

SESSION II: SPEAKER ABSTRACTS

Investigating the Installation of Hydrazine in Fosfazinomycin Biosynthesis

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Fosfazinomycin is a natural product that contains a unique structural feature: a hydrazine linkage joins a valine-arginine dipeptide with methyl-2-hydroxyl-phosphono-acetic acid. There are more than 200 known natural products that contain nitrogen-nitrogen (N-N) bonds; these N-N bond-containing molecules are extremely structurally diverse and display a variety of bioactivities. We discovered using a combination of *in vitro* enzymatic assays and stable isotope labeling experiments that one of the nitrogen atoms in the N-N bond in fosfazinomycin originates from aspartic acid, which is used to form acetylhydrazine in a pathway that involves nitrous acid but that has yet to be fully understood. Acetylhydrazine is then condensed onto the side chain carboxyl group of glutamic acid, and subsequent deacetylation yields glutamylhydrazine. In fosfazinomycin biosynthesis, hydrazine can then be transferred from glutamylhydrazine onto the carboxyl group of arginine. Further, the genes encoding the set of enzymes responsible for the formation of glutamylhydrazine can also be found in the biosynthetic gene clusters of other N-N bond-containing natural products such as kinamycin. Thus, this pathway represents a modular strategy in which the N-N bond is preformed as a discrete synthon before being funneled into disparate biosynthetic routes.

