Targeted therapy for pulmonary alveolar proteinosis: the time is now

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Shareable abstract (@ERSpublications)
Gene therapy and impaired pathway correction are promising treatments for selected patients with pulmonary alveolar proteinosis syndrome https://bit.ly/3d9hjdS

Cite this article as: Bonella F, Borie R. Targeted therapy for pulmonary alveolar proteinosis: the time is now. *Eur Respir J* 2022; 59: 2102971 [DOI: 10.1183/13993003.02971-2021].

Received: 19 Nov 2021
Accepted: 24 Nov 2021

Pulmonary alveolar proteinosis (PAP) is a rare syndrome with a complex pathogenesis leading, at the end, to accumulation of surfactant phospholipids and lipoproteins in the alveoli, and causing progressive respiratory insufficiency [1]. Alongside the most common autoimmune form, affecting more than 90% of patients and characterised by the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies, there are severe forms associated with genetic mutations, which are usually diagnosed in children. The landscape of genetic mutations underlying PAP is rapidly evolving and advances in this field from the past decade are impressive [2, 3]. In terms of frequency, the most common mutations, associated with primary hereditary PAP, affect genes coding for the a- and b-subunit of GM-CSF receptor (CSF2RA and CSF2RB), followed by surfactant (SFTPB, SFTPC, SFTPA1 and SFTPA2), ABCA3 and NKX2.1 gene mutations; PAP syndrome occurs sporadically in the latter two. Further, GATA-2 mutations, associated with a genetic immunodeficiency syndrome (MonoMAC) [4–6], SLC7A7, MARS, FARSB and NPC 2 gene mutations (causing lysinuric protein intolerance, methionine deficit, phenylalanine-tRNA synthetase deficit and Niemann–Pick disease, respectively) [2], and telomerase reverse transcriptase (TERT) mutations [7, 8] can also be revealed by PAP.