Inhibition of Airway Mucus Production: a Magnetic Nanoparticle Approach

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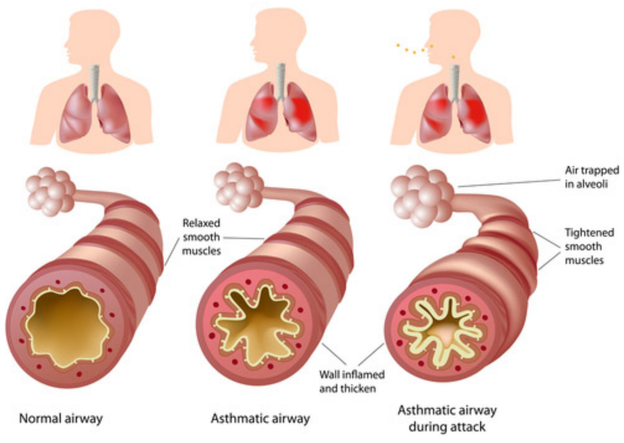
1) Lung diseases with excessive airway mucus.

Pathology of Asthma



Lung diseases with excessive airway mucus production afflict over 24 million people in the US and result in over $50 billion in healthcare costs annually.

Excessive mucus production is a common and significant problem for several prominent human lung diseases such as asthma and chronic obstructive pulmonary disease (COPD).

The mucus barrier poses a significant challenge to drug delivery, leading to increased healthcare cost and poor quality of life for patients.

Common features of asthma and COPD

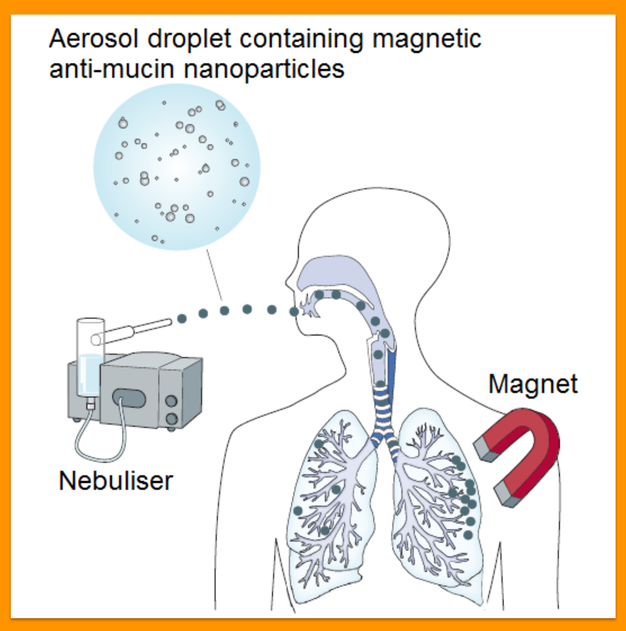
- **Inflammation:** neutrophils, lymphocytes
- **Remodeling**: mucus overproduction
- **Infection:** a major cause of exacerbations

Bacteria: *Nontypeable Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella catarrhalis, Mycoplasma pneumoniae*

Viruses: Rhinovirus, respiratory syncytial virus

Magnetic nanoparticles may provide a mechanism to overcome structural and fluid resistance of mucus to penetration.

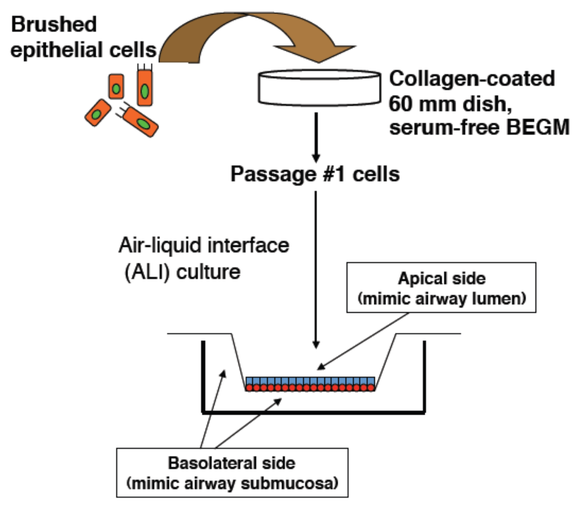
2) Targeted delivery of magnetic aerosol droplets.



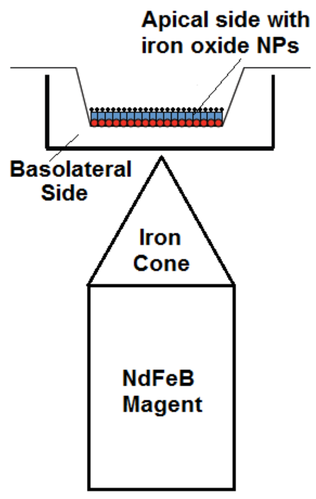
Dolovich M. D., Lancet 377: 1032-45 (2011)

3) Experimental model system

Primary bronchial epithelial culture (bronchial brushing)



Iron-oxide (Fe_3O_4) magnetic nanoparticle (NP) delivery system.



Previous experimental studies [Kircha]:
No mucus penetration with magnetic field gradients of 10 T/m.

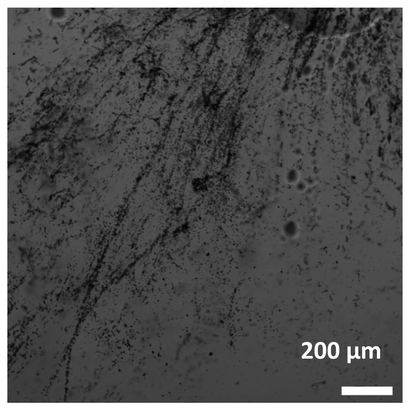
Our permanent neodymium (NdFeB) magnet with an iron cone generates 238 T/m.

Kircha et al.PNAS 109:18355 (2012).

4) Results: conventional 30 nm Fe_3O_4 NPs.

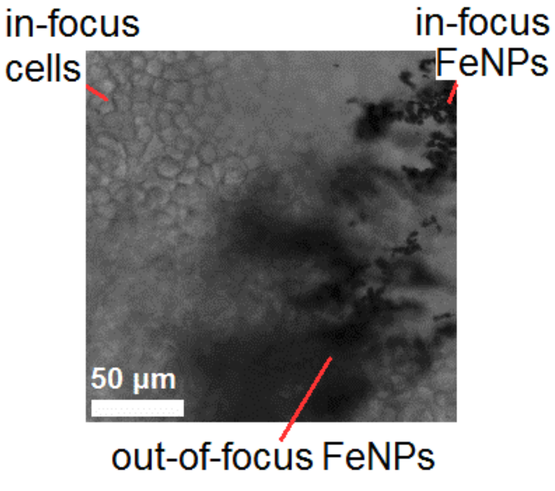
Harvested mucus:

- Disrupted mucus structure
- Successful penetration of large % of NPs
- NP chaining



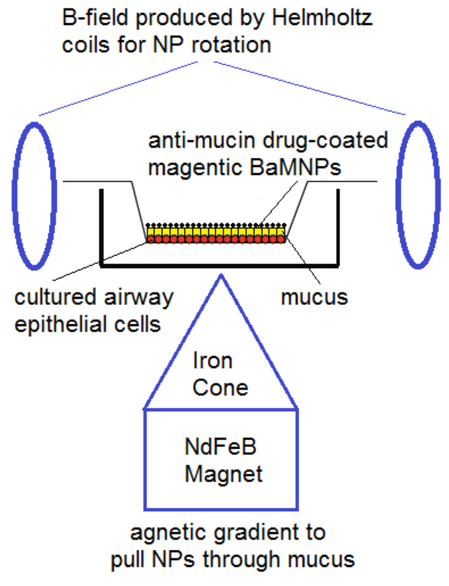
Mucus layer on top of cells:

- Un-disrupted mucus structure
- successful penetration of small % of NPs
- NP chaining



Experiments suggest that the rigid mucin scaffold needs to be disrupted for successful penetration.

5) Next Steps: Use high anisotropy magnetic NPs to increase efficiency of mucus penetration.



-generate M-type Barium hexagonal ferrite (BaM) NPs (30-100 nm).

- BaMNPs can physically oscillate and rotate.

maximum torque density:
$M_s \times H_{app}$

magnetic force density:
$M_s * dH_{app}/dz$

M_s...BaMNP saturation magnetization
H_{app}... applied magnetic field
z... pulling direction through mucus

Estimate for oscillating $|H_{app}| = 0.05$ mT: BaNP rotates at a rate of 6 rotations/minute.