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Perspective

Lung Protection by Cathepsin C Inhibition: A New Hope for COVID-19 and ARDS?

Miniperspective

Brice Korkmaz,* Adam Lesner, Sylvain Marchand-Adam, Celia Moss, and Dieter E. Jenne

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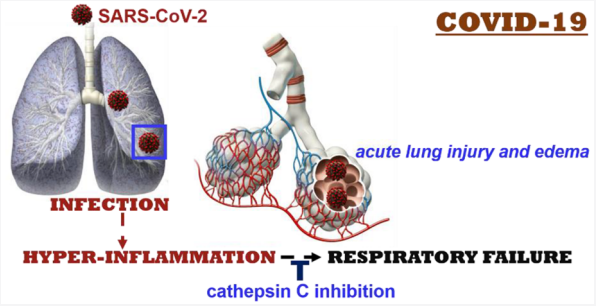
ABSTRACT: Cathepsin C (CatC) is a cysteine dipeptidyl aminopeptidase that activates most of tissue-degrading elastase-related serine proteases. Thus, CatC appears as a potential therapeutic target to impair protease-driven tissue degradation in chronic inflammatory and autoimmune diseases. A depletion of proinflammatory elastase-related proteases in neutrophils is observed in patients with CatC deficiency (Papillon–Lefèvre syndrome). To address and counterbalance unwanted effects of elastase-related proteases, chemical inhibitors of CatC are being evaluated in preclinical and clinical trials. Neutrophils may contribute to the diffuse alveolar inflammation seen in acute respiratory distress syndrome (ARDS) which is currently a growing challenge for intensive care units due to the outbreak of the COVID-19 pandemic. Elimination of elastase-related neutrophil proteases may reduce the progression of lung injury in these patients. Pharmacological CatC inhibition could be a potential therapeutic strategy to prevent the irreversible pulmonary failure threatening the life of COVID-19 patients.



INTRODUCTION

The infectious respiratory tract disease COVID-19 (coronavirus disease 2019) caused by a newly emergent coronavirus SARS-CoV-2 is a global pandemic, and it is urgent and vital for the medical scientific community to investigate new therapies. COVID-19 is the third emergence of a coronavirus in less than 20 years. Its clinical spectrum ranges from unapparent to very severe signs of a life-threatening disease presenting as acute respiratory distress syndrome (ARDS) due to a generalized viral pneumonia. The latter disease manifestation necessitates admission to a hospital in 20% and intensive care therapies in 5% of all infected persons.[1] ARDS, the major cause of morbidity and mortality of COVID-19 patients, is a type of respiratory failure characterized by acute lung injury and edema (Figure 1). While the mechanism that causes the most severe forms of COVID-19 is not yet fully understood, accumulating evidence points to an inappropriate exaggerated response of the innate immune system leading to severe and potentially irreversible lung injury and death from respiratory failure.

The development of viral hyperinflammation resulting in increased influx of neutrophils and monocyte-macrophages was observed in severe cases of COVID-19[2] as well as in previous coronavirus infections (SARS, severe acute respiratory syndrome, or MERS, Middle East respiratory syndrome).[3] Every minute, 30 billion neutrophils (assuming a cardiac output of 5 L/min and 6000 neutrophils/μL blood) with a large arsenal of mature, ready to use proteases are squeezed through lung capillaries and are at the forefront of sensing subtle changes in the lung tissue and local cytokine production. In addition to the freely circulating neutrophils, a large fraction of neutrophils are tethered to the lining of the lung vasculature, and this so-called marginated pool represents the most prominent reservoir and almost 40% of total body neutrophils.[4] As shown by pulmonary intravital microscopy, neutrophils firmly associated with lung endothelial cells form an efficient vascular antibacterial filter to remove circulating bacteria and endotoxin.[5] Neutrophil activation and neutrophil-initiated local proteolysis often at very low but sometimes at a very fast pace are a common theme in chronic inflammatory and autoimmune diseases of the lung.[6−8] On the basis of the accumulated data from preclinical and clinical studies, neutrophils indeed play a crucial role in acute lung injury by releasing elastase-related serine proteases and reactive oxygen

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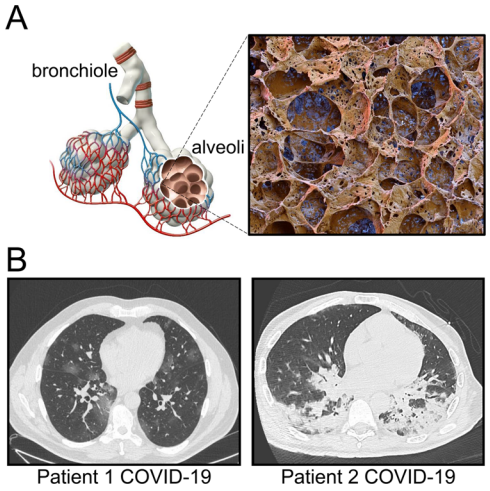

Figure 1. Lung structure in health and chest computed tomography scans from patients with COVID-19 pneumonia. (A) (Left) Lung alveoli, computer artwork. The bronchiole becomes smaller, finally ending in alveoli (tiny air sacs, bulbous), which are the site of gaseous exchange. Oxygen dissolves in the moist surface of the alveoli and passes into capillaries (red blood vessels) that carry it into the bloodstream. Carbon dioxide passes out of venules (blue blood vessels) into the alveoli and is exhaled through the lungs. (Right) Colored scanning electron micrograph (SEM) of a section through a lung, showing numerous alveoli (hollows) and alveolar ducts. (B) Computed tomography (CT) images from two patients showing bilateral multifocal ground-glass opacities (GGO) (patient 1) and consolidation lesions (patient 2). Chest CT of patient 1 was performed 10 days after initial onset of symptoms. The survival and functional outcome of the patient 1 were favorable after 20 days in the intensive care unit. Chest CT of patient 2 was performed 16 days after initial onset of symptoms. Patient 2 died on day 31 despite thorough treatment in the intensive care unit. GGO is a nonspecific finding on CT scans consisting of a hazy opacity that does not obscure the underlying bronchial structures or pulmonary vessels and indicates a partial filling of air spaces in the lung by exudate, transudate, fibrosis, or malignancy. Pulmonary consolidation is a region of normally compressible lung tissue that has filled with liquid or cells instead of air.

species under rapidly evolving deteriorating health conditions.[6,7,9] Decondensation of nuclear chromatin is promoted by neutrophil elastase released from primary granules and leads to neutrophil extracellular trap formation[10] which very recently has been inferred as a driver of severe COVID-19 pneumonia.[11−14] Neutrophil elastase-related serine proteases recognized as pharmacological targets in neutrophilic inflammatory diseases thus appear as promising targets of therapeutic intervention in COVID-19.

PHARMACOLOGICAL INHIBITION OF NEUTROPHIL ELASTASE-RELATED PROTEASES

Direct Inhibition. As proteases are easily understood as major actors in the degradation of tissue, their targeting by therapeutic inhibitors appears to represent a straightforward, easy to achieve goal.[7,15,16] Unexpectedly, direct inhibition of neutrophil elastase-related serine proteases has faced a lot of unresolved difficulties regarding the selection of the most relevant protease targets and their respective inhibitors with an appropriate physicochemical profile, prompting proposals for alternative approaches.[7] Many studies have been conducted with an elastase-selective competitor inhibitor, called sivelestat (*N*-[2-[4-(2,2-dimethylpropionyloxy)phenylsulfonylamino]-aminoacetic acid, research name ONO-5046 marketed as Elaspol, IC_{50}-elastase = 0.044 μM, K_i = 0.2 μM).[17,18] While approved in Japan for the treatment of acute respiratory failure, Eli Lilly stopped the development of this drug in the U.S. in view of disappointing results.[19] Destructive proteolytic processes with organ damage are mediated by multiple proteases, and hence inhibition of a single entity is not appropriate and unlikely to be effective in neutrophil-mediated lung injury. Nonetheless, monospecific highly selective inhibitors developed by the pharmaceutical industry were extraordinarily successful with small compounds inhibiting nonredundant proteases of proteolytic cascades like thrombin or the clotting factor Xa.

Indirect Inhibition. An original and innovative recent strategy was dedicated to the development of an efficient antiproteolytic therapy upstream of elastase-related serine proteases by blocking their maturing enzyme, cathepsin C (CatC, EC 3.4.14.1),[7] during the promyelocytic stage of neutrophil maturation in the bone marrow. CatC, also known as dipeptidyl peptidase I, is a lysosomal tetrameric (Figure 2) amino peptidase belonging to the papain family of cysteine peptidases (family C1, clan CA).[20] CatC is initially synthesized as a ∼60 kDa single chain glycosylated monomer (Asp_1-Leu_{439}) that associates to form the inactive proCatC homodimer.[21] ProCatC dimer is processed and converted to its proteolytically active, mature form by proteolytic activities of CatL-like cysteine proteases in two steps.[21,22] This maturation is initiated by an almost complete excision of the internal propeptide (Thr_{120}-His_{206}) (step 1) and then continued by the processing of the catalytic papain-like structure (Asp_{207}-Leu_{439}) (step 2). The three generated chains of mature CatC, the exclusion domain (Asp_1-Gly_{119}), the heavy (Asp_{207}-Arg_{370}) and the light (Asp_{370}-Leu_{439}) chains, are tightly associated by noncovalent interactions. The processing of papain-like structure in the second step is essential for achievement of active tetrameric CatC in which the N-terminal exclusion domain responsible for the diaminopeptidase activity is localized and stabilized[22] beyond the S2 pocket[20] according to the nomenclature of Schechter and Berger.[23]

CatC, which is ubiquitously expressed in mammals, is recognized as a major intracellular processing protease.[20] CatC catalyzes the dipeptide removal of two residues from the free N-termini of peptides and proteins. The best known function of CatC is the activation of immune cell-associated serine proteases such as proinflammatory neutrophil elastase-related serine proteases (elastase, proteinase 3, cathepsin G, and NSP4) by the removal of their N-terminal dipropeptide.[24,25] Loss of function mutations in the CatC gene (gene symbol *CTSC*) in humans cause Papillon−Lefèvre syndrome (PLS, OMIM 245000) characterized by a severe prepubertal periodontitis and palmoplantar keratoderma without marked immunodeficiency.[26,27] The lack of CatC activity results in an almost total elimination of elastase-related serine proteases in neutrophils from PLS patients[25,28,29] (Figure 3A). Moreover, PLS cells are incapable of producing neutrophil extracellular traps (NETs), networks of fibers, primarily composed of DNA.[30,31] In spite of their deficiency in CatC, PLS patients do not present marked immunodeficiency or recurrent viral infections which means that a transitory pharmacological inhibition of CatC activity in the precursor cells of the bone marrow could well be an attractive therapeutic strategy to regulate activity of elastase-related serine proteases in inflammatory and immune disorders.[6,7] Small molecule

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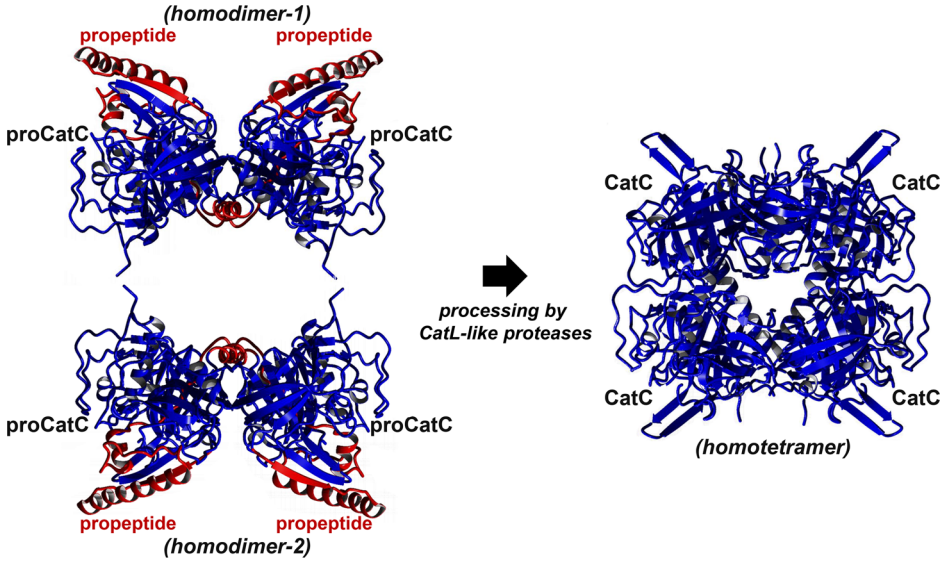

Figure 2. 3D structures of dimeric proCatC and functional tetrameric CatC. (Left) Ribbon representation of unprocessed single chain proCatC monomer model structures in homodimers (PDB file, ref 22). The propeptide (residues Thr_{120}-His_{206}) in ribbon plot is shown in red. After synthesis two monomers of single chain proCatC each composed of an N-terminal exclusion domain, a propeptide segment, and a papain-like structure are associated with formation of a dimeric zymogen. The propeptide segment that participates in the dimerization process prevents tetramerization. Proteolytically active mature CatC in the dimer is generated by proteolytic cleavages at several sites in each proCatC monomer resulting in almost complete excision of the internal propeptide and processing of the papain-like structure. Cathepsins L, S, K, V, and F are identified as proCatC converting proteases.[22] (Right) Ribbon representation of processed CatC monomer structures in functional homotetramer (PDB code 2DJF[39]). Each mature processed CatC is composed of three chains: exclusion domain, heavy and light chains. The images were created with Yasara (http://www.yasara.org).

chemical inhibitors of CatC resulted in similar protection of knockout mice against neutrophil-mediated tissue damage.[32]

NITRILE INHIBITORS OF CATHEPSIN C APPROVED IN PRECLINICAL AND CLINICAL STUDIES

Several chemical inhibitors of CatC have been synthesized,[33−36] some of which are now being tested in preclinical/clinical trials.[6] Most are based on particular dipeptide substrates and carry electrophilic warheads that form reversible or irreversible covalent bonds with the enzyme's active site Cys234.[33,35] The main issue in developing CatC inhibitors is metabolic stability which comes at the cost of inhibitory activity. Different cell assays were used including rat liver microsomes in an attempt to optimize stability, and a small number of compounds progressed to *in vivo* studies of pharmacokinetics or biological effects.[6]

Design and Synthesis of Brensocatib and $IcatC_{XPZ\text{-}01}$. Nitrile-based inhibitors of cysteine cathepsins, which react reversibly with the Cys active site to form a thioimidate adduct, have been studied the most (Figure 4A). Investigators have focused on three chemical classes of nitrile (cyanamides, aryl or heteroaryl nitriles, and amino- or amidoacetonitriles), which differ in their electrophilic effects.[6,34] Nitrile-based inhibitors of CatC are mostly dipeptidyl nitriles with a P2 side chain which determines inhibitory potency.[33,37,38] The S2 subsite of CatC presents as a deep pocket (Figure 4B) containing a chloride ion at the bottom[20,39] and an Asp1 with a carboxylic side chain which interacts with the free N-terminal amino group on the inhibitor. The S1 subsite at the surface of CatC is exposed to solvent[39] so it can accommodate P1 residues bearing aliphatic, hydrophobic, polar, basic, or acidic natural amino acid side chains[40] but might not tolerate long aliphatic side chains directed at proline 3 at the P1 position[32] (Figure 4B).

The first dipeptidyl nitrile compounds, derived from Abu-Bip-CN (Figure 5A) with an aminobutyric acid (Abu) residue at P2 and biphenyl (Bip) at P1, were not stable in plasma because the amide bond was rapidly hydrolyzed.[33,34,37] Stabilization of the peptide bond can be achieved by substituting the N-terminal amino acid with one displaying a piperidine or cyclohexyl ring as side chain[33−36] or by inserting a 1,1-cyclopropylaminonitrile moiety in P1.[41,42] By use of these strategies, brensocatib (formerly INS1007/AZD7986, (*S*)-*N*-((*S*)-1-cyano-2-(4-(3-methyl-2-oxo-2,3-dihydrobenzo[*d*]-oxazol-5-yl)phenyl)ethyl)-1,4-oxazepane-2-carboxamide, IC_{50}-CatC = 22 nM)[43] (Figure 5B) and cyclopropyl inhibitor $IcatC_{XPZ\text{-}01}$ ((*S*)-2-amino-*N*-((1*R*,2*R*)-1-cyano-2-(4′-(4-methylpiperazin-1-ylsulfonyl)biphenyl-4-yl)cyclopropyl)-butanamide), IC_{50}-CatC = 15 nM)[32] (Figure 5C) were developed by AstraZeneca and Neuprozyme Therapeutics, respectively. These appear to be potent CatC inhibitors with good species crossover for rodent CatC, suitable metabolic stability, and resistance to hydrolytic degradation.

Evaluation of $IcatC_{XPZ\text{-}01}$ and Brensocatib in Cell-Based Assays. *$IcatC_{XPZ\text{-}01}$*. In studies using human immature myeloid PLB-985 cells and HL-60 promyelocytic leukemia cells as a model for neutrophilic precursors at different stages of maturation, $IcatC_{XPZ\text{-}01}$ almost completely inhibited the activation of elastase-related proteases.[44] However, the protease levels achieved by pharmacological CatC inhibition using $IcatC_{XPZ\text{-}01}$ were not as low as those observed in neutrophils from PLS patients.[42,44] This may be explained by a difference in protease content of immortalized cell lines compared with bone marrow precursor cells. To test this, we pulse-chased neutrophil progenitors from human bone marrow up to 5 days in the presence of $IcatC_{XPZ\text{-}01}$.[45] There was no disturbance of neutrophil differentiation and almost total disappearance of proteolytic degradation as seen in PLS

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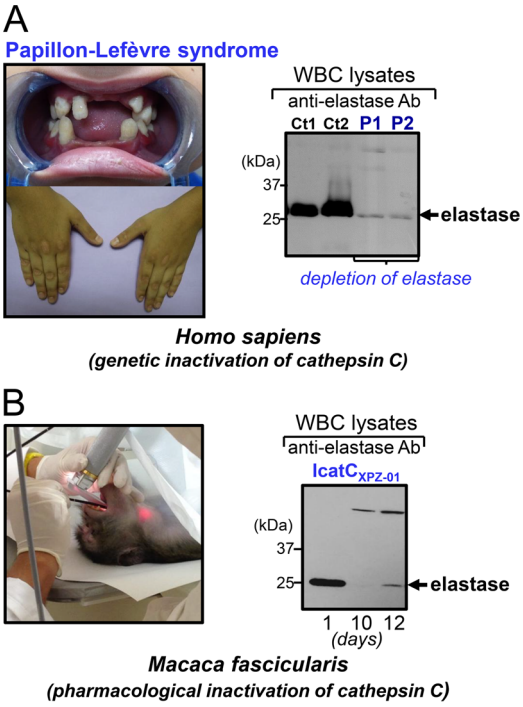

Figure 3. Consequences of genetic or pharmacological inactivation of CatC. (A) Genetic deficiency of CatC in human, showing the dental and dermatological features of PLS. Immunoblot of white blood cell (WBC) lysates using an antielastase Ab: blood samples were collected from two healthy controls (Ct) and two PLS patients (P). The cells from PLS patients were lacking elastase zymogens which were degraded during neutrophil differentiation in the bone marrow. The blood samples and pictures were taken after informed consent was obtained, and the study was conducted according to Declaration of Helsinki principles.[29] (B) Pharmacological inactivation of CatC by prolonged administration of $IcatC_{XPZ-01}$ in a *Macaca fascicularis* experimental model of acute lung inflammation. The image shows broncho-alveolar lavage of an anesthetized macaque. After 11 days administration of $IcatC_{XPZ-01}$ no dental or dermatological manifestations were observed. For the immunoblot of white blood cell (WBC) lysates using an antielastase Ab, blood samples were collected at days 1, 10, 12 from the macaque treated with $IcatC_{XPZ-01}$. CatC inhibition resulted in elimination of elastase zymogens as observed in PLS. All primate experiments and procedures were approved by the local animal experimentation ethic committee (Committee d'Ethique de Val de Loire (CEFA VdL, no. 2013-01-2).[45] The Western-blot results shown in the figure are partially modified and reproduced with permission from *Biochemical Pharmacology* (https://www.sciencedirect.com/journal/biochemical-pharmacology),[45] Copyright 2017 Elsevier, and from *Pharmacology & Therapeutics* (https://www.sciencedirect.com/journal/pharmacology-and-therapeutics),[6] Copyright 2018 Elsevier.

patients. Treating human $CD34^+$ hematopoietic stem cells from umbilical cord blood with $IcatC_{XPZ-01}$ for 10 days during neutrophil differentiation gave similar results.

Brensocatib. In a study using human primary bone marrow-derived $CD34^+$ neutrophil progenitor cells, brensocatib almost completely inhibited the activation of elastase-related proteases in a concentration-dependent manner.[43]

Evaluation of $IcatC_{XPZ-01}$ and Brensocatib *in Vivo*. *$IcatC_{XPZ-01}$.* In mice, $IcatC_{XPZ-01}$ reached high enough levels in bone marrow to inhibit CatC. In a murine model of rheumatoid arthritis induced by anti-collagen antibodies, subcutaneous administration of $IcatC_{XPZ-01}$ (1.2 or 4.8 mg/kg twice daily) resulted in sustained antiarthritic activity measured as reduced mean total and rear paw arthritis scores and mean rear paw thickness.[32] This demonstrates that incomplete CatC inhibition with 60−80% reduction of elastase-related protease activity can have a therapeutic effect and that total elimination of the proteases may not be necessary.

Neutrophil elastase-related proteases are implicated in vascular compromise and inflammation following lung transplantation, the so-called ischemia−reperfusion response with primary graft dysfunction.[9] We hypothesized that $IcatC_{XPZ-01}$, by blocking elastase maturation in the bone marrow, might minimize this damage. We tested this in an orthotopic mouse lung transplantation (LTx) model after 18 h of cold storage of the graft. Recipient mice treated with subcutaneous $IcatC_{XPZ-01}$ for 10 days (1.2 mg/kg; twice daily) prior to LTx showed reduced proteolytic activity in bone marrow neutrophils, improved early graft function, and disappearance of active elastase-related proteases in the transplanted lung. Pretreatment with a CatC inhibitor to reduce elastase-related proteases might be a therapeutically useful strategy to minimize the immediate ischemia−reperfusion response to LTx.

Inhibition of elastase-related proteases by $IcatC_{XPZ-01}$ has also been demonstrated in a non-human primate model of acute lung inflammation. Subcutaneous administration of $IcatC_{XPZ-01}$ (4.5 mg/kg; twice daily; 12 days) resulted in almost complete elimination of elastase-related proteases in white blood cells (Figure 3B) which could still be recruited to the lung in response to lipopolysachharide-induced airway inflammation.[45] These preclinical results confirm that a reduction in elastase-like proteases comparable to that seen in PLS patients is possible using pharmacological inhibitors of bone marrow CatC. Temporary inhibition of CatC to rebalance the protease load during chronic inflammatory diseases might offer new therapeutic possibilities in humans.

Brensocatib. The effect of CatC inhibition by brensocatib on downstream elastase-related protease activation was studied *in vivo* in naïve rats: brensocatib administered twice daily for 8 days resulted in a dose-dependent decrease in protease activity in bone-marrow cell lysates.

Brensocatib was the first nitrile CatC inhibitor to reach clinical trials[43] with randomized, placebo controlled human phase 1 studies commencing in 2014. The safety, tolerability, and pharmacokinetics/pharmacodynamics of single and multiple oral doses were assessed in 81 healthy subjects treated for 28 days with brensocatib or placebo.[46] Daily doses of 10, 25, and 40 mg of brensocatib resulted in 30%, 49%, and 59% reduction in whole blood neutrophil elastase activity.[46] Several dose-dependent, nonserious skin manifestations were observed, including peeling and hyperkeratosis. These symptoms seem unrelated to elastase activity and were not considered sufficiently significant to prohibit further clinical development.[46]

In 2016, the biotechnology company Insmed Incorporated announced a licensing agreement with the pharmaceutical company AstraZeneca for global exclusive rights to brensocatib. In the WILLOW phase 2 study evaluating safety, efficacy, and pharmacokinetics, 256 adults with noncystic fibrosis bronchiectasis were treated once daily for 24 weeks with 10 mg or 25 mg of brensocatib or placebo. Results from this international, randomized, double-blind placebo-controlled trial were announced recently. As well as achieving the primary and a key secondary end point, there was a significant reduction in sputum neutrophil elastase which is an important biomarker for CatC inhibition (www.insmed.com). The

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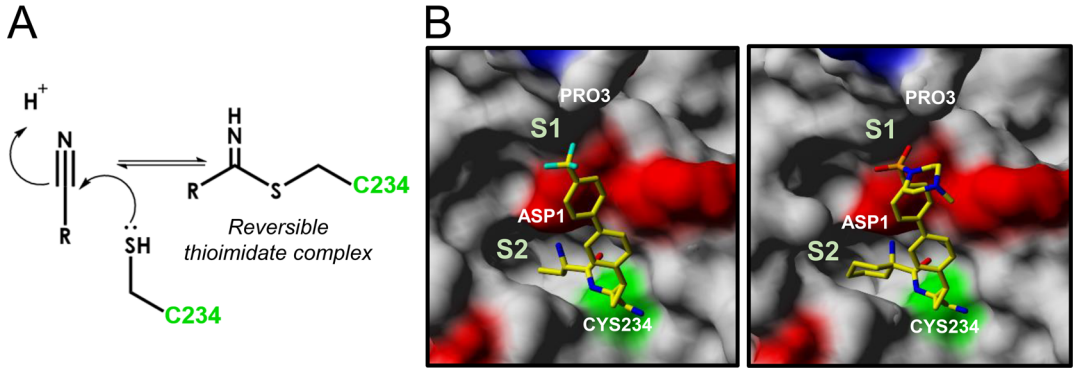

Figure 4. X-ray structures of two dipeptidyl cyclopropyl nitrile inhibitors of CatC. (A) Formation of a reversible thioimidate complex resulting in the reaction of the nitrile function with the active site cysteine 234. (B) Solvent-accessible surfaces of CatC complexed with the inhibitors (1*R*,2*R*)-methyl-(*S*)-2-(*tert*-butyloxycarbonylamino)butanamido)-2-(4′-(4-methylpiperazin-1-ylsulfonyl)phenyl-4-yl)cyclopropanecarboxylate (PDB code 6IC6[32]) or 1-amino-*N*-((1*R*,2*R*)-1-cyano-2-(4′-((4-methylpiperazin-1-yl)sulfonyl)-[1,′-biphenyl]-4-yl)cyclopropyl)cyclohexane-1-carboxamide (PDB code 6IC7[32]). Positive and negative electrostatic potential is represented in blue and red, respectively. The Cys234 is colored in green. The images were created with Yasara (http://www.yasara.org).

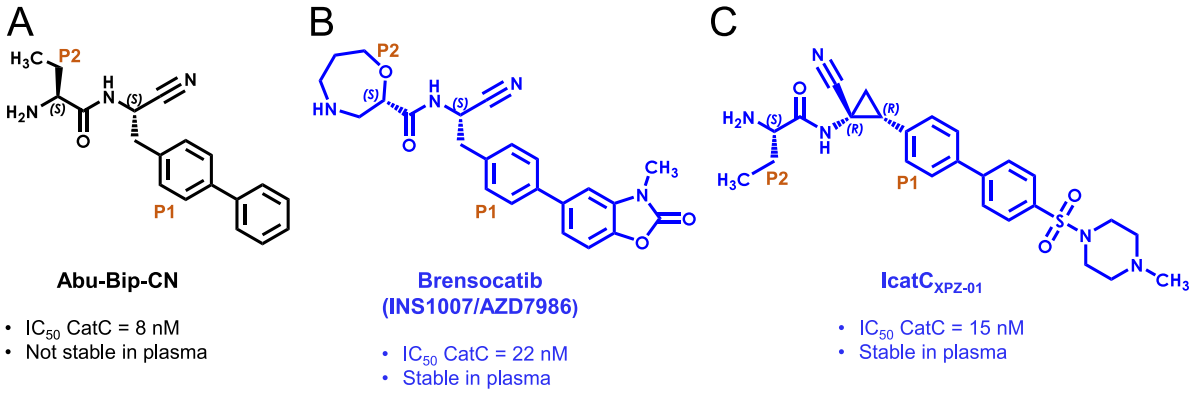

Figure 5. Chemical structures of Abu-Bip-CN (A), brensocatib (INS1007/AZD7986) (B), and $IcatC_{XPZ-01}$ (C).

company plans to advance brensocatib to phase 3 trials for the treatment of noncystic fibrosis bronchiectasis. Moreover, the company announced very recently that brensocatib will be evaluated in the STOP-COVID19 (Superiority Trial of Protease Inhibition in COVID-19, EudraCT no. 2020-001643-13) trial in up to 300 hospitalized patients with COVID-19.

These preclinical and clinical results provide a powerful argument for testing CatC inhibitors in other neutrophil-driven inflammatory conditions.

CONCLUSION

CatC, which is ubiquitously expressed in mammals, is considered to be a major intracellularly located, tetrameric dipeptidyl exopeptidase processing a small restricted subset of substrates at the amino terminus.[20] This unique property distinguishes it from other lysosomal and endosomal cathepsins with a broader substrate profile. After cellular uptake of viral particles, endosomal cathepsins, in particular cathepsin L, can cleave the coronavirus surface spike glycoprotein, which is required for membrane fusion and entry of the corona virus mRNA into the cytosol of host cells.[47] The spike protein of SARS-COV-2, however, is susceptible to structurally diverse proteases and to furin-like and trypsin-like TMPRSS2 proteases.[48,49] However, these proteases cannot be inhibited collectively to prevent the virus from spreading.

In many cases, the initiation and progression of pulmonary disease are the result of an excessive and uncontrolled inflammatory response. The molecular and cellular mechanisms involved can culminate in complete respiratory failure. The pathology of viral pneumonia COVID-19 is typical of inflammatory deregulation in the lungs often culminating in ARDS and sometimes death. ARDS is characterized by diffuse alveolar damage with severe hypoxia requiring hospitalization for oxygen therapy administered if necessary by artificial ventilation on an intensive care unit. It appears that COVID-19 can lead to a deadly cytokine release ("cytokine storm"). Neutrophils seem to play a central role in this hyper-inflammation which results in acute lung injury and sometimes irreversible degradation of lung tissue. Their recruitment in the respiratory tract is associated with a poor prognosis. Thus, the major threat is not the SARS-CoV-2 virus per se but the inappropriately exaggerated response of the innate immune system. Neutrophils produce proinflammatory cytokines, NETs and proteases, in particular elastase-related serine proteases whose proteolytic activities contribute to acute lung injury and escalate inflammation. Inhibiting elastase-related serine proteases represents a particularly promising approach to combating inflammatory processes in lung diseases characterized by neutrophilic inflammation. CatC increasingly attracts the attention of both scientists and clinicians because of its role in the activation of proinflammatory neutrophil elastase-related serine proteases im-

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plicated in specific chronic inflammatory and autoimmune disorders. Pharmacological CatC inhibition could, moreover, be regarded as a potential therapeutic strategy to prevent the irreversible pulmonary failure threatening the lives and survival of COVID-19 patients during the second and third week of hospitalization and mechanical ventilation.

AUTHOR INFORMATION

Corresponding Author

Brice Korkmaz − *INSERM UMR-1100, Centre d'Etude des Pathologies Respiratoires and Universitéde Tours, 37032 Tours, France;* orcid.org/0000-0002-5159-8706; Phone: 0033 2 47 36 63 86; Email: brice.korkmaz@inserm.fr

Authors

Adam Lesner − *Faculty of Chemistry, University of Gdansk, 80-398 Gdansk, Poland;* orcid.org/0000-0001-8335-3431

Sylvain Marchand-Adam − *INSERM UMR-1100, Centre d'Etude des Pathologies Respiratoires and Universitéde Tours, 37032 Tours, France; Service de Pneumologie, CHRU de Tours, 37032 Tours, France;* orcid.org/0000-0002-9522-3738

Celia Moss − *Birmingham Children's Hospital and University of Birmingham, B4 6NH Birmingham, U.K.*

Dieter E. Jenne − *Comprehensive Pneumology Center, Institute of Lung Biology and Disease, German Center for Lung Research (DZL), Munich and Max-Planck Institute of Neurobiology, 82152 Planegg-Martinsried, Germany;* orcid.org/0000-0002-1125-9144

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jmedchem.0c00776

Notes

The authors declare the following competing financial interest(s): Brice Korkmaz has been paid for the time spent as a committee member for advisory boards, other forms of consulting, symposium organization, and lectures or presentations. These payments were made directly to the University of Tours, and no personal payments were received in relation to these activities. All other authors declare no competing interests.

Biographies

Brice Korkmaz received his Ph.D. from the University of Tours in 2005 (supervisor: Prof Francis Gauthier). He was recruited by INSERM (French National Institute of Health and Medical Research) in 2009 after postdoctoral placements in France (INSERM U618), U.S. (Seattle, University of Washington; medical genetics; supervisor, Prof Marshall Horwitz), and Germany (Munich, Max Planck Institute of Neurobiology; supervisor, Dr. Dieter Jenne). He has extensive expertise in biochemistry/enzymology and in neutrophilic chronic inflammatory/autoimmune diseases. He is responsible for a research group (therapeutic targeting of neutrophilic proteases) in team 2 of INSERM-U1100 since 2012. He is the chair of the International Cathepsin C Consortium ICat-CC since 2016.

Adam Lesner received his Ph.D. at the Faculty of Chemistry, University of Gdansk, Poland, in 2001. In 2001−2004 he worked as postdoctoral researcher in the group of Dr. Margaret Simm in the Virology Department led by Dr. J. Volsky at Columbia University, New York, U.S. In 2014, he became Full Professor, at the Faculty of Chemistry, University of Gdansk. He leads the Analytical Biochemistry Lab. His research is dedicated to the design, synthesis, and evaluation of novel peptide and peptidomimetics with broad activity. He focuses on novel artificial chromogenic and fluorogenic substrate and inhibitors activity-based probes of several proteases. He is also involved in developing the anti-inflammatory and antimicrobial compounds.

Sylvain Marchand-Adam completed his pneumology internship in Paris from 1995 to 2001, and he carried out a science thesis at the Inserm U408 unit under the supervision of Pr. Bruno Crestani on the mechanisms of pulmonary repair and implications during idiopathic pulmonary fibrosis. He was then recruited to the faculty of medicine in Tours and appointed professor at the Universities of Tours in 2012. He has been managing the pulmonology department of the CHU of Tours since 2016. He works in team 2 of INSERM-U1100 on the role of proteases during rare pulmonary diseases such as pulmonary fibrosis or granulomatosis with polyangiitis.

Celia Moss obtained a first class honours degree in physiology at the University of Oxford in 1972 and graduated in medicine from the University of London in 1975. She trained in dermatology under Prof. Sam Shuster in Newcastle-upon-Tyne and was appointed consultant dermatologist at Birmingham Children's Hospital in 1993 and honorary professor at the University of Birmingham in 2008. She chaired the British Society for Paediatric Dermatology from 1997 to 2000. Now semiretired she still lectures, advises, and publishes widely on genetic and paediatric dermatology. In 2016 she was awarded the British Association of Dermatologists' Sir Archibald Gray Medal and was appointed Officer of the Order of the British Empire (OBE) for services to pediatric dermatology.

Dieter E. Jenne received his Dr.Med. from the Department of Clinical Pharmacology (Prof. Ellen Weber) and his Dr.Habil. from the Institute of Immunology (Prof. K. Rother) at the University of Heidelberg. In 2003 he was awarded the Venia Legendi in Experimental Immunology (Priv.Doz.) from the Ludwig-Maximilians University in Munich. He was a postdoctoral research fellow at the European Molecular Biology Laboratory in Heidelberg in the cell biology program of Dr. K. Simons and in Prof. Dr. Jürg Tschopp's team at the Institute of Biochemistry, University of Lausanne. In 1992, he was selected for a staff scientist position at the Max-PIanck-Institute of Neurobiology. Since 2012, Dr. Jenne has been a guest scientist at the Institute of Lung Biology and Disease (iLBD) of the Helmholtz Center Munich.

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ABBREVIATIONS USED

ARDS, acute respiratory distress syndrome; CatC, cathepsin C; COVID-19, coronavirus disease 2019; CT, computed tomography; LTx, lung transplantation; NET, neutrophil extracellular trap; PLS, Papillon−Lefèvre syndrome; WBC, white blood cell

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