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DELIVERING NANOMEDICINE THROUGH THE LUNGS: A PROMISING ROUTE OF ADMINISTRATION

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Introduction

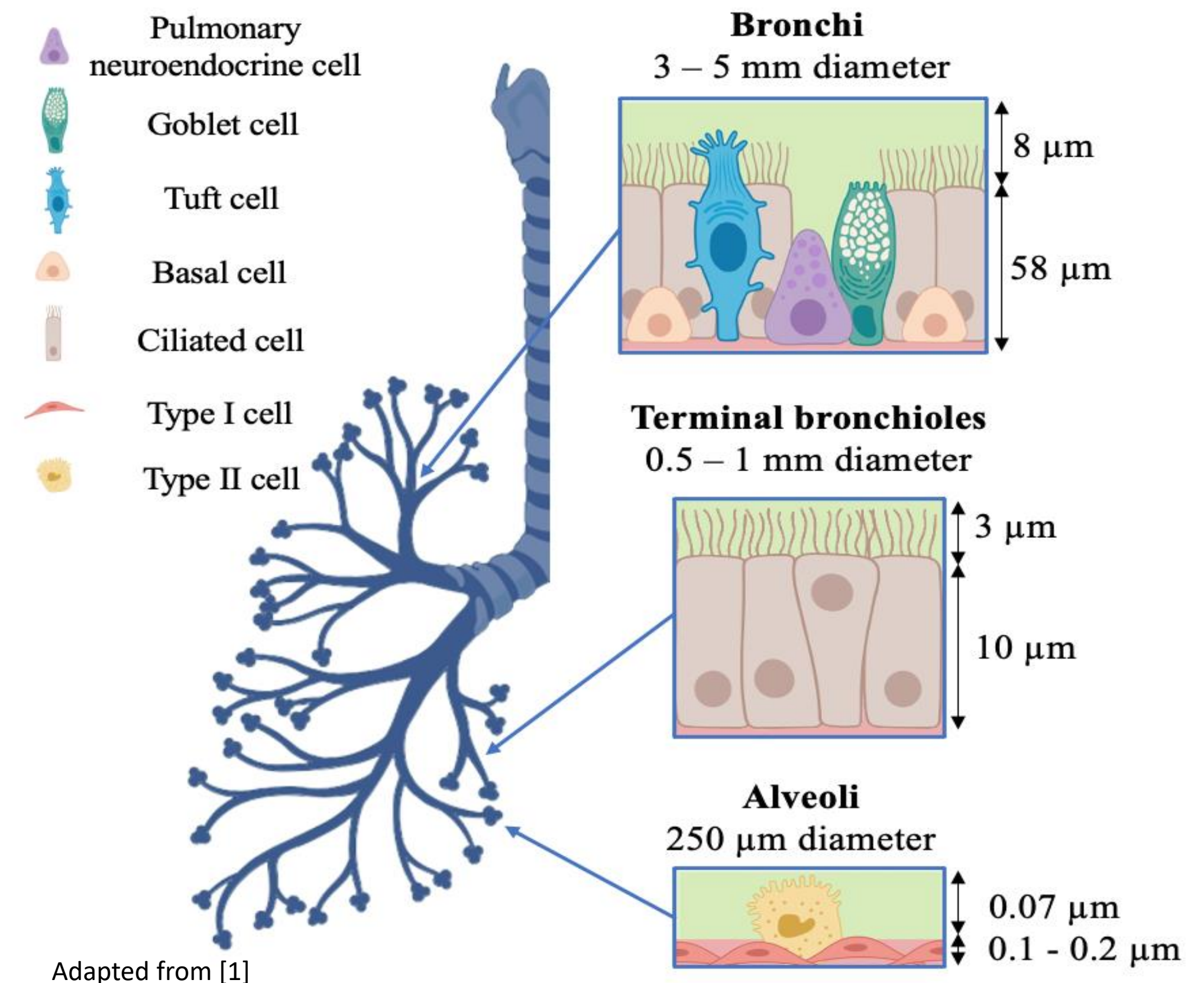
Nanomedicines can be aerosolized and pass through the air-blood barrier, reaching the bloodstream. Indeed, the pulmonary route is direct and allows to reach organs, such as the heart. It avoids stomach acidity and immune response observed with other administration ways. The inhalation strategy had been 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

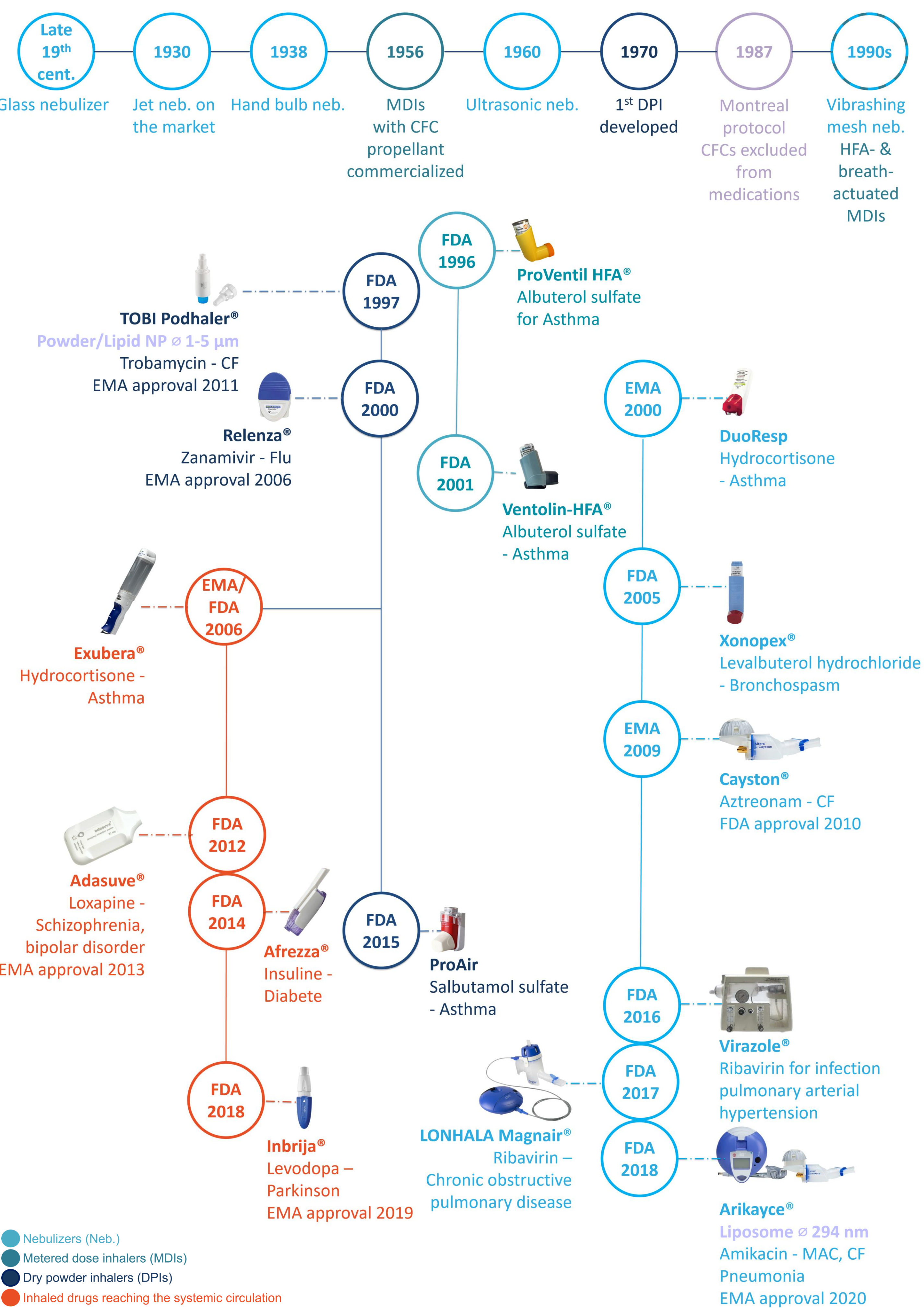
- To avoid clearance by macrophages, particle diameter should be less than 0.5 μm
- To be translocated from the lung to the systemic circulation or lymph nodes, particles have to be negatively charged or neutral



Adapted from [1]

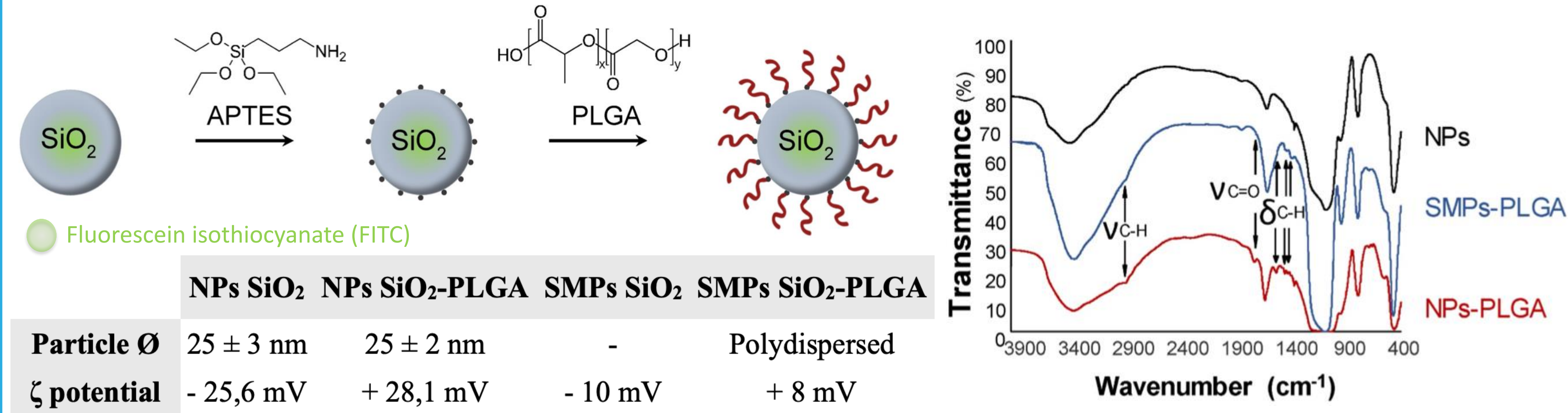
Adapted from [1]

2. Timeline of device evolution and inhalation market

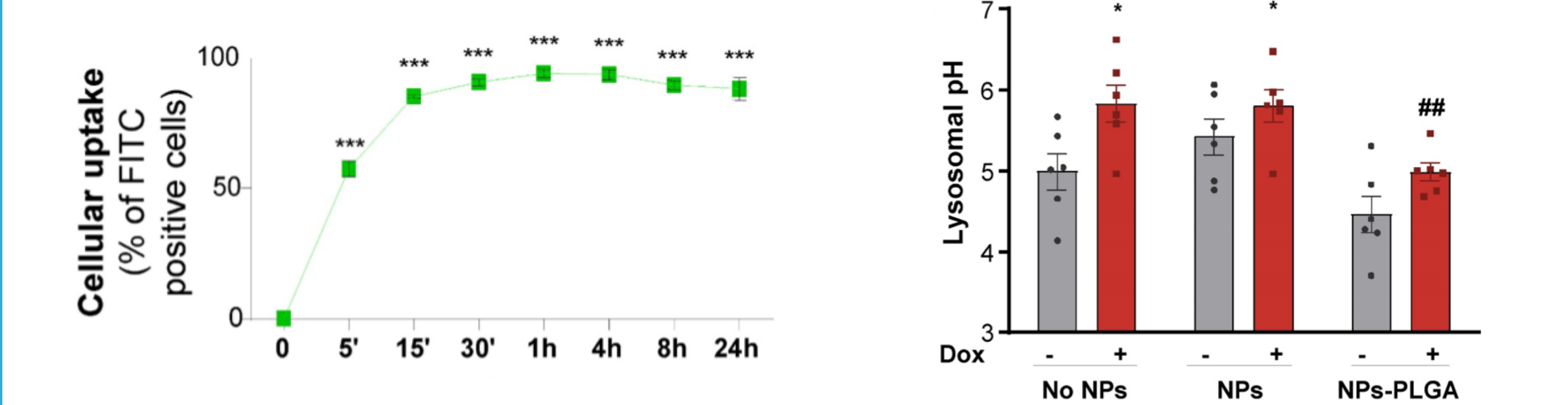


3. Through the respiratory system to the systemic circulation: the heart as a target

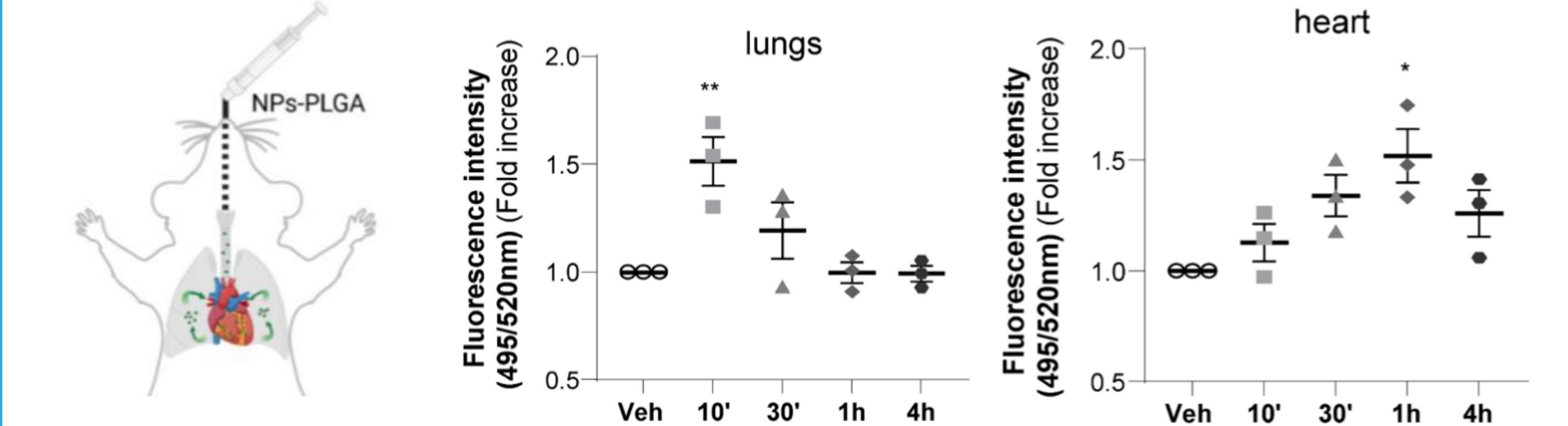
Doxorubicin is effective to treat cancers by damaging DNA and cellular structures. However, it can induce lethal cardiomyopathy by disrupting autophagic flux [2].



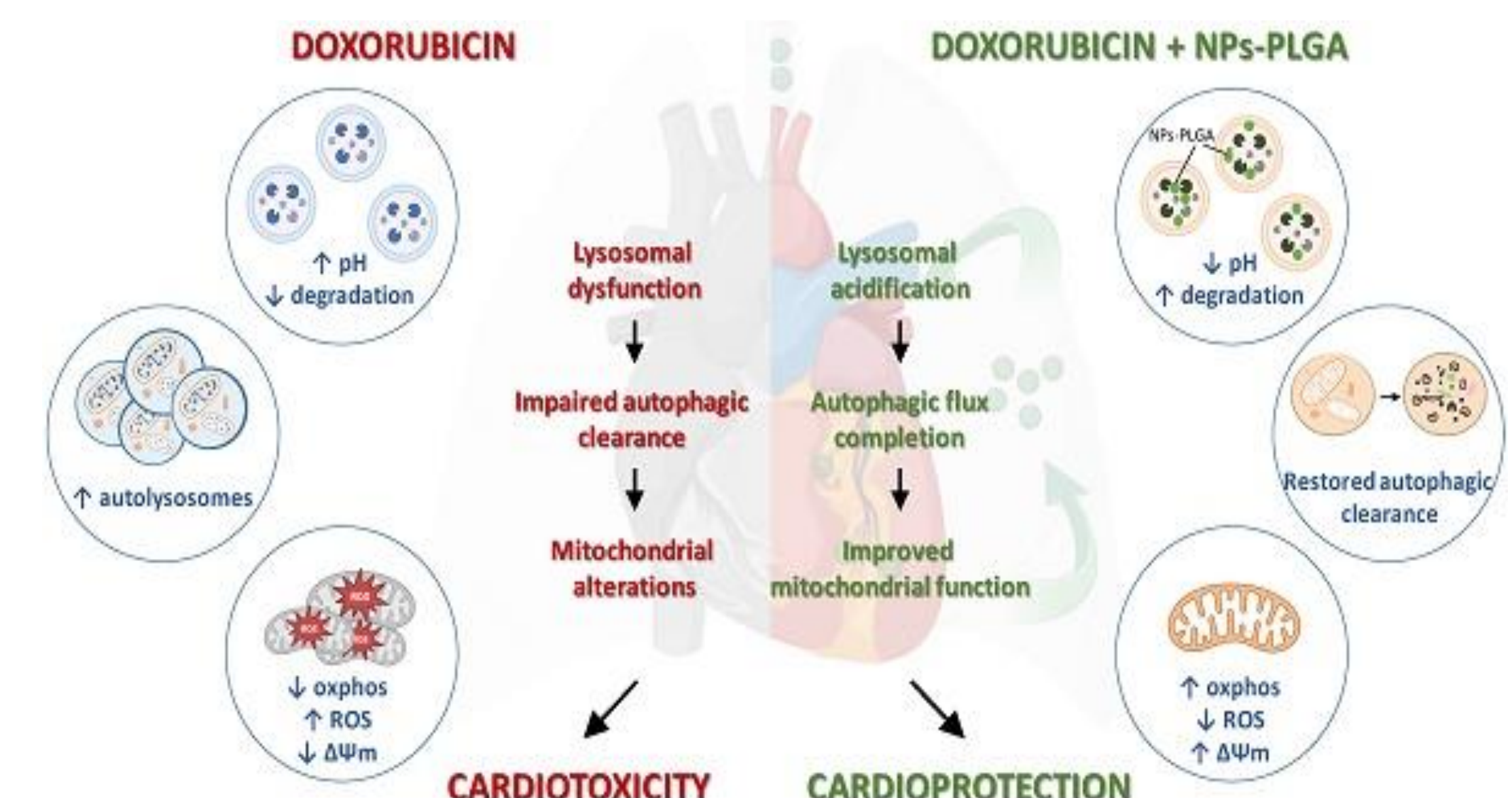
To counter this, PLGA-grafted silica nanoparticles (NPs-PLGA) and submicronic particles (SMPs-PLGA) were used to target and restore lysosomal function, preventing cardiotoxicity when co-administered with doxorubicin in mice [2].



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].

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.