Supplemental limitation section

This is a preliminary single-experiment animal study, and as such, it has several limitations. First, we need to interpret its findings with caution in the context of a clinical human setting. The primary focus of this study was on the pathophysiological concept of NETs, and therefore it was not powered to detect a difference in clinical disease between treatment groups. In addition, none of the current existing animal models, including our used bovine model, mimics all the features of human RSV disease (1). Finally, dornase alfa may also affect 'normal' extracellular DNA from necrotic cells in addition to NETs. Taken together, more studies are needed to address the role of NETs and potential clinical benefit to target them (e.g. by dornase alfa).

A second limitation of our study was the unexpected need to sacrifice this number of animals prematurely as a result of rapid LRTD deterioration at day 7-8, as observed mostly in the control group. This led to a complete dataset of blood and BAL samples up to day 7, and to different time points of histological analysis. However, as mentioned and shown in the supplemental data, the observed differences between the dornase alfa and control treated animals were not attributable to this.

In the present study we used the clinical available (and cystic fibrosis FDA-registered) human recombinant dornase alfa (Pulmozyme®) as treatment. The dose was within therapeutic range for humans, delivered directly intratracheally (2) and by nebulisation. Due to ethical reasons we could not deliver both administrations intratracheally. Thus we chose to administer the second dose by nebulization to ascertain maximal treatment effect. Future research must determine if single dose or double dose via nebulization only, will result in equal NET-lysis.

References

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