

# ***In vitro* activity of the $\beta$ -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](mailto:christine.miossec@novoxel.com)

**Background:** NXL104 is a novel-structure  $\beta$ -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  $\beta$ -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  $\beta$ -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  $\beta$ -lactamases, class C enzymes and class A carbapenemases. Given the limited therapeutic options available for infections caused by multiresistant Enterobacteriaceae isolates, NXL104  $\beta$ -lactamase inhibitor is a promising agent to be used in combination with a  $\beta$ -lactam to protect its antibacterial activity.