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Poster Number

23 **Using Polyanionic Heparin Mimetics for the treatment of COPD**

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COPD patients suffer from sustained inflammation leading to airway damage and deteriorating lung function caused by unopposed protease activity resulting from a1-antitrypsin resistant supramolecular complexes of neutrophil elastase and shed syndecan-1 in the airway. It was further shown that the action of the GAG digesting enzyme heparanase facilitates syndecan-1 shedding.

We hypothesize that the use of a polyanionic heparin mimetic would 1) displace neutrophil elastase from syndecan-1 rendering it susceptible to a1-antitrypsin inhibition and 2) inhibit heparanase activity in the airway.

In vitro tests show that the heparin mimetic successfully displaced neutrophil elastase from high molecular weight supramolecular complexes with syndecan-1. The dissociated neutrophil elastase was then rapidly inhibited by endogenous a1-antitrypsin. A similar degree of complex dissociation and resultant neutrophil inhibition was also shown to be present in BA samples of COPD patients. We also demonstrate that the heparin mimetic was capable of reducing heparanase activity and heparanase-induced syndecan-1 shedding using an air-liquid interface model of the lung.

To assess the feasibility of using the mimetic as a treatment for COPD, we treated cigarette smoke-induced COPD rats with an aerosol preparation of the mimetic. Preliminary results indicated that the number of neutrophils and neutrophil elastase amount in the lung was significantly decreased compared to rats treated with carrier alone. This suggests that our preparation can serve as a potential drug for the treatment of COPD.

24 **Timeless interacts with Parp1 to promote homologous recombination repair**

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Both Parp1 and Timeless have been implicated in DNA damage response, while there is no report that Parp1 could function together with Timeless. We have, for the first time, provided the evidence that Parp1 binds to Timeless both in vitro and in vivo. In addition, we present the crystal structure of Timeless in complex with Parp1, and demonstrate that Timeless-Parp1 complex facilitates homologous recombination repair.