New Horizon Session #3
Nanomedicine Applications for Allergy and Vaccines

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Intellectual Property
- Co-inventor (10 patents-USF & ~12 pending),

Co-founder & Chairman of the Board (Consultant)
- TranGenex Nanobiotech Inc
Lung Disease Burden

- Lung Cancer (2011): Estd New cases: 221,130; Deaths: 156,940
- An estd 24 million US adults have COPD
  - 12 million physician-diagnosed and 12 undiagnosed.
  - Past Year Morbidity: chronic bronchitis: 9.9 million emphysema: 4.9 million
  - Past year Mortality: bronchitis: 667, emphysema: 12,790 other chronic lower respiratory diseases (excluding asthma): 111,020
- An estd. 23 million individuals have asthma
  - 12 million of them experienced at least one asthma attack during the survey year.
- Approx. 30,000 people have cystic fibrosis
  - 1 in 3,000 babies are born with the disease;
- ~40,000 infants and 150,000 adults have respiratory distress syndrome
- ~12 million persons have obstructive sleep apnea
What is Nanomedicine?
Challenges in drug delivery to the lung

- **Lungs expel materials** reducing efficiency
- **Patients need to inhale correctly**
- **Drugs need to get into deep lung** which they do not
- **Payload versatility** needs to be increased
- **Particles should range from 1-3 μm** for optimal deposition/delivery
- **Aerosol systems deliver only 10-30% of the dispensed drug**
- **Aerosol systems deliver <100 μg of drug per puff** (mg/dose needed)
- **Inhalers often impart a stigma to the user** (especially young people)
Nanotechnology can change the entire healthcare scene.
Polymeric Nanoparticles: Vehicles for Drug Delivery

- A natural biocompatible cationic polysaccharide from crustacean shells,
- Slowly biodegradable & Nuclease resistant
- Increases transcellular and paracellular transport across mucosal epithelium (mucosal gene delivery)
- Immunostimulatory & Anti-microbial
- Anticoagulant & wound-healing
- Non-toxic, non-hemolytic & Safe
- Cost-effective

Kumar & Mohapatra Human Gene Therapy, 2003
What are some of the examples of potential applications to allergy and asthma?
Thiolated chitosan nanoparticles enhance anti-inflammatory effects of intranasally delivered theophylline


Lee et al Respir Res., 2007
How can NANOTECHNOLOGY help develop novel vaccine for therapies to decrease severity of RSV?

- **Vaccines**
  - Live-attenuated
  - Subunit
  - DNA Vaccines *(Kumar et al. 2002)*

- **Prophylactics**
  - IFN-gamma *(Kumar et al. 2000)*
  - 2-5 OAS *(Behera et al. 2002)*
  - si-RNA *(Zhang et al. 2005, Kong et al. 2007)*

- **Anti-Inflammatory**
  - LTRAs *(Behera et al. 1997)*
  - FP/ Salmeterol *(Singham et al. 2006)*
Nanoparticle-complexed siNS1 Exhibits Antiviral Activity In Vivo

Zhang et al, Nature Medicine 2005

- siNS1 Nanoparticles
  - Reduced RSV replication
- Rx with siNS1 nanoparticles before or after infection with RSV showed
  - decreased virus titers
  - decreased inflammation and AHR.
- human dendritic cells, upon RSV infection, produced
  - elevated type-1 IFN and
  - induced differentiation of naive CD4+ T cells to T helper type 1 (TH1) cells.
NPRA Signaling: A New Target for anti-inflammatory Target

- DNAs:
  - pNPRAi (pNP73102)
  - siNPRA/psiNPRA

- Peptide:
  - KP73-102
  - VD
  - Anantin

- Small molecule:
  - Isatin
  - Isatin-derivatives

Decreased NPRA Expression/Signaling: an Approach to Treat pulmonary inflammation

- Intranasal or oral Administration of KP73-102 or pKP73-102 protects from Ovalbumin-Induced AHR and Eosinophilia.

- Nano-siNPRA Cream modulates eosinophilia and Inflammation in Asthma (Wang et al GVT 2008)

- Vessel Dilator decreases lung resistance and inflammation in the lung in Ovalbumin – induced asthma model (Wang et al Res Res 2009)

A new approach to delivering drugs to the deep lung
Multifunctional Chitosan Nanoparticles

- Passive targeting
  - use peptides such as PVGLIG, a substrate for MMPs, to target tumor vasculature
  - increase retention in blood circulation by coating with polyethylene glycol

- Active targeting
  - antibodies, peptides, ligands to target delivery specifically to cancer cells
1) avoid immune rejection: Inhibit cell-mediated immunity, target cell apoptosis and complement-mediated cell lysis
2) provide for the immunoprotection of allo- and xenogeneic cell transplants,
3) SCs (30-50 µm) appear to become entrapped in the pre-capillary vascular bed of the lung, where the lysed cells are cleared within 15 minutes from the system without deleterious effects to the individual.  

Mohapatra et al, Technol & Innov, 2011
Mouse lung 15 minutes after injection of DiO-labeled rat SCs

SCs take up nanoparticles and they are seen mouse lung 15 minutes post-injection
Electron micrograph of mouse lung 1 hr after injection of pre-loaded, pre-labeled rat Sertoli cells

Quantitation of FITC-labeled nanoparticles and Curcumin-labeled therapeutic drug in mouse organs 1 hr post-injection

Specific Absorbance Assay

% of Total Delivered

Lung  Kidney  Liver  Spleen  Thymus  Control

Mouse Organs

Histology of Lung Sections of Control and Mice treated with SNAP


Ova-Induced Asthmatic Mouse

SNAP THERANOSTICS: THE CONCEPT

Label rat SC
DiL (red) or DiO (green)

Multifunctional Chitosan Nanoaparticle

Xenogen Imaging
Control IR820-1 IR820-2

SNAP (IR820) Control
Summary and Concluding Remarks

- Nanomedicine provides solutions to delivering drugs to lungs more effectively.
- Targeted drug/gene delivery to diseased lung cells can increase effectiveness, be safer and less expensive.
- Pre-clinical studies have shown efficacy and safety in different models.
- IV injection of nanoparticle pre-loaded Sertoli cells (coupled with drug of choice) can provide a new approach to delivering drugs to the deep lung.
- Drugs get to deep lung, SCs deliver >80% of dispensed drug.
- SCs are cleared from the system after delivering nanoparticle load in ~1 hour.
- No inflammation associated with injected or transplanted SCs.