Glycosylation represents one of the most abundant posttranslational modification of proteins. Glycosylation products are diverse and are regulated by the cooperative action of various glycosyltransferases, glycosidases, substrates thereof: nucleoside sugars and their transporters, and chaperons. In this article, we focus on a glycosyltransferase, \( \alpha_{1,6} \)-fucosyltransferase (Fut8) and its product, the core fucose structure on N-glycans, and summarize the potential protective functions of this structure against emphysema and chronic obstructive pulmonary disease (COPD). Studies of FUT8 and its enzymatic product, core fucose, are becoming an emerging area of interest in various fields of research including inflammation, cancer and therapeutics. This article discusses what we can learn from studies of Fut8 and core fucose by using knockout mice or \textit{in vitro} studies that were conducted by our group as well as other groups. We also include a discussion of the potential protective functions of the keratan sulfate (KS) disaccharide, namely L4, against emphysema and COPD as a glycomimetic. Glycomimetics using glycan analogs is one of the more promising therapeutics that compensate for the usual therapeutic strategy that involves targeting the genome and the proteome. These typical glycans using KS derivatives as glycomimetics, will likely become a clue to the development of novel and effective therapeutic strategies.

## Introduction

In the human body, there are several types of protein modifications that involve glycans being attached to glycoproteins, such as N-glycosylation, O-glycosylation, glycosylphosphatidylinositol (GPI)-anchor and glycosaminoglycan chains and others attaching to protein molecules [1]. These glycan modifications are regulated by the tissue- or cell type-dependent expression pattern of multiple glycosyltransferases, which are required for glycoproteins to express tissue- or cell type-dependent functions. Our group focused on glycosyltransferases that are associated with branching enzymes of N-glycans [2] and major enzymes including N-acetylglucosaminyltransferases referred to as GnT-III, GnT-IV, GnT-V, GnT-VI and \( \alpha_{1,6} \)-Fucosyltransferase (N-acetyl-\( \beta \)-D-glucosamine \( \alpha_{1,6} \) fucosyltransferase, FUT8). They were purified to homogeneity, and GnT-IX (Vb) was identified by molecular cloning. Among them the cDNA of GnT-III, GnT-V and FUT8 were cloned and their genes identified in our group [3–9].

FUT8 attaches a fucose residue onto N-linked-type complex glycoproteins (N-glycans) [8], is expressed ubiquitously in mammalian tissues and is the sole enzyme responsible for generating a core fucose structure. The core fucose structure has a variety of functions that have been demonstrated in studies of Fut8 knockout mice (Fut8\(^{-/-}\)). Fut8\(^{-/-}\) mice showed semi-lethal phenotypes with severe growth retardation and emphysematous phenotypic changes [9], aberrant B cell development [10], defects in T cell receptor signaling [11–14], long term potentiation [15] and enhancement of
neuroinflammation with schizophrenia phenotypes [16]. In human patients with congenital disorders of glycosylation (CDG) caused by FUT8 mutations, lung dysfunction was reported [17,18] as was observed in Fut8 knockout mice [9]. These findings facilitated the development of therapeutics using cancer immunotherapy and tumor biomarkers. An excellent article on FUT8 was recently published [19]. Typical target proteins of FUT8 are the immunoglobulin G (IgG)-B receptor [20], μ-heavy chain [21], IgG1 [22,23], TGF-β-receptor [9], epidermal growth factor receptor (EGFR) [24,25], αβ3 integrin/VCAM-1 [10], α3β1 integrin [26,27], T cell receptors (TCRs) [13,28], E-cadherin [29-32], Dectin-1 [33] and program cell death 1 (PD-1) [34].

It is well known that the aberrant glycan modifications of proteins are strongly related to the onset and progression of certain diseases [35-38]. This suggests that targeting those aberrant glycans is a potentially useful strategy for developing novel and effective therapies [39]. In fact, most of the cancer biomarkers in use today are glycan-based molecules, examples include, CEA, CA19-9, CA15-3, CA-125, PSA and α-fetoprotein L3 [40,41]. These glycans are not just biomarkers but are functional molecules involved in tumorigenesis and the malignant properties in some cancers [38,42]. The attachment of a core fucose to specific glycoproteins are likely candidates for various cancer biomarkers in non-small cell lung cancer (NSCLC) [43-45], castration-resistant and aggressive prostate cancer [46-48], papillary cancer of the thyroid [49], colorectal cancer [32,50], pancreatic ductal adenocarcinoma [50-52], breast cancer [53], ovarian cancer [54], hepatocellular carcinoma [44,55-60].

Research to identify unique disease-related glycans are ongoing concerning many other diseases as well because they could be biomarkers and may be available for developing targeting therapies [60,61]. Concerning this, we extensively investigated emphysema because our research group was the first in the world to generate Fut8 knockout mice and we found severe emphysema and chronic obstructive pulmonary disease (COPD)-like phenotypes in these model animals [9,62-64].

COPD is the third most common cause of death in the world between 1990 and 2010 [65]. In this disease, the development of chronic bronchitis leads to bronchial obstruction and respiratory failure that are not fully reversible [66]. Most COPD cases are associated with emphysema and chronic bronchitis, which is exacerbation by viral or bacterial infections [67] and have an increased risk of primary lung cancer [68]. In any case, the major cause of COPD is exposure to cigarette smoke, secondhand smoke and air pollutions [69]. Importantly, cigarette smoke can strongly activate a variety of immune cells such as macrophages, neutrophils, T-lymphocytes, B-lymphocytes and dendritic cells (DCs) in the bronchi. Those activated immune cells secrete many inflammatory mediators and proteolytic enzymes, which further damage the bronchi and alveoli.

In the first half of this review, we summarize the protective role of Fut8, as reported in our studies using Fut8−/− mice. Additionally, we also summarize our recent data regarding the potential therapeutic effects of the keratan sulfate (KS) disaccharide against emphysema and COPD, and discuss its potential use in the treatment of COPD as a candidate glycomimetic in the second half of this report.

**Emphysema phenotypes in Fut8 knockout mice**

FUT8 generates a core fucose structure by transferring a fucose moiety from GDP-fucose to the innermost GlcNAc residue in N-glycans [70] (Figure 1A). Regarding the molecular structure of human FUT8, the putative catalytic domain is located approximately in the middle of its protein primary structure, and also FUT8 contains other two characteristic domains: An N-terminal α-helical coiled-coil domain and a C-terminal Src homology 3 (SH3) domain [71,72]. The existing of SH3 domain is characteristic for FUT8, but a recent study reported that the SH3 domain is required for its enzymatic activity and identified candidate binding molecules that bind to the SH3 domain [73]. Our research group had generated Fut8−−/ mice and analyzed them in order to address the physiological functions of Fut8 as well as its product: the core fucose structure, in *in vivo.*

Embryogenesis of Fut8−−/ mice does not appear to be impaired, hence they are born with an apparent normal pregnancy period. However, most newborn Fut8−−/ mice died within a few days after birth. The survivors showed severe growth retardation. To determine the reason for this, we examined Fut8−−/ mice and identified severe emphysema phenotypes that include the attenuation of the inhalation and exhalation activity, as well as the structural collapse of alveoli of the lung [9]. In a further study, we demonstrated that an impairment in TGF-β receptor-II/Smad signaling was one of the molecular mechanisms by which emphysema was spontaneously induced in Fut8−−/ mice. TGF-β receptor-II is a transmembrane kinase and forms heteromeric complexes with the TGF-β receptor-I for ligand binding. Murine TGF-β receptor-II contains three N-linked glycans on its extracellular region, and a lack of a core fucose structure results in a lower binding affinity of the ligand:
TGF-β1, to TGF-β receptor-II in the lungs of Fut8−/- mice. This weak ligand stimulation results in low levels of the phosphorylation of Smad2 and the up-regulation of the matrix metalloprotease (Mmp) family genes such as Mmp1, Mmp9 and Mmp12. The strong expression of these proteolytic enzymes effectively breaks down...
the connective tissue components of the bronchi, which induces severe emphysema phenotypes in the lungs of Fut8−/− mice (Figure 1B). These data demonstrate the protective roles of Fut8 and the core fucose structure on TGF-β receptor-II against emphysema and COPD. A study using mutant mice with a lung epithelium-specific deletion of the TGF-β receptor-II also demonstrated the protective roles of the TGF-β receptor-II/Smad signaling against emphysema [74].

In COPD patients, decreased levels of expression of TGF-β1 in the bronchiolar epithelium and alveolar macrophages and TGF-β receptor-II in bronchial glands as well as TGF-β receptor-I were observed [75–77]. While these studies indicate that the down-regulation of TGF-β receptor/Smad signaling is associated with the disease state in humans as well, these studies did not focus on the Fut8 gene and the core fucose structure. Notably, a Thr267Lys polymorphism in human Fut8 gene was also reported to be associated with the development of emphysema in humans. A significantly increased frequency of Thr267Lys polymorphisms in Fut8 in subjects with emphysema compared with subjects without emphysema was found (subjects with emphysema vs. subjects without emphysema = 18.7% vs. 14.2%) [78]. The Thr267Lys polymorphism is located in the proline-rich region of Fut8 and is conserved among glycosyltransferases [79,80], indicating that this amino acid change has an impact on its catalytic activity. Other recent studies reported that patients with a Fut8−CDG were found to show respiratory abnormalities [17,18]. In one allele, a substitution in the coding region of Fut8 (c.943C > T) contains a stop codon (p.Arg315*). As a result, the catalytic activity of Fut8 in this individual was completely deficient [18]. There have not been any studies showing the direct involvement of the core fucose structure on TGF-β receptor in the disease state of patients of emphysema and COPD. However, those studies strongly suggest Fut8 and/or core fucose structure in humans have potential protective roles in humans as well as in experimental animals.

Emphysema mouse model using Fut8 mutant mice

Cigarette smoke is the major cause of emphysema and COPD, therefore, research to address how cigarette smoke is associated with the onset and progression of this disease is a particularly important subject. Interestingly, it was reported that cigarette smoke decreases the level of expression of Fut8 gene and its enzymatic activity in the lungs of mice that were exposed to cigarette smoke [64]. Depending on this Fut8 suppression, the lasting up-regulation of Mmp9 was observed in the lungs during the period of exposure to cigarette smoke, which is consistent with the results of a Fut8−/− mice study as described above. This indicates the potential of using Fut8 mutant mice as an emphysema model. Importantly, the emphysema-like phenotypes induced by exposure to cigarette smoke actually appeared in Fut8 heterozygous knockout (Fut8+/−) mice earlier than in wild type mice [64].

Instead of a cigarette smoke-exposure model, an elastase-induced model is also commonly used in the research field of emphysema and COPD [79]. Elastase is a proteolytic enzyme that digests elastin that is present in the extracellular matrix [81,82]. Thus, the administration of elastase to the mice by intratracheal spray induces the breakdown of connective tissue components in the lungs, which results in the development of emphysema-like phenotypes such as bronchial obstruction, respiratory failure and bronchitis. In addition to the above conventional model, we developed other models for exacerbation induced by viral and bacterial infections. During the pathogenesis and clinical course of COPD, a vicious circle of infection and inflammation is thought to lead to the exacerbation of the disease [69]. Therefore, our group reported that the combined administration of a one shot administration of LPS and elastase to the murine bronchi induced more severe emphysema phenotypes [62] (Figure 2). Based on this and the protective roles of Fut8 gene, as outlined above, the intratracheal administration of elastase combined with LPS to the WT or Fut8−/− mice would be predicted to be an exacerbation model for emphysema and COPD (Figure 2). This model would be desirable in terms of developing effective therapies for the treatment of serious cases of emphysema and COPD patients with bacterial and viral infections.

Keratan sulfate proteoglycan in emphysema and COPD

Unfortunately, there are still significant hurdles to the develop an effective therapy for emphysema and COPD targeting FUT8 and/or core fucose structure on TGF-β receptor-II. Thus, we studied other glycan candidates and identified KS proteoglycan because the expression levels of KS were significantly decreased in the lungs of mice that had been exposed to cigarette smoke [83]. This indicates that KS expression is down-regulated by cigarette smoke and is somehow involved in the onset and progression of emphysema. Based on this, our
hypothesis was that KS exerted protective functions against emphysema and COPD and the supplementation of KS into the lungs would mitigate the clinical phenotypes of the disease.

The KS proteoglycan is one of the proteoglycans that was identified in corneal extracts in 1939 [26]. The KS is made up of a linear polymer of repeating N-acetyllactosamine (LacNAc) unit which is composed of β1,4 linked to a GlcNAc and is sulfated at different positions [80]. KS is now classified into three types, corneal KS-I, skeletal KS-II and brain KS-III. KS-I is attached to N-linked glycans, whereas KS-II and KS-III are attached to mucin type O-linked glycan chains and O-mannose type glycans, respectively [84,85]. The large and diverse structure of glycans of KS seemed to be unsuitable, hence our particular focus was on the simpler di-sulfated KS disaccharide called L4 which consists of a galactose-6-sulfate unit and a β1-4 linked GlcNAc-6-sulfate unit (Figure 3A). Xu et al. [86] reported that the treatment of model mice of autoimmune disease with L4 modulates Interleukin 12 (IL-12) production by macrophages. Shirato et al. [87] suggested that L4 specifically blocks the interaction of flagellin with the toll-like receptor 5, and subsequently suppresses IL-8 production in primary normal human bronchial epithelial cells. Taking these collective issues into account, L4 represents a potential molecule that could be used for the prevention and treatment of airway inflammatory responses to bacterial infections including COVID-19 [39], which play a critical role in the exacerbation of COPD [87]. L4 was obtained from KS of shark fin cartilage after a keratanase II treatment [86] and provided from the Seikagaku Corporation which is a collaborator of our group, and we identified it as a potential functional ligand of Langerin, a C-type lectin receptor that is expressed on DCs [88].

**Figure 2. Three types of mice model were used in this study.**

Model A: Cigarette smoke model. Exposure of wild type mice (WT) to cigarette smoke induces COPD-like phenotypes within approximately 6 months. When heterozygous Fut8 KO (Fut8+/-) mice are exposed to cigarette smoke, however, emphysematous changes are induced within 3 months indicating these mice are sensitive to cigarette smoke [62]. Model B: The conventional method for producing a porcine pancreatic elastase-induced emphysema model. When given a single dose of an elastase treatment, emphysema was produced after 3 weeks. Model C: Exacerbation model. Heterozygous Fut8 knockout (Fut8+/-) mice or porcine pancreatic elastase-induced model mice plus the administration of one dose of an intratracheal administration of LPS. To the mice with emphysema caused by the cigarette exposure for 3 month or by the elastase treatment for 3 weeks, one shot LPS was administered intravenously.
Potential protective functions of keratan sulfate disaccharide L4 through Langerin in emphysema

Langerin, which was identified as a C-type lectin receptor in 2000 [89], is a type II membrane protein and has one C-terminal carbohydrate recognition domain (CRD) in its extracellular region. Physiologically, the expression of Langerin is selective and highly enriched in Langerhans cells (LCs), a subset of DCs that are localized in the dermis. DCs, including LCs, are antigen-presenting cells that function to initiate specific T cell immunity, and LCs are particularly characterized by the presence of a unique pentalamellar cytoplasmic organelle, the Birbeck granule, that mediates the intracellular transport of antigens. The precise roles of Birbeck granule have not been demonstrated, but importantly, Langerin is required for the formation of Birbeck granules and antigen presentation for nonpeptide antigens of Mycobacterium leprae in LCs [90]. However, the issue of how interactions between Langerin and its endogenous and exogenous sugar ligands modulate DC and LC functions and immune responses currently remain unclear.

Several studies have identified various candidates for sugar ligands of Langerin. Langerin recognizes a broad range of glycans that contain mannose, fucose or sulfated sugars, such as oligomannose type N-glycans, the blood group B epitope and glycosaminoglycans. Carbohydrates on gp120 of the human immunodeficiency virus (HIV) and the hemagglutinin glycoprotein of influenza A virus that were also reported to be recognized by Langerin [91,92], and the Langerin-mediated capture of those glycan ligands was proposed to function as a barrier against HIV and influenza A virus [91]. On the other hands, Langerin also binds the teichoic acid of staphylococcus aureus to enhance the inflammatory process [92] and heparin production. The binding of Langerin to glycosaminoglycans, especially heparin, has been extensively studied and the high-affinity binding of heparin to Langerin (dissociation constants ~2.4 nM) as judged by surface plasmon resonance was reported [93].

Figure 3. Keratan sulfate in emphysema and COPD.

(A) The structure of keratan sulfate, KS-1, L4 consists of galactose-6-sulfate unit and β1-4 linked to GlcNAc-6-sulfate. (B) A scheme for the potential protective functions of the keratan sulfate disaccharide L4 and derivatives thereof: triangle-L4 and pendant-L4 against emphysema and COPD. L4 shows anti-proteolytic activity caused by the inhibition of Mmp-2 and Mmp-9 activities. Triangle-L4 and pendant-L4 bind to Langerin more strongly than the L4 monomer and may result in an enhanced down-regulation of TNFα in dendritic cells. These two functions of L4 shown by squares contribute to the mitigation of emphysema phenotypes in the elastase-induced mouse model. The suppressed signal transduction through Langerin is not currently understood. Langerin is required for Birbeck granule formation. 6S: the sulfate group on carbon number 6.

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Among many reports regarding the sugar-binding properties of Langerin, a comprehensive glycoconjugate microarray revealed that galactose-6-sulfate, a component of KS, was a unique sugar ligand of Langerin [94], suggesting that Langerin-KS interactions play important roles in the development of immunity. Interestingly, we previously characterized the interaction between L4 and recombinant trimeric Langerin in in vitro binding assays. Competitive enzyme-linked immunosorbent assay revealed that L4 binds to Langerin that was expressed and purified from *Escherichia coli* with an IC50 value of 3.5 mM. This high IC50 value indicates that the binding between Langerin and the L4 monomer is weak, as is the case of many lectin–sugar interactions, and we expected that the chemical oligomerization of L4 would overcome this weak affinity and lead to the development of high-affinity L4-related Langerin ligands for further functional analysis and clinical applications.

Therefore, we synthesized two L4 oligomers: triangle-L4 (L4 trimer) and pendant-L4 (L4 polymer). As expected, the triangle-L4 and the pendant-L4 bound more strongly to recombinant Langerin than the L4 monomer. The IC50 value for pendant-L4 was 2.1 nM [88], which is a sufficiently low concentration to allow further in vivo analyses to be conducted.

We recently demonstrated that the administration of L4 mitigated the disease state of elastase-induced emphysema and the emphysema in the LPS-induced COPD exacerbation model [62]. In these studies, the intratracheal administration of L4 to the mice decreased the number of infiltrating immune cells, namely, neutrophils and macrophages and the amount of an inflammatory cytokine: tumor necrosis factor α (TNFα) in the bronchoalveolar lavage fluid (BALF). In addition, the activity of Mmp-9 and Mmp-12 in BALF of elastase- or LPS-treated mice was also attenuated by the administration of L4. These anti-inflammatory and anti-proteolytic effects of L4 attenuated severe bronchitis and the pathological collapse of alveoli (Figure 3B). These current pre-clinical data strongly indicate that L4 could serve as a drug for the treatment of emphysema and COPD. However, further investigations will be needed to determine whether Langerin is indeed a functional receptor of L4 in these mouse models as well as in humans.

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**Figure 4. Proposed interaction between glycan-based PAMP and DAMP (virus and/or bacteria) and C-type lectins, Langerin and DC-SIGN.**

PAMP and DAMP can bind to DC-SIGN and Langerin but L4 binds specifically to Langerin and blocks hijacking by PAMP and DAMP thus allowing Langerin to remain active in endocytosis and degradation of the pathogens. The structure information of DC-SIGN is cited from the Uniprot database.
Undesirable roles of FUT8 in cancer tissues and cells

Patients with COPD are at increased risk for the development of primary lung cancer [95–97]. Although the down-regulation of FUT8 is involved in the disease state of emphysema and COPD as described above, the overexpression of FUT8 and/or core fucose-containing glycans was reported in lung cancer and prostate cancer [45,98]. Moreover, a correlation of the expression of core fucose structure with poor survival outcome in some cancer has been reported [45,52,99]. Importantly, FUT8 was also identified as a driver of metastasis of melanoma cells [98].

Epithelial–mesenchymal transition (EMT) and its reversion process MET (mesenchymal–epithelial transition) are important in embryonal development, wound healing and cancer. The overexpression of FUT8 gene in breast cancer cells drives strong TGF-β signals and EMT due to excess levels of core fucose structures on TGF-β receptors in breast cancer cells [54]. In relation to EMT, our group summarized the role of glycosyltransferases involved in N-glycan branching and emphasized the roles of above glycosyltransferases including FUT8 in EMT and MET as transition state as well as biomarkers [99]. Moreover, the overexpression of FUT8 in cancer-associated fibroblasts (CAFs) can promote the malignancy of NSCLC through the activation of EGFR signaling in CAFs [100]. A knockdown study of FUT8 also revealed that weakened EGFR signaling in CAFs attenuated the malignancy of NSCLC [100].

Core fucose unit of N-linked glycan has a unique function in modulating anti-cancer immune responses, for instance, the core fucose structure of N-linked glycan on the TCR is required for the activation of TCR signaling [11–13]. Based on these reports, the inhibition of the core fucose structure considered to be one of the novel therapeutic strategies for cancer patients, but these trials are still in progress. TCR is required for the activation of TCR signaling, and the core fucose structure of PD-1 is essential for cancer immunotherapy [34]. Based on these reports, the inhibition of the core fucose structure is considered to be one of the novel therapeutic strategies for cancer patients [101], but these trials are still in progress.

Glycomimetic using two C-type lectin receptors on dendritic cells as targets

Rational of Langerin as a glycomimetic target

DCs contain two major C-type lectin receptors, Langerin and ICAM-3 grabbing non-integrin (DC-SIGN) [102]. On the cell surface of DCs, both receptors can recognize pathogen- and danger-associated molecular patterns (PAMS and DMPS, respectively) [103] and function to regulate immune responses. However, if some receptor(s) are hijacked by viruses or bacteria, these functions are blocked. Therefore, the development of a specific ligand for binding to a receptor that would protect against this hijacking. This would be a candidate for a glycomimetic drug [39]. In HIV infections, DC-SIGN and Langerin have opposing effects, and DC-SIGN acts on the facilitating of viral survival transmission and infection, whereas Langerin acts on the promotion of viral uptake and degradation [104]. Wamhoff et al. [105] analyzed 275 sugar compounds using the bacterially produced and fluorescence-labeled monomeric carbohydrate recognition domain of DC-SIGN and Langerin, and found that the carbohydrate specificity for Langerin were a terminal mannose, a terminal N-acetylglucosamine and a 6-sulfogalactose residue. Portolabo et al. reported on a specific inhibitor against DC-SIGN, and Wen et al. [106] also reported on a highly specific inhibitor against DC-SIGN with a polyproline tetra helix macrocyte scaffold. Additionally, Pottelverge et al. [107] reported that there are two segregated subsets of tissue-resident pulmonary myeloid DCs and these cells were identified in subcell cell suspensions by flowcytometry. In those patients with COPD, Langerhans-type DCs were accumulated selectively in small airways. Therefore, as a target for COPD, Langerin would play a key role. In this respect, KS derivatives are specific ligands for Langerin and protect hijacking by viruses or bacteria as shown in Figure 4.

Perspectives

- The molecular mechanisms responsible for the onset and progression of emphysema and COPD have not been completely revealed, and there is still no fundamental therapy for curing these diseases. This has already become one of the crucial issues for world health.
From the glycoscience point of view, the core fucose structure and KS are prospective targets for novel and effective drug discovery. It is particularly noteworthy that the KS disaccharide L4: a specific glycan ligand to Langerin, can be administered through the trachea as well as intravenously, and the protective functions against emphysema and COPD have been demonstrated in mouse models.

Although studies are needed to be continued to clarify the role of Langerin as well and to verify the anti-inflammatory effects and safety of L4 more substantially, we believe that L4 has the potential to be developed as a breakthrough glycan-based drug and vaccine for the subjects who are suffering from inflammatory diseases including COPD and cancer in near future.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution
Y.O. drafted this article. Y.H. and N.T. reviewed and revised. All of the authors have read and agree with the submission of this article.

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Abbreviations
BALF, bronchoalveolar lavage fluid; CAFs, cancer-associated fibroblasts; CDG, congenital disorders of glycosylation; COPD, chronic obstructive pulmonary disease; DCs, dendritic cells; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; HIV, human immunodeficiency virus; IgG, immunoglobulin G; KS, keratan sulfate; LCs, Langerhans cells; NSCLC, non-small cell lung cancer; PD-1, program cell death 1; SH3, Src homology 3; TCR, T cell receptor.

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