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Opracowanie drobnocząsteczkowego inhibitora chitotriozydazy (CHIT1) oraz weryfikacja CHIT1 jako nowego celu terapeutycznego w leczeniu śródmiąższowych chorób płuc

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

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Pracę wykonano w laboratoriach Molecure S.A
w ramach programu Doktorat Wdrożeniowy
realizowanym w Studium Medycyny Molekularnej
Warszawskiego Uniwersytetu Medycznego

Obrona rozprawy doktorskiej przed Radą Dyscypliny Nauk Medycznych
Warszawskiego Uniwersytetu Medycznego

Warszawa 2022 r.

3 Streszczenie w języku angielskim

Discovery and development of small-molecule chitotriosidase 1 (CHIT1) inhibitor and validation of CHIT1 as a new therapeutic target for the treatment of interstitial lung diseases

Interstitial lung diseases comprise a heterogeneous group of disorders characterized by the presence of inflammation of varying degrees, in some cases with accompanying irreversible fibrosis affecting the pulmonary interstitium. These diseases differ in etiology, clinical manifestation and outcome. Numerous interstitial lung diseases are considered to be rare, but collectively they affect a significant number of patients and remain a considerable social and medical problem despite the progress in diagnosis and therapy. Chitotriosidase (CHIT1) belongs to the GH18 glycoside hydrolase family and is one of two enzymatically active chitinases in mammals. CHIT1 is a protein involved in inflammatory and fibrotic processes in the lungs and it is considered a potential new therapeutic target in those diseases in which pathology is linked to abnormal immune response or excessive accumulation of extracellular matrix proteins. Due to the limited effectiveness or side effects of currently available therapies, new drugs with novel mechanism of action are pursued. CHIT1 inhibition may represent a new therapeutic approach in the treatment of several conditions that are classified as interstitial lung diseases.

This PhD thesis presents the results of studies on the expression and activity of CHIT1 in biological materials from patients with interstitial lung diseases, describes the process of the identification of a small-molecule CHIT1 inhibitor and presents the characterization of the pharmacokinetic, pharmacodynamic and pharmacological properties of the selected compound using *in vitro* and *in vivo* models. The results of the conducted experiments and analyzes were presented in the form of a series of original research articles, which constitute an integral part of this thesis.

The results of the studies indicate a significant increase in the activity and concentration of CHIT1 in serum and induced sputum in patients with idiopathic pulmonary fibrosis, with *CHIT1* gene being a marker of a subpopulation of profibrotic macrophages specific for patients with fibrosing interstitial lung diseases. Patients with sarcoidosis are characterized by a significantly increased chitinolytic activity and serum CHIT1 concentration. Moreover, a strong expression of CHIT1 was demonstrated in pathological granulomas present in biopsy specimens of mediastinal lymph nodes and bronchial mucosa. OATD-01 is a novel small-molecule CHIT1 inhibitor with a favorable pharmacokinetic and pharmacodynamic profile. The compound was shown to be active *in vitro* and to reduce the secretion of pro-inflammatory mediators by macrophages isolated from the bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis and sarcoidosis. Administration of OATD-01 inhibitor

reduced pulmonary fibrosis and decreased the number of lung lesions in murine models of lung fibrosis and granulomatous inflammation, respectively.

In summary, CHIT1 is a protein with expression upregulated in patients with interstitial lung diseases such as idiopathic pulmonary fibrosis and sarcoidosis. Inhibition of CHIT1 with OATD-01 - a novel inhibitor with a favorable pharmacological profile, may serve as an effective therapeutic approach in this group of diseases.