Flocel

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DIV-BBB 2.0: TEER Measurement and Fluid Perfusion System
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Introduction:

Each year pharmaceutical companies spend millions of dollars to test drugs using in-vitro models of the blood brain barrier (BBB). Flocel's family of Dynamic In Vitro Blood-Brain Barrier (DIV-BBB) products offer a unique and superior approach to this method by utilizing real human endothelial cells and the formation of tight junctions within its dynamic system, resulting in a physiologically accurate reflection of true BBB characteristics.

Version 2.0 of the DIV-BBB model boasts a highly-modular subsystem design that allows the user to assemble and modify their experimental setup in a manner most befitting their test-specific needs:

Fluid Perfusion:

The *DIV-BBB 2.0* operates with a fluid perfusion system that can be supplied from either a piezo micro-pump for single-cartridge experiments (Fig. 1, left) or four peristaltic pumps simultaneously for concurrent trials (Fig. 1, right). These pumps can provide steady-state and peristaltic (pulsatile) fluid flow through the cell culture modules, and can be user-controlled for flow rate and beats-per-minute. With the peristaltic pump, the user may also select amongst a variety of output pressures and tubing diameters, which are displayed on our website.

Figure 1: User may choose between single piezo micropump (left) or four peristaltic pumps (right).

In-Vitro Cell Culture Modules:

Flocel offers a wide array of single-use cell culture modules which are designed to perform reliably and consistently in both pharmaceutical and immunological testing conditions. These products range from the single fiber transmural cartridge for on-stage microscopy and drug extravasation trials (Fig. 2, left) to the multi-fiber environment for high-throughput pharmacokinetic experiments (Fig. 2, right). All varieties of cell culture module -in accordance with the Fluid Perfusion system- promise a high-quality and confluent growth of luminal cells.

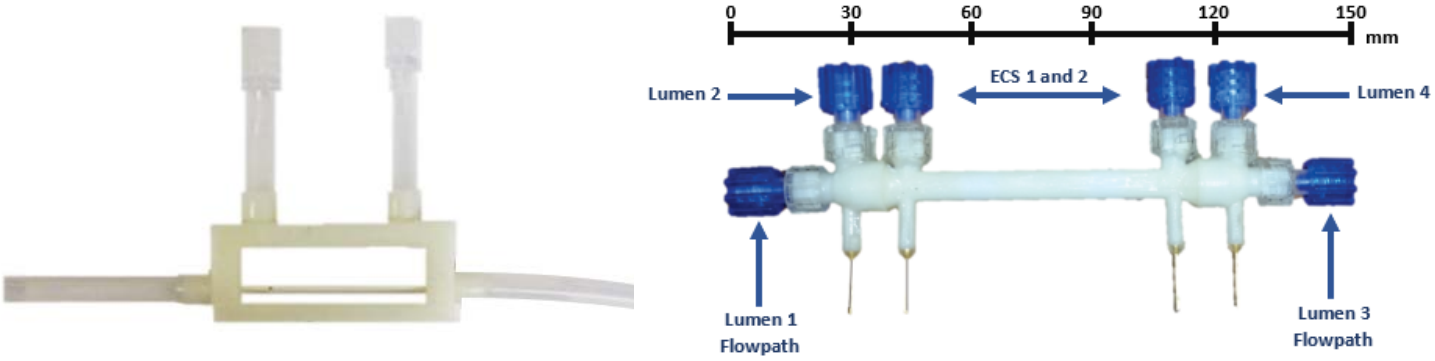


Figure 2: Example of the single fiber transmural cartridge (left) and multi-fiber cartridge (right), compatible with both piezo and peristaltic pump setups.

Trans-Endothelial/Epithelial Electrical Resistance (TEER):

A favored approach to analyzing cell culture modules is Trans-Endothelial/Epithelial Electrical Resistance (TEER), which provides rapid evaluation of the cell layer's integrity by measuring impedance across its boundary. The *DIV-BBB 2.0* comes equipped with a TEER Measurement Unit and four docking platforms, which translates to the concurrent testing of up to four cell culture modules. Trials can be performed at sampling frequencies up to 1 kHz for any duration of time, and data is automatically logged to a saved file of the user's preference. These systems are controlled via the *DIV-BBB 2.0* software package which is received upon purchase of the model.

DIV-BBB 2.0 Software:

Operation of the system is performed within the *DIV-BBB 2.0* software package, an intuitive interface for the dynamic modification of TEER and pump testing parameters (Fig. 3). *The TEER Measurement User Interface* displays separate test pages for parameter selection and calibration of raw data output (upper left), frequency sweeps (upper right) and time sweeps (lower left). The *Fluid Perfusion User Interface* (lower right) simplifies the task of directing up to four fluid perfusion channels by allowing flow rate and type of flow to be selected for each pump head. In the event of a bug report, Flocel offers a rapid patching and redistribution of the software.

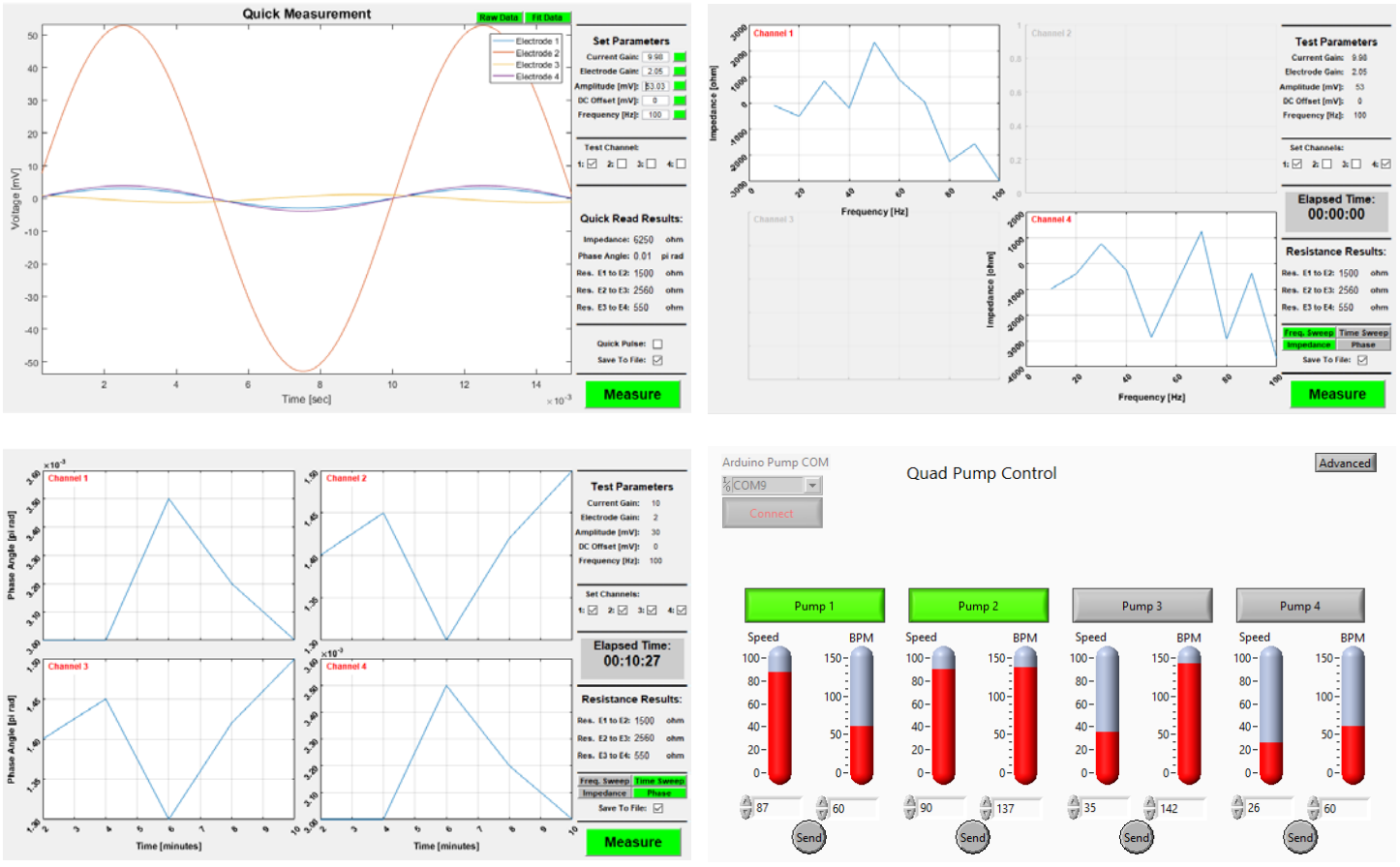
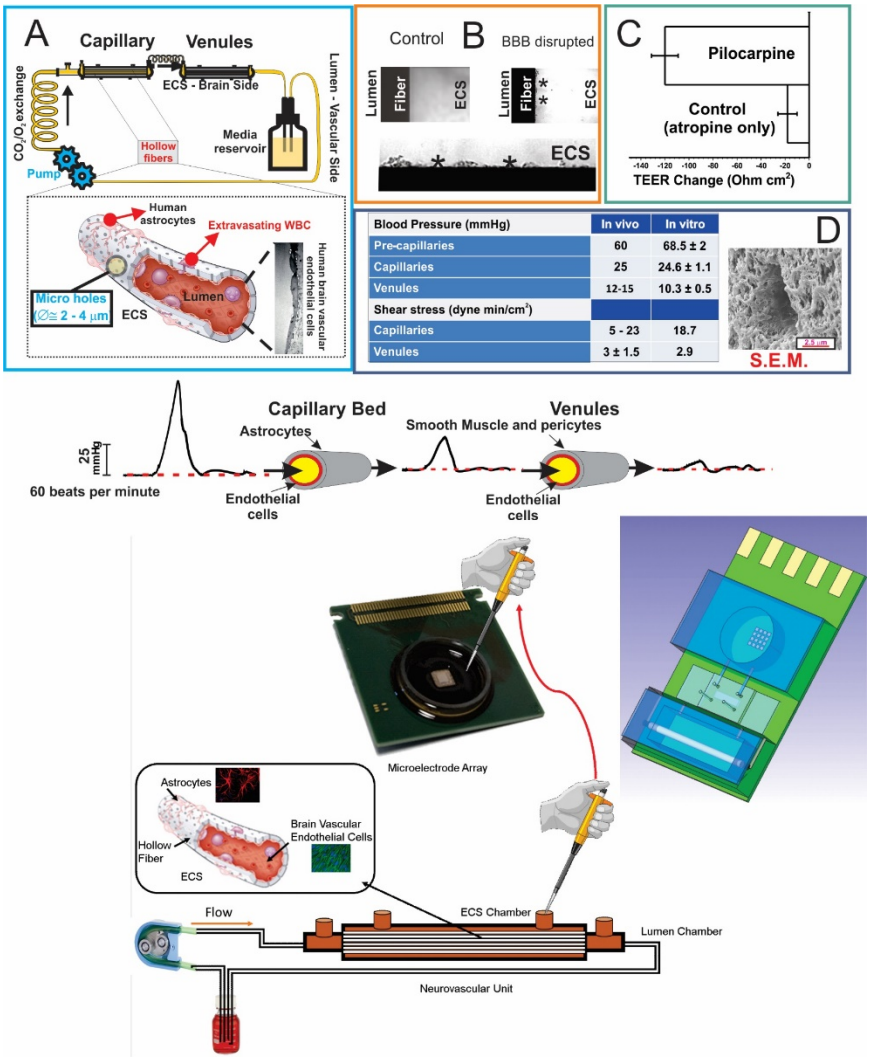


Figure 3: TEER parameter selection and calibration screen (upper left), frequency sweep screen with 2 of 4 channels selected (upper right), time sweep screen with all 4 channels selected (lower left) and interface for controlling fluid perfusion with up to four independent pump heads (lower right).

Testing Capabilities of the DIV-BBB 2.0:

Examples of in-vitro studies that can be performed with the *DIV-BBB 2.0* include:

1. The isolation, growth and identification of cells derived from multicellular organisms. The *DIV-BBB 2.0* is permissive for the growth of endothelial, epithelial, glial and tumor cells, as well as pericytes.
2. The use of surgical samples isolated from human brain or other organs where blood flow is of essence.
3. Effect of shear stress in arteries and veins.
4. Study of metastatic tumor migration from peripheral organs to the brain.
5. Prediction of efficacy and toxicity antitumor drugs.
6. In-vitro testing has been used to characterize the effects of drug transporters in human or rodent brain.
7. Drug delivery via nanospheres, viral vectors and siRNA have been studied in humanized and rodent models of the BBB.
8. Efficacy and penetration of antibody drugs or other large molecular weight protein.
9. Distribution, metabolism, and excretion processes of drugs in a model of human body with hepatocytes, brain barriers and other peripheral organ systems.



Overall, the *DIV-BBB 2.0* enables more accurate pharmacokinetic and toxicological studies and reflects in vivo blood-brain barrier properties. Its replication of important endothelial cell-astrocyte interactions and ability to sustain 4 cell culture modules at once will substantially reduce drug development cost and experimental time.