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Strategies for Nasal and Pulmonary Delivery of Proteins and Viral Vaccines

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Outline

- **Pulmonary and Nasal Delivery**
  - Anatomy of Nose and Lung
  - Delivery Losses
  - Uptake Limitations

- **Strategies**
  - Particle Engineering
  - Penetration Enhancers and Transporters
  - Active Transport

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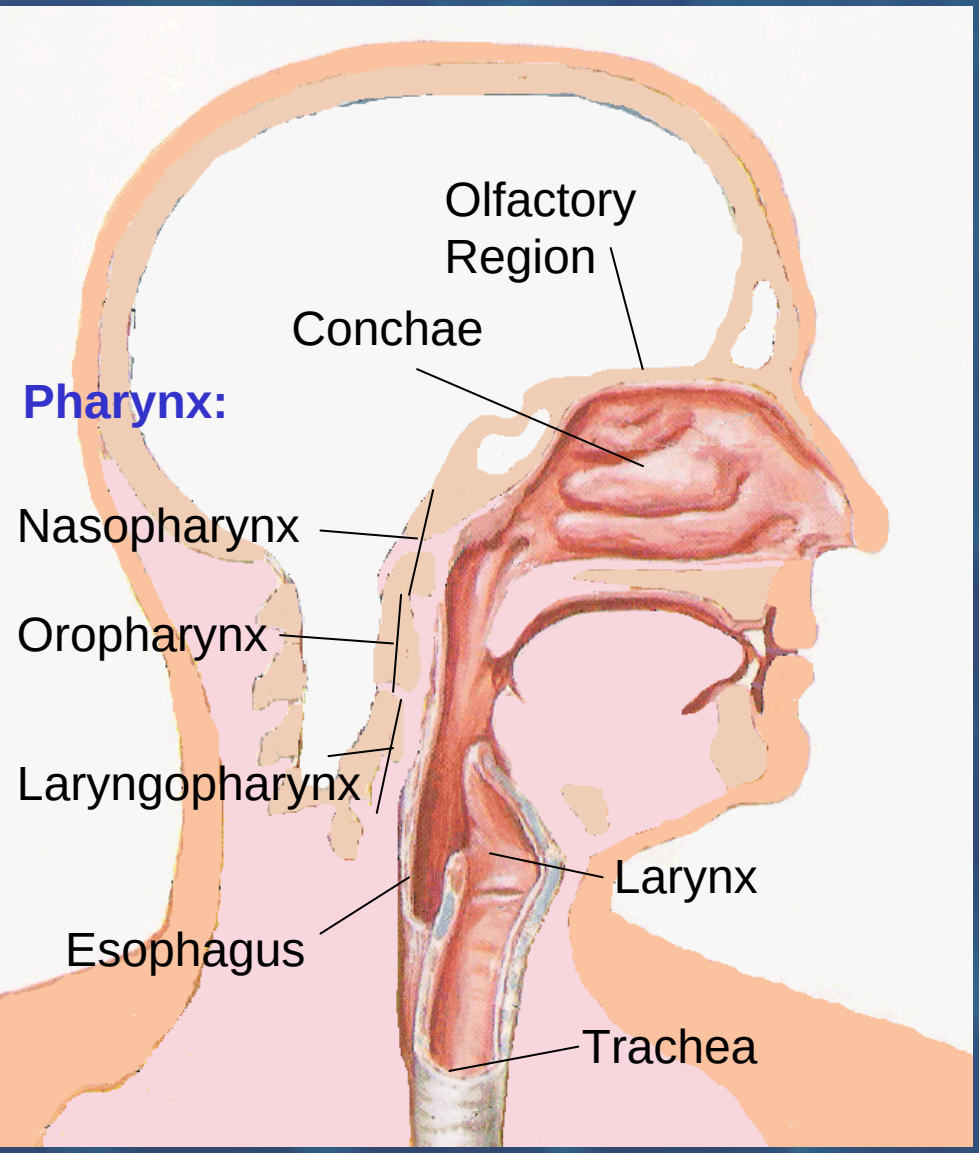
Anatomy of the Nose



- **Warms, humidifies and filters air**
  - Captures > 50 % of particles with an aerodynamic diameter d_a > 3 µm
  - Captures > 90 % of particles with d_a > 10 µm
- **Surface area: 150 cm²**
- **Volume: 15 cm³**

Aerodynamic Diameter

$$d_a = \sqrt{\rho_p} d_g$$

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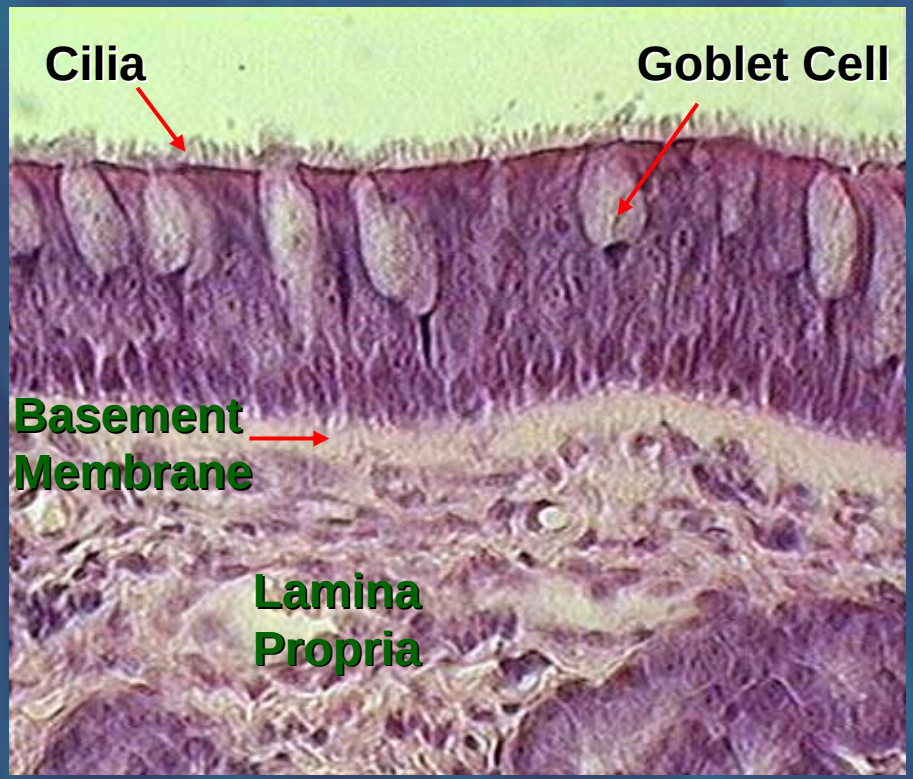
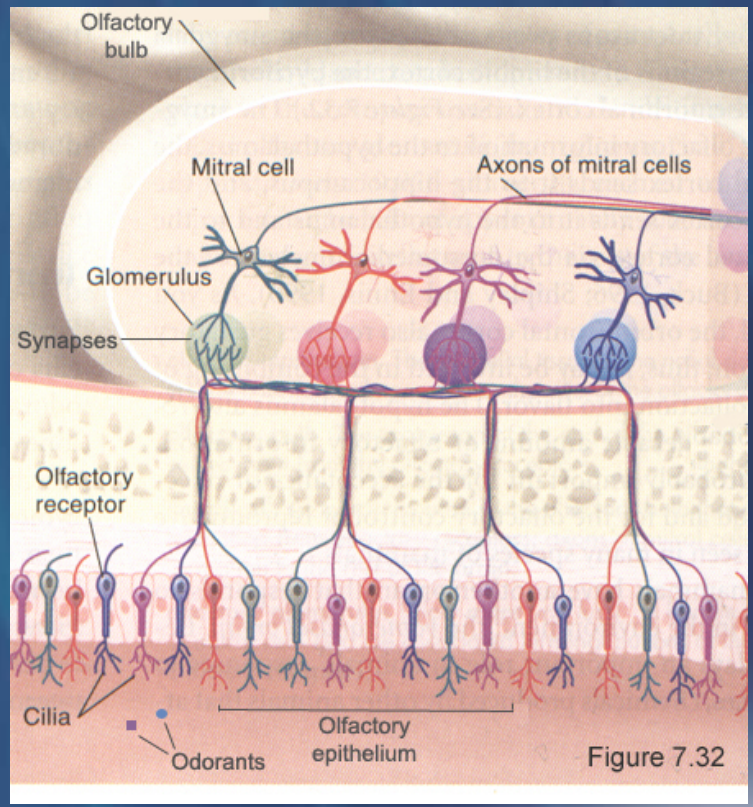
Nose Ultrastructure

- Cilia and mucus transport particles to the pharnyx.
- Mucociliary clearance takes 15 – 20 min.

3 – 5 % of total nasal surface



Columnar ciliated epithelium



Olfactory Region

casweb.cas.ou.edu/pbell/Histology/Captions/Respiratory/106.nasal.epithel.40x.html
www.colorado.edu/epob/epob3730rlynch/image/figure8-18.jpg

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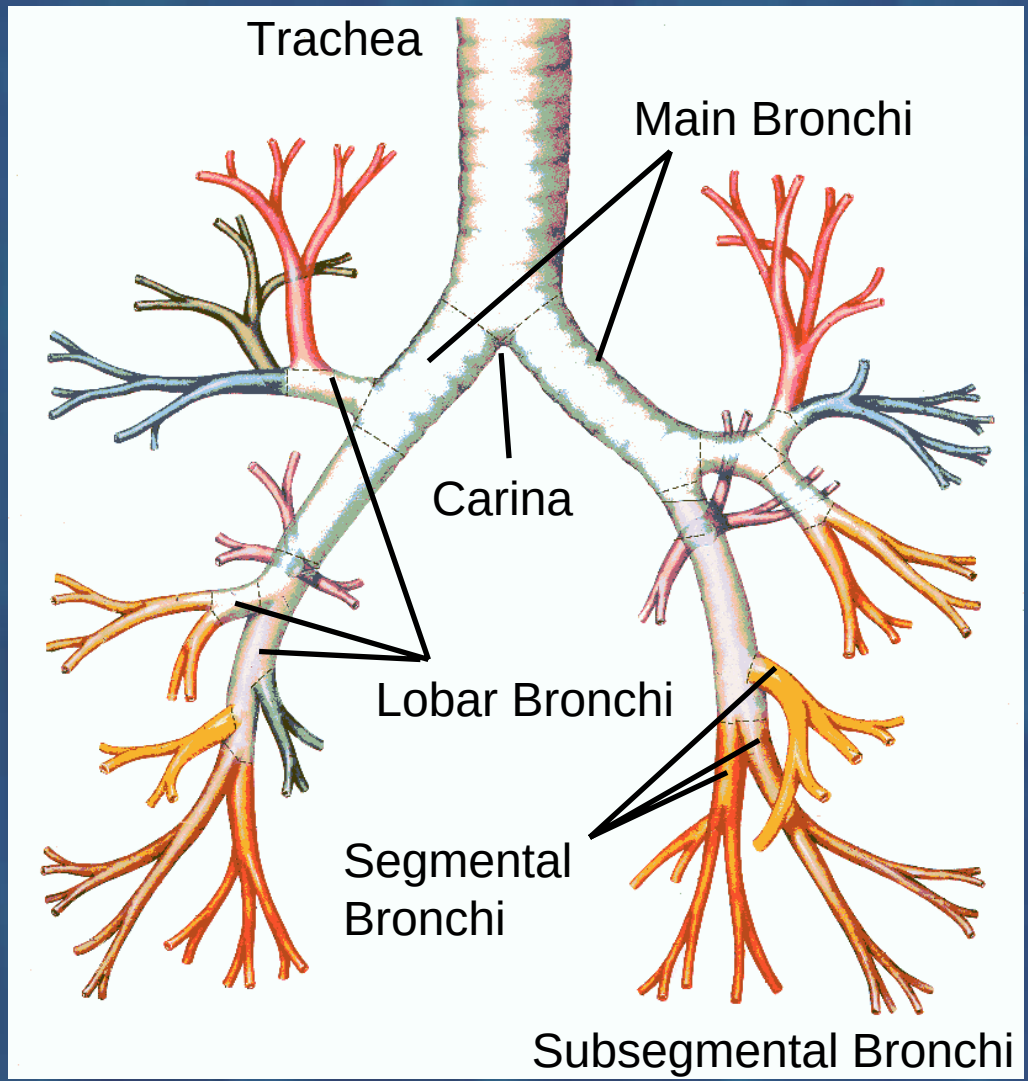
Lung - Conducting Airways



- **Conducting Zone**
  - Consists of Trachea, Bronchi, Bronchioles, Terminal Bronchioles
  - Ciliated
  - Surface area: 3500 cm^2
  - Volume 175 cm^3

Adapted from: F.H. Netter, Respiratory System, Ciba Geigy, 1992

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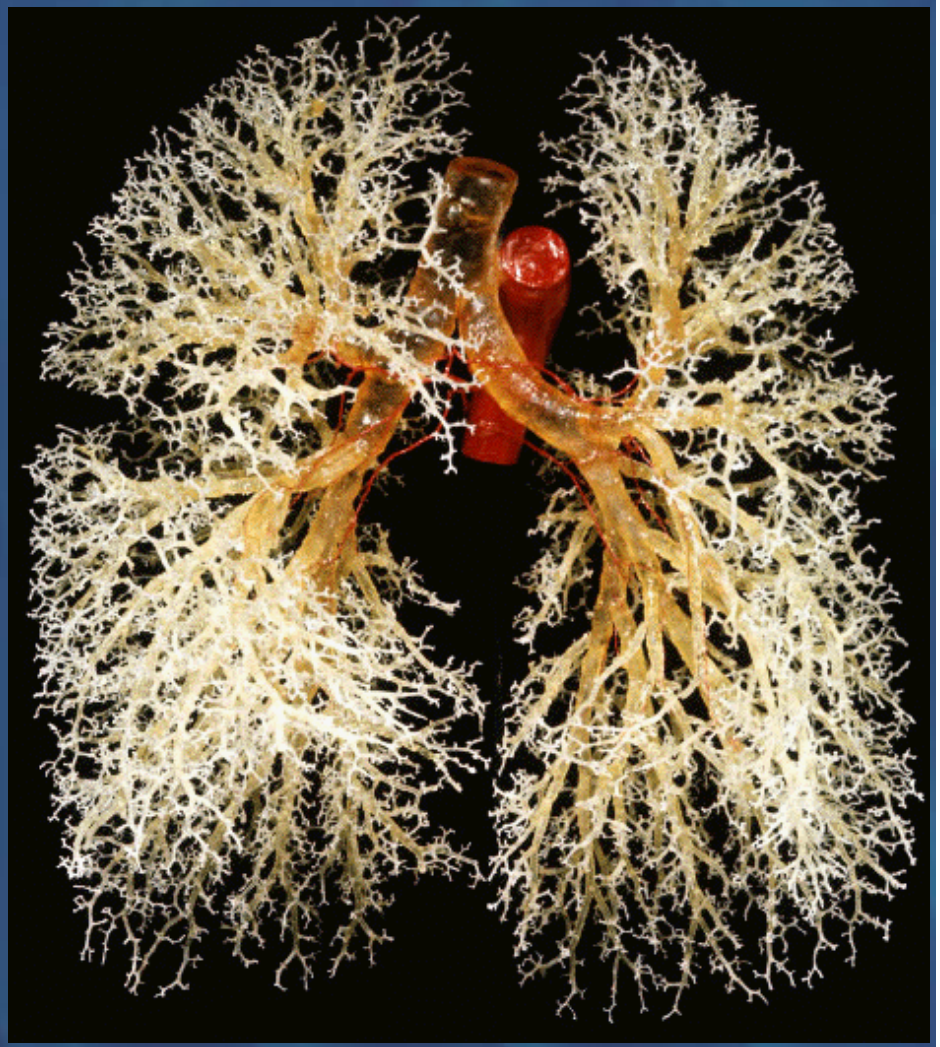
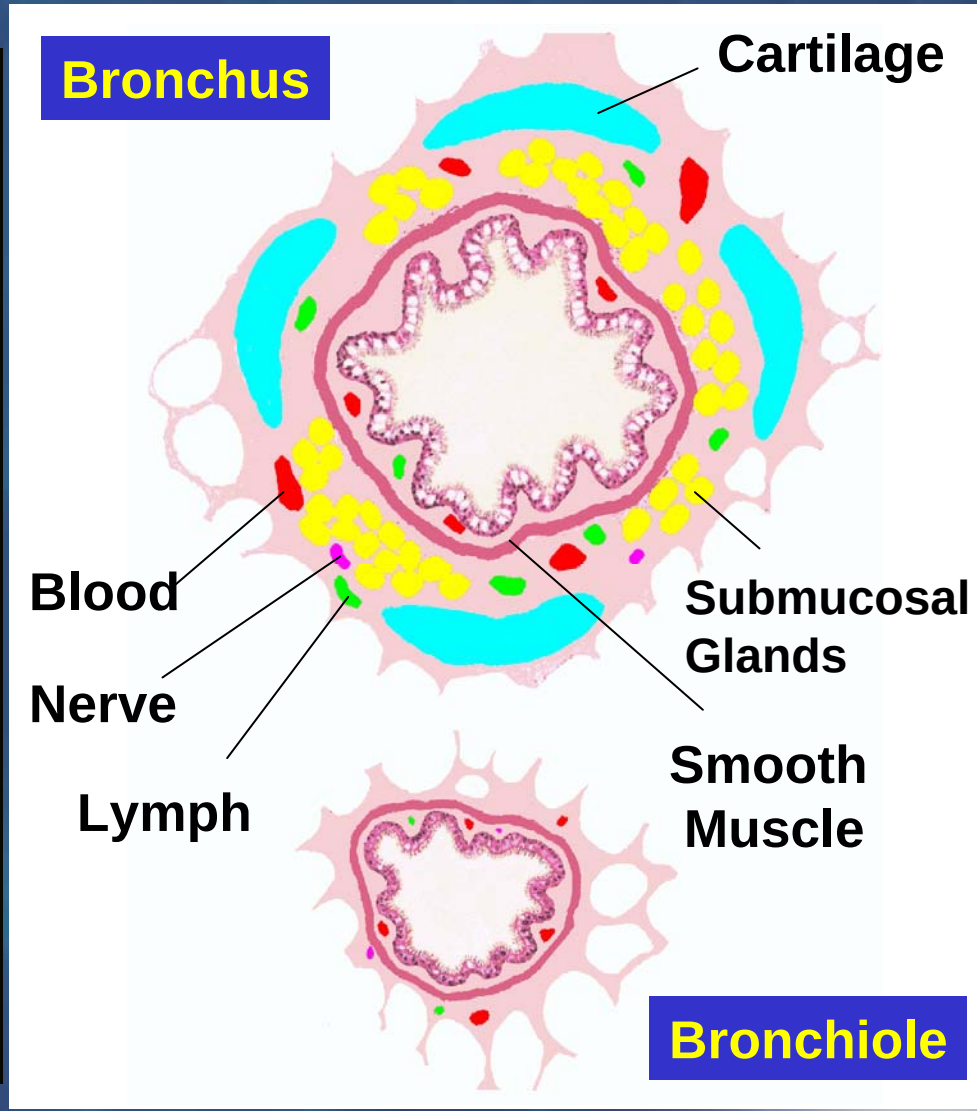
Conducting Airways





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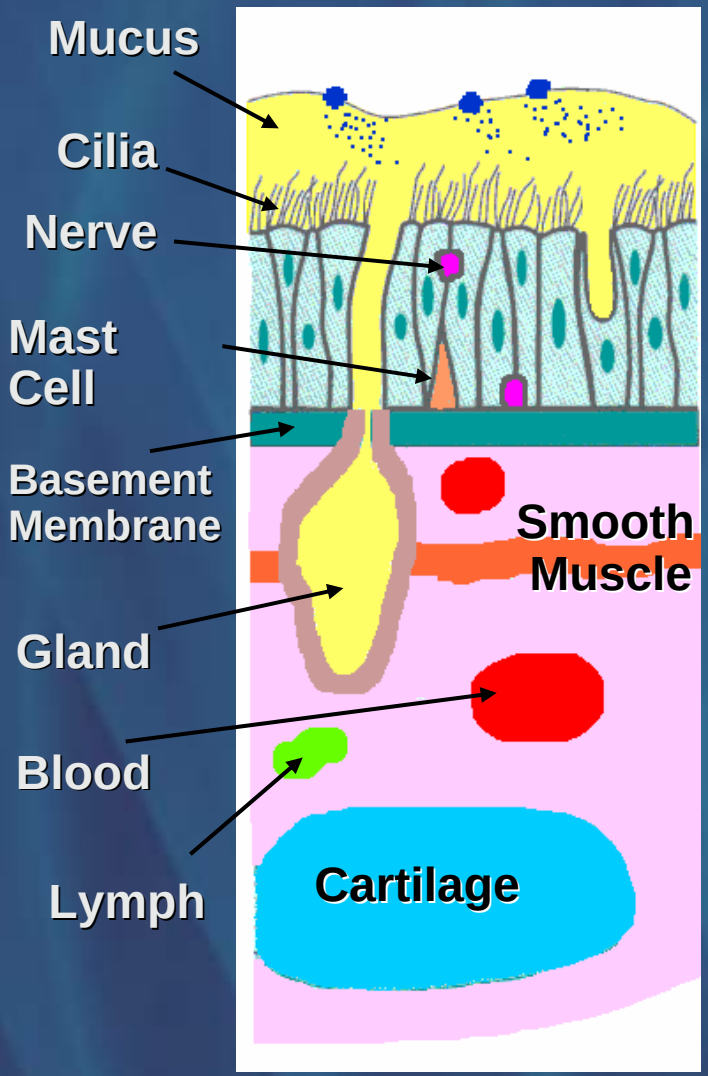
Ultrastructure of the Conducting Airways



- Diffusion through mucus layer competes with mucociliary clearance
- Transport can be paracellular, transcellular or receptor mediated
- Larger distances favor small molecules
- Bioavaliability depends on location of local target

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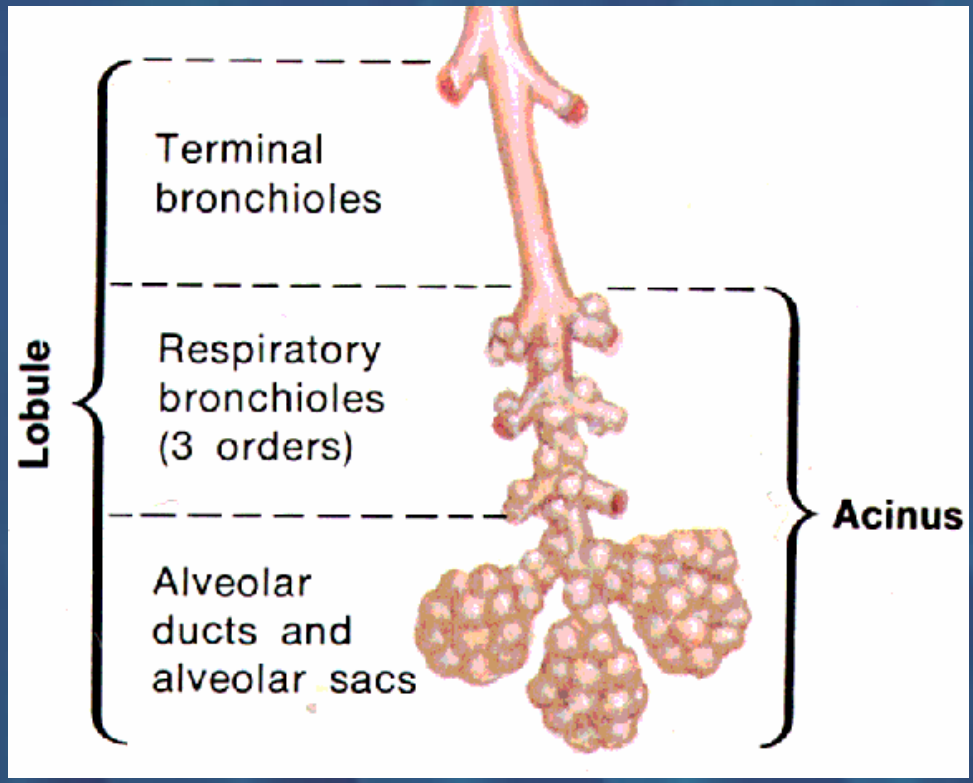
Lung - Respiratory Zone



- Respiratory Bronchioles, Alveolar Ducts, Alveoli (300 million)
- Volume: 5,000 cm^3, Surface Area: 100 m^2
- The entire blood volume of the body passes through the lungs each minute
- Fast, IV-like absorption kinetics

Adapted from: F.H. Netter, Respiratory System, Ciba Geigy, 1992

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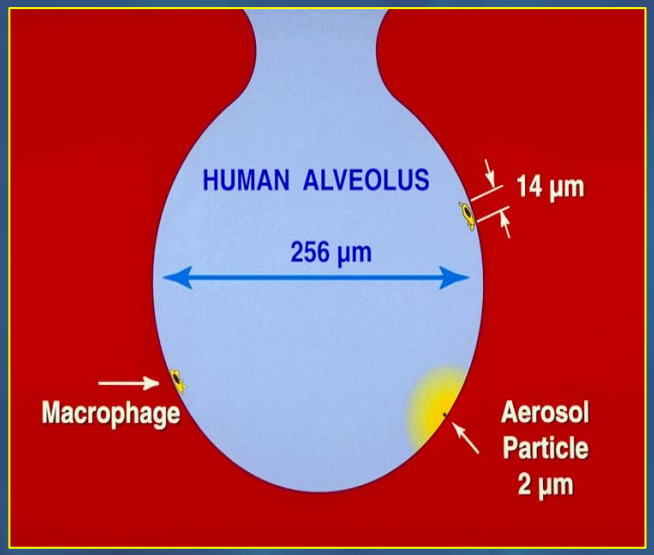
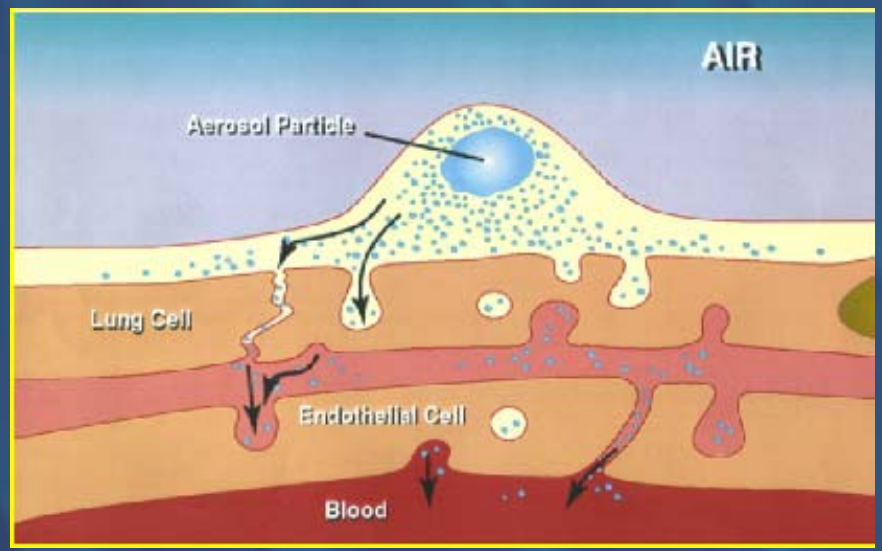
Ultrastructure and Pharmacology of the Respiratory Zone



A typical aerosol dose (1 – 50 mg) deposits only a few particles per alveolus into the lining fluid of a thin alveolar wall (200 nm)



- **Transport mechanisms**
  - Paracellular
    - Tight junctions – epithelium
    - Loose junctions – endothelium
  - Transcellular
    - Diffusion
    - Transcytosis
    - Receptor mediated
  - Bioavailability depends on molecular weight, solubility, and partition coefficient

Vehring, et al., AAPS 1st Annual Pharmaceutics and Drug Delivery Conference, Arlington, VA, 2002

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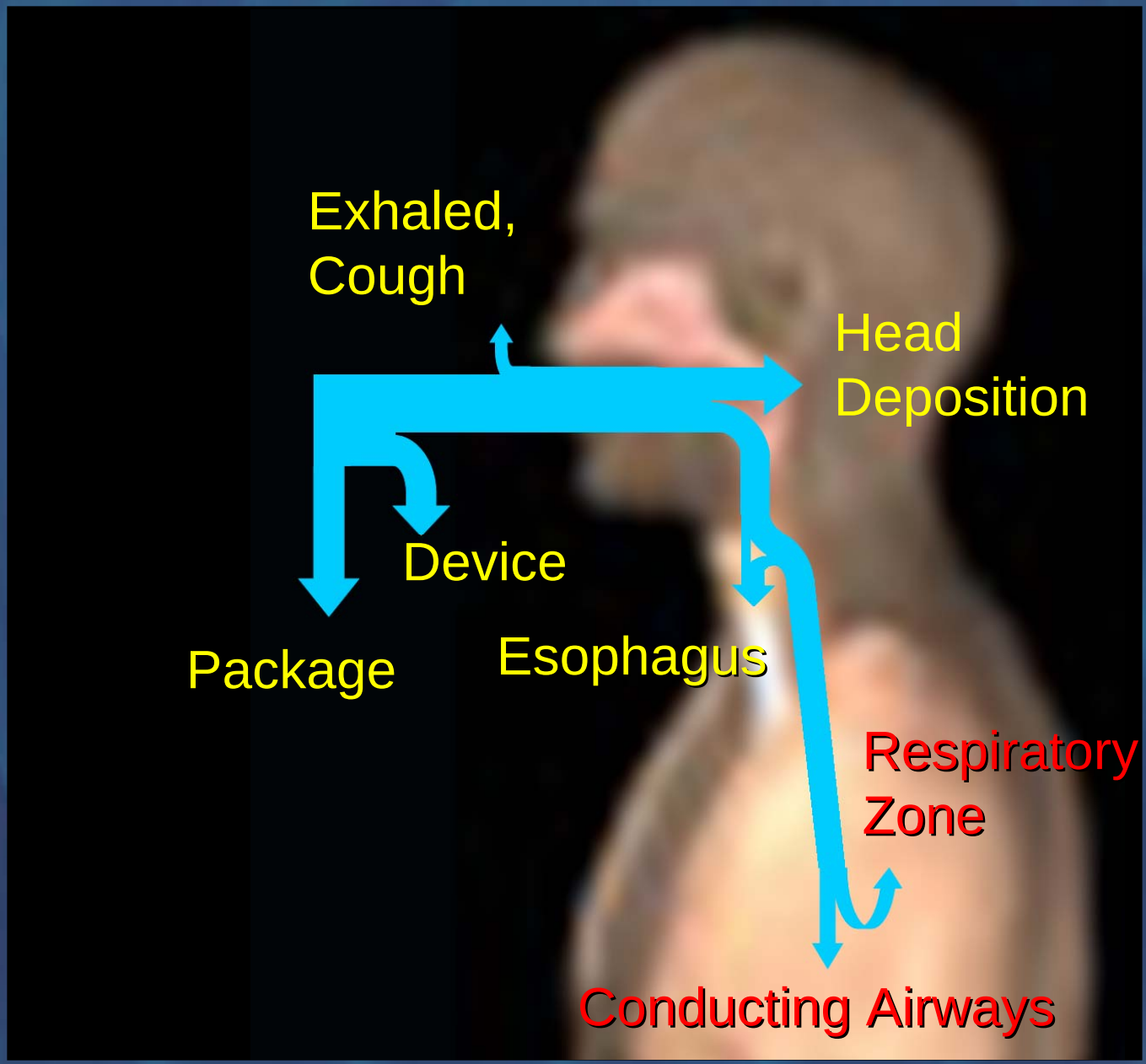
Losses in Pulmonary Delivery



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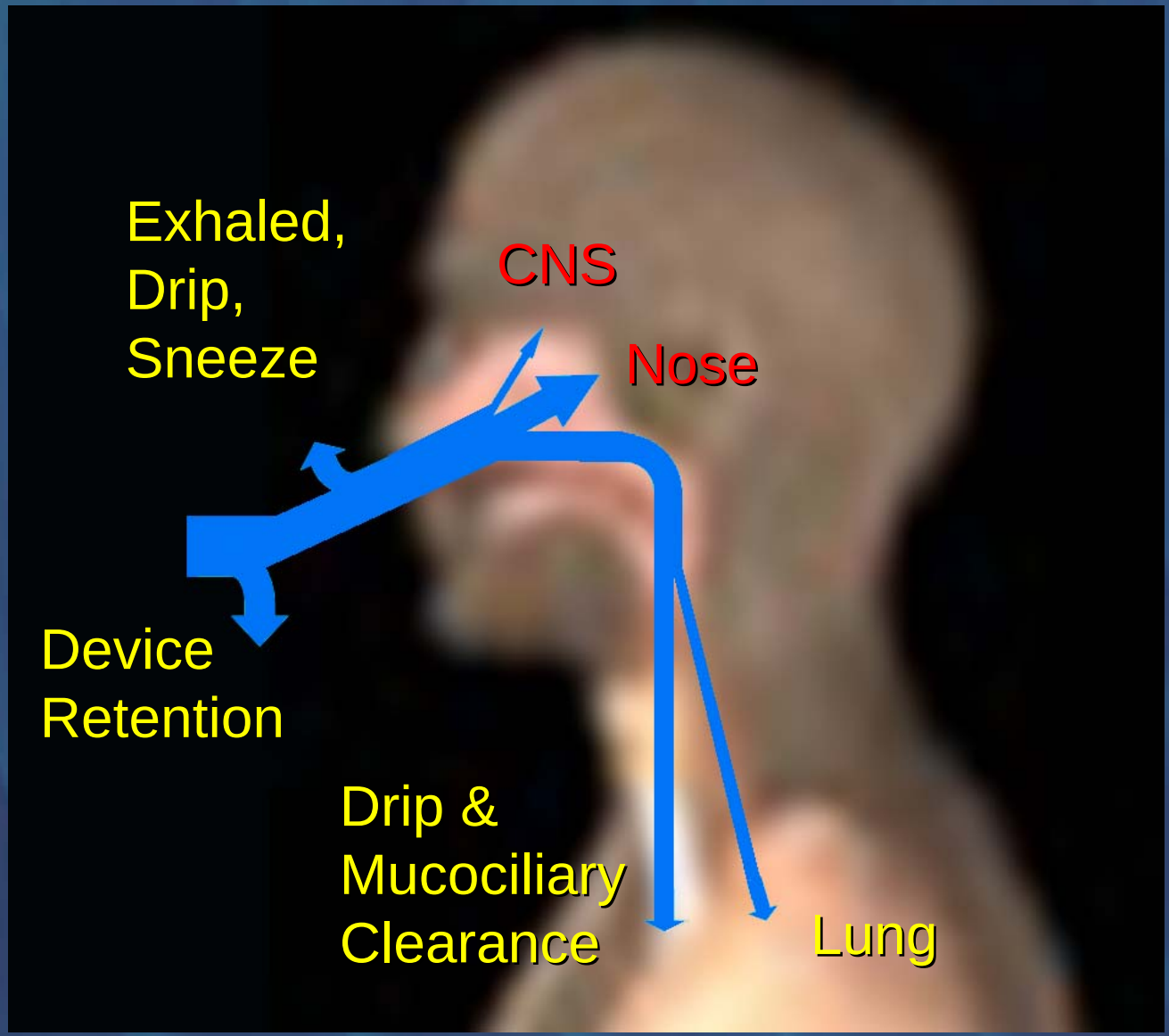
Losses in Nasal Delivery



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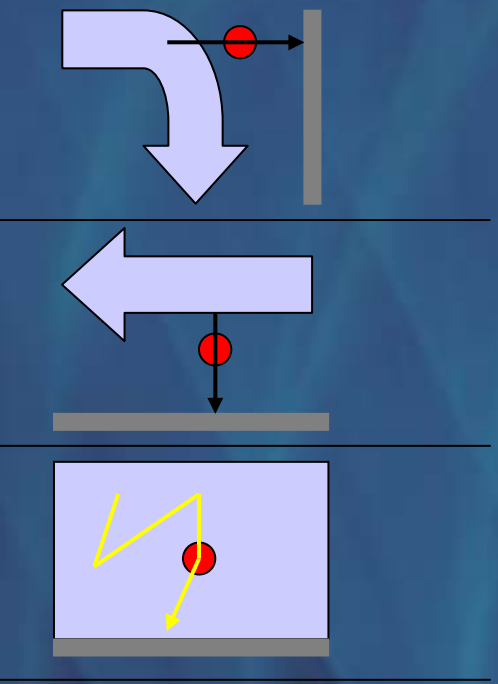
Loss and Deposition Mechanisms



Impaction
Primary mechanism for big particles and upper airways

Sedimentation
More important in small airways. Affected by breath-hold

Diffusion
Main mechanism in the respiratory zone

Factors affecting lung and nose deposition

- Aerodynamic particle / droplet diameter
  (rule of thumb: > 10 μm nasal, < 5 μm pulmonary)
- Inspiratory flow
- Lung / Nose volume
- Aerosol concentration and initial velocity

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Further Defense Mechanisms

- **Mucus / Mucociliary Clearance**
- **Phagocytosis**
- **Cellular Barrier**
  - Tight Junctions
  - Cell Wall
- **Lysosomal Proteases**

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Virus, Proteins, and Peptides in Development for Pulmonary Delivery

Phase I	Phase II	Phase III	Approved
Insulin (Qdose)	Insulin (KOS)	Insulin (Novo Nordisk) Insulin (Alkermes) Insulin (MannKind)	Insulin (Nektar)
Ostabolin-C (Nektar) PTH (Alkermes) PTH (Mannkind) Calcitonin (Mannkind) Leuprolide (Nektar) hGH (Alkermes) CC10 (Claragen) DNA nanoparticles (Copernicus)	α-1-antitrypsin (Arriva) Sinapultide (Discovery Labs)	Lucinactant (Discovery Labs) Interferon-γ (Intermune) Denufosol (Inspire)	Measles Vaccine (WHO) rhDNase (Genentech)

Liquid
Dry powder

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Virus, Proteins, and Peptides for Nasal Delivery

Phase I	Phase II	Phase III	Approved
PTH 1-34 (Nastech)	Bremelanotide (Palatin Tech.)	Influenza LAV (MedImmune)	Calcitonin (Novartis)
Insulin (Nastech)	YY 3-36 (Nastech)		Nafarelin (Pfizer)
Epo-Fc (Syntonix)	Leuprolide (Archimedes)		Desmopressin (ZLB Behring)
RSV / PIV vaccine (MedImmune)	Insulin (Bentley)		Influenza LAV (MedImmune)
Influenza WIV (DelSite)	Influenza subunit (GSK)		

Penetration Enhancer / Active Transport

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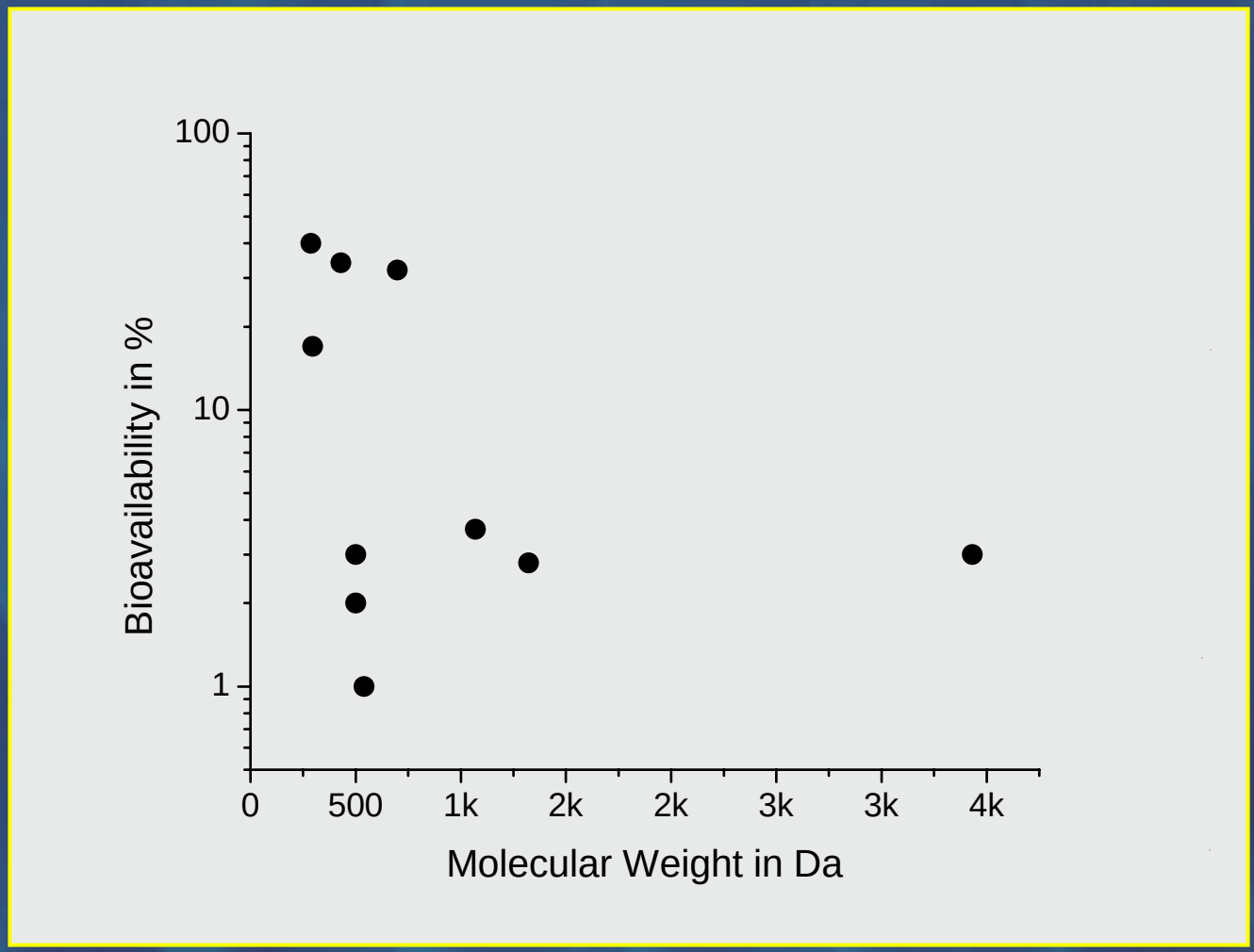
Bioavailability of Nasal Drugs on the Market



- Bioavailability for molecules > 1 kDa is very low
- High Variability

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Delivery Strategies – Particle Engineering

- Low Density Particles
- Prevention of Macrophage Uptake
- Trojan Horses / Nanoparticles

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First Generation Particles - Poor Delivery Efficiency

Typically not more than 10 – 20 % delivered to the lung.
The active was typically milled to achieve the required particle size.
The resulting dense, poorly dispersing particles were blended with carrier particles to facilitate dispersion.

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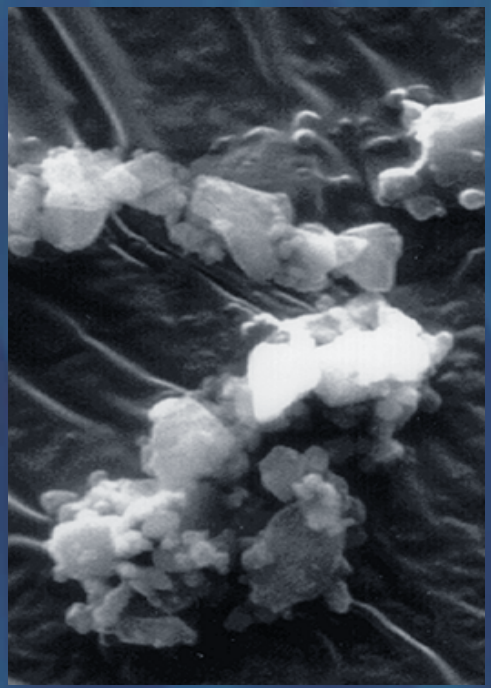
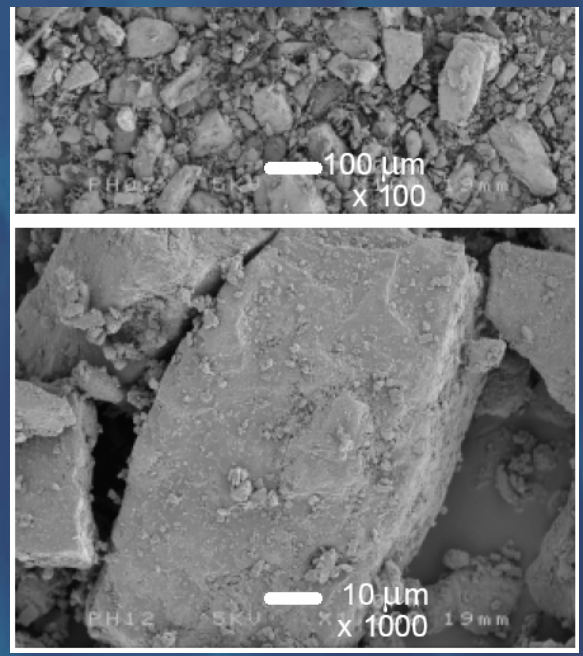


Micronized Budesonide



Lactose Blend

Vehring, et al., AAPS 1st Annual Pharmaceutics and Drug Delivery Conference, Arlington, VA, 2002

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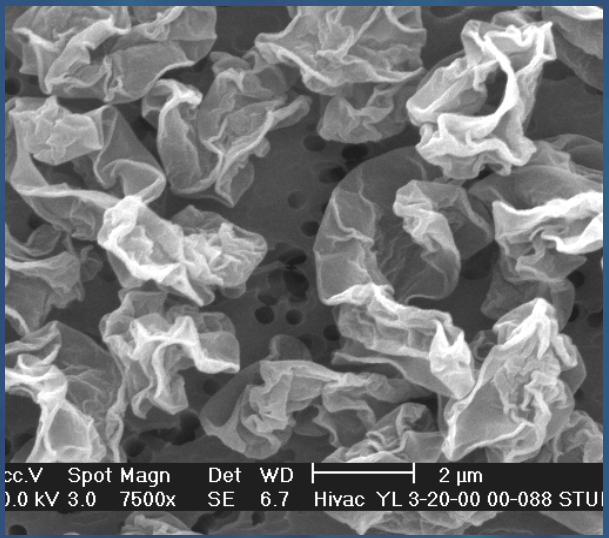
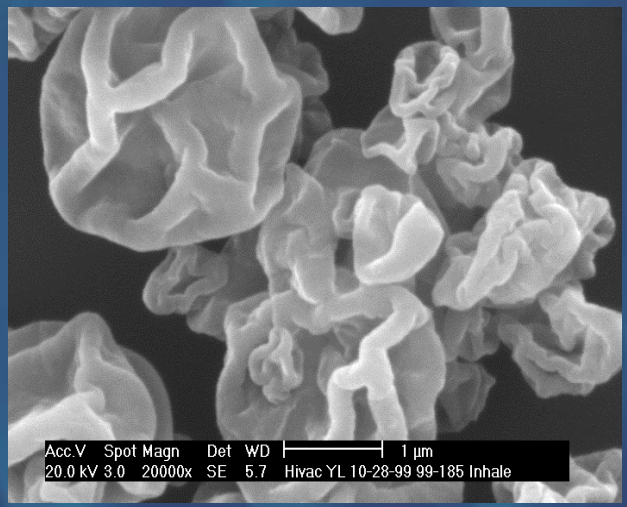
Highly Dispersible, Low Density Particles (Nektar Therapeutics)

Trileucine Shell

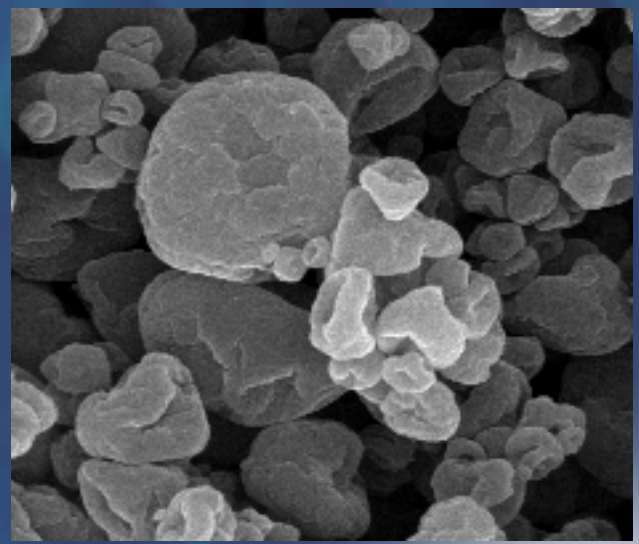


Protein Shell



Structured Microparticles

Crystalline Amino Acid Shell



- **< 5 % device retention**
- **Up to 80 % delivered to lung**

US Pat.: 6,685,967; 6,673,335; 6,589,560; 6,136,346, 6,372,258, 6,518,239

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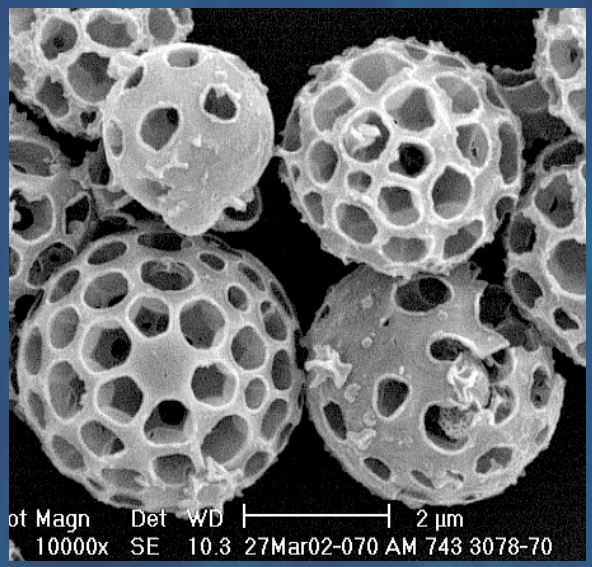
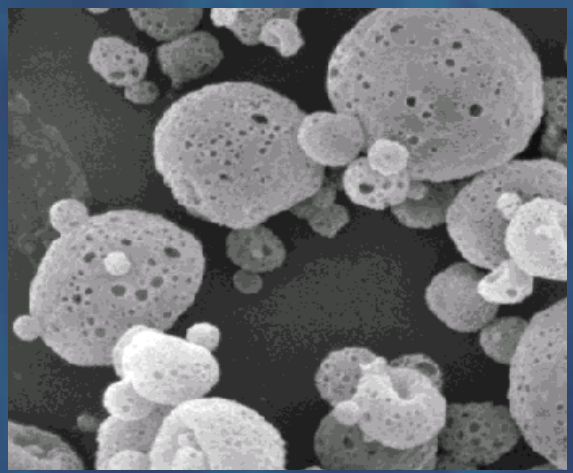
Lipid Based Particles (Nektar Therapeutics)



Small Molecule Formulation



Calcitonin

- Small porous particles provide good dispersibility and facilitate transport to the peripheral lung
- Main excipient is a lung surfactant (DSPC)
- May use blowing agent to lower and control particle density
- High bioavailability -Increased transcellular transport ?

Vehring, R. IBC 4th Annual Conference, Delivery Strategies for Proteins and Peptides, Boston, MA, 2004

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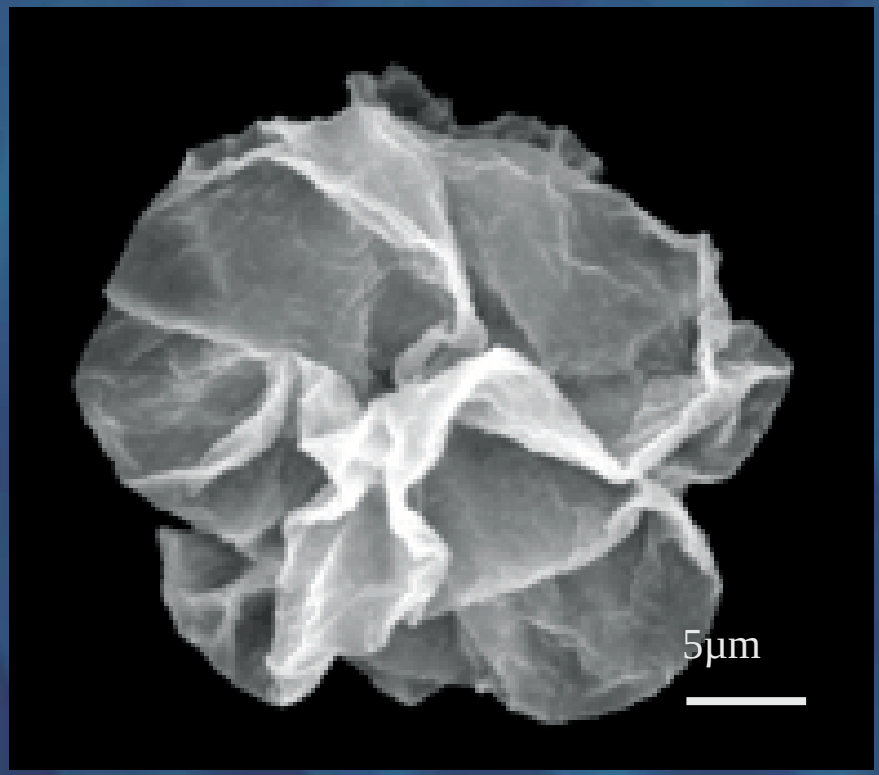
Large Particles Avoid Macrophage Uptake (Alkermes / AIR)



- d_p = 5-30 µm
- d_a = 1-5 µm

- Large particles with small aerodynamic diameter
- Low solubility
- Macrophages cannot internalize particles that are larger than ~ 15 µm

Edwards et al. **Large porous particles for pulmonary drug delivery.** *Science* 1997, **276**:1868-1871.

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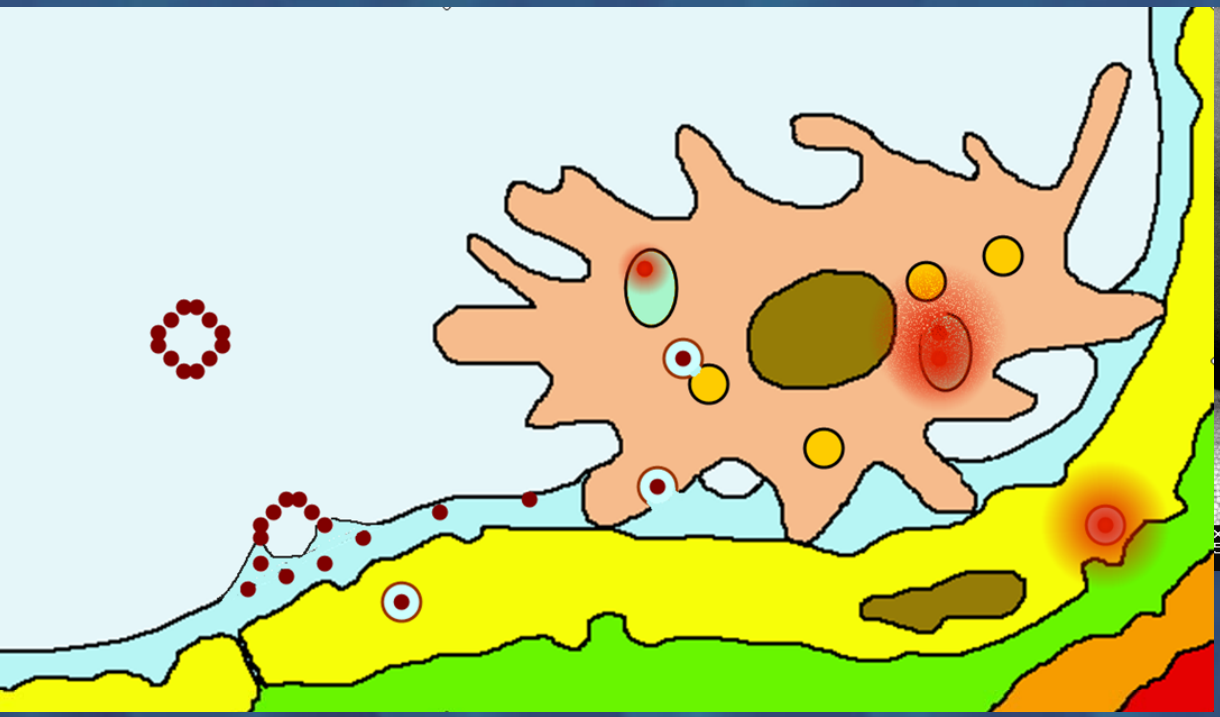
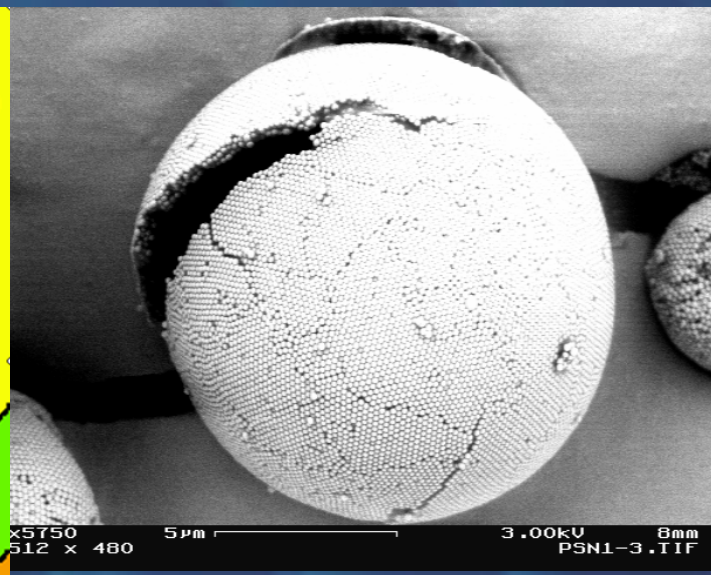
Trojan Horses and Composite Particles





Microparticle
composed of nanoparticles

- Macrophage targeting (tuberculosis)
- Controlled release

http://people.deas.harvard.edu/~ntsapis/AIR.html
N. Tsapis et al. PNAS **99**, 12001, 2002

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Delivery Strategies – Penetration Enhancers

- **Tight Junction Modulators**
  - Irreversible (toxicity concerns)
  - Reversible, targeting extracellular tight junction proteins (occludin, claudin family)
- **Bioadhesives**
  - Carbopol, cellulose agents, starch, dextran, chitosan, gelatin microspheres, ionic polysaccharides
- **Transduction Agents**
  - TAT, VP22, penetratin (Antp), transportan, MAP, haptides

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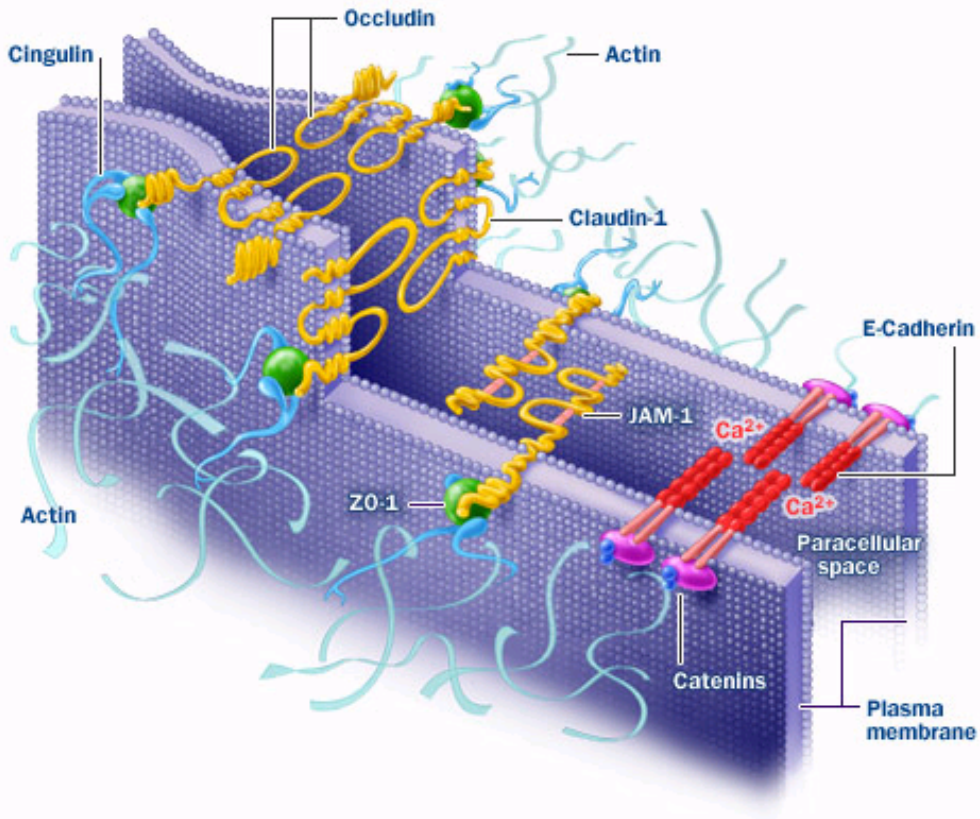
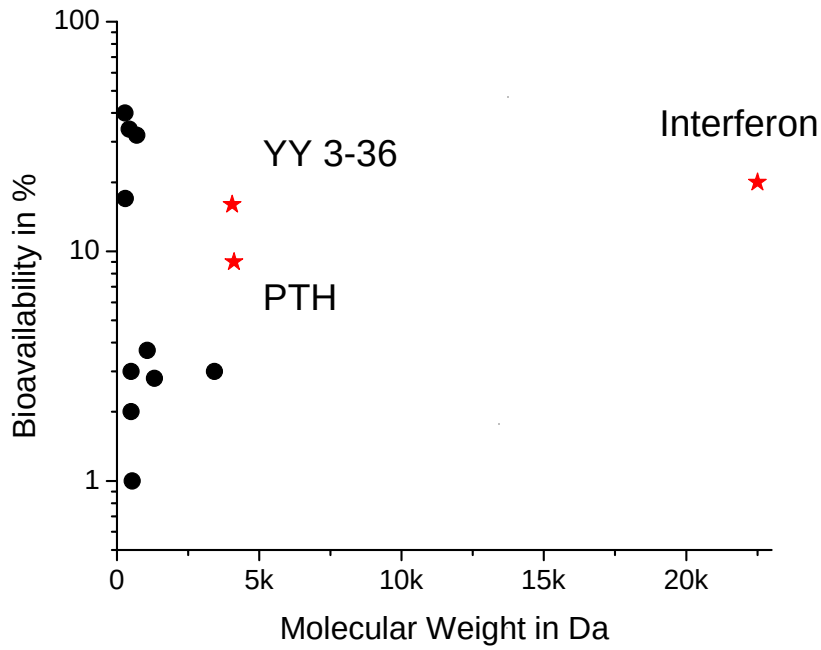
Tight Junction Modulation (Nastech)





http://www.nastech.com/nastech/junctions_biology

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Bioadhesives

- Enhance absorption by increasing residence time at mucosal surfaces
- Enhances immune response of vaccines

- Examples:
  - ChiSys™ (Archimedes)
    16 – 21 % bioavailability for Leuprolide
  - GelSite™ polysaccharide purified from aloe (DelSite)
    In situ gelling

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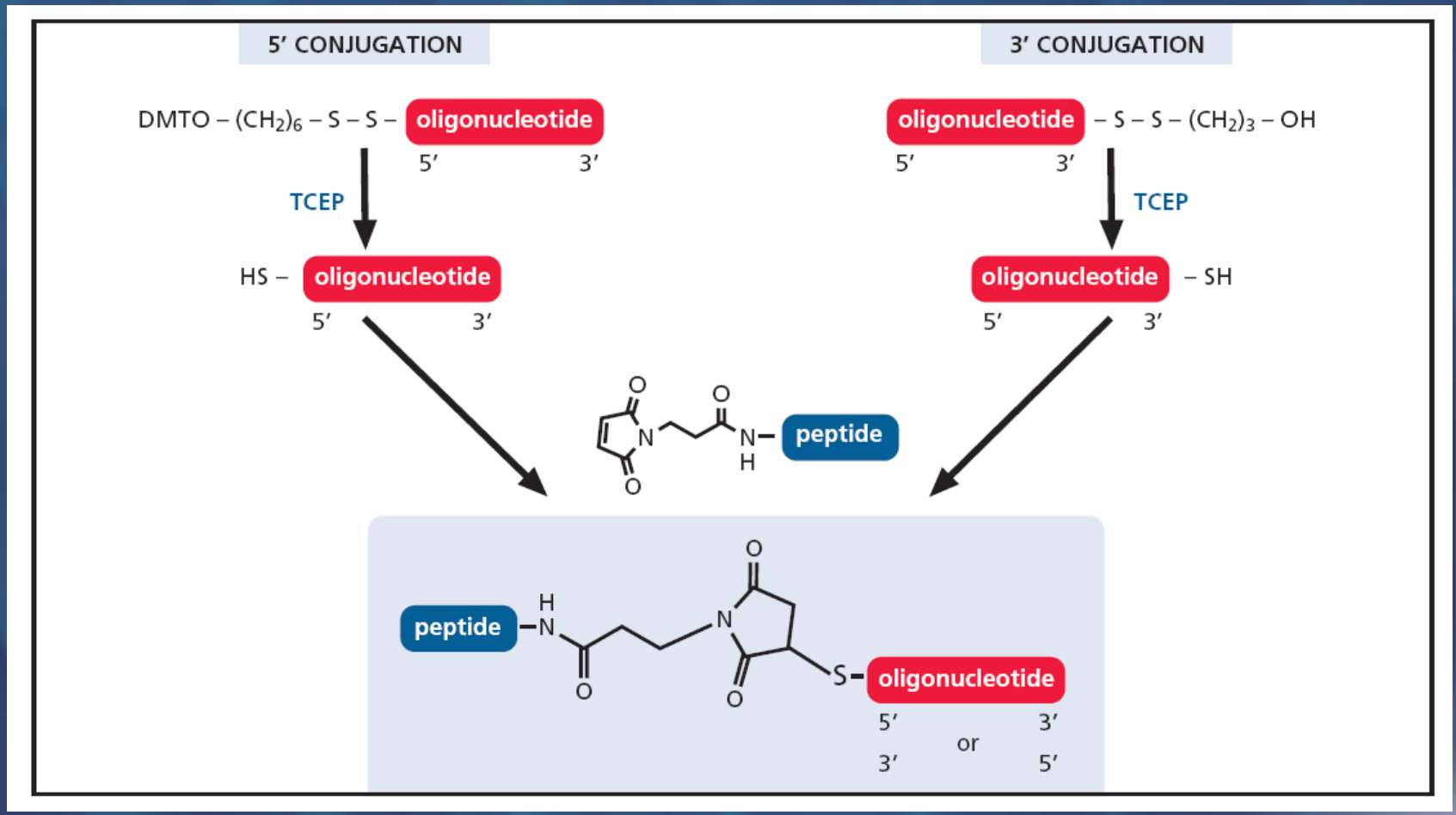
Transporters: siRNA – peptide conjugation (Nastech)



R. T. Witkowska, et al., Peptide – Mediated Delivery of siRNA via Noncovalent Complexes and Covalent Conjugates. American Peptide Symposium, June 20, 2005

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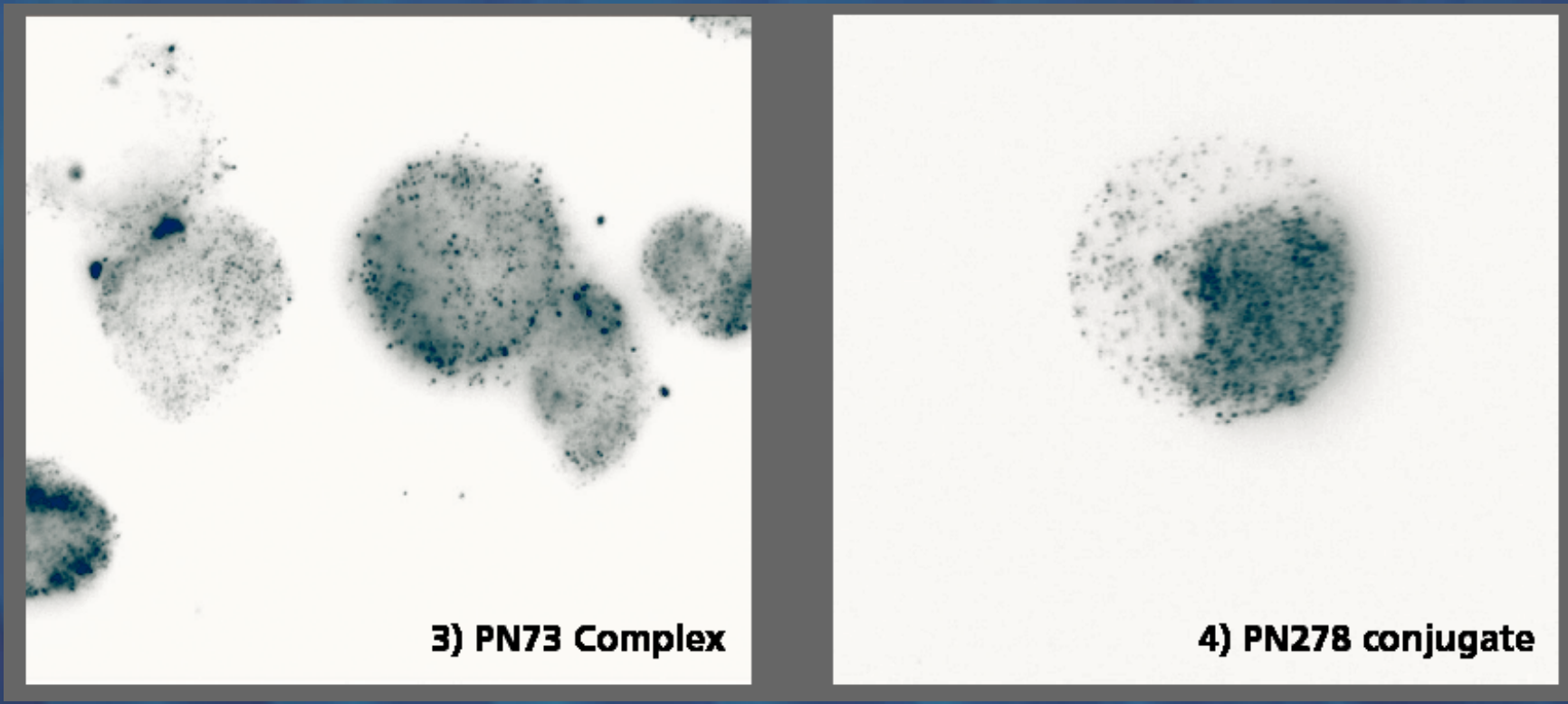
siRNA Delivery to the Cytoplasm (Nastech)



siRNA in the cell visualized by fluorescent microscopy

R. T. Witkowska, et al., Peptide – Mediated Delivery of siRNA via Noncovalent Complexes and Covalent Conjugates. American Peptide Symposium, June 20, 2005

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Delivery Strategies – Active Transport

- **FcRn Pathway**
  - Albumin
  - Antibodies
  - Fc Fusion molecules
- **Blood Brain Barrier**

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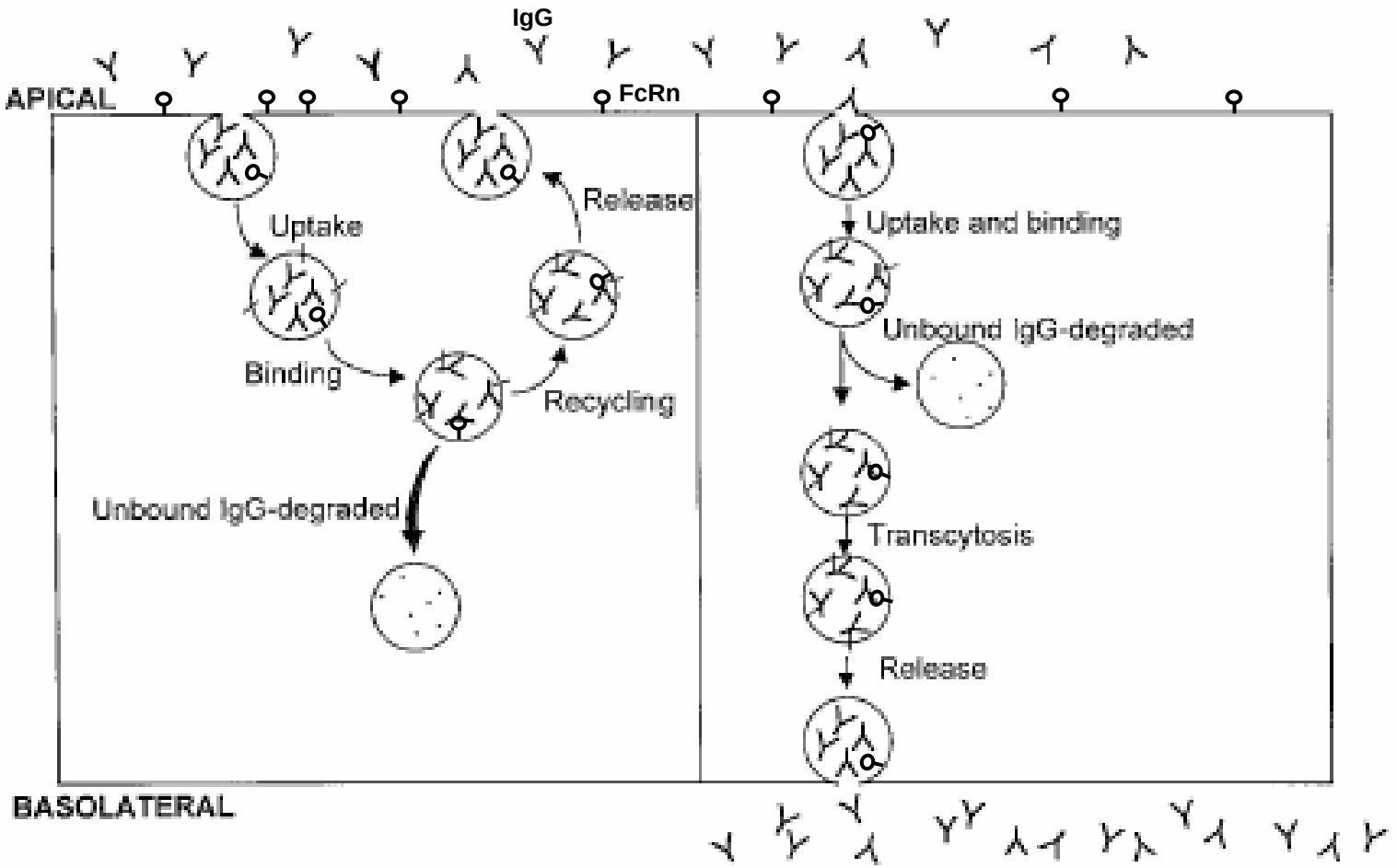
FcRn Trafficking



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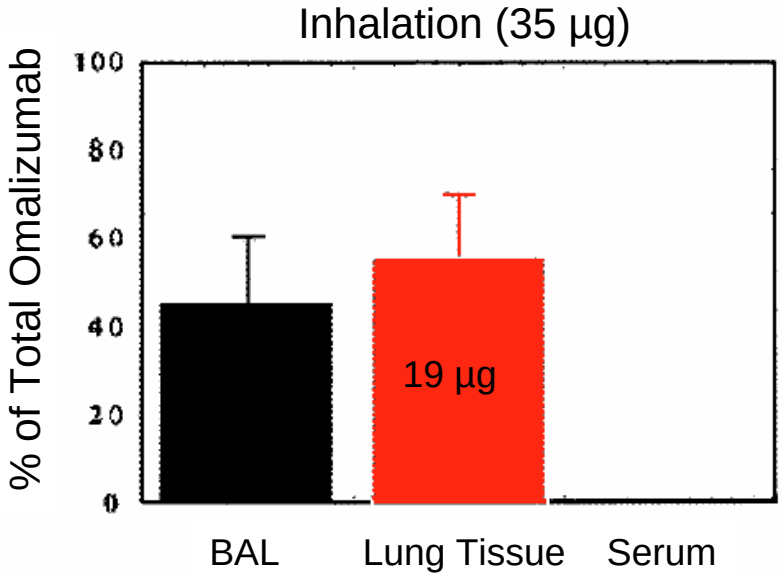
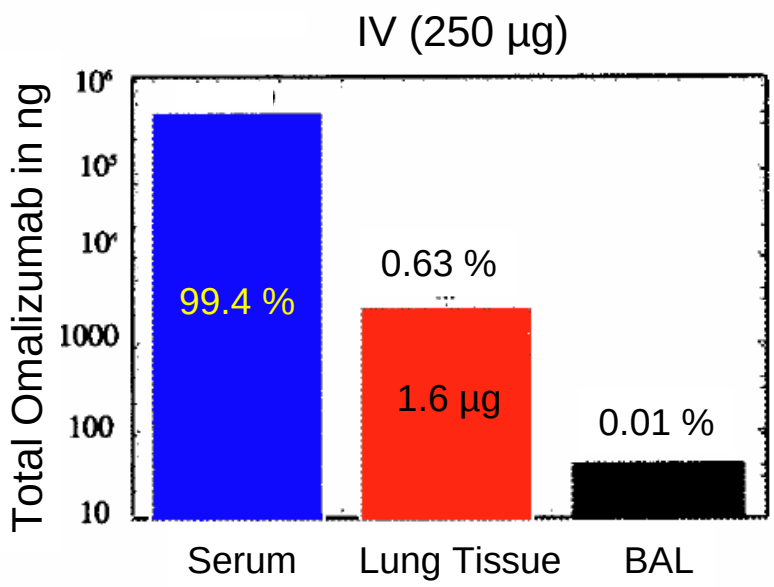
Local IgG1 Delivery (Genentech)





Distribution of anti-IgE in brochoalveolar lavage fluid, lung tissue, and serum 1 hour after administration by inhalation or IV in the rat.

- Clinical study did not show efficacy

Sweeney, T.D., et al., RDD VII, 59, 2000; Fahy, J. V., et al., Am J Respir Crit Care Med **160**, 1023, 1999.

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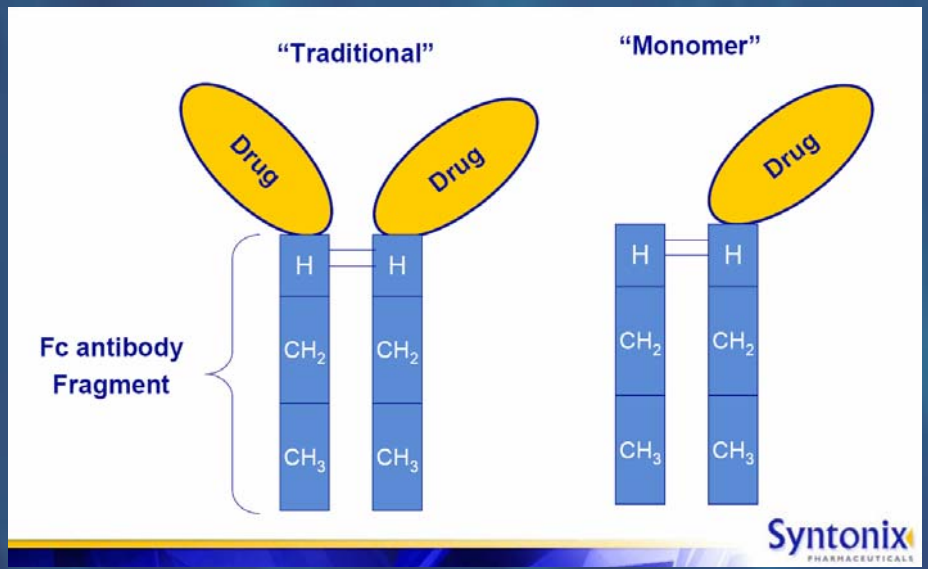
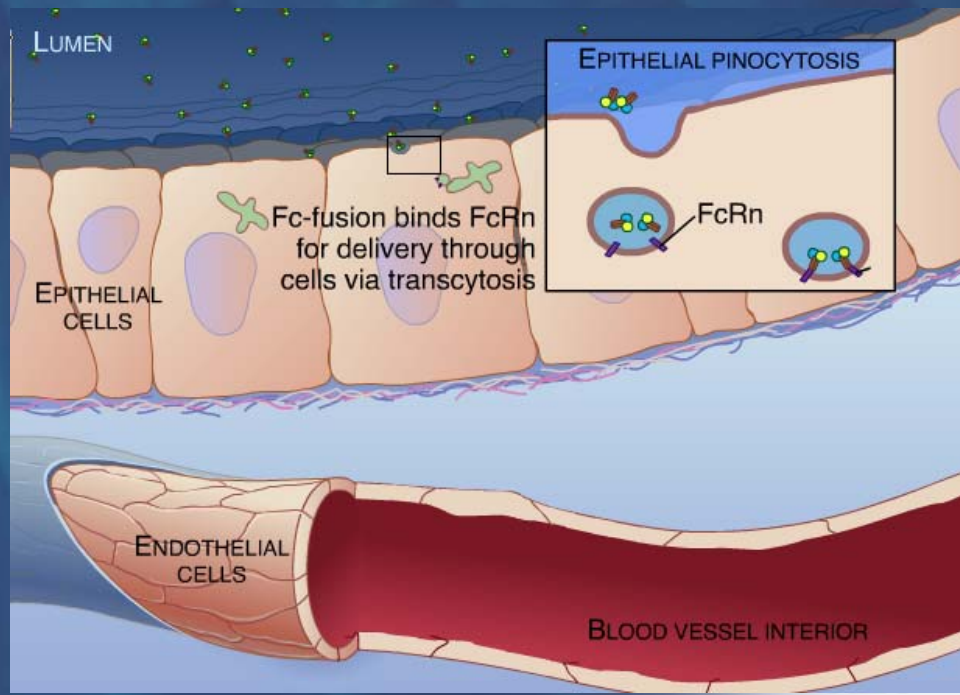
Systemic Delivery of Fc-Fusion Molecules (Syntonix)

- Fc-fusion molecules: API attached to Fc fragment.
- 5 to 50 % bioavailability depends on type of fusion molecule, monomeric vs. dimeric.
- Receptor saturation occurs at doses ~ 1-2 mg/kg
- Limited capacity for systemic delivery





http://www.syntnx.com/tech.php

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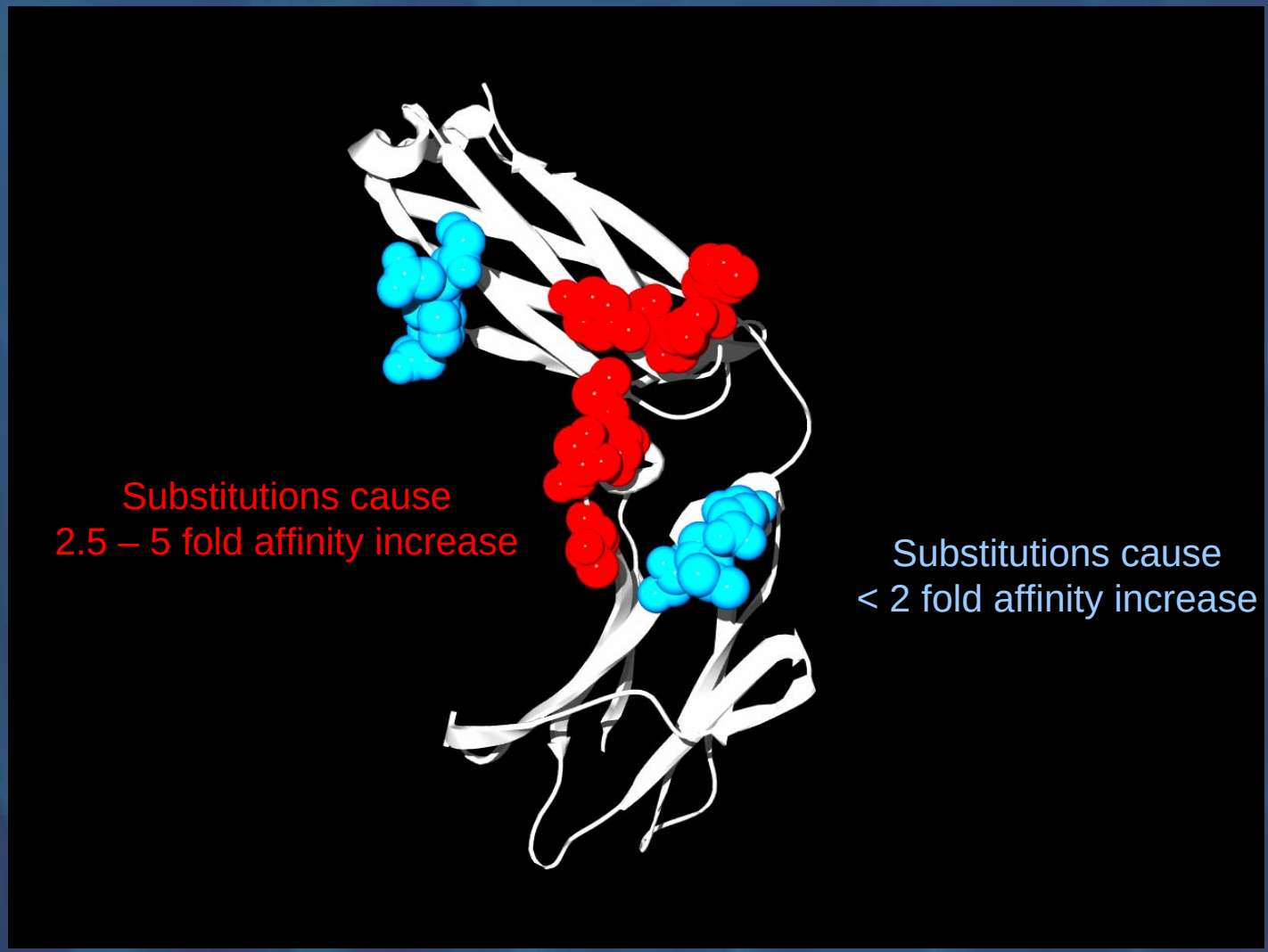
FcRn – Antibody Affinity Modulation



IgG1 Fc - FcRn docking surface

W. F. Dall'Aqua et al. J. Immunol. **169**, 5171, 2002

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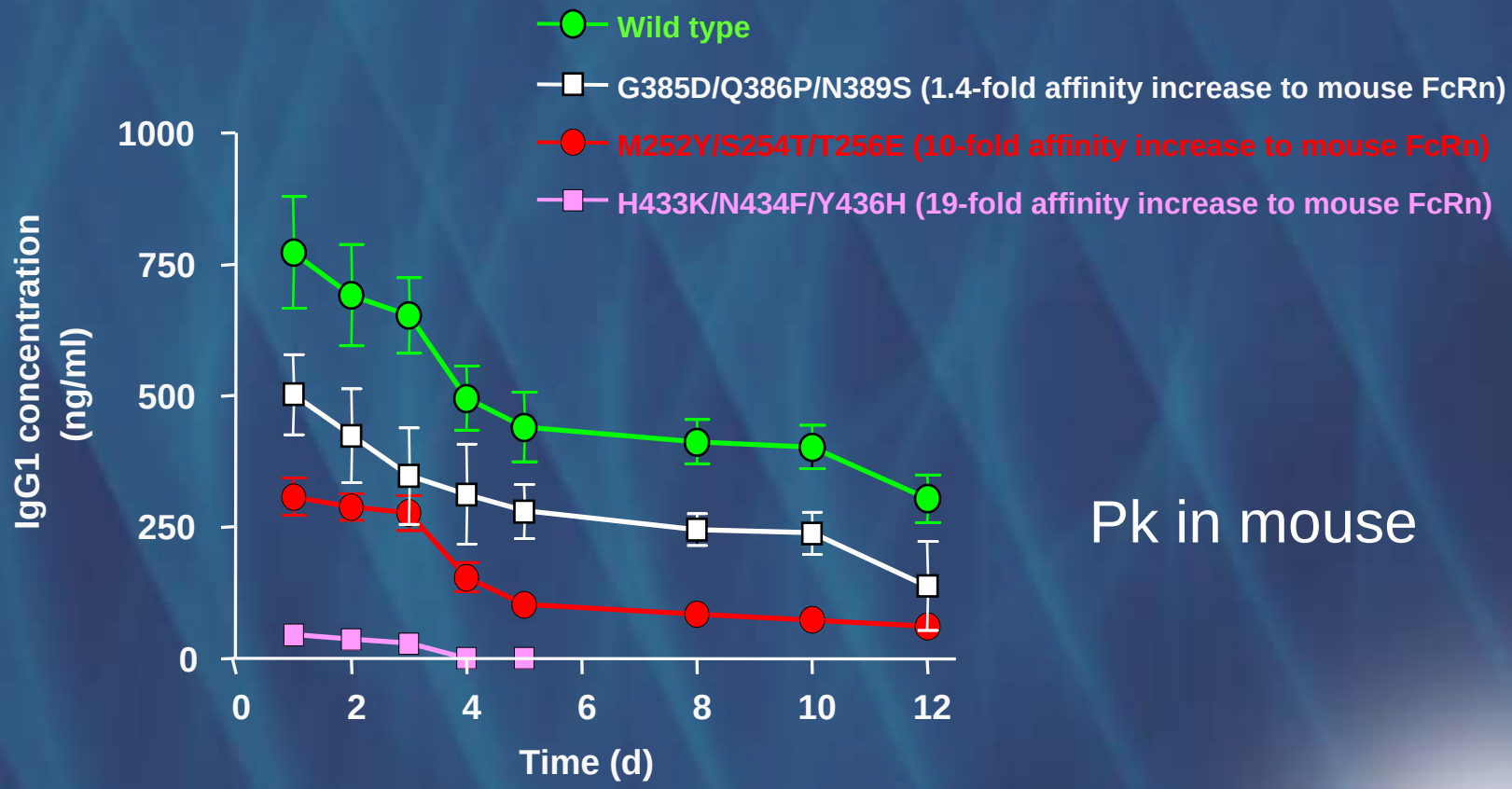
Increasing the Affinity of Human IgG1 to Mouse FcRn Affects Pharmacokinetics



Pk in mouse

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Summary

- Pulmonary and nasal delivery are attractive routes for some systemically or locally acting protein therapeutics or vaccines
- Delivery issues regarding anatomic filter functions and device efficiency are largely solved
- Bioavailability limits systemic delivery to small proteins and peptides
- Penetration enhancers for nasal delivery are in clinical development
- Multiple novel approaches for controlled release, active transport, and targeting are in the research stage.

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