Big Changes on a Small Scale: Microbiome-Targeted Therapies for Lung Disease

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TARGETED and personalised therapies are expanding into a new area, focused not just on molecular receptors or immune signatures, but on the complex microbial communities that live inside us. In a 'hot topic' session presented at the European Respiratory Society (ERS) Congress 2025, researchers offered a compelling look at how the respiratory microbiome is reshaping our understanding of airway disease pathogenesis and opening novel therapeutic avenues. Together, their talks moved from precision pathogen targeting, to early-life microbial imprinting, to the potential of 'beneficial bacteria' in the chronically diseased lung.

PHAGE THERAPY: PATHOGEN TARGETING WITHOUT COLLATERAL DAMAGE?

The session opened with Georgia Mitropoulou, Lausanne University Hospital, Switzerland, who brought the clinical urgency of precision antibacterial therapy into focus. Her talk centred on one of the most challenging scenarios in respiratory medicine: a child with cystic fibrosis (CF) and multidrug-resistant *Pseudomonas aeruginosa*, for whom no conventional antimicrobial options remained.

Mitropoulou described the rationale and real-world execution of bacteriophage therapy, a highly targeted approach in which viruses that naturally infect bacteria are used therapeutically. Unlike broad-spectrum antibiotics, phages are narrow in host range, leaving commensal bacteria largely untouched. This makes phage therapy uniquely compatible with the principles of personalised, microbiome-sparing intervention.

In her case example, inhaled phage therapy was delivered under compassionate use, combined with standard antibiotics. Clinical improvement followed, and sputum monitoring showed early increases in phage titres. Yet the story quickly became more complex. Over repeated cycles, the patient developed increasing levels of anti-phage antibodies (IgA, IgG, and IgM), which correlated with a steady decline in recoverable phage in sputum. Ultimately, phage neutralisation diminished therapeutic effect.

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From this, Mitropoulou explored one of the central challenges in phage therapy: immune recognition. While phages can evolve alongside bacteria, they cannot escape a host immune response that flags them as foreign. Experimental frameworks are now emerging to quantify this risk. One such tool, a 'phage immunogenicity risk index', based on specific genetic features, may eventually help clinicians choose phages that are less likely to be neutralised.

She contextualised these clinical observations within the broader evidence base. Across hundreds of case reports, observational success rates appear high

(up to 80% achieving infection control or eradication), but randomised trials report more modest outcomes, reflecting publication bias and the concomitant use of antibiotics in nearly all cases. Notably, the first randomised, inhaled phage therapy trial in humans (BioMIX BX004 for chronic CF-associated *Pseudomonas*) demonstrated safety, tolerability, and preliminary microbiological signals, though efficacy results remain pending.[1]

Mitropoulou concluded with a nuanced message: phage therapy holds great promise as a personalised, targeted antibacterial intervention, especially for drug-resistant infections in CF and bronchiectasis, but its implementation required rigorous phage-host matching, immune-aware treatment planning, and much stronger clinical trial data.

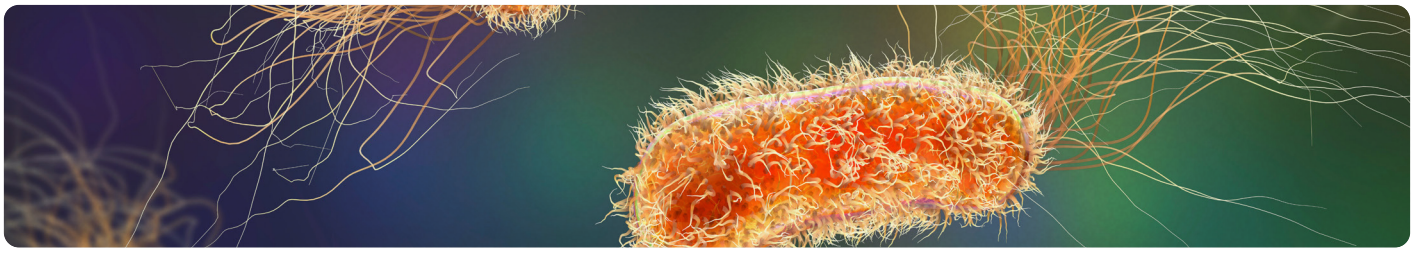
EARLY-LIFE IMPRINTING AND RESTORING LOST MICROBIAL SIGNALS

Olaf Perdijk, Utrecht University, the Netherlands, extended the concept of targeted therapy from targeting microbes to replacing the molecular signals they provide. His research shines light on a complex paradox: when early-life antibiotics are given to young mice, the microbiome composition eventually normalises, yet the animals retain a heightened vulnerability to allergic airway disease. Something in those early-life interactions imprints a long-lasting susceptibility, even when the microbial community appears restored.

Perdijk's mouse model, which uses a short antibiotic course followed by cohousing to allow complete microbial recovery, enabled his team to identify the crucial missing link: epithelial memory. Airway structural cells from mice treated with early-life antibiotics showed exaggerated chemokine release and heightened inflammatory responses long after microbial normalisation. Single-cell sequencing revealed mitochondrial stress signatures and altered metabolic pathways in epithelial subsets, signs of a tissue 'stress imprint' beneath an apparently healthy surface.[2]

Untargeted metabolomics provided a clue to this imprint: mice treated with early-life antibiotics exhibited reduced levels of indole-3-propionic acid (IPA), a microbially derived, tryptophan-based antioxidant with strong reactive oxygen species-scavenging properties. IPA supplementation during the early-life antibiotic window prevented mitochondrial dysfunction, normalised epithelial transcriptional signatures, and protected mice from developing exaggerated allergic inflammation. Interestingly, microbial dysbiosis and exacerbated airway inflammation were absent when antibiotics were given in adulthood, pointing to a narrow developmental window during which microbial metabolites shape epithelial resilience.[2]

Perdijk's findings position microbial metabolites, not just microbes themselves, as personalised therapeutic targets. Restoring these missing metabolic 'messages', whether via metabolite supplementation, engineered probiotics, or defined microbial consortia, may one day allow clinicians to correct early-life perturbations that predispose individuals to asthma and allergic disease.



BENEFICIAL BACTERIA IN CHRONIC LUNG DISEASE: PROTECTING THE 'GOOD ONES'

The third speaker, Aurélie Crabbé, University of Antwerp, Belgium, extended the discussion into chronic lung conditions such as COPD, CF, and bronchiectasis, asking a central question: while pathogens fuel the well-known vicious circle of chronic airway inflammation, could non-pathogenic members of the lung microbiome play a modulating, or even protective, role?

Chronic airway disease microbiomes (such as in bronchiectasis) typically include a substantial proportion of pathogens like *P. aeruginosa*, *Haemophilus*, and *Streptococcus pneumoniae*.[3] But alongside them exist an overlooked second half composed of commensal or opportunistic microbes. Over the past decade, multiple studies have reported associations between certain airway bacteria and lower inflammation, better lung function, or improved prognosis. However, study heterogeneity makes it difficult to evaluate which findings are robust.

To address this, Crabbé and colleagues conducted a systematic review and meta-analysis of chronic lung microbiome studies, synthesising data from 34 studies and over 4,000 participants (submitted, unpublished data). Across diseases spanning CF, COPD, asthma, and bronchiectasis, six genera were consistently associated with lower inflammation or better clinical outcomes. Three stood out: *Prevotella*, linked with lower cytokine levels, reduced neutrophil elastase activity, and better lung function; *Rothia*, associated with reduced inflammatory biomarkers and shown experimentally to protect against viral infection; and non-pathogenic *Streptococcus*, correlated with lower inflammation and capable of suppressing *Pseudomonas* through metabolic by-products.

Understanding how beneficial bacteria function requires credible *in vitro* systems that mimic the architecture and behaviour of human airway tissue. Using a variety of sophisticated platforms, including a rotating-wall bioreactor that produces highly differentiated airway tissue, Crabbé and her team found how specific non-pathogenic bacteria exert protective effects. *Prevotella* dampened epithelial inflammatory responses and inhibited *Pseudomonas* biofilms;[4] *Rothia* reduced cytokine production and protected mice from influenza-induced mortality by lowering viral loads;[5] and certain *Streptococcus* strains inhibited *Pseudomonas* growth via acetate production.[6] Importantly, these effects are strain-specific: genus-level sequencing cannot distinguish protective strains from neutral or even pro-inflammatory ones. This complicates interpretation of microbiome data and reinforces the need for precision approaches that function at strain resolution.

Crabbé closed with a real-world example illustrating why this nuance matters. In the CFMATTERS trial,[7] patients were randomised to either standard *Pseudomonas*-targeted therapy or an intensified regimen targeting *Pseudomonas* plus the next-most-abundant genera, which in many individuals included *Prevotella*, *Rothia*, *Veillonella*, and commensal *Streptococcus*. The broader regimen showed no benefit in lung function. More worryingly, extended follow-up revealed more exacerbations and lower quality of life in patients who received the broader antimicrobials.

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While causality cannot be proven, the pattern is consistent with the possibility that eliminating commensal strains removed ecological buffers that protect against pathogen overgrowth or inflammation. As Crabbé summarised: "Let's not kill the good ones."

A NEW ERA OF MICROBIOME-INFORMED PRECISION MEDICINE

Across these talks, a conceptual shift emerged, redefining the targets of respiratory therapeutics. Mitropoulou highlighted the promise of precision pathogen killing that spares the wider microbial ecosystem. Perdijk demonstrated that microbial metabolites, not just microbes, are essential signals that shape immune development and disease susceptibility. Crabbé argued for recognising and protecting beneficial commensals that actively modulate inflammation and pathogen behaviour.

Together, they point toward a future where respiratory medicine embraces the lung as a dynamic ecosystem. The next generation of personalised therapies may involve not only eradicating harmful microbes, but cultivating protective ones, restoring missing metabolites, and respecting the ecological balance that underpins respiratory health.

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