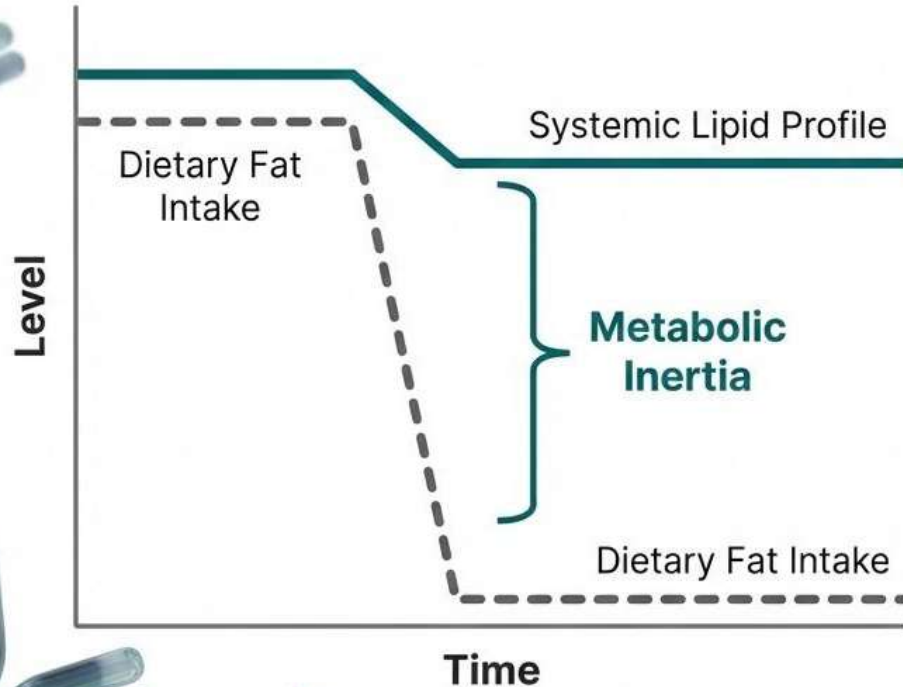


# Breaking Metabolic Inertia

Targeting the Gut FcRn-IgG Interface  
to Reset Metabolic History

Presenter: Hong-Hsing Liu, MD, PhD

# The Clinical Reality: Metabolic Inertia



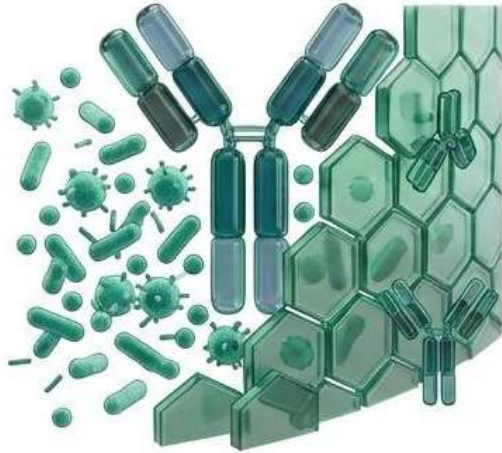
## Diet Switch $\neq$ Metabolic Reset

Even when dietary fat is removed, the body “remembers” the obese state.

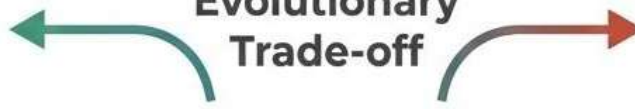
We have identified the mechanism of this biological memory.

# The Hypothesis: Immune Memory as a Double-Edged Sword

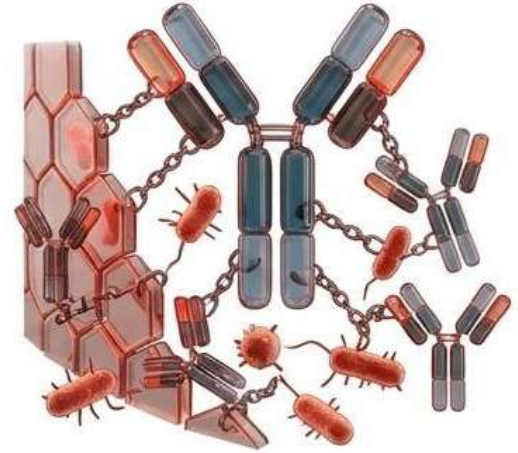
**Protection During Stress**  
(Stabilizes the Gut)



**Evolutionary  
Trade-off**



**Inertia During Recovery**  
(Prevents Adaptation)



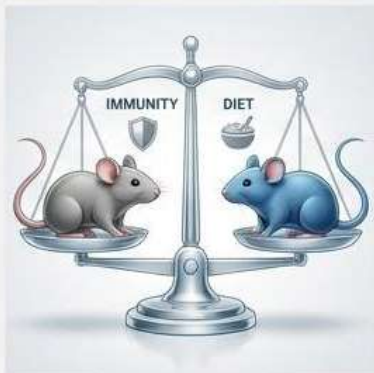
The immune system “remembers” dietary history to protect us.  
But does this protective memory become a trap when we try to recover?

# In Vivo Validation Strategy

## 1. The Phenotype

### NSG vs. BALB/c on HFD

Comparing immunodeficient vs. immunocompetent hosts to establish the immune system's role in diet-induced metabolic changes.



## 2. Proof of Causality

### Adoptive IgG Transfer

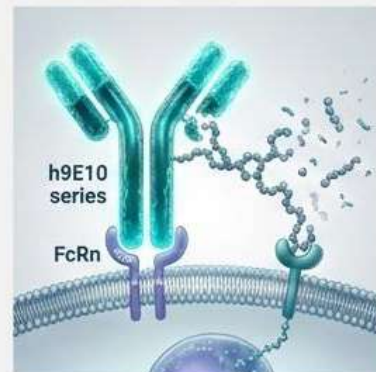
Transferring HFD-conditioned IgG into naive SCID mice to prove IgG alone is sufficient to transfer the microbial and metabolic lock.



## 3. Therapeutic Rescue

### Diet-Switch + FcRn Modulators

Testing if targeted disruption of the gut FcRn-IgG anchor (h9E10 series) can overcome metabolic inertia after dietary correction.



**A systematic approach: From defining the biology to validating the therapeutic intellectual property.**

# The Baseline: Immunity is Required for Microbiome Stability

## Dietary Input



**Normal Chow**  
(Standard Diet)



**High-Fat Diet**  
(HFD Stressor)



**NSG Mice**  
(No Immunity)



**BALB/c Mice**  
(Intact Immunity)

**Result: Unchecked Functional Drift**



**Week 4**



**Week 12**



**Week 20**

**Result: Functional Stabilization**



**Week 4**



**Week 12**



**Week 20**

## Analysis



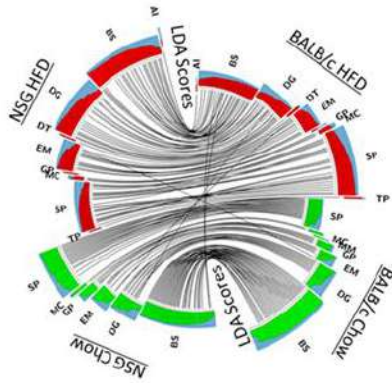
**16S Sequencing**



**Functional Inference**

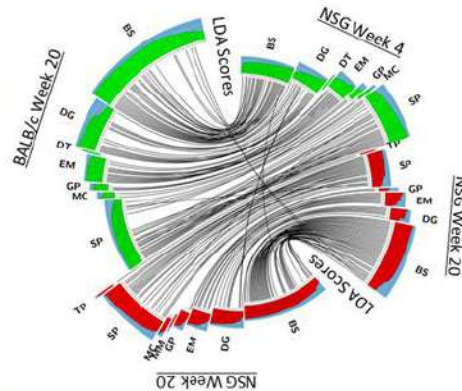
# Identification of the Conserved Immunometabolic Core

## Step 1: The Universal Shock (Week 4)



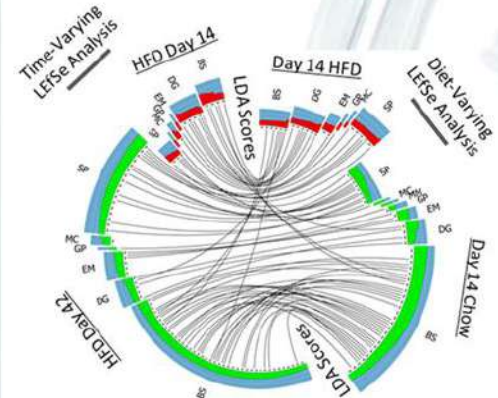
Week 4 HFD vs. Chow LefSe

## Step 2: Immune Stabilization (Week 20)



HFD Week 4 vs. 20 LefSe

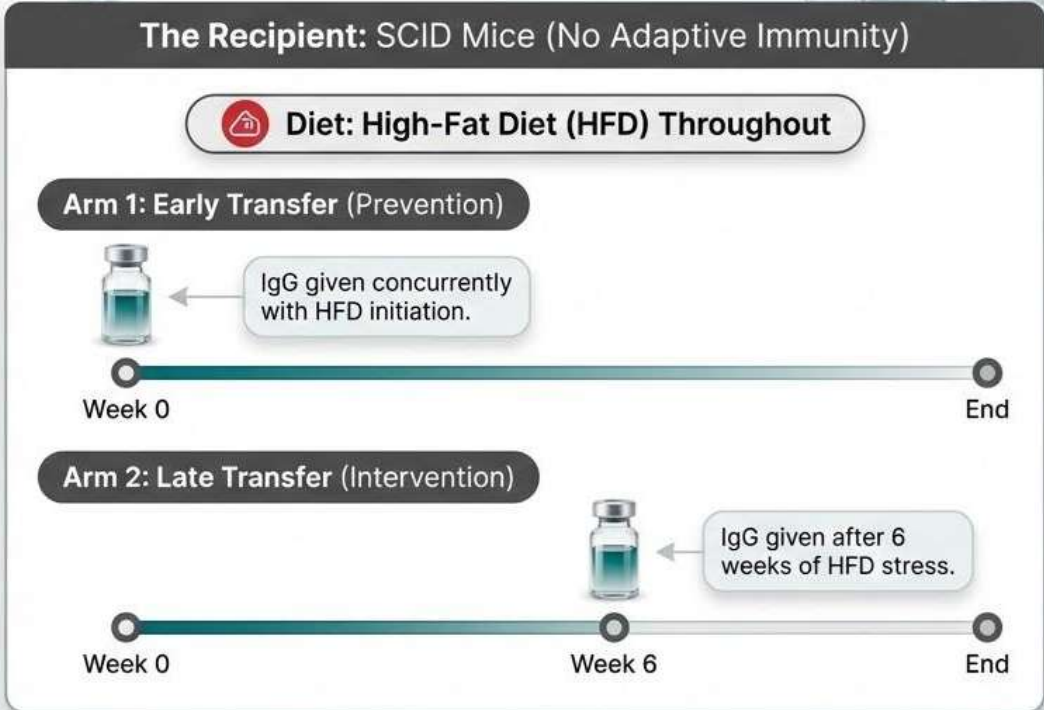
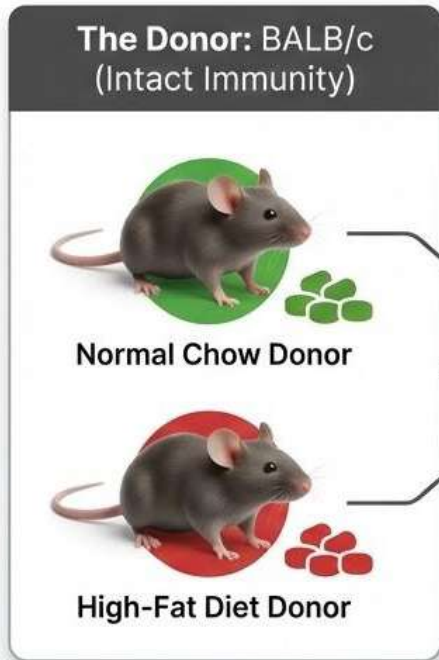
## Step 3: Cross-Strain Validation



Diet/Time LefSe for C57BL/6

The Discovery: 17 Core  
Immune-Dependent Pathways

# Proving Causality: IgG Transfer Strategy



**Key Question: Is immune memory sufficient to stabilize the microbiome against HFD stress?**



# The Double-Edged Sword: Stability becomes Inertia

During HFD Stress



**IgG Stabilizes the Microbiome**  
(Protective)

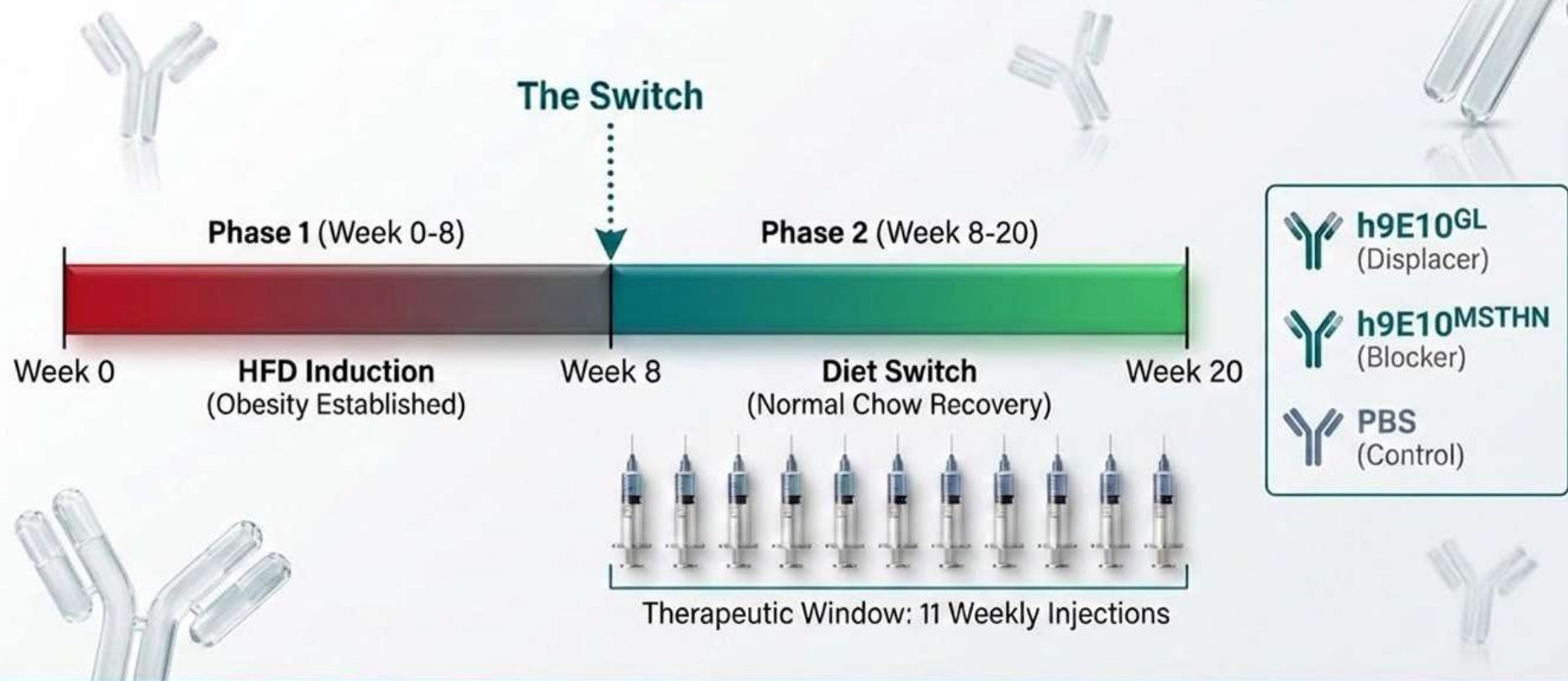
During Dietary Recovery



**IgG Prevents Reset**  
(Maladaptive)

**Hypothesis: To cure metabolic inertia, we must physically unlock the immune memory.**

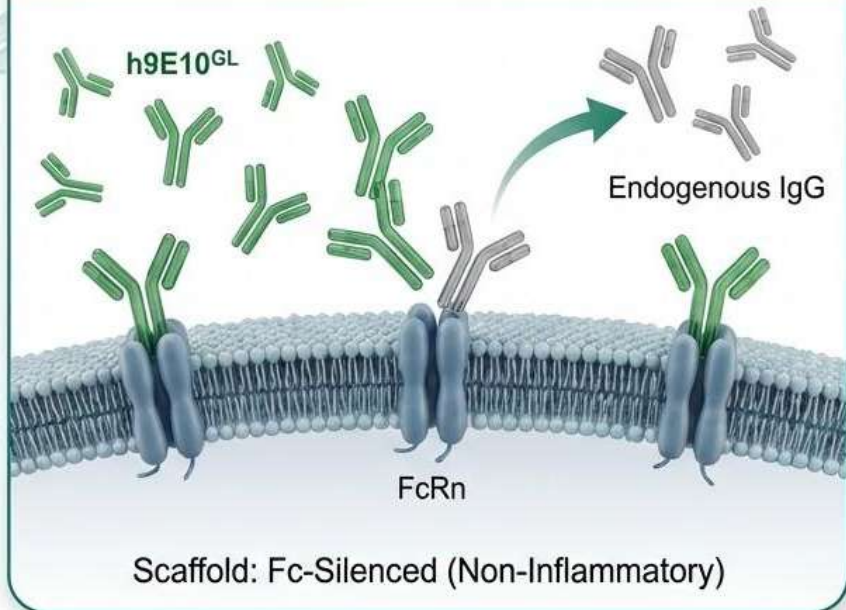
# The Hysteresis Check: Diet Switch Protocol



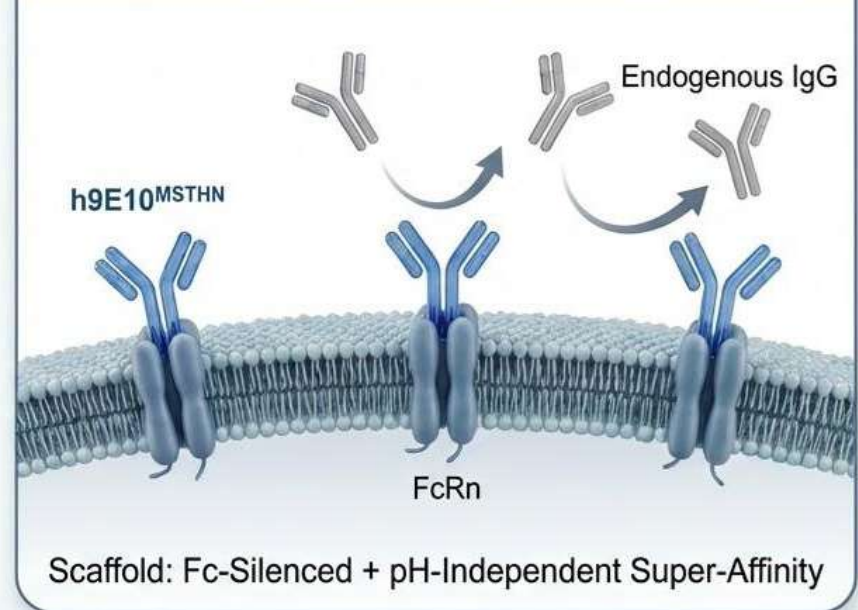
Can we break the metabolic memory even after the diet has improved?

# Two Distinct Mechanisms to Disrupt the “Anchor”

## h9E10<sup>GL</sup>: Competitive Displacement



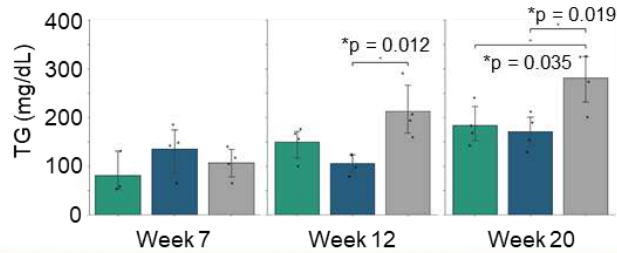
## h9E10<sup>MSTHN</sup>: Functional Blockade



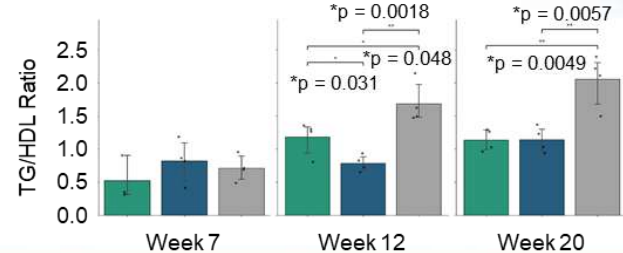
**Objective: Targeted modulation of the intestinal FcRn-IgG interface.**

# Therapeutic Efficacy: Overcoming Metabolic Inertia

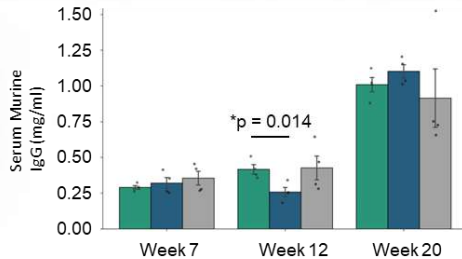
## Serum Triglycerides (TG)



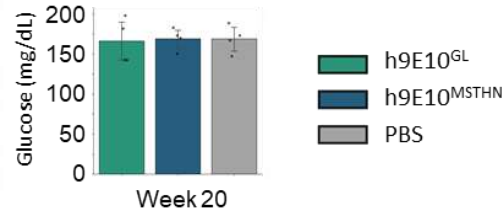
## Cardiovascular Risk (TG/HDL Ratio)



## Serum IgG Levels



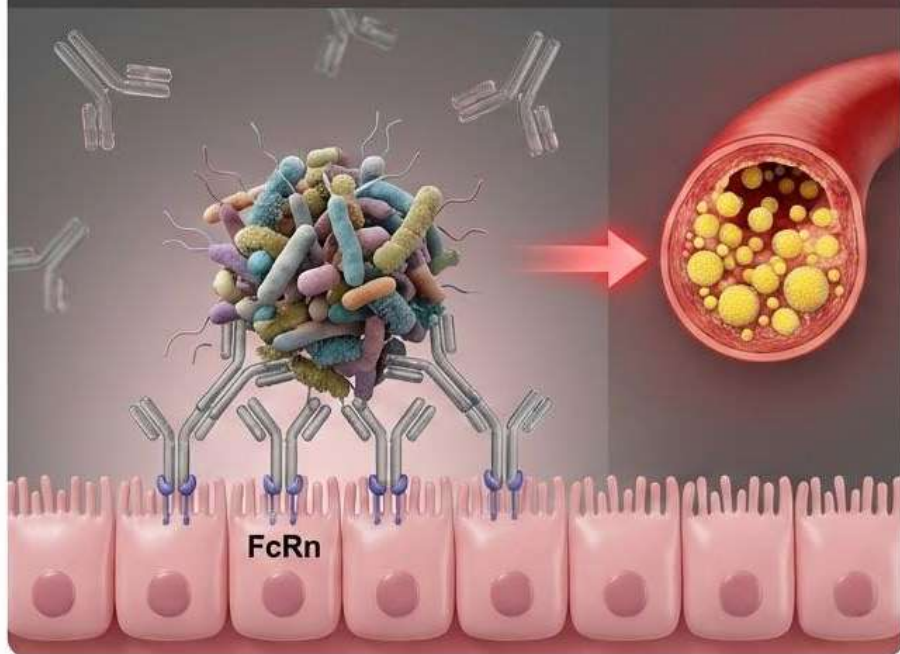
## Serum Glucose



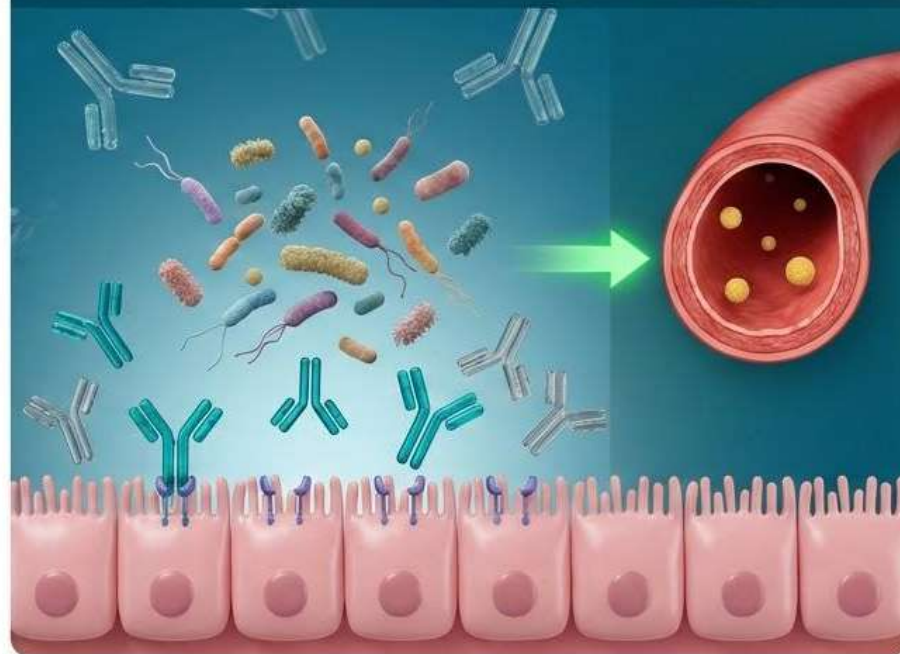
**Conclusion: Disconnecting the immune memory resets the lipid trajectory, overcoming metabolic inertia.**

# The Paradigm Shift: Targeting the Gut-Immune-Metabolic Axis

## The Pathogenic Lock (Metabolic Inertia)



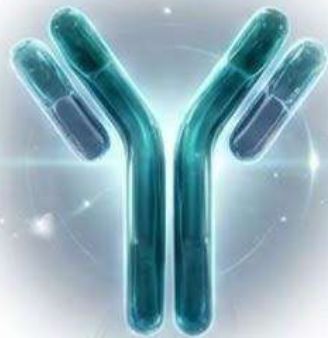
## The Therapeutic Reset



**Conclusion: Disrupting the intestinal FcRn-IgG interface breaks the immune memory lock, restoring microbial flexibility and resetting systemic lipid trajectories.**

# Future Horizons: Expanding the Therapeutic Landscape

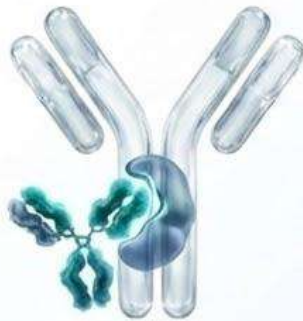
## Pillar 1 Receptor Blockade



Repurposing clinical-stage anti-FcRn antibodies.

Proof-of-Concept Established  
(h9E10 series)

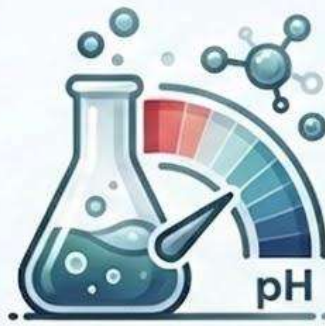
## Pillar 2 Fc-Targeting Agents



\* **Concept:** Directly masking or capping the Fc region of the IgG.

**Advantage:** Avoids targeting the receptor itself; highly specific to the “cargo”.

## Pillar 3 Environmental Disruption



\* **Concept:** Modulating the local mucosal pH to prevent IgG docking.

**Advantage:** Enables non-systemic, oral small-molecule formulations.

**Vision:** A flexible platform allowing multiple ways to disrupt the metabolic lock—biological, chemical, or physical.

2016 – 2026: A DECADE OF DISCOVERY

Thank  You

Ready to uncouple the past and reset the future.