THE IMPACT OF EXPRESSION VECTOR POSITION ON TRANSGENE TRANSCRIPTION ALLOWS FOR RATIONAL EXPRESSION VECTOR DESIGN IN A TARGETED INTEGRATION SYSTEM

Kathryn Beal, Pfizer, Inc.
Kathryn.Beal@pfizer.com

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Site-specific integration (SSI) technology has emerged as an effective approach by the pharmaceutical industry for the development of recombinant Chinese hamster ovary (CHO) cell lines. While SSI systems have been demonstrated to be effective for the development of CHO cell lines, they can be limiting in terms of both transgene expression and in the case of multi-specifics, the ability to generate the correct product of interest. To maximize the performance of Pfizer's dual SSI expression system for the development of monoclonal and multi-specific antibodies, we investigated the positional effect of transgenes within the expression vectors in the context of this system. We observed that the transcript level from the 2nd gene in a dual-gene expression vector decreased compared to when the same gene occupied the 1st gene position. The amount of transcriptional repression observed was dependent upon the sequence of the transgene in the 1st position as well as chromosome location. To our knowledge, this is the first demonstration of the positional effect of transgenes within a dual-gene expression vector using an SSI system. We then applied these learnings to rationally design expression vectors for 5 different mAbs and a multi-specific antibody. We showed enhanced productivity and optimal product quality when compared to a conventional expression vector topology. Progressing forward, the learnings gained here can potentially aid in the determination of optimal vector topologies for several IgG-like multi-specific formats.