Defences to pathogens such as SarCoV2 in mammals involves interactions between immune functions and metabolic pathways to eradicate infection while preventing hyperinflammation. Amino acid metabolic pathways represent with other antimicrobial agent potential targets for therapeutic strategies. iNOS-mediated production of NO from Arg is involved in the innate inflammatory response to pathogens and NO overproduction can induce hyperinflammation. The two Arg- and Trp-catabolising enzymes Arg1 and IDO1 reduce the hyperinflammation by an immunosuppressive effect via either Arg starvation (for Arg1) or via the immunomodulatory activity of the Trp-derived metabolites Kyn (for IDO1). In response to amino acid abundance mTOR activates the host protein translation and Coronaviruses use this machinery for their own protein synthesis and replication. In contrast GCN2, the sensor of amino acid starvation, activates pathways that restrict inflammation and viral replication. Glu depletion alters the immune response that become more suppressive, by favouring a regulatory T phenotype rather than a Th1 phenotype. Proliferating activated immune cells are highly dependent on Ser, activation and differentiation of T cells need enough Ser and dietary Ser restriction can inhibit their proliferation. Cys is strictly required for T-cell proliferation because they cannot convert Met to Cys. Restricting Met inhibits both viral RNA cap methylation and replication, and the proliferation of infected cells with an increased requirement for Met. Phe catabolism produces antimicrobial metabolites resulting in the inhibition of microbial growth and an immunosuppressive activity towards T lymphocytes.

INTRODUCTION
Host defences to pathogen invasion, including bacteria or virus such as SarCoV2, involves in mammals a combination of initial innate immune and protective responses to eradicate infection that proceeds by directly acting on the pathogens and with locally induced inflammation, subsequently balanced by different mechanisms of immunomodulation and disease tolerance to prevent secondary harmful hyperinflammation. These processes include for a part a series of complex interactions between immune functions and metabolic pathways resulting from a convergent evolution of the two systems [1, 2]. This is particularly illustrated by the strategy exploited by higher organisms in response to pathogens infection using amino acid metabolic and signalling pathways to both restrict pathogen invasion and modulate the time-course of the immune response. Mammals control the immune response and the intracellular availability of amino acids through different mechanisms including an increase in their local catabolism and the production of amino acid-derived metabolites with both antimicrobial cytotoxic and immunomodulatory activities. Interestingly, it has been shown that these mechanisms not only result in pathogen starvation and control of infection, but also participate in regulating the potentially harmful hyperinflammatory reactivity [3]. In this context, amino acid depletion or repletion, and/or targeting different amino acid metabolites and signalling pathways can represent, in association with other antimicrobial agents, potential therapeutic strategies against microbial pathogens (Table 1).

ARGININE AND ARGININE-CATABOLIZING ENZYMES INOS AND ARG1
Arginine (Arg) is a non-essential amino acid for healthy humans involved in the synthesis of proteins and in the urea cycle and acting as precursor for different molecules including glutamate (Glu), citrulline (Cit), and nitric oxide (NO), an important bioactive molecule with both cardiovascular, immunological, and neurological signalling functions, and antimicrobial cytotoxic activity [4]. In humans, Arg is supplied by the diet and by an endogenous synthesis that proceeds by two major steps, with an initial conversion in intestinal epithelial cells of dietary proline (Pro), Glu, and glutamine (Gln) to ornithine (Orn) and Cit, and the subsequent conversion of Cit to Arg both in the proximal tubules of the kidney, and in immune cells for the synthesis of NO as signalling molecule of the immune responses [5]. Arg is taken-up and transported into the cells by the solute carrier family 7 (SLC7), and the cationic amino acid transporters (CAT-1, CAT-2, and CAT-3). CAT-1 is constitutively expressed by most tissues, while CAT-2 is upregulated in murine dendritic
Arg catabolism involves in mammals four enzymes including nitric oxide synthase (NOS1, NOS2, NOS3), arginase (Arg1, Arg2), arginine decarboxylase (ADC), and arginine glycine amidino-transferase (AGAT) [8]. The three NOS isoforms produce NO and cit from Arg and are referred as neuronal (NOS1, or nNOS), inducible (NOS2, or iNOS), and endothelial (NOS3, or eNOS) enzymes [9]. NOS1 and NOS3 are constitutive enzymes, while NOS2 (iNOS) is induced by pro-inflammatory cytokines (including IFN-γ and IL-1β) and microbial-associated products (Lipopolysaccharide, LPS). Arginase hydrolyses Arg into urea and Orn and is a key enzyme involved in macrophages polarisation, such as Gln or serine, for their role into TCA cycle and one-carbon metabolism, respectively [3]. Arg is the substrate for iNOS-mediated production of NO involved in the initial innate inflammatory immune response to viral infections [19]. In this initial phase of the innate immune response, NO production of NO by iNOS and the extent of the hyperinflammation causally related to morbidity [20]. Severe cases of COVID-19 are also characterised by NO overproduction, lung hyperinflammation and local tissue damage [21]. Arg depletion using Arg-depleting enzymes represents a promising therapeutic antiviral approach in patients with SARSCoV-2 infection. Reduction of plasma Arg and NO-dependant hyperinflammation and viral replication: - Activation of GCN2 can limit hyperinflammation and reduce viral replication.

Ser Proliferating activated immune cells are dependent on Ser and activation and differentiation of T cells need enough Ser

Cys Cys availability is critical for T-cell functions because T cells lack the enzyme converting Met to Cys.

Met The proper methylation of RNA cap structure of SarCoV2 depends on the level of Met in the host to form SAM:
- Restriction of Met availability inhibit viral replication.

Phe Phe catabolism leads to Phe depletion and the production of H2O2 with antimicrobial toxic effects resulting in the inhibition of microbial growth and to an immunosuppressive activity towards T lymphocytes.

mTOR Coronavirus exploits the cellular machinery for their own protein synthesis and replication:
- Inhibition of mTOR can inhibit viral replication.

GCN2 GCN2 senses amino acid starvation and activates downstream pathways that restrict inflammation and viral replication:
- Activation of GCN2 can limit hyperinflammation and reduce viral replication.
In the second phase of the immune response to pathogen infection, Arg1-expressing macrophages dominate in response to Th2-type cytokines and provide Pro and polyamines that participate to modulate the hyperinflammation and to tissue repair [18]. However, viruses and hosts compete for polyamines that are involved in the repair of host tissues but are also critical for the virus genome packaging and viral enzymatic activity. Thus, any pharmacological antiviral strategy targeting Arg and polyamines production should favor the host while restricting the use of polyamines for virus replication [28].

TRYPTOPHAN AND THE TRYPTOPHAN-CATABOLIZING ENZYME IDO1

The essential amino acid tryptophan (Trp) is a precursor for the synthesis of proteins and for several molecules involved in the regulation of diverse biological processes, including the amino acid kynurenine (Kyn), NAD, serotonin and melatonin [29]. In mammals, the Kyn pathway is the major route for Trp catabolism while a lower amount is catabolized via the methoxyindole pathway. The conversion of Trp into Kyn involves the two enzymes, indoleamine-2,3-dioxygenase 1 (IDO1) and tryptophan-2,3-dioxygenase (TDO) (Fig. 2). IDO1 is a monomeric, haem-containing enzyme that catalyzes the initial, rate-limiting step in the degradation of Trp into L-Kyn [30, 31]. Alternatively, Trp can be converted by tryptophan hydroxylase-1 to 5-hydroxytryptophan, a precursor in the pathway for the synthesis of serotonin and melatonin [32].

The enzyme IDO1, mainly expressed by DCs, is involved in the control of acute inflammation by an immunoregulatory immunosuppressive effect linked to its catabolic activity that induce a rapid change of Trp and Kyn levels that causes Trp deprivation in the microenvironment and the generation of immunoreactive Kyn metabolites [33]. Kyn is an endogenous ligand for aryl hydrocarbon receptor (AhR) that affects the biology of immune cells and cancer cells [34]. The Kyn-derived metabolites such as quinolinic acid and 3-hydroxyanthranilic acid have different biological activities, acting as immunosuppressive factors and inhibiting T-cell proliferation [35, 36]. The cytokine γ-IFN activates intense short-term IDO1-competent DCs-mediated immunosuppressive activity on T lymphocytes, including inhibition of proliferation, apoptosis, and differentiation towards a regulatory phenotype Treg [37]. A main effect of a defective IDO1 catalytic activity is the low generation of Kyn-type ligands of the AhR and of Treg cells [37, 38]. A defective activity of IDO1 was previously shown in autoimmune and chronic inflammatory diseases [39, 40].

Identification of mechanisms that control the functions and fate of IDO1 opens new strategies for the pharmacologic control of IDO1 functioning and its immunoregulatory effect and modulating IDO1 catalytic activity is a promising therapeutic approach to modulate the immune response during the different steps of the immune response to pathogens infection. For some viral infections high IDO1 activity represents a main cause of immune unresponsiveness during the initial immune responses that aims to eradicate pathogens and downregulation of the short-term immunosuppressive regulatory effects of IDO1 should improve this short-term immune response. In contrast, during the second phase of the response, upregulating and increasing the activity of IDO1 could participate to prevent harmful hyperinflammation.

At the crossroad between Arg and Trp metabolism and their regulatory effects, the two enzymes Arg1 and IDO1 are involved in the secondary control of acute hyperinflammation associated to pathogens infection by an immunoregulatory immunosuppressive effect via either amino acid depletion (as for Arg1) or via the combined effects of immunoregulatory Kyn and signalling.
activity (as for IDO1) [3, 32]. However, these two pathways may have separate functions according to different environment conditions and could be complementary associated in therapeutic approaches. Interestingly, an IL4-dominated cellular environments promote Arg1 expression (mainly in macrophages/MDCs) [14], while a γ-IFN-dominated cellular environments promote IDO1 (DCs) expression [41]. The interaction between Arg and Trp metabolism in the immunoregulatory processes is also illustrated by the observation that spermidine activates molecular pathways related to the activation of IDO1 and confers to DCs a tolerogenic phenotype [42].

GLUTAMINE AND HOST DEFENCE
Rapidly proliferating cells, including several immune cells, require a supply of some amino acids such as Gln and upregulate metabolic pathways providing these amino acids, and these processes can be used as therapeutic targets against infection [43]. The amino acid Gln is a non-essential amino acid that can become conditionally essential during periods of physiological stress or under critical illness and injury [44]. Gln is essential for proliferating cells, including lymphocytes, thymocytes, and colonocytes, where it is actively used in several important metabolic processes. Gln is involved in the synthesis of protein, is the precursor for nucleotides and amino sugars, is degraded by glutaminase to Glu that is further metabolised to different products including γ-amino butyrate, glutathione, and folic acid, and is a main source of energy by providing intermediates components of the tricarboxylic acid cycle. Gln is the most abundant free amino acid in human muscles and plasma and is utilised at high rates by rapidly dividing cells, including leucocytes, to provide energy and for nucleotide biosynthesis. The expression of several genes in immune system cells is largely dependent on Gln availability.

The degradation of Gln leads to the formation of NH₃ and aspartate and to the synthesis of the nucleotides purines and pyrimidines involved in the synthesis of DNA and RNA. Gln acts as a nitrogen donor for rapidly dividing cells, such as lymphocytes, in which it is critical for nucleotide synthesis and energy production [45] and this critically impacts the efficiency of immune cell responses [46]. Glutaminases catalyse the hydrolytic deamidation of Gln to Glu that is further metabolised to different products including γ-amino butyrate, glutathione, and folic acid, and is a main source of energy by providing intermediates components of the tricarboxylic acid cycle. Gln is the most abundant free amino acid in human muscles and plasma and is utilised at high rates by rapidly dividing cells, including leucocytes, to provide energy and for nucleotide biosynthesis. The expression of several genes in immune system cells is largely dependent on Gln availability.

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responses by inhibiting T cell receptor-activated mTORC1 [52]. Ser can be de novo synthesised from glycine transamination by the serine hydroxymethyltransferase (SHMT1/2) or produced from 3-phosphoglycerate (3-PG), an intermediate of glycolysis [72]. Ser directly modulates adaptive immunity by controlling T cell proliferative capacity by supplying one-carbon units for de novo nucleotide biosynthesis in proliferating T cells [71] and for the generation of SAM to maintain a high SAM:S-adenosyl-homocysteine ratio to support the epigenetic methylation of histone and the production of some immune cytokines, including IL-1β. SAM appears essential for inflammatory macrophages and reducing SAM generation has an anti-inflammatory effect [73, 74]. Interestingly, Epstein–Barr virus infection induces a control of NADPH levels in infected cells by maintaining intracellular Ser level to augment one-carbon flux for B cell proliferation [75].

In the same way, the two sulphur-containing amino acids, the essential amino acid methionine (Met) and the semi-essential amino cysteine (Cys), are also involved in immunoregulation. Cys is strictly required for T-cell proliferation because T cells lack the enzyme converting Met to Cys and must import Cys via their transport system [76]. Cys availability is therefore critical for T-cell functions, with cells either providing (as is the case for antigen-presenting cells) or sequestering (in particular, MDSCs) this amino acid, resulting in stimulatory or suppressive effects, respectively. Cys dioxygenase (CDO) catabolises Cys to cysteine sulfenic acid, and further to hypotaurine or to taurine, or to pyruvate and sulfate. Thus, CDO not only removes Cys cytotoxic excess, but is also necessary to produce hypotaurine/taurine and sulfite/ sulfate from Cys [77]. The combination of copper, N-acetylcysteine, colchicine, and NO associated to currently used experimental antiviral agents, has been proposed as a potential treatment in SARS-CoV-2-infected patients [78]. Moreover, the coronavirus RNA cap structure is methylated by two viral methyltransferases that transfer methyl groups provided by S-adenosylmethionine (SAM). The proper methylation of the virus depends on the level of Met availability in the host to form SAM and it has been proposed to restrict Met availability by treating Covid-19 patients with oral recombinant metioninase [79]. Restricting Met not only inhibits viral replication, which depends on the viral RNA cap methylation, but also inhibits the proliferation of the infected cells, which have an increased requirement for Met. Most importantly, the virally induced T-cell- and macrophage-mediated cytokine storm, a significant cause of morbidity, can also be inhibited by Met depletion, since T-cell and macrophages activation requires a supply of Met. Moreover, the interleukin 4-inducible 1 enzyme, secreted or localised in lysosomes, catalyses the catabolism leading Phe depletion and to the production of the a-ketoacid phenylpyruvate, and H2O2 with antibacterial toxic effects potentiated by the associated production of NH3 and basification of the medium [76, 80]. These processes result in the inhibition of microbial bacterial growth and to an immunosuppressive activity towards T lymphocytes [81].

CONCLUSION
Amino acid metabolism and signalling processes participate to the control of pathogen infection and to the regulation of the inflammation induced by activation of innate, adaptive, and regulatory immune responses. The crosstalk between catabolism of amino acids and the immune system represents an important process for tuning immune reactivity and reducing hyperinflammation-associated immune responses to infections. Among amino acids, Arg availability and the catabolic enzyme iNOS are involved in the inflammatory innate response through the production of NO, while Arg and Trp availability, associated to the two catabolic enzymes Arg1 and IDO1, represent catabolic pathways involved in modulating immune reactivity and exerting regulatory effect on inflammation and on the adaptive immune responses. Moreover, the amino acids Gln, Ser, Cys, Met, and Phe are also being considered as amino acids involved in pathogen development and in the balance of the immune reactivity. Overall, excess amino acid and mTOR hyperactivation appear as an environment favouring virus invasion while amino acid starvation and GCN2 activation restrict viral invasion. These different mechanisms represent potential therapeutic targets to control infection and associated hyperinflammatory response causally related to morbidity and mortality induced by pathogens, including coronavirus.

REFERENCES
1. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542:177–85.
2. Ferrante AW Jr. Macrophages, fat, and the emergence of immunometabolism. J Clin Investig. 2013;123:4992–3.
3. Grohmann U, Mondanelli G, Belladonna ML, Orabona C, Pallotta MT, Iacono A, et al. Amino-acid sensing and degrading pathways in immune regulation. Cytokine Growth Factor Rev. 2017;35:37–45.
4. Wu G, Morris SM Jr. Arginine metabolism: nitric oxide and beyond. Biochemical J. 1998;336:–1–17.
5. Husson A, Brasse-Lag nel C, Fairand A, Renouf S, Lavo inne A. Argininosuccinate synthetase from the urea cycle to the citrulline-NO cycle. Eur J Biochem. 2003;270:1887–99.
6. Yeramian A, Martin L, Serrat N, Arpa C, Bertrand J, et al. Arginine transport via cationic amino acid transporter 2 plays a critical regulatory role in classical or alternative activation of macrophages. J Immunol. 2006;176:5918–24.
7. Chang J, Thangamani S, Kim MH, Ulrich B, Morris SM Jr., Kim CH. Retinoic acid promotes the development of Arg1-expressing dendritic cells for the regulation of T-cell differentiation. Eur J Immunol. 2013;43:967–78.
8. Gogoi M, Datey A, Wilson KT, Chakravorty D. Dual role of arginine metabolism in establishing pathogenesis. Curr Opin Microbiol. 2016;29:43–8.
9. Bogdan C. Nitric oxide and the immune response. Nat Immunol. 2001;2:907–16.
10. Dzik JM. Evolutionary roots of arginine expression and regulation. Front Immunol. 2014;5:544.
11. Munder M. Arginase: an emerging key player in the mammalian immune system. Br J Pharmacol. 2009;158:638–51.
12. Monticelli LA, Buck MD, Flamar-L-A, Saenz SA, Wojno ED, Yudanin NA, et al. Arginase 1 is an innate lymphoid-cell-intrinsic metabolic checkpoint controlling type 2 inflammation. Nat Immunol. 2016;17:656–65.
13. Gray MJ, Poljakovic M, Kepka-Lenhart D, Morris SM Jr. Induction of arginase I transcription by IL-4 requires a composite DNA response element for STAT6 and CREBPβ. Gene. 2005;353:98–106.
14. Bronte V, Zunovello P. Regulation of immune responses by L-arginine metabolism. Nat Rev Immunol. 2005;5:641–54.
15. Jacobsen LC, Theilgaard-Møch K, Christensen EJ, Borregaard N. Arginase 1 is expressed in myelocytes/metamyelocytes and localized in gelatinase granules of human neutrophils. Blood. 2007;109:3084–7.
16. Rotondo R, Bertolotto M, Barisione G, Astigiano S, Mandruzatto S, Ottoleno L, et al. Exocytosis of azurphil and arginase 1-containing granules by activated polymorphonuclear neutrophils is required to inhibit T lymphocyte proliferation. J Leukoc Biol. 2011;89:721–7.
17. Rouzaut A, Subirat ML, De Miguel C, Domingo-de-Miguel E, González A, Santiago E, et al. Co-expression of inducible nitric oxide synthase and arginases in human monocytic subsets. Apoptosis regulated by endogenous NO. Biochim et Biophys Acta. 1999;1451:319–33.
18. Kieler M, Hofmann M, Schab Bauer G. More than just protein building blocks: How amino acids and related metabolic pathways fuel macrophage polarization. FEBS J. 2021. https://doi.org/10.1111/febs.15715. Epub ahead of print. PMID: 33460504.
19. Ricciardolo FL, Di Stefano A, Sabatini F, Folkerts G. Reactive nitrogen species in inflammation induced by activation of innate, adaptive, and regulatory immune responses. Biophys Acta. 1999;1451:319–33.
20. Perrone LA, Belser JA, Wadford DA, Katz JM, Tumpey TM. Inducible nitric oxide synthetase from the urea cycle to the citrulline-NO cycle. Eur J Biochem. 2003;270:1887–99.
21. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8:420–2.
22. Izzo F, Montella M, Orlando AP, Nasti G, Bene duc e G, Castello G, et al. Pegylated arginine deiminase lowers hepatitis C viral titers and inhibits nitric oxide synthesis. J Gastroenterol Hepatol. 2007;22:86–91.
23. Grimes JM, Khan S, Badeaux M, Rao RM, Rowlinson SW, Carvalho RD. Arginine depletion as a therapeutic approach for patients with coronavirus COVID-19. Int J Infect Dis. 2021;102:566–70.

24. McBride R, Van Zyl M, Fielding B. The coronavirus nucleocapsid is a multifunctional protein. Viruses. 2014;6:2991–3018.

25. Saha P, Banerjee AK, Tripathi PP, Srivastava AK, Ray U. A virus that has gone viral: amino acid substitution in S protein of Indian isolate of Coronavirus COVID-19 might impact receptor binding, and thus, infectivity. Biosci Rep. 2020;40:BSR20201312.

26. Khan MI, Khan ZA, Baig MH, Ahmad I, Farouk A-E, Song YG, et al. Comparative genome analysis of novel coronavirus (SARS-CoV-2) from different geographical locations and the effect of mutations on major target proteins: an in silico insight. PLoS One. 2020;15:e0238344.

27. Hofmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol Cell. 2020;27:7879–84. e5.

28. Firpo MR, Mounce BC. Diverse functions of polyamines in virus infection. Bio- molecules. 2020;10:628.

29. Oxenkrug GF. Genetic and hormonal regulation of tryptophan–kynurenine metabolism: implications for vascular cognitive impairment, major depressive disorder, and aging. Ann N. Y Acad Sci. 2007;1122:35–49.

30. Schwarz R. The kynurenine pathway of tryptophan degradation as a drug target. Curr Opin Pharmacol. 2004;4:12–7.

31. Fallarino F, Grohmann U, Puccetti P. Indoleamine 2, 3-dioxygenase: from catalyst to signaling function. Eur J Immunol. 2012;42:1932–7.

32. Grohmann U, Bronte V. Control of immune response by amino acid metabolism. Immunol Rev. 2010;236:243–64.

33. Fiore A, Murray PJ. Tryptophan and indole metabolism in immune regulation. Curr Immunol Rev. 2021;70:7–14.

34. Opitz CA, Litzenburger UM, Sahn F, Ott M, Tritschler I, Trump S, et al. An endogenous promoter-tumorigenic ligand of the human aryl hydrocarbon receptor. Nature. 2011;478:197–203.

35. Frumento G, Rotondo R, Tonetti M, Damante G, Benatti U, Femras GS. Tryptophan-derived catalytics are responsible for inhibition of T and natural killer cell proliferation induced by indoleamide 2, 3-dioxygenase. J Exp Med. 2002;196:459–68.

36. Fallarino F, Grohmann U, Hwang KW, Orabona C, Vacca C, Bianchi R, et al. Modulation of tryptophan catabolism by regulatory T cells. Nat Immunol. 2003;4:1206–12.

37. Grohmann U, Puccetti P. The coevolution of IDO1 and AhR in the emergence of immune response. Trends Immunol. 2003;24:242–8.

38. Hoffmann M, Kleine-Weber H, Albert R, Emili E, Shi Y-B, Taylor PM, Cantrell DA. Control of amino-acid transport by antigen receptors coordinates the metabolic reprogramming essential for T cell differentiation. Nat Immunol. 2013;14:4500–8.

39. Chang W-K, Yang KD, Shaio M-F. Effect of glutamine on TH1 and TH2 cytokine responses of human peripheral blood mononuclear cells. Clin Immunol. 1999;93:294–301.

40. Höög H, Spagnoli GC, Filgueira L, Babst R, Gallati H, Harder F, et al. Exogenous glutamine requirement is confined to late events of T cell activation. J Cell Biochem. 1993;53:433–51.

41. Kudsk KA. Effect of route and type of nutrition on intestine-derived inflammatory responses. Am J Surg. 2003;185:16–21.

42. Wu G, Yang F-Z, Yang S, Lupton JR, Turner ND. Recent Advances in Nutritional Sciences-Glutathione Metabolism and Its Implications for Health. J Nutr. 2004;134:489–92.

43. Uyangaa E, Lee H-K, Eo SK. Glutamine and leucine provide enhanced protective immunity against mucosal infection with herpes simplex virus type 1. Immune Netw. 2012;12:196.

44. Bringhurst RM, Dominguez AA, Schaffer PA. Glutamine deprivation causes enhanced plating efficiency of a herpes simplex virus type 1 ICPO-null mutant. J Virol. 2008;82:11472–5.
79. Hoffman RM, Han Q. Oral methioninase for Covid-19 methionine-restriction therapy. Vivo. 2020;34:1593–6.
80. Boulland M-L, Marquet J, Molinier-Frenkel V, Möller P, Guiter C, Lasoudris F, et al. Human IL4I1 is a secreted L-phenylalanine oxidase expressed by mature dendritic cells that inhibits T-lymphocyte proliferation. Blood. 2007;110:220–7.
81. Puiffe M-L, Lachaise I, Molinier-Frenkel V, Castellano F. Antibacterial properties of the mammalian L-amino acid oxidase IL4I1. PloS One. 2013;8:e54589.

COMPETING INTERESTS
The author declares no competing interests.

ADDITIONAL INFORMATION
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