FROM BIOREACTORS FOR PROTEIN THERAPEUTIC PRODUCTION TO BIOREACTORS FOR TESTING EFFICACY AND SAFETY OF PROTEIN THERAPEUTICS

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The tremendous successes of mammalian cell culture engineering since the 1980's made our modern era of protein therapeutics a reality, bringing tremendous new possibilities for targeted intervention, but also additional challenges in pre-clinical development due to the species specificity of biologics. While the efficacy and safety of all drugs intended for humans is often difficult to extrapolate from assays in animal models and traditional cell cultures, the situation is significantly more difficult for biologics. Traditional cell culture modes, even with human cells, often fail to capture the complexity of pathways, which may involve multiple cell types and cross-talk between different organ systems. The species specificity of most biologics precludes testing in most common animal models. Thus, adverse events are observed in the clinic due to lack of adequate predictive models. For example, the anti IL-6 receptor Tocilizumab, developed to treat chronic inflammatory diseases like arthritis, earned a warning label from the FDA after clinical evidence that the metabolism of statins and other drugs was altered by Tocilizumab in ways that were not predicted by pre-clinical models. (Long, Cosgrove et al. 2016).

The modern field of "organs-on-chips" or "microphysiological systems (MPS)" is poised to address these gaps, and is coming full circle back to the wealth of knowledge about cell culture bioreactor performance produced by the therapeutic protein field. The field of "organs on chips" had its origins several decades ago with demonstrations by Michael Shuler and others that facets of human drug pharmacokinetics could be replicated by interconnected cultures of various cell lines (liver, fat, etc). These initial demonstrations were powerful but ultimately limited by the simplicity of the cell cultures – cell lines that mimicked only modest facets of the functions of the in vivo organ system. Over the past decades, tremendous advances in microfluidics, biomaterials, and technologies to process and make available primary human cells have dramatically increased the human-ness of in vitro cultures. Interestingly, cell lines are also still commonly used, and there has not yet been a thoughtful appreciation of how the basic metabolic functions of the tissue engineered constructs may affect the performance of these systems. Special challenges exist in formulating common media, for example, in interconnected organ systems where some cells are primary, some are tumor-derived lines, and yet others are from iPS-derived sources.

In this talk, I will highlight the past, present and future interplay between these two dynamic, vibrant fields, with illustrations in particular of how the organs-on-chips technologies are poised to aid the therapeutic protein production field.

Long, T., P. Cosgrove, R. N. Dunn, D. Stolz, H. Hamadeh, C. Afshari, H. McBride and L. Griffith (2016). "Modeling Therapeutic Antibody-Small Molecule Drug-Drug Interactions Using a Three Dimensional Perfusable Human Liver Coculture Platform." Drug Metab Dispos 44: 1940-1948.