（様式５）Form 5

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

博士の専攻分野の名称：博士（感染症学）　　氏名：エディ　ソロ
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学位論文題名
The title of the doctoral dissertation

Molecular characterization of *Mycobacterium tuberculosis* isolates and their association to multidrug resistance in Lusaka, Zambia

（ザンビア共和国 Lusaka 市で分離された患者由来結核菌株の遺伝学的特徴と多剤耐性との関連に関する研究）

World Health organization (WHO) has described tuberculosis as one of the leading causes of death from a single infectious microorganism known as *Mycobacterium tuberculosis*. In 2019, 10.0 million new tuberculosis cases 1.4 million deaths were estimated globally. Most tuberculosis cases occurred in South-East Asia (44%), Africa (25%) and the Western Pacific (18%). Although effective drugs for treatment of tuberculosis exist, tuberculosis strains with drug resistance are threatening global progress towards set target of ending tuberculosis by 2035. In 2019, 3.4% of new tuberculosis cases and 18% of previously treated cases had multi-drug resistant tuberculosis (MDR-TB).

In Zambia, the burden of MDR-TB is increasing. The proportions of MDR-TB rates have risen from 0.3% among new cases and 8.1% among previously treated cases in 2014 to 2.8% and 18% in 2019, respectively. Factors contributing to the increasing number of MDR-TB cases in this Sub-Saharan African nation are currently unknown.

Molecular studies have demonstrated ability to improve knowledge related to the *M. tuberculosis* genotypes prevailing in a specific region and drug

resistance phenomenon to inform the development of effective control strategies, new drugs and diagnostic tools.

Using spoligotyping, large sequence polymorphism and gene sequencing, *M. tuberculosis* isolates stored (2013-2017) at the University Teaching Hospital in Lusaka Zambia were characterized.

In chapter 1, Spoligotyping of *M. tuberculosis* isolates from Lusaka, Zambia revealed the dominance of LAM family in Lusaka (54.4%) followed by CAS (16.1%) and T (14.2%). Furthermore, three *M. bovis* among human isolates, and interestingly a first case of Beijing genotype were identified among the Zambian population. CAS-Kili (SIT 21) and LAM1 (SIT 20) demonstrated propensity to becoming MDR-TB (p=0.0001 and 0.001, respectively).

In chapter 2, Sequencing of *rpo*B gene showed that the types of mutations in *rpo*B gene conferring drug resistance to rifampicin in Lusaka are similar to those described globally. Ser 531 Leu was the most dominant mutation at 55.6% followed by mutations at codons His 526 and Asp 516 (each at 18.2%). Overall the sensitivity of genotypic testing for rifampicin resistance was 98% and specificity was 100%. Therefore, Zambia can customize molecular tools (e.g., XpertMTB/RIF and Line Probe Assay) targeting polymorphisms in *rpo*B gene for quick detection rifampicin resistance. For isoniazid resistance, *kat*G gene displayed higher mutational frequencies (96%) than what has been reported in the region. This unique feature identified in *kat*G gene can be exploited to design a rapid isoniazid resistance diagnostic tool fit for the local population. Such a tool would complement the widely employed Xpert/MTB RIF, which currently only detects resistance to rifampicin. On the other hand, *inh*A regulatory region showed low mutational frequencies (2%) compared to the postulated range (15 -35%).

In conclusion, the national tuberculosis control program in Zambia is recommended to implement molecular epidemiological surveillance by genotyping *M. tuberculosis* isolates to help monitor and formulate effective control strategies against the spread of strains that are prone to becoming MDR-TB.