Medical University of Graz

Precision Medicine for People with Muco-Obstructive Lung Diseases

Summary

Florian Singer, Division of Paediatric Pulmonology and Allergology, Medical University of Graz, Austria

Supervisor:	PD Dr. Florian Singer
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 03, 2022 00:00 and September 20, 2022 23:59 (Europe/Zurich)

Description

Background: In people with muco-obstructive lung diseases (pwMOLD), Cystic Fibrosis (CF) and Primary Ciliary Dyskinesia (PCD) account for the most prevalent genetic etiologies. Chronic bacterial and fungal infection, neutrophilic inflammation, and mucus in peripheral small airways account for increased respiratory morbidity and mortality. We and others have extensively characterized biomarkers of small airway dysfuncion in pwMOLD using novel lung-physiology and imaging methods[1,2]. With the advent of precision medicine, *i.e.* modulator therapy for specific CFTR gene mutations, lung function decline is attenuated and survival may increase in people with CF. However, due to certain severe CFTR mutations, age restrictions and lack of specific treatment for people with PCD, approximately half of the population of pwMOLD worldwide are not eligible for modulators. Therefore, populations of pwMOLD currently undergo a dramatic shift into an increased heterogeneity of modulated vs. naïve disease endotypes. There is an urgent need to precisely characterize these heterogeneous disease endotypes using novel biomarker development and implementation approaches. On the basis of biomarkers that distinguish a given individual from other pwMOLD, effective and safe treatments should be precisely targeted to the needs of individuals.

Hypothesis and Objectives:

Biomarker Implementation - Small airway dysfuncion quantified by the Lung Clearance Index (LCI) from multiple-breath washout is an ideal candidate “treatable trait” for precise healthcare decisions in pwMOLD [3]. We aim to establish a study allocating pwMOLD to LCI guided vs. traditional care. We hypothesize that LCI guided care improves important respiratory domains in pwMOLD. We further hypothesize that this improvements exceed natural variability thresholds.

Objective I: To develop clinical decision algorithms with or without LCI including public and patient involvement (PPI).

Objective II: To develop the minimal clinically important difference in LCI using anchor based methods by PPI.

Objective III: To assess the difference in structural, functional and clinical domains of the lungs between pwMOLD undergoing LCI guided vs. traditional care in longitudinal analyses.

Biomarker Development – (i) Concurrent, (ii) discriminate, and (iii) predictive validity and (iv) responsiveness are important clinimetric properties which need to be established during the process of biomarker development. Our research institutes already have great experience and established reliable lipidome[4], microbiome, and neutrophilic marker protocols [5–7]. We aim to apply a systematic multi-domain characterization using lipidomics, microbiome, and neutrophil activity (elastase) in airway secretions, and lipidomics and elastase in peripheral blood [8,9].

Objective I: To assess the concurrent validity of lipidomics, microbiome, and elastase activity according to structural and functional lung disease domains in pwMOLD in cross-sectional and longitudinal analyses.

Objective II: To assess the discriminate validity of lipidomics, microbiome, and elastase activity to differentiate between pwMOLD stratified by modulator treatment in cross-sectional analyses.

Objective III: To assess the discriminate validity of lipidomics, microbiome, and elastase activity to differentiate between pwMOLD undergoing LCI guided vs. traditional care in longitudinal analyses.

Medical University of Graz

Objective IV: To assess the predictive validity and responsiveness of lipidomics, microbiome, and neutrophil activity to estimate the future risk of pulmonary exacerbations and response to exacerbation treatment in pwMOLD in longitudinal analyses.

Methodology:

Study design: International, prospective, multi-center observational study with sampling and testing embedded into clinical routine outpatient programs. Study sites: Graz, Zurich, and Berlin. Backup site: Innsbruck. Sample size based on non-inferiority lung function thresholds. Study duration: 3 years. Inclusion criteria: Established CF or PCD diagnoses, age > 4 years, not listed for lung transplant, ability to adhere to the protocols. At baseline, random allocation stratified by modulator treatment of pwMOLD to LCI-guided vs. traditional clinical care. Single-blinding of pwMOLD regarding the allocation of care programs. Clinical decision algorithm based on individual baseline and change in LCI vs standard algorithms in accordance to recommendations.

Assessments

Sampling is scheduled according to clinical routine care programs at all sites (Table 1). Functional and structural magnetic resonance imaging of the lung, together with Univ. Basel and Graz. Lung function tests: nitrogen multiple-breath washout and spirometry. Induced sputum samples for biobanking in Graz and later longitudinal 16S rRNA gene profiles, i.e. microbial diversity, and quantitative analyses together with BioTechMed Graz. Blood serum samples for biobanking in Graz and later profiling of lipid mediators by liquid chromatography coupled to tandem mass spectrometry for untargeted comprehensive lipidomics and targeted biomarker panels together with the Core Facility Mass Spectrometry Graz. Symptom and quality of life questionnaires.

References

1. Singer, F. *et al.* Lung clearance index predicts pulmonary exacerbations in individuals with primary ciliary dyskinesia: A multicentre cohort study. *Thorax* 1–8 (2021) doi:10.1136/thoraxjnl-2020-215504.

2. Kurz, J. M. *et al.* Association of lung clearance index with survival in individuals with cystic fibrosis. *European Respiratory Journal* **59**, 2100432 (2022).

3. Nyilas, S. *et al.* Physiological phenotyping of pediatric chronic obstructive airway diseases. *Journal of Applied Physiology* **121**, 324–332 (2016).

4. Brandsma, J. *et al.* Lipid phenotyping of lung epithelial lining fluid in healthy human volunteers. *Metabolomics* **14**, (2018).

5. Mahnert, A. *et al.* Man-made microbial resistances in built environments. *Nature Communications* **10**, 1–12 (2019).

6. Warncke, G. *et al.* Volatile organic compounds, bacterial airway microbiome, spirometry and exercise performance of patients after surgical repair of congenital diaphragmatic hernia. *Molecules* **26**, (2021).

7. Kumpitsch, C., Koskinen, K., Schöpf, V. & Moissl-Eichinger, C. The microbiome of the upper respiratory tract in health and disease. *BMC Biology* vol. 17 Preprint at https://doi.org/10.1186/s12915-019-0703-z (2019).

8. Kargl, J. *et al.* Neutrophils dominate the immune cell composition in non-small cell lung cancer. *Nature Communications* **8**, (2017).

9. Haudum, C. W. *et al.* Cohort profile: 'Biomarkers of Personalised Medicine' (BioPersMed): a single-centre prospective observational cohort study in Graz/Austria to evaluate novel biomarkers in cardiovascular and metabolic diseases. *BMJ Open* **12**, e058890 (2022).

To get more information or to apply online, visit https://mug.glowbase.com/positions/255 or scan the the code on the left with your smartphone.