Molecular Therapy
Methods & Clinical Development
Editorial

Pulmonary macrophage transplant therapy in parenchymal lung diseases

Pulmonary alveolar proteinosis (PAP) is a rare syndrome where surfactant accumulates in the alveolar macrophages, leading to impaired gas exchange, dyspnea, hypoxia, and respiratory failure in some cases. The key regulator of alveolar macrophage maturity and function is granulocyte macrophage colony-stimulating factor (GM-CSF), and dysfunctional signaling is the key pathogenic driver of primary PAP.[1,2] Primary PAP can be caused by either anti-GM-CSF autoantibodies in autoimmune PAP or mutations in CSF2RA or CSF2RB, encoding the α and β subunits of the GM-CSF receptor, respectively, in hereditary PAP (hPAP).[3,4] Whole-lung lavage is the current treatment for hPAP but is not FDA approved, and while bone marrow, stem cell, and lung transplantations have been trialed in hPAP with some success, these therapies are limited by infection and graft rejection.

Almost a decade ago, Suzuki et al. demonstrated that pulmonary macrophage transplantation (PMT) of either wild-type or *Csf2rb*-gene-corrected macrophages into *Csf2rb*$^{-/-}$ mice was a potential therapeutic solution for hPAP. They showed that this was safe and well tolerated and that a single administration corrected the lung disease without the need for myeloablation. Moreover, the PMT-derived alveolar macrophages and the associated benefits persisted for at least 12 months.[5] Importantly, *CSF2RA* mutations affecting the α subunit of the GM-CSF receptor account for almost 90% cases of hPAP.[6] This group created a *Csf2ra*$^{-/-}$ mouse model[7] and subsequently implanted lentiviral gene-corrected bone-marrow-derived macrophages. They demonstrated correction of PAP-specific histological, cytological, and biomarker findings.[8] This led to calls for human trials and thus the current study by Arumugam et al.,[6] which was designed in support of an investigational new drug (IND) application, and the first-in-human clinical trial (ClinicalTrials.gov: NCT05761899).

This comprehensive toxicology study has successfully demonstrated the efficacy and safety of PMT using *Csf2ra*-gene-corrected macrophages at different dosing intervals and with substantial long-term follow-up data. A dose of 500,000 cells, the lowest effective dose, was chosen as the target dose, with 5,000,000 cells as the 10-fold safety margin. PMT was therapeutically efficacious in *Csf2ra*$^{-/-}$ mice with reduction in pulmonary surfactant burden, lung weight, bronchoalveolar lavage (BAL) turbidity, surfactant protein D (SP-D), GM-CSF, macrophage colony stimulating factor (M-CSF), and monocyte chemoattractant protein-1 (MCP-1) levels. It was safe and well tolerated, and while transient pulmonary neutrophilia and exacerbation of pre-existing hPAP-related lymphocytosis were observed 14 days after PMT, this was seen only with the safety-margin dose and not the target dose.[6] Critically, the center that performed this study utilized the Vector Production Facility at Cincinnati Children's Hospital Medical Center. This center provides scale-up and manufacturing services for gene transfer vectors under conditions compliant with good manufacturing practices (GMPs) and in accordance with US Food and Drug Administration (FDA) and European Medicine Agency (EMEA) guidelines for use in human clinical trials. Crucially, this will be the same facility and site of the recently approved trial (ClinicalTrials.gov: NCT05761899).

These are exciting and promising first steps toward advancing treatment for this previously difficult-to-treat, devastating disease. The advancement of PMT to clinical trials follows huge innovation over recent years with the emergence of autologous cell-based therapies, such as chimeric antigen receptor (CAR) T cell therapy,[9] that have paved a new road to gene-corrected therapy. For decades, attempts at direct gene therapies for diseases including cystic fibrosis (CF) and Duchenne muscular dystrophy have had varying results. Despite a lack of success in the gene therapy clinical trials performed to date, recombinant adeno-associated virus (rAAV) appears to be the most promising human gene therapy vector.[10] However, a significant limitation remains potential immune-related adverse events such as acute respiratory distress syndrome (ARDS) when given at higher doses.[11]

The emergence of cell-based gene therapies opens a whole new raft of possibilities. It is possible that the use of PMT could extend to other parenchymal lung diseases including progressive pulmonary fibrosis and even potentially to difficult-to-treat infections such as mycobacterium. The translation of the results by Arumugam et al. into in-human trials is the first step of an exciting new journey in both cell-based therapies and parenchymal lung disease.

Marissa O'Callaghan[1,2] and Cormac McCarthy[1,2]

[1]Department of Respiratory Medicine, St. Vincent's University Hospital, Dublin 4, Ireland; [2]School of Medicine, University College Dublin, Dublin 4, Ireland

Correspondence: Cormac McCarthy, School of Medicine, University College Dublin, Dublin 4, Ireland.
E-mail: cormac.mccarthy@ucd.ie

https://doi.org/10.1016/j.omtm.2023.101180

REFERENCES

1. Trapnell, B.C., Nakata, K., Bonella, F., Campo, I., Griese, M., Hamilton, J., Wang, T., Morgan, C., Cottin, V., and McCarthy, C. (2019). Pulmonary alveolar proteinosis. Nat. Rev. Dis. Prim. *5*, 16.

2. McCarthy, C., Carey, B.C., and Trapnell, B.C. (2022). Autoimmune Pulmonary Alveolar Proteinosis. Am. J. Respir. Crit. Care Med. *205*, 1016–1035.

3. Suzuki, T., Sakagami, T., Young, L.R., Carey, B.C., Wood, R.E., Luisetti, M., Wert, S.E., Rubin, B.K., Kevill, K., Chalk, C., et al. (2010). Hereditary pulmonary alveolar proteinosis: pathogenesis, presentation, diagnosis, and therapy. Am. J. Respir. Crit. Care Med. *182*, 1292–1304.

4. Suzuki, T., Maranda, B., Sakagami, T., Catellier, P., Couture, C.Y., Carey, B.C., Chalk, C., and Trapnell, B.C. (2011). Hereditary pulmonary alveolar proteinosis caused by recessive CSF2RB mutations. Eur. Respir. J. *37*, 201–204.

5. Suzuki, T., Arumugam, P., Sakagami, T., Lachmann, N., Chalk, C., Sallese, A., Abe, S., Trapnell, C., Carey, B., Moritz, T., et al. (2014). Pulmonary macrophage transplantation therapy. Nature *514*, 450–454.

6. Paritha Arumugam, P., Brenna Carey, P., Kathryn, A., Wikenheiser-Brokamp, M., Jeffrey Krischer, P., Matthew Wessendarp, M., Kenjiro Shima, M., Claudia Chalk, M., Jennifer Stock, M., Yan Ma, B., et al. (2023). A Toxicology Study of Csf2ra Complementation and Pulmonary Macrophage Transplantation Therapy of Hereditary PAP in Mice. Mol. Ther. Methods Clin. Dev.

7. Shima, K., Arumugam, P., Sallese, A., Horio, Y., Ma, Y., Trapnell, C., Wessendarp, M., Chalk, C., McCarthy, C., Carey, B.C., et al. (2022). A murine model of hereditary pulmonary alveolar proteinosis caused by homozygous Csf2ra gene disruption. Am. J. Physiol. Lung Cell Mol. Physiol. *322*, L438–l448.

8. Arumugam, P., Suzuki, T., Shima, K., McCarthy, C., Sallese, A., Wessendarp, M., Ma, Y., Meyer, J., Black, D., Chalk, C., et al. (2019). Long-Term Safety and Efficacy of Gene-Pulmonary Macrophage Transplantation Therapy of PAP in Csf2ra(-/-) Mice. Mol. Ther. *27*, 1597–1611.

9. Michels, A., Ho, N., and Buchholz, C.J. (2022). Precision medicine: In vivo CAR therapy as a showcase for receptor-targeted vector platforms. Mol. Ther. *30*, 2401–2415.

10. Sui, H., Xu, X., Su, Y., Gong, Z., Yao, M., Liu, X., Zhang, T., Jiang, Z., Bai, T., Wang, J., et al. (2022). Gene therapy for cystic fibrosis: Challenges and prospects. Front. Pharmacol. *13*, 1015926.

11. Lek, A., Wong, B., Keeler, A., Blackwood, M., Ma, K., Huang, S., Sylvia, K., Batista, A.R., Artinian, R., Kokoski, D., et al. (2023). Death after High-Dose rAAV9 Gene Therapy in a Patient with Duchenne's Muscular Dystrophy. N. Engl. J. Med. *389*, 1203–1210.