

***In vitro* activity of the β -lactamase inhibitor NXL104 against KPC-2 carbapenemase and Enterobacteriaceae expressing KPC carbapenemases**

Thérèse Stachyra, Premavathy Levasseur, Marie-Claude Péchereau, Anne-Marie Girard, Monique Claudon, Christine Miossec* and Michael T. Black

Novoxel SA, Parc Biocitech, 102 avenue Gaston Roussel, 93230 Romainville, France

Received 7 April 2009; returned 29 April 2009; revised 5 May 2009; accepted 7 May 2009

* Corresponding author. Tel: +33-1-5714-0747; Fax: +33-1-5714-0725; E-mail: christine.miossec@novoxel.com

Background: NXL104 is a novel-structure β -lactamase inhibitor with potent activity against both class A and class C enzymes. Among the class A carbapenemases, KPC-type enzymes are now spreading rapidly and KPC-related carbapenemase resistance is an emerging phenomenon of great clinical importance. The activity of NXL104 against KPC β -lactamases was examined.

Methods: Enzymatic activity of purified recombinant KPC-2 was measured with nitrocefin as reporter substrate and inhibition by NXL104 was measured by determination of IC_{50} values. Antimicrobial susceptibility testing of various β -lactams combined with a fixed concentration of NXL104 at 4 mg/L against strains producing KPC enzymes was performed by the broth microdilution method.

Results: NXL104 was a potent inhibitor of KPC-2 with an IC_{50} of 38 nM. NXL104 restored the antimicrobial activity of ceftazidime, ceftriaxone, imipenem and piperacillin against Enterobacteriaceae strains producing KPC-2 or KPC-3. MIC values of ceftazidime against KPC producers were reduced by up to 1000-fold by combination with NXL104.

Conclusions: NXL104 inhibitory activity is unique in terms of spectrum, encompassing class A extended-spectrum β -lactamases, class C enzymes and class A carbapenemases. Given the limited therapeutic options available for infections caused by multiresistant Enterobacteriaceae isolates, NXL104 β -lactamase inhibitor is a promising agent to be used in combination with a β -lactam to protect its antibacterial activity.