

GSDMD VHHs prevent pyroptosis

Single domain antibodies (sdAbs) against GSDMD prevent pyroptosis

Invention

Human GSDMD is a key mediator of pyroptosis, a pro-inflammatory form of cell death. GSDMD has a pivotal role in a broad range of diseases, including autoimmune, metabolic and neurodegenerative diseases as well as cancer. Hence GSDMD is an attractive drug target for the treatment of such diseases and excessive inflammation. The present invention provides single domain antibodies (VHH) targeting the oligomerization interface of GSDMD, enabling efficient inhibition of GSDMD pore formation, pyroptosis and IL-1 β release. GSDMD targeting VHHs demonstrate binding affinities in the subnanomolar range. GSDMD inhibition is observed following expression of GSDMD nanobodies in the target cell. Importantly, however, recombinant VHHs added to cultured target cells also block cell death. Inhibition of intracellular GSDMD via extracellular addition of VHHs may be promoted by a mechanism that involves anti-GSDMD VHHs entering through GSDMD pores and subsequent inhibition of additional pore formation.

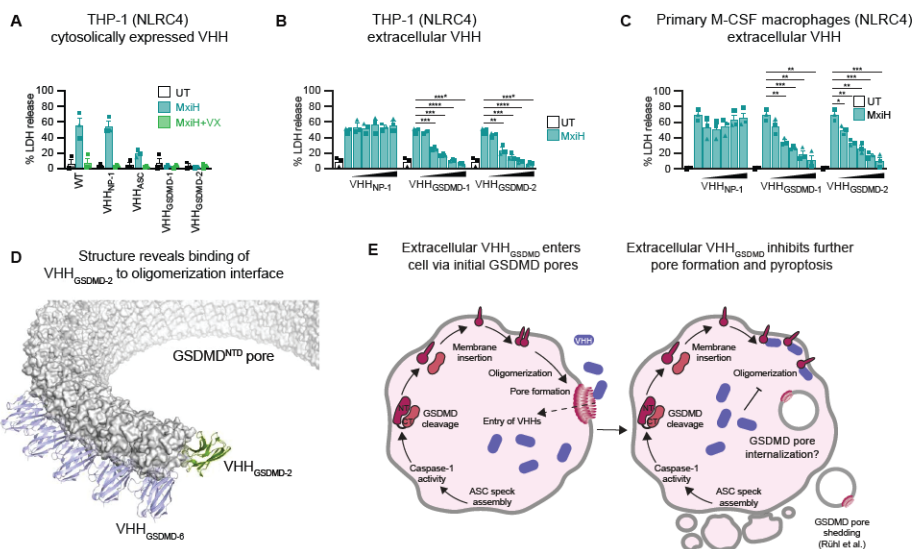


Figure 1: Single domain antibodies against GSDMD prevent pyroptosis and GSDMD pore formation.

Commercial Opportunities

The invention offers single domain antibodies for the efficient inhibition of GSDMD in inflammatory diseases and is available for licensing or further development together with the researchers.

Current Status

Several VHHs against different epitopes are available and have been characterized using a variety of biophysical, biochemical and cell-based methods. Tool compounds targeting murine GSDMD for in vivo experiments are in development.

Relevant Publications

A European Patent application has been filed on 15.02.2023 and a PCT application has been filed on 14.02.2024.

Schiffelers et al., Nat Commun (2024). doi: <https://doi.org/10.1038/s41467-024-52110-1>

Kopp et al., Nat Commun (2023). doi: <https://www.nature.com/articles/s41467-023-43707-z>

An invention from the Rheinische Friedrich-Wilhelms-University Bonn.

Advantages

- High affinity VHHs (subnanomolar)
- VHHs efficiently block GSDMD following intracellular expression in target cells
- VHHs inhibit GSDMD activity inside target cells following extracellular application
- Variety of VHHs against different epitopes available

Technology Readiness Level

1 2 3 4 5 6 7 8 9

Experimental proof of concept

Sector(s)

- Biotechnology
- Research
- Pharmaceutical industry

Ref.-No.

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