Liposomes and nanoparticles as delivery vehicles for the treatment of lung diseases

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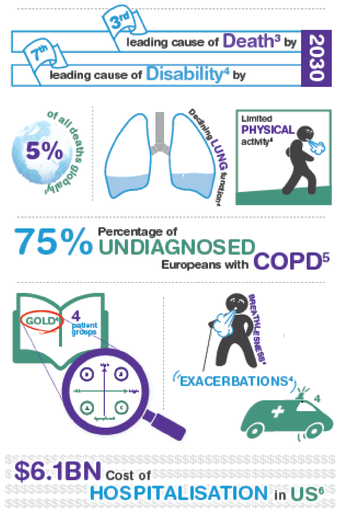
Introduction

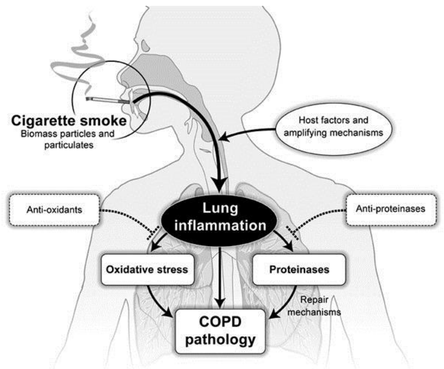
- Reactive oxygen species (ROS) are greatly involved in important physiological and pathophysiological processes.
- **Overproduction of most toxic ROS** - superoxide radicals - leads to a variety of detrimental health conditions including cardiovascular disease, neurodegenerative disorders, and extensive oxidative inflammation.
- Inhaled toxic agents stimulate the generation of reactive oxygen/nitrogen species (ROS/RNS), which in turn provoke inflammatory responses resulting in the release of proinflammatory cytokines and chemokines.



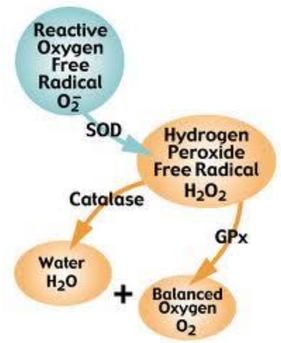
COPD fact sheet[1]

- l**COPD**, or **chronic obstructive pulmonary disease**, is a major global health problem that causes significant disability. It is the 4th leading cause of death in the US.
- Oxidative stress derived from either environmental or cellular origins results in inflammation.

Superoxide dismutases (SODs) are the only enzymatic system that hypothesized to play a significant role against oxidant stress, especially in the lung.



Inflammation in lungs[2]



Oxidative stress pathway[3]

Challenges of drug delivery to the lungs:

- Low time of contact of administered agents with the respiratory mucosa;
- Low bioavailability due to enzymatic degradation;
- Airway geometry, humidity, mucociliary clearance and alveolar macrophages are barriers to the therapeutic effectiveness of inhaled medications.

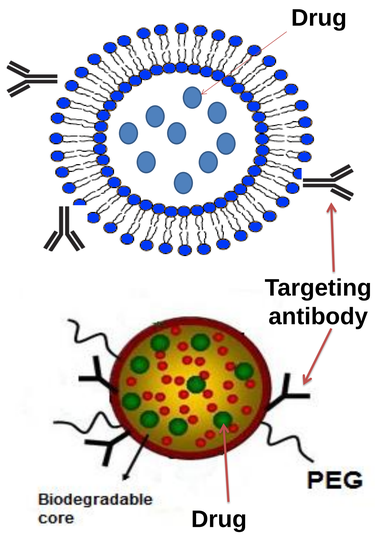
Nanoparticulate systems to overcome the limitations of drug therapy

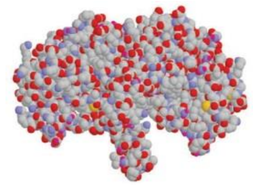
Improvement of the therapeutic index of drugs via several mechanisms such as:

- Increasing their stability in the Biological environment;
- Enhancing cellular/tissue uptake;
- Providing sustained release;
- Reducing toxicity.

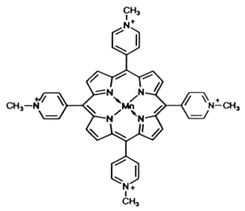
Solution and experimental setup

- Preparation and characterization of antioxidant PLGA nanoparticles (NPs) and liposomes loaded by SOD or SOD mimetic and surface modified with anti-MUC1 antibody.



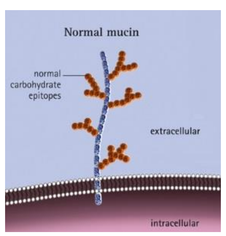


Human Mn-SOD enzyme[4]

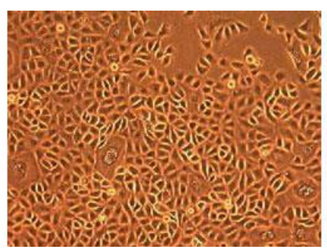


Mn(III)tetrakis(1-methyl-4-pyridyl)porphyrin (MnTMPyP)

- Investigation of the targeting effect and protective antioxidant efficacy of prepared nanoparticulate systems in vitro.



Anti-MUC1 antibody



Normal human bronchial epithelial cells

Results and discussion

Synthesis of NPs and liposomes and their main characteristics

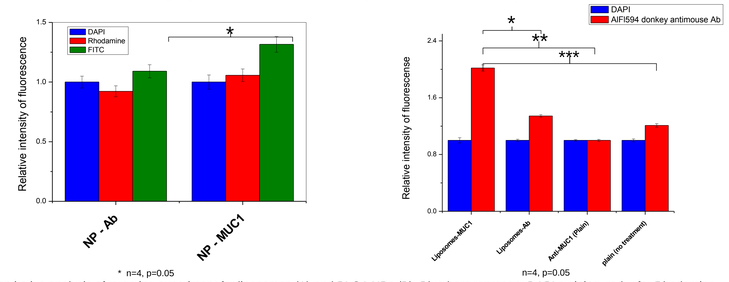
- We have successfully synthesized PLGA NPs and liposomes modified with SOD or SOD mimetic (MnTM-2-PyP) and attached targeting or control antibody.
- In our experiments the hydrodynamic diameter of NPs and liposomes was measured using photon-correlation spectroscopy or dynamic light scattering (DLS) technique that was performed on 90 Plus Particle Size Analyzer (Brookhaven Instruments Corporation, Holtsville, NY, USA).
- The colloidal stability was analyzed through estimation of Zeta potential of nanoparticles.

Table 1. Main characteristics of nanoparticulate systems

	L-SOD	L-SOD-Ab	L-SOD-MUC1	NP-SOD	NP-SOD-Ab	NP-SOD-MUC1
Actual size, hm	130±15	135±15	135±15	220±10	250±25	230±20
SOD activity, U/ml	3000±100	3550±100	3270±100	800±70	800±50	800±50
Concentration of antibody (μg/ml)/ molecules per liposome						
Rabbit anti-bovine antibody	-	53	-	-	50	-
ANTI-MUC-1	-	-	14	-	-	45

Targeted drug delivery in vitro

- To study the potential of targeting treatment we have tested PLGA NPs and liposomes surface modified with anti-MUC1 antibody (L-MUC1 and NP-MUC1) in comparison with nanoparticles modified with control antibody (L-Ab and NP-Ab). Results are presented below.



* n=4, p=0.05 n=4, p=0.05

Quantitative analysis of targeting experiment for liposomes (A) and PLGA NPs (B). Blue bars represent DAPI staining, red – for Rhodamine, and green is for AlFl594 (A)/FITC (B).

Conclusions

- We have synthesized PLGA NPs and liposomes modified with SOD or SOD mimetic (MnTM-2-PyP) and attached targeting or control antibody.
- Modification of liposomes and PLGA NPs with anti-MUC1 antibody is suitable for the targeting purposes. These nanoparticulate systems have shown to have better targeting compare to the plain nanoparticles and samples with control antibodies.

References

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