

A



B

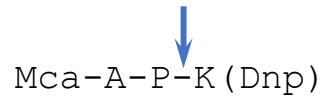
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C

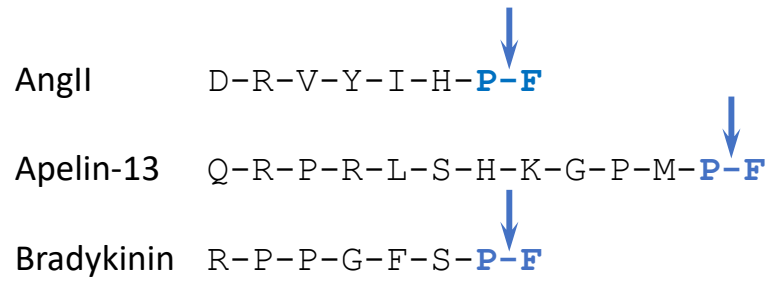
|                  |                  |                  |                  |
|------------------|------------------|------------------|------------------|
| <b>Glu145Ala</b> | <b>Arg273Ala</b> | <b>His345Ala</b> | <b>Pro346Ala</b> |
| <b>Asp368Ala</b> | <b>His374Ala</b> | <b>His378Ala</b> | <b>Glu402Ala</b> |
| <b>His505Ala</b> |                  |                  |                  |

**Supplementary Figure S1. Summary of ACE2-Fc mutagenesis.** **A.** Schematics of ACE2-Fc fusion construct: in an N-to-C-terminus order, ACE2-Fc is comprised of signal peptide and ACE2 ectodomain of human sequence, followed by Fc derived from human IgG1. **B.** The amino acid sequence of wild-type ACE2-Fc, showing signal peptide, ACE2 ectodomain and Fc with distinct font colors. The single amino acids in red fonts were individually mutated to alanine. **C.** List of the 9 mutants of ACE2-Fc.

A



B



**Supplementary Figure S2. The consensus substrate motif of ACE2 . A.** ACE2 cleaves surrogate peptide of Mca-APK-(Dnp) between proline (P) and lysine (K) residues (arrow). **B.** ACE2 cleaves proline-phenylalanine (P-F) peptide bonds at the C-termini of its physiological peptides.