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Recombinant uromodulin to prevent vascular calcification in chronic kidney disease

uromodulin, chronic kidney disease, calcification, pharmaceutical application

INVENTION NOVELTY

Accelerated medial arterial calcification in patients with chronic kidney disease (CKD) strongly correlates with increased arterial stiffness and cardiovascular mortality. Although the mechanism of vascular calcification is not fully understood, several lines of evidence highlight an association of low serum levels of uromodulin with elevated rates of cardiovascular mortality in CKD-patients. To date, no specific treatment that can prevent or even reverse vascular calcification is available for this patient population.
It was surprisingly found that overexpression of uromodulin after AAV-mediated transduction in a mouse model blunted cholecalciferol overload-induced aortic calcification and mRNA expression of osteogenic markers Cbfa1 and Alpl without significantly modifying serum calcium and phosphorus concentration.

VALUE PROPOSITION

The data of the invention suggest that uromodulin provides a direct molecular link between impaired kidney function, chronic inflammation and vascular pathology. There is emerging evidence for beneficial effects of uromodulin provoking vasculo-protective and inflammation modulatory properties conceiving as an anti-inflammatory therapy to reduce vascular calcification and improve cardiovascular outcome.

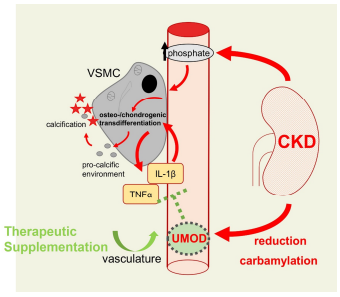

***Fig. 1**: Graphical abstract of uromodulin supplementation to counter calcification.*

TECHNOLOGY DESCRIPTION

Recent scientific advances suggest that systemic supplementation of uromodulin can dramatically ameliorate vascular calcification. This novel approach utilizes the protective function of systemic elevation of uromodulin for CKD patients at risk of progressive vascular calcification. It could be successfully demonstrated that uromodulin counteracts and prevents calcification by blocking the signalling cascade of TNFα and IL1β, which in turn could improve cardiovascular health progression to reduce cardiovascular morbidity for CKD patients predisposed to hypertension, coronary artery disease, diabetes mellitus and aging. This therapeutic approach shows following benefits:

- Means for reducing cardiovascular risk and inflammation in CKD-patients;
- Utilization of endogenous protective mechanisms, reducing risk of side effects;
- Novel approach to improve the cardiovascular risk management of kidney patients.

COMMERCIAL OPPORTUNITY

The invention offers an opportunity for direct entry into translational drug development of a therapeutic protein. We seek especially support and collaboration to validate the data using AAV-based overexpression in using systemically applied recombinant uromodulin. Recombinant production of uromodulin to conduct pre-clinical animal studies is therefore an essential need. In addition, collaboration is also sought to establish a GMP-compliant production of recombinant human uromodulin and future clinical studies.

DEVELOPMENT STATUS

Chronic renal failure in mice tended to reduce serum uromodulin concentrations, while uromodulin overexpression ameliorated the reduced uromodulin levels. Uromodulin supplementation was effective in reducing osteo-/chondrogenic signaling in vascular smooth muscle cells (VSMCs) during uremic conditions.

PATENT SITUATION

Patents are granted in US (US11161887) and EP (EP3589306) with effect in CH, DE, ES, FR, GB and IT.

FURTHER READING

Alesutan et al. (2021), Cardiovasc. Res. 117:930-941.

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

Ascenion GmbH
Herzogstraße 64
D-80803 München
info@ascenion.de
www.ascenion.de

Licensing Contact
Dr. Hubert Müller
Technology Manager
T: +49 89 318814-32
mueller@ascenion.de