

Title: A Long-acting ACE2–Fc Fusion Biologic Provides Organ Protection in Hypertensive Mice

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Angiotensin-converting enzyme 2 (ACE2) is a membrane carboxypeptidase that potently degrades angiotensin II (Ang II) to form Ang-(1-7). Mouse studies showed injection of recombinant ACE2 enzymatic ectodomain (rACE2) provides organ protection against harmful activation of the renin-angiotensin system (RAS). However, due to very short plasma half-life of rACE2, its therapeutic potentials are limited. To circumvent this problem, we generated a chimeric fusion of rACE2 and the immunoglobulin fragment crystallizable region (Fc segment) to increase its plasma stability. This rACE2-Fc fusion protein retained full peptidase activity meanwhile, as expected, exhibited greatly extended plasma half-life in mice, from less than two hours of the original rACE2, to over a week of rACE2-Fc. A single injection of 2mg/kg rACE2-Fc elevated the overall Ang II-conversion activities in blood by ~100 folds that lasted for two weeks. Consequently, only rACE2-Fc, but not rACE2 injection, achieved sustained prevention of blood pressure spike in response to bolus of Ang II. In a follow-up study of chronic hypertensive mice of RenTgMK transgenic driven by the expression of synthetic renin cDNA, we further demonstrated that weekly injections of rACE2-Fc effectively eliminated Ang II in blood, ameliorated albuminuria, and reduced kidney and lung fibrosis. These results suggest that this chimeric fusion strategy for rACE2-Fc may be suitable for future development of new RAS therapies.

Biography

Jing Jin has completed his PhD from the University of Toronto and postdoctoral studies from the Mount Sinai Hospotal in Toronto Canada. He is currently assistant professor of medicine in Northwestern University in the USA, and his research focues on recombinant protein engineering in diagnosis and treatments of kidney diseases. He has published 29 papers in reputed journals including *Cell, Developmental Cell, Nature Reviews in Molecular Biology*, *PNAS*.

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