Due to the complex nature of balancing >50 individual media components, the development and optimization of bioreactor medium for high performing perfusion bioreactors is a resource intensive, multivariate problem that greatly benefits from the availability of predictive high through-put scale-down models that simulate the bioreactor system. For that purpose, both a 10 mL long-term block model and 50 mL shaker tube model were developed and optimized to settings that balance oxygen transfer, culture health, and productivity. The long-term block model was limited by the volume needed for culture sampling; as a result, the shaker tube model was developed with a 7.5x increase in working volume. This shaker tube model was then applied to adequately characterize cell nutrient consumption profiles and subsequently inform medium development through multivariate design of experiments (DOE). Within two rounds of studies in the scale-down models, Regeneron’s first-generation perfusion medium formulation achieved approximately 100% increase in productivity compared to the initial medium. The improved nutrient strategy optimized in shaker tubes translated to several cell lines in the benchtop and pilot scale bioreactor perfusion system, indicating the predictive capabilities of the small-scale model. These results highlight the benefits of using small-scale models to shorten development time for perfusion process implementation.