Introduction:
The receptor for advanced glycation end-products (RAGE) is highly expressed in lung alveolar type (AT)-I cells where it can bind multiple ligands. Whether RAGE plays a role in lung alveolar epithelial repair following injury remains unknown. Here, we investigated whether RAGE modulation has an impact on lung alveolar epithelial repair and examined the influence of RAGE on the proliferation, migration, and differentiation of AT-II cells into AT-I cells.

Methods:
A549 cells were grown in culture to confluence and treated with RAGE agonists HMGB1 and AGEs, alone or combined with RAGE antagonist peptide. Lung epithelial repair, cell migration and cell proliferation were studied. Immunostaining of caveolin 1 and surfactant protein-C was used to investigate the expression of markers of AT-I and AT-II cells, respectively.

Results:
HMGB1 promoted healing of the A549 cell monolayer compared to the control condition at 24h (p=0.04) and 48h (p <0.0001), and treatment with RAP reduced this effect. AGEs stimulated wound repair at 24h (p=0.005) and 48h (p=0.0001); RAP suppressed the positive effect of AGEs at all time points. A549 cells treated with HMGB1 had higher migration capacity at 12h (p=0.0015), but not at 48h (p=0.7), and co-treatment with RAP had no influence. Treatment with AGEs decreased cell migration at 12h (p=0.002) but increased it at 48h (p=0.004); RAP inhibited this effect at 48h (p=0.005). HMGB1 increased cell proliferation at 12h (p = 0.0001) and 48h (p = 0.0003), and this effect was reversed by RAP treatment; the effects of AGEs on cell proliferation followed exactly the same patterns. Immunostaining of caveolin 1 seemed more important after treatment with HMGB1 and AGEs.

Conclusion:
Our results suggest that RAGE ligation may impact wound repair of lung alveolar epithelial A549 cells through multiple mechanisms including cell proliferation and cell differentiation.