Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
The physiological role of Ang1–7 has been controversial and linked with upregulation of ACE2 [5], and cardiac myocyte levels in failing human heart ventricles has been correlated with disruption of gap junctions and the destruction of the vasodilator bradykinin [1,2]. It is perhaps surprising, therefore, that the discovery of its homologue, ACE2, did not take place until almost half a century later. It took the application of two independent genomics-based approaches to reveal the presence of ACE2 in the human genome [3,4]. The high incidence of sudden death in knockout mice supports this hypothesis [8]. Ace2 knockout mice show major cardiac contractility defects and increased levels of Ang II [8] and, overall, studies in these mice suggest that ACE2 is a key regulator of cardiac function, although the mechanism by which this is mediated is unclear. However, double knockouts, in which both Ace and Ace2 genes have been deleted, do not show the cardiac defects of the Ace2 knockout alone [8], emphasizing the Yin–Yang nature of ACE and ACE2 expression. When Ace2 is transgenically overexpressed in mouse heart, cardiac defects are again observed, most notably a lethal ventricular arrhythmia, which is associated with disruption of gap junction formation [9]. The high incidence of sudden death in these mice correlated with the levels of Ace2 transgene expression. Surviving older mice showed a spontaneous downregulation of the transgene and restoration of normal gene expression. In vivo downregulation of the transgene and restoration of normal

ACE2 is transgenically overexpressed in mouse heart, cardiac defects are again observed, most notably a lethal ventricular arrhythmia, which is associated with disruption of gap junction formation [9]. The high incidence of sudden death in these mice correlated with the levels of Ace2 transgene expression. Surviving older mice showed a spontaneous downregulation of the transgene and restoration of normal gene expression. In vivo downregulation of the transgene and restoration of normal ACE2 activity. Despite its close similarity to ACE and conservation of many of the key active site features, ACE2 displayed a distinct preference for substrates, operating exclusively as a carboxypeptidase, removing single amino acids, unlike ACE, which removes dipeptides from the C-terminus of a peptide [3,4]. Hence, ACE2 could not convert angiotensin I (Ang I) to Ang II and was unable to inactivate bradykinin. Furthermore, ACE2 was not susceptible to inhibition by any ACEIs tested. What has been revealed about the pharmacology of ACE2 in the subsequent three years?

ACE2 and vasopeptide metabolism

A key role for ACE2 is emerging in the conversion of the octapeptide Ang II to its metabolite angiotensin(1–7) (Ang1–7). For example, a compensatory increase in Ang1–7 levels in failing human heart ventricles has been correlated with upregulation of ACE2 [5], and cardiac myocyte Ang1–7 levels are increased in ischaemic cardiomyopathy [6]. The physiological role of Ang1–7 has been controversial but it generally appears to oppose the pressor, proliferative and pro-fibrotic actions of Ang II [7], and acts through its own G-protein-coupled receptor. This would suggest that ACE and ACE2 might act as counterbalances in the renin–angiotensin system (RAS) (Figure 1). The successful production of Ace2 null (Ace2−/−) mice supports this hypothesis [8]. Ace2 knockout mice show major cardiac contractility defects and increased levels of Ang II [8] and, overall, studies in these mice suggest that ACE2 is a key regulator of cardiac function, although the mechanism by which this is mediated is unclear. However, double knockouts, in which both Ace and Ace2 genes have been deleted, do not show the cardiac defects of the Ace2 knockout alone [8], emphasizing the Yin–Yang nature of ACE and ACE2 expression. When Ace2 is transgenically overexpressed in mouse heart, cardiac defects are again observed, most notably a lethal ventricular arrhythmia, which is associated with disruption of gap junction formation [9]. The high incidence of sudden death in these mice correlated with the levels of Ace2 transgene expression. Surviving older mice showed a spontaneous downregulation of the transgene and restoration of normal gene expression. In vivo downregulation of the transgene and restoration of normal gene expression. In vivo downregulation of the transgene and restoration of normal...
cardiac function. There are also indirect associations of Ace2 expression with hypertension. In particular, Crackower et al. [8] noted that, in the rat, the Ace2 gene maps to a defined quantitative trait locus associated with hypertension and, additionally, two single nucleotide polymorphisms in the Ace2 gene locus have been associated with human cardiovascular disease [10]. Another disease model in which ACE2 expression has recently been studied is diabetes. In streptozotocin-induced diabetes in the rat, expression of renal tubule ACE2 mRNA and protein was substantially reduced whereas an increase in ACE2 protein expression was seen in the diabetic glomeruli [11]. The significance of these changes, and the underlying mechanisms involved, remain to be elucidated. Clearly, searches for possible correlations of ACE2 mRNA and protein over- or under-expression with human cardiovascular and renal disease are warranted to determine whether these correlations mirror the effects observed in rodent models. Several potent and relatively selective inhibitors of ACE2 have been described [12,13], and the modelling of the active site of ACE2 [14], based on the recently reported structure of human ACE [15], will facilitate the development of new classes of specific inhibitors. The active site model also provides an explanation for the differences in substrate specificity and inhibitor sensitivity between ACE and ACE2 [14].

ACE2 as a gateway to SARS
During several months of 2003, the virus that caused the newly identified illness severe acute respiratory syndrome (SARS) spread rapidly from China throughout Asia to Canada and beyond, causing almost 800 deaths and disrupting travel, economics and even scientific conventions. The death rate following infection approached almost 10%. Almost as mysteriously as it appeared, perhaps as a result of public health measures, the disease faded away only to re-emerge in China this year. The speed with which the infection spread and the severity of the symptoms led to a massive effort to identify the agent responsible. Within months it had been identified as a positive strand RNA virus, classified as a member of the coronavirus family (SARS-CoV); its genome was positive strand RNA virus, classified as a member of the coronavirus family (SARS-CoV); its genome was sequenced [16,17] and the search was underway to identify the cellular receptor for the virus. As with other coronaviruses, it is the N-terminal portion (S1 domain) of the viral spike (S) glycoprotein that mediates the initial high-affinity binding to a receptor on the surface of susceptible cells. The spike sits in the viral envelope and projects outwards to give a ‘corona’-like appearance to the virus, hence its name. The replication strategy of the virus is summarized in Figure 2, and Figure 3 depicts the coronavirus-infected cell.

Michael Farzan and colleagues [18] demonstrated that the S1 domain of the SARS-CoV S protein bound to the African Green monkey kidney cell line Vero E6, which is permissive for viral replication. They were then able to co-immunoprecipitate the protein responsible for viral binding and entry. This SARS-CoV receptor, a glycoprotein of M, 110 000, was identified by mass spectrometry as ACE2. Its identity was confirmed by showing that, when ACE2 was overexpressed in human cells non-permissive for viral infection, SARS-CoV entry and replication were facilitated; this process was blocked by an ACE2 antibody [18]. The tissue distribution of ACE2 also appears to show some correlation with the sites of SARS-CoV infection and disease pathology. Independently, Xiao et al. [19] confirmed that ACE2 was a SARS-CoV receptor and showed that the receptor-binding domain was probably located between residues 272 and 537 of the spike glycoprotein. Farzan’s group [20] has now established the recognition region within a 193 amino acid sequence (residues 318–510) and smaller fragments were unable to bind ACE2. A crucial aspartic acid in this region was essential for binding with ACE2. Modelling of the ACE2 structure based on the known structure of ACE has provided another approach to predicting potential binding contacts between ACE2 and the SARS-CoV S protein [21] but ultimately experimental studies are essential to identify the nature of the interactions between these two proteins. The recent solution of the structure of ACE2 [22], which supports much of the earlier modelling of the active site of the enzyme [14], should facilitate studies of ACE2 and S protein interactions. Two unexpected features of ACE2 inhibitor binding arise from the structural studies [22]. First, inhibitor binding induced a large conformational change in the enzyme that
expressed on certain cell types: for example, APN are heavily glycosylated. They are also abundantly catalytic domain, faces the extracellular space, and they ectoenzymes in which the bulk of the protein, including the membrane peptidases as viral receptors. They exist as Several features probably facilitate the usurping of plasma homology and show a different membrane topology. region, APN and ACE2 bear no discernible sequence sites of infection. However, apart from the zinc-binding with this receptor, its distribution can be correlated with immunoreactivity in the kidney has been shown to double ACE2 are also appearing. Recently, for example, ACE2 similarity to ACE. Other physiological correlations for cardiovascular origin as originally predicted from its close prominence in several disease states and not just those of ACE2 to produce Ang1–7 from Ang II. Future ability of ACE2 to produce Ang1–7 from Ang II. Future analysis of the physiological roles of ACE2 needs to bear in mind that it can metabolize a range of biologically active peptides other than angiotensin-related peptides [14,25]. For example, it can hydrolyse (des-Arg9)-bradykinin, which is the endogenous ligand of the bradykinin B1 receptor. In this context, the availability of potent and selective inhibitors of ACE2 [12,13] will provide valuable pharmacological tools for exploring the physiology and pathology of the enzyme. The therapeutic potential of ACE2 inhibitors in cardiovascular-related diseases, however, is questionable given the apparent cardioprotective nature of ACE2 activity; much further study is needed in this area. Indeed, mechanisms for selectively increasing cardiac or renal ACE2 levels might be desirable in some conditions; this will require an understanding of the factors that regulate its tissue-specific expression.

The biggest surprise, however, was the identification of ACE2 as a viral receptor [18] and, although current data are consistent with ACE2 as a SARS-CoV receptor, there might be other receptors or co-receptors for this virus that are yet to be discovered. Effective therapies against SARS are urgently required should further major outbreaks occur. From studies on other coronaviruses, a vaccination approach might be viable, although not without limitations [26]. Hence, soluble ACE2 fragments or ACE2 antibodies might provide alternative anti-viral therapeutic approaches, although the possible side-effects of blocking ACE2 are unknown. Indeed, infection by SARS-CoV might affect ACE2 function adversely, which could in turn contribute to some of the pathology of the disease. Given the ability of viruses to usurp cell-surface peptidases and the prevalence of ACE in respiratory and other tissues, ACE itself might have a role as a receptor for an as yet unidentified virus.

Future perspectives
In a relatively short space of time, ACE2 has gained prominence in several disease states and not just those of cardiovascular origin as originally predicted from its close similarity to ACE. Other physiological correlations for ACE2 are also appearing. Recently, for example, ACE2 immunoreactivity in the kidney has been shown to double during pregnancy in rats, leading to the suggestion that ACE2 might contribute to the localized overproduction of Ang1–7 in the kidney observed in pregnancy, which might protect against rises in blood pressure [24]. It is therefore conceivable that deficient expression of ACE2 might underlie pathological conditions of pregnancy such as pre-eclampsia.

Perhaps too much attention to date has focused on the ability of ACE2 to produce Ang1–7 from Ang II. Future analysis of the physiological roles of ACE2 needs to bear in mind that it can metabolize a range of biologically active

### References
1. Turner, A.J. and Hooper, N.M. (2002) The angiotensin-converting enzyme gene family: genomics and pharmacology. *Trends Pharmacol. Sci.* 23, 177–183
2. Acharya, K.R. *et al.* (2003) ACE revisited: a new target for structure-based drug design. *Nat. Rev. Drug Discov.* 2, 891–902
3. Tipnis, S.R. *et al.* (2000) A human homolog of angiotensin-converting enzyme.
S-Adenosylhomocysteine hydrolase as a target for intracellular adenosine action

Doris Kloor and Hartmut Osswald

Department of Pharmacology and Toxicology, Faculty of Medicine, University of Tübingen, Wilhelmstrasse 56, D-72074 Tübingen, Germany

S-Adenosylhomocysteine hydrolase (AdoHcyase) controls intracellular levels of S-adenosylhomocysteine (AdoHcy). AdoHcy is a potent product inhibitor of some S-adenosylmethionine-dependent methyltransferases. Pharmacological modulation of AdoHcyase to indirectly inhibit methyltransferases can be guided by the fact that adenosine binds with high affinity to AdoHcyase and inhibits enzyme activity. cAMP can compete with adenosine and can counteract the adenosine-induced inhibition of AdoHcyase. Thus, the ratio between adenosine and cAMP, which can vary under different physiological conditions, might result in changes in, for example, DNA promoter methylation and therefore transcription.

S-Adenosylhomocysteine hydrolase (AdoHcyase; EC 3.3.1.1) is a cytoplasmic enzyme that catalyzes the reversible hydrolysis of S-adenosylhomocysteine (AdoHcy) to adenosine and homocysteine [1]. The thermodynamic equilibrium of the reaction in vitro favors the synthesis of AdoHcy [2]. However, hydrolysis of AdoHcy to adenosine and homocysteine prevails under physiological in vivo conditions because both reaction products are removed rapidly. Adenosine can be deaminated by adenosine deaminase or enters the purine nucleotide pool by the action of adenosine kinase. Homocysteine can enter the trans-sulfuration pathway and be metabolized to cystathionine or can be re-methylated to methionine (Figure 1).

S-Adenosylhomocysteine hydrolase (AdoHcyase) as a target for intracellular adenosine action

Doris Kloor and Hartmut Osswald

Department of Pharmacology and Toxicology, Faculty of Medicine, University of Tübingen, Wilhelmstrasse 56, D-72074 Tübingen, Germany

S-Adenosylhomocysteine hydrolase (AdoHcyase) controls intracellular levels of S-adenosylhomocysteine (AdoHcy). AdoHcy is a potent product inhibitor of some S-adenosylmethionine-dependent methyltransferases. Pharmacological modulation of AdoHcyase to indirectly inhibit methyltransferases can be guided by the fact that adenosine binds with high affinity to AdoHcyase and inhibits enzyme activity. cAMP can compete with adenosine and can counteract the adenosine-induced inhibition of AdoHcyase. Thus, the ratio between adenosine and cAMP, which can vary under different physiological conditions, might result in changes in, for example, DNA promoter methylation and therefore transcription.

S-Adenosylhomocysteine hydrolase (AdoHcyase; EC 3.3.1.1) is a cytoplasmic enzyme that catalyzes the reversible hydrolysis of S-adenosylhomocysteine (AdoHcy) to adenosine and homocysteine [1]. The thermodynamic equilibrium of the reaction in vitro favors the synthesis of AdoHcy [2]. However, hydrolysis of AdoHcy to adenosine and homocysteine prevails under physiological in vivo conditions because both reaction products are removed rapidly. Adenosine can be deaminated by adenosine deaminase or enters the purine nucleotide pool by the action of adenosine kinase. Homocysteine can enter the trans-sulfuration pathway and be metabolized to cystathionine or can be re-methylated to methionine (Figure 1).

S-Adenosylhomocysteine hydrolase (AdoHcyase; EC 3.3.1.1) is a cytoplasmic enzyme that catalyzes the reversible hydrolysis of S-adenosylhomocysteine (AdoHcy) to adenosine and homocysteine [1]. The thermodynamic equilibrium of the reaction in vitro favors the synthesis of AdoHcy [2]. However, hydrolysis of AdoHcy to adenosine and homocysteine prevails under physiological in vivo conditions because both reaction products are removed rapidly. Adenosine can be deaminated by adenosine deaminase or enters the purine nucleotide pool by the action of adenosine kinase. Homocysteine can enter the trans-sulfuration pathway and be metabolized to cystathionine or can be re-methylated to methionine (Figure 1).

S-Adenosylhomocysteine hydrolase (AdoHcyase; EC 3.3.1.1) is a cytoplasmic enzyme that catalyzes the reversible hydrolysis of S-adenosylhomocysteine (AdoHcy) to adenosine and homocysteine [1]. The thermodynamic equilibrium of the reaction in vitro favors the synthesis of AdoHcy [2]. However, hydrolysis of AdoHcy to adenosine and homocysteine prevails under physiological in vivo conditions because both reaction products are removed rapidly. Adenosine can be deaminated by adenosine deaminase or enters the purine nucleotide pool by the action of adenosine kinase. Homocysteine can enter the trans-sulfuration pathway and be metabolized to cystathionine or can be re-methylated to methionine (Figure 1).