POLYCLONAL PRODUCTION OF ANTIBODIES USING CHO CELL LINE MIXTURES

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Physicians use polyclonal antibodies in many clinical applications including fighting cancer and infectious diseases. An example where a mixture of antibodies is critical is snake antivenom, neutralizing a broad spectrum of toxins. Synthetic anti-venoms made of multiple humanized monoclonal antibodies (mAbs) produced by individual CHO cell lines would overcome the issue of xeno-immunogenicity of conventional antivenoms (derived from horses), while targeting multiple snake toxins and/ or species. Producing individual batches of mAbs and mixing them afterwards is associated with significant validation costs and single batch production of mAb cocktails would thus be attractive. We selected four snake toxin-specific antibodies against Sub-Saharan African snake species (mamba and cobra) and generated stable anti-toxin producer clones through targeted integration in CHO cells, creating isogenic cell lines. In this way, we aim to reduce clonal variation with the hypothesis of similar behavior of the different clones in a mixture. We use the same constant regions for all antibodies and the only difference in the inserted constructs is the variable regions of the antibodies (V_L and V_H). The resulting cell lines were cultivated in single batches to compare the growth and antibody production and maximum growth rates (μ_{max}) were not significantly different. As the antibodies originated from a human library, they were not optimized. Titers differed significantly and presence of monomers indicated varying stress levels in the different cell lines. Changing vector elements led to increasing (transient) titers, where each antibody exhibited a different critical element. However, stable cell line engineering for more uniform antibody production is still ongoing and we attempted a mixture of the cell lines already generated. Cell population dynamics analysis revealed that the cell line ratios stayed stable over time in the mixture (*Figure 1*). Initial antibody ratio investigation suggested that the antibody ratios stayed stable over time as well, though we are still optimizing the method. Results will be presented at the conference.

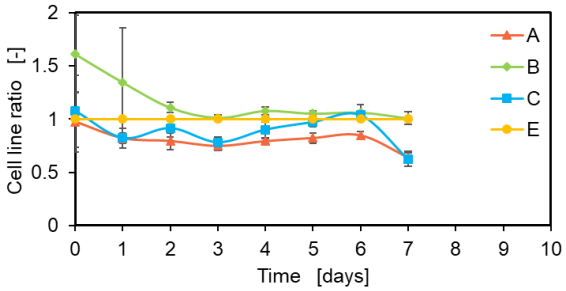

Figure 1 Cell line ratios in a mixed Batch cultivation after mixing equal amounts of inoculum.