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Covalent inhibition of bacterial type I dehydroquinase – Opportunities for anti-virulence therapies

The loss of effectiveness of current antibiotics caused by the development of drug resistance, along with the evident decline in antibiotic research by the major pharmaceutical companies during the last 50 years, has triggered the search for novel antibiotics and alternative therapies. Targeting bacterial virulence is an attractive choice that is increasingly being explored. The inhibition of virulence factors will lead to a loss of the ability of bacteria to cause infection in the host and, as a consequence, they could be more easily eliminated by the immune system. A promising target for the development of new anti-virulence agents is the type I dehydroquinase enzyme (EC 4.2.1.10, aroD gene, DHQ1). This enzyme does not have any counterpart in human cells and seems to act as a virulence factor *in vivo* as the deletion of the aroD gene has been proven to afford satisfactory live oral vaccines. In this talk, several irreversible inhibitors of this enzyme that cause the covalent modification of the DHQ1 from Salmonella typhi and Staphylococcus aureus and that are able to reduce the ability of Salmonella enteritidis to kill A459 respiratory cells will be presented. The resolution of diverse crystal structures of DHQ1 from Salmonella typhi chemically modified by those compounds, the detection by mass spectroscopy of the reaction intermediates, in conjunction with the results of molecular dynamics simulations, allowed us to explain the inhibition mechanism of those compounds. Our recent results on this project will be presented.

Biography

Concepción González-Bello has obtained her PhD at the University of Santiago de Compostela (USC, Spain) in 1994. She did two predoctoral stays in the University of Gent (Belgium) with Prof. Vandewalle and in the Scripps Research Institute (USA) with Prof. Nicolaou. After a postdoctoral stay in the University of Cambridge (UK) with Prof. Abell, she joined USC as an Assistant Professor, and was promoted to Associate Professor in 2003 and obtained the Spanish habilitation to full Professor in 2011. In 2011, she joined the CIQUS, a new USC research center, as a group leader. She is author of about 70 papers and several patents and book chapters.

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