



Intratumoral *Enterobacter hormaechei* drives gemcitabine resistance in pancreatic cancer via *cdd_L*-mediated drug inactivation

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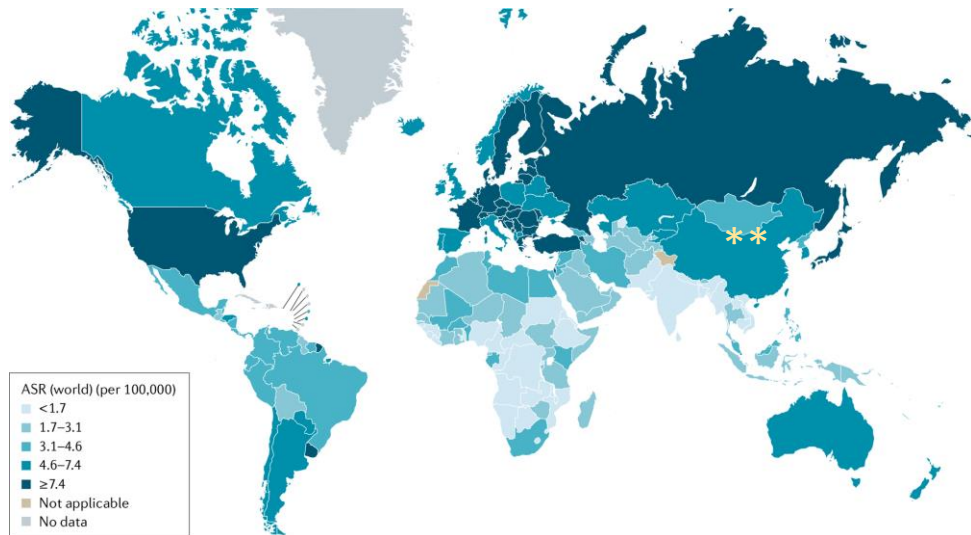
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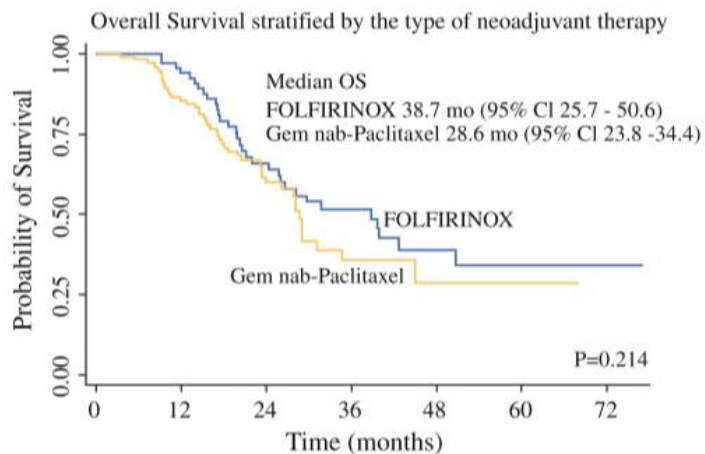
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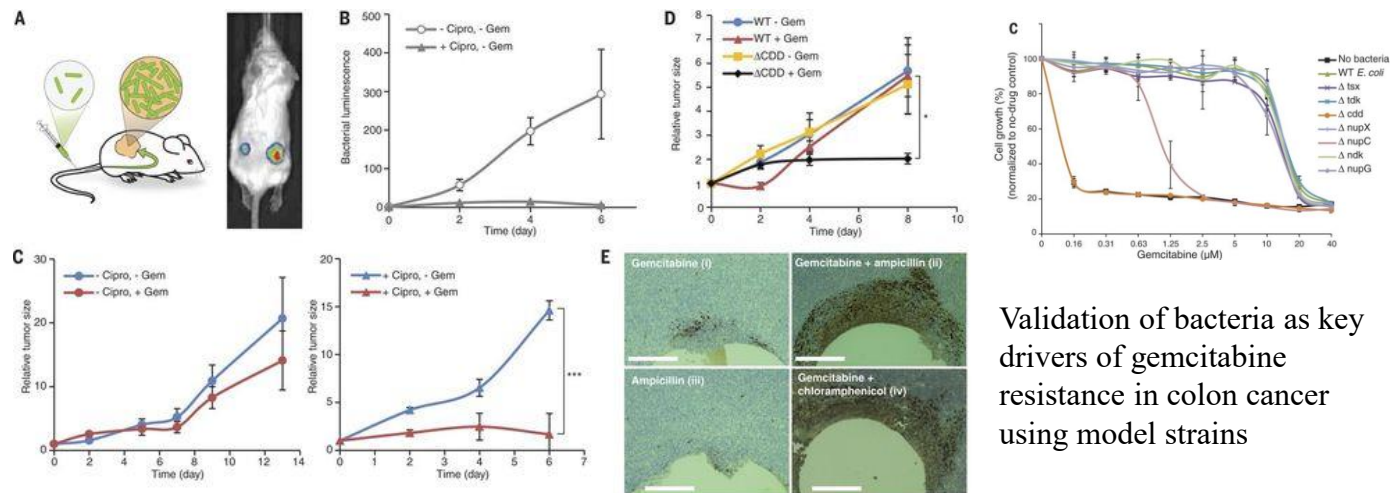
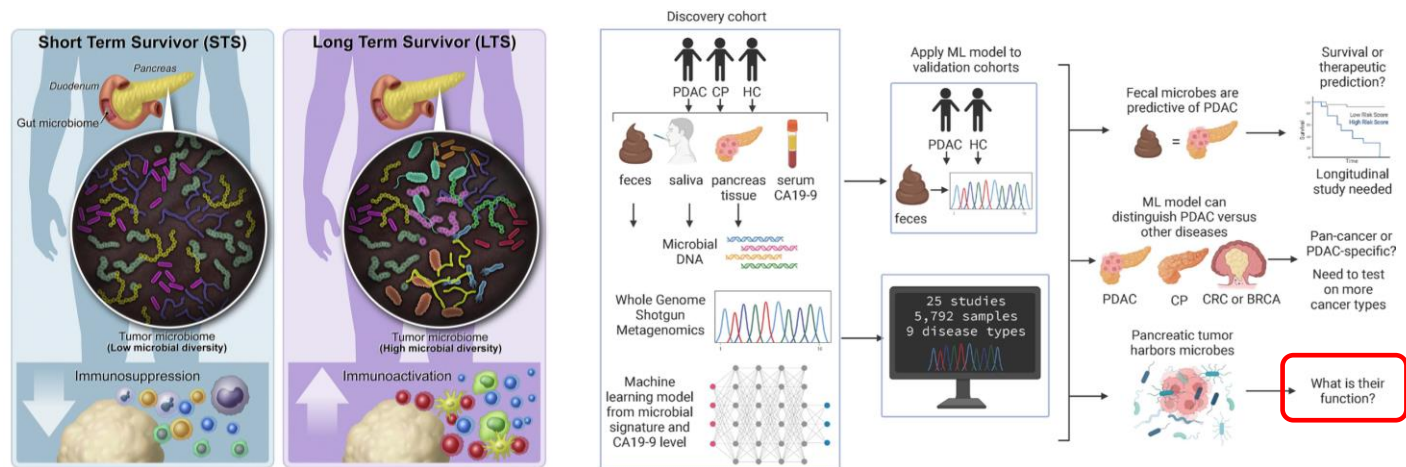
Introduction



Global trends in pancreatic cancer



Chemotherapy is an effective treatment for pancreatic cancer

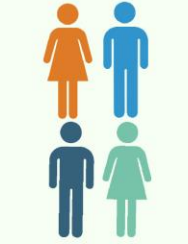


Which specific clinical isolates drive PDAC chemoresistance, and how?

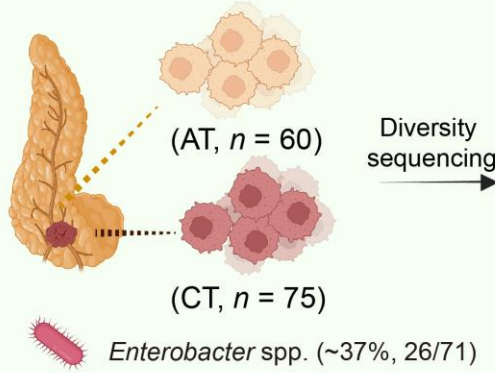


Highlights

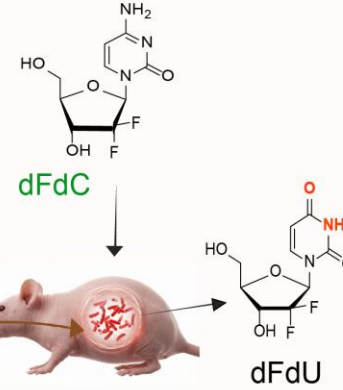
From 2017 to 2021



71 pancreatic cancer patients



In vivo resistance

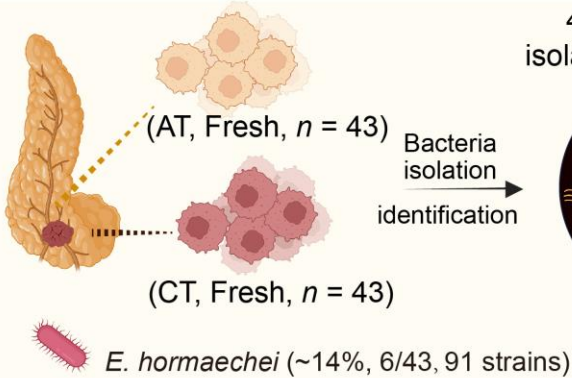


E. hormaechei coexists with tumor

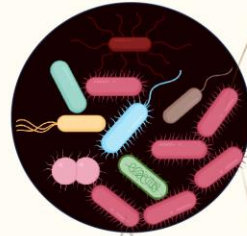
From 2021 to 2022



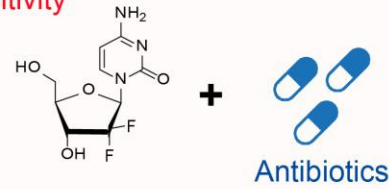
43 pancreatic cancer patients



431 strains are isolated and identified

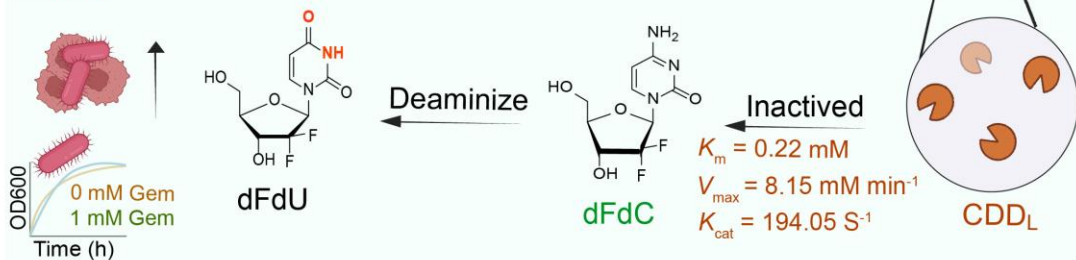


Sensitivity



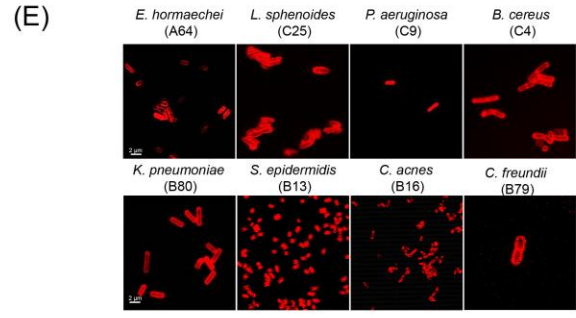
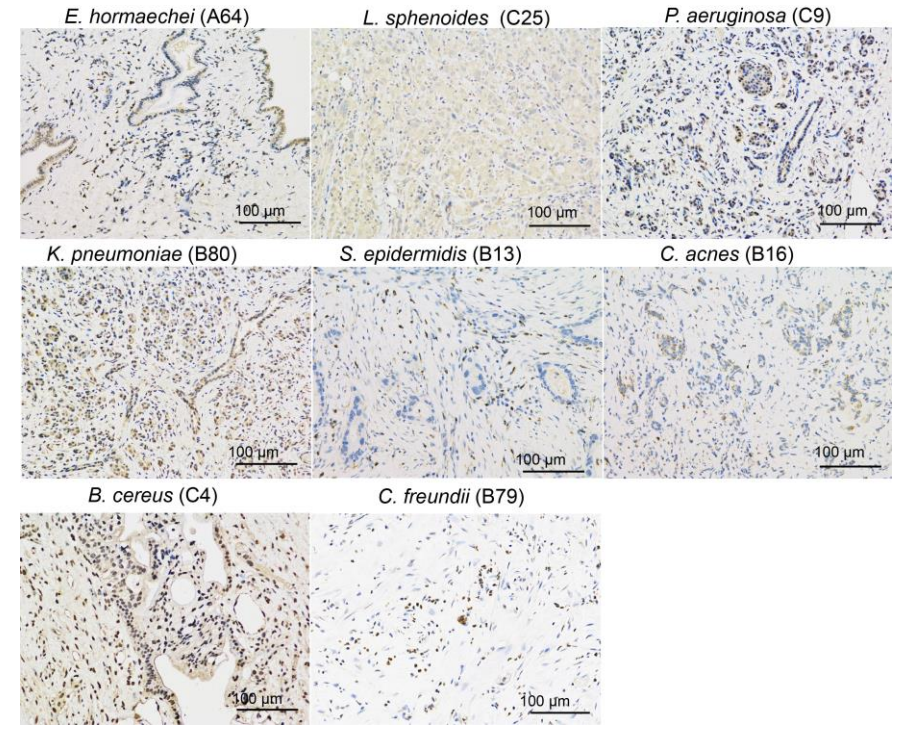
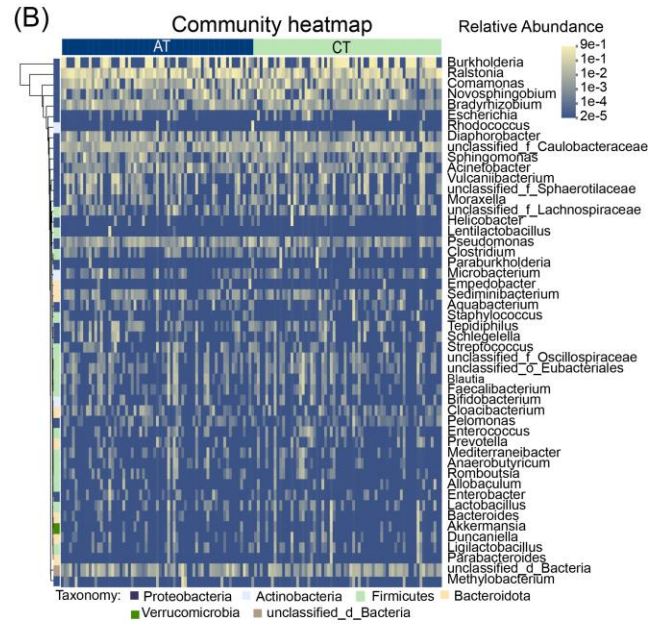
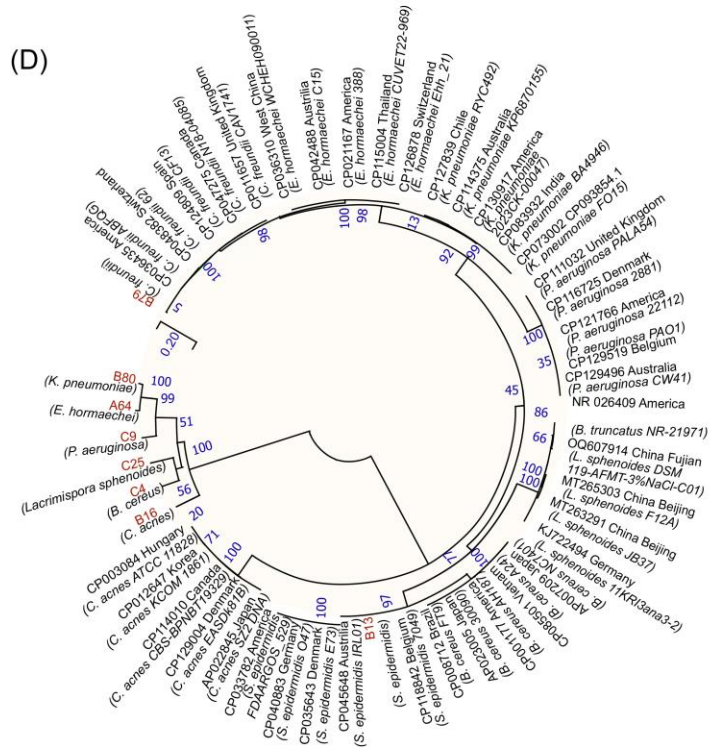
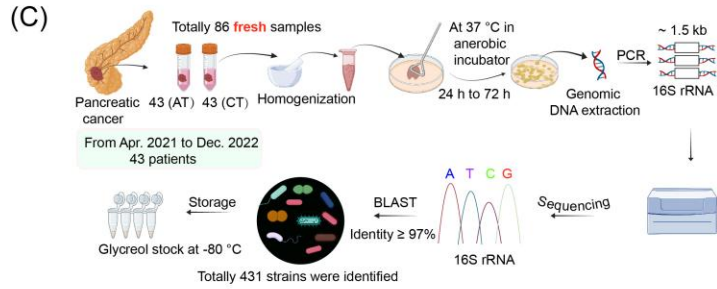
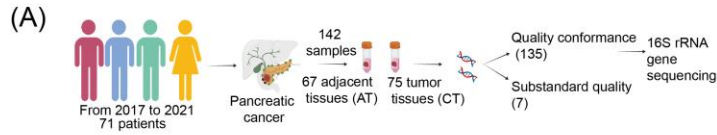
Tumor growth is inhibited

In vitro



- ✓ Multi-omics identifies intratumoral *E. hormaechei* driving PDAC chemoresistance.
- ✓ Bacterial CDD_L inactivates gemcitabine; *cdd_L* ablation completely reverses resistance.
- ✓ Antibiotic co-treatment eradicates bacteria and halves the required chemo-dosage.
- ✓ Pan-cancer presence of *Enterobacter* spp. indicates a ubiquitous resistance mechanism.

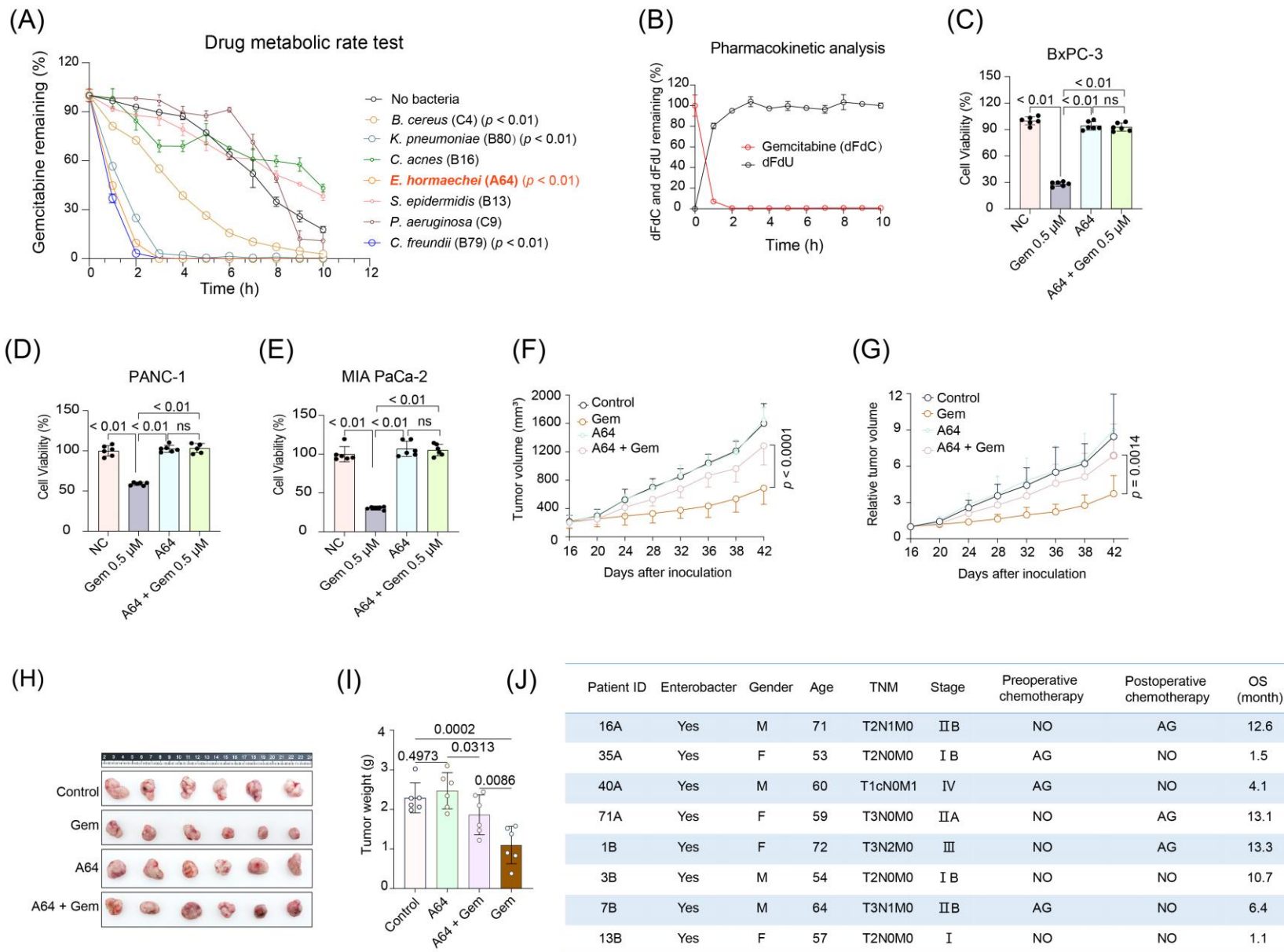
Profiling and isolation of intratumoral *Enterobacter hormaechei*



- Microbiome profiling & target identification.
- Viability confirmation via culturomics.
- Correlation with adverse clinical prognosis.
- *In Situ* localization and phylogenetic validation.

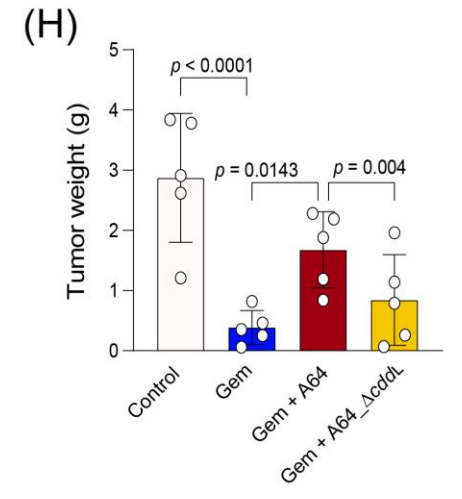
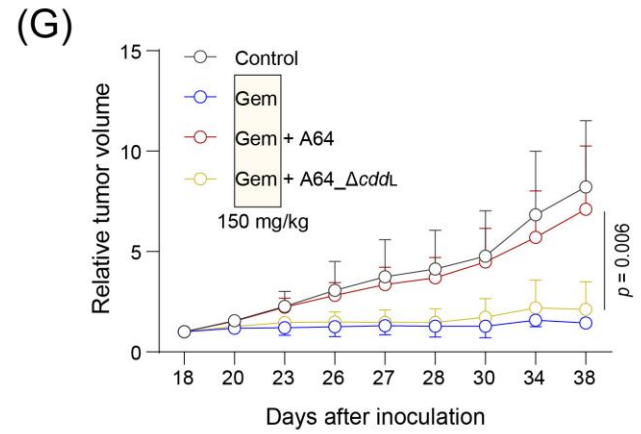
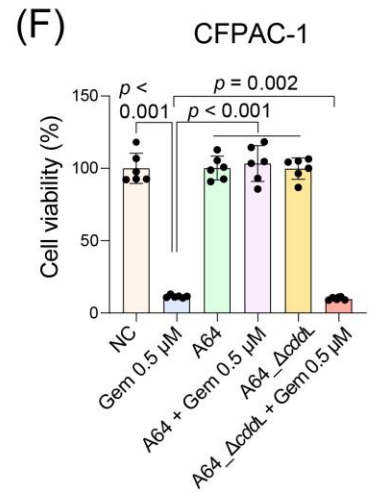
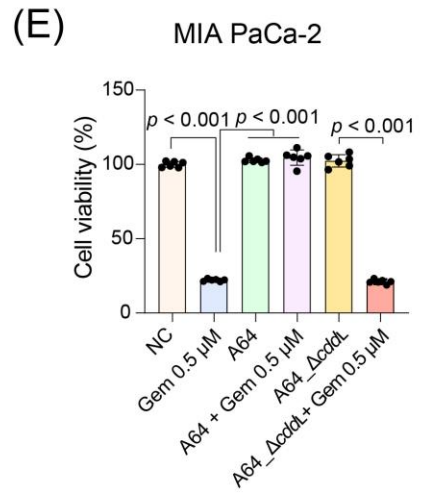
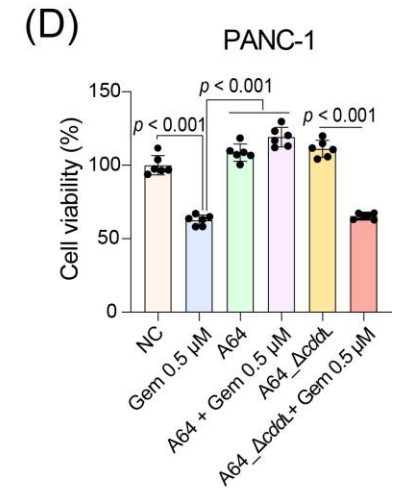
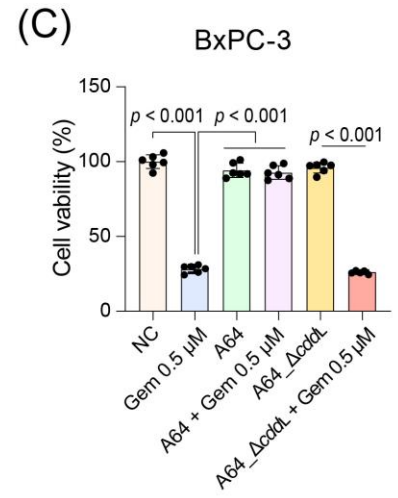
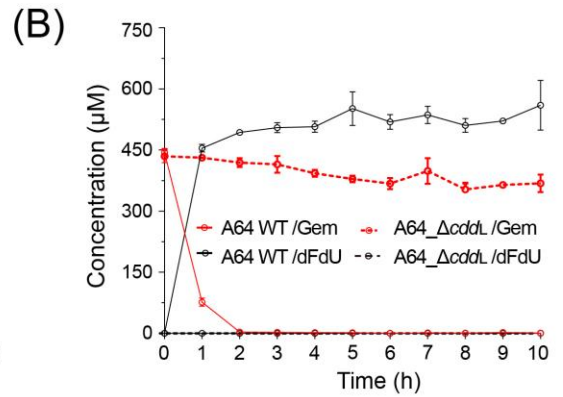
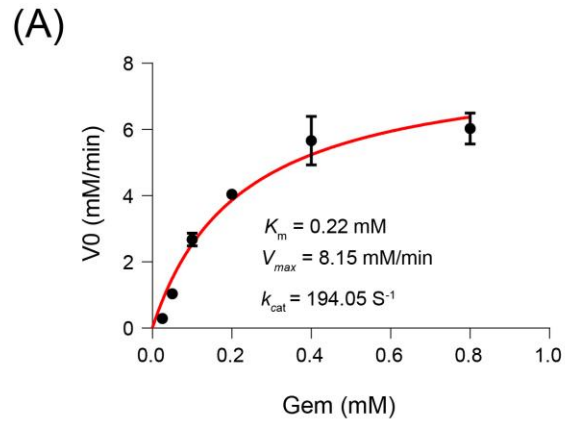


Intratatumoral *Enterobacter hormaechei* drives gemcitabine resistance



- Screening and identification of the most potent drug-inactivating strain
- Rapid pharmacokinetic metabolic conversion
- Severe chemoresistance validated *in vitro* and *in vivo*
- Identification *Enterobacter* spp. as an independent clinical risk factor

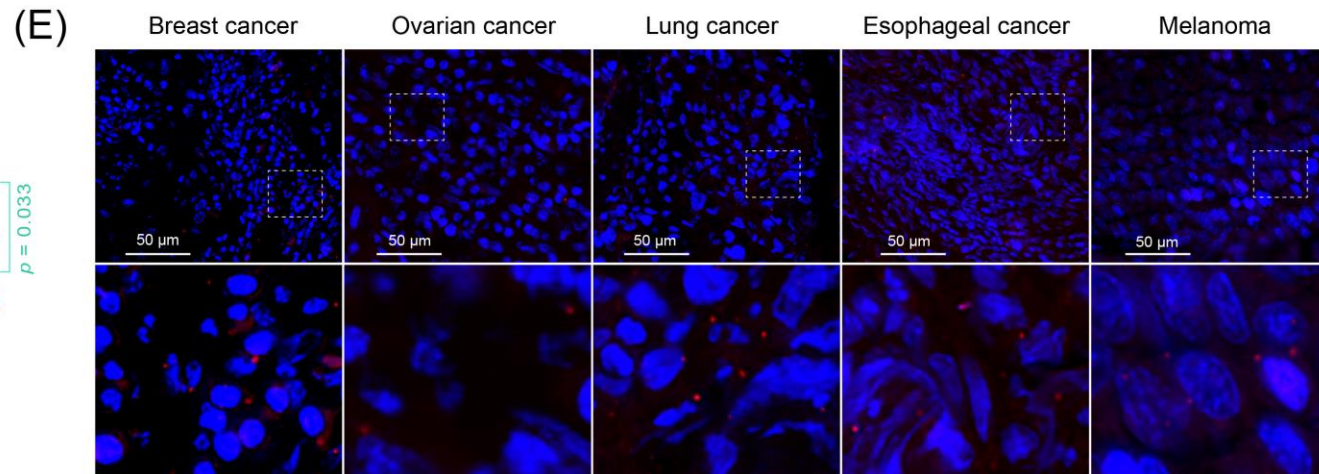
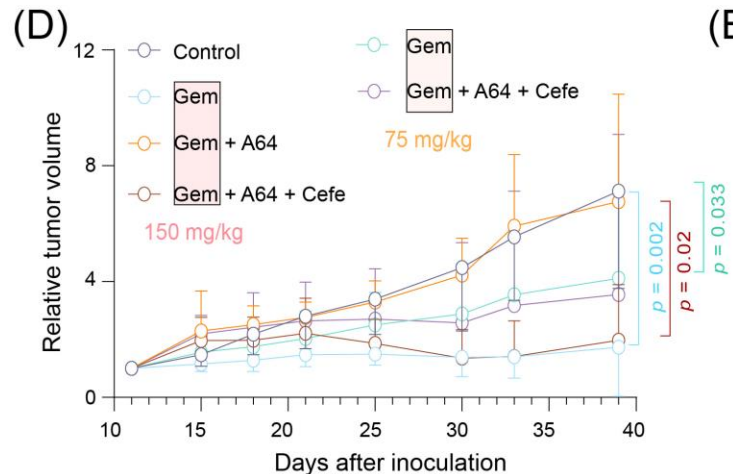
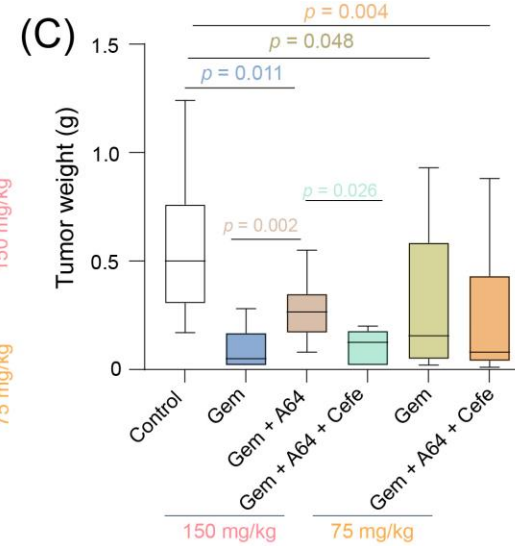
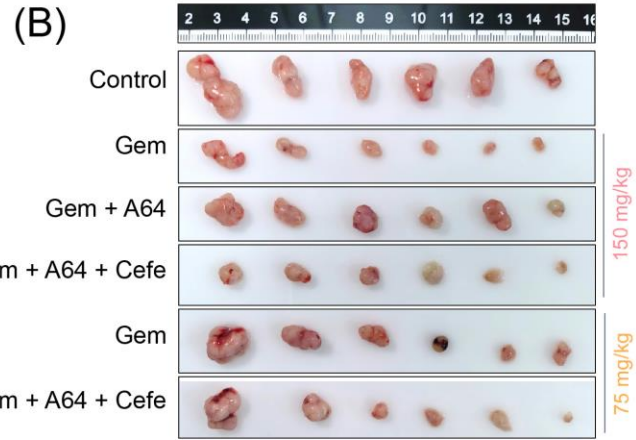
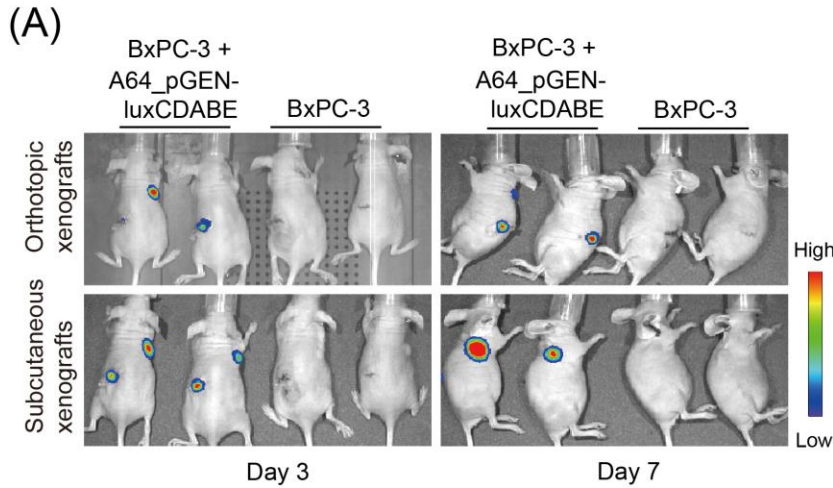
Cytidine deaminase drives gemcitabine resistance in *Enterobacter hormaechei*



- Identification of a unique long-isoform deaminase gene
- Establishment of causality via knockout mutant
- High catalytic efficiency of the purified protein
- Full restoration of drug efficacy *in vitro* and *in vivo*



Antibiotic-mediated eradication restores gemcitabine efficacy and implicates *Enterobacter* as a pan-cancer therapeutic target



✓ Therapeutic targeting reverses chemoresistance and optimizes dosage.

✓ Pan-Cancer ubiquity of *Enterobacter*-mediated chemoresistance.



Summary

- This study demonstrates that intratumoral *E. hormaechei*, prevalent across a spectrum of solid tumors, drives chemoresistance through highly efficient CDD_L-mediated inactivation of gemcitabine.
- Targeted bacteria eradication with antibiotics not only fully reverses this resistance but also enables a 50% reduction in the effective chemotherapy dose, offering a highly clinically translatable paradigm to overcome microbe-driven treatment failure.

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