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Special thanks to OMICS Organizing Committee for the sponsorship!

New Frontier of Therapeutic Intervention for Retinal Disease.

Tina Guanting Qiu, MD PhD

Ophthalmic Executive Consultant

Greater Boston Area, Massachusetts, USA



The 273rd OMICS International Conference
Eye Disorders and Treatment (Eye-2015)
Double Tree by Hilton Baltimore, USA.
July 13-15, 2015



Financial Disclosure

Ophthalmic Executive Consultant for

- Inotek Pharmaceuticals, MA.
- LambdaVision Inc. CT.
- Gerson Lehman Group.

Previously, Ophthalmology Medical Consultant for

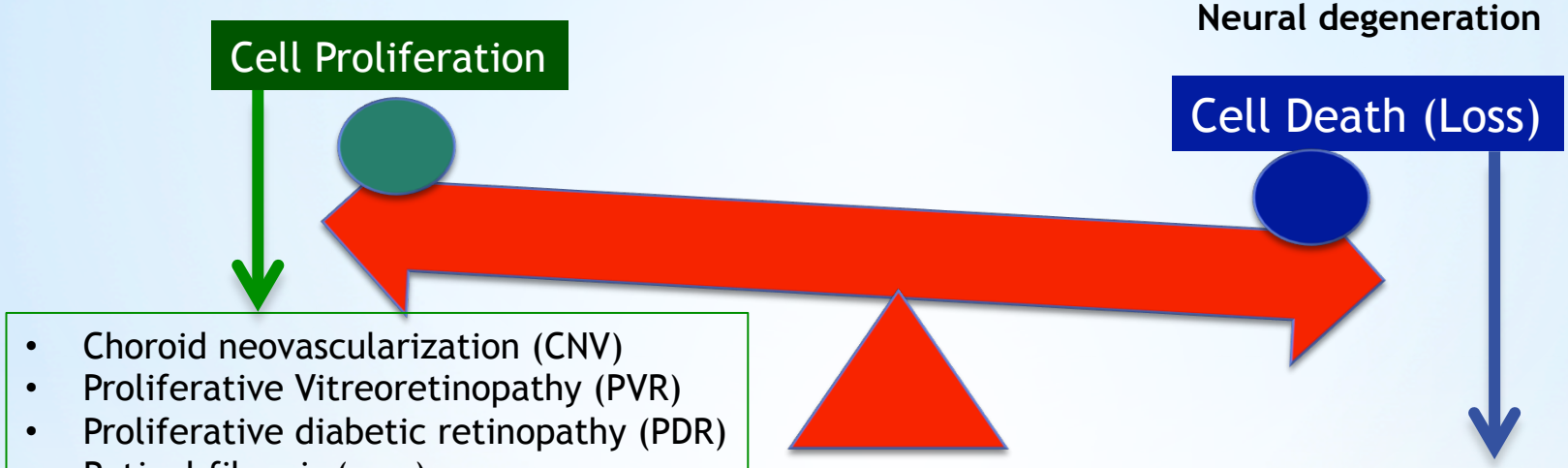
- Sucampo Pharma, D.C.
- Ocata Therapeutics, MA.

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Key Problems in the Retina

NEI audacious goal-2014

Neural degeneration



- Choroid neovascularization (CNV)
- Proliferative Vitreoretinopathy (PVR)
- Proliferative diabetic retinopathy (PDR)
- Retinal fibrosis (scar)
- Inflammation

- Retinal ganglion cell loss
  - Glaucoma
  - Diabetic macular edema (DME)
- Photoreceptor loss
  - Age-related macular degeneration (AMD)
  - Retinitis Pigmentosa (RP)
  - DME

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Paradigm Shift on Focus

- 1. Three most important advancements in AMD.
  - New appreciation of dry AMD clinical sub phenotypes (n=4).
  - Anti-VEGF: switch from “wet” to “dry” phenotype (anti-PDGF, hRPE transplant).
  - Ocular drug delivery innovation & gene/RNA based protein delivery.
- 2. Three most important things in glaucoma.
  - IOP stability & sustained-release ocular drug delivery.
  - Non-IOP dependent factors (preventing RGC loss)- Adenosine A1R .
  - MIGS/Phaco on early stage glaucoma.
- 3. A rising wave of steroids in refractory macular edema.
  - A new recognition of Muller glia “pump”- inner retina.
  - RPE/Bruch’s membrane is the outer layer water “pump”.
  - Para inflammation & anti-oxidative stress (unoprostone).
- 4. Game ends: neuronal cell loss (RGC and photoreceptor).
  - Retinal Prosthesis (Second Sight), LambdaVision and stem cell replacement.

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AMD Clinical Phenotypes & Predominant Pathological Entity

AMD Hallmark



Drusen

1. RPE Atrophy

2. Bruch's Membrane Thickening

Prof. John Marshall (UCL)

Para inflammation
(Aging & Oxidative Stress)

3. Photoreceptor (cones) Loss

4. Choroid Ischemia

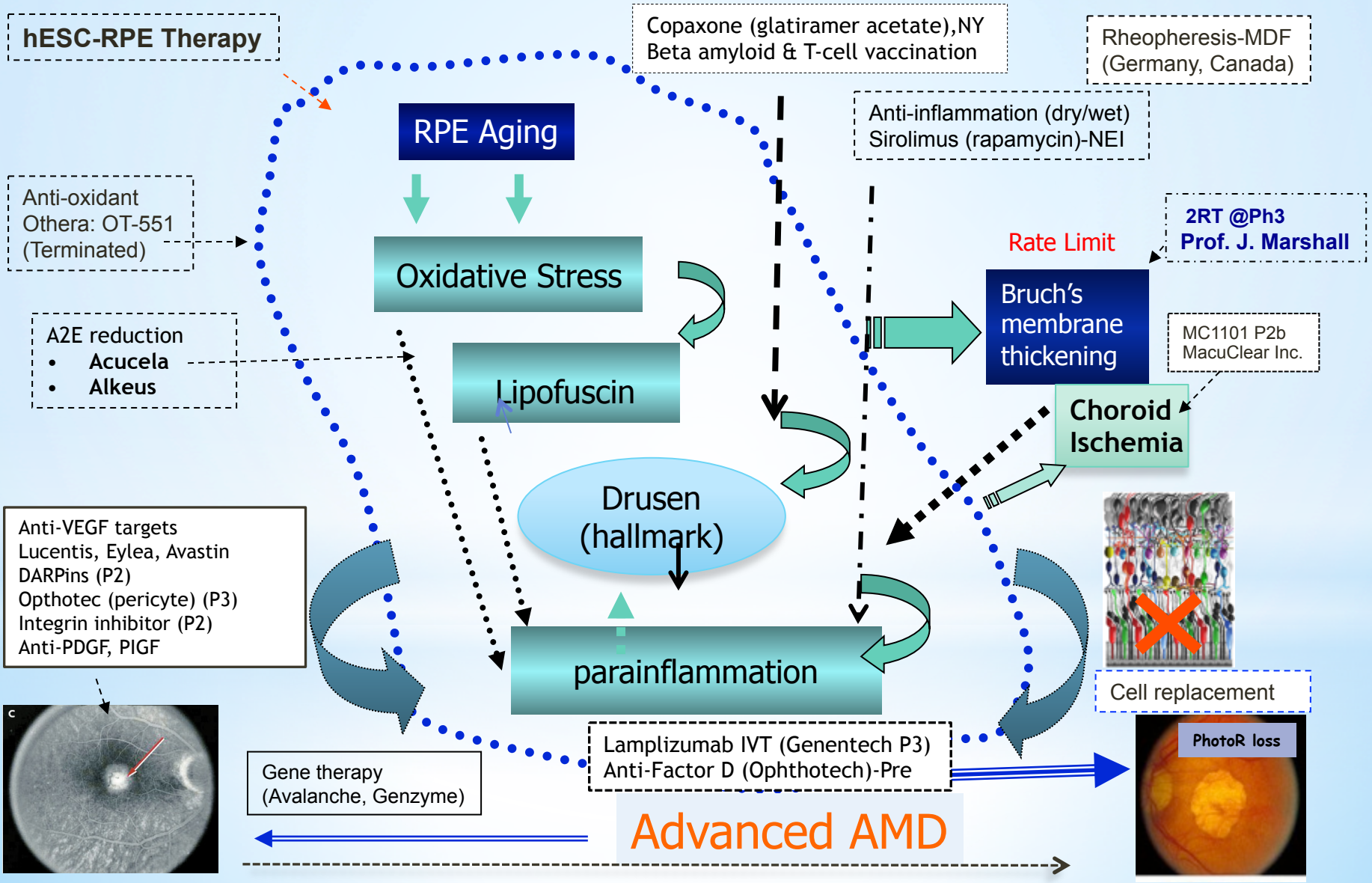
Hidden Devil

Prof. Alan Bird (UCL)

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Targeting on Pathophysiological Root Causes of AMD



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Switch from "Wet" to Dry" Clinical Phenotype

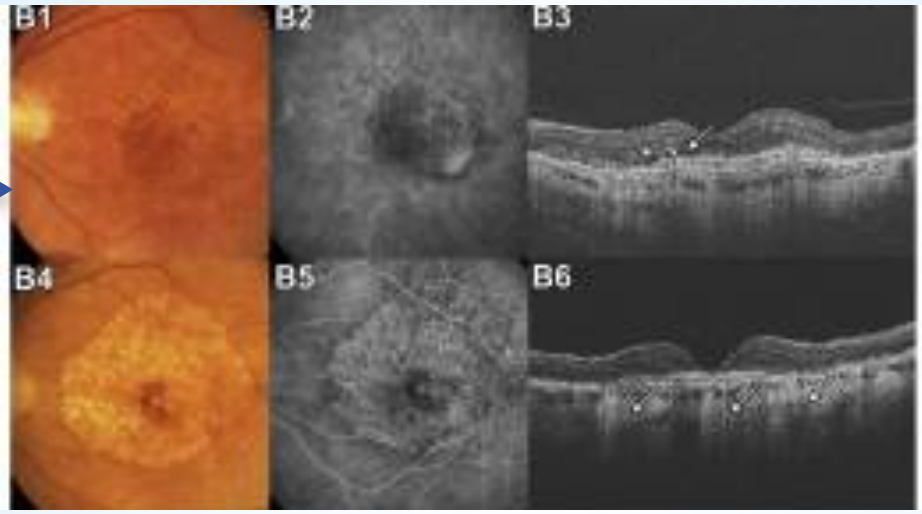
CNV lesion evolved with increased RPE loss and progressive macular atrophy

- CATT Research Group-2014

B1-3: Baseline

Anti-VEGF Therapy

B4-6: 2-year later



Future Solution

hESC-RPE Transplant @ Phase 2b. (Ocata Therapeutics)

Image courtesy by Dr. Grunwald and CATT Research Group

Ref: Juan E. Grunwald et al. 2014 Ophthal,

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Anti-VEGF non-Responders: Subretinal Fibrosis

Sustained vision loss due to fovea scar, increased GA, pigment changes.

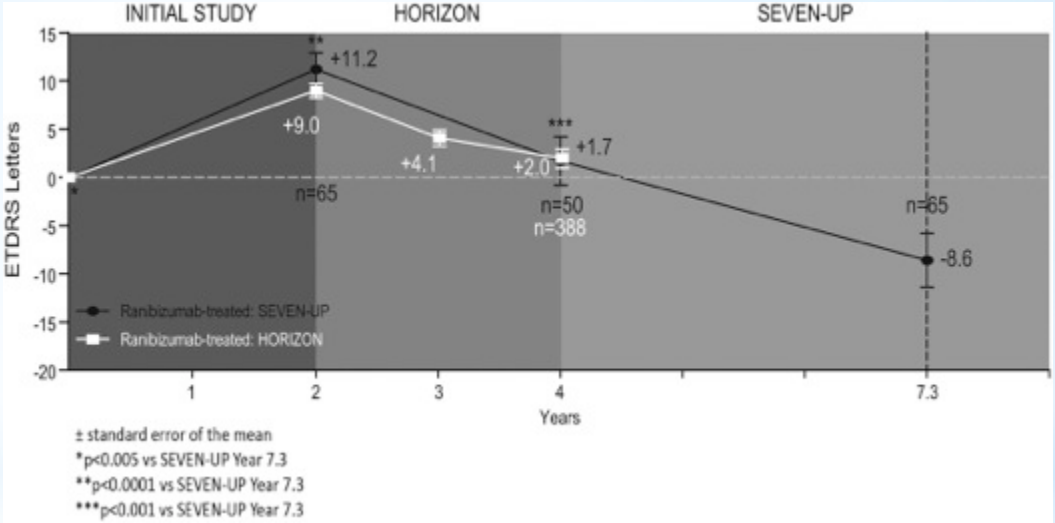
- Macrophage/microglia infiltration
- Muller glia remodeling
- Fibroblast proliferation

Preventive Solution

Anti-PDGF (Fovista) + Lucentis @ Ph3

Ophthotech Pharm

Seven -up study:
1/3: Poor VA outcome.



❖ Seven-Year Outcomes in Ranibizumab-Treated Patients in ANCHOR, MARINA, and HORIZON: A Multicenter Cohort Study (Seven-up Study)-2013.

PDGF: platelet derived growth factor

◆ S. Rofagha et al, Seven-up Study Group

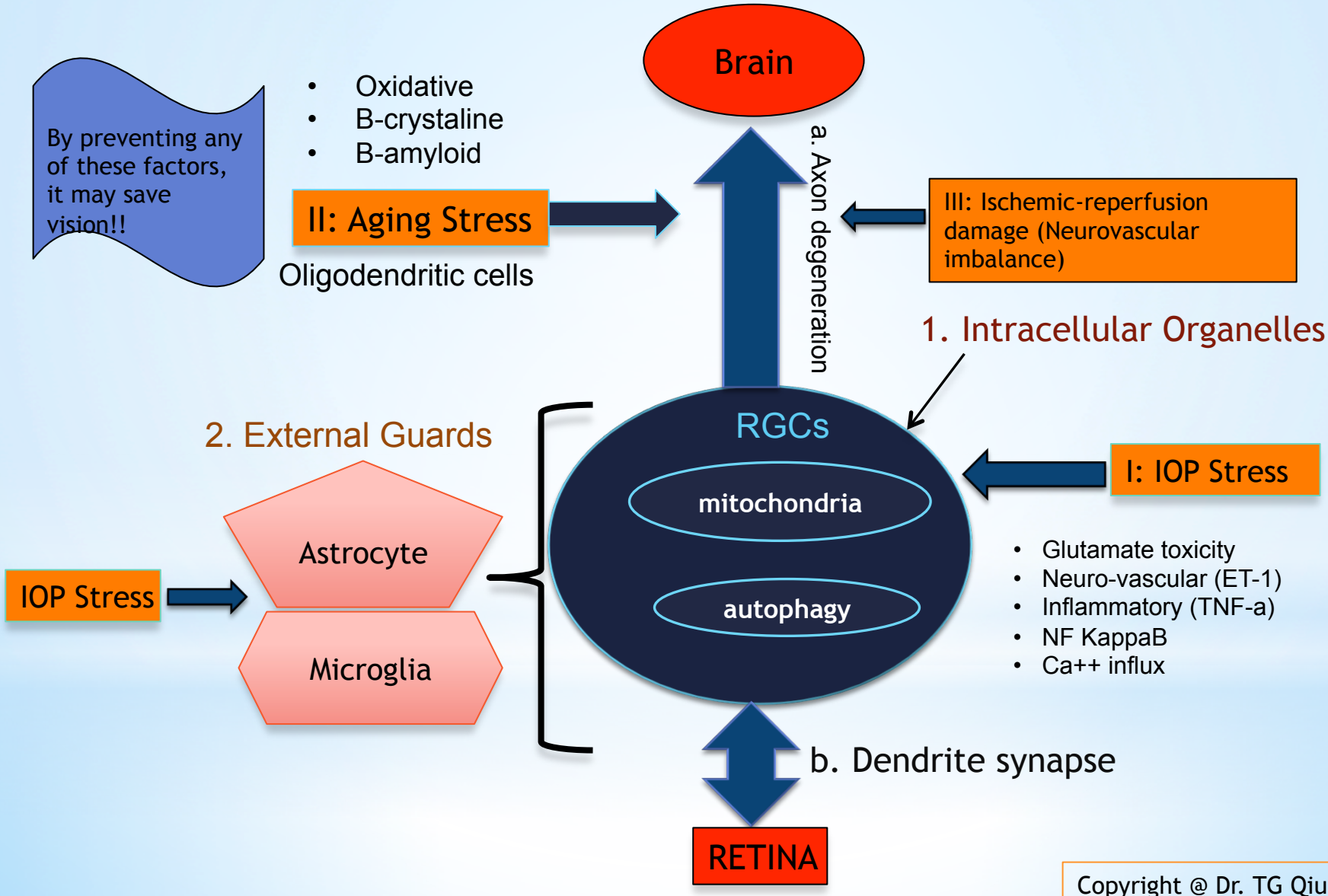
Ophthalmology 2013 120, 2292-2299DOI: (10.1016/j.ophtha.2013.03.046)

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IOP Dependent and IOP Independent Factors

Key Cellular Compartments Involved RGCs/Complex Apoptosis



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New Prospect of Neural Protection in Glaucoma/Retina

Late 20th century is an era of neurotrophin related neural protection via tyrosine signaling (NGF, BDNF, NT3, NT4/5 and CNTF)- not successful so far.

New hope in the 21st century: via proactive or regenerative approach.

- Three new targets: **Trabodenoson vs Unoprostone vs Brimonidine**.
  - MOA: Adenosine (A1R) vs B-K channel activator vs a-adrenergic agonist.

- **Current Status:**
- 1. Trabodenoson (Inotek Pharma) is a new class small molecule adenosine mimetic specific to A1 receptor (A1R), through A1R mediated neurovascular modulation may have broad clinical implications.
  - Trabodenoson is being developed as first-in-class adenosine-based therapy for glaucoma (Phase 3).
  - With evidence of rescuing RGC loss from ischemia-reperfusion damage in preclinical model- a new promising prospect.
- 2. 0.12% Unoprostone has been approved for POAG/OH (since 1994). Currently the same formulation is being repositioned for the treatment of retinitis pigmentosa @Phase 3 in JP (R-Tech Ueno)- promising.
- 3: Brimonidine sustained release implant (IVT) for neural protection in the retina – various Ph2 trials completed by Allergan - not promising.
  - E.g.: trials on dry AMD, RP, glaucomateous optic neuropathy, macular-off retinal detachment.

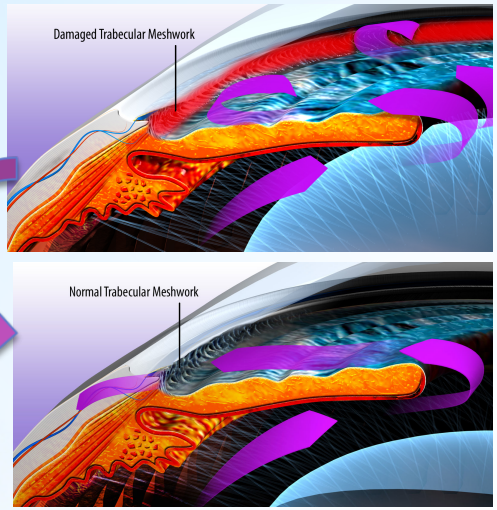
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An Eye on Basement Membrane Rejuvenation

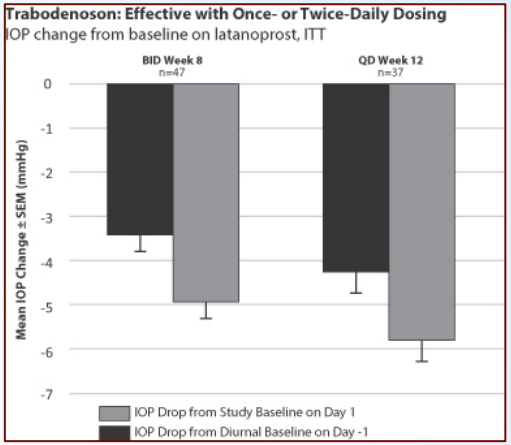
Trabecular Meshwork Rejuvenation

I: Adenosine (A1R) on TM rejuvenation via MMP activation to increase TM outflow facility (ref. 3,4).

MMP: Matrix Metalloproteinase



Trabodenoson in POAG/OH (Switch from BID to QD @3mo).



INOTEK Pharma

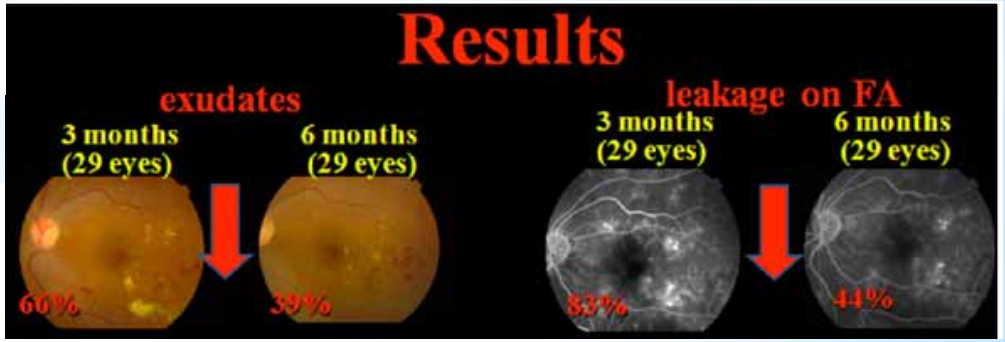
- Long-term TM Health Benefit

Data Source: Ph2 Trials, Inotek IPO, Feb. 2015.

II: "Ellex" 2RT nanopulse laser on Bruch's membrane rejuvenation via MMP activation (ref. 1,2).

2RT: Retinal Rejuvenation Therapy.

2. The First 2RT-DME London Trial (Kings College London).



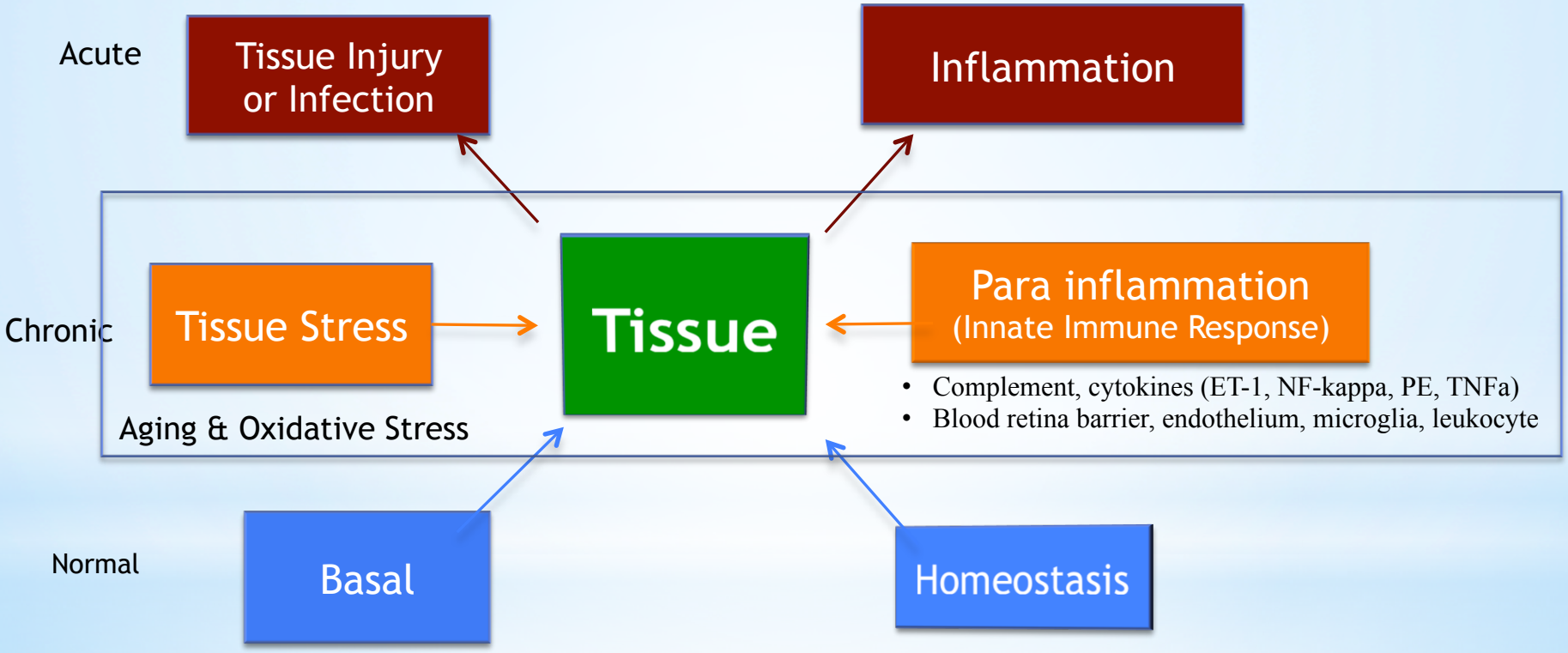
(A. Hamilton, L Pelosini, J Marshall*, AAO, 2008).

1.J Marshall, The 2014 Bowman Lecture—Bowman's and Bruch's: a tale of two membranes during the laser revolution. Eye (2015).
2. L. Pelosini, R. Hamilton, A Hamilton, J. Marshall, et al. Retina. 2013.
3. Crosson CE et al. Mechanisms linking adenosine A1 receptors and extracellular signal-regulated kinase 1/2 activation in human trabecular meshwork cells. J Pharmacol Exp Ther. 2007.
4. Crosson CE et al: Ocular effects associated with the chronic adminstration of A1 agonist, cyclohexyladenosine. Curr Eye Res. 2000.

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Para-inflammation: Neglected

- The role of para inflammation in AMD, glaucoma and diabetic macular edema.



Ref: H Xu et al. Prog. in Retinal and Eye Res. 2009.

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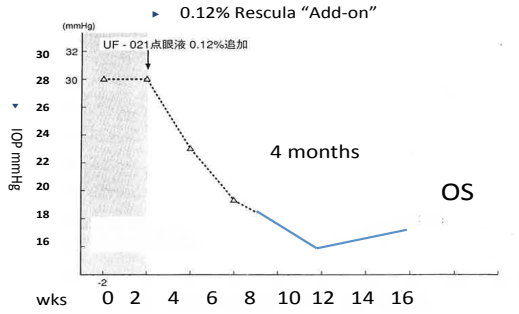
Rescula on Refractory Glaucoma via Para inflammation Pathway

Rescula, BK channel activator, restores tissue hemostasis and targets on anti-inflammatory pathway.

N=138 patients in this report (Azuma I., J. Jpn Ophthal Soc. 1993).

Case Example: Rescula on Refractory POAG and OHT (JP)

Patient 1: POAG 66 yrs, Male (OS)

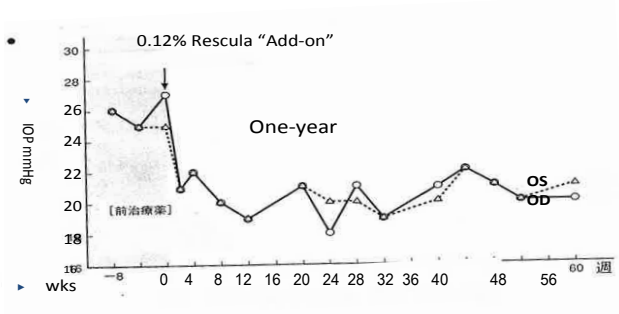


IOP Changes in Patient with POAG (66 Yrs, male)

Before:
0.5% Timolol
2% Dorzolamide

After:
0.5% Timolol
2% Dorzolamide
0.12% Rescula

Patient 2: OHT 58 yrs, Male (OU)



IOP Changes in Patient with OHT (58 yrs, male)

Before:
0.5% Timolol
1% Brimonidine

After:
0.5% Timolol
1% brimonidine
0.12% Rescula

Ref: Azuma I, J. Jpn Ophthalmol Soc 97:232-238, 1993

Dr. TG Qiu: Mechanism of IOP lowering in these patients may be through modulating para inflammatory pathological process within the TM (e.g. ET-1, NF-KappaB, TNFa).

Sucampo Pharma & R-Tech Ueno (JP)

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Steroids: Good and Bad.

- Good: we still need steroids!
  - Steroid & retina edema.
  - Steroid & Muller glia (inner pump).
  - Steroid & blood retina barrier (outer pump): via ILs
  - Iluvien vs Ozudex, vs Triam intravitreal (off label).
- Bad: high incidence of AEs (adverse events).
  - IOP elevation and cataract
  - Disease “re-bounce”
- Solutions:
  - Superochoroidal delivery to minimize the side effects.
  - Pathway based anti-inflammatory targets.
  - Address “parainflammation” early.

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Steroids Alleviate Persistent Intraretinal Cysts via Müller Glia "Pump"

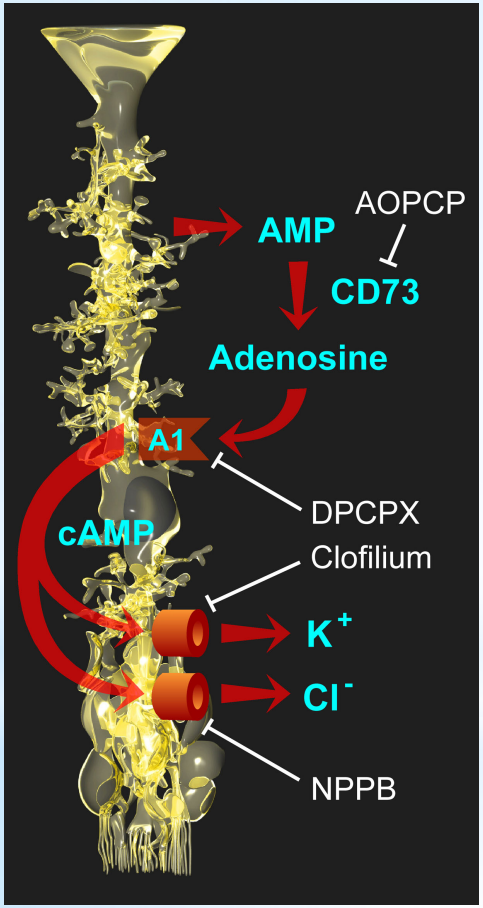
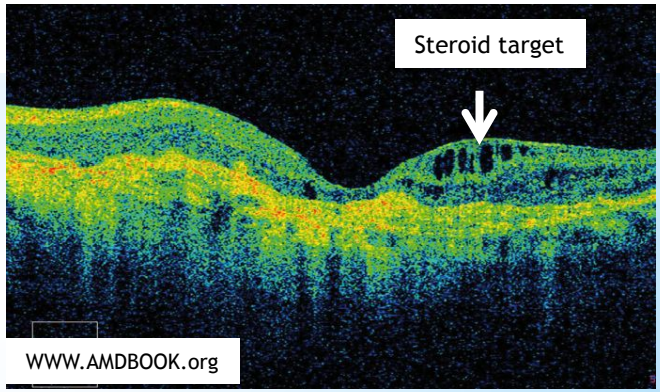


Image courtesy @ Ref: A Wurm et al, Mol. Vis 2009.

- Regulation of the **Müller glia** volume has great importance for the homeostasis of the extracellular space volume under conditions of intense neural activity.
- **Triamcinolone:** inner retinal edema via A1R mediated adenosine effect (K-ATP hydro-conductance).
- **Müller** glia ensheathed with retinal arterioles. Its end-feet has high potassium conductance (ref: TG. Qiu, Ocriplasmin & Muller Glia. AOVS, 2014).



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Ocular Drug Delivery: Huge Unmet Medical Needs

Glaucomatous Neuropathy



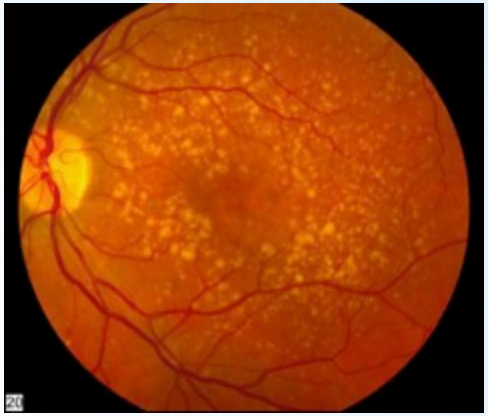
Targets

Neural Protection

Inflammation

Angiogenesis

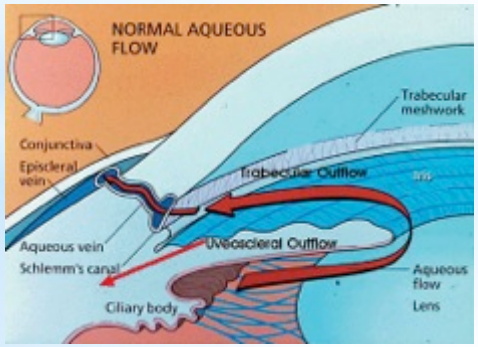
Dry AMD ("Drusen")



Wet AMD (CNV)



Intraocular Hypertension



IOP control: tips

Iluvien 0.19mg (2 drops)=3 years

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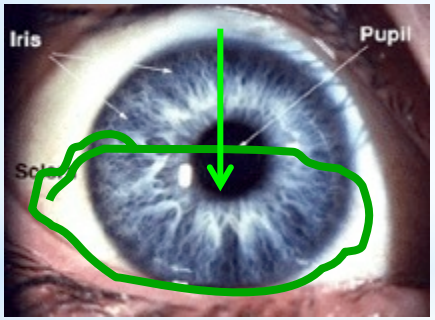
Does Eye Drop Work for AMD?

Reasons to believe…..

- Sclera is much more permeable than what we thought before.
- However…..

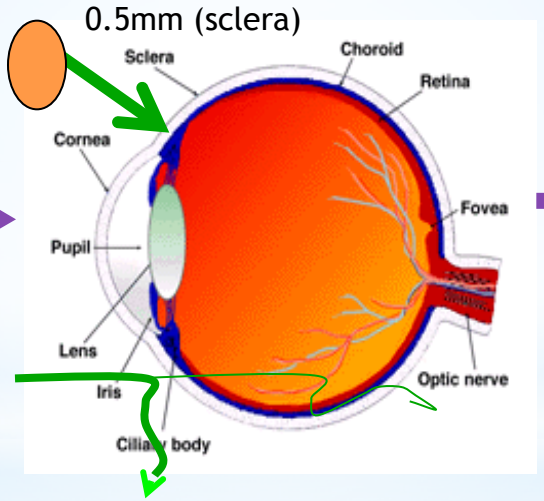
Cul-de-sac delivery

drop

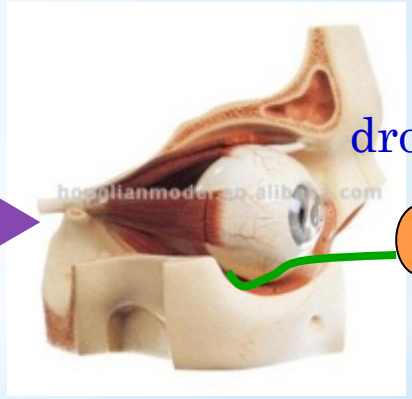


1. Cornea penetration

>80% immediate loss



2. Limbal vascular absorption



3. Posterior sclera diffusion

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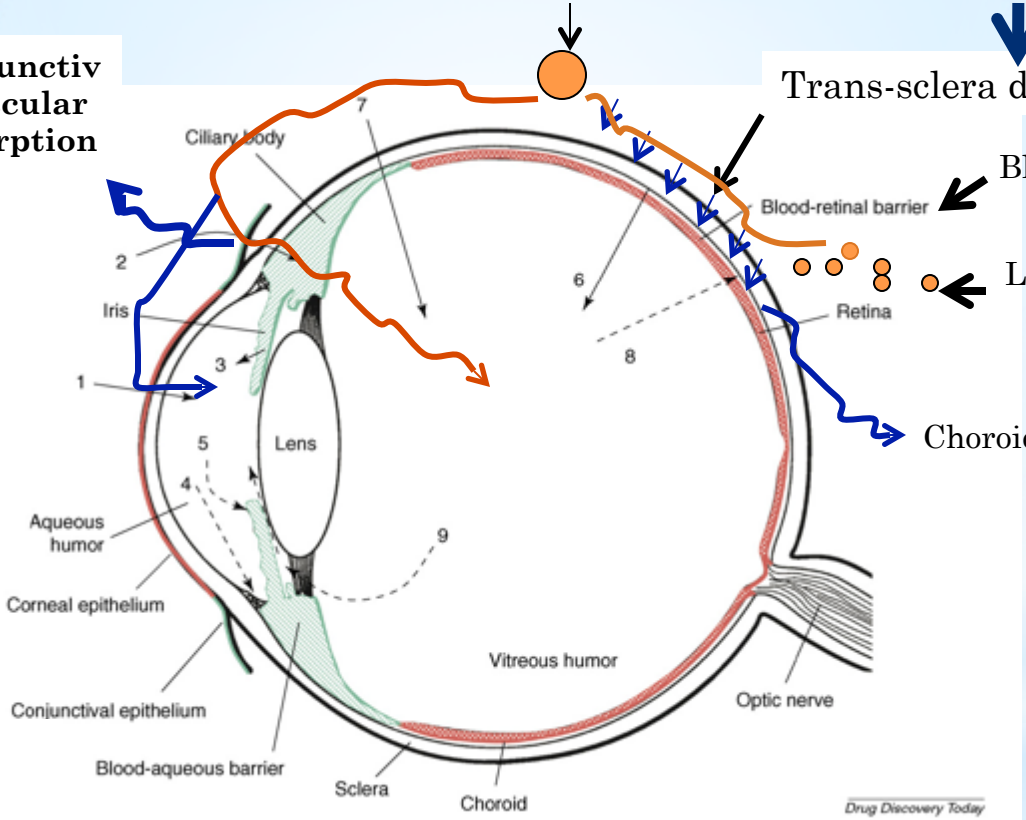
Trans-sclera Drug Delivery

Advantages

Periocular Delivery

Challenges

Conjunctiva vascular absorption



Trans-sclera diffusion

Blood retinal barrier

Lymphatic drainage

Choroid vascular drainage

Dr. TG Qiu Insight

- Ocular reservoirs
- **Melanin binding**
- **Retrabulbar fatty tissue**

For half of the commercial drugs, the dose label in Japanese market is lower than that in the US and EU markets (NIH, 2010).

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Superochoroidal Drug Delivery (New)

- ** I. Unique advantage to RPE gene delivery (LCA).
- II. Extend a new life to "steroids" (triamcinolone).
  - Eliminate steroid induced cataract and IOP elevation.

Microneedle for Drug Delivery
(Clearside Bio. @ Ph 2)

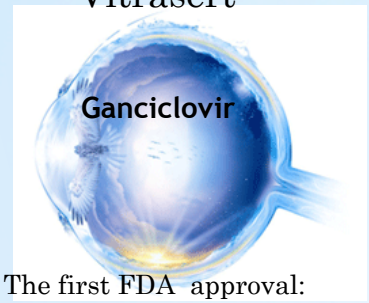


** Dr. TG Qiu Insight

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Sustained Release Ocular Drug Delivery Technologies

Vitrasert



The first FDA approval:
pSivida/B&L, 2005

Bausch & Lomb
Retisert
(fluocinolone acetonide intravitreal implant) 0.59 mg

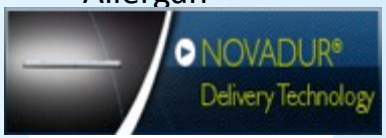
FDA-approval intravitreal implant (2009)

Iluvien (fluorcinolone)



pSivida/Alimira
(DME Approved)

Allergan



* Azurdex (DEX-ITV-2009)-RVO/ Uveitis.
* Brimonidine IVT

Punctal Plug Delivery -Prostaglandin (L-PPDS, QLT, Ocular Therapeutics)



Iontophoresis-Eyegate



Neurotech-ECT

SiRNA IVT (Quark)
AntiVEGF (sflt-01) IVT (Genzyme)
sflt-01 SubR (Avalanche)

Lucentis slow release (P1)-DME

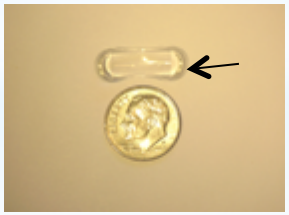
Future Opportunities: Nanotechnology (biodegradable)



Forsight Vision 5.
(Anterior Segment)

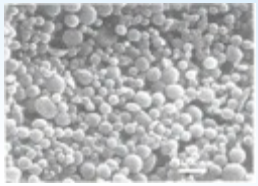
Mucus Penetration Platform (MPP)

Kala Pharma, MA



Contact lens alike insert
Amorphex LLC, MA

Nano-medicine
(Rod/disc/spheres)



10 nm ~1000 nm

Ocular Gene Delivery

Avalanche
Genzyme
Oxford Biomedica

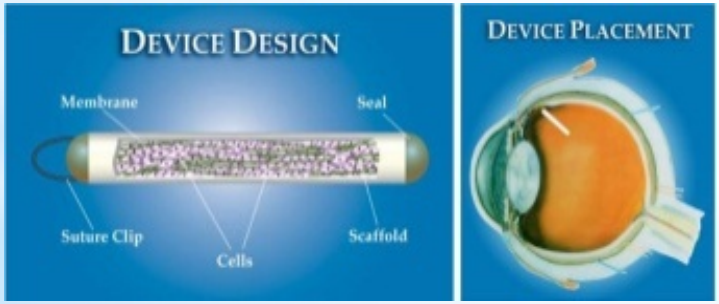
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Sustained Protein Delivery & Biotherapeutics

- Genetic Engineering

sflt-01 wet AMD @Ph2
- **Avalanche Bio (SubR)-promising**
- Genzyme (IVT)

- Subretina
- IVT



Encapsulated cell technology (Ph2)

Neurotech

- RNA based Therapy

VEGF SiRNA for DME (Ph2)
Quark Therapeutics

CTGF RNAi for Retina Scarring
(connective tissue growth factor)
RXi Pharmaceuticals

Exploratory Research

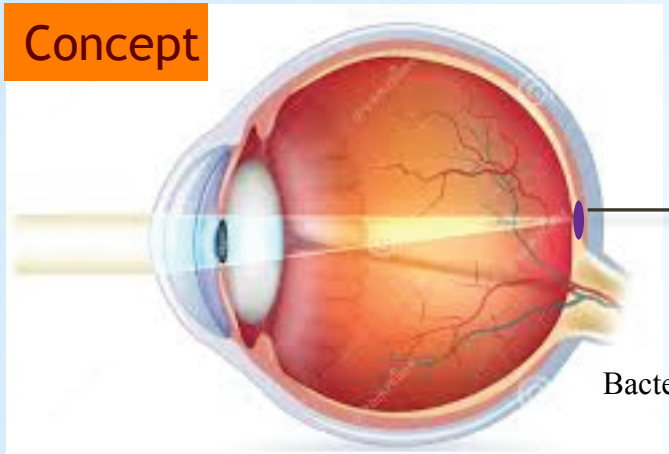
- Edidas (DNA editing)
- Moderna (mRNA based therapy)

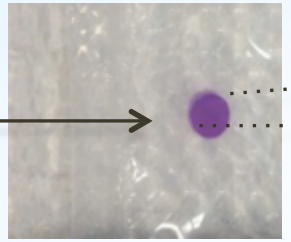
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Latest in Nanobiotechnology Innovation (Eye).

LambdaVision –Artificial Retina Implant

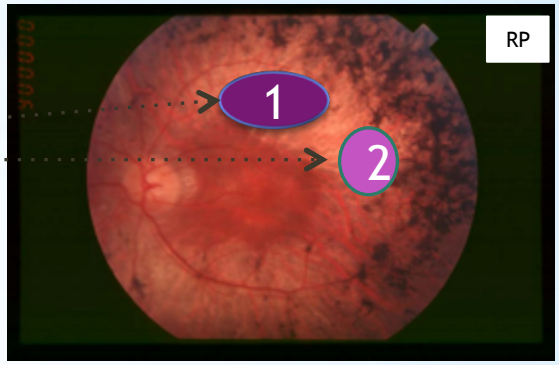
Concept





Bacteriorhodopsin (BR) Implant

Diagram of BR Subretinal Implant

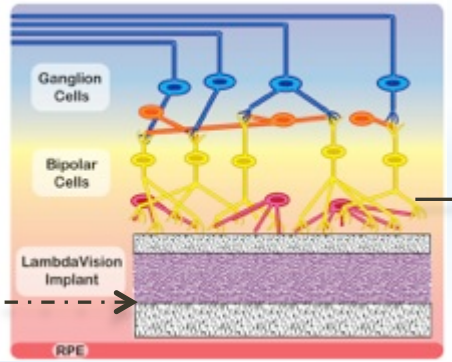


Status

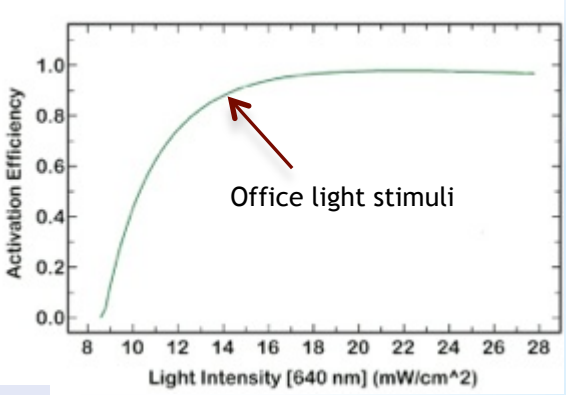
A Thin BR "Sheet" under Sensory Retina

Neural Sensory Retina

Multilayer BR Fabrication



Single RGC recording from P23H rat flat mount.



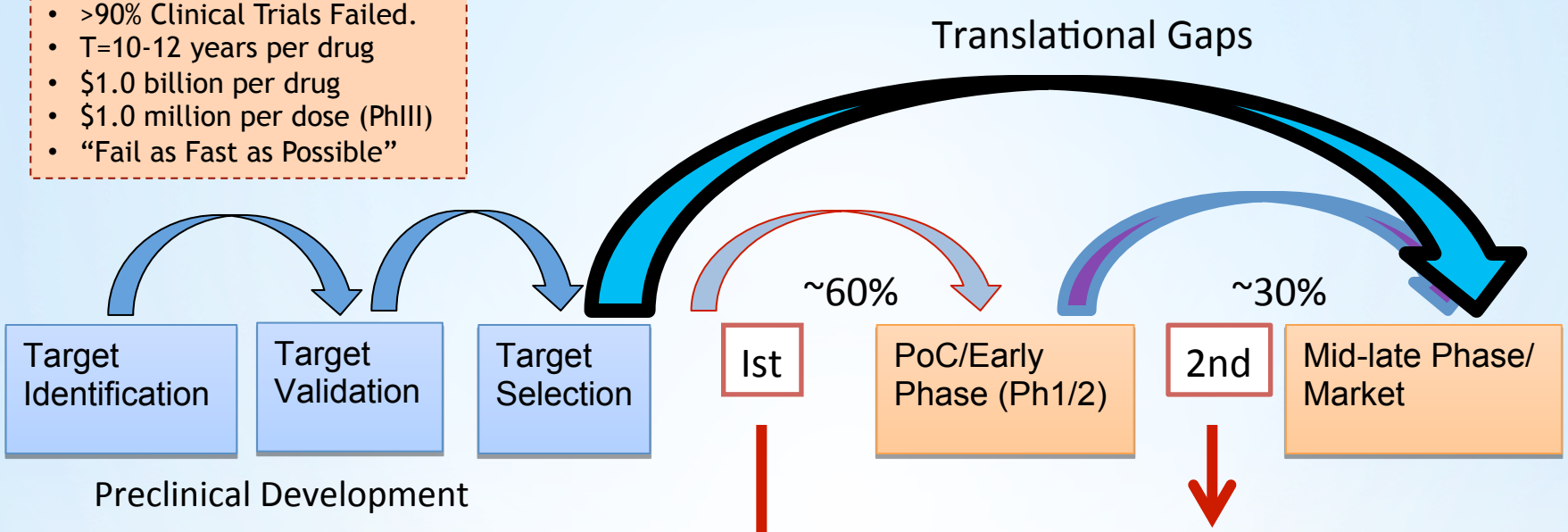
BR: bateriorhodopsin

- BR image data provided by the courtesy of Dr. Nicole Wagner.

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Bridge Gaps for Translational Efficiency

Facts:
- >90% Clinical Trials Failed.
- T=10-12 years per drug
- $1.0 billion per drug
- $1.0 million per dose (PhIII)
- "Fail as Fast as Possible"



The 1st Gap

- Disease root causes are unclear.
- Limitations of animal model.
- Ocular delivery is at its infancy
- Need better surrogate biomarkers for "Go/No Go" decision making.

The 2nd Gap

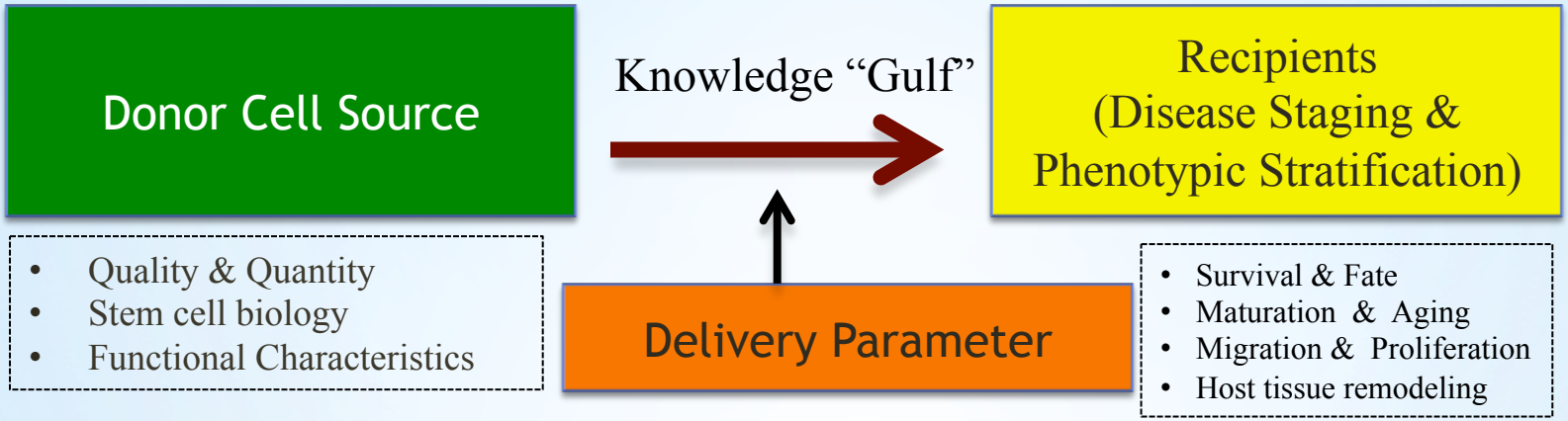
* Precision match failed
* Efficacy failure: Small sensitive to large complex clinical phenotype
* Safety challenges: elderly people, everything has nearly "worn out".
* Ocular pharmacotherapy is at its infancy.

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Knowledge "Gulf": Stem Cell & Regenerative Medicine

A Steep Learning Curve on Clinical Regulatory & Reimbursement Landscape.



"Retina" Innovation Horizons

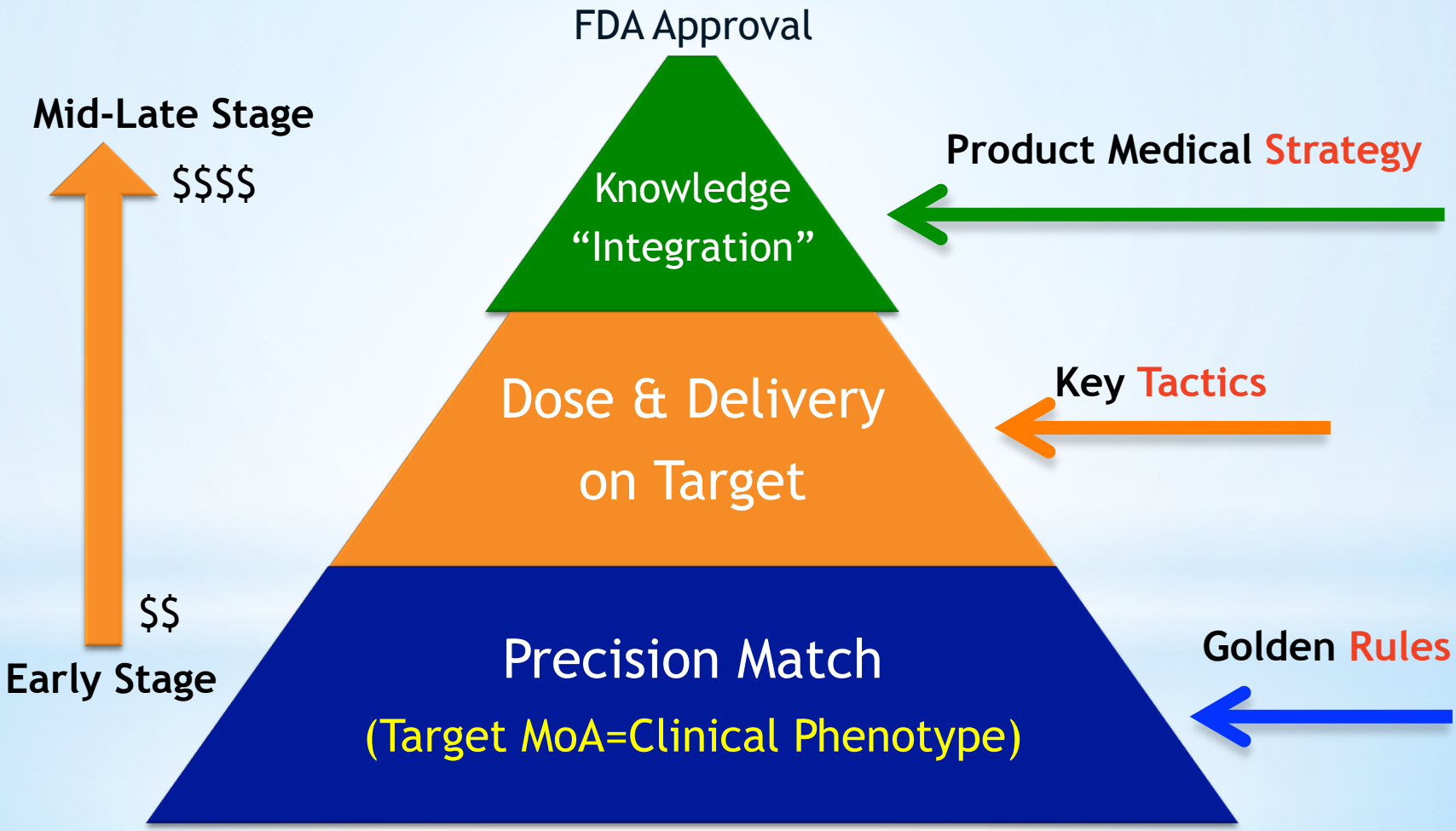
hESC-RPE Therapy@ Ph2b (AMD, SMD, MMD) (OCATA Therapeutics)	CNS Neural Progenitor@ Ph2b (AMD) (Stem Cell Inc.)	Blood Born Stem Cells The Biggest Market Segment

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Dr. QIU Insight

Therapeutic Product Development

Unlocking the mystery of a black box. *"Does It Work, Is It Safe?"*



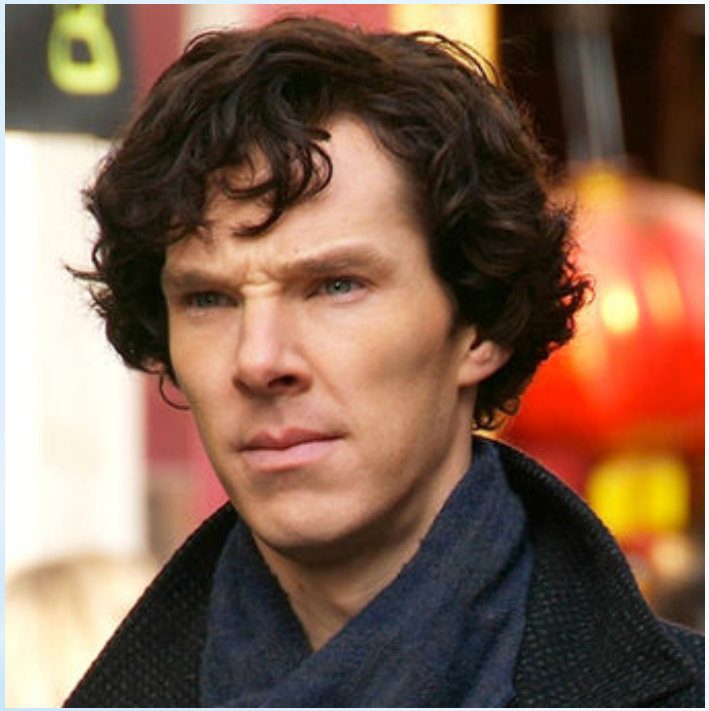
"Creativity is Connecting Things" by Steve Jobs.

Golden Rule, Tactic & Strategy by Dr. TG Qiu, 2015.

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Medicine Development Needs Super "Stars"!!!

Sherlock Holmes

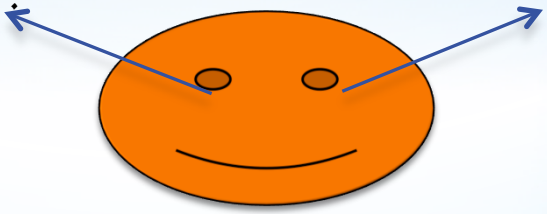


"I can't wait for a big murder!"

James Bond



"He is The Best"



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THANK YOU!

The End

Dr. Tina Guanting Qiu
Ophthalmic Executive Consultant
Greater Boston Area, USA
Expert @ YourEncore Inc.
Council Member @ Gerson Lehman Group
Principal Advisor@ Directional Healthcare Advisors LLC.

Email: Tina70qiu@gmail.com
Tina.Qiu@directionalhealthcare.com
Phone: 001-978 998 0624
Contact me @Linkedin http://www.linkedin.com/profile/view?id=7687436&trk=nav_responsive_tab_profile

Ophthalmic Product Innovation



Pivotal Preclinical

Strategy, Tactic, Principle

- Drug Repurposing Strategy
- Ocular Drug Delivery
- Formulation Strategy
- Stem Cell/Gene Therapy
- PK/PD, Safety & Efficacy
- Product Development Profile

Due Diligence & SWOT

Clinical Development (cross-function)

- Strategy, Protocol Synopsis
- **Adaptive Clinical Trials**
- Data Analysis & Integration
- High Level Content Strategy

- Bridging "Gaps" in Translation
- Disease staging & "Combo"
- Efficacy & Safety Pool-Integration
- IND, NDA Review & Label

Commercial Medical

- Commercial Medical Affairs
- Product Medical Strategy
- KOLs Penetration & Ad-board
- Global Communication
- Medical Inquiry & Training
- Risk-Benefit Assessment

Competitive Intelligence

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Directional Healthcare Advisors, LLC

Email: tina70qiu@gmail.com

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