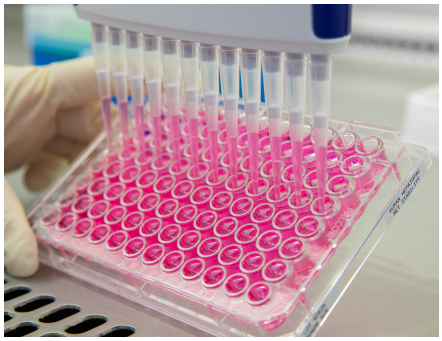
HEPATOMUNE Cultures

A Long-Term, Stable *In Vitro* Hepatic Inflammation Model

HEPATOMUNE® cultures are a tri-culture of hepatocytes, stromal cells and Kupffer cells in 24- and 96-well plate formats. The system mimics the physiological microenvironment of the liver, and provides a unique model to study cytokinesand cytokine modulators.



Features and Benefits

HEPATOMUNE cultures offer superior performance compared to conventional hepatocyte models, including suspension, monolayer or sandwich cultures. Convenient, ready-to-use HEPATOMUNE kits include plated cells and required maintenance and application media. A detailed step-by-step instruction guide is available online. HEPATOMUNE cultures remain viable for up to ten days with the following characteristics:

- Display *in vivo* like morphology
- Express liver-specific genes
- Exhibit transporter activity
- Secrete diverse liver-specific products
- Retain functional phase I/II drug metabolizing enzymes
- Maintain functional Kupffer cells that respond to inflammatory stimuli and are able to perform phagocytosis

Research Applications

Our HEPATOMUNE cultures are a unique research tool for evaluating long-term immune-related and inflammation-mediated liver injury and may be used for numerous *in vitro* models, including:

- Healthy liver physiology and inflammation
- Inflammation-related diseases, including NAFLD / NASH
- Long-term hepatotoxicity of drug candidates assessed using ALT, ATP, urea or GSH as study endpoints
- Protein and small molecule drug-drug interactions
- Mechanisms of toxicity

HEPATOMUNE Cultures

Manufacturing Process and Validation

HEPATOMUNE cultures are engineered using a microfabrication method developed and patented at MIT. In each well, human hepatocytes are organized into colonies with empirically optimized dimensions. The hepatocytes are surrounded with murine fibroblasts. After the hepatocyte-fibroblast co-culture is established, primary human Kupffer cells are added at a precise ratio of 10:4.

Kupffer cells serve as resident macrophages of the liver; their activation leads to the release of inflammatory mediators. The ratio of Kupffer cells to hepatocytes in HEPATOMUNE culture mimics those seen in an inflamed state.

Kupffer cell functionality is confirmed via pHrodo-S. *aureus* phagocytosis and CD68 staining.

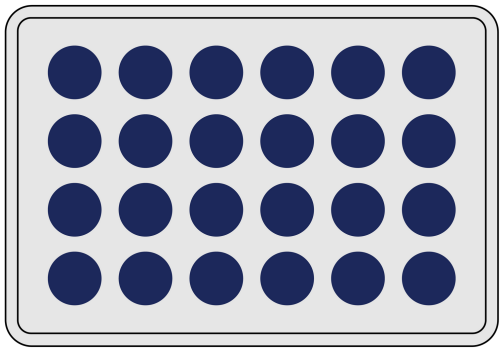
Hepatocytes within the culture demonstrate normal metabolic function, as assessed by CPY3A4 activity and urea synthesis.

HEPATOMUNE Plate Options

"Full" HEPATOMUNE Plates

All wells have HEPATOMUNE® cultures and can accommodate numerous experimental designs.

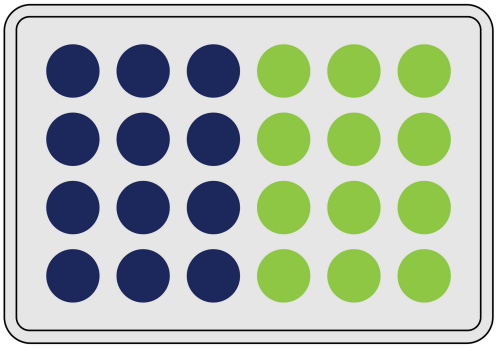
"Full" HEPATOMUNE plates



"Half and Half" HEPATOMUNE Plates

Half the wells have HEPATOMUNE cultures, and the other half do not, making them standard HEPATOPAC® cultures. This allows side-by-side comparison of cultures with and without Kupffer cells.

"Half and Half" HEPATOMUNE plates



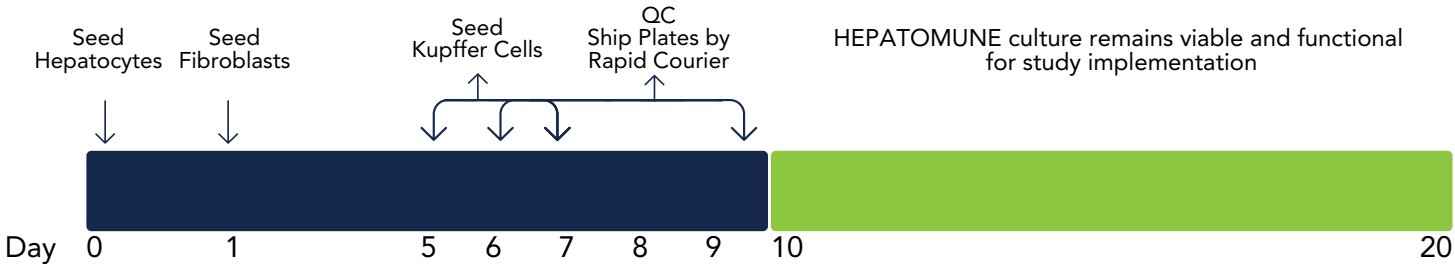
The 96-well format is available in high-content imaging (HCI) plates as well as standard plates.

The following human hepatocyte cell types may be used:

- Cryoplateable hepatocytes
- TRANSPORTER CERTIFIED™ hepatocytes
- LIVERPOOL® cryoplateable hepatocytes

HEPATOMUNE Plate Timeline

HEPATOMUNE kit delivery is timed to meet your needs. It takes approximately 10 days from the initial cell seeding to plate delivery. After delivery, you have an additional 10 days to implement your studies.



Long-term Culture Validation Studies

As shown in Figure A, LPS stimulation of HEPATOMUNE (HM) cultures exacerbated trovafloxacin toxicity, marked by a leftward shift in the ATP dose-response curve, as compared to HEPATOPAC (HP) cultures. Figure B shows that IL-6 release remained stable for at least 15 days post plating and at least 10 days after receipt of the plate.

Figure A

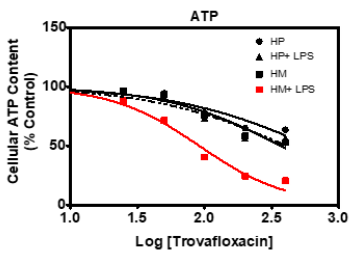
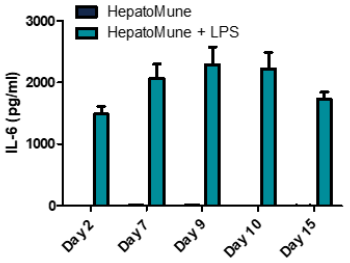


Figure B



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