IDENTIFYING THE BEST *PICHIA PASTORIS* BASE STRAIN USING FUNCTIONAL GENOMICS

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Market sizes for novel breakthrough therapies and growing demand for existing treatments in emerging markets promise to challenge the current capacity for production of biologics. These trends dictate the need for a concomitant paradigm shift in biomanufacturing toward greater productivity for lower cost. Strain engineering is a promising means to realize the greatest returns by increasing the product titer going into downstream processes. Current cellular hosts are approaching saturation of optimal productivity due to lack of deep biological understanding or limitations of the host's intrinsic secretion capacity. We demonstrate an approach informed by functional genomics to understand key performance differences between interchangeably-used variants of the host, *Pichia pastoris*. Genomic variant calling on all USDA-banked and commercially-available strains revealed varying numbers of SNPs relative to the WT strain, Y-11430. Combining transcriptomics and traditional phenotypic assays, the functional impact of these SNPs can inform which host strain is best suited for a given application. Taken together, we have identified key, beneficial SNPs that can be introduced into a WT background to create an IP-free host primed for optimal protein production.