Liposomal Form of Prostaglandin E2 for Inhalation Treatment of Pulmonary Fibrosis

V. Ivanova, O. B. Garbuzenko, K. R. Reuhl, and T. Minko

Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ, 08854, USA
vivanova@eden.rutgers.edu

ABSTRACT SUMMARY
The present investigation is aimed at studying administration of liposomal prostaglandin E2 (PGE2) locally through inhalation versus intravenous administration to the mice with idiopathic pulmonary fibrosis (IPF). An IPF model was created by intratracheal instillation of bleomycin (1.5 U/kg). Liposomal PGE2 normalized the disturbances in the expression of many genes involved in the development of IPF, substantially restricted inflammation and fibrotic injury in the lung tissues, prevented decrease in body mass, limited hydroxyproline accumulation in the lungs, and finally eliminated mortality of animals after intratracheal injection of bleomycin.

INTRODUCTION
Idiopathic pulmonary fibrosis (IPF), a chronic, progressive, and often fatal form of interstitial lung disease, is the most common form of idiopathic interstitial pneumonias [1]. Treatment of IPF still represents a major clinical challenge since this disorder does not have reliable therapeutic options.

Prostaglanding E2 (PGE2), a cyclooxygenase-derived lipid mediator, attracts considerable attention for its role in the development and progression of IPF and as a possible therapeutic for this disease [2]. Systemic delivery of PGE2, as well as other drugs intended to fight lung diseases, has several disadvantages including but not limited to low accumulation in the lungs and possible adverse side effects on other organs and tissues. In contrast, local inhalation delivery of PGE2 directly to the lungs has the potential to enhance the treatment of IPF by increasing its local concentration in the lungs and preventing or at least limiting its penetration into the bloodstream and accumulation in other healthy organs.

However, free native PGE2 cannot be delivered into the lungs by inhalation requiring a special dosage form/formulation or delivery system that can be inhaled. We hypothesize that the local lung delivery of liposomes containing PGE2 can be used for the effective treatment of IPF and will limit its adverse side effects on other organs. To test this hypothesis, we designed and tested in bleomycin induced murine model of IPF liposomal drug delivery system which delivers PGE2 by inhalation topically to the lungs.

EXPERIMENTAL METHODS
Liposomes were prepared as previously described [3-6]. PGE2 was incorporated in the membranes of liposomes in the ratio of 1:1. The diameter, shape, and charge of liposomes were characterized by dynamic light scattering, and zeta-potential measurement respectively.

RESULTS AND DISCUSSION
It was found that 24 hours after intravenous injection, liposomes predominately accumulated in the kidneys and liver while substantially less content of liposomes was found in the spleen, heart and lungs (Fig. 2). Only trace amount of liposomes registered in the brain. In contrast, after inhalation delivery, liposomes predominately retained in the lungs with minimal amounts found in other organs including the liver, kidneys spleen, heart, and brain. Liposomes were registered by TEM inside the cytoplasm of lung cells. In the present experimental work, at the first time we showed that treatment of pulmonary fibrosis by liposomal PGE2 delivered to the lungs by inhalation led to the substantial elimination of all studied symptoms of IPF developed after intratracheal injection of bleomycin. The data show that liposomal PGE2 delivered locally to the lungs eliminated the
increase in the mouse body mass, substantially limited hydroxyproline content in the lungs, disturbances in the mRNA and protein expression, restricted lung tissue damage (Fig. 3), normalized body weight and completely prevented animal mortality (Fig. 4). These effects of PGE2 can be a result of its ability to limit fibroblast proliferation, activation, migration, collagen secretion, myofibroblast differentiation.

Fig. 2. Relative tissue content of liposomes delivered to mice by intravenous injection (A) or inhalation (B).

Fig. 3. Lung histology (hematoxylin and eosin). A- Healthy mice (control). B- Lung fibrosis (induced by intratracheal injection of 1.5 u/kg of bleomycin). C- Mice treated with inhalation of liposomal PGE2 within 3 weeks twice a week starting one day after the bleomycin administration.

Fig. 4. Inhalation treatment of mice with experimental lung fibrosis by liposomal PGE2 (Lip PGE2) prevents animal mortality.

CONCLUSION
Our data provide an evidence that pulmonary fibrosis can be effectively treated by inhalation of the liposomal form of PGE2 delivered locally into the lungs. The results of the present investigations make liposomal form of PGE2 an attractive drug for effective inhalation treatment of idiopathic pulmonary fibrosis.

REFERENCES

ACKNOWLEDGMENTS
We thank Dr. D. C. Reimer from Rutgers Lab Animal Services for his help with the development and implementation of orthotopic mouse model of lung fibrosis and Valentyn Starovoytov for the help with obtaining and analysis of transmission electron microscopy images. This work was supported in part by the grant R01 CA111766 from National Institutes of Health.