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学　位　論　文　要　旨

獣医学　専攻　博士後期　課程
学籍番号　19185004
氏　名　Shengwei JI　印

論文題目：Discovery and evaluating new drugs for babesiosis treatment（バベシア症に対する新薬候補の特定と評価）

要旨

Babesiosis has a wide geographical distribution and is a host-specific zoonotic disease. Essentially, the disease causes economic losses in livestock industry and notably threatens human health. To date the lack of effective vaccine, leaves the use of chemical treatment as the most commonly used control strategy. However, there are concerns about the side effects and drug resistance of currently used anti-*Babesia* drugs. Hence, discovery and development of more effective therapeutic drugs or druggable targets are urgent needed. In this research project, I screened two potential anti-*Babesia* drugs from currently used and under development anti-*Plasmodium* compounds, as well as evaluate their activity against *Babesia* species. Likewise, I identified and evaluated promising anti-*Babesia* druggable targets, with a specific direction toward eradicating parasites.

In chapter 1, I found NQP, which currently used for malaria treatment, showed anti-*Babesia* activity. I evaluated the efficacy of NQP on *B. gibsoni in vitro* and *B. rodhaini in vivo*. The IC_{50} of NQP against *B. gibsoni* was 3.3 ± 0.5 μM and five days treatment with NQP at a dose of 40 mg/kg significantly inhibited *B. rodhaini* growth in a mouse model. These results demonstrated that NQP can be a candidate for babesiosis treatment. Future study can focus on elucidating the mechanism of NQP to provide a new druggable target for the development of more drugs.

In chapter 2, I evaluated the inhibitory effects of MMV390048 on *in vitro* cultured *B. gibsoni*, as well as, *B. rodhaini* and *B. microti in vivo*. MMV390048 is an anti-malaria compound that is under evaluation in clinical trials. In this study, MMV390048 against *B. gibsoni* with a IC_{50} value of 6.9 ± 0.9 μM. Moreover, MMV390048 showed comparable anti-*Babesia* activity with ATO plus AZI and TAF *in vivo* study of *B. microti* and *B. rodhaini*, respectively. Furthermore, I isolated a MMV390048-resistant strain and revealed the target of MMV390048 as well as its mechanism. Overall, this finding provided an alternative drug for babesiosis treatment and a new druggable target for babesiosis treatment.

In chapter 3, I evaluated the efficacy of uninterrupted targeting *Babesia* PI4K treatment. After 64 days consecutively treating *B. microti*-infected SCID mice with MMV390048, the PCR detection targeting *B. microti* 18S-RNA was negative until the end of the trial. Furthermore, I isolated a *B. microti* ATO-resistant strain from the control group and a genetic mutation in Y272C in *Cytb* gene was detected by sequencing. This mutation has been reported in clinical case of human babesiosis. I further confirmed that MMV390048 also showed potent inhibition against the ATO-resistant strain. These results demonstrated that PI4K is a promising target for eliminating parasites from immunocompromised hosts, especially in relapsing infections caused by ATO-resistant *B. microti*.

In summary, I have found and evaluated two drugs that showed inhibition against *Babesia* spp. which can be candidates for babesiosis treatment. Moreover, the new drug target identified in this study will provide insights to accelerate the development of next-generation anti-babesiosis therapeutics.