Breathomics of Respiratory Diseases

ABSTRACT

Respiratory diseases are common in humans. Rapid, and rather inexpensive diagnostics of respiratory diseases observed in the patient's exhaled air is extremely important today. The following exhaled biomarkers are discussed: fractional exhaled nitric oxide (FENO), volatile organic compounds, carbon monoxide, hydrocarbons, and hydrogen peroxide. Breathomics from exhaled volatile organic compounds and oximeters are also shortly discussed. FENO monitors made of WO_3 are discussed. They are large-scale produced and widely used in medical centers and clinics for diagnostics of respiratory diseases. Promising semiconductor sensors are manufactured from SnO_2, doped with Pd, Au, or Pt or multi walls carbon nanotubes, gold nanoparticles with single wall carbon nanotubes, quartz microbalance devices with porphyrin, ITO –ZnO <Pt> films, and surface acoustic wave devices with isobutylene. A combination of VOCs is considered a “molecular fingerprint” of breath. The electronic nose on metal oxide detectors allows investigation lung cancer and tuberculous.

Keywords: Obstructive sleep apnea syndrome; ypertension; tuberculosis; cystic fibrosis; bronchiectasis; rhinitis; interstitial lung disease; panbronchioliti; obstructive sleep apnea syndrome.

1. INTRODUCTION

Respiratory diseases include asthma, chronic obstructive pulmonary disease, lung cancer, pulmonary arterial hypertension, tuberculosis, cystic fibrosis, bronchiectasis, rhinitis, interstitial lung disease, chronic cough, lung transplant rejection, adult respiratory distress syndrome, diffuse panbronchioliti, obstructive sleep apnea syndrome and pneumoconiosis. Rapid and inexpensive diagnostics of respiratory diseases observed in the patient's exhaled air are very important today [1, 2]. It is impossible within the frames of this article to provide detailed information on the achievements in the field of respiratory diseases [1-3].

Detection of diseases at an early stage can significantly reduce the consequences of the disease and mortality [1, 4], as well as allows achieving the best possible therapeutic outcome. The development of new expensive and invasive tests, biomarkers, highly qualified medical workers, and special equipment are necessary [1, 5]. An ideal respiratory disease test should be highly accurate, low cost, non-invasive, and easily reproducible.

2. FRACTIONAL EXHALED NITRIC OXIDE BIOMARKER

Much attention has been paid recently to metal oxide gas sensors, which are promising for use in medicine (see, e.g., [6-8]). The most popular biomarker for respiratory disease today is fractional exhaled nitric oxide NO (FENO). Possibilities of to use tungsten trioxide (WO_3) gas sensors for breath analysis are discussed in [9]. WO_3 is one of the most commonly used materials for the manufacture of semiconductor gas sensors, which are promising for manufacture of portable medical diagnostic detectors. WO_3 responds to several biomarkers found in exhaled air (nitric oxide, acetone, ammonia, carbon monoxide, hydrogen sulfide, toluene, etc.) and allows obtaining probing results without the use of much more expensive analytical devices. Analyzing a patient's breathing is an extremely important field of application of such small-sized instruments allowing carry out real-time measurements.

Breath analysis of asthma using WO_3 was reported in [8, 30–32]. The resistance of such detectors decreased when exposed to reducing gas and increased in the presence of oxidizing gases [39]. For example, it is known that CO reduces the WO_3 lattice [40]. Akamatsu et al. investigated the surface of WO_3 in the air with NO_2 and NO. Oxidation of the surface was visible during exposure to NO_2 [9].

During inhalation air enters through the mouth and nostrils into the pharynx, then passes the epiglottis into the trachea, and finally enters the bronchi which branch into bronchioles that end in clusters of alveoli (see Fig. 1). The exchange of air with the bloodstream takes place in the alveoli [9].

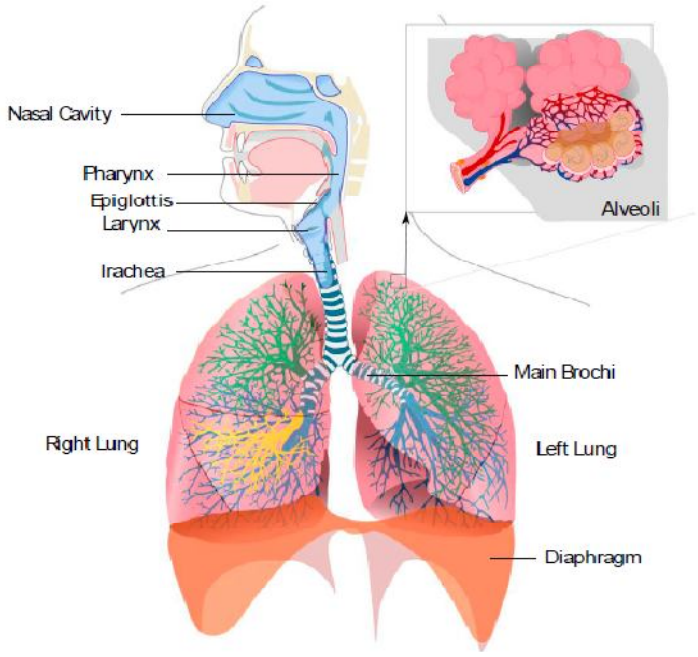

Fig. 1. Basic picture of the respiratory system [9]

Asthmatic patients exhale between 20 and 25 ppb of NO [17]. Portable NO-selective sensors used to detect asthma are sensitive to NO levels of <1 ppb, and have a rapid response time [68]. There are sensor arrays with high diagnostic accuracy for asthma [14, 44]. Most popular detectors for measuring the amount of NO detectors are produced by the Siemens and Bosch companies (Figs. 2 and 3) [21, 22]. The Siemens device is the size of a mobile phone and works by analyzing a patient's breath and measuring the amount of NO. The Siemens devices help asthma sufferers predict attacks, and can measure amounts of NO as small as one ppb.

Fig. 2. Breath measurements in Siemens [21, 22]

The device is allowing analyze their breath themselves at it minimum amount.

Fig. 3. Bedfont NObreath FeNO Monitor [23]

Specification of the monitor: Concentration range: 5-300ppb nitric oxide, Sensor sensitivity: 5ppb, Breath test time: Adult 12 seconds, Child 10 seconds, Operating temperature range: 10-30°C (ambient), Maximum ambient operating level: 350ppb NO.

Bosch Healthcare Solutions (USA) also developed small-size devices for measuring the amount of nitrogen monoxide (NO) (see Fig. 4).

Fig. 4. The Bosch detector [21, 22]

3. VOLATILE ORGANIC COMPOUNDS BIOMARKERS FOR RESPIRATORY DISEASES AND THEIR SPECIFIC

Volatile organic compounds (VOCs) are known as biomarkers for respiratory diseases. The monitoring of them by breath analysis is non-invasive. Specific of respiratory diseases are discussed below.

Obstructive pulmonary disease (COPD) is characterized by the production of VOCs secreted by the lungs [1]. Since both COPD and asthma patients have chronic airway inflammation, COPD patients could be misdiagnosed as asthmatics and vice versa. It is essential to clearly differentiate COPD from asthma in the case of elderly people who have systemic corticosteroids [1]. Is proposed to use an array of quartz crystal microbalance sensors coated with metal porphyrins in order to solve this problem. VOCs have been found in the exhaled breath of lung cancer patients [8, 24-33], and efforts have been realized in the early detection of lung cancer using exhaled breath [34-36]. Di Natale et al. reported in [37] how it is possible to differ healthy patients with lung cancer by using eight quartz crystal microbalance sensors coated with different metal porphyrins. The Pt-, Pd-, and Au-loaded SnO_2 sensors were used for PCA and discriminate analysis [38]. A surface acoustic wave (SAW) detector correctly diagnosed patients with lung cancer at room temperature and sub-ppb concentration [39, 40]. Haick et al. [41–44] differed early and late stages of lung cancer, small cell lung, and non-small cell carcinoma, as well as adenocarcinoma and squamous cell carcinoma with high accuracy, respectively. One gold nanoparticle (GNP) sensor, and Single-walled carbon nanotubes (CNTs) - based sensors array differentiated patients with lung cancer before and after surgery [42, 45].

Exhaled breath of patients with pulmonary arterial hypertension (PAH) had raised concentrations of 2-nonene, 2-propanol, acetaldehyde, ammonia, and pentane compared with control subjects, whereas 1-decene and 1-octene were significantly lower [46-50]. Cohen-Kaminsky et al. [51] have established that GNP-based sensors can successfully detect and classify PAH. The results showed that the breath signatures of patients with lung cancer differed from PAH [52]. All results were not influenced by the sex, and age of patients.

New devices for diagnosis and tuberculosis (TB) screening of were proposed [53-55]. Phillips et al. [56] suggested new biomarkers. GNP and molecularly modified single-walled CNTs were proposed for the detection of active TB [55]. The array- based on metalloporphyrin - coated QMB sensors successfully analyzed the exhaled breath of patients with TB [54].

The polymer composite- and quartz-based sensors array were utilized in the discrimination of obstructive sleep apnea syndrome (OSAS) between healthy controls [57, 58]. Breath prints of patients with OSAS largely depend upon diabetes mellitus, metabolic syndrome, and chronic heart failure [59]. Inflammation during monitoring of cystic fibrosis arises before clinical symptoms appear [60, 61]. Note that FeNO is the main marker in exhaled breath in some pulmonary diseases, including cystic fibrosis [62].

The detection and monitoring of therapy of patients with respiratory diseases is impossible today without machine-learning methods, disease-specific reference libraries and databases, and the use of different respiratory disease biomarkers discussed below [63-65]. The sensor response to VOCs can be analyzed by pattern recognition algorithms to classify different cases individually, in which the principal component reduction and subsequent pattern recognition are possible using discriminant analysis, machine-learning algorithms, artificial neural network data analysis, and neural networks [66].

4. EXHALED CARBON MONOXIDE BIOMARKERS

The degradation of hemoglobin leads to the exhalation of carbon monoxide (CO) via the

alveoli [61]. The measurements of CO in humans give reproducible results [67] using a laser spectrophotometer [68], or by a near-infrared CO analyzer [69]. Sensitive and stable near-IR instruments are used for continuous monitoring of stable asthma [70,71] and patients treated with inhaled corticosteroids. The cigarette smoking masks influence of CO when the COPD, chronic bronchitis, and bronchiectasis diseases are investigated [72[. Note that exhaled CO levels were markedly increased in patients with stable cystic fibrosis (CF) and allergic rhinitis [73-75], and reduced with antibacterial and corticosteroid treatment, which is related to lung function deterioration [74, 75].

5. EXHALED HYDROCARBONS MARKERS

Studies of ethane and pentane in exhaled breath were carried out on newborns [76]. Pentane and isoprene are increased in normal smokers and ethane in patients with COPD who smoke. Exhaled markers NO and pentane are used to distinguish asthma from obstructive sleep apnea, [77]. Elevated levels of NO [73], and ethane[78] for patients with sleep apnea CF obstruction and lung cancer were detected, correspondingly. Exhaled breath profile of different hydrocarbons has been shown in patients. An increase of pentane, but a decrease in isoprene concentration were observed in the case of pulmonary infection in comparison with patients without pulmonary infection. A significant increase in exhaled ethane was observed in patients undergoing cardiopulmonary bypass operations.

6. HYDROGEN PEROXIDE MARKERS

Exhaled H_2O_2 has been observed in exhaled condensate for patients with increased concentrations in asthma [79, 80]. More high levels of H_2O_2 has been detected in the breath condensate of smokers with stable COPD [81] as well as concentrations of 8-isoprostane in the breath condensate of patients with stable CF are increased [83].

Different sensors were developed based on fuel cell aldehyde sensor [84], and spin-coated ZnO<Pt> layer on ITO (indium tin oxide) substrate [85]. An electronic nose is used in the detection of patients with non-small cell lung cancer and COPD [86, 87]. Exhaled breath analysis using electronic nose was carried out for non-invasive diagnosis of chronic kidney disease, and diabetes mellitus [88]. Our patent [89] is suggested for detection of respiratory diseases.

7. BREATHOMICS FROM EXHALED VOLATILE ORGANIC COMPOUNDS

A combination of VOCs is necessary for the monitoring of respiratory diseases. It can be considered as a “molecular fingerprint” of exhaled breath. A “breathome” termin is proposed for such fingerprint, and “breathomics” describing for its [90-92]. The analysis of VOCs in exhaled by asthmatic breath is a non-invasive approach, that has not yet reached clinical practice.

Rather complicated and expensive optical techniques are commonly used to collect, detect and analyze exhaled VOCs of respiratory diseases [93–99]. Semiconductor chemical sensors for the breath analysis are proposed today, that, as usually, dramatically changed their electrical resistivity when they contact with VOCs [100], including SAW sensors were used as a detector, as well as acoustic and colorimetric sensors [101, 102].

8. OXYMETERS

A pulse oximeter can measure the level of oxygen (or oxygen saturation) in the blood in the case of respiratory disease [103] (Fig. 5). Pulse oximetry is often used in surgeries and bronchoscopy, and may also recommend if patient uses a ventilator to support breathing, suffer from sleep apnea, COPD, lung cancer, asthma, or pneumonia as well as heart attack, congestive heart failure, anemia disease. So, oximeters are used in all cases when it is necessary to measure the level of oxygen in the body.

A device contains a light source, light detector, and microprocessor, which compares and calculates the differences in oxygen-rich versus oxygen-poor hemoglobin. Two different types of light- infrared and red are transmitted through the body's tissues to the light detector on the other side of the probe.

Hemoglobin without oxygen absorbs more red light, and the microprocessor in the probe calculates the differences and converts the information to a digital value. The readings of the last 3 seconds are then averaged out. Several

different types of pulse oximeters can be purchased in drug stores.

Fig. 5. Pulse oximeter [103]

9. CONCLUSIONS

Rapid, and potentially inexpensive diagnostics of respiratory diseases observed in the patient's exhaled air are extremely important today. The following exhaled biomarkers are discussed: fractional exhaled nitric oxide (FENO), volatile organic compounds, carbon monoxide, hydrocarbons, and hydrogen peroxide. Breathomics from exhaled VOCs and oximeters are also shortly discussed.

FENO monitors made of WO_3 are large-scale produced and widely used in medical centers and clinics for diagnostics of respiratory diseases. Promising semiconductor sensors are manufactured from SnO_2, doped with Pd, Au, or Pt or multi walls carbon nanotubes, gold nanoparticles with single wall carbon nanotubes, quartz microbalance devices with porphyrin, ITO –Zno-Pt films, and surface acoustic wave devices with isobutylene. A combination of VOCs is considered as a “molecular fingerprint” of breath. The electronic nose on metal oxide detectors allows investigation lung cancer and tuberculous.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

Please insert paper title all highlighted references number

1. D. Hashoul and H. Haick Eur Respir Rev. 28: 1900110) (2019).
2. R. Gasparri, G. Sedda, L. Spaggiari Sensors (Basel) 18: E3029 (2018).
3. Y.Y. Broza, R. Vishinkin, O. Barash, et al. Chem Soc Rev; 47: 4781 (2018).
4. F.E. Azar, S. Azami-Aghdash, F. Pournaghi-Azar, et al. BMC Health Serv Res. 17, 413. (2017).
5. I. Nardi-Agmon, N. Peled. Lung Cancer; 8, 31 (2017).
6. V. M. Aroutiounian Journal of Nanomedicine and Nanotechnology, 11, 1 (2020).
7. V. M. Aroutiounian Journal of Contemporary Physics (Armenian Academy of Sciences), 55, 213 (2020).
8. V. M. Aroutiounian Ibid 56. 4 (2021).
9. A. Staerz, U. Weimar, and N. Barsan Sensors, 16, 1815 (2016).
10. M. Righettoni, A. Amann, S.E. Pratsini Mater. Today, 18, 163 (2015).
11. P. I. Gouma, K. A. Kalyanasundaram. Appl. Phys. Lett. 93,1 (2008).
12. H.G. Moon, Y.R. Choi, Y.S. Shim et al. ACS Appl. Mater. Interfaces 5, 10591 (2013).
13. B. Fruhberger, N. Stirling, F.G. Grillo et al Sens. Actuators B Chem., 76, 226 (2001).
14. H. Long, W. Zeng, H. Zhang J. Mater. Sci. Mater. Electron. 26, 4698 (2015).
15. M. Hübner, C.E. Simion, A. Haensch et al Sens. Actuators B Chem. 151, 103 (2010).
16. 41. T. Akamatsu, T. Itoh, N. Izu, W. Shin Sensors 13, 12467 (2013).
17. V. M. D. Struben, M. H. Wieringa, C. J. Mantingh et al. Eur. Respir. J. 26, 453 (2005).
18. P. Gouma,; S. Sood, M. Stanacevic, et al. Med. Rep. 2, 56 (2010).
19. X.-L. Li, T.-J. Lou, X.-M. Sun Inorg. Chem. 43, 5442 (2004).
20. N. Barsan, U. Weimar J. Electroceramics7, 13 (201).
21. www.healthcare.siemens.com/laboratory-diagnostics
22. www.vivaatmo.com Bosch Healthcare Solutions GmbH Techniks fur Leben
23. Bedfont® NObreath® FeNO Monitor
24. Z. Jia, H. Zhang, C. N. Ong, et al. ACS Omega 3, 5131 (2018).
25. W. Miekisch, J. K. Schubert, G. F. Noeldge-Schomburg Clin Chim Acta 347, 25 (2004).

26. B.M. Kesy. T. Ligor, et al. Biomed Chromatogr; 21, 553 2007).
27. S. Kischkel, W. Miekisch, A, Sawacki et al. Clin Chim Acta 411, 1637 (2010).
28. G. Peng, M. Hakim, Y.Y. Broza, et al. Br J Cancer 103, 542 (2010).
29. A. Bajtarevic, C. Ager, M. Pienz, et al. BMC Cancer; 9, 348 (2009).
30. A. Amann, M. Corradi, P. Mazzone, et al. Expert Rev Mol Diagn 11, 207 (2011).
31. M. Phillips, J. Herrera, S. Krishnan, et al. J. Chromatogr B Biomed Sci Appl; 729, 75 (1999).
32. S. Mendis, P.A. Sobotka, D.E. Euler Clin Chem Acta; 40, 1485 (1994).
33. D. Smith, T. Wang, J. Sule-Suso, et al. Rapid Commun Mass Spectrom 17, 845 (2003).
34. M. Phillips, N. Altorki, J. H. Austin, et al. Clin Chim Acta 393, 76 (2008).
35. M. Phillips, R. N. Cataneo, A. R. Cummin, et al. Chest 123, 2115 (2003).
36. P. Devillier, H. Salvator, E. Naline, et al. Curr Pharm Des 23, 2050 (2017).
37. C. Di Natale, A. Macagnano, E.Martinelli et al. Biosens Bioelectron 18, 1209 (2003).
38. T. Itoh, T. Nakashima, T. Akamatsu et al. Sens. Actuators B Chem. 187, 135 (2013).
39. Y. Y. Broza, R. Vishinkin, O. Barash, et al. Chem Soc Rev 47, 4781 (2018).
40. M. Hakim, O. Barash, et al. Chem Rev 112, 5949 (2012)
41. Peled N, Hakim M, Bunn PA, et al. J Thorac Oncol. 7,1528 (2012).
42. Broza YY, Kremer R, Tisch U. et al. Nanomedicine 9, 15 (2013).
43. O. Barash, N. Peled, F. R. Hirsch, et al. Small 5, 2618 (2009).
44. D. Shlomi, M. Abud, O. Liran, et al. J Thorac Oncol 12, 1544 (2017).
45. I. Nardi-Agmon, M. Abud-Hawa, O. Liran, et al. Ibid, 11, 827 (2016).
46. M. K. Nakhleh, H. Amal, R. Jeries, et al. ACS Nano 11, 112 (2017).
47. M. K. Nakhleh, H. Haick, M. Humbert, et al. Eur Respir J; 49, 1601897 (2017) .
48. Y. Lai, K.C. Potoka, H .C. Champion, et al. Circ Res 115, 115(2014).
49. N. Galie,. M. Humbert, J. L. Vachiery, et al. Eur Heart J; 37, 67(2016).
50. F. SJr. Cikach, A. R Tonelli, J. Barnes, et al. Chest 145, 551 (2014).
51. S. Cohen-Kaminsky, M. Nakhleh, F. Perros, et al. Am J Respir Crit Care Med. 188, 756 (2013).
52. P. J. Mazzone, J. Hammel, R. Dweik, et al. Thorax 62, 565 (2007).
53. N.M. Zetola, C. Modongo, O. Matsiri, et al. J Infect; 74, 367 (2017)
54. M. Bruins, Z. Rahim, A Bos, et al. Tuberculosis 93, 232 (2013).
55. M. K. Nakhleh, R. Jeries, A. Gharra, et al. Eur Respir J. 43 1522 (2014).
56. M. Phillips, R.N. Cataneo, R. Condos, et al. Tuberculosis 87, 44 (2007).
57. T. Greulich, A. Hattesohl, A Grabisch, et al. Ibid., 42, 145 (2013).
58. S. Dragonieri, F. Porcelli, F. Longobardi, et al. J Breath Res. 9, 026005 (2015).
59. R. Antonelli Incalzi, G. Pennazza, S. Scarlata, et al. Breath 19, 623 (2015).
60. D. Smith, K. Sovova, K. Dryahina, et al. J Breath Res 10, 021002 (2016).
61. K. D. van de Kant, L. J. van der Sande, Q. Jobsis, et al. Respir Res 13, 117 (2012).
62. L. T. McGrath, R. Patrick, P. Mallon, et al. Eur Respir J. 16, 1065 (2000).
63. Miekisch, J. K. Schubert, G. F. Noeldge-Schomburg Clin Chim Acta 347 25 (2004).
64. M. Zhang, J. J. Sun, M. Khatib, et al. Nat Commun. 10, 1120 (2019).
65. A. Wilson, M. Baietto Sensors 9, 5099 (2009).
66. S. Dragonieri, G. Pennazza, P. Carratu, et al. Lung 195, 157 (2017).
67. S. A. Kharitonov and P. J. Barnes Am J Respir Crit Care Med 163, 1693 (2001).
68. A. G. Chuchalin, N. Voznesenskiy, K. Dulin, et al. Am J Respir Crit Care Med 159, A410 (1999).
69. K. Alving, W. Zetterquist, P. Wennerholm, J. Lundberg. Ibid. A841.
70. K. Zayasu, K. Sekizawa, S. Okinaga, et al. Ibid 156, 1140 (1997).
71. I. Horvath, L. E. Donnelly, A. Kiss, et al. Thorax 53, 668 (1998).
72. I. Horvath, S. Loukides, T. Wodehouse, et al. Ibid. 870.
73. P. Paredi, S. A. Kharitonov, D. Leak, et al. Am J Respir Crit Care Med 161, 1247 (2000).
74. J. D. Antuni, A. B. Du Bois, S. Ward, et al. Ibid 159, A510 (1999).
75. M. Monma, M .Yamaya, K Sekizawa, et al. Clin Exp Allergy 29, 1537 (1999).
76. O. M. Pitkanen, M. Hallman, S. M. Andersson J. Pediatry 116,760 (1990).
77. M. S. Ip, B. Lam, L.Y. Chan, et al. Am J RespirCrit Care Med 162, 2166 (2000).
78. M. Phillips, K. Gleeson, J. Hughes, et al, Lancet 353, 1930 (1999).

79. I. Horvath, L. E. Donnelly, A. Kiss, et al. Am J Respir Crit Care Med 158, 1042 (1998).
80. Q. Jöbsis, H. C. Raatgeep, S. L. Schellekens, et al. Eur Respir J 12, 483 (1998).
81. P. N. Dekhuijzen, K. K. Aben, I. Dekker, et al. Am J Respir Crit Care Med 154, 813 (1996).
82. J. Hull, P. Vervaart, K. Grimwood, P. Phelan Thorax 52, 557 (1997).
83. C. E. Collins, P. Quaggiotto, L. Wood, et al. Lipids 34, 551 (1999).
84. B. Li, Q. Dong, R. Scott Downen. Sensors & Actuators: B. Chemical 287 584 (2019).
85. C. H. Sai Sravya, Y. Sai Navya Keerthan, and B.M. Nandini International Journal of Modern Trends in Engineering and Research 03, 6 (2016).]
86. S. Dragonieria, T. Jouke Annema, R. Schot. Lung Cancer 64, 166 (2009).
87. T. Itoh, T. Miwa, A. Tsuruta. Sensors 16, 1891 (2016).
88. S.Tarik, Z. Omar, M. Moufid Sensors and Actuators B 257 178 (2018).
89. M. Aleksanyan, V. Aroutiounian, G. Shahnazaryan Patent of Armenia No. AM20210018 24.02,2021
90. P. Brinkman, A. Hilse M. van der Zee, and A. H. Wagener Current opinion 25, 1 (2019).
91. A. H. Neerincx , S. J. H. Vijverberg, D. J. Lieuwe et al. Pulmonology 1(2017).
92. C. E. Wheelock, V. M. Goss, D. Balgoma, et al. Eur Respir J. 42, 802 (2013).
93. K. D. van de Kant, J. J. van Berkel, Q. Jöbsis, et al. Eur Respir J. 41 (2013).
94. B. Buszewski, M.Kęsy, T. Ligor, A. Amann Biomed Chromatogr. 21, 553 (2007).
95. P. Španěl, D. Smith Mass Spectrom Rev. 30, 236 (2011).
96. I. Buryakov, E. Krylov, E. Nazarov, U. Rasulev Int. J .Mass Spectrom Ion Processes 128, 143 (1993).
97. Y. Zrodnikov, C. E. Davis J. Nanomed. Nanotechnol. 3,109 (2012).
98. M. P. van der Schee, T. Paff, P. Brinkman et al CHEST J. 147, 224 (2015).
99. F. Gahleitner, C. Guallar-Hoyas, C. S. Beardsmore et al Bioanalysis 5, 2239 (2013).
100. L. Buck, R. Axel Cell 65, 175 (1991).
101. J. Wojtas, Z, Bielecki, T. Stacewicz, et al. Opto-Electron Rev. 20, 26 (2012).
102. M. R. McCurdy, Y. Bakhirkin, G. Wysocki, et al. J Breath Res.1, 014001 (2007).
103. Available:http://www.hopkinsmedicine.org/healthlibrary/test_procedures/pulmonary/oximetry_92,p07754/