Executive Summary of MSS 227 R

Project Title:
The level of GFAP as a specific biomarker of neuroAIDS among Chinese patients

Objectives:

1) To establish an easy, sensitive and cost-effective enzyme-linked immunosorbent assay (ELISA) for quantifying the concentration of Glial Fibrillary Acidic Protein (GFAP) in cerebrospinal fluid (CSF)
2) To validate GFAP as a biomarker of neuroAIDS among Chinese HIV-1/AIDS patients.

Design and setting:

The concentration of GFAP in CSF (CSF-GFAP) was measured by ELISA established in our laboratory. The degree of HIV-associated neurocognitive disorder (HAND) was determined by Head magnetic resonance imaging (H-MRI) and Montreal Cognitive Assessment (MoCA). Brain lesions were determined by H-MRI. The potential of CSF-GFAP for predicting HAND development and the progression of brain lesions were investigated by a longitudinal study. The clinical status of patients was diagnosed by the clinical doctors in Shenzhen Third People's Hospital. The concentration of soluble CD163 in CSF (CSF-sCD163) was measured by ELISA.

Participants:

CSF specimens from 162 HIV-1 patients were recruited at Shenzhen Third people's Hospital. Among them, 76 patients were HAART naïve, 66 patients were HAART treated and 20 patients were undetermined at the time of CSF collection. This study was approved by the ethics review committee of Shenzhen Third People's Hospital.

Results:

The 162 specimens were first divided into CSF-GFAP concentration <4.5 ng/ml and >4.5 ng/ml groups followed by classifying into 7 neuroAIDS subsets: No HAND, HAND, Taxoplasmaosis, Cryptococcosis, Lymphoma, Tuberculosis and Progress multifocal leukoencephalopathy. Although CSF-GFAP concentration in >4.5 group was higher in the patients from Toxoplasmaosis, Cryptococcosis and Tuberculosis

subsets, patients of these groups were also found in the <4.5 group. These results suggested CSF-GFAP concentration might be related to opportunistic infections and dependent on patients' conditions at the time of CSF collection. To investigate the potential of CSF-GFAP for predicting HAND development and brain lesion progression, 13 patients from HAND subset were recruited for H-MRI and MoCA, and 37 patients from different subsets were recruited for H-MRI in the longitudinal study, respectively. No major changes in H-MRI and MoCA results against time were found among CSF-GFAP positive patients with HAND and for reference, one patient from tuberculosis subset with CSF-GFAP >900ng/ml achieved high MoCA scores. Besides, brain lesion progression was observed in patients of <4.5 and >4.5 groups. These results suggested CSF-GFAP was unlikely effective to be a biomarker for these two settings. We also evaluate other related biomarkers for comparison, we found that CSF-sCD163 concentration was significantly correlated with CSF HIV-RNA and was significantly increased in patients with neurological complications. Also, CSFsCD163, but not CSF-GFAP was significantly increased in patients with meningitis from Cryptococcosis and Tuberculosis subsets when compared with those without mycobacterium tuberculosis, bacterial, fungal infection and viral meningitis.

Outcomes and conclusions:

In summary, although CSF-GFAP is unlikely a strong biomarker for neuroAIDS due to complicated clinical situations, we identified that CSF-sCD163 could be a useful biomarker for a neuroAIDS subset (Cryptococcal and Tuberculous meningitis) in Chinese HIV-1/AIDS patients.

Publication:

Wu X, Liu L, Cheung KW, *et al.* Brain Invasion by CD4(+) T Cells Infected with a Transmitted/Founder HIV-1BJZS7 During Acute Stage in Humanized Mice. *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology* 2016, **11**(3)**:** 572-583.

Project Title:
The level of GFAP as a specific biomarker of neuroAIDS among Chinese patients

Objectives:
1) 構建一個靈敏及具成本效益的 ELISA 以測量腦脊液 (CSF) 中 Glial Fibrillary Acidic Protein (GFAP) 的濃度
2) 驗證 GFAP 在中國愛滋病病人中作為 neuroAIDS 生物標誌物 (biomarker) 的資質。

Design and setting:

CSF 中的 GFAP 濃度 (CSF-GFAP) 是用我們建立的 ELISA 定量。 HIV 相關神經認知障礙 (HAND) 的病情是用頭顱核磁共振成像(H-MRI)及蒙特利爾認知評估(MoCA)作判斷。腦損傷是以 H-MRI 作判斷。 CSF-GFAP 作為預測 HAND 及腦損傷病情的 biomarker 的資質是利用縱向研究方法檢定。臨床診斷是由深圳第三人民醫院的醫生負責。CSF 中的 CD163 (CSF-sCD163) 是利用 ELISA 定量。

Participants:

162 份愛滋病病人的腦脊液樣本是從深圳第三人民醫院收集所得。其中，76 人是未接受抗 HIV 藥物治療，66 人為已治療的，20 人的藥物治療情況在樣本收集時為不能確定的。此研究是在取得深圳第三人民醫院倫理委員會批准後進行的。

Results:

我們首先將 162 份樣本分為 CSF-GFAP 濃度 <4.5 ng/ml 和 >4.5 ng/ml 兩組，然後按診斷結果再分為：非 HAND，HAND，弓型蟲，隱球菌，淋巴瘤，結核及進行性多灶性白質腦病 7 個 neuroAIDS 亞群。在>4.5 組中，弓型蟲，隱球菌及結核感染的病人有較高的 CSF-GFAP，然而這類病人亦出現在<4.5 組中。此結果說明 CSF-GFAP 濃度或與機會性感染及取樣時病人的病情有關。此外，縱向研究結果顯示，CSF-GFAP 呈陽性的病人的 H-MRI 結果並無隨時間變異，而且有一名來自結核組，CSF-GFAP 濃度達 900ng/ml 的病人在兩次的 MoCA 評估中都取得高分。腦損傷變差的情況亦可於來自不同亞群的<4.5 及 >4.5 組的病人中發現。這些結果均指出 CSF-GFAP 未必可作為預測 HAND 及腦損傷病情進展的 biomarker。
另外，我們發現 CSF-sCD163 濃度不單與 CSF HIV-RNA 有相關性，更於有神經系統病變的病人中明顯升高。同時，我們發現有別於 CSF-GFAP, 在當與那些沒

有肺結核，細菌及真菌共感染及病毒性腦膜炎的病人相比時，CSF-sCD163 於隱球菌腦膜炎及結核性腦膜炎的病人中明顯上升。

Outcomes and conclusions:

由於病人複雜的臨床表症，CSF-GFAP 不算是一個很強的 neuroAIDS 生物標誌物，但我們發現 CSF-sCD163 是一個可能作為中國愛滋病病人檢定隱球菌和結核性腦膜炎的生物標誌物。

Publication:

Wu X, Liu L, Cheung KW, *et al.* Brain Invasion by CD4(+) T Cells Infected with a Transmitted/Founder HIV-1BJZS7 During Acute Stage in Humanized Mice. *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology* 2016, **11**(3)**:** 572-583.