# Breathomics in Respiratory Medicine

*Paolo Montuschi, M.D.*
*Department of Pharmacology, Faculty of Medicine, Catholic University of the Sacred Heart, Largo Francesco Vito, 1 – 00168, Roma, Italy*
*Pharmacology Unit, University Hospital Agostino Gemelli Foundation IRCCS, Largo Agostino Gemelli, 8 – 00168 Roma, Italy*

Breathomics, the multidimensional molecular analysis of exhaled breath [1], includes measurement of volatile (e.g., ethane, penthane, isoprene, limonene) or semi-volatile compounds (e.g., ethanol, acetone, 2-propanol) in the gaseous phase of exhaled breath with electronic noses (e-noses) or gas chromatography/mass spectrometry (GC/MS) and measurement of non-volatile (e.g., acetate, propionate, aminoacids) or semivolatile compounds with high-resolution nuclear magnetic resonance (NMR) spectroscopy or liquid chromatography/mass spectrometry (LC/MS) of exhaled breath condensate (EBC), a non-invasive technique which provides information on the composition of airway lining fluid, [2,3]. Metabolomics is the identification and quantification of small molecular weight metabolites in a biofluid. Specific profiles of volatile compounds in exhaled breath and metabolites in EBC (breathprints) are potentially useful surrogate markers of inflammatory respiratory diseases, including asthma and chronic obstructive pulmonary disease (COPD) [4,5]. Electronic noses (e-noses) are artificial sensor systems, usually consisting of chemical cross-reactive sensor arrays for characterization of patterns of breath volatile compounds, and algorithms for breathprints classification [6]. E-noses are handheld, portable, and provide real-time data. E-nose breathprints can reflect respiratory inflammation [4,5].
E-noses and NMR-based metabolomics of EBC can distinguish patients with respiratory diseases such as asthma [7-9], COPD [10,11], and lung cancer [12-14], or diseases with a clinically relevant respiratory component including cystic fibrosis [15] and primary ciliary dyskinesia [16], and healthy individuals.
Breathomics provides a unique tool for exploring the pathophysiology of respiratory diseases [11,15,16] and can be useful for molecular phenotyping of patients with respiratory disease, including asthma [4]. In combination with other omics platforms, breathomics might help identify disease pathways (endotypes), which might lead to mechanism-driven therapeutic approaches and foster drug discovery, by pinpointing new therapeutic targets. A pilot proof of concept study shows that breathomics is useful for assessing the effects of inhaled pharmacotherapies in patients COPD at the molecular level [17].
Validation in prospective independent cohorts is essential for development of e-nose and EBC NMR-based metabolomics techniques

## References

[1] Santini G, Mores N, Penas A, Capuano R, Mondino C, Trové A, Macagno F, Zini G, Cattani P, Martinelli E, Motta A, Macis G, Ciabattoni G, Montuschi P, Electronic Nose and Exhaled Breath NMR-based Metabolomics Applications in Airways Disease. Curr Top Med Chem 16, 1610-1630 (2016)
[2] Montuschi P (Editor), New perspectives in monitoring lung inflammation: analysis of exhaled breath condensate. CRC Press, Boca Raton, 1-219 (2004)
[3] Montuschi P, Indirect monitoring of lung inflammation. Nat Rev Drug Discov 1, 238-242, 2002.
[4] Brinkman P, Wagener AH, Hekking PP, Bansal AT, Maitland-van der Zee AH, Wang Y, Weda H, Knobel HH, Vink TJ, Rattray NJ, D'Amico A, Pennazza G, Santonico M, Lefaudeux D, De Meulder B, Auffray C, Bakke PS, Caruso M, Chanez P, Chung KF, Corfield J, Dahlén SE, Djukanovic R, Geiser T, Horvath I, Krug N, Musial J, Sun K, Riley JH, Shaw DE, Sandström T, Sousa AR, Montuschi P, Fowler SJ, Sterk PJ; U-BIOPRED Study Group, Identification and prospective stability of electronic nose (eNose)-derived inflammatory phenotypes in patients with severe asthma. J Allergy Clin Immunol 143, 1811-1820.e7 (2019)

[5] Fens N, de Nijs SB, Peters S, Dekker T, Knobel HH, Vink TJ, Willard NP, Zwinderman AH, Krouwels FH, Janssen HG, Lutter R, Sterk PJ, Exhaled air molecular profiling in relation to inflammatory subtype and activity in COPD. Eur Respir J 38, 1301-1309 (2011)
[6] Montuschi P, Mores N, Trové A, Mondino C, Barnes PJ, The electronic nose in respiratory medicine. Respiration 85, 72-84 (2013)
[7] Montuschi P, Santonico M, Mondino C, Pennazza G, Mantini G, Martinelli E, Capuano R, Ciabattoni G, Paolesse R, Di Natale C, Barnes PJ, D'Amico A, Diagnostic performance of an electronic nose, fractional exhaled nitric oxide and lung function testing in asthma. Chest 137, 790-796 (2010)
[8] Ibrahim B, Marsden P, Smith JA, Custovic A, Nilsson M, Fowler SJ, Breath metabolomic profiling by nuclear magnetic resonance spectroscopy in asthma. Allergy 68, 1050-1056 (2013)
[9] Sinha A, Krishnan V, Sethi T, Roy S, Ghosh B, Lodha R, Kabra S, Agrawal A, Metabolomic signatures in nuclear magnetic resonance spectra of exhaled breath condensate identify asthma. Eur Respir J 39, 500-502 (2012)
[10] Fens N, Zwinderman AH, van der Schee MP, de Nijs SB, Dijkers E, Roldaan AC, Cheung D, Bel EH, Sterk PJ, Exhaled breath profiling enables discrimination of chronic obstructive pulmonary disease and asthma. Am J Respir Crit Care Med 180, 1076-1082 (2009)
[11] Motta A, Paris D, Melck D, de Laurentiis G, Maniscalco M, Sofia M, Montuschi P, Nuclear magnetic resonance-based metabolomics of exhaled breath condensate: methodological aspects. Eur Respir J 39, 498-500 (2012)
[12] Kort S, Tiggeloven MM, Brusse-Keizer M, Gerritsen JW, Schouwink JH, Citgez E, de Jongh FHC, Samii S, van der Maten J, van den Bogart M, van der Palen J, Multi-centre prospective study on diagnosing subtypes of lung cancer by exhaled-breath analysis. Lung Cancer 125, 223-229 (2018)
[13] Tirzïte M, Bukovskis M, Strazda G, Jurka N, Taivans I, Detection of lung cancer with electronic nose and logistic regression analysis. J Breath Res 20, 13(1):016006 (2018)
[14] D'Amico A, Pennazza G, Santonico M, Martinelli E, Roscioni C, Galluccio G, Paolesse R, Di Natale C, An investigation on electronic nose diagnosis of lung cancer. Lung Cancer 68, 170-176 (2010)
[15] Montuschi P, Paris D, Melck D, Lucidi V, Ciabattoni G, Raia V, Calabrese C, Bush A, Barnes PJ, Motta A, NMR spectroscopy metabolomic profiling of exhaled breath condensate in patients with stable and unstable cystic fibrosis. Thorax 67, 222-228 (2012)
[16] Montuschi P, Paris D, Montella S, Melck D, Mirra V, Santini G, Mores N, Montemitro E, Majo F, Lucidi V, Bush A, Motta A, Santamaria F, Nuclear magnetic resonance-based metabolomics discriminates primary ciliary dyskinesia from cystic fibrosis. Am J Respir Crit Care Med 190, 229-233 (2014)
[17] Montuschi P, Santini G, Mores N, Vignoli A, Macagno F, Shoreh R, Tenori L, Zini G, Fuso L, Mondino C, Di Natale C, D'Amico A, Luchinat C, Barnes PJ, Higenbottam T, Breathomics for Assessing the Effects of Treatment and Withdrawal With Inhaled Beclomethasone/Formoterol in Patients With COPD. Front Pharmacol 9:258 (2018)