氏　　名	DINH THI QUYEN
授与した学位	博　士
専攻分野の名称	薬　学
学位授与番号	博甲第 7373 号
学位授与の日付	令和 7 年 9 月 25 日
学位授与の要件	医歯薬学総合研究科病態制御科学専攻 （学位規則第５条第１項該当）
学位論文の題目	Investigating the effect of N-89 as a transdermal antimalarial drug on gametocytes of *Plasmodium berghei*-infected mice（マラリア病態モデルを用いた環状過酸化物・N-89 のガメトサイト原虫に対する解析）
論文審査委員	垣内　力　　教授　　竹内　綾子　　教授　　堀口　道子　　教授

学位論文内容の要旨

Transdermal 1,2,6,7-tetraoxaspiro [7.11] nonadecane (td N-89) was reported as a novel antimalarial candidate against the asexual stage of parasites *in vitro* and *in vivo.* My study aimed to investigate the effect of td N-89 on gametocytes, the sexual stage responsible for malaria transmission. I used 5-8 weeks old ICR mice for all experiments. An ointment formulation containing compounds (approximately 70 mg/application) was topically applied to a shaved area of around 4cm^2. The control group received only the vehicle (polyethylene glycol-based formulation). I checked the change in parasitemia in mice during treatment time by light microscopy. To monitor the expression of gametocyte-related genes, I employed a standard curve-based method for relative RT-qPCR to assess changes in gene expression level during treatment under different regimens.

I. To establish a suitable rodent malaria model for evaluating the effect of td N-89, I carried out the following three experiments with *P. berghei* NK65 and ANKA strains on ICR mice: (1) evaluation of responses to a 4-day suppressive treatment with either td N-89 or ART; (2) analysis of parasitemia curves, and (3) changes in gametocyte-related gene expression levels during the post-infection period. Finally, *P. berghei* NK65 strain-infected mouse is a suitable rodent malaria model for testing gametocytes *in vivo*.

II. I assesed three monotherapy regimens of td N-89 initiated approximately 1-2% parasitemia; (1) at doses of ED_{90} values (46 mg/kg, tiwce daily for 2 days), the reference compound are td ART (ED_{90} value; 21.8 mg/kg), and td lumefantrine (ED_{90} value; 2.9 mg/kg); (2) curative dose (60 mg/kg, twice daily for 4 days); (3) insufficient therapy (60 mg/kg, twice daily for only 2 days).

Conclusion, my study demonstrates that td N-89 maintained efficacy even at 1.7% parasitemia, although with a lower cure rate (33.3%). Notably, the transmission-blocking potential of td N-89 appears to be associated with sustained trophozoite clearance rather than direct gametocidal activity. I reported for the first time that gametocyte-related gene expression progressively changes in the td N-89 group and can be detected for a long period. Conversely, td ART which exhibited stronger anti-asexual activity than td N-89 but failed to prevent

recrudescence. Moreover, in mice with td artemisinin as a reference, Pbs21 and GCS expression levels were higher than those in the td N-89 group, indicating that td N-89 may exhibit a less side effect compared to td artemisinin.

論文審査結果の要旨

本論文は、N-89のマラリア原虫のガメトサイト形成に与える影響を解析している。ガメトサイトはマラリア原虫がヒト宿主内で形成する有性生殖細胞であり、蚊の中で有性生殖を行うために必要となる。N-89の処理は、血中でのマラリア原虫の数を減少させ、マウスの感染死を抑制する効果を示す一方で、ガメトサイト形成に関わる遺伝子発現は促進する結果が得られた。このことは、N-89は抗マラリア活性以外に、ガメトサイト形成を促進し、マラリア原虫の有性生殖を増やすという副作用を有することを示唆する。本論文は、十分な解析データを元に、抗マラリア候補薬N-89のガメトサイトサイト関連遺伝子に対する発現増強作用を初めて明らかにしたものであり、論文の質・量、ならびに新規性・進歩性の点から博士論文に値するものと判断した。