CAT-BLAST: Engineered Bacteria for Robust Targeting and Elimination of Cancer-Associated Fibroblasts

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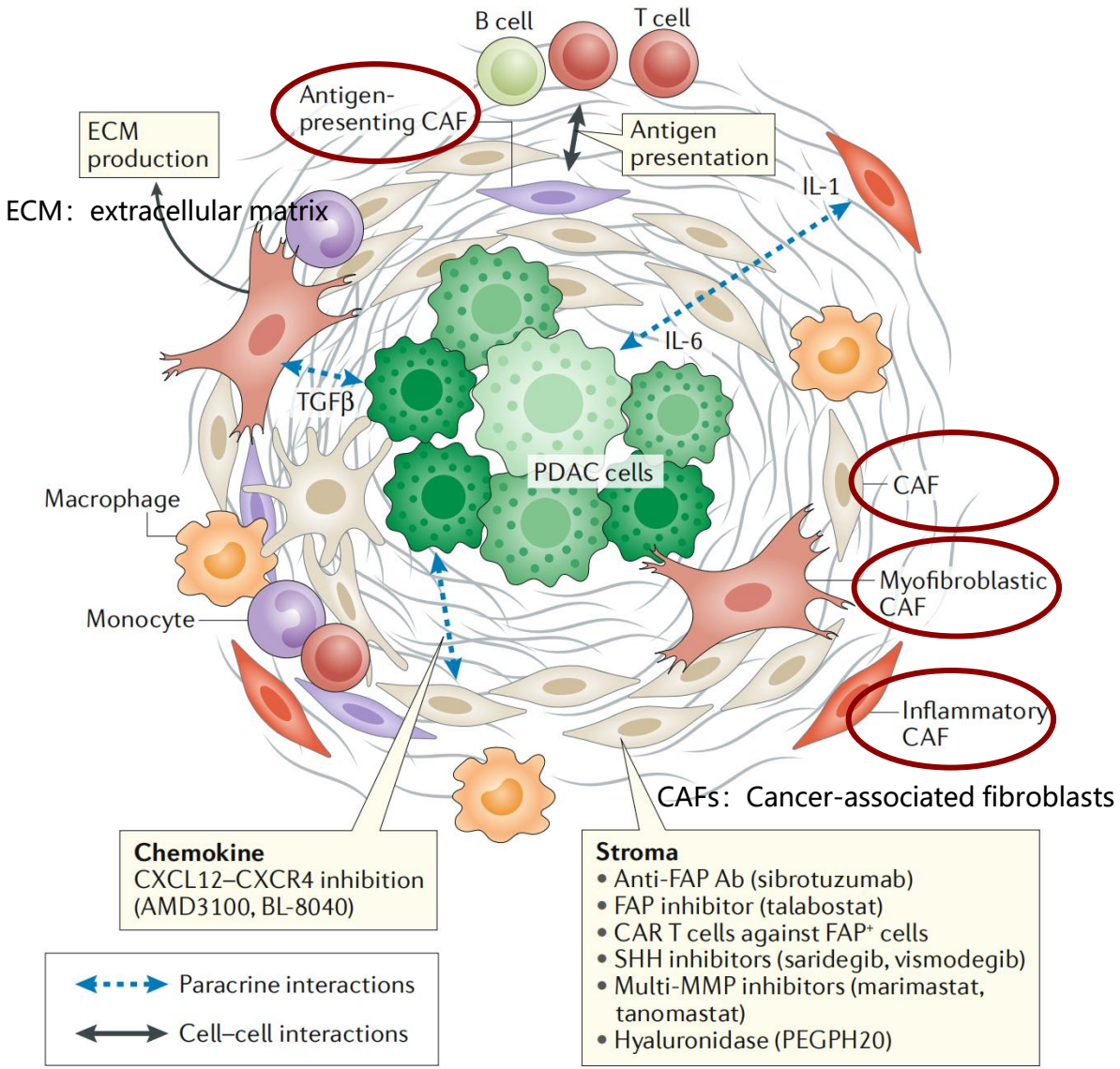
The tumor stroma plays a protective barrier role for tumor cells



Won Jin Ho et al., 2020, *Nat Rev Clin Oncol*

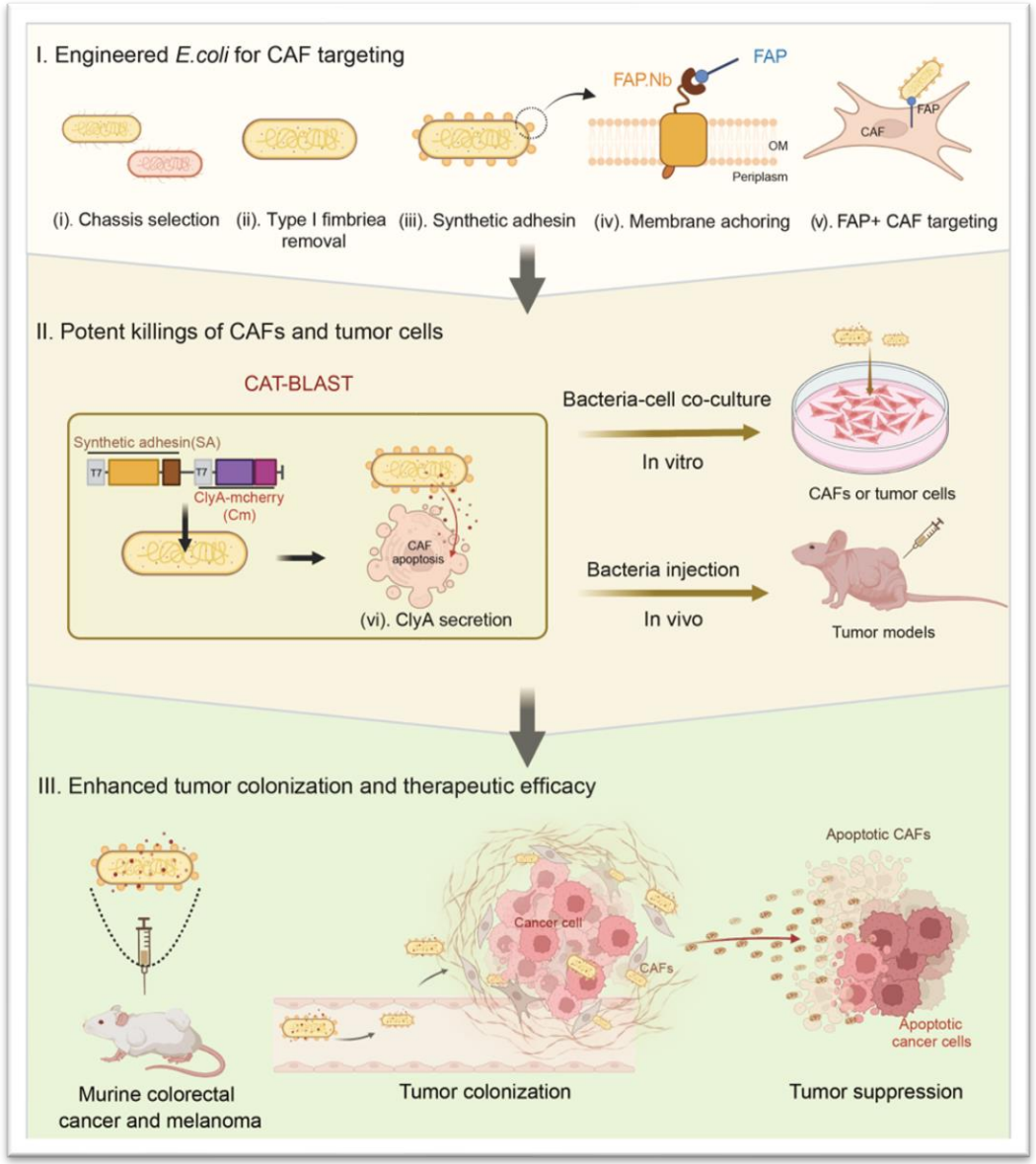
The tumor microenvironment (TME)

Tumor stromal cells ⇄ (mutual / promotion) Tumor cell

- Currently, the treatment model targeting tumor cells is usually insufficient to completely eradicate malignant tumors, as tumor stromal cells can enhance tumor recurrence and treatment resistance;
- The tumor stroma is composed of infiltrating immune cells (such as macrophages, dendritic cells, and lymphocytes), cancer-related stromal cells (such as cancer-associated fibroblasts), endothelial cells and adipocytes, as well as extracellular matrix and various signaling molecules.

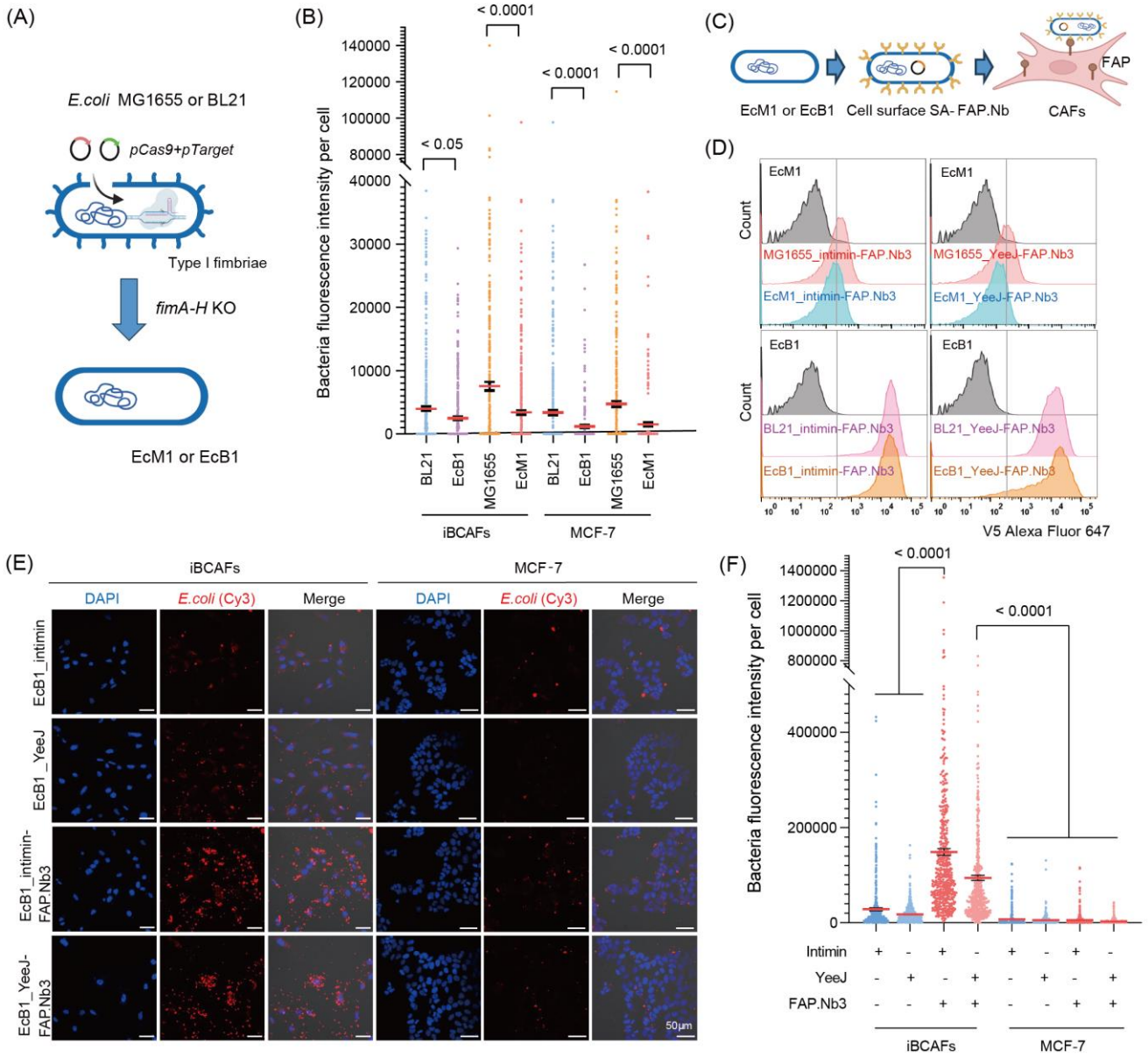
CAFs：Cancer-associated fibroblasts

Engineering CAT-BLAST bacteria to target CAFs and dismantle the tumor stromal barrier



- CAT-BLAST utilizes engineered bacteria to specifically target and colonize FAP-positive cancer-associated fibroblasts (CAFs);
- Secretion of the pore-forming toxin ClyA eliminates CAFs and induces potent bystander killing of adjacent tumor cells;
- The platform demonstrates robust tumor colonization and therapeutic efficacy across diverse tumor mice models.

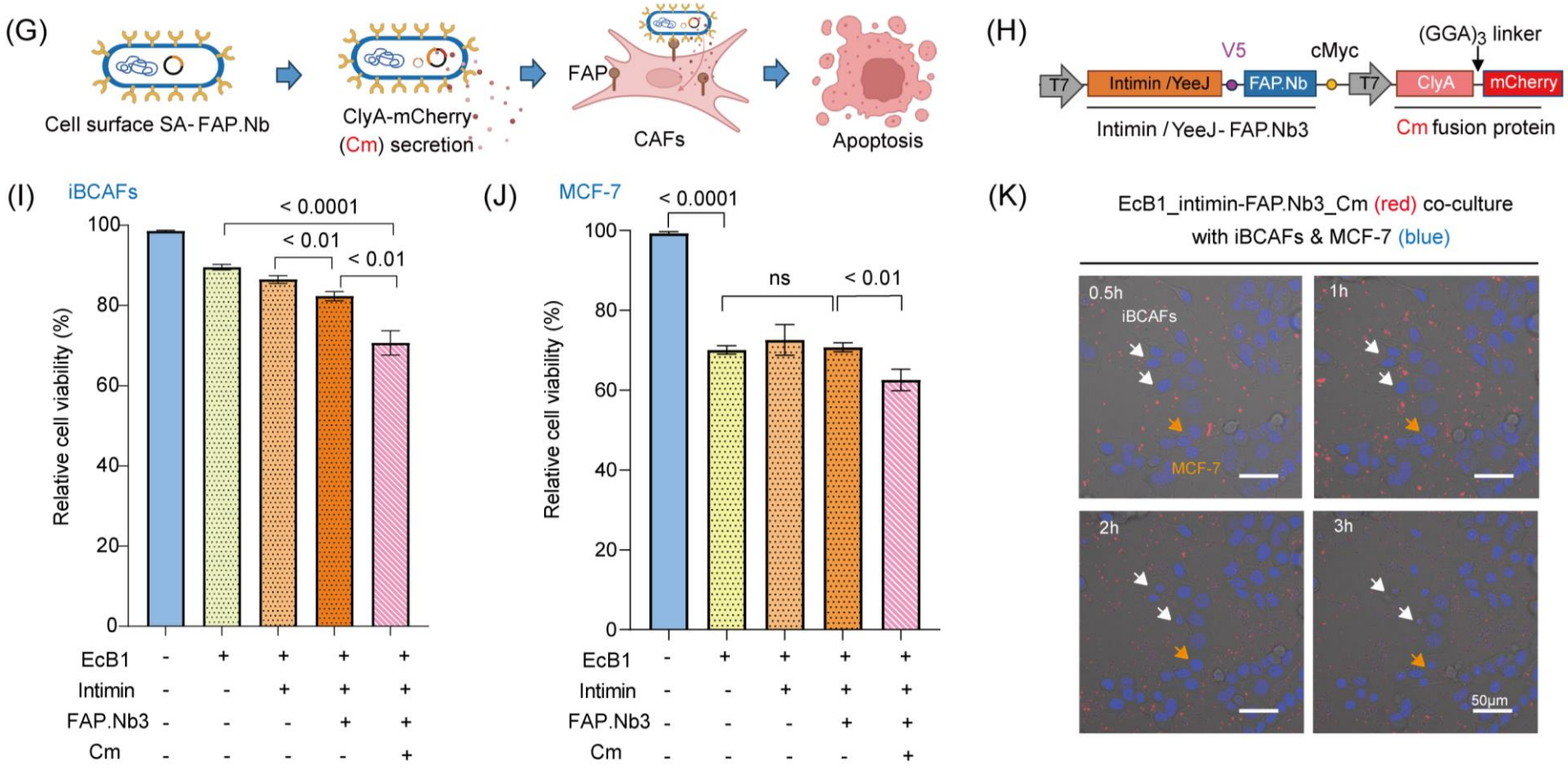
Engineered bacteria with enhanced biological safety and specifically target FAP-positive CAFs



- Knocking out the natural fimbriae encoded by the *fimA-H* operon to reduce bacterial non-specific adhesion and enhances the safety of the host bacteria;
- Designing synthetic adhesin (SA) that fuse the FAP nanobody with the membrane-anchored protein (intimin/YeeJ);
- EcB1 has a higher and more stable expression level of SA compared to EcM1;
- The engineered bacteria expressing SA can specifically target FAP-positive iBCAFs, and intimin is more effective than YeeJ.

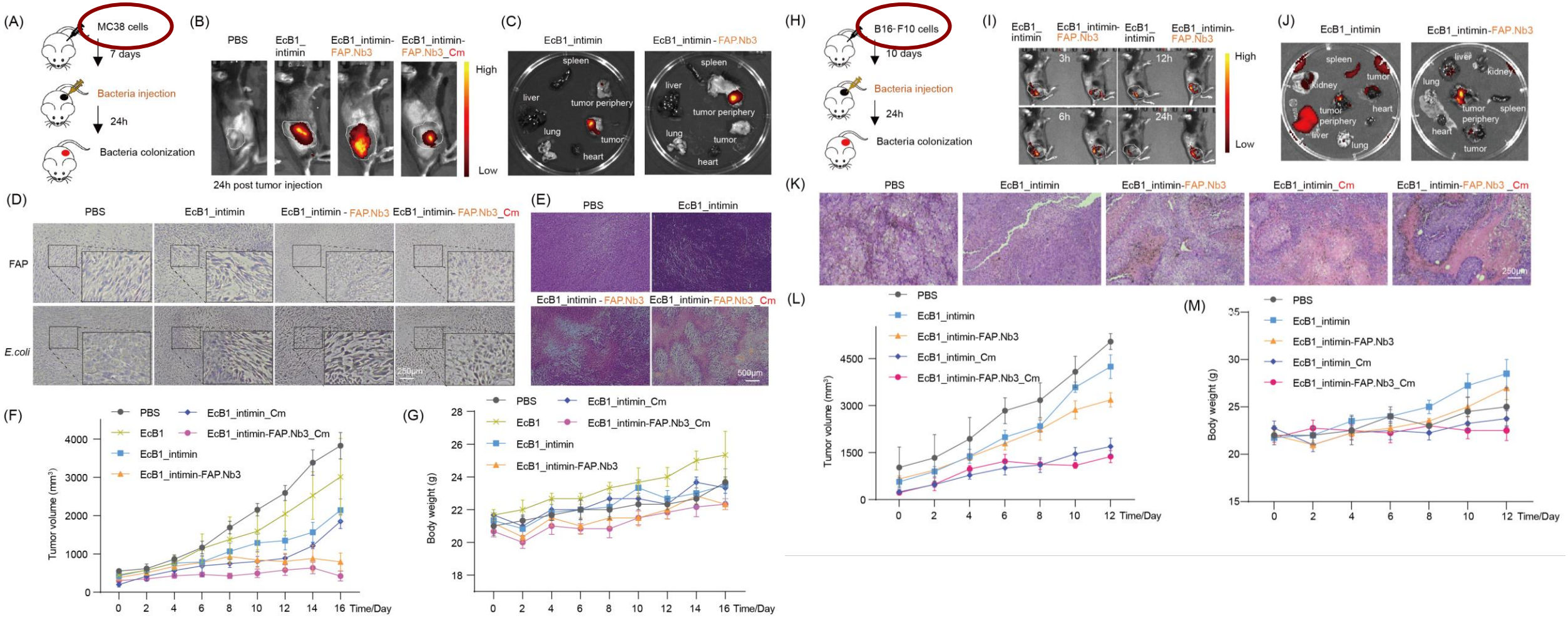
Secretion of ClyA toxin enables potent killings of CAFs and adjacent tumor cells

- Further modification of the engineered bacteria resulted in the formation of a complete CAT-BLAST. It expresses the synthetic adhesin that target FAP-positive CAFs, while secreting the cytotoxic perforin toxin ClyA, inducing apoptosis of CAFs and exerting a bystander killing effect on surrounding FAP-negative tumor cells.



CAT-BLAST potently suppresses colorectal tumor and melanoma

- EcB1_intimin-FAP.Nb can target and enrich in the tumor periphery region with high expression of FAP.
- EcB1_intimin-FAP.Nb3_Cm (**CAT-BLAST**) can significantly damage tumor tissues and effectively suppress the growth of colon cancer and melanoma.



Summary

- In this study, we introduce CAT-BLAST, an engineered bacterium designed to remodel the tumor microenvironment by dismantling cancer-associated fibroblasts.

- By combining a FAP-specific adhesin for precision targeting with a secretable ClyA toxin, CAT-BLAST effectively kills both cancer-associated fibroblasts and adjacent tumor cells.

- This dual-action engineered bacterium demonstrated robust tumor colonization and potent anti-tumor efficacy across diverse *in vivo* models, offering a new strategy for overcoming stromal barriers in cancer therapy.

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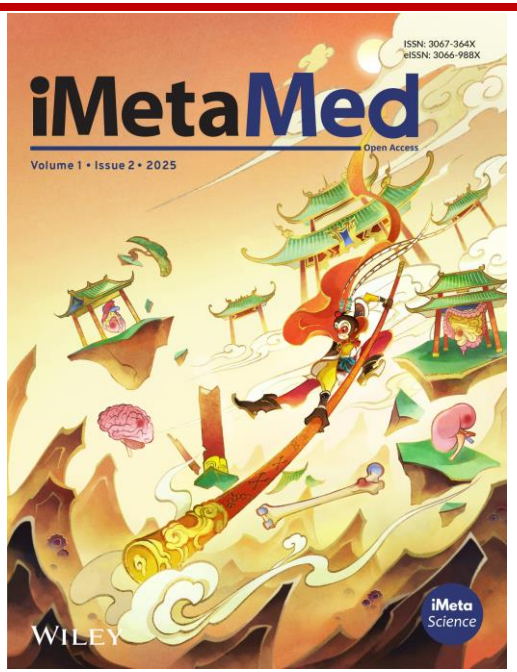

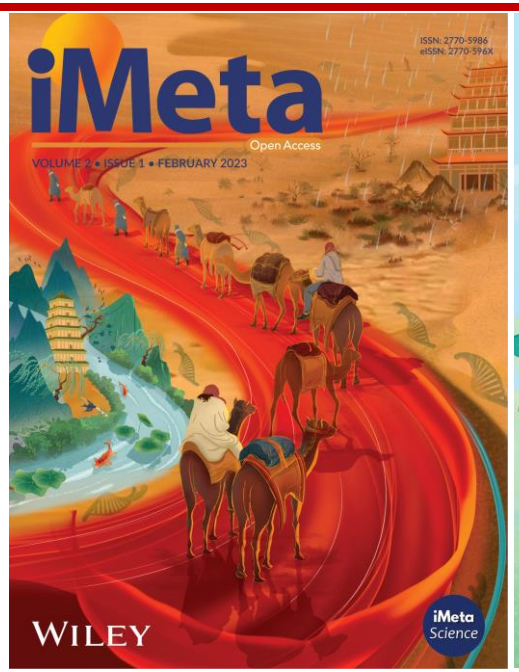

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