



A New Evaluation System for Drug-microbiota Interactions

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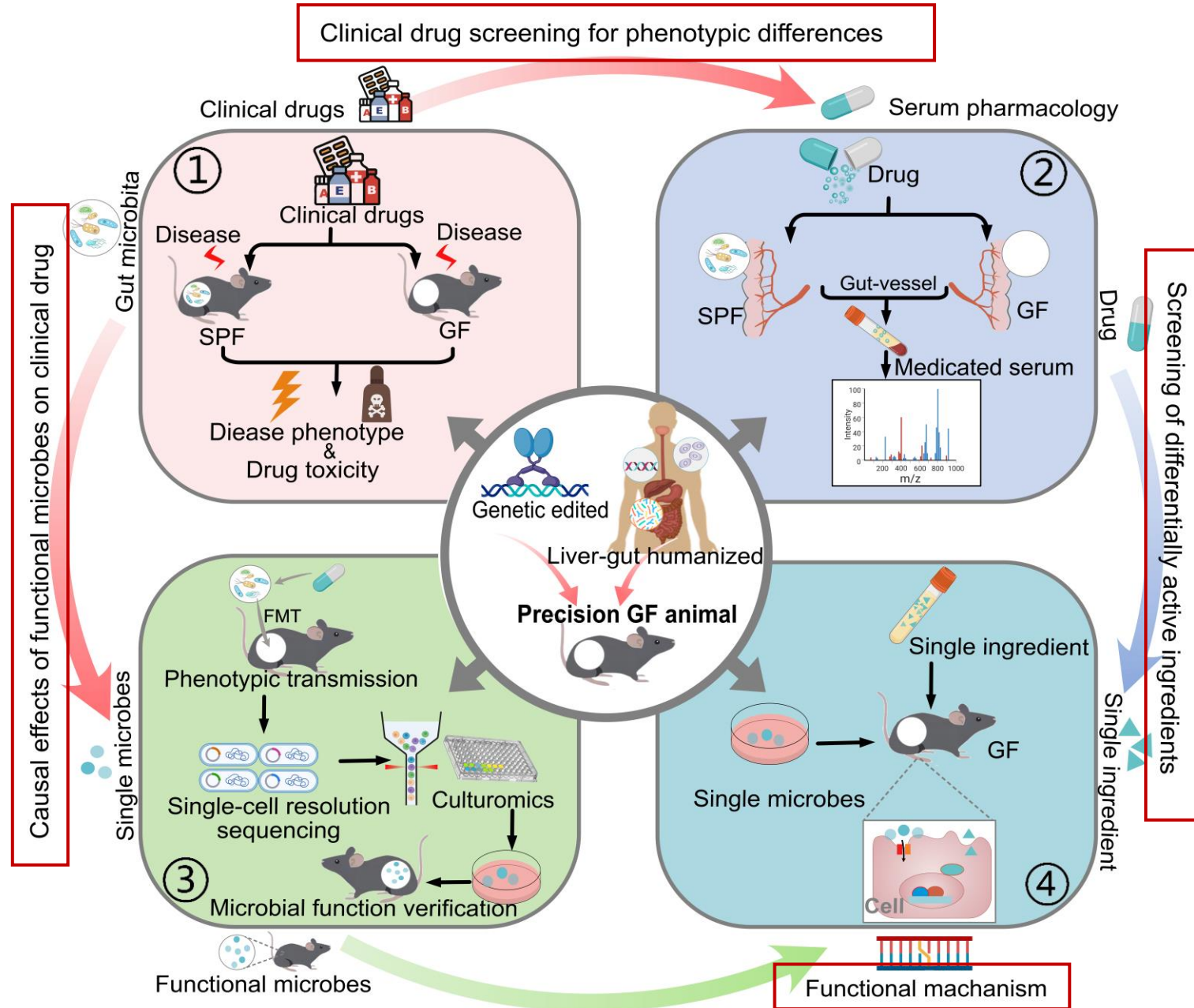
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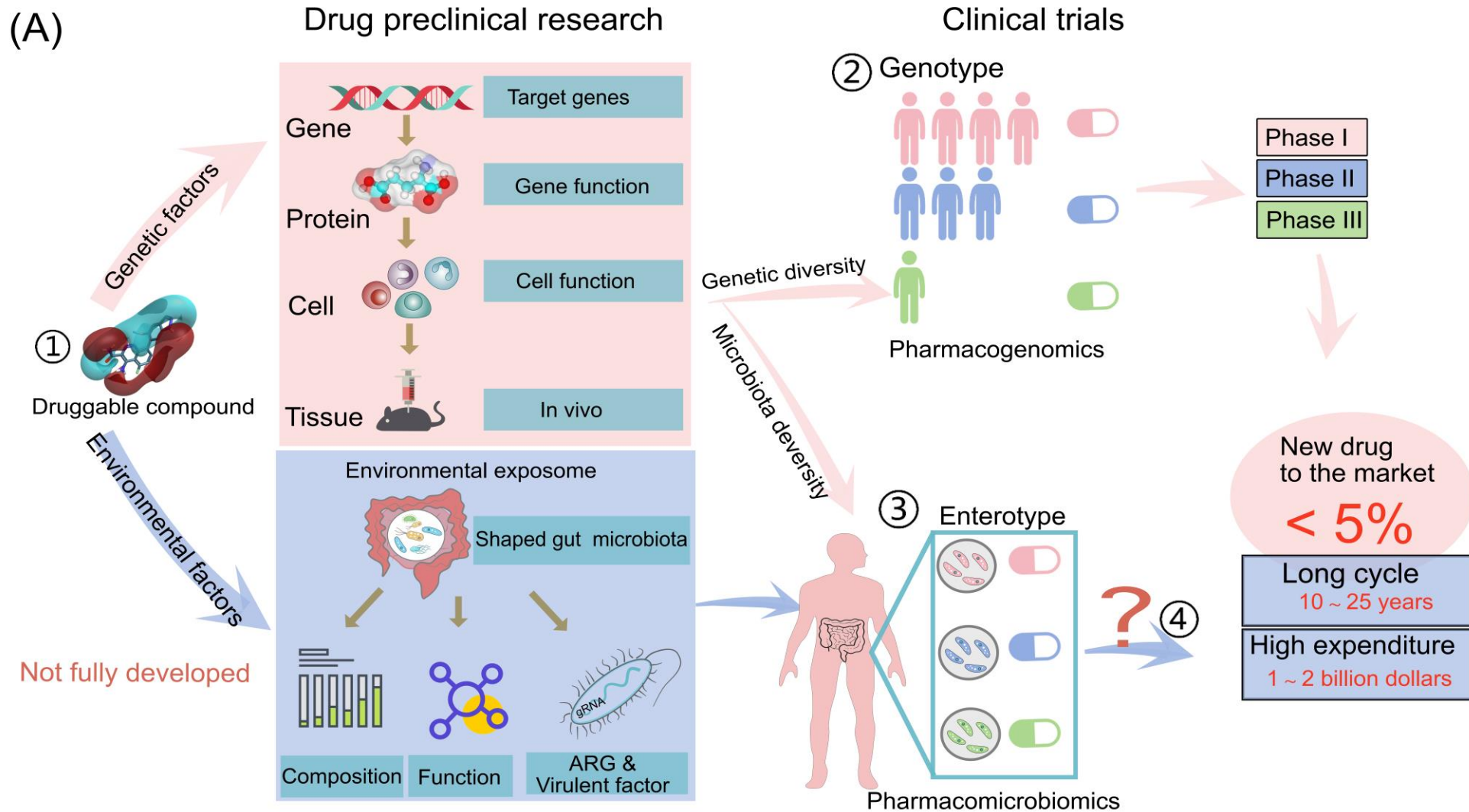
Introduction





Clinical significance of gut microbiota

—pharmacological studies & drug-targeting genes regulation



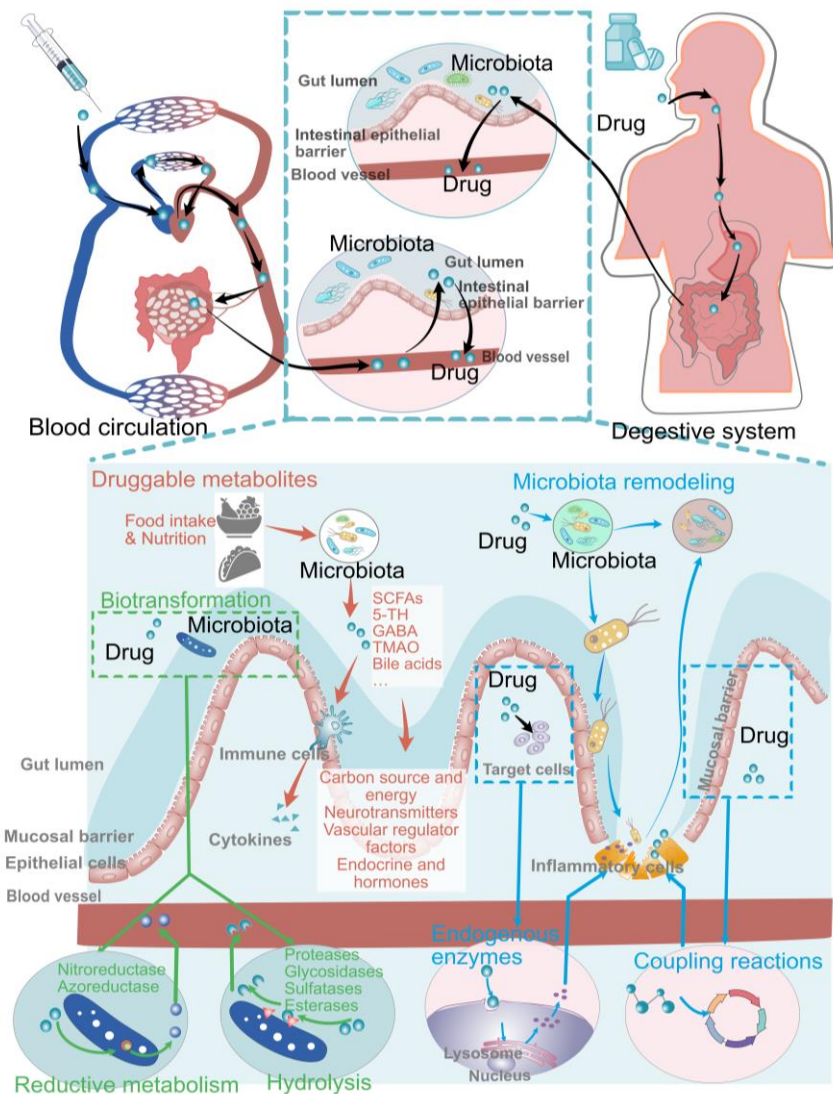
Gut microbiota, a vital interface between human body and environment, intuitively mirrors human adaptation to it.

Maximize gut microbiota's value in drug efficacy evaluation & cut new drug development waste.

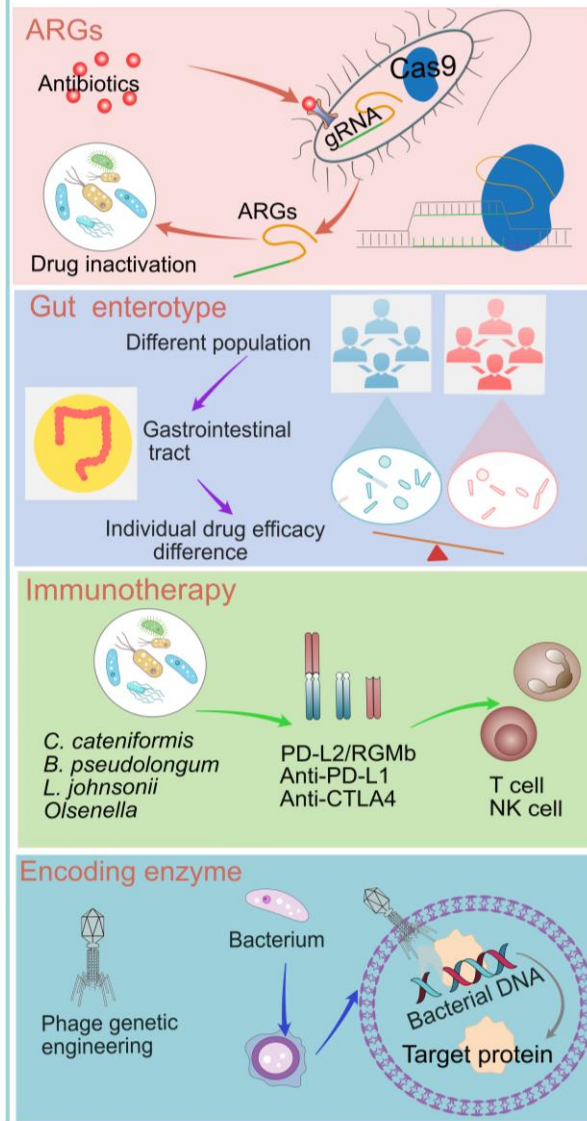
Clinical significance of gut microbiota

— pharmacological studies & drug-targeting genes regulation

(B) Gut microbiota — host IVDR — drug ADME



(C) Gut microbiota — drug — genes



Potential feasibility of gut microbiota as an evaluation criterion for evaluating individual differences in drug efficacy:

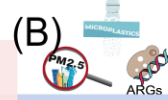
- ★ Involvement of gut flora in drug ADME;
- ★ Interaction of gut flora with drug-targeting genes.

Environmental factors affecting gut microbiota



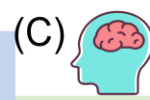
(A) Natural conditions

| | |
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| <p><i>Collinsella</i> ↑ <i>Bifidobacterium</i> ↑ Lachnospiraceae ↑ Veillonellaceae ↑ Clostridiales ↑ <i>Akkermansia</i> ↑ Ruminococcaceae ↑ Prevotellaceae ↑ Muribaculaceae ↑ <i>Rikenellaceae</i> ↑ Bacteroidaceae ↑ <i>Quinella</i> ↑ <i>Rothia</i> ↑ <i>Senegalimassilia</i> ↑ <i>Sutterella</i> ↓ <i>Escherichia</i> ↓ <i>Shigella</i> ↓ Cyanobacteria ↓ Comamonadaceae ↓ Sinobacteraceae ↓ Lactobacillaceae ↓ <i>Erysipelotrichaceae</i> ↓ <i>Lactobacillus</i> ↓ Lachnospiraceae ↓ Ruminococcaceae ↓</p> | <p>Cold exposure and stress -- Thermoregulation -- Energy saving and homeostasis -- Brown adipose tissue and white fat browning -- Glucose and lipid metabolism -- Colonic mucosal barrier -- Brain gut peptide neuroregulation -- Cold-induced hypertension -- SCFAs such as butyric and isovaleric acids -- Insulin sensitivity -- Isovaleric acids and arginine and proline metabolism pathway -- Rheumatoid arthritis</p> |
| <p><i>Lactobacillus</i> ↑ <i>Oscillospira</i> ↑ <i>Escherichia Shigella</i> ↑ <i>Acinetobacter</i> ↑ <i>Klebsiella</i> ↑ <i>Ruminiclostridium</i> ↓ <i>Blautia</i> ↓ Lachnospiraceae NK4A136 group ↓ <i>Clostridium VadinBB60</i> ↓ Muribaculaceae ↓ <i>Blautia</i> ↓ <i>Allobaculum</i> ↓ <i>Peptostreptococcus anaerobius</i> ↓ <i>Streptococcus</i> ↑ Ratio of Firmicutes and Proteobacteria ↑ Bile acids producing gut microbiota ↑</p> | <p>Heat exposure and stress -- Heat illness -- Host resistance to viral pathogens including influenza virus and SARS-CoV-2 -- Neural development in early life -- Inflammation and renal injury -- Intestinal barrier -- Glycolipid metabolism and mitochondrial dysfunction during pregnancy</p> |
| <p><i>Prevotella</i> ↑ Prevotellaceae ↑ Porphyromonadaceae ↑ Streptococcaceae ↑ <i>L. johnsonii YH1136</i> (-) Enteric fermenting anaerobes ↑ <i>Odoribacter</i> ↑ Bacteroides ↑ Parabacteroides ↑ <i>Alistipes</i> ↑ <i>Akkermansia</i> ↑ <i>Weissella</i> ↓ <i>Saccharibacteria</i> ↓ <i>Enterobacter</i> ↓ <i>Gemella</i> ↓</p> | <p>High altitude hypoxia -- GI function -- Acute mountain sickness -- High-altitude heart disease -- SCFAs and BAs -- Drug metabolism such as aspirin and irbesartan -- Intestinal injury -- Alcohol metabolism</p> |



(B) Environmental pollution

| | |
|---|---|
| <p><i>Oribacterium</i> ↓ <i>Shuttleworthia</i> ↓ <i>Cyanobacteria</i> ↓ <i>Deferribacteres</i> ↓ Bacteroides ↓ <i>Lactobacillus</i> ↓ <i>Prevotella</i> ↓ <i>Butyrivibrio</i> ↓ <i>Paraprevotella</i> ↓ <i>Enterococcus</i> ↑ <i>Ruminococcus</i> ↑</p> | <p>PM 2.5 exposure -- Insulin resistance and sphingolipid metabolism -- Pulmonary microbiota imbalance and metabolic disorders -- Allergic asthma -- SCFAs -- Lung cancer -- Glucose metabolism -- Obesity during pregnancy</p> |
| <p><i>Staphylococcus</i> ↑ <i>Parabacteroides</i> ↓ Firmicutes ↓ α-Proteobacteria ↓ Bacteroides ↑ <i>Dethiosulfonitroreductase</i> ↑ Enterobacteriaceae ↑ Lachnospiraceae NK4A136 group ↑ <i>Akkermansia</i> ↓ Bacteroides ↓ Ruminococcaceae UCG014 ↓ <i>Mucispirillum</i> ↓ <i>Helicobacter</i> ↓ Bacteroides ↑ <i>Prevotellaceae</i> UCG001 ↓</p> | <p>Microplastic exposure -- Colon and duodenum inflammation -- Hepatic lipid disorder -- Colonic mucin -- Intestinal function in children -- Insulin resistance -- Hepatotoxicity -- Hematopoietic function -- Male testicular disorder</p> |
| <p>Resistance genes Sulfonamide Multidrug Vancomycin</p> | <p>ARGs exposure -- Water environment -- Aquatic environment -- Contaminated soils</p> |
| <p><i>Lactobacillus</i> ↓ <i>Bacteroides acidifaciens</i> ↑ <i>Ruminococcus gauvreauii</i> ↑ <i>Akkermansia</i> ↓ Parabacteroides ↓ Enterobacteriaceae ↓ <i>Blautia</i> ↓ <i>Erysipelatoclostridium</i> ↓ <i>Parasutterella</i> ↑ Ruminococcaceae ↑ Lachnospiraceae ↓ Enterococcaceae ↓</p> | <p>Radiation exposure -- Gut microbiota-derived indole 3-propionic acid -- Gut commensal derived-valeric acid -- Concentrations of microbially derived propionate and tryptophan metabolites -- Gut microbiota-derived L-Histidine and its secondary metabolite imidazole propionate (ImP) -- Drug metabolism such as yellow wine polyphenolic compound, baicalein, quercetin, D-galactose and botanical lycium barbarum, etc.</p> |
| <p>Environmental heavy metal exposure -- Lead (Pb), cadmium, mercury, etc.</p> | |



(C) Psychological factors & stress

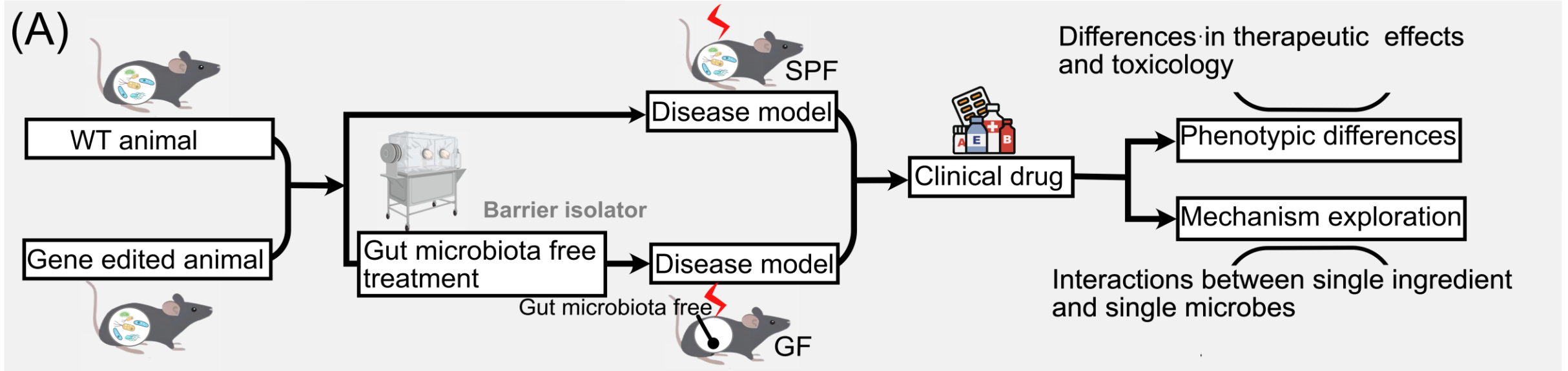
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|---|---|
| <p><i>Akkermansia</i> ↓ <i>Lactobacillus</i> ↓ Enterobacteriaceae ↑ <i>E. coli</i> ↑ <i>Tuncibacter</i> ↑ Ruminococcaceae ↑ <i>Candidatus Arthromitus</i> ↑ <i>Enterobacter</i> ↑ <i>Lactobacillus</i> ↓ <i>Muribaculum</i> ↓ <i>Monoglobus</i> ↓ <i>Parasutterella</i> ↓ <i>Helicobacter</i> ↑ <i>Oscillibacter</i> ↑ Parabacteroides ↓ Ruminococcus ↓ <i>Prevotella</i> ↓ <i>Bacteroides acidifaciens</i> ↓ Erysipelotrichaceae ↓ <i>Akkermansia muciniphila</i> ↑ <i>Anaerostipes</i> ↑ <i>Lactobacillus reuteri</i> ↓</p> | <p>Neuroinflammatory and immunity -- Increased differentiation in colonic interleukin (IL)-17-producing γδ T cells (γδ17 T cells) and their meningeal accumulation -- Interferon-γ (IFN-γ) and the tumor necrosis factor-alpha (TNF-α) in the hippocampus -- IL-22 and mucosal barrier integrity in Crohn's disease -- Regulatory T cell (Th17/Treg) imbalance promoting resilience to stress-induced anxiety- and depressive-like behaviors -- Autophagy in inflammatory bowel disease -- Inflammatory signals in acute sleep deprivation -- Neurotransmitters and inflammatory factors in chronic restraint stress (CRS)-induced depression -- Serotonin and dopamine neurotransmission pathways in the brainstem and adult hippocampal (HPC) neurogenesis -- Inflammation and hyperglycemia caused by social overcrowding</p> |
| <p><i>Segmented filamentous</i> ↑ <i>Enterococcus faecalis</i> ↓ Bacteroides ↑ <i>Prevotellaceae</i> UCG001 ↑ <i>Quinella</i> ↑ Veillonellaceae ↑ Bacteroidia ↑ Campylobacteria ↑ Negativicutes ↑ Bacteroidales ↑ Campylobacteriales ↑ <i>Alistipes</i> (-) <i>Clostridium IV</i> (-) <i>Clostridium XI</i> (-) <i>Faecalibacterium Blautia</i> (-)</p> | <p>Hypothalamic-pituitary-adrenal (HPA) axis -- IL-17A/Th17 cells and stress-induced vaso-occlusive episodes -- Corticosterone production and social behaviour -- Estrogen receptor β (ERβ) in inflammatory bowel disease -- Stress-induced hypertension -- Glucocorticoid receptor</p> |
| <p>Ruminococcaceae ↑ Porphyromonadaceae ↑ Lactobacillaceae ↓</p> | <p>Endocannabinoid (eCB) signaling -- Depressive-like behaviors</p> |
| <p>Drug metabolism -- Probiotics, prebiotics, and neurotransmitter metabolites derived from gut microbiota, such as 5-HT, indole, glutamatergic and gamma-aminobutyric acid (GABA), and SCFAs -- Antidepressants such as Venlafaxine, (R)-ketamine, Lanicemine, Fluoxetine and Agomelatine (AGO)</p> | |



(D) Life style

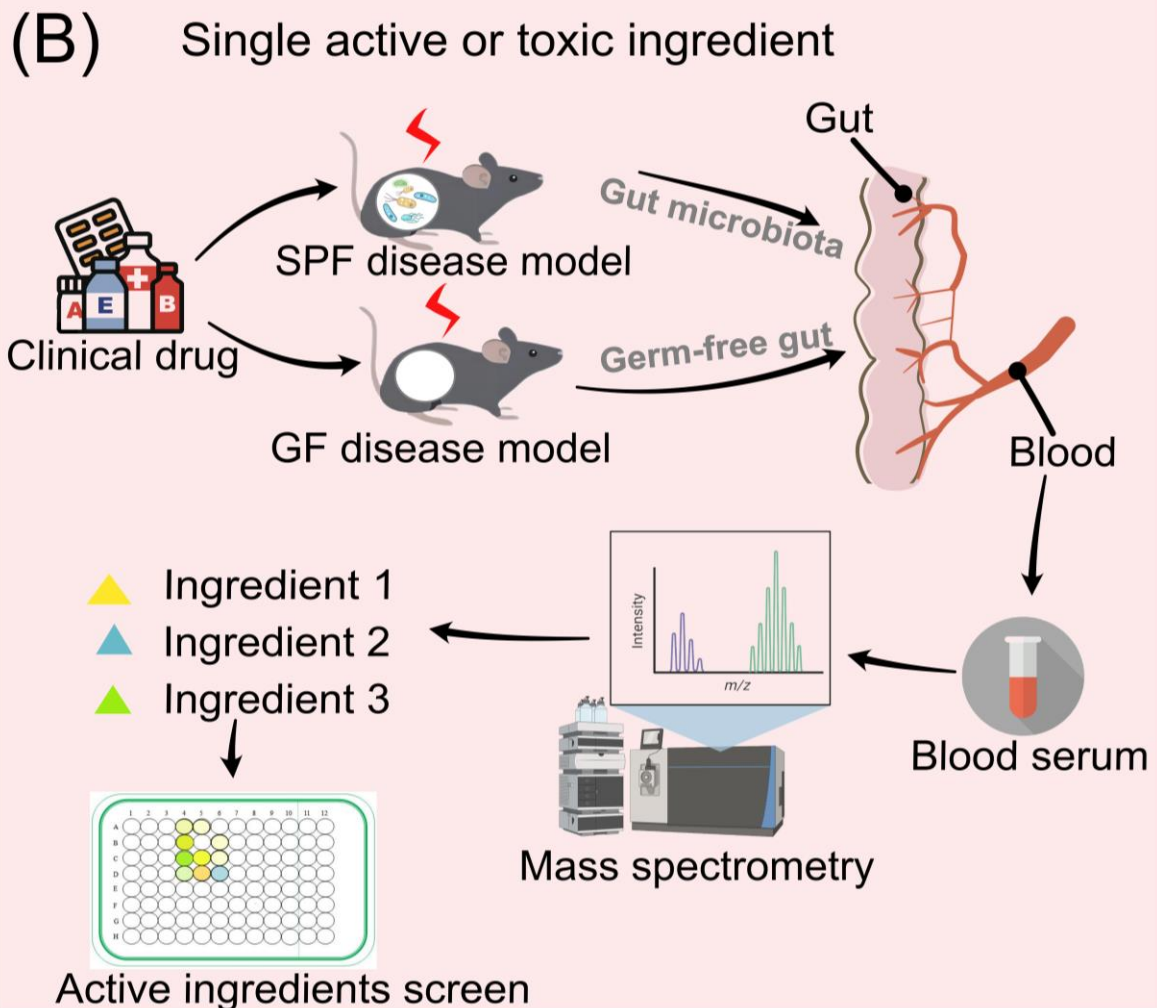
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| <p>Firmicutes ↑ Bacteroidetes ↓ <i>Blautia producta</i> ↑ Clostridia ↓ Ruminococcaceae ↓ <i>Akkermansia</i> ↓ <i>Eubacterium fissicatena</i> group ↑ <i>Romboutsia</i> ↑ <i>Erysipelatoclostridium</i> ↓ <i>Escherichia coli</i> ↑ <i>Proteobacteria</i> ↑</p> | <p>Western diets (High fat and high sugar) -- Hypothalamic inflammation and adaptation -- Obesity and leptin sensitivity -- Non-alcoholic steatohepatitis -- Necrotising pancreatitis -- Paneth cell defects in Crohn's disease and other IBD -- Peripheral tryptophan-kynurenine metabolism -- Glucose intolerance</p> |
| <p>Lachnospiraceae NK4A136 ↑ <i>Faecalibacterium prausnitzii</i> ↑ <i>Eubacterium</i> ↑ <i>Roseburia</i> ↓ <i>Ruminococcus torques</i> ↓ <i>Prevotella</i> ↑</p> | <p>Mediterranean diet -- Weight loss -- Reduce frailty and inflammation -- Cardiometabolic health -- IBD</p> |
| <p><i>Intestinimonas</i> ↑ <i>Catenibacterium</i> ↑ Ruminococcaceae ↑ <i>Eggerthella lenta</i> ↑ Parabacteroides distasonis ↓ <i>Lactobacillus</i> spp ↓ Parabacteroides goldsteinii ↓</p> | <p>Smoking habits -- Neurotransmitter-associated metabolites -- Promote colon cancer -- Activate oncogenic MAPK/ERK signalling in colonic epithelium -- COPD -- Weight gain</p> |
| <p>Clostridiales order ↓ Bacteroidales order ↓</p> | <p>Alcohol dependence -- Alcoholic liver disease -- Altered sociability and depression -- Cardiometabolic health -- IBD -- Neuroinflammation -- Osteoporosis</p> |
| <p>Firmicutes ↑ Actinobacteria ↓ Proteobacteria ↓ Ascomycota ↑ Basidiomycota ↓</p> | <p>Sedentary behaviors</p> |
| <p>Drug metabolism -- Antibiotics (Rifaximin, Isoalantolactone, and Minocycline) and proton pump inhibitors (Esomeprazole, etc.) protects against depression -- Traditional Chinese medicine formulas (decoction Xiaoyaosan, Shugan granule, etc.) and herbal medicines and their monomers or compounds (Berberine, Lycium barbarum polysaccharide, etc.)</p> | |

Drug preclinical research strategies based on precise germ-free animal models

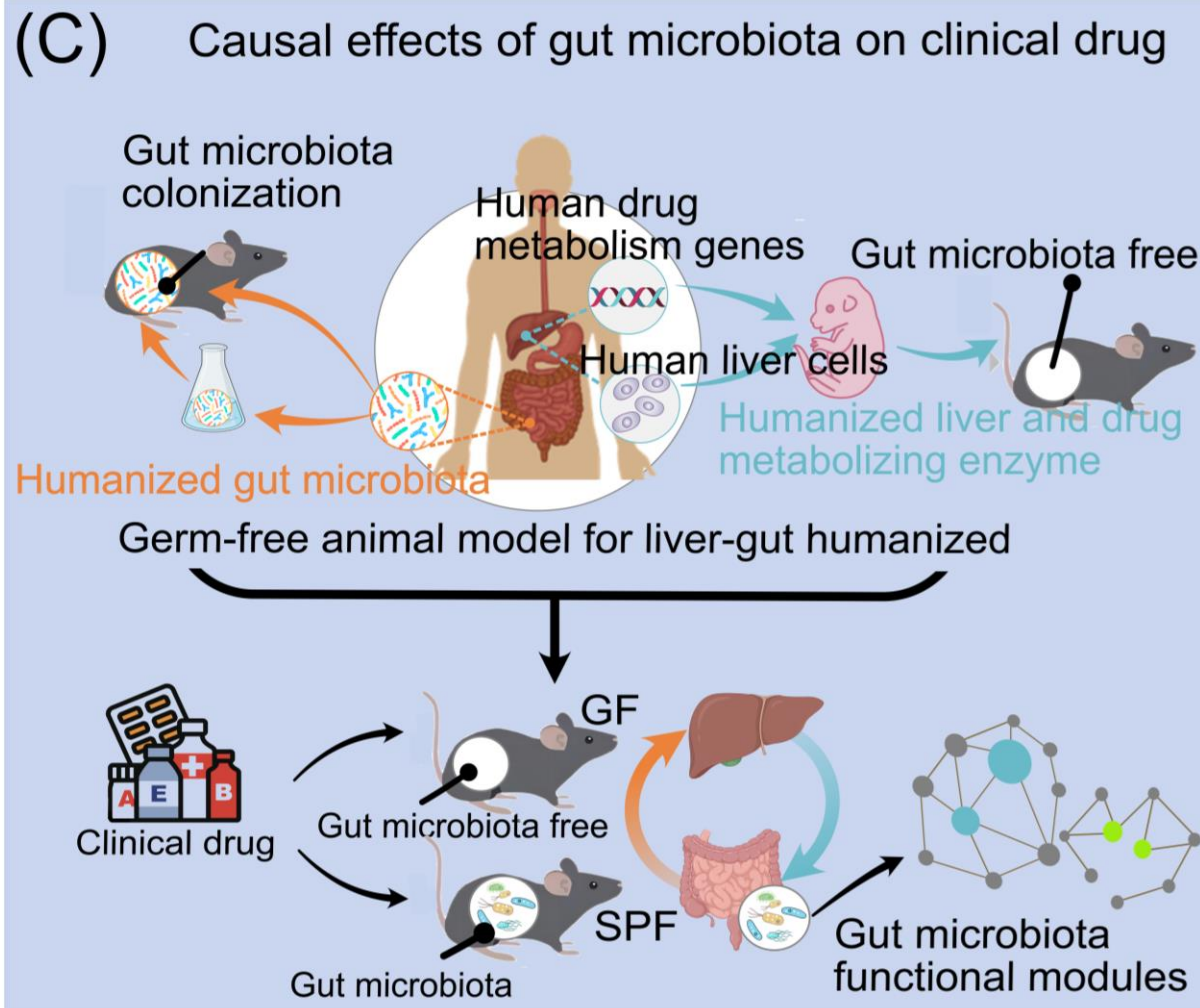


Exploring drug phenotypic differences and confirming the involvement of gut microbes in **drug efficacy** and **toxicology** using precise germ-free animal models.

Drug preclinical research strategies based on precise germ-free animal models

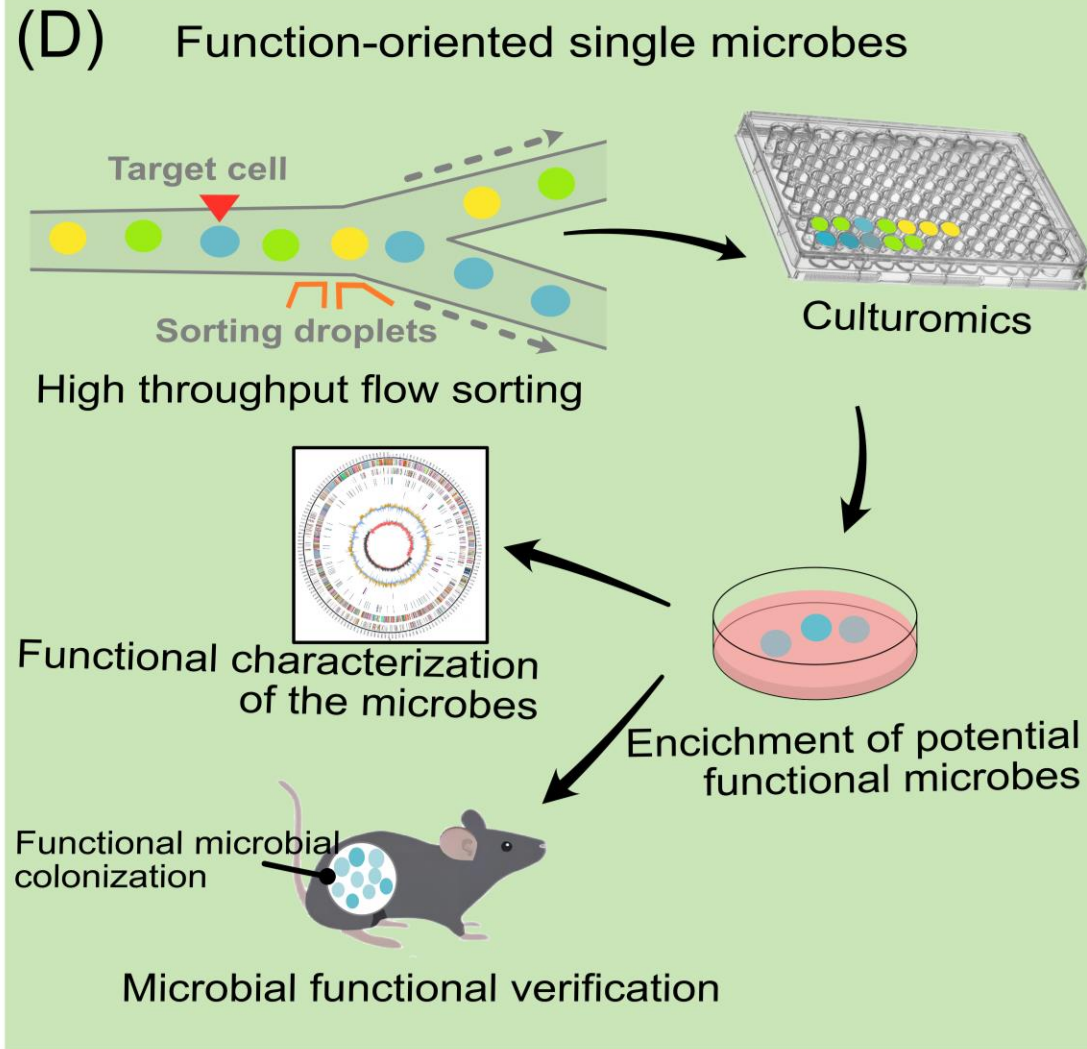


In vivo function exploration and component screening of gut microbiota drug metabolism

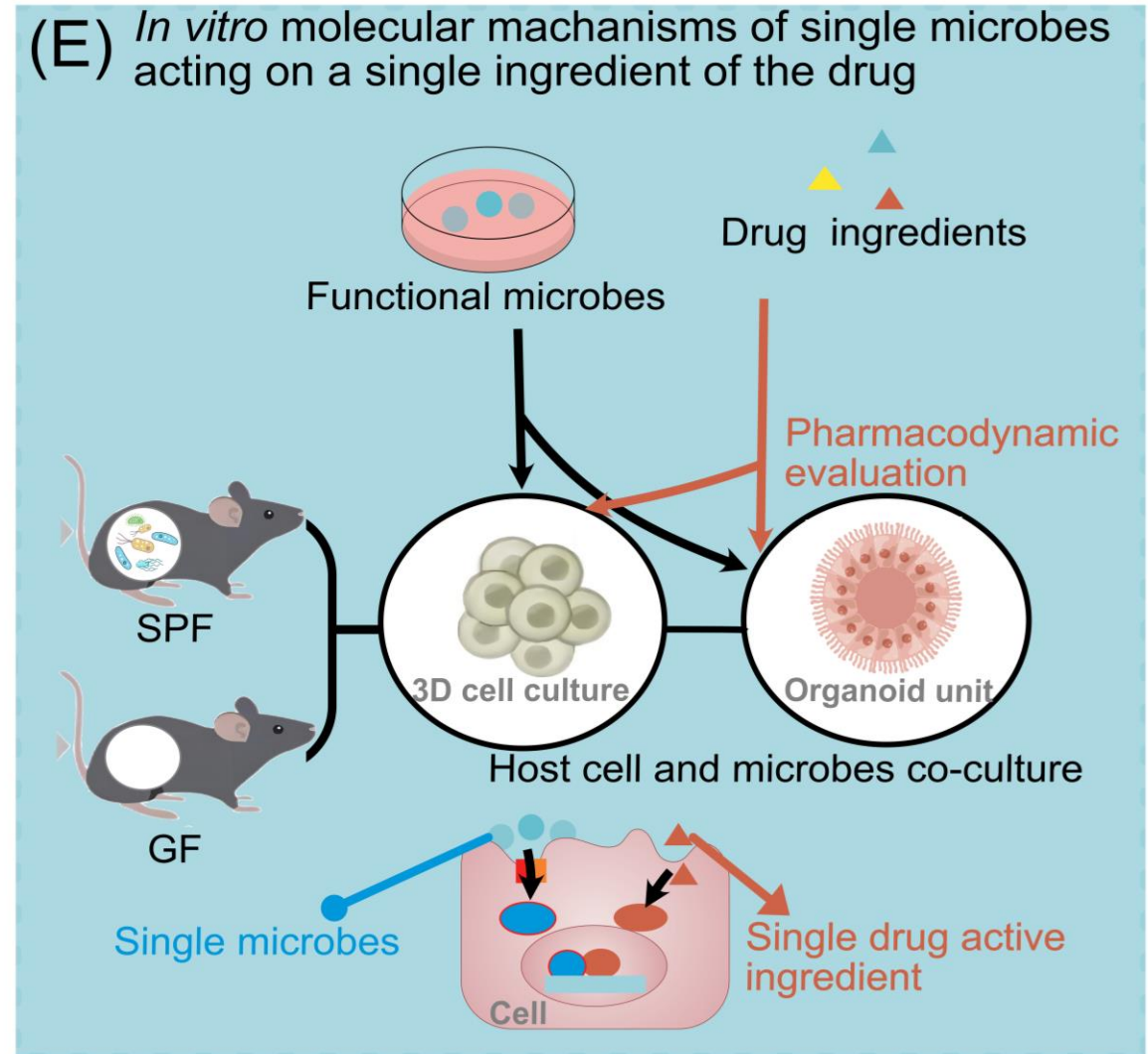


Investigating the "causal" relationship between gut microbiota and drug metabolism based on **microbial sorting, culturomics** and precision monoculture colonisation of germ-free animals.

Drug preclinical research strategies based on precise germ-free animal models



Function-oriented precise bacterial culture and *in vivo* functional verification

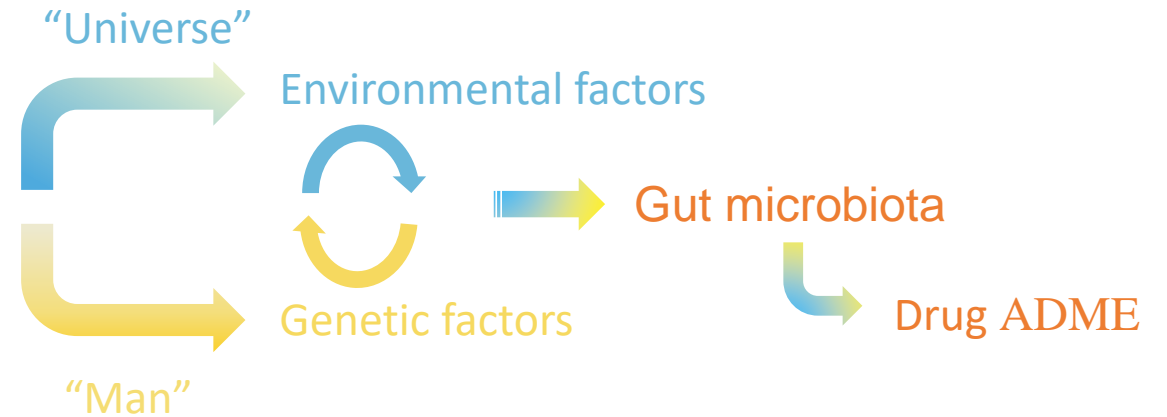


Co-culture based on the *in vivo* function of gut microbiota

conclusion



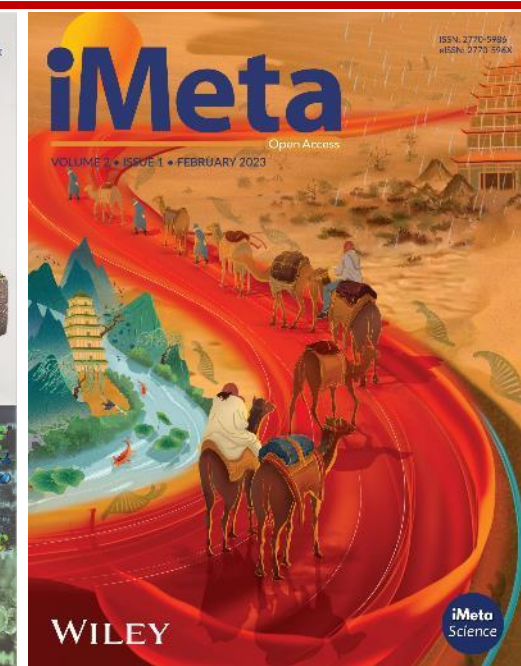
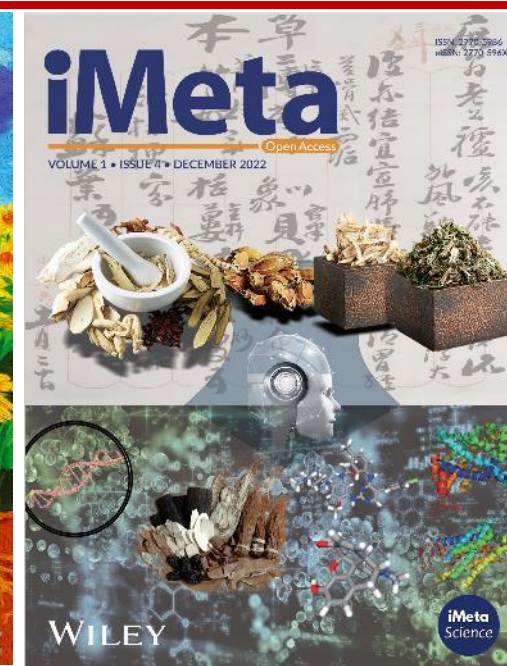
“Correspondence between man and universe”



- Gut microbiota is influenced by genetic and environmental factors that significantly influence the host microenvironment of **drug absorption, distribution, metabolism, and excretion** of the host. This highlights the necessity of establishing a new evaluation system for drug-microbiota interactions.
- To study the complex nature of the interaction between gut microbiota and drugs in the body, we propose a new top-down research model using precise germ-free animals.

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