DELIVERY OF HUMAN AMNIOTIC STEM CELLS CORRECTS CFTR FUNCTION IN CF MOUSE NASAL AIRWAYS *IN VIVO*

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Background

- Many mutations that cause CF lung disease may not be treatable by oral drugs, and a stem cell therapy is one option being explored.
- Human amnion epithelial cells (hAEC) are immune-privileged epithelial cells that can be readily harvested from placenta after birth.
- Our *in vitro* studies (Kicic et al, unpublished) suggest that when CF airway epithelium is co-cultured with hAEC, hAEC can improve CFTR-associated defects such as increasing a low airway surface liquid (ASL) depth and renewing defective epithelial chloride-ion transport.
- This study tested if delivery of hAEC to the (CFTR-defective) nasal airways of CF mice could improve the standard functional indicator of CFTR protein expression in CF airways - the nasal airway potential difference (PD) under low chloride perfusion.

Methods

- We employed a repeated-measures study design to measure the change in the bioelectrical defect in nasal airways in CF mice using an *in vivo* airway PD assay (total n=24 CF mice, 12 mice/ group (10 M, 14 F)).
- Nasal PD was measured using Krebs (KRB) solutions with or without chloride, infused into the nasal airway at a rate of 1µl/min (Figure 1).
- Nasal PD was performed prior to treatment (baseline).
- Mice received either: a) 30 µl of conditioned-media alone (media derived from hAEC cultures), or b) 0.5 -1.1 x10^6 cells/ml in 30µl of hAEC in conditioned-media.
- Treatment was instilled into the right nostril in 3 x10µl aliquots, delivered at 10 minute intervals.
- PD was again measured at 1 at 7 days after delivery.

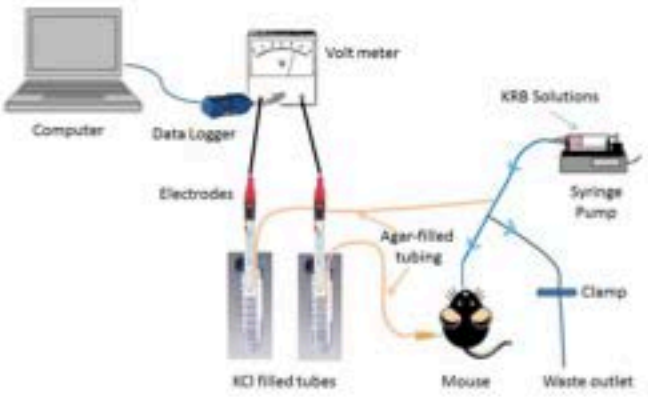

Figure 1: Diagrammatic representation of nasal PD setup

Results

- For the mice that received conditioned-media, nasal airway PD was significantly improved after 1 day (ΔPD 0.46 ± 2.55; Mean± SEM, *p<0.05 vs baseline, RM ANOVA, n=12) compared to pre-treatment baseline ΔPD: 7.38 ± 1.24. However after 7 days the nasal PD (ΔPD 2.83 ± 1.79) was not significantly different to baseline (Figure 2a).
- Nasal PD tested in the same animals following hAEC delivery (Figure 2b) retained a significantly-improved level of airway PD at both 1 day (ΔPD 0.68 ± 2.05, **p<0.01) and 7 days (ΔPD -0.45± 2.38, ***p<0.001) compared to baseline.

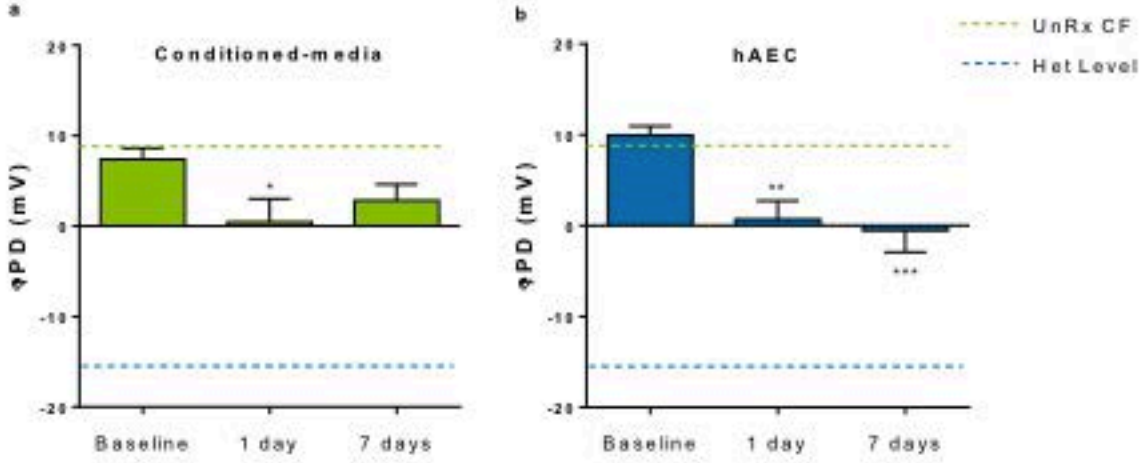

*Figure 2: The change in nasal PD in mice that received either a) conditioned-media or b) hAEC compared to pre-treatment (baseline). *p<0.05, **p<0.01, ***p<0.001, RM ANOVA vs baseline, n=12.*

Conclusion

- Improvement in CFTR functional expression in CF mouse airway as measured by airway PD, together with *in vitro* data (Kicic et al, unpublished) suggests that hAEC can produce improvement in airway CFTR function.
- Interestingly, conditioned-media derived from hAEC culture can transiently improve airway PD. Future studies of these two potential therapeutic approaches for CF airway disease treatment (short, and longer term) will further examine airway epithelial ion channel function *in vivo* to help determine the mechanisms of action.

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