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# Higher throughput drug screening for rare respiratory diseases: readthrough therapy in primary ciliary dyskinesia

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**Primary cell culture of nasal epithelial cells (including differentiation to multiciliated cells) from patients with primary ciliary dyskinesia enabled immunofluorescence-based screening in miniaturised air–liquid interface cultures** https://bit.ly/3rjoxBF

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## Abstract

***Background*** Development of therapeutic approaches for rare respiratory diseases is hampered by the lack of systems that allow medium-to-high-throughput screening of fully differentiated respiratory epithelium from affected patients. This is a particular problem for primary ciliary dyskinesia (PCD), a rare genetic disease caused by mutations in genes that adversely affect ciliary movement and consequently mucociliary transport. Primary cell culture of basal epithelial cells from nasal brush biopsies followed by ciliated differentiation at the air–liquid interface (ALI) has proven to be a useful tool in PCD diagnostics but the technique's broader utility, including in pre-clinical PCD research, has been restricted by the limited number of basal cells that can be expanded from such biopsies.

***Methods*** We describe an immunofluorescence screening method, enabled by extensive expansion of basal cells from PCD patients and the directed differentiation of these cells into ciliated epithelium in miniaturised 96-well transwell format ALI cultures. As proof-of-principle, we performed a personalised investigation in a patient with a rare and severe form of PCD (reduced generation of motile cilia), in this case caused by a homozygous nonsense mutation in the *MCIDAS* gene.

***Results*** Initial analyses of ciliary ultrastructure, beat pattern and beat frequency in the 96-well transwell format ALI cultures indicate that a range of different PCD defects can be retained in these cultures. The screening system in our proof-of-principal investigation allowed drugs that induce translational readthrough to be evaluated alone or in combination with nonsense-mediated decay inhibitors. We observed restoration of basal body formation but not the generation of cilia in the patient's nasal epithelial cells *in vitro*.

***Conclusion*** Our study provides a platform for higher throughput analyses of airway epithelia that is applicable in a range of settings and suggests novel avenues for drug evaluation and development in PCD caused by nonsense mutations.