A Global View of *Streptomyces coelicolor* M145: Transcription, Translation, and Metabolic Analysis of Natural Product Biosynthesis

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Streptomyces coelicolor M145 is a model organism of the genus *Steptomyces*, one of the most prolific producers of natural products. These privileged molecules have a tremendous impact on human health with approximately ⅔ of all FDA approved therapeutics being either natural products or derivatives thereof. While the production of these compounds has been extensively studied and optimized for commercial production of therapeutically relevant compounds, relatively little is known about the course of biosynthesis of these structures. We have developed a time-resolved study of the first nine days of growth of the organism. We have performed quantitative transcriptomics, proteomics, primary, and secondary metabolomics. This immense amount of information has allowed, for the first time, a characterization of the entire biosynthesis process, from when translation is triggered, to when transcription occurs, to when the bacteria synthesize compounds and finally expel them into the extracellular matrix.

We present here several case studies on important biosynthetic clusters including desferrioxamine, actinorhodin, germicidin, and prodigiosin. Each cluster has unique behaviors related to delays between the various stages of the central dogma and in what way the compounds are finally secreted. Ferrioxamine, for example, is expelled at a high level during initial growth but then decreases before finally increasing toward the end of the experiment as the media is depleted of iron. Prodigiosin is built up to high concentrations in the cell before being expelled in a concerted burst, resulting in a tremendous spike in concentration, and a depleted intracellular concentration. The biosynthetic proteins of germicidin are produced at a near constant level over the entire growth of the organism, but secreted levels do not appear for many days, before ramping up exponentially, implying regulation of the biosynthesis not by the proteins themselves, but by availability of precursors shunted from primary metabolism at a specific stage of growth.

These snapshots of transcription, translation, and primary and secondary metabolites over the entire life cycle of this model organism provide an unprecedented understanding of the biosynthesis of natural products. These untargeted studies provide quantitative characterization of not only the case studies presented here, but of the entirety of the *S. coelicolor* machinery, and additional gene clusters remain to be explored. Due to the broad interest in this organism, and the wealth of different focuses, we aim to make all the data obtained publicly available so that other researchers may benefit from these studies and be allowed to focus on their own area of interest, be that amino acid synthesis, carbon utilization, or regulatory mechanisms.