Inhibition of quorum sensing and pyoverdine signalling as an anti-virulence strategy against *Pseudomonas aeruginosa*

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Pseudomonas aeruginosa is a major opportunistic pathogen responsible for a broad range of infections in humans. Chronic lung infection by *P. aeruginosa* is also the main cause of mortality in cystic fibrosis patients. *P. aeruginosa* infections are difficult to eradicate by conventional antibiotic therapy, due to the inherent antimicrobial resistance of the bacterium and its propensity to acquire new resistance determinants, and this calls for the development of innovative anti-*P. aeruginosa* therapies.
An appealing approach for identifying novel antibacterial drugs is to search for inhibitors of specific adaptive or virulence-related traits, as opposed to inhibitors of growth *per se*. Selective targeting of the pathogenic potential has the advantage of reducing the severity of the infection without creating the strong selective pressure imposed by conventional antibiotics. Given that *P. aeruginosa* produces an impressive array of virulence factors, all playing a role in its pathogenicity, a suitable strategy to efficiently inhibit *P. aeruginosa* virulence is to target regulatory networks that coordinate the expression of several virulence traits, rather than to inhibit a specific one.
In this work, we explored two well-characterized global regulatory systems which are crucial for *P. aeruginosa* pathogenicity (*i.e.* quorum sensing and pyoverdine signalling) as targets for anti-virulence compounds. To this aim, we developed specific high-throughput screening systems and used them to screen a commercial library of more than 1,000 FDA-approved drugs, according to the selective optimization of side activities (SOSA) approach, which relies on the search for novel side activities in "old" drugs already approved for use in humans. This led to the identification of two promising drugs which significantly inhibited either the quorum sensing (QSI-1) or the pyoverdine (PI-1) screening system. Both molecules proved to be effective in reducing quorum sensing or pyoverdine-regulated virulence gene expression *in vitro*, as well as *P. aeruginosa* pathogenicity in different animal models. Experiments are in progress to unravel the molecular mechanisms of QSI-1 and PI-1 mediated inhibition.