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Nanobodies that block gating of the P2X7 ion channel ameliorate inflammation

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ABSTRACT: Ion channels are desirable therapeutic targets, yet ion channel–directed drugs with high selectivity and few side effects are still needed. Unlike small-molecule inhibitors, antibodies are highly selective for target antigens but mostly fail to antagonize ion channel functions. Nanobodies—small, single-domain antibody fragments—may overcome these problems. P2X7 is a ligand-gated ion channel that, upon sensing adenosine 5′-triphosphate released by damaged cells, initiates a proinflammatory signaling cascade, including release of cytokines, such as interleukin-1b (IL- 1b). To further explore its function, we generated and characterized nanobodies against mouse P2X7 that effectively blocked (13A7) or potentiated (14D5) gating of the channel. Systemic injection of nanobody 13A7 in mice blocked P2X7 on T cells and macrophages in vivo and ameliorated experimental glomerulonephritis and allergic contact dermatitis. We also generated nanobody Dano1, which specifically inhibited human P2X7. In endotoxin-treated human blood, Dano1 was 1000 times more potent in preventing IL-1b release than small-molecule P2X7 antagonists currently in clinical development. Our results show that nanobody technology can generate potent, specific therapeutics against ion channels, confirm P2X7 as a therapeutic target for inflammatory disorders, and characterize a potent new drug candidate that targets P2X7.

STATEMENT: *"Our study provides a proof of principle that nanobodies are potent tools to block ion channels. The P2X7-blocking nanobodies reported in our study represent a new class of anti-inflammatory drugs."*

BACKGROUND: This work was performed at the Institute of Immunology in the group of Friedrich Koch-Nolte who holds a professorship at UKE since 1996. It was part of the PhD thesis of Dipl. Biochem. Welbeck Danquah. Both authors have strong research interests in the field of antibody engineering. This is an interdisciplinary study with the Departments of Nephrology and Neurology at the UKE, the University of Bordeaux and the Belgian start up company Ablynx, which develops nanobody-based therapeutics. The nanobodies described in this paper have been jointly patented by the UKE and Ablynx (WO2013178783).