Microbiome—pancreatic cancer crosstalk: from tumor biology to therapeutic intervention

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Introduction

The Intratumoral Microbiome in Pancreatic Cancer: Mechanisms, Clinical Impact, and Therapeutic Strategies

Origin & Composition

Gut/oral microbes translocate via ductal, hematogenous & biliary routes

Pro-tumor taxa (Pseudomonas, F. nucleatum) vs. protective taxa (Lactobacillus, Bifidobacterium)

Mechanisms Driving Progression

Immune suppression: MDSCs/M2 polarization → $CD8^+$ T-cell exhaustion

Metabolic reprogramming: H_2S/acetaldehyde promote; 3-IAA sensitizes to chemotherapy

Stromal remodeling: CAF activation → desmoplasia → drug barrier

Therapeutic Strategies

Precision antibiotics (ciprofloxacin, metronidazole)

Fecal microbiota transplantation (FMT)

Dietary modulation (tryptophan, Mediterranean diet)

Engineered microbes / EVs (preclinical)

Clinical Impact

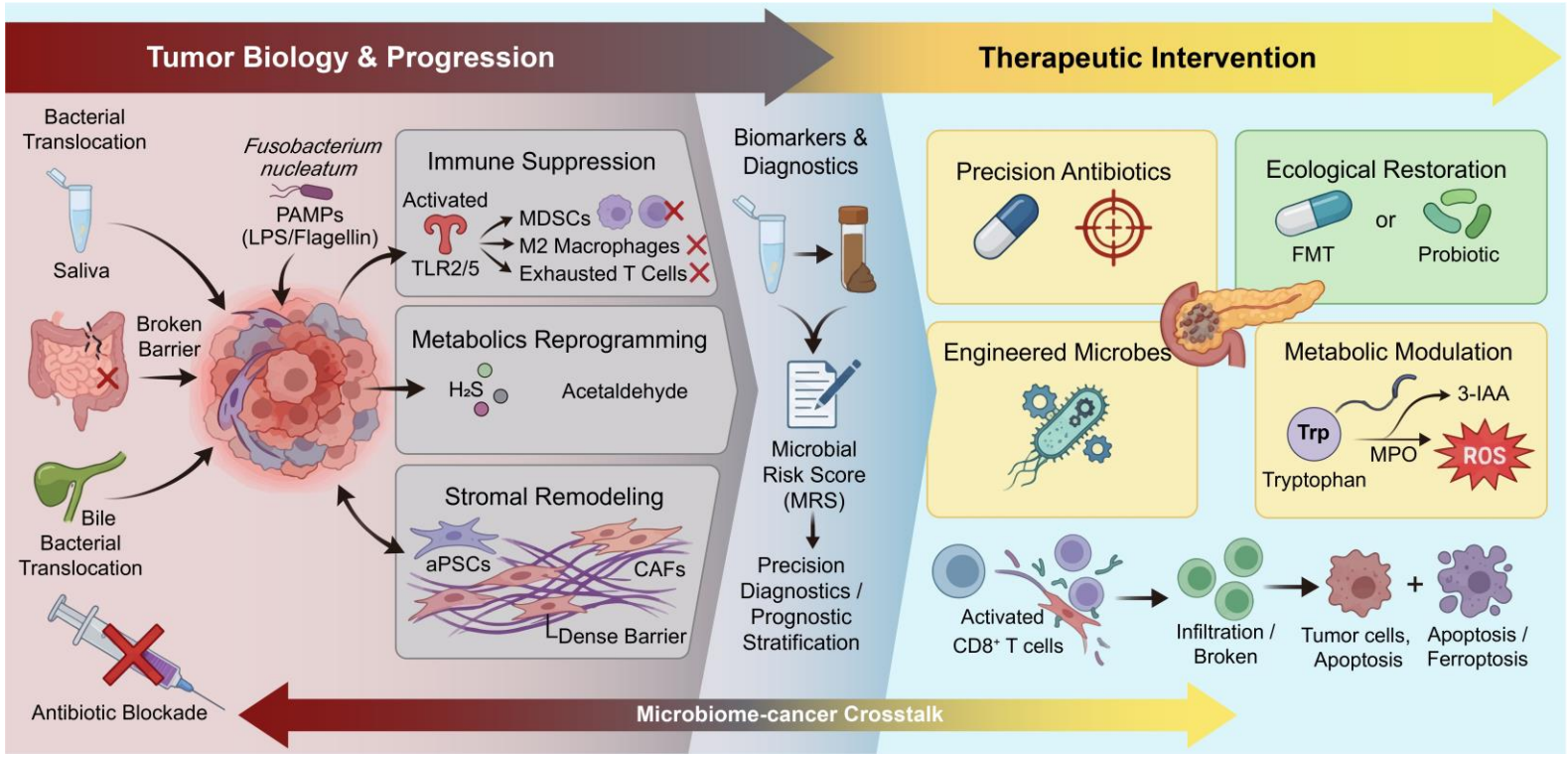
- Chemoresistance: γ-proteobacteria inactivate gemcitabine via CDA
- Immunotherapy failure: *F. nucleatum* drives PD-1/PD-L1 resistance
- Prognosis: 11-taxa microbial risk score predicts survival

Challenge: **From correlation to causation: standardization & multi-cohort validation**

Targeting the microbiome offers new hope to overcome therapy resistance in pancreatic cancer.

Highlights

- The intratumoral microbiome of pancreatic tumors originates primarily via ductal, hematogenous, and biliary routes, and its composition differs significantly from that of normal pancreatic tissue as well as the gut and oral microbiomes.
- Intratumoral microorganisms drive the initiation and progression of pancreatic cancer through multiple mechanisms, including immunosuppression, metabolic reprogramming, and pro-fibrotic stromal remodeling.
- Specific microbial species and their metabolites can substantially weaken the efficacy of standard chemotherapy and immunotherapy.
- Although most microbiome-targeted therapeutic strategies—including precision antibiotics, fecal microbiota transplantation, and engineered bacteria—remain at the preclinical stage, they represent an emerging direction for overcoming therapeutic resistance.



Intratumoral Microbiome in Pancreatic Cancer: Mechanisms and Clinical Intervention Strategies

This work elucidates the biological mechanisms by which the microbiome drives pancreatic cancer progression and therapeutic resistance, systematically reviews the latest non-invasive diagnostic biomarkers, and highlights the strategic advantages of remodeling the tumor microenvironment through microbiome-targeted interventions, thereby providing a comprehensive and cutting-edge framework for addressing this formidable clinical challenge.

Figure 1. Origins and Migratory Routes of the Intratumoral Microbiome in Pancreatic Cancer

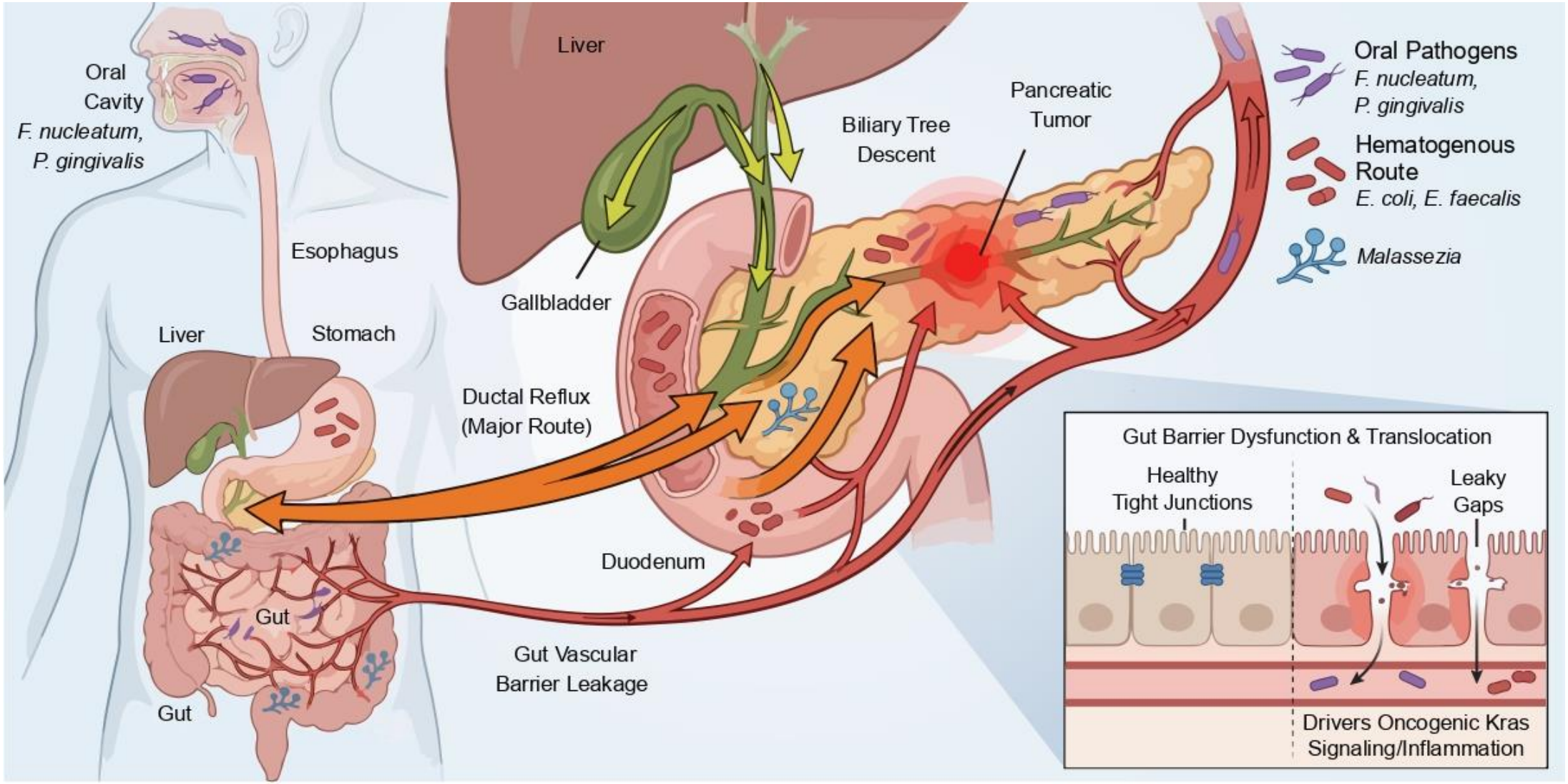


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Figure 2. Host, Lifestyle, and Environmental Determinants of the Pancreatic Cancer-Associated Microbiome

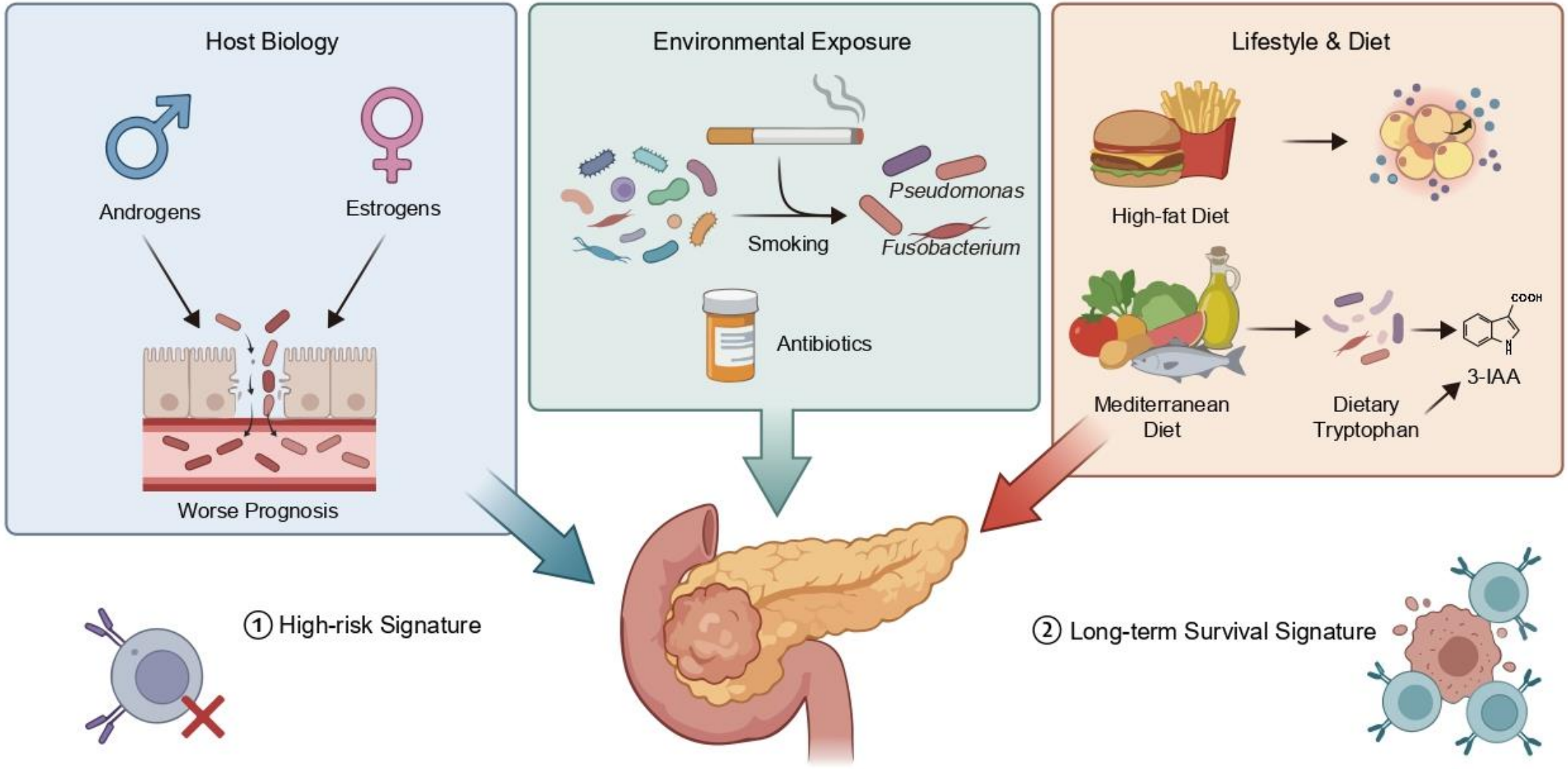

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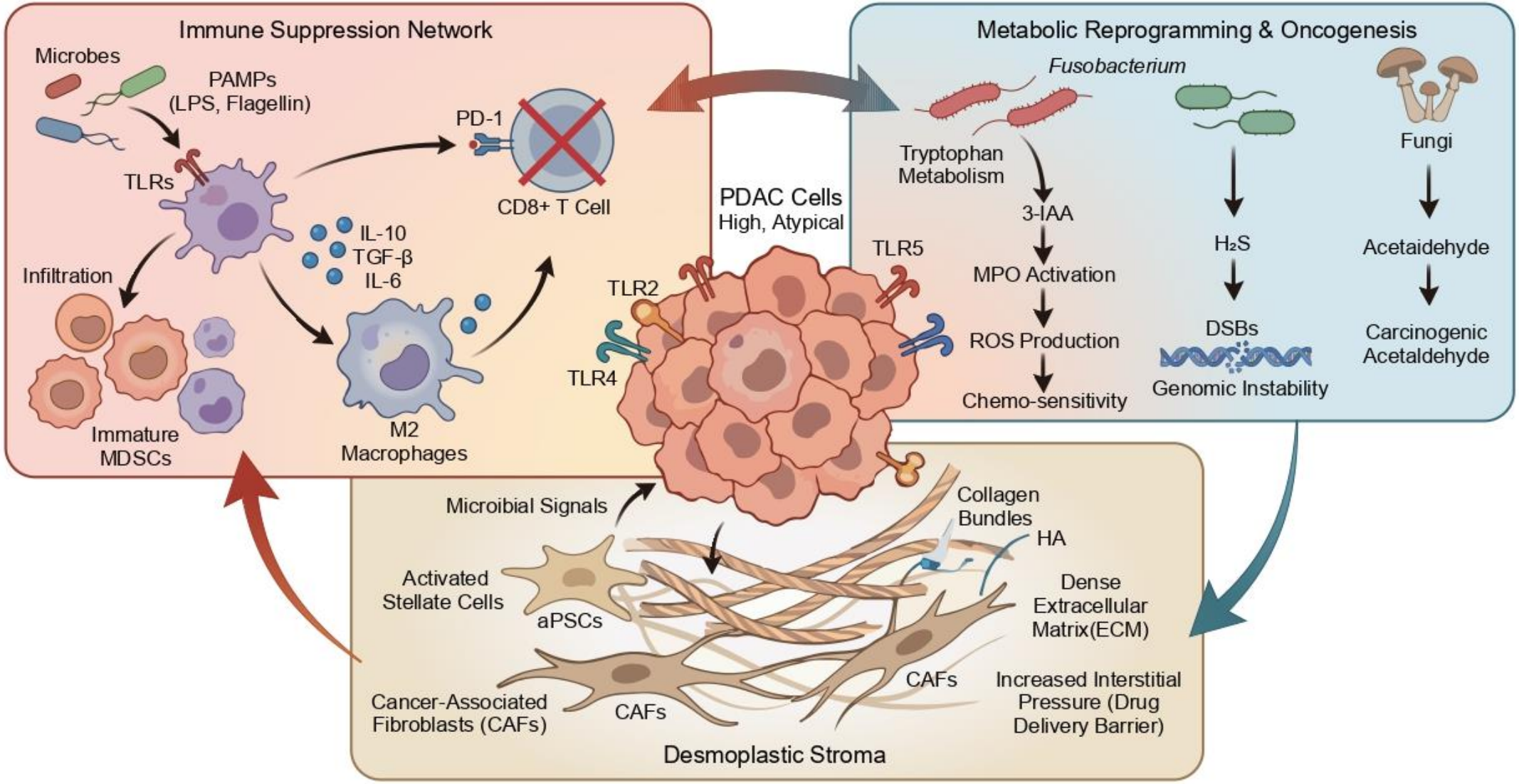
Figure 3. Integrated Mechanisms of Microbiome-Driven Tumor Microenvironment Remodeling



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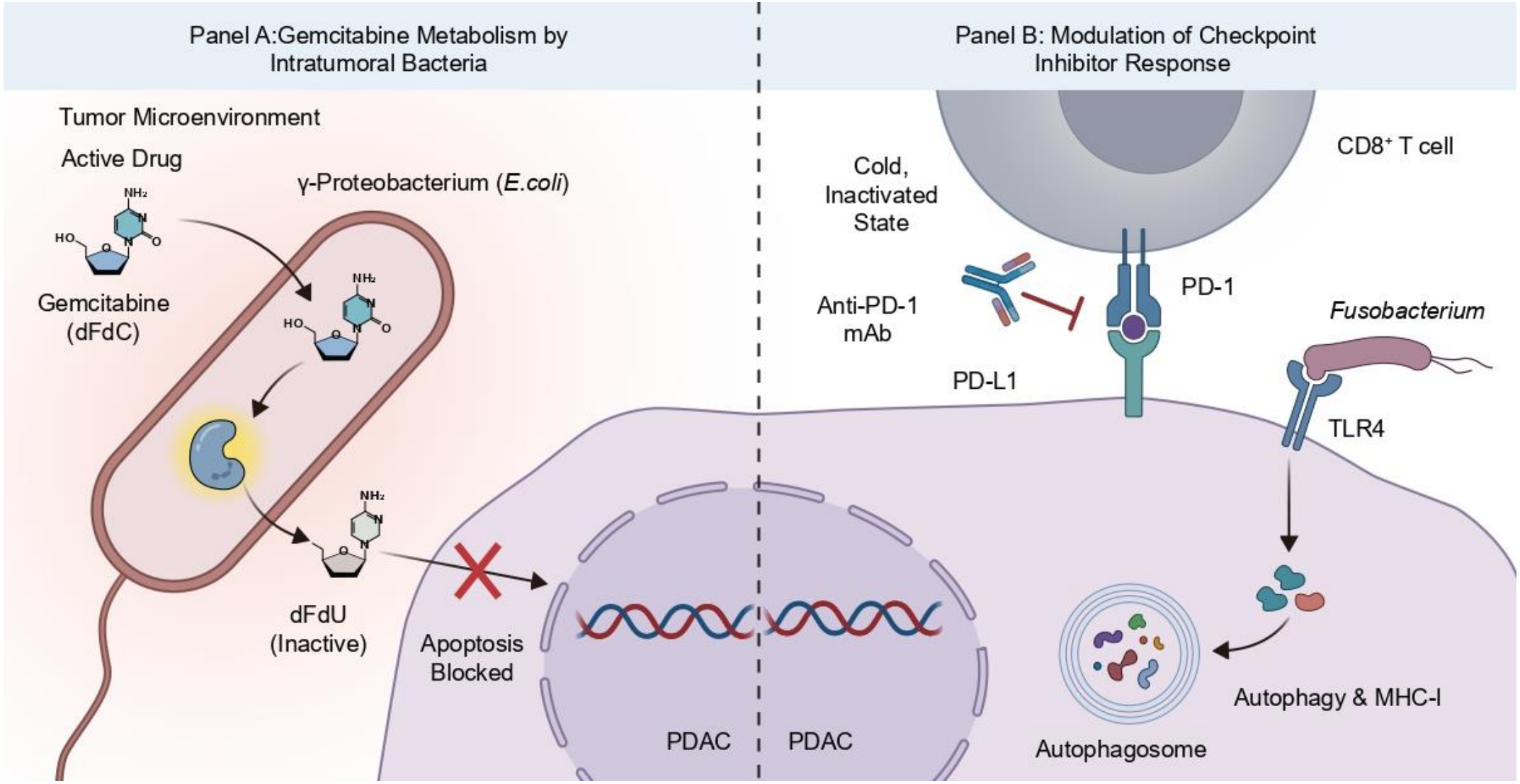

Figure 4. Microbial Mechanisms of Therapeutic Resistance in Pancreatic Cancer

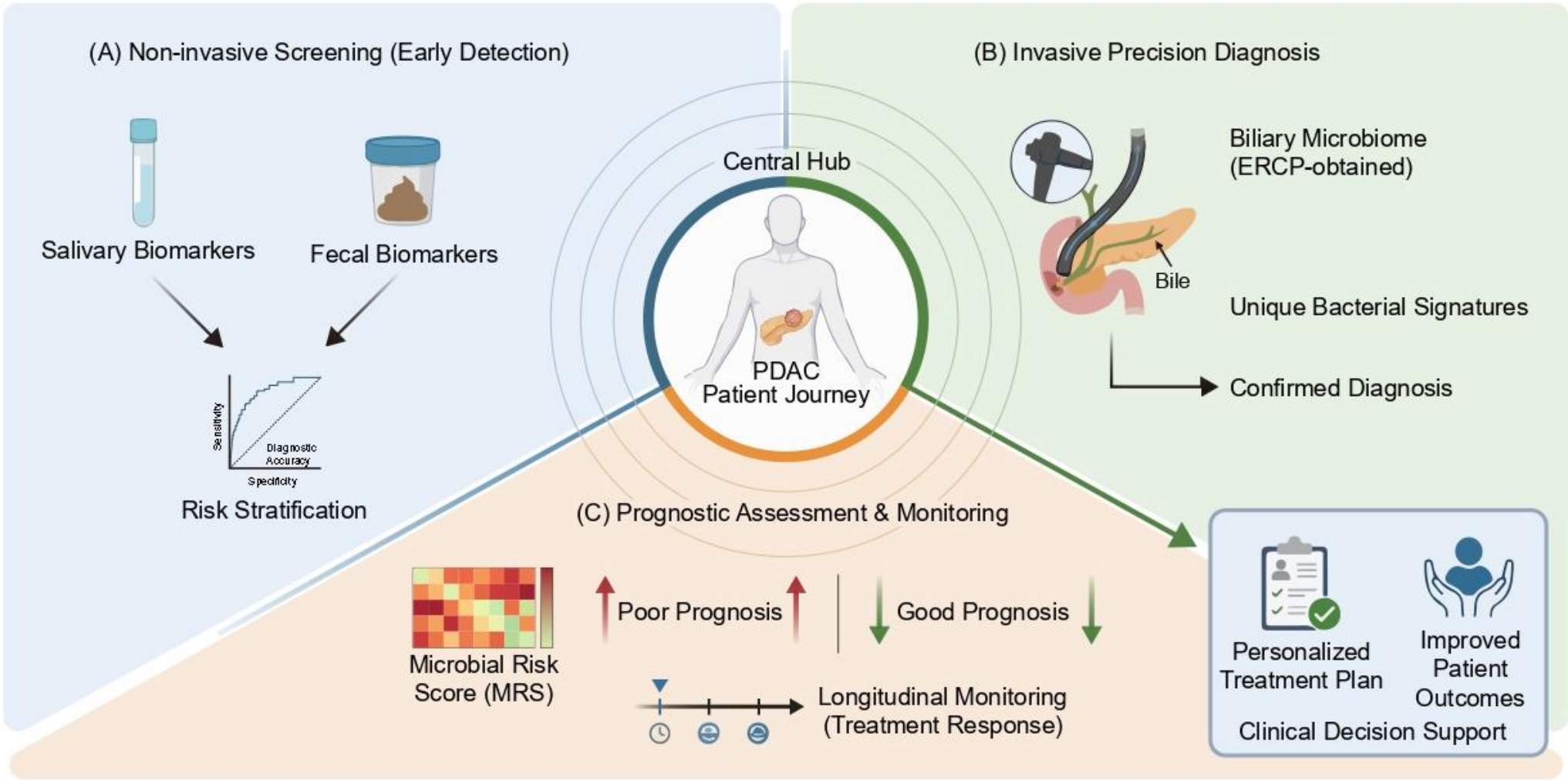

Figure 5. Clinical Application of Microbiome-Based Biomarkers in Pancreatic Cancer

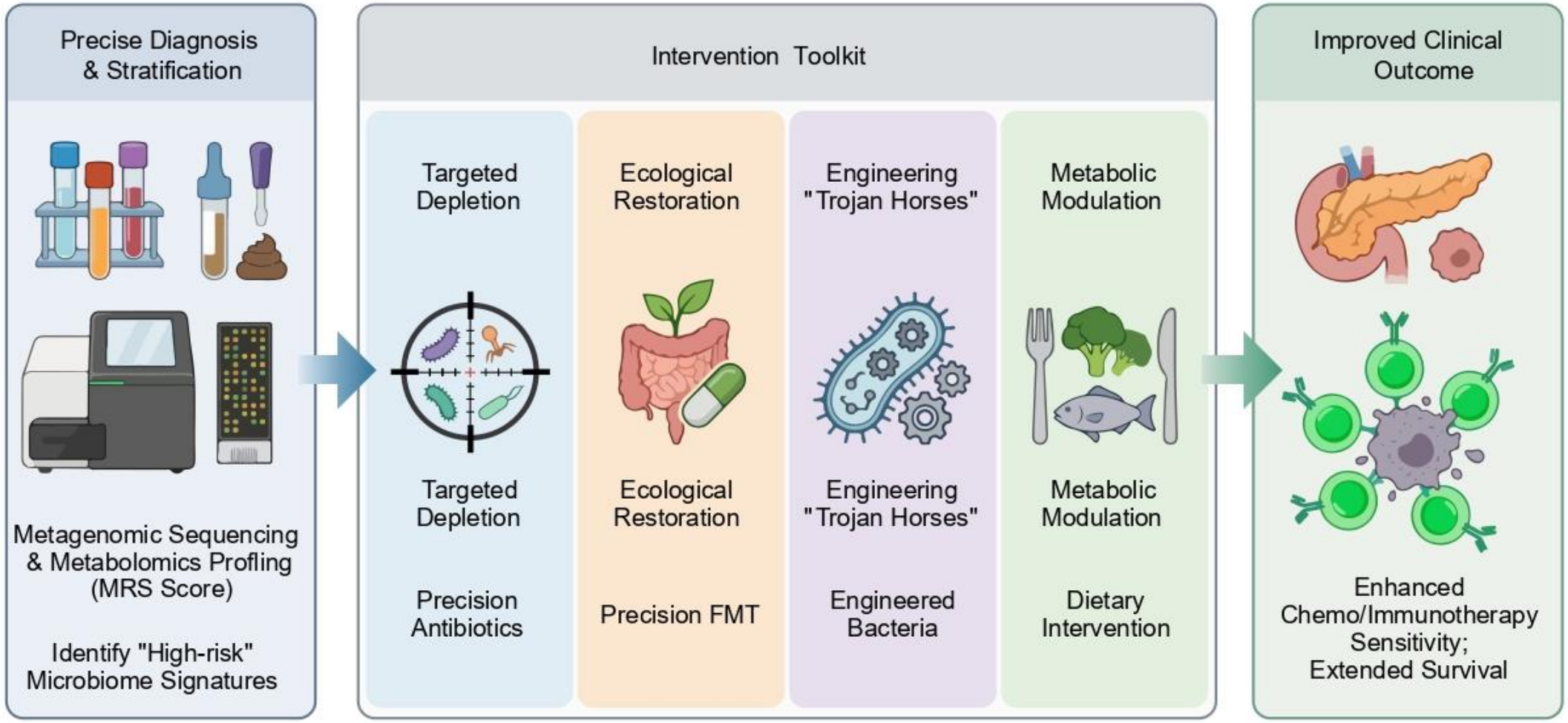

Figure 6. Toward Microbiome-Based Personalized Interventions for Pancreatic Cancer

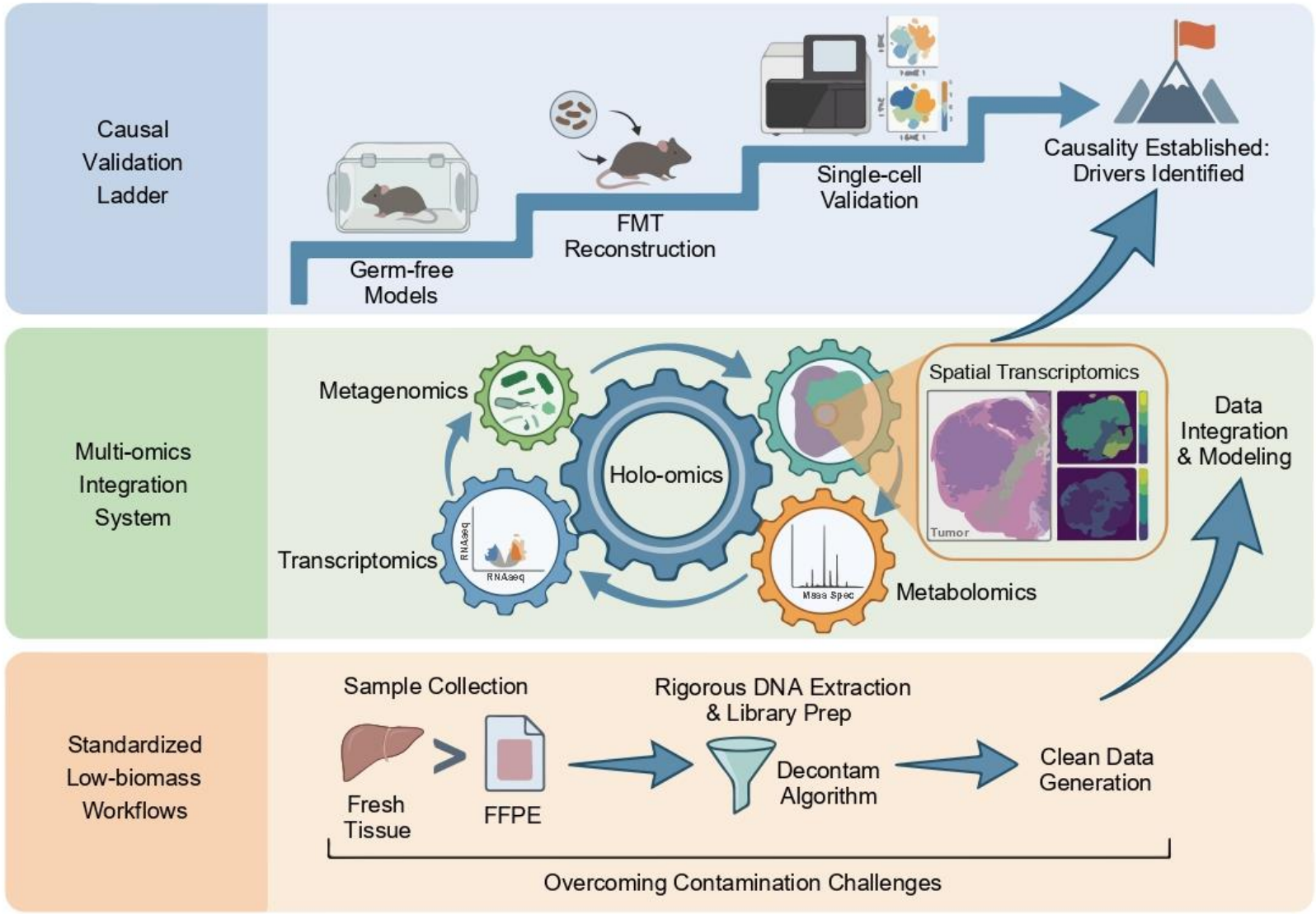

Figure 7. Methodological Framework for Establishing Causal Microbiome–Tumor Interactions in Pancreatic Cancer

Summary

- **Tumor Microbiome Characteristics**
  Proteobacteria-dominated composition with reduced diversity, enrichment of Pseudomonas and Fusobacterium, and protective association with Lactobacillus.
- **Three Major Sources and the "Gut–Pancreas Axis"**
  Translocation of oral and gut microbiota to the pancreas via the pancreatic duct, hematogenous route, and biliary tract; pancreatic enzyme insufficiency leading to dysbiosis, which in turn establishes a vicious cycle.
- **Driving Mechanisms: Immune + Metabolic + Stromal**
  TLR → MDSC/M2 → $CD8^+$ exhaustion; H_2S/acetaldehyde promotes DNA damage; CAF activation → fibrotic barrier
- **Therapeutic Resistance**

Gammaproteobacteria inactivate gemcitabine; Fusobacterium nucleatum induces autophagy, leading to ICI failure.

- **Clinical Translation**

Early screening using salivary and fecal microbiota; a risk score based on 11 microbial species for prognosis; precision antibiotics, fecal microbiota transplantation (FMT), engineered bacteria, and dietary interventions.

- **Challenges and Future Directions**

Low-biomass contamination requires standardization; transitioning from correlation to causation (using germ-free mice, FMT, and single-cell approaches); incorporation of fungi and viruses.

The intrapancreatic microbiome serves as a "hidden regulator," and its systematic characterization combined with targeted intervention holds promise for breaking through current therapeutic bottlenecks in pancreatic cancer.

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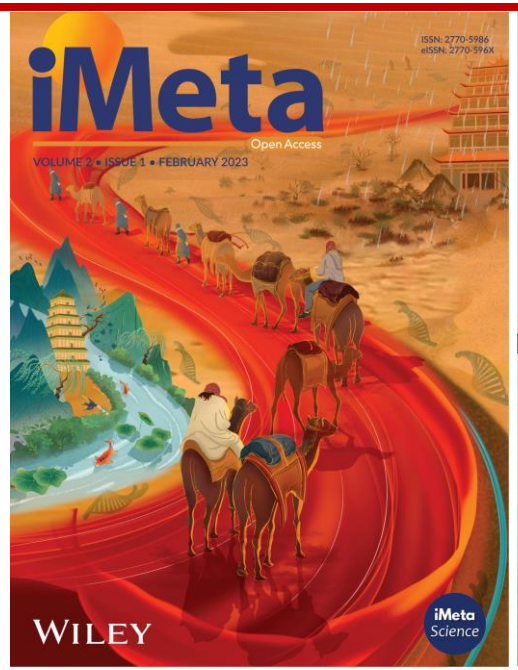

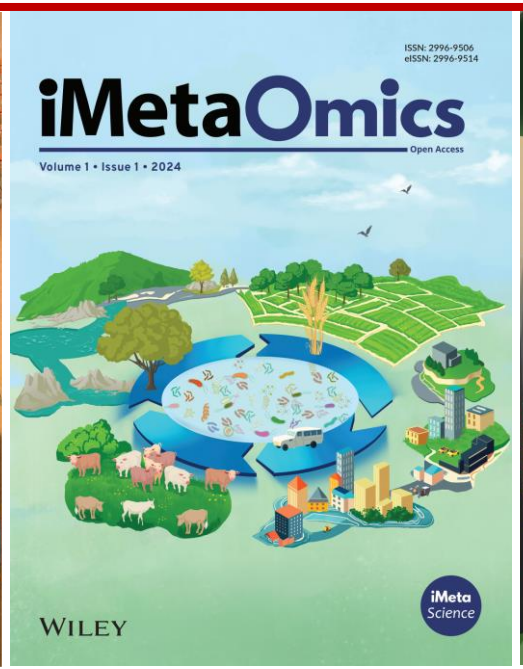

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