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(54)名稱

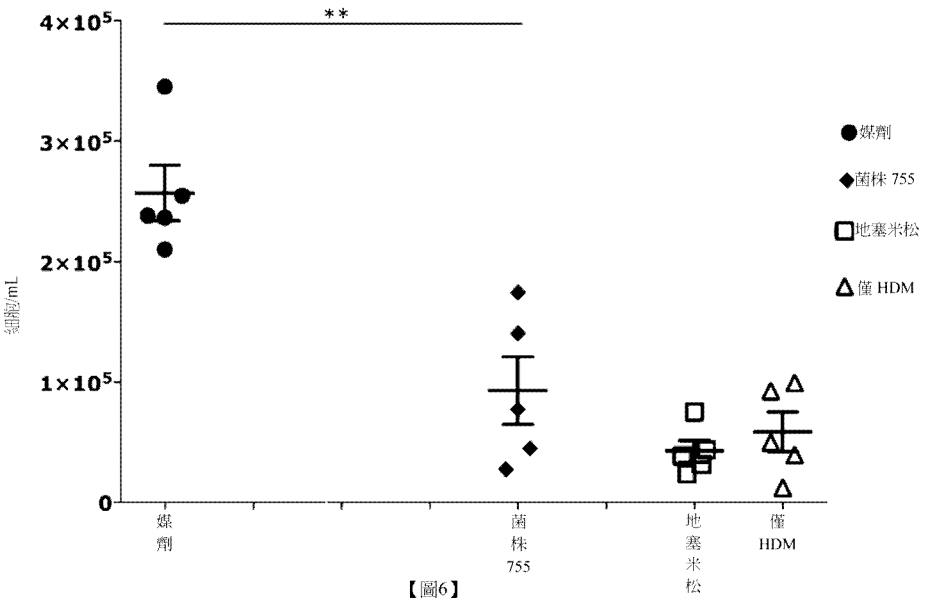
包含細菌菌株之組合物

(57)摘要

本發明提供包含細菌菌株之組合物，其用於治療及預防發炎及自體免疫疾病。

The invention provides compositions comprising bacterial strains for treating and preventing inflammatory and autoimmune diseases.

指定代表圖：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4×10^5
3×10^5
2×10^5
1×10^5
0
細胞/mL
媒劑
菌株755
地塞米松
僅HDM
媒劑
菌株 755
地塞米松
僅 HDM

【圖6】

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公告本

【發明摘要】

【中文發明名稱】

包含細菌菌株之組合物

【英文發明名稱】

COMPOSITIONS COMPRISING BACTERIAL STRAINS

【中文】

本發明提供包含細菌菌株之組合物，其用於治療及預防發炎及自體免疫疾病。

【英文】

The invention provides compositions comprising bacterial strains for treating and preventing inflammatory and autoimmune diseases.

【指定代表圖】

圖6

【代表圖之符號簡單說明】

無

【特徵化學式】

無

【發明說明書】

【中文發明名稱】

包含細菌菌株之組合物

【英文發明名稱】

COMPOSITIONS COMPRISING BACTERIAL STRAINS

【技術領域】

【0001】 本發明屬於包含自哺乳動物消化道分離之細菌菌株之組合物及此類組合物用於治療疾病之用途的領域。

【先前技術】

【0002】 雖然認為人類腸道在子宮內無菌，但在出生後其立刻暴露於大量母體及環境微生物。此後，出現微生物定殖及演替的動態期，其受諸如分娩模式、環境、飲食及宿主基因型之因素影響，所有因素均影響腸微生物叢之組成，特別在童年期間。隨後，微生物叢穩定化且變成成人樣[1]。人類腸微生物叢含有超過500-1000個基本上屬於兩大細菌分類脆弱擬桿菌(Bacteroidete)及厚壁門菌(Firmicute)之不同種系型[2]。由人類腸之細菌定殖產生的成功共生關係產生多種代謝、結構、保護及其他有益功能。定殖於腸之增強代謝活性確保降解以其他方式無法攝取之飲食組分，同時釋放副產物，為宿主提供重要的營養物來源。類似地，充分認識到腸微生物叢之免疫重要性，且在免疫系統減弱之無菌動物中例示，其免疫系統在引入共生細菌後在功能上復原[3-5]。

【0003】 微生物叢組成之顯著變化已在諸如發炎性腸病(IBD)之腸胃病症中證明。舉例而言，在IBD患者中梭菌屬(*Clostridium*)XIVa

簇細菌之含量降低，而大腸桿菌數目增加，表明腸內共生體與病原性共生體之平衡的變化[6-9]。有趣地，此微生物生態失調亦與效應T細胞群體之不平衡相關。

【0004】 認識到某些細菌菌株對動物腸可具有潛在積極作用，已提議各種菌株用於治療各種疾病(參見例如[10-13])。亦已提議某些菌株，包括大部分乳桿菌屬(*Lactobacillus*)及雙歧桿菌屬(*Bifidobacterium*)菌株，用於治療不直接與腸相關之各種發炎及自體免疫疾病(綜述參見[14]及[15])。然而，不同疾病及不同細菌菌株之間的關係及在全身層面上特定細菌菌株對腸及對任何特定類型疾病之準確作用尚未很好地表徵。

【0005】 此項技術中需要治療發炎及自體免疫疾病之新方法。亦需要待表徵之腸細菌之潛在作用，以可研發使用腸細菌之新療法。

【發明內容】

【0006】 本發明者已研發用於治療及預防發炎及自體免疫疾病之新療法。詳言之，本發明者已研發用於治療及預防由IL-17或Th17路徑介導之疾病及病狀的新療法。詳言之，本發明者已鑑別來自副擬桿菌屬(*Parabacteroides*)之細菌菌株可有效減少Th17發炎反應。如實例中所描述，經口投與包含狄氏副擬桿菌(*Parabacteroides distasonis*)之組合物可降低氣喘、類風濕性關節炎及多發性硬化之小鼠模型中包括Th17發炎反應之發炎反應之嚴重程度。亦如實例中所描述，經口投與包含狄氏副擬桿菌之組合物可降低葡萄膜炎之小鼠模型中包括Th17發炎反應之發炎反應的嚴重程度。

【0007】 因此，在第一實施例中，本發明提供一種包含副擬桿菌

屬之細菌菌株的組合物，其用於治療或預防由IL-17或Th17路徑介導之疾病或病狀的方法中。本發明者已鑑別用來自該屬之細菌菌株治療可降低作為Th17路徑(包括IL-17)之一部分之細胞介素的含量，可減輕Th17發炎反應且在由IL-17及Th17路徑介導之發炎及自體免疫疾病之小鼠模型中可提供臨床益處。

【0008】 在特定實施例中，本發明提供一種包含副擬桿菌屬之細菌菌株的組合物，其用於治療或預防選自由以下組成之群之疾病或病狀的方法中：多發性硬化；關節炎，諸如類風濕性關節炎、骨關節炎、牛皮癬性關節炎或幼年特發性關節炎；視神經脊髓炎(德維克氏病(Devic's disease))；強直性脊椎炎；脊椎關節炎；牛皮癬；全身性紅斑狼瘡；發炎性腸病，諸如克羅恩氏病(Crohn's disease)或潰瘍性結腸炎；乳糜瀉；氣喘，諸如過敏性氣喘或中性粒細胞性氣喘；慢性阻塞性肺病(COPD)；癌症，諸如乳癌、結腸癌、肺癌或卵巢癌；葡萄膜炎；鞏膜炎；血管炎；白塞氏病(Behcet's disease)；動脈粥樣硬化；異位性皮炎；肺氣腫；牙周炎；過敏性鼻炎；及同種異體移植排斥。來自副擬桿菌屬之細菌菌株展示之對Th17發炎反應的作用可為由IL-17及Th17路徑介導之疾病及病狀，諸如上列疾病及病狀提供治療益處。

【0009】 在較佳實施例中，本發明提供一種包含副擬桿菌屬之細菌菌株的組合物，其用於治療或預防氣喘，諸如中性粒細胞性氣喘或過敏性氣喘的方法中。本發明者已鑑別用副擬桿菌屬菌株治療可減少中性粒細胞及嗜酸細胞募集至肺中，此可幫助治療或預防氣喘。此外，本發明者已測試及證明副擬桿菌屬菌株在氣喘之小鼠模型中的功

效。在某些實施例中，組合物用於治療或預防中性粒細胞性氣喘或嗜酸性粒細胞性氣喘之方法中。本發明之組合物展示的對中性粒細胞及嗜酸性粒細胞之作用意謂其可特別有效治療或預防中性粒細胞性氣喘及嗜酸性粒細胞性氣喘。實際上，在某些實施例中，組合物用於在治療或預防氣喘中降低中性粒細胞性發炎反應之方法中，或組合物用於在治療或預防氣喘中降低嗜酸性粒細胞性發炎反應之方法中。在較佳實施例中，本發明提供一種包含物種狄氏副擬桿菌之細菌菌株的組合物，其用於治療氣喘且尤其中性粒細胞性氣喘。狄氏副擬桿菌在氣喘模型中展示對中性粒細胞具有特別深遠之作用，且用狄氏副擬桿菌治療可特別有效治療中性粒細胞性氣喘。

【0010】 在其他較佳實施例中，本發明提供一種包含副擬桿菌屬之細菌菌株的組合物，其用於治療或預防類風濕性關節炎之方法中。本發明者已確定用副擬桿菌屬菌株治療可在類風濕性關節炎之小鼠模型中提供臨床益處且可減少關節腫脹。在較佳實施例中，本發明提供一種包含物種狄氏副擬桿菌之細菌菌株的組合物，其用於治療類風濕性關節炎。使用物種狄氏副擬桿菌之組合物可特別有效治療類風濕性關節炎。

【0011】 在其他較佳實施例中，本發明提供一種包含副擬桿菌屬之細菌菌株的組合物，其用於治療或預防多發性硬化之方法中。本發明者已確定用副擬桿菌屬菌株治療可在多發性硬化之小鼠模型中降低發病率及疾病嚴重程度。在較佳實施例中，本發明提供一種包含物種狄氏副擬桿菌之細菌菌株的組合物，其用於治療多發性硬化。使用物種狄氏副擬桿菌之組合物可特別有效治療多發性硬化。

【0012】在其他較佳實施例中，本發明提供一種包含副擬桿菌屬之細菌菌株的組合物，其用於治療或預防葡萄膜炎、諸如後葡萄膜炎之方法中。本發明者已確定用副擬桿菌屬菌株治療可在葡萄膜炎之小鼠模型中降低發病率及疾病嚴重程度且可預防或減少視網膜損傷。在較佳實施例中，本發明提供一種包含物種狄氏副擬桿菌之細菌菌株的組合物，其用於治療葡萄膜炎。

【0013】在其他較佳實施例中，本發明提供一種包含副擬桿菌屬之細菌菌株的組合物，其用於治療或預防癌症、諸如乳癌、肺癌或肝癌之方法中。包含副擬桿菌屬之細菌菌株的組合物可在乳癌、肺癌或肝癌之小鼠模型中降低腫瘤生長。在某些實施例中，組合物用於癌症治療中減小腫瘤尺寸或預防腫瘤生長之方法中。在某些實施例中，本發明提供一種包含物種狄氏副擬桿菌之細菌菌株的組合物，其用於治療癌症。

【0014】在某些實施例中，本發明之組合物用於由IL-17或Th17路徑介導之疾病或病狀的治療或預防中減少IL-17產生或減少Th17細胞分化之方法中。詳言之，本發明之組合物可用於氣喘、類風濕性關節炎或多發性硬化或氣喘、類風濕性關節炎、多發性硬化、葡萄膜炎或癌症之治療或預防中減少IL-17產生或減少Th17細胞分化。較佳地，本發明提供包含物種狄氏副擬桿菌之細菌菌株的組合物，其用於氣喘、類風濕性關節炎或多發性硬化之治療或預防中減少IL-17產生或減少Th17細胞分化。本發明亦提供包含物種狄氏副擬桿菌之細菌菌株的組合物，其用於葡萄膜炎之治療或預防中減少IL-17產生或減少Th17細胞分化。

【0015】在某些實施例中，組合物用於具有升高之IL-17含量或Th17細胞的患者中。副擬桿菌屬菌株展示之對Th17發炎反應的作用可特別有益於此類患者。

【0016】在本發明之較佳實施例中，組合物中之細菌菌株為狄氏副擬桿菌。亦可使用緊密相關之菌株，諸如具有與狄氏副擬桿菌之細菌菌株之16s rRNA序列至少95%、96%、97%、98%、99%、99.5%或99.9%一致之16s rRNA序列的細菌菌株。較佳地，細菌菌株具有與SEQ ID NO:1、2、3、4、5、6、7、8或9至少95%、96%、97%、98%、99%、99.5%或99.9%一致之16s rRNA序列。較佳地，用於本發明之細菌菌株具有由SEQ ID NO:9表示之16s rRNA序列。

【0017】在某些實施例中，本發明之組合物用於經口投與。經口投與本發明之菌株可有效治療IL-17或Th17路徑介導之疾病及病狀。此外，經口投與便於患者及開業醫師且允許傳遞至腸及/或部分或全部定殖於腸。

【0018】在某些實施例中，本發明之組合物包含一或多種醫藥學上可接受之賦形劑或載劑。

【0019】在某些實施例中，本發明之組合物包含已凍乾之細菌菌株。凍乾為一項製備允許傳遞細菌之穩定組合物的有效及便利技術。

【0020】在某些實施例中，本發明提供一種包含如上所述之組合物的食品。

【0021】在某些實施例中，本發明提供一種包含如上所述之組合物的疫苗組合物。

【0022】另外，本發明提供一種治療或預防由IL-17或Th17路徑

介導之疾病或病狀的方法，其包括投與包含副擬桿菌屬之細菌菌株的組合物。

【0023】 在研發以上發明時，本發明者已鑑別及表徵特別適用於療法之細菌菌株。本發明之狄氏副擬桿菌菌株展示有效治療本文中描述之疾病，諸如關節炎、氣喘、多發性硬化及葡萄膜炎。因此，在另一個態樣中，本發明提供一種以登記號NCIMB 42382寄存之狄氏副擬桿菌菌株或其衍生物的細胞。本發明亦提供包含此類細胞之組合物或此類細胞之生物純培養物。本發明亦提供一種以登記號NCIMB 42382寄存之狄氏副擬桿菌菌株或其衍生物的細胞，其用於療法中，尤其用於本文中描述之疾病。

【圖式簡單說明】

【0024】 **圖1**：房塵蟎誘發之氣喘的小鼠模型-總BAL流體細胞計數。

【0025】 **圖2**：房塵蟎誘發之氣喘的小鼠模型-BALF中總嗜酸性粒細胞計數。

【0026】 **圖3**：房塵蟎誘發之氣喘的小鼠模型-BALF中嗜酸性粒細胞比例。

【0027】 **圖4**：房塵蟎誘發之氣喘的小鼠模型-BALF中總巨噬細胞計數。

【0028】 **圖5**：房塵蟎誘發之氣喘的小鼠模型-BALF中巨噬細胞比例。

【0029】 **圖6**：房塵蟎誘發之氣喘的小鼠模型-BALF中總中性粒細胞計數。

【0030】 **圖7**：房塵蟎誘發之氣喘的小鼠模型-BALF中中性粒細胞比例。

【0031】 **圖8**：房塵蟎誘發之氣喘的小鼠模型-BALF中總淋巴細胞計數。

【0032】 **圖9**：房塵蟎誘發之氣喘的小鼠模型-BALF中淋巴細胞比例。

【0033】 **圖10**：嚴重中性粒細胞性氣喘之小鼠模型-總BAL流體細胞計數。

【0034】 **圖11**：嚴重中性粒細胞性氣喘之小鼠模型-BALF中總嗜酸性粒細胞計數。

【0035】 **圖12**：嚴重中性粒細胞性氣喘之小鼠模型-BALF中嗜酸性粒細胞比例。

【0036】 **圖13**：嚴重中性粒細胞性氣喘之小鼠模型-BALF中總巨噬細胞計數。

【0037】 **圖14**：嚴重中性粒細胞性氣喘之小鼠模型-BALF中巨噬細胞比例。

【0038】 **圖15**：嚴重中性粒細胞性氣喘之小鼠模型-BALF中總中性粒細胞計數。

【0039】 **圖16**：嚴重中性粒細胞性氣喘之小鼠模型-BALF中中性粒細胞比例。

【0040】 **圖17**：嚴重中性粒細胞性氣喘之小鼠模型-BALF中總淋巴細胞計數。

【0041】 **圖18**：嚴重中性粒細胞性氣喘之小鼠模型-BALF中淋巴

細胞比例。

【0042】 **圖19**：類風濕性關節炎之小鼠模型-體重，第-14天至第0天。資料呈現為初始(第-14天)體重之平均值±SEM百分比。

【0043】 **圖20**：類風濕性關節炎之小鼠模型-體重，第0天至第42天。資料呈現為初始(第0天)體重之平均值±SEM百分比。•••• $p < 0.0001$，當與媒劑處理組比較時。

【0044】 **圖21**：類風濕性關節炎之小鼠模型-臨床評分。資料呈現為平均值±SEM。****$p < 0.0001$，當與媒劑處理組中第21天比較時。♦,O $p < 0.05$，當既定日與媒劑處理組比較時。

【0045】 **圖22**：類風濕性關節炎之小鼠模型-對II型膠原蛋白之脾細胞增殖反應。基於3H-TdR併入之每分鐘減去培養基背景[CII刺激-培養基背景]計數。所有資料呈現為平均值±SEM。***$p < 0.001$，與媒劑組相比。

【0046】 **圖23**：類風濕性關節炎之小鼠模型-組織培養上清液中IFNγ之含量。線表示組中位值。

【0047】 **圖24**：類風濕性關節炎之小鼠模型-組織培養上清液中IL-17A之含量。線表示組中位值。

【0048】 **圖25**：類風濕性關節炎之小鼠模型-組織培養上清液中IL-10之含量。線表示組中位值。

【0049】 **圖26**：類風濕性關節炎之小鼠模型-組織培養上清液中IL-6之含量。線表示組中位值。

【0050】 **圖27**：房塵蟎誘發之氣喘的小鼠模型-血清中總IgE。

【0051】 **圖28**：房塵蟎誘發之氣喘的小鼠模型-血清中HDM特異

性IgG1。

【0052】 **圖29**：房塵蟎誘發之氣喘的小鼠模型-BALF中總IgE。

【0053】 **圖30**：房塵蟎誘發之氣喘的小鼠模型-BALF中HDM特異性IgG1。

【0054】 **圖31**：房塵蟎誘發之氣喘的小鼠模型-組織學分析-平均細枝氣管周浸潤評分。

【0055】 **圖32**：房塵蟎誘發之氣喘的小鼠模型-組織學分析-平均血管周浸潤評分。

【0056】 **圖33**：房塵蟎誘發之氣喘的小鼠模型-組織學分析-平均發炎評分(細枝氣管周與血管周浸潤評分之平均值)。

【0057】 **圖34**：房塵蟎誘發之氣喘的小鼠模型-組織學分析-黏液評分。

【0058】 **圖35**：房塵蟎誘發之氣喘的小鼠模型-肺組織中IL-9含量。

【0059】 **圖36**：房塵蟎誘發之氣喘的小鼠模型-肺組織中IL-1a含量。

【0060】

【0061】 **圖38**：房塵蟎誘發之氣喘的小鼠模型-肺組織中IL-17A含量。

【0062】 **圖39**：房塵蟎誘發之氣喘的小鼠模型-肺組織中IL-4含量。

【0063】 **圖40**：房塵蟎誘發之氣喘的小鼠模型-肺組織中IL-5含量。

【0064】 **圖41**：房塵蟎誘發之氣喘的小鼠模型-肺組織中IL-1b含量。

【0065】 **圖42**：房塵蟎誘發之氣喘的小鼠模型-肺組織中RANTES含量。

【0066】 **圖43**：房塵蟎誘發之氣喘的小鼠模型-肺組織中MIP-1a含量。

【0067】 **圖44**：房塵蟎誘發之氣喘的小鼠模型-肺組織中KC含量。

【0068】 **圖45**：房塵蟎誘發之氣喘的小鼠模型-肺組織中MIP-2含量。

【0069】 **圖46**：嚴重中性粒細胞性氣喘之小鼠模型-血清中HDM特異性IgG1。

【0070】 **圖47**：嚴重中性粒細胞性氣喘-血清中HDM特異性IgG2a。

【0071】 **圖48**：嚴重中性粒細胞性氣喘-BALF中HDM特異性IgG1。

【0072】 **圖49**：嚴重中性粒細胞性氣喘-BALF中HDM特異性IgG2a。

【0073】 **圖50**：嚴重中性粒細胞性氣喘之小鼠模型-組織學分析-平均細枝氣管周浸潤評分

【0074】 **圖51**：嚴重中性粒細胞性氣喘之小鼠模型-組織學分析-平均血管周浸潤評分

【0075】 **圖52**：嚴重中性粒細胞性氣喘之小鼠模型-組織學分析-

平均發炎評分(細枝氣管周與血管周浸潤評分之平均值)。

【0076】 **圖53**：嚴重中性粒細胞性氣喘之小鼠模型-肺組織中TNFα含量。

【0077】 **圖54**：嚴重中性粒細胞性氣喘之小鼠模型-肺組織中IL-1a含量。

【0078】 **圖55**：嚴重中性粒細胞性氣喘之小鼠模型-肺組織中IFNγ含量。

【0079】 **圖56**：嚴重中性粒細胞性氣喘之小鼠模型-肺組織中IL-17F含量。

【0080】 **圖57**：嚴重中性粒細胞性氣喘之小鼠模型-肺組織中IL-1b含量。

【0081】 **圖58**：嚴重中性粒細胞性氣喘之小鼠模型-肺組織中RANTES含量。

【0082】 **圖59**：嚴重中性粒細胞性氣喘之小鼠模型-肺組織中MIP-2含量。

【0083】 **圖60**：嚴重中性粒細胞性氣喘之小鼠模型-肺組織中KC含量。

【0084】 **圖61**：嚴重中性粒細胞性氣喘之小鼠模型-肺組織中IL-17A含量。

【0085】 **圖62**：嚴重中性粒細胞性氣喘之小鼠模型-肺組織中MIP-1a含量。

【0086】 **圖63**：嚴重中性粒細胞性氣喘之小鼠模型-肺組織中IL-33含量。

【0087】 **圖64**：類風濕性關節炎之小鼠模型-組織病理學評分之目測模板。代表性影像展示膠原蛋白誘發之關節炎研究中來自小鼠跗關節之綜合評分。

【0088】 **圖65**：類風濕性關節炎之小鼠模型-組織病理學：發炎評分。資料呈現為平均值±SEM。*p < 0.05，當與媒劑處理組比較時。

【0089】 **圖66**：類風濕性關節炎之小鼠模型-組織病理學：軟骨評分。資料呈現為平均值±SEM。*p < 0.05，當與媒劑處理組比較時。

【0090】 **圖67**：類風濕性關節炎之小鼠模型-組織病理學：骨骼評分。資料呈現為平均值±SEM。*p < 0.05，當與媒劑處理組比較時。

【0091】 **圖68**：類風濕性關節炎之小鼠模型-組織病理學：總評分。資料呈現為平均值±SEM。* p < 0.05，當與媒劑處理組比較時。

【0092】 **圖69**：類風濕性關節炎之小鼠模型-組織病理學：代表性圖。在括弧之間指示動物ID (#n.n)及四肢(R為右，L為左)。左影像(媒劑)：發炎及纖維化延伸至關節周圍之軟組織之大範圍關節及骨骼破壞。

【0093】 **圖70**：多發性硬化之小鼠模型-臨床評分。

【0094】 **圖71**：多發性硬化之小鼠模型-發病率。

【0095】 **圖72**：葡萄膜炎之小鼠模型-對照組中之TEFI評分。資料呈現為平均值±SEM。

【0096】 **圖73**：葡萄膜炎之小鼠模型-第28天之TEFI評分。資料

呈現為平均值±SEM。

【實施方式】

細菌菌株

【0097】本發明之組合物包含副擬桿菌屬之細菌菌株。該等實例證明該屬之細菌可用於治療或預防由IL-17或Th17路徑介導之疾病及病狀。較佳細菌菌株為物種狄氏副擬桿菌菌株。

【0098】用於本發明之副擬桿菌屬物種之實例包括狄氏副擬桿菌、戈氏副擬桿菌(*Parabacteroides goldsteinii*)、糞副擬桿菌(*Parabacteroides merdae*)及約氏副擬桿菌(*Parabacteroides johnsonii*)。副擬桿菌屬類似於擬桿菌屬，且為革蘭氏陰性、專性厭氧、不形成孢子、不運動且呈杆狀，且尺寸上為0.8-1.6×1.2-12 μm。狄氏副擬桿菌為人類糞便中最常見物種之一。狄氏副擬桿菌之模式菌株為JCM 5825^T (=CCUG 4941^T=DSM 20701^T=ATCC 8503^T)。狄氏副擬桿菌菌株JCM 5825T、JCM 13400、JCM 13401、JCM 13402、JCM 13403及JCM 13404及糞副擬桿菌菌株JCM 9497T及JCM 13405之16S rRNA基因序列的GenBank/EMBL/DDBJ登記號分別為AB238922–AB238929 (本文中揭示為SEQ ID NO:1-8)。示例性菌株亦描述於[16]中。

【0099】以登記號NCIMB 42382寄存之狄氏副擬桿菌細菌在該等實例中進行測試且在本文中亦稱為菌株755或MRX005。測試之755菌株的16S rRNA序列在SEQ ID NO:9中提供。菌株755由GT Biologics Ltd. (Life Sciences Innovation Building, Aberdeen, AB25 2ZS, Scotland)以「副擬桿菌屬755」在2015年3月12日寄存在國際寄存局NCIMB,

Ltd. (Ferguson Building, Aberdeen, AB21 9YA, Scotland)且分配登記號NCIMB 42382。GT Biologics Ltd.隨後將其名稱改為4D Pharma Research Limited。

【0100】 菌株755之基因組序列提供於SEQ ID NO:10中。此序列使用PacBio RS II平臺產生。

【0101】 亦預期與實例中測試之菌株緊密相關的細菌菌株有效治療或預防由IL-17或Th17路徑介導之疾病及病狀。在某些實施例中，用於本發明之細菌菌株具有與狄氏副擬桿菌之細菌菌株之16s rRNA序列至少95%、96%、97%、98%、99%、99.5%或99.9%一致的16s rRNA序列。較佳地，用於本發明之細菌菌株具有與SEQ ID NO:1、2、3、4、5、6、7、8或9至少95%、96%、97%、98%、99%、99.5%或99.9%一致之16s rRNA序列。較佳地，序列一致性係針對SEQ ID NO:9。較佳地，用於本發明之細菌菌株具有由SEQ ID NO:9表示之16s rRNA序列。

【0102】 亦預期作為以登記號42382寄存之細菌之生物型的細菌菌株有效治療或預防由IL-17或Th17路徑介導之疾病及病狀。生物型為具有相同或極類似之生理及生物化學特性的密切相關菌株。

【0103】 作為以登記號NCIMB 42382寄存之細菌之生物型且適合用於本發明中的菌株可藉由對以登記號NCIMB 42382寄存之細菌之其他核苷酸序列進行定序來鑑別。舉例而言，基本上全基因組可定序，且用於本發明之生物型菌株可在其全基因組之至少80%上(例如在至少85%、90%、95%或99%上或在其全基因組上)具有至少95%、96%、97%、98%、99%、99.5%或99.9%序列一致性。用於鑑別生物型菌株

之其他適合序列可包括hsp60或重複順序，諸如BOX、ERIC、$(GTG)_5$或REP或[17]。生物型菌株可具有與以登記號NCIMB 42382寄存之細菌之對應序列至少95%、96%、97%、98%、99%、99.5%或99.9%序列一致性的序列。

【0104】在某些實施例中，用於本發明之細菌菌株具有與SEQ ID NO:10有序列一致性之基因組。在較佳實施例中，用於本發明之細菌菌株具有在SEQ ID NO:10之至少60% (例如至少65%、70%、75%、80%、85%、95%、96%、97%、98%、99%或100%)上與SEQ ID NO:10具有至少90%序列一致性(例如至少92%、94%、95%、96%、97%、98%、99%或100%序列一致性)的基因組。舉例而言，用於本發明之細菌菌株可具有在SEQ ID NO:10 70%上與SEQ ID NO:10至少90%序列一致，或在SEQ ID NO:10 80%上與SEQ ID NO:10至少90%序列一致，或在SEQ ID NO:10 90%上與SEQ ID NO:10至少90%序列一致，或在SEQ ID NO:10 100%上與SEQ ID NO:10至少90%序列一致，或在SEQ ID NO:10 70%上與SEQ ID NO:10至少95%序列一致，或在SEQ ID NO:10 80%上與SEQ ID NO:10至少95%序列一致，或在SEQ ID NO:10 90%上與SEQ ID NO:10至少95%序列一致，或在SEQ ID NO:10 100%上與SEQ ID NO:10至少95%序列一致，或在SEQ ID NO:10 70%上與SEQ ID NO:10至少98%序列一致，或在SEQ ID NO:10 80%上與SEQ ID NO:10至少98%序列一致，或在SEQ ID NO:10 90%上與SEQ ID NO:10至少98%序列一致，或在SEQ ID NO:10 100%上與SEQ ID NO:10至少98%序列一致的基因組。

【0105】或者，作為以登記號NCIMB 42382寄存之細菌之生物型

且適用於本發明中的菌株可藉由使用登記號NCIMB 42382寄存物及限制片段分析及/或PCR分析，例如藉由使用螢光增強之片段長度多態現象(FAFLP)及重複DNA元件(rep)-PCR指紋或蛋白質型態分析或部分16S或23s rDNA定序來鑑別。在較佳實施例中，此類技術可用於鑑別其他狄氏副擬桿菌菌株。

【0106】 在某些實施例中，作為以登記號NCIMB 42382寄存之細菌之生物型且適用於本發明中的菌株為當藉由增強之核蛋白體DNA限制分析(ARDRA)分析時，例如當使用Sau3AI限制酶(關於示例性方法及指導參見例如[18])時提供與以登記號NCIMB 42382寄存之細菌相同模式的菌株。或者，生物型菌株確定為具有與以登記號NCIMB 42382寄存之細菌相同的碳水化合物發酵模式的菌株。

【0107】 適用於本發明之組合物及方法的其他副擬桿菌屬菌株，諸如以登記號NCIMB 42382寄存之細菌之生物型，可使用任何適當方法或策略，包括實例中描述之分析鑑別。舉例而言，用於本發明中之菌株可藉由在厭氧YCFA中培養及/或投與細菌至II型膠原蛋白誘發之關節炎小鼠模型且接著評估細胞介素含量來鑑別。詳言之，具有與以登記號NCIMB 42382寄存之細菌類似的生長模式、代謝類型及/或表面抗原之細菌菌株可用於本發明。適用菌株將具有與NCIMB 42382菌株可比的免疫調節活性。詳言之，生物型菌株將對氣喘、關節炎、多發性硬化及葡萄膜炎疾病模型引起與實例中所示之作用可比的作用，且對細胞介素含量引起與實例中所示之作用可比的作用，其可藉由使用實例中描述之培養及投與方案來鑑別。

【0108】 本發明之一種尤其較佳之菌株為以登記號NCIMB 42382

寄存之狄氏副擬桿菌菌株。此為實例中測試之示例性755菌株且展示有效治療疾病。因此，本發明提供以登記號NCIMB 42382寄存之狄氏副擬桿菌菌株或其衍生物之細胞，諸如分離細胞。本發明亦提供一種組合物，其包含以登記號NCIMB 42382寄存之狄氏副擬桿菌菌株或其衍生物之細胞。本發明亦提供一種以登記號NCIMB 42382寄存之狄氏副擬桿菌菌株之生物純培養物。本發明亦提供以登記號NCIMB 42382寄存之狄氏副擬桿菌菌株或其衍生物之細胞，其用於療法中，尤其用於本文中描述之疾病。

【0109】 以登記號NCIMB 42382寄存之菌株之衍生物可為子代菌株(子代)或自原始培養(次選殖)之菌株。本發明菌株之衍生物可例如在基因層面下修飾，而不消除生物活性。詳言之，本發明之衍生菌株為治療活性的。衍生菌株將具有與原始NCIMB 42382菌株可比的免疫調節活性。詳言之，衍生物菌株將對氣喘、關節炎、多發性硬化及葡萄膜炎疾病模型引起與實例中所示之作用可比的作用，且對細胞介素含量引起與實例中所示之作用可比的作用，其可藉由使用實例中描述之培養及投與方案來鑑別。NCIMB 42382菌株之衍生物一般將為NCIMB 42382菌株之生物型。

【0110】 對以登記號NCIMB 42382寄存之狄氏副擬桿菌菌株之細胞的提及涵蓋具有與以登記號NCIMB 42382寄存之菌株相同的安全性及治療功效特性的任何細胞，且本發明涵蓋此類細胞。

【0111】 在較佳實施例中，本發明組合物中之細菌菌株為活的且能夠部分或全部定殖於腸。

治療用途

【0112】 如實例中證明，本發明之細菌組合物有效減少Th17發炎反應。詳言之，用本發明之組合物治療實現IL-17A含量及其他Th17路徑細胞介素減少，及由IL-17及Th17路徑介導之病狀之動物模型中的臨床改善。因此，本發明之組合物可用於治療或預防發炎自體免疫疾病及尤其由IL-17介導之疾病或病狀。詳言之，本發明之組合物可用於減少或預防IL-17發炎反應升高。

【0113】 Th17細胞為產生例如IL-17A、IL17-F、IL-21及IL-22之T輔助細胞子集。Th17細胞分化及IL-17表現可由IL-23驅動。此等細胞介素及其他形成Th17路徑之重要部分，Th17路徑為公認之發炎信號傳導路徑，其促進且引起大量發炎及自體免疫疾病(如例如[19-24]中所述)。Th17路徑活化之疾病為Th17路徑介導之疾病。Th17路徑介導之疾病可藉由抑制Th17路徑改善或減輕，其可經由減少Th17細胞分化或降低其活性或減少Th17路徑細胞介素之含量。藉由Th17路徑介導之疾病可藉由Th17細胞產生之細胞介素，諸如IL-17A、IL-17F、IL-21、IL-22、IL-26、IL-9之含量增加表徵([25]中評述)。藉由Th17路徑介導之疾病可藉由Th-17相關基因，諸如Stat3或IL-23R之表現增加表徵。藉由Th17路徑介導之疾病可與增加之Th17細胞含量相關。

【0114】 IL-17為一種促發炎細胞介素，其促進若干發炎及自體免疫疾病及病狀之發病機理。如本文所用，IL-17可指IL-17家族之任何成員，包括IL-17A、IL-17B、IL-17C、IL-17D、IL-17E及IL-17F。IL-17介導之疾病及病狀特徵在於罹患該疾病或病狀之組織中IL-17之高表現及/或IL-17陽性細胞之累積或存在。類似地，IL-17介導之疾病及病狀為藉由高IL-17含量或IL-17含量增加而加重且藉由低IL-17含量

或IL-17含量減少而減輕的疾病及病狀。IL-17發炎反應可為局部或全身性的。

【0115】 可藉由IL-17或Th17路徑介導之疾病及病狀之實例包括多發性硬化；關節炎，諸如類風濕性關節炎、骨關節炎、牛皮癬性關節炎或幼年特發性關節炎；視神經脊髓炎(德維克氏病)；強直性脊椎炎；脊椎關節炎；牛皮癬；全身性紅斑狼瘡；發炎性腸病，諸如克羅恩氏病或潰瘍性結腸炎；乳糜瀉；氣喘，諸如過敏性氣喘或中性粒細胞性氣喘；慢性阻塞性肺病(COPD)；癌症，諸如乳癌、結腸癌、肺癌或卵巢癌；葡萄膜炎；鞏膜炎；血管炎；白塞氏病；動脈粥樣硬化；異位性皮炎；肺氣腫；牙周炎；過敏性鼻炎；及同種異體移植排斥。在較佳實施例中，本發明之組合物用於治療或預防此等病狀或疾病中之一或多者。在其他較佳實施例中，病狀或疾病藉由IL-17或Th17路徑介導。

【0116】 在某些實施例中，本發明之組合物用於由IL-17或Th17路徑介導之疾病或病狀的治療或預防中減少IL-17產生或減少Th17細胞分化之方法中。在某些實施例中，本發明之組合物用於治療或預防發炎或自體免疫疾病，其中該治療或預防藉由減少Th17發炎反應或預防其升高來實現。在某些實施例中，本發明之組合物用於治療患有發炎或自體免疫疾病之患者中，其中該患者具有升高之IL-17含量或升高之Th17細胞或展現Th17發炎反應。在某些實施例中，患者可經診斷患有慢性發炎或自體免疫疾病或病狀，或本發明之組合物可用於預防發展成為慢性發炎或自體免疫疾病或病狀之發炎或自體免疫疾病或病狀。在某些實施例中，疾病或病狀可不對用TNF-α抑制劑治療起反

應。本發明之此等用途可應用於前段中列出之任何特定疾病或病狀。

【0117】 IL-17及Th17路徑常常與慢性發炎及自體免疫疾病相關，因此本發明之組合物可特別適用於治療或預防如上列出之慢性疾病或病狀。在某些實施例中，組合物用於患有慢性疾病之患者中。在某些實施例中，組合物用於預防慢性疾病發展。

【0118】 本發明之組合物可用於治療藉由IL-17或Th17路徑介導之疾病及病狀且對付Th17發炎反應，因此本發明之組合物可特別適用於治療或預防慢性疾病、治療或預防患者之對其他療法(諸如用TNF-α抑制劑治療)起反應之疾病，及/或治療或預防與IL-17及Th17細胞相關之組織損傷及症狀。舉例而言，已知IL-17活化軟骨及骨組織中基質破壞且IL-17對軟骨細胞及成骨細胞中基質產生具有抑制作用，因此本發明之組合物可用於治療或預防骨質侵蝕或軟骨破壞。

【0119】 在某些實施例中，用本發明之組合物治療減少IL-17含量、尤其IL-17A含量或預防其升高。在某些實施例中，用本發明之組合物治療減少IFN-γ、IL-1β或IL-6含量或預防其升高。此等細胞介素之含量的此類減少或預防含量升高可用於治療或預防發炎及自體免疫疾病及病狀，尤其藉由IL-17或Th17路徑介導之疾病及病狀。

氣喘

【0120】 在較佳實施例中，本發明之組合物用於治療或預防氣喘。實例證明本發明之組合物減少敏化及用房塵蟎提取物激發後中性粒細胞及/或嗜酸性粒細胞募集至氣道中，因此其可用於治療或預防氣喘。氣喘為一種特徵為氣道發炎及限制之慢性疾病。氣喘發炎可藉由IL-17及/或Th17細胞介導，因此本發明之組合物可特別有效預防或

治療氣喘。氣喘發炎可藉由嗜酸性粒細胞及/或中性粒細胞介導。

【0121】 在某些實施例中，氣喘為嗜酸性粒細胞或過敏性氣喘。嗜酸性粒細胞及過敏性氣喘之特徵為外周血及氣道分泌物中嗜酸性粒細胞數目增加且病理學上與基底膜區域變厚及藥理學上與皮質類固醇反應相關[26]。減少或抑制嗜酸性粒細胞募集或活化之組合物可用於治療或預防嗜酸性粒細胞及過敏性氣喘。

【0122】 在其他實施例中，本發明之組合物用於治療或預防中性粒細胞性氣喘(或非嗜酸性粒細胞性氣喘)。高中性粒細胞數目與可對皮質類固醇治療不敏感之嚴重氣喘有關。減少或抑制中性粒細胞募集或活化之組合物可用於治療或預防中性粒細胞性氣喘。

【0123】 嗜酸性粒細胞及中性粒細胞性氣喘並非互斥病狀且一般幫助對付任一嗜酸性粒細胞及中性粒細胞反應之治療可用於治療氣喘。

【0124】 增加之IL-17含量及Th17路徑活化與嚴重氣喘有關，因此本發明之組合物可用於預防嚴重氣喘之發展或用於治療嚴重氣喘。

【0125】 在某些實施例中，本發明之組合物用於在治療或預防氣喘中降低嗜酸性粒細胞發炎反應的方法中，或用於在治療或預防氣喘中降低中性粒細胞性發炎反應的方法中。如上所指出，氣喘中高含量嗜酸性粒細胞在病理學上與基底膜區域變厚相關，因此在治療或預防氣喘中減少嗜酸性粒細胞發炎反應也許能特別地對付該疾病之此特徵。此外，與升高之嗜酸性粒細胞組合或其不存在的升高之嗜中性粒細胞與嚴重氣喘及慢性氣道變窄有關。因此，減少中性粒細胞性發炎反應可特別適用於對付嚴重氣喘。

【0126】在某些實施例中，組合物減少過敏性氣喘中細枝氣管周浸透，或用於在過敏性氣喘之治療中減少細枝氣管周浸透。在某些實施例中，組合物減少中性粒細胞性氣喘中細枝氣管周及/或血管周浸透，或用於在過敏性中性粒細胞性氣喘之治療中減少細枝氣管周及/或血管周浸透。

【0127】在某些實施例中，用本發明之組合物治療減少IL-1b或IFNγ含量或預防其升高。

【0128】在某些實施例中，本發明之組合物用於減少嗜酸性粒細胞及/或中性粒細胞性發炎反應之氣喘治療方法中。在某些實施例中，待治療之患者已經或先前已經鑑別為具有升高之嗜中性粒細胞或嗜酸性粒細胞含量，例如如經由採血或唾液分析來鑑別。

【0129】本發明之組合物在投與新生兒或孕婦時可用於預防新生兒中氣喘發展。組合物可用於預防兒童中氣喘發展。本發明之組合物可用於治療或預防成年發作型氣喘。本發明之組合物可用於管理或減輕氣喘。本發明之組合物可特別適用於減少與由諸如房塵蟎之過敏原加重之氣喘相關的症狀。

【0130】治療或預防氣喘可指例如減輕症狀嚴重程度或減小對患者而言成問題之惡化頻率或觸發範圍。

關節炎

【0131】在較佳實施例中，本發明之組合物用於治療或預防類風濕性關節炎(RA)。實例證明本發明之組合物減少小鼠模型中RA臨床徵象，減少軟骨及骨骼破壞，且減少IL-17發炎反應，因此其可用於治療或預防RA。RA為一種主要影響關節之全身性發炎病症。RA與引

起關節腫脹、滑液增生及軟骨及骨骼破壞之發炎反應有關。IL-17及Th17在RA中可具有關鍵作用，例如因為IL-17抑制軟骨細胞及成骨細胞中基質產生，且活化基質金屬蛋白酶之產生及功能，且因為RA疾病活動與IL-17含量及Th-17細胞數相關[27,28]，因此本發明之組合物可特別有效預防或治療RA。

【0132】在某些實施例中，本發明之組合物用於在RA治療或預防中降低IL-17含量或預防IL-17含量升高。在某些實施例中，用本發明之組合物治療減少IL-17含量、尤其IL-17A含量或預防其升高。在某些實施例中，用本發明之組合物治療減少IFN-γ或IL-6含量或預防其升高。

【0133】在某些實施例中，用本發明之組合物治療減少關節腫脹。在某些實施例中，本發明之組合物用於關節腫脹之患者或經鑑別為處於關節腫脹風險中之患者中。在某些實施例中，本發明之組合物用於減少RA中關節腫脹之方法中。

【0134】在某些實施例中，用本發明之組合物治療減少軟骨破壞或骨骼破壞。在某些實施例中，本發明之組合物用於在RA治療中減少或預防軟骨或骨骼破壞。在某些實施例中，組合物用於治療患有嚴重RA之處於軟骨或骨骼破壞風險中的患者。

【0135】增加之IL-17含量及Th17細胞數與RA中軟骨及骨組織破壞有關[27,28]。已知IL-17活化軟骨及骨組織中基質破壞且IL-17對軟骨細胞及成骨細胞中基質產生具有抑制作用。因此，在某些實施例中，本發明之組合物用於在RA治療中預防骨質侵蝕或軟骨破壞。在某些實施例中，組合物用於治療展現骨質侵蝕或軟骨破壞之患者或經

鑑別為處於骨質侵蝕或軟骨破壞風險中的患者。

【0136】 TNF-α亦與RA相關，但TNF-α不參與該疾病後期之發病機理。相比之下，IL-17在整個慢性疾病階段具有作用[29]。因此，在某些實施例中，本發明之組合物用於治療慢性RA或晚期RA，諸如包括關節破壞及軟骨喪失之疾病。在某些實施例中，本發明之組合物用於治療先前已接受抗TNF-α療法之患者。在某些實施例中，尚未治療之患者不或不再對抗TNF-α療法起反應。

【0137】 本發明之組合物可用於調節患者之免疫系統，因此，在某些實施例中，本發明之組合物用於預防已經鑑別為處於RA風險中或已經診斷患有早期RA之患者的RA。本發明之組合物可用於預防RA發展。

【0138】 本發明之組合物可用於管理或減輕RA。本發明之組合物可特別適用於減少與關節腫脹或骨組織破壞相關之症狀。治療或預防RA可指例如減輕症狀嚴重程度或減小對患者而言成問題之惡化頻率或觸發範圍。

多發性硬化

【0139】 在較佳實施例中，本發明之組合物用於治療或預防多發性硬化。實例證明本發明之組合物減少多發性硬化小鼠模型(EAE模型)中發病率及疾病嚴重程度，因此其可用於治療或預防多發性硬化。多發性硬化為一種與特別腦及脊柱中神經元髓鞘破壞相關之發炎病症。多發性硬化為一種慢性疾病，其逐步喪失活動能力且連串進展。IL-17及Th17細胞在多發性硬化中可具有關鍵作用，例如因為IL-17含量可與多發性硬化病變相關，IL-17可破壞血腦屏障內皮細胞緊

密接頭，且Th17細胞可遷移至中樞神經系統中且引起神經元喪失[30,31]。因此、本發明之組合物可特別有效預防或治療多發性硬化。

【0140】在某些實施例中，用本發明之組合物治療降低發病率或疾病嚴重程度。在某些實施例中，本發明之組合物用於降低發病率或疾病嚴重程度。在某些實施例中，用本發明之組合物治療預防運動功能衰退或改善運動功能。在某些實施例中，本發明之組合物用於預防運動功能衰退或用於改善運動功能。在某些實施例中，用本發明之組合物治療預防出現癱瘓。在某些實施例中，本發明之組合物在多發性硬化治療中用於預防癱瘓。

【0141】本發明之組合物可用於調節患者之免疫系統，因此，在某些實施例中，本發明之組合物用於預防已鑑別為處於多發性硬化風險中或已經診斷患有早期多發性硬化或「復發緩解型」多發性硬化之患者的多發性硬化。本發明之組合物可用於預防出現硬化症。實際上，實例展示投與本發明之組合物預防許多小鼠中出現疾病。

【0142】本發明之組合物可用於管理或減輕多發性硬化。本發明之組合物可特別適用於減少與多發性硬化相關之症狀。治療或預防多發性硬化可指例如減輕症狀嚴重程度或減小對患者而言成問題之惡化頻率或觸發範圍。

葡萄膜炎

【0143】在較佳實施例中，本發明之組合物用於治療或預防葡萄膜炎。實例證明本發明之組合物降低葡萄膜炎之動物模型中發病率及疾病嚴重程度，因此其可用於治療或預防葡萄膜炎。葡萄膜炎為葡萄膜發炎且可引起視網膜組織破壞。其可以不同解剖形式(前部、中

間、後部或擴散)存在且由不同但相關之病因引起，包括全身性自體免疫病狀。IL-17及Th17路徑主要與葡萄膜炎相關，因此本發明之組合物可特別有效預防或治療葡萄膜炎。參考文獻[32-39]描述葡萄膜炎患者中升高血清含量之介白素-17A，IL17A遺傳變異體與全葡萄膜炎特定相關，Th17相關之細胞介素在實驗自體免疫葡萄膜炎之發病機理中的作用，在單相實驗自體免疫葡萄膜炎期間Th17細胞與調節T細胞之間的不平衡，葡萄膜炎及活動性亞當=白塞及沃格特-小柳-原田(Vogt-Koyanagi-Harada，VKH)疾病患者中IL-17A上調，用蘇金單抗(secukinumab) (抗IL-17A抗體)治療非感染性葡萄膜炎，及葡萄膜炎眼睛中之Th17。

【0144】在某些實施例中，葡萄膜炎為後葡萄膜炎。後葡萄膜炎主要存在視網膜及脈絡膜發炎，且實例證明本發明之組合物有效減少視網膜發炎及破壞。

【0145】在某些實施例中，用本發明之組合物治療減少視網膜損傷。在某些實施例中，本發明之組合物在葡萄膜炎治療中用於減少或預防視網膜損傷。在某些實施例中，組合物用於治療處於視網膜損傷風險中的嚴重葡萄膜炎患者。在某些實施例中，用本發明之組合物治療減少視神經盤發炎。在某些實施例中，本發明之組合物用於治療減少或預防視神經盤發炎。在某些實施例中，用本發明之組合物治療減少發炎細胞浸透視網膜組織。在某些實施例中，本發明之組合物用於減少發炎細胞浸透視網膜組織。在某些實施例中，用本發明之組合物治療維持或改善視力。在某些實施例中，本發明之組合物用於維持或改善視力。

【0146】在某些實施例中，組合物用於治療或預防與非感染性或自體免疫疾病，諸如白塞氏病、克羅恩氏病、富克斯異色性虹膜睫狀體炎(Fuchs heterochromic iridocyclitis)、肉芽腫病伴多血管炎、HLA-B27相關葡萄膜炎、幼年特發性關節炎、結節病、脊椎關節炎、交感性眼炎、小管間質性腎炎及葡萄膜炎症候群或沃格特-小柳-原田症候群相關之葡萄膜炎。IL-17A已顯示與例如白塞氏病及沃格特-小柳-原田疾病相關。

【0147】葡萄膜炎之治療或預防可指例如減輕症狀嚴重程度或預防復發。

癌症

【0148】在較佳實施例中，本發明之組合物用於治療或預防癌症。IL-17及Th17路徑在癌症發展及進展中具有重要作用，因此本發明之組合物可用於治療或預防癌症。

【0149】雖然IL-17及Th17在癌症中之作用尚未完全瞭解，但已知IL-17及Th17細胞之許多促腫瘤作用。舉例而言，Th17細胞及IL-17可促進血管生成，增加增生及腫瘤細胞存活且活化促腫瘤轉錄因子[40-42]。

【0150】在某些實施例中，用本發明之組合物治療減少腫瘤尺寸或減少腫瘤生長。在某些實施例中，本發明之組合物用於減少腫瘤尺寸或減少腫瘤生長。本發明之組合物可有效減少腫瘤尺寸或生長。在某些實施例中，本發明之組合物用於具有實體腫瘤之患者中。在某些實施例中，本發明之組合物在癌症治療中用於減少或預防血管生成。IL-17及Th17細胞在血管生成中具有重要作用。在某些實施例中，本

發明之組合物用於預防轉移。

【0151】在某些實施例中，本發明之組合物用於治療或預防乳癌。本發明之組合物可有效治療乳癌，且IL-17及Th17細胞在乳癌中具有重要作用[43]。在某些實施例中，本發明之組合物用於在乳癌治療中減少腫瘤尺寸，減少腫瘤生長，或減少血管生成。在較佳實施例中，癌症為乳癌。在較佳實施例中，癌症為IV期乳癌。

【0152】在某些實施例中，本發明之組合物用於治療或預防肺癌。本發明之組合物可有效治療肺癌，且IL-17及Th17細胞在肺癌中具有重要作用[44]。在某些實施例中，本發明之組合物用於在肺癌治療中減少腫瘤尺寸，減少腫瘤生長，或減少血管生成。在較佳實施例中，癌症為肺癌。

【0153】在某些實施例中，本發明之組合物用於治療或預防肝癌。本發明之組合物可有效治療肝癌，且IL-17及Th17細胞在肝癌中具有重要作用[45]。在某些實施例中，本發明之組合物用於在肝癌治療中減少腫瘤尺寸，減少腫瘤生長，或減少血管生成。在較佳實施例中，癌症為肝癌(肝細胞癌)。

【0154】在某些實施例中，本發明之組合物用於治療或預防癌瘤。本發明之組合物可尤其有效治療癌瘤。在某些實施例中，本發明之組合物用於治療或預防非免疫原性癌。本發明之組合物可有效治療非免疫原性癌。

【0155】在其他實施例中，本發明之組合物用於治療或預防急性淋巴母細胞性白血病(ALL)、急性骨髓性白血病、腎上腺皮質癌、基細胞癌瘤、膽管癌、膀胱癌、骨腫瘤、骨肉瘤/惡性纖維組織細胞

瘤、腦幹神經膠質瘤、腦腫瘤、小腦星形細胞瘤、大腦星形細胞瘤/惡性神經膠質瘤、室管膜瘤、髓母細胞瘤、幕上原始神經外胚層腫瘤、乳癌、枝氣管腺瘤/類癌瘤、伯基特氏淋巴瘤(Burkitt's lymphoma)、類癌瘤腫瘤、子宮頸癌、慢性淋巴細胞性白血病、慢性骨髓性白血病、慢性脊髓增生病、結腸癌、皮膚T細胞淋巴瘤、子宮內膜癌、室管膜瘤、食道癌、尤因肉瘤(Ewing's sarcoma)、眼內黑色素瘤、視網膜母細胞瘤、膽囊癌、胃癌、胃腸道類癌腫瘤、胃腸基質腫瘤(GIST)、生殖細胞腫瘤、兒童期視覺路徑及下丘腦神經膠質瘤、霍奇金氏淋巴瘤(Hodgkin lymphoma)、黑色素瘤、胰島細胞癌瘤、卡波西氏肉瘤(Kaposi sarcoma)、腎細胞癌症、喉癌、白血病、淋巴瘤、間皮瘤、神經母細胞瘤、非霍奇金淋巴瘤、口咽癌、骨肉瘤、卵巢癌、胰臟癌、甲狀旁腺癌、咽癌、垂體腺瘤、漿細胞瘤形成、前列腺癌、腎細胞癌瘤、視網膜母細胞瘤、肉瘤、睾丸癌、甲狀腺癌或子宮癌。

【0156】本發明之組合物在與其他治療劑組合使用時可特別有效。本發明組合物之免疫調節作用在與更直接抗癌藥劑組合時可有效。因此，在某些實施例中，本發明提供一種組合物，其包含副擬桿菌屬之細菌菌株及抗癌劑。在較佳實施例中，抗癌劑為免疫檢查點抑制劑、靶向抗體免疫療法、CAR-T細胞療法、溶瘤病毒或抑制細胞生長藥物。在較佳實施例中，組合物包含選自由以下組成之群的抗癌藥劑：Yervoy (易普利單抗(ipilimumab)，BMS)；Keytruda (派姆單抗(pembrolizumab)，Merck)；Opdivo (納武單抗(nivolumab)，BMS)；MEDI4736 (AZ/MedImmune)；MPDL3280A (Roche/Genentech)；曲美

目單抗(Tremelimumab) (AZ/MedImmune)；CT-011 (皮利珠單抗(pidilizumab)，CureTech)；BMS-986015 (利魯單抗(lirilumab)，BMS)；MEDI0680 (AZ/MedImmune)；MSB-0010718C (Merck)；PF-05082566 (Pfizer)；MEDI6469 (AZ/MedImmune)；BMS-986016 (BMS)；BMS-663513 (優瑞路單抗(urelumab)，BMS)；IMP321 (Prima Biomed)；LAG525 (Novartis)；ARGX-110 (arGEN-X)；PF-05082466 (Pfizer)；CDX-1127 (瓦利路單抗(varlilumab)；CellDex Therapeutics)；TRX-518 (GITR Inc.)；MK-4166 (Merck)；JTX-2011 (Jounce Therapeutics)；ARGX-115 (arGEN-X)；NLG-9189 (英多莫德(indoximod)，NewLink Genetics)；INCB024360 (Incyte)；IPH2201 (Innate Immotherapeutics/AZ)；NLG-919 (NewLink Genetics)；抗VISTA (JnJ)；依帕斯塔特(Epacadostat) (INCB24360，Incyte)；F001287 (Flexus/BMS)；CP 870893 (University of Pennsylvania)；MGA271 (Macrogenix)；依瑪珠單抗(Emactuzumab) (Roche/Genentech)；加尼斯替(Galunisertib) (Eli Lilly)；優庫路單抗(Ulocuplumab) (BMS)；BKT140/BL8040 (Biokine Therapeutics)；巴維昔單抗(Bavituximab) (Peregrine Pharmaceuticals)；CC 90002 (Celgene)；852A (Pfizer)；VTX-2337 (VentiRx Pharmaceuticals)；IMO-2055 (Hybridon，Idera Pharmaceuticals)；LY2157299 (Eli Lilly)；EW-7197 (Ewha Women's University，Korea)；威羅菲尼(Vemurafenib) (Plexxikon)；達拉菲尼(Dabrafenib) (Genentech/GSK)；BMS-777607 (BMS)；BLZ945 (Memorial Sloan-Kettering Cancer Centre)；Unituxin (地土昔單抗(dinutuximab)，United Therapeutics

Corporation)；Blincyto（布林莫單抗(blinatumomab)，Amgen)；Cyramza (雷莫蘆單抗(ramucirumab)，Eli Lilly)；Gazyva (歐努珠單抗(obinutuzumab)，Roche/Biogen)；Kadcyla (阿多曲妥珠單抗恩他新(ado-trastuzumab emtansine)，Roche/Genentech)；Perjeta (帕妥珠單抗(pertuzumab)，Roche/Genentech)；Adcetris（布瑞西單抗維多新(brentuximab vedotin)，Takeda/Millennium)；Arzerra（奧法木單抗(ofatumumab)，GSK)；Vectibix (帕尼單抗(panitumumab)，Amgen)；Avastin (貝伐單抗(bevacizumab)，Roche/Genentech)；Erbitux (西妥昔單抗(cetuximab)，BMS/Merck)；Bexxar (托西莫單抗(tositumomab)-I131，GSK)；Zevalin (替伊莫單抗(ibritumomab tiuxetan)，Biogen)；Campath (阿侖單抗(alemtuzumab)，Bayer)；Mylotarg (吉妥珠單抗奧唑米星(gemtuzumab ozogamicin)，Pfizer)；Herceptin (曲妥珠單抗(trastuzumab)，Roche/Genentech)；Rituxan (利妥昔單抗(rituximab)，Genentech/Biogen)；伏洛昔單抗(volociximab) (Abbvie)；艾那維單抗(Enavatuzumab) (Abbvie)；ABT-414 (Abbvie)；埃羅妥珠單抗(Elotuzumab) (Abbvie/BMS)；ALX-0141 (Ablynx)；奧紮利單抗(Ozaralizumab) (Ablynx)；埃替單抗(Actimab)-C (Actinium)；埃替單抗-P (Actinium)；米拉珠單抗-多柔比星(Milatuzumab-dox) (Actinium)；Emab-SN-38 (Actinium)；伊土莫單抗(Naptumonmab estafenatox) (Active Biotech)；AFM13 (Affimed)；AFM11 (Affimed)；AGS-16C3F (Agensys)；AGS-16M8F (Agensys)；AGS-22ME (Agensys)；AGS-15ME (Agensys)；GS-67E (Agensys)；ALXN6000 (薩瑪利單抗(samalizumab)，Alexion)；ALT-836 (Altor Bioscience)；

ALT-801 (Altor Bioscience)；ALT-803 (Altor Bioscience)；AMG780 (Amgen)；AMG 228 (Amgen)；AMG820 (Amgen)；AMG172 (Amgen)；AMG595 (Amgen)；AMG110 (Amgen)；AMG232 (阿達木單抗(adecatumumab)，Amgen)；AMG211 (Amgen/MedImmune)；BAY20-10112 (Amgen/Bayer)；瑞洛土單抗(Rilotumumab) (Amgen)；戴諾素單抗(Denosumab) (Amgen)；AMP-514 (Amgen)；MEDI575 (AZ/MedImmune)；MEDI3617 (AZ/MedImmune)；MEDI6383 (AZ/MedImmune)；MEDI551 (AZ/MedImmune)；帕莫西單抗(Moxetumomab pasudotox) (AZ/MedImmune)；MEDI565 (AZ/MedImmune)；MEDI0639 (AZ/MedImmune)；MEDI0680 (AZ/MedImmune)；MEDI562 (AZ/MedImmune)；AV-380 (AVEO)；AV203 (AVEO)；AV299 (AVEO)；BAY79-4620 (Bayer)；拉安土單抗(Anetumab ravtansine) (Bayer)；萬替珠單抗(vantictumab) (Bayer)；BAY94-9343 (Bayer)；西羅珠單抗(Sibrotuzumab) (Boehringer Ingleheim)；BI-836845 (Boehringer Ingleheim)；B-701 (BioClin)；BIIB015 (Biogen)；歐努珠單抗(Biogen/Genentech)；BI-505 (Bioinvent)；BI-1206 (Bioinvent)；TB-403 (Bioinvent)；BT-062 (Biotest) BIL-010t (Biosceptre)；MDX-1203 (BMS)；MDX-1204 (BMS)；奈西莫單抗(Necitumumab) (BMS)；CAN-4 (Cantargia AB)；CDX-011 (Celldex)；CDX1401 (Celldex)；CDX301 (Celldex)；U3-1565 (Daiichi Sankyo)；帕曲土單抗(patritumab) (Daiichi Sankyo)；替加土單抗(tigatuzumab) (Daiichi Sankyo)；尼妥珠單抗(nimotuzumab) (Daiichi Sankyo)；DS-8895 (Daiichi Sankyo)；DS-8873 (Daiichi

Sankyo)；DS-5573 (Daiichi Sankyo)；MORab-004 (Eisai)；MORab-009 (Eisai)；MORab-003 (Eisai)；MORab-066 (Eisai)；LY3012207 (Eli Lilly)；LY2875358 (Eli Lilly)；LY2812176 (Eli Lilly)；LY3012217(Eli Lilly)；LY2495655 (Eli Lilly)；LY3012212 (Eli Lilly)；LY3012211 (Eli Lilly)；LY3009806 (Eli Lilly)；西妥木單抗(cixutumumab) (Eli Lilly)；法拉維單抗(Flanvotumab) (Eli Lilly)；IMC-TR1 (Eli Lilly)；雷莫蘆單抗Eli Lilly)；塔巴木單抗(Tabalumab) (Eli Lilly)；紮諾利單抗(Zanolimumab) (Emergent Biosolution)；FG-3019 (FibroGen)；FPA008 (Five Prime Therapeutics)；FP-1039 (Five Prime Therapeutics)；FPA144 (Five Prime Therapeutics)；卡妥索單抗(catumaxomab) (Fresenius Biotech)；IMAB362 (Ganymed)；IMAB027 (Ganymed)；HuMax-CD74 (Genmab)；HuMax-TFADC (Genmab)；GS-5745 (Gilead)；GS-6624 (Gilead)；OMP-21M18 (登西珠單抗(demcizumab)，GSK)；馬帕木單抗(mapatumumab) (GSK)；IMGN289 (ImmunoGen)；IMGN901 (ImmunoGen)；IMGN853 (ImmunoGen)；IMGN529 (ImmunoGen)；IMMU-130 (Immunomedics)；米拉珠單抗-多柔比星(Immunomedics)；IMMU-115 (Immunomedics)；IMMU-132 (Immunomedics)；IMMU-106 (Immunomedics)；IMMU-102 (Immunomedics)；依帕珠單抗(Epratuzumab) (Immunomedics)；克利瓦單抗(Clivatuzumab) (Immunomedics)；IPH41 (Innate Immunotherapeutics)；達拉土單抗(Daratumumab) (Janssen/Genmab)；CNTO-95 (Intetumumab，Janssen)；CNTO-328 (西妥昔單抗(siltuximab)，Janssen)；KB004 (KaloBios)；莫加利單抗

(mogamulizumab) (Kyowa Hakko Kirrin)；KW-2871 (依美昔單抗(ecromeximab)，Life Science)；索奈珠單抗(Sonepcizumab) (Lpath)；馬土西單抗(Margetuximab) (Macrogenics)；恩利珠單抗(Enoblituzumab) (Macrogenics)；MGD006 (Macrogenics)；MGF007 (Macrogenics)；MK-0646 (dalotuzumab，Merck)；MK-3475 (Merck)；Sym004 (Symphogen/Merck Serono)；DI17E6 (Merck Serono)；MOR208 (Morphosys)；MOR202 (Morphosys)；Xmab5574 (Morphosys)；BPC-1C (恩斯土單抗(ensituximab)，Precision Biologics)；TAS266 (Novartis)；LFA102 (Novartis)；BHQ880 (Novartis/Morphosys)；QGE031 (Novartis)；HCD122 (盧卡木單抗(lucatumumab)，Novartis)；LJM716 (Novartis)；AT355 (Novartis)；OMP-21M18 (登西珠單抗，OncoMed)；OMP52M51 (Oncomed/GSK)；OMP-59R5 (Oncomed/GSK)；萬替珠單抗(Oncomed/Bayer)；CMC-544 (奧英妥珠單抗(inotuzumab ozogamicin)，Pfizer)；PF-03446962 (Pfizer)；PF-04856884 (Pfizer)；PSMA-ADC (Progenics)；REGN1400 (Regeneron)；REGN910 (奈瓦庫單抗(nesvacumab)，Regeneron/Sanofi)；REGN421 (恩替庫單抗(enoticumab)，Regeneron/Sanofi)；RG7221、RG7356、RG7155、RG7444、RG7116、RG7458、RG7598、RG7599、RG7600、RG7636、RG7450、RG7593、RG7596、DCDS3410A、RG7414 (帕薩珠單抗(parsatuzumab))、RG7160 (伊佳珠單抗(imgatuzumab))、RG7159 (歐賓珠單抗(obintuzumab))、RG7686、RG3638 (歐奈珠單抗(onartuzumab))、RG7597 (Roche/Genentech)；SAR307746 (Sanofi)；

SAR566658 (Sanofi)；SAR650984 (Sanofi)；SAR153192 (Sanofi)；SAR3419 (Sanofi)；SAR256212 (Sanofi)，SGN-LIV1A (林妥珠單抗(lintuzumab)，Seattle Genetics)；SGN-CD33A (Seattle Genetics)；SGN-75 (馬維珠單抗(vorsetuzumab mafodotin)，Seattle Genetics)；SGN-19A (Seattle Genetics)；SGN-CD70A (Seattle Genetics)；SEA-CD40 (Seattle Genetics)；替伊莫單抗(Spectrum)；MLN0264 (Takeda)；加尼妥單抗(ganitumab) (Takeda/Amgen)；CEP-37250 (Teva)；TB-403 (Thrombogenic)；VB4-845 (Viventia)；Xmab2512 (Xencor)；Xmab5574 (Xencor)；尼妥珠單抗(YM Biosciences)；卡路單抗(Carlumab) (Janssen)；NY-ESO TCR (Adaptimmune)；MAGE-A-10 TCR (Adaptimmune)；CTL019 (Novartis)；JCAR015 (Juno Therapeutics)；KTE-C19 CAR (Kite Pharma)；UCART19 (Cellectis)；BPX-401 (Bellicum Pharmaceuticals)；BPX-601 (Bellicum Pharmaceuticals)；ATTCK20 (Unum Therapeutics)；CAR-NKG2D (Celyad)；Onyx-015 (Onyx Pharmaceuticals)；H101 (Shanghai Sunwaybio)；DNX-2401 (DNAtrix)；VCN-01 (VCN Biosciences)；Colo-Ad1 (PsiOxus Therapeutics)；ProstAtak (Advantagene)；Oncos-102 (Oncos Therapeutics)；CG0070 (Cold Genesys)；Pexa-vac (JX-594，Jennerex Biotherapeutics)；GL-ONC1 (Genelux)；T-VEC (Amgen)；G207 (Medigene)；HF10 (Takara Bio)；SEPREHVIR (HSV1716，Virttu Biologics)；OrienX010 (OrienGene Biotechnology)；Reolysin (Oncolytics Biotech)；SVV-001 (Neotropix)；Cacatak (CVA21，Viralytics)；Alimta (Eli Lilly)、順鉑

(cisplatin)、奧沙利鉑(oxaliplatin)、伊立替康(irinotecan)、亞葉酸(folinic acid)、甲胺喋呤(methotrexate)、環磷醯胺(cyclophosphamide)、5-氟尿嘧啶(5-fluorouracil)、Zykadia (Novartis)、Tafinlar (GSK)、Xalkori (Pfizer)、Iressa (AZ)、Gilotrif (Boehringer Ingelheim)、Tarceva (Astellas Pharma)、Halaven (Eisai Pharma)、Veliparib (Abbvie)、AZD9291 (AZ)、阿雷替尼(Alectinib) (Chugai)、LDK378 (Novartis)、蓋納特皮(Genetespib) (Synta Pharma)、Tergenpumatucel-L (NewLink Genetics)、GV1001 (Kael-GemVax)、替瓦替尼(Tivantinib) (ArQule)；Cytoxan (BMS)；Oncovin (Eli Lilly)；阿黴素(Adriamycin) (Pfizer)；Gemzar (Eli Lilly)；Xeloda (Roche)；Ixempra (BMS)；Abraxane (Celgene)；Trelstar (Debiopharm)；Taxotere (Sanofi)；Nexavar (Bayer)；IMMU-132 (Immunomedics)；E7449 (Eisai)；Thermodox (Celsion)；Cometriq (Exellxis)；Lonsurf (Taiho Pharmaceuticals)；Camptosar (Pfizer)；UFT (Taiho Pharmaceuticals)；及TS-1 (Taiho Pharmaceuticals)。

投與模式

【0157】較佳地，本發明之組合物待施用於胃腸道，以能夠傳遞至腸及/或使本發明之細菌菌株部分或全部定殖於腸。一般地，雖然本發明之組合物經口投與，但其可直腸、鼻內或經由頰或舌下途徑投與。

【0158】在某些實施例中，本發明之組合物可呈泡沫、噴霧或凝膠形式投與。

【0159】在某些實施例中，本發明之組合物可呈栓劑，諸如直腸

栓劑，例如呈可可豆油(可可脂)、合成硬脂(例如suppocire、witepsol)、甘油基-明膠、聚乙二醇或肥皂甘油組合物之形式投與。

【0160】在某些實施例中，本發明之組合物經由管，諸如鼻飼管、口胃管、胃管、空腸造口管(J型管)、經皮內窺鏡胃造口術(PEG)或埠，諸如通向胃、空腸及其他適合進入埠之胸壁埠投與胃腸道。

【0161】本發明之組合物可投與一次，或其可作為治療方案一部分連續投與。在某些實施例中，本發明之組合物將每日投與。

【0162】在本發明之某些實施例中，根據本發明之治療伴隨有患者腸微生物叢之評估。若本發明之菌株傳遞及/或部分或全部定殖未實現，使得功效未觀測到，則可重複治療，或若傳遞及/或部分或全部定殖成功且觀測到功效，則可停止治療。

【0163】在某些實施例中，本發明之組合物可投與懷孕動物，例如哺乳動物，諸如人類，以預防發炎或自體免疫疾病在其子女中在子宮內及/或其出生後出現。

【0164】本發明之組合物可投與經診斷患有由IL-17或Th17路徑介導之疾病或病狀或已鑑別為處於由IL-17或Th17路徑介導之疾病或病狀風險中的患者。組合物亦可作為預防措施投與以預防健康患者中由IL-17或Th17路徑介導之疾病或病狀出現。

【0165】本發明之組合物可投與已鑑別為具有異常腸微生物叢之患者。舉例而言，患者可具有減少或缺乏之副擬桿菌屬且尤其狄氏副擬桿菌之細菌定殖。

【0166】本發明之組合物可作為食品，諸如營養增補劑投與。

【0167】一般地，本發明之組合物用於治療人類，不過其可用於

治療動物，包括單胃哺乳動物，諸如家禽、豬、貓、犬、馬或兔。本發明之組合物可用於增強動物之生長及效能。若投與動物，則可使用經口管飼法。

組合物

【0168】一般地，本發明之組合物包含細菌。在本發明之較佳實施例中，組合物呈凍乾形式調配。舉例而言，本發明之組合物可包含含有本發明之細菌菌株的顆粒或明膠膠囊，例如硬明膠膠囊。

【0169】較佳地，本發明之組合物包含凍乾細菌。細菌凍乾為公知程序且相關指導可於例如參考文獻[46-48]中獲得。

【0170】或者，本發明之組合物可包含活的活性細菌培養物。

【0171】在較佳實施例中，本發明之組合物經囊封以能夠傳遞細菌菌株至腸。囊封保護組合物免於降解，直至經由例如用化學或物理刺激，諸如壓力、酶活性或物理性崩解(其可藉由pH值改變而觸發)進行破裂，在目標位置傳遞。可使用任何適當囊封法。示例性囊封技術包括截留在多孔基質內、附著或吸附在固體載體表面上、藉由絮凝或利用交聯劑而自我凝聚以及機械容納在微孔膜或微膠囊後。關於可用於製備本發明之組合物的囊封之指導可於例如參考文獻[49]及[50]中獲得。

【0172】組合物可經口投與且可呈錠劑、膠囊或散劑形式。囊封產品為較佳，因為副擬桿菌屬為厭氧菌。其他成分(諸如維生素C)可作為除氧劑及益生基質包括以改善活體內傳遞及/或部分或全部定殖及存活。或者，本發明之益生組合物可作為食品或營養產品，諸如基於牛奶或乳清之發酵乳製品，或作為藥品經口投與。

【0173】 組合物可調配為益生菌。

【0174】 本發明之組合物包括治療有效量之本發明之細菌菌株。治療有效量之細菌菌株足以對患者發揮有益作用。治療有效量之細菌菌株可足夠傳遞至患者腸及/或部分或全部定殖於患者腸。

【0175】 例如適合於成年人之細菌日劑量可為約1×10^{3}至約1×10^{11}菌落形成單位(CFU)；例如約1×10^{7}至約1×10^{10}CFU；在另一實例中，約1×10^{6}至約1×10^{10} CFU。

【0176】 在某些實施例中，組合物含有相對於組合物之重量，約1×10^{6}至約1×10^{11} CFU/g，例如約1×10^{8}至約1×10^{10} CFU/g之量的細菌菌株。劑量可為例如1 g、3 g、5 g及10 g。

【0177】 通常，益生菌，諸如本發明之組合物，視情況與至少一種適合益生化合物組合。益生化合物通常為不易消化之碳水化合物，諸如寡醣或多醣，或糖醇，其在上部消化道中不降解或吸收。已知之益生菌包括商業產品，諸如菊糖及反式半乳寡醣。

【0178】 在某些實施例中，本發明之益生菌組合物包括相對於組合物總重量，約1至約30重量% (例如5至20重量%)之量的益生菌化合物。碳水化合物可選自由以下組成之群：果寡糖(或FOS)、短鏈果寡醣、菊糖、異麥芽寡糖、果膠、木寡醣(或XOS)、幾丁寡醣(或COS)、β-葡聚糖、阿拉伯膠改性及抗性澱粉、聚葡萄糖、D-塔格糖、阿拉伯膠纖維、角豆樹、燕麥及柑桔纖維。在一個態樣中，益生菌為短鏈果糖-寡醣(下文中簡單起見展示為FOSs-c.c)；該等FOSs-c.c為不可消化之碳水化合物，一般由甜菜糖轉變獲得且包括三個葡萄糖分子鍵結之蔗糖分子。

【0179】本發明之組合物可包含醫藥學上可接受之賦形劑或載劑。此類適合賦形劑之實例可見於參考文獻[51]中。用於治療用途之可接受之載劑或稀釋劑為醫藥技術中所熟知且描述於例如參考文獻[52]中。適合載劑之實例包括乳糖、澱粉、葡萄糖、甲基纖維素、硬脂酸鎂、甘露糖醇、山梨糖醇等等。適合稀釋劑之實例包括乙醇、甘油及水。醫藥載劑、賦形劑或稀釋劑之選擇可針對預期投藥途徑及標準醫藥實踐來選擇。醫藥組合物可包含任何適合黏合劑、潤滑劑、懸浮劑、包被劑、增溶劑作為載劑、賦形劑或稀釋劑或除載劑、賦形劑或稀釋劑之外可包含該等物質。適合黏合劑之實例包括澱粉、明膠、天然糖(諸如葡萄糖、無水乳糖、自由流動乳糖、β-乳糖、玉米甜味劑)、天然及合成樹膠(諸如阿拉伯膠、黃蓍膠)或海藻酸鈉、羧甲基纖維素及聚乙二醇。適合潤滑劑之實例包括油酸鈉、硬脂酸鈉、硬脂酸鎂、苯甲酸鈉、乙酸鈉、氯化鈉等等。防腐劑、穩定劑、染料及甚至調味劑可提供於醫藥組合物中。防腐劑之實例包括苯甲酸鈉、山梨酸及對羥基苯甲酸酯。亦可使用抗氧化劑及懸浮劑。

【0180】本發明之組合物可調配為食品。舉例而言，除本發明之治療作用之外，食品可提供營養益處，諸如營養增補劑中。類似地，食品可經調配以增強本發明組合物之口味，或藉由使其更類似於常見食品而非醫藥組合物，使得組合物食用起來更具吸引力。在某些實施例中，本發明之組合物調配為基於牛奶之產品。術語「基於牛奶之產品」意謂具有變化脂肪含量之任何液體或半固體基於牛奶或乳清之產品。基於牛奶之產品可為例如奶牛奶、山羊奶、綿羊奶、脫脂乳、全乳、無任何加工下奶粉與乳清重組之牛奶或加工產品，諸如酸乳酪、

凝乳、凝塊、酸牛奶、酸全乳、酪乳及其他酸牛奶產品。另一重要組包括乳製飲料，諸如乳清飲料、發酵牛奶、煉乳、嬰兒或嬰孩牛奶；增香乳、霜淇淋；含牛奶之食品，諸如甜食。

【0181】在某些實施例中，本發明之組合物含有單一細菌菌株或物種且不含有任何其他細菌菌株或物種。此類組合物可僅僅包含最低限度或生物學上不相關量之其他細菌菌株或物種。此類組合物可為基本上不含其他生物體物種之培養物。

【0182】根據本發明使用之組合物可需要或可不需要銷售批准。

【0183】在一些情況下，凍乾細菌菌株在投與之前復原。在一些情況下，復原係藉由使用本文中描述之稀釋劑。

【0184】本發明之組合物可包含醫藥學上可接受之賦形劑、稀釋劑或載劑。

【0185】在某些實施例中，本發明提供一種醫藥組合物，其包含：本發明之細菌菌株；及醫藥學上可接受之賦形劑、載劑或稀釋劑；其中細菌菌株在投與有需要之受試者時量足夠治療病症；且其中病症係選自由以下組成之群：氣喘、過敏性氣喘、中性粒細胞性氣喘、骨關節炎、牛皮癬性關節炎、幼年特發性關節炎、視神經脊髓炎(德維克氏病)、強直性脊椎炎、脊椎關節炎、全身性紅斑狼瘡、乳糜瀉、慢性阻塞性肺病(COPD)、癌症、乳癌、結腸癌、肺癌、卵巢癌、葡萄膜炎、鞏膜炎、血管炎、白塞氏病、動脈粥樣硬化、異位性皮炎、肺氣腫、牙周炎、過敏性鼻炎及同種異體移植排斥。

【0186】在某些實施例中，本發明提供醫藥組合物，其包含：本發明之細菌菌株；及醫藥學上可接受之賦形劑、載劑或稀釋劑；其中

細菌菌株之量足夠治療或預防由IL-17或Th17路徑介導之疾病或病狀。在較佳實施例中，該疾病或病狀選自由以下組成之群：類風濕性關節炎、多發性硬化、牛皮癬、發炎性腸病、克羅恩氏病、潰瘍性結腸炎、乳糜瀉、氣喘、過敏性氣喘、中性粒細胞性氣喘、骨關節炎、牛皮癬性關節炎、幼年特發性關節炎、視神經脊髓炎(德維克氏病)、強直性脊椎炎、脊椎關節炎、全身性紅斑狼瘡、慢性阻塞性肺病(COPD)、癌症、乳癌、結腸癌、肺癌、卵巢癌、葡萄膜炎、鞏膜炎、血管炎、白塞氏病、動脈粥樣硬化、異位性皮炎、肺氣腫、牙周炎、過敏性鼻炎及同種異體移植排斥。

【0187】 在某些實施例中，本發明提供以上醫藥組合物，其中細菌菌株之量為相對於組合物之重量每公克約1×10^{3}至約1×10^{11}菌落形成單位。

【0188】 在某些實施例中，本發明提供以上醫藥組合物，其中組合物以1 g、3 g、5 g或10 g之劑量投與。

【0189】 在某些實施例中，本發明提供以上醫藥組合物，其中組合物藉由選自由口腔、直腸、皮下、鼻、頰及舌下組成之群的方法投與。

【0190】 在某些實施例中，本發明提供以上醫藥組合物，其包含選自由乳糖、澱粉、葡萄糖、甲基纖維素、硬脂酸鎂、甘露糖醇及山梨糖醇組成之群的載劑。

【0191】 在某些實施例中，本發明提供以上醫藥組合物，其包含選自由乙醇、甘油及水組成之群的稀釋劑。

【0192】 在某些實施例中，本發明提供以上醫藥組合物，其包含

選自由以下組成之群的賦形劑：澱粉、明膠、葡萄糖、無水乳糖、自由流動之乳糖、β-乳糖、玉米甜味劑、阿拉伯膠、黃蓍膠、海藻酸鈉、羧甲基纖維素、聚乙二醇、油酸鈉、硬脂酸鈉、硬脂酸鎂、苯甲酸鈉、乙酸鈉及氯化鈉。

【0193】 在某些實施例中，本發明提供以上醫藥組合物，其進一步包含防腐劑、抗氧化劑及穩定劑中之至少一種。

【0194】 在某些實施例中，本發明提供以上醫藥組合物，其包含選自由苯甲酸鈉、山梨酸及對羥基苯甲酸酯組成之群的防腐劑。

【0195】 在某些實施例中，本發明提供以上醫藥組合物，其中該細菌菌株係凍乾的。

【0196】 在某些實施例中，本發明提供以上醫藥組合物，其中當組合物儲存在密封容器中約4℃或約25℃下且容器置於具有50%相對濕度之氛圍中時，在至少約1個月、3個月、6個月、1年、1.5年、2年、2.5年或3年時期後如以菌落形成單位量測之至少80%細菌菌株殘留。

培養方法

【0197】 用於本發明之細菌菌株可使用如例如參考文獻[53-55]中詳述之標準微生物學技術培養。

【0198】 用於培養之固體或液體培養基可為YCFA瓊脂或YCFA培養基。YCFA培養基可包括(每100 ml，近似值)：酪胰(1.0 g)、酵母提取物(0.25 g)、$NaHCO_3$ (0.4 g)、半胱胺酸(0.1 g)、K_2HPO_4 (0.045 g)、KH_2PO_4 (0.045 g)、NaCl (0.09 g)、$(NH_4)_2SO_4$ (0.09 g)、$MgSO_4 \cdot 7H_2O$ (0.009 g)、$CaCl_2$ (0.009 g)、刃天青(0.1 mg)、氯化血紅素(1 mg)、生

物素(1 μg)、鈷胺素(1 μg)、對胺基苯甲酸(3 μg)、葉酸(5 μg)及吡哆胺(15 μg)。

用於疫苗組合物中之細菌菌株

【0199】 本發明者已確定本發明之細菌菌株可用於治療或預防由IL-17或Th17路徑介導之疾病或病狀。此可能為本發明之細菌菌株作用於宿主免疫系統之結果。因此，當作為疫苗組合物投與時，本發明之組合物亦可用於預防由IL-17或Th17路徑介導之疾病或病狀。在某些此類實施例中，本發明之細菌菌株可為殺死的、滅活的或減毒的。在某些此類實施例中，組合物可包含疫苗佐劑。在某些實施例中，組合物用於經由注射，諸如經由皮下注射投與。

通則

【0200】 除非另外指明，否則本發明之實施將採用在此項技術技能內之習知化學、生物化學、分子生物學、免疫學及藥理學方法。此類技術在文獻中充分解釋。參見例如參考文獻[56]及[57-63]等。

【0201】 術語「包含」涵蓋「包括」以及「由.....組成」，例如「包含」X之組合物可僅僅由X組成，或可包括其他某物，例如X + Y。

【0202】 關於數值 x之術語「約」為視情況選用的且意謂例如 x ±10%。

【0203】 詞語「基本上」不排除「完全」，例如「基本上不含」Y之組合物可完全不含Y。必要時，詞語「基本上」可自本發明之定義省略。

【0204】 提及兩種核苷酸序列之間的序列一致性百分比意謂在比

對時，比較兩種序列中相同的核苷酸百分比。此比對及同源性或序列一致性百分比可使用此項技術中已知之軟體程式，例如參考文獻[64]之部分7.7.18中描述的軟體程式確定。較佳比對藉由Smith-Waterman同源性搜索演算法使用仿射空位搜索(其中開放空位罰分為12且空位延伸罰分為2、BLOSUM 62矩陣)來確定。Smith-Waterman同源性搜索演算法在參考文獻[65]中揭示。

【0205】 除非特別陳述，否則包括多個步驟之製程或方法可在方法開始或結束包括其他步驟，或可包括其他插入步驟。此外，適當時步驟可組合，省去或以替代次序進行。

【0206】 本文中描述本發明之多個實施例。應瞭解每個實施例中說明之特徵均可與其他所說明之特徵組合以提供其他實施例。詳言之，本文中強調為適合、典型或較佳之實施例可彼此組合(除非其互斥時)。

用於進行本發明之模式

實例1-房塵蟎誘發之氣喘之小鼠模型中細菌接種物之功效

概述

【0207】 向小鼠投與包含根據本發明之細菌菌株的組合物，且隨後用房塵蟎(HDM)提取物激發以引起過敏性發炎反應。對HDM之發炎反應包括嗜酸性粒細胞及中性粒細胞性組分，由IL-17及Th17路徑介導，且為氣喘模型。將用本發明組合物治療之小鼠所展現的發炎反應之量值及特徵與對照組相比。發現本發明之組合物減輕發炎反應，且減少嗜酸性粒細胞及嗜中性粒細胞募集，表明其可用於治療IL-17及Th17介導之病狀，諸如嗜酸性粒細胞增多、中性粒細胞增多及氣

喘。

菌株

【0208】 755：狄氏副擬桿菌

研究設計

【0209】 組：

1. 陰性對照組。用媒劑對照處理(經口)。

5. 用治療性細菌接種物菌株755處理(經口)。

7. 陽性對照組。用地塞米松處理(腹膜內)。

8. 未處理之對照組。

【0210】 每組小鼠數目 = 5

【0211】 第-14天至第13天：每日經口投與媒劑對照(組1)。

【0212】 第-14天至第13天：每日經口投與治療性細菌接種物(組2-6)。

【0213】 第0、2、4、7、9、11天，經鼻投與於30 ul體積PBS中之15 ug HDM (房塵蟎提取物-目錄號：XPB70D3A25，批號：231897，Greer Laboratories, Lenoir, NC, USA) (組1-8)。

【0214】 第0、2、4、7、9、11天投與地塞米松(腹膜內，3 mg/kg，Sigma-Aldrich，目錄號D1159) (組7)。

【0215】 第14天處死所有動物用於分析。

【0216】 小鼠總數= 40。

終點及分析

【0217】 在第14天，藉由腹膜內注射致命戊巴比妥(pentabarbitol)(Streuli Pharma AG, Uznach, 目錄號：1170139A)處死動

物，接著立刻進行枝氣管肺泡灌洗(BAL)。

【0218】 細胞與BAL (枝氣管肺泡灌洗)流體分離且進行細胞分類計數(200個細胞計數/樣品)。

材料與方法

【0219】 **小鼠**。自Charles River Laboratories購買雌性7週齡BALB/c小鼠且隨機分配至籠，每籠均5隻小鼠(通風籠來源於Indulab AG, Gams, Switzerland籠型：“TheSealsafeTM - IVC籠。產品號1248L)。籠標記有研究號、組號及實驗開始日期。每週監測小鼠且適應設施7天，接著開始研究(研究第-14天)。在研究第-14天動物為8週齡。飲用水及食物可隨意取用。存在籠富集。根據地方特許牌照號2283.1 (經Service de la consommation et des affaires vétérinaires du Canton de Vaud頒予及批准)進行動物之每日護理。飲用水及食物可隨意取用且每日補充一次。存在籠富集。觀測到如瑞士官方根據FVO (Federal Veterinary Office)關於實驗動物飼養管理、遺傳修飾動物產生及動物實驗方法之條例455.163所給出的動物福利規定。

【0220】 **培養細菌接種物**。在無菌工作站內，藉由將手套手溫熱使細菌之低溫小瓶解凍且約0.7 ml內含物注射至含有8 ml厭氧YCFA之亨蓋特管(Hungate tube)(目錄號1020471，Glasgerätebau Ochs, Bovenden-Lenglern, Germany)中。通常每個菌株準備兩個管。接著亨蓋特管在37℃下培育(靜止) 16小時(菌株755)。

【0221】 **培養媒劑對照**。將含有8 ml厭氧YCFA之亨蓋特管在37℃下培育(靜止) 16小時。

【0222】 **投與細菌接種物或媒劑對照**。將400 ul培養之細菌接種

物或媒劑對照每天根據經口管飼法投與。

【0223】 **鼻內敏化**。藉由腹膜內注射每公斤9.75 mg xylasol及48.75 mg ketasol (Dr. E. Graeub AG, Bern, Switzerland)使小鼠麻醉且每個鼻投與於30 ul體積PBS中之15 ug HDM (目錄號：XPB70D3A25，批號：231897，Greer Laboratories, Lenoir, NC, USA)。

【0224】 **製備及投與陽性對照化合物地塞米松**。地塞米松21-磷酸二鈉鹽(Sigma-Aldrich，目錄號D1159，貨號N° SLBD.1030V)溶解在H_2O中，且以3 mg/kg之劑量於200 ul體積中在以上研究方案中所指示之日經口投與動物。

【0225】 **終末程序**。在第14天，藉由腹膜內注射致命戊巴比妥(Streuli PharmaAG, Uznach,目錄號：1170139A)處死動物，接著立刻進行500 ul生理食鹽水中枝氣管肺泡灌洗(BAL)。

【0226】 **量測BAL中之細胞浸潤**。細胞與BAL流體分離且基於標準形態學及細胞化學標準進行細胞分類計數。

【0227】 **圖表及統計分析**。所有圖表均用Graphpad Prism第6版產生且應用單向ANOVA。來自統計分析之結果具備個別資料表。誤差線表示平均標準誤差(SEM)。

結果及分析

【0228】 實驗結果展示於圖1-9中。

【0229】 在用細菌或媒劑處理之小鼠中未記錄到發病或死亡。兩種對照媒劑處理(陰性對照)及地塞米松處理(陽性對照)如所預期表現，其中地塞米松處理後記錄到嗜酸性粒細胞增多及中性粒細胞增多減弱。

【0230】 此實驗之最重要結果展現在圖6及7中，圖6及7報告在用HDM激發後在枝氣管灌洗中偵測到之嗜中性粒細胞之總數及百分比。投與菌株755使得相對於僅僅媒劑之對照，BAL中嗜中性粒細胞總量及嗜中性粒細胞之比例統計學上顯著減少。

實例2-嚴重中性粒細胞性氣喘之小鼠模型中細菌接種物之功效

概述

【0231】 向小鼠投與包含根據本發明之細菌菌株之組合物且隨後藉由皮下投與房塵蟎(HDM)提取物來敏化，且藉由鼻內投與HDM激發，以模擬嚴重中性粒細胞性氣喘之發炎反應。將用本發明組合物治療之小鼠所展現的發炎反應之量值及特徵與對照組相比。發現本發明之組合物減輕發炎反應，且尤其減少嗜中性粒細胞之募集，方式與包括投與抗IL-17抗體之陽性對照相當。因此，資料表明本發明之組合物可用於治療IL-17及Th17介導之病狀，諸如中性粒細胞增多及氣喘。

菌株

【0232】 755：狄氏副擬桿菌

研究設計

【0233】 組：

1. 陰性對照組。用媒劑對照處理(經口)。

5. 用治療性細菌接種物菌株755處理(經口)。

7. 陽性對照組。用抗IL-17處理(腹膜內)。

8. 未處理之對照組。

9: 健康小鼠(基線)。

【0234】 每組小鼠數目(組1-8) = 5

【0235】 第-14天至第17天：每日經口投與媒劑對照(組1)。

【0236】 第-14天至第17天：每日經口投與治療性細菌接種物(組2-6)。

【0237】 第0天：用CFA中HDM敏化(皮下) (組1-8)

【0238】 第7天：用CFA中HDM敏化(皮下) (組1-8)

【0239】 第13、15、17天：經腹膜內投與抗IL-17中和抗體(組7)。

【0240】 第14、15、16、17天：經鼻用30 ul PBS中HDM激發(組1-8)。

【0241】 第18天：處死所有動物用於分析。

終點及分析：

【0242】 在第14天，藉由腹膜內注射致命戊巴比妥(Streuli Pharma AG, Uznach, 目錄號：1170139A)處死動物，接著立刻進行枝氣管肺泡灌洗(BAL)。細胞與BAL流體分離且進行細胞分類計數(200個細胞計數/樣品)。

材料與方法

【0243】 **小鼠**。自Charles River Laboratories購買雌性7週齡C57BL/6小鼠且隨機分配至籠，每籠均5隻小鼠(通風籠來源於Indulab AG, Gams, Switzerland 籠型：“TheSealsafeTM-IVC籠。產品號1248L)。籠標記有研究號、組號及實驗開始日期。每週監測小鼠且適應設施7天，接著開始研究(研究第-14天)。在研究第-14天動物為8週齡。飲用水及食物可隨意取用。存在籠富集。根據地方特許牌照號

2283.1 (經Service de la consommation et des affaires vétérinaires du Canton de Vaud頒予及批准)進行動物之每日護理。飲用水及食物可隨意取用且每日補充一次。存在籠富集。觀測到如瑞士官方根據FVO (Federal Veterinary Office)關於實驗動物飼養管理、遺傳修飾動物產生及動物實驗方法之條例455.163所給出的動物福利規定。

【0244】 **培養細菌接種物**。在無菌工作站內，藉由將手套手溫熱使細菌之低溫小瓶解凍且約0.7 ml內含物注射至含有8 ml厭氧YCFA之亨蓋特管(目錄號1020471，Glasgerätebau Ochs, Bovenden-Lenglern, Germany)中。通常每個菌株準備兩個管。接著亨蓋特管在37℃下培育(靜止) 16小時(菌株755)。

【0245】 **培養媒劑對照**。含有8 ml厭氧YCFA之亨蓋特管在37℃下培育(靜止) 16小時。

【0246】 **投與細菌接種物或媒劑對照**。將400 ul培養之細菌接種物或媒劑對照每天根據經口管飼法投與。

【0247】 **HDM敏化**。將PBS中50 μg HDM (目錄號：XPB70D3A25，批號：231897, Greer Laboratories, Lenoir, NC, USA)在等體積完全弗氏佐劑(complete Freund'sadjuvant，CFA Chondrex Inc. Washington, USA)中乳化，且在兩週內在對側腰窩上以200 μl體積皮下投與兩次。第二次免疫接種後一週，藉由腹膜內注射每公斤9.75 mg xylasol及48.75 mg ketasol (Dr. E. Graeub AG, Bern, Switzerland)使小鼠麻醉，接著連續4日，以30 ul體積PBS中15 μg HDM鼻內激發。最終激發後一天進行分析。

【0248】 **陽性對照化合物抗小鼠IL-17抗體之製備及投與**。抗IL-

17中和抗體來源於Bio X Cell且儲存在4℃下(純系17F3，目錄號BE0173，Bio X Cell)，且經腹膜內以12.5 mg/kg之劑量在以上研究方案中指示之日投與。

【0249】**終末程序**。在第18天，藉由腹膜內注射致命戊巴比妥(Streuli Pharma AG, Uznach, 目錄號：1170139A)處死動物，接著立刻進行500 ul生理食鹽水中枝氣管肺泡灌洗(BAL)。

【0250】**量測BAL中之細胞浸潤**。細胞與BAL流體分離且基於標準形態學及細胞化學標準進行細胞分類計數。

【0251】**圖表及統計分析**。所有圖表均用Graphpad Prism第6版產生且應用單向ANOVA。來自統計分析之結果具備個別資料表。誤差線表示平均標準誤差(SEM)。

結果及分析

【0252】實驗結果展示於圖10-18中。

【0253】在用細菌或媒劑處理之小鼠中未記錄到發病或死亡。如圖15及16中所示，菌株755高度有效地減輕中性粒細胞性發炎反應之程度。另外，菌株755相對於對照減少嗜酸性粒細胞數目，如圖11及12中所示。

實例3-II型膠原蛋白誘發之關節炎小鼠模型中細菌接種物治療關節炎之功效

材料與方法

菌株

【0254】755：狄氏副擬桿菌

細菌培養物

【0255】細菌培養物在厭氧工作站(Don Whitley Scientific)中生長用於投與。

【0256】細菌菌株#755使用甘油原液生長。甘油原液儲存在-80℃下。每週三次，甘油原液在室溫下解凍且在YCFA盤上劃線。每次使用新的甘油等分試樣。使細菌在給定盤上生長多達72小時。

【0257】待投與動物之溶液每日製備兩次，上午(AM)及下午(PM)處理具有八小時時間間隔。自劃線盤挑選菌落，且轉移至含有YCFA培養基之管中。使細菌菌株#755生長24小時，接著AM投與。細菌以1%傳代培養至YCFA培養基中進行PM投與。在上午及下午處理製備後記錄每一菌株之OD值。

II型膠原蛋白誘發之關節炎小鼠模型

【0258】成年雄性DBA/1小鼠隨機分配至實驗組其使其適應兩週。在第0天，藉由皮下注射100微升含有100微克II型膠原蛋白(CII)於補充有4 mg/ml結核分枝桿菌(*Mycobacterium tuberculosis*) H37Ra的不完全弗氏佐劑中之乳液來投與動物。在第21天，藉由皮下注射含有100 μg II型膠原蛋白於不完全弗氏佐劑中之加強乳液來投與動物。

【0259】根據以下投與時程給與處理。自第-14天直至第45天實驗結束，將動物每週稱重三次。自第21天直至實驗結束，每週針對關節炎之臨床徵象，包括後爪及前爪、橈腕(腕)關節及脛跗(踝)關節之腫脹對動物評分三次。

【0260】在第45天，挑選小鼠且取終末血液樣品用於細胞介素分析。

【0261】在第-14天、第0天及第45天，收集糞便樣品用於微生物

分析，立刻迅速冰凍且儲存在-80℃下。

【0262】膠原蛋白誘發之關節炎(CIA)小鼠模型為公認的類風濕性關節炎小鼠模型[66]。用CII免疫接種引起包括類風濕性關節炎之若干重要病理學特徵，包括滑液增生、單核細胞浸潤及軟骨退變之發病機理。重要地，CIA之發展藉由Th17細胞，經由分泌IL-17A介導[67]。潛於關節炎模型之免疫反應藉由使用補充有結核分枝桿菌之弗氏佐劑增強。

【0263】在第21天，自每組中三個衛星動物收集脾。細胞在II型膠原蛋白存在或不存在下培養72小時。藉由Luminex定量培養物上清液中及終末血清中之包括TNF-α、IL-6、IFN-γ、IL-4、IL-10及IL-17之細胞介素。使用氚化胸腺嘧啶併入法定量細胞增殖。

處理組及劑量

【0264】所有組n = 15 (主要研究組n = 12且衛星組n = 3)。

【0265】用於生物治療劑之媒劑為酵母提取物-酪腖-脂肪酸(YCFA)培養基。

	組	*劑量*	*投與*		*疾病誘發*
			途徑	*方案*	
1	*媒劑*	*5 ml/kg*	*PO*	*BID：* *第-14天-結束*	*第0天：膠原蛋白/CFA，一次，SC* *第21天：膠原蛋白/IFA，一次，SC*
5	*生物治療劑#755*	*5 ml/kg*			

PO：經口管飼法，SC：皮下注射，BID：每天兩次，CFA：完全弗氏佐劑

體重

【0266】自第-14天直至實驗結束，將動物每週稱重三次。將資

料繪圖(平均值±SEM)。

非特定之臨床觀測結果

【0267】自第-14天至實驗結束，每日檢查動物之非特定臨床徵象，包括姿勢異常(弓背)、異常皮毛情況(豎毛)及異常活動程度(活動減少或增加)。

臨床觀測結果

【0268】自第21天直至第45天實驗結束，每週針對關節炎之臨床徵象，包括後爪及前爪、橈腕(腕)關節及脛跗(踝)關節之腫脹對動物評分三次。使用以下量表對每肢評分：(0)正常，(1)輕微腫脹，(2)輕度腫脹，(3)中度腫脹及(4)嚴重腫脹。藉由加入每肢評分計算臨床評分。動物之最大可能臨床評分為(16)。挑選兩個連續時刻之評分等於(12)之動物及任一時刻評分超過(12)之動物。將資料繪圖(平均值±SEM)。

細胞增殖分析

【0269】第21天，每組挑選三個衛星動物且將脾解剖出。脾細胞在II型膠原蛋白存在或不存在下培養72小時。72小時後，細胞在氚化胸腺嘧啶存在下脈衝隔夜。藉由量測胸苷併入來定量細胞增殖。將資料繪圖(平均值±SEM)。取上清液且測試關鍵細胞介素之存在。

細胞介素分析

【0270】藉由Luminex測試來自脾細胞培養物之終末上清液以定量TNF-α、IL-6、IFN-γ、IL-4、IL-10及IL-17。將資料繪圖(平均值±SEM)。

微生物分析

【0271】在第-14天、第0天及第45天，自每個動物收集糞便樣品，立刻迅速冰凍且儲存在-80℃下。盲腸(包括內含物)立刻迅速冰凍且儲存在80℃下。每日藉由塗鋪細菌進行細菌鑑別測試。

組織病理學

【0272】在實驗結束時，後爪儲存在組織固定劑中。樣品轉移至脫鈣溶液中。將組織樣品加工，切片，且用蘇木精與曙紅染色。藉由對實驗設計不知情之合格組織病理學家，針對關節炎徵象，包括發炎、關節軟骨破壞及下層幹骺端骨骼之破壞，對切片評分。使用詳述評分系統(見下文)。將資料繪圖(平均值±SEM)。提供原始及分析資料以及代表性圖。

表1：組織病理學評分系統

級別	描述
發炎	
0	正常關節
1	具有嗜中性粒細胞主宰之發炎的輕度滑液增生。關節間隙中少量嗜中性粒細胞及巨噬細胞。
2	具有涉及嗜中性粒細胞與巨噬細胞之中度至顯著發炎的滑液增生。關節間隙中嗜中性粒細胞及巨噬細胞；可能為一些壞死組織碎片。
3	具有涉及嗜中性粒細胞與巨噬細胞之顯著發炎的滑液增生。喪失滑膜細胞內層。發炎可自滑膜延伸至包括肌肉之周圍組織。關節間隙中許多嗜中性粒細胞及巨噬細胞，連同明顯的壞死組織碎片。
關節軟骨破壞	
0	正常關節
1	關節軟骨僅僅展示輕度退行性改變。可能周邊存在早期血管翳形成。
2	關節軟骨展示中度退行性改變及局灶損失。局灶上存在血管翳形成。
3	關節軟骨顯著破壞及喪失，大範圍血管翳形成。
下層幹骺端骨骼之破壞	
0	正常關節
1	下層幹骺端骨骼無變化

2	可能為幹骺端骨骼之局灶性壞死或纖維化。
3	幹骺端骨骼破壞或塌縮。大範圍發炎、壞死或纖維化，延伸至幹骺端之髓腔。

結果及分析

存活及非特異性臨床觀測結果

【0273】 一些動物因關節炎之臨床徵象的嚴重程度或因非特定臨床觀測結果之嚴重程度而在研究時程結束之前淘汰。

【0274】 3隻動物淘汰或發現在預處理時期(第-14天至第0天)期間死亡：組1中之1隻動物(媒劑處理之動物自供應者處到達後斷腿且淘汰)及組5中之兩隻動物(生物治療劑#755處理)。

【0275】 7隻動物因關節炎臨床徵象之嚴重程度而淘汰：組1中之5隻動物(媒劑處理)及組5中之2隻動物(生物治療劑#755處理)。

【0276】 組1中之3隻動物(媒劑處理)因包括姿勢異常(弓背)、異常皮毛情況(豎毛)、異常活動程度(活動減少)之非特定臨床徵象之嚴重程度而淘汰。

體重

【0277】 自第-14天直至第0天記錄體重資料，且表示為初始(第-14天)體重之百分比，藉由雙向ANOVA，接著鄧尼特事後檢驗(Dunnett's post-test)分析，以與第-14天進行多重比較，接著與媒劑處理組進行多重比較。資料呈現於圖19中。來自實驗時程結束之前淘汰之動物的資料自分析中排除。

【0278】 當與第-14天比較時，在媒劑處理組中，在第-9天及第-7天，藉由經口管飼法每日投與兩次誘發顯著體重損失。

【0279】 自第0天直至第28天記錄體重資料，且表示為初始(第0

天)體重之百分比，藉由雙向ANOVA，接著鄧尼特事後檢驗分析，以與媒劑組中第0天進行多重比較，接著與媒劑處理組進行多重比較。資料呈現於圖20中。來自實驗時程結束之前淘汰之動物及來自衛星動物的資料自分析中排除。第28天、第35天及第42天資料藉由單向ANOVA，接著鄧尼特事後檢驗進一步分析，以與媒劑處理組進行多重比較。

【0280】 當與媒劑處理組中第0天比較時，在第26天及第28天關節炎臨床徵象之發作與顯著體重喪失有關($p < 0.0001$)。

【0281】 當與媒劑處理組比較時，在第28天體重在組5 (生物治療劑#755處理)中顯著更高(< 0.0001)。

臨床觀測結果

【0282】 藉由雙向ANOVA，接著鄧尼特事後檢驗分析臨床評分資料，以在媒劑處理組中各天之間進行多重比較，接著在實驗組與媒劑處理組之間每天進行多重比較。資料呈現於圖21中。自實驗結束之前淘汰之動物記錄的資料自分析中排除。當動物因關節炎臨床徵象之嚴重程度而淘汰時，報告以下天之最後記錄評分且用於統計分析中。

【0283】 當與第21天比較時，自第28天直至第45天，在媒劑處理組中觀測到臨床評分顯著增加($p < 0.0001$)。

【0284】 當自第28天直至第45天與媒劑處理組比較時，生物治療劑#755誘發臨床評分減少。第31天及第38天減少為統計學上顯著($p < 0.05$)。

細胞增殖分析

【0285】 為使有效該分析，脾細胞在作為陽性對照刺激物之可溶

性抗CD3及抗CD28 (抗CD3/CD28)存在下培養以證實細胞之增殖潛能。

【0286】 在所有實驗組中均看到對抗CD3/CD28之強烈增殖反應，展示細胞健康、有活力且能夠對活化信號作出反應。

【0287】 為測試在II型膠原蛋白 (CII)存在下之增殖反應，脾細胞在50 μg/ml CII存在下培養。藉由雙向ANOVA，接著斯達克事後檢驗(Sydak's post-test)，分析對CII之脾細胞增殖反應，以在未刺激與CII刺激之脾細胞之間進行多重比較，且藉由單向ANOVA，接著鄧尼特事後檢驗分析，以將不同實驗組與媒劑處理組中CII刺激之反應進行比較。資料呈現於圖22中。

【0288】 當與媒劑處理組中未刺激脾細胞比較時，CII誘發^{3}H-胸苷併入(cpm)極顯著增加($p < 0.0001$)。

【0289】 用生物治療劑#755處理之組證明CII誘發之脾細胞增殖水準顯著低於媒劑處理組。

組織培養上清液中細胞介素含量

【0290】 藉由luminex分析，在來源於抗CD3/CD28刺激之培養物的組織培養上清液中，量測每種細胞介素之含量。此等展示所有量測之細胞介素的穩固反應(媒劑組中平均含量如下：IL-4 = 6,406 pg/ml；IL-6 = 306 pg/ml；IL-10 = 10,987 pg/ml；IL-17A = 11,447 pg/ml；IFN-γ = 15,581 pg/ml；TNF-α = 76 pg/ml)。

【0291】 以下部分概括自II型膠原蛋白刺激之培養物獲得的資料。適用時，未刺激及CII刺激之脾細胞之上清液中細胞介素含量之間的差異統計分析使用雙向ANOVA，接著斯達克事後檢驗進行，以

進行多重比較，而單向ANOVA、接著鄧尼特事後檢驗用於比較生物治療劑處理組與媒劑處理組之CII刺激之反應。在兩種情況下該等組之間的細胞介素含量無顯著差異。此可能歸因於使用之樣本尺寸小(n = 3)。

【0292】 為更精確地呈現細胞介素之資料分佈與資料之大體佈置，此作為散佈圖呈現。

【0293】 在用CII刺激後組織培養上清液中IL-4之組平均值<5 pg/ml。此等不視為生物學上顯著的且此處不包括。用膠原蛋白刺激後組織培養上清液中TNF-α之組平均值低於定量限度。

IFN-γ之上清液含量(圖23)

【0294】 與IL-17一起，IFN-γ為CIA模型中驅動疾病之主要細胞介素。圖23中之散佈圖證明CII刺激後IFN-γ含量，與生物治療劑比較，媒劑處理組之組中位數更高。

IL-17A之上清液含量(圖24)

【0295】 在媒劑處理組之CII刺激之培養物中IL-17A含量為50 pg/ml。與媒劑處理組比較，在生物治療劑組中此細胞介素之含量似乎較低。

IL-10之上清液含量(圖25)

【0296】 媒劑處理組中CII刺激及培養基對照培養物之IL-10含量分別為13 pg/ml及2.1 pg/ml。可預期媒劑處理組之IL-10 (其為消炎細胞介素)含量較高，因為發炎及促炎細胞介素誘發可以伴隨有消炎回饋機制。

IL-6之上清液含量(圖26)

【0297】 諸如IL-6及TNF-α之發炎細胞介素在抗CII培養物中通常不高含量產生。然而，其含量可能由於免疫調節而改變。CII刺激之培養物中IL-6含量少，達到10 pg/ml。雖然高於培養基對照培養物，但此等差異太小，以致於無法提供進行統計分析之基本原理。

微生物分析

【0298】 藉由使用光譜儀量測600 nm下光密度來證實細菌生長。藉由比較劃線盤圖像與參考圖像，證實細菌身份。

【0299】 在改良之細菌製備方法後，如量測之高OD值所指示，自第-2天及第-3天投與一致高劑量之細菌菌株。

【0300】 在第-14天、第0天及終止時收集糞便樣品且迅速冰凍。

組織病理學

【0301】 組織病理學結果展示於圖65-69中。如對此模型所預期，根據關節炎存在/不存在或存在之改變嚴重程度，觀測個體內及個體間變化性。

【0302】 病理性質如針對此模型所預期，滑膜及滑液囊大範圍混合型慢性活動性發炎，延伸至涉及關節周圍之軟組織(肌肉、脂肪組織、皮膚膠原蛋白)。在最嚴重受影響之關節中，存在關節軟骨退化及喪失，具有關節內碎片及發炎及關節及骨結構因纖維化及發炎而破壞。

【0303】 組織病理學改變之發生率為：媒劑-80% (16/20)；生物治療劑#755-41% (9/22)。當與媒劑處理組比較時，用生物治療劑#755處理減少小鼠後肢中組織病理學評分之發生率(參見圖65-68)。藉由單向ANOVA，針對非參數資料(克魯斯凱-沃利斯檢驗(Kruskal-Wallis

test))分析組織病理學評分，接著鄧尼特事後檢驗，與媒劑處理組進行多重比較。當與媒劑處理組比較時，生物治療劑#755誘發在組織病理學中觀測到之關節發炎評分顯著減少($p < 0.05$)。當與媒劑處理組比較時，生物治療劑#755誘發在組織病理學中觀測到之軟骨破壞評分顯著減少($p < 0.05$)。當與媒劑處理組比較時，生物治療劑#755誘發在組織病理學中觀測到之骨骼破壞評分顯著減少($p < 0.05$)。當與媒劑處理組比較時，生物治療劑#755誘發總組織病理學評分顯著減少($p < 0.05$)。

概述

【0304】 如DBA/1小鼠中關節炎模型中所預期，自II型膠原蛋白第一次投與後第28天觀測到臨床評分增加。生物治療劑#755展示在此模型中有效治療關節炎，生物治療劑#755有效減少臨床評分之嚴重程度且有效減少關節中之病理性疾病，如組織病理學分析中所證明。

【0305】 在來自所有實驗組之脾細胞培養物中均看到對II型膠原蛋白之增殖回憶反應。膠原蛋白特定之反應在用生物治療劑#755處理後顯著減少(組5)。

【0306】 大部分所測試之T細胞細胞介素展示在媒劑處理組中II型膠原蛋白刺激之培養基與培養基對照之間可偵測之增加。此等增加在生物治療劑處理組中不如此明顯。此廣泛證明上述對II型膠原蛋白之增殖回憶反應。

【0307】 有證據證明抑制Th1/Th17軸，Th1/Th17軸為此模型及人類RA中病原性反應。降低之細胞介素含量與減少之增殖的相關性暗示免疫調節。無證據證明此調節由Th2相關之IL-4含量增加或免疫調

節細胞介素IL-10增加引起。

實例4-房塵蟎誘發之氣喘之小鼠模型中細菌接種物之作用的進一步分析

【0308】 在實例1中測試之小鼠進行進一步分析以進一步表徵本發明之組合物對過敏性氣喘發炎反應之作用。

材料與方法

【0309】 **在第14天抽血及血清製備**。動物之血液樣品經由心臟刺穿收集。藉由在14000g下離心5分鐘，將血清自血液樣品分離且儲存在-20℃下。

【0310】 **在第14天移除器官**。左肺葉收集在福馬林中以進行改進型組織學分析。收集右肺葉(所有剩餘葉)及移除血清以迅速冰凍及用於改進型分析。剩餘BAL流體迅速冰凍用於改進型分析。

血清及BAL流體中抗體含量之量測

【0311】 藉由ELISA分析，在BAL及血清中量測全部IgE及房塵蟎(HDM)特異性IgG1抗體產生。

肺分離及組織學分析

【0312】 左肺葉固定在福馬林中，接著埋入石蠟中，切片，且用蘇木精及曙紅及PAS染色。如下盲法進行隨後組織學評分：針對發炎(枝氣管周浸潤及血管周浸潤)及黏液產生，對每個樣品之5個隨機視場評分。發炎浸潤用以下分級系統評分：

0 - 正常

1 - 輕度發炎浸潤

2 - 中度發炎浸潤

3 - 顯著發炎浸潤

4 - 嚴重發炎浸潤

5 - 非常嚴重發炎浸潤

【0313】 在每個視場中，氣道以尺寸量測且黏液細胞數以uM定量。

量測肺組織中發炎介體

【0314】 分離用於定量發炎介體之右肺葉(所有剩餘葉)迅速冰凍，用於隨後藉由市售多工分析(Merck-Millipore)量測CCL11、IFN-γ、IL-1α、IL-1β、IL-4、IL-5、IL-9、IL-17A、CXCL1、CCL3、CXCL2及CCL5。根據製造商之說明書進行分析。

結果及分析

【0315】 實驗結果展示於圖27-45中。

【0316】 支援實例1中描述之發現，用菌株755處理之小鼠之肺組織中細胞浸潤物之分析展示平均發炎評分顯著及統計上顯著之減少(參見圖31及33)。

【0317】 分析BAL流體及血清中抗體含量(參見圖27-30)。觀測到細菌處理對血清抗體含量無明確作用。此可反映實驗失敗，因為資料之散佈及每一處理之誤差線大，且陽性及陰性對照似乎未如預期起作用。此外，基線血清抗體含量可已遮罩任何改變。

【0318】 類似地，觀測到細菌處理對肺組織中細胞介素含量無明確作用(參見圖35-45)。再次，此可反映實驗失敗，因為資料之散佈及每一處理之誤差線大，且陽性及陰性對照似乎未如預期起作用。亦可能涉及之作用機制影響較早細胞介素反應，該等細胞介素反應在最終

HDM氣道激發後第4天不再可偵測。歸因於所偵測之含量的變化性，當解釋當前研究中細胞介素資料時應謹慎一些。此變化性可藉由以下事實解釋：分離肺組織用於不同分析，且歸因於發炎之分佈不規則，因此一個肺葉可能不具充分代表性或可與其他小鼠中相同葉匹敵。

實例5-嚴重中性粒細胞性氣喘之小鼠模型中細菌接種物之作用的進一步分析

【0319】 在實例2中測試之小鼠進行進一步分析以進一步表徵本發明之組合物對與嚴重氣喘相關之中性粒細胞性反應之作用。

材料與方法

【0320】 **在第18天移除器官**。左肺葉收集在福馬林中以進行改進型組織學分析。收集右肺葉(所有剩餘葉)及移除血清以迅速冰凍及用於改進型分析。剩餘BAL流體迅速冰凍用於改進型分析。

【0321】 **肺組織中發炎介體之量測(改進型分析)**。分離用於定量發炎介體之右肺葉(所有剩餘葉)迅速冰凍，用於隨後藉由市售多工分析(Merck-Millipore)量測IFN-γ、IL-1α、IL-1β、CXCL1、CCL3、CXCL2、CCL5、IL-17A、TNF-α、IL-17F、IL -23及IL-33。根據製造商之說明書進行分析。

【0322】 **血清及BAL流體中抗體含量之量測(改進型分析)**。藉由ELISA分析，在BAL及血清中量測房塵蟎(HDM)特異性IgG1及IgG2a抗體產生。

【0323】 **肺分離及組織學分析(改進型分析)**。左肺葉固定在福馬林中，接著埋入石蠟中，切片，且用蘇木精及曙紅及PAS染色。如下盲法進行隨後組織學評分：針對發炎(枝氣管周浸潤及血管周浸潤)及

黏液產生，對每個樣品之5個隨機視場評分。發炎浸潤用以下分級系統評分：

0 - 正常

1 - 輕度發炎浸潤

2 - 中度發炎浸潤

3 - 顯著發炎浸潤

4 - 嚴重發炎浸潤

5 - 非常嚴重發炎浸潤

結果及分析

【0324】 實驗結果展示於圖46-63中。

【0325】 抗體含量之進一步分析揭露細菌菌株755之功效亦反映在BAL流體及血清中HDM特異性IgG1含量降低(參見圖46及48)。關於對IgG2a含量之作用的確定結論無法繪圖。總體而言，來自抗體分析之資料表明與對抗體同型切換之選擇性作用相對比，與總體減少之發炎反應相關的減少。

【0326】 組織學分析證明來自BAL流體之細胞分類計數，展示用菌株755處理之小鼠中細胞浸潤減少(參見圖50-52)。

【0327】 關於細胞介素含量，如針對實例4，資料之散佈及每一處理之誤差線大，且陽性及陰性對照似乎未如預期必要地起作用。亦可能涉及之作用機制影響較早細胞介素反應，該等細胞介素反應在最終HDM氣道激發後第4天不再可偵測。歸因於所偵測之含量的變化性，當解釋當前研究中解釋細胞介素資料時應謹慎一些。此變化性可藉由以下事實解釋：分離肺組織用於不同分析，且歸因於發炎之分佈

不規則，因此一個肺葉可能不具充分代表性或可與其他小鼠中相同葉匹敵。儘管此變化性，展示菌株755對細胞介素含量之明確消炎作用，且陽性對照抗IL-17 Ab一般如預期起作用。

【0328】 在以上告誡下，圖55及57中之資料表明用菌株755處理可實現IL-1b及IFNγ之含量減少，此可表明與對基質或先天免疫細胞之趨化因子釋放(及因此細胞募集)之影響相關的作用機制。此等細胞介素屬於Th17路徑。將此資料集聯繫在一起，可得出以下明確結論：在嚴重中性粒細胞性氣喘之此小鼠模型中菌株755高度有效保護小鼠避免發炎。

實例6-多發性硬化之小鼠模型中細菌接種物之功效

概述

【0329】 向小鼠投與包含根據本發明之細菌菌株的組合物且隨後用髓磷脂少突神經膠質細胞醣蛋白將小鼠免疫接種以誘發實驗自體免疫腦脊髓炎(EAE)。EAE為人類多發性硬化最常用之實驗模型。發現本發明之組合物對發病率及疾病嚴重程度具有顯著作用。

菌株

【0330】 755：以登記號NCIMB 42382寄存之細菌

研究設計

【0331】 組：

1. 陰性對照組。用媒劑對照處理(經口)。

5. 用治療性細菌接種物菌株755處理(經口)。

9. 陽性對照組。用地塞米松處理(腹膜內)。

10. 未處理之對照組。

【0332】 每組小鼠數目 = 10

【0333】 第-14天至第27天：每日經口投與媒劑對照(組1)。

【0334】 第-14天至第27天：每日經口投與治療性細菌接種物(組5)。

【0335】 第0-28天：一週投與地塞米松(腹膜內)三次(組9)

【0336】 第0天：MOG35-55 (髓磷脂少突神經膠質細胞醣蛋白-2mg/ml)及CFA (2 mg/ml MTB) 1:1混合，產生1 mg/ml溶液。100 μl肽-CFA混合物皮下注射至每個後腿中。腹膜內投與百日咳毒素(300 ng)。

【0337】 第1天：腹膜內投與百日咳毒素(300 ng)。

【0338】 第7天-向前：量測發病率及稱重，一週三次。

終點及分析

【0339】 分析小鼠之發病率及疾病嚴重程度，一週三次。評分盲法進行。使用在0至5範圍內之臨床評分評估疾病嚴重程度，其中5指示小鼠死亡(參見以下臨床評分系統)。

監測

【0340】 在指示天數，將小鼠稱重且觀測疾病活動評分及發病率。

【0341】 疾病活動評分觀測結果：

0 - 與未免疫接種小鼠比較，運動功能無明顯變化。

0.5 - 尾部尖端柔弱。

1.0 - 尾巴無力。

1.5 - 尾巴無力及後腿抑制。

2.0 - 尾巴無力及後腿虛弱。

或-當觀測行走時存在明顯頭部傾斜徵象。平衡性差。

2.5 - 尾巴無力及後腿打滑。

- 或-存在強烈頭部傾斜，引起小鼠有時跌倒。

3.0 - 尾巴無力及後腿完全麻痹。

3.5 - 尾巴無力及後腿完全麻痹。

外加：小鼠繞籠移動，但當置於其側面上時，不能恢復常態。

後腿一起在身體一側上。

4.0 - 尾巴無力、後腿完全癱瘓及前腿部分癱瘓。

- 小鼠最低限度地繞籠移動，但似乎警覺且進食

4.5 - 後腿完全癱瘓及前腿部分癱瘓，不繞籠運動。

立刻對小鼠執行安樂死且自籠移除。

5.0 因嚴重癱瘓而對小鼠執行安樂死。

【0342】 當動物具有等於或大於1之疾病活動評分時，認為其具有正發病評分。

結果

【0343】 研究結果展示於圖70及71中。

【0344】 陰性對照組中疾病誘發成功，其中媒劑對照及未處理之對照展示高分。用菌株755處理之作用顯著且用菌株755處理之小鼠展現顯著降低之發病率及疾病嚴重程度。實際上，發病率及疾病嚴重程度降低可與陽性對照組相當。此等資料指示菌株755可用於治療或預防多發性硬化。

實例7-小鼠葡萄膜炎模型中細菌接種物之功效

概述

【0345】 此研究使用光感受器間類視黃醇結合蛋白(IRBP)誘發之葡萄膜炎之小鼠模型測試細菌投與對葡萄膜炎之作用。葡萄膜炎為一種由眼內發炎及視網膜組織破壞引起之威脅視力之病狀。此疾病可在齧齒動物中在實驗自體免疫葡萄膜視網膜炎(EAU)之模型中研究[68]。EAU為一種器官特異性病症，其中Th1/Th17細胞係針對視網膜抗原且產生活化固有及浸潤單核細胞之細胞介素，引起組織破壞。EAU可藉由用包括光感受器間類視黃醇結合蛋白肽(IRBPp)之視網膜抗原激發而在小鼠中誘發。疾病發作通常在第8-9天出現，且在14-15天後達到峰值。臨床疾病之徵象可使用局部內窺鏡眼底成像(TEFI)來監測。

菌株

【0346】 MRX005：狄氏副擬桿菌，以登記號NCIMB42382寄存之細菌。

【0347】 生物治療劑提供于甘油原液中。微生物生長培養基(YCFA)用於培養該藥劑。

小鼠

【0348】 小鼠為菌株C57BL/6且在研究開始時超過6週。使用72只小鼠(+ 36只衛星動物)。自研究中排除不健康動物。將動物圈養在恒溫監測之保藏室(22±4℃)中無特定病原體(spf)條件下。在使用之前使動物適應標準畜舍條件最少一週。在整個此時期內監測動物之健康狀態且在研究開始之前評估每個動物對於實驗使用之適合性。在整個

研究時期內將小鼠以每籠多達10只動物一組來圈養。在整個適應及研究時期輻照顆粒飼料(實驗室飼料，EU齧齒動物飼料22%，5LF5)及水隨意取用。飲食或水之任何成分不能干擾研究。

實驗概述

【0349】 成年雌性C57BL/6小鼠隨機分配至實驗組且使其適應1週。根據以下時程投與處理。在第0天，藉由皮下注射向動物投與含有200 μg光感受器間類視黃醇結合蛋白肽1-20 (IRBP p1-20)於補充有2.5 mg/ml結核分枝桿菌H37 Ra之完全弗氏佐劑(complete Freund'sadjuvant，CFA)中之乳液。亦在第0天，藉由腹膜內注射，向動物投與1.5 μg百日咳桿菌毒素。自第-14天起，將動物每週稱重三次。自第-1天直至第42天實驗結束，使用局部內窺鏡眼底成像(TEFI)，針對葡萄膜炎之臨床徵象每週監測動物兩次。

投與時程

【0350】 所有組均為n = 12

【0351】 經口投與媒劑為YCFA培養基。

【0352】 每日經口投與兩次之投與體積為5 ml/kg。

組	*處理*	*劑量*	*途徑*	*頻率*	*疾病誘發*
1	*媒劑*	*5 ml/kg*	*PO*	*BID* *第-14天-結束*	*第0天：IRBP/CFA，SC* *第0天：PTx，IP*
2	*MRX005*	*5 ml/kg*			

PO：經口投與，BID：每日兩次，SC：皮下注射，IP：腹膜內注射，IRBP：光感受器間結合蛋白，CFA：完全弗氏佐劑，PTx：百日咳毒素

【0353】 亦使用藥物環孢菌素A處理測試陽性對照組。

读出

【0354】 **體重**. 自第-14天起，將動物一週稱重三次。淘汰連續兩個時刻之體重損失等於或超過其初始(第0天)體重15%之動物。

【0355】 **非特定之臨床觀測結果.** 自第-14天至實驗結束，每日檢查動物之非特定臨床徵象，包括姿勢異常(弓背)、異常皮毛情況(豎毛)及異常活動程度(活動減少或增加)。

【0356】 **臨床評分：藉由局部內窺鏡眼底成像(TEFI)使視網膜成像。**自第-1天至實驗結束，針對葡萄膜炎之臨床徵象，每週將動物評分兩次。在未麻醉但束縛之動物中，在使用托品醯胺1%、接著鹽酸苯腎上腺素2.5%擴張瞳孔後使用TEFI捕捉視網膜影像。使用以下系統對視網膜影像評分。最大累積評分為20。

評分	視神經盤發炎	視網膜血管	視網膜組織浸潤	結構破壞
1	最低	1-4個輕度袖套	1-4個小病灶或1個線狀病灶	涉及¼至¾視網膜區域之視網膜病灶或萎縮
2	輕度	>4個輕度袖套或1-3個中度袖套	5-10個小病灶或2-3個線狀病灶	具有多個小病灶(瘢痕)或≤3個線狀病灶(瘢痕)之全視網膜萎縮
3	中度	>3個中度袖套	>10個小病灶或>3個線狀病灶	具有>3個線狀病灶或匯合病灶(瘢痕)之全視網膜萎縮
4	嚴重	>1個嚴重袖套	線狀病灶彙合	具有摺疊之視網膜脫落
5	不可見(白視或嚴重脫落)			

結果

【0357】 研究結果展示於圖72及73中。

【0358】 **臨床評分：藉由局部內窺鏡眼底成像(TEFI)使視網膜成像。**藉由克魯斯凱-沃利斯檢驗，針對非參數資料，接著鄧尼特事後

檢驗，針對實驗天數之間的多重比較，來分析在對照組中自第0天至第28天量測之TEFI評分資料。

【0359】 當與第0天對照組中比較時，IRBP投與誘發自第14天($p < 0.01$)及在第28天($p < 0.0001$)量測之TEFI評分顯著增加(圖72)。

【0360】 在第28天在實驗組中量測之TEFI評分使用單向ANOVA分析。如所預期，在陽性對照環孢素A組中觀測到評分顯著下降。相對於陰性對照，MRX005處理組之評分亦在統計學上顯著下降($p<0.01$) (圖73)。

結論.藉由TEFI確定之臨床評分自第14天起增加，如在IRBP誘發之葡萄膜炎的此模型中所預期。截至第28天，在MRX005處理組中觀測到發病率及疾病嚴重程度顯著且在統計學上顯著的減少，此減少與陽性對照組所見到之減少相當。詳言之，此等資料表明用菌株MRX005處理減少視網膜損傷、視神經盤發炎及/或發炎細胞對視網膜組織浸潤(參見以上TEFI視網膜影像評分系統)。此等資料表明菌株MRX005可用於治療或預防葡萄膜炎。

實例8-穩定性測試

【0361】 含有至少一種本文中描述之細菌菌株的本文中描述之組合物儲存在密封容器中25℃或4℃下且容器置於具有30%、40%、50%、60%、70%、75%、80%、90%或95%相對濕度之氛圍中。1個月、2個月、3個月、6個月、1年、1.5年、2年、2.5年或3年後，至少50%、60%、70%、80%或90%之細菌菌株應殘留，如以藉由標準方案測定之菌落形成單位量測。

序列

【0362】 SEQ ID NO:1 (狄氏副擬桿菌16S核糖體RNA基因，部分序列，菌株：JCM 5825 - AB238922)

1 agagtttgat cctggctcag gatgaacgct agcgacaggc ttaacacatg caagtcgagg

61 ggcagcgggg tgtagcaata caccgccggc gaccggcgca cgggtgagta acgcgtatgc

121 aacttgccta tcagaggggg ataacccggc gaaagtcgga ctaataccgc atgaagcagg

181 gatcccgcat gggaatattt gctaaagatt catcgctgat agataggcat gcgttccatt

241 aggcagttgg cggggtaacg gcccaccaaa ccgacgatgg atagggggttc tgagaggaag

301 gtcccccaca ttggtactga gacacggacc aaactcctac gggaggcagc agtgaggaat

361 attggtcaat gggcgtaagc ctgaaccagc caagtcgcgt gagggatgaa ggttctatgg

421 atcgtaaacc tcttttataa gggaataaag tgcgggacgt gtcccgtttt gtatgtacct

481 tatgaataag gatcggctaa ctccgtgcca gcagccgcgg taatacggag gatccgagcg

541 ttatccggat ttattgggtt taaagggtgc gtaggcggcc ttttaagtca gcggtgaaag

601 tctgtggctc aaccatagaa ttgccgttga aactgggggg cttgagtatg tttgaggcag

661 gcggaatgcg tggtgtagcg gtgaaatgca tagatatcac gcagaacccc gattgcgaag

721 gcagcctgcc aagccattac tgacgctgat gcacgaaagc gtggggatca aacaggatta

781 gataccctgg tagtccacgc agtaaacgat gatcactagc tgtttgcgat acactgtaag

841 cggcacagcg aaagcgttaa gtgatccacc tggggagtac gccggcaacg gtgaaactca

901 aaggaattga cgggggcccg cacaagcgga ggaacatgtg gtttaattcg atgatacgcg

961 aggaacctta cccgggtttg aacgcattcg gaccgaggtg gaaacacctt ttctagcaat

1021 agccgtttgc gaggtgctgc atggttgtcg tcagctcgtg ccgtgaggtg tcggcttaag

1081 tgccataacg agcgcaaccc ttgccactag ttactaacag gttaggctga ggactctggt

1141 gggactgcca gcgtaagctg cgaggaaggc ggggatgacg tcaaatcagc acggcccttа

1201 catccggggc gacacacgtg ttacaatggc gtggacaaag ggaggccacc tggcgacagg

1261 gagcgaatcc ccaaaccacg tctcagttcg gatcggagtc tgcaacccga ctccgtgaag

1321 ctggattcgc tagtaatcgc gcatcagcca tggcgcggtg aatacgttcc cgggccttgt

1381 acacaccgcc cgtcaagcca tgggagccgg gggtacctga agtccgtaac cgaaaggatc

1441 ggcctagggt aaaactggtg actggggcta agtcgtaaca aggtaacc

【0363】 SEQ ID NO:2 (狄氏副擬桿菌16S核糖體RNA基因，部分序列，菌株：JCM 13400 - AB238923)

1 agagtttgat cctggctcag gatgaacgct agcgacaggc ttaacacatg caagtcgagg

61 ggcagcacag gtagcaatac cgggtggcga ccggcgcacg ggtgagtaac gcgtatgcaa

121 cttacctatc agagggggat aacccggcga aagtcggact aataccgcat gaagcagggg

181 ccccgcatgg ggatatttgc taaagattca tcgctgatag ataggcatgc gttccattag

241 gcagttggcg gggtaacggc ccaccaaacc gacgatggat aggggttctg agaggaaggt

301 cccccacatt ggtactgaga cacggaccaa actcctacgg gaggcagcag tgaggaatat

361 tggtcaatgg gcgtaagcct gaaccagcca agtcgcgtga gggatgaagg ttctatggat

421 cgtaaacctc ttttataagg gaataaagtg cgggacgtgt cctgttttgt atgtacctta

481 tgaataagga tcggctaact ccgtgccagc agccgcggta atacggagga tccgagcgtt

541 atccggattt attgggttta aagggtgcgt aggcggcctt ttaagtcagc ggtgaaagtc

601 tgtggctcaa ccatagaatt gccgttgaaa ctgggggggct tgagtatgtt tgaggcaggc

661 ggaatgcgtg gtgtagcggt gaaatgctta gatatcacgc agaaccccga ttgcgaaggc

721 agcctgccaa gccatgactg acgctgatgc acgaaagcgt ggggatcaaa caggattaga

781 taccctggta gtccacgcag taaacgatga tcactagctg tttgcgatac agtgtaagcg

841 gcacagcgaa agcgttaagt gatccacctg gggagtacgc cggcaacggt gaaactcaaa

901 ggaattgacg ggggcccgca caagcggagg aacatgtggt ttaattcgat gatacgcgag

961 gaaccttacc cgggtttgaa cgcattcgga ccgaggtgga aacacctttt ctagcaatag

1021 ccgtttgcga ggtgctgcat ggttgtcgtc agctcgtgcc gtgaggtgtc ggcttaagtg

1081 ccataacgag cgcaaccctt gccactagtt actaacaggt aaagctgagg actctggtgg

1141 gactgccagc gtaagctgcg aggaaggcgg ggatgacgtc aaatcagcac ggcccttaca

1201 tccggggcga cacacgtgtt acaatggcgt ggacaaaggg aagccacctg gcgacaggga

1261 gcgaatcccc aaaccacgtc tcagttcgga tcggagtctg caacccgact ccgtgaagct

1321 ggattcgcta gtaatcgcgc atcagccatg gcgcggtgaa tacgttcccg ggccttgtac

1381 acaccgcccg tcaagccatg ggagccgggg gtacctgaag tccgtaaccg aaaggatcgg

1441 cctagggtaa aactggtgac tggggctaag tcgtaacaag gtaacc

【0364】 SEQ ID NO:3 (狄氏副擬桿菌16S核糖體RNA基因，部分序列，菌株：JCM 13401 - AB238924)

1 agagtttgat cctggctcag gatgaacgct agcgacaggc ttaacacatg caagtcgagg

61 ggcagcacag gtagcaatac ccgccggcga ccggcgcacg ggtgagtaac gcgtatgcaa

121 cttgcctatc agaggggggat aacccggcga aagtcggact aataccgcat gaagcagggg

181 ccccgcatgg ggatatttgc taaagattca tcgctgatag ataggcatgc gttccattag

241 gcagttggcg gggtaacggc ccaccaaacc gacgatggat aggggttctg agaggaaggt

301 cccccacatt ggtactgaga cacggaccaa actcctacgg gaggcagcag tgaggaatat

361 tggtcaatgg gcgtaagcct gaaccagcca agtcgcgtga gggatgaagg ttctatggat

421 cgtaaacctc ttttataagg gaataaagtg tgggacgtgt cctgttttgt atgtaccttа

481 tgaataagga tcggctaact ccgtgccagc agccgcggta atacggagga tccgagcgtt

541 atccggattt attgggttta aagggtgcgt aggcggcctt ttaagtcagc ggtgaaagtc

601 tgtggctcaa ccatagaatt gccgttgaaa ctgggaggct tgagtatgtt tgaggcaggc

661 ggaatgcgtg gtgtagcggt gaaatgctta gatatcacgc agaaccccga ttgcgaaggc

721 agcctgccaa gccatgactg acgctgatgc acgaaagcgt ggggatcaaa caggattaga

781 taccctggta gtccacgcag taaacgatga tcactagctg tttgcgatac actgtaagcg

841 gcacagcgaa agcgttaagt gatccacctg gggagtacgc cggcaacggt gaaactcaaa

901 ggaattgacg ggggcccgca caagcggagg aacatgtggt ttaattcgat gatacgcgag

961 gaaccttacc cgggtttgaa cgcattcgga ccgaggtgga aacacctttt ctagcaatag

1021 ccgtttgcga ggtgctgcat ggttgtcgtc agctcgtgcc gtgaggtgtc ggcttaagtg

1081 ccataacgag cgcaaccctt gccactagtt actaacaggt gatgctgagg actctggtgg

1141 gactgccagc gtaagctgcg aggaaggcgg ggatgacgtc aaatcagcac ggcccttaca

1201 tccggggcga cacacgtgtt acaatggcgt ggacaaaggg atgccacctg gcgacaggga

1261 gcgaatcccc aaaccacgtc tcagttcgga tcggagtctg caacccgact ccgtgaagct

1321 ggattcgcta gtaatcgcgc atcagccatg gcgcggtgaa tacgttcccg ggccttgtac

1381 acaccgcccg tcaagccatg ggagccgggg gtacctgaag tccgtaaccg aaaggatcgg

1441 cctagggtaa aactggtgac tggggctaag tcgtaacaag gtaacc

【0365】 SEQ ID NO:4 (狄氏副擬桿菌16S核糖體RNA基因，部分序列，菌株：JCM 13402 - AB238925)

1 agagtttgat cctggctcag gatgaacgct agcgacaggc ttaacacatg caagtcgagg

61 ggcagcacag gtagcaatac cgggtggcga ccggcgcacg ggtgagtaac gcgtatgcaa

121 cttacctatc agagggggat aacccggcga aagtcggact aataccgcat gaagcagggg

181 ccccgcatgg ggatatttgc taaagattca tcgctgatag ataggcatgc gttccattag

241 gcagttggcg gggtaacggc ccaccaaacc gacgatggat aggggttctg agaggaaggt

301 cccccacatt ggtactgaga cacggaccaa actcctacgg gaggcagcag tgaggaatat

361 tggtcaatgg gcgtaagcct gaaccagcca agtcgcgtga gggatgaagg ttctatggat

421 cgtaaacctc ttttataagg gaataaagtg cgggacgtgt cccgttttgt atgtacctta

481 tgaataagga tcggctaact ccgtgccagc agccgcggta atacggagga tccgagcgtt

541 atccggattt attgggttta aagggtgcgt aggcggcctt ttaagtcagc ggtgaaagtc

601 tgtggctcaa ccatagaatt gccgttgaaa ctgggaggct tgagtatgtt tgaggcaggc

661 ggaatgcgtg gtgtagcggt gaaatgctta gatatcacgc agaaccccga ttgcgaaggc

721 agcctgccaa gccatgactg acgctgatgc acgaaagcgt ggggatcaaa caggattaga

781 taccctggta gtccacgcag taaacgatga tcactagctg tttgcgatac actgtaagcg

841 gcacagcgaa agcgttaagt gatccacctg gggagtacgc cggcaacggt gaaactcaaa

901 ggaattgacg gggcccgca caagcggagg aacatgtggt ttaattcgat gatacgcgag

961 gaaccttacc cgggtttgaa cgcattcgga ccgaggtgga aacacctttt ctagcaatag

1021 ccgtttgcga ggtgctgcat ggttgtcgtc agctcgtgcc gtgaggtgtc ggcttaagtg

1081 ccataacgag cgcaaccctt gccactagtt actaacaggt aaagctgagg actctggtgg

1141 gactgccagc gtaagctgcg aggaaggcgg ggatgacgtc aaatcagcac ggcccttaca

1201 tccggggcga cacacgtgtt acaatggcgt ggacaaaggg aggccacctg gcgacaggga

1261 gcgaatcccc aaaccacgtc tcagttcgga tcggagtctg caacccgact ccgtgaagct

1321 ggattcgcta gtaatcgcgc atcagccatg gcgcggtgaa tacgttcccg ggccttgtac

1381 acaccgcccg tcaagccatg ggagccgggg gtacctgaag tccgtaaccg aaaggatcgg

1441 cctagggtaa aactggtgac tggggctaag tcgtaacaag gtaacc

【0366】 SEQ ID NO:5 (狄氏副擬桿菌16S核糖體RNA基因，部分序列，菌株：JCM 13403 - AB238926)

1 agagtttgat cctggctcag gatgaacgct agcgacaggc ttaacacatg caagtcgagg

61 ggcagcacag gtagcaatac cgggtggcga ccggcgcacg ggtgagtaac gcgtatgcaa

121 cttacctatc agaggggggat aacccggcga aagtcggact aataccgcat gaagcagggg

181 ccccgcatgg ggatatttgc taaagattca tcgctgatag ataggcatgc gttccattag

241 gcagttggcg gggtaacggc ccaccaaacc gacgatggat aggggttctg agaggaaggt

301 cccccacatt ggtactgaga cacggaccaa actcctacgg gaggcagcag tgaggaatat

361 tggtcaatgg gcgtaagcct gaaccagcca agtcgcgtga gggatgaagg ttctatggat

421 cgtaaacctc ttttataagg gaataaagtg tgggacgtgt cccgttttgt atgtacctta

481 tgaataagga tcggctaact ccgtgccagc agccgcggta atacggagga tccgagcgtt

541 atccggattt attgggttta aagggtgcgt aggcggcctt ttaagtcagc ggtgaaagtc

601 tgtggctcaa ccatagaatt gccgttgaaa ctgggaggct tgagtatgtt tgaggcaggc

661 ggaatgcgtg gtgtagcggt gaaatgctta gatatcacgc agaaccccga ttgcgaaggc

721 agcctgccaa gccatgactg acgctgatgc acgaaagcgt ggggatcaaa caggattaga

781 taccctggta gtccacgcag taaacgatga tcactagctg tttgcgatac attgtaagcg

841 gcacagcgaa agcgttaagt gatccacctg gggagtacgc cggcaacggt gaaactcaaa

901 ggaattgacg gggcccgca caagcggagg aacatgtggt ttaattcgat gatacgcgag

961 gaaccttacc cgggtttgaa cgcattcgga ccgaggtgga aacacctttt ctagcaatag

1021 ccgtttgcga ggtgctgcat ggttgtcgtc agctcgtgcc gtgaggtgtc ggcttaagtg

1081 ccataacgag cgcaaccctt gccactagtt actaacaggt aaagctgagg actctggtgg

1141 gactgccagc gtaagctgcg aggaaggcgg ggatgacgtc aaatcagcac ggcccttaca

1201 tccggggcga cacacgtgtt acaatggcgt ggacaaaggg aggccacctg gcgacaggga

1261 gcgaatcccc aaaccacgtc tcagttcgga tcggagtctg caacccgact ccgtgaagct

1321 ggattcgcta gtaatcgcgc atcagccatg gcgcggtgaa tacgttcccg ggccttgtac

1381 acaccgcccg tcaagccatg ggagccgggg gtacctgaag tccgtaaccg aaaggatcgg

1441 cctagggtaa aactggtgac tggggctaag tcgtaacaag gtaacc

【0367】 SEQ ID NO:6 (狄氏副擬桿菌16S核糖體RNA基因，部分序列，菌株：JCM 13404 - AB238927)

1 agagtttgat cctggctcag gatgaacgct agcgacaggc ttaacacatg caagtcgagg

61 ggcagcacag gtagcaatac cgggtggcga ccggcgcacg ggtgagtaac gcgtatgcaa

121 cttacctatc agaggggggat aacccggcga aagtcggact aataccgcat gaagcagggg

181 ccccgcatgg ggatatttgc taaagattca tcgctgatag ataggcatgc gttccattag

241 gcagttggcg gggtaacggc ccaccaaacc gacgatggat aggggttctg agaggaaggt

301 cccccacatt ggtactgaga cacggaccaa actcctacgg gaggcagcag tgaggaatat

361 tggtcaatgg gcgtaagcct gaaccagcca agtcgcgtga gggatgaagg ttctatggat

421 cgtaaacctc ttttataagg gaataaagtg tgggacgtgt cccgttttgt atgtacctta

481 tgaataagga tcggctaact ccgtgccagc agccgcggta atacggagga tccgagcgtt

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【符號說明】

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【生物材料寄存】

國內寄存資訊[請依寄存機構、日期、號碼順序註記]

(1) 食品工業發展研究所；105年9月20日；BCRC 910743

國外寄存資訊[請依寄存國家、機構、日期、號碼順序註記]

(1) 英國；國家食品工業和海洋細菌中心(National Collection of Industrial, Food and Marine Bacteria；NCIMB)；104年3月12日；NCIMB 42382

【序列表】

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<210> 4
<211> 1486
<212> DNA
<213> 狄氏副擬桿菌

<400> 4
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<210> 5
<211> 1486

<212> DNA
<213> 狄氏副擬桿菌

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<210> 6
<211> 1486
<212> DNA
<213> 狄氏副擬桿菌

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<210> 7
<211> 1492
<212> DNA
<213> 糞副擬桿菌

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<210> 8
<211> 1492
<212> DNA
<213> 糞副擬桿菌

<400> 8

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<210> 9
<211> 1403
<212> DNA
<213> 狄氏副擬桿菌

<400> 9
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<210> 10
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<212> DNA
<213> 狄氏副擬桿菌

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【發明申請專利範圍】

【請求項1】

一種包含狄氏副擬桿菌(*Parabacteroides distasonis*)菌種之細菌菌株之組合物之用途，其係用於製備治療或預防結腸癌之藥劑。

【請求項2】

如請求項1之用途，其中該細菌菌株具有與SEQ ID NO:9至少98%、99%、99.5%或99.9%一致性之16s rRNA序列。

【請求項3】

如請求項1或2之用途，其中該組合物係用於減少IL-17產生或減少Th17細胞分化以治療或預防該癌症。

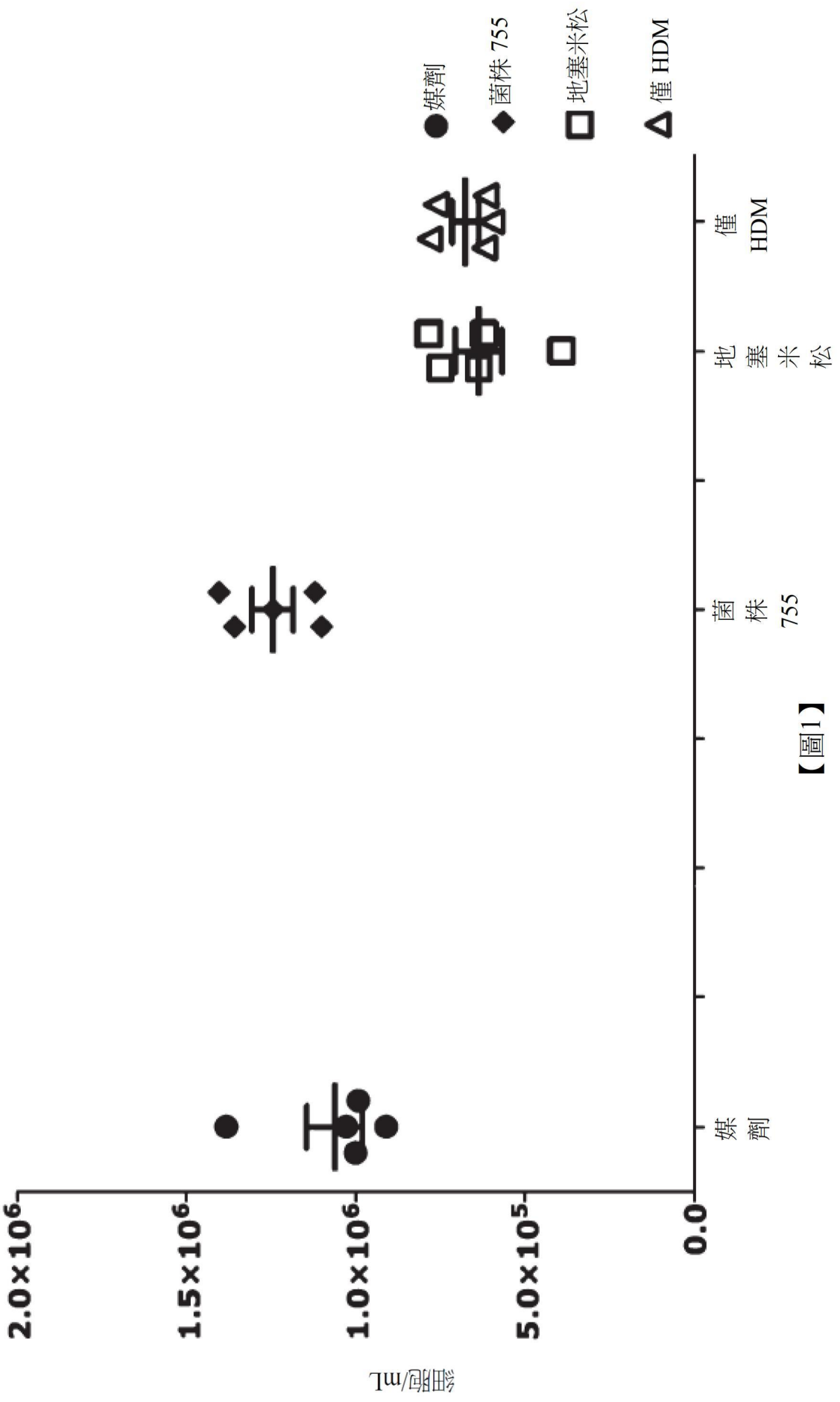
【請求項4】

如請求項1或2之用途，其中該組合物係用於具有升高之IL-17含量或Th17細胞之患者。

【請求項5】

如請求項3之用途，其中該組合物係用於具有升高之IL-17含量或Th17細胞之患者。

【發明圖式】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媒劑
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地塞米松
僅 HDM
媒劑
菌株 755
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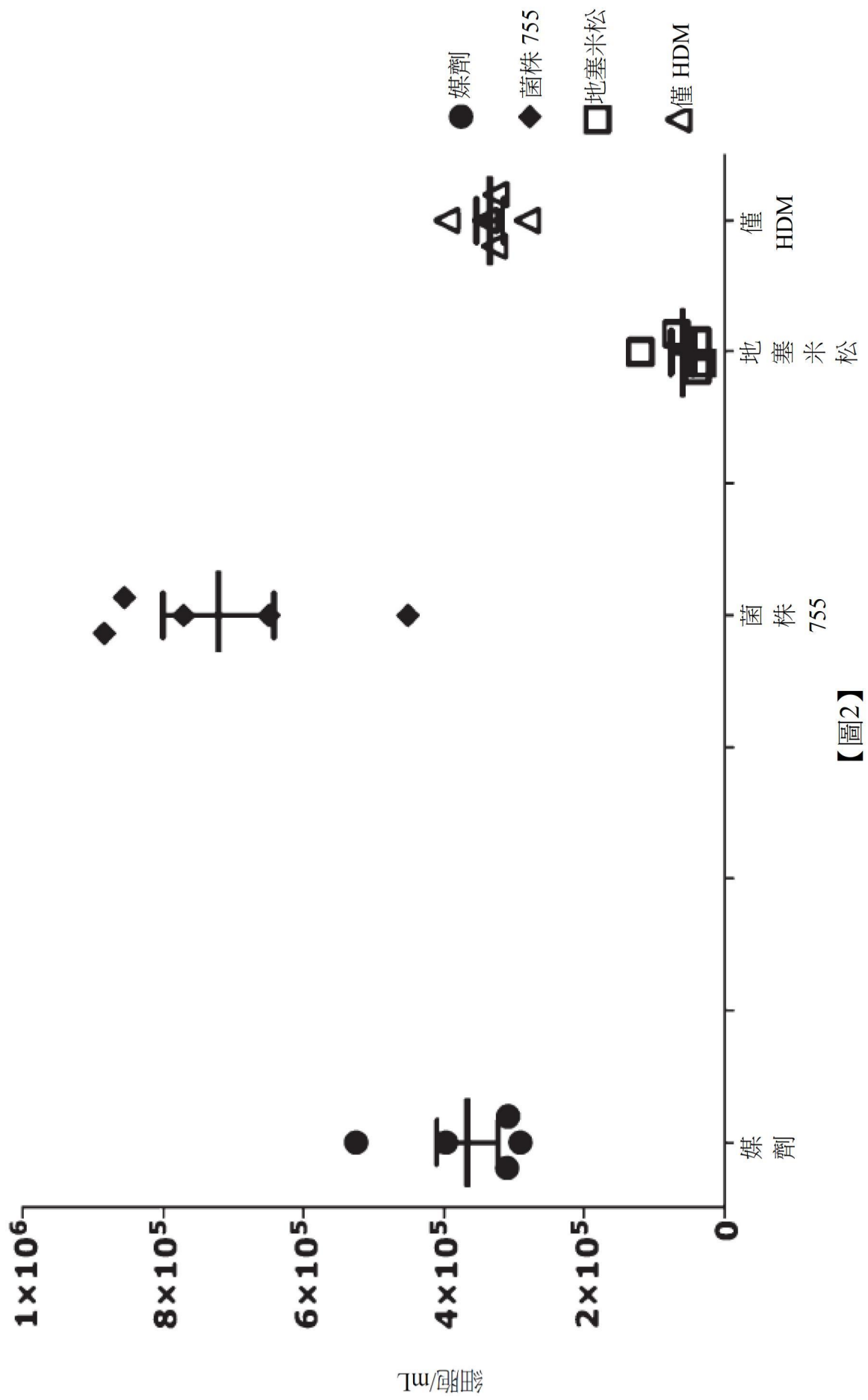
僅 HDM

【圖1】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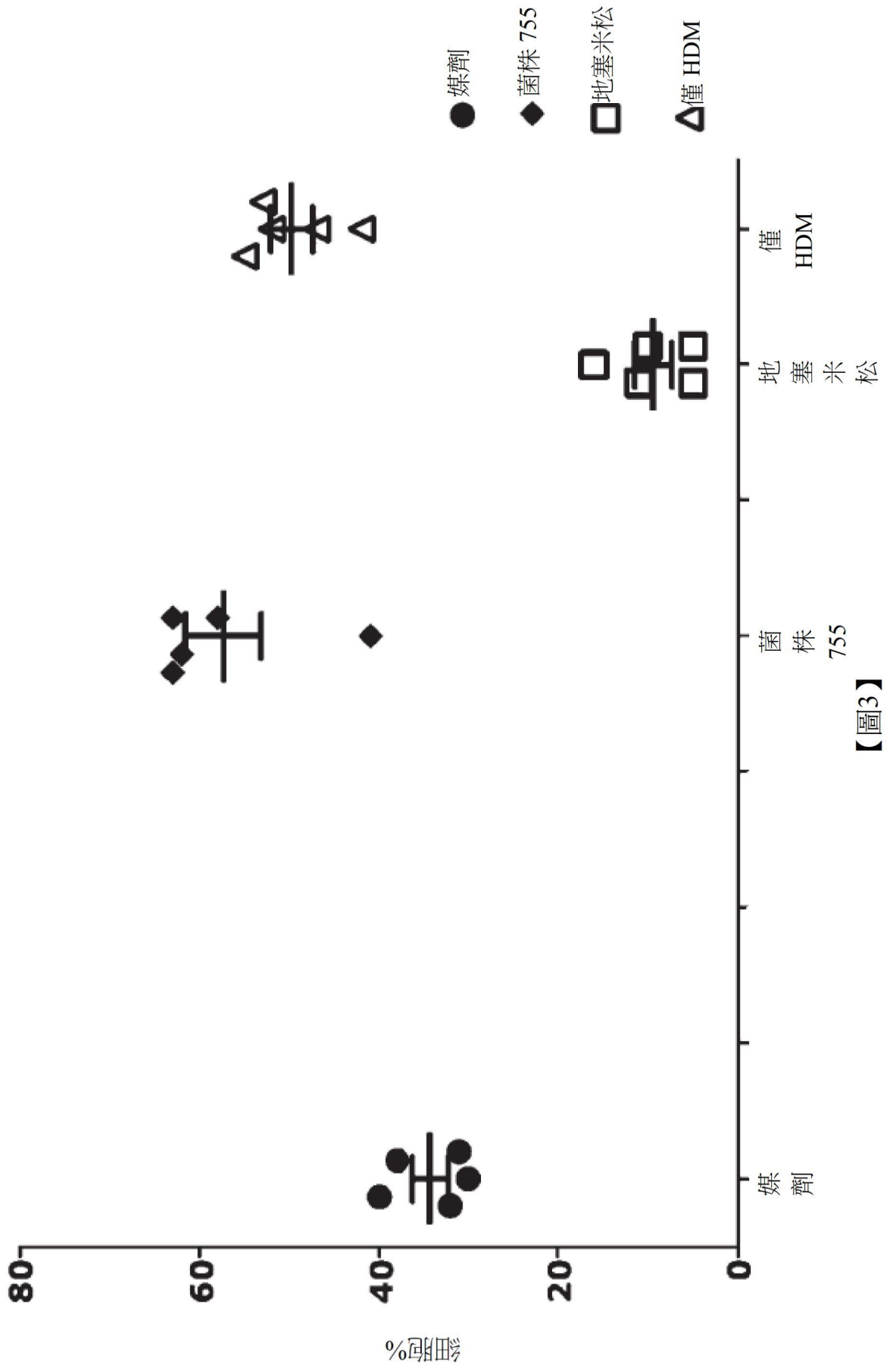
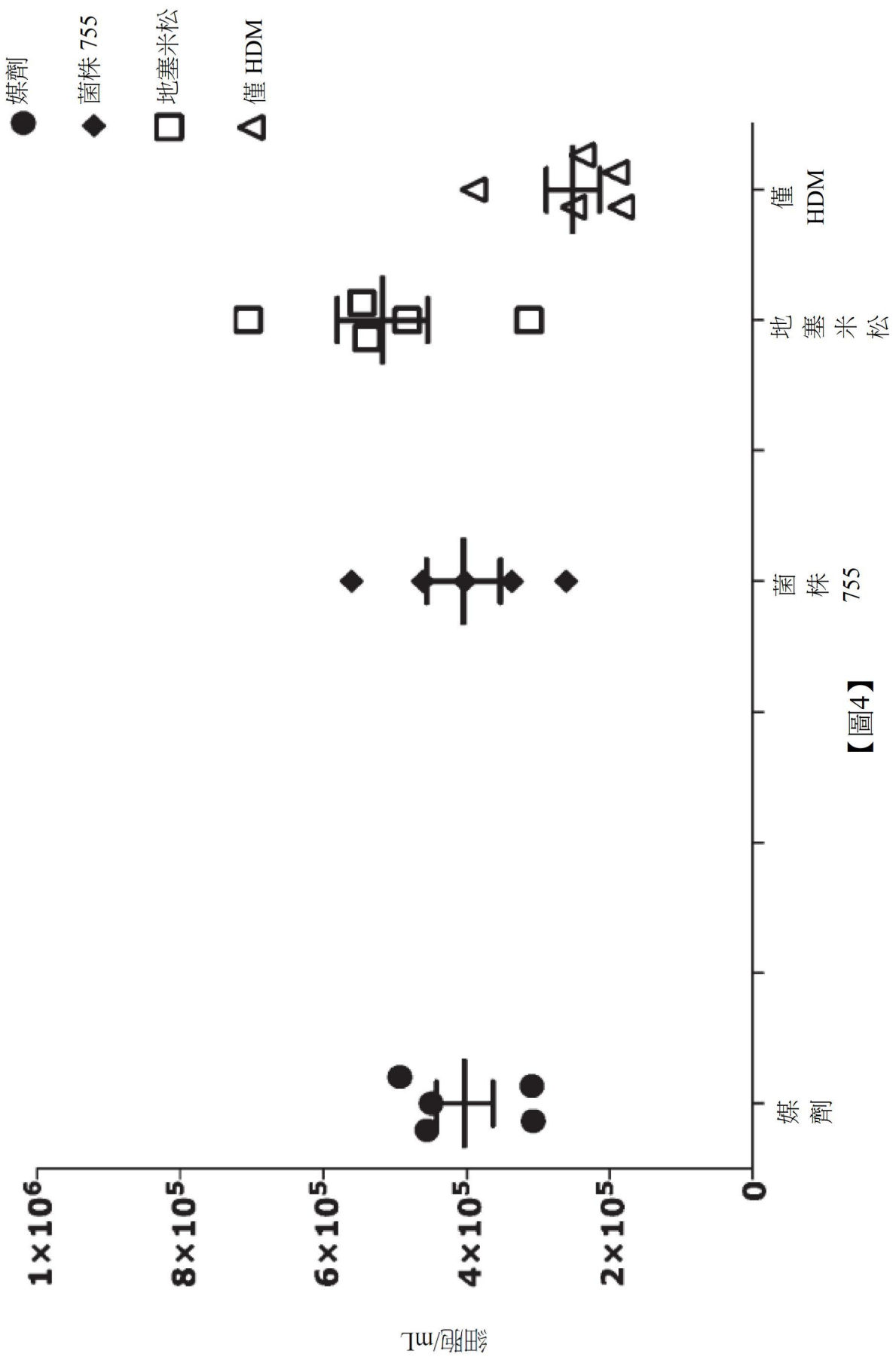
僅 HDM
●媒劑
◆菌株 755
□地塞米松
△僅 HDM

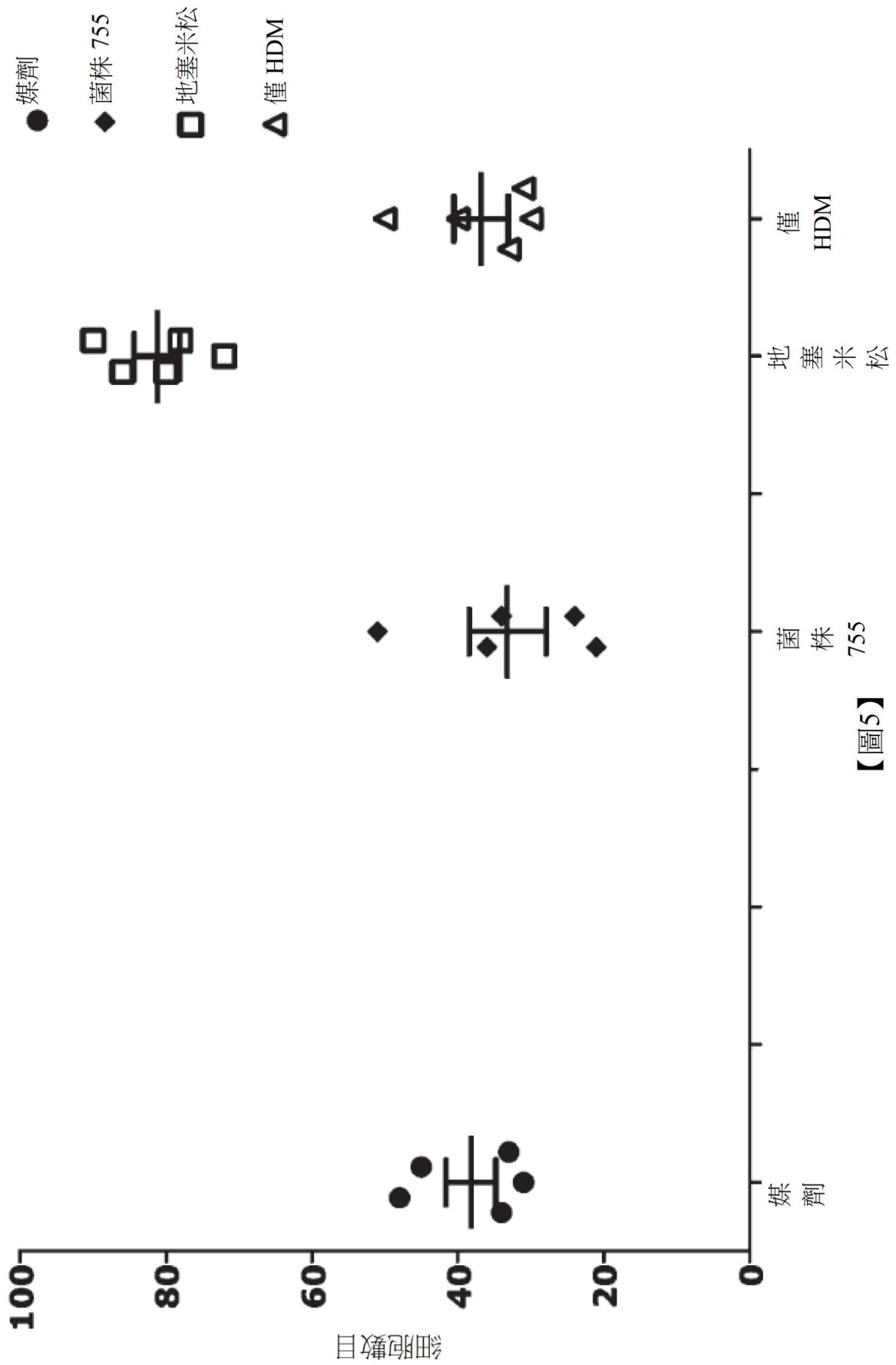
【圖2】



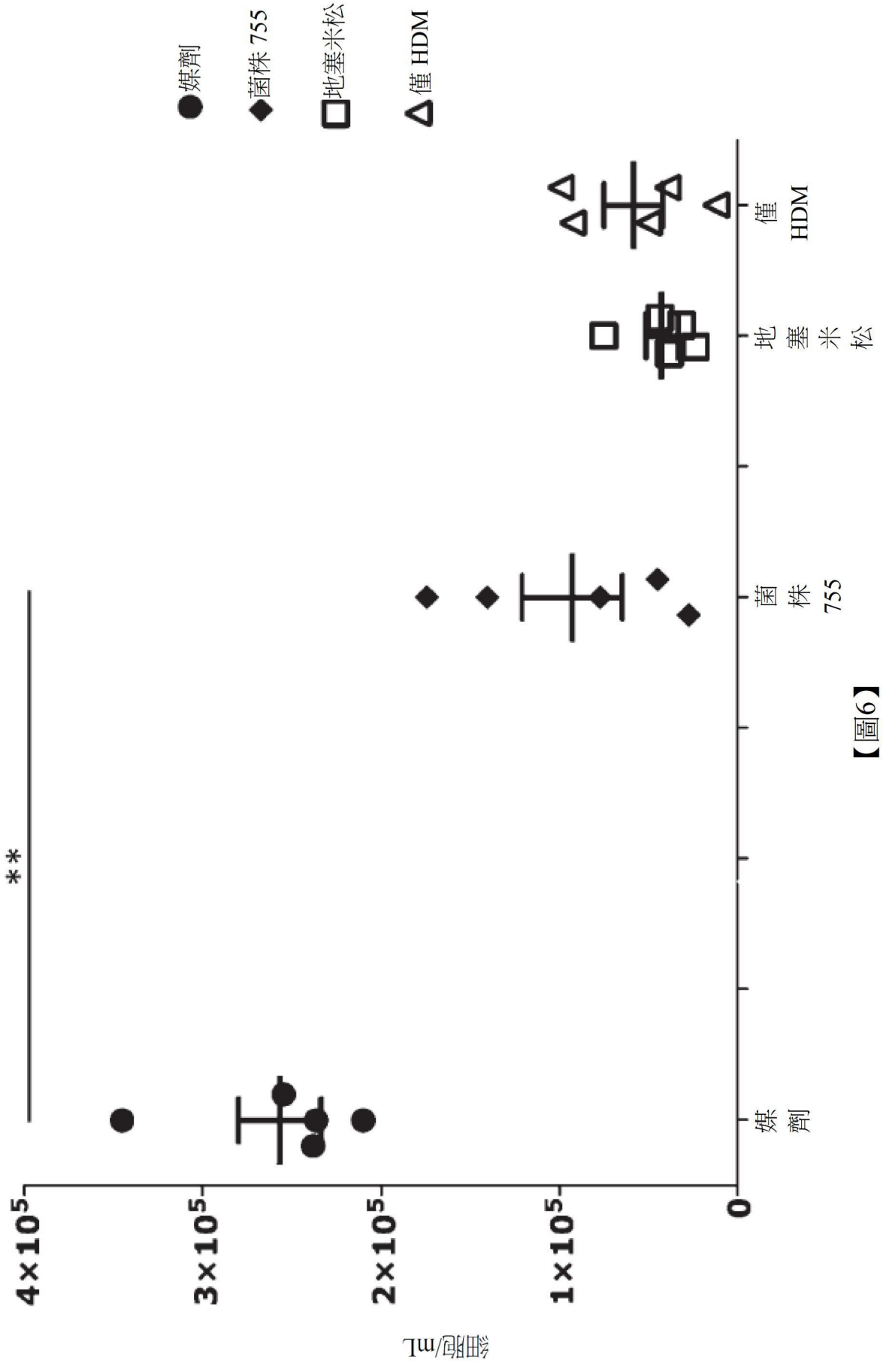
【圖3】


媒劑
菌株 755
地塞米松
僅 HDM
1×10⁶
8×10⁵
6×10⁵
4×10⁵
2×10⁵
0
媒劑
菌株 755
地塞米松
僅 HDM
細胞/mL

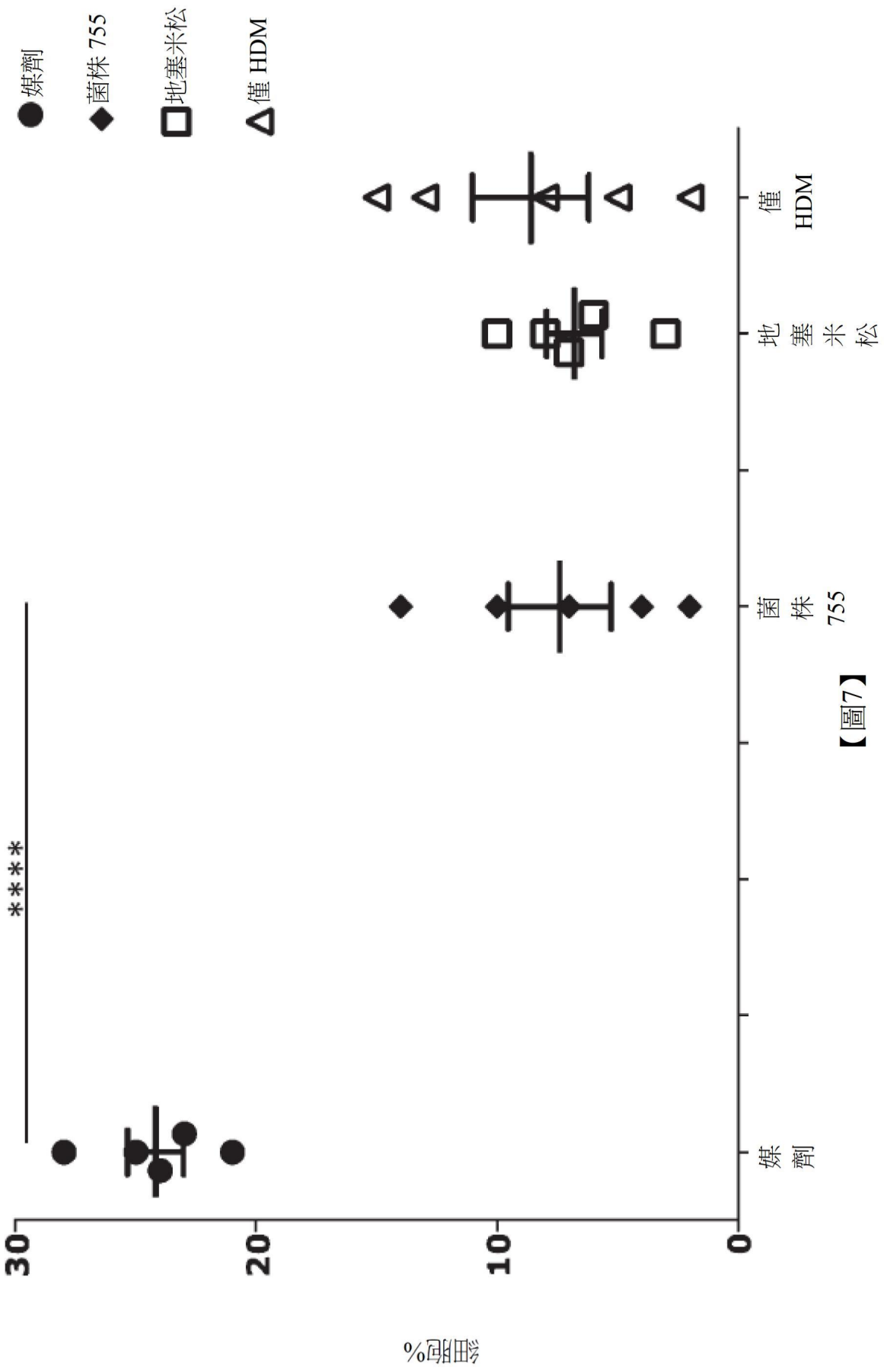
【圖4】



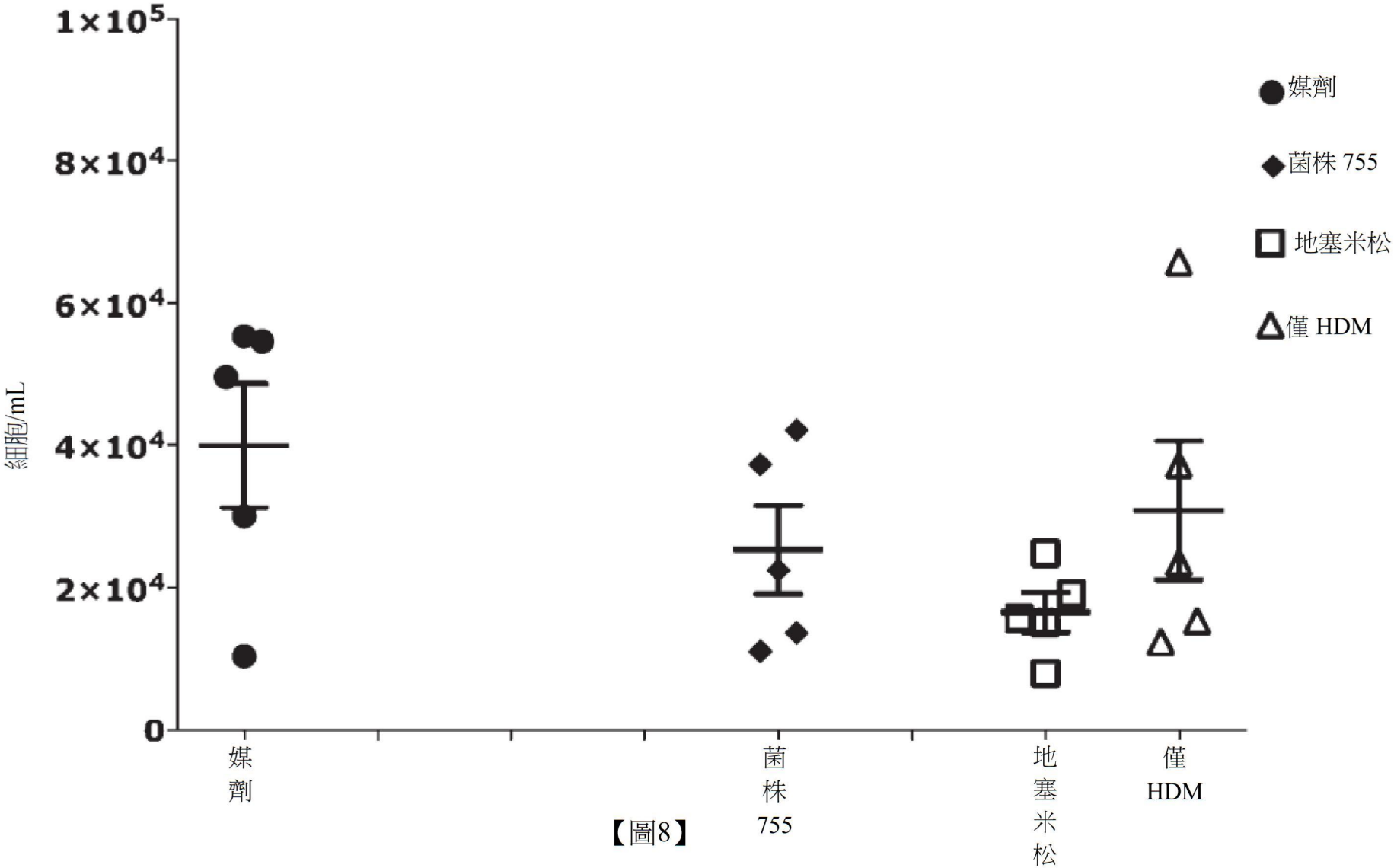
【圖5】


媒劑
菌株 755
地塞米松
僅 HDM
**
4×10^5
3×10^5
2×10^5
1×10^5
0
細胞/mL
媒劑
菌株 755
地塞米松
僅 HDM

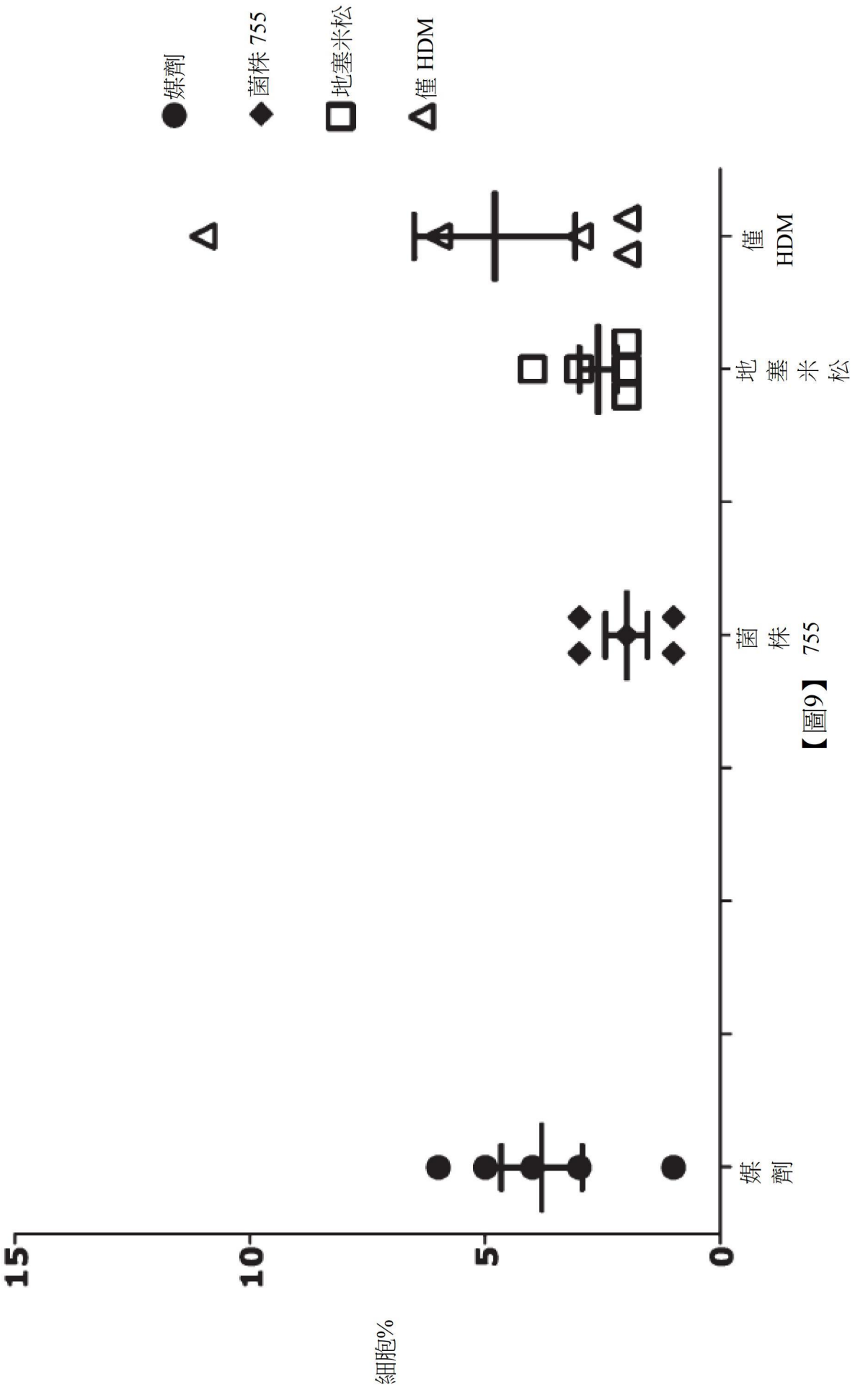
【圖6】



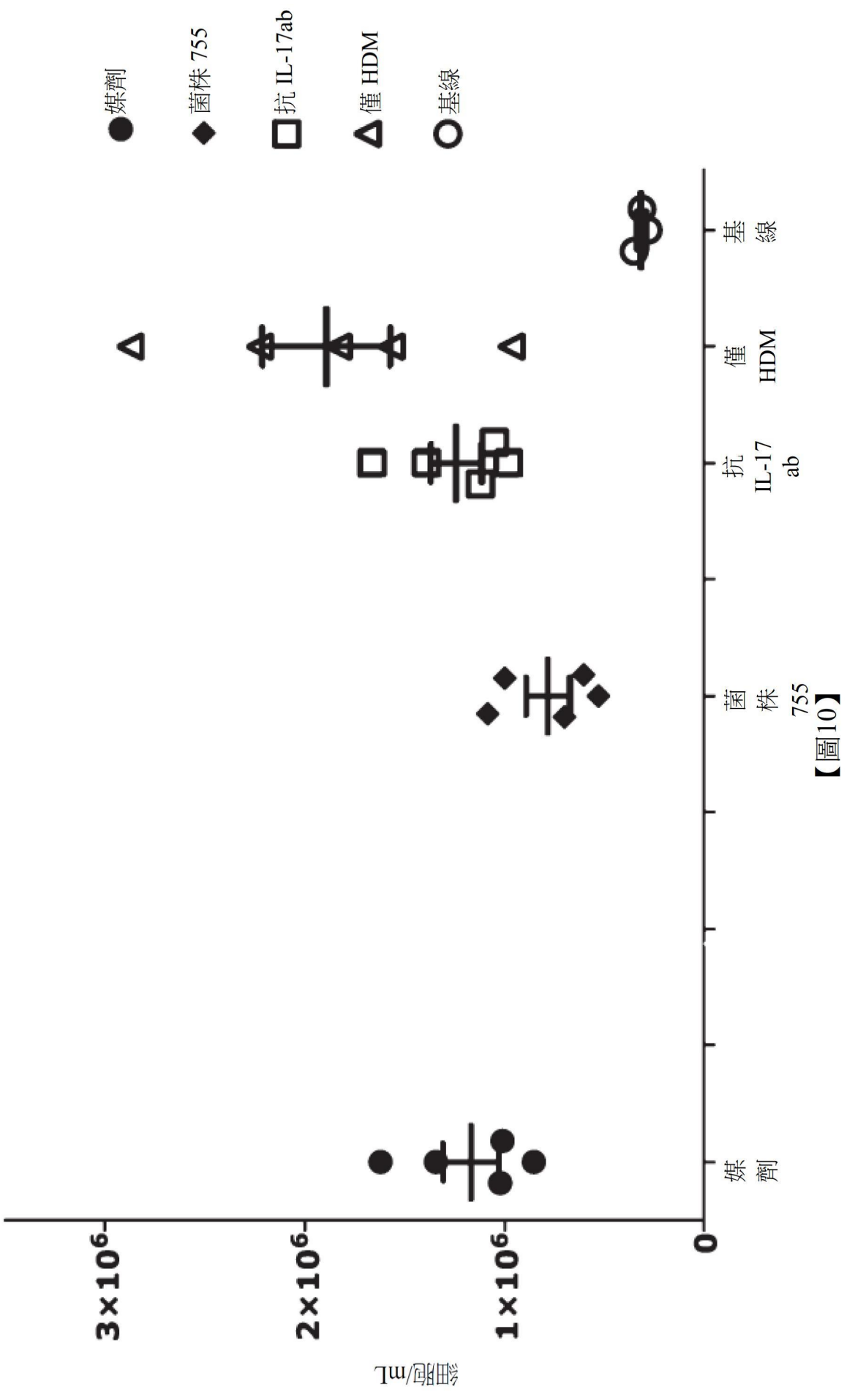
【圖7】


1×10^5
8×10^4
6×10^4
4×10^4
2×10^4
0
細胞/mL
媒劑
菌株 755
地塞米松
僅 HDM
媒劑
菌株 755
地塞米松
僅 HDM

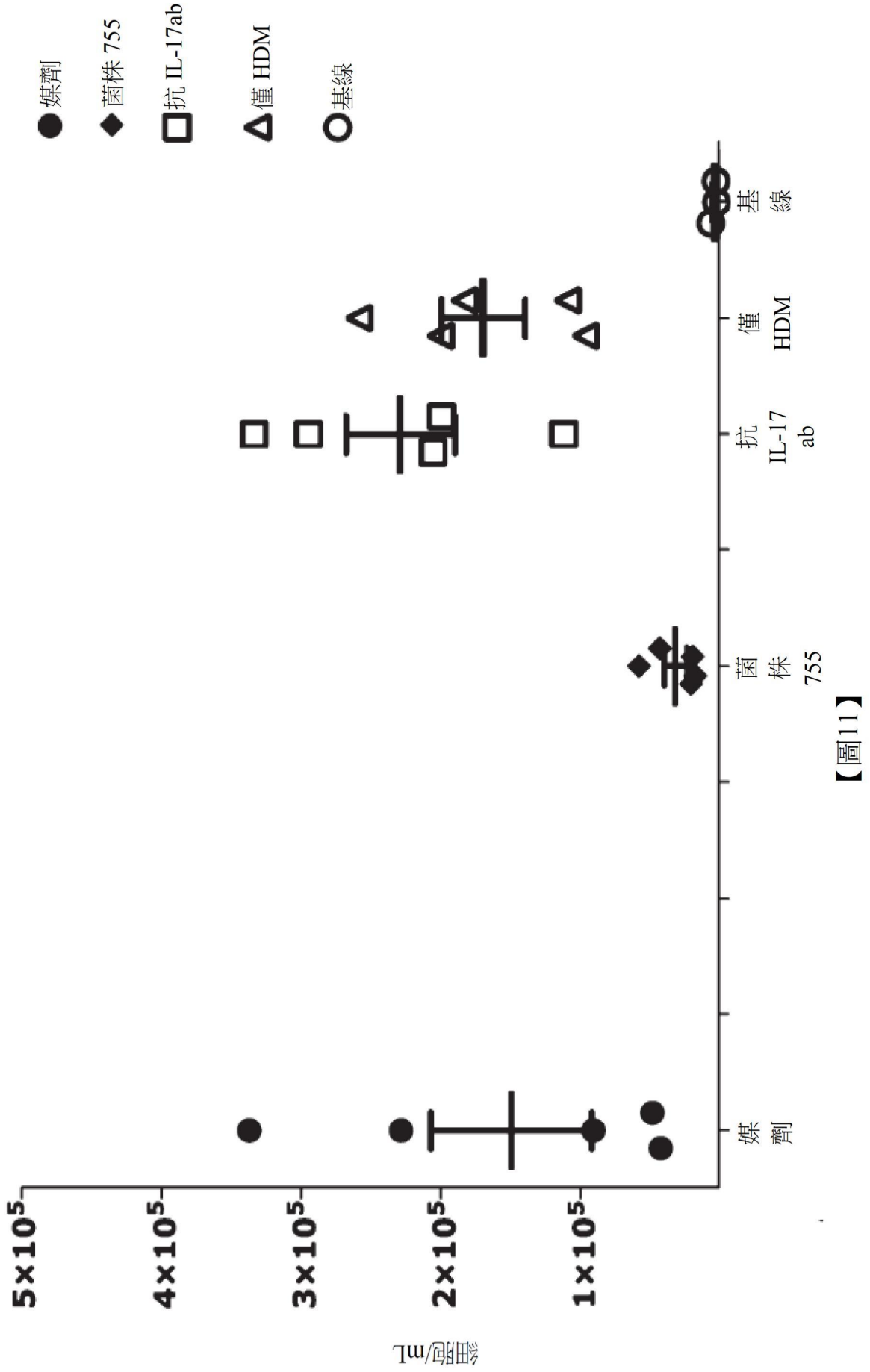
【圖8】



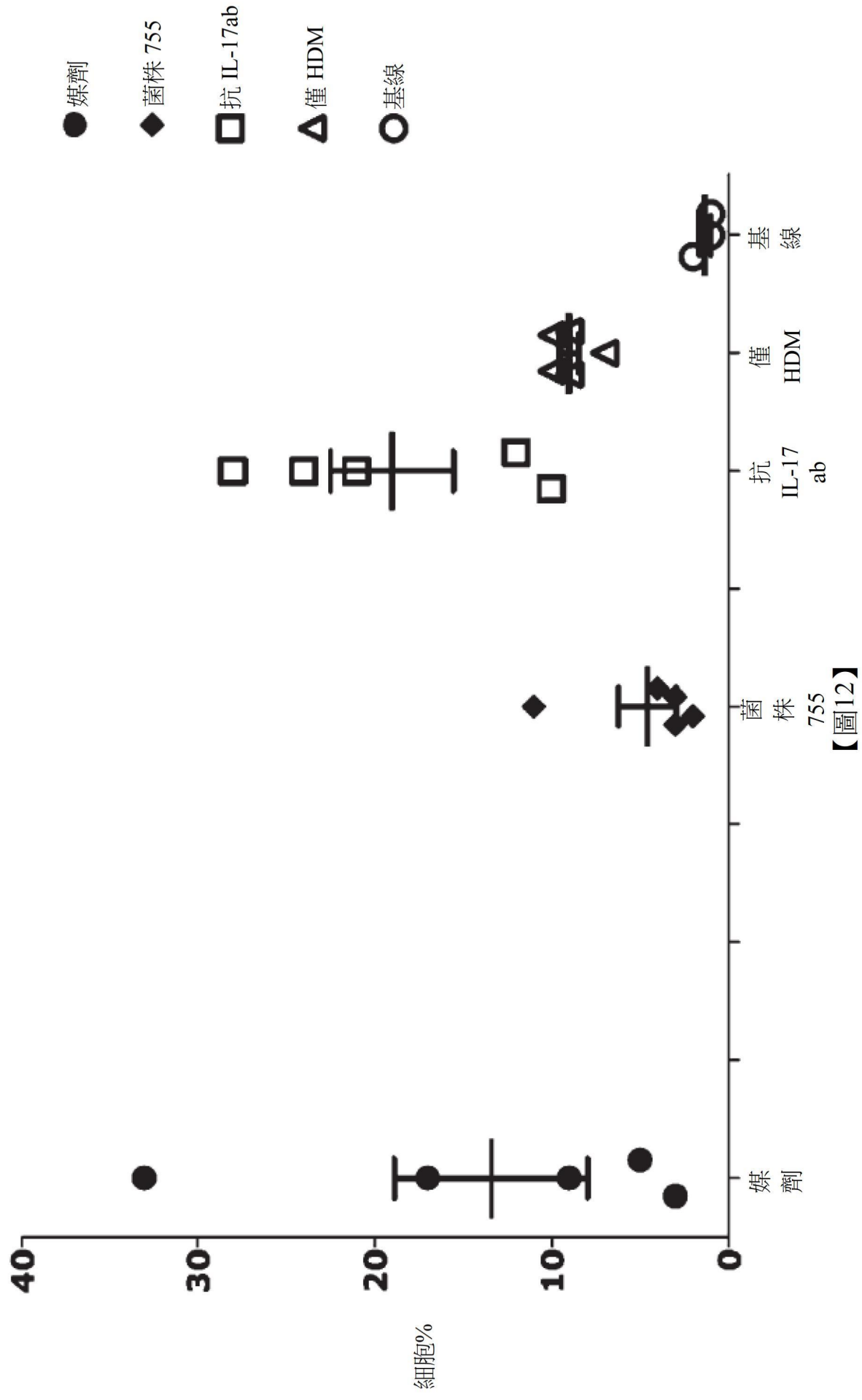
【圖9】


●媒劑
◆菌株 755
□抗 IL-17ab
△僅 HDM
○基線
3×10⁶
2×10⁶
1×10⁶
0
細胞/mL
媒劑
菌株755
抗IL-17ab
僅HDM
基線

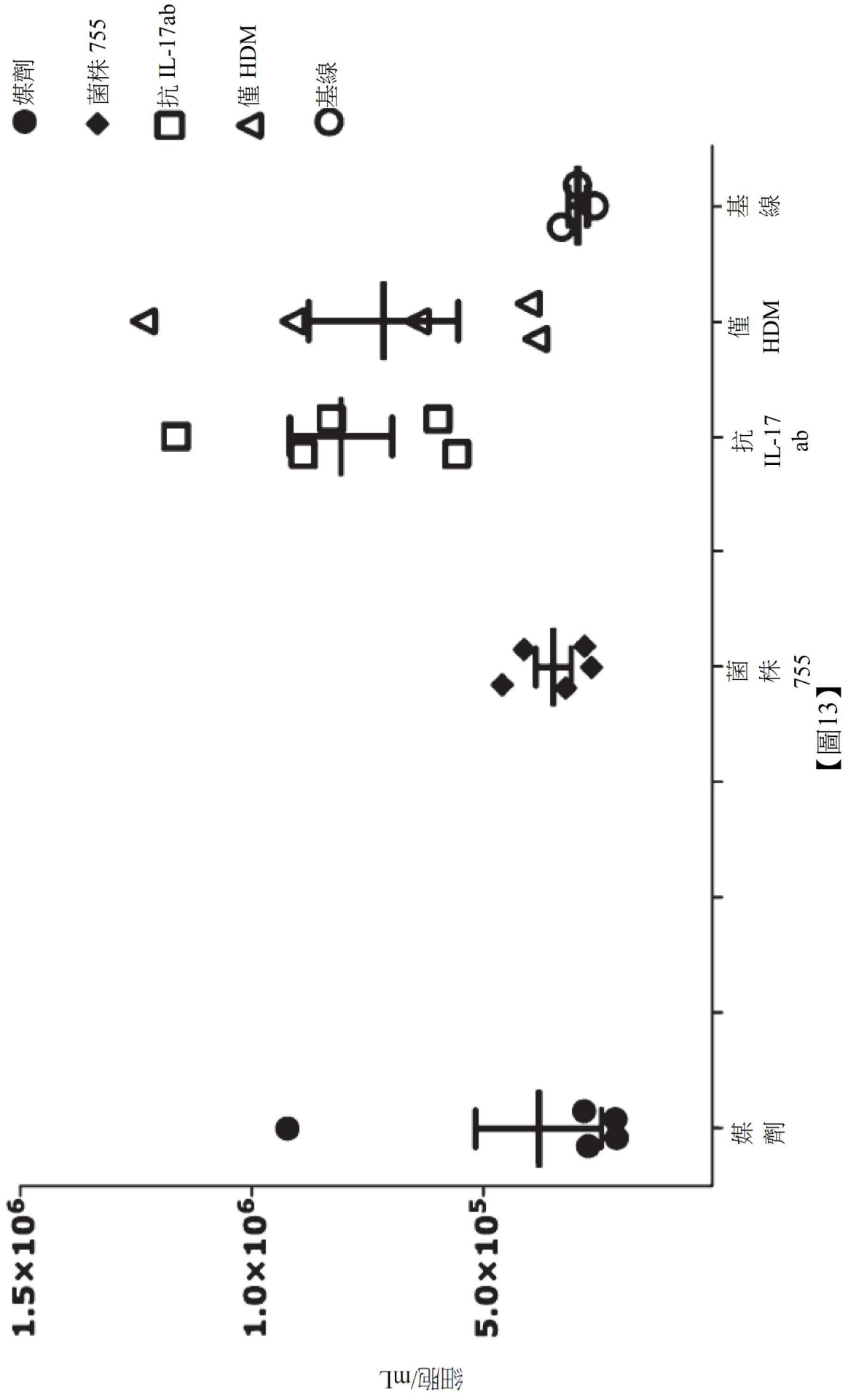
【圖10】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
5×10^5
4×10^5
3×10^5
2×10^5
1×10^5
細胞/mL
媒劑
菌株 755
抗 IL-17 ab
僅 HDM
基線

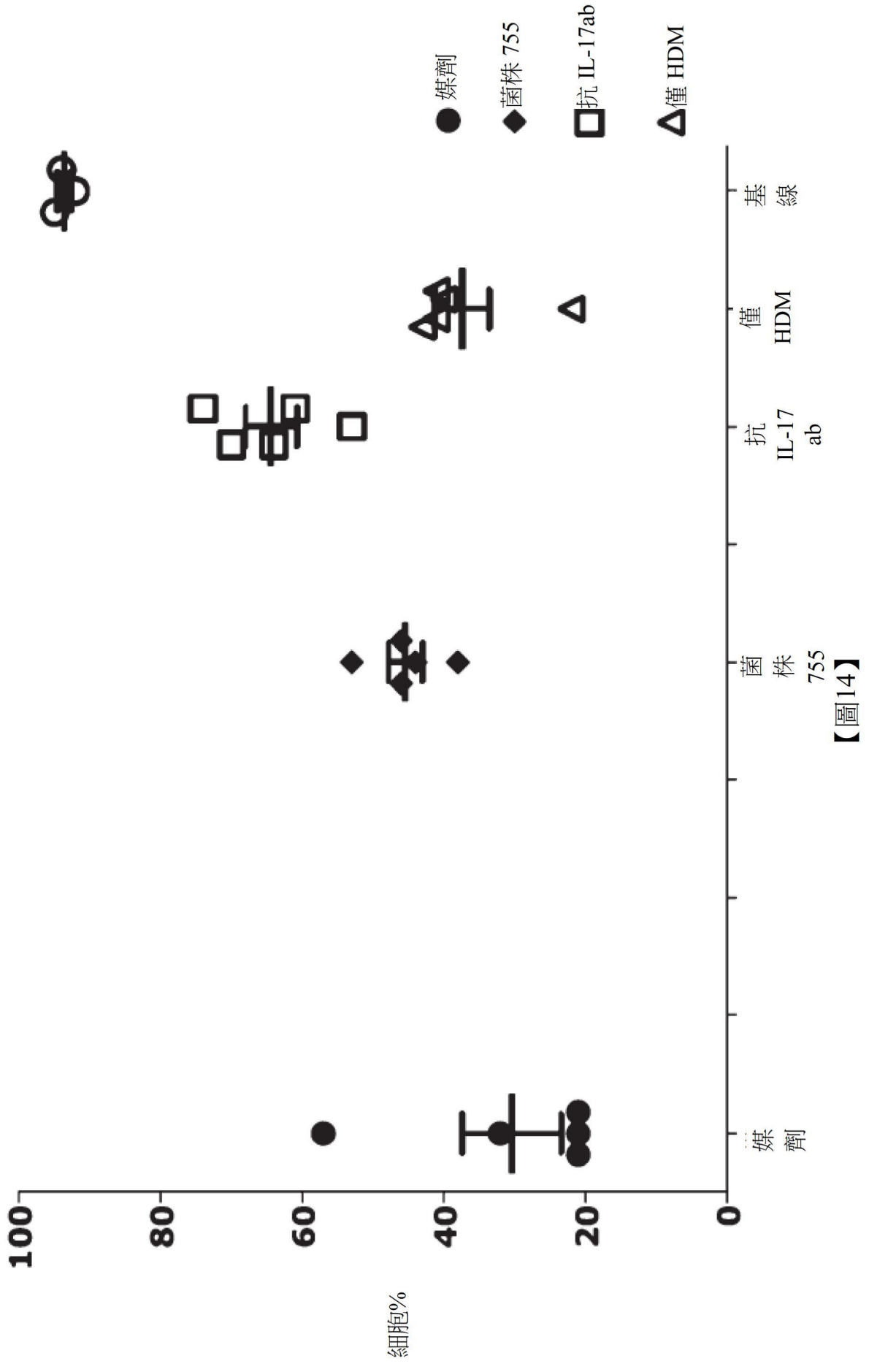
【圖11】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
細胞%
40
30
20
10
0
媒劑
菌株 755
抗 IL-17 ab
僅 HDM
基線

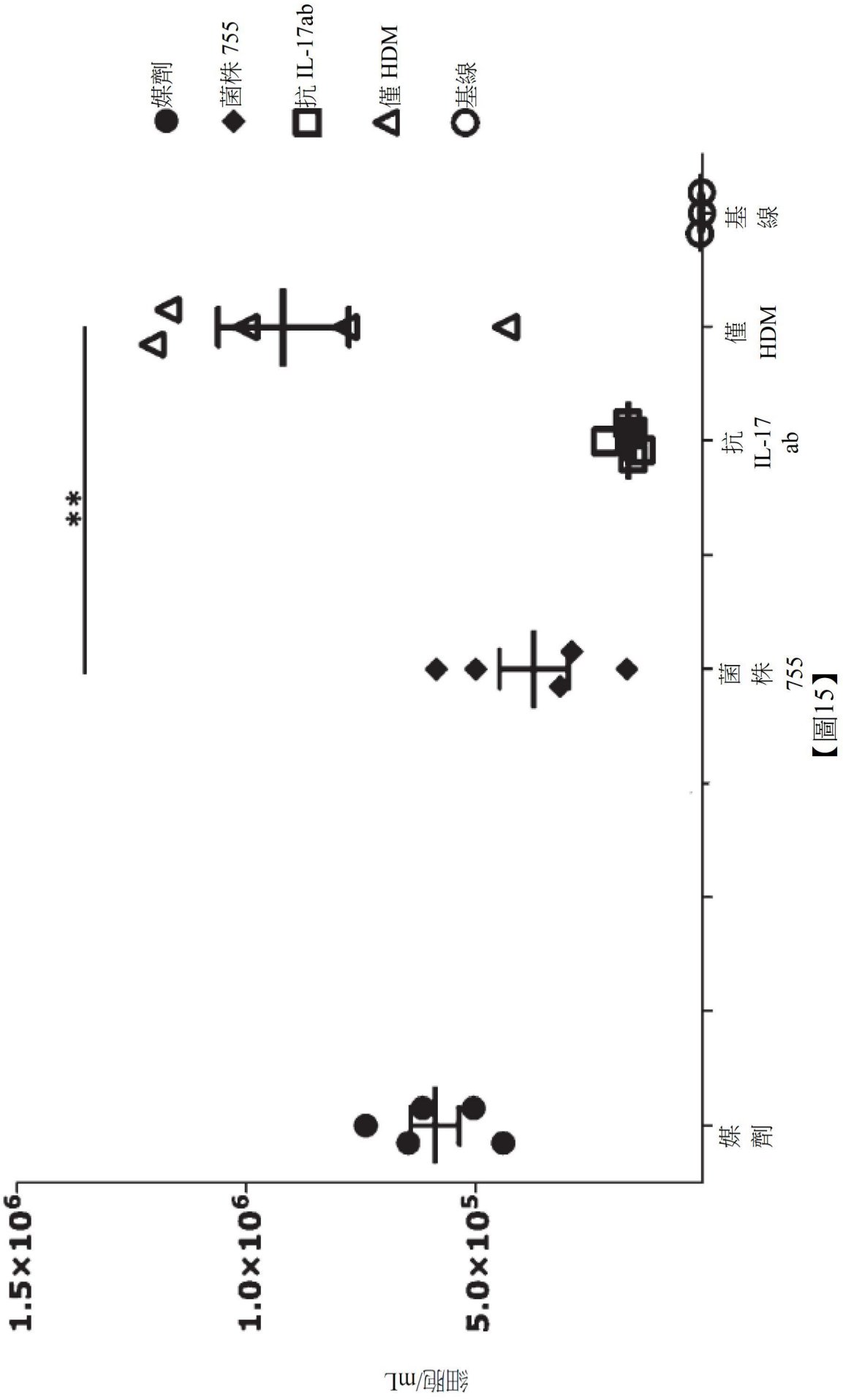
【圖12】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
1.5×10^6
1.0×10^6
5.0×10^5
細胞/mL
媒劑
菌株755
抗IL-17ab
僅HDM
基線

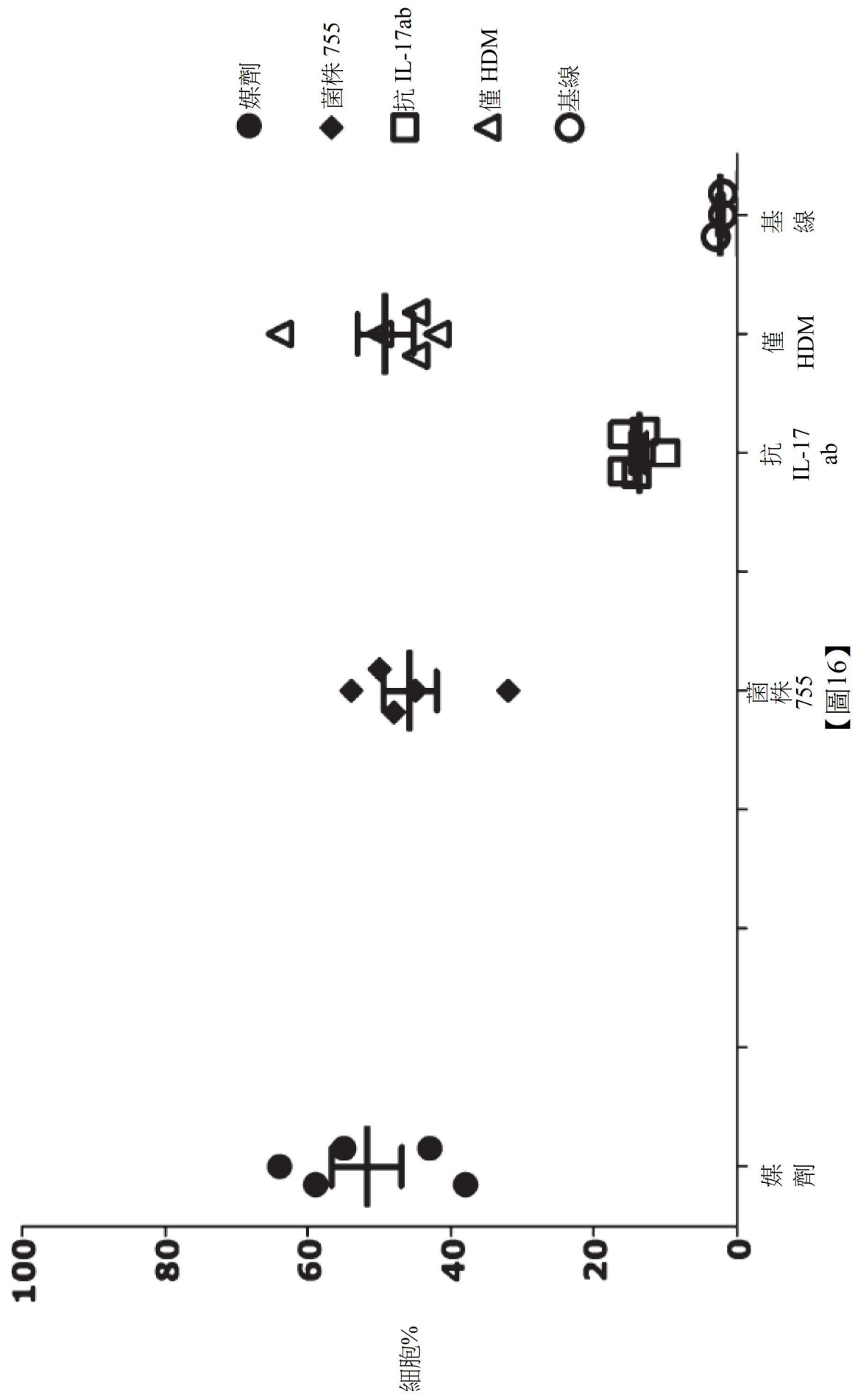
【圖13】


100
80
60
40
20
0
細胞%
媒劑
菌株 755
抗 IL-17 ab
僅 HDM
基線
媒劑
菌株 755
抗 IL-17ab
僅 HDM

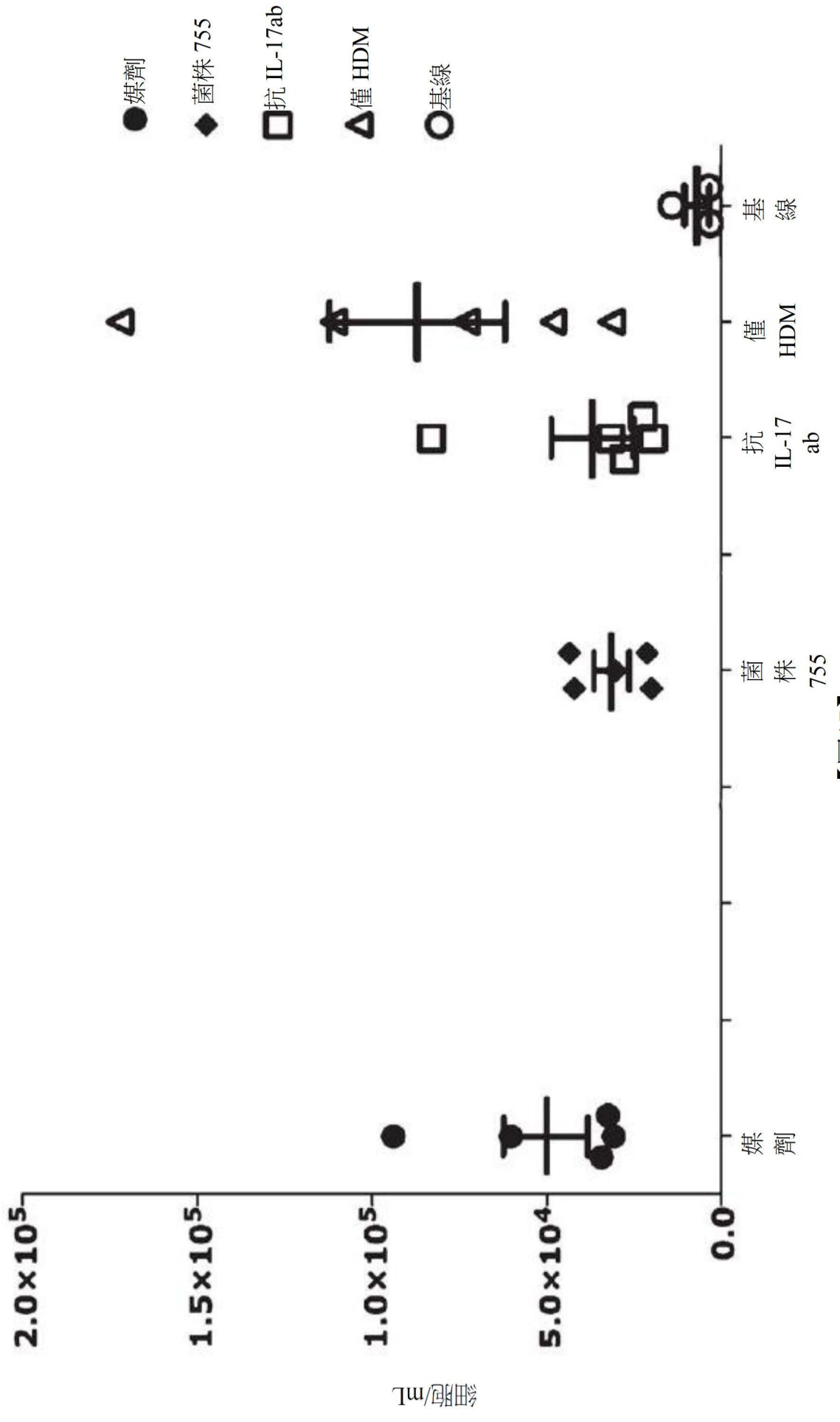
【圖14】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
**
1.5×10^6
1.0×10^6
5.0×10^5
細胞/mL
媒劑
菌株 755
抗 IL-17 ab
僅 HDM
基線

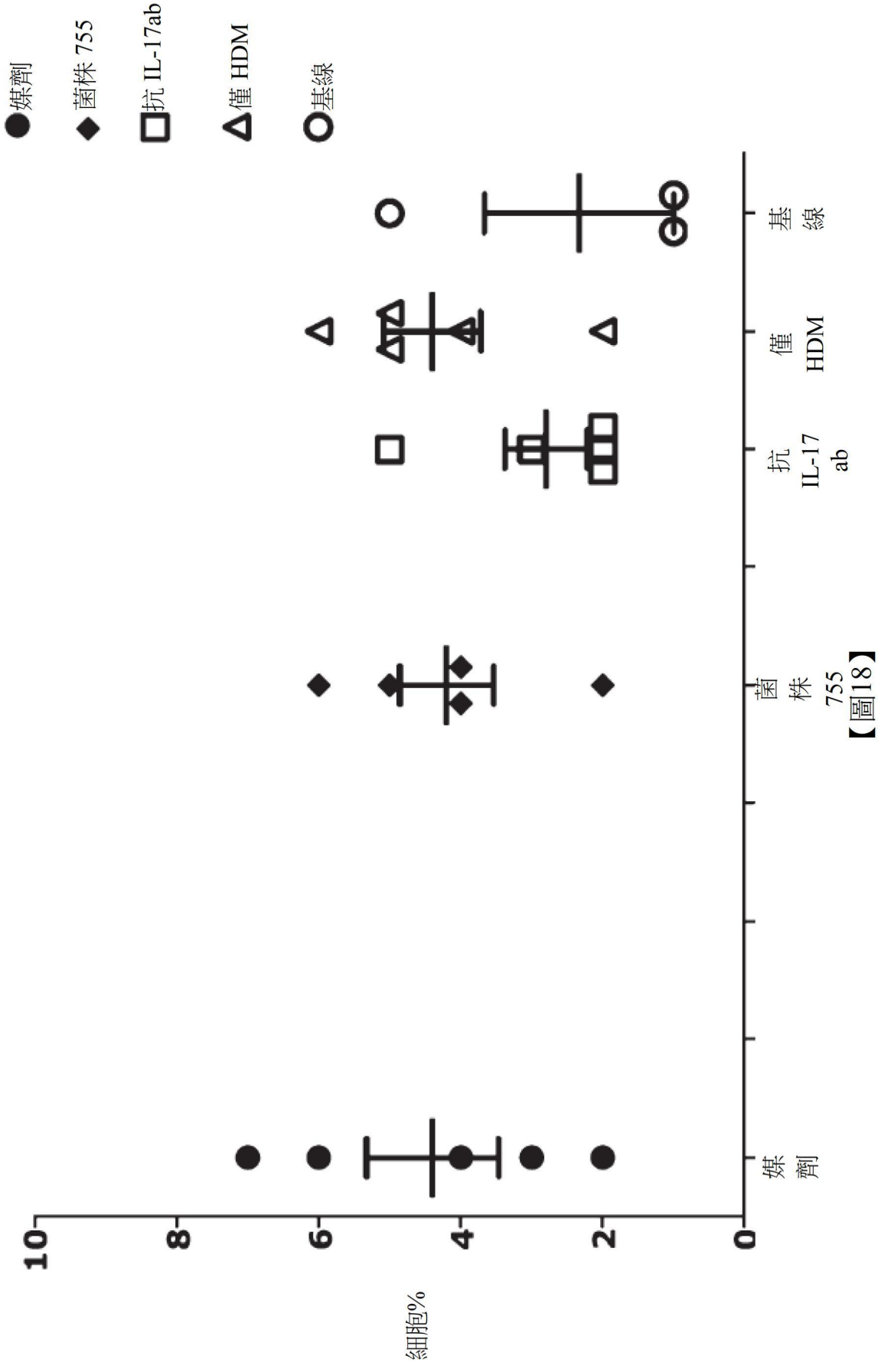
【圖15】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
細胞%
100
80
60
40
20
0
媒劑
菌株755
抗IL-17 ab
僅HDM
基線

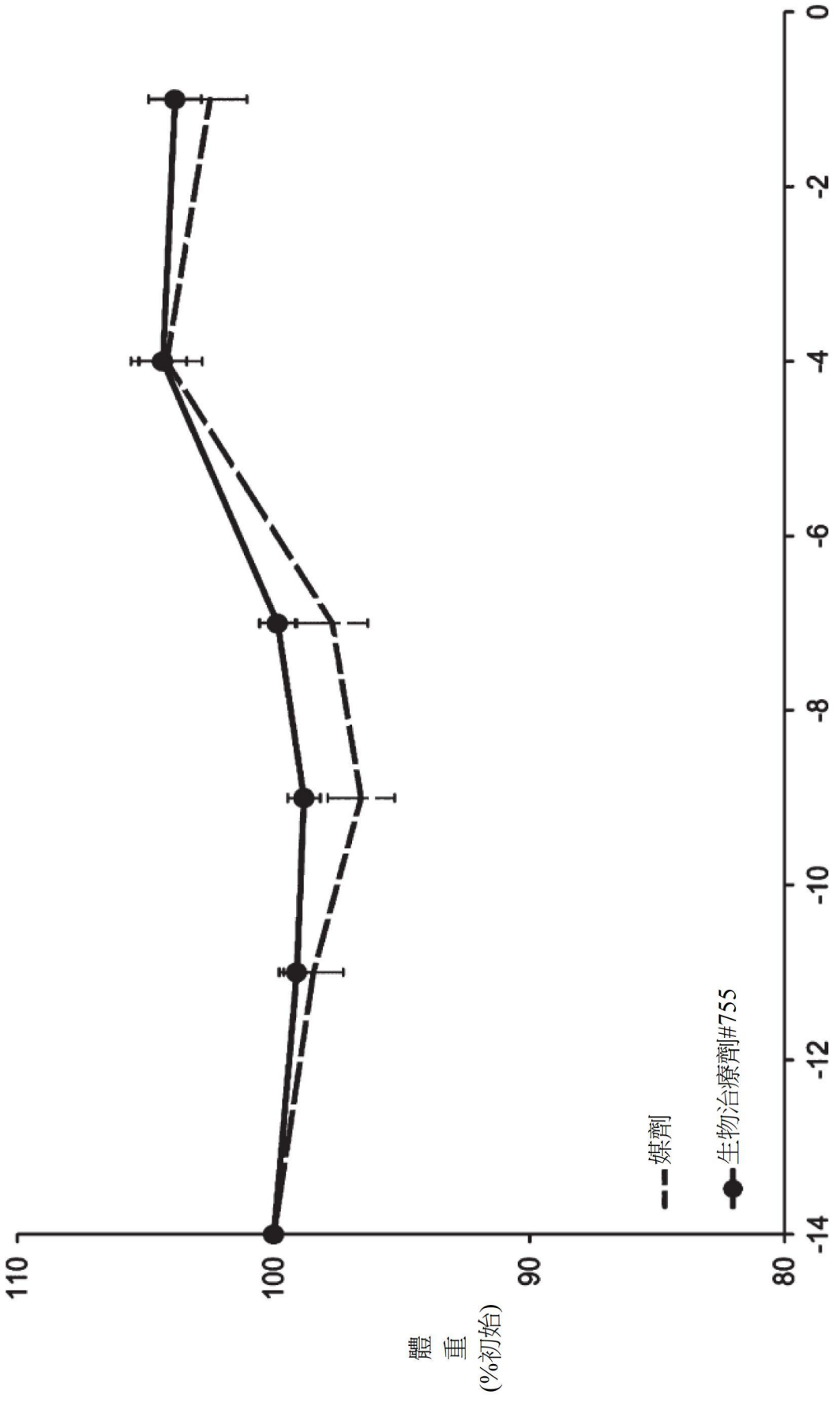
【圖16】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
細胞/mL
2.0×10^5
1.5×10^5
1.0×10^5
5.0×10^4
0.0
媒劑
菌株 755
抗 IL-17 ab
僅 HDM
基線

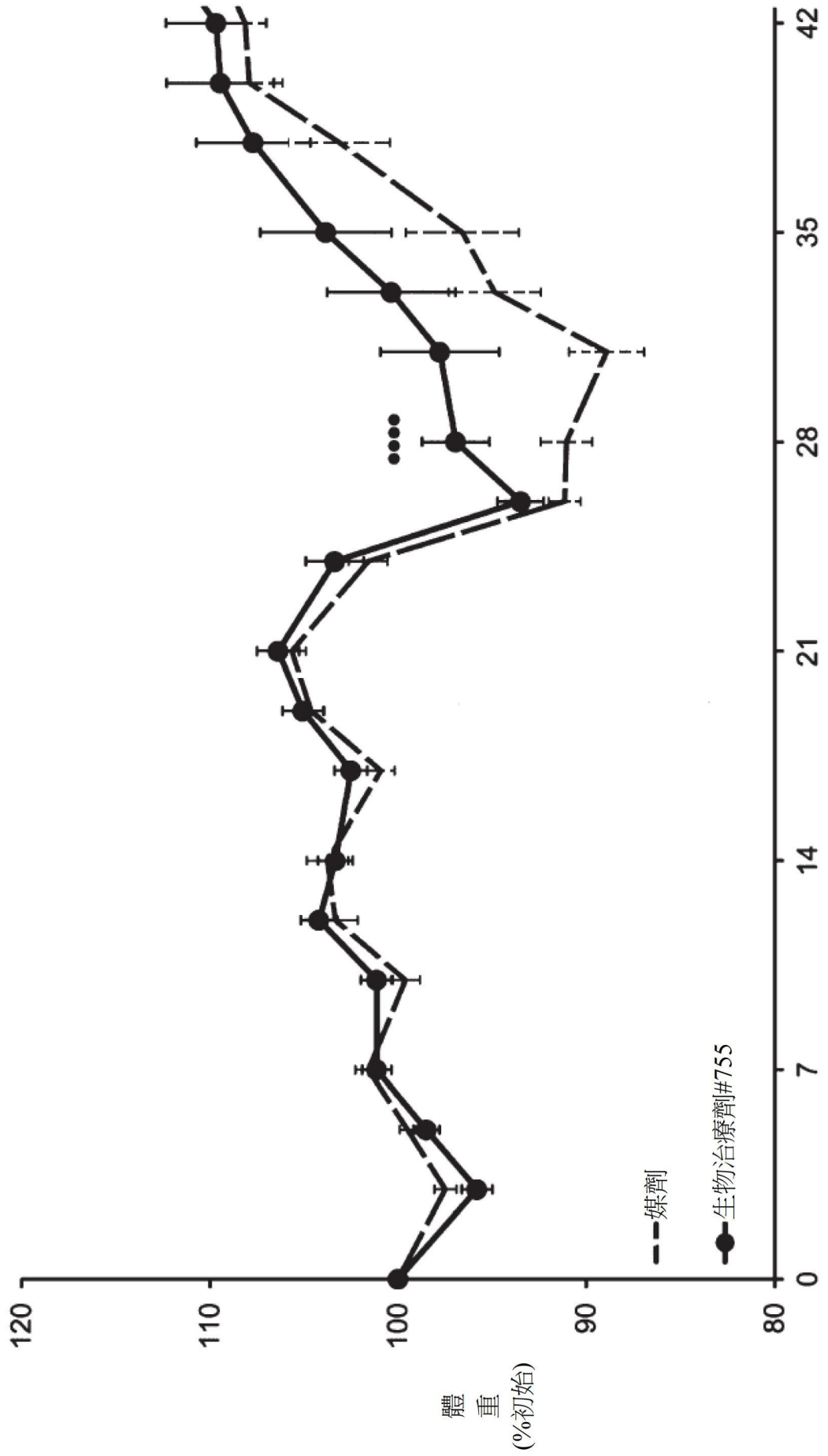
【圖17】



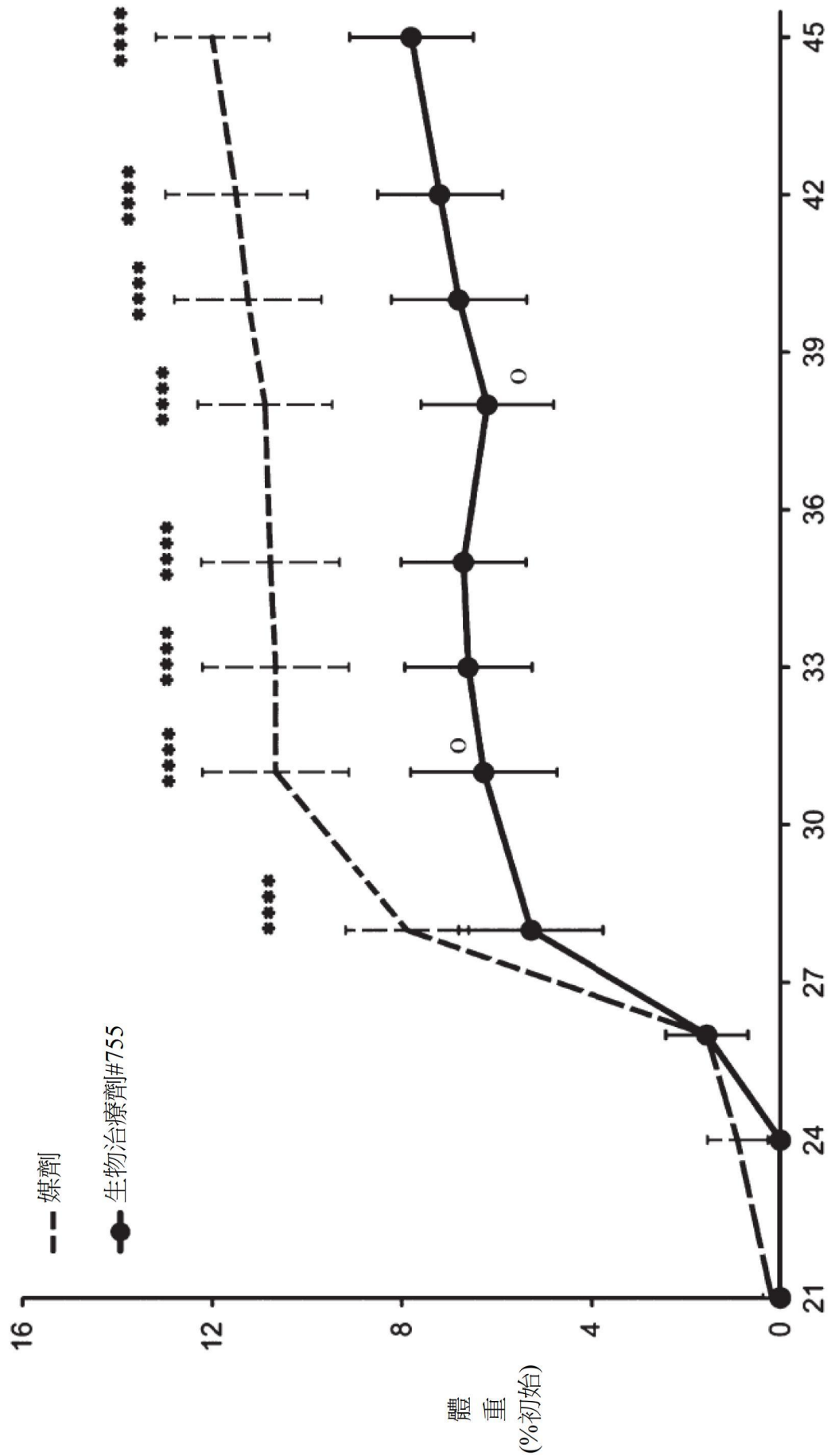
【圖18】



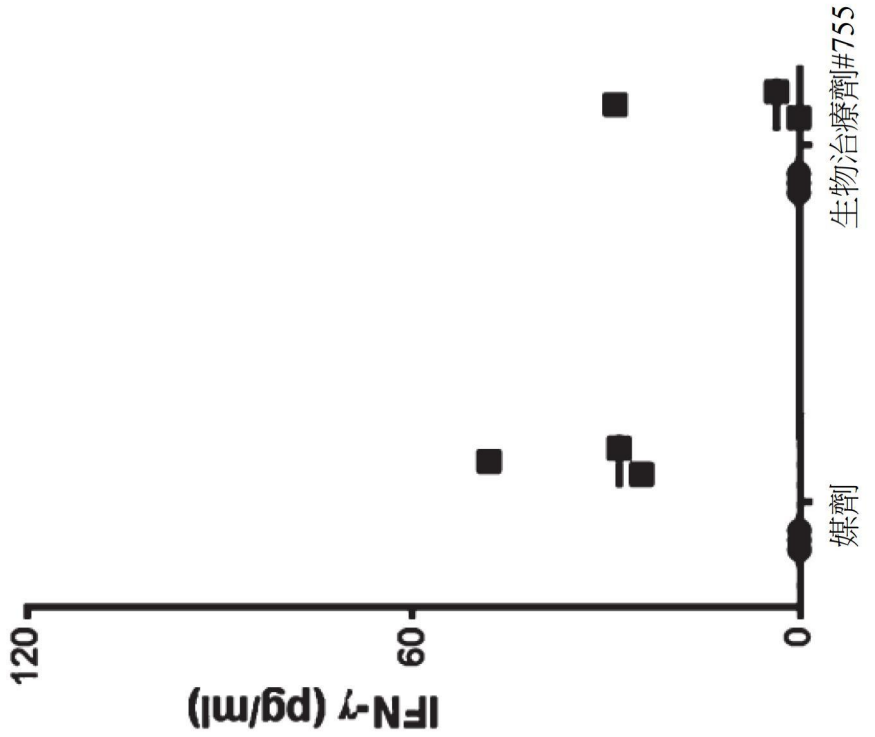
【圖19】



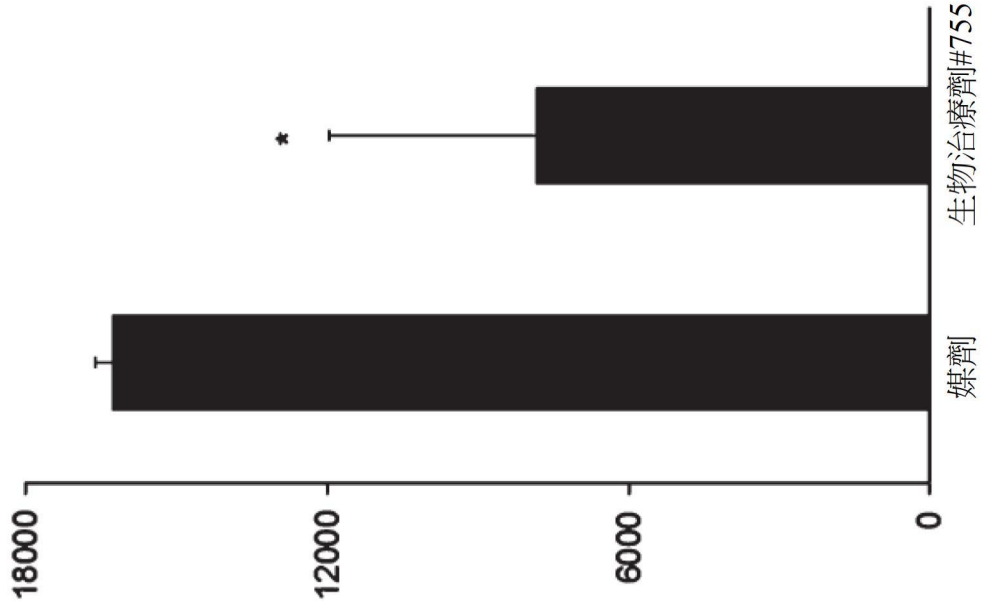
【圖20】



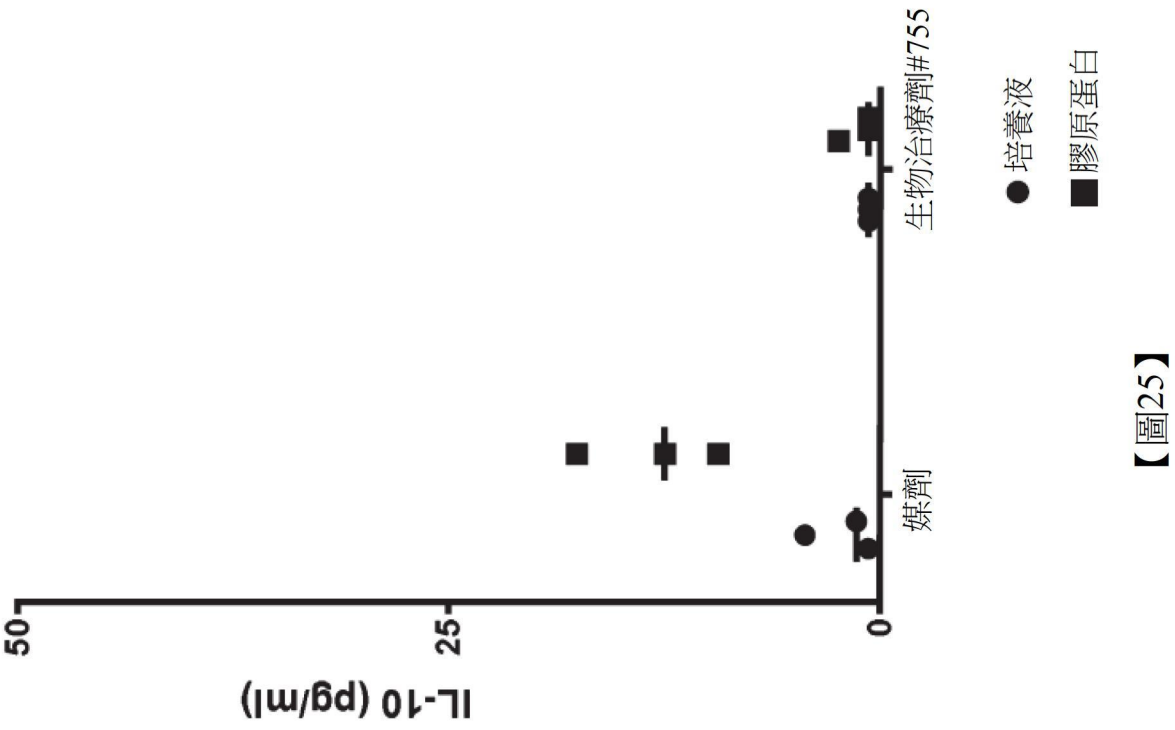
【圖21】


IFN-γ (pg/ml)
120
60
0
媒劑
生物治療劑#755
●培養液
■膠原蛋白

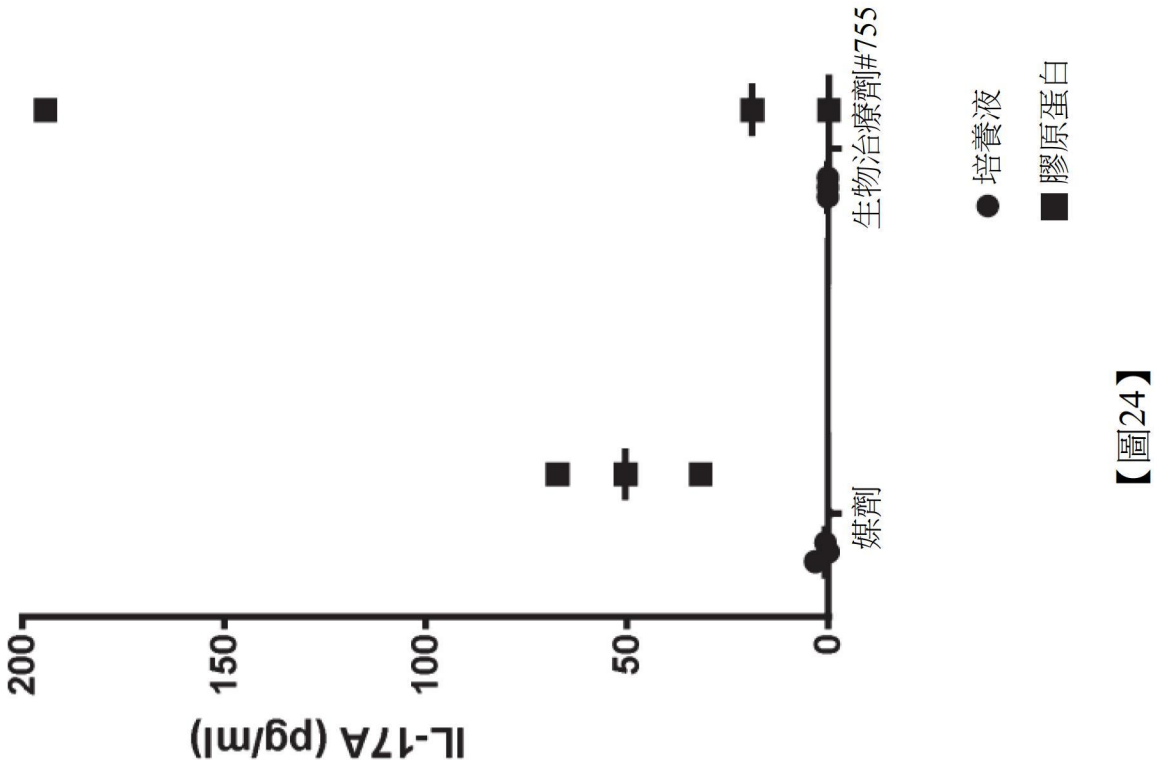
【圖23】


18000
12000
6000
0
*
媒劑
生物治療劑#755

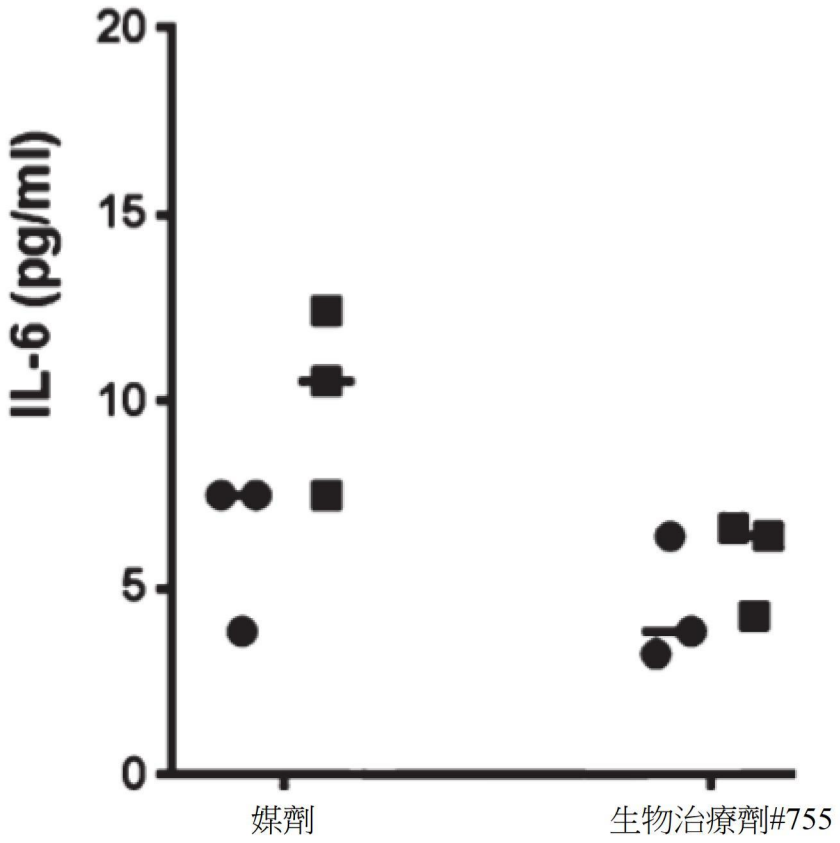
【圖22】


IL-10 (pg/ml)
50
25
0
媒劑
生物治療劑#755
●培養液
■膠原蛋白

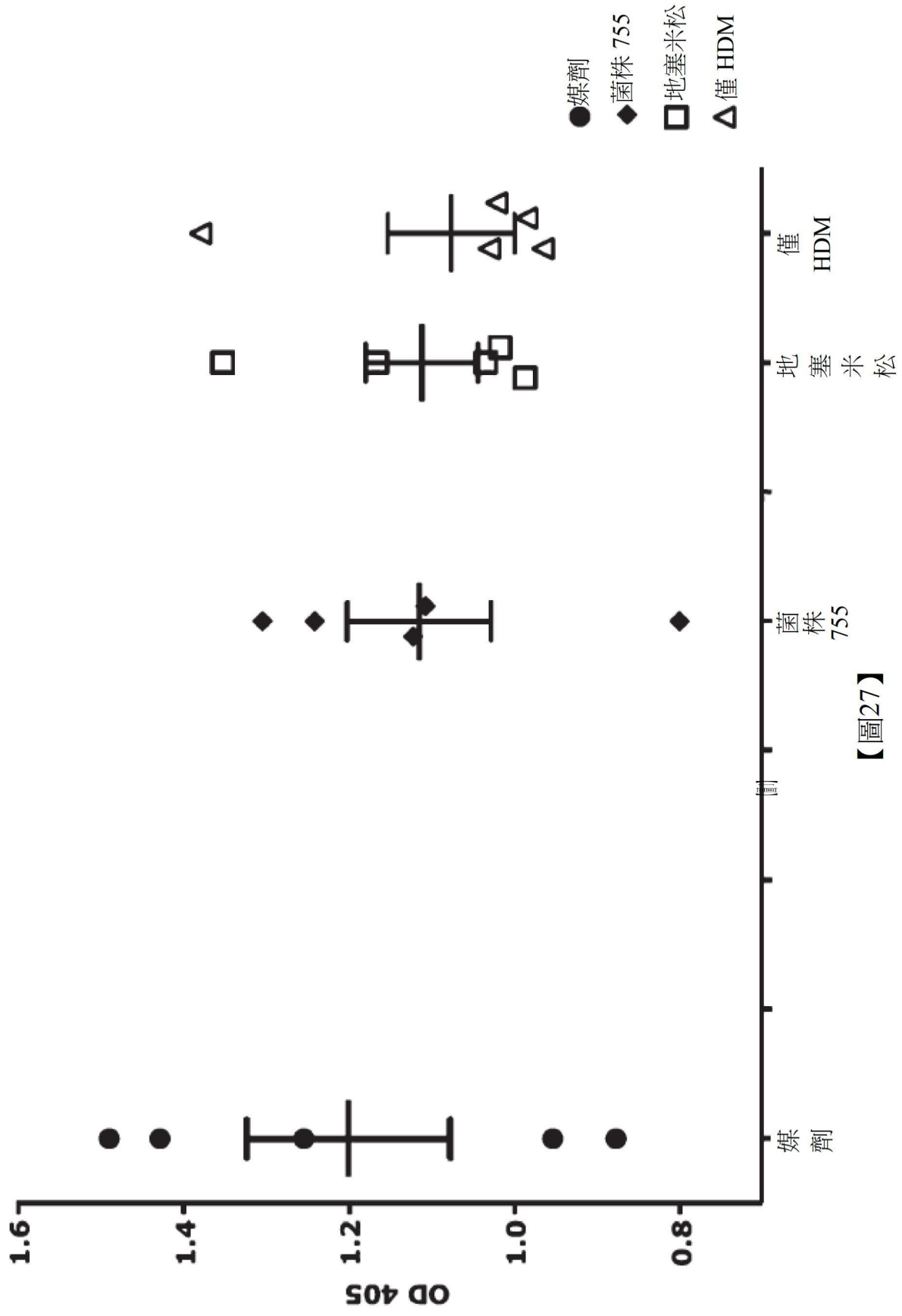
【圖25】


IL-17A (pg/ml)
200
150
100
50
0
媒劑
生物治療劑#755
●培養液
■膠原蛋白

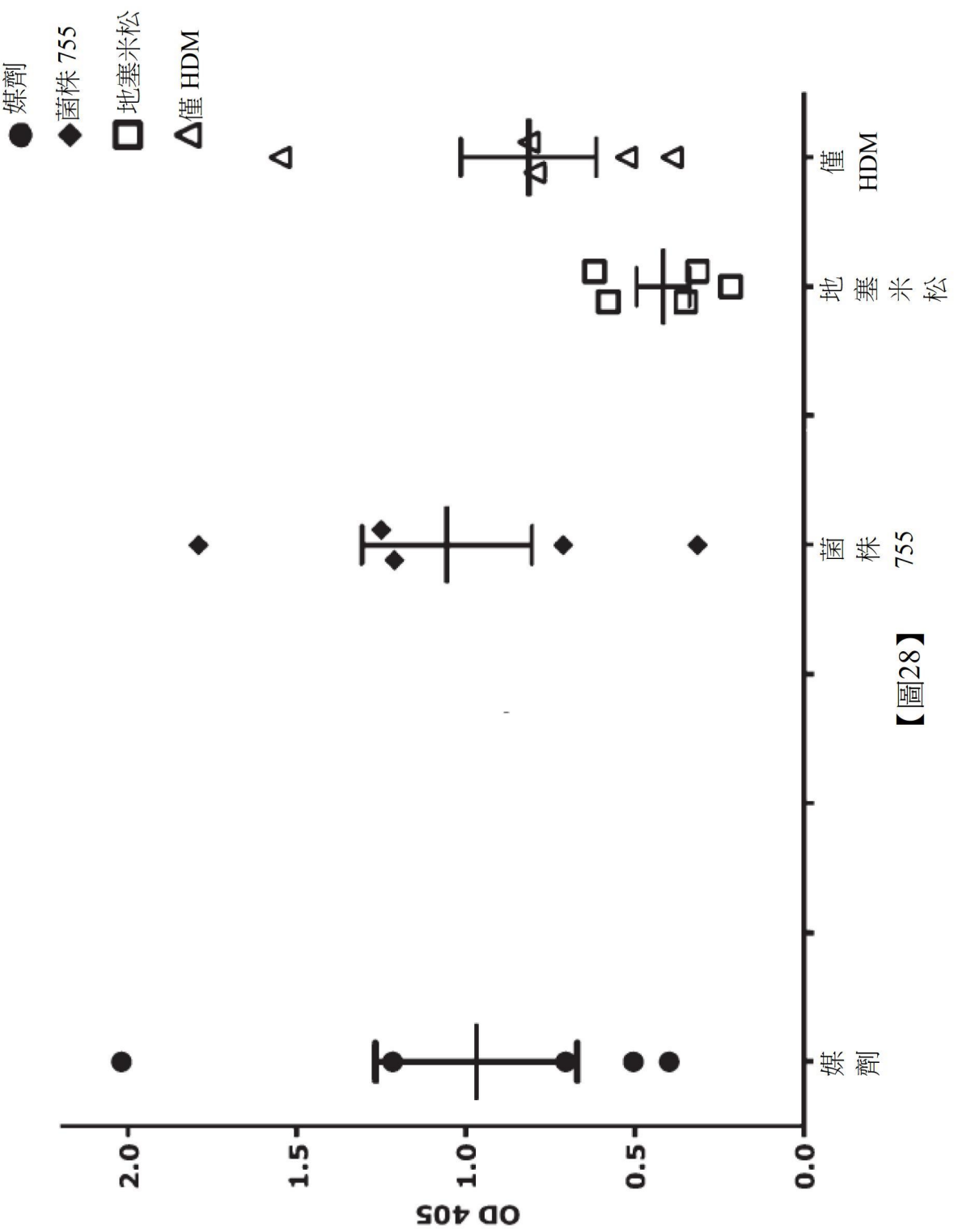
【圖24】



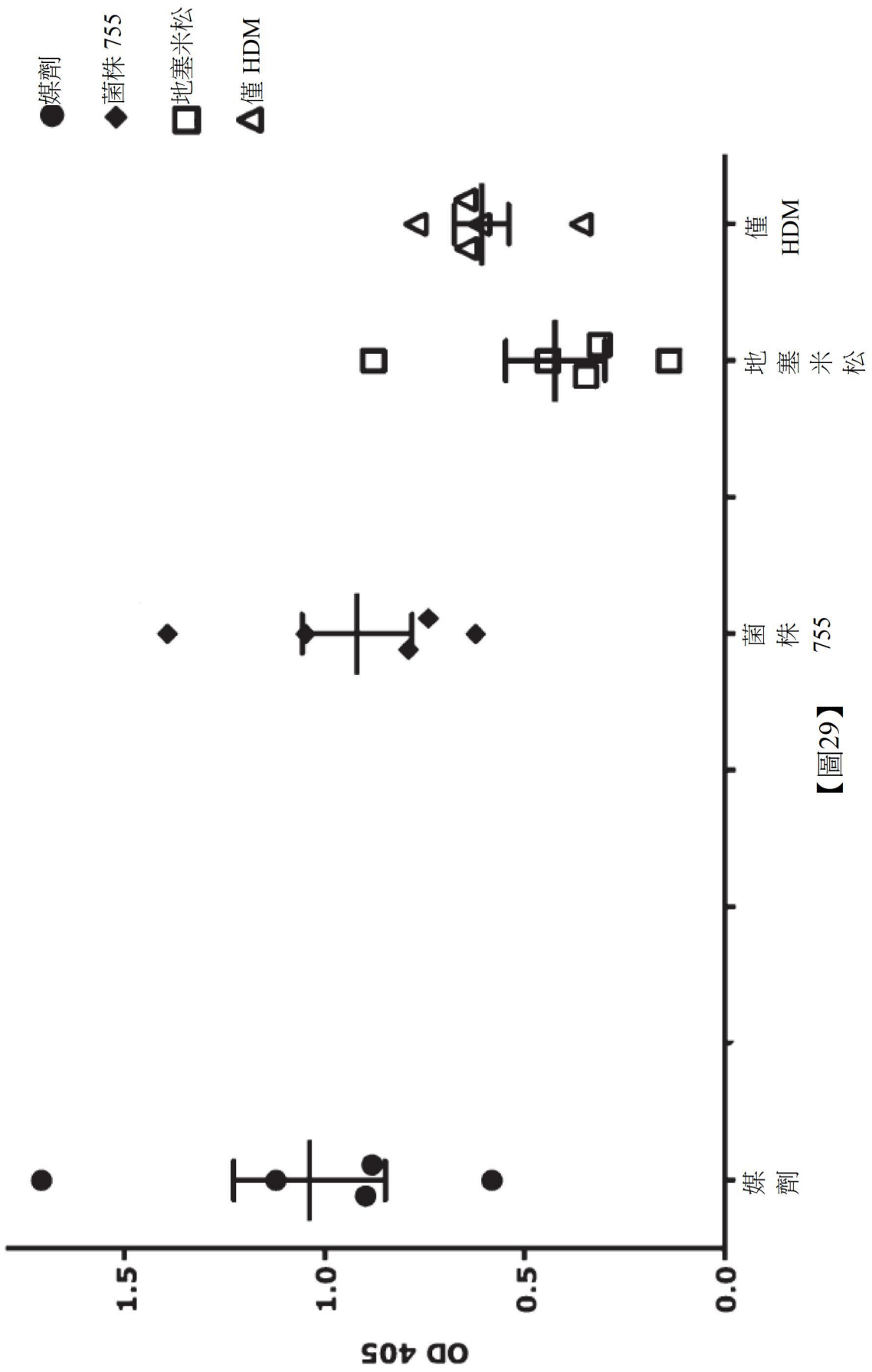
【圖26】



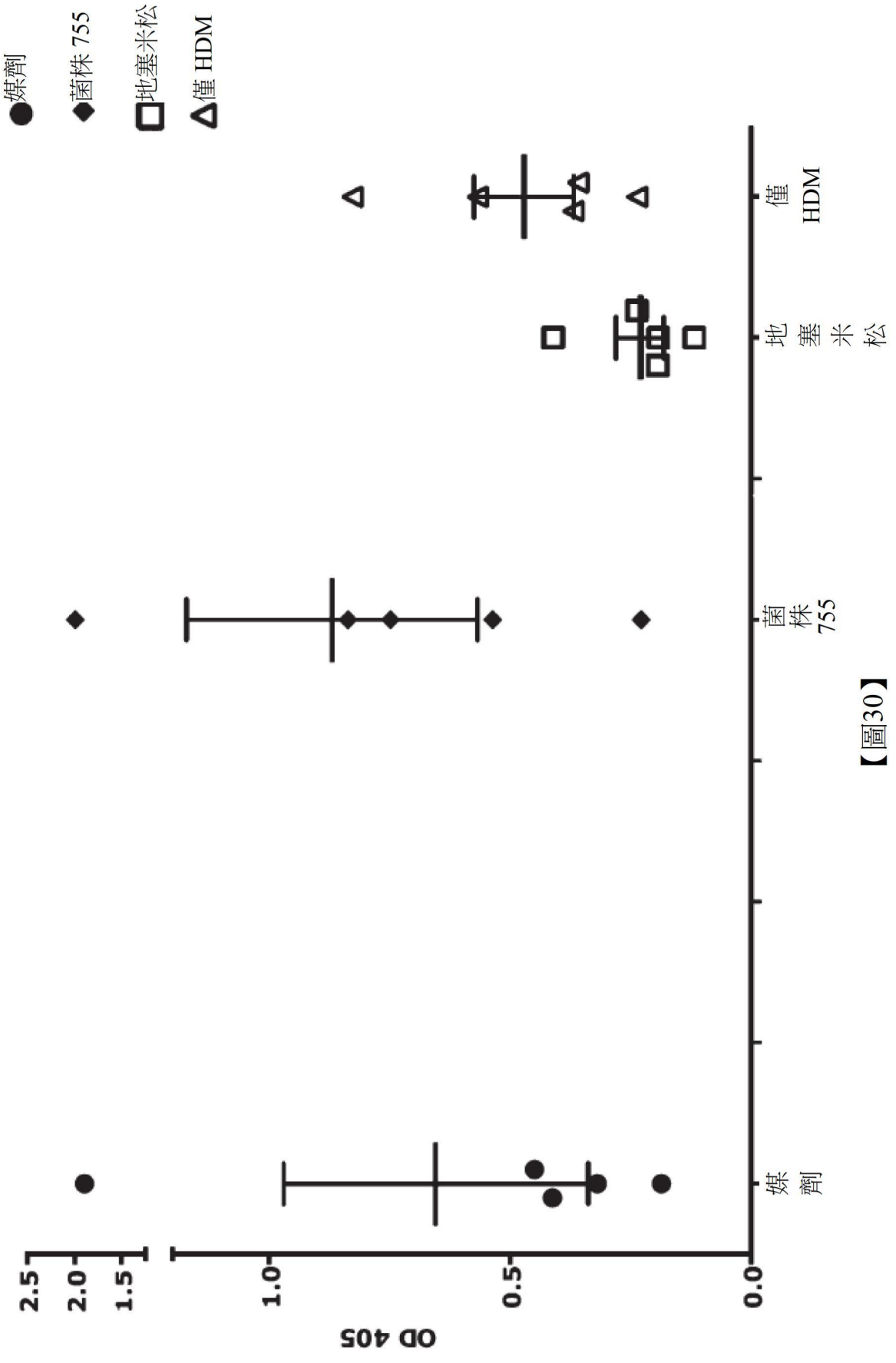
【圖27】



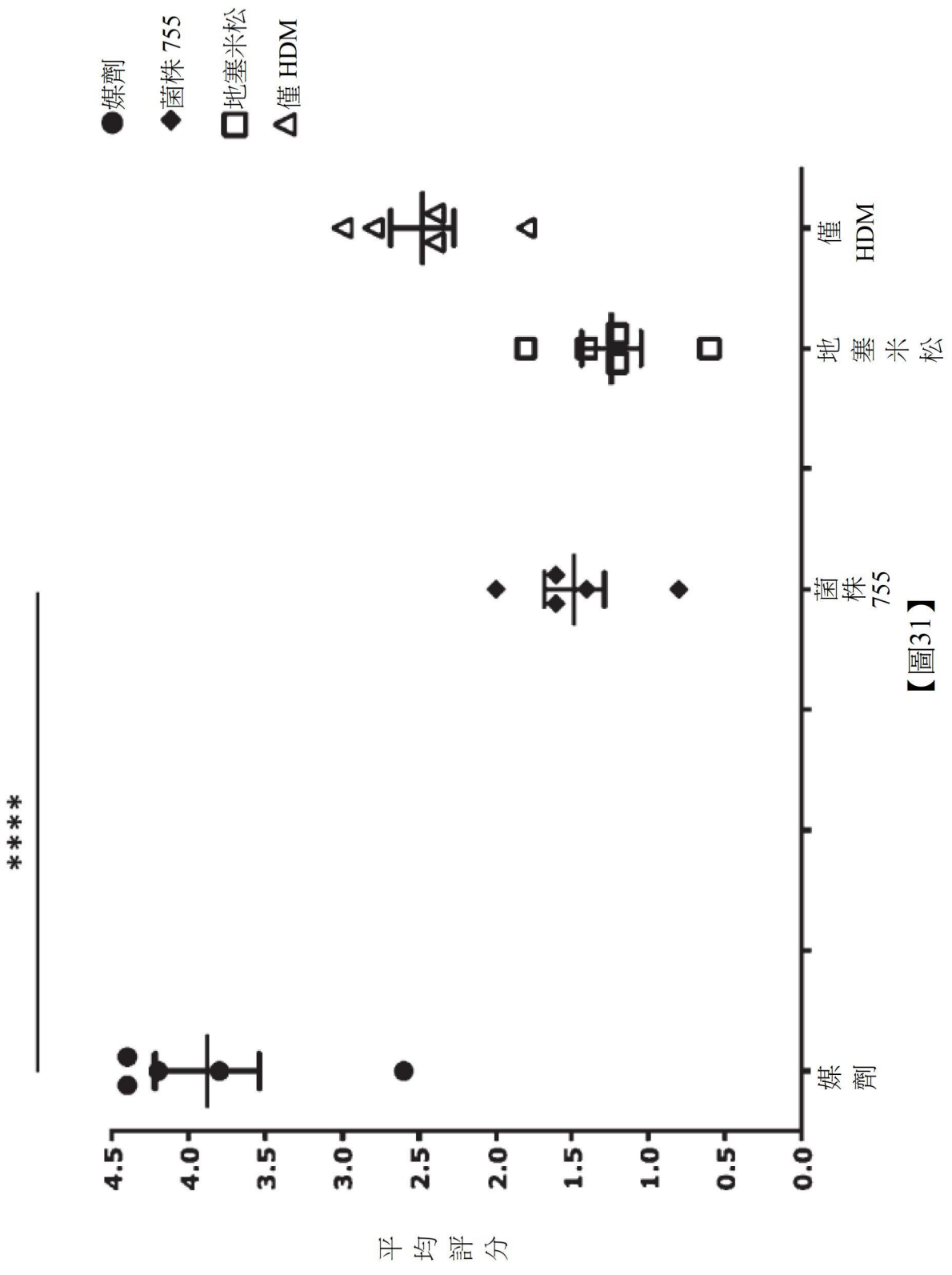
【圖28】



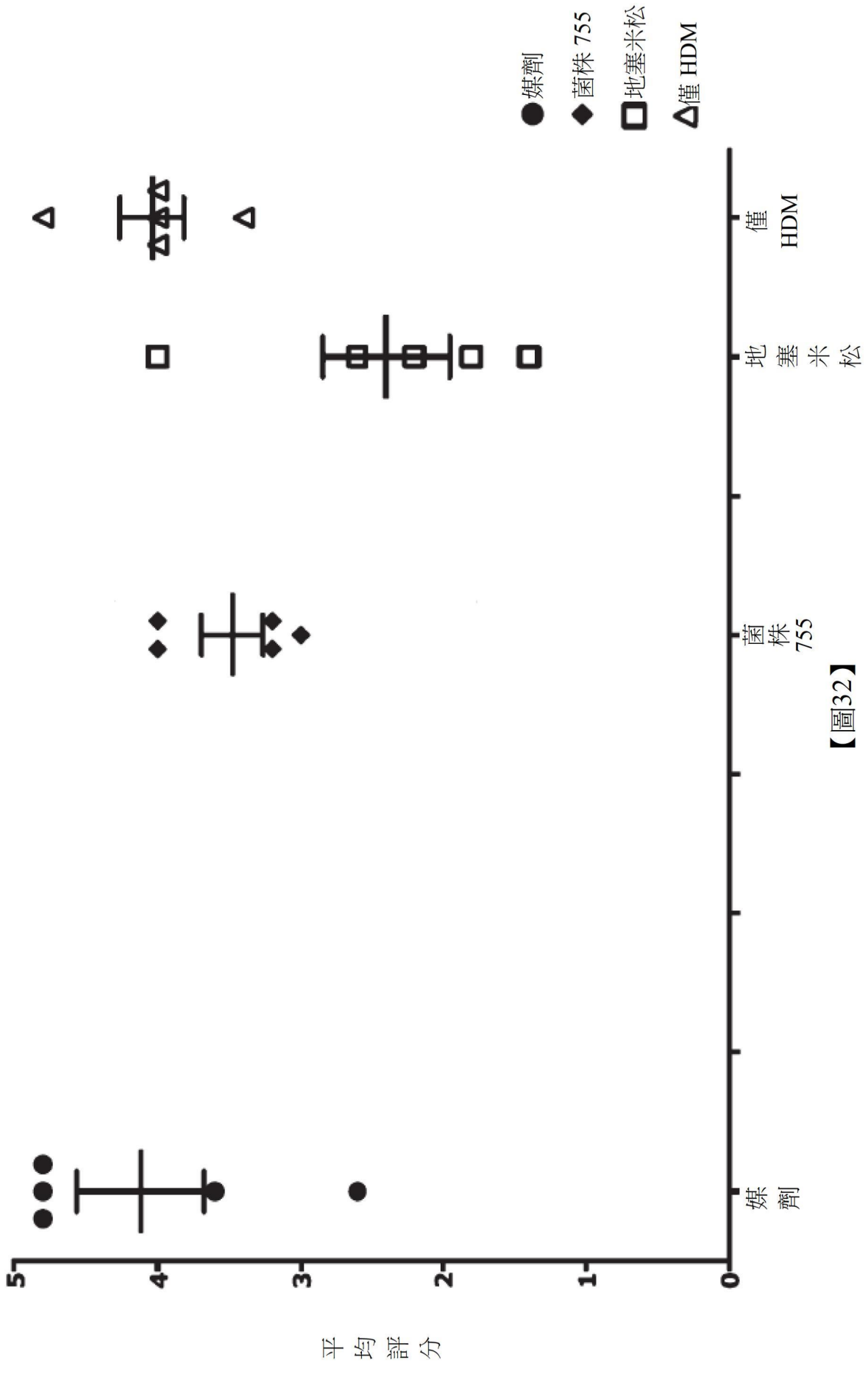
【圖29】



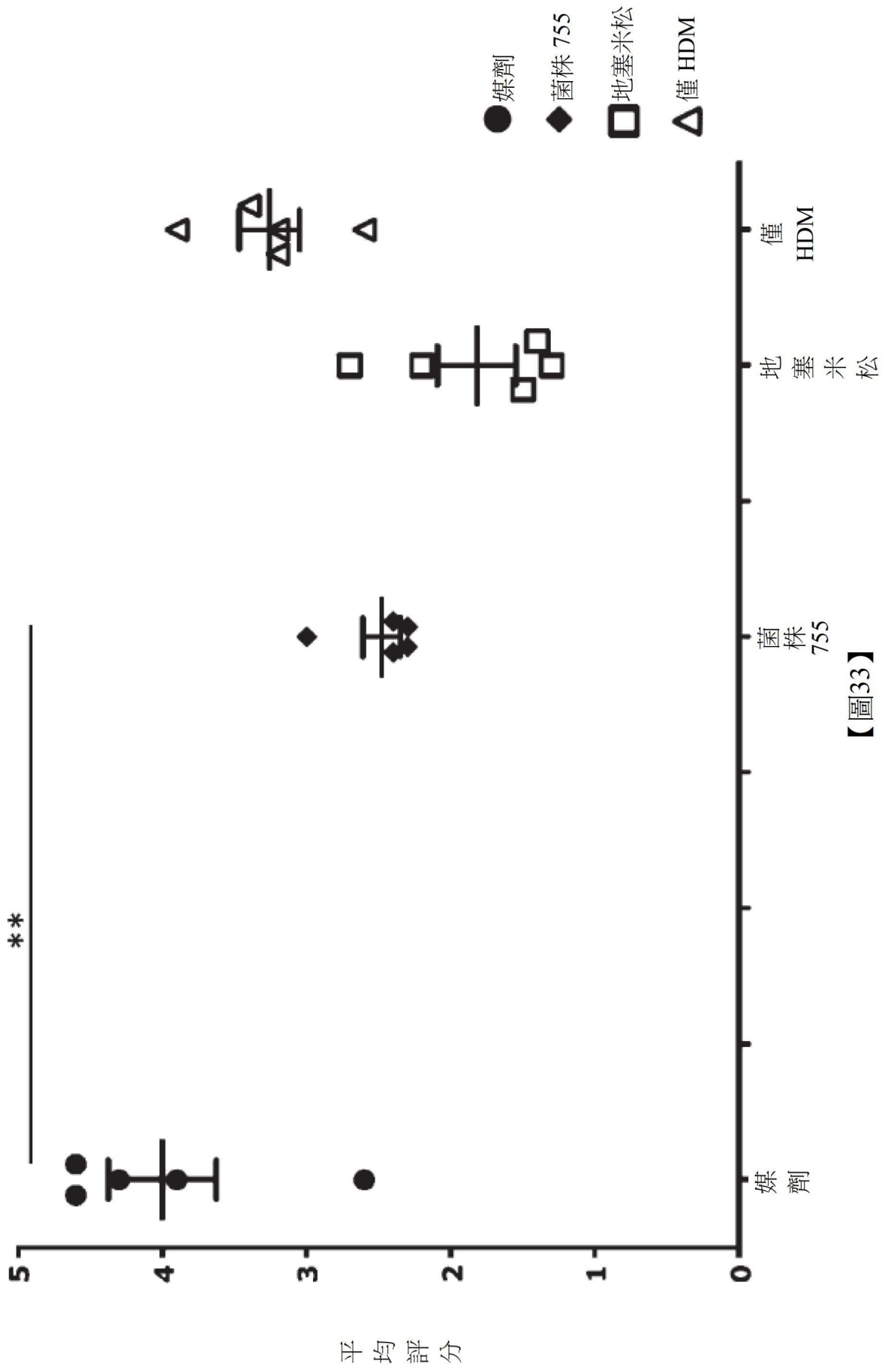
【圖30】


●媒劑
◆菌株 755
□地塞米松
△僅 HDM
****
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
平均評分
媒劑
菌株755
地塞米松
僅HDM

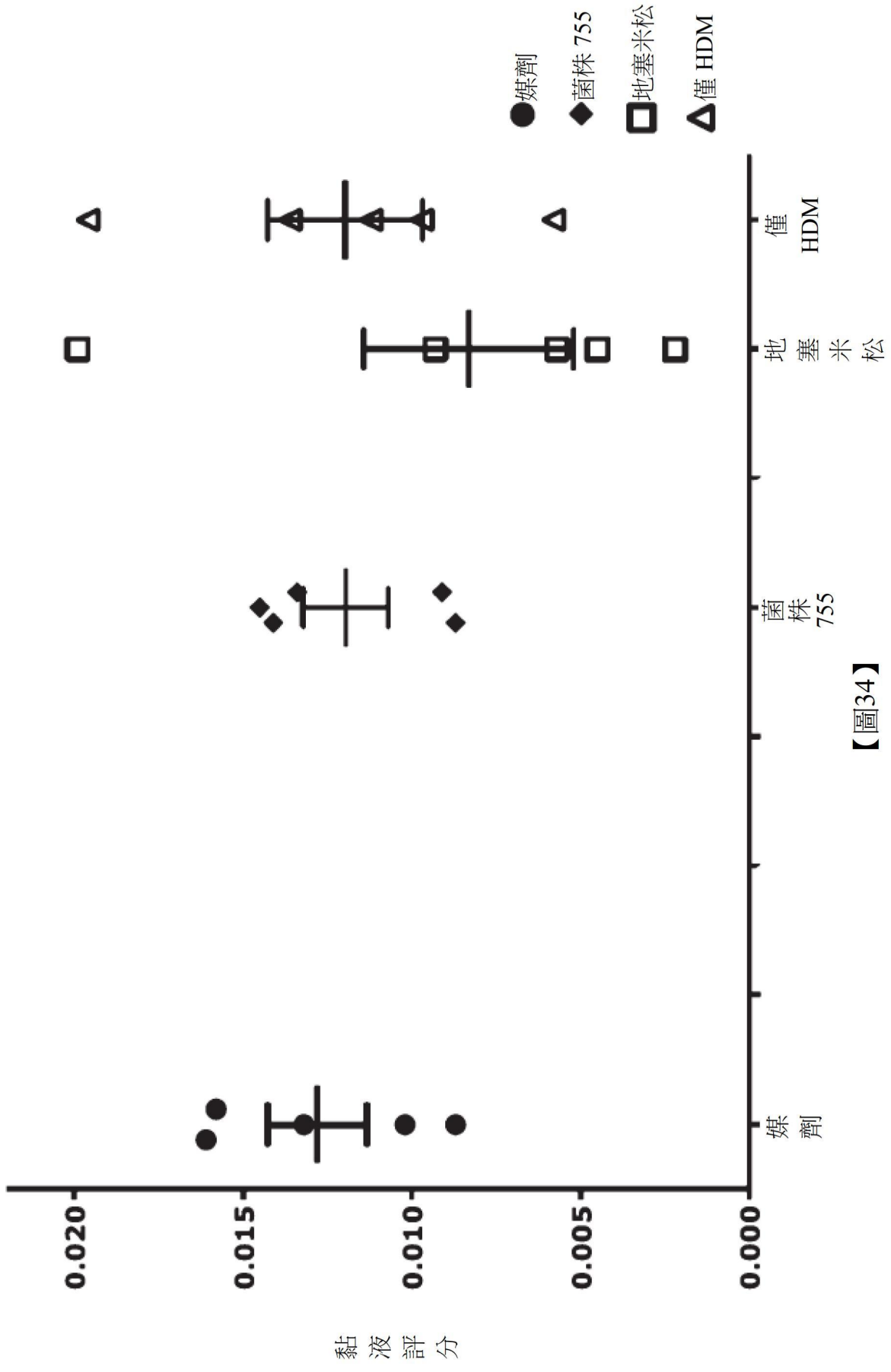
【圖31】



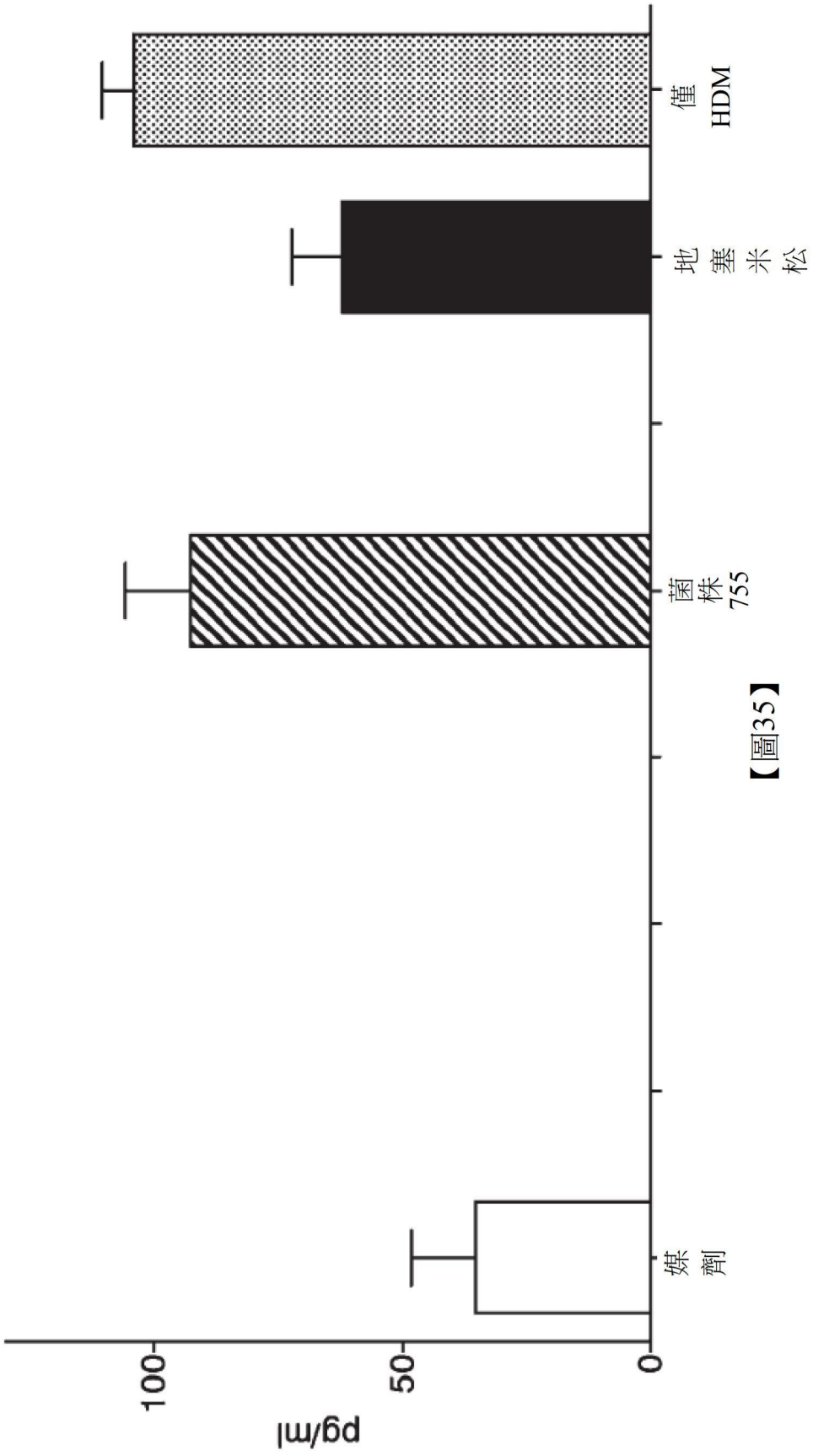
【圖32】



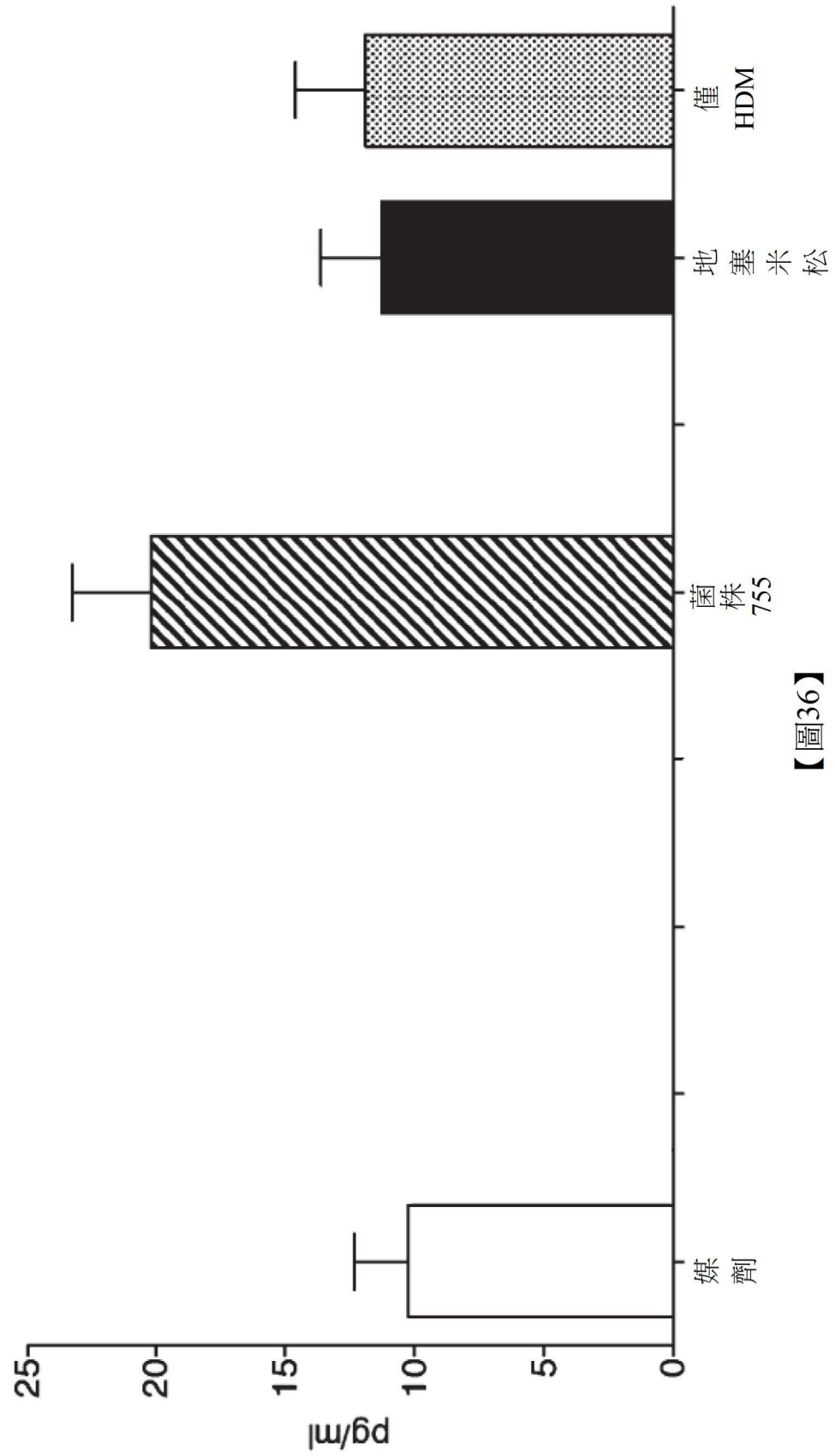
【圖33】


●媒劑
◆菌株 755
□地塞米松
△僅 HDM
黏液評分
0.020
0.015
0.010
0.005
0.000
媒劑
菌株755
地塞米松
僅HDM

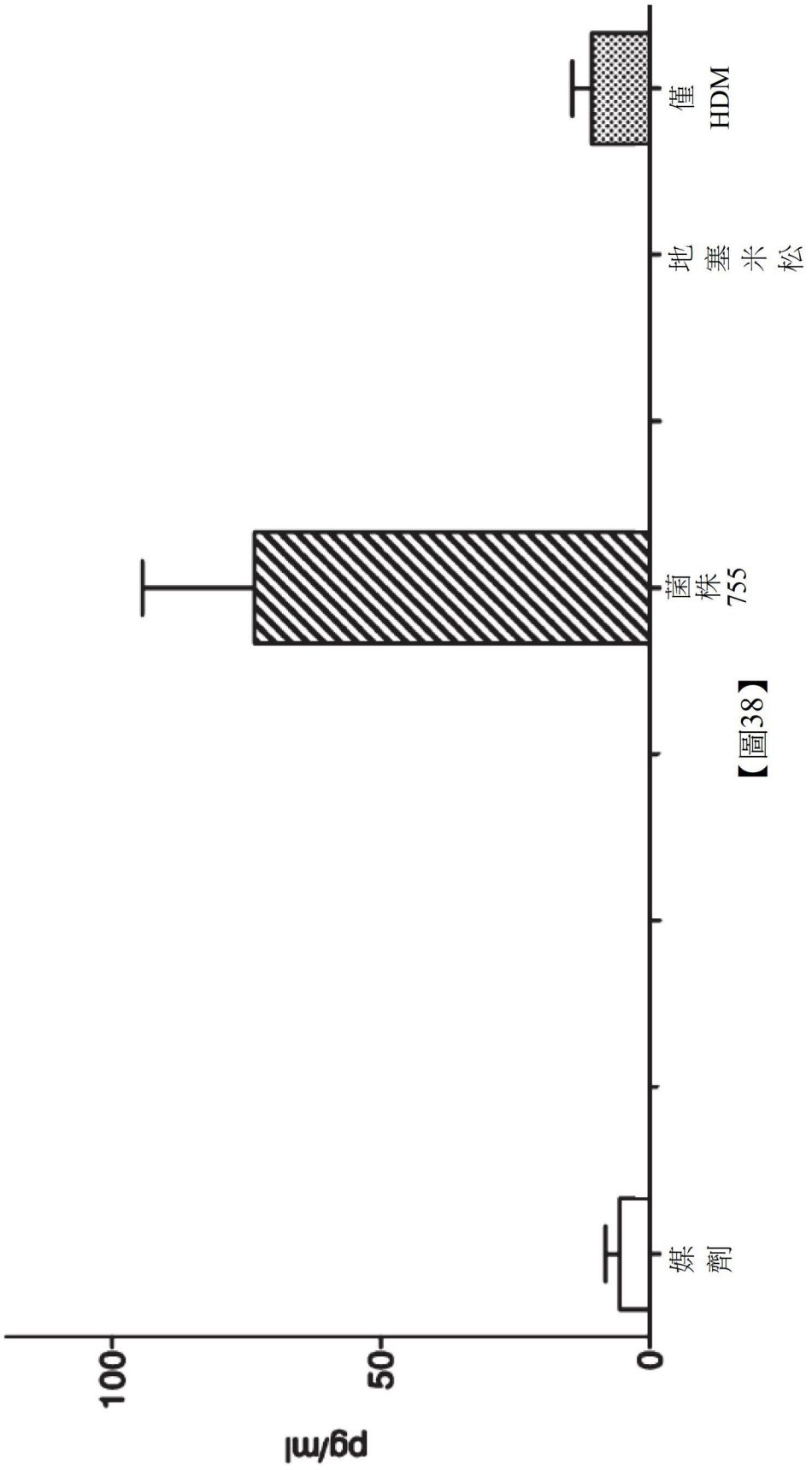
【圖34】



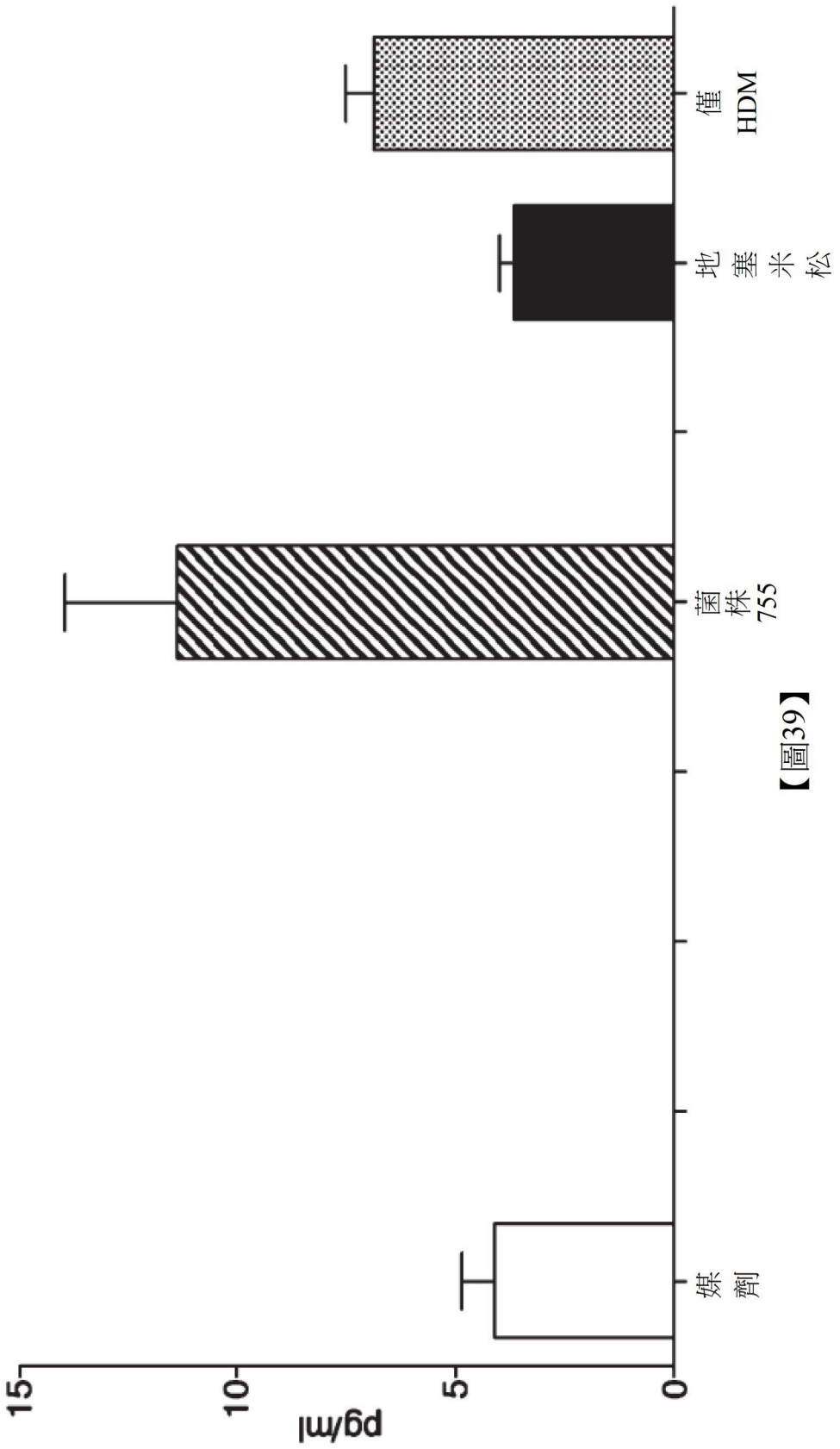
【圖35】



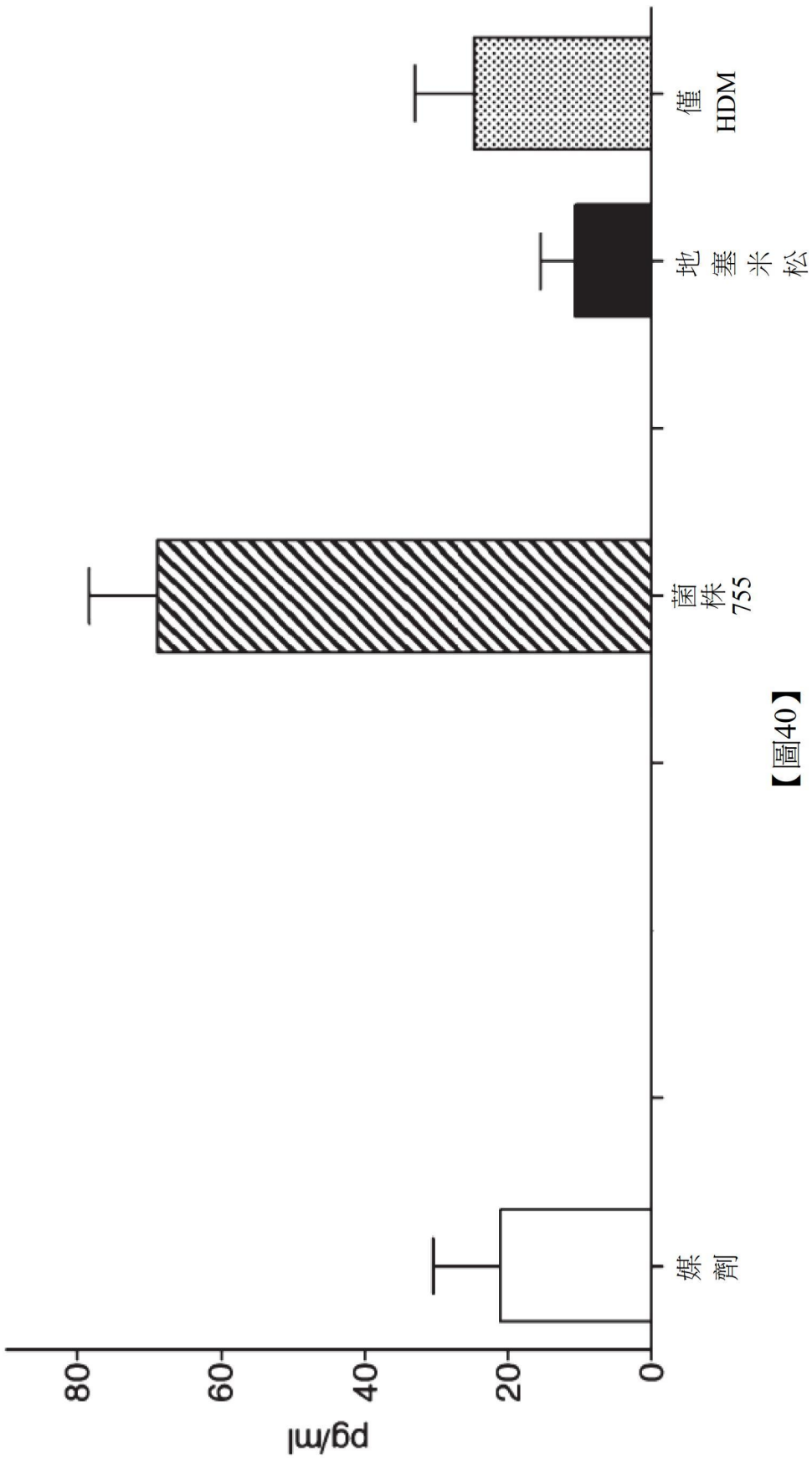
【圖36】



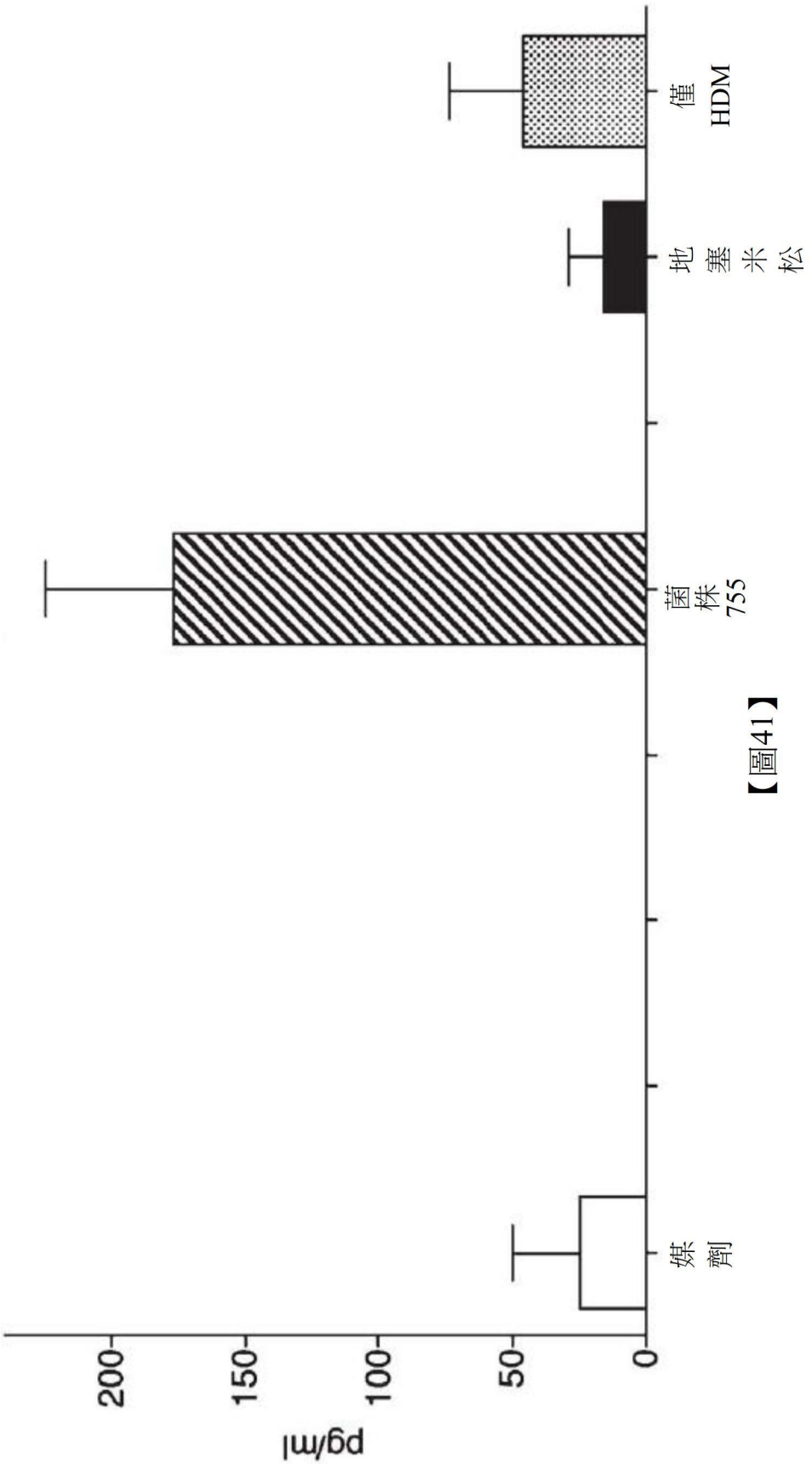
【圖38】



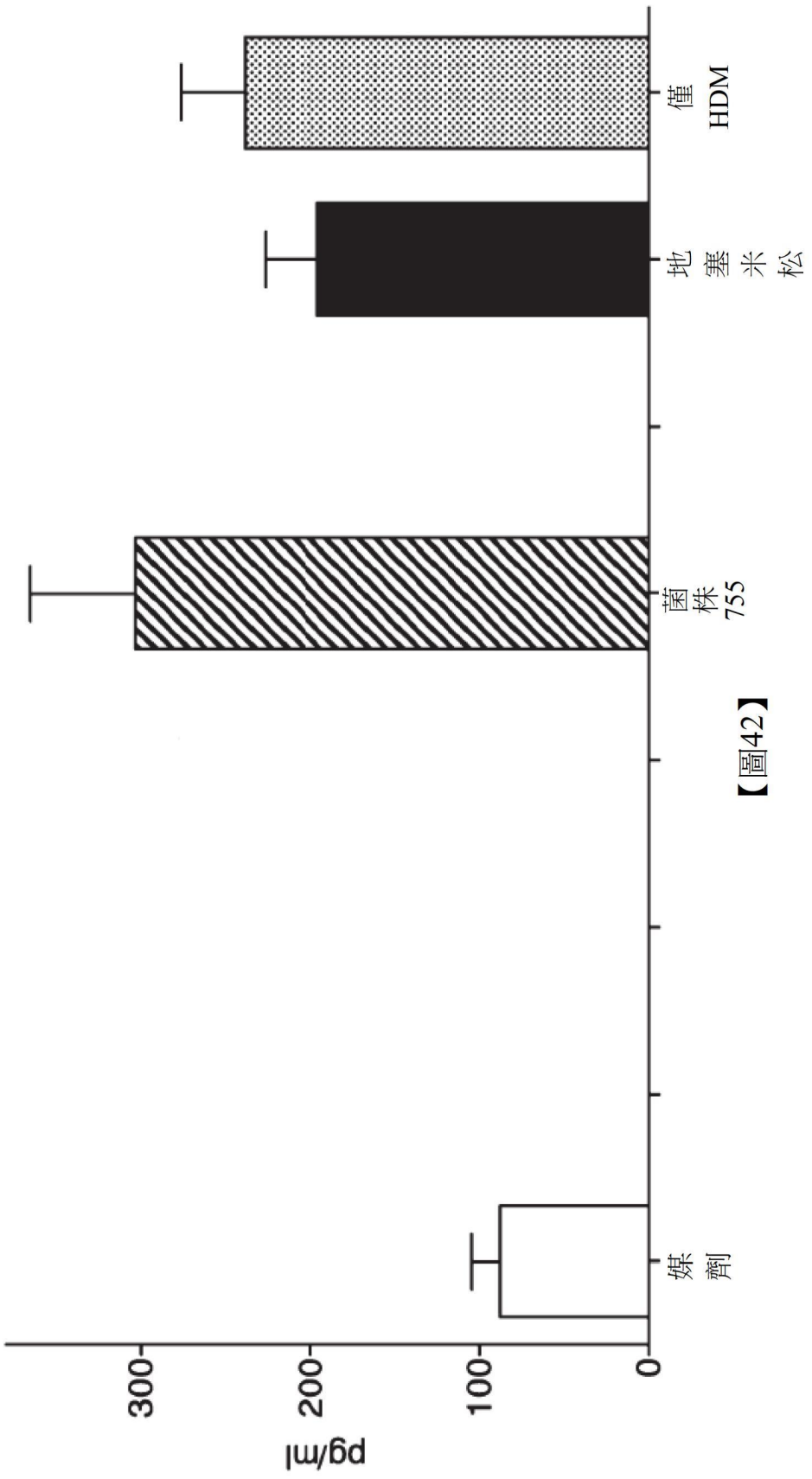
【圖39】



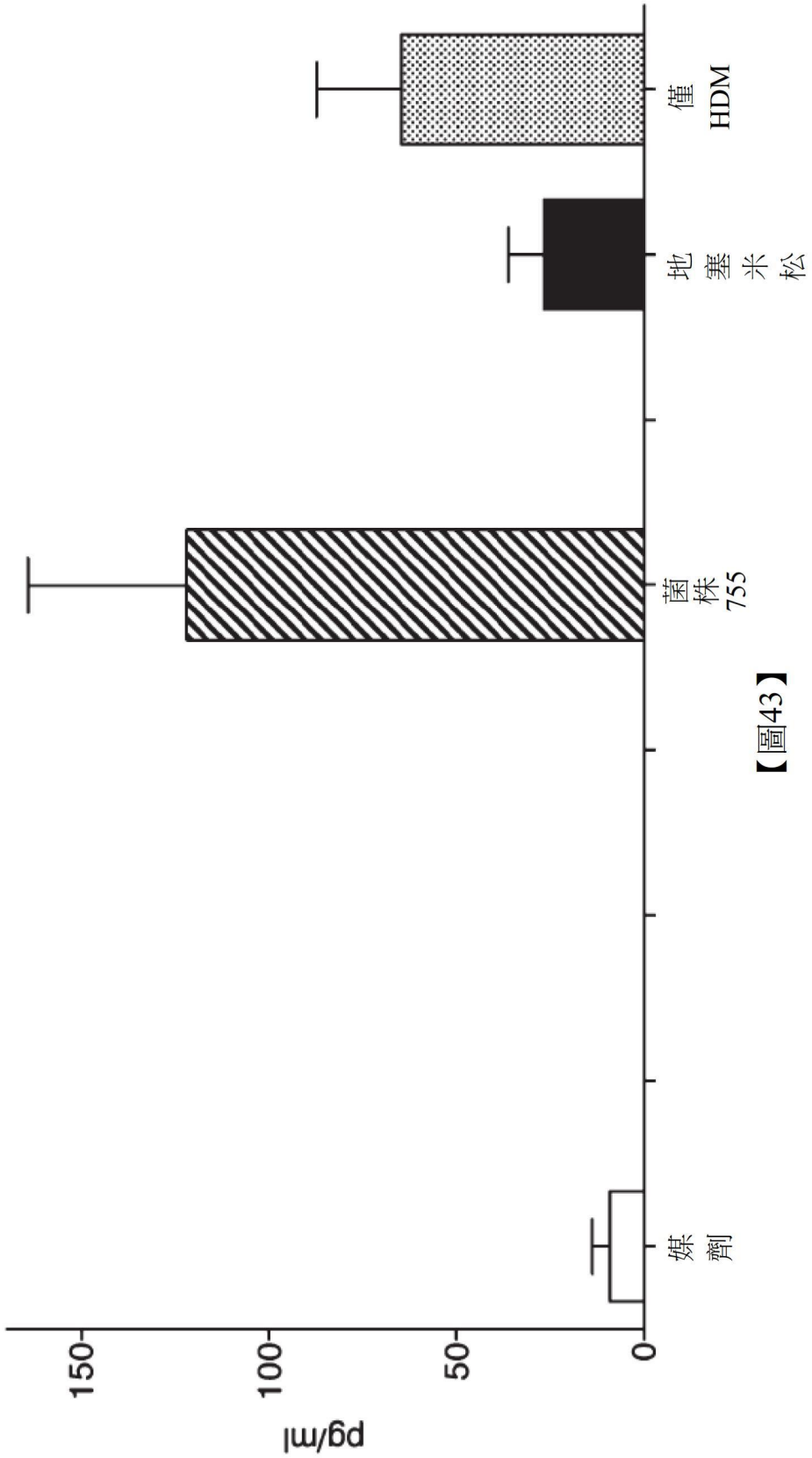
【圖40】



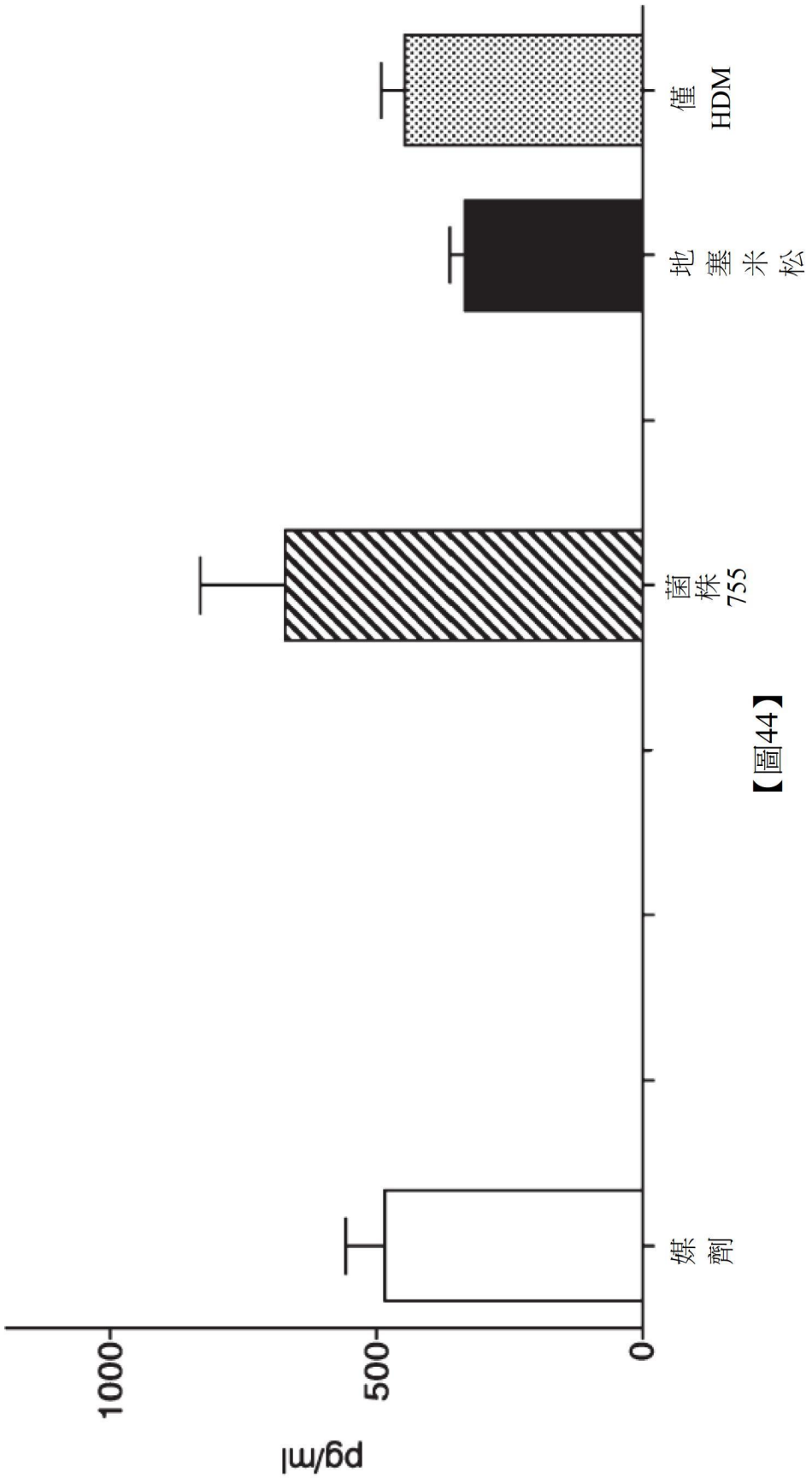
【圖41】



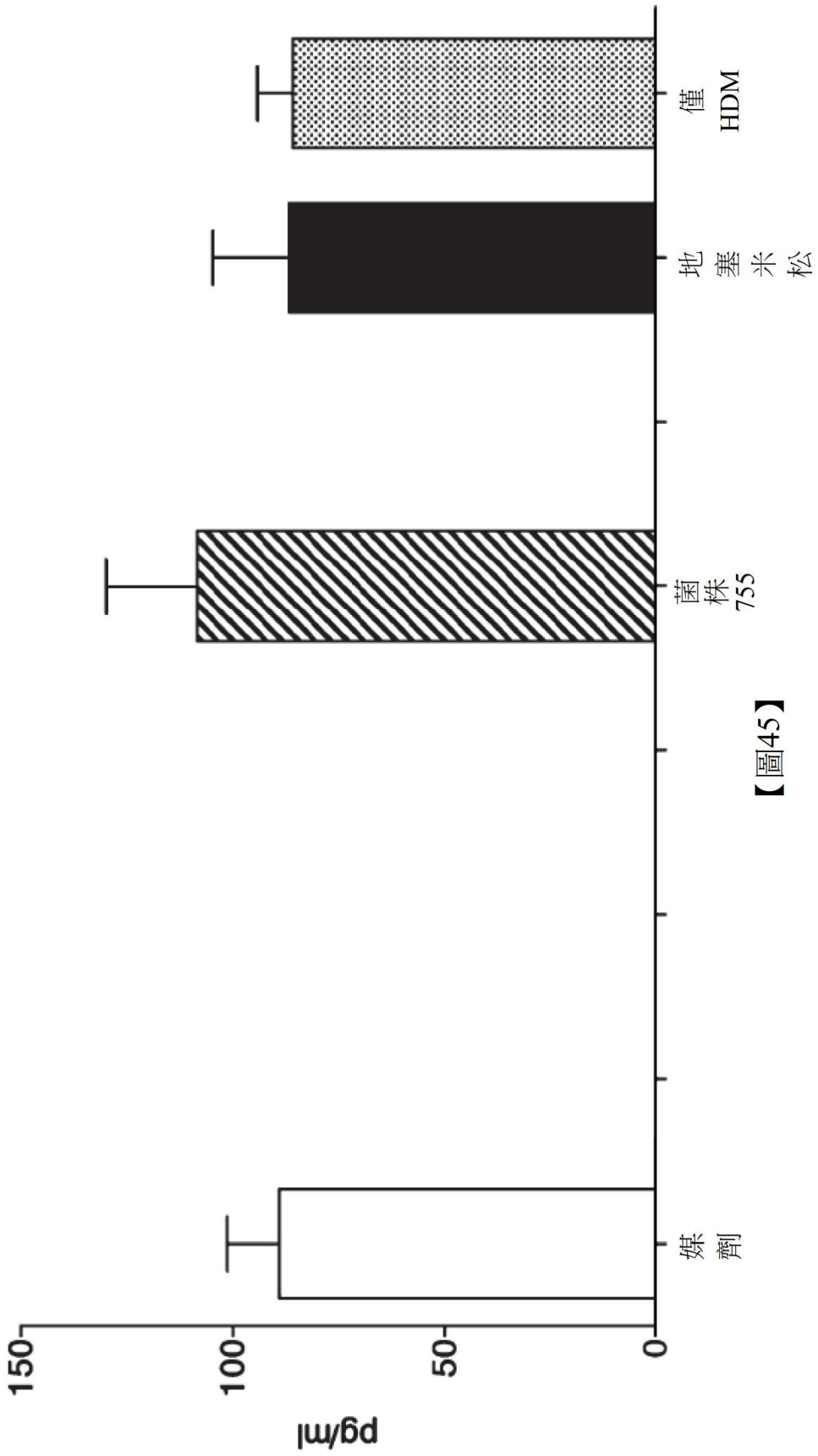
【圖42】



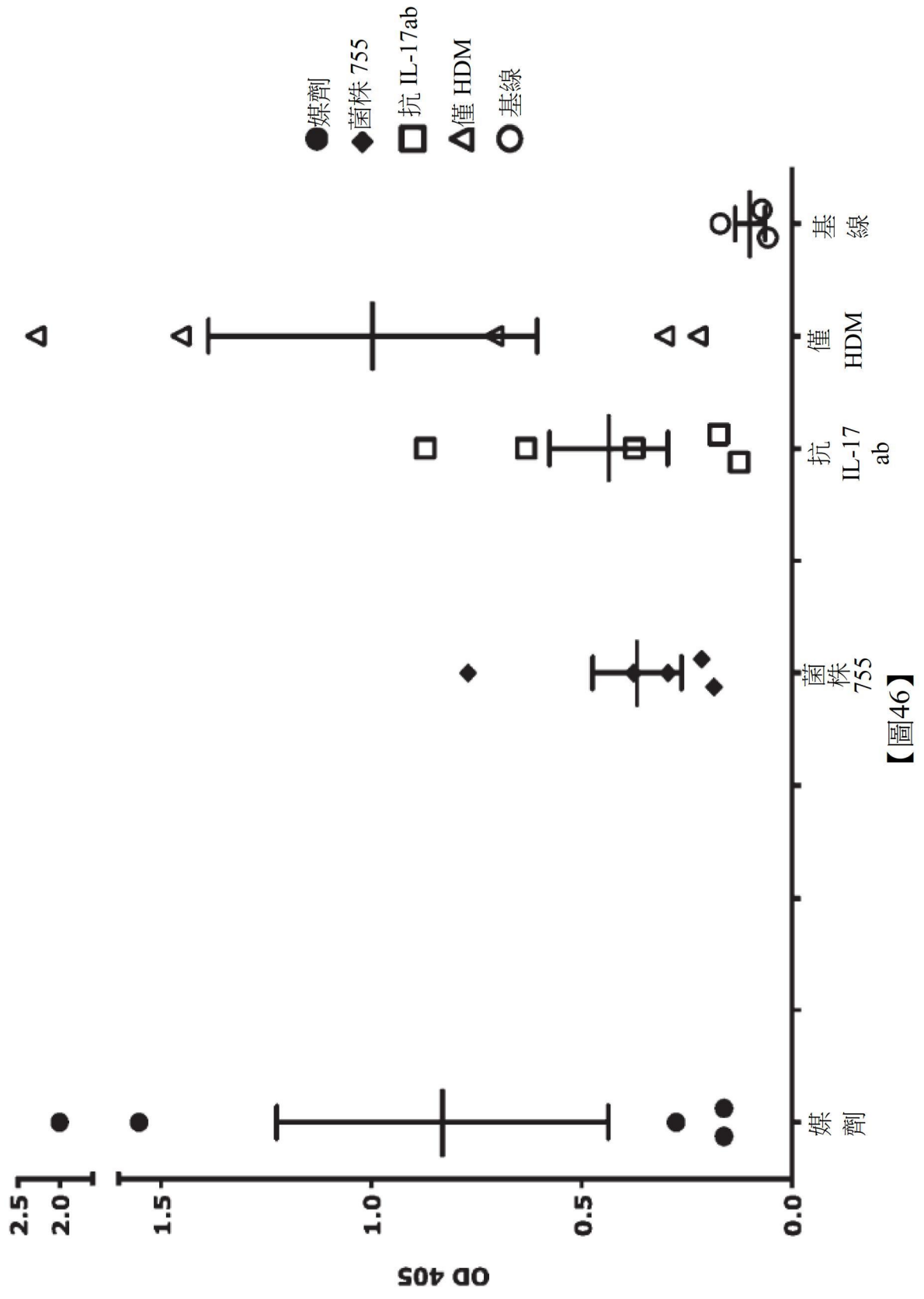
【圖43】



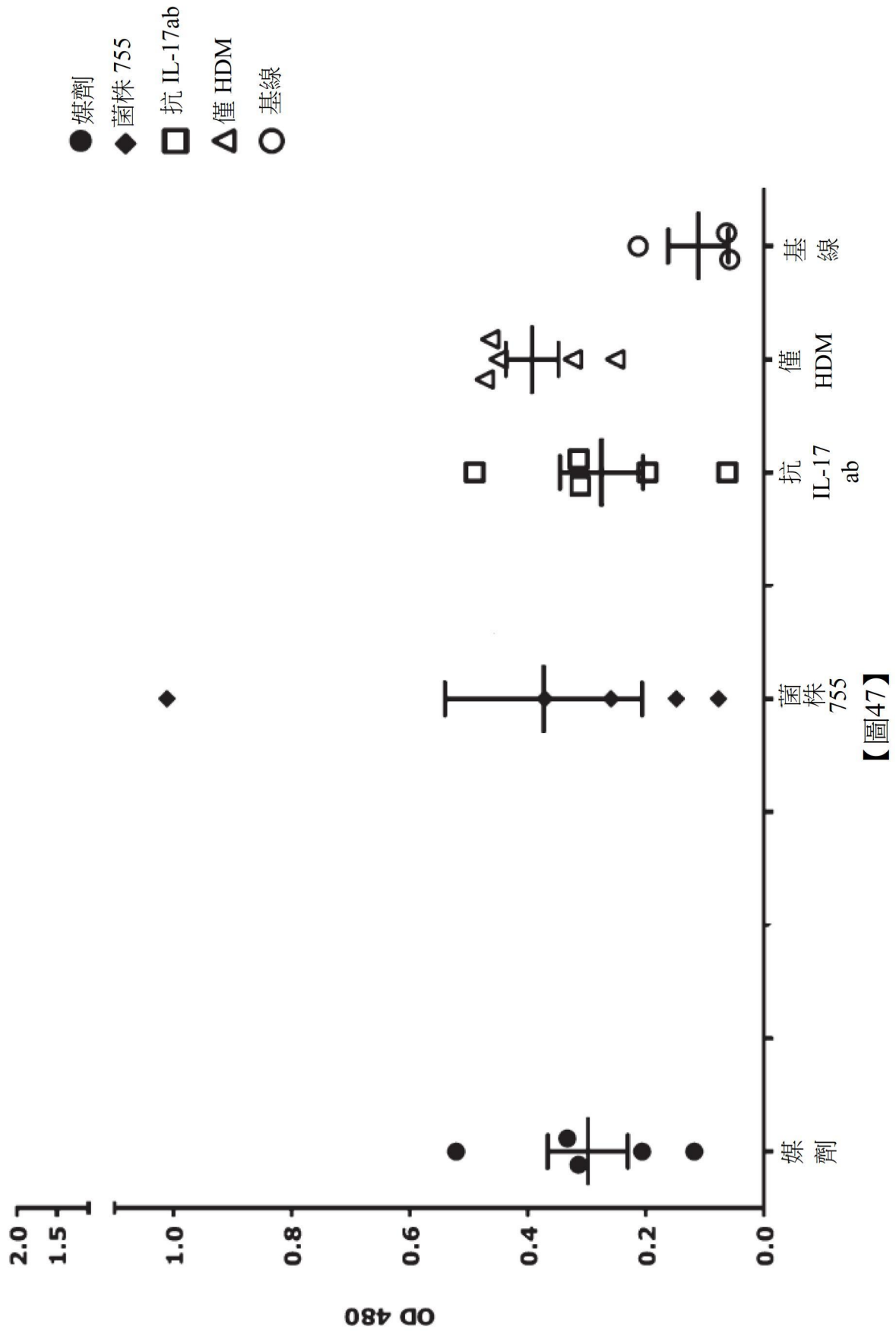
【圖44】



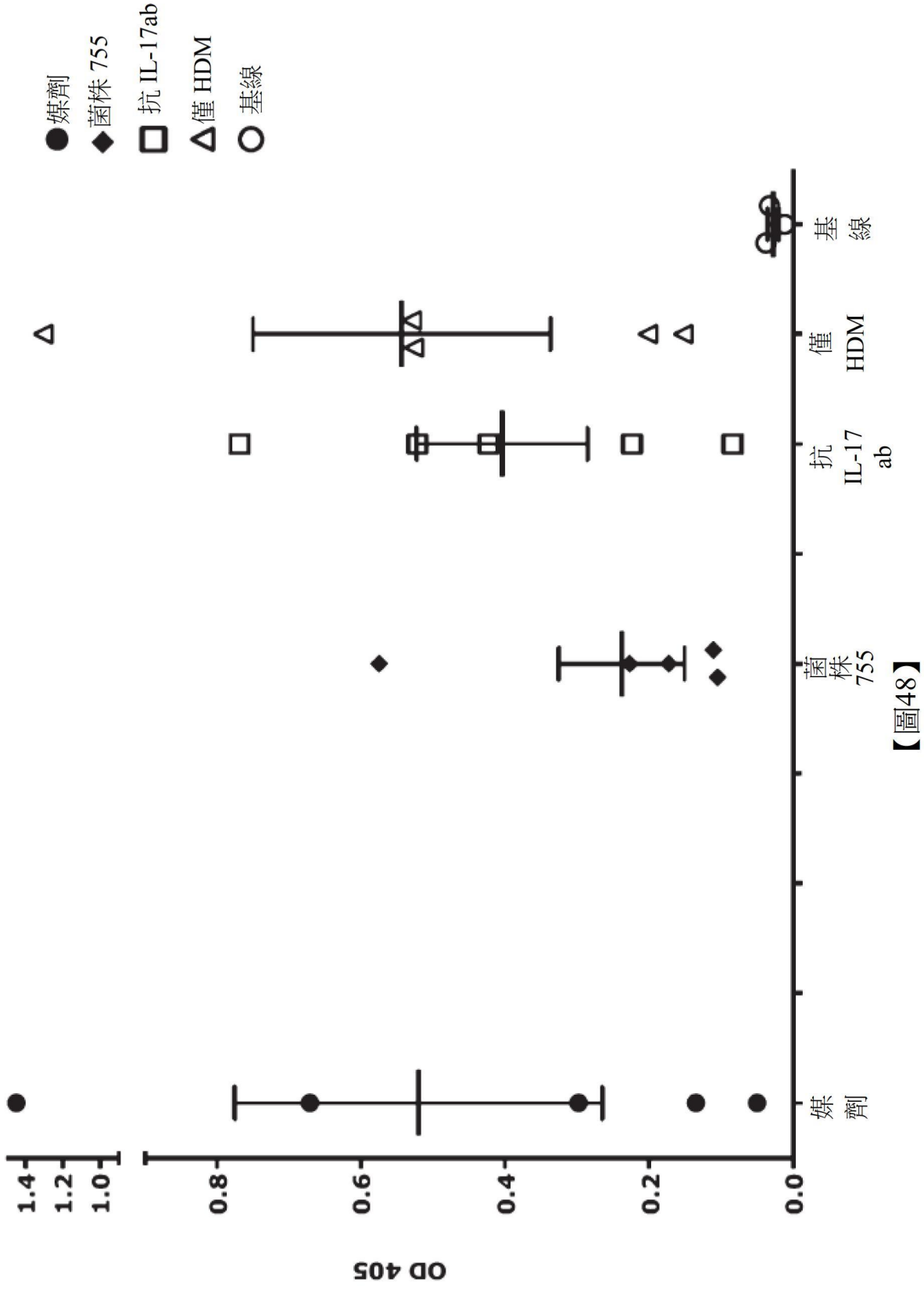
【圖45】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
OD 405
2.5
2.0
1.5
1.0
0.5
0.0
媒劑
菌株 755
抗 IL-17 ab
僅 HDM
基線

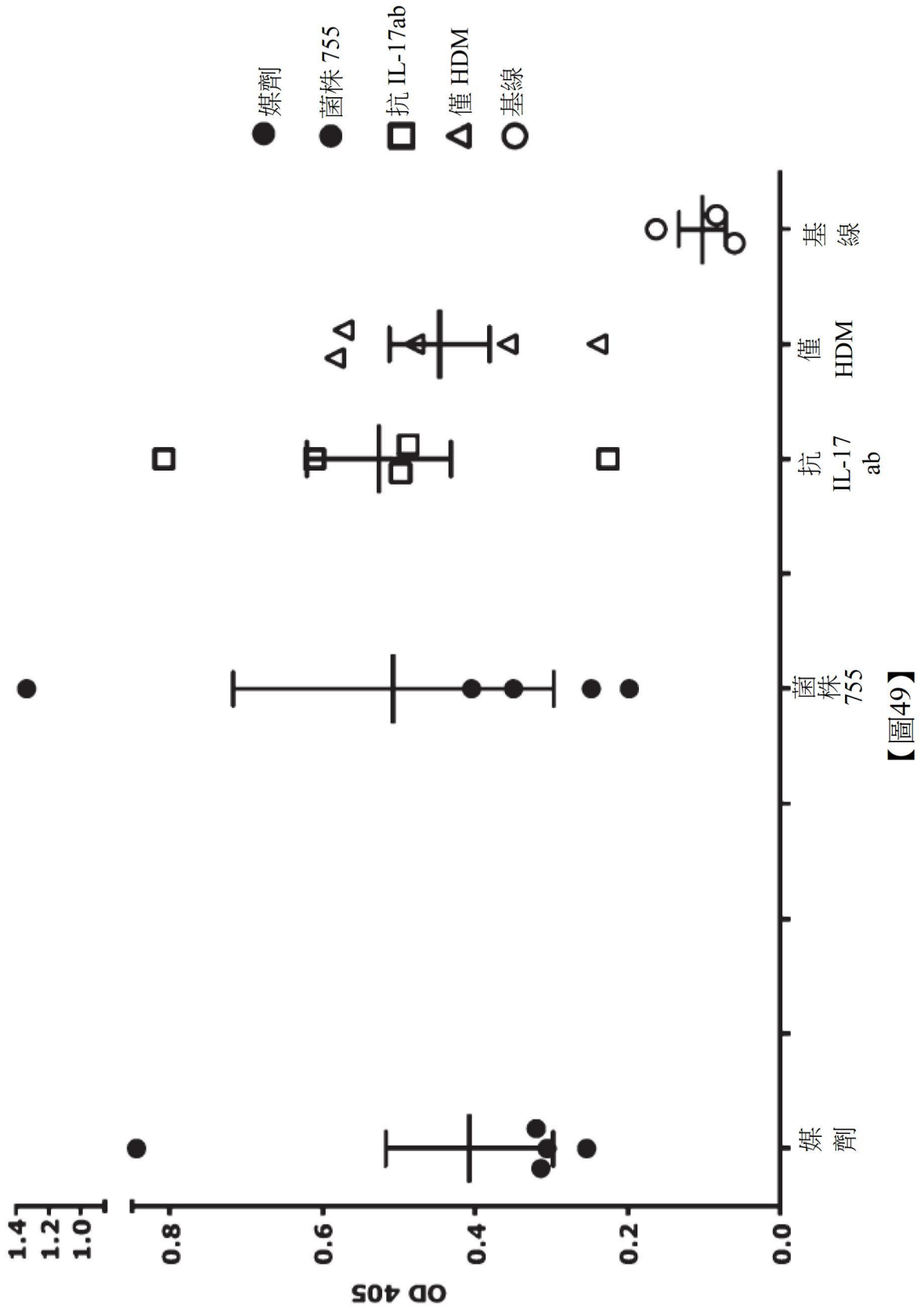
【圖46】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
OD 480
2.0
1.5
1.0
0.8
0.6
0.4
0.2
0.0
媒劑
菌株 755
抗 IL-17 ab
僅 HDM
基線

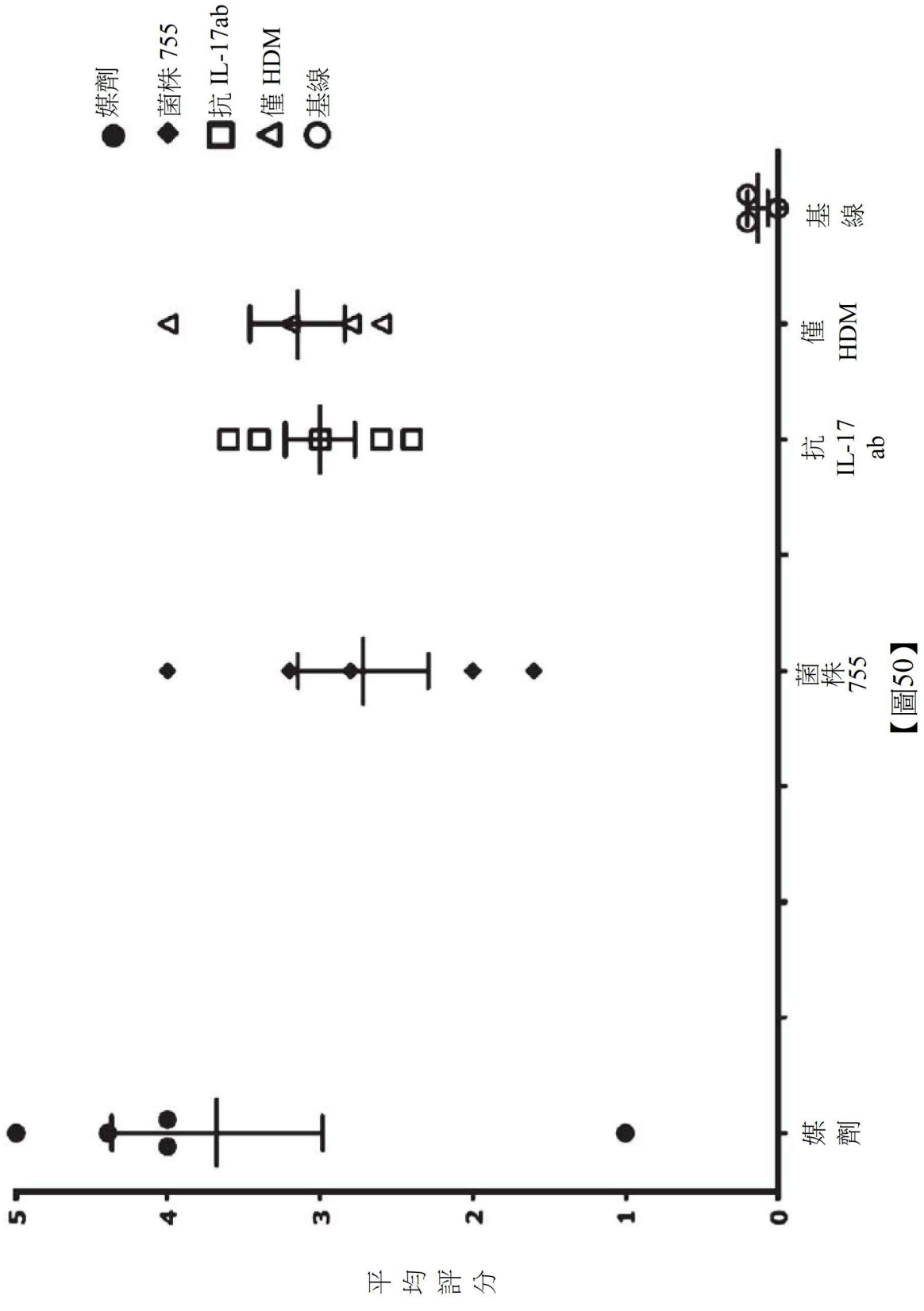
【圖47】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
OD 405
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
媒劑
菌株 755
抗 IL-17 ab
僅 HDM
基線

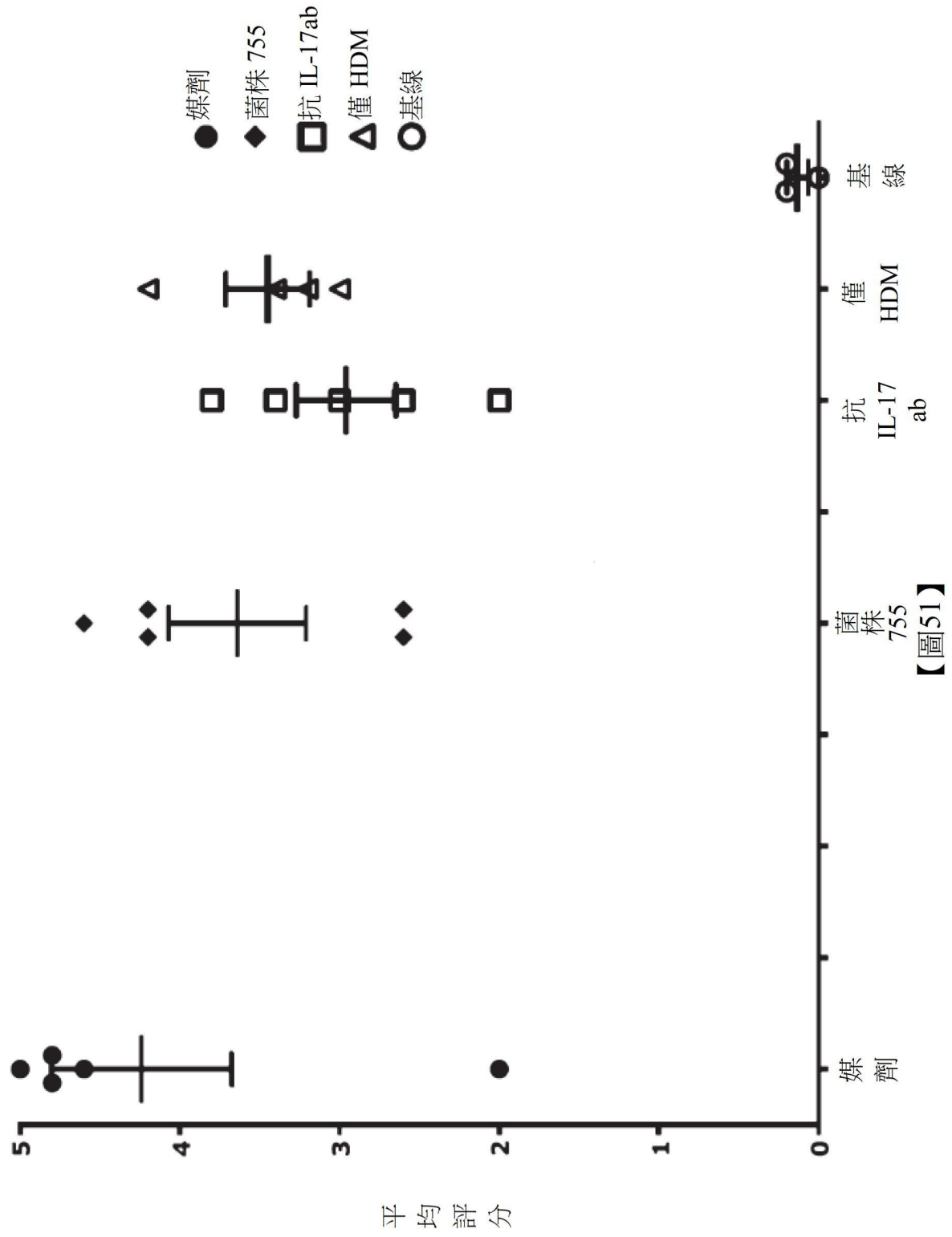
【圖48】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
OD 405
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
媒劑
菌株 755
抗 IL-17 ab
僅 HDM
基線

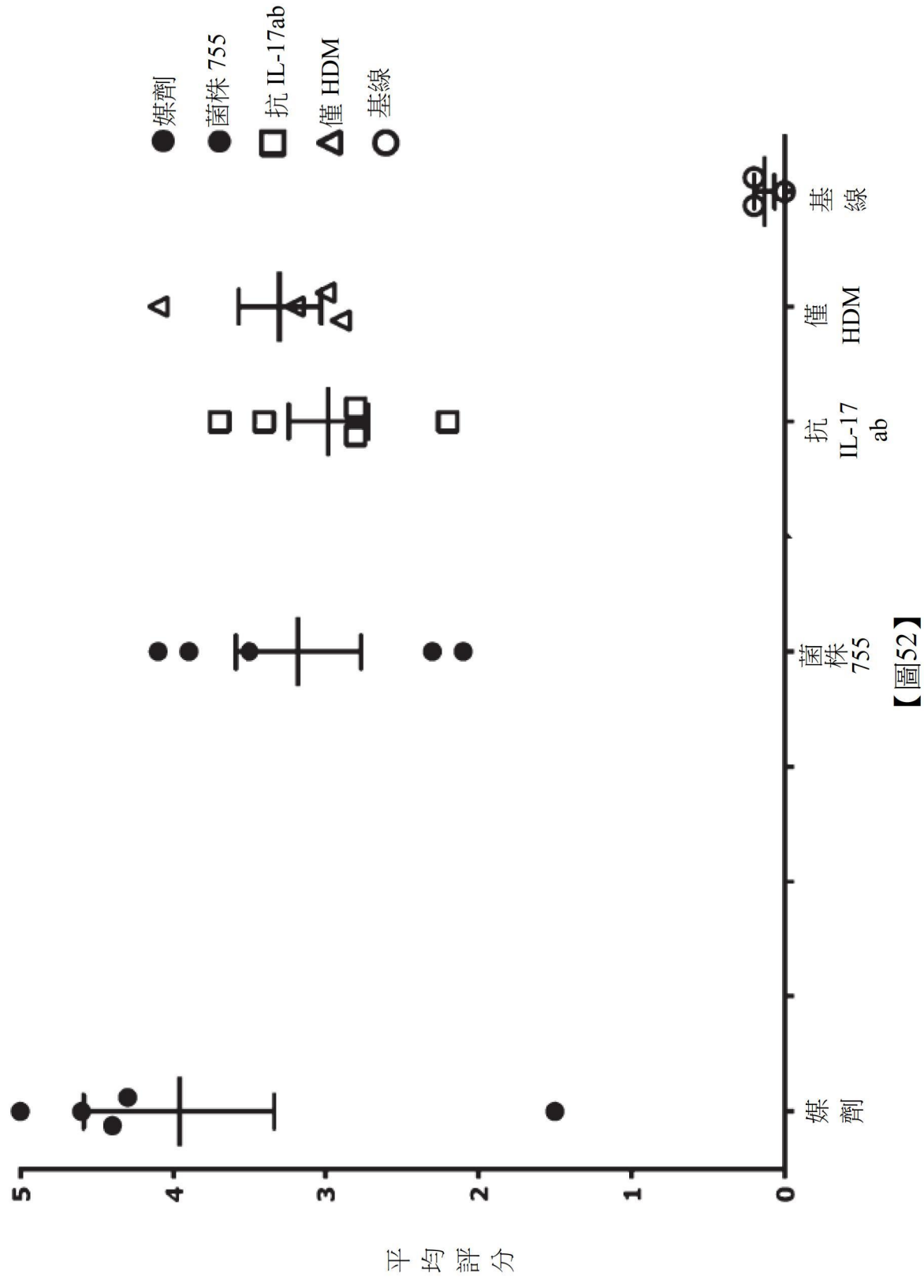
【圖49】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
平均評分
0
1
2
3
4
5
媒劑
菌株755
抗IL-17 ab
僅HDM
基線

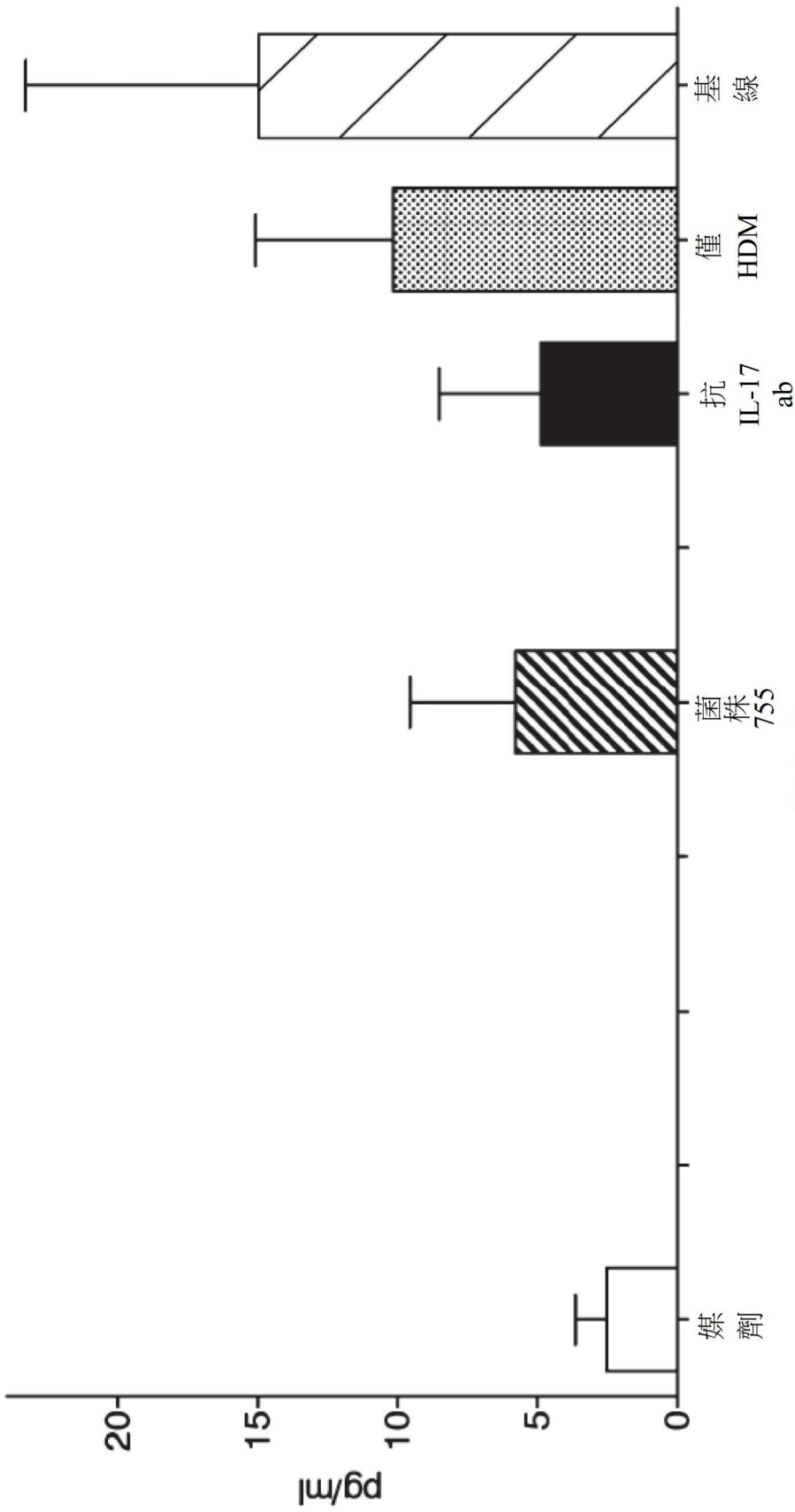
【圖50】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
平均評分
0
1
2
3
4
5
媒劑
菌株755
抗IL-17 ab
僅HDM
基線

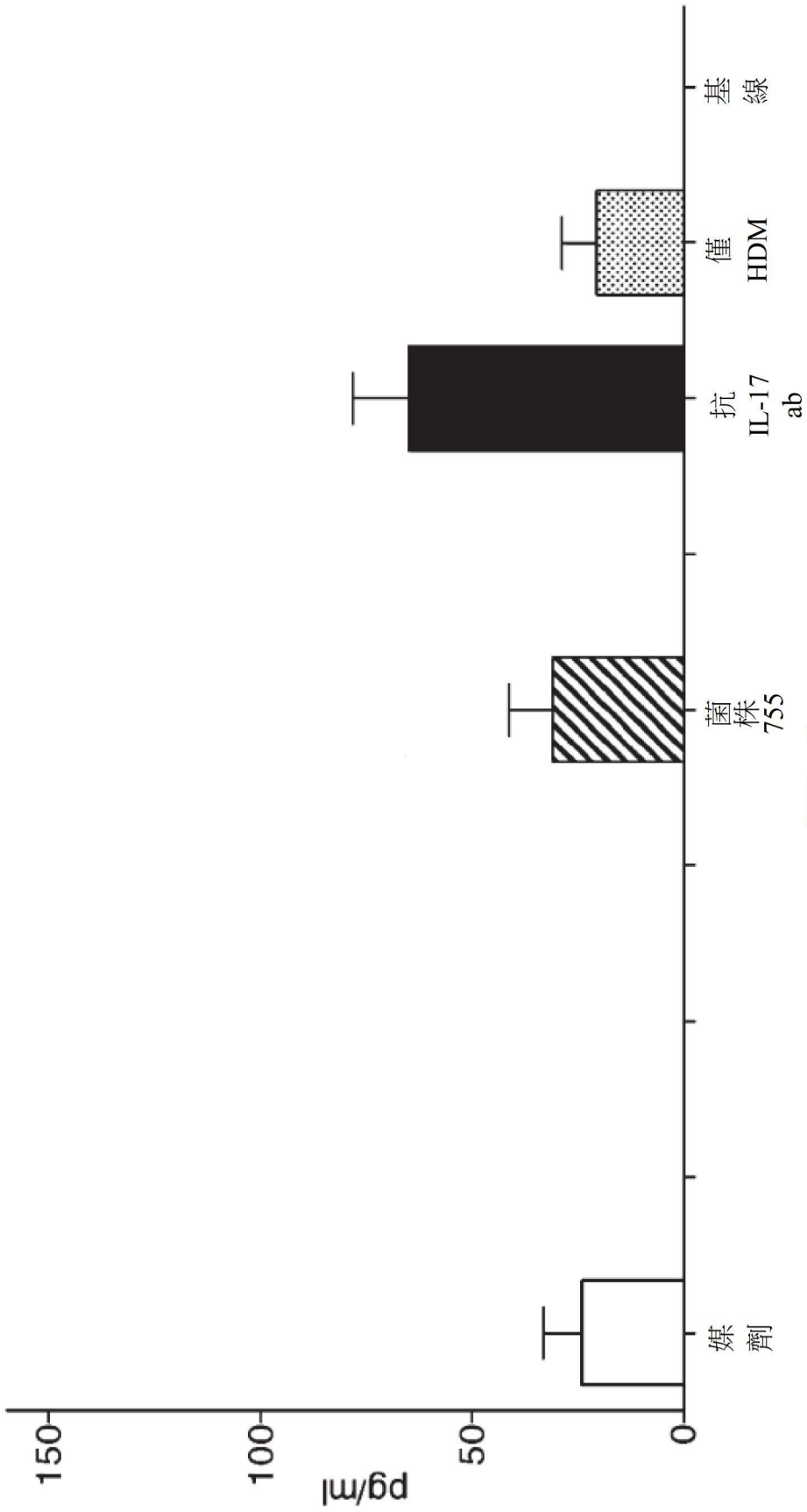
【圖51】


媒劑
菌株 755
抗 IL-17ab
僅 HDM
基線
平均評分
0
1
2
3
4
5
媒劑
菌株 755
抗 IL-17 ab
僅 HDM
基線

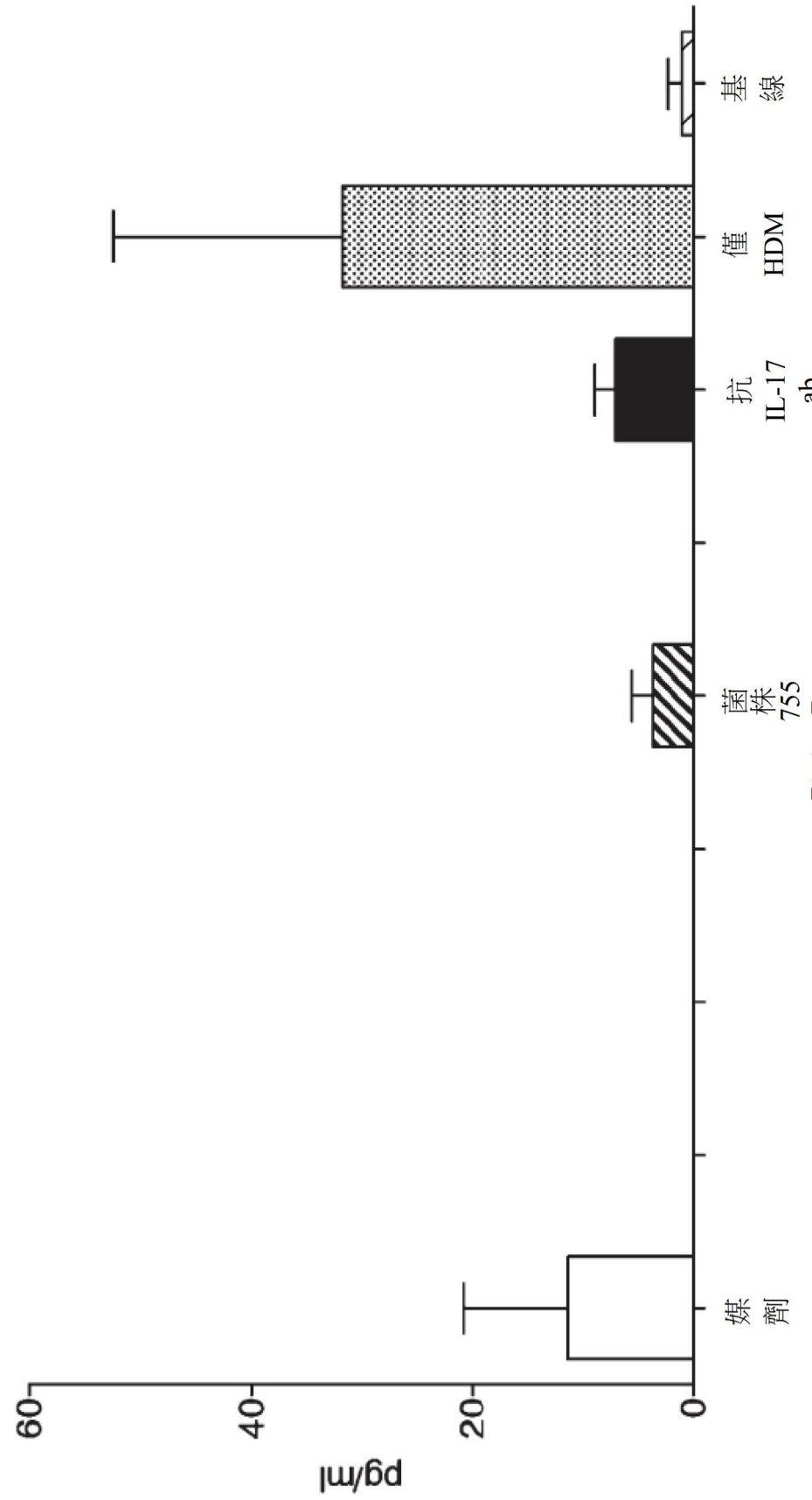
【圖52】



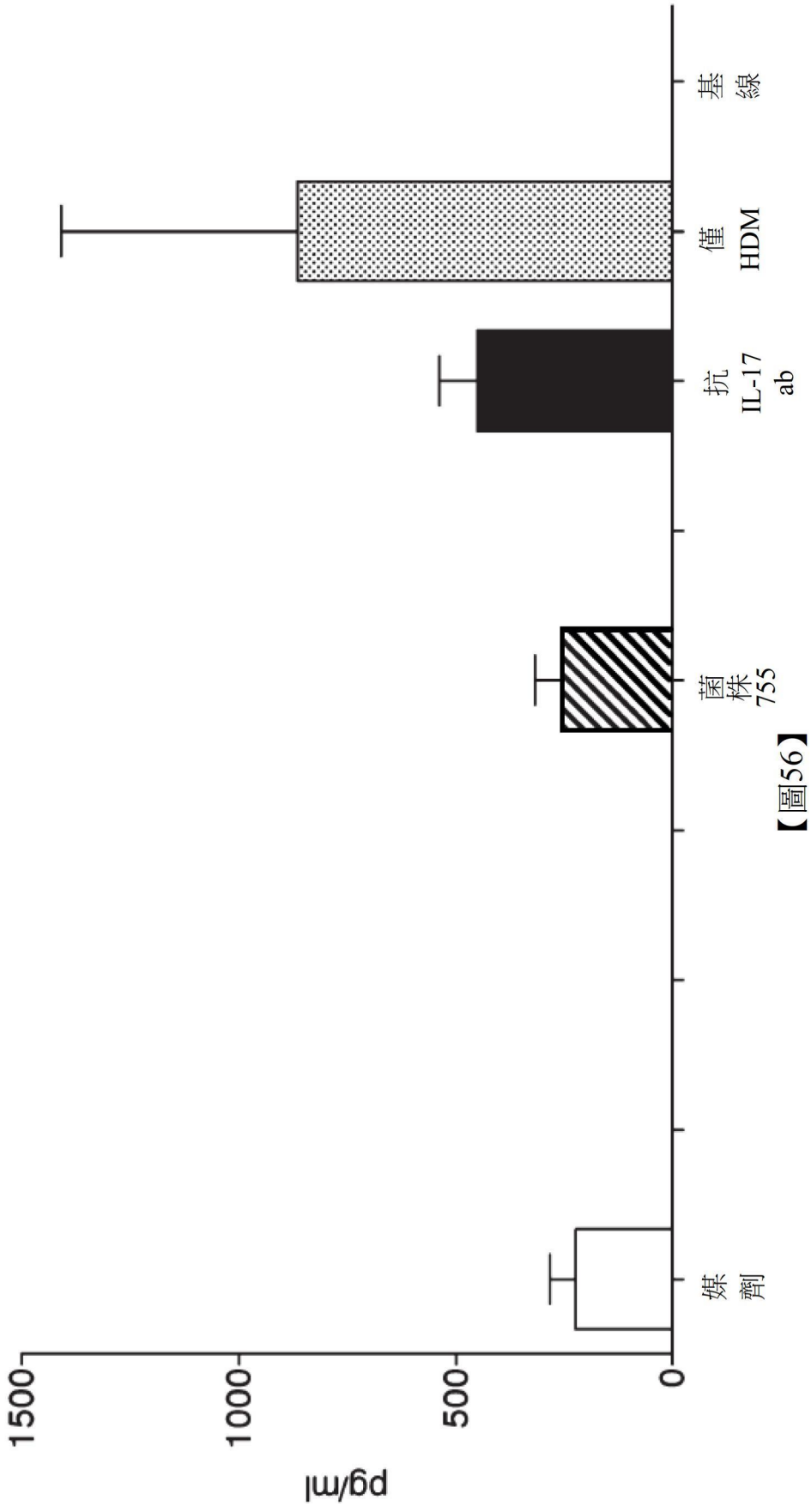
【圖53】



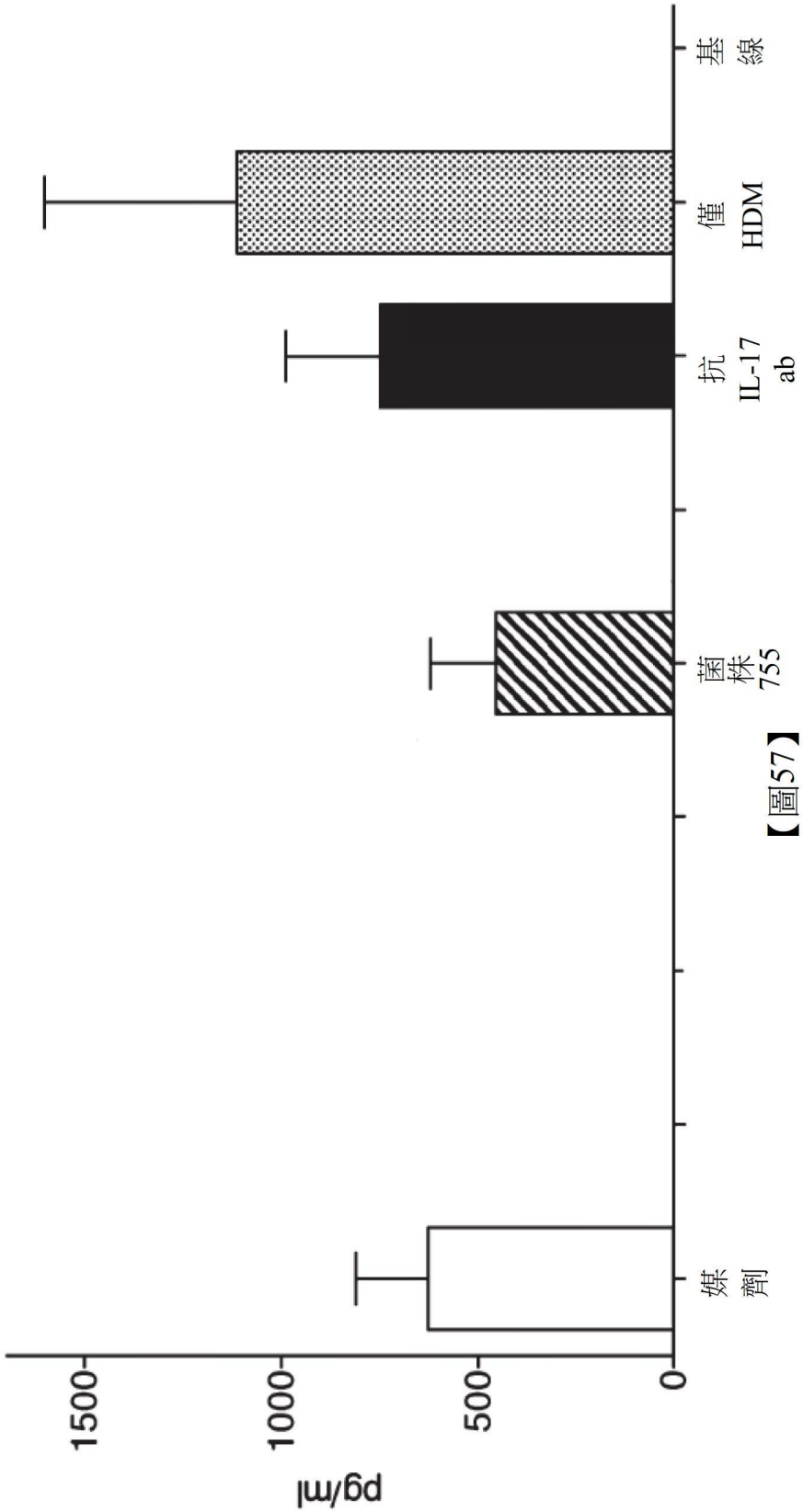
【圖54】



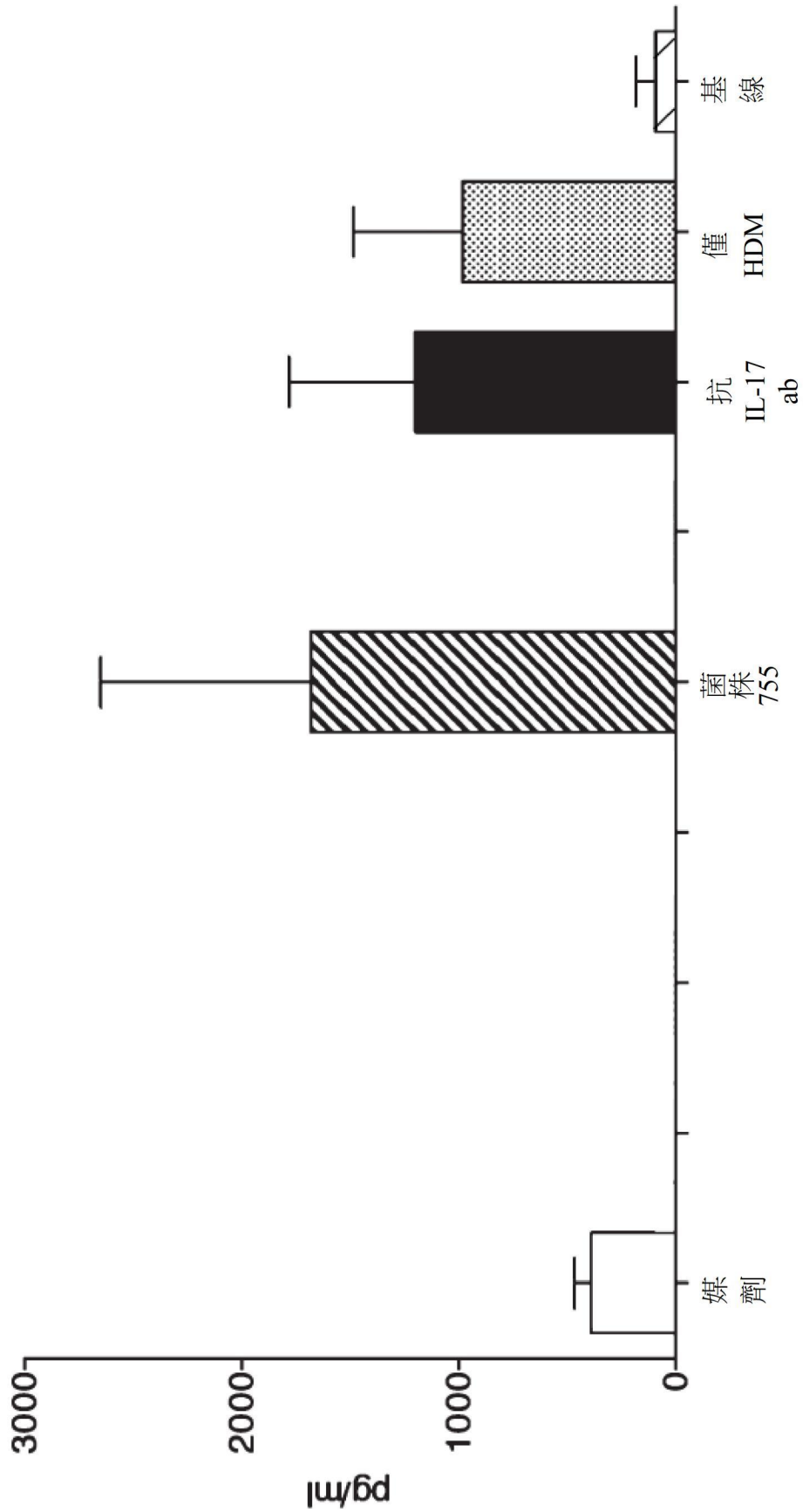
【圖55】



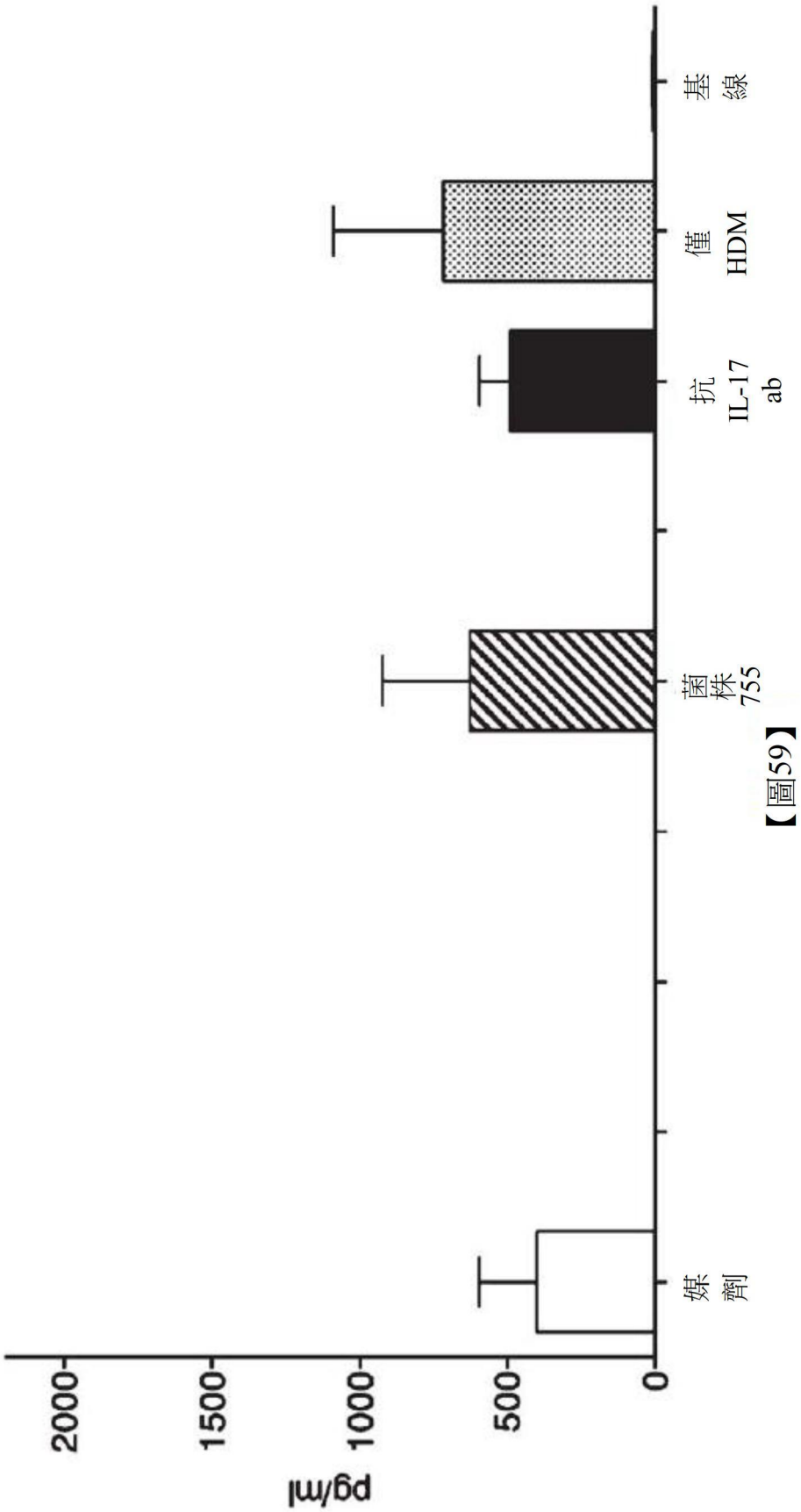
【圖56】



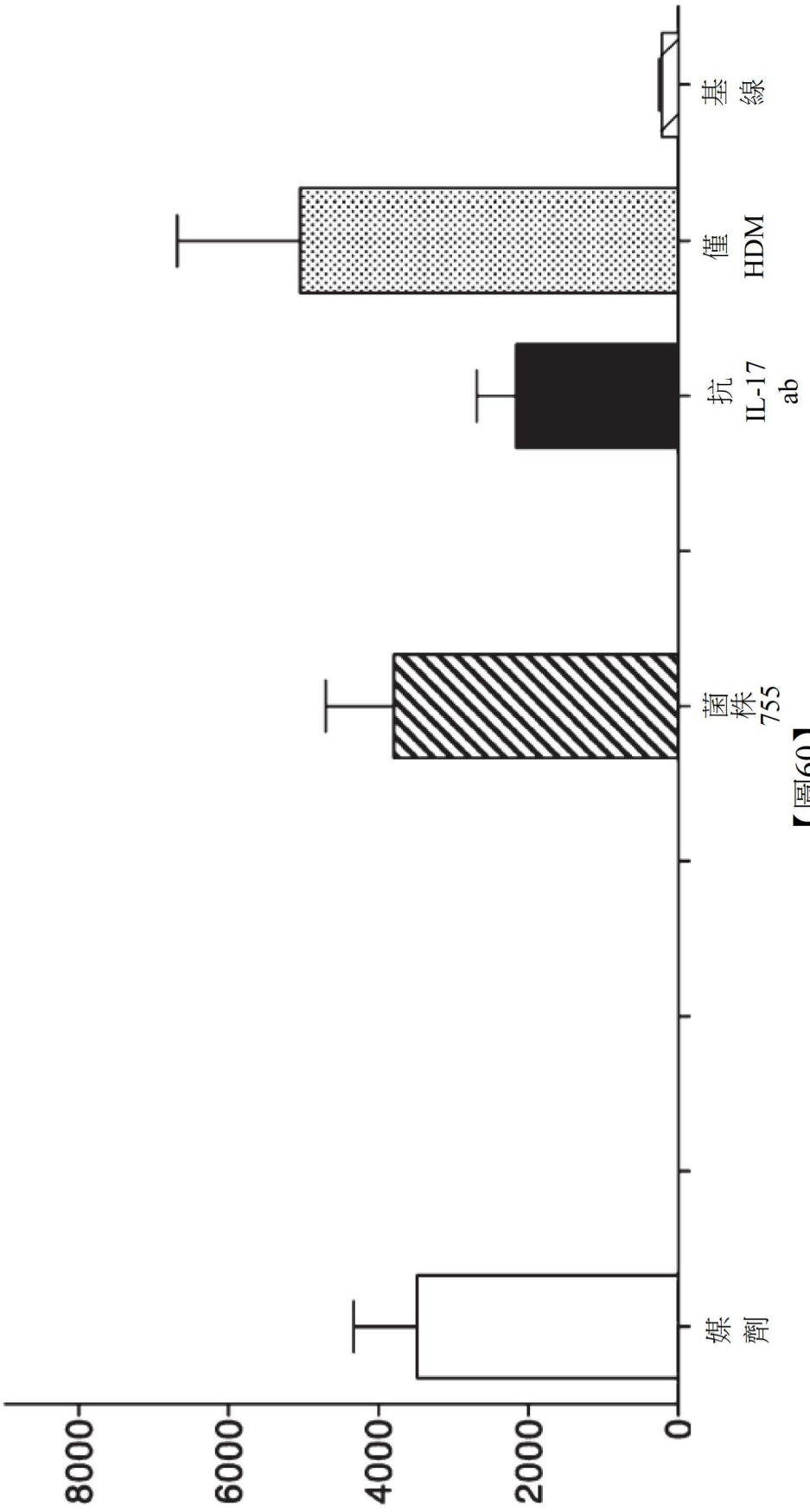
【圖57】



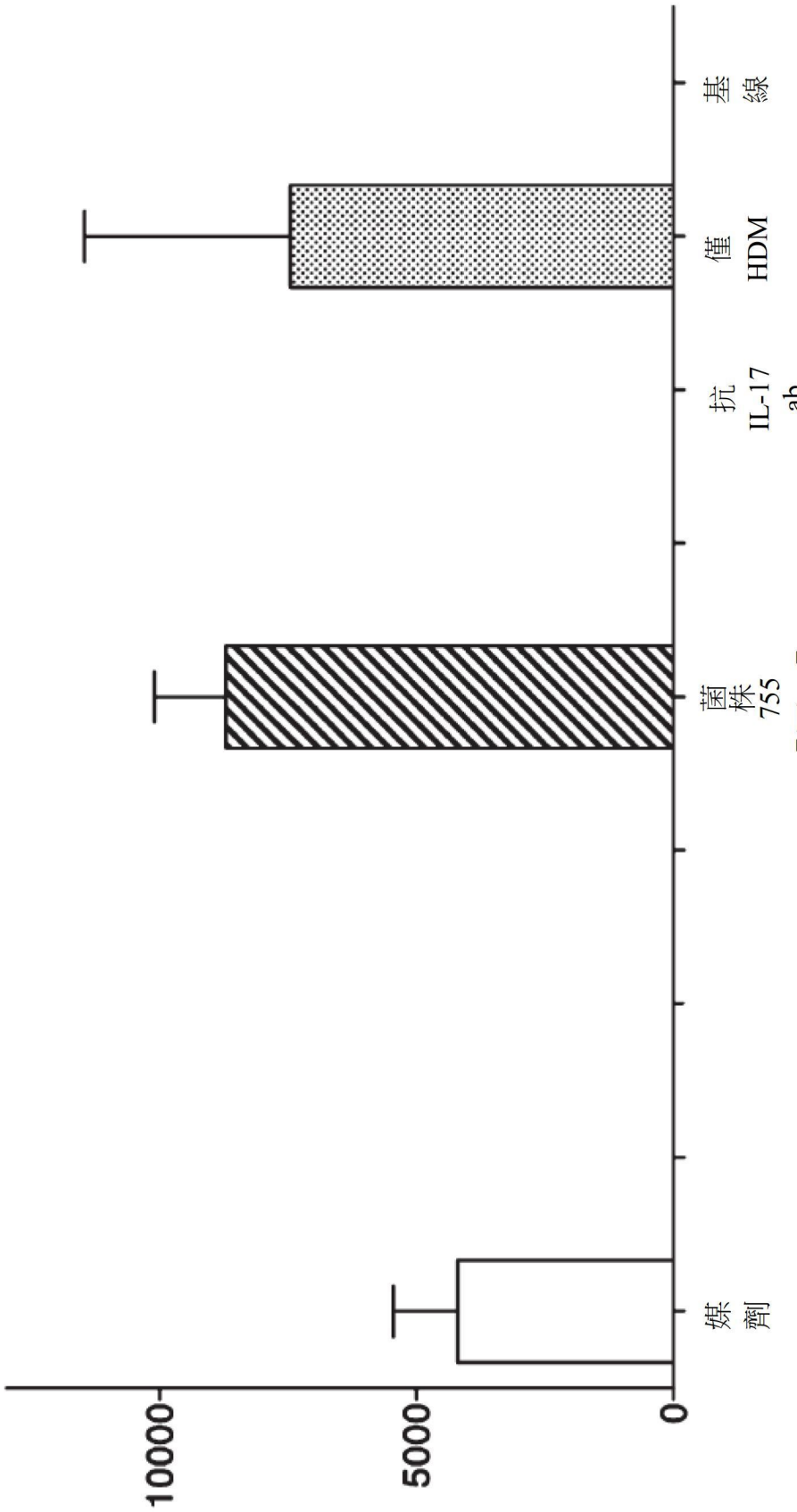
【圖58】



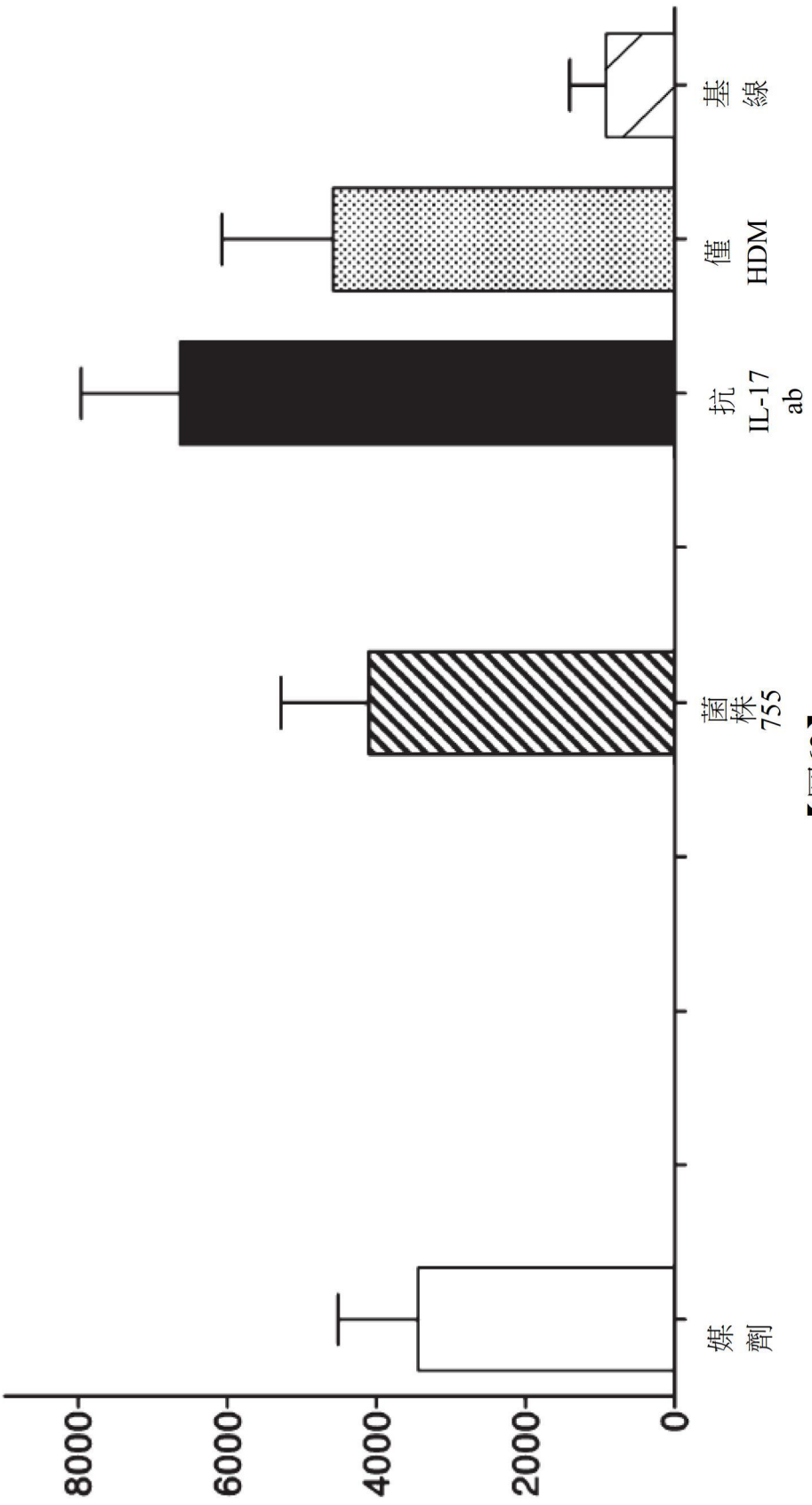
【圖59】



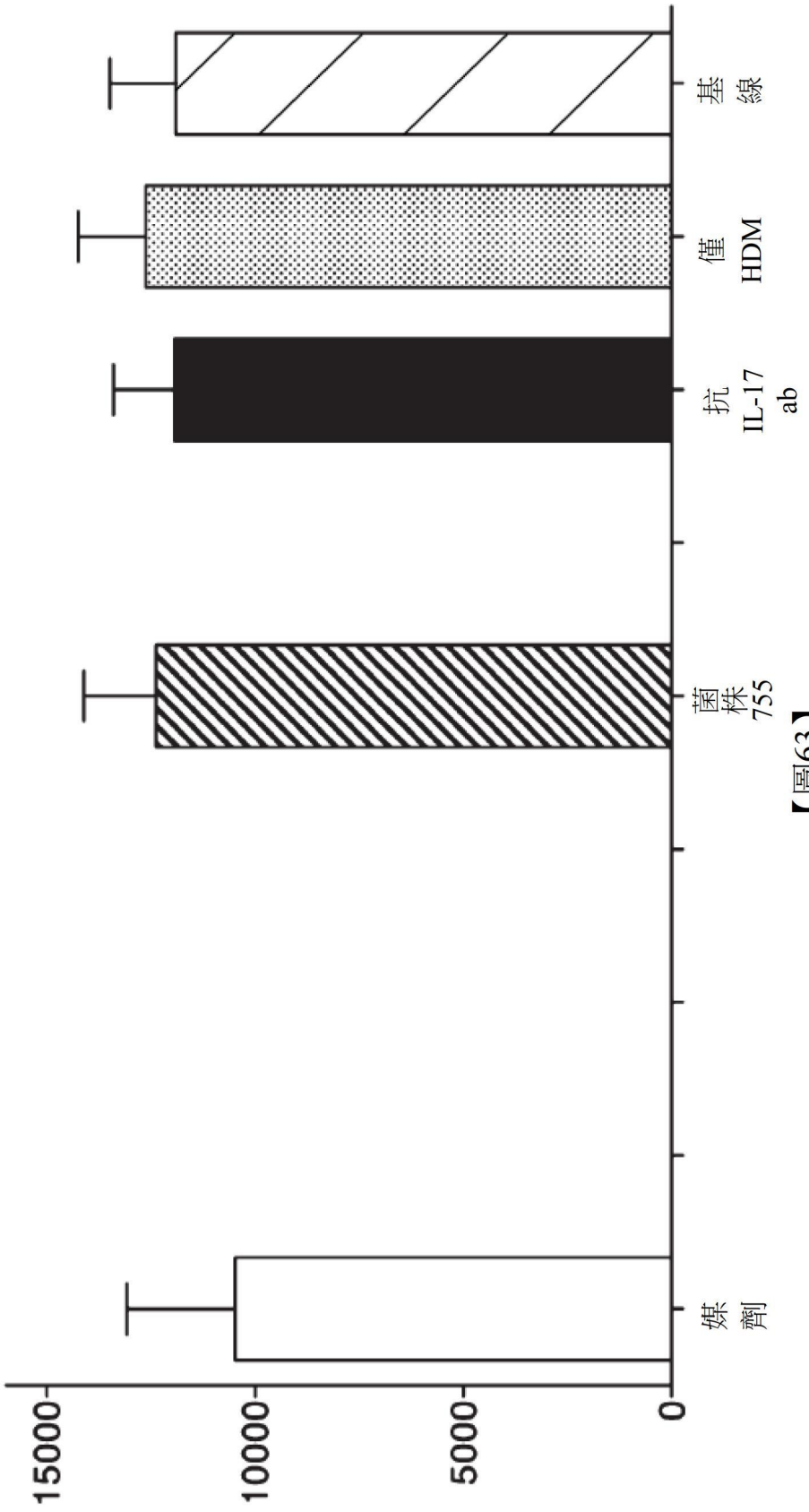
【圖60】



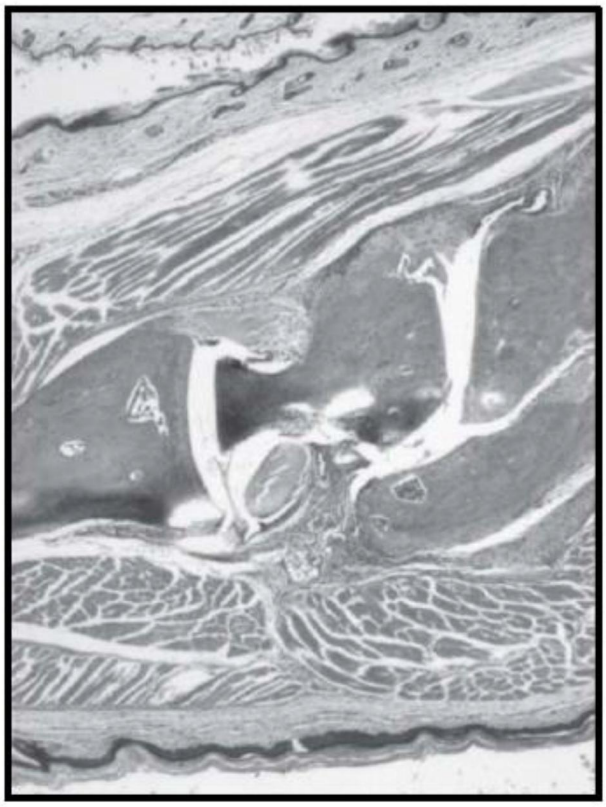
【圖61】

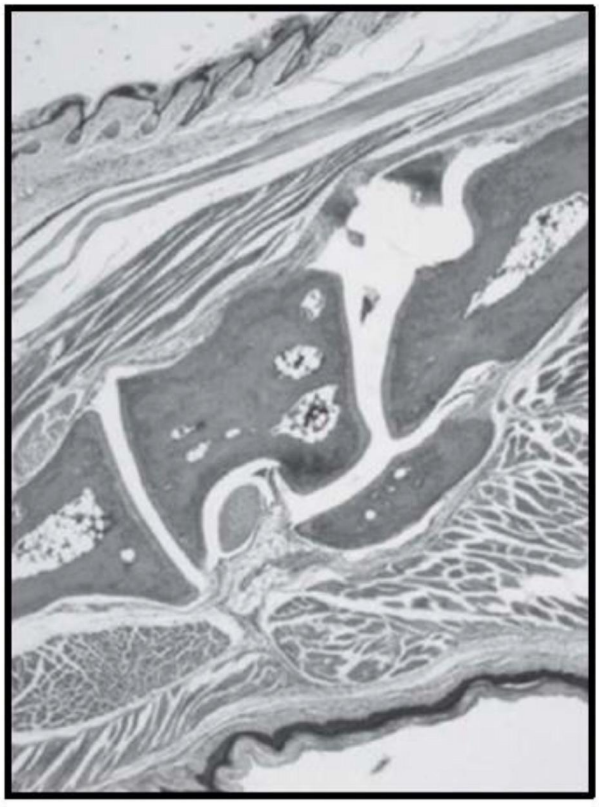


【圖62】

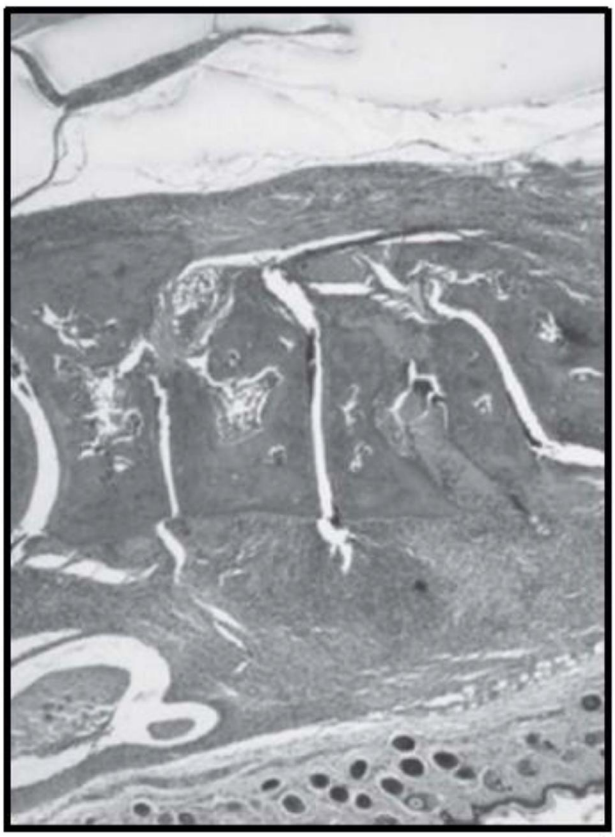


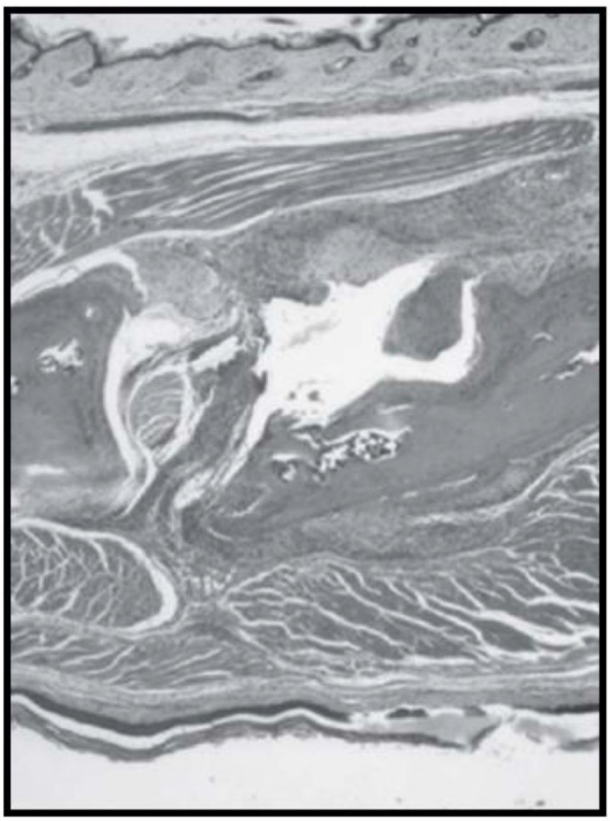
【圖63】



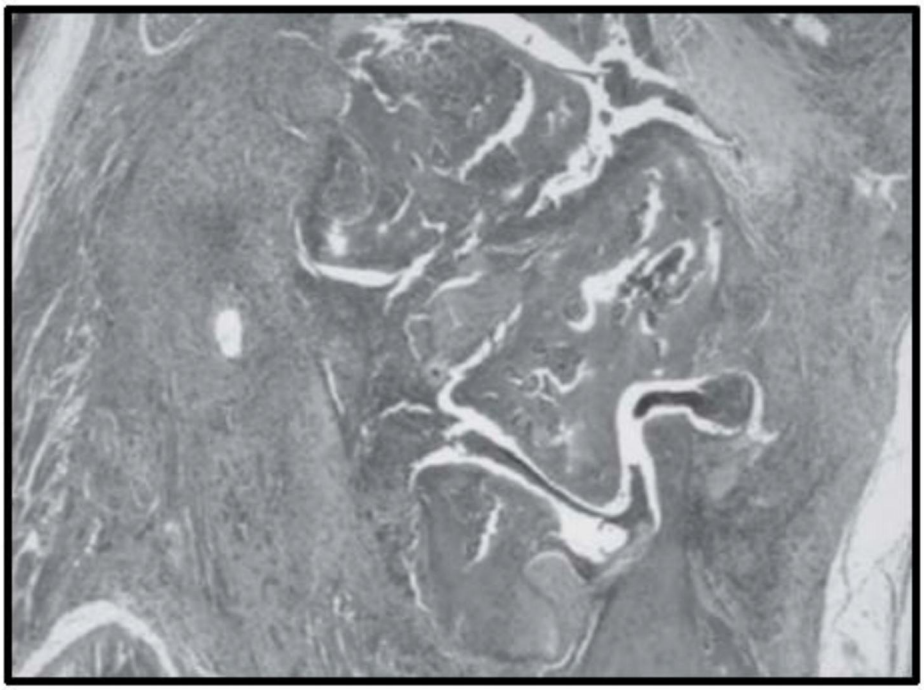


【圖64】

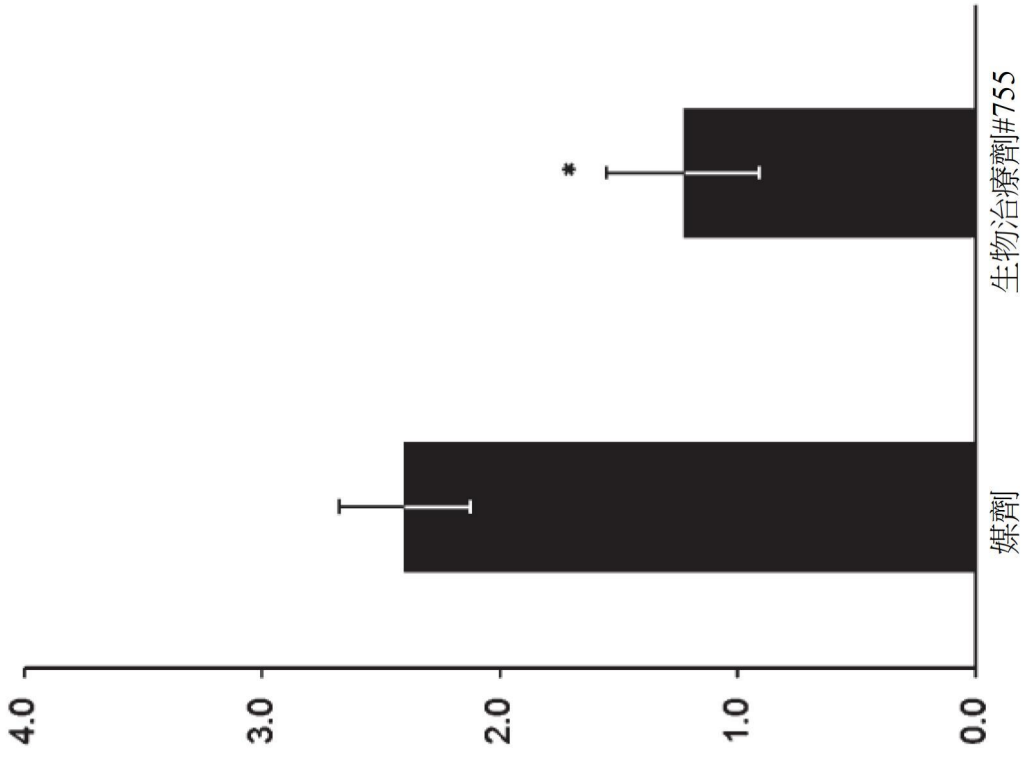




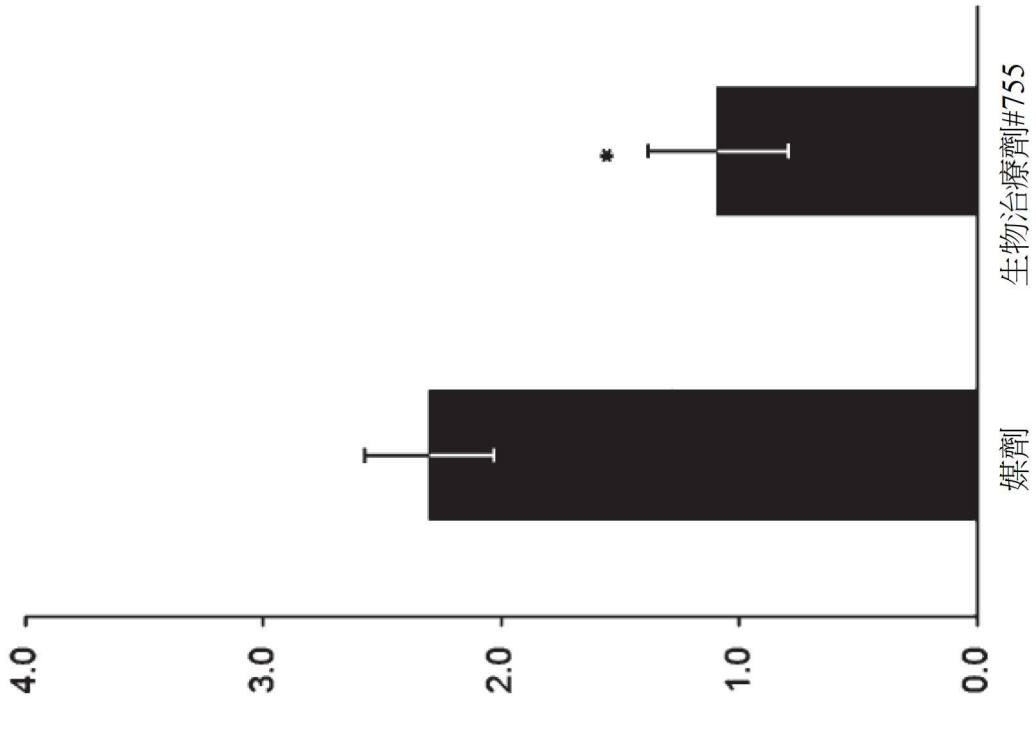
【圖64】



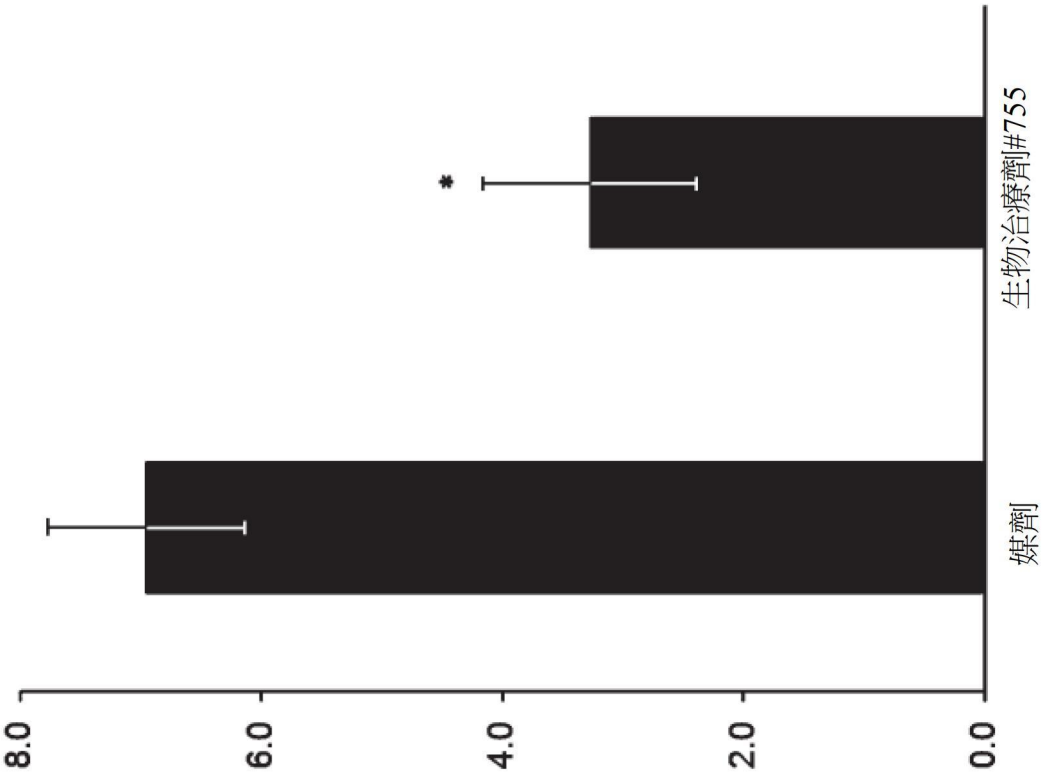
【圖64】



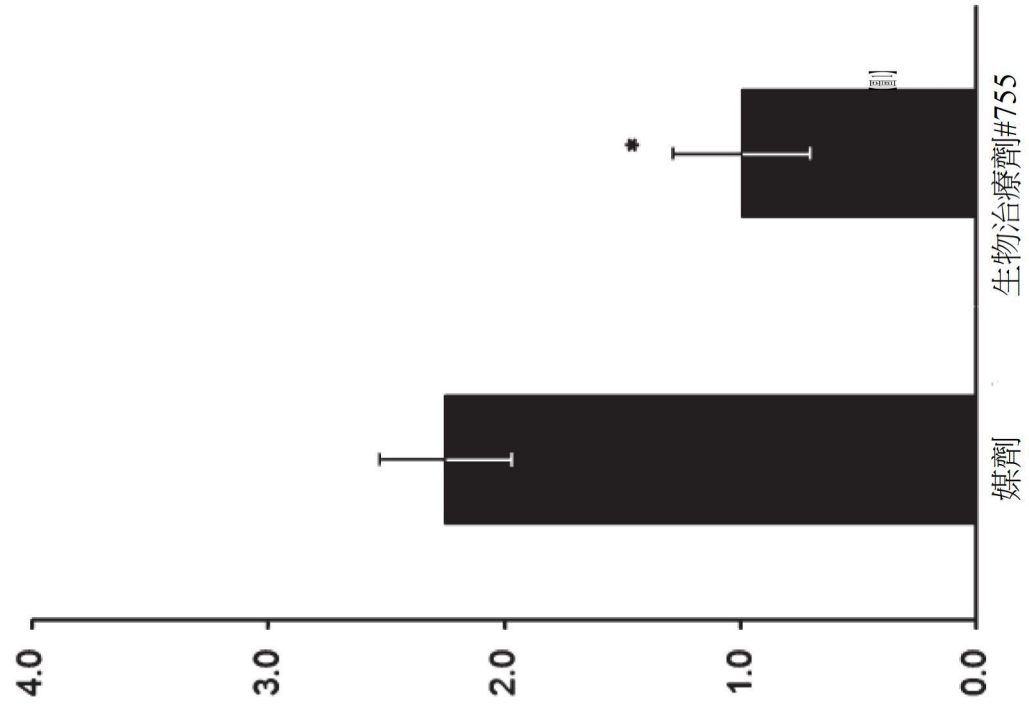
【圖65】



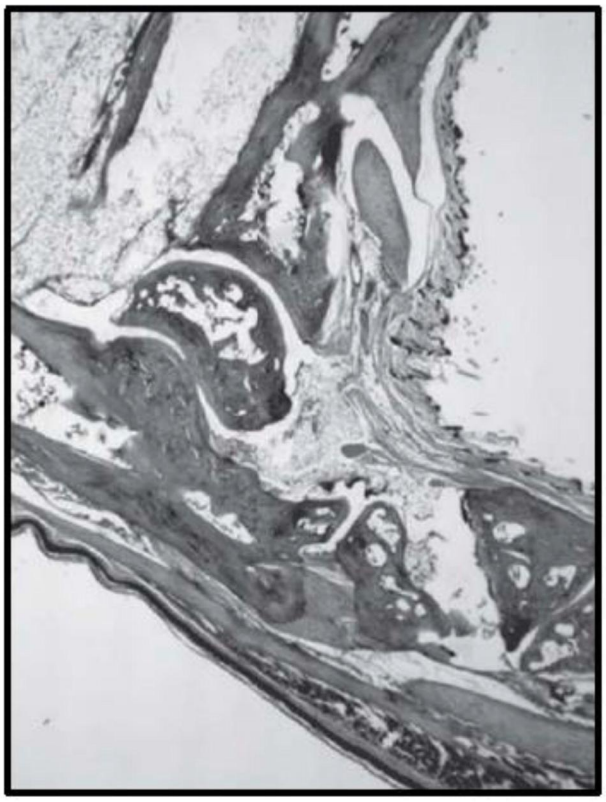
【圖66】

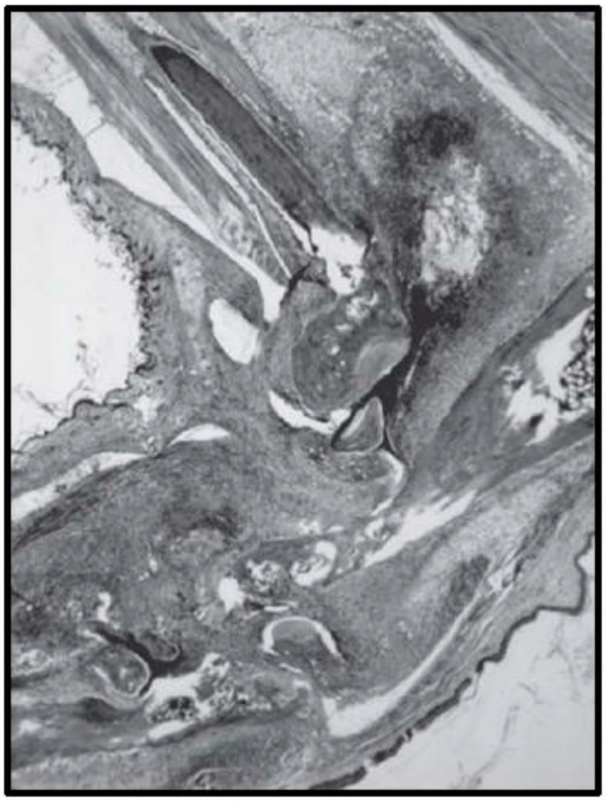


【圖68】

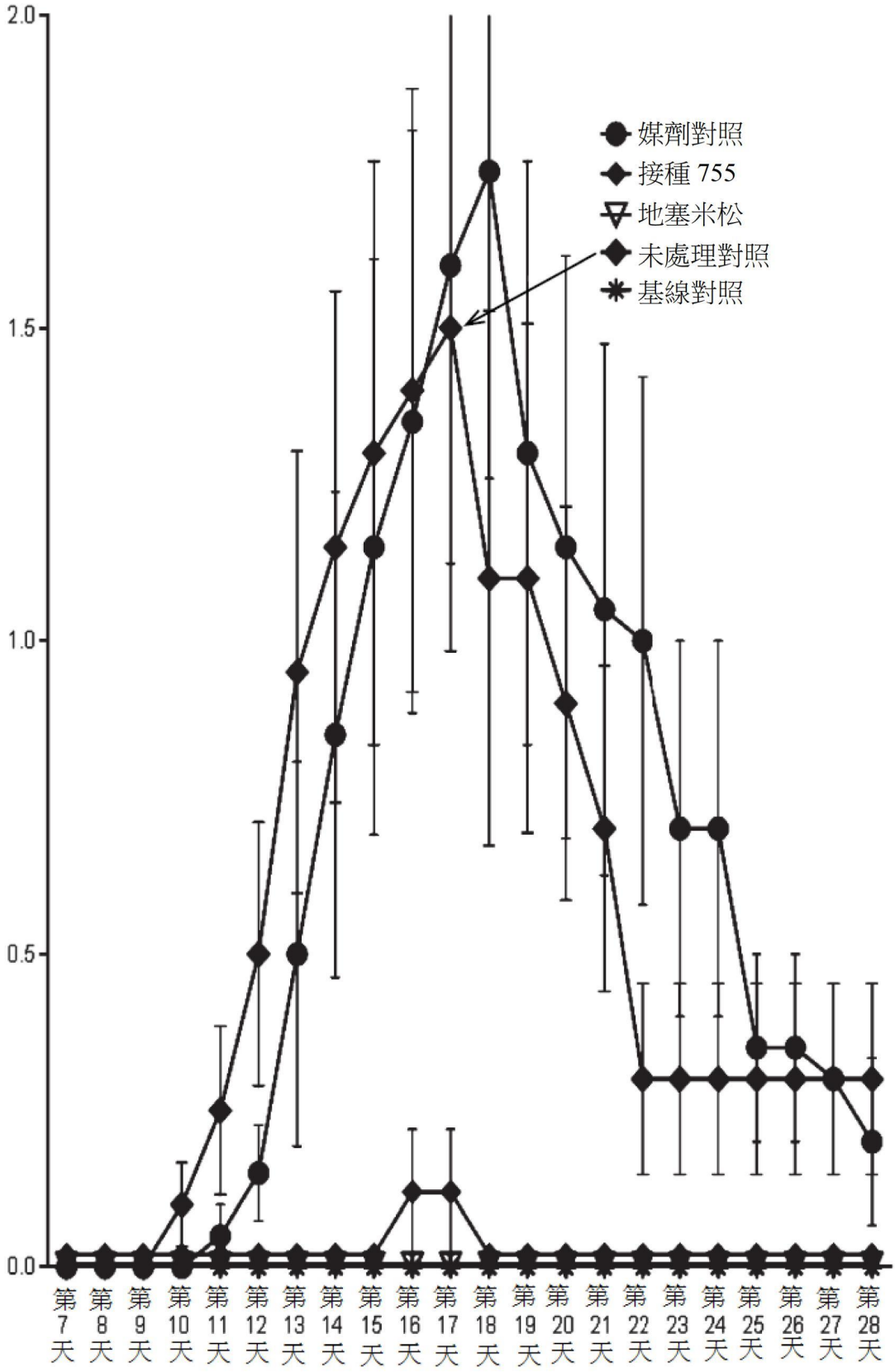


【圖67】

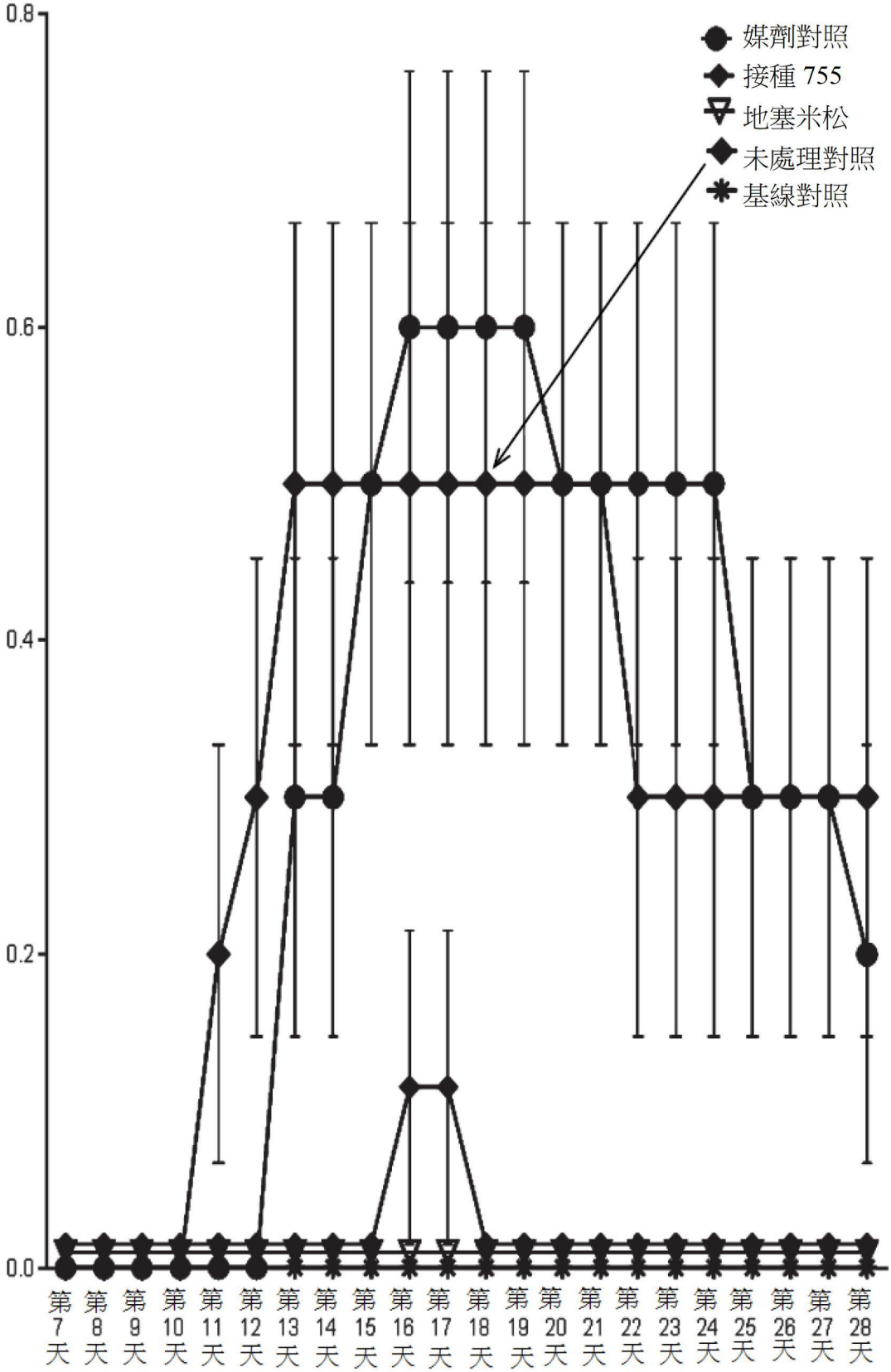




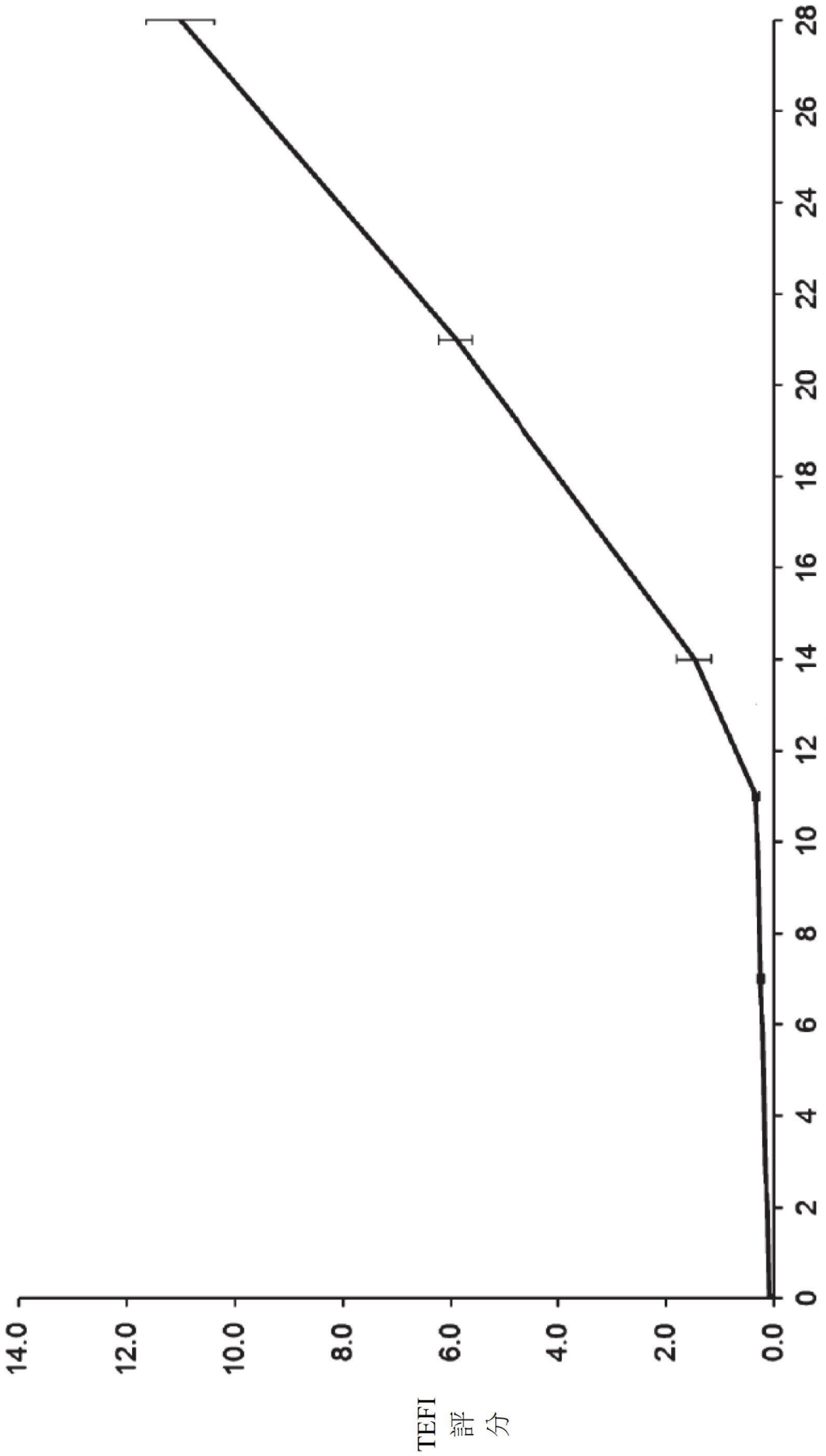
【圖69】


2.0
1.5
1.0
0.5
0.0
媒劑對照
接種 755
地塞米松
未處理對照
基線對照
第7天
第8天
第9天
第10天
第11天
第12天
第13天
第14天
第15天
第16天
第17天
第18天
第19天
第20天
第21天
第22天
第23天
第24天
第25天
第26天
第27天
第28天

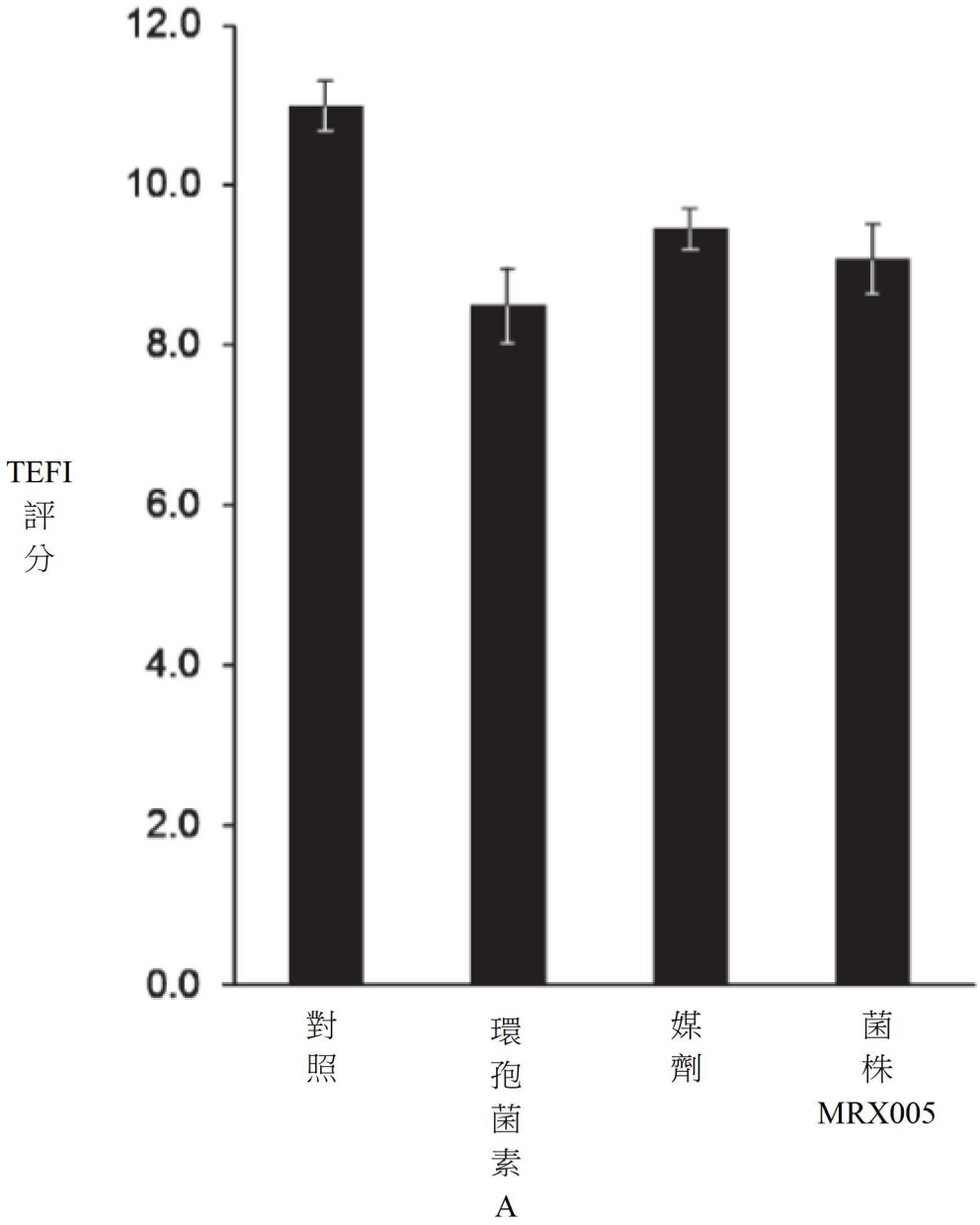
【圖70】


媒劑對照
接種 755
地塞米松
未處理對照
基線對照
0.8
0.6
0.4
0.2
0.0
第7天
第8天
第9天
第10天
第11天
第12天
第13天
第14天
第15天
第16天
第17天
第18天
第19天
第20天
第21天
第22天
第23天
第24天
第25天
第26天
第27天
第28天

【圖71】


TEFI
評分
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
時間(天)

【圖72】



【圖73】