A method of evaluating cytocompatibility of devices for the delivery of cells

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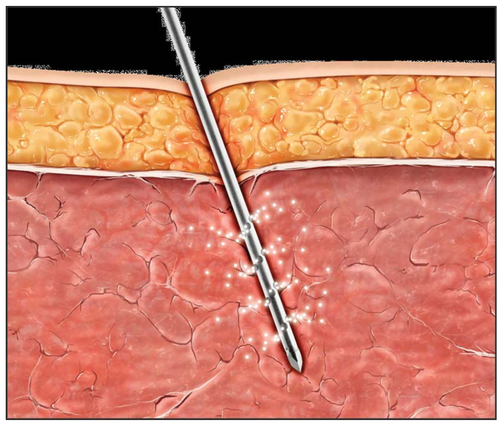
ABSTRACT

The current device biocompatibility testing, while necessary, is not sufficient in addressing cell delivery compatibility. As such, a series of tests were devised to examine cell delivery capabilities focusing on cell recovery, viability, and functionality. Multiple cell sources have been tested, including point-of-use and human-blood-derived total nucleated cells (TNC, HemaTrate™ Blood Filtration System). Human bone marrow mesenchymal stem cells (hBMMSC, RoosterBio) were utilized as model cells. The ProFusion™ Therapeutic Infusion Needle, a sideported infusion needle designed for the delivery of cells or other therapeutic agents into tissues in a distributed manner, and the Compass® CT Disposable Pressure Transducer in-line pressure monitor have been evaluated as test devices. Recovery was determined by counting total cell quantity before and after injection. Viability was determined concurrently using either trypan blue exclusion or acridine orange and propidium iodide staining. Functionality testing was conducted in a cell dependent manner. For the blood-derived TNC concentrate, functionality consisted of cell analysis characterization. For the hBMMSC, functionality consisted of proliferation. Devices were tested in numbers and conditions sufficient to characterize the performance in a worst case situation. For example, ProFusion was tested to represent worst case, with a 19-gauge x 15cm needle tested at 30mL/min flowrate and a 25-gauge x 7.5cm needle tested at 11.5mL/min. Both the ProFusion and the Compass CT passed the acceptance criteria for the recovery, viability, and functionality tests indicating cytocompatibility. These results show that the ProFusion and Compass CT are compatible with cell delivery and these analyses provide a basis for future testing of devices used in cell delivery applications.

MATERIALS and METHODS

ProFusion™ Therapeutic Infusion Needle



Compass® CT Disposable Pressure Transducer

HemaTrate™ Blood Filtration System

ProFusion Cytocompatibility Testing with hBMMSC

- hBMMSC (RoosterBio) at one million cells/mL tested
- ProFusion (21-gauge x 15cm and 25-gauge x 7.5cm) were tested against single lumen BD Spinal needles (20-gauge x 15cm and 25-gauge x 7.5cm)
- 18 x 1mL injections were performed for each needle type
- Injection rate was 30mL/min for the 20/21-gauge needles, 11.5mL/min for 25-gauge ProFusion, and 13.0mL/min for the 25-gauge Spinal needle (sufficient to create 825mmHg injection pressure)
- Cells were immediately assayed (hemocytometer) for recovery and viability, and at seven days for proliferation

ProFusion Cytocompatibility Testing with HemaTrate Total Nucleated Cell (TNC) Concentrate

- TNC preparations were obtained with HemaTrate from six donors with 110mL of whole blood anticoagulated with 10mL ACD-A
- ProFusion (19-gauge x 15cm and 25-gauge x 7.5cm) were tested against single lumen BD Spinal needles (20-gauge x 15cm and 25-gauge x 7.5cm)
- 18 x 0.5mL injections were performed for each needle type at the above flow rates
- Samples were immediately assayed (Cellometer® Auto 2000) for recovery, viability, and white blood cell (WBC) differential

Compass CT Cytocompatibility Testing with hBMMSC

- hBMMSC (RoosterBio) at one million cells per mL tested
- Compass CT and Compass CT Port were tested in conjunction with a Cantata® Microcatheter (2.5Fr, Cook® Medical)
- 18 x 1mL injections were performed for each Compass CT type and control
- Injection rate was 11mL/min (sufficient to create 825mmHg injection pressure)
- Cells were assayed (hemocytometer) immediately for recovery and viability, and at seven days for proliferation

All tests were conducted in accordance with ASTM 3206-17 Standard Guide for Assessing Medical Device Cytocompatibility with Delivered Cellular Therapies.

RESULTS

ProFusion Cytocompatibility Testing with hBMMSC

- ProFusion tested as non-inferior compared to the control needles
- Overall recovery was greater than 85% for all samples
- Overall viability was greater than 95% for all samples
- hBMMSC ability to proliferate was unaffected by injection

Table 1. hBMMSC recovery, viability, and proliferation comparison after injection through needles. ProFusion 21-gauge compared against Spinal 20-gauge on top. ProFusion 25-gauge compared to Spinal 25-gauge on bottom. Average (SD)

Needle	Recovery	Viability	Population Doublings
ProFusion 21-gauge x 15cm	90% (15%)	96% (2%)	3.4 (0.5)
Spinal 20-gauge x 15cm	89% (13%)	97% (1%)	3.4 (0.4)
ProFusion 25-gauge x 7.5cm	87% (20%)	95% (2%)	3.5 (0.3)
Spinal 25-gauge x 7.5cm	90% (23%)	96% (2%)	3.3 (0.4)

ProFusion Cytocompatibility Testing with TNC Concentrate

- ProFusion tested as non-inferior compared to the control needles
- Overall recovery was greater than 99% for all samples
- Overall viability was greater than 99.5% for all samples
- WBC differentials were not altered as measured by change in ratio of lymphocyte concentration to neutrophil concentration

Table 2. TNC recovery, viability, and change in lymphocyte/neutrophil ratio comparison after injection through needles. ProFusion 21-gauge compared against Spinal 20-gauge on top. ProFusion 25-gauge compared to Spinal 25-gauge on bottom. Average (SD)

Needle	Recovery	Viability	Change in Lymphocyte/Neutrophil ratio
ProFusion 19-gauge x 15cm	100% (3%)	99.7% (0.2%)	5.4% (5.5%)
Spinal 20-gauge x 15cm	100% (2%)	99.8% (0.3%)	5.3% (4.6%)
ProFusion 25-gauge x 7.5cm	99% (3%)	99.6% (0.4%)	6.3% (7.8%)
Spinal 25-gauge x 7.5cm	99% (2%)	99.7% (0.2%)	4.9% (4.1%)

Compass CT Cytocompatibility Testing with hBMMSC

- Compass CT and Compass CT Port tested as cytocompatible with no decrease in recovery, viability, or proliferation compared to Cantata injection alone
- Overall recovery was greater than 90% for all samples
- Overall viability was greater than 85% for all samples
- hBMMSC ability to proliferate was unaffected by injection

Table 3. hMMSC recovery, viability, and proliferation comparison after injection through Cantata with or without Compass CT. Average (SD)

Device	Recovery	Viability	Population Doublings
Compass CT	99% (13%)	86% (4%)	3.9 (0.5)
Compass CT Port	93% (15%)	85% (4%)	4.0 (0.5)
Cantata (Control)	96% (18%)	87% (4%)	3.7 (0.5)

CONCLUSION

- Ensuring cell compatibility with intended use may help provide confidence in devices used for clinical cell delivery
- ProFusion and Compass CT are compatible with cell injections
  - As tested with hBMMSC (ProFusion and Compass CT) and TNC concentrate (ProFusion)
  - Minimal effect on cell recovery and viability
  - Minimal effect on cell functionality as measured by proliferation or WBC differentials

CONTACT INFORMATION

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