（報告様式４）

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平 成 ２ ８ 年 度　委 託 研 究 開 発 成 果 報 告 書

I. 基本情報

事　業　名：（日本語）エイズ対策実用化研究事業
（英　語）Research Program on HIV/AIDS

研究開発課題名：（日本語）適正なHIV療法開発のための研究
（英　語）Study for Development of Appropriate Anti-HIV Therapy

研究開発担当者　（日本語）国立国際医療研究センター　治療開発室長　潟永博之
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実 施 期 間：平成２８年　４月　１日　～　平成２９年　３月３１日

分 担 研 究　（日本語）抗HIV療法の適正化のための研究
開 発 課 題 名：（英　語）Study for Adjustment of Anti-HIV Therapy

研究開発分担者　（日本語）国立国際医療研究センター　治療開発室長　潟永博之
所属 役職 氏名：（英　語）Hiroyuki Gatanaga, Chief, National Center for Global Health and Medicine

分 担 研 究　（日本語）抗HIV薬による有害事象の解析
開 発 課 題 名：（英　語）Analysis of Adverse Events Caused by Anti-HIV Drugs

研究開発分担者　（日本語）帝京大学医学部内科学講座　教授　太田康男
所属 役職 氏名：（英　語）Yasuo Ota, Professor, Department of Internal Medicine, Teikyo University

分 担 研 究　（日本語）感染予防法開発のための研究
開 発 課 題 名：（英　語）Study for Development of Prevention of HIV Infection

研究開発分担者　（日本語）山梨大学医学部総合研究部　教授　川村龍吉
所属 役職 氏名：（英　語）Tatsuyoshi Kawamura, Professor, Yamanashi University
分 担 研 究　（日本語）新規抗HIV薬の開発

開 発 課 題 名： （英　語）Development of Novel Anti-HIV Agents

研究開発分担者　（日本語）東北大学災害科学国際研究所災害感染症分野　教授　児玉栄一
所属 役職 氏名：（英　語）Eiichi Kodama, Professor, International Research Institute of Disaster Science, Tohoku University

II. 成果の概要（総括研究報告）

和文

日本人に適した抗 HIV 療法(antiretroviral therapy: ART)を実践可能にするため、「柱１：安全な治療法開発のための研究」、「柱２：効果的な治療法開発のための研究」を行った。また、日本における新規感染者の一方的な増加に歯止めをかけるため、「柱３：感染予防法開発のための研究」を行った。

「柱１：安全な治療法開発のための研究」国立国際医療研究センターにおいて、tenofovir disoproxil fumarate (TDF)を含む抗 HIV 療法を開始した患者 655 人の治療開始後最初の尿中 β2-microglobulin (U-b2MG)とその後の予測糸球体濾過率 (estimated glomerular filtration rate: eGFR) を比較したところ、U-b2MG>1,700μg/L の患者では、U-b2MG<1,700μg/L の患者に比較し、より大きく eGFR の低下が認められた。これにより、治療開始後最初の U-b2MG により TDF 投与患者の腎機能の予後が推測できることが明らかとなった。また、lopinavir (LPV)・ritonavir (RTV)を含む抗 HIV 療法を二年以上継続した後、raltegravir (RAL)に変更した症例で、変更前と、変更後半年の時点の骨代謝マーカーを解析したところ、骨芽細胞による骨生成不全を示すペントシジンと低カルボキシル化オステオカルシン (undercarboxylated osteocalcin: ucOC) が低下し改善していた。更に、RTV は培養骨芽細胞の骨生成を阻害した。これらの結果より、LPV・RTV の治療は骨生成を阻害することにより骨密度の低下をもたらすと考えられた。太田康男教授（帝京大学医学部内科学講座）のグループとともに、抗 HIV 療法導入後一年以上の 54 症例について、173 person years の骨密度変化のデータを解析した（観察期間の中央値：3.1 年)。腰椎と大腿骨頸部の骨密度の変化の中央値は、それぞれ 0%と-0.52%であり、大部分の患者で骨密度の変化（低下）はほとんど認めなかった。しかしながら、一部の患者では骨密度の低下を認めた。多変量解析により、血清 bone-specific alkaline phosphatase (BAP)の低下や尿中 N-terminal telopeptide of type I collagen (NTx)排泄量の増加が、骨密度の低下と相関していた。骨密度低下の早期マーカーとして利用できる可能性が示された。

「柱２:効果的な治療法開発のための研究」国立国際医療研究センターにて、ATP-binding cassette sub-family B member 1 (ABCB1)遺伝子の 4 つの SNP、1236 C>T、2677 G>T/A、3435 C>T、4036 A>G、ABCG2 遺伝子の SNP、421 C>A、合計 5 つの SNP と、RAL 常用量 (800mg/2x) を 2 週間以上内服している 31 人の trough（内服前）と 41 人の peak（内服後 2-4 時間）の RAL 血中濃度の相関を解析した。trough の濃度はいずれの SNP とも関連しなかったが、peak は ABCB1 遺伝子の 4063 A>G と ABCG2 遺伝子の 421 C>A と関連し、両方の SNP を homozygote か heterozygote で持つ患者は、有意に高い RAL 濃度を示した。児玉栄一教授（東北大学災害科学国際研究所災害感染症分野）のグループとともに、天然化合物のスクリーニングを行い、新たな抗 HIV 薬開発の基となる新規低分子化合物を見いだした。既存の抗 HIV 薬と作用機序が異なる可能性が示唆されており、今後の開発が期待される。

「柱３：感染予防法開発のための研究」川村龍吉教授（山梨大学医学部総合研究部）らのグループ

とともに、EFdA、 darunavir(DRV)、dolutegravir(DTG) が低濃度 (10 nM) でもランゲルハンス細胞の HIV 感染を強力に抑制することを確認した。組み合わせでは、maraviroc＋DTG で強力な相乗効果が認められた。他の性感染症があると HIV の感染性が高まるため、近年増加している梅毒のコントロールも重要である。通常、梅毒感染後 10 年以上を経て生じるといわれている脳梅毒のゴム腫が、梅毒感染後 5 か月以内で生じた HIV 感染者の一例を症例報告した。また、診断が難しいとされている眼梅毒の 20 症例について、後方視的に解析し、診断が 4 週間以上遅れた症例では、視力に後遺症を残す率が 80%であり、4 週間以内に診断された症例では、全例視力障害無く完治していることを示した。梅毒の早期診断が、HIV 感染のためにも、梅毒患者本人の予後のためにも重要である。

英文

In order to make it possible to develop the anti-HIV therapy suitable for Japanese patients, we performed 'the study for development of safe therapy' and 'the study for efficient therapy'. Further, in order to stop the increase of newly infected individuals, we also performed 'the study for development of prevention methods of HIV infection'.

'The study for development of safe therapy'. In 655 HIV-infected patients in National Center for Global Health and Medicine, U-β2MG just after the introduction of TDF-containing anti-HIV therapy and eGFR afterwards were compared. The patients with U-β2MG>1,700μg/L showed the larger decrease of eGFR than those with U-β2MG<1,700μg/L, indicating that it is possible to predict the prognosis of renal function by measuring U-β2MG just after the introduction of TDF-containing anti-HIV therapy. In the patients who have been treated with lopinavir (LPV) and ritonavir (RTV)-containing anti-HIV therapy longer than two years and afterwards treated with raltegravir (RAL), the bone metabolizing markers were measured. Pentosidine and undercarboxylated osteocalcin (ucOC) were decreased after switching from LPV and RTV to RAL. Further, in vitro experiment, the bone production of cultured osteoblasts were inhibited with RTV. These results suggested that LPV and RTV decrease the bone mineral density by inhibiting the bone formation of osteoblasts. Professor Yasuo Ota, Department of Internal Medicine, Teikyo University, and his colleagues measured the bone mineral density in 54 cases longer than one year after the introduction of anti-HIV therapy (observation person-year: 173 person years, median observation period: 3.1 years). The median changes of bone mineral density of lumbar and hip were 0% and -0.52%, respectively, and no significant change was observed in most of observed patients. However, significant changes were observed in some patients. Multiple regression analysis revealed that the decrease of bone-specific alkaline phosphatase and the increase of urinary N-terminal telopeptide of type I collagen were positively related with decrease of bone mineral density, indicating that these markers can be used as early markers of decrease of bone mineral density.

'The study for efficient therapy'. In National Center for Global Health and Medicine, 4 SNPs of ATP-binding cassette sub-family B member 1 (ABCB1) and 1 SNP of ABCG2 were analyzed and its relation with trough and peak RAL concentrations in the patients treated with RAL longer than two weeks. Trough concentrations were not related with any of analyzed SNPs but peak concentrations were related with 4063 A>G of ABCB1 and 421 C>A of ABCG2 and homozygote

and heterozygote holders had significantly high peak RAL concentration. Professor Eiichi Kodama, International Research Institute of Disaster Science, Tohoku University, and his colleagues performed screening of natural compounds and identified a novel small molecular compound which can inhibit HIV replication in vitro. They obtained some data suggesting the compound inhibiting through a novel mechanism.

'The study for development of prevention methods of HIV infection'. Professor Tatsuyoshi Kawamura, Faculty of Medicine, University of Yamanashi, and his colleagues revealed that EFdA, darunavir, and dolutegravir can inhibit HIV infection in Langerhans cells at low concentrations (10nM). Further, the combination of maraviroc and dolutegravir showed synergy effect. When other sexually transmitted diseases coexist, HIV can transmit more easily. Therefore, it is important to control the syphilis epidemic. We reported one case of cerebral gumma which developed within five months after syphilis infection. Further, we performed retrospective analysis of ophthalmic syphilis and reported that the cases diagnosed within four months of ophthalmic symptoms can be treated without remaining any complication but 80% of other cases remained complications. These results indicate that early diagnosis of syphilis is important not only for the prognosis of the patients themselves but also for prevention of spreading HIV infection.

III. 成果の外部への発表

（1）学会誌・雑誌等における論文一覧（国内誌　　件、国際誌　　件）

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（2）学会・シンポジウム等における口頭・ポスター発表

該当なし

（3）「国民との科学・技術対話社会」に対する取り組み

該当なし

（4）特許出願

該当なし