学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Impact of QnrB19, a pentapeptide repeat protein mimicking double stranded DNA, on the quinolone resistance in *Salmonella* Typhimurium
（二重鎖DNAを模倣するペンタペプチド繰返し蛋白QnrB19のネズミチフス菌キノロン耐性化への影響）

Fluoroquinolones have been used for the drugs of choice to treat non-typhoidal *Salmonella* (NTS) infection in humans and animals. However, plasmid-mediated quinolone resistance (PMQR) mechanism has emerged in Enterobacteriaceae. Plasmid-encoded quinolone resistance protein Qnr is an important factor among PMQR in bacterial resistance to quinolones. This protein interacts with DNA gyrase and reduces susceptibility to quinolones.

However, as there are limited information of the predominant Qnr types in *Salmonella* isolates, I investigated the prevalence of Qnr in 692 reports published from 2008 to 2017 and found that 4,459 Enterobacteriaceae isolates had Qnrs (1,917 QnrB, 1,545 QnrS, 498 QnrA, 459 QnrD, 27 QnrVC, 12 QnrC and 1 QnrE). And QnrB19 was found in the highest number of isolates among Qnr reported in *Salmonella* isolates.

In Chapter I, *in vitro* assays for wild type *S.* Typhimurium DNA gyrases, QnrB19 and quinolones were performed. The IC_{50}s of norfloxacin and ciprofloxacin against DNA gyrases were increased around 3-fold by the addition of QnrB19 and the results exhibited that the contribution of QnrB19 did not associate with the difference between R1 group of these two quinolones. The IC_{50} of nalidixic acid was 59- and 110-folds higher than norfloxacin and of ciprofloxacin in the absence of QnrB19, respectively, and this was similar to the that in the presence of 18 nM QnrB19. These results showed that the fluorine at R6 and/or piperazine at R7 and/or hydrogen at R8 group might associate with the ability

of QnrB19 to increase IC_{50}s. QnrB19 was shown for the first time *in vitro* to have ability to grant non-classical quinolone resistance to *S.* Typhimurium DNA gyrase in connection with the structure at R6 and/or R7 and/or R8.

In Chapter II, I identified the activity of novel fluoroquinolones with the potentiality attributed by unique R1 group, 6-amino-3,5-difluoropyridine-2-yl, by *in vitro* assay. I compared IC_{50} of WQ-3810, WQ-3334 and WQ-4065 with specific features of quinolones at positions R1, R6, R7 or R8. WQ-3810 and WQ-3334 (6-amino-3,5-difluoropyridine-2-yl at the R1 group) showed stronger inhibitory activity against *S.* Typhimurium DNA gyrases with a lower IC_{50}s than WQ-4065 (6-ethylamino-3,5-difluoropyridine-2-yl at the R1). Moreover, WQ-3810 and WQ-3334 showed greater inhibitory activity against *S.* Typhimurium DNA gyrases even in the presence of QnrB19. The results suggested that novel fluoroquinolones, WQ-3810 and WQ-3334 could be the good candidate drug for wild type *Salmonella* and *Salmonella* carrying QnrB19.

Comparison of conventional quinolones (nalidixic acid, norfloxacin and ciprofloxacin) in Chapter I and novel fluoroquinolones (WQ-3810, WQ-3334 and WQ-4065) in Chapter II showed that 6-amino-3,5-difluoropyridine-2-yl group at the R1 in WQ-3810 and WQ-3334 added a strong inhibitory activity against *S.* Typhimurium DNA gyrases to quinolones with very low IC_{50}. IC_{50}s of WQ-3810 and WQ-3334 were greatly increased in the presence of QnrB19, however, similar to those of ciprofloxacin and norfloxacin. Structural at R1 may cause the different impact by QnrB19 on the inhibitory activities of quinolones against DNA gyrase. The knowledge obtained in my study can be applied to design new compounds against bacteria carrying QnrB19 or other pentapeptide repeat proteins.