ACOUSTIC CELL WASHING AND RAMAN SPECTROSCOPY TECHNOLOGIES TO ADDRESS CELL THERAPY BIOPROCESS CHALLENGES

James M. Piret, Felix Trampler, SonoSep Technologies Inc.
james.piret@ubc.ca, Department of Chemical & Biological Engineering
Michael Smith Laboratories, University of British Columbia
Mitchell Braam, Catherine Gordon, Amarandi H. Morales, June Wong, Christopher Sherwood,
Stanislav O. Konorov, Shreyas Rangan, Sepehr Kamal, H. Georg Schulze
Timothy Kieffer, Michael W. Blades and Robin F.B. Turner
Departments of Cellular & Physiological Sciences, Chemistry, Electrical & Computer Engineering
Michael Smith Laboratories, University of British Columbia
Vancouver, BC Canada

Many organizations are confronting the challenges of economically ensuring the manufacture of safe and efficacious cell therapy products. These processes often depend on devices and methods that were developed for only related applications, such as blood cell processing or scientific research. Thus, we are in a window of opportunity to tailor innovative technologies to address the emerging specialized needs of cell therapy manufacturing.

The most frequent unit operation is to wash cells between process stages, such as from DMSO containing cryopreservation medium to culture expansion medium. In particular for relatively small-scale autologous cell therapy processing, cell washing is imperfectly performed by closed system blood cell centrifuges or filters. We previously developed an acoustic cell separation device, widely used for over 15 years in CHO cell perfusion cultures. This technology acts as a non-fouling filter for months of operation, by using the forces generated in ultrasonic standing wave fields. These forces separate cells from medium based on differences in density and compressibility. Greater than 99.9% cell washing with 95% washed cell recovery efficiencies have been provided by our device. We also have recently enhanced the acoustic technology to perfuse 100 million cell/mL cultures, maintaining >99% cell separation efficiencies. This provides an alternative high performance closed manufacturing system, to perfuse, concentrate and wash cells, with no physical filter barrier or mechanical moving parts.

While many clinical trials have had few adverse events, the great promise of cellular therapies comes with grave risks, such as from potentially oncogenic pluripotent cells present in embryonic stem cell derived populations. There is an urgent need for process analytical technologies to non-invasively monitor mammalian cell populations and improve the reliability of manufactured cell products. This includes to monitor both the expected differentiation as well as to detect unexpected cells in the process. Recently, technological advances have led to an explosive growth in the capabilities of Raman spectroscopy, increasing the potential for novel applications. We are developing the use of this spectroscopic technique to track cell development, by measuring macromolecular changes in cell samples from cultures where stem cells are differentiated towards insulin-producing cells for the treatment of diabetes. Raman spectroscopy has great potential to provide continuous on-line assessment of cell quality during the manufacture of cell-derived therapeutic cells.