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NOVEL AGENTS FOR THE TREATMENT OF ASTHMA

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Progress regarding improved outcomes for asthma patients globally has slowed significantly in the last decade, due in part to the prevalence of treating it as a homogenous disease (Custovic et al, 2019, p.26). The problem lies in the clinical approach; endotyping asthma is currently dichotomised between type 2 (eosinophilic) response and non-type 2 (neutrophilic) response, which has proven to be a simplified categorisation that fails to reflect the complexity of the pathological process (Jeong et al., 2019, p.3). A better understanding of the mechanisms of asthma pathogenesis is particularly important for patients currently categorised as non-type 2 for whom there is no effective therapeutic modality despite comprising approximately 50% of all asthma patients (Jeong et al., 2019, p.10). The standard comprehensive management of asthma depends on a stepwise approach and comprises inhaled corticosteroids (ICSs), B₂ - agonists and leukotriene receptor antagonists (LRTAs) for symptom control (Eyerich et al., 2019, p.547). Recent developments in the research of asthma focusing on its heterogeneity and classification of its specific endotypes have led to new approaches, such as stratified medicine, and novel treatments based on biologicals. It is accepted that humanized monoclonal antibody (mAb) treatments are safe in adult patients with moderate-to-severe asthma (Varricchi et al., 2019, p. 2801). Many mAb treatments have been approved after favourable trials; existing medications with a good safety profile include omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab, which have been shown to reduce exacerbations in patients (adult and pediatric) with severe persistent uncontrolled asthma (Delimpoura et al., 2018; Eyerich et al., 2019). Thymic stromal lymphopoietin (TSLP) has been associated with asthma pathophysiology; tezepelumab is a promising new mAb that specifically targets TSLP (Marone et al., 2019, p.1). A phase 2, randomized, double-blind, placebo-controlled trial carried out by Corren and co-authors (2017, p.936) compared exacerbation events per patient-year in patients who were given three dose levels with placebo over a 52-week treatment period. The trial showed favourable outcomes; exacerbation rates in the tezepelumab groups were lower by 62%, 71%, and 66% than the rate in the placebo group, providing clinical evidence

that inhibition of TSLP with tezepelumab leads to a lower rate of asthma exacerbations than in placebo control (Corren et al., 2017, p.946). Tezepelumab is currently undergoing phase 3 trials (Wechsler et al., 2020; Menzies-Gow et al., 2020). A key pathological feature of severe asthma and chronic obstructive pulmonary disease is airway remodeling (AR) which is unaffected by current therapies (ICSs, B₂ - agonists, LRTAs or mAbs). Novel treatments aim to regulate inflammation-driven AR by targeting the pericyte-myofibroblast transition triggered by the binding of NF-κB/ReA with bromodomain - containing protein 4 (BRD4) associated with toll-like receptor TLR3. By inhibiting BRD4, studies have shown chronic inflammation-induced pericyte-myofibroblast transition can be blocked and thus show potential for inflammation-driven AR (Zhao et al., 2019). A recent review found BRD4 to be a promising therapeutic target for use in patients with diseases characterized by AR based on studies demonstrating the benefits of selective BRD4 inhibitors in disrupting epithelial mesenchymal transition and myofibroblast transition (Brais, A., J. Zhou 2020). Another mechanism by which AR can be regulated is by targeting bitter taste receptors (TAS2Rs) located in the airway smooth muscle (ASM). Kim and co-authors studied the TAS2R5 receptor in particular, prevalent in ASM, and found the bronchodilatory effects of interaction with 1,10-Phenanthroline-5,6-dione showed >1000-fold improvement over the other research compounds. A recent review of current research around TAS2R agonists found research demonstrating “robust” bronchodilatory, anti-inflammatory and ASM regulatory effects in vitro and in animal models, while a review of the clinical role of TAS2Rs agonists called for their potential to be further examined (Jeruzal-Świątecka et al., 2020, p.10).

References:

- [1] Brasier, A. R., & Zhou, J. (2020). Validation of the epigenetic reader bromodomain-containing protein 4 (BRD4) as a therapeutic target for treatment of airway remodeling. *Drug discovery today*, 25(1): 126–132. <https://doi.org/10.1016/j.drudis.2019.11.002>.
- [2] Corren, J., Parnes, J. R., Wang, L., Mo, M., Roseti, S. L., Griffiths, J. M., & van der Merwe, R. (2017). Tezepelumab in Adults with Uncontrolled Asthma. *The New England journal of medicine*, 377(10): 936–946. <https://doi.org/10.1056/NEJMoa1704064>.
- [3] Custovic, A., Henderson, J., Simpson, A. (2019) Does understanding endotypes translate to better asthma management options for all? *Journal of Allergy and Clinical Immunology*, 144 (1): 25-33. <https://doi.org/10.1016/j.jaci.2019.05.016>.
- [4] Delimpoura, V., Bostantzoglou, C., Liu, N., & Nenna, R. (2018). Novel therapies for severe asthma in children and adults. *Breathe (Sheffield, England)*, 14(1): 59–62. <https://doi.org/10.1183/20734735.018917>.
- [5] Eyerich, S., Metz, M., Bossios, A., & Eyerich, K. (2020). New biological treatments for asthma and skin allergies. *Allergy*, 75(3): 546–560. <https://doi.org/10.1111/all.14027>.
- [6] Jeruzal-Świątecka, J., Fendler, W., & Pietruszewska, W. (2020). Clinical Role of Extraoral Bitter Taste Receptors. *International journal of molecular sciences*, 21(14): 5156. <https://doi.org/10.3390/ijms21145156>.
- [7] Jeong, J. S., Kim, S. R., Cho, S. H., & Lee, Y. C. (2019). A Novel Insight on Endotyping Heterogeneous Severe Asthma Based on Endoplasmic Reticulum Stress: Beyond the "Type 2/Non-Type 2 Dichotomy". *International Journal of Molecular Sciences*, 20(3): 713. <https://doi.org/10.3390/ijms20030713>.
- [8] Menzies-Gow, A., Colice, G., Griffiths, J. M., Almqvist, G., Ponnambal, S., Kaur, P., Ruberto, G., Bowen, K., Hellqvist, Å., Mo, M., & Garcia Gil, E. (2020). NAVIGATOR: a phase 3 multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe, uncontrolled asthma. *Respiratory research*, 21(1): 266. <https://doi.org/10.1186/s12931-020-01526-6>.
- [9] Marone, G., Spadaro, G., Braile, M., Poto, R., Criscuolo, G., Pahima, H., Loffredo, S., Levi-Schaffer, F., & Varricchi, G. (2019). Tezepelumab: a novel biological therapy for the treatment of severe uncontrolled asthma. *Expert opinion on investigational drugs*, 28(11): 931–940. <https://doi.org/10.1080/13543784.2019.1672657>.

- [10] Varricchi, G., Marone, G., Spadaro, G., Russo, M., Granata, F., Genovese, A., & Marone, G. (2019). Novel Biological Therapies in Severe Asthma: Targeting the Right Trait. *Current Medicinal Chemistry*, 26(16): 2801–2822. <https://doi.org/10.2174/0929867325666180110094542>.
- [11] Wechsler, M. E., Colice, G., Griffiths, J. M., Almqvist, G., Skärby, T., Piechowiak, T., Kaur, P., Bowen, K., Hellqvist, Å., Mo, M., & Garcia Gil, E. (2020). SOURCE: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of tezepelumab in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma. *Respiratory Research*, 21(1): 264. DOI: 10.1186/s12931-020-01503-z.
- [12] Zhao, Y., Tian, B., Sun, H., Zhang, J., Zhang, Y., Ivannikov, M., Motamedi, M., Liu, Z., Zhou, J., Kaphalia, L., Calhoun, W. J., Maroto, R., & Brasier, A. R. (2019). Pharmacoproteomics reveal novel protective activity of bromodomain containing 4 inhibitors on vascular homeostasis in TLR3-mediated airway remodeling. *Journal of proteomics*, 205: 103415. <https://doi.org/10.1016/j.jprot.2019.103415>.