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Kim Le
Amgen

Hannah Victor
Amgen

Kristi Daris
Amgen

Trent Munro
Amgen

Increasing Diversity of Production Cell Lines through Miniaturization, Automation, and High-Throughput Analytics

Kim Le, Hannah Victor, Kristi Daris, Trent Munro

Pre-Pivotal Drug Substance Process Development, Amgen Inc. One Amgen Center Drive, Thousand Oaks, CA 91320

The development of a successful biologic therapeutic manufacturing process begins with the creation of a stable clonal cell line. Since attributes of the production cell line will significantly impact upstream and downstream processes, researchers must find ways to generate several candidate lines with diverse properties. However, a wide diversity is difficult to achieve since cultures are commonly selected, maintained, and screened as populations. In these populations, robust sub-populations can overtake the overall culture and reduce diversity. To combat this, sub-populations must be physically separated by splitting or subcloning, and maintained in individual vessels requiring intensive labor and infrastructure. As a result, researchers must balance between either increasing diversity vs. increasing resources need to maintain and screen hundreds of cultures. In order to shift this balance towards greater diversity, we have developed systems that combines miniaturization of culture vessels, targeted use of automation, and single cell analysis to allow for hundreds of cell lines to be isolated, maintained, and analyzed. We demonstrate cell lines can be easily maintained in simple low volume formats with no impact on cells. We show that we can significantly improve and maintain diversity through separation and isolation of hundreds of cultures. Additionally, higher throughputs allows to assess cell line phenotypes of multiple candidate lines early in development. Benefits achieved through this approach did not increase resources or timelines. Moving towards miniaturization combined with single cell analysis will also enable future possibilities for more precise cell engineering and gene editing.