# New compounds discovered as candidates for new antimicrobial drugs against Listeria infection

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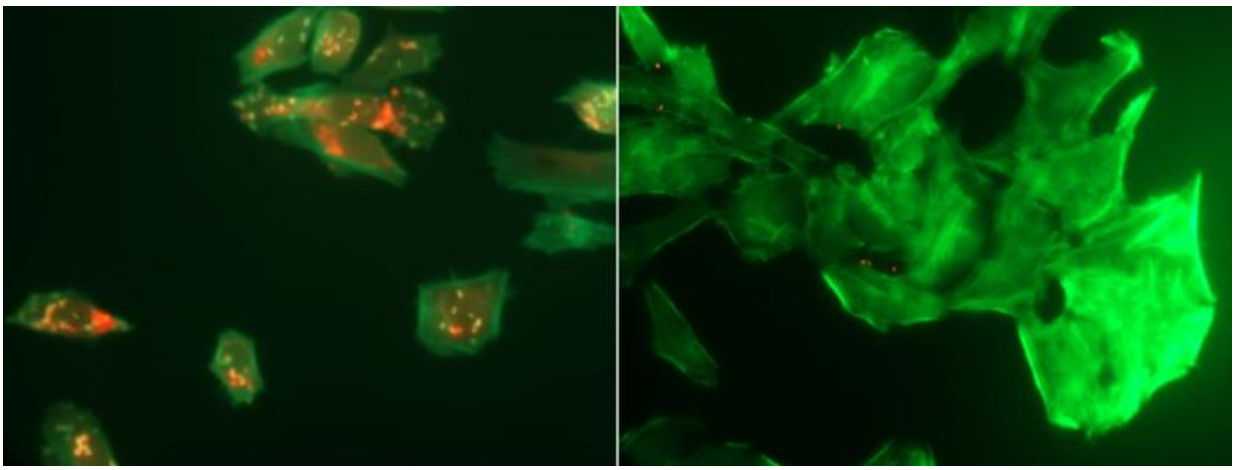

The infection and ability to grow inside the human epithelial cells with *L. monocytogenes*, in absence (left picture) or presence (right picture) of 2-pyridones. Bacteria are shown in orange and Hep-2 cells in green. Credit: Johnny Mikaelsson

Scientists at Umeå Centre for Microbial Research (UCMR) have discovered chemical compounds which are able to attenuate the virulence of the bacterial human pathogen Listeria monocytogenes. Their findings are published today in the high impact journal *Cell Chemical Biology*.

The dramatic increase of antibiotic resistance makes new antimicrobial strategies necessary. The researchers at Umeå University in Sweden are studying an alternative approach, to inhibit the disease capacity (virulence) of bacteria but not their viability. Compared with traditional antibiotics, which often kill the bacteria, the risk of resistance development in disarmed bacteria is lower, since their survival does not depend on resistance against the new drug.

A Listeria infection can be very severe, particularly among patients such as elderly, infants, immunocompromised or pregnant women. Although disease occurrence is relatively low, Listeria's severe and sometimes fatal health consequences make it among the most serious foodborne infections, with a mortality of 30%. Listeria is found in unpasteurized dairy products and various ready-to-eat foods, and can grow at refrigeration temperatures. In Sweden, 60-90 people per year get infected and the statistics show that the number of outbreaks is increasing.

The study involved several different Umeå University research groups with diverse specialties: Microbiology, Chemistry and Structural Biology. The group of Jörgen Johansson, professor at the laboratory for Molecular Infection Medicine Sweden (MIMS) and the Department of Molecular Biology collaborated with the research groups of Elisabeth Sauer-Eriksson and Fredrik Almqvist, both professors at the Department of Chemistry.

The researchers tested a large number of possible candidates, which could inhibit expression of the Listeria virulence factors. For the test, they screened Listeria infection of human cells with a collection of ring-fused 2-pyridones. The scientists could prove that the ring-fused 2-pyridones could both attenuate the uptake of Listeria in the cell and the activity of the virulence regulator PrfA, which control the pathogenic abilities of Listeria.

The researchers also identified the first crystal structure of PrfA together with an inhibitor. Binding of the inhibitor to PrfA blocked its ability to interact with DNA, thereby preventing expression of virulence factors. As a consequence, Listeria bacteria were not able to bind and infect the human cells.

"This study means a lot for future development of 'disarming compounds', not only in Listeria. In fact, our study is the first example on a structural level of an inhibition of any virulence regulator in bacteria," says Jörgen Johansson about the impact of the findings.

"The first results are very promising. We have been able to use the structural information to design and synthesize new improved candidates that are now being evaluated", added Fredrik Almqvist.

"We now know that this class of compounds (2-pyridones) constitute a great platform for the development of virulence blocking compounds. We have developed methods that allow us to fine-tune the substitution pattern and compound properties in such a way that we can direct these compounds towards several different pathogens e.g. E. coli and Chlamydia. And more studies are ongoing with other pathogens," adds Fredrik Almqvist.

"Through this very fruitful research collaboration, we showed that Umeå has all the tools and expertise needed to understand and develop new antimicrobial strategies," says Elisabeth Sauer-Eriksson.

**More information:** *Cell Chemical Biology*, dx.doi.org/10.1016/j.chembiol201602013

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