204b Analysis of Mab Production-Enhancing Compounds

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Increasing the specific productivity of mammalian cells producing biopharmaceuticals, such as monoclonal antibodies (MAbs) is an important endeavor for reducing development and production costs. A first step toward realizing these efficiency gains is to increase our knowledge of essential pathways that directly or indirectly control specific productivity. Knowledge regarding the metabolic pathways can be used to identify compounds that may directly or indirectly influence MAb production. Several compounds have been reported to increase productivity and more are to be uncovered. The enhancement of titer using enhancing compounds as additives during a bioprocess is an immediate endpoint for this work. However, analysis of all compounds that have observable, positive or negative, effects on MAb constitutes a longer-term objective of defining the metabolic pathways that regulate MAb production and then exploiting this knowledge for metabolic engineering of new, higher-producing cell lines.

In the current work, a first goal is to analyze the activity of compounds reported to enhance MAb production in hybridomas, namely rapamycin, sodium butyrate, and DMSO. The investigation begins with testing for effects on growth, death, and metabolism using an 18-hour, 96-well plate sublethal metabolic activity assay. The results of the 18-hour screen are then used to choose concentrations that will be tested for increases or decreases in MAb titer over a 72-hour batch cultures conducted in 96-well plates. Utilizing 96-well plates for initial characterization provides necessary throughput to test many chemicals in parallel and at the same time have ample replicates for thorough statistical analysis.

The second goal of this research is aimed at understanding possible mechanisms for how compounds increase or decrease MAb production. In theory, any given compound that causes a change in the overall pathway for MAb productivity indicates that it impinges on at least one direct or indirect pathway that leads to the observed change. Literature reports of tested compounds with regard to mechanisms as well as data collected will be used to discuss how direct or indirect the compounds may be in regards to specific productivity pathways. In addition, some possible/potential key regulatory reactions will be discussed.