Advancing Biologics Production Through Nanopore Whole Genome Sequencing

Vrljičak P, Boddireddy M, Alfred A, Di Cara A, Fabian DK et al.
Lonza Biologics plc, Cambridge, UK

Lonza
Integrated Biologics

BACKGROUND

Chinese Hamster Ovary (CHO) cells are widely used in biopharmaceutical production, particularly for monoclonal antibodies (mAbs). A better understanding of CHO clone genetics can support efforts to enhance productivity, stability, and product quality.

Whole genome sequencing (WGS) provides a comprehensive analysis of the transfected CHO cell genome, identifying mutations, structural variations, and gene copy number changes that impact cell line performance and titre.

APPROACH

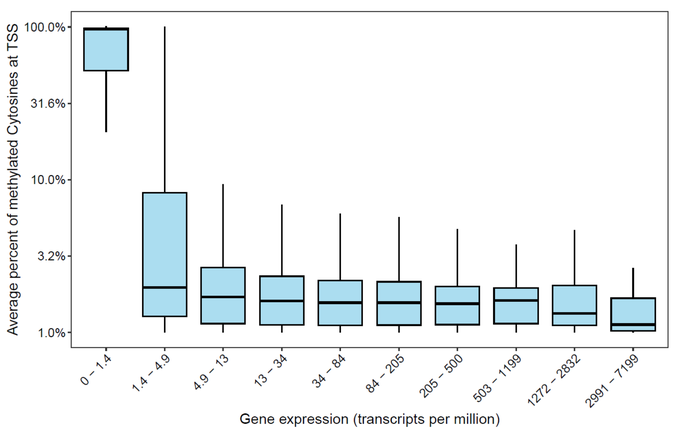
Here, we explore the use of DNA methylation data derived from Nanopore long read WGS to characterise a panel of 22 of Lonza's CHOK1SV GS-KO® clones expressing mAbs through transposon-mediated integration.

KEY FINDINGS

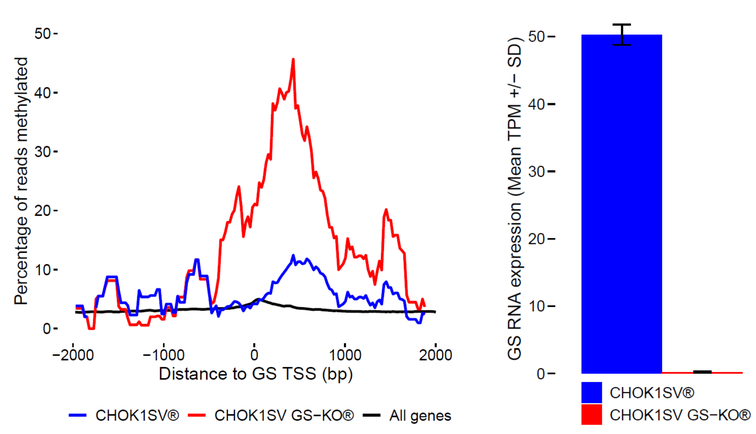
Within our panel of CHO clones:

1. DNA methylation is correlated with gene expression in CHO cells.
2. There is variation in methylation patterns across transgene integration sites.
3. Methylation in transgenes does not affect mAb product titre.

DNA methylation is correlated to endogenous gene inactivation in CHO cells



DNA hypermethylation marks inactive genes in CHOK1SV GS-KO® cells

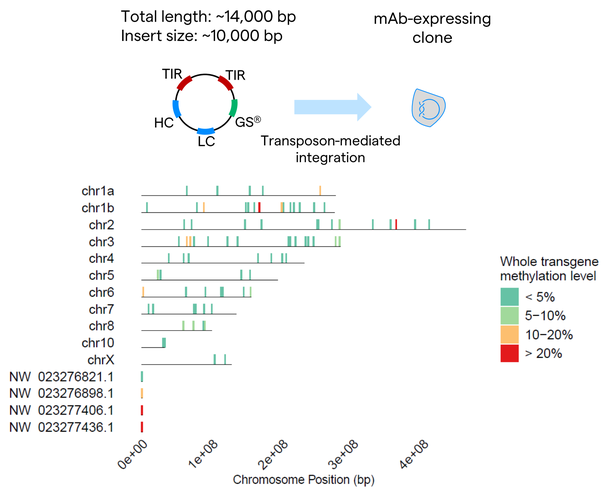


Targeted knockout of GS gene in CHOK1SV GS-KO® cells results in increased DNA methylation and reduced GS expression

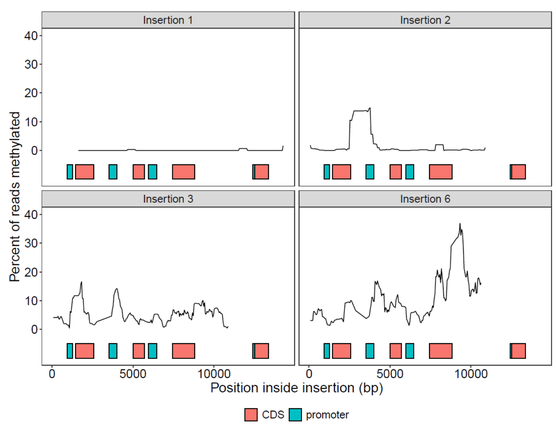
TAKE-AWAY

Lonza's use of Nanopore long read WGS provides valuable insights into transgene integration sites in CHO.

Mapping genomic transgene integration sites and their DNA methylation patterns

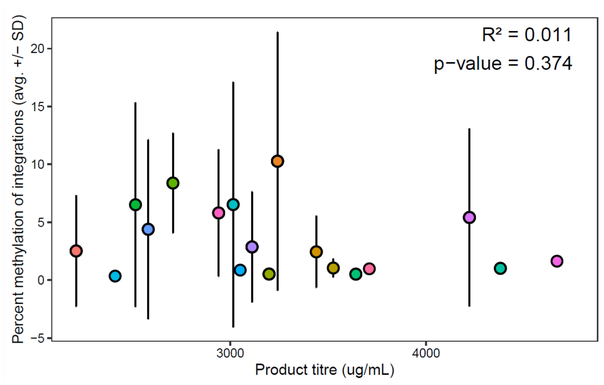


Over 80% of integration sites show low overall methylation (n = 110)



Examples of methylation patterns for a mAb expressing clone

Transgene methylation does not impact overall product titre



Analysis of CHO clones revealed no significant correlation between transgene DNA methylation and titre. This suggests that other factors might play a more prominent role than methylation-driven silencing in determining productivity.

Dr. Pavle Vrljičak

pavle.vrljicak@lonza.com

Lonza Biologics plc, Cambridge

Pavle's LinkedIn