PROCESS ANALYTICAL UTILITY OF RAMAN SPECTROSCOPY FOR CELL THERAPY MANUFACTURING

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New clinical therapies based on implanting living cells into patients offer great promise to cure degenerative and deadly diseases, including Type I diabetes and cancers, with hundreds of clinical trials initiated yearly. However, populations of living cells are far more complex (and inherently variable) than any molecular therapeutic and they cannot be either purified or analyzed anywhere near as stringently. The long-term success of cell-based therapeutics will depend largely on the development of improved methods to validate both the final cell product quality as well as the expected critical process parameter levels during manufacturing processes. Raman spectroscopy offers a label-free approach to distinguish cell types and physiological states by analyzing cellular macromolecular composition changes. This optical analytical method has already been implemented as a noninvasive CHO cell process analytical technology. Using Raman microscopy, we have shown that spectral markers, such as the ratio of nucleic acid to lipid-associated band intensities can discriminate between various types of cell death. In our work towards developing process analytical technologies for stem cell and T-cell based therapies, we have also shown that the ratio of nucleic acid to protein-associated band intensities, can discriminate between stem cells and their differentiated progeny, as well as T-cell subtypes and activation stateseither stem cells or naïve T-cells and their differentiated progeny. We have used Raman microscopy to analyze the directed differentiation of stem cells to yield insulin-producing pancreatic cells for treating Type I diabetes, a manufacturing process that involves seven stages of differentiation. We were able to distinguish with Raman spectral markers off-target cell type emergence, whereas spectral features assigned to disulfide bond content correlate strongly with increasing insulin levels in on-target differentiated cells. Thus, Raman measurements can be used to infer the purity and even the potency of manufactured cells, potentially feedback controlling the harvest and other timing of manufacturing processes. Raman spectroscopy thus offers a promising approach to provide a highly informative, non-destructive means to enhance our ability to monitor, validate and control the quality of cell therapy manufacturing.

Rangan et al., "Applications of Raman Spectroscopy in the Development of Cell Therapies: State of the Art and Future Perspectives", Analyst, 145:2070-2105, 2020.