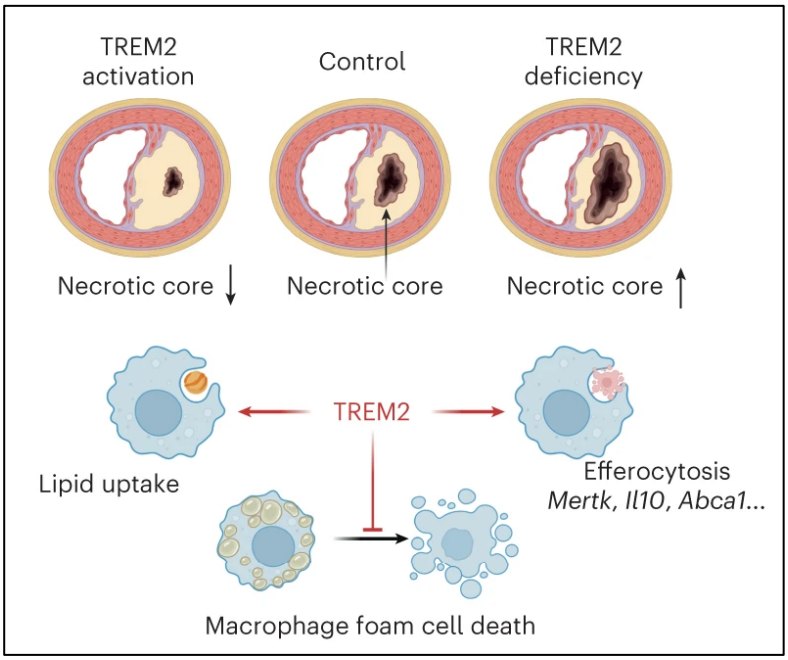
Marie Piollet*, Florentina Porsch*, Giuseppe Rizzo, Frederieke Kapser, Dirk J. J. Schulz, Máté G. Kiss, Kai Schlepckow, Estrella Morenas-Rodriguez, Mustafa Orkun Sen, Julius Gropper, Sourish Reddy Bandi, Sarah Schäfer, Tobias Krammer, Alexander M. Leipold, Matthias Hoke, Mária Ozsvár-Kozma, Hannah Beneš, Martin Schillinger, Erich Minar, Melanie Roesch, Laura Göderle, Anastasiya Hladik, Sylvia Knapp, Marco Colonna, Rudolf Martini, Antoine-Emmanuel Saliba, Christian Haass, Alma Zernecke#, Christoph J. Binder# & Clément Cochain#

TREM2 protects from atherosclerosis by limiting necrotic core formation *Nature Cardiovascular Research,* 3, 269–282 (2024). https://doi.org/10.1038/s44161-024-00429-9



The present study garners deeper insight into the critical role TREM2 plays in the pathogenesis of atherosclerosis, providing evidence that TREM2 agonism represents a promising therapeutic target to promote plaque stability and highlighting the clinical relevance of circulating soluble TREM2 as a potential marker for atherosclerosis progression. The paper is the result of a collaboration by the labs of Dr. Clément Cochain and Prof. Alma Zernecke at the University Hospital of Würzburg and Prof. Christoph Binder at the Medical University of Vienna.

- The authors investigated atherosclerotic plaque formation in *Ldlr*$^{-/-}$ mice with haematopoietic or global TREM2 deficiency, demonstrating increased necrotic core formation independently of lesion size, macrophage content and systemic lipid levels particularly at earlier and intermediate disease stages. In line with the observed increased necrotic core formation indicative of the accumulation of dying cells, the team find impaired cellular survival upon cholesterol loading and reduced primary and continuous efferocytotic capacities of TREM2-deficient macrophages in *in vitro* assays.
- Importantly, they provide evidence that treatment with an agonistic antibody against TREM2, 4D9, limits necrotic core formation in *Ldlr*$^{-/-}$ mice, suggesting that TREM2 agonism could be a promising therapeutic strategy.
- Finally, the team also measured the levels of soluble TREM2 (sTREM2) in the serum of patients enrolled in a prospective clinical cohort who underwent carotid duplex ultrasound at multiple timepoints, revealing that elevated sTREM2 levels were associated with an increased risk of plaque progression in clinical setting.
- In summary, the present paper suggests that activating TREM2 protects from necrotic core formation by avoiding foam cell death and enhancing efferocytosis, indicating that this pathway represents a putative therapeutic target to enhance plaque stability.