

## Recommendations of RAAS Blockers Use Amidst the Coronavirus Pandemic

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### Abstract

Currently, there are gaps in the knowledge regarding the safety of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for COVID-19 patients due to concern of ACE2, which is critical for viral entry and their levels are upregulated when using these renin-angiotensin-aldosterone system blockers. ACE2, a glycoprotein metalloprotease that is ubiquitously found in human organs, played an essential role in physiologic and pathological states. Despite sharing homology, ACE2 is different from ACE, and while the latter cleaves angiotensin I to angiotensin 2, the former cleaves angiotensin 2 to angiotensin 1-7. Extrapolated from experimental animal studies, ACE2 and angiotensin 1-7 are important and protective for the lung physiology based on mice model of acute lung injury by various causes. Other evidence also demonstrates harm over benefits when ceasing RAAS blockers, particularly in patients with pre-existed cardiovascular disease, in which these drugs are proven to be life-saving. In paucity of evidence derived from well-designed study, majority of societies have recommended to continue RAAS blockers until new evidence says otherwise.

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**Keyword:** SARS-Cov-2, COVID-19, ACEi, ARB, ACE2

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## Introduction

On 31st December 2019, the health authorities in China notified the World Health Organization (WHO) of an outbreak of pneumonia of unknown causes in Wuhan, Hubei Provinces, China.<sup>1</sup> A new type of coronavirus is responsible for this viral respiratory

disease initially called as a novel coronavirus (nCoV) but now identified as severe acute respiratory syndrome coronavirus – 2 (SARS-CoV2).<sup>2</sup> This virus is responsible for SARS-like disease called coronavirus disease 2019 (COVID-19). Since then, WHO has declared it a public health emergency of international concern and raised its status as a pandemic.<sup>3</sup> As of 13th April 2020, SARS-CoV2 has spread to more than 210 countries/areas/

territories with total global cases of nearly 1.7 million cases, and the overall mortality has surpassed 100.000 deaths.<sup>4,5</sup>

Currently, there are gaps in the knowledge regarding the safety of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for COVID-19 patients that are medically indicated. Controversies whether to continue or discontinue ACEi/ARBs usage exist because the main pathway of viral entry into pneumocyte, mainly the type 2, is via ACE2, which their levels are upregulated when using these RAAS blockers.<sup>6,7</sup>

Furthermore, both drugs are widely used for various indications, particularly in cardiovascular diseases.<sup>8,9</sup> Therefore, guidance on the use of these drugs in COVID-19 patients is sorely needed. In this review, we explain the interaction of SARS-CoV2 and ACE, the benefit of continuing vs. harm of discontinuing of RAAS blockers, and we presented summaries of recommendations from various societies and colleges around the world regarding the use of ACEi/ARB in COVID-19 patients.

### **SARS-CoV2 and Angiotensin Converting Enzyme (ACE)**

Coronaviruses are positive-stranded RNA viruses with a crown-like appearance under an electron microscope. Among the structural elements, there are spike glycoproteins composed of two subunits (S1 and S2).<sup>10</sup> Cell entry of SARS-CoV-2 requires the binding of S1 glycoprotein to ACE2 and the serine protease TMPRSS2 for S protein priming.<sup>11</sup> ACE 2 is expressed in many organs, including intestine, endothelium, heart, kidney, and lung as well, specifically in type 2 pneumocytes and macrophages.<sup>12,13</sup> ACE2 shares considerable homology to ACE, but unlike ACE, it does not convert angiotensin I (Ang I) to angiotensin II (Ang II). ACE2 degrades angiotensin I to angiotensin-(1-9) and angiotensin II to angiotensin-(1-7).<sup>12,14</sup>

The renin-angiotensin-aldosterone system (RAAS) is a critical regulator of blood volume and systemic vascular resistance. RAAS is responsible for more chronic alterations while baroreceptor reflex responds in the short-term to decreased arterial pressure.<sup>15</sup> The modern concept of the RAS includes renin, angiotensin-converting enzyme [ACE], angiotensin I, angiotensin II, and angiotensin type 1 and type 2 receptors, novel

enzymes, peptides, and receptors (ACE2,<sup>3,4</sup> Ang-(1-7), pro-renin receptor, and Mas).<sup>16</sup>

ACE2 degrades angiotensin I to angiotensin-(1-9) and angiotensin II to angiotensin-(1-7). Actions of angiotensin-(1-7) are not restricted to the cardiovascular system as it also affects other systems such as renal hemodynamic, inflammation, and fibrosis.<sup>16</sup> While renin, angiotensin II, and aldosterone renin, angiotensin II, and aldosterone act to elevate arterial pressure in response to decreased renal blood pressure, reduced salt delivery to the distal convoluted tubule, and/or beta-agonism, ACE2 counterbalances the function of ACE and negatively regulates angiotensin II production.<sup>13,15</sup> ACE2 deficiency causes augmentation in vascular inflammation, and inflammatory responses detrimental in cardiovascular diseases, and kidney disease, as well as enhances pulmonary, cardiac, and renal injuries. Expression of ACE2 preserves cardiac function, ventricular wall motion, and contractility, and protects from remodelling.<sup>17</sup>

ACE 2 is a glycoprotein metalloprotease that exists mostly as membrane-bound and with low blood solubility.<sup>18</sup> The soluble level of ACE2 is often increased in pathological states due to membrane bound ACE2 shedding. In mice model injected with SARS-CoV, it was found that due to ACE2 being a critical negative regulatory factor for severity of lung edema and acute lung failure, SARS-CoV spike protein-mediated ACE2 downregulation contributes to the severity of lung pathologies.<sup>19</sup> It was found that ACE2 is a crucial receptor for SARS-CoV-2 and increased angiotensin I and II levels are thought to upregulate ACE2 activity, which then attenuates lung failure.<sup>19</sup>

In 2006, a study regarding ACE2 as SARS-CoV entry suggested that inhibition of ACE2 might be capable of blocking SARS-CoV infection.<sup>18</sup> Tseng et. al, in 2007 found that in transgenic mice expressing human ACE2, a functional receptor to the virus, there were high susceptibility towards SARS-CoV infection.<sup>20</sup>

Recently, it is known that COVID-19 has three phases of the disease. As stated earlier<sup>7</sup>, phase one (infection), constitutes SARS-CoV-2 binding to ACE2 to infect cells, which then initiates localized inflammation, endothelial activation, tissue damage, and disordered cytokine release.<sup>21</sup> Furthermore, the fusion of membrane interrupts angiotensin II metabolism, causing an increase in angiotensin II and a decrease in angiotensin-(1-7),

augmenting inflammation, endothelial activation, and leukocyte and platelet recruitment.<sup>21</sup>

Afterward, phase two (dysregulated inflammation) is commenced by activation of pulmonary endothelial then leads to ACE1 shedding phenomenon, where ACE1 is rapidly liberated from the cell membrane, producing an initial rapid rise in angiotensin II. This can induce a positive feedback loop enhancing local inflammation, coagulation, and capillary leak.<sup>21</sup>

The final phase (hypo-inflammation – endothelial dysfunction) is marked by the dissipation of transiently increased ACE1 leads to lower angiotensin II concentrations. Low systemic angiotensin II leads to vasodilation, worsened capillary leak, and impaired endothelial conductance and autoregulation.<sup>21</sup>

Low angiotensin II also upregulates ACE2, possibly

increasing susceptibility to SARS-CoV-2 in remote tissue.<sup>21</sup> Although ACE2 shares some homology with an angiotensin-converting enzyme (ACE), it is not inhibited by ACEi and ARBs.<sup>14</sup> Theoretically, RAAS blockade might cause an increase in host susceptibility towards SARS-CoV-2. Despite the lack of evidence, there have been advocates for both the use and cessation of ACEIs, ARBs, or both during the treatment for COVID-19.<sup>13</sup>

**The Harm of Discontinuing ACE-i or ARB Therapy for Cardiovascular Indication in COVID - 19 patients.**

Angiotensin II, a neurohumoral agent, plays a pivotal role in heart failure, primarily in ventricular remodeling (ventricular hypertrophy and dilatation). Both ACE-I

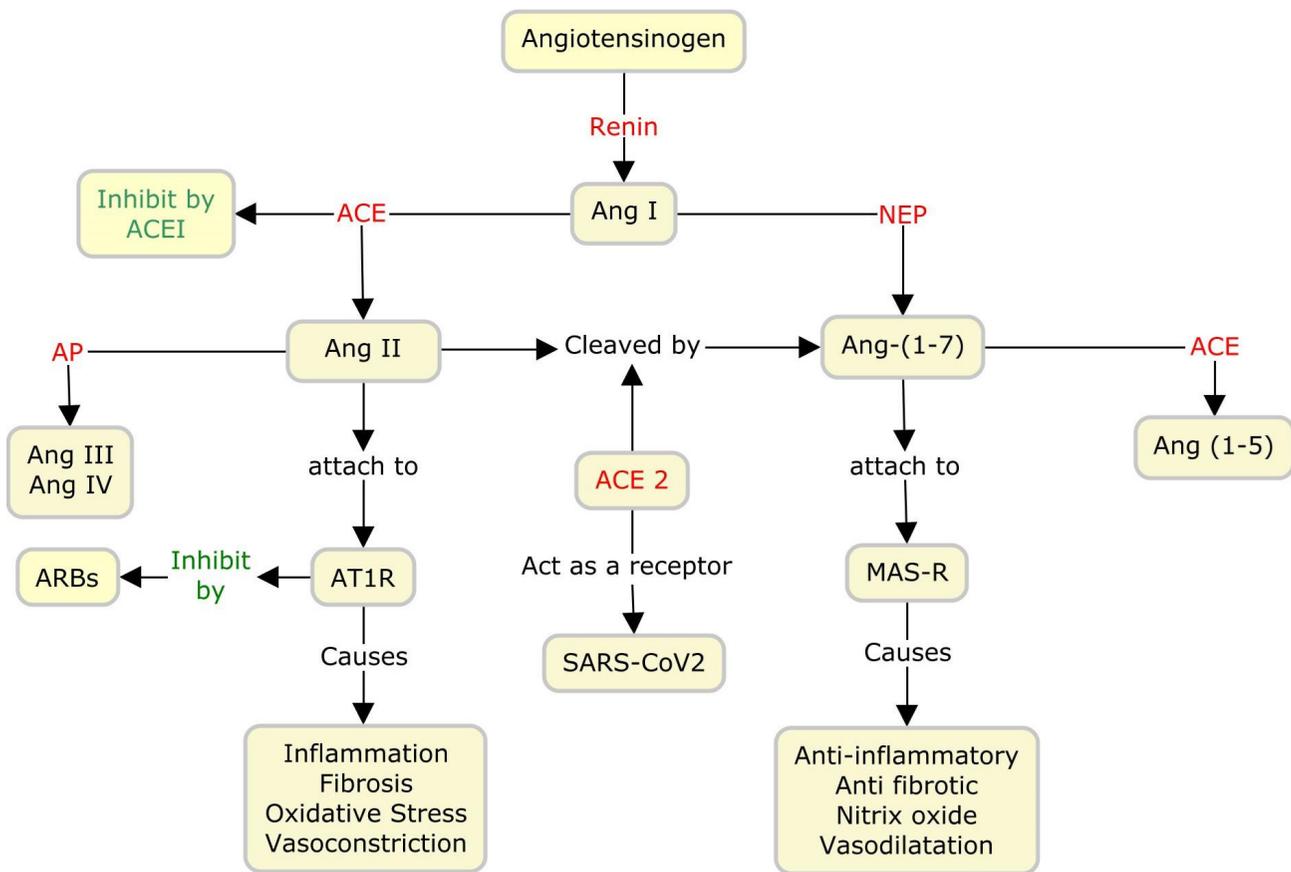


Figure 1. Renin Angiotensin System (RAS)

This figure depicts the RAS system. The words that are highlighted with red color are enzymes responsible for converting corresponding peptides. The words that are highlighted with green color are the inhibitors for enzyme/receptor corresponding to the arrows. Ang; angiotensinogen, ACE; angiotensin-converting enzyme, NEP; neprilysin, AP; activator protein, AT1R; angiotensin II receptor 1, MAS-R; MAS receptor, SARS-CoV2; severe acute respiratory syndrome-coronavirus 2.

and ARB can be used to prevent this phenomenon in heart failure.<sup>22</sup> Furthermore, ACE-I and ARB can prevent the progression of renal failure and can act as an antihypertensive agent by inhibiting angiotensin-converting enzyme and blocking angiotensin receptor, respectively.<sup>23,24</sup>

Diabetes mellitus, hypertension, cardiovascular diseases, and respiratory disease are often found in severe COVID-19 patients.<sup>25</sup> Based on a pooled analysis, hypertension was independently associated with a nearly 2.5-fold significantly increased risk of severe and mortality in COVID-19 disease.<sup>26</sup> In line with hypertension, cardiovascular diseases were also independently associated with approximately 2.5-fold significantly increased risk of mortality based on multivariate analysis of prospective cohort study.<sup>27</sup>

This can be explained, in part, by increased susceptibility due to enhanced expression of ACE2, especially those who are taking RAAS blockers and consequently causing local acute respiratory distress syndrome (ARDS) and systemic (multi-organ failure (MOF)/ systemic inflammatory response syndrome (SIRS)) complications.<sup>28</sup> Meanwhile, others argued that ACE2 expression is already reduced in hypertensive patients and decreases even more when bound to the SARS-CoV-2 virus, tipping the balance off towards Ang II, which contributes to lung injury and cardiovascular disorders.<sup>29</sup>

Although ACE-i or ARB theoretically can cause increased susceptibility to SARS-CoV-2 infection, the cessation of these drugs in patients with cardiovascular disease during a COVID-19 pandemic does not have robust evidence yet.<sup>30</sup> Discontinuation of ACEi or ARB therapy can worsen cardiac function, thereby increasing the risk of rehospitalization and mortality in patients with heart failure.<sup>31</sup> Furthermore, abrupt discontinuation of ACE-i or ARB in hypertensive patients can cause spikes in blood pressure and uncontrolled blood pressure rendering the patients an increased risk of sequelae.<sup>32,33</sup>

### **The Benefit of Continuing ACEi/ARB for Cardiovascular Indication in COVID - 19 patients.**

Although human evidence evaluating the safety of ACEi/ARB in the setting of SARS CoV2 infection is still lacking, we can extrapolate from other experimental animal studies, albeit with great caution because findings from basic medical science do not always translate to

human physiology.

Angiotensin-converting enzyme 2 (ACE 2) is known to have protective effects on lung physiology. In a mice model of acute lung injury induced by H5N1 virus infection and acid aspiration that is deficient from ACE2, increased levels of ACE, angiotensin II, and angiotensin II type 1a receptor (AT1a) induced lung edema and impaired lung function. However, this condition is readily reversed by infusion of human recombinant ACE2 protein.<sup>34,35</sup> Furthermore, lung injury induced by a respiratory syncytial virus (RSV) in ACE2 deficient mice is reduced by human recombinant ACE2 supplementation and angiotensin II receptor (AT1R) inhibition, in terms of reduced leukocyte cell count, inflammatory reaction, viral titers, and lung edema.<sup>36</sup> In a model of acute respiratory distress syndrome (ARDS) done in pigs, ACE2 protein significantly improved the respiratory failure outcome by increasing the oxygen levels by almost 40%.<sup>37</sup>

Losartan, an ARB, when used as a pretreatment for mice model of acute lung injury induced by lipopolysaccharides (LPS) has shown to reduce the inflammatory process in terms of IL-6 and prevent histological changes such as alveolar wall thickening caused by edema, striking inflammatory cell infiltration, and severe interstitial hemorrhage. Thus, preventing the action of angiotensin II indirectly on pneumocytes by blocking the AT1R by an ARB proved to be protective against acute lung injury.<sup>38</sup>

In experimental animal studies, Angiotensin-(1-7), a degradation product of angiotensin II by ACE2, acts through MAS receptor and attenuate the severity of acute lung injury through reduced lung edema, myeloperoxidase activity, histological lung injury score, pulmonary vascular resistance, inflammatory mediator response, lung injury scores, and improved lung function.<sup>39-42</sup>

In another experimental animal study, ACE2 can improve lung function after acute lung injury by antagonizing vascular endothelial growth factor antagonist (VEGFa), a mediator that responsible for increasing permeability of vascular endothelium.<sup>43</sup> The protective effects of ACE2 are also shown in the model of lung injury induced by H7N9. Whereas of its absence, lung injury is more severe. In addition, AT1 inhibition also attenuates the severity of lung injury.<sup>44</sup> Moreover,

ACE2 can prevent pulmonary vascular endothelial apoptosis by inhibiting the angiotensin II cascade, and thus protect the lung from injury.<sup>45</sup>

The Renin angiotensin aldosterone systems (RAAS) are known to play an essential role in the pathogenesis of inflammatory diseases. Blocking the action of angiotensin II by ARBs can prevent its downstream effect of NF- $\kappa$ B transcription factors and activating protein 1 (AP-1) activation.<sup>46</sup> Furthermore, pro-inflammatory activities orchestrated by multiple cell functions and molecular signalling pathways can be avoided, including progression of lung injury which is already marked in COVID-19 patients. Conversely, Angiotensin (1-7) mediated by the MAS receptor causes non-pro-inflammatory effect through the reduction of leukocyte migration and pro-inflammatory cytokines such as TNF- $\alpha$ , IFN- $\gamma$ , and IL-1 $\beta$  and IL-6. Angiotensin-(1-7) also exerts its anti-inflammatory effect through increasing the anti-inflammatory cytokine, such as IL-10.<sup>47-49</sup>

The protective effect was also found in a study of patients with underlying hypertension. A retrospective, multi-center study in China compared the mortality outcome of 1128 adult patients with hypertension diagnosed with COVID-19, including 188 taking RAAS blockers and 940 without using RAAS blockers. They found that inpatient use of ACEi/ARB was unlikely associated with increased mortality risk but was instead associated with a lower risk of all-cause mortality compared with ACEi/ARB non-users.<sup>50</sup>

The three different phases of COVID-19 should be taken into account while we are scrutinizing effects of RAAS blockers in such population. In the first phase, although RAAS blockers can increase ACE2, thereby promoting viral infection, both also prevent Ang II from building-up by increasing ACE2, which metabolizes it to become Ang 1-7. In the second phase, ACE 1 and Ang II are the main culprits, which can be inhibited and blocked by ACE-i and ARB, respectively.<sup>21</sup> Interestingly, whereas ACE-i/ARB could be detrimental if used in phase three, Ang II is useful in this phase, because it prevents vasodilatation, worsened capillary leak, and impaired endothelial conductance and autoregulation.<sup>21</sup> Therefore, it is judicious to use RAS blockers in the first two phases. Nevertheless, in phase three, both should be avoided, and Angiotensin II putatively could be utilized for COVID-19 patients who progressed to shock.

In conclusion, angiotensin II is detrimental to lung physiology, but ACE2 and Angiotensin (1-7) counterbalance its effects.<sup>51</sup> Thus, ACE-I and ARBs have been speculated to be beneficial in COVID-19 patients not just by preventing severe pneumonia but also avoid the negative consequences of cardiovascular diseases. With a caveat that they could be useful in the first two phases of COVID-19 and detrimental for the third phase. In contrast, the contrary is true for Angiotensin II. Nevertheless, further research is needed to investigate the potential therapeutic effect of Angiotensin II.

### **Latest summary of recommendations from world-wide Societies/Colleges**

Numerous publications related to this issue have been released recently. In general, they are in accordance with continuing ACEi/ARB for patients with distinctive indications, regardless of SARS-CoV2 infection.

## **Conclusion**

Emerging concerns about RAAS blockers prescription for patients infected by SARS-CoV-2 are based merely on hypothesis-generating data which indicates that ACE2 receptors are critical for viral entry and their levels are upregulated when using these RAAS blockers. Regarding to the scarcity of clinical evidence upon this issue, several world-wide societies have released recommendations to carry on RAAS blockers in patients with obvious cardiovascular indications regardless of COVID-19 status, until later evidences show otherwise. Discontinuing RAAS blockers might cause more harm over benefits, particularly in patients with heart failure in which these agents have been proven to reduce long-term mortality.

### **Publication Statements**

#### **Publication approval**

All authors read and approved the final manuscript.

#### **Conflict of interest**

None

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Table 1. Summaries of recommendation regarding ACEI/ARB for Antihypertensive in Patient with COVID19

Societies/Colleges	Recommendations	Latest Update
Indonesian Heart Association <sup>52</sup>	Recommends continuing ACEi/ARBs according to standard clinical practice guidelines due to inconclusive evidence and without adding/omitting treatment related to RAAS antagonist	March 26, 2020
Australian Diabetes Society <sup>53</sup>	Recommends that usual antihypertensive therapy is continued	March 29, 2020
High Blood Pressure Research Council of Australia <sup>54</sup>	Recommends that the routine use of ACE-Inhibitors or ARBs should continue, and patients should not cease blood pressure-lowering medications unless advised to do so by their physician.	March 17, 2020
American Society of Pediatric Nephrology <sup>55</sup>	Strongly recommends that patients continue to take their ACE inhibitors and ARBs, until new evidence to the contrary becomes available.	March 16, 2020
American College of Physicians <sup>56</sup>	Encourages continuing ACEis/ARBs because the mortality of patient confirmed COVID-19 with the cardiovascular disease treated with or without the use of ACEI/ARB did not show a significant difference in the outcome, and discontinuing or changing antihypertensive therapy without medical indication and supervision could lead to adverse effects and may be harmful	March 16, 2020
AHA/HFSA/ACC <sup>57</sup>	Recommends continuation of ACE-I and ARBs in a patient with hypertension, heart failure, or ischemic heart disease who are diagnosed with COVID-19	March 17, 2020
The Renal Association, United Kingdom <sup>58</sup>	Supports for continuing ACE-i and ARB in hypertensive patients because there is no data on the drug will increase the risk of COVID-19	March 15, 2020
International Society of Hypertension <sup>59</sup>	Does not support changing ACEi or ARB in hypertensive patients to treat or prevent SARS-CoV-2 infection because there is no evidence	March 16, 2020
Canada Cardiovascular Society <sup>60</sup>	Encourages to continue ACEi, ARB, and ARNI for hypertensive patients during the COVID-19 pandemic	March 20,2020
Hypertension Canada <sup>61</sup>	Endorses patients to continue ACEi/ARBs due to lack of evidence that patient with hypertension and those treated with ACEi/ARBs are at higher risk of adverse outcomes from COVID-19 infection	March 13, 2020
Spanish Society of Hypertension <sup>62</sup>	Treatments with ACEI or ARBs should not be suspended preventively in stable patients. Otherwise, in a patient with hemodynamic instability or need for admission due to severity criteria, changes of treatment should be made on a case-by-case	March 16, 2020
European Renal Association/ European Dialysis and Transplant Association <sup>63</sup>	Recommends that patients who are prescribed ACEi/ARB therapy continue to take these medications at this time unless there is a compelling, evidence-based indication to discontinue treatment.	March 17, 2020
European Society of Cardiology Council on Hypertension <sup>64</sup>	Strongly recommends that physicians and patients should continue treatment with their usual antihypertensive therapy. More evidence is needed to support the discontinuing of RAAS blockers.	March 13, 2020
European Society of Hypertension <sup>65</sup>	Still following the March 13, 2020 guideline, which is to continue ACEi/ARBs due to lack of evidence. In those with with severe symptoms or sepsis, antihypertensive decisions should be made on a case-by-case basis taking into account current guidelines	March 19, 2020

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### Ethical Clearance

Not Applicable

### List Of Abbreviations

COVID-19	: coronavirus disease of 2019
SARS-CoV2	: severe acute respiratory syndrome coronavirus - 2
ACE	: angiotensin-converting enzyme
ARBs	: angiotensin receptor blockers
RAAS	: renin angiotensin aldosterone system
WHO	: world health organization
nCov	: novel coronavirus
Ang I	: angiotensin I
Ang II	: angiotensin II
ARDS	: acute respiratory distress syndrome
MOF	: multi organ failure
SIRS	: systemic inflammatory response syndrome
AT1a	: angiotensin II receptor type 1a receptor
RSV	: respiratory syncytial virus
LPS	: lipopolysaccharides
VEGFa	: vascular endothelial growth factor antagonist
AP-1	: activating protein-1

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