

Insights into Nucleocidin Biosynthesis by *Streptomyces sp.*

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Nucleocidin is a natural product analog of adenosine that is notable for having 4'-fluorine and 5'-*O*-sulfamate groups. Both modifications are rarely seen in nature, but appear widely in pharmaceuticals and drug candidates such as 4'-fluorouridine, which was recently shown to have potential as a COVID-19 therapeutic. The biosynthesis of the sulfamate and fluorine substituents in nucleocidin remains unknown. Within the nucleocidin biosynthetic gene cluster there are several genes predicted to encode chemistry related to sulfamate biosynthesis or fluorination, including four sulfate transfer enzymes (*nucGIKO*), an amidinotransferase (*nucN*), and a radical SAM / Fe-S cluster dependent enzyme (*nucJ*). Through recent gene inactivation experiments in *Streptomyces virens*, we show that *nucI*, *nucG*, and *nucJ* are essential for sulfamate biosynthesis, but not fluorination. Recent results towards understanding nucleocidin biosynthesis and characterization of related derivatives will be discussed.

