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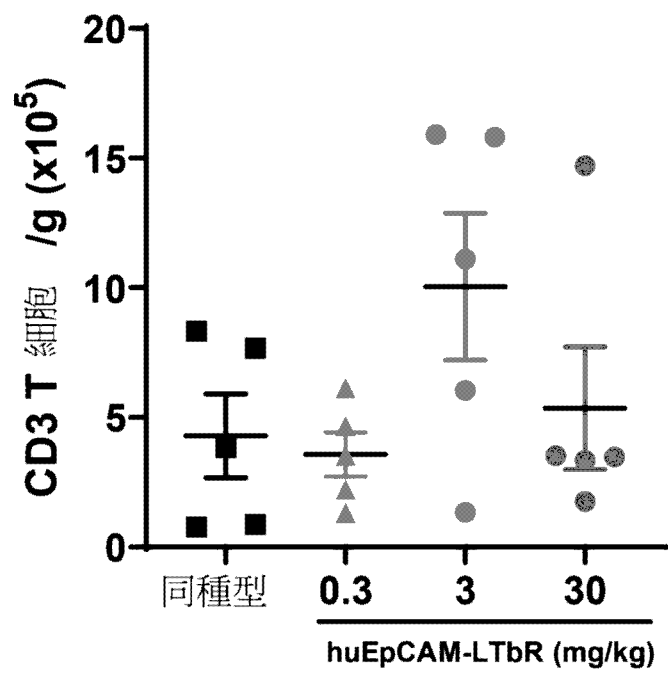
(54)名稱
淋巴毒素 β 受體促效劑結合蛋白

(57)摘要

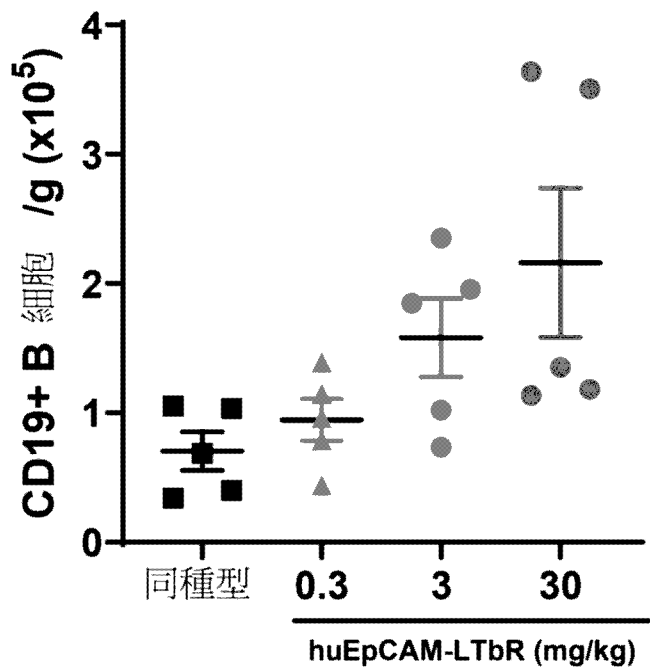
本揭露描述了與淋巴毒素 β 受體 (LTβR) 相互作用並使其激動的 LTβR 結合蛋白，以及製備和使用這樣的 LTβR 結合蛋白之方法。還描述了治療患有實性瘤的受試者之方法，其涉及投與藥學上有效量的 LTβR 結合蛋白。

LTβR binding proteins that interact with and agonize lymphotoxin beta receptor (LTβR) are described as well as methods of making and using such LTβR binding proteins. Methods of treating a subject having a solid tumor that involve administering a pharmaceutically effective amount of LTβR binding protein are also described.

指定代表圖：



【圖1A】



【圖1B】

【發明摘要】

【中文發明名稱】 淋巴毒素 β 受體促效劑結合蛋白

【英文發明名稱】 LYMPHOTOXIN BETA RECEPTOR AGONIST

BINDING PROTEINS

【中文】

本揭露描述了與淋巴毒素 β 受體(LT β R)相互作用並使其激動的LT β R結合蛋白，以及製備和使用這樣的LT β R結合蛋白之方法。還描述了治療患有實性瘤的受試者之方法，其涉及投與藥學上有效量的LT β R結合蛋白。

【英文】

LT β R binding proteins that interact with and agonize lymphotoxin beta receptor (LT β R) are described as well as methods of making and using such LT β R binding proteins. Methods of treating a subject having a solid tumor that involve administering a pharmaceutically effective amount of LT β R binding protein are also described.

【指定代表圖】 圖1A和1B

【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】 淋巴毒素β受體促效劑結合蛋白

【英文發明名稱】 LYMPHOTOXIN BETA RECEPTOR AGONIST

BINDING PROTEINS

【技術領域】

【0001】 本發明之領域關於與淋巴毒素β受體（「LTβR」或「LTBR」）結合蛋白相關的組成物和方法。

【先前技術】

【0002】 癌症免疫療法藉由誘導或增強患者的有效抗腫瘤免疫反應來增強癌症患者的存活率。免疫檢查點抑制係免疫療法的一種形式，其已經改變了許多腫瘤的治療前景。該療法藉由阻斷介導腫瘤免疫逃避的免疫檢查點蛋白（例如細胞毒性T淋巴細胞抗原4（CTLA-4）、計畫性細胞死亡蛋白1（PD-1）和計畫性細胞死亡配體1（PD-L1））的免疫抑制訊息起作用。阻斷這種免疫抑制傳訊可恢復和/或增強身體的自然抗腫瘤反應，以促進腫瘤根除。雖然這種形式的免疫療法在許多患者中產生了持久的反應，但它未能在許多其他患者中產生治療反應。特別地，患有「冷腫瘤」，即以缺乏浸潤性T細胞和存在其他免疫抑制細胞為特徵的腫瘤之患者通常對免疫檢查點抑制劑療法具有耐藥性。因此，本領域需要如下抗癌療法：其可以誘導T細胞浸潤到腫瘤微環境中，以使這樣的冷腫瘤發炎並克服這種耐藥性，從而使腫瘤適合免疫療法。

【發明內容】

【0003】 本揭露之第一方面涉及促效劑淋巴毒素 β 受體(LT β R)結合蛋白。本揭露之促效劑LT β R結合蛋白結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R富含半胱胺酸結構域4(CRD4)的一或多個胺基酸殘基，並且(a)不抑制LIGHT與LT β R結合或(b)不抑制LT α 1 β 2與LT β R結合。

【0004】 本揭露之另一方面涉及雙特異性促效劑LT β R結合蛋白。該雙特異性結合蛋白包含LT β R結合結構域，其中該LT β R結合結構域結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R CRD4的一或多個胺基酸殘基；和腫瘤相關抗原結合結構域。這種雙特異性結合蛋白激動LT β R活性，並且(a)不抑制LIGHT與LT β R結合或(b)不抑制LT α 1 β 2與LT β R結合。

【0005】 本揭露之其他方面涉及編碼本揭露之促效劑LT β R結合蛋白和雙特異性LT β R結合蛋白的多核苷酸；包含該等多核苷酸的載體；以及包含該等載體的宿主細胞。

【0006】 本揭露之額外的方面涉及藥物組成物，該等藥物組成物包含本文所述之促效劑LT β R結合蛋白、雙特異性促效劑LT β R結合蛋白或編碼其的多核苷酸或載體。

【0007】 本揭露之另一方面涉及治療受試者癌症之方法，該等方法涉及向患有癌症的受試者投與促效劑LT β R結合蛋白。該等方法中使用的促效劑LT β R結合蛋白結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R富含半胱胺酸結構域4(CRD4)的一或多個胺基酸殘基，並且(a)不抑制LIGHT與LT β R結合或(b)不抑制LT α 1 β 2與LT β R結合。

【0008】 本揭露之另一方面涉及治療受試者癌症之方法，該等方法涉及向患有癌症的受試者投與雙特異性促效劑LT β R結合蛋白。該雙特異性促效劑LT β R

結合蛋白包含LT β R結合結構域和腫瘤相關抗原結合結構域。該LT β R結合結構域結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R富含半胱胺酸結構域(CRD4)的一或多個胺基酸殘基。雙特異性LT β R結合蛋白進一步包含腫瘤相關抗原結合結構域。雙特異性LT β R結合蛋白激動LT β R活性，並且 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT1 α 2 β 與LT β R結合。

【0009】 LT β R激動作用作為抗腫瘤療法之潛在效用早在20多年前就被提出（參見例如，Browning等人，「Signaling through the Lymphotoxin β Receptor Induces the Death of Some Adenocarcinoma Tumor Lines[通過淋巴毒素 β 受體的傳訊誘導一些腺癌腫瘤系的死亡],」 *J. Exp. Med.*[實驗醫學雜誌] 183:867 (1996)）。儘管如此，只有一種LT β R抗體進入了I期臨床試驗，並且該試驗提前結束。LT β R在全身多種細胞上普遍表現，並在淋巴器官和多種免疫細胞群的形成和維持中起著關鍵作用。因此，為了使LT β R抗體具有治療有效性和安全性，它必須選擇性地激活腫瘤微環境中的LT β R傳訊，而不會破壞腫瘤微環境外的正常LT β R傳訊。雖然可以使用提供交聯特異性LT β R激活的雙特異性模式來實現將激動作用靶向腫瘤環境；但如果設計不當，交聯依賴性促效劑將在以靶標非依賴性方式結合LT β R時充當拮抗劑。鑒於LT β R在維持免疫功能中的重要性，對其活性進行拮抗造成嚴重的安全問題。

【0010】 本文揭露的促效劑LT β R結合蛋白藉由以交聯靶標依賴性方式發揮促效劑活性而不拮抗正常LT β R傳訊活性來克服這個問題。這藉由特異性選擇和工程化LT β R結合蛋白來實現，當與LT β R的富含半胱胺酸的結構域4 (CRD4) 結合時，該LT β R結合蛋白以交聯特異性方式激動LT β R，而不阻斷內源性LT β R配體（即LIGHT或LT α 1 β 2）結合和傳訊活性。

【圖式簡單說明】

【0011】 [圖1A-1B]顯示了靶向腫瘤相關抗原 (TAA) 的LTβR激動作用增加表現人EpCAM的B16F10黑色素瘤腫瘤模型中的淋巴細胞浸潤。如圖1A的圖表所示，相對於投與同種型對照抗體，在3 mg/kg劑量的人EpCAM x 鼠LTβR雙特異性抗體的情況下，浸潤腫瘤組織的T細胞 (CD3⁺ T細胞) 的總數增加。如圖1B的圖表所示，相對於投與同種型對照抗體，浸潤腫瘤組織的B細胞 (CD19⁺ B細胞) 的總數隨著huEpCAM x muLTβR BsAb的劑量 (0.3、3和30 mg/kg) 的增加而增加。

【0012】 [圖2]顯示了在表現人EpCAM的B16F10黑色素瘤腫瘤模型中，靶向腫瘤相關抗原 (TAA) 的LTβR激動作用誘導HEV形成。圖2顯示了同種型對照治療 (上圖像) 和3 mg/kg的huEpCAM-muLTβR雙特異性抗體治療 (下圖像) 後，腫瘤組織中HEV形成的免疫組織化學分析，如本文實例1所描述的。

【0013】 [圖3]顯示了靶向腫瘤相關抗原 (TAA) 的LTβR激動作用在人KPC胰臟腫瘤模型中增加T細胞浸潤。圖3的圖表顯示了在向攜帶KPC M5腫瘤的小鼠投與兩種不同工具huLRRC15 x muLTβR BsAb後，每克腫瘤組織的T細胞計數增加。在用流動式細胞分析術評估腫瘤之前，每週投與兩次huLRRC15 x muLTβR BsAb，共3劑。Dunnett多重比較檢驗的單因子變異數分析 (One-way ANOVA) 顯示了相對於同種型沒有顯著差異，但治療確實顯示出T細胞浸潤的上升趨勢。圖表中表示了平均值和SEM。

【0014】 [圖4]顯示了靶向腫瘤相關抗原 (TAA) 的LTβR激動作用在人KPC胰臟腫瘤模型中抑制腫瘤生長。圖4的圖表顯示了用PD-1抗體、huLRRC15 x muLTβR BsAb或該等抗體的組合治療的KPC M5胰臟腫瘤模型的平均腫瘤體積。huLRRC15 x muLTβR BsAb單一療法 (▼) 比PD-1單一療法 (■) 產生的效果更大。huLRRC15 x muLTβR BsAb和PD-1 Ab組合確實顯示出更大的TGI，但兩個治療組之間的差異沒有統計學顯著性。Tukey多重比較檢驗的雙因子變異數分析

(Two-way ANOVA) 表明, huLRRC15 x muLTbR BsAb和huLRRC15 x muLTbR BsAb + PD-1 Ab抗體相對於同種型的顯著性 ($p < 0.0001$)。N = 10, 圖表中表示了平均值和SEM。

【0015】 [圖5]包含表A和表B, 總結了在第一輪融合瘤篩選中鑒定的LTβR抗體的表徵數據。表A包含功能效力值 (EC_{50}) 和結合數據, 即LTβR抗體與TNFRSF1和TNFRSF2、小鼠LTβR和食蟹猴LTβR結合。數據呈現為模擬轉染細胞的GeoMean倍數。表A還顯示了在指示LTβR抗體存在下, 使用基於單點FACS珠粒的受體-配體測定評估的人LIGHT或人LTα1β2配體與人LTβR結合的抑制百分比, 如實例4.6中所述。表B顯示了LTβR抗體與人和食蟹猴LTβR的結合親和力測量值 (k_a 、 k_d 和KD)。

【0016】 [圖6]鑒定了參與同LTβR抗體, LIBC No. 218990 (Bio. Reg. No. 19320 / Well ID 30H1) 之結合相互作用的LTβR胞外結構域 (ECD) (SEQ ID NO: 4) 的區域, 如藉由氫-氬交換 (HDX) 質譜 (MS) 確定的 (參見實例6.1.1)。顯示了對應於單獨或與抗體複合的LTβR胞外結構域 (ECD) 的殘基56-64和81-101的肽之氬攝取圖表。相對於非複合肽, 複合物衍生肽中免於氬交換表明, LTβR ECD的該等區域內的一或多個殘基, 即殘基57-64和82-101參與結合相互作用 (注意, 肽的N端殘基沒有用於測量的醯胺氬, 因此在報告表位區域時被排除在外)。

【0017】 [圖7]鑒定了參與同LTβR抗體, LIBC No. 218944 (Bio. Reg No. 19321 / Well ID 31A3) 之結合相互作用的LTβR ECD (SEQ ID NO: 4) 的區域, 如藉由HDX MS確定的 (參見實例6.1.1)。顯示了對應於單獨或與抗體複合的LTβR ECD的殘基3-9、20-29和38-47的肽之氬攝取圖表。相對於非複合肽, 複合物衍生肽中免於氬交換表明, LTβR ECD的該等區域內的一或多個殘基, 即殘基4-9、21-29和39-47參與結合相互作用 (注意, 肽的N端殘基沒有用於測量的醯胺氬, 因此在報告表位區域時被排除在外)。

【0018】[圖8]鑒定了參與同LT β R抗體，LIBC No. 219058 (Bio. Reg. No. 19324 / Well ID 36G2) 之結合相互作用的LT β R ECD (SEQ ID NO: 4) 的區域，如藉由HDX MS確定的 (參見實例6.1.1)。顯示了對應於單獨或與抗體複合的LT β R ECD的殘基56-64和81-101的肽之氘攝取圖表。相對於非複合肽，複合物衍生肽中免於氘交換表明，LT β R ECD的該等區域內的一或多個殘基，即殘基57-64和82-101參與結合相互作用 (注意，肽的N端殘基沒有用於測量的氘胺氘，因此在報告表位區域時被排除在外)。

【0019】[圖9]鑒定了參與同LT β R抗體，LIBC No. 219081 (Bio Reg. No. 19325 / Well ID 41B2) 之結合相互作用的LT β R ECD (SEQ ID NO: 4) 的區域，如藉由HDX MS確定的 (參見實例6.1.1)。顯示了對應於單獨或與抗體複合的LT β R ECD的殘基167-179的肽之氘攝取圖表。相對於非複合肽，複合物衍生肽中免於氘交換表明，LT β R ECD的該等區域內的一或多個殘基，即殘基168-179參與結合相互作用 (注意，肽的N端殘基沒有用於測量的氘胺氘，因此在報告表位區域時被排除在外)。

【0020】[圖10]鑒定了參與同LT β R抗體，LIBC No. 219097 (Bio. Reg. No. 19326 / Well ID 43D9) 之結合相互作用的LT β R ECD (SEQ ID NO: 4) 的區域，如藉由HDX MS確定的 (參見實例6.1.1)。顯示了對應於單獨或與抗體複合的LT β R ECD的殘基38-42、37-47、56-64和65-70的肽之氘攝取圖表。相對於非複合肽，複合物衍生肽中免於氘交換表明，LT β R ECD的該等區域內的一或多個殘基，即殘基39-42和57-70參與結合相互作用 (注意，肽的N端殘基沒有用於測量的氘胺氘，因此在報告表位區域時被排除在外)。

【0021】[圖11]鑒定了參與同LT β R抗體，LIBC No. 218979 (Bio. Reg. No. 19319 / Well ID 23E9) 之結合相互作用的LT β R ECD (SEQ ID NO: 4) 的區域，如藉由HDX MS確定的 (參見實例6.1.2)。顯示了對應於單獨或與抗體複合的

LT β R ECD的殘基154-166、167-177、167-181和178-193的肽之氘攝取圖表。相對於非複合肽，複合物衍生肽中免於氘交換表明，LT β R ECD的該等區域內的一或多個殘基，即殘基168-178參與結合相互作用（注意，肽的N端殘基沒有用於測量的醯胺氘，因此在報告表位區域時被排除在外）。

【0022】[圖12]鑒定了參與同LT β R抗體，LIBC No. 219051（Bio. Reg. No. 19323 / Well ID 35F5）之結合相互作用的LT β R ECD（SEQ ID NO: 4）的區域，如藉由HDX MS確定的（參見實例6.1.2）。顯示了對應於單獨或與抗體複合的LT β R ECD的殘基1-9、1-20（未糖基化和糖基化）、10-20和19-28的肽之氘攝取圖表。相對於非複合肽，複合物衍生肽中免於氘交換表明，LT β R ECD的區域1-19內的一或多個殘基參與結合相互作用（注意，Q1已轉化為pyro-Q，其含有可測量的醯胺氘）。

【0023】[圖13]鑒定了參與同LT β R結合相互作用的LIBC No. 218990（19320/30H1）的可變重（VH）和可變輕（VL）結構域區域。顯示了單獨或與LT β R結合的VH和VL結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH和VL序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0024】[圖14A-14B]鑒定了參與同LT β R結合相互作用的LIBC No. 218944（19321/31A3）的可變重（VH）和可變輕（VL）結構域區域。顯示了單獨或與LT β R結合的VH（圖14A）和VL（圖14B）結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH（圖14A）和VL（圖14B）序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0025】[圖15]鑒定了參與同LT β R結合相互作用的LIBC No. 219058

(19324/36G2)的可變重(VH)和可變輕(VL)結構域區域。顯示了單獨或與LT β R結合的VH和VL結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH和VL序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0026】 [圖16A-16B]鑒定了參與同LT β R結合相互作用的LIBC No. 219081 (19325/41B2)的可變重(VH)和可變輕(VL)結構域區域。顯示了單獨或與LT β R結合的VH(圖16A)和VL(圖16B)結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH(圖16A)和VL(圖16B)序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0027】 [圖17A-17B]鑒定了參與同LT β R結合相互作用的LIBC No. 219097 (19326/43D9)的可變重(VH)和可變輕(VL)結構域區域。顯示了單獨或與LT β R結合的VH(圖17A)和VL(圖17B)結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH(圖17A)和VL(圖17B)序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0028】 [圖18A-18B]鑒定了參與同LT β R結合相互作用的LIBC No. 218979 (Bio. Reg. No. 19319 / Well ID 23E9)的可變重(VH)和可變輕(VL)結構域區域。顯示了單獨或與LT β R結合的VH(圖18A)和VL(圖18B)結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH(圖18A)和VL(圖18B)序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0029】[圖19A-19B]鑒定了參與同LT β R結合相互作用的LIBC No. 219051 (Bio. Reg. No. 19323 / Well ID 35F5) 的可變重 (VH) 和可變輕 (VL) 結構域區域。顯示了單獨或與LT β R結合的VH (圖19A) 和VL (圖19B) 結構域肽之氬攝取圖表。相對於非複合肽，複合肽中免於氬交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH (圖19A) 和VL (圖19B) 序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0030】[圖20]係顯示huLT β R x huCLDN6雙特異性抗體 (PUR149204-4、PUR149205-4、PUR149212-5和PUR149213-4) 之效力的圖表。在所指示的huLT β R x huCLDN6雙特異性抗體濃度增加的情況下，藉由與表現CLDN6的倉鼠卵巢細胞 (CHO) 共培養的表現LT β R之人黑色素瘤細胞釋放的IL-8來測量效力。y軸的「訊號」表示藉由665 nm處訊號與615 nm處訊號的比率計算的相對IL-8釋放。

【0031】[圖21]係顯示huLT β R x huCLDN18.2雙特異性抗體 (PUR149206-4、PUR149214-4和PUR149215-4) 之效力的圖表。在所指示的huLT β R x huCLDN18.2雙特異性抗體濃度增加的情況下，藉由與表現CLDN18.2的CHO細胞共培養的表現LT β R之人黑色素瘤細胞釋放的IL-8來測量效力。y軸的「訊號」表示藉由665 nm處訊號與615 nm處訊號的比率計算的相對IL-8釋放。

【0032】[圖22]係顯示huLT β R x huMUC17雙特異性抗體 (PUR149211-4、PUR149218-4和PUR149219-4) 之效力的圖表。在所指示的huLT β R x huMUC17雙特異性抗體濃度增加的情況下，藉由與表現MUC17的CHO細胞共培養的表現LT β R之人黑色素瘤細胞釋放的IL-8來測量效力。y軸的「訊號」表示藉由665 nm處訊號與615 nm處訊號的比率計算的相對IL-8釋放。

【0033】[圖23]係顯示huLT β R x huLRRC15雙特異性抗體 (44245-5、45147-3和52208-3) 之效力的圖表。在huLT β R x huLRRC15雙特異性抗體濃度增加的情

況下，藉由與表現LRRC15的Saos-2細胞共培養的表現LT β R之人黑色素瘤細胞釋放的IL-8來測量效力。y軸的「訊號」表示藉由665 nm處訊號與615 nm處訊號的比率計算的相對IL-8釋放。

【0034】 [圖24A-24C]係顯示在本文所描述各種LT β R抗體濃度增加的情況下，LIGHT（圖24A）和LT α 1 β 2（圖24B）抑制作用的圖表。圖24C係顯示抗LT β R抗體與由HEK293細胞表現的LT β R結合的圖表，以證實非配體阻斷活性不是由於測試抗體的非受體結合所致。

【0035】 [圖25A-25C]係顯示在如本文所描述的各種LT β R-LRRC15雙特異性抗體濃度增加的情況下，LIGHT（圖25A）和LT α 1 β 2（圖25B）抑制作用的圖表。圖25C係顯示LT β R-LRRC15雙特異性抗體與HEK293細胞表現的LT β R結合的圖表，以證實非配體阻斷活性不是由於測試雙特異性抗體的非受體結合所致。

【0036】 [圖26A-26C]係顯示在如本文所描述的所指定LT β R-LRRC15雙特異性抗體（52208）濃度增加的情況下，LT α 1 β 2（圖26A）和LIGHT（圖26B）抑制作用的圖表。圖26C係顯示LT β R-LRRC15雙特異性抗體與HEK293細胞表現的LT β R結合的圖表，以證實非配體阻斷活性不是由於測試雙特異性抗體的非受體結合所致。

【0037】 [圖27]提供了總結在重新篩選XenoMouse[®]融合瘤池中鑒定的額外促效劑結合LT β R CRD4的非配體阻斷抗體的表格。使用實例9.3中描述的基於細胞的測定和實例9.4中描述的Caterpillar測定評估抗體的非配體阻斷活性。

【實施方式】

【0038】 根據35 U.S.C. §119(e)特此要求2023年6月12日提交的美國臨時申請案號63/472,565之權益，並且將其揭露內容藉由引用特此併入本文。

【0039】 本揭露關於結合和激動淋巴毒素 β 受體（LT β R）的蛋白分子。本揭露提供了促效劑LT β R結合蛋白，其結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R富含半胱胺酸結構域4（CRD4）的一或多個胺基酸殘基，並且 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT α 1 β 2與LT β R結合。本揭露還提供了雙特異性促效劑LT β R結合蛋白，其包含與人LT β R CRD4的一或多個胺基酸殘基結合並且 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT1 α 2 β 與LT β R結合的LT β R結合結構域，以及腫瘤相關抗原結合結構域。

【0040】 本揭露進一步關於治療人受試者癌症之方法。該等方法包括向患有癌症的受試者投與促效劑LT β R結合蛋白，例如如本文所描述的促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白，以誘導或增強受試者的抗腫瘤免疫反應。如本文所證明的，腫瘤微環境中的LT β R激動作用誘導高內皮微靜脈形成，以增強免疫細胞浸潤到腫瘤微環境中。這種LT β R介導的抗腫瘤免疫反應足以減少腫瘤生長。

【0041】 本揭露進一步提供了與結合人LT β R的促效劑LT β R結合蛋白相關的組成物、套組（kit）和方法。還提供了包含編碼本文揭露的促效劑LT β R結合蛋白的全部或一部分之多核苷酸序列的核酸分子。本揭露進一步提供了包含這樣的核酸的載體和質體，以及包含這樣的核酸和/或載體和質體的細胞或細胞系。所提供的方法進一步包括，例如，製備、鑒定和分離促效劑LT β R結合蛋白之方法，以及用於向人受試者投與本揭露之促效劑LT β R結合蛋白之方法。

【0042】 應理解，如所聲明的前述一般描述以及以下的詳細描述均僅為示例性和說明性的，而不限制所揭露的發明。

【0043】 除非本文另外定義，否則結合本揭露使用的科技術語應當具有熟悉該項技術者通常所理解的含義。通常，結合本文所描述的細胞及組織培養、分子生物學、免疫學、微生物學、遺傳學以及蛋白質及核酸化學及雜交而使用的命

名法及其技術係本領域中所熟知且通常使用的那些命名法及技術。除非另外指示，否則本揭露之方法和技術通常根據本領域熟知且如貫穿本說明書所引用和討論的各種通用和更特別參考文獻中所述之常規方法來進行。參見例如 Sambrook 等人, *Molecular Cloning: A Laboratory Manual* [分子選殖：實驗室手冊], 第2版, Cold Spring Harbor Laboratory Press [冷泉港實驗室出版社], 冷泉港, 紐約 (1989) 和 Ausubel 等人, *Current Protocols in Molecular Biology* [分子生物學現代方法], Greene Publishing Associates [格林出版聯合公司] (1992), 以及 Harlow 和 Lane *Antibodies: A Laboratory Manual* [抗體：實驗室手冊] Cold Spring Harbor Laboratory Press [冷泉港實驗室出版社], 冷泉港, 紐約 (1990), 該等所有都藉由引用併入本文。酶促反應及純化技術係根據製造商之說明書、如本領域中通常所實現或如本文所描述來進行。結合本文中所描述的分析化學、合成有機化學以及醫學及藥物化學而使用的術語及其實驗程式和技術係本領域中眾所周知且通常使用的那些術語以及實驗程式和技術。

【0044】 在本揭露中，除非另有明確說明，否則單數術語的使用包括複數，並且複數術語應包括單數。除非上下文另外明確指示，否則如本文所用，單數形式「一個」、「一種」和「該」包括單數和複數個指示物。

【0045】 在本揭露中，術語「包括 (including)」、「以及其他形式如「包括 (includes)」和「包括 (included)」之使用不是限制性的。同樣，除非另外特別說明，否則術語如「元件」或「組分」涵蓋包含一個單位的元件和組分以及包含超過一個亞單位的元件和組分兩者。而且，術語「部分 (portion)」的使用可包括一部分 (moiety) 或整個部分 (moiety)。

【0046】 藉由端點表述的數值範圍包括歸入到各自範圍內的所有數值和分數，以及所述端點。

【0047】 如本文所用，術語「約」在指可測量值例如參數、數量、持續時

間等時，意在涵蓋指定值 $\pm 10\%$ 或更小，較佳的是 $\pm 1\%-5\%$ 或更小的變化，只要這樣的變化適合在所揭露的實施方式中執行。應理解，修飾詞「約」所指的值本身也是特別地，而且較佳的是揭露的。

【0048】 使用標準的一或三字母縮寫表示多核苷酸和多肽序列。除非另有說明，否則多肽序列的胺基末端位於左側，其羧基末端位於右側。單鏈核酸序列以及雙鏈核酸序列的頂鏈的5'末端位於左側，其3'末端位於右側。多肽的特定部分可藉由胺基酸殘基數（如胺基酸1至50）或該位點的實際殘基（如天冬醯胺至脯胺酸）來指定。特定的多肽或多核苷酸序列也可以藉由解釋其與參考序列的差異來描述。

【0049】 除非另有說明，否則以下術語應理解為具有以下含義：

【0050】 「序列同一性」係指兩個或更多個胺基酸（多肽或蛋白質）序列或兩個或更多個核酸（多核苷酸）序列之間的關係，如藉由比較序列確定的。兩個序列之間的同一性較佳的是藉由評估它們在如本文所鑒定的序列的整個長度上的同一性來定義。

【0051】 在比較兩個或更多個核苷酸或胺基酸序列的同一性時，第一序列和第二序列之間的序列同一性百分比可以使用熟悉該項技術者已知的方法計算，例如，藉由將第一序列中與第二序列中相應位置的殘基相同的殘基數除以第一序列中殘基的總數乘以100%或藉由使用已知的電腦演算法進行序列比對，例如NCBI Blast，例如BLASTN和BLASTP（Altschul, S. F.等人, *J. Mol. Biol.*[分子生物學雜誌] 215:403-410 (1990))、GCG套裝程式（Devereux, J.,等人, *Nucleic Acids Research*[核酸研究] 12 (1): 387 (1984))、BestFit、FASTA和EMBOSS Needle（Madeira, F.,等人, *Nucleic Acids Research*[核酸研究] 47(W1): W636-W641 (2019)）。

【0052】 「結合親和力」通常係指分子（例如，如本文所描述的LT β R結合

蛋白)的單個結合位點與其結合配偶體(例如,人LTβR)之間的非共價相互作用的總和的強度。除非另有說明,否則如本文所用,「結合親和力」係指內在結合親和力,其反映了結合對成員(例如,LTβR結合蛋白和LTβR)之間的1:1相互作用。分子X對其配偶體Y的親和力通常可以表示為解離常數(KD)。親和力可以用本領域已知的多種方式測量和/或表示,包括但不限於平衡解離常數(KD)和平衡締合常數(KA)。KD係根據k_{off}/k_{on}的商計算的,而KA係根據k_{on}/k_{off}的商計算的。K_{on}係指例如抗體與抗原的締合速率常數,而K_{off}係指例如抗體從抗原中的解離。結合親和力可以使用如本文所描述的和本領域已知的多種技術來確定,例如但不限於平衡方法,例如酶聯免疫吸附測定(ELISA)、KinExA(參見,例如,Rathanaswami等人 *Analytical Biochemistry*[分析生物化學], 373:52-60 (2008),特此藉由引用將其全部併入)和放射免疫測定(RIA);表面電漿共振測定;或其他基於動力學的測定(例如,BIACORE®分析或Octet®分析(forteBIO))。親和力也可以使用其他方法確定,例如間接結合測定、競爭性結合測定、螢光共振能量轉移(FRET)、凝膠電泳和層析(例如凝膠過濾)。該等方法和其他方法可以對一或多種待檢查的組分使用標記和/或使用多種檢測方法,包括但不限於發色標記、螢光標記、發光標記或者同位素標記。結合親和力和動力學的詳細描述可見於Paul, W. E.編輯, *Fundamental Immunology* [基礎免疫學], 第4版, Lippincott-Raven [Lippincott-Raven出版社], 費城(1999),其集中於抗體-免疫原相互作用。

【0053】如本文所用,術語「結合蛋白」係指本領域已知的多種形式的結合蛋白中的任一種。在示例性方面,本揭露之結合蛋白包括(i)全長免疫球蛋白分子,即抗體,(ii)抗體的表位結合片段,以及(iii)抗體衍生物,例如多特異性抗體。

【0054】如本文所用,術語「抗體」係指具有常規免疫球蛋白形式、包含

重鏈及輕鏈且包含可變區及恒定區的蛋白質。例如，抗體可為IgG，其係兩對相同多肽鏈的「Y形」結構，每對具有一條「輕」鏈（典型地具有約25 kDa的分子量）和一條「重」鏈（典型地具有約50-70 kDa的分子量）。抗體具有可變區和恒定區。在IgG形式中，可變區通常是約100-110個或更多個胺基酸，包含三個互補決定區（CDR），並且主要負責抗原識別。

【0055】本領域已經描述了抗體CDR的一般結構和特性。簡言之，在抗體支架中，CDR嵌埋於重鏈及輕鏈可變區中的框架內，在這裡其構成主要負責抗原結合及識別的區域。可變區典型地包含至少三個重鏈CDR或輕鏈CDR（Kabat等人, 1991, Sequences of Proteins of Immunological Interest [有免疫學意義的蛋白質序列], Public Health Service [公共衛生署] N.I.H., Bethesda [貝塞斯達], Md. [馬里蘭州]；還參見Chothia和Lesk, 1987, J. Mol. Biol.[分子生物學雜誌] 196:901-917；Chothia等人, 1989, Nature [自然] 342: 877-883），位於框架區內（由Kabat等人, 1991指定框架區1-4、FR1、FR2、FR3、和FR4；還參見Chothia和Lesk, 1987, 同上）。

【0056】抗體可以包含本領域已知的任何恒定區。人輕鏈分類為 κ 輕鏈及 λ 輕鏈。重鏈分類為 μ 、 δ 、 γ 、 α 或 ϵ ，並且將抗體的同種型分別定義為IgM、IgD、IgG、IgA和IgE。在本發明中，抗體為IgG同種型。IgG具有若干個亞類，包括但不限於IgG1、IgG2、IgG3和IgG4。輕鏈恒定區可為例如 κ 型或 λ 型輕鏈恒定區，例如人 κ 型或 λ 型輕鏈恒定區。

【0057】抗體的「表位結合片段」涵蓋全長抗體的任何多肽片段、區域、部分或結構域，其表現出與全長抗體相同或基本相似的結合特性，並且可以例如藉由蛋白酶切割完整親本抗體來獲得。

【0058】「抗體衍生物」係含有至少一個抗體表位結合結構域的蛋白質或多肽，通常使用重組技術或經由親本抗體或其部分的化學修飾形成。抗體衍生物

包含與一或多種親本抗體或其相關部分的胺基酸序列基本相似的胺基酸序列。本揭露之示例性抗體衍生物包括多特異性結合蛋白，例如雙特異性結合蛋白。

【0059】如本文所用，術語「表位」係指抗體結合的蛋白質的位點或部分。表位可以由形成構象空間單元的連續胺基酸殘基或不連續胺基酸殘基中的一個或兩個組成。對於不連續表位，來自抗原線性序列不同部分的胺基酸通過蛋白質分子的折疊在3維空間中非常接近。LT β R結合蛋白結合的表位可以藉由如本文所描述的氫/氘交換與質譜偶合來確定。

【0060】如本文所用，術語「互補位」係指結合蛋白，例如抗體，與蛋白靶標的表位結合的部分。互補位本質上可為線性的或可為不連續的，由抗體的非連續胺基酸殘基之間的空間關係形成，而不是由一系列線性胺基酸形成。如本文所提及的，「輕鏈互補位胺基酸殘基」、「重鏈互補位胺基酸殘基」或「互補位介面殘基」係指參與同蛋白質靶標結合相互作用的抗體輕鏈和/或重鏈殘基。互補位可以包含單個重鏈CDR，例如重鏈CDR3的胺基酸殘基，或來自重鏈CDR（HCDR1、CDR2、HCDR3）和輕鏈CDR（LCDR1、LCDR2和LCDR3）的胺基酸殘基的組合。如本文所證明的，互補位不需要CDR的所有胺基酸殘基，並且不需要來自所有六個CDR的胺基酸殘基。

LT β R結合蛋白

【0061】本文的揭露涵蓋促效劑淋巴毒素 β 受體（LT β R）結合蛋白。LT β R（也稱為腫瘤壞死因子（TNF）受體超家族成員3和腫瘤壞死因子受體III型（TNFR-III））是TNF家族成員，在大多數細胞類型（包括成纖維細胞、上皮細胞、單核細胞、樹突狀細胞和髓系細胞）上表現。LT β R不被T或B淋巴細胞表現。LT β R係兩種TNF家族細胞介素配體的受體。該等LT β R配體中的第一個配體係淋巴毒素 α 和淋巴毒素 β 亞基的異源三聚體，稱為LT α 1 β 2。LT β R的第二個配體係LIGHT（腫瘤壞死因子配體超家族成員14（TNFSF14））的同源三聚體。LT α 1 β 2

和LIGHT與LTβR的結合激活主要涉及NFκB途徑的訊息傳遞途徑。LTβR傳訊參與發育過程中的淋巴結（LN）器官發生和成年後淋巴器官和多種免疫細胞（包括嗜中性球、自然殺手（NK）細胞和恒定自然殺手T（iNKT）細胞）的維持。LTβR在非淋巴器官中稱為三級淋巴結構（TLS）的LN樣細胞簇的形成、以及T細胞跨內皮遷移的關鍵基因的誘導中也發揮著關鍵作用，這兩者均為促進有效抗腫瘤反應的關鍵。

【0062】 人LTβR係61 kDa跨膜蛋白，其具有SEQ ID NO: 1（同種型1）或SEQ ID NO: 2（同種型2）的胺基酸序列，如下所示。如本文所描述的LTβR結合蛋白與人LTβR結合。在一個實施方式中，本揭露之LTβR結合蛋白與人LTβR的胞外結構域內的一或多個表位（包含SEQ ID NO: 1之胺基酸殘基31-227）結合，所述胞外結構域包含四個富含半胱胺酸的結構域（即CRD1-CRD4）。

人LTβR同種型1（UniProtKB No. P36941-1）

MLLPWATSAPGLAWGPLVLGLFGLLAASQPQAVPPYASENQTCRDQEKEYYEPQHRICCS
RCPPGTYVSAKCSRIRDTCATCAENSYNEHWNLYLTICQLCRPCDPVMGLEEIAPCTSKR
KTQCRCQPGMFCAAWALECTHCELLSDCPPGTEAELKDEVGKGNNHCVPCKAGHFQNTSS
PSARCQPHTRCENQGLVEAAPGTAQSDTTCKNPLEPLPPEMSGTMLMLAVLLPLAFFLLL
ATVFSCIWKSHPSLCRKLGSLLKRRPQGEGPNPVAGSWEPPKAHPYFPDLVQPLLPISGD
VSPVSTGLPAAPVLEAGVPQQQSPLDLTREPQLEPGEQSQVAHGTTNGIHVTGGSMTITGN
IYIYNGPVLGGPPGPGDLPATPEPPYPIPEEGDPGPPGLSTPHQEDGKAHHLAETEHCGA
TPSNRGPRNQFITHD (SEQ ID NO: 1)

人LTβR同種型2（UniProtKB No. P36941-2）

MEATGISLASQLKVPPYASENQTCRDQEKEYYEPQHRICCSRCPPGTYVSAKCSRIRDTC
CATCAENSYNEHWNLYLTICQLCRPCDPVMGLEEIAPCTSKRKTQCRCQPGMFCAAWALEC
THCELLSDCPPGTEAELKDEVGKGNNHCVPCKAGHFQNTSSPSARCQPHTRCENQGLVEA

APGTAQSDTTCKNPLEPLPPEMSGTMLMLAVLLPLAFFLLLATVFSCIWKSHPSLCRKLGSLLKRRPQGE
GPNPVAGSWEPPKAHPYFPDLVQPLLPISGDVSPVSTGLPAAPVLEAGVPQQQSPLDLTREPQLE
PGEQSQVAHGTNGIHVTGGSMTITGNIYIYNGPVLGGPPGPGDLPATPEPPYPIPEEGDPGPPGLSTPHQ
EDGKAWHLAETEHCGATPSNRGPRNQFITHD (SEQ ID NO: 2)

【0063】 在一個實施方式中，本文所描述的LTβR結合蛋白也結合食蟹猴（cyno）LTβR。cyno LTβR之胺基酸序列如下提供（SEQ ID NO: 3）。在一個實施方式中，本文所描述的LTβR結合蛋白不結合鼠LTβR。在一個實施方式中，本文所描述的LTβR結合蛋白結合人LTβR和食蟹猴LTβR，但不結合鼠LTβR。

Macaca fascicularis（食蟹猴）UniProtKB No. A0A2K5VGQ6（SEQ ID NO:3）

MRLPWATSAPGLAWGPLVLGLFGLLAASQPQVVRKGPVPPYGSSENQTCRDQEKEYYEPRH
RICCSRCPPGTYVSAKCSRSRDTVCATCAENSYNEHWNLYLTICQLCRPCDPVMGLEE
IAPCTSKRKTQCRCQPGMFCAAWALECTHCELLSDCPPGTEAELKDEVGKGNNHCV
PCKAGHFNQNTSSPSARCQPHTRCEDQGLVEAAPGTAQSDTTTCRNPSESLPPEMSGTMLMLAILLPLA
FFLLLATIFACIWKSHPSLCRKLGSLLKRHPQGE
GPNPVAAGRDPKANKQYPDLVEPLLPISGDVSPVSTGLPTALVSEEGVPQQQSPLDLTTEPQLEPGEQ
NQVAHGTNGIHVTGGSMTITGNIYIYNGPVLGGPPGPGDLPATPDPPYPIPEEGDPGPPGLSTPHQEDGKA
WHLAETEHCGATPSNRGPRSQFITYD

【0064】 根據本揭露，LTβR結合蛋白為促效劑LTβR結合蛋白，例如，促效劑LTβR抗體、抗體的促效劑LTβR表位結合片段、或促效劑LTβR抗體衍生物（例如，促效劑LTβR雙特異性結合蛋白）。如本文所用，「促效劑LTβR結合蛋白」係一種LTβR結合分子，其藉由與受體結合直接誘導LTβR介導的傳訊，或經由與受體結合並例如藉由使用交聯抗體在細胞表面誘導其更高級的簇集間接誘導LTβR介導的傳訊。本揭露之LTβR結合蛋白與LTβR的結合誘導NFκB傳訊、與

T細胞跨內皮遷移相關的基因表現和/或TLS簇形成。用於測量本揭露結合蛋白對LT β R激活和/或LT β R傳訊誘導之測定係本領域已知的並在本文中描述。

【0065】 在一個實施方式中，藉由測定與促效劑LT β R結合蛋白孵育後表現LT β R的細胞釋放的白血球介素-8 (IL8) 來測量LT β R激動作用，如本文實例7所述。與不存在相比，在存在本揭露之LT β R結合蛋白的情況下，細胞IL8釋放水平的增加表明LT β R結合蛋白作為促效劑LT β R結合蛋白。在另一個實施方式中，藉由測定內皮細胞之反式激活來測量LT β R激動作用。LT β R介導的內皮細胞反式激活可以藉由測定以下來測量：黏附分子（例如血管細胞黏附蛋白1 (VCAM1；也稱為CD106) 和/或細胞內黏附分子1 (ICAM；也稱為CD54)) 的內皮細胞表現，和/或炎性趨化因子例如CCL5、CCL2和CXCL10的表現或分泌。與不存在促效劑LT β R結合蛋白相比，在存在其的情況下，內皮細胞VCAM或ICAM表現增加表明LT β R結合蛋白作為促效劑LT β R結合蛋白。類似地，與不存在LT β R結合蛋白相比，在存在其的情況下，CCL5、CCL2和/或CXCL10的內皮細胞表現或分泌增加表明LT β R結合蛋白作為促效劑LT β R結合蛋白。

【0066】 在一個實施方式中，相對於在不存在促效劑LT β R結合蛋白情況下的LT β R傳訊活性，本文所描述的LT β R結合蛋白的促效劑活性誘導LT β R傳訊活性增加至少10%，如藉由例如IL8釋放或內皮細胞反式激活測量的。在一個實施方式中，相對於在不存在促效劑LT β R結合蛋白的情況下的LT β R傳訊水平，本文所描述的LT β R結合蛋白使LT β R傳訊活性增加至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少55%、至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%。在一個實施方式中，相對於在不存在促效劑LT β R結合蛋白的情況下的LT β R傳訊水平，本文所描述的LT β R結合蛋白使LT β R傳訊活性增加至少100%。

【0067】 在一個實施方式中，本文所描述的LT β R結合蛋白的促效劑活性使

用如上文所述之一或多個體外功能終點來測量，並且該活性表示為半最大有效濃度（EC₅₀）。在一個實施方式中，本文所描述的LTβR結合蛋白的EC₅₀在約1 pM至約500 pM、約1 pM至約250 pM、約1 pM至約200 pM、約1 pM至約150 pM、約1 pM至約125 pM、約1 pM至約100 pM、約1 pM至約90 pM、約1 pM至約80 pM、約1 pM至約70 pM、約1 pM至約60 pM、約1 pM至約50 pM、約1 pM至約40 pM、約1 pM至約30 pM、約1 pM至約200 pM、約10 pM至約200 pM、約20 pM至約200 pM、約30 pM至約200 pM、約40 pM至約200 pM、約50 pM至約200 pM、約60 pM至約200 pM內。在一個實施方式中，如本文所描述的促效劑LTβR結合蛋白介導的IL-8釋放的EC₅₀為約10 pM至約200 pM、約20 pM至約150 pM、或約30 pM至約140 pM。

【0068】 在一個實施方式中，如本文所描述的LTβR結合蛋白結合並激動人LTβR，同時允許內源性LTβR配體與受體結合並產生活性。如上所述，LTβR結合至少兩種不同的內源性配體，即LIGHT和LTα1β2。當本揭露之LTβR結合蛋白與LTβR的其相應表位結合時，LIGHT或LTα1β2中的至少一種也可以與LTβR結合以激活內源性配體介導的傳訊活性。因此，在一個實施方式中，本文所描述的LTβR結合蛋白的結合不抑制、阻止或排除LTα1β2與LTβR的結合。在一個實施方式中，本文所描述的LTβR結合蛋白的結合不抑制、阻止或排除LIGHT與LTβR的結合。在一個較佳的實施方式中，本文所描述的LTβR結合蛋白的結合不抑制、阻止或排除LIGHT與LTβR的結合或LTα1β2與LTβR的結合。

【0069】 促效劑LTβR結合蛋白的這種功能特徵，本文稱為「非配體阻斷活性」，係本揭露之促效劑LTβR結合蛋白的有益特徵，因為它在將結合蛋白投與給例如患者時使安全性最大化。此外，本文所描述的LTβR結合蛋白優先以交聯依賴性方式激動LTβR，即結合分子必須與LTβR和另一種蛋白（例如，Fc受體或靶向蛋白）結合以誘導LTβR激活。從安全角度來看，這兩個特性提供了優越的

分子。如果結合分子以非交聯依賴性方式結合LT β R，例如，它僅與LT β R結合，則其結合不會激動受體。此外，由於LT β R結合蛋白以不阻斷內源性配體結合的方式結合LT β R，因此其結合也將不會無意中拮抗或阻斷內源性配體介導的活性。

【0070】 在一個實施方式中，如本文所描述的促效劑LT β R結合蛋白的非配體阻斷活性之特徵在於其結合對LIGHT和LT α 1 β 2與LT β R結合的抑制百分比。在一個實施方式中，本揭露之結合蛋白與LT β R結合對LIGHT與LT β R結合（ $\leq 20\%$ 抑制）或LT α 1 β 2與LT β R結合（ $\leq 20\%$ 抑制）的抑制或阻斷可忽略不計，如藉由下文所描述的基於細胞的受體-配體測定測量的（另參見實例8）。例如，如本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $\leq 20\%$ 、LT α 1 β 2與LT β R結合的 $\leq 20\%$ 、或LIGHT和LT α 1 β 2與LT β R結合的 $\leq 20\%$ ，如藉由本文所描述的基於細胞的受體-配體測定測量的。在一個實施方式中，如本文所描述的LT β R結合蛋白抑制LIGHT與LT β R結合或LT α 1 β 2與LT β R結合的 $< 20\%$ 、 $< 15\%$ 、 $< 10\%$ 、 $< 9\%$ 、 $< 8\%$ 、 $< 7\%$ 、 $< 6\%$ 、 $< 5\%$ 、 $< 4\%$ 、 $< 3\%$ 、 $< 2\%$ 或 $< 1\%$ 。在一個實施方式中，如本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $< 15\%$ 或抑制LT α 1 β 2與LT β R結合的 $< 15\%$ ，如藉由本文所描述且實例8.2中示例的基於細胞的受體配體測定測量的。在一個實施方式中，如本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $< 15\%$ 且抑制LT α 1 β 2與LT β R結合的 $< 15\%$ ，如藉由本文所描述且實例8.2中示例的基於細胞的受體配體測定測量的。在一個實施方式中，本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $< 10\%$ 或抑制LT α 1 β 2與LT β R結合的 $< 10\%$ ，如藉由本文所描述的基於細胞的受體配體測定測量的。在一個實施方式中，本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $< 10\%$ 且抑制LT α 1 β 2與LT β R結合的 $< 10\%$ ，如藉由本文所描述的基於細胞的受體配體測定法測量的。在一個實施方式中，本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $< 5\%$ 或抑制LT α 1 β 2與LT β R結

合的 < 5%，如藉由本文所描述的基於細胞的受體配體測定測量的。在一個實施方式中，本文所描述的結合蛋白與LTβR結合抑制LIGHT與LTβR結合的 < 5%且抑制LTα1β2與LTβR結合的 < 5%，如藉由本文所描述的基於細胞的受體配體測定法測量的。較佳的是，本文所描述的結合蛋白與LTβR結合抑制LIGHT與LTβR結合的0%或抑制LTα1β2與LTβR結合的0%，如藉由本文所描述的基於細胞的受體配體測定測量的。更較佳的是，本文所描述的結合蛋白與LTβR結合抑制LIGHT與LTβR結合的0%且抑制LTα1β2與LTβR結合的0%，如藉由本文所描述的基於細胞的受體配體測定測量的。不抑制LIGHT與LTβR結合且不抑制LTα1β2與LTβR結合（即，表現出對LIGHT與LTβR結合0%抑制且對LTα1β2與LTβR結合0%抑制）的本文所描述的示例性LTβR結合蛋白包括但不限於與LTβR的CRD4結構域結合的促效劑LTβR結合蛋白。

【0071】 可替代地，如本文所描述的促效劑LTβR結合蛋白的非配體阻斷活性之特徵在於，在結合促效劑LTβR結合蛋白存在下發生的內源性LTβR配體結合的百分比。在一個實施方式中，如本文所描述的結合蛋白與LTβR結合允許發生至少80%的內源性LTβR配體（即LIGHT或LTα1β2）結合，如藉由本文所描述的基於細胞的受體-配體測定測量的（參見實例8.2）。在一個實施方式中，如本文所描述的結合蛋白與LTβR結合允許發生至少80%、至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%的LIGHT與LTβR結合或LTα1β2與LTβR結合。在一個實施方式中，如本文所描述的結合蛋白與LTβR結合允許發生至少90%的LIGHT與LTβR結合或允許發生至少90%的LTα1β2配體與LTβR結合，如藉由本文所描述且實例8中示例的基於細胞的受體-配體測定測量的。在一個實施方式中，如本文所描述的結合蛋白與LTβR結合允許發生至少90%的LIGHT與LTβR結合且允許發生至少90%的LTα1β2配體與LTβR結合，如藉由本文所描述且實例8中示例的基於細

胞的受體-配體測定測量的。在一個實施方式中，如本文所描述的結合蛋白與LTβR結合允許發生至少95%的LIGHT與LTβR結合或允許發生至少95%的LTα1β2配體與LTβR結合，如藉由本文所描述且實例8中示例的基於細胞的受體-配體測定測量的。在一個實施方式中，如本文所描述的結合蛋白與LTβR結合允許發生至少95%的LIGHT與LTβR結合且允許發生至少95%的LTα1β2配體與LTβR結合，如藉由本文所描述且實例8中示例的基於細胞的受體-配體測定測量的。較佳的是，如本文所描述的結合蛋白與LTβR結合允許發生100%的LIGHT與LTβR結合或允許發生100%的LTα1β2配體與LTβR結合，如藉由實例8中所描述的基於細胞的基於受體-配體的測定測量的。更較佳的是，如本文所描述的結合蛋白與LTβR結合允許發生100%的LIGHT與LTβR結合且允許發生100%的LTα1β2配體與LTβR結合，如藉由實例8中所描述的基於細胞的基於受體-配體的測定測量的。允許LIGHT與LTβR結合的100%和LTα1β2與LTβR結合的100%的本文所描述的示例性促效劑LTβR結合蛋白係與LTβR的CRD4結構域結合的促效劑LTβR結合蛋白。

【0072】 本文所描述的促效劑LTβR結合蛋白的非配體阻斷活性使用基於細胞的受體-配體結合測定進行測量和定量。該測定測量在本揭露之促效劑LTβR結合蛋白存在下對LIGHT和/或LTα1β2與LTβR結合的抑制百分比（參見實例8）。這種基於細胞的受體-配體結合測定涉及將表現LTβR的細胞與含有促效劑LTβR結合蛋白的細胞培養基在4° C下孵育1小時，以使促效劑LTβR結合蛋白結合細胞上表現的LTβR。合適的表現LTβR的細胞包括任何自然表現LTβR的細胞類型，例如內皮細胞、巨噬細胞、自然殺手細胞等，以及被工程化以表現LTβR的細胞，例如用LTβR表現載體轉染的細胞系（例如CHO細胞、HEK 293細胞、黑色素瘤細胞等）。細胞培養基中促效劑LTβR結合蛋白的濃度為有效地使表現LTβR的細胞表現的所有LTβR的結合飽和的濃度。例如，細胞培養基中促效劑LTβR結合蛋

白的濃度為濃度5-30 nM，以使表現LTβR的細胞表現的所有LTβR的結合飽和。該測定進一步涉及在與促效劑LTβR結合蛋白孵育後，在配體與LTβR有效結合的條件下，將表現LTβR的細胞與可檢測的LIGHT配體、可檢測的LTα1β2配體或兩者（即可檢測的LIGHT和LTα1β2配體）相互作用。藉由將LIGHT和LTα1β2配體直接偶合到可檢測的標記（例如螢光標記或標籤）使其係可檢測的。使用合適的手段（例如，螢光激活的細胞分選），在促效劑LTβR結合蛋白存在下，對可檢測的LIGHT和/或LTα1β2配體與表現LTβR的細胞的結合進行檢測。配體結合抑制的定量評估係藉由將在存在促效劑LTβR結合蛋白下LIGHT和/或LTα1β2與LTβR的結合水平與在不存在促效劑LTβR結合蛋白下LIGHT和/或LTα1β2與LTβR的相應結合水平進行比較來確定的。最低限度抑制（≤20%抑制）或不抑制（0%抑制）LIGHT或LTα1β2配體與LTβR結合的促效劑LTβR結合蛋白被鑒定為適用於本文所描述之方法。在流式細胞儀上經由FAC，在存在或不存在LTβR結合蛋白的情況下，對可檢測的LIGHT和/或LTα1β2配體與表現LTβR的細胞的結合進行檢測。

【0073】 本文所描述的示例性促效劑LTβR結合蛋白表現出所期望的功能特性（例如，cyno和人LTβR結合和非配體阻斷活性），部分原因是LTβR的表位與促效劑LTβR結合蛋白結合。在一個實施方式中，本文所揭露的LTβR結合蛋白與包含胞外結構域的富含半胱氨酸結構域（CRD）的一或多個片段的LTβR的表位結合，即CRD1、CRD2、CRD3或CRD4的一或多個殘基。人LTβR胞外結構域如下SEQ ID NO: 4所示。在一個實施方式中，本揭露之促效劑LTβR結合蛋白與包含LTβR的CRD1殘基的表位結合。LTβR的CRD1包含SEQ ID NO: 4的殘基12-51，其對應於SEQ ID NO: 1之全長LTβR的殘基42-81。在一個實施方式中，本揭露之LTβR結合蛋白與包含LTβR CRD2的殘基的表位結合。LTβR CRD2包含SEQ ID NO: 4的殘基52-94，其對應於SEQ ID NO: 1之全長LTβR的殘基82-124。在一

個實施方式中，本揭露之LTβR結合蛋白與包含LTβR CRD3的殘基的表位結合。LTβR CRD3包含SEQ ID NO: 4的殘基95-138，其對應於SEQ ID NO: 1之全長LTβR的殘基125-168。在一個實施方式中，本揭露之LTβR結合蛋白與包含LTβR CRD4的殘基的表位結合。LTβR CRD4包含SEQ ID NO: 4的殘基139-181，其對應於SEQ ID NO: 1之全長LTβR胺基酸序列的殘基168-211。

QAVPPYASENQTCRDQEKEYYEPQHRICCSRCPPGTYSKCSRIKDTVCATCAENSYNEHW
NYLTICQLCRPCDPVMGLEEIIAPCTSKRKTQCRCQPGMFCAAWALECTHCELLSDCPPGTEA
ELKDEVGKGNHCVPCAGHFQNTSSPSARCQPHTRCENQGLVEAAPGTAQSDTTCKNPLEP
LPPEMSGTMLM (SEQ ID NO: 4)

【0074】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白與包含人LTβR的胞外CRD2和CRD3的殘基的表位結合。在一個實施方式中，該促效劑LTβR結合蛋白與包含SEQ ID NO: 4之位置56-64處的一或多個殘基的CRD2內的表位結合，並與包含SEQ ID NO: 4之位置81-101處的一或多個殘基的跨越CRD2和CRD3的表位結合，如藉由氫/氘交換（HDX）質譜（MS）確定的。在一個實施方式中，該促效劑LTβR結合蛋白與CRD2和CRD3的上述區域結合，而不與CRD2和CRD3之外的LTβR區域結合。換句話說，在一個實施方式中，該促效劑LTβR結合蛋白與LTβR中由CRD2和CRD3內的一或多個殘基組成的區域結合。LTβR結合蛋白與LTβR的已鑒定區域的結合激動受體傳訊，同時允許內源性LTβR配體結合。結合該表位的促效劑LTβR結合蛋白也結合cyno LTβR。具有該等特性之示例性促效劑LTβR結合蛋白在本文中被鑒定為LIBC219058（19324）和LIBC218990（19320）。

【0075】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白與包含人LTβR的胞外CRD1的殘基的表位結合。在一個實施方式中，本文所描述的促效劑LTβR結合蛋白與包含SEQ ID NO: 4之位置3-9、20-29和/或38-47處的一或多個殘

基的CRD1內的表位結合，如藉由HDX MS確定的。在一個實施方式中，該促效劑LTβR結合蛋白與CRD1的上述區域結合，而不與CRD1之外的LTβR區域結合。換句話說，在一個實施方式中，該促效劑LTβR結合蛋白與LTβR中由CRD1內的殘基組成的區域結合。LTβR結合蛋白與LTβR的該表位的結合激動受體傳訊，同時允許內源性LIGHT配體與LTβR結合，並最低限度地抑制LTα1β2配體結合（≤20%）。結合該表位的促效劑LTβR結合蛋白也結合cyno LTβR。具有該等特性的示例性促效劑LTβR結合蛋白在本文中被鑒定為LIBC218994（19321）。

【0076】在另一個實施方式中，本揭露之促效劑LTβR結合蛋白與包含人LTβR的胞外CRD1的殘基的表位結合。在一個實施方式中，本文所描述的促效劑LTβR結合蛋白與包含SEQ ID NO: 4之位置1-19處的一或多個殘基的CRD1內的表位結合，如藉由HDX MS確定的。在一個實施方式中，該促效劑LTβR結合蛋白與CRD1的上述區域結合，而不與CRD1之外的LTβR區域結合。換句話說，在一個實施方式中，該促效劑LTβR結合蛋白與LTβR中由CRD1內的殘基組成的區域結合。LTβR結合蛋白與LTβR的該表位的結合激動受體傳訊，並且不抑制內源性LIGHT與LTβR結合，以及不抑制內源性LTα1β2與LTβR結合。結合該表位的促效劑LTβR結合蛋白也結合cyno LTβR。具有該等特性的示例性促效劑LTβR結合蛋白在本文中被鑒定為LIBC219051（19323）。

【0077】在另一個實施方式中，本揭露之促效劑LTβR結合蛋白與包含人LTβR的胞外CRD4的殘基的表位結合。在一個實施方式中，本文所描述的促效劑LTβR結合蛋白與包含LTβR的胞外結構域（SEQ ID NO: 4）（SEQ ID NO: 1的殘基197-209）的位置168-179處的一或多個殘基的CRD4內的表位結合，如藉由HDX MS確定的。在一個實施方式中，該促效劑LTβR結合蛋白與CRD4的上述區域結合，而不與CRD4之外的LTβR區域結合。換句話說，在一個實施方式中，該促效劑LTβR結合蛋白與LTβR中由CRD4內的殘基組成的區域結合。促效劑LTβR結合

蛋白與LT β R的該表位的結合激動受體傳訊，並且不抑制內源性LIGHT與LT β R結合，以及不抑制內源性LT α 1 β 2與LT β R結合。結合該表位的促效劑LT β R結合蛋白也結合cyno LT β R。具有該等特性的示例性促效劑LT β R結合蛋白在本文中被鑒定為LIBC219081（19325）和LIBC218979（19319）。

【0078】與本文揭露的示例性促效劑LT β R結合蛋白具有相同或重疊表位的LT β R結合蛋白將相互競爭結合LT β R。因此，在一個實施方式中，本揭露之示例性促效劑LT β R結合蛋白與LIBC219081（19325）和/或LIBC218979（19319）競爭結合CRD4。「競爭」或「與.....競爭」意指LT β R結合蛋白競爭靶標上的相同表位或結合位點。這樣的競爭可以藉由其中參考促效劑LT β R結合蛋白（例如促效劑LT β R結合蛋白LIBC219081（19325）和LIBC218979（19319））阻止或抑制測試LT β R結合蛋白的特異性結合的測定來確定。本文在實例9.2中描述了示例性競爭性結合測定，其可用於鑒定本揭露所涵蓋的競爭性結合LT β R的CRD4的促效劑LT β R結合蛋白。通常，當競爭性LT β R結合蛋白過量存在時，其將抑制參考促效劑LT β R結合蛋白與共同表位的結合至少50%、至少55%、至少60%、至少65%、至少70%、或至少75%。在一些情況下，參考促效劑LT β R結合蛋白與LT β R的結合被抑制至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或更多。本文描述了本揭露之示例性促效劑LT β R結合蛋白，其與本文鑒定為LIBC219081（19325）和LIBC218979（19319）的結合蛋白競爭結合LT β R的CRD4結構域（參見表2-4和6-8）。

【0079】本揭露之促效劑LT β R結合蛋白係結合並激動LT β R的蛋白質，而不阻斷或抑制一種或兩種內源性LT β R配體結合LT β R。本文所描述的LT β R結合蛋白包含一或多個胺基酸結合結構域，該等胺基酸結合結構域單獨或組合結合LT β R區域並激活受體的傳訊活性。視需要，該促效劑LT β R結合蛋白進一步包含支架或框架部分，其允許一或多個結合結構域採用促進一或多個結合結構域和

LT β R之間結合相互作用的構象。示例性LT β R結合蛋白包括但不限於LT β R抗體（即免疫球蛋白）、LT β R抗體的表位結合片段、和LT β R抗體衍生物，本文更詳細地描述了其中的每一種。

【0080】 本文揭露的促效劑LT β R結合蛋白與LT β R的胞外結構域內的其相應表位結合。在一個實施方式中，本揭露之促效劑LT β R結合蛋白比替代表位更頻繁、更快速、以更長持續時間和/或更大親和力或親合力結合LT β R的胞外結構域的CRD4內的表位殘基（即SEQ ID NO: 4（ECD）的殘基139-181；SEQ ID NO: 1（全長LT β R）的殘基169-211）。在一個實施方式中，本文所描述的促效劑LT β R結合蛋白與LT β R的胞外CRD4結構域的任何2、3、4、5、6、7、8、9、10個或更多個胺基酸殘基結合，特別是SEQ ID NO: 4的168-179的一或多個殘基或SEQ ID NO: 4的168-178的一或多個殘基。

【0081】 根據本揭露，促效劑LT β R結合蛋白以緊密結合親和力結合LT β R，如由 10^{-7} M或更小的平衡解離常數（ K_D ）值確定的。在一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，LT β R抗體、表位結合片段或抗體衍生物）以小於 10^{-7} M、小於 10^{-8} M、小於 10^{-9} M、小於 10^{-10} M、或小於 10^{-11} M、小於 10^{-12} M或小於 10^{-13} M的平衡解離常數或 K_D （ k_{off}/k_{on} ）（值越低指示結合親和力越緊密）結合人LT β R。

【0082】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，抗體、表位結合片段和抗體衍生物）結合人LT β R，其平衡解離常數或 K_D （ k_{off}/k_{on} ）在約 10^{-7} M和約 10^{-11} M之間、約 10^{-7} M和約 10^{-10} M之間、約 10^{-7} M和約 10^{-9} M之間、約 10^{-7} M和約 10^{-8} M之間、約 10^{-8} M和約 10^{-9} M之間、約 10^{-9} M和約 10^{-10} M之間、約 10^{-10} M和約 10^{-11} M之間、約 10^{-11} M和約 10^{-12} M之間、約 10^{-12} M和約 10^{-13} M之間。在任何實施方式中，本揭露之促效劑LT β R結合蛋白特異性結合人LT β R，其 K_D 在約 10^{-8} M和約 10^{-11} M之間或在約 10^{-9} M和約 10^{-10} M之間。

【0083】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，抗體、表位結合片段和抗體衍生物）特異性結合人LT β R，其平衡解離常數或 K_D (k_{off}/k_{on}) 在約0.01 mM和約10 nM之間、約0.01 nM和約9 nM之間、約0.01 nM和約8 nM之間、約0.01 nM和約7 nM之間、約0.01 nM和約6 nM之間、約0.01 nM和約5 nM之間、約0.01 nM和約4 nM之間、約0.01 nM和約3 nM之間、約0.01 nM和約2 nM之間、約0.01 nM和約1 nM之間、約0.1 nM和約10 nM之間、約0.1 nM和約9 nM之間、約0.1 nM和約8 nM之間、約0.1 nM和約7 nM之間、約0.1 nM和約6 nM之間、約0.1 nM和約5 nM之間、約0.1 nM和約4 nM之間、約0.1 nM和約3 nM之間、約0.1 nM和約2 nM之間、約0.1 nM和約1 nM之間、或約0.01 nM和約0.1 nM之間。

【0084】 與人LT β R結合的本揭露之促效劑LT β R結合蛋白也以相同或相似的親和力與食蟹猴（cyno）LT β R結合。cyno LT β R的胺基酸序列在本文中提供為 SEQ ID NO: 3。在示例性方面，本文所描述的促效劑LT β R結合蛋白與食蟹猴LT β R結合，其 K_D 在約 10^{-7} M和約 10^{-8} M之間、約 10^{-8} M和約 10^{-9} M之間、約 10^{-9} M和約 10^{-10} M之間、約 10^{-10} M和約 10^{-11} M之間、約 10^{-11} M和約 10^{-12} M之間。在任何實施方式中，本揭露之LT β R結合蛋白特異性結合cyno LT β R，其 K_D 在約 10^{-8} M和約 10^{-10} M之間。

【0085】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，抗體、表位結合片段和抗體衍生物）與食蟹猴（cyno）LT β R結合，其平衡解離常數或 K_D (k_{off}/k_{on}) 在約0.1 nM和約30 nM之間、約0.1 nM和約20 nM之間、約0.1 nM和約10 nM之間、約0.1 nM和約9 nM之間、約0.1 nM和約8 nM之間、約0.1 nM和約7 nM之間、約0.1 nM和約6 nM之間、約0.1 nM和約5 nM之間、約0.1 nM和約4 nM之間、約0.1 nM和約3 nM之間、約0.1 nM和約2 nM之間、或約0.1 nM和約1 nM之間。

【0086】 本揭露之促效劑LT β R結合蛋白以高親和力與人LT β R和cyno

LTβR結合。例如，該促效劑LTβR結合蛋白對人LTβR的K_D係在促效劑LTβR結合蛋白對cyno LTβR的K_D的約100倍、約50倍、約25倍、約10倍、約5倍或約2倍或更少以內。在一個實施方式中，該促效劑LTβR結合蛋白對人LTβR的K_D係促效劑LTβR結合蛋白對cyno LTβR的K_D的約10倍或更少。

【0087】 如本文揭露的促效劑LTβR結合蛋白與LTβR胞外結構域結合，其親和力的K_D對應於比其與非特異性抗原（例如，TNFR-I或TNFR-II等）結合的親和力低至少10倍，例如低至少100倍，例如低至少1,000倍，例如低至少10,000倍，例如低至少100,000倍。親和力降低的量取決於結合蛋白對LTβR的K_D，因此當該促效劑LTβR結合蛋白的K_D非常低（即結合蛋白具有高度特異性）時，對LTβR的親和力低於對非特異性抗原的親和力的量可能為至少10,000倍。

【0088】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白為LTβR抗體、LTβR抗體的表位結合片段（例如，結合LTβR的Fab、Fab'、F(ab')₂）或LTβR抗體衍生物（例如，LTβR scFv、微抗體、雙特異抗體或多特異性結合蛋白），如本文所描述的。

【0089】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係如本文所定義的抗體。術語「抗體」還包括在重鏈和/或輕鏈的N端和/或C端包含1、2、3、4或5個胺基酸殘基插入或缺失的抗體，其保留與包含不包含該等胺基酸殘基取代、插入或缺失的兩個重鏈和兩個輕鏈的抗體相同或相似的結合和/或功能。

【0090】 本文所描述的抗體和其他結合分子（即抗體的表位結合片段和抗體衍生物）的重鏈和輕鏈可變區（分別為V_H和V_L）負責LTβR識別和結合，而重鏈和輕鏈恒定區介導免疫球蛋白與宿主組織或因子的結合，包括免疫系統的多種細胞（例如，效應細胞）和經典補體系統的第一組分（C1q）。在輕鏈和重鏈中，可變區（V）和恒定區（C）由約12個或更多個胺基酸的「J」區連接，重鏈還包括約10個以上胺基酸的「D」區（一般參見Fundamental Immunology [基礎免

疫學] 第7章 (Paul, W., 編輯, 第2版 Raven Press, 紐約 (1989), 特此藉由引用將其全部併入)。每個輕鏈/重鏈對的可變區形成抗體結合位點, 使得完整的免疫球蛋白具有兩個結合位點。

【0091】如本文所描述的LT β R抗體和其他LT β R結合蛋白的V_H和V_L區進一步細分為高變區, 稱為「互補決定區」或「CDR」, 其散佈在更保守序列的區域內, 該區域稱為「框架區」(FR)。重鏈和輕鏈的一或多個可變區CDR內的一或多個殘基形成與抗原(例如LT β R)相互作用的結合結構域。下文更詳細地描述了本揭露之LT β R抗體和結合蛋白的示例性V_H和V_L結構域序列以及V_H和V_L CDR序列。

【0092】在一個實施方式中, 本揭露之促效劑LT β R結合蛋白係LT β R抗體的表位結合片段。如本文所用, 術語「片段」、「區域」、「部分」和「結構域」通常旨在係同義詞, 除非它們的使用上下文另有說明。例如, 可以藉由完整親本抗體的蛋白酶切割來獲得表現出LT β R結合能力的抗體片段(例如, Fab和(Fab')₂片段)。可替代地, LT β R抗體的表位結合片段係胺基酸序列, 其包含這樣的親本抗體的一部分胺基酸序列。本揭露所涵蓋的示例性LT β R結合片段包括但不限於(i) Fab'或Fab片段, 其係包含如上所述之VL、VH、CL和CH1結構域的單價片段; (ii) F(ab')₂片段, 其係包含藉由鉸鏈區的二硫鍵連接的兩個Fab片段的二價片段; (iii) 基本上由VH和CH1結構域組成的Fd片段; (iv) 基本上由VL和VH結構域組成的Fv片段; (v) 單個結構域抗體或dAb片段(Ward等人「Binding Activities Of A Repertoire Of Single Immunoglobulin Variable Domains Secreted From Escherichia coli [大腸桿菌分泌的單個免疫球蛋白可變結構域的庫的結合活性],」*Nature* [自然] 341 :544-546 (1989), 特此藉由引用將其全部併入), 其基本上由VH或VL結構域(或VH或VL的表位結合部分)組成, 也被稱為結構域抗體或奈米抗體(Holt等人「Domain Antibodies: Proteins For Therapy [結構域抗體: 治療用蛋白質],」

Trends Biotechnol.[生物技術趨勢] 21(11):484-490 (2003); Revets等人「Nanobodies As Novel Agents For Cancer Therapy [奈米抗體作為癌症治療的新型藥物],」*Expert Opin. Biol. Ther.*[生物治療專家觀點] 5(1):111-124 (2005), 特此藉由引用將其全部併入); 和 (vi) 分離的互補決定區 (CDR)。

【0093】 本揭露之促效劑LTβR表位結合片段可以包含如本文揭露的LTβR抗體之1、2、3、4、5或全部6個CDR結構域。在一個實施方式中，LTβR抗體的表位結合片段包含，基本上由，或由親本LTβR抗體的30至100個胺基酸殘基、或50至150個胺基酸殘基、或70至200個胺基酸殘基組成。在一個實施方式中，LTβR抗體的表位結合片段的長度為LTβR抗體長度的至少40%、50%、60%、70%、80%、90%或95%。在一個實施方式中，本揭露之LTβR表位結合片段引發與該片段來源的LTβR抗體相同或相似的活性。在一個實施方式中，如本文所描述的促效劑LTβR表位結合片段和LTβR抗體引發可檢測的LTβR結合活性並誘導LTβR傳訊，如本文揭露的。

【0094】 LTβR抗體的表位結合片段可以使用熟悉該項技術者已知的常規技術獲得。例如，促效劑LTβR F(ab')₂片段可以藉由用胃蛋白酶處理促效劑LTβR抗體而產生。可以處理所得LTβR F(ab')₂片段以還原二硫鍵以產生LTβR Fab'片段。促效劑LTβR Fab片段可以藉由用木瓜酶處理促效劑LTβR抗體來獲得，LTβR Fab'片段可以藉由胃蛋白酶消化促效劑LTβR抗體來獲得。促效劑LTβR Fab'片段可以藉由用還原劑如二硫蘇糖醇處理促效劑LTβR F(ab')₂片段來獲得。LTβR結合片段也可以藉由在重組細胞中表現編碼這樣的片段的核酸而產生（參見例如，Evans等人「Rapid Expression Of An Anti-Human C5 Chimeric Fab Utilizing A Vector That Replicates In COS And 293 Cells [利用在COS和293細胞中複製的載體快速表現抗人C5嵌合Fab],」*J. Immunol. Meth.*[免疫學方法雜誌] 184:123-38 (1995), 特此藉由引用將其全部併入)。例如，編碼LTβR F(ab')₂片段一部分的嵌

合基因可以包括編碼重鏈的CH1結構域和鉸鏈區的DNA序列，然後係翻譯終止密碼子以產生這種截短的抗體片段分子。可以以與抗體相同的方式容易地篩選能夠與LT β R的所需表位結合的合適片段的效用。本揭露之LT β R抗體及其表位結合片段係「分離的」，以便存在於不同於其產生或將天然存在的物理環境中。

【0095】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白為抗體衍生物。促效劑LT β R抗體衍生物包括含有促效劑LT β R抗體的至少一個表位結合結構域的蛋白質或多肽，其通常使用重組技術形成。促效劑LT β R抗體衍生物也可以或可替代地通過親本LT β R抗體或其部分的化學修飾而獲得。促效劑LT β R抗體衍生物包含與該親本抗體或親本抗體的相關部分的胺基酸序列基本相似的胺基酸序列，例如與該親本LT β R抗體或其相關部分相差小於30%、小於20%、小於10%或小於5%，或與該親本分子或其相關部分相差10個胺基酸殘基，或相差少於10、9、8、7、6、5、4、3或2個胺基酸殘基。

【0096】 本揭露之示例性促效劑LT β R抗體衍生物係單鏈Fv (scFv)。促效劑LT β R scFv由Fv片段的兩個結構域，即V_L區和V_H區形成的，該等結構域可能由單獨的基因編碼。使用重組方法，藉由柔性連接基（通常為約10、12、15個或更多個胺基酸殘基）連接這樣的基因序列或其編碼cDNA，使它們能夠製成單個蛋白質鏈，其中V_L和V_H區結合形成單價表位結合蛋白（參見例如，Bird等人「Single-Chain Antigen-Binding Proteins [單鏈抗原結合蛋白],」 *Science* [科學] 242:423-426 (1988)；和Huston等人「Protein Engineering Of Antibody Binding Sites: Recovery Of Specific Activity In An Anti-Digoxin Single-Chain Fv Analogue Produced In *Escherichia coli* [抗體結合位點的蛋白質工程：在大腸桿菌中產生的抗地高辛單鏈Fv類似物中比活性的恢復],」 *Proc. Natl. Acad. Sci. (U.S.A.)*[美國國家科學院院刊] 85:5879-5883 (1988)，特此藉由引用將其全部併入）。

【0097】 本揭露之另一種示例性促效劑LT β R抗體衍生物係雙特異性scFv。

雙特異性LT β R scFv可以藉由使用柔性連接基形成，該柔性連接基使不同單個多肽鏈的V_L和V_H區（每個具有不同的表位結合特異性）聯繫在一起。

【0098】 在另一個實施方式中，本揭露之促效劑LT β R抗體衍生物係二價或雙價單鏈可變片段，藉由將兩個scFv串聯連接在一起來工程化（即串聯scFv）或使它們二聚化形成雙特異抗體（Holliger等人「『Diabodies[雙特異抗體]』: Small Bivalent And Bispecific Antibody Fragments [小的雙價和雙特異性抗體片段],」*Proc. Natl. Acad. Sci. (U.S.A.)*[美國國家科學院院刊] 90(14), 6444-8 (1993)；特此藉由引用將其全部併入）。根據本實施方式，雙價串聯scFv或雙特異抗體中的每個scFv可為相同的，即識別相同的LT β R靶表位，或者可為不同的，即識別和結合不同的靶表位。在又另一個實施方式中，該促效劑LT β R抗體衍生物係三抗體，即三價單鏈可變片段，藉由以串聯或三聚體形式將三個scFv連接在一起以形成三抗體來工程化。根據本實施方式，三抗體中的每個scFv可為相同的，即識別相同的靶表位，或者可為不同的，即識別和結合不同的靶表位。在另一個實施方式中，該促效劑LT β R抗體衍生物係四個單鏈可變片段的四抗體，其中每個scFv識別相同或不同的靶表位。在另一個實施方式中，該促效劑LT β R抗體衍生物係「線性抗體」，其係包含一對串聯Fd片段（VH-CH1-VH-CH1）的抗體，其與互補的輕鏈多肽一起形成一對抗原結合區（參見Zapata等人 *Protein Eng.*[蛋白質工程] 8(10): 1057-1062 (1995)，特此藉由引用將其全部併入）。在另一個實施方式中，該促效劑LT β R抗體衍生物係微抗體，包含與CH3區耦合的單鏈Fv區（即scFv-CH3）。在另一個實施方式中，該促效劑LT β R抗體衍生物係修飾的結構域抗體，例如，修飾的單個VL或VH結構域或藉由肽連接基連接的兩個或更多個VH結構域（參見例如，Ward等人, *Nature* [自然], 341:544-546 (1989)，特此藉由引用將其全部併入）；大抗體，即與Fc區融合的兩個scFv（參見例如，Fredericks等人, *Protein Engineering, Design & Selection* [蛋白質工程化、設計和選擇], 17:95-106 (2004)和

Powers等人, J. Immunol. Methods [免疫學方法雜誌], 251:123-135 (2001), 特此藉由引用將其全部併入); 或肽體(附接到Fc區的一或多個肽, 參見Feige的PCT申請公開案號WO 00/024782, 特此藉由引用將其全部併入)。在另一個實施方式中, 該促效劑LT β R抗體衍生物係免疫球蛋白融合蛋白, 其包含與鉸鏈區多肽和一或多個免疫球蛋白恒定區偶合的促效劑LT β R結合結構域(即, 包含一或多個重鏈和/或輕鏈CDR的多肽, 如本文所描述的)(參見例如, 美國專利申請公開案號20030133939, 特此藉由引用將其全部併入)。示例性免疫球蛋白融合蛋白形式包括但不限於IgG-scFv、IgG-Fab、2scFv-IgG、4scFv-IgG、VH-IgG、IgG-VH和Fab-scFv-Fc。

【0099】本揭露之另一種示例性促效劑LT β R抗體衍生物係多特異性結合抗體, 例如雙特異性或三特異性結合蛋白。本揭露之多特異性促效劑LT β R結合蛋白包含結合LT β R並與一或多個額外結合結構域偶合的第一結合結構域, 其中每個額外結合結構域結合非LT β R的靶部分。本揭露之示例性促效劑LT β R多特異性結合蛋白係雙特異性促效劑LT β R結合蛋白, 其包含LT β R結合結構域和腫瘤相關抗原結合結構域。雙特異性促效劑LT β R結合蛋白之示例性LT β R結合結構域包括來自本文揭露的任一種LT β R抗體的結合結構域。在一個實施方式中, 雙特異性促效劑LT β R結合蛋白包含LT β R結合結構域, 該LT β R結合結構域結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R富含半胱胺酸的結構域4(CRD4)的一或多個胺基酸殘基。該雙特異性促效劑結合蛋白不抑制LIGHT與LT β R結合, 而且不抑制LT1 α 2 β 與LT β R結合。

【0100】根據本揭露, 促效劑LT β R結合蛋白為人促效劑LT β R結合蛋白。人促效劑LT β R結合蛋白包含可變區和恒定區或結構域, 其基本上對應於本領域已知的人種系免疫球蛋白序列, 包括例如Kabat等人(1991)所描述的那些。本文揭露的人促效劑LT β R結合蛋白可以包括非人種系免疫球蛋白序列編碼的胺基酸

殘基（例如，藉由體外隨機或位點特異性誘變或藉由體內體細胞突變引入的突變），例如在CDR中，特別是CDR3。本揭露之人促效劑LTβR結合蛋白可以具有至少一個、兩個、三個、四個、五個或更多個被非人種系免疫球蛋白序列編碼的胺基酸殘基替換的位置。本文所用的人促效劑結合蛋白的定義還考慮了完全人抗體，其包括非人工和/或非基因改變的人抗體序列，因為該等可以藉由使用本領域已知的技術或系統（例如，噬菌體展示技術或轉基因小鼠技術，包括但不限於XenoMouse[®]，其是能夠產生人抗體的轉基因小鼠）衍生。

【0101】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白為IgG同種型。同種型的選擇通常將由所期望的效應物功能來指導，例如抗體依賴性細胞毒性（ADCC）誘導。示例性IgG同種型係IgG1、IgG2、IgG3和IgG4。在一個實施方式中，本揭露之促效劑LTβR結合蛋白為IgG1同種型。在一個實施方式中，本揭露之促效劑LTβR結合蛋白為IgG2同種型。

【0102】 根據本揭露之所有方面，本文揭露的示例性促效劑LTβR結合蛋白之結合結構域包含一或多個VH和VL CDR，其可以使用本領域已知的任一種標準方法來描述，包括但不限於Kabat編號方案（Kabat等人, Sequences of Proteins of Immunological Interest [免疫學感興趣的蛋白質序列], 第5版, U.S. Dept. of Health and Human Services [美國衛生與公眾服務部], NIH (1991)）、Chothia編號方案（Chothia等人, J. Mol. Biol.[分子生物學雜誌] 196: 901-917 (1987)和Al-Lazikani等人, J. Mol. Biol.[分子生物學雜誌] 273: 927-948 (1997)，特此藉由引用將其全部併入）、Abhinandan編號方案（Abhinandan等人, Mol. Immunol.[分子免疫學] 45: 3832-3839 (2008)，特此藉由引用將其全部併入）、免疫遺傳學（IMGT）數據庫編號方案（Giudicelli等人, Nucl. Acids Res.[核酸研究] 34: D781-784 (2006)和Lefranc等人, Dev. Comp. Immunol.[發育和比較免疫學] 27: 55-77 (2003)，特此藉由引用將其全部併入）、Aho編號方案（Honegger等人, J. Mol. Biol.[分子生物

學雜誌] 309: 657-670 (2001)，特此藉由引用將其全部併入) 和Contact編號方案 (MacCallum等人, J. Mol. Biol.[分子生物學雜誌] 262 732-745 (1996)，特此藉由引用將其全部併入)。根據每個系統，包含CDR的VH和VL區的殘基在下表1中提供。

[表1].根據已知編號方案的VH和VL CDR殘基

環	Kabat	AbM	Chothia	Contact	IMGT
L1	L24-L34	L24-L34	L26-L32	L30-L36	L27-L32
L2	L50-L56	L50-L56	L50-L52	L46-L55	L50-L51
L3	L89-L97	L89-L97	L91-L96	L89-L96	L89-L97
H1	H31-H35B (Kabat編號)	H26-H35B	H26-H32...34	H30-H35B	H26-H35B
H1	H31-H35 (Chothia編號)	H26-H35	H26-H32	H30-H35	H26-H33
H2	H50-H65	H50-H58	H52-H56	H47-H58	H51-H56
H3	H95-H102	H95-H102	H96-H101	H93-H101	H93-H102

【0103】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含表4、8和12中提供的重鏈可變區序列中之任一個的HCDR1、HCDR2和HCDR3，以及表4、8和12中也提供的相應輕鏈可變區的LCDR1、LCDR2和LCDR3，其中CDR由Kabat編號方案定義。在另一個實施方式中，本揭露之促效劑LTβR結合蛋白包含表4、8和12中提供的重鏈可變區序列中之任一個的HCDR1、HCDR2和HCDR3，以及表4、8和12中也提供的相應輕鏈可變區的LCDR1、LCDR2和LCDR3，其中CDR由Chothia編號方案定義。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含表4、8和12中提供的重鏈可變區序列中之任一個的HCDR1、HCDR2和HCDR3，以及表4、8和12中提供的相應輕鏈可變區的LCDR1、LCDR2和LCDR3，其中CDR由AbM編號方案定義。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含表4、8和12中提供的重鏈可變區序列中之任一個的HCDR1、HCDR2和

HCDR3，以及表4、8和12中也提供的相應輕鏈可變區的LCDR1、LCDR2和LCDR3，其中CDR由IMGT編號方案定義。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含表4、8和12中提供的重鏈可變區序列中之任一個的HCDR1、HCDR2和HCDR3，以及表4、8和12中也提供的相應輕鏈可變區的LCDR1、LCDR2和LCDR3，其中CDR由Contact編號方案定義。在一個實施方式中，該促效劑LT β R結合蛋白為抗體。在一個實施方式中，該促效劑LT β R結合蛋白為雙特異性抗體。

結合CRD4的LT β R促效劑結合蛋白

【0104】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白與包含LT β R的CRD4殘基的表位結合。LT β R的CRD4跨越SEQ ID NO: 4 (LT β R ECD) 的殘基139-181，其對應於SEQ ID NO: 1 (全長LT β R) 的殘基169-211。在一個實施方式中，本文所描述的促效劑LT β R結合蛋白與包含LT β R的胞外結構域 (SEQ ID NO: 4) (SEQ ID NO: 1的殘基197-209) 的位置168-179處的一或多個CRD4殘基的表位結合，如藉由HDX MS確定的。在一個實施方式中，本揭露之促效劑LT β R結合蛋白與包含LT β R CRD4殘基的表位結合，並且還與CRD4外的一或多個殘基結合。例如，在一個實施方式中，該促效劑LT β R結合蛋白與包含LT β R的CRD4殘基和相鄰CRD3殘基的表位結合。LT β R的CRD3包含SEQ ID NO: 4的殘基95-138，其對應於SEQ ID NO: 1之全長LT β R的殘基125-168。

【0105】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白與LT β R的CRD4內的LT β R表位結合，而不與如本文定義的CRD4外的LT β R區域結合。換句話說，在一個實施方式中，該促效劑LT β R結合蛋白與由LT β R的CRD4內的殘基組成的表位結合。

【0106】 促效劑LT β R結合蛋白與LT β R的CRD4結合激動受體傳訊，並且不抑制內源性LT β R配體 (即LIGHT或LT α 1 β 2) 與受體結合。在一些實施方式中，具有該等特性的促效劑LT β R結合蛋白係抗體。本文揭露了具有該等功能特徵的

示例性促效劑LTβR抗體（參見表2-4和6-8）。在一些實施方式中，具有該等特性的促效劑LTβR結合蛋白係雙特異性結合蛋白。具有該等功能特徵的示例性促效劑LTβR雙特異性結合蛋白包含來自本文揭露的示例性促效劑LTβR抗體的LTβR結合結構域。

【0107】 根據本揭露，具有該等功能特性的促效劑LTβR結合蛋白，即結合LTβR的CRD4殘基且不阻斷LIGHT與LTβR結合或LTα1β2與LTβR結合的結合蛋白，藉由其共用的重鏈可變區（V_H）CDR結構定義。該等促效劑LTβR結合蛋白可以藉由其共用的輕鏈可變區（V_L）CDR結構進一步定義。這種共用的CDR結構，表現為共有的V_H CDR和V_L CDR序列，來源於本文揭露的示例性促效劑LTβR結合蛋白的V_H和V_L結構域的比對（表4），其 (i) 具有上述功能特徵，以及 (ii) 包含分別與LTβR結合蛋白LIBC219081和LIBC 218979的V_H和V_L胺基酸序列具有至少90%序列同一性的V_H和V_L胺基酸序列。

【0108】 因此，在一個實施方式中，本揭露之促效劑LTβR結合蛋白，其 (i) 結合LTβR CRD4的殘基和 (ii) 不阻斷LIGHT與LTβR結合，並且不阻斷LTα1β2與LTβR結合，包含由以下定義的共用V_H CDR結構：HCDR1胺基酸序列：X₁YX₃MX₅（SEQ ID NO: 5），其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺基酸序列：X₁IX₃YDX₆X₇X₈X₉YX₁₁X₁₂DSVKG（SEQ ID NO: 6），其中X₁為A或V；X₃為W或R；X₆為E或G；X₇為S、R或T；X₈為N或K；X₉為K、R或Q；X₁₁為H或Y；並且X₁₂為A或E；以及HCDR3胺基酸序列：X₁RX₃X₄X₅X₆X₇X₈X₉YYGX₁₃X₁₄V（SEQ ID NO: 7），其中X₁為D或E；X₃為V、G或I；X₄為V、P或A；X₅為A、Y或G；X₆為R、A、G或H；X₇為P或G；X₈為G、N、D、Y、A或H；X₉為Y、T或F；X₁₃為L或M；並且X₁₄為D或A。在一些實施方式中，該促效劑LTβR結合蛋白係抗體。在一些實施方式中，該促效劑LTβR結合蛋白係雙特異性結合蛋白。

【0109】 示例性促效劑LTβR結合蛋白（例如，抗體或雙特異性結合蛋白）的重鏈CDR序列在下表2中提供，其結合LTβR的CRD4，不阻斷LIGHT或LTα1β2結合或活性，並且包含SEQ ID NO: 5的HCDR1、SEQ ID NO: 6的HCDR2和SEQ ID NO: 7的HCDR3。

[表2]：LTβR CRD4結合物的重鏈CDR序列，其與LIBC219081和LIBC218979的Fv結構域具有90%序列同一性

LIBC 編號	HCDR1		HCDR2		HCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
共有的	X ₁ YX ₃ MX ₅ X ₁ 為S、N； X ₃ 為G、A、D X ₅ 為H、Y	5	X ₁ IX ₃ YDX ₆ X ₇ X ₈ X ₉ Y X ₁₁ X ₁₂ DSVKG X ₁ 為A、V X ₃ 為W、R X ₆ 為E、G X ₇ 為S、R、T X ₈ 為N、K X ₉ 為K、R、Q X ₁₁ 為H、Y X ₁₂ 為A、E	6	X ₁ RX ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ YYGX ₁₃ X ₁₄ V X ₁ 為D、E X ₃ 為V、I、G X ₄ 為V、A、P X ₅ 為A、G、Y X ₆ 為R、A、H、G X ₇ 為P、G X ₈ 為G、N、D、Y、A、H X ₉ 為Y、F、T X ₁₃ 為L、M X ₁₄ 為D、A	7
219081 (19325)	SYAMH	8	VIWYDGSNQYYADSVKG	9	DRVAAHPAYYYGLDV	10
218979 (19319)	SYGMH	11	VIWYDGSNKYYADSVKG	12	ERIAAAPYYYYGMDV	13
1318341	SYAMH	14	VIWYDGTNKYYADSVKG	15	DRVAARPDYYYYGMDV	16
1318409	SYAMH	17	VIWYDGSNKYYADSVKG	18	DRVVARPDYYYYGMDV	19
1318412	SYAMH	20	VIWYDGRKRYADSVKG	21	DRIAARPNYYYYGLDV	22
1318738	SYDMH	23	VIRYDGSNKYYEDSVKG	24	ERGPYGGNTYYGMDV	25
1319003	SYGMH	26	VIWYDGRKRYADSVKG	27	DRIAARPNYYYYGLDV	28

LIBC 編號	HCDR1		HCDR2		HCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
1319078	SYAMH	29	VIWYDGSNKYYADSVKG	30	DRVAARPNYYYGMAV	31
1319182	SYAMH	32	VIWYDGSNKYYADSVKG	33	DRVVARPDYYYGMDV	34
1319275	SYAMH	35	VIWYDGSNKYYEDSVKG	36	DRVAARPNFYYGMDV	37
1319390	SYAMH	38	VIWYDGSNKYYEDSVKG	39	DRVAARPNFYYGMDV	40
1319499	NYGMY	41	VIWYDESNKYYADSVKG	42	DRIAGRPGYYYGMDV	43
1319908	SYAMH	44	VIWYDGRKRYADSVKG	45	DRIAARPNYYYGLDV	46
1318496	SYAMH	47	AIWYDGSNKYHADSVKG	48	DRIAARPNYYYGMDV	49
1320038	SYAMH	50	AIWYDGSNKYHADSVKG	51	DRIAARPNYYYGMDV	52
1308929	SYAMH	53	VIWYDGSNKYYADSVKG	54	DRVAARPHYYYGLDV	55
1309633	SYAMH	56	VIWYDGSNKYYADSVKG	57	DRVAARPHYYYGLDV	58
1309682	SYAMH	59	VIWYDGSNKYYADSVKG	60	DRVAARPHYYYGLDV	61

【0110】 在一個實施方式中，該促效劑LTβR結合蛋白，其 (i) 結合LTβR CRD4的殘基和 (ii) 不阻斷LIGHT與LTβR結合，並且不阻斷LTα1β2與LTβR結合，包含由以下定義的共用V_L CDR結構：LCDR1胺基酸序列：SGDX₄LPX₇X₈YX₁₀Y（SEQ ID NO: 62），其中X₄為A或T；X₇為E、K、Q、D或N；X₈為Q或H；並且X₁₀為A或T；LCDR2胺基酸序列：KDNERPS（SEQ ID NO: 63）；以及LCDR3胺基酸序列：QSX₃DX₅SX₇X₈YX₁₀X₁₁（SEQ ID NO: 64），其中X₃為A或T；X₅為S、G或N；X₇為G或A；X₈為T、S或A；X₁₀為V或M；並且X₁₁為I或V。

【0111】 下表3中提供了示例性促效劑LTβR結合蛋白的輕鏈CDR序列，其結合LTβR的CRD4，不阻斷LIGHT或LTα1β2結合或活性，並且包含SEQ ID NO: 62的LCDR1、SEQ ID NO: 63的LCDR2和SEQ ID NO: 64的LCDR3。

[表3]：示例性LTβR CRD4結合物的輕鏈CDR，其與LIBC219081和LIBC218979的Fv結構域具有90%序列同一性

LIBC 編號	LCDR1		LCDR2		LCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
共有的	SGDX ₄ LPX ₇ X ₈ YX ₁₀ Y X ₄ 為A、T X ₇ 為E、K、Q、D、N X ₈ 為Q、H X ₁₀ 為A、T	62	KDNERPS	63	Q SX ₃ DX ₅ SX ₇ X ₈ YX ₁₀ X ₁₁ X ₃ 為A、T X ₅ 為S、G、N X ₇ 為G、A X ₈ 為T、S、A X ₁₀ 為V、M X ₁₁ 為I、V	64
219081 (19325)	SGDALPNHYAY	65	KDNERPS	66	QSADSSGSYVI	67
218979 (19319)	SGDALPKHYAY	68	KDNERPS	69	QSADNTGSYMV	70
1318341	SGDALPDHYTY	71	KDNERPS	72	QSADSSGAYVI	73
1318409	SGDALPQHYTY	74	KDNERPS	75	QSADGSGTYVV	76
1318412	SGDTLPEHYTY	77	KDNERPS	78	QSADSSGAYVV	79
1318738	SGDALPKHYAY	80	KDNERPS	81	QSTDSSATYVV	82
1319003	SGDTLPDHYTY	83	KDNERPS	84	QSADSSGAYVV	85
1319078	SGDTLPNHYTY	86	KDNERPS	87	QSADSSGTYVL	88
1319182	SGDTLPQHYTY	89	KDNERPS	90	QSADSSGSYVV	91
1319275	SGDALPKHYAY	92	KDNERPS	93	QSADSSGTYVV	94
1319390	SGDALPKHYAY	95	KDNERPS	96	QSADSSGTYVV	97
1319499	SGDALPKQYAY	98	KDNERPS	99	QSADSSGAYVV	100
1319908	SGDTLPEHYTY	101	KDNERPS	102	QSADSSGAYVV	103
1318496	SGDTLPNHYTY	104	KDNERPS	105	QSADSSGSYVV	106
1320038	SGDTLPNHYTY	107	KDNERPS	108	QSADSSGSYVV	109
1308929	SGDALPNHYAY	110	KDNERPS	111	QSADSSGSYVV	112
1309633	SGDALPNQYAY	113	KDNERPS	114	QSADSSGSYVV	115
1309682	SGDALPNQYAY	116	KDNERPS	117	QSADSSGSYVV	118

【0112】 在一個實施方式中，促效劑LTβR結合蛋白，其結合人LTβR CRD4

的殘基和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC219081的VH和VL胺基酸序列（分別為SEQ ID NO: 121和122）具有至少80%序列同一性的VH和VL胺基酸序列的結合蛋白。在一個實施方式中，促效劑LT β R結合蛋白，其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC218979的VH和VL胺基酸序列（分別為SEQ ID NO: 123和124）具有至少80%序列同一性的VH和VL胺基酸序列的結合蛋白。在一個實施方式中，促效劑LT β R結合蛋白，其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC219081（分別為SEQ ID NO: 121和122）和LIBC218979（分別為SEQ ID NO: 123和124）的VH和VL胺基酸序列具有至少80%序列同一性的VH和VL胺基酸序列的結合蛋白。

【0113】 在一個實施方式中，促效劑LT β R結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合或 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC219081的VH和VL胺基酸序列（分別為SEQ ID NO: 121和122）具有至少85%序列同一性的VH和VL胺基酸序列的結合蛋白。在一個實施方式中，促效劑LT β R結合蛋白，其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC218979的VH和VL胺基酸序列（分別為SEQ ID NO: 123和124）具有至少85%序列同一性的VH和VL胺基酸序列的結合蛋白。在一個實施方式中，促效劑LT β R結合蛋白，其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC219081（分別為SEQ ID NO: 121和122）和LIBC218979（分別為SEQ ID NO: 123和124）的VH和VL胺基酸序列具有至少85%

序列同一性的VH和VL胺基酸序列的結合蛋白。

【0114】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包括那些具有分別與LTβR結合蛋白LIBC219081和LIBC218979的VH和VL胺基酸序列具有至少90%序列同一性的VH和VL胺基酸序列的結合蛋白。因此，在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 121之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。與SEQ ID NO: 121和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的示例性VH胺基酸序列提供在下表4中。

【0115】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包括那些包含與SEQ ID NO: 121之胺基酸序列具有至少90%序列同一性的VH胺基酸序列的結合蛋白。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。與SEQ ID NO: 121和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的示例性VH胺基酸序列提供在下表4中。

【0116】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻

斷LT α 1 β 2與LT β R結合，包括那些包含與SEQ ID NO: 122之胺基酸序列具有至少90%序列同一性的VL胺基酸序列的結合蛋白。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 122之胺基酸序列和SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。與SEQ ID NO: 122和SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的示例性VL胺基酸序列提供在下表4中。

【0117】 在一個實施方式中，促效劑LT β R結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含與SEQ ID NO: 121之胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 121之胺基酸序列具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少95%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 121之胺基酸序列具有至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少98%序列同一性的VL胺基酸序列。

【0118】 在一個實施方式中，促效劑LT β R結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含與SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 123之胺基酸序列具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 124之胺基酸序列具有至少95%序列同一性的VL胺基酸序列。在一個

個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 123之胺基酸序列具有至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 124之胺基酸序列具有至少98%序列同一性的VL胺基酸序列。

【0119】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列和SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列和SEQ ID NO: 124之胺基酸序列具有至少95%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列和SEQ ID NO: 124之胺基酸序列具有至少98%序列同一性的VL胺基酸序列。

【0120】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含與SEQ ID NO: 121或SEQ ID NO: 123的VH胺基酸序列具有至少90%序列同一性的VH胺基酸序列並且包含如下HCDR1胺基酸序列：X₁YX₃MX₅（SEQ ID NO: 5），其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺基酸序列：X₁IX₃YDX₆X₇X₈X₉Y X₁₁X₁₂DSVKG（SEQ ID NO: 6），其中X₁為A或V；X₃為W或R；X₆為E或G；X₇為S、R或T；X₈為N或K；X₉為K、R或Q；X₁₁為H或Y；並且X₁₂為A或E；以及HCDR3胺基酸序列：X₁RX₃X₄X₅X₆

X₇X₈X₉YYGX₁₃X₁₄V (SEQ ID NO: 7)，其中X₁為D或E；X₃為V、G或I；X₄為V、P或A；X₅為A、Y或G；X₆為R、A、G或H；X₇為P或G；X₈為G、N、D、Y、A或H；X₉為Y、T或F；X₁₃為L或M；並且X₁₄為D或A。與SEQ ID NO: 121或SEQ ID NO: 123之胺基酸序列的VH具有90%序列同一性和包含SEQ ID NO: 5、6和7的HCDR序列的促效劑LTβR結合蛋白的示例性VH胺基酸序列提供在下表4中。

【0121】該等促效劑LTβR結合蛋白進一步可以包含與SEQ ID NO: 122或SEQ ID NO: 124的VL胺基酸序列具有至少90%序列同一性的VL胺基酸序列並且包含以下LCDR1胺基酸序列：SGDX₄LPX₇X₈YX₁₀Y (SEQ ID NO: 62)，其中X₄為A或T；X₇為E、K、Q、D或N；X₈為Q或H；並且X₁₀為A或T；LCDR2胺基酸序列：KDNERPS (SEQ ID NO: 63)；以及LCDR3胺基酸序列：QSX₃DX₅SX₇X₈YX₁₀X₁₁ (SEQ ID NO: 64)，其中X₃為A或T；X₅為S、G或N；X₇為G或A；X₈為T、S或A；X₁₀為V或M；並且X₁₁為I或V。與SEQ ID NO: 122或SEQ ID NO: 124之胺基酸序列的VL具有90%序列同一性和包含SEQ ID NO: 62、63和64的LCDR序列的促效劑LTβR結合蛋白的示例性VL胺基酸序列提供在下表4中。

【0122】在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含以下VH胺基酸序列：QVQLVESGGGVVQPGRSLRLSCAASGFTFSX₃₁YX₃₃MX₃₅WVRQAPGKGLEWVAX₅₀IX₅₂YDX₅₅X₅₆X₅₇X₅₈YX₆₀X₆₁DSVKGRFTISRDN SKNTLSLQMNSLRAEDTAVYYCARX₉₉RX₁₀₁X₁₀₂X₁₀₃X₁₀₄X₁₀₅X₁₀₆X₁₀₇YYGX₁₁₁X₁₁₂VWGQGTTVTVSS (SEQ ID NO: 119)，其中X₃₁為S或N；X₃₃為G或A；X₃₅為H或Y；X₅₀為A或V；X₅₂為W或R；X₅₅為E或G；X₅₆為S、R或T；X₅₇為N或K；X₅₈為K、R或Q；X₆₀為H或Y；X₆₁為A或E；X₉₉為D或E；X₁₀₁為V、G或I；X₁₀₂為V、P或A；X₁₀₃為A、Y或G；X₁₀₄為R、A、G或H；X₁₀₆為G、N、D、Y、A或H；X₁₀₇為Y、T或F；X₁₁₁為

L或M；並且X₁₁₂為D或A。

【0123】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷 LTα1β2 與 LTβR 結合，包含以下 VL 胺基酸序列：
SYELTQPPSVSVSPRQTARITCSGDX₂₆LPX₂₉X₃₀YX₃₂YWYQQKPGQAPVLVIY
KDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSX₉₀DX₉₂SX₉₄X₉₅YX₉₇X₉₈FGGGTKLTVLG (SEQ ID NO: 120)，其中X₂₆為A或T；X₂₉為E、K、Q、D或N；X₃₀為Q或H；X₃₂為A或T；X₉₀為A或T；X₉₂為S、G或N；X₉₄為G或A；X₉₅為T、S或A；X₉₇為V或M；並且X₉₈為I或V。

【0124】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含VH，其中該VH包含SEQ ID NO: 119之胺基酸序列，並且與SEQ ID NO: 121的VH胺基酸序列和/或SEQ ID NO: 123的VH胺基酸序列共用至少90%序列同一性。該促效劑LTβR結合蛋白進一步包含VL，其中該VL包含SEQ ID NO: 120之胺基酸序列，並且與SEQ ID NO: 122的VL胺基酸序列和/或SEQ ID NO: 124的VL胺基酸序列共用至少90%序列同一性。

【0125】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含VH，其中該VH包含SEQ ID NO: 119之胺基酸序列，並且與SEQ ID NO: 121的VH胺基酸序列和/或SEQ ID NO: 123的VH胺基酸序列共用至少95%序列同一性。該促效劑LTβR結合蛋白進一步包含VL，其中該VL包含SEQ ID NO: 120之胺基酸序列，並且與SEQ ID NO: 122的VL胺基酸序列和/或SEQ ID NO: 124的VL胺基酸序列共用至少95%序列同一性。

【0126】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白，其結合人

LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含可變輕鏈（VL）結構域、可變重鏈（VH）結構域或VL和VH結構域的組合。表4中提供了與LIBC219081和LIBC218979的VH和VL胺基酸序列共用90%序列同一性的示例性促效劑LTβR結合蛋白的VH和VL胺基酸序列。在一些實施方式中，該促效劑LTβR結合蛋白的VH結構域包含表4中提供的VH胺基酸序列中的任一個，或與表4中列出的VH胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%或至少95%相同的胺基酸序列。在一些實施方式中，該促效劑LTβR結合蛋白的VL結構域包含下表4中提供的VL胺基酸序列中的任一個，或與表4中列出的VL胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%、至少95%相同的胺基酸序列。

[表4]：共用90%序列同一性的LTβR CRD4結合蛋白的VH和VL序列

LIBC編號	結構域	序列	SEQ ID
共有的	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSX ₃₁ YX ₃₃ MX ₃₅ WVRQ APGKGLEWVAX ₅₀ IX ₅₂ YDX ₅₅ X ₅₆ X ₅₇ X ₅₈ YX ₆₀ X ₆₁ DSVKGRFTISRDN SKNTLSLQMNSLRAEDTAVYYCARX ₉₉ RX ₁₀₁ X ₁₀₂ X ₁₀₃ X ₁₀₄ X ₁₀₅ X ₁₀₆ X ₁₀₇ YYGX ₁₁₁ X ₁₁₂ VWGQGTTVTVSS	119
	V _L	SYELTQPPSVSVSPRQTARITCSGDX ₂₆ LPX ₂₉ X ₃₀ YX ₃₂ Y WYQQKPGQAPVLVIYKDX ₅₁ ERPSGIPERFSGSSSGTTVTLTISGV QAEDEADYYCQSX ₉₀ DX ₉₂ SX ₉₄ X ₉₅ YX ₉₇ X ₉₈ FGGGTKLTVLG	120
219081 19325	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSYAMHWVRQAPG KGLEWVAVIWDGSGNQYYADSVKGRFIISRDN SKNTLYLQMNS LRAEDTAVYYCARDRVAAHPAYYYGLDVWGQGTTVTVSS	121
	V _L	SYELTQPPSVSLSPGQTARITCSGDALPNHYAYWYQQKPGQAPV LVIFKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSA DSSGSYVIFGGGTKLTVLG	122
218979 19319	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSYGMHWVRQAPG KGLEWVAVIWDGSGNKYYADSVKGRFTISRDN SKNTLSLQMNS LRAEDTAVYYCARERIAA PYYYYYGM DVWGQGTTVTVSS	123

LIBC編號	結構域	序列	SEQ ID
	V _L	SYELTQPPSVSVSPRQTARITCSGDALPKHYAYWYQQKPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQS ADNTGSYMVFGGGTKLTVLG	124
1308929	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLDWVGVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDRVAARPHYYYGLDVWGQGTTVTVSS	125
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPNHYAYWYQQKPGQAP VLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ SADSSGSYVVFVFGGGTKLTVLG	126
1318341	V _H	LVQLVESGGGVVQPGRSLRLSCAASGFTFRSYAMHWVRQAPG KGLEWVAVIWYDGTNKYYADSVKGRFTISRDN SKNTLYLQMN TLRADDTAVYFCAKDRVAARPDYYYGMDVWGQGTTVTVSS	127
	V _L	SYELTQPPSVSVSPGQTARIACSGDALPDHYTYWYQQKPGQAP VLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ SADSSGAYVIFGGGTKLTVLG	128
1318409	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKDTLHLQMN SLRAEDMAVYFCAKDRVVARPDYYYGMDVWGQGTTVTVSS	129
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPQHYTYWYQQKPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQS ADGSGTYVVFVFGGGTKLTVLG	130
1318412	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGRKRYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCAKDRIAARPNYYYGLDVWGQGTTVTVSS	131
	V _L	SYELIQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPIL VIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSA DSSGAYVVFVFGGGTKLTVLG	132
1318738	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYDMHWVRQAPG KGLEWVAVIRYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMNS LRVEDTAVYYCARERGPYGGNTYYGMDVWGQGTTVTVSS	133
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPKHYAYWYQQKPGQAP	134

LIBC編號	結構域	序列	SEQ ID
		VMVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ STDSSATYVVFGGGTKLTVLR	
1319003	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPG KGLEWVAVIWYDGRKRYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDRIAARPNYYYGLDVWGQGTTVTVSS	135
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPDHYTYWYQQRPGQAPIL VIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSA DSSGAYVVFGGGTKLTVLR	136
1319078	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDRVAARPNYYYGMAVWGQGTTVTVSS	137
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQKPGQAPV MVIYKDNERPSGIPERFSGFSSGTTVTLTITGVQAEDEADYYCQS ADSSGTYYVLFGGGTKLTVLG	138
1319182	V _H	QVHLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKDTLHLQMN SLRAEDMAVYFCAKDRVVARPDYYYGMDVWGQGTTVTVSS	139
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPQHYYTYWYQQNPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTISRVAEDEADYYCQS ADSSGSYVVFGGGTKLTVLG	140
1319275	V _H	QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCAKDRVAARPNFYYGMDVWGQGTTVTVSS	141
	V _L	SYELTQPPSVSLSPGHSARITCSGDALPKHYAYWYQQKPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQS ADSSGTYYVVFGGGTKLTVLG	142
1319390	V _H	QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCAKDRVAARPNFYYGMDVWGQGTTVTVSS	143
	V _L	SYELTQPPSVSLSPGHSARITCSGDALPKHYAYWYQQKPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQS	144

LIBC編號	結構域	序列	SEQ ID
		ADSSGTYVVFGGGTKLTVLG	
1319499	V _H	QVQLVESGGGVVQPGRSLRLSCVASGFTFSNYGMYWVRQAPG KGLEWVAVIWYDESNKYYADSVKGRFTISRDKNTLYLQMN SLRAEDTAVYYCARDRIAGRPGYGYGMDVWGQGTTVTVSS	145
	V _L	SYELTQPPSVSVSPGQTARISCSGDALPKQYAYWYQQKPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQS ADSSGAYVVFGGGTKLTVLG	146
1319908	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGRKRYADSVKGRFTISRDNKNTLYLQMN SLRAEDTAVYYCAKDRIAARPNYYYGLDVWGQGTTVTVSS	147
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPIL VIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSA DSSGAYVVFGGGTKLTVLG	148
1318496	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAIWIYDGSNKYHADSVKGRFTISRDNKNTLYLQMN SLRAEDTAVYYCARDRIAARPNYYYGMDVWGQGTTVTVSS	149
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQEPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQS ADSSGSYVVFGGGTKLTVLG	150
1320038	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAIWIYDGSNKYHADSVKGRFTISRDNKNTLYLQMN SLRAEDTAVYYCARDRIAARPNYYYGMDVWGQGTTVTVSS	151
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQEPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQS ADSSGSYVVFGGGTKLTVLG	152
1308929	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLDWVGVIWYDGSNKYYADSVKGRFTISRDNKNTLYLQMN SLRAEDTAVYYCARDRVAARPHYYYGLDVWGQGTTVTVSS	153
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPNHYAYWYQQKPGQAP VLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ SADSSGSYVVFGGGTKLTVLG	154

LIBC編號	結構域	序列	SEQ ID
1309633	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFRSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDRVAARPHYYYGLDVWGQGTTVTVSS	155
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPNQYAYWYQQKPGQAP VLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ SADSSGSYVVFVGGGTKLTVLG	156
1309682	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFRSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDRVAARPHYYYGLDVWGQGTTVTVSS	157
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPNQYAYWYQQKPGQAP VLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ SADSSGSYVVFVGGGTKLTVLG	158

【0127】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白）結合人LTβR CRD4，包括對應於SEQ ID NO: 1的殘基198-209（SEQ ID NO: 4的殘基168-179）的一或多個殘基，並且 (a) 不阻斷LIGHT與LTβR結合和 (b) 不阻斷LTα1β2與LTβR結合。該促效劑LTβR結合蛋白包含V_H，其中該V_H包含與SEQ ID NO: 8的序列具有至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 9的序列具有至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 10的序列具有至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該促效劑LTβR結合蛋白的V_H包含SEQ ID NO: 5的HCDR1序列，SEQ ID NO: 6的HCDR2序列和SEQ ID NO: 7的HCDR3序列。在一個實施方式中，該促效劑LTβR結合蛋白的V_H包含SEQ ID NO: 8的HCDR1序列，SEQ ID NO: 9的HCDR2序列和SEQ ID NO: 10的HCDR3序列。

【0128】根據前述實施方式，本揭露之促效劑LT β R結合蛋白進一步包含VL，其中該VL包含與SEQ ID NO: 65的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 66的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 67的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 62的LCDR1序列，SEQ ID NO: 63的LCDR2和SEQ ID NO: 64的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 65的LCDR1序列，SEQ ID NO: 66的LCDR2和SEQ ID NO: 67的LCDR3序列。包含該實施方式的VH和VL的示例性LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219081 (BR# 19325 ; 41B2) 的LT β R抗體。

【0129】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白）結合人LT β R CRD4，包括對應於SEQ ID NO: 1的殘基197-209（即SEQ ID NO: 4的殘基167-179）的一或多個殘基，並且 (a) 不阻斷LIGHT與LT β R結合和 (b) 不阻斷LT α 1 β 2與LT β R結合。該LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 11的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 12的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 13的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該LT β R結合蛋白的VH包含SEQ ID NO: 5的HCDR1序列，SEQ ID NO: 6的HCDR2序列和SEQ ID NO: 7的HCDR3序列。在一個實施方式中，該

LTβR結合蛋白的VH包含SEQ ID NO: 11的HCDR1序列, SEQ ID NO: 12的HCDR2序列和SEQ ID NO: 13的HCDR3序列。

【0130】 根據前述實施方式，本揭露之促效劑LTβR結合蛋白進一步包含VL，其中該VL包含與SEQ ID NO: 68的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 69的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 70的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 62的LCDR1序列，SEQ ID NO: 63的LCDR2和SEQ ID NO: 64的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 68的LCDR1序列，SEQ ID NO: 69的LCDR2和SEQ ID NO: 70的LCDR3序列。包含該實施方式的VH和VL的示例性LTβR結合蛋白包括但不限於本文鑒定為LIBC No. 218979（BR#19319；23E9）的LTβR抗體。

【0131】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和(a)不阻斷LIGHT與LTβR結合並且(b)不阻斷LTα1β2與LTβR結合，包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合：(i)分別為SEQ ID NO: 14、SEQ ID NO: 15、SEQ ID NO: 16、SEQ ID NO: 71、SEQ ID NO: 72和SEQ ID NO: 73，(ii)分別為SEQ ID NO: 17、SEQ ID NO: 18、SEQ ID NO: 19、SEQ ID NO: 74、SEQ ID NO: 75和SEQ ID NO: 76；(iii)分別為SEQ ID NO: 20、SEQ ID NO: 21、SEQ ID NO: 22、SEQ ID NO: 77、SEQ ID NO: 78和SEQ ID NO: 79；(iv)分別為SEQ ID NO: 23、SEQ ID NO: 24、SEQ ID NO: 25、SEQ ID NO: 80、SEQ ID NO: 81和SEQ ID NO: 82；(v)分別為SEQ ID NO: 26、SEQ ID NO:

NO: 27、SEQ ID NO: 28、SEQ ID NO: 83、SEQ ID NO: 84和SEQ ID NO: 85；(vi) 分別為SEQ ID NO: 29、SEQ ID NO: 30、SEQ ID NO: 31、SEQ ID NO: 86、SEQ ID NO: 87和SEQ ID NO: 88；(vii) 分別為SEQ ID NO: 32、SEQ ID NO: 33、SEQ ID NO: 34、SEQ ID NO: 89、SEQ ID NO: 90和SEQ ID NO: 91；(viii) 分別為SEQ ID NO: 35、SEQ ID NO: 36、SEQ ID NO: 37、SEQ ID NO: 92、SEQ ID NO: 93和SEQ ID NO: 94；(vix) 分別為SEQ ID NO: 38、SEQ ID NO: 39、SEQ ID NO: 40、SEQ ID NO: 95、SEQ ID NO: 96和SEQ ID NO: 97；(x) 分別為SEQ ID NO: 41、SEQ ID NO: 42、SEQ ID NO: 43、SEQ ID NO: 98、SEQ ID NO: 99和SEQ ID NO: 100；(xi) 分別為SEQ ID NO: 44、SEQ ID NO: 45、SEQ ID NO: 46、SEQ ID NO: 101、SEQ ID NO: 102和SEQ ID NO: 103；(xii) 分別為SEQ ID NO: 47、SEQ ID NO: 48、SEQ ID NO: 49、SEQ ID NO: 104、SEQ ID NO: 105和SEQ ID NO: 106；(xiii) 分別為SEQ ID NO: 50、SEQ ID NO: 51、SEQ ID NO: 52、SEQ ID NO: 107、SEQ ID NO: 108和SEQ ID NO: 109；(xiv) 分別為SEQ ID NO: 53、SEQ ID NO: 54、SEQ ID NO: 55、SEQ ID NO: 110、SEQ ID NO: 111和SEQ ID NO: 112；(xv) 分別為SEQ ID NO: 56、SEQ ID NO: 57、SEQ ID NO: 58、SEQ ID NO: 113、SEQ ID NO: 114和SEQ ID NO: 115；以及 (xvi) 分別為SEQ ID NO: 59、SEQ ID NO: 60、SEQ ID NO: 61、SEQ ID NO: 116、SEQ ID NO: 117和SEQ ID NO: 118。

【0132】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含選自以下的VH胺基酸序列和VL胺基酸序列：SEQ ID NO: 119的VH胺基酸序列和SEQ ID NO: 120的VL胺基酸序列；SEQ ID NO: 121的VH胺基酸序列和SEQ ID NO: 122的VL胺基酸序列；SEQ ID NO: 123的VH胺基酸序列和SEQ ID NO: 124的VL胺基酸序列；SEQ ID NO: 125的VH胺基酸序列和SEQ ID NO: 126的VL胺基酸序

列；SEQ ID NO: 127的VH胺基酸序列和SEQ ID NO: 128的VL胺基酸序列；SEQ ID NO: 129的VH胺基酸序列和SEQ ID NO: 130的VL胺基酸序列；SEQ ID NO: 131的VH胺基酸序列和SEQ ID NO: 132的VL胺基酸序列；SEQ ID NO: 133的VH胺基酸序列和SEQ ID NO: 134的VL胺基酸序列；SEQ ID NO: 135的VH胺基酸序列和SEQ ID NO: 136的VL胺基酸序列；SEQ ID NO: 137的VH胺基酸序列和SEQ ID NO: 138的VL胺基酸序列；SEQ ID NO: 139的VH胺基酸序列和SEQ ID NO: 140的VL胺基酸序列；SEQ ID NO: 141的VH胺基酸序列和SEQ ID NO: 142的VL胺基酸序列；SEQ ID NO: 143的VH胺基酸序列和SEQ ID NO: 144的VL胺基酸序列；SEQ ID NO: 145的VH胺基酸序列和SEQ ID NO: 146的VL胺基酸序列；SEQ ID NO: 147的VH胺基酸序列和SEQ ID NO: 148的VL胺基酸序列；SEQ ID NO: 149的VH胺基酸序列和SEQ ID NO: 150的VL胺基酸序列；SEQ ID NO: 151的VH胺基酸序列和SEQ ID NO: 152的VL胺基酸序列；SEQ ID NO: 153的VH胺基酸序列和SEQ ID NO: 154的VL胺基酸序列；SEQ ID NO: 155的VH胺基酸序列和SEQ ID NO: 156的VL胺基酸序列；以及SEQ ID NO: 157的VH胺基酸序列和SEQ ID NO: 158的VL胺基酸序列。

【0133】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含如上所述之VH區和/或VL區，並且進一步包含與VH區偶合的一或多個重鏈恒定區和/或與VL區偶合的輕鏈恒定區。例如，在一個實施方式中，該LT β R結合蛋白係Fab，其包含VH和與VL偶合的第一重鏈恒定結構域（CH1）以及輕鏈恒定區（CL）。在另一個實施方式中，該LT β R結合蛋白係F(ab')₂，其包含藉由鉸鏈區偶合的完全抗體的兩個LT β R結合區，其中每個結合區包含VH-CH1和VL-CL。在另一個實施方式中，該LT β R結合蛋白係包含完全輕鏈（VL-CL）和完全重鏈（VH-CH1-

CH2-CH3) 的抗體。

【0134】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含人IgG1重鏈。在另一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含人IgG2重鏈。在一個實施方式中，該人IgG重鏈被修飾以防止或減少與Fcγ受體的相互作用。在一個實施方式中，該人IgG係穩定效應物無功能 (SEFL) IgG (Liu等人, *J Biol. Chem.* [生物化學雜誌] 292(5):1876-1883，特此藉由引用將其全部併入)。下表5提供了本揭露之LTβR結合蛋白之示例性輕鏈恒定區和重鏈恒定區的胺基酸序列。

[表5]：示例性LC和HC恒定結構域區

描述	SEQ ID NO:	胺基酸序列
λLC恒定區	299	QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV ETTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS
κLC恒定區	300	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
IgG1 SEFL2 (CH1-Fc)	301	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSV MHEALHNHYTQKSLSLSPGK

【0135】 本文表9中提供了本揭露之LTβR抗體之示例性胺基酸序列，該抗體結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合。

【0136】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白）與LTβR結合物LIBC219081和LIBC218979競爭結合人LTβR CRD4，以及 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合。

【0137】 根據本揭露，具有該等功能特性的促效劑LTβR結合蛋白，即與LTβR結合物LIBC219081和LIBC218979競爭結合LTβR的CRD4，並且不阻斷LIGHT或LTα1β2與LTβR結合，由其結構相似的VH和VL結構域定義。這種共用的可變區結構，表現為共有的VH和VL CDR序列以及共有的VH和VL序列，來源於本文揭露的示例性促效劑LTβR結合蛋白的比對（參見表6、7和8），其 (i) 具有該等功能特徵以及 (ii) 包含在其各自的整個長度上共用至少90%序列同一性的VH和VL胺基酸序列，即在FR1、CDR1、FR2、CDR2、FR3、CDR3和FR4上從N端到C端。

【0138】 因此，在一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含由以下定義的共用VH CDR結構：HCDR1胺基酸序列：GX₂YMH（SEQ ID NO: 159），其中X₂為Y或F；HCDR2胺基酸序列：WINPNX₆GGTNYAQKFQG（SEQ ID NO: 160），其中X₆為S、N或R；以及HCDR3胺基酸序列：X₁X₂X₃X₄GX₆X₇X₈YYGMDV（SEQ ID NO: 161），其中X₁為D或A；X₂為R或D；X₃為N、S或A；X₄為G或S；X₆為V或W；X₇為Y或不存在；X₈為Y或不存在。下表6中提供了示例性促效劑LTβR結合蛋白的重鏈CDR序列，其結合LTβR CRD4，不阻斷LIGHT與LTβR結

合，不阻斷LT α 1 β 2與LT β R結合，並且包含SEQ ID NO: 159的HCDR1、SEQ ID NO: 160的HCDR2和SEQ ID NO: 161的HCDR3。

【0139】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含分別為SEQ ID NO: 159-161的HCDR 1-3，進一步包含由以下定義的共用VL CDR結構：LCDR1胺基酸序列TGTX₄SDVGSYNLVS（SEQ ID NO: 278），其中X₄為T、N或S；LCDR2胺基酸序列EVX₃X₄RPS（SEQ ID NO: 279），其中X₃為T或S且X₄為K或V；以及LCDR3胺基酸序列CSYX₄X₅SX₇TX₉V（SEQ ID NO: 280），其中X₄為A或V；X₅為D或E；X₇為S或K；X₉為L或W。下表7中提供了示例性促效劑LT β R結合蛋白的輕鏈CDR序列，其結合LT β R CRD4，不阻斷LIGHT與LT β R結合，不阻斷LT α 1 β 2與LT β R結合，並且包含SEQ ID NO: 278的LCDR1、SEQ ID NO: 279的LCDR2和SEQ ID NO: 280的LCDR3。

【0140】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含分別為SEQ ID NO: 159-161的HCDR 1-3，進一步包含由以下定義的共用VL CDR結構：LCDR1胺基酸序列SGDX₄LPX₇X₈YX₁₀Y（SEQ ID NO: 308），其中X₄為A或T；X₇為Q、E、N、R或K；X₈為H或Q；X₁₀為V、T或A；LCDR2胺基酸序列KDX₃X₄RPS（SEQ ID NO: 309），其中X₃為N或S；X₄為D或E；以及LCDR3胺基酸序列QSADX₅SGX₈X₉VV（SEQ ID NO: 310），其中X₅為I、N或S；X₈為S、A、I或T；並且X₉為F或Y。下表7中提供了示例性促效劑LT β R結合蛋白的輕鏈CDR序列，其結合LT β R CRD4，不阻斷LIGHT與LT β R結合，不阻斷LT α 1 β 2與LT β R結合，並且包含SEQ ID NO: 308的LCDR1、SEQ ID NO: 309的LCDR2和SEQ ID NO: 310的LCDR3。

[表6].結合人LT β R CRD4且不阻斷LIGHT或LT α 1 β 2與LT β R結合的促效劑LT β R結合蛋白的重鏈CDR序列

LIBC 編號	HCDR1		HCDR2		HCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
共有的 VH進化 枝1	GX ₂ YMH	159	WINPNX ₆ GGTNYAQKFQG	160	X ₁ X ₂ X ₃ X ₄ GX ₆ X ₇ X ₈ YYGMDV	161
	X ₂ 為Y或F		X ₆ 為S、N或R		X ₁ 為D、A	
					X ₂ 為R、D	
					X ₃ 為N、S、A	
					X ₄ 為G、S	
					X ₆ 為V、W	
					X ₇ 為Y、不存在	
					X ₈ 為Y、不存在	
1303255	GYMH	162	WINPNNGGTNYAQKFQG	163	ADNSGWYYYYGMDV	164
1303574	GYMH	165	WINPNNGGTNYAQKFQG	166	ADNSGWYYYYGMDV	167
1303613	GYMH	168	WINPNNGGTNYAQKFQG	169	ADNSGWYYYYGMDV	170
1303507	GYMH	171	WINPNNGGTNYAQKFQG	172	ADNSGWYYYYGMDV	173
1303716	GYMH	174	WINPNNGGTNYAQKFQG	175	ADNSGWYYYYGMDV	176
1308640	GYMH	177	WINPNNGGTNYAQKFQG	178	ADSSGWYYYYGMDV	179
1308591	GFYMH	180	WINPNNGGTNYAQKFQG	181	ADSSGWYYYYGMDV	182
1303446	GYMH	183	WINPNNGGTNYAQKFQG	184	ADNSGWYYYYGMDV	185
1306164	GYMH	186	WINPNSGGTNYAQKFQG	187	DRAGGVYYGMDV	188
1306253	GYMH	189	WINPNRGGTNYAQKFQG	190	DRAGGVYYGMDV	191
1306424	GYMH	192	WINPNRGGTNYAQKFQG	193	DRAGGVYYGMDV	194
共有的 VH進化 枝4	X ₁ YGMH	195	X ₁ IWYDGNNKYYX ₁₂ DSVK	196	DRITX ₅ VRGVTNYGMDV	197
	X ₁ 為A或S		G		X ₅ 為M、R	
			X ₁ 為L或V			
			X ₁₂ 為E或A			
1306053	AYGMH	197	LIWYDGNNKYYADSVKG	198	DRITRVRGVTNYGMDV	199
1306153	AYGMH	200	LIWYDGNNKYYADSVKG	201	DRITRVRGVTNYGMDV	202
1306251	AYGMH	203	LIWYDGNNKYYADSVKG	204	DRITRVRGVTNYGMDV	205
1306674	AYGMH	206	LIWYDGNNKYYADSVKG	207	DRITRVRGVTNYGMDV	208
1307329	AYGMH	209	LIWYDGNNKYYADSVKG	210	DRITRVRGVTNYGMDV	211

LIBC 編號	HCDR1		HCDR2		HCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
1306622	AYGMH	212	LIWYDGNNKYYADSVKG	213	DRITRVRGVTNYGMDV	214
1306800	AYGMH	215	LIWYDGNNKYYADSVKG	216	DRITRVRGVTNYGMDV	217
1306965	AYGMH	218	LIWYDGNNKYYADSVKG	219	DRITRVRGVTNYGMDV	220
1306294	SYGMH	221	VIWYDGNNKYYEDSVKG	222	DRITMVRGVTNYGMDV	223
共有的 VH進化 枝7	SX ₂ AMH X ₂ 為Y或F	224	VIWYX ₅ X ₆ X ₇ NX ₉ FYADSVK G X ₅ 為D、A、N X ₆ 為R、E X ₇ 為N、S X ₉ 為K、N	225	GDX ₃ X ₄ YX ₆ YX ₈ YGX ₁₁ DX ₁₃ X ₃ 為W、R X ₄ 為N、D X ₆ 為S、H、Y X ₈ 為Y、Q、K X ₁₁ 為M、V X ₁₃ 為L、V	226
1307739	SYAMH	227	VIWYDRNNKFYADSVKG	228	GDRDYHYQYGMDV	229
1310489	SYAMH	230	VIWYDRNNKFYADSVKG	231	GDRDYHYQYGMDV	232
1308006	SYAMH	233	VIWYNRNNNFYADSVKG	234	GDRDYYYYYGMDV	235
1308236	SYAMH	236	VIWYNRNNNFYADSVKG	237	GDRDYYYYYGMDV	238
1308563	SYAMH	239	VIWYNRNNNFYADSVKG	240	GDRDYYYYYGMDV	241
1308943	SYAMH	242	VIWYNRNNNFYADSVKG	243	GDRDYYYYYGMDV	244
1318301	SFAMH	245	VIWYAESNKFYADSVKG	246	GDWNYSYKYGVDL	247
1319279	SFAMH	257	VIWYAESNKFYADSVKG	258	GDWNYSYKYGVDL	259
1318394	SYGMH	248	VIWYDRSNKYYADSVKG	249	GISGYRYGTDMDV	250
1318693	SYGMH	251	VIWYDRSNKYYADSVKG	252	GISGYRYGTDMDV	253
1318991	SYGMH	254	VIWYDRSNKYYADSVKG	255	GISGYRYGTDMDV	256
1318188	SDGYFWS	266	FIYFTGITYYNPSLQS	267	VIPGEDAFDI	268
1318198	SDGYFWS	275	FIYFTGITYYNPSLQS	276	VIPGEDAFDI	277
1318253	GFYMH	260	WLNPNNTGGTSYVQKFQG	261	GTGTTAFFDF	262
1318209	SYVMN	263	GISGSDGSTYYADSVKG	264	EEDWNYGFDY	265
1319569	SYDIN	269	WMNPNTGNTGYPQKFQG	270	GGLTMKVVGAGWFDP	271
1307105	SYGMD	272	VISYDGNKYKYADSVKG	273	DDYSTLDY	274

[表7].結合人LTβR CRD4且不阻斷LIGHT或LTα1β2與LTβR結合的促效劑LTβR
結合蛋白的輕鏈CDR序列

LIBC 編號	LCDR1		LCDR2		LCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
共有的 VL進化 枝1	TGTX ₄ SDVGSYNLVS X ₄ 為T、N、S	278	EVX ₃ X ₄ RPS X ₃ 為S、T X ₄ 為K、V	279	CSYX ₄ X ₅ SX ₇ TX ₉ V X ₄ 為A、V X ₅ 為D、E X ₇ 為S、K X ₉ 為L、W	280
1303255	TGTTSDVGSYNLVS	281	EVSKRPS	282	CSYAESSTLV	283
1303574	TGTTSDVGSYNLVS	284	EVSKRPS	285	CSYAESSTLV	286
1303613	TGTTSDVGSYNLVS	287	EVSKRPS	288	CSYAESSTLV	289
1303507	TGTTSDVGSYNLVS	290	EVSKRPS	291	CSYAESSTLV	292
1303716	TGTTSDVGSYNLVS	293	EVSKRPS	294	CSYAESSTLV	295
1308640	TGTSSDVGSYNLVS	296	EVSKRPS	297	CSYADSSTLV	298
1318394	TGTSSDVGSYNLVS	380	EVTVRPS	381	CSYVDSKTWV	382
1318693	TGTSSDVGSYNLVS	383	EVTVRPS	384	CSYVDSKTWV	385
1318991	TGTSSDVGSYNLVS	386	EVTVRPS	387	CSYVDSKTWV	388
1318198	TGTNSDVGSYNLVS	398	EVTVRPS	399	CSYVDSKTWV	400
1308591	TGTSSDVGSYNLVS	302	EVSKRPS	303	CSYADRSTLV	304
1303446	TGTTSDVGSYNLVS	305	EVSKRPS	306	CSYAESSTLV	307
共有的 VL進化 枝4	SGDX ₄ LPX ₇ X ₈ YX ₁₀ Y X ₄ 為A、T X ₇ 為Q、E、N、R、K X ₈ 為H、Q X ₁₀ 為V、T、A	308	KDX ₃ X ₄ RPS X ₃ 為N、S X ₄ 為D、E	309	QSADX ₅ SGX ₈ X ₉ VV X ₅ 為I、N、S、 X ₈ 為S、A、I、T X ₉ 為F、Y	310
1306164	SGDALPKQYAY	311	KDSERPS	312	QSADNSGTFVV	313
1306253	SGDALPKQYAY	314	KDSERPS	315	QSADSSGTYVV	316
1306424	SGDALPKQYAY	317	KDSERPS	318	QSADSSGTYVV	319
1306053	SGDTLPKQYVY	320	KDNERPS	321	QSADNSGIYVV	322
1306153	SGDTLPKHYAY	323	KDNERPS	324	QSADNSGIYVV	325

LIBC 編號	LCDR1		LCDR2		LCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
1306251	SGDTLPKHYAY	326	KDNERPS	327	QSADNSGIYVV	328
1306674	SGDTLPKHYAY	329	KDNERPS	330	QSADNSGIYVV	331
1307329	SGDTLPKHYAY	332	KDNERPS	333	QSADNSGIYVV	334
1306622	SGDALPRHYAY	335	KDNERPS	336	QSADSSGIYVV	337
1306800	SGDALPKHYAY	338	KDNERPS	339	QSADNSGIYVV	340
1306965	SGDALPNHYAY	341	KDNERPS	342	QSADSSGIYVV	343
1306294	SGDALPKHYTY	344	KDNDRPS	345	QSADISGIYVV	346
1318253	SGDALPQHYTY	347	KDNERPS	348	QSADSSGSYVV	349
1318209	SGDTLPEHYTY	350	KDNERPS	351	QSADSSGAYVV	352
1318188	SGDALPQHYTY	353	KDNERPS	354	QSADISGTYVV	355
共有的 VL進化 枝2	TGX ₃ X ₄ SDVGSYNLV S X ₃ 為S、T X ₄ 為N、S、I	356	EVX ₃ KRPS X ₃ 為T、N、S	357	CSYAX ₅ X ₆ X ₇ TYV X ₅ 為D、G X ₆ 為T、S X ₇ 為R、S、K、	358
1307739	TGTSSDVGSYNLVS	359	EVSKRPS	360	CSYADSSTYV	361
1310489	TGTSSDVGSYNLVS	362	EVSKRPS	363	CSYAGSSTYV	364
1308006	TGTISDVGSYNLVS	365	EVNKRPS	366	CSYADTKTYV	367
1308236	TGTISDVGSYNLVS	368	EVSKRPS	369	CSYADTKTYV	370
1308563	TGTISDVGSYNLVS	371	EVSKRPS	372	CSYADTKTYV	373
1308943	TGTISDVGSYNLVS	374	EVSKRPS	375	CSYADTKTYV	376
1318301	TGSNSDVGSYNLVS	377	EVTKRPS	378	CSYADSRTYV	379
1319279	TGSNSDVGSYNLVS	389	EVNKRPS	390	CSYADSRTYV	391
1319569	SGDKLGDKYAF	392	QDKKRPS	393	QAWDISTGV	394
1307105	TGTSRDVGGINYVS	395	EVSNRPS	396	SSYISGNSHV	397

【0141】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含由以下定義的共用VH CDR結構：HCDR1胺基酸序列：X₁YGMH（SEQ ID NO: 195），其中

X₁為A或S；HCDR2胺基酸序列：X₁IWYDGNKYYX₁₂DSVKG（SEQ ID NO: 196），其中X₁為L或V，並且X₁₂為E或A；以及HCDR3胺基酸序列：DRITX₅VRGVTNYGMDV（SEQ ID NO: 197），其中X₅為M或R。上表6中提供了示例性促效劑LTβR結合蛋白的重鏈CDR序列，其結合人LTβR CRD4，不阻斷LIGHT與LTβR結合，不阻斷LTα1β2與LTβR結合，並且包含SEQ ID NO: 195的HCDR1、SEQ ID NO: 196的HCDR2和SEQ ID NO: 197的HCDR3。

【0142】在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含分別為SEQ ID NO: 195-197的HCDR 1-3，進一步包含由以下定義的共用VL CDR結構：LCDR1胺基酸序列SGDX₄LPX₇X₈YX₁₀Y（SEQ ID NO: 308），其中X₄為A或T；X₇為Q、E、N、R或K；X₈為H或Q；並且X₁₀為V、T或A；LCDR2胺基酸序列KDX₃X₄RPS（SEQ ID NO: 309），其中X₃為N或S且X₄為D或E；以及LCDR3胺基酸序列QSADX₅SGX₈X₉VV（SEQ ID NO: 310），其中X₅為I、N或S；X₈為S、A、I或T；X₉為F或Y。上表7中提供了示例性促效劑LTβR結合蛋白的輕鏈可變區CDR序列，其結合人LTβR CRD4，不阻斷LIGHT與LTβR結合，不阻斷LTα1β2與LTβR結合，並且包含SEQ ID NO: 308的LCDR1、SEQ ID NO: 309的LCDR2和SEQ ID NO: 310的LCDR3。

【0143】在另一個實施方式中，促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含由以下定義的共用VH CDR結構：HCDR1胺基酸序列：SX₂AMH（SEQ ID NO: 224），其中X₂為Y或F；HCDR2胺基酸序列：VIWYX₅X₆X₇NX₉FYADSVKG（SEQ ID NO: 225），其中X₅為D、A或N；X₆為R或E；X₇為N或S；X₉為K或N；HCDR3胺基酸序列：GDX₃X₄YX₆YX₈YGX₁₁DX₁₃（SEQ ID NO: 226），其中X₃為W或R；X₄為N或D；X₆為S、H或Y；X₈為Y、Q或K；X₁₁為M或V；X₁₃為L或V。上表6中提供了示例

性促效劑LTβR結合蛋白的重鏈CDR序列，其結合人LTβR CRD4，不阻斷LIGHT與LTβR結合，不阻斷LTα1β2與LTβR結合，並且包含SEQ ID NO: 224的HCDR1、SEQ ID NO: 225的HCDR2和SEQ ID NO: 226的HCDR3。

【0144】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含分別為SEQ ID NO: 224-226的HCDR 1-3，進一步包含由以下定義的共用VL CDR結構：LCDR1胺基酸序列TGX₃X₄SDVGSYNLVS（SEQ ID NO: 356），其中X₃為S或T；X₄為N、S或I；LCDR2胺基酸序列：EVX₃KRPS（SEQ ID NO: 357），其中X₃為T、N或S；以及LCDR3胺基酸序列：CSYAX₅X₆X₇TYV（SEQ ID NO: 358），其中X₅為D或G；X₆為T或S；X₇為R、S或K。上表7中提供了示例性促效劑LTβR結合蛋白的輕鏈可變區CDR序列，其結合人LTβR CRD4，不阻斷LIGHT與LTβR結合，不阻斷LTα1β2與LTβR結合，並且包含SEQ ID NO: 356的LCDR1、SEQ ID NO: 357的LCDR2和SEQ ID NO: 358的LCDR3。

【0145】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含可變輕鏈（VL）結構域、可變重鏈（VH）結構域或VL和VH結構域的組合。在任何實施方式中，該促效劑LTβR結合蛋白的VH結構域包含下表8中提供的VH胺基酸序列中的任一個，或與表8中列出的VH胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%或至少95%相同的胺基酸序列。在任何實施方式中，該促效劑LTβR結合蛋白的VL結構域包含下表8中提供的VL胺基酸序列中的任一個，或與表8中列出的VL胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%、至少95%相同的胺基酸序列。

【0146】 本揭露之示例性促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT

與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合：(i) 分別為SEQ ID NO: 159、SEQ ID NO: 160、SEQ ID NO: 161、SEQ ID NO: 278、SEQ ID NO: 279和SEQ ID NO: 280；(ii) 分別為SEQ ID NO: 162、SEQ ID NO: 163、SEQ ID NO: 164、SEQ ID NO: 281、SEQ ID NO: 282和SEQ ID NO: 283；(iii) 分別為SEQ ID NO: 165、SEQ ID NO: 166、SEQ ID NO: 167、SEQ ID NO: 284、SEQ ID NO: 285和SEQ ID NO: 286；(iv) 分別為SEQ ID NO: 168、SEQ ID NO: 169、SEQ ID NO: 170、SEQ ID NO: 287、SEQ ID NO: 288和SEQ ID NO: 289；(v) 分別為SEQ ID NO: 171、SEQ ID NO: 172、SEQ ID NO: 173、SEQ ID NO: 290、SEQ ID NO: 291和SEQ ID NO: 292；(vi) 分別為SEQ ID NO: 174、SEQ ID NO: 175、SEQ ID NO: 176、SEQ ID NO: 293、SEQ ID NO: 294和SEQ ID NO: 295；(vii) 分別為SEQ ID NO: 177、SEQ ID NO: 178、SEQ ID NO: 179、SEQ ID NO: 296、SEQ ID NO: 297和SEQ ID NO: 298；(viii) 分別為SEQ ID NO: 180、SEQ ID NO: 181、SEQ ID NO: 182、SEQ ID NO: 302、SEQ ID NO: 303和SEQ ID NO: 304；(ix) 分別為SEQ ID NO: 183、SEQ ID NO: 184、SEQ ID NO: 185、SEQ ID NO: 305、SEQ ID NO: 306和SEQ ID NO: 307。

【0147】 在一個實施方式中，促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些包含分別為SEQ ID NO: 159-161的HCDR1、HCDR2和HCDR3胺基酸序列以及分別為SEQ ID NO: 278-280的LCDR1、LCDR2和LCDR3胺基酸序列的結合蛋白。該等促效劑LT β R結合蛋白進一步包含選自以下的VH和VL胺基酸序列：與SEQ ID NO: 401的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 402的VL胺基酸序列具有至少90%、至少95%或至少98%序列

同一性的VL胺基酸序列；與SEQ ID NO: 403的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 404的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 405的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 406的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 407的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 408的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 409的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 410的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 411的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 412的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 413的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 414的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 415的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 416的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列。下表8中提供了本文所述之VH和VL胺基酸序列。

【0148】 在一個實施方式中，本揭露之示例性促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合：

(i) 分別為SEQ ID NO: 159、SEQ ID NO: 160、SEQ ID NO: 161、SEQ ID NO: 308、

SEQ ID NO: 309和SEQ ID NO: 310；(ii) 分別為SEQ ID NO: 189、SEQ ID NO: 190、SEQ ID NO: 191、SEQ ID NO: 314、SEQ ID NO: 315和SEQ ID NO: 316；(iii) 分別為SEQ ID NO: 186、SEQ ID NO: 187、SEQ ID NO: 188、SEQ ID NO: 311、SEQ ID NO: 312和SEQ ID NO: 313；(iv) 分別為SEQ ID NO: 192、SEQ ID NO: 193、SEQ ID NO: 194、SEQ ID NO: 317、SEQ ID NO: 318和SEQ ID NO: 319。

【0149】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些包含分別為SEQ ID NO: 159-161的HCDR1、HCDR2和HCDR3胺基酸序列以及分別為SEQ ID NO: 308-310的LCDR1、LCDR2和LCDR3胺基酸序列的結合蛋白。該等促效劑LT β R結合蛋白進一步包含選自以下的VH和VL胺基酸序列：與SEQ ID NO: 417的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 418的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 419的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 420的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；以及與SEQ ID NO: 421的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 422的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列。下表8中提供了本文所述之VH和VL胺基酸序列。

【0150】 在一個實施方式中，本揭露之示例性促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合：

(i) SEQ ID NO: 195、SEQ ID NO: 196、SEQ ID NO: 197、SEQ ID NO: 308、SEQ ID NO: 309和SEQ ID NO: 310；(ii) SEQ ID NO: 197、SEQ ID NO: 198、SEQ ID NO: 199、SEQ ID NO: 320、SEQ ID NO: 321和SEQ ID NO: 322；(iii) 分別為SEQ ID NO: 200、SEQ ID NO: 201、SEQ ID NO: 202、SEQ ID NO: 323、SEQ ID NO: 324和SEQ ID NO: 325；(iv) 分別為SEQ ID NO: 203、SEQ ID NO: 204、SEQ ID NO: 205、SEQ ID NO: 326、SEQ ID NO: 327和SEQ ID NO: 328；(v) 分別為SEQ ID NO: 206、SEQ ID NO: 207、SEQ ID NO: 208、SEQ ID NO: 329、SEQ ID NO: 330和SEQ ID NO: 331；(vi) 分別為SEQ ID NO: 209、SEQ ID NO: 210、SEQ ID NO: 211、SEQ ID NO: 332、SEQ ID NO: 333和SEQ ID NO: 334；(vii) 分別為SEQ ID NO: 212、SEQ ID NO: 213、SEQ ID NO: 214、SEQ ID NO: 335、SEQ ID NO: 336和SEQ ID NO: 337；(viii) 分別為SEQ ID NO: 215、SEQ ID NO: 216、SEQ ID NO: 217、SEQ ID NO: 338、SEQ ID NO: 339和SEQ ID NO: 340；(ix) 分別為SEQ ID NO: 218、SEQ ID NO: 219、SEQ ID NO: 220、SEQ ID NO: 341、SEQ ID NO: 342和SEQ ID NO: 343；(x) 分別為SEQ ID NO: 221、SEQ ID NO: 222、SEQ ID NO: 223、SEQ ID NO: 343、SEQ ID NO: 344和SEQ ID NO: 345。

【0151】在一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含分別為SEQ ID NO: 195-197的HCDR1、HCDR2和HCDR3胺基酸序列以及分別為SEQ ID NO: 308-310的LCDR1、LCDR2和LCDR3胺基酸序列。該等促效劑LT β R結合蛋白進一步包含選自以下的VH和VL胺基酸序列：與SEQ ID NO: 423的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 424的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 425的VH胺基酸序列具有至少90%、至少95%或至少

98%序列同一性的VH胺基酸序列和與SEQ ID NO: 426的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 427的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 428的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 429的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 430的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 431的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 432的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 433的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 434的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 435的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 436的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 437的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 438的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 439的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 440的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列。下表8中提供了本文所述之VH和VL胺基酸序列。

【0152】 在一個實施方式中，本揭露之示例性促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含選自以

下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合：

(i) 分別為SEQ ID NO: 224、SEQ ID NO: 225、SEQ ID NO: 226、SEQ ID NO: 356、SEQ ID NO: 357和SEQ ID NO: 358；(ii) 分別為SEQ ID NO: 227、SEQ ID NO: 228、SEQ ID NO: 229、SEQ ID NO: 359、SEQ ID NO: 360和SEQ ID NO: 361；(iii) 分別為SEQ ID NO: 230、SEQ ID NO: 231、SEQ ID NO: 232、SEQ ID NO: 362、SEQ ID NO: 363和SEQ ID NO: 364；(iv) 分別為SEQ ID NO: 233、SEQ ID NO: 234、SEQ ID NO: 235、SEQ ID NO: 365、SEQ ID NO: 366和SEQ ID NO: 367；(v) 分別為SEQ ID NO: 236、SEQ ID NO: 237、SEQ ID NO: 238、SEQ ID NO: 368、SEQ ID NO: 369和SEQ ID NO: 370；(vi) 分別為SEQ ID NO: 239、SEQ ID NO: 240、SEQ ID NO: 241、SEQ ID NO: 371、SEQ ID NO: 372和SEQ ID NO: 373；(vii) 分別為SEQ ID NO: 242、SEQ ID NO: 243、SEQ ID NO: 244、SEQ ID NO: 374、SEQ ID NO: 375和SEQ ID NO: 376；(viii) 分別為SEQ ID NO: 245、SEQ ID NO: 246、SEQ ID NO: 247、SEQ ID NO: 377、SEQ ID NO: 378和SEQ ID NO: 379；(ix) 分別為SEQ ID NO: 248、SEQ ID NO: 249、SEQ ID NO: 250、SEQ ID NO: 380、SEQ ID NO: 381和SEQ ID NO: 382；(x) 分別為SEQ ID NO: 251、SEQ ID NO: 252、SEQ ID NO: 253、SEQ ID NO: 383、SEQ ID NO: 384和SEQ ID NO: 385；(xi) 分別為SEQ ID NO: 254、SEQ ID NO: 255、SEQ ID NO: 256、SEQ ID NO: 386、SEQ ID NO: 387和SEQ ID NO: 388；(xii) 分別為SEQ ID NO: 180、SEQ ID NO: 181、SEQ ID NO: 182、SEQ ID NO: 302、SEQ ID NO: 303和SEQ ID NO: 304；(xiii) 分別為SEQ ID NO: 183、SEQ ID NO: 184、SEQ ID NO: 185、SEQ ID NO: 305、SEQ ID NO: 306和SEQ ID NO: 307；(xiv) 分別為SEQ ID NO: 257、SEQ ID NO: 258、SEQ ID NO: 259、SEQ ID NO: 389、SEQ ID NO: 390和SEQ ID NO: 391。

【0153】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效

劑LT β R抗體或促效劑LT β R雙特異性結合蛋白)，其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含分別為SEQ ID NO: 224-226的HCDR1、HCDR2和HCDR3胺基酸序列以及分別為SEQ ID NO: 356-358的LCDR1、LCDR2和LCDR3胺基酸序列。該等促效劑LT β R結合蛋白進一步包含選自以下的VH和VL胺基酸序列：與SEQ ID NO: 441的VH胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 442的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 443的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 444的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 445的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 446的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 447的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 448的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 449的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 450的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 451的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 452的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 453的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 454的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 455的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 456的VL胺基酸序列具有至少

90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 457的VH胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 458的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 459的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 460的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 461的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 462的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列。下表8中提供了本文所述之VH和VL胺基酸序列。

【0154】 在一個實施方式中，本揭露之示例性促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合：

(i) 分別為SEQ ID NO: 257、SEQ ID NO: 258、SEQ ID NO: 259、SEQ ID NO: 389、SEQ ID NO: 390和SEQ ID NO: 391（1319279）；(ii) 分別為SEQ ID NO: 260、SEQ ID NO: 261、SEQ ID NO: 262、SEQ ID NO: 347、SEQ ID NO: 348和SEQ ID NO: 349（1318253）；(iii) 分別為SEQ ID NO: 263、SEQ ID NO: 264、SEQ ID NO: 265、SEQ ID NO: 350、SEQ ID NO: 351和SEQ ID NO: 352（1318209）；(iv) 分別為SEQ ID NO: 266、SEQ ID NO: 267、SEQ ID NO: 268、SEQ ID NO: 353、SEQ ID NO: 354和SEQ ID NO: 355（1318188）；(v) 分別為SEQ ID NO: 269、SEQ ID NO: 270、SEQ ID NO: 271、SEQ ID NO: 392、SEQ ID NO: 393和SEQ ID NO: 394（1319569）；(vi) 分別為SEQ ID NO: 272、SEQ ID NO: 273、SEQ ID NO: 274、SEQ ID NO: 395、SEQ ID NO: 396和SEQ ID NO: 397（1317105）；(vii) 分別為SEQ ID NO: 275、SEQ ID NO: 276、SEQ ID NO: 277、SEQ ID NO: 398、SEQ ID

NO: 399和SEQ ID NO: 400 (1318198) ;

【0155】 在另一個實施方式中，本揭露之LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含選自以下的VH胺基酸序列和VL胺基酸序列：SEQ ID NO: 401的VH胺基酸序列和SEQ ID NO: 402的VL胺基酸序列；SEQ ID NO: 403的VH胺基酸序列和SEQ ID NO: 404的VL胺基酸序列；SEQ ID NO: 405的VH胺基酸序列和SEQ ID NO: 406的VL胺基酸序列；SEQ ID NO: 407的VH胺基酸序列和SEQ ID NO: 408的VL胺基酸序列；SEQ ID NO: 409的VH胺基酸序列和SEQ ID NO: 410的VL胺基酸序列；SEQ ID NO: 411的VH胺基酸序列和SEQ ID NO: 412的VL胺基酸序列；SEQ ID NO: 413的VH胺基酸序列和SEQ ID NO: 414的VL胺基酸序列；SEQ ID NO: 415的VH胺基酸序列和SEQ ID NO: 416的VL胺基酸序列；SEQ ID NO: 417的VH胺基酸序列和SEQ ID NO: 418的VL胺基酸序列；SEQ ID NO: 419的VH胺基酸序列和SEQ ID NO: 420的VL胺基酸序列；SEQ ID NO: 421的VH胺基酸序列和SEQ ID NO: 422的VL胺基酸序列；SEQ ID NO: 423的VH胺基酸序列和SEQ ID NO: 424的VL胺基酸序列；SEQ ID NO: 425的VH胺基酸序列和SEQ ID NO: 426的VL胺基酸序列；SEQ ID NO: 427的VH胺基酸序列和SEQ ID NO: 428的VL胺基酸序列；SEQ ID NO: 429的VH胺基酸序列和SEQ ID NO: 430的VL胺基酸序列；SEQ ID NO: 431的VH胺基酸序列和SEQ ID NO: 432的VL胺基酸序列；SEQ ID NO: 433的VH胺基酸序列和SEQ ID NO: 434的VL胺基酸序列；SEQ ID NO: 435的VH胺基酸序列和SEQ ID NO: 436的VL胺基酸序列；SEQ ID NO: 437的VH胺基酸序列和SEQ ID NO: 438的VL胺基酸序列；SEQ ID NO: 439的VH胺基酸序列和SEQ ID NO: 440的VL胺基酸序列；SEQ ID NO: 441的VH胺基酸序列和SEQ ID NO: 442的VL胺基酸序列；SEQ ID NO: 443的VH胺基酸序列和SEQ ID NO: 444的VL胺基酸序列；SEQ

ID NO: 445的VH胺基酸序列和SEQ ID NO: 446的VL胺基酸序列；SEQ ID NO: 447的VH胺基酸序列和SEQ ID NO: 448的VL胺基酸序列；SEQ ID NO: 449的VH胺基酸序列和SEQ ID NO: 450的VL胺基酸序列；SEQ ID NO: 451的VH胺基酸序列和SEQ ID NO: 452的VL胺基酸序列；SEQ ID NO: 453的VH胺基酸序列和SEQ ID NO: 454的VL胺基酸序列；SEQ ID NO: 455的VH胺基酸序列和SEQ ID NO: 456的VL胺基酸序列；SEQ ID NO: 457的VH胺基酸序列和SEQ ID NO: 458的VL胺基酸序列；SEQ ID NO: 459的VH胺基酸序列和SEQ ID NO: 460的VL胺基酸序列；SEQ ID NO: 461的VH胺基酸序列和SEQ ID NO: 462的VL胺基酸序列；SEQ ID NO: 463的VH胺基酸序列和SEQ ID NO: 464的VL胺基酸序列；SEQ ID NO: 465的VH胺基酸序列和SEQ ID NO: 466的VL胺基酸序列；SEQ ID NO: 467的VH胺基酸序列和SEQ ID NO: 468的VL胺基酸序列；SEQ ID NO: 469的VH胺基酸序列和SEQ ID NO: 470的VL胺基酸序列；SEQ ID NO: 471的VH胺基酸序列和SEQ ID NO: 472的VL胺基酸序列；以及SEQ ID NO: 473的VH胺基酸序列和SEQ ID NO: 474的VL胺基酸序列。下表8中提供了本文所述之VH和VL胺基酸序列。

[表8]：與LTβR結合物LIBC219081和LIBC218979競爭結合LTβR的CRD4並且不阻斷LIGHT或LTα1β2結合的LTβR結合蛋白的VH和VL胺基酸序列

LIBC編號	結構域	序列	SEQ ID
1303255	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	401
	V _L	QSALTQPASVSGSPGQSITISCTGTSDVGSYNLVSQYQHPGKVPK FMIYEVSKRPSGVSNRFGSGKSGNTASLTISGLQAEDEADYHCCSYA ESSTLVFGGGTKLTVLG	402
1303574	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	403

LIBC編號	結構域	序列	SEQ ID
	V _L	QSALTQPASVSGSPGQSITISCTGTTSADVGSYNLVSWYQQHPGKVPK FMIYEVSKRPSGVSNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYA ESSTLVFGGGTKLTVLG	404
1303613	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	405
	V _L	QSALTQPASVSGSPGQSITISCTGTTSADVGSYNLVSWYQQHPGKVPK FMIYEVSKRPSGVYNRFSGSKSGNTASLTISGLQAEDEADYHCCSY AESSTLVFGGGTKLTVLG	406
1303507	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	407
	V _L	QSALTQPASVSGSPGQSITISCTGTTSADVGSYNLVSWYQQHPGKVPK FMIYEVSKRPSGVFNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYA ESSTLVFGGGTKLTVLG	408
1303716	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	409
	V _L	QSALTQPASVSGSPGQSITISCTGTTSADVGSYNLVSWYQQHPGKVPK FMIYEVSKRPSGVFNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYA ESSTLVFGGGTKLTVLG	410
1308640	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADSSGWYYYYGMDVWGQGTTVTVSS	411
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKVPK FMIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYHCCSYA DSSTLVFGGGTKLTVLG	412
1308591	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGFYMHWRQAPGQG LKWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADSSGWYYYYGMDVWGQGTTVTVSS	413
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKVPK	414

LIBC編號	結構域	序列	SEQ ID
		FMIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCSYA DRSTLVFGGGTKLTVLG	
1303446	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	415
	V _L	QSALTQPASVFGSPGQSITISCTGTTSDVGSYNLVSQYQHPGKVPK FMIYEVSKRPSGVYNRFSGSKSGNTASLTIFGLQAEDEADYHCCSY AESSTLVFGGGTKLTVLG	416
1306164	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQ GLEWMGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVFYCAKDRAGGVYYGMDVWGQGTTVTVSS	417
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQKKPGQAPVRV IYKDSERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADNSG TFVVFGGGTKLTVLG	418
1306253	V _H	QVQLVQSGAEVKKPGASVKVSCRASGYTFTGYYMHWVRQAPGQG LEWMGWINPNRGGTNYAQKFQGRVTMTRDTSISTAYMELSRLISD DTAVYYCAKDRAGGVYYGMDVWGQGTTVTVSS	419
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQKPDQAPVM VISKDSERPSGIPERFSGSSSGTTVTLTISGVQAEDESYYCQSADSS GTYYVFGGGTKLTVLG	420
1306424	V _H	QVQLVQSGAEVKKPGASVKVSCRASGYTFTGYYMHWVRQAPGQG LEWMGWINPNRGGTNYAQKFQGRVTMTRDTSISTAYMELSRLISD DTAVYYCAKDRAGGVYYGMDVWGQGTTVTVSS	421
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQKPDQAPVM VISKDSERPSGIPERFSGSSSGTTVTLTISGVQAEDESYYCQSADSS GTYYVFGGGTKLTVLG	422
1306053	V _H	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGL EWVALIWYDGNKYYADSVKGRFTISRDNKNTLYLQMSSLRAED TAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	423
	V _L	SYELTQPPSMVSPGQTARITCSGDTLPKQYVYWYRQKPGQAPVLV IYKDNERPSGILERFSGSSSGATVTLTISGVQAEDEADYFCQSADNS	424

LIBC編號	結構域	序列	SEQ ID
		GIYVVFGGGTKLTVLG	
1306153	V _H	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGL EWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMSSLRAED TAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	425
	V _L	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKAGQAPVL VIYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADN SGIYVVFGGGTKLTVLG	426
1306251	V _H	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGL EWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMSSLRAED TAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	427
	V _L	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKAGQAPVL VIYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADN SGIYVVFGGGTKLTVLG	428
1306674	V _H	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGL EWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMSSLRAED TAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	429
	V _L	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKPGQAPVLV IYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNS GIYVVFGGGTKLTVLG	430
1307329	V _H	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGL EWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMSSLRAED TAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	431
	V _L	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKPGQAPVLV IYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNS GIYVVFGGGTKLTVLG	432
1306622	V _H	QVQLVESGGGVVQFGRSLRLSCAASGFTFSAYGMHWVRQAPGKG LEWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAE DTAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	433
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPRHYAYWYRQKPGQAPVLV IYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADSSG IYVVFGGGTKLTVLG	434

LIBC編號	結構域	序列	SEQ ID
1306800	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKG LEWVALIWYDGN NKYYADSVKGRFTISRDN SKNTLYLQMNSLRAE DTAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	435
	V _L	SYELTQPPSMSVSPGQTARITCSGDALPKHYAYWYRQKPGQAPVL VIYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADN SGIYVVFGGG TKLTVLG	436
1306965	V _H	QVQVVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKG LEWVALIWYDGN NKYYADSVKGRFTISRDN SKNTLYLQMNSLRAE DTAIYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	437
	V _L	SYELTQPPSVSLSPGQTARITCSGDALPNHYAYWYRQKPGQAPVLV IYKDNERPSGIPERFSGSSSGATVTLTITGVQAEDEADYFCQSADSSG IYVVFGGG TKLTVLG	438
1306294	V _H	QEQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGL EWVAVIWYDGN NKYYEDSVKGRFTISRDN SKNTLYLQMNSLRAE DTAVYYCARDRITMVRGVTNYGMDVWGQGTTVTVSS	439
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPKHYTYWYQQKPGQAPLLV IYKDNDRPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADISG IYVVFGGG TKLTVLG	440
1307739	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAVIWYDRNNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDRDYHYQYGMDVWGQGTTVTVSS	441
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNL VSWYQQHPGKAPQ LMIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYA DSSTYVFGTGTKVTVLG	442
1310489	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAVIWYDRNNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDRDYHYQYGMDVWGQGTTVTVSS	443
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNL VSWYQQHPGKAPQ LMIYEVSKRPSGVSSRFSVSKSGNTASLTISGLRAEDEADYYCCSYA GSSTYVFGSGTKVTVLG	444
1308006	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL	445

LIBC編號	結構域	序列	SEQ ID
		EWVAVIWYNRRNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDRDY YYYYGMDVWGQGTTVTVSS	
	V _L	QSALTQPASVSGSPGQSITISCTGTISDVGSYNL VSWYQQHPGKAPQ LMIYEVNKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSY ADTKTYVFGTGTKVTVLG	446
1308236	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAVIWYNRRNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDRDY YYYYGMDVWGQGTTVTVSS	447
	V _L	QSALTQPASVSGSPGQSITISCTGTISDVGSYNL VSWYQQHPGKAPQ LMIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYA DTKTYVFGTGTKVTVLG	448
1308563	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAVIWYNRRNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAED AAVYYCARGDRDY YYYYGMDVWGQGTTVTVSS	449
	V _L	QSALTQPASVSGSPGQSITISCTGTISDVGSYNL VSWYQQHPGKAPQ LMIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYA DTKTYVFGTGTKVTVLG	450
1308943	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAVIWYNRRNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAED AAVYYCARGDRDY YYYYGMDVWGQGTTVTVSS	451
	V _L	QSALTQPASVSGSPGQSITISCTGTISDVGSYNL VSWYQQHPGKAPQ LMIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYA DTKTYVFGTGTKVTVLG	452
1318301	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFAMHWVRQAPGKGL DWVAVIWYAESNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDWNYSYKYGVDLWGQGTTVTVSS	453
	V _L	QSALTQPASVSGSPGQSITISCTGSNSDVGSYNL VSWYQQDPGKAP KLMIYEVTKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCS YADSRTYVFGTGTKVTVLG	454
1318394	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGL EWMTVIWYDRSNKY YADSVKGRFTISRDN SKNTLYLQMNSLRAED	455

LIBC編號	結構域	序列	SEQ ID
		TAVYYCARGISGYRYGTDMDVWGQGTTVTVSS	
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKAPK FMIYEVTVRPSGVSNRFGSKSGNTAYLTISGLQAEDEADYYCCSY VDSKTWVFGGGTKLTVLG	456
1318693	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGL EWMTVIWYDRSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGISGYRYGTDMDVWGQGTTVTVSS	457
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKAPK FMIYEVTVRPSGVSNRFGSKSGNTAYLTISGLQAEDEADYYCCSY VDSKTWVFGGGTKLTVLG	458
1318991	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGL EWMTVIWYDRSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGISGYRYGTDMDVWGQGTTVTVSS	459
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKAPK FMIYEVTVRPSGVSNRFGSKSGNTAYLTISGLQAEDEADYYCCSY VDSKTWVFGGGTKLTVLG	460
1319279	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFAMHWVRQAPGKGL DWVAVIWYAESNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDWNYSYKYGVDLWGQGTTVTVSS	461
	V _L	QSALTQPASVSGSPGQSITISCTGSNSDVGSYNLVSWYQQDPGKAP KLMIYEVNKRPSGVYNCFFGSKSGNTASLTICGLQGEEEGDYY*CS YADSRTYVFGSGTKVTVLG	462
1318253	V _H	QMQLVQSGTEVKKPGASVKVSCEASGYAFTGFYMHWRQAPGQG LEWMGWLNPNTGGTSYVQKFQGRVTMTRDTSISTAYMELSRLRSD DTAVYFCASGTGTTAFDFWGQGTMTVTVSS	463
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPQHYTYWYQQKPGRAPVLV IYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSG SYVVFGGGTKLTVLG	464
1318209	V _H	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYVMNWVRQAPGKGL EWVSGISGSDGSTYYADSVKGRFTISSDN SKNTLYLQMNSLRAEDT AVYYCAKEEDWNYGFDYWGQGLTVTVSS	465

LIBC編號	結構域	序列	SEQ ID
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPILVI YKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSG AYVVFGGGTKLTVLG	466
1318188	V _H	QVQLQESGPGLVKPSQTLSTCTVSGGSISSDGYFWSWIRQHPGKG LEWIGFIYFTGITYYNPSLQSRVTISVDTSKNQFSLKLNSVTAADTAV YYCARVIPGEDAFDIWGQGTMTVTVSS	467
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPQHYTYWYQQKPGQAPVLV IYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADISG TYVVFGGGTKLTVLG	468
1319569	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGL EWMGWMNPNTGNTGYPQKFQGRVTMTNRNTSISTAYMELSSLRSE DTAVYYCARGGLTMKVVGAGWFDWPWGQGTLLTVTVSS	469
	V _L	SYELTQPPSVSVSPGQTASITCSGDKLGDKYAFWYQQKPGQSPLLVI YQDKKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDIS TGVFGGGTKLTVLG	470
1307105	V _H	QVQVVESGGGVVQPGRSLRLSCAASGFTFRSYGMDWVRQAPGKG LEWVAVISYDGNKYKYADSVKGRFTISRDN SKNTLYLQMNSLRAE DTAVYYCARD DYSTLDYWGQGTLLTVTVSS	471
	V _L	QSALTQPASVSGSPGQSITISCTGTSRDVGGYNYVSWYQQHPGKAP KLMIYEVS NRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSY ISGN SHVFGTGTKVTPG	472
1318198	V _H	QVQLQESGPGLVKPSQTLSTCTVSGGSISSDGYFWSWIRQHPGKG LEWIGFIYFTGITYYNPSLQSRVTISVDTSKNQFSLKLNSVTAADTAV YYCARVIPGEDAFDIWGQGTMTVTVSS	473
	V _L	QSALTQPASVSGSPGQSITISCTGTNSDVGSYNLVSWYQQHPGKAP KFMIYEVTVRPSGV SNRFSGSKSGNTAYLTISGLQAEDEADYYCCS YVDSKTWVFGGGTKLTVLG	474

【0156】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含如上所述之

VH區和/或VL區，並且進一步包含與VH區偶合的一或多個重鏈恒定區和/或與VL區偶合的輕鏈恒定區。例如，在一個實施方式中，該LTβR結合蛋白係Fab，其包含VH和與VL偶合的第一重鏈恒定結構域（CH1）以及輕鏈恒定區（CL）。在另一個實施方式中，該LTβR結合蛋白係F(ab')₂，其包含藉由鉸鏈區偶合的完全抗體的兩個LTβR結合區，其中每個結合區包含VH-CH1和VL-CL。在另一個實施方式中，該LTβR結合蛋白係包含完全輕鏈（VL-CL）和完全重鏈（VH-CH1-CH2-CH3）的抗體。下表9中提供了本揭露之LTβR抗體之示例性胺基酸序列，該抗體結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合。

[表9]. LTβR CRD4結合抗體的抗體HC和LC序列

LIBC編號	描述	序列	SEQ ID
219081 19325	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGSNQYYADSVKGRFIISRDN SKNTLYLQMNSLRAEDTA VYYCARDRVAAHPAYYYGLDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWKVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	747
	LC	SYELTQPPSVSLSPGQTARITCSGDALPNHYAYWYQQKPGQAPVLVIF KDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGSYV IFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV TVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS	748
218979 19319	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLE WVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLSLQMNSLRAEDTA	749

LIBC編號	描述	序列	SEQ ID
		VYYCARERIAAAPYYYYGMDVWGQGTTTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPRQTARITCSGDALPKHYAYWYQQKPGQAPVLVI YKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADNTGS YMFVGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	750
1308929	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLD WVGVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARDRVAARPHYYYGLDVWGQGTTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKF N WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	751
	LC	SYELTQPPSVSVSPGQTARITCSGDALPNHYAYWYQQKPGQAPVLVI YKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGSY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	752
1318341	HC	LVQLVESGGGVVQPGRSLRLSCAASGFTFRSYAMHWVRQAPGKGLE WVAVIWYDGTNKYYADSVKGRFTISRDN SKNTLYLQMNTLRADDT	753

LIBC編號	描述	序列	SEQ ID
		AVYFCAKDRVAARPDYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARIACSGDALPDHYTYWYQQKPGQAPVLVI YKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGA YVIFGGGKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	754
1318409	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGSNKYYADSVKGRFTISRDN SKDTLHLQMNSLRAEDM AVYFCAKDRVVARPDYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	755
	LC	SYELTQPPSVSVSPGQTARITCSGDALPQHYTYWYQQKPGQAPVLVIY KDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADGSGTY VVFGGGKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	756
1318412	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGRKRYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	757

LIBC編號	描述	序列	SEQ ID
		VYYCAKDRIAARPNYYYGLDVWGQGTTTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELIQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPILVIYK DNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGAYV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS	758
1318738	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYDMHWVRQAPGKGLE WVAVIRYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMNSLRVEDTA VYYCARERGPYGGNTYYGMDVWGQGTTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKF NWXVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	759
	LC	SYELTQPPSVSVSPGQTARITCSGDALPKHYAYWYQQKPGQAPVMVI YKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSTDSSATY VVFGGGTKLTVLRQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	760
1319003	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLE WVAVIWDGRKRYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	761

LIBC編號	描述	序列	SEQ ID
		VYYCARDRIAARPNYYYGLDVWGQGTTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPDHYTYWYQQRPGQAPILVIY KDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGAY VVFGGGTKLTVLRQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	762
1319078	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARDRVAARPNYYYGMAVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF N WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	763
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQKPGQAPVMVI YKDNERPSGIPERFSGFSSSGTTVTLTITGVQAEDEADYYCQSADSSGT YVLFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	764
1319182	HC	QVHLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGSNKYYADSVKGRFTISRDN SKDTLHLQMNSLRAEDM	765

LIBC編號	描述	序列	SEQ ID
		AVYFCAKDRVVARPDYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPQHYTYWYQQNPGQAPVLVIY KDNERPSGIPERFSGSSSGTTVTLTISRVAEDEADYYCQSADSSGSYV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS	766
1319275	HC	QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCAKDRVAARP NFYYGMDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	767
	LC	SYELTQPPSVSLSPGHSARITCSGDALPKHYAYWYQQKPGQAPVLVIY KDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGTY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	768
1319390	HC	QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	769

LIBC編號	描述	序列	SEQ ID
		VYYCAKDRVAARPNFYYGMDVWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVLSLSPGHSARITCSGDALPKHYAYWYQQKPGQAPVLIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGTYVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	770
1319499	HC	QVQLVESGGGVVQPGRSLRLSCVASGFTFSNYGMYWVRQAPGKGLEWVAVIWYDESNKYYADSVKGRFTISRDKNTLYLQMNSLRAEDTAVYYCARDRIAGRPGYYYGMDVWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	771
	LC	SYELTQPPSVSVSPGQTARISCSGDALPKQYAYWYQQKPGQAPVLIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGAYVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	772
1319908	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVIWYDGRKRYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTA	773

LIBC編號	描述	序列	SEQ ID
		VYYCAKDRIAARPNYYYYGLDVWGQGTTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPILVIY KDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGAY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	774
1318496	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAAIWYDGSNKYHADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARDRIAARPNYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF N WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	775
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQEPGQAPVLVIY KDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGSY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	776
1320038	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAAIWYDGSNKYHADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	777

LIBC編號	描述	序列	SEQ ID
		VYYCARDRIAARPNYYYYGMDVWGQGTTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWKYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQEPGQAPVLVIY KDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGSY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	778
1308929	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLD WVGVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARDRVAARPHYYYGLDVWGQGTTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWKYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	779
	LC	SYELTQPPSVSVSPGQTARITCSGDALPNHYAYWYQQKPGQAPVLVI YKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGSY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	780
1309633	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFRSYAMHWVRQAPGKGLE WVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	781

LIBC編號	描述	序列	SEQ ID
		VYYCARDRVAARPHYYYGLDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWXVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDALPNQYAYWYQQKPGQAPVLI YKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGSY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	782
1303255	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	783
	LC	QSALTQPASVSGSPGQSITISCTGTSDVGSYNLVSQYQHPGKVPKF MIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYHCCSYAES STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	784
1303574	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT	785

LIBC編號	描述	序列	SEQ ID
		AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSDVGSYNLVSQYQHPGKVPKF MIYEVSKRPSGVSNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYAES STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	786
1303613	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	787
	LC	QSALTQPASVSGSPGQSITISCTGTSDVGSYNLVSQYQHPGKVPKF MIYEVSKRPSGVYNRFSGSKSGNTASLTISGLQAEDEADYHCCSYAES STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	788
1303507	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT	789

LIBC編號	描述	序列	SEQ ID
		AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTTSDVGSYNLVSQYQHPGKVPKF MIYEVSKRPSGVFNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYAES STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	790
1303716	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	791
	LC	QSALTQPASVSGSPGQSITISCTGTTSDVGSYNLVSQYQHPGKVPKF MIYEVSKRPSGVFNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYAES STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	792
1308640	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT	793

LIBC編號	描述	序列	SEQ ID
		AVYYCAKADSSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSQYQHPGKVPKF MIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYHCCSYADS STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTTPSKQSNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	794
1308591	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGFYMHWVRQAPGQGL KWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRRLSDDT AVYYCAKADSSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	795
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSQYQHPGKVPKF MIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCSYADR STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTTPSKQSNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	796
1303446	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRRLSDDT	797

LIBC編號	描述	序列	SEQ ID
		AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVFGSPGQSITISCTGTTSDVGSYNLVSWEYQHPGKVPKFMIEVSKRPSGVYNRFSGSKSGNTASLTIFGLQAEEADYHCCSYAESTLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	798
1306164	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNSSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSSDTAVFYCAKDRAGGVYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	799
	LC	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQKKPGQAPVRVIYKDSERPSGIPERFSGSSSGTTVTLTISGVQAEEADYCYQSADNSGTFVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	800
1306253	HC	QVQLVQSGAEVKKPGASVKVSCRASGYTFTGYYMHWVRQAPGQGLEWMGWINPNRGGTNYAQKFQGRVTMTRDTSISTAYMELSRLISDDT	801

LIBC編號	描述	序列	SEQ ID
		AVYYCAKDRAGGVYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQQKPDQAPVMVI SKDSERPSGIPERFSGSSSGTTVTLTISGVQAEDES DY CQSADSSGTY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	802
1306424	HC	QVQLVQSGAEVKKPGASVKVSCRASGYTFTGYMHWRQAPGQGL EWMGWINPNRGGTNYAQKFQGRVTMTRDTSISTAYMELSRLLSDDT AVYYCAKDRAGGVYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	803
	LC	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQQKPDQAPVMVI SKDSERPSGIPERFSGSSSGTTVTLTISGVQAEDES DY CQSADSSGTY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	804
1306053	HC	QEHLVESGGGVVQGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMSSLRAEDTA	805

LIBC編號	描述	序列	SEQ ID
		VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSMSVSPGQTARITCSGDTLPKQYVYWYRQKPGQAPVLVI YKDNERPSGILERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	806
1306153	HC	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGNKNKYADSVKGRFTISRDN SKNTLYLQMSSLRAEDTA VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	807
	LC	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKAGQAPVLVI YKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	808
1306251	HC	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGNKNKYADSVKGRFTISRDN SKNTLYLQMSSLRAEDTA	809

LIBC編號	描述	序列	SEQ ID
		VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKAGQAPVLVI YKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	810
1306674	HC	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGNKNKYADSVKGRFTISRDN SKNTLYLQMSSLRAEDTA VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	811
	LC	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKPGQAPVLVI YKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	812
1307329	HC	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGNKNKYADSVKGRFTISRDN SKNTLYLQMSSLRAEDTA	813

LIBC編號	描述	序列	SEQ ID
		VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKPGQAPVLVI YKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	814
1306622	HC	QVQLVESGGGVVQFGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGNKNKYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	815
	LC	SYELTQPPSVSVSPGQTARITCSGDALPRHYAYWYRQKPGQAPVLVIY KDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADSSGIYV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS	816
1306800	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGNKNKYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	817

LIBC編號	描述	序列	SEQ ID
		VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSMSVSPGQTARITCSGDALPKHYAYWYRQKPGQAPVLVI YKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	818
1306965	HC	QVQVVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA IYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	819
	LC	SYELTQPPSVSLSPGQTARITCSGDALPNHYAYWYRQKPGQAPVLVIY KDNERPSGIPERFSGSSSGATVTLTITGVQAEDEADYFCQSADSSGIYV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS	820
1306294	HC	QEQLVESGGGVVQPGRSLRLSCAASGFTFSYGMHWVRQAPGKGLE WVAWIWYDGNNKYYEDSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	821

LIBC編號	描述	序列	SEQ ID
		VYYCARDRITMVRGVNTNYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDALPKHYTYWYQQKPGQAPLLVIYKDNDRPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADISGIYVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	822
1307739	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVIWYDRNNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGDRDYHYQYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	823
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKAPQLMIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYADSTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	824
1310489	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVIWYDRNNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGDRDYHYQYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	825

LIBC編號	描述	序列	SEQ ID
		VYYCARGDRDYHYQYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWEYQHPGKAPQL MIYEVSKRPSGVSSRFSVSKSGNTASLTISGLRAEDEADYYCCSYAGS STYVFGSGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	826
1308006	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARGDRDYHYHYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	827
	LC	QSALTQPASVSGSPGQSITISCTGTISDVGSYNLVSWEYQHPGKAPQL MIYEVNKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYADT KTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	828
1308236	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	829

LIBC編號	描述	序列	SEQ ID
		VYYCARGDRDYYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTISDVGSYNLVSWYQQHPGKAPQL MIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYADT KTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	830
1308563	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDAA VYYCARGDRDYYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	831
	LC	QSALTQPASVSGSPGQSITISCTGTISDVGSYNLVSWYQQHPGKAPQL MIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYADT KTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	832
1308943	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDAA	833

LIBC編號	描述	序列	SEQ ID
		VYYCARGDRDYYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTISDVGSYNLVSWYQQHPGKAPQL MIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYADT KTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	834
1318301	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFAMHWVRQAPGKGLD WVAVIWYAESNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARGDWNYSYKYGVDLWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	835
	LC	QSALTQPASVSGSPGQSITISCTGSNSDVGSYNLVSWYQQDPGKAPKL MIYEVTKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCSYADS RTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	836
1318394	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLE WMTVIWYDRSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	837

LIBC編號	描述	序列	SEQ ID
		VYYCARGISGYRYGTDMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWEYQHPGKAPKFMIEVTVRPSGVSNRFGSKSGNTAYLTISGLQAEEADYYCCSYVDSKTWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	838
1318693	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLIEWMTVIWYDRSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGISGYRYGTDMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	839
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWEYQHPGKAPKFMIEVTVRPSGVSNRFGSKSGNTAYLTISGLQAEEADYYCCSYVDSKTWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	840
1318991	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLIEWMTVIWYDRSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGISGYRYGTDMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	841

LIBC編號	描述	序列	SEQ ID
		VYYCARGISGYRYGTDMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWEYQHPGKAPKFMIEVTVRPSGVSNRFSGSKSGNTAYLTISGLQAEDEADYYCCSYVDSKTWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	842
1319279	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFAMHWVRQAPGKGLDWVAVIWYAESNKFYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARGDWNYSYKYGVDLWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	843
	LC	QSALTQPASVSGSPGQSITISCTGSNSDVGSYNLVSWEYQDHPGKAPKLMIEVVKRPSGVYNCFFGSKSGNTASLTICGLQGEEEGDYY*CSYADSRITYVFGSGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	844
1318253	HC	QMQLVQSGTEVKKPGASVKVSCEASGYAFTGFYMHWRQAPGQGLEWMGWLNPNTGGTSYVQKFQGRVTMTRDTSISTAYMELSRLRSDDT	845

LIBC編號	描述	序列	SEQ ID
		AVYFCASGTGTTAFDFWQGTMVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV DGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDALPQHYTYWYQQKPGRAPVLVIY KDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGSYV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS	846
1318209	HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYVMNWVRQAPGKGLE WVSGISGSDGSTYYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAV YYCAKEEDWNYGFDYWQGQTLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVD GVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK	847
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPILVIY KDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGAY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	848
1318188	HC	QVQLQESGPGLVKPSQTLSTCTVSGGSISSDGYFWSWIRQHPGKGLE WIGFIYFTGITYYNPSLQSRVTISVDTSKNQFSLKLNSVTAADTAVYYC	849

LIBC編號	描述	序列	SEQ ID
		ARVIPGEDAFDIWGQGTMTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVH NAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDALPQHYYTYWYQQKPGQAPVLIY KDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADISGT YVVFVGGGKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	850
1319569	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLE WMGWMNPNTGNTGYPQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARGGLTMKVVGAGWFDPWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKF NWXVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSR WQQGNVFSCSV MHEALHNHYTQKSLSLSPGK	851
	LC	SYELTQPPSVSVSPGQTASITCSGDKLGDKYAFWYQQKPGQSPLLVIY QDKKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDISTG VFVGGGKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	852
1307105	HC	QVQVVESGGGVVQPGRSLRLSCAASGFTFRSYGMDWVRQAPGKGLE WVAVISYDGNKYKYADSVKGRFTISRDNKNTLYLQMNSLRAEDTA	853

LIBC編號	描述	序列	SEQ ID
		VYYCARDDYSTLDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDG VEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSRDVGGYNYVSWYQQHPGKAPK LMIYEVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYISG NSHVFGTGTKVTVPGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	854
1318198	HC	QVQLQESGPGLVKPSQTLSTCTVSGGSISSDGYFWSWIRQHPGKGLE WIGFIYFTGITYYNPSLQSRVTISVDTSKNQFSLKLNSVTAADTAVYYC ARVIPGEDAFDIWGQGTMTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVH NAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK	855
	LC	QSALTQPASVSGSPGQSITISCTGTNSDVGSYNLVSQYQQHPGKAPKF MIYEVTVRPSGVSNRFSGSKSGNTAYLTISGLQAEDEADYYCCSYVDS KTWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	856

結合CRD1、CRD2和/或CRD3的LTβR促效劑結合蛋白

【0157】 根據本揭露之所有方面，如本文所描述的促效劑LTβR結合蛋白包含結合並激動LTβR活性的一或多個結合結構域。在一個實施方式中，該結合結構域包含重鏈可變區（VH）或其片段，其中該VH包含結合LTβR的一或多個互補決定區（即HCDR1、HCDR2和/或HCDR3）或其部分。在一個實施方式中，該VH包含SEQ ID NO: 475-498、740-742或其修飾序列中任一個的HCDR1胺基酸序列，其中與SEQ ID NO: 475-498和740-742中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。在一個實施方式中，該VH包含SEQ ID NO: 499-528、743或其修飾序列中任一個的HCDR2胺基酸序列，其中與SEQ ID NO: 499-528和743中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。在一個實施方式中，該VH包含SEQ ID NO: 529-558、744-746或其修飾序列中任一個的HCDR3胺基酸序列，其中與SEQ ID NO: 529-558和744-746中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。下表10中提供了本文所描述的示例性促效劑LTβR結合蛋白的重鏈CDR序列。

【0158】 如本文實例中所描述的，本文揭露的幾種LTβR抗體的互補位作圖研究表明，在某些情況下，特定LTβR抗體與LTβR的結合不涉及或需要抗體的所有三個重鏈CDR區和/或不涉及一或多個重鏈CDR的所有殘基。顯示不參與LTβR抗體結合相互作用的重鏈CDR在下表10中用星號表示。藉由互補位作圖或突變分析鑒定的顯示不參與或不需要LTβR抗體結合相互作用的重鏈CDR區的殘基被鑒定為可變殘基（X）。表10序列內的X殘基的同一性在本文實例12的表18-25中提供。

[表10]. LTβR結合蛋白的重鏈CDR序列

LIBC編號	Well ID	HCDR1		HCDR2		HCDR3	
		SEQ	ID	SEQ	ID	SEQ	ID
218990 (19320)	30H1	GDYMY*	475	WINPX ₅ SGGTNX ₁₁ -X ₁₇	499	EGSSGWSAEYX ₁₁ X ₁₂ X ₁₃	529
				WINPX ₅ SGGTNX ₁₁ -X ₁₇	500	EGSSGWSAEYX ₁₁ X ₁₂ X ₁₃	530

LIBC編號	Well ID	HCDR1		HCDR2		HCDR3	
		SEQ	ID	SEQ	ID	SEQ	ID
				WINPNSGGTNYAKKFQG	501	EGSSGWSAEYFQH	531
218994 (19321)	31A3	SYX ₈ X ₉ X ₁₀	476	IIWYX ₅ X ₆ SDX ₉ -X ₁₇	502	GDSEDFYYYDX ₁₁ X ₁₂ X ₁₃	532
		SYX ₈ X ₉ X ₁₀	477	IIWYX ₅ X ₆ SDX ₉ -X ₁₇	503	GDSEDFYYYDX ₁₁ X ₁₂ X ₁₃	533
		SYGMH	478	IIWYDGSDEYYADSVKG	504	GDSEDFYYDFDV	534
219058 (19324)	36G2	TSGMN	479	SVSSSGSYX ₉ -X ₁₇	505	AX ₂ YNWHFDASX ₁₁ X ₁₂	535
				SVSSSGSYX ₉ -X ₁₇	506	AX ₂ YNWHFDASX ₁₁ X ₁₂	536
				SVSSSGSYIYYADSVKG	507	ARYNWHFDASDI	537
219037 (19322)	34D1	SGGYFWS	480	YSHYSGTTYYNPSLKS	508	VPDGEDYFDY	538
219098 (19327)	44B1	SYAMS	481	TISGSGGSTYYADSVKG	509	VRDNWNYX ₈ X ₉ MDV	539
						VRDNWNYX ₈ X ₉ MDV	540
						VRDNWNYDGMDV	541
219098. 001		SYAMS	482	TISGSGGSTYYADSVKG	510	VRDNWNYDGMDV	542
219097 (19326)	43D9	DAWX ₉ X ₁₀	740	RIKTKTDGGTTDYAAPV KG*	743	DYGDYX ₆ X ₇	744
		DAWX ₉ X ₁₀	741			DYGDYX ₆ X ₇	745
		DAWMS	742			DYGDYDY	746
219051 (19323)	35F5	GYYLH	483	WINPNIGVTDX ₁₁ AQKFQ D	511	RGYNDDYDFDY	543
				WINPNIGVTDX ₁₁ AQKFQ D	512		
				WINPNIGVTDSAQKFQD	513		
218989- 1	29G8	TSGMGVG	484	LIYWNGGKLYSPSLKN	514	SGYYDNSGYYWDGMDV	544
218967	17F5	SYFWT	485	YIYYSGSTNYNPSLKS	515	VETIMAFDAFDI	545
218981	25C9	SGGYFWS	486	YTHYIGSTYYNPSLKS	516	VDTAMVDAFDI	546
218995	31C9	SRNWWG	487	YIHYIGNTYYNPSLKS	517	ETGSDGDDTFDI	547
218996	31B10	NYDMH	488	TIWYDGSNKYYADSVKG	518	LSTVTTGDYYGMDV	548
218998	32A2	SGGYFWG	489	YIHYIGSPYYNPSLKS	519	DCSSVNCQDAFDI	549
219083	41H7	SDGYFWS	490	FIYYSGTTYYNPSLKS	520	VCGGDCYDAFDI	550

LIBC編 號	Well ID	HCDR1		HCDR2		HCDR3	
		SEQ	ID	SEQ	ID	SEQ	ID
219092	43C1	NSIWWG	491	YIHYSGNTYYNPSLKS	521	NFGDVDAFDI	551
219023	33G6	SNSAAWN	492	RTYCRSKCYSDYALSVK	522	AVADHYSYALDV	552
				S			
219023.001		SNSAAWN	493	RTYYRSKWYSYALSVK	523	AVADHYSYALDV	553
219095	43G5	NYAMN	494	VISDSGGSSNYADSVKG	524	DRSIAGYYGMDV	554
219102	44G11	SYYWS	495	YIYYGGSTNYNPSLKS	525	SYSSAWYGSAY	555
218973	21A5	SYGIH	496	VIWYDGSKKYYADSVKG	526	DPSHYYGSGSYNYFYGM	556
						V	
219044	34F10	DNYMS	497	VIYSGGNTYYGDSVKG	527	PFFDY	557
218997	31E12	SGGYYS	498	YIYYSGSTYYNPSLMG	528	RGPVAGGFDY	558
*本文所描述的HDX互補位作圖實驗表明CDR不參與結合LTβR							

【0159】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含輕鏈可變區（VL），其中VL包含單獨或與VH CDR一起結合LTβR的一或多個互補決定區（即LCDR1、LCDR2和/或LCDR3）或其部分。在一個實施方式中，該VL包含SEQ ID NO: 559-589或其修飾序列中任一個的LCDR1胺基酸序列，其中與SEQ ID NO: 559-589中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。在一個實施方式中，該VL包含SEQ ID NO: 590-618或其修飾序列中任一個的LCDR2胺基酸序列，其中與SEQ ID NO: 590-618中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。在一個實施方式中，該VL包含SEQ ID NO: 619-643或其修飾序列中任一個的LCDR3胺基酸序列，其中與SEQ ID NO: 619-643中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。下表11中提供了本文所述之示例性促效劑LTβR結合蛋白的輕鏈CDR序列。

【0160】 如本文實例中所描述的，本文揭露的幾種LTβR抗體的互補位作圖研究表明，在某些情況下，特定LTβR抗體與LTβR的結合不涉及或需要抗體的所

有三個輕鏈CDR區和/或不涉及一或多個輕鏈CDR的所有殘基。顯示不參與LTβR抗體結合相互作用的輕鏈CDR在下表11中用星號表示。藉由互補位作圖或突變分析鑒定的顯示不參與LTβR抗體結合相互作用或其不需要的輕鏈CDR區的殘基被鑒定為可變殘基（X）。表11序列內的X殘基的同一性在本文實例12的表18-25中提供。

[表11]. LTβR結合蛋白的輕鏈CDR序列

LIBC編號	Well	LCDR1		LCDR2		LCDR3	
		SEQ	ID	SEQ	ID	SEQ	ID
218990 (19320)	30H1	X ₁ X ₂ X ₃ X ₄ SVSSSFX ₁₁ X ₁₂	559	GASRRAT*	590	QQYGTSPLS	619
		X ₁ X ₂ X ₃ X ₄ SVSSSFX ₁₁ X ₁₂	560				
		RASQSVSSSFLA	561				
218994 (19321)	31A3	SGSSSNIGKNX ₁₁ X ₁₂ X ₁₃	562	DNNX ₄ X ₅ PS	591	X ₁ X ₂ X ₃ DHSLSASX ₁₁ X ₁₂	620
		SGSSSNIGKNX ₁₁ X ₁₂ X ₁₃	563	DNNX ₄ X ₅ PS	592	X ₁ X ₂ X ₃ DHSLSASX ₁₁ X ₁₂	621
		SGSSSNIGKNYVS	564	DNNKRPS	593	GTWDHSLSASYV	622
219058 (19324)	36G2	RASQSISSDLN*	565	AASSLX ₆ X ₇	594	QQSYNTPLT*	623
				AASSLX ₆ X ₇	595		
				AASSLHS	596		
219097 (19326)	43D9	RTSQSISRYLN	566	GASSLX ₆ X ₇	597	HQSYSTPPT*	624
				GASSLX ₆ X ₇	598		
				GASSLQS	599		
219037 (19322)	34D1	RASQTISSYLN	567	DASSLQS	600	QQSFSAFIT	625
219098 (19327)	44B1	RX ₂ SQSLLYSSGYID LD	568	LGSNRAS	601	MQTIQTPLT	626
		RX ₂ SQSLLYSSGYID LD	569				

LIBC編號	Well ID	LCDR1		LCDR2		LCDR3	
		SEQ	ID	SEQ	ID	SEQ	ID
		RCSQSLLYSSGYIDL D	570				
219098.00 1		RSSQSLLYSSGYIDL D	571	LGSNRAS	602	MQTIQTPLT	627
219051 (19323)	35F5	KSRQSLLHRX ₁₀ X ₁₁ K TYLY	572	EVSNRFS	603	MQSIQLPLI	628
		KSRQSLLHRX ₁₀ X ₁₁ K TYLY	573				
		KSRQSLLHRDGTKY LY	574				
218989	29G8	RASQSLISDYLV	575	GASSRPT	604	QQYDTSLN	629
218967	17F5	RASQSVGSSYLA	576	GASSRAT	605	QQYDTSPIT	630
218981	25C9	RASQNIDSSYLA	577	DTSSRAT	606	QQYGGSPIT	631
218995	31C9	RASQSIGSSYLA	578	GASGRAT	607	QQCYSSPIT	632
218996	31B1 0	SGSRSNIGNNYVS	579	DNSKRPS	608	GTWDSSLSAVV	633
218998	32A2	WSSQSIDSTYLA	580	GASTRAT	609	QQYSSSPIT	634
219083	41H7	RASQNISNTYLA	581	GASSRAT	610	QQYFSSPIT	635
219092	43C1	RASQSISSSYLA	582	GASSRAT	611	QQYYLSPLT	636
219023	33G6	RASQTIRTYLN	583	AASSLQS	612	QQSYSSPIT	637
219023.00 1		RASQTIRTYLN	584	AASSLQS	613	QQSYSSPIT	638
219095	43G5	RASQSISSDLN	585	AASSLHS	614	QQSYNTPLT	639
219102	44G1 1	QASQDISNYLI	586	DASNLET	615	QQYDHLPI	640
218973	21A5	SGSSSNIGNTYVS	587	DNNERPS	616	GTWDNSLTAVV	641
219044	34F10	RASQTVWSNYLA	588	GASRRVI	617	QQYGSSSIT	642
218997	31E12	RASQNVYNNYLA	589	GTSSRAT	618	QQYGSSLLCS	643
* 本文所描述的HDX互補位作圖實驗表明CDR不參與結合LTβR							

【0161】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合人LTβR的CRD2和CRD3，包括對應於SEQ ID NO: 4的殘基56-64和81-101（對應於SEQ ID NO: 1的殘基86-94和111-131）的一或多個殘基，並允許如本文所定義的內源性LTβR配體結合活性。該促效劑LTβR結合蛋白包含可變重鏈結構域（VH），其包含與SEQ ID NO: 501的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 531的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。視需要，該VH進一步包含與SEQ ID NO: 475的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列。在一個實施方式中，該LTβR結合蛋白的VH包含SEQ ID NO: 499的HCDR2序列和SEQ ID NO: 529的HCDR3序列；或如SEQ ID NO: 500的HCDR2序列和SEQ ID NO: 530的HCDR3序列進一步定義的。在一個實施方式中，該LTβR結合蛋白的VH包含SEQ ID NO: 501的HCDR2序列和SEQ ID NO: 531的HCDR3序列。視需要，該示例性促效劑LTβR結合蛋白的VH進一步包含SEQ ID NO: 475的HCDR1。

【0162】 根據前述實施方式，該促效劑LTβR結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 561的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，以及與SEQ ID NO: 619的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。視需要，該VL進一步包含與SEQ ID NO: 590的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列。在一個實施方式中，該VL包含SEQ ID NO: 559的LCDR1序列和SEQ ID NO: 619的LCDR3序列；或如SEQ ID NO: 560的LCDR1序列和SEQ ID NO: 619的LCDR3

序列進一步定義的；或如SEQ ID NO: 560的LCDR1序列和SEQ ID NO: 619的LCDR3序列進一步定義的。視需要，該VL進一步包含SEQ ID NO: 590的LCDR2。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218990（19320；30H1）的LT β R抗體。

【0163】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白係結合LT β R的CRD1的結合蛋白，包括對應於SEQ ID NO: 4的殘基3-9、20-29和38-47（對應於SEQ ID NO: 1的殘基33-39、50-59和68-77）的一或多個殘基。在一個實施方式中，該LT β R結合蛋白不阻斷或抑制內源性LIGHT與LT β R結合發生，以及至少或約80%的內源性LT α 1 β 2與LT β R結合發生。該LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 478的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 504的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 534的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該LT β R結合蛋白的VH包含SEQ ID NO: 476的HCDR1序列，SEQ ID NO: 502的HCDR2序列和SEQ ID NO: 532的HCDR3序列；或如SEQ ID NO: 477的HCDR1序列、SEQ ID NO: 503的HCDR2序列和SEQ ID NO: 533的HCDR3序列進一步定義的；或如SEQ ID NO: 478的HCDR1序列、SEQ ID NO: 504的HCDR2序列和SEQ ID NO: 534的HCDR3序列進一步定義的。

【0164】根據前述實施方式，本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 564的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 593的序列共用至少80%、至少85%、至少90%、至少95%、

至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 622的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 562的LCDR1序列、SEQ ID NO: 591的LCDR2和SEQ ID NO: 620的LCDR3序列；或如SEQ ID NO: 563的LCDR1序列、SEQ ID NO: 592的LCDR2和SEQ ID NO: 621的LCDR3序列進一步定義的；或如SEQ ID NO: 564的LCDR1序列、SEQ ID NO: 593的LCDR2和SEQ ID NO: 622的LCDR3序列進一步定義的。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218994 (19321; 31A3) 的LT β R抗體

【0165】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白結合人LT β R的CRD2和CRD3，包括對應於SEQ ID NO: 4的殘基56-64和81-101（對應於SEQ ID NO: 1的殘基86-94和111-131）的一或多個殘基。在一個實施方式中，該促效劑LT β R結合蛋白在< 8 nM的濃度下不阻斷內源性LIGHT或LT α 1 β 2與LT β R結合，如本文所描述的基於細胞的受體-配體測定所測量的（參見例如，實例8.2）。該LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 479的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 507的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 537的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該LT β R結合蛋白的VH包含SEQ ID NO: 479的HCDR1序列，SEQ ID NO: 505的HCDR2序列和SEQ ID NO: 535的HCDR3序列；或如SEQ ID NO: 479的HCDR1序列、SEQ ID NO: 506的HCDR2序列和SEQ ID NO: 536的HCDR3序列進一步定義的；或如SEQ ID NO: 479的HCDR1序列、SEQ ID NO: 507

的HCDR2序列和SEQ ID NO: 537的HCDR3序列進一步定義的。

【0166】 根據前述實施方式，本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 596的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列。視需要，該VL包含與SEQ ID NO: 565的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，以及視需要包含與SEQ ID NO: 623的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 594的LCDR2，或如SEQ ID NO: 595的LCDR2進一步定義的，或如SEQ ID NO: 596的LCDR2進一步定義的。視需要，該VL包含SEQ ID NO: 565的LCDR1序列，SEQ ID NO: 596的LCDR2和SEQ ID NO: 623的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219058 (19324; 36G2) 的LT β R抗體。

【0167】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白係結合LT β R且不阻斷或抑制LIGHT與LT β R結合發生的結合蛋白。該促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 480的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 508的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 538的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 408的HCDR1序列，SEQ ID NO: 508的HCDR2和SEQ ID NO: 538的HCDR3序列。

【0168】 根據前述實施方式，本揭露之促效劑LT β R結合蛋白視需要進一步

包含VL，其中該VL包含與SEQ ID NO: 567的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 600的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 625的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 567的LCDR1序列，SEQ ID NO: 600的LCDR2和SEQ ID NO: 625的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219037（19322；34D1）的LT β R抗體。

【0169】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白係結合LT β R且不阻斷或抑制如本文定義的LIGHT與LT β R結合的結合蛋白。在一個實施方式中，該促效劑LT β R結合蛋白不阻斷或抑制LIGHT與LT β R結合。該LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 4812的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 509的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 539的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 481的HCDR1序列、SEQ ID NO: 509的HCDR2和SEQ ID NO: 539的HCDR3序列，或如SEQ ID NO: 481的HCDR1序列、SEQ ID NO: 509的HCDR2和SEQ ID NO: 540的HCDR3序列進一步定義的；或如SEQ ID NO: 481的HCDR1序列、SEQ ID NO: 509的HCDR2和SEQ ID NO: 541的HCDR3序列進一步定義的。

【0170】 根據前述實施方式，本揭露之促效劑LT β R結合蛋白視需要進一步

包含VL，其中該VL包含與SEQ ID NO: 570的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 601的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 626的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 568的LCDR1序列、SEQ ID NO: 601的LCDR2和SEQ ID NO: 626的LCDR3序列；或如SEQ ID NO: 569的LCDR1序列、SEQ ID NO: 601的LCDR2和SEQ ID NO: 626的LCDR3序列進一步定義的；或如SEQ ID NO: 570的LCDR1序列、SEQ ID NO: 601的LCDR2和SEQ ID NO: 626的LCDR3序列進一步定義的；或如SEQ ID NO: 571的LCDR1序列、SEQ ID NO: 602的LCDR2和SEQ ID NO: 627的LCDR3序列進一步定義的。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219098（19327；44B1）的LT β R抗體。

【0171】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白）結合人LT β R CRD1，包括對應於SEQ ID NO: 4的殘基1-19（對應於SEQ ID NO: 1的殘基31-49）的一或多個殘基。該促效劑LT β R結合蛋白不阻斷LIGHT與LT β R結合並且不阻斷LT α 1 β 2與LT β R結合。該促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 483的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 513的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 543的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一

性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO:483的HCDR1序列、SEQ ID NO: 511的HCDR2和SEQ ID NO: 543的HCDR3序列；或如SEQ ID NO: 483的HCDR1序列、SEQ ID NO: 512的HCDR2和SEQ ID NO: 543的HCDR3序列進一步定義的；或如SEQ ID NO: 483的HCDR1序列、SEQ ID NO: 513的HCDR2和SEQ ID NO: 543的HCDR3序列進一步定義的。

【0172】 根據前述實施方式，本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 574的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 603的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 628的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO:57217的LCDR1序列、SEQ ID NO: 603的LCDR2和SEQ ID NO: 628的LCDR3序列；或如SEQ ID NO: 573的LCDR1序列、SEQ ID NO: 603的LCDR2和SEQ ID NO: 628的LCDR3序列進一步定義的；或如SEQ ID NO: 574的LCDR1序列、SEQ ID NO: 603的LCDR2和SEQ ID NO: 628的LCDR3序列進一步定義的。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219051（19323；35F5）的LT β R抗體。

【0173】 在另一個實施方式中，本揭露之LT β R結合蛋白係結合LT β R CRD1和CRD2的基於抗體的分子，包括對應於SEQ ID NO: 4的殘基38-42和56-70的一或多個殘基。該基於LT β R抗體的分子包含VH，其中該VH包含與SEQ ID NO: 742的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，以及與SEQ ID NO: 746的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或

至少99%序列同一性的HCDR3序列。視需要，該LT β R結合蛋白的VH進一步包含與SEQ ID NO: 743的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列。在任何實施方式中，該LT β R結合蛋白的VH包含SEQ ID NO: 740的HCDR1序列和SEQ ID NO: 744的HCDR3序列；或如SEQ ID NO: 741的HCDR1序列和SEQ ID NO: 745的HCDR3序列進一步定義的；或如SEQ ID NO: 742的HCDR1序列和SEQ ID NO: 746的HCDR3序列進一步定義的。視需要，該示例性LT β R結合蛋白的VH進一步包含SEQ ID NO: 743的HCDR2。

【0174】 根據前述實施方式，本揭露之該基於LT β R抗體的分子視需要進一步包含VL，其中該VL包含與SEQ ID NO: 566的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 599的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列。視需要，該VL進一步包含與SEQ ID NO: 624的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在任何實施方式中，該VL包含SEQ ID NO: 566的LCDR1序列和SEQ ID NO: 597的LCDR2；或如SEQ ID NO: 566的LCDR1序列和SEQ ID NO: 598的LCDR2進一步定義的；或如SEQ ID NO: 566的LCDR1序列和SEQ ID NO: 599的LCDR2進一步定義的。視需要，該VL進一步包含SEQ ID NO: 624的LCDR3。包含該實施方式的VH和VL之示例性基於LT β R抗體的分子包括但不限於本文鑒定為LIBC No. 219097 (19326; 43D9) 的LT β R抗體。

【0175】 在另一個實施方式中，該促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 484的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID

NO: 514的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 544的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 484的HCDR1序列，SEQ ID NO: 514的HCDR2和SEQ ID NO: 544的HCDR3序列。該促效劑LT β R結合蛋白進一步包含VL，其中該VL包含與SEQ ID NO: 575的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 604的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 629的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 575的LCDR1序列，SEQ ID NO: 604的LCDR2和SEQ ID NO: 629的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218989的LT β R抗體。

【0176】在另一個實施方式中，該促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 485的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 515的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 545的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 485的HCDR1序列，SEQ ID NO: 515的HCDR2和SEQ ID NO: 545的HCDR3序列。本揭露之促效劑LT β R結合蛋白進一步包含VL，其中該VL包含與

SEQ ID NO: 576的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 605的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 630的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 576的LCDR1序列，SEQ ID NO: 605的LCDR2和SEQ ID NO: 630的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218967的LT β R抗體。

【0177】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 486的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 516的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 546的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 486的HCDR1序列，SEQ ID NO: 516的HCDR2和SEQ ID NO: 546的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 577的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 606的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 631的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含

SEQ ID NO: 577的LCDR1序列，SEQ ID NO: 6068的LCDR2和SEQ ID NO: 631的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218981的LT β R抗體。

【0178】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 487的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 517的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 547的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 487的HCDR1序列，SEQ ID NO: 517的HCDR2和SEQ ID NO: 547的HCDR3序列。本揭露之促效劑LT β R結合蛋白進一步包含VL，其中該VL包含與SEQ ID NO: 578的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 607的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 632的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 578的LCDR1序列，SEQ ID NO: 607的LCDR2和SEQ ID NO: 632的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218995的LT β R抗體。

【0179】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 488的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，

與SEQ ID NO: 518的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 548的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 488的HCDR1序列，SEQ ID NO: 518的HCDR2和SEQ ID NO: 548的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 579的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 608的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 633的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 579的LCDR1序列，SEQ ID NO: 608的LCDR2和SEQ ID NO: 633的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218996的LT β R抗體。

【0180】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 489的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 519的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 549的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 489的HCDR1序列，SEQ ID NO: 519的HCDR2和SEQ ID NO: 549的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中

該VL包含與SEQ ID NO: 580的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 609的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 634的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 580的LCDR1序列，SEQ ID NO: 609的LCDR2和SEQ ID NO: 634的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218998的LT β R抗體。

【0181】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 490的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 520的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 550的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 490的HCDR1序列，SEQ ID NO: 520的HCDR2和SEQ ID NO: 550的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 581的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 610的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 635的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含

SEQ ID NO: 581的LCDR1序列，SEQ ID NO: 610的LCDR2和SEQ ID NO: 635的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219083的LT β R抗體。

【0182】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 491的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 521的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 551的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 491的HCDR1序列，SEQ ID NO: 521的HCDR2和SEQ ID NO: 551的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 582的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 611的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 636的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 582的LCDR1序列，SEQ ID NO: 611的LCDR2和SEQ ID NO: 636的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219092的LT β R抗體。

【0183】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白係結合LT β R並允許內源性LT β R配體結合活性的結合蛋白，如本文所定義的。該LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 492的序列共用至少80%、至少

85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 522的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 552的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 492的HCDR1序列，SEQ ID NO: 522的HCDR2和SEQ ID NO: 552的HCDR3序列。在一個實施方式中，SEQ ID NO: 522的HCDR2被修飾以取代SEQ ID NO: 522中的位置4和8處的半胱胺酸殘基。在一個實施方式中，該LTβR結合蛋白的HCDR2包含SEQ ID NO: 523的HCDR2。本揭露之促效劑LTβR結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 583的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 612的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 637的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 583的LCDR1序列，SEQ ID NO: 612的LCDR2和SEQ ID NO: 637的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LTβR結合蛋白包括但不限於本文鑒定為LIBC No. 219023的LTβR抗體。

【0184】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白包含VH，其中該VH包含與SEQ ID NO: 494的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 524的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID

NO: 554的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 494的HCDR1序列，SEQ ID NO: 524的HCDR2和SEQ ID NO: 554的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 585的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 614的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 639的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 585的LCDR1序列，SEQ ID NO: 614的LCDR2和SEQ ID NO: 639的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219095的LT β R抗體。

【0185】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 495的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 525的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 555的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 495的HCDR1序列，SEQ ID NO: 525的HCDR2和SEQ ID NO: 555的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 586的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與

SEQ ID NO: 615的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 640的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 586的LCDR1序列，SEQ ID NO: 615的LCDR2和SEQ ID NO: 640的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219102的LT β R抗體。

【0186】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 496的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 526的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 556的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 496的HCDR1序列，SEQ ID NO: 526的HCDR2和SEQ ID NO: 556的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 587的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 616的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 641的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 587的LCDR1序列，SEQ ID NO: 616的LCDR2和SEQ ID NO: 641的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但

不限於本文鑒定為LIBC No. 218973的LT β R抗體。

【0187】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 497的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 527的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 557的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 497的HCDR1序列，SEQ ID NO: 527的HCDR2和SEQ ID NO: 557的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 588的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 617的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 642的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 588的LCDR1序列，SEQ ID NO: 617的LCDR2和SEQ ID NO: 642的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219044的LT β R抗體。

【0188】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 498的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 528的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID

NO: 558的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 498的HCDR1序列，SEQ ID NO: 528的HCDR2和SEQ ID NO: 558的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 589的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 618的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 643的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 589的LCDR1序列，SEQ ID NO: 618的LCDR2和SEQ ID NO: 643的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218997的LT β R抗體。

【0189】 對本文揭露的LT β R結合蛋白的重鏈CDR序列和/或輕鏈CDR序列的合適的胺基酸修飾包括，例如，保守取代或功能等效的胺基酸殘基取代，該等取代導致變體CDR序列具有與上文描述的CDR序列的那些相似或增強的結合特徵。本揭露涵蓋的是含有1、2、3、4、5或更多個胺基酸取代（取決於CDR的長度）的表2、3、6、7、9和10的CDR，該等取代維持或增強抗體的LT β R結合。所得修飾的CDR在序列上與表2、3、6、7、9和10中提供的CDR係至少70%、至少75%、至少80%、至少85%、至少90%、至少95%相似。

【0190】 對本文揭露的重鏈和輕鏈CDR序列的合適的胺基酸修飾包括，例如，保守取代或功能等效的胺基酸殘基取代，該等取代導致變體CDR序列具有與本文揭露的CDR序列的那些相似或增強的結合特徵。保守取代係發生在與其側鏈相關的胺基酸家族中的取代。基因編碼的胺基酸可分為四個家族：(1) 酸性（天

冬胺酸、麩胺酸)；(2) 鹼性 (離胺酸、精胺酸、組胺酸)；(3) 非極性 (丙胺酸、纈胺酸、白胺酸、異白胺酸、脯胺酸、苯丙胺酸、蛋胺酸、色胺酸)；以及 (4) 不帶電荷的極性 (甘胺酸、天冬醯胺、麩醯胺酸、半胱胺酸、絲胺酸、蘇胺酸、酪胺酸)。苯丙胺酸、色胺酸和酪胺酸有時被共同分類為芳香族胺基酸。可替代地，胺基酸庫可以分組為 (1) 酸性 (天冬胺酸、麩胺酸)；(2) 鹼性 (離胺酸、精胺酸、組胺酸)，(3) 脂肪族 (甘胺酸、丙胺酸、纈胺酸、白胺酸、異白胺酸、絲胺酸、蘇胺酸)，其中絲胺酸和蘇胺酸視需要地單獨分組為脂肪族羥基；(4) 芳香族 (苯丙胺酸、酪胺酸、色胺酸)；(5) 醯胺 (天冬醯胺、麩醯胺酸)；以及 (6) 含硫 (半胱胺酸和蛋胺酸) (Stryer (編輯), Biochemistry[生物化學], 第2版, WH Freeman and Co., 1981，特此藉由引用將其全部併入)。也可以對本文揭露的重鏈CDR序列和輕鏈CDR序列進行非保守取代。非保守取代涉及用來自不同類別胺基酸的一或多個胺基酸殘基取代CDR的一或多個胺基酸殘基，以改善或增強CDR的結合特性。本文揭露的重鏈可變區CDR和/或輕鏈可變區CDR的胺基酸序列可進一步包含維持或增強LTβR結合的一或多個內部中性胺基酸插入或缺失。

【0191】如本文所描述的結合LTβR的LTβR結合蛋白可以包含可變輕鏈 (VL)、可變重鏈 (VH) 或VL鏈和VH鏈的組合。在一個實施方式中，該LTβR結合蛋白的VH鏈包含下表12中提供的VH胺基酸序列中的任一個，或與表12中列出的VH胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%或至少95%相同的胺基酸序列。在一個實施方式中，該LTβR結合蛋白的VL鏈包含下表12中提供的VL胺基酸序列中的任一個，或與表12中列出的VL胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%、至少95%相同的胺基酸序列。

【0192】在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人LTβR (SEQ ID NO: 1)，同時允許內源性LTβR配體結合和活性 (即LIGHT或LTα1β2結合)，如本文所描述的，並且包含與表12中所列的VH結構域胺基酸序

列中的任一個具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域。在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人LTβR(SEQ ID NO: 1)，同時允許內源性LTβR配體結合和活性（即LIGHT或LTα1β2結合），如本文所描述的，並且包含與表12中所列的VL結構域胺基酸序列中的任一個具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人LTβR（SEQ ID NO: 1），同時允許內源性LTβR配體結合和活性（即LIGHT或LTα1β2結合），如本文所描述的，並且包含與表12中所列的VH結構域胺基酸序列中的任一個具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域，以及與表12中所列的相應VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。

[表12]. LTβR結合蛋白VH和VL胺基酸序列

LIBC 編號	Well ID	結構域	序列	SEQ ID
218990	30H1 19320	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGDYMYWVRQAPG QGLEWMGWINPNSGGTNYAKKFQGRVTMTRDTSISTAYMELSR LRSDDTAVYYCAREGSSGWSAEYFQHWGQGTLVTVFS	644
		V _L	EIVLTQSPGTLSPGERATLSCRASQSVSSSFLAWYQQKLGQAP RLLMYGASRRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGTSPLSFGGGGTKVEIKR	645
218994	31A3/ 19321	V _H	QVQLVESGGAVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGK GLEWVAIIWYDGSDEYYADSVKGRFTISRDN SKNTLYLQMNSV RDEDTALYYCVRGDSSEDFYYDFDVWGQGTTVTVSS	646
		V _L	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGKNYVSWYQHLPGTAP KLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCG TWDHSLSASYVFGTGKVTVLG	647
219058	36G2/ 19324	V _H	EVQLVESGGGLVKPGGSLRLSCAASGFTFSTSGMNWVRQAPGK GLEWVSSVSSSGSYIYYADSVKGRFTISRDN AKNSLYLQMNSLR	648

LIBC 編號	Well ID	結構域	序列	SEQ ID
			AEDTAVYYCAGARYNWHFDASDIWGQGTVVTVSS	
		V _L	DIQMTQSPSSLSASVGDRVTTTCRASQSISSDLNWFYQQKPGKAPN LLIYAASSLHSGVPSRFSGSGSGTDFTLTISLLPEDFATYYCQQS YNTPLTFGGGTKVEIKR	649
219097	43D9/ 19326	V _H	EVQLVESGGGLVKPGGSLRLSCAASGFTFNDAWMSWVRQAPGK GLEWVGRIKTKTDGGTTDYAAPVKGRITISRDDSKNTLYLQMNS LKTEDTAVYYCTTDYGDYEWGQGTLLTVSS	650
		V _L	DIQMTQSPSSLSASVGDRVTTTCRTSQSISRYLNWFYQQKPGKAPK LLIYGASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCHQS YSTPPTFGQGTVEIKR	651
219037	34D1/ 19322	V _H	QVQLQESGPGRVKPSQTLSTCTVSGGSINSGGYFWSWIRQHPG KVLEWIGYSHYSGTTYNPSLKSRTISVDTSKNQLSLKLSNVN AADTAVYYCARVPDGEDYFDYWGQALVTVSS	652
		V _L	DLQLTQSPSSLSASVGDRVTTTCRASQTISSYLNWFYQQKPGKAPK LLIYDASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFETYYCQQSF SAPITFGQGTVEIKR	653
219098	44B1/ 19327	V _H	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK GLEWVSTISGSGGSTYYADSVKGRFTISRDN SKNTLNLQMNSLR AEDTAVYYCAKVRDNWNYDGMDVWGQGTTVTVSS	654
		V _L	DIVMTQSPLSLPVTLGESASISCRCSQSLLYSSGYIDL DWYLQKPG QSPQLLIYLG SNRASGV PDRFSGSGSGTDFTLKISRVEAEDVGVY YCMQTIQTPLTFGGGTKVEIKR	655
219098. 001		V _H	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK GLEWVSTISGSGGSTYYADSVKGRFTISRDN SKNTLNLQMNSLR AEDTAVYYCAKVRDNWNYDGMDVWGQGTTVTVSS	656
		V _L	DIVMTQSPLSLPVTLGESASISCRSSQSLLYSSGYIDL DWYLQKPG QSPQLLIYLG SNRASGV PDRFSGSGSGTDFTLKISRVEAEDVGVY YCMQTIQTPLTFGGGTKVEIKR	657
219051	35F5/ 19323	V _H	QVQLVQSGAEVKKPGASVKVSKASGYTFTGYLHWVRQAPG QGLEWMGWINPNIGVTDSAQKFQDRVMTTRDTSISTAYMELSR	658

LIBC 編號	Well ID	結構域	序列	SEQ ID
			LISDDTAVYYCTVRGYNDYDFDYWGQGLVTVSS	
		V _L	DVVMQTPLSLSVTPGPASISCKSRQSLLRDGGKTYLYWYLQK PGQPPQLLIYEVSNNRFSGVNRFSGSGSGTDFTLKISRVEAEDVGV YYCMQSIQLPLIFGGGTRVDIKR	659
218989	29G8	V _H	QITLKESGPTLVKPTQTLTLTCTFTGFSLSSTSGMGVGVIRQPPGK ALEWLALIYWNGGKLYSPSLKNRLTITKDTSKNQVVLMTNMD PVDATYYCAHSGYYDNSGYWWDGMDVWGQGTITVTVSP	660
		V _L	EIVLTQSPVTLSPGERATLSCRASQSLISDYLWVYQQKPGQAP RLLIYGASSRPTGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQ YDTSLNFGGGTKVEIKR	661
218967	17F5	V _H	QVQLQESGPGVVKPSETLSLTCTVSGGSISSYFWTWIRQPPGKGL EWIGYIYYSGSTNYNPSLKSRTFSVDTSKNQFSLKLSVTAADT AVYYCARVETIMAFDAFDIWGQGTMTVTVSS	662
		V _L	EIVLTQSPGTLSPGERATLSCRASQSVGSSYLAWEYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYFCQQ YDTSPITFGQGTRLDIKR	663
218981	25C9	V _H	QVQLQESGPGLVKPSQTLTLTCTVSGGSISSGGYFWSWIRQHPGK GLEWIGYTHYIGSTYYNPSLKSRTAFSVDTSKNQFSLKLSVTAADT DTAVYYCARVDTAMVDAFDIWGQGTMTVTVSS	664
		V _L	EIMLTQSPGTLSPGERATLSCRASQSNIDSSYLAWEYQQTPGQAP RLLIYDTSSRATGIPDRFSGSGSGTDFTLTISRLEPEDFVYYCQQ YGGSPITFGQGTRLDIKR	665
218995	31C9	V _H	QVQLQESGPGLVKPSDTLSLTCAVSGYSISRNWWGIRQPPGK GLEWIGYIHYIGNTYNPSLKSRTMSVDTSKNQFSLKLSVTAV DTAVYYCARETGSDGDDTFDIWGQGTMTVTVSS	666
		V _L	EIVLTQSPVTLSPGERATLSCRASQSIGSSYLAWEYQQKPGQAP RLLIYGASGRATGIPDRFSGSGSGTDFTLTISRLEPEDFALYYCQQ CYSSPITFGHGTRLDIKR	667
218996	31B1 0	V _H	QVQLVESGGGVVQPRSLRLSCAASGFTFSNYDMHWVRQAPGK GLEWVTTIWYDGSNKYYADSVKGRFTISRDNKNTLFLQMNSL	668

LIBC 編號	Well ID	結構域	序列	SEQ ID
			RAEDTAVYYCPTLSTVTTGDYYGMDVWGQGTAVTVSS	
		V _L	QSVLTQPPSVSAAPGQKVTISCSGSRSNIGNNYVSWYQQLPGTVP KLLIYDNSKRPSGIPDRFSGSKSGTSVTLGITGLQTGDEADYYCG TWDSSLSAVVFGGGTKLTVLS	669
218998	32A2	V _H	QVQLQESGPGQVKPSQTLSTCTVSGGSISSGGYFWGWIRQHPG KGLEWIGYIHYIGSPYYNPSLKSRTTISVDTSKNQFSLKLSSVIAA DTAVYYCARDCSSVNCQDAFDIWGQGTMTVTVSS	670
		V _L	EIVLTQSPGTLSPGERASLSCWSSQSIDSTYLAWYHQKPGQAP RLLIYGASTRATGIPDRFSGSGSGTDFTLSISRLEPEDFAVYYCQQ YSSSPITFGQGTRLEIKR	671
219083	41H7	V _H	QVQLQESGPGLVKPSQTLSTCTVSGGSIRSDGYFWSWIRQHPG KGLEWLGFIYYSGTTYYNPSLKSRTTISVDTSKNQFSLKLTSVTV ADTAVYYCARVCGGDCYDAFDIWGQGTMTVTVSS	672
		V _L	DIVLTQSPGTLSPGEGATLSCRASQNISNTYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYDCQQ YFSSPITFGGGTRVEIKR	673
219092	43C1	V _H	QVQVQESGPGLVKPSDTLSLTCAVSGYSISNSIWWGWIRQPPGK GLEWIGYIHYSGNTYYNPSLKSRTTMSVDTSKNQFSLKLNSVTA VDTAVYYCARNFGDVDAFDIWGQGTMTVTVSS	674
		V _L	EIVLTQSPGTLSPGERATLSCRASQSISSSYLAWYQQKPGQAPR LLIYGASSRATGIPDRFSGSGSGTDFTLNISRLEPEDFVYYCQQY YLSPLTFGGGTKVEIKR	675
219023	33G6	V _H	QVQLQQSGPGLVKPSQTLSTCAISGDSVFSNSAAWNWIRQSPSR GLEWLGRTYCRSKCYSDYALSVKSRATINPDTSENQFSLQLNSV TPEDTAVYYCARAVADHYSYALDVWGQGTTVNVSS	676
		V _L	DIQMNQSPSSLSASVGDRVTITCRASQTIRTYLNWYQQKPGKAP KVLIIYAASSLQSGVPSRFSGTGSGTDFTLTITSLQPEDFATYSCQQ SYSSPITFGGGTKVEIKR	677
219023. 001		V _H	QVQLQQSGPGLVKPSQTLSTCAISGDSVFSNSAAWNWIRQSPSR GLEWLGRTYYSKWYSYALSVKSRATINPDTSENQFSLQLNSV	678

LIBC 編號	Well ID	結構域	序列	SEQ ID
			TPEDTAVYYCARAVADHYSYALDVWGQGTTVTVSS	
		V _L	DIQMTQSPSSLSASVGDRVTTTCRASQTIRTYLNWYQQKPGKAPK VLIYAASSLQSGVPSRFSGTGSGTDFTLTITSLQPEDFATYSCQQS YSSPITFGGGTKVEIKR	679
219095	43G5	V _H	EVQLLESGGNLVQPGGSLRLSCVVS GFTFN NYAMNWVRQAPGK GLEWVSVISDSGGSSNYADSVKGRFTISRDN SKKTLYLQMNSLR AEDTAVYYCAKDRSIAGYYGMDVWGQGTTVTVSS	680
		V _L	DIQMTQSPSSLSASVGDRVTTTCRASQSISSDLNWYQQKPGKAPN LLIYAASSLHSGVPSRFSGSGSGTDFTLTISLLPEDFATYYCQQS YNTPLTFGGGTKVEIKR	681
219102	44G1 1	V _H	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRLPPGKGL EWIGYIYYGGSTNYNPSLKSRVSM SVDTSKNQFSLKLSYVTAAD TAVYYCARSYSSAWYGSAYWGQGT LVIVSS	682
		V _L	DIQMTQSPSSLSASLGDRVTTTCQASQDISNYLIWYQLKPGKAPK VLIYDASNLETGVPSRFSGNGSGTDFTFTISSLPEDIATYYCQQY DHLPTFGQGTRLDIKR	683
219102. 001		V _H	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRLPPGKGL EWIGYIYYGGSTNYNPSLKSRVSM SVDTSKNQFSLKLSYVTAAD TAVYYCARSYSSAWYGSAYWGQGT LVIVSS	684
		V _L	DIQMTQSPSSLSASLGDRVTTTCQASQDISNYLIWYQLKPGKAPK VLIYDASNLETGVPSRFSGSGSGTDFTFTISSLPEDIATYYCQQY DHLPTFGQGTRLDIKR	685
218973	21A5	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGIHWVRQAPGKG LEWVAVIWYDGSKKYYADSVKGRFTISRDN SKSTLYLQMNSLR AEDTAVYYCARDPSHYYGSGSYNYFYGMDVWGQGTTVTVSS	686
		V _L	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNTYVSWYQQLPGTAP KLLIYDNNERPSGIPDRFSGSKSDTSATLGITGLQTGDEADYYCG TWDNSLTAVVFGGGTKLTVLG	687
219044	34F1 0	V _H	EVQLVESGGGLIQPGGSLRLSCAASGFTVSDNYMSWVRQAPGK GLEWVSVIYSGGNTYYGDSVKGRFTISRDN SKNTLYLQMNSLRA	688

LIBC 編號	Well ID	結構域	序列	SEQ ID
			EDTAVYFCTGPFFDYWGPGTLVTVSS	
		V _L	EIVLTQFPGTLSLSPGEGGTLSRASQTVWSNYLAWYQQKPGQA PRLLIYGASRRVIGIPDRFSGSGSGTDNLTSSLEPGDFAVYYCQ QYGSSSITFGQGTRLEIKR	689
218997	31E1 2	V _H	QVQVQESGPGLVKPSQTLSTCTVSGGSISSGGYYWSWIRQHPG KGLEWIGYIYYSGSTYYNPSLMGRVTISVDTSKNQFSLRLSSVTA ADTAVYYCARRGPVAGGFDYWGQGTSLVTVSS	690
		V _L	EIVLTQSPGTLSLSPGERATLSRASQNVYNNYLAWYQQKPRQA PRLLIYGTSSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSLLCSFGQGTKLEIKR	691

【0193】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR。該促效劑LTβR結合蛋白在表位結合人LTβR的CRD2和CRD3，該表位包含SEQ ID NO: 4之位置56-64和81-101（對應於SEQ ID NO: 1的殘基86-94和111-131）處的一或多個殘基或由其組成。該促效劑LTβR結合蛋白包含與SEQ ID NO: 644的VH結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 645的VL結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 644至少95%相同的VH胺基酸序列和與SEQ ID NO: 645至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 644的VH胺基酸序列和SEQ ID NO: 645的VL胺基酸序列（30H1/19320）。

【0194】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR。該促效劑LTβR結合蛋白在表位結合人LTβR的CRD1，該表位包含SEQ ID NO: 4之位置3-9、12-29和38-47（對應於SEQ ID NO: 1的殘基33-39、50-59和68-77）處的一或多個殘基或由其組成。該促效劑LTβR結合蛋白允許發生

100%的LIGHT與LTβR結合和/或至少或約80%的LTα1β2與LTβR結合，並且包含與SEQ ID NO: 646的VH結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域。該LTβR結合蛋白進一步包含與SEQ ID NO: 647的VL結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 646至少95%相同的VH胺基酸序列和與SEQ ID NO: 647至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 646的VH胺基酸序列和SEQ ID NO: 647的VL胺基酸序列（19321）。

【0195】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR。該促效劑LTβR結合蛋白在表位結合人LTβR的CRD2和CRD3，該表位包含SEQ ID NO: 4之位置56-64和81-101（對應於SEQ ID NO: 1的殘基86-94和111-131）處的一或多個殘基或由其組成。該促效劑LTβR結合蛋白在基於細胞的受體-配體測定中在< 8 nM濃度下不抑制LIGHT和LTα1β2與LTβR結合，如本文所描述的。該LTβR結合蛋白包含與SEQ ID NO: 648的VH結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 649的VL結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 648至少95%相同的VH胺基酸序列和與SEQ ID NO: 649至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 648的VH胺基酸序列和SEQ ID NO: 649的VL胺基酸序列（19324）。

【0196】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR。該LTβR結合蛋白在表位結合人LTβR的CRD1和CRD2，該表位包含SEQ ID NO: 4之位置38-42、56-65和65-70處的一或多個殘基或由其組成。該促效劑LTβR結合蛋白包含與SEQ ID NO: 650的VH結構域胺基酸序列具有至少

80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 651的VL結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 650至少95%相同的VH胺基酸序列和與SEQ ID NO: 651至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 650的VH胺基酸序列和SEQ ID NO: 651的VL胺基酸序列。

【0197】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR，並且不抑制內源性LIGHT與LTβR結合。該促效劑LTβR結合蛋白包含與SEQ ID NO: 652的VH結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 653的VL結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 652至少95%相同的VH胺基酸序列和與SEQ ID NO: 653至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 652的VH胺基酸序列和SEQ ID NO: 653的VL胺基酸序列（19322）。

【0198】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR，並且不抑制內源性LIGHT與LTβR結合。該促效劑LTβR結合蛋白包含與SEQ ID NO: 654至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 655或SEQ ID NO: 657至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 654至少95%相同的VH胺基酸序列和與SEQ ID NO: 657至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 654的VH胺基酸序列和SEQ ID NO: 657的VL胺基酸序列（19327）。

【0199】 在一個實施方式中，本揭露之LTβR結合蛋白結合並激動人和cyno

LT β R，以及不抑制LT α 1 β 2與LT β R結合且不抑制LIGHT與LT β R結合。該促效劑LT β R結合蛋白包含與SEQ ID NO: 658的VH結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 659的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 658至少95%相同的VH胺基酸序列和與SEQ ID NO: 659至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 658的VH胺基酸序列和SEQ ID NO: 659的VL胺基酸序列（35F5/19323）。

【0200】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白結合並激動人和cyno LT β R，並包含與SEQ ID NO: 660至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 661至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 660至少95%相同的VH胺基酸序列和與SEQ ID NO: 661至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 660的VH胺基酸序列和SEQ ID NO: 661的VL胺基酸序列。

【0201】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白結合並激動人和cyno LT β R，並包含與SEQ ID NO: 662至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 663至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 662至少95%相同的VH胺基酸序列和與SEQ ID NO: 663至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 662的VH胺基酸序列和SEQ ID NO: 663的VL胺基酸序列。

【0202】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 664至少80%、至少85%或至少90%相

同的VH胺基酸序列和與SEQ ID NO: 665至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 664至少95%相同的VH胺基酸序列和與SEQ ID NO: 665至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 664的VH胺基酸序列和SEQ ID NO: 665的VL胺基酸序列。

【0203】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 666至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 667至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 666至少95%相同的VH胺基酸序列和與SEQ ID NO: 667至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 666的VH胺基酸序列和SEQ ID NO: 667的VL胺基酸序列。

【0204】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 668至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 669至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 668至少95%相同的VH胺基酸序列和與SEQ ID NO: 669至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 668的VH胺基酸序列和SEQ ID NO: 669的VL胺基酸序列。

【0205】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 670至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 671至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 670至少95%相同的VH胺基酸序列和與SEQ ID NO: 671至少95%相同的VL胺基

酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 670的VH胺基酸序列和SEQ ID NO: 671的VL胺基酸序列。

【0206】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 672至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 673至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 672至少95%相同的VH胺基酸序列和與SEQ ID NO: 673至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 672的VH胺基酸序列和SEQ ID NO: 673的VL胺基酸序列。

【0207】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 674至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 675至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 674至少95%相同的VH胺基酸序列和與SEQ ID NO: 675至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 674的VH胺基酸序列和SEQ ID NO: 675的VL胺基酸序列。

【0208】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 676至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 677至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 676至少95%相同的VH胺基酸序列和與SEQ ID NO: 677至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 676的VH胺基酸序列和SEQ ID NO: 677的VL胺基酸序列。

【0209】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合

蛋白，其結合LTβR，並包含與SEQ ID NO: 678至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 679至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 678至少95%相同的VH胺基酸序列和與SEQ ID NO: 679至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 678的VH胺基酸序列和SEQ ID NO: 679的VL胺基酸序列。

【0210】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係促效劑結合蛋白，其結合LTβR，並包含與SEQ ID NO: 680至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 681至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 680至少95%相同的VH胺基酸序列和與SEQ ID NO: 681至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 680的VH胺基酸序列和SEQ ID NO: 681的VL胺基酸序列。

【0211】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係促效劑結合蛋白，其結合LTβR，並包含與SEQ ID NO: 682至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 683或SEQ ID NO: 685至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 682至少95%相同的VH胺基酸序列和與SEQ ID NO: 683或SEQ ID NO: 685至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 682的VH胺基酸序列和SEQ ID NO: 683或SEQ ID NO: 685的VL胺基酸序列。

【0212】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係促效劑結合蛋白，其結合LTβR，並包含與SEQ ID NO: 686至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 687至少80%、至少85%或至少90%相同的

VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 686至少95%相同的VH胺基酸序列和與SEQ ID NO: 687至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 686的VH胺基酸序列和SEQ ID NO: 687的VL胺基酸序列。

【0213】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係促效劑結合蛋白，其結合LTβR，並包含與SEQ ID NO: 688至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 689至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 688至少95%相同的VH胺基酸序列和與SEQ ID NO: 689至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 688的VH胺基酸序列和SEQ ID NO: 689的VL胺基酸序列。

【0214】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係促效劑結合蛋白，其結合LTβR，並包含與SEQ ID NO: 690至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 691至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 690至少95%相同的VH胺基酸序列和與SEQ ID NO: 691至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 690的VH胺基酸序列和SEQ ID NO: 691的VL胺基酸序列。

【0215】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含如上所描述的VH區和/或VL區，並且進一步包含與VH區偶合的一或多個重鏈恒定區和/或與VL區偶合的輕鏈恒定區。例如，在一個實施方式中，該促效劑LTβR結合蛋白係Fab，其包含VH和與VL偶合的第一重鏈恒定結構域（CH1）以及輕鏈恒定區（CL）。在另一個實施方式中，該促效劑LTβR結合蛋白係F(ab')₂，其包含藉由鉸鏈區偶合的完全抗體的兩個LTβR結合區，其中每個結合區包含VH-CH1和VL-

CL。本文表13中提供了本揭露之示例性促效劑LTβR抗體的完全重鏈和輕鏈胺基酸序列。

[表13]. LTβR抗體的全長胺基酸序列

LIBC編號	Well ID	鏈	序列	SEQ ID
218990	30H1 19320	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGDYMYWVRQA PGQGLEWMGWINPNSGGTNYAKKFQGRVTMTRDTSISTAYM ELSRLRSDDTAVYYCAREGSSGWSAEYFQHWGQGTLVTVFS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV D HKPSNTKVDKTVERKCCVECPCPAPPVAGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIE KTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	692
		LC	EIVLTQSPGTLSPGERATLSCRASQSVSSSFLAWYQQKLGQ APRLLMYGASRRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVY YCQQYGTSPLSFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	693
218994	31A3/ 19321	HC	QVQLVESGGAVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAIIWYDGSDEYYADSVKGRFTISRDNKNTLYLQM NSVRDEDTALYYCVRGDSSEDFYYYDFDVGQGTTTVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV D HKPSNTKVDKTVERKCCVECPCPAPPVAGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK	694

LIBC編號	Well ID	鏈	序列	SEQ ID
		LC	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGKNYVSWYQHLPGT APKLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADY YCGTWDHSLSASYVFGTGTKVTVLGQPKAAPSVTLFPPSSEEL QANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ SNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPT ECS	695
219058	36G2/ 19324	HC	EVQLVESGGGLVKPGGSLRLSCAASGFTFSTSGMNWVRQAPG KGLEWVSSVSSSGSYIYYADSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCAGARYNWHFDASDIWGQGTVVTVSSASTK GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVDPHKPS NTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQ FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNV FSCSVMEALHNHYTQKSLSLGLGK	696
		LC	DIQMTQSPSSLSASVGDRVITTCRASQSISSDLNWHYQQKPGKA PNLLIYAASSLHSGVPSRFRSGSGSGTDFTLTISLLPEDFATYYC QQSYNTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKIDSTY SLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	697
219097	43D9/1 9326/	HC	EVQLVESGGGLVKPGGSLRLSCAASGFTFNDAWMSWVRQAP GKGLEWVGRIKTKTDGGTTDYAAPVKGRITISRDDSKNTLYL QMNSLKTEDTAVYYCTTDYGDYEWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSNFGTQTYTCNVDPHKPSNT KVDKTVERKCCVECPAPPVAGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFN STFRVVSFLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISK KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW	698

LIBC編號	Well ID	鏈	序列	SEQ ID
			ESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK	
		LC	DIQMTQSPSSLSASVGDRVITTCRTSQSISRYLNWYQQKPGKA PKLLIYGASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC HQSYSTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	699
219037	34D1/ 19322	HC	QVQLQESGPGRVKPSQTLSTCTVSGGSINSGGYFWSWIRQHP GKVLEWIGYSHYSGTTYYNPSLKSRTVISVDTSKNQLSLKLNS VNAADTAVYYCARVPDGEDYFDYWQGALVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGKTKYTCNVDHKPSNTK VDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTP EVTCTVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPDIAVEWES NGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC SVMHEALHNHYTQKSLSLSLGK	700
		LC	DLQLTQSPSSLSASVGDRVITTCRASQTISSYLNWYQQKPGKA PKLLIYDASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFETYYC QQSFSAPITFGQGRLEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	701
219098	44B1/ 19327	HC	EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSTISGSGGSTYYADSVKGRFTISRDN SKNTLNLQMN SLRAEDTAVYYCAKVRDNWNYDGMDVWGQGTTVTVSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKP SNTKVDKTKVERKCCVECPAPPVAGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI	702

LIBC編號	Well ID	鏈	序列	SEQ ID
			SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK	
		LC	DIVMTQSPLSLPVTLGESASISCRCSQSLLYSSGYIDLWDWYLQK PGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDV GVYYCMQTIQTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC	703
219098.001		HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSTISGSGGSTYYADSVKGRFTISRDN SKNTLNLMN SLRAEDTAVYYCAKVRDNWNYDGM DVWGQGTTVTVSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSNFGTQTYTCNV DHKP SNTKVDKTVERKCCVECPAPPVAGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTFRVVS VLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK	704
		LC	DIVMTQSPLSLPVTLGESASISCRSSQSLLYSSGYIDLWDWYLQK PGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDV GVYYCMQTIQTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC	705
219051	35F5/19 323	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYLHWVRQAP GQGLEWMGWINPNIGVTD SAQKFQDRVTMTRDTSISTAYME LSRLISDDTAVYYCTVRGYND D YDFDYWGQGT LVT VSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNV DHKP	706

LIBC編號	Well ID	鏈	序列	SEQ ID
			SNTKVDKRVESKYGPPCPSCAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGN VFSCSVMHEALHNHYTQKSLSLGLGK	
		LC	DVVMQTQTPLSLSVTPGQPASISCKSRQSLHHRDGKTYLYWYL QKPGQPPQLLIYEVSNRFSGVPNRFSGSGSGTDFTLKISRVEAE DVGVIYCMQSIQLPLIFGGGTRVDIKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC	707
218989	29G8	HC	QITLKESGPTLVKPTQTLTLTCTFTGFSLSSTSGMGVGWIRQPPG KALEWLALIYWNGGKLYSPSLKNRLTITKDTSKNQVVLMTN MDPVDATYYCAHSGYYDNSGYYWDGMDVWGQGTTVTVS PASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVPSSNFGTQTYTCNV DHKPSNTKVDKTVKCCVECPAPPVAGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPI EKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	708
		LC	EIVLTQSPVTLSPGERATLSCRASQSLISDYLWVYQQKPGQ APRLLIYGASSRPTGIPDRFSGSGSGTDFTLTISRLEPEDFAVYY CQQYDTSLNFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	709
218967	17F5	HC	QVQLQESGPVVKPSETSLTCTVSGGSISSYFWTWIRQPPGK GLEWIGYIYYSGSTNYPNPSLKSRTFSVDTSKNQFSLKLNSVT AADTAVYYCARVETIMAFDAFDIWGQGTMTVSSASTKGPS	710

LIBC編號	Well ID	鏈	序列	SEQ ID
			VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTK VDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNST FRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK	
		LC	EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQ APRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYF CQQYDTSPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	711
218981	25C9	HC	QVQLQESGPGLVKPSQTLSTCTVSGGSISSGGYFWSWIRQHP GKGLEWIGYTHYIGSTYYNPSLKSRAFSVDTSKNQFSLKLSS VTAADTAVYYCARVDTAMVDAFDIWGQGTMTVSSASTKG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSN TKVDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISK TKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK	712
		LC	EIMLTQSPGTLSLSPGERATLSCRASQNIDSSYLAWYQQTPGQ APRLLIYDTSSRATGIPDRFSGSGSGTDFTLTISRLEPEDFSVYY CQQYGGSPITFGQGTRLDIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	713
218995	31C9	HC	QVQLQESGPGLVKPSDTLSLTCAVSGYSISSRNWWGWIRQPP GKGLEWIGYIHYIGNTYYNPSLKSRTMSVDTSKNQFSLKLSS	714

LIBC編號	Well ID	鏈	序列	SEQ ID
			VTAVDTAVYYCARETGSDGDDTFDIWGQGTMTVTVSSASTKG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSN TKVDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISK TKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPMLDSDGSSFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK	
		LC	EIVLTQSPVTLSLSPGERATLSCRASQSIGSSYLAWYQQKPGQ APRLLIYGASGRATGIPDRFSGSGSGTDFTLTISRLEPEDFALYY CQQCYSSPITFGHGTRLDIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	715
218996	31B10	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYDMHWVRQAP GKGLEWVTTIWYDGSNKYYADSVKGRFTISRDN SKNTLFLQ MNSLRAEDTAVYYCPTLSTVTTGDYYGMDVWGQGTAVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPI EKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPMLDSDGSSFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	716
		LC	QSVLTQPPSVSAAPGQKVTISCSGSRSNIGNNYVSWYQQLPGT VPKLLIYDNSKRPSGIPDRFSGSKSGTSVTLGITGLQTGDEADY YCGTWDSSLSAVVFGGGTKLTVLSQPKAAPSVTLFPPSSEELQ ANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTE CS	717

LIBC編號	Well ID	鏈	序列	SEQ ID
218998	32A2	HC	QVQLQESGPGQVKPSQTLSTCTVSGGSISSGGYFWGWIRQHP GKGLEWIGYIHYIGSPYYNPSLKSRTTISVDTSKNQFSLKLSSVI AADTAVYYCARDCSSVNCQDAFDIWGQGTMTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPKPSNT KVDKTVRKCCVECPAPPVAGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFN STFRVVSIVLTQVHVDWLNQKEYKCKVSNKGLPAPIEKTISK KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK	718
		LC	EIVLTQSPGTLSPGERASLSCWSSQSIDSTYLAWYHQKPGQ APRLLIYGASTRATGIPDRFSGSGSGTDFTLISRLEPEDFAVYY CQQYSSSPITFGQGRLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKIDSTY SLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	719
219083	41H7	HC	QVQLQESGPGLVKPSQTLSTCTVSGGSIRSDGYFWSWIRQHP GKGLEWLGFIIYSGTTYNPSLKSRVTISVDTSKNQFSLKLTS VTVADTAVYYCARVCGGDCYDAFDIWGQGTMTVTVSSASTK GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPKPS NTKVDKTVRKCCVECPAPPVAGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQ FNSTFRVVSIVLTQVHVDWLNQKEYKCKVSNKGLPAPIEKTIS KTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK	720
		LC	DIVLTQSPGTLSPGEGATLSCRASQNISNTYLAWYQQKPGQ APRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYD CQQYFSSPITFGGGRVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKIDSTY	721

LIBC編號	Well ID	鏈	序列	SEQ ID
			SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
219092	43C1	HC	QVQVQESGPGLVKPSDTLSLTCAVSGYSISNSIWGWIRQPPG KGLEWIGYIHYSGNTYYNPSLKSRTMSVDTSKNQFSLKLNS VTAVDTAVYYCARNFGDVDAFDIWGQGTMTVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDPHKPSNTK VDKTVRKKCCVECPAPPVAGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNST FRVVSVLTVVHQQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK	722
		LC	EIVLTQSPGTLSLSPGERATLSCRASQSISSSYLAWYQQKPGQA PRLLIYGASSRATGIPDRFSGSGSGTDFTLNISRLEPEDFVYYC QQYYLSPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKIDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	723
219023	33G6	HC	QVQLQQSGPGLVKPSQTLTLTCAISGDSVFSNSAAWNWIRQSP SRGLEWLGRTYCRSKCYSDYALSVKSRATINPDTSNQFSLQL NSVTPEDTAVYYCARAVADHYSYALDVWGQGTTVNVSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKTYTCNVDPHKP SNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGN VFSCSVMEALHNHYTQKSLSLSPGK	724
		LC	DIQMNQSPSSLSASVGDRVTITCRASQTIRTYLNWYQQKPGKA PKVLIYAASSLQSGVPSRFSGTSGTDFLTITSLQPEDFATYSC QQSYSSPITFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV	725

LIBC編號	Well ID	鏈	序列	SEQ ID
			VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
219023.001		HC	QVQLQQSGPGLVKPSQTLSTCAISGDSVFSNSAAWNWIRQSP SRGLEWLGRITYYRSKWYSDYALSVKSRATINPDTSENQFSLQ LNSVTPEDTAVYYCARAVADHYSYALDVWGQGTTVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTCTYTCNVDPHK PSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPR EEQFNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSPGK	726
		LC	DIQMTQSPSSLSASVGDRVITTCRASQTIRTYLNWYQQKPGKA PKVLIYAASSLQSGVPSRFSGTGSGTDFTLTITSLQPEDFATYSC QQSYSSPITFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	727
219095	43G5	HC	EVQLLESGGNLVQPGGSLRLSCVVSQGTFFNNYAMNWVRQAP GKGLEWVSVISDSGGSSNYADSVKGRFTISRDNSSKTLYLQM NSLRAEDTAVYYCAKDRSIAGYYGMDVWGQGTTVTVSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKP SNTKVDKTVERKCCVECPAPPVAGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTFRVVSIVLVHVDWLNQKEYKCKVSNKGLPAPIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK	728
		LC	DIQMTQSPSSLSASVGDRVITTCRASQSISSDLNWYQQKPGKA PNLLIYAASSLHSGVPSRFSGSGSGTDFTLTISLLPEDFATYYC	729

LIBC編號	Well ID	鏈	序列	SEQ ID
			QQSYNTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
219102	44G11	HC	QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWSWIRLPPGK GLEWIGYIYYGGSTNYPNPSLKSRVSMVSDTSKNQFSLKLSYVT AADTAVYYCARSYSSAWYGSAYWGQGLVIVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLGLGK	730
		LC	DIQMTQSPSSLSASLGDRVITITCQASQDISNYLIWYQLKPGKAP KVLIIYDASNLETGVPSRFSNGSGTDFTFTISSLQPEDIATYYC QQYDHLPIITFGQGTRLDIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	731
219102.001		HC	QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWSWIRLPPGK GLEWIGYIYYGGSTNYPNPSLKSRVSMVSDTSKNQFSLKLSYVT AADTAVYYCARSYSSAWYGSAYWGQGLVIVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLGLGK	732
		LC	DIQMTQSPSSLSASLGDRVITITCQASQDISNYLIWYQLKPGKAP	733

LIBC編號	Well ID	鏈	序列	SEQ ID
			KVLIYDASNLETGVPSRFSGSGSGTDFTFITSSSLQPEDIATYYC QQYDHLPIITFGQGTRLDIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
218973	21A5	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGIHWVRQAPG KGLEWVAVIWYDGSKKYYADSVKGRFTISRDNKSTLYLQM NSLRAEDTAVYYCARDPSHYGSGSYNYFYGMDEVWGQGT VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSNFGTQTYT CNVDHKPSNTKVDKTKVERKCCVECPAPPVAGPSVFLFPPK PKDTLMISRTPEVTCVVDVSHEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGL PAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	734
		LC	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNTYVSWYQQLPGT APKLLIYDNNERPSGIPDRFSGSKSDTSATLGITGLQTGDEADY YCGTWDNSLTAVVFGGGTKLTVLGQPKAAPSVTLFPPSSEEL QANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ SNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPT ECS	735
219044	34F10	HC	EVQLVESGGGLIQPGGSLRLSCAASGFTVSDNYMSWVRQAPG KGLEWVSVIYSGGNTYYGDSVKGRFTISRDNKNTLYLQMNS LRAEDTAVYFCTGPFFDYWGPGLTVTVSSASTKGPSVFPLAPC SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVTPSSSLGKTYTCNVDHKPSNTKVDKRVES KYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVD DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQ VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTPPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMHEA	736

LIBC編號	Well ID	鏈	序列	SEQ ID
			LHNHYTQKSLSLSLGK	
		LC	EIVLTQFPGTLSLSPGEGGTLSRASQTVWSNYLAWYQQKPG QAPRLLIYGASRRVIGIPDRFSGSGSGTDNLTISLEPGDFAVY YCQQYGSSSITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	737
218997	31E12	HC	QVQVQESGPGLVKPSQTLSTCTVSGGSISSGGYYWSWIRQHP GKGLEWIGYIYYSGSTYYNPSLMGRVTISVDTSKNQFSLRLSS VTAADTAVYYCARRGPVAGGFDYWGQGLVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSKV HTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDPKPSNTK VDKTVRKKCCVECPKPPVAGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNST FRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTTPMLDSGSSFFLYSKLTVDKSRWQQGNVSCS VMHEALHNHYTQKSLSLSPGK	738
		LC	EIVLTQSPGTLSLSPGERATLSCRASQNVYNNYLAWYQQKPR QAPRLLIYGTSSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVY YCQQYGSSLLCSFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	739

多特異性LTβR結合分子

【0216】 在本揭露之另一方面，該促效劑LTβR結合蛋白為多特異性促效劑LTβR結合蛋白。根據本揭露之此方面，該多特異性促效劑LTβR結合蛋白包含與人LTβR（SEQ ID NO: 1）結合的第一結合結構域和與非LTβR蛋白靶標（即LTβR以外的蛋白質）結合的第二結合結構域，其中該多特異性結合蛋白激動LTβR活性並且 (a) 不抑制LIGHT與LTβR結合，以及 (b) 不抑制LT1α2β與LTβR結合。如

本文所描述的示例性LT β R多特異性結合蛋白的第二結合結構域與非LT β R蛋白靶標結合。在一個實施方式中，該LT β R多特異性結合蛋白的第二結合結構域與腫瘤微環境（TME）的腫瘤細胞或其他細胞優先表現的蛋白或抗原結合。

【0217】 在一個實施方式中，該多特異性促效劑LT β R結合蛋白對於由該第一和第二結合結構域多特異性結合蛋白結合的每個蛋白靶標係單價的。在一個實施方式中，該多特異性促效劑LT β R結合蛋白對於LT β R配體結合結構域係單價的，而對於非LT β R結合結構域係二價的。

【0218】 在一個實施方式中，本揭露之多特異性促效劑LT β R結合蛋白進一步包含一或多個額外的結合結構域。在一個實施方式中，本文所描述的多特異性促效劑LT β R結合蛋白包含第三結合結構域，其中該第三結合結構域結合與該第一或第二結合結構域相同的蛋白靶標，以形成對於由雙特異性結合蛋白結合的蛋白靶標之一為二價的雙特異性結合蛋白。在另一個實施方式中，該第三結合結構域結合與該第一和第二結合結構域不同的蛋白靶標，從而形成單價三特異性結合蛋白。在一個實施方式中，該多特異性促效劑LT β R結合蛋白可以進一步包含第四結合結構域，其中該第四結合結構域結合與該第一、第二或第三結合結構域相同的蛋白靶標。

【0219】 根據本揭露之此方面，該多特異性促效劑LT β R結合蛋白可以採用本領域已知的任何多特異性結合蛋白形式。例如，在一個實施方式中，該多特異性促效劑LT β R結合蛋白係促效劑LT β R雙特異性結合蛋白或三特異性促效劑LT β R結合蛋白。在一個實施方式中，該多特異性促效劑LT β R結合結構域的第一、第二和/或第三結合結構域係Fab。可替代地，該多特異性促效劑LT β R結合結構域的第一、第二和/或第三結合結構域係scFv。在一個實施方式中，該第一結合結構域是Fab，該第二結合結構域係scFv，並且視需要存在的第三結合結構域係Fab或scFv。在一個實施方式中，該第二結合結構域係Fab，該第一結合結構域係scFv，

並且視需要存在的第三結合結構域係Fab或scFv。在一個實施方式中，該第一和第二結合結構域係Fab，並且視需要存在的第三結合結構域係Fab或scFv。在一個實施方式中，該第一和第二結合結構域係scFv，並且視需要存在的第三結合結構域係Fab或scFv。

【0220】 在本揭露之一個實施方式中，該多特異性促效劑LT β R結合蛋白係雙特異性促效劑LT β R結合蛋白。如本文所指的「雙特異性結合蛋白」係同時與兩種不同抗原結合的結合蛋白。本揭露之雙特異性促效劑LT β R結合蛋白涵蓋了本領域已知的任何雙特異性分子形式（參見例如，Spiess等人, *Mol. Immunol.*[分子免疫學] 67(2): 95-106 (2015)，特此藉由引用將其全部併入）。該等分子形式包括保留具有兩個Fab臂和一個Fc區的傳統單株抗體結構的IgG樣形式、含有附加的額外抗原結合部分的IgG形式、雙特異性結合蛋白片段、雙特異性融合蛋白及其組合。

【0221】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的第一和/或第二結合結構域係Fab。可替代地，該雙特異性促效劑LT β R結合蛋白的第一和/或第二結合結構域係scFv。在一個實施方式中，該第一結合結構域係Fab，並且該第二結合結構域係scFv。在一個實施方式中，該第二結合結構域係Fab，並且該第一結合結構域係scFv。在一個實施方式中，該第一和第二結合結構域均為Fab。在一個實施方式中，該第一和第二結合結構域均為scFv。

【0222】 在一個實施方式中，本揭露之雙特異性促效劑LT β R結合蛋白係全長雙特異性IgG或包含IgG樣結構。在一個實施方式中，該雙特異性促效劑LT β R結合蛋白係對於由雙特異性結合蛋白結合的每個靶蛋白係單價的異源IgG。包含經工程化以增強異二聚體形成的Fc結構域的示例性異源IgG雙特異性形式在本領域中係熟知的，並且係本揭露之雙特異性促效劑LT β R結合蛋白的合適形式。該等異源IgG形式包括但不限於旋鈕入孔形式(參見例如，Ridgway等人, 「Knobs-

into-holes' engineering of antibody CH3 domains for heavy chain heterodimerization[用於重鏈異二聚化的抗體CH3結構域的'旋鈕入孔'工程化],」 *Protein Eng.*[蛋白工程] 9:617-621 (1996)和Atwell等人,「Stable heterodimers from remodeling the domain interface of a homodimer using a phage display library[使用噬菌體展示文庫 重塑同源二聚體結構域介面的穩定異二聚體],」 *J. Mol. Biol.*[分子生物學雜誌] 270:26-35 (1997),特此藉由引用將其全部併入)、DuoBody形式(參見例如,Labriijn等人,「Efficient generation of stable bispecific IgG1 by controlled Fab-arm exchange[藉由受控的Fab-arm交換有效產生穩定的雙特異性IgG1],」 *Proc. Natl. Acad. Sci. U.S.A.*[美國國家科學院院刊], 110: 5145-5150 (2013),特此藉由引用將其全部併入); Azymetric形式(參見例如, Von Kreudenstein等人,「Improving biophysical properties of a bispecific antibody scaffold to aid developability: quality by molecular design[提高雙特異性抗體支架的生物物理特性以說明可開發性: 分子設計品質],」 *mAbs*[單株抗體] 5:646-654 (2013),特此藉由引用將其全部併入);帶電的Fc對(參見例如, Gunasekaran等人,「Enhancing antibody Fc heterodimer formation through electrostatic steering effects: applications to bispecific molecules and monovalent IgG[藉由靜電轉向效應增強抗體Fc異二聚體的形成: 對雙特異性分子和單價IgG的應用],」 *J. Biol. Chem.*[生物化學雜誌], 285: 19637-46 (2010)和Strop等人,「Generating bispecific human IgG1 and IgG2 antibodies from any antibody pair[從任何抗體對生成雙特異性人IgG1和IgG2抗體],」 *J. Mol. Biol.*[分子生物學雜誌], 420:204-219 (2012),特此藉由引用將其全部併入);mAb-Fv(參見例如, Close等人,「A novel bispecific antibody format enables simultaneous bivalent and monovalent co-engagement of distinct target antigens[一種新型雙特異性抗體形式能夠使不同靶抗原同時二價和單價共接合],」 *mAbs*[單株抗體] 3: 546-557 (2011),特此藉由引用將其全部併入);鏈交換工程化結構域

(SEED)CH3異二聚體形式(參見例如,「Davis等人,「SEEDbodies: fusion proteins based on strand-exchange engineered domain (SEED) CH3 heterodimers in an Fc analogue platform for asymmetric binders or immunofusions and bispecific antibodies[SEED體:基於Fc類似物平臺中鏈交換工程化結構域(SEED)CH3異二聚體的融合蛋白,用於不對稱結合物或免疫融合物和雙特異性抗體],」*Protein Eng. Des. Sel.*[蛋白質工程設計與選擇]23:195-202 (2010),特此藉由引用將其全部併入);和蛋白A差別親和力(參見例如,Davis等人的美國專利案號8,586,713,特此藉由引用將其全部併入)。

【0223】在一個實施方式中,本揭露之雙特異性促效劑LTβR結合蛋白係包含一或多個結合蛋白片段的構建體。本揭露之合適的LTβR雙特異性結合蛋白片段構建體包括但不限於包含經由肽連接基連接的兩個單可變(VHH)結構域的奈米抗體(Els Conrath等人,「Camel single-domain antibodies as modular building units in bispecific and bivalent antibody constructs[駱駝單結構域抗體作為雙特異性和二價抗體構建體中的模組化構建單元],」*J. Biol. Chem.*[生物化學雜誌]276:7346-50 (2001),特此藉由引用將其全部併入),以及包含兩個偶合在一起的scFv片段的雙特異抗體(Holliger等人,「‘Diabodies’: small bivalent and bispecific antibody fragments[‘雙特異抗體’:小的二價和雙特異性抗體片段],」*Proc. Natl. Acad. Sci. U.S.A.*[美國國家科學院院刊],90: 6444-6448 (1993),特此藉由引用將其全部併入)。合適的雙特異抗體LTβR雙特異性構建體包括但不限於單鏈雙特異抗體(參見例如,Alt等人,「Novel tetravalent and bispecific IgG-like antibody molecules combining single-chain diabodies with the immunoglobulin gamma1 Fc or CH3 region[將單鏈雙特異抗體與免疫球蛋白γ1 Fc或CH3區結合的新型四價和雙特異性IgG樣抗體分子],」*FEBS Lett.*[歐洲生物化學會聯合會快報]454: 90-94 (1999),特此藉由引用將其全部併入)、雙親和力重新靶向雙特異抗體(DART)

(參見例如, Johnson等人, 「Effector cell recruitment with novel Fv-based dual-affinity re-targeting protein leads to potent tumor cytotoxicity and in vivo B-cell depletion[用新型基於Fv的雙親和力重新靶向蛋白募集效應細胞導致有效的腫瘤細胞溶解和體內B細胞耗竭],」 J. Mol. Biol.[分子生物學雜誌] 399: 436-449 (2010), 特此藉由引用將其全部併入)、串聯雙特異抗體和包含連接在單多肽鏈中的兩對VL和VH結構域的四價串聯雙特異抗體(TandAb)(參見例如, Arndt等人, 「A bispecific diabody that mediates natural killer cell cytotoxicity against xenotransplanted human Hodgkin's tumors[介導自然殺手細胞對異種移植的人霍奇金腫瘤的細胞毒性的雙特異性雙特異抗體],」 Blood[血液] 94: 2562-2568 (1999), 特此藉由引用將其全部併入)。合適的LT β R雙特異性構建體還包括與Fc部分偶合(例如, 微抗體、雙特異抗體-CH3、sc雙特異抗體-CH3、scFv-CH3、微抗體)或與一或多個其他部分融合以延長半衰期(例如, 與血清白蛋白或白蛋白結合蛋白融合)的scFv片段或雙特異抗體。

【0224】在一個實施方式中, 本揭露之雙特異性促效劑LT β R結合蛋白係工程化為雙特異性的單特異性IgG抗體(例如, 含有雙特異性抗體的第一或第二結合結構域), 通過將包含例如VHH、scFv、2scFv、Fv、Fab或抗體模擬物結合結構域的額外結合結構域(例如, 分別為該第二或第一結合結構域)與抗體的一或多個輕鏈或重鏈的胺基或羧基末端偶合。示例性工程化雙特異性結合蛋白包括但不限於雙可變結構域(DVD)-IgG、IgG(H)-scFv、ScFv-(H)IgG、IgG(L)-scFv、scFv-(L)IgG、IgG((L,H)-Fv、IgG(H)-V、V(H)-IgG、IgG(L)-V、V(L)-IgG、IgG-scFab、2scFv-IgG、IgG-2scFv、scFv4-Ig(參見例如, Spiess等人, 「Alternative molecular formats and therapeutic applications for bispecific antibodies[雙特異性抗體的替代分子形式和治療應用],」 Mol. Immunol.[分子免疫學] 67(2): 95-106 (2015), 特此藉由引用將其全部併入)。

【0225】 在一個實施方式中，本揭露之多特異性促效劑LT β R結合蛋白係雙特異性促效劑LT β R結合蛋白。該雙特異性促效劑LT β R結合蛋白包含 (i) LT β R結合結構域，其中該LT β R結合結構域結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R CRD4的一或多個胺基酸殘基，和 (ii) 腫瘤相關抗原結合結構域。該雙特異性LT β R結合蛋白激動LT β R活性，並且 (a) 不抑制LIGHT與LT β R結合和 (b) 不抑制LT1 α 2 β 與LT β R結合。

【0226】 上文描述了結合人LT β R的CRD4的示例性LT β R結合結構域，即HCDR和LCDR，以及VH和VL結構域，包括但不限於LIBC219081和LIBC218979的結合結構域以及表2-4和6-8中提供的LT β R結合蛋白的結合結構域。特別地，如本文所描述的雙特異性促效劑LT β R結合蛋白的合適的第一結合結構域可包含重鏈可變結構域(VH)或其片段，其包含表2或表6的單行中所列的HCDR1、HCDR2和/或HCDR3中的一或多個或其部分。在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的第一結合結構域包含表2或表6的單行中所列的HCDR1、HCDR2和HCDR3的全部三個或其部分。在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的第一結合結構域包含輕鏈可變結構域(VL)或其片段，其包含表3或表7的單行中所列的LCDR1、LCDR2和/或LCDR3中的一或多個或其部分。在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的第一結合結構域包含表3或表7的單行中所列的LCDR1、LCDR2和LCDR3的全部三個或其部分。在一個實施方式中，如本文所描述的雙特異性促效劑LT β R結合蛋白的第一結合結構域包含VH或其片段，其包含表2或表6的單行中所列的HCDR1、HCDR2和/或HCDR3中的一或多個或其部分，以及VL或其片段，其包含表3或表7的單行中所列的相應結合分子的LCDR1、LCDR2和/或LCDR3中的一或多個或其部分。在一個實施方式中，如本文所描述的雙特異性促效劑LT β R結合蛋白的第一結合結構域包含VH或其片段，其包含表2或表6的單行中所列的HCDR1、HCDR2和HCDR3

的全部三個或其部分，以及VL或其片段，其包含表3或表7的單行中所列的相應結合分子的LCDR1、LCDR2和LCDR3的全部三個或其部分。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0227】 在一個實施方式中，結合人LTβR的CRD4的雙特異性促效劑LTβR結合蛋白的第一結合結構域包含重鏈可變結構域 (VH)、輕鏈可變結構域 (VL) 或VH和VL結構域的組合。在一個實施方式中，該雙特異性促效劑LTβR結合蛋白的第一結合結構域的VH結構域包含表4或表8中提供的VH胺基酸序列中的任一個，或與表4或表8中列出的VH胺基酸序列中的任一個至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%相同的胺基酸序列。在一個實施方式中，該雙特異性促效劑LTβR結合蛋白的第一結合結構域的VL結構域包含表4或表8中提供的VL胺基酸序列中的任一個，或與表4或表8中列出的VL胺基酸序列中的任一個至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%相同的胺基酸序列。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0228】 在一個實施方式中，結合人LTβR的CRD4的雙特異性促效劑LTβR結合蛋白的第一結合結構域包含與表4或表8中列出的VH結構域胺基酸序列中的任一個具有至少85%、至少90%、至少95%或100%序列同一性的重鏈可變結構域，和與表4或表8中列出的相應VL結構域胺基酸序列具有至少85%、至少90%、至少95%或100%序列同一性的輕鏈可變結構域。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0229】 在一個實施方式中，結合人LTβR的CRD4的雙特異性促效劑LTβR結合蛋白的LTβR結合結構域包含VH，其包含HCDR1胺基酸序列：X₁YX₃MX₅ (SEQ ID NO: 5)，其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺

基酸序列：X₁IX₃YDX₆X₇X₈X₉Y X₁₁X₁₂DSVKG (SEQ ID NO: 6)，其中X₁為A或V；X₃為W或R；X₆為E或G；X₇為S、R或T；X₈為N或K；X₉為K、R或Q；X₁₁為H或Y；並且X₁₂為A或E；以及HCDR3胺基酸序列：X₁RX₃X₄X₅X₆X₇X₈X₉YYGX₁₃X₁₄V (SEQ ID NO: 7)，其中X₁為D或E；X₃為V、G或I；X₄為V、P或A；X₅為A、Y或G；X₆為R、A、G或H；X₇為P或G；X₈為G、N、D、Y、A或H；X₉為Y、T或F；X₁₃為L或M；並且X₁₄為D或A。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0230】 在一個實施方式中，結合人LTβR的CRD4的雙特異性促效劑LTβR結合蛋白的LTβR結合結構域進一步包含VL，其包含LCDR1胺基酸序列：SGDX₄LPX₇X₈YX₁₀Y (SEQ ID NO: 62)，其中X₄為A或T；X₇為E、K、Q、D或N；X₈為Q或H；並且X₁₀為A或T；LCDR2胺基酸序列：KDNERPS (SEQ ID NO: 63)；以及LCDR3胺基酸序列：QSX₃DX₅SX₇X₈YX₁₀X₁₁ (SEQ ID NO: 64)，其中X₃為A或T；X₅為S、G或N；X₇為G或A；X₈為T、S或A；X₁₀為V或M；並且X₁₁為I或V。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0231】 在一個實施方式中，結合人LTβR的CRD4的雙特異性促效劑LTβR結合蛋白的LTβR結合結構域包含與SEQ ID NO: 121之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。在一個實施方式中，LTβR結合結構域包含與SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。在一個實施方式中，LTβR結合結構域包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。與SEQ ID NO: 121和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的示例性VH胺基酸序列提供在上表4中。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0232】 在一個實施方式中，該結合人LTβR的CRD4的雙特異性促效劑LTβR結合蛋白的LTβR結合結構域包含與SEQ ID NO: 122之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，該LTβR結合結構域包含與SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，該LTβR結合結構域包含與SEQ ID NO: 122之胺基酸序列和SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。與SEQ ID NO: 122和SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的示例性VL胺基酸序列提供在上表4中。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0233】 在一個實施方式中，該結合人LTβR的CRD4的雙特異性促效劑LTβR結合蛋白的LTβR結合結構域包含與SEQ ID NO: 121之胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，該LTβR結合結構域包含與SEQ ID NO: 121之胺基酸序列具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少95%序列同一性的VL胺基酸序列。在一個實施方式中，LTβR結合結構域包含與SEQ ID NO: 121之胺基酸序列具有至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少98%序列同一性的VL胺基酸序列。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0234】 在一個實施方式中，該雙特異性促效劑LTβR結合蛋白的LTβR結合結構域包含與SEQ ID NO: 123具有至少90%序列同一性的VH胺基酸序列，以及SEQ ID NO: 5 (X₁YX₃MX₅) 的HCDR1胺基酸序列，SEQ ID NO: 6 (X₁IX₃YDX₆X₇X₈X₉YX₁₁X₁₂DSVKG) 的HCDR2胺基酸序列，以及SEQ ID NO: 7 (X₁RX₃X₄X₅X₆X₇X₈X₉YYGX₁₃X₁₄V) 的HCDR3胺基酸序列。在一個實施方式

中，該LTβR結合結構域進一步包含與SEQ ID NO: 124具有至少90%序列同一性的VL胺基酸序列，以及SEQ ID NO: 62 (SGDX₄LPX₇X₈YX₁₀Y)的LCDR1胺基酸序列，SEQ ID NO: 63 (KDX₃ERPS)的LCDR2胺基酸序列，以及SEQ ID NO: 64 (QSX₃DX₅SX₇X₈YX₁₀X₁₁)的LCDR3胺基酸序列。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0235】 在一個實施方式中，該雙特異性促效劑LTβR結合蛋白的LTβR結合結構域包含VH，其包含分別為SEQ ID NO: 11-13的HCDR1、HCDR2和HCDR3胺基酸序列，以及VL，其包含分別為SEQ ID NO: 68-70的LCDR1、LCDR2和LCDR3胺基酸序列。在一個實施方式中，該LTβR結合結構域包含VH，其包含分別為SEQ ID NO: 8-10的HCDR1、HCDR2和HCDR3胺基酸序列，以及VL，其包含分別為SEQ ID NO: 65-67的LCDR1、LCDR2和LCDR3胺基酸序列。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0236】 在一個實施方式中，該雙特異性促效劑LTβR結合蛋白的LTβR結合結構域與示例性LTβR結合物LIBC219081和LIBC218979競爭結合LTβR。在一個實施方式中，該第一結合結構域包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列：(i) SEQ ID NO: 159、SEQ ID NO: 160、SEQ ID NO: 161、SEQ ID NO: 278、SEQ ID NO: 279和SEQ ID NO: 280；(ii) SEQ ID NO: 159、SEQ ID NO: 160、SEQ ID NO: 161、SEQ ID NO: 299、SEQ ID NO: 300和SEQ ID NO: 301；(iii) SEQ ID NO: 159、SEQ ID NO: 160、SEQ ID NO: 161、SEQ ID NO: 308、SEQ ID NO: 309和SEQ ID NO: 310；(iv) SEQ ID NO: 195、SEQ ID NO: 196、SEQ ID NO: 197、SEQ ID NO: 308、SEQ ID NO: 309和SEQ ID NO: 310；(v) SEQ ID NO: 224、SEQ ID NO: 225、SEQ ID NO: 226、SEQ ID NO: 356、SEQ ID NO: 357和SEQ ID NO: 358。包含具有上述重鏈和輕鏈CDR的第一結合

結構域的雙特異性促效劑LT β R結合蛋白不抑制LIGHT與LT β R結合，而且不抑制LT α 1 β 2與LT β R結合。

【0237】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R CRD1，並包含與SEQ ID NO: 646的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 647的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。該雙特異性LT β R結合蛋白不抑制內源性LIGHT與LT β R結合，並允許發生80%的內源性LT α 1 β 2與LT β R結合。

【0238】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R，並包含與SEQ ID NO: 652的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 653的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。該雙特異性LT β R結合蛋白不抑制內源性LIGHT與LT β R結合。

【0239】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R，並包含與SEQ ID NO: 654的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 655的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。該雙特異性LT β R結合蛋白不抑制內源性LIGHT與LT β R結合。

【0240】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R CRD1，並包含與SEQ ID NO: 658的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 659的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。該雙特異性LT β R結合蛋白不抑制內源性LIGHT與LT β R結合，而且不抑制LT α 1 β 2與LT β R結合。

【0241】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R CRD2和CRD3，並包含與SEQ ID NO: 648的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 649的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。該LT β R結合蛋白在基於細胞的受體-配體測定中在< 8 nM濃度下不抑制LIGHT和LT α 1 β 2與LT β R結合，如本文所描述的。

【0242】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R CRD2和CRD3，並包含與SEQ ID NO: 644的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 645的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。

【0243】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的腫瘤相關結合結構域與腫瘤相關抗原（TAA）結合。在一個實施方式中，該TAA係實性瘤TAA。合適的TAA係本領域已知的，並包括但不限於甲型胎兒蛋白（AFP）、CD44v6、碳酸酐酶IX（CAIX）、癌胚抗原（CEA）、CD133、肝細胞生長因子受體（c-MET）、密連蛋白18.2（CLDN18.2）、密連蛋白6（CLDN6）、含富胺酸重複序列的蛋白15（LRRC15）、表皮生長因子受體（EGFR）、III型變體表皮生長因子受體（EGFRvIII）、促紅血球生成素產生肝細胞癌A2（EphA2）、上皮細胞黏附分子（EpCAM）、胎兒乙醯膽鹼受體、葉酸受體 α （FR α ）、神經節苷脂GD2（GD2）、蛋白多糖-3（GPC3）、鳥苷酸環化酶C（GUCY2C）、人表皮生長因子受體1（HER1）、人表皮生長因子受體2（ERBB2/HER2）、細胞間黏附分子1（ICAM-1）、白血球介素13受體 α 2（IL13R α 2）、白血球介素11受體 α （IL11R α ）、Kirsten大鼠肉瘤病毒癌基因同源物（KRAS）、KRAS G12D、L1細胞黏附分子（L1CAM）、MAGE、MET、黏蛋白1（MUC1）、黏蛋白16（MUC16）、

黏蛋白17 (MUC17)、自然殺手組2成員D (NKG2D)、NYESO-1、前列腺幹細胞抗原 (PSCA)、腎母細胞瘤1 (WT-1)、半乳糖凝集素9 (Gal9)、計畫性細胞死亡1配體1 (PD-L1)、滋養層糖蛋白 (5T4癌胚抗原)、葉酸受體 α (FOLR1) 和腫瘤相關鈣訊息傳遞子2 (TROP2)。

【0244】能夠結合該等TAA的結合蛋白在實例中進行了描述，並且在本領域中係已知的。任何該等已知的結合蛋白或從其衍生的TAA結合結構域可以方便地用作本文所描述的雙特異性促效劑LT β R結合蛋白的TAA結合結構域。例如，且不限於，該TAA結合結構域可包含本文實例7中描述的CLDN6結合結構域、CLDN18.2結合結構域、LRRC15結合結構域或MUC17結合結構域。其他合適的TAA結合結構域包括但不限於抗甲型胎兒蛋白 (AFP) 抗體或其結合結構域 (參見例如，Hansen等人的美國專利案號8,268,312，特此藉由引用將其全部併入)；抗CD44v6抗體或其結合結構域 (參見例如，Adolf等人的美國專利案號6,972,324，特此藉由引用將其全部併入)；抗碳酸酐酶IX (CAIX) 抗體或其結合結構域 (參見例如，Renner的WO 2011139375和Lenferink的美國專利案號10,487,153，特此藉由引用將其全部併入)；抗癌胚抗原 (CEA) 抗體或其結合結構域 (參見例如，Mossner等人的美國專利申請公開案號20160075795，特此藉由引用將其全部併入)；抗CD133抗體或其結合結構域 (參見例如，Vallera的美國專利案號11,098,109和Pfister等人的美國專利申請公開案號20200354468，特此藉由引用將其全部併入)；抗肝細胞生長因子受體 (c-MET) 抗體或其結合結構域 (參見例如，Harms等人的美國專利案號9,458,245，和Neijssen等人的美國專利案號9,068,011，特此藉由引用將其全部併入)；抗密連蛋白18.2抗體或其結合結構域 (參見例如，Dahlhoff等人的美國專利申請公開案號20200055932，和Hu等人的美國專利案號10,421,817，特此藉由引用將其全部併入)；抗密連蛋白6抗體或其結合結構域 (參見例如，Chambers等人的美國專利案號11,248,046，特此藉由引用將其全部併入)。

入)；抗表皮生長因子受體(EGFR)抗體或其結合結構域(參見例如，Chiu等人的美國專利案號9,695,242，和van de Winkel等人的美國專利案號9,458,236，特此藉由引用將其全部併入)；抗III型變體表皮生長因子受體(EGFRvIII)抗體或其結合結構域(參見例如，Kirschner等人的美國專利案號10,738,124，和Ellwanger等人的美國專利案號10,273,309，特此藉由引用將其全部併入)；抗促紅血球生成素產生肝細胞癌A2(EphA2)抗體或其結合結構域(參見例如，Bouchard等人的美國專利案號9,676,864，和Zhou和Marks的美國專利案號10,406,225，特此藉由引用將其全部併入)；抗上皮細胞黏附分子(EpCAM)抗體或其結合結構域(參見例如，Gunnarsson等人的美國專利案號8,637,017，和Harvey等人的美國專利案號9,790,274，特此藉由引用將其全部併入)；抗胎兒乙醯膽鹼受體抗體或其結合結構域(參見例如，Martinez-Martinez的WO 2013011030，特此藉由引用將其全部併入)；抗葉酸受體 α (FR α)結合結構域(參見例如，O'Shannessy的美國專利案號8,475,795，特此藉由引用將其全部併入)；抗神經節苷脂GD2(GD2)抗體或其結合結構域(參見例如，Scholz等人的美國專利申請公開案號20210189000，和Leusen等人的美國專利申請公開案號20210179732，特此藉由引用將其全部併入)；抗蛋白多糖-3(GPC3)抗體或其結合結構域(參見例如，Terrett等人的美國專利案號9,217,033，特此藉由引用將其全部併入)；抗鳥苷酸環化酶C(GUCY2C)抗體或其結合結構域(參見例如，Chang等人的美國專利申請公開案號20200010566，特此藉由引用將其全部併入)；抗人表皮生長因子受體1(HER1)抗體或其結合結構域(參見例如，Bossenmaier等人的美國專利申請公開案號20180100022，特此藉由引用將其全部併入)；抗人表皮生長因子受體2(ERBB2/HER2)抗體或其結合結構域(參見例如，Goeij等人的美國專利案號11,046,771，和Alper的美國專利案號8,722,362，特此藉由引用將其全部併入)；抗細胞間黏附分子1(ICAM-1)抗體或其結合結構域(參見例如，Hansson等人

的美國專利申請公開案號20160280788，和Abulrob等人的美國專利案號8,623,369，特此藉由引用將其全部併入）；抗白血球介素13受體 $\alpha 2$ （IL13R $\alpha 2$ ）抗體或其結合結構域（參見例如，Balyasnikova等人的美國專利申請公開案號20200181227，特此藉由引用將其全部併入）；抗白血球介素11受體 α （IL11R α ）抗體或其結合結構域（參見例如，Edwards等人的美國專利案號9,340,618，特此藉由引用將其全部併入）；抗Kirsten大鼠肉瘤病毒癌基因同源物（KRAS）抗體或其結合結構域（參見例如，Zhou等人的美國專利案號11,174,314，特此藉由引用將其全部併入）；抗L1細胞黏附分子（L1CAM）抗體或其結合結構域（參見例如，Hong等人的美國專利申請公開案號20220033494，特此藉由引用將其全部併入）；抗MAGE抗體或其結合結構域（參見例如，Bergeron等人的美國專利案號8,987,423，和Esslinger等人的美國專利申請公開案號20140093514，特此藉由引用將其全部併入）；抗肝細胞生長因子受體（HGF受體/MET）抗體或其結合結構域（參見例如，Burgess等人的美國專利案號8,609,090，和Goetsch等人的美國專利案號8,545,839，特此藉由引用將其全部併入）；抗黏蛋白1（MUC1）抗體或其結合結構域（參見例如，Denardo等人的美國專利案號7,183,388，和Yonezawa的美國專利案號8,951,526，特此藉由引用將其全部併入）；抗黏蛋白16（MUC16）抗體或其結合結構域（參見例如，Haber等人的美國專利案號10,941,208，特此藉由引用將其全部併入）；抗黏蛋白17（MUC17）抗體或其結合結構域（參見例如，Raum等人的美國專利申請公開案號20210130465，特此藉由引用將其全部併入）；抗自然殺手組2成員D（NKG2D）抗體或其結合結構域（參見例如，Urso等人的美國專利案號10,526,409，特此藉由引用將其全部併入）；抗癌/睪丸抗原1（CT6.1）抗體或其結合結構域（參見例如，美國專利申請公開案號20190382504，特此藉由引用將其全部併入）；抗前列腺幹細胞抗原（PSCA）抗體或其結合結構域（參見例如，Gudas等人的美國專利案號8,013,128，

特此藉由引用將其全部併入)；抗腎母細胞瘤1(WT-1)抗體或其結合結構域(參見例如，Benz等人的美國專利案號11,192,957，特此藉由引用將其全部併入)；抗半乳糖凝集素9(Gal9)抗體或其結合結構域(參見例如，Koide等人的美國專利案號10,344,091，特此藉由引用將其全部併入)；抗計畫性細胞死亡1配體1(PD-L1)抗體或其結合結構域(參見例如，Freeman等人的美國專利案號9,988,452，特此藉由引用將其全部併入)；抗滋養層糖蛋白(5T4癌胚抗原)抗體或其結合結構域(參見例如，Boghaert等人的美國專利案號8,044,178，特此藉由引用將其全部併入)；抗葉酸受體 α (FOLR1)抗體或其結合結構域(參見例如，Ando等人的美國專利案號9,207,238，特此藉由引用將其全部併入)；和抗腫瘤相關鈣訊息傳遞子2(滋養層細胞表面抗原2；TROP2)抗體或其結合結構域(參見例如，Tang等人的美國專利案號11,192,954，特此藉由引用將其全部併入)。

【0245】在另一個實施方式中，該雙特異性LT β R結合蛋白的腫瘤相關抗原結合結構域與腫瘤微環境(TME)的基質相關抗原(SAA)結合。合適的SAA包括但不限於纖連蛋白(FN1)、基質金屬蛋白酶-2(MMP2)、血小板衍生的生長因子受體- β (PDGFR β)、dickkopf相關蛋白3(DKK3)、血小板衍生的生長因子亞基B(PDGFB)、NUAK家族SNF1樣激酶1(NUAK1)、成纖維細胞生長因子(FGF1)、PDZ和LIM結構域蛋白4(PDLIM4)、gremlin 1(Grem1)和骨膜蛋白(POSTN)。

【0246】能夠結合該等SAA的結合蛋白在本領域中已經係已知的，並且可以容易地用作本文所描述的LT β R雙特異性結合蛋白的第二結合結構域。例如，且不限於，該第二結合結構域可包含抗纖連蛋白抗體或其結合結構域(參見例如，Kato等人的美國專利申請公開案號20100248262，特此藉由引用將其全部併入)、抗基質金屬蛋白酶-2抗體或其結合結構域(參見例如，Devy的美國專利案號8,013,125，特此藉由引用將其全部併入)、抗血小板衍生的生長因子受體- β

(PDGFR β)抗體或其結合結構域(參見例如,Zhu等人的美國專利案號7,740,850,特此藉由引用將其全部併入)、抗dickkopf相關蛋白3抗體或其結合結構域(參見例如,Hwang等人的美國專利申請公開案號20210340232,特此藉由引用將其全部併入)、抗血小板衍生的生長因子亞基B抗體或其結合結構域(參見例如,Arch等人的美國專利案號9,428,577,特此藉由引用將其全部併入)、抗NUAK家族SNF1樣激酶1(NUAK1)抗體或其結合結構域、抗成纖維細胞生長因子抗體或其結合結構域(參見例如,Ashkenazi等人的美國專利案號8,410,250,和Weng等人的美國專利案號8,481,168,特此藉由引用將其全部併入)、抗PDZ和LIM結構域蛋白4(PDLIM4)抗體或其結合結構域、抗gremlin 1抗體或其結合結構域(參見例如,Chalothorn等人的美國專利申請公開案號20180057580,和Dedi等人的美國專利申請公開案號20210163586,特此藉由引用將其全部併入)、以及抗骨膜蛋白抗體或其結合結構域(參見例如,Taniyama等人的美國專利案號8,372,957,特此藉由引用將其全部併入)。

【0247】在一個實施方式中,本揭露之多特異性LT β R結合蛋白係對於LT β R結合係單價的雙特異性LT β R結合蛋白。對於本文所描述的LT β R結合結構域,已經發現包含該等呈單價形式(但不是二價形式)的LT β R結合結構域的雙特異性分子表現出交聯依賴性LT β R激動作用。換句話說,包含單價LT β R結合結構域的雙特異性分子需要第一和第二結合結構域的結合以誘導LT β R受體聚集並實現LT β R激動作用。這種對LT β R具有單價的雙特異性構建體特別有利於將LT β R激動作用靶向特定組織,例如腫瘤微環境,因為活性取決於第一和第二結合結構域的結合。此外,本文揭露的LT β R結合物係基於它們與LT β R在不會抑制內源性LT β R配體結合和傳訊的區域(例如CRD4)的結合進行專門篩選和選擇的。本文揭露的LT β R結合蛋白的該等特性共同確保了,如果LT β R雙特異性結合蛋白在靶向腫瘤微環境之外結合LT β R, (i) 在不存在第二結合結構域與其靶標結

合的情況下，結合不會誘導脫靶LT β R傳訊，以及 (ii) 這樣的結合不會阻斷脫靶組織中的內源性LT β R配體（即，LIGHT和LT α 1 β 2）傳訊。該等設計特性提供了相對於先前描述的LT β R結合蛋白具有優異的安全性和功效性質的LT β R結合蛋白。

衍生物、變體和模擬物

【0248】 在一個實施方式中，本文所描述的LT β R結合蛋白在重鏈恒定區中包含一或多個胺基酸修飾，其提高半衰期/穩定性或使抗體更適用於表現/可製造性。在一個實施方式中，該LT β R結合蛋白被設計為防止或減少與Fc受體的相互作用。在示例性情況中，該結合蛋白係包含缺乏與Fc γ 受體相互作用能力的恒定區的穩定效應物無功能（SEFL）結合蛋白。胺基酸突變和製備SEFL抗體之方法在本領域中係已知的，參見例如，Liu等人, J. Biol. Chem[生物化學雜誌]. 292: 1876-1883 (2016)；和Jacobsen等人, J. Biol. Chem[生物化學雜誌]. 292: 1865-1875 (2017)，特此藉由引用將其全部併入。在示例性方面，本文所描述的LT β R結合蛋白被修飾為包含以下突變中的一或多個，根據EU系統進行編號：L242C、A287C、R292C、N297G、V302C、L306C和/或K334C。在示例性方面，本文所描述的LT β R結合蛋白包含N297G取代以形成SEFL結合蛋白。在示例性方面，本文所描述的LT β R結合蛋白包含A287C、N297G和L306C取代以形成SEFL結合蛋白。在其他示例性方面，該LT β R結合蛋白包含R292C、N297G和V302C取代以形成基於SEFL2-2抗體的分子。

【0249】 在一個實施方式中，如本文所描述的促效劑LT β R結合蛋白可以包含其他半衰期延長（HLE）修飾。在一個實施方式中，該HLE修飾發生在重鏈恒定區中，並包含以下胺基酸取代中的一或多個，根據EU系統編號：M252Y、S254T和T256E。在示例性情況中，該LT β R結合蛋白包含M252Y、S254T和T256E取代中的一個或兩個。在示例性情況中，本揭露之LT β R結合蛋白包含M252Y、S254T

和T256E中的全部三個。在一個實施方式中，該HLE修飾發生在重鏈恒定區中，並包含以下取代中的一或多個，根據EU系統編號：L309D、Q311H和N434S。在示例性情況中，本揭露之LT β R結合蛋白包含L309D、Q311H和N434S取代中的一個、兩個或全部三個。在示例性情況中，該LT β R結合蛋白包含L309D、Q311H和N434S取代中的全部三個。在一個實施方式中，本文揭露的LT β R結合蛋白包含SEFL或SEFL2-2修飾與本文所描述的任何HLE修飾的組合。

【0250】 在某些實施方式中，該促效劑LT β R結合蛋白的變體包括糖基化變體，其中糖基化位點的數量和/或類型與親本多肽的胺基酸序列相比已經改變。在某些實施方式中，變體包含比天然蛋白質更多或更少數目的N連接的糖基化位點。可替代地，消除此序列的取代將移除已存在的N連接的碳水化合物鏈。還提供了N連接的碳水化合物鏈的重排，其中消除一或多個N連接的糖基化位點（典型地天然存在的那些）並且創造一或多個新的N連接的位點。額外的結合蛋白變體包括半胱胺酸變體，其中與親本胺基酸序列相比，一或多個半胱胺酸殘基缺失或被取代為另一種胺基酸（例如絲胺酸）。當抗體必須重新折疊成生物學上活性構象時，如在分離不溶性包涵體之後，半胱胺酸變體可能有用。半胱胺酸變體一般具有少於天然蛋白質的半胱胺酸殘基，且典型地具有偶數個以使由未配對的半胱胺酸引起的相互作用最小。

【0251】 在一個實施方式中，本文揭露的促效劑LT β R結合蛋白（例如，促效劑LT β R抗體和雙特異性促效劑LT β R結合蛋白）包括翻譯後修飾的變體。例如，在一個實施方式中，包含重鏈的促效劑LT β R結合蛋白的C末端離胺酸殘基已缺失。

【0252】 其他期望的胺基酸取代（無論是保守的還是非保守的）和缺失可以由熟悉該項技術者在需要這樣的取代或缺失時來確定。在某些實施方式中，胺基酸取代可用於例如鑑定與功能相關的結合蛋白的重要殘基、增加或降低抗體

對本文所描述的感興趣靶標的親和力、降低對蛋白水解的易感性、降低對氧化的易感性、改變形成蛋白複合物的結合親和力，和/或賦予或修飾此類多肽的其他物理化學或功能性質。根據某些實施方式，可在天然存在的序列中（在某些實施方式中，在形成分子間接觸的一或多個結構域外的多肽部分中）進行單個或多個胺基酸取代（在某些實施方式中為保守胺基酸取代）。在某些實施方式中，保守胺基酸取代通常可能不會實質性地改變親本序列的結構特徵（例如，替換胺基酸不應傾向於破壞親本序列中發生的螺旋或破壞表徵親本序列的其他類型的二級結構）。領域公認的多肽二級和三級結構之實例描述於Proteins, Structures and Molecular Principles [蛋白質、結構和分子原理] (Creighton編輯, W. H. Freeman and Company [W.H.弗裡曼公司], 紐約 (1984))；Introduction to Protein Structure [蛋白質結構簡介] (C.Branden及J.Tooze編, Garland Publishing [加蘭出版社], 紐約, 紐約州。(1991))；以及Thornton等人 Nature [自然] 354:105 (1991)，將該等文獻各自藉由引用併入本文。

編碼LTβR結合蛋白的核酸分子

【0253】 本揭露進一步提供了包含編碼本揭露之促效劑LTβR結合蛋白的核苷酸序列的核酸分子。本文所用的「核酸分子」涵蓋多核苷酸和寡核苷酸，通常係指DNA或RNA的聚合物，或其修飾形式，其可為單鏈或雙鏈，從天然來源合成或獲得（例如，分離和/或純化），其可以含有天然、非天然或改變的核苷酸，並且其可以含有天然的、非天然或改變的核苷酸間鍵，例如磷酸醯胺鍵或硫代磷酸鍵，而不是在未修飾的寡核苷酸的核苷酸之間發現的磷酸二酯。核酸分子可以包含編碼本揭露之任何促效劑LTβR結合蛋白的任何核苷酸序列。在一些實施方式中，核酸不包含任何插入、缺失、倒位和/或取代。在其他實施方式中，核酸包含一或多個插入、缺失、倒位和/或取代。

【0254】 在一些方面，本揭露之核酸分子係重組的。如本文所用，術語「重

組」係指藉由使用實驗室方法連接天然或合成核酸片段以形成自然界中未發現的核酸分子而在活細胞外構建的分子。

【0255】 在一些方面，本揭露之核酸分子係使用本領域已知的程式基於化學合成和/或酶連接反應構建的。參見例如，Sambrook等人, *Molecular Cloning: A Laboratory Manual* [分子選殖：實驗室手冊].第3版, Cold Spring Harbor Press, Cold Spring Harbor [冷泉港實驗室出版社], NY 2001；和Ausubel等人, *Current Protocols in Molecular Biology* [分子生物學現代方法], Greene Publishing Associates [格林出版公司] 和John Wiley & Sons [約翰·威利父子公司], NY [紐約州], 1994。例如，核酸分子可以使用天然存在的核苷酸或多種修飾的核苷酸進行化學合成，該等核苷酸旨在提高分子的生物穩定性或增加雜交時形成的雙鏈體的物理穩定性（例如，硫代磷酸衍生物和吡啶取代的核苷酸）。可用於生成核酸的修飾核苷酸之實例包括但不限於5-氟尿嘧啶、5-溴尿嘧啶、5-氯碘尿嘧啶、5-碘尿嘧啶、次黃嘌呤、黃嘌呤、4-乙醯胞嘧啶、5-(羧基羥甲基)尿嘧啶、5-羧甲基胺基甲基-2-硫尿苷、5-羧甲基胺基甲基尿嘧啶、二氫尿嘧啶、 β -D-半乳糖基Q核苷(queosine)、肌苷、 N^6 -異戊烯基腺嘌呤、1-甲基鳥嘌呤、1-甲基肌苷、2,2-二甲基鳥嘌呤、2-甲基腺嘌呤、2-甲基鳥嘌呤、3-甲基胞嘧啶、5-甲基胞嘧啶、N-取代的腺嘌呤、7-甲基鳥嘌呤、5-甲基胺基尿嘧啶、5-甲氧基胺基甲基-2-硫尿嘧啶、 β -D-甘露糖基Q核苷(queosine)、5'-甲氧基羧甲基尿嘧啶、5-甲氧基尿嘧啶、2-甲硫基- N^6 -異戊烯基腺嘌呤、尿嘧啶-5-氧乙酸(v)、wybutoxosine、假尿嘧啶、Q核苷(queosine)、2-硫胞嘧啶、5-甲基-2-硫尿嘧啶、2-硫尿嘧啶、4-硫尿嘧啶、5-甲基尿嘧啶、尿嘧啶-5-氧乙酸甲酯、3-(3-胺基-3-N-2-羧丙基)尿嘧啶和2,6-二胺基嘌呤。

【0256】 在一個實施方式中，該核酸分子包含一或多個多核苷酸，其編碼促效劑LT β R結合蛋白之全部或部分，例如如本文揭露的結合蛋白的一條或兩條

鏈。多核苷酸可為適合所期望用途或功能的任何長度，並且可以可操作地偶合到一或多個額外序列（例如調節序列）和/或是較大核酸分子（例如載體）的一部分。如果調節序列影響多核苷酸序列的表現（例如，表現的水平、時間或位置），則多核苷酸「可操作地偶合」或「可操作地連接」至調節序列。多核苷酸分子可為單鏈或雙鏈，並且可以包含RNA和/或DNA核苷酸以及其人工變體（例如，肽核酸）。

【0257】 在一個實施方式中，本揭露之多核苷酸編碼上文揭露的促效劑LT β R結合蛋白，並包含編碼上文所描述的CDR中的任一個、任兩個、任三個、任四個、任五個或任六個的序列，包括表2、6和10中提供的重鏈CDR和表3、7和11中提供的輕鏈CDR。

【0258】 在一個實施方式中，本揭露之多核苷酸分子包含編碼與LT β R的CRD4結合的LT β R結合蛋白的VH結構域和VL結構域的核苷酸序列。因此，在一個實施方式中，該多核苷酸分子包含選自以下的編碼VH和VL結構域的核苷酸序列：SEQ ID NO: 119的VH胺基酸序列和SEQ ID NO: 120的VL胺基酸序列；SEQ ID NO: 121的VH胺基酸序列和SEQ ID NO: 122的VL胺基酸序列；SEQ ID NO: 123的VH胺基酸序列和SEQ ID NO: 124的VL胺基酸序列；SEQ ID NO: 125的VH胺基酸序列和SEQ ID NO: 126的VL胺基酸序列；SEQ ID NO: 127的VH胺基酸序列和SEQ ID NO: 128的VL胺基酸序列；SEQ ID NO: 129的VH胺基酸序列和SEQ ID NO: 130的VL胺基酸序列；SEQ ID NO: 131的VH胺基酸序列和SEQ ID NO: 132的VL胺基酸序列；SEQ ID NO: 133的VH胺基酸序列和SEQ ID NO: 134的VL胺基酸序列；SEQ ID NO: 135的VH胺基酸序列和SEQ ID NO: 136的VL胺基酸序列；SEQ ID NO: 137的VH胺基酸序列和SEQ ID NO: 138的VL胺基酸序列；SEQ ID NO: 139的VH胺基酸序列和SEQ ID NO: 140的VL胺基酸序列；SEQ ID NO: 141的VH胺基酸序列和SEQ ID NO: 142的VL胺基酸序列；SEQ ID NO: 143的VH

胺基酸序列和SEQ ID NO: 144的VL胺基酸序列；SEQ ID NO: 145的VH胺基酸序列和SEQ ID NO: 146的VL胺基酸序列；SEQ ID NO: 147的VH胺基酸序列和SEQ ID NO: 148的VL胺基酸序列；SEQ ID NO: 149的VH胺基酸序列和SEQ ID NO: 150的VL胺基酸序列；SEQ ID NO: 151的VH胺基酸序列和SEQ ID NO: 152的VL胺基酸序列；SEQ ID NO: 153的VH胺基酸序列和SEQ ID NO: 154的VL胺基酸序列；SEQ ID NO: 155的VH胺基酸序列和SEQ ID NO: 156的VL胺基酸序列；以及SEQ ID NO: 157的VH胺基酸序列和SEQ ID NO: 158的VL胺基酸序列。

【0259】 在一個實施方式中，本揭露之多核苷酸分子包含編碼促效劑LTβR結合蛋白的VH結構域和VL結構域的核苷酸序列，該促效劑LTβR結合蛋白與LIBC219081和LIBC218979示例性LTβR結合物競爭結合LTβR的CRD4。因此，在一個實施方式中，該多核苷酸分子包含選自以下的編碼VH和VL結構域的核苷酸序列：SEQ ID NO: 401的VH胺基酸序列和SEQ ID NO: 402的VL胺基酸序列；SEQ ID NO: 403的VH胺基酸序列和SEQ ID NO: 404的VL胺基酸序列；SEQ ID NO: 405的VH胺基酸序列和SEQ ID NO: 406的VL胺基酸序列；SEQ ID NO: 407的VH胺基酸序列和SEQ ID NO: 408的VL胺基酸序列；SEQ ID NO: 409的VH胺基酸序列和SEQ ID NO: 410的VL胺基酸序列；SEQ ID NO: 411的VH胺基酸序列和SEQ ID NO: 412的VL胺基酸序列；SEQ ID NO: 413的VH胺基酸序列和SEQ ID NO: 414的VL胺基酸序列；SEQ ID NO: 415的VH胺基酸序列和SEQ ID NO: 416的VL胺基酸序列；SEQ ID NO: 417的VH胺基酸序列和SEQ ID NO: 418的VL胺基酸序列；SEQ ID NO: 419的VH胺基酸序列和SEQ ID NO: 420的VL胺基酸序列；SEQ ID NO: 421的VH胺基酸序列和SEQ ID NO: 422的VL胺基酸序列；SEQ ID NO: 423的VH胺基酸序列和SEQ ID NO: 424的VL胺基酸序列；SEQ ID NO: 425的VH胺基酸序列和SEQ ID NO: 426的VL胺基酸序列；SEQ ID NO: 427的VH胺基酸序列和SEQ ID NO: 428的VL胺基酸序列；SEQ ID NO: 429的VH胺基酸序

列和SEQ ID NO: 430的VL胺基酸序列；SEQ ID NO: 431的VH胺基酸序列和SEQ ID NO: 432的VL胺基酸序列；SEQ ID NO: 433的VH胺基酸序列和SEQ ID NO: 434的VL胺基酸序列；SEQ ID NO: 435的VH胺基酸序列和SEQ ID NO: 436的VL胺基酸序列；SEQ ID NO: 437的VH胺基酸序列和SEQ ID NO: 438的VL胺基酸序列；SEQ ID NO: 439的VH胺基酸序列和SEQ ID NO: 440的VL胺基酸序列；SEQ ID NO: 441的VH胺基酸序列和SEQ ID NO: 442的VL胺基酸序列；SEQ ID NO: 443的VH胺基酸序列和SEQ ID NO: 444的VL胺基酸序列；SEQ ID NO: 445的VH胺基酸序列和SEQ ID NO: 446的VL胺基酸序列；SEQ ID NO: 447的VH胺基酸序列和SEQ ID NO: 448的VL胺基酸序列；SEQ ID NO: 449的VH胺基酸序列和SEQ ID NO: 450的VL胺基酸序列；SEQ ID NO: 451的VH胺基酸序列和SEQ ID NO: 452的VL胺基酸序列；SEQ ID NO: 453的VH胺基酸序列和SEQ ID NO: 454的VL胺基酸序列；SEQ ID NO: 455的VH胺基酸序列和SEQ ID NO: 456的VL胺基酸序列；SEQ ID NO: 457的VH胺基酸序列和SEQ ID NO: 458的VL胺基酸序列；SEQ ID NO: 459的VH胺基酸序列和SEQ ID NO: 460的VL胺基酸序列；SEQ ID NO: 461的VH胺基酸序列和SEQ ID NO: 462的VL胺基酸序列；SEQ ID NO: 463的VH胺基酸序列和SEQ ID NO: 464的VL胺基酸序列；SEQ ID NO: 465的VH胺基酸序列和SEQ ID NO: 466的VL胺基酸序列；SEQ ID NO: 467的VH胺基酸序列和SEQ ID NO: 468的VL胺基酸序列；SEQ ID NO: 469的VH胺基酸序列和SEQ ID NO: 470的VL胺基酸序列；SEQ ID NO: 471的VH胺基酸序列和SEQ ID NO: 472的VL胺基酸序列；以及SEQ ID NO: 473的VH胺基酸序列和SEQ ID NO: 474的VL胺基酸序列。

【0260】 在一個實施方式中，本揭露之多核苷酸分子包含編碼結合人LTβR的促效劑LTβR結合蛋白的VH結構域和VL結構域的核苷酸序列。因此，在一個實施方式中，該多核苷酸包含選自以下的編碼VH和VL結構域的核苷酸序列：

SEQ ID NO: 644的VH胺基酸序列和SEQ ID NO: 645的VL胺基酸序列；SEQ ID NO: 646的VH胺基酸序列和SEQ ID NO: 647的VL胺基酸序列；SEQ ID NO: 648的VH胺基酸序列和SEQ ID NO: 649的VL胺基酸序列；SEQ ID NO: 650的VH胺基酸序列和SEQ ID NO: 651的VL胺基酸序列；SEQ ID NO: 652的VH胺基酸序列和SEQ ID NO: 653的VL胺基酸序列；SEQ ID NO: 654的VH胺基酸序列和SEQ ID NO: 655的VL胺基酸序列；SEQ ID NO: 656的VH胺基酸序列和SEQ ID NO: 657的VL胺基酸序列；SEQ ID NO: 658的VH胺基酸序列和SEQ ID NO: 659的VL胺基酸序列；SEQ ID NO: 660的VH胺基酸序列和SEQ ID NO: 661的VL胺基酸序列；SEQ ID NO: 662的VH胺基酸序列和SEQ ID NO: 663的VL胺基酸序列；SEQ ID NO: 664的VH胺基酸序列和SEQ ID NO: 665的VL胺基酸序列；SEQ ID NO: 666的VH胺基酸序列和SEQ ID NO: 667的VL胺基酸序列；SEQ ID NO: 668的VH胺基酸序列和SEQ ID NO: 669的VL胺基酸序列；SEQ ID NO: 670的VH胺基酸序列和SEQ ID NO: 671的VL胺基酸序列；SEQ ID NO: 672的VH胺基酸序列和SEQ ID NO: 673的VL胺基酸序列；SEQ ID NO: 674的VH胺基酸序列和SEQ ID NO: 675的VL胺基酸序列；SEQ ID NO: 676的VH胺基酸序列和SEQ ID NO: 677的VL胺基酸序列；SEQ ID NO: 678的VH胺基酸序列和SEQ ID NO: 679的VL胺基酸序列；SEQ ID NO: 680的VH胺基酸序列和SEQ ID NO: 681的VL胺基酸序列；SEQ ID NO: 682的VH胺基酸序列和SEQ ID NO: 683的VL胺基酸序列；SEQ ID NO: 684的VH胺基酸序列和SEQ ID NO: 685的VL胺基酸序列；SEQ ID NO: 686的VH胺基酸序列和SEQ ID NO: 687的VL胺基酸序列；SEQ ID NO: 688的VH胺基酸序列和SEQ ID NO: 689的VL胺基酸序列；SEQ ID NO: 690的VH胺基酸序列和SEQ ID NO: 691的VL胺基酸序列。下表14中提供了編碼本文揭露的促效劑LTβR結合蛋白的VH和VL結構域的示例性核酸序列。

[表14]. LTβR結合蛋白的核酸序列

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第 187 頁，共 297 頁(發明說明書)

LIBC. 編號	鏈	序列	SEQ ID
218990	HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGG GCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCG GCGACTATATGTACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGA GTGGATGGGATGGATCAACCCTAACAGTGGTGGCACAACTATGCA AAGAAGTTTCAGGGCAGGGTCACCATGACCAGGGACACGTCCATC AGCACAGCCTACATGGAGCTGAGCAGGCTGAGATCTGACGACACG GCCGTGTATTACTGTGCGAGAGAAGGGAGCAGTGGCTGGTCCGCCG AATACTTCCAGCACTGGGGCCAGGGCACCTGGTCACCGTCTTTTC AGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAG GACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAATCAGGCGCTC TGACCAGCGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGG ACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTC GGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAAC ACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCC CACCGTGCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCCTCTTC CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGG TCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCA GTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACA AAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGC GTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACA AGTGCAAGGTCAGCAACAAAGGCCTCCCAGCCCCCATCGAGAAAA CCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACA CCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCT GACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCT CCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCAC CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCC GTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCT CCCTGTCTCCGGGCAAATAG	857
	LC	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTNTCNTGCAGGGCCAGTCAGAGTGTTAGCAG CAGCTTCTTAGCCTGGTACCAGCAGAACTTGGCCAGGCTCCCAGG CTCCTCATGTATGGTGCATCCCGCAGGGCCACAGGCATCCCAGACA	858

LIBC. 編號	鏈	序列	SEQ ID
		GGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAG CAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTAT GGTACCTCACCTCTCTCTTTTCGGCGGAGGGACCAAGGTGGAGATCA AACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT GAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATA ACTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACG CCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACA GCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCA AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCC ATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG AGTGTTAG	
218994	HC	CAGGTGCAACTGGTGGAGTCTGGGGGAGCCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAG CTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAATTATATGGTATGATGGAAGTGATGAATACTATGCAG ACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAA CACGTTGTATCTGCAAATGAACAGTGTGAGAGACGAGGACACGGCT CTGTATTACTGTGTGAGAGGGGACAGTGAGGACTTCTACTACTACG ATTTGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGC CTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGG AGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACT ACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCTCTGAC CAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTC TACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCA CCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAA GGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCACCG TGCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCC AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACG TGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCA ACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGC CACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCT CACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTG CAAGGTCAGCAACAAAGGCCTCCCAGCCCCATCGAGAAAACCAT CTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT	859

LIBC. 編號	鏈	序列	SEQ ID
		GCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGAC CTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGG GAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCC ATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGT GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC TGTCTCCGGGCAAATAG	
	LC	CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGAC AGAAGGTCACCATCTCCTGTCTGGAAGCAGCTCCAACATTGGGAA GAATTATGTTTCCTGGTACCAACACCTCCCAGGCACAGCCCCAAA CTCCTCATTTATGACAATAATAAGCGACCCTCAGGAATTCCTGACC GATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCATCAC CGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGG GATCACAGCCTGAGTGCTAGTTATGTCTTCGGAAGTGGGACCAAGG TCACCGTCCTAGGTGAGCCCAAGGCTGCACCCTCGGTCACTCTGTTC CCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGT GTCTCATCAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAA GGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAAACCACCACACC CTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAG CCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAG GTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCCTACA GAATGTTCATAG	860
219058	HC	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGG GGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAC CTCTGGCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGA GTGGGTCTCATCCGTTAGTAGTAGTGGTAGTTACATATACTACGCA GACTCAGTGAAGGGCCGATTACCATCTCCAGAGACAACGCCAAG AACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACG GCTGTCTATTACTGTGCTGGAGCTCGGTATAACTGGCACTTTGATGC TTCTGATATCTGGGGCCAAGGGACAGTGGTCAACCGTCTCTTCAGCC AGCACCAAGGGGCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTA CTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCCCTGACC AGCGGCGTGACACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCT	861

LIBC. 編號	鏈	序列	SEQ ID
219081		ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCAC GAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAA GGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCATCA TGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCC CCCAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTC ACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAG TTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAA AGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCG TCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAA GTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACC ATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACC CTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTG ACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGT GGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTC CCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTAACC GTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTC CCTGTCTCTGGGCAAATAG	
	LC	GACATCCAGATGACCCAGTCTCCGTCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGC GATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAACCTCC TGATCTATGCTGCATCCAGTTTGCACAGTGGGGTCCCATCAAGGTTT AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTC TCCTACCTGAGGATTTTGAACCTTACTACTGTCAACAGAGTTACAAT ACCCCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA G	862
219081	HC	CCGATTCATCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTG	863

LIBC. 編號	鏈	序列	SEQ ID
		CAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTATATTACTGTG CGCGAGATCGGGTAGCAGCTCATCCGGCCTACTACTACGGTCTGGA CGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCACC AAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCT CCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCC CGAACCGGTGACGGTGTCTGTGGAACTCAGGCGCTCTGACCAGCGGC GTGCACACCTTCCCAGCTGTCTACAGTCCTCAGGACTCTACTCCCT CAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACC TACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGAC AAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCACCGTGCCAG CACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCAAACCC AAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGG TGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTA CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGA GGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTT GTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTC AGCAACAAAGGCCTCCCAGCCCCATCGAGAAAACCATCTCCAAA ACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCAT CCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAA TGGGCAGCCGGAGAACAATAACAAGACCACACCTCCCATGCTGGA CTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAG AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATG AGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCC GGGCAAATAG	
	LC	TCCTATGAGCTGACACAGCCACCCTCGGTGTCATTGTCCCCAGGAC AGACGGCCAGGATCACCTGCTCTGGAGATGCATTGCCAAACCATTA TGCTTATTGGTACCAGCAGAAGCCAGGCCAGGCCCTGTACTGGTG ATATTTAAAGACAATGAGAGGCCCTCAGGGATCCCTGAGCGATTCT CTGGCTCCAGTTCAGGGACAACAGTCACGTTGACCATCAGTGGAGT CCAGGCAGAAGACGAGGCTGACTATTACTGTCAATCAGCAGACAG CAGTGGTTCTTATGTGATTTTCGGCGGAGGGACCAAAGTACCGTC CTAGGTCAGCCAAGGCTGCACCCTCGGTCACTCTGTTCCCGCCCTC CTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATC	864

LIBC. 編號	鏈	序列	SEQ ID
		AGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATA GCAGCCCCGTCAAGGCGGGAGTGGAACCACCACACCCTCCAAAC AAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGC CTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGC ATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCCTACAGAATGTT CATAG	
219097	HC	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTAAAGCCTGGG GGGTCCCTTAGACTCTCCTGTGCAGCCTCTGGATTCACTTTCAATGA CGCCTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGA GTGGGTTGGCCGTATTAAAACCAAACTGATGGTGGGACAACAGA CTACGCTGCACCCGTGAAAGGCAGAATCACCATCTCAAGAGATGAT TCAAAAAACACGCTGTATCTGCAAATGAACAGCCTGAAAACCGAG GACACAGCCGTGTATTACTGTACCACCGACTACGGTGACTACGAGT ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAA GGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC GAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG AACCGGTGACGGTGTCTGTGGAATCAGGCGCTCTGACCAGCGGCGT GCACACCTTCCCAGCTGTCTACAGTCCTCAGGACTCTACTCCCTCA GCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTA CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAA GACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCA CCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCCTAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGT GGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTAC GTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAG GAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTG TGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCA GCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAAC CAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCC CGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTC AAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGGCAGCCGGAGAACAACACTACAAGACCACACCTCCCATGCTGGAC TCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGA GCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGA	865

LIBC. 編號	鏈	序列	SEQ ID
		GGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCG GGCAAATAG	866
	LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGACAAGTCAGAGCATTAGTAGA TATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCCTAAACTCC TGATCTATGGTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTT CAGTGGCAGTGGATCTGGGACAGATTCTACTCTCACCATCAGCAGT CTGCAACCTGAAGATTTTGCAACTTACTATTGTCATCAGAGTTACAG TACCCCTCCGACGTTCTGGCCAAGGGACCAAGGTGGAAATCAAACG AACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGC AGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTC TATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTC CAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAG GACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCA GACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAG GGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTT AG	
218979	HC	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTAG CTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAG ACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAA CACGCTGTCTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCT GTGTATTACTGTGCGAGAGAGCGTATAGCAGCAGCCCCTTACTACT ACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCAGCCAGCACCAAGGGGCCATCCGTCTTCCCCCTGGCGCCCTGC TCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCA AGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCAAGGCGC CCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCT TGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCA ACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATG CCCATCATGCCCAGCACCTGAGTTCTTGGGGGGACCATCAGTCTTC CTGTTCCCCCAAAACCAAGGACACTCTCATGATCTCCCGGACCC	867

LIBC. 編號	鏈	序列	SEQ ID
		CTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCG AGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGT GGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCG AGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGG TGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGT CAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACC ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAG GCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTC ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAG AGCCTCTCCCTGTCTCTGGGCAAATAG	
	LC	TCCTATGAACTGACACAGCCACCCTCGGTGTCGGTGTCCCCAAGAC AGACGGCCAGGATCACCTGCTCTGGAGATGCATTGCCAAAGCATT TGCTTATTGGTACCAGCAGAAGCCAGGCCAGGCCCTGTGCTGGTG ATATATAAAGACAATGAGAGGCCCTCAGGGATCCCTGAGCGATTCT CTGGCTCCAGCTCAGGGACAACGTGTCACGTTGACCATCAGTGGAGT CCAGGCAGAAGACGAGGCTGACTATTACTGTCAATCAGCAGACAA CACTGGTTCTTATATGGTATTTCGGCGGAGGGACCAAGCTGACCGTC CTAGGTCAGCCCAAGGCTGCACCCTCGGTCACTCTGTTCCCGCCCTC CTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATC AGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATA GCAGCCCCGTCAAGGCGGGAGTGGAACCACCACACCCTCCAAAC AAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGC CTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGC ATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTT CATAG	868
219037	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACGGGTGAAGCCTTCA CAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAACAG TGGTGGTTACTTCTGGAGCTGGATCCGCCAGCACCCAGGGAAGGTC CTGGAGTGGATTGGGTACAGCCATTACAGTGGTACCACCTACTACA ATCCGTCCCTCAAGAGTCGAGTAACCATATCAGTAGACACGTCTAA GAACCAGCTCTCCCTGAAGCTGAACTCTGTGAATGCCGCGGACACG	869

LIBC. 編號	鏈	序列	SEQ ID
		GCCGTGTATTACTGTGCGAGAGTGCCTGATGGGGAAGACTACTTTG ACTACTGGGGCCAGGGAGCCCTGGTCACCGTCTCCTCAGCCAGCAC CAAGGGGCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACC TCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCC CCGAACCGGTGACGGTGTCTGTGGAAGTCAAGGCGCCCTGACCAGCGG CGTGACACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCC TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGAC CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGA CAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCATCATGCCCA GCACCTGAGTTCCTGGGGGGACCATCAGTCTTCTGTTCCCCCCAA AACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTG CGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAA CTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCC GCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTC ACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGC AAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCT CCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGC CCCCATCCCAGGAGGAGATGACCAAGAACCAGGTACGCCTGACCT GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGA GAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGT GCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTAACCGTG GACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGA TGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCT GTCTCTGGGCAAATAG	
	LC	GACCTCCAGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGACCATTAGTAGT TATTTAAATTGGTATCAGCAGAAACCGGGGAAAGCCCCCTAAACTCC TGATCTATGATGCCTCAAGTTTGCAAAGTGGGGTCCCATCAAGGTT CAGTGGCAGTGGATCTGGGACAGATTTACTCTCACCATCAGCAGT CTGCAACCTGAAGATTTTGAAACTTACTACTGTCAACAGAGTTTCA GTGCCCCGATCACCTTCGGCCAAGGGACACGACTGGAAATTAAACG AACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGC AGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTC TATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTC	870

LIBC. 編號	鏈	序列	SEQ ID
		CAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAG GACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCA GACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAG GGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTT AG	
219098	HC	GAGGTGCAGTTGTTGGAGTCTGGGGGAGGCTTGGTTCAGCCTGGGG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGC TATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGT GGGTCTCAACTATTAGTGGTAGTGGTGGTAGCACATACTACGCAGA CTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAAC ACGCTGAATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCC GTATATTACTGTGCGAAAGTTAGGGATAACTGGAACACTACGACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTC CACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGC ACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACT TCCCCGAACCGGTGACGGTGTCGTGGAACCTCAGGCGCTCTGACCAG CGGCGTGACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACT CCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCA GACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGT GGACAAGACAGTTGAGCGCAAATGTTGTGTGCGAGTGCCACCGTGC CCAGCACCACTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCCTAA AACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTG CGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAAC TGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCA CGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCA CCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCA AGGTCAGCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTC CAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG AGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCCATG CTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA CAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATG CATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT	871

LIBC. 編號	鏈	序列	SEQ ID
		CTCCGGGCAAATAG	
	LC	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTCACCCTTGG AGAGTCGGCCTCCATCTCCTGTAGGTGTAGTCAGAGCCTCCTGTAT AGTAGTGGATACATCGATTTGGATTGGTACCTGCAGAAGCCAGGGC AGTCTCCACAGCTCCTGATCTATTTGGGTTCTAATCGGGCCTCCGGG GTCCCTGACAGGTTCA GTGGCAGTGGATCAGGCACAGATTTTACAC TGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTG CATGCAAAC TATACAACTCCGCTCACTTTCGGCGGAGGGACCAAG GTGGAGATCAAACGAACGGTGGCTGCACCATCTGTCTTCATCTTCC CGCCATCTGATGAGCAGTTGAAATCTGGA ACTGCCTCTGTTGTGTG CCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAG GTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAG AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGA CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCG AAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAA CAGGGGAGAGTGTTAG	872
219098.0 01	HC	GAGGTGCAGTTGTTGGAGTCTGGGGGAGGCTTG GTTCAGCCTGGGG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGC TATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGT GGGTCTCAACTATTAGTGGTAGTGGTGGTAGCACATACTACGCAGA CTCCGTGAAGGGCCGGTTCAACCATCTCCAGAGACAATTCCAAGAAC ACGCTGAATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCC GTATATTACTGTGCGAAAGTTAGGGATAACTGGA ACTACGACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTC CACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGC ACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACT TCCCCGAACCGGTGACGGTGTCGTGGA ACTCAGGCGCTCTGACCAG CGGCGTGACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACT CCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCA GACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGT GGACAAGACAGTTGAGCGCAAATGTTGTGTGCGAGTGCCACCGTGC CCAGCACCACCTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCAA AACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACAGTG CGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAAC	873

LIBC. 編號	鏈	序列	SEQ ID
		TGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCA CGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCA CCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCA AGGTCAGCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTC CAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG AGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCCATG CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTACCGTGGA CAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATG CATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT CTCCGGGCAAATAG	
	LC	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTCACCCTTGG AGAGTCGGCCTCCATCTCCTGTAGGAGCAGTCAGAGCCTCCTGTAT AGTAGTGGATACATCGATTTGGATTGGTACCTGCAGAAGCCAGGGC AGTCTCCACAGCTCCTGATCTATTTGGGTTCTAATCGGGCCTCCGGG GTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACAC TGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTG CATGCAAACACTATACAACTCCGCTCACTTTCGGCGGAGGGACCAAG GTGGAGATCAAACGAACGGTGGCTGCACCATCTGTCTTCATCTTCC CGCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTG CCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAG GTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAG AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGA CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCG AAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAA CAGGGGAGAGTGTTAG	874
219051	HC	CAGGTGCAACTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGG GCCTCAGTGAAGGTCTCTTGCAAGGCTTCTGGATACACCTTCACCG GCTACTATCTACACTGGGTGCGACAGGCCCTGGACAAGGGCTTGA GTGGATGGGATGGATCAACCCTAATATTGGTGTACAGACTGTGCA CAGAAGTTTCAGGACAGGGTCACCATGACCAGGGACACGTCCATCA GTACAGCCTACATGGAGCTGAGCAGGCTGATATCTGACGACACGGC CGTGTATTACTGTACGGTACGTGGATATAATGATGATTACGACTTTG	875

LIBC. 編號	鏈	序列	SEQ ID
		ACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCAGCAC CAAGGGGGCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACC TCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCC CCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCCCTGACCAGCGG CGTGACACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCC TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGAC CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGA CAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCATCATGCCCA GCACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCCAA AACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTG CGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAA CTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCC GCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTC ACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGC AAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCT CCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGC CCCCATCCCAGGAGGAGATGACCAAGAACCAGGTACGCCTGACCT GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGA GAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGT GCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTAACCGTG GACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGA TGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCT GTCTCTGGGCAAATAG	
	LC	GATGTTGTGATGACCCAGACTCCACTCTCTCTGTCCGTCACCCCTGG ACAGCCGGCCTCCATCTCCTGCAAGTCTCGTCAGAGCCTCCTGCAT AGAGATGGAAAGACCTATTTGTATTGGTACCTGCAGAAGCCAGGCC AGCCTCCACAACCTCCTGATCTATGAAGTTTCCAACCGGTTCTCTGGA GTGCCAAATAGATTCAGTGGCAGCGGGTCAGGGACAGATTTACAC TGAAAATCAGCCGGGTGGAGGCTGAAGATGTTGGGGTTTATTACTG CATGCAAAGTATACAGCTTCCGCTCATTTTCGGCGGAGGGACCAGG GTTGACATCAAACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCC GCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGC CTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGG TGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGA	876

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218989	HC	CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAACCCACAC AGACCCCTCACGCTGACCTGCACCTTCACTGGGTTTTCACTCAGCACT AGTGGAATGGGTGTGGGCTGGATCCGTCAGCCCCCAGGAAAGGCC CTGGAGTGGCTTGCACTCATTTATTGGAATGGTGGTAAGCTCTACA GCCCATCTCTGAAGAACAGGGCTCACCATCACCAAGGACACCTCCAA AAACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACA GCCACATATTACTGTGCACACAGTGGATACTATGATAATAGTGGCT ATTACTGGGACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCAC CGTCTCCCCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGC CCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCT GGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGA ACTCA GGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGT CCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAG CAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCC AGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTC GAGTGCCCAACCGTGCCCAAGCACCTGTGGCAGGACCGTCAGTCT TCCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGAC CCCTGAGGTACAGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCC GAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG CCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTG TGGTACAGGTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAA GGAGTACAAGTGCAAGGTCAGCAACAAAGGCCTCCCAGCCCCCAT CGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCA GGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATC GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA ACTACAAG ACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAG CAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAG AAGAGCCTCTCCCTGTCTCCGGGCAAATAG	877

LIBC. 編號	鏈	序列	SEQ ID
	LC	GAAATTGTGTTGACGCAGTCTCCAGTCACCCTGTCTTTGTCGCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTCTTATCAGC GACTACTTAGTCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCAGCAGGCCCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAATATG ATACCTCCCTCAATTTTCGGCGGAGGGACCAAGGTGGAGATCAAACG AACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGC AGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTC TATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTC CAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAG GACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCA GACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAG GGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTT AG	878
218967	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGAGTGGTGAAGCCTTCG GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAG TTACTTCTGGACCTGGATCCGGCAGCCCCAGGGAAGGGACTGGAA TGGATTGGCTATATCTATTACAGTGGGAGCACCAACTACAACCCCT CCCTCAAGAGTCGAGTCACGTTTTTCAGTAGACACGTCCAAGAACCA GTTCTCCCTGAAGTTGAATTCTGTGACCGCTGCGGACACGGCCGTG TATTACTGTGCGAGAGTGGAACAATTATGGCCTTTGATGCTTTTGA TATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCTCCACC AAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCT CCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCC CGAACCGGTGACGGTGTCTGTGGAAGTCAAGCGCTCTGACCAGCGGC GTGCACACCTTCCCAGCTGTCTACAGTCCTCAGGACTCTACTCCCT CAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACC TACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGAC AAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCACCGTGCCAG CACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCAAACCC AAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGG TGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTA CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGA	879

LIBC. 編號	鏈	序列	SEQ ID
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	LC	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTGGCAGC AGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCTAGGC TCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTGCAGTGTATTTCTGTCAGCAGTATG ATACCTCACCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	880
218981	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCAC AGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGT GGTGGTTACTTCTGGAGCTGGATCCGTCAGCACCCAGGGAAGGGCC TGGAGTGGATTGGGTACACCCATTACATTGGGAGCACCTACTACAA CCCGTCCCTCAAGAGTCGAGTTGCCTTTTCAGTAGACACGTCTAAG AACCAGTTCTCCCTGAAGTTGAGCTCTGTGACTGCCGCGGACACGG CCGTGTATTACTGTGCGAGAGTGGATAACAGCTATGGTGGATGCTTT TGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCTCC	881

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	LC	GAAATTATGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAATATTGACAGC AGCTACTTAGCCTGGTACCAGCAGACACCTGGCCAGGCTCCCAGGC TCCTCATCTATGATACATCCAGCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTTCAGTGTATTACTGTCAGCAGTATG GTGGCTCACCTATCACCTTCGGCCAAGGGACACGACTGGACATTAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAA	882

LIBC. 編號	鏈	序列	SEQ ID
		GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	
218995	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG GACACCCTGTCCCTCACCTGCGCTGTCTCTGGTTACTCCATCAGTAG TCGTAACCTGGTGGGGCTGGATCCGGCAGCCCCAGGGAAGGGACT GGAGTGGATCGGGTACATCCATTATATTGGGAACACCTACTACAAC CCGTCCCTCAAGAGTCGAGTCACCATGTCAGTAGACACGTCCAAGA ACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCCGTGGACACGGC CGTGTATTACTGTGCGAGAGAGACTGGTAGCGATGGTGATGATACT TTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCT CCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAG CACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTAC TTCCCCGAACCGGTGACGGTGTCGTGGAACCTCAGGCGCTCTGACCA GCGGCGTGCACACCTTCCAGCTGTCCTACAGTCCTCAGGACTCTA CTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACC CAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAG GTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCACCGT GCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCA AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGT GCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCA ACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGC CACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCT CACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTG CAAGGTCAGCAACAAAGGCCTCCCAGCCCCATCGAGAAAACCAT CTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT GCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGAC CTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGG GAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCC ATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGT GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC TGTCTCCGGGCAAATAG	883
	LC	GAAATTGTGTTGACGCAGTCTCCAGTCACCCTGTCTTTGTCTCCAGG	884

LIBC. 編號	鏈	序列	SEQ ID
		GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTATTGGCAGC AGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCGGCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTGCCTGTATTACTGTCAGCAGTGTT ATAGCTCACCGATCACCTTCGGCCACGGGACACGACTGGACATTAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	
218996	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCAC AGACCCTGTCCCTCACCTGCACTGTCTCTGGTGTCTCTGTCTCTGGT GGCTCCATCAACAGTGGTAATTACTACTGGAGCTGGATCCGCCAGC ACCCAGGAAAGGGCCTGGAGTGGATTGGGTACATCCATTACAGTGG GAACACCTACTACAACCCGTCCCTCAAGAGTCGAGTTACCATATCA GTAGACACGTCTAAGAACCAGTTCTCCCTGAAGCTGGACTCTGTGA CTGCCGCGGACACGGCCGTGTATTACTGTGCGGTGGCTACGGAATA CTACTACTACGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACC GTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCC CTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTG GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTACAG GCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTC CTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGC AACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCA GCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCG AGTGCCACCGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTT CCTCTTCCCCCAAACCCAAAGGACACCCTCATGATCTCCCGGACC CCTGAGGTACAGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCG AGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGC CAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGT	885

LIBC. 編號	鏈	序列	SEQ ID
		GGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCAGCAACAAAGGCCTCCCAGCCCCCATC GAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAG GTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCG CCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAATACTACAAGA CCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTC TCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGA AGAGCCTCTCCCTGTCTCCGGGCAAATAG	
	LC	CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGAC AGAAGGTCACCATCTCCTGCTCTGGAAGCAGCTCCAACATTGGGAA TAATTATGTATCCTGGTACCAGCAGTTCCCAGGAACAGCCCCAAA CTCCTCATTTATGACAATAATAAGCGACCCTCAGGGATTCTGACC GATTCTCTGGCTCCAAGTCTGGCACGTACGCCACCCTGGGCATCAC CGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGG GATCGCAGCCTGAGTGCTGTGATATTGCGCGGAGGGACCAAGCTGA CCGTCTAGGTACGCCAAGGCTGCACCCTCGGTCACTCTGTTCCCG CCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTC TCATCAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGC AGATAGCAGCCCCGTCAAGGCGGGAGTGGAACCACCACACCCTC CAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCT GACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGT CACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGA ATGTTTCATAG	886
218998	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACAGGTGAAGCCTTCA CAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAG TGGTGGTTACTTCTGGGGCTGGATCCGCCAGCACCCAGGGAAGGGC CTGGAATGGATTGGGTACATCCATTATATTGGGAGCCCCTACTACA ATCCGTCTCTCAAGAGTCGAACCTACCATATCAGTAGACACGTCTAA GAACCAGTTCTCCCTGAAGCTAAGCTCTGTGATTGCCGCGGACACG GCCGTATATTACTGTGCGAGAGATTGTAGTAGTGTCAACTGCCAAG ATGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTC AGCCTCCACCAAGGGCCCCATCGGTCTTCCCCCTGGCGCCCTGCTCC	887

LIBC. 編號	鏈	序列	SEQ ID
		AGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAG GACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCTC TGACCAGCGGCGTGACACCTTCCCAGCTGTCCTACAGTCCTCAGG ACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTC GGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAAC ACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCC CACCGTGCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCCTCTTC CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGG TCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCGAGGTCCA GTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACA AAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGC GTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACA AGTGCAAGGTCAGCAACAAAGGCCTCCCAGCCCCCATCGAGAAAA CCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACA CCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCT GACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCT CCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCAC CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCC GTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCT CCCTGTCTCCGGGCAAATAG	
	LC	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCTCCCTCTCCTGCTGGTCCAGTCAGAGTATTGACAGC ACCTACTTAGCCTGGTACCACCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCACCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCAGCATCAGC AGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAATATA GTAGCTCACCTATCACCTTCGGCCAAGGGACACGACTGGAGATTAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC	888

LIBC. 編號	鏈	序列	SEQ ID
		AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	
219083	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCAC AGACCCCTGTCCCTCACCTGTACCGTCTCTGGTGGCTCCATCAGAAGT GATGGTTACTTCTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCC TGGAGTGGCTTGGGTTTCATCTATTACAGTGGGACCACCTACTACAA CCCGTCCCTCAAGAGTCGAGTTACTATATCAGTAGACACGTCTAAG AACCAGTTCTCCCTGAAGCTGACCTCTGTGACTGTGCGGGACACGG CCGTGTATTATTGTGCGAGAGTTTTGTGGTGGTGAAGTGTACGATGCT TTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCT CCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAG CACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTAC TTCCCCGAACCGGTGACGGTGTGCTGGAAGTCAAGGCGCTCTGACCA GCGGCGTGCACACCTTCCCAGCTGTCTACAGTCCTCAGGACTCTA CTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACC CAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAG GTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCACCGT GCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCA AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACAGT GCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCA ACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGC CACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCT CACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTG CAAGGTCAGCAACAAAGGCCTCCCAGCCCCATCGAGAAAACCAT CTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGAC CTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGG GAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCC ATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGT GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC TGTCTCCGGGCAAATAG	889
	LC	GACATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAGGAGCCACCCTCTCCTGCAGGGCCAGTCAAAATATTAGCAAC	890

LIBC. 編號	鏈	序列	SEQ ID
		ACCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTGCAGTGTATGACTGTCAGCAGTATT TTAGCTCACCGATCACTTTCGGCGGAGGGACCAGGGTGGAGATCAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	
219092	HC	CAGGTGCAGGTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG GACACCCTGTCCCTCACCTGCGCTGTCTCTGGTTACTCCATCAGCAA TAGTATCTGGTGGGGCTGGATCCGGCAGCCCCAGGGAAGGGACTG GAGTGGATTGGGTACATCCATTATAGTGGGAACACCTACTATAATC CGTCCCTCAAGAGTCGAGTCACCATGTCAGTAGACACGTCCAAGAA CCAGTTCTCCCTGAAGCTGAACTCTGTGACCGCCGTGGACACGGCC GTGTATTACTGTGCGAGAAATTTCCGGTGACGTTGATGCTTTTGATAT CTGGGGCCAAGGGACAATGGTCAACGCTCTCTTCAGCCTCCACCAAG GGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCG AGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGA ACCGGTGACGGTGTCGTGGAAGTCAAGGCGCTCTGACCAGCGGCGTG CACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAG CAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTAC ACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTGCGAGTGCCACCGTGCCAGCAC CACCTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCAAAACCCAA GGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTG GTGGACGTGAGCCACGAAGACCCGAGGTCCAGTTCAACTGGTACG TGGACGGCGTGAGGTGCATAATGCCAAGACAAAGCCACGGGAGG AGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGT GCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCAG	891

LIBC. 編號	鏈	序列	SEQ ID
		CAACAAAGGCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAACC AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCATCCC GGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCA AAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATG GGCAGCCGGAGAACAACACTACAAGACCACACCTCCCATGCTGGACTC CGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGC AGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGG CTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGG CAAATAG	
	LC	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTATTAGCAGC AGCTATTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCAACATCAGC AGACTGGAGCCTGAAGATTTTGTGTGTATTACTGTCAGCAGTATTA TCTCTACCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA CGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA GCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAACT TCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT CCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAA GGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGC AGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCA GGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTG TTAG	892
219023	HC	CAAGTGCAGCTGCAACAGTCAGGTCCAGGACTGGTGAAGCCCTCGC AGACCCTCTCACTCACCTGTGCCATCTCCGGTGACAGTGTCTTTAGC AACAGTGCTGCTTGGAACCTGGATCAGGCAGTCCCCCTCGAGAGGCC TTGAGTGGCTGGGAAGGACATATTGTAGGTCCAAGTGTTATAGTGA TTATGCATTATCTGTGAAAAGTCGAGCAACCATCAACCCAGACACA TCCGAGAACCAGTTCTCCCTGCAGCTGAACTCTGTGACTCCCGAGG ACACGGCTGTGTATTACTGTGCAAGAGCAGTGGCTGACCACTACTC CTACGCTTTGGACGTCTGGGGCCAAGGGACCACGGTCAATGTCTCC TCAGCCAGCACCAAGGGGCCATCCGTCTTCCCCCTGGCGCCCTGCT CCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAA	893

LIBC. 編號	鏈	序列	SEQ ID
		GGACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCC CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAG GACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTT GGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAA CACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGC CCATCATGCCCAGCACCTGAGTTCTTGGGGGGACCATCAGTCTTCC TGTTCCCCCAAACCCAAGGACACTCTCATGATCTCCCGGACCCC TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGA GGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCC AAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGG AGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGA GAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGT GTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTC AGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCG TGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCA CGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGG CTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCAT GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAG CCTCTCCCTGTCTCTGGGCAAATAG	
	LC	GACATCCAGATGAACCAGTCTCCATCCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGACCATTAGAACT TATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGGTCC TGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCTTCAAGGTTC AGTGGCACTGGATCTGGGACAGATTTCACTCTCACCATCACCAGTC TGCAACCTGAAGATTTTGCAACTTACTCCTGTCAACAGAGTTACAG TTCACCGATCACTTTCGGCGGGGGGACCAAGGTCGAGATCAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA	894

LIBC. 編號	鏈	序列	SEQ ID
		G	
219023.0 01	HC	CAAGTGCAGCTGCAACAGTCAGGTCCAGGACTGGTGAAGCCCTCGC AGACCCCTCTCACTCACCTGTGCCATCTCCGGTGACAGTGTCTTTAGC AACAGTGCTGCTTGGAAGTGGATCAGGCAGTCCCCCTCGAGAGGCC TTGAGTGGCTGGGAAGGACATATTACAGGTCCAAGTGGTATAGTGA TTATGCATTATCTGTGAAAAGTCGAGCAACCATCAACCCAGACACA TCCGAGAACCAGTTCTCCCTGCAGCTGAACTCTGTGACTCCCGAGG ACACGGCTGTGTATTACTGTGCAAGAGCAGTGGCTGACCACTACTC CTACGCTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCC TCAGCCAGCACCAAGGGGCCATCCGTCTTCCCCCTGGCGCCCTGCT CCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAA GGACTACTTCCCCGAACCGGTGACGGTGTCTGTGAACTCAGGCGCC CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAG GACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTT GGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAA CACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGC CCATCATGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCC TGTTCCCCC AAAACCCAAGGACACTCTCATGATCTCCCGGACCCC TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCGA GGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCC AAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTG GTCAGCGTCCTACCGTCCTGCACCAGGACTGGCTGAACGGCAAGG AGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGA GAAAACCATCTCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGT GTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTC AGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCG TGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA ACTACAAGACCA CGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTCCTCTACAGCAGG CTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCAT GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAG CCTCTCCCTGTCTCTGGGCAAATAG	895
	LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGACCATTAGAACT TATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCCTAAGGTCC	896

LIBC. 編號	鏈	序列	SEQ ID
		TGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCTTCAAGGTTC AGTGGCACTGGATCTGGGACAGATTTCACTCTCACCATCACCAGTC TGCAACCTGAAGATTTTGCAACTTACTCCTGTCAACAGAGTTACAG TTCACCGATCACTTTCGGCGGGGGGACCAAGGTCGAGATCAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA G	
219095	HC	GAGGTGCAGCTGTTGGAGTCTGGGGGAAACTTGGTACAGCCTGGGG GGTCCCTGAGACTCTCCTGTGTAGTCTCTGGATTACCTTTAACAAC TATGCCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGT GGGTCTCAGTTATTAGTGATAGTGGTGGTAGCTCAAACCTACGCAGA CTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAAA ACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCC GTATATTACTGTGCGAAAGATCGGAGTATAGCCGGCTACTACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTC CACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGC ACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACT TCCCCGAACCGGTGACGGTGTCGTGGAAGTCAAGGCGCTCTGACCAG CGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACT CCCTCAGCAGCGTGTTGACCGTGCCCTCCAGCAACTTCGGCACCCA GACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGT GGACAAGACAGTTGAGCGCAAATGTTGTGTGAGTGCCACCGTGC CCAGCACCACTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCAA AACCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTG CGTGGTGGTGGACGTGAGCCACGAAGACCCGAGGTCCAGTTCAAC TGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCA CGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCA CCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCA AGGTCAGCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTC	897

LIBC. 編號	鏈	序列	SEQ ID
		CAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG AGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCCATG CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGA CAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATG CATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT CTCCGGGCAAATAG	
	LC	GACATCCAGATGACCCAGTCTCCGTCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGC GATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAACCTCC TGATCTATGCTGCATCCAGTTTGCACAGTGGGGTCCCATCAAGGTTT AGTGGCAGTGGATCTGGGACAGATTTCCTCTCACCATCAGCAGTC TCCTACCTGAGGATTTTGCAACTTACTACTGTCAACAGAGTTACAAT ACCCCGCTCACTTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACCTCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA G	898
219102	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAG TTACTACTGGAGCTGGATCCGGCTGCCCCCAGGGAAGGGACTGGAG TGGATTGGGTATATCTATTATGGTGGGAGCACCAACTACAACCCT CCCTCAAGAGTCGGGTCTCCATGTCAGTAGACACGTCCAAGAACCA GTTCTCCCTGAAGCTGAGCTATGTGACCGCCGCGGACACGGCCGTG TATTACTGTGCGAGATCGTATAGCAGCGCCTGGTACGGCTCTGCAT ACTGGGGCCAGGGAACCCTGGTCATCGTCTCCTCGGCCAGCACCAA GGGGCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC GAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG AACCGGTGACGGTGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGT	899

LIBC. 編號	鏈	序列	SEQ ID
		GCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTACTCCCTCA GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTA CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAA GAGAGTTGAGTCCAAATATGGTCCCCCATGCCCATCATGCCCAGCA CCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCC AAAACC CAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTG GTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG AGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGT CCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGT CTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAA GCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCAT CCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA TGGGCAGCCGGAGAACAATAACAAGACCACGCCTCCCGTGCTGGA CTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTAACCGTGGACAAG AGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATG AGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCT GGGCAAATAG	
	LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTTTAGG AGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGACATTAGCAAC TATTTAATTTGGTATCAGCTGAAACCAGGGAAAGCCCCTAAGGTCC TGATCTACGATGCATCCAATTTGGAAACAGGGGTCCCATCAAGGTT CAGTGGAATGGATCTGGGACAGATTTTACTTTTACCATCAGCAGC CiGCAGCCTGAAGATATTGCAACATATTACTGTCAACAGTATGATCA TCTCCCGATCACCTTCGGCCAAGGGACACGACTGGACATTAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA G	900

LIBC. 編號	鏈	序列	SEQ ID
219102.0 01	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAG TTACTACTGGAGCTGGATCCGGCTGCCCCAGGGAAGGGACTGGAG TGGATTGGGTATATCTATTATGGTGGGAGCACCAACTACAACCCCT CCCTCAAGAGTCGGGTCTCCATGTCAGTAGACACGTCCAAGAACCA GTTCTCCCTGAAGCTGAGCTATGTGACCGCCGCGGACACGGCCGTG TATTACTGTGCGAGATCGTATAGCAGCGCCTGGTACGGCTCTGCAT ACTGGGGCCAGGGAACCCTGGTCATCGTCTCCTCGGCCAGCACCAA GGGGCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC GAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG AACCGGTGACGGTGTCTGTGGAACCTCAGGCGCCCTGACCAGCGGCGT GCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTACTCCCTCA GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTA CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAA GAGAGTTGAGTCCAAATATGGTCCCCCATGCCCATCATGCCCAGCA CCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCCCTAAACC CAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTG GTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG AGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGT CCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGT CTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAA GCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCAT CCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA TGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGCTGGA CTCCGACGGCTCCTTCTTCTCTACAGCAGGCTAACCGTGGACAAG AGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATG AGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCT GGGCAAATAG	901
	LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTTTAGG AGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGACATTAGCAAC TATTTAATTTGGTATCAGCTGAAACCAGGGAAAGCCCCTAAGGTCC TGATCTACGATGCATCCAATTTGGAAACAGGGGTCCCATCAAGGTT	902

LIBC. 編號	鏈	序列	SEQ ID
		CAGTGGAAGCGGATCTGGGACAGATTTTACTTTCACCATCAGCAGC CiGCAGCCTGAAGATATTGCAACATATTACTGTCAACAGTATGATCA TCTCCCGATCACCTTCGGCCAAGGGACACGACTGGACATTAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA G	
218973	HC	CAGGTGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAG CTATGGCATACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATGGTATGATGGAAGTAAAAAATACTATGCAG ACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAG CACGCTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGACACGGCT GTGTATTACTGTGCGAGAGATCCCTCCCATTACTATGGTTCGGGGA GTTATAACTACTTCTACGGTATGGACGTCTGGGGCCAAGGGACCAC GGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCC TGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGG CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGG AACTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCC CTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCAC AAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGT TGTGTGAGTGTCCACCGTGCCAGCACCACTGTGGCAGGACCGT CAGTCTTCCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCC CGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAA GACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC ATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGT TCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAA CGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGGCCTCCCAGC CCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGA	903

LIBC. 編號	鏈	序列	SEQ ID
		ACCACAGGTGTACACCCTGCCCCATCCCGGGAGGAGATGACCAAG AACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCG ACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAAC ACAAGACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTC TACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAAC GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC GCAGAAGAGCCTCTCCCTGTCTCCGGGCAAATAG	
	LC	CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGAC AGAAGGTCACCATCTCCTGCTCTGGAAGCAGCTCCAACATTGGGAA TACTTATGTATCCTGGTACCAGCAACTCCCAGGAACAGCCCCAAA CTCCTCATTTATGACAATAATGAGCGACCCTCAGGGATTCTGACC GATTCTCTGGCTCCAAGTCTGACACGTCAGCCACCCTGGGCATCAC CGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACCTGG GATAACAGCCTGACTGCTGTGGTATTTCGGCGGAGGGACCAAGCTGA CCGTCTTAGGTCAGCCCAAGGCTGCACCCTCGGTCACTCTGTTCCCG CCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTC TCATCAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGC AGATAGCAGCCCCGTCAAGGCGGGAGTGGAACCACCACACCCTC CAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCT GACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGT CACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGA ATGTTCATAG	904
219044	HC	GAGGTGCAGTTGGTGGAGTCTGGAGGAGGCTTGATCCAGCCTGGGG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGGTTACCGTCAGTGAC AACTACATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAG TGGGTCTCAGTTATTTATAGCGGTGGTAACACATACTACGGAGACT CCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCCAAGAACAC GCTCTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTG TATTTCTGTACTGGCCCCCTTCTTTGACTACTGGGGCCCGGGAACCCT GGTCACCGTCTCCTCAGCCAGCACCAAGGGGCCATCCGTCTTCCCC CTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGG GCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTG GAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTC CTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGC	905

LIBC. 編號	鏈	序列	SEQ ID
		CCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCA CAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATA TGGTCCCCCATGCCCATCATGCCCAGCACCTGAGTTCCTGGGGGA CCATCAGTCTTCCTGTTCCCCCAAAACCCAAGGACACTCTCATGAT CTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAG GAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAG GTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGC ACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGC TGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCC CGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCG AGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACC AAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCA GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA ACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC CTCTACAGCAGGCTAACCCTGGACAAGAGCAGGTGGCAGGAGGGG AATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA CACACAGAAGAGCCTCTCCCTGTCTCTGGGCAAATAG	
	LC	GAAATTGTGTTGACGCAGTTTCCAGGCACCCTGTCTTTGTCTCCGGG GGAAGGAGGCACCCTCTCCTGCAGGGCCAGTCAGACTGTTTGGAGC AACTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCAGGAGGGTCATTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCAATCTCACCATCAGC AGCCTGGAGCCTGGAGATTTTGCAGTGTATTACTGTCAGCAGTATG GTAGTTCATCGATTACCTTCGGCCAAGGGACACGACTGGAGATTAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	906
218997	HC	CAGGTGCAGGTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCA CAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAG	907

LIBC. 編號	鏈	序列	SEQ ID
		TGGTGGTTACTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGC CTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTACTACA ACCCGTCCCTCATGGGTTCGAGTTACCATATCAGTAGACACGTCTAA GAACCAGTTTTCCCTGAGGCTGAGCTCTGTGACTGCCGCGGACACG GCCGTGTATTATTGTGCGAGAAGGGGGCCAGTGGCTGGTGGATTTG ACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCAC CAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACC TCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCC CCGAACCGGTGACGGTGTCTGTGGAAGTCAAGGCGCTCTGACCAGCGG CGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCC TCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGAC CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGA CAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCACCGTGCCCA GCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCAAAC CCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGT GGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTG GTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACG GGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAG GTCAGCAACAAAGGCCTCCCAGCCCCATCGAGAAAACCATCTCCA AAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCC CATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCT GGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGC AATGGGCAGCCGGAGAACAATAAGACCACACCTCCCATGCTG GACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACA AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT CCGGGCAAATAG	
	LC	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAATGTTTACAAC AACTACTTAGCCTGGTACCAGCAGAAACCTCGCCAGGCTCCCAGGC TCCTCATCTATGGTACATCCAGTAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAACAGTATG	908

LIBC. 編號	鏈	序列	SEQ ID
		GTAGCTCACTTCTGTGCAGTTTTGGCCAGGGGACCAAGCTGGAGAT CAAACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTG ATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAA TAACTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAAC GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACACAGAGCAGGAC AGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGC AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACC CATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGA GAGTGTTAG	

【0261】 可以藉由突變將變化引入本文揭露的核酸分子中，從而導致其編碼的多肽（例如，LTβR結合蛋白）的胺基酸序列發生變化。可使用本領域中已知的任何技術來引入突變。在一個實施方式中，使用例如定點誘變方案來改變一或多個特定胺基酸殘基。在另一個實施方式中，使用例如隨機誘變方案使一或多個隨機選擇的殘基改變。無論是如何製備的，可以表現並篩選出突變多肽的所需特性。

【0262】 可以將突變引入本文揭露的核酸分子中，而不顯著改變其編碼的多肽的生物活性。例如，可進行核苷酸取代，從而在非必需胺基酸殘基處進行胺基酸取代。在一個實施方式中，本揭露之促效劑LTβR結合蛋白之一的本文提供的核苷酸序列發生突變，使得其編碼的胺基酸序列包含如本文所示的本揭露之LTβR結合蛋白的輕鏈和/或重鏈的胺基酸殘基的一或多個缺失或取代。在另一個實施方式中，該誘變插入與本文所示的本揭露之促效劑LTβR結合蛋白的輕鏈和/或重鏈的一或多個胺基酸殘基相鄰的胺基酸。可替代地，可以將一或多個突變引入本文揭露的核酸分子中，其選擇性地改變其編碼的促效劑LTβR結合蛋白的生物活性。

【0263】 編碼本揭露之抗體的相應胺基酸序列的本揭露之促效劑LTβR結

合蛋白的核苷酸序列可以例如藉由隨機誘變或定點誘變來改變，以產生與未突變的多核苷酸相比包含一或多個特定核苷酸取代、缺失或插入的改變的多核苷酸。用於進行這樣的改變的技術的實例描述於以下中：Walder等人, *Gene*[基因] 42:133 (1986)；Bauer等人 *Gene*[基因] 37:73 (1985)；Smith等人, 1981, *Genetic Engineering: Principles and Methods*[基因工程：原理與方法], Plenum Press；以及美國專利案號4,518,584和4,737,462。例如，該等和其他方法可用於製備具有期望的特性（例如，與未衍生的抗體相比，對所期望靶標的親和力、親合力或特異性增加，體內或體外活性或穩定性增加，或體內副作用減少）的LT β R結合蛋白的衍生物。

【0264】在另一個實施方式中，本揭露提供了包含編碼本文揭露的促效劑LT β R結合蛋白的多核苷酸的載體。載體係用於將另一個核酸引入細胞的核酸分子。載體之實例包括但不限於質體、病毒載體、非附加型哺乳動物載體和表現載體，例如重組表現載體。

【0265】包含本揭露之多核苷酸的載體可以使用以下中描述的標準重組DNA技術來製備：例如，Sambrook等人, *Molecular Cloning: A Laboratory Manual*[分子選殖：實驗室手冊]. 第3版, 冷泉港出版社, 紐約冷泉港 (2001)；以及Ausubel等人, *Current Protocols in Molecular Biology*[分子生物學的當前方案], Greene Publishing Associates和John Wiley & Sons, NY (1994)，特此藉由引用將其全部併入。呈圓形或線性的表現載體的構建體可經製備以含有在原核或真核宿主細胞中發揮功能的複製系統。複製系統可來源於例如CoIE1、2 μ 質體、 λ 、SV40、牛乳頭瘤病毒等。

【0266】在一個實施方式中，該表現載體係圓形質體（參見例如，Muthumani等人, 「Optimized and Enhanced DNA Plasmid Vector Based In vivo Construction of a Neutralizing anti-HIV-1 Envelope Glycoprotein Fab[中和抗HIV-1

包膜糖蛋白Fab的基於優化和增強DNA質體載體的體內構建],」 *Hum. Vaccin. Immunother*[人類疫苗和免疫療法]. 9: 2253-2262 (2013), 特此藉由引用將其全部併入)。質體可以藉由整合到細胞基因組中來轉化靶細胞或存在於染色體外(例如, 具有複製起點的自主複製質體)。示例性質體載體包括但不限於pCEP4、pREP4、pVAX、pcDNA3.0、provax或能夠表現由重組核酸序列構建體編碼的重鏈多肽和/或輕鏈多肽的任何其他表現載體。

【0267】 在另一個實施方式中, 該表現載體係線性表現盒(「LEC」)。LEC能夠經由電穿孔有效地遞送到受試者, 以表現由重組核酸序列構建體編碼的重鏈多肽和/或輕鏈多肽。LEC可為任何沒有磷酸骨架的線性DNA。在一個實施方式中, 該LEC不含有任何抗生素抗性基因和/或磷酸骨架。在另一個實施方式中, 該LEC不含有與所需基因表現無關的其他核酸序列。

【0268】 LEC可以衍生自任何能夠線性化的質體。質體可能能夠表現由重組核酸序列構建體編碼的重鏈多肽和/或輕鏈多肽。示例性質體包括但不限於pNP (Puerto Rico/34)、pM2 (New Caledonia/99)、WLV009、pVAX、pcDNA3.0或provax, 或任何其他能夠表現由重組核酸序列構建體編碼的重鏈多肽和/或輕鏈多肽的表現載體。

【0269】 在另一個實施方式中, 該表現載體係病毒載體。能夠表現全長抗體或其結合部分的合適病毒載體包括, 例如, 腺相關病毒(AAV)載體(參見例如, Lewis等人, 「Generation of Neutralizing Activity against Human Immunodeficiency Virus Type I in Serum by Antibody Gene Transfer[藉由抗體基因轉移在血清中產生對人類免疫缺乏病毒I型的中和活性],」 *J. Virol.*[病毒學雜誌] 76:8769-775 (2002); Fang等人, 「An Antibody Delivery System for Regulated Expression of Therapeutic Levels of Monoclonal Antibodies In vivo[一種用於調節治療水平單株抗體體內表現的抗體遞送系統],」 *Mol. Ther.*[分子療法]15(6): 1153-9

(2007)；Buning等人，「Recent Developments in Adeno-associated Virus Vector Technology[腺相關病毒載體技術的最新發展],」 *J. Gene Med.*[基因醫學雜誌] 10:717-733 (2008))、慢病毒載體（參見例如，Joseph等人，「Inhibition of In vivo HIV Infection in Humanized Mice by Gene Therapy of Human Hematopoietic Stem Cells with a Lentiviral Vector Encoding a Broadly Neutralizing anti-HIV Antibody[藉由用編碼廣泛中和抗HIV抗體的慢病毒載體對人類造血幹細胞進行基因治療來抑制人源化小鼠體內HIV感染],」 *J. Virol.*[病毒學雜誌], 84: 6645-53 (2010)；以及Luo等人，「Engineering Human Hematopoietic Stem/Progenitor Cells to Produce a Broadly Neutralizing anti-HIV Antibody after In vivo Maturation to Human B Lymphocytes[工程化人類造血幹細胞/先驅細胞以在體內成熟為人B淋巴細胞後產生廣泛中和的抗HIV抗體],」 *Blood*[血液] 113: 1422-1431 (2009))、反轉錄病毒載體、複製缺陷型腺病毒載體和無腸腺病毒載體（參見例如，美國專利案號5,872,005）。用於生成和分離適合用作載體的腺相關病毒（AAV）的方法係本領域已知的（參見例如，Grieger和Samulski，「Adeno-associated Virus as a Gene Therapy Vector: Vector Development, Production and Clinical Applications[腺相關病毒作為基因治療載體：載體開發，生產和臨床應用],」 *Adv.Biochem. EnginBiotechnol.*[生物化學工程/生物技術的進展]99: 119-145 (2005)；Buning等人，「Recent Developments in Adeno-associated Virus Vector Technology[腺相關病毒載體技術的最新發展],」 *J. Gene Med.*[基因醫學雜誌] 10:717-733 (2008))。

【0270】編碼如本文所描述的促效劑LTβR結合蛋白的表現載體構建體可包括編碼重鏈多肽、重鏈可變區或其片段的多核苷酸。重鏈多肽可以包括可變重鏈（VH）區和/或至少一個恒定重鏈（CH）區。至少一個恒定重鏈區可以包括恒定重鏈區1（CH1）、恒定重鏈區2（CH2）、和恒定重鏈區3（CH3）和/或鉸鏈區。在一些實施方式中，該重鏈多肽可以包括VH區和CH1區。在其他實施方式

中，該重鏈多肽可以包括VH區、CH1區、鉸鏈區、CH2區和CH3區。表現構建體還可以包括編碼輕鏈多肽、輕鏈可變區或其片段的多核苷酸序列。輕鏈多肽可以包括可變輕鏈（VL）區和/或恒定輕鏈（CL）區。

【0271】 在一些方面，載體包含一或多個調節序列。「調節序列」係影響與其可操作地連接的核酸的表現（例如，表現的水平、時間或位置）的核酸。示例性調節序列包括轉錄和翻譯起始和終止密碼子，其對於載體要引入的宿主類型（例如，細菌、真菌、植物或動物）係特定的，視情況而定，並考慮載體係基於DNA還是基於RNA。基於待用於表現的宿主細胞而選擇合適的調節序列，並且可操作地連接至要表現的核酸序列。調節序列包括在許多類型的宿主細胞中直接組成型表現核苷酸序列的那些（例如，SV40早期基因強化子、Rous肉瘤病毒啟動子和巨細胞病毒啟動子），僅在某些宿主細胞中直接表現核苷酸序列的那些（例如，組織特異性調節序列），以及響應於特定治療或條件而指導核苷酸序列誘導表現的那些（例如，哺乳動物細胞中的金屬硫蛋白啟動子以及原核和真核系統中的tet反應和/或鏈黴素反應啟動子（參見例如，Voss等人, *Trends Biochem. Sci.* [生化科學趨勢] 11:287 (1986), Maniatis 等人, *Science* [科學] 236:1237 (1987)））。熟悉該項技術者將理解，表現載體的設計可以取決於諸如待轉化的宿主細胞的選擇、所期望的蛋白表現水平等因素。可以將本揭露之表現載體引入宿主細胞中，從而產生由如本文所描述的核酸編碼的蛋白或肽。

【0272】 表現構建體可以進一步編碼蛋白酶切割位點。蛋白酶切割位點可以被蛋白酶或肽酶識別。蛋白酶可為內肽酶或內切蛋白酶，例如但不限於弗林蛋白酶、彈性蛋白酶、HtrA、鈣蛋白酶、胰蛋白酶、糜蛋白酶、胰蛋白酶和胃蛋白酶。在其他實施方式中，蛋白酶可為絲胺酸蛋白酶、蘇胺酸蛋白酶、半胱胺酸蛋白酶、天冬胺酸蛋白酶、金屬蛋白酶、麩胺酸蛋白酶或任何切割內部肽鍵的蛋白酶（即，不切割N末端或C末端肽鍵）。蛋白酶切割位點可以包括一或多個促進

或提高切割效率的胺基酸序列。

【0273】 表現構建體可以進一步編碼連接模體列。該連接模體列可以編碼在空間上分離和/或連接表現構建體的一或多個組分（編碼抗體的重鏈和輕鏈組分）的胺基酸序列。

【0274】 在一個實施方式中，第一表現載體構建體編碼包括VH和CH1的重鏈多肽，第二表現載體構建體編碼包括VL和CL的輕鏈多肽。替代排列包括編碼包括VH、CH1、鉸鏈區、CH2和CH3的重鏈多肽的第一載體和編碼包括VL和CL的輕鏈多肽的第二載體。

【0275】 在另一個實施方式中，該表現載體構建體編碼包括VH和CH1的重鏈多肽，以及包括VL和CL的輕鏈多肽，並且連接模體列位於編碼重鏈多肽的核酸序列和編碼輕鏈多肽的核酸序列之間。

【0276】 在替代實施方式中，該表現載體構建體編碼包括VH和CH1的重鏈多肽，以及包括VL和CL的輕鏈多肽，並且編碼蛋白酶切割位點的核酸序列位於編碼重鏈多肽的核酸序列和編碼輕鏈多肽的核酸序列之間。

【0277】 在另一個實施方式中，該表現載體構建體編碼包括VH、CH1、鉸鏈區、CH2和CH3的重鏈多肽，以及包括VL和CL的輕鏈多肽，並且連接模體列位於編碼重鏈多肽的核酸序列和編碼輕鏈多肽的核酸序列之間。

【0278】 在又另一個實施方式中，該表現載體構建體編碼包括VH、CH1、鉸鏈區、CH2和CH3的重鏈多肽，以及包括VL和CL的輕鏈多肽，並且編碼蛋白酶切割位點的異源核酸序列位於編碼重鏈多肽的核酸序列和編碼輕鏈多肽的核酸序列之間。

【0279】 載體可包括一或多種標記基因，其允許選擇轉化或轉染的宿主。標記基因包括殺生物劑抗性（例如針對抗生素、重金屬等的抗性）、營養缺陷型宿主中提供原營養的補充等。適用於本揭露之表現載體的標記基因包括例如新

黴素/G418抗性基因、潮黴素抗性基因（hygromycin resistance gene）、組胺醇抗性基因、四環素抗性基因和安比西林抗性基因（ampicillin resistance gene）。

【0280】載體可以包含可操作地連接到編碼促效劑LT β R結合蛋白的核苷酸序列的天然或標準啟動子。啟動子（例如強啟動子、弱啟動子、誘導型啟動子、組織特異性啟動子和發育特異性啟動子）的選擇在技術者之普通技術範圍內。類似地，核苷酸序列與啟動子組合還在技術者之技術範圍內。啟動子可為非病毒啟動子或病毒啟動子，例如巨細胞病毒（CMV）啟動子、SV40啟動子、RSV啟動子和在鼠科幹細胞病毒的長末端重複序列中發現的啟動子。

【0281】在另一個實施方式中，本揭露提供了已將本揭露之重組表現載體引入其中的宿主細胞。宿主細胞係用於表現核酸的細胞，例如，編碼如本文所描述的LT β R結合蛋白的多核苷酸。合適的宿主細胞包括原核細胞和真核細胞，如下文更詳細描述的。宿主細胞不僅指含有感興趣核酸分子的特定細胞，還指這種細胞的後代或潛在後代。因為由於例如突變或環境影響，在後代中可能發生某些修飾，因此這樣的後代實際上可能與親本細胞不同，但仍包含在本文使用的「宿主細胞」範圍內。

【0282】原核生物宿主細胞包括革蘭氏陰性或革蘭氏陽性生物體，例如大腸桿菌或桿菌。在示例性方面，該細胞係真核細胞，包括但不限於酵母細胞、絲狀真菌細胞、原生動物細胞、藻類細胞、昆蟲細胞或哺乳動物細胞。本領域中描述了這樣的宿主細胞。參見例如，Frenzel,等人, *Front Immunol*[免疫學前沿] 4: 217 (2013)。在示例性方面中，該等真核細胞為哺乳動物細胞。在示例性方面中，該等真核細胞為非人類哺乳動物細胞。在一些方面，該等細胞係中國倉鼠卵巢（CHO）細胞及其衍生物（例如，CHO-K1、CHO pro-3、CS9）、小鼠骨髓瘤細胞（例如，NS0、GS-NS0、Sp2/0），工程化為缺乏二氫葉酸還原酶（DHFR）活性的細胞（例如，DUKX-X11、DG44）、人胚胎腎293（HEK293）細胞或其衍

生物（例如，HEK293T、HEK293-EBNA）、綠色非洲猴腎細胞（例如，COS細胞、VERO細胞）、人子宮頸癌細胞（例如HeLa）、人骨肉瘤上皮細胞U2-OS、腺癌人肺泡基底上皮細胞A549、人纖維肉瘤細胞HT1080、小鼠腦腫瘤細胞CAD、胚胎癌細胞P19、小鼠胚胎成纖維細胞NIH 3T3、小鼠成纖維細胞L929、小鼠神經母細胞瘤細胞N2a、人乳癌細胞MCF-7、視網膜母細胞瘤細胞Y79、人視網膜母細胞瘤細胞SO-Rb50、人肝癌細胞Hep G2、小鼠B骨髓瘤細胞J558L或幼倉鼠腎（BHK）細胞（Gaillet等人 2007；Khan, Adv Pharm Bull [高級藥物通報] 3(2): 257-263 (2013)）。在一個特定實施方式中，該宿主細胞係CS9（CHO細胞系）。

【0283】可經由常規轉化或轉染技術將載體DNA引入原核或真核細胞中。為了穩定轉染哺乳動物細胞，已知取決於所使用的表現載體及轉染技術，僅一小部分細胞可將外來DNA整合至其基因組中。為了鑒定和選擇該等整合體，通常將編碼選擇性標誌物（例如針對抗生素抗性）的基因與目的基因一起引入宿主細胞中。另外的選擇性標誌物包括賦予藥物（如G418、潮黴素和胺甲喋呤）抗性的那些。除其他方法以外，可藉由藥物選擇（例如已併入選擇性標記基因的細胞將倖存，而其他細胞則死亡）來鑒別經所引入的核酸穩定轉染的細胞。

【0284】轉化的細胞可以在促進LTβR結合蛋白表現的條件下培養，並且藉由常規蛋白純化程式回收結合蛋白。

LTβR結合蛋白的生產方法

【0285】本文揭露的LTβR結合蛋白可以藉由本領域已知的、合成結合蛋白和/或蛋白的任何方法，特別是藉由化學合成或較佳的是，藉由重組表現技術進行生產。從頭合成多肽的合適方法在以下中描述，例如，Chan等人, Fmoc Solid Phase Peptide Synthesis[Fmoc固相肽合成], Oxford University Press[牛津大學出版社], 英國牛津, 2005；以及Peptide and Protein Drug Analysis[肽和蛋白質藥物分析], Reid, R.編輯, Marcel Dekker, Inc., 2000。

【0286】 重組表現技術涉及構建含有編碼如本文所描述的促效劑LTβR結合蛋白的多核苷酸的表現載體。一旦獲得了編碼促效劑LTβR結合蛋白的多核苷酸，就可以藉由重組DNA技術生產用於生產促效劑LTβR結合蛋白的載體。構建含有促效劑LTβR結合蛋白編碼序列和適當的轉錄和翻譯控制訊號的表現載體。該等方法包括例如體外重組DNA技術、合成技術、以及體內基因重組。

【0287】 藉由常規技術將表現載體轉移到宿主細胞，然後藉由常規技術培養轉染的細胞以產生本揭露之促效劑LTβR結合蛋白。在本揭露之一個實施方式中，可以將編碼抗體的重鏈和輕鏈的載體在宿主細胞中共表現，以表現整個免疫球蛋白分子。

【0288】 多種宿主表現載體系統可用於表現本揭露之促效劑LTβR結合蛋白。這樣的宿主表現系統代表了可以產生感興趣的編碼序列並隨後純化的媒介物，也代表了當用適當的核苷酸編碼序列轉化或轉染時，可以原位表現本揭露之結合蛋白的細胞。細菌細胞(如大腸桿菌)和真核細胞常用於表現重組抗體分子，尤其是用於表現整個重組抗體分子。例如，哺乳動物細胞如中國倉鼠卵巢細胞(CHO)，與載體(如來自人類巨細胞病毒的主要中間早期基因啟動子元件)相結合，係抗體的有效表現系統(Foecking等人, *Gene*[基因] 45:101 (1986); Cockett等人, *Nat. Biotech.*[自然生物技術] 8:2 (1990))。

【0289】 此外，還可以選擇調節插入序列的表現或以所期望方式修飾和加工基因產物的宿主細胞株。蛋白產物之這樣的修飾(例如，糖基化)和加工(例如，切割)對於結合蛋白的功能可能是重要的。不同宿主細胞對於蛋白和基因產物的翻譯後加工和修飾具有特徵和特定機制。可選擇適當細胞系或宿主系統以確保所表現的外源蛋白的正確修飾和加工。為此，可以使用具有用於初級轉錄物的適當加工、基因產物的糖基化和磷酸化的細胞機器的真核宿主細胞。這樣的哺乳動物宿主細胞包括但不限於CHO細胞、COS細胞、293細胞、3T3細胞、NS0細

胞、VERO細胞、BHK細胞或骨髓瘤細胞。

【0290】對於重組蛋白(如本揭露之LT β R結合蛋白)的長期、高產量生產，穩定表現係較佳的。例如，可以對穩定表現LT β R抗體分子的細胞系進行工程化。代替使用含有病毒複製起點的表現載體，宿主細胞可以使用由適當表現控制元件(例如啟動子、強化子、序列、轉錄終止子、聚腺苷酸化位點等)和選擇性標誌物來控制的DNA來轉化。在引入外源DNA後，可以允許工程化的細胞在富集的培養基中生長1-2天，並且然後切換至選擇性培養基。重組質體中的選擇性標誌物賦予對選擇的抗性，並且允許細胞穩定地將質體整合到其染色體中並生長以形成病灶，進而其可以進行選殖並擴展成細胞系。該方法可有利地用於工程化表現LT β R結合蛋白的細胞系。這樣的工程化的細胞系可以特別地用於篩選和評估與抗體分子直接或間接相互作用的化合物。

【0291】可以使用許多選擇系統，包括但不限於單純疱疹病毒胸苷激酶(參見例如，Wigler等人, *Cell*[細胞] 11:223 (1977))、次黃嘌呤鳥嘌呤磷酸核糖基轉移酶(參見例如，Szybalska和Szybalski, *Proc. Natl. Acad. Sci. USA*[美國國家科學院院刊] 48:202 (1992))和腺嘌呤磷酸核糖基轉移酶(參見例如，Lowy等人, *Cell*[細胞] 22:817 (1980))基因可分別用於tk、hgp^rt或ap^rt細胞。另外，可以將抗代謝藥抗性作為選擇以下基因的依據：dhfr，其賦予對胺甲喋呤的抗性(參見例如，Wigler等人, *Proc. Natl. Acad. Sci. USA*[美國國家科學院院刊] 77:357 (1980)；O'Hare等人, *Proc. Natl. Acad. Sci. USA*[美國國家科學院院刊] 78:1527 (1981))；gpt，其賦予對黴酚酸的抗性(參見例如，Mulligan和Berg, *Proc. Natl. Acad. Sci. USA*[美國國家科學院院刊] 78:2072 (1981))；neo，其賦予對胺基糖苷G-418的抗性(參見例如，Wu和Wu, *Biotherapy* [生物療法] 3:87-95 (1991))；以及hygro，其賦予對潮黴素的抗性(參見例如，Santerre等人, *Gene* [基因] 30:147 (1984))。可以將本領域公知的重組DNA技術的方法常規地應用於選擇所希望的重組選

殖，並且此類方法描述於例如，Ausubel等人(編輯), *Current Protocols in Molecular Biology* [分子生物學現代方法], John Wiley & Sons [約翰•威利父子公司], 紐約 (1993)；Kriegler, *Gene Transfer and Expression, A Laboratory Manual* [基因轉移和表現：實驗室手冊], Stockton Press [密斯托克頓出版社], 紐約 (1990)；以及第12和13章, Dracopoli等人(編輯), *Current Protocols in Human Genetics* [當代人類遺傳學實驗手冊], John Wiley & Sons [約翰•威利父子公司], 紐約 (1994)；Colberre-Garapin等人, *J. Mol. Biol.* [分子生物學雜誌] 150:1 (1981)。

【0292】 宿主細胞可以用本揭露之兩種表現載體進行共轉染，例如，第一載體編碼如本文所描述的促效劑LT β R結合蛋白重鏈或其可變結構域，第二載體編碼如本文所描述的LT β R結合蛋白輕鏈或其可變結構域。這兩種載體可含有相同的選擇性標誌物，這使得重鏈和輕鏈多肽能相等表現。可替代地，可以使用編碼並能夠表現例如重鏈和輕鏈多肽的單個載體。在這種情況下，輕鏈應置於重鏈之前，以避免過量的無毒重鏈（參見例如，Proudfoot, *Nature* [自然] 322:52 (1986)；Kohler, *Proc. Natl. Acad. Sci. USA* [美國國家科學院院刊] 77:2197 (1980)）。重鏈和輕鏈的編碼序列可以包含cDNA或基因組DNA。

【0293】 LT β R單鏈結合蛋白可以經由胺基酸橋（短肽連接基）藉由連接重鏈和輕鏈可變結構域（Fv區）片段形成，從而產生單個多肽鏈。這樣的單鏈Fv（scFv）已藉由在編碼兩個可變結構域多肽（V_L和V_H）的DNA之間融合編碼肽連接基的DNA來製備。所得多肽可以自身折疊以形成抗原結合單體，或者它們可以形成多聚體（例如，二聚體、三聚體或四聚體），這取決於兩個可變結構域之間的柔性連接基的長度（參見例如，Kortt等人, *Prot. Eng.* [蛋白質工程] 10:423 (1997)；Kortt等人, *Biomol. Eng.* [生物分子工程] 18:95-108 (2001)）。藉由組合包含不同V_L和V_H的多肽，可以形成與不同表位結合的多聚體scFv（Kriangkum等人, *Biomol. Eng.* [生物分子工程] 18:31-40 (2001)）。為生產單鏈結合蛋白而開發的技

術包括以下中描述的那些：美國專利案號4,946,778；Bird等人, *Science*[科學] 242:423 (1988)；Huston等人, *Proc. Natl. Acad. Sci. USA*[美國國家科學院院刊] 85:5879 (1988)；Ward等人, *Nature* [自然] 334:544 (1989)；de Graaf等人, *Methods Mol Biol.*[分子生物學方法] 178:379-87 (2002)。

【0294】在一個實施方式中，如本文所描述的能夠結合LT β R和TAA或SAA的雙特異性LT β R結合蛋白可以使用本領域已知的方法生產，例如參見，Yan等人的美國專利申請公開案號20200071425，或Kannan等人的美國專利案號8,592,562。在一個實施方式中，如本文所描述的雙特異性促效劑LT β R結合蛋白係使用以下中描述的方法生產：Wu等人的美國專利申請公開案號20100233173；Allan等人的美國專利申請公開案號20100105873；或Wu等人的美國專利申請公開案號20090155275。在一些實施方式中，如本文所描述的能夠結合LT β R和TAA或SAA的雙特異性促效劑LT β R結合蛋白使用以下中描述的方法生產：Thompson等人的美國專利申請公開案號20090175867和Thompson等人的美國專利申請公開案號20110033483。

【0295】本文所描述的雙特異性促效劑LT β R結合蛋白可以可替代地藉由直接回收例如在大腸桿菌中重組表現的Fab'片段產生，並且可以以化學偶合以形成雙特異性抗體（參見例如，Carter等人, *Applications for Escherichia coli-Derived Humanized Fab' Fragments: Efficient Construction of Bispecific Antibodies*[大腸桿菌衍生的人源化Fab'片段的應用：雙特異性抗體的高效構建]. 於：Rosenberg, M., Moore, G.P. (編輯) *The Pharmacology of Monoclonal Antibodies*[單株抗體的藥理學]. *Handbook of Experimental Pharmacology*[實驗藥理學手冊], v. 113. 施普林格，柏林，海德堡）。

【0296】一旦藉由本文所描述的任何方法生產促效劑LT β R結合蛋白，就使用標準免疫球蛋白純化方法進行純化。合適的純化方法包括但不限於層析法（例

如，離子交換、親和力，特別是藉由蛋白A後對特定抗原的親和力，以及大小排除層析法）、離心或差分溶解度。此外，本揭露之結合蛋白可以融合到本文所描述的或本領域已知的異源多肽序列，以促進純化。

藥物組成物

【0297】 本文提供了包含呈多肽、核酸、載體、宿主細胞或其組合的形式的促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白）的組成物。在一個實施方式中，本揭露之藥物組成物包含呈分離和/或純化的形式的促效劑LT β R結合蛋白或編碼其的多核苷酸。在一個實施方式中，該組成物包含本揭露之兩種或更多種不同的結合蛋白（例如，不同結構）和/或多核苷酸的組合。

【0298】 本揭露之藥物組成物包含增強促效劑LT β R結合蛋白或編碼其的多核苷酸的化學物理特性的藥劑，例如，經由在特定溫度（例如，室溫）下穩定、增加保質期、減少降解（例如，氧化蛋白酶介導的降解）、增加促效劑LT β R結合蛋白的半衰期等。

【0299】 在本揭露之示例性方面中，該組成物另外包含藥學上可接受的載劑、稀釋劑或賦形劑。在一些實施方式中，將如本文揭露的LT β R結合蛋白或編碼其的多核苷酸（以下稱為「活性劑」）配製成包含活性劑以及藥學上可接受的載劑、稀釋劑或賦形劑的藥物組成物。就此而言，本揭露進一步提供了包含活性劑的藥物組成物，該藥物組成物旨在投與至受試者，例如哺乳動物。

【0300】 在一些實施方式中，該活性劑以適合於投與至患者的純度水平存在於藥物組成物中。在一些實施方式中，該活性劑具有至少約90%、約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%的純度水平，和藥學上可接受的稀釋劑、載劑或賦形劑。在一些實施方式中，該等組成物含有約0.001至約30.0 mg/ml的濃度的活性劑。

【0301】在示例性方面中，該等藥物組成物包含藥學上可接受的載劑。如本文所用，術語「藥學上可接受的載劑」包括任一標準藥物載劑，例如磷酸鹽緩衝鹽水溶液、水、乳液（例如油/水或水/油乳液）和各種類型潤濕劑。該術語還涵蓋經美國聯邦政府的管理機構批准或在美國藥典中列出的用於包括人類的動物的任一試劑。

【0302】該藥物組成物可以包含任何藥學上可接受的成分，包括例如酸化劑、添加劑、吸附劑、氣溶膠推進劑、空氣置換劑、鹼化劑、抗結塊劑、抗凝劑、抗微生物防腐劑、抗氧化劑、防腐劑、基質、黏合劑、緩衝劑、螯合劑、包衣劑、著色劑、乾燥劑、洗滌劑、稀釋劑、消毒劑、崩解劑、分散劑、溶解增強劑、染料、潤膚劑、乳化劑、乳化穩定劑、填充劑、成膜劑、增味劑、調味劑、流動促進劑、膠凝劑、造粒劑、保濕劑、潤滑劑、黏膜黏附劑、軟膏基質、軟膏、含油載體、有機基質、錠劑基質、色素、增塑劑、拋光劑、防腐劑、螯合劑、增溶劑、溶劑、穩定劑、栓劑基質、界面活性劑（surface active agent）、界面活性劑（surfactant）、懸浮劑、增稠劑、張力劑、毒性劑、增黏劑、水吸收劑、水混溶性共溶劑、水軟化劑或潤濕劑（例如參見，the Handbook of Pharmaceutical Excipients[藥用賦形劑手冊], 第三版, A. H. Kibbe (Pharmaceutical出版社, 英國倫敦, 2000); Remington's Pharmaceutical Sciences[雷明頓製藥科學], 第十六版, E. W. Martin (Mack Publishing Co., 賓夕法尼亞州伊斯頓, 1980)）。

【0303】在示例性方面中，該藥物組成物包含在所採用的劑量和濃度下對接受者無毒的配製物材料。在一個實施方式中，藥物組成物包含活性劑和一或多種藥學上可接受的鹽、多元醇、界面活性劑、滲透平衡劑、張力劑、抗氧化劑、抗生素、抗真菌劑、填充劑；凍乾保護劑；消泡劑；螯合劑；防腐劑；色料；鎮痛劑；或另外的藥劑。在示例性方面，除了上文提到的賦形劑中的一或多種之外，該藥物組成物視需要包含一或多種多元醇和/或一或多種界面活性劑。

【0304】在某些實施方式中，該藥物組成物可含有用於改變、維持或保持例如組成物的pH值、滲透性、黏性、透明度、顏色、等滲性、氣味、無菌性、穩定性、分解或釋放速率、表面吸收或滲透的配製物材料。在這樣的實施方式中，合適的配製物材料包括但不限於胺基酸（例如甘胺酸、麩醯胺酸、天冬醯胺、精胺酸或離胺酸）；抗微生物劑；抗氧化劑（如抗壞血酸、亞硫酸鈉或亞硫酸氫鈉）；緩衝劑（如硼酸鹽、碳酸氫鹽、Tris-HCl、檸檬酸鹽、磷酸鹽或其他有機酸）；疏鬆劑（如甘露糖醇或甘胺酸）；螯合劑（如乙二胺四乙酸（EDTA））；複合劑（如咖啡因、聚乙烯吡咯啶酮、 β -環糊精或羥丙基- β -環糊精）；填充劑；單糖；二糖；和其他碳水化合物（諸如葡萄糖、甘露糖或糊精）；蛋白質（諸如血清白蛋白、明膠或免疫球蛋白）；著色劑、調味劑和稀釋劑；乳化劑；親水聚合物（如聚乙烯吡咯啶酮）；低分子量多肽；成鹽抗衡離子（如鈉）；防腐劑（諸如殺藻胺、苯甲酸、水楊酸、硫柳汞、苯乙醇、對羥基苯甲酸甲酯、對羥基苯甲酸丙酯、氯己定（chlorhexidine）、山梨酸或過氧化氫）；溶劑（如甘油、丙二醇或聚乙二醇）；糖醇（如甘露糖醇或山梨糖醇）；懸浮劑；界面活性劑或潤濕劑（例如 pluronics、PEG、脫水山梨醇酯、聚山梨醇酯例如聚山梨醇酯20、triton、胺丁三醇、卵磷脂、膽固醇、泰洛沙泊）；穩定性增強劑；張力增強劑（如鹼金屬鹵化物、較佳的是氯化鈉或氯化鉀，甘露糖醇，山梨糖醇）；遞送媒介物；稀釋劑；賦形劑和/或藥用輔助劑。參見REMINGTON'S PHARMACEUTICAL SCIENCES [雷明頓藥物科學], 第18版, (A. R. Genrmo編), 1990, Mack Publishing Company [麥克出版公司]。

【0305】藥物組成物可經配製以實現生理學上相容的pH值。在一些實施方式中，藥物組成物的pH值可例如在約4或約5與約8.0之間或約4.5與約7.5之間或約5.0至約7.5。

治療方法

【0306】 本揭露之另一方面涉及治療有需要的受試者之方法，其中該方法包括向有需要的受試者投與有效量的如本文所描述的促效劑LT β R結合蛋白，例如促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白或包含其的藥物組成物。在一個實施方式中，該促效劑LT β R結合蛋白係與人LT β R的CRD4結合的蛋白，並且 (a) 不抑制LIGHT與LT β R結合，以及 (b) 不抑制LT1 α 2 β 與LT β R結合。在一個實施方式中，該促效劑LT β R結合蛋白係促效劑LT β R抗體。在一個實施方式中，該促效劑LT β R結合蛋白係雙特異性LT β R結合蛋白，其包含 (i) LT β R結合結構域，其中該LT β R結合結構域結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R CRD4的一或多個胺基酸殘基；和 (ii) 腫瘤相關抗原結合結構域。該雙特異性LT β R結合蛋白激動LT β R活性，並且 (a) 不抑制LIGHT與LT β R結合和 (b) 不抑制LT1 α 2 β 與LT β R結合。在一個實施方式中，這種雙特異性促效劑LT β R結合蛋白對於LT β R結合係單價的。

【0307】 在一個實施方式中，有需要的受試者係患有癌症的受試者。在一個實施方式中，該受試者患有實體瘤。不受限於特定理論，在腫瘤微環境中激動LT β R活性增強了T細胞對腫瘤微環境的浸潤並誘導三級淋巴結構(TLS)的形成。LT β R的這種活性增強和/或提供了腫瘤微環境中的抗腫瘤T細胞活性。因此，在一個實施方式中，投與促效劑LT β R結合蛋白或包含其的藥物組成物適合於在患有腫瘤的受試者中誘導和/或增強抗腫瘤免疫反應。如本文所用，術語「受試者」係指包括人的哺乳動物，並且可與術語「患者」互換使用。

【0308】 因此，本文提供了增強受試者腫瘤微環境中T細胞數量和活性、增強受試者腫瘤微環境中T細胞存活和效應物功能、以及增強受試者腫瘤微環境中對靶細胞（例如，癌細胞）的細胞毒性之方法。在示例性實施方式中，該等方法包括向受試者投與有效量的本揭露之藥物組成物。在示例性方面中，T細胞活性或免疫反應係針對癌細胞或癌症組織或腫瘤細胞或腫瘤。在示例性方面中，免疫

反應為體液免疫反應。在示例性方面中，免疫反應為先天性免疫反應。在示例性方面中，增強的免疫反應為T細胞介導的免疫反應。

【0309】如本文所用，術語「增強」及其衍生詞不需要或推斷出100%或完全增強或增加。更確切些，存在本領域中普通技術者認為具有潛在益處或治療作用的不同程度的增強。就此而言，本揭露之藥物組成物可以增強例如T細胞活性或免疫反應到任何量或水平，超過在沒有用如本文所描述的LT β R結合蛋白治療的情況下存在的T細胞活性或免疫反應的量或水平。在示例性實施方式中，藉由本揭露之方法提供的抗腫瘤免疫的增強係抗腫瘤免疫增強至少或約10%、增強至少或約20%、增強至少或約30%、增強至少或約40%、增強至少或約50%、增強至少或約60%、增強至少或約70%、增強至少或約80%、增強至少或約90%、增強至少或約95%、增強至少或約98%。

【0310】測量T細胞活性和免疫反應的方法為本領域中已知。T細胞活性可以藉由例如細胞毒性測定法來測量，例如Fu等人, *PLoS ONE*[公共科學圖書館綜合] 5(7): e11867 (2010)中描述的那些。適用於測量響應的其他T細胞活性測定在Bercovici等人, *Clin Diagn Lab Immunol.*[臨床診斷實驗室免疫學] 7(6): 859-864 (2000)中進行了描述。測量免疫反應的合適方法包括例如Macatangay等人, *Clin Vaccine Immunol*[臨床和疫苗免疫學] 17(9): 1452-1459 (2010)和Clay等人, *Clin Cancer Res.*[臨床癌症研究]7(5):1127-35 (2001)中描述的那些。

【0311】需要用如本文所描述的促效劑LT β R結合蛋白治療的受試者包括但不限於患有癌症的受試者，特別是患有實性瘤的受試者。在示例性實施方式中，該方法包括向受試者投與促效劑LT β R結合蛋白或包含促效劑LT β R結合蛋白的藥物組成物，其量可有效治療受試者中的癌症或實性瘤。藉由本文揭露的方法和促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白）可治療的癌症可為任何癌症，例如由異常和不受控制的細胞分裂引起的任

何惡性生長或腫瘤，其可以藉由淋巴系統或血流擴散到身體的其他部位。在一個實施方式中，該癌症或實性瘤係「冷」腫瘤，即被抑制抗腫瘤免疫反應的細胞包圍的腫瘤。

【0312】 在一個實施方式中，要用如本文所描述的促效劑LTβR結合蛋白治療的受試者患有選自間皮瘤、胰臟腫瘤、卵巢腫瘤、肺腫瘤、食管腫瘤、胃腫瘤、肝腫瘤、結直腸腫瘤、宮頸腫瘤、子宮內膜腫瘤、乳房腫瘤、腎腫瘤、膀胱腫瘤、睪丸腫瘤、前列腺腫瘤、腦腫瘤、骨腫瘤和頭頸部腫瘤的腫瘤。在一個實施方式中，該癌症選自齒槽橫紋肌肉瘤、肛門癌、肛管癌或肛腸癌、眼癌、肝內膽管癌、關節癌、頸部癌、膽囊癌或胸膜癌、鼻癌、鼻腔癌或中耳癌、口腔癌、外陰癌、大腸癌、食道癌、子宮頸癌、胃腸道類癌、下嚥癌、腎癌、喉癌、肝癌、肺癌（例如，非小細胞肺癌（NSCLC））、惡性間皮瘤、黑色素瘤、鼻咽癌、卵巢癌、胰臟癌、腹膜癌、網膜癌和腸系膜癌、咽癌、前列腺癌、直腸癌、腎癌（例如，腎細胞癌（RCC））、小腸癌、軟組織癌、胃癌、睪丸癌、甲狀腺癌、輸尿管癌和膀胱癌。在示例性實施方式中，該受試者患有實性瘤，並且將促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或雙特異性促效劑LTβR結合蛋白）以有效治療受試者腫瘤的量投與至受試者。

【0313】 術語「治療」涵蓋減輕病症的至少一種症狀或其他實施方式、或降低疾病嚴重程度等。根據本揭露之促效劑LTβR結合蛋白，特別是結合人LTβR的CRD4並且不阻斷內源性LTβR配體結合的促效劑LTβR抗體或雙特異性結合蛋白，不需要完全治癒，或根除疾病的每種症狀或表現，即可構成可行的治療劑。正如在相關領域中所認識到的，治療劑可以降低特定疾病狀態的嚴重程度，但不需要消除疾病的每種表現才能被視為有用的治療劑。僅僅降低疾病的影響（例如藉由減少其症狀的次數或降低其症狀的嚴重度，或藉由增加另一治療的有效性，或藉由產生另一有益作用）或降低疾病在受試者中發生或惡化的可能性即為足

夠。本揭露之一個實施方式涉及一種方法，該方法包括向患者投與一定量的促效劑LT β R結合蛋白一段時間，該促效劑LT β R結合蛋白投與的量和時間足以誘導與反映特定病症嚴重程度的指標的基線相比的持續改善。在一個實施方式中，該方法包括向患者投與一定量的如本文揭露的促效劑LT β R結合蛋白一段時間，該促效劑LT β R結合蛋白投與的量和時間足以藉由增加腫瘤微環境中的免疫細胞浸潤和/或免疫細胞抗腫瘤活性將冷腫瘤轉化為熱腫瘤。在一個實施方式中，該方法進一步涉及將促效劑LT β R結合蛋白與一或多種免疫調節劑（例如PD(L)1-軸抑制劑）組合投與，以進一步刺激免疫細胞浸潤到腫瘤微環境中。

【0314】術語「預防」涵蓋預防病症的至少一種症狀或其他實施方式等。併入了如本文揭露的結合LT β R的CRD4並且不阻斷內源性LT β R配體結合活性的促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白）的預防性投與的治療不需要完全有效地預防病況的發作以構成可行的預防劑。僅僅降低疾病在受試者中發生或惡化的可能性即為足夠。在一個實施方式中，如本文所描述的促效劑LT β R結合蛋白的預防性投與藉由增強免疫細胞浸潤到腫瘤微環境中有效地防止腫瘤轉變為冷腫瘤。在一個實施方式中，如本文所描述的促效劑LT β R結合蛋白的預防性投與藉由在腫瘤微環境中增強免疫細胞浸潤和增強抗腫瘤免疫反應來有效地預防腫瘤生長。

【0315】如在相關領域中所理解的，將包含如本文揭露的促效劑LT β R結合蛋白的藥物組成物以適合於適應症和組成物的方式投與給受試者。在一個實施方式中，包含結合LT β R的CRD4並且不抑制內源性LT β R配體結合的促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白）的藥物組成物藉由任何合適的技術投與，包括但不限於胃腸外、靜脈內、肌內、病變內、腹膜內或皮下途徑、藉由推注或連續輸注。藉由吸入遞送包括，例如經鼻或經口吸入、使用霧化器、以氣溶膠形式吸入的促效劑LT β R結合蛋白等。其他替代品

包括口服製劑，包括丸劑、糖漿或錠劑。

【0316】 有利地，促效劑LTβR結合蛋白可以以組成物的形式投與，該組成物包含一或多種額外組分，例如生理上可接受的載劑、賦形劑或稀釋劑。視需要，該組成物另外包含一或多種生理活性劑。在各種特定實施方式中，除了一或多種促效劑LTβR結合蛋白外，該組成物還包含一種、兩種、三種、四種、五種或六種生理活性劑。

【0317】 提供了用於由執業醫師使用的套組，該等套組包括一或多種促效劑LTβR結合蛋白和用於治療本文所討論的任何病況的標記或其他說明書。在一個實施方式中，該等套組包括一或多種促效劑LTβR結合蛋白的無菌製劑，其可為如本文揭露的組成物的形式，並且可以在一或多個小瓶中。

【0318】 投與的劑量和頻率可根據諸如投與途徑、所採用的特定促效劑LTβR結合蛋白、待治療的疾病的性質和嚴重程度、病況是急性還是慢性、以及受試者的體型和一般狀況等因素而變化。適當的劑量可以藉由相關領域中（例如，在可能涉及劑量遞增研究的臨床試驗中）已知的程式來確定。

【0319】 如本文揭露的結合LTβR的CRD4並且不抑制內源性LTβR配體結合活性的促效劑LTβR結合蛋白可以例如一次或多次投與，例如在一段時間內以規則的間隔投與。在特定實施方式中，LTβR結合蛋白在至少每月一次或更長時間內投與，例如，持續一個月、兩個月或三個月或甚至無限期。對於治療慢性病，長期治療通常是最有效的。然而，對於治療急性病，較短時間投與（例如，一到六週）可能就足夠了。一般來說，投與促效劑LTβR結合蛋白，直到患者對所選一或多種指標表現出醫學相關的改善程度（相對於基線）。

【0320】 如本文揭露的結合LTβR的CRD4和/或不抑制內源性LTβR配體結合活性的促效劑LTβR結合蛋白可較佳的是與免疫調節治療劑的投與結合投與。在一個實施方式中，該免疫調節治療劑係檢查點抑制劑。合適的檢查點抑制劑係

本領域已知的，包括例如且不限於PD-1抑制劑、PD-L1抑制劑、CTLA-4抑制劑、TIM-3抑制劑、LAG-3抑制劑、NKG2A抑制劑、CD73抑制劑和TIGIT抑制劑以及其任何組合。下文更詳細地描述了合適的組合療法。

組合療法

【0321】 本揭露之方法和組成物的特定實施方式涉及使用至少一種促效劑LTβR結合蛋白和一或多種可用於治療或預防癌症的其他治療劑。在一個實施方式中，促效劑LTβR結合蛋白單獨投與或與可用於治療患有實性瘤的受試者的其他藥劑組合投與。這樣的藥劑之實例包括蛋白質和非蛋白質藥物。當共投與多種治療劑時，如相關技術中所認識到的，可以相應地調整劑量。「共投與」和組合療法不限於同時投與，還包括在涉及向患者投與至少一種其他治療劑的治療過程中至少投與一次促效劑LTβR結合蛋白的治療方案。在某些實施方式中，促效劑LTβR結合蛋白在投與至少一種其他治療劑之前投與。在某些實施方式中，促效劑LTβR結合蛋白與投與至少一種其他治療劑同時投與。在某些實施方式中，促效劑LTβR結合蛋白在投與至少一種其他治療劑之後投與。

【0322】 在一個實施方式中，該至少一種其他治療劑係免疫調節治療劑，特別是檢查點抑制劑或T細胞接合治療劑。合適的檢查點抑制劑係本領域已知的，包括例如且不限於PD-1抑制劑、PD-L1抑制劑、CTLA-4抑制劑、TIM-3抑制劑、LAG-3抑制劑、NKG2A抑制劑、CD73抑制劑和TIGIT抑制劑以及其任何組合。

【0323】 在一個實施方式中，如本文揭露的結合LTβR的CRD4且不抑制內源性LTβR配體結合活性的促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或雙特異性促效劑LTβR結合蛋白）與PD-1抑制劑（例如抗PD-1抗體）組合投與。合適的抗PD-1抗體之實例包括但不限於納武單抗（Opdivo®/KEGG D10316）、派姆單抗（Keytruda®/KEGG D10574）、西米普利單抗（Libtayo®/KEGG D11108）、

多塔利單抗（TSR-042/KEGG D11366）、斯巴達珠單抗（KEGG D11605）和匹地利珠單抗（CT-011；KEGG D10390）。

【0324】在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與PD-L1抑制劑（例如抗PD-L1抗體）組合投與。合適的抗PD-L1抗體之實例包括但不限於阿替利珠單抗（Tecentriq[®]；KEGG D10773）、阿維魯單抗（Bavencio[®]；KEGG D10817）和德瓦魯單抗（Imfinzi[®]；KEGG D10808）。

【0325】在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與CTLA-4抑制劑組合投與。合適的CTLA-4抑制劑係單株抗體伊匹單抗（Yervoy；KEGG D04603）。

【0326】在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與TIM-3抑制劑（例如抗TIM-3抗體）組合投與。合適的抗TIM-3抗體之實例包括但不限於沙巴托利單抗（MBG453；諾華公司（Novartis））；LY3321367（禮來公司（Eli Lilly））和TSR-022（Tesaro）。

【0327】在一個實施方式中，如本文揭露的結合LT β R的CRD4和/或不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與LAG-3抑制劑（例如抗LAG-3抗體）組合投與。適用於與本文所描述的LT β R結合蛋白組合使用的示例性抗LAG-3抗體包括但不限於瑞拉利單抗（KEGG D11350）。

【0328】在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與NKG2-A/NKG2-B II型整合膜蛋白（NKG2A）抑制劑（例如抗NKG2A抗體）組合投與。適用於與本文所描述的LT β R結合蛋白組合使用的示例性抗NKG2A抗體包括但不限於BMS-986315（Bristol Myers Squibb[®]）。

【0329】 在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與CD73抑制劑組合投與。與本文所描述的LT β R結合蛋白組合使用的合適的CD73抑制劑包括但不限於小分子CD73抑制劑OP-5244（Du等人, *J. Med. Chem.*[藥物化學雜誌] 63:10433-10459 (2020)，特此藉由引用將其全部併入）和LY-3475070（禮來公司（Eli Lilly））。

【0330】 在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與TIGIT抑制劑（例如抗TIGIT抗體）組合投與。合適的抗TIGIT抗體之實例包括但不限於BMS-986207（百時美施貴寶公司（Bristol-Myers Squibb））；Tiragolumab（羅氏公司（Roche））、MK-7684（默克公司（Merck））和COM902（Compugen公司）。

【0331】 在已經描述了本揭露以後，藉由說明而非限制的方式提供以下實施方式和實例。

實施方式

【0332】 本揭露提供了以下非限制性實施方式。

【0333】 本揭露之實施方式1涉及一種促效劑淋巴毒素 β 受體（LT β R）結合蛋白，其中所述結合蛋白結合包含人LT β R富含半胱胺酸結構域4（CRD4）的一或多個殘基的表位，其中人LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211，並且其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT α 1 β 2與LT β R結合。

【0334】 實施方式2係如實施方式1所述之促效劑LT β R結合蛋白，其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合且 (b) 不抑制LT α 1 β 2與LT β R結合。

【0335】 實施方式3係如實施方式1或2所述之促效劑LT β R結合蛋白，其中所述結合蛋白結合包含SEQ ID NO: 1的殘基197-209的LT β R CRD4的一或多個殘基。

【0336】實施方式4係如實施方式1-3所述之促效劑LT β R結合蛋白，其中在該促效劑LT β R結合蛋白存在下對LIGHT和/或LT α 1 β 2與LT β R結合的抑制在基於細胞的受體-配體結合測定中測量，所述測定包括以下步驟：將表現LT β R的細胞與含有該促效劑LT β R結合蛋白的培養基孵育1小時；在所述孵育後，使該等表現LT β R的細胞與可檢測的LIGHT配體、可檢測的LT α 1 β 2配體或其組合接觸，以允許該等可檢測的配體與LT β R結合；在所述接觸後，在該LT β R結合蛋白存在下，檢測與表現LT β R的細胞結合的可檢測的LIGHT和/或LT α 1 β 2配體；以及基於所述檢測將該促效劑LT β R結合蛋白鑒定為不抑制LIGHT或LT α 1 β 2與LT β R結合。

【0337】實施方式5係如實施方式1-4中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：與SEQ ID NO: 121或SEQ ID NO: 123具有至少90%序列同一性的重鏈可變結構域（VH）胺基酸序列和與SEQ ID NO: 122或SEQ ID NO: 124具有至少90%序列同一性的輕鏈可變結構域（VL）胺基酸序列。

【0338】實施方式6係如實施方式1-4中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：與SEQ ID NO: 121和SEQ ID NO: 123具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 122和SEQ ID NO: 124具有至少90%序列同一性的VL胺基酸序列。

【0339】實施方式7係如實施方式1-4中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：與SEQ ID NO: 121和SEQ ID NO: 123具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 122和SEQ ID NO: 124具有至少95%序列同一性的VL胺基酸序列。

【0340】實施方式8係如實施方式1-7中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：VH，其包含HCDR1胺基酸序列X₁YX₃MX₅（SEQ ID NO: 5），其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺基酸序

列X₁IX₃YDX₆X₇X₈X₉Y X₁₁X₁₂DSVKG (SEQ ID NO: 6) , 其中X₁為A或V ; X₃為W或R ; X₆為E或G ; X₇為S、R或T ; X₈為N或K ; X₉為K、R或Q ; X₁₁為H或Y ; 並且X₁₂為A或E ; 以及HCDR3胺基酸序列X₁RX₃X₄X₅X₆ X₇X₈X₉YYGX₁₃X₁₄V (SEQ ID NO: 7) , 其中X₁為D或E ; X₃為V、G或I ; X₄為V、P或A ; X₅為A、Y或G ; X₆為R、A、G或H ; X₇為P或G ; X₈為G、N、D、Y、A或H ; X₉為Y、T或F ; X₁₃為L或M ; 並且X₁₄為D或A ; VL , 其包含LCDR1胺基酸序列SGDX₄LPX₇X₈YX₁₀Y (SEQ ID NO: 62) , 其中X₄為A或T ; X₇為E、K、Q、D或N ; X₈為Q或H ; 並且X₁₀為A或T ; LCDR2胺基酸序列KDNERPS (SEQ ID NO: 63) ; 以及LCDR3胺基酸序列QSX₃DX₅SX₇X₈YX₁₀X₁₁ (SEQ ID NO: 64) , 其中X₃為A或T ; X₅為S、G或N ; X₇為G或A ; X₈為T、S或A ; X₁₀為V或M ; 並且X₁₁為I或V。

【0341】 實施方式9係如實施方式1-8中任一項所述之促效劑LTβR結合蛋白，其中所述結合蛋白包含：與SEQ ID NO: 121具有至少90%序列同一性的VH胺基酸序列、以及SEQ ID NO: 5的HCDR1胺基酸序列、SEQ ID NO: 6的HCDR2胺基酸序列和SEQ ID NO: 7的HCDR3胺基酸序列；以及與SEQ ID NO: 122具有至少90%序列同一性的VL胺基酸序列、以及SEQ ID NO: 62的LCDR1胺基酸序列、SEQ ID NO: 63的LCDR2胺基酸序列和SEQ ID NO: 64的LCDR3胺基酸序列。

【0342】 實施方式10係如實施方式1-9中任一項所述之促效劑LTβR結合蛋白，其中所述結合蛋白包含：VH，其包含分別為SEQ ID NO: 11-13的HCDR1、HCDR2和HCDR3胺基酸序列，以及VL，其包含分別為SEQ ID NO: 68-70的LCDR1、LCDR2和LCDR3胺基酸序列；或VH，其包含分別為SEQ ID NO: 8-10的HCDR1、HCDR2和HCDR3胺基酸序列，以及VL，其包含分別為SEQ ID NO: 65-67的LCDR1、LCDR2和LCDR3胺基酸序列。

【0343】 實施方式11係如實施方式1-10中任一項所述之促效劑LTβR結合蛋白，其中該結合蛋白係抗體。

【0344】實施方式12係如實施方式1-10中任一項所述之促效劑LT β R結合蛋白，其中該結合蛋白係雙特異性結合蛋白。

【0345】實施方式13涉及雙特異性淋巴毒素 β 受體（LT β R）結合蛋白，所述結合蛋白包含：LT β R結合結構域，其中該LT β R結合結構域結合包含人LT β R富含半胱氨酸結構域4（CRD4）的一或多個殘基的表位，其中所述LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211；和腫瘤相關抗原結合結構域，其中該雙特異性結合蛋白激動LT β R活性，並且 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT α 1 β 2與LT β R結合。

【0346】實施方式14係如實施方式13所述之雙特異性促效劑LT β R結合蛋白，其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合且 (b) 不抑制LT α 1 β 2與LT β R結合。

【0347】實施方式15係如實施方式13所述之雙特異性促效劑LT β R結合蛋白，其中該表位包含SEQ ID NO: 1之位置197-209處的LT β R CRD4的一或多個殘基。

【0348】實施方式16係如實施方式13-15中任一項所述之雙特異性促效劑LT β R結合蛋白，其中在該雙特異性促效劑LT β R結合蛋白存在下對LIGHT和/或LT α 1 β 2與LT β R結合的抑制在基於細胞的受體-配體結合測定中測量，所述測定包括以下步驟：將表現LT β R的細胞與含有該雙特異性促效劑LT β R結合蛋白的培養基孵育1小時；在所述孵育後，使該等表現LT β R的細胞與可檢測的LIGHT配體、可檢測的LT α 1 β 2配體或其組合接觸，以允許該等可檢測的配體與LT β R結合；在所述接觸後，在該雙特異性促效劑LT β R結合蛋白存在下，檢測與表現LT β R的細胞結合的可檢測的LIGHT和/或LT α 1 β 2配體；以及基於所述檢測將該雙特異性促效劑LT β R結合蛋白鑒定為不抑制LIGHT或LT α 1 β 2與LT β R結合。

【0349】實施方式17係如實施方式13-15中任一項所述之雙特異性促效劑

LTβR結合蛋白，其中該LTβR結合結構域包含：與SEQ ID NO: 121或SEQ ID NO: 123具有至少90%序列同一性的VH胺基酸序列，和與SEQ ID NO: 122或SEQ ID NO: 124具有至少90%序列同一性的VL胺基酸序列。

【0350】 實施方式18係如實施方式13所述之雙特異性促效劑LTβR結合蛋白，其中該LTβR結合結構域包含：與SEQ ID NO: 121和SEQ ID NO: 123具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 122和SEQ ID NO: 124具有至少90%序列同一性的VL胺基酸序列。

【0351】 實施方式19係如實施方式13所述之雙特異性促效劑LTβR結合蛋白，其中該LTβR結合結構域包含：與SEQ ID NO: 121和SEQ ID NO: 123具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 122和SEQ ID NO: 124具有至少95%序列同一性的VL胺基酸序列。

【0352】 實施方式20係如實施方式13-19中任一項所述之雙特異性促效劑LTβR結合蛋白，其中該LTβR結合結構域包含：VH，其包含HCDR1胺基酸序列X₁YX₃MX₅（SEQ ID NO: 5），其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺基酸序列X₁IX₃YDX₆X₇X₈X₉Y X₁₁X₁₂DSVKG（SEQ ID NO: 6），其中X₁為A或V；X₃為W或R；X₆為E或G；X₇為S、R或T；X₈為N或K；X₉為K、R或Q；X₁₁為H或Y；並且X₁₂為A或E；以及HCDR3胺基酸序列X₁RX₃X₄X₅X₆X₇X₈X₉YYGX₁₃X₁₄V（SEQ ID NO: 7），其中X₁為D或E；X₃為V、G或I；X₄為V、P或A；X₅為A、Y或G；X₆為R、A、G或H；X₇為P或G；X₈為G、N、D、Y、A或H；X₉為Y、T或F；X₁₃為L或M；並且X₁₄為D或A；VL，其包含LCDR1胺基酸序列SGDX₄LPX₇X₈YX₁₀Y（SEQ ID NO: 62），其中X₄為A或T；X₇為E、K、Q、D或N；X₈為Q或H；並且X₁₀為A或T；LCDR2胺基酸序列KDNERPS（SEQ ID NO: 63）；以及LCDR3胺基酸序列QSX₃DX₅SX₇X₈YX₁₀X₁₁（SEQ ID NO: 64），其中X₃為A或T；X₅為S、G或N；X₇為G或A；X₈為T、S或A；X₁₀為V或M；並且X₁₁為

I或V。

【0353】實施方式21係如實施方式13-20中任一項所述之雙特異性促效劑LT β R結合蛋白，其中所述結合蛋白包含：與SEQ ID NO: 121具有至少90%序列同一性的VH胺基酸序列、以及SEQ ID NO: 5的HCDR1胺基酸序列、SEQ ID NO: 6的HCDR2胺基酸序列和SEQ ID NO: 7的HCDR3胺基酸序列；以及與SEQ ID NO: 122具有至少90%序列同一性的VL胺基酸序列、以及SEQ ID NO: 62的LCDR1胺基酸序列、SEQ ID NO: 63的LCDR2胺基酸序列和SEQ ID NO: 64的LCDR3胺基酸序列。

【0354】實施方式22係如實施方式13所述之雙特異性促效劑LT β R結合蛋白，其中該VH包含分別為SEQ ID NO: 11-13的HCDR1、HCDR2和HCDR3胺基酸序列，以及該VL包含分別為SEQ ID NO: 68-70的LCDR1、LCDR2和LCDR3胺基酸序列；或該VH包含分別為SEQ ID NO: 8-10的HCDR1、HCDR2和HCDR3胺基酸序列，以及該VL包含分別為SEQ ID NO: 65-67的LCDR1、LCDR2和LCDR3胺基酸序列。

【0355】實施方式23係如實施方式13-22中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該雙特異性結合蛋白僅包含一個LT β R結合結構域。

【0356】實施方式24係如實施方式13-22中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域係Fab。

【0357】實施方式25係如實施方式13-24中任一項所述之雙特異性促效劑LT β R結合蛋白，其中結合蛋白包含一個腫瘤相關抗原結合結構域。

【0358】實施方式26係如實施方式25所述之雙特異性促效劑LT β R結合蛋白，其中該腫瘤相關抗原結合結構域係Fab。

【0359】實施方式27係如實施方式13-24中任一項所述之雙特異性促效劑LT β R結合蛋白，其中結合蛋白包含兩個腫瘤相關抗原結合結構域。

【0360】實施方式28係如實施方式13-22中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域係Fab，並且該腫瘤相關抗原結合結構域係Fab。

【0361】實施方式29係如實施方式13-28中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域和該腫瘤相關抗原結合結構域各自偶合到Fc部分。

【0362】實施方式30係如實施方式29所述之雙特異性促效劑LT β R結合蛋白，其中該Fc部分不與Fc γ 受體結合。

【0363】實施方式31涉及編碼如實施方式1-12中任一項所述之促效劑LT β R結合蛋白的多核苷酸。

【0364】實施方式32係包含如實施方式31所述之多核苷酸的載體。

【0365】實施方式33係包含如實施方式31所述之多核苷酸或如實施方式32所述之載體的宿主細胞。

【0366】實施方式34係編碼如實施方式13-30中任一項所述之雙特異性促效劑LT β R結合蛋白的一或多種多核苷酸。

【0367】實施方式35係包含如實施方式34所述之一或多種多核苷酸的載體。

【0368】實施方式36係包含如實施方式34所述之一或多種多核苷酸或如實施方式35所述之載體的宿主細胞。

【0369】實施方式37係一種藥物組成物，其包含：如實施方式1-12中任一項所述之促效劑LT β R結合蛋白，如實施方式13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，如實施方式31或34所述之一或多種多核苷酸，或如實施方式32或35所述之載體，以及藥學上可接受的載劑。

【0370】實施方式38係如實施方式1-12中任一項所述之促效劑LT β R結合

蛋白，用作藥物。

【0371】實施方式39係如實施方式1-12中任一項所述之促效劑LT β R結合蛋白，用於治療癌症。

【0372】實施方式40係如實施方式1-12中任一項所述之促效劑LT β R結合蛋白，用於製備用於治療癌症的藥物。

【0373】實施方式41係如實施方式13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，用作藥物。

【0374】實施方式42係如實施方式13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，用於治療癌症。

【0375】實施方式43係如實施方式13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，用於製備用於治療癌症的藥物。

【0376】實施方式44涉及一種治療受試者癌症之方法，所述方法包括：向患有癌症的受試者投與促效劑淋巴毒素 β 受體（LT β R）結合蛋白，其中所述結合蛋白結合包含人LT β R富含半胱胺酸結構域4（CRD4）的一或多個殘基的表位，其中人LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211，並且其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT α 1 β 2與LT β R結合。

【0377】實施方式45係一種治療受試者癌症之方法，所述方法包括：向患有癌症的受試者投與雙特異性淋巴毒素 β 受體（LT β R）結合蛋白，其中所述結合蛋白包含：LT β R結合結構域，其中該LT β R結合結構域結合包含人LT β R富含半胱胺酸結構域4（CRD4）的一或多個胺基酸殘基的表位，其中人LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211；和腫瘤相關抗原結合結構域，其中該雙特異性結合蛋白激動LT β R活性，並且 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT1 α 2 β 與LT β R結合。

【0378】實施方式46係如實施方式44或實施方式45所述之方法，進一步包

括：與所述促效劑LT β R結合蛋白或雙特異性LT β R結合蛋白結合投與免疫調節治療劑。

【0379】實施方式47係如實施方式41或42所述之方法，其中該受試者患有選自由以下組成之群組的實性瘤：間皮瘤、胰臟腫瘤、卵巢腫瘤、肺腫瘤、食管腫瘤、胃腫瘤、肝腫瘤、結直腸腫瘤、宮頸腫瘤、子宮內膜腫瘤、乳房腫瘤、腎腫瘤、膀胱腫瘤、睪丸腫瘤、前列腺腫瘤、腦腫瘤、骨腫瘤和頭頸部腫瘤。

實例

【0380】給出以下實例僅用於說明本發明，而不以任何方式限制其範圍。

實例1：靶向腫瘤相關抗原（TAA）的LT β R激動作用在體內腫瘤模型中表現出治療功效

【0381】**1.1 靶向EpCAM的LT β R激動作用在鼠B16F10黑色素瘤模型中誘導HEV形成並增加淋巴細胞浸潤。**在研究第0天，將huEpCAM-B16F10腫瘤細胞皮下植入雌性野生型C57BL/6動物的右側腹部。在第10天將腫瘤分為不同的治療組（n=10/組），平均腫瘤體積為約100 mm³。每三天一次給動物靜脈給藥30 mg/kg的對照同種型mIgG1（美商安進公司（Amgen），PL-11445-3）或增加劑量（0.3、3和30 mg/kg）的huEpCAM-muLT β R（5G11）雙特異性促效劑LT β R工具抗體（美商安進公司，7622-1）。在第20天收穫腫瘤。將一半的腫瘤解離進行流動式細胞分析術分析，並且另一半用福馬林固定進行組織學分析。如圖1所示，浸潤到腫瘤環境中的CD3⁺ T細胞的總數（圖1A）在3 mg/kg劑量下增加，並且浸潤到腫瘤環境中的CD19⁺ B細胞的總數（圖1B）以劑量依賴性方式增加。使用流動式細胞分析術評估T和B細胞浸潤。如圖2所示，huEpCAM-LT β R治療誘導了腫瘤環境中高內皮小靜脈（HEV）的形成（下圖）。在同種型對照治療的腫瘤組織中未觀察到HEV的存在（圖2，上圖）。使用抗PNAd（Meca79）mAb藉由免疫組織化學染

色來評估HEV的存在。

【0382】 1.2 靶向LRRC15的LTβR激動作用在KPC M5腫瘤模型中誘導淋巴細胞浸潤並抑制腫瘤生長。在研究的第0天，將KPC M5胰臟腫瘤細胞皮下植入雌性野生型C57BL/6小鼠的右側腹部。使腫瘤生長10天，達到大約100 mm³，然後隨機分為相應組（n = 5/組）。每週兩次向動物以3 mpk給藥三劑小鼠工具LRRC15 x LTβR雙特異性抗體（BsAb）（36017-1和28786-1/64506-1）或同種型對照mIgG1 N297G（PL-57469）。在最後一劑LRRC15 x LTβR BsAb（第20天）後三天收穫腫瘤和血清。收集皮膚附著在外周的腫瘤。去除附著的皮膚，並且解離腫瘤以進行流動式細胞分析術分析。如圖3所示，與同種型對照相比，觀察到LRRC15 x LTβR雙特異性抗體治療後，T細胞浸潤（CD3⁺細胞）到腫瘤中的增加。

【0383】 在另一項研究中，在第0天將KPC M5胰臟腫瘤細胞（100k/小鼠）皮下植入雌性野生型C57BL/6小鼠的右側腹部。使腫瘤生長10天，直到平均腫瘤體積達到100 mm³。將動物隨機分組以接受LRRC15 x LTβR BsAb（36017-1）或同種型對照治療（n = 10/組）。對動物進行腹膜內給藥，每週兩次，共9劑（或直到該等動物退出），使用3 mg/kg的對照同種型mIgG1（11445-3），每週兩次，共9劑，使用3 mg/kg的LRRC15 x LTβR BsAb，或每三天一次，共3劑，使用100 μg/小鼠的抗PD1抗體（7358-1）。每週兩次測量腫瘤並稱量體重，直到腫瘤達到大於或等於2000 mm³或動物達到中位存活極限的兩倍。如圖4所示，與同種型(●)相比，PD-1抗體治療(■)沒有顯著抑制腫瘤生長，僅產生4.64%的腫瘤生長抑制（TGI）。與同種型相比，用LRRC15 x LTβR BsAb單一療法(▼)治療的腫瘤確實產生了20.76%的統計學顯著TGI。LRRC15 x LTβR BsAb和PD-1抗體組合確實導致了32.37%的更大TGI，但兩個治療組之間沒有統計學顯著性。

實例2：人LTβR結合蛋白的產生

【0384】 藉由免疫XenoMouse®轉基因小鼠產生針對人LTβR的完全人抗

體。XenoMouse®及其用於產生人抗體的效用在以下中公開：美國專利案號 6,114,598 ； 6,162,963 ； 6,833,268 ； 7,049,426 ； 7,064,244 和 Green 等人, *Nature Genetics*[自然遺傳學] 7:13-21 (1994)；Mendez等人, *Nature Genetics*[自然遺傳學] 15:146-156 (1997)；Green和Jakobovitis, *J. Ex. Med*[實驗醫學雜誌], 188:483-495 (1998)；Kellerman和Green, *Current Opinion in Biotechnology*[生物技術的當前觀點] 13, 593-597 (2002)，特此藉由引用將其全部併入。多種免疫原和免疫途徑用於產生抗人LTβR免疫反應。使用GeneGun（BioRad）方案在6-8週內對產生人免疫球蛋白G（IgG）2或IgG 4抗體的轉基因XenoMouse®進行12-16次皮內免疫，該方案遞送包有編碼人LTβR的質體DNA和分子佐劑的金微粒。可替代地，用暫態轉染人或cyno LTβR表現載體的CHO-S細胞對動物進行皮下免疫。對於可溶性蛋白免疫，對小鼠皮下注射人LTβR重組蛋白，每次增強5 μg蛋白質，每週兩次，持續6-8週。在第4週將Cyno LTβR抗原引入小鼠，並與人LTβR抗原以交替的時間表進行注射。為了選擇產生對LTβR特異的抗體的動物，測試了來自免疫小鼠的血清與暫態轉染的HEK 293細胞上表現的人和cyno LTβR的結合，並藉由螢光激活細胞分選（FACS）進行分析。應用相對於背景的倍數GeoMean變化來選擇對人和cyno LTβR具有最高天然效價的響應小鼠。所選的小鼠在組織收穫前4天接受最後的增強，隨後進行B細胞富集。收穫和免疫原的詳細資訊列於表15中。

[表15]. XenoMouse®免疫和抗體收穫總結

收穫組	免疫原	佐劑	菌株	收穫
收穫2.3	編碼hu LTβR的質體DNA + 編碼cyno LTβR的質體DNA	CpG + mGM-CSF	G4K	10隻小鼠
			G4KL	5隻小鼠
收穫3.4	暫態表現hu LTβR的CHO-S + 暫態表現cyno LTβR的 CHO-S	Alum + CpG	G2K	2隻小鼠
			G2KL	8隻小鼠
收穫4.4	暫態表現hu LTβR的CHO-S	Alum + CpG	G4K	4隻小鼠

	+ 暫態表現cyno LTβR的 CHO-S		G4KL	6隻小鼠
收穫5.2	重組人LTβR Fc嵌合體 + 重 組Cyno LTβR Fc嵌合體	Alum + CpG	G2K	4隻小鼠
			G2KL	4隻小鼠

實例3：單株抗體融合瘤產生的製備。

【0385】 鑒別展現合適血清效價的動物且自脾和/或引流淋巴結獲得淋巴細胞。藉由在合適的培養基（例如，RPMI 1640培養基；加利福尼亞州卡爾斯巴德的英傑公司（Invitrogen, Carlsbad, CA））中研磨，將彙集的淋巴細胞（來自每次收穫）從淋巴組織中解離。使用標準方法選擇和/或擴增B細胞，並使用本領域已知的技術與合適的融合配偶體融合。

實例4：用於LTβR結合物鑒定的融合瘤池的第一輪篩選

【0386】 4.1從融合瘤池中產生選殖抗LTβR融合瘤。將來自收穫1至6的XenoMouse®融合瘤培養物解凍，並在DMEM選擇培養基中生長3-4天。在FACS富集分選前一天將培養基改為BDQY融合瘤培養基。將細胞在10 mL無菌FACS緩衝液中洗滌，然後與生物素標記的重組人LTβR（R&D系統公司（R&D Systems），目錄號：7538LR）以2-5 μg/mL濃度在1 mL反應體積中在4°C下孵育30分鐘。對於收穫5和6融合瘤培養物，在該步驟中還添加100 μg/mL多選殖人IgG（傑克遜免疫研究公司（Jackson ImmunoResearch），目錄號：009-000-003）以阻斷抗Fc結合物。在10 mL FACS緩衝液中洗滌一次後，將1 mL抗體混合物添加到細胞中，該抗體混合物含有各5 μg/mL的Alexa Fluor 488軛合的山羊抗人IgG Fc Fab（傑克遜免疫研究公司，目錄號：109-547-008）和Alexa Fluor 647軛合的鏈黴親和素（傑克遜免疫研究公司，目錄號：016-600-084）。然後將細胞在4°C下孵育30分鐘。孵育後，將細胞在10 mL FACS緩衝液中洗滌，重懸於2 mL含有5 μL 7-AAD（BD Pharmingen公司，目錄號：559925）的BDQY融合瘤培養基中，

然後通過40微米細胞過濾器以去除任何團塊。藉由對Alexa Fluor 488和Alexa Fluor 647螢光訊號雙陽性的活細胞群體進行門控，在BD FACSAria®上對細胞進行批量分選。在第一輪富集分選以使目標群體從< 1%到> 20%之後，將靶細胞單細胞分選到含有BDQY融合瘤培養基的384孔微量滴定板上，並培養長達2週，然後收集上清液進行篩選。

【0387】 4.2 LTβR特異性結合抗體的初始選擇。藉由按照製造商制定的方案使用表現載體、Opti-MEM®培養基(Gibco™，目錄號31985088)和293Fectin™試劑(英傑公司，目錄號12347019)轉染，在宿主人胚胎腎293細胞上表現人LTβR (pTT5.2:VK1O2O12::huLTβR(31-435) C-173003 (DNA-38098))。轉染後二十四小時，每15 μL體積FACS緩衝液(磷酸鹽緩衝鹽水(1X) 0.0067M (PO4) (賽提瓦公司(Cytiva) 目錄號:SH30256.02)、2%胎牛血清(海選殖公司(Hyclone) 目錄號:SH30396.03)和30 μg/mL的Hoechst核染劑(Hoechst 33342溶液(20 mM)，賽默飛世爾公司(ThermoFisher) 目錄號:62249))重懸13000個轉染細胞。將細胞與15 μL融合瘤上清液在室溫下在Corning® 384孔平底透明黑聚苯乙烯TC處理的微孔板中孵育1小時。使用AquaMax 4000平板洗滌機(分子儀器公司(Molecular Devices))用50 μL PBS洗滌細胞兩次。在室溫下以5 μg/mL最終濃度添加到Alexa Fluor 488軛合的AffiniPure山羊抗人IgG(Jackson 109-545-098)，持續20分鐘。用50 μL PBS洗滌細胞兩次以去除未結合的檢測試劑，並添加額外的30 μL FACS緩衝液以用微孔板軌道板振盪器(Big Bear Automation Model HT-91000)重懸細胞。在CellInsight CX7高含量篩選(HCS)平臺上使用Acquire only and Cell Health Profiling Bio-Apps HCS Studio 2.0軟體讀取平板。表16列出了每次收穫的結合物數量。

[表16].每次收穫的LTβR結合物

收穫編號	總共陽性#
2.3	364個天然結合物
3.4	679個天然結合物
4.4	651個天然結合物
5.2	350個天然結合物

【0388】 **4.3 LTβR單點和效力功能測定** 在測定第1天，將人黑色素瘤A375細胞（ATCC，CRL-1619）以10,000個細胞/孔（50 μL）接種在384孔測定板中生長培養基（DMEM，10% FBS，4 mM L-麩醯胺酸，1.5 g/L碳酸氫鈉，4.5 g/L葡萄糖）中。將板在37°C/5% CO2下孵育過夜。在測定第2天，從384孔測定板中取出40 μL/孔的培養上清液。在測定培養基（含有2% FBS的生長培養基）中以最終濃度0.5 μg/mL製備蛋白G（西格瑪公司（Sigma），目錄號P4689）。抗LTβR mAb（R&D系統公司，選殖71315和選殖31G4D8）分別以最終濃度為1 μg/mL和5 μg/mL製備，以1：3向下滴定共8個點。對於單點篩選，添加最終濃度為1 μg/mL的含有抗huLTβR抗體的耗盡上清液（ESN）。在添加或不添加蛋白G作為交聯劑的情況下，將測試樣本轉移到384孔測定板中的所期望的孔中。384孔測定板中的最終總體積為50 μL/孔。將測定板在37°C/5% CO2下孵育過夜。在測定第3天，藉由機器人將16 μL上清液從384孔測定板轉移到384孔低體積板。根據製造商之說明，藉由檢測套組（希思公司（Cisbio），目錄號62IL8PEC）測量趨化因子IL-8釋放，並藉由微孔板讀取器在665 nm和615 nm處讀取。相對IL-8釋放表示為在665 nm/615 nm處獲得的訊號的比率。在沒有蛋白G交聯的情況下表現出低活性，但在蛋白G交聯的情況下表現出高活性的抗體被用於效力測試。

【0389】 對於功能效力篩選，先將ESN歸一化至10 μg/mL，然後在測定培養基中進一步稀釋至最終濃度1 μg/mL，以1：3向下滴定共8個點。抗LTβR抗體的插值EC50、轉運EC50（當訊號=4時）和最大活性（當ENS以1 μg/mL使用時）

藉由Genedata Screener (Smart fit公司) 的四參數邏輯擬合模型確定。LTβR抗體的功能效力分析、Transit EC₅₀和最大活性 (在665 nm/615 nm獲得的訊號比率) 的結果提供於圖5的表A中。

【0390】 4.4 LTβR特異性結合抗體的選擇性和交叉反應性 食蟹猴主要LTβR (pTT5.2:VK1O2O12::cyLTβR (31-253) C173083 (DNA-38100))、食蟹猴次要LTβR(pTT5.2:VK1O2O12::cyLTβR_minor (31-434) C173082(DNA-38099))、鼠LTβR (pTT5.2:VK1O2O12::muLTβR_native(31-415) - DNA-37605) 、腫瘤壞死受體超家族1 (pTT5:huTNFRp55 (huTNFRSF1) C-159747 - DNA-22292) 和腫瘤壞死受體超家族2 (pTT5:huTNFRp75-FL (TNFRSF2) C-159746 - DNA-22291) 分別藉由按照製造商制定的方案使用表現載體、Opti-MEM®培養基 (Gibco™, 目錄號31985088) 和293Fectin™試劑(英傑公司, 目錄號12347019) 轉染在宿主HEK 293細胞上表現。藉由在每個轉染細胞上孵育抗體1小時, 然後進行兩個洗滌步驟以去除一抗, 來篩選融合瘤上清液中是否存在結合cyno主要LTβR、cyno次要LTβR, Mu LTβR、TNFRSF1和TNFRSF2的單株抗體。然後將細胞與軛合於Alexa647 (傑克遜免疫化學 (Jackson Immunochemical) 109-605-098) 的山羊抗人Fc抗體一起孵育15分鐘, 並洗滌兩次以去除未結合的檢測試劑。使用Intellicyt公司Accuri iQue™平臺藉由FACS檢測結合。使用Intellicyt公司ForeCyt®企業客戶版軟體進行數據分析。包括使用空pTT5表現載體轉染的HEK 293細胞 (模擬轉染), 數據呈現為模擬轉染細胞的GeoMean倍數。如圖5的表A所示, LTβR抗體均未表現出與TNFRSF1或TNFRSF2的結合。

【0391】 4.5 相對表位分組/分析。將生物素醃化的重組可溶性人LTβR蛋白Fc嵌合體 (R&D系統公司7538-LR-100) 以2 μg/mL濃度與鏈黴親和素包被的、經獨特條碼編碼的LumAvidin Beads® (LumAvidin Microspheres, 路明克斯公司 (Luminex Corp.) , 美國德克薩斯州奧斯丁) 在室溫下在黑暗中偶合30分鐘, 並

洗滌兩次。將5 µg/mL濃度的參考抗體融合瘤上清液樣本與抗原包被的珠粒在室溫下在黑暗中孵育1小時，並洗滌三次。將珠粒重懸於含有免疫測定穩定劑溶液（Stabilguard™，舒爾默迪克斯公司（SurModics））的FACS緩衝液中。將抗原包被的參考抗體結合珠粒合併，然後將該等珠粒分到含有歸一化的（2 µg/ml）測試抗體（融合瘤上清液）樣本（或陰性對照）的單個樣本孔中，在室溫下在黑暗中孵育1小時，並洗滌兩次。然後將樣本與Mo抗HuG2、G3、G4（PL-46339，由已停產的卡爾生物化學公司（Calbiochem）HP6030抗體序列製成）在室溫下在黑暗中孵育1小時，並洗滌兩次。將樣本與軛合於Alexa488（傑克遜免疫化學115-545-071）的山羊抗小鼠Fc抗體在室溫下在黑暗中孵育15分鐘，並洗滌兩次以去除未結合的檢測試劑，並重懸於FACS緩衝液中。使用Intellicyt公司iQue™ Screener平臺對樣本進行分析。為了確定各個測試抗體的抗體競爭/結合譜，從每個競爭/結合反應（即整個參考抗體組）的參考抗體加測試抗體訊號中減去僅參考抗體結合訊號。單個抗體結合譜被定義為每個競爭/結合反應的淨結合值的集合。然後藉由計算每個測試抗體譜之間的決定係數來評估單個譜之間的相似程度。然後將顯示彼此高度相似（ $R^2 > 0.8$ ）的測試抗體分組到共同的分組譜中。使用這種方法，將LTβR結合抗體細分為6個獨特的分組譜（A、B、C、D、E和F）。表現出獨特的分組譜（如上文所描述的）但與另一個譜共用相對高度相似（ $R^2 = 0.7-0.8$ ）的抗體被歸類為該譜的子組（即A.1、A.2等）。LTβR抗體的相對表位分組結果如圖5的表A所示。

【0392】 4.6 使用基於單點FACS珠粒的受體-配體測定鑒定LTβR受體-配體非阻斷抗體。藉由按照製造商制定的方案使用Alexa Fluor 647 Microscale蛋白質標記套組（賽默飛世爾科技公司（Thermo Fisher Scientific），目錄號A30009）軛合人LIGHT（R&D系統公司，目錄號664-LI/CF）和人LTα1β2（R&D系統公司，目錄號8884-LY/CF）來製備人LIGHT-Alexa 647和人LTα1β2-Alexa 647。經由基

於FACS的受體-配體測定，測定含有人LT β R結合抗體的融合瘤上清液阻斷人LIGHT和人LT α 1 β 2與人LT β R-His結合的能力。如果LT β R抗體阻止人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647與人LT β R-His結合，則流動式細胞分析術幾何平均值（GeoMean）訊號相對於在不存在LT β R抗體的情況下獲得的GeoMean訊號降低，從而由於競爭而導致配體結合的高百分比抑制值。圖5的表A顯示了選定的融合瘤上清液樣本的受體-配體相互作用阻斷能力，並反映了在指示的融合瘤上清液存在下，人LIGHT或人LT α 1 β 2與人LT β R-His結合的抑制百分比。

【0393】簡言之，在室溫下，將生物素醯化的人LT β R-His在FACS緩衝液[1 x 磷酸鹽緩衝鹽水（賽提瓦公司，目錄號SH30256.02）+ 2%胎牛血清（海選殖公司目錄號SH30396.03）]中的鏈黴親和素（SA）包被的珠粒（Spherotech公司，目錄號SVP-60-5）上捕獲30分鐘。然後將珠粒在FACS緩衝液中藉由在3500 RPM下離心2分鐘洗滌兩次。將包被的珠粒重懸於免疫測定穩定溶液（StabilGuard™舒爾默迪克斯公司，目錄號SG01）中。將人LT β R特異性單株抗體（15 μ L，10 μ g/mL）與15 μ L包被的珠粒混合，使LT β R抗體的最終濃度為5 μ g/mL，並使用96孔V底聚苯乙烯FACS板（康寧公司，目錄號3897）在室溫下孵育1小時。然後將30 μ L人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647以9 μ g/mL添加到FACS緩衝液中，並在室溫下在黑暗中孵育30分鐘。人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647的最終濃度為4.5 μ g/mL。將FACS板加入140 μ L FACS緩衝液，然後在FACS緩衝液中藉由以3500 RPM離心2分鐘洗滌一次。根據製造商之建議，將樣本重懸在30 μ L FACS緩衝液中，並在帶有Intellicyt公司自動進樣器的iQue流式細胞儀上讀取；在Intellicyt公司ForeCyt®企業客戶6.2版（R3）上進行數據分析。

【0394】將人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647的量藉由流動式細胞分析術分析由GeoMean螢光訊號定量，並將該訊號轉換為受體-配體（R-L）相互作用的抑制百分比。在LT β R抗體存在下配體結合訊號的損失計算為R-L結合

的抑制百分比。藉由對12個重複的配體-Alexa 647訊號的GeoMean訊號取平均值來確定人LIGHT-Alexa 647或人LTα1β2-Alexa 647的最大GeoMean訊號，該等重複與結合了生物素醃化的人LTβR-His的不相關耗盡上清液（ESN）一起孵育。人LIGHT-Alexa 647或人LTα1β2-Alexa 647的最小GeoMean訊號係從與結合了不相關的生物素醃化的人TREM1-His的不相關的人IgG2對照一起孵育的配體-Alexa 647訊號的GeoMean訊號確定的。使用以下等式計算人LTβR抗體或同種型對照抗體對生物素醃化的人LTβR-His：配體（人LIGHT或人LTα1β2）的抑制百分比：

$$\text{抑制百分比 (\%)} = 1 - (\text{實驗GeoMean} - \text{最小GeoMean}) / (\text{最大GeoMean} - \text{最小GeoMean})$$

對於一些LTβR抗體，當實驗GeoMean訊號高於最大GeoMean訊號時，獲得了負抑制百分比值，這可能是由於LTβR抗體與生物素醃化的人LTβR-His結合的確認性變化，從而可能導致更高的配體-Alexa 647 GeoMean訊號（即，允許更高水平的內源性配體結合）。使用不相關的ESN不會看到任何潛在的確認性變化，因為不相關的抗體不會與生物素醃化的人LTβR-His結合。

【0395】 由於使用不相關的樣本代替ESN來確定測定的最小訊號，發現該測定中的背景訊號對於LIGHT高達約20%，以及對於LTα1β2高達約15%。從該最小值中減去ESN樣本以確定淨測定訊號，從而計算抑制%。由於背景水平高，因此經由該測定表現出約20%抑制的LTβR抗體經由該基於細胞的測定被認為是非阻斷物。開發實例8中描述的基於細胞的測定，以確定LTβR抗體的非阻斷活性。

【0396】 4.7 親和力差距分析。 親和力係在通用電氣醫療公司（GE Healthcare）的BIAcore® 3000上測量的。實驗在25°C下進行。運行緩衝液為補充有0.5% BSA的HBS-P（10 mM HEPES，pH 7.4，150 mM NaCl，0.05%界面活性劑P-20；賽提瓦公司目錄號BR100827），並且動力學以高流速（100 μl/min）進行。使用pH 1.7的10 mM甘胺酸進行再生。將小鼠抗人抗體在10 nM乙酸鈉（pH

5) 中稀釋至0.065 mg/mL，並使用胺偶合試劑（賽提瓦公司目錄號BR100050）共價偶合至CM5感測器晶片（賽提瓦公司目錄號29104988）的樣本和參考流動池（Fc1）。將未純化的抗LT β R mAb在HBS-P中稀釋至1 μ g/ml，並在流動池2、3或4上捕獲，以獲得100 RU - 200 RU的捕獲水平。Fc1用作參考。將靶標（人或cyno LT β R）作為分析物以150 nM、50 nM、16.7 nM、5.6 nM和1.85 nM進樣，其50 nM濃度運行兩次以測量再現性。解離時間為10分鐘，以允許篩選大抗體組。數據係雙重背景參考，因為從數據中減去了參考Fc和0 nM分析物濃度。在BIAcore®評估軟體中使用1:1朗格繆爾傳質結合模型來分析數據。人和cyno主要的結果顯示在圖5的表B中。

【0397】 4.8 LT β R促效劑抗體的分子拯救和定序。使用Qiagen RNeasy微型套組或Invitrogen mRNA catcher plus套組，從含有產生促效劑LT β R抗體的融合瘤細胞的孔中純化出RNA（總RNA或mRNA）。經純化的RNA用於使用經由逆轉錄的cDNA合成、接著聚合酶鏈反應（RT-PCR）來擴增抗體重鏈和輕鏈可變區（V）基因。使用Qiagen單步逆轉錄酶PCR套組（凱傑公司（Qiagen））獲得完全人抗體 γ 重鏈。此方法用於自RNA模板產生第一鏈cDNA，接著使用多重PCR擴增 γ 重鏈的可變區。將5' γ 鏈特異性引物與抗體重鏈的訊息序列退火，而3'引物與 γ 恒定結構域的區域退火。使用Qiagen單步逆轉錄酶PCR套組（凱傑公司）獲得完全人 κ 和 λ 輕鏈。該方法用於自RNA模板產生第一鏈cDNA，接著使用多重PCR擴增輕鏈的可變區。將5'輕鏈特異性引物與抗體輕鏈的訊息序列退火，而3'引物與輕鏈的恒定區退火。

【0398】 使用核酸外切酶I和鹼性磷酸酶以酶法純化擴增的cDNA並對純化的PCR產物直接定序。通過生物資訊學方法，自對應核酸序列推導出胺基酸序列。各融合瘤樣本完成兩次另外的獨立的RT-PCR擴增和定序循環，以證實觀察到的任何突變並非PCR的結果。接著分析衍生的胺基酸序列，以確定抗體的種系

序列起源，且鑒別與種系序列的偏差。

實例5：LTβR抗體工程化

【0399】藉由將VH結構域與CH1-CH2-CH3序列融合並將VL結構域與到CL或CK序列融合，將選定的抗LTβR抗體轉化為IgG1亞型的標準抗體形式。該抗體同種型的CH2結構域藉由引入N297G突變被工程化以降低效應子功能，並藉由工程化的二硫鍵（R292C，V302C）以提高熱穩定性；該抗體同種型被命名為SEFL2.2。

【0400】對抗LTβR抗體進行另外工程化，以去除通過計算預測或經驗確定會影響分子表現、純化、均一性、熱穩定性、膠體穩定性、長期儲存穩定性、體內藥物動力學和/或免疫性的「熱點」或殘基。可變重鏈（VH）和可變輕鏈（VL）結構域中該等熱點的各種胺基酸突變係基於保守性、共變異性、化學相似性、結構建模的預測以及來自其他抗體工程活動的先驗知識設計的。設計的工程化的抗體包括單一突變和突變組合兩者。表17（下文）提供了引入LTβR抗體亞群的單個和組合突變以及工程化抗體的結合親和力（KD）的總結。所鑒定的取代的位置相對於源自以下的參考序列：Honegger和Pluckthun, 「Yet Another Numbering Scheme for Immunoglobulin Variable Domains: An Automatic Modeling and Analysis Tool[免疫球蛋白可變結構域的又另一種編號方案：自動建模和分析工具],」 *J. Mol. Biol.* [分子生物學雜誌] 309: 657-670 (2001)，特此藉由引用將其全部併入。

[表17]. LTβR抗體熱點工程化

BioReg ID	Fab描述	親本	KD (nM)
huLTβR LIBC218979 (19319 -- 23E9)		X	11.43723782
26985-1	VH:D61E_D72Q_S90Y,VL:R16G_N111I_M137V		弱
26986-1	VH:D61E_D72Q_S90Y,VL:R16G		弱
26988-1	VH:D61E_S90Y,VL:R16G		弱
26990-1	VH:D61L_S90Y,VL:R16G		弱

BioReg ID	Fab描述	親本	KD (nM)
26991-1	VH:D72Q_S90Y,VL:R16G		15.43514472
26992-1	VH:D72V_S90Y,VL:R16G		16.40551694
26993-1	VH:G65A_D72Q_S90Y_R110T,VL:R16G_N111I_M137V		弱
26995-1	VH:G65A_S90Y,VL:R16G		19.79679887
26998-1	VH:G65L_S90Y,VL:R16G		弱
26999-1	VH:S90Y,VL:R16G_M137I		31.04580415
27000-1	VH:S90Y,VL:R16G_M137V		28.00773125
27001-1	VH:S90Y,VL:R16G_N111I		15.01961755
27002-1	VH:S90Y,VL:R16G_N111L		17.30011157
27003-1	VH:S90Y,VL:R16G		16.07352296
27004-1	VL:R16G		12.2143522
huLTβR LIBC218990 (19320 -- 30H1)		X	3.27501537
27006-1	VH:F148S,VL:M56I		5.202407838
27007-1	VH:K72Q_F148S,VL:M56I		9.410228152
27008-1	VH:K72V_F148S,VL:M56I		9.144188517
27009-1	VH:N61Q_F148S,VL:M56I		5.399789949
27010-1	VH:N61Q_K72Q_F148S,VL:M56I		11.09048764
27011-1	VH:N61Q_K72V_F148S,VL:M56I		7.958937509
27012-1	VL:M56I		4.505336548
huLTβR LIBC218994 (19321 -- 31A3)		X	0.403443251
27014-1	VH:A110G_D61E_D72E_V96L,VL:K69I		4.696555145
27015-1	VH:A110G_D61E_D72E_V96L,VL:K69L_R70I		2.591425519
27016-1	VH:A110G_D61E_D72E_V96L,VL:R70I		3.627320222
27017-1	VH:A110G_D61E_D72E_V96L,VL:R70V		3.662808057
27018-1	VH:A110G_D61E_D72E_V96L		3.360797418
27019-1	VH:A110G_D61E_D72T_V96L,VL:K69I_R70V		4.328156944
27020-1	VH:A110G_D61E_D72T_V96L,VL:K69L		4.58220395
27021-1	VH:A110G_D61E_D72T_V96L,VL:R70L		3.275583582
27022-1	VH:A110G_D61E_D72T_V96L,VL:R70V		3.509973423
27023-1	VH:A110G_D61E_D72T_V96L		3.500158829
27024-1	VH:A110G_D61E_S73L_V96L		2.941727972

BioReg ID	Fab描述	親本	KD (nM)
27025-1	VH:A110G_G65A_D72E_V96L		0.284150703
27026-1	VH:A110G_G65A_D72T_V96L		0.381976978
27027-1	VH:A11G_G65A_S73L_V96L		0.336655454
27028-1	VH:A110G_V96L,VL:W109I		0.212721493
27029-1	VH:A110G_V96L,VL:W109Q		0.161329478
27030-1	VH:V96L		0.318844229
huLTβR LIBC219037 (19322 -- 34D1)		X	0.190412769
27032-1	VH:L89F_A143T		0.404416306
27033-1	VH:R12L_V51G_L89F_A143T		0.367707031
27034-1	VH:R12L_V51G_L89F_N94S_A143T		0.516807652
huLTβR LIBC219051 (19323 -- 35F5)		X	0.684584722
27036-1	VH:C70Y_I97R,VL:D35E_R144K		5.471490372
27037-1	VH:C70Y_I97R,VL:D35V_R144K		1.935658966
27038-1	VH:C70Y_I97R,VL:G37A_R144K		2.006767197
27039-1	VH:C70Y_I97R,VL:R144K		0.795696731
27040-1	VH:C70Y_I97R		0.293820496
huLTβR LIBC219058 (19324 -- 36G2)		X	0.326818905
27042-1	VH:K14Q_R110I,VL:L97Q		0.296413116
27043-1	VH:K14Q_R110I,VL:N53K_L97Q		0.300532627
27044-1	VH:K14Q,VL:L97Q		0.235652803
27045-1	VH:K14Q,VL:N53K_L97Q		0.247290188
27046-1	VH:R110I,VL:L97Q		0.354185514
27047-1	VL:L97Q		0.2950519
huLTβR LIBC219081 (19325 -- 41B2)		X	0.580223924
27049-1	VH:I79T,VL:H39Q_S111A		1.286345586
27050-1	VH:I79T,VL:H39Q_S111I		1.459335319
27051-1	VH:I79T,VL:H39Q		1.294832574
27052-1	VH:I79T,VL:N33E_S111A		1.092138935
27053-1	VH:I79T,VL:N33E_S111I		0.990274196
27054-1	VH:I79T,VL:N33E		1.648852277
27055-1	VH:I79T,VL:N33Q_S111A		0.938002565

BioReg ID	Fab描述	親本	KD (nM)
27056-1	VH:I79T,VL:N33Q_S111I		0.771084585
27057-1	VH:I79T,VL:N33Q		0.699522384
27058-1	VH:I79T,VL:S111A		0.738710315
27059-1	VH:I79T,VL:S111I		0.600474948
27060-1	VH:I79T		0.788530019
huLTβR LIBC219097 (19326 -- 43D9)		X	12.00579103
27062-1	VH:I78F_D84N_S85A_T98A		12.13646339
27063-1	VH:I78F		14.0569778
huLTβR LIBC219098 (19327 -- 44B1)		X	3.005941052
27065-1	VH:D134E,VL:C25S		32.43914293
27066-1	VH:D134E,VL:S18P_C25S		178.166033
27067-1	VH:G135V,VL:C25S		37.5613709
27068-1	VH:G135V,VL:S18P_C25S		17.72182401
27069-1	VL:C25S		0.330403122
27070-1	VL:S18P_C25S		0.323484073
27071-1	VL:N53K_L97Q		0.311045523

實例6：LTβR促效劑抗體的表位和互補位作圖

【0401】 6.1 氫/氘交換（HDX）質譜（MS）。使用HDX MS進行選擇促效劑LTβR抗體的表位和互補位作圖。HDX MS測量蛋白質骨架醯胺氫的氘交換率。HDX MS實驗使用Twin HTS PAL HDX系統（LEAP技術公司（LEAP Technologies），北卡羅來納州卡勃羅）進行，該系統被配置為在胃蛋白酶柱上進行線上消化，並與Orbitrap質譜儀（Elite，賽默飛世爾科技公司，加利福尼亞州聖約瑟）介面，如前文所描述（參見例如，Chalmers等人, *Anal. Chem.*[分析化學] 78: 1005-1014 (2006)和Zhang等人, *Structure*[結構] 18: 1332-1341 (2010)，特此藉由引用將其全部併入）或Twin HTS PAL HDX系統，該系統被配置為進行溶液內消化，並與Orbitrap Eclipse質譜儀（賽默飛世爾科技公司，加利福尼亞州聖約

瑟) 介面，其方式類似於先前所述 (Zhang 等人, *Anal. Chem.*[分析化學] 84(11):4942-4949 (2012)，特此藉由引用將其全部併入)。

【0402】 6.1.1 使用具有柱上消化的Twin HTS PAL HDX系統 (「系統1」)
進行HDX MS實驗：用於LTβR抗體 (LIBC218990、LIBC218944、LIBC219058、LIBC219081和LIBC219097) 的表位/互補位作圖的HDX反應分別在三個條件下進行：分別是僅LTβR胞外結構域 (ECD) 抗原、LTβR ECD/抗體結構域複合物和僅抗體Fab。考慮到LTβR和評估的抗體具有 k_D 在低nM範圍內的高結合親和力，並且結合比為2:1，藉由分別以約20 μM和約10 μM的最終濃度預孵育LTβR與抗體，可以容易地形成LTβR/抗體複合物。H/D交換反應藉由在25°C下如所指示的用10 mM乙酸鹽的D2O (pD 5.2) 將蛋白質樣本5倍稀釋預定時間 (10 s、1 min、10 min、1 h、4 h和12 h) 來激活。藉由與冰冷的200 mM磷酸鈉、4 M鹽酸胍、0.5 M三(2-羧乙基)膦 (TCEP) 在pH 2.4下1:1混合來淬滅交換反應。將淬滅的蛋白質混合物以200 μL/min的流速通過定制填充的2 mm×2 cm胃蛋白酶 (世爾科技公司 (Fisher Scientific)，賓夕法尼亞州匹茲堡) 柱 (安捷倫技術公司 (Agilent Technologies)，加利福尼亞州聖克拉拉)。在2 mm×1 cm C18捕獲柱 (沃特斯公司 (Waters Corporation)，麻塞諸塞州米爾福德) 上捕獲消化的肽，並以0.2 mL/min的流速脫鹽3分鐘。然後藉由使用2.1 mm × 5 cm C18柱 (1.9 μm Hypersil Gold；賽默飛世爾科技公司，麻塞諸塞州沃爾瑟姆)，9.5分鐘線性梯度的5%-40%乙腈的0.1%甲酸溶液，以0.2 mL/min的流速來分離肽。蛋白質消化和肽分離在保持在1°C下的熱室中進行，以減少反向交換。對於m/z 400的離子，以60,000的品質分辨能力獲得LC-MS數據。每個實驗都一式兩份進行，以提供對變化的估計。

【0403】 串聯質譜 (MS/MS) 實驗在與如上文描述的相同的條件下進行。在數據依賴性模式下獲取產物離子光譜，並選擇10個最豐富的離子進行產物離子分析。所有數據均使用軟體MassAnalyzer (Zhang 等人, *Anal. Chem.*[分析化學]

84: 4942-4949 (2012), 特此藉由引用將其全部併入) 處理, 用於肽鑒定和氘水平計算。分析了大約500個肽, 所有mAb2多肽鏈的序列覆蓋率為至少97%。將所有HDX-MS數據歸一化為100%氘濃度, 並用Prism v 6.02 (圖形軟體公司 (GraphPad Software), 加利福尼亞州拉荷亞) 以對數標度繪製針對標記時間的氘摻入百分比。

【0404】 6.1.2 使用具有溶液內消化的Twin HTS PAL HDX系統 (「系統2」) 進行HDX MS實驗: 對於互補位作圖, 藉由將抗體Fab結構域與過量 (1.5倍) 的LTβR胞外結構域 (ECD) 抗原孵育形成LTβR/抗體複合物, 並與游離抗體Fab結構域並行分析。藉由將每個樣本在D₂O中的100 mM磷酸鹽緩衝液中稀釋10倍來開始氘標記。在一定長度的標記時間 (6次標記時間, 從15 s到2 h, 每次至少一式兩份) 後, 藉由在1°C下在含有0.625 M三(2-羧乙基)膦 (TCEP) 和約5.8 M尿素的淬滅/變性緩衝液 (pH 2.7) 中稀釋4倍來淬滅標記。然後將胃蛋白酶添加到淬滅的溶液中, 然後在1°C下注入樣本環路中, 並在環路線上切換用於梯度洗脫之前進行6 min消化延遲。在1°C下在1 mm×5 cm C18柱 (Waters CSH, 1.7 μM) 上, 用9.5分鐘線性梯度的5%-40%乙腈的在0.035%三氟乙酸 (TFA)、0.1%甲酸溶液, 以0.2 mL/min的流速來分離肽。三種肽, 包括緩激肽、血管收縮素和白胺酸腦啡肽, 用作內標來校正反向交換。

【0405】 對於表位作圖, 藉由將LTβR ECD抗原與過量 (1.5倍) 的每種抗體Fab一起孵育形成LTβR/抗體複合物, 並與游離抗原並行分析。H/D交換標記和消化以與如上文所描述的相同的方式進行, 不同之處在於使用1:1胃蛋白酶/XIII型蛋白酶混合物進行消化, 並且在注入樣本回路之前, 在約7°C下進行消化6 min, 這是因為使用標準條件難以用胃蛋白酶消化LTβR ECD。

【0406】 所有MS數據均為在賽默飛世爾科技公司Orbitrap Eclipse高解析度質譜儀上收集的, 該質譜儀具有電灑游離介面。在120k解析度設置下收集MS

數據。對於每個互補位或表位實驗，還從兩個未標記的樣本（游離和複合物）中的每一個中收集三次注射的數據依賴性MS/MS，用於肽鑒定。

【0407】所有數據均在軟體MassAnalyzer上處理，用於肽鑒定、氘水平計算、使用內標的反向交換校正和全氘化對照（Zhang等人, *Anal. Chem.* [分析化學] 84(11):4942-4949 (2012)，特此藉由引用將其全部併入）。

【0408】 **6.2 表位作圖結果**。表位作圖實驗的結果提供在圖4-8中。來源於單獨LT β R和與抗體複合的LT β R的肽之氘交換圖的比較鑒定了被檢測抗體結合的表位區域，其中被抗體結合的LT β R區域受到保護免於氘交換。應注意的是，肽的N-末端殘基不具有用於測量的醯胺氫，並且在報告表位區域時被排除在外。如圖6和8中所示，LT β R抗體LIBC218990-1（19320）和LIBC219058（19324）與LT β R的CRD2內的殘基結合，如由LT β R ECD（SEQ ID NO: 4）的胺基酸殘基56-64和81-101組成的複合肽中存在的氘的減少所示。因此，LIBC218990-1的表位和LIBC219058的表位包含SYNEHWNY（SEQ ID NO: 4的殘基57-64）的胺基酸序列內的一或多個殘基和EIAPCTSKRKTQCRCQPGMF（SEQ ID NO: 4的殘基82-101）的胺基酸序列內的一或多個殘基。LT β R：LT β R-抗體複合物的其他區域沒有受到保護免於氘交換（數據未顯示）。

【0409】LT β R抗體LIBC218994（19321）結合CRD1內的殘基，特別是LT β R ECD（SEQ ID NO: 4）的殘基4-9、21-29和39-47內的一或多個殘基（參見圖7）。因此，LIBC218944的表位包含PPYASE（SEQ ID NO: 4的殘基4-9）、YEPQHRICC（SEQ ID NO: 4的殘基21-29）和SAKCSRIRD（SEQ ID NO: 4的殘基39-47）的胺基酸序列內的一或多個殘基。LT β R：LT β R-抗體複合物的其他區域沒有受到保護免於氘交換（數據未顯示）。

【0410】LT β R抗體LIBC219081（19325）結合CRD4內的殘基，特別是LT β R ECD（SEQ ID NO: 4）的位置168-179處的殘基片段內的殘基（參見圖9）。因此，

LIBC219081的表位包含EAAPGTAQSDDT (SEQ ID NO: 4的殘基168-179) 的胺基酸序列內的一或多個殘基。LTβR : LTβR-抗體複合物的其他區域沒有受到保護免於氘交換 (數據未顯示) 。

【0411】 LTβR抗體LIBC219097 (19326) 結合跨越CRD1和CRD2的LTβR區域，該區域包含LTβR ECD (SEQ ID NO: 4) 的39-42和57-70區域中的殘基 (參見圖10) 。包含殘基38-42和殘基37-47的肽之氘攝取曲線的比較顯示了，殘基38-42的較短肽具有相對大的保護而免於氘交換，而較長肽37-47具有相對小的保護。這表明保護主要發生在重疊的較短肽中，因此將表位區域縮小到LTβR ECD的殘基39-42。因此，LIBC219097的表位包含SAKC (SEQ ID NO: 4的殘基39-42) 和SYNEHWNYLTICQL (SEQ ID NO: 4的殘基57-70) 的胺基酸序列內的一或多個殘基。LTβR : LTβR-抗體複合物的其他區域沒有受到保護免於氘交換 (數據未顯示) 。

【0412】 LTβR抗體LIBC218979 (19319) 與LTβR ECD (SEQ ID NO: 4) 的CRD4內的LTβR殘基結合。LIBC218979與LTβR ECD結合後，LTβR肽167-177和167-181中的氘攝取減少，但肽154-166和178-193中沒有，這表明保護區在殘基168-178內 (圖11) 。LTβR : LTβR-抗體複合物的其他區域沒有受到保護免於氘交換 (數據未顯示) 。因此，表位包含EAAPGTAQSDDT (SEQ ID NO: 4的殘基168-179) 的胺基酸序列內的一或多個殘基。

【0413】 LTβR抗體LIBC219051 (19323) 與包括CRD1在內的LTβR ECD的N末端區域結合。LIBC219051與LTβR ECD結合後，LTβR肽1-9、1-20和10-20中的氘攝取減少，但肽19-28中沒有，這表明保護區在殘基1-19內 (圖12) 。LTβR : LTβR-抗體複合物的其他區域沒有受到保護免於氘交換 (數據未顯示) 。因此，表位包含QAVPPYASENQTCRDQEKE (SEQ ID NO: 4的殘基1-19) 的胺基酸序列內的一或多個殘基。應注意的是，Q1已轉換為pyro-E，其含有可測量的醯胺氫。

數據還表明，結合與殘基N10上的糖基化狀態無關。

【0414】 6.3 互補位作圖結果。互補位作圖實驗的結果提供在圖13-19中。與表位作圖類似，來源於未結合和LT β R結合抗體的重鏈和輕鏈可變結構域肽中氘攝取的比較用於鑒定所檢測抗體的互補位區域。與未結合抗體相比，結合抗體的肽區域內氘攝取的減少表明所檢測肽的至少一些區域參與結合相互作用。如上文所述，所檢測肽的N末端殘基不具有用於測量的醯胺氘，因此在報告互補位區域時被排除在外。因為這種方法檢測微抗體衍生肽（而不是單個殘基）中的氘交換，所以互補位的解析不在殘基水平上。然而，該方法可以可靠地鑒定不參與結合相互作用的殘基片段。

【0415】圖13顯示了來源於未結合和結合的LT β R抗體LIBC218990（19320）的肽之一系列氘攝取圖。受到保護免於氘交換的結合抗體（即抗體-LT β R複合物）的肽在圖底部的相應重鏈和輕鏈可變序列中進行鑒定（參見加框殘基）。每個可變區序列內的CDR位置加下劃線。由SEQ ID NO: 644的殘基27-34組成的重鏈肽的氘攝取圖顯示沒有免於氘攝取。該重鏈肽跨越HCDR1殘基31-35，表明LIBC218990的HCDR1不參與同LT β R的結合相互作用。類似地，SEQ ID NO: 645的殘基50-70的複合輕鏈肽中的氘攝取也顯示沒有免於氘攝取。該輕鏈肽跨越LCDR2殘基51-57，表明LIBC218990的LCDR2也不參與該抗體與LT β R的結合相互作用。

【0416】LIBC218990的HCDR2包含SEQ ID NO: 644的殘基50-66。然而，只有該HCDR2區域的前半部分內的殘基參與結合相互作用（即，殘基51-59），如在SEQ ID NO: 644的殘基50-59的複合重鏈肽中觀察到的受到保護免於氘交換和在殘基60-66的複合重鏈肽中觀察不到的缺乏保護所示（圖13）。類似地，雖然LIBC218990的LCDR1跨越VL殘基24-35（SEQ ID NO: 645），但基於與該區域重疊的肽之氘攝取，僅SEQ ID NO: 645的殘基29-33似乎參與LCDR1與LT β R的相

互作用(圖13)。在LIBC218990的HCDR3和LCDR3區域中檢測的肽包括各自CDR區域的一端或兩端的框架區。雖然該等框架殘基已被包括在加框區域中，但它們參與結合相互作用不能使用這種方法來解決。

【0417】 類似於LIBC218990，LIBC219058 (19324) (圖15)和LIBC219097 (19326) (圖17)的互補位定位顯示了，並非該等抗體的所有六個CDR都參與了該等各自抗體與LTβR之間的結合相互作用。特別地，對於LIBC219058(圖15)，由SEQ ID NO: 649的殘基23-33組成的VL的複合肽沒有受到保護免於氘交換，這表明LCDR1不參與同LTβR的相互作用。同樣，由SEQ ID NO: 649的殘基87-116和107-116組成的VL的複合肽也顯示出沒有受到保護免於氘交換，這表明LCDR3不參與抗體與LTβR的結合。對於LIBC219097 (圖17)，由SEQ ID NO: 650的殘基47-61和62-75組成的VH的複合肽沒有受到保護免於氘交換，這表明HCDR2不參與抗體與LTβR的相互作用(圖17A)。類似地，由SEQ ID NO: 651的殘基87-112組成的複合VL肽沒有受到保護免於氘交換，這表明LIBC219097的LCDR3不參與同LTβR的結合(圖17B)。

【0418】 圖14和16顯示了來源於未結合和結合的LTβR抗體LIBC218994 (19321) (圖14A-14B)和LTβR抗體LIBC219081 (19325) (圖16A-16B)的肽之氘攝取圖。受到保護免於氘交換的結合抗體(即抗體-LTβR複合物)的肽在每個圖底部的相應重鏈和輕鏈可變序列中進行鑒定(參見加框殘基)。每個可變區序列內的CDR位置加下劃線。與LIBC218990、LIBC219058和LIBC219097相比，LIBC218994和LIBC219081抗體的互補位作圖顯示，三個VH和VL CDR中的每一個內的殘基都參與了與LTβR的結合相互作用。在一些情況下，當多個肽覆蓋CDR區域時，還鑒定了不參與結合相互作用的特定CDR中的殘基。參見例如SEQ ID NO: 646的VH肽48-57和58-68的圖(圖14A)，其顯示HCDR2的殘基49-57而非58-66參與LIBC218994與LTβR的結合相互作用。還參見SEQ ID NO: 121的VH

肽49-59和60-68的圖（圖16A），其顯示HCDR2的殘基50-59而非60-66參與LIBC219081與LTβR的結合相互作用。

【0419】圖18A-18B顯示了來源於未結合和結合的LTβR抗體LIBC218979（19319）的肽之氘攝取圖。受到保護免於氘交換的結合抗體（即抗體-LTβR複合物）的肽在每個圖底部的相應重鏈（圖18A）和輕鏈（圖18B）可變序列中進行鑒定（參見加框殘基）。每個可變區序列內的CDR位置加下劃線。氘攝取圖的分析表明，LIBC218979的三個VH和VL CDR中的每一個內的殘基都參與了與LTβR的結合相互作用。

【0420】圖19A-19B顯示了來源於未結合和結合的LTβR抗體LIBC219051（19323）的肽之氘攝取圖。受到保護免於氘交換的結合抗體（即抗體-LTβR複合物）的肽在每個圖底部的相應重鏈（圖19A）和輕鏈（圖19B）可變序列中進行鑒定（參見加框殘基）。每個可變區序列內的CDR位置加下劃線。氘攝取圖的分析表明，LIBC219051的三個VH和VL CDR中的每一個內的殘基都參與了與LTβR的結合相互作用。

【0421】基於互補位定位和熱點工程化，對LTβR結合相互作用重要的LTβR抗體LBC218990、LIBC218994、LIBC219058、LIBC219081、LIBC219097、LIBC218979、LIBC219098和LIBC219051的CDR殘基總結在下表16-22中。未被鑒定為參與或對LTβR結合相互作用至關重要的抗體的CDR殘基（在表16-22的CDR序列中被鑒定為「X」）可以被任何胺基酸殘基、保守胺基酸取代或熱點補救的胺基酸殘基取代，如下表18-25中的每一個所鑒定的。

表18.LTβR抗體LIBC218990（19320/30H1）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
GDYMY *基於HDX分析不 是互補位的一部分	475	WINPX ₅ SGGTNX ₁₁ -X ₁₇ X ₅ 和X ₁₁ -X ₁₇ 獨立地選自任何 胺基酸殘基	499	EGSSGWSAEYX ₁₁ X ₁₂ X ₁₃ X ₁₁ -X ₁₃ 獨立地選自任何 胺基酸殘基	529

		WINPX₅SGGTNX₁₁-X₁₇ X₅為N、G、D、E、T、S、R、K、Q、H，較佳的是N或Q X₁₁為Y、H、M、I、L、F、W X₁₂為A、G、S、T、V X₁₃為K、D、E、N、Q、R、V，較佳的是K、V或Q X₁₄為K、D、E、N、Q、R X₁₅為F、M、V、I、L、W、Y X₁₆為Q、D、E、N、H、M、S、R、K X₁₇為G、A、S、N X₅和X₁₃各自係如上表17中針對該抗體所定義的熱點殘基（即N61和K72）。	500	EGSSGWSAEYX₁₁X₁₂X₁₃ X₁₁為F、M、V、I、L、W、Y X₁₂為Q、D、E、N、H、M、S、R、K X₁₃為H、D、E、N、M、R、Q	530
		WINPNSGGTNYAKKFQG	501	EGSSGWSAEYFQH	531
LCDR1	ID	LCDR2	ID	LCDR3	ID
X₁X₂X₃X₄SVSSSFX₁₁X₁₂ X₁-X₄和X₁₁-X₁₂獨立地選自任何胺基酸殘基	559	GASRRAT <i>*基於HDX分析不是互補位的一部分</i>	590	QQYGTSPLS	619
X₁X₂X₃X₄SVSSSFX₁₁X₁₂ X₁為R、E、N、H、Q、K X₂為A、G、S、T、V	560				

X ₃ 為S、G、D、 E、N、Q、A、T X ₄ 為Q、D、E、 N、H、M、S、 R、K X ₁₁ 為L、M、V、 I、Y、F X ₁₂ 為A、G、S、 T、V					
RASQSVSSSFLA	561				

[表19]. LTβR抗體LIBC218994（19321/31A3）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
SYX ₃ X ₄ X ₅ X ₃ 、X ₄ 和X ₅ 獨立地選 自任何胺基酸殘基	476	IIWYX ₅ X ₆ SDX ₉ -X ₁₇ X ₅ 、X ₆ 和X ₉ -X ₁₇ 獨立地選自 任何胺基酸殘基	502	GDSEDFYYYDX ₁₁ X ₁₂ X ₁₃ X ₁₁ -X ₁₃ 獨立地選自任何 胺基酸殘基	532
SYX ₃ X ₄ X ₅ X ₃ 為G、A、S、N X ₄ 為M、H、Q、Y、 F、L、I、V X ₅ 為H、D、E、N、 M、R、Q	477	IIWYX ₅ X ₆ SDX ₉ -X ₁₇ X ₅ 為D、S、K、Q、H、N 或E，較佳的是D或E X ₆ 為G、S、N或A，較佳的 是G或A X ₉ 為E、P、D、S、R、K、 Q、H、N X ₁₀ 為Y、H、M、I、L、 F、W X ₁₁ 為Y、H、M、I、L、 F、W X ₁₂ 為A、G、S、T、V X ₁₃ 為D、S、K、Q、H、	503	GDSEDFYYYDX ₁₁ X ₁₂ X ₁₃ X ₁₁ 為F、M、V、I、L、 W、Y X ₁₂ 為D、S、K、Q、H、 N、E X ₁₃ 為V、T、A、 M、F、L、I	533

		N、E、T，較佳的是D、E或T X₁₄為S、G、D、E、N、Q、A、T、L，較佳的是S或L X₁₅為V、T、A、M、F、L、I X₁₆為K、D、E、N、Q、R X₁₇為G、A、S、N X₅、X₆、X₁₃和X₁₄各自係如上表17中針對該抗體所定義的熱點殘基（即D61、G65、D72和S73）。			
SYGMH	478	IIWYDGSDEYYADSVKG	504	GDSSEDFYYYDFDV	534
LCDR1	ID	LCDR2	ID	LCDR3	ID
SGSSSNIGKNX ₁₁ X ₁₂ X ₁₃ X ₁₁ -X ₁₃ 各自獨立地選自任何胺基酸殘基	562	DNNX ₄ X ₅ PS X ₄ 和X ₅ 為任何胺基酸	591	X ₁ X ₂ X ₃ DHSLSASX ₁₁ X ₁₂ X ₁ -X ₃ 、X ₁₁ 和X ₁₂ 各自獨立地選自任何胺基酸殘基	620
SGSSSNIGKNX ₁₁ X ₁₂ X ₁₃ X ₁₁ 為Y、H、M、I、L、F、W X ₁₂ 為V、T、A、M、F、L、I X ₁₃ 為S、G、D、E、N、Q、A、T	563	DNNX ₄ X ₅ PS X ₄ 為K、D、E、N、Q、R、I、L，較佳的是K、I或L X ₅ 為R、E、N、H、Q、K、V、L、I，較佳的是R、V、L或I X ₄ 和X ₅ 各自係如上表17中針對該抗體所定義的熱點殘基（即K69和R70）。	592	X ₁ X ₂ X ₃ DHSLSASX ₁₁ X ₁₂ X ₁ 為G、A、S、N X ₂ 為T、N、S、V、A X ₃ 為W、F、Y、Q、I，較佳的是W、Q或I X ₁₁ 為Y、H、M、I、L、F、W X ₁₂ 為V、T、A、M、F、L、I X ₃ 係如上表17中針對該抗體所定義的熱點殘基（即W109）。	621

SGSSSNIGKNYVS	564	DNNKRPS	593	GTWDHSLSASYV	622
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[表20]. LTβR抗體LIBC219058（19324/36G2）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
TSGMN	479	SVSSSGSYX ₉ -X ₁₇ X ₉ -X ₁₇ 中每一個獨立地選自任何胺基酸殘基	505	AX ₂ YNWHFDASX ₁₁ X ₁₂	535
		SVSSSGSYX ₉ -X ₁₇ X ₉ 為I、M、V、Y、F、L X ₁₀ 為Y、H、M、I、L、F、W X ₁₁ 為Y、H、M、I、L、F、W X ₁₂ 為A、G、S、T、V X ₁₃ 為D、S、K、Q、H、N、E X ₁₄ 為S、G、D、E、N、Q、A、T X ₁₅ 為V、T、A、M、F、L、I X ₁₆ 為K、D、E、N、Q、R X ₁₇ 為G、A、S、N	506	AX ₂ YNWHFDASX ₁₁ X ₁₂ X ₂ 為R、E、N、H、Q、K或I，較佳的是R或I X ₁₁ 為D、S、K、Q、H、N、E X ₁₂ 為I、M、V、Y、F、L X ₂ 係如上表17中針對該抗體所定義的熱點殘基（即R110）。	536
		SVSSSGSYIYYADSVKG	507	ARYNWHFDASDI	537
LCDR1	ID	LCDR2	ID	LCDR3	ID
RASQSISSDLN <i>*基於HDX分析不是互補位的一部分</i>	565	AASSLX ₆ X ₇ X ₆ 和X ₇ 各自為任何胺基酸殘基	594	QQSYNTPLT <i>*基於HDX分析不是互補位的一部分</i>	623
		AASSLX ₆ X ₇ X ₆ 為H、D、E、N、M、R、Q X ₇ 為S、G、D、E、N、Q、	595		

		A、T			
		AASSLHS			

[表21]. LTβR抗體LIBC219081（19325/41B2）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
SYAX ₄ X ₅ X ₄ 和X ₅ 各自為任何胺基酸殘基	927	VIWYDGSNQYX ₁₁ -X ₁₇ X ₁₁ -X ₁₇ 中每一個獨立地選自任何胺基酸殘基	930	DRVAAHPAYYX ₁₁ -X ₁₅ X ₁₁ -X ₁₅ 中每一個獨立地選自任何胺基酸殘基	933
SYA X ₄ X ₅ X ₁ 為M、H、Q、Y、F、L、I、V X ₂ 為H、D、E、N、M、R、Q	928	VIWYDGSNQYX ₁₁ -X ₁₇ X ₁₁ 為Y、H、M、I、L、F、W X ₁₂ 為A、G、S、T、V X ₁₃ 為D、S、K、Q、H、N、E X ₁₄ 為S、G、D、E、N、Q、A、T X ₁₅ 為V、T、A、M、F、L、I X ₁₆ 為K、D、E、N、Q、R X ₁₇ 為G、A、S、N	931	DRVAAHPAYYX ₁₁ -X ₁₅ X ₁₁ 為Y、H、M、I、L、F、W X ₁₂ 為G、A、S、N X ₁₃ 為L、M、V、I、Y、F X ₁₄ 為D、S、K、Q、H、N、E X ₁₅ 為V、T、A、M、F、L、I	934
SYAMH	8	VIWYDGSNQYYADSVKG	9	DRVAAHPAYYYGLDV	10
LCDR1	ID	LCDR2	ID	LCDR3	ID
X ₁ X ₂ DALPX ₇ X ₈ Y AY X ₁ 、X ₂ 、X ₇ 、X ₈ 各自獨立地為任何胺基酸殘基	934	KDNERPS	66	QSADX ₅ SGSYVI X ₅ 為任何胺基酸殘基	936
X ₁ X ₂ DALPX ₇ X ₈ Y AY X ₁ 為S、G、D、E、N、Q、A、T	935			QSADX ₅ SGSYVI X ₅ 為S、G、D、E、N、Q、A、T、I，較佳的是S、A或I	937

X ₂ 為G、A、S、N X ₇ 為N、G、D、 T、S、R、K、 H、E、Q，較佳 的是N、E或Q X ₈ 為H、D、E、 N、M、R、Q， 較佳的是H或Q X ₇ 和X ₈ 各自係如 上表17中針對該 抗體所定義的熱 點殘基（即N33和 H39）。				X ₅ 係如上表17中針對該 抗體所定義的熱點殘基 （即S111）。	
SGDALPNHYAY	65			QSADSSGSYVI	67

[表22]. LTβR抗體LIBC219097（19326/43D9）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
DAWX ₉ X ₁₀ X ₉ 和X ₁₀ 為任何胺 基酸殘基	740	RIKTKTDGGTTDYAAPVKG *不是互補位的一部分	743	DYGDYX ₆ X ₇ X ₆ 和X ₇ 為任何胺基酸殘基	744
DAWX ₉ X ₁₀ X ₉ 為M、H、Q、Y、 F、L、I、V X ₁₀ 為S、G、D、E、 N、Q、A、T	741			DYGDYX ₆ X ₇ X ₆ 為E、P、D、S、R、K、 Q、H、N X ₇ 為Y、H、M、I、L、F、 W	745
DAWMS	742			DYGDYEEY	746
LCDR1	ID	LCDR2	ID	LCDR3	ID

RTSQSISRYLN	566	GASSLX ₆ X ₇	597	HQSYSTPPT	624
		X ₆ 和X ₇ 為任何胺基酸殘基		<i>*基於HDX 分析不是互補位的一部分</i>	
		GASSLX ₆ X ₇	598		
		X ₆ 為Q、D、E、N、H、M、S、 R、K X ₇ 為S、G、D、E、N、Q、A、 T			
		GASSLQS	599		

[表23]. LTβR抗體LIBC218979（19319/23E9）的關鍵CDR殘基的總結

HCDR1	ID	HCDR2	ID	HCDR3	ID
SYGMH	11	VIWYX ₅ X ₆ SNKY _Y AX ₁₃ SVKG X ₅ 、X ₆ 和X ₁₃ 各自為任何胺基酸殘基	938	ERIAAAPYYYYGMDV	13
		VIWY X ₅ X ₆ SNKY _Y AX ₁₃ SVKG X ₅ 為D、S、K、Q、H、N、E、L，較佳的是D、E或L X ₆ 為G、S、N或A，較佳的是G或A X ₁₃ 為D、S、K、Q、H、N、E、V或Q，較佳的是D、Q或V X ₅ 、X ₆ 和X ₁₃ 各自係如上表17中針對該抗體所定義的熱點殘基（即D61、G65和	939		

		D72) 。			
		VIWYDGSNKYYADSVKG	12		
LCDR1	ID	LCDR2	ID	LCDR3	ID
SGDALPKHYAY	68	KDNERPS	69	QSADX ₅ TGSYX ₁₀ V X ₅ 和X ₁₀ 為任何胺基酸殘基	940
				QSADX ₅ TGSYX ₁₀ V X ₅ 為N、G、D、E、T、S、R、K、Q、H、I、L，較佳的是N或I X ₁₀ 為M、H、Q、Y、F、L、I、V，較佳的是M或V X ₅ 和X ₁₀ 係如上表17中針對該抗體所定義的熱點殘基（即N111和M137）。	941
				QSADNTGSYMV	70

[表24]. LTβR抗體LIBC219098（19327/44B1）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
SYAMS	481	TISGSGGSTYYADSVKG	509	VRDNWNYX ₈ X ₉ MDV X ₈ 和X ₉ 為任何胺基酸殘基	539
				VRDNWNYX ₈ X ₉ MDV X ₈ 為D、S、K、Q、H、N、E，較佳的是D或E X ₉ 為G、A、S、N、V，較佳的是G或V X ₈ 和X ₉ 各自係如上表17	540

				中針對該抗體所定義的熱點殘基（即D134和G135）。	
				VRDNWNYDGMDV	541
LCDR1	ID	LCDR2	ID	LCDR3	ID
RX ₂ SQSLLYSSGYI DLD X ₂ 為任何胺基酸殘基	568	LGSNRAS	601	MQTIQTPLT	627
RX ₂ SQSLLYSSGYI DLD X ₂ 為C或S X ₂ 係如上表17中針對該抗體所定義的熱點殘基（即C25）。	569				
RCSQSLLYSSGYI DLD	570				
RSSQSLLYSSGYI DLD	571				

[表25]. LTβR抗體LIBC219051（19323/35F5）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
GYYLH	483	WINPNIGVTDX ₁₁ AQKFQD X ₁₁ 為任何胺基酸殘基	511	RGYNDDYDFDY	543
		WINPNIGVTDX ₁₁ AQKFQD X ₁₁ 為C、S或Y	512		
		WINPNIGVTDSAQKFQD	513		
LCDR1	ID	LCDR2	ID	LCDR3	ID
KSRQSLLHRX ₁₀ X ₁₁ KTY	572	EVSNRFS	603	MQSIQLPLI	628

LY X ₁₀ 為任何胺基酸殘基 X ₁₁ 為任何胺基酸殘基					
KSRQSLLHRX ₁₀ X ₁₁ KTY LY X ₁₀ 為D、E或V X ₁₁ 為G或A	573				
KSRQSLLHRDGGKTYL Y	574				

實例7：雙特異性分子生產和功能測試

【0422】 靶向腫瘤抗原相關(TAA)或基質抗原相關(SAA)的促效劑LTβR結合蛋白能夠結合 (i) 人LTβR (huLTβR) 和人Claudin 18.2 (CLDN18.2)，(ii) huLTβR和人Claudin 6 (CLDN6)，(iii) huLTβR和人MUC17，或 (iv) huLTβR和LRRC15，以AmAb形式(即Fab x scFv)或異源IgG形式產生。該等結合蛋白係使用本文所描述的LTβR抗體(即LTβR抗體36G2(19324)、31A3(19321)、23E9(19319)和41B2(19325))的可變區結合結構域和下表26中提供的相應SAA或TAA的可變區產生的。CLDN18.2、CLDN6、MUC17和LRRC15可變區的胺基酸序列提供在下表27中。

【0423】 在體外共培養測定中，評估了以AmAb或異源IgG形式產生的促效劑LTβR雙特異性結合蛋白組(見表26)的交聯依賴性LTβR傳訊活性。在該測定中，與穩定表現相關SAA或TAA的CHO或Saos-2細胞共培養的表現LTβR之人黑色素瘤細胞的趨化因子IL-8釋放表明測試抗體的交聯依賴性LTβR傳訊活性。

[表26].親本和雙特異性抗體

ID	描述
PUR149194-4	LTBR(36G2) IgG1 SEFL2
PUR149195-4	LTBR(31A3) IgG1 SEFL2
PUR149197-4	huClaudin-6(57103 (VH:C51G,VL:C141Q)_IgG1_SEFL2

PUR149198-4	huClaudin-6(57104 (VH:C51G,VL:C141Q))_IgG1_SEFL2
	huCLDN18.2(32698
PUR149199-4	(VH:G9R_S57A_V103E,VL:N39K_F103V))_IgG1_SEFL2
PUR149200-4	huCLDN18.2(32698)_IgG1_SEFL2
PUR149202-4	huMUC17(57105 (VH:C51G,VL:C141G_Q149R))_IgG1_SEFL2
PUR149203-4	huMUC17(57107 (VH:C51G,VL:C141G_Q149R))_IgG1_SEFL2
PUR149204-4	huLTBR(31A3)_ Fab x huClaudin-6(57103)_scFv_AmAb_CC
PUR149205-4	huLTBR(31A3)_ Fab x huClaudin-6(57104)_scFv_AmAb_CC
PUR149206-4	huLTBR(31A3)_ Fab x huCLDN18.2(32698) scFv_AmAb_no_CC
PUR149210-4	huLTBR(31A3)_ Fab x huMUC17(57105)_scFv_AmAb_CC
PUR149211-4	huLTBR(31A3)_ Fab x huMUC17(57107)_scFv_AmAb_CC
PUR149212-5	huLTBR(36G2)_ Fab x huClaudin-6(57103)_scFv_AmAb_CC
PUR149213-4	huLTBR(36G2)_ Fab x huClaudin-6(57104)_scFv_AmAb_CC
PUR149214-4	huLTBR(36G2)_ Fab x huCLDN18.2(32698)scFv_AmAb_no_CC
PUR149215-4	huLTBR(36G2)_ Fab x huCLDN18.2(32698)scFv_AmAb_no_CC
PUR149218-4	huLTBR(36G2)_ Fab x huMUC17(57105))_scFv_AmAb_CC
PUR149219-4	huLTBR(36G2)_ Fab x huMUC17(57107)_scFv_AmAb_CC
44245	huLTBR(41B2) x LRRC15(25851) AmAb CC
45147	huLTBR_19325 x huLRRC15_36779(VH:C98S) Hetero IgG1z SEFL2
52208	huLRRC15_36789(VL:C137S)_huLTBR_19319_Hetero IgG1z SEFL2

[表27]. SAA和TAA結合物的胺基酸序列

結合物名稱	VH	SEQ ID	VL	SEQ ID
		NO:		NO:
huClaudin-6 (57103)	QVQLVQSGAEVKKPGAS VKVSCKASGYTFTGYYV HWVRQAPGQGLEWMGW INPNSGATNYAQKFQGRV TMTRDTSISTAYMELSRL RSDDTAVYYCVRDALIVE APATRDYYYYGMDVWG	909	EIVLTQSPGTLSPGERA TLSCRASQSVRSTYLAW YQQKPGQAPRLLIYGASS RATGIPDRFSGSGSGTDF TLTISRLEPEDFAVYYCQ QYDASPITFGQGTRLEIK R	910

	QGTTVTVSS			
huClaudin-6 (57104)	QVQLVQSGAEVKKPGAS VKVSCKASGYTFTGYYV HWVRQAPGQGLEWMGW INPNSGATNYAQKFQGRV TMTRDTSISTAYMELSRL RSDDTAVYYCVRDRLIVE APATRDYYYYGMDVWG QGTTVTVSS	911	EIVLTQSPGTLSSLSPGERA TLSCRASQSVRSTYLAW YQQKPGQAPRLLIYGASS RATGIPDRFSGSGSGTDF TLTISRLEPEDFAVYYCQ QYDASPITFGQGTRLEIK R	912
huMUC17(57105)	QVQLVESGGGVVQPGRS LRLSCAASGFTFSNHGMH WVRQAPGKGLEWVAGIW SEGSNKYYADAVKGRFTI SRDNSKNTLYLQMNSLR AEDTAVYYCARATYTTG WSYFDYWGQGTLVTVSS	913	SYELTQPPSVSVSPGQTA SITCSGDKLGDKYASWY QQKSGQSPVLVIYQDAK RPSGIPERFSGSNSGNTA TLTISGTQAMDEADYYC QAFHQSTWVFGGGTQLT VLR	914
huMUC17(57107)	QLQQWGAGLLKPSETLSL TCAVYGGSFSGYYWSWI RQPPGKGLEWIGDIDASG STKYNPSLKSRTISLDT KNQFSLKLNSVTAADTAV YFCARKKYSTVWSYFDY WGQGTLVTVSS	915	SYELTQPPSVSVPPGQTA SITCSGDKLGDKYASWY QQKPGQSPVLIYQDRKR PSGVPERFSGSNSGNTAT LTISGTQAMDEADYYCQ AWGSSTAVFGGGTKLTV LR	916
huCLDN18.2 (32698)	EVQLLESRGGLVQPGGSL RLSCAASGFTFSNYAMSW VRQAPGKGLEWVSAISGS GGSTYYADSVKGRFTISR DNSKNTLYLQMSSLRAED TAEYYCAKGDWKYGY GMDVWGKGTTVTVSS	917	DIVMTQSPLSLPVTGPGE ASISCRSSQSLHSNGYK YLDWYLQKPGQSPQLLI YLGSNRASGVDPDRFSGS GSGTDFTLKISRLEAEDV GVYYCMQALQTPLTFGG GTKVEIKR	918
huCLDN18.2	EVQLLESGGGLVQPGGSL	919	DIVMTQSPLSLPVTGPGE	920

(32698)	RLSCAASGFTFSNYAMSW VRQAPGKGLEWVSSISGS GGSTYYADSVKGRFTISR DNSKNTLYLQMSSLRAED TAVYYCAKGDWKYGY GMDVWGKGTTVTVSS		ASISCRSSQSLLHSNGYN YLDWYLQKPGQSPQLLI YLGSNRASGVDPDRFSGS GSGTDFTLKISRLEAEDV GFYYCMQALQTPLTFGG GTKVEIKR	
huLRR15 (25851)	EVQLVQSGAEVKKPGAS VKVSCKASGYTFTDYYIH WMRQAPGQGLEWMGWI NPNSGGTNYAQKFLGRV TMTRDTSISTAYLELRRLR SDDTAVYYCARERRYNS GGFDYWGQGTLLTVSS	921	DIVMTQSPLSLSVTPGQP ASISCKSSQSLLHSNGKN YLDWYLQKPGQSPQLLI FLGSNRASGVDPDRFSGSG SGTDFTLKISRVEAEDVG VYYCMQAQQTPTFTGPG TKVEIKR	922
huLRR15 (36779)	QVQLVQSGAEVKKPGAS VKVSCKVSGNTLTVSM HWVRQAPGKGLEWMGG FDPEDGETIYAQKFQGRIT MTEDTSTDYAYMELNSLR CEDTAVYFCATLYSSGW NYYYGVVDVWGQGTAVT VSS	923	DIQMTQSPSSLSASVGDR VTITCRASQGIRNDLGW YQQKPGKAPKRLIYGASI FQIGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCL QHYSYPWTFGQGTREI KR	924
huLRR15 (36789)	QVQLVESGGGVVQPGRS LRLSCAASGFTFSNYGMH WVRQAPGKGLEWVAVIS YDGSNEYADSVKGRFTI SRDNSKNTLYLQMDSLRL AEDTAVYYCARDGAVAY YYYYGLDVWGQGTTVTV SS	925	DIVMTQSPLSLPVTGPGE ASISCRSSQSLLHRNGYN YLDWYLQKPGQSPQLLI YLGSNRASGVDPDRFSGS GSGTDFTLKISRVEAEDV GLYYCMQGLQTMCSFG QGTKLEIKR	926

【0424】 在該測定的第1天，收穫、計數表現LTβR的人黑色素瘤A375細胞

(ATCC, CRL-1619)，並將該等細胞以10,000個細胞/孔 (50 µL) 在生長培養基 (DMEM, 10% FBS, 4 mM L-麩醯胺酸, 1.5 g/L碳酸氫鈉, 4.5 g/L葡萄糖) 中接種於384孔測定板 (科斯塔公司 (Costar), 目錄號3701)。將板在37°C/5% CO₂下孵育過夜。在測定的第2天, 在測定培養基 (DMEM、2% FBS、4 mM L-麩醯胺酸、1.5 g/L碳酸氫鈉、4.5 g/L葡萄糖) 中從10 nM 1:3向下滴定測試分子11個點。以40 µL從384孔測定板的每個孔中去除培養上清液。然後將滴定的測試分子轉移到預先接種有表現LTβR的A375細胞的384孔測定板, 並在室溫下孵育30分鐘。收穫並計數穩定表現靶標的倉鼠卵巢細胞 (CHO) 或人骨肉瘤Saos-2細胞, 將該等細胞重懸在測定培養基中, 並按照板佈局轉移到測定板上。然後將測定板在37°C/5% CO₂下孵育過夜。基於測定開發數據, LTβR與表現CLDN6、CLDN18.2、MUC17、LRRC15的細胞或相應的非表現細胞的比率設置為1:1。各種表現靶標的細胞為測試分子提供交聯, 相應的非表現靶標的細胞用於確定測試分子的交聯獨立性。在測定第3天, 按照製造商之說明, 藉由檢測套組 (希思公司, 目錄號62IL8PEC) 測量測定孔上清液中趨化因子IL-8釋放, 並由EnVision (珀金埃爾默公司 (PerkinElmer)) 在665 nm和615 nm下讀取。相對IL-8釋放由比率 = 訊號665 nm/訊號615 nm表示。

【0425】為了分析, 藉由Genedata Screener (Smart fit公司) 的四參數邏輯擬合模型確定測試分子的插值EC₅₀、轉運EC₅₀和最大活性。插值EC₅₀係基於每種結合蛋白的劑量曲線中的回折點, 轉運EC₅₀係Y軸上特定點的值, 對於大多數分子來說, 該值為約EC₅₀。EC₉₀係使用插值EC₅₀和希爾斜率以以下公式計算的: $EC_{90} = (90/100-90)^{\frac{1}{\text{希爾斜率}}} EC_{50}$ 。

【0426】雙特異性抗體的最大活性係藉由將每種分子的最高訊號除以相應中性對照的平均訊號來計算的。下表28提供了個體抗體效力的總結, 如圖20-23所示。

【0427】 LTβR x CLDN6 BsAb的大部分最大活性在中性對照的2.98至4.12倍之間（圖20）。含有huLTβR 31A3的分子具有最佳EC₅₀值，為約75 pM。具有huLTβR 36G2的分子的EC₅₀值範圍為90.65至183.10 pM。所有分子均表現出交聯依賴性活性。

【0428】 LTβR x CLDN18.2 BsAb的大部分最大活性在中性對照的4.14至4.32倍之間（圖21）。所有LTβR x CLDN18.2分子具有相似的EC₅₀值，並表現出交聯依賴性活性。

【0429】 LTβR x MUC17 BsAb的大部分最大活性在中性對照的2.70至3.26倍之間（圖22）。所有LTβR x MUC17 BsAb分子具有相似的EC₅₀值，並表現出交聯依賴性活性。

【0430】 LTβR x LRRC15 BsAb的大部分最大活性在中性對照的4.46至5.37倍之間（圖23）。LTβR x LRRC15 BsAb分子的EC₅₀值範圍為46.42至108.12。所有LTβR x LRRC15 BsAb分子均表現出交聯依賴性活性。

[表28]：LTβR雙特異性分子效力總結

CHO CLDN 6 ⁺ 細胞					CHO K1 (CLDN6)
LTβR x CLDN6 BsAb ID	最大活性	EC50 [pM]	EC90 [pM]	暫態EC50 (pM) Y=2.2	最大活性
PUR149204-4	3.43	74.42	266.45	1575.87	1.06
PUR149205-4	3.70	75.10	340.54	822.36	1.03
PUR149212-5	2.98	90.65	208.03	1514.50	1.07
PUR149213-4	4.12	183.10	3441.46	847.30	1.29
CHO CLDN 18.2 ⁺ 細胞					CHO K1 (CLDN18.2)
LTβR x CLDN18.2 BsAb ID	最大活性	EC50 [pM]	EC90 [pM]	暫態EC50 (pM) Y=2.2	最大活性

PUR149206-4	4.26	50.16	124.96	58.81	1.04
PUR149214-4	4.32	69.98	268.62	81.15	1.14
PUR149215-4	4.14	49.13	196.95	57.65	1.05
CHO MUC17 ⁺ 細胞					CHO K1 (MUC17 ⁻)
LTβR x MUC17 BsAb ID	最大活性	EC50 [pM]	EC90 [pM]	暫態EC (pM) Y=2.5	最大活性
PUR149211-4	3.26	46.64	295.19	39.99	0.97
PUR149218-4	2.70	43.53	232.93	64.61	1.05
PUR149219-4	3.09	31.61	211.59	30.21	0.97
Saos-2 LRRC15 ⁺ 細胞					Saos-2 (LRRC15 ⁻)
LTβR x LRRC15 BsAb ID	最大活性	EC50 [pM]	EC90 [pM]	暫態EC (pM) Y=8	最大活性
44245	5.08	80.82	276.94	76.54	1.02
45147	5.37	46.42	708.17	36.98	0.92
52208	4.46	108.12	560.27	120.53	0.94

實例8：使用基於細胞的測定確認LTβR受體-配體非阻斷活性。

【0431】藉由按照製造商制定的方案使用Alexa Fluor 647 Microscale蛋白質標記套組（賽默飛世爾科技公司，目錄號A30009）軛合人LIGHT（R&D系統公司，目錄號664-LI/CF）和人LTα1β2（R&D系統公司，目錄號8884-LY/CF）來製備人LIGHT-Alexa 647和人LTα1β2-Alexa 647。經由基於FACS的受體-配體測定，測定人LTβR結合抗體或包含LTβR結合抗體的雙特異性抗體不阻斷人LIGHT和人LTα1β2與HEK 293T細胞上暫態表現的人LTβR結合的能力。將樣本與人IgG共染色，以另外評估配體的非阻斷是否係由於LTβR抗體與HEK293T細胞上暫態表現的人LTβR不結合。如果LTβR抗體不阻止人LIGHT-Alexa 647或人LTα1β2-Alexa 647與HEK 293T細胞上暫態表現的人LTβR結合，則流動式細胞分析術幾

何平均值（GeoMean）訊號相對於在不存在LT β R抗體的情況下獲得的GeoMean訊號降低，從而由於非競爭而導致配體結合的低百分比抑制值。

【0432】簡言之，藉由按照製造商制定的方案使用表現 huLT β R cDNA[pTT5.2:VK1O2O12::huLT β R(31-435) C173003 (DNA-38098)]的表現載體以及Opti-MEM®減少血清培養基（吉布柯公司（Gibco），目錄號：31985-088）和293Fectin™試劑（吉布柯公司 REF:12347-019，P/N 53020LT）轉染，在宿主入胚胎腎293細胞上表現人LT β R。將7.5 uL人LT β R特異性單株抗體在劑量滴定曲線中滴定，並在4°C下與7.5 uL轉染的hu LT β R細胞在FACS緩衝液[1XPBS+2%胎牛血清（西格瑪奧德里奇公司（Sigma-Aldrich），目錄號F2442-500 mL）]中使用96孔FACS板（康寧公司（Corning）目錄號3702）孵育1小時。然後，在FACS緩衝液中以1.112 μ g/mL添加15 μ L人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647，以及5 μ g/mL Alexa Fluor 488軛合的AffiniPure山羊抗人IgG（傑克遜免疫研究公司，目錄號：109-545-098），並在室溫下在黑暗中孵育20分鐘。人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647的最終濃度為0.556 μ g/mL，Alexa 488山羊抗人IgG的最終濃度係2.5 μ g/mL。將FACS板加入170 uL FACS緩衝液，然後在FACS緩衝液中藉由以2500 RPM離心2分鐘洗滌一次。根據製造商之建議，將樣本重懸在45 μ L FACS緩衝液中，並在帶有Intellicyt公司自動進樣器的iQue流式細胞儀上讀取；在Intellicyt公司ForeCyt®企業客戶6.2版（R3）上進行數據分析。

【0433】將人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647的量藉由流動式細胞分析術分析由GeoMean螢光訊號定量，並將該訊號轉換為受體-配體（R-L）相互作用的抑制百分比。在LT β R抗體存在下配體結合訊號的損失計算為R-L結合的抑制百分比。藉由對4個重複的配體-Alexa 647訊號的GeoMean訊號取平均值來確定人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647的最大GeoMean訊號，該等重複與HEK 293T細胞上暫態表現的人LT β R一起孵育。人LIGHT-Alexa 647或人

LTα1β2-Alexa 647的最小GeoMean訊號係由與用模擬載體轉染的HEK 293T細胞一起孵育的配體-Alexa 647訊號的GeoMean訊號確定的。使用以下等式計算人LTβR抗體或同種型對照抗體對人LTβR-His：配體（人LIGHT或人LTα1β2）的抑制百分比：

$$\text{抑制百分比 (\%)} = 1 - (\text{實驗GeoMean} - \text{最小GeoMean}) / (\text{最大GeoMean} - \text{最小GeoMean})$$

【0434】對於一些LTβR抗體，當實驗GeoMean訊號高於最大GeoMean訊號時，獲得了負抑制百分比值，這可能是由於LTβR抗體與HEK 293T細胞上暫態表現的人LTβR結合的確認性變化，從而可能導致更高的配體-Alexa 647 GeoMean訊號（即，與不存在LTβR抗體相比，在其存在下允許更高水平的內源性配體結合）。

【0435】使用Alexa 488山羊抗人IgG染劑評估與HEK293T細胞上暫態表現的與人LTβR結合的LTβR抗體的量，並使用相對於不相關上清液的GeoMean特異性倍數的計算，藉由流動式細胞分析術分析的GeoMean螢光訊號進行定量。大於2.0的GeoMean計算值用作LTβR抗體與HEK293T細胞上暫態表現的人LTβR結合的臨界值。

【0436】圖24A和24B係繪製隨著所指示的促效劑LTβR結合蛋白濃度的增加，LIGHT（圖24A）和LTα1β2（圖24B）與HEK293T細胞上暫態表現的LTβR的結合受到抑制的圖。人IgG1同種型和市售大鼠抗人LTβR抗體（Carlos-1；英傑公司；目錄號MA125845）分別作為陰性和陽性對照。下表29中提供了測試促效劑LTβR結合蛋白的配體阻斷活性的總結。圖24C顯示了所指示結合分子的濃度依賴性LTβR結合。

[表29].選擇促效劑LTβR結合蛋白的LTβR配體阻斷活性的總結

LTβR結合物ID	形式	LTα1β2	LIGHT
19323 (35F5)	單株抗體	在任何測試濃度下均無阻斷活性	在任何測試濃度下均無阻斷活性
19324 (36G2)	單株抗體	僅在> 8 nM濃度下觀察到阻斷活性（在< 8 nM濃度下為非阻斷物）	僅在> 8 nM濃度下觀察到阻斷活性（在< 8 nM濃度下為非阻斷物）
19321 (31A3)	單株抗體	在> 0.3 nM下，表現出LTα1β2結合的低水平（20%）抑制	在任何測試濃度下均無阻斷活性
19322 (34D1)	單株抗體	在所有測試濃度下阻斷LTα1β2-LTβR結合	在任何測試濃度下均無LIGHT阻斷活性。
19327 (44B1)	單株抗體	在高濃度下阻斷LTα1β2-LTβR	在任何測試濃度下均無LIGHT阻斷活性
19326 (56577)	雙特異性結合蛋白	濃度依賴性LTα1β2-LTβR阻斷	濃度依賴性LIGHT-LTβR阻斷
19325 (56575)	雙特異性結合蛋白	在任何測試濃度下均無LTα1β2阻斷活性。	在任何測試濃度下均無LIGHT阻斷活性。
19319 (52208)	雙特異性結合蛋白	在任何測試濃度下均無LTα1β2阻斷活性。	在任何測試濃度下均無LIGHT阻斷活性。

【0437】 還評估了雙特異性LTβR結合蛋白的LTβR配體阻斷活性。圖25A和26A係顯示所指示的LTβR-LRRC15雙特異性結合物抑制LTα1β2與細胞表現的LTβR結合的圖，圖25B和26B顯示了相同的LTβR-LRRC15雙特異性結合物抑制LIGHT與細胞表現的LTβR結合。上表29中提供了所測試的LTβR雙特異性結合蛋白的配體阻斷活性的總結。圖25C和26C顯示了所指示的雙特異性結合蛋白的濃度依賴性LTβR結合。

【0438】 該數據顯示，結合CRD4的LTβR抗體19325(LIBC219081)和19319（ LIBC218979 ）在以抗體和雙特異性結合蛋白形式測試的所有濃度下均不抑制

LT α 1 β 2或LIGHT與LT β R結合。

實例9：重新篩選融合瘤池以鑒定額外的LT β R CRD4結合非配體阻斷抗體

【0439】 9.1 從融合瘤池中產生選殖抗LT β R融合瘤。將來自收穫1至6的XenoMouse®融合瘤培養物解凍，並在DMEM選擇培養基中生長3-4天。在FACS富集分選前一天將培養基改為BDQY融合瘤培養基。在10 mL無菌FACS緩衝液中洗滌細胞，然後在4°C下，在2 mL反應體積中與3 μ g/mL濃度的生物素標記的重組人LT β R（R&D系統公司，目錄號：7538LR）和20 μ g/mL濃度的人LT α 1 β 2-Alexa 647（R&D系統公司，目錄號8884-LY/CF）一起孵育30分鐘。對於所有融合瘤培養物，在此步驟中還添加了100 μ g/mL多選殖人IgG（傑克遜免疫研究公司，目錄號：009-000-003）以阻斷抗Fc結合物。在10 mL FACS緩衝液中洗滌一次後，將1 mL抗體混合物添加到細胞中，該抗體混合物含有各5 μ g/mL Alexa Fluor 488軛合的山羊抗人IgG Fc Fab（傑克遜免疫研究公司，目錄號：109-547-008）和BV421軛合的鏈黴親和素（BD生物科學公司（BD biosciences），目錄號：563259）。然後將細胞在4°C下孵育30分鐘。孵育後，將細胞在10 mL FACS緩衝液中洗滌，重懸於2 mL含有5 μ L 7-AAD（BD Pharmingen公司，目錄號：559925）的BDQY融合瘤培養基中，然後通過40微米細胞過濾器以去除任何團塊。藉由對活細胞群體進行門控在BD FACSAria上對細胞進行批量分選，然後對雙陽性Alexa Fluor 488 IgG和BV421 LT β R螢光訊號進行分選，最後對Alexa Fluor 647 LT α 1 β 2和BV421 LT β R螢光訊號進行分選。在第一輪富集分選以使目標群體從< 1%到> 20%之後，將靶細胞單細胞分選到含有BDQY融合瘤培養基的384孔微量滴定板上，並培養長達2週，然後收集上清液進行篩選。

【0440】 9.2 相對表位分組/分析。將生物素醯化山羊抗人IgG Fc捕獲抗體（傑克遜免疫研究公司，目錄號：109-065-098）以2 μ g/mL濃度與鏈黴親和素包被的、經獨特條碼編碼LumAvidin Beads®（LumAvidin Microspheres，路明克斯

公司，美國德克薩斯州奧斯丁）在室溫下在黑暗中偶合30分鐘，並洗滌兩次。將4 µg/mL濃度的參考抗體融合瘤上清液樣本與山羊抗人IgG Fc包被的珠粒在室溫下在黑暗中孵育30分鐘，並洗滌三次。將His-標記的人LTβR抗原（VK1O2O12::huLTβR(31-227)::8xHis，46449-2）以60 nM製備，並與5 ug/mL Chrompure人IgG全分子（傑克遜免疫研究公司，目錄號：009-000-003）結合，在室溫下在黑暗中與包被的珠粒孵育30分鐘，並洗滌兩次。將珠粒重懸於含有Stabilguard®（舒爾默迪克斯公司（SurModics）SG01）的FACS緩衝液中。

【0441】將含有歸一化（4 ug/mL）測試抗體（融合瘤上清液）的樣本孔與Zenon™抗人Fab（Zenon™ Alexa Fluor™ 488人IgG標記套組，賽默飛世爾科技公司，目錄號：Z25402）以0.06 ug標記/孔在室溫下在黑暗中孵育15分鐘。然後將Chrompure人IgG全分子（傑克遜免疫研究公司，目錄號：009-000-003）以7.2 ug塊/孔添加到Zenon™標記的樣本孔中，並在室溫下在黑暗中孵育15分鐘。

【0442】將抗原包被的參考抗體結合珠粒合併，然後將該等珠粒分到含有Zenon™標記的測試抗體（融合瘤上清液）樣本（或陰性對照）的單個樣本孔中，在室溫下在黑暗中孵育30分鐘，並洗滌兩次。測試抗體（融合瘤上清液）的最終濃度為1 ug/mL。將樣本洗滌兩次以去除未結合的檢測試劑，並重懸於FACS緩衝液中。使用Intellicyt公司iQue™ Screener平臺對樣本進行分析。為了確定各個測試抗體的抗體競爭/結合譜，從每個競爭/結合反應（即整個參考抗體組）的參考抗體加測試抗體訊號中減去僅參考抗體結合訊號。單個抗體結合譜被定義為每個競爭/結合反應的淨結合值的集合。然後藉由計算每個測試抗體譜之間的決定係數來評估單個譜之間的相似程度。然後將彼此顯示高度相似性（ $R^2 > 0.7$ ）的測試抗體分組到共同的分組譜中。使用這種方法，將LTβR結合抗體細分為7個獨特的分組譜（A、B、C、D、F、G和H）。已鑒定出與本文鑒定為19325（41B2）和19319（23E9）的LTβR抗體具有共同分組譜的候選抗體，該等抗體藉由HDX-

MS分析（見實例6.2）與LTβR的CRD4結合，並在圖27的表中提供。使用內部表位定位測定確認該等候選抗體結合LTβR的CRD4。

【0443】 9.3 使用基於細胞的測定確認在重新篩選中鑒定出的LTβR抗體的非配體阻斷活性。經由實例8中描述的基於FACS的受體-配體測定，測定含有人LTβR結合抗體(5 μg/mL)的融合瘤上清液不阻斷人LIGHT和人LTα1β2與HEK 293T細胞上暫態表現的人LTβR結合的能力。一式兩份測試每種含有人LTβR結合抗體的融合瘤上清液的配體阻斷活性。圖27的表中提供了與和LTβR的CRD4結合的、本文鑒定為19325（41B2）和19319（23E9）的LTβR抗體具有表位分組譜的每種LTβR結合抗體的抑制百分比。如上文所描述的，當實驗GeoMean訊號高於最大GeoMean訊號時，獲得了負抑制百分比值，這可能是由於LTβR抗體與HEK 293T細胞上暫態表現的人LTβR結合的確認性變化，從而可能導致更高的配體-Alexa 647 GeoMean訊號（即，與不存在LTβR抗體相比，在其存在下允許更高水平的內源性配體結合）。

【0444】 9.4 使用Carterra測定確認在重新篩選中鑒定的LTβR抗體的非配體阻斷活性。為了進一步確認LTβR抗體的非配體阻斷活性，經由基於Carterra的受體-配體測定，測定含有LTβR結合抗體的融合瘤上清液阻斷人LIGHT（R&D系統公司，目錄號664-LI/CF）和人LTα1β2（R&D系統公司，目錄號8884-LY/CF）與人LTβR-His結合的能力。如果LTβR抗體阻止人LIGHT或人LTα1β2與人LTβR-His結合，則將受體暴露於抗體後注射配體的響應（RU）不會相對於存在單獨LTβR受體時達到的RU增加，從而防止由於競爭而形成三組分夾層複合物。圖27的表顯示了藉由此Catterra方法測量的選定融合瘤上清液樣本的受體-配體相互作用阻斷能力。

【0445】 簡言之，在25°C下在Carterra® LSA上，在預載入生物素醯化抗huFc VHH（Chromotek公司，目錄號：shurbGB-1）的HBSTE緩衝液[10 mM HEPES，

pH7.4，150 mM NaCl，0.05% tween-20和1 mM EDTA；自製]的鏈黴親和素（SA）晶片（SAHC30M，Carterra零件號4294）上捕獲人LTβR結合抗體組。將抗體歸一化並稀釋至2 μg/mL，並藉由96通道打印頭在晶片的斑點上列印15 min。然後使用單個流通池以300 nM向晶片注射人LTβR-His，結合時間為5 min，以使受體結合達到飽和，解離時間為1 min，這是軟體使解離最小化所允許的最小值。隨後立即以150 nM注射人LIGHT或人LTα1β2配體，結合5 min，解離1 min。在重新列印用於其他配體測定的抗體之前，使用10 mM甘胺酸，pH 1.5（Carterra零件號3639）進行再生。

【0446】 使用Kinetics軟體（Carterra公司）藉由RU定量LTβR抗體載入、人LTβR-His受體結合和人LIGHT或人LTα1β2配體夾層。夾層水平計算為配體RU與受體RU的比率。用在相同實驗設置中測量的不相關人IgG1對照確定最低夾層水平。對於一些LTβR抗體，夾層水平值較低，可能是由於抗體濃度低、注射體積變化效應、對LTβR的弱結合物或LTβR解離速度快。由於無法確定該等抗體係非阻斷物還是阻斷物，因此，在結果表中被標記為「NA」。

【0447】 9.5 親和力差距分析。在25°C下在Carterra LSA上，在HBSTE運行緩衝液[10 mM HEPES，pH7.4，150 mM NaCl，0.05% tween-20和1 mM EDTA]中測量親和力。使用10 mM甘胺酸（pH 1.5）（Carterra零件號3639）進行再生。將含有LTβR結合抗體的融合瘤上清液歸一化並稀釋至0.3 μg/mL，並使用96通道打印頭將該等上清液在預先裝載有生物素醯化抗huFc VHH（Chromotek公司，目錄號：shurbGB-1）的鏈黴親和素（SA）晶片（SAHC30M，Carterra零件號4294）的斑點上列印10 min。緩衝液孔和不相關人IgG1樣本用作陰性對照。將靶標、人或cyno LTβR作為分析物以243 nM、81 nM、27 nM、9 nM、3 nM和1 nM注射。結合時間為5 min，解離時間為30分鐘。數據係雙背景參考，因為從數據中減去了晶片上的參考斑點和0 nM分析物濃度。使用1：1朗格繆爾傳質結合模型在

Kinetics軟體（Carterra公司）中分析數據。人和cyno親和力差距的結果顯示在圖27的表中。

【0448】 本文引用的每個參考文獻針對它所教導的全部內容和出於所有目的均特此藉由引用將其全部併入。

【0449】 本揭露之範圍不受本文所述之特定實施方式的限制，該等實施方式旨在作為本揭露之各個實施方式的單個說明，並且揭露了功能上等效的方法和組分。實際上，除了本文中顯示和描述的那些之外，根據前述描述和附圖，本發明之各種修改對於熟悉該項技術者將變得顯而易見。這類改變旨在落入所附申請專利範圍之範圍內。

【符號說明】

【0450】 無

【生物材料寄存】

【0451】 無

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【發明申請專利範圍】

【請求項1】一種促效劑淋巴毒素 β 受體 (LT β R) 結合蛋白，其中所述結合蛋白結合包含人LT β R富含半胱氨酸結構域4 (CRD4) 的一或多個殘基的表位，其中人LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211，並且其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT α 1 β 2與LT β R結合。

【請求項2】如請求項1所述之促效劑LT β R結合蛋白，其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合且 (b) 不抑制LT α 1 β 2與LT β R結合。

【請求項3】如請求項1所述之促效劑LT β R結合蛋白，其中該表位包含SEQ ID NO: 1之位置197-209處的LT β R CRD4的一或多個殘基。

【請求項4】如請求項1-3中任一項所述之促效劑LT β R結合蛋白，其中在該促效劑LT β R結合蛋白存在下對LIGHT和/或LT α 1 β 2與LT β R結合的抑制在基於細胞的受體-配體結合測定中進行測量，所述測定包括以下步驟：

將表現LT β R的細胞與含有該促效劑LT β R結合蛋白的培養基孵育1小時；

在所述孵育後，使該等表現LT β R的細胞與可檢測的LIGHT配體、可檢測的LT α 1 β 2配體或其組合接觸，以允許該等可檢測的配體與LT β R結合；

在所述接觸後，在該LT β R結合蛋白存在下，檢測與表現LT β R的細胞結合的可檢測的LIGHT和/或LT α 1 β 2配體；以及

基於所述檢測將該促效劑LT β R結合蛋白鑒定為不抑制LIGHT或LT α 1 β 2與LT β R結合。

【請求項5】如請求項1-3中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：

與SEQ ID NO: 121或SEQ ID NO: 123具有至少90%序列同一性的重鏈可變結構域 (VH) 胺基酸序列，和

與SEQ ID NO: 122或SEQ ID NO: 124具有至少90%序列同一性的輕鏈可變結構域（VL）胺基酸序列。

【請求項6】如請求項1-3中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：

與SEQ ID NO: 121和SEQ ID NO: 123具有至少90%序列同一性的VH胺基酸序列，和

與SEQ ID NO: 122和SEQ ID NO: 124具有至少90%序列同一性的VL胺基酸序列。

【請求項7】如請求項1-3中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：

與SEQ ID NO: 121和SEQ ID NO: 123具有至少95%序列同一性的VH胺基酸序列，和

與SEQ ID NO: 122和SEQ ID NO: 124具有至少95%序列同一性的VL胺基酸序列。

【請求項8】如請求項1-7中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：

VH，其包含HCDR1胺基酸序列X₁YX₃MX₅（SEQ ID NO: 5），其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺基酸序列X₁IX₃YDX₆X₇X₈X₉YX₁₁X₁₂DSVKG（SEQ ID NO: 6），其中X₁為A或V；X₃為W或R；X₆為E或G；X₇為S、R或T；X₈為N或K；X₉為K、R或Q；X₁₁為H或Y；並且X₁₂為A或E；以及HCDR3胺基酸序列X₁RX₃X₄X₅X₆X₇X₈X₉YYGX₁₃X₁₄V（SEQ ID NO: 7），其中X₁為D或E；X₃為V、G或I；X₄為V、P或A；X₅為A、Y或G；X₆為R、A、G或H；X₇為P或G；X₈為G、N、D、Y、A或H；X₉為Y、T或F；X₁₃為L或M；並且X₁₄為D或A；

VL，其包含LCDR1胺基酸序列SGDX₄LPX₇X₈YX₁₀Y（SEQ ID NO: 62），其

中X₄為A或T；X₇為E、K、Q、D或N；X₈為Q或H；並且X₁₀為A或T；LCDR2胺基酸序列 KDNERPS（SEQ ID NO: 63）；以及 LCDR3 胺基酸序列 QSX₃DX₅SX₇X₈YX₁₀X₁₁（SEQ ID NO: 64），其中X₃為A或T；X₅為S、G或N；X₇為G或A；X₈為T、S或A；X₁₀為V或M；並且X₁₁為I或V。

【請求項9】如請求項1-8中任一項所述之促效劑LTβR結合蛋白，其中所述結合蛋白包含：

與SEQ ID NO: 121具有至少90%序列同一性的VH胺基酸序列、以及SEQ ID NO: 5的HCDR1胺基酸序列、SEQ ID NO: 6的HCDR2胺基酸序列和SEQ ID NO: 7的HCDR3胺基酸序列；以及

與SEQ ID NO: 122具有至少90%序列同一性的VL胺基酸序列、以及SEQ ID NO: 62的LCDR1胺基酸序列、SEQ ID NO: 63的LCDR2胺基酸序列和SEQ ID NO: 64的LCDR3胺基酸序列。

【請求項10】如請求項1-9中任一項所述之促效劑LTβR結合蛋白，其中所述結合蛋白包含：

VH，其包含分別為SEQ ID NO: 11-13的HCDR1、HCDR2和HCDR3胺基酸序列，以及VL，其包含分別為SEQ ID NO: 68-70的LCDR1、LCDR2和LCDR3胺基酸序列；或

VH，其包含分別為SEQ ID NO: 8-10的HCDR1、HCDR2和HCDR3胺基酸序列，以及VL，其包含分別為SEQ ID NO: 65-67的LCDR1、LCDR2和LCDR3胺基酸序列。

【請求項11】如請求項1-10中任一項所述之促效劑LTβR結合蛋白，其中該結合蛋白係抗體。

【請求項12】如請求項1-10中任一項所述之促效劑LTβR結合蛋白，其中該結合蛋白係雙特異性結合蛋白。

【請求項13】 一種雙特異性淋巴毒素 β 受體（LT β R）結合蛋白，所述結合蛋白包含：

LT β R結合結構域，其中該LT β R結合結構域結合包含人LT β R富含半胱氨酸結構域4（CRD4）的一或多個殘基的表位，其中所述LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211；以及

腫瘤相關抗原結合結構域，

其中該雙特異性結合蛋白激動LT β R活性，並且 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT α 1 β 2與LT β R結合。

【請求項14】 如請求項13所述之雙特異性促效劑LT β R結合蛋白，其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合且 (b) 不抑制LT α 1 β 2與LT β R結合。

【請求項15】 如請求項13所述之雙特異性促效劑LT β R結合蛋白，其中該表位包含SEQ ID NO: 1之位置197-209處的LT β R CRD4的一或多個殘基。

【請求項16】 如請求項13-15中任一項所述之雙特異性促效劑LT β R結合蛋白，其中在該雙特異性促效劑LT β R結合蛋白存在下對LIGHT和/或LT α 1 β 2與LT β R結合的抑制在基於細胞的受體-配體結合測定中進行測量，所述測定包括以下步驟：

將表現LT β R的細胞與含有該雙特異性促效劑LT β R結合蛋白的培養基孵育1小時；

在所述孵育後，使該等表現LT β R的細胞與可檢測的LIGHT配體、可檢測的LT α 1 β 2配體或其組合接觸，以允許該等可檢測的配體與LT β R結合；

在所述接觸後，在該雙特異性促效劑LT β R結合蛋白存在下，檢測與表現LT β R的細胞結合的可檢測的LIGHT和/或LT α 1 β 2配體；以及

基於所述檢測將該雙特異性促效劑LT β R結合蛋白鑒定為不抑制LIGHT或LT α 1 β 2與LT β R結合。

【請求項17】 如請求項13所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域包含：

與SEQ ID NO: 121或SEQ ID NO: 123具有至少90%序列同一性的VH胺基酸序列，和

與SEQ ID NO: 122或SEQ ID NO: 124具有至少90%序列同一性的VL胺基酸序列。

【請求項18】 如請求項13所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域包含：

與SEQ ID NO: 121和SEQ ID NO: 123具有至少90%序列同一性的VH胺基酸序列，和

與SEQ ID NO: 122和SEQ ID NO: 124具有至少90%序列同一性的VL胺基酸序列。

【請求項19】 如請求項13所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域包含：

與SEQ ID NO: 121和SEQ ID NO: 123具有至少95%序列同一性的VH胺基酸序列，和

與SEQ ID NO: 122和SEQ ID NO: 124具有至少95%序列同一性的VL胺基酸序列。

【請求項20】 如請求項13-19中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域包含：

VH，其包含HCDR1胺基酸序列X₁YX₃MX₅（SEQ ID NO: 5），其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺基酸序列X₁IX₃YDX₆X₇X₈X₉YX₁₁X₁₂DSVKG（SEQ ID NO: 6），其中X₁為A或V；X₃為W或R；X₆為E或G；X₇為S、R或T；X₈為N或K；X₉為K、R或Q；X₁₁為H或Y；並且X₁₂為A或E；以及HCDR3

胺基酸序列X₁RX₃X₄X₅X₆X₇X₈X₉YYGX₁₃X₁₄V (SEQ ID NO: 7)，其中X₁為D或E；X₃為V、G或I；X₄為V、P或A；X₅為A、Y或G；X₆為R、A、G或H；X₇為P或G；X₈為G、N、D、Y、A或H；X₉為Y、T或F；X₁₃為L或M；並且X₁₄為D或A；

VL，其包含LCDR1胺基酸序列SGDX₄LPX₇X₈YX₁₀Y (SEQ ID NO: 62)，其中X₄為A或T；X₇為E、K、Q、D或N；X₈為Q或H；並且X₁₀為A或T；LCDR2胺基酸序列KDNERPS (SEQ ID NO: 63)；以及LCDR3胺基酸序列QSX₃DX₅SX₇X₈YX₁₀X₁₁ (SEQ ID NO: 64)，其中X₃為A或T；X₅為S、G或N；X₇為G或A；X₈為T、S或A；X₁₀為V或M；並且X₁₁為I或V。

【請求項21】 如請求項13-20中任一項所述之雙特異性促效劑LTβR結合蛋白，其中所述結合蛋白包含：

與SEQ ID NO: 121具有至少90%序列同一性的VH胺基酸序列、以及SEQ ID NO: 5的HCDR1胺基酸序列、SEQ ID NO: 6的HCDR2胺基酸序列和SEQ ID NO: 7的HCDR3胺基酸序列；以及

與SEQ ID NO: 122具有至少90%序列同一性的VL胺基酸序列、以及SEQ ID NO: 62的LCDR1胺基酸序列、SEQ ID NO: 63的LCDR2胺基酸序列和SEQ ID NO: 64的LCDR3胺基酸序列。

【請求項22】 如請求項13所述之雙特異性促效劑LTβR結合蛋白，其中該VH包含分別為SEQ ID NO: 11-13的HCDR1、HCDR2和HCDR3胺基酸序列，以及該VL包含分別為SEQ ID NO: 68-70的LCDR1、LCDR2和LCDR3胺基酸序列；或

該VH包含分別為SEQ ID NO: 8-10的HCDR1、HCDR2和HCDR3胺基酸序列，以及該VL包含分別為SEQ ID NO: 65-67的LCDR1、LCDR2和LCDR3胺基酸序列。

【請求項23】 如請求項13-22中任一項所述之雙特異性促效劑LTβR結合蛋白，其中該雙特異性結合蛋白僅包含一個LTβR結合結構域。

【請求項24】 如請求項13-22中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域係Fab。

【請求項25】 如請求項13-24中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該結合蛋白包含一個腫瘤相關抗原結合結構域。

【請求項26】 如請求項25所述之雙特異性促效劑LT β R結合蛋白，其中該腫瘤相關抗原結合結構域係Fab。

【請求項27】 如請求項13-24中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該結合蛋白包含兩個腫瘤相關抗原結合結構域。

【請求項28】 如請求項13-22中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域係Fab，並且該腫瘤相關抗原結合結構域係Fab。

【請求項29】 如請求項13-28中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域和該腫瘤相關抗原結合結構域各自偶合到Fc部分。

【請求項30】 如請求項29所述之雙特異性促效劑LT β R結合蛋白，其中該Fc部分不與Fc- γ 受體結合。

【請求項31】 一種多核苷酸，該多核苷酸編碼如請求項1-12中任一項所述之促效劑LT β R結合蛋白。

【請求項32】 一種載體，該載體包含如請求項31所述之多核苷酸。

【請求項33】 一種宿主細胞，該宿主細胞包含如請求項31所述之多核苷酸或如請求項32所述之載體。

【請求項34】 一或多種多核苷酸，該一或多種多核苷酸編碼如請求項13-30中任一項所述之雙特異性促效劑LT β R結合蛋白。

【請求項35】 一種載體，該載體包含如請求項34所述之一或多種多核苷酸。

【請求項36】 一種宿主細胞，該宿主細胞包含如請求項34所述之一或多種多核苷酸或如請求項35所述之載體。

【請求項37】 一種藥物組成物，該藥物組成物包含：

如請求項1-12中任一項所述之促效劑LT β R結合蛋白，如請求項13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，如請求項31或34所述之一或多種多核苷酸，或如請求項32或35所述之載體，以及

藥學上可接受的載劑。

【請求項38】 如請求項1-12中任一項所述之促效劑LT β R結合蛋白，用作藥物。

【請求項39】 如請求項1-12中任一項所述之促效劑LT β R結合蛋白，用於治療癌症。

【請求項40】 如請求項1-12中任一項所述之促效劑LT β R結合蛋白，用於製備用於治療癌症的藥物。

【請求項41】 如請求項13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，用作藥物。

【請求項42】 如請求項13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，用於治療癌症。

【請求項43】 如請求項13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，用於製造用於治療癌症的藥物。

【請求項44】 一種治療受試者癌症之方法，所述方法包括：

向患有癌症的受試者投與促效劑淋巴毒素 β 受體（LT β R）結合蛋白，其中所述結合蛋白結合包含人LT β R富含半胱氨酸結構域4（CRD4）的一或多個殘基的表位，其中人LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211，並且其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT α 1 β 2與LT β R結合。

【請求項45】 一種治療受試者癌症之方法，所述方法包括：

向患有癌症的受試者投與雙特異性淋巴毒素 β 受體（LT β R）結合蛋白，其中

所述結合蛋白包含：

LT β R結合結構域，其中該LT β R結合結構域結合包含人LT β R富含半胱氨酸結構域4（CRD4）的一或多個胺基酸殘基的表位，其中人LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211；以及

腫瘤相關抗原結合結構域，

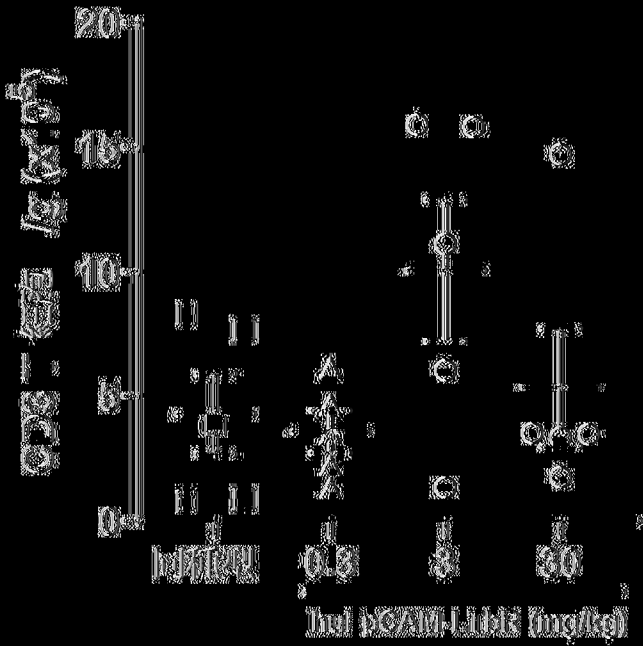
其中該雙特異性結合蛋白激動LT β R活性，並且 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT1 α 2 β 與LT β R結合。

【請求項46】 如請求項44或請求項45所述之方法，所述方法進一步包括：

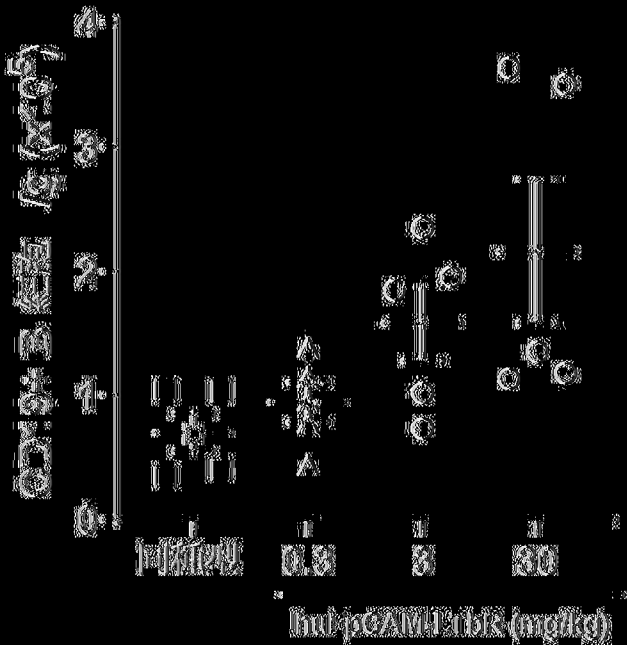
與所述促效劑LT β R結合蛋白或雙特異性LT β R結合蛋白結合投與免疫調節治療劑。

【請求項47】 如請求項41或42所述之方法，其中該受試者患有選自由以下組成之群組的實性瘤：間皮瘤、胰臟腫瘤、卵巢腫瘤、肺腫瘤、食管腫瘤、胃腫瘤、肝腫瘤、結直腸腫瘤、宮頸腫瘤、子宮內膜腫瘤、乳房腫瘤、腎腫瘤、膀胱腫瘤、睪丸腫瘤、前列腺腫瘤、腦腫瘤、骨腫瘤和頭頸部腫瘤。

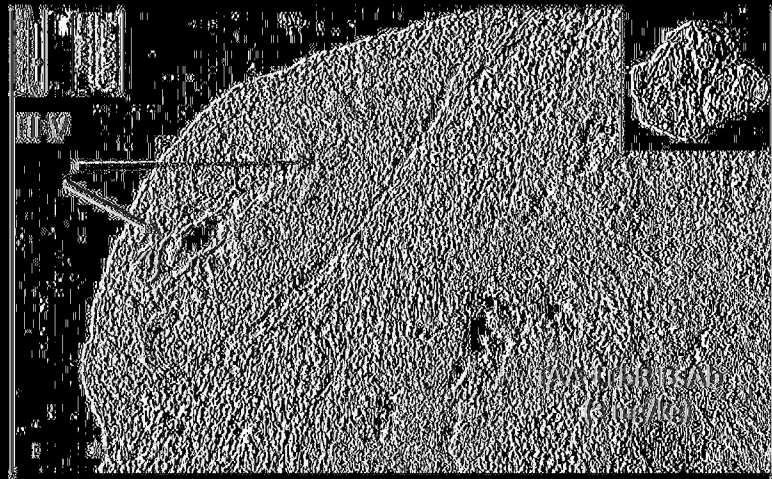
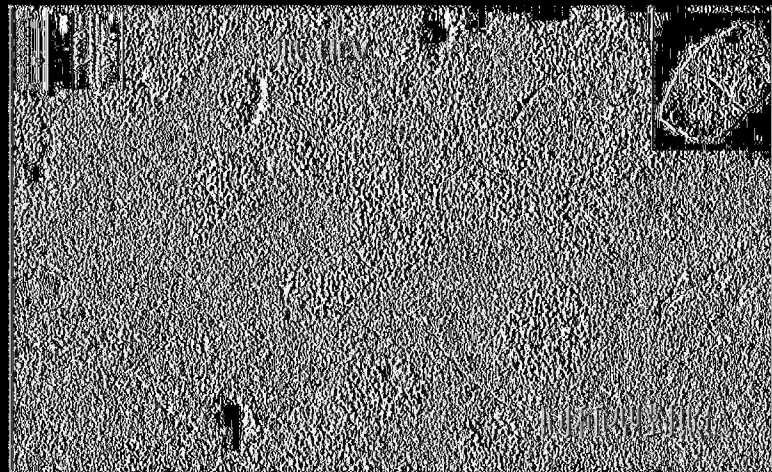
[(發明圖式)]



[(圖1A)]



[(圖1B)]



|(圖2)|

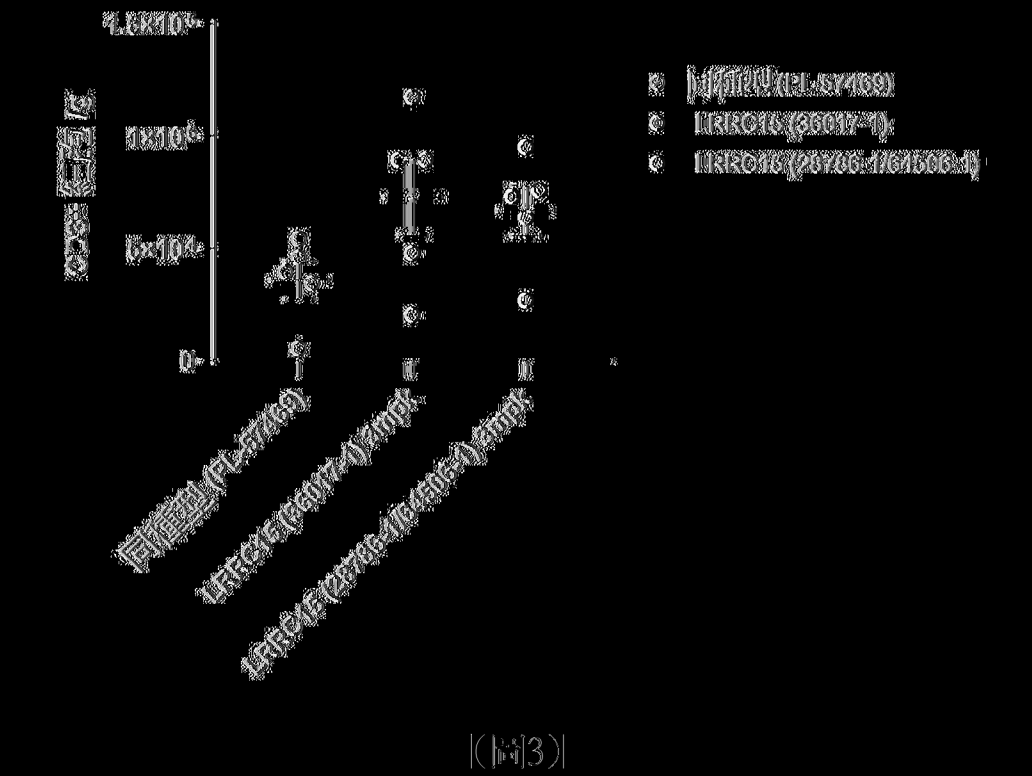


図3

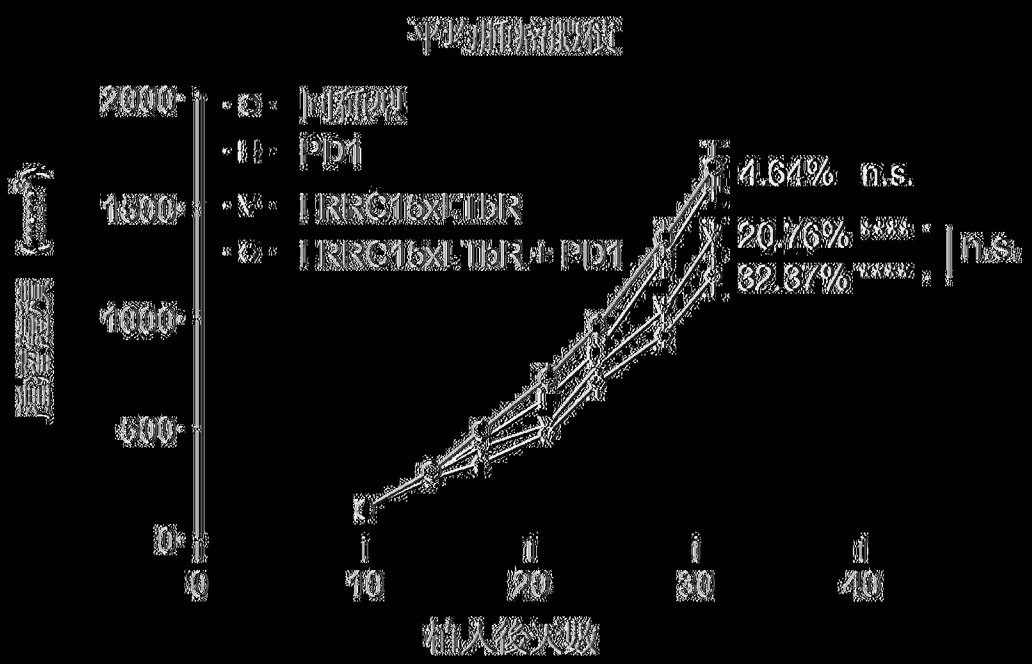
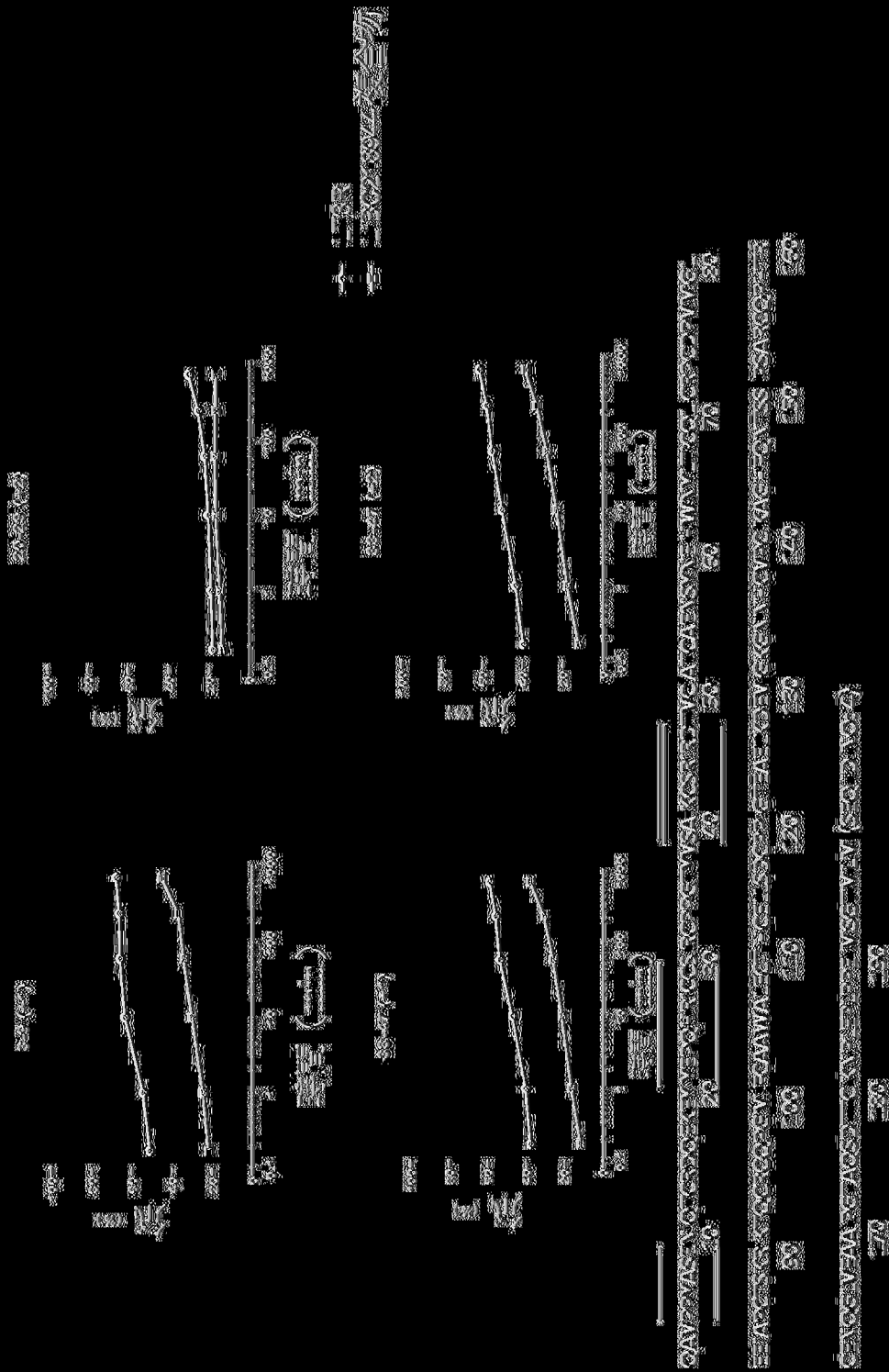
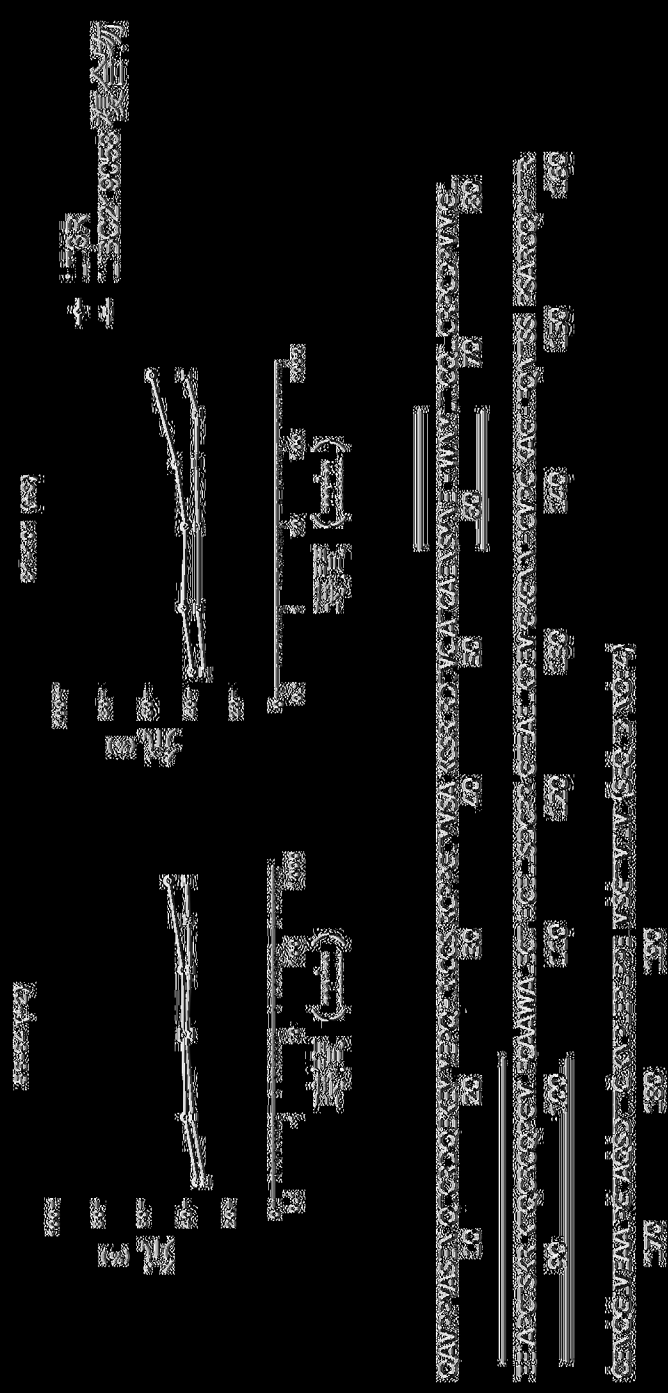


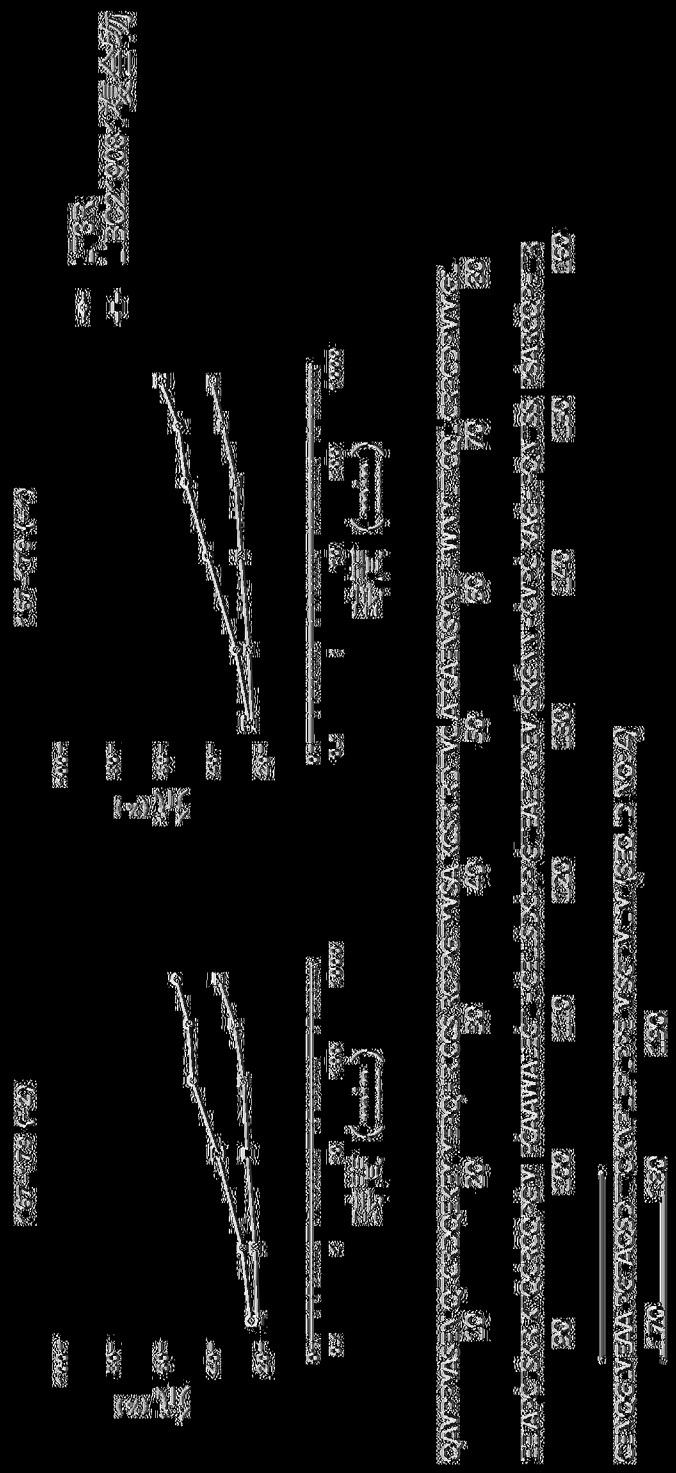
図4



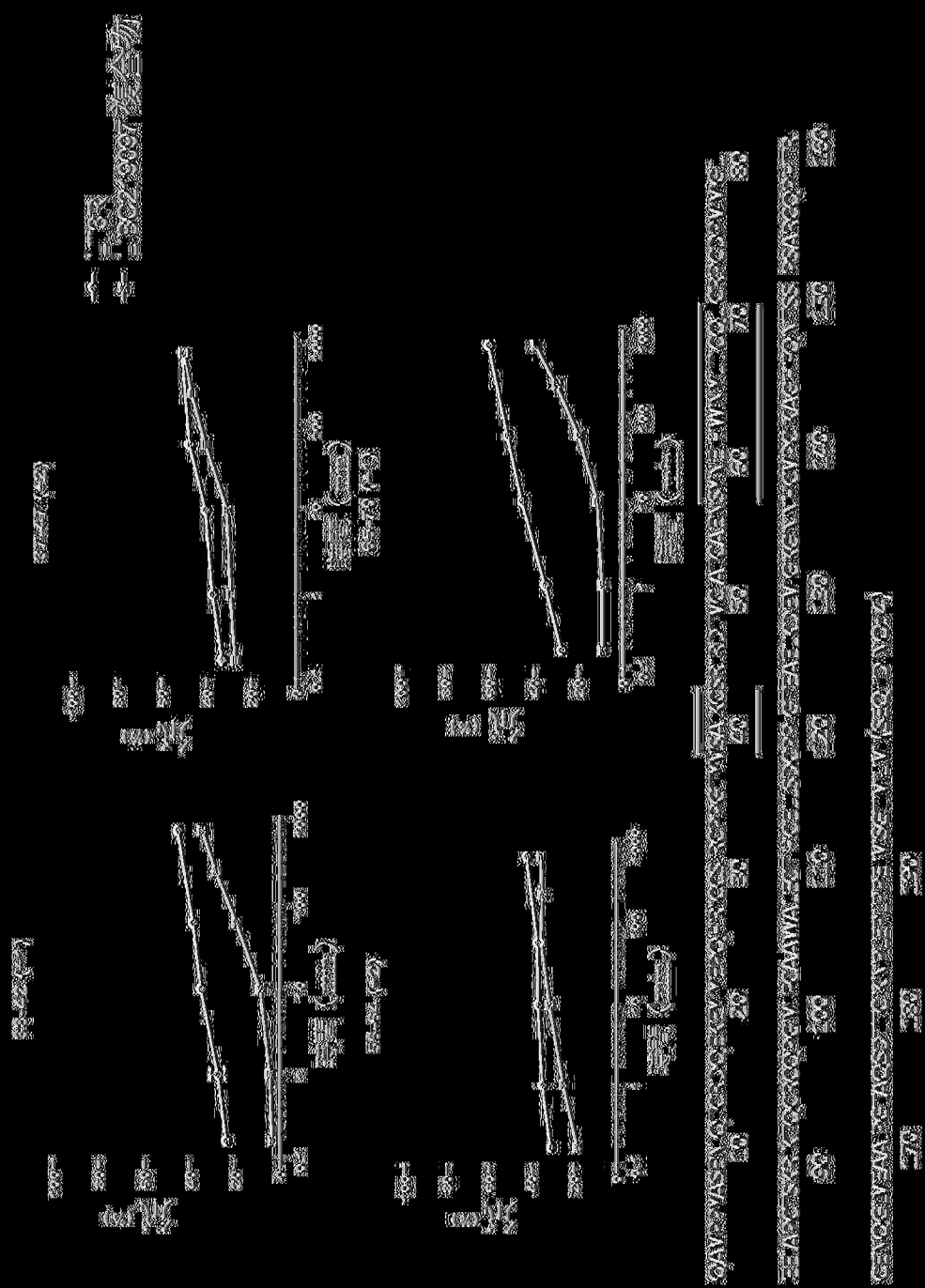
[圖 7]



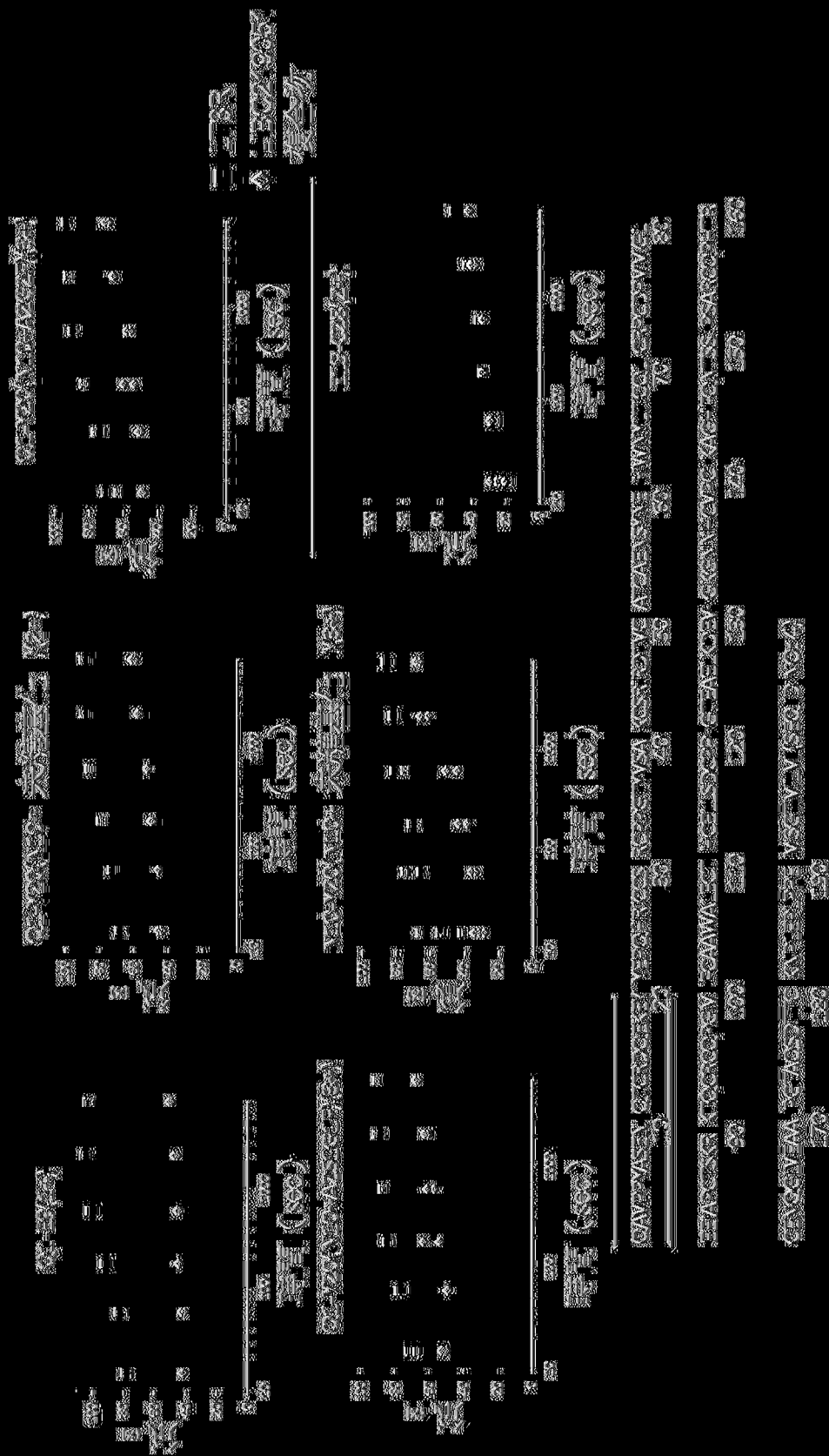
[図 8]



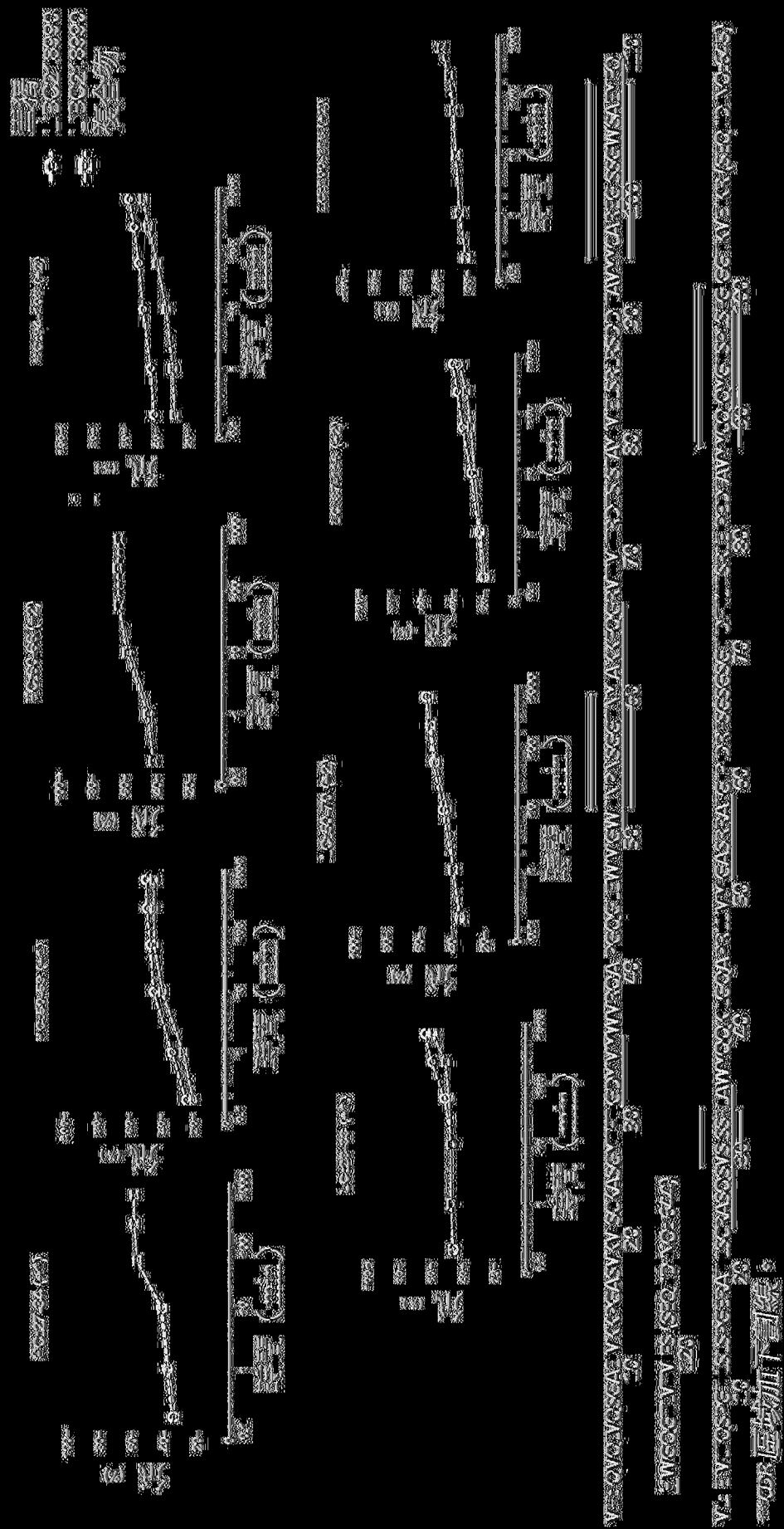
[6]



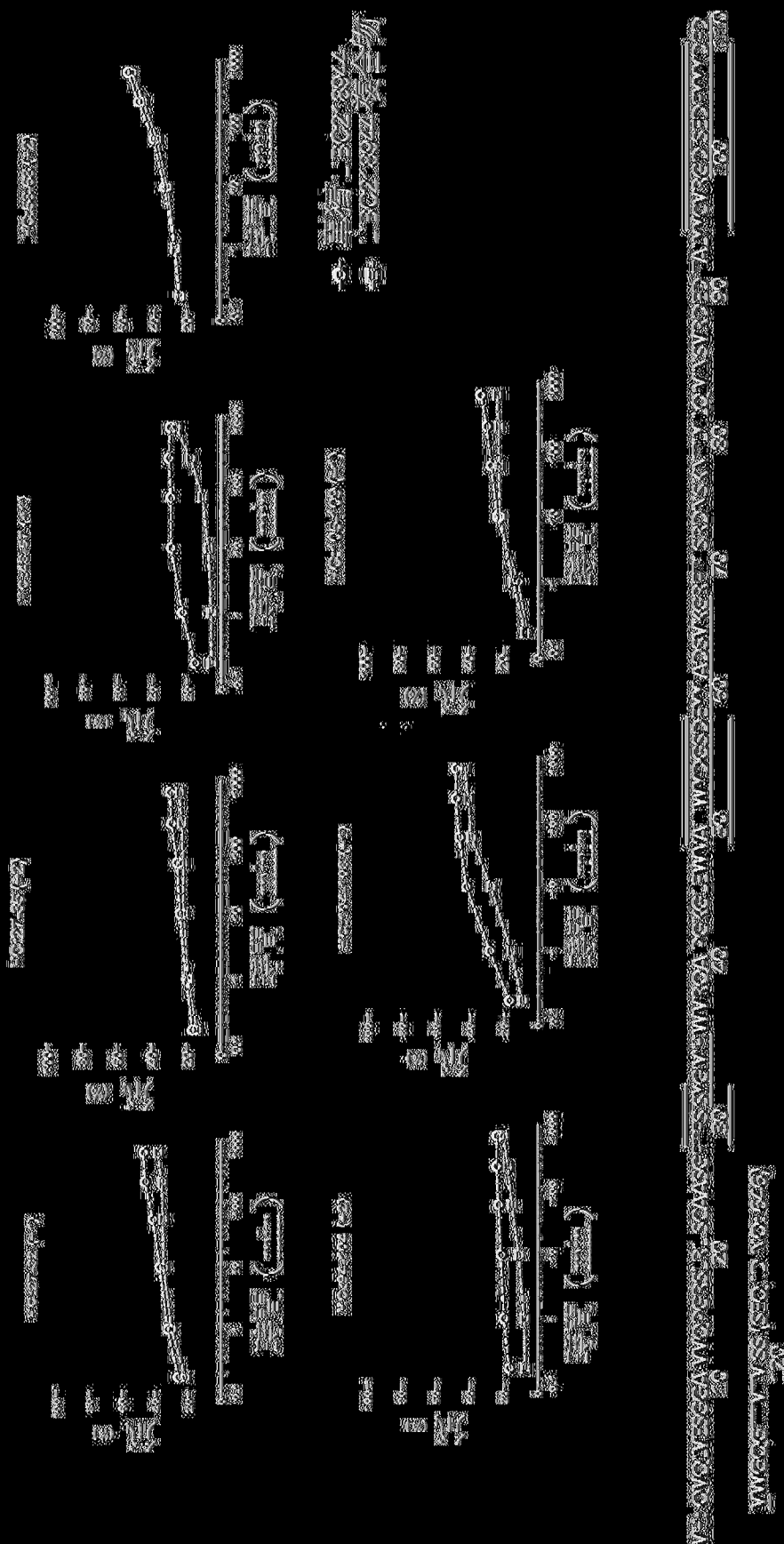
[圖 10]

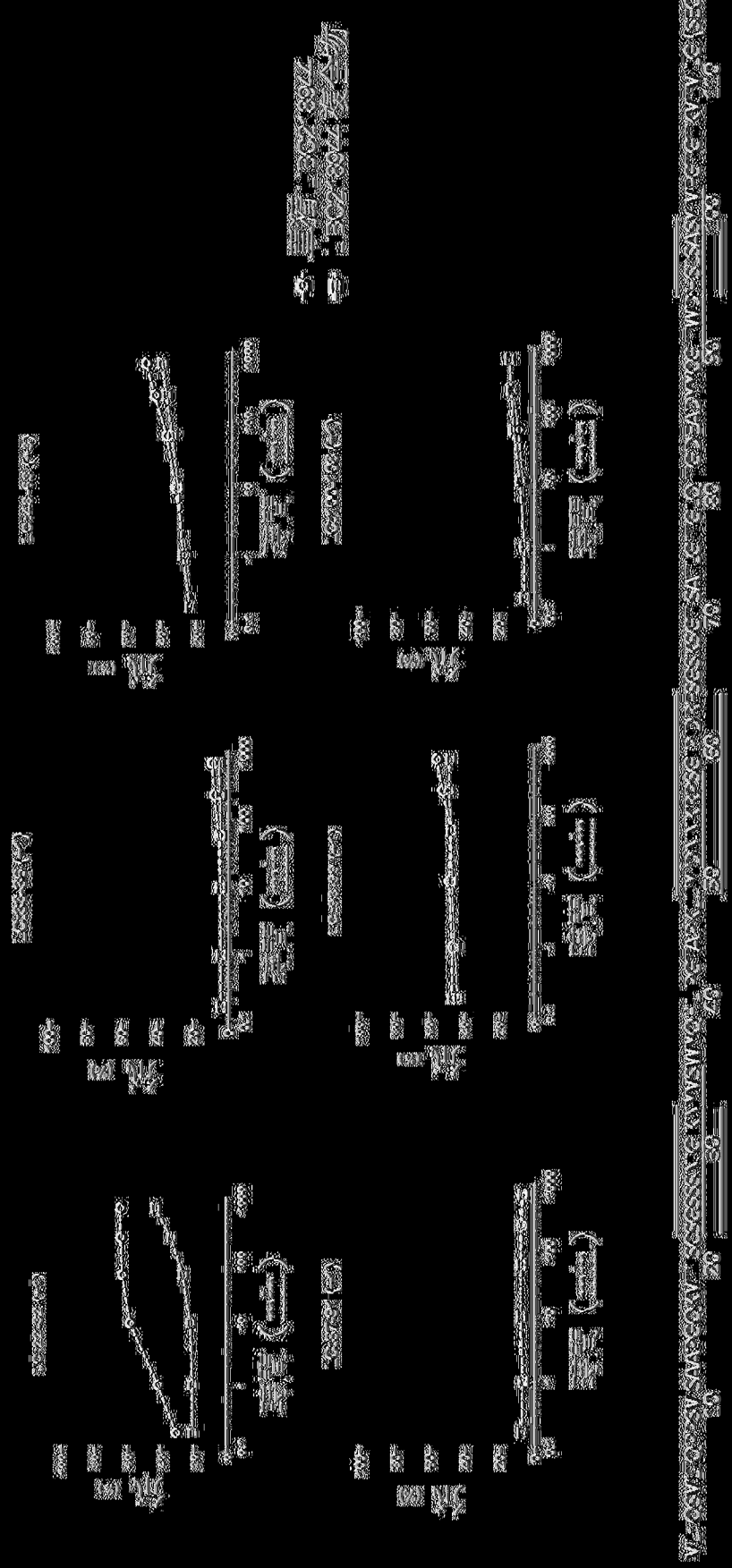


[圖 2]

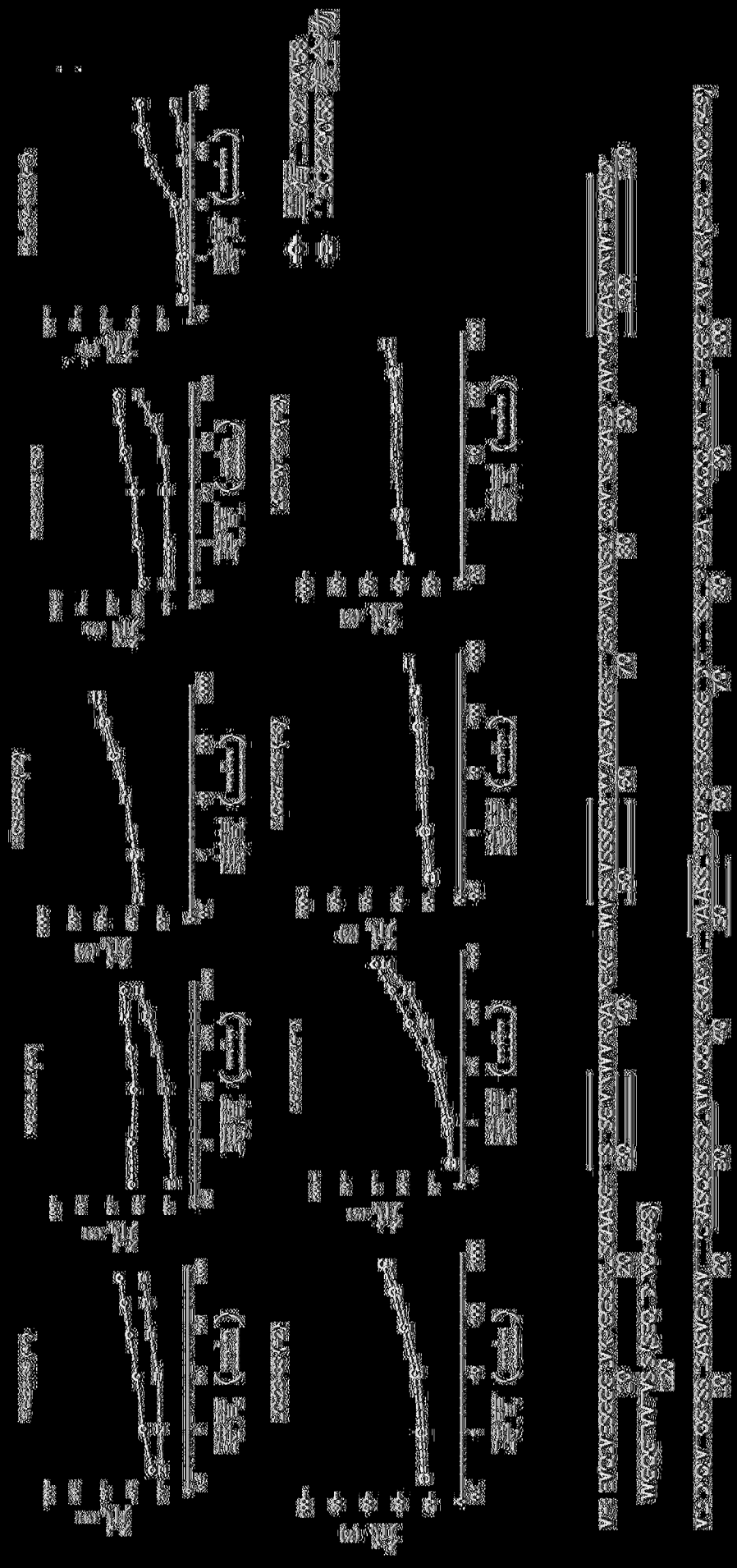


[圖 13]

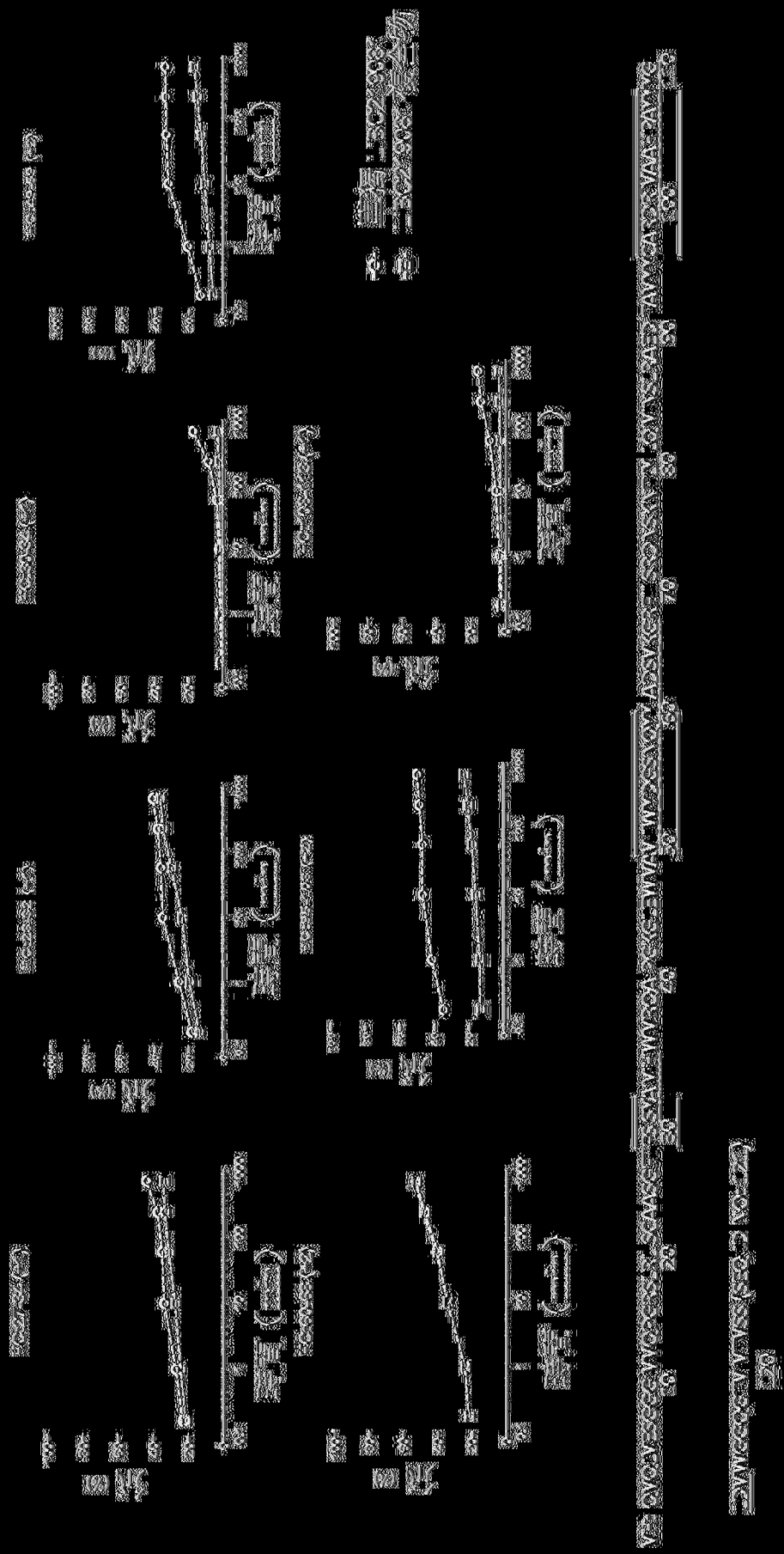
[Δ] [Σ]



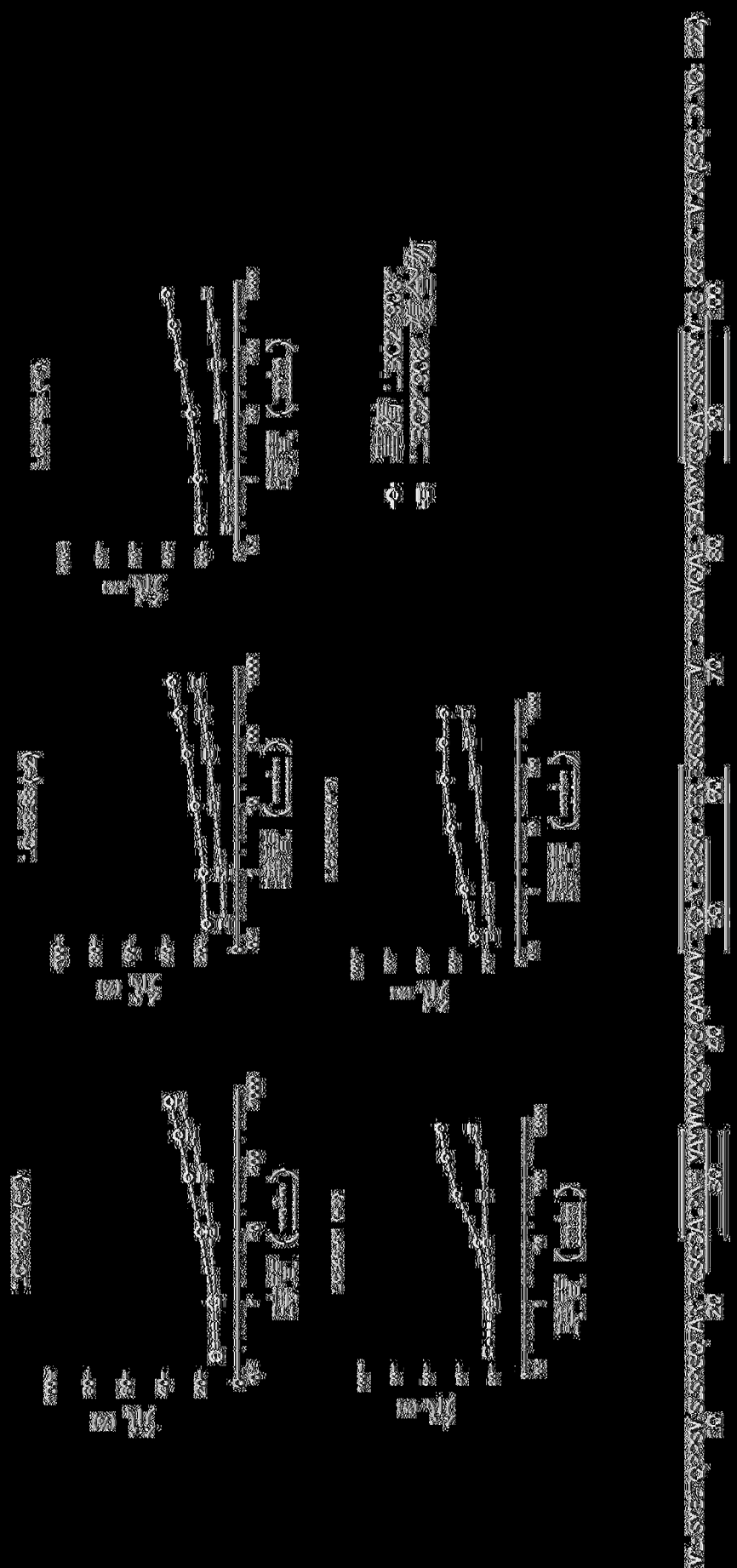
【圖 43】



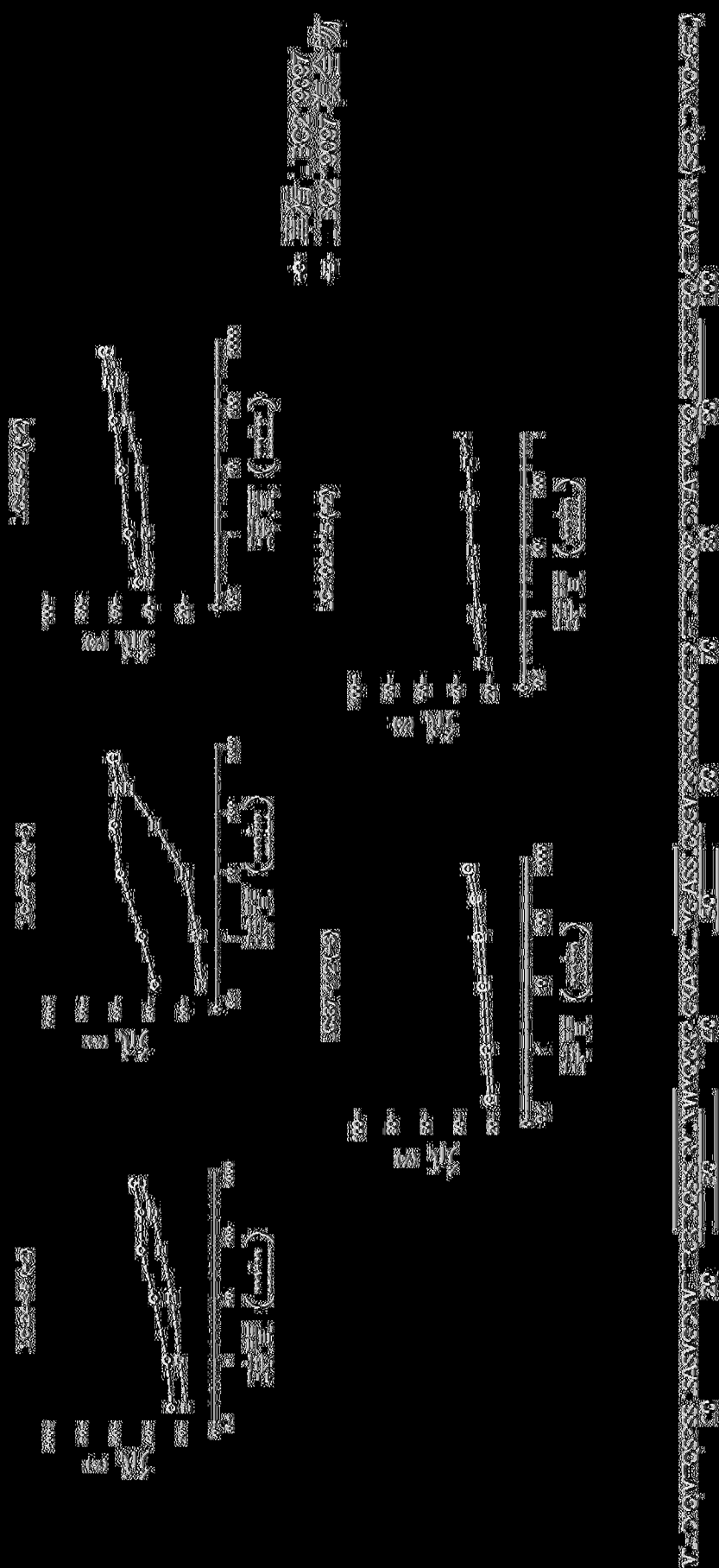
【図15】



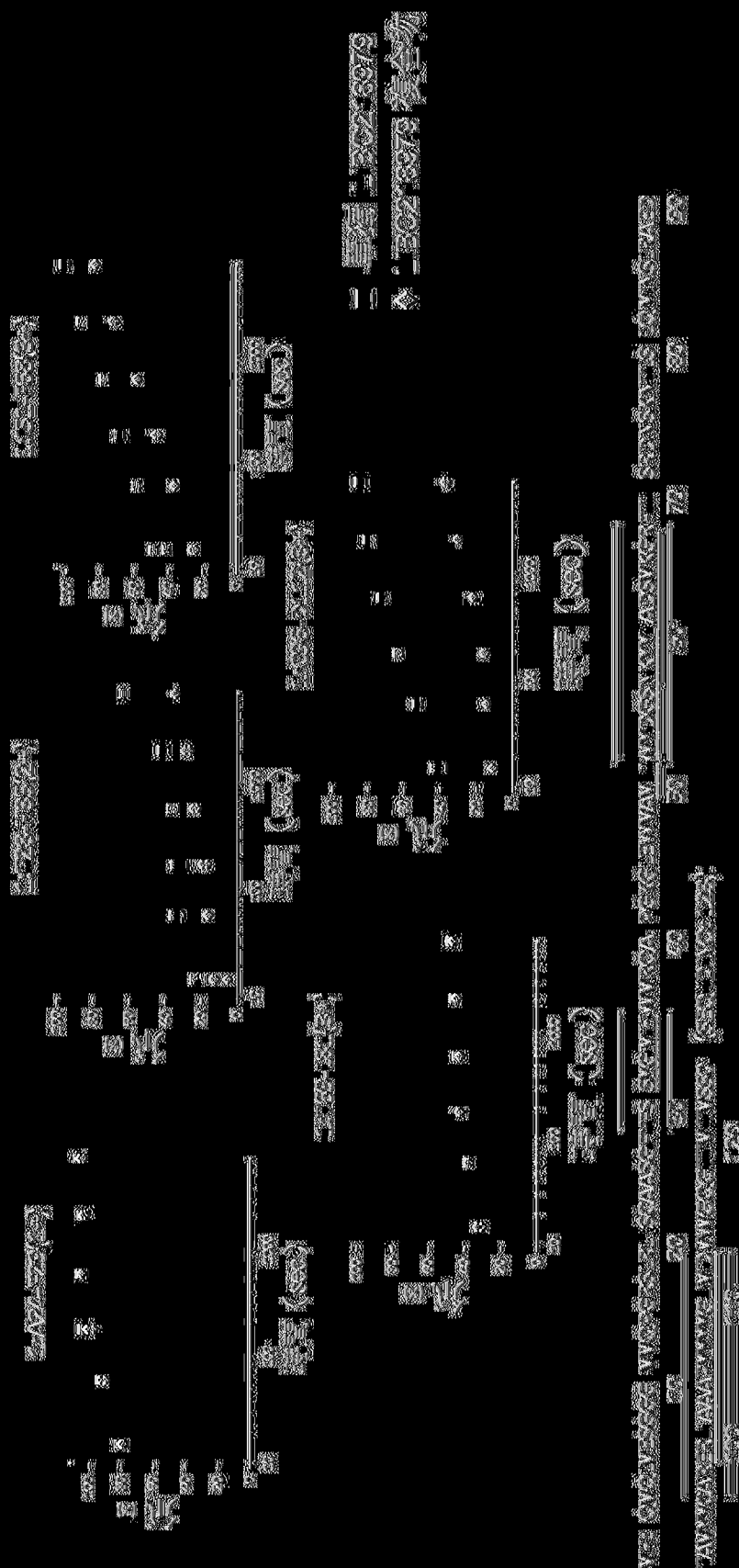
[圖 6A]



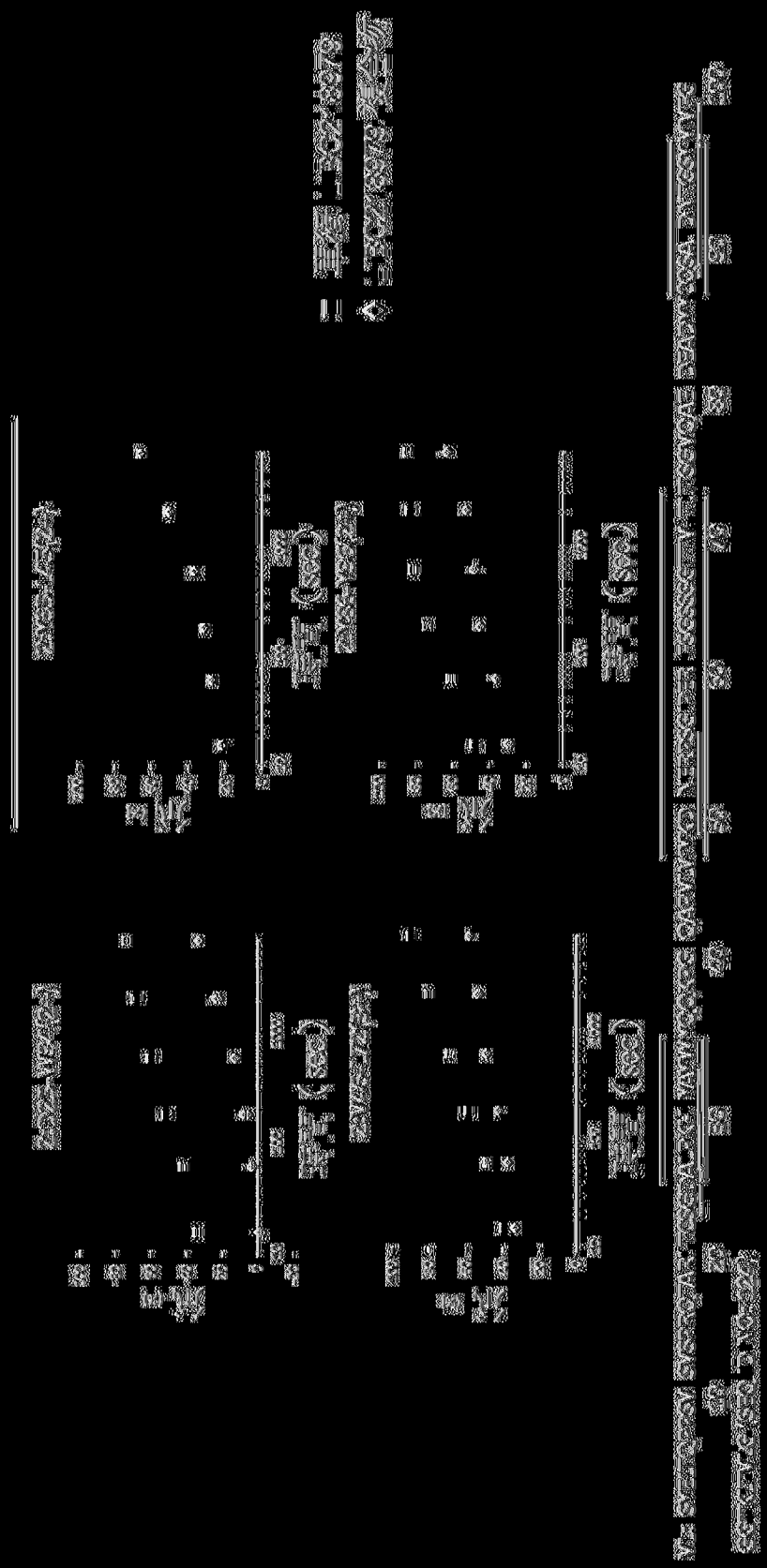
[圖 163]



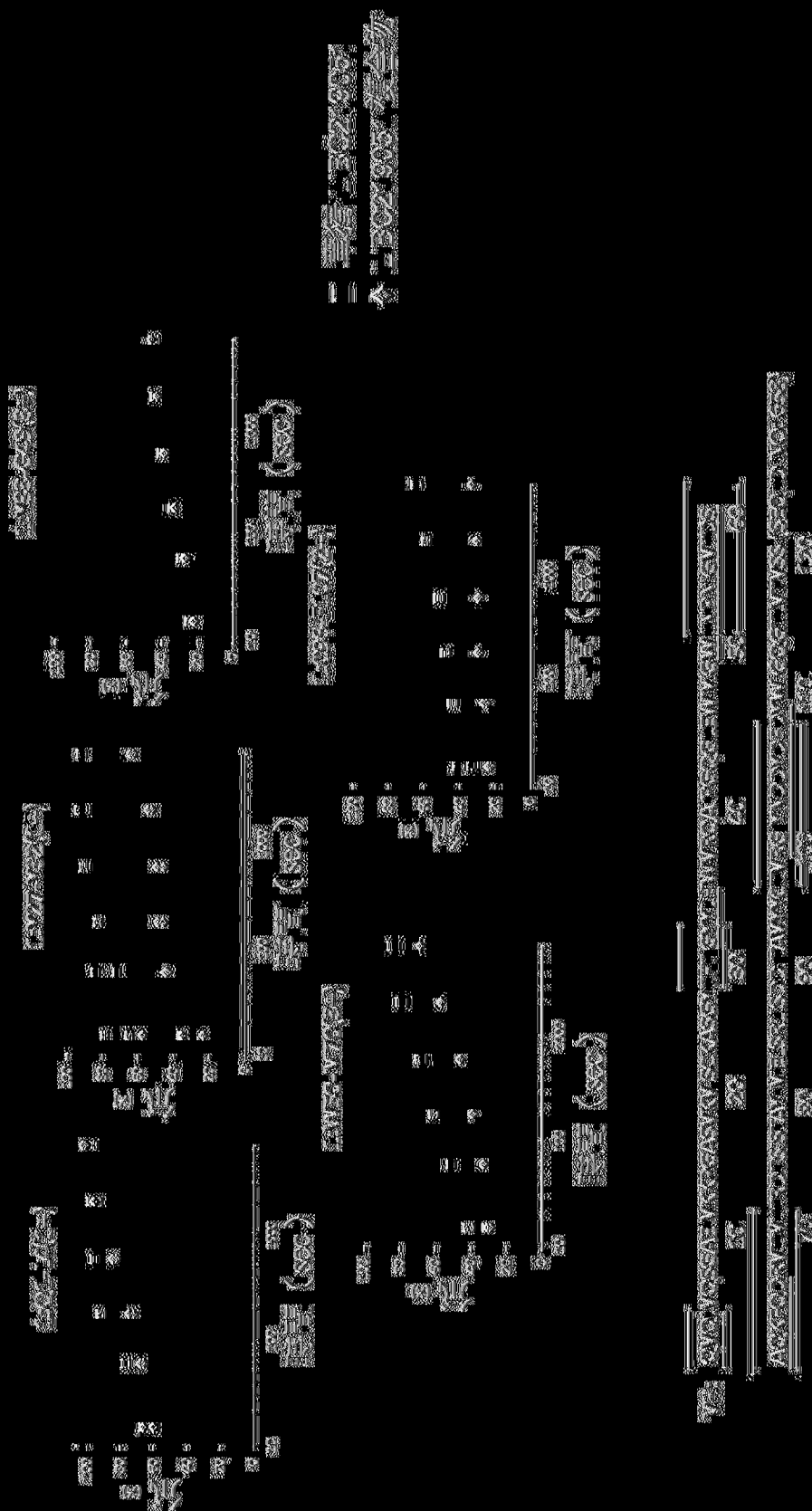
[213]



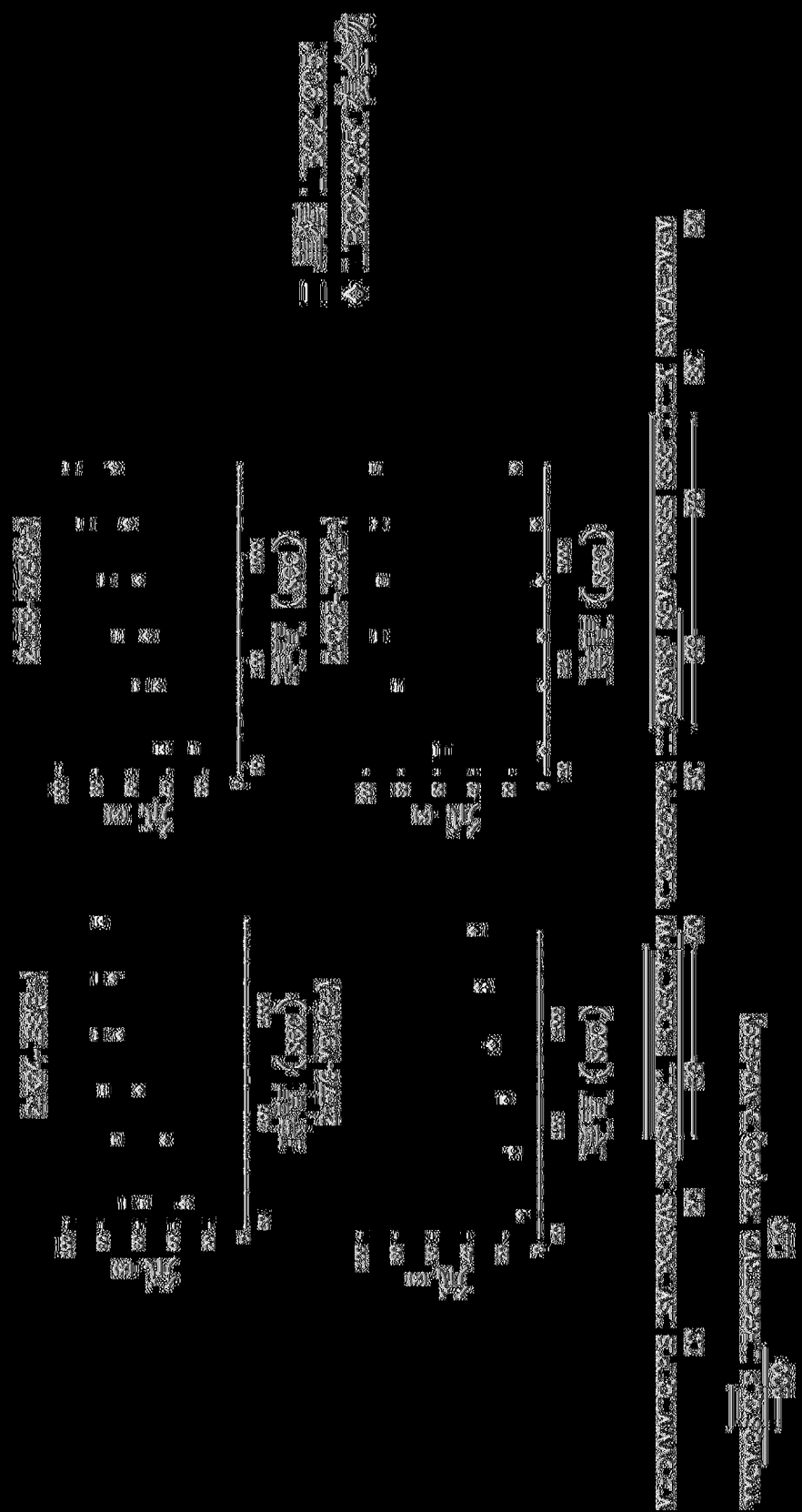
【A】
【B】



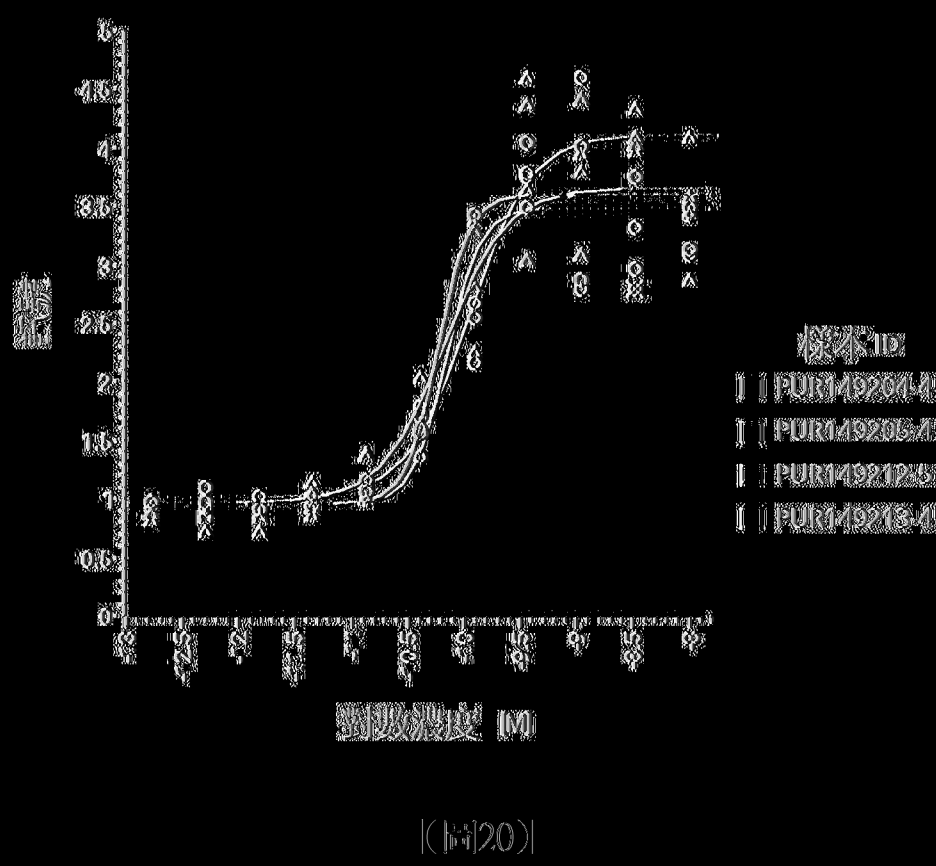
[圖 183]

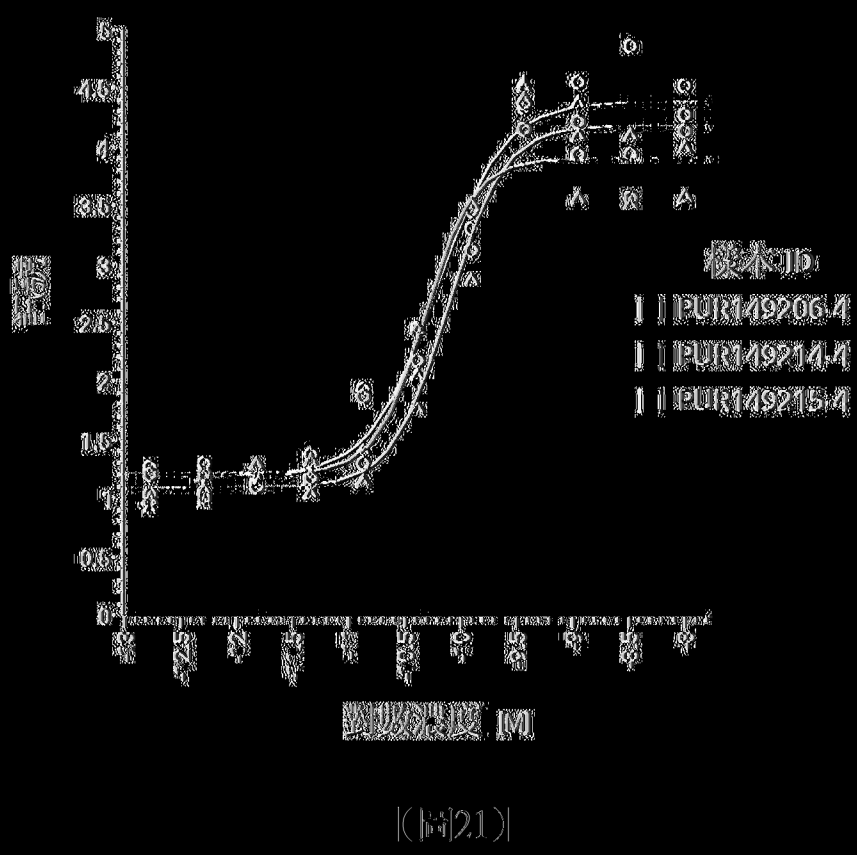


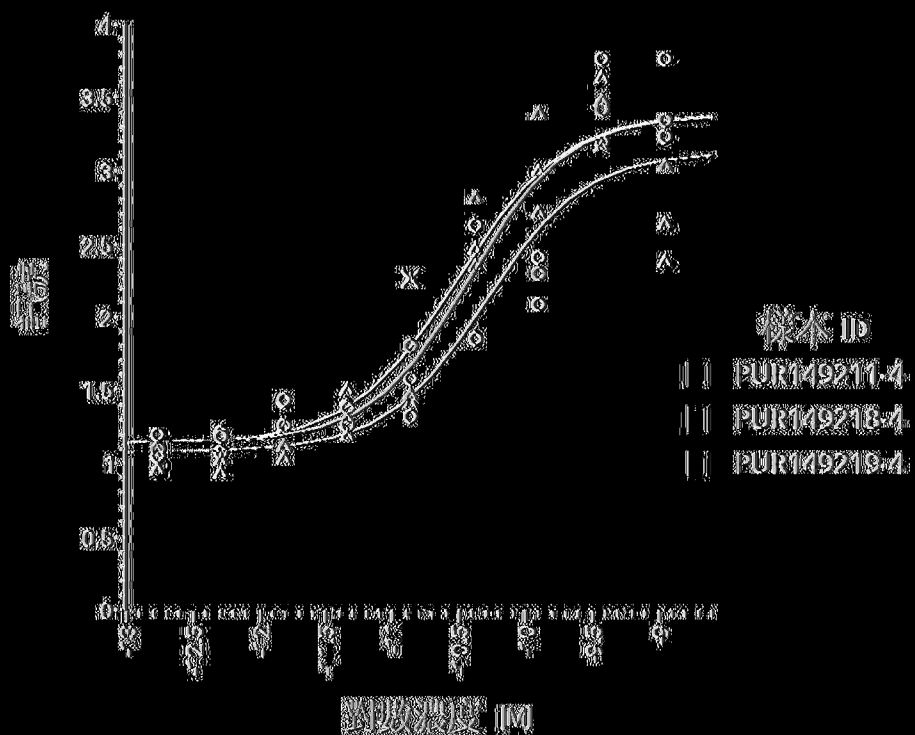
[9A]



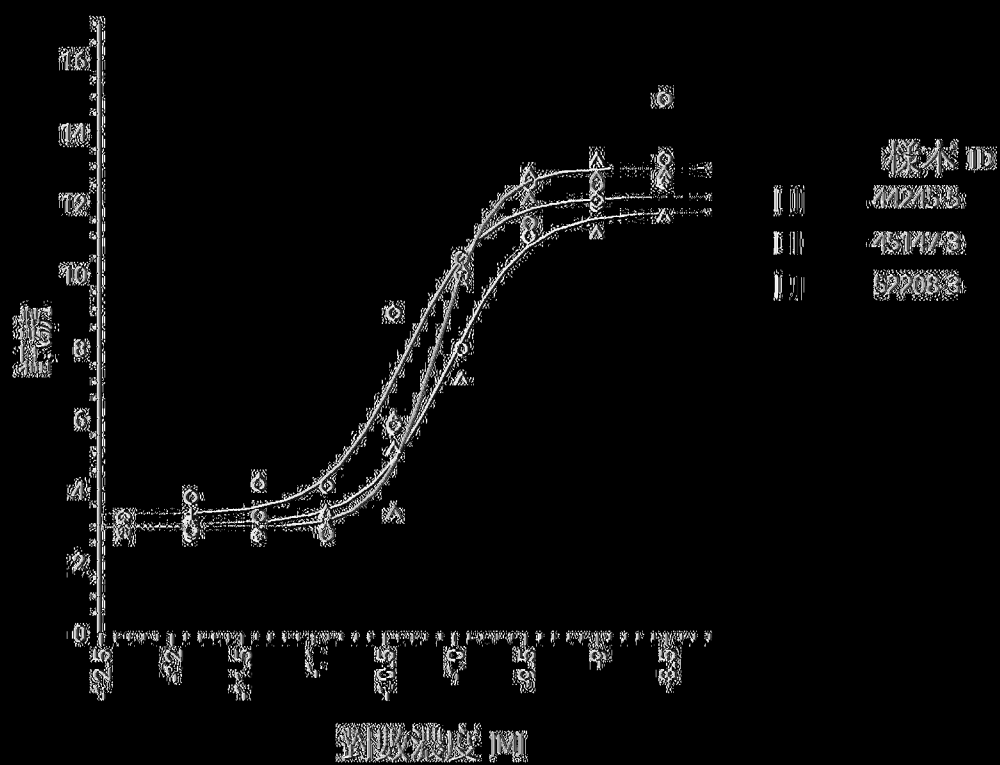
【圖 93】



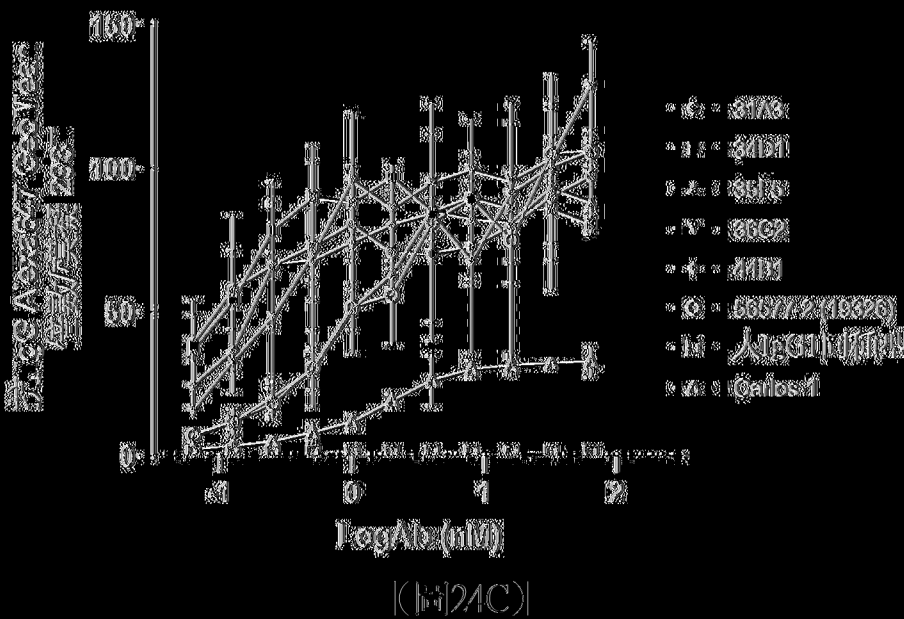
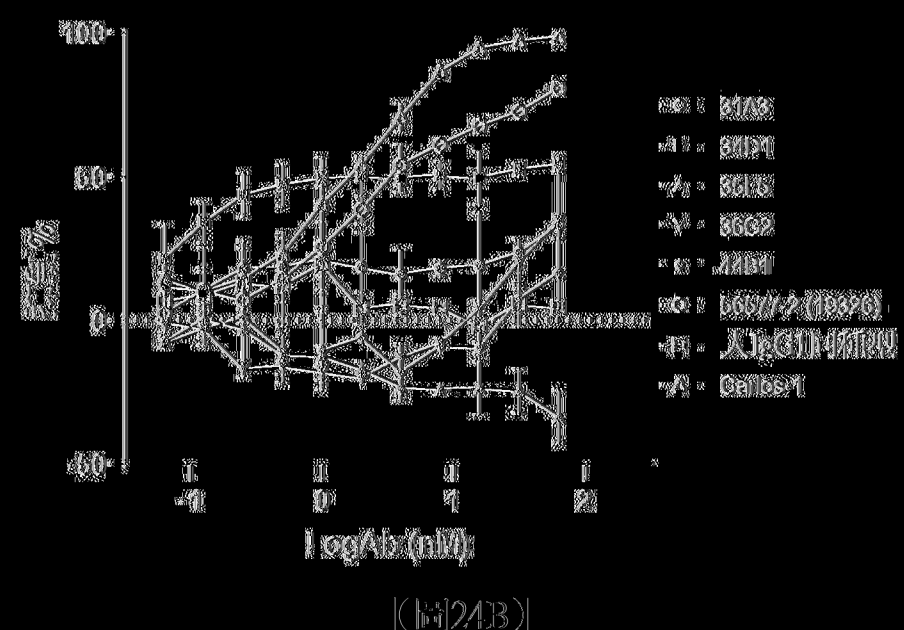
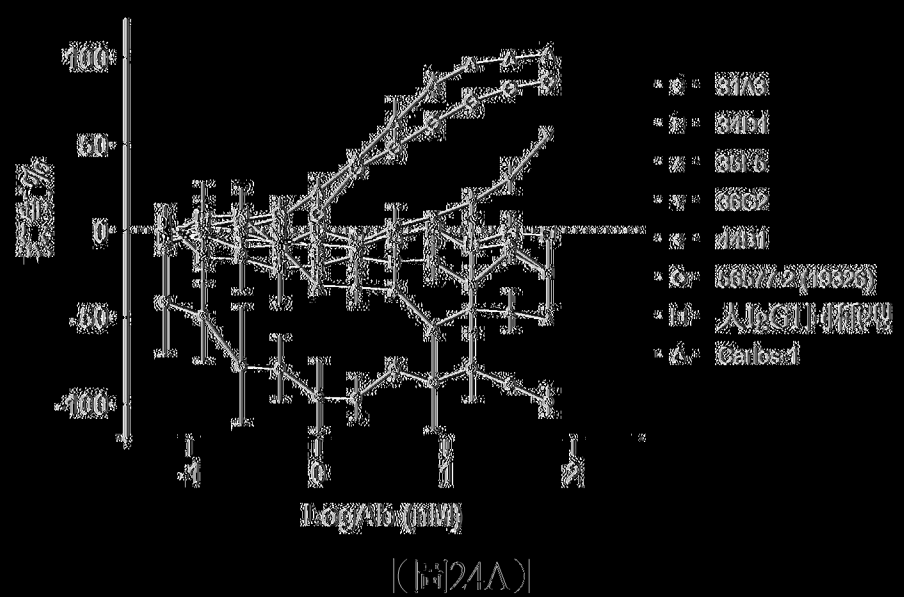


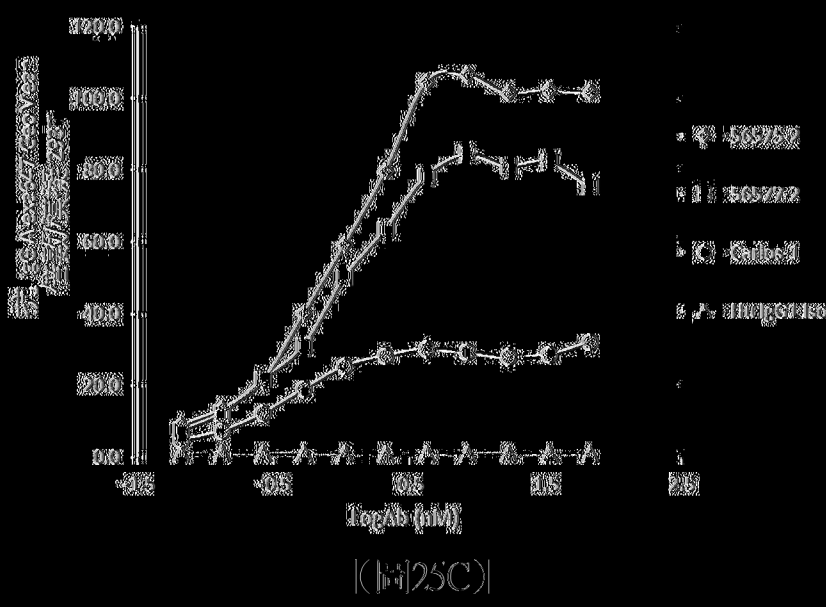
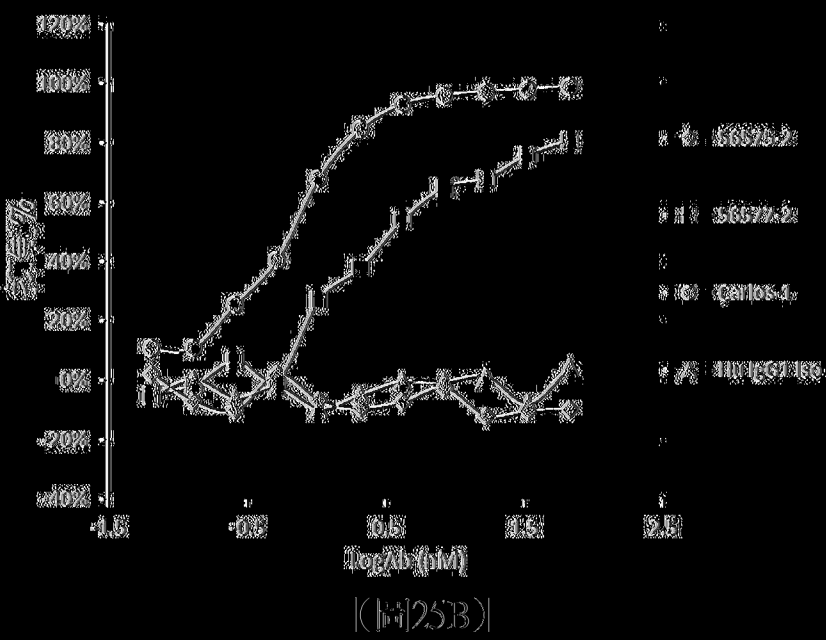
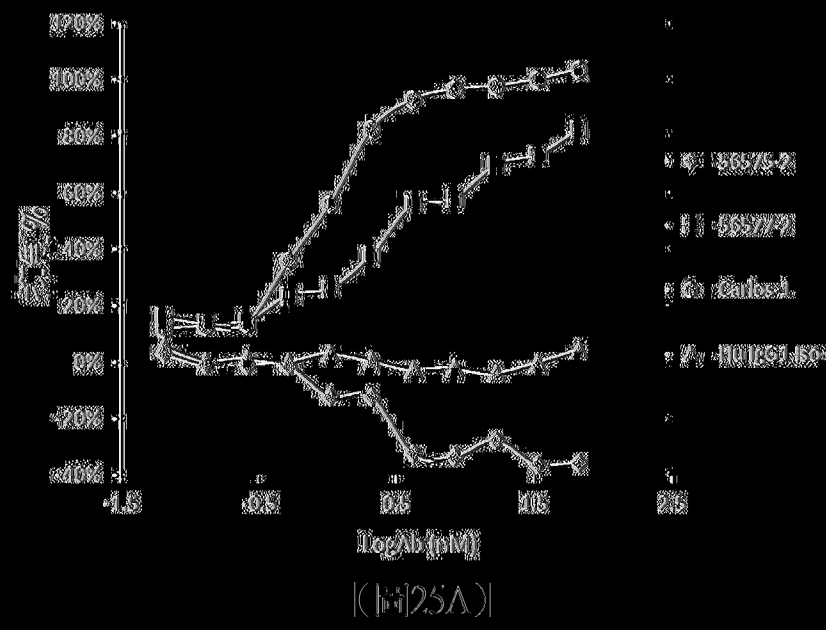


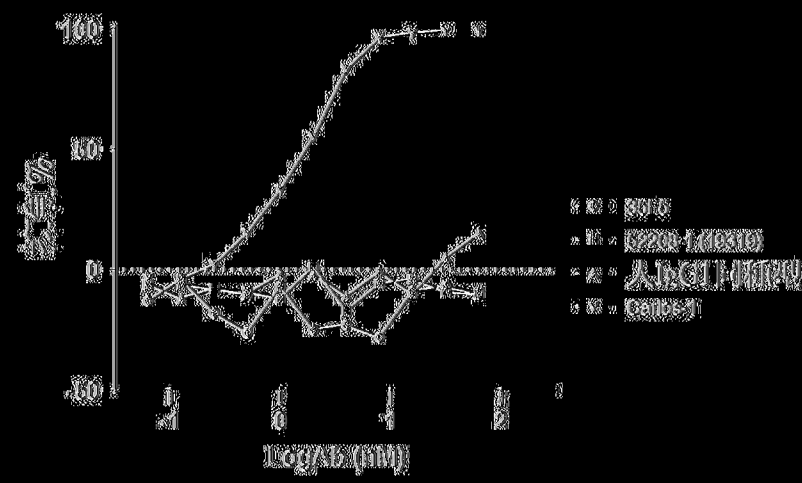
[(H)22]



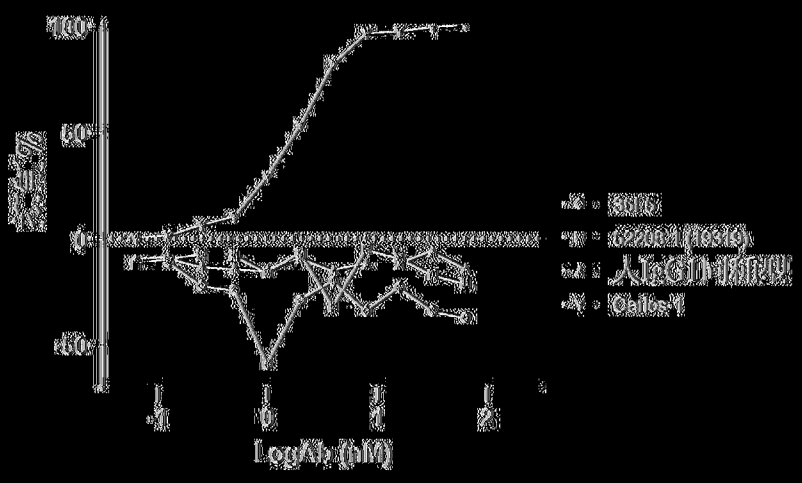
|(図)23|



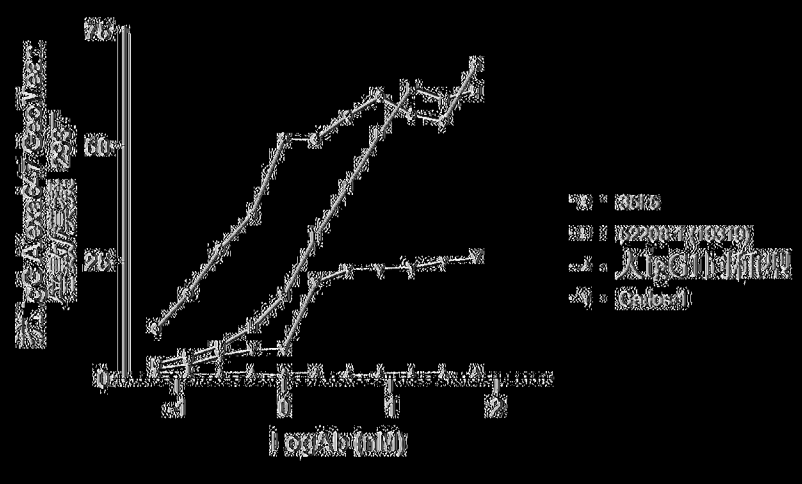




|(a)|26A|



|(b)|26B|



|(c)|26C|

[illegible]

[27]

[illegible]

[圖 27 (續)]

【發明說明書】

【中文發明名稱】 淋巴毒素β受體促效劑結合蛋白

【英文發明名稱】 LYMPHOTOXIN BETA RECEPTOR AGONIST
BINDING PROTEINS

【技術領域】

【0001】 本發明之領域關於與淋巴毒素β受體（「LTβR」或「LTBR」）結合蛋白相關的組成物和方法。

【先前技術】

【0002】 癌症免疫療法藉由誘導或增強患者的有效抗腫瘤免疫反應來增強癌症患者的存活率。免疫檢查點抑制係免疫療法的一種形式，其已經改變了許多腫瘤的治療前景。該療法藉由阻斷介導腫瘤免疫逃避的免疫檢查點蛋白（例如細胞毒性T淋巴細胞抗原4（CTLA-4）、計畫性細胞死亡蛋白1（PD-1）和計畫性細胞死亡配體1（PD-L1））的免疫抑制訊息起作用。阻斷這種免疫抑制傳訊可恢復和/或增強身體的自然抗腫瘤反應，以促進腫瘤根除。雖然這種形式的免疫療法在許多患者中產生了持久的反應，但它未能在許多其他患者中產生治療反應。特別地，患有「冷腫瘤」，即以缺乏浸潤性T細胞和存在其他免疫抑制細胞為特徵的腫瘤之患者通常對免疫檢查點抑制劑療法具有耐藥性。因此，本領域需要如下抗癌療法：其可以誘導T細胞浸潤到腫瘤微環境中，以使這樣的冷腫瘤發炎並克服這種耐藥性，從而使腫瘤適合免疫療法。

【發明內容】

【0003】 本揭露之第一方面涉及促效劑淋巴毒素 β 受體(LT β R)結合蛋白。本揭露之促效劑LT β R結合蛋白結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R富含半胱胺酸結構域4(CRD4)的一或多個胺基酸殘基，並且(a)不抑制LIGHT與LT β R結合或(b)不抑制LT α 1 β 2與LT β R結合。

【0004】 本揭露之另一方面涉及雙特異性促效劑LT β R結合蛋白。該雙特異性結合蛋白包含LT β R結合結構域，其中該LT β R結合結構域結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R CRD4的一或多個胺基酸殘基；和腫瘤相關抗原結合結構域。這種雙特異性結合蛋白激動LT β R活性，並且(a)不抑制LIGHT與LT β R結合或(b)不抑制LT α 1 β 2與LT β R結合。

【0005】 本揭露之其他方面涉及編碼本揭露之促效劑LT β R結合蛋白和雙特異性LT β R結合蛋白的多核苷酸；包含該等多核苷酸的載體；以及包含該等載體的宿主細胞。

【0006】 本揭露之額外的方面涉及藥物組成物，該等藥物組成物包含本文所述之促效劑LT β R結合蛋白、雙特異性促效劑LT β R結合蛋白或編碼其的多核苷酸或載體。

【0007】 本揭露之另一方面涉及治療受試者癌症之方法，該等方法涉及向患有癌症的受試者投與促效劑LT β R結合蛋白。該等方法中使用的促效劑LT β R結合蛋白結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R富含半胱胺酸結構域4(CRD4)的一或多個胺基酸殘基，並且(a)不抑制LIGHT與LT β R結合或(b)不抑制LT α 1 β 2與LT β R結合。

【0008】 本揭露之另一方面涉及治療受試者癌症之方法，該等方法涉及向患有癌症的受試者投與雙特異性促效劑LT β R結合蛋白。該雙特異性促效劑LT β R

結合蛋白包含LT β R結合結構域和腫瘤相關抗原結合結構域。該LT β R結合結構域結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R富含半胱胺酸結構域(CRD4)的一或多個胺基酸殘基。雙特異性LT β R結合蛋白進一步包含腫瘤相關抗原結合結構域。雙特異性LT β R結合蛋白激動LT β R活性，並且(a)不抑制LIGHT與LT β R結合或(b)不抑制LT1 α 2 β 與LT β R結合。

【0009】 LT β R激動作用作為抗腫瘤療法之潛在效用早在20多年前就被提出（參見例如，Browning等人，「Signaling through the Lymphotoxin β Receptor Induces the Death of Some Adenocarcinoma Tumor Lines[通過淋巴毒素 β 受體的傳訊誘導一些腺癌腫瘤系的死亡],」 *J. Exp. Med.*[實驗醫學雜誌] 183:867 (1996)）。儘管如此，只有一種LT β R抗體進入了I期臨床試驗，並且該試驗提前結束。LT β R在全身多種細胞上普遍表現，並在淋巴器官和多種免疫細胞群的形成和維持中起著關鍵作用。因此，為了使LT β R抗體具有治療有效性和安全性，它必須選擇性地激活腫瘤微環境中的LT β R傳訊，而不會破壞腫瘤微環境外的正常LT β R傳訊。雖然可以使用提供交聯特異性LT β R激活的雙特異性模式來實現將激動作用靶向腫瘤環境；但如果設計不當，交聯依賴性促效劑將在以靶標非依賴性方式結合LT β R時充當拮抗劑。鑒於LT β R在維持免疫功能中的重要性，對其活性進行拮抗造成嚴重的安全問題。

【0010】 本文揭露的促效劑LT β R結合蛋白藉由以交聯靶標依賴性方式發揮促效劑活性而不拮抗正常LT β R傳訊活性來克服這個問題。這藉由特異性選擇和工程化LT β R結合蛋白來實現，當與LT β R的富含半胱胺酸的結構域4（CRD4）結合時，該LT β R結合蛋白以交聯特異性方式激動LT β R，而不阻斷內源性LT β R配體（即LIGHT或LT α 1 β 2）結合和傳訊活性。

【圖式簡單說明】

【0011】 [圖1A-1B]顯示了靶向腫瘤相關抗原 (TAA) 的LT β R激動作用增加表現人EpCAM的B16F10黑色素瘤腫瘤模型中的淋巴細胞浸潤。如圖1A的圖表所示，相對於投與同種型對照抗體，在3 mg/kg劑量的人EpCAM x 鼠LT β R雙特異性抗體的情況下，浸潤腫瘤組織的T細胞 (CD3⁺ T細胞) 的總數增加。如圖1B的圖表所示，相對於投與同種型對照抗體，浸潤腫瘤組織的B細胞 (CD19⁺ B細胞) 的總數隨著huEpCAM x muLT β R BsAb的劑量 (0.3、3和30 mg/kg) 的增加而增加。

【0012】 [圖2]顯示了在表現人EpCAM的B16F10黑色素瘤腫瘤模型中，靶向腫瘤相關抗原 (TAA) 的LT β R激動作用誘導HEV形成。圖2顯示了同種型對照治療 (上圖像) 和3 mg/kg的huEpCAM-muLT β R雙特異性抗體治療 (下圖像) 後，腫瘤組織中HEV形成的免疫組織化學分析，如本文實例1所描述的。

【0013】 [圖3]顯示了靶向腫瘤相關抗原 (TAA) 的LT β R激動作用在人KPC胰臟腫瘤模型中增加T細胞浸潤。圖3的圖表顯示了在向攜帶KPC M5腫瘤的小鼠投與兩種不同工具huLRRC15 x muLT β R BsAb後，每克腫瘤組織的T細胞計數增加。在用流動式細胞分析術評估腫瘤之前，每週投與兩次huLRRC15 x muLT β R BsAb，共3劑。Dunnett多重比較檢驗的單因子變異數分析 (One-way ANOVA) 顯示了相對於同種型沒有顯著差異，但治療確實顯示出T細胞浸潤的上升趨勢。圖表中表示了平均值和SEM。

【0014】 [圖4]顯示了靶向腫瘤相關抗原 (TAA) 的LT β R激動作用在人KPC胰臟腫瘤模型中抑制腫瘤生長。圖4的圖表顯示了用PD-1抗體、huLRRC15 x muLT β R BsAb或該等抗體的組合治療的KPC M5胰臟腫瘤模型的平均腫瘤體積。huLRRC15 x muLT β R BsAb單一療法 (▼) 比PD-1單一療法 (■) 產生的效果更大。huLRRC15 x muLT β R BsAb和PD-1 Ab組合確實顯示出更大的TGI，但兩個治療組之間的差異沒有統計學顯著性。Tukey多重比較檢驗的雙因子變異數分析

(Two-way ANOVA) 表明, huLRRC15 x muLTbR BsAb和huLRRC15 x muLTbR BsAb + PD-1 Ab抗體相對於同種型的顯著性 ($p < 0.0001$)。N = 10, 圖表中表示了平均值和SEM。

【0015】 [圖5]包含表A和表B, 總結了在第一輪融合瘤篩選中鑒定的LTβR抗體的表徵數據。表A包含功能效力值 (EC_{50}) 和結合數據, 即LTβR抗體與TNFRSF1和TNFRSF2、小鼠LTβR和食蟹猴LTβR結合。數據呈現為模擬轉染細胞的GeoMean倍數。表A還顯示了在指示LTβR抗體存在下, 使用基於單點FACS珠粒的受體-配體測定評估的人LIGHT或人LTα1β2配體與人LTβR結合的抑制百分比, 如實例4.6中所述。表B顯示了LTβR抗體與人和食蟹猴LTβR的結合親和力測量值 (k_a 、 k_d 和KD)。

【0016】 [圖6]鑒定了參與同LTβR抗體, LIBC No. 218990 (Bio. Reg. No. 19320 / Well ID 30H1) 之結合相互作用的LTβR胞外結構域 (ECD) (SEQ ID NO: 4) 的區域, 如藉由氫-氘交換 (HDX) 質譜 (MS) 確定的 (參見實例6.1.1)。顯示了對應於單獨或與抗體複合的LTβR胞外結構域 (ECD) 的殘基56-64和81-101的肽之氘攝取圖表。相對於非複合肽, 複合物衍生肽中免於氘交換表明, LTβR ECD的該等區域內的一或多個殘基, 即殘基57-64和82-101參與結合相互作用 (注意, 肽的N端殘基沒有用於測量的醯胺氘, 因此在報告表位區域時被排除在外)。

【0017】 [圖7]鑒定了參與同LTβR抗體, LIBC No. 218944 (Bio. Reg No. 19321 / Well ID 31A3) 之結合相互作用的LTβR ECD (SEQ ID NO: 4) 的區域, 如藉由HDX MS確定的 (參見實例6.1.1)。顯示了對應於單獨或與抗體複合的LTβR ECD的殘基3-9、20-29和38-47的肽之氘攝取圖表。相對於非複合肽, 複合物衍生肽中免於氘交換表明, LTβR ECD的該等區域內的一或多個殘基, 即殘基4-9、21-29和39-47參與結合相互作用 (注意, 肽的N端殘基沒有用於測量的醯胺氘, 因此在報告表位區域時被排除在外)。

【0018】 [圖8]鑒定了參與同LT β R抗體，LIBC No. 219058 (Bio. Reg. No. 19324 / Well ID 36G2) 之結合相互作用的LT β R ECD (SEQ ID NO: 4) 的區域，如藉由HDX MS確定的 (參見實例6.1.1)。顯示了對應於單獨或與抗體複合的LT β R ECD的殘基56-64和81-101的肽之氘攝取圖表。相對於非複合肽，複合物衍生肽中免於氘交換表明，LT β R ECD的該等區域內的一或多個殘基，即殘基57-64和82-101參與結合相互作用 (注意，肽的N端殘基沒有用於測量的氘胺氫，因此在報告表位區域時被排除在外)。

【0019】 [圖9]鑒定了參與同LT β R抗體，LIBC No. 219081 (Bio Reg. No. 19325 / Well ID 41B2) 之結合相互作用的LT β R ECD (SEQ ID NO: 4) 的區域，如藉由HDX MS確定的 (參見實例6.1.1)。顯示了對應於單獨或與抗體複合的LT β R ECD的殘基167-179的肽之氘攝取圖表。相對於非複合肽，複合物衍生肽中免於氘交換表明，LT β R ECD的該等區域內的一或多個殘基，即殘基168-179參與結合相互作用 (注意，肽的N端殘基沒有用於測量的氘胺氫，因此在報告表位區域時被排除在外)。

【0020】 [圖10]鑒定了參與同LT β R抗體，LIBC No. 219097 (Bio. Reg. No. 19326 / Well ID 43D9) 之結合相互作用的LT β R ECD (SEQ ID NO: 4) 的區域，如藉由HDX MS確定的 (參見實例6.1.1)。顯示了對應於單獨或與抗體複合的LT β R ECD的殘基38-42、37-47、56-64和65-70的肽之氘攝取圖表。相對於非複合肽，複合物衍生肽中免於氘交換表明，LT β R ECD的該等區域內的一或多個殘基，即殘基39-42和57-70參與結合相互作用 (注意，肽的N端殘基沒有用於測量的氘胺氫，因此在報告表位區域時被排除在外)。

【0021】 [圖11]鑒定了參與同LT β R抗體，LIBC No. 218979 (Bio. Reg. No. 19319 / Well ID 23E9) 之結合相互作用的LT β R ECD (SEQ ID NO: 4) 的區域，如藉由HDX MS確定的 (參見實例6.1.2)。顯示了對應於單獨或與抗體複合的

LTβR ECD的殘基154-166、167-177、167-181和178-193的肽之氘攝取圖表。相對於非複合肽，複合物衍生肽中免於氘交換表明，LTβR ECD的該等區域內的一或多個殘基，即殘基168-178參與結合相互作用（注意，肽的N端殘基沒有用於測量的醯胺氘，因此在報告表位區域時被排除在外）。

【0022】 [圖12] 鑒定了參與同LTβR抗體，LIBC No. 219051（Bio. Reg. No. 19323 / Well ID 35F5）之結合相互作用的LTβR ECD（SEQ ID NO: 4）的區域，如藉由HDX MS確定的（參見實例6.1.2）。顯示了對應於單獨或與抗體複合的LTβR ECD的殘基1-9、1-20（未糖基化和糖基化）、10-20和19-28的肽之氘攝取圖表。相對於非複合肽，複合物衍生肽中免於氘交換表明，LTβR ECD的區域1-19內的一或多個殘基參與結合相互作用（注意，Q1已轉化為pyro-Q，其含有可測量的醯胺氘）。

【0023】 [圖13] 鑒定了參與同LTβR結合相互作用的LIBC No. 218990（19320/30H1）的可變重（VH）和可變輕（VL）結構域區域。顯示了單獨或與LTβR結合的VH和VL結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH和VL序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0024】 [圖14A-14B] 鑒定了參與同LTβR結合相互作用的LIBC No. 218944（19321/31A3）的可變重（VH）和可變輕（VL）結構域區域。顯示了單獨或與LTβR結合的VH（圖14A）和VL（圖14B）結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH（圖14A）和VL（圖14B）序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0025】 [圖15] 鑒定了參與同LTβR結合相互作用的LIBC No. 219058

(19324/36G2)的可變重(VH)和可變輕(VL)結構域區域。顯示了單獨或與LT β R結合的VH和VL結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH和VL序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0026】 [圖16A-16B]鑒定了參與同LT β R結合相互作用的LIBC No. 219081 (19325/41B2)的可變重(VH)和可變輕(VL)結構域區域。顯示了單獨或與LT β R結合的VH(圖16A)和VL(圖16B)結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH(圖16A)和VL(圖16B)序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0027】 [圖17A-17B]鑒定了參與同LT β R結合相互作用的LIBC No. 219097 (19326/43D9)的可變重(VH)和可變輕(VL)結構域區域。顯示了單獨或與LT β R結合的VH(圖17A)和VL(圖17B)結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH(圖17A)和VL(圖17B)序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0028】 [圖18A-18B]鑒定了參與同LT β R結合相互作用的LIBC No. 218979 (Bio. Reg. No. 19319 / Well ID 23E9)的可變重(VH)和可變輕(VL)結構域區域。顯示了單獨或與LT β R結合的VH(圖18A)和VL(圖18B)結構域肽之氘攝取圖表。相對於非複合肽，複合肽中免於氘交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH(圖18A)和VL(圖18B)序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0029】[圖19A-19B]鑒定了參與同LT β R結合相互作用的LIBC No. 219051 (Bio. Reg. No. 19323 / Well ID 35F5) 的可變重 (VH) 和可變輕 (VL) 結構域區域。顯示了單獨或與LT β R結合的VH (圖19A) 和VL (圖19B) 結構域肽之氙攝取圖表。相對於非複合肽，複合肽中免於氙交換表明，抗體的該等區域內的一或多個CDR殘基參與結合相互作用。將包括該等一或多個殘基的區域在所示的VH (圖19A) 和VL (圖19B) 序列中加框，並且將每個可變結構域的三個CDR區域加下劃線。

【0030】[圖20]係顯示huLT β R x huCLDN6雙特異性抗體 (PUR149204-4、PUR149205-4、PUR149212-5和PUR149213-4) 之效力的圖表。在所指示的huLT β R x huCLDN6雙特異性抗體濃度增加的情況下，藉由與表現CLDN6的倉鼠卵巢細胞 (CHO) 共培養的表現LT β R之人黑色素瘤細胞釋放的IL-8來測量效力。y軸的「訊號」表示藉由665 nm處訊號與615 nm處訊號的比率計算的相對IL-8釋放。

【0031】[圖21]係顯示huLT β R x huCLDN18.2雙特異性抗體 (PUR149206-4、PUR149214-4和PUR149215-4) 之效力的圖表。在所指示的huLT β R x huCLDN18.2雙特異性抗體濃度增加的情況下，藉由與表現CLDN18.2的CHO細胞共培養的表現LT β R之人黑色素瘤細胞釋放的IL-8來測量效力。y軸的「訊號」表示藉由665 nm處訊號與615 nm處訊號的比率計算的相對IL-8釋放。

【0032】[圖22]係顯示huLT β R x huMUC17雙特異性抗體 (PUR149211-4、PUR149218-4和PUR149219-4) 之效力的圖表。在所指示的huLT β R x huMUC17雙特異性抗體濃度增加的情況下，藉由與表現MUC17的CHO細胞共培養的表現LT β R之人黑色素瘤細胞釋放的IL-8來測量效力。y軸的「訊號」表示藉由665 nm處訊號與615 nm處訊號的比率計算的相對IL-8釋放。

【0033】[圖23]係顯示huLT β R x huLRRC15雙特異性抗體 (44245-5、45147-3和52208-3) 之效力的圖表。在huLT β R x huLRRC15雙特異性抗體濃度增加的情

況下，藉由與表現LRRC15的Saos-2細胞共培養的表現LT β R之人黑色素瘤細胞釋放的IL-8來測量效力。y軸的「訊號」表示藉由665 nm處訊號與615 nm處訊號的比率計算的相對IL-8釋放。

【0034】 [圖24A-24C]係顯示在本文所描述的各种LT β R抗體濃度增加的情況下，LIGHT（圖24A）和LT α 1 β 2（圖24B）抑制作用的圖表。圖24C係顯示抗LT β R抗體與由HEK293細胞表現的LT β R結合的圖表，以證實非配體阻斷活性不是由於測試抗體的非受體結合所致。

【0035】 [圖25A-25C]係顯示在如本文所描述的各种LT β R-LRRC15雙特異性抗體濃度增加的情況下，LIGHT（圖25A）和LT α 1 β 2（圖25B）抑制作用的圖表。圖25C係顯示LT β R-LRRC15雙特異性抗體與HEK293細胞表現的LT β R結合的圖表，以證實非配體阻斷活性不是由於測試雙特異性抗體的非受體結合所致。

【0036】 [圖26A-26C]係顯示在如本文所描述的所指定LT β R-LRRC15雙特異性抗體（52208）濃度增加的情況下，LT α 1 β 2（圖26A）和LIGHT（圖26B）抑制作用的圖表。圖26C係顯示LT β R-LRRC15雙特異性抗體與HEK293細胞表現的LT β R結合的圖表，以證實非配體阻斷活性不是由於測試雙特異性抗體的非受體結合所致。

【0037】 [圖27]提供了總結在重新篩選XenoMouse[®]融合瘤池中鑒定的額外促效劑結合LT β R CRD4的非配體阻斷抗體的表格。使用實例9.3中描述的基於細胞的測定和實例9.4中描述的Caterpillar測定評估抗體的非配體阻斷活性。

【實施方式】

【0038】 根據35 U.S.C. §119(e)特此要求2023年6月12日提交的美國臨時申請案號63/472,565之權益，並且將其揭露內容藉由引用特此併入本文。

【0039】 本揭露關於結合和激動淋巴毒素 β 受體 (LT β R) 的蛋白分子。本揭露提供了促效劑LT β R結合蛋白，其結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R富含半胱胺酸結構域4 (CRD4) 的一或多個胺基酸殘基，並且 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT α 1 β 2與LT β R結合。本揭露還提供了雙特異性促效劑LT β R結合蛋白，其包含與人LT β R CRD4的一或多個胺基酸殘基結合並且 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT1 α 2 β 與LT β R結合的LT β R結合結構域，以及腫瘤相關抗原結合結構域。

【0040】 本揭露進一步關於治療人受試者癌症之方法。該等方法包括向患有癌症的受試者投與促效劑LT β R結合蛋白，例如如本文所描述的促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白，以誘導或增強受試者的抗腫瘤免疫反應。如本文所證明的，腫瘤微環境中的LT β R激動作用誘導高內皮微靜脈形成，以增強免疫細胞浸潤到腫瘤微環境中。這種LT β R介導的抗腫瘤免疫反應足以減少腫瘤生長。

【0041】 本揭露進一步提供了與結合人LT β R的促效劑LT β R結合蛋白相關的組成物、套組 (kit) 和方法。還提供了包含編碼本文揭露的促效劑LT β R結合蛋白的全部或一部分之多核苷酸序列的核酸分子。本揭露進一步提供了包含這樣的核酸的載體和質體，以及包含這樣的核酸和/或載體和質體的細胞或細胞系。所提供的方法進一步包括，例如，製備、鑒定和分離促效劑LT β R結合蛋白之方法，以及用於向人受試者投與本揭露之促效劑LT β R結合蛋白之方法。

【0042】 應理解，如所聲明的前述一般描述以及以下的詳細描述均僅為示例性和說明性的，而不限制所揭露的發明。

【0043】 除非本文另外定義，否則結合本揭露使用的科技術語應當具有熟悉該項技術者通常所理解的含義。通常，結合本文所描述的細胞及組織培養、分子生物學、免疫學、微生物學、遺傳學以及蛋白質及核酸化學及雜交而使用的命

名法及其技術係本領域中所熟知且通常使用的那些命名法及技術。除非另外指示，否則本揭露之方法和技術通常根據本領域熟知且如貫穿本說明書所引用和討論的各種通用和更特別參考文獻中所述之常規方法來進行。參見例如 Sambrook 等人, *Molecular Cloning: A Laboratory Manual* [分子選殖：實驗室手冊], 第2版, Cold Spring Harbor Laboratory Press [冷泉港實驗室出版社], 冷泉港, 紐約 (1989) 和 Ausubel 等人, *Current Protocols in Molecular Biology* [分子生物學現代方法], Greene Publishing Associates [格林出版聯合公司] (1992), 以及 Harlow 和 Lane *Antibodies: A Laboratory Manual* [抗體：實驗室手冊] Cold Spring Harbor Laboratory Press [冷泉港實驗室出版社], 冷泉港, 紐約 (1990), 該等所有都藉由引用併入本文。酶促反應及純化技術係根據製造商之說明書、如本領域中通常所實現或如本文所描述來進行。結合本文中所描述的分析化學、合成有機化學以及醫學及藥物化學而使用的術語及其實驗程式和技術係本領域中眾所周知且通常使用的那些術語以及實驗程式和技術。

【0044】 在本揭露中，除非另有明確說明，否則單數術語的使用包括複數，並且複數術語應包括單數。除非上下文另外明確指示，否則如本文所用，單數形式「一個」、「一種」和「該」包括單數和複數個指示物。

【0045】 在本揭露中，術語「包括 (including)」、「以及其他形式如「包括 (includes)」和「包括 (included)」之使用不是限制性的。同樣，除非另外特別說明，否則術語如「元件」或「組分」涵蓋包含一個單位的元件和組分以及包含超過一個亞單位的元件和組分兩者。而且，術語「部分 (portion)」的使用可包括一部分 (moiety) 或整個部分 (moiety)。

【0046】 藉由端點表述的數值範圍包括歸入到各自範圍內的所有數值和分數，以及所述端點。

【0047】 如本文所用，術語「約」在指可測量值例如參數、數量、持續時

間等時，意在涵蓋指定值 $\pm 10\%$ 或更小，較佳的是 $\pm 1\%-5\%$ 或更小的變化，只要這樣的變化適合在所揭露的實施方式中執行。應理解，修飾詞「約」所指的值本身也是特別地，而且較佳的是揭露的。

【0048】 使用標準的一或三字母縮寫表示多核苷酸和多肽序列。除非另有說明，否則多肽序列的胺基末端位於左側，其羧基末端位於右側。單鏈核酸序列以及雙鏈核酸序列的頂鏈的5'末端位於左側，其3'末端位於右側。多肽的特定部分可藉由胺基酸殘基數（如胺基酸1至50）或該位點的實際殘基（如天冬醯胺至脯胺酸）來指定。特定的多肽或多核苷酸序列也可以藉由解釋其與參考序列的差異來描述。

【0049】 除非另有說明，否則以下術語應理解為具有以下含義：

【0050】 「序列同一性」係指兩個或更多個胺基酸（多肽或蛋白質）序列或兩個或更多個核酸（多核苷酸）序列之間的關係，如藉由比較序列確定的。兩個序列之間的同一性較佳的是藉由評估它們在如本文所鑒定的序列的整個長度上的同一性來定義。

【0051】 在比較兩個或更多個核苷酸或胺基酸序列的同一性時，第一序列和第二序列之間的序列同一性百分比可以使用熟悉該項技術者已知的方法計算，例如，藉由將第一序列中與第二序列中相應位置的殘基相同的殘基數除以第一序列中殘基的總數乘以100%或藉由使用已知的電腦演算法進行序列比對，例如NCBI Blast，例如BLASTN和BLASTP（Altschul, S. F.等人, *J. Mol. Biol.*[分子生物學雜誌] 215:403-410 (1990)）、GCG套裝程式（Devereux, J.,等人, *Nucleic Acids Research*[核酸研究] 12 (1): 387 (1984)）、BestFit、FASTA和EMBOSS Needle（Madeira, F.,等人, *Nucleic Acids Research*[核酸研究] 47(W1): W636-W641 (2019)）。

【0052】 「結合親和力」通常係指分子（例如，如本文所描述的LT β R結合

蛋白)的單個結合位點與其結合配偶體(例如,人LTβR)之間的非共價相互作用的總和的強度。除非另有說明,否則如本文所用,「結合親和力」係指內在結合親和力,其反映了結合對成員(例如,LTβR結合蛋白和LTβR)之間的1:1相互作用。分子X對其配偶體Y的親和力通常可以表示為解離常數(KD)。親和力可以用本領域已知的多種方式測量和/或表示,包括但不限於平衡解離常數(KD)和平衡締合常數(KA)。KD係根據k_{off}/k_{on}的商計算的,而KA係根據k_{on}/k_{off}的商計算的。K_{on}係指例如抗體與抗原的締合速率常數,而K_{off}係指例如抗體從抗原中的解離。結合親和力可以使用如本文所描述的和本領域已知的多種技術來確定,例如但不限於平衡方法,例如酶聯免疫吸附測定(ELISA)、KinExA(參見,例如,Rathanaswami等人 *Analytical Biochemistry*[分析生物化學], 373:52-60 (2008),特此藉由引用將其全部併入)和放射免疫測定(RIA);表面電漿共振測定;或其他基於動力學的測定(例如,BIACORE®分析或Octet®分析(forteBIO))。親和力也可以使用其他方法確定,例如間接結合測定、競爭性結合測定、螢光共振能量轉移(FRET)、凝膠電泳和層析(例如凝膠過濾)。該等方法和其他方法可以對一或多種待檢查的組分使用標記和/或使用多種檢測方法,包括但不限於發色標記、螢光標記、發光標記或者同位素標記。結合親和力和動力學的詳細描述可見於Paul, W. E.編輯, *Fundamental Immunology* [基礎免疫學], 第4版, Lippincott-Raven [Lippincott-Raven出版社], 費城(1999),其集中於抗體-免疫原相互作用。

【0053】如本文所用,術語「結合蛋白」係指本領域已知的多種形式的結合蛋白中的任一種。在示例性方面,本揭露之結合蛋白包括(i)全長免疫球蛋白分子,即抗體,(ii)抗體的表位結合片段,以及(iii)抗體衍生物,例如多特異性抗體。

【0054】如本文所用,術語「抗體」係指具有常規免疫球蛋白形式、包含

重鏈及輕鏈且包含可變區及恒定區的蛋白質。例如，抗體可為IgG，其係兩對相同多肽鏈的「Y形」結構，每對具有一條「輕」鏈（典型地具有約25 kDa的分子量）和一條「重」鏈（典型地具有約50-70 kDa的分子量）。抗體具有可變區和恒定區。在IgG形式中，可變區通常是約100-110個或更多個胺基酸，包含三個互補決定區（CDR），並且主要負責抗原識別。

【0055】本領域已經描述了抗體CDR的一般結構和特性。簡言之，在抗體支架中，CDR嵌埋於重鏈及輕鏈可變區中的框架內，在這裡其構成主要負責抗原結合及識別的區域。可變區典型地包含至少三個重鏈CDR或輕鏈CDR（Kabat等人, 1991, Sequences of Proteins of Immunological Interest [有免疫學意義的蛋白質序列], Public Health Service [公共衛生署] N.I.H., Bethesda [貝塞斯達], Md. [馬里蘭州]；還參見Chothia和Lesk, 1987, J. Mol. Biol.[分子生物學雜誌] 196:901-917；Chothia等人, 1989, Nature [自然] 342: 877-883），位於框架區內（由Kabat等人, 1991指定框架區1-4、FR1、FR2、FR3、和FR4；還參見Chothia和Lesk, 1987, 同上）。

【0056】抗體可以包含本領域已知的任何恒定區。人輕鏈分類為 κ 輕鏈及 λ 輕鏈。重鏈分類為 μ 、 δ 、 γ 、 α 或 ϵ ，並且將抗體的同種型分別定義為IgM、IgD、IgG、IgA和IgE。在本發明中，抗體為IgG同種型。IgG具有若干個亞類，包括但不限於IgG1、IgG2、IgG3和IgG4。輕鏈恒定區可為例如 κ 型或 λ 型輕鏈恒定區，例如人 κ 型或 λ 型輕鏈恒定區。

【0057】抗體的「表位結合片段」涵蓋全長抗體的任何多肽片段、區域、部分或結構域，其表現出與全長抗體相同或基本相似的結合特性，並且可以例如藉由蛋白酶切割完整親本抗體來獲得。

【0058】「抗體衍生物」係含有至少一個抗體表位結合結構域的蛋白質或多肽，通常使用重組技術或經由親本抗體或其部分的化學修飾形成。抗體衍生物

包含與一或多種親本抗體或其相關部分的胺基酸序列基本相似的胺基酸序列。本揭露之示例性抗體衍生物包括多特異性結合蛋白，例如雙特異性結合蛋白。

【0059】如本文所用，術語「表位」係指抗體結合的蛋白質的位點或部分。表位可以由形成構象空間單元的連續胺基酸殘基或不連續胺基酸殘基中的一個或兩個組成。對於不連續表位，來自抗原線性序列不同部分的胺基酸通過蛋白質分子的折疊在3維空間中非常接近。LT β R結合蛋白結合的表位可以藉由如本文所描述的氫/氘交換與質譜偶合來確定。

【0060】如本文所用，術語「互補位」係指結合蛋白，例如抗體，與蛋白靶標的表位結合的部分。互補位本質上可為線性的或可為不連續的，由抗體的非連續胺基酸殘基之間的空間關係形成，而不是由一系列線性胺基酸形成。如本文所提及的，「輕鏈互補位胺基酸殘基」、「重鏈互補位胺基酸殘基」或「互補位介面殘基」係指參與同蛋白質靶標結合相互作用的抗體輕鏈和/或重鏈殘基。互補位可以包含單個重鏈CDR，例如重鏈CDR3的胺基酸殘基，或來自重鏈CDR（HCDR1、CDR2、HCDR3）和輕鏈CDR（LCDR1、LCDR2和LCDR3）的胺基酸殘基的組合。如本文所證明的，互補位不需要CDR的所有胺基酸殘基，並且不需要來自所有六個CDR的胺基酸殘基。

LT β R結合蛋白

【0061】本文的揭露涵蓋促效劑淋巴毒素 β 受體（LT β R）結合蛋白。LT β R（也稱為腫瘤壞死因子（TNF）受體超家族成員3和腫瘤壞死因子受體III型（TNFR-III））是TNF家族成員，在大多數細胞類型（包括成纖維細胞、上皮細胞、單核細胞、樹突狀細胞和髓系細胞）上表現。LT β R不被T或B淋巴細胞表現。LT β R係兩種TNF家族細胞介素配體的受體。該等LT β R配體中的第一個配體係淋巴毒素 α 和淋巴毒素 β 亞基的異源三聚體，稱為LT α 1 β 2。LT β R的第二個配體係LIGHT（腫瘤壞死因子配體超家族成員14（TNFSF14））的同源三聚體。LT α 1 β 2

和LIGHT與LTβR的結合激活主要涉及NFκB途徑的訊息傳遞途徑。LTβR傳訊參與發育過程中的淋巴結（LN）器官發生和成年後淋巴器官和多種免疫細胞（包括嗜中性球、自然殺手（NK）細胞和恒定自然殺手T（iNKT）細胞）的維持。LTβR在非淋巴器官中稱為三級淋巴結構（TLS）的LN樣細胞簇的形成、以及T細胞跨內皮遷移的關鍵基因的誘導中也發揮著關鍵作用，這兩者均為促進有效抗腫瘤反應的關鍵。

【0062】 人LTβR係61 kDa跨膜蛋白，其具有SEQ ID NO: 1（同種型1）或SEQ ID NO: 2（同種型2）的胺基酸序列，如下所示。如本文所描述的LTβR結合蛋白與人LTβR結合。在一個實施方式中，本揭露之LTβR結合蛋白與人LTβR的胞外結構域內的一或多個表位（包含SEQ ID NO: 1之胺基酸殘基31-227）結合，所述胞外結構域包含四個富含半胱胺酸的結構域（即CRD1-CRD4）。

人LTβR同種型1（UniProtKB No. P36941-1）

MLLPWATSAPGLAWGPLVLGLFGLLAASQPQAVPPYASENQTCRDQEKEYYEPQHRICCS
RCPPGTYVSAKCSRIRDTCATCAENSYNEHWNLYLTICQLCRPCDPVMGLEEIAPCTSKR
KTQCRCQPGMFCAAWALECTHCELLSDCPPGTEAELKDEVGKGNNHCVPCKAGHFQNTSS
PSARCQPHTRCENQGLVEAAPGTAQSDTTCKNPLEPLPPEMSGTMLMLAVLLPLAFFLLL
ATVFSCIWKSHPSLCRKLGSLKRRPQGEGPNPVAGSWEPPKAHPYFPDLVQPLLPISGD
VSPVSTGLPAAPVLEAGVPQQQSPLDLTREPQLEPGEQSQVAHGTTNGIHVTGGSMTITGN
IYIYNGPVLGGPPGPGDLPATPEPPYPIPEEGDPGPPGLSTPHQEDGKAHHLAETEHCGA
TPSNRGPRNQFITHD (SEQ ID NO: 1)

人LTβR同種型2（UniProtKB No. P36941-2）

MEATGISLASQLKVPPYASENQTCRDQEKEYYEPQHRICCSRCPPGTYVSAKCSRIRDTC
CATCAENSYNEHWNLYLTICQLCRPCDPVMGLEEIAPCTSKRKTQCRCQPGMFCAAWALEC
THCELLSDCPPGTEAELKDEVGKGNNHCVPCKAGHFQNTSSPSARCQPHTRCENQGLVEA

APGTAQSDTTCKNPLEPLPPEMSGTMLMLAVLLPLAFFLLLATVVFSCIWKSHPSLCRKLG
SLLKRRPQGEGPNPVAGSWEPPKAHPYFPDLVQPLLPISGDVSPVSTGLPAAPVLEAGVP
QQQSPLDLTREPQLEPGEQSQVAHGTNGIHVTGGSMTITGNIYIYNGPVLGGPPGPGDLP
ATPEPPYPIPEEGDPGPPGLSTPHQEDGKAHHLAETEHCGATPSNRGPRNQFITHD (SEQ ID
NO: 2)

【0063】 在一個實施方式中，本文所描述的LTβR結合蛋白也結合食蟹猴（cyno）LTβR。cyno LTβR之胺基酸序列如下提供（SEQ ID NO: 3）。在一個實施方式中，本文所描述的LTβR結合蛋白不結合鼠LTβR。在一個實施方式中，本文所描述的LTβR結合蛋白結合人LTβR和食蟹猴LTβR，但不結合鼠LTβR。

Macaca fascicularis（食蟹猴）UniProtKB No. A0A2K5VGQ6（SEQ ID NO:3）

MRLPWATSAPGLAWGPLVLGLFGLLAASQPQVVRKGPVPPYGSENQTCRDQEKEYYEPRH
RICCSRCPPGTIVSAKCSRSRDTVCATCAENSYNEHWNLTICQLCRPCDPVMGLEEIAIP
CTSKRKTQCRCQPGMFCAAWALECTHCELLSDCPPGTEAELKDEVGKGNNHCVCKAGHF
QNTSSPSARCQPHTRCEDQGLVEAAPGTAQSDTTTCRNPSESLPPEMSGTMLMLAILLPLA
FFLLLATIFACIWKSHPSLCRKLGSLKRRHPQGEGPNPVAAGRDPKANKPYPDVLEPLL
PISGDVSPVSTGLPTALVSEEGVPQQQSPLDLTTEPQLEPGEQNQVAHGTNGIHVTGGSMT
TITGNIYIYNGPVLGGPPGPGDLPATPDPPYPIPEEGDPGPPGLSTPHQEDGKAHHLAET
EHCGATPSNRGPRSQFITYD

【0064】 根據本揭露，LTβR結合蛋白為促效劑LTβR結合蛋白，例如，促效劑LTβR抗體、抗體的促效劑LTβR表位結合片段、或促效劑LTβR抗體衍生物（例如，促效劑LTβR雙特異性結合蛋白）。如本文所用，「促效劑LTβR結合蛋白」係一種LTβR結合分子，其藉由與受體結合直接誘導LTβR介導的傳訊，或經由與受體結合並例如藉由使用交聯抗體在細胞表面誘導其更高級的簇集間接誘導LTβR介導的傳訊。本揭露之LTβR結合蛋白與LTβR的結合誘導NFκB傳訊、與

T細胞跨內皮遷移相關的基因表現和/或TLS簇形成。用於測量本揭露結合蛋白對LT β R激活和/或LT β R傳訊誘導之測定係本領域已知的並在本文中描述。

【0065】 在一個實施方式中，藉由測定與促效劑LT β R結合蛋白孵育後表現LT β R的細胞釋放的白血球介素-8 (IL8) 來測量LT β R激動作用，如本文實例7所述。與不存在相比，在存在本揭露之LT β R結合蛋白的情況下，細胞IL8釋放水平的增加表明LT β R結合蛋白作為促效劑LT β R結合蛋白。在另一個實施方式中，藉由測定內皮細胞之反式激活來測量LT β R激動作用。LT β R介導的內皮細胞反式激活可以藉由測定以下來測量：黏附分子（例如血管細胞黏附蛋白1 (VCAM1；也稱為CD106) 和/或細胞內黏附分子1 (ICAM；也稱為CD54)) 的內皮細胞表現，和/或炎性趨化因子例如CCL5、CCL2和CXCL10的表現或分泌。與不存在促效劑LT β R結合蛋白相比，在存在其的情況下，內皮細胞VCAM或ICAM表現增加表明LT β R結合蛋白作為促效劑LT β R結合蛋白。類似地，與不存在LT β R結合蛋白相比，在存在其的情況下，CCL5、CCL2和/或CXCL10的內皮細胞表現或分泌增加表明LT β R結合蛋白作為促效劑LT β R結合蛋白。

【0066】 在一個實施方式中，相對於在不存在促效劑LT β R結合蛋白情況下的LT β R傳訊活性，本文所描述的LT β R結合蛋白的促效劑活性誘導LT β R傳訊活性增加至少10%，如藉由例如IL8釋放或內皮細胞反式激活測量的。在一個實施方式中，相對於在不存在促效劑LT β R結合蛋白的情況下的LT β R傳訊水平，本文所描述的LT β R結合蛋白使LT β R傳訊活性增加至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少55%、至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%。在一個實施方式中，相對於在不存在促效劑LT β R結合蛋白的情況下的LT β R傳訊水平，本文所描述的LT β R結合蛋白使LT β R傳訊活性增加至少100%。

【0067】 在一個實施方式中，本文所描述的LT β R結合蛋白的促效劑活性使

用如上文所述之一或多個體外功能終點來測量，並且該活性表示為半最大有效濃度（EC₅₀）。在一個實施方式中，本文所描述的LTβR結合蛋白的EC₅₀在約1 pM至約500 pM、約1 pM至約250 pM、約1 pM至約200 pM、約1 pM至約150 pM、約1 pM至約125 pM、約1 pM至約100 pM、約1 pM至約90 pM、約1 pM至約80 pM、約1 pM至約70 pM、約1 pM至約60 pM、約1 pM至約50 pM、約1 pM至約40 pM、約1 pM至約30 pM、約1 pM至約200 pM、約10 pM至約200 pM、約20 pM至約200 pM、約30 pM至約200 pM、約40 pM至約200 pM、約50 pM至約200 pM、約60 pM至約200 pM內。在一個實施方式中，如本文所描述的促效劑LTβR結合蛋白介導的IL-8釋放的EC₅₀為約10 pM至約200 pM、約20 pM至約150 pM、或約30 pM至約140 pM。

【0068】 在一個實施方式中，如本文所描述的LTβR結合蛋白結合並激動人LTβR，同時允許內源性LTβR配體與受體結合並產生活性。如上所述，LTβR結合至少兩種不同的內源性配體，即LIGHT和LTα1β2。當本揭露之LTβR結合蛋白與LTβR的其相應表位結合時，LIGHT或LTα1β2中的至少一種也可以與LTβR結合以激活內源性配體介導的傳訊活性。因此，在一個實施方式中，本文所描述的LTβR結合蛋白的結合不抑制、阻止或排除LTα1β2與LTβR的結合。在一個實施方式中，本文所描述的LTβR結合蛋白的結合不抑制、阻止或排除LIGHT與LTβR的結合。在一個較佳的實施方式中，本文所描述的LTβR結合蛋白的結合不抑制、阻止或排除LIGHT與LTβR的結合或LTα1β2與LTβR的結合。

【0069】 促效劑LTβR結合蛋白的這種功能特徵，本文稱為「非配體阻斷活性」，係本揭露之促效劑LTβR結合蛋白的有益特徵，因為它在將結合蛋白投與給例如患者時使安全性最大化。此外，本文所描述的LTβR結合蛋白優先以交聯依賴性方式激動LTβR，即結合分子必須與LTβR和另一種蛋白（例如，Fc受體或靶向蛋白）結合以誘導LTβR激活。從安全角度來看，這兩個特性提供了優越的

分子。如果結合分子以非交聯依賴性方式結合LT β R，例如，它僅與LT β R結合，則其結合不會激動受體。此外，由於LT β R結合蛋白以不阻斷內源性配體結合的方式結合LT β R，因此其結合也將不會無意中拮抗或阻斷內源性配體介導的活性。

【0070】在一個實施方式中，如本文所描述的促效劑LT β R結合蛋白的非配體阻斷活性之特徵在於其結合對LIGHT和LT α 1 β 2與LT β R結合的抑制百分比。在一個實施方式中，本揭露之結合蛋白與LT β R結合對LIGHT與LT β R結合（ $\leq 20\%$ 抑制）或LT α 1 β 2與LT β R結合（ $\leq 20\%$ 抑制）的抑制或阻斷可忽略不計，如藉由下文所描述的基於細胞的受體-配體測定測量的（另參見實例8）。例如，如本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $\leq 20\%$ 、LT α 1 β 2與LT β R結合的 $\leq 20\%$ 、或LIGHT和LT α 1 β 2與LT β R結合的 $\leq 20\%$ ，如藉由本文所描述的基於細胞的受體-配體測定測量的。在一個實施方式中，如本文所描述的LT β R結合蛋白抑制LIGHT與LT β R結合或LT α 1 β 2與LT β R結合的 $< 20\%$ 、 $< 15\%$ 、 $< 10\%$ 、 $< 9\%$ 、 $< 8\%$ 、 $< 7\%$ 、 $< 6\%$ 、 $< 5\%$ 、 $< 4\%$ 、 $< 3\%$ 、 $< 2\%$ 或 $< 1\%$ 。在一個實施方式中，如本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $< 15\%$ 或抑制LT α 1 β 2與LT β R結合的 $< 15\%$ ，如藉由本文所描述且實例8.2中示例的基於細胞的受體配體測定測量的。在一個實施方式中，如本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $< 15\%$ 且抑制LT α 1 β 2與LT β R結合的 $< 15\%$ ，如藉由本文所描述且實例8.2中示例的基於細胞的受體配體測定測量的。在一個實施方式中，本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $< 10\%$ 或抑制LT α 1 β 2與LT β R結合的 $< 10\%$ ，如藉由本文所描述的基於細胞的受體配體測定測量的。在一個實施方式中，本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $< 10\%$ 且抑制LT α 1 β 2與LT β R結合的 $< 10\%$ ，如藉由本文所描述的基於細胞的受體配體測定法測量的。在一個實施方式中，本文所描述的結合蛋白與LT β R結合抑制LIGHT與LT β R結合的 $< 5\%$ 或抑制LT α 1 β 2與LT β R結

合的 < 5%，如藉由本文所描述的基於細胞的受體配體測定測量的。在一個實施方式中，本文所描述的結合蛋白與LTβR結合抑制LIGHT與LTβR結合的 < 5%且抑制LTα1β2與LTβR結合的 < 5%，如藉由本文所描述的基於細胞的受體配體測定法測量的。較佳的是，本文所描述的結合蛋白與LTβR結合抑制LIGHT與LTβR結合的0%或抑制LTα1β2與LTβR結合的0%，如藉由本文所描述的基於細胞的受體配體測定測量的。更較佳的是，本文所描述的結合蛋白與LTβR結合抑制LIGHT與LTβR結合的0%且抑制LTα1β2與LTβR結合的0%，如藉由本文所描述的基於細胞的受體配體測定測量的。不抑制LIGHT與LTβR結合且不抑制LTα1β2與LTβR結合(即，表現出對LIGHT與LTβR結合0%抑制且對LTα1β2與LTβR結合0%抑制)的本文所描述的示例性LTβR結合蛋白包括但不限於與LTβR的CRD4結構域結合的促效劑LTβR結合蛋白。

【0071】可替代地，如本文所描述的促效劑LTβR結合蛋白的非配體阻斷活性之特徵在於，在結合促效劑LTβR結合蛋白存在下發生的內源性LTβR配體結合的百分比。在一個實施方式中，如本文所描述的結合蛋白與LTβR結合允許發生至少80%的內源性LTβR配體(即LIGHT或LTα1β2)結合，如藉由本文所描述的基於細胞的受體-配體測定測量的(參見實例8.2)。在一個實施方式中，如本文所描述的結合蛋白與LTβR結合允許發生至少80%、至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%的LIGHT與LTβR結合或LTα1β2與LTβR結合。在一個實施方式中，如本文所描述的結合蛋白與LTβR結合允許發生至少90%的LIGHT與LTβR結合或允許發生至少90%的LTα1β2配體與LTβR結合，如藉由本文所描述且實例8中示例的基於細胞的受體-配體測定測量的。在一個實施方式中，如本文所描述的結合蛋白與LTβR結合允許發生至少90%的LIGHT與LTβR結合且允許發生至少90%的LTα1β2配體與LTβR結合，如藉由本文所描述且實例8中示例的基於細

胞的受體-配體測定測量的。在一個實施方式中，如本文所描述的結合蛋白與LT β R結合允許發生至少95%的LIGHT與LT β R結合或允許發生至少95%的LT α 1 β 2配體與LT β R結合，如藉由本文所描述且實例8中示例的基於細胞的受體-配體測定測量的。在一個實施方式中，如本文所描述的結合蛋白與LT β R結合允許發生至少95%的LIGHT與LT β R結合且允許發生至少95%的LT α 1 β 2配體與LT β R結合，如藉由本文所描述且實例8中示例的基於細胞的受體-配體測定測量的。較佳的是，如本文所描述的結合蛋白與LT β R結合允許發生100%的LIGHT與LT β R結合或允許發生100%的LT α 1 β 2配體與LT β R結合，如藉由實例8中所描述的基於細胞的基於受體-配體的測定測量的。更較佳的是，如本文所描述的結合蛋白與LT β R結合允許發生100%的LIGHT與LT β R結合且允許發生100%的LT α 1 β 2配體與LT β R結合，如藉由實例8中所描述的基於細胞的基於受體-配體的測定測量的。允許LIGHT與LT β R結合的100%和LT α 1 β 2與LT β R結合的100%的本文所描述的示例性促效劑LT β R結合蛋白係與LT β R的CRD4結構域結合的促效劑LT β R結合蛋白。

【0072】 本文所描述的促效劑LT β R結合蛋白的非配體阻斷活性使用基於細胞的受體-配體結合測定進行測量和定量。該測定測量在本揭露之促效劑LT β R結合蛋白存在下對LIGHT和/或LT α 1 β 2與LT β R結合的抑制百分比（參見實例8）。這種基於細胞的受體-配體結合測定涉及將表現LT β R的細胞與含有促效劑LT β R結合蛋白的細胞培養基在4° C下孵育1小時，以使促效劑LT β R結合蛋白結合細胞上表現的LT β R。合適的表現LT β R的細胞包括任何自然表現LT β R的細胞類型，例如內皮細胞、巨噬細胞、自然殺手細胞等，以及被工程化以表現LT β R的細胞，例如用LT β R表現載體轉染的細胞系（例如CHO細胞、HEK 293細胞、黑色素瘤細胞等）。細胞培養基中促效劑LT β R結合蛋白的濃度為有效地使表現LT β R的細胞表現的所有LT β R的結合飽和的濃度。例如，細胞培養基中促效劑LT β R結合蛋

白的濃度為濃度5-30 nM，以使表現LT β R的細胞表現的所有LT β R的結合飽和。該測定進一步涉及在與促效劑LT β R結合蛋白孵育後，在配體與LT β R有效結合的條件下，將表現LT β R的細胞與可檢測的LIGHT配體、可檢測的LT α 1 β 2配體或兩者（即可檢測的LIGHT和LT α 1 β 2配體）相互作用。藉由將LIGHT和LT α 1 β 2配體直接偶合到可檢測的標記（例如螢光標記或標籤）使其係可檢測的。使用合適的手段（例如，螢光激活的細胞分選），在促效劑LT β R結合蛋白存在下，對可檢測的LIGHT和/或LT α 1 β 2配體與表現LT β R的細胞的結合進行檢測。配體結合抑制的定量評估係藉由將在存在促效劑LT β R結合蛋白下LIGHT和/或LT α 1 β 與LT β R的結合水平與在不存在促效劑LT β R結合蛋白下LIGHT和/或LT α 1 β 與LT β R的相應結合水平進行比較來確定的。最低限度抑制（ $\leq 20\%$ 抑制）或不抑制（0%抑制）LIGHT或LT α 1 β 2配體與LT β R結合的促效劑LT β R結合蛋白被鑒定為適用於本文所描述之方法。在流式細胞儀上經由FAC，在存在或不存在LT β R結合蛋白的情況下，對可檢測的LIGHT和/或LT α 1 β 2配體與表現LT β R的細胞的結合進行檢測。

【0073】 本文所描述的示例性促效劑LT β R結合蛋白表現出所期望的功能特性（例如，cyno和人LT β R結合和非配體阻斷活性），部分原因是LT β R的表位與促效劑LT β R結合蛋白結合。在一個實施方式中，本文所揭露的LT β R結合蛋白與包含胞外結構域的富含半胱氨酸結構域（CRD）的一或多個片段的LT β R的表位結合，即CRD1、CRD2、CRD3或CRD4的一或多個殘基。人LT β R胞外結構域如下SEQ ID NO: 4所示。在一個實施方式中，本揭露之促效劑LT β R結合蛋白與包含LT β R的CRD1殘基的表位結合。LT β R的CRD1包含SEQ ID NO: 4的殘基12-51，其對應於SEQ ID NO: 1之全長LT β R的殘基42-81。在一個實施方式中，本揭露之LT β R結合蛋白與包含LT β R CRD2的殘基的表位結合。LT β R CRD2包含SEQ ID NO: 4的殘基52-94，其對應於SEQ ID NO: 1之全長LT β R的殘基82-124。在一

個實施方式中，本揭露之LTβR結合蛋白與包含LTβR CRD3的殘基的表位結合。LTβR CRD3包含SEQ ID NO: 4的殘基95-138，其對應於SEQ ID NO: 1之全長LTβR的殘基125-168。在一個實施方式中，本揭露之LTβR結合蛋白與包含LTβR CRD4的殘基的表位結合。LTβR CRD4包含SEQ ID NO: 4的殘基139-181，其對應於SEQ ID NO: 1之全長LTβR胺基酸序列的殘基168-211。

QAVPPYASENQTCRDQEKEYYEPQHRICCSRCPPGTYSKCSRIKDTVCATCAENSYNEHW
NYLTICQLCRPCDFVMGLEEIIAPCTSKRKTQCRCQPGMFCAAWALECTHCELLSDCPPGTEA
ELKDEVGKGNNHCVPCAGHFGNTSSPSARCQPHTRCENQGLVEAAPGTAQSDTTCKNPLEP
LPPEMSGTMLM (SEQ ID NO: 4)

【0074】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白與包含人LTβR的胞外CRD2和CRD3的殘基的表位結合。在一個實施方式中，該促效劑LTβR結合蛋白與包含SEQ ID NO: 4之位置56-64處的一或多個殘基的CRD2內的表位結合，並與包含SEQ ID NO: 4之位置81-101處的一或多個殘基的跨越CRD2和CRD3的表位結合，如藉由氫/氘交換（HDX）質譜（MS）確定的。在一個實施方式中，該促效劑LTβR結合蛋白與CRD2和CRD3的上述區域結合，而不與CRD2和CRD3之外的LTβR區域結合。換句話說，在一個實施方式中，該促效劑LTβR結合蛋白與LTβR中由CRD2和CRD3內的一或多個殘基組成的區域結合。LTβR結合蛋白與LTβR的已鑒定區域的結合激動受體傳訊，同時允許內源性LTβR配體結合。結合該表位的促效劑LTβR結合蛋白也結合cyno LTβR。具有該等特性之示例性促效劑LTβR結合蛋白在本文中被鑒定為LIBC219058（19324）和LIBC218990（19320）。

【0075】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白與包含人LTβR的胞外CRD1的殘基的表位結合。在一個實施方式中，本文所描述的促效劑LTβR結合蛋白與包含SEQ ID NO: 4之位置3-9、20-29和/或38-47處的一或多個殘

基的CRD1內的表位結合，如藉由HDX MS確定的。在一個實施方式中，該促效劑LTβR結合蛋白與CRD1的上述區域結合，而不與CRD1之外的LTβR區域結合。換句話說，在一個實施方式中，該促效劑LTβR結合蛋白與LTβR中由CRD1內的殘基組成的區域結合。LTβR結合蛋白與LTβR的該表位的結合激動受體傳訊，同時允許內源性LIGHT配體與LTβR結合，並最低限度地抑制LTα1β2配體結合（≤20%）。結合該表位的促效劑LTβR結合蛋白也結合cyno LTβR。具有該等特性的示例性促效劑LTβR結合蛋白在本文中被鑒定為LIBC218994（19321）。

【0076】在另一個實施方式中，本揭露之促效劑LTβR結合蛋白與包含人LTβR的胞外CRD1的殘基的表位結合。在一個實施方式中，本文所描述的促效劑LTβR結合蛋白與包含SEQ ID NO: 4之位置1-19處的一或多個殘基的CRD1內的表位結合，如藉由HDX MS確定的。在一個實施方式中，該促效劑LTβR結合蛋白與CRD1的上述區域結合，而不與CRD1之外的LTβR區域結合。換句話說，在一個實施方式中，該促效劑LTβR結合蛋白與LTβR中由CRD1內的殘基組成的區域結合。LTβR結合蛋白與LTβR的該表位的結合激動受體傳訊，並且不抑制內源性LIGHT與LTβR結合，以及不抑制內源性LTα1β2與LTβR結合。結合該表位的促效劑LTβR結合蛋白也結合cyno LTβR。具有該等特性的示例性促效劑LTβR結合蛋白在本文中被鑒定為LIBC219051（19323）。

【0077】在另一個實施方式中，本揭露之促效劑LTβR結合蛋白與包含人LTβR的胞外CRD4的殘基的表位結合。在一個實施方式中，本文所描述的促效劑LTβR結合蛋白與包含LTβR的胞外結構域（SEQ ID NO: 4）（SEQ ID NO: 1的殘基197-209）的位置168-179處的一或多個殘基的CRD4內的表位結合，如藉由HDX MS確定的。在一個實施方式中，該促效劑LTβR結合蛋白與CRD4的上述區域結合，而不與CRD4之外的LTβR區域結合。換句話說，在一個實施方式中，該促效劑LTβR結合蛋白與LTβR中由CRD4內的殘基組成的區域結合。促效劑LTβR結合

蛋白與LT β R的該表位的結合激動受體傳訊，並且不抑制內源性LIGHT與LT β R結合，以及不抑制內源性LT α 1 β 2與LT β R結合。結合該表位的促效劑LT β R結合蛋白也結合cyno LT β R。具有該等特性的示例性促效劑LT β R結合蛋白在本文中被鑒定為LIBC219081（19325）和LIBC218979（19319）。

【0078】與本文揭露的示例性促效劑LT β R結合蛋白具有相同或重疊表位的LT β R結合蛋白將相互競爭結合LT β R。因此，在一個實施方式中，本揭露之示例性促效劑LT β R結合蛋白與LIBC219081（19325）和/或LIBC218979（19319）競爭結合CRD4。「競爭」或「與.....競爭」意指LT β R結合蛋白競爭靶標上的相同表位或結合位點。這樣的競爭可以藉由其中參考促效劑LT β R結合蛋白（例如促效劑LT β R結合蛋白LIBC219081（19325）和LIBC218979（19319））阻止或抑制測試LT β R結合蛋白的特異性結合的測定來確定。本文在實例9.2中描述了示例性競爭性結合測定，其可用於鑒定本揭露所涵蓋的競爭性結合LT β R的CRD4的促效劑LT β R結合蛋白。通常，當競爭性LT β R結合蛋白過量存在時，其將抑制參考促效劑LT β R結合蛋白與共同表位的結合至少50%、至少55%、至少60%、至少65%、至少70%、或至少75%。在一些情況下，參考促效劑LT β R結合蛋白與LT β R的結合被抑制至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或更多。本文描述了本揭露之示例性促效劑LT β R結合蛋白，其與本文鑒定為LIBC219081（19325）和LIBC218979（19319）的結合蛋白競爭結合LT β R的CRD4結構域（參見表2-4和6-8）。

【0079】本揭露之促效劑LT β R結合蛋白係結合並激動LT β R的蛋白質，而不阻斷或抑制一種或兩種內源性LT β R配體結合LT β R。本文所描述的LT β R結合蛋白包含一或多個胺基酸結合結構域，該等胺基酸結合結構域單獨或組合結合LT β R區域並激活受體的傳訊活性。視需要，該促效劑LT β R結合蛋白進一步包含支架或框架部分，其允許一或多個結合結構域採用促進一或多個結合結構域和

LT β R之間結合相互作用的構象。示例性LT β R結合蛋白包括但不限於LT β R抗體（即免疫球蛋白）、LT β R抗體的表位結合片段、和LT β R抗體衍生物，本文更詳細地描述了其中的每一種。

【0080】 本文揭露的促效劑LT β R結合蛋白與LT β R的胞外結構域內的其相應表位結合。在一個實施方式中，本揭露之促效劑LT β R結合蛋白比替代表位更頻繁、更快速、以更長持續時間和/或更大親和力或親合力結合LT β R的胞外結構域的CRD4內的表位殘基（即SEQ ID NO: 4（ECD）的殘基139-181；SEQ ID NO: 1（全長LT β R）的殘基169-211）。在一個實施方式中，本文所描述的促效劑LT β R結合蛋白與LT β R的胞外CRD4結構域的任何2、3、4、5、6、7、8、9、10個或更多個胺基酸殘基結合，特別是SEQ ID NO: 4的168-179的一或多個殘基或SEQ ID NO: 4的168-178的一或多個殘基。

【0081】 根據本揭露，促效劑LT β R結合蛋白以緊密結合親和力結合LT β R，如由 10^{-7} M或更小的平衡解離常數（ K_D ）值確定的。在一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，LT β R抗體、表位結合片段或抗體衍生物）以小於 10^{-7} M、小於 10^{-8} M、小於 10^{-9} M、小於 10^{-10} M、或小於 10^{-11} M、小於 10^{-12} M或小於 10^{-13} M的平衡解離常數或 K_D （ k_{off}/k_{on} ）（值越低指示結合親和力越緊密）結合人LT β R。

【0082】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，抗體、表位結合片段和抗體衍生物）結合人LT β R，其平衡解離常數或 K_D （ k_{off}/k_{on} ）在約 10^{-7} M和約 10^{-11} M之間、約 10^{-7} M和約 10^{-10} M之間、約 10^{-7} M和約 10^{-9} M之間、約 10^{-7} M和約 10^{-8} M之間、約 10^{-8} M和約 10^{-9} M之間、約 10^{-9} M和約 10^{-10} M之間、約 10^{-10} M和約 10^{-11} M之間、約 10^{-11} M和約 10^{-12} M之間、約 10^{-12} M和約 10^{-13} M之間。在任何實施方式中，本揭露之促效劑LT β R結合蛋白特異性結合人LT β R，其 K_D 在約 10^{-8} M和約 10^{-11} M之間或在約 10^{-9} M和約 10^{-10} M之間。

【0083】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，抗體、表位結合片段和抗體衍生物）特異性結合人LT β R，其平衡解離常數或 K_D (k_{off}/k_{on}) 在約0.01 mM和約10 nM之間、約0.01 nM和約9 nM之間、約0.01 nM和約8 nM之間、約0.01 nM和約7 nM之間、約0.01 nM和約6 nM之間、約0.01 nM和約5 nM之間、約0.01 nM和約4 nM之間、約0.01 nM和約3 nM之間、約0.01 nM和約2 nM之間、約0.01 nM和約1 nM之間、約0.1 nM和約10 nM之間、約0.1 nM和約9 nM之間、約0.1 nM和約8 nM之間、約0.1 nM和約7 nM之間、約0.1 nM和約6 nM之間、約0.1 nM和約5 nM之間、約0.1 nM和約4 nM之間、約0.1 nM和約3 nM之間、約0.1 nM和約2 nM之間、約0.1 nM和約1 nM之間、或約0.01 nM和約0.1 nM之間。

【0084】 與人LT β R結合的本揭露之促效劑LT β R結合蛋白也以相同或相似的親和力與食蟹猴（cyno）LT β R結合。cyno LT β R的胺基酸序列在本文中提供為 SEQ ID NO: 3。在示例性方面，本文所描述的促效劑LT β R結合蛋白與食蟹猴LT β R結合，其 K_D 在約 10^{-7} M和約 10^{-8} M之間、約 10^{-8} M和約 10^{-9} M之間、約 10^{-9} M和約 10^{-10} M之間、約 10^{-10} M和約 10^{-11} M之間、約 10^{-11} M和約 10^{-12} M之間。在任何實施方式中，本揭露之LT β R結合蛋白特異性結合cyno LT β R，其 K_D 在約 10^{-8} M和約 10^{-10} M之間。

【0085】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，抗體、表位結合片段和抗體衍生物）與食蟹猴（cyno）LT β R結合，其平衡解離常數或 K_D (k_{off}/k_{on}) 在約0.1 nM和約30 nM之間、約0.1 nM和約20 nM之間、約0.1 nM和約10 nM之間、約0.1 nM和約9 nM之間、約0.1 nM和約8 nM之間、約0.1 nM和約7 nM之間、約0.1 nM和約6 nM之間、約0.1 nM和約5 nM之間、約0.1 nM和約4 nM之間、約0.1 nM和約3 nM之間、約0.1 nM和約2 nM之間、或約0.1 nM和約1 nM之間。

【0086】 本揭露之促效劑LT β R結合蛋白以高親和力與人LT β R和cyno

LTβR結合。例如，該促效劑LTβR結合蛋白對人LTβR的K_D係在促效劑LTβR結合蛋白對cyno LTβR的K_D的約100倍、約50倍、約25倍、約10倍、約5倍或約2倍或更少以內。在一個實施方式中，該促效劑LTβR結合蛋白對人LTβR的K_D係促效劑LTβR結合蛋白對cyno LTβR的K_D的約10倍或更少。

【0087】如本文揭露的促效劑LTβR結合蛋白與LTβR胞外結構域結合，其親和力的K_D對應於比其與非特異性抗原（例如，TNFR-I或TNFR-II等）結合的親和力低至少10倍，例如低至少100倍，例如低至少1,000倍，例如低至少10,000倍，例如低至少100,000倍。親和力降低的量取決於結合蛋白對LTβR的K_D，因此當該促效劑LTβR結合蛋白的K_D非常低（即結合蛋白具有高度特異性）時，對LTβR的親和力低於對非特異性抗原的親和力的量可能為至少10,000倍。

【0088】在一個實施方式中，本揭露之促效劑LTβR結合蛋白為LTβR抗體、LTβR抗體的表位結合片段（例如，結合LTβR的Fab、Fab'、F(ab')₂）或LTβR抗體衍生物（例如，LTβR scFv、微抗體、雙特異抗體或多特異性結合蛋白），如本文所描述的。

【0089】在一個實施方式中，本揭露之促效劑LTβR結合蛋白係如本文所定義的抗體。術語「抗體」還包括在重鏈和/或輕鏈的N端和/或C端包含1、2、3、4或5個胺基酸殘基插入或缺失的抗體，其保留與包含不包含該等胺基酸殘基取代、插入或缺失的兩個重鏈和兩個輕鏈的抗體相同或相似的結合和/或功能。

【0090】本文所描述的抗體和其他結合分子（即抗體的表位結合片段和抗體衍生物）的重鏈和輕鏈可變區（分別為V_H和V_L）負責LTβR識別和結合，而重鏈和輕鏈恒定區介導免疫球蛋白與宿主組織或因子的結合，包括免疫系統的多種細胞（例如，效應細胞）和經典補體系統的第一組分（C1q）。在輕鏈和重鏈中，可變區（V）和恒定區（C）由約12個或更多個胺基酸的「J」區連接，重鏈還包括約10個以上胺基酸的「D」區（一般參見Fundamental Immunology [基礎免

疫學] 第7章 (Paul, W., 編輯, 第2版 Raven Press, 紐約 (1989), 特此藉由引用將其全部併入)。每個輕鏈/重鏈對的可變區形成抗體結合位點, 使得完整的免疫球蛋白具有兩個結合位點。

【0091】如本文所描述的LT β R抗體和其他LT β R結合蛋白的V_H和V_L區進一步細分為高變區, 稱為「互補決定區」或「CDR」, 其散佈在更保守序列的區域內, 該區域稱為「框架區」(FR)。重鏈和輕鏈的一或多個可變區CDR內的一或多個殘基形成與抗原(例如LT β R)相互作用的結合結構域。下文更詳細地描述了本揭露之LT β R抗體和結合蛋白的示例性V_H和V_L結構域序列以及V_H和V_L CDR序列。

【0092】在一個實施方式中, 本揭露之促效劑LT β R結合蛋白係LT β R抗體的表位結合片段。如本文所用, 術語「片段」、「區域」、「部分」和「結構域」通常旨在係同義詞, 除非它們的使用上下文另有說明。例如, 可以藉由完整親本抗體的蛋白酶切割來獲得表現出LT β R結合能力的抗體片段(例如, Fab和(Fab')₂片段)。可替代地, LT β R抗體的表位結合片段係胺基酸序列, 其包含這樣的親本抗體的一部分胺基酸序列。本揭露所涵蓋的示例性LT β R結合片段包括但不限於(i) Fab'或Fab片段, 其係包含如上所述之VL、VH、CL和CH1結構域的單價片段; (ii) F(ab')₂片段, 其係包含藉由鉸鏈區的二硫鍵連接的兩個Fab片段的二價片段; (iii) 基本上由VH和CH1結構域組成的Fd片段; (iv) 基本上由VL和VH結構域組成的Fv片段; (v) 單個結構域抗體或dAb片段(Ward等人「Binding Activities Of A Repertoire Of Single Immunoglobulin Variable Domains Secreted From Escherichia coli [大腸桿菌分泌的單個免疫球蛋白可變結構域的庫的結合活性],」*Nature* [自然] 341 :544-546 (1989), 特此藉由引用將其全部併入), 其基本上由VH或VL結構域(或VH或VL的表位結合部分)組成, 也被稱為結構域抗體或奈米抗體(Holt等人「Domain Antibodies: Proteins For Therapy [結構域抗體: 治療用蛋白質],」

Trends Biotechnol.[生物技術趨勢] 21(11):484-490 (2003); Revets等人「Nanobodies As Novel Agents For Cancer Therapy [奈米抗體作為癌症治療的新型藥物],」*Expert Opin. Biol. Ther.*[生物治療專家觀點] 5(1):111-124 (2005), 特此藉由引用將其全部併入); 和 (vi) 分離的互補決定區 (CDR)。

【0093】 本揭露之促效劑LT β R表位結合片段可以包含如本文揭露的LT β R抗體之1、2、3、4、5或全部6個CDR結構域。在一個實施方式中，LT β R抗體的表位結合片段包含，基本上由，或由親本LT β R抗體的30至100個胺基酸殘基、或50至150個胺基酸殘基、或70至200個胺基酸殘基組成。在一個實施方式中，LT β R抗體的表位結合片段的長度為LT β R抗體長度的至少40%、50%、60%、70%、80%、90%或95%。在一個實施方式中，本揭露之LT β R表位結合片段引發與該片段來源的LT β R抗體相同或相似的活性。在一個實施方式中，如本文所描述的促效劑LT β R表位結合片段和LT β R抗體引發可檢測的LT β R結合活性並誘導LT β R傳訊，如本文揭露的。

【0094】 LT β R抗體的表位結合片段可以使用熟悉該項技術者已知的常規技術獲得。例如，促效劑LT β R F(ab')₂片段可以藉由用胃蛋白酶處理促效劑LT β R抗體而產生。可以處理所得LT β R F(ab')₂片段以還原二硫鍵以產生LT β R Fab'片段。促效劑LT β R Fab片段可以藉由用木瓜酶處理促效劑LT β R抗體來獲得，LT β R Fab'片段可以藉由胃蛋白酶消化促效劑LT β R抗體來獲得。促效劑LT β R Fab'片段可以藉由用還原劑如二硫蘇糖醇處理促效劑LT β R F(ab')₂片段來獲得。LT β R結合片段也可以藉由在重組細胞中表現編碼這樣的片段的核酸而產生（參見例如，Evans等人「Rapid Expression Of An Anti-Human C5 Chimeric Fab Utilizing A Vector That Replicates In COS And 293 Cells [利用在COS和293細胞中複製的載體快速表現抗人C5嵌合Fab],」*J. Immunol. Meth.*[免疫學方法雜誌] 184:123-38 (1995), 特此藉由引用將其全部併入)。例如，編碼LT β R F(ab')₂片段一部分的嵌

合基因可以包括編碼重鏈的CH1結構域和鉸鏈區的DNA序列，然後係翻譯終止密碼子以產生這種截短的抗體片段分子。可以以與抗體相同的方式容易地篩選能夠與LT β R的所需表位結合的合適片段的效用。本揭露之LT β R抗體及其表位結合片段係「分離的」，以便存在於不同於其產生或將天然存在的物理環境中。

【0095】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白為抗體衍生物。促效劑LT β R抗體衍生物包括含有促效劑LT β R抗體的至少一個表位結合結構域的蛋白質或多肽，其通常使用重組技術形成。促效劑LT β R抗體衍生物也可以或可替代地通過親本LT β R抗體或其部分的化學修飾而獲得。促效劑LT β R抗體衍生物包含與該親本抗體或親本抗體的相關部分的胺基酸序列基本相似的胺基酸序列，例如與該親本LT β R抗體或其相關部分相差小於30%、小於20%、小於10%或小於5%，或與該親本分子或其相關部分相差10個胺基酸殘基，或相差少於10、9、8、7、6、5、4、3或2個胺基酸殘基。

【0096】 本揭露之示例性促效劑LT β R抗體衍生物係單鏈Fv (scFv)。促效劑LT β R scFv由Fv片段的兩個結構域，即V_L區和V_H區形成的，該等結構域可能由單獨的基因編碼。使用重組方法，藉由柔性連接基（通常為約10、12、15個或更多個胺基酸殘基）連接這樣的基因序列或其編碼cDNA，使它們能夠製成單個蛋白質鏈，其中V_L和V_H區結合形成單價表位結合蛋白（參見例如，Bird等人「Single-Chain Antigen-Binding Proteins [單鏈抗原結合蛋白],」 *Science* [科學] 242:423-426 (1988)；和Huston等人「Protein Engineering Of Antibody Binding Sites: Recovery Of Specific Activity In An Anti-Digoxin Single-Chain Fv Analogue Produced In *Escherichia coli* [抗體結合位點的蛋白質工程：在大腸桿菌中產生的抗地高辛單鏈Fv類似物中比活性的恢復],」 *Proc. Natl. Acad. Sci. (U.S.A.)*[美國國家科學院院刊] 85:5879-5883 (1988)，特此藉由引用將其全部併入）。

【0097】 本揭露之另一種示例性促效劑LT β R抗體衍生物係雙特異性scFv。

雙特異性LT β R scFv可以藉由使用柔性連接基形成，該柔性連接基使不同單個多肽鏈的V_L和V_H區（每個具有不同的表位結合特異性）聯繫在一起。

【0098】 在另一個實施方式中，本揭露之促效劑LT β R抗體衍生物係二價或雙價單鏈可變片段，藉由將兩個scFv串聯連接在一起來工程化（即串聯scFv）或使它們二聚化形成雙特異抗體（Holliger等人「『Diabodies[雙特異抗體]』: Small Bivalent And Bispecific Antibody Fragments [小的雙價和雙特異性抗體片段],」 Proc. Natl. Acad. Sci. (U.S.A.)[美國國家科學院院刊] 90(14), 6444-8 (1993)；特此藉由引用將其全部併入）。根據本實施方式，雙價串聯scFv或雙特異抗體中的每個scFv可為相同的，即識別相同的LT β R靶表位，或者可為不同的，即識別和結合不同的靶表位。在又另一個實施方式中，該促效劑LT β R抗體衍生物係三抗體，即三價單鏈可變片段，藉由以串聯或三聚體形式將三個scFv連接在一起以形成三抗體來工程化。根據本實施方式，三抗體中的每個scFv可為相同的，即識別相同的靶表位，或者可為不同的，即識別和結合不同的靶表位。在另一個實施方式中，該促效劑LT β R抗體衍生物係四個單鏈可變片段的四抗體，其中每個scFv識別相同或不同的靶表位。在另一個實施方式中，該促效劑LT β R抗體衍生物係「線性抗體」，其係包含一對串聯Fd片段（VH-CH1-VH-CH1）的抗體，其與互補的輕鏈多肽一起形成一對抗原結合區（參見Zapata等人 *Protein Eng.*[蛋白質工程] 8(10): 1057-1062 (1995)，特此藉由引用將其全部併入）。在另一個實施方式中，該促效劑LT β R抗體衍生物係微抗體，包含與CH3區耦合的單鏈Fv區（即scFv-CH3）。在另一個實施方式中，該促效劑LT β R抗體衍生物係修飾的結構域抗體，例如，修飾的單個VL或VH結構域或藉由肽連接基連接的兩個或更多個VH結構域（參見例如，Ward等人, *Nature* [自然], 341:544-546 (1989)，特此藉由引用將其全部併入）；大抗體，即與Fc區融合的兩個scFv（參見例如，Fredericks等人, *Protein Engineering, Design & Selection* [蛋白質工程化、設計和選擇], 17:95-106 (2004)和

Powers等人, J. Immunol. Methods [免疫學方法雜誌], 251:123-135 (2001), 特此藉由引用將其全部併入); 或肽體(附接到Fc區的一或多個肽, 參見Feige的PCT申請公開案號WO 00/024782, 特此藉由引用將其全部併入)。在另一個實施方式中, 該促效劑LT β R抗體衍生物係免疫球蛋白融合蛋白, 其包含與鉸鏈區多肽和一或多個免疫球蛋白恒定區偶合的促效劑LT β R結合結構域(即, 包含一或多個重鏈和/或輕鏈CDR的多肽, 如本文所描述的)(參見例如, 美國專利申請公開案號20030133939, 特此藉由引用將其全部併入)。示例性免疫球蛋白融合蛋白形式包括但不限於IgG-scFv、IgG-Fab、2scFv-IgG、4scFv-IgG、VH-IgG、IgG-VH和Fab-scFv-Fc。

【0099】本揭露之另一種示例性促效劑LT β R抗體衍生物係多特異性結合抗體, 例如雙特異性或三特異性結合蛋白。本揭露之多特異性促效劑LT β R結合蛋白包含結合LT β R並與一或多個額外結合結構域偶合的第一結合結構域, 其中每個額外結合結構域結合非LT β R的靶部分。本揭露之示例性促效劑LT β R多特異性結合蛋白係雙特異性促效劑LT β R結合蛋白, 其包含LT β R結合結構域和腫瘤相關抗原結合結構域。雙特異性促效劑LT β R結合蛋白之示例性LT β R結合結構域包括來自本文揭露的任一種LT β R抗體的結合結構域。在一個實施方式中, 雙特異性促效劑LT β R結合蛋白包含LT β R結合結構域, 該LT β R結合結構域結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R富含半胱胺酸的結構域4 (CRD4)的一或多個胺基酸殘基。該雙特異性促效劑結合蛋白不抑制LIGHT與LT β R結合, 而且不抑制LT1 α 2 β 與LT β R結合。

【0100】根據本揭露, 促效劑LT β R結合蛋白為人促效劑LT β R結合蛋白。人促效劑LT β R結合蛋白包含可變區和恒定區或結構域, 其基本上對應於本領域已知的人種系免疫球蛋白序列, 包括例如Kabat等人(1991)所描述的那些。本文揭露的人促效劑LT β R結合蛋白可以包括非人種系免疫球蛋白序列編碼的胺基酸

殘基（例如，藉由體外隨機或位點特異性誘變或藉由體內體細胞突變引入的突變），例如在CDR中，特別是CDR3。本揭露之人促效劑LT β R結合蛋白可以具有至少一個、兩個、三個、四個、五個或更多個被非人種系免疫球蛋白序列編碼的胺基酸殘基替換的位置。本文所用的人促效劑結合蛋白的定義還考慮了完全人抗體，其包括非人工和/或非基因改變的人抗體序列，因為該等可以藉由使用本領域已知的技術或系統（例如，噬菌體展示技術或轉基因小鼠技術，包括但不限於XenoMouse[®]，其是能夠產生人抗體的轉基因小鼠）衍生。

【0101】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白為IgG同種型。同種型的選擇通常將由所期望的效應物功能來指導，例如抗體依賴性細胞毒性（ADCC）誘導。示例性IgG同種型係IgG1、IgG2、IgG3和IgG4。在一個實施方式中，本揭露之促效劑LT β R結合蛋白為IgG1同種型。在一個實施方式中，本揭露之促效劑LT β R結合蛋白為IgG2同種型。

【0102】 根據本揭露之所有方面，本文揭露的示例性促效劑LT β R結合蛋白之結合結構域包含一或多個VH和VL CDR，其可以使用本領域已知的任一種標準方法來描述，包括但不限於Kabat編號方案（Kabat等人, Sequences of Proteins of Immunological Interest [免疫學感興趣的蛋白質序列], 第5版, U.S. Dept. of Health and Human Services [美國衛生與公眾服務部], NIH (1991)）、Chothia編號方案（Chothia等人, J. Mol. Biol.[分子生物學雜誌] 196: 901-917 (1987)和Al-Lazikani等人, J. Mol. Biol.[分子生物學雜誌] 273: 927-948 (1997)，特此藉由引用將其全部併入）、Abhinandan編號方案（Abhinandan等人, Mol. Immunol.[分子免疫學] 45: 3832-3839 (2008)，特此藉由引用將其全部併入）、免疫遺傳學（IMGT）數據庫編號方案（Giudicelli等人, Nucl. Acids Res.[核酸研究] 34: D781-784 (2006)和Lefranc等人, Dev. Comp. Immunol.[發育和比較免疫學] 27: 55-77 (2003)，特此藉由引用將其全部併入）、Aho編號方案（Honegger等人, J. Mol. Biol.[分子生物

學雜誌] 309: 657-670 (2001)，特此藉由引用將其全部併入) 和Contact編號方案 (MacCallum等人, J. Mol. Biol.[分子生物學雜誌] 262 732-745 (1996)，特此藉由引用將其全部併入)。根據每個系統，包含CDR的VH和VL區的殘基在下表1中提供。

[表1].根據已知編號方案的VH和VL CDR殘基

環	Kabat	AbM	Chothia	Contact	IMGT
L1	L24-L34	L24-L34	L26-L32	L30-L36	L27-L32
L2	L50-L56	L50-L56	L50-L52	L46-L55	L50-L51
L3	L89-L97	L89-L97	L91-L96	L89-L96	L89-L97
H1	H31-H35B (Kabat編號)	H26-H35B	H26-H32...34	H30-H35B	H26-H35B
H1	H31-H35 (Chothia編號)	H26-H35	H26-H32	H30-H35	H26-H33
H2	H50-H65	H50-H58	H52-H56	H47-H58	H51-H56
H3	H95-H102	H95-H102	H96-H101	H93-H101	H93-H102

【0103】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含表4、8和12中提供的重鏈可變區序列中之任一個的HCDR1、HCDR2和HCDR3，以及表4、8和12中也提供的相應輕鏈可變區的LCDR1、LCDR2和LCDR3，其中CDR由Kabat編號方案定義。在另一個實施方式中，本揭露之促效劑LTβR結合蛋白包含表4、8和12中提供的重鏈可變區序列中之任一個的HCDR1、HCDR2和HCDR3，以及表4、8和12中也提供的相應輕鏈可變區的LCDR1、LCDR2和LCDR3，其中CDR由Chothia編號方案定義。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含表4、8和12中提供的重鏈可變區序列中之任一個的HCDR1、HCDR2和HCDR3，以及表4、8和12中提供的相應輕鏈可變區的LCDR1、LCDR2和LCDR3，其中CDR由AbM編號方案定義。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含表4、8和12中提供的重鏈可變區序列中之任一個的HCDR1、HCDR2和

HCDR3，以及表4、8和12中也提供的相應輕鏈可變區的LCDR1、LCDR2和LCDR3，其中CDR由IMGT編號方案定義。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含表4、8和12中提供的重鏈可變區序列中之任一個的HCDR1、HCDR2和HCDR3，以及表4、8和12中也提供的相應輕鏈可變區的LCDR1、LCDR2和LCDR3，其中CDR由Contact編號方案定義。在一個實施方式中，該促效劑LT β R結合蛋白為抗體。在一個實施方式中，該促效劑LT β R結合蛋白為雙特異性抗體。

結合CRD4的LT β R促效劑結合蛋白

【0104】在一個實施方式中，本揭露之促效劑LT β R結合蛋白與包含LT β R的CRD4殘基的表位結合。LT β R的CRD4跨越SEQ ID NO: 4 (LT β R ECD) 的殘基139-181，其對應於SEQ ID NO: 1 (全長LT β R) 的殘基169-211。在一個實施方式中，本文所描述的促效劑LT β R結合蛋白與包含LT β R的胞外結構域 (SEQ ID NO: 4) (SEQ ID NO: 1的殘基197-209) 的位置168-179處的一或多個CRD4殘基的表位結合，如藉由HDX MS確定的。在一個實施方式中，本揭露之促效劑LT β R結合蛋白與包含LT β R CRD4殘基的表位結合，並且還與CRD4外的一或多個殘基結合。例如，在一個實施方式中，該促效劑LT β R結合蛋白與包含LT β R的CRD4殘基和相鄰CRD3殘基的表位結合。LT β R的CRD3包含SEQ ID NO: 4的殘基95-138，其對應於SEQ ID NO: 1之全長LT β R的殘基125-168。

【0105】在一個實施方式中，本揭露之促效劑LT β R結合蛋白與LT β R的CRD4內的LT β R表位結合，而不與如本文定義的CRD4外的LT β R區域結合。換句話說，在一個實施方式中，該促效劑LT β R結合蛋白與由LT β R的CRD4內的殘基組成的表位結合。

【0106】促效劑LT β R結合蛋白與LT β R的CRD4結合激動受體傳訊，並且不抑制內源性LT β R配體 (即LIGHT或LT α 1 β 2) 與受體結合。在一些實施方式中，具有該等特性的促效劑LT β R結合蛋白係抗體。本文揭露了具有該等功能特徵的

示例性促效劑LTβR抗體（參見表2-4和6-8）。在一些實施方式中，具有該等特性的促效劑LTβR結合蛋白係雙特異性結合蛋白。具有該等功能特徵的示例性促效劑LTβR雙特異性結合蛋白包含來自本文揭露的示例性促效劑LTβR抗體的LTβR結合結構域。

【0107】 根據本揭露，具有該等功能特性的促效劑LTβR結合蛋白，即結合LTβR的CRD4殘基且不阻斷LIGHT與LTβR結合或LTα1β2與LTβR結合的結合蛋白，藉由其共用的重鏈可變區（V_H）CDR結構定義。該等促效劑LTβR結合蛋白可以藉由其共用的輕鏈可變區（V_L）CDR結構進一步定義。這種共用的CDR結構，表現為共有的V_H CDR和V_L CDR序列，來源於本文揭露的示例性促效劑LTβR結合蛋白的V_H和V_L結構域的比對（表4），其 (i) 具有上述功能特徵，以及 (ii) 包含分別與LTβR結合蛋白LIBC219081和LIBC 218979的V_H和V_L胺基酸序列具有至少90%序列同一性的V_H和V_L胺基酸序列。

【0108】 因此，在一個實施方式中，本揭露之促效劑LTβR結合蛋白，其 (i) 結合LTβR CRD4的殘基和 (ii) 不阻斷LIGHT與LTβR結合，並且不阻斷LTα1β2與LTβR結合，包含由以下定義的共用V_H CDR結構：HCDR1胺基酸序列：X₁YX₃MX₅（SEQ ID NO: 5），其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺基酸序列：X₁IX₃YDX₆X₇X₈X₉Y X₁₁X₁₂DSVKG（SEQ ID NO: 6），其中X₁為A或V；X₃為W或R；X₆為E或G；X₇為S、R或T；X₈為N或K；X₉為K、R或Q；X₁₁為H或Y；並且X₁₂為A或E；以及HCDR3胺基酸序列：X₁RX₃X₄X₅X₆X₇X₈X₉YYGX₁₃X₁₄V（SEQ ID NO: 7），其中X₁為D或E；X₃為V、G或I；X₄為V、P或A；X₅為A、Y或G；X₆為R、A、G或H；X₇為P或G；X₈為G、N、D、Y、A或H；X₉為Y、T或F；X₁₃為L或M；並且X₁₄為D或A。在一些實施方式中，該促效劑LTβR結合蛋白係抗體。在一些實施方式中，該促效劑LTβR結合蛋白係雙特異性結合蛋白。

【0109】 示例性促效劑LTβR結合蛋白（例如，抗體或雙特異性結合蛋白）的重鏈CDR序列在下表2中提供，其結合LTβR的CRD4，不阻斷LIGHT或LTα1β2結合或活性，並且包含SEQ ID NO: 5的HCDR1、SEQ ID NO: 6的HCDR2和SEQ ID NO: 7的HCDR3。

[表2]：LTβR CRD4結合物的重鏈CDR序列，其與LIBC219081和LIBC218979的Fv結構域具有90%序列同一性

LIBC 編號	HCDR1		HCDR2		HCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
共有的	X ₁ YX ₃ MX ₅ X ₁ 為S、N； X ₃ 為G、A、D X ₅ 為H、Y	5	X ₁ IX ₃ YDX ₆ X ₇ X ₈ X ₉ Y X ₁₁ X ₁₂ DSVKG X ₁ 為A、V X ₃ 為W、R X ₆ 為E、G X ₇ 為S、R、T X ₈ 為N、K X ₉ 為K、R、Q X ₁₁ 為H、Y X ₁₂ 為A、E	6	X ₁ RX ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ YYGX ₁₃ X ₁₄ V X ₁ 為D、E X ₃ 為V、I、G X ₄ 為V、A、P X ₅ 為A、G、Y X ₆ 為R、A、H、G X ₇ 為P、G X ₈ 為G、N、D、Y、A、H X ₉ 為Y、F、T X ₁₃ 為L、M X ₁₄ 為D、A	7
219081 (19325)	SYAMH	8	VIWYDGSNQYYADSVKG	9	DRVAAHPAYYYGLDV	10
218979 (19319)	SYGMH	11	VIWYDGSNKYYADSVKG	12	ERIAAAPYYYYGMDV	13
1318341	SYAMH	14	VIWYDGTNKYYADSVKG	15	DRVAARPDYYYYGMDV	16
1318409	SYAMH	17	VIWYDGSNKYYADSVKG	18	DRVVARPDYYYYGMDV	19
1318412	SYAMH	20	VIWYDGRKRYYADSVKG	21	DRIAARPNYYYYGLDV	22
1318738	SYDMH	23	VIRYDGSNKYYEDSVKG	24	ERGPYGGNTYYGMDV	25
1319003	SYGMH	26	VIWYDGRKRYYADSVKG	27	DRIAARPNYYYYGLDV	28

LIBC 編號	HCDR1		HCDR2		HCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
1319078	SYAMH	29	VIWYDGSNKYYADSVKG	30	DRVAARPNYYYGMAV	31
1319182	SYAMH	32	VIWYDGSNKYYADSVKG	33	DRVVARPDYYYGMDV	34
1319275	SYAMH	35	VIWYDGSNKYYEDSVKG	36	DRVAARPNFYYGMDV	37
1319390	SYAMH	38	VIWYDGSNKYYEDSVKG	39	DRVAARPNFYYGMDV	40
1319499	NYGMY	41	VIWYDESNKYYADSVKG	42	DRIAGRPGYYYGMDV	43
1319908	SYAMH	44	VIWYDGRKRYADSVKG	45	DRIAARPNYYYGLDV	46
1318496	SYAMH	47	AIWYDGSNKYHADSVKG	48	DRIAARPNYYYGMDV	49
1320038	SYAMH	50	AIWYDGSNKYHADSVKG	51	DRIAARPNYYYGMDV	52
1308929	SYAMH	53	VIWYDGSNKYYADSVKG	54	DRVAARPHYYYGLDV	55
1309633	SYAMH	56	VIWYDGSNKYYADSVKG	57	DRVAARPHYYYGLDV	58
1309682	SYAMH	59	VIWYDGSNKYYADSVKG	60	DRVAARPHYYYGLDV	61

【0110】 在一個實施方式中，該促效劑LTβR結合蛋白，其 (i) 結合LTβR CRD4的殘基和 (ii) 不阻斷LIGHT與LTβR結合，並且不阻斷LTα1β2與LTβR結合，包含由以下定義的共用V_L CDR結構：LCDR1胺基酸序列：SGDX₄LPX₇X₈YX₁₀Y（SEQ ID NO: 62），其中X₄為A或T；X₇為E、K、Q、D或N；X₈為Q或H；並且X₁₀為A或T；LCDR2胺基酸序列：KDNERPS（SEQ ID NO: 63）；以及LCDR3胺基酸序列：QSX₃DX₅SX₇X₈YX₁₀X₁₁（SEQ ID NO: 64），其中X₃為A或T；X₅為S、G或N；X₇為G或A；X₈為T、S或A；X₁₀為V或M；並且X₁₁為I或V。

【0111】 下表3中提供了示例性促效劑LTβR結合蛋白的輕鏈CDR序列，其結合LTβR的CRD4，不阻斷LIGHT或LTα1β2結合或活性，並且包含SEQ ID NO: 62的LCDR1、SEQ ID NO: 63的LCDR2和SEQ ID NO: 64的LCDR3。

[表3]：示例性LTβR CRD4結合物的輕鏈CDR，其與LIBC219081和LIBC218979的Fv結構域具有90%序列同一性

LIBC 編號	LCDR1		LCDR2		LCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
共有的	SGDX ₄ LPX ₇ X ₈ YX ₁₀ Y X ₄ 為A、T X ₇ 為E、K、Q、D、N X ₈ 為Q、H X ₁₀ 為A、T	62	KDNERPS	63	Q SX ₃ DX ₅ SX ₇ X ₈ YX ₁₀ X ₁₁ X ₃ 為A、T X ₅ 為S、G、N X ₇ 為G、A X ₈ 為T、S、A X ₁₀ 為V、M X ₁₁ 為I、V	64
219081 (19325)	SGDALPNHYAY	65	KDNERPS	66	QSADSSGSYVI	67
218979 (19319)	SGDALPKHYAY	68	KDNERPS	69	QSADNTGSYMV	70
1318341	SGDALPDHYTY	71	KDNERPS	72	QSADSSGAYVI	73
1318409	SGDALPQHYTY	74	KDNERPS	75	QSADGSGTYVV	76
1318412	SGDTLPEHYTY	77	KDNERPS	78	QSADSSGAYVV	79
1318738	SGDALPKHYAY	80	KDNERPS	81	QSTDSSATYVV	82
1319003	SGDTLPDHYTY	83	KDNERPS	84	QSADSSGAYVV	85
1319078	SGDTLPNHYTY	86	KDNERPS	87	QSADSSGTYVL	88
1319182	SGDTLPQHYTY	89	KDNERPS	90	QSADSSGSYVV	91
1319275	SGDALPKHYAY	92	KDNERPS	93	QSADSSGTYVV	94
1319390	SGDALPKHYAY	95	KDNERPS	96	QSADSSGTYVV	97
1319499	SGDALPKQYAY	98	KDNERPS	99	QSADSSGAYVV	100
1319908	SGDTLPEHYTY	101	KDNERPS	102	QSADSSGAYVV	103
1318496	SGDTLPNHYTY	104	KDNERPS	105	QSADSSGSYVV	106
1320038	SGDTLPNHYTY	107	KDNERPS	108	QSADSSGSYVV	109
1308929	SGDALPNHYAY	110	KDNERPS	111	QSADSSGSYVV	112
1309633	SGDALPNQYAY	113	KDNERPS	114	QSADSSGSYVV	115
1309682	SGDALPNQYAY	116	KDNERPS	117	QSADSSGSYVV	118

【0112】 在一個實施方式中，促效劑LTβR結合蛋白，其結合人LTβR CRD4

的殘基和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC219081的VH和VL胺基酸序列（分別為SEQ ID NO: 121和122）具有至少80%序列同一性的VH和VL胺基酸序列的結合蛋白。在一個實施方式中，促效劑LT β R結合蛋白，其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC218979的VH和VL胺基酸序列（分別為SEQ ID NO: 123和124）具有至少80%序列同一性的VH和VL胺基酸序列的結合蛋白。在一個實施方式中，促效劑LT β R結合蛋白，其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC219081（分別為SEQ ID NO: 121和122）和LIBC218979（分別為SEQ ID NO: 123和124）的VH和VL胺基酸序列具有至少80%序列同一性的VH和VL胺基酸序列的結合蛋白。

【0113】 在一個實施方式中，促效劑LT β R結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合或 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC219081的VH和VL胺基酸序列（分別為SEQ ID NO: 121和122）具有至少85%序列同一性的VH和VL胺基酸序列的結合蛋白。在一個實施方式中，促效劑LT β R結合蛋白，其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC218979的VH和VL胺基酸序列（分別為SEQ ID NO: 123和124）具有至少85%序列同一性的VH和VL胺基酸序列的結合蛋白。在一個實施方式中，促效劑LT β R結合蛋白，其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些具有分別與LT β R結合蛋白LIBC219081（分別為SEQ ID NO: 121和122）和LIBC218979（分別為SEQ ID NO: 123和124）的VH和VL胺基酸序列具有至少85%

序列同一性的VH和VL胺基酸序列的結合蛋白。

【0114】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包括那些具有分別與LTβR結合蛋白LIBC219081和LIBC218979的VH和VL胺基酸序列具有至少90%序列同一性的VH和VL胺基酸序列的結合蛋白。因此，在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 121之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。與SEQ ID NO: 121和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的示例性VH胺基酸序列提供在下表4中。

【0115】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包括那些包含與SEQ ID NO: 121之胺基酸序列具有至少90%序列同一性的VH胺基酸序列的結合蛋白。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。與SEQ ID NO: 121和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的示例性VH胺基酸序列提供在下表4中。

【0116】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻

斷LT α 1 β 2與LT β R結合，包括那些包含與SEQ ID NO: 122之胺基酸序列具有至少90%序列同一性的VL胺基酸序列的結合蛋白。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 122之胺基酸序列和SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。與SEQ ID NO: 122和SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的示例性VL胺基酸序列提供在下表4中。

【0117】 在一個實施方式中，促效劑LT β R結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含與SEQ ID NO: 121之胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 121之胺基酸序列具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少95%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 121之胺基酸序列具有至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少98%序列同一性的VL胺基酸序列。

【0118】 在一個實施方式中，促效劑LT β R結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含與SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 123之胺基酸序列具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 124之胺基酸序列具有至少95%序列同一性的VL胺基酸序列。在一個

個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 123之胺基酸序列具有至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 124之胺基酸序列具有至少98%序列同一性的VL胺基酸序列。

【0119】 在一個實施方式中，促效劑LT β R結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列和SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列和SEQ ID NO: 124之胺基酸序列具有至少95%序列同一性的VL胺基酸序列。在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列和SEQ ID NO: 124之胺基酸序列具有至少98%序列同一性的VL胺基酸序列。

【0120】 在一個實施方式中，促效劑LT β R結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含與SEQ ID NO: 121或SEQ ID NO: 123的VH胺基酸序列具有至少90%序列同一性的VH胺基酸序列並且包含如下HCDR1胺基酸序列：X₁YX₃MX₅（SEQ ID NO: 5），其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺基酸序列：X₁IX₃YDX₆X₇X₈X₉Y X₁₁X₁₂DSVKG（SEQ ID NO: 6），其中X₁為A或V；X₃為W或R；X₆為E或G；X₇為S、R或T；X₈為N或K；X₉為K、R或Q；X₁₁為H或Y；並且X₁₂為A或E；以及HCDR3胺基酸序列：X₁RX₃X₄X₅X₆

X₇X₈X₉YYGX₁₃X₁₄V (SEQ ID NO: 7)，其中X₁為D或E；X₃為V、G或I；X₄為V、P或A；X₅為A、Y或G；X₆為R、A、G或H；X₇為P或G；X₈為G、N、D、Y、A或H；X₉為Y、T或F；X₁₃為L或M；並且X₁₄為D或A。與SEQ ID NO: 121或SEQ ID NO: 123之胺基酸序列的VH具有90%序列同一性和包含SEQ ID NO: 5、6和7的HCDR序列的促效劑LTβR結合蛋白的示例性VH胺基酸序列提供在下表4中。

【0121】該等促效劑LTβR結合蛋白進一步可以包含與SEQ ID NO: 122或SEQ ID NO: 124的VL胺基酸序列具有至少90%序列同一性的VL胺基酸序列並且包含以下LCDR1胺基酸序列：SGDX₄LPX₇X₈YX₁₀Y (SEQ ID NO: 62)，其中X₄為A或T；X₇為E、K、Q、D或N；X₈為Q或H；並且X₁₀為A或T；LCDR2胺基酸序列：KDNERPS (SEQ ID NO: 63)；以及LCDR3胺基酸序列：QSX₃DX₅SX₇X₈YX₁₀X₁₁ (SEQ ID NO: 64)，其中X₃為A或T；X₅為S、G或N；X₇為G或A；X₈為T、S或A；X₁₀為V或M；並且X₁₁為I或V。與SEQ ID NO: 122或SEQ ID NO: 124之胺基酸序列的VL具有90%序列同一性和包含SEQ ID NO: 62、63和64的LCDR序列的促效劑LTβR結合蛋白的示例性VL胺基酸序列提供在下表4中。

【0122】在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含以下VH胺基酸序列：QVQLVESGGGVVQPGRSLRLSCAASGFTFSX₃₁YX₃₃MX₃₅WVRQAPGKGLEWVAX₅₀IX₅₂YDX₅₅X₅₆X₅₇X₅₈YX₆₀X₆₁DSVKGRFTISRDN SKNTLSLQMNSLRAEDTAVYYCARX₉₉RX₁₀₁X₁₀₂X₁₀₃X₁₀₄X₁₀₅X₁₀₆X₁₀₇YYGX₁₁₁X₁₁₂VWGQGTTVTVSS (SEQ ID NO: 119)，其中X₃₁為S或N；X₃₃為G或A；X₃₅為H或Y；X₅₀為A或V；X₅₂為W或R；X₅₅為E或G；X₅₆為S、R或T；X₅₇為N或K；X₅₈為K、R或Q；X₆₀為H或Y；X₆₁為A或E；X₉₉為D或E；X₁₀₁為V、G或I；X₁₀₂為V、P或A；X₁₀₃為A、Y或G；X₁₀₄為R、A、G或H；X₁₀₆為G、N、D、Y、A或H；X₁₀₇為Y、T或F；X₁₁₁為

L或M；並且X₁₁₂為D或A。

【0123】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷 LTα1β2 與 LTβR 結合，包含以下 VL 胺基酸序列：
SYELTQPPSVSVSPRQTARITCSGDX₂₆LPX₂₉X₃₀YX₃₂YWYQQKPGQAPVLVIY
KDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSX₉₀DX₉₂SX₉₄X₉₅YX₉₇X₉₈FGGGTKLTVLG (SEQ ID NO: 120)，其中X₂₆為A或T；X₂₉為E、K、Q、D或N；X₃₀為Q或H；X₃₂為A或T；X₉₀為A或T；X₉₂為S、G或N；X₉₄為G或A；X₉₅為T、S或A；X₉₇為V或M；並且X₉₈為I或V。

【0124】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含VH，其中該VH包含SEQ ID NO: 119之胺基酸序列，並且與SEQ ID NO: 121的VH胺基酸序列和/或SEQ ID NO: 123的VH胺基酸序列共用至少90%序列同一性。該促效劑LTβR結合蛋白進一步包含VL，其中該VL包含SEQ ID NO: 120之胺基酸序列，並且與SEQ ID NO: 122的VL胺基酸序列和/或SEQ ID NO: 124的VL胺基酸序列共用至少90%序列同一性。

【0125】 在一個實施方式中，促效劑LTβR結合蛋白（例如抗體或雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含VH，其中該VH包含SEQ ID NO: 119之胺基酸序列，並且與SEQ ID NO: 121的VH胺基酸序列和/或SEQ ID NO: 123的VH胺基酸序列共用至少95%序列同一性。該促效劑LTβR結合蛋白進一步包含VL，其中該VL包含SEQ ID NO: 120之胺基酸序列，並且與SEQ ID NO: 122的VL胺基酸序列和/或SEQ ID NO: 124的VL胺基酸序列共用至少95%序列同一性。

【0126】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白，其結合人

LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含可變輕鏈（VL）結構域、可變重鏈（VH）結構域或VL和VH結構域的組合。表4中提供了與LIBC219081和LIBC218979的VH和VL胺基酸序列共用90%序列同一性的示例性促效劑LTβR結合蛋白的VH和VL胺基酸序列。在一些實施方式中，該促效劑LTβR結合蛋白的VH結構域包含表4中提供的VH胺基酸序列中的任一個，或與表4中列出的VH胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%或至少95%相同的胺基酸序列。在一些實施方式中，該促效劑LTβR結合蛋白的VL結構域包含下表4中提供的VL胺基酸序列中的任一個，或與表4中列出的VL胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%、至少95%相同的胺基酸序列。

[表4]：共用90%序列同一性的LTβR CRD4結合蛋白的VH和VL序列

LIBC編號	結構域	序列	SEQ ID
共有的	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSX ₃₁ YX ₃₃ MX ₃₅ WVRQ APGKGLEWVAX ₅₀ IX ₅₂ YDX ₅₅ X ₅₆ X ₅₇ X ₅₈ YX ₆₀ X ₆₁ DSVKGRFTISRDN SKNTLSLQMNSLRAEDTAVYYCARX ₉₉ RX ₁₀₁ X ₁₀₂ X ₁₀₃ X ₁₀₄ X ₁₀₅ X ₁₀₆ X ₁₀₇ YYGX ₁₁₁ X ₁₁₂ VWGQGTTVTVSS	119
	V _L	SYELTQPPSVSVSPRQTARITCSGDX ₂₆ LPX ₂₉ X ₃₀ YX ₃₂ Y WYQQKPGQAPVLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQ AEDEADYYCQSX ₉₀ DX ₉₂ SX ₉₄ X ₉₅ YX ₉₇ X ₉₈ FGGGTKLTVLG	120
219081 19325	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGSNQYYADSVKGRFIISRDN SKNTLYLQMNS LRAEDTAVYYCARDRVAAHPAYYYGLDVWGQGTTVTVSS	121
	V _L	SYELTQPPSVSLSPGQTARITCSGDALPNHYAYWYQQKPGQAPV LVIFKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSA DSSGSYVIFGGGTKLTVLG	122
218979 19319	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPG KGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLSLQMNS LRAEDTAVYYCARERIAAAPYYYYGMDVWGQGTTVTVSS	123

LIBC編號	結構域	序列	SEQ ID
	V _L	SYELTQPPSVSVSPRQTARITCSGDALPKHYAYWYQQKPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQS ADNTGSYMVFGGGTKLTVLG	124
1308929	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLDWVGVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDRVAARPHYYYGLDVWGQGTTVTVSS	125
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPNHYAYWYQQKPGQAP VLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ SADSSGSYVVFSGGGTKLTVLG	126
1318341	V _H	LVQLVESGGGVVQPGRSLRLSCAASGFTFRSYAMHWVRQAPG KGLEWVAVIWYDGTNKYYADSVKGRFTISRDN SKNTLYLQMN TLRADDTAVYFCAKDRVAARPDYYYGMDVWGQGTTVTVSS	127
	V _L	SYELTQPPSVSVSPGQTARIACSGDALPDHYTYWYQQKPGQAP VLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ SADSSGAYVIFGGGTKLTVLG	128
1318409	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKDTLHLQMN SLRAEDMAVYFCAKDRVVARPDYYYGMDVWGQGTTVTVSS	129
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPQHYTYWYQQKPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQS ADGSGTYVVFSGGGTKLTVLG	130
1318412	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGRKRYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCAKDRIAARPNYYYGLDVWGQGTTVTVSS	131
	V _L	SYELIQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPIL VIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSA DSSGAYVVFSGGGTKLTVLG	132
1318738	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYDMHWVRQAPG KGLEWVAVIRYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMNS LRVEDTAVYYCARERGPYGGNTYYGMDVWGQGTTVTVSS	133
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPKHYAYWYQQKPGQAP	134

LIBC編號	結構域	序列	SEQ ID
		VMVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ STDSSATYVVFGGGTKLTVLR	
1319003	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPG KGLEWVAVIWYDGRKRYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDRIAARPNYYYGLDVWGQGTTVTVSS	135
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPDHYTYWYQQRPGQAPIL VIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSA DSSGAYVVFGGGTKLTVLR	136
1319078	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDRVAARPNYYYGMAVWGQGTTVTVSS	137
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQKPGQAPV MVIYKDNERPSGIPERFSGFSSGTTVTLTITGVQAEDEADYYCQS ADSSGTYYVLFGGGTKLTVLG	138
1319182	V _H	QVHLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKDTLHLQMN SLRAEDMAVYFCAKDRVVARPDYYYGMDVWGQGTTVTVSS	139
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPQHYYTYWYQQNPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTISRVAEDEADYYCQS ADSSGSYVVFGGGTKLTVLG	140
1319275	V _H	QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCAKDRVAARPNFYYGMDVWGQGTTVTVSS	141
	V _L	SYELTQPPSVSLSPGHSARITCSGDALPKHYAYWYQQKPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQS ADSSGTYYVVFGGGTKLTVLG	142
1319390	V _H	QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCAKDRVAARPNFYYGMDVWGQGTTVTVSS	143
	V _L	SYELTQPPSVSLSPGHSARITCSGDALPKHYAYWYQQKPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQS	144

LIBC編號	結構域	序列	SEQ ID
		ADSSGTYVVFGGGTKLTVLG	
1319499	V _H	QVQLVESGGGVVQPGRSLRLSCVASGFTFSNYGMYWVRQAPG KGLEWVAVIWYDESNKYYADSVKGRFTISRDKNTLYLQMN SLRAEDTAVYYCARDRIAGRPGYGYGMDVWGQGTTVTVSS	145
	V _L	SYELTQPPSVSVSPGQTARISCSGDALPKQYAYWYQQKPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQS ADSSGAYVVFGGGTKLTVLG	146
1319908	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAVIWYDGRKRYADSVKGRFTISRDNKNTLYLQMN SLRAEDTAVYYCAKDRIAARPNYYYGLDVWGQGTTVTVSS	147
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPIL VIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSA DSSGAYVVFGGGTKLTVLG	148
1318496	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAAIWYDGSNKYHADSVKGRFTISRDNKNTLYLQMN SLRAEDTAVYYCARDRIAARPNYYYGMDVWGQGTTVTVSS	149
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQEPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQS ADSSGSYVVFGGGTKLTVLG	150
1320038	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVAAIWYDGSNKYHADSVKGRFTISRDNKNTLYLQMN SLRAEDTAVYYCARDRIAARPNYYYGMDVWGQGTTVTVSS	151
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQEPGQAPV LVIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQS ADSSGSYVVFGGGTKLTVLG	152
1308929	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPG KGLDWVGVIWYDGSNKYYADSVKGRFTISRDNKNTLYLQMN SLRAEDTAVYYCARDRVAARPHYYYGLDVWGQGTTVTVSS	153
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPNHYAYWYQQKPGQAP VLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ SADSSGSYVVFGGGTKLTVLG	154

LIBC編號	結構域	序列	SEQ ID
1309633	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFRSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDRVAARPHYYYGLDVWGQGTTVTVSS	155
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPNQYAYWYQQKPGQAP VLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ SADSSGSYVVFSGGGTKLTVLG	156
1309682	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFRSYAMHWVRQAPG KGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDRVAARPHYYYGLDVWGQGTTVTVSS	157
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPNQYAYWYQQKPGQAP VLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQ SADSSGSYVVFSGGGTKLTVLG	158

【0127】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白）結合人LTβR CRD4，包括對應於SEQ ID NO: 1的殘基198-209（SEQ ID NO: 4的殘基168-179）的一或多個殘基，並且 (a) 不阻斷LIGHT與LTβR結合和 (b) 不阻斷LTα1β2與LTβR結合。該促效劑LTβR結合蛋白包含V_H，其中該V_H包含與SEQ ID NO: 8的序列具有至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 9的序列具有至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 10的序列具有至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該促效劑LTβR結合蛋白的V_H包含SEQ ID NO: 5的HCDR1序列，SEQ ID NO: 6的HCDR2序列和SEQ ID NO: 7的HCDR3序列。在一個實施方式中，該促效劑LTβR結合蛋白的V_H包含SEQ ID NO: 8的HCDR1序列，SEQ ID NO: 9的HCDR2序列和SEQ ID NO: 10的HCDR3序列。

【0128】 根據前述實施方式，本揭露之促效劑LT β R結合蛋白進一步包含VL，其中該VL包含與SEQ ID NO: 65的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 66的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 67的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 62的LCDR1序列，SEQ ID NO: 63的LCDR2和SEQ ID NO: 64的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 65的LCDR1序列，SEQ ID NO: 66的LCDR2和SEQ ID NO: 67的LCDR3序列。包含該實施方式的VH和VL的示例性LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219081 (BR# 19325 ; 41B2) 的LT β R抗體。

【0129】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白）結合人LT β R CRD4，包括對應於SEQ ID NO: 1的殘基197-209（即SEQ ID NO: 4的殘基167-179）的一或多個殘基，並且 (a) 不阻斷LIGHT與LT β R結合和 (b) 不阻斷LT α 1 β 2與LT β R結合。該LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 11的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 12的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 13的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該LT β R結合蛋白的VH包含SEQ ID NO: 5的HCDR1序列，SEQ ID NO: 6的HCDR2序列和SEQ ID NO: 7的HCDR3序列。在一個實施方式中，該

LT β R結合蛋白的VH包含SEQ ID NO: 11的HCDR1序列, SEQ ID NO: 12的HCDR2序列和SEQ ID NO: 13的HCDR3序列。

【0130】 根據前述實施方式, 本揭露之促效劑LT β R結合蛋白進一步包含VL, 其中該VL包含與SEQ ID NO: 68的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列, 與SEQ ID NO: 69的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列, 以及與SEQ ID NO: 70的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中, 該VL包含SEQ ID NO: 62的LCDR1序列, SEQ ID NO: 63的LCDR2和SEQ ID NO: 64的LCDR3序列。在一個實施方式中, 該VL包含SEQ ID NO: 68的LCDR1序列, SEQ ID NO: 69的LCDR2和SEQ ID NO: 70的LCDR3序列。包含該實施方式的VH和VL的示例性LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218979 (BR#19319; 23E9) 的LT β R抗體。

【0131】 在另一個實施方式中, 本揭露之促效劑LT β R結合蛋白(例如, 促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白), 其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合, 包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合:(i) 分別為SEQ ID NO: 14、SEQ ID NO: 15、SEQ ID NO: 16、SEQ ID NO: 71、SEQ ID NO: 72和SEQ ID NO: 73, (ii) 分別為SEQ ID NO: 17、SEQ ID NO: 18、SEQ ID NO: 19、SEQ ID NO: 74、SEQ ID NO: 75和SEQ ID NO: 76; (iii) 分別為SEQ ID NO: 20、SEQ ID NO: 21、SEQ ID NO: 22、SEQ ID NO: 77、SEQ ID NO: 78和SEQ ID NO: 79; (iv) 分別為SEQ ID NO: 23、SEQ ID NO: 24、SEQ ID NO: 25、SEQ ID NO: 80、SEQ ID NO: 81和SEQ ID NO: 82; (v) 分別為SEQ ID NO: 26、SEQ ID

NO: 27、SEQ ID NO: 28、SEQ ID NO: 83、SEQ ID NO: 84和SEQ ID NO: 85；(vi) 分別為SEQ ID NO: 29、SEQ ID NO: 30、SEQ ID NO: 31、SEQ ID NO: 86、SEQ ID NO: 87和SEQ ID NO: 88；(vii) 分別為SEQ ID NO: 32、SEQ ID NO: 33、SEQ ID NO: 34、SEQ ID NO: 89、SEQ ID NO: 90和SEQ ID NO: 91；(viii) 分別為SEQ ID NO: 35、SEQ ID NO: 36、SEQ ID NO: 37、SEQ ID NO: 92、SEQ ID NO: 93和SEQ ID NO: 94；(vix) 分別為SEQ ID NO: 38、SEQ ID NO: 39、SEQ ID NO: 40、SEQ ID NO: 95、SEQ ID NO: 96和SEQ ID NO: 97；(x) 分別為SEQ ID NO: 41、SEQ ID NO: 42、SEQ ID NO: 43、SEQ ID NO: 98、SEQ ID NO: 99和SEQ ID NO: 100；(xi) 分別為SEQ ID NO: 44、SEQ ID NO: 45、SEQ ID NO: 46、SEQ ID NO: 101、SEQ ID NO: 102和SEQ ID NO: 103；(xii) 分別為SEQ ID NO: 47、SEQ ID NO: 48、SEQ ID NO: 49、SEQ ID NO: 104、SEQ ID NO: 105和SEQ ID NO: 106；(xiii) 分別為SEQ ID NO: 50、SEQ ID NO: 51、SEQ ID NO: 52、SEQ ID NO: 107、SEQ ID NO: 108和SEQ ID NO: 109；(xiv) 分別為SEQ ID NO: 53、SEQ ID NO: 54、SEQ ID NO: 55、SEQ ID NO: 110、SEQ ID NO: 111和SEQ ID NO: 112；(xv) 分別為SEQ ID NO: 56、SEQ ID NO: 57、SEQ ID NO: 58、SEQ ID NO: 113、SEQ ID NO: 114和SEQ ID NO: 115；以及 (xvi) 分別為SEQ ID NO: 59、SEQ ID NO: 60、SEQ ID NO: 61、SEQ ID NO: 116、SEQ ID NO: 117和SEQ ID NO: 118。

【0132】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含選自以下的VH胺基酸序列和VL胺基酸序列：SEQ ID NO: 119的VH胺基酸序列和SEQ ID NO: 120的VL胺基酸序列；SEQ ID NO: 121的VH胺基酸序列和SEQ ID NO: 122的VL胺基酸序列；SEQ ID NO: 123的VH胺基酸序列和SEQ ID NO: 124的VL胺基酸序列；SEQ ID NO: 125的VH胺基酸序列和SEQ ID NO: 126的VL胺基酸序

列；SEQ ID NO: 127的VH胺基酸序列和SEQ ID NO: 128的VL胺基酸序列；SEQ ID NO: 129的VH胺基酸序列和SEQ ID NO: 130的VL胺基酸序列；SEQ ID NO: 131的VH胺基酸序列和SEQ ID NO: 132的VL胺基酸序列；SEQ ID NO: 133的VH胺基酸序列和SEQ ID NO: 134的VL胺基酸序列；SEQ ID NO: 135的VH胺基酸序列和SEQ ID NO: 136的VL胺基酸序列；SEQ ID NO: 137的VH胺基酸序列和SEQ ID NO: 138的VL胺基酸序列；SEQ ID NO: 139的VH胺基酸序列和SEQ ID NO: 140的VL胺基酸序列；SEQ ID NO: 141的VH胺基酸序列和SEQ ID NO: 142的VL胺基酸序列；SEQ ID NO: 143的VH胺基酸序列和SEQ ID NO: 144的VL胺基酸序列；SEQ ID NO: 145的VH胺基酸序列和SEQ ID NO: 146的VL胺基酸序列；SEQ ID NO: 147的VH胺基酸序列和SEQ ID NO: 148的VL胺基酸序列；SEQ ID NO: 149的VH胺基酸序列和SEQ ID NO: 150的VL胺基酸序列；SEQ ID NO: 151的VH胺基酸序列和SEQ ID NO: 152的VL胺基酸序列；SEQ ID NO: 153的VH胺基酸序列和SEQ ID NO: 154的VL胺基酸序列；SEQ ID NO: 155的VH胺基酸序列和SEQ ID NO: 156的VL胺基酸序列；以及SEQ ID NO: 157的VH胺基酸序列和SEQ ID NO: 158的VL胺基酸序列。

【0133】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含如上所述之VH區和/或VL區，並且進一步包含與VH區偶合的一或多個重鏈恒定區和/或與VL區偶合的輕鏈恒定區。例如，在一個實施方式中，該LT β R結合蛋白係Fab，其包含VH和與VL偶合的第一重鏈恒定結構域（CH1）以及輕鏈恒定區（CL）。在另一個實施方式中，該LT β R結合蛋白係F(ab')₂，其包含藉由鉸鏈區偶合的完全抗體的兩個LT β R結合區，其中每個結合區包含VH-CH1和VL-CL。在另一個實施方式中，該LT β R結合蛋白係包含完全輕鏈（VL-CL）和完全重鏈（VH-CH1-

CH2-CH3) 的抗體。

【0134】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含人IgG1重鏈。在另一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含人IgG2重鏈。在一個實施方式中，該人IgG重鏈被修飾以防止或減少與Fcγ受體的相互作用。在一個實施方式中，該人IgG係穩定效應物無功能(SEFL)IgG(Liu等人, *J Biol. Chem.*[生物化學雜誌] 292(5):1876-1883，特此藉由引用將其全部併入)。下表5提供了本揭露之LTβR結合蛋白之示例性輕鏈恒定區和重鏈恒定區的胺基酸序列。

[表5]：示例性LC和HC恒定結構域區

描述	SEQ ID NO:	胺基酸序列
λLC恒定區	299	QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV ETTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS
κLC恒定區	300	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
IgG1 SEFL2 (CH1-Fc)	301	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK

【0135】 本文表9中提供了本揭露之LTβR抗體之示例性胺基酸序列，該抗體結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合。

【0136】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白）與LTβR結合物LIBC219081和LIBC218979競爭結合人LTβR CRD4，以及 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合。

【0137】 根據本揭露，具有該等功能特性的促效劑LTβR結合蛋白，即與LTβR結合物LIBC219081和LIBC218979競爭結合LTβR的CRD4，並且不阻斷LIGHT或LTα1β2與LTβR結合，由其結構相似的VH和VL結構域定義。這種共用的可變區結構，表現為共有的VH和VL CDR序列以及共有的VH和VL序列，來源於本文揭露的示例性促效劑LTβR結合蛋白的比對（參見表6、7和8），其 (i) 具有該等功能特徵以及 (ii) 包含在其各自的整個長度上共用至少90%序列同一性的VH和VL胺基酸序列，即在FR1、CDR1、FR2、CDR2、FR3、CDR3和FR4上從N端到C端。

【0138】 因此，在一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含由以下定義的共用VH CDR結構：HCDR1胺基酸序列：GX₂YMH（SEQ ID NO: 159），其中X₂為Y或F；HCDR2胺基酸序列：WINPNX₆GGTNYAQKFQG（SEQ ID NO: 160），其中X₆為S、N或R；以及HCDR3胺基酸序列：X₁X₂X₃X₄GX₆X₇X₈YYGMDV（SEQ ID NO: 161），其中X₁為D或A；X₂為R或D；X₃為N、S或A；X₄為G或S；X₆為V或W；X₇為Y或不存在；X₈為Y或不存在。下表6中提供了示例性促效劑LTβR結合蛋白的重鏈CDR序列，其結合LTβR CRD4，不阻斷LIGHT與LTβR結

合，不阻斷LTα1β2與LTβR結合，並且包含SEQ ID NO: 159的HCDR1、SEQ ID NO: 160的HCDR2和SEQ ID NO: 161的HCDR3。

【0139】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含分別為SEQ ID NO: 159-161的HCDR 1-3，進一步包含由以下定義的共用VL CDR結構：LCDR1胺基酸序列TGTX4SDVGSYNLVS（SEQ ID NO: 278），其中X₄為T、N或S；LCDR2胺基酸序列EVX₃X₄RPS（SEQ ID NO: 279），其中X₃為T或S且X₄為K或V；以及LCDR3胺基酸序列CSYX₄X₅SX₇TX₉V（SEQ ID NO: 280），其中X₄為A或V；X₅為D或E；X₇為S或K；X₉為L或W。下表7中提供了示例性促效劑LTβR結合蛋白的輕鏈CDR序列，其結合LTβR CRD4，不阻斷LIGHT與LTβR結合，不阻斷LTα1β2與LTβR結合，並且包含SEQ ID NO: 278的LCDR1、SEQ ID NO: 279的LCDR2和SEQ ID NO: 280的LCDR3。

【0140】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含分別為SEQ ID NO: 159-161的HCDR 1-3，進一步包含由以下定義的共用VL CDR結構：LCDR1胺基酸序列SGDX₄LPX₇X₈YX₁₀Y（SEQ ID NO: 308），其中X₄為A或T；X₇為Q、E、N、R或K；X₈為H或Q；X₁₀為V、T或A；LCDR2胺基酸序列KDX₃X₄RPS（SEQ ID NO: 309），其中X₃為N或S；X₄為D或E；以及LCDR3胺基酸序列QSADX₅SGX₈X₉VV（SEQ ID NO: 310），其中X₅為I、N或S；X₈為S、A、I或T；並且X₉為F或Y。下表7中提供了示例性促效劑LTβR結合蛋白的輕鏈CDR序列，其結合LTβR CRD4，不阻斷LIGHT與LTβR結合，不阻斷LTα1β2與LTβR結合，並且包含SEQ ID NO: 308的LCDR1、SEQ ID NO: 309的LCDR2和SEQ ID NO: 310的LCDR3。

[表6].結合人LTβR CRD4且不阻斷LIGHT或LTα1β2與LTβR結合的促效劑LTβR結合蛋白的重鏈CDR序列

LIBC 編號	HCDR1		HCDR2		HCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
共有的 VH進化 枝1	GX ₂ YMH	159	WINPNX ₆ GGTNYAQKFQG	160	X ₁ X ₂ X ₃ X ₄ GX ₆ X ₇ X ₈ YYGMDV	161
	X ₂ 為Y或F		X ₆ 為S、N或R		X ₁ 為D、A	
					X ₂ 為R、D	
					X ₃ 為N、S、A	
					X ₄ 為G、S	
					X ₆ 為V、W	
					X ₇ 為Y、不存在	
					X ₈ 為Y、不存在	
1303255	GYMH	162	WINPNNGGTNYAQKFQG	163	ADNSGWYYYYGMDV	164
1303574	GYMH	165	WINPNNGGTNYAQKFQG	166	ADNSGWYYYYGMDV	167
1303613	GYMH	168	WINPNNGGTNYAQKFQG	169	ADNSGWYYYYGMDV	170
1303507	GYMH	171	WINPNNGGTNYAQKFQG	172	ADNSGWYYYYGMDV	173
1303716	GYMH	174	WINPNNGGTNYAQKFQG	175	ADNSGWYYYYGMDV	176
1308640	GYMH	177	WINPNNGGTNYAQKFQG	178	ADSSGWYYYYGMDV	179
1308591	GFYMH	180	WINPNNGGTNYAQKFQG	181	ADSSGWYYYYGMDV	182
1303446	GYMH	183	WINPNNGGTNYAQKFQG	184	ADNSGWYYYYGMDV	185
1306164	GYMH	186	WINPNSGGTNYAQKFQG	187	DRAGGVYYGMDV	188
1306253	GYMH	189	WINPNRGGTNYAQKFQG	190	DRAGGVYYGMDV	191
1306424	GYMH	192	WINPNRGGTNYAQKFQG	193	DRAGGVYYGMDV	194
共有的 VH進化 枝4	X ₁ YGMH	195	X ₁ IWYDGNNKYYX ₁₂ DSVK	196	DRITX ₅ VRGVTNYGMDV	197
	X ₁ 為A或S		G		X ₅ 為M、R	
			X ₁ 為L或V			
			X ₁₂ 為E或A			
1306053	AYGMH	200	LIWYDGNNKYYADSVKG	198	DRITRVRGVTNYGMDV	199
1306153	AYGMH	200	LIWYDGNNKYYADSVKG	201	DRITRVRGVTNYGMDV	202
1306251	AYGMH	203	LIWYDGNNKYYADSVKG	204	DRITRVRGVTNYGMDV	205
1306674	AYGMH	206	LIWYDGNNKYYADSVKG	207	DRITRVRGVTNYGMDV	208
1307329	AYGMH	209	LIWYDGNNKYYADSVKG	210	DRITRVRGVTNYGMDV	211

LIBC 編號	HCDR1		HCDR2		HCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
1306622	AYGMH	212	LIWYDGNNKYYADSVKG	213	DRITRVRGVTNYGMDV	214
1306800	AYGMH	215	LIWYDGNNKYYADSVKG	216	DRITRVRGVTNYGMDV	217
1306965	AYGMH	218	LIWYDGNNKYYADSVKG	219	DRITRVRGVTNYGMDV	220
1306294	SYGMH	221	VIWYDGNNKYYEDSVKG	222	DRITMVRGVTNYGMDV	223
共有的 VH進化 枝7	SX ₂ AMH X ₂ 為Y或F	224	VIWYX ₅ X ₆ X ₇ NX ₉ FYADSVK G X ₅ 為D、A、N X ₆ 為R、E X ₇ 為N、S X ₉ 為K、N	225	GDX ₃ X ₄ YX ₆ YX ₈ YGX ₁₁ DX ₁₃ X ₃ 為W、R X ₄ 為N、D X ₆ 為S、H、Y X ₈ 為Y、Q、K X ₁₁ 為M、V X ₁₃ 為L、V	226
1307739	SYAMH	227	VIWYDRNNKFYADSVKG	228	GDRDYHYQYGMDV	229
1310489	SYAMH	230	VIWYDRNNKFYADSVKG	231	GDRDYHYQYGMDV	232
1308006	SYAMH	233	VIWYNRNNNFYADSVKG	234	GDRDYYYYYGMDV	235
1308236	SYAMH	236	VIWYNRNNNFYADSVKG	237	GDRDYYYYYGMDV	238
1308563	SYAMH	239	VIWYNRNNNFYADSVKG	240	GDRDYYYYYGMDV	241
1308943	SYAMH	242	VIWYNRNNNFYADSVKG	243	GDRDYYYYYGMDV	244
1318301	SFAMH	245	VIWYAESNKFYADSVKG	246	GDWNYSYKYGVDL	247
1319279	SFAMH	257	VIWYAESNKFYADSVKG	258	GDWNYSYKYGVDL	259
1318394	SYGMH	248	VIWYDRSNKYYADSVKG	249	GISGYRYGTDMDV	250
1318693	SYGMH	251	VIWYDRSNKYYADSVKG	252	GISGYRYGTDMDV	253
1318991	SYGMH	254	VIWYDRSNKYYADSVKG	255	GISGYRYGTDMDV	256
1318188	SDGYFWS	266	FIYFTGITYYNPSLQS	267	VIPGEDAFDI	268
1318198	SDGYFWS	275	FIYFTGITYYNPSLQS	276	VIPGEDAFDI	277
1318253	GFYMH	260	WLNPNNTGGTSYVQKFQG	261	GTGTTAFFDF	262
1318209	SYVMN	263	GISGSDGSTYYADSVKG	264	EEDWNYGFDY	265
1319569	SYDIN	269	WMNPNTGNTGYPQKFQG	270	GGLTMKVVGAGWFDP	271
1307105	SYGMD	272	VISYDGNYKYYADSVKG	273	DDYSTLDY	274

[表7].結合人LTβR CRD4且不阻斷LIGHT或LTα1β2與LTβR結合的促效劑LTβR
結合蛋白的輕鏈CDR序列

LIBC 編號	LCDR1		LCDR2		LCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
共有的 VL進化 枝1	TGTX ₄ SDVGSYNLVS	278	EVX ₃ X ₄ RPS	279	CSYX ₄ X ₅ SX ₇ TX ₉ V	280
	X ₄ 為T、N、S		X ₃ 為S、T		X ₄ 為A、V	
			X ₄ 為K、V		X ₅ 為D、E	
					X ₇ 為S、K	
					X ₉ 為L、W	
1303255	TGTTSDVGSYNLVS	281	EVSKRPS	282	CSYAESSTLV	283
1303574	TGTTSDVGSYNLVS	284	EVSKRPS	285	CSYAESSTLV	286
1303613	TGTTSDVGSYNLVS	287	EVSKRPS	288	CSYAESSTLV	289
1303507	TGTTSDVGSYNLVS	290	EVSKRPS	291	CSYAESSTLV	292
1303716	TGTTSDVGSYNLVS	293	EVSKRPS	294	CSYAESSTLV	295
1308640	TGTSSDVGSYNLVS	296	EVSKRPS	297	CSYADSSTLV	298
1318394	TGTSSDVGSYNLVS	380	EVTVRPS	381	CSYVDSKTWV	382
1318693	TGTSSDVGSYNLVS	383	EVTVRPS	384	CSYVDSKTWV	385
1318991	TGTSSDVGSYNLVS	386	EVTVRPS	387	CSYVDSKTWV	388
1318198	TGTNSDVGSYNLVS	398	EVTVRPS	399	CSYVDSKTWV	400
1308591	TGTSSDVGSYNLVS	302	EVSKRPS	303	CSYADRSTLV	304
1303446	TGTTSDVGSYNLVS	305	EVSKRPS	306	CSYAESSTLV	307
共有的 VL進化 枝4	SGDX ₄ LPX ₇ X ₈ YX ₁₀ Y	308	KDX ₃ X ₄ RPS	309	QSADX ₅ SGX ₈ X ₉ VV	310
	X ₄ 為A、T		X ₃ 為N、S		X ₅ 為I、N、S、	
	X ₇ 為Q、E、N、R、K		X ₄ 為D、E		X ₈ 為S、A、I、T	
	X ₈ 為H、Q				X ₉ 為F、Y	
	X ₁₀ 為V、T、A					
1306164	SGDALPKQYAY	311	KDSERPS	312	QSADNSGTFVV	313
1306253	SGDALPKQYAY	314	KDSERPS	315	QSADSSGTYVV	316
1306424	SGDALPKQYAY	317	KDSERPS	318	QSADSSGTYVV	319
1306053	SGDTLPKQYVY	320	KDNERPS	321	QSADNSGIYVV	322
1306153	SGDTLPKHYAY	323	KDNERPS	324	QSADNSGIYVV	325

LIBC 編號	LCDR1		LCDR2		LCDR3	
	SEQ	ID	SEQ	ID	SEQ	ID
1306251	SGDTLPKHYAY	326	KDNERPS	327	QSADNSGIYVV	328
1306674	SGDTLPKHYAY	329	KDNERPS	330	QSADNSGIYVV	331
1307329	SGDTLPKHYAY	332	KDNERPS	333	QSADNSGIYVV	334
1306622	SGDALPRHYAY	335	KDNERPS	336	QSADSSGIYVV	337
1306800	SGDALPKHYAY	338	KDNERPS	339	QSADNSGIYVV	340
1306965	SGDALPNHYAY	341	KDNERPS	342	QSADSSGIYVV	343
1306294	SGDALPKHYTY	344	KDNDRPS	345	QSADISGIYVV	346
1318253	SGDALPQHYTY	347	KDNERPS	348	QSADSSGSYVV	349
1318209	SGDTLPEHYTY	350	KDNERPS	351	QSADSSGAYVV	352
1318188	SGDALPQHYTY	353	KDNERPS	354	QSADISGTYVV	355
共有的 VL進化 枝2	TGX ₃ X ₄ SDVGSYNLV S X ₃ 為S、T X ₄ 為N、S、I	356	EVX ₃ KRPS X ₃ 為T、N、S	357	CSYAX ₅ X ₆ X ₇ TYV X ₅ 為D、G X ₆ 為T、S X ₇ 為R、S、K、	358
1307739	TGTSSDVGSYNLVS	359	EVSKRPS	360	CSYADSSTYV	361
1310489	TGTSSDVGSYNLVS	362	EVSKRPS	363	CSYAGSSTYV	364
1308006	TGTISDVGSYNLVS	365	EVNKRPS	366	CSYADTKTYV	367
1308236	TGTISDVGSYNLVS	368	EVSKRPS	369	CSYADTKTYV	370
1308563	TGTISDVGSYNLVS	371	EVSKRPS	372	CSYADTKTYV	373
1308943	TGTISDVGSYNLVS	374	EVSKRPS	375	CSYADTKTYV	376
1318301	TGSNSDVGSYNLVS	377	EVTKRPS	378	CSYADSRTYV	379
1319279	TGSNSDVGSYNLVS	389	EVNKRPS	390	CSYADSRTYV	391
1319569	SGDKLGDKYAF	392	QDKKRPS	393	QAWDISTGV	394
1307105	TGTSRDVGGINYVS	395	EVSNRPS	396	SSYISGNSHV	397

【0141】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含由以下定義的共用VH CDR結構：HCDR1胺基酸序列：X₁YGMH（SEQ ID NO: 195），其中

X₁為A或S；HCDR2胺基酸序列：X₁IWYDGNKYYX₁₂DSVKG（SEQ ID NO: 196），其中X₁為L或V，並且X₁₂為E或A；以及HCDR3胺基酸序列：DRITX₅VRGVTNYGMDV（SEQ ID NO: 197），其中X₅為M或R。上表6中提供了示例性促效劑LTβR結合蛋白的重鏈CDR序列，其結合人LTβR CRD4，不阻斷LIGHT與LTβR結合，不阻斷LTα1β2與LTβR結合，並且包含SEQ ID NO: 195的HCDR1、SEQ ID NO: 196的HCDR2和SEQ ID NO: 197的HCDR3。

【0142】在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含分別為SEQ ID NO: 195-197的HCDR 1-3，進一步包含由以下定義的共用VL CDR結構：LCDR1胺基酸序列SGDX₄LPX₇X₈YX₁₀Y（SEQ ID NO: 308），其中X₄為A或T；X₇為Q、E、N、R或K；X₈為H或Q；並且X₁₀為V、T或A；LCDR2胺基酸序列KDX₃X₄RPS（SEQ ID NO: 309），其中X₃為N或S且X₄為D或E；以及LCDR3胺基酸序列QSADX₅SGX₈X₉VV（SEQ ID NO: 310），其中X₅為I、N或S；X₈為S、A、I或T；X₉為F或Y。上表7中提供了示例性促效劑LTβR結合蛋白的輕鏈可變區CDR序列，其結合人LTβR CRD4，不阻斷LIGHT與LTβR結合，不阻斷LTα1β2與LTβR結合，並且包含SEQ ID NO: 308的LCDR1、SEQ ID NO: 309的LCDR2和SEQ ID NO: 310的LCDR3。

【0143】在另一個實施方式中，促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含由以下定義的共用VH CDR結構：HCDR1胺基酸序列：SX₂AMH（SEQ ID NO: 224），其中X₂為Y或F；HCDR2胺基酸序列：VIWYX₅X₆X₇NX₉FYADSVKG（SEQ ID NO: 225），其中X₅為D、A或N；X₆為R或E；X₇為N或S；X₉為K或N；HCDR3胺基酸序列：GDX₃X₄YX₆YX₈YGX₁₁DX₁₃（SEQ ID NO: 226），其中X₃為W或R；X₄為N或D；X₆為S、H或Y；X₈為Y、Q或K；X₁₁為M或V；X₁₃為L或V。上表6中提供了示例

性促效劑LTβR結合蛋白的重鏈CDR序列，其結合人LTβR CRD4，不阻斷LIGHT與LTβR結合，不阻斷LTα1β2與LTβR結合，並且包含SEQ ID NO: 224的HCDR1、SEQ ID NO: 225的HCDR2和SEQ ID NO: 226的HCDR3。

【0144】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含分別為SEQ ID NO: 224-226的HCDR 1-3，進一步包含由以下定義的共用VL CDR結構：LCDR1胺基酸序列TGX₃X₄SDVGSYNLVS（SEQ ID NO: 356），其中X₃為S或T；X₄為N、S或I；LCDR2胺基酸序列：EVX₃KRPS（SEQ ID NO: 357），其中X₃為T、N或S；以及LCDR3胺基酸序列：CSYAX₅X₆X₇TYV（SEQ ID NO: 358），其中X₅為D或G；X₆為T或S；X₇為R、S或K。上表7中提供了示例性促效劑LTβR結合蛋白的輕鏈可變區CDR序列，其結合人LTβR CRD4，不阻斷LIGHT與LTβR結合，不阻斷LTα1β2與LTβR結合，並且包含SEQ ID NO: 356的LCDR1、SEQ ID NO: 357的LCDR2和SEQ ID NO: 358的LCDR3。

【0145】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含可變輕鏈（VL）結構域、可變重鏈（VH）結構域或VL和VH結構域的組合。在任何實施方式中，該促效劑LTβR結合蛋白的VH結構域包含下表8中提供的VH胺基酸序列中的任一個，或與表8中列出的VH胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%或至少95%相同的胺基酸序列。在任何實施方式中，該促效劑LTβR結合蛋白的VL結構域包含下表8中提供的VL胺基酸序列中的任一個，或與表8中列出的VL胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%、至少95%相同的胺基酸序列。

【0146】 本揭露之示例性促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT

與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合：(i) 分別為SEQ ID NO: 159、SEQ ID NO: 160、SEQ ID NO: 161、SEQ ID NO: 278、SEQ ID NO: 279和SEQ ID NO: 280；(ii) 分別為SEQ ID NO: 162、SEQ ID NO: 163、SEQ ID NO: 164、SEQ ID NO: 281、SEQ ID NO: 282和SEQ ID NO: 283；(iii) 分別為SEQ ID NO: 165、SEQ ID NO: 166、SEQ ID NO: 167、SEQ ID NO: 284、SEQ ID NO: 285和SEQ ID NO: 286；(iv) 分別為SEQ ID NO: 168、SEQ ID NO: 169、SEQ ID NO: 170、SEQ ID NO: 287、SEQ ID NO: 288和SEQ ID NO: 289；(v) 分別為SEQ ID NO: 171、SEQ ID NO: 172、SEQ ID NO: 173、SEQ ID NO: 290、SEQ ID NO: 291和SEQ ID NO: 292；(vi) 分別為SEQ ID NO: 174、SEQ ID NO: 175、SEQ ID NO: 176、SEQ ID NO: 293、SEQ ID NO: 294和SEQ ID NO: 295；(vii) 分別為SEQ ID NO: 177、SEQ ID NO: 178、SEQ ID NO: 179、SEQ ID NO: 296、SEQ ID NO: 297和SEQ ID NO: 298；(viii) 分別為SEQ ID NO: 180、SEQ ID NO: 181、SEQ ID NO: 182、SEQ ID NO: 302、SEQ ID NO: 303和SEQ ID NO: 304；(ix) 分別為SEQ ID NO: 183、SEQ ID NO: 184、SEQ ID NO: 185、SEQ ID NO: 305、SEQ ID NO: 306和SEQ ID NO: 307。

【0147】 在一個實施方式中，促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包括那些包含分別為SEQ ID NO: 159-161的HCDR1、HCDR2和HCDR3胺基酸序列以及分別為SEQ ID NO: 278-280的LCDR1、LCDR2和LCDR3胺基酸序列的結合蛋白。該等促效劑LT β R結合蛋白進一步包含選自以下的VH和VL胺基酸序列：與SEQ ID NO: 401的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 402的VL胺基酸序列具有至少90%、至少95%或至少98%序列

同一性的VL胺基酸序列；與SEQ ID NO: 403的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 404的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 405的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 406的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 407的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 408的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 409的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 410的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 411的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 412的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 413的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 414的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 415的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 416的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列。下表8中提供了本文所述之VH和VL胺基酸序列。

【0148】 在一個實施方式中，本揭露之示例性促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合：

(i) 分別為SEQ ID NO: 159、SEQ ID NO: 160、SEQ ID NO: 161、SEQ ID NO: 308、

SEQ ID NO: 309和SEQ ID NO: 310 ; (ii) 分別為SEQ ID NO: 189、SEQ ID NO: 190、SEQ ID NO: 191、SEQ ID NO: 314、SEQ ID NO: 315和SEQ ID NO: 316 ; (iii) 分別為SEQ ID NO: 186、SEQ ID NO: 187、SEQ ID NO: 188、SEQ ID NO: 311、SEQ ID NO: 312和SEQ ID NO: 313 ; (iv) 分別為SEQ ID NO: 192、SEQ ID NO: 193、SEQ ID NO: 194、SEQ ID NO: 317、SEQ ID NO: 318和SEQ ID NO: 319。

【0149】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包括那些包含分別為SEQ ID NO: 159-161的HCDR1、HCDR2和HCDR3胺基酸序列以及分別為SEQ ID NO: 308-310的LCDR1、LCDR2和LCDR3胺基酸序列的結合蛋白。該等促效劑LTβR結合蛋白進一步包含選自以下的VH和VL胺基酸序列：與SEQ ID NO: 417的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 418的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 419的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 420的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；以及與SEQ ID NO: 421的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 422的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列。下表8中提供了本文所述之VH和VL胺基酸序列。

【0150】 在一個實施方式中，本揭露之示例性促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合：

(i) SEQ ID NO: 195、SEQ ID NO: 196、SEQ ID NO: 197、SEQ ID NO: 308、SEQ ID NO: 309和SEQ ID NO: 310；(ii) SEQ ID NO: 197、SEQ ID NO: 198、SEQ ID NO: 199、SEQ ID NO: 320、SEQ ID NO: 321和SEQ ID NO: 322；(iii) 分別為SEQ ID NO: 200、SEQ ID NO: 201、SEQ ID NO: 202、SEQ ID NO: 323、SEQ ID NO: 324和SEQ ID NO: 325；(iv) 分別為SEQ ID NO: 203、SEQ ID NO: 204、SEQ ID NO: 205、SEQ ID NO: 326、SEQ ID NO: 327和SEQ ID NO: 328；(v) 分別為SEQ ID NO: 206、SEQ ID NO: 207、SEQ ID NO: 208、SEQ ID NO: 329、SEQ ID NO: 330和SEQ ID NO: 331；(vi) 分別為SEQ ID NO: 209、SEQ ID NO: 210、SEQ ID NO: 211、SEQ ID NO: 332、SEQ ID NO: 333和SEQ ID NO: 334；(vii) 分別為SEQ ID NO: 212、SEQ ID NO: 213、SEQ ID NO: 214、SEQ ID NO: 335、SEQ ID NO: 336和SEQ ID NO: 337；(viii) 分別為SEQ ID NO: 215、SEQ ID NO: 216、SEQ ID NO: 217、SEQ ID NO: 338、SEQ ID NO: 339和SEQ ID NO: 340；(ix) 分別為SEQ ID NO: 218、SEQ ID NO: 219、SEQ ID NO: 220、SEQ ID NO: 341、SEQ ID NO: 342和SEQ ID NO: 343；(x) 分別為SEQ ID NO: 221、SEQ ID NO: 222、SEQ ID NO: 223、SEQ ID NO: 343、SEQ ID NO: 344和SEQ ID NO: 345。

【0151】在一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含分別為SEQ ID NO: 195-197的HCDR1、HCDR2和HCDR3胺基酸序列以及分別為SEQ ID NO: 308-310的LCDR1、LCDR2和LCDR3胺基酸序列。該等促效劑LT β R結合蛋白進一步包含選自以下的VH和VL胺基酸序列：與SEQ ID NO: 423的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 424的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 425的VH胺基酸序列具有至少90%、至少95%或至少

98%序列同一性的VH胺基酸序列和與SEQ ID NO: 426的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 427的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 428的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 429的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 430的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 431的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 432的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 433的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 434的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 435的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 436的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 437的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 438的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 439的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 440的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列。下表8中提供了本文所述之VH和VL胺基酸序列。

【0152】 在一個實施方式中，本揭露之示例性促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含選自以

下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合：

(i) 分別為SEQ ID NO: 224、SEQ ID NO: 225、SEQ ID NO: 226、SEQ ID NO: 356、SEQ ID NO: 357和SEQ ID NO: 358；(ii) 分別為SEQ ID NO: 227、SEQ ID NO: 228、SEQ ID NO: 229、SEQ ID NO: 359、SEQ ID NO: 360和SEQ ID NO: 361；(iii) 分別為SEQ ID NO: 230、SEQ ID NO: 231、SEQ ID NO: 232、SEQ ID NO: 362、SEQ ID NO: 363和SEQ ID NO: 364；(iv) 分別為SEQ ID NO: 233、SEQ ID NO: 234、SEQ ID NO: 235、SEQ ID NO: 365、SEQ ID NO: 366和SEQ ID NO: 367；(v) 分別為SEQ ID NO: 236、SEQ ID NO: 237、SEQ ID NO: 238、SEQ ID NO: 368、SEQ ID NO: 369和SEQ ID NO: 370；(vi) 分別為SEQ ID NO: 239、SEQ ID NO: 240、SEQ ID NO: 241、SEQ ID NO: 371、SEQ ID NO: 372和SEQ ID NO: 373；(vii) 分別為SEQ ID NO: 242、SEQ ID NO: 243、SEQ ID NO: 244、SEQ ID NO: 374、SEQ ID NO: 375和SEQ ID NO: 376；(viii) 分別為SEQ ID NO: 245、SEQ ID NO: 246、SEQ ID NO: 247、SEQ ID NO: 377、SEQ ID NO: 378和SEQ ID NO: 379；(ix) 分別為SEQ ID NO: 248、SEQ ID NO: 249、SEQ ID NO: 250、SEQ ID NO: 380、SEQ ID NO: 381和SEQ ID NO: 382；(x) 分別為SEQ ID NO: 251、SEQ ID NO: 252、SEQ ID NO: 253、SEQ ID NO: 383、SEQ ID NO: 384和SEQ ID NO: 385；(xi) 分別為SEQ ID NO: 254、SEQ ID NO: 255、SEQ ID NO: 256、SEQ ID NO: 386、SEQ ID NO: 387和SEQ ID NO: 388；(xii) 分別為SEQ ID NO: 180、SEQ ID NO: 181、SEQ ID NO: 182、SEQ ID NO: 302、SEQ ID NO: 303和SEQ ID NO: 304；(xiii) 分別為SEQ ID NO: 183、SEQ ID NO: 184、SEQ ID NO: 185、SEQ ID NO: 305、SEQ ID NO: 306和SEQ ID NO: 307；(xiv) 分別為SEQ ID NO: 257、SEQ ID NO: 258、SEQ ID NO: 259、SEQ ID NO: 389、SEQ ID NO: 390和SEQ ID NO: 391。

【0153】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效

劑LT β R抗體或促效劑LT β R雙特異性結合蛋白)，其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含分別為SEQ ID NO: 224-226的HCDR1、HCDR2和HCDR3胺基酸序列以及分別為SEQ ID NO: 356-358的LCDR1、LCDR2和LCDR3胺基酸序列。該等促效劑LT β R結合蛋白進一步包含選自以下的VH和VL胺基酸序列：與SEQ ID NO: 441的VH胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 442的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 443的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 444的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 445的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 446的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 447的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 448的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 449的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 450的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 451的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 452的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 453的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 454的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 455的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 456的VL胺基酸序列具有至少

90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 457的VH胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 458的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 459的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 460的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列；與SEQ ID NO: 461的VH胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 462的VL胺基酸序列具有至少90%、至少95%或至少98%序列同一性的VL胺基酸序列。下表8中提供了本文所述之VH和VL胺基酸序列。

【0154】 在一個實施方式中，本揭露之示例性促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列的組合：

(i) 分別為SEQ ID NO: 257、SEQ ID NO: 258、SEQ ID NO: 259、SEQ ID NO: 389、SEQ ID NO: 390和SEQ ID NO: 391（1319279）；(ii) 分別為SEQ ID NO: 260、SEQ ID NO: 261、SEQ ID NO: 262、SEQ ID NO: 347、SEQ ID NO: 348和SEQ ID NO: 349（1318253）；(iii) 分別為SEQ ID NO: 263、SEQ ID NO: 264、SEQ ID NO: 265、SEQ ID NO: 350、SEQ ID NO: 351和SEQ ID NO: 352（1318209）；(iv) 分別為SEQ ID NO: 266、SEQ ID NO: 267、SEQ ID NO: 268、SEQ ID NO: 353、SEQ ID NO: 354和SEQ ID NO: 355（1318188）；(v) 分別為SEQ ID NO: 269、SEQ ID NO: 270、SEQ ID NO: 271、SEQ ID NO: 392、SEQ ID NO: 393和SEQ ID NO: 394（1319569）；(vi) 分別為SEQ ID NO: 272、SEQ ID NO: 273、SEQ ID NO: 274、SEQ ID NO: 395、SEQ ID NO: 396和SEQ ID NO: 397（1317105）；(vii) 分別為SEQ ID NO: 275、SEQ ID NO: 276、SEQ ID NO: 277、SEQ ID NO: 398、SEQ ID

NO: 399和SEQ ID NO: 400 (1318198) ;

【0155】 在另一個實施方式中，本揭露之LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白），其結合人LT β R CRD4和 (a) 不阻斷LIGHT與LT β R結合並且 (b) 不阻斷LT α 1 β 2與LT β R結合，包含選自以下的VH胺基酸序列和VL胺基酸序列：SEQ ID NO: 401的VH胺基酸序列和SEQ ID NO: 402的VL胺基酸序列；SEQ ID NO: 403的VH胺基酸序列和SEQ ID NO: 404的VL胺基酸序列；SEQ ID NO: 405的VH胺基酸序列和SEQ ID NO: 406的VL胺基酸序列；SEQ ID NO: 407的VH胺基酸序列和SEQ ID NO: 408的VL胺基酸序列；SEQ ID NO: 409的VH胺基酸序列和SEQ ID NO: 410的VL胺基酸序列；SEQ ID NO: 411的VH胺基酸序列和SEQ ID NO: 412的VL胺基酸序列；SEQ ID NO: 413的VH胺基酸序列和SEQ ID NO: 414的VL胺基酸序列；SEQ ID NO: 415的VH胺基酸序列和SEQ ID NO: 416的VL胺基酸序列；SEQ ID NO: 417的VH胺基酸序列和SEQ ID NO: 418的VL胺基酸序列；SEQ ID NO: 419的VH胺基酸序列和SEQ ID NO: 420的VL胺基酸序列；SEQ ID NO: 421的VH胺基酸序列和SEQ ID NO: 422的VL胺基酸序列；SEQ ID NO: 423的VH胺基酸序列和SEQ ID NO: 424的VL胺基酸序列；SEQ ID NO: 425的VH胺基酸序列和SEQ ID NO: 426的VL胺基酸序列；SEQ ID NO: 427的VH胺基酸序列和SEQ ID NO: 428的VL胺基酸序列；SEQ ID NO: 429的VH胺基酸序列和SEQ ID NO: 430的VL胺基酸序列；SEQ ID NO: 431的VH胺基酸序列和SEQ ID NO: 432的VL胺基酸序列；SEQ ID NO: 433的VH胺基酸序列和SEQ ID NO: 434的VL胺基酸序列；SEQ ID NO: 435的VH胺基酸序列和SEQ ID NO: 436的VL胺基酸序列；SEQ ID NO: 437的VH胺基酸序列和SEQ ID NO: 438的VL胺基酸序列；SEQ ID NO: 439的VH胺基酸序列和SEQ ID NO: 440的VL胺基酸序列；SEQ ID NO: 441的VH胺基酸序列和SEQ ID NO: 442的VL胺基酸序列；SEQ ID NO: 443的VH胺基酸序列和SEQ ID NO: 444的VL胺基酸序列；SEQ

ID NO: 445的VH胺基酸序列和SEQ ID NO: 446的VL胺基酸序列；SEQ ID NO: 447的VH胺基酸序列和SEQ ID NO: 448的VL胺基酸序列；SEQ ID NO: 449的VH胺基酸序列和SEQ ID NO: 450的VL胺基酸序列；SEQ ID NO: 451的VH胺基酸序列和SEQ ID NO: 452的VL胺基酸序列；SEQ ID NO: 453的VH胺基酸序列和SEQ ID NO: 454的VL胺基酸序列；SEQ ID NO: 455的VH胺基酸序列和SEQ ID NO: 456的VL胺基酸序列；SEQ ID NO: 457的VH胺基酸序列和SEQ ID NO: 458的VL胺基酸序列；SEQ ID NO: 459的VH胺基酸序列和SEQ ID NO: 460的VL胺基酸序列；SEQ ID NO: 461的VH胺基酸序列和SEQ ID NO: 462的VL胺基酸序列；SEQ ID NO: 463的VH胺基酸序列和SEQ ID NO: 464的VL胺基酸序列；SEQ ID NO: 465的VH胺基酸序列和SEQ ID NO: 466的VL胺基酸序列；SEQ ID NO: 467的VH胺基酸序列和SEQ ID NO: 468的VL胺基酸序列；SEQ ID NO: 469的VH胺基酸序列和SEQ ID NO: 470的VL胺基酸序列；SEQ ID NO: 471的VH胺基酸序列和SEQ ID NO: 472的VL胺基酸序列；以及SEQ ID NO: 473的VH胺基酸序列和SEQ ID NO: 474的VL胺基酸序列。下表8中提供了本文所述之VH和VL胺基酸序列。

[表8]：與LTβR結合物LIBC219081和LIBC218979競爭結合LTβR的CRD4並且不阻斷LIGHT或LTα1β2結合的LTβR結合蛋白的VH和VL胺基酸序列

LIBC編號	結構域	序列	SEQ ID
1303255	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	401
	V _L	QSALTQPASVSGSPGQSITISCTGTSDVGSYNLVSWYQQHPGKVPK FMIYEVSKRPSGVSNRFGSGKSGNTASLTISGLQAEDEADYHCCSYA ESSTLVFGGGTKLTVLG	402
1303574	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	403

LIBC編號	結構域	序列	SEQ ID
	V _L	QSALTQPASVSGSPGQSITISCTGTTSADVGSYNLVSWYQQHPGKVPK FMIYEVSKRPSGVSNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYA ESSTLVFGGGTKLTVLG	404
1303613	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWVRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	405
	V _L	QSALTQPASVSGSPGQSITISCTGTTSADVGSYNLVSWYQQHPGKVPK FMIYEVSKRPSGVYNRFSGSKSGNTASLTISGLQAEDEADYHCCSY AESSTLVFGGGTKLTVLG	406
1303507	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWVRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	407
	V _L	QSALTQPASVSGSPGQSITISCTGTTSADVGSYNLVSWYQQHPGKVPK FMIYEVSKRPSGVFNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYA ESSTLVFGGGTKLTVLG	408
1303716	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWVRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	409
	V _L	QSALTQPASVSGSPGQSITISCTGTTSADVGSYNLVSWYQQHPGKVPK FMIYEVSKRPSGVFNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYA ESSTLVFGGGTKLTVLG	410
1308640	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWVRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADSSGWYYYYGMDVWGQGTTVTVSS	411
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKVPK FMIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYHCCSYA DSSTLVFGGGTKLTVLG	412
1308591	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGFYMHWVRQAPGQG LKWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADSSGWYYYYGMDVWGQGTTVTVSS	413
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKVPK	414

LIBC編號	結構域	序列	SEQ ID
		FMIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCSYA DRSTLVFGGGTKLTVLG	
1303446	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQ GLEWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAKADNSGWYYYYGMDVWGQGTTVTVSS	415
	V _L	QSALTQPASVFGSPGQSITISCTGTTSDVGSYNLVSQYQHPGKVPK FMIYEVSKRPSGVYNRFSGSKSGNTASLTIFGLQAEDEADYHCCSY AESSTLVFGGGTKLTVLG	416
1306164	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQ GLEWMGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVFYCAKDRAGGVYYGMDVWGQGTTVTVSS	417
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQKKPGQAPVRV IYKDSERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADNSG TFVVFGGGTKLTVLG	418
1306253	V _H	QVQLVQSGAEVKKPGASVKVSCRASGYTFTGYYMHWVRQAPGQG LEWMGWINPNRGGTNYAQKFQGRVTMTRDTSISTAYMELSRLISD DTAVYYCAKDRAGGVYYGMDVWGQGTTVTVSS	419
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQKQPDQAPVM VISKDSERPSGIPERFSGSSSGTTVTLTISGVQAEDESDYYCQSADSS GTYYVFGGGTKLTVLG	420
1306424	V _H	QVQLVQSGAEVKKPGASVKVSCRASGYTFTGYYMHWVRQAPGQG LEWMGWINPNRGGTNYAQKFQGRVTMTRDTSISTAYMELSRLISD DTAVYYCAKDRAGGVYYGMDVWGQGTTVTVSS	421
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQKQPDQAPVM VISKDSERPSGIPERFSGSSSGTTVTLTISGVQAEDESDYYCQSADSS GTYYVFGGGTKLTVLG	422
1306053	V _H	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGL EWVALIWYDGNKYYADSVKGRFTISRDN SKNTLYLQMSSLRAED TAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	423
	V _L	SYELTQPPSMSVSPGQTARITCSGDTLPKQYVYWYRQKPGQAPVLV IYKDNERPSGILERFSGSSSGATVTLTISGVQAEDEADYFCQSADNS	424

LIBC編號	結構域	序列	SEQ ID
		GIYVVFGGGTKLTVLG	
1306153	V _H	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGL EWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMSSLRAED TAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	425
	V _L	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKAGQAPVL VIYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADN SGIYVVFGGGTKLTVLG	426
1306251	V _H	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGL EWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMSSLRAED TAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	427
	V _L	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKAGQAPVL VIYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADN SGIYVVFGGGTKLTVLG	428
1306674	V _H	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGL EWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMSSLRAED TAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	429
	V _L	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKPGQAPVLV IYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNS GIYVVFGGGTKLTVLG	430
1307329	V _H	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGL EWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMSSLRAED TAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	431
	V _L	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKPGQAPVLV IYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNS GIYVVFGGGTKLTVLG	432
1306622	V _H	QVQLVESGGGVVQFGRSLRLSCAASGFTFSAYGMHWVRQAPGKG LEWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAE DTAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	433
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPRHYAYWYRQKPGQAPVLV IYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADSSG IYVVFGGGTKLTVLG	434

LIBC編號	結構域	序列	SEQ ID
1306800	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKG LEWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAE DTAVYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	435
	V _L	SYELTQPPSMSVSPGQTARITCSGDALPKHYAYWYRQKPGQAPVL VIYKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADN SGIYVVFGGGTKLTVLG	436
1306965	V _H	QVQVVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKG LEWVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAE DTAIYYCARDRITRVRGVTNYGMDVWGQGTTVTVSS	437
	V _L	SYELTQPPSVSLSPGQTARITCSGDALPNHYAYWYRQKPGQAPVLV IYKDNERPSGIPERFSGSSSGATVTLTITGVQAEDEADYFCQSADSSG IYVVFGGGTKLTVLG	438
1306294	V _H	QEQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGL EWVAVIWYDGNNKYYEDSVKGRFTISRDN SKNTLYLQMNSLRAE DTAVYYCARDRITMVRGVTNYGMDVWGQGTTVTVSS	439
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPKHYTYWYQQKPGQAPLLV IYKDNDRPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADISG IYVVFGGGTKLTVLG	440
1307739	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAVIWYDRNNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDRDYHYQYGMDVWGQGTTVTVSS	441
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWEYQHPGKAPQ LMIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYA DSSTYVFGTGKTVTLG	442
1310489	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAVIWYDRNNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDRDYHYQYGMDVWGQGTTVTVSS	443
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWEYQHPGKAPQ LMIYEVSKRPSGVSSRFSVSKSGNTASLTISGLRAEDEADYYCCSYA GSSTYVFGSGTKTVTLG	444
1308006	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL	445

LIBC編號	結構域	序列	SEQ ID
		EWVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDRDY YYYYGMDVWGQGTTVTVSS	
	V _L	QSALTQPASVSGSPGQSITISCTGTISDVGSYNL VSWYQQHPGKAPQ LMIYEVNKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSY ADTKTYVFGTGTKVTVLG	446
1308236	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDRDY YYYYGMDVWGQGTTVTVSS	447
	V _L	QSALTQPASVSGSPGQSITISCTGTISDVGSYNL VSWYQQHPGKAPQ LMIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYA DTKTYVFGTGTKVTVLG	448
1308563	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAED AAVYYCARGDRDY YYYYGMDVWGQGTTVTVSS	449
	V _L	QSALTQPASVSGSPGQSITISCTGTISDVGSYNL VSWYQQHPGKAPQ LMIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYA DTKTYVFGTGTKVTVLG	450
1308943	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAED AAVYYCARGDRDY YYYYGMDVWGQGTTVTVSS	451
	V _L	QSALTQPASVSGSPGQSITISCTGTISDVGSYNL VSWYQQHPGKAPQ LMIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYA DTKTYVFGTGTKVTVLG	452
1318301	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFAMHWVRQAPGKGL DWVAVIWYAESNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDWNYSYKYGVDLWGQGTTVTVSS	453
	V _L	QSALTQPASVSGSPGQSITISCTGSNSDVGSYNL VSWYQQDPGKAP KLMIYEVTKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCS YADSRTYVFGTGTKVTVLG	454
1318394	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGL EWMTVIWYDRSNKY YADSVKGRFTISRDN SKNTLYLQMNSLRAED	455

LIBC編號	結構域	序列	SEQ ID
		TAVYYCARGISGYRYGTDMDVWGQGTTVTVSS	
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKAPK FMIYEVTVRPSGVSNRFGSKSGNTAYLTISGLQAEDEADYYCCSY VDSKTWVFGGGTKLTVLG	456
1318693	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGL EWMTVIWYDRSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGISGYRYGTDMDVWGQGTTVTVSS	457
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKAPK FMIYEVTVRPSGVSNRFGSKSGNTAYLTISGLQAEDEADYYCCSY VDSKTWVFGGGTKLTVLG	458
1318991	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGL EWMTVIWYDRSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGISGYRYGTDMDVWGQGTTVTVSS	459
	V _L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKAPK FMIYEVTVRPSGVSNRFGSKSGNTAYLTISGLQAEDEADYYCCSY VDSKTWVFGGGTKLTVLG	460
1319279	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFAMHWVRQAPGKGL DWVAVIWYAESNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAED TAVYYCARGDWNYSYKYGVDLWGQGTTVTVSS	461
	V _L	QSALTQPASVSGSPGQSITISCTGSNSDVGSYNLVSWYQQDPGKAP KLMIYEVNKRPSGVYNCFFGSKSGNTASLTICGLQGEEEGDYY*CS YADSRTYVFGSGTKVTVLG	462
1318253	V _H	QMQLVQSGTEVKKPGASVKVSCEASGYAFTGFYMHWVRQAPGQG LEWMGWLNPNTGGTSYVQKFQGRVTMTRDTSISTAYMELSRLRSD DTAVYFCASGTGTTAFDFWGQGTMTVTVSS	463
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPQHYTYWYQQKPGRAPVLV IYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSG SYVVFGGGTKLTVLG	464
1318209	V _H	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYVMNWVRQAPGKGL EWVSGISGSDGSTYYADSVKGRFTISSDN SKNTLYLQMNSLRAEDT AVYYCAKEEDWNYGFDYWGQGLTVTVSS	465

LIBC編號	結構域	序列	SEQ ID
	V _L	SYELTQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPILVI YKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSG AYVVFGGGTKLTVLG	466
1318188	V _H	QVQLQESGPGLVKPSQTLSTCTVSGGSISSDGYFWSWIRQHPGKG LEWIGFIYFTGITYYNPSLQSRVTISVDTSKNQFSLKLNSVTAADTAV YYCARVIPGEDAFDIWGQGTMTVTVSS	467
	V _L	SYELTQPPSVSVSPGQTARITCSGDALPQHYTYWYQQKPGQAPVLV IYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADISG TYVVFGGGTKLTVLG	468
1319569	V _H	QVQLVQSGAEVKKPGASVKVCKASGYTFTSYDINWVRQATGQGL EWMGWMNPNTGNTGYPQKFQGRVTMTRNTSISTAYMELSSLRSE DTAVYYCARGGLTMKVVGAGWFDWPWGQGTLLTVTVSS	469
	V _L	SYELTQPPSVSVSPGQTASITCSGDKLGDKYAFWYQQKPGQSPLLVI YQDKKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDIS TGVFGGGTKLTVLG	470
1307105	V _H	QVQVVESGGGVVQPGRSLRLSCAASGFTFRSYGMDWVRQAPGKG LEWVAVISYDGNKYKYADSVKGRFTISRDN SKNTLYLQMNSLRAE DTAVYYCARD DYSTLDYWGQGTLLTVTVSS	471
	V _L	QSALTQPASVSGSPGQSITISCTGTSRDVGGYNYVSWYQQHPGKAP KLMIYEVS NRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSY ISGNSHVFGTGTKVTPVG	472
1318198	V _H	QVQLQESGPGLVKPSQTLSTCTVSGGSISSDGYFWSWIRQHPGKG LEWIGFIYFTGITYYNPSLQSRVTISVDTSKNQFSLKLNSVTAADTAV YYCARVIPGEDAFDIWGQGTMTVTVSS	473
	V _L	QSALTQPASVSGSPGQSITISCTGTNSDVGSYNLVSWYQQHPGKAP KFMIYEVTVRPSGV SNRFSGSKSGNTAYLTISGLQAEDEADYYCCS YVDSKTWVFGGGTKLTVLG	474

【0156】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或促效劑LTβR雙特異性結合蛋白），其結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合，包含如上所述之

VH區和/或VL區，並且進一步包含與VH區偶合的一或多個重鏈恒定區和/或與VL區偶合的輕鏈恒定區。例如，在一個實施方式中，該LTβR結合蛋白係Fab，其包含VH和與VL偶合的第一重鏈恒定結構域（CH1）以及輕鏈恒定區（CL）。在另一個實施方式中，該LTβR結合蛋白係F(ab')₂，其包含藉由鉸鏈區偶合的完全抗體的兩個LTβR結合區，其中每個結合區包含VH-CH1和VL-CL。在另一個實施方式中，該LTβR結合蛋白係包含完全輕鏈（VL-CL）和完全重鏈（VH-CH1-CH2-CH3）的抗體。下表9中提供了本揭露之LTβR抗體之示例性胺基酸序列，該抗體結合人LTβR CRD4和 (a) 不阻斷LIGHT與LTβR結合並且 (b) 不阻斷LTα1β2與LTβR結合。

[表9]. LTβR CRD4結合抗體的抗體HC和LC序列

LIBC編號	描述	序列	SEQ ID
219081 19325	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTSSYAMHWVRQAPGKGLE WVAVIWYDGSNQYYADSVKGRFIISRDNSKNTLYLQMNSLRAEDTA VYYCARDRVAAHPAYYYGLDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWKVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	747
	LC	SYELTQPPSVSLSPGQTARITCSGDALPNHYAYWYQQKPGQAPVLVIF KDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGSYV IFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV TVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS	748
218979 19319	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTSSYGMHWVRQAPGKGLE WVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLSLQMNSLRAEDTA	749

LIBC編號	描述	序列	SEQ ID
		VYYCARERIAAAPYYYYGMDVWGQGTTTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPRQTARITCSGDALPKHYAYWYQQKPGQAPVLVI YKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADNTGS YMFVGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	750
1308929	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLD WVGVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARDRVAARPHYYYGLDVWGQGTTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKF NWXVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	751
	LC	SYELTQPPSVSVSPGQTARITCSGDALPNHYAYWYQQKPGQAPVLVI YKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGSY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	752
1318341	HC	LVQLVESGGGVVQPGRSLRLSCAASGFTFRSYAMHWVRQAPGKGLE WVAVIWYDGTNKYYADSVKGRFTISRDN SKNTLYLQMNTLRADDT	753

LIBC編號	描述	序列	SEQ ID
		AVYFCAKDRVAARPDYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARIACSGDALPDHYTYWYQQKPGQAPVLVI YKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGA YVIFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	754
1318409	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGSNKYYADSVKGRFTISRDN SKDTLHLQMNSLRAEDM AVYFCAKDRVVARPDYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	755
	LC	SYELTQPPSVSVSPGQTARITCSGDALPQHYTYWYQQKPGQAPVLVIY KDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADGSGTY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	756
1318412	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGRKRYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	757

LIBC編號	描述	序列	SEQ ID
		VYYCAKDRIAARPNYYYGLDVWGQGTTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELIQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPILVIYK DNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGAYV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS	758
1318738	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYDMHWVRQAPGKGLE WVAVIRYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMNSLRVEDTA VYYCARERGPYGGNTYYGMDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWXVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	759
	LC	SYELTQPPSVSVSPGQTARITCSGDALPKHYAYWYQQKPGQAPVMVI YKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSTDSSATY VVFGGGTKLTVLRQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	760
1319003	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLE WVAVIWYDGRKRYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	761

LIBC編號	描述	序列	SEQ ID
		VYYCARDRIAARPNYYYGLDVWGQGTTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPVLDS DGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPDHYTYWYQQRPGQAPILVIY KDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGAY VVFGGGTKLTVLRQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	762
1319078	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARDRVAARPNYYYGMAVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF N WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDS DGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	763
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQKPGQAPVMVI YKDNERPSGIPERFSGFSSSGTTVTLTITGVQAEDEADYYCQSADSSGT YVLFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	764
1319182	HC	QVHLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGSNKYYADSVKGRFTISRDN SKDTLHLQMNSLRAEDM	765

LIBC編號	描述	序列	SEQ ID
		AVYFCAKDRVVARPDYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPQHYTYWYQQNPGQAPVLVIY KDNERPSGIPERFSGSSSGTTVTLTISRVAEDEADYYCQSADSSGSYV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS	766
1319275	HC	QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCAKDRVAARP NFYYGMDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	767
	LC	SYELTQPPSVSLSPGHSARITCSGDALPKHYAYWYQQKPGQAPVLVIY KDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGTY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	768
1319390	HC	QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYAMHWVRQAPGKGLE WVAVIWYDGSNKYYEDSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	769

LIBC編號	描述	序列	SEQ ID
		VYYCAKDRVAARPNFYYGMDVWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSLSPGHSARITCSGDALPKHYAYWYQQKPGQAPVLIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGTYVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	770
1319499	HC	QVQLVESGGGVVQPGRSLRLSCVASGFTFSNYGMYWVRQAPGKGLEWVAVIWYDESNKYYADSVKGRFTISRDKNTLYLQMNSLRAEDTAVYYCARDRIAGRPGYYYGMDVWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	771
	LC	SYELTQPPSVSVSPGQTARISCSGDALPKQYAYWYQQKPGQAPVLIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGAYVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	772
1319908	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVIWYDGRKRYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTA	773

LIBC編號	描述	序列	SEQ ID
		VYYCAKDRIAARPNYYYYGLDVWGQGTTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPILVIY KDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGAY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	774
1318496	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAAIWYDGSNKYHADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARDRIAARPNYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF N WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	775
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQEPGQAPVLVIY KDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGSY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	776
1320038	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAAIWYDGSNKYHADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	777

LIBC編號	描述	序列	SEQ ID
		VYYCARDRIAARPNYYYYGMDVWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPNHYTYWYQQEPGQAPVLVIYKDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGSYVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	778
1308929	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLDWVGVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRVAARPHYYYGLDVWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	779
	LC	SYELTQPPSVSVSPGQTARITCSGDALPNHYAYWYQQKPGQAPVLVIYKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGSYVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	780
1309633	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFRSYAMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	781

LIBC編號	描述	序列	SEQ ID
		VYYCARDRVAARPHYYYGLDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWyVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDALPNQYAYWYQQKPGQAPVLI YKDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGSY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	782
1303255	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	783
	LC	QSALTQPASVSGSPGQSITISCTGTSDVGSYNLVSWYQQHPGKVPKF MIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYHCCSYAES STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	784
1303574	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT	785

LIBC編號	描述	序列	SEQ ID
		AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSDVGSYNLVSQYQHPGKVPKF MIYEVSKRPSGVSNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYAES STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	786
1303613	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	787
	LC	QSALTQPASVSGSPGQSITISCTGTSDVGSYNLVSQYQHPGKVPKF MIYEVSKRPSGVYNRFSGSKSGNTASLTISGLQAEDEADYHCCSYAES STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	788
1303507	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT	789

LIBC編號	描述	序列	SEQ ID
		AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTTSDVGSYNLVSQYQHPGKVPKF MIYEVSKRPSGVFNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYAES STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	790
1303716	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	791
	LC	QSALTQPASVSGSPGQSITISCTGTTSDVGSYNLVSQYQHPGKVPKF MIYEVSKRPSGVFNRFSGSKSGNTASLTIFGLQAEDEADYHCCSYAES STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	792
1308640	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT	793

LIBC編號	描述	序列	SEQ ID
		AVYYCAKADSSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKVPKF MIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYHCCSYADS STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	794
1308591	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGFYMHWVRQAPGQGL KWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAKADSSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	795
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKVPKF MIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCSYADR STLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	796
1303446	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWVRQAPGQGL EWMGWINPNNGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDT	797

LIBC編號	描述	序列	SEQ ID
		AVYYCAKADNSGWYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVFGSPGQSITISCTGTTSDVGSYNLVSWEYQHPGKVPKFMIEVSKRPSGVYNRFSGSKSGNTASLTIFGLQAEEADYHCCSYAESTLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	798
1306164	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNSSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVFYCAKDRAGGVYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	799
	LC	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQKKPGQAPVRVIYKDSERPSGIPERFSGSSSGTTVTLTISGVQAEEADYCYQSADNSGTFVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	800
1306253	HC	QVQLVQSGAEVKKPGASVKVSCRASGYTFTGYYMHWVRQAPGQGLEWMGWINPNRGGTNYAQKFQGRVTMTRDTSISTAYMELSRLISDDT	801

LIBC編號	描述	序列	SEQ ID
		AVYYCAKDRAGGVYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQQKPDQAPVMVI SKDSERPSGIPERFSGSSSGTTVTLTISGVQAEDESDYYCQSADSSGT YVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	802
1306424	HC	QVQLVQSGAEVKKPGASVKVSCRASGYTFTGYMHWRQAPGQGL EWMGWINPNRGGTNYAQKFQGRVTMTRDTSISTAYMELSRLISDDT AVYYCAKDRAGGVYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	803
	LC	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQQKPDQAPVMVI SKDSERPSGIPERFSGSSSGTTVTLTISGVQAEDESDYYCQSADSSGT YVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	804
1306053	HC	QEHLVESGGGVVQGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGNKYYADSVKGRFTISRDN SKNTLYLQMSSLRAEDTA	805

LIBC編號	描述	序列	SEQ ID
		VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSMSVSPGQTARITCSGDTLPKQYVYWYRQKPGQAPVLVI YKDNERPSGILERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	806
1306153	HC	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGN NKYYADSVKGRFTISRDN SKNTLYLQMSSLRAEDTA VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	807
	LC	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKAGQAPVLVI YKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	808
1306251	HC	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGN NKYYADSVKGRFTISRDN SKNTLYLQMSSLRAEDTA	809

LIBC編號	描述	序列	SEQ ID
		VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKAGQAPVLVI YKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	810
1306674	HC	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGN NKYYADSVKGRFTISRDN SKNTLYLQMSSLRAEDTA VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	811
	LC	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKPGQAPVLVI YKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	812
1307329	HC	QEHLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGN NKYYADSVKGRFTISRDN SKNTLYLQMSSLRAEDTA	813

LIBC編號	描述	序列	SEQ ID
		VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSMSVSPGQTARITCSGDTLPKHYAYWYRQKPGQAPVLVI YKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	814
1306622	HC	QVQLVESGGGVVQFGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGN NKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	815
	LC	SYELTQPPSVSVSPGQTARITCSGDALPRHYAYWYRQKPGQAPVLVIY KDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADSSGIYV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS	816
1306800	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGN NKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	817

LIBC編號	描述	序列	SEQ ID
		VYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSMSVSPGQTARITCSGDALPKHYAYWYRQKPGQAPVLVI YKDNERPSGIPERFSGSSSGATVTLTISGVQAEDEADYFCQSADNSGIY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	818
1306965	HC	QVQVVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLE WVALIWYDGNNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA IYYCARDRITRVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	819
	LC	SYELTQPPSVSLSPGQTARITCSGDALPNHYAYWYRQKPGQAPVLVIY KDNERPSGIPERFSGSSSGATVTLTITGVQAEDEADYFCQSADSSGIYV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS	820
1306294	HC	QEQLVESGGGVVQPGRSLRLSCAASGFTFSYGMHWVRQAPGKGLE WVAWIWYDGNNKYYEDSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	821

LIBC編號	描述	序列	SEQ ID
		VYYCARDRITMVRGVTNYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDALPKHYTYWYQQKPGQAPLLVIYKDNDRPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADISGIYVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	822
1307739	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVIWYDRNNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGDRDYHYQYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	823
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKAPQLMIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYADSTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	824
1310489	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVIWYDRNNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGDRDYHYQYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	825

LIBC編號	描述	序列	SEQ ID
		VYYCARGDRDYHYQYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWEYQHPGKAPQL MIYEVSKRPSGVSSRFSVSKSGNTASLTISGLRAEDEADYYCCSYAGS STYVFGSGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS	826
1308006	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARGDRDYHYHYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	827
	LC	QSALTQPASVSGSPGQSITISCTGTISDVGSYNLVSWEYQHPGKAPQL MIYEVNKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYADT KTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	828
1308236	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	829

LIBC編號	描述	序列	SEQ ID
		VYYCARGDRDYYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTISDVGSYNLVSWYQQHPGKAPQL MIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYADT KTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	830
1308563	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDAA VYYCARGDRDYYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	831
	LC	QSALTQPASVSGSPGQSITISCTGTISDVGSYNLVSWYQQHPGKAPQL MIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYADT KTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	832
1308943	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVAVIWYNRNNNFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDAA	833

LIBC編號	描述	序列	SEQ ID
		VYYCARGDRDYYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTISDVGSYNLVSWYQQHPGKAPQL MIYEVSKRPSGVSNRFSVSKSGNTASLTISGLRAEDEADYYCCSYADT KTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAFTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	834
1318301	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFAMHWVRQAPGKGLD WVAVIWYAESNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARGDWNYSYKYGVDLWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	835
	LC	QSALTQPASVSGSPGQSITISCTGSNSDVGSYNLVSWYQQDPGKAPKL MIYEVTKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCSYADS RTYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAFTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	836
1318394	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLE WMTVIWYDRSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	837

LIBC編號	描述	序列	SEQ ID
		VYYCARGISGYRYGTDMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWEYQHPGKAPKFMIEVTVRPSGVSNRFGSKSGNTAYLTISGLQAEEADYYCCSYVDSKTWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	838
1318693	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLIEWMTVIWYDRSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGISGYRYGTDMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	839
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWEYQHPGKAPKFMIEVTVRPSGVSNRFGSKSGNTAYLTISGLQAEEADYYCCSYVDSKTWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	840
1318991	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLIEWMTVIWYDRSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGISGYRYGTDMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	841

LIBC編號	描述	序列	SEQ ID
		VYYCARGISGYRYGTDMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWEYQQHPGKAPKFMIEVTVRPSGVSNRFSGSKSGNTAYLTISGLQAEEADYYCCSYVDSKTWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	842
1319279	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFAMHWVRQAPGKGLDWVAVIWYAESNKFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGDWNYSYKYGVDLWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	843
	LC	QSALTQPASVSGSPGQSITISCTGSNSDVGSYNLVSWEYQQDPGKAPKLMIEVNKRPSGVYNCFFGSKSGNTASLTICGLQGEEEGDY*CSYADSRITYVFGSGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	844
1318253	HC	QMQLVQSGTEVKKPGASVKVSCEASGYAFTGFYMHWRQAPGQGLEWMGWLNPNTGGTSYVQKFQGRVTMTRDTSISTAYMELSRLRSDDT	845

LIBC編號	描述	序列	SEQ ID
		AVYFCASGTGTTAFDFWQGTMVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV DGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDALPQHYTYWYQQKPGRAPVLVIY KDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGSYV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS	846
1318209	HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYVMNWVRQAPGKGLE WVSGISGSDGSTYYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAV YYCAKEEDWNYGFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVD GVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK	847
	LC	SYELTQPPSVSVSPGQTARITCSGDTLPEHYTYWYQQRPGQAPILVIY KDNERPSGIPERFSGSSSGTTVTLTIRGVQAEDEADYYCQSADSSGAY VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS	848
1318188	HC	QVQLQESGPGLVKPSQTLSTCTVSGGSISSDGYFWSWIRQHPGKGLE WIGFIYFTGITYYNPSLQSRVTISVDTSKNQFSLKLNSVTAADTAVYYC	849

LIBC編號	描述	序列	SEQ ID
		ARVIPGEDAFDIWGQGTMTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVH NAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK	
	LC	SYELTQPPSVSVSPGQTARITCSGDALPQHYYTYWYQQKPGQAPVLIY KDNERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADISGT YVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	850
1319569	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLE WMGWMNPNTGNTGYPQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARGGLTMKVVGAGWFDPWGQGTLLTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKF FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	851
	LC	SYELTQPPSVSVSPGQTASITCSGDKLGDKYAFWYQQKPGQSPLLVIY QDKKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDISTG VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	852
1307105	HC	QVQVVESGGGVVQPGRSLRLSCAASGFTFRSYGMDWVRQAPGKGLE WVAVISYDGNKYKYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA	853

LIBC編號	描述	序列	SEQ ID
		VYYCARDDYSTLDYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDG VEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPVLDSDGSEFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSRDVGGYNYVSWYQQHPGKAPK LMIYEVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYISG NSHVFGTGTKVTVPGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	854
1318198	HC	QVQLQESGPGLVKPSQTLSTCTVSGGSISSDGYFWSWIRQHPGKGLE WIGFIYFTGITYYNPSLQSRVTISVDTSKNQFSLKLNSVTAADTAVYYC ARVIPGEDAFDIWGQGTMTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVH NAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSDGSEFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK	855
	LC	QSALTQPASVSGSPGQSITISCTGTNSDVGSYNLVSQYQQHPGKAPKF MIYEVTVRPSGVSNRFSGSKSGNTAYLTISGLQAEDEADYYCCSYVDS KTWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS	856

結合CRD1、CRD2和/或CRD3的LTβR促效劑結合蛋白

【0157】 根據本揭露之所有方面，如本文所描述的促效劑LTβR結合蛋白包含結合並激動LTβR活性的一或多個結合結構域。在一個實施方式中，該結合結構域包含重鏈可變區（VH）或其片段，其中該VH包含結合LTβR的一或多個互補決定區（即HCDR1、HCDR2和/或HCDR3）或其部分。在一個實施方式中，該VH包含SEQ ID NO: 475-498、740-742或其修飾序列中任一個的HCDR1胺基酸序列，其中與SEQ ID NO: 475-498和740-742中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。在一個實施方式中，該VH包含SEQ ID NO: 499-528、743或其修飾序列中任一個的HCDR2胺基酸序列，其中與SEQ ID NO: 499-528和743中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。在一個實施方式中，該VH包含SEQ ID NO: 529-558、744-746或其修飾序列中任一個的HCDR3胺基酸序列，其中與SEQ ID NO: 529-558和744-746中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。下表10中提供了本文所描述的示例性促效劑LTβR結合蛋白的重鏈CDR序列。

【0158】 如本文實例中所描述的，本文揭露的幾種LTβR抗體的互補位作圖研究表明，在某些情況下，特定LTβR抗體與LTβR的結合不涉及或需要抗體的所有三個重鏈CDR區和/或不涉及一或多個重鏈CDR的所有殘基。顯示不參與LTβR抗體結合相互作用的重鏈CDR在下表10中用星號表示。藉由互補位作圖或突變分析鑒定的顯示不參與或不需要LTβR抗體結合相互作用的重鏈CDR區的殘基被鑒定為可變殘基（X）。表10序列內的X殘基的同一性在本文實例12的表18-25中提供。

[表10]. LTβR結合蛋白的重鏈CDR序列

LIBC編號	Well ID	HCDR1		HCDR2		HCDR3	
		SEQ	ID	SEQ	ID	SEQ	ID
218990 (19320)	30H1	GDYMY*	475	WINPX ₅ SGGTNX ₁₁ -X ₁₇	499	EGSSGWSAEYX ₁₁ X ₁₂ X ₁₃	529
				WINPX ₅ SGGTNX ₁₁ -X ₁₇	500	EGSSGWSAEYX ₁₁ X ₁₂ X ₁₃	530

LIBC編號	Well ID	HCDR1		HCDR2		HCDR3	
		SEQ	ID	SEQ	ID	SEQ	ID
				WINPNSGGTNYAKKFQG	501	EGSSGWSAEYFQH	531
218994 (19321)	31A3	SYX ₈ X ₉ X ₁₀	476	IIWYX ₅ X ₆ SDX ₉ -X ₁₇	502	GDSEDFYYDX ₁₁ X ₁₂ X ₁₃	532
		SYX ₈ X ₉ X ₁₀	477	IIWYX ₅ X ₆ SDX ₉ -X ₁₇	503	GDSEDFYYDX ₁₁ X ₁₂ X ₁₃	533
		SYGMH	478	IIWYDGSDEYYADSVKG	504	GDSEDFYYDFDV	534
219058 (19324)	36G2	TSGMN	479	SVSSSGSYX ₉ -X ₁₇	505	AX ₂ YNWHFDASX ₁₁ X ₁₂	535
				SVSSSGSYX ₉ -X ₁₇	506	AX ₂ YNWHFDASX ₁₁ X ₁₂	536
				SVSSSGSYIYYADSVKG	507	ARYNWHFDASDI	537
219037 (19322)	34D1	SGGYFWS	480	YSHYSGTTYYNPSLKS	508	VPDGEDYFDY	538
219098 (19327)	44B1	SYAMS	481	TISGSGGSTYYADSVKG	509	VRDNWNYX ₈ X ₉ MDV	539
						VRDNWNYX ₈ X ₉ MDV	540
						VRDNWNYDGMDV	541
219098. 001		SYAMS	482	TISGSGGSTYYADSVKG	510	VRDNWNYDGMDV	542
219097 (19326)	43D9	DAWX ₉ X ₁₀	740	RIKTKTDGGTTDYAAPV KG*	743	DYGDYX ₆ X ₇	744
		DAWX ₉ X ₁₀	741			DYGDYX ₆ X ₇	745
		DAWMS	742			DYGDYXY	746
219051 (19323)	35F5	GYYLH	483	WINPNIGVTDX ₁₁ AQKFQ D	511	RGYNDDYDFDY	543
				WINPNIGVTDX ₁₁ AQKFQ D	512		
				WINPNIGVTDSAQKFQD	513		
218989- 1	29G8	TSGMGVG	484	LIYWNGGKLYSPSLKN	514	SGYYDNSGYYWDGMDV	544
218967	17F5	SYFWT	485	YIYYSGSTNYNPSLKS	515	VETIMAFDAFDI	545
218981	25C9	SGGYFWS	486	YTHYIGSTYYNPSLKS	516	VDTAMVDAFDI	546
218995	31C9	SRNWWG	487	YIHYIGNTYYNPSLKS	517	ETGSDGDDTFDI	547
218996	31B10	NYDMH	488	TIWYDGSNKYYADSVKG	518	LSTVTTGDYYGMDV	548
218998	32A2	SGGYFWG	489	YIHYIGSPYYNPSLKS	519	DCSSVNCQDAFDI	549
219083	41H7	SDGYFWS	490	FIYYSGTTYYNPSLKS	520	VCGGDCYDAFDI	550

LIBC編 號	Well ID	HCDR1		HCDR2		HCDR3	
		SEQ	ID	SEQ	ID	SEQ	ID
219092	43C1	NSIWWG	491	YIHYSGNTYYNPSLKS	521	NFGDVDAFDI	551
219023	33G6	SNSAAWN	492	RTYCRSKCYSDYALSVK	522	AVADHYSYALDV	552
				S			
219023.001		SNSAAWN	493	RTYYRSKWYSYALSVK	523	AVADHYSYALDV	553
219095	43G5	NYAMN	494	VISDSGGSSNYADSVKG	524	DRSIAGYYGMDV	554
219102	44G11	SYYWS	495	YIYYGGSTNYNPSLKS	525	SYSSAWYGSAY	555
218973	21A5	SYGIH	496	VIWYDGSKKYYADSVKG	526	DPSHYYGSGSYNYFYGM	556
						V	
219044	34F10	DNYMS	497	VIYSGGNTYYGDSVKG	527	PFFDY	557
218997	31E12	SGGYYS	498	YIYYSGSTYYNPSLMG	528	RGPVAGGFDY	558
*本文所描述的HDX互補位作圖實驗表明CDR不參與結合LTβR							

【0159】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白包含輕鏈可變區（VL），其中VL包含單獨或與VH CDR一起結合LTβR的一或多個互補決定區（即LCDR1、LCDR2和/或LCDR3）或其部分。在一個實施方式中，該VL包含SEQ ID NO: 559-589或其修飾序列中任一個的LCDR1胺基酸序列，其中與SEQ ID NO: 559-589中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。在一個實施方式中，該VL包含SEQ ID NO: 590-618或其修飾序列中任一個的LCDR2胺基酸序列，其中與SEQ ID NO: 590-618中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。在一個實施方式中，該VL包含SEQ ID NO: 619-643或其修飾序列中任一個的LCDR3胺基酸序列，其中與SEQ ID NO: 619-643中的任一個相比，所述修飾序列含有1、2或3個胺基酸殘基修飾。下表11中提供了本文所述之示例性促效劑LTβR結合蛋白的輕鏈CDR序列。

【0160】 如本文實例中所描述的，本文揭露的幾種LTβR抗體的互補位作圖研究表明，在某些情況下，特定LTβR抗體與LTβR的結合不涉及或需要抗體的所

有三個輕鏈CDR區和/或不涉及一或多個輕鏈CDR的所有殘基。顯示不參與LTβR抗體結合相互作用的輕鏈CDR在下表11中用星號表示。藉由互補位作圖或突變分析鑒定的顯示不參與LTβR抗體結合相互作用或其不需要的輕鏈CDR區的殘基被鑒定為可變殘基（X）。表11序列內的X殘基的同一性在本文實例12的表18-25中提供。

[表11]. LTβR結合蛋白的輕鏈CDR序列

LIBC編號	Well	LCDR1		LCDR2		LCDR3	
		SEQ	ID	SEQ	ID	SEQ	ID
218990 (19320)	30H1	X ₁ X ₂ X ₃ X ₄ SVSSSFX ₁₁	559	GASRRAT*	590	QQYGTSPLS	619
		X ₁₂					
		X ₁ X ₂ X ₃ X ₄ SVSSSFX ₁₁	560				
		X ₁₂					
		RASQSVSSSFLA	561				
218994 (19321)	31A3	SGSSSNIGKNX ₁₁ X ₁₂ X ₁₃	562	DNNX ₄ X ₅ PS	591	X ₁ X ₂ X ₃ DHSLSASX ₁₁ X ₁₂	620
		SGSSSNIGKNX ₁₁ X ₁₂ X ₁₃	563	DNNX ₄ X ₅ PS	592	X ₁ X ₂ X ₃ DHSLSASX ₁₁ X ₁₂	621
		SGSSSNIGKNYVS	564	DNNKRPS	593	GTWDHSLSASYV	622
219058 (19324)	36G2	RASQSISSDLN*	565	AASSLX ₆ X ₇	594	QQSYNTPLT*	623
				AASSLX ₆ X ₇	595		
				AASSLHS	596		
219097 (19326)	43D9	RTSQSISRYLN	566	GASSLX ₆ X ₇	597	HQSYSTPPT*	624
				GASSLX ₆ X ₇	598		
				GASSLQS	599		
219037 (19322)	34D1	RASQTISSYLN	567	DASSLQS	600	QQSFSAFIT	625
219098 (19327)	44B1	RX ₂ SQSLLYSSGYID	568	LGSNRAS	601	MQTIQTPLT	626
		LD					
		RX ₂ SQSLLYSSGYID	569				
		LD					

LIBC編號	Well	LCDR1		LCDR2		LCDR3	
	ID	SEQ	ID	SEQ	ID	SEQ	ID
		RCSQSLLYSSGYIDL D	570				
219098.00 1		RSSQSLLYSSGYIDL D	571	LGSNRAS	602	MQTIQTPLT	627
219051 (19323)	35F5	KSRQSLLHRX ₁₀ X ₁₁ K TYLY	572	EVSNRFS	603	MQSIQLPLI	628
		KSRQSLLHRX ₁₀ X ₁₁ K TYLY	573				
		KSRQSLLHRDGTKY LY	574				
218989	29G8	RASQSLISDYLV	575	GASSRPT	604	QQYDTSLN	629
218967	17F5	RASQSVGSSYLA	576	GASSRAT	605	QQYDTSPIT	630
218981	25C9	RASQNIDSSYLA	577	DTSSRAT	606	QQYGGSPIT	631
218995	31C9	RASQSIGSSYLA	578	GASGRAT	607	QQCYSSPIT	632
218996	31B1 0	SGSRSNIGNNYVS	579	DNSKRPS	608	GTWDSSLSAVV	633
218998	32A2	WSSQSIDSTYLA	580	GASTRAT	609	QQYSSSPIT	634
219083	41H7	RASQNISNTYLA	581	GASSRAT	610	QQYFSSPIT	635
219092	43C1	RASQSISSSYLA	582	GASSRAT	611	QQYYLSPLT	636
219023	33G6	RASQTIRTYLN	583	AASSLQS	612	QQSYSSPIT	637
219023.00 1		RASQTIRTYLN	584	AASSLQS	613	QQSYSSPIT	638
219095	43G5	RASQSISSDLN	585	AASSLHS	614	QQSYNTPLT	639
219102	44G1 1	QASQDISNYLI	586	DASNLET	615	QQYDHLPI	640
218973	21A5	SGSSSNIGNTYVS	587	DNNERPS	616	GTWDNSLTAVV	641
219044	34F10	RASQTVWSNYLA	588	GASRRVI	617	QQYGSSSIT	642
218997	31E12	RASQNVYNNYLA	589	GTSSRAT	618	QQYGSSLLCS	643
* 本文所描述的HDX互補位作圖實驗表明CDR不參與結合LTβR							

【0161】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白結合人LT β R的CRD2和CRD3，包括對應於SEQ ID NO: 4的殘基56-64和81-101（對應於SEQ ID NO: 1的殘基86-94和111-131）的一或多個殘基，並允許如本文所定義的內源性LT β R配體結合活性。該促效劑LT β R結合蛋白包含可變重鏈結構域（VH），其包含與SEQ ID NO: 501的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 531的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。視需要，該VH進一步包含與SEQ ID NO: 475的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列。在一個實施方式中，該LT β R結合蛋白的VH包含SEQ ID NO: 499的HCDR2序列和SEQ ID NO: 529的HCDR3序列；或如SEQ ID NO: 500的HCDR2序列和SEQ ID NO: 530的HCDR3序列進一步定義的。在一個實施方式中，該LT β R結合蛋白的VH包含SEQ ID NO: 501的HCDR2序列和SEQ ID NO: 531的HCDR3序列。視需要，該示例性促效劑LT β R結合蛋白的VH進一步包含SEQ ID NO: 475的HCDR1。

【0162】 根據前述實施方式，該促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 561的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，以及與SEQ ID NO: 619的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。視需要，該VL進一步包含與SEQ ID NO: 590的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列。在一個實施方式中，該VL包含SEQ ID NO: 559的LCDR1序列和SEQ ID NO: 619的LCDR3序列；或如SEQ ID NO: 560的LCDR1序列和SEQ ID NO: 619的LCDR3

序列進一步定義的；或如SEQ ID NO: 560的LCDRI序列和SEQ ID NO: 619的LCDRI序列進一步定義的。視需要，該VL進一步包含SEQ ID NO: 590的LCDRI。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218990（19320；30H1）的LT β R抗體。

【0163】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白係結合LT β R的CRDI的結合蛋白，包括對應於SEQ ID NO: 4的殘基3-9、20-29和38-47（對應於SEQ ID NO: 1的殘基33-39、50-59和68-77）的一或多個殘基。在一個實施方式中，該LT β R結合蛋白不阻斷或抑制內源性LIGHT與LT β R結合發生，以及至少或約80%的內源性LT α 1 β 2與LT β R結合發生。該LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 478的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDRI序列，與SEQ ID NO: 504的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDRI序列，以及與SEQ ID NO: 534的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDRI序列。在一個實施方式中，該LT β R結合蛋白的VH包含SEQ ID NO: 476的HCDRI序列，SEQ ID NO: 502的HCDRI序列和SEQ ID NO: 532的HCDRI序列；或如SEQ ID NO: 477的HCDRI序列、SEQ ID NO: 503的HCDRI序列和SEQ ID NO: 533的HCDRI序列進一步定義的；或如SEQ ID NO: 478的HCDRI序列、SEQ ID NO: 504的HCDRI序列和SEQ ID NO: 534的HCDRI序列進一步定義的。

【0164】根據前述實施方式，本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 564的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDRI序列，與SEQ ID NO: 593的序列共用至少80%、至少85%、至少90%、至少95%、

至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 622的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO:562的LCDR1序列、SEQ ID NO: 591的LCDR2和SEQ ID NO: 620的LCDR3序列；或如SEQ ID NO: 563的LCDR1序列、SEQ ID NO: 592的LCDR2和SEQ ID NO: 621的LCDR3序列進一步定義的；或如SEQ ID NO: 564的LCDR1序列、SEQ ID NO: 593的LCDR2和SEQ ID NO: 622的LCDR3序列進一步定義的。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218994 (19321; 31A3) 的LT β R抗體

【0165】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白結合人LT β R的CRD2和CRD3，包括對應於SEQ ID NO: 4的殘基56-64和81-101（對應於SEQ ID NO: 1的殘基86-94和111-131）的一或多個殘基。在一個實施方式中，該促效劑LT β R結合蛋白在< 8 nM的濃度下不阻斷內源性LIGHT或LT α 1 β 2與LT β R結合，如本文所描述的基於細胞的受體-配體測定所測量的（參見例如，實例8.2）。該LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 479的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 507的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 537的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該LT β R結合蛋白的VH包含SEQ ID NO: 479的HCDR1序列，SEQ ID NO: 505的HCDR2序列和SEQ ID NO: 535的HCDR3序列；或如SEQ ID NO: 479的HCDR1序列、SEQ ID NO: 506的HCDR2序列和SEQ ID NO: 536的HCDR3序列進一步定義的；或如SEQ ID NO: 479的HCDR1序列、SEQ ID NO: 507

的HCDR2序列和SEQ ID NO: 537的HCDR3序列進一步定義的。

【0166】 根據前述實施方式，本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 596的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列。視需要，該VL包含與SEQ ID NO: 565的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，以及視需要包含與SEQ ID NO: 623的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 594的LCDR2，或如SEQ ID NO: 595的LCDR2進一步定義的，或如SEQ ID NO: 596的LCDR2進一步定義的。視需要，該VL包含SEQ ID NO: 565的LCDR1序列，SEQ ID NO: 596的LCDR2和SEQ ID NO: 623的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219058 (19324; 36G2) 的LT β R抗體。

【0167】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白係結合LT β R且不阻斷或抑制LIGHT與LT β R結合發生的結合蛋白。該促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 480的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 508的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 538的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 408的HCDR1序列，SEQ ID NO: 508的HCDR2和SEQ ID NO: 538的HCDR3序列。

【0168】 根據前述實施方式，本揭露之促效劑LT β R結合蛋白視需要進一步

包含VL，其中該VL包含與SEQ ID NO: 567的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 600的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 625的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 567的LCDR1序列，SEQ ID NO: 600的LCDR2和SEQ ID NO: 625的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LTβR結合蛋白包括但不限於本文鑒定為LIBC No. 219037 (19322; 34D1) 的LTβR抗體。

【0169】 在另一個實施方式中，本揭露之促效劑LTβR結合蛋白係結合LTβR且不阻斷或抑制如本文定義的LIGHT與LTβR結合的結合蛋白。在一個實施方式中，該促效劑LTβR結合蛋白不阻斷或抑制LIGHT與LTβR結合。該LTβR結合蛋白包含VH，其中該VH包含與SEQ ID NO: 4812的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 509的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 539的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 481的HCDR1序列、SEQ ID NO: 509的HCDR2和SEQ ID NO: 539的HCDR3序列，或如SEQ ID NO: 481的HCDR1序列、SEQ ID NO: 509的HCDR2和SEQ ID NO: 540的HCDR3序列進一步定義的；或如SEQ ID NO: 481的HCDR1序列、SEQ ID NO: 509的HCDR2和SEQ ID NO: 541的HCDR3序列進一步定義的。

【0170】 根據前述實施方式，本揭露之促效劑LTβR結合蛋白視需要進一步

包含VL，其中該VL包含與SEQ ID NO: 570的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 601的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 626的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 568的LCDR1序列、SEQ ID NO: 601的LCDR2和SEQ ID NO: 626的LCDR3序列；或如SEQ ID NO: 569的LCDR1序列、SEQ ID NO: 601的LCDR2和SEQ ID NO: 626的LCDR3序列進一步定義的；或如SEQ ID NO: 570的LCDR1序列、SEQ ID NO: 601的LCDR2和SEQ ID NO: 626的LCDR3序列進一步定義的；或如SEQ ID NO: 571的LCDR1序列、SEQ ID NO: 602的LCDR2和SEQ ID NO: 627的LCDR3序列進一步定義的。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219098 (19327; 44B1) 的LT β R抗體。

【0171】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或促效劑LT β R雙特異性結合蛋白）結合人LT β R CRD1，包括對應於SEQ ID NO: 4的殘基1-19（對應於SEQ ID NO: 1的殘基31-49）的一或多個殘基。該促效劑LT β R結合蛋白不阻斷LIGHT與LT β R結合並且不阻斷LT α 1 β 2與LT β R結合。該促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 483的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 513的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 543的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一

性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO:483的HCDR1序列、SEQ ID NO: 511的HCDR2和SEQ ID NO: 543的HCDR3序列；或如SEQ ID NO: 483的HCDR1序列、SEQ ID NO: 512的HCDR2和SEQ ID NO: 543的HCDR3序列進一步定義的；或如SEQ ID NO: 483的HCDR1序列、SEQ ID NO: 513的HCDR2和SEQ ID NO: 543的HCDR3序列進一步定義的。

【0172】根據前述實施方式，本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 574的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 603的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 628的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO:57217的LCDR1序列、SEQ ID NO: 603的LCDR2和SEQ ID NO: 628的LCDR3序列；或如SEQ ID NO: 573的LCDR1序列、SEQ ID NO: 603的LCDR2和SEQ ID NO: 628的LCDR3序列進一步定義的；或如SEQ ID NO: 574的LCDR1序列、SEQ ID NO: 603的LCDR2和SEQ ID NO: 628的LCDR3序列進一步定義的。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219051（19323；35F5）的LT β R抗體。

【0173】在另一個實施方式中，本揭露之LT β R結合蛋白係結合LT β R CRD1和CRD2的基於抗體的分子，包括對應於SEQ ID NO: 4的殘基38-42和56-70的一或多個殘基。該基於LT β R抗體的分子包含VH，其中該VH包含與SEQ ID NO: 742的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，以及與SEQ ID NO: 746的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或

至少99%序列同一性的HCDR3序列。視需要，該LT β R結合蛋白的VH進一步包含與SEQ ID NO: 743的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列。在任何實施方式中，該LT β R結合蛋白的VH包含SEQ ID NO: 740的HCDR1序列和SEQ ID NO: 744的HCDR3序列；或如SEQ ID NO: 741的HCDR1序列和SEQ ID NO: 745的HCDR3序列進一步定義的；或如SEQ ID NO: 742的HCDR1序列和SEQ ID NO: 746的HCDR3序列進一步定義的。視需要，該示例性LT β R結合蛋白的VH進一步包含SEQ ID NO: 743的HCDR2。

【0174】根據前述實施方式，本揭露之該基於LT β R抗體的分子視需要進一步包含VL，其中該VL包含與SEQ ID NO: 566的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 599的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列。視需要，該VL進一步包含與SEQ ID NO: 624的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在任何實施方式中，該VL包含SEQ ID NO: 566的LCDR1序列和SEQ ID NO: 597的LCDR2；或如SEQ ID NO: 566的LCDR1序列和SEQ ID NO: 598的LCDR2進一步定義的；或如SEQ ID NO: 566的LCDR1序列和SEQ ID NO: 599的LCDR2進一步定義的。視需要，該VL進一步包含SEQ ID NO: 624的LCDR3。包含該實施方式的VH和VL之示例性基於LT β R抗體的分子包括但不限於本文鑒定為LIBC No. 219097 (19326; 43D9) 的LT β R抗體。

【0175】在另一個實施方式中，該促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 484的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID

NO: 514的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 544的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 484的HCDR1序列，SEQ ID NO: 514的HCDR2和SEQ ID NO: 544的HCDR3序列。該促效劑LT β R結合蛋白進一步包含VL，其中該VL包含與SEQ ID NO: 575的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 604的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 629的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 575的LCDR1序列，SEQ ID NO: 604的LCDR2和SEQ ID NO: 629的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218989的LT β R抗體。

【0176】在另一個實施方式中，該促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 485的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 515的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 545的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 485的HCDR1序列，SEQ ID NO: 515的HCDR2和SEQ ID NO: 545的HCDR3序列。本揭露之促效劑LT β R結合蛋白進一步包含VL，其中該VL包含與

SEQ ID NO: 576的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 605的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 630的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 576的LCDR1序列，SEQ ID NO: 605的LCDR2和SEQ ID NO: 630的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218967的LT β R抗體。

【0177】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 486的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 516的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 546的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 486的HCDR1序列，SEQ ID NO: 516的HCDR2和SEQ ID NO: 546的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 577的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 606的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 631的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含

SEQ ID NO: 577的LCDR1序列，SEQ ID NO: 6068的LCDR2和SEQ ID NO: 631的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218981的LT β R抗體。

【0178】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 487的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 517的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 547的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 487的HCDR1序列，SEQ ID NO: 517的HCDR2和SEQ ID NO: 547的HCDR3序列。本揭露之促效劑LT β R結合蛋白進一步包含VL，其中該VL包含與SEQ ID NO: 578的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 607的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 632的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 578的LCDR1序列，SEQ ID NO: 607的LCDR2和SEQ ID NO: 632的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218995的LT β R抗體。

【0179】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 488的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，

與SEQ ID NO: 518的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 548的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 488的HCDR1序列，SEQ ID NO: 518的HCDR2和SEQ ID NO: 548的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 579的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 608的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 633的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 579的LCDR1序列，SEQ ID NO: 608的LCDR2和SEQ ID NO: 633的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218996的LT β R抗體。

【0180】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 489的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 519的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 549的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 489的HCDR1序列，SEQ ID NO: 519的HCDR2和SEQ ID NO: 549的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中

該VL包含與SEQ ID NO: 580的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 609的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 634的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 580的LCDR1序列，SEQ ID NO: 609的LCDR2和SEQ ID NO: 634的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218998的LT β R抗體。

【0181】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 490的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 520的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 550的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 490的HCDR1序列，SEQ ID NO: 520的HCDR2和SEQ ID NO: 550的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 581的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 610的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 635的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含

SEQ ID NO: 581的LCDR1序列，SEQ ID NO: 610的LCDR2和SEQ ID NO: 635的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219083的LT β R抗體。

【0182】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 491的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 521的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 551的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 491的HCDR1序列，SEQ ID NO: 521的HCDR2和SEQ ID NO: 551的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 582的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 611的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 636的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 582的LCDR1序列，SEQ ID NO: 611的LCDR2和SEQ ID NO: 636的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219092的LT β R抗體。

【0183】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白係結合LT β R並允許內源性LT β R配體結合活性的結合蛋白，如本文所定義的。該LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 492的序列共用至少80%、至少

85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 522的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 552的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 492的HCDR1序列，SEQ ID NO: 522的HCDR2和SEQ ID NO: 552的HCDR3序列。在一個實施方式中，SEQ ID NO: 522的HCDR2被修飾以取代SEQ ID NO: 522中的位置4和8處的半胱胺酸殘基。在一個實施方式中，該LT β R結合蛋白的HCDR2包含SEQ ID NO: 523的HCDR2。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 583的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 612的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 637的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 583的LCDR1序列，SEQ ID NO: 612的LCDR2和SEQ ID NO: 637的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219023的LT β R抗體。

【0184】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 494的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 524的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID

NO: 554的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 494的HCDR1序列，SEQ ID NO: 524的HCDR2和SEQ ID NO: 554的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 585的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 614的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 639的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 585的LCDR1序列，SEQ ID NO: 614的LCDR2和SEQ ID NO: 639的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219095的LT β R抗體。

【0185】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 495的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 525的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 555的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 495的HCDR1序列，SEQ ID NO: 525的HCDR2和SEQ ID NO: 555的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 586的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與

SEQ ID NO: 615的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 640的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 586的LCDR1序列，SEQ ID NO: 615的LCDR2和SEQ ID NO: 640的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219102的LT β R抗體。

【0186】在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 496的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 526的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 556的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 496的HCDR1序列，SEQ ID NO: 526的HCDR2和SEQ ID NO: 556的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 587的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 616的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 641的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 587的LCDR1序列，SEQ ID NO: 616的LCDR2和SEQ ID NO: 641的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但

不限於本文鑒定為LIBC No. 218973的LT β R抗體。

【0187】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 497的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 527的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID NO: 557的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 497的HCDR1序列，SEQ ID NO: 527的HCDR2和SEQ ID NO: 557的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 588的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 617的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 642的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 588的LCDR1序列，SEQ ID NO: 617的LCDR2和SEQ ID NO: 642的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 219044的LT β R抗體。

【0188】 在另一個實施方式中，本揭露之促效劑LT β R結合蛋白包含VH，其中該VH包含與SEQ ID NO: 498的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR1序列，與SEQ ID NO: 528的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR2序列，以及與SEQ ID

NO: 558的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的HCDR3序列。在一個實施方式中，該VH包含SEQ ID NO: 498的HCDR1序列，SEQ ID NO: 528的HCDR2和SEQ ID NO: 558的HCDR3序列。本揭露之促效劑LT β R結合蛋白視需要進一步包含VL，其中該VL包含與SEQ ID NO: 589的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR1序列，與SEQ ID NO: 618的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR2序列，以及與SEQ ID NO: 643的序列共用至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%序列同一性的LCDR3序列。在一個實施方式中，該VL包含SEQ ID NO: 589的LCDR1序列，SEQ ID NO: 618的LCDR2和SEQ ID NO: 643的LCDR3序列。包含該實施方式的VH和VL之示例性促效劑LT β R結合蛋白包括但不限於本文鑒定為LIBC No. 218997的LT β R抗體。

【0189】 對本文揭露的LT β R結合蛋白的重鏈CDR序列和/或輕鏈CDR序列的合適的胺基酸修飾包括，例如，保守取代或功能等效的胺基酸殘基取代，該等取代導致變體CDR序列具有與上文描述的CDR序列的那些相似或增強的結合特徵。本揭露涵蓋的是含有1、2、3、4、5或更多個胺基酸取代（取決於CDR的長度）的表2、3、6、7、9和10的CDR，該等取代維持或增強抗體的LT β R結合。所得修飾的CDR在序列上與表2、3、6、7、9和10中提供的CDR係至少70%、至少75%、至少80%、至少85%、至少90%、至少95%相似。

【0190】 對本文揭露的重鏈和輕鏈CDR序列的合適的胺基酸修飾包括，例如，保守取代或功能等效的胺基酸殘基取代，該等取代導致變體CDR序列具有與本文揭露的CDR序列的那些相似或增強的結合特徵。保守取代係發生在與其側鏈相關的胺基酸家族中的取代。基因編碼的胺基酸可分為四個家族：(1) 酸性（天

冬胺酸、麩胺酸)；(2) 鹼性 (離胺酸、精胺酸、組胺酸)；(3) 非極性 (丙胺酸、纈胺酸、白胺酸、異白胺酸、脯胺酸、苯丙胺酸、蛋胺酸、色胺酸)；以及 (4) 不帶電荷的極性 (甘胺酸、天冬醯胺、麩醯胺酸、半胱胺酸、絲胺酸、蘇胺酸、酪胺酸)。苯丙胺酸、色胺酸和酪胺酸有時被共同分類為芳香族胺基酸。可替代地，胺基酸庫可以分組為 (1) 酸性 (天冬胺酸、麩胺酸)；(2) 鹼性 (離胺酸、精胺酸、組胺酸)，(3) 脂肪族 (甘胺酸、丙胺酸、纈胺酸、白胺酸、異白胺酸、絲胺酸、蘇胺酸)，其中絲胺酸和蘇胺酸視需要地單獨分組為脂肪族羥基；(4) 芳香族 (苯丙胺酸、酪胺酸、色胺酸)；(5) 醯胺 (天冬醯胺、麩醯胺酸)；以及 (6) 含硫 (半胱胺酸和蛋胺酸) (Stryer (編輯), Biochemistry[生物化學], 第2版, WH Freeman and Co., 1981，特此藉由引用將其全部併入)。也可以對本文揭露的重鏈CDR序列和輕鏈CDR序列進行非保守取代。非保守取代涉及用來自不同類別胺基酸的一或多個胺基酸殘基取代CDR的一或多個胺基酸殘基，以改善或增強CDR的結合特性。本文揭露的重鏈可變區CDR和/或輕鏈可變區CDR的胺基酸序列可進一步包含維持或增強LTβR結合的一或多個內部中性胺基酸插入或缺失。

【0191】如本文所描述的結合LTβR的LTβR結合蛋白可以包含可變輕鏈 (VL)、可變重鏈 (VH) 或VL鏈和VH鏈的組合。在一個實施方式中，該LTβR結合蛋白的VH鏈包含下表12中提供的VH胺基酸序列中的任一個，或與表12中列出的VH胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%或至少95%相同的胺基酸序列。在一個實施方式中，該LTβR結合蛋白的VL鏈包含下表12中提供的VL胺基酸序列中的任一個，或與表12中列出的VL胺基酸序列中的任一個至少75%、至少80%、至少85%、至少90%、至少95%相同的胺基酸序列。

【0192】在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人LTβR (SEQ ID NO: 1)，同時允許內源性LTβR配體結合和活性 (即LIGHT或LTα1β2結合)，如本文所描述的，並且包含與表12中所列的VH結構域胺基酸序

列中的任一個具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域。在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人LTβR(SEQ ID NO: 1)，同時允許內源性LTβR配體結合和活性（即LIGHT或LTα1β2結合），如本文所描述的，並且包含與表12中所列的VL結構域胺基酸序列中的任一個具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人LTβR（SEQ ID NO: 1），同時允許內源性LTβR配體結合和活性（即LIGHT或LTα1β2結合），如本文所描述的，並且包含與表12中所列的VH結構域胺基酸序列中的任一個具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域，以及與表12中所列的相應VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。

[表12]. LTβR結合蛋白VH和VL胺基酸序列

LIBC 編號	Well ID	結構域	序列	SEQ ID
218990	30H1 19320	V _H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGDYMYWVRQAPG QGLEWMGWINPNSGGTNYAKKFQGRVTMTRDTSISTAYMELSR LRSDDTAVYYCAREGSSGWSAEYFQHWGQGTLVTVFS	644
		V _L	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFLAWYQQKLGQAP RLLMYGASRRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGTSPLSFGGGGTKVEIKR	645
218994	31A3/ 19321	V _H	QVQLVESGGAVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGK GLEWVAIIWYDGSDEYYADSVKGRFTISRDN SKNTLYLQMNSV RDEDTALYYCVRGDSSEDFYYDFDVWGQGTTVTVSS	646
		V _L	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGKNYVSWYQHLPGTAP KLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCG TWDHSLSASYVFGTGKVTVLG	647
219058	36G2/ 19324	V _H	EVQLVESGGGLVKPGGSLRLSCAASGFTFSTSGMNWVRQAPGK GLEWVSSVSSSGSYIYYADSVKGRFTISRDN AKNSLYLQMNSLR	648

LIBC 編號	Well ID	結構域	序列	SEQ ID
			AEDTAVYYCAGARYNWHFDASDIWGQGTVVTVSS	
		V _L	DIQMTQSPSSLSASVGDRVTTTCRASQSISSDLNWFYQQKPGKAPN LLIYAASSLHSGVPSRFSGSGSGTDFTLTISLLPEDFATYYCQQS YNTPLTFGGGTKVEIKR	649
219097	43D9/ 19326	V _H	EVQLVESGGGLVKPGGSLRLSCAASGFTFNDAWMSWVRQAPGK GLEWVGRIKTKTDGGTTDYAAPVKGRITISRDDSKNTLYLQMNS LKTEDTAVYYCTTDYGDYEWGQGTLLTVSS	650
		V _L	DIQMTQSPSSLSASVGDRVTTTCRTSQSISRYLNWFYQQKPGKAPK LLIYGASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCHQS YSTPPTFGQGTKVEIKR	651
219037	34D1/ 19322	V _H	QVQLQESGPGRVKPSQTLSTCTVSGGSINSGGYFWSWIRQHPG KVLEWIGYSHYSGTTYNPSLKSRTISVDTSKNQLSLKLSNVN AADTAVYYCARVPDGEDYFDYWGQALVTVSS	652
		V _L	DLQLTQSPSSLSASVGDRVTTTCRASQTISSYLNWFYQQKPGKAPK LLIYDASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFETYYCQQSF SAPITFGQGTTRLEIKR	653
219098	44B1/ 19327	V _H	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK GLEWVSTISGSGGSTYYADSVKGRFTISRDN SKNTLNLQMNSLR AEDTAVYYCAKVRDNWNYDGMDVWGQGTTVTVSS	654
		V _L	DIVMTQSPLSLPVTLGESASISCRCSQSLLYSSGYIDL DWYLQKPG QSPQLLIYLG SNRASGV PDRFSGSGSGTDFTLKISRVEAEDVGVY YCMQTIQTPLTFGGGTKVEIKR	655
219098. 001		V _H	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK GLEWVSTISGSGGSTYYADSVKGRFTISRDN SKNTLNLQMNSLR AEDTAVYYCAKVRDNWNYDGMDVWGQGTTVTVSS	656
		V _L	DIVMTQSPLSLPVTLGESASISCRSSQSLLYSSGYIDL DWYLQKPG QSPQLLIYLG SNRASGV PDRFSGSGSGTDFTLKISRVEAEDVGVY YCMQTIQTPLTFGGGTKVEIKR	657
219051	35F5/ 19323	V _H	QVQLVQSGAEVKKPGASVKVSKASGYTFTGYLHWVRQAPG QGLEWMGWINPNIGVTDSAQKFQDRVMTMTRDTSISTAYMELSR	658

LIBC 編號	Well ID	結構域	序列	SEQ ID
			LISDDTAVYYCTVRGYNDYDFDYWGQGLVTVSS	
		V _L	DVVMTQTPLSLSVTPGPASISCKSRQSLLRDGGKTYLYWYLQK PGQPPQLLIYEVSNNRFSGVNRFSGSGSGTDFTLKISRVEAEDVGV YYCMQSIQLPLIFGGGTRVDIKR	659
218989	29G8	V _H	QITLKESGPTLVKPTQTLTLTCTFTGFSLSSTSGMGVGVIRQPPGK ALEWLALIYWNGGKLYSPSLKNRLTITKDTSKNQVVLMTNMD PVDATYYCAHSGYYDNSGYWGDMDVWGQGTITVTVSP	660
		V _L	EIVLTQSPVTLSPGERATLSCRASQSLIDYLVWYQQKPGQAP RLLIYGASSRPTGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQ YDTSLNFGGGTKVEIKR	661
218967	17F5	V _H	QVQLQESGPGVVKPSETLSLTCTVSGGSISSYFWTWIRQPPGKGL EWIGYIYYSGSTNYNPSLKSRTFSVDTSKNQFSLKLSVTAADT AVYYCARVETIMAFDAFDIWGQGTMTVTVSS	662
		V _L	EIVLTQSPGTLSPGERATLSCRASQSVGSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYFCQQ YDTSPITFGQGTRLEIKR	663
218981	25C9	V _H	QVQLQESGPGLVKPSQTLTLTCTVSGGSISSGGYFWSWIRQHPGK GLEWIGYTHYIGSTYYNPSLKSRTAFSVDTSKNQFSLKLSSVTAA DTAVYYCARVDTAMVDAFDIWGQGTMTVTVSS	664
		V _L	EIMLTQSPGTLSPGERATLSCRASQNIDSSYLAWYQQTPGQAP RLLIYDTSSRATGIPDRFSGSGSGTDFTLTISRLEPEDFSVYYCQQ YGGSPITFGQGTRLDIKR	665
218995	31C9	V _H	QVQLQESGPGLVKPSDTLSLTCAVSGYSSRNWWGIRQPPGK GLEWIGYIHYIGNTYYNPSLKSRTMSVDTSKNQFSLKLSSVTAV DTAVYYCARETGSDGDDTFDIWGQGTMTVTVSS	666
		V _L	EIVLTQSPVTLSPGERATLSCRASQSIGSSYLAWYQQKPGQAP RLLIYGASGRATGIPDRFSGSGSGTDFTLTISRLEPEDFALYYCQQ CYSSPITFGHGTRLDIKR	667
218996	31B1 0	V _H	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYDMHWVRQAPGK GLEWVTTIWYDGSNKYYADSVKGRFTISRDN SKNTLFLQMNSL	668

LIBC 編號	Well ID	結構域	序列	SEQ ID
			RAEDTAVYYCPTLSTVTTGDYYGMDVWGQGTAVTVSS	
		V _L	QSVLTQPPSVSAAPGQKVTISCSGSRSNIGNNYVSWYQQLPGTVP KLLIYDNSKRPSGIPDRFSGSKSGTSVTLGITGLQTGDEADYYCG TWDSSLSAVVFGGGTKLTVLS	669
218998	32A2	V _H	QVQLQESGPGQVKPSQTLSTCTVSGGSISSGGYFWGWIRQHPG KGLEWIGYIHYIGSPYYNPSLKSRTTISVDTSKNQFSLKLSSVIAA DTAVYYCARDCSSVNCQDAFDIWGQGTMTVTVSS	670
		V _L	EIVLTQSPGTLSPGERASLSCWSSQSIDSTYLAWYHQKPGQAP RLLIYGASTRATGIPDRFSGSGSGTDFTLSISRLEPEDFAVYYCQQ YSSSPITFGQGTRLEIKR	671
219083	41H7	V _H	QVQLQESGPGLVKPSQTLSTCTVSGGSIRSDGYFWSWIRQHPG KGLEWLGFIYYSGTTYYNPSLKSRTTISVDTSKNQFSLKLTSVTV ADTAVYYCARVCGGDCYDAFDIWGQGTMTVTVSS	672
		V _L	DIVLTQSPGTLSPGEGATLSCRASQNISNTYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYDCQQ YFSSPITFGGGTRVEIKR	673
219092	43C1	V _H	QVQVQESGPGLVKPSDTLSLTCAVSGYSISNSIWWGWIRQPPGK GLEWIGYIHYSGNTYYNPSLKSRTTMSVDTSKNQFSLKLNSVTA VDTAVYYCARNFGDVDAFDIWGQGTMTVTVSS	674
		V _L	EIVLTQSPGTLSPGERATLSCRASQSISSSYLAWYQQKPGQAPR LLIYGASSRATGIPDRFSGSGSGTDFTLNISRLEPEDFVYYCQQY YLSPLTFGGGTKVEIKR	675
219023	33G6	V _H	QVQLQQSGPGLVKPSQTLSTCAISGDSVFSNSAAWNWIRQSPSR GLEWLGRTYCRSKCYSDYALSVKSRATINPDTSENQFSLQLNSV TPEDTAVYYCARAVADHYSYALDVWGQGTTVNVSS	676
		V _L	DIQMNQSPSSLSASVGDRVTTICRASQTIRTYLNWYQQKPGKAP KVLIIYAASSLQSGVPSRFSGTGSGTDFTLTITSLQPEDFATYSCQQ SYSSPITFGGGTKVEIKR	677
219023. 001		V _H	QVQLQQSGPGLVKPSQTLSTCAISGDSVFSNSAAWNWIRQSPSR GLEWLGRTYYSKWYSYALSVKSRATINPDTSENQFSLQLNSV	678

LIBC 編號	Well ID	結構域	序列	SEQ ID
			TPEDTAVYYCARAVADHYSYALDVWGQGTTVTVSS	
		V _L	DIQMTQSPSSLSASVGDRVTTTCRASQTIRTYLNWYQQKPGKAPK VLIYAASSLQSGVPSRFSGTGSGTDFTLTITSLQPEDFATYSCQQS YSSPITFGGGTKVEIKR	679
219095	43G5	V _H	EVQLLESGGNLVQPGGSLRLSCVVS GFTFN NYAMNWVRQAPGK GLEWVSVISDSGGSSNYADSVKGRFTISRDN SKKTLYLQMNSLR AEDTAVYYCAKDRSIAGYYGMDVWGQGTTVTVSS	680
		V _L	DIQMTQSPSSLSASVGDRVTTTCRASQSISSDLNWYQQKPGKAPN LLIYAASSLHSGVPSRFSGSGSGTDFTLTISLLPEDFATYYCQQS YNTPLTFGGGTKVEIKR	681
219102	44G1 1	V _H	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRLPPGKGL EWIGYIYYGGSTNYNPSLKSRVSM SVDTSKNQFSLKLSYVTAAD TAVYYCARSYSSAWYGSAYWGQGT LVIVSS	682
		V _L	DIQMTQSPSSLSASLGDRVTTTCQASQDISNYLIWYQLKPGKAPK VLIYDASNLETGVPSRFSGNGSGTDFTFTISSLPEDIATYYCQQY DHLPTFGQGTRLDIKR	683
219102. 001		V _H	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRLPPGKGL EWIGYIYYGGSTNYNPSLKSRVSM SVDTSKNQFSLKLSYVTAAD TAVYYCARSYSSAWYGSAYWGQGT LVIVSS	684
		V _L	DIQMTQSPSSLSASLGDRVTTTCQASQDISNYLIWYQLKPGKAPK VLIYDASNLETGVPSRFSGSGSGTDFTFTISSLPEDIATYYCQQY DHLPTFGQGTRLDIKR	685
218973	21A5	V _H	QVQLVESGGGVVQGRSLRLSCAASGFTFSSYGIHWVRQAPGKG LEWVAVIWYDGSKKYYADSVKGRFTISRDN SKSTLYLQMNSLR AEDTAVYYCARDPSHYYGSGSYNYFYGMDVWGQGTTVTVSS	686
		V _L	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNTYVSWYQQLPGTAP KLLIYDNNERPSGIPDRFSGSKSDTSATLGITGLQTGDEADYYCG TWDNSLTAVVFGGGTKLTVLG	687
219044	34F1 0	V _H	EVQLVESGGGLIQPGGSLRLSCAASGFTVSDNYMSWVRQAPGK GLEWVSVIYSGGNTYYGDSVKGRFTISRDN SKNTLYLQMNSLRA	688

LIBC 編號	Well ID	結構域	序列	SEQ ID
			EDTAVYFCTGPFFDYWGPGTLVTVSS	
		V _L	EIVLTQFPGTLSLSPGEGGTLSCRASQTVWSNYLAWYQQKPGQA PRLLIYGASRRVIGIPDRFSGSGSGTDNFLTISSLEPGDFAVYYCQ QYGSSSITFGQGTRLEIKR	689
		V _H	QVQVQESGPGLVKPSQTLSTCTVSGGSISSGGYYWSWIRQHPG KGLEWIGYIYYSGSTYYNPSLMGRVTISVDTSKNQFSLRLSSVTA ADTAVYYCARRGPVAGGFDYWQGQTLVTVSS	690
218997	31E1 2	V _L	EIVLTQSPGTLSLSPGERATLSCRASQNVYNNYLAWYQQKPRQA PRLLIYGTSSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSLLCSFGQGTKLEIKR	691

【0193】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR。該促效劑LTβR結合蛋白在表位結合人LTβR的CRD2和CRD3，該表位包含SEQ ID NO: 4之位置56-64和81-101（對應於SEQ ID NO: 1的殘基86-94和111-131）處的一或多個殘基或由其組成。該促效劑LTβR結合蛋白包含與SEQ ID NO: 644的VH結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 645的VL結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 644至少95%相同的VH胺基酸序列和與SEQ ID NO: 645至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 644的VH胺基酸序列和SEQ ID NO: 645的VL胺基酸序列（30H1/19320）。

【0194】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR。該促效劑LTβR結合蛋白在表位結合人LTβR的CRD1，該表位包含SEQ ID NO: 4之位置3-9、12-29和38-47（對應於SEQ ID NO: 1的殘基33-39、50-59和68-77）處的一或多個殘基或由其組成。該促效劑LTβR結合蛋白允許發生

100%的LIGHT與LTβR結合和/或至少或約80%的LTα1β2與LTβR結合，並且包含與SEQ ID NO: 646的VH結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域。該LTβR結合蛋白進一步包含與SEQ ID NO: 647的VL結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 646至少95%相同的VH胺基酸序列和與SEQ ID NO: 647至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 646的VH胺基酸序列和SEQ ID NO: 647的VL胺基酸序列（19321）。

【0195】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR。該促效劑LTβR結合蛋白在表位結合人LTβR的CRD2和CRD3，該表位包含SEQ ID NO: 4之位置56-64和81-101（對應於SEQ ID NO: 1的殘基86-94和111-131）處的一或多個殘基或由其組成。該促效劑LTβR結合蛋白在基於細胞的受體-配體測定中在< 8 nM濃度下不抑制LIGHT和LTα1β2與LTβR結合，如本文所描述的。該LTβR結合蛋白包含與SEQ ID NO: 648的VH結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 649的VL結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 648至少95%相同的VH胺基酸序列和與SEQ ID NO: 649至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 648的VH胺基酸序列和SEQ ID NO: 649的VL胺基酸序列（19324）。

【0196】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR。該LTβR結合蛋白在表位結合人LTβR的CRD1和CRD2，該表位包含SEQ ID NO: 4之位置38-42、56-65和65-70處的一或多個殘基或由其組成。該促效劑LTβR結合蛋白包含與SEQ ID NO: 650的VH結構域胺基酸序列具有至少

80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 651的VL結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 650至少95%相同的VH胺基酸序列和與SEQ ID NO: 651至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 650的VH胺基酸序列和SEQ ID NO: 651的VL胺基酸序列。

【0197】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR，並且不抑制內源性LIGHT與LTβR結合。該促效劑LTβR結合蛋白包含與SEQ ID NO: 652的VH結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 653的VL結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 652至少95%相同的VH胺基酸序列和與SEQ ID NO: 653至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 652的VH胺基酸序列和SEQ ID NO: 653的VL胺基酸序列（19322）。

【0198】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白結合並激動人和cyno LTβR，並且不抑制內源性LIGHT與LTβR結合。該促效劑LTβR結合蛋白包含與SEQ ID NO: 654至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 655或SEQ ID NO: 657至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 654至少95%相同的VH胺基酸序列和與SEQ ID NO: 657至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 654的VH胺基酸序列和SEQ ID NO: 657的VL胺基酸序列（19327）。

【0199】 在一個實施方式中，本揭露之LTβR結合蛋白結合並激動人和cyno

LT β R，以及不抑制LT α 1 β 2與LT β R結合且不抑制LIGHT與LT β R結合。該促效劑LT β R結合蛋白包含與SEQ ID NO: 658的VH結構域胺基酸序列具有至少80%、至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 659的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 658至少95%相同的VH胺基酸序列和與SEQ ID NO: 659至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 658的VH胺基酸序列和SEQ ID NO: 659的VL胺基酸序列（35F5/19323）。

【0200】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白結合並激動人和cyno LT β R，並包含與SEQ ID NO: 660至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 661至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 660至少95%相同的VH胺基酸序列和與SEQ ID NO: 661至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 660的VH胺基酸序列和SEQ ID NO: 661的VL胺基酸序列。

【0201】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白結合並激動人和cyno LT β R，並包含與SEQ ID NO: 662至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 663至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 662至少95%相同的VH胺基酸序列和與SEQ ID NO: 663至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 662的VH胺基酸序列和SEQ ID NO: 663的VL胺基酸序列。

【0202】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 664至少80%、至少85%或至少90%相

同的VH胺基酸序列和與SEQ ID NO: 665至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 664至少95%相同的VH胺基酸序列和與SEQ ID NO: 665至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 664的VH胺基酸序列和SEQ ID NO: 665的VL胺基酸序列。

【0203】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係促效劑結合蛋白，其結合LTβR，並包含與SEQ ID NO: 666至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 667至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 666至少95%相同的VH胺基酸序列和與SEQ ID NO: 667至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 666的VH胺基酸序列和SEQ ID NO: 667的VL胺基酸序列。

【0204】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係促效劑結合蛋白，其結合LTβR，並包含與SEQ ID NO: 668至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 669至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 668至少95%相同的VH胺基酸序列和與SEQ ID NO: 669至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 668的VH胺基酸序列和SEQ ID NO: 669的VL胺基酸序列。

【0205】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係促效劑結合蛋白，其結合LTβR，並包含與SEQ ID NO: 670至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 671至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 670至少95%相同的VH胺基酸序列和與SEQ ID NO: 671至少95%相同的VL胺基

酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 670的VH胺基酸序列和SEQ ID NO: 671的VL胺基酸序列。

【0206】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 672至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 673至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 672至少95%相同的VH胺基酸序列和與SEQ ID NO: 673至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 672的VH胺基酸序列和SEQ ID NO: 673的VL胺基酸序列。

【0207】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 674至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 675至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 674至少95%相同的VH胺基酸序列和與SEQ ID NO: 675至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 674的VH胺基酸序列和SEQ ID NO: 675的VL胺基酸序列。

【0208】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 676至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 677至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 676至少95%相同的VH胺基酸序列和與SEQ ID NO: 677至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 676的VH胺基酸序列和SEQ ID NO: 677的VL胺基酸序列。

【0209】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合

蛋白，其結合LTβR，並包含與SEQ ID NO: 678至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 679至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 678至少95%相同的VH胺基酸序列和與SEQ ID NO: 679至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 678的VH胺基酸序列和SEQ ID NO: 679的VL胺基酸序列。

【0210】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係促效劑結合蛋白，其結合LTβR，並包含與SEQ ID NO: 680至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 681至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 680至少95%相同的VH胺基酸序列和與SEQ ID NO: 681至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 680的VH胺基酸序列和SEQ ID NO: 681的VL胺基酸序列。

【0211】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係促效劑結合蛋白，其結合LTβR，並包含與SEQ ID NO: 682至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 683或SEQ ID NO: 685至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含與SEQ ID NO: 682至少95%相同的VH胺基酸序列和與SEQ ID NO: 683或SEQ ID NO: 685至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LTβR結合蛋白包含SEQ ID NO: 682的VH胺基酸序列和SEQ ID NO: 683或SEQ ID NO: 685的VL胺基酸序列。

【0212】 在一個實施方式中，本揭露之促效劑LTβR結合蛋白係促效劑結合蛋白，其結合LTβR，並包含與SEQ ID NO: 686至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 687至少80%、至少85%或至少90%相同的

VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 686至少95%相同的VH胺基酸序列和與SEQ ID NO: 687至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 686的VH胺基酸序列和SEQ ID NO: 687的VL胺基酸序列。

【0213】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 688至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 689至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 688至少95%相同的VH胺基酸序列和與SEQ ID NO: 689至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 688的VH胺基酸序列和SEQ ID NO: 689的VL胺基酸序列。

【0214】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白係促效劑結合蛋白，其結合LT β R，並包含與SEQ ID NO: 690至少80%、至少85%或至少90%相同的VH胺基酸序列和與SEQ ID NO: 691至少80%、至少85%或至少90%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含與SEQ ID NO: 690至少95%相同的VH胺基酸序列和與SEQ ID NO: 691至少95%相同的VL胺基酸序列。在一個實施方式中，該促效劑LT β R結合蛋白包含SEQ ID NO: 690的VH胺基酸序列和SEQ ID NO: 691的VL胺基酸序列。

【0215】 在一個實施方式中，本揭露之促效劑LT β R結合蛋白包含如上所描述的VH區和/或VL區，並且進一步包含與VH區偶合的一或多個重鏈恒定區和/或與VL區偶合的輕鏈恒定區。例如，在一個實施方式中，該促效劑LT β R結合蛋白係Fab，其包含VH和與VL偶合的第一重鏈恒定結構域（CH1）以及輕鏈恒定區（CL）。在另一個實施方式中，該促效劑LT β R結合蛋白係F(ab')₂，其包含藉由鉸鏈區偶合的完全抗體的兩個LT β R結合區，其中每個結合區包含VH-CH1和VL-

CL。本文表13中提供了本揭露之示例性促效劑LTβR抗體的完全重鏈和輕鏈胺基酸序列。

[表13]. LTβR抗體的全長胺基酸序列

LIBC編號	Well ID	鏈	序列	SEQ ID
218990	30H1 19320	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGDYMYWVRQA PGQGLEWMGWINPNSGGTNYAKKFQGRVTMTRDTSISTAYM ELSRLRSDDTAVYYCAREGSSGWSAEYFQHWGQGTLVTVFS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV D HKPSNTKVDKTVERKCCVECPCPAPPVAGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIE KTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	692
		LC	EIVLTQSPGTLSPGERATLSCRASQSVSSFLAWYQQKLGQ APRLLMYGASRRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVY YCQQYGTSPLSFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	693
218994	31A3/ 19321	HC	QVQLVESGGAVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAIIWYDGSDEYYADSVKGRFTISRDNKNTLYLQM NSVRDEDTALYYCVRGDSSEDFYYYDFDVGQGTTTVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV D HKPSNTKVDKTVERKCCVECPCPAPPVAGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK	694

LIBC編號	Well ID	鏈	序列	SEQ ID
		LC	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGKNYVSWYQHLPGT APKLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADY YCGTWDHSLSASYVFGTGTKVTVLGQPKAAPSVTLFPPSSEEL QANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ SNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPT ECS	695
219058	36G2/ 19324	HC	EVQLVESGGGLVKPGGSLRLSCAASGFTFSTSGMNWVRQAPG KGLEWVSSVSSSGSYIYYADSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCAGARYNWHFDASDIWGQGTVVTVSSASTK GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPCCPSCAPEFLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQ FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNV FSCSVMEALHNHYTQKSLSLGLGK	696
		LC	DIQMTQSPSSLSASVGDRVTTTCRASQSISSDLNWWYQQKPGKA PNLLIYAASSLHSGVPSRFRSGSGSGTDFTLTISLLPEDFATYYC QQSYNTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKIDSTY SLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	697
219097	43D9/1 9326/	HC	EVQLVESGGGLVKPGGSLRLSCAASGFTFNDAWMSWVRQAP GKGLEWVGRIKTKTDGGTTDYAAPVKGRITISRDDSKNTLYL QMNSLKTEDTAVYYCTTDYGDYEWGQGLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNT KVDKTVERKCCVECPCPAPPVAGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFN STFRVVSIVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW	698

LIBC編號	Well ID	鏈	序列	SEQ ID
			ESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK	
		LC	DIQMTQSPSSLSASVGDRVTTTCRTSQSISRYLNWYQQKPGKA PKLLIYGASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC HQSYSTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	699
219037	34D1/ 19322	HC	QVQLQESGPGRVKPSQTLSTCTVSGGSINSGGYFWSWIRQHP GKVLEWIGYSHYSGTTYYNPSLKSRTVISVDTSKNQLSLKLNS VNAADTAVYYCARVPDGEDYFDYWQGALVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVDHKPSNTK VDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTP EVTCTVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSC SVMHEALHNHYTQKSLSLSLGK	700
		LC	DLQLTQSPSSLSASVGDRVTTICRASQTISSYLNWYQQKPGKA PKLLIYDASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFETYYC QQSFSAPITFGQGRLEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	701
219098	44B1/ 19327	HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSTISGSGGSTYYADSVKGRFTISRDN SKNTLNLQMN SLRAEDTAVYYCAKVRDNWNYDGMDVWGQGTTVTVSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSNFGTQTYTCNVDHKP SNTKVDKTKVERKCCVECPAPPVAGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI	702

LIBC編號	Well ID	鏈	序列	SEQ ID
			SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK	
		LC	DIVMTQSPLSLPVTLGESASISCRCSQSLLYSSGYIDLWDWYLQK PGQSPQLLIYLGSNRASGVDPDRFSGSGSGTDFTLKISRVEAEDV GVYYCMQTIQTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC	703
219098.001		HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSTISGSGGSTYYADSVKGRFTISRDN SKNTLNLMN SLRAEDTAVYYCAKVRDNWNYDGMDVWGQGTTVTVSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSNFGTQTYTCNVDHKP SNTKVDKTV ERKCCVECP PAPPVAGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTFRVVS VLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK	704
		LC	DIVMTQSPLSLPVTLGESASISCRSSQSLLYSSGYIDLWDWYLQK PGQSPQLLIYLGSNRASGVDPDRFSGSGSGTDFTLKISRVEAEDV GVYYCMQTIQTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC	705
219051	35F5/19 323	HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYLHWVRQAP GQGLEWMGWINPNIGVTD SAQKFQDRVTMTRDTSISTAYME LSRLISDDTAVYYCTVRGYND D YDFDYWGQGT LVT VSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNVDHKP	706

LIBC編號	Well ID	鏈	序列	SEQ ID
			SNTKVDKRVESKYGPPCPSCAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGN VFSCSVMHEALHNHYTQKSLSLGLGK	
		LC	DVVMQTQTPLSLSVTPGQPASISCKSRQSLHHRDGKTYLYWYL QKPGQPPQLLIYEVSNRFSGVPNRFSGSGSGTDFTLKISRVEAE DVGVIYCMQSIQLPLIFGGGTRVDIKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC	707
218989	29G8	HC	QITLKESGPTLVKPTQTLTLTCTFTGFSLSTSGMGVGWIRQPPG KALEWLALIYWNGGKLYSPSLKNRLTITKDTSKNQVVLMTN MDPVDATYYCAHSGYYDNSGYYWDGMDVWGQGTTVTVS PASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVPSSNFGTQTYTCNV DHKPSNTKVDKTVKCCVECPAPPVAGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPI EKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	708
		LC	EIVLTQSPVTLSLSPGERATLSCRASQSLISDYLWVYQQKPGQ APRLLIYGASSRPTGIPDRFSGSGSGTDFTLTISRLEPEDFAVYY CQQYDTSLNFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	709
218967	17F5	HC	QVQLQESGPGVVKPSETLSLTCTVSGGSISSYFWTWIRQPPGK GLEWIGYIYYSGSTNYPNPSLKSRTFSVDTSKNQFSLKLNSVT AADTAVYYCARVETIMAFDAFDIWGQGTMTVSSASTKGPS	710

LIBC編號	Well ID	鏈	序列	SEQ ID
			VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTK VDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNST FRVVSVLTVVHQQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK	
		LC	EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQ APRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYF CQQYDTSPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	711
218981	25C9	HC	QVQLQESGPGLVKPSQTLSTCTVSGGSISSGGYFWSWIRQHP GKGLEWIGYTHYIGSTYYNPSLKSRAFSVDTSKNQFSLKLSS VTAADTAVYYCARVDTAMVDAFDIWGQGTMTVSSASTKG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSN TKVDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTFRVVSVLTVVHQQDWLNGKEYKCKVSNKGLPAPIEKTISK TKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK	712
		LC	EIMLTQSPGTLSLSPGERATLSCRASQNIDSSYLAWYQQTPGQ APRLLIYDTSSRATGIPDRFSGSGSGTDFTLTISRLEPEDFSVYY CQQYGGSPITFGQGTRLDIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	713
218995	31C9	HC	QVQLQESGPGLVKPSDTLSLTCAVSGYISSRNWWGWIRQPP GKGLEWIGYIHYIGNTYYNPSLKSRTMSVDTSKNQFSLKLSS	714

LIBC編號	Well ID	鏈	序列	SEQ ID
			VTAVDTAVYYCARETGSDGDDTFDIWGQGTMTVTVSSASTKG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSN TKVDKTVERKCCVECPCPAPPVAGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISK TKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPMLDSDGSSFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK	
		LC	EIVLTQSPVTLSLSPGERATLSCRASQSIGSSYLAWYQQKPGQ APRLLIYGASGRATGIPDRFSGSGSGTDFTLTISRLEPEDFALYY CQQCYSSPITFGHGTRLDIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	715
218996	31B10	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYDMHWVRQAP GKGLEWVTTIWYDGSNKYYADSVKGRFTISRDN SKNTLFLQ MNSLRAEDTAVYYCPTLSTVTTGDYYGMDVWGQGTAVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCCVECPCPAPPVAGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPI EKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPMLDSDGSSFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	716
		LC	QSVLTQPPSVSAAPGQKVTISCSGSRSNIGNNYVSWYQQLPGT VPKLLIYDNSKRPSGIPDRFSGSKSGTSVTLGITGLQTGDEADY YCGTWDSSLSAVVFGGGTKLTVLSQPKAAPSVTLFPPSSEELQ ANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTE CS	717

LIBC編號	Well ID	鏈	序列	SEQ ID
218998	32A2	HC	QVQLQESGPGQVKPSQTLSTCTVSGGSISSGGYFWGWIRQHP GKGLEWIGYIHYIGSPYYNPSLKSRTTISVDTSKNQFSLKLSSVI AADTAVYYCARDCSSVNCQDAFDIWGQGTMTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPKPSNT KVDKTVRKCCVECPAPVAGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFN STFRVVSIVLTQVHQLDNLGKEYKCKVSNKGLPAPIEKTISK KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK	718
		LC	EIVLTQSPGTLSPGERASLSCWSSQSIDSTYLAWYHQKPGQ APRLLIYGASTRATGIPDRFSGSGSGTDFTLISRLEPEDFAVYY CQQYSSSPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKIDSTY SLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	719
219083	41H7	HC	QVQLQESGPGVLVKPSQTLSTCTVSGGSIRSDGYFWSWIRQHP GKGLEWLGFIIYSGTTYYNPSLKSRVTISVDTSKNQFSLKLTS VTVADTAVYYCARVCGGDCYDAFDIWGQGTMTVTVSSASTK GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPKPS NTKVDKTVRKCCVECPAPVAGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQ FNSTFRVVSIVLTQVHQLDNLGKEYKCKVSNKGLPAPIEKTIS KTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK	720
		LC	DIVLTQSPGTLSPGEGATLSCRASQNISNTYLAWYQQKPGQ APRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYD CQQYFSSPITFGGTRVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKIDSTY	721

LIBC編號	Well ID	鏈	序列	SEQ ID
			SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
219092	43C1	HC	QVQVQESGPGLVKPSDTLSLTCAVSGYSISNSIWGWIRQPPG KGLEWIGYIHYSGNTYYNP SLKSRVTMSVDTSKNQFSLKLNS VTAVDTAVYYCARNFGDVDAFDIWGQGTMTVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVTPSSNFGTQTYTCNVDPHKPSNTK VDKTVRKKCCVECPKPPVAGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNST FRVVSVLTVVHQQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK	722
		LC	EIVLTQSPGTLSLSPGERATLSCRASQSISSSYLAWYQQKPGQA PRLLIYGASSRATGIPDRFSGSGSGTDFTLNISRLEPEDFVYYC QQYYLSPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKIDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	723
219023	33G6	HC	QVQLQQSGPGLVKPSQTLTLTCAISGDSVFSNSAAWNWIRQSP SRGLEWLGRTYCRSKCYSDYALSVKSRATINPDTSNQFSLQL NSVTPEDTAVYYCARAVADHYSYALDVWGQGTTVNVSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKTKYTCNVDPHKP SNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGN VFSCSVMEALHNHYTQKSLSLSPGK	724
		LC	DIQMNQSPSSLSASVGDRVTITCRASQTIRTYLNWYQQKPGKA PKVLIYAASSLQSGVPSRFSGTSGTDFLTITSLQPEDFATYSC QQSYSSPITFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV	725

LIBC編號	Well ID	鏈	序列	SEQ ID
			VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
219023.001		HC	QVQLQQSGPGLVKPSQTLSTCAISGDSVFNSAAWNWIRQSP SRGLEWLGRITYYRSKWYSDYALSVKSRATINPDTSENQFSLQ LNSVTPEDTAVYYCARAVADHYSYALDVWGQGTTVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNVDPHK PSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPR EEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSPGK	726
		LC	DIQMTQSPSSLSASVGDRVITTCRASQTIRTYLNWYQQKPGKA PKVLIYAASSLQSGVPSRFSGTGSGTDFTLTITSLQPEDFATYSC QQSYSSPITFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	727
219095	43G5	HC	EVQLLESGGNLVQPGGSLRLSCVVSQGTFFNNYAMNWVRQAP GKGLEWVSVISDSGGSSNYADSVKGRFTISRDNSSKTLYLQM NSLRAEDTAVYYCAKDRSIAGYYGMDVWGQGTTVTVSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSNFGTQTYTCNVDPHKP SNTKVDKTVERKCCVECPAPPVAGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK	728
		LC	DIQMTQSPSSLSASVGDRVITTCRASQSISSDLNWYQQKPGKA PNLLIYAASSLHSGVPSRFSGSGSGTDFTLTISLLPEDFATYYC	729

LIBC編號	Well ID	鏈	序列	SEQ ID
			QQSYNTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDESTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
219102	44G11	HC	QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWSWIRLPPGK GLEWIGYIYYGGSTNYNPSLKSRVSMVDTSKNQFSLKLSYVT AADTAVYYCARSYSSAWYGSAYWGQGLVIVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLGLGK	730
		LC	DIQMTQSPSSLSASLGDRVITITCQASQDISNYLIWYQLKPGKAP KVLIIYDASNLETGVPSRFSGNGSGTDFTFTISSLQPEDIATYYC QQYDHLPIITFGQGTRLDIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDESTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	731
219102.001		HC	QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWSWIRLPPGK GLEWIGYIYYGGSTNYNPSLKSRVSMVDTSKNQFSLKLSYVT AADTAVYYCARSYSSAWYGSAYWGQGLVIVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLGLGK	732
		LC	DIQMTQSPSSLSASLGDRVITITCQASQDISNYLIWYQLKPGKAP	733

LIBC編號	Well ID	鏈	序列	SEQ ID
			KVLIYDASNLETGVPSRFSGSGSGTDFTFITISLQPEDATYYC QQYDHLPTFGQGTRLDIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKIDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
218973	21A5	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGIHWVRQAPG KGLEWVAVIWYDGSKKYYADSVKGRFTISRDNISKSTLYLQM NSLRAEDTAVYYCARDPSHYGSGSYNYFYGMDEVWGQGT VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSNFGTQTYT CNVDHKPSNTKVDKTKVERKCCVECPAPPVAGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGL PAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	734
		LC	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNTYVSWYQQLPGT APKLLIYDNNRPSGIPDRFSGSKSDTSATLGITGLQTGDEADY YCGTWDNSLTAVVFGGGTKLTVLGQPKAAPSVTLFPPSSEEL QANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ SNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPT ECS	735
219044	34F10	HC	EVQLVESGGGLIQPGGSLRLSCAASGFTVSDNYMSWVRQAPG KGLEWVSVIYSGGNTYYGDSVKGRFTISRDNISKNTLYLQMNS LRAEDTAVYFCTGPFDDYWGPGLTVTVSSASTKGPSVFPLAPC SRSTSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVTPSSSLGTKTYTCNVDHKPSNTKVDKRVES KYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQ VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTPPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMHEA	736

LIBC編號	Well ID	鏈	序列	SEQ ID
			LHNHYTQKSLSLSLGK	
		LC	EIVLTQFPGTLSLSPGEGGTLSCRASQTVWSNYLAWYQQKPG QAPRLLIYGASRRVIGIPDRFSGSGSGTDNLTISLEPGDFAVY YCQQYGSSSITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	737
218997	31E12	HC	QVQVQESGPGLVKPSQTLSTCTVSGGSISSGGYYWSWIRQHP GKGLEWIGYIYYSGSTYYNPSLMGRVTISVDTSKNQFSLRLSS VTAADTAVYYCARRGPVAGGFDYWGGTLVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSNFGTQTYTCNVDPHKPSNTK VDKTVRKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNST FRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTTPMLDSGDSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK	738
		LC	EIVLTQSPGTLSLSPGERATLSCRASQNVYNNYLAWYQQKPR QAPRLLIYGTSSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVY YCQQYGSSLLCSFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	739

多特異性LTβR結合分子

【0216】 在本揭露之另一方面，該促效劑LTβR結合蛋白為多特異性促效劑LTβR結合蛋白。根據本揭露之此方面，該多特異性促效劑LTβR結合蛋白包含與人LTβR（SEQ ID NO: 1）結合的第一結合結構域和與非LTβR蛋白靶標（即LTβR以外的蛋白質）結合的第二結合結構域，其中該多特異性結合蛋白激動LTβR活性並且 (a) 不抑制LIGHT與LTβR結合，以及 (b) 不抑制LT1α2β與LTβR結合。如

本文所描述的示例性LT β R多特異性結合蛋白的第二結合結構域與非LT β R蛋白靶標結合。在一個實施方式中，該LT β R多特異性結合蛋白的第二結合結構域與腫瘤微環境（TME）的腫瘤細胞或其他細胞優先表現的蛋白或抗原結合。

【0217】 在一個實施方式中，該多特異性促效劑LT β R結合蛋白對於由該第一和第二結合結構域多特異性結合蛋白結合的每個蛋白靶標係單價的。在一個實施方式中，該多特異性促效劑LT β R結合蛋白對於LT β R配體結合結構域係單價的，而對於非LT β R結合結構域係二價的。

【0218】 在一個實施方式中，本揭露之多特異性促效劑LT β R結合蛋白進一步包含一或多個額外的結合結構域。在一個實施方式中，本文所描述的多特異性促效劑LT β R結合蛋白包含第三結合結構域，其中該第三結合結構域結合與該第一或第二結合結構域相同的蛋白靶標，以形成對於由雙特異性結合蛋白結合的蛋白靶標之一為二價的雙特異性結合蛋白。在另一個實施方式中，該第三結合結構域結合與該第一和第二結合結構域不同的蛋白靶標，從而形成單價三特異性結合蛋白。在一個實施方式中，該多特異性促效劑LT β R結合蛋白可以進一步包含第四結合結構域，其中該第四結合結構域結合與該第一、第二或第三結合結構域相同的蛋白靶標。

【0219】 根據本揭露之此方面，該多特異性促效劑LT β R結合蛋白可以採用本領域已知的任何多特異性結合蛋白形式。例如，在一個實施方式中，該多特異性促效劑LT β R結合蛋白係促效劑LT β R雙特異性結合蛋白或三特異性促效劑LT β R結合蛋白。在一個實施方式中，該多特異性促效劑LT β R結合結構域的第一、第二和/或第三結合結構域係Fab。可替代地，該多特異性促效劑LT β R結合結構域的第一、第二和/或第三結合結構域係scFv。在一個實施方式中，該第一結合結構域是Fab，該第二結合結構域係scFv，並且視需要存在的第三結合結構域係Fab或scFv。在一個實施方式中，該第二結合結構域係Fab，該第一結合結構域係scFv，

並且視需要存在的第三結合結構域係Fab或scFv。在一個實施方式中，該第一和第二結合結構域係Fab，並且視需要存在的第三結合結構域係Fab或scFv。在一個實施方式中，該第一和第二結合結構域係scFv，並且視需要存在的第三結合結構域係Fab或scFv。

【0220】 在本揭露之一個實施方式中，該多特異性促效劑LT β R結合蛋白係雙特異性促效劑LT β R結合蛋白。如本文所指的「雙特異性結合蛋白」係同時與兩種不同抗原結合的結合蛋白。本揭露之雙特異性促效劑LT β R結合蛋白涵蓋了本領域已知的任何雙特異性分子形式（參見例如，Spiess等人, *Mol. Immunol.*[分子免疫學] 67(2): 95-106 (2015)，特此藉由引用將其全部併入）。該等分子形式包括保留具有兩個Fab臂和一個Fc區的傳統單株抗體結構的IgG樣形式、含有附加的額外抗原結合部分的IgG形式、雙特異性結合蛋白片段、雙特異性融合蛋白及其組合。

【0221】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的第一和/或第二結合結構域係Fab。可替代地，該雙特異性促效劑LT β R結合蛋白的第一和/或第二結合結構域係scFv。在一個實施方式中，該第一結合結構域係Fab，並且該第二結合結構域係scFv。在一個實施方式中，該第二結合結構域係Fab，並且該第一結合結構域係scFv。在一個實施方式中，該第一和第二結合結構域均為Fab。在一個實施方式中，該第一和第二結合結構域均為scFv。

【0222】 在一個實施方式中，本揭露之雙特異性促效劑LT β R結合蛋白係全長雙特異性IgG或包含IgG樣結構。在一個實施方式中，該雙特異性促效劑LT β R結合蛋白係對於由雙特異性結合蛋白結合的每個靶蛋白係單價的異源IgG。包含經工程化以增強異二聚體形成的Fc結構域的示例性異源IgG雙特異性形式在本領域中係熟知的，並且係本揭露之雙特異性促效劑LT β R結合蛋白的合適形式。該等異源IgG形式包括但不限於旋鈕入孔形式(參見例如，Ridgway等人, 「Knobs-

into-holes' engineering of antibody CH3 domains for heavy chain heterodimerization[用於重鏈異二聚化的抗體CH3結構域的'旋鈕入孔'工程化],」 *Protein Eng.*[蛋白工程] 9:617-621 (1996)和Atwell等人,「Stable heterodimers from remodeling the domain interface of a homodimer using a phage display library[使用噬菌體展示文庫 重塑同源二聚體結構域介面的穩定異二聚體],」 *J. Mol. Biol.*[分子生物學雜誌] 270:26-35 (1997),特此藉由引用將其全部併入)、DuoBody形式(參見例如,Labriijn等人,「Efficient generation of stable bispecific IgG1 by controlled Fab-arm exchange[藉由受控的Fab-arm交換有效產生穩定的雙特異性IgG1],」 *Proc. Natl. Acad. Sci. U.S.A.*[美國國家科學院院刊], 110: 5145-5150 (2013),特此藉由引用將其全部併入); Azymetric形式(參見例如, Von Kreudenstein等人,「Improving biophysical properties of a bispecific antibody scaffold to aid developability: quality by molecular design[提高雙特異性抗體支架的生物物理特性以說明可開發性:分子設計的品質],」 *mAbs*[單株抗體] 5:646-654 (2013),特此藉由引用將其全部併入);帶電的Fc對(參見例如, Gunasekaran等人,「Enhancing antibody Fc heterodimer formation through electrostatic steering effects: applications to bispecific molecules and monovalent IgG[藉由靜電轉向效應增強抗體Fc異二聚體的形成:對雙特異性分子和單價IgG的應用],」 *J. Biol. Chem.*[生物化學雜誌], 285: 19637-46 (2010)和Strop等人,「Generating bispecific human IgG1 and IgG2 antibodies from any antibody pair[從任何抗體對生成雙特異性人IgG1和IgG2抗體],」 *J. Mol. Biol.*[分子生物學雜誌], 420:204-219 (2012),特此藉由引用將其全部併入);mAb-Fv(參見例如, Close等人,「A novel bispecific antibody format enables simultaneous bivalent and monovalent co-engagement of distinct target antigens[一種新型雙特異性抗體形式能夠使不同靶抗原同時二價和單價共接合],」 *mAbs*[單株抗體] 3: 546-557 (2011),特此藉由引用將其全部併入);鏈交換工程化結構域

(SEED)CH3異二聚體形式(參見例如,「Davis等人,「SEEDbodies: fusion proteins based on strand-exchange engineered domain (SEED) CH3 heterodimers in an Fc analogue platform for asymmetric binders or immunofusions and bispecific antibodies[SEED體:基於Fc類似物平臺中鏈交換工程化結構域(SEED)CH3異二聚體的融合蛋白,用於不對稱結合物或免疫融合物和雙特異性抗體],」*Protein Eng. Des. Sel.*[蛋白質工程設計與選擇]23:195-202 (2010),特此藉由引用將其全部併入);和蛋白A差別親和力(參見例如,Davis等人的美國專利案號8,586,713,特此藉由引用將其全部併入)。

【0223】在一個實施方式中,本揭露之雙特異性促效劑LTβR結合蛋白係包含一或多個結合蛋白片段的構建體。本揭露之合適的LTβR雙特異性結合蛋白片段構建體包括但不限於包含經由肽連接基連接的兩個單可變(VHH)結構域的奈米抗體(Els Conrath等人,「Camel single-domain antibodies as modular building units in bispecific and bivalent antibody constructs[駱駝單結構域抗體作為雙特異性和二價抗體構建體中的模組化構建單元],」*J. Biol. Chem.*[生物化學雜誌]276:7346-50 (2001),特此藉由引用將其全部併入),以及包含兩個偶合在一起的scFv片段的雙特異抗體(Holliger等人,「‘Diabodies’: small bivalent and bispecific antibody fragments[‘雙特異抗體’:小的二價和雙特異性抗體片段],」*Proc. Natl. Acad. Sci. U.S.A.*[美國國家科學院院刊],90: 6444-6448 (1993),特此藉由引用將其全部併入)。合適的雙特異抗體LTβR雙特異性構建體包括但不限於單鏈雙特異抗體(參見例如,Alt等人,「Novel tetravalent and bispecific IgG-like antibody molecules combining single-chain diabodies with the immunoglobulin gamma1 Fc or CH3 region[將單鏈雙特異抗體與免疫球蛋白γ1 Fc或CH3區結合的新型四價和雙特異性IgG樣抗體分子],」*FEBS Lett.*[歐洲生物化學會聯合會快報]454: 90-94 (1999),特此藉由引用將其全部併入)、雙親和力重新靶向雙特異抗體(DART)

(參見例如, Johnson等人, 「Effector cell recruitment with novel Fv-based dual-affinity re-targeting protein leads to potent tumor cytotoxicity and in vivo B-cell depletion[用新型基於Fv的雙親和力重新靶向蛋白募集效應細胞導致有效的腫瘤細胞溶解和體內B細胞耗竭],」 J. Mol. Biol.[分子生物學雜誌] 399: 436-449 (2010), 特此藉由引用將其全部併入)、串聯雙特異抗體和包含連接在單多肽鏈中的兩對VL和VH結構域的四價串聯雙特異抗體(TandAb)(參見例如, Arndt等人, 「A bispecific diabody that mediates natural killer cell cytotoxicity against xenotransplanted human Hodgkin's tumors[介導自然殺手細胞對異種移植的人霍奇金腫瘤的細胞毒性的雙特異性雙特異抗體],」 Blood[血液] 94: 2562-2568 (1999), 特此藉由引用將其全部併入)。合適的LT β R雙特異性構建體還包括與Fc部分偶合(例如, 微抗體、雙特異抗體-CH3、sc雙特異抗體-CH3、scFv-CH3、微抗體)或與一或多個其他部分融合以延長半衰期(例如, 與血清白蛋白或白蛋白結合蛋白融合)的scFv片段或雙特異抗體。

【0224】在一個實施方式中, 本揭露之雙特異性促效劑LT β R結合蛋白係工程化為雙特異性的單特異性IgG抗體(例如, 含有雙特異性抗體的第一或第二結合結構域), 通過將包含例如VHH、scFv、2scFv、Fv、Fab或抗體模擬物結合結構域的額外結合結構域(例如, 分別為該第二或第一結合結構域)與抗體的一或多個輕鏈或重鏈的胺基或羧基末端偶合。示例性工程化雙特異性結合蛋白包括但不限於雙可變結構域(DVD)-IgG、IgG(H)-scFv、ScFv-(H)IgG、IgG(L)-scFv、scFv-(L)IgG、IgG((L,H)-Fv、IgG(H)-V、V(H)-IgG、IgG(L)-V、V(L)-IgG、IgG-scFab、2scFv-IgG、IgG-2scFv、scFv4-Ig(參見例如, Spiess等人, 「Alternative molecular formats and therapeutic applications for bispecific antibodies[雙特異性抗體的替代分子形式和治療應用],」 Mol. Immunol.[分子免疫學] 67(2): 95-106 (2015), 特此藉由引用將其全部併入)。

【0225】 在一個實施方式中，本揭露之多特異性促效劑LT β R結合蛋白係雙特異性促效劑LT β R結合蛋白。該雙特異性促效劑LT β R結合蛋白包含 (i) LT β R結合結構域，其中該LT β R結合結構域結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R CRD4的一或多個胺基酸殘基，和 (ii) 腫瘤相關抗原結合結構域。該雙特異性LT β R結合蛋白激動LT β R活性，並且 (a) 不抑制LIGHT與LT β R結合和 (b) 不抑制LT1 α 2 β 與LT β R結合。

【0226】 上文描述了結合人LT β R的CRD4的示例性LT β R結合結構域，即HCDR和LCDR，以及VH和VL結構域，包括但不限於LIBC219081和LIBC218979的結合結構域以及表2-4和6-8中提供的LT β R結合蛋白的結合結構域。特別地，如本文所描述的雙特異性促效劑LT β R結合蛋白的合適的第一結合結構域可包含重鏈可變結構域(VH)或其片段，其包含表2或表6的單行中所列的HCDR1、HCDR2和/或HCDR3中的一或多個或其部分。在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的第一結合結構域包含表2或表6的單行中所列的HCDR1、HCDR2和HCDR3的全部三個或其部分。在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的第一結合結構域包含輕鏈可變結構域(VL)或其片段，其包含表3或表7的單行中所列的LCDR1、LCDR2和/或LCDR3中的一或多個或其部分。在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的第一結合結構域包含表3或表7的單行中所列的LCDR1、LCDR2和LCDR3的全部三個或其部分。在一個實施方式中，如本文所描述的雙特異性促效劑LT β R結合蛋白的第一結合結構域包含VH或其片段，其包含表2或表6的單行中所列的HCDR1、HCDR2和/或HCDR3中的一或多個或其部分，以及VL或其片段，其包含表3或表7的單行中所列的相應結合分子的LCDR1、LCDR2和/或LCDR3中的一或多個或其部分。在一個實施方式中，如本文所描述的雙特異性促效劑LT β R結合蛋白的第一結合結構域包含VH或其片段，其包含表2或表6的單行中所列的HCDR1、HCDR2和HCDR3

的全部三個或其部分，以及VL或其片段，其包含表3或表7的單行中所列的相應結合分子的LCDR1、LCDR2和LCDR3的全部三個或其部分。該雙特異性促效劑LT β R結合蛋白 (a) 不抑制LIGHT與LT β R結合，而且 (b) 不抑制LT1 α 2 β 與LT β R結合。

【0227】 在一個實施方式中，結合人LT β R的CRD4的雙特異性促效劑LT β R結合蛋白的第一結合結構域包含重鏈可變結構域(VH)、輕鏈可變結構域(VL)或VH和VL結構域的組合。在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的第一結合結構域的VH結構域包含表4或表8中提供的VH胺基酸序列中的任一個，或與表4或表8中列出的VH胺基酸序列中的任一個至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%相同的胺基酸序列。在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的第一結合結構域的VL結構域包含表4或表8中提供的VL胺基酸序列中的任一個，或與表4或表8中列出的VL胺基酸序列中的任一個至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%相同的胺基酸序列。該雙特異性促效劑LT β R結合蛋白 (a) 不抑制LIGHT與LT β R結合，而且 (b) 不抑制LT1 α 2 β 與LT β R結合。

【0228】 在一個實施方式中，結合人LT β R的CRD4的雙特異性促效劑LT β R結合蛋白的第一結合結構域包含與表4或表8中列出的VH結構域胺基酸序列中的任一個具有至少85%、至少90%、至少95%或100%序列同一性的重鏈可變結構域，和與表4或表8中列出的相應VL結構域胺基酸序列具有至少85%、至少90%、至少95%或100%序列同一性的輕鏈可變結構域。該雙特異性促效劑LT β R結合蛋白 (a) 不抑制LIGHT與LT β R結合，而且 (b) 不抑制LT1 α 2 β 與LT β R結合。

【0229】 在一個實施方式中，結合人LT β R的CRD4的雙特異性促效劑LT β R結合蛋白的LT β R結合結構域包含VH，其包含HCDR1胺基酸序列：X₁YX₃MX₅ (SEQ ID NO: 5)，其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺

基酸序列：X₁IX₃YDX₆X₇X₈X₉Y X₁₁X₁₂DSVKG（SEQ ID NO: 6），其中X₁為A或V；X₃為W或R；X₆為E或G；X₇為S、R或T；X₈為N或K；X₉為K、R或Q；X₁₁為H或Y；並且X₁₂為A或E；以及HCDR3胺基酸序列：X₁RX₃X₄X₅X₆X₇X₈X₉YYGX₁₃X₁₄V（SEQ ID NO: 7），其中X₁為D或E；X₃為V、G或I；X₄為V、P或A；X₅為A、Y或G；X₆為R、A、G或H；X₇為P或G；X₈為G、N、D、Y、A或H；X₉為Y、T或F；X₁₃為L或M；並且X₁₄為D或A。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0230】 在一個實施方式中，結合人LTβR的CRD4的雙特異性促效劑LTβR結合蛋白的LTβR結合結構域進一步包含VL，其包含LCDR1胺基酸序列：SGDX₄LPX₇X₈YX₁₀Y（SEQ ID NO: 62），其中X₄為A或T；X₇為E、K、Q、D或N；X₈為Q或H；並且X₁₀為A或T；LCDR2胺基酸序列：KDNERPS（SEQ ID NO: 63）；以及LCDR3胺基酸序列：QSX₃DX₅SX₇X₈YX₁₀X₁₁（SEQ ID NO: 64），其中X₃為A或T；X₅為S、G或N；X₇為G或A；X₈為T、S或A；X₁₀為V或M；並且X₁₁為I或V。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0231】 在一個實施方式中，結合人LTβR的CRD4的雙特異性促效劑LTβR結合蛋白的LTβR結合結構域包含與SEQ ID NO: 121之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。在一個實施方式中，LTβR結合結構域包含與SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。在一個實施方式中，LTβR結合結構域包含與SEQ ID NO: 121之胺基酸序列和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的VH胺基酸序列。與SEQ ID NO: 121和SEQ ID NO: 123之胺基酸序列具有至少90%序列同一性的示例性VH胺基酸序列提供在上表4中。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0232】 在一個實施方式中，該結合人LTβR的CRD4的雙特異性促效劑LTβR結合蛋白的LTβR結合結構域包含與SEQ ID NO: 122之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，該LTβR結合結構域包含與SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，該LTβR結合結構域包含與SEQ ID NO: 122之胺基酸序列和SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。與SEQ ID NO: 122和SEQ ID NO: 124之胺基酸序列具有至少90%序列同一性的示例性VL胺基酸序列提供在上表4中。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0233】 在一個實施方式中，該結合人LTβR的CRD4的雙特異性促效劑LTβR結合蛋白的LTβR結合結構域包含與SEQ ID NO: 121之胺基酸序列具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少90%序列同一性的VL胺基酸序列。在一個實施方式中，該LTβR結合結構域包含與SEQ ID NO: 121之胺基酸序列具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少95%序列同一性的VL胺基酸序列。在一個實施方式中，LTβR結合結構域包含與SEQ ID NO: 121之胺基酸序列具有至少98%序列同一性的VH胺基酸序列和與SEQ ID NO: 122之胺基酸序列具有至少98%序列同一性的VL胺基酸序列。該雙特異性促效劑LTβR結合蛋白 (a) 不抑制LIGHT與LTβR結合，而且 (b) 不抑制LT1α2β與LTβR結合。

【0234】 在一個實施方式中，該雙特異性促效劑LTβR結合蛋白的LTβR結合結構域包含與SEQ ID NO: 123具有至少90%序列同一性的VH胺基酸序列，以及SEQ ID NO: 5 (X₁YX₃MX₅) 的HCDR1胺基酸序列，SEQ ID NO: 6 (X₁IX₃YDX₆X₇X₈X₉YX₁₁X₁₂DSVKG) 的HCDR2胺基酸序列，以及SEQ ID NO: 7 (X₁RX₃X₄X₅X₆X₇X₈X₉YYGX₁₃X₁₄V) 的HCDR3胺基酸序列。在一個實施方式

中，該LT β R結合結構域進一步包含與SEQ ID NO: 124具有至少90%序列同一性的VL胺基酸序列，以及SEQ ID NO: 62 (SGDX₄LPX₇X₈YX₁₀Y)的LCDR1胺基酸序列，SEQ ID NO: 63 (KDX₃ERPS)的LCDR2胺基酸序列，以及SEQ ID NO: 64 (Q SX₃DX₅SX₇X₈YX₁₀X₁₁)的LCDR3胺基酸序列。該雙特異性促效劑LT β R結合蛋白 (a) 不抑制LIGHT與LT β R結合，而且 (b) 不抑制LT1 α 2 β 與LT β R結合。

【0235】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域包含VH，其包含分別為SEQ ID NO: 11-13的HCDR1、HCDR2和HCDR3胺基酸序列，以及VL，其包含分別為SEQ ID NO: 68-70的LCDR1、LCDR2和LCDR3胺基酸序列。在一個實施方式中，該LT β R結合結構域包含VH，其包含分別為SEQ ID NO: 8-10的HCDR1、HCDR2和HCDR3胺基酸序列，以及VL，其包含分別為SEQ ID NO: 65-67的LCDR1、LCDR2和LCDR3胺基酸序列。該雙特異性促效劑LT β R結合蛋白 (a) 不抑制LIGHT與LT β R結合，而且 (b) 不抑制LT1 α 2 β 與LT β R結合。

【0236】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域與示例性LT β R結合物LIBC219081和LIBC218979競爭結合LT β R。在一個實施方式中，該第一結合結構域包含選自以下的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3胺基酸序列：(i) SEQ ID NO: 159、SEQ ID NO: 160、SEQ ID NO: 161、SEQ ID NO: 278、SEQ ID NO: 279和SEQ ID NO: 280；(ii) SEQ ID NO: 159、SEQ ID NO: 160、SEQ ID NO: 161、SEQ ID NO: 299、SEQ ID NO: 300和SEQ ID NO: 301；(iii) SEQ ID NO: 159、SEQ ID NO: 160、SEQ ID NO: 161、SEQ ID NO: 308、SEQ ID NO: 309和SEQ ID NO: 310；(iv) SEQ ID NO: 195、SEQ ID NO: 196、SEQ ID NO: 197、SEQ ID NO: 308、SEQ ID NO: 309和SEQ ID NO: 310；(v) SEQ ID NO: 224、SEQ ID NO: 225、SEQ ID NO: 226、SEQ ID NO: 356、SEQ ID NO: 357和SEQ ID NO: 358。包含具有上述重鏈和輕鏈CDR的第一結合

結構域的雙特異性促效劑LT β R結合蛋白不抑制LIGHT與LT β R結合，而且不抑制LT α 1 β 2與LT β R結合。

【0237】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R CRD1，並包含與SEQ ID NO: 646的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 647的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。該雙特異性LT β R結合蛋白不抑制內源性LIGHT與LT β R結合，並允許發生80%的內源性LT α 1 β 2與LT β R結合。

【0238】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R，並包含與SEQ ID NO: 652的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 653的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。該雙特異性LT β R結合蛋白不抑制內源性LIGHT與LT β R結合。

【0239】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R，並包含與SEQ ID NO: 654的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 655的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。該雙特異性LT β R結合蛋白不抑制內源性LIGHT與LT β R結合。

【0240】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R CRD1，並包含與SEQ ID NO: 658的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 659的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。該雙特異性LT β R結合蛋白不抑制內源性LIGHT與LT β R結合，而且不抑制LT α 1 β 2與LT β R結合。

【0241】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R CRD2和CRD3，並包含與SEQ ID NO: 648的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 649的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。該LT β R結合蛋白在基於細胞的受體-配體測定中在< 8 nM濃度下不抑制LIGHT和LT α 1 β 2與LT β R結合，如本文所描述的。

【0242】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的LT β R結合結構域結合人LT β R CRD2和CRD3，並包含與SEQ ID NO: 644的VH結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的重鏈可變結構域和與SEQ ID NO: 645的VL結構域胺基酸序列具有至少85%、至少90%或至少95%序列同一性的輕鏈可變結構域。

【0243】 在一個實施方式中，該雙特異性促效劑LT β R結合蛋白的腫瘤相關結合結構域與腫瘤相關抗原（TAA）結合。在一個實施方式中，該TAA係實性瘤TAA。合適的TAA係本領域已知的，並包括但不限於甲型胎兒蛋白（AFP）、CD44v6、碳酸酐酶IX（CAIX）、癌胚抗原（CEA）、CD133、肝細胞生長因子受體（c-MET）、密連蛋白18.2（CLDN18.2）、密連蛋白6（CLDN6）、含富胺酸重複序列的蛋白15（LRRC15）、表皮生長因子受體（EGFR）、III型變體表皮生長因子受體（EGFRvIII）、促紅血球生成素產生肝細胞癌A2（EphA2）、上皮細胞黏附分子（EpCAM）、胎兒乙醯膽鹼受體、葉酸受體 α （FR α ）、神經節苷脂GD2（GD2）、蛋白多糖-3（GPC3）、鳥苷酸環化酶C（GUCY2C）、人表皮生長因子受體1（HER1）、人表皮生長因子受體2（ERBB2/HER2）、細胞間黏附分子1（ICAM-1）、白血球介素13受體 α 2（IL13R α 2）、白血球介素11受體 α （IL11R α ）、Kirsten大鼠肉瘤病毒癌基因同源物（KRAS）、KRAS G12D、L1細胞黏附分子（L1CAM）、MAGE、MET、黏蛋白1（MUC1）、黏蛋白16（MUC16）、

黏蛋白17 (MUC17)、自然殺手組2成員D (NKG2D)、NYESO-1、前列腺幹細胞抗原 (PSCA)、腎母細胞瘤1 (WT-1)、半乳糖凝集素9 (Gal9)、計畫性細胞死亡1配體1 (PD-L1)、滋養層糖蛋白 (5T4癌胚抗原)、葉酸受體 α (FOLR1) 和腫瘤相關鈣訊息傳遞子2 (TROP2)。

【0244】能夠結合該等TAA的結合蛋白在實例中進行了描述，並且在本領域中係已知的。任何該等已知的結合蛋白或從其衍生的TAA結合結構域可以方便地用作本文所描述的雙特異性促效劑LT β R結合蛋白的TAA結合結構域。例如，且不限於，該TAA結合結構域可包含本文實例7中描述的CLDN6結合結構域、CLDN18.2結合結構域、LRRC15結合結構域或MUC17結合結構域。其他合適的TAA結合結構域包括但不限於抗甲型胎兒蛋白 (AFP) 抗體或其結合結構域 (參見例如，Hansen等人的美國專利案號8,268,312，特此藉由引用將其全部併入)；抗CD44v6抗體或其結合結構域 (參見例如，Adolf等人的美國專利案號6,972,324，特此藉由引用將其全部併入)；抗碳酸酐酶IX (CAIX) 抗體或其結合結構域 (參見例如，Renner的WO 2011139375和Lenferink的美國專利案號10,487,153，特此藉由引用將其全部併入)；抗癌胚抗原 (CEA) 抗體或其結合結構域 (參見例如，Mossner等人的美國專利申請公開案號20160075795，特此藉由引用將其全部併入)；抗CD133抗體或其結合結構域 (參見例如，Vallera的美國專利案號11,098,109和Pfister等人的美國專利申請公開案號20200354468，特此藉由引用將其全部併入)；抗肝細胞生長因子受體 (c-MET) 抗體或其結合結構域 (參見例如，Harms等人的美國專利案號9,458,245，和Neijssen等人的美國專利案號9,068,011，特此藉由引用將其全部併入)；抗密連蛋白18.2抗體或其結合結構域 (參見例如，Dahlhoff等人的美國專利申請公開案號20200055932，和Hu等人的美國專利案號10,421,817，特此藉由引用將其全部併入)；抗密連蛋白6抗體或其結合結構域 (參見例如，Chambers等人的美國專利案號11,248,046，特此藉由引用將其全部併入)。

入)；抗表皮生長因子受體(EGFR)抗體或其結合結構域(參見例如，Chiu等人的美國專利案號9,695,242，和van de Winkel等人的美國專利案號9,458,236，特此藉由引用將其全部併入)；抗III型變體表皮生長因子受體(EGFRvIII)抗體或其結合結構域(參見例如，Kirschner等人的美國專利案號10,738,124，和Ellwanger等人的美國專利案號10,273,309，特此藉由引用將其全部併入)；抗促紅血球生成素產生肝細胞癌A2(EphA2)抗體或其結合結構域(參見例如，Bouchard等人的美國專利案號9,676,864，和Zhou和Marks的美國專利案號10,406,225，特此藉由引用將其全部併入)；抗上皮細胞黏附分子(EpCAM)抗體或其結合結構域(參見例如，Gunnarsson等人的美國專利案號8,637,017，和Harvey等人的美國專利案號9,790,274，特此藉由引用將其全部併入)；抗胎兒乙醯膽鹼受體抗體或其結合結構域(參見例如，Martinez-Martinez的WO 2013011030，特此藉由引用將其全部併入)；抗葉酸受體 α (FR α)結合結構域(參見例如，O'Shannessy的美國專利案號8,475,795，特此藉由引用將其全部併入)；抗神經節苷脂GD2(GD2)抗體或其結合結構域(參見例如，Scholz等人的美國專利申請公開案號20210189000，和Leusen等人的美國專利申請公開案號20210179732，特此藉由引用將其全部併入)；抗蛋白多糖-3(GPC3)抗體或其結合結構域(參見例如，Terrett等人的美國專利案號9,217,033，特此藉由引用將其全部併入)；抗鳥苷酸環化酶C(GUCY2C)抗體或其結合結構域(參見例如，Chang等人的美國專利申請公開案號20200010566，特此藉由引用將其全部併入)；抗人表皮生長因子受體1(HER1)抗體或其結合結構域(參見例如，Bossenmaier等人的美國專利申請公開案號20180100022，特此藉由引用將其全部併入)；抗人表皮生長因子受體2(ERBB2/HER2)抗體或其結合結構域(參見例如，Goeij等人的美國專利案號11,046,771，和Alper的美國專利案號8,722,362，特此藉由引用將其全部併入)；抗細胞間黏附分子1(ICAM-1)抗體或其結合結構域(參見例如，Hansson等人

的美國專利申請公開案號20160280788，和Abulrob等人的美國專利案號8,623,369，特此藉由引用將其全部併入）；抗白血球介素13受體 $\alpha 2$ （IL13R $\alpha 2$ ）抗體或其結合結構域（參見例如，Balyasnikova等人的美國專利申請公開案號20200181227，特此藉由引用將其全部併入）；抗白血球介素11受體 α （IL11R α ）抗體或其結合結構域（參見例如，Edwards等人的美國專利案號9,340,618，特此藉由引用將其全部併入）；抗Kirsten大鼠肉瘤病毒癌基因同源物（KRAS）抗體或其結合結構域（參見例如，Zhou等人的美國專利案號11,174,314，特此藉由引用將其全部併入）；抗L1細胞黏附分子（L1CAM）抗體或其結合結構域（參見例如，Hong等人的美國專利申請公開案號20220033494，特此藉由引用將其全部併入）；抗MAGE抗體或其結合結構域（參見例如，Bergeron等人的美國專利案號8,987,423，和Esslinger等人的美國專利申請公開案號20140093514，特此藉由引用將其全部併入）；抗肝細胞生長因子受體（HGF受體/MET）抗體或其結合結構域（參見例如，Burgess等人的美國專利案號8,609,090，和Goetsch等人的美國專利案號8,545,839，特此藉由引用將其全部併入）；抗黏蛋白1（MUC1）抗體或其結合結構域（參見例如，Denardo等人的美國專利案號7,183,388，和Yonezawa的美國專利案號8,951,526，特此藉由引用將其全部併入）；抗黏蛋白16（MUC16）抗體或其結合結構域（參見例如，Haber等人的美國專利案號10,941,208，特此藉由引用將其全部併入）；抗黏蛋白17（MUC17）抗體或其結合結構域（參見例如，Raum等人的美國專利申請公開案號20210130465，特此藉由引用將其全部併入）；抗自然殺手組2成員D（NKG2D）抗體或其結合結構域（參見例如，Urso等人的美國專利案號10,526,409，特此藉由引用將其全部併入）；抗癌/睪丸抗原1（CT6.1）抗體或其結合結構域（參見例如，美國專利申請公開案號20190382504，特此藉由引用將其全部併入）；抗前列腺幹細胞抗原（PSCA）抗體或其結合結構域（參見例如，Gudas等人的美國專利案號8,013,128，

特此藉由引用將其全部併入)；抗腎母細胞瘤1(WT-1)抗體或其結合結構域(參見例如，Benz等人的美國專利案號11,192,957，特此藉由引用將其全部併入)；抗半乳糖凝集素9(Gal9)抗體或其結合結構域(參見例如，Koide等人的美國專利案號10,344,091，特此藉由引用將其全部併入)；抗計畫性細胞死亡1配體1(PD-L1)抗體或其結合結構域(參見例如，Freeman等人的美國專利案號9,988,452，特此藉由引用將其全部併入)；抗滋養層糖蛋白(5T4癌胚抗原)抗體或其結合結構域(參見例如，Boghaert等人的美國專利案號8,044,178，特此藉由引用將其全部併入)；抗葉酸受體 α (FOLR1)抗體或其結合結構域(參見例如，Ando等人的美國專利案號9,207,238，特此藉由引用將其全部併入)；和抗腫瘤相關鈣訊息傳遞子2(滋養層細胞表面抗原2；TROP2)抗體或其結合結構域(參見例如，Tang等人的美國專利案號11,192,954，特此藉由引用將其全部併入)。

【0245】在另一個實施方式中，該雙特異性LT β R結合蛋白的腫瘤相關抗原結合結構域與腫瘤微環境(TME)的基質相關抗原(SAA)結合。合適的SAA包括但不限於纖連蛋白(FN1)、基質金屬蛋白酶-2(MMP2)、血小板衍生的生長因子受體- β (PDGFR β)、dickkopf相關蛋白3(DKK3)、血小板衍生的生長因子亞基B(PDGFB)、NUAK家族SNF1樣激酶1(NUAK1)、成纖維細胞生長因子(FGF1)、PDZ和LIM結構域蛋白4(PDLIM4)、gremlin 1(Grem1)和骨膜蛋白(POSTN)。

【0246】能夠結合該等SAA的結合蛋白在本領域中已經係已知的，並且可以容易地用作本文所描述的LT β R雙特異性結合蛋白的第二結合結構域。例如，且不限於，該第二結合結構域可包含抗纖連蛋白抗體或其結合結構域(參見例如，Kato等人的美國專利申請公開案號20100248262，特此藉由引用將其全部併入)、抗基質金屬蛋白酶-2抗體或其結合結構域(參見例如，Devy的美國專利案號8,013,125，特此藉由引用將其全部併入)、抗血小板衍生的生長因子受體- β

(PDGFR β)抗體或其結合結構域(參見例如,Zhu等人的美國專利案號7,740,850,特此藉由引用將其全部併入)、抗dickkopf相關蛋白3抗體或其結合結構域(參見例如,Hwang等人的美國專利申請公開案號20210340232,特此藉由引用將其全部併入)、抗血小板衍生的生長因子亞基B抗體或其結合結構域(參見例如,Arch等人的美國專利案號9,428,577,特此藉由引用將其全部併入)、抗NUAK家族SNF1樣激酶1(NUAK1)抗體或其結合結構域、抗成纖維細胞生長因子抗體或其結合結構域(參見例如,Ashkenazi等人的美國專利案號8,410,250,和Weng等人的美國專利案號8,481,168,特此藉由引用將其全部併入)、抗PDZ和LIM結構域蛋白4(PDLIM4)抗體或其結合結構域、抗gremlin 1抗體或其結合結構域(參見例如,Chalothorn等人的美國專利申請公開案號20180057580,和Dedi等人的美國專利申請公開案號20210163586,特此藉由引用將其全部併入)、以及抗骨膜蛋白抗體或其結合結構域(參見例如,Taniyama等人的美國專利案號8,372,957,特此藉由引用將其全部併入)。

【0247】在一個實施方式中,本揭露之多特異性LT β R結合蛋白係對於LT β R結合係單價的雙特異性LT β R結合蛋白。對於本文所描述的LT β R結合結構域,已經發現包含該等呈單價形式(但不是二價形式)的LT β R結合結構域的雙特異性分子表現出交聯依賴性LT β R激動作用。換句話說,包含單價LT β R結合結構域的雙特異性分子需要第一和第二結合結構域的結合以誘導LT β R受體聚集並實現LT β R激動作用。這種對LT β R具有單價的雙特異性構建體特別有利於將LT β R激動作用靶向特定組織,例如腫瘤微環境,因為活性取決於第一和第二結合結構域的結合。此外,本文揭露的LT β R結合物係基於它們與LT β R在不會抑制內源性LT β R配體結合和傳訊的區域(例如CRD4)的結合進行專門篩選和選擇的。本文揭露的LT β R結合蛋白的該等特性共同確保了,如果LT β R雙特異性結合蛋白在靶向腫瘤微環境之外結合LT β R,(i) 在不存在第二結合結構域與其靶標結

合的情況下，結合不會誘導脫靶LT β R傳訊，以及 (ii) 這樣的結合不會阻斷脫靶組織中的內源性LT β R配體（即，LIGHT和LT α 1 β 2）傳訊。該等設計特性提供了相對於先前描述的LT β R結合蛋白具有優異的安全性和功效性質的LT β R結合蛋白。

衍生物、變體和模擬物

【0248】 在一個實施方式中，本文所描述的LT β R結合蛋白在重鏈恒定區中包含一或多個胺基酸修飾，其提高半衰期/穩定性或使抗體更適用於表現/可製造性。在一個實施方式中，該LT β R結合蛋白被設計為防止或減少與Fc受體的相互作用。在示例性情況中，該結合蛋白係包含缺乏與Fc γ 受體相互作用能力的恒定區的穩定效應物無功能（SEFL）結合蛋白。胺基酸突變和製備SEFL抗體之方法在本領域中係已知的，參見例如，Liu等人, J. Biol. Chem[生物化學雜誌]. 292: 1876-1883 (2016)；和Jacobsen等人, J. Biol. Chem[生物化學雜誌]. 292: 1865-1875 (2017)，特此藉由引用將其全部併入。在示例性方面，本文所描述的LT β R結合蛋白被修飾為包含以下突變中的一或多個，根據EU系統進行編號：L242C、A287C、R292C、N297G、V302C、L306C和/或K334C。在示例性方面，本文所描述的LT β R結合蛋白包含N297G取代以形成SEFL結合蛋白。在示例性方面，本文所描述的LT β R結合蛋白包含A287C、N297G和L306C取代以形成SEFL結合蛋白。在其他示例性方面，該LT β R結合蛋白包含R292C、N297G和V302C取代以形成基於SEFL2-2抗體的分子。

【0249】 在一個實施方式中，如本文所描述的促效劑LT β R結合蛋白可以包含其他半衰期延長（HLE）修飾。在一個實施方式中，該HLE修飾發生在重鏈恒定區中，並包含以下胺基酸取代中的一或多個，根據EU系統編號：M252Y、S254T和T256E。在示例性情況中，該LT β R結合蛋白包含M252Y、S254T和T256E取代中的一個或兩個。在示例性情況中，本揭露之LT β R結合蛋白包含M252Y、S254T

和T256E中的全部三個。在一個實施方式中，該HLE修飾發生在重鏈恒定區中，並包含以下取代中的一或多個，根據EU系統編號：L309D、Q311H和N434S。在示例性情況中，本揭露之LT β R結合蛋白包含L309D、Q311H和N434S取代中的一個、兩個或全部三個。在示例性情況中，該LT β R結合蛋白包含L309D、Q311H和N434S取代中的全部三個。在一個實施方式中，本文揭露的LT β R結合蛋白包含SEFL或SEFL2-2修飾與本文所描述的任何HLE修飾的組合。

【0250】 在某些實施方式中，該促效劑LT β R結合蛋白的變體包括糖基化變體，其中糖基化位點的數量和/或類型與親本多肽的胺基酸序列相比已經改變。在某些實施方式中，變體包含比天然蛋白質更多或更少數目的N連接的糖基化位點。可替代地，消除此序列的取代將移除已存在的N連接的碳水化合物鏈。還提供了N連接的碳水化合物鏈的重排，其中消除一或多個N連接的糖基化位點（典型地天然存在的那些）並且創造一或多個新的N連接的位點。額外的結合蛋白變體包括半胱胺酸變體，其中與親本胺基酸序列相比，一或多個半胱胺酸殘基缺失或被取代為另一種胺基酸（例如絲胺酸）。當抗體必須重新折疊成生物學上活性構象時，如在分離不溶性包涵體之後，半胱胺酸變體可能有用。半胱胺酸變體一般具有少於天然蛋白質的半胱胺酸殘基，且典型地具有偶數個以使由未配對的半胱胺酸引起的相互作用最小。

【0251】 在一個實施方式中，本文揭露的促效劑LT β R結合蛋白（例如，促效劑LT β R抗體和雙特異性促效劑LT β R結合蛋白）包括翻譯後修飾的變體。例如，在一個實施方式中，包含重鏈的促效劑LT β R結合蛋白的C末端離胺酸殘基已缺失。

【0252】 其他期望的胺基酸取代（無論是保守的還是非保守的）和缺失可以由熟悉該項技術者在需要這樣的取代或缺失時來確定。在某些實施方式中，胺基酸取代可用於例如鑑定與功能相關的結合蛋白的重要殘基、增加或降低抗體

對本文所描述的感興趣靶標的親和力、降低對蛋白水解的易感性、降低對氧化的易感性、改變形成蛋白複合物的結合親和力，和/或賦予或修飾此類多肽的其他物理化學或功能性質。根據某些實施方式，可在天然存在的序列中（在某些實施方式中，在形成分子間接觸的一或多個結構域外的多肽部分中）進行單個或多個胺基酸取代（在某些實施方式中為保守胺基酸取代）。在某些實施方式中，保守胺基酸取代通常可能不會實質性地改變親本序列的結構特徵（例如，替換胺基酸不應傾向於破壞親本序列中發生的螺旋或破壞表徵親本序列的其他類型的二級結構）。領域公認的多肽二級和三級結構之實例描述於Proteins, Structures and Molecular Principles [蛋白質、結構和分子原理] (Creighton編輯, W. H. Freeman and Company [W.H.弗裡曼公司], 紐約 (1984))；Introduction to Protein Structure [蛋白質結構簡介] (C.Branden及J.Tooze編, Garland Publishing [加蘭出版社], 紐約, 紐約州。(1991))；以及Thornton等人 Nature [自然] 354:105 (1991)，將該等文獻各自藉由引用併入本文。

編碼LTβR結合蛋白的核酸分子

【0253】 本揭露進一步提供了包含編碼本揭露之促效劑LTβR結合蛋白的核苷酸序列的核酸分子。本文所用的「核酸分子」涵蓋多核苷酸和寡核苷酸，通常係指DNA或RNA的聚合物，或其修飾形式，其可為單鏈或雙鏈，從天然來源合成或獲得（例如，分離和/或純化），其可以含有天然、非天然或改變的核苷酸，並且其可以含有天然的、非天然或改變的核苷酸間鍵，例如磷酸醯胺鍵或硫代磷酸鍵，而不是在未修飾的寡核苷酸的核苷酸之間發現的磷酸二酯。核酸分子可以包含編碼本揭露之任何促效劑LTβR結合蛋白的任何核苷酸序列。在一些實施方式中，核酸不包含任何插入、缺失、倒位和/或取代。在其他實施方式中，核酸包含一或多個插入、缺失、倒位和/或取代。

【0254】 在一些方面，本揭露之核酸分子係重組的。如本文所用，術語「重

組」係指藉由使用實驗室方法連接天然或合成核酸片段以形成自然界中未發現的核酸分子而在活細胞外構建的分子。

【0255】 在一些方面，本揭露之核酸分子係使用本領域已知的程式基於化學合成和/或酶連接反應構建的。參見例如，Sambrook等人, *Molecular Cloning: A Laboratory Manual* [分子選殖：實驗室手冊].第3版, Cold Spring Harbor Press, Cold Spring Harbor [冷泉港實驗室出版社], NY 2001；和Ausubel等人, *Current Protocols in Molecular Biology* [分子生物學現代方法], Greene Publishing Associates [格林出版公司] 和John Wiley & Sons [約翰·威利父子公司], NY [紐約州], 1994。例如，核酸分子可以使用天然存在的核苷酸或多種修飾的核苷酸進行化學合成，該等核苷酸旨在提高分子的生物穩定性或增加雜交時形成的雙鏈體的物理穩定性（例如，硫代磷酸衍生物和吡啶取代的核苷酸）。可用於生成核酸的修飾核苷酸之實例包括但不限於5-氟尿嘧啶、5-溴尿嘧啶、5-氯碘尿嘧啶、5-碘尿嘧啶、次黃嘌呤、黃嘌呤、4-乙醯胞嘧啶、5-(羧基羥甲基)尿嘧啶、5-羧甲基胺基甲基-2-硫尿苷、5-羧甲基胺基甲基尿嘧啶、二氫尿嘧啶、 β -D-半乳糖基Q核苷(queosine)、肌苷、 N^6 -異戊烯基腺嘌呤、1-甲基鳥嘌呤、1-甲基肌苷、2,2-二甲基鳥嘌呤、2-甲基腺嘌呤、2-甲基鳥嘌呤、3-甲基胞嘧啶、5-甲基胞嘧啶、N-取代的腺嘌呤、7-甲基鳥嘌呤、5-甲基胺基尿嘧啶、5-甲氧基胺基甲基-2-硫尿嘧啶、 β -D-甘露糖基Q核苷(queosine)、5'-甲氧基羧甲基尿嘧啶、5-甲氧基尿嘧啶、2-甲硫基- N^6 -異戊烯基腺嘌呤、尿嘧啶-5-氧乙酸(v)、wybutoxosine、假尿嘧啶、Q核苷(queosine)、2-硫胞嘧啶、5-甲基-2-硫尿嘧啶、2-硫尿嘧啶、4-硫尿嘧啶、5-甲基尿嘧啶、尿嘧啶-5-氧乙酸甲酯、3-(3-胺基-3-N-2-羧丙基)尿嘧啶和2,6-二胺基嘌呤。

【0256】 在一個實施方式中，該核酸分子包含一或多個多核苷酸，其編碼促效劑LT β R結合蛋白之全部或部分，例如如本文揭露的結合蛋白的一條或兩條

鏈。多核苷酸可為適合所期望用途或功能的任何長度，並且可以可操作地偶合到一或多個額外序列（例如調節序列）和/或是較大核酸分子（例如載體）的一部分。如果調節序列影響多核苷酸序列的表現（例如，表現的水平、時間或位置），則多核苷酸「可操作地偶合」或「可操作地連接」至調節序列。多核苷酸分子可為單鏈或雙鏈，並且可以包含RNA和/或DNA核苷酸以及其人工變體（例如，肽核酸）。

【0257】 在一個實施方式中，本揭露之多核苷酸編碼上文揭露的促效劑LTβR結合蛋白，並包含編碼上文所描述的CDR中的任一個、任兩個、任三個、任四個、任五個或任六個的序列，包括表2、6和10中提供的重鏈CDR和表3、7和11中提供的輕鏈CDR。

【0258】 在一個實施方式中，本揭露之多核苷酸分子包含編碼與LTβR的CRD4結合的LTβR結合蛋白的VH結構域和VL結構域的核苷酸序列。因此，在一個實施方式中，該多核苷酸分子包含選自以下的編碼VH和VL結構域的核苷酸序列：SEQ ID NO: 119的VH胺基酸序列和SEQ ID NO: 120的VL胺基酸序列；SEQ ID NO: 121的VH胺基酸序列和SEQ ID NO: 122的VL胺基酸序列；SEQ ID NO: 123的VH胺基酸序列和SEQ ID NO: 124的VL胺基酸序列；SEQ ID NO: 125的VH胺基酸序列和SEQ ID NO: 126的VL胺基酸序列；SEQ ID NO: 127的VH胺基酸序列和SEQ ID NO: 128的VL胺基酸序列；SEQ ID NO: 129的VH胺基酸序列和SEQ ID NO: 130的VL胺基酸序列；SEQ ID NO: 131的VH胺基酸序列和SEQ ID NO: 132的VL胺基酸序列；SEQ ID NO: 133的VH胺基酸序列和SEQ ID NO: 134的VL胺基酸序列；SEQ ID NO: 135的VH胺基酸序列和SEQ ID NO: 136的VL胺基酸序列；SEQ ID NO: 137的VH胺基酸序列和SEQ ID NO: 138的VL胺基酸序列；SEQ ID NO: 139的VH胺基酸序列和SEQ ID NO: 140的VL胺基酸序列；SEQ ID NO: 141的VH胺基酸序列和SEQ ID NO: 142的VL胺基酸序列；SEQ ID NO: 143的VH

胺基酸序列和SEQ ID NO: 144的VL胺基酸序列；SEQ ID NO: 145的VH胺基酸序列和SEQ ID NO: 146的VL胺基酸序列；SEQ ID NO: 147的VH胺基酸序列和SEQ ID NO: 148的VL胺基酸序列；SEQ ID NO: 149的VH胺基酸序列和SEQ ID NO: 150的VL胺基酸序列；SEQ ID NO: 151的VH胺基酸序列和SEQ ID NO: 152的VL胺基酸序列；SEQ ID NO: 153的VH胺基酸序列和SEQ ID NO: 154的VL胺基酸序列；SEQ ID NO: 155的VH胺基酸序列和SEQ ID NO: 156的VL胺基酸序列；以及SEQ ID NO: 157的VH胺基酸序列和SEQ ID NO: 158的VL胺基酸序列。

【0259】 在一個實施方式中，本揭露之多核苷酸分子包含編碼促效劑LTβR結合蛋白的VH結構域和VL結構域的核苷酸序列，該促效劑LTβR結合蛋白與LIBC219081和LIBC218979示例性LTβR結合物競爭結合LTβR的CRD4。因此，在一個實施方式中，該多核苷酸分子包含選自以下的編碼VH和VL結構域的核苷酸序列：SEQ ID NO: 401的VH胺基酸序列和SEQ ID NO: 402的VL胺基酸序列；SEQ ID NO: 403的VH胺基酸序列和SEQ ID NO: 404的VL胺基酸序列；SEQ ID NO: 405的VH胺基酸序列和SEQ ID NO: 406的VL胺基酸序列；SEQ ID NO: 407的VH胺基酸序列和SEQ ID NO: 408的VL胺基酸序列；SEQ ID NO: 409的VH胺基酸序列和SEQ ID NO: 410的VL胺基酸序列；SEQ ID NO: 411的VH胺基酸序列和SEQ ID NO: 412的VL胺基酸序列；SEQ ID NO: 413的VH胺基酸序列和SEQ ID NO: 414的VL胺基酸序列；SEQ ID NO: 415的VH胺基酸序列和SEQ ID NO: 416的VL胺基酸序列；SEQ ID NO: 417的VH胺基酸序列和SEQ ID NO: 418的VL胺基酸序列；SEQ ID NO: 419的VH胺基酸序列和SEQ ID NO: 420的VL胺基酸序列；SEQ ID NO: 421的VH胺基酸序列和SEQ ID NO: 422的VL胺基酸序列；SEQ ID NO: 423的VH胺基酸序列和SEQ ID NO: 424的VL胺基酸序列；SEQ ID NO: 425的VH胺基酸序列和SEQ ID NO: 426的VL胺基酸序列；SEQ ID NO: 427的VH胺基酸序列和SEQ ID NO: 428的VL胺基酸序列；SEQ ID NO: 429的VH胺基酸序

列和SEQ ID NO: 430的VL胺基酸序列；SEQ ID NO: 431的VH胺基酸序列和SEQ ID NO: 432的VL胺基酸序列；SEQ ID NO: 433的VH胺基酸序列和SEQ ID NO: 434的VL胺基酸序列；SEQ ID NO: 435的VH胺基酸序列和SEQ ID NO: 436的VL胺基酸序列；SEQ ID NO: 437的VH胺基酸序列和SEQ ID NO: 438的VL胺基酸序列；SEQ ID NO: 439的VH胺基酸序列和SEQ ID NO: 440的VL胺基酸序列；SEQ ID NO: 441的VH胺基酸序列和SEQ ID NO: 442的VL胺基酸序列；SEQ ID NO: 443的VH胺基酸序列和SEQ ID NO: 444的VL胺基酸序列；SEQ ID NO: 445的VH胺基酸序列和SEQ ID NO: 446的VL胺基酸序列；SEQ ID NO: 447的VH胺基酸序列和SEQ ID NO: 448的VL胺基酸序列；SEQ ID NO: 449的VH胺基酸序列和SEQ ID NO: 450的VL胺基酸序列；SEQ ID NO: 451的VH胺基酸序列和SEQ ID NO: 452的VL胺基酸序列；SEQ ID NO: 453的VH胺基酸序列和SEQ ID NO: 454的VL胺基酸序列；SEQ ID NO: 455的VH胺基酸序列和SEQ ID NO: 456的VL胺基酸序列；SEQ ID NO: 457的VH胺基酸序列和SEQ ID NO: 458的VL胺基酸序列；SEQ ID NO: 459的VH胺基酸序列和SEQ ID NO: 460的VL胺基酸序列；SEQ ID NO: 461的VH胺基酸序列和SEQ ID NO: 462的VL胺基酸序列；SEQ ID NO: 463的VH胺基酸序列和SEQ ID NO: 464的VL胺基酸序列；SEQ ID NO: 465的VH胺基酸序列和SEQ ID NO: 466的VL胺基酸序列；SEQ ID NO: 467的VH胺基酸序列和SEQ ID NO: 468的VL胺基酸序列；SEQ ID NO: 469的VH胺基酸序列和SEQ ID NO: 470的VL胺基酸序列；SEQ ID NO: 471的VH胺基酸序列和SEQ ID NO: 472的VL胺基酸序列；以及SEQ ID NO: 473的VH胺基酸序列和SEQ ID NO: 474的VL胺基酸序列。

【0260】 在一個實施方式中，本揭露之多核苷酸分子包含編碼結合人LTβR的促效劑LTβR結合蛋白的VH結構域和VL結構域的核苷酸序列。因此，在一個實施方式中，該多核苷酸包含選自以下的編碼VH和VL結構域的核苷酸序列：

SEQ ID NO: 644的VH胺基酸序列和SEQ ID NO: 645的VL胺基酸序列；SEQ ID NO: 646的VH胺基酸序列和SEQ ID NO: 647的VL胺基酸序列；SEQ ID NO: 648的VH胺基酸序列和SEQ ID NO: 649的VL胺基酸序列；SEQ ID NO: 650的VH胺基酸序列和SEQ ID NO: 651的VL胺基酸序列；SEQ ID NO: 652的VH胺基酸序列和SEQ ID NO: 653的VL胺基酸序列；SEQ ID NO: 654的VH胺基酸序列和SEQ ID NO: 655的VL胺基酸序列；SEQ ID NO: 656的VH胺基酸序列和SEQ ID NO: 657的VL胺基酸序列；SEQ ID NO: 658的VH胺基酸序列和SEQ ID NO: 659的VL胺基酸序列；SEQ ID NO: 660的VH胺基酸序列和SEQ ID NO: 661的VL胺基酸序列；SEQ ID NO: 662的VH胺基酸序列和SEQ ID NO: 663的VL胺基酸序列；SEQ ID NO: 664的VH胺基酸序列和SEQ ID NO: 665的VL胺基酸序列；SEQ ID NO: 666的VH胺基酸序列和SEQ ID NO: 667的VL胺基酸序列；SEQ ID NO: 668的VH胺基酸序列和SEQ ID NO: 669的VL胺基酸序列；SEQ ID NO: 670的VH胺基酸序列和SEQ ID NO: 671的VL胺基酸序列；SEQ ID NO: 672的VH胺基酸序列和SEQ ID NO: 673的VL胺基酸序列；SEQ ID NO: 674的VH胺基酸序列和SEQ ID NO: 675的VL胺基酸序列；SEQ ID NO: 676的VH胺基酸序列和SEQ ID NO: 677的VL胺基酸序列；SEQ ID NO: 678的VH胺基酸序列和SEQ ID NO: 679的VL胺基酸序列；SEQ ID NO: 680的VH胺基酸序列和SEQ ID NO: 681的VL胺基酸序列；SEQ ID NO: 682的VH胺基酸序列和SEQ ID NO: 683的VL胺基酸序列；SEQ ID NO: 684的VH胺基酸序列和SEQ ID NO: 685的VL胺基酸序列；SEQ ID NO: 686的VH胺基酸序列和SEQ ID NO: 687的VL胺基酸序列；SEQ ID NO: 688的VH胺基酸序列和SEQ ID NO: 689的VL胺基酸序列；SEQ ID NO: 690的VH胺基酸序列和SEQ ID NO: 691的VL胺基酸序列。下表14中提供了編碼本文揭露的促效劑LTβR結合蛋白的VH和VL結構域的示例性核酸序列。

[表14]. LTβR結合蛋白的核酸序列

LIBC. 編號	鏈	序列	SEQ ID
218990	HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGG GCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCG GCGACTATATGTACTGGGTGCGACAGGCCCTGGACAAGGGCTTGA GTGGATGGGATGGATCAACCCTAACAGTGGTGGCACAACTATGCA AAGAAGTTTCAGGGCAGGGTCACCATGACCAGGGACACGTCCATC AGCACAGCCTACATGGAGCTGAGCAGGCTGAGATCTGACGACACG GCCGTGTATTACTGTGCGAGAGAAGGGAGCAGTGGCTGGTCCGCCG AATACTTCCAGCACTGGGGCCAGGGCACCTGGTCACCGTCTTTTC AGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAG GACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAATCAGGCGCTC TGACCAGCGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGG ACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTC GGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAAC ACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCC CACCGTGCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCCTCTTC CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGG TCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCA GTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACA AAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGC GTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACA AGTGCAAGGTCAGCAACAAAGGCCTCCCAGCCCCCATCGAGAAAA CCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACA CCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCT GACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCT CCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCAC CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCC GTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCT CCCTGTCTCCGGGCAAATAG	857
	LC	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTNTCNTGCAGGGCCAGTCAGAGTGTTAGCAG CAGCTTCTTAGCCTGGTACCAGCAGAACTTGGCCAGGCTCCCAGG CTCCTCATGTATGGTGCATCCCGCAGGGCCACAGGCATCCCAGACA	858

LIBC. 編號	鏈	序列	SEQ ID
		GGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAG CAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTAT GGTACCTCACCTCTCTCTTTTCGGCGGAGGGACCAAGGTGGAGATCA AACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT GAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATA ACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACG CCCTCCAATCGGGTAACTCCCAGGAGAGTGTACACAGAGCAGGACA GCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCA AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCC ATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG AGTGTTAG	
218994	HC	CAGGTGCAACTGGTGGAGTCTGGGGGAGCCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAG CTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAATTATATGGTATGATGGAAGTGATGAATACTATGCAG ACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAA CACGTTGTATCTGCAAATGAACAGTGTGAGAGACGAGGACACGGCT CTGTATTACTGTGTGAGAGGGGACAGTGAGGACTTCTACTACTACG ATTTGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGC CTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGG AGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACT ACTTCCCCGAACCGGTGACGGTGTGCGTGGAACCTCAGGCGCTCTGAC CAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTC TACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCA CCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAA GGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCACCG TGCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCC AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACG TGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCA ACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGC CACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCT CACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTG CAAGGTCAGCAACAAAGGCCTCCCAGCCCCATCGAGAAAACCAT CTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT	859

LIBC. 編號	鏈	序列	SEQ ID
		GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGAC CTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGG GAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCC ATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGT GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC TGTCTCCGGGCAAATAG	
	LC	CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGAC AGAAGGTCACCATCTCCTGTCTGGAAGCAGCTCCAACATTGGGAA GAATTATGTTTCCTGGTACCAACACCTCCCAGGCACAGCCCCAAA CTCCTCATTTATGACAATAATAAGCGACCCTCAGGAATTCCTGACC GATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCATCAC CGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGG GATCACAGCCTGAGTGCTAGTTATGTCTTCGGAAC TGGGACCAAGG TCACCGTCCTAGGTCAGCCCAAGGCTGCACCCTCGGTCACTCTGTTC CCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGT GTCTCATCAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAA GGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAAACCACCACACC CTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAG CCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAG GTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCCTACA GAATGTTCATAG	860
219058	HC	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGG GGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAC CTCTGGCATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGA GTGGGTCTCATCCGTTAGTAGTAGTGGTAGTTACATATACTACGCA GACTCAGTGAAGGGCCGATTACCATCTCCAGAGACAACGCCAAG AACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACG GCTGTCTATTACTGTGCTGGAGCTCGGTATAACTGGCACTTTGATGC TTCTGATATCTGGGGCCAAGGGACAGTGGTCAACCGTCTCTTCAGCC AGCACCAAGGGGCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGA GCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTA CTTCCCCGAACCGGTGACGGTGTCTGTGGAAC TACAGGCGCCCTGACC AGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCT	861

LIBC. 編號	鏈	序列	SEQ ID
219081		ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCAC GAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAA GGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCATCA TGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCC CCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTC ACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAG TTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAA AGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCG TCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAA GTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACC ATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACC CTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTG ACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGT GGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTC CCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTAACC GTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCG TGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTC CCTGTCTCTGGGCAAATAG	
	LC	GACATCCAGATGACCCAGTCTCCGTCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGC GATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAACCTCC TGATCTATGCTGCATCCAGTTTGCACAGTGGGGTCCCATCAAGGTTT AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTC TCCTACCTGAGGATTTTGCAACTTACTACTGTCAACAGAGTTACAAT ACCCCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA G	862
219081	HC	CCGATTCATCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTG	863

LIBC. 編號	鏈	序列	SEQ ID
		CAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTATATTACTGTG CGCGAGATCGGGTAGCAGCTCATCCGGCCTACTACTACGGTCTGGA CGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCACC AAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCT CCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCC CGAACCGGTGACGGTGTCTGTGGAACTCAGGCGCTCTGACCAGCGGC GTGCACACCTTCCCAGCTGTCTTACAGTCCTCAGGACTCTACTCCCT CAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACC TACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGAC AAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCACCGTGCCAG CACCACCTGTGGCAGGACCGTCAGTCTTCTTCCCCCAAACCC AAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGG TGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTA CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGA GGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTT GTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTC AGCAACAAAGGCCTCCCAGCCCCATCGAGAAAACCATCTCCAAA ACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCAT CCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA TGGGCAGCCGGAGAACAATAACAAGACCACACCTCCCATGCTGGA CTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAG AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATG AGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCC GGGCAAATAG	
	LC	TCCTATGAGCTGACACAGCCACCCTCGGTGTCATTGTCCCCAGGAC AGACGGCCAGGATCACCTGCTCTGGAGATGCATTGCCAAACCATTA TGCTTATTGGTACCAGCAGAAGCCAGGCCAGGCCCTGTACTGGTG ATATTTAAAGACAATGAGAGGCCCTCAGGGATCCCTGAGCGATTCT CTGGCTCCAGTTCAGGGACAACAGTCACGTTGACCATCAGTGAGT CCAGGCAGAAGACGAGGCTGACTATTACTGTCAATCAGCAGACAG CAGTGGTTCTTATGTGATTTTCGGCGGAGGGACCAAAGTACCGTC CTAGGTCAGCCAAGGCTGCACCCTCGGTCACTCTGTTCCCGCCCTC CTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATC	864

LIBC. 編號	鏈	序列	SEQ ID
		AGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATA GCAGCCCCGTCAAGGCGGGAGTGGAACCACCACACCCTCCAAAC AAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGC CTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGC ATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCCTACAGAATGTT CATAG	
219097	HC	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTAAAGCCTGGG GGGTCCCTTAGACTCTCCTGTGCAGCCTCTGGATTCACTTTCAATGA CGCCTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGA GTGGGTTGGCCGTATTAAAACCAAACTGATGGTGGGACAACAGA CTACGCTGCACCCGTGAAAGGCAGAATCACCATCTCAAGAGATGAT TCAAAAAACACGCTGTATCTGCAAATGAACAGCCTGAAAACCGAG GACACAGCCGTGTATTACTGTACCACCGACTACGGTGACTACGAGT ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAA GGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC GAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG AACCGGTGACGGTGTCTGTGGAATCAGGCGCTCTGACCAGCGGCGT GCACACCTTCCCAGCTGTCTACAGTCCTCAGGACTCTACTCCCTCA GCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTA CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAA GACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCA CCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCCTAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGT GGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTAC GTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAG GAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTG TGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCA GCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAAC CAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCC CGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTC AAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGGCAGCCGGAGAACAACACTACAAGACCACACCTCCCATGCTGGAC TCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGA GCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGA	865

LIBC. 編號	鏈	序列	SEQ ID
		GGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCG GGCAAATAG	
	LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGACAAGTCAGAGCATTAGTAGA TATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCCTAAACTCC TGATCTATGGTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTT CAGTGGCAGTGGATCTGGGACAGATTCTACTCTCACCATCAGCAGT CTGCAACCTGAAGATTTTGCAACTTACTATTGTCATCAGAGTTACAG TACCCCTCCGACGTTCTGGCCAAGGGACCAAGGTGGAAATCAAACG AACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGC AGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTC TATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTC CAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAG GACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCA GACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAG GGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTT AG	866
218979	HC	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAG CTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAG ACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAA CACGCTGTCTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCT GTGTATTACTGTGCGAGAGAGCGTATAGCAGCAGCCCCTTACTACT ACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCAGCCAGCACCAAGGGGCCATCCGTCTTCCCCCTGGCGCCCTGC TCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCA AGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCAAGGCGC CCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCT TGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCA ACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATG CCCATCATGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTC CTGTTCCCCCCTAAACCAAGGACACTCTCATGATCTCCCGGACCC	867

LIBC. 編號	鏈	序列	SEQ ID
		CTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCG AGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGT GGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCG AGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGG TGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGT CAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACC ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAG GCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTC ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAG AGCCTCTCCCTGTCTCTGGGCAAATAG	
	LC	TCCTATGAACTGACACAGCCACCCTCGGTGTCGGTGTCCCCAAGAC AGACGGCCAGGATCACCTGCTCTGGAGATGCATTGCCAAAGCATT TGCTTATTGGTACCAGCAGAAGCCAGGCCAGGCCCTGTGCTGGTG ATATATAAAGACAATGAGAGGCCCTCAGGGATCCCTGAGCGATTCT CTGGCTCCAGCTCAGGGACAACGTGTCACGTTGACCATCAGTGGAGT CCAGGCAGAAGACGAGGCTGACTATTACTGTCAATCAGCAGACAA CACTGGTTCTTATATGGTATTTCGGCGGAGGGACCAAGCTGACCGTC CTAGGTCAGCCCAAGGCTGCACCCTCGGTCACTCTGTTCCCGCCCTC CTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATC AGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATA GCAGCCCCGTCAAGGCGGGAGTGGAACCACCACACCCTCCAAAC AAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGC CTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGC ATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCCTACAGAATGTT CATAG	868
219037	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACGGGTGAAGCCTTCA CAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAACAG TGGTGGTTACTTCTGGAGCTGGATCCGCCAGCACCCAGGGAAGGTC CTGGAGTGGATTGGGTACAGCCATTACAGTGGTACCACCTACTACA ATCCGTCCCTCAAGAGTCGAGTAACCATATCAGTAGACACGTCTAA GAACCAGCTCTCCCTGAAGCTGAACTCTGTGAATGCCGCGGACACG	869

LIBC. 編號	鏈	序列	SEQ ID
		GCCGTGTATTACTGTGCGAGAGTGCCTGATGGGGAAGACTACTTTG ACTACTGGGGCCAGGGAGCCCTGGTCACCGTCTCCTCAGCCAGCAC CAAGGGGCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACC TCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCC CCGAACCGGTGACGGTGTCTGTGGAAGTCAAGGCGCCCTGACCAGCGG CGTGACACACCTTCCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCC TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGAC CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGA CAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCATCATGCCCA GCACCTGAGTTCCTGGGGGGACCATCAGTCTTCTGTTCCCCCCAA AACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTG CGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAA CTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCC GCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTC ACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGC AAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCT CCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGC CCCCATCCCAGGAGGAGATGACCAAGAACCAGGTACGCCTGACCT GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGA GAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGT GCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTAACCGTG GACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGA TGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCT GTCTCTGGGCAAATAG	
	LC	GACCTCCAGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGACCATTAGTAGT TATTTAAATTGGTATCAGCAGAAACCGGGGAAAGCCCCTAAACTCC TGATCTATGATGCCTCAAGTTTGCAAAGTGGGGTCCCATCAAGGTT CAGTGGCAGTGGATCTGGGACAGATTTACTCTCACCATCAGCAGT CTGCAACCTGAAGATTTTGAAACTTACTACTGTCAACAGAGTTTCA GTGCCCCGATCACCTTCGGCCAAGGGACACGACTGGAAATTAAACG AACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGC AGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTC TATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTC	870

LIBC. 編號	鏈	序列	SEQ ID
		CAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAG GACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCA GACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAG GGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTT AG	
219098	HC	GAGGTGCAGTTGTTGGAGTCTGGGGGAGGCTTGGTTCAGCCTGGGG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGC TATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGT GGGTCTCAACTATTAGTGGTAGTGGTGGTAGCACATACTACGCAGA CTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAAC ACGCTGAATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCC GTATATTACTGTGCGAAAGTTAGGGATAACTGGA ACTACGACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTC CACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGC ACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACT TCCCCGAACCGGTGACGGTGTCGTGGA ACTCAGGCGCTCTGACCAG CGGCGTGACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACT CCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCA GACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGT GGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGC CCAGCACCACTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCC AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTG CGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAAC TGGTACGTGGACGGCGTGAGGTGCATAATGCCAAGACAAAGCCA CGGGAGGAGCAGTTCAACAGCACGTTCCTGTGGTCAGCGTCCTCA CCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCA AGGTCAGCAACAAAGGCCTCCAGCCCCCATCGAGAAAACCATCTC CAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG AGCAATGGGCAGCCGGAGAACA ACTACAAGACCACACCTCCCATG CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGA CAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATG CATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT	871

LIBC. 編號	鏈	序列	SEQ ID
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	LC	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTCACCCTTGG AGAGTCGGCCTCCATCTCCTGTAGGTGTAGTCAGAGCCTCCTGTAT AGTAGTGGATACATCGATTTGGATTGGTACCTGCAGAAGCCAGGGC AGTCTCCACAGCTCCTGATCTATTTGGGTTCTAATCGGGCCTCCGGG GTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACAC TGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTG CATGCAAACCTATACAACTCCGCTCACTTTCGGCGGAGGGACCAAG GTGGAGATCAAACGAACGGTGGCTGCACCATCTGTCTTCATCTTCC CGCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTG CCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAG GTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAG AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGA CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCG AAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAA CAGGGGAGAGTGTTAG	872
219098.0 01	HC	GAGGTGCAGTTGTTGGAGTCTGGGGGAGGCTTGGTTCAGCCTGGGG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGC TATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGT GGGTCTCAACTATTAGTGGTAGTGGTGGTAGCACATACTACGCAGA CTCCGTGAAGGGCCGGTTACCATCTCCAGAGACAATTCCAAGAAC ACGCTGAATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCC GTATATTACTGTGCGAAAGTTAGGGATAACTGGAACCTACGACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTC CACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGC ACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACT TCCCCGAACCGGTGACGGTGTCGTGGAACCTCAGGCGCTCTGACCAG CGGCGTGACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACT CCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCA GACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGT GGACAAGACAGTTGAGCGCAAATGTTGTGTGCGAGTGCCACCGTGC CCAGCACCACTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCAA AACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACAGTG CGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAAC	873

LIBC. 編號	鏈	序列	SEQ ID
		TGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCA CGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCA CCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCA AGGTCAGCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTC CAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG AGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCCATG CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTACCGTGGA CAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATG CATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT CTCCGGGCAAATAG	
	LC	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTCACCCTTGG AGAGTCGGCCTCCATCTCCTGTAGGAGCAGTCAGAGCCTCCTGTAT AGTAGTGGATACATCGATTTGGATTGGTACCTGCAGAAGCCAGGGC AGTCTCCACAGCTCCTGATCTATTTGGGTTCTAATCGGGCCTCCGGG GTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACAC TGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTG CATGCAAACACTATACAAACTCCGCTCACTTTCGGCGGAGGGACCAAG GTGGAGATCAAACGAACGGTGGCTGCACCATCTGTCTTCATCTTCC CGCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTG CCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAG GTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAG AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGA CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCG AAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAA CAGGGGAGAGTGTTAG	874
219051	HC	CAGGTGCAACTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGG GCCTCAGTGAAGGTCTCTTGCAAGGCTTCTGGATACACCTTCACCG GCTACTATCTACACTGGGTGCGACAGGCCCTGGACAAGGGCTTGA GTGGATGGGATGGATCAACCCTAATATTGGTGTACAGACTGTGCA CAGAAGTTTCAGGACAGGGTCACCATGACCAGGGACACGTCCATCA GTACAGCCTACATGGAGCTGAGCAGGCTGATATCTGACGACACGGC CGTGTATTACTGTACGGTACGTGGATATAATGATGATTACGACTTTG	875

LIBC. 編號	鏈	序列	SEQ ID
		ACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCAGCAC CAAGGGGCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACC TCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCC CCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCCCTGACCAGCGG CGTGACACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCC TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGAC CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGA CAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCATCATGCCCA GCACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCCAA AACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTG CGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAA CTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCC GCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTC ACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGC AAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCT CCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGC CCCCATCCCAGGAGGAGATGACCAAGAACCAGGTACGCCTGACCT GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGA GAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGT GCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTAACCGTG GACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGA TGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCT GTCTCTGGGCAAATAG	
	LC	GATGTTGTGATGACCCAGACTCCACTCTCTCTGTCCGTCACCCCTGG ACAGCCGGCCTCCATCTCCTGCAAGTCTCGTCAGAGCCTCCTGCAT AGAGATGGAAAGACCTATTTGTATTGGTACCTGCAGAAGCCAGGCC AGCCTCCACAACCTCCTGATCTATGAAGTTTCCAACCGGTTCTCTGGA GTGCCAAATAGATTCAGTGGCAGCGGGTCAGGGACAGATTTACAC TGAAAATCAGCCGGGTGGAGGCTGAAGATGTTGGGGTTTATTACTG CATGCAAAGTATACAGCTTCCGCTCATTTTCGGCGGAGGGACCAGG GTTGACATCAAACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCC GCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGC CTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGG TGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGA	876

LIBC. 編號	鏈	序列	SEQ ID
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218989	HC	CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAACCCACAC AGACCCCTCACGCTGACCTGCACCTTCACTGGGTTTTCACTCAGCACT AGTGGAATGGGTGTGGGCTGGATCCGTCAGCCCCCAGGAAAGGCC CTGGAGTGGCTTGCACTCATTTATTGGAATGGTGGTAAGCTCTACA GCCCATCTCTGAAGAACAGGGCTCACCATCACCAAGGACACCTCCAA AAACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACA GCCACATATTACTGTGCACACAGTGGATACTATGATAATAGTGGCT ATTACTGGGACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCAC CGTCTCCCCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGC CCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCT GGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAActCA GGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGT CCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAG CAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCC AGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTC GAGTGCCCAACCGTGCCCAAGCACCTGTGGCAGGACCGTCAGTCT TCCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGAC CCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCC GAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG CCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTG TGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAA GGAGTACAAGTGCAAGGTCAGCAACAAAGGCCTCCCAGCCCCCAT CGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCA GGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATC GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAActACAAG ACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAG CAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAG AAGAGCCTCTCCCTGTCTCCGGGCAAATAG	877

LIBC. 編號	鏈	序列	SEQ ID
	LC	GAAATTGTGTTGACGCAGTCTCCAGTCACCCTGTCTTTGTCGCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTCTTATCAGC GACTACTTAGTCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCAGCAGGCCCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAATATG ATACCTCCCTCAATTTTCGGCGGAGGGACCAAGGTGGAGATCAAACG AACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGC AGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTC TATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTC CAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAG GACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCA GACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAG GGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTT AG	878
218967	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGAGTGGTGAAGCCTTCG GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAG TTACTTCTGGACCTGGATCCGGCAGCCCCCAGGGAAGGGACTGGAA TGGATTGGCTATATCTATTACAGTGGGAGCACCAACTACAACCCCT CCCTCAAGAGTCGAGTCACGTTTTTCAGTAGACACGTCCAAGAACCA GTTCTCCCTGAAGTTGAATTCTGTGACCGCTGCGGACACGGCCGTG TATTACTGTGCGAGAGTGGAACAATTATGGCCTTTGATGCTTTTGA TATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCTCCACC AAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCT CCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCC CGAACCGGTGACGGTGTCTGTGGAAGTCAAGCGCTCTGACCAGCGGC GTGCACACCTTCCCAGCTGTCTACAGTCCTCAGGACTCTACTCCCT CAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACC TACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGAC AAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCAACCGTGCCAG CACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCAAACCC AAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGG TGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTA CGTGGACGGCGTGAGGTGCATAATGCCAAGACAAAGCCACGGGA	879

LIBC. 編號	鏈	序列	SEQ ID
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	LC	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTGGCAGC AGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCTAGGC TCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTGCAGTGTATTTCTGTCAGCAGTATG ATACCTCACCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	880
218981	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCAC AGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGT GGTGGTTACTTCTGGAGCTGGATCCGTCAGCACCCAGGGAAGGGCC TGGAGTGGATTGGGTACACCCATTACATTGGGAGCACCTACTACAA CCCGTCCCTCAAGAGTCGAGTTGCCTTTTCAGTAGACACGTCTAAG AACCAGTTCTCCCTGAAGTTGAGCTCTGTGACTGCCGCGGACACGG CCGTGTATTACTGTGCGAGAGTGGATACAGCTATGGTGGATGCTTT TGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCTCC	881

LIBC. 編號	鏈	序列	SEQ ID
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	LC	GAAATTATGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAATATTGACAGC AGCTACTTAGCCTGGTACCAGCAGACACCTGGCCAGGCTCCCAGGC TCCTCATCTATGATACATCCAGCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTTCAGTGTATTACTGTCAGCAGTATG GTGGCTCACCTATCACCTTCGGCCAAGGGACACGACTGGACATTAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAA	882

LIBC. 編號	鏈	序列	SEQ ID
		GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	
218995	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG GACACCCTGTCCCTCACCTGCGCTGTCTCTGGTTACTCCATCAGTAG TCGTAACCTGGTGGGGCTGGATCCGGCAGCCCCCAGGGAAGGGACT GGAGTGGATCGGGTACATCCATTATATTGGGAACACCTACTACAAC CCGTCCCTCAAGAGTCGAGTCACCATGTCAGTAGACACGTCCAAGA ACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCCGTGGACACGGC CGTGTATTACTGTGCGAGAGAGACTGGTAGCGATGGTGATGATACT TTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCT CCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAG CACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTAC TTCCCCGAACCGGTGACGGTGTCGTGGAACCTCAGGCGCTCTGACCA GCGGCGTGCACACCTTCCAGCTGTCCTACAGTCCTCAGGACTCTA CTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACC CAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAG GTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCACCGT GCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCA AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGT GCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCA ACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGC CACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCT CACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTG CAAGGTCAGCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCAT CTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGAC CTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGG GAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACACCTCCC ATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGT GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC TGTCTCCGGGCAAATAG	883
	LC	GAAATTGTGTTGACGCAGTCTCCAGTCACCCTGTCTTTGTCTCCAGG	884

LIBC. 編號	鏈	序列	SEQ ID
		GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTATTGGCAGC AGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCGGCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTGCCTGTATTACTGTCAGCAGTGTT ATAGCTCACCGATCACCTTCGGCCACGGGACACGACTGGACATTAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	
218996	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCAC AGACCCTGTCCCTCACCTGCACTGTCTCTGGTGTCTCTGTCTCTGGT GGCTCCATCAACAGTGGTAATTACTACTGGAGCTGGATCCGCCAGC ACCCAGGAAAGGGCCTGGAGTGGATTGGGTACATCCATTACAGTGG GAACACCTACTACAACCCGTCCCTCAAGAGTCGAGTTACCATATCA GTAGACACGTCTAAGAACCAGTTCTCCCTGAAGCTGGACTCTGTGA CTGCCGCGGACACGGCCGTGTATTACTGTGCGGTGGCTACGGAATA CTACTACTACGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACC GTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCC CTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTG GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCTCAG GCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTC CTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGC AACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCA GCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCG AGTGCCACCGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTT CCTCTTCCCCCAAACCCAAAGGACACCCTCATGATCTCCCGGACC CCTGAGGTACAGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCG AGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGC CAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGT	885

LIBC. 編號	鏈	序列	SEQ ID
		GGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCAGCAACAAAGGCCTCCCAGCCCCCATC GAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAG GTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCG CCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAATACTACAAGA CCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTC TCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGA AGAGCCTCTCCCTGTCTCCGGGCAAATAG	
	LC	CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGAC AGAAGGTCACCATCTCCTGTCTTGGAAGCAGCTCCAACATTGGGAA TAATTATGTATCCTGGTACCAGCAGTTCCCAGGAACAGCCCCAAA CTCCTCATTTATGACAATAATAAGCGACCCTCAGGGATTCTGACC GATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCATCAC CGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGG GATCGCAGCCTGAGTGCTGTGATATTGCGCGGAGGGACCAAGCTGA CCGTCTAGGTGAGCCCAAGGCTGCACCCTCGGTCACTCTGTTCCCG CCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTC TCATCAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGC AGATAGCAGCCCCGTCAAGGCGGGAGTGGAACCACCACACCCTC CAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCT GACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGT CACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGA ATGTTCATAG	886
218998	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACAGGTGAAGCCTTCA CAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAG TGGTGGTTACTTCTGGGGCTGGATCCGCCAGCACCCAGGGAAGGGC CTGGAATGGATTGGGTACATCCATTATATTGGGAGCCCCTACTACA ATCCGTCTCTCAAGAGTCGAACTACCATATCAGTAGACACGTCTAA GAACCAGTTCTCCCTGAAGCTAAGCTCTGTGATTGCCGCGGACACG GCCGTATATTACTGTGCGAGAGATTGTAGTAGTGTCAACTGCCAAG ATGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTC AGCCTCCACCAAGGGCCCCATCGGTCTTCCCCCTGGCGCCCTGCTCC	887

LIBC. 編號	鏈	序列	SEQ ID
		AGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAG GACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCTC TGACCAGCGGCGTGACACACCTTCCCAGCTGTCCTACAGTCCTCAGG ACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTC GGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAAC ACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCC CACCGTGCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCCTCTTC CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGG TCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCA GTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACA AAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGC GTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACA AGTGCAAGGTCAGCAACAAAGGCCTCCCAGCCCCCATCGAGAAAA CCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACA CCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTTCAGCCT GACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCT CCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCAC CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCC GTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCT CCCTGTCTCCGGGCAAATAG	
	LC	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCTCCCTCTCCTGCTGGTCCAGTCAGAGTATTGACAGC ACCTACTTAGCCTGGTACCACCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCACCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCAGCATCAGC AGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAATATA GTAGCTCACCTATCACCTTCGGCCAAGGGACACGACTGGAGATTAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC	888

LIBC. 編號	鏈	序列	SEQ ID
		AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	
219083	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCAC AGACCCTGTCCCTCACCTGTACCGTCTCTGGTGGCTCCATCAGAAGT GATGGTTACTTCTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCC TGGAGTGGCTTGGGTTTCATCTATTACAGTGGGACCACCTACTACAA CCCGTCCCTCAAGAGTCGAGTTACTATATCAGTAGACACGTCTAAG AACCAGTTCTCCCTGAAGCTGACCTCTGTGACTGTGCGGACACGG CCGTGTATTATTGTGCGAGAGTTTGTGGTGGTGAAGTGTACGATGCT TTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCT CCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAG CACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTAC TTCCCCGAACCGGTGACGGTGTGCTGGAAGTCAAGGCGCTCTGACCA GCGGCGTGCACACCTTCCCAGCTGTCTACAGTCCTCAGGACTCTA CTCCCTCAGCAGCGTGGTGACCGTGGCCCTCCAGCAACTTCGGCACC CAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAG GTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCACCGT GCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCA AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGT GCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCA ACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGC CACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCT CACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTG CAAGGTCAGCAACAAAGGCCTCCCAGCCCCATCGAGAAAACCAT CTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGAC CTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGG GAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCC ATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGT GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC TGTCTCCGGGCAAATAG	889
	LC	GACATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAGGAGCCACCCTCTCCTGCAGGGCCAGTCAAAATATTAGCAAC	890

LIBC. 編號	鏈	序列	SEQ ID
		ACCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTGCAGTGTATGACTGTCAGCAGTATT TTAGCTCACCGATCACTTTCGGCGGAGGGACCAGGGTGGAGATCAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	
219092	HC	CAGGTGCAGGTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG GACACCCTGTCCCTCACCTGCGCTGTCTCTGGTTACTCCATCAGCAA TAGTATCTGGTGGGGCTGGATCCGGCAGCCCCAGGGAAGGGACTG GAGTGGATTGGGTACATCCATTATAGTGGGAACACCTACTATAATC CGTCCCTCAAGAGTCGAGTCACCATGTCAGTAGACACGTCCAAGAA CCAGTTCTCCCTGAAGCTGAACTCTGTGACCGCCGTGGACACGGCC GTGTATTACTGTGCGAGAAATTTCCGGTGACGTTGATGCTTTTGATAT CTGGGGCCAAGGGACAATGGTCAACGCTCTCTTCAGCCTCCACCAAG GGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCG AGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGA ACCGGTGACGGTGTCGTGGAAGTCAAGGCGCTCTGACCAGCGGCGTG CACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAG CAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTAC ACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAG ACAGTTGAGCGCAAATGTTGTGTGCGAGTGCCACCGTGCCAGCAC CACCTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCAAACCCAA GGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTG GTGGACGTGAGCCACGAAGACCCGAGGTCCAGTTCAACTGGTACG TGGACGGCGTGAGGTGCATAATGCCAAGACAAAGCCACGGGAGG AGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGT GCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCAG	891

LIBC. 編號	鏈	序列	SEQ ID
		CAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACC AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCC GGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCA AAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATG GGCAGCCGGAGAACAACACTACAAGACCACACCTCCCATGCTGGACTC CGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGC AGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGG CTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGG CAAATAG	
	LC	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTATTAGCAGC AGCTATTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCAACATCAGC AGACTGGAGCCTGAAGATTTTGTGTGTATTACTGTCAGCAGTATTA TCTCTACCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA CGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA GCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAACT TCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT CCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAA GGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGC AGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCA GGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTG TTAG	892
219023	HC	CAAGTGCAGCTGCAACAGTCAGGTCCAGGACTGGTGAAGCCCTCGC AGACCCTCTCACTCACCTGTGCCATCTCCGGTGACAGTGTCTTTAGC AACAGTGCTGCTTGGAACCTGGATCAGGCAGTCCCCCTCGAGAGGCC TTGAGTGGCTGGGAAGGACATATTGTAGGTCCAAGTGTTATAGTGA TTATGCATTATCTGTGAAAAGTCGAGCAACCATCAACCCAGACACA TCCGAGAACCAGTTCTCCCTGCAGCTGAACTCTGTGACTCCCGAGG ACACGGCTGTGTATTACTGTGCAAGAGCAGTGGCTGACCACTACTC CTACGCTTTGGACGTCTGGGGCCAAGGGACCACGGTCAATGTCTCC TCAGCCAGCACCAAGGGGCCATCCGTCTTCCCCCTGGCGCCCTGCT CCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAA	893

LIBC. 編號	鏈	序列	SEQ ID
		GGACTACTTCCCCGAACCGGTGACGGTGTCGTGGA ACTCAGGCGCC CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAG GACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTT GGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAA CACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGC CCATCATGCCCAGCACCTGAGTTCTCTGGGGGGACCATCAGTCTTCC TGTTCCCCC AAAACCCAAGGACACTCTCATGATCTCCCGGACCCC TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGA GGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCC AAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGG AGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGA GAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGT GTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTC AGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCG TGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA ACTACAAGACCA CGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGG CTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCAT GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAG CCTCTCCCTGTCTCTGGGCAAATAG	
	LC	GACATCCAGATGAACCAGTCTCCATCCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGACCATTAGAACT TATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGGTCC TGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCTTCAAGGTTC AGTGGCACTGGATCTGGGACAGATTTCACTCTCACCATCACCAGTC TGCAACCTGAAGATTTTGCAACTTACTCCTGTCAACAGAGTTACAG TTCACCGATCACTTTCGGCGGGGGGACCAAGGTCGAGATCAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGA ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA	894

LIBC. 編號	鏈	序列	SEQ ID
		G	
219023.0 01	HC	CAAGTGCAGCTGCAACAGTCAGGTCCAGGACTGGTGAAGCCCTCGC AGACCCCTCTCACTCACCTGTGCCATCTCCGGTGACAGTGTCTTTAGC AACAGTGCTGCTTGGAAGTGGATCAGGCAGTCCCCCTCGAGAGGCC TTGAGTGGCTGGGAAGGACATATTACAGGTCCAAGTGGTATAGTGA TTATGCATTATCTGTGAAAAGTCGAGCAACCATCAACCCAGACACA TCCGAGAACCAGTTCTCCCTGCAGCTGAACTCTGTGACTCCCGAGG ACACGGCTGTGTATTACTGTGCAAGAGCAGTGGCTGACCACTACTC CTACGCTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCC TCAGCCAGCACCAAGGGGCCATCCGTCTTCCCCCTGGCGCCCTGCT CCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAA GGACTACTTCCCCGAACCGGTGACGGTGTCTGTGAACTCAGGCGCC CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAG GACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTT GGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAA CACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGC CCATCATGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCC TGTTCCCCC AAAACCCAAGGACACTCTCATGATCTCCCGGACCCC TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCGA GGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCC AAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTG GTCAGCGTCCTACCGTCCTGCACCAGGACTGGCTGAACGGCAAGG AGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGA GAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGT GTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTC AGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCG TGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA ACTACAAGACCA CGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGG CTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCAT GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAG CCTCTCCCTGTCTCTGGGCAAATAG	895
	LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGACCATTAGAACT TATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCCTAAGGTCC	896

LIBC. 編號	鏈	序列	SEQ ID
		TGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCTTCAAGGTTC AGTGGCACTGGATCTGGGACAGATTTCACTCTCACCATCACCAGTC TGCAACCTGAAGATTTTGCAACTTACTCCTGTCAACAGAGTTACAG TTCACCGATCACTTTCGGCGGGGGGACCAAGGTCGAGATCAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA G	
219095	HC	GAGGTGCAGCTGTTGGAGTCTGGGGGAAACTTGGTACAGCCTGGGG GGTCCCTGAGACTCTCCTGTGTAGTCTCTGGATTCACCTTTAACAAC TATGCCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGT GGGTCTCAGTTATTAGTGATAGTGGTGGTAGCTCAAACCTACGCAGA CTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAAA ACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCC GTATATTACTGTGCGAAAGATCGGAGTATAGCCGGCTACTACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTC CACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGC ACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACT TCCCCGAACCGGTGACGGTGTCGTGGAAGTCAAGGCGCTCTGACCAG CGGCGTGACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACT CCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCA GACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGT GGACAAGACAGTTGAGCGCAAATGTTGTGTGAGTGCCACCGTGC CCAGCACCACTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCAA AACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTG CGTGGTGGTGGACGTGAGCCACGAAGACCCGAGGTCCAGTTCAAC TGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCA CGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCA CCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCA AGGTCAGCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTC	897

LIBC. 編號	鏈	序列	SEQ ID
		CAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG AGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCCATG CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGA CAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATG CATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT CTCCGGGCAAATAG	
	LC	GACATCCAGATGACCCAGTCTCCGTCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGC GATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAACCTCC TGATCTATGCTGCATCCAGTTTGCACAGTGGGGTCCCATCAAGGTTCT AGTGGCAGTGGATCTGGGACAGATTTCCTCTCACCATCAGCAGTC TCCTACCTGAGGATTTTGCAACTTACTACTGTCAACAGAGTTACAAT ACCCCGCTCACTTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACCTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA G	898
219102	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAG TTACTACTGGAGCTGGATCCGGCTGCCCCCAGGGAAGGGACTGGAG TGGATTGGGTATATCTATTATGGTGGGAGCACCAACTACAACCCT CCCTCAAGAGTCGGGTCTCCATGTCAGTAGACACGTCCAAGAACCA GTTCTCCCTGAAGCTGAGCTATGTGACCGCCGCGGACACGGCCGTG TATTACTGTGCGAGATCGTATAGCAGCGCCTGGTACGGCTCTGCAT ACTGGGGCCAGGGAACCCTGGTCATCGTCTCCTCGGCCAGCACCAA GGGGCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC GAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG AACCGGTGACGGTGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGT	899

LIBC. 編號	鏈	序列	SEQ ID
		GCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTACTCCCTCA GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTA CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAA GAGAGTTGAGTCCAAATATGGTCCCCCATGCCCATCATGCCCAGCA CCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCC AAAACC CAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTG GTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG AGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGT CCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGT CTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAA GCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCAT CCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA TGGGCAGCCGGAGAACA ACTACAAGACCACGCCTCCCGTGCTGGA CTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTAACCGTGGACAAG AGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATG AGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCT GGGCAAATAG	
	LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTTTAGG AGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGACATTAGCAAC TATTTAATTTGGTATCAGCTGAAACCAGGGAAAGCCCCTAAGGTCC TGATCTACGATGCATCCAATTTGGAAACAGGGGTCCCATCAAGGTT CAGTGGAATGGATCTGGGACAGATTTTACTTTTACCATCAGCAGC CiGCAGCCTGAAGATATTGCAACATATTACTGTCAACAGTATGATCA TCTCCCGATCACCTTCGGCCAAGGGACACGACTGGACATTAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGA ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA G	900

LIBC. 編號	鏈	序列	SEQ ID
219102.0 01	HC	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAG TTACTACTGGAGCTGGATCCGGCTGCCCCAGGGAAGGGACTGGAG TGGATTGGGTATATCTATTATGGTGGGAGACCAACTACAACCCCT CCCTCAAGAGTCGGGTCTCCATGTCAGTAGACACGTCCAAGAACCA GTTCTCCCTGAAGCTGAGCTATGTGACCGCCGCGGACACGGCCGTG TATTACTGTGCGAGATCGTATAGCAGCGCCTGGTACGGCTCTGCAT ACTGGGGCCAGGGAACCCTGGTCATCGTCTCCTCGGCCAGCACCAA GGGGCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC GAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG AACCGGTGACGGTGTCTGTGGAATCAGGCGCCCTGACCAGCGGCGT GCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTACTCCCTCA GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTA CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAA GAGAGTTGAGTCCAAATATGGTCCCCCATGCCCATCATGCCCAGCA CCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCC AAAACC CAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTG GTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGT ACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG AGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGT CCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGT CTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAA GCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCAT CCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA TGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGA CTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTAACCGTGGACAAG AGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATG AGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCT GGGCAAATAG	901
	LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTTTAGG AGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGACATTAGCAAC TATTTAATTTGGTATCAGCTGAAACCAGGGAAAGCCCCTAAGGTCC TGATCTACGATGCATCCAATTTGGAAACAGGGGTCCCATCAAGGTT	902

LIBC. 編號	鏈	序列	SEQ ID
		CAGTGGAAGCGGATCTGGGACAGATTTTACTTTCACCATCAGCAGC CiGCAGCCTGAAGATATTGCAACATATTACTGTCAACAGTATGATCA TCTCCCGATCACCTTCGGCCAAGGGACACGACTGGACATTAAACGA ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAAGTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTA G	
218973	HC	CAGGTGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAG CTATGGCATACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATGGTATGATGGAAGTAAAAAATACTATGCAG ACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAG CACGCTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGACACGGCT GTGTATTACTGTGCGAGAGATCCCTCCCATTACTATGGTTCGGGGA GTTATAACTACTTCTACGGTATGGACGTCTGGGGCCAAGGGACCAC GGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCC TGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGG CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGG AACTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCC CTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCAC AAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGT TGTGTCGAGTGCCACCGTGCCAGCACCACTGTGGCAGGACCGT CAGTCTTCCTCTTCCCCCAAACCCAAGGACACCCTCATGATCTCC CGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAA GACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC ATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGT TCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAA CGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGGCCTCCCAGC CCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGA	903

LIBC. 編號	鏈	序列	SEQ ID
		ACCACAGGTGTACACCCTGCCCCATCCCCGGGAGGAGATGACCAAG AACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCG ACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACT ACAAGACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTC TACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAAC GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC GCAGAAGAGCCTCTCCCTGTCTCCGGGCAAATAG	
	LC	CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGAC AGAAGGTCACCATCTCCTGCTCTGGAAGCAGCTCCAACATTGGGAA TACTTATGTATCCTGGTACCAGCAACTCCCAGGAACAGCCCCAAA CTCCTCATTTATGACAATAATGAGCGACCCTCAGGGATTCTGACC GATTCTCTGGCTCCAAGTCTGACACGTCAGCCACCCTGGGCATCAC CGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACCTGG GATAACAGCCTGACTGCTGTGGTATTTCGGCGGAGGGACCAAGCTGA CCGTCTTAGGTCAGCCCAAGGCTGCACCCTCGGTCACTCTGTTCCCG CCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTC TCATCAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGC AGATAGCAGCCCCGTCAAGGCGGGAGTGGAACCACCACACCCTC CAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCT GACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGT CACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGA ATGTTCATAG	904
219044	HC	GAGGTGCAGTTGGTGGAGTCTGGAGGAGGCTTGATCCAGCCTGGGG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGGTTACCGTCAGTGAC AACTACATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAG TGGGTCTCAGTTATTTATAGCGGTGGTAACACATACTACGGAGACT CCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCCAAGAACAC GCTCTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTG TATTTCTGTACTGGCCCCCTTCTTTGACTACTGGGGCCCGGGAACCCT GGTCACCGTCTCCTCAGCCAGCACCAAGGGGCCATCCGTCTTCCCC CTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGG GCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTG GAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTC CTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGC	905

LIBC. 編號	鏈	序列	SEQ ID
		CCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCA CAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATA TGGTCCCCCATGCCCATCATGCCCAGCACCTGAGTTCCTGGGGGA CCATCAGTCTTCCTGTTCCCCCAAAACCCAAGGACACTCTCATGAT CTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAG GAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAG GTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGC ACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGC TGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCC CGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCG AGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACC AAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCA GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA ACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC CTCTACAGCAGGCTAACCCTGGACAAGAGCAGGTGGCAGGAGGGG AATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA CACACAGAAGAGCCTCTCCCTGTCTCTGGGCAAATAG	
	LC	GAAATTGTGTTGACGCAGTTTCCAGGCACCCTGTCTTTGTCTCCGGG GGAAGGAGGCACCCTCTCCTGCAGGGCCAGTCAGACTGTTTGGAGC AACTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGC TCCTCATCTATGGTGCATCCAGGAGGGTCATTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCAATCTCACCATCAGC AGCCTGGAGCCTGGAGATTTTGCAGTGTATTACTGTCAGCAGTATG GTAGTTCATCGATTACCTTCGGCCAAGGGACACGACTGGAGATTAA ACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG AGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT GTTAG	906
218997	HC	CAGGTGCAGGTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCA CAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAG	907

LIBC. 編號	鏈	序列	SEQ ID
		TGGTGGTTACTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGC CTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTACTACA ACCCGTCCCTCATGGGTCGAGTTACCATATCAGTAGACACGTCTAA GAACCAGTTTTCCCTGAGGCTGAGCTCTGTGACTGCCGCGGACACG GCCGTGTATTATTGTGCGAGAAGGGGGCCAGTGGCTGGTGGATTTG ACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCAC CAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACC TCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCC CCGAACCGGTGACGGTGTCTGTGGAAGTCAAGGCGCTCTGACCAGCGG CGTGACACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCC TCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGAC CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGA CAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCAACCGTGCCCA GCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCAAAC CCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGT GGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTG GTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACG GGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAG GTCAGCAACAAAGGCCTCCCAGCCCCATCGAGAAAACCATCTCCA AAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCC CATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCT GGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGC AATGGGCAGCCGGAGAACAATAAGACCACACCTCCCATGCTG GACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACA AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT CCGGGCAAATAG	
	LC	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAATGTTTACAAC AACTACTTAGCCTGGTACCAGCAGAAACCTCGCCAGGCTCCCAGGC TCCTCATCTATGGTACATCCAGTAGGGCCACTGGCATCCCAGACAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC AGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAACAGTATG	908

LIBC. 編號	鏈	序列	SEQ ID
		GTAGCTCACTTCTGTGCAGTTTTGGCCAGGGGACCAAGCTGGAGAT CAAACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTG ATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAA TAACTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAAC GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACACAGAGCAGGAC AGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGC AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACC CATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGA GAGTGTTAG	

【0261】 可以藉由突變將變化引入本文揭露的核酸分子中，從而導致其編碼的多肽（例如，LTβR結合蛋白）的胺基酸序列發生變化。可使用本領域中已知的任何技術來引入突變。在一個實施方式中，使用例如定點誘變方案來改變一或多個特定胺基酸殘基。在另一個實施方式中，使用例如隨機誘變方案使一或多個隨機選擇的殘基改變。無論是如何製備的，可以表現並篩選出突變多肽的所需特性。

【0262】 可以將突變引入本文揭露的核酸分子中，而不顯著改變其編碼的多肽的生物活性。例如，可進行核苷酸取代，從而在非必需胺基酸殘基處進行胺基酸取代。在一個實施方式中，本揭露之促效劑LTβR結合蛋白之一的本文提供的核苷酸序列發生突變，使得其編碼的胺基酸序列包含如本文所示的本揭露之LTβR結合蛋白的輕鏈和/或重鏈的胺基酸殘基的一或多個缺失或取代。在另一個實施方式中，該誘變插入與本文所示的本揭露之促效劑LTβR結合蛋白的輕鏈和/或重鏈的一或多個胺基酸殘基相鄰的胺基酸。可替代地，可以將一或多個突變引入本文揭露的核酸分子中，其選擇性地改變其編碼的促效劑LTβR結合蛋白的生物活性。

【0263】 編碼本揭露之抗體的相應胺基酸序列的本揭露之促效劑LTβR結

合蛋白的核苷酸序列可以例如藉由隨機誘變或定點誘變來改變，以產生與未突變的多核苷酸相比包含一或多個特定核苷酸取代、缺失或插入的改變的多核苷酸。用於進行這樣的改變的技術的實例描述於以下中：Walder等人, *Gene*[基因] 42:133 (1986)；Bauer等人 *Gene*[基因] 37:73 (1985)；Smith等人, 1981, *Genetic Engineering: Principles and Methods*[基因工程：原理與方法], Plenum Press；以及美國專利案號4,518,584和4,737,462。例如，該等和其他方法可用於製備具有期望的特性（例如，與未衍生的抗體相比，對所期望靶標的親和力、親合力或特異性增加，體內或體外活性或穩定性增加，或體內副作用減少）的LT β R結合蛋白的衍生物。

【0264】在另一個實施方式中，本揭露提供了包含編碼本文揭露的促效劑LT β R結合蛋白的多核苷酸的載體。載體係用於將另一個核酸引入細胞的核酸分子。載體之實例包括但不限於質體、病毒載體、非附加型哺乳動物載體和表現載體，例如重組表現載體。

【0265】包含本揭露之多核苷酸的載體可以使用以下中描述的標準重組DNA技術來製備：例如，Sambrook等人, *Molecular Cloning: A Laboratory Manual*[分子選殖：實驗室手冊]. 第3版, 冷泉港出版社, 紐約冷泉港 (2001)；以及Ausubel等人, *Current Protocols in Molecular Biology*[分子生物學的當前方案], Greene Publishing Associates和John Wiley & Sons, NY (1994)，特此藉由引用將其全部併入。呈圓形或線性的表現載體的構建體可經製備以含有在原核或真核宿主細胞中發揮功能的複製系統。複製系統可來源於例如CoIE1、2 μ 質體、 λ 、SV40、牛乳頭瘤病毒等。

【0266】在一個實施方式中，該表現載體係圓形質體（參見例如，Muthumani等人, 「Optimized and Enhanced DNA Plasmid Vector Based In vivo Construction of a Neutralizing anti-HIV-1 Envelope Glycoprotein Fab[中和抗HIV-1

包膜糖蛋白Fab的基於優化和增強DNA質體載體的體內構建],」 *Hum. Vaccin. Immunother*[人類疫苗和免疫療法]. 9: 2253-2262 (2013), 特此藉由引用將其全部併入)。質體可以藉由整合到細胞基因組中來轉化靶細胞或存在於染色體外(例如, 具有複製起點的自主複製質體)。示例性質體載體包括但不限於pCEP4、pREP4、pVAX、pcDNA3.0、provax或能夠表現由重組核酸序列構建體編碼的重鏈多肽和/或輕鏈多肽的任何其他表現載體。

【0267】 在另一個實施方式中, 該表現載體係線性表現盒(「LEC」)。LEC能夠經由電穿孔有效地遞送到受試者, 以表現由重組核酸序列構建體編碼的重鏈多肽和/或輕鏈多肽。LEC可為任何沒有磷酸骨架的線性DNA。在一個實施方式中, 該LEC不含有任何抗生素抗性基因和/或磷酸骨架。在另一個實施方式中, 該LEC不含有與所需基因表現無關的其他核酸序列。

【0268】 LEC可以衍生自任何能夠線性化的質體。質體可能能夠表現由重組核酸序列構建體編碼的重鏈多肽和/或輕鏈多肽。示例性質體包括但不限於pNP (Puerto Rico/34)、pM2 (New Caledonia/99)、WLV009、pVAX、pcDNA3.0或provax, 或任何其他能夠表現由重組核酸序列構建體編碼的重鏈多肽和/或輕鏈多肽的表現載體。

【0269】 在另一個實施方式中, 該表現載體係病毒載體。能夠表現全長抗體或其結合部分的合適病毒載體包括, 例如, 腺相關病毒(AAV)載體(參見例如, Lewis等人, 「Generation of Neutralizing Activity against Human Immunodeficiency Virus Type I in Serum by Antibody Gene Transfer[藉由抗體基因轉移在血清中產生對人類免疫缺乏病毒I型的中和活性],」 *J. Virol.*[病毒學雜誌] 76:8769-775 (2002); Fang等人, 「An Antibody Delivery System for Regulated Expression of Therapeutic Levels of Monoclonal Antibodies In vivo[一種用於調節治療水平單株抗體體內表現的抗體遞送系統],」 *Mol. Ther.*[分子療法]15(6): 1153-9

(2007)；Buning等人，「Recent Developments in Adeno-associated Virus Vector Technology[腺相關病毒載體技術的最新發展],」 *J. Gene Med.*[基因醫學雜誌] 10:717-733 (2008))、慢病毒載體（參見例如，Joseph等人，「Inhibition of In vivo HIV Infection in Humanized Mice by Gene Therapy of Human Hematopoietic Stem Cells with a Lentiviral Vector Encoding a Broadly Neutralizing anti-HIV Antibody[藉由用編碼廣泛中和抗HIV抗體的慢病毒載體對人類造血幹細胞進行基因治療來抑制人源化小鼠體內HIV感染],」 *J. Virol.*[病毒學雜誌], 84: 6645-53 (2010)；以及Luo等人，「Engineering Human Hematopoietic Stem/Progenitor Cells to Produce a Broadly Neutralizing anti-HIV Antibody after In vivo Maturation to Human B Lymphocytes[工程化人類造血幹細胞/先驅細胞以在體內成熟為人B淋巴細胞後產生廣泛中和的抗HIV抗體],」 *Blood*[血液] 113: 1422-1431 (2009))、反轉錄病毒載體、複製缺陷型腺病毒載體和無腸腺病毒載體（參見例如，美國專利案號5,872,005）。用於生成和分離適合用作載體的腺相關病毒（AAV）的方法係本領域已知的（參見例如，Grieger和Samulski，「Adeno-associated Virus as a Gene Therapy Vector: Vector Development, Production and Clinical Applications[腺相關病毒作為基因治療載體：載體開發，生產和臨床應用],」 *Adv.Biochem. EnginBiotechnol.*[生物化學工程/生物技術的進展]99: 119-145 (2005)；Buning等人，「Recent Developments in Adeno-associated Virus Vector Technology[腺相關病毒載體技術的最新發展],」 *J. Gene Med.*[基因醫學雜誌] 10:717-733 (2008))。

【0270】編碼如本文所描述的促效劑LTβR結合蛋白的表現載體構建體可包括編碼重鏈多肽、重鏈可變區或其片段的多核苷酸。重鏈多肽可以包括可變重鏈（VH）區和/或至少一個恒定重鏈（CH）區。至少一個恒定重鏈區可以包括恒定重鏈區1（CH1）、恒定重鏈區2（CH2）、和恒定重鏈區3（CH3）和/或鉸鏈區。在一些實施方式中，該重鏈多肽可以包括VH區和CH1區。在其他實施方式

中，該重鏈多肽可以包括VH區、CH1區、鉸鏈區、CH2區和CH3區。表現構建體還可以包括編碼輕鏈多肽、輕鏈可變區或其片段的多核苷酸序列。輕鏈多肽可以包括可變輕鏈（VL）區和/或恒定輕鏈（CL）區。

【0271】 在一些方面，載體包含一或多個調節序列。「調節序列」係影響與其可操作地連接的核酸的表現（例如，表現的水平、時間或位置）的核酸。示例性調節序列包括轉錄和翻譯起始和終止密碼子，其對於載體要引入的宿主類型（例如，細菌、真菌、植物或動物）係特定的，視情況而定，並考慮載體係基於DNA還是基於RNA。基於待用於表現的宿主細胞而選擇合適的調節序列，並且可操作地連接至要表現的核酸序列。調節序列包括在許多類型的宿主細胞中直接組成型表現核苷酸序列的那些（例如，SV40早期基因強化子、Rous肉瘤病毒啟動子和巨細胞病毒啟動子），僅在某些宿主細胞中直接表現核苷酸序列的那些（例如，組織特異性調節序列），以及響應於特定治療或條件而指導核苷酸序列誘導表現的那些（例如，哺乳動物細胞中的金屬硫蛋白啟動子以及原核和真核系統中的tet反應和/或鏈黴素反應啟動子（參見例如，Voss等人, *Trends Biochem. Sci.* [生化科學趨勢] 11:287 (1986), Maniatis 等人, *Science* [科學] 236:1237 (1987)））。熟悉該項技術者將理解，表現載體的設計可以取決於諸如待轉化的宿主細胞的選擇、所期望的蛋白表現水平等因素。可以將本揭露之表現載體引入宿主細胞中，從而產生由如本文所描述的核酸編碼的蛋白或肽。

【0272】 表現構建體可以進一步編碼蛋白酶切割位點。蛋白酶切割位點可以被蛋白酶或肽酶識別。蛋白酶可為內肽酶或內切蛋白酶，例如但不限於弗林蛋白酶、彈性蛋白酶、HtrA、鈣蛋白酶、胰蛋白酶、糜蛋白酶、胰蛋白酶和胃蛋白酶。在其他實施方式中，蛋白酶可為絲胺酸蛋白酶、蘇胺酸蛋白酶、半胱胺酸蛋白酶、天冬胺酸蛋白酶、金屬蛋白酶、麩胺酸蛋白酶或任何切割內部肽鍵的蛋白酶（即，不切割N末端或C末端肽鍵）。蛋白酶切割位點可以包括一或多個促進

或提高切割效率的胺基酸序列。

【0273】 表現構建體可以進一步編碼連接模體列。該連接模體列可以編碼在空間上分離和/或連接表現構建體的一或多個組分（編碼抗體的重鏈和輕鏈組分）的胺基酸序列。

【0274】 在一個實施方式中，第一表現載體構建體編碼包括VH和CH1的重鏈多肽，第二表現載體構建體編碼包括VL和CL的輕鏈多肽。替代排列包括編碼包括VH、CH1、鉸鏈區、CH2和CH3的重鏈多肽的第一載體和編碼包括VL和CL的輕鏈多肽的第二載體。

【0275】 在另一個實施方式中，該表現載體構建體編碼包括VH和CH1的重鏈多肽，以及包括VL和CL的輕鏈多肽，並且連接模體列位於編碼重鏈多肽的核酸序列和編碼輕鏈多肽的核酸序列之間。

【0276】 在替代實施方式中，該表現載體構建體編碼包括VH和CH1的重鏈多肽，以及包括VL和CL的輕鏈多肽，並且編碼蛋白酶切割位點的核酸序列位於編碼重鏈多肽的核酸序列和編碼輕鏈多肽的核酸序列之間。

【0277】 在另一個實施方式中，該表現載體構建體編碼包括VH、CH1、鉸鏈區、CH2和CH3的重鏈多肽，以及包括VL和CL的輕鏈多肽，並且連接模體列位於編碼重鏈多肽的核酸序列和編碼輕鏈多肽的核酸序列之間。

【0278】 在又另一個實施方式中，該表現載體構建體編碼包括VH、CH1、鉸鏈區、CH2和CH3的重鏈多肽，以及包括VL和CL的輕鏈多肽，並且編碼蛋白酶切割位點的異源核酸序列位於編碼重鏈多肽的核酸序列和編碼輕鏈多肽的核酸序列之間。

【0279】 載體可包括一或多種標記基因，其允許選擇轉化或轉染的宿主。標記基因包括殺生物劑抗性（例如針對抗生素、重金屬等的抗性）、營養缺陷型宿主中提供原營養的補充等。適用於本揭露之表現載體的標記基因包括例如新

黴素/G418抗性基因、潮黴素抗性基因 (hygromycin resistance gene)、組胺醇抗性基因、四環素抗性基因和安比西林抗性基因 (ampicillin resistance gene)。

【0280】載體可以包含可操作地連接到編碼促效劑LTβR結合蛋白的核苷酸序列的天然或標準啟動子。啟動子(例如強啟動子、弱啟動子、誘導型啟動子、組織特異性啟動子和發育特異性啟動子)的選擇在技術者之普通技術範圍內。類似地,核苷酸序列與啟動子組合還在技術者之技術範圍內。啟動子可為非病毒啟動子或病毒啟動子,例如巨細胞病毒(CMV)啟動子、SV40啟動子、RSV啟動子和在鼠科幹細胞病毒的長末端重複序列中發現的啟動子。

【0281】在另一個實施方式中,本揭露提供了已將本揭露之重組表現載體引入其中的宿主細胞。宿主細胞係用於表現核酸的細胞,例如,編碼如本文所描述的LTβR結合蛋白的多核苷酸。合適的宿主細胞包括原核細胞和真核細胞,如下文更詳細描述的。宿主細胞不僅指含有感興趣核酸分子的特定細胞,還指這種細胞的後代或潛在後代。因為由於例如突變或環境影響,在後代中可能發生某些修飾,因此這樣的後代實際上可能與親本細胞不同,但仍包含在本文使用的「宿主細胞」範圍內。

【0282】原核生物宿主細胞包括革蘭氏陰性或革蘭氏陽性生物體,例如大腸桿菌或桿菌。在示例性方面,該細胞係真核細胞,包括但不限於酵母細胞、絲狀真菌細胞、原生動物細胞、藻類細胞、昆蟲細胞或哺乳動物細胞。本領域中描述了這樣的宿主細胞。參見例如, Frenzel,等人, *Front Immunol*[免疫學前沿] 4: 217 (2013)。在示例性方面中,該等真核細胞為哺乳動物細胞。在示例性方面中,該等真核細胞為非人類哺乳動物細胞。在一些方面,該等細胞係中國倉鼠卵巢(CHO)細胞及其衍生物(例如, CHO-K1、CHO pro-3、CS9)、小鼠骨髓瘤細胞(例如, NS0、GS-NS0、Sp2/0),工程化為缺乏二氫葉酸還原酶(DHFR)活性的細胞(例如, DUKX-X11、DG44)、人胚胎腎293(HEK293)細胞或其衍

生物（例如，HEK293T、HEK293-EBNA）、綠色非洲猴腎細胞（例如，COS細胞、VERO細胞）、人子宮頸癌細胞（例如HeLa）、人骨肉瘤上皮細胞U2-OS、腺癌人肺泡基底上皮細胞A549、人纖維肉瘤細胞HT1080、小鼠腦腫瘤細胞CAD、胚胎癌細胞P19、小鼠胚胎成纖維細胞NIH 3T3、小鼠成纖維細胞L929、小鼠神經母細胞瘤細胞N2a、人乳癌細胞MCF-7、視網膜母細胞瘤細胞Y79、人視網膜母細胞瘤細胞SO-Rb50、人肝癌細胞Hep G2、小鼠B骨髓瘤細胞J558L或幼倉鼠腎（BHK）細胞（Gaillet等人 2007；Khan, Adv Pharm Bull [高級藥物通報] 3(2): 257-263 (2013)）。在一個特定實施方式中，該宿主細胞係CS9（CHO細胞系）。

【0283】可經由常規轉化或轉染技術將載體DNA引入原核或真核細胞中。為了穩定轉染哺乳動物細胞，已知取決於所使用的表現載體及轉染技術，僅一小部分細胞可將外來DNA整合至其基因組中。為了鑒定和選擇該等整合體，通常將編碼選擇性標誌物（例如針對抗生素抗性）的基因與目的基因一起引入宿主細胞中。另外的選擇性標誌物包括賦予藥物（如G418、潮黴素和胺甲喋呤）抗性的那些。除其他方法以外，可藉由藥物選擇（例如已併入選擇性標記基因的細胞將倖存，而其他細胞則死亡）來鑒別經所引入的核酸穩定轉染的細胞。

【0284】轉化的細胞可以在促進LT β R結合蛋白表現的條件下培養，並且藉由常規蛋白純化程式回收結合蛋白。

LT β R結合蛋白的生產方法

【0285】本文揭露的LT β R結合蛋白可以藉由本領域已知的、合成結合蛋白和/或蛋白的任何方法，特別是藉由化學合成或較佳的是，藉由重組表現技術進行生產。從頭合成多肽的合適方法在以下中描述，例如，Chan等人, Fmoc Solid Phase Peptide Synthesis[Fmoc固相肽合成], Oxford University Press[牛津大學出版社], 英國牛津, 2005；以及Peptide and Protein Drug Analysis[肽和蛋白質藥物分析], Reid, R.編輯, Marcel Dekker, Inc., 2000。

【0286】 重組表現技術涉及構建含有編碼如本文所描述的促效劑LT β R結合蛋白的多核苷酸的表現載體。一旦獲得了編碼促效劑LT β R結合蛋白的多核苷酸，就可以藉由重組DNA技術生產用於生產促效劑LT β R結合蛋白的載體。構建含有促效劑LT β R結合蛋白編碼序列和適當的轉錄和翻譯控制訊號的表現載體。該等方法包括例如體外重組DNA技術、合成技術、以及體內基因重組。

【0287】 藉由常規技術將表現載體轉移到宿主細胞，然後藉由常規技術培養轉染的細胞以產生本揭露之促效劑LT β R結合蛋白。在本揭露之一個實施方式中，可以將編碼抗體的重鏈和輕鏈的載體在宿主細胞中共表現，以表現整個免疫球蛋白分子。

【0288】 多種宿主表現載體系統可用於表現本揭露之促效劑LT β R結合蛋白。這樣的宿主表現系統代表了可以產生感興趣的編碼序列並隨後純化的媒介物，也代表了當用適當的核苷酸編碼序列轉化或轉染時，可以原位表現本揭露之結合蛋白的細胞。細菌細胞(如大腸桿菌)和真核細胞常用於表現重組抗體分子，尤其是用於表現整個重組抗體分子。例如，哺乳動物細胞如中國倉鼠卵巢細胞(CHO)，與載體(如來自人類巨細胞病毒的主要中間早期基因啟動子元件)相結合，係抗體的有效表現系統(Foecking等人, *Gene*[基因] 45:101 (1986); Cockett等人, *Nat. Biotech.*[自然生物技術] 8:2 (1990))。

【0289】 此外，還可以選擇調節插入序列的表現或以所期望方式修飾和加工基因產物的宿主細胞株。蛋白產物之這樣的修飾(例如，糖基化)和加工(例如，切割)對於結合蛋白的功能可能是重要的。不同宿主細胞對於蛋白和基因產物的翻譯後加工和修飾具有特徵和特定機制。可選擇適當細胞系或宿主系統以確保所表現的外源蛋白的正確修飾和加工。為此，可以使用具有用於初級轉錄物的適當加工、基因產物的糖基化和磷酸化的細胞機器的真核宿主細胞。這樣的哺乳動物宿主細胞包括但不限於CHO細胞、COS細胞、293細胞、3T3細胞、NS0細

胞、VERO細胞、BHK細胞或骨髓瘤細胞。

【0290】對於重組蛋白(如本揭露之LTβR結合蛋白)的長期、高產量生產,穩定表現係較佳的。例如,可以對穩定表現LTβR抗體分子的細胞系進行工程化。代替使用含有病毒複製起點的表現載體,宿主細胞可以使用由適當表現控制元件(例如啟動子、強化子、序列、轉錄終止子、聚腺苷酸化位點等)和選擇性標誌物來控制的DNA來轉化。在引入外源DNA後,可以允許工程化的細胞在富集的培養基中生長1-2天,並且然後切換至選擇性培養基。重組質體中的選擇性標誌物賦予對選擇的抗性,並且允許細胞穩定地將質體整合到其染色體中並生長以形成病灶,進而其可以進行選殖並擴展成細胞系。該方法可有利地用於工程化表現LTβR結合蛋白的細胞系。這樣的工程化的細胞系可以特別地用於篩選和評估與抗體分子直接或間接相互作用的化合物。

【0291】可以使用許多選擇系統,包括但不限於單純疱疹病毒胸苷激酶(參見例如,Wigler等人, *Cell*[細胞] 11:223 (1977))、次黃嘌呤鳥嘌呤磷酸核糖基轉移酶(參見例如, Szybalska和Szybalski, *Proc. Natl. Acad. Sci. USA*[美國國家科學院院刊] 48:202 (1992))和腺嘌呤磷酸核糖基轉移酶(參見例如, Lowy等人, *Cell*[細胞] 22:817 (1980))基因可分別用於tk、hgp^rt或ap^rt細胞。另外,可以將抗代謝藥抗性作為選擇以下基因的依據:dhfr,其賦予對胺甲喋呤的抗性(參見例如,Wigler等人, *Proc. Natl. Acad. Sci. USA*[美國國家科學院院刊] 77:357 (1980); O'Hare等人, *Proc. Natl. Acad. Sci. USA*[美國國家科學院院刊] 78:1527 (1981)); gpt,其賦予對黴酚酸的抗性(參見例如, Mulligan和Berg, *Proc. Natl. Acad. Sci. USA*[美國國家科學院院刊] 78:2072 (1981)); neo,其賦予對胺基糖苷G-418的抗性(參見例如, Wu和Wu, *Biotherapy* [生物療法] 3:87-95 (1991)); 以及hygro,其賦予對潮黴素的抗性(參見例如, Santerre等人, *Gene* [基因] 30:147 (1984))。可以將本領域公知的重組DNA技術的方法常規地應用於選擇所希望的重組選

殖，並且此類方法描述於例如，Ausubel等人(編輯), *Current Protocols in Molecular Biology* [分子生物學現代方法], John Wiley & Sons [約翰•威利父子公司], 紐約 (1993)；Kriegler, *Gene Transfer and Expression, A Laboratory Manual* [基因轉移和表現：實驗室手冊], Stockton Press [密斯托克頓出版社], 紐約 (1990)；以及第12和13章, Dracopoli等人(編輯), *Current Protocols in Human Genetics* [當代人類遺傳學實驗手冊], John Wiley & Sons [約翰•威利父子公司], 紐約 (1994)；Colberre-Garapin等人, *J. Mol. Biol.* [分子生物學雜誌] 150:1 (1981)。

【0292】 宿主細胞可以用本揭露之兩種表現載體進行共轉染，例如，第一載體編碼如本文所描述的促效劑LT β R結合蛋白重鏈或其可變結構域，第二載體編碼如本文所描述的LT β R結合蛋白輕鏈或其可變結構域。這兩種載體可含有相同的選擇性標誌物，這使得重鏈和輕鏈多肽能相等表現。可替代地，可以使用編碼並能夠表現例如重鏈和輕鏈多肽的單個載體。在這種情況下，輕鏈應置於重鏈之前，以避免過量的無毒重鏈（參見例如，Proudfoot, *Nature* [自然] 322:52 (1986)；Kohler, *Proc. Natl. Acad. Sci. USA* [美國國家科學院院刊] 77:2197 (1980)）。重鏈和輕鏈的編碼序列可以包含cDNA或基因組DNA。

【0293】 LT β R單鏈結合蛋白可以經由胺基酸橋（短肽連接基）藉由連接重鏈和輕鏈可變結構域（Fv區）片段形成，從而產生單個多肽鏈。這樣的單鏈Fv（scFv）已藉由在編碼兩個可變結構域多肽（V_L和V_H）的DNA之間融合編碼肽連接基的DNA來製備。所得多肽可以自身折疊以形成抗原結合單體，或者它們可以形成多聚體（例如，二聚體、三聚體或四聚體），這取決於兩個可變結構域之間的柔性連接基的長度（參見例如，Kortt等人, *Prot. Eng.* [蛋白質工程] 10:423 (1997)；Kortt等人, *Biomol. Eng.* [生物分子工程] 18:95-108 (2001)）。藉由組合包含不同V_L和V_H的多肽，可以形成與不同表位結合的多聚體scFv（Kriangkum等人, *Biomol. Eng.* [生物分子工程] 18:31-40 (2001)）。為生產單鏈結合蛋白而開發的技

術包括以下中描述的那些：美國專利案號4,946,778；Bird等人, *Science*[科學] 242:423 (1988)；Huston等人, *Proc. Natl. Acad. Sci. USA*[美國國家科學院院刊] 85:5879 (1988)；Ward等人, *Nature* [自然] 334:544 (1989)；de Graaf等人, *Methods Mol Biol.*[分子生物學方法] 178:379-87 (2002)。

【0294】在一個實施方式中，如本文所描述的能夠結合LT β R和TAA或SAA的雙特異性LT β R結合蛋白可以使用本領域已知的方法生產，例如參見，Yan等人的美國專利申請公開案號20200071425，或Kannan等人的美國專利案號8,592,562。在一個實施方式中，如本文所描述的雙特異性促效劑LT β R結合蛋白係使用以下中描述的方法生產：Wu等人的美國專利申請公開案號20100233173；Allan等人的美國專利申請公開案號20100105873；或Wu等人的美國專利申請公開案號20090155275。在一些實施方式中，如本文所描述的能夠結合LT β R和TAA或SAA的雙特異性促效劑LT β R結合蛋白使用以下中描述的方法生產：Thompson等人的美國專利申請公開案號20090175867和Thompson等人的美國專利申請公開案號20110033483。

【0295】本文所描述的雙特異性促效劑LT β R結合蛋白可以可替代地藉由直接回收例如在大腸桿菌中重組表現的Fab'片段產生，並且可以以化學偶合以形成雙特異性抗體（參見例如，Carter等人, *Applications for Escherichia coli-Derived Humanized Fab' Fragments: Efficient Construction of Bispecific Antibodies*[大腸桿菌衍生的人源化Fab'片段的應用：雙特異性抗體的高效構建]. 於: Rosenberg, M., Moore, G.P. (編輯) *The Pharmacology of Monoclonal Antibodies*[單株抗體的藥理學]. *Handbook of Experimental Pharmacology*[實驗藥理學手冊], v. 113. 施普林格，柏林，海德堡）。

【0296】一旦藉由本文所描述的任何方法生產促效劑LT β R結合蛋白，就使用標準免疫球蛋白純化方法進行純化。合適的純化方法包括但不限於層析法（例

如，離子交換、親和力，特別是藉由蛋白A後對特定抗原的親和力，以及大小排除層析法）、離心或差分溶解度。此外，本揭露之結合蛋白可以融合到本文所描述的或本領域已知的異源多肽序列，以促進純化。

藥物組成物

【0297】 本文提供了包含呈多肽、核酸、載體、宿主細胞或其組合的形式的促效劑LTβR結合蛋白（例如，促效劑LTβR抗體或雙特異性促效劑LTβR結合蛋白）的組成物。在一個實施方式中，本揭露之藥物組成物包含呈分離和/或純化的形式的促效劑LTβR結合蛋白或編碼其的多核苷酸。在一個實施方式中，該組成物包含本揭露之兩種或更多種不同的結合蛋白（例如，不同結構）和/或多核苷酸的組合。

【0298】 本揭露之藥物組成物包含增強促效劑LTβR結合蛋白或編碼其的多核苷酸的化學物理特性的藥劑，例如，經由在特定溫度（例如，室溫）下穩定、增加保質期、減少降解（例如，氧化蛋白酶介導的降解）、增加促效劑LTβR結合蛋白的半衰期等。

【0299】 在本揭露之示例性方面中，該組成物另外包含藥學上可接受的載劑、稀釋劑或賦形劑。在一些實施方式中，將如本文揭露的LTβR結合蛋白或編碼其的多核苷酸（以下稱為「活性劑」）配製成包含活性劑以及藥學上可接受的載劑、稀釋劑或賦形劑的藥物組成物。就此而言，本揭露進一步提供了包含活性劑的藥物組成物，該藥物組成物旨在投與至受試者，例如哺乳動物。

【0300】 在一些實施方式中，該活性劑以適合於投與至患者的純度水平存在於藥物組成物中。在一些實施方式中，該活性劑具有至少約90%、約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%的純度水平，和藥學上可接受的稀釋劑、載劑或賦形劑。在一些實施方式中，該等組成物含有約0.001至約30.0 mg/ml的濃度的活性劑。

【0301】在示例性方面中，該等藥物組成物包含藥學上可接受的載劑。如本文所用，術語「藥學上可接受的載劑」包括任一標準藥物載劑，例如磷酸鹽緩衝鹽水溶液、水、乳液（例如油/水或水/油乳液）和各種類型潤濕劑。該術語還涵蓋經美國聯邦政府的管理機構批准或在美國藥典中列出的用於包括人類的動物的任一試劑。

【0302】該藥物組成物可以包含任何藥學上可接受的成分，包括例如酸化劑、添加劑、吸附劑、氣溶膠推進劑、空氣置換劑、鹼化劑、抗結塊劑、抗凝劑、抗微生物防腐劑、抗氧化劑、防腐劑、基質、黏合劑、緩衝劑、螯合劑、包衣劑、著色劑、乾燥劑、洗滌劑、稀釋劑、消毒劑、崩解劑、分散劑、溶解增強劑、染料、潤膚劑、乳化劑、乳化穩定劑、填充劑、成膜劑、增味劑、調味劑、流動促進劑、膠凝劑、造粒劑、保濕劑、潤滑劑、黏膜黏附劑、軟膏基質、軟膏、含油載體、有機基質、錠劑基質、色素、增塑劑、拋光劑、防腐劑、螯合劑、增溶劑、溶劑、穩定劑、栓劑基質、界面活性劑（surface active agent）、界面活性劑（surfactant）、懸浮劑、增稠劑、張力劑、毒性劑、增黏劑、水吸收劑、水混溶性共溶劑、水軟化劑或潤濕劑（例如參見，the Handbook of Pharmaceutical Excipients[藥用賦形劑手冊], 第三版, A. H. Kibbe (Pharmaceutical出版社, 英國倫敦, 2000); Remington's Pharmaceutical Sciences[雷明頓製藥科學], 第十六版, E. W. Martin (Mack Publishing Co., 賓夕法尼亞州伊斯頓, 1980)）。

【0303】在示例性方面中，該藥物組成物包含在所採用的劑量和濃度下對接受者無毒的配製物材料。在一個實施方式中，藥物組成物包含活性劑和一或多種藥學上可接受的鹽、多元醇、界面活性劑、滲透平衡劑、張力劑、抗氧化劑、抗生素、抗真菌劑、填充劑；凍乾保護劑；消泡劑；螯合劑；防腐劑；色料；鎮痛劑；或另外的藥劑。在示例性方面，除了上文提到的賦形劑中的一或多種之外，該藥物組成物視需要包含一或多種多元醇和/或一或多種界面活性劑。

【0304】 在某些實施方式中，該藥物組成物可含有用於改變、維持或保持例如組成物的pH值、滲透性、黏性、透明度、顏色、等滲性、氣味、無菌性、穩定性、分解或釋放速率、表面吸收或滲透的配製物材料。在這樣的實施方式中，合適的配製物材料包括但不限於胺基酸（例如甘胺酸、麩醯胺酸、天冬醯胺、精胺酸或離胺酸）；抗微生物劑；抗氧化劑（如抗壞血酸、亞硫酸鈉或亞硫酸氫鈉）；緩衝劑（如硼酸鹽、碳酸氫鹽、Tris-HCl、檸檬酸鹽、磷酸鹽或其他有機酸）；疏鬆劑（如甘露糖醇或甘胺酸）；螯合劑（如乙二胺四乙酸（EDTA））；複合劑（如咖啡因、聚乙烯吡咯啶酮、 β -環糊精或羥丙基- β -環糊精）；填充劑；單糖；二糖；和其他碳水化合物（諸如葡萄糖、甘露糖或糊精）；蛋白質（諸如血清白蛋白、明膠或免疫球蛋白）；著色劑、調味劑和稀釋劑；乳化劑；親水聚合物（如聚乙烯吡咯啶酮）；低分子量多肽；成鹽抗衡離子（如鈉）；防腐劑（諸如殺藻胺、苯甲酸、水楊酸、硫柳汞、苯乙醇、對羥基苯甲酸甲酯、對羥基苯甲酸丙酯、氯己定（chlorhexidine）、山梨酸或過氧化氫）；溶劑（如甘油、丙二醇或聚乙二醇）；糖醇（如甘露糖醇或山梨糖醇）；懸浮劑；界面活性劑或潤濕劑（例如 pluronics、PEG、脫水山梨醇酯、聚山梨醇酯例如聚山梨醇酯20、triton、胺丁三醇、卵磷脂、膽固醇、泰洛沙泊）；穩定性增強劑；張力增強劑（如鹼金屬鹵化物、較佳的是氯化鈉或氯化鉀，甘露糖醇，山梨糖醇）；遞送媒介物；稀釋劑；賦形劑和/或藥用輔助劑。參見REMINGTON'S PHARMACEUTICAL SCIENCES [雷明頓藥物科學], 第18版, (A. R. Genrmo編), 1990, Mack Publishing Company [麥克出版公司]。

【0305】 藥物組成物可經配製以實現生理學上相容的pH值。在一些實施方式中，藥物組成物的pH值可例如在約4或約5與約8.0之間或約4.5與約7.5之間或約5.0至約7.5。

治療方法

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第 236 頁，共 297 頁(發明說明書)

【0306】 本揭露之另一方面涉及治療有需要的受試者之方法，其中該方法包括向有需要的受試者投與有效量的如本文所描述的促效劑LT β R結合蛋白，例如促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白或包含其的藥物組成物。在一個實施方式中，該促效劑LT β R結合蛋白係與人LT β R的CRD4結合的蛋白，並且 (a) 不抑制LIGHT與LT β R結合，以及 (b) 不抑制LT1 α 2 β 與LT β R結合。在一個實施方式中，該促效劑LT β R結合蛋白係促效劑LT β R抗體。在一個實施方式中，該促效劑LT β R結合蛋白係雙特異性LT β R結合蛋白，其包含 (i) LT β R結合結構域，其中該LT β R結合結構域結合包含SEQ ID NO: 1之胺基酸殘基169-211的人LT β R CRD4的一或多個胺基酸殘基；和 (ii) 腫瘤相關抗原結合結構域。該雙特異性LT β R結合蛋白激動LT β R活性，並且 (a) 不抑制LIGHT與LT β R結合和 (b) 不抑制LT1 α 2 β 與LT β R結合。在一個實施方式中，這種雙特異性促效劑LT β R結合蛋白對於LT β R結合係單價的。

【0307】 在一個實施方式中，有需要的受試者係患有癌症的受試者。在一個實施方式中，該受試者患有實體瘤。不受限於特定理論，在腫瘤微環境中激動LT β R活性增強了T細胞對腫瘤微環境的浸潤並誘導三級淋巴結構(TLS)的形成。LT β R的這種活性增強和/或提供了腫瘤微環境中的抗腫瘤T細胞活性。因此，在一個實施方式中，投與促效劑LT β R結合蛋白或包含其的藥物組成物適合於在患有腫瘤的受試者中誘導和/或增強抗腫瘤免疫反應。如本文所用，術語「受試者」係指包括人的哺乳動物，並且可與術語「患者」互換使用。

【0308】 因此，本文提供了增強受試者腫瘤微環境中T細胞數量和活性、增強受試者腫瘤微環境中T細胞存活和效應物功能、以及增強受試者腫瘤微環境中對靶細胞（例如，癌細胞）的細胞毒性之方法。在示例性實施方式中，該等方法包括向受試者投與有效量的本揭露之藥物組成物。在示例性方面中，T細胞活性或免疫反應係針對癌細胞或癌症組織或腫瘤細胞或腫瘤。在示例性方面中，免疫

反應為體液免疫反應。在示例性方面中，免疫反應為先天性免疫反應。在示例性方面中，增強的免疫反應為T細胞介導的免疫反應。

【0309】如本文所用，術語「增強」及其衍生詞不需要或推斷出100%或完全增強或增加。更確切些，存在本領域中普通技術者認為具有潛在益處或治療作用的不同程度的增強。就此而言，本揭露之藥物組成物可以增強例如T細胞活性或免疫反應到任何量或水平，超過在沒有用如本文所描述的LT β R結合蛋白治療的情況下存在的T細胞活性或免疫反應的量或水平。在示例性實施方式中，藉由本揭露之方法提供的抗腫瘤免疫的增強係抗腫瘤免疫增強至少或約10%、增強至少或約20%、增強至少或約30%、增強至少或約40%、增強至少或約50%、增強至少或約60%、增強至少或約70%、增強至少或約80%、增強至少或約90%、增強至少或約95%、增強至少或約98%。

【0310】測量T細胞活性和免疫反應的方法為本領域中已知。T細胞活性可以藉由例如細胞毒性測定法來測量，例如Fu等人, *PLoS ONE*[公共科學圖書館綜合] 5(7): e11867 (2010)中描述的那些。適用於測量響應的其他T細胞活性測定在Bercovici等人, *Clin Diagn Lab Immunol.*[臨床診斷實驗室免疫學] 7(6): 859-864 (2000)中進行了描述。測量免疫反應的合適方法包括例如Macatangay等人, *Clin Vaccine Immunol*[臨床和疫苗免疫學] 17(9): 1452-1459 (2010)和Clay等人, *Clin Cancer Res.*[臨床癌症研究]7(5):1127-35 (2001)中描述的那些。

【0311】需要用如本文所描述的促效劑LT β R結合蛋白治療的受試者包括但不限於患有癌症的受試者，特別是患有實性瘤的受試者。在示例性實施方式中，該方法包括向受試者投與促效劑LT β R結合蛋白或包含促效劑LT β R結合蛋白的藥物組成物，其量可有效治療受試者中的癌症或實性瘤。藉由本文揭露的方法和促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白）可治療的癌症可為任何癌症，例如由異常和不受控制的細胞分裂引起的任

何惡性生長或腫瘤，其可以藉由淋巴系統或血流擴散到身體的其他部位。在一個實施方式中，該癌症或實性瘤係「冷」腫瘤，即被抑制抗腫瘤免疫反應的細胞包圍的腫瘤。

【0312】 在一個實施方式中，要用如本文所描述的促效劑LT β R結合蛋白治療的受試者患有選自間皮瘤、胰臟腫瘤、卵巢腫瘤、肺腫瘤、食管腫瘤、胃腫瘤、肝腫瘤、結直腸腫瘤、宮頸腫瘤、子宮內膜腫瘤、乳房腫瘤、腎腫瘤、膀胱腫瘤、睪丸腫瘤、前列腺腫瘤、腦腫瘤、骨腫瘤和頭頸部腫瘤的腫瘤。在一個實施方式中，該癌症選自齒槽橫紋肌肉瘤、肛門癌、肛管癌或肛腸癌、眼癌、肝內膽管癌、關節癌、頸部癌、膽囊癌或胸膜癌、鼻癌、鼻腔癌或中耳癌、口腔癌、外陰癌、大腸癌、食道癌、子宮頸癌、胃腸道類癌、下嚥癌、腎癌、喉癌、肝癌、肺癌（例如，非小細胞肺癌（NSCLC））、惡性間皮瘤、黑色素瘤、鼻咽癌、卵巢癌、胰臟癌、腹膜癌、網膜癌和腸系膜癌、咽癌、前列腺癌、直腸癌、腎癌（例如，腎細胞癌（RCC））、小腸癌、軟組織癌、胃癌、睪丸癌、甲狀腺癌、輸尿管癌和膀胱癌。在示例性實施方式中，該受試者患有實性瘤，並且將促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白）以有效治療受試者腫瘤的量投與至受試者。

【0313】 術語「治療」涵蓋減輕病症的至少一種症狀或其他實施方式、或降低疾病嚴重程度等。根據本揭露之促效劑LT β R結合蛋白，特別是結合人LT β R的CRD4並且不阻斷內源性LT β R配體結合的促效劑LT β R抗體或雙特異性結合蛋白，不需要完全治癒，或根除疾病的每種症狀或表現，即可構成可行的治療劑。正如在相關領域中所認識到的，治療劑可以降低特定疾病狀態的嚴重程度，但不需要消除疾病的每種表現才能被視為有用的治療劑。僅僅降低疾病的影響（例如藉由減少其症狀的次數或降低其症狀的嚴重度，或藉由增加另一治療的有效性，或藉由產生另一有益作用）或降低疾病在受試者中發生或惡化的可能性即為足

夠。本揭露之一個實施方式涉及一種方法，該方法包括向患者投與一定量的促效劑LT β R結合蛋白一段時間，該促效劑LT β R結合蛋白投與的量和時間足以誘導與反映特定病症嚴重程度的指標的基線相比的持續改善。在一個實施方式中，該方法包括向患者投與一定量的如本文揭露的促效劑LT β R結合蛋白一段時間，該促效劑LT β R結合蛋白投與的量和時間足以藉由增加腫瘤微環境中的免疫細胞浸潤和/或免疫細胞抗腫瘤活性將冷腫瘤轉化為熱腫瘤。在一個實施方式中，該方法進一步涉及將促效劑LT β R結合蛋白與一或多種免疫調節劑（例如PD(L)1-軸抑制劑）組合投與，以進一步刺激免疫細胞浸潤到腫瘤微環境中。

【0314】術語「預防」涵蓋預防病症的至少一種症狀或其他實施方式等。併入了如本文揭露的結合LT β R的CRD4並且不阻斷內源性LT β R配體結合活性的促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白）的預防性投與的治療不需要完全有效地預防病況的發作以構成可行的預防劑。僅僅降低疾病在受試者中發生或惡化的可能性即為足夠。在一個實施方式中，如本文所描述的促效劑LT β R結合蛋白的預防性投與藉由增強免疫細胞浸潤到腫瘤微環境中有效地防止腫瘤轉變為冷腫瘤。在一個實施方式中，如本文所描述的促效劑LT β R結合蛋白的預防性投與藉由在腫瘤微環境中增強免疫細胞浸潤和增強抗腫瘤免疫反應來有效地預防腫瘤生長。

【0315】如在相關領域中所理解的，將包含如本文揭露的促效劑LT β R結合蛋白的藥物組成物以適合於適應症和組成物的方式投與給受試者。在一個實施方式中，包含結合LT β R的CRD4並且不抑制內源性LT β R配體結合的促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白）的藥物組成物藉由任何合適的技術投與，包括但不限於胃腸外、靜脈內、肌內、病變內、腹膜內或皮下途徑、藉由推注或連續輸注。藉由吸入遞送包括，例如經鼻或經口吸入、使用霧化器、以氣溶膠形式吸入的促效劑LT β R結合蛋白等。其他替代品

包括口服製劑，包括丸劑、糖漿或錠劑。

【0316】 有利地，促效劑LT β R結合蛋白可以以組成物的形式投與，該組成物包含一或多種額外組分，例如生理上可接受的載劑、賦形劑或稀釋劑。視需要，該組成物另外包含一或多種生理活性劑。在各種特定實施方式中，除了一或多種促效劑LT β R結合蛋白外，該組成物還包含一種、兩種、三種、四種、五種或六種生理活性劑。

【0317】 提供了用於由執業醫師使用的套組，該等套組包括一或多種促效劑LT β R結合蛋白和用於治療本文所討論的任何病況的標記或其他說明書。在一個實施方式中，該等套組包括一或多種促效劑LT β R結合蛋白的無菌製劑，其可為如本文揭露的組成物的形式，並且可以在一或多個小瓶中。

【0318】 投與的劑量和頻率可根據諸如投與途徑、所採用的特定促效劑LT β R結合蛋白、待治療的疾病的性質和嚴重程度、病況是急性還是慢性、以及受試者的體型和一般狀況等因素而變化。適當的劑量可以藉由相關領域中（例如，在可能涉及劑量遞增研究的臨床試驗中）已知的程式來確定。

【0319】 如本文揭露的結合LT β R的CRD4並且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白可以例如一次或多次投與，例如在一段時間內以規則的間隔投與。在特定實施方式中，LT β R結合蛋白在至少每月一次或更長時間內投與，例如，持續一個月、兩個月或三個月或甚至無限期。對於治療慢性病，長期治療通常是最有效的。然而，對於治療急性病，較短時間投與（例如，一到六週）可能就足夠了。一般來說，投與促效劑LT β R結合蛋白，直到患者對所選一或多種指標表現出醫學相關的改善程度（相對於基線）。

【0320】 如本文揭露的結合LT β R的CRD4和/或不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白可較佳的是與免疫調節治療劑的投與結合投與。在一個實施方式中，該免疫調節治療劑係檢查點抑制劑。合適的檢查點抑制劑係

本領域已知的，包括例如且不限於PD-1抑制劑、PD-L1抑制劑、CTLA-4抑制劑、TIM-3抑制劑、LAG-3抑制劑、NKG2A抑制劑、CD73抑制劑和TIGIT抑制劑以及其任何組合。下文更詳細地描述了合適的組合療法。

組合療法

【0321】本揭露之方法和組成物的特定實施方式涉及使用至少一種促效劑LT β R結合蛋白和一或多種可用於治療或預防癌症的其他治療劑。在一個實施方式中，促效劑LT β R結合蛋白單獨投與或與可用於治療患有實體瘤的受試者的其他藥劑組合投與。這樣的藥劑之實例包括蛋白質和非蛋白質藥物。當共投與多種治療劑時，如相關技術中所認識到的，可以相應地調整劑量。「共投與」和組合療法不限於同時投與，還包括在涉及向患者投與至少一種其他治療劑的治療過程中至少投與一次促效劑LT β R結合蛋白的治療方案。在某些實施方式中，促效劑LT β R結合蛋白在投與至少一種其他治療劑之前投與。在某些實施方式中，促效劑LT β R結合蛋白與投與至少一種其他治療劑同時投與。在某些實施方式中，促效劑LT β R結合蛋白在投與至少一種其他治療劑之後投與。

【0322】在一個實施方式中，該至少一種其他治療劑係免疫調節治療劑，特別是檢查點抑制劑或T細胞接合治療劑。合適的檢查點抑制劑係本領域已知的，包括例如且不限於PD-1抑制劑、PD-L1抑制劑、CTLA-4抑制劑、TIM-3抑制劑、LAG-3抑制劑、NKG2A抑制劑、CD73抑制劑和TIGIT抑制劑以及其任何組合。

【0323】在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白（例如，促效劑LT β R抗體或雙特異性促效劑LT β R結合蛋白）與PD-1抑制劑（例如抗PD-1抗體）組合投與。合適的抗PD-1抗體之實例包括但不限於納武單抗（Opdivo®/KEGG D10316）、派姆單抗（Keytruda®/KEGG D10574）、西米普利單抗（Libtayo®/KEGG D11108）、

多塔利單抗（TSR-042/KEGG D11366）、斯巴達珠單抗（KEGG D11605）和匹地利珠單抗（CT-011；KEGG D10390）。

【0324】在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與PD-L1抑制劑（例如抗PD-L1抗體）組合投與。合適的抗PD-L1抗體之實例包括但不限於阿替利珠單抗（Tecentriq[®]；KEGG D10773）、阿維魯單抗（Bavencio[®]；KEGG D10817）和德瓦魯單抗（Imfinzi[®]；KEGG D10808）。

【0325】在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與CTLA-4抑制劑組合投與。合適的CTLA-4抑制劑係單株抗體伊匹單抗（Yervoy；KEGG D04603）。

【0326】在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與TIM-3抑制劑（例如抗TIM-3抗體）組合投與。合適的抗TIM-3抗體之實例包括但不限於沙巴托利單抗（MBG453；諾華公司（Novartis））；LY3321367（禮來公司（Eli Lilly））和TSR-022（Tesaro）。

【0327】在一個實施方式中，如本文揭露的結合LT β R的CRD4和/或不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與LAG-3抑制劑（例如抗LAG-3抗體）組合投與。適用於與本文所描述的LT β R結合蛋白組合使用的示例性抗LAG-3抗體包括但不限於瑞拉利單抗（KEGG D11350）。

【0328】在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與NKG2-A/NKG2-B II型整合膜蛋白（NKG2A）抑制劑（例如抗NKG2A抗體）組合投與。適用於與本文所描述的LT β R結合蛋白組合使用的示例性抗NKG2A抗體包括但不限於BMS-986315（Bristol Myers Squibb[®]）。

【0329】 在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與CD73抑制劑組合投與。與本文所描述的LT β R結合蛋白組合使用的合適的CD73抑制劑包括但不限於小分子CD73抑制劑OP-5244（Du等人, *J. Med. Chem.*[藥物化學雜誌] 63:10433-10459 (2020)，特此藉由引用將其全部併入）和LY-3475070（禮來公司（Eli Lilly））。

【0330】 在一個實施方式中，如本文揭露的結合LT β R的CRD4且不抑制內源性LT β R配體結合活性的促效劑LT β R結合蛋白與TIGIT抑制劑（例如抗TIGIT抗體）組合投與。合適的抗TIGIT抗體之實例包括但不限於BMS-986207（百時美施貴寶公司（Bristol-Myers Squibb））；Tiragolumab（羅氏公司（Roche））、MK-7684（默克公司（Merck））和COM902（Compugen公司）。

【0331】 在已經描述了本揭露以後，藉由說明而非限制的方式提供以下實施方式和實例。

實施方式

【0332】 本揭露提供了以下非限制性實施方式。

【0333】 本揭露之實施方式1涉及一種促效劑淋巴毒素 β 受體（LT β R）結合蛋白，其中所述結合蛋白結合包含人LT β R富含半胱氨酸結構域4（CRD4）的一或多個殘基的表位，其中人LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211，並且其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT α 1 β 2與LT β R結合。

【0334】 實施方式2係如實施方式1所述之促效劑LT β R結合蛋白，其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合且 (b) 不抑制LT α 1 β 2與LT β R結合。

【0335】 實施方式3係如實施方式1或2所述之促效劑LT β R結合蛋白，其中所述結合蛋白結合包含SEQ ID NO: 1的殘基197-209的LT β R CRD4的一或多個殘基。

【0336】 實施方式4係如實施方式1-3所述之促效劑LT β R結合蛋白，其中在該促效劑LT β R結合蛋白存在下對LIGHT和/或LT α 1 β 2與LT β R結合的抑制在基於細胞的受體-配體結合測定中測量，所述測定包括以下步驟：將表現LT β R的細胞與含有該促效劑LT β R結合蛋白的培養基孵育1小時；在所述孵育後，使該等表現LT β R的細胞與可檢測的LIGHT配體、可檢測的LT α 1 β 2配體或其組合接觸，以允許該等可檢測的配體與LT β R結合；在所述接觸後，在該LT β R結合蛋白存在下，檢測與表現LT β R的細胞結合的可檢測的LIGHT和/或LT α 1 β 2配體；以及基於所述檢測將該促效劑LT β R結合蛋白鑒定為不抑制LIGHT或LT α 1 β 2與LT β R結合。

【0337】 實施方式5係如實施方式1-4中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：與SEQ ID NO: 121或SEQ ID NO: 123具有至少90%序列同一性的重鏈可變結構域（VH）胺基酸序列和與SEQ ID NO: 122或SEQ ID NO: 124具有至少90%序列同一性的輕鏈可變結構域（VL）胺基酸序列。

【0338】 實施方式6係如實施方式1-4中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：與SEQ ID NO: 121和SEQ ID NO: 123具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 122和SEQ ID NO: 124具有至少90%序列同一性的VL胺基酸序列。

【0339】 實施方式7係如實施方式1-4中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：與SEQ ID NO: 121和SEQ ID NO: 123具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 122和SEQ ID NO: 124具有至少95%序列同一性的VL胺基酸序列。

【0340】 實施方式8係如實施方式1-7中任一項所述之促效劑LT β R結合蛋白，其中所述結合蛋白包含：VH，其包含HCDR1胺基酸序列X₁YX₃MX₅（SEQ ID NO: 5），其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺基酸序

列X₁IX₃YDX₆X₇X₈X₉Y X₁₁X₁₂DSVKG (SEQ ID NO: 6) , 其中X₁為A或V ; X₃為W或R ; X₆為E或G ; X₇為S、R或T ; X₈為N或K ; X₉為K、R或Q ; X₁₁為H或Y ; 並且X₁₂為A或E ; 以及HCDR3胺基酸序列X₁RX₃X₄X₅X₆ X₇X₈X₉YYGX₁₃X₁₄V (SEQ ID NO: 7) , 其中X₁為D或E ; X₃為V、G或I ; X₄為V、P或A ; X₅為A、Y或G ; X₆為R、A、G或H ; X₇為P或G ; X₈為G、N、D、Y、A或H ; X₉為Y、T或F ; X₁₃為L或M ; 並且X₁₄為D或A ; VL , 其包含LCDR1胺基酸序列SGDX₄LPX₇X₈YX₁₀Y (SEQ ID NO: 62) , 其中X₄為A或T ; X₇為E、K、Q、D或N ; X₈為Q或H ; 並且X₁₀為A或T ; LCDR2胺基酸序列KDNERPS (SEQ ID NO: 63) ; 以及LCDR3胺基酸序列QSX₃DX₅SX₇X₈YX₁₀X₁₁ (SEQ ID NO: 64) , 其中X₃為A或T ; X₅為S、G或N ; X₇為G或A ; X₈為T、S或A ; X₁₀為V或M ; 並且X₁₁為I或V。

【0341】 實施方式9係如實施方式1-8中任一項所述之促效劑LTβR結合蛋白，其中所述結合蛋白包含：與SEQ ID NO: 121具有至少90%序列同一性的VH胺基酸序列、以及SEQ ID NO: 5的HCDR1胺基酸序列、SEQ ID NO: 6的HCDR2胺基酸序列和SEQ ID NO: 7的HCDR3胺基酸序列；以及與SEQ ID NO: 122具有至少90%序列同一性的VL胺基酸序列、以及SEQ ID NO: 62的LCDR1胺基酸序列、SEQ ID NO: 63的LCDR2胺基酸序列和SEQ ID NO: 64的LCDR3胺基酸序列。

【0342】 實施方式10係如實施方式1-9中任一項所述之促效劑LTβR結合蛋白，其中所述結合蛋白包含：VH，其包含分別為SEQ ID NO: 11-13的HCDR1、HCDR2和HCDR3胺基酸序列，以及VL，其包含分別為SEQ ID NO: 68-70的LCDR1、LCDR2和LCDR3胺基酸序列；或VH，其包含分別為SEQ ID NO: 8-10的HCDR1、HCDR2和HCDR3胺基酸序列，以及VL，其包含分別為SEQ ID NO: 65-67的LCDR1、LCDR2和LCDR3胺基酸序列。

【0343】 實施方式11係如實施方式1-10中任一項所述之促效劑LTβR結合蛋白，其中該結合蛋白係抗體。

【0344】 實施方式12係如實施方式1-10中任一項所述之促效劑LT β R結合蛋白，其中該結合蛋白係雙特異性結合蛋白。

【0345】 實施方式13涉及雙特異性淋巴毒素 β 受體（LT β R）結合蛋白，所述結合蛋白包含：LT β R結合結構域，其中該LT β R結合結構域結合包含人LT β R富含半胱氨酸結構域4（CRD4）的一或多個殘基的表位，其中所述LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211；和腫瘤相關抗原結合結構域，其中該雙特異性結合蛋白激動LT β R活性，並且 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT α 1 β 2與LT β R結合。

【0346】 實施方式14係如實施方式13所述之雙特異性促效劑LT β R結合蛋白，其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合且 (b) 不抑制LT α 1 β 2與LT β R結合。

【0347】 實施方式15係如實施方式13所述之雙特異性促效劑LT β R結合蛋白，其中該表位包含SEQ ID NO: 1之位置197-209處的LT β R CRD4的一或多個殘基。

【0348】 實施方式16係如實施方式13-15中任一項所述之雙特異性促效劑LT β R結合蛋白，其中在該雙特異性促效劑LT β R結合蛋白存在下對LIGHT和/或LT α 1 β 2與LT β R結合的抑制在基於細胞的受體-配體結合測定中測量，所述測定包括以下步驟：將表現LT β R的細胞與含有該雙特異性促效劑LT β R結合蛋白的培養基孵育1小時；在所述孵育後，使該等表現LT β R的細胞與可檢測的LIGHT配體、可檢測的LT α 1 β 2配體或其組合接觸，以允許該等可檢測的配體與LT β R結合；在所述接觸後，在該雙特異性促效劑LT β R結合蛋白存在下，檢測與表現LT β R的細胞結合的可檢測的LIGHT和/或LT α 1 β 2配體；以及基於所述檢測將該雙特異性促效劑LT β R結合蛋白鑒定為不抑制LIGHT或LT α 1 β 2與LT β R結合。

【0349】 實施方式17係如實施方式13-15中任一項所述之雙特異性促效劑

LTβR結合蛋白，其中該LTβR結合結構域包含：與SEQ ID NO: 121或SEQ ID NO: 123具有至少90%序列同一性的VH胺基酸序列，和與SEQ ID NO: 122或SEQ ID NO: 124具有至少90%序列同一性的VL胺基酸序列。

【0350】 實施方式18係如實施方式13所述之雙特異性促效劑LTβR結合蛋白，其中該LTβR結合結構域包含：與SEQ ID NO: 121和SEQ ID NO: 123具有至少90%序列同一性的VH胺基酸序列和與SEQ ID NO: 122和SEQ ID NO: 124具有至少90%序列同一性的VL胺基酸序列。

【0351】 實施方式19係如實施方式13所述之雙特異性促效劑LTβR結合蛋白，其中該LTβR結合結構域包含：與SEQ ID NO: 121和SEQ ID NO: 123具有至少95%序列同一性的VH胺基酸序列和與SEQ ID NO: 122和SEQ ID NO: 124具有至少95%序列同一性的VL胺基酸序列。

【0352】 實施方式20係如實施方式13-19中任一項所述之雙特異性促效劑LTβR結合蛋白，其中該LTβR結合結構域包含：VH，其包含HCDR1胺基酸序列X₁YX₃MX₅（SEQ ID NO: 5），其中X₁為S或N；X₃為G、D或A；並且X₅為H或Y；HCDR2胺基酸序列X₁IX₃YDX₆X₇X₈X₉Y X₁₁X₁₂DSVKG（SEQ ID NO: 6），其中X₁為A或V；X₃為W或R；X₆為E或G；X₇為S、R或T；X₈為N或K；X₉為K、R或Q；X₁₁為H或Y；並且X₁₂為A或E；以及HCDR3胺基酸序列X₁RX₃X₄X₅X₆X₇X₈X₉YYGX₁₃X₁₄V（SEQ ID NO: 7），其中X₁為D或E；X₃為V、G或I；X₄為V、P或A；X₅為A、Y或G；X₆為R、A、G或H；X₇為P或G；X₈為G、N、D、Y、A或H；X₉為Y、T或F；X₁₃為L或M；並且X₁₄為D或A；VL，其包含LCDR1胺基酸序列SGDX₄LPX₇X₈YX₁₀Y（SEQ ID NO: 62），其中X₄為A或T；X₇為E、K、Q、D或N；X₈為Q或H；並且X₁₀為A或T；LCDR2胺基酸序列KDNERPS（SEQ ID NO: 63）；以及LCDR3胺基酸序列QSX₃DX₅SX₇X₈YX₁₀X₁₁（SEQ ID NO: 64），其中X₃為A或T；X₅為S、G或N；X₇為G或A；X₈為T、S或A；X₁₀為V或M；並且X₁₁為

I或V。

【0353】實施方式21係如實施方式13-20中任一項所述之雙特異性促效劑LT β R結合蛋白，其中所述結合蛋白包含：與SEQ ID NO: 121具有至少90%序列同一性的VH胺基酸序列、以及SEQ ID NO: 5的HCDR1胺基酸序列、SEQ ID NO: 6的HCDR2胺基酸序列和SEQ ID NO: 7的HCDR3胺基酸序列；以及與SEQ ID NO: 122具有至少90%序列同一性的VL胺基酸序列、以及SEQ ID NO: 62的LCDR1胺基酸序列、SEQ ID NO: 63的LCDR2胺基酸序列和SEQ ID NO: 64的LCDR3胺基酸序列。

【0354】實施方式22係如實施方式13所述之雙特異性促效劑LT β R結合蛋白，其中該VH包含分別為SEQ ID NO: 11-13的HCDR1、HCDR2和HCDR3胺基酸序列，以及該VL包含分別為SEQ ID NO: 68-70的LCDR1、LCDR2和LCDR3胺基酸序列；或該VH包含分別為SEQ ID NO: 8-10的HCDR1、HCDR2和HCDR3胺基酸序列，以及該VL包含分別為SEQ ID NO: 65-67的LCDR1、LCDR2和LCDR3胺基酸序列。

【0355】實施方式23係如實施方式13-22中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該雙特異性結合蛋白僅包含一個LT β R結合結構域。

【0356】實施方式24係如實施方式13-22中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域係Fab。

【0357】實施方式25係如實施方式13-24中任一項所述之雙特異性促效劑LT β R結合蛋白，其中結合蛋白包含一個腫瘤相關抗原結合結構域。

【0358】實施方式26係如實施方式25所述之雙特異性促效劑LT β R結合蛋白，其中該腫瘤相關抗原結合結構域係Fab。

【0359】實施方式27係如實施方式13-24中任一項所述之雙特異性促效劑LT β R結合蛋白，其中結合蛋白包含兩個腫瘤相關抗原結合結構域。

【0360】實施方式28係如實施方式13-22中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域係Fab，並且該腫瘤相關抗原結合結構域係Fab。

【0361】實施方式29係如實施方式13-28中任一項所述之雙特異性促效劑LT β R結合蛋白，其中該LT β R結合結構域和該腫瘤相關抗原結合結構域各自偶合到Fc部分。

【0362】實施方式30係如實施方式29所述之雙特異性促效劑LT β R結合蛋白，其中該Fc部分不與Fc γ 受體結合。

【0363】實施方式31涉及編碼如實施方式1-12中任一項所述之促效劑LT β R結合蛋白的多核苷酸。

【0364】實施方式32係包含如實施方式31所述之多核苷酸的載體。

【0365】實施方式33係包含如實施方式31所述之多核苷酸或如實施方式32所述之載體的宿主細胞。

【0366】實施方式34係編碼如實施方式13-30中任一項所述之雙特異性促效劑LT β R結合蛋白的一或多種多核苷酸。

【0367】實施方式35係包含如實施方式34所述之一或多種多核苷酸的載體。

【0368】實施方式36係包含如實施方式34所述之一或多種多核苷酸或如實施方式35所述之載體的宿主細胞。

【0369】實施方式37係一種藥物組成物，其包含：如實施方式1-12中任一項所述之促效劑LT β R結合蛋白，如實施方式13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，如實施方式31或34所述之一或多種多核苷酸，或如實施方式32或35所述之載體，以及藥學上可接受的載劑。

【0370】實施方式38係如實施方式1-12中任一項所述之促效劑LT β R結合

蛋白，用作藥物。

【0371】實施方式39係如實施方式1-12中任一項所述之促效劑LT β R結合蛋白，用於治療癌症。

【0372】實施方式40係如實施方式1-12中任一項所述之促效劑LT β R結合蛋白，用於製備用於治療癌症的藥物。

【0373】實施方式41係如實施方式13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，用作藥物。

【0374】實施方式42係如實施方式13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，用於治療癌症。

【0375】實施方式43係如實施方式13-30中任一項所述之雙特異性促效劑LT β R結合蛋白，用於製備用於治療癌症的藥物。

【0376】實施方式44涉及一種治療受試者癌症之方法，所述方法包括：向患有癌症的受試者投與促效劑淋巴毒素 β 受體（LT β R）結合蛋白，其中所述結合蛋白結合包含人LT β R富含半胱胺酸結構域4（CRD4）的一或多個殘基的表位，其中人LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211，並且其中所述結合蛋白 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT α 1 β 2與LT β R結合。

【0377】實施方式45係一種治療受試者癌症之方法，所述方法包括：向患有癌症的受試者投與雙特異性淋巴毒素 β 受體（LT β R）結合蛋白，其中所述結合蛋白包含：LT β R結合結構域，其中該LT β R結合結構域結合包含人LT β R富含半胱胺酸結構域4（CRD4）的一或多個胺基酸殘基的表位，其中人LT β R CRD4包含SEQ ID NO: 1之胺基酸殘基169-211；和腫瘤相關抗原結合結構域，其中該雙特異性結合蛋白激動LT β R活性，並且 (a) 不抑制LIGHT與LT β R結合或 (b) 不抑制LT1 α 2 β 與LT β R結合。

【0378】實施方式46係如實施方式44或實施方式45所述之方法，進一步包

括：與所述促效劑LT β R結合蛋白或雙特異性LT β R結合蛋白結合投與免疫調節治療劑。

【0379】實施方式47係如實施方式41或42所述之方法，其中該受試者患有選自由以下組成之群組的實性瘤：間皮瘤、胰臟腫瘤、卵巢腫瘤、肺腫瘤、食管腫瘤、胃腫瘤、肝腫瘤、結直腸腫瘤、宮頸腫瘤、子宮內膜腫瘤、乳房腫瘤、腎腫瘤、膀胱腫瘤、睪丸腫瘤、前列腺腫瘤、腦腫瘤、骨腫瘤和頭頸部腫瘤。

實例

【0380】給出以下實例僅用於說明本發明，而不以任何方式限制其範圍。

實例1：靶向腫瘤相關抗原（TAA）的LT β R激動作用在體內腫瘤模型中表現出治療功效

【0381】**1.1 靶向EpCAM的LT β R激動作用在鼠B16F10黑色素瘤模型中誘導HEV形成並增加淋巴細胞浸潤。**在研究第0天，將huEpCAM-B16F10腫瘤細胞皮下植入雌性野生型C57BL/6動物的右側腹部。在第10天將腫瘤分為不同的治療組（n=10/組），平均腫瘤體積為約100 mm³。每三天一次給動物靜脈給藥30 mg/kg的對照同種型mIgG1（美商安進公司（Amgen），PL-11445-3）或增加劑量（0.3、3和30 mg/kg）的huEpCAM-muLT β R（5G11）雙特異性促效劑LT β R工具抗體（美商安進公司，7622-1）。在第20天收穫腫瘤。將一半的腫瘤解離進行流動式細胞分析術分析，並且另一半用福馬林固定進行組織學分析。如圖1所示，浸潤到腫瘤環境中的CD3⁺ T細胞的總數（圖1A）在3 mg/kg劑量下增加，並且浸潤到腫瘤環境中的CD19⁺ B細胞的總數（圖1B）以劑量依賴性方式增加。使用流動式細胞分析術評估T和B細胞浸潤。如圖2所示，huEpCAM-LT β R治療誘導了腫瘤環境中高內皮小靜脈（HEV）的形成（下圖）。在同種型對照治療的腫瘤組織中未觀察到HEV的存在（圖2，上圖）。使用抗PNAd（Meca79）mAb藉由免疫組織化學染

色來評估HEV的存在。

【0382】 1.2 靶向LRRC15的LTβR激動作用在KPC M5腫瘤模型中誘導淋巴細胞浸潤並抑制腫瘤生長。在研究的第0天，將KPC M5胰臟腫瘤細胞皮下植入雌性野生型C57BL/6小鼠的右側腹部。使腫瘤生長10天，達到大約100 mm³，然後隨機分為相應組（n = 5/組）。每週兩次向動物以3 mpk給藥三劑小鼠工具LRRC15 x LTβR雙特異性抗體（BsAb）（36017-1和28786-1/64506-1）或同種型對照mIgG1 N297G（PL-57469）。在最後一劑LRRC15 x LTβR BsAb（第20天）後三天收穫腫瘤和血清。收集皮膚附著在外周的腫瘤。去除附著的皮膚，並且解離腫瘤以進行流動式細胞分析術分析。如圖3所示，與同種型對照相比，觀察到LRRC15 x LTβR雙特異性抗體治療後，T細胞浸潤（CD3⁺細胞）到腫瘤中的增加。

【0383】 在另一項研究中，在第0天將KPC M5胰臟腫瘤細胞（100k/小鼠）皮下植入雌性野生型C57BL/6小鼠的右側腹部。使腫瘤生長10天，直到平均腫瘤體積達到100 mm³。將動物隨機分組以接受LRRC15 x LTβR BsAb（36017-1）或同種型對照治療（n = 10/組）。對動物進行腹膜內給藥，每週兩次，共9劑（或直到該等動物退出），使用3 mg/kg的對照同種型mIgG1（11445-3），每週兩次，共9劑，使用3 mg/kg的LRRC15 x LTβR BsAb，或每三天一次，共3劑，使用100 μg/小鼠的抗PD1抗體（7358-1）。每週兩次測量腫瘤並稱量體重，直到腫瘤達到大於或等於2000 mm³或動物達到中位存活極限的兩倍。如圖4所示，與同種型(●)相比，PD-1抗體治療(■)沒有顯著抑制腫瘤生長，僅產生4.64%的腫瘤生長抑制（TGI）。與同種型相比，用LRRC15 x LTβR BsAb單一療法(▼)治療的腫瘤確實產生了20.76%的統計學顯著TGI。LRRC15 x LTβR BsAb和PD-1抗體組合確實導致了32.37%的更大TGI，但兩個治療組之間沒有統計學顯著性。

實例2：人LTβR結合蛋白的產生

【0384】 藉由免疫XenoMouse®轉基因小鼠產生針對人LTβR的完全人抗

體。XenoMouse®及其用於產生人抗體的效用在以下中公開：美國專利案號 6,114,598；6,162,963；6,833,268；7,049,426；7,064,244和Green等人, *Nature Genetics*[自然遺傳學] 7:13-21 (1994)；Mendez等人, *Nature Genetics*[自然遺傳學] 15:146-156 (1997)；Green和Jakobovitis, *J. Ex. Med*[實驗醫學雜誌], 188:483-495 (1998)；Kellerman和Green, *Current Opinion in Biotechnology*[生物技術的當前觀點] 13, 593-597 (2002)，特此藉由引用將其全部併入。多種免疫原和免疫途徑用於產生抗人LTβR免疫反應。使用GeneGun（BioRad）方案在6-8週內對產生人免疫球蛋白G（IgG）2或IgG 4抗體的轉基因XenoMouse®進行12-16次皮內免疫，該方案遞送包有編碼人LTβR的質體DNA和分子佐劑的金微粒。可替代地，用暫態轉染人或cyno LTβR表現載體的CHO-S細胞對動物進行皮下免疫。對於可溶性蛋白免疫，對小鼠皮下注射人LTβR重組蛋白，每次增強5 μg蛋白質，每週兩次，持續6-8週。在第4週將Cyno LTβR抗原引入小鼠，並與人LTβR抗原以交替的時間表進行注射。為了選擇產生對LTβR特異的抗體的動物，測試了來自免疫小鼠的血清與暫態轉染的HEK 293細胞上表現的人和cyno LTβR的結合，並藉由螢光激活細胞分選（FACS）進行分析。應用相對於背景的倍數GeoMean變化來選擇對人和cyno LTβR具有最高天然效價的響應小鼠。所選的小鼠在組織收穫前4天接受最後的增強，隨後進行B細胞富集。收穫和免疫原的詳細資訊列於表15中。

[表15]. XenoMouse®免疫和抗體收穫總結

收穫組	免疫原	佐劑	菌株	收穫
收穫2.3	編碼hu LTβR的質體DNA + 編碼cyno LTβR的質體DNA	CpG + mGM-CSF	G4K	10隻小鼠
			G4KL	5隻小鼠
收穫3.4	暫態表現hu LTβR的CHO-S + 暫態表現cyno LTβR的 CHO-S	Alum + CpG	G2K	2隻小鼠
			G2KL	8隻小鼠
收穫4.4	暫態表現hu LTβR的CHO-S	Alum + CpG	G4K	4隻小鼠

	+ 暫態表現cyno LTβR的 CHO-S		G4KL	6隻小鼠
收穫5.2	重組人LTβR Fc嵌合體 + 重組Cyno LTβR Fc嵌合體	Alum + CpG	G2K	4隻小鼠
			G2KL	4隻小鼠

實例3：單株抗體融合瘤產生的製備。

【0385】鑒別展現合適血清效價的動物且自脾和/或引流淋巴結獲得淋巴細胞。藉由在合適的培養基（例如，RPMI 1640培養基；加利福尼亞州卡爾斯巴德的英傑公司（Invitrogen, Carlsbad, CA））中研磨，將彙集的淋巴細胞（來自每次收穫）從淋巴組織中解離。使用標準方法選擇和/或擴增B細胞，並使用本領域已知的技術與合適的融合配偶體融合。

實例4：用於LTβR結合物鑒定的融合瘤池的第一輪篩選

【0386】4.1從融合瘤池中產生選殖抗LTβR融合瘤。將來自收穫1至6的XenoMouse®融合瘤培養物解凍，並在DMEM選擇培養基中生長3-4天。在FACS富集分選前一天將培養基改為BDQY融合瘤培養基。將細胞在10 mL無菌FACS緩衝液中洗滌，然後與生物素標記的重組人LTβR（R&D系統公司（R&D Systems），目錄號：7538LR）以2-5 μg/mL濃度在1 mL反應體積中在4°C下孵育30分鐘。對於收穫5和6融合瘤培養物，在該步驟中還添加100 μg/mL多選殖人IgG（傑克遜免疫研究公司（Jackson ImmunoResearch），目錄號：009-000-003）以阻斷抗Fc結合物。在10 mL FACS緩衝液中洗滌一次後，將1 mL抗體混合物添加到細胞中，該抗體混合物含有各5 μg/mL的Alexa Fluor 488軛合的山羊抗人IgG Fc Fab（傑克遜免疫研究公司，目錄號：109-547-008）和Alexa Fluor 647軛合的鏈黴親和素（傑克遜免疫研究公司，目錄號：016-600-084）。然後將細胞在4°C下孵育30分鐘。孵育後，將細胞在10 mL FACS緩衝液中洗滌，重懸於2 mL含有5 μL 7-AAD（BD Pharmingen公司，目錄號：559925）的BDQY融合瘤培養基中，

然後通過40微米細胞過濾器以去除任何團塊。藉由對Alexa Fluor 488和Alexa Fluor 647螢光訊號雙陽性的活細胞群體進行門控，在BD FACSAria®上對細胞進行批量分選。在第一輪富集分選以使目標群體從< 1%到> 20%之後，將靶細胞單細胞分選到含有BDQY融合瘤培養基的384孔微量滴定板上，並培養長達2週，然後收集上清液進行篩選。

【0387】 4.2 LTβR特異性結合抗體的初始選擇。藉由按照製造商制定的方案使用表現載體、Opti-MEM®培養基(Gibco™，目錄號31985088)和293Fectin™試劑(英傑公司，目錄號12347019)轉染，在宿主人胚胎腎293細胞上表現人LTβR (pTT5.2:VK1O2O12::huLTβR(31-435) C-173003 (DNA-38098))。轉染後二十四小時，每15 μL體積FACS緩衝液(磷酸鹽緩衝鹽水(1X) 0.0067M (PO4)(賽提瓦公司(Cytiva)目錄號:SH30256.02)、2%胎牛血清(海選殖公司(Hyclone)目錄號:SH30396.03)和30 μg/mL的Hoechst核染劑(Hoechst 33342溶液(20 mM)，賽默飛世爾公司(ThermoFisher)目錄號:62249))重懸13000個轉染細胞。將細胞與15 μL融合瘤上清液在室溫下在Corning® 384孔平底透明黑聚苯乙烯TC處理的微孔板中孵育1小時。使用AquaMax 4000平板洗滌機(分子儀器公司(Molecular Devices))用50 μL PBS洗滌細胞兩次。在室溫下以5 μg/mL最終濃度添加到Alexa Fluor 488軛合的AffiniPure山羊抗人IgG(Jackson 109-545-098)，持續20分鐘。用50 μL PBS洗滌細胞兩次以去除未結合的檢測試劑，並添加額外的30 μL FACS緩衝液以用微孔板軌道板振盪器(Big Bear Automation Model HT-91000)重懸細胞。在CellInsight CX7高含量篩選(HCS)平臺上使用Acquire only and Cell Health Profiling Bio-Apps HCS Studio 2.0軟體讀取平板。表16列出了每次收穫的結合物數量。

[表16].每次收穫的LTβR結合物

收穫編號	總共陽性#
2.3	364個天然結合物
3.4	679個天然結合物
4.4	651個天然結合物
5.2	350個天然結合物

【0388】 **4.3 LTβR單點和效力功能測定** 在測定第1天，將人黑色素瘤A375細胞（ATCC，CRL-1619）以10,000個細胞/孔（50 μL）接種在384孔測定板中生長培養基（DMEM，10% FBS，4 mM L-麩醯胺酸，1.5 g/L碳酸氫鈉，4.5 g/L葡萄糖）中。將板在37°C/5% CO2下孵育過夜。在測定第2天，從384孔測定板中取出40 μL/孔的培養上清液。在測定培養基（含有2% FBS的生長培養基）中以最終濃度0.5 μg/mL製備蛋白G（西格瑪公司（Sigma），目錄號P4689）。抗LTβR mAb（R&D系統公司，選殖71315和選殖31G4D8）分別以最終濃度為1 μg/mL和5 μg/mL製備，以1：3向下滴定共8個點。對於單點篩選，添加最終濃度為1 μg/mL的含有抗huLTβR抗體的耗盡上清液（ESN）。在添加或不添加蛋白G作為交聯劑的情況下，將測試樣本轉移到384孔測定板中的所期望的孔中。384孔測定板中的最終總體積為50 μL/孔。將測定板在37°C/5% CO2下孵育過夜。在測定第3天，藉由機器人將16 μL上清液從384孔測定板轉移到384孔低體積板。根據製造商之說明，藉由檢測套組（希思公司（Cisbio），目錄號62IL8PEC）測量趨化因子IL-8釋放，並藉由微孔板讀取器在665 nm和615 nm處讀取。相對IL-8釋放表示為在665 nm/615 nm處獲得的訊號的比率。在沒有蛋白G交聯的情況下表現出低活性，但在蛋白G交聯的情況下表現出高活性的抗體被用於效力測試。

【0389】 對於功能效力篩選，先將ESN歸一化至10 μg/mL，然後在測定培養基中進一步稀釋至最終濃度1 μg/mL，以1：3向下滴定共8個點。抗LTβR抗體的插值EC50、轉運EC50（當訊號=4時）和最大活性（當ENS以1 μg/mL使用時）

藉由Genedata Screener (Smart fit公司) 的四參數邏輯擬合模型確定。LTβR抗體的功能效力分析、Transit EC₅₀和最大活性 (在665 nm/615 nm獲得的訊號比率) 的結果提供於圖5的表A中。

【0390】 4.4 LTβR特異性結合抗體的選擇性和交叉反應性 食蟹猴主要LTβR (pTT5.2:VK1O2O12::cyLTβR (31-253) C173083 (DNA-38100)) 、食蟹猴次要LTβR(pTT5.2:VK1O2O12::cyLTβR_minor (31-434) C173082(DNA-38099)) 、鼠LTβR (pTT5.2:VK1O2O12::muLTβR_native(31-415) - DNA-37605) 、腫瘤壞死受體超家族1 (pTT5:huTNFRp55 (huTNFRSF1) C-159747 - DNA-22292) 和腫瘤壞死受體超家族2 (pTT5:huTNFRp75-FL (TNFRSF2) C-159746 - DNA-22291) 分別藉由按照製造商制定的方案使用表現載體、Opti-MEM®培養基 (Gibco™，目錄號31985088) 和293Fectin™試劑(英傑公司，目錄號12347019) 轉染在宿主HEK 293細胞上表現。藉由在每個轉染細胞上孵育抗體1小時，然後進行兩個洗滌步驟以去除一抗，來篩選融合瘤上清液中是否存在結合cyno主要LTβR、cyno次要LTβR，Mu LTβR、TNFRSF1和TNFRSF2的單株抗體。然後將細胞與軛合於Alexa647 (傑克遜免疫化學 (Jackson Immunochemical) 109-605-098) 的山羊抗人Fc抗體一起孵育15分鐘，並洗滌兩次以去除未結合的檢測試劑。使用Intellicyt公司Accuri iQue™平臺藉由FACS檢測結合。使用Intellicyt公司ForeCyt®企業客戶版軟體進行數據分析。包括使用空pTT5表現載體轉染的HEK 293細胞 (模擬轉染) ，數據呈現為模擬轉染細胞的GeoMean倍數。如圖5的表A所示，LTβR抗體均未表現出與TNFRSF1或TNFRSF2的結合。

【0391】 4.5 相對表位分組/分析。將生物素醃化的重組可溶性人LTβR蛋白Fc嵌合體 (R&D系統公司7538-LR-100) 以2 μg/mL濃度與鏈黴親和素包被的、經獨特條碼編碼的LumAvidin Beads® (LumAvidin Microspheres，路明克斯公司 (Luminex Corp.) ，美國德克薩斯州奧斯丁) 在室溫下在黑暗中偶合30分鐘，並

洗滌兩次。將5 µg/mL濃度的參考抗體融合瘤上清液樣本與抗原包被的珠粒在室溫下在黑暗中孵育1小時，並洗滌三次。將珠粒重懸於含有免疫測定穩定劑溶液（Stabilguard™，舒爾默迪克斯公司（SurModics））的FACS緩衝液中。將抗原包被的參考抗體結合珠粒合併，然後將該等珠粒分到含有歸一化的（2 µg/ml）測試抗體（融合瘤上清液）樣本（或陰性對照）的單個樣本孔中，在室溫下在黑暗中孵育1小時，並洗滌兩次。然後將樣本與Mo抗HuG2、G3、G4（PL-46339，由已停產的卡爾生物化學公司（Calbiochem）HP6030抗體序列製成）在室溫下在黑暗中孵育1小時，並洗滌兩次。將樣本與軛合於Alexa488（傑克遜免疫化學115-545-071）的山羊抗小鼠Fc抗體在室溫下在黑暗中孵育15分鐘，並洗滌兩次以去除未結合的檢測試劑，並重懸於FACS緩衝液中。使用Intellicyt公司iQue™ Screener平臺對樣本進行分析。為了確定各個測試抗體的抗體競爭/結合譜，從每個競爭/結合反應（即整個參考抗體組）的參考抗體加測試抗體訊號中減去僅參考抗體結合訊號。單個抗體結合譜被定義為每個競爭/結合反應的淨結合值的集合。然後藉由計算每個測試抗體譜之間的決定係數來評估單個譜之間的相似程度。然後將顯示彼此高度相似（ $R^2 > 0.8$ ）的測試抗體分組到共同的分組譜中。使用這種方法，將LTβR結合抗體細分為6個獨特的分組譜（A、B、C、D、E和F）。表現出獨特的分組譜（如上文所描述的）但與另一個譜共用相對高度相似（ $R^2 = 0.7-0.8$ ）的抗體被歸類為該譜的子組（即A.1、A.2等）。LTβR抗體的相對表位分組結果如圖5的表A所示。

【0392】 4.6 使用基於單點FACS珠粒的受體-配體測定鑒定LTβR受體-配體非阻斷抗體。藉由按照製造商制定的方案使用Alexa Fluor 647 Microscale蛋白質標記套組（賽默飛世爾科技公司（Thermo Fisher Scientific），目錄號A30009）軛合人LIGHT（R&D系統公司，目錄號664-LI/CF）和人LTα1β2（R&D系統公司，目錄號8884-LY/CF）來製備人LIGHT-Alexa 647和人LTα1β2-Alexa 647。經由基

於FACS的受體-配體測定，測定含有人LT β R結合抗體的融合瘤上清液阻斷人LIGHT和人LT α 1 β 2與人LT β R-His結合的能力。如果LT β R抗體阻止人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647與人LT β R-His結合，則流動式細胞分析術幾何平均值（GeoMean）訊號相對於在不存在LT β R抗體的情況下獲得的GeoMean訊號降低，從而由於競爭而導致配體結合的高百分比抑制值。圖5的表A顯示了選定的融合瘤上清液樣本的受體-配體相互作用阻斷能力，並反映了在指示的融合瘤上清液存在下，人LIGHT或人LT α 1 β 2與人LT β R-His結合的抑制百分比。

【0393】簡言之，在室溫下，將生物素醯化的人LT β R-His在FACS緩衝液[1 x 磷酸鹽緩衝鹽水（賽提瓦公司，目錄號SH30256.02）+ 2%胎牛血清（海選殖公司目錄號SH30396.03）]中的鏈黴親和素（SA）包被的珠粒（Spherotech公司，目錄號SVP-60-5）上捕獲30分鐘。然後將珠粒在FACS緩衝液中藉由在3500 RPM下離心2分鐘洗滌兩次。將包被的珠粒重懸於免疫測定穩定溶液（StabilGuard™舒爾默迪克斯公司，目錄號SG01）中。將人LT β R特異性單株抗體（15 μ L，10 μ g/mL）與15 μ L包被的珠粒混合，使LT β R抗體的最終濃度為5 μ g/mL，並使用96孔V底聚苯乙烯FACS板（康寧公司，目錄號3897）在室溫下孵育1小時。然後將30 μ L人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647以9 μ g/mL添加到FACS緩衝液中，並在室溫下在黑暗中孵育30分鐘。人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647的最終濃度為4.5 μ g/mL。將FACS板加入140 μ L FACS緩衝液，然後在FACS緩衝液中藉由以3500 RPM離心2分鐘洗滌一次。根據製造商之建議，將樣本重懸在30 μ L FACS緩衝液中，並在帶有Intellicyt公司自動進樣器的iQue流式細胞儀上讀取；在Intellicyt公司ForeCyt®企業客戶6.2版（R3）上進行數據分析。

【0394】將人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647的量藉由流動式細胞分析術分析由GeoMean螢光訊號定量，並將該訊號轉換為受體-配體（R-L）相互作用的抑制百分比。在LT β R抗體存在下配體結合訊號的損失計算為R-L結合

的抑制百分比。藉由對12個重複的配體-Alexa 647訊號的GeoMean訊號取平均值來確定人LIGHT-Alexa 647或人LTα1β2-Alexa 647的最大GeoMean訊號，該等重複與結合了生物素醯化的人LTβR-His的不相關耗盡上清液（ESN）一起孵育。人LIGHT-Alexa 647或人LTα1β2-Alexa 647的最小GeoMean訊號係從與結合了不相關的生物素醯化的人TREM1-His的不相關的人IgG2對照一起孵育的配體-Alexa 647訊號的GeoMean訊號確定的。使用以下等式計算人LTβR抗體或同種型對照抗體對生物素醯化的人LTβR-His：配體（人LIGHT或人LTα1β2）的抑制百分比：

抑制百分比（%）= 1-（實驗GeoMean-最小GeoMean）/（最大GeoMean-最小GeoMean）

對於一些LTβR抗體，當實驗GeoMean訊號高於最大GeoMean訊號時，獲得了負抑制百分比值，這可能是由於LTβR抗體與生物素醯化的人LTβR-His結合的確認性變化，從而可能導致更高的配體-Alexa 647 GeoMean訊號（即，允許更高水平的內源性配體結合）。使用不相關的ESN不會看到任何潛在的確認性變化，因為不相關的抗體不會與生物素醯化的人LTβR-His結合。

【0395】 由於使用不相關的樣本代替ESN來確定測定的最小訊號，發現該測定中的背景訊號對於LIGHT高達約20%，以及對於LTα1β2高達約15%。從該最小值中減去ESN樣本以確定淨測定訊號，從而計算抑制%。由於背景水平高，因此經由該測定表現出約20%抑制的LTβR抗體經由該基於細胞的測定被認為是非阻斷物。開發實例8中描述的基於細胞的測定，以確定LTβR抗體的非阻斷活性。

【0396】 4.7 親和力差距分析。親和力係在通用電氣醫療公司（GE Healthcare）的BIAcore® 3000上測量的。實驗在25°C下進行。運行緩衝液為補充有0.5% BSA的HBS-P（10 mM HEPES，pH 7.4，150 mM NaCl，0.05%界面活性劑P-20；賽提瓦公司目錄號BR100827），並且動力學以高流速（100 μl/min）進行。使用pH 1.7的10 mM甘胺酸進行再生。將小鼠抗人抗體在10 nM乙酸鈉（pH

5) 中稀釋至0.065 mg/mL，並使用胺偶合試劑（賽提瓦公司目錄號BR100050）共價偶合至CM5感測器晶片（賽提瓦公司目錄號29104988）的樣本和參考流動池（Fc1）。將未純化的抗LTβR mAb在HBS-P中稀釋至1 μg/ml，並在流動池2、3或4上捕獲，以獲得100 RU - 200 RU的捕獲水平。Fc1用作參考。將靶標（人或cyno LTβR）作為分析物以150 nM、50 nM、16.7 nM、5.6 nM和1.85 nM進樣，其50 nM濃度運行兩次以測量再現性。解離時間為10分鐘，以允許篩選大抗體組。數據係雙重背景參考，因為從數據中減去了參考Fc和0 nM分析物濃度。在BIAcore®評估軟體中使用1:1朗格繆爾傳質結合模型來分析數據。人和cyno主要的結果顯示在圖5的表B中。

【0397】 4.8 LTβR促效劑抗體的分子拯救和定序。使用Qiagen RNeasy微型套組或Invitrogen mRNA catcher plus套組，從含有產生促效劑LTβR抗體的融合瘤細胞的孔中純化出RNA（總RNA或mRNA）。經純化的RNA用於使用經由逆轉錄的cDNA合成、接著聚合酶鏈反應（RT-PCR）來擴增抗體重鏈和輕鏈可變區（V）基因。使用Qiagen單步逆轉錄酶PCR套組（凱傑公司（Qiagen））獲得完全人抗體γ重鏈。此方法用於自RNA模板產生第一鏈cDNA，接著使用多重PCR擴增γ重鏈的可變區。將5'γ鏈特異性引物與抗體重鏈的訊息序列退火，而3'引物與γ恒定結構域的區域退火。使用Qiagen單步逆轉錄酶PCR套組（凱傑公司）獲得完全人κ和λ輕鏈。該方法用於自RNA模板產生第一鏈cDNA，接著使用多重PCR擴增輕鏈的可變區。將5'輕鏈特異性引物與抗體輕鏈的訊息序列退火，而3'引物與輕鏈的恒定區退火。

【0398】 使用核酸外切酶I和鹼性磷酸酶以酶法純化擴增的cDNA並對純化的PCR產物直接定序。通過生物資訊學方法，自對應核酸序列推導出胺基酸序列。各融合瘤樣本完成兩次另外的獨立的RT-PCR擴增和定序循環，以證實觀察到的任何突變並非PCR的結果。接著分析衍生的胺基酸序列，以確定抗體的種系

序列起源，且鑒別與種系序列的偏差。

實例5：LTβR抗體工程化

【0399】藉由將VH結構域與CH1-CH2-CH3序列融合並將VL結構域與到CL或CK序列融合，將選定的抗LTβR抗體轉化為IgG1亞型的標準抗體形式。該抗體同種型的CH2結構域藉由引入N297G突變被工程化以降低效應子功能，並藉由工程化的二硫鍵（R292C，V302C）以提高熱穩定性；該抗體同種型被命名為SEFL2.2。

【0400】對抗LTβR抗體進行另外工程化，以去除通過計算預測或經驗確定會影響分子表現、純化、均一性、熱穩定性、膠體穩定性、長期儲存穩定性、體內藥物動力學和/或免疫性的「熱點」或殘基。可變重鏈（VH）和可變輕鏈（VL）結構域中該等熱點的各種胺基酸突變係基於保守性、共變異性、化學相似性、結構建模的預測以及來自其他抗體工程活動的先驗知識設計的。設計的工程化的抗體包括單一突變和突變組合兩者。表17（下文）提供了引入LTβR抗體亞群的單個和組合突變以及工程化抗體的結合親和力（KD）的總結。所鑒定的取代的位置相對於源自以下的參考序列：Honegger和Pluckthun,「Yet Another Numbering Scheme for Immunoglobulin Variable Domains: An Automatic Modeling and Analysis Tool[免疫球蛋白可變結構域的又另一種編號方案：自動建模和分析工具],」 *J. Mol. Biol.* [分子生物學雜誌] 309: 657-670 (2001)，特此藉由引用將其全部併入。

[表17]. LTβR抗體熱點工程化

BioReg ID	Fab描述	親本	KD (nM)
huLTβR LIBC218979 (19319 -- 23E9)		X	11.43723782
26985-1	VH:D61E_D72Q_S90Y,VL:R16G_N111I_M137V		弱
26986-1	VH:D61E_D72Q_S90Y,VL:R16G		弱
26988-1	VH:D61E_S90Y,VL:R16G		弱
26990-1	VH:D61L_S90Y,VL:R16G		弱

BioReg ID	Fab描述	親本	KD (nM)
26991-1	VH:D72Q_S90Y,VL:R16G		15.43514472
26992-1	VH:D72V_S90Y,VL:R16G		16.40551694
26993-1	VH:G65A_D72Q_S90Y_R110T,VL:R16G_N111I_M137V		弱
26995-1	VH:G65A_S90Y,VL:R16G		19.79679887
26998-1	VH:G65L_S90Y,VL:R16G		弱
26999-1	VH:S90Y,VL:R16G_M137I		31.04580415
27000-1	VH:S90Y,VL:R16G_M137V		28.00773125
27001-1	VH:S90Y,VL:R16G_N111I		15.01961755
27002-1	VH:S90Y,VL:R16G_N111L		17.30011157
27003-1	VH:S90Y,VL:R16G		16.07352296
27004-1	VL:R16G		12.2143522
huLTβR LIBC218990 (19320 -- 30H1)		X	3.27501537
27006-1	VH:F148S,VL:M56I		5.202407838
27007-1	VH:K72Q_F148S,VL:M56I		9.410228152
27008-1	VH:K72V_F148S,VL:M56I		9.144188517
27009-1	VH:N61Q_F148S,VL:M56I		5.399789949
27010-1	VH:N61Q_K72Q_F148S,VL:M56I		11.09048764
27011-1	VH:N61Q_K72V_F148S,VL:M56I		7.958937509
27012-1	VL:M56I		4.505336548
huLTβR LIBC218994 (19321 -- 31A3)		X	0.403443251
27014-1	VH:A110G_D61E_D72E_V96L,VL:K69I		4.696555145
27015-1	VH:A110G_D61E_D72E_V96L,VL:K69L_R70I		2.591425519
27016-1	VH:A110G_D61E_D72E_V96L,VL:R70I		3.627320222
27017-1	VH:A110G_D61E_D72E_V96L,VL:R70V		3.662808057
27018-1	VH:A110G_D61E_D72E_V96L		3.360797418
27019-1	VH:A110G_D61E_D72T_V96L,VL:K69I_R70V		4.328156944
27020-1	VH:A110G_D61E_D72T_V96L,VL:K69L		4.58220395
27021-1	VH:A110G_D61E_D72T_V96L,VL:R70L		3.275583582
27022-1	VH:A110G_D61E_D72T_V96L,VL:R70V		3.509973423
27023-1	VH:A110G_D61E_D72T_V96L		3.500158829
27024-1	VH:A110G_D61E_S73L_V96L		2.941727972

BioReg ID	Fab描述	親本	KD (nM)
27025-1	VH:A110G_G65A_D72E_V96L		0.284150703
27026-1	VH:A110G_G65A_D72T_V96L		0.381976978
27027-1	VH:A11G_G65A_S73L_V96L		0.336655454
27028-1	VH:A110G_V96L,VL:W109I		0.212721493
27029-1	VH:A110G_V96L,VL:W109Q		0.161329478
27030-1	VH:V96L		0.318844229
huLTβR LIBC219037 (19322 -- 34D1)		X	0.190412769
27032-1	VH:L89F_A143T		0.404416306
27033-1	VH:R12L_V51G_L89F_A143T		0.367707031
27034-1	VH:R12L_V51G_L89F_N94S_A143T		0.516807652
huLTβR LIBC219051 (19323 -- 35F5)		X	0.684584722
27036-1	VH:C70Y_I97R,VL:D35E_R144K		5.471490372
27037-1	VH:C70Y_I97R,VL:D35V_R144K		1.935658966
27038-1	VH:C70Y_I97R,VL:G37A_R144K		2.006767197
27039-1	VH:C70Y_I97R,VL:R144K		0.795696731
27040-1	VH:C70Y_I97R		0.293820496
huLTβR LIBC219058 (19324 -- 36G2)		X	0.326818905
27042-1	VH:K14Q_R110I,VL:L97Q		0.296413116
27043-1	VH:K14Q_R110I,VL:N53K_L97Q		0.300532627
27044-1	VH:K14Q,VL:L97Q		0.235652803
27045-1	VH:K14Q,VL:N53K_L97Q		0.247290188
27046-1	VH:R110I,VL:L97Q		0.354185514
27047-1	VL:L97Q		0.2950519
huLTβR LIBC219081 (19325 -- 41B2)		X	0.580223924
27049-1	VH:I79T,VL:H39Q_S111A		1.286345586
27050-1	VH:I79T,VL:H39Q_S111I		1.459335319
27051-1	VH:I79T,VL:H39Q		1.294832574
27052-1	VH:I79T,VL:N33E_S111A		1.092138935
27053-1	VH:I79T,VL:N33E_S111I		0.990274196
27054-1	VH:I79T,VL:N33E		1.648852277
27055-1	VH:I79T,VL:N33Q_S111A		0.938002565

BioReg ID	Fab描述	親本	KD (nM)
27056-1	VH:I79T,VL:N33Q_S111I		0.771084585
27057-1	VH:I79T,VL:N33Q		0.699522384
27058-1	VH:I79T,VL:S111A		0.738710315
27059-1	VH:I79T,VL:S111I		0.600474948
27060-1	VH:I79T		0.788530019
huLTβR LIBC219097 (19326 -- 43D9)		X	12.00579103
27062-1	VH:I78F_D84N_S85A_T98A		12.13646339
27063-1	VH:I78F		14.0569778
huLTβR LIBC219098 (19327 -- 44B1)		X	3.005941052
27065-1	VH:D134E,VL:C25S		32.43914293
27066-1	VH:D134E,VL:S18P_C25S		178.166033
27067-1	VH:G135V,VL:C25S		37.5613709
27068-1	VH:G135V,VL:S18P_C25S		17.72182401
27069-1	VL:C25S		0.330403122
27070-1	VL:S18P_C25S		0.323484073
27071-1	VL:N53K_L97Q		0.311045523

實例6：LTβR促效劑抗體的表位和互補位作圖

【0401】 6.1 氫/氬交換（HDX）質譜（MS）。使用HDX MS進行選擇促效劑LTβR抗體的表位和互補位作圖。HDX MS測量蛋白質骨架醯胺氫的氬交換率。HDX MS實驗使用Twin HTS PAL HDX系統（LEAP技術公司（LEAP Technologies），北卡羅來納州卡勃羅）進行，該系統被配置為在胃蛋白酶柱上進行線上消化，並與Orbitrap質譜儀（Elite，賽默飛世爾科技公司，加利福尼亞州聖約瑟）介面，如前文所描述（參見例如，Chalmers等人, *Anal. Chem.*[分析化學] 78: 1005-1014 (2006)和Zhang等人, *Structure*[結構] 18: 1332-1341 (2010)，特此藉由引用將其全部併入）或Twin HTS PAL HDX系統，該系統被配置為進行溶液內消化，並與Orbitrap Eclipse質譜儀（賽默飛世爾科技公司，加利福尼亞州聖約

瑟) 介面, 其方式類似於先前所述 (Zhang 等人, *Anal. Chem.*[分析化學] 84(11):4942-4949 (2012), 特此藉由引用將其全部併入)。

【0402】 6.1.1 使用具有柱上消化的Twin HTS PAL HDX系統 (「系統1」)
進行HDX MS實驗: 用於LT β R抗體 (LIBC218990、LIBC218944、LIBC219058、LIBC219081和LIBC219097) 的表位/互補位作圖的HDX反應分別在三個條件下進行: 分別是僅LT β R胞外結構域 (ECD) 抗原、LT β R ECD/抗體結構域複合物和僅抗體Fab。考慮到LT β R和評估的抗體具有 k_D 在低nM範圍內的高結合親和力, 並且結合比為2:1, 藉由分別以約20 μ M和約10 μ M的最終濃度預孵育LT β R與抗體, 可以容易地形成LT β R/抗體複合物。H/D交換反應藉由在25°C下如所指示的用10 mM乙酸鹽的D₂O (pD 5.2) 將蛋白質樣本5倍稀釋預定時間 (10 s、1 min、10 min、1 h、4 h和12 h) 來激活。藉由與冰冷的200 mM磷酸鈉、4 M鹽酸胍、0.5 M三(2-羧乙基)膦 (TCEP) 在pH 2.4下1:1混合來淬滅交換反應。將淬滅的蛋白質混合物以200 μ L/min的流速通過定制填充的2 mm $\times$ 2 cm胃蛋白酶 (世爾科技公司 (Fisher Scientific), 賓夕法尼亞州匹茲堡) 柱 (安捷倫技術公司 (Agilent Technologies), 加利福尼亞州聖克拉拉)。在2 mm $\times$ 1 cm C18捕獲柱 (沃特斯公司 (Waters Corporation), 麻塞諸塞州米爾福德) 上捕獲消化的肽, 並以0.2 mL/min的流速脫鹽3分鐘。然後藉由使用2.1 mm $\times$ 5 cm C18柱 (1.9 μ m Hypersil Gold; 賽默飛世爾科技公司, 麻塞諸塞州沃爾瑟姆), 9.5分鐘線性梯度的5%-40%乙腈的0.1%甲酸溶液, 以0.2 mL/min的流速來分離肽。蛋白質消化和肽分離在保持在1°C下的熱室中進行, 以減少反向交換。對於m/z 400的離子, 以60,000的品質分辨能力獲得LC-MS數據。每個實驗都一式兩份進行, 以提供對變化的估計。

【0403】 串聯質譜 (MS/MS) 實驗在與如上文描述的相同的條件下進行。在數據依賴性模式下獲取產物離子光譜, 並選擇10個最豐富的離子進行產物離子分析。所有數據均使用軟體MassAnalyzer (Zhang 等人, *Anal. Chem.*[分析化學]

84: 4942-4949 (2012), 特此藉由引用將其全部併入) 處理, 用於肽鑒定和氘水平計算。分析了大約500個肽, 所有mAb2多肽鏈的序列覆蓋率為至少97%。將所有HDX-MS數據歸一化為100%氘濃度, 並用Prism v 6.02 (圖形軟體公司 (GraphPad Software), 加利福尼亞州拉荷亞) 以對數標度繪製針對標記時間的氘摻入百分比。

【0404】 6.1.2 使用具有溶液內消化的Twin HTS PAL HDX系統 (「系統2」) 進行HDX MS實驗：對於互補位作圖, 藉由將抗體Fab結構域與過量 (1.5倍) 的LTβR胞外結構域 (ECD) 抗原孵育形成LTβR/抗體複合物, 並與游離抗體Fab結構域並行分析。藉由將每個樣本在D₂O中的100 mM磷酸鹽緩衝液中稀釋10倍來開始氘標記。在一定長度的標記時間 (6次標記時間, 從15 s到2 h, 每次至少一式兩份) 後, 藉由在1°C下在含有0.625 M三(2-羧乙基)膦 (TCEP) 和約5.8 M尿素的淬滅/變性緩衝液 (pH 2.7) 中稀釋4倍來淬滅標記。然後將胃蛋白酶添加到淬滅的溶液中, 然後在1°C下注入樣本環路中, 並在環路線上切換用於梯度洗脫之前進行6 min消化延遲。在1°C下在1 mm×5 cm C18柱 (Waters CSH, 1.7 μM) 上, 用9.5分鐘線性梯度的5%-40%乙腈的在0.035%三氟乙酸 (TFA)、0.1%甲酸溶液, 以0.2 mL/min的流速來分離肽。三種肽, 包括緩激肽、血管收縮素和白胺酸腦啡肽, 用作內標來校正反向交換。

【0405】 對於表位作圖, 藉由將LTβR ECD抗原與過量 (1.5倍) 的每種抗體Fab一起孵育形成LTβR/抗體複合物, 並與游離抗原並行分析。H/D交換標記和消化以與如上文所描述的相同的方式進行, 不同之處在於使用1:1胃蛋白酶/XIII型蛋白酶混合物進行消化, 並且在注入樣本回路之前, 在約7°C下進行消化6 min, 這是因為使用標準條件難以用胃蛋白酶消化LTβR ECD。

【0406】 所有MS數據均為在賽默飛世爾科技公司Orbitrap Eclipse高解析度質譜儀上收集的, 該質譜儀具有電灑游離介面。在120k解析度設置下收集MS

數據。對於每個互補位或表位實驗，還從兩個未標記的樣本（游離和複合物）中的每一個中收集三次注射的數據依賴性MS/MS，用於肽鑒定。

【0407】所有數據均在軟體MassAnalyzer上處理，用於肽鑒定、氘水平計算、使用內標的反向交換校正和全氘化對照（Zhang等人, *Anal. Chem.* [分析化學] 84(11):4942-4949 (2012)，特此藉由引用將其全部併入）。

【0408】 **6.2 表位作圖結果**。表位作圖實驗的結果提供在圖4-8中。來源於單獨LT β R和與抗體複合的LT β R的肽之氘交換圖的比較鑒定了被檢測抗體結合的表位區域，其中被抗體結合的LT β R區域受到保護免於氘交換。應注意的是，肽的N-末端殘基不具有用於測量的醯胺氫，並且在報告表位區域時被排除在外。如圖6和8中所示，LT β R抗體LIBC218990-1（19320）和LIBC219058（19324）與LT β R的CRD2內的殘基結合，如由LT β R ECD（SEQ ID NO: 4）的胺基酸殘基56-64和81-101組成的複合肽中存在的氘的減少所示。因此，LIBC218990-1的表位和LIBC219058的表位包含SYNEHWNY（SEQ ID NO: 4的殘基57-64）的胺基酸序列內的一或多個殘基和EIAPCTSKRKTQCRCQPGMF（SEQ ID NO: 4的殘基82-101）的胺基酸序列內的一或多個殘基。LT β R：LT β R-抗體複合物的其他區域沒有受到保護免於氘交換（數據未顯示）。

【0409】LT β R抗體LIBC218994（19321）結合CRD1內的殘基，特別是LT β R ECD（SEQ ID NO: 4）的殘基4-9、21-29和39-47內的一或多個殘基（參見圖7）。因此，LIBC218944的表位包含PPYASE（SEQ ID NO: 4的殘基4-9）、YEPQHRICC（SEQ ID NO: 4的殘基21-29）和SAKCSRIRD（SEQ ID NO: 4的殘基39-47）的胺基酸序列內的一或多個殘基。LT β R：LT β R-抗體複合物的其他區域沒有受到保護免於氘交換（數據未顯示）。

【0410】LT β R抗體LIBC219081（19325）結合CRD4內的殘基，特別是LT β R ECD（SEQ ID NO: 4）的位置168-179處的殘基片段內的殘基（參見圖9）。因此，

LIBC219081的表位包含EAAPGTAQSDDT (SEQ ID NO: 4的殘基168-179) 的胺基酸序列內的一或多個殘基。LT β R: LT β R-抗體複合物的其他區域沒有受到保護免於氘交換 (數據未顯示)。

【0411】 LT β R抗體LIBC219097 (19326) 結合跨越CRD1和CRD2的LT β R區域, 該區域包含LT β R ECD (SEQ ID NO: 4) 的39-42和57-70區域中的殘基 (參見圖10)。包含殘基38-42和殘基37-47的肽之氘攝取曲線的比較顯示了, 殘基38-42的較短肽具有相對大的保護而免於氘交換, 而較長肽37-47具有相對小的保護。這表明保護主要發生在重疊的較短肽中, 因此將表位區域縮小到LT β R ECD的殘基39-42。因此, LIBC219097的表位包含SAKC (SEQ ID NO: 4的殘基39-42) 和SYNEHWNYLTICQL (SEQ ID NO: 4的殘基57-70) 的胺基酸序列內的一或多個殘基。LT β R: LT β R-抗體複合物的其他區域沒有受到保護免於氘交換 (數據未顯示)。

【0412】 LT β R抗體LIBC218979 (19319) 與LT β R ECD (SEQ ID NO: 4) 的CRD4內的LT β R殘基結合。LIBC218979與LT β R ECD結合後, LT β R肽167-177和167-181中的氘攝取減少, 但肽154-166和178-193中沒有, 這表明保護區在殘基168-178內 (圖11)。LT β R: LT β R-抗體複合物的其他區域沒有受到保護免於氘交換 (數據未顯示)。因此, 表位包含EAAPGTAQSDDT (SEQ ID NO: 4的殘基168-179) 的胺基酸序列內的一或多個殘基。

【0413】 LT β R抗體LIBC219051 (19323) 與包括CRD1在內的LT β R ECD的N末端區域結合。LIBC219051與LT β R ECD結合後, LT β R肽1-9、1-20和10-20中的氘攝取減少, 但肽19-28中沒有, 這表明保護區在殘基1-19內 (圖12)。LT β R: LT β R-抗體複合物的其他區域沒有受到保護免於氘交換 (數據未顯示)。因此, 表位包含QAVPPYASENQTCRDQEKE (SEQ ID NO: 4的殘基1-19) 的胺基酸序列內的一或多個殘基。應注意的是, Q1已轉換為pyro-E, 其含有可測量的醯胺氫。

數據還表明，結合與殘基N10上的糖基化狀態無關。

【0414】 6.3 互補位作圖結果。互補位作圖實驗的結果提供在圖13-19中。與表位作圖類似，來源於未結合和LT β R結合抗體的重鏈和輕鏈可變結構域肽中氘攝取的比較用於鑒定所檢測抗體的互補位區域。與未結合抗體相比，結合抗體的肽區域內氘攝取的減少表明所檢測肽的至少一些區域參與結合相互作用。如上文所述，所檢測肽的N末端殘基不具有用於測量的醯胺氘，因此在報告互補位區域時被排除在外。因為這種方法檢測微抗體衍生肽（而不是單個殘基）中的氘交換，所以互補位的解析不在殘基水平上。然而，該方法可以可靠地鑒定不參與結合相互作用的殘基片段。

【0415】圖13顯示了來源於未結合和結合的LT β R抗體LIBC218990（19320）的肽之一系列氘攝取圖。受到保護免於氘交換的結合抗體（即抗體-LT β R複合物）的肽在圖底部的相應重鏈和輕鏈可變序列中進行鑒定（參見加框殘基）。每個可變區序列內的CDR位置加下劃線。由SEQ ID NO: 644的殘基27-34組成的重鏈肽的氘攝取圖顯示沒有免於氘攝取。該重鏈肽跨越HCDR1殘基31-35，表明LIBC218990的HCDR1不參與同LT β R的結合相互作用。類似地，SEQ ID NO: 645的殘基50-70的複合輕鏈肽中的氘攝取也顯示沒有免於氘攝取。該輕鏈肽跨越LCDR2殘基51-57，表明LIBC218990的LCDR2也不參與該抗體與LT β R的結合相互作用。

【0416】LIBC218990的HCDR2包含SEQ ID NO: 644的殘基50-66。然而，只有該HCDR2區域的前半部分內的殘基參與結合相互作用（即，殘基51-59），如在SEQ ID NO: 644的殘基50-59的複合重鏈肽中觀察到的受到保護免於氘交換和在殘基60-66的複合重鏈肽中觀察不到的缺乏保護所示（圖13）。類似地，雖然LIBC218990的LCDR1跨越VL殘基24-35（SEQ ID NO: 645），但基於與該區域重疊的肽之氘攝取，僅SEQ ID NO: 645的殘基29-33似乎參與LCDR1與LT β R的相

互作用(圖13)。在LIBC218990的HCDR3和LCDR3區域中檢測的肽包括各自CDR區域的一端或兩端的框架區。雖然該等框架殘基已被包括在加框區域中，但它們參與結合相互作用不能使用這種方法來解決。

【0417】類似於LIBC218990，LIBC219058(19324)(圖15)和LIBC219097(19326)(圖17)的互補位定位顯示了，並非該等抗體的所有六個CDR都參與了該等各自抗體與LT β R之間的結合相互作用。特別地，對於LIBC219058(圖15)，由SEQ ID NO: 649的殘基23-33組成的VL的複合肽沒有受到保護免於氘交換，這表明LCDR1不參與同LT β R的相互作用。同樣，由SEQ ID NO: 649的殘基87-116和107-116組成的VL的複合肽也顯示出沒有受到保護免於氘交換，這表明LCDR3不參與抗體與LT β R的結合。對於LIBC219097(圖17)，由SEQ ID NO: 650的殘基47-61和62-75組成的VH的複合肽沒有受到保護免於氘交換，這表明HCDR2不參與抗體與LT β R的相互作用(圖17A)。類似地，由SEQ ID NO: 651的殘基87-112組成的複合VL肽沒有受到保護免於氘交換，這表明LIBC219097的LCDR3不參與同LT β R的結合(圖17B)。

【0418】圖14和16顯示了來源於未結合和結合的LT β R抗體LIBC218994(19321)(圖14A-14B)和LT β R抗體LIBC219081(19325)(圖16A-16B)的肽之氘攝取圖。受到保護免於氘交換的結合抗體(即抗體-LT β R複合物)的肽在每個圖底部的相應重鏈和輕鏈可變序列中進行鑒定(參見加框殘基)。每個可變區序列內的CDR位置加下劃線。與LIBC218990、LIBC219058和LIBC219097相比，LIBC218994和LIBC219081抗體的互補位作圖顯示，三個VH和VL CDR中的每一個內的殘基都參與了與LT β R的結合相互作用。在一些情況下，當多個肽覆蓋CDR區域時，還鑒定了不參與結合相互作用的特定CDR中的殘基。參見例如SEQ ID NO: 646的VH肽48-57和58-68的圖(圖14A)，其顯示HCDR2的殘基49-57而非58-66參與LIBC218994與LT β R的結合相互作用。還參見SEQ ID NO: 121的VH

肽49-59和60-68的圖（圖16A），其顯示HCDR2的殘基50-59而非60-66參與LIBC219081與LTβR的結合相互作用。

【0419】圖18A-18B顯示了來源於未結合和結合的LTβR抗體LIBC218979（19319）的肽之氘攝取圖。受到保護免於氘交換的結合抗體（即抗體-LTβR複合物）的肽在每個圖底部的相應重鏈（圖18A）和輕鏈（圖18B）可變序列中進行鑒定（參見加框殘基）。每個可變區序列內的CDR位置加下劃線。氘攝取圖的分析表明，LIBC218979的三個VH和VL CDR中的每一個內的殘基都參與了與LTβR的結合相互作用。

【0420】圖19A-19B顯示了來源於未結合和結合的LTβR抗體LIBC219051（19323）的肽之氘攝取圖。受到保護免於氘交換的結合抗體（即抗體-LTβR複合物）的肽在每個圖底部的相應重鏈（圖19A）和輕鏈（圖19B）可變序列中進行鑒定（參見加框殘基）。每個可變區序列內的CDR位置加下劃線。氘攝取圖的分析表明，LIBC219051的三個VH和VL CDR中的每一個內的殘基都參與了與LTβR的結合相互作用。

【0421】基於互補位定位和熱點工程化，對LTβR結合相互作用重要的LTβR抗體LBC218990、LIBC218994、LIBC219058、LIBC219081、LIBC219097、LIBC218979、LIBC219098和LIBC219051的CDR殘基總結在下表16-22中。未被鑒定為參與或對LTβR結合相互作用至關重要的抗體的CDR殘基（在表16-22的CDR序列中被鑒定為「X」）可以被任何胺基酸殘基、保守胺基酸取代或熱點補救的胺基酸殘基取代，如下表18-25中的每一個所鑒定的。

表18.LTβR抗體LIBC218990（19320/30H1）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
GDYMY *基於HDX分析不 是互補位的一部分	475	WINPX ₅ SGGTNX ₁₁ -X ₁₇ X ₅ 和X ₁₁ -X ₁₇ 獨立地選自任何 胺基酸殘基	499	EGSSGWSAEYX ₁₁ X ₁₂ X ₁₃ X ₁₁ -X ₁₃ 獨立地選自任何 胺基酸殘基	529

		WINPX ₅ SGGTNX ₁₁ -X ₁₇ X ₅ 為N、G、D、E、T、S、 R、K、Q、H，較佳的是N 或Q X ₁₁ 為Y、H、M、I、L、 F、W X ₁₂ 為A、G、S、T、V X ₁₃ 為K、D、E、N、Q、 R、V，較佳的是K、V或Q X ₁₄ 為K、D、E、N、Q、R X ₁₅ 為F、M、V、I、L、 W、Y X ₁₆ 為Q、D、E、N、H、 M、S、R、K X ₁₇ 為G、A、S、N X ₅ 和X ₁₃ 各自係如上表17中 針對該抗體所定義的熱點殘 基（即N61和K72）。	500	EGSSGWSAEYX ₁₁ X ₁₂ X ₁₃ X ₁₁ 為F、M、V、I、L、 W、Y X ₁₂ 為Q、D、E、N、H、 M、S、R、K X ₁₃ 為H、D、E、N、 M、R、Q	530
		WINPNSGGTNYAKKFQG	501	EGSSGWSAEYFQH	531
LCDR1	ID	LCDR2	ID	LCDR3	ID
X ₁ X ₂ X ₃ X ₄ SVSSSFX ₁₁ X ₁₂ X ₁ -X ₄ 和X ₁₁ -X ₁₂ 獨立 地選自任何胺基酸 殘基	559	GASRRAT *基於HDX分析不是互補位 的一部分	590	QQYGTSPLS	619
X ₁ X ₂ X ₃ X ₄ SVSSSFX ₁₁ X ₁₂ X ₁ 為R、E、N、 H、Q、K X ₂ 為A、G、S、 T、V	560				

X ₃ 為S、G、D、 E、N、Q、A、T X ₄ 為Q、D、E、 N、H、M、S、 R、K X ₁₁ 為L、M、V、 I、Y、F X ₁₂ 為A、G、S、 T、V				
RASQSVSSSFLA	561			

[表19]. LTβR抗體LIBC218994（19321/31A3）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
SYX ₃ X ₄ X ₅ X ₃ 、X ₄ 和X ₅ 獨立地選 自任何胺基酸殘基	476	IIWYX ₅ X ₆ SDX ₉ -X ₁₇ X ₅ 、X ₆ 和X ₉ -X ₁₇ 獨立地選自 任何胺基酸殘基	502	GDSEDFYYYDX ₁₁ X ₁₂ X ₁₃ X ₁₁ -X ₁₃ 獨立地選自任何 胺基酸殘基	532
SYX ₃ X ₄ X ₅ X ₃ 為G、A、S、N X ₄ 為M、H、Q、Y、 F、L、I、V X ₅ 為H、D、E、N、 M、R、Q	477	IIWYX ₅ X ₆ SDX ₉ -X ₁₇ X ₅ 為D、S、K、Q、H、N 或E，較佳的是D或E X ₆ 為G、S、N或A，較佳的 是G或A X ₉ 為E、P、D、S、R、K、 Q、H、N X ₁₀ 為Y、H、M、I、L、 F、W X ₁₁ 為Y、H、M、I、L、 F、W X ₁₂ 為A、G、S、T、V X ₁₃ 為D、S、K、Q、H、	503	GDSEDFYYYDX ₁₁ X ₁₂ X ₁₃ X ₁₁ 為F、M、V、I、L、 W、Y X ₁₂ 為D、S、K、Q、H、 N、E X ₁₃ 為V、T、A、 M、F、L、I	533

		N、E、T，較佳的是D、E或T X₁₄為S、G、D、E、N、Q、A、T、L，較佳的是S或L X₁₅為V、T、A、M、F、L、I X₁₆為K、D、E、N、Q、R X₁₇為G、A、S、N X₅、X₆、X₁₃和X₁₄各自係如上表17中針對該抗體所定義的熱點殘基（即D61、G65、D72和S73）。			
SYGMH	478	IIWYDGSDEYYADSVKG	504	GDSEDFYYYDFDV	534
LCDR1	ID	LCDR2	ID	LCDR3	ID
SGSSSNIGKNX ₁₁ X ₁₂ X ₁₃ X ₁₁ -X ₁₃ 各自獨立地選自任何胺基酸殘基	562	DNNX ₄ X ₅ PS X ₄ 和X ₅ 為任何胺基酸	591	X ₁ X ₂ X ₃ DHSLSASX ₁₁ X ₁₂ X ₁ -X ₃ 、X ₁₁ 和X ₁₂ 各自獨立地選自任何胺基酸殘基	620
SGSSSNIGKNX ₁₁ X ₁₂ X ₁₃ X ₁₁ 為Y、H、M、I、L、F、W X ₁₂ 為V、T、A、M、F、L、I X ₁₃ 為S、G、D、E、N、Q、A、T	563	DNNX ₄ X ₅ PS X ₄ 為K、D、E、N、Q、R、I、L，較佳的是K、I或L X ₅ 為R、E、N、H、Q、K、V、L、I，較佳的是R、V、L或I X ₄ 和X ₅ 各自係如上表17中針對該抗體所定義的熱點殘基（即K69和R70）。	592	X ₁ X ₂ X ₃ DHSLSASX ₁₁ X ₁₂ X ₁ 為G、A、S、N X ₂ 為T、N、S、V、A X ₃ 為W、F、Y、Q、I，較佳的是W、Q或I X ₁₁ 為Y、H、M、I、L、F、W X ₁₂ 為V、T、A、M、F、L、I X ₃ 係如上表17中針對該抗體所定義的熱點殘基（即W109）。	621

SGSSSNIGKNYVS	564	DNNKRPS	593	GTWDHSLSASYV	622
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[表20]. LTβR抗體LIBC219058（19324/36G2）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
TSGMN	479	SVSSSGSYX ₉ -X ₁₇ X ₉ -X ₁₇ 中每一個獨立地選自任何胺基酸殘基	505	AX ₂ YNWHFDASX ₁₁ X ₁₂	535
		SVSSSGSYX ₉ -X ₁₇ X ₉ 為I、M、V、Y、F、L X ₁₀ 為Y、H、M、I、L、F、W X ₁₁ 為Y、H、M、I、L、F、W X ₁₂ 為A、G、S、T、V X ₁₃ 為D、S、K、Q、H、N、E X ₁₄ 為S、G、D、E、N、Q、A、T X ₁₅ 為V、T、A、M、F、L、I X ₁₆ 為K、D、E、N、Q、R X ₁₇ 為G、A、S、N	506	AX ₂ YNWHFDASX ₁₁ X ₁₂ X ₂ 為R、E、N、H、Q、K或I，較佳的是R或I X ₁₁ 為D、S、K、Q、H、N、E X ₁₂ 為I、M、V、Y、F、L X ₂ 係如上表17中針對該抗體所定義的熱點殘基（即R110）。	536
		SVSSSGSYIYYADSVKG	507	ARYNWHFDASDI	537
LCDR1	ID	LCDR2	ID	LCDR3	ID
RASQSISSDLN *基於HDX分析不是互補位的一部分	565	AASSLX ₆ X ₇ X ₆ 和X ₇ 各自為任何胺基酸殘基	594	QQSYNTPLT *基於HDX分析不是互補位的一部分	623
		AASSLX ₆ X ₇ X ₆ 為H、D、E、N、M、R、Q X ₇ 為S、G、D、E、N、Q、	595		

		A、T			
		AASSLHS			

[表21]. LTβR抗體LIBC219081（19325/41B2）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
SYAX ₄ X ₅ X ₄ 和X ₅ 各自為任何胺基酸殘基	927	VIWYDGSNQYX ₁₁ -X ₁₇ X ₁₁ -X ₁₇ 中每一個獨立地選自任何胺基酸殘基	930	DRVAAHPAYYX ₁₁ -X ₁₅ X ₁₁ -X ₁₅ 中每一個獨立地選自任何胺基酸殘基	933
SYA X ₄ X ₅ X ₁ 為M、H、Q、Y、F、L、I、V X ₂ 為H、D、E、N、M、R、Q	928	VIWYDGSNQYX ₁₁ -X ₁₇ X ₁₁ 為Y、H、M、I、L、F、W X ₁₂ 為A、G、S、T、V X ₁₃ 為D、S、K、Q、H、N、E X ₁₄ 為S、G、D、E、N、Q、A、T X ₁₅ 為V、T、A、M、F、L、I X ₁₆ 為K、D、E、N、Q、R X ₁₇ 為G、A、S、N	931	DRVAAHPAYYX ₁₁ -X ₁₅ X ₁₁ 為Y、H、M、I、L、F、W X ₁₂ 為G、A、S、N X ₁₃ 為L、M、V、I、Y、F X ₁₄ 為D、S、K、Q、H、N、E X ₁₅ 為V、T、A、M、F、L、I	934
SYAMH	8	VIWYDGSNQYYADSVKG	9	DRVAAHPAYYYGLDV	10
LCDR1	ID	LCDR2	ID	LCDR3	ID
X ₁ X ₂ DALPX ₇ X ₈ Y AY X ₁ 、X ₂ 、X ₇ 、X ₈ 各自獨立地為任何胺基酸殘基	932	KDNERPS	66	QSADX ₅ SGSYVI X ₅ 為任何胺基酸殘基	936
X ₁ X ₂ DALPX ₇ X ₈ Y AY X ₁ 為S、G、D、E、N、Q、A、T	935			QSADX ₅ SGSYVI X ₅ 為S、G、D、E、N、Q、A、T、I，較佳的是S、A或I	937

X ₂ 為G、A、S、N X ₇ 為N、G、D、 T、S、R、K、 H、E、Q，較佳 的是N、E或Q X ₈ 為H、D、E、 N、M、R、Q， 較佳的是H或Q X ₇ 和X ₈ 各自係如 上表17中針對該 抗體所定義的熱 點殘基（即N33和 H39）。			X ₅ 係如上表17中針對該 抗體所定義的熱點殘基 （即S111）。	
SGDALPNHYAY	65		QSADSSGSYVI	67

[表22]. LTβR抗體LIBC219097（19326/43D9）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
DAWX ₉ X ₁₀ X ₉ 和X ₁₀ 為任何胺 基酸殘基	740	RIKTKTDGGTTDYAAPVKG *不是互補位的一部分	743	DYGDYX ₆ X ₇ X ₆ 和X ₇ 為任何胺基酸殘基	744
DAWX ₉ X ₁₀ X ₉ 為M、H、Q、Y、 F、L、I、V X ₁₀ 為S、G、D、E、 N、Q、A、T	741			DYGDYX ₆ X ₇ X ₆ 為E、P、D、S、R、K、 Q、H、N X ₇ 為Y、H、M、I、L、F、 W	745
DAWMS	742			DYGDY EY	746
LCDR1	ID	LCDR2	ID	LCDR3	ID

RTSQSISRYLN	566	GASSLX ₆ X ₇	597	HQSYSTPPT	624
		X ₆ 和X ₇ 為任何胺基酸殘基		*基於HDX分析不是互補位的一部分	
		GASSLX ₆ X ₇	598		
		X ₆ 為Q、D、E、N、H、M、S、 R、K X ₇ 為S、G、D、E、N、Q、A、 T			
		GASSLQS	599		

[表23]. LTβR抗體LIBC218979（19319/23E9）的關鍵CDR殘基的總結

HCDR1	ID	HCDR2	ID	HCDR3	ID
SYGMH	11	VIWYX ₅ X ₆ SNKY _Y AX ₁₃ SVKG X ₅ 、X ₆ 和X ₁₃ 各自為任何胺基酸殘基	938	ERIAAAPYYYYGMDV	13
		VIWY X ₅ X ₆ SNKY _Y AX ₁₃ SVKG X ₅ 為D、S、K、Q、H、N、E、L，較佳的是D、E或L X ₆ 為G、S、N或A，較佳的是G或A X ₁₃ 為D、S、K、Q、H、N、E、V或Q，較佳的是D、Q或V X ₅ 、X ₆ 和X ₁₃ 各自係如上表17中針對該抗體所定義的熱點殘基（即D61、G65和	939		

		D72) 。			
		VIWYDGSNKYYADSVKG	12		
LCDR1	ID	LCDR2	ID	LCDR3	ID
SGDALPKHYAY	68	KDNERPS	69	QSADX ₅ TGSYX ₁₀ V X ₅ 和X ₁₀ 為任何胺基酸殘基	940
				QSADX ₅ TGSYX ₁₀ V X ₅ 為N、G、D、E、T、S、R、K、Q、H、I、L，較佳的是N或I X ₁₀ 為M、H、Q、Y、F、L、I、V，較佳的是M或V X ₅ 和X ₁₀ 係如上表17中針對該抗體所定義的熱點殘基（即N111和M137）。	941
				QSADNTGSYMV	70

[表24]. LTβR抗體LIBC219098（19327/44B1）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
SYAMS	481	TISGSGGSTYYADSVKG	509	VRDNWNYX ₈ X ₉ MDV X ₈ 和X ₉ 為任何胺基酸殘基	539
				VRDNWNYX ₈ X ₉ MDV X ₈ 為D、S、K、Q、H、N、E，較佳的是D或E X ₉ 為G、A、S、N、V，較佳的是G或V X ₈ 和X ₉ 各自係如上表17	540

				中針對該抗體所定義的熱點殘基（即D134和G135）。	
				VRDNWNYDGMDV	541
LCDR1	ID	LCDR2	ID	LCDR3	ID
RX ₂ SQSLLYSSGYI DLD X ₂ 為任何胺基酸殘基	568	LGSNRAS	601	MQTIQTPLT	627
RX ₂ SQSLLYSSGYI DLD X ₂ 為C或S X ₂ 係如上表17中針對該抗體所定義的熱點殘基（即C25）。	569				
RCSQSLLYSSGYI DLD	570				
RSSQSLLYSSGYI DLD	571				

[表25]. LTβR抗體LIBC219051（19323/35F5）的關鍵CDR殘基的總結					
HCDR1	ID	HCDR2	ID	HCDR3	ID
GYYLH	483	WINPNIGVTDX ₁₁ AQKFQD X ₁₁ 為任何胺基酸殘基	511	RGYNDDYDFDY	543
		WINPNIGVTDX ₁₁ AQKFQD X ₁₁ 為C、S或Y	512		
		WINPNIGVTDSAQKFQD	513		
LCDR1	ID	LCDR2	ID	LCDR3	ID
KSRQSLLHRX ₁₀ X ₁₁ KTY	572	EVSNRFS	603	MQSIQLPLI	628

LY X ₁₀ 為任何胺基酸殘基 X ₁₁ 為任何胺基酸殘基					
KSRQSLLHRX ₁₀ X ₁₁ KTY LY X ₁₀ 為D、E或V X ₁₁ 為G或A	573				
KSRQSLLHRDGGKTYL Y	574				

實例7：雙特異性分子生產和功能測試

【0422】 靶向腫瘤抗原相關(TAA)或基質抗原相關(SAA)的促效劑LTβR結合蛋白能夠結合 (i) 人LTβR (huLTβR) 和人Claudin 18.2 (CLDN18.2) , (ii) huLTβR和人Claudin 6 (CLDN6) , (iii) huLTβR和人MUC17 , 或 (iv) huLTβR和LRRC15 , 以AmAb形式 (即Fab x scFv) 或異源IgG形式產生。該等結合蛋白係使用本文所描述的LTβR抗體 (即LTβR抗體36G2 (19324) 、31A3 (19321) 、23E9 (19319) 和41B2 (19325)) 的可變區結合結構域和下表26中提供的相應SAA或TAA的可變區產生的。CLDN18.2、CLDN6、MUC17和LRRC15可變區的胺基酸序列提供在下表27中。

【0423】 在體外共培養測定中,評估了以AmAb或異源IgG形式產生的促效劑LTβR雙特異性結合蛋白組 (見表26) 的交聯依賴性LTβR傳訊活性。在該測定中,與穩定表現相關SAA或TAA的CHO或Saos-2細胞共培養的表現LTβR之人黑色素瘤細胞的趨化因子IL-8釋放表明測試抗體的交聯依賴性LTβR傳訊活性。

[表26].親本和雙特異性抗體

ID	描述
PUR149194-4	LTBR(36G2) IgG1 SEFL2
PUR149195-4	LTBR(31A3) IgG1 SEFL2
PUR149197-4	huClaudin-6(57103 (VH:C51G,VL:C141Q)_IgG1_SEFL2

PUR149198-4	huClaudin-6(57104 (VH:C51G,VL:C141Q))_IgG1_SEFL2
	huCLDN18.2(32698
PUR149199-4	(VH:G9R_S57A_V103E,VL:N39K_F103V))_IgG1_SEFL2
PUR149200-4	huCLDN18.2(32698)_IgG1_SEFL2
PUR149202-4	huMUC17(57105 (VH:C51G,VL:C141G_Q149R))_IgG1_SEFL2
PUR149203-4	huMUC17(57107 (VH:C51G,VL:C141G_Q149R))_IgG1_SEFL2
PUR149204-4	huLTBR(31A3)_ Fab x huClaudin-6(57103)_scFv_AmAb_CC
PUR149205-4	huLTBR(31A3)_ Fab x huClaudin-6(57104)_scFv_AmAb_CC
PUR149206-4	huLTBR(31A3)_ Fab x huCLDN18.2(32698) scFv_AmAb_no_CC
PUR149210-4	huLTBR(31A3)_ Fab x huMUC17(57105)_scFv_AmAb_CC
PUR149211-4	huLTBR(31A3)_ Fab x huMUC17(57107)_scFv_AmAb_CC
PUR149212-5	huLTBR(36G2)_ Fab x huClaudin-6(57103)_scFv_AmAb_CC
PUR149213-4	huLTBR(36G2)_ Fab x huClaudin-6(57104)_scFv_AmAb_CC
PUR149214-4	huLTBR(36G2)_ Fab x huCLDN18.2(32698)scFv_AmAb_no_CC
PUR149215-4	huLTBR(36G2)_ Fab x huCLDN18.2(32698)scFv_AmAb_no_CC
PUR149218-4	huLTBR(36G2)_ Fab x huMUC17(57105))_scFv_AmAb_CC
PUR149219-4	huLTBR(36G2)_ Fab x huMUC17(57107)_scFv_AmAb_CC
44245	huLTBR(41B2) x LRRC15(25851) AmAb CC
45147	huLTBR_19325 x huLRRC15_36779(VH:C98S) Hetero IgG1z SEFL2
52208	huLRRC15_36789(VL:C137S)_huLTBR_19319_Hetero IgG1z SEFL2

[表27]. SAA和TAA結合物的胺基酸序列

結合物名稱	VH	SEQ ID	VL	SEQ ID
		NO:		NO:
huClaudin-6 (57103)	QVQLVQSGAEVKKPGAS	909	EIVLTQSPGTLSPGERA	910
	VKVSCKASGYTFTGYYV		TLSCRASQSVRSTYLAW	
	HWVRQAPGQGLEWMGW		YQQKPGQAPRLLIYGASS	
	INPNSGATNYAQKFQGRV		RATGIPDRFSGSGSGTDF	
	TMTRDTSISTAYMELSRL		TLTISRLEPEDFAVYYCQ	
	RSDDTAVYYCVRDALIVE		QYDASPITFGQGTRLEIK	
	APATRDYYYYGMDVWG		R	

	QGTTVTVSS			
huClaudin-6 (57104)	QVQLVQSGAEVKKPGAS VKVSCKASGYTFTGYYV HWVRQAPGQGLEWMGW INPNSGATNYAQKFQGRV TMTRDTSISTAYMELSRL RSDDTAVYYCVRDRLIVE APATRDYYYYGMDVWG QGTTVTVSS	911	EIVLTQSPGTLSLSPGERA TLSCRASQSVRSTYLAW YQQKPGQAPRLLIYGASS RATGIPDRFSGSGSGTDF TLTISRLEPEDFAVYYCQ QYDASPITFGQGTRLEIK R	912
huMUC17(57105)	QVQLVESGGGVVQPGRS LRLSCAASGFTFSNHGMH WVRQAPGKGLEWVAGIW SEGSNKYYADAVKGRFTI SRDNSKNTLYLQMNSLR AEDTAVYYCARATYTTG WSYFDYWGQGTLVTVSS	913	SYELTQPPSVSVSPGQTA SITCSGDKLGDKYASWY QQKSGQSPVLVIYQDAK RPSGIPERFSGSNSGNTA TLTISGTQAMDEADYYC QAFHQSTWVFGGGTQLT VLR	914
huMUC17(57107)	QLQQWGAGLLKPSETLSL TCAVYGGSFSGYYWSWI RQPPGKGLEWIGDIDASG STKYNPSLKSRTVISLDT KNQFSLKLNSVTAADTAV YFCARKKYSTVWSYFDY WGQGTLVTVSS	915	SYELTQPPSVSVPPGQTA SITCSGDKLGDKYASWY QQKPGQSPVLIIYQDRKR PSGVPERFSGSNSGNTAT LTISGTQAMDEADYYCQ AWGSSTAVFGGGTKLTV LR	916
huCLDN18.2 (32698)	EVQLLESRGGLVQPGGSL RLSCAASGFTFSNYAMSW VRQAPGKGLEWVSAISGS GGSTYYADSVKGRFTISR DNSKNTLYLQMSSLRAED TAEYYCAKGDWKYGYG GMDVWGKGTTVTVSS	917	DIVMTQSPLSLPVTGPGE ASISCRSSQSLLSNGYK YLDWYLQKPGQSPQLLI YLGSNRASGVDPDRFSGS GSGTDFTLKISRLEAEDV GVYYCMQALQTPLTFGG GTKVEIKR	918
huCLDN18.2	EVQLLESGGGLVQPGGSL	919	DIVMTQSPLSLPVTGPGE	920

(32698)	RLSCAASGFTFSNYAMSW VRQAPGKGLEWVSSISGS GGSTYYADSVKGRFTISR DNSKNTLYLQMSSLRAED TAVYYCAKGDWKYGY GMDVWGKGTTVTVSS		ASISCRSSQSLLHSNGYN YLDWYLQKPGQSPQLLI YLGSNRASGVDPDRFSGS GSGTDFTLKISRLEAEDV GFYYCMQALQTPLTFGG GTKVEIKR	
huLRRC15 (25851)	EVQLVQSGAEVKKPGAS VKVSCKASGYTFTDYYIH WMRQAPGQGLEWMGWI NPNSGGTNYAQKFLGRV TMTRDTSISTAYLELRRLR SDDTAVYYCARERRYNS GGFDYWGGQGLTVTVSS	921	DIVMTQSPLSLSVTPGQP ASISCKSSQSLLHSNGKN YLDWYLQKPGQSPQLLI FLGSNRASGVDPDRFSGSG SGTDFTLKISRVEAEDVG VYYCMQAQQTPTFTFGPG TKVEIKR	922
huLRRC15 (36779)	QVQLVQSGAEVKKPGAS VKVSCKVSGNTLTEVSM HWVRQAPGKGLEWMGG FDPEDGETIYAQKFQGRIT MTEDTSTDATYMEINSLR CEDTAVYFCATLYSSGW NYYYGVDVWGQGTAVT VSS	923	DIQMTQSPSSLSASVGDR VTITCRASQGIRNDLGW YQQKPGKAPKRLIYGASI FQIGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCL QHYSYPWTFGQGTREI KR	924
huLRRC15 (36789)	QVQLVESGGGVVQPGRS LRLSCAASGFTFSNYGMH WVRQAPGKGLEWVAVIS YDGSNEYADSVKGRFTI SRDNSKNTLYLQMDSLRL AEDTAVYYCARDGAVAY YYYYGLDVWGQGTTVTV SS	925	DIVMTQSPLSLPVTGPGE ASISCRSSQSLLHRNGYN YLDWYLQKPGQSPQLLI YLGSNRASGVDPDRFSGS GSGTDFTLKISRVEAEDV GLYYCMQGLQTMCSFG QGTKLEIKR	926

【0424】 在該測定的第1天，收穫、計數表現LTβR的人黑色素瘤A375細胞

(ATCC, CRL-1619)，並將該等細胞以10,000個細胞/孔(50 μL)在生長培養基(DMEM, 10% FBS, 4 mM L-麩醯胺酸, 1.5 g/L碳酸氫鈉, 4.5 g/L葡萄糖)中接種於384孔測定板(科斯塔公司(Costar), 目錄號3701)。將板在37°C/5% CO₂下孵育過夜。在測定的第2天, 在測定培養基(DMEM、2% FBS、4 mM L-麩醯胺酸、1.5 g/L碳酸氫鈉、4.5 g/L葡萄糖)中從10 nM 1:3向下滴定測試分子11個點。以40 μL從384孔測定板的每個孔中去除培養上清液。然後將滴定的測試分子轉移到預先接種有表現LTβR的A375細胞的384孔測定板, 並在室溫下孵育30分鐘。收穫並計數穩定表現靶標的倉鼠卵巢細胞(CHO)或人骨肉瘤Saos-2細胞, 將該等細胞重懸在測定培養基中, 並按照板佈局轉移到測定板上。然後將測定板在37°C/5% CO₂下孵育過夜。基於測定開發數據, LTβR與表現CLDN6、CLDN18.2、MUC17、LRRC15的細胞或相應的非表現細胞的比率設置為1:1。各種表現靶標的細胞為測試分子提供交聯, 相應的非表現靶標的細胞用於確定測試分子的交聯獨立性。在測定第3天, 按照製造商之說明, 藉由檢測套組(希思公司, 目錄號62IL8PEC)測量測定孔上清液中趨化因子IL-8釋放, 並由EnVision(珀金埃爾默公司(PerkinElmer))在665 nm和615 nm下讀取。相對IL-8釋放由比率 = 訊號665 nm/訊號615 nm表示。

【0425】為了分析, 藉由Genedata Screener (Smart fit公司)的四參數邏輯擬合模型確定測試分子的插值EC₅₀、轉運EC₅₀和最大活性。插值EC₅₀係基於每種結合蛋白的劑量曲線中的回折點, 轉運EC₅₀係Y軸上特定點的值, 對於大多數分子來說, 該值為約EC₅₀。EC₉₀係使用插值EC₅₀和希爾斜率以以下公式計算的: $EC_{90} = (90/100-90)^{\frac{1}{\text{希爾斜率}}} EC_{50}$ 。

【0426】雙特異性抗體的最大活性係藉由將每種分子的最高訊號除以相應中性對照的平均訊號來計算的。下表28提供了個體抗體效力的總結, 如圖20-23所示。

【0427】 LTβR x CLDN6 BsAb的大部分最大活性在中性對照的2.98至4.12倍之間（圖20）。含有huLTβR 31A3的分子具有最佳EC₅₀值，為約75 pM。具有huLTβR 36G2的分子的EC₅₀值範圍為90.65至183.10 pM。所有分子均表現出交聯依賴性活性。

【0428】 LTβR x CLDN18.2 BsAb的大部分最大活性在中性對照的4.14至4.32倍之間（圖21）。所有LTβR x CLDN18.2分子具有相似的EC₅₀值，並表現出交聯依賴性活性。

【0429】 LTβR x MUC17 BsAb的大部分最大活性在中性對照的2.70至3.26倍之間（圖22）。所有LTβR x MUC17 BsAb分子具有相似的EC₅₀值，並表現出交聯依賴性活性。

【0430】 LTβR x LRRC15 BsAb的大部分最大活性在中性對照的4.46至5.37倍之間（圖23）。LTβR x LRRC15 BsAb分子的EC₅₀值範圍為46.42至108.12。所有LTβR x LRRC15 BsAb分子均表現出交聯依賴性活性。

[表28]：LTβR雙特異性分子效力總結

		CHO CLDN 6 ⁺ 細胞			CHO K1 (CLDN6)
LTβR x CLDN6 BsAb ID	最大活性	EC50 [pM]	EC90 [pM]	暫態EC50 (pM) Y=2.2	最大活性
PUR149204-4	3.43	74.42	266.45	1575.87	1.06
PUR149205-4	3.70	75.10	340.54	822.36	1.03
PUR149212-5	2.98	90.65	208.03	1514.50	1.07
PUR149213-4	4.12	183.10	3441.46	847.30	1.29
		CHO CLDN 18.2 ⁺ 細胞			CHO K1 (CLDN18.2)
LTβR x CLDN18.2 BsAb ID	最大活性	EC50 [pM]	EC90 [pM]	暫態EC50 (pM) Y=2.2	最大活性

PUR149206-4	4.26	50.16	124.96	58.81	1.04
PUR149214-4	4.32	69.98	268.62	81.15	1.14
PUR149215-4	4.14	49.13	196.95	57.65	1.05
CHO MUC17 ⁺ 細胞					CHO K1 (MUC17 ⁻)
LTβR x MUC17 BsAb ID	最大活性	EC50 [pM]	EC90 [pM]	暫態EC (pM) Y=2.5	最大活性
PUR149211-4	3.26	46.64	295.19	39.99	0.97
PUR149218-4	2.70	43.53	232.93	64.61	1.05
PUR149219-4	3.09	31.61	211.59	30.21	0.97
Saos-2 LRRC15 ⁺ 細胞					Saos-2 (LRRC15 ⁻)
LTβR x LRRC15 BsAb ID	最大活性	EC50 [pM]	EC90 [pM]	暫態EC (pM) Y=8	最大活性
44245	5.08	80.82	276.94	76.54	1.02
45147	5.37	46.42	708.17	36.98	0.92
52208	4.46	108.12	560.27	120.53	0.94

實例8：使用基於細胞的測定確認LTβR受體-配體非阻斷活性。

【0431】藉由按照製造商制定的方案使用Alexa Fluor 647 Microscale蛋白質標記套組（賽默飛世爾科技公司，目錄號A30009）軛合人LIGHT（R&D系統公司，目錄號664-LI/CF）和人LTα1β2（R&D系統公司，目錄號8884-LY/CF）來製備人LIGHT-Alexa 647和人LTα1β2-Alexa 647。經由基於FACS的受體-配體測定，測定人LTβR結合抗體或包含LTβR結合抗體的雙特異性抗體不阻斷人LIGHT和人LTα1b2與HEK 293T細胞上暫態表現的人LTβR結合的能力。將樣本與人IgG共染色，以另外評估配體的非阻斷是否係由於LTβR抗體與HEK293T細胞上暫態表現的人LTβR不結合。如果LTβR抗體不阻止人LIGHT-Alexa 647或人LTα1β2-Alexa 647與HEK 293T細胞上暫態表現的人LTβR結合，則流動式細胞分析術幾

何平均值 (GeoMean) 訊號相對於在不存在LT β R抗體的情況下獲得的GeoMean 訊號降低，從而由於非競爭而導致配體結合的低百分比抑制值。

【0432】簡言之，藉由按照製造商制定的方案使用表現 huLT β R cDNA[pTT5.2:VK1O2O12::huLT β R(31-435) C173003 (DNA-38098)]的表現載體以及Opti-MEM®減少血清培養基（吉布柯公司（Gibco），目錄號：31985-088）和293Fectin™試劑（吉布柯公司 REF:12347-019，P/N 53020LT）轉染，在宿主 人胚胎腎293細胞上表現人LT β R。將7.5 uL人LT β R特異性單株抗體在劑量滴定曲線中滴定，並在4°C下與7.5 uL轉染的hu LT β R細胞在FACS緩衝液[1XPBS+2%胎牛血清（西格瑪奧德里奇公司（Sigma-Aldrich），目錄號F2442-500 mL）]中使用96孔FACS板（康寧公司（Corning）目錄號3702）孵育1小時。然後，在FACS緩衝液中以1.112 μ g/mL添加15 μ L人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647，以及5 μ g/mL Alexa Fluor 488軛合的AffiniPure山羊抗人IgG（傑克遜免疫研究公司，目錄號：109-545-098），並在室溫下在黑暗中孵育20分鐘。人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647的最終濃度為0.556 μ g/mL，Alexa 488山羊抗人IgG的最終濃度係2.5 μ g/mL。將FACS板加入170 uL FACS緩衝液，然後在FACS緩衝液中藉由以2500 RPM離心2分鐘洗滌一次。根據製造商之建議，將樣本重懸在45 μ L FACS緩衝液中，並在帶有Intellicyt公司自動進樣器的iQue流式細胞儀上讀取；在Intellicyt公司ForeCyt®企業客戶6.2版（R3）上進行數據分析。

【0433】將人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647的量藉由流動式細胞分析術分析由GeoMean螢光訊號定量，並將該訊號轉換為受體-配體（R-L）相互作用的抑制百分比。在LT β R抗體存在下配體結合訊號的損失計算為R-L結合的抑制百分比。藉由對4個重複的配體-Alexa 647訊號的GeoMean訊號取平均值來確定人LIGHT-Alexa 647或人LT α 1 β 2-Alexa 647的最大GeoMean訊號，該等重複與HEK 293T細胞上暫態表現的人LT β R一起孵育。人LIGHT-Alexa 647或人

LT α 1 β 2-Alexa 647的最小GeoMean訊號係由與用模擬載體轉染的HEK 293T細胞一起孵育的配體-Alexa 647訊號的GeoMean訊號確定的。使用以下等式計算人LT β R抗體或同種型對照抗體對人LT β R-His：配體（人LIGHT或人LT α 1 β 2）的抑制百分比：

抑制百分比（%）= 1 - （實驗GeoMean-最小GeoMean） / （最大GeoMean-最小GeoMean）

【0434】對於一些LT β R抗體，當實驗GeoMean訊號高於最大GeoMean訊號時，獲得了負抑制百分比值，這可能是由於LT β R抗體與HEK 293T細胞上暫態表現的人LT β R結合的確認性變化，從而可能導致更高的配體-Alexa 647 GeoMean訊號（即，與不存在LT β R抗體相比，在其存在下允許更高水平的內源性配體結合）。

【0435】使用Alexa 488山羊抗人IgG染劑評估與HEK293T細胞上暫態表現的與人LT β R結合的LT β R抗體的量，並使用相對於不相關上清液的GeoMean特異性倍數的計算，藉由流動式細胞分析術分析的GeoMean螢光訊號進行定量。大於2.0的GeoMean計算值用作LT β R抗體與HEK293T細胞上暫態表現的人LT β R結合的臨界值。

【0436】圖24A和24B係繪製隨著所指示的促效劑LT β R結合蛋白濃度的增加，LIGHT（圖24A）和LT α 1 β 2（圖24B）與HEK293T細胞上暫態表現的LT β R的結合受到抑制的圖。人IgG1同種型和市售大鼠抗人LT β R抗體（Carlos-1；英傑公司；目錄號MA125845）分別作為陰性和陽性對照。下表29中提供了測試促效劑LT β R結合蛋白的配體阻斷活性的總結。圖24C顯示了所指示結合分子的濃度依賴性LT β R結合。

[表29].選擇促效劑LT β R結合蛋白的LT β R配體阻斷活性的總結

LTβR結合物ID	形式	LTα1β2	LIGHT
19323 (35F5)	單株抗體	在任何測試濃度下均無阻斷活性	在任何測試濃度下均無阻斷活性
19324 (36G2)	單株抗體	僅在> 8 nM濃度下觀察到阻斷活性（在< 8 nM濃度下為非阻斷物）	僅在> 8 nM濃度下觀察到阻斷活性（在< 8 nM濃度下為非阻斷物）
19321 (31A3)	單株抗體	在> 0.3 nM下，表現出LTα1β2結合的低水平（20%）抑制	在任何測試濃度下均無阻斷活性
19322 (34D1)	單株抗體	在所有測試濃度下阻斷LTα1β2-LTβR結合	在任何測試濃度下均無LIGHT阻斷活性。
19327 (44B1)	單株抗體	在高濃度下阻斷LTα1β2-LTβR	在任何測試濃度下均無LIGHT阻斷活性
19326 (56577)	雙特異性結合蛋白	濃度依賴性LTα1β2-LTβR阻斷	濃度依賴性LIGHT-LTβR阻斷
19325 (56575)	雙特異性結合蛋白	在任何測試濃度下均無LTα1β2阻斷活性。	在任何測試濃度下均無LIGHT阻斷活性。
19319 (52208)	雙特異性結合蛋白	在任何測試濃度下均無LTα1β2阻斷活性。	在任何測試濃度下均無LIGHT阻斷活性。

【0437】 還評估了雙特異性LTβR結合蛋白的LTβR配體阻斷活性。圖25A和26A係顯示所指示的LTβR-LRRC15雙特異性結合物抑制LTα1β2與細胞表現的LTβR結合的圖，圖25B和26B顯示了相同的LTβR-LRRC15雙特異性結合物抑制LIGHT與細胞表現的LTβR結合。上表29中提供了所測試的LTβR雙特異性結合蛋白的配體阻斷活性的總結。圖25C和26C顯示了所指示的雙特異性結合蛋白的濃度依賴性LTβR結合。

【0438】 該數據顯示，結合CRD4的LTβR抗體19325(LIBC219081)和19319（ LIBC218979 ）在以抗體和雙特異性結合蛋白形式測試的所有濃度下均不抑制

LT α 1 β 2或LIGHT與LT β R結合。

實例9：重新篩選融合瘤池以鑒定額外的LT β R CRD4結合非配體阻斷抗體

【0439】 **9.1 從融合瘤池中產生選殖抗LT β R融合瘤。**將來自收穫1至6的XenoMouse®融合瘤培養物解凍，並在DMEM選擇培養基中生長3-4天。在FACS富集分選前一天將培養基改為BDQY融合瘤培養基。在10 mL無菌FACS緩衝液中洗滌細胞，然後在4°C下，在2 mL反應體積中與3 μ g/mL濃度的生物素標記的重組人LT β R（R&D系統公司，目錄號：7538LR）和20 μ g/mL濃度的人LT α 1 β 2-Alexa 647（R&D系統公司，目錄號8884-LY/CF）一起孵育30分鐘。對於所有融合瘤培養物，在此步驟中還添加了100 μ g/mL多選殖人IgG（傑克遜免疫研究公司，目錄號：009-000-003）以阻斷抗Fc結合物。在10 mL FACS緩衝液中洗滌一次後，將1 mL抗體混合物添加到細胞中，該抗體混合物含有各5 μ g/mL Alexa Fluor 488軛合的山羊抗人IgG Fc Fab（傑克遜免疫研究公司，目錄號：109-547-008）和BV421軛合的鏈黴親和素（BD生物科學公司（BD biosciences），目錄號：563259）。然後將細胞在4°C下孵育30分鐘。孵育後，將細胞在10 mL FACS緩衝液中洗滌，重懸於2 mL含有5 μ L 7-AAD（BD Pharmingen公司，目錄號：559925）的BDQY融合瘤培養基中，然後通過40微米細胞過濾器以去除任何團塊。藉由對活細胞群體進行門控在BD FACSAria上對細胞進行批量分選，然後對雙陽性Alexa Fluor 488 IgG和BV421 LT β R螢光訊號進行分選，最後對Alexa Fluor 647 LT α 1 β 2和BV421 LT β R螢光訊號進行分選。在第一輪富集分選以使目標群體從< 1%到> 20%之後，將靶細胞單細胞分選到含有BDQY融合瘤培養基的384孔微量滴定板上，並培養長達2週，然後收集上清液進行篩選。

【0440】 **9.2 相對表位分組/分析。**將生物素醯化山羊抗人IgG Fc捕獲抗體（傑克遜免疫研究公司，目錄號：109-065-098）以2 μ g/mL濃度與鏈黴親和素包被的、經獨特條碼編碼LumAvidin Beads®（LumAvidin Microspheres，路明克斯

公司，美國德克薩斯州奧斯丁）在室溫下在黑暗中偶合30分鐘，並洗滌兩次。將4 µg/mL濃度的參考抗體融合瘤上清液樣本與山羊抗人IgG Fc包被的珠粒在室溫下在黑暗中孵育30分鐘，並洗滌三次。將His-標記的人LTβR抗原（VK1O2O12::huLTβR(31-227)::8xHis，46449-2）以60 nM製備，並與5 ug/mL Chrompure人IgG全分子（傑克遜免疫研究公司，目錄號：009-000-003）結合，在室溫下在黑暗中與包被的珠粒孵育30分鐘，並洗滌兩次。將珠粒重懸於含有Stabilguard®（舒爾默迪克斯公司（SurModics）SG01）的FACS緩衝液中。

【0441】將含有歸一化（4 ug/mL）測試抗體（融合瘤上清液）的樣本孔與Zenon™抗人Fab（Zenon™ Alexa Fluor™ 488人IgG標記套組，賽默飛世爾科技公司，目錄號：Z25402）以0.06 ug標記/孔在室溫下在黑暗中孵育15分鐘。然後將Chrompure人IgG全分子（傑克遜免疫研究公司，目錄號：009-000-003）以7.2 ug塊/孔添加到Zenon™標記的樣本孔中，並在室溫下在黑暗中孵育15分鐘。

【0442】將抗原包被的參考抗體結合珠粒合併，然後將該等珠粒分到含有Zenon™標記的測試抗體（融合瘤上清液）樣本（或陰性對照）的單個樣本孔中，在室溫下在黑暗中孵育30分鐘，並洗滌兩次。測試抗體（融合瘤上清液）的最終濃度為1 ug/mL。將樣本洗滌兩次以去除未結合的檢測試劑，並重懸於FACS緩衝液中。使用Intellicyt公司iQue™ Screener平臺對樣本進行分析。為了確定各個測試抗體的抗體競爭/結合譜，從每個競爭/結合反應（即整個參考抗體組）的參考抗體加測試抗體訊號中減去僅參考抗體結合訊號。單個抗體結合譜被定義為每個競爭/結合反應的淨結合值的集合。然後藉由計算每個測試抗體譜之間的決定係數來評估單個譜之間的相似程度。然後將彼此顯示高度相似性（ $R^2 > 0.7$ ）的測試抗體分組到共同的分組譜中。使用這種方法，將LTβR結合抗體細分為7個獨特的分組譜（A、B、C、D、F、G和H）。已鑒定出與本文鑒定為19325（41B2）和19319（23E9）的LTβR抗體具有共同分組譜的候選抗體，該等抗體藉由HDX-

MS分析（見實例6.2）與LTβR的CRD4結合，並在圖27的表中提供。使用內部表位定位測定確認該等候選抗體結合LTβR的CRD4。

【0443】 9.3 使用基於細胞的測定確認在重新篩選中鑒定出的LTβR抗體的非配體阻斷活性。經由實例8中描述的基於FACS的受體-配體測定，測定含有人LTβR結合抗體(5 μg/mL)的融合瘤上清液不阻斷人LIGHT和人LTα1β2與HEK 293T細胞上暫態表現的人LTβR結合的能力。一式兩份測試每種含有人LTβR結合抗體的融合瘤上清液的配體阻斷活性。圖27的表中提供了與和LTβR的CRD4結合的、本文鑒定為19325（41B2）和19319（23E9）的LTβR抗體具有表位分組譜的每種LTβR結合抗體的抑制百分比。如上文所描述的，當實驗GeoMean訊號高於最大GeoMean訊號時，獲得了負抑制百分比值，這可能是由於LTβR抗體與HEK 293T細胞上暫態表現的人LTβR結合的確認性變化，從而可能導致更高的配體-Alexa 647 GeoMean訊號（即，與不存在LTβR抗體相比，在其存在下允許更高水平的內源性配體結合）。

【0444】 9.4 使用Carterra測定確認在重新篩選中鑒定的LTβR抗體的非配體阻斷活性。為了進一步確認LTβR抗體的非配體阻斷活性，經由基於Carterra的受體-配體測定，測定含有LTβR結合抗體的融合瘤上清液阻斷人LIGHT（R&D系統公司，目錄號664-LI/CF）和人LTα1β2（R&D系統公司，目錄號8884-LY/CF）與人LTβR-His結合的能力。如果LTβR抗體阻止人LIGHT或人LTα1β2與人LTβR-His結合，則將受體暴露於抗體後注射配體的響應（RU）不會相對於存在單獨LTβR受體時達到的RU增加，從而防止由於競爭而形成三組分夾層複合物。圖27的表顯示了藉由此Catterra方法測量的選定融合瘤上清液樣本的受體-配體相互作用阻斷能力。

【0445】簡言之，在25°C下在Carterra® LSA上，在預載入生物素醯化抗huFc VHH（Chromotek公司，目錄號：shurbGB-1）的HBSTE緩衝液[10 mM HEPES，

pH7.4，150 mM NaCl，0.05% tween-20和1 mM EDTA；自製]的鏈黴親和素（SA）晶片（SAHC30M，Carterra零件號4294）上捕獲人LT β R結合抗體組。將抗體歸一化並稀釋至2 μ g/mL，並藉由96通道打印頭在晶片的斑點上列印15 min。然後使用單個流通池以300 nM向晶片注射人LT β R-His，結合時間為5 min，以使受體結合達到飽和，解離時間為1 min，這是軟體使解離最小化所允許的最小值。隨後立即以150 nM注射人LIGHT或人LT α 1 β 2配體，結合5 min，解離1 min。在重新列印用於其他配體測定的抗體之前，使用10 mM甘胺酸，pH 1.5（Carterra零件號3639）進行再生。

【0446】 使用Kinetics軟體（Carterra公司）藉由RU定量LT β R抗體載入、人LT β R-His受體結合和人LIGHT或人LT α 1 β 2配體夾層。夾層水平計算為配體RU與受體RU的比率。用在相同實驗設置中測量的不相關人IgG1對照確定最低夾層水平。對於一些LT β R抗體，夾層水平值較低，可能是由於抗體濃度低、注射體積變化效應、對LT β R的弱結合物或LT β R解離速度快。由於無法確定該等抗體係非阻斷物還是阻斷物，因此，在結果表中被標記為「NA」。

【0447】 **9.5 親和力差距分析。**在25°C下在Carterra LSA上，在HBSTE運行緩衝液[10 mM HEPES，pH7.4，150 mM NaCl，0.05% tween-20和1 mM EDTA]中測量親和力。使用10 mM甘胺酸（pH 1.5）（Carterra零件號3639）進行再生。將含有LT β R結合抗體的融合瘤上清液歸一化並稀釋至0.3 μ g/mL，並使用96通道打印頭將該等上清液在預先裝載有生物素醯化抗huFc VHH（Chromotek公司，目錄號：shurbGB-1）的鏈黴親和素（SA）晶片（SAHC30M，Carterra零件號4294）的斑點上列印10 min。緩衝液孔和不相關人IgG1樣本用作陰性對照。將靶標、人或cyno LT β R作為分析物以243 nM、81 nM、27 nM、9 nM、3 nM和1 nM注射。結合時間為5 min，解離時間為30分鐘。數據係雙背景參考，因為從數據中減去了晶片上的參考斑點和0 nM分析物濃度。使用1：1朗格繆爾傳質結合模型在

Kinetics軟體（Carterra公司）中分析數據。人和cyno親和力差距的結果顯示在圖27的表中。

【0448】 本文引用的每個參考文獻針對它所教導的全部內容和出於所有目的均特此藉由引用將其全部併入。

【0449】 本揭露之範圍不受本文所述之特定實施方式的限制，該等實施方式旨在作為本揭露之各個實施方式的單個說明，並且揭露了功能上等效的方法和組分。實際上，除了本文中顯示和描述的那些之外，根據前述描述和附圖，本發明之各種修改對於熟悉該項技術者將變得顯而易見。這類改變旨在落入所附申請專利範圍之範圍內。

【符號說明】

【0450】 無

【生物材料寄存】

【0451】 無