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# Gene editing of the proteinase 3 autoantigen as a novel treatment for ANCA-associated vasculitis

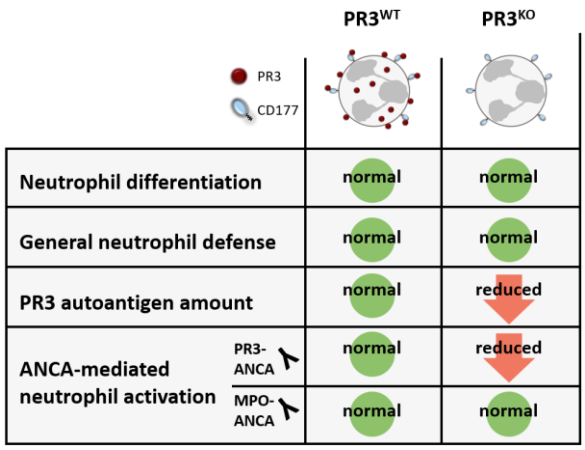
Keywords: anti-neutrophil cytoplasmic autoantibody, PR3, hematopoietic stem cells, gene editing, autoimmune disease, rare disease, vasculitis

## INVENTION NOVELTY

The technology provides a novel approach for treating proteinase 3 (PR3)-specific anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) via an autologous cell therapy. AAV are severe, systemic autoimmune diseases causing inflammation of small blood vessels. Triggered by autoantibodies against PR3 or myeloperoxidase (MPO) on neutrophils and monocytes, it leads to cell overactivation and, if untreated, can cause multi-organ damage and death within months.

## VALUE PROPOSITION

Unlike conventional treatments that suppress the immune system non-specifically and are often associated with disease relapses, this innovative approach precisely targets the molecular disease trigger PR3. The approach deletes the PR3 autoantigen thereby avoiding long-term immunosuppression that is associated with treatment-associated morbidity and mortality. This novel strategy offers a potentially curative alternative aimed at achieving long-term, drug-free remission - particularly valuable for patients with refractory or relapsing disease. The strategy developed by scientists at Charité and the Max Delbrück Center involves *ex vivo* gene editing of CD34+ hematopoietic stem and progenitor cells (HSPCs) of the PR3-AAV patient, which could then be reintroduced to regenerate a neutrophil population devoid of the pathogenic PR3 autoantigen.




*Effects of PR3 gene editing in HSPC-derived neutrophils. Source: Jerke et al., Kidney Int. 2025*

## TECHNOLOGY DESCRIPTION

Human HSPCs were edited using a ribonucleoprotein (RNP) complex composed of Cas9 and a single-guide RNA targeting the PR3 gene. Editing leads to effective elimination of PR3 protein expression in differentiated neutrophils. Experimental results demonstrate that PR3-knockout (PR3KO) HSPCs maintain a normal developmental behavior, and *in vitro* differentiated neutrophils were not impaired in viability and functionality, including phagocytosis, oxidative burst, degranulation, and constitutive apoptosis. Importantly, PR3KO neutrophils exhibit highly diminished PR3-ANCA binding and show a significantly reduced activation response to PR3-ANCA antibodies, while MPO-ANCA stimulation was not affected.

## COMMERCIAL OPPORTUNITY

We are looking for a licensing and/or collaboration partner.

## DEVELOPMENT STATUS

*In vitro* proof-of-principle established. Only low-risk off-targets have been predicted and are currently being analyzed.

## PATENT SITUATION

A European patent application was filed in September 2024 (EP24202670.6). PCT application filed.

## FURTHER READING

Jerke et al., Kidney Int. 2025, DOI: 10.1016/j.kint.2025.03.020

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