ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Review Article

Pulmonology and Respiratory Medicine Assessment from the Genetic, Environmental Factor, Drug, Pathway Perspective to Utilize New Therapeutic Systems

Rassol Housen Pure[1]*, Reza Safari Dizaj[2], Milad Hosseinpour[2] and Farzaneh Soleimani Dargani[3]

[1]*Department of Basic Science, Faculty of Biology, Payame Noor University, Iran*

[2]*Department of Medical Genetics and Molecular Biology, Faculty of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran*

[3]*Department of Medical Genetics, Faculty of Medicine, Mashhad University of Medical Sciences (MUMS), Mashhad, Iran*

***Corresponding Author**: Rassol Housen Pure, Department of Basic Science, Faculty of Biology, Payame Noor University, Iran.

Received: October 30, 2018; **Publisshed:** November 19, 2018

Abstract

Recent researches have shown that by deep understanding of the structural and functional biological molecular properties relationship such as Genetics, Environmental factor, Drug, Pathway it is possible to regulate signaling pathways which control cell proliferation, wound healing and angiogenesis. In addition, they can be used for pulmonary and respiratory therapy. The main aim of this research is to collect the Genetics, Environmental factor, Drug, Pathway information regarding the contribution in pulmonary and respiratory therapy. Molecular targeted therapy in pulmonary and respiratory diseases is a type of treatment based on advanced Extra Potential personalized medical therapy. In some pulmonary and respiratory diseases several molecular targets are known and some still being identified. molecular Targeted therapy provides a better way to customize pulmonary and respiratory treatment. Targeted therapies that block the growth and spread of pulmonary and respiratory by interfering with the particular molecule that is involved in the progression and growth of diseases.

Keywords: *Genetic; Environmental Factor; Drug; Pathway; Pulmonary and Respiratory*

Introduction

Diagnostic of Pulmonary and Respiratory diseases involves not only physical examination, chest radiography, history and bronchoscopy however the selective use of various imaging tests such as computed tomography of the chest, bone scans, ultrasound, radiography for suspected diseases, mediastinoscopy, or explorative thoracotomy and molecular diagnostics.

New advances have been made in the diagnostic assessment and staging of lung malignancies with metabolic imaging methods using positron emitting drugs such as 2-deoxyglucose labelled with 18F (FDG), which is preferentially taken up in metabolically active tissues such as malignancies [1].

Pathway

Connective tissue growth factor, promotes chemotactic recruitment and wound repair by an integrin-mediated pathway and increase of cells involved in angiogenesis [2].

Cell migration can widely be qualified as the translation of cells from one location to another and it is a main component for the tissue homeostasis.

Cell migration strongly depends on factors such as substratum, adhesion strength and migratory signals and is controlled by complex signaling pathways. different kinases and phosphatases play main roles in the regulation of cell migration which are localized and activated by membrane lipids, protein associations, multidomain adapter proteins. Another part of components such as microtubules, actin filaments and lipid vesicles also as contribution to cell migration [3].

The phosphoinositide 3-kinase(s) (PI3K) are a family of proteins that involved in significant cellular functions to the generation of lipids and control intracellular signaling pathways. Recent studies from many components of the PI3K shows the pathway plays a serious obligation for corticosteroid insensitivity in chronic inflammatory respiratory disease. PI3K inhibitors have been expanded that decrease inflammation and even some Characteristic features of the disease in empirical animal models. Targeting specific PI3K isoforms allow the researchers pay attention for new molecular treatment of respiratory diseases. the suggestion of this study is that inhibitors of PI3K/Akt may demonstrate to be helpful new therapies in the treatment of asthma, chronic obstructive pulmonary disease [4].

Pathways integrated care or clinical pathways particularity responsibility, timescales, sequences, disciplines and encompass a checklist of all obligatory functions [5].

Drug delivery

Antibiotics are other popular examples of pulmonary drug delivery in the situation of local disease [6].

Pulmonary drug delivery system extensively utilized for the lung diseases treatment and is applauded for the asthma cure and chronic obstructive pulmonary diseases. This method can be done without any needle or other related instruments. Therapy with inhalation originated by Indian about 4000 years ago where their patients with cough have smoked the *Atropa belladonna* leaves to relief it. In the early 20th century, asthmatic patients have smoked a kind of cigarettes that include Stramonium powder pulse tobacco to relief the asthmatic signs [7].

Currently drug delivery to pulmonary system field is a useful, amazing and cutting-edge method in functional pharmaceutical research [8,9].

The lungs are an attractive path for non-invasive drug delivery with advantages for both systemic and local utilization. Incorporating modern therapeutics with polymeric nanoparticles offers extra degrees of utilization for delivery systems, providing sustained release and the potency to target specific organs and cells. in addition, nanoparticle delivery to the lungs has plenty of challenges containing formulation instability due to particle-particle interactions and insignificant delivery proficiency due to exhalation of low-inertia nanoparticles. Thus, recent methods formulating nanoparticles into the shape of micron-scale dry powders have been developed. These carrier nanoparticles perform improved handling and delivery system, while releasing nanoparticles upon deposition in the lungs [10].

Environmental factor

Practically, healthy city and sustainable development significance take into consideration social, economic, cultural issues and environmental and how these affect individuals, communities and populations' lives [11].

Risk of Lung cancer associated with smoking and depends on many factors such as age at starting to smoke, the term of smoking, number and kind of cigarettes smoked (tar and nicotine contents, filter and non-filter cigarettes), and smoking behavior [12].

Effects of environmental factors on children's respiratory system and pulmonary tests have been performed [13].

O_3 has powerful oxidation activity because it enhances the permeability of the epithelial cells and reduces the mucociliary apparatus. NO_2 is a weak and less reactive oxidant agent, which can disturb the epithelial cells and alveolar macrophage functions. Oxidative stress in macrophages and epithelial cells can be triggered by PM, In the other side of this that agent induces interleukin (IL)-6, tumor necrosis factor-β, interferon-γ and transforming growth factor-β. Another important agent that be present in PM is diesel exhaust particle which can induce the production of IL-8. The higher level of the SO_2 dosage enhances the releasing of the Reactive oxygen species in the pulmonary system. Finally, air pollution absolutely hinders with innate and specific lung defenses, thus accelerating the progress of lung diseases, such as exacerbation of chronic obstructive pulmonary disease, asthma and allergy [14].

Genetic

Gene therapy is a new personalized medical approach in which gene nucleotide is transferred to the somatic cells of an exclusive to accurate a hereditary specific genetic disease or treat an attained disorder [15,16].

Genetic transformation into target cell can be occurred *in vivo* or *in vitro*. Impressive gene transfer initiates demonstrating that gene expression to target cells [16]. Transgenes and different type of promoters have been assessed in human gene transformation experiments. many of the expression cassettes have used extremely active, constitutive strong promoters [17].

The utility of adenovirus vector-mediated transfer for CFTR gene to the respiratory epithelium of patients with cystic fibrosis disease as *in vivo* clinical utilization of human gene therapy [18,19].

Guide for pulmonary and respiratory diseases

Some diseases such as, Urban-Rifkin-Davis syndrome, Interstitial lung and liver disease, Diffuse panbronchiolitis are in table 1. Content of genes part and diseases such, Congenital pulmonary alveolar proteinosis, Alpha-1-antitrypsin deficiency, Bronchiectasis with or without elevated sweat chloride are in table 2. Contents of genes, Environmental factors, Pathways parts and disease such, Chronic obstructive pulmonary disease (COPD) are in table 3. Contents of genes, Environmental factors, drugs part and disease, such as Primary ciliary dyskinesia (PCD) are in table 4. Contents of gene part and diseases such as, Idiopathic pulmonary fibrosis, Pulmonary alveolar microlithiasis, Pneumothorax, Obliterative bronchiolitis are in table 5. Contents of genes, Environmental factor, drugs parts.

Diseases	Gene	Reference
Urban-Rifkin-Davis syndrome	LTBP4	[20]
Interstitial lung and liver disease (ILLD)	MARS	[21,22]
Diffuse panbronchiolitis (DPB)	HLA-A(polymorphism) HLA-B(polymorphism) MUC22(polymorphism) HCG22(polymorphism)	[23,24]

Table 1

Diseases	Gene	Environmental factor	Pathway	Reference
Congenital pulmonary alveolar proteinosis	(SMDP1) SFTPB (SMDP2) SFTPC (SMDP3) ABCA3 (SMDP4) CSF2RA (SMDP5) CSF2RB	Inhalation of inorganic dust or toxic fumes hematologic malignancies pharmacologic immunosuppression certain infections	Cytokine-cytokine receptor interaction JAK-STAT signaling pathway	[25-27]
Alpha-1-antitrypsin deficiency	SERPINA1	Cigarette smoke	Complement and coagulation cascades	[28-30]
Bronchiectasis with or without elevated sweat chloride	SCNN1B SCNN1A SCNN1G		Aldosterone-regulated sodium reabsorption	[31,32]

Table 2

Diseases	Gene	Environmental factor	Drug	Reference
Chronic obstructive pulmonary disease (COPD)	SERPINA1	Cigarette smoking	Glycopyrrolate Prednisolone sodium phosphate Prednisone Salmeterol xinafoate - fluticasone propionate mixt Ipratropium bromide Metaproterenol sulfate Salmeterol xinafoate Formoterol fumarate Formoterol fumarate hydrate Indacaterol maleate Olodaterol hydrochloride Budesonide - formoterol fumarate dihydrate mixt Fluticasone furoate - vilanterol trifenatate mixt Albuterol sulfate - ipratropium bromide mixt Umeclidinium bromide - vilanterol mixt Glycopyrronium bromide - indacaterol maleate mixt Tiotropium - olodaterol mixt Glycopyrrolate - formoterol mixt Fluticasone furoate - umeclidinium bromide - vilanterol mixt Tiotropium bromide hydrate Aclidinium bromide Umeclidinium bromide Aminophylline hydrate Theophylline - dextrose mixt Roflumilast /Arformoterol tartrate	[33,34]

Table 3

Discussion

Caring for patients with pulmonary and Respiratory diseases will be a major challenge over the future. Due to a mixture of factors including Genetic, Environmental factor, Drug, Pathway past and present effective habits and an ageing population it is still associated with rising mortality. plenty of drugs are being tested for the treatment of pulmonary and Respiratory diseases some seems to be near to being marketed. The clinical development plan has involved mainly studies in patients had already pulmonary and Respiratory diseases [66-68].

Rising rates of harmful factors in the world on functioning of the respiratory system. This review focuses primarily on Genetic, Environmental factor, Drug, Pathway, where in each case recent evidence has been and associated with advances in clinical management for pulmonary and Respiratory diseases.

Diseases	Gene	Reference
Primary ciliary dyskinesia (PCD)	(CILD1) DNAI1 (CILD2) DNAAF3 (CILD3) DNAH5 (CILD5) HYDIN (CILD6) TXNDC3 (CILD7) DNAH11 (CILD9) DNAI2 (CILD10) KTU (CILD11) RSPH4A (CILD12) RSPH9 (CILD13) LRRC50 (CILD14) CCDC39 (CILD15) CCDC40 (CILD16) DNAL1 (CILD17) CCDC103 (CILD18) HEATR2 (CILD19) LRRC6 (CILD20) CCDC114 (CILD21) DRC1 (CILD22) ZMYND10 (CILD23) ARMC4 (CILD24) RSPH1 (CILD25) DYX1C1 (CILD26) C21ORF59 (CILD27) CCDC65 (CILD28) SPAG1 (CILD29) CCNO (CILD30) CCDC151 (CILD32) RSPH3 (CILD33) GAS8 (CILD34) DNAJB13 (CILD35) TTC25 (CILD36) PIH1D3	[35-57]

Table 4

Diseases	Gene	Environmental factor	Drug	Reference
Idiopathic pulmonary fibrosis	TERC TERT SFTPA1 SFTPA2 SFTPC MUC5B	Prednisolone Sodium phosphate Prednisone Nintedanib esylate Pirfenidone		[58-62]
Pulmonary alveolar microlithiasis (PALM)	SLC34A2			[63]
Pneumothorax	FLCN	Smoking		[64]
Obliterative bronchiolitis (OB)			Prednisolone sodium phosphate	[65]

Table 5

Conclusion

After discussion within large group of pulmonary and Respiratory diseases we selected subjects under four broad headings containing Genetic, Environmental factor, Drug, Pathway Some of these such as Drug, Genetic and Pathway to determine prospect of molecular engineering for treatment But in case of Environmental factor as we added a fourth primarily focuse for treatment were chosen because of the of Prevention and diagnosis of environmental factors within prevalence of the diseases.

Bibliography

1. Valk Peter E., *et al*. "Staging non-small cell lung cancer by whole-body positron emission tomographic imaging". *The Annals of Thoracic Surgery* 60.6 (1995): 1573-1582.

2. Jedsadayanmata Arom., *et al*. "Activation-dependent adhesion of human platelets to Cyr61 and Fisp12/mouse connective tissue growth factor is mediated through integrin αIIbβ3". *Journal of Biological Chemistry* 274.34 (1999): 24321-24327.

3. Saarikangas Juha., *et al*. "Regulation of the actin cytoskeleton-plasma membrane interplay by phosphoinositides". *Physiological Reviews* 90.1 (2010): 259-289.

4. Ito Kazuhiro., *et al*. "Therapeutic potential of phosphatidylinositol 3-kinase inhibitors in inflammatory respiratory disease". *Journal of Pharmacology and Experimental Therapeutics* 321.1 (2007): 1-8.

5. Campbell Harry., *et al*. "Integrated care pathways". *BMJ: British Medical Journal* 316.7125 (1998): 133-137.

6. Ciucă Adrian G., *et al*. "Nanostructures for drug delivery: pharmacokinetic and toxicological aspects". *Nanostructures for Drug Delivery* (2017): 941-957.

7. Chandel Arvind Kumar Singh. "Devices for Controlled Release Advancements and Effectiveness". Design and Development of Affordable Healthcare Technologies. IGI Global (2018): 103-134.

8. Swarbrick James. Encyclopedia of pharmaceutical technology. CRC Press (2013).

9. Niven Ralph W. "Delivery of biotherapeutics by inhalation aerosol". *Critical Reviews™ in Therapeutic Drug Carrier Systems* 12.2-3 (1995): 151-231.

10. Sung Jean C., *et al*. "Nanoparticles for drug delivery to the lungs". *Trends in Biotechnology* 25.12 (2007): 563-570.

11. Basaran Ismail. "Sağlıklı Kentler Kavramının Gelişiminde Sağlıklı Kentler Projesi" (2007).

12. Peto Richard. "Influence of dose and duration of smoking on lung cancer rates". *IARC Scientific Publications* 74 (1986): 23-33.

13. Guneser S., *et al*. "Effects of indoor environmental factors on respiratory systems of children". *Journal of Tropical Pediatrics* 40.2 (1994): 114-116.

14. Olivieri D and E Scoditti. "Impact of environmental factors on lung defences". *European Respiratory Review* 14.95 (2005): 51-56.

15. Mulligan Richard C. "The basic science of gene therapy". *Science* 260.5110 (1993): 926-932.

16. Crystal Ronald G. "Gene therapy strategies for pulmonary disease". *The American Journal of Medicine* 92.6 (1992): S44-S52.

17. Crystal Ronald G. "Transfer of genes to humans: early lessons and obstacles to success". *Science* 270.5235 (1995): 404-410.

18. Rosenfeld Melissa A., *et al*. "In vivo transfer of the human cystic fibrosis transmembrane conductance regulator gene to the airway epithelium". *Cell* 68.1 (1992): 143-155.

19. Crystal Ronald G., *et al*. "Administration of an adenovirus containing the human CFTR cDNA to the respiratory tract of individuals with cystic fibrosis". *Nature Genetics* 8.1 (1994): 42-51.

20. Urban Zsolt., *et al*. "Mutations in LTBP4 cause a syndrome of impaired pulmonary, gastrointestinal, genitourinary, musculoskeletal, and dermal development". *The American Journal of Human Genetics* 85.5 (2009): 593-605.

21. Rips Jonathan., *et al*. "MARS variant associated with both recessive interstitial lung and liver disease and dominant Charcot-Marie-Tooth disease". *European Journal of Medical Genetics* 61.10 (2018): 616-620.

22. Hadchouel Alice., *et al*. "Biallelic mutations of methionyl-tRNA synthetase cause a specific type of pulmonary alveolar proteinosis prevalent on Reunion Island". *The American Journal of Human Genetics* 96.5 (2015): 826-831.

23. Sugimoto Seiichiro., *et al*. "Lung transplantation for diffuse panbronchiolitis: 5 cases from a single centre". *Interactive Cardiovascular and Thoracic Surgery* 22.5 (2016): 679-681.

24. Lin Xiufang., *et al*. "Macrolides for diffuse panbronchiolitis". *Cochrane Database of Systematic Reviews* 12 (2015): CD007716.

25. Borie R., *et al*. "Pulmonary alveolar proteinosis". *European Respiratory Review* 20.120 (2011): 98-107.

26. Martinez-Moczygemba Margarita and David P Huston. "Immune dysregulation in the pathogenesis of pulmonary alveolar proteinosis". *Current Allergy and Asthma Reports* 10.5 (2010): 320-325.

27. Tanaka Takeshi., *et al*. "Adult-onset hereditary pulmonary alveolar proteinosis caused by a single-base deletion in CSF2RB". *Journal of Medical Genetics* 48.3 (2011): 205-209.

28. Greene Catherine M., *et al*. "Alpha-1 antitrypsin deficiency: a conformational disease associated with lung and liver manifestations". *Journal of Inherited Metabolic Disease* 31.1 (2008): 21-34.

29. Mulgrew Alan T., *et al*. "Alpha-1-antitrypsin deficiency: current concepts". *Lung* 185.4 (2007): 191-201.

30. Lockett Angelia D., *et al*. "Effect of cigarette smoke exposure and structural modifications on the α-1 antitrypsin interaction with caspases". *Molecular Medicine* 18.1 (2012): 445-454.

31. Rademacher Jessica and Tobias Welte. "Bronchiectasis-diagnosis and treatment". *Deutsches* Ärzteblatt *International* 108.48 (2011): 809-815.

32. Fajac Isabelle., *et al*. "Could a defective epithelial sodium channel lead to bronchiectasis". *Respiratory Research* 9.1 (2008): 46.

33. Smith Jaclyn and Ashley Woodcock. "Cough and its importance in COPD". *International Journal of Chronic Obstructive Pulmonary Disease* 1.3 (2006): 305-314.

34. Tsuchida Tomoko., *et al*. "Pathologically confirmed, early-onset, severe chronic obstructive pulmonary disease". *Internal Medicine* 51.24 (2012): 3411-3414.

35. Zariwala Maimoona A., *et al*. "Genetic defects in ciliary structure and function". *Annual Review of Physiology* 69 (2007): 423-450.

36. Mitchison Hannah M., *et al*. "Mutations in axonemal dynein assembly factor DNAAF3 cause primary ciliary dyskinesia". *Nature Genetics* 44.4 (2012): 381-389.

37. Olbrich Heike., *et al*. "Recessive HYDIN mutations cause primary ciliary dyskinesia without randomization of left-right body asymmetry". *The American Journal of Human Genetics* 91.4 (2012): 672-684.

38. Antony Dinu., *et al*. "Mutations in CCDC39 and CCDC40 are the major cause of primary ciliary dyskinesia with axonemal disorganization and absent inner dynein arms". *Human Mutation* 34.3 (2013): 462-472.

39. Mazor Masha., *et al*. "Primary ciliary dyskinesia caused by homozygous mutation in DNAL1, encoding dynein light chain 1". *The American Journal of Human Genetics* 88.5 (2011): 599-607.

40. Panizzi Jennifer R., *et al*. "CCDC103 mutations cause primary ciliary dyskinesia by disrupting assembly of ciliary dynein arms". *Nature Genetics* 44.6 (2012): 714-719.

41. Horani Amjad., *et al*. "Whole-exome capture and sequencing identifies HEATR2 mutation as a cause of primary ciliary dyskinesia". *The American Journal of Human Genetics* 91.4 (2012): 685-693.

42. Kott Esther., *et al*. "Loss-of-function mutations in LRRC6, a gene essential for proper axonemal assembly of inner and outer dynein arms, cause primary ciliary dyskinesia". *The American Journal of Human Genetics* 91.5 (2012): 958-964.

43. Knowles Michael R., *et al*. "Exome sequencing identifies mutations in CCDC114 as a cause of primary ciliary dyskinesia". *The American Journal of Human Genetics* 92.1 (2013): 99-106.

44. Wirschell Maureen., *et al*. "The nexin-dynein regulatory complex subunit DRC1 is essential for motile cilia function in algae and humans". *Nature Genetics* 45.3 (2013): 262-268.

45. Moore Daniel J., *et al*. "Mutations in ZMYND10, a gene essential for proper axonemal assembly of inner and outer dynein arms in humans and flies, cause primary ciliary dyskinesia". *The American Journal of Human Genetics* 93.2 (2013): 346-356.

46. Hjeij Rim., *et al*. "ARMC4 mutations cause primary ciliary dyskinesia with randomization of left/right body asymmetry". *The American Journal of Human Genetics* 93.2 (2013): 357-367.

47. Kott Esther., *et al*. "Loss-of-function mutations in RSPH1 cause primary ciliary dyskinesia with central-complex and radial-spoke defects". *The American Journal of Human Genetics* 93.3 (2013): 561-570.

48. Tarkar Aarti., *et al*. "DYX1C1 is required for axonemal dynein assembly and ciliary motility". *Nature Genetics* 45.9 (2013): 995-1003.

49. Niederberger Craig. "Re: zebrafish ciliopathy screen plus human mutational analysis identifies C21orf59 and CCDC65 defects as causing primary ciliary dyskinesia". *The Journal of Urology* 191.5 (2014): 1355.

50. Knowles Michael R., *et al*. "Mutations in SPAG1 cause primary ciliary dyskinesia associated with defective outer and inner dynein arms". *The American Journal of Human Genetics* 93.4 (2013): 711-720.

51. Wallmeier Julia., *et al*. "Mutations in CCNO result in congenital mucociliary clearance disorder with reduced generation of multiple motile cilia". *Nature Genetics* 46.6 (2014): 646-651.

52. Jerber Julie., *et al*. "The coiled-coil domain containing protein CCDC151 is required for the function of IFT-dependent motile cilia in animals". *Human Molecular Genetics* 23.3 (2013): 563-577.

53. Jeanson Ludovic., *et al*. "RSPH3 mutations cause primary ciliary dyskinesia with central-complex defects and a near absence of radial spokes". *The American Journal of Human Genetics* 97.1 (2015): 153-162.

54. Olbrich Heike., *et al*. "Loss-of-function GAS8 mutations cause primary ciliary dyskinesia and disrupt the nexin-dynein regulatory complex". *The American Journal of Human Genetics* 97.4 (2015): 546-554.

55. El Khouri Elma., *et al*. "Mutations in DNAJB13, encoding an HSP40 family member, cause primary ciliary dyskinesia and male infertility". *The American Journal of Human Genetics* 99.2 (2016): 489-500.

56. Wallmeier Julia., *et al*. "TTC25 deficiency results in defects of the outer dynein arm docking machinery and primary ciliary dyskinesia with left-right body asymmetry randomization". *The American Journal of Human Genetics* 99.2 (2016): 460-469.

57. Olbrich Claudius Werner., *et al*. "Mutations in PIH1D3 Cause X-Linked Primary Ciliary Dyskinesia with Outer and Inner Dynein Arm Defects". *The American Journal of Human Genetics* 100.1 (2017): 160-168.

58. Wang Yongyu., *et al*. "Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer". *The American Journal of Human Genetics* 84.1 (2009): 52-59.

59. Lawson William E., *et al*. "Genetics in pulmonary fibrosis-familial cases provide clues to the pathogenesis of idiopathic pulmonary fibrosis". *The American Journal of the Medical Sciences* 341.6 (2011): 439-443.

60. Heinrich S., *et al*. "Surfactant protein A-from genes to human lung diseases". *Current Medicinal Chemistry* 13.27 (2006): 3239-3252.

61. Zhang Yingze., *et al*. "A variant in the promoter of MUC5B and idiopathic pulmonary fibrosis". *The New England Journal of Medicine* 364.16 (2011): 1576-1577.

62. Lehtonen Siri T., *et al*. "Pirfenidone and nintedanib modulate properties of fibroblasts and myofibroblasts in idiopathic pulmonary fibrosis". *Respiratory Research* 17.1 (2016): 14.

63. Corut Ayse., *et al*. "Mutations in SLC34A2 cause pulmonary alveolar microlithiasis and are possibly associated with testicular microlithiasis". *The American Journal of Human Genetics* 79.4 (2006): 650-656.

64. Grundy Seamus., *et al*. "Primary spontaneous pneumothorax: a diffuse disease of the pleura". *Respiration* 83.3 (2012): 185-189.

65. Aguilar Patrick R., *et al*. "Obliterative bronchiolitis". *Transplantation* 100.2 (2016): 272-283.

66. Milgrom Henry., *et al*. "Treatment of allergic asthma with monoclonal anti-IgE antibody". *New England Journal of Medicine* 341.26 (1999): 1966-1973.

67. Bishop Naomi B., *et al*. "Alveolar capillary dysplasia". *American Journal of Respiratory and Critical Care Medicine* 184.2 (2011): 172-179.

68. Hung Shih-Pin., *et al*. "Misalignment of lung vessels and alveolar capillary dysplasia: a case report with autopsy". *Pediatrics and Neonatology* 52.4 (2011): 232-236.

Volume 7 Issue 12 December 2018