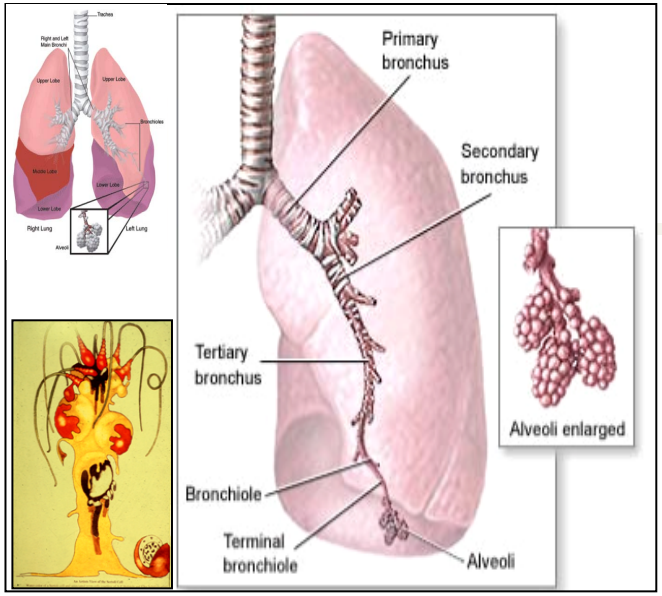
New Horizon Session #3

Nanomedicine Applications for Allergy and Vaccines



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World Allergy Congresss , Cancun, Mexico
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Relevant Disclosures

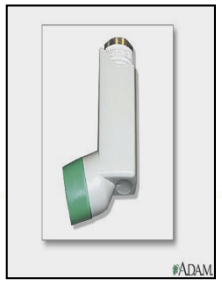
- Current Support:
  - NIH-NCI (1RO1CA152005-01)
  - NIH-NHLBI (1P30HL101265-01)
  - NIH (1R41CA139785-01A1)
  - ONR (N00014-09-1-1008)
  - VA Merit Review (1I01BX000954-01A1)
  - VA Research Career Scientist Award
  - FL Biomed. Res. Foundation (09BW-07)
- Intellectual Property
  - Co-inventor (10 patents-USF & ~12 pending),
- Co-founder & Chairman of the Board (Consultant)
  - TranGenex Nanobiotech Inc

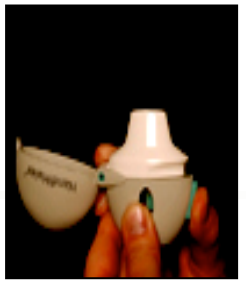
Lung Disease Burden

- 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


MDIs

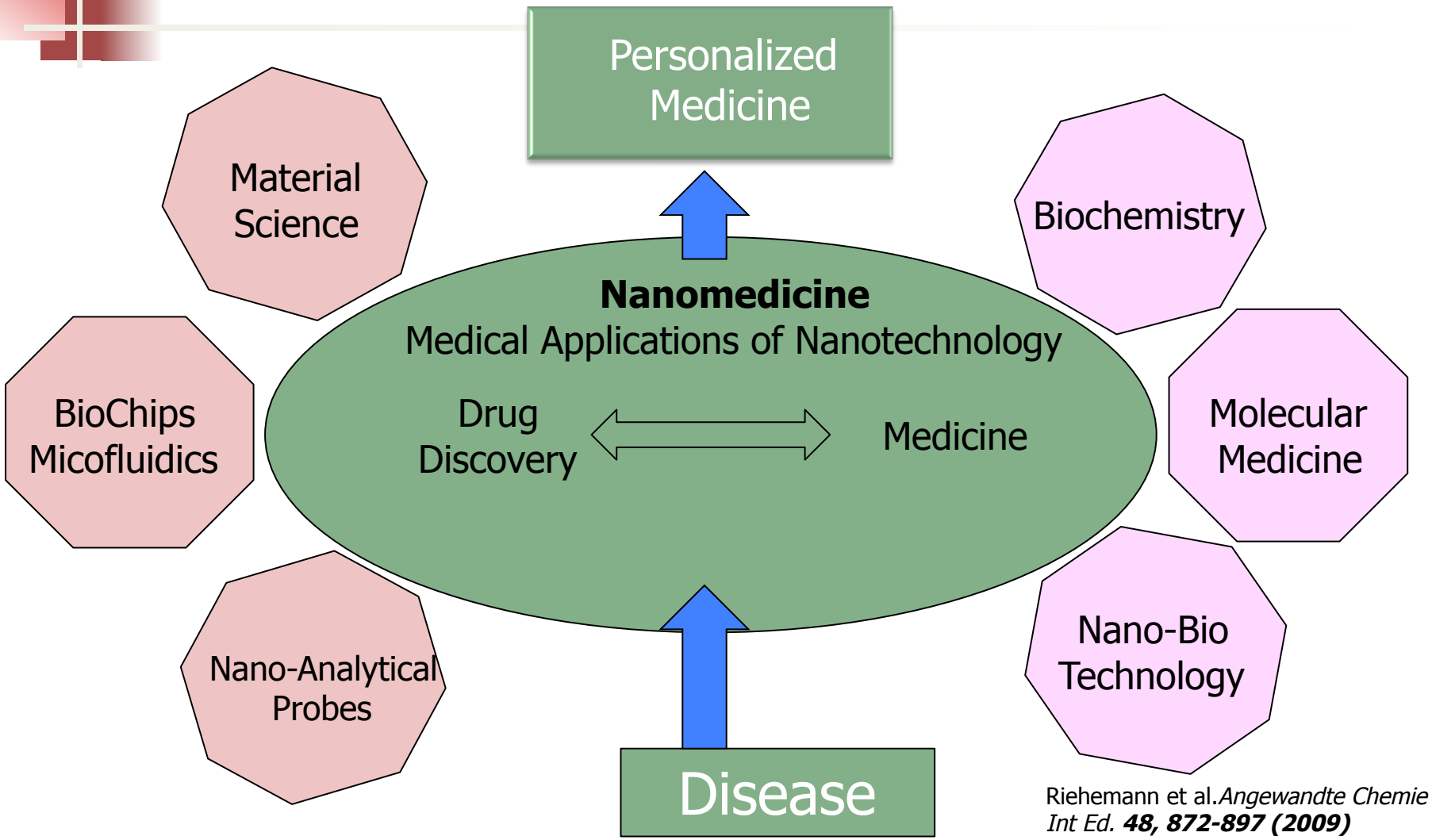

DPIs


Ultrasonic Nebulizers

- **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)

Nanomedicine

Nanotechnology can change the entire healthcare scene



Riehemann et al. *Angewandte Chemie Int Ed.* ***48, 872-897 (2009)***

Polymeric Nanoparticles: Vehicles for Drug Delivery

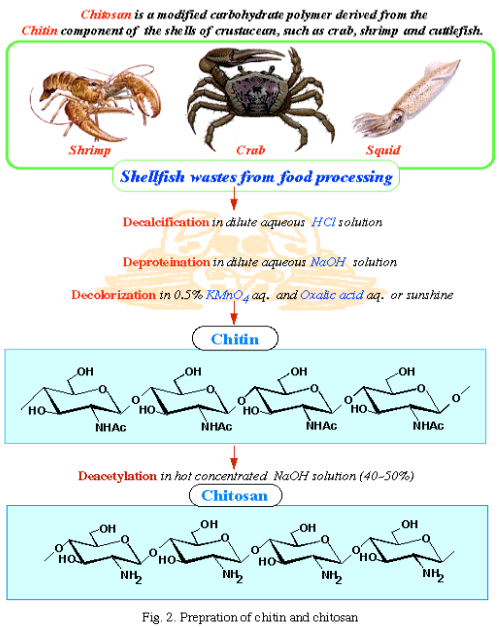
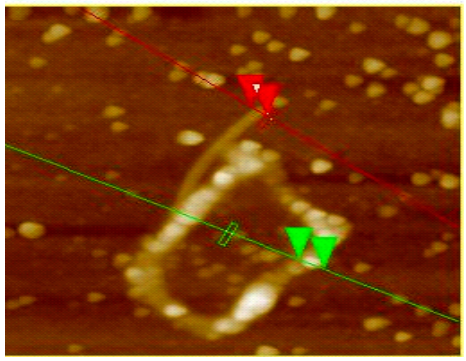
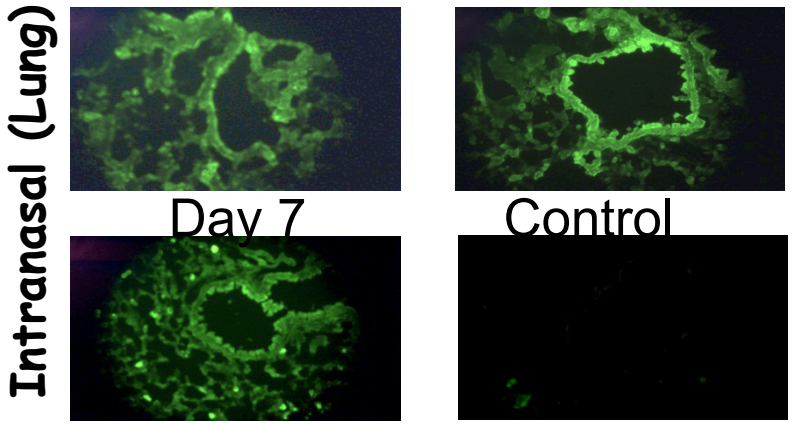


Fig. 2. Prepration of chitin and chitosan

- **Targeted delivery**
- **Lower dosage**
- **Non-invasive**
- **Long shelf-life**
- **Cost-effective**

AFM



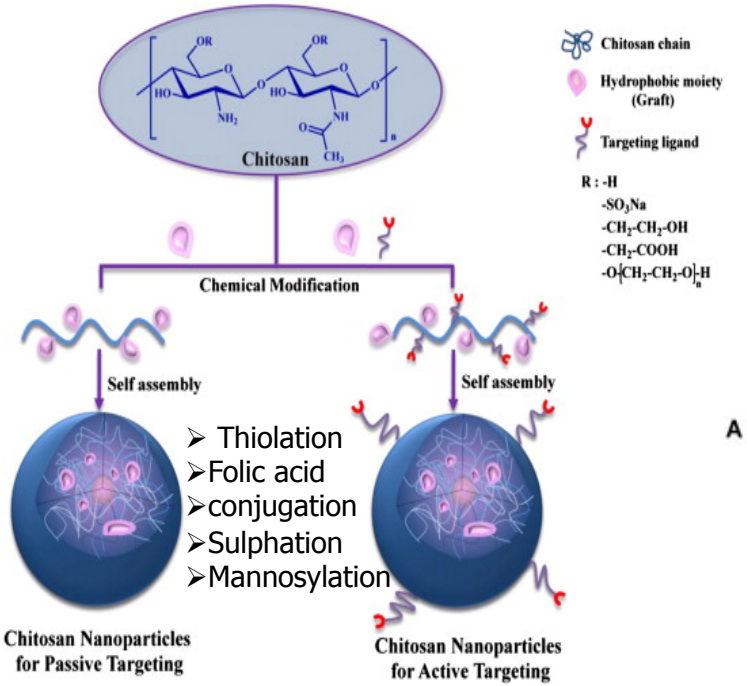


- A natural biocompatible cationic polysaccharide from crustacean shells,
- Slowly biodegradable & Nuclease resistant
- Increases transcellular and paracellular transport across mucosal epithelium (mucosal gene delivery)
- Immunostimulatory & Anti-microbial
- Anticoagulant & wound-healing
- Non-toxic,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

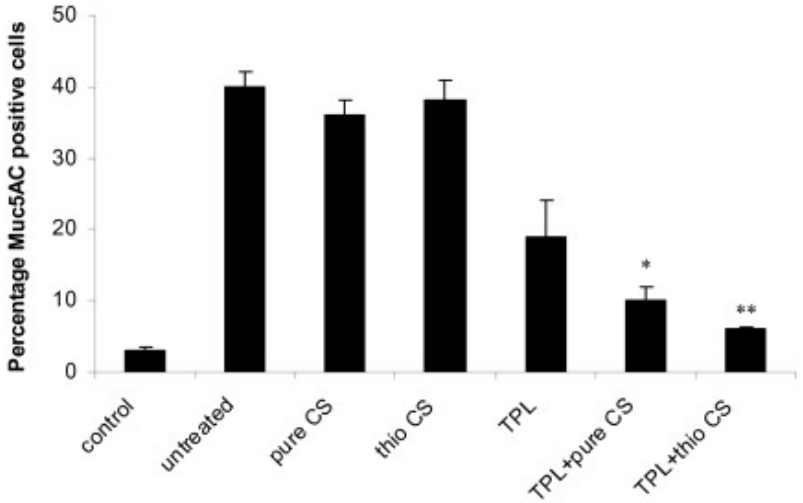
Kumar & Mohapatra Human Gene Therapy, 2003

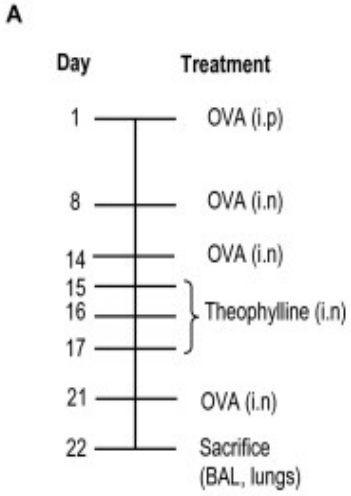
What are some of the examples of potential applications to allergy and asthma?

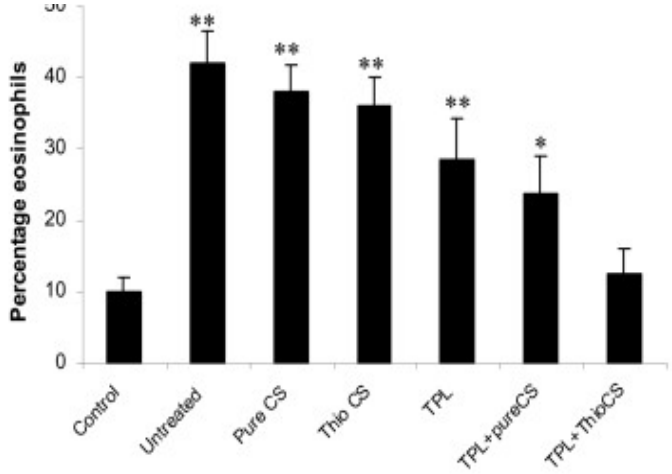
Thiolated chitosan nanoparticles enhance anti-inflammatory effects of intranasally delivered theophylline



Kumar et al. Human Gene Therapy 2002;
Kumar et al. Gen Vacc & Ther, 2003;
Zhang et al Nature Medicine, 2005;
Lee etal, Respiratory Res, 2006,
Lee et al, J Nanosci & Nanotech, 2006
Lee et al, Pharm Res 2007,



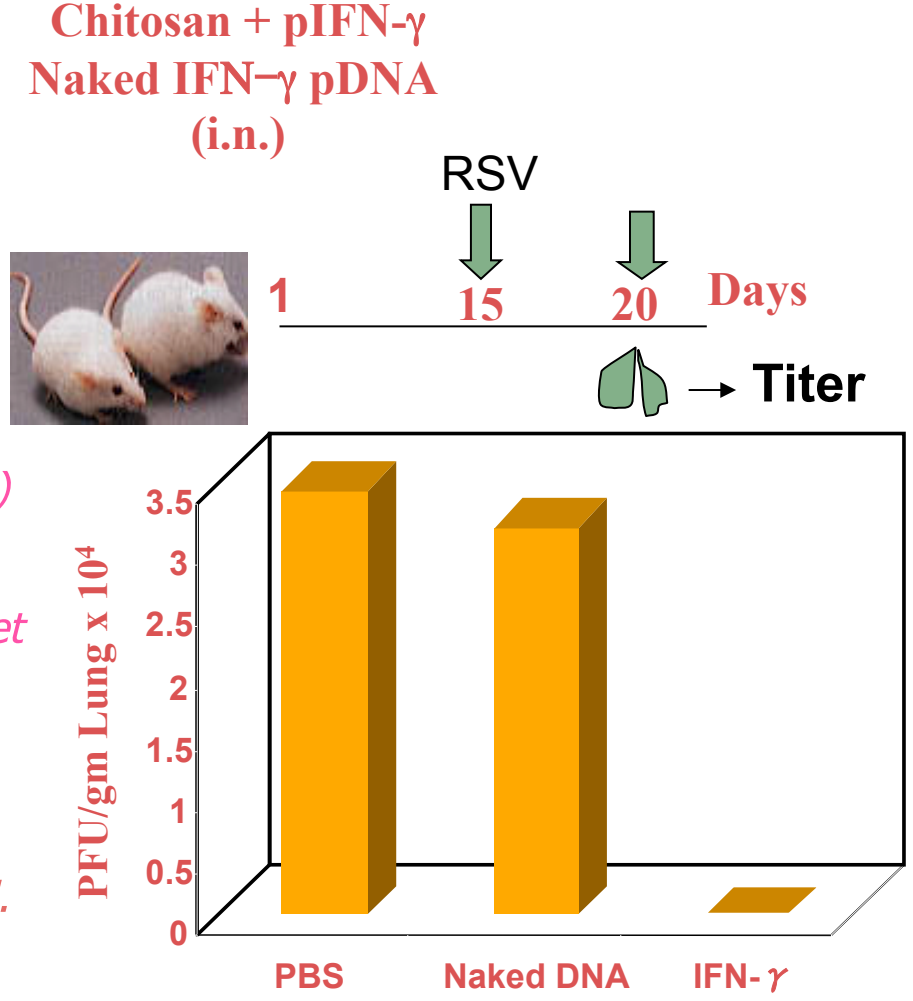




Lee et al Respir Res., 2007

How can NANOTECHNOLOGY help develop novel vaccine for therapies to decrease severity of RSV?

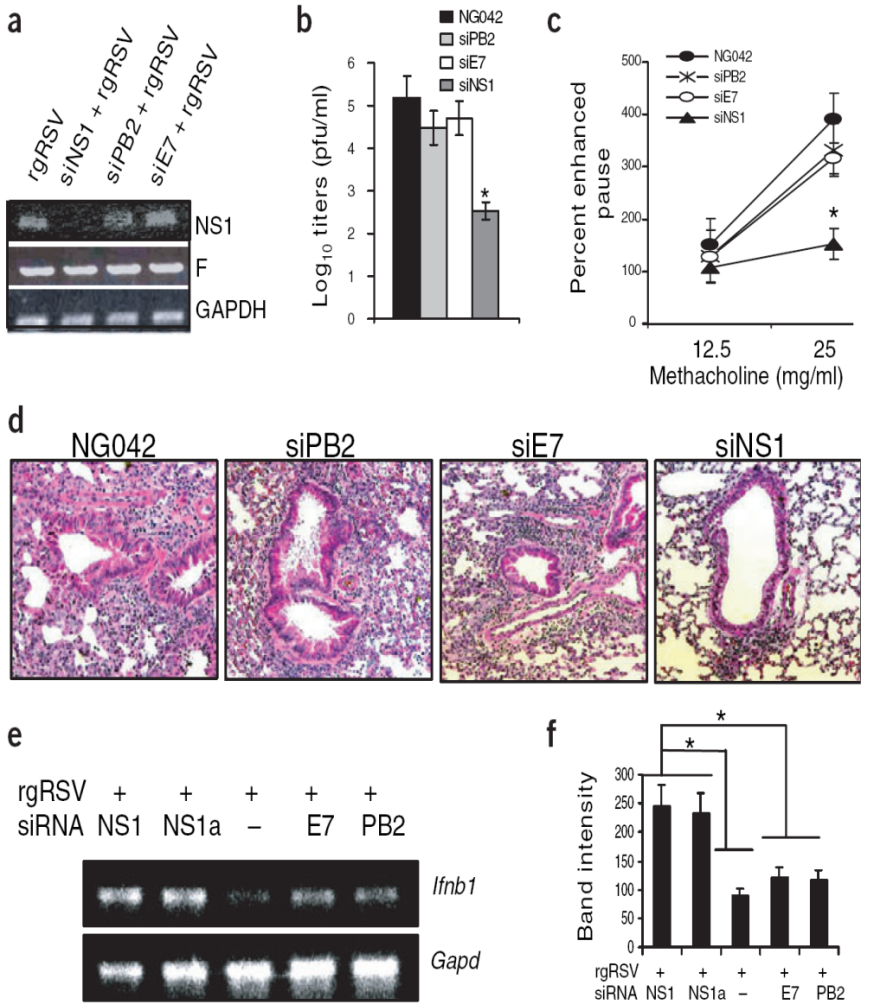
- Vaccines
  - Live-attenuated
  - Subunit
  - **DNA Vaccines** *(Kumar et al. 2002)*
- Prophylactics
  - **IFN-gamma** *(Kumar et al. 2000)*
  - **2-5 OAS** *(Behera et al. 2002)*
  - **si-RNA** *(Zhang et al. 2005, Kong et al 2007)*
- Anti-Inflammatory
  - **LTRAs** *(Behera et al. 1997)*
  - **FP/ Salmeterol** *(Singham et al. 2006)*



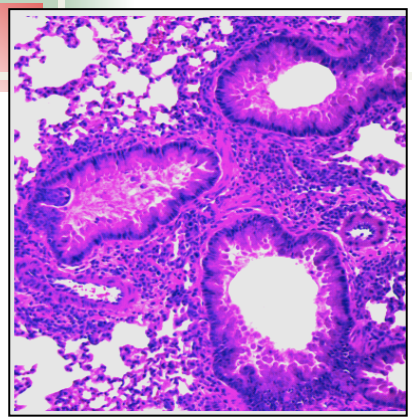
Nanoparticle-complexed siNS1 Exhibits Antiviral Activity In Vivo

Zhang et al, Nature Medicine 2005

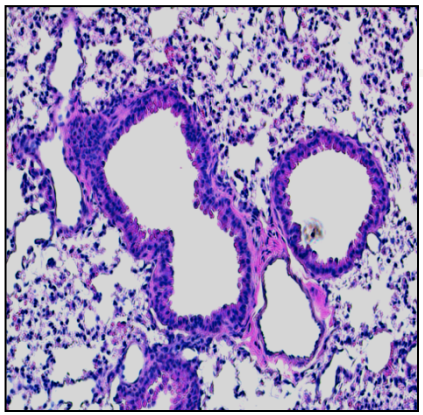
- siNS1 Nanoparticles
  - Reduced RSV replication
- Rx with siNS1 nanoparticles before or after infection with RSV showed
  - decreased virus titers
  - decreased inflammation and AHR.
- human dendritic cells, upon RSV infection, produced
  - elevated type-1 IFN and
  - induced differentiation of naive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



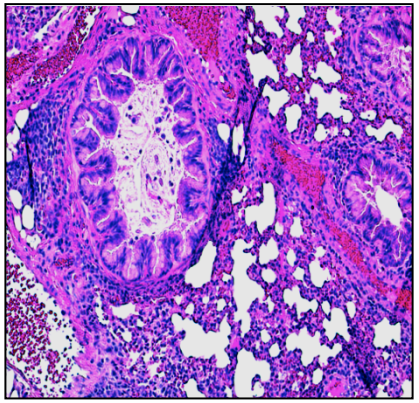
NPRA Signaling: A New Target for anti-inflammatory Target



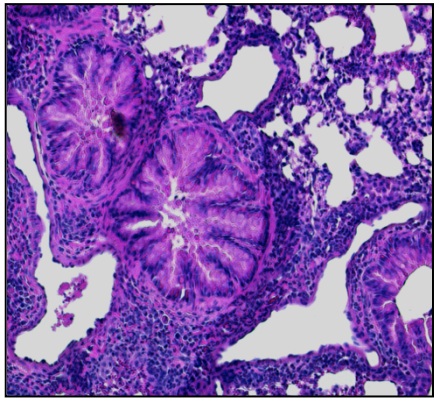
WT (+/+)



NPRA -/-



WT (+/+)

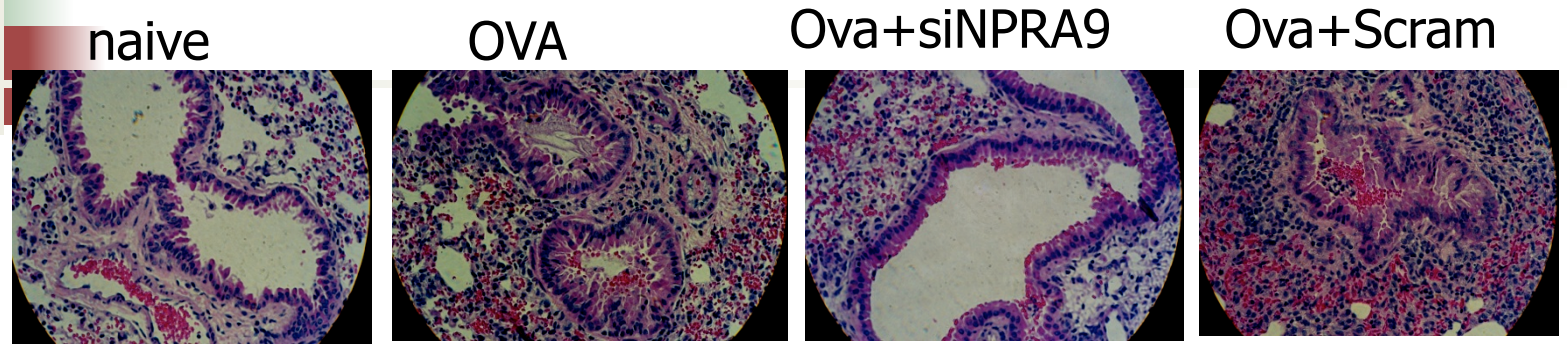


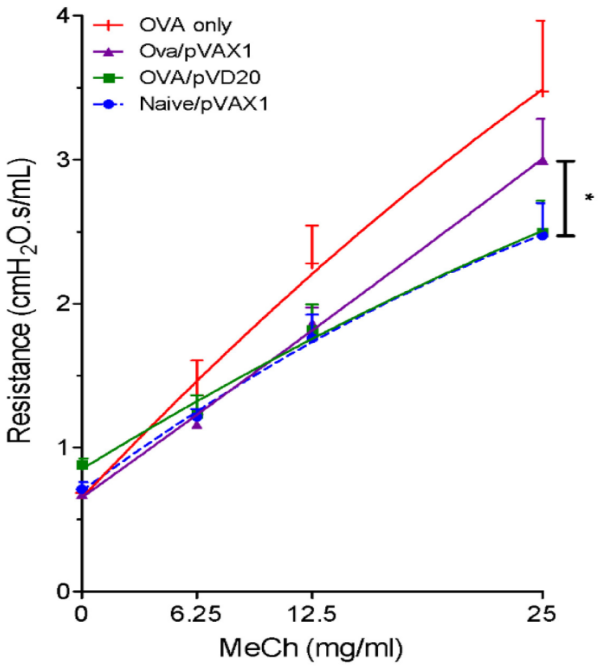
NPRC -/-

- DNAs:
  - pNPRAi (pNP73102)
  - siNPRA/psiNPRA
- Peptide:
  - KP73-102
  - VD
  - Anantin
- Small molecule:
  - Isatin
  - Isatin-derivatives

Wang et al Mol Cancer. 2011;Zhang et al. GVT. 2011; Kandasamy et al Int Immunopharmacol. 2010; Wang et al Respir Res. 2009; Wang et al GVT. 2008; Kong et al Cancer Res. 2008; Mohapatra SS. Can J Physiol Pharmacol. 2007; Mohapatra SS et al J A C I. 2004;

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.

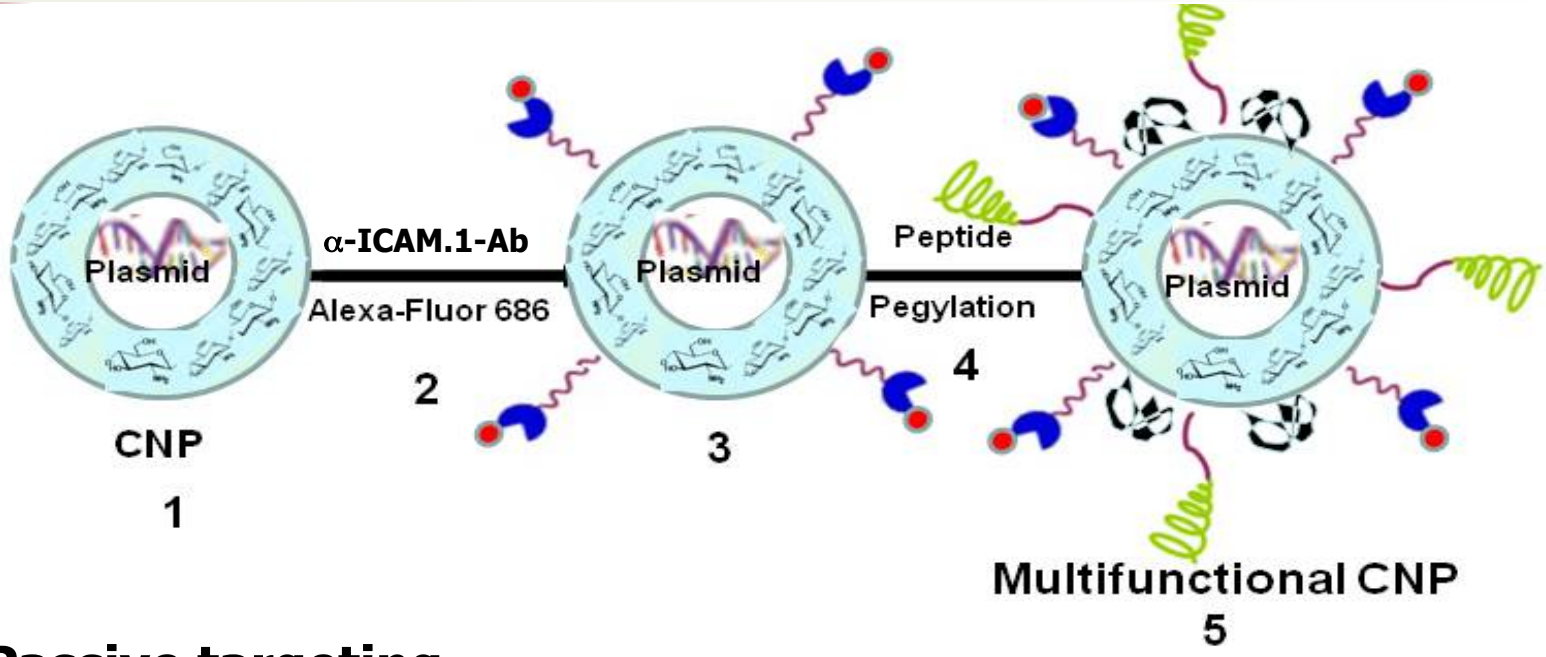
✓ Nano-siNPRA Cream modulates eosinophilia and Inflammation in Asthma (Wang et al GVT 2008)

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

Kandasamy et al Int Immunopharmacol. 2010; Wang et al Respir Res. 2009; Wang et al GVT. 2008

A new approach to delivering drugs to the deep lung

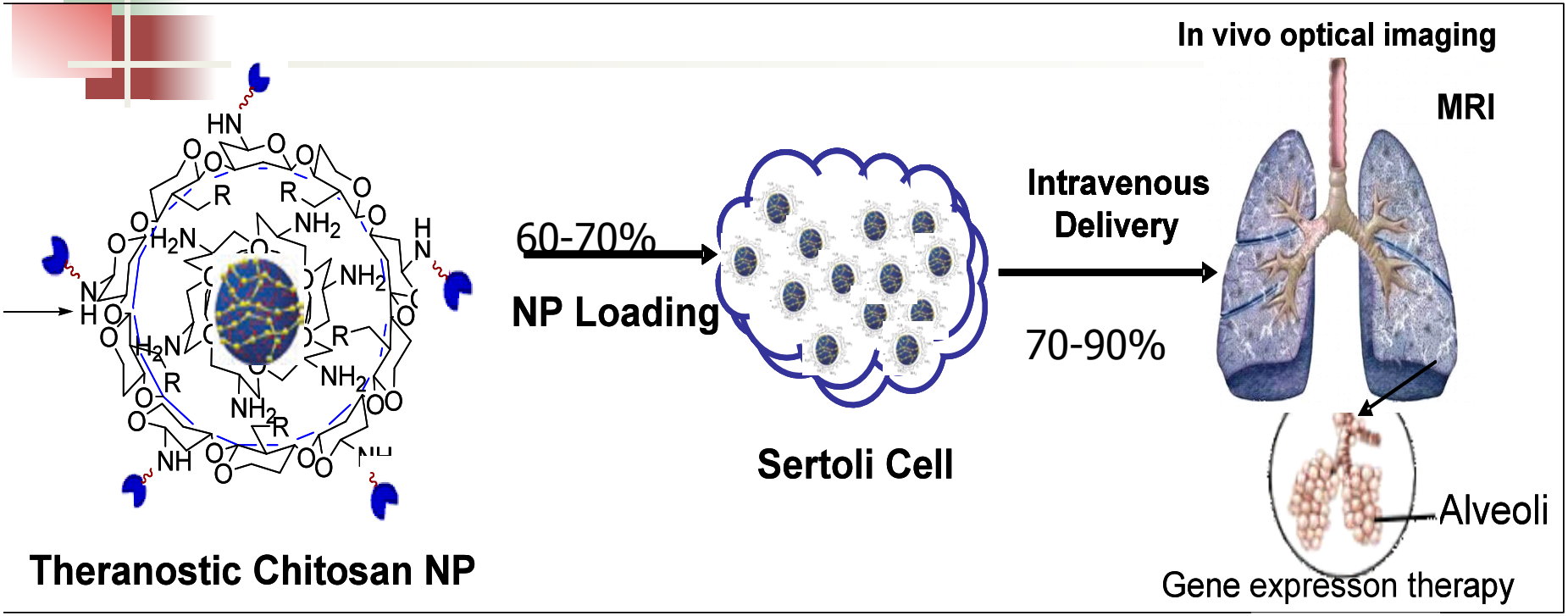
Multifunctional Chitosan Nanoparticles



- **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

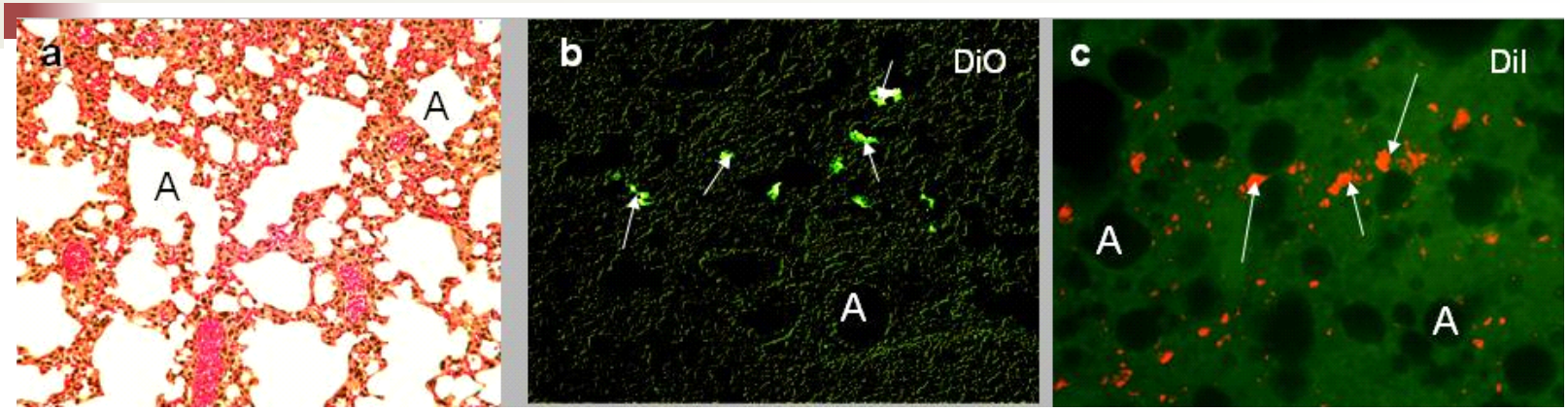
Schematic of "Nano-Cell" strategy: Development of polymer theranostics for lung

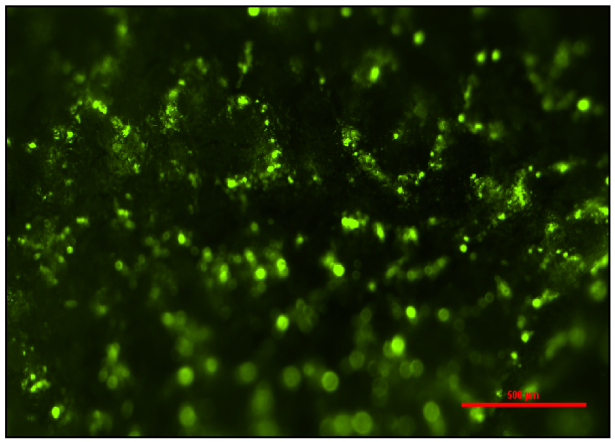
Mohapatra et al, Technol & Innov, 2011

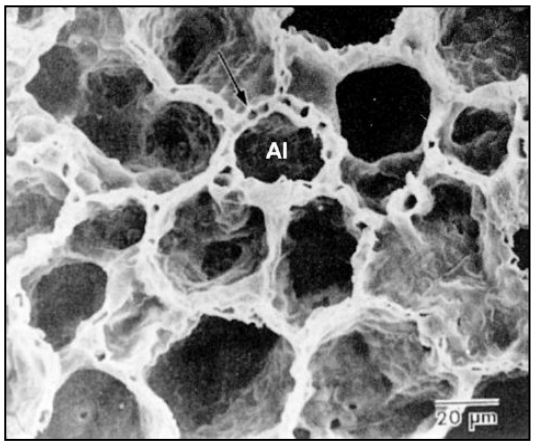


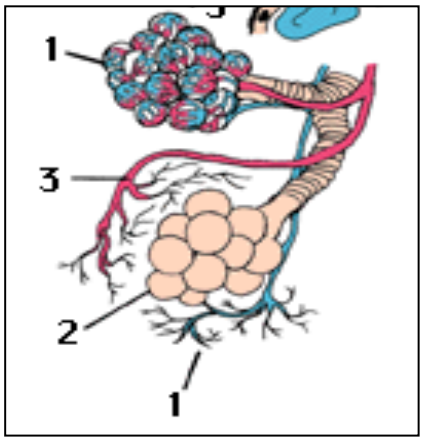
1) avoid immune rejection: Inhibit cell-mediated immunity, target cell apoptosis and complement-mediated cell lysis
2) provide for the immunoprotection of allo- and xenogeneic cell transplants,
3) SCs (30-50 μm) appear to become entrapped in the pre-capillary vascular bed of the lung, where the lysed 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





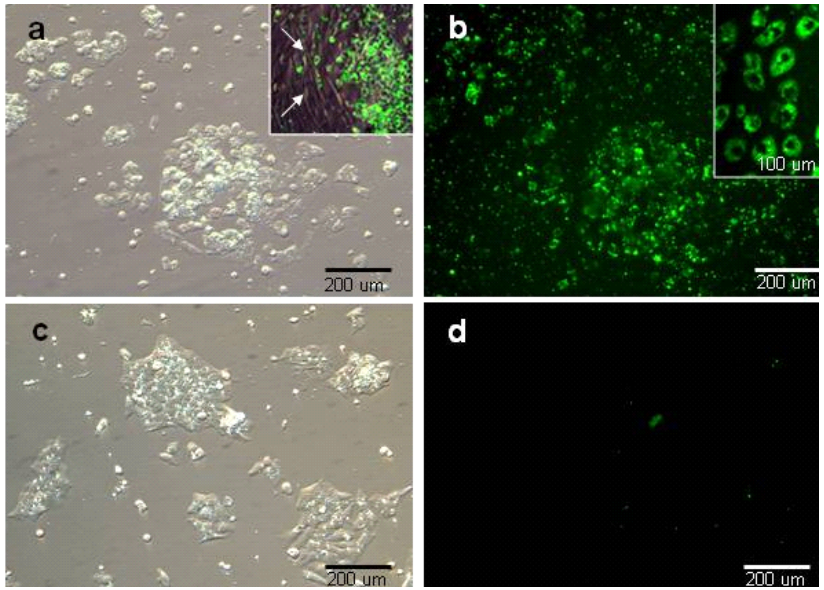




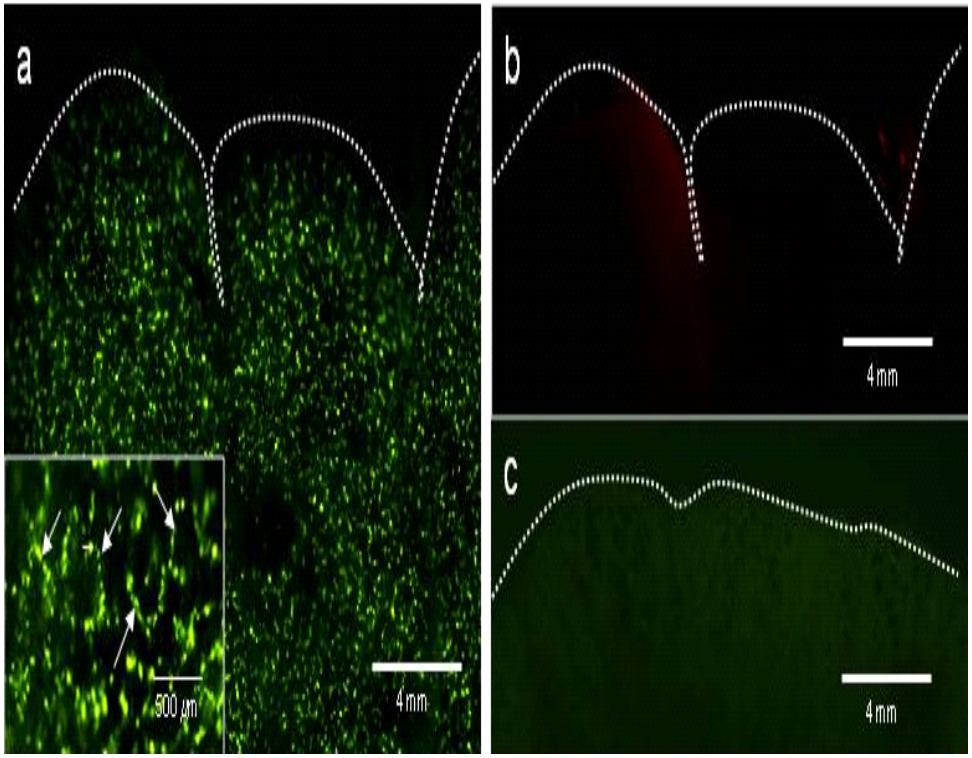
Kumar A. et al. Cell Transplant. 2011

SCs take up nanoparticles and they are seen mouse lung 15 minutes post-injection

In Vitro

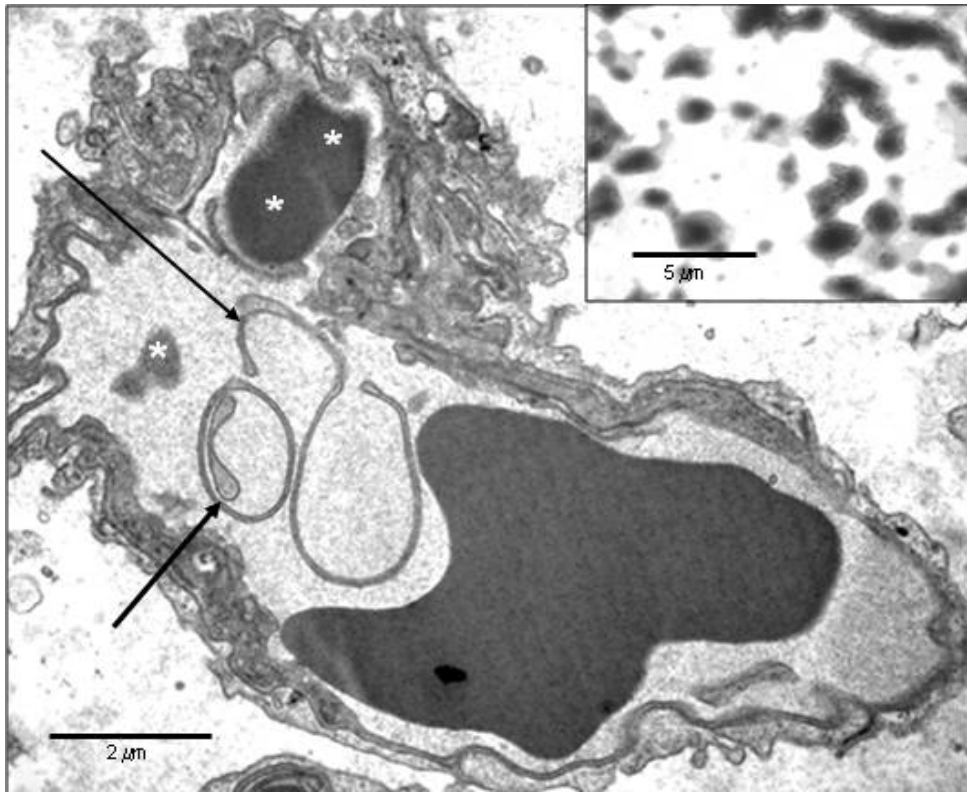


In Vivo



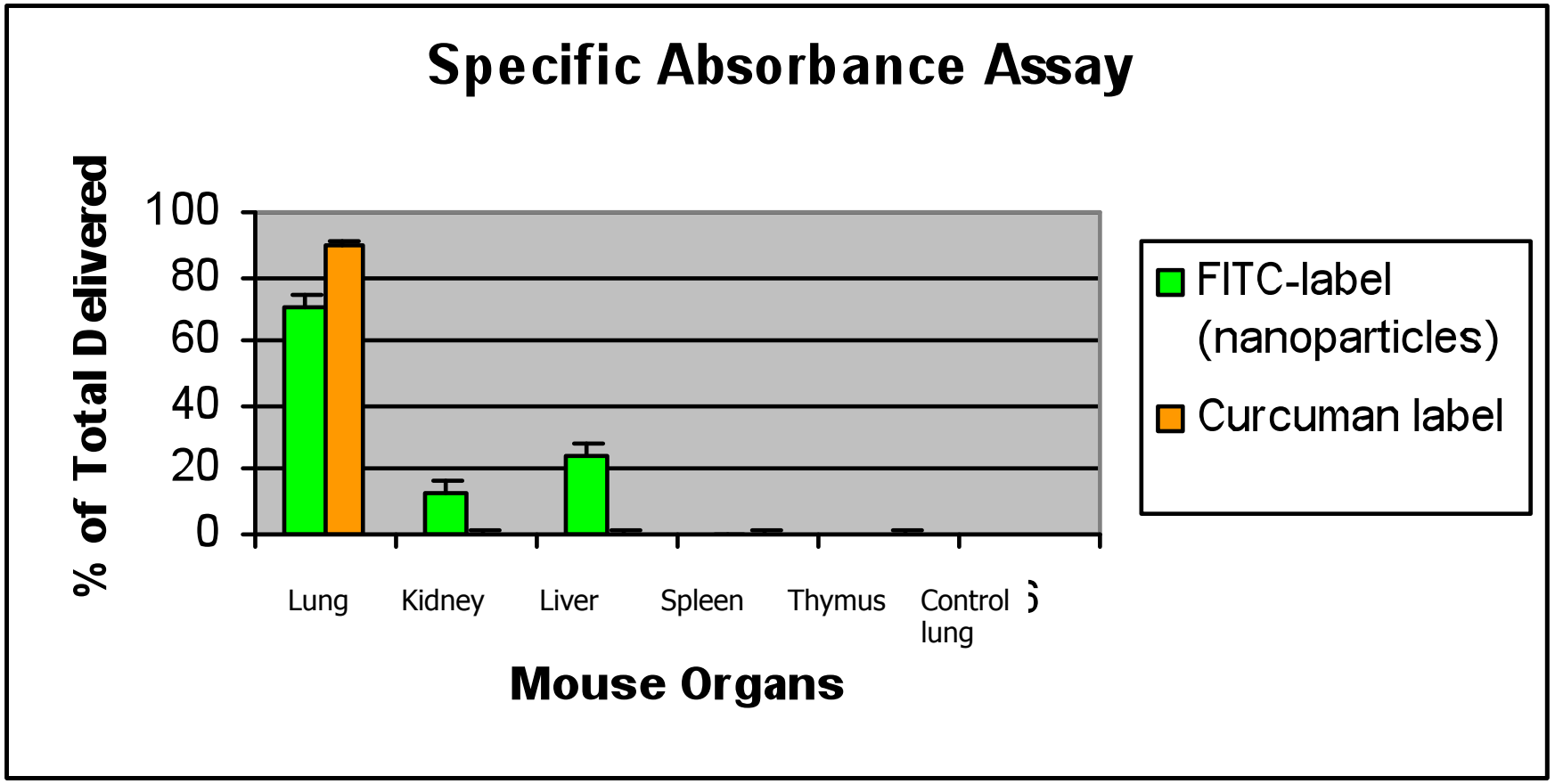
Kumar A. et al. Cell Transplant. 2011

Electron micrograph of mouse lung 1 hr after injection of pre-loaded, pre-labeled rat Sertoli cells



Kumar A. et al. Cell Transplant. 2011

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

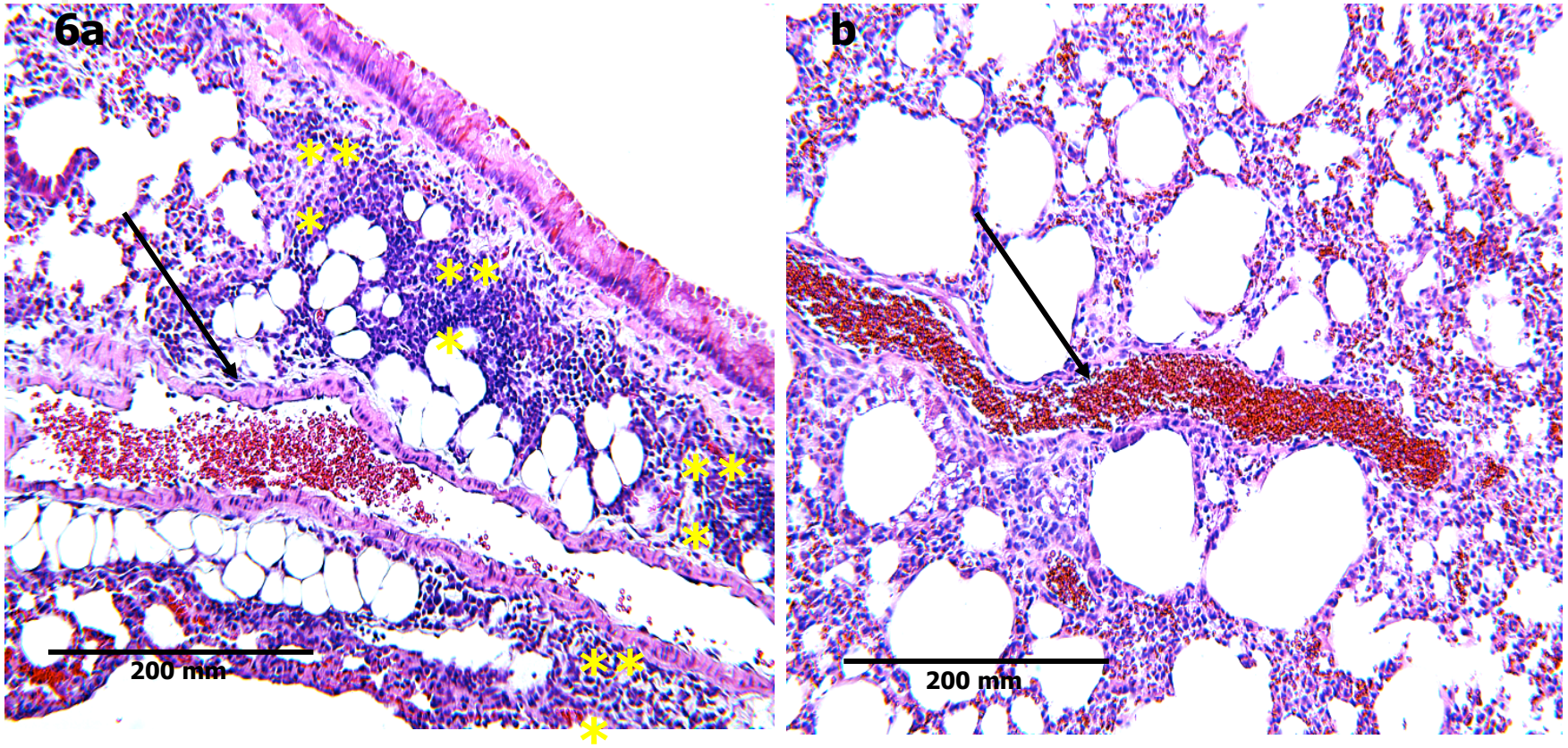


Kumar A. et al. Cell Transplant. 2011

Histology of Lung Sections of Control and Mice treated with SNAP

Asthma

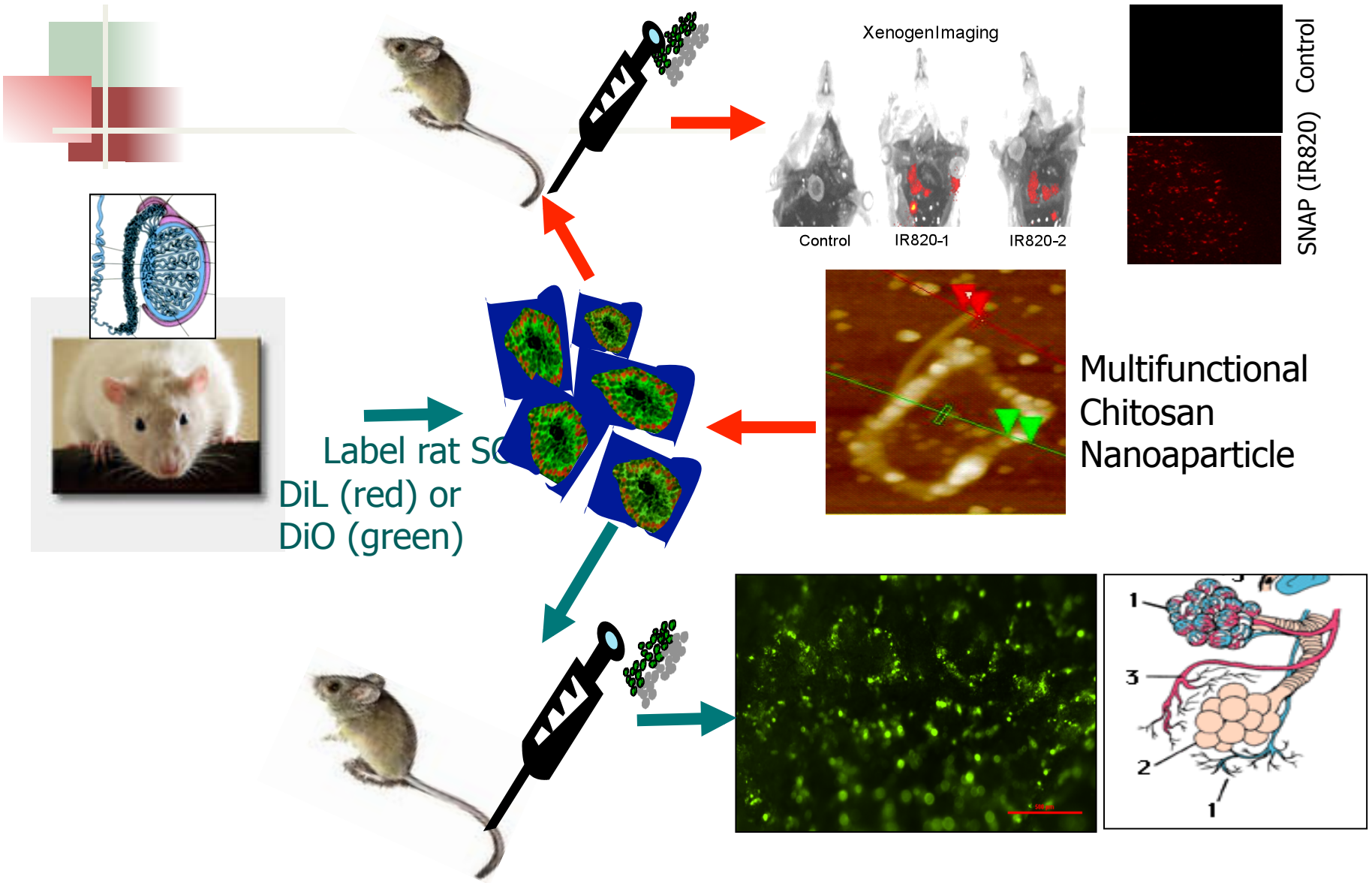
Control



Ova-Induced Asthmatic Mouse

Kumar A. et al. Cell Transplant. 2011

SNAP THERANOSTICS: THE CONCEPT



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.**