Identification of new drugs and novel targets for *Burkholderia cenocepacia*

The development of novel antibiotics remains a major issue for the treatment of infectious lung disease, such as that in CF.

The current research involves the synthesis of new molecules effective against *B. cenocepacia*. We found that a pyridine compound (11026103) and a benzothiadiazol compound (10126109) are very active and we identified a mechanism of resistance, which relies on the extrusion by RND-4 and RND-9 transporters (Scoffone *et al*., 2014. Antimicrob. Agents Chemother.58: 2415-17; Scoffone *et al*., 2015. Front. Microbiol. 6: 815). 10126109 is active against clinical isolates and other members of the *B. cepacia* complex (Bcc), as well as against other Gram-negative and -positive bacteria. We recently identified the mechanism of action, which relies on the inhibition of the activity of FtsZ cell division (Hogan *et al*., 2018. Antimicrob. Agents Chemother. 62 pii: e01231-18). In collaboration with Dr. V. Makarov (Russian Academy of Sciences, Moscow, Russia) we would like to synthetize new derivatives that are not recognized by the pumps as a substrate.

New inhalable formulations of the latter compound are being developed in collaboration with Prof. F. Ungaro (Naples University). The *in vivo* efficacy of this compound is currently under investigation in collaboration with Dr. A. Bragonzi (San Raffaele Hospital, Milan).

Moreover, the characterization of the quorum sensing enzymes of *B. cenocepacia*, as target of anti-virulence compounds, could represent a new promising therapeutic approach. The two enzymes CepI and DfsA have been obtained in recombinant form and, for the latter the crystal structure has been resolved (Spadaro *et al*. 2016. Biochemistry 55: 3241-50). The activity assay of both enzymes has been assessed, allowing the screening of potential inhibitors. These screen led to new compounds active in vitro against CepI, which are able to dramatically decrease the virulence of the bacteria in an *in vivo C. elegans* model (Scoffone *et al*., 2016. Sci. Rep. 6: 32487; Buroni *et al*., 2018. Front. Pharmacol. 9: 836).