

AN INTEGRATED STRAIN IMPROVEMENT AND PROCESS DEVELOPMENT PROGRAM FOR THE PRODUCTION OF UK-2A, THE PRECURSOR OF THE FUNGICIDE INATREQ™ ACTIVE

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Key Words: natural product, secondary metabolite, fermentation, fungicide

Secondary metabolites produced by Actinobacteria serve a variety of functions including molecules having agricultural applications. *Streptomyces sp. 517-02* produces a novel fungicidal compound called UK-2A, which through a single step chemical reaction is converted to Inatreq™ active. Inatreq utilizes a unique target site of action, ubiquinone reductase Qi site (inner side of membrane), and is intended for use in cereals and banana markets with strong residual protectant and curative activity in wheat against *Zymoseptoria tritici*, with additional activity on rust and other diseases. To achieve a commercially viable process an integrated multidiscipline approach was applied in parallel including mutagenesis, high-throughput (HTP) screening, fermentation process optimization, and targeted genetic engineering. The presentation will review how the integrated approach contributed to a rapid acceleration in productivity gains resulting in a 75% improvement in titer over a one-year period, more than a 2 fold improvement in 4 years and successful scale-up to the final commercial production plant.

Examples of topics to be discussed:

- Development, deployment, and optimization of the mutagenesis and high-throughput screening process for the selection of improved strains.
- Deployment of targeted genetic engineering to alleviate biosynthesis bottlenecks identified using approaches such as biosynthetic gene overexpression and precursor feeding.
- Use of “omics” tools to identify native promoters which permit temporal gene expression suitable for enhanced precursor production and increased UK-2A production.
- Vetting of new strains and fermentation process improvements both in bioreactors at multiple scales and in the downstream process for product recovery.
- Use of experimental results from across the integrated program to guide prioritization of strain and process improvement targets.
- Incorporation of final product design and performance requirements into the program with a line of sight to manufacturing process constraints.

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