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Microporous Scaffold-Mediated Myeloid Cell Activation in Situ for Robust Peptide-Based Cancer Vaccine

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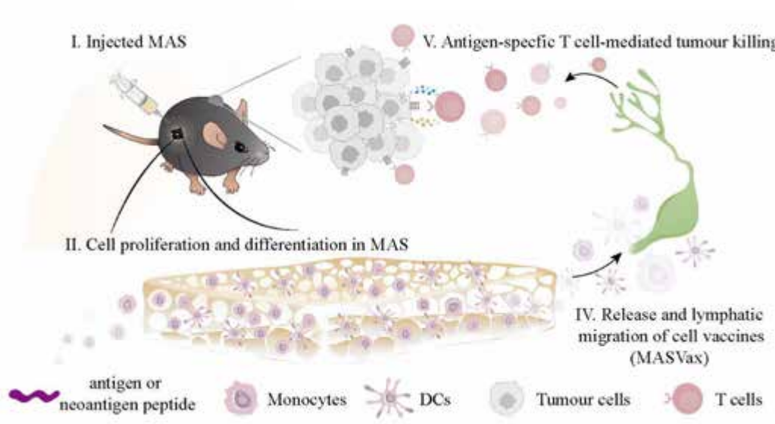
Abstract

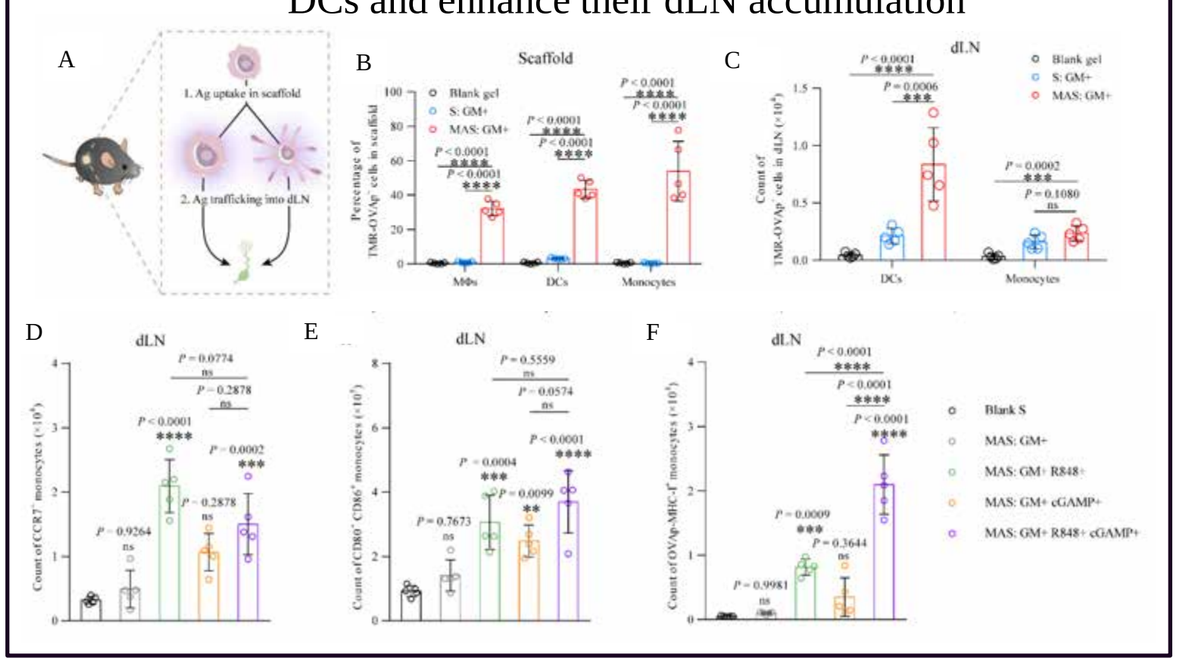
Neoantigen research is crucial for advancing custom cancer vaccines and immunotherapies, offering tumor-specific immune responses. Despite their potential, these therapies have had limited success due to challenges in neoantigen prediction and cancer's immune evasion. Neoantigen vaccines, like peptide and dendritic cell vaccines, effectively boost anti-tumor immunity but face manufacturing complexities. In vivo cell engineering simplifies this process, with myeloid cells showing promise for enhancing immune responses. We developed an injectable microporous scaffold for in vivo monocyte and DC vaccine generation, promoting antigen presentation and T-cell activation. Furthermore, the production of intracellular neoantigens in DCs can be achieved generally via mRNA transfection or mRNA electroporation, which are not suitable for in vivo cell engineering. Subsequently, surface-modified but not encapsulated peptide antigen or neoantigen are released and ingested by extensive antigen presenting cells, regardless of their phagocytic abilities, via cell membrane sulfhydryl group-promoted disulfide bond exchange. Consequently, this promotes cell differentiation, activation, and migration from the produced monocyte and DC vaccines (MASVax) to stimulate antitumor T-cell immunity. Neoantigen-based MASVax combined with immune checkpoint blockade induces rejection of established tumors and long-term immune protection.

Design of MAS and its function

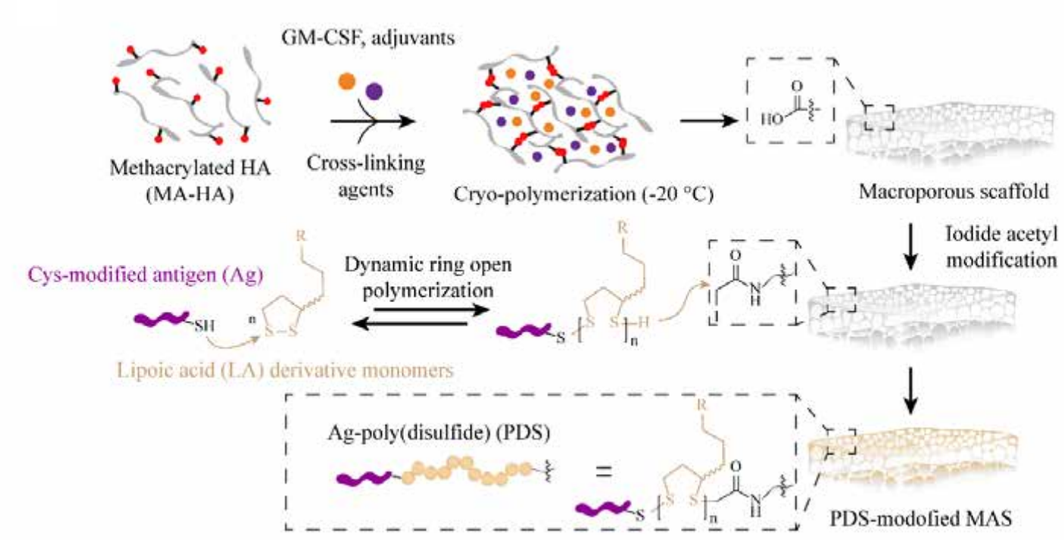


We designed an injectable macroporous myeloid cell adoptive scaffold (MAS) that acts as *in vivo* monocyte and DC vaccine.

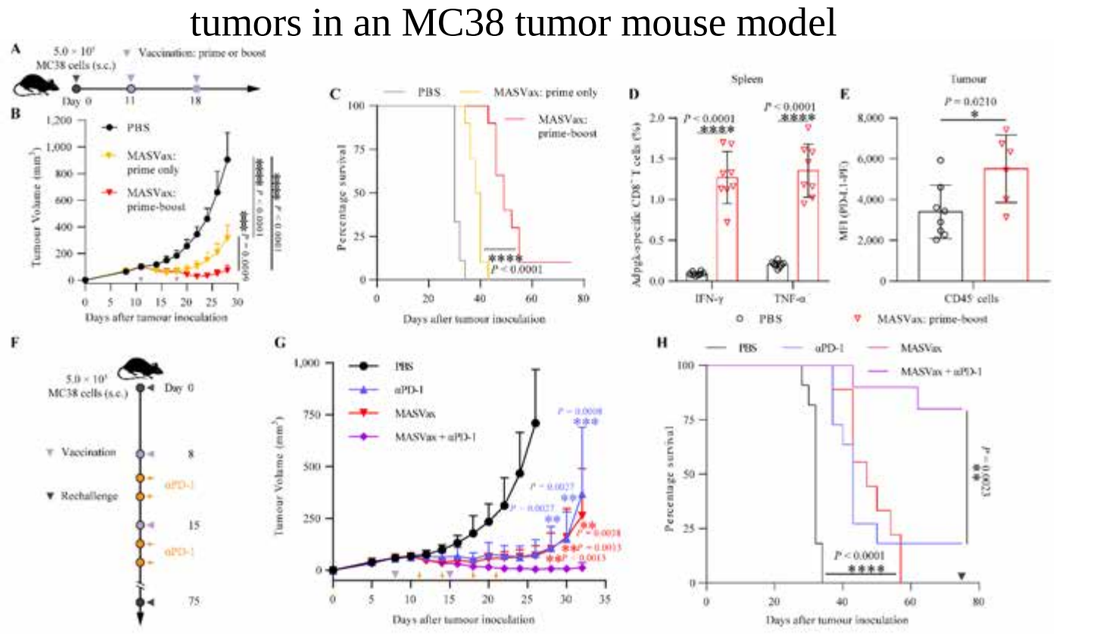
Optimized MAS components activate monocytes and DCs and enhance their dLN accumulation



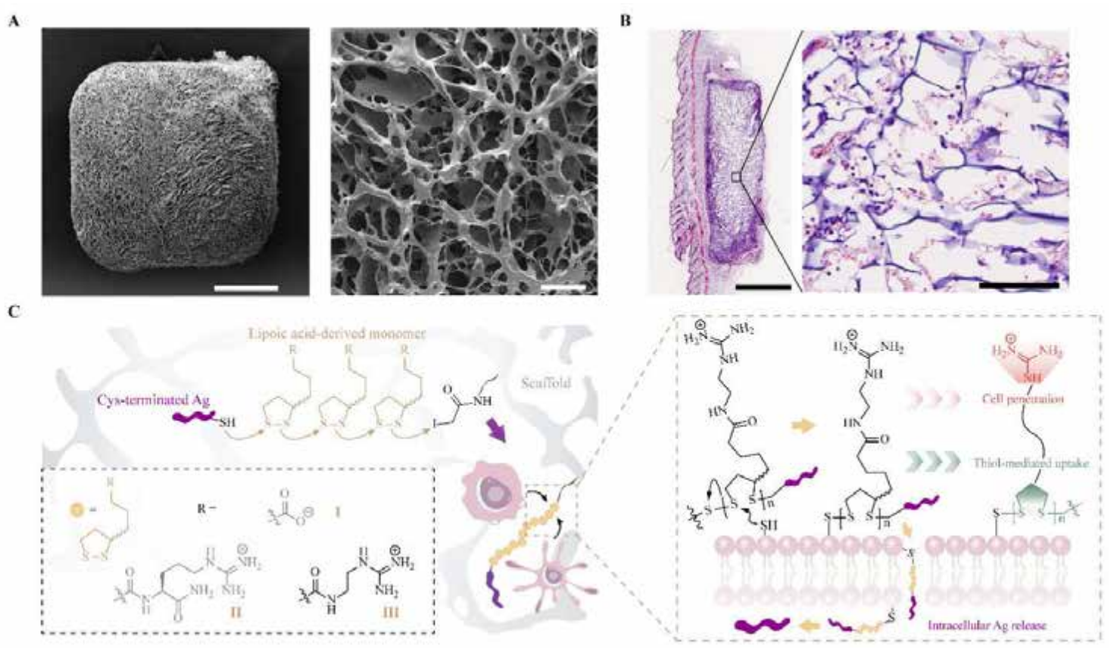
Poly(disulfide) (PDS) modification on MAS



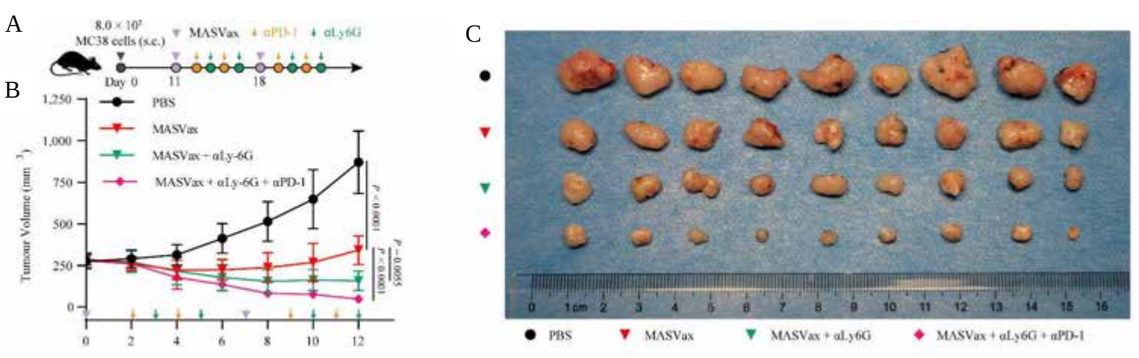
MASVax-based neoantigen therapies eradiate tumors in an MC38 tumor mouse model



Antigen loading and release through dynamic disulfide exchange



Depletion of PMN-MDSC by αLy-6G augments MASVax-based neoantigen therapies



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[1] W.-H. Li, J.-Y. Su, B.-D. Zhang, L. Zhao, S.-H. Zhuo, T.-Y. Wang, H.-G. Hu, Y.-M. Li, Adv. Mater. 2024, 36, 2308155.