一种新的药物-微生物相互作用评价系统

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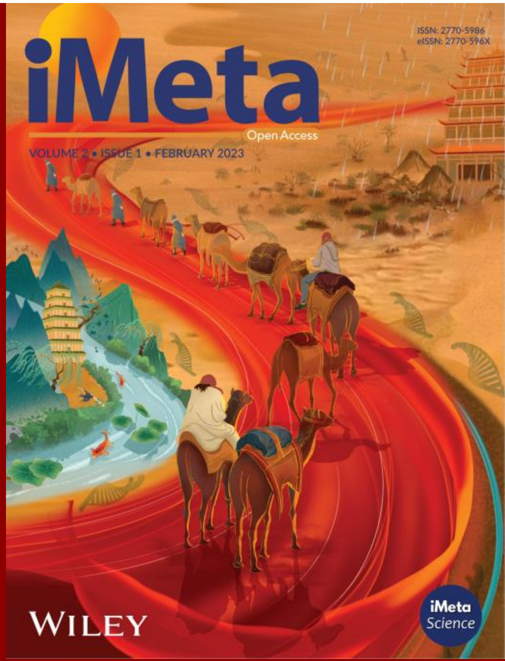

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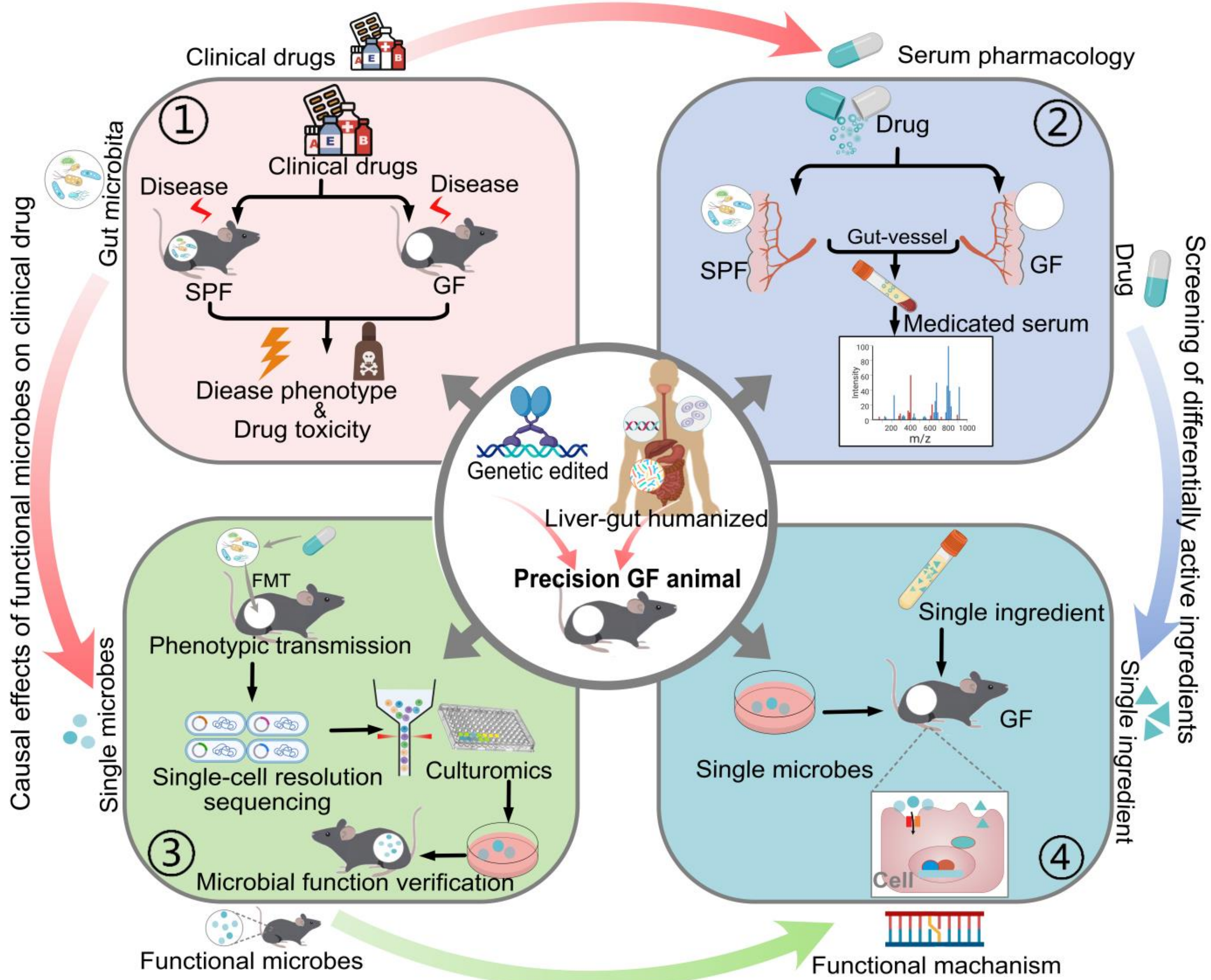
简介

① 有表型差异的临床药物筛选

Clinical drug screening for phenotypic differences

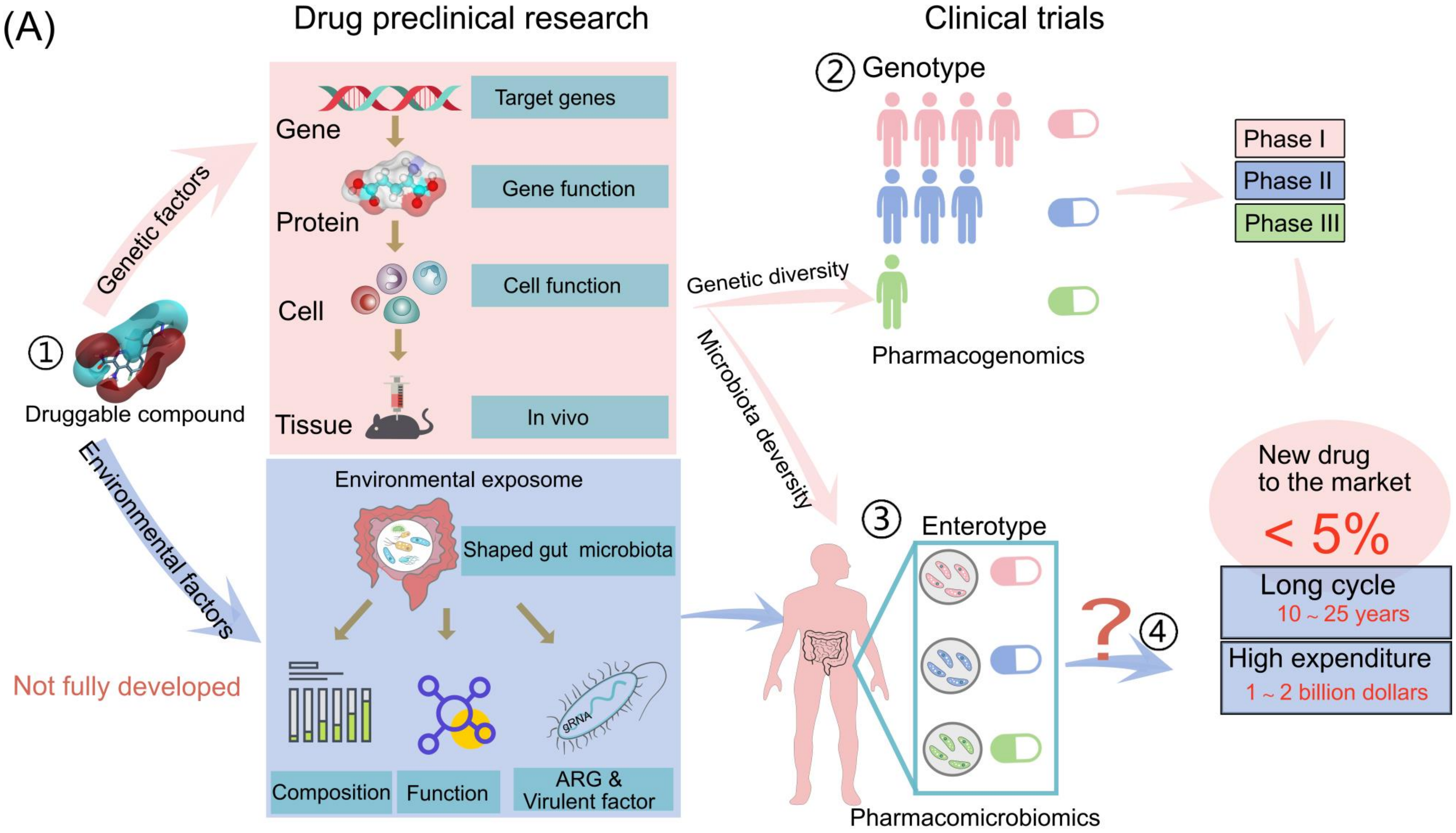
② 差异性药效/毒理成分的筛选

③ 肠道菌群对临床药物作用的因果关系



④ 单一微生物与单一药物成分相互作用的功能机制研究

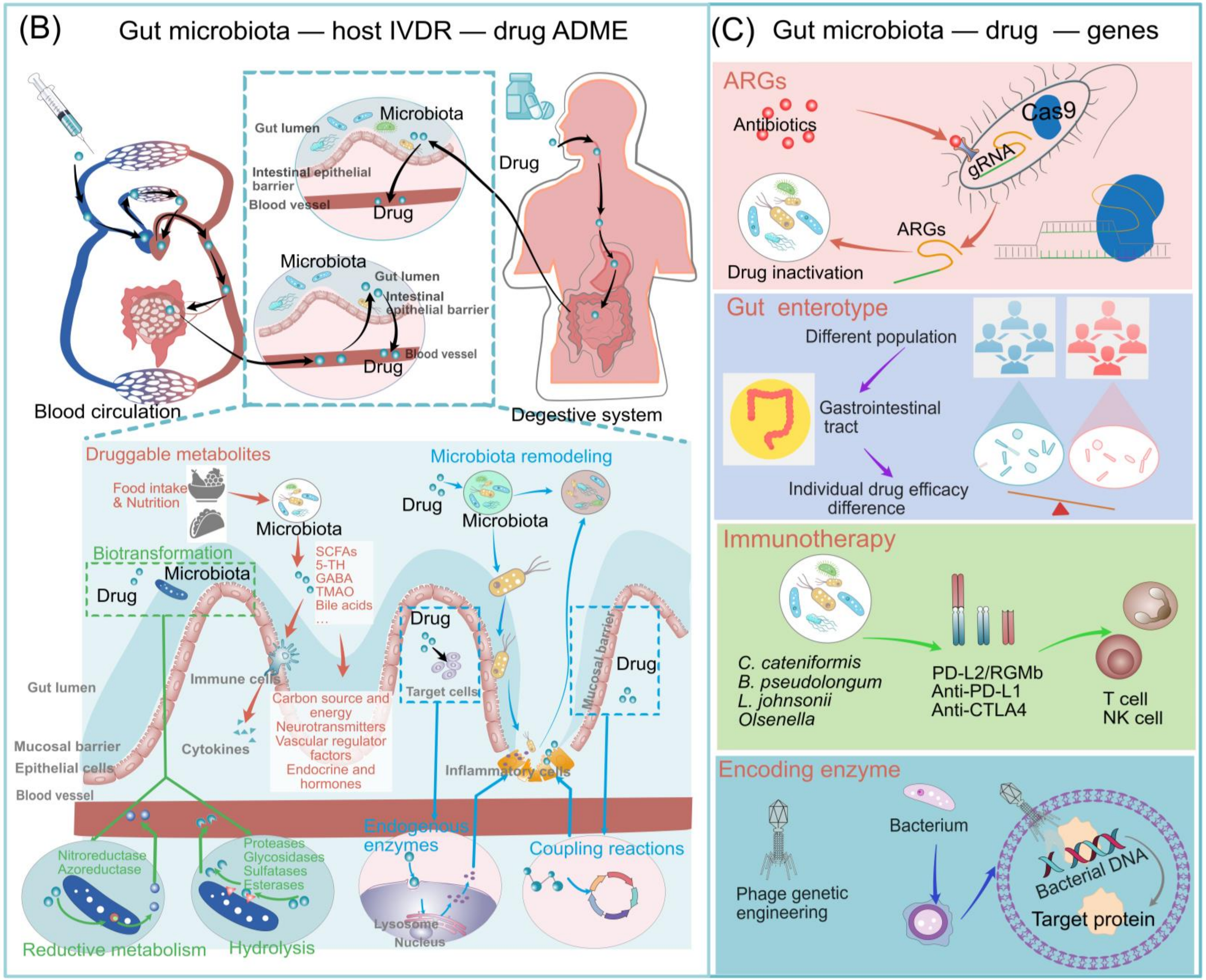
肠道菌群在药理学研究和药物靶基因调控中的临床意义



肠道菌群作为人体与环境相互作用的重要场所，可以最直观反应人体对环境的适应性改变。

充分挖掘肠道菌群作为评价药效个体差异标准的价值，缓解新药研发成本的资源浪费。

肠道菌群在药理学研究和药物靶基因调控中的临床意义



肠道菌群作为评价药效个体差异评价标准的潜在可行性：

★肠道菌群参与药物ADME；

★肠道菌群与药物靶向基因的相互作用。

影响肠道菌群的环境因素

(A) Natural conditions

Collinsella ↑ *Bifidobacterium* ↑ Lachnospiraceae ↑ Veillonellaceae ↑ *Clostridiales* ↑ *Akkermansia* ↑ Ruminococcaceae ↑ Prevotellaceae ↑ Muribaculaceae ↑ *Rikenellaceae* ↑ *Bacteroidaceae* ↑ *Quinella* ↑ *Rothia* ↑ *Senegalimassilia* ↑ *Sutterella* ↓ *Escherichia* ↓ *Shigella* ↓ Cyanobacteria ↓ Comamonadacea ↓ Sinobacteraceae ↓ *Lactobacillaceae* ↓ *Erysipelotrichacea* ↓ *Lactobacillus* ↓ *Lachnospiraceae* ↓ *Ruminococcaceae* ↓	**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
Lactobacillus ↑ *Oscillospira* ↑ *Escherichia Shigella* ↑ *Acinetobacter* ↑ *Klebsiella* ↑ *Ruminiclostridium* ↓ *Blautia* ↓ *Lachnospiraceae NK4A136 group* ↓ *Clostridium VadinBB60* ↓ *Muribaculaceae* ↓ *Blautia* ↓ *Allobaculum* ↓ *Peptostreptococcu sanaerobius* ↓ *Streptococcus* ↑ Ratio of Firmicutes and Proteobacteria ↑ Bile acids producing gut microbiota ↑	**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
Prevotella ↑ Prevotellaceae ↑ Porphyromonadaceae ↑ Streptococcaceae ↑ *L. johnsonii YH1136* (-) Enteric fermenting anaerobes ↑ *Odoribacter* ↑ *Bacteroides* ↑ *Parabacteroides* ↑ *Alistipes* ↑ *Akkermansia* ↑ *Weissella* ↓ *Saccharibacteria* ↓ *Enterobacter* ↓ *Gemella* ↓	**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

(B) Environmental pollution

Oribacterium ↓ *Shuttleworthia* ↓ *Cyanobacteria* ↑ *Deferribacteres* ↓ *Bacteroides* ↓ *Lactobacillus* ↓ *Prevotella* ↓ *Butyricicoccus* ↓ *Paraprevotella* ↓ *Enterococcus* ↑ *Ruminococcus* ↑	**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
Staphylococcus ↑ *Parabacteroides* ↓ Firmicutes ↓ α-Proteobacteria ↓ Bacteroides ↑ *Dethiosulfovibrionaceae* ↑ Enterobacteriaceae ↑ lachnospiraceae NK4A136 group ↑ Akkermansia ↓ Bacteroides ↓ Ruminococceae UCG014 ↓ Mucispirillum ↓ Helicobacter ↓ Bacteroides ↑ *Prevotellaceae UCG001* ↑	**Microplastic exposure** -- Colon and duodenum inflammation -- Hepatic lipid disorder -- Colonic mucin -- Intestinal function in children -- Insulin resistance -- Hepatotoxicity -- Hematopoietic function -- Male testicular disorder
Resistance genes Sulfonamide Multidrug Vancomycin	**ARGs exposure** -- Water environment -- Aquatic environment -- Contaminated soils
Lactobacillus ↓ *Bacteroides acidifaciens* ↑ *Ruminococcus gauvreauii* ↑ *Akkermansia* ↓ *Parabacteroides* ↓ *Enterobacteriaceae* ↓ *Blautia* ↓ *Erysipelatoclostridium* ↓ *Parasutterella* ↑ *Ruminococcaceae* ↑ *Lachnospiraceae* ↓ *Enterococcaceae* ↓	**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.

Environmental heavy metal exposure
-- Lead (Pb), cadmium, mercury, etc.

(C) Psychological factors & stress

Akkermansia ↑ *Lactobacillus* ↓ Enterobacteriaceae ↑ *E. coli* ↑ *Turicibacter* ↑ *Ruminococcaceae* ↑ *Candidatus Arthromitus* ↑ *Enterobacter* ↑ *Lactobacillus Muribaculum* ↓ *Monoglobus* ↓ *Parasutterella* ↓ *Helicobacter* ↑ *Oscillibacter* ↑ *Parabacteroides* ↓ *Ruminococcus* ↓ *Prevotella* ↓ *Bacteroides acidifaciens* ↓ Erysipelotrichaceae ↓ *Akkermansia muciniphila* ↑ *Anaerostipes* ↑ *Lactobacillus reuteri* ↓	**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
Segmented filamentous ↑ *Enterococcus faecalis* ↓ *Bacteroides* ↑ *Prevotellaceae UCG001* ↑ *Quinella* ↑ *Veillonellaceae* ↑ *Bacteroidia* ↑ *Campylobacteria* ↑ *Negativicutes* ↑ *Bacteroidales* ↑ *Campylobacterales* ↑ *Alistipes* (-) *Clostridium IV* (-) *Clostridium XI* (-) Faecalibacterium Blautia(-)	**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
Ruminococcaceae ↑ *Porphyromonodaceae* ↑ *Lactobacillaceae* ↓	**Endocannabinoid (eCB) signaling** --Depressive-like behaviors

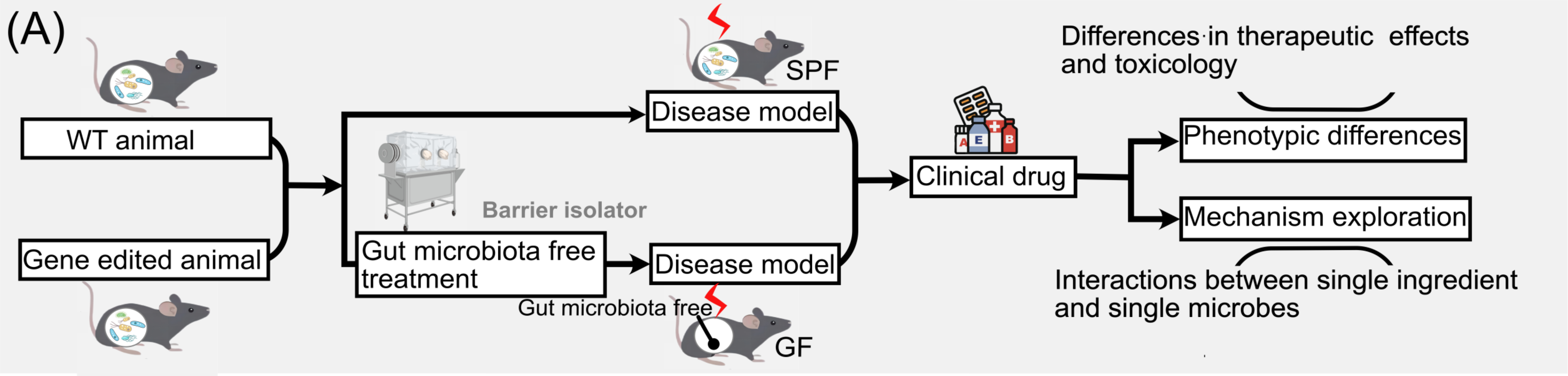
Drug metabolism
-- Probiotics, prebiotics, and neurotransmitter metabolites derived from gut microbiota, such as 5-TH, indole, glutamatergic and gamma-aminobutyric acid (GABA), and SCFAs
-- Antidepressants such as Venlafaxine, (R)-ketamine, Lanicemine, Fluoxetine and Agomelatine （AGO)

(D) Life style

Firmicutes ↑ Bacteroidetes ↓ *Blautia producta* ↑ *Clostridia* ↓ *Ruminococcaceae* ↓ *Akkermansia* ↓ *Eubacterium fissicatena group* ↑ *Romboutsia* ↑ *Erysipelatoclostridium* ↑ *Escherichia coli* ↑ *Proteobacteria* ↑	**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
Lachnospiraceae NK4A136 ↑ *Faecalibacterium prausnitzii* ↑ *Eubacterium* ↑ *Roseburia* ↑ *Ruminococcus torques* ↓ *Prevotella* ↑	**Mediterranean diet** -- Weight loss -- Reduce frailty and inflammation -- Cardiometabolic health -- IBD
Intestinimonas ↑ *Catenibacterium* ↑ *Ruminococcaceae* ↑ *Eggerthella lenta* ↑ *Parabacteroides distasonis* ↓ *Lactobacillus spp* ↓ *Parabacteroides goldsteinii* ↓	**Smoking habits** -- Neurotransmitter-associated metabolites -- Promote colon cancer -- Activate oncogenic MAPK/ERK signalling in colonic epithelium -- COPD -- Weight gain
Clostridiales order ↓ *Bacteroidales order* ↓	**Alcohol dependence** -- Alcoholic liver disease -- Altered sociability and depression -- Cardiometabolic health -- IBD -- Neuroinflammation -- Osteoporosis
Firmicutes ↑ *Actinobacteria* ↓ *Proteobacteria* ↓ *Ascomycota* ↑ *Basidiomycota* ↓	**Sedentary behaviors**

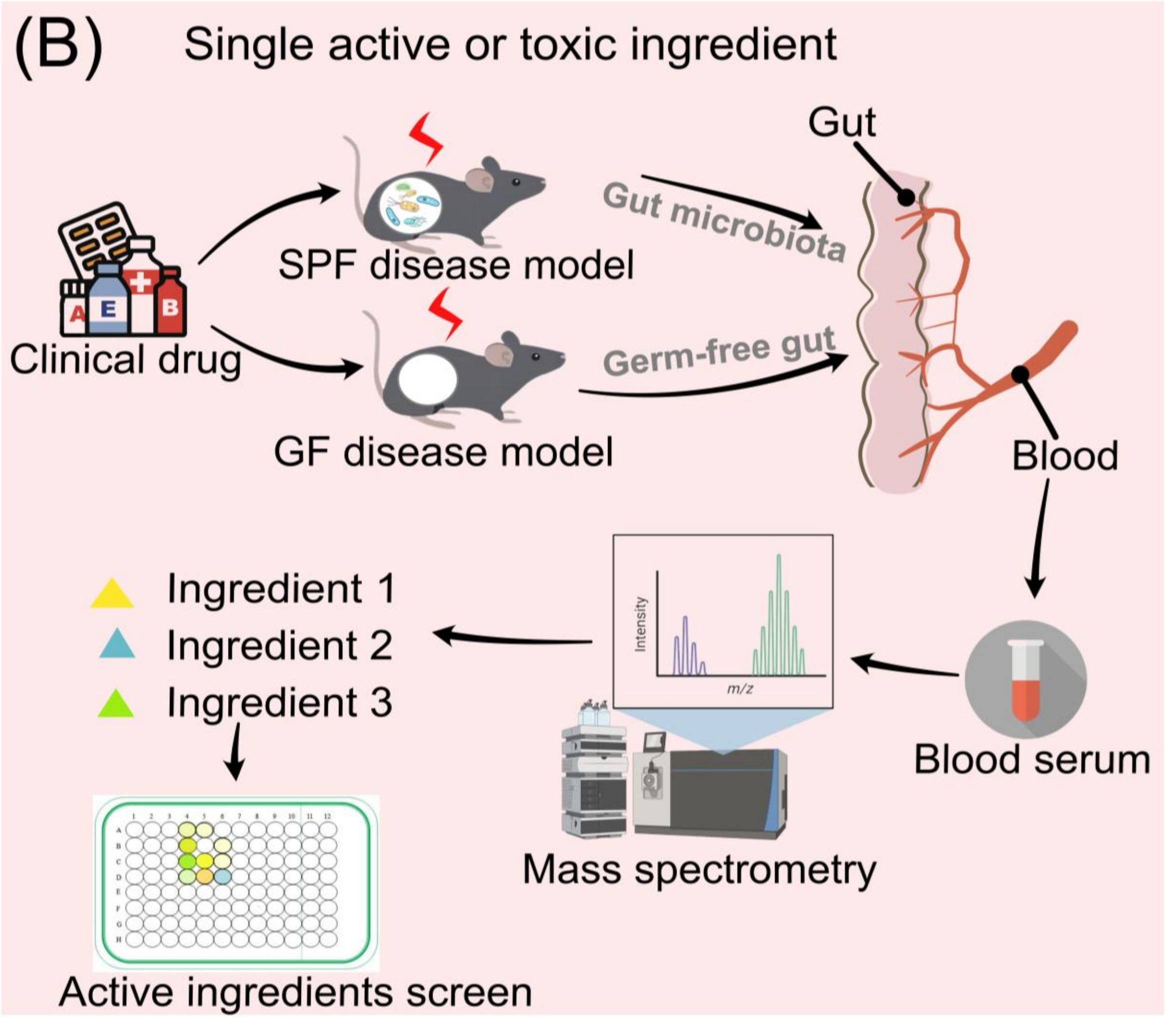
Drug metabolism
-- Antibiotics (Rifaximin, Isoalantolactone, and Minocycline) and proton pump inhibitors (Esomeprazole, etc.） protects against depression
-- Traditional Chinese medicine formulas （decoction Xiaoyaosan, Shugan granule, etc.） and herbal medicines and their monomers or compounds (Berberine, Lycium barbarum polysaccharide, etc.)

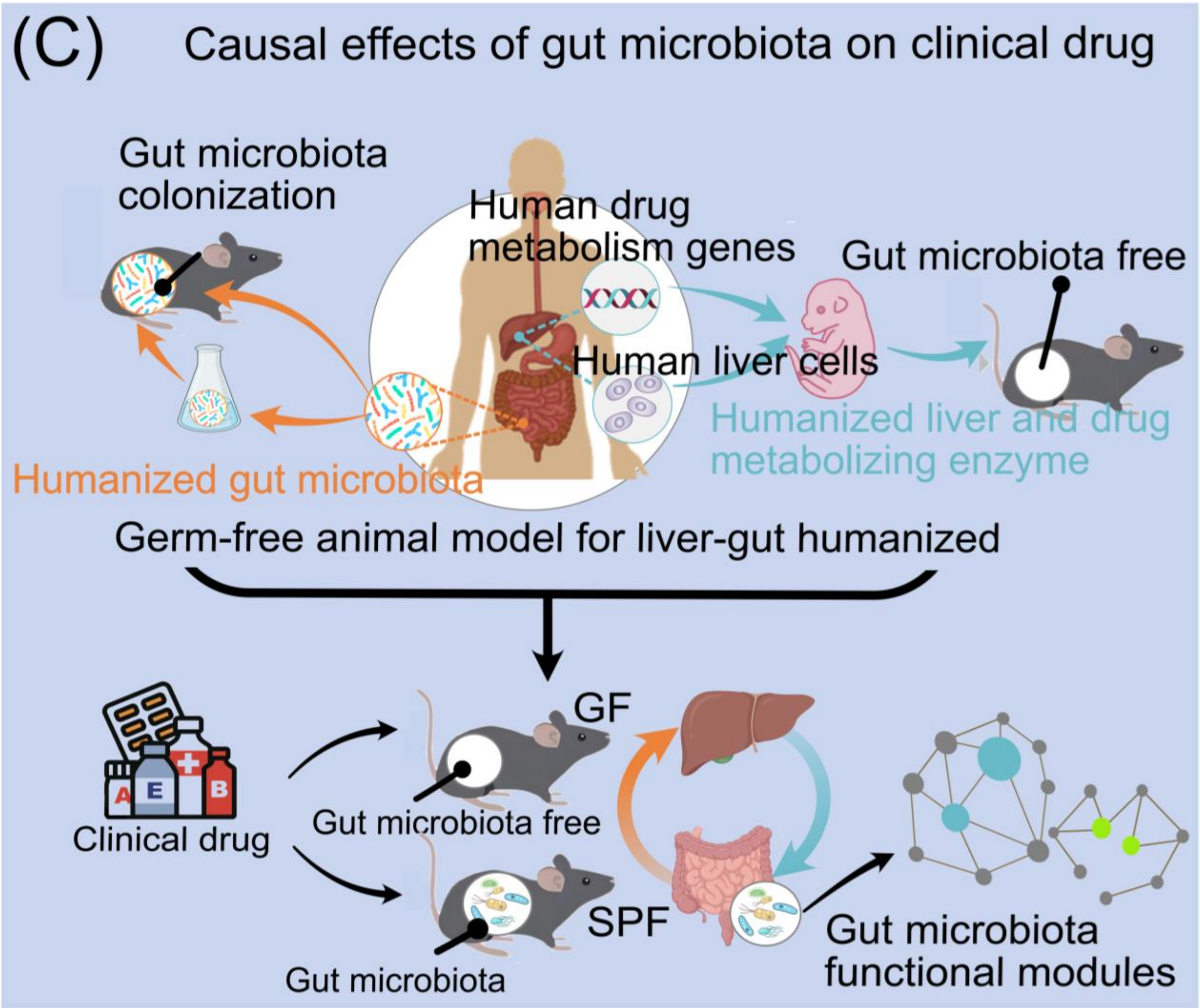
基于精确无菌动物模型的药物临床前研究策略



利用精准化无菌动物模型探索药物表型差异，确证肠道微生物参与药物药效和毒理的作用。

基于精确无菌动物模型的药物临床前研究策略

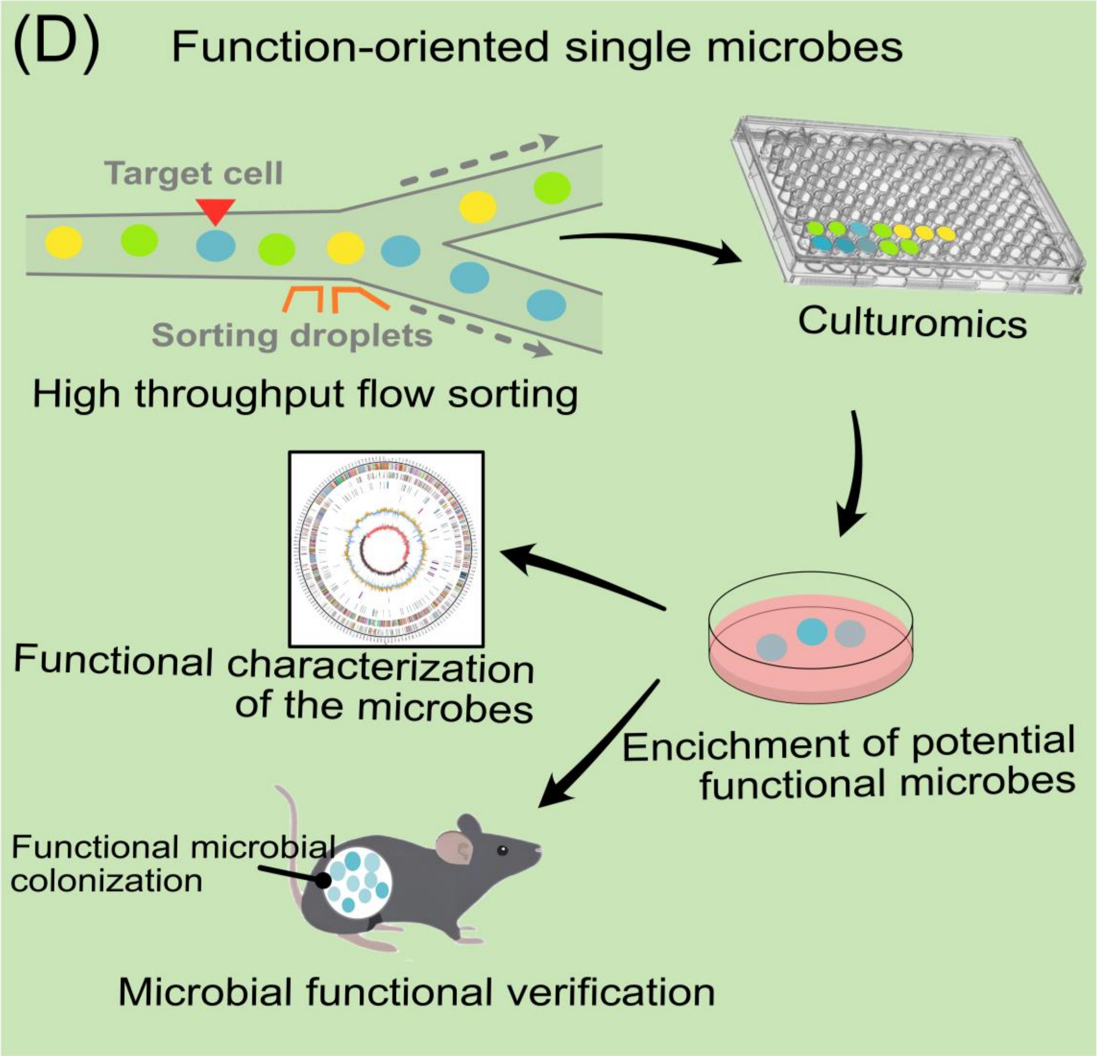


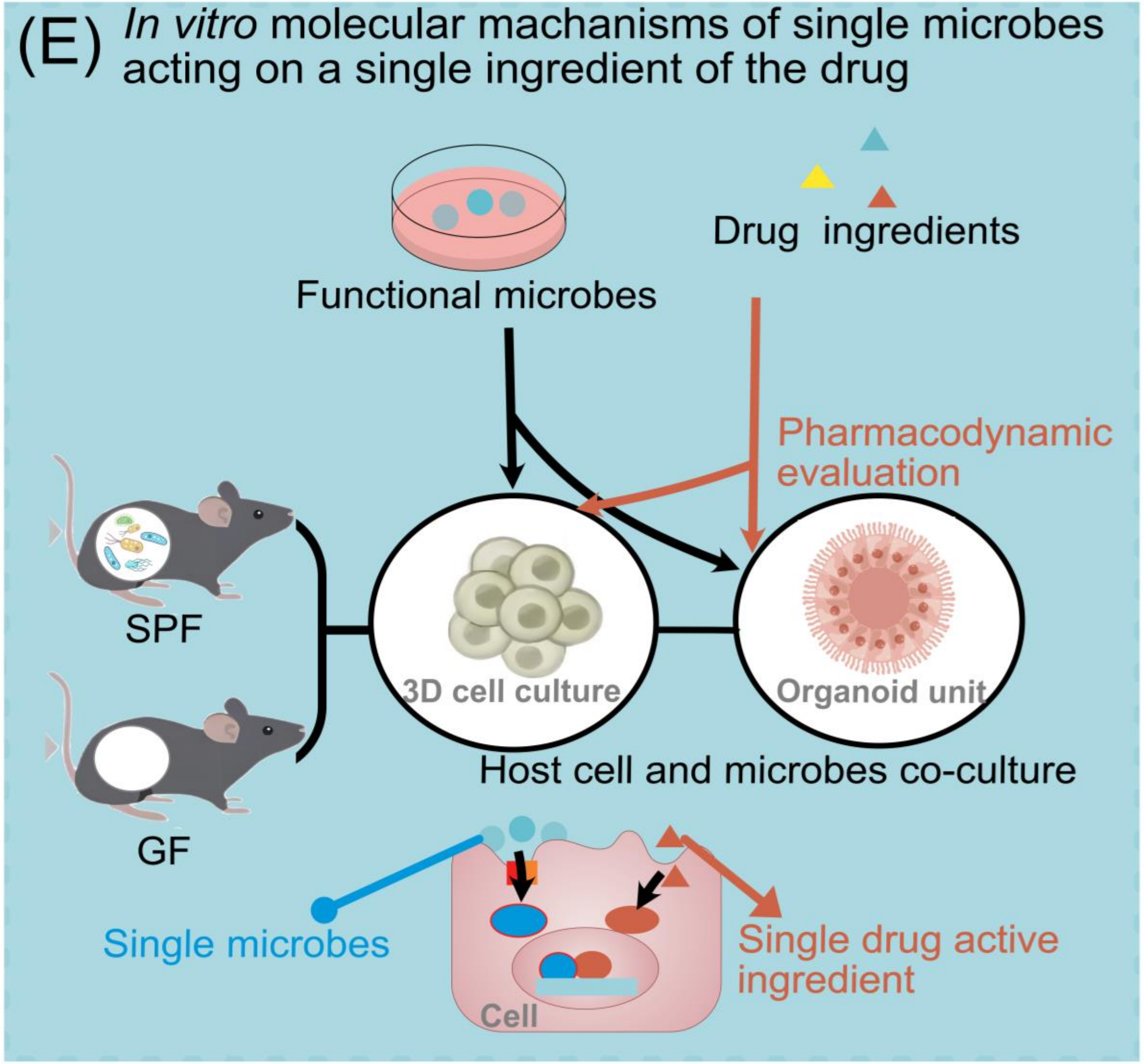


肠道菌群药物代谢的体内功能探索及成分筛选。

基于微生物分选、培养组学和精准化无菌动物单菌定植，研究菌群和药物代谢的“因果”关系

基于精确无菌动物模型的药物临床前研究策略

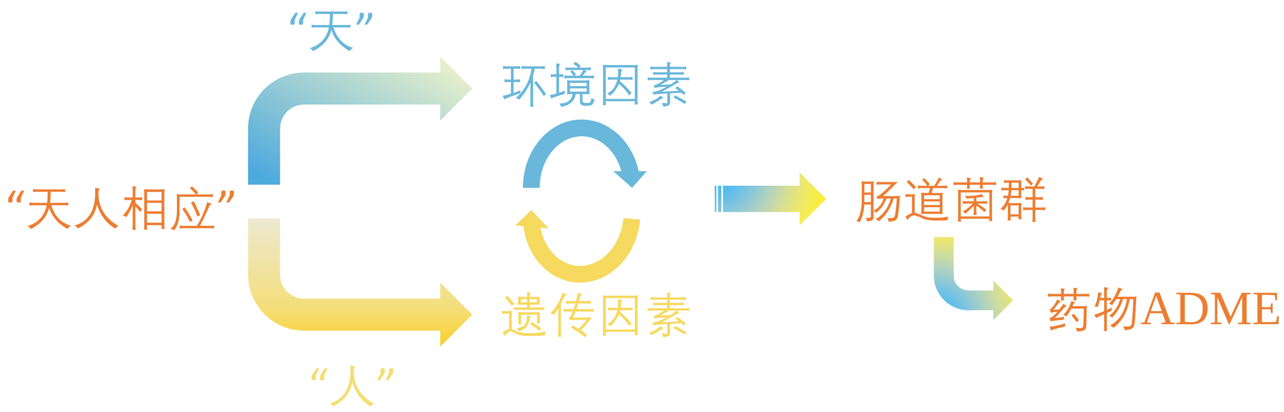




功能导向的精确细菌培养及单菌定植、体内功能验证。

建立“单菌-单成分-细胞”相互作用的现代分子机制研究“接口”。

总结



- 肠道微生物群受遗传和环境因素的共同影响，以及肠道微生物群对宿主的药物吸收、分布、代谢和排泄微环境产生显著影响，这凸显了建立药物-微生物相互作用新评估体系的必要性。

- 为了研究肠道微生物群与药物在体内相互作用的复杂性质，本文提出了一种新的利用精准化无菌动物的自上而下研究模式。

Tianhao Liu, Chenyang Zhang, Hang Zhang, Jing Jin, Xue Li, Shiqiang Liang, Yuzheng Xue, Fenglai Yuan, Yahong Zhou, Xiuwu Bian, Hong Wei. 2024. A new evaluation system for drug–microbiota interactions. ***iMeta*** 3: e199.

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iMeta: 整合宏组学重新认识生命和环境科学

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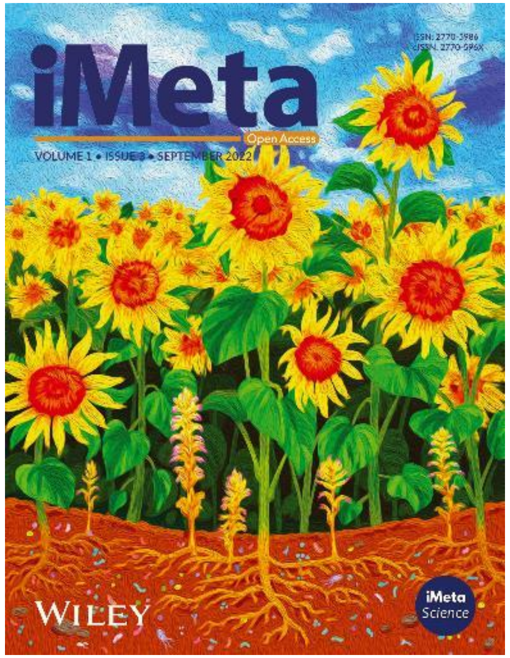

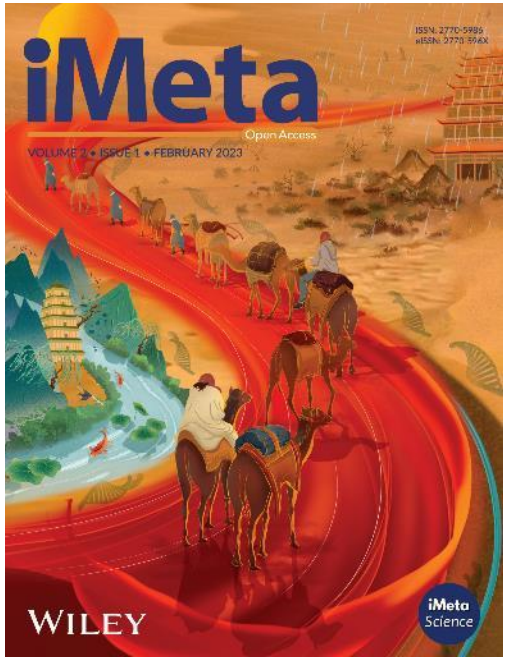

“*iMeta*” 由威立、肠菌分会和华人科学家出版的开放获取期刊，主编由中科院微生物所刘双江和荷兰格罗宁根大学傅静远教授共同担任。目的是发表原创研究、方法和综述以促进宏基因组学、微生物组和生物信息学发展。目标是发表前10%(IF>20)的高影响力论文。期刊特色包括视频投稿、可重复分析、图片打磨、青年编委、中英双语、50万用户的社交媒体宣传等。2022年2月发行，相继被**ESCI**、Google Scholar、DOAJ、Scopus等数据库收录，发文161篇，被引2316次(Dimension, 2024/2/19)!

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