Researchers develop new generation tumor-specific pro-IL-12

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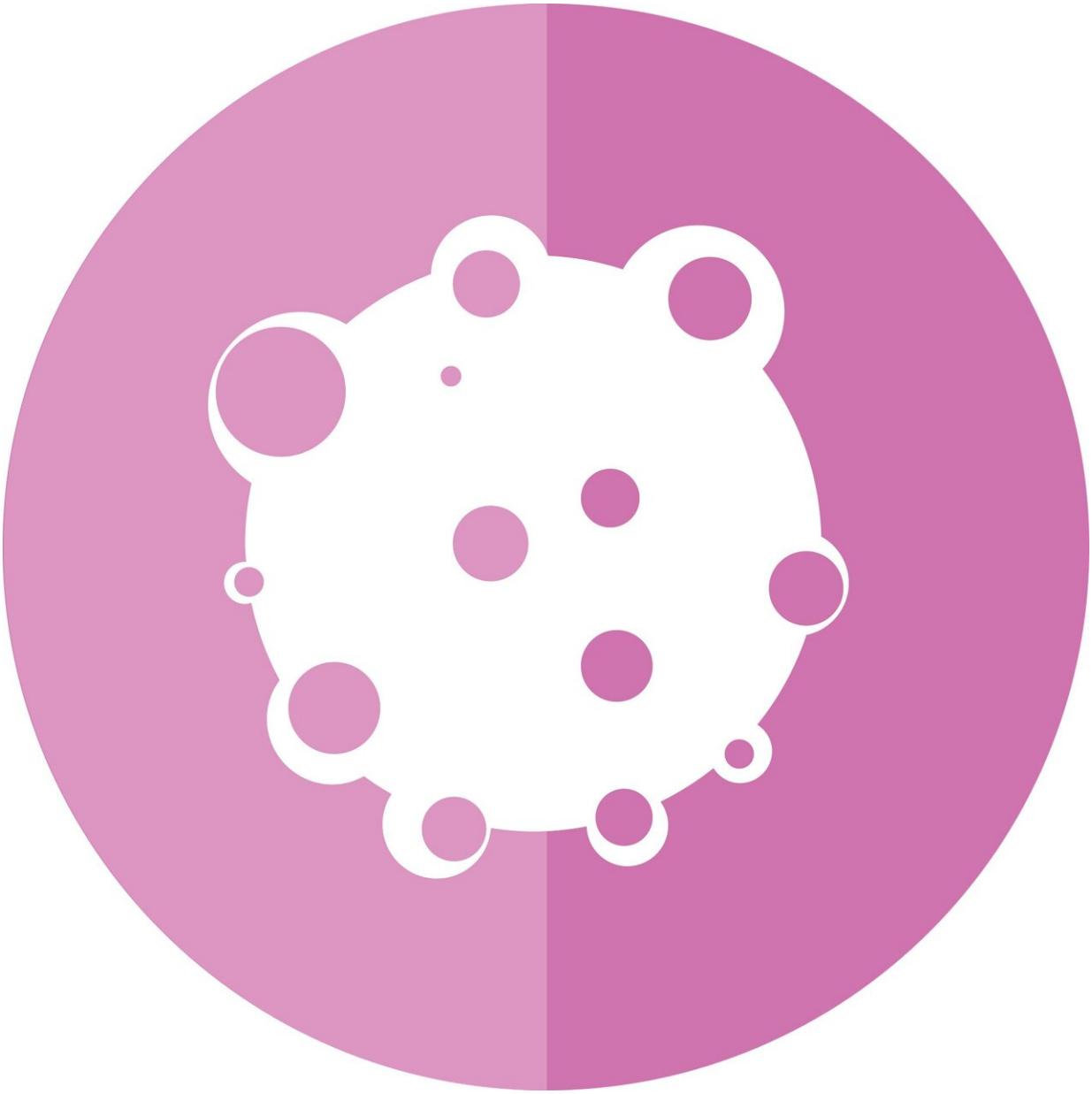

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Interleukin-12 (IL-12), a potent inducer of cell-mediated immunity, can stimulate the anti-tumor effector functions of the activated T and NK cells for solid tumors rejection. However, clinical administration of IL-12 has been limited because of its short half-life, low efficacy, and dose-limiting systemic toxicity.

In a study published in *Science Immunology*, Prof. Peng Hua at the Institute of Biophysics of the Chinese Academy of Sciences and Prof. Fu Yangxin at the University of Texas Southwestern Medical Center, and collaborators, developed a new generation IL-12, the pro-IL-12, with low toxicity, tumor restriction, and high anti-tumor efficiency.

The researchers first constructed an IL-12-Fc fusion protein to extend the in vivo half-life of IL-12 and further engineered a pro-IL-12 with the functional site blocked by an MMP-cleavable peptide-linked IL-12 natural extracellular receptor-binding domains. Pro-IL-12 could be reactivated when the linker was cleaved by tumor-enriched MMP14. Systemic treatment with pro-IL-12 resulted in effective tumor control and prolonged mouse survival.

This next-generation IL-12 directly activated the preexisting intratumoral tumor-specific CD8+ T cells to release IFNγ within the TME. Pro-IL-12 could improve the therapeutic outcomes when combined with both tyrosine kinase inhibitors (TKI)-targeted therapy and immune checkpoint blockade (ICB) therapy, providing a new therapeutic regimen to reduce tumor resistance to the existing treatments.

Overall, this study showed a tumor-conditional pro-IL-12 to overcome

the limitations of IL-12-based therapies and provided a platform for future anti-tumor procytokine design.

More information: Diyuan Xue et al, A tumor-specific pro-IL-12 activates preexisting cytotoxic T cells to control established tumors, *Science Immunology* (2022). DOI: 10.1126/sciimmunol.abi6899