

Biomolecular engineering in the design of novel therapies to treat coagulation disorders and inflammatory diseases

Citation for published version (APA):

Wildhagen, K. C. A. A. (2014). *Biomolecular engineering in the design of novel therapies to treat coagulation disorders and inflammatory diseases*. [Doctoral Thesis, Maastricht University]. Uitgeverij BOXPRESS. <https://doi.org/10.26481/dis.20141125kw>

Document status and date:

Published: 01/01/2014

DOI:

[10.26481/dis.20141125kw](https://doi.org/10.26481/dis.20141125kw)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Stellingen behorende bij het proefschrift

Biomolecular engineering in the design of novel therapies to treat coagulation disorders and inflammatory diseases

1. *In silico* structure-based virtual screening is a successful approach to discover small molecule inhibitors of protein-protein interaction for the interaction between coagulation factor Va and APC (this thesis).
2. Wild type- and S360A-(A)PC express protective properties in a mouse model for acute myocardial I/R injury and have the potential to inhibit development of chronic inflammation as occurring during atherosclerosis (this thesis).
3. The minor beneficial effects of unfractionated heparin observed in a randomized clinical trial for treatment of sepsis (HETRASE study) might be attributed to its histone-neutralizing capacity and independent of its anticoagulant properties (this thesis).
4. AADH, a low anticoagulant fraction of UFH, should be developed for use in a therapy to treat sepsis and other hyperinflammatory conditions in which excessive neutrophil activation with release of histones is part of the host response (this thesis).
5. Thrombin can initiate anti-inflammatory and barrier protective signaling via PAR-1, when EPCR is occupied by its natural ligand (A)PC (J.S. Bae et al. *Thromb Haemost* 2008).
6. Extracellular histones released in response to inflammatory challenge contribute to endothelial dysfunction, organ failure and death during sepsis (J. Xu et al. *Nature Med* 2009).
7. Neutrophils generate neutrophil extracellular traps (NETs), structures composed of DNA, histones and granule constituents, to disarm and kill bacteria extracellularly (V. Brinkmann et al. *Science* 2004).
8. S360A-APC can reduce the infarcted area of the heart even further than wt-APC, because its dose of administration can be higher than that of wt-APC due to its reduced anticoagulant activity (this thesis, valorisation).
9. The important thing in science is not so much to obtain new facts, as to discover new ways of thinking about them (William Lawrence Bragg).
10. There are no secrets to success. It is the result of preparation, hard work and learning from failure (Colin Powell).
11. How often in life we complete a task that was beyond the capability of the person we were when we started it (Robert Brault).

