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DELIVERING NANOMEDICINE THROUGH THE LUNGS: A PROMISING ROUTE OF ADMINISTRATION

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Introduction

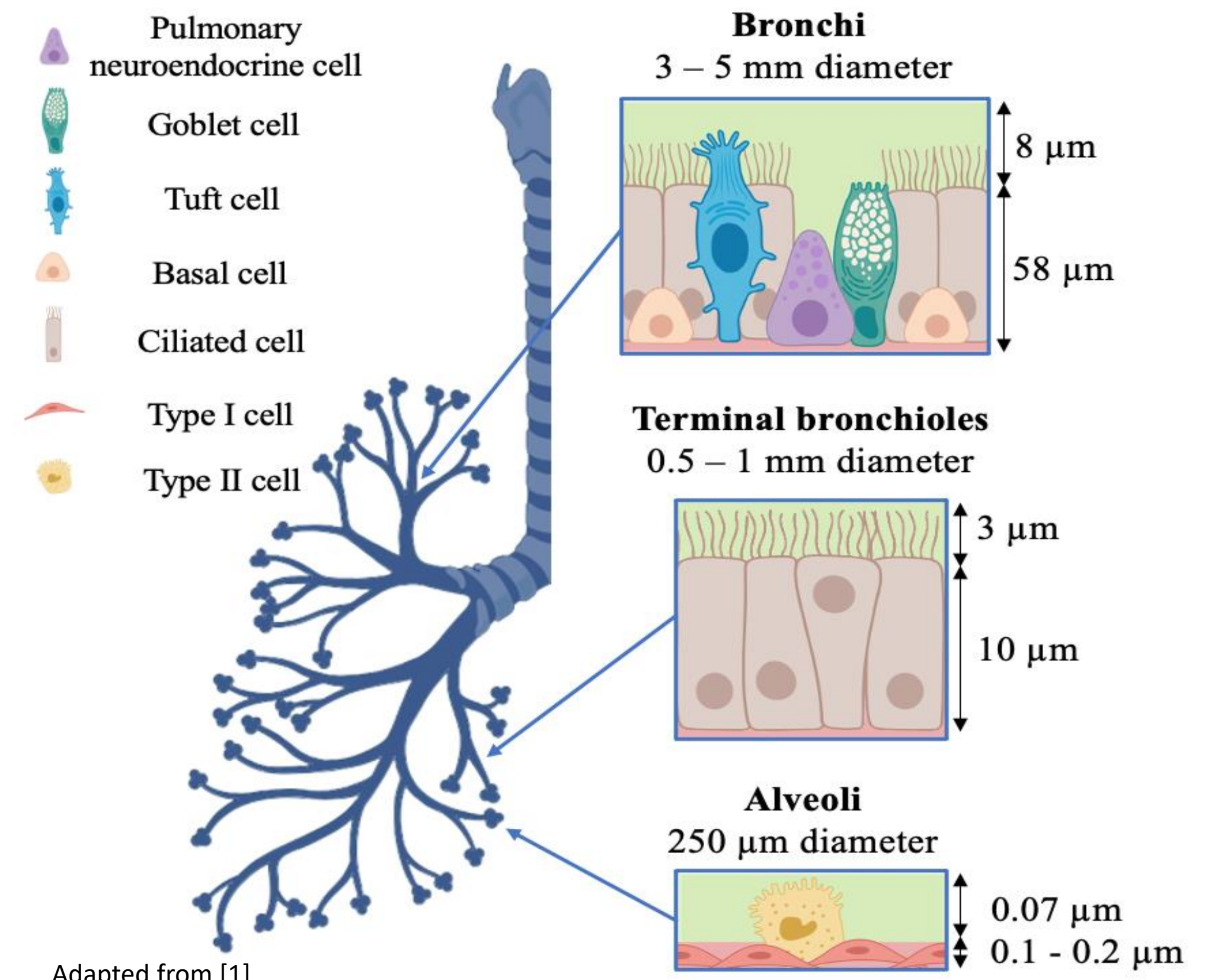
Nanomedicines can be aerosolized and pass through the air-blood barrier, reaching the bloodstream. Indeed, the pulmonary route is direct and allows to reach organs, such as the heart. It avoids stomach acidity and immune response observed with other administration ways. The inhalation strategy had been tested to mitigate doxorubicin cardiac toxicity. Silica nanoparticles with a fluorescein isothiocyanate core were synthesized, grafted with PLGA, and characterized. The resulting SiO₂-PLGA-NPs, suitable for nebulization, exhibited promising results in restoring cardiomyocyte lysosome activity *in vitro* and *in vivo*.

1. The respiratory system and its clearance

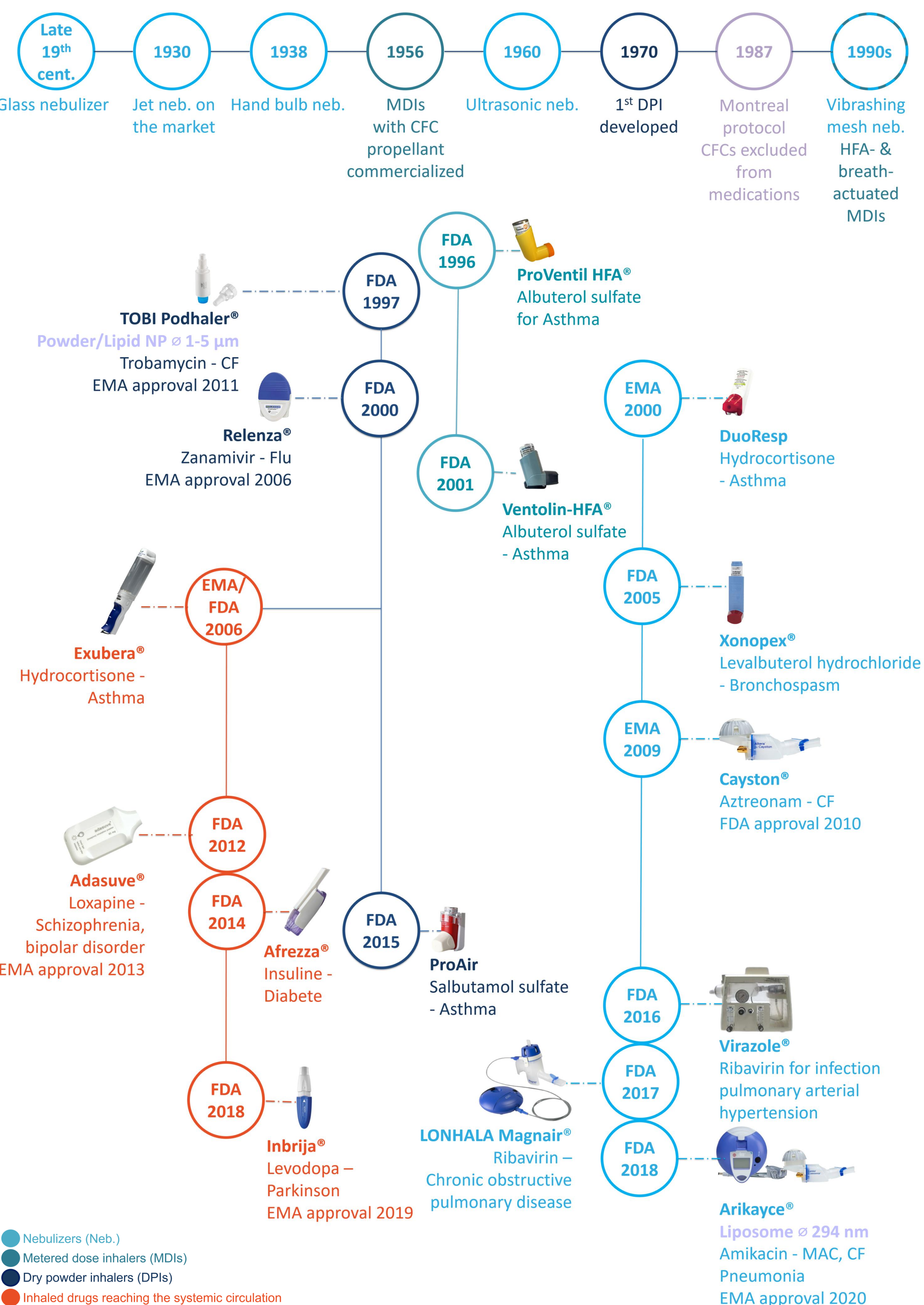
| Diameter | Zone | Force | Clearance | |
|----------|----------------------------|--------------------|--------------------------------------|--|
| | | | Hydrophobic surfaces | Hydrophilic surfaces |
| > 6 μm | Tracheal region | Inertial impaction | Mucociliary | Diffusion, pinocytosis |
| | Bronchi area | | Endocytosis (epithelial macrophages) | Cough, mucociliary |
| 2 – 6 μm | Tracheo-bronchial region | Sedimentation | Cough | Chemical binding (epithelial, sub-epithelial, secretion) |
| | Bronchioles area | | Phagocytosis (alveolar macrophages) | Diffusion, pinocytosis |
| < 2 μm | Terminal of bronchial area | Diffusion | Endocytosis (type I cells) | Endocytosis (alveolar macrophages, type I cells) |
| | Respiratory zone | | Fluid flux | Diffusion, pinocytosis |
| | Alveolar ducts | | | |
| | Alveolar sacs | | | |

Systemic circulation

- To avoid clearance by macrophages, particle diameter should be less than 0.5 μm
- To be translocated from the lung to the systemic circulation or lymph nodes, particles have to be negatively charged or neutral



2. Timeline of device evolution and inhalation market



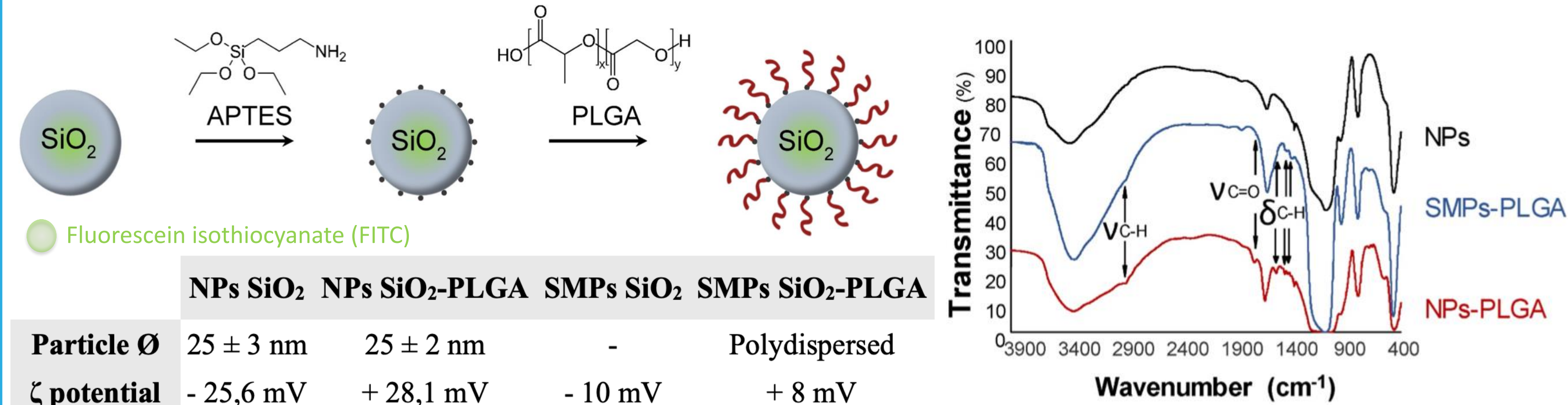
Time line of inhalation devices evolution and non-exhaustive list of inhaled drugs allowed by the Food and Drugs Administration (FDA) and European Medicines Agency (EMA). Adapted from [1]. Nebulizers (Neb.); Metered-dose inhalers (MDIs); Dry-powder inhalers (DPIs); Chlorofluorocarbon (CFC), Cystic fibrosis (CF); Mycobacterium avium complex (MAC).

Conclusion

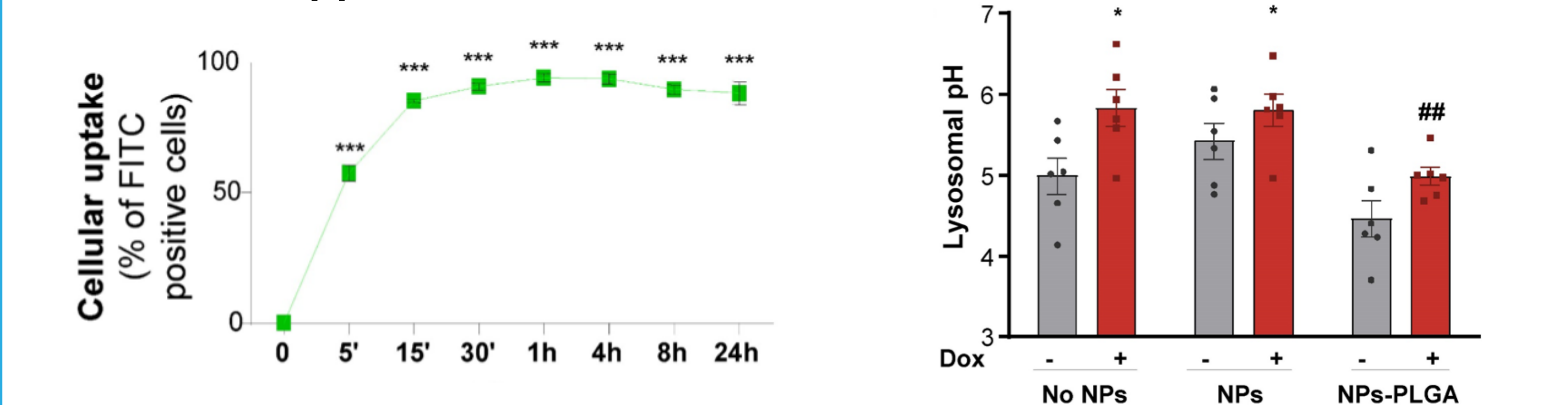
Inhalation is a promising route for drug delivery, with numerous advantages. While some drugs are common for local administration in the lungs, only a few are developed for systemic delivery. Further development and exploration are still to be achieved to exploit more this innovative way of administration.

3. Through the respiratory system to the systemic circulation: the heart as a target

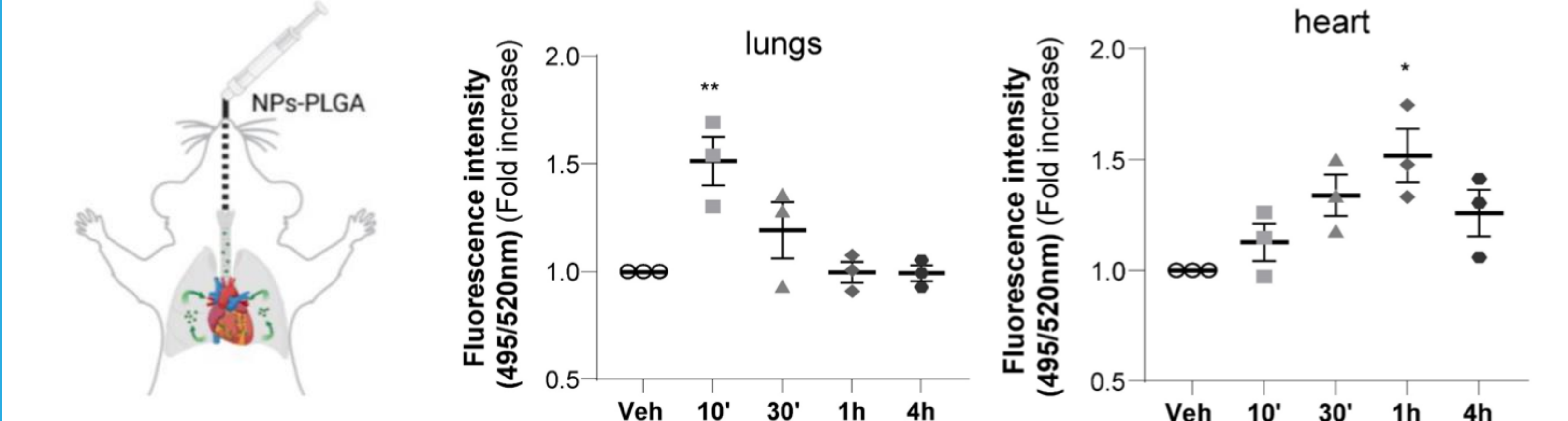
Doxorubicin is effective to treat cancers by damaging DNA and cellular structures. However, it can induce lethal cardiomyopathy by disrupting autophagic flux [2].



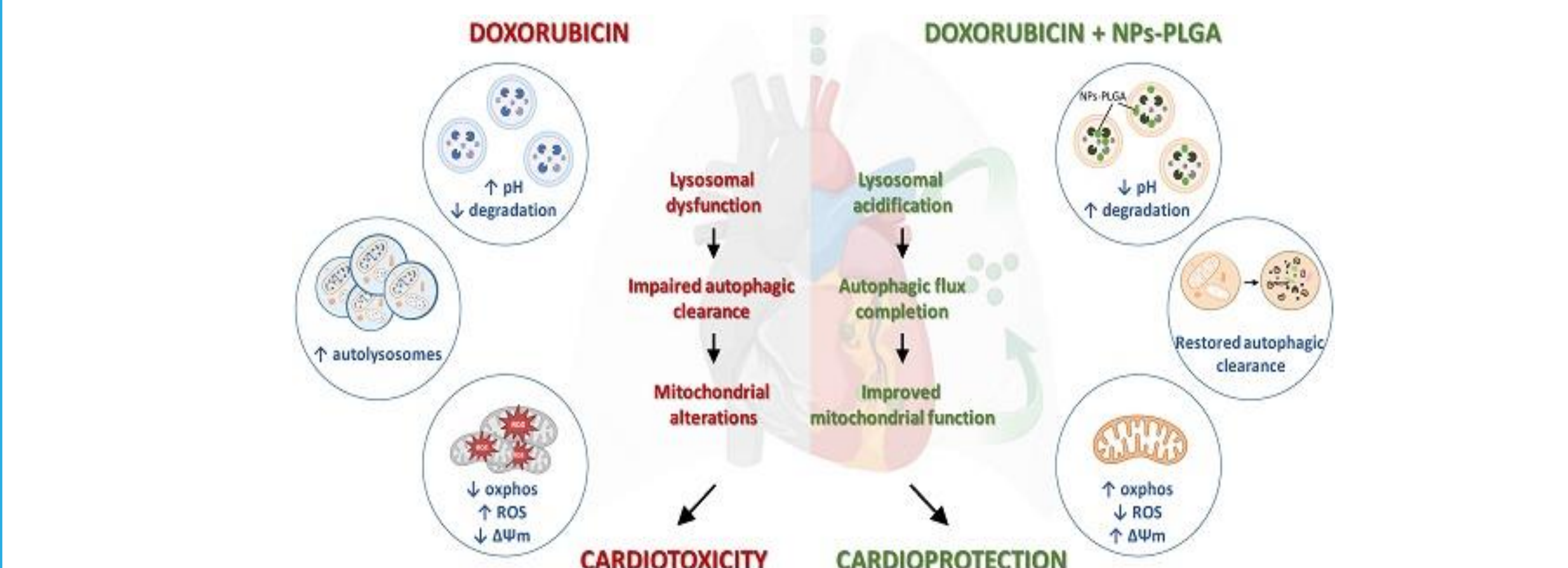
To counter this, PLGA-grafted silica nanoparticles (NPs-PLGA) and submicronic particles (SMPs-PLGA) were used to target and restore lysosomal function, preventing cardiotoxicity when co-administered with doxorubicin in mice [2].



The formulations were administrated to mice by nebulization and were able to directly reach the heart, bypassing intravenous and oral administration barriers, and in preserving mitochondrial function [2].



Fluorescence of NPs-PLGA-FITC in lungs and hearts of mice treated with vehicle (Veh) or 1 mg/kg of NPs-PLGA-FITC through intratracheal nebulization for 10', 30', 1 h or 4 h [2].



Schematic conclusion of the doxorubicin side effects on heart (red) and the improvement obtained when the anticancer drug is co-administrated with NPs-PLGA (green) [2].