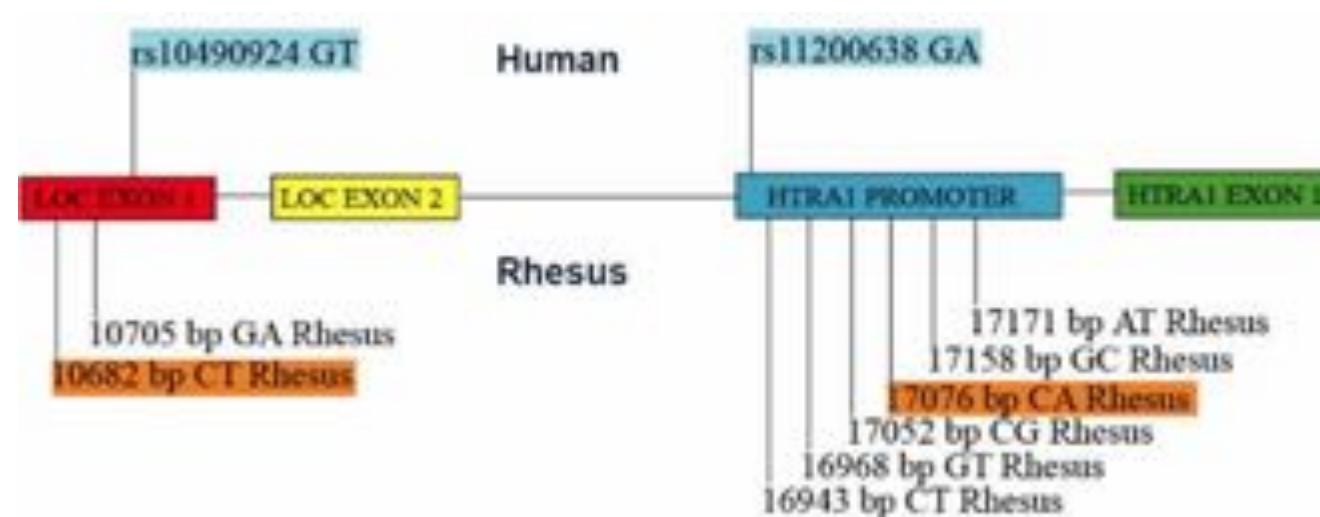


	Location	Total Animals	Age Range	Drusen Frequency	Pigment Change
El Mofty 1978	CPRC (free-ranging)	105	1-21	30%	32%
Stafford 1984	Various (most indoor)	574	10-31	5.9%	NR
Engel 1988	CPRC (free-ranging)	29	13-27	74%	NR
Monaco 1990	Naval Aerospace Lab (indoor & free-ranging)	100	1-13	31%	10%
Hope 1992	CPRC (free-ranging)	246	1-30	57.7%	NR
Olin 1995	CRPRC & WRPRC (indoor)	62	20-33	47%	NR
Gouras 2008	NIH & ONPRC (indoor)	121	10-39	61%	NR

Similarities between monkey drusen and AMD



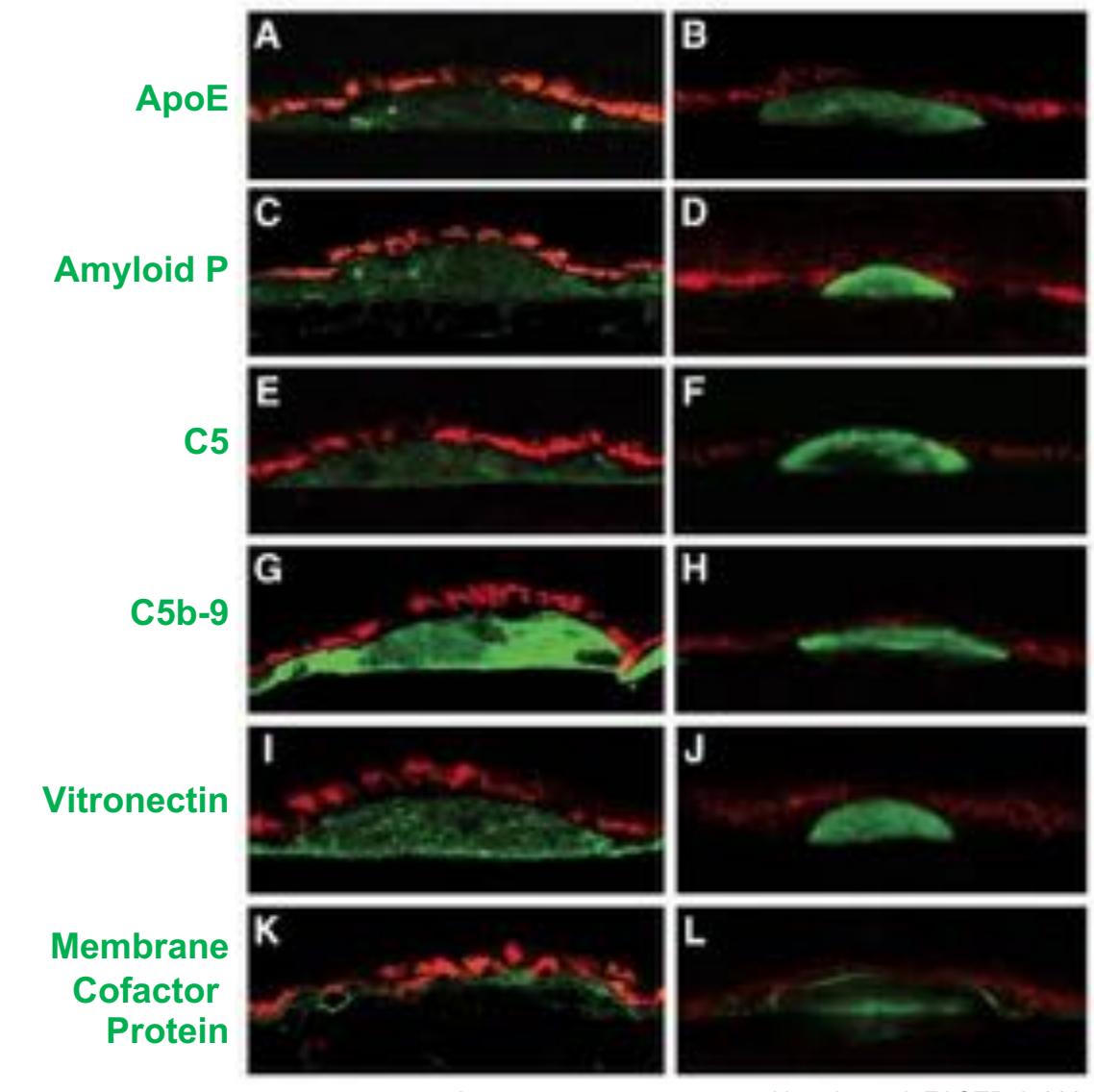
Monkeys with drusen share similar genetic risk alleles as AMD patients



		Controls		Cases		Odds Ratio (CI)	p-value
		#	%	#	%		
ARMS2	TT	4	8	4	6	1.00	
SNP 10682	CT	41	85	41	60	1.00 (0.36-2.79)	1.0000
	CC	3	6	23	34	7.67 (2.09-28.07)	0.0020
HTRA1	CC	18	42	22	36	1.00	
SNP 17076	AC	25	58	35	57	1.14 (0.65-2.03)	0.6600
	AA	0	0	4	7	[cannot compute]	0.0200

Francis et al., *Hu Mol Gen*, 2008

Monkey drusen have similar components as human drusen



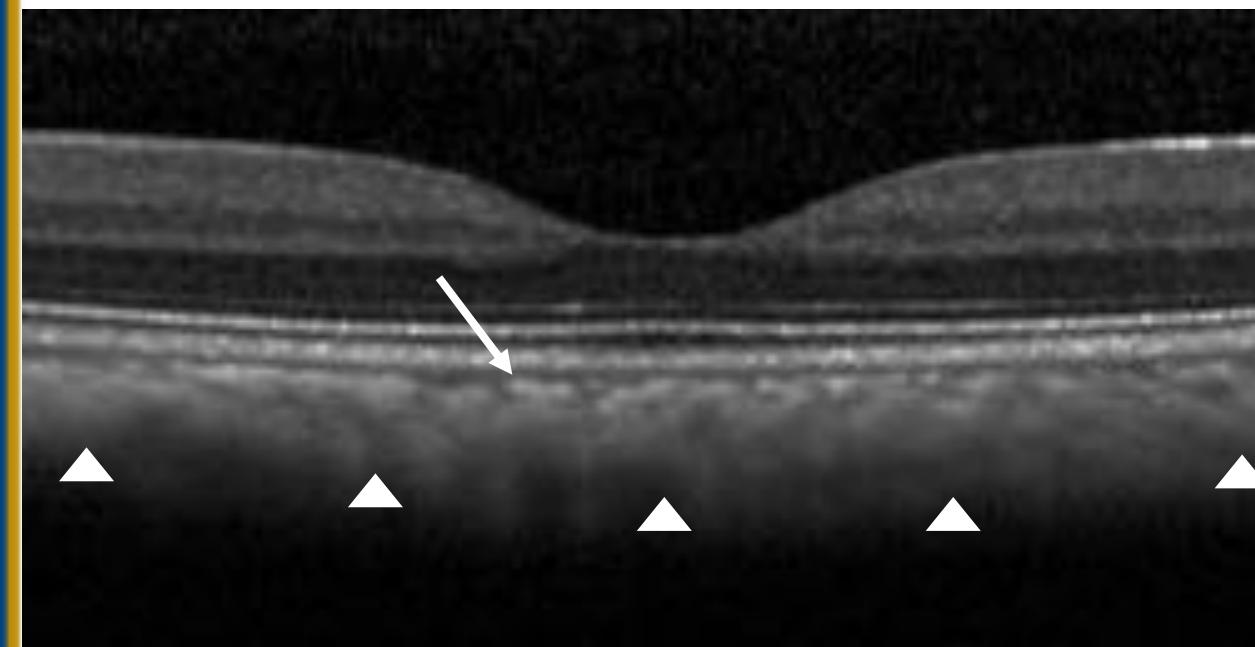
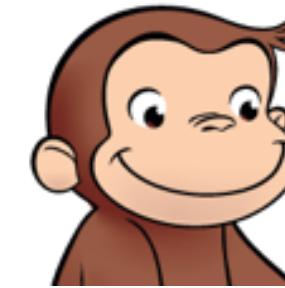
Lipofuscin

Umeda et al, *FASEB J*, 2005

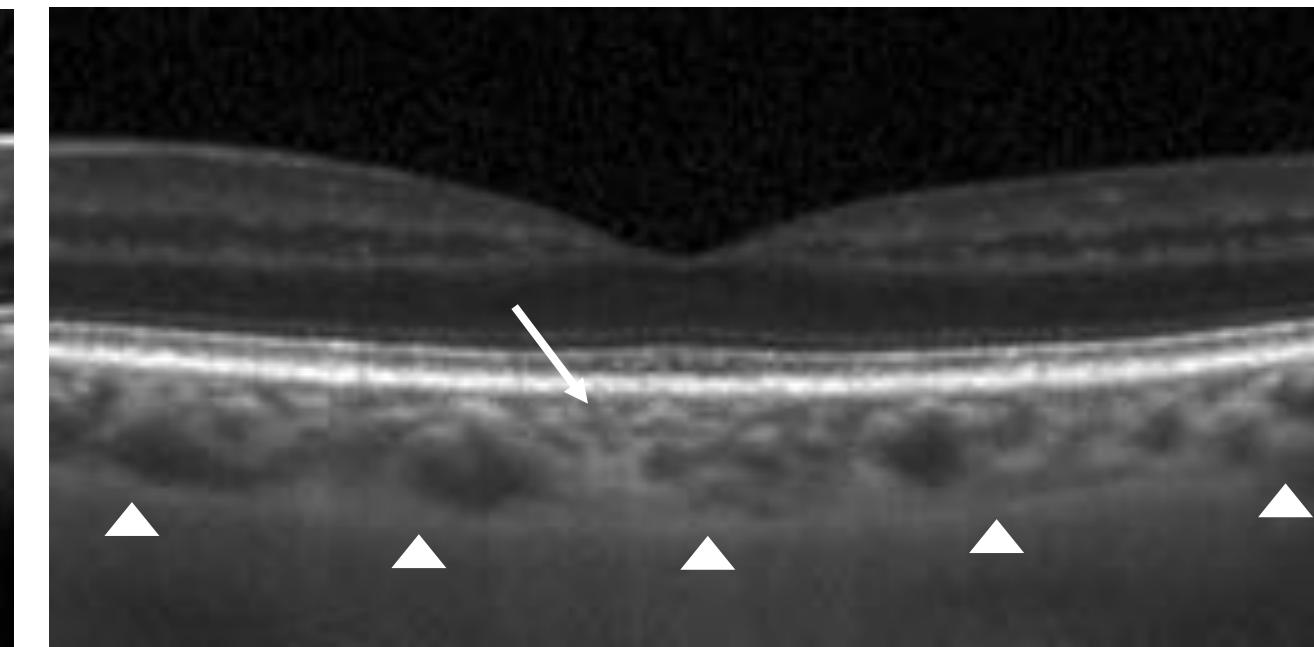
OCT imaging in monkeys vs human



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EYE CENTER

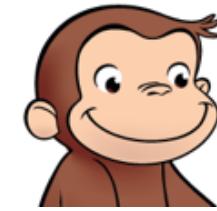
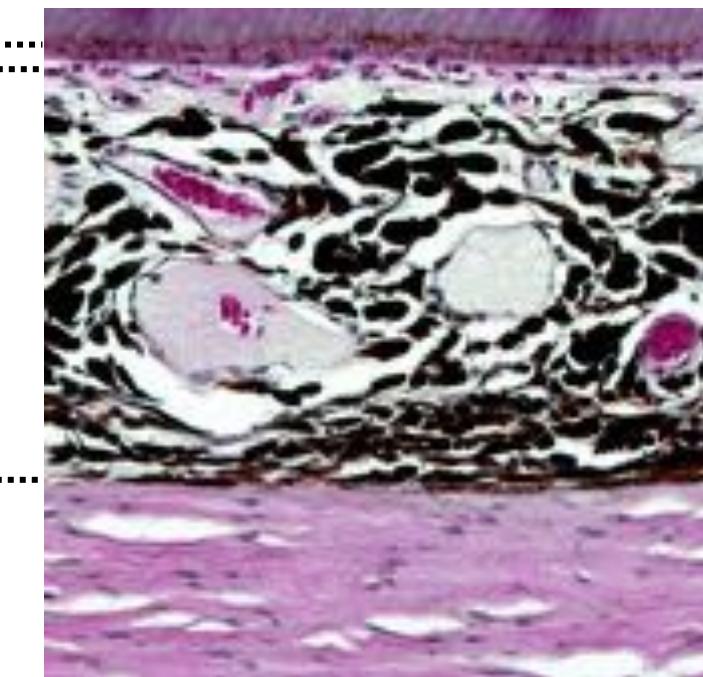
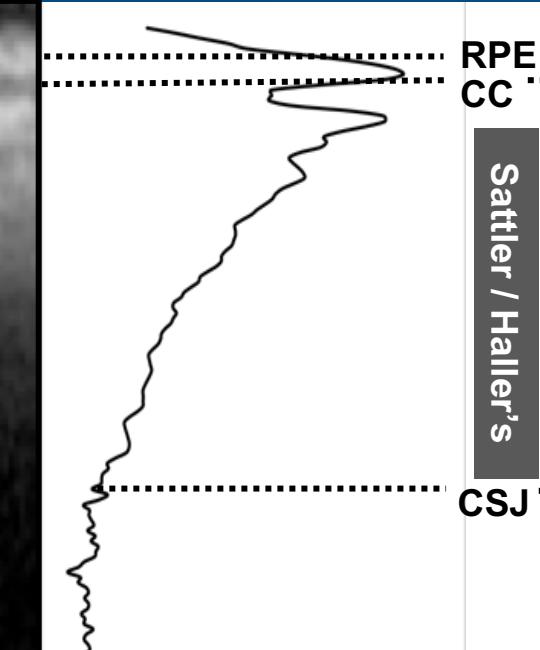
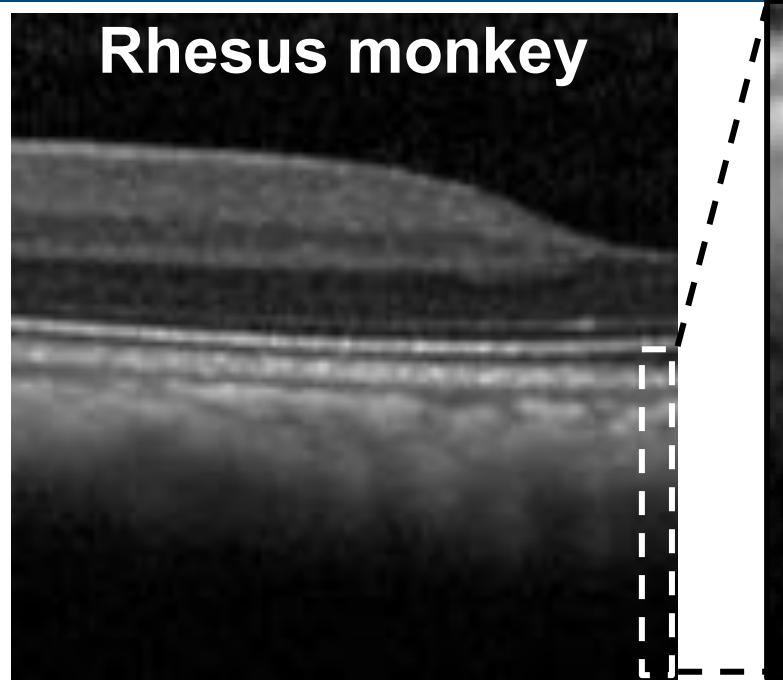
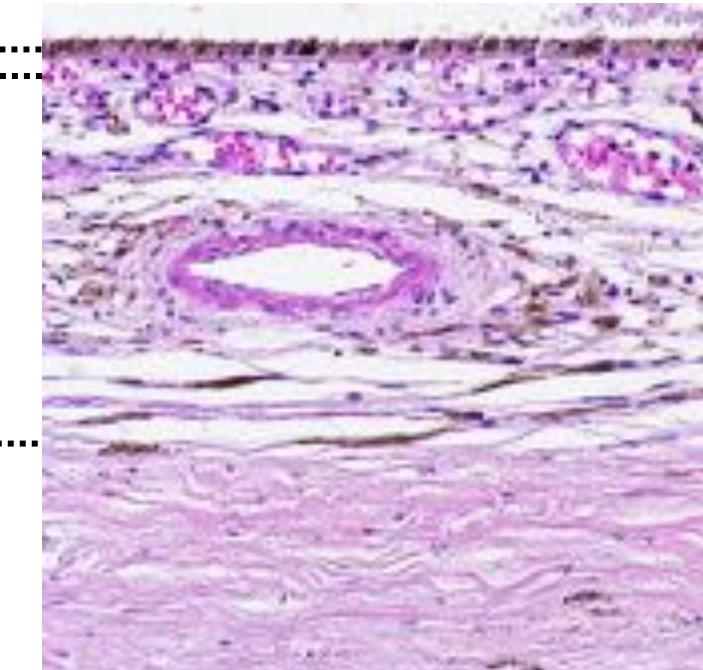
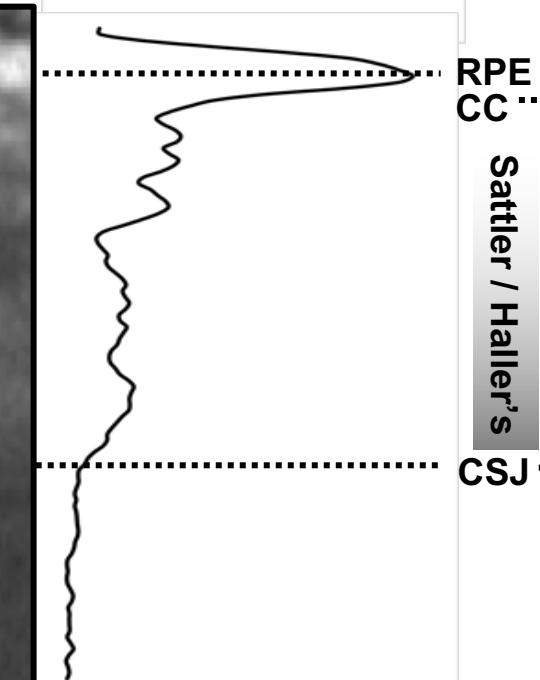
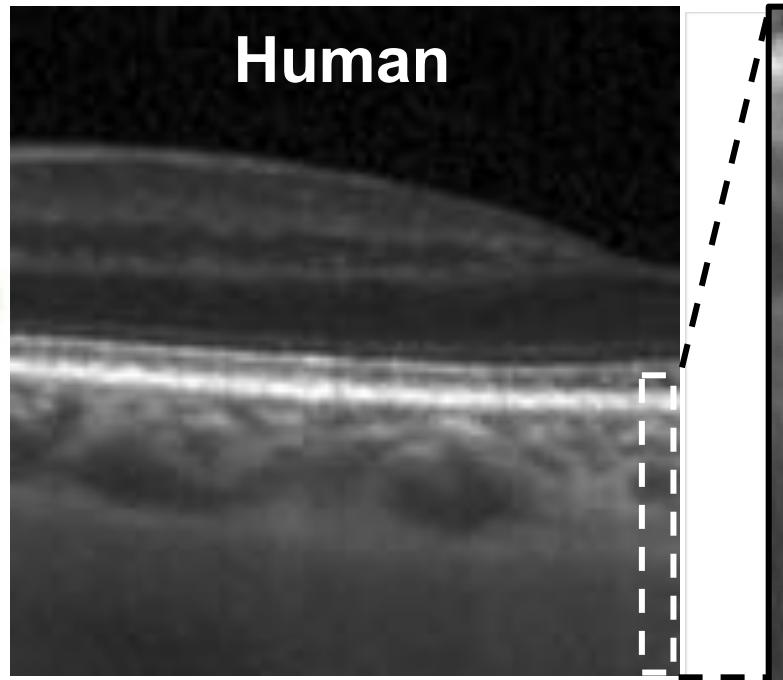


Rhesus monkey



Human

Uveal melanocytes affect OCT choroidal morphology

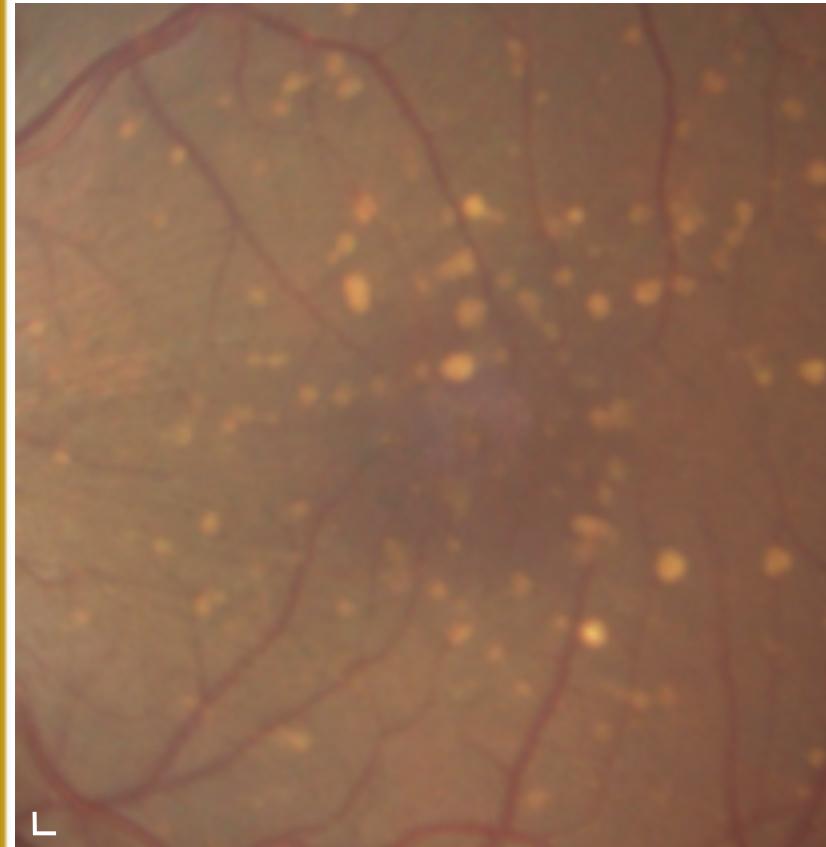
UCDAVIS
EYE CENTER**Rhesus monkey****Human**

Drusenoid lesions in monkeys

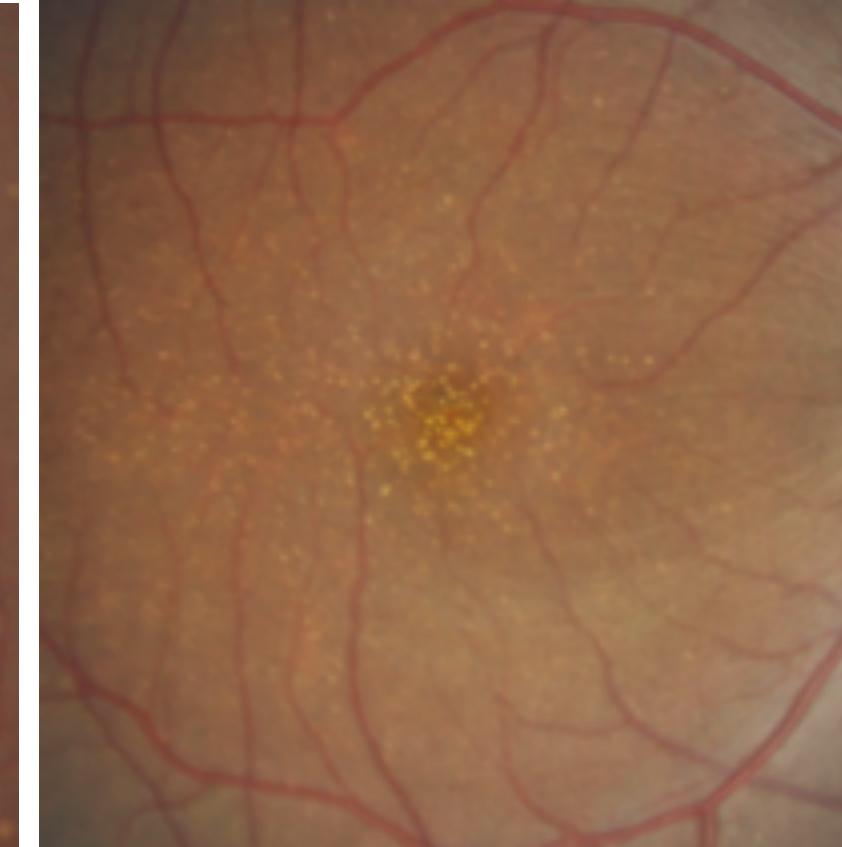


UCDAVIS
EYE CENTER

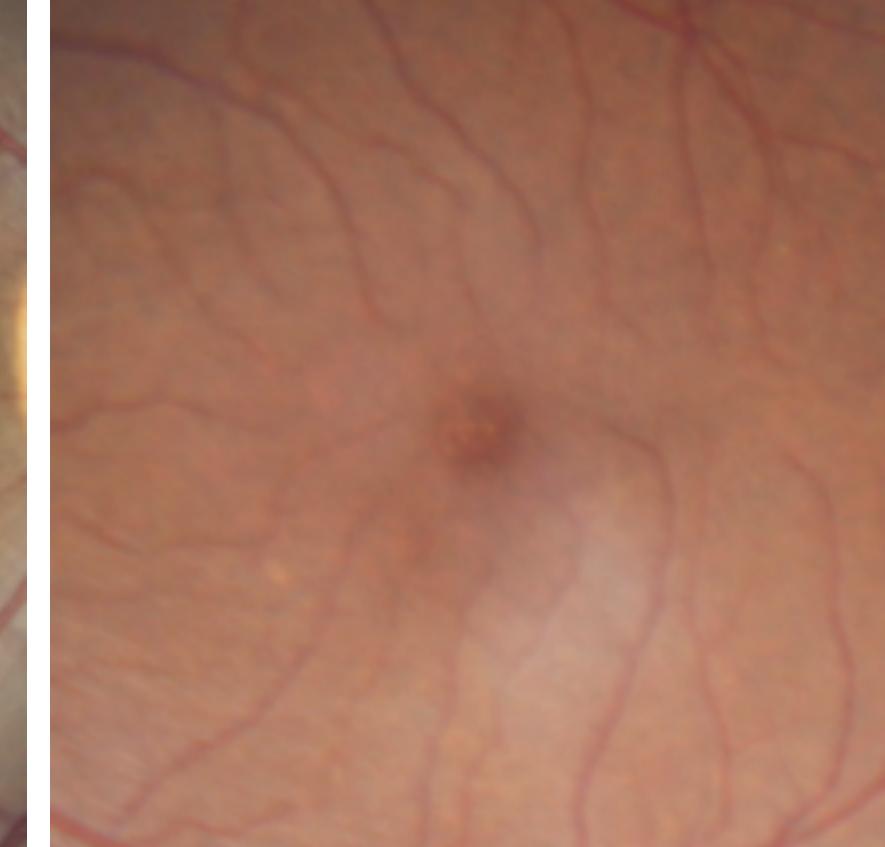
Soft Drusen



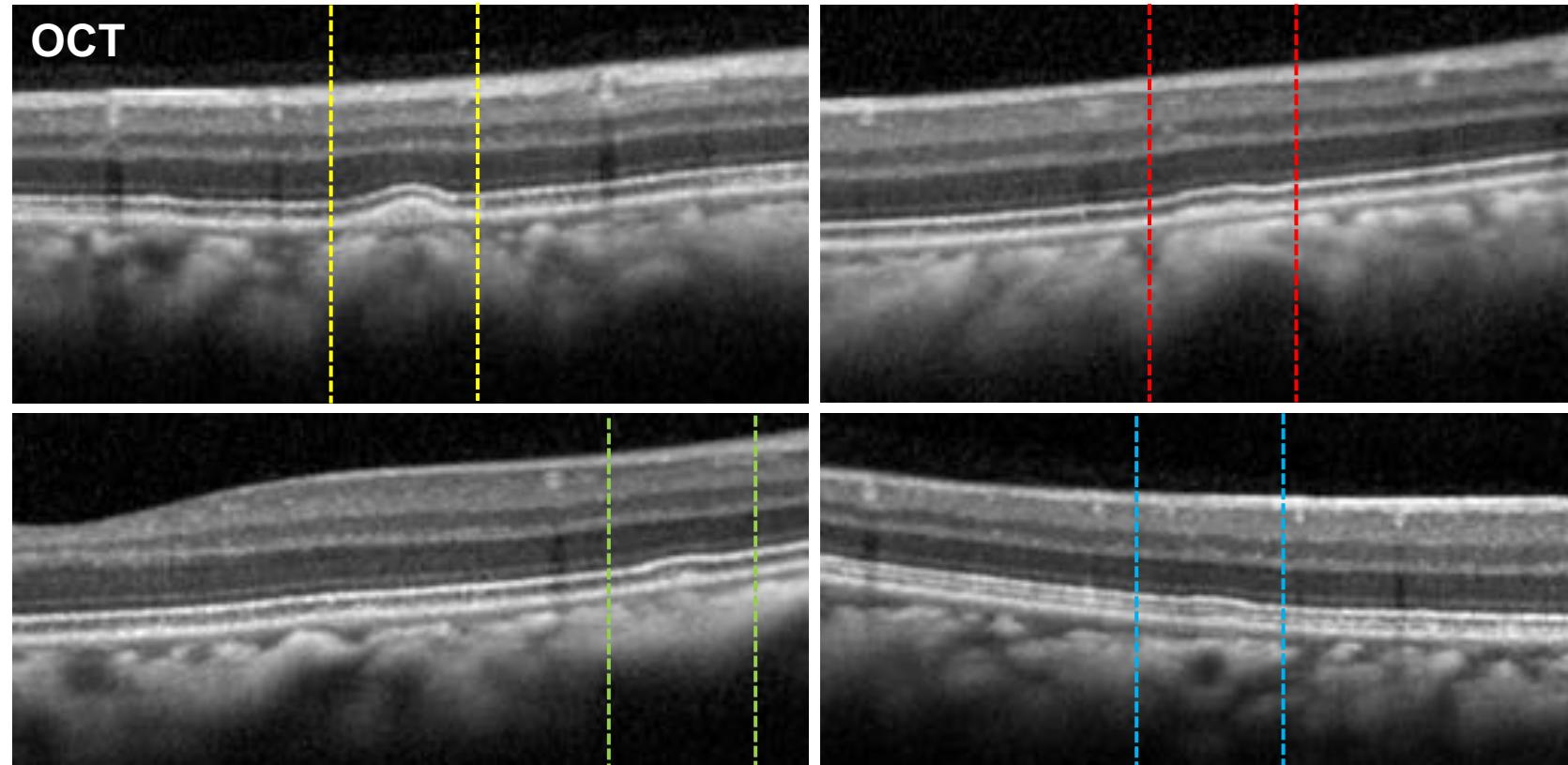
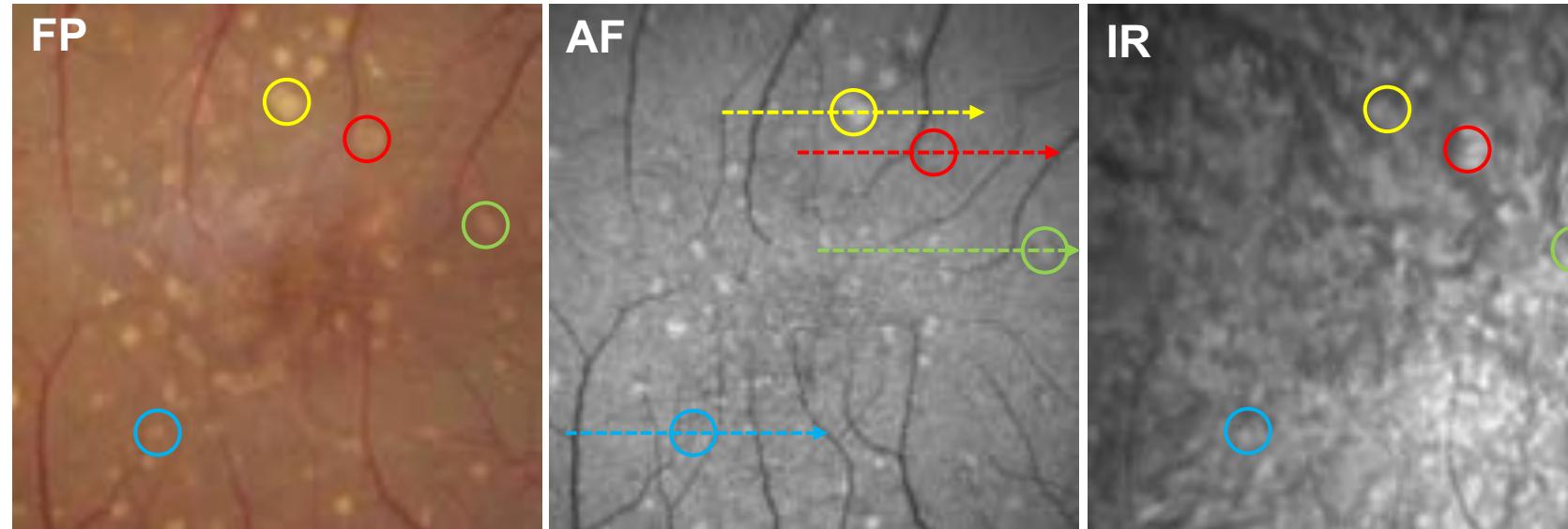
Punctate Lesions



Normal Aging



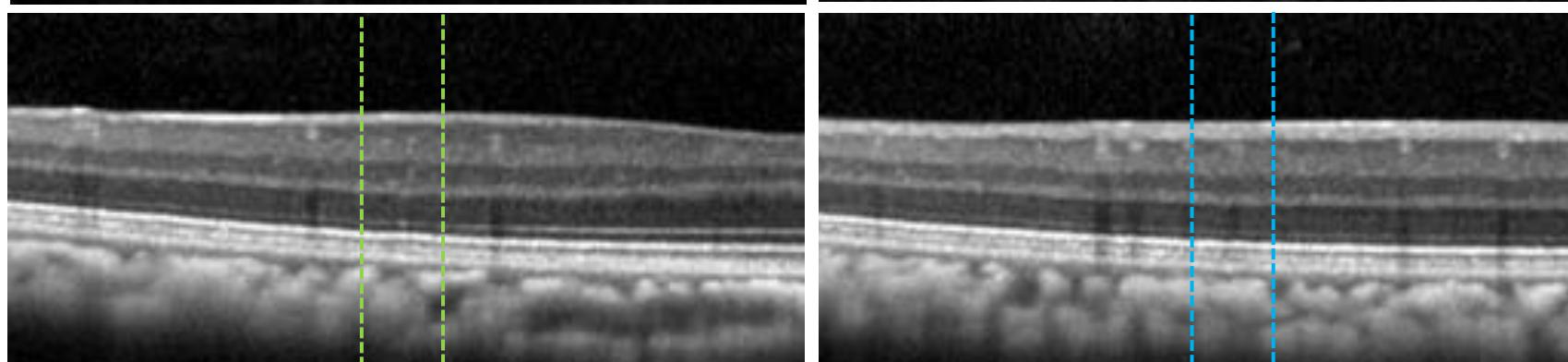
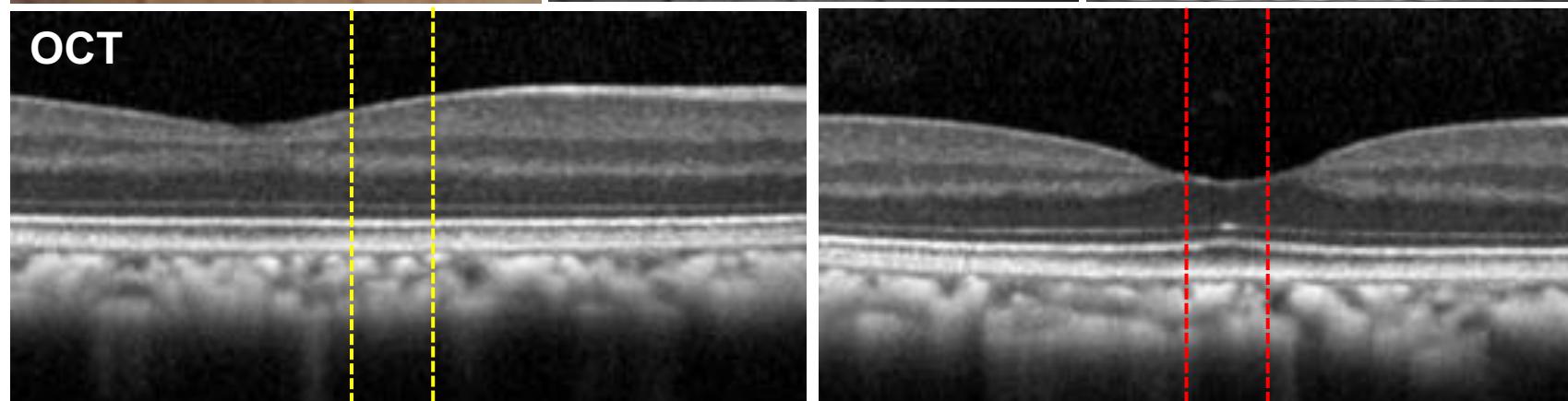
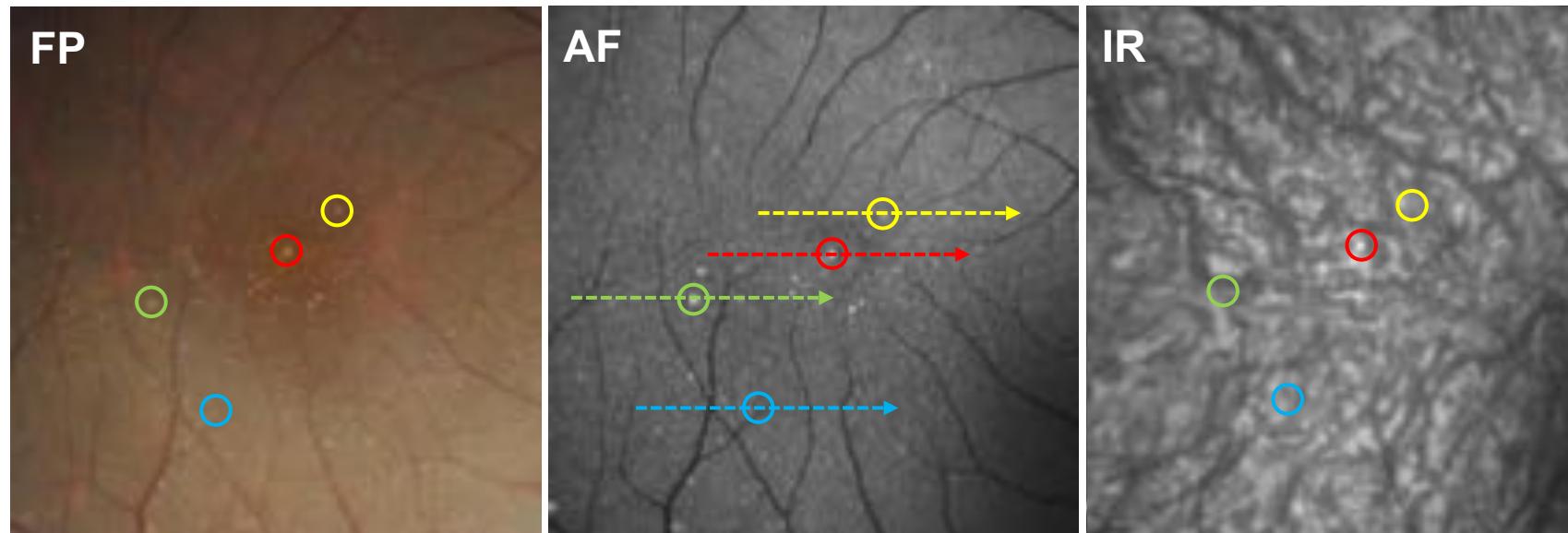
OCT demonstrates soft drusen in monkeys

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Soft drusen

- Large size
- Soft edge
- under RPE
- occ hyperFAF

OCT demonstrates hard lesions in monkeys



Soft drusen

- Large size
- Soft edge
- under RPE
- occ hyperFAF

Punctate lesions

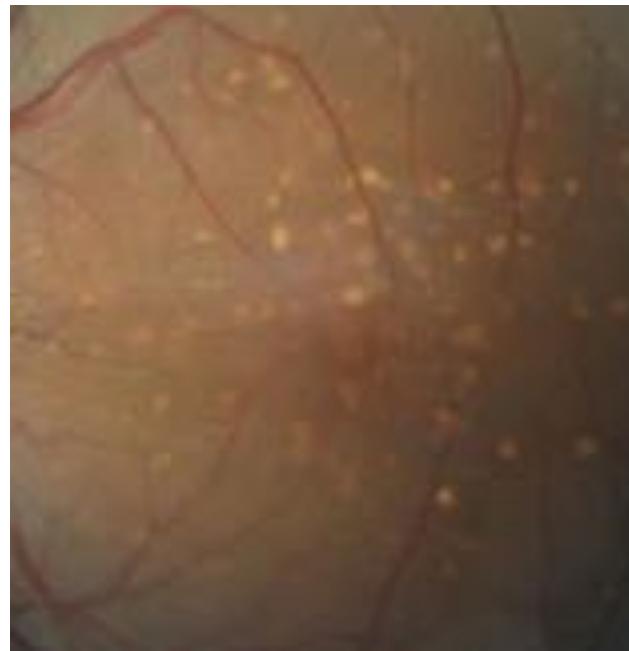
- Tiny size
- sharp edge
- not on OCT
- rare hyperFAF

Evolution of soft drusen in primates over 2 years

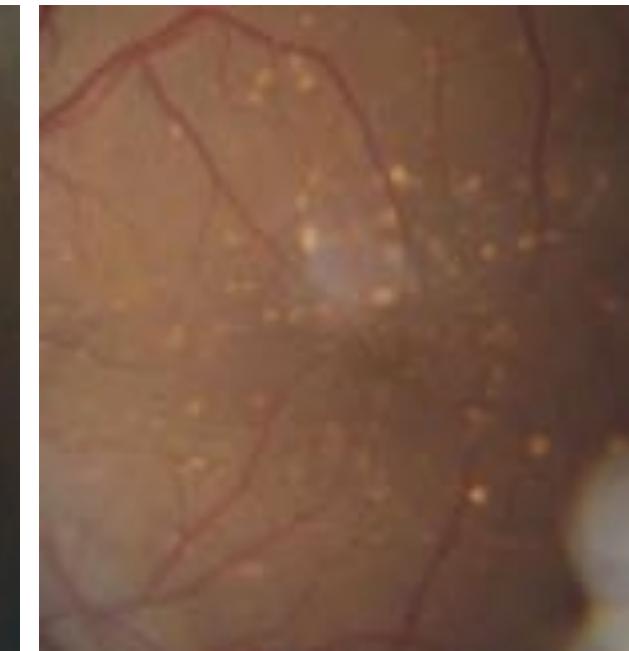


Fundus Photo

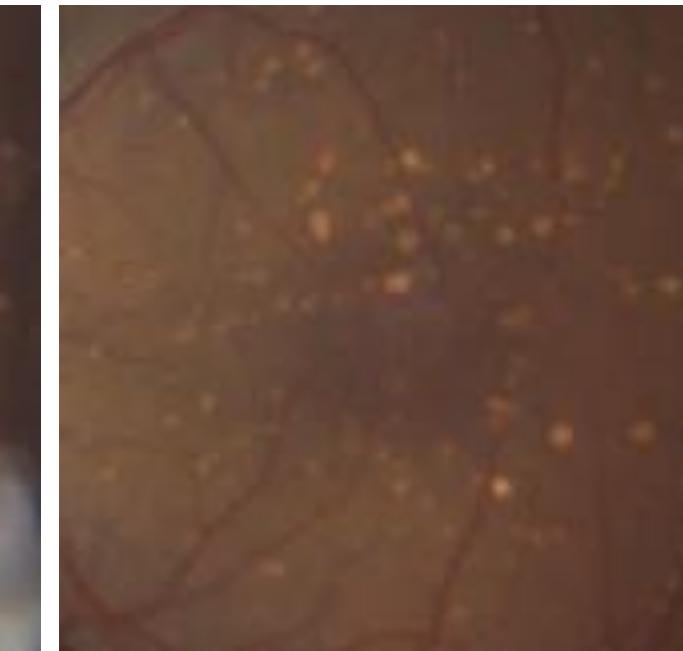
Year 0



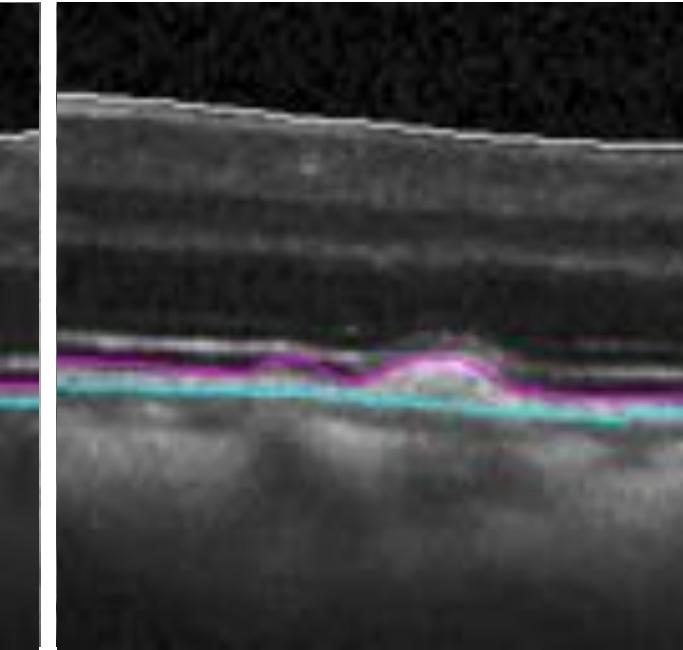
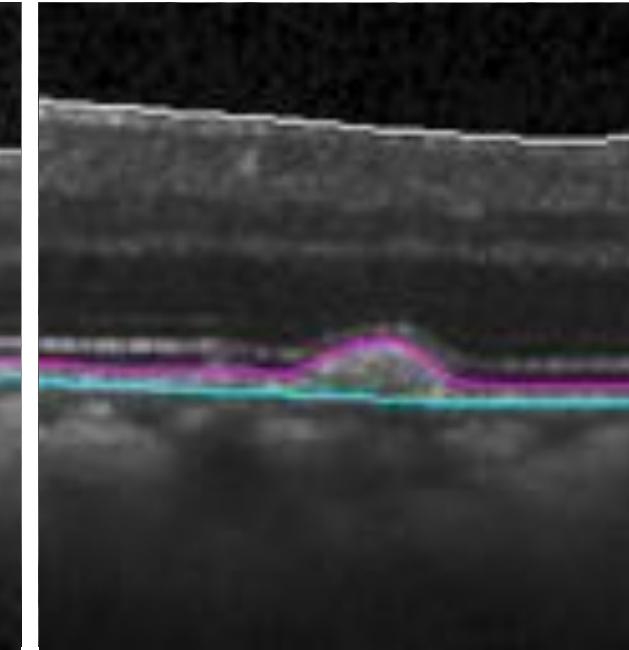
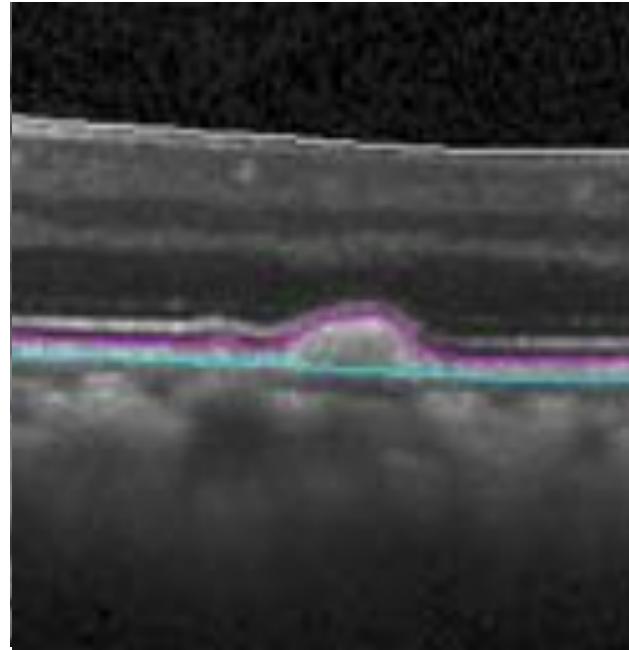
Year 1



Year 2



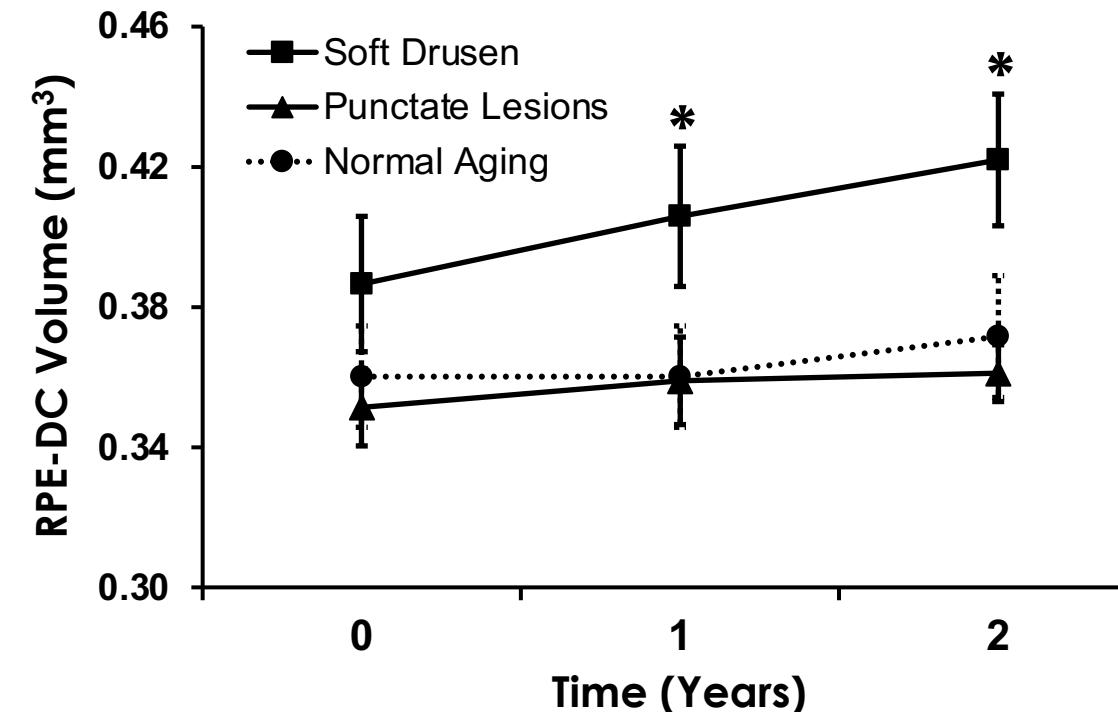
Autofluorescence



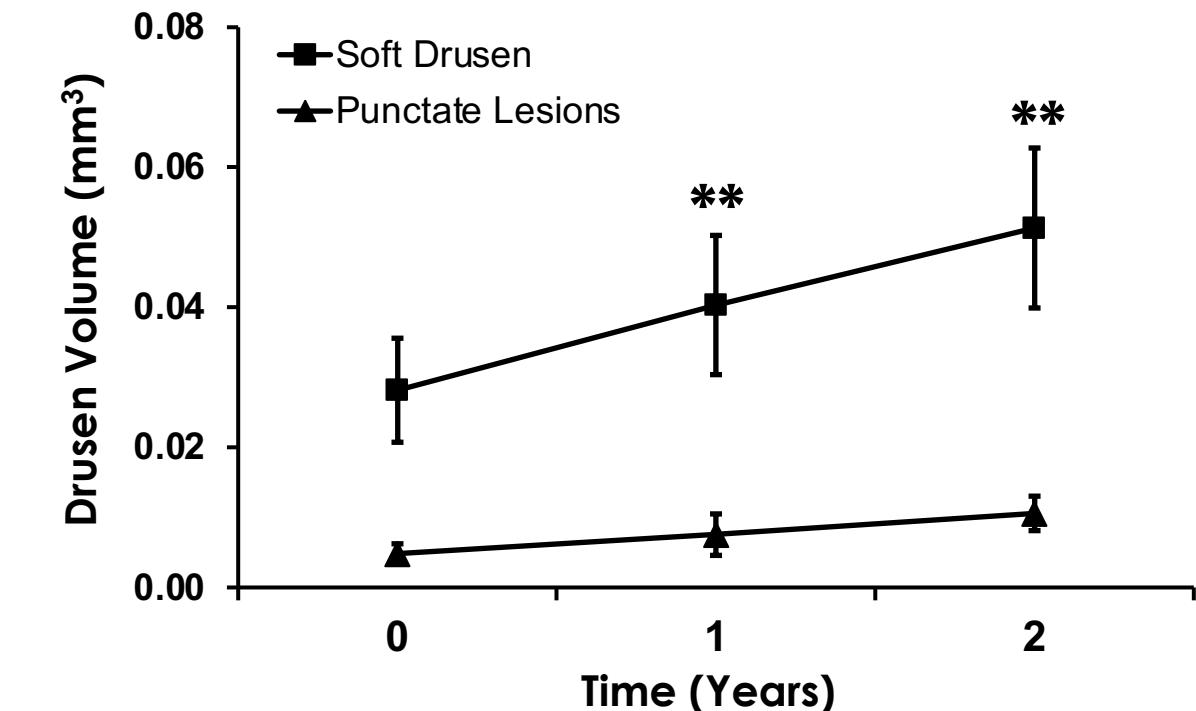
Evolution of soft drusen in primates over 2 years



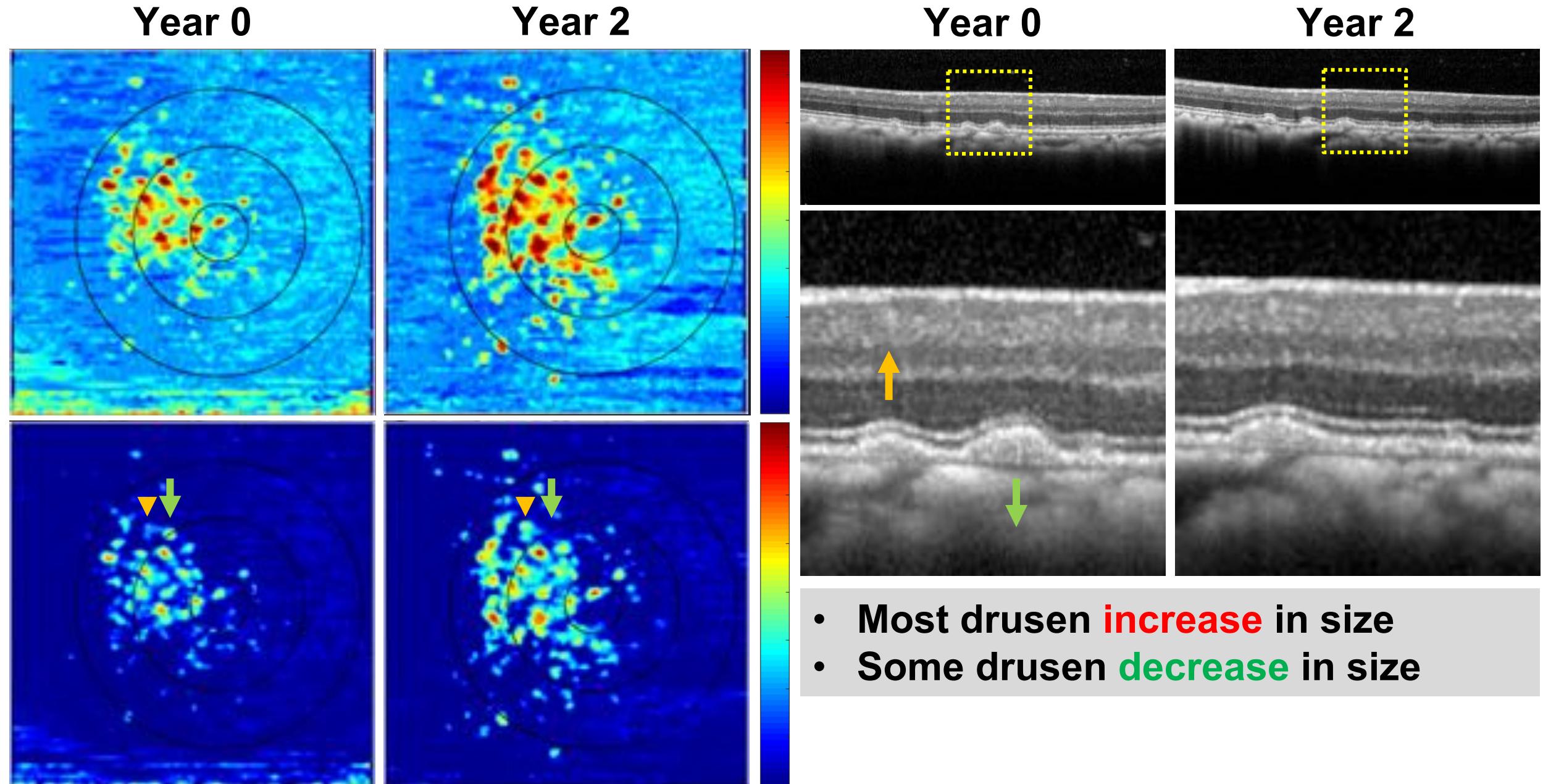
RPE-Drusen Complex Volume



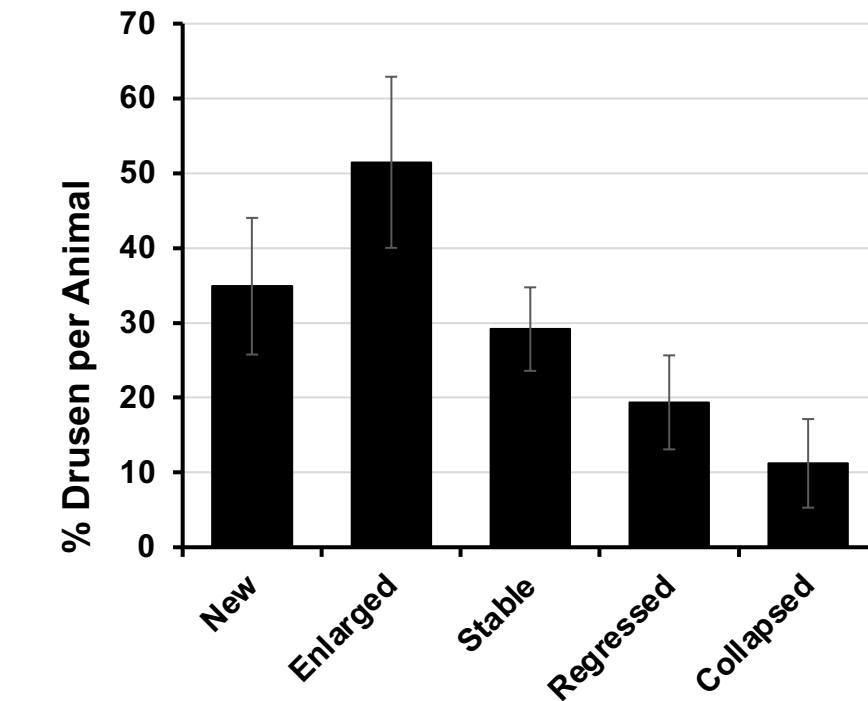
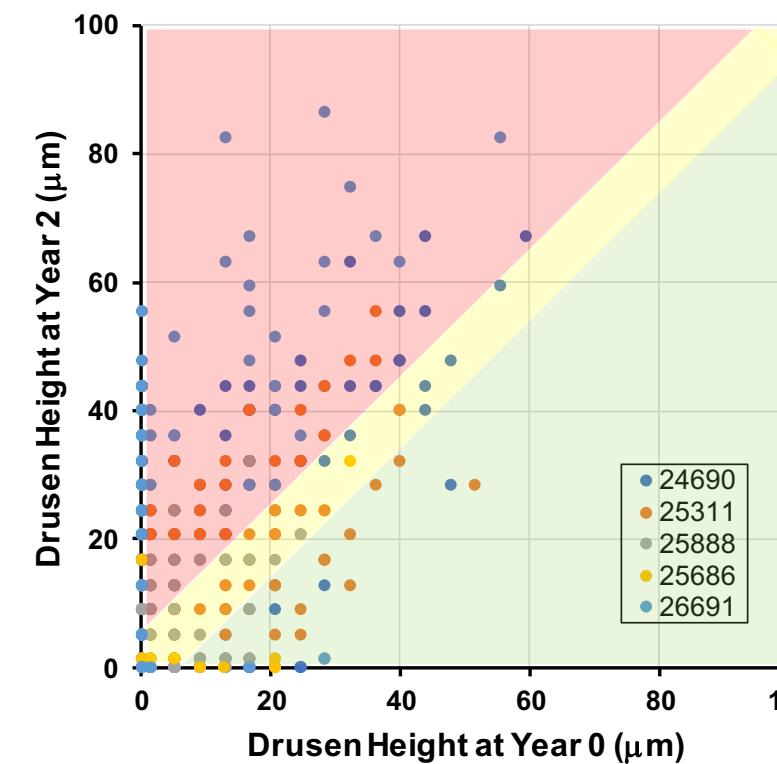
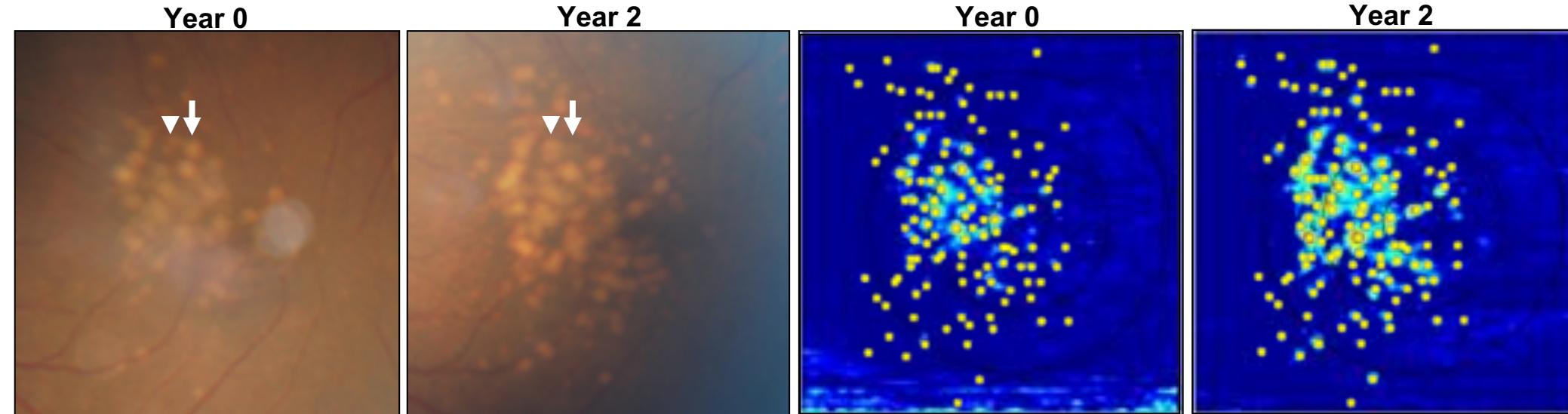
Drusen Volume



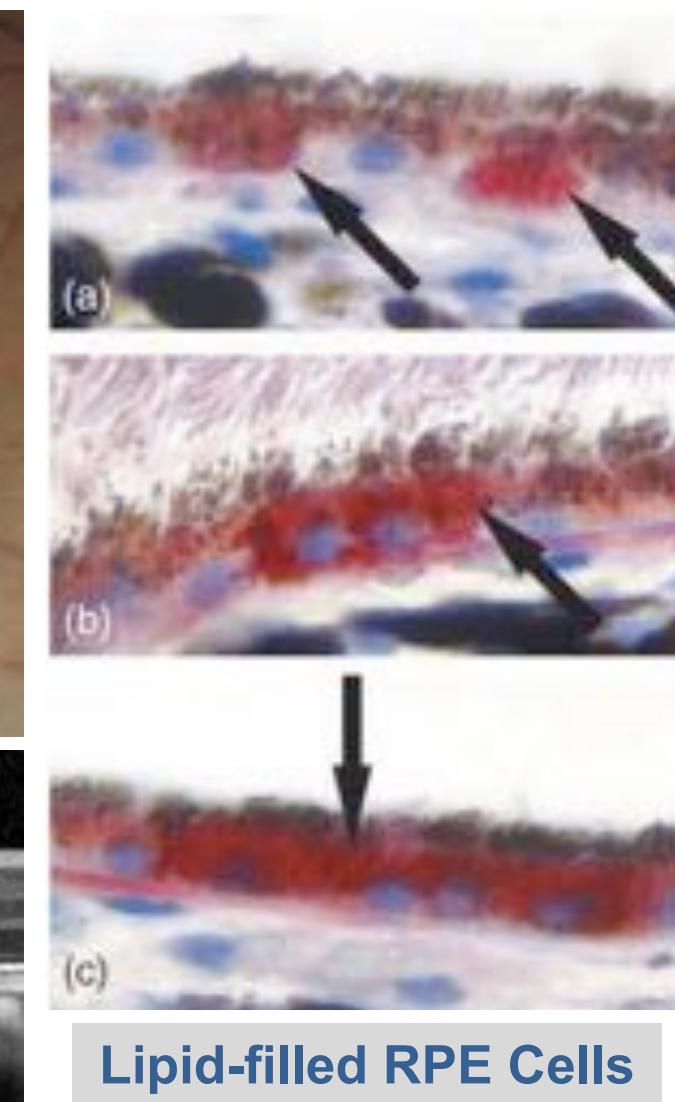
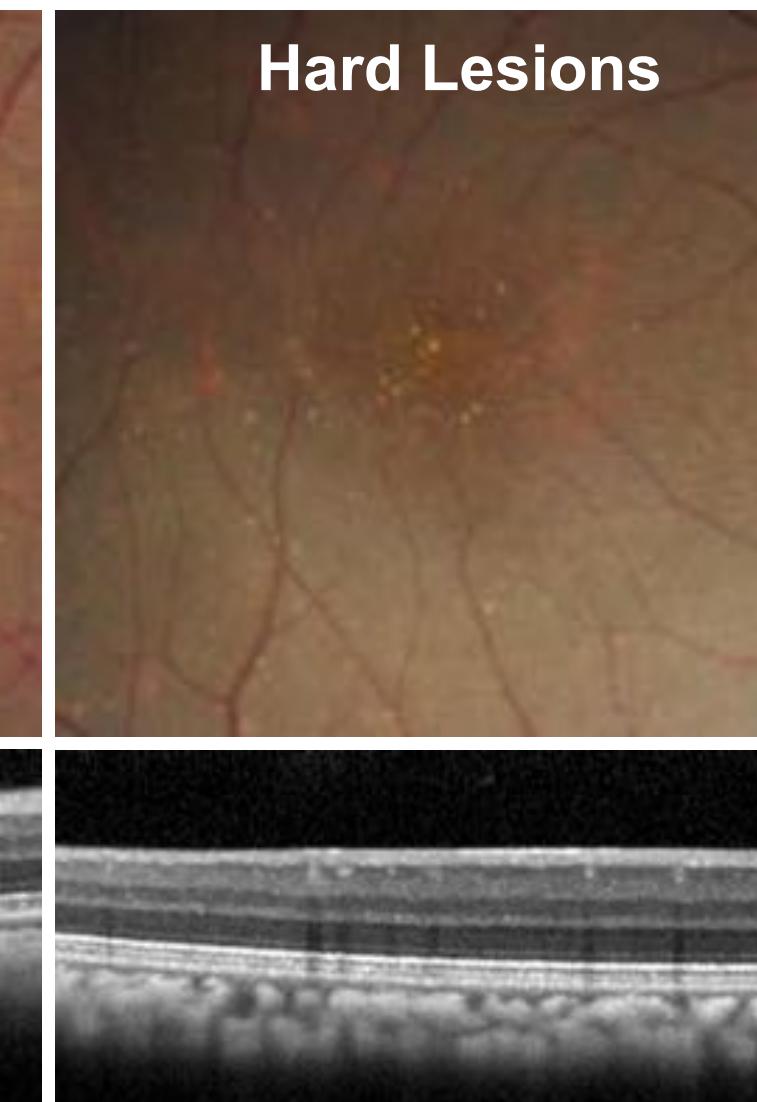
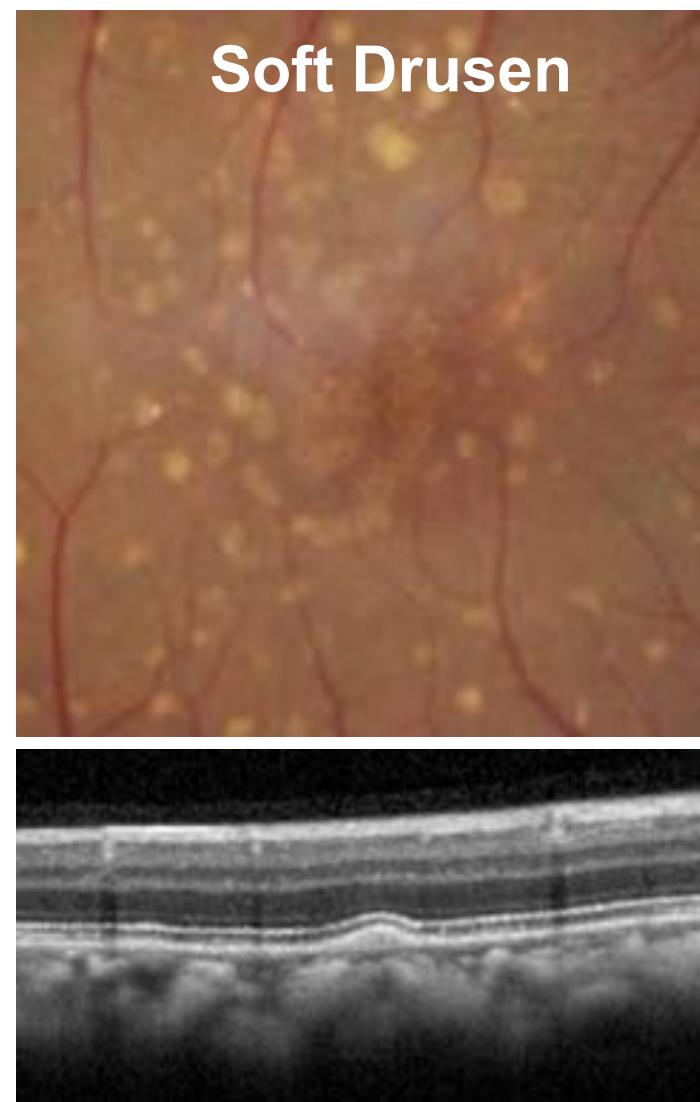
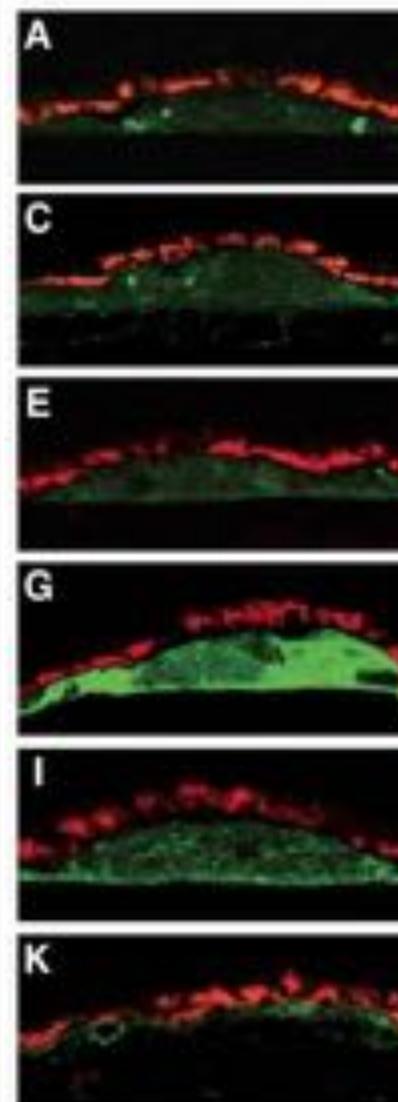
Evolution of soft drusen in primates over 2 years



Remodeling of Drusen in Primates over 2 years



Soft drusen vs. hard lesions in rhesus monkeys



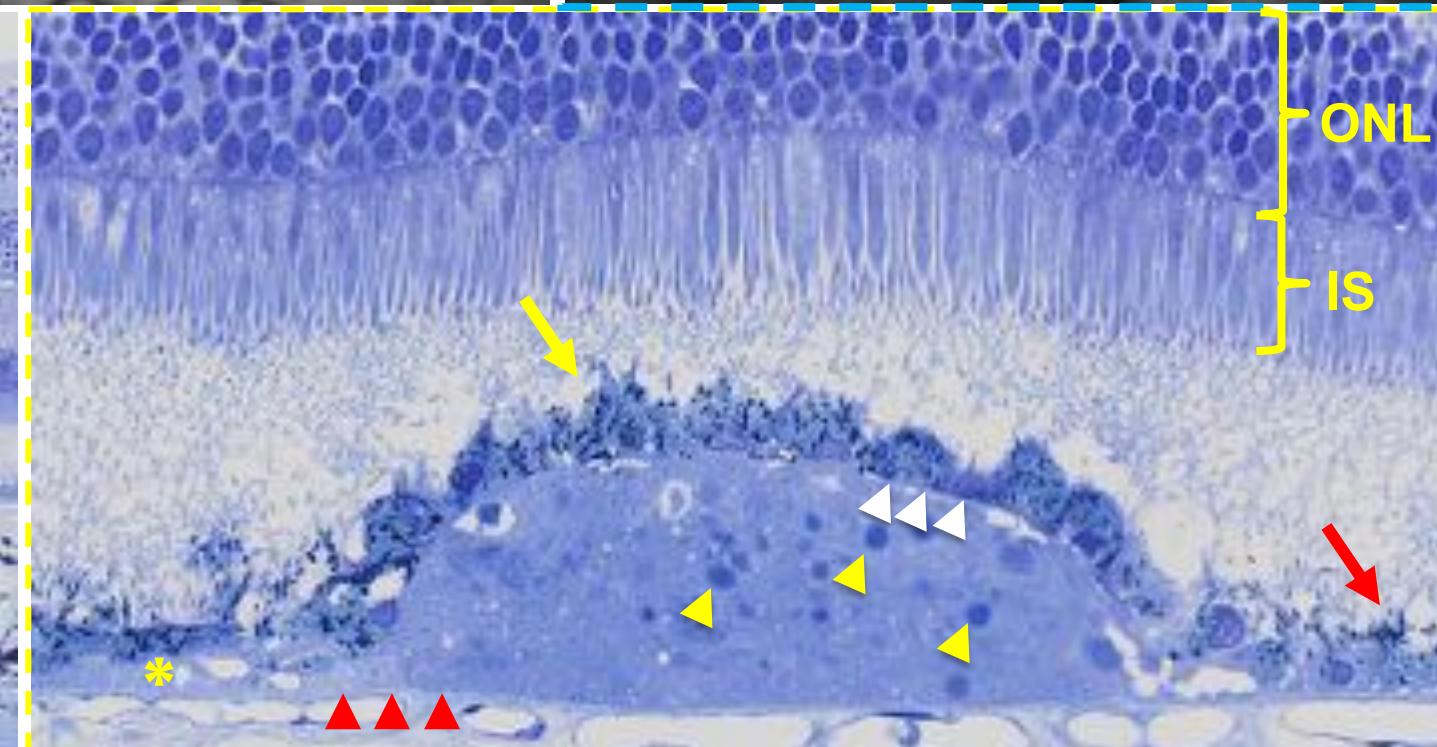
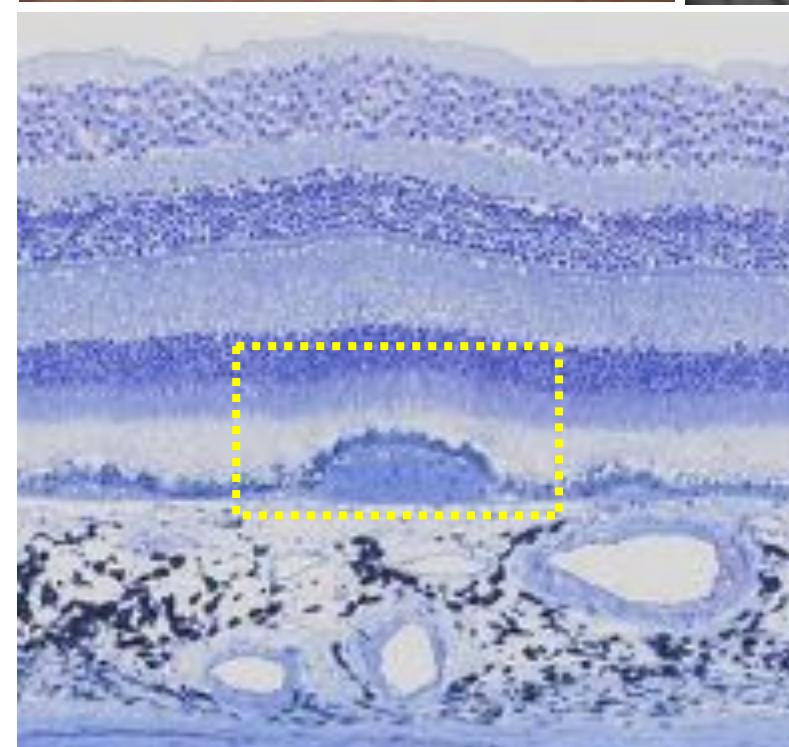
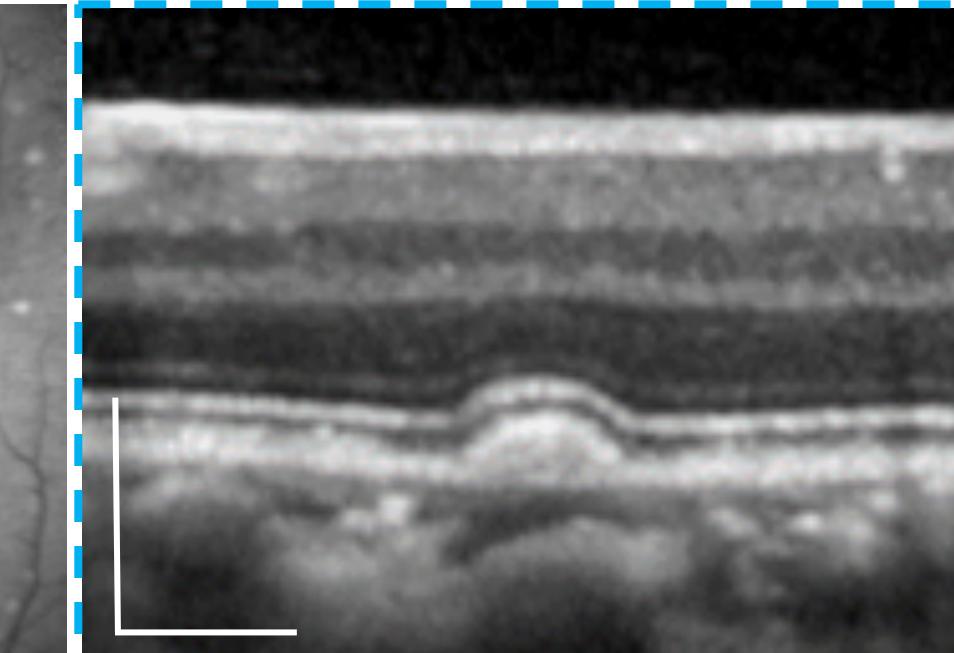
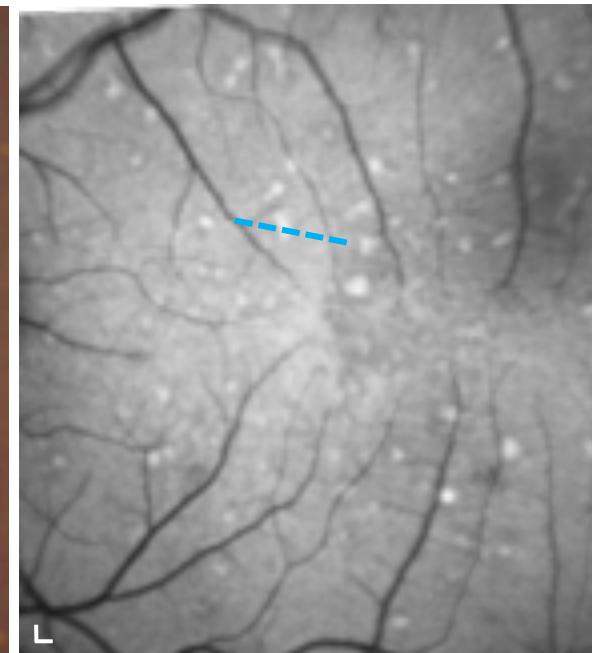
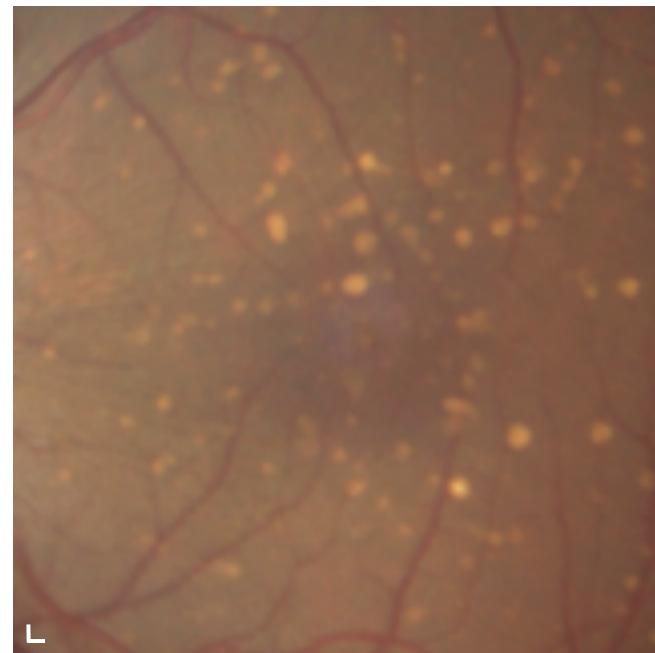
Umeda et al, FASEB J, 2005

Yiu et al, Sci Rep, 2017

Anderson et al., Vet Ophthalmol, 2006

Lipid-filled RPE Cells

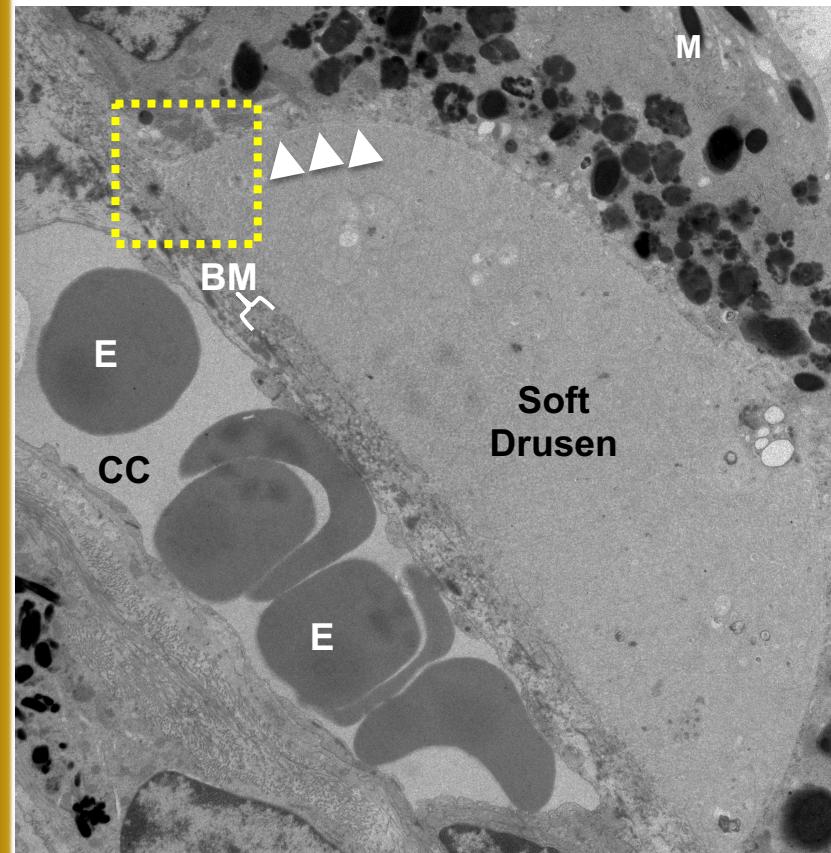
Semi-thin histology of primate soft drusen



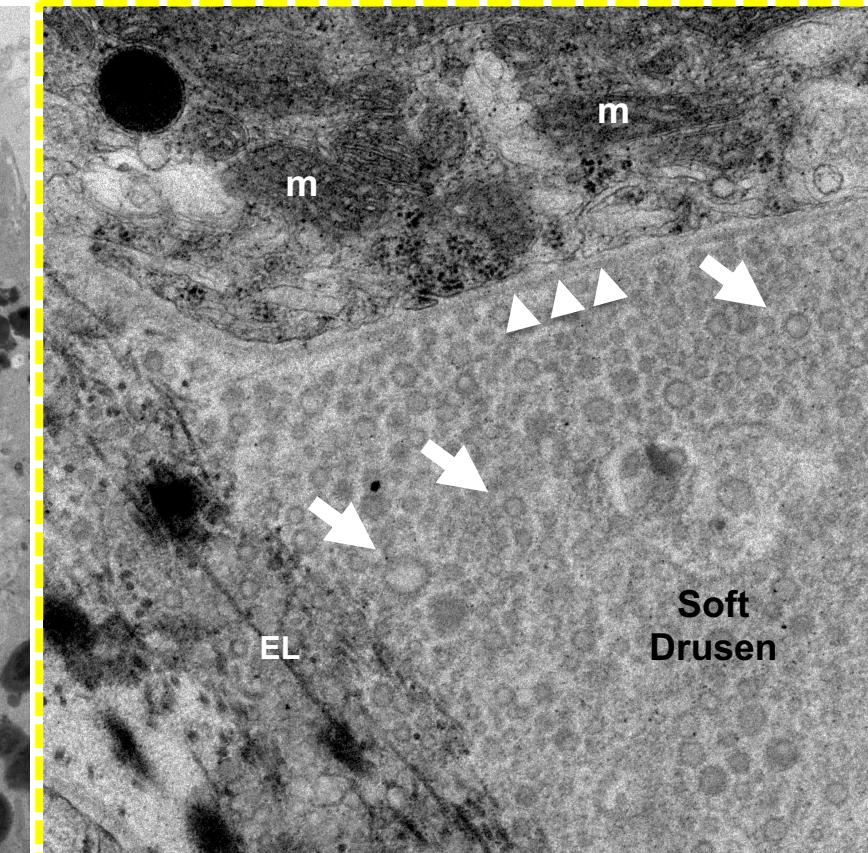
Electron microscopy of primate soft drusen



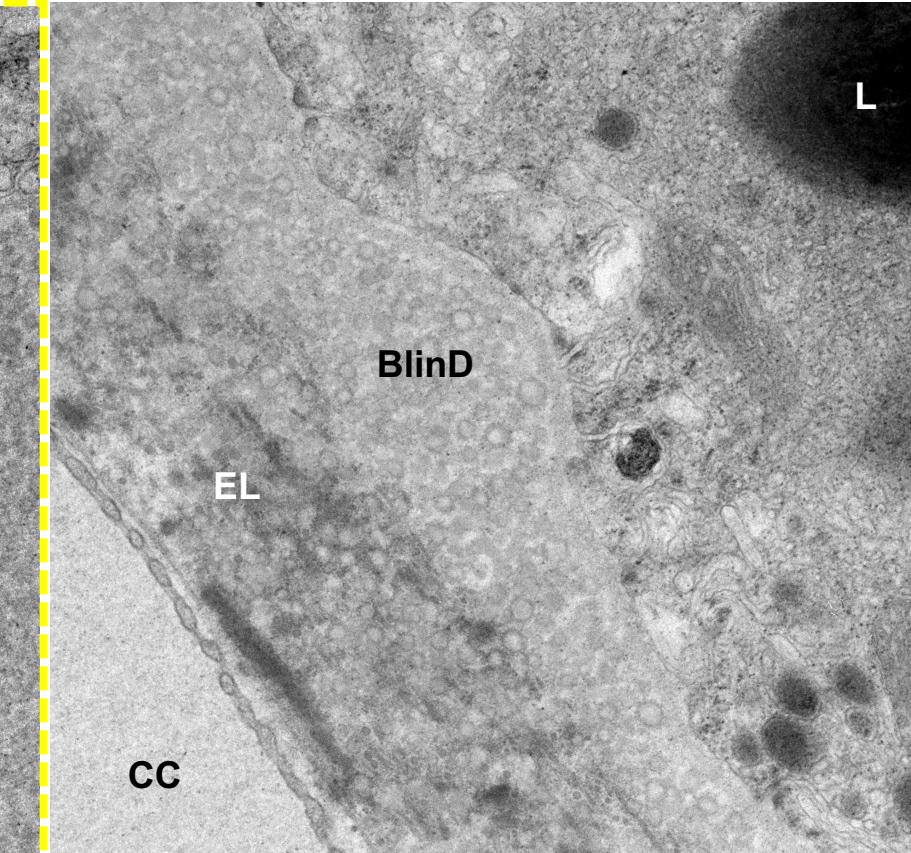
Soft drusen



Lipid particles



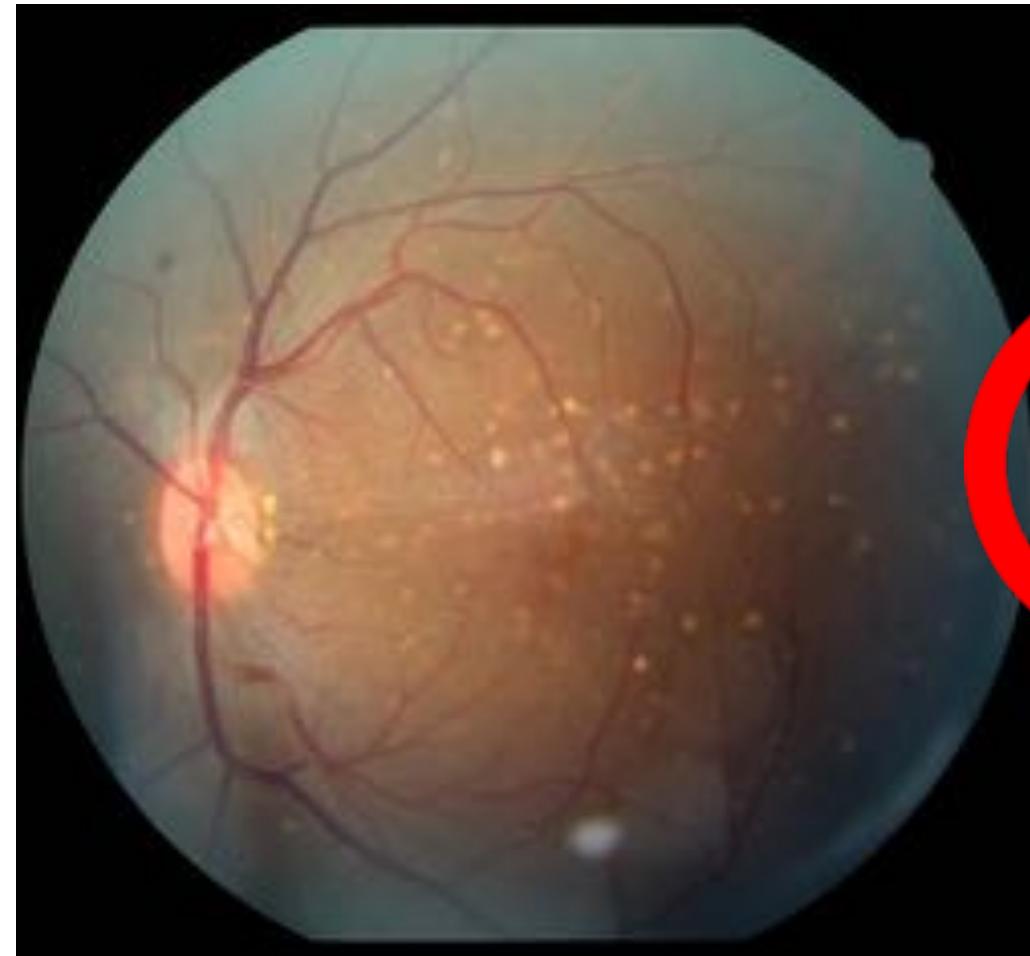
Basal linear deposits



Monkeys do NOT develop CNV or GA



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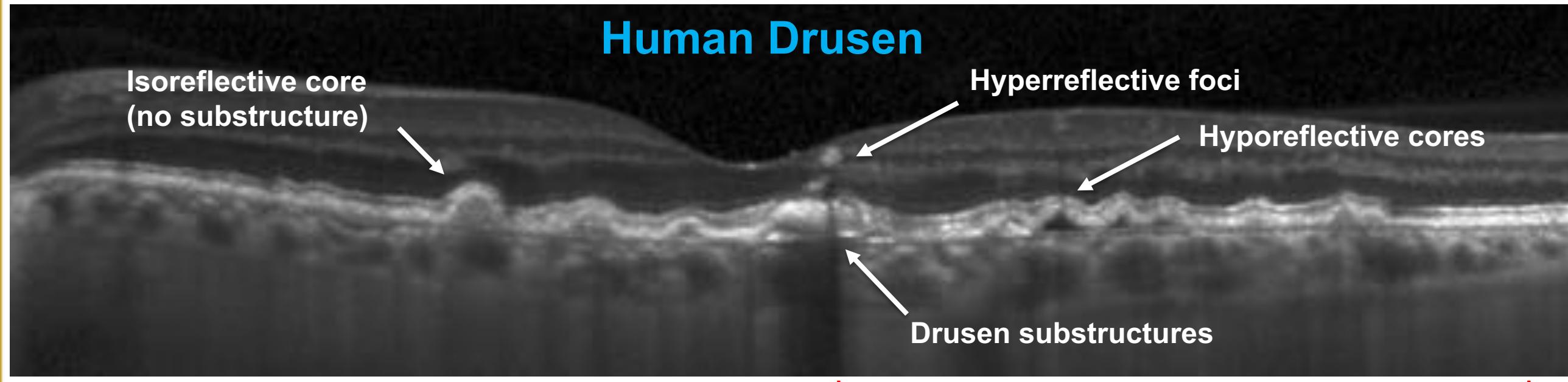
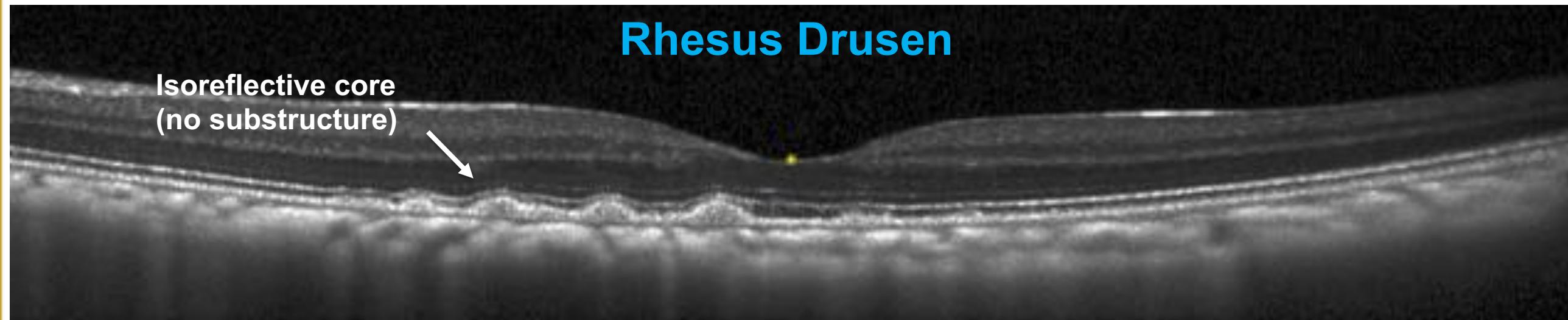


Macaque Drusen



Human Geographic Atrophy

Why do primates not develop advanced AMD?



Insight into human AMD from monkey drusen



Rhesus monkeys

- Life expectancy ~25yrs
- Regular diet / exposures
- Dark uveal pigment
- Simple drusen structure



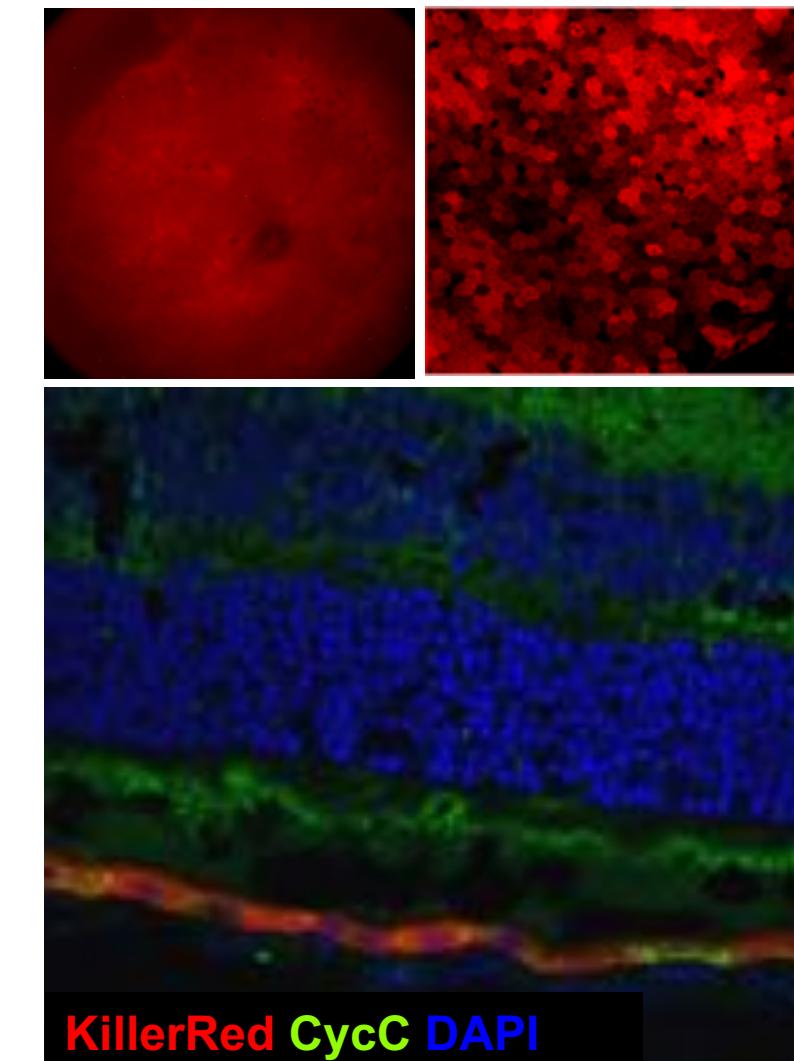
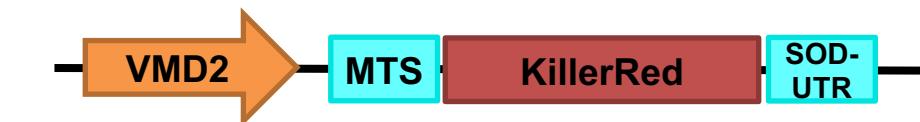
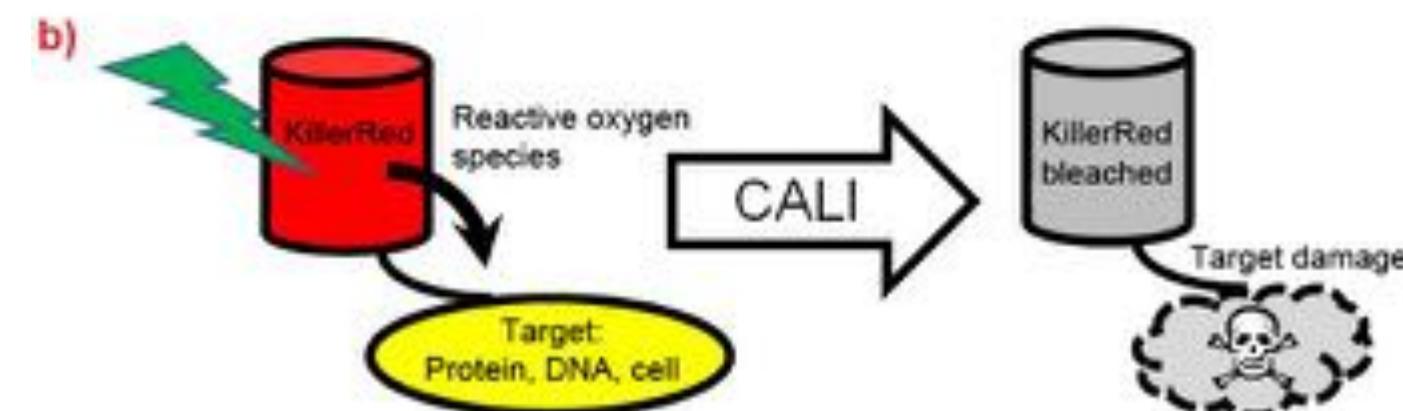
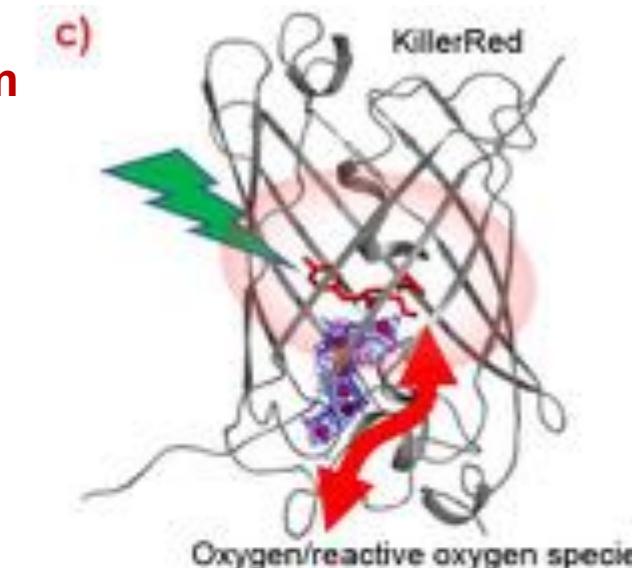
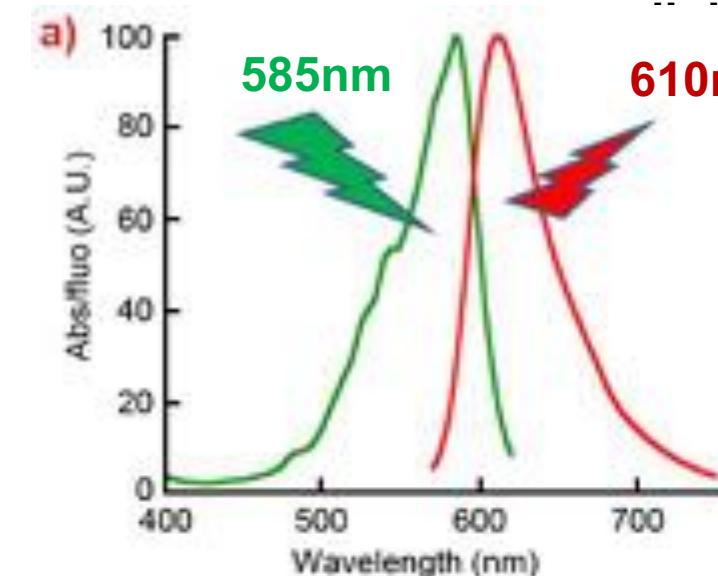
Humans

- Life expectancy ~80yrs
- Poor diet / exposures
- Light uveal pigment
- Complex drusen structure

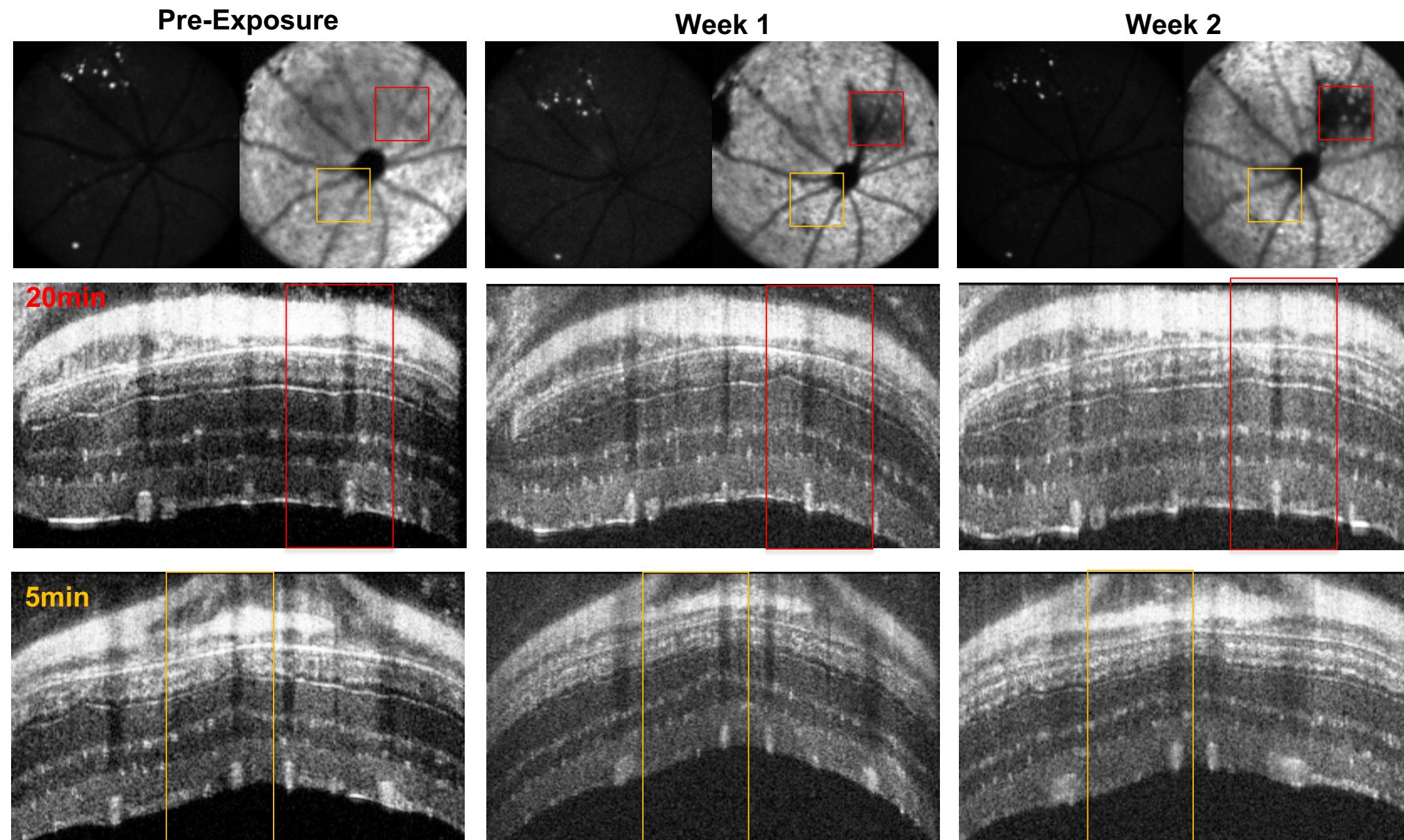
Optogenetic control of oxidative stress as GA model



KillerRed is a genetically-encoded ROS-generating protein that produces superoxide ROS with induction with 585nm



Optogenetic control of oxidative stress as GA model

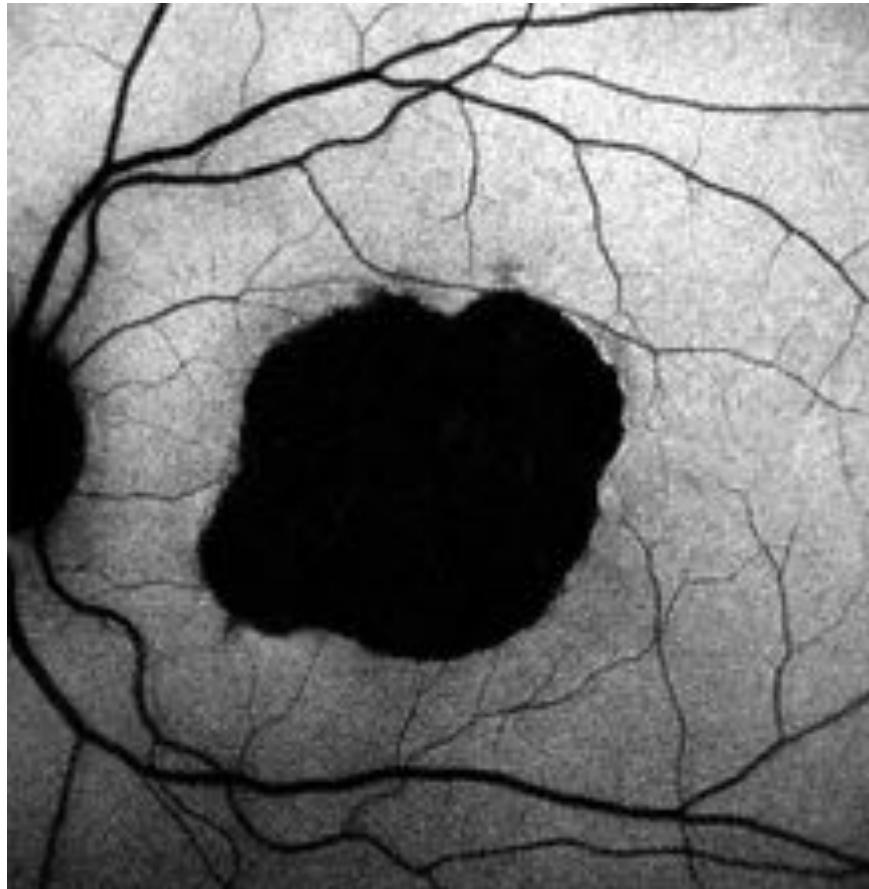


An optogenetic animal model of GA

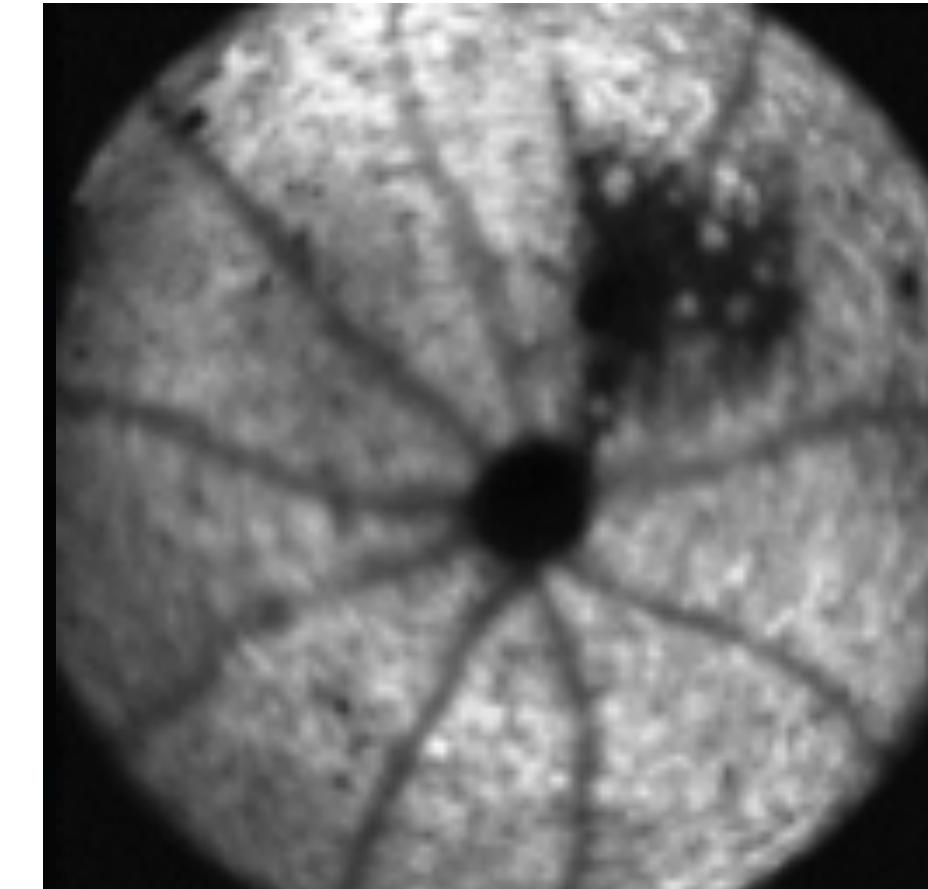


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EYE CENTER

Human

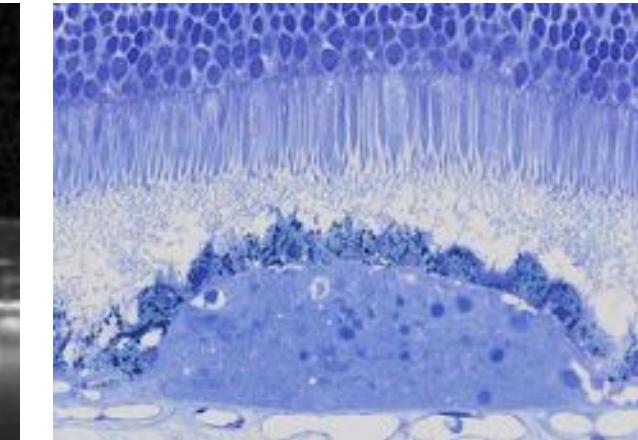
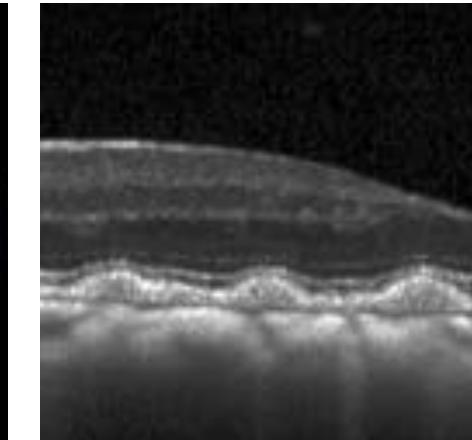
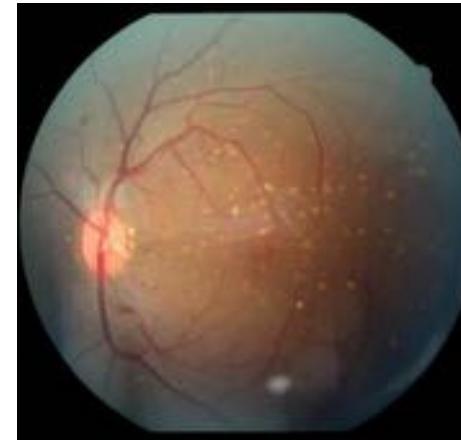


Mouse





Summary



- Primates are the only mammals to possess a macula, and are the premier animal model to study dry AMD
- Rhesus macaques develop soft drusen with age, and share genetic risk alleles with human AMD
- Macaque drusen exhibit dynamic remodeling with time, with imaging/histological features resembling human drusen
- Macaques with drusen do not progress to CNV or GA, but efforts are underway to simulate these features

Thank You



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