PC-158

DESIGNING NOVEL INHIBITORS FOR CARBAPENEMASES: A MULTIDISCIPLINARY APPROACH

Spyrakis, N.;[a,b] Bellio, P.;[c] Vicario, M.;[d] Cendron, L.;[d] Marcoccia, F.;[c] Perilli, MG.;[c] Cruciani, G.;[e] Costi, MP.;[a] Celenza, G.[c] and Tondi, D.[a]

[a]Dipartimento di Scienze della Vita, Università degli Studi di Modena e Reggio Emilia, Via Campi 103, 41100, Modena, Italy; [b]Dipartimento di Scienze degli Alimenti, Università degli Studi di Parma, Parco Area delle Scienze, 59/A - 43124 Parma, Italy; [c]Dipartimento di Biologia, Università degli Studi di Padova,Viale G. Colombo 3 Padova, Italy; [d]Dipartimento di Scienze cliniche applicate e biotecnologiche, Università dell'Aquila, Via Vetoio 1, 67100 L'Aquila, Italy; [e]Department of Chemistry, Biology and Biotechnology, University of Perugia, Via Elce di Sotto 8, 06123, Perugia, Italy.
tondi.donatella@unimore.it

The extensive use of *beta*-lactam antibiotics has created major resistance problems leading to increased morbidity, mortality and health-care costs. Resistance is most often mediated by *beta*-lactamases (BLs), which have emerged in both Gram-positive and Gram-negative bacteria [1,2]. Medicinal chemists have introduced *beta*-lactam-based molecules that inhibit or are stable to their action. These molecules are themselves *beta*-lactams, making it easier for bacteria to respond by adapting previously evolved mechanisms. Many bacteria are now resistant to these anti-resistance compounds. Thus there is a growing need for new broad-spectrum *beta*-lactamases inhibitors in general and especially against carbapenemases (i.e KPC, NDM-1, VIM)[3,4]. Their substrate promiscuity, their resistance to available drugs, the easiness of variants appearance and transferability make carbapenemases the most worrisome BLs [2].
Focusing on the de novo, non *beta*-lactam like derivatives we identified, through a structure-based *in silico* screening of commercially available library using FLAP, several promising candidates active against class A and class B carbapenemases. The binding affinities of the high scoring hits were measured *in vitro* revealing, for some of them,low micromolar affinity towards BLs.
To investigate the potential of these compounds to reverse antibiotic resistance, we are undertaking antimicrobial activity studies in bacterial cell culture. The ability of novel compounds to synergize antibiotics against pathogenic resistant bacteria, as well as their ability to evade those mechanisms normally involved in resistance to *beta*-lactam-based inhibitors are now under evaluation. Moreover, since our inhibitors are novel, non *beta*-lactam based, we expect them to do not up-regulate *beta*-lactamase expression in cell culture.
X-ray crystallography studies are now in progress to confirm our docking prediction and to deeply investigate the structural requirement necessary for proficuous hit to lead generation.

Keywords: carbapenemases resistance, SBDD, in silico screening, enzyme inhibition, antimicrobial activity, x-ray crystallography

References

1.Frère, J.M.; Sauvage, E.; Kerff, F. *Curr. Drug Targets* **2016.***17, no. 9.*
2. Bonomo, R.A. *Clin. Infect. Dis.* **2011**. *52 (4): 485-487*
3. Tondi,D.; Venturelli,A.; Bonnet,R.; Pozzi, C.; Shoichet, BK.; Costi, M.P. *J. Med. Chem.* **2014**. *57 (12), pp 5449–5458.*
4. Tondi, D.; Cross, S.; Venturelli, A.; Costi, MP; Cruciani, G.; Spyrakis, F. *Curr. Drug Targets* **2016** 17, *no. 9.*