

Supplemental Material

Literatur

- 1 Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000–2016. Geneva: World Health Organization; 2018.
- 2 Agusti A, Sobradillo P, Celli B: Addressing the complexity of chronic obstructive pulmonary disease: from phenotypes and biomarkers to scale-free networks, systems biology, and P4 medicine. *Am J Respir Crit Care Med* 2011;183(9):1129–1137.
- 3 Jones PW, Agusti AG: Outcomes and markers in the assessment of chronic obstructive pulmonary disease. *Eur Respir J* 2006;27(4):822–832.
- 4 Mendy A, Forno E, Niyonsenga T, et al.: Blood biomarkers as predictors of long-term mortality in COPD. *Clin Respir J* 2018;12(5):1891–1899.
- 5 Haldar K, Bafadhel M, Lau K, et al.: Microbiome balance in sputum determined by PCR stratifies COPD exacerbations and shows potential for selective use of antibiotics. *PLoS One* 2017;12(8):e0182833.
- 6 Lakhdar R, McGuinness D, Drost EM, et al.: Role of accelerated aging in limb muscle wasting of patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2018;13:1987–1998.
- 7 Chalela R, Gea J, Barreiro E: Immune phenotypes in lung cancer patients with COPD: potential implications for immunotherapy. *J Thorac Dis* 2018;10(S18 Suppl 18):S2186–9.
- 8 Seijo LM, Zulueta JJ: Understanding the Links Between Lung Cancer, COPD, and Emphysema: A Key to More Effective Treatment and Screening. *Oncology (Williston Park)*. 2017; 31(2):93–102.
- 9 Yong PC, Sigel K, de-Torres JP, et al.: The effect of radiographic emphysema in assessing lung cancer risk. *Thorax* 2019;pii:thoraxjnl-2018-212457.
- 10 Hogg JC, Paré PD, Hackett TL: The Contribution of Small Airway Obstruction to the Pathogenesis of Chronic Obstructive Pulmonary Disease. *Physiol Rev* 2017;97(2):529–552.
- 11 Hogg JC, Timens W: The pathology of chronic obstructive pulmonary disease. *Annu Rev Pathol* 2009;4(1):435–459.
- 12 Suzuki M, Sze MA, Campbell JD, et al.: The cellular and molecular determinants of emphysematous destruction in COPD. *Sci Rep* 2017;7(1): 9562.
- 13 Caramori G, Casolari P, Barczyk A, et al.: COPD immunopathology. *Semin Immunopathol* 2016;38(4):497–515.
- 14 Barnes PJ: Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2016;138(1):16–27.
- 15 Yamasaki K, Eeden SF: Lung Macrophage Phenotypes and Functional Responses: role in the Pathogenesis of COPD. *Int J Mol Sci* 2018;19(2):E582.
- 16 Miyata R, van Eeden SF: The innate and adaptive immune response induced by alveolar macrophages exposed to ambient particulate matter. *Toxicol Appl Pharmacol* 2011;257(2):209–226.
- 17 Meijer M, Rijkers GT, van Overveld FJ: Neutrophils and emerging targets for treatment in chronic obstructive pulmonary disease. *Expert Rev Clin Immunol* 2013;9(11):1055–1068.
- 18 Rosales C, Demaurex N, Lowell CA, et al.: Neutrophils: their role in innate and adaptive immunity. *J Immunol Res* 2016;2016:1469780.
- 19 Stockley RA, Mannino D, Barnes PJ: Burden and pathogenesis of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2009;6(6):524–526.
- 20 Ortega H, Llanos JP, Lefeuvre MH, et al.: Burden of disease associated with a COPD eosinophilic phenotype. *Int J Chron Obstruct Pulmon Dis* 2018; 13:2425–4233.
- 21 Hogg JC: Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* 2004;364(9435):709–721.
- 22 Ning W, Li CJ, Kaminski N, et al.: Comprehensive gene expression profiles reveal pathways related to the pathogenesis of chronic obstructive pulmonary disease. *Proc Natl Acad Sci USA* 2004;101(41):14895–14900.
- 23 Eriksson Ström J, Pourazar J, Linder R, et al.: Cytotoxic lymphocytes in COPD airways: increased NK cells associated with disease, iNKT and NKT-like cells with current smoking. *Respir Res* 2018;19(1):244.
- 24 Knight DA, Holgate ST: The airway epithelium: structural and functional properties in health and disease. *Respirology* 2003;8(4):432–446.
- 25 Holtzman MJ, Byers DE, Alexander-Brett J, et al.: The role of airway epithelial cells and innate immune cells in

- chronic respiratory disease. *Nat Rev Immunol* 2014;14(10):686–698.
- 26 Fujii T, Hayashi S, Hogg JC, et al.: Particulate matter induces cytokine expression in human bronchial epithelial cells. *Am J Respir Cell Mol Biol* 2001;25(3):265–271.
- 27 Ishii H, Fujii T, Hogg JC, et al.: Contribution of IL-1 beta and TNF-alpha to the initiation of the peripheral lung response to atmospheric particulates (PM10). *Am J Physiol Lung Cell Mol Physiol* 2004;287(1):L176–183.
- 28 Corfield AP: Mucins: a biologically relevant glycan barrier in mucosal protection. *Biochim Biophys Acta* 2015;1850(1):236–252.
- 29 Gohy ST, Hupin C, Pilette C, et al.: Chronic inflammatory airway diseases: the central role of the epithelium revisited. *Clin Exp Allergy* 2016;46(4):529–542.
- 30 Brasier AR: Therapeutic targets for inflammation-mediated airway remodeling in chronic lung disease. *Expert Rev Respir Med* 2018;12(11):931–939.
- 31 Aoshiba K, Yokohori N, Nagai A: Alveolar wall apoptosis causes lung destruction and emphysematous changes. *Am J Respir Cell Mol Biol* 2003;28(5):555–562.
- 32 Plataki M, Tzortzaki E, Rytla P, et al.: Apoptotic mechanisms in the pathogenesis of COPD. *Int J Chron Obstruct Pulmon Dis.* 2006;1(2):161–171.
- 33 Gordon C, Gudi K, Krause A, et al.: Circulating endothelial microparticles as a measure of early lung destruction in cigarette smokers. *Am J Respir Crit Care Med* 2011;184(2):224–232.
- 34 Strulovici-Barel Y, Staudt MR, Krause A, et al.: Persistence of circulating endothelial microparticles in COPD despite smoking cessation. *Thorax* 2016;71(12):1137–1144.
- 35 McDonough JE, Yuan R, Suzuki M, et al.: Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med* 2011;365(17):1567–1575.
- 36 Ikonomou L, Wagner DE, Turner L, et al.: Translating Basic Research into Safe and Effective Cell-based Treatments for Respiratory Diseases. *Ann Am Thorac Soc* 2019;16(6):657–668.
- 37 Kajstura J, Rota M, Hall SR, et al.: Evidence for human lung stem cells. *N Engl J Med* 2011;364(19):1795–806.
- 38 Antunes MA, Lapa E Silva JR, Rocco PR: Mesenchymal stromal cell therapy in COPD: from bench to bedside. *Int J Chron Obstruct Pulmon Dis* 2017;12:3017–3027.
- 39 de Oliveira HG, Cruz FF, Antunes MA, et al.: Combined bone marrow-derived mesenchymal stromal cell therapy and one-way endobronchial valve placement in patients with pulmonary emphysema: a phase I clinical trial. *Stem Cells Transl Med* 2017;6(3):962–969.
- 40 Weiss DJ, Casaburi R, Flannery R, et al.: A placebo-controlled, randomized trial of mesenchymal stem cells in COPD. *Chest* 2013;143(6):1590–1598.
- 41 Vitenberga Z, Pilmane M, Babjoniševa A: The evaluation of inflammatory, anti-inflammatory and regulatory factors contributing to the pathogenesis of COPD in airways. *Pathol Res Pract* 2019;215(1):97–105.
- 42 Moore SA, Strieter RM, Rolfe MW, et al.: Expression and regulation of human alveolar macrophage-derived interleukin-1 receptor antagonist. *Am J Respir Cell Mol Biol.*1992;6(6):569–575.
- 43 Jiang S, Shan F, Zhang Y, et al.: Increased serum IL-17 and decreased serum IL-10 and IL-35 levels correlate with the progression of COPD. *Int J Chron Obstruct Pulmon Dis* 2018;13:2483–2494.
- 44 Ding L, Linsley PS, Huang LY, et al.: IL-10 inhibits macrophage costimulatory activity by selectively inhibiting the up-regulation of B7 expression. *J Immunol* 1993;151(3):1224–1234.
- 45 Silva BS, Lira FS, Ramos D, et al.: Severity of COPD and its relationship with IL-10. *Cytokine* 2018;106:95–100.
- 46 Miotto D, Ruggieri MP, Boschetto P, et al.: Interleukin-13 and -4 expression in the central airways of smokers with chronic bronchitis. *Eur Respir J* 2003;22(4):602–8.
- 47 Nakanishi K, Yoshimoto T, Tsutsui H, et al.: Interleukin-18 regulates both Th1 and Th2 responses. *Annu Rev Immunol* 2001;19(1):423–474.
- 48 Imaoka H, Hoshino T, Takei S, et al.: Interleukin-18 production and pulmonary function in COPD. *Eur Respir J* 2008;31(2):287–297.
- 49 Hilty M, Burke C, Pedro H, et al.: Disordered microbial communities in asthmatic airways. *PLoS One* 2010;5(1):e8578.
- 50 Sethi S, Maloney J, Grove L, et al.: Airway inflammation and bronchial bacterial colonization in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173(9):991–998.
- 51 Rosell A, Monsó E, Soler N, et al.: Microbiologic determinants of exacerbation in chronic obstructive pulmonary disease. *Arch Intern Med* 2005;165(8):891–897.
- 52 Dy R, Sethi S. The lung microbiome and exacerbations of COPD. *Curr Opin Pulm Med.* 2016 May;22(3):196–202.
- 53 Toczyska I, Zwolińska E, Chcialowski A: Influence of Inhaled Corticosteroids on Bronchial Inflammation and Pulmonary Function in Chronic Obstructive Pulmonary Disease with Moderate Obstruction [J]. *Adv Exp Med Biol* 2018;1047:41–52.
- 54 Brightling CE, Monteiro W, Ward R, et al.: Sputum eosinophilia and short-

- term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2000;356(9240):1480–1485.
- 55 Siva R, Green RH, Brightling CE, et al.: Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. *Eur Respir J* 2007; 29(5):906–913.
- 56 Leigh R, Pizzichini MM, Morris MM, et al.: Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment. *Eur Respir J* 2006;27(5):964–971.
- 57 Brightling CE, Bleecker ER, Panettieri RA Jr, et al.: Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. *Lancet Respir Med* 2014;2(11):891–901.
- 58 Criner GJ, Celli BR, Brightling CE, et al.: GALATHEA and TERRANOVA Study Investigators. Benralizumab for the Prevention of COPD Exacerbations. *N Engl J Med* 2019, Epub ahead of print.
- 59 Singh R, Mackay AJ, Patel AR, et al.: Inflammatory thresholds and the species-specific effects of colonising bacteria in stable chronic obstructive pulmonary disease. *Respir Res*.2014;15:114.
- 60 Cui Y, Luo L, Li C, et al.: Long-term macrolide treatment for the prevention of acute exacerbations in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2018;13:3813–29.
- 61 Kusano S, Kadota J, Kohno S, et al.: Effect of roxithromycin on peripheral neutrophil adhesion molecules in patients with chronic lower respiratory tract disease. *Respiration* 1995;62 (4):217–222.
- 62 Hodge S, Hodge G, Brozyna S, et al.: Azithromycin increases phagocytosis of apoptotic bronchial epithelial cells by alveolar macrophages. *Eur Respir J* 2006;28(3):486–495.
- 63 Feola DJ, Garvy BA, Cory TJ, et al.: Azithromycin alters macrophage phenotype and pulmonary compartmentalization during lung infection with *Pseudomonas*. *Antimicrob Agents Chemother* 2010;54(6):2437–2447.
- 64 Hodge S, Hodge G, Jersmann H, et al.: Azithromycin improves macrophage phagocytic function and expression of mannose receptor in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;178(2):139–148.
- 65 Balloy V, Deveaux A, Lebeaux D, et al.: Azithromycin analogue CSY0073 attenuates lung inflammation induced by LPS challenge. *Br J Pharmacol* 2014; 171(7):1783–1794.
- 66 Kobayashi Y, Wada H, Rossios C, et al.: A novel macrolide/fluoroketolide, solithromycin (CEM-101), reverses corticosteroid insensitivity via phosphoinositide 3-kinase pathway inhibition. *Br J Pharmacol* 2013;169(5):1024–1034.
- 67 Lusamba Kalonji N, Nomura K, Kawase T, et al.: The non-antibiotic macrolide EM900 inhibits rhinovirus infection and cytokine production in human airway epithelial cells. *Physiol Rep* 2015;3(10):e12557.
- 68 Yamaya M, Nomura K, Arakawa K, et al.: Clarithromycin decreases rhinovirus replication and cytokine production in nasal epithelial cells from subjects with bronchial asthma: effects on IL-6, IL-8 and IL-33. *Arch Pharm Res* 2017. DOI: 10.1007/s12272-017-0950-x.
- 69 Tojima I, Shimizu S, Ogawa T, et al.: Anti-inflammatory effects of a novel non-antibiotic macrolide, EM900, on mucus secretion of airway epithelium. *Auris Nasus Larynx* 2015;42(4):332–336.
- 70 Sun X, Chen L, He Z: PI3K/Akt-Nrf2 and Anti-Inflammation Effect of Macrolides in Chronic Obstructive Pulmonary Disease. *Curr Drug Metab* 2019;20(4):301–304.
- 71 Sugiyama K, Shirai R, Mukae H, et al.: Differing effects of clarithromycin and azithromycin on cytokine production by murine dendritic cells. *Clin Exp Immunol* 2007;147(3):540–546.
- 72 Barnes PJ: Theophylline. *Am J Respir Crit Care Med* 2013;188(8):901–906.
- 73 Houslay MD, Adams DR: PDE4 cAMP phosphodiesterases: modular enzymes that orchestrate signalling cross-talk, desensitization and compartmentalization. *Biochem J* 2003;370(Pt 1):1–18.
- 74 Sanz MJ, Cortijo J, Morcillo EJ: PDE4 inhibitors as new anti-inflammatory drugs: effects on cell trafficking and cell adhesion molecules expression. *Pharmacol Ther* 2005;106(3):269–297.
- 75 Matera MG, Page CP, Cazzola M: Novel bronchodilators for the treatment of chronic obstructive pulmonary disease. *Trends Pharmacol Sci* 2011;32(8):495–506.
- 76 Fan Chung K: Phosphodiesterase inhibitors in airways disease. *Eur J Pharmacol* 2006;533(1–3):110–117.
- 77 Brightling CE, McKenna S, Hargadon B, et al.: Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. *Thorax* 2005;60(3):193–198.
- 78 Bujarski S, Parulekar AD, Sharafkhaneh A, et al.: The asthma COPD overlap syndrome (ACOS). *Curr Allergy Asthma Rep* 2015;15(3):509.
- 79 Singh D, Kolsum U, Brightling CE, et al.; ECLIPSE investigators: Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J* 2014;44(6):1697–1700.
- 80 Wechsler ME: Current and Emerging Biologic Therapies for Asthma and

- COPD. *Respir Care* 2018;63(6):699–707.
- 81 Pavord ID, Korn S, Howarth P, et al.: Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380(9842):651–659.
- 82 Castro M, Wenzel SE, Bleecker ER, et al.: Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014;2(11):879–890.
- 83 Deeks ED, Brusselle G: Reslizumab in Eosinophilic Asthma: A Review. *Drugs* 2017;77(7):777–784.
- 84 Pavord ID, Chanez P, Criner GJ, et al.: Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2017;377(17):1613–1629.
- 85 Wenzel S, Castro M, Corren J, et al.: Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β 2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet* 2016;388(10039):31–44.
- 86 Bafadhel M, McKenna S, Terry S, et al.: Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011;184(6):662–671.
- 87 Bautista MV, Chen Y, Ivanova VS, et al.: IL-8 regulates mucin gene expression at the posttranscriptional level in lung epithelial cells. *J Immunol* 2009;183(3):2159–2166.
- 88 Schneider D, Ganesan S, Comstock AT, et al.: Increased cytokine response of rhinovirus-infected airway epithelial cells in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;182(3):332–340.
- 89 Zhang X, Zheng H, Zhang H, et al.: Increased interleukin (IL)-8 and decreased IL-17 production in chronic obstructive pulmonary disease (COPD) provoked by cigarette smoke. *Cytokine* 2011;56(3):717–725.
- 90 Huang AX, Lu LW, Liu WJ, et al.: Plasma Inflammatory Cytokine IL-4, IL-8, IL-10, and TNF- α Levels Correlate with Pulmonary Function in Patients with Asthma-Chronic Obstructive Pulmonary Disease (COPD) Overlap Syndrome. *Med Sci Monit* 2016;22:2800–2808.
- 91 Mahler DA, Huang S, Tabrizi M, et al.: Efficacy and safety of a monoclonal antibody recognizing interleukin-8 in COPD: a pilot study. *Chest* 2004;126(3):926–934.
- 92 Lazaar AL, Miller BE, Tabberer M, et al.: Effect of the CXCR2 antagonist danirixin on symptoms and health status in COPD. *Eur Respir J* 2018;52(4):pii:1801020.
- 93 Chapman KR, Stockley RA, Dawkins C, et al.: Augmentation therapy for alpha1 antitrypsin deficiency: a meta-analysis. *COPD* 2009;6(3):177–184.
- 94 Götzsche PC, Johansen HK: Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. *Cochrane Database Syst Rev* 2016;9(9):CD007851.
- 95 Green CE, Parr DG, Edgar RG, et al.: Lung density associates with survival in alpha 1 antitrypsin deficient patients. *Respir Med* 2016;112:81–87.
- 96 Strauss P, Stolk J, McElvaney G, et al.: Phase II/III, double-blind, randomized, placebo-controlled, international study evaluating the safety and efficacy of inhaled, human, alpha-1 antitrypsin (AAT) in alpha-1 antitrypsin deficient patients (AATD) [Abstract]. *Am J Respir Crit Care Med* 2014:A5790.
- 97 Owen CA: Roles for proteinases in the pathogenesis of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2008;3(2):253–268.
- 98 Polverino F, Rojas-Quintero J, Wang X, et al.: A Disintegrin and Metalloproteinase Domain-8: A Novel Protective Proteinase in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2018;198(10):1254–1267.
- 99 Wang X, Polverino F, Rojas-Quintero J, et al.: A Disintegrin and A Metalloproteinase-9 (ADAM9): A Novel Proteinase Culprit with Multifarious Contributions to COPD. *Am J Respir Crit Care Med* 2018, Epub ahead of print.
- 100 Marsland BJ, Gollwitzer ES: Host-microorganism interactions in lung diseases. *Nat Rev Immunol* 2014;14(12):827–835.
- 101 Mammen MJ, Sethi S: COPD and the microbiome. *Respirology*. 2016;21(4):590–599.
- 102 Surette MG: The cystic fibrosis lung microbiome. *Ann Am Thorac Soc* 2014;11 Suppl 1:S61–65.
- 103 Han MK, Zhou Y, Murray S, Tayob N, Noth I, Lama VN, et al.; COMET Investigators: Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study. *Lancet Respir Med* 2014;2(7):548–556.
- 104 Su YC, Jalalvand F, Thegerström J, et al.: The Interplay Between Immune Response and Bacterial Infection in COPD: Focus Upon Non-typeable *Haemophilus influenzae*. *Front Immunol* 2018;9:2530.
- 105 Marjanović N, Bosnar M, Michielin F, et al.: Macrolide antibiotics broadly and distinctively inhibit cytokine and chemokine production by COPD sputum cells in vitro. *Pharmacol Res* 2011;63(5):389–397.
- 106 Segal LN, Clemente JC, Wu BG, et al.: Randomised, double-blind, placebo-

- controlled trial with azithromycin selects for anti-inflammatory microbial metabolites in the emphysematous lung. *Thorax* 2017;72(1):13–22.
- 107 Llor C, Moragas A, Hernández S, et al.: Efficacy of antibiotic therapy for acute exacerbations of mild to moderate chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186(8):716–723.
- 108 Stefan MS, Rothberg MB, Shieh MS, et al.: Association between antibiotic treatment and outcomes in patients hospitalized with acute exacerbation of COPD treated with systemic steroids. *Chest* 2013;143(1):82–90.
- 109 Wang JX, Zhang SM, Li X, et al.: Acute exacerbations of chronic obstructive pulmonary disease with low serum procalcitonin values do not benefit from antibiotic treatment: a prospective randomized controlled trial. *Int J Infect Dis* 2016;48:40–45.
- 110 van de Geijn GM, Denker S, Meuleman-van Waning V, et al.: Evaluation of new laboratory tests to discriminate bacterial from nonbacterial chronic obstructive pulmonary disease exacerbations. *Int J Lab Hematol* 2016;38(6):616–628.
- 111 Aloisi F, Pujol-Borrell R: Lymphoid neogenesis in chronic inflammatory diseases. *Nat Rev Immunol.* 2006;6(3):205–217.
- 112 Caramori G, Ruggeri P, Di Stefano A, et al.: Autoimmunity and COPD: clinical Implications. *Chest* 2018;153(6):1424–1431.
- 113 Kunz LI, Ten Hacken NH, Lapperre TS, et al.: GLUCOLD Study Group. Airway inflammation in COPD after long-term withdrawal of inhaled corticosteroids. *Eur Respir J* 2017;49(1):1600839.
- 114 Kanoh S, Rubin BK: Mechanisms of action and clinical application of macro-
- lides as immunomodulatory medications. *Clin Microbiol Rev* 2010;23(3):590–615.
- 115 Durham AL, Caramori G, Chung KF, et al.: Targeted anti-inflammatory therapeutics in asthma and chronic obstructive lung disease. *Transl Res* 2016;167(1):192–203.
- 116 Steri M, Orrù V, Idda ML et al.: Overexpression of the Cytokine BAFF and Autoimmunity Risk. *N Engl J Med* 2017;376(17):1615–1626.
- 117 Polverino F: Deconvoluting Chronic Obstructive Pulmonary Disease: Are B Cells the Frontrunners? *Am J Respir Crit Care Med* 2019;199(9):1170–1171.
- 118 Seys LJ, Verhamme FM, Schinwald A, et al.: Role of B Cell-Activating Factor in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015;192(6):706–718.
- 119 Guerreiro Castro S, Isenberg DA: Belimumab in systemic lupus erythematosus (SLE): evidence-to-date and clinical usefulness. *Ther Adv Musculoskelet Dis* 2017;9(3):75–85.
- 120 Morissette MC, Gao Y, Shen P, et al.: Role of BAFF in pulmonary autoantibody responses induced by chronic cigarette smoke exposure in mice. *Physiol Rep* 2016;4(24):e13057.
- 121 Kurschus FC, Moos S: IL-17 for therapy. *J Dermatol Sci* 2017;87(3):221–227.
- 122 Yadava K, Pattaroni C, Sichelstiel AK, et al.: Microbiota Promotes Chronic Pulmonary Inflammation by Enhancing IL-17A and Autoantibodies. *Am J Respir Crit Care Med* 2016;193(9):975–987.
- 123 Yadava K, Bollyky P, Lawson MA: The formation and function of tertiary lymphoid follicles in chronic pulmonary inflammation. *Immunology* 2016;149(3):262–269.
- 124 Schaad UB, Mütterlein R, Goffin H; BV-Child Study Group: Immunostimulation with OM-85 in children with recurrent infections of the upper respiratory tract: a double-blind, placebo-controlled multicenter study. *Chest* 2002;122(6):2042–2049.
- 125 Pan L, Jiang XG, Guo J, et al.: Effects of OM-85 BV in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. *J Clin Pharmacol* 2015;55(10):1086–1092.
- 126 Pasquali C, Salami O, Taneja M, et al.: Enhanced Mucosal Antibody Production and Protection against Respiratory Infections Following an Orally Administered Bacterial Extract. *Front Med (Lausanne)* 2014;1:41.
- 127 Bessler WG, Vor dem Esche U, Masihi N: The bacterial extract OM-85 BV protects mice against influenza and Salmonella infection. *Int Immunopharmacol* 2010;10(9):1086–1090.
- 128 Dang AT, Pasquali C, Ludigs K, et al.: OM-85 is an immunomodulator of interferon- β production and inflammasome activity. *Sci Rep* 2017;7(1):43844.
- 129 Huber M, Mossmann H, Bessler WG: Th1-orientated immunological properties of the bacterial extract OM-85-BV. *Eur J Med Res.* 2005 May;10(5):209–17.
- 130 van Eeden SF, Sin DD: Chronic obstructive pulmonary disease: a chronic systemic inflammatory disease. *Respiration* 2008;75(2):224–238.
- 131 Man SF, Van Eeden S, Sin DD: Vascular risk in chronic obstructive pulmonary disease: role of inflammation and other mediators. *Can J Cardiol* 2012;28(6):653–661.
- 132 Donaldson GC, Seemungal TA, Patel IS, et al.: Airway and systemic inflammation and decline in lung function in patients with COPD. *Chest* 2005;128(4):1995–2004.

- 133 Dahl M, Vestbo J, Lange P, et al.: C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175(3):250–255.
- 134 Agustí A, Edwards LD, Rennard SI, et al.: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012;7(5):e37483.
- 135 Thomsen M, Ingebrigtsen TS, Marott JL, et al.: Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. *JAMA* 2013;309(22):2353–2361.
- 136 Fu JJ, McDonald VM, Baines KJ, et al.: Airway $\text{IL-1}\beta$ and systemic inflammation as predictors of future exacerbation risk in asthma and COPD. *Chest* 2015;148(3):618–629.
- 137 Van Eeden S, Leipsic J, Paul Man SF, et al.: The relationship between lung inflammation and cardiovascular disease. *Am J Respir Crit Care Med* 2012;186(1):11–16.