# Microbiota-Gut-Brain Axis Multi-Organ Chip Construction and Applications in Drug Evaluation

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# Introduction

## Microbiota-Gut-Brain Axis (MGBA)

◈Trillions of microorganisms coexist with the host in the human gut, and microbial dysbiosis impacts human health.

◈The gut microbiota engages in bidirectional regulation with the brain through pathways such as the **neural, endocrine, immune, and metabolic** systems, thereby influencing central nervous system functions.

◈The MGBA theory offers novel microbiome-targeted approaches for the treatment of neurological disorders.

## Microfluidic Organ-on-a-Chip

◈Limited by ethical standards and experimental conditions, traditional in vivo and in vitro models **struggle to replicate** the complex human physiological environment and cellular interactions.

◈Organ-on-a-chips, based on microfluidic technology, can **dynamically simulate the microenvironmental characteristics of human organs**, offering advantages such as high biomimicry, high throughput, and low sample consumption.

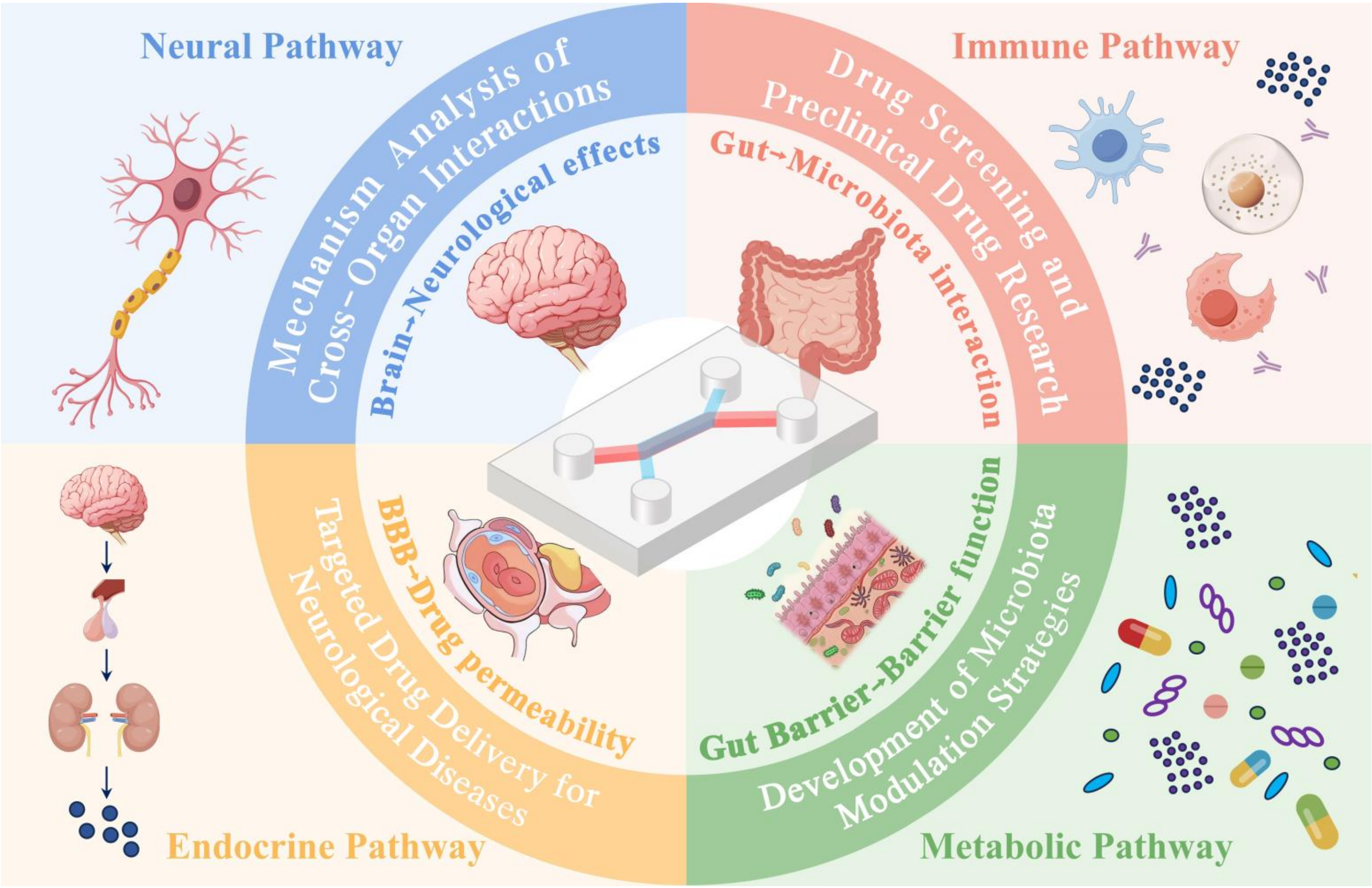
◈The MGBA chip system will drive research into complex pathologies, gut microphysiology, and new drugs.

## Core of the Review

●Based on the research pathway from simulating basic physiological structures to reconstructing complex physiological processes, and then to clinical translation, this paper elaborates on **the mechanisms of the MGBA**, as well as the research progress and practical applications of **gut-on-a-chips**, **blood-brain barrier-on-a-chips**, **brain-on-a-chips**, and **multi-organ chips**.

●Systematically integrating **MGBA with multi-organ chip technology**, this paper analyzes the design innovations and application scope of the gut-blood-brain barrier-brain cascade MGBA chip.

# Highlights




- Systematically integrating the Microbiota-gut-brain axis (MGBA) with multi-organ chip technology to construct a research paradigm for elucidating the mechanisms of cross-organ interactions.
- Providing a comprehensive elaboration on the technical iterations and current development status of core models, including gut-on-a-chip, blood-brain barrier-on-a-chip, brain-on-a-chip, as well as multi-organ cascading techniques.
- Discussing the critical application value of MGBA organ-on-a-chip platforms in drug screening and preclinical drug research, including pharmacokinetic studies, pharmacodynamic profiling, and toxicity evaluation.

# Overview of Microbiota-Gut-Brain Axis Mechanisms

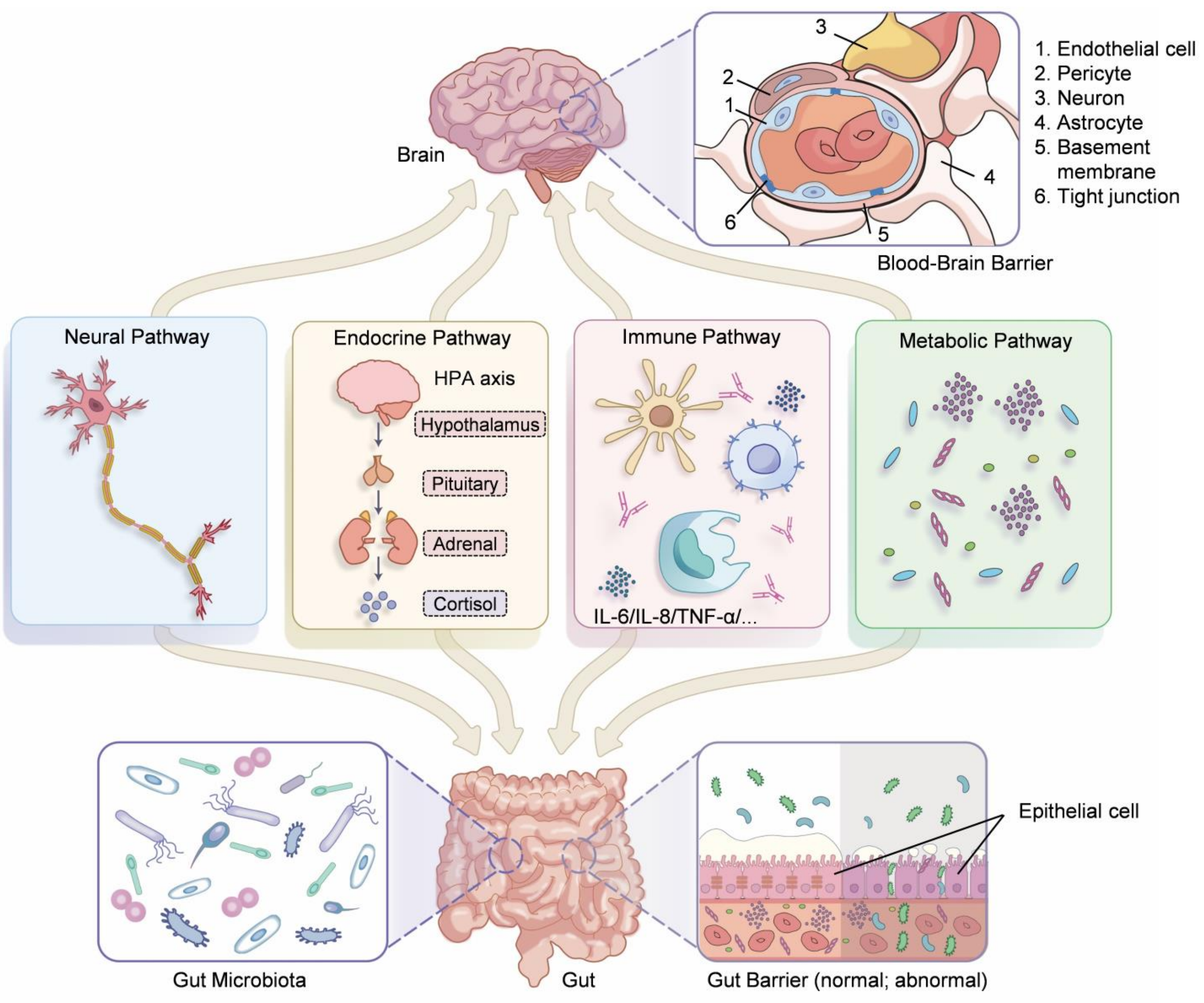



Figure 1. The communication pathways of the microbiota-gut-brain axis.

## Main Components

**Four Major Systems**

Nervous; Endocrine; Immune; Metabolic

**Two Barriers**

Gut Barrier; Blood-Brain Barrier

## Primary Pathways

### Vagus Nerve Transmission

Afferent fibers transmit peripheral signals to the central nervous system, while the parasympathetic nervous system regulates organs such as the gut.

### Endocrine Regulation

Environmental stimuli activate the HPA axis, releasing cortisol, which alters the composition and metabolic activity of the gut microbiota.

### Immune Interaction

Dysbiosis of the microbiota generates pro-inflammatory substances, disrupts barrier permeability, and induces neuroinflammation.

### Microbiota Metabolites

Produce short-chain fatty acids and various bio-active substances that participate in the regulation of the nervous, endocrine, and immune systems.

# Gut-on-a-Chip

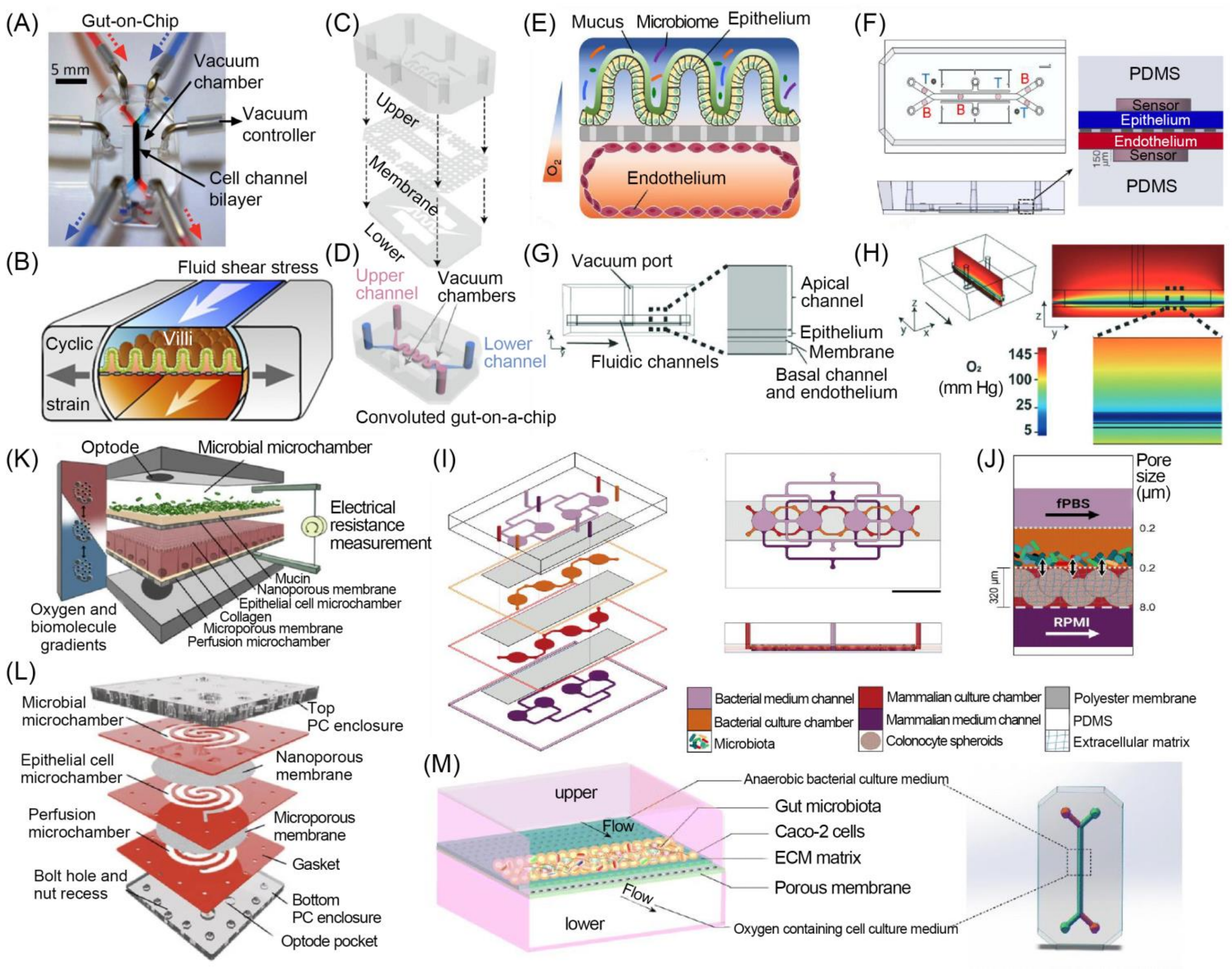



Figure 2. Schematic diagram of the related Gut-on-a-Chip structure.

## Model Elements

### Structural and Functional Basis

⦿Small intestinal villi and microvilli structure;
⦿Resident gut microbiota;
⦿Mucous layer secretion.

### Mechanical Stimulation Simulation

⦿Laminar flow and periodic mechanical deformation simulate intestinal peristalsis.

### Anaerobic Environment Construction

⦿Nitrogen flushing establishes an oxygen gradient within the chamber;
⦿Computer simulation and impermeable membranes regulate oxygen permeability;
⦿Time difference controlled oxygen;
⦿Real-time monitoring of oxygen sensor.

## Practical Applications

⦿Intestinal disease research;
⦿Pharmacokinetic studies;
⦿Probiotic screening.

## Technical Challenges

⦿Model Simplification Limitations;
⦿ Material Limitations.

# Blood-Brain Barrier-on-a-Chip

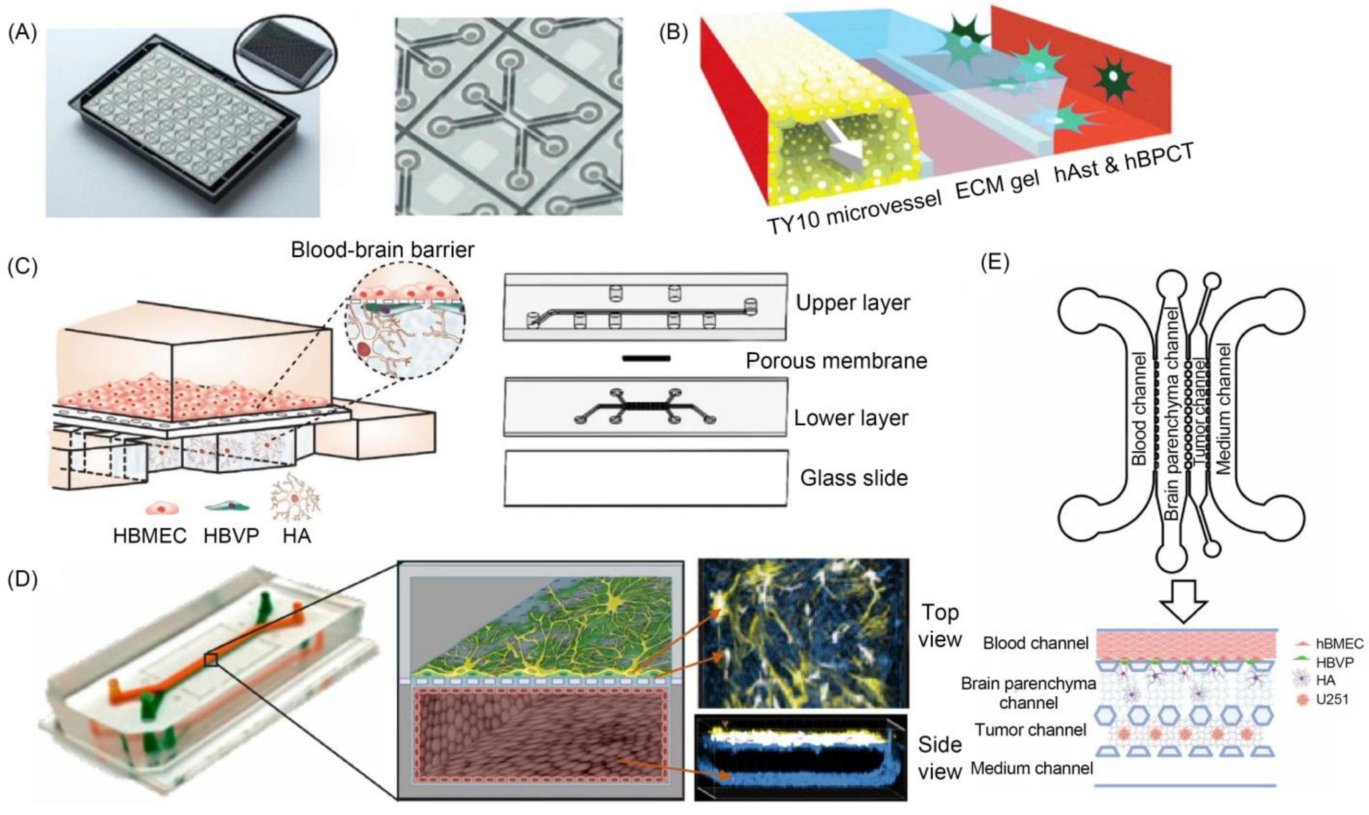



Figure 3. Schematic diagram of the related Blood-Brain Barrier-on-a-Chip structure.

## Model Elements

### Components and Function

⦿Includes brain microvascular endothelial cells with intercellular tight junctions, astrocytes, pericytes, and the basement membrane.

⦿Exhibits selective permeability, isolating peripheral blood from brain parenchyma and maintaining the stability of the neuronal microenvironment.

### Chip Design

⦿The vascular and neural chambers are separated by a porous membrane.

⦿Fluid shear stress mimics in vivo hemodynamics, promoting the formation of 3D vessel-like structures.

## Practical Applications

⦿Targeted drug design;
⦿Evaluation of drug active ingredient transport efficiency across the barrier and therapeutic efficacy;
⦿Construction of disease-specific models.

## Technical Challenges

⦿Traditional chip flow limitations;
⦿Complexity of cell co-culture;
⦿Structural integration design.

# Brain-on-a-Chip

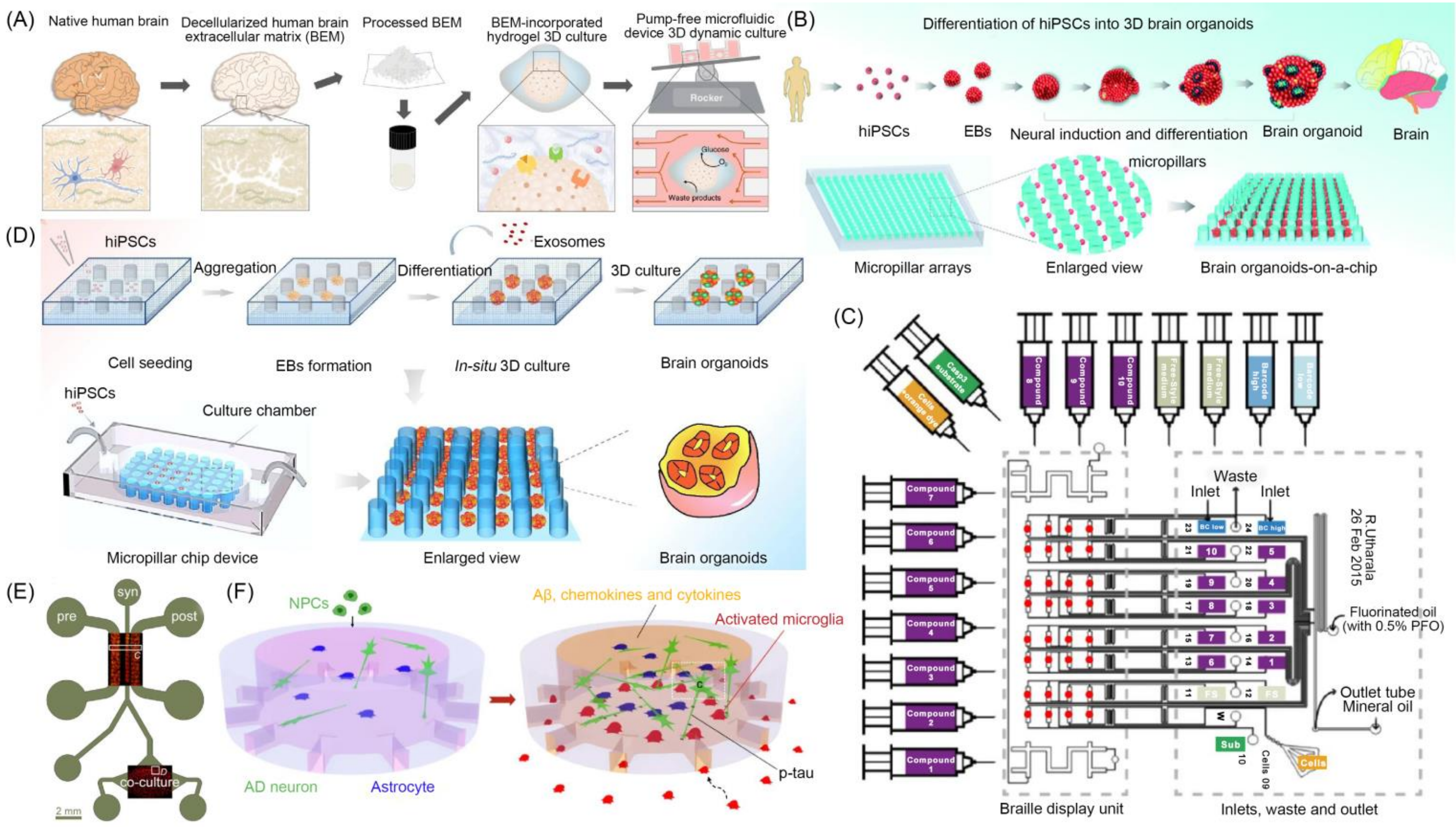



Figure 4. Schematic diagram of the related Brain-on-a-Chip structure.

## Model Elements

### Structural and Functional Basis

⦿Neurons (information integration, transmission) collaborate with glial cells (support, nutrition, protection) to govern the body's coordination and interaction with the external environment.

### Chip Design

⦿A 3D hydrogel matrix combined with bidirectional fluid perfusion promotes the formation of brain-like structures;

⦿In situ differentiation of hiPSCs forms functional human brain organoids;

⦿Co-culture of neurons and glial cells promotes brain synapse formation and spontaneous neural activity.

## Practical Applications

⦿Simulation of various neurological diseases and pathological studies;

⦿Brain development and brain injury research.

## Technical Challenges

⦿Real-time monitoring of brain tissue metabolism;

⦿Precise simulation of complex brain disease pathologies.

# Multi-Organ Chip Cascade Technology

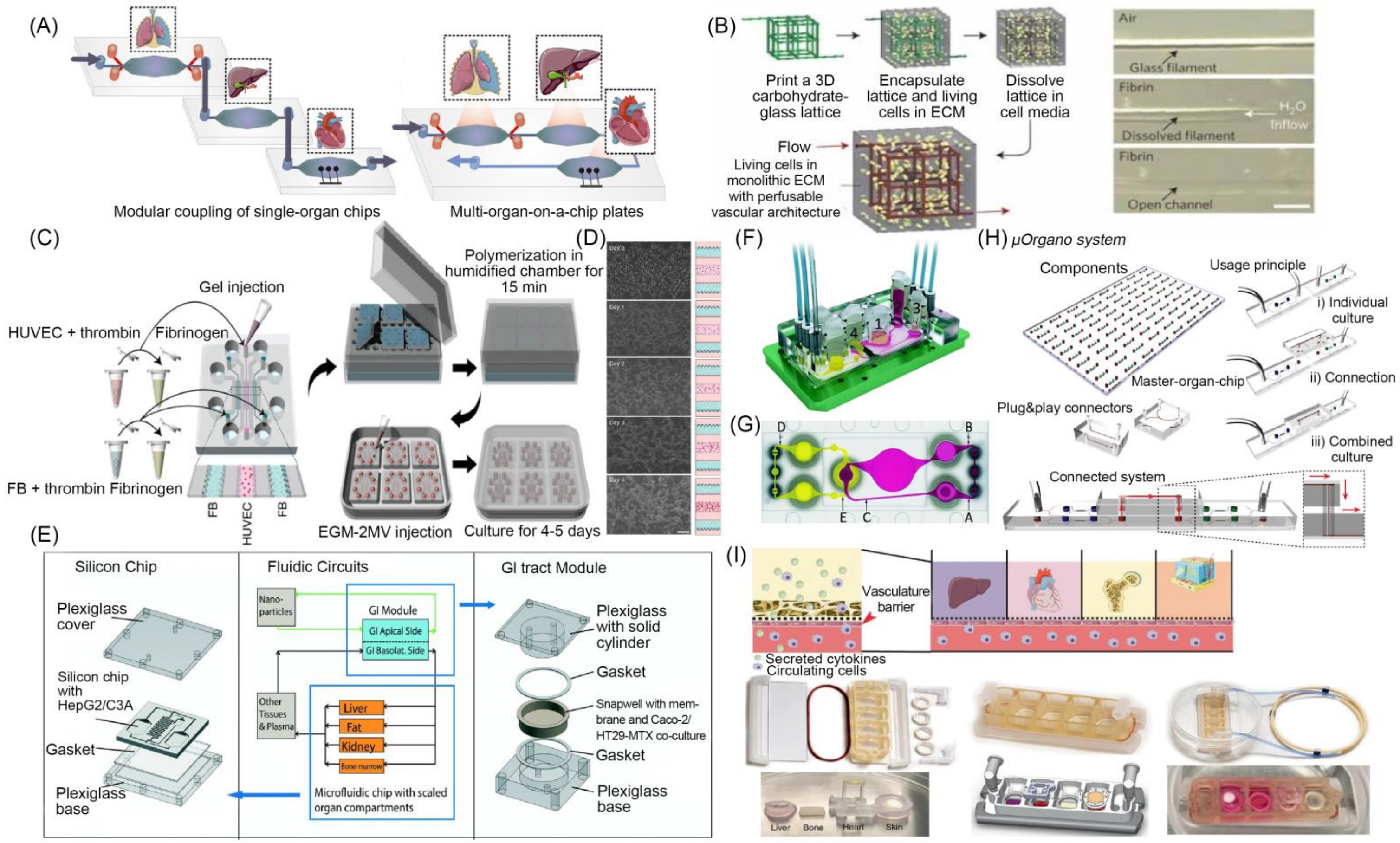



Figure 5. Schematic diagram of the related multi-organ chip structure.

## Technical Challenges

⦿Organ scaling ratio; ⦿Pheromone integration;
⦿Realizing the "human body on a chip."

## System Classification

### Single-organ chip coupling system

⦿Flexible reconfiguration for dynamic studies.

### Multi-Organ-on-a-Chip Plates

⦿Compact structure reduces leakage risk and simulates minimal systemic circulation.

## Vascularized Cascade Technology

⦿3D printing constructs large-scale blood vessels (>100μm); ⦿Endothelial cells generate microvessels (<100μm).

## Cascade Types

⦿**Static cascade**: Specific organs are fixed in single-chip chambers;
⦿**Semi-static cascade**: Organs are pre-cultured and then integrated;
⦿**Flexible cascade**: Plug-and-play modular design.

## Practical Applications

⦿Multi-organ interstitial chip reproduces the pharmacokinetic and pharmacodynamic characteristics of drugs in the body.

# Microbiota-Gut-Brain Axis-Multi-Organ Chip Integration and Applications in Drug Evaluation

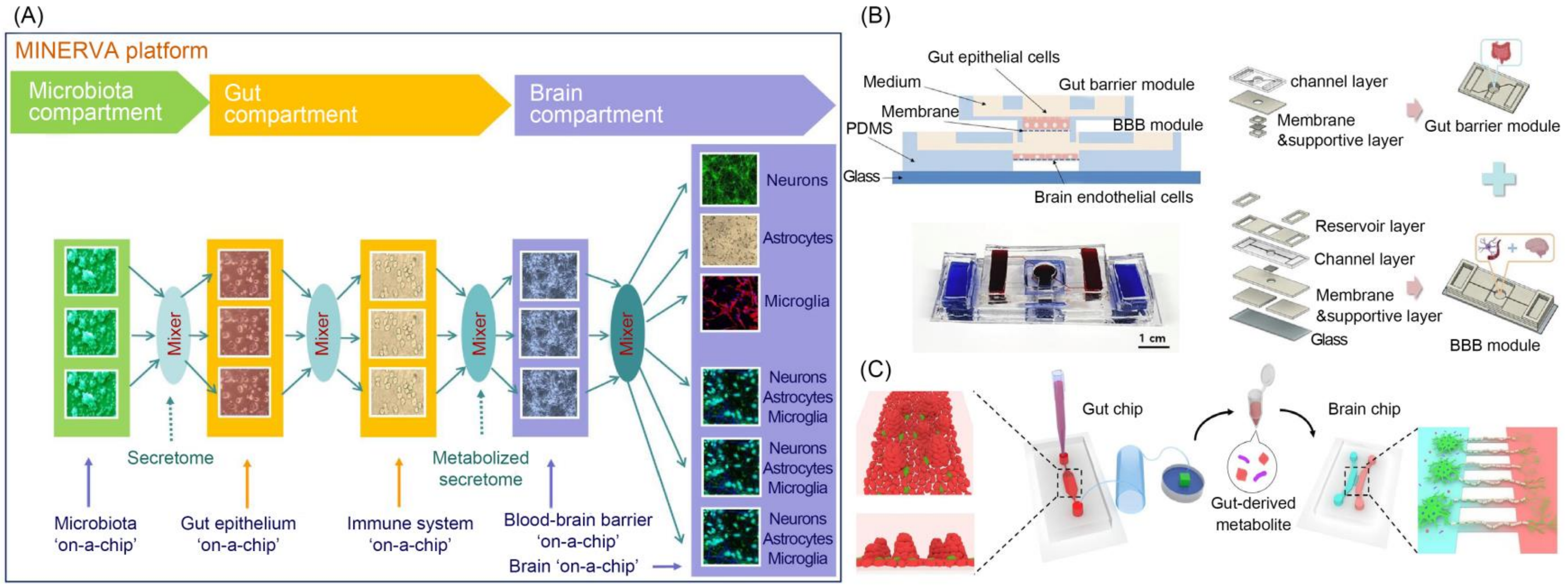



Figure 6. Schematic diagram of the related microbiota-gut-brain axis-multi-organ chips.

## Application Research

⦿MINERVA platform (funded by ERC);
⦿Split-type Gut-Brain Axis-on-a-Chip.

## Mechanism Research

⦿Reveals the impact of gut-derived substances on neurodevelopment and neurodegenerative diseases.

## Drug Screening

⦿Evaluates the regulatory effects of psychotropic drugs and probiotics on the microbiota-gut-brain axis, exploring the potential of microbiota-assisted therapy for neurological disorders.

## Technical Challenges

⦿**Materials and Processing**: Microenvironment requirements for different cell types.
⦿**Cell Growth**: Activity and functional stability of cells in long-term co-culture.
⦿**Fluid Control**: Balancing the regulation of flow rate and pressure at the microscale to match the fluid dynamics of multi-organ modules.
⦿**Signal Analysis**: Real-time monitoring and analysis technology for multi-channel dynamic signals.

# Summary and Outlook

## ❑ Research Significance and Technological Applications

- Reveals the mechanisms of gut-brain interactions, advancing the frontiers of gut science;
- Constructs dynamic cell culture systems, simulating the human physiological environment;
- Applicable to basic research on brain diseases, drug toxicity prediction, and ADME optimization.

## ❑ Future Challenges and Development Directions

### Technical Challenges

- Enhanced precision of physiological environment simulation;
- Stable maintenance of long-term cell activity.

### Innovative Strategies

- Technological Integration:

Microfluidic chips + Tissue engineering + Stem cell culture + Biosensing + Advanced manufacturing.

- Focus Areas:

Functionalization of organoids; Development of real-time monitoring systems; Construction of standardized platforms.

### Expected Impact

- Promotes personalized medicine and precision drug development;
- Reshapes the treatment paradigm for complex diseases.

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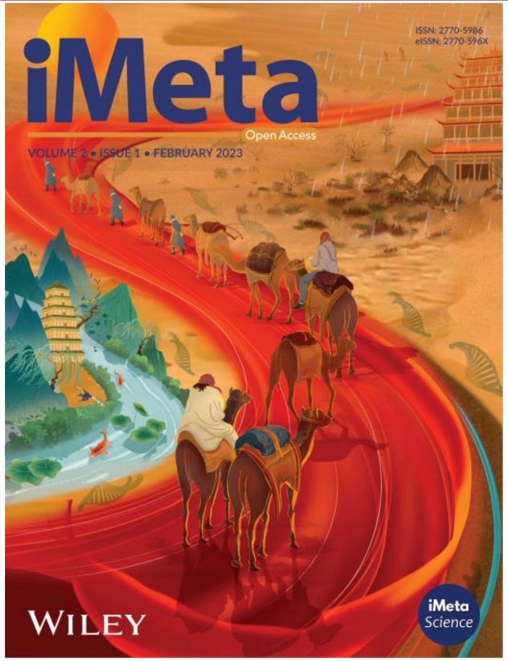
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