CEPR
Centre d'étude des pathologies respiratoires

5th International Symposium on Cathepsin C

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In Memory of Prof. Carl-Bertil Laurel

15 > 17 April 2026 | Tours, France

THERAPEUTIC TARGETING OF CATHEPSIN C

FROM PATHOPHYSIOLOGY TO TREATMENT

CELEBRATING 10 years ICat-CC Consortium

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Symposium organised by

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5TH INTERNATIONAL SYMPOSIUM ON CATHEPSIN C

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SUMMARY

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RÉGION CENTRE VAL DE LOIRE

Cathepsin C: advances in therapeutic targeting and the 10-year journey of the ICat-C Consortium

Cathepsin C, also known as dipeptidyl peptidase 1 (DPP1), is attracting increasing attention from both scientists and clinicians due to its central role in activating proinflammatory neutrophil serine proteases (NSPs; elastase, proteinase 3, cathepsin G, and NSP-4), which are implicated in various chronic inflammatory/autoimmune diseases and certain cancers. Promising preclinical and clinical data suggest that pharmacological inhibition of neutrophil serine proteases may help ameliorate these conditions. Patients with Papillon-Lefèvre syndrome have a genetically determined deficiency in cathepsin C but, reassuringly, do not exhibit significant immunodeficiency despite the absence of neutrophil serine proteases in immune cells.Thus, pharmacological control of cathepsin C activity in bone marrow precursor cells represents a promising therapeutic strategy for NSP-mediated disorders, including chronic obstructive pulmonary disease (COPD), bronchiectasis, T2-low asthma, cystic fibrosis, ANCA-associated vasculitis, pulmonary arterial hypertension, inflammatory bowel diseases, and rheumatoid arthritis. Chronic inflammatory respiratory diseases affect over 1 billion people worldwide and are responsible for approximately 4 million deaths annually, with mortality expected to increase through 2030, particularly due to COPD.

Several cathepsin C inhibitors have been developed by pharmaceutical companies and academic teams and are currently being evaluated in preclinical and clinical studies. Among the most advanced is brensocatib (Brinsupri), an oral cathepsin C inhibitor. Results from the Phase 3 ASPEN trial in patients with non-cystic fibrosis bronchiectasis showed significant efficacy, and the drug has now been approved in the USA and EU, making it the first validated targeted treatment for this disease. Two other inhibitors, verducatib and HSK31858, are currently in Phase 3 trials, both demonstrating efficacy and a good safety profile in earlier Phase 2 studies in adults with non-cystic fibrosis bronchiectasis.

The validation of clinically effective cathepsin C inhibitors represents a major breakthrough. This progress is highly encouraging for the scientific community—biochemists studying cathepsin C functionality, cell biologists investigating its maturation and tissue localization, chemists developing selective inhibitors, and clinicians managing NSP-mediated disorders. Reducing constitutively produced neutrophil serine proteases via pharmacological cathepsin C inhibition holds great promise for future therapies. It is gratifying to see that the sustained efforts of academic laboratories, industry, and patient advocacy in the field of cathepsin C may now lead to tangible clinical benefits.

From the perspective of unmet medical needs, drug repurposing for rare diseases offers an important opportunity, as more than 95 % of the >7,000 rare diseases lack an approved therapy. Drug repositioning remains particularly attractive for rare diseases for both scientific and commercial reasons. A special issue on "Neutrophil serine proteases and cathepsin C in rare diseases" was published following the 3rd International Symposium on Cathepsin C (ISyCatC III, Tours/France, April 2022).

In 2016, we initiated the International Cathepsin C Consortium (ICat-CC) to promote collaborative research on therapeutic co-targeting of cathepsin C. The 2026 symposium marks the 10th anniversary of the consortium, celebrating a decade of joint progress in understanding and targeting this key enzyme. We sincerely thank all the academic and industry researchers involved in the consortium for their dedication, as well as the organizations providing financial and institutional support, which have been essential to advancing research on cathepsin C over the past decade.

Since its creation, the consortium has successfully organized four International Cathepsin C Symposia, bringing together scientists, clinicians, and industry partners from around the world to share knowledge, foster collaborations, and advance the field. This 2026 symposium will be the fifth edition, and it is with great joy and pride that we celebrate ten years of scientific progress, discovery, and partnership. We look forward to inspiring discussions, new ideas, and continued collaboration that will further accelerate the development of therapies targeting cathepsin C for patients in need.

Brice Korkmaz
On behalf of Scientific Committee

Kingwell K. Neutrophil-targeting drug seeks first approval in an inflammatory lung disease. Nat Rev Drug Discov. 2025;24(7):487–489.

Chalmers JD, et al. Phase 3 trial of the DPP 1 inhibitor brensocatib in bronchiectasis. N Engl J Med. 2025;392:1569–1581.

Zhong NS, et al. Effects of the DPP 1 inhibitor HSK31858 in adults with bronchiectasis (SAVE BE): Phase 2 randomized trial. Lancet Respir Med. 2025;13:414–424.

Chalmers JD, et al. Cathepsin C (DPP 1) inhibition in adults with bronchiectasis: AIRLEAF Phase 2 Study. Eur Respir J. 2025;65:2401551.

ISyCatC V

Wednesday April 15th

Tours City Hall

19:00 Welcome coctail reception

20:00 **OPENING AND WELCOME SPEECH**

Brice Korkmaz [France]
- The past, present and future of pharmacological targeting of cathepsin C

Représentant Région Centre Val-de-Loire [France]
Fonction du représentant

Daniel Alquier Université de Tours [France]
Vice-président en charge de la recherche

Paola De Carli Vaincre la Mucoviscidose [France]
Scientific Director

Daniel Sojka International Proteolysis Society [Czech Republic]
IPS Council member

- **Prof. Carl-Bertil Laurell's biography** by **Robert Stockley** [UK]

Award ceremony

20:30 **KEYNOTE LECTURE**

James D. Chalmers [UK]
- Targeting cathepsin C: latest clinical advances
Presentation on clinical trial results and disease mechanisms, followed by a discussion on pathophysiology and therapeutic approaches

Thursday April 16th

Hotel Océania | Room Eugénie

08:30 Registration

09:00 Session 1

PATHOPHYSIOLOGY OF CATHEPSIN C

Chair: G. Lalmanach [France]

09:00 **M. Novinec** [Slovenia]
- Oligomeric composition and dynamics of human cathepsin C

09:20 **P. Eickholz** [Germany]
- How does Papillon-Lefèvre syndrom look?

09:40 **A. Gilmour** [UK]
- Cathepsin C activity in pleural infection

10:00 **G. Médard** [Greece]
- Chemoproteomics for characterization of NSPs-AAP-1

10:25 | 11:00 Coffee break

11:00 **D. Sojka** [Czech Republic]
- Cathepsin C–type dipeptidyl peptidases in blood-feeding parasites: emerging roles and therapeutic opportunities

11:20 **C. Taggart** [UK]
- Pharmacological inhibition of cathepsin S and consequences for cathepsin C maturation and myeloid cell function

11:40 ***Selected 5 min Talk:***
***C. Hughes** [UK]: Cathepsin C activity in the airway inflammation*

11:50 Session 2

PATHOPHYSIOLOGY OF CATHEPSIN C TARGETS

Chair: G. Kwapiszewska [Austria]

11:50 **P. McDonald** [Canada]
- A wider-ranging inhibition of cathepsin C and of its substrates in inflammation

12:10 **M. Sienczyk** [Poland]
- Neutrophil serine proteases targeted by various phosphonates - the good and not that bad

12:30 | 14:30 Lunch Buffet

14:30 **M. Selsted** [USA]
- Unexpected role of cathepsin C in the biosynthetic maturation of alpha- and theta-defensins

14:50 **L. Sabirova** [France]
- Differential proteolytic processing, stability, and activation of neutrophil serine proteases in human myelomonocytic cells

15:10 **M. Mall** [Germany]
- Neutrophil serine proteases in cystic fibrosis: role in disease pathogenesis and rationale as therapeutic target

15:30 ***Selected 5 min Talk:***
***T. Chazeirat** [France]: Quantification of neutrophil serine proteases in bronchiectasis*

15:35 **C.H. Chen** [UK]
- Investigating pharmacological inhibition of cathepsin S on human macrophage function and its potential as a target for alpha-1 antitrypsin deficiency

15:55 | 16:30 Coffee break

16:30 **A. Ö. Yildirim** [Germany]
- Neutrophil serine proteases in bronchiolitis obliterans syndrome

16:50 **M. Wegmann** [Germany]
- New therapeutic targets in neutrophil asthma

17:10 **R. Vanbever** [Belgium]
- A single-domain antibody better protects the lung tissue against neutrophil elastase-mediated damage than alpha1-antitrypsin

20:00 Dinner

Friday April 17th

Hotel Océania | Room Rockefeller

09:00 Session 3

PHARMACOLOGICAL TARGETING OF CATHEPSIN C

Chairs: L. Hellman [Sweden] & A. Gieldon [Poland]

09:00 **J.D. Chalmers** [UK]
- Cathepsin C inhibition using BI 1291583 in adults with bronchiectasis: AIRLEAF, a phase II randomised, double-blind, placebo-controlled, dose-finding study

09:20 **V. Sutton** [Australia]
- Pharmacologic inhibition of cathepsin C in CD8T or NK cells

09:40 ***Selected 5 min Talk:***
R. Domain *[Luxembourg]: Alternative cathepsin C–independent pathways for granzyme zymogen maturation in cytotoxic lymphocytes*

09:50 **M. Long** [UK]
- Investigating the impact of DPP1/Cathepsin C or direct neutrophil elastase inhibition in humans using multiomics

10:10 | 11:00 Coffee break

11:00 **M. Rhimi** [France]
- Inactivation of cathepsin C in inflammatory bowel diseases

11:20 **I. Borek** [Austria]
- Inactivation of cathepsin C in pulmonary arterial hypertension

11:40 **Y. Terada** [Japan]
- Pharmacological targeting of cathepsin C in rat model of ANCA-vasculitis

12:00 **K.J. Chen** [USA]
- *In vivo* evaluation of novel cathepsin C inhibitors across preclinical models of inflammatory diseases

12:30 | 14:30 Lunch Buffet

14:30 **B. Liu** [Germany]
- Pharmacological inhibition of the cysteine protease cathepsin C on non-renal vasculature in a rat model of polycystic kidney disease

14:50 **A. Shoemark** [UK]
- Investigating the impact of cathepsin C inhibition on azurocidin

15:10 **E. Johnson** [UK]
- Broad immunomodulatory effects of the cathepsin C inhibitor, brensocatib in bronchiectasis: Data from the Phase 2, double-blind, placebo-controlled WILLOW Trial

15:30 **J. Cichy** [Poland]
- Targeting cathepsin C in neutrophil differentiation and function

15:50 ***Selected 5 min Talk:***
A. Kutlu *[Turkey]: Dual targeting of cathepsin C and S in COPD: design and evaluation of novel cathepsin S inhibitors*

15:55 | 16:15 Coffee break

16:15 **CONCLUDING REMARKS & FUTURE PERSPECTIVES**

B. Korkmaz [France]

20:00 Dinner Gala - Tours City Hall

Prof. Carl-Bertil Laurell (1919-2001)

Carl-Bertil Laurell's (CB's) achievements starting in Uppsala with a paper on the location of vitamin B1 in wheat grains, continuing in Lund where he defended a thesis describing total iron binding capacity, TIBC. He also discovered transferrin and ceruloplasmin. Working in Malmö from 1954 he created Sweden's leading laboratory of Clinical Chemistry. He remained there until 1984, when he retired, holding the titles of Chairman of the Department of Clinical Chemistry and Professor at Lund University in Malmo, Sweden.

Paper electrophoresis became an early signal method perfected by Laurell and developed the quantitative method known as rocket immunoelectrophoresis, which became a mainstay for quantifying many proteins. Another method that he developed for separating and identifying proteins, called crossed immunoelectrophoresis, led to major progress in elucidating the role of proteolytic enzymes and the regulation of their activity. This method led to the discovery and improved diagnosis of diseases caused by disruptions in those regulatory systems including immunoglobulins and the relationship of kappa and lamda chains with IgG abnormalities, albumin and IgG interpretation in CSF.

Dr. Laurell published over 200 scientific papers in international journals in a career that stretched over decades. However, the most important was his discovery of a1-antitrypsin deficiency, the most common hereditary disease in his native Sweden.

The discovery of alpha-1-antitrypsin deficiency was made in 1962 identifying what we now refer to as the ZZ variant although Laurell subsequently identified other phenotypic variants. The clinical development of this observation formed the basis of the PhD thesis for Sten Eriksson (an ENT surgeon) in 1964 and Eriksson's student Chister Larsson who discovered intracellular retention of defective alpha-1-antitrypsin as background for the deficiency in 1975.

Laurells flair for research is illustrated by an incident in which a technician mistakenly used tap water instead of distilled water in an electrophoresis buffer. The anomalies in the results led Dr. Laurell's team to the realisation that the addition of calcium ions to the electrophoresis buffer could cause the splitting of the b-fraction in ways that supplied better clinical information, a discovery that influences the performance of electrophoresis to this day

Carl-Bertil Laurell, MD, PhD received the fourth annual Edwin F. Ullman Award at the AACC in recognition of his outstanding contributions to the technology of clinical laboratory science.

Carl-Bertil was a devoted systematic researcher, excelling in the development of new techniques including agarose gel electrophoresis, crossed immunoelectrophoresis and electroimmuno assay or "Laurell rock-ets." For these innovations he became one of the most cited authors in medical research for years, although he rarely and reluctantly attended scientific meetings. He also had a broad and burning interest in the biochemical basis of clinical conditions. As advisor for numerous colleagues he instigated clinical, metabolic, psychiatric, genetic, and population studies related to protein abnormalities he had seen. At the time of his retirement, Carl-Bertil began investigating aspects of fertility, leading to the delineation of several seminal proteins, in-cluding PSA, and culminating in June 1984 with the opening of a clinical Fertility Center in Malmö.

Carl-Bertil was a fierce proponent of high academic standards and could terrify unprepared students (a man after my own heart). For those who worked closely with him, he was an excellent listener, delighted by new ideas and supportive in times of crisis. Despite numerous awards and memberships in honorable scientific societies, Carl-Bertil derived greatest pleasure from his lab bench and from the successes of his students. A most important survivor is the Swedish tradition of clinical chemistry, which has largely been moulded by his example, his teaching and his textbook.

Prof. Robert Stockley

15th April 2026

James D. Chalmers

Targeting cathepsin C: latest clinical advances

notes

Targeting cathepsin C: latest clinical advances

James D. Chalmers

Asthma and Lung UK Chair of Respiratory Research, University of Dundee, Division of Molecular and Clinical Medicine, School of Medicine, Dundee, Scotland, UK

Abstract

The dipeptidyl peptidase-1 [cathepsin C] inhibitor brensocatib has recently become the first licensed therapy for bronchiectasis by regulatory authorities in the United State and Europe, a major landmark in a previous neglected disease. These drugs are now being used in clinical practice on the basis of a phase 3 trial showing reduced exacerbations and slowing down of lung function decline in patients with this chronic lung disease. This has become an exciting trial space, with Verducatib also entering phase 3 trials in bronchiectasis and cystic fibrosis, HSK31858 entering phase 3 trials in bronchiectasis and a recently announced phase 2 trial in COPD. These drugs are likely to make a major contribution to the management of chronic lung diseases. This presentation will review the results of these clinical trials, with a focus on the many unanswered questions for the research community : which patients are most likely to respond? Can we develop biomarkers of response? What is their mechanism of action in the airways? Why do Asian patients appear to be super-responders? What does long term safety look like? This is an exciting time for science in this area and for patients benefiting from these treatments.

16th April 2026

Marko Novinec

Oligomeric composition and dynamics of human cathepsin C

notes

Oligomeric composition and dynamics of human cathepsin C

Milena Stojkovska Docevska[1], Filip Maciejowski[2], Marcin Skoreński[2], Marcin Sieńczyk[2], **Marko Novinec[1]**

[1] University of Ljubljana, Faculty of Chemistry and Chemical Technology, Ljubljana, Slovenia. | [2] Wroclaw University of Science and Technology, Faculty of Chemistry, Wroclaw, Poland.

Abstract

Cathepsin C is a papain-like cysteine peptidase with several unique structural and functional features. In its active form, it exists as a homotetramer organized as a dimer of dimers, formed through two distinct subunit interfaces called head-to-tail and lateral. This arrangement is facilitated by its unique exclusion domain, which participates in both subunit interfaces and also determines its dipeptidyl peptidase activity. Cathepsin C assembles through a two-step process involving a dimeric zymogen form called procathepsin C. During zymogen maturation, the propeptide is removed, and the exclusion domain remains noncovalently attached to the catalytic domain, which is then cleaved into heavy and light chains.

The objective of our work is to determine the sequence and importance of events during cathepsin C maturation and the significance of the tetrameric form for its biochemical properties. To this end, we introduced targeted mutations at various functionally and structurally important regions of cathepsin C, including key activation-site residues, N-glycosylation sites, and C-terminal extensions designed to disrupt the head-to-tail subunit interface.

We used size-exclusion chromatography and mass photometry to characterize the resulting oligomeric states, and active site labeling with the probe WKS-762 to detect cathepsin C species during activation. These experiments identified two distinct dimeric forms of procathepsin C, demonstrating that cathepsin C maturation follows two alternative assembly pathways. The equilibrium dissociation constant K_d of the head-to-tail dimer of procathepsin C was in the nanomolar range, while the K_d of the lateral dimer was two orders of magnitude higher, reflecting the lower but still significant affinity of this form.

After activation, wild-type cathepsin C assembled into a high-affinity tetramer. The K_d value for the dimer-tetramer equilibrium was about 0.2 nM, and monomers were not detected by the methods used. Failure to cleave the catalytic domain into heavy and light chains prevented tetramerization, highlighting the importance of proteolytic processing in forming the mature tetramer. Nonetheless, low catalytic activity was detectable in vitro even for the mutant form. Removal of one or two N-glycosylation sites did not affect the processing, oligomeric state, or activity of cathepsin C, whereas removal of three or four N-glycosylation sites adversely affected oligomer formation but still resulted in a catalytically active enzyme.

By defining the structural requirements and assembly pathways that govern cathepsin C oligomerization, this study provides a framework for understanding how homooligomeric proteases mature and establishes a foundation for future research into the physiological and pathological significance of the oligomeric state of cathepsin C.

16th April 2026

Peter Eickholz

How does Papillon-Lefèvre syndrome look?

notes

How does Papillon-Lefèvre syndrome look?

Peter Eickholz

Johann Wolfgang Goethe University Frankfurt am Main | Center for Dentistry and Oral Medicine (Carolinum), Dept. of Periodontology | Theodor-Stern-Kai 7 (Haus 29), 60596 Frankfurt am Main

Abstract

How does Papillon-Lefèvre syndrome (PLS) look? How may PLS be detected? Characteristic symptoms are palmo-plantar hyperkeratosis and severe periodontitis that may manifest already in the deciduous dentition in early childhood. Periodontitis is the inflammatory destruction of tooth supporting tissues triggered by a dysbiotic biofilm. Whereas hyperkeratosis at palms and feed may be easily noticed early. Detection of periodontitis in children requires attentative dentists. PLS is a rare autosomal recessive disease, with an incidence of 1–4 cases/million people that is unlikely to be detected by pediatritions. PLS is caused by lost-of-function mutations in the cathepsin C gene. To date, more than 50 different mutations have been identified and since cathepsin C activity is essential for activation of neutrophil elastase, cathepsin G, protease 3 and neutrophil serine protease 4, PLS neutrophils show no or severely reduced activity of these four enzymes. Untreated patients frequently harbor *Aggregatibacter actinomycetemcomitans* in the subgingival microflora. In PLS LL-37 a bactericidal peptide against *A. actinomycetemcomitans* is not activated. Textbooks state that early loss of all teeth is inevitable in PLS patients. However, early detection and consequent treatment may result in in long-term tooth retention.

16th April 2026

Amy Gilmour

Cathepsin C activity and pleural infection

notes

Cathepsin C activity and pleural infection

Amy Gilmour

Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Dundee, Scotland, UK

Abstract

Pleural infection is a neutrophil dominated pathology but there has been limited characterisation of neutrophil function or activity in this disease. Here we present the results of the PIRATE (Pleural Infection Registry and Translational Endpoint Study) which investigated neutrophilic inflammation and the role of cathepsin C targets in pleural disease. Patients with pleural infection, confirmed by established criteria, non-infected pleural effusions and healthy controls were enrolled. Matched blood and pleural fluid were obtained for measurement of inflammatory markers including cathepsin C targets such as neutrophil elastase and azurocidin-1. Neutrophil activity in the peripheral blood was profiled using flow cytometry, and whole blood and neutrophil transcriptomics. An assay to measure cathepsin C enzyme activity directly in patients samples was validated in sputum from patients with bronchiectasis and subsequently applied to pleural infection samples. The results of the PIRATE study will be presented investigating the role of cathepsin C targets and neutrophilic inflammation in pleural infection.

16th April 2026

Guillaume Médard

Chemoproteomics for characterization of NSPs-AAP-1

notes

Chemoproteomics for characterization of NSPs-AAP-1

Guillaume Médard

Proteomics Core Facility, National and Kapodistrian University of Athens, Greece

Abstract

A novel alternative protease, NSPs-AAP-1, has recently been shown to activate neutrophil serine proteases (NSPs) even in the absence of cathepsin C (CatC) activity. Data point to NSPs-AAP-1 as a cysteine protease that is inhibited by reversible covalent nitrile compounds designed for CatC inhibition. The major therapeutic implication of the unveiling of this CatC-independent proteolytic pathway(s) in the activation of proNSPs calls for the leveraging of chemoproteomics strategies to reveal the identity of the protease so as 1) to engage in medicinal chemistry campaigns to create chemical tools and drugs targeting NSPs-AAP-1 and 2) to unlock the molecular biology toolbox necessary to dissect NSPs-AAP-1 action.

Chemoproteomics identification of NSPs-AAP-1 relies on its specific enrichment out of biological samples, thanks to its strong interaction with dual inhibitors of CatC/ NSPs-AAP-1 used as baits. Untargeted bottom-up proteomics measurement by mass-spectrometry then allows to map the peptidic sequences to the genome and thereby identify the protein. Competition for enrichment of NSPs-AAP-1 between the bait and other inhibitors allow to validate the specificity of the drugs-protease interaction. This presentation will detail the principles of affinity-based chemoproteomics at play, while applying the approach to the identification of NSPs-AAP-1.

16th April 2026

Daniel Sojka

Cathepsin C–type dipeptidyl peptidases in blood-feeding parasites: emerging roles and therapeutic opportunities

notes

Cathepsin C–type dipeptidyl peptidases in blood-feeding parasites: emerging roles and therapeutic opportunities

Daniel Sojka

Institute of Parasitology, Biology Centre of the Czech Academy of Sciences, České Budějovice, Czech Republic

Abstract

Blood feeding has evolved multiple times independently across metazoan and protist lineages, including helminths, hematophagous arthropods, and protozoan parasites. Despite their distant evolutionary origins, these organisms face a common physiological challenge: the digestion of host hemoglobin and other blood proteins as a primary nutrient source. This requirement has driven the emergence of specialized intracellular proteolytic systems, often composed of coordinated networks of cysteine and aspartic proteases that operate within acidic digestive compartments.

While endopeptidases such as cathepsins B and L have long been recognized as central components of these digestive pathways, increasing evidence points to a broader role for cathepsin C–type dipeptidyl peptidases within these proteolytic systems.

In blood-feeding helminths, including schistosomes, cathepsin C homologues are expressed in the parasite gut and participate in intestinal proteolysis associated with hemoglobin digestion. Comparable proteolytic architectures are found in ticks, where blood digestion occurs intracellularly within acidic endolysosomal vesicles of midgut digestive cells. Transcriptomic and biochemical analyses of the *Ixodes ricinus* midgut reveal a complex digestive protease network dominated by cathepsin B and L enzymes, accompanied by cathepsin C–like exopeptidases that likely contribute to downstream peptide processing.

Related enzymes are also present in apicomplexan parasites, where cathepsin C–like dipeptidyl aminopeptidases (DPAPs) have been implicated in hemoglobin degradation and host-cell invasion processes. Notably, pharmacological inhibition of DPAP enzymes in malaria parasites has demonstrated strong antiparasitic activity, highlighting the vulnerability of these proteolytic pathways.

Together, these observations suggest that cathepsin C–type enzymes are conserved components of proteolytic systems across diverse blood-feeding parasites. Because these enzymes operate within pathways essential for nutrient acquisition and parasite survival, they represent attractive and potentially underexplored targets for antiparasitic intervention.

16th April 2026

Cliff Taggart

Pharmacological inhibition of cathepsin S and consequences for cathepsin C maturation and myeloid cell function

notes

Pharmacological inhibition of cathepsin S and consequences for cathepsin C maturation and myeloid cell function

Cliff Taggart

Wellcome Wolfson Institute for Experimental Medicine, Queen's University Belfast

Abstract

Cathepsin S (CTSS) is a potent elastolytic protease that plays a role in inflammation, tissue destruction and antigen presentation. We have previously demonstrated upregulated CTSS activity and protein in the lungs of patients with Cystic Fibrosis (CF), Chronic Obstructive Pulmonary Disease (COPD) and Acute Respiratory Distress Syndrome (ARDS). Utilising murine models of acute (direct instillation of lipopolysaccharide) and chronic (ENaC-Tg and smoking) lung disease, we have demonstrated a role for CTSS in lung inflammation, mucus production and lung damage. Notably, in all murine models of lung disease we have observed a significant decrease in lung neutrophil recruitment which is due, in part, to activation of the protease activated receptors, PAR-1 and PAR-2. In recent data, we have shown that neutrophils can also produce CTSS which suggests a role for CTSS in neutrophil function. We have focused on the involvement of CTSS in the processing of Cathepsin C (CTSC), which itself is an integral protease for the activation of the Neutrophil Serine Proteases (NSPs), which are integral and critical to the normal function of neutrophilic cells. Initial investigations were carried out in the neutrophil precursor-like cell lines, HL-60 and PLB-985, as the processing of CTSC and NSPs occurs early in the neutrophil maturation process. In these cells we have shown that inhibition of CTSS activity leads to an arrest in CTSC processing, as confirmed by the appearance of a processing intermediate via Western blot and a reduction in CTSC activity via fluorometric activity assay. More recently, we have evaluated a role for CTSS in CTSC processing in U937 cells and, similar to PLB-985 cells, we also show inhibition of CTSC in these cells suggesting that CTSS regulates CTSC in monocytic, as well as neutrophilic, cells. The effect of these inhibitors on NSP activity was then also investigated via fluorometric activity assay and reductions in the activity of NSP activity were noticeable with CTSS inhibitor treatment. Future investigations will involve analysing the effect of CTSS inhibition on neutrophil and monocytic function. The findings of this study could implicate myeloid-derived CTSS in the pathogenesis of acute and chronic lung disease.

16th April 2026

Chloe Hughes

Cathepsin C targets and neutrophilic inflammation in patients with bronchiectasis

notes

Cathepsin C targets and neutrophilic inflammation in patients with bronchiectasis

Chloe Hughes

Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Dundee, Scotland, UK

Abstract

DPP1/Cathepsin C inhibitors are now licensed for treatment of bronchiectasis. While nearly all attention has focused on the impact of these therapies on the levels of airway inflammation there are few if any studies investigating systemic neutrophilic inflammation and DPP1 targets in people with this disease. This is highly clinically relevant since DPP1 inhibitors are systemically acting drugs and so may be expected to have effects also on systemic inflammation. In a European study (EMBARC-BRIDGE) profiling systemic inflammation we show an association between systemic neutrophilic inflammation including DPP1 targets such as Proteinase-3 and azurocidin-1 associated with worse lung function and symptom burden. We demonstrate an altered neutrophil phenotype in the systemic circulation of patients with bronchiectasis and associations with important clinical outcomes. Our data suggest that neutrophil dysfunction is not limited to the airway compartment and suggests that studies should examine the impact of DPP1 targeting also on the systemic component of the disease.

16th April 2026

Patrick P McDonald

Impact of dipeptidyl peptidase i on human and mouse neutrophil functional responses

notes

Impact of dipeptidyl peptidase i on human and mouse neutrophil functional responses

Patrick P McDonald[1,2], Dedong Li[1], Mei Fong Pang[1], Vanessa de Carvalho Oliveira[2], Kuan-Ju Chen[1], David C Cipolla[1]

[1] Dept of Research, Insmed Incorporated, Bridgewater, NJ, USA | [2] Immunology Graduate Program, Faculty of Medicine, Université de Sherbrooke, Canada

Abstract

Dipeptidyl peptidase-1 (DPP1) is a lysosomal cysteine protease essential for activating neutrophil serine proteases (NSPs), including neutrophil elastase, cathepsin G, and proteinase 3, during neutrophil differentiation in the bone marrow. Because NSP-mediated tissue damage contributes to chronic inflammatory and autoimmune diseases, targeting NSPs has emerged as a therapeutic strategy. In this regard, small molecule drugs have been developed such as brensocatib – a competitive, reversible DPP1 inhibitor. Active DPP1 is expressed and catalytically active in mature neutrophils, which raises the possibility that its inhibition might affect more than just NSP activities.

We investigated the effects of DPP1 inhibition, or of NSP inhibition or ablation, on neutrophil function. As expected, DPP1 inhibition with brensocatib during mouse bone marrow hematopoietic stem cell differentiation dose-dependently reduced NSP activities in the resulting neutrophils; a similar outcome was observed using DPP1 knockout and triple NSP knockout (NE-/-CatG-/-Pr3-/-) mice. Exposure to brensocatib during granulocytic differentiation suppressed the ability of the resulting mouse neutrophils to generate neutrophil extracellular traps (NETs), and this response was also absent in neutrophis from DPP1 knockout or triple NSP knockout mice. By contrast, DPP1 inhibition, or the ablation of DPP1 or all three NSPs, had no significant impact on granulocytic differentiation, migration, phagocytosis, reactive oxygen species production, or bacterial killing. In human neutrophils, brensocatib had no effect on any of the above responses, including NET formation, and also did not affect NET-mediated bacterial killing. These findings suggest that while DPP1 is crucial for NSP activation during early neutrophilic differentiation, it does not substantially influence differentiation itself or core neutrophil functions, except for NET formation in mice. This study advances our understanding of the roles of DPP1 and NSPs in neutrophil biology and further emphasizes the high selectivity of brensocatib in its main target cells.

16th April 2026

Marcin Sieńczyk

Serine proteases targeted by various phosphonates - the good and not that bad

notes

Serine proteases targeted by various phosphonates - the good and not that bad

Marcin Sieńczyk

Wroclaw University of Science and Technology, Faculty of Chemistry, Wyb. Wyspianskiego 27, 50-370 Wrocław, Poland

Abstract

Although 1-aminoalkylphosphonate diaryl esters have a history spanning nearly 50 years, they remain one of the premier classes of specific, irreversible, active-site-directed inhibitors. Their hallmark is an exquisite selectivity: they react exclusively with serine proteases while remaining completely inert toward other classes of proteolytic enzymes. Furthermore, their high chemical stability, combined with virtually limitless possibilities for structural modification, makes them an invaluable tool for studying serine proteases of diverse origins—human, bacterial, and viral—both in vitro and within living cells.

Historically, phosphonic activity-based probes (ABPs) were first designed and implemented to investigate proteases secreted by immune cells, including granzymes, elastase, and chymase. Subsequent research shifted focus toward developing inhibitors and probes targeting neutrophil serine proteases (NSPs), specifically proteinase 3, neutrophil elastase, cathepsin G, and NSP4. Since the structural diversification of phosphonates is constrained primarily by the researcher's imagination, numerous highly potent and selective compounds have been synthesized. These tools have proven essential in distinguishing between proteases with similar or overlapping substrate specificities.

Beyond their traditional role as inhibitors, 1-aminoalkylphosphonates have demonstrated utility in the development of catalytic antibodies and, more recently, as functional components in PROTACs (Proteolysis Targeting Chimeras). This latter application significantly expands the scope of phosphonate utility in targeted protein degradation. This presentation will explore the discovery, chemical evolution, and diverse applications of 1-aminoalkylphosphonates, while also addressing their inherent limitations.

16th April 2026

Michael E. Selsted

Unexpected role of cathepsin C in the biosynthetic maturation of neutrophil alpha- and theta-defensins

notes

Unexpected role of cathepsin C in the biosynthetic maturation of neutrophil alpha- and theta-defensins

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Abstract

Myeloid alpha (α)- and theta (θ)-defensins are host defense peptides that contribute to innate immune functions of neutrophils and monocytes. Although α- and θ- defensins are closely related genetically, the mature peptides are structurally distinct: human α-defensins (HNPs) are linear 29-30 amino acid, arginine-rich, tri-disulfide peptides, whereas θ-defensins are 18-amino acid backbone cyclized, tri-disulfide macrocycles expressed uniquely in Old World monkeys.

In previous studies on the maturation of human HNPs, we showed that recombinant HNP propeptides are processed with high fidelity by serine proteases neutrophil elastase (NE) and proteinase 3 (PR3). In contrast, pro-HNP treatment with the closely related serine protease cathepsin G (CG) resulted in a two-amino acid amino terminal extension. Since CatC is a dipeptidyl aminopeptidase, we hypothesized that its absence in Papillon-Lefevre syndrome (PLS) neutrophils might result in incomplete HNP processing. Extracts of neutrophils from three PLS patients and two controls were analyzed for their mature HNP content by RP-HPLC and LC-MS/MS.

Neutrophils from all three PLS patients contained HNPs with N-terminal extensions of one or two amino acids, demonstrating incomplete peptide maturation, whereas these processing variants were not observed in control neutrophils. In studies to delineate the maturation of cyclic θ-defensins, we synthesized putative θ-defensin precursor peptides which were cyclized when incubated with microsomal preparations of baboon bone marrow cells. Chromatographic purification and proteomic analysis of tissue lysates identified CatC as a cycloconvertase that cyclized several putative θ-defensin precursors. The requirement for CatC in θ-defensin biosynthesis was confirmed by metabolic labeling studies of rhesus macaque bone marrow cells in the presence of CatC-specific inhibitor BI-9740 which blocked mature θ-defensin biosynthesis. Thus CatC is a maturase required for the biosynthesis of linear α-defensins and macrocyclic θ-defensins.

16th April 2026

Lada Sabirova **Differential proteolytic processing, stability, and activation of neutrophil serine proteases in human myelomonocytic cells**

notes

Differential proteolytic processing, stability, and activation of neutrophil serine proteases in human myelomonocytic cells

Lada Sabirova, Cécile Croix and Brice Korkmaz

INSERM UMR-1100, Research Center for Respiratory Diseases, Tours, France | University of Tours, Tours, France

Abstract

Neutrophil serine proteases (NSPs), elastase, proteinase 3, and cathepsin G, are key effectors of innate immunity. Most NSPs are activated by cathepsin C, and to a lesser extent by NSPs-AAP-1, through proteolytic cleavage of their prodipeptides within promyelocyte granules during neutrophil differentiation. Here, we investigated the relative contributions of cathepsin C- and NSPs-AAP-1-dependent pathways in NSP activation in human myelomonocytic cell lines U937, THP-1, and MonoMac-6. We targeted proteolytic mechanisms using chemical inhibitors and employed biochemical assays, Western blotting, confocal microscopy, and mass spectrometry-based proteomics to assess NSP activation and stability. Striking differences were observed among these cell lines. U937 cells contained high intracellular levels of active NSPs, whereas THP-1 and MonoMac-6 cells exhibited very low amounts, likely due to rapid proteolytic degradation. Post-translational regulation, including proteolytic degradation, acts as a major checkpoint controlling NSP availability and function in THP-1 and MonoMac-6 cells. In U937 cells, NSP activation mirrored that of neutrophils, involving both cathepsin C and NSPs-AAP-1 pathways. In THP-1 and MonoMac-6 cells, chemical stabilization revealed a cathepsin C- and NSPs-AAP-1–independent pathway that activates elastase and proteinase 3, whereas cathepsin G activation remained dependent on NSPs-AAP-1. These findings demonstrate that NSP stability and activation are strongly cell type–dependent, reflecting intrinsic differences in protease processing, maturation, and degradation. This study provides a framework for interpreting NSP function in myeloid cellular models and highlights cell type–specific regulatory mechanisms relevant to both physiological and pathological contexts.

16th April 2026

Marcus A. Mall

Neutrophil serine proteases in cystic fibrosis: role in disease pathogenesis and rationale as therapeutic target

notes

Neutrophil serine proteases in cystic fibrosis: role in disease pathogenesis and rationale as therapeutic target

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Abstract

Chronic neutrophilic airway inflammation is a key feature of cystic fibrosis (CF) and increased activity of neutrophil elastase (NE) secreted by activated neutrophils has been identified as a major risk factor of CF lung disease severity and progression acting via multiple mechanisms including protease/antiprotease imbalance, degradation of extracellular matrix, mucus hypersecretion, impaired pathogen clearance and impaired epithelial ion transport via CFTR and the epithelial sodium channel ENaC.

In addition to NE, emerging evidence supports that the two other neutrophil serine proteases (NSPs), i.e. cathepsin G and proteinase 3, are also elevated in the airways and contribute to the pathogenesis of CF lung disease. All three NSPs are produced as inactive precursors during neutrophil differentiation in the bone marrow and are activated by cathepsin C (CatC; also known as dipeptidyl peptidase 1, DPP-1), stored in azurophil granules and secreted upon neutrophil activation in the muco-inflammatory environment of CF airways. Besides increased "free" NSP activity in extracellular milieu of the airway lumen, "membrane-bound" NSP activity on the surface of airway neutrophils was also found to be increased and to contribute to lung damage and lung function impairment in mice with CF-like lung disease and patients with CF, even at early stages of disease when the antiprotease shield remains intact.

In recent years, the introduction of highly effective CFTR modulator therapy has led to unprecedented improvements in clinical outcomes of people with CF. Despite this breakthrough, emerging evidence from real-world observational studies suggests that neutrophilic inflammation and elevated NSP activity persists in people with CF treated with CFTR modulators at levels that are probably similar to people with non-CF bronchiectasis.

Collectively, these data highlight the ongoing need for new therapies targeting neutrophilic inflammation in CF lung disease and support pharmacological inhibition of all three NSPs by CatC (DPP-1) inhibitors as promising anti-inflammatory strategy, which is currently tested in the AIRTIVITY trial of verducatib (NCT06872892) in bronchiectasis including people with CF.

16th April 2026

T. Chazeirat

Quantification of neutrophil serine proteases in bronchiectasis

notes

Quantification of neutrophil serine proteases in bronchiectasis

T. Chazeirat

France

Abstract

16th April 2026

Celine H. Chen

Investigating pharmacological inhibition of cathepsin S on human macrophage function and its potential as a target for alpha-1 antitrypsin deficiency

notes

Investigating pharmacological inhibition of cathepsin S on human macrophage function and its potential as a target for alpha-1 antitrypsin deficiency

Celine H. Chen

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Abstract

Cathepsin S (CTSS) is an elastolytic proteinase associated with inflammation and tissue destruction. The role of CTSS in neutrophils is as an upstream regulator of neutrophil serine proteinases production via cathepsin C activation. However, its role in macrophages remains less well delineated, despite these cells containing an abundance of CTSS.

Alpha-1 antitrypsin (AAT) is a major proteinase inhibitor in blood and airways that protects against serine proteinase damage. This manifests in patients with alpha-1 antitrypsin deficiency (AATD), who have increased susceptibility to developing chronic obstructive pulmonary disease (COPD) and emphysema. However, it has been reported that CTSS activity and protein is increased in the lungs of COPD patients and CTSS knockout mice are protected against smoke-induced emphysema, suggesting CTSS may also play a role – especially as AAT can negate CTSS production in various immune cells, including macrophages.

Firstly, we established that human monocyte-derived macrophages (MDMs) from AATD patients had higher levels of intracellular CTSS, compared to MDMs from healthy age-matched subjects, without corresponding increase in extracellular CTSS. Consistent with the recognised defect in AATD macrophage efferocytosis, pharmacological inhibition of CTSS during monocyte-to-macrophage maturation improved clearance of apoptotic neutrophils.

We subsequently developed a human cellular differentiation model to investigate how CTSS shapes macrophage development and function under conditions relevant to the AATD lung, including under oxidative stress and inflammatory challenges and assessment of potential detrimental effects. Together, these data support a mechanistic link between CTSS activity during macrophage maturation and defective efferocytosis, suggesting that targeting CTSS may promote resolution of neutrophil-mediated inflammation, a pathway linked to emphysema progression in AATD.

16th April 2026

Önder A. Yildirim

Neutrophil serine proteases in bronchiolitis obliterans syndrome

notes

Neutrophil serine proteases in bronchiolitis obliterans syndrome

Önder A. Yildirim

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Abstract

Lung transplantation (LTx) is a life-saving therapy for end-stage lung disease, yet long-term outcomes remain limited by primary graft dysfunction (PGD) and the subsequent development of bronchiolitis obliterans syndrome (BOS). Early ischemia–reperfusion injury triggers innate immune activation, particularly neutrophil-driven inflammation. Neutrophil serine proteases (NSPs), released during degranulation and neutrophil extracellular trap (NET) formation, contribute to epithelial injury, tissue remodeling, and chronic graft dysfunction. Activation of NSPs is critically dependent on the lysosomal cysteine protease cathepsin C (CatC), positioning CatC as a central regulator of protease-mediated lung injury.

We investigated whether dysregulation of cysteine protease inhibition contributes to early lung graft injury and downstream pathways associated with BOS. Lung transplant recipients exhibited reduced levels of the endogenous cysteine protease inhibitor cystatin C (CysC), accompanied by increased expression of γ-H2AX and ACSL4, markers of DNA damage and ferroptosis, respectively, which correlated with poorer outcomes. Using an orthotopic LTx model, we engineered an albumin-fused, cell-permeable CysC derivative (CysC-Alb) to enhance lung preservation. Addition of CysC-Alb to preservation solutions during cold storage and ex vivo lung perfusion significantly improved oxygenation, reduced DNA damage, and limited ferroptotic cell death, particularly in alveolar type II epithelial cells. In murine grafts, CysC-Alb treatment decreased γ-H2AX and ACSL4 expression.

Beyond immune cells, CatC is expressed by structural cells and is upregulated during chronic inflammation, amplifying neutrophil recruitment, NSP activity, and NET formation. Pharmacologic CatC inhibition is clinically feasible, as genetic CatC deficiency causes minimal systemic toxicity, and CatC inhibitors are in advanced clinical trials for inflammatory lung disease. Together, these findings identify loss of cysteine protease control as a key driver of early lung graft injury and support CysC-based strategies to improve graft preservation and potentially limit progression toward BOS following LTx.

16th April 2026

Michael Wegmann

New therapeutic targets in neutrophil asthma

notes

New therapeutic targets in neutrophil asthma

Michael Wegmann

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Abstract

Asthma is one of the most common chronic diseases worldwide and is characterized by recurrent respiratory symptoms that comprise chest tightness, cough, shortness of breath, wheeze, and a variable degree of broncho-obstruction. This complex symptomology arises on the basis of chronicvairway inflammation, which is commonly associated with high numbers of eosinophils and high levels of T2 cytokines such as interleukin (IL) 4 and IL-13. However, approximately 20% of all patients with asthma display an increased proportion of neutrophils. Though the role of neutrophils in asthma is not fully understood yet, clinical observations suggest these cells as critical targets for therapeutic intervention: (I) In adult patients with asthma sputum neutrophilia is associated with more severe lung disease and the requirement for higher doses of controler medication. (II) Most acute asthma exacerbations are predominantly by nature. (III) Neutrophilic asthma is associated with a higher degree of refractoryness to the corticoid based standart therapy.

Since neutrophils also represent a critical part of the defense against infection targeting these cells remains problematic. Nevertheless, novel strategies for neutrophilic asthma and asthma exacerbation adress cytokines that are involved in superior levels of immuno-regulation and include neutralisation of proinflammatory cytokines or support of antiinflammatory mediators, but also mechanisms of neutrophil recruitment. Very recent studies also suggest cathepsin C to be critically involved in neutrophil associated deterioration of asthma, making it a new aim for therapeutic intervention.

16th April 2026

Rita Vanbever **A single-domain antibody better protects the lung tissue against neutrophil elastase-mediated damage than alpha1-antitrypsin**

notes

A single-domain antibody better protects the lung tissue against neutrophil elastase-mediated damage than alpha1-antitrypsin

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Abstract

Muco-obstructive lung diseases are characterized by chronic neutrophilic inflammation and an imbalance between proteolytic enzymes and their inhibitors, thereby causing lung damages and perpetuating inflammation. We measured protease concentrations and activities in sputa from patients with cystic fibrosis (CF), bronchiectasis and chronic obstructive pulmonary disease (COPD) and found that neutrophil elastase (NE) and proteinase 3 (PR3) were more abundant than cathepsin G and matrix metalloproteinases. In addition, the active form of NE was more abundant in sputa than the active form of PR3. NE and PR3 concentrations and activities largely increased during exacerbation episodes in COPD while they were low in stable COPD.

With the purpose to inhibit NE activity and prevent its deleterious effects, we recently identified and characterized a single domain antibody (variable domain of heavy-chain only antibody from camelids or Nanobody®), called NbE201, able to tightly, selectively and competitively inhibit human NE (Ki 4 nM) and murine NE (Ki 37 nM)[1].

NbE201 preserved its capacity to neutralize NE in sputa from patients with CF, bronchiectasis and COPD and its inhibition potency was superior to that of alpha1 antitrypsin (AAT), the main endogenous NE inhibitor. AAT rapidly oxidized and hydrolysed upon incubation in sputa, explaining its limited NE neutralization efficiency. NbE201 protected elastin from proteolysis in sputa and prevented sputum-induced damages in monolayers of bronchial epithelial cells as effectively as AAT even tough AAT primarily inhibits NE but also inhibits PR3 and cathepsin G, the other major neutrophil serine proteases. NbE201 better protected mice against cigarette smoke-induced neutrophil influx in the lungs than AAT. Therefore, NbE201 has the potential to significantly improve the treatment of muco-obstructive lung diseases by protecting the lungs against NE-mediated damage, especially during exacerbation episodes.

[1] Redeghieri, et al. Enzymatic, structural, and biophysical characterization of a single-domain antibody (VHH) selectively and tightly inhibiting neutrophil elastase and exhibiting favorable developability properties. Protein Sci 2024, 33, (12), e5227.

17th April 2026

James D. Chalmers

Neutrophil elastase activity following cathepsin C (CatC, or DPP1) inhibition with BI 1291583 in people with bronchiectasis

notes

Neutrophil elastase activity following cathepsin C (CatC, or DPP1) inhibition with BI 1291583 in people with bronchiectasis

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Abstract

Background:
Neutrophil elastase (NE) is activated by CatC, and increased airway NE activity is linked to poor outcomes in people with bronchiectasis (BE). We report the effects of the CatC inhibitor BI 1291583 on NE activity in people with BE in the AIRLEAF® study.

Methods:
AIRLEAF® enrolled 322 adults with BE, examining once-daily BI 1291583 administration (1/2.5/5 mg doses) vs placebo up to 48 weeks. Participants had a history of pulmonary exacerbations (PExs) requiring antibiotic treatment in the year prior to screening (≥2 PExs or 1 PEx with St. George's Respiratory Questionnaire (SGRQ) Symptoms score >40). Free sputum NE activity was measured at baseline and over time, using a fluorescent substrate-based enzymatic activity assay. Descriptive statistics for absolute NE activity over time were calculated; change from baseline in sputum NE activity and corresponding NE inhibition were estimated using a mixed model with repeated measures.

Results:
At baseline, mean sputum NE activity was similar across all treatment groups, with no differences in participants who had ≥2 PExs or 1 PEx with SGRQ Symptoms score >40. Higher baseline NE activity ($p<0.01$) was observed in those positive for P. aeruginosa and those from East Asia. At Weeks 12 and 24, placebo-corrected-mean-adjusted NE inhibition was 24.1% and 44.9%, 78.4% and 78.9%, and 80.2% and 90.8% in the BI 1291583 1 mg, 2.5 mg, and 5 mg groups, respectively.

Conclusions:
Dose-dependent NE inhibition was seen with BI 1291583. However, the 2.5 mg dose achieved the greatest clinical efficacy in AIRLEAF®[1]; several mechanisms may be responsible for this.

[1] Chalmers JD. et al. Eur Respir J 2025;65:2401551

Footnotes:
This topic was first presented at the 2025 ERS Congress.

17th April 2026

Vivien R Sutton

Pharmacological inhibition of DPP1 does not block target cell killing by human cytotoxic T lymphocytes and natural killer cells

notes

Pharmacological inhibition of DPP1 does not block target cell killing by human cytotoxic T lymphocytes and natural killer cells

Joseph A Trapani, Sally V Watt, Hedieh Akhlaghi, David C Cipolla*, Kuan-Ju Chen*, Daniel LaSala*, Patrick P McDonald*, Paul A Beavis, Isabelle Munoz, Adrian W Hodel, Tahereh Noori, Ilia Voskoboinik, **Vivien R Sutton**

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Abstract

Recently developed small-molecule inhibitors of the lysosomal protease dipeptidyl peptidase 1 (DPP1), can suppress suppurative inflammation *in vivo* by blocking the processing of zymogenic (pro-) forms of neutrophil serine proteases (NSPs) including neutrophil elastase, proteinase 3, and cathepsin G. DPP1 also plays an important role in activating granzyme serine proteases that are expressed by cytotoxic T lymphocytes (CTL) and natural killer (NK) cells and share extensive structural and catalytic features with NSPs. Therefore, it is critical to determine whether DPP1 inhibition can also cause off-target suppression of CTL/NK-cell-mediated killing of virus-infected or malignant cells. Using gene knock-out and pharmacological means, we found that the processing of human granzymes A and B from zymogens to active proteases is not solely dependent on DPP1. Thus, the killing of target cells by primary human $CD8^+$ T cells, NK cells, and gene-engineered anti-CD19 CAR T cells was not blocked *in vitro* after prior exposure to high concentrations of the DPP1 inhibitor brensocatib. Consistent with this observation, the turnover of model granzyme A/B peptide substrates in human CTL/NK cell lysates was not significantly reduced by brensocatib. In contrast, preincubation with brensocatib almost entirely abolished (>90%) both the cytotoxic activity of mouse $CD8^+$ T cells and granzyme substrate turnover. Overall, our finding that the effects of DPP1 inhibition on human cytotoxic lymphocytes are attenuated in comparison to those of mice indicates that granzyme processing/activation pathways differ substantially between mice and humans. Moreover, the *in vitro* data suggest that human subjects treated with reversible DPP1 inhibitors such as brensocatib are unlikely to experience any appreciable deficits in CTL/NK-cell-mediated immunity.

17th April 2026

Roxane Domain

Alternative cathepsin C–independent pathways for granzyme zymogen maturation in cytotoxic lymphocytes

notes

Alternative cathepsin C–independent pathways for granzyme zymogen maturation in cytotoxic lymphocytes

Roxane Domain[1,2], Brice Korkmaz[1,2].

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Abstract

Granzymes are serine proteinases expressed in cytotoxic lymphocytes and play a critical role in the elimination of virus-infected and cancerous cells. Like other immune cell-derived serine proteinases, granzymes are classically matured *in vitro* by cathepsin C (CatC). However, biochemical characterization of granzymes A and B in cytotoxic lymphocytes from patients with Papillon-Lefèvre syndrome (PLS), who are deficient in CatC, has revealed the existence of a CatC-independent processing and maturation pathway. Cytotoxic lymphocytes from PLS patients retained significant granzyme activity (~50–60%) and exhibited normal cytotoxicity toward cancer cells[1].

These findings indicate that CatC is not the sole protease responsible for pro-granzyme maturation in human lymphocytes. The presence of CatC-like protease(s) may therefore provide a molecular explanation for the absence of a generalized defect in cytotoxic T-cell function in PLS patients. Data on the proteolytic cascades involved in CatC maturation and granzyme zymogen activation will be presented.

1. Pham CT et al., Papillon-Lefèvre syndrome: correlating the molecular, cellular, and clinical consequences of cathepsin C/dipeptidyl peptidase I deficiency in humans. J Immunol. 2004 Dec 15;173(12):7277-81. doi: 10.4049/jimmunol.173.12.7277.

17th April 2026

Merete Long

Investigating the impact of DPP1/Cathepsin C or direct neutrophil elastase inhibition in humans using multiomics

notes

Investigating the impact of DPP1/Cathepsin C or direct neutrophil elastase inhibition in humans using multiomics

Merete Long

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Abstract

This presentation will discuss recently published work investigating the impact of DPP1/Cathepsin C inhibition in humans using a combination of neutrophil proteomics, peripheral blood transcriptomics and targeted measurement of biomarkers. We show the impact of DPP1 inhibition on the neutrophil proteome including demonstrating previous unreported DPP1 targets and downstream effects. Azurocidin-1 was identified as a novel DPP1 target markedly reduced at the protein level in neutrophils and peripheral blood (further characterisation of the importance of this finding will be discussed in Prof Shoemarks presentation). Defensin-A3 was found to be upregulated within neutrophils with potential impacts on host defence. This work illustrates the translational value of embedding detailed multiomic profiling including clinical trials, an approach which has broader applicability, including to recent trials of directly targeting neutrophil elastase with alpha-1 antitrypsin supplementation or antimicrobial targets in bronchiectasis.

17th April 2026

Merete Long

Cathepsin C inhibition: paving the way to better ibd care

notes

Cathepsin C inhibition: paving the way to better ibd care

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Abstract

Inflammatory bowel diseases (IBD) represent a growing global health concern with rising incidence and a complex, poorly understood etiology. Current therapeutic options are often limited by suboptimal efficacy and tolerability. In the absence of a definitive cure, both the economic and personal burden of IBD continues to increase. This underscores the urgent need for novel therapeutic strategies. Mounting evidence highlights the pivotal role of neutrophil serine proteases in driving IBD pathology, suggesting that modulation of the proteolytic balance could be essential for disease control. Cathepsin C functions as a central regulator for the activation of the majority of tissue-degrading neutrophil serine proteases. It has been implicated in promoting neutrophil recruitment as well as the release of chemokines and cytokines associated with IBD. Consequently, Cathepsin C emerges as a promising target to mitigate protease-mediated tissue damage. To explore this, we evaluated the effects of Cathepsin C inhibition in mouse models of colitis. Strikingly, mice lacking Cathepsin C displayed substantial protection against colitis development. These findings not only reinforce the critical role of proteolytic regulation in IBD but also highlight Cathepsin C inhibition as a potential therapeutic approach for managing the disease.

17th April 2026

Izabela Borek

Therapeutic targeting of cathepsin C in pulmonary arterial hypertension

notes

Therapeutic targeting of cathepsin C in pulmonary arterial hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a severe clinical condition characterized by pronounced pulmonary vascular remodeling and a persistent elevation of mean pulmonary arterial pressure. Immune cell–derived inflammatory serine proteases have been shown to play a central pathogenic role in the development of PAH. The primary objective of this study is to investigate the therapeutic potential of inhibiting cathepsin C (CatC also known as dipeptidyl peptidase 1/DPP1), an upstream activator of serine proteases, as a novel treatment strategy for PAH.

Our transcriptomic screening identified elevated levels of CatC in lung tissue from patients with PAH. Single-cell RNA sequencing revealed that, compared with healthy donor lungs, pulmonary arteries in PAH exhibit an altered immune cell composition characterized by an expansion of CatC-positive cells. Protein analyses further confirmed increased CatC expression in PAH lung samples and demonstrated the presence of proteolytically active CatC in pulmonary arterial smooth muscle cells (PASMCs). The increased autophagy and proliferation are characteristic features of PAH-associated PASMCs implicated in vascular remodeling. In our vitro experiments, treatment with active recombinant human CatC enhanced PASMC proliferation, whereas pharmacological inhibition of CatC suppressed both autophagy and proliferation. Importantly, therapeutic inhibition of CatC in both chronic hypoxia–induced pulmonary hypertension in mice and the monocrotaline rat PAH model significantly ameliorated disease severity, as evidenced by reduced right ventricular systolic pressure, attenuated right heart remodeling, and decreased pulmonary vascular remodeling.

Our findings demonstrate a critical role for CatC in PAH pathophysiology and identify it as a potential novel therapeutic target. Notably, our in vitro experiments using primary human PASMCs suggest that the beneficial effects of CatC inhibition extend beyond the suppression of inflammatory serine protease activation to include direct modulation of PASMC behavior.

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17th April 2026

Yoh Terada

Pharmacological targeting of cathepsin C in rat model of ANCA-associated vasculitis

notes

Pharmacological targeting of cathepsin C in rat model of ANCA-associated vasculitis

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Abstract

Neutrophils are essential for host defense but also drive tissue injury in inflammatory diseases, making direct neutrophil targeting a therapeutic "double-edged sword." Cathepsin C (CatC) regulates the maturation of neutrophil serine proteases (NSPs) that are central to neutrophil activation. Notably, CatC deficiency in humans is not typically associated with profound impairment of host defense, supporting CatC inhibition as a potentially safer strategy to attenuate pathogenic neutrophil effector functions.

Here, we report the discovery and preclinical characterization of MOD06051, a novel, potent, and highly selective CatC inhibitor. MOD06051 inhibited CatC activity in vitro and produced dose-dependent suppression of cellular CatC activity. In human CD34* hematopoietic stem cell–derived neutrophils, MOD06051 reduced NSP activities and decreased cell-surface expression of proteinase 3 (PR3), consistent with impaired NSP maturation. *In vivo*, oral administration of MOD06051 in rats suppressed neutrophil elastase (NE) activity and reduced neutrophil extracellular trap (NET) formation in *ex vivo* neutrophils isolated from treated animals.

Importantly, MOD06051 conferred robust therapeutic benefit in a rat model of myeloperoxidase (MPO)-anti-neutrophil cytosolic antibody (ANCA)–associated vasculitis (AAV). Treatment dose-dependently ameliorated vasculitis in lung and kidney and significantly decreased NET burden in affected tissues.

Collectively, these data demonstrate that selective CatC inhibition can attenuate neutrophil activation programs -including NET formation- while improving end-organ injury caused by vasculitis in MPO-AAV. CatC inhibition therefore represents a promising mechanism-based approach for neutrophil-driven inflammatory diseases.

notes

KJ CHEN

Abstract

17th April 2026

Baoer Liu

Effects of cathepsin C inhibition on extra-renal vascular function in a rat model of polycystic kidney disease

notes

Effects of Cathepsin C inhibition on extra-renal vascular function in a rat model of polycystic kidney disease

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Abstract

Background: Polycystic kidney disease (PKD) is a hereditary disorder of the kidneys. Patients with PKD are also at higher risk of cardiovascular complications. Inflammatory processes contribute to both PKD progression and endothelial dysfunction by excessive release of pro-inflammatory neutrophil serine proteases (NSPs). Cathepsin C is an enzyme that regulates the maturation of NSPs, which are essential for neutrophil activation. In the present study, we hypothesized that the cathepsin C inhibitor, BI9740 (BI) (OpnMe/Boehringer Ingelheim) improves vascular dysfunction in a rat model of PKD.

Methods: The PCK rat is a Sprague–Dawley (SD)–derived PKD model. Nine-month-old male PCK rats and age-matched SD controls received either BI (20 mg/kg body weight) or placebo once daily for 12 days. On day 13, thoracic aortae were harvested for ex vivo assessment of vascular function using an organ bath system. Serum samples were also collected.

Results: The PCK rats have significantly lower body weight compared with SD controls (581±21g vs. 743±12g, $p<0.05$). 12-day BI or placebo administration did not affect body weight in PCK rats (570±8g vs. 581±21g, $p>0.05$). BI treatment significantly reduced serum creatinine and urea levels compared with placebo-treated PCK rats (creatinine: 32±1 vs. 43±4 µmol/l; urea: 2981±198 vs. 3816±259 µmol/l; both $p<0.05$). Endothelium-dependent relaxation to acetylcholine was impaired in PCK rats at higher concentrations, reflected by reduced maximal response (R_{max}), compared with SD controls, and was improved by BI treatment (SD: 79±1%, PCK: 61±2%, PCK+BI: 70±2%, $p<0.05$). Maximum contractile responses to the alpha-1-adrenergic receptor phenylephrine were significantly lower in the PCK-BI group (SD: 92±2%, PCK: 90±2%, PCK+BI: 78±3%, $p<0.05$). Endothelium-independent relaxation to sodium nitroprusside did not differ in maximal response among groups. However, BI group treatment induced a leftward shift of the concentration–response curve compared with placebo-treated PCK rats. The vascular sensitivity to sodium nitroprusside, expressed as the pD_2 value (-log EC_{50}), was significantly increased in the PCK+BI group (SD: 8.9±0.2, PCK: 8.4±0.1, PCK+BI: 9.6±0.3, $p<0.05$).

Conclusion: Cathepsin C inhibition with BI9740 enhances vascular function in a nine-month-old rat model of autosomal recessive polycystic kidney disease.

17th April 2026

Amelia Schoemark

Investigating the impact of cathepsin C inhibition on azurocidin

notes

Investigating the impact of cathepsin C inhibition on azurocidin

Amelia Schoemark

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Abstract

Background: Cathepsin C activates neutrophil serine proteases contributing to airway inflammation and tissue injury in chronic lung diseases. Cat-C inhibitors reduce exacerbations in bronchiectasis, including in Phase 3 trials, but their downstream mechanisms remain incompletely defined. We investigated the mechanistic effects of Cat-C inhibition on the neutrophil pseudoenzyme azurocidin-1 (AZU1) and explored the role of AZU1 in the pathophysiology of bronchiectasis and COPD.

Methods: Biomarker analyses were performed in the placebo-controlled phase 2 WILLOW trial (NCT03218917) evaluating brensocatib 10 mg and 25 mg in bronchiectasis. Sputum was collected at baseline, weeks 4 and 24 of treatment and week 28 (4 weeks post-treatment) and proteomics performed by LCMS. Findings were supported by prior neutrophil proteomic analyses (STOP-COVID19, NCT04817332). Sputum AZU1 was quantified by ELISA. Associations between sputum AZU1 and disease severity and outcomes were examined in two observational bronchiectasis cohorts (EMBARC cohort 1 and 2), a COPD cohort, and an experimental rhinovirus challenge study. In vitro experiments assessed the effects of AZU1 on airway epithelial integrity and ciliary function.

Results: Neutrophil proteomics identified AZU1 as the most downregulated protein with the CatC inhibitor brensocatib versus placebo. In the WILLOW trial, sputum AZU1 was markedly reduced by both 10 mg and 25 mg brensocatib by week 4 ($p<0.001$), with sustained suppression to week 24. AZU1 was associated with bronchiectasis severity index, lung function and exacerbation frequency (all $p<0.001$), and with radiological severity, symptoms and bacterial infection. AZU1 levels were increased during bacterial and viral exacerbations, associated with COPD severity, and increased following experimental rhinovirus challenge. In vitro, AZU1 impaired epithelial integrity and ciliary function, indicating a mechanism by which AZU1 drives disease pathogenesis.

Conclusion: Cathepsin C inhibition significantly reduces airway AZU-1. AZU1 is a novel mechanistic mediator of airway injury and a biomarker of disease severity and exacerbation risk in bronchiectasis and COPD.

17th April 2026

Emma Johnson

Broad immunomodulatory effects of the DPP1 inhibitor brensocatib in patients with bronchiectasis: data from the phase 2 WILLOW study

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Broad immunomodulatory effects of the DPP1 inhibitor brensocatib in patients with bronchiectasis: data from the phase 2 WILLOW study

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Abstract

Brensocatib has recently become the first licensed therapy in the USA and Europe for the management of bronchiectasis having shown reductions in exacerbations and slowing in decline in lung function. Using data from two independent cohorts we investigated the downstream effects of DPP1 inhibition on the inflammatory response in patients with bronchiectasis. We show that patients receiving brensocatib have significantly reduced MUC5AC, a major proinflammatory mucin, and increased levels of the antimicrobial peptides SLPI and defensin A3. Interestingly, a number of cytokines are increased with DPP1 inhibition with many reported to be cleaved by neutrophil serine proteases. Investigating in a European multicentre cohort study confirmed that low levels of these cytokines are generally associated with more severe disease and increased neutrophilic inflammation. Taken together these data suggest that DPP1 inhibitors have broad immunomodulatory effects which may be beneficial in the context of bronchiectasis.

17th April 2026

Joanna Cichy

Targeting cathepsin C in neutrophil differentiation and function

notes

Targeting cathepsin C in neutrophil differentiation and function

Joanna Cichy

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Abstract

Neutrophil differentiation in the bone marrow is critical for supplying sufficient cells to effectively control bacterial and fungal infections. Persistently low neutrophil numbers are observed in patients with neutropenia. In addition to reduced neutrophil counts, our data indicate that circulating neutrophils in patients with neutropenia also exhibit alterations in phenotype and function, particularly with respect to their proteolytic phenotype and activity. Here, using an iPSC-based system and CRISPR–Cas-mediated gene editing, we review the impact of proteases—such as those regulated by cathepsin C—and their synthetic and endogenous inhibitors on neutrophil pathophysiology.

17th April 2026

Asli Kutlu

Dual targeting of cathepsin C and S in COPD: design and evaluation of novel cathepsin S inhibitors

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Dual targeting of cathepsin C and S in COPD: design and evaluation of novel cathepsin S inhibitors

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Abstract

Chronic obstructive pulmonary disease (COPD) is a major global health burden and the third leading cause of mortality worldwide. Current therapies relieve symptoms but do not halt disease progression. Dysregulated protease networks drive COPD pathogenesis, with cathepsin C (CatC) activating neutrophil serine proteases and cathepsin S (CatS) degrading extracellular matrix and generating neutrophil chemotactic elastokines. The CatC inhibitor brensocatib (brinsupri) was approved in the US in August 2025 and in the EU in November 2025, confirming the therapeutic potential of protease inhibition. This project proposes a dual-targeting strategy combining systemic CatC inhibition and local (inhaled) CatS inhibition to reduce neutrophil-mediated tissue damage and potentially modify COPD progression. By selectively inhibiting CatS in the lung, this approach aims to limit elastin degradation while avoiding systemic immunosuppression. The project will focus on the rational design of novel CatS inhibitors optimized for pulmonary delivery and high selectivity. Computational modeling and predictive pharmacokinetic analyses will guide compound selection and optimization. Integrating CatS inhibition with established CatC targeting is expected to disrupt the self-amplifying protease–inflammation loop characteristic of COPD. Overall, this strategy seeks to lay the groundwork for a disease-modifying therapeutic approach addressing a major unmet clinical need in COPD.

Dr. Kutlu, a laureate of the Prestij 2026 Program from the Embassy of France in Turkey, will present this collaborative work in a selected oral session, highlighting her expertise in medicinal chemistry, computational modeling, and compound screening.

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