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

THE CENTER FOR NANOMEDICINE AT JOHNS HOPKINS
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

Drugs More Effective Even at Much Lower Doses
The Center for Nanomedicine occupies the 6th floor of the state-of-the-art, 207,000 ft² Robert H. and Clarice Smith Building of the Wilmer Eye Institute on the Johns Hopkins School of Medicine Campus in Baltimore, MD. The 1st 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.
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

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
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

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 Adhesive

Nanoporous mesh*

Highly Viscoelastic+

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

![Image of human mucus](image1)

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

Nanoparticles do not penetrate human CF sputum
Dawson et al. (Hanes Lab), *J. Biol. Chem*, 2003

![Image of nanoparticle diffusion](image2)

THE CENTER FOR NANOMEDICINE AT JOHNS HOPKINS
The Sensational Six + Key Early Collaborators


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

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

Key Papers:
- Tang, *PNAS* 2009
- Lai, *PNAS* 2010
- Yang, *Angew Chem* 2011
- Ensign, *Adv Matl* 2012
- Kim, *Angew Chem* 2013

Key News Stories:
- *JAMA*
- Science (Editor’s Choice)
- Sci-Bx (Nature)
- Nature Materials
- Nature Nanotechnology
- *PNAS*
- NCI Nano Alliance

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

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Ensign, *Sci Transl Med* 2012
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

<table>
<thead>
<tr>
<th>Grant ID</th>
<th>Principal Investigator(s)</th>
<th>Agency</th>
<th>Title</th>
<th>Start Date</th>
<th>End Date</th>
<th>Funding Amount</th>
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<tbody>
<tr>
<td>U19 (Hanes &amp; Cone)</td>
<td>PI’s of Project 2; Hendrix, PD</td>
<td>NIH</td>
<td>Development of Rectal Enema as Microbicide (DREAM)</td>
<td>07/01/2014 - 06/30/2019</td>
<td>$21,105,233</td>
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<tr>
<td>R21/R33 AI094519 (Hanes &amp; Cone)</td>
<td>NIH (NIAID/NIMH/ODNIH)</td>
<td>Development of Rectal Enema as Microbicide</td>
<td>05/01/11 - 04/30/16</td>
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<td>R01 HD062844 (Hanes &amp; Cone)</td>
<td>NIH (NICHHD/NIAID)</td>
<td>Mucus Penetrating Particles for Rectal Microbicides</td>
<td>04/01/10 - 01/31/15</td>
<td>$2,050,000</td>
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<td>R01 HL105847 (Rowe, UAB, PI; Hanes PI of Subaward)</td>
<td>NIH (NHLBI)</td>
<td>Pathogen trapping by genital mucus secretions</td>
<td>02/01/11 - 01/31/16</td>
<td>$1,378,200 ($ to JHU)</td>
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<td>U54CA151838 (Hanes, PI of Project 4; Searson, PD)</td>
<td>NIH (NCI)</td>
<td>Molecular Pathogenesis and Phenotype of Acquired CFTR dysfunction in COPD</td>
<td>11/01/11 - 10/31/15</td>
<td>US-ISRAEL BINATL FOUNDATION $188,000</td>
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<td>P01HL51811 (Hanes-PI Project 2; Guggino, PD)</td>
<td>NIH (NHLBI)</td>
<td>Center for Cancer Nanotechnology Excellence</td>
<td>08/25/10 - 07/31/15</td>
<td>~$15,000,000 ($2,021,109 Project 4)</td>
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<td>HANES07XX0 (Hanes)</td>
<td>Cystic Fibrosis Foundation</td>
<td>Particle Delivery to Optimize Small Airway Mucociliary Transport</td>
<td>01/01/08 - 12/31/14</td>
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<td>P50 HL107190 (Neptune)</td>
<td>NIH (NHLBI)</td>
<td>TGFβ Modulation: Therapeutic Targeting for COPD-Emphysema</td>
<td>07/01/11 - 05/31/14</td>
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<td>Nanoparticles</td>
<td>Corneal Grafts: Protection</td>
<td>Glaucoma: Protection of RGC</td>
<td>Wet AMD: Reduce Angiogenesis</td>
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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

- Hypoxia/Ischemia (AMD, DR)

HIF-1 Activity

- PDGF
- VEGF
- Ang-1
- Ang-2
- PDGF-B

- VEGF-R1
- VEGF-R2
- TIE2
- PDGF-R

Endothelial Cell Function, Growth and Survival

Cell-Cell Interactions required for vessel formation

Neovascularization

HIF-1 inhibitor causes NV regression!

Diagram Modified from Kelly et al., 2003

Lucentis

Eylea

HIF-1 Inhibitor

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

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

Iwase, Fu, et al., to be submitted
HIF-1i Polymer Nanoparticles Highly Effective in Animals

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

Iwase, et al., J Control Release 2014
HIFi Nanoparticles Cause Regression of New Blood Vessels

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

Area of CNV (mm²)

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<th>Dose (µg/eye)</th>
<th>n (eyes)</th>
<th>1</th>
<th>0</th>
<th>0 Base line</th>
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P<0.001
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

Iwase, et al., J Control Release 2014
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- Prof. Sujatha Kannan
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- Prof. TC Wu
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- Prof. Don Zack

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- Samuel K. Lai, Ph.D.
- Ben Tang, Ph.D.
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- Anthony Kim, Ph.D.
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