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發明

全 21 頁

【54】名稱：HER2 標靶藥物

【21】申請案號：114129312

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日本

2020-198044

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日本

國立大學法人東北大學

TOHOKU UNIVERSITY

日本

【74】代理人：陳長文

【56】參考文獻：

期刊 Shinji Yamada et al., Establishment of H2Mab-119, an Anti-Human Epidermal Growth Factor Receptor 2 Monoclonal Antibody, Against Pancreatic Cancer. Monoclon Antib Immunodiagn Immunother. 36(6): doi: 10.1089/mab.2017.0050. 2017 Dec; Epub 2017 Nov 27. 287-290.

期刊 Shunsuke Itai et al., H2Mab-77 is a Sensitive and Specific Anti-HER2 Monoclonal Antibody Against Breast Cancer. Monoclon Antib Immunodiagn Immunother. 36(4): doi: 10.1089/mab.2017.0026. 2017 Aug; Epub 2017 Jul 12. 143-148.

審查人員：吳淑君

【57】申請專利範圍

1. 一種特異性結合於 HER2 之經單離之抗體或其抗原結合性片段，其包含重鏈可變區及輕鏈可變區，上述重鏈可變區包含
為序列編號：24 之胺基酸序列之重鏈 CDR1、
為序列編號：25 之胺基酸序列之重鏈 CDR2、及
為序列編號：26 之胺基酸序列之重鏈 CDR3，
上述輕鏈可變區包含
為序列編號：27 之胺基酸序列之輕鏈 CDR1、
為序列編號：28 之胺基酸序列之輕鏈 CDR2、及
為序列編號：29 之胺基酸序列之輕鏈 CDR3，且
該抗體之抗原結合性片段為 Fab 或 scFv(單鏈 Fv)。
2. 如請求項 1 之抗體或其抗原結合性片段，其為 scFv。

(2)

3. 一種醫藥組合物，其含有包含如請求項 1 或 2 之抗體或其抗原結合性片段之 HER2 標靶藥物作為有效成分。
4. 如請求項 3 之醫藥組合物，其係用於治療癌。
5. 一種癌之治療劑，其包含如請求項 1 或 2 之抗體或其抗原結合性片段作為有效成分。
6. 一種核酸分子，其編碼如請求項 1 或 2 之抗體或其抗原結合性片段。

圖式簡單說明

圖 1A 係實施例中所使用之 pCAG/PA-HER2-RAP-MAP 之向量圖。

圖 1B 係實施例中所使用之 pCAG/PA-HER2ec-RAP-MAP 之向量圖。

圖 2 表示本發明之抗體之一例(H₂Mab-214 及 H₂Mab-250)結合於在乳癌細胞株(SK-BR-3 細胞)上表現之 HER2，另一方面，與於正常人類表皮角化細胞株(HaCaT 細胞)上表現之 HER2 完全不反應。

圖 3 表示免疫組織化學染色(IHC)之結果，該免疫組織化學染色(IHC)之結果表示本發明之抗體之一例(H₂Mab-214 及 H₂Mab-250)將由調查癌細胞之 HER2 表現狀況之先前之診斷試劑診斷為 HER2 陰性的癌細胞染色。

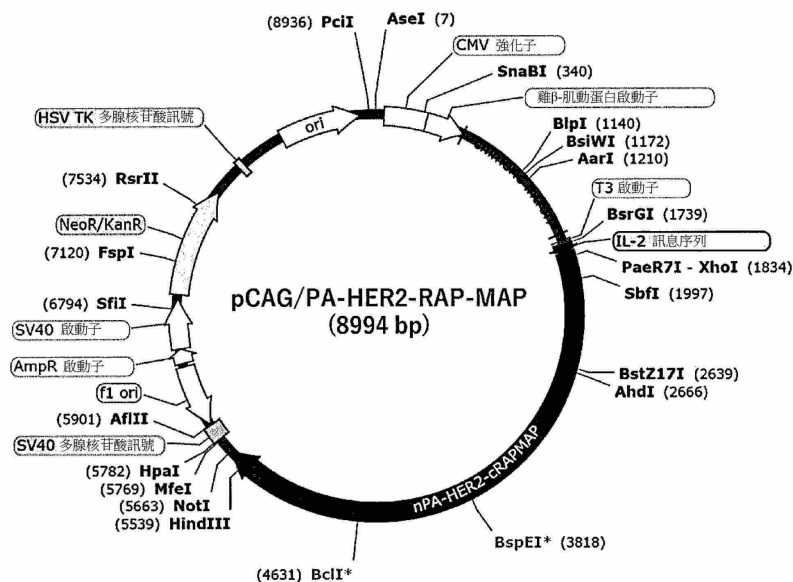
圖 4 表示 H₂Mab-214 及 H₂Mab-250 與各種 HER2 之部分肽之結合性。

圖 5 表示使用使各種 HER2 之丙胺酸置換突變體(W614A、K615A、F616A)表現之 CHO-K1 細胞而分別對於 PA 標籤之抗體(NZ-1)、H₂Mab-214 抗體、H₂Mab-250 抗體、陽性對照抗體(曲妥珠單抗)之流式細胞分析(FACS)解析結果。最左使用使野生型 HER2 表現之 CHO-K1 細胞作為細胞之陽性對照。

圖 6A ~ E 表示實施例 6 中所獲得之抗體群之表位解析結果。

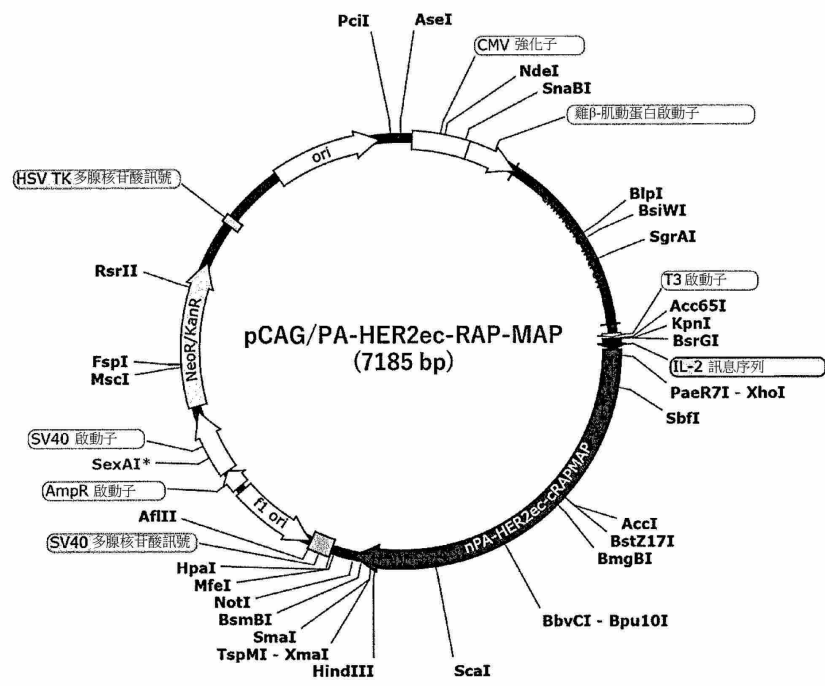
圖 7A ~ G 表示實施例 6 中所獲得之抗體群之流式細胞分析(FACS)解析結果。

圖 8A ~ F 表示實施例 6 中所獲得之抗體群之癌細胞與正常細胞中之免疫組織化學染色(IHC)之結果。

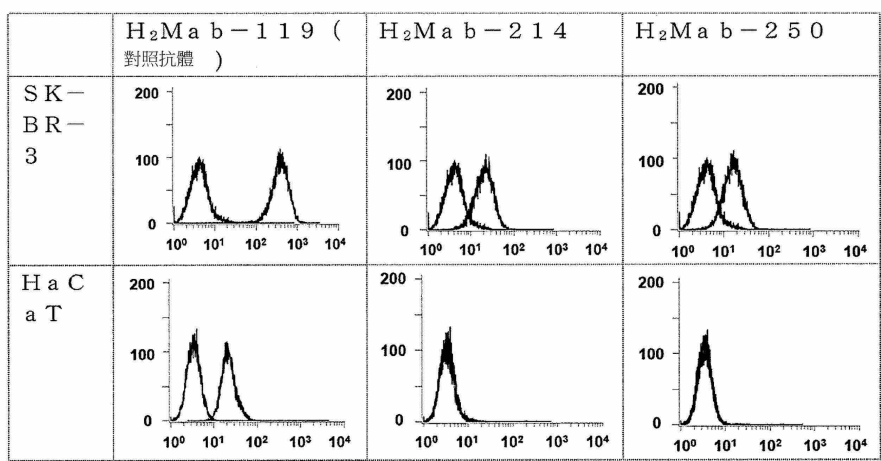


【圖1A】

(3)

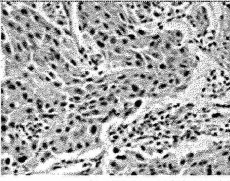
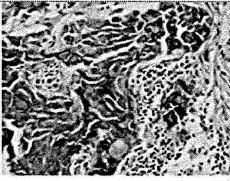
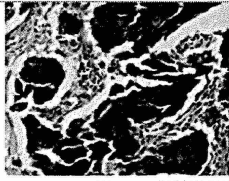
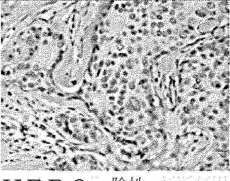
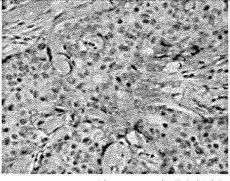


【圖1B】

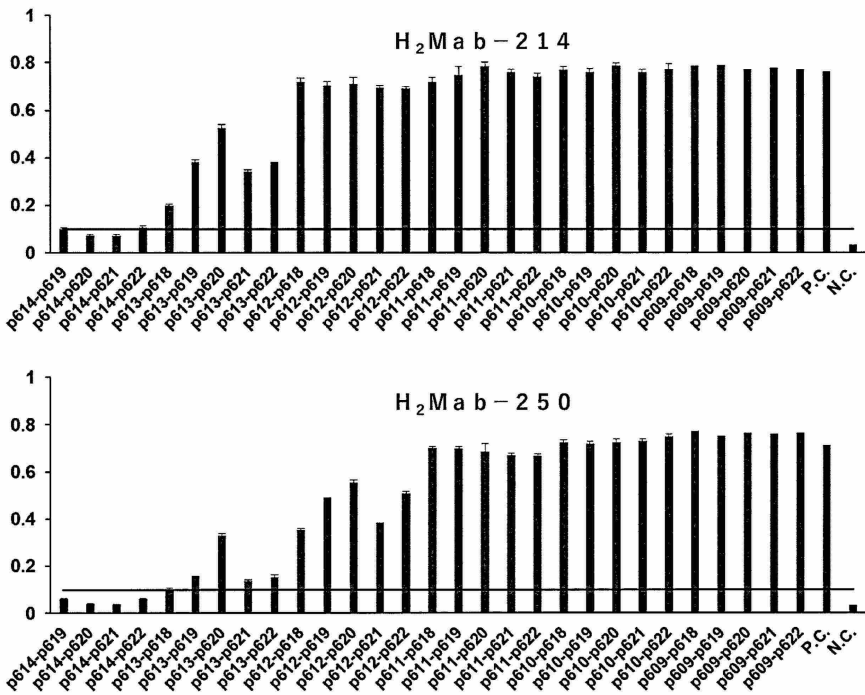


【圖2】

(4)

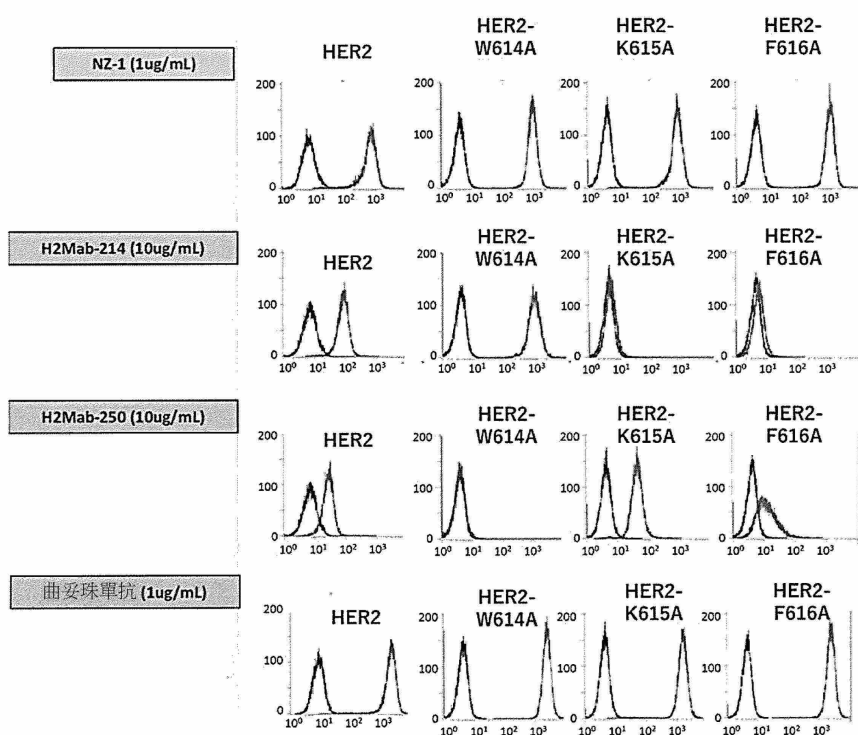
HER2陰性乳癌	H ₂ Ma b-119 (對照抗體)	H ₂ Ma b-214	H ₂ Ma b-250
TMA 核心 F10			
	HER 2 陰性	HER 2 2+	HER 2 3+
TMA 核心 F11			
	HER 2 陰性	HER 2 1+	HER 2 1+

【圖3】



【圖4】

(5)

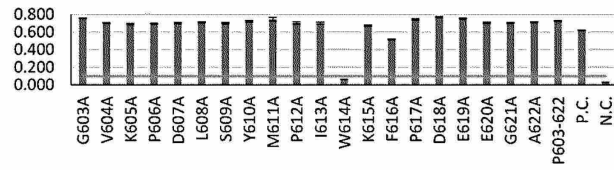


【圖5】

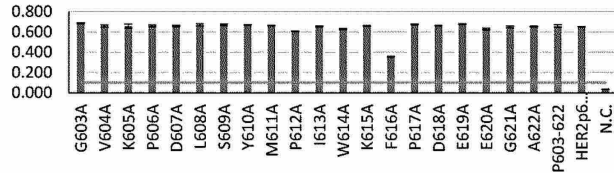
(6)

表位映射之結果

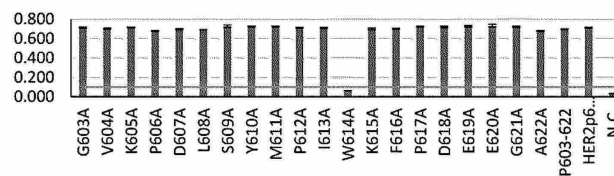
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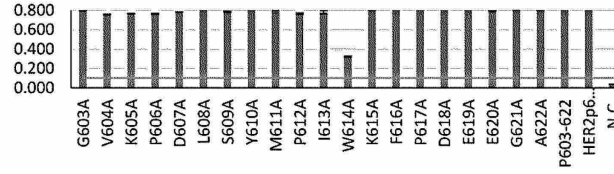
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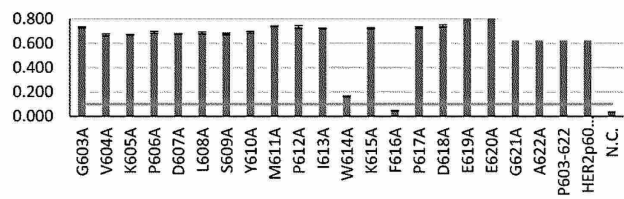
H₂Mab-280 推定表位 : GVKPDLSYMPIWKFPDEEGA



H₂Mab-281 推定表位 : GVKPDLSYMPIWKFPDEEGA

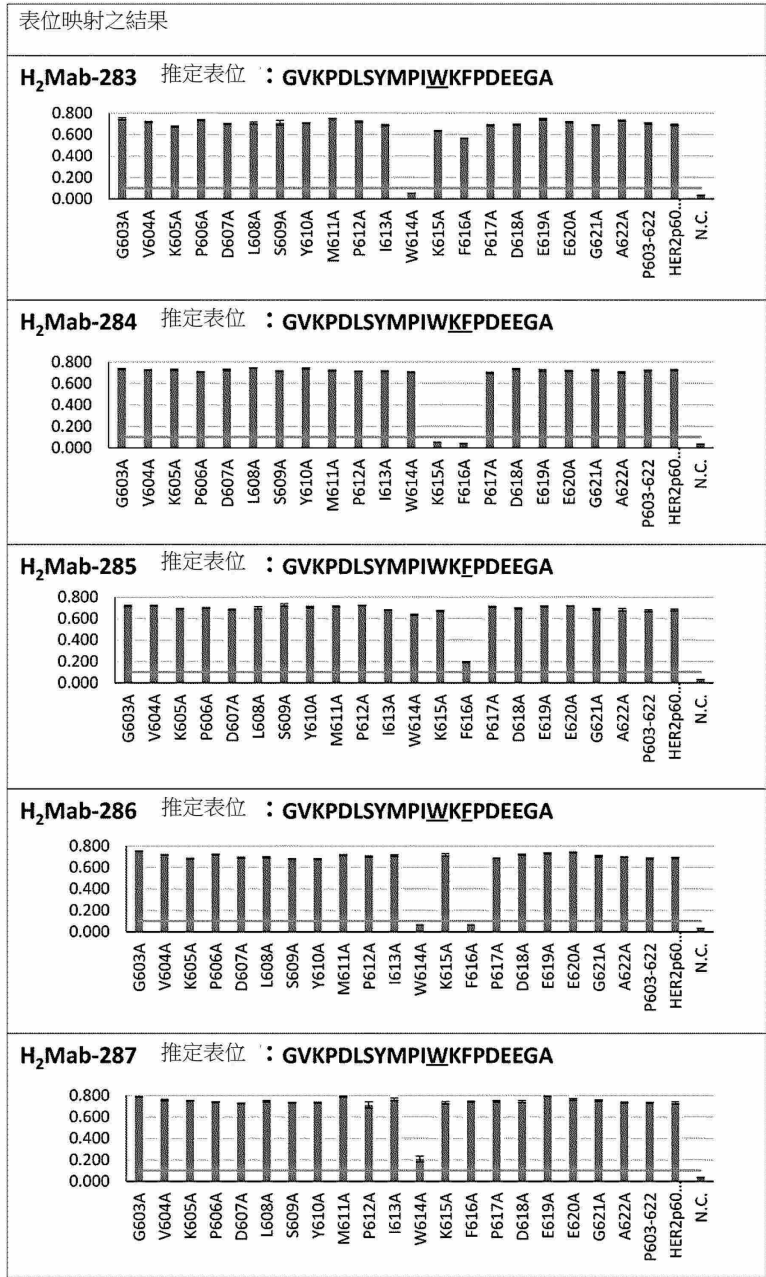


H₂Mab-282 推定表位 : GVKPDLSYMPIWKFPDEEGA



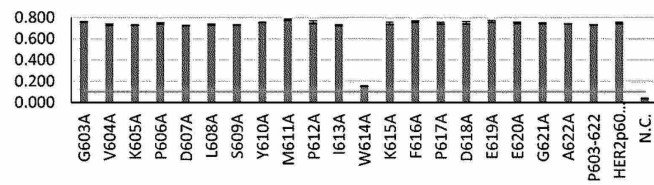
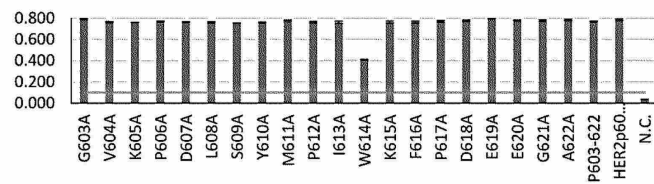
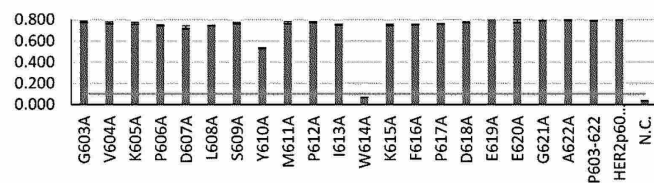
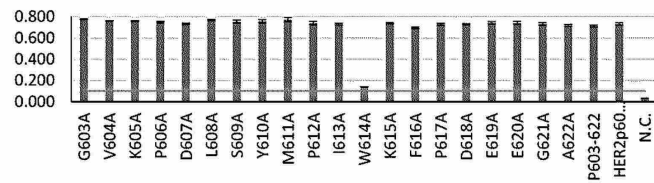
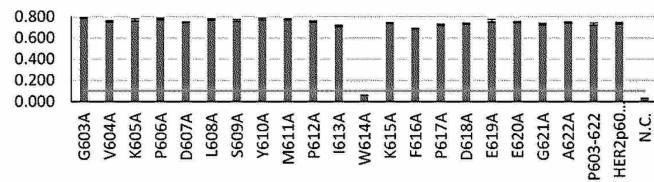
【圖6A】

(7)



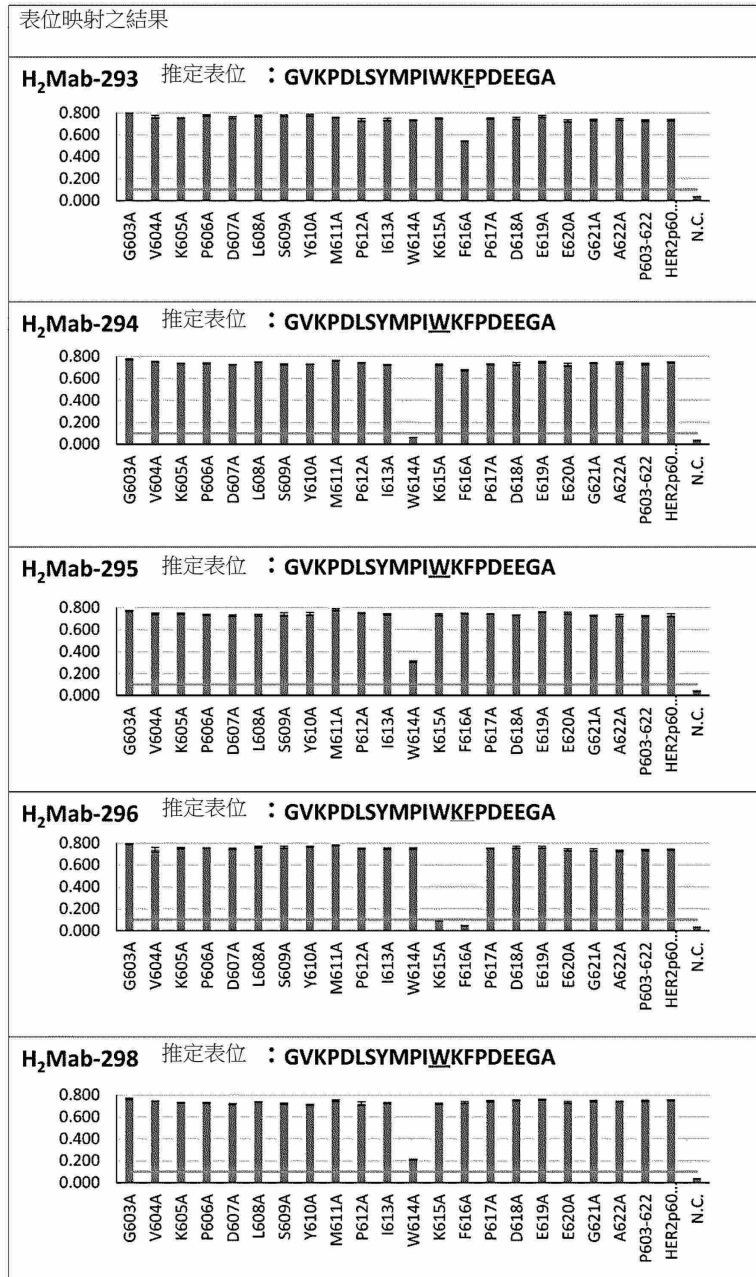
【圖6B】

表位映射之結果

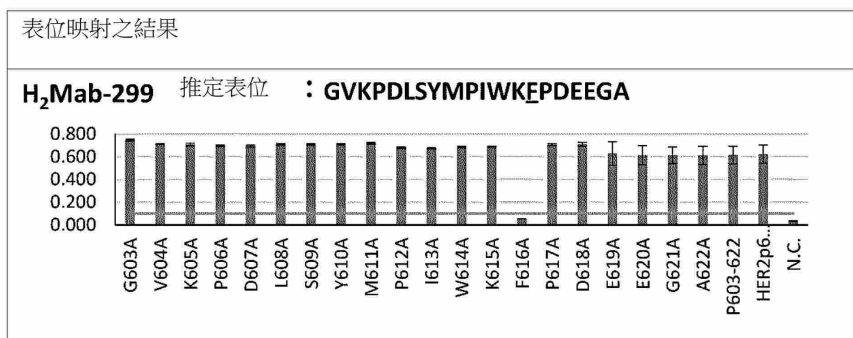
H₂Mab-288 推定表位 : GVKPDLSYMPIWKFPDEEGA**H₂Mab-289** 推定表位 : GVKPDLSYMPIWKFPDEEGA**H₂Mab-290** 推定表位 : GVKPDLSYMPIWKFPDEEGA**H₂Mab-291** 推定表位 : GVKPDLSYMPIWKFPDEEGA**H₂Mab-292** 推定表位 : GVKPDLSYMPIWKFPDEEGA

【圖6C】

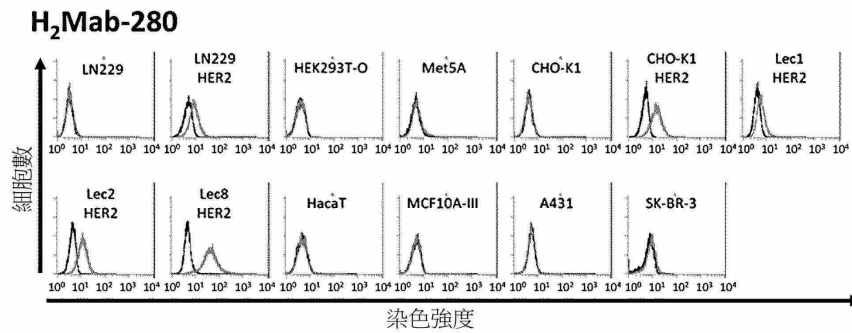
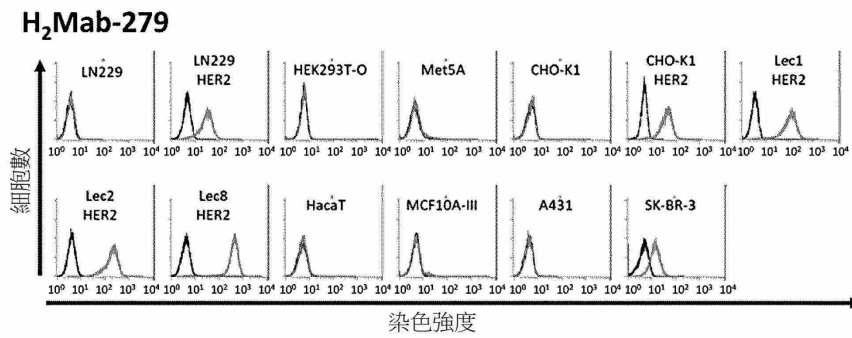
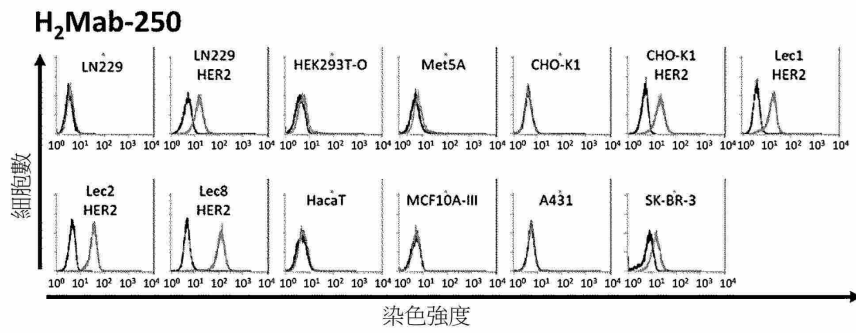
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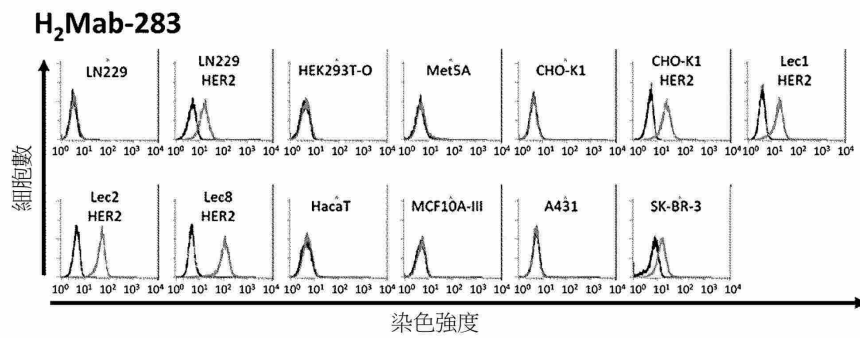
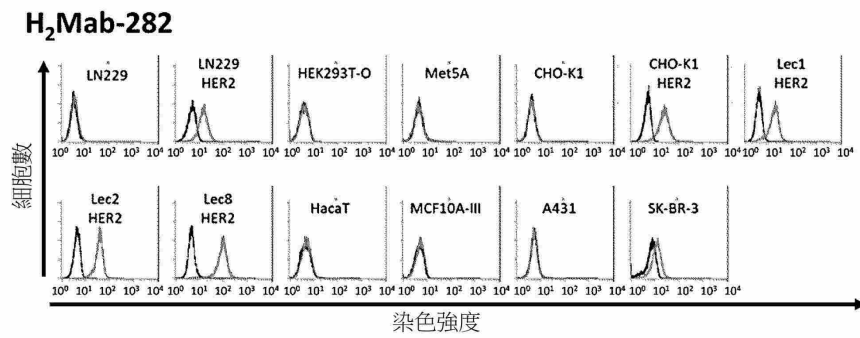
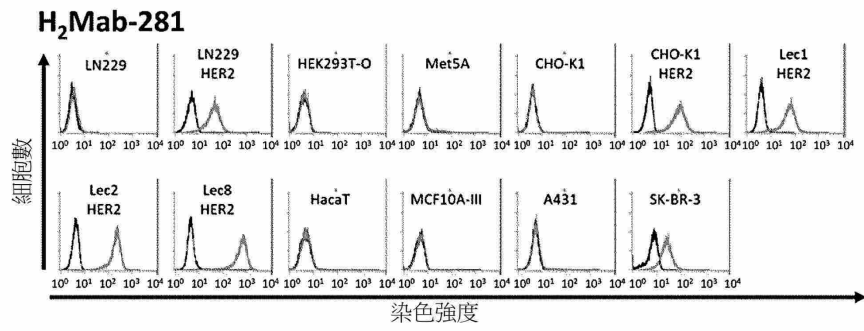
【圖6D】



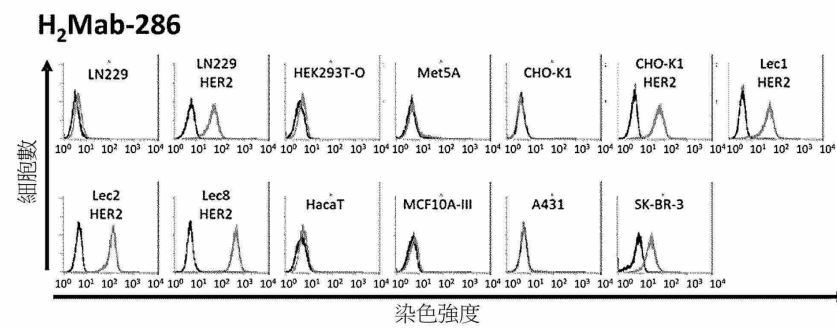
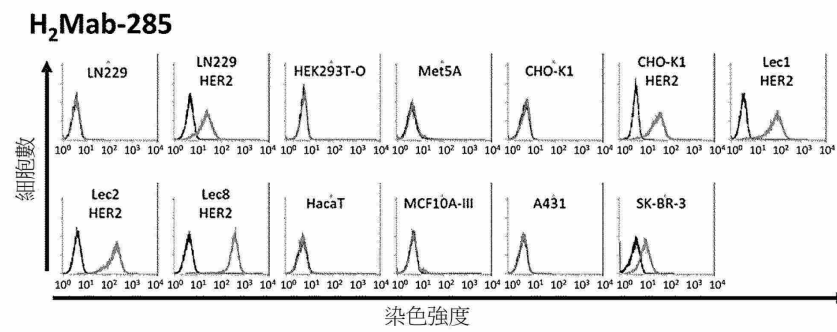
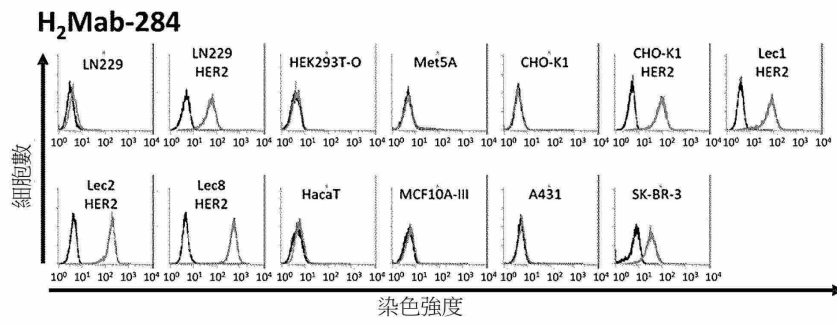
【圖6E】



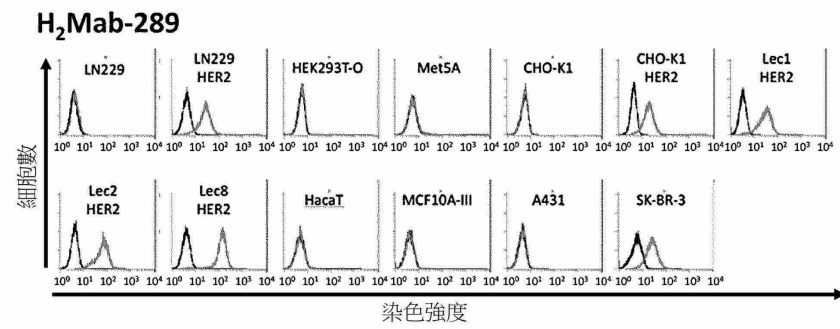
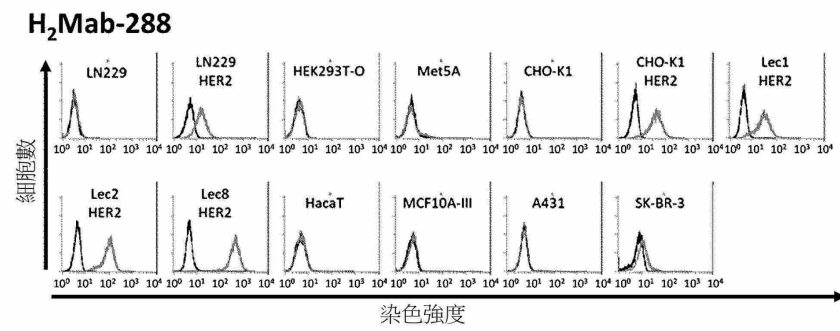
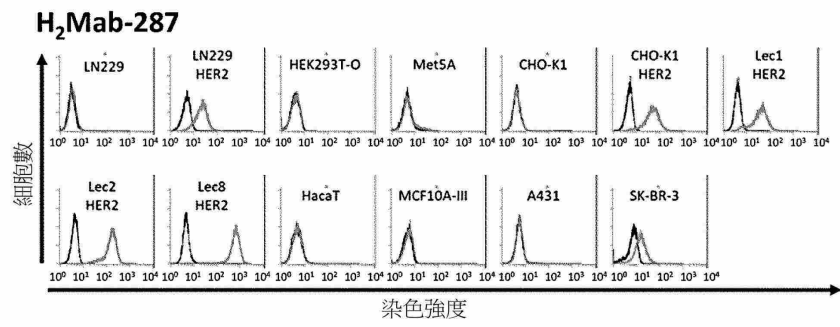
【圖7A】



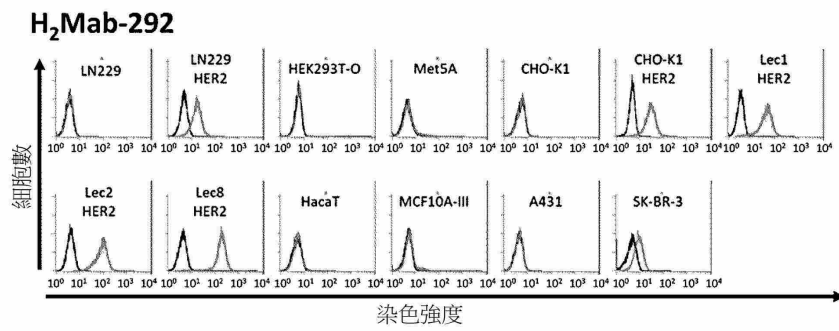
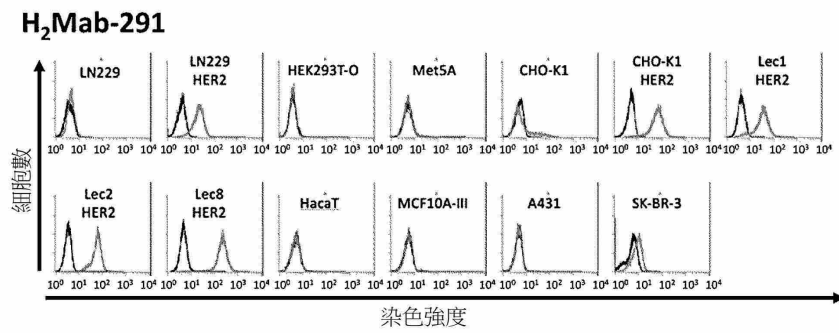
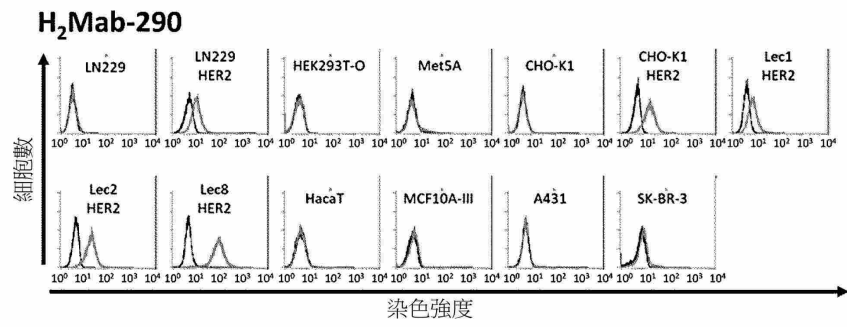
【圖7B】



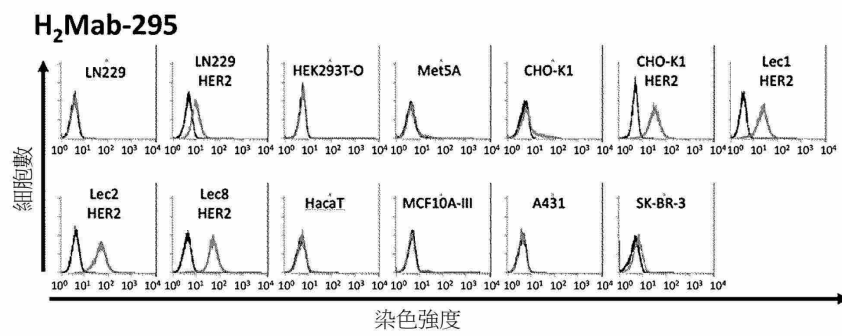
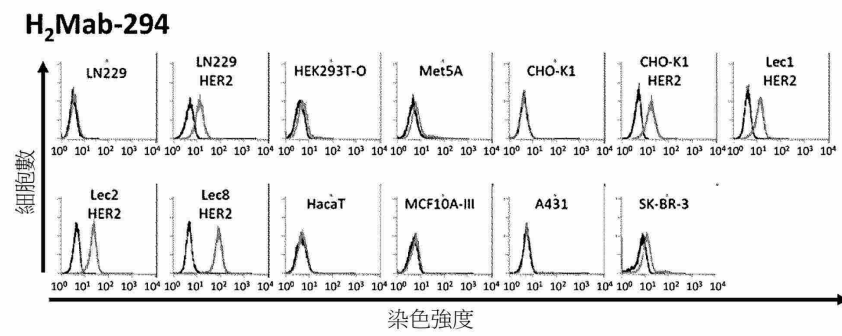
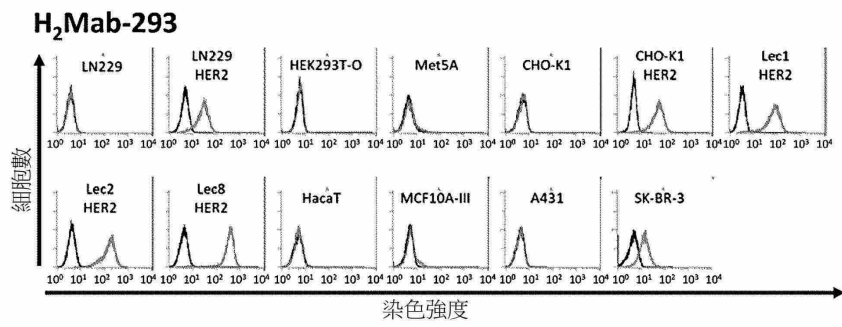
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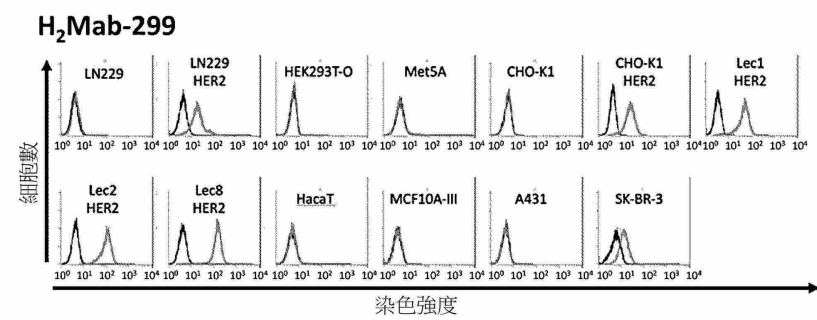
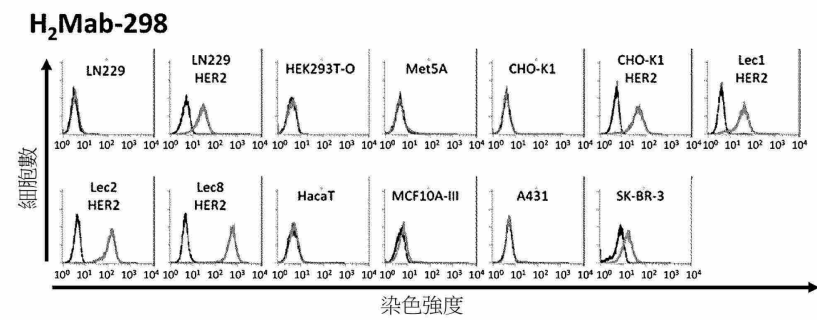
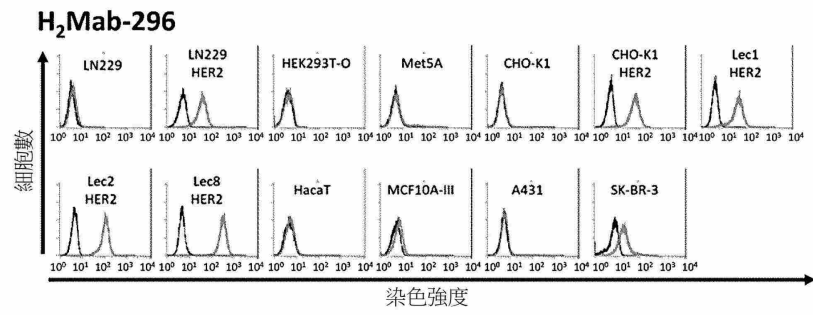
【圖7D】



【圖7E】

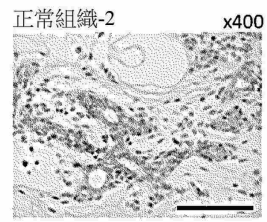
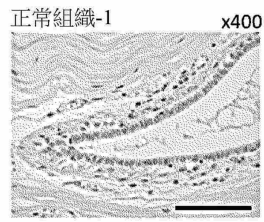
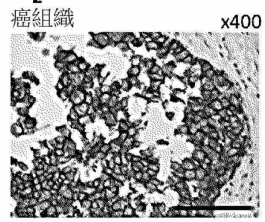


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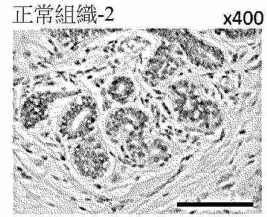
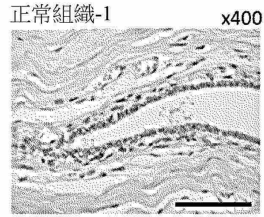
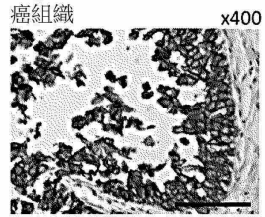
【圖7G】

H₂Mab-250



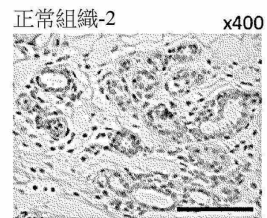
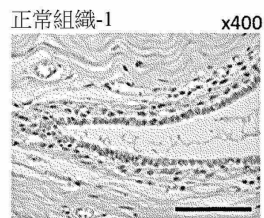
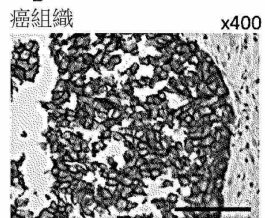
比例尺: 100 μm

H₂Mab-279



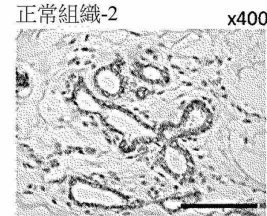
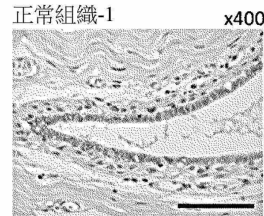
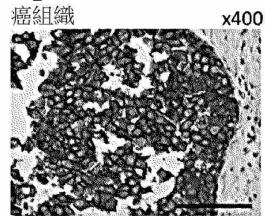
比例尺: 100 μm

H₂Mab-280



比例尺: 100 μm

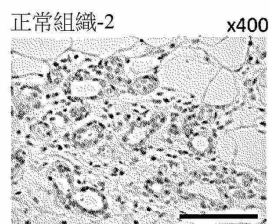
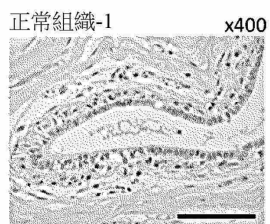
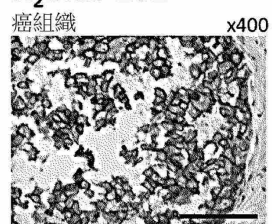
H₂Mab-281



比例尺: 100 μm

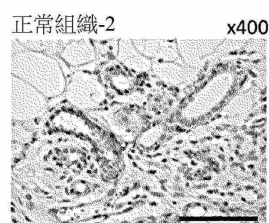
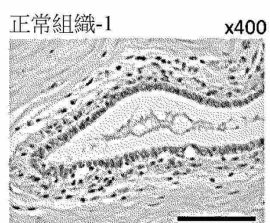
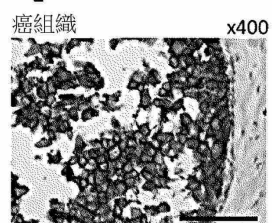
【圖8A】

H₂Mab-282



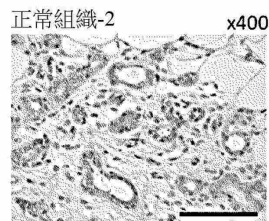
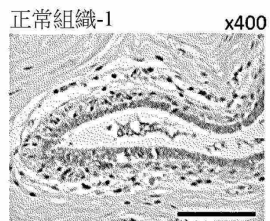
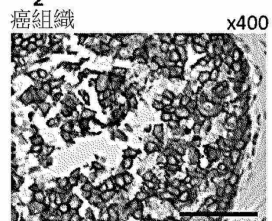
比例尺: 100 μm

H₂Mab-283



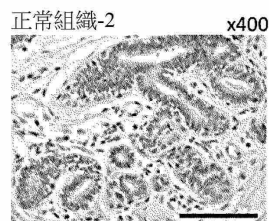
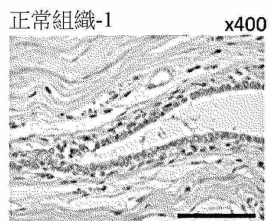
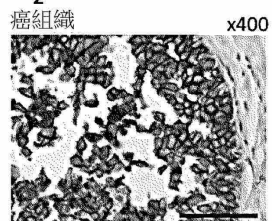
比例尺: 100 μm

H₂Mab-284



比例尺: 100 μm

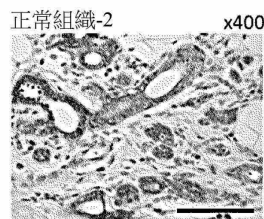
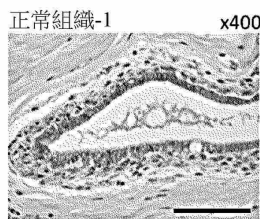
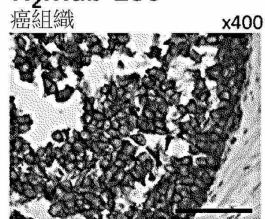
H₂Mab-285



比例尺: 100 μm

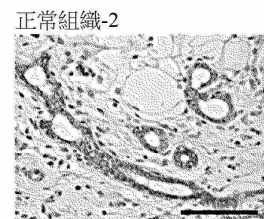
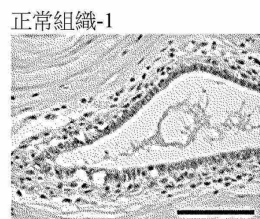
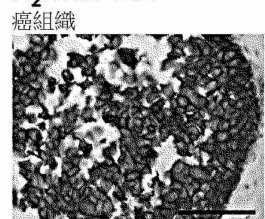
【圖8B】

H₂Mab-286



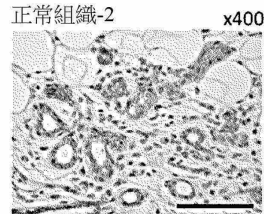
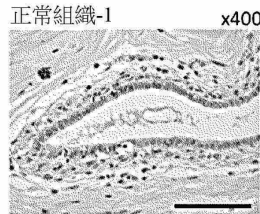
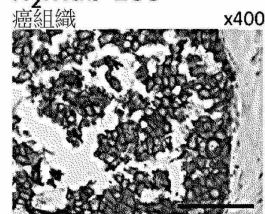
比例尺: 100 μm

H₂Mab-287



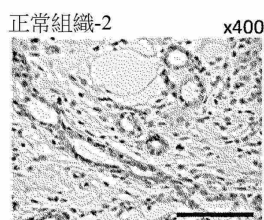
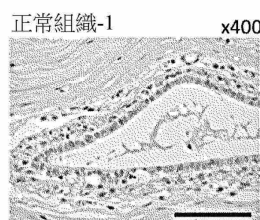
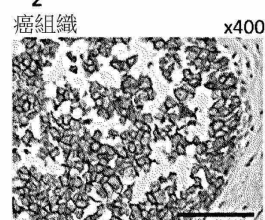
比例尺: 100 μm

H₂Mab-288



比例尺: 100 μm

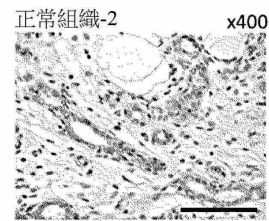
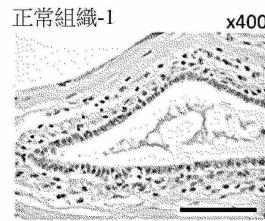
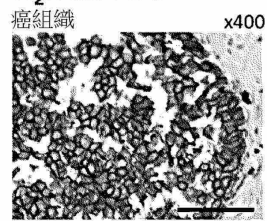
H₂Mab-289



比例尺: 100 μm

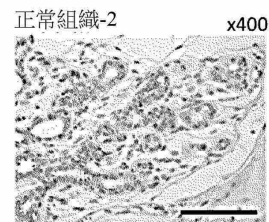
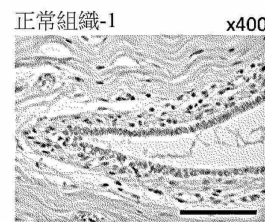
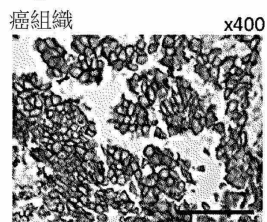
【圖8C】

H₂Mab-290



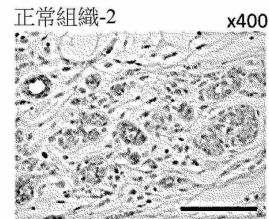
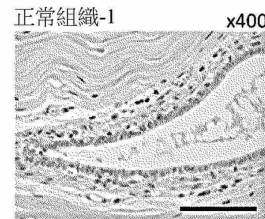
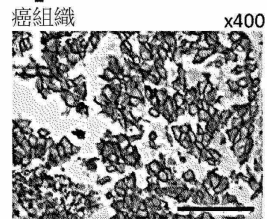
比例尺: 100 μm

H₂Mab-291



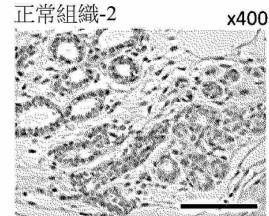
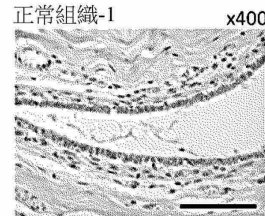
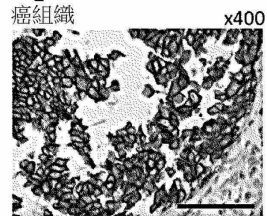
比例尺: 100 μm

H₂Mab-292



比例尺: 100 μm

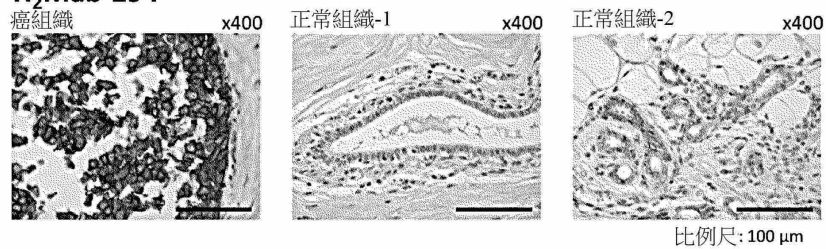
H₂Mab-293



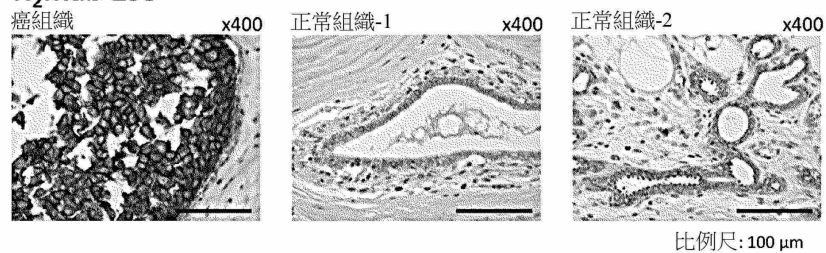
比例尺: 100 μm

【圖8D】

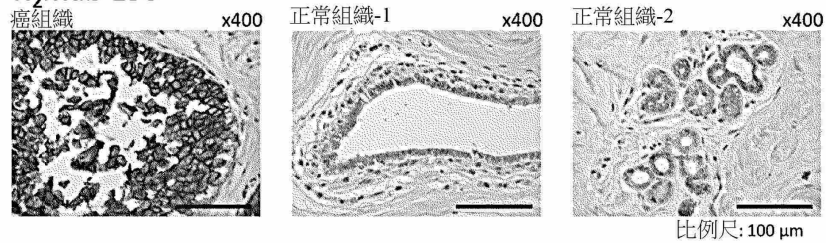
H₂Mab-294



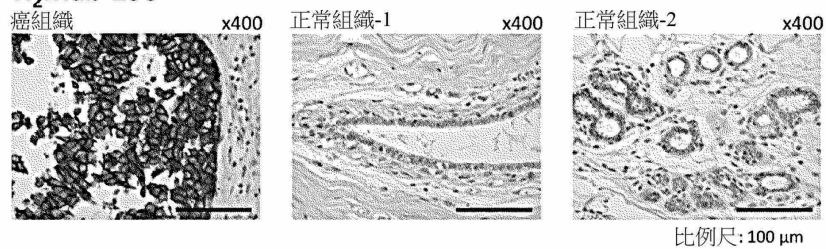
H₂Mab-295



H₂Mab-296

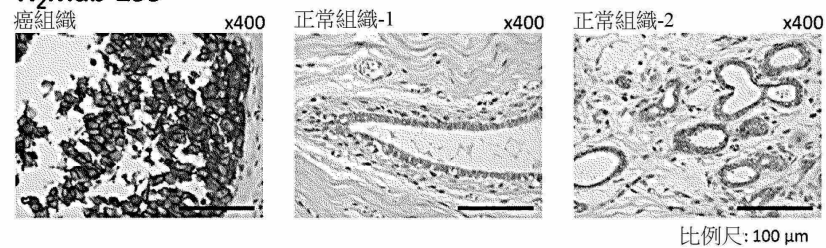


H₂Mab-298



【圖8E】

H₂Mab-299



【圖8F】