

# Nanomedicine: Making Drugs and Biologics Safer and More Effective



Justin Hanes, Ph.D.

The Center for Nanomedicine at Wilmer Eye Institute

ICTR Drugs/Biologics/Vaccines/Devices Translational Research Community

July 9, 2014

# Financial Interest Disclosure



**December 2009**

Hanes, Cone, Fu, Lai



**June 2011**

Hanes, Campochiaro, Fu, McDonnell, Wyskiel



**April 2014**

Lee, Hanes, Pomper

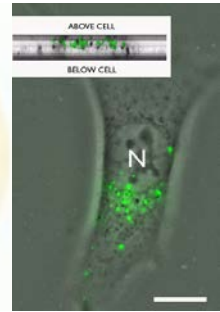
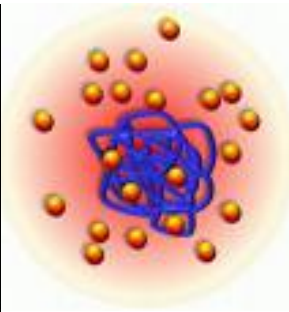
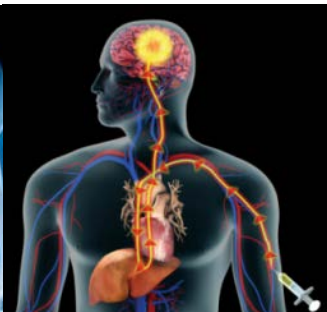
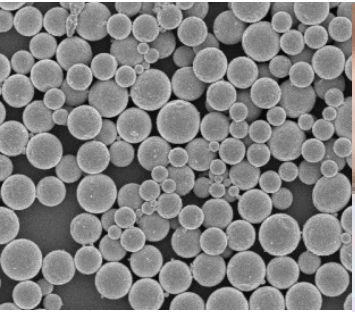


**April 2014**

Lee, Hanes, Pomper

Dr. Hanes is a founder and owns company stock in Kala Pharmaceuticals, GrayBug, Theraly Pharmaceuticals, and Theraly Diabetes, some of which is subject to certain restrictions under University policy. The terms of these arrangements are managed by the Johns Hopkins University in accordance with its conflict of interest policies.

# Medicine Should Go Only Where it is Needed... *and it Should Last*



Nanoparticles

Ocular  
Delivery

Respiratory  
Delivery

Targeted  
Delivery

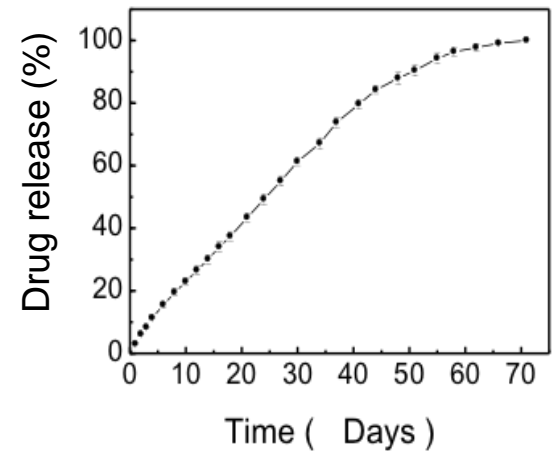
Controlled  
Release

Gene  
Therapy

Nanoparticles Allow *Local Delivery + Timed Release*:  
Drugs More Effective + Side Effects Reduced

# Major Advantages of “Nanomedicine”

- Small Molecules, Biologics, Nucleic Acids
- Highly Localized or “Targeted” Delivery
- Controlled Delivery (hours to years)
  - Greatly Improved PK
- Enhanced Tissue Penetration
- Intracellular Delivery
- Proprietary Product Extension



**Drug Release Kinetics**

Drugs More Effective Even at Much Lower Doses



THE CENTER FOR NANOMEDICINE AT JOHNS HOPKINS  
 MEDICAL INNOVATIONS THROUGH ENGINEERING, SCIENCE AND MEDICINE



HOME PEOPLE RESEARCH COMMERCIALIZATION NEWS + EVENTS CONTACT US DONATE



RESPIRATORY



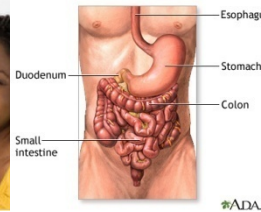
BRAIN



EYE



WOMEN'S HEALTH



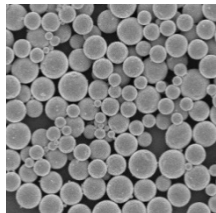
GASTROINTESTINAL



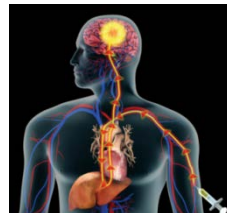
SINUSES

*HOME...*

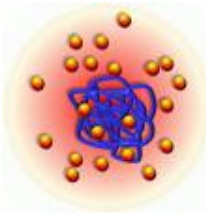
The Center for Nanomedicine occupies the 6<sup>th</sup> floor of the state-of-the-art, 207,000 ft<sup>2</sup> **Robert H. and Clarice Smith Building** of the Wilmer Eye Institute on the Johns Hopkins School of Medicine Campus in Baltimore, MD. The 1<sup>st</sup> floor is dedicated to eye surgery, and the top five floors are dedicated to research. The open floor plan enhances everyday interaction among its more than 350 inhabitants, including basic scientists, biomedical engineers and clinician-scientists.



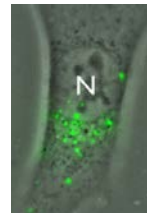
NANOPARTICLES



DISEASE TARGETING



TIMED RELEASE



GENE THERAPY



CANCER



INFLAMMATION

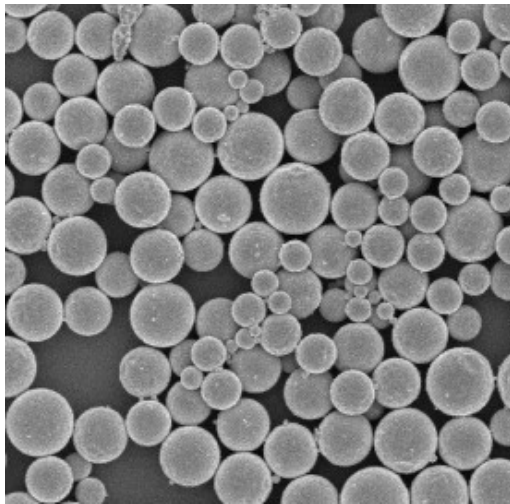


CARDIOVASCULAR



# How Small is “Nano”?

Nanoparticles



~100 nm  
( $10^{-7}$  m)

Soccer Ball



~0.1 to 1 m

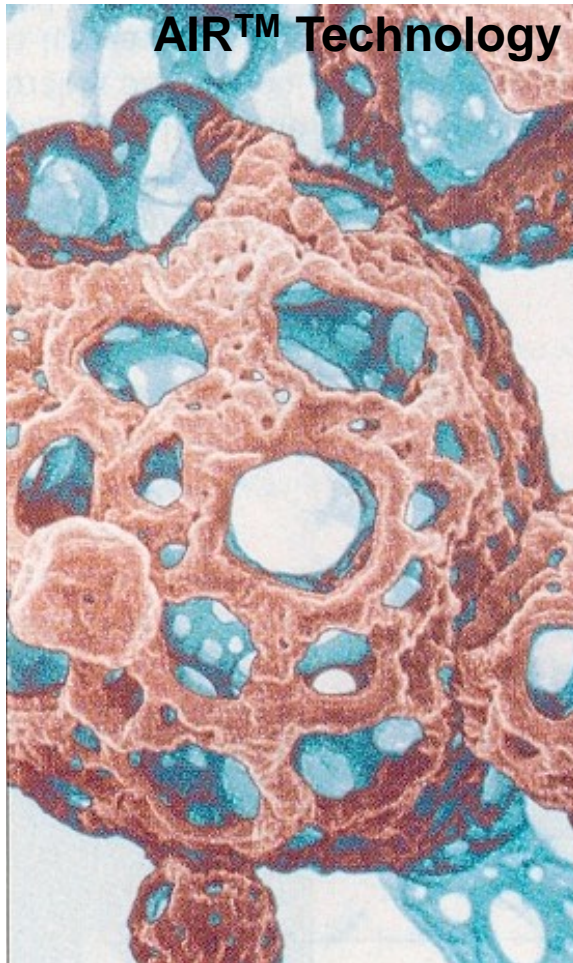
Earth



~ $10^7$  m

Yet, >1 Million Drug Molecules can be Packaged in a Nanoparticle

# Large Porous Particles for Pulmonary Drug Delivery



Edwards, *Science* 1997

Large Porous Particles Aerosolize Easily from Low Tech Inhalers into Deep Lung

> 50% Respirable (vs. 10-15%)

Provide Long-Term Drug Release into the blood

Insulin: 96 h (vs. 6 h for liposomes)

87% Relative Bioavailability

Alkermes Purchased AIR in Feb 1999



Bob Langer



David Edwards



Advanced Inhalation Research, Inc.

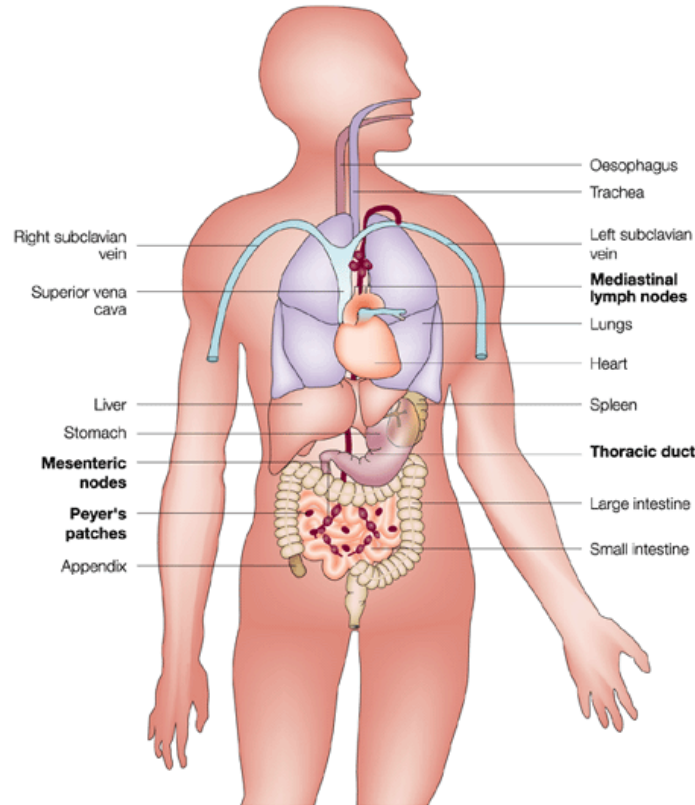
# The Beginning: Graduate Student Working on CF Gene Therapy Insists on Working with Mucus



Michelle Dawson, Ph.D., 2000-2005  
(Currently: Assistant Professor, Georgia Tech)



# Mucus Coats Entry Points to Body not Covered by Skin

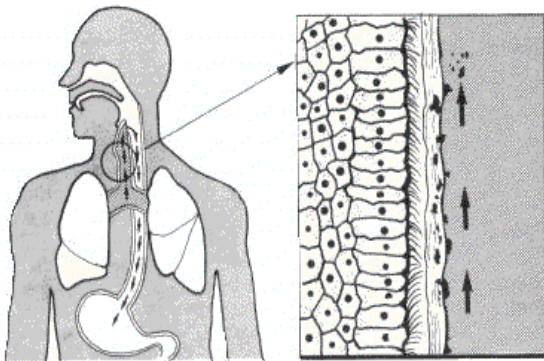


Nature Reviews | Immunology

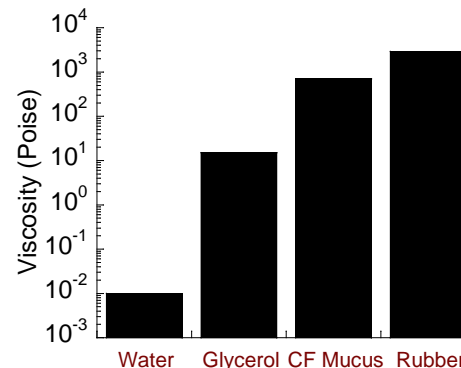
Eye surface  
Respiratory Tract  
-Nose  
-Sinuses  
-Trachea  
-Lung Airways  
Gastrointestinal Tract  
-Mouth to Anus  
Female Reproductive Tract  
Inner Ear

Mucus Barrier Protects Body from Constant Assault by Infectious + Toxic Agents

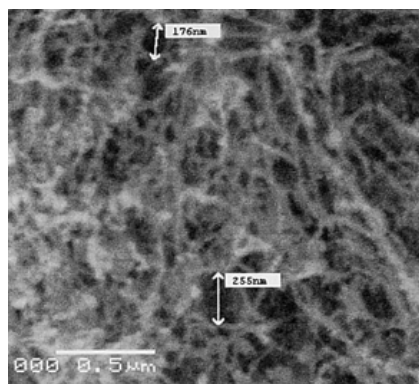
# The Mucus Barrier to Drug and Gene Delivery



Mucus coats entry points



Highly Viscoelastic<sup>+</sup>



Nanoporous mesh\*



Highly Adhesive

Mucus traps particles which are then removed (sec-hr)

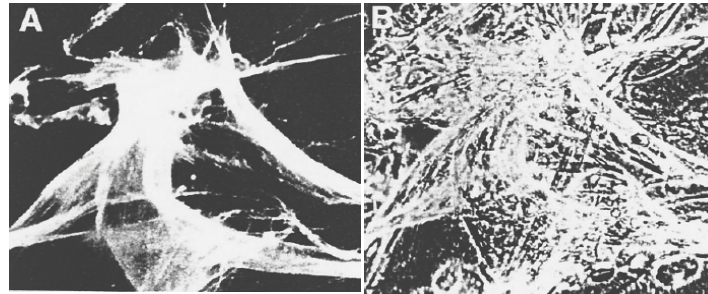
\*Sanders *et al.*, **AJRCCM**, 2000

+Cone, **Mucosal Immunology**, 1999

# Human Mucus Traps Standard Particles

Nanoparticles completely immobile in undiluted human mucus

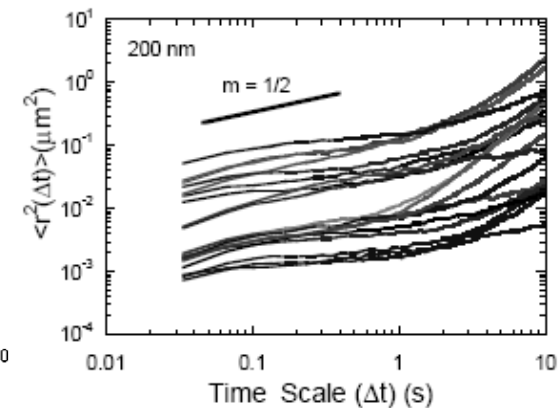
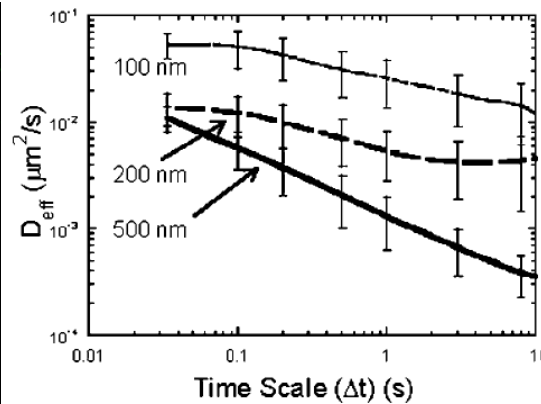
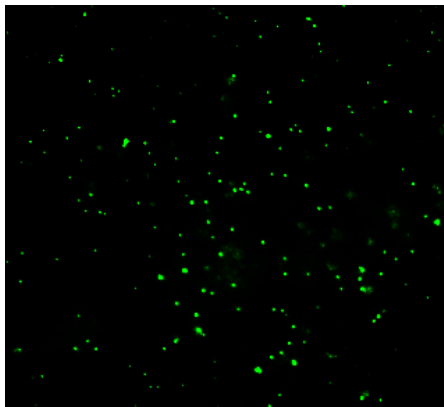
Olmsted et al. (Cone Lab), *Biophys J*, 2001



**Diffusivity = 0  
for particle size  
59 – 1000 nm**

Nanoparticles do not penetrate human CF sputum

Dawson et al. (Hanes Lab), *J. Biol. Chem*, 2003



# The Sensational Six + Key Early Collaborators



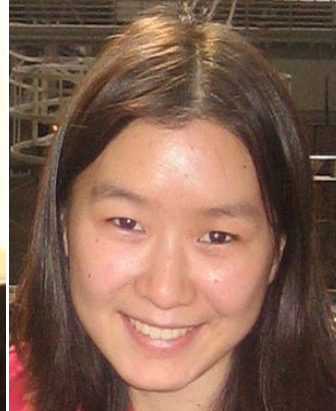
Sam Lai  
(2007)



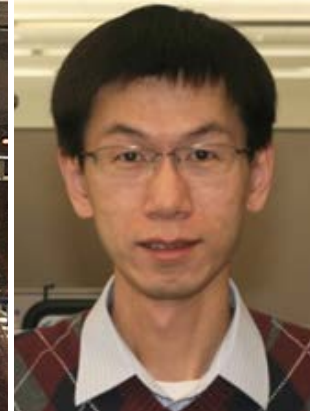
Ben Tang  
(2009)



Jung Soo Suk  
(2011)



Ying-Ying Wang  
(2011)



Ming Yang  
(2011)



Laura Ensign  
(2012)



Richard Cone



Jie Fu



Bill Guggino



Denis Wirtz



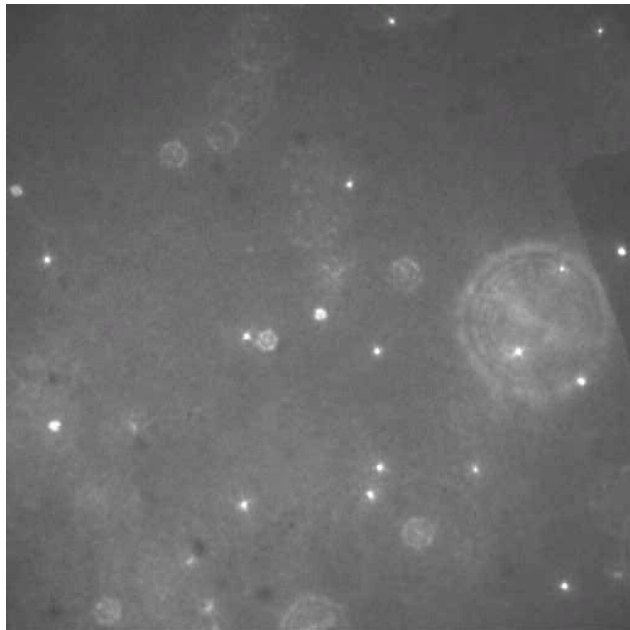
Pam Zeitlin



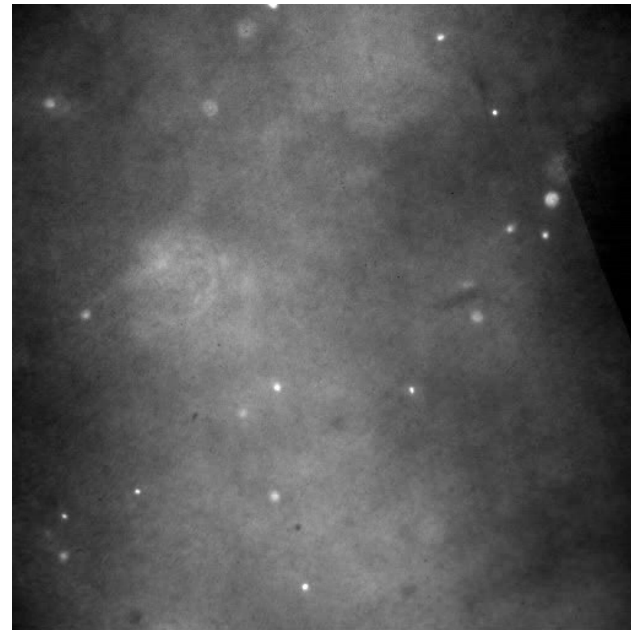
# Nanoparticles that Penetrate the Mucus Barrier

## “Mucus-Penetrating Particles”

Enable Localized + Sustained Drug & Gene Delivery



**Uncoated Particles**



**Coated Particles**

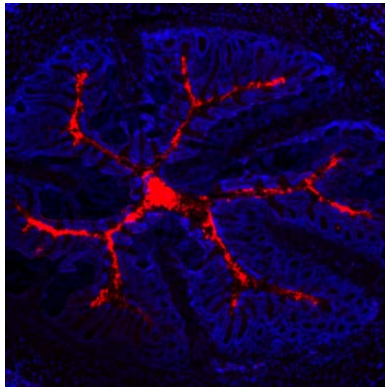
**Mucus Types:** Lungs, Eyes, Sinuses, Cervicovaginal, GI Tract

Lai, *PNAS* 2007; Wang, *Angew Chem* 2008; Tang, *PNAS* 2009; Suk, *Biomaterials* 2010;  
Yang, *Angew Chem*, 2011; Lai, *Biomaterials* 2011; Ensign, *Sci Transl Med* 2012

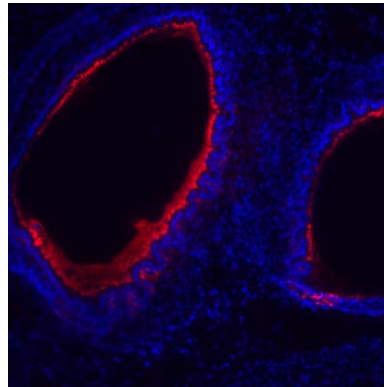


# Nanomedicines that Bypass the Mucus Barrier: “Mucus Penetrating Particles”

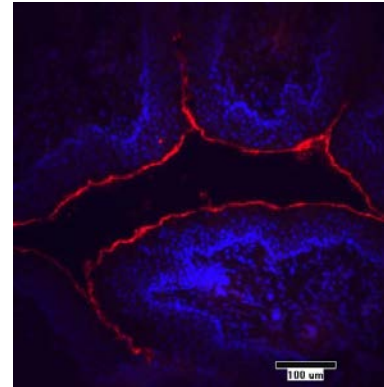
GI Tract



Lung Airways



Vagina



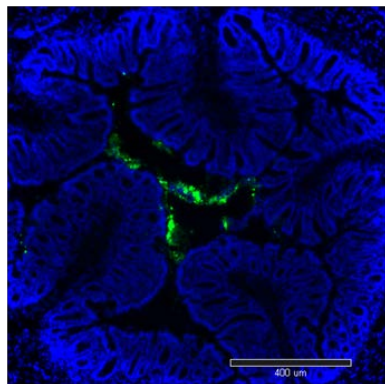
**Key Papers:**

Lai, *PNAS* 2007  
Wang, *Angew Chem* 2008  
Tang, *PNAS* 2009  
Lai, *PNAS* 2010  
Yang, *Angew Chem* 2011  
Ensign, *Adv Matls* 2012  
Nance, *Sci Transl Med* 2012  
Ensign, *Sci Transl Med* 2012  
Kim, *Angew Chem* 2013

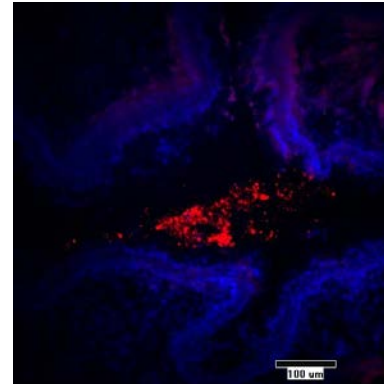
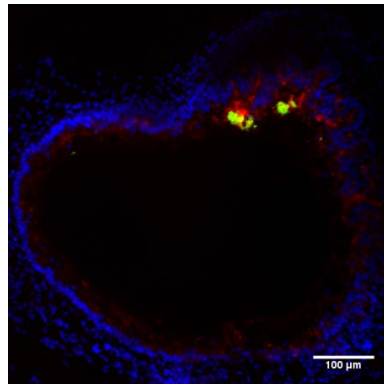
**Key News Stories:**

JAMA  
Science (Editor's Choice)  
Sci-Bx (Nature)  
Nature Materials  
Nature Nanotechnology  
PNAS  
NCI Nano Alliance

MPP

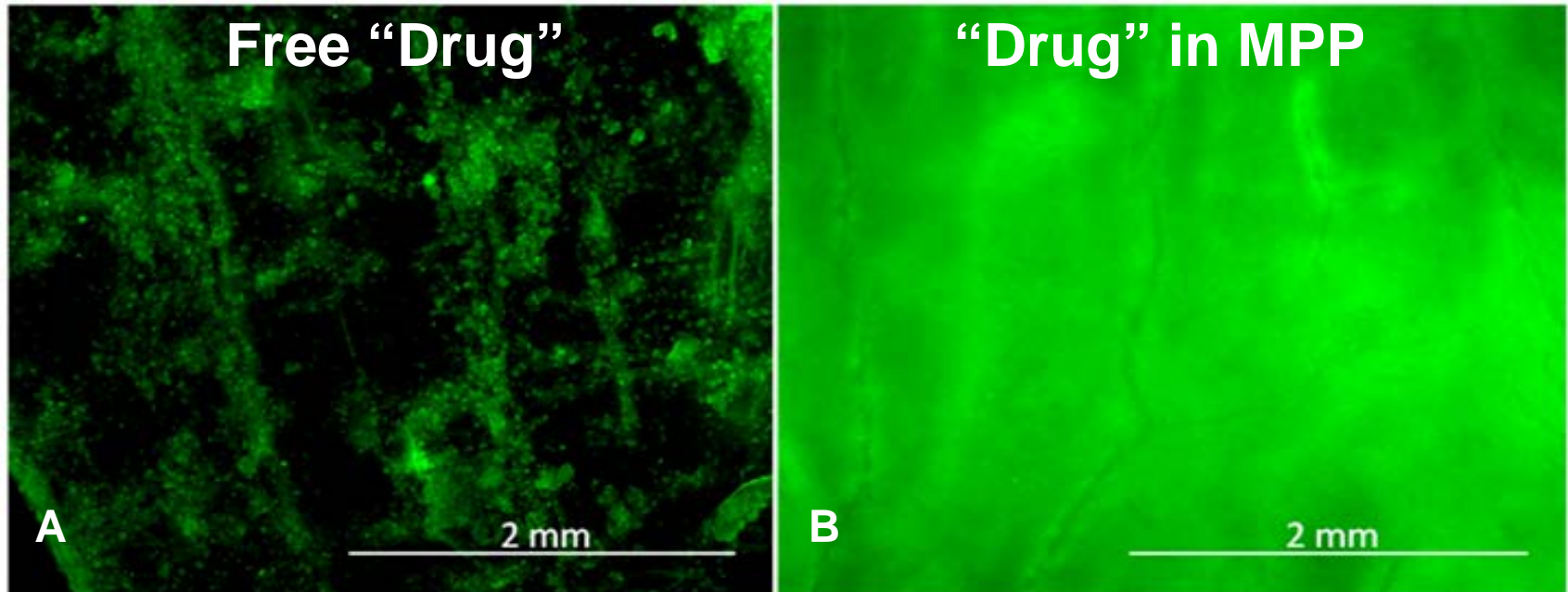


CP



Drug PK Improved by >40-fold in Lungs, Vagina, Peritoneal Cavity

# Mucus Penetrating Particles Deliver Drugs for Longer Times (>24h)



Better Protection Against HSV Infection with 10-fold Less Drug

# Many Diseases May be Treated More Effectively by Localized Drug Delivery to Mucosal Surfaces

- Respiratory tract:
  - Inflammation (Asthma, CF, COPD, Emphysema, ILD)  
>100 mil people worldwide for Asthma alone
  - Lung cancer  
1.3 mil deaths each yr
  - Cystic Fibrosis  
70,000 patients worldwide (30,000 in US)
  - Sinusitis (including chronic sinusitis)  
14% of Americans (~40 Million in US)
- Gastrointestinal tract:
  - Inflammatory bowel disease (IBD) / Crohn's / Colitis  
0.5-1% of Western population (> 1 Mil in US)
  - Gastrointestinal cancer  
250,000+ new cases in U.S. each yr
- Cervicovaginal tract:
  - Sexually transmitted diseases (e.g. HIV, Herpes, HPV, Chlamydia)  
> 46 mil people with HIV
  - Cervical cancer  
230,000 deaths/yr

# An “MPP” Company Formed



Technology: Mucus Penetrating Nanoparticles

>\$45M raised in venture capital

Phase III trial 2014: Post Cataract Surgery Pain and Inflammation

Phase II trial 2014: Dry Eye

Phase II trial 2014: Blepharitis

Phase II trial 2015: Diabetic Macular Edema

# Current “MPP” Grant Funding

U19 (Hanes & Cone, PI's of Project 2; Hendrix, PD) NIH <i>Development of Rectal Enema as Microbicide (DREAM)</i>	07/01/2014 – 06/30/2019 \$21,105,233
R21/R33 AI094519 (Hanes & Cone) NIH (NIAID/NIMH/ODNIH) <i>Mucus Penetrating Particles for Rectal Microbicides</i>	05/01/11 – 04/30/16 \$1,869,428
R01HD062844 (Hanes & Cone) NIH (NICHD/NIAID) <i>Pathogen trapping by genital mucus secretions</i>	04/01/10 – 01/31/15 \$2,050,000
R01 HL105847 (Rowe, UAB, PI; Hanes PI of Subaward) NIH (NHLBI) <i>Molecular Pathogenesis and Phenotype of Acquired CFTR dysfunction in COPD</i>	02/01/11 – 01/31/16 \$1,378,200 (\$ to JHU)
(Jelinek & Hanes) US-ISRAEL BINATL FOUNDATION <i>Mucus Permeation and Membrane Interactions of Stealth Nano-Carriers for Cystic Fibrosis Gene Therapy</i>	11/01/11 – 10/31/15 \$188,000
U54CA151838 (Hanes, PI of Project 4; Searson, PD) NIH (NCI) Center for Cancer Nanotechnology Excellence Project 4 Title: <i>Mucus Penetrating Nanoparticles for Small Cell Lung Cancer</i>	08/25/10 – 07/31/15 ~\$15,000,000 (\$2,021,109 Project 4)
P01HL51811 (Hanes-PI Project 2; Guggino, PD) NIH (NHLBI) <i>Project 2: New Approaches to Overcome the Sputum Barrier to Gene Delivery</i>	06/01/09 – 04/30/14 ~\$7,200,000 (\$1,320,200 Project 2)
HANES07XX0 (Hanes) Cystic Fibrosis Foundation <i>Particle Delivery to Optimize Small Airway Mucociliary Transport</i>	01/01/08 – 12/31/14 \$490,000
P50 HL107190 (Neptune) NIH (NHLBI) <i>TGF<math>\beta</math> Modulation: Therapeutic Targeting for COPD-Emphysema</i>	07/01/11 – 05/31/14 \$1,470,000



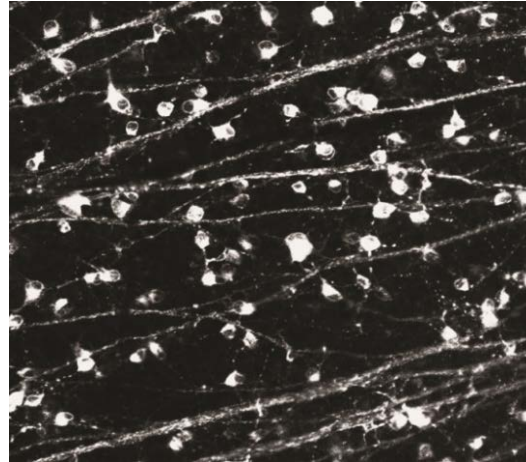
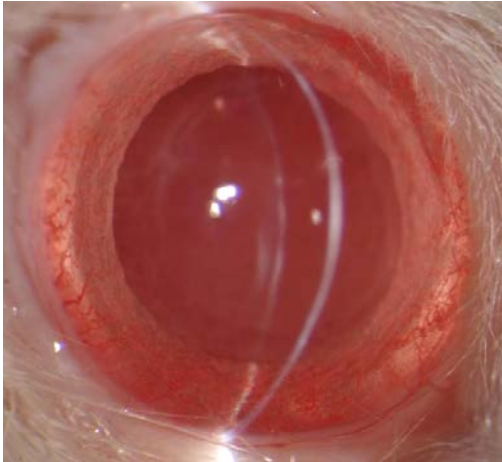
# Saving Vision: The Promise of Nanomedicine

Corneal Grafts:  
Protection

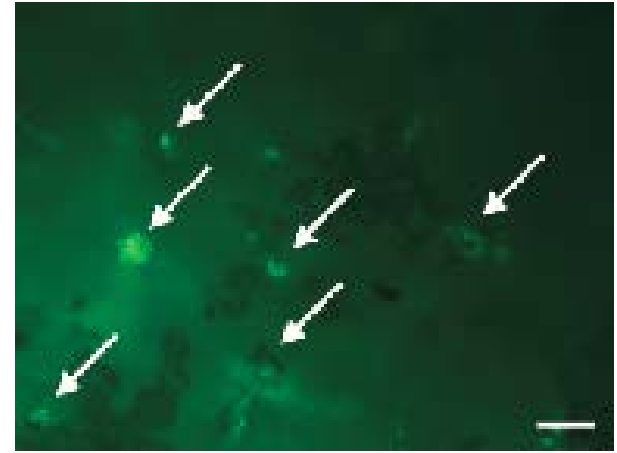
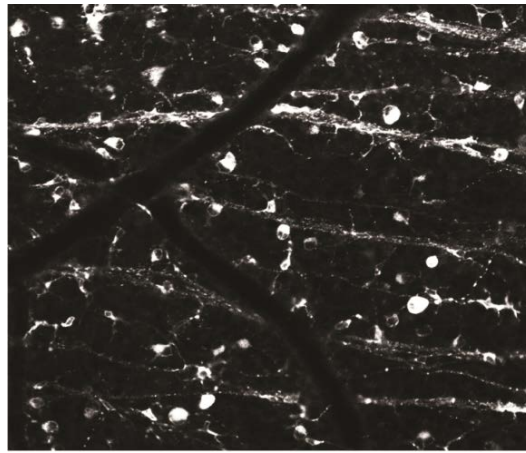
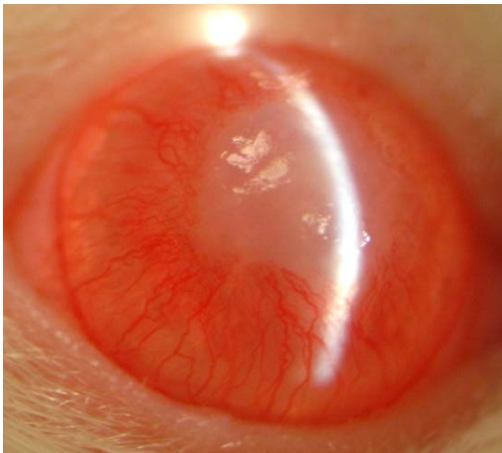
Glaucoma:  
Protection of RGC

Wet AMD:  
Reduce Angiogenesis

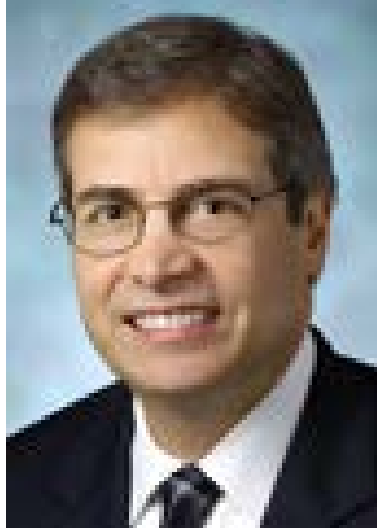
Nanoparticles



Controls



# New Therapy for Ocular Neovascularization



Peter A.  
Campochiaro



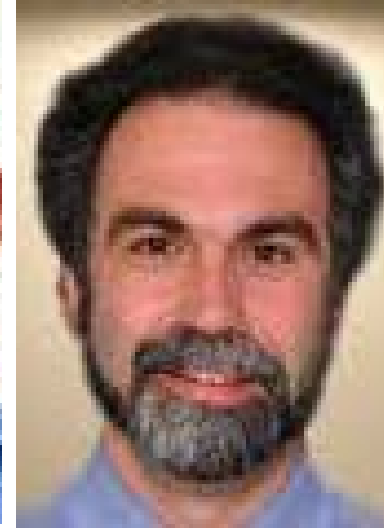
Jie Fu



Justin Hanes



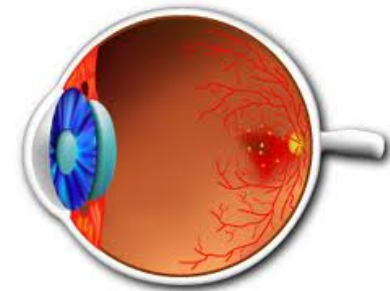
Takeshi Iwase



Gregg  
Semenza

# Angiogenesis: Major Problem in Eye Diseases

- Choroidal Neovascularization (CNV) occurs in diseases of the retinal pigmented epithelium/Bruch's membrane complex
  - Characterized by new blood vessel growth through Bruch's Membrane
  - **AMD** is most common cause of blindness in elderly in Western World (>20M)
- Retinal NV occurs in ischemic retinopathies
  - **Diabetic retinopathy (DR), retinopathy of prematurity, retinal vein occlusions**
  - **DR** most common cause of moderate-severe vision loss in working-age Americans
- The Unmet Need
  - Need for reduced frequency of injection
    - Reduce burden on patients + reduce complications
    - VEGF Trap-Eye (Eylea) >\$1B in sales in 2013
  - Current therapies all anti-VEGF—do not cause blood vessel regression
  - Combinations of expensive biologics major burden on healthcare system



# New Therapy for AMD and other Ocular NV Diseases

HIF-1 functions as the master regulator of neovascularization by controlling multiple pro-angiogenic growth factors

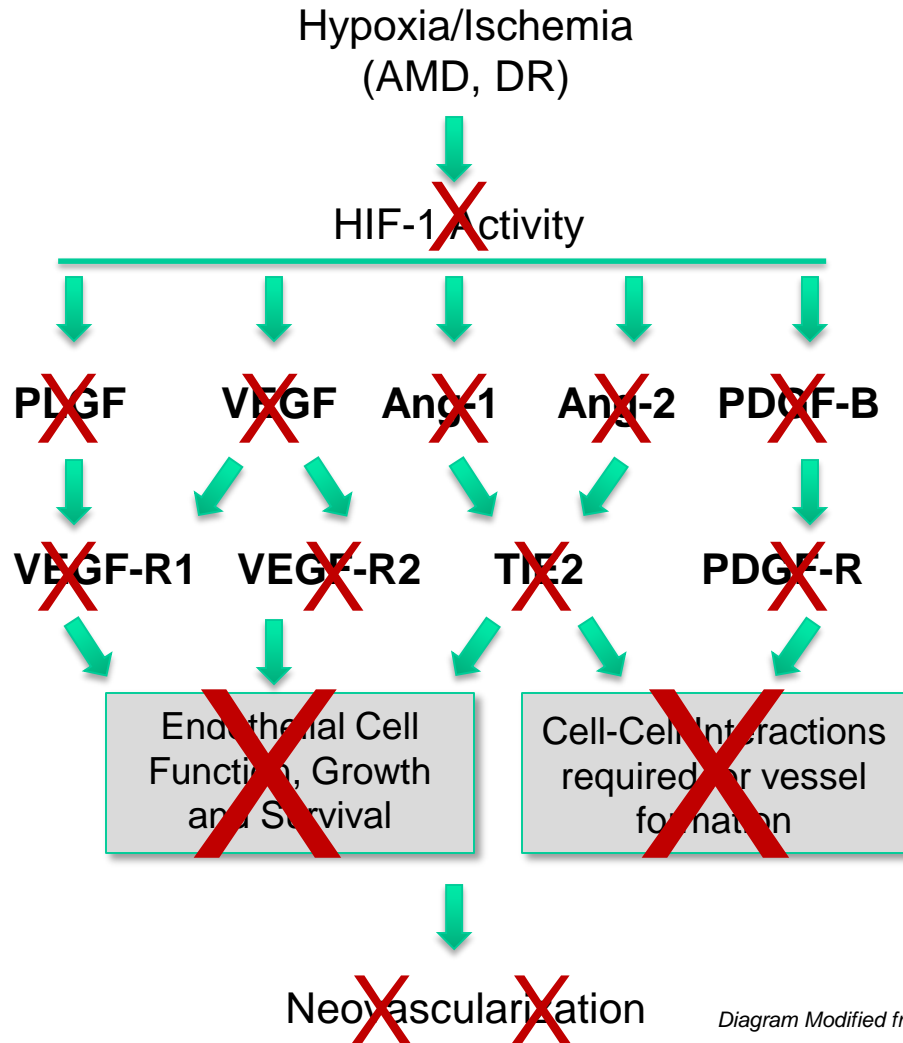
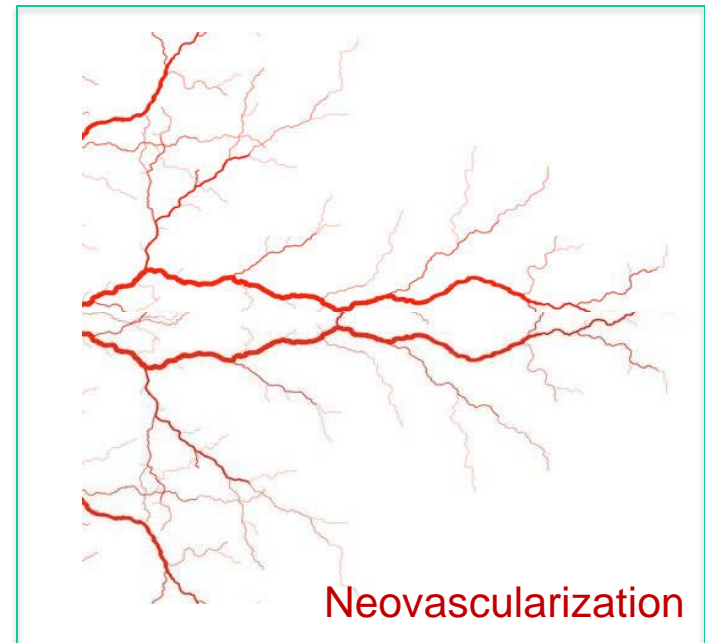


Diagram Modified from Kelly et al., 2003

**Lucentis**

**Eylea**

**HIF-1 Inhibitor**



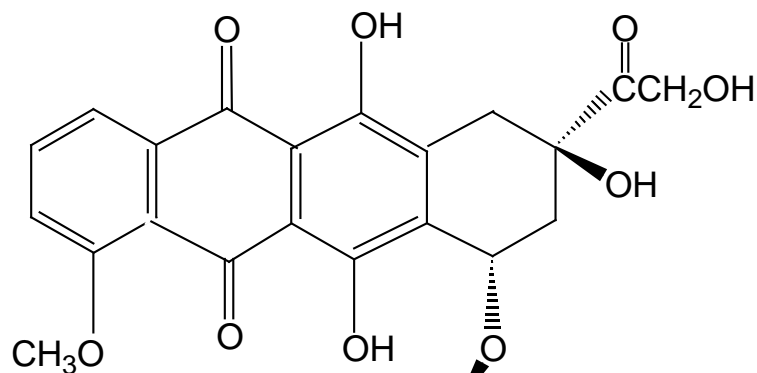
Neovascularization

HIF-1 inhibitor causes NV regression!

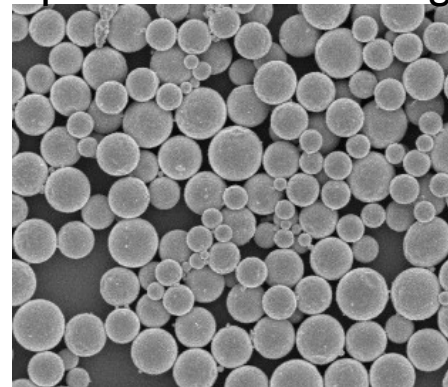
**Pioneering work:**  
Gregg Semenza &  
Peter Campochiaro

# Polymerized HIF-1 Inhibitor (HIF-1i)

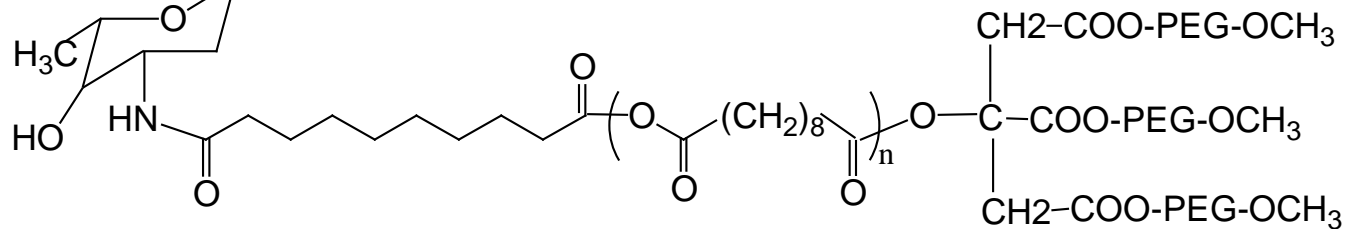
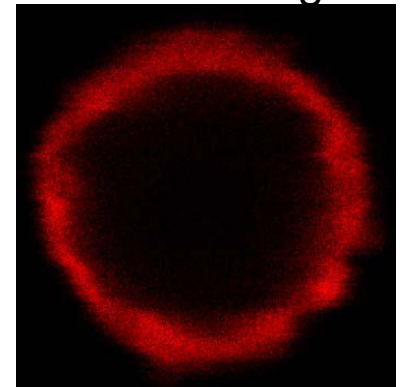
To achieve long-lasting therapy, we developed a polymer that contains a potent HIF-1 Inhibitor



Up to 23.6% Loading



PEG Coatings

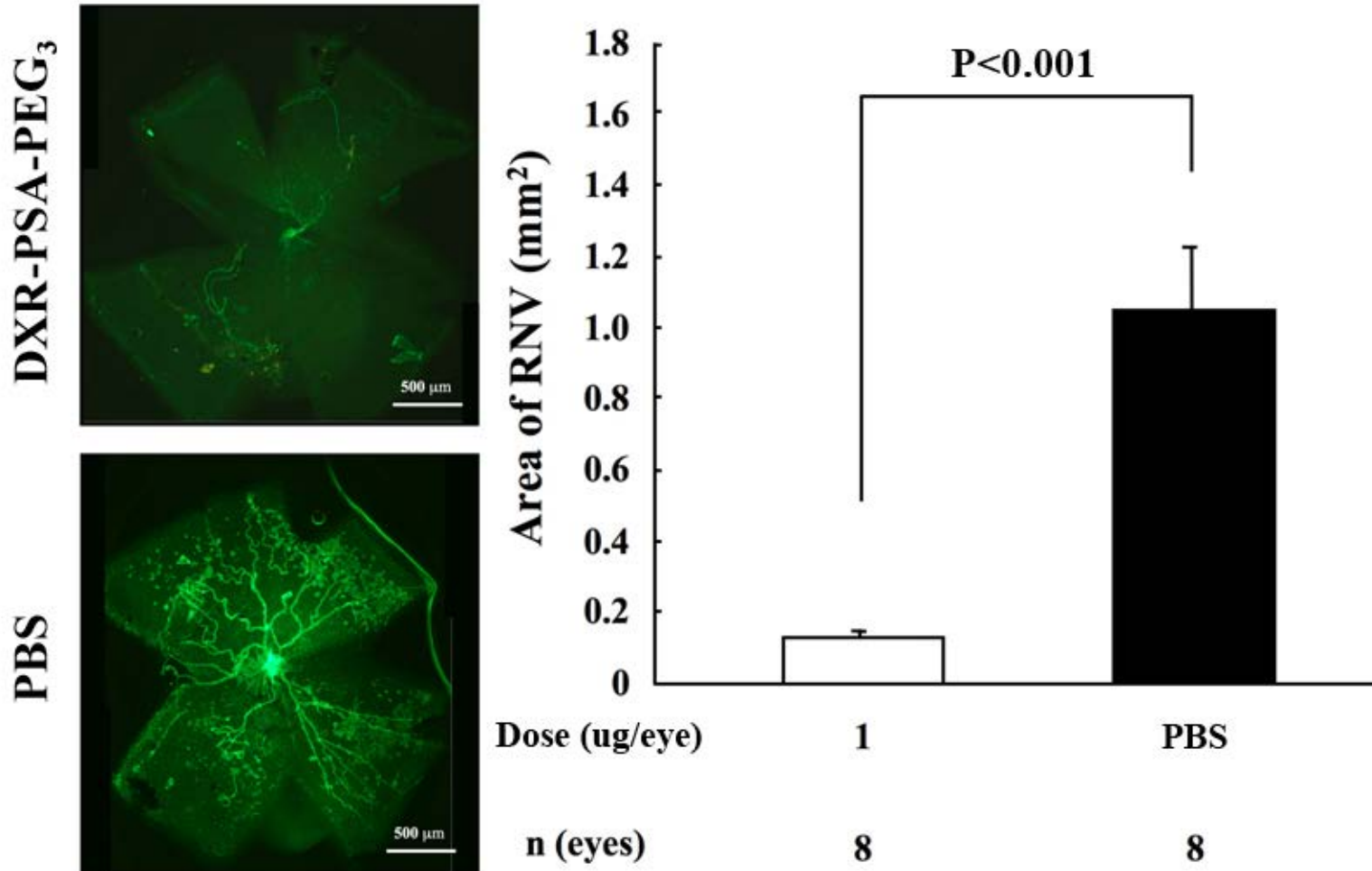


QA/QC Includes: NMR, FTIR, GPC, DLS, Stability, Drug Content, *In Vitro* Release, etc.



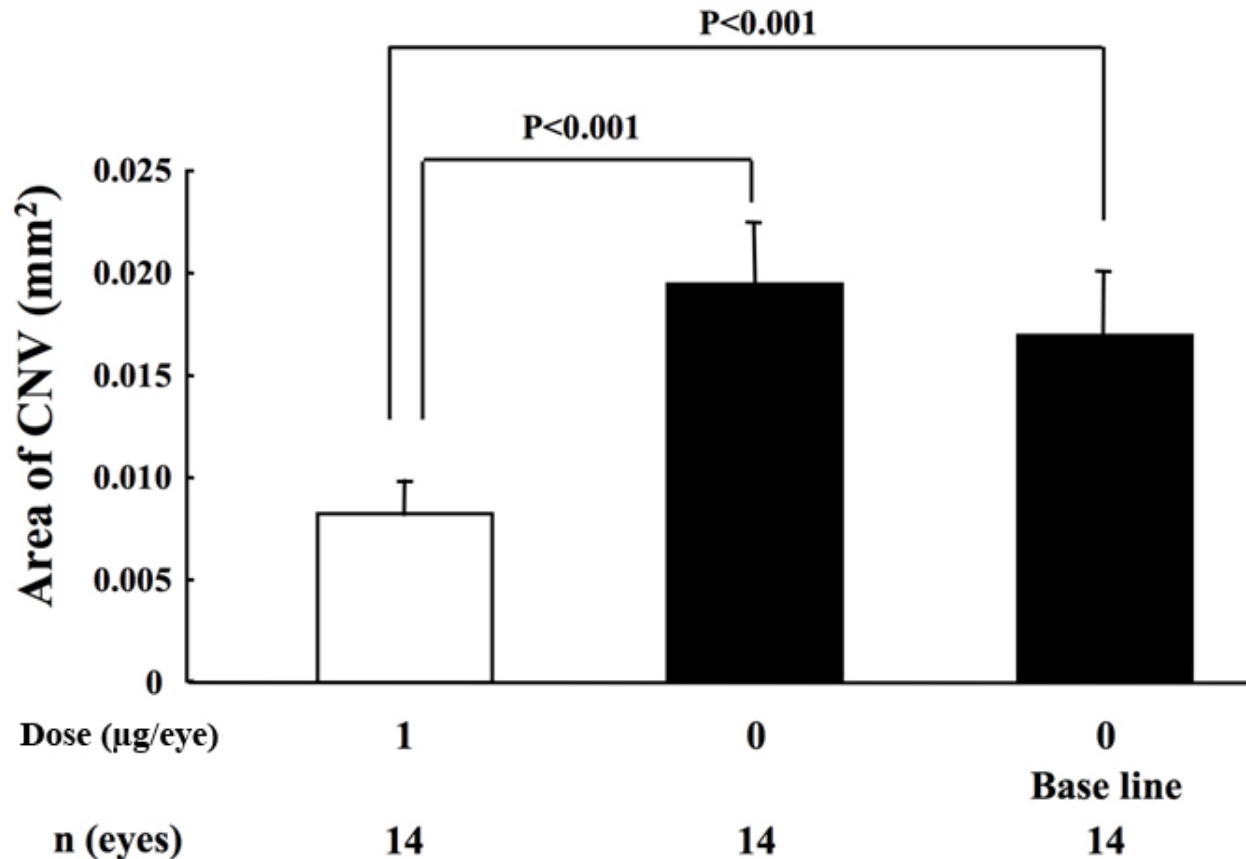
# HIF-1i Polymer Nanoparticles Highly Effective in Animals

Oxygen-Induced Ischemic Retinopathy Model (**ROP** and **DR** Model)



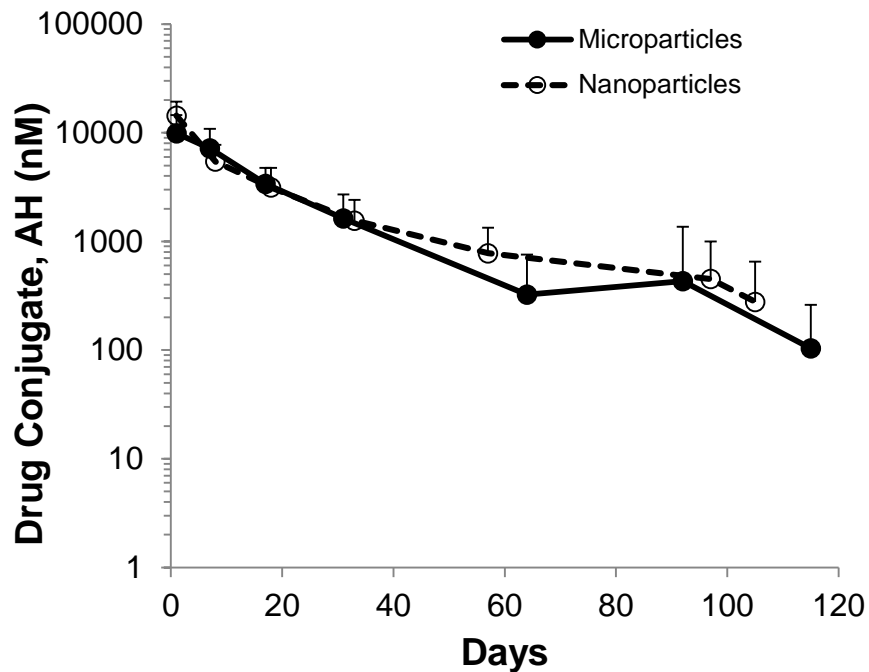
# HIFi Nanoparticles Cause *Regression* of New Blood Vessels

Laser-induced Bruch's Membrane Rupture Model (NV **AMD** Model)

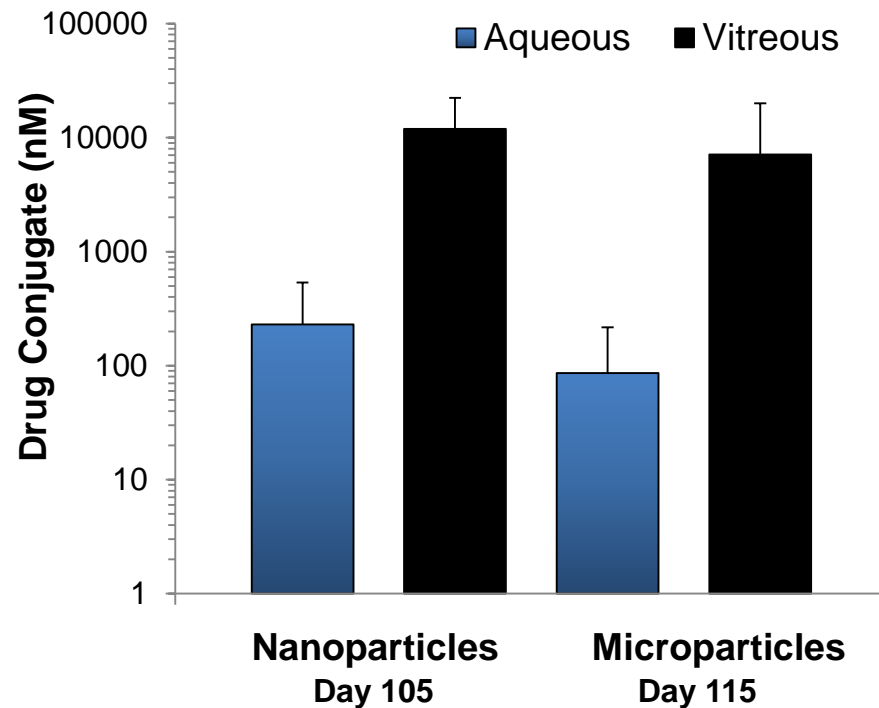


# Sustained HIF-1i Drug Levels in Rabbits

## Drug Levels in Aqueous Humor



## Drug Levels in Aqueous vs. Vitreous



Drug release sustained >115 days in rabbits

# GrayBug, LLC

[graybug.com](http://graybug.com)



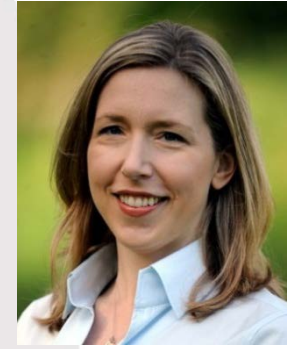
**Justin Hanes, PhD**



**Peter Campochiaro, MD**



**Peter McDonnell, MD**



**Christy Wyskiel**



**Gerald Cagle, PhD**



**Michael O'Rourke**



**Judy Gordon, DVM**



**Mark Tracy, PhD**

# Ocular Drug Delivery Innovations

# Acknowledgements

## **PI of Collaborating Groups**

Prof. Henry Brem  
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Prof. Charles Eberhart  
Prof. Laura Ensign  
Prof. Jie Fu  
Prof. Bill Guggino  
Prof. Craig Hendrix  
Prof. Chien-Fu Hung  
Prof. Rangaramanujam Kannan  
Prof. Sujatha Kannan  
Prof. Michael McMahon  
Prof. Peter J. McDonnell  
Prof. Enid Neptune  
Prof. Drew Pardoll  
Prof. Craig Peacock  
Prof. Martin Pomper  
Prof. Richard J. Price, UVA  
Prof. Gregg L. Semenza  
Prof. Walter Stark  
Prof. Betty Tyler  
Prof. Peter van Zijl  
Prof. Denis Wirtz  
Prof. TC Wu  
Prof. Qingguo Xu  
Prof. Don Zack

## **Hanes Lab**

Jennifer Fiegel, Ph.D.  
Junghae Suh, Ph.D.  
Yah-el Har-el, Ph.D.  
Michelle Dawson, Ph.D.  
Samuel K. Lai, Ph.D.  
Ben Tang, Ph.D.  
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