

Nanoparticles and the lung: friend or foe?

Y. S. Prakash^{1,2} and Sadis Matalon³

¹Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota; ²Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota; and ³Department of Anesthesiology, University of Alabama Birmingham, Birmingham, Alabama

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Prakash YS, Matalon S. Nanoparticles and the lung: friend or foe? *Am J Physiol Lung Cell Mol Physiol* 306: L393–L396, 2014. First published January 24, 2014; doi:10.1152/ajplung.00013.2014.—Nanomedicine is a rapidly evolving field with high potential for developing novel research, diagnosis, and/or therapeutic approaches for lung diseases. However, for engineered nanomaterials to reach their true potential, there are still a number of unanswered questions regarding nanomaterial vs. tissue properties that dictate lung cellular uptake, distribution, and intracellular effects, and particle vs. tissue factors that determine toxicity vs. beneficial effects in the lung. Some of these key questions are highlighted in this Perspectives. Addressing these important issues will help improve nanoparticle design and enhance enthusiasm for more widespread use of nanotechnology in pulmonary medicine.

THE NATIONAL NANOTECHNOLOGY INITIATIVE (39) defines nanotechnology as “the understanding and control of matter at the nanoscale, at dimensions between ~1 and 100 nm, in which unique phenomena enable novel applications.” Such technology allows for exploitation of material properties at the “nano” scale level that are distinct from bulk or macroscopic material systems. In this regard, engineered nanotechnology is a rapidly evolving field in science and medicine where the unique, size-dependent properties of engineered nanomaterials such as nanoparticles, nanotubes, dendrimers, and fullerenes offer the possibility of developing novel tools for research, diagnosis, and therapy for a range of diseases, including those afflicting the lung (4, 10, 12, 15, 19, 23, 56, 57, 64). Here, the ability to carefully engineer and “custom design” nanoparticles in terms of their core materials (e.g., carbon, ceramics, gold, silver, titanium), core size/surface area, surface properties (charge, hydrophobicity), aggregation, and the increasing capacity for incorporating drugs or other “payloads” into nanomaterial-based carrier systems (3, 18, 24, 30) have all created new paradigms in medicine. In terms of diagnostics, nanoparticles can be used as contrast agents in medical imaging and can also allow for “molecular” imaging of body structures based on our ability to engineer and coat particles with moieties that target specific organs, tissues, and cell types (14, 40, 42). Nanoparticle-based pharmacological therapeutics, particularly in the context of drug delivery to specific cell types or tissues that are not readily targeted by conventional pharmacological approaches, are thus now within the realm of reality. Such novel strategies may further allow for the concentration of drugs at desired target sites, e.g., by coating nanoparticles with ligands for or antibodies against cell surface proteins including receptors and channels, thus minimizing systemic side effects and

toxicity. This aspect of nanomaterial-based therapy is particularly appealing for the targeting of focal lung diseases such as cancers, and even chronic diseases such as asthma, chronic obstructive pulmonary disease (COPD), or pulmonary fibrosis that involve much of the lung, without introducing substantial toxicity to other organs, as would occur by parenteral or other systemic administration of drugs (3, 25, 30, 43, 55). Indeed, given the unique juxtaposition of the airways to the pulmonary vasculature, targeting diseases such as pulmonary hypertension by using nanoparticles may also be a consideration (35).

Thus the overall potential for nanoparticles (or other nanomaterials) in medicine is substantial and ever growing. On the other hand a number of studies have outlined significant long-term health effects of engineered nanoparticles, including detrimental effects in the lung (e.g., 7, 9, 13, 29, 47–50, 62). Furthermore, there is evidence for detrimental effects on fetal and postnatal lung growth by nanoparticles (2, 46, 52). These significant concerns have resulted in a less than enthusiastic embracement of nanoparticle technology in pulmonary medicine and oncology. In this regard, although engineered nanotechnology for medicine per se may be seen as an exciting and burgeoning field, particles <100 nm in diameter have been recognized and studied for much longer in the context of environmental exposures (ultrafine particles derived from pollution, fires, viruses, etc.) as by-products of industrial processes (e.g., engine exhaust, power plant output), and as components of consumer products (particularly dyes, pigments, powders, toothpaste, sunscreen). Nanoparticles can thus gain access to the human body through the skin, the gastrointestinal tract, and, particularly, the lung. Indeed, given the large surface area of the lung that is in contact with the environment, the lung has been an organ of particular interest for studies on the distribution, uptake, and toxicity of nanoparticles (8, 27, 44, 45, 53, 54, 60, 61). Furthermore, the sole alveolar-capillary transport barrier in the distal lung may allow for entry of nanoparticles into the pulmonary circulation, particularly if the air-blood barrier is disrupted, or perhaps through vesicular pathways (17, 63). In addition, nanoparticles may initiate local as well as systemic inflammatory responses (1, 13, 33), which may prove detrimental to the systemic circulation.

From the perspective of “environmental” nanoparticles (be it natural or human designed) the issue of pulmonary toxicity has been prominently in the forefront. These ideas would then suggest that it is important to understand the biological effects of engineered nanoparticles in the lung before the targeting of lung diseases with nanomedicine becomes widely accepted. This issue is particularly relevant in a number of lung diseases such as asthma or COPD in which a range of pharmacological and other therapies currently in use are already quite effective, and the bar for establishing nanomaterial-based therapies is likely to be quite high. However, crossing this threshold is

Address for reprint requests and other correspondence: Y. S. Prakash, Dept. of Anesthesiology, Mayo Clinic, Rochester, MN 55905 (e-mail: prakash.ys@mayo.edu).

currently hindered by a substantial knowledge gap in our understanding of what factors determine the relative beneficial effects of nanoparticles in lung tissues (be it normal or pathological) vs. the toxicity of such nanoparticles, particularly as unintended consequences in normal tissues. This key question envelops many more fundamental issues:

1) Which nanoparticle properties are most important in determining their distribution, uptake, and half-life within different lung compartments: core vs. overall particle size, nature of ligands, surface charge, hydrophobicity, tendency toward aggregation, etc. (5, 21, 22, 26, 51)?

2) How do nanoparticle interactions with biological fluids (mucus, blood) or cell surfaces affect the nanoparticle surface

itself (concepts such as the protein “corona”) and its further ability to interact with tissues (11, 16, 34, 38, 58, 59)?

3) What lung cellular properties are important in nanoparticle-cell interactions, uptake, and intracellular processing and targeting (20, 31, 36, 37, 63)? Here, an important corollary issue is what nanoparticle vs. cellular properties determine intracellular fate vs. unobstructed translocation of nanoparticles across the bronchial vs. alveolar epithelium. This is particularly relevant for design of nanoparticle-based drug delivery systems for proximal airways (where the epithelium as well as underlying structures such as smooth muscle, fibroblasts, and immune cells may need to be targeted) vs. the distal lung parenchyma.

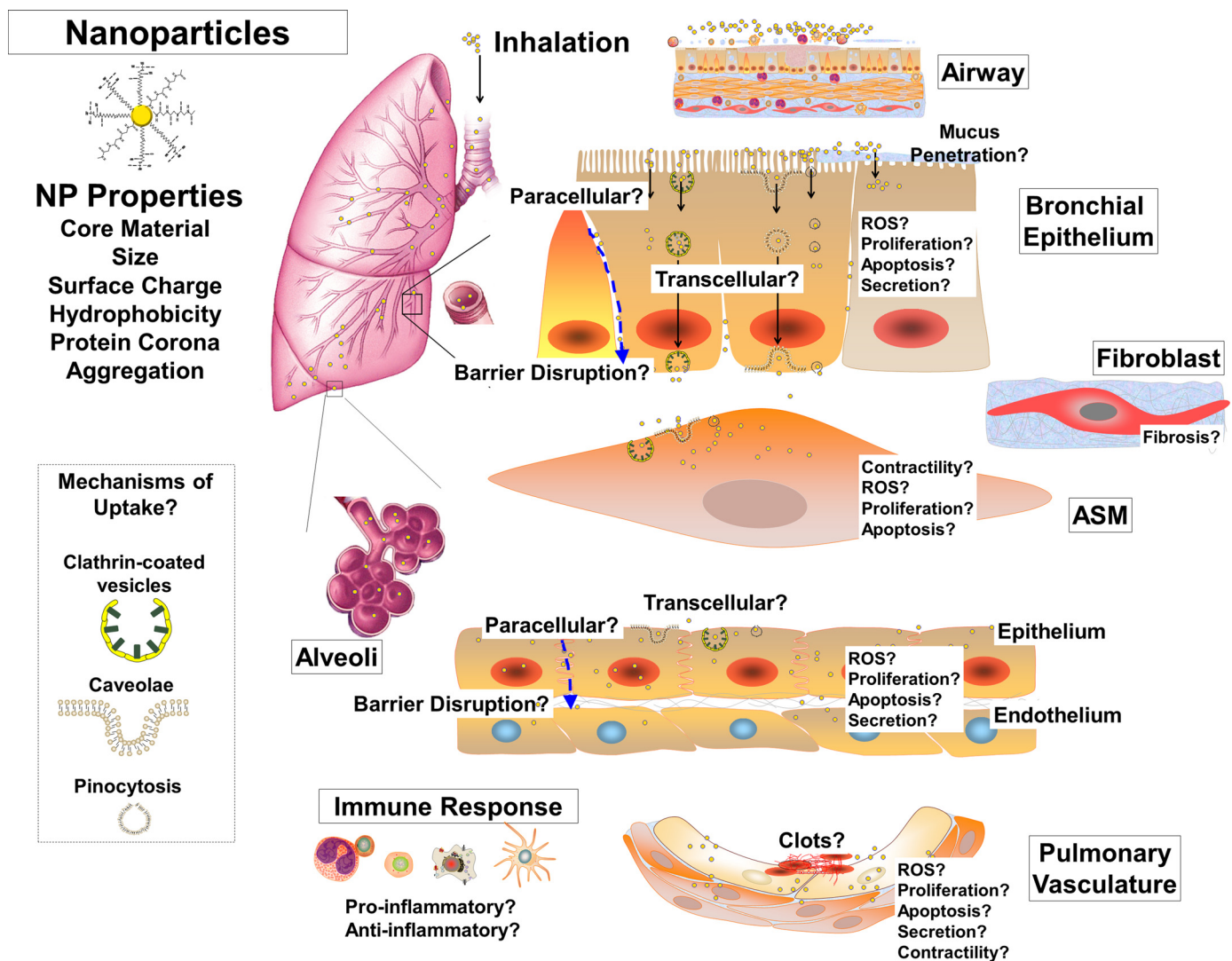


Fig. 1. Issues in identifying nanoparticles (NP) as friends vs. foes. Inhalation of nanoparticles, be it intentional or not, can result in widespread distribution within the lung, where their eventual effects on different lung compartments are driven by a host of nanoparticle- vs. host-dependent factors. In terms of the nanoparticle itself, factors such as core material, core vs. overall size (following conjugation of ligands with surface engineering), tendencies to collect proteins within biological media (corona) and toward aggregation may all play an important role in the uptake, distribution, cellular effects, and elimination of nanoparticles. At the level of the proximal airway, nanoparticles will need to penetrate the mucus and epithelial ciliary layer to produce effects. This requirement may drive nanoparticle design if the intent is to target bronchial epithelium and underlying structures with the goal of therapies for inflammatory or fibrotic airway diseases. At the alveolar level, penetration of nanoparticles may lead to effects in the pulmonary vasculature as well. Within different areas of the lung, nanoparticles may modulate the immune response. In all of these processes, cellular uptake, translocation, and transfer of nanoparticles may be driven by mechanisms such as clathrin-coated vesicles, caveolae, and pinocytosis. Intracellular effects of nanoparticles may be cell and context specific, overall resulting in a balance between detrimental and potentially beneficial effects in the lung. ROS, reactive oxygen species; ASM, airway smooth muscle.

4) What are the key cellular mechanisms that underlie nanoparticle effects in lung cells (reactive oxygen species, physical interactions, inflammasome pathways, mitochondria) (6, 25, 29, 41)?

5) What are the detrimental/pathological effects of nanoparticles in the lung (e.g., inflammation, fibrosis, cancer) (29, 33, 49, 50)?

6) Do normal lung cells and tissues differ from pathological tissues in nanoparticle interactions (e.g., in the presence of thicker mucus as occurs in cystic fibrosis or bronchitis, in the presence of blood, or remodeled, thicker epithelium as in asthma)? These issues may help us design nanoparticles to be largely beneficial with negligible toxicity, whether as drug delivery systems or as self-therapeutic moieties.

7) How should we design nanoparticles in a “target-specific” manner? Presumably if the goal is to target diseases such as asthma in which it is normal airway and immune cells gone awry, this will require nanoparticle therapies that do not disrupt normal epithelial barrier function or worsen immune responses in the airway. On the other hand, if the target is focal cancers, the goal would be intentional but targeted cellular toxicity, with minimal effects on surrounding normal tissues.

8) What are the systemic/nonpulmonary effects of nanoparticles with local or systemic administration (inflammation, thrombosis, neurogenic effects)? A particularly important concern may be whether nanoparticles can cross placental barriers and influence development of the fetus.

9) What are the best techniques for measuring nanoparticle concentrations and distribution in lung compartments (28)?

In addition to the above concepts of nanoparticles in diagnostic and therapeutic medicine, there is increasing interest in the idea of their use in in vitro screening and identification of biomarkers (1, 32). Here, our understanding of how nanoparticle interactions with biological materials (blood, serum, sputum, cell surfaces, lysates) affect nanoparticle themselves (e.g., formation of a protein corona) could be used advantageously to develop novel testing platforms. Conversely, development of tests and biomarkers for nanoparticle effects in the lung will also be necessary. Here, in vitro lung cell test platforms (e.g., alveolar cell, fibroblast, or endothelial monolayers) and identification of relevant serum or sputum biomarkers will be of particular interest. These novel approaches will also be instrumental in identifying the mechanisms by which nanoparticles influence lung cells.

The above discussion, although necessarily brief and certainly not comprehensive, nonetheless emphasizes the overall urgent need for much deeper and greater understanding of nanoparticles in the lung in order for nanomedicine to become a reality. This will require interdisciplinary and collaborative research between material scientists/nanoparticle engineers, lung cell and molecular biologists and physiologists, and immunologists. Studies are clearly needed to identify and highlight key concepts of nanoparticle design, implementation, and utilization in targeting lung diseases (the friend) with minimal pulmonary or vascular toxicity (the foe) and the current and future challenges in making this a reality (Fig. 1).

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