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(54) 발명의 명칭 다중특이적 탈면역화된 CD3-바인더

(57) 요 약
본 발명은 인간 CD3에 특이적으로 결합하는 제1 도메인 및 Ig-유래의 제2 결합 도메인을 포함하는, 세포독성적으로 활성인 CD3 특이적 결합 구조체에 관한 것이다. 또한, 본 발명의 CD3 특이적 결합 구조체를 인코드하는 핵산 서열을 제공한다. 본 발명의 또다른 측면들은 상기 핵산 서열을 포함하는 벡터들 및 숙주 세포들, 본 발명의 구조체를 생산하는 방법 및 상기 구조체를 포함하는 조성물이다. 본 발명은 또한 특정 질환들을 치료하는 약학적 조성물들을 제조하기 위한 상기 구조체의 용도, 특정 질환들을 치료하는 방법 및 본 발명의 결합 구조체를 포함하는 키트를 제공한다.
특허청구의 범위

청구항 1

인간 CD3에 특이적으로 결합하는 제1 도메인 및 Ig-유래의 제2 결합 도메인을 포함하는 세포독성적으로 활성인 CD3 특이적 결합 구조체(binding construct)에 있어서,

상기 제1 도메인은 탈면역화되고, CDR-H1 영역, CDR-H2 영역 및 CDR-H3 영역을 포함하고,

상기 CDR-H1 영역은 서열번호 88의 아미노산 서열을 포함하고,

상기 CDR-H2 영역은 서열번호 90 또는 92의 아미노산 서열을 포함하고,

상기 CDR-H3 영역은 서열번호: 96, 108, 119, 120, 121, 122, 123, 124, 125, 126, 또는 127의 아미노산 서열을 포함하고;

상기 제1 도메인은 그것의 골격(framework) H1에 서열 VKK를 더 포함하고, 골격 H1 및 CDRH1 영역 간의 전이 서열(transition sequence)이 서열 Ala-Ser-Gly-Tyr-Thr-Phe (ASGYTF; 서열번호: 233)을 포함하는 것인,

세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 2

청구항 1에 있어서, 상기 제1 도메인 내에, 서열 Met-Glu-Leu-Ser (MELS; 서열번호: 234)을 포함하는 골격 H3를 더 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 3

청구항 1 또는 2에 있어서, 상기 제1 도메인 내에, 서열 Ile-Thr-Thr-Asp-Lys (ITTDK; 서열번호: 235)을 포함하는 골격 H3를 더 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 4

청구항 1에 있어서, 상기 인간 CD3에 특이적으로 결합하는 제1 도메인이, 서열번호: 152 또는 153에 나타낸 골격 H1을 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 5

청구항 1에 있어서, 상기 인간 CD3에 특이적으로 결합하는 제1 도메인이, 서열번호: 156 또는 157에 나타낸 골격 H2를 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 6

청구항 1에 있어서, 상기 인간 CD3에 특이적으로 결합하는 제1 도메인이, 서열번호: 160 또는 161에 나타낸 골격 H3를 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 7

청구항 1에 있어서, 상기 인간 CD3에 특이적으로 결합하는 제1 도메인이, 서열번호: 164 또는 165에 나타낸 골격 H4를 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 8

삭제

청구항 9

청구항 1에 있어서, 상기 구조체가 서열번호: 74 또는 76에 도시된 Vh-영역을 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 10
청구항 1에 있어서, 상기 구조체가 서열번호: 98 또는 100 에 도시된 CDR-L1 을 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 11
청구항 1에 있어서, 상기 구조체가 서열번호: 102 에 도시된 CDR-L2 를 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 12
청구항 1에 있어서, 상기 구조체가 서열번호: 104 에 도시된 CDR-L3 을 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 13
청구항 1에 있어서, CD3-특이적 부분에 V_{L} 영역을 포함하고, 상기 V_{L} 영역은 서열번호: 78, 서열번호: 80, 서열 번호: 82 및 서열번호: 112 로 이루어지는 그룹으로부터 선택되는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 14
청구항 1에 있어서, 상기 Ig-유래의 제2 도메인이 scFv 인 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 15
청구항 1에 있어서, 상기 Ig-유래의 제2 도메인 또는 연결 링커-영역(들) 또는 둘다가 인간화된 또는 탈면역화된 또는 인간화되고 탈면역화된 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 16
청구항 1에 있어서, 상기 Ig-유래의 제2 도메인이 세포 표면 분자에 대해 특이성을 갖는, 항원을 특이적으로 인식하는 항원-상호작용-부위(antigen-interaction-site)를 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 17
청구항 16에 있어서, 상기 세포 표면 분자가 종양 특이적 마커인 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 18
청구항 16에 있어서, 상기 Ig-유래의 제2 결합 도메인이 EpCAM, CCR5, CD19, HER-2, HER-2 neu, HER-3, HER-4, EGFR, PSMA, CEA, MUC-1(śmycin), MUC2, MUC3, MUC4, MUC5ac, MUC5b, MUC7, βhCG, Lewis-Y, CD20, CD33, CD30, 강글리오시드(ganglioside) GD3, 9-O-아세틸-GD3, GM2, 글로브(Globo) II, 루코보(fucosyl) GM1, 콜리(Poly) SA, GD2, 카르보안하이드라트(2OSSone hydrase) IX (MN/CA IX), CD44v6, 소니 헤지호그(Sonic Hedgehog) (Shh), Wue-1, 형질 세포 항원(Plasma Cell Antigen), (막-결합) IgE, 축삭중 콘도미호른 창단에 프로페오글리칸(Melanoma Chondroitin Sulfate Proteoglycan) (MCSP), CCR8, TNF-알파 항체구체, STEAP, 메소텔린 (mesothelin), A33 항원, 전립선 중기세포 항원 (PSCA), Ly-6: 데스모글레인(desmoglein) 4, E-카드헤린 나오-에피토프(neo-epitope), 태아 아세틸콜린(Fetal Acetylcholine) 수용체, CD25, CA19-9 마커, CA-125 마커 및 필러산 역제 물질 (MIS) 수용체 타입 II, sTn (시알릴화(sialylated) Tn 항원, TAG72), FAP (심유아세포 활성화 항원), 엔도시밀린(endosialin), EGFRvIII, L6, SAS, CD63, TAG72, TF-항원, Cora 항원, CD7, CD22, Igα, Igβ, G250, gp100, MT-MMPs, F19-항원, CO-29 및 EphA2 로 이루어지는 그룹으로부터 선택되는 분자에 대해 특이성을 갖는, 항원을 특이적으로 인식하는 항원-상호작용 부위를 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 19
청구항 1에 있어서, 상기 Ig-유래의 제2 결합 도메인은 EpCAM에 대해 독이성을 갖는, 항원을 독이적으로 인식하는 항원-상호작용-부위를 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 20
청구항 19에 있어서, 상기 CD3 특이적 결합 구조체가
(c) 상기 (b)의 뉴클레오티드 서열에 대한 유전자 코드(genetic code)의 결과로 축퇴(degenerate)하는 핵산 서열에 의해 인코딩된 아미노산 서열.

의 그룹으로부터 선택되는 아미노산 서열을 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 21
청구항 1에 있어서, 상기 Ig-유래의 제2 결합 도메인은 CCR5에 특이성을 갖는, 항원을 특이적으로 인식하는 항원-상호작용 부위를 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 22
청구항 21에 있어서, 상기 CD3 특이적 결합 구조체가:
(a) 서열번호: 206, 208, 210, 212, 214 또는 216 중 어느 하나의 아미노산 서열: 및
(b) 서열번호: 205, 207, 209, 211, 213 또는 215 중 어느 하나의 핵산 서열에 의해 인코딩된 아미노산 서열: 및
(c) 상기 (b)의 뉴클레오티드 서열에 대한 유전자 코드의 결과로서 축퇴하는 핵산 서열에 의해 인코딩된 아미노산 서열.

의 그룹으로부터 선택되는 아미노산 서열을 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 23
청구항 1에 있어서, 상기 Ig-유래의 제2 결합 도메인은 CD19에 대한 독이성을 갖는, 항원을 독이적으로 인식하는 항원-상호작용 부위를 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 24
청구항 23에 있어서, 상기 CD3 특이적 결합 구조체가:
(c) 상기 (b)의 뉴클레오티드 서열에 대한 유전자 코드의 결과로 축퇴하는 핵산 서열에 의해 인코딩된 아미노산 서열.
서열.
의 그룹으로부터 선택되는 아미노산 서열을 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 25
청구항 1에 있어서, 상기 Ig-유래의 제2 결합 도메인은 CD20에 대해 특이성을 갖는, 항원을 특이적으로 인식하는 항원-상호작용 부위를 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 26
청구항 25에 있어서, 상기 CD3 특이적 결합 구조체가:
(a) 서열번호: 218, 220, 222, 224, 226, 또는 228 중 어느 하나의 아미노산 서열; 및
(b) 서열번호: 217, 219, 221, 223, 225 또는 227 중 어느 하나의 핵산 서열에 의해 인코드된 아미노산 서열; 및
(c) 상기 (b)의 뉴클레오티드 서열에 대한 유전자 코드의 결과로서 촉매하는 핵산 서열에 의해 인코드된 아미노산 서열.
의 그룹으로부터 선택되는 아미노산 서열을 포함하는 것인, 세포독성적으로 활성인 CD3 특이적 결합 구조체.

청구항 27
청구항 1에 기재된 CD3 특이적 결합 구조체를 인코드하는 핵산 서열.

청구항 28
청구항 27에 기재된 핵산 서열을 포함하는 벡터.

청구항 29
청구항 28에 있어서, 청구항 27 기재의 상기 핵산 서열에 작동적으로 연결된(operably-linked) 조절 서열(regulatory sequence)인 핵산 서열을 더 포함하는 것인 벡터.

청구항 30
청구항 28에 있어서, 상기 벡터가 발현 벡터인 것인 벡터.

청구항 31
청구항 28에 기재된 벡터로 형질전환된(transformed) 또는 트랜스페кт된(transfected) 숙주.

청구항 32
CD3 특이적 결합 구조체의 생산 방법으로서, 상기 방법은 폴리펩티드 구조체의 발현을 허용하는 조건하에서 청구항 31 기재의 숙주로 배양하는 단계 및 상기 배양으로부터 생산된 폴리펩티드 구조체를 회수하는 단계를 포함하는 것인 방법.

청구항 33
청구항 1에 기재된 CD3 특이적 결합 구조체, 청구항 27 기재의 핵산 분자, 청구항 28에 기재된 벡터, 또는 청구항 31 기재의 숙주를 포함하는 조성물로서, 중식성 질환, 중양성 질환, 염증성 질환, 면역학적 장애, 자기면역 질환, 감염성 질환, 바이러스 질환, 알레르기 반응, 기생충 반응(parasitic reaction), 이식대숙주병 또는 숙주 대이식병의 예방, 치료 또는 개선을 위한 조성물.

청구항 34
청구항 33에 있어서, 상기 조성물은 약학 조성물이고, 담체, 안정화제, 부형제, 및 이들의 조합으로 이루어진 그룹으로부터 선택된 적합한 재료를 더 포함하는 것인 조성물.
청구항 35
청구항 33에 있어서, 상기 조성물은 진단 조성물이고, 검출을 위한 수단 및 방법을 더 포함하는 것인 조성물.

청구항 36
삭제

청구항 37
삭제

청구항 38
삭제

청구항 39
삭제

청구항 40
삭제

청구항 41
청구항 1에 기재된 CD3 특이적 결합 구조체, 청구항 27 기재의 핵산 분자, 청구항 28에 기재된 벡터 또는 청구항 31 기재의 숙주를 포함하는 키트로서, 증식성 질환, 종양성 질환, 염증성 질환, 면역학적 장애, 자가면역 질환, 감염성 질환, 바이러스 질환, 알레르기 반응, 기생충 반응(parasitic reaction), 이식세종관중 또는 숙주대 이식병의 예방, 치료 또는 개선을 위한 키트.

명세서

기술 분야

본 발명은 인간 CD3에 특이적으로 결합하는 제1 도메인 및 Ig-유래의 제2 결합 도메인을 포함하는 세포독성적으로 활성인 CD3 특이적 결합 구조체에 관한 것이다. 또한, 본 발명의 CD3 특이적 결합 구조체를 인코드하는 핵산 서열을 제공한다. 본 발명의 또다른 측면은 상기 핵산 서열을 포함하는 벡터들 및 숙주세포들, 본 발명의 구조체를 생산하는 방법 및 상기 구조체를 포함하는 조성물이다. 본 발명은 또한 특정 질환들을 치료하기 위한 약학적 조성물을 제조하기 위한 상기 구조체의 용도, 특정 질환들을 치료하는 방법 및 본 발명의 결합 구조체를 포함하는 키트를 제공한다.

배경 기술


그러나, CD3에 대해 지시되는 선행 기술의 항체들은 비-인간 근원으로부터 유래된 것이다. 이것은 상기 항-CD3 항체들을 인간에서 치료요법의 일부로서 사용할 때 몇 가지 적절한 문제들을 가져온다.

그러한 문제 중 하나는 "사이토카인 방출 증후군(CRS)"이다. CRS는 항-CD3 항체의 최초 몇 번 투여 후 관찰되어 온 임상 증후군이며, CD3에 대해 지시된 많은 항체들이 분열을 촉진한다는 사실과 관련되어 있다. 시험관내 에서, CD3에 대해 지시된 분열촉진 항체들은 T-세포 쥐식 및 사이토카인 생산을 유도한다. 생체 내에서 이러한 분열 촉진 환경은 항체의 최초 주입 후 초기 시간 내에, 다수의 T-세포-유래의 사이토카인들을 포함하여, 사이토 카인들의 대량 방출을 가져온다. CD3-특이적 항체들의 분열 촉진 능력은 단핵세포/대식세포 의존적이며, 이들 세포들에 의한 IL-6 및 IL-1β의 생산과 관련되어 있다.

CRS 증후군은 빈번하게 보고된 가벼운 "독감-유사"증후군에서부터 덜 보고된 심각한 "쇼크-유사" 반응(이것은 심장혈관 및 중추신경계 소견을 포함한다)까지 범위가 넓다. 증상은 특히 두통, 떨림, 구역/구토, 설사, 복통, 관절 통증 및 주요/관절의 아픔 및 통증, 전신 약함(generalized weakness), 심장 고장(cardiorespiratory events) 뿐 아니라, 신경정신적 고장(neuro-psychiatric events)을 포함한다. 각각의 증상들은 빈번하게 보고되었으며, CRS 증후군은 심장혈관계 및 중추신경계 소견을 보이며, CD3 특이적 항체들의 치료소견은 두통, 떨림, 구역/구토, 설사, 복통, 관절 통증 및 주요/관절의 아픔 및 통증, 전신 약함이 특징이다. CRS 증후군은 인간 CD3에 특이적으로 결합하는 제1 도메인 및 Ig-유래의 제2 결합 도메인을 포함하는, 세포독성적으로 활성인 CD3 특이적 결합 구조체에 관한 것이며, 여기에서 상기 제1 도메인은 탈면역화되고, CDR-H1 영역, CDR-H2 영역 및 CDR-H3 영역을 포함하며, 상기 CDR-H3 영역은 서열번호: 96, 108, 119, 120, 121, 122, 123, 124, 125, 126, 또는 127의 아미노산 서열을 포함하고; 상기 제1 도메인은 그 골격 내에 서열 CTVK (Cys-Thr-Val-Lys)를 추가로 포함하고, 여기에서 골격 H1 및 CDR-H1 영역 간 전이 서열(transition sequence)은 서열 Ala-Ser-Gly-Tyr-Thr-Phe (ASGYTF; 서열번호: 23 3)를 포함한다.
의 탈면역화 되지 않은 서열과 비교했을 때 감소된 면역원성을 보이지만, 놀랍게도 독성 활성을 보유하는, 탈면역화된 CD3 특이적 결합 분자를 초래하는 것을 발견했다. 이러한 발견은 모든 가능한 탈면역 프로토콜이 두려운 독성 활성을 보이는, 생물학적(bioactive) 활성(activating) 성분의 특징이기 때문에 특히 놀라운 것이었다. 무작위 실험을 통해, 탈면역화된 CD3 특이적 결합 분자를 포함한 세포의 면역계 내에서의 활성을 관찰한 결과, 정상 면역계 내에서의 활성을 보이는 특성의 극大地의 특성을 보였다. 본 발명에 따라, 탈면역화되지 않은 혈청체의 특정 서열이, 여기서 상기 기술된 서열들로 대체되거나, 상기 기술된 서열들로 변형되었다. 특히, 곤충 H1 영역에서 원래의 서열 Leu-Ala-Arg (LAR)는 서열 Val-Lys-Lys (VKK)로 변형되었다. (도 14 참조) 밝혔다. 변형된 CD3-특이적 결합 구조체는 적어도 두 개의 결합 특성을 포함하며, 여기서 제2 결합 특성은 Ig-유래인 것을 특징으로 한다. 게다가, 상기 변형한 구조체는 편리한 특정 아미노산 서열을 특징으로 한다. 일부 실시예들에 쓰여져 있는 바와 같이, 여기서 제공된 구조들은 그들의 면역반응/탈면역화된 형식에서도 여전히 생존성을 보유한다. 특히, 모든 탈면역화가 생존성 분자들에 초래하는 것은 아님을, 기술분야에 공지된 방법들(WO 92/10755, WO 00/34317, WO 98/52976, WO 02/079415 또는 WO 02/012899)에 의해 측정하여, 서술하고 있다: 특히 실험 2 및 5 참조.

여기에서 사용한 용어 "생물학적으로 활성인 CD3 결합 구조체"는 T-세포 상에 발현된 인간 CD3 복합체에 결합할 수 있고, 표적 세포의 세포/상호작용을 유도할 수 있는 CD3/C3 복합체의 CD3 특이적 바인더(예를 들면, 항체, 항체 유도체 또는 항체 단편)의 결합은 기술분야에 공지된 것과 같이 T-세포의 활성을 가져온다. (예를 들면, FACS에 기초한 프로피디움 요오드화물(propidium Iodide) 측정법, 트리판 블루 유입(trypan Blue influx) 측정법, 포토메트릭(photometric) 효소 방출 측정법(LDH), 방사성측정(3H-Thd 편입) 측정법 및 칼세인(Calcein)AM 방출 측정법) 추가적인 측정법은 예를 들면, 광도측정(photometric) MTT, XTT, WST-1 및 알라마 블루(alamarBlue) 측정법, 방사성측정(125I) 방출 측정법, 형광 측정법(fluorescent Europium) 방출 및 칼세인(Calcein)AM 방출 측정법) 추가적인 측정법은 예를 들면, 광도측정(photometric) MTT, XTT, WST-1 및 알라마 블루(alamarBlue) 측정법, 방사성측정(125I) 방출 측정법, 형광 측정법(fluorescent Europium) 방출 측정법, 세포 분열 활성을 측정하는 클론생성(clonogenic) 측정법, 및 미토COND라리아의 밸런스 구배(transmembrane gradient)를 측정하는 형광측정 로다민(Rhodamine) 측정법에 의해, 세포의 세기를 측정하는 필수적인 도구이다. 또한, 방사성 측정법(autoradiography)에 의해 둔한 FACS에 기초한 포츠피터질해년 노출 측정법, ELISA에 기초한 TUNEL 검사, 카르파제 화학 측정법(광도, 형광 측정 또는 ELISA에 기초한) 또는 변환된 세포 형식 분석(수축, 세포막 기포(bubbling))에 의해 측정할 수 있다. 이는 특히, 세포로의 화학적 측정법은 형광세포의 임기-결합의 영역에의 측정법여기에 의해 측정할 수 있다. 이는 특이적으로 인식하는 특성을 보이는 항체분자의 특정 영역을 분별하는 능력에 관한 것이다. 형광을 측정한 세포들은 매개체(hinge region)로서의 B형반응과의 관련성에 의해 측정한다. 본 발명의 세포복합체로 활성화된 이중특이적 CD3 결합 구조체의 존재에 의한 혈청체의 본질은 Tem-1에 기반한 T세포주를 포함하며, 해당 배양은 형광활성화에 의해 측정한다. 본 발명의 세포복합체로 활성화된 이중특이적 CD3 결합 구조체의 흔적을 보였거나 또는 표적 세포들의 특성을 가지지 않은 유사한 구조체의 생존성을 보유하고, 양의 비교된 값을 특징으로 한다.

본 발명의 내용에 사용된 "-에 결합하는/-와 상호작용하는"이라는 용어는 적어도 두 개의 "항원-상호작용-부위(antigen-interaction-site)"가 서로 결합/상호작용하는 것을 정의한다. 본 발명에 따른, 용어 "항원-상호작용-부위"는 특정 항원 또는 특정 항원군과 특이적으로 상호작용하는 능력을 보이는 종합바디의 모티프(motif)를 정의한다. 상기 결합/상호작용은 또한 "특이적 인식"을 정의하는 것으로 이해한다. "특이적으로 인식하는"이란 용어는 본 발명에 따르면, 여기서 정의된 각각의 인간 표적 분자의 적어도 두 개의 아미노산 포지션에서 특이적으로 상호작용 및/또는 결합할 수 있는 것을 의미한다. 항체들은, 단일한 표적분자의 다른 모티포들을 인식, 상호작용 및/또는 결합할 수 있다. 상기 용어는, 항체 분자의 특성, 즉 여기서 정의된 인간 표적 분자의 특정 영역을 분별하는 능력에 관한 것이다. 항원-상호작용-부위의 특정 항원의 특이적 상호작용은, 예를
들어 항원의 구조(conformation)의 변화, 항원의 올리고머화(oligomerization) 등의 유도에 기인하여, 신호의 개시를 가져올 수 있다. 그래서, 항원-상호작용-부위의 아미노산 서열의 특이적 모티프 및 항원은 그들의 1차, 2차 또는 3차 구조의 결과뿐 아니라 상기 구조의 2차 변형의 결과로 서로 결합한다.

본 발명에서 사용된 "특이적 상호작용"이란 용어는, 본 발명의 CD3 특이적 결합 구조체가 유사한 구조체들의 (폴리)펩티드들에 교차-반응(cross-react)하지 않거나, 또는 본질적으로 교차-반응하지 않을 수 없음을 의미한다. 따라서, 본 발명의 구조체는 인간 CD3와 특이적으로 결합/상호작용하여, 제2의, Ig-유래의 도메인에 기인하여, 특정 특정의 선택된 다른 화합물들, 항원들, 세포 표면 마커(marker)들, 종양 마커들 등과 상호작용하는 것이 가능하다. 상기 제2의, Ig-유래의 도메인이 지시되는 상기 분자들의 특정 예들은 여기서 이하에 제공된다.


용어 "에 결합하는/과 상호작용하는"은 선형(linear) 에피토프에 관한 것뿐 아니라, 임체구조(conformational) 에피토프, 구조적 에피토프 또는 인간 표면 분자의 특이적인 두 개 이상의 불연속(discontinuous) 에피토프에 관한 것으로 전달된다. 본 발명에서, 임체구조구조의 특이적 에피토프는 폴리펩티드가 원래의 단백질로 접히는 경우에 분자의 표면상에서 회합하는 임체구조구조의 특이적인 두 개 이상의 불연속(discrete) 아미노산 서열로 정의된다 (Sela, (1969) Science 166, 1365 및 Laver, (1990) Cell 61, 553-6).

용어 "불연속 에피토프"는 본 발명에서 폴리펩티드 쇄의 원격 부분의 잔기들로 조합되는 비-선형 에피토프들을 의미한다. 이들 잔기들은 폴리펩티드 쇄가 삼차 구조로 접히면서 임체구조구조의 특이적 에피토프를 구성할 때 분자의 표면상에서 회합한다.

본 발명의 구조체는 또한 하기에 기술되는 바와 같이 본원에 기술된 인간 CD3 복합체 또는 그 일부 또는 이와 동일한 역할을 수행하는 임체구조구조의 특이적 에피토프를 포함할 수 있다. 이에 따르는 임체구조구조의 특이적 에피토프는 항원의 특이적 결합 및/또는 항체의 항원 결합 영역을 포함한다.

따라서 특이성은 기술 분야에 공지된 방법 및 본 명세서에 기재된 방법에 의해 실험적으로 측정할 수 있다. 이러한 방법은 웨스턴 블롯, ELISA-, RIA-, ECL-, IRMA-시험 및 펩티드 스캔을 포함한다. 이에 제한되는 것은 아니다.

용어 "Ig-유래의 제2 결합 도메인"은 "면역글로불린-유래의 도메인"에 관한 것이며, 특히 항체 또는 그들의 단편, 단일 체 항체, 항산 항체, Fab, F(ab′)2, Fv 또는 scFv 단편 등과 같은 항체 단편, 또는 이들 중 어느 하나의 회화적으로 변형된 유도체에 관한 것이다. 이러한 항체 분자는 상이한 종들로부터 유래되거나, 기예외 기원(chimeric origin)일 수 있다. 가장 바람직하게는 (이하에서 설명한 바와 같이), 본 발명의 CD3 특이적 결합

의 T-세포 에피토프의 제거도 감소된 면역원성을 가져온다. 바람직하게는, 상기 분자는 VL 쇄의 CDR2 영역에서 탈면역화되고, 더욱 바람직하게는 VH 쇄의 CDR2 영역에서, 더욱 바람직하게는 VL 쇄의 CDR1 영역에서, 더욱 바람직하게는 VH 쇄의 CDR1 영역에서, 더욱 바람직하게는 VL 쇄의 골격 영역(FR)에서, 가장 바람직하게는 VH 쇄의 골격 영역(FR)에서 탈면역화된다.


본 발명에 따르면, 골격 영역은 항원과 접촉시키는 초가변(hypervariable) 상보성 결정 영역(CDR)에 대한 단백질 스케폴드(scaffold)를 제공하는, 면역글로불린 및 T-세포 수용체의 V 도메인(VH 또는 VL 도메인) 내의 영역에 관련된 것이다. 각각의 V 도메인에는, FR1, FR2, FR3 및 FR4로 지정된 4개의 골격 영역이 있다. 골격 1은 V 도메인의 N-말단으로부터 CDR1의 시작까지의 영역을 포함하고(encode), 골격 2는 CDR1 및 CDR2 사이의 영역에 관련된 것이고, 골격 3은 CDR2 및 CDR3 사이의 영역을 포함하고, 골격 4는 CDR3의 끝에서부터 V 도메인의 C-말단까지의 영역을 의미한다; 특히 Janeway, Immunobiology, Garland Publishing, 2001, 5th ed. 참조. 그러므로, 골격 영역은 VH 또는 VL 도메인 내의 CDR 영역 바깥의 모든 영역을 포함한다. 또한, 음용 "골격 및 CDR 영역 사이의 전이"은 골격 및 CDR 영역 사이의 직접 연결(direct junction)에 관한 것이다. 특히, 음용 "골격 및 CDR 영역 사이의 전이"은 CDR 영역을 둘러싸는 아미노산 또는 CDR 영역의 N- 또는 C- 말단에 직접적으로 위치하는 서열을 의미한다. 그러므로, 골격은 또한 상이한 CDR 영역 간의 서열을 포함할 수 있다. 당업자는 손쉽게 주어진 서열로부터 골격 영역, CDR 및 대응하는 전이 서열을 추론할 수 있다; Kabat (1991) Sequences
바람직한 본 발명의 세포독성적으로 활성인 CD3 특이적 결합 구조체는 또한 상기 제1 도메인 내에 서열 Met-Glu-Leu-Ser (MELS; 서열번호: 234)를 포함하는 곡적 H3을 포함한다. 보다 더 바람직한 본 발명의 구조체는 상기 제1 도메인 내에 서열 11e-Thr-Thr-Asp-Lys (ITTDK; 서열번호: 235)를 포함하는 곡적 H3을 포함한다.

본 발명에 따라, 인간 CD3에 특이적으로 결합/상호작용하고, T-세포 에피토프를 생성하는 감소된 성향을 갖는 본 발명 구조체의 제1 도메인은 여기서 정의한 CDR-H1, CDR-H2 및 CDR-H3 영역을, 바람직한 구체예에서는, 전술한 VH-곡적 (곡적 1.2.3.4), 특히 서열번호: 152 또는 153, 156 또는 157, 160 또는 161 및/또는 164 또는 165의 어느 하나에 나타낸 것과 같은 것을 포함한다. 그러므로, 본 발명의 CD3 특이적 결합 구조체는 인간 CD3에 특이적으로 결합하고, 서열번호 152 또는 153에 나타낸 것과 같은 곡적 영역 1, 서열번호 156 또는 157에 나타낸 것과 같은 곡적 영역 2, 서열번호 160 또는 161에 나타낸 것과 같은 곡적 영역 3 및/또는 서열번호 164 또는 165에 나타낸 것과 같은 곡적 영역 4를 포함하는 제1 도메인을 포함한다.

본 발명의 특히 바람직한 구체예에서, 세포독성적으로 활성인 탈면역화된 CD3 특이적 결합 구조체는 그 제1 도메인에 (a) 서열번호: 88로 나타낸 CDR-H1; 및 (b) 서열번호 90 또는 92로 나타낸 CDR-H2를 포함한다.

따라서, 변형된 CDR-H1 및 CDR-H2 영역은 T-세포 에피토프를 생성하는 감소된 성향을 가지며, CD3-ε쇄 특이적 항체로서의 CDR-H1 및 CDR-H2 영역은 T-세포 에피토프를 생성하는 감소된 성향을 가지며, 본 발명에 따라, 가장 바람직하게는 상기 (모(parental)) 항체는 TCR 복합체의 환경 중에 존재하는 인간 CD3의 입체구조 에피토프 또는 원래 또는 거의 원래의 구조를 반영하는 에피토프를 특이적으로 결합할 수 있어야 한다.

바람직하게는, 본 발명의 CD3 특이적 결합 구조체는 서열번호 74 또는 76으로 나타낸 VH-영역을 포함한다. 서열번호 74는 예시가 되는 탈면역화된 가변 중 영역(heavy region)을 나타내며, 이와 유사하게, 서열번호 76은 시가 되는 탈면역화된 가변 중 영역을 나타낸다.

바람직하게는, 본 발명의 CD3 특이적 결합 구조체는 서열번호 98 또는 100에 나타낸 것과 같은 CDR-L1, 서열번호 102에 나타낸 CDR-L2 및/또는 서열번호 104에 나타낸 CDR-L3을 포함한다.

본 발명의 CD3 특이적 결합 구조체는, 바람직한 구체예에서, VL 영역과 그 CD3-특이적 부위에 포함하며, 여기서 상기 VL 영역은 서열번호 78, 서열번호 80, 서열번호 82 및 서열번호 112를 포함하는 그룹으로부터 선택된다. 서열번호 78에 특징화된 바와 같은 VL1, 서열번호 80에 특징화된 바와 같은 VL2 및 서열번호 82에 특징화된 바와 같은 VL3은 본 발명에 따른 모두 탈면역화된 VL 영역에 관한 것이며, 또한 이들은 전술한 VH 영역과 다양하게 조합되어 사용될 수 있다. 그러나, 탈면역화 되지 않은 VL 영역을, 본 발명에 따라, 전술한 탈면역화된 VH 영역과 조합하는 것이 또한 예견된다. 본 발명의 세포독성적으로 활성인 CD3 결합 구조체에 바람직하게 사용된 탈면역화 되지 않은 VL영역은, 서열번호 112에 나타난다. 따라서, 본 발명의 CD3 구조체의 전술한 "제1 도메인"의 중세 부분만이 T-세포 에피토프를 생성하는 감소된 성향을 갖도록 변형될 수 있는 것은 아니다. 상기 도메인은 대응하는 가변 경제 부문들을 포함하는 것이 또한 예견된다. 서열번호 78, 80, 82, 88, 90, 92는 예를 들어, WO 99/54440에 기재된 구조체의 CD3 결합 부분의 탈면역화된 VL1, VL2, VL3 영역들을 나타낸다.

장학과 같이, 본 발명의 CD3 특이적 결합 구조체는, 가장 바람직하게는, scFv인 Ig-유래의 제2 도메인을 포함한다. 따라서, 본 발명의 가장 바람직한 구체예에서는, 인간 CD3에 대해 하나의 특이성 및 제2 scFv에 의해 매개되며, 추가적인 분자/화합물이 주로 상호작용하는 도메인, 즉 이중특이적 단일 쇄 항체 구조체에 관한 것이다. 이중특이적 구조체 내의 2 도메인/영역, 바람직하게는 단일 쇄로 서로 공유 결합된다. 이 결합은 직접적으로, 보다 더 바람직한 본 발명의 구조체는 단일 쇄로 서로 공유 결합된다. 이 결합은 직접적으로.

본 발명에 따라 사용되는 용어 "단일 체"는 이중특이적 단일 체 구조체의 상기 제1 및 제2 도메인이 바람직하게는 단일 핵산 분자에 의해 인코딩된 공-선형(co-linear) 아미노산 서열의 형태로 공유 결합되는 것을 의미한다.

본 발명의 구조체는 여기서 정의된 제1 도메인 및 Ig-유래의 제2 도메인에 대하여, 예를 들면, 재조합으로 생성된 도메인의 분리 및/또는 제조용의 추가적인 도메인을 포함할 수 있음을 주목해야 한다.

본 발명에 따라, 본 발명의 CD3 구조체의 인간 CD3에 특이적으로 결합하는 전술한 제1 도메인만이 T-세포 에피토프 생성에 대해 감소된 성향을 갖는 것이 아님을 주목해야 한다. Ig-유래의 제2 도메인 및/또는 (a) 연결 링커-영역(들)은, 예를 들어 인간화 및/또는 또한 탈면역화되어 변형되는 것이 또한 예정된다. 전술과 같이, 일반화대한 수법은 특히 WO 00/34317, WO 98/52976, WO 02/079415 및 WO 02/012899 및 첨부한 실시예들에 개시되어 있다. 이러한 수법은 잠재적 T-체포에 에피토프 내의 아미노산의 치환의 수행을 수반한다. 이런 식으로, 주어진 서열이 세포 내 단백질 가공시 T-세포 에피토프 생성시킬 가능성은 감소한다. 또한, WO 92/10755는 단백질 상의 항원 결정기를 처리하는 수법을 기재하고 있다. 특히, 단백질들은 에피토프 매핑되고, 그들의 아미노산 서열은 유전공학을 통해 변경된다.

접하게 닮기 위해 비-인간으로부터 유래된 하나 이상의 아미노산을 그 안에 도입하여 가진다. 항체/항체 분자의
들면 EpCAM에 대해 지식되는 항체는 기술분야에서 공지되어 있다. 예를 들어, (LoBuglio, Proceedings of the
American Society of Clinical Oncology (Abstract), 1997, 1562 및 Khor, Proceedings of the American

따라서, 본 발명의 내용에는, 특히 이중특이적 단일 쇄 항체 구조체들이 제공되며, 이들은 탈면역화되고, 약학
적 조성물에 성공적으로 사용될 수 있다.

전술한 바와 같이, 전술한 CD3 특이적 결합 구조체의 Ig-유래의 제2 도메인은 세포 표면 분자에 특이성을 갖는
항원-상호작용-부위를 포함할 수 있다.

여기서 사용된 용어 "세포 표면 분자"는 또한 세포의 표면상에 존재하는 분자를 나타낸다. 용어 "세포 표면 분자"
는 세포의 표면상에 존재하여 Ig-유래의 결합 도메인에, 바람직하게는 항체, 항체 단편 또는 유도체들에 (생
체 외 또는 생체 내에서) 접근할 수 있는 도메인 또는 에피토프를 포함하는, 분자에 관한 것이다. 전술한 바와
같이, 가장 바람직하게는 상기 Ig-유래의 도메인은 scFv이다. 상기 세포 표면 분자들에 대한 예는 또한, 막 및 막
합 단백질, 상기 표면 또는 세포 표면 등에 적용된(adapted) 요소들이 있다. 본 발명의 다른 바람직한 구체에
에 따라 상기 세포 표면 분자는 종양 특이적 마커이다. 본 발명의 내용에서, 용어 "종양 특이적 마커"는 분자에
관한 것이며, 이는 종양 세포의 표면에 존재 및/또는 위치하거나 또는 어디에서도 발현되지만 종양 세포의 표
면상에서 항체, 항체 단편 또는 항체 유도체의 결합에 대해서도 이용할 수 있다. 종양 마커의 예들은 이하에 제
공되며, 여기에 한정되는 것은 아니지만, EpCAM, CD19, HER-2, HER-2 neu, HER-3, HER-4, EGFR, PSMA, CEA,
MUC-1 (뮤신(mucin)), MUC2, MUC3, MUC4, MUC5ac, MUC5b, MUC7, Lewis-Y, CD20, CD23, CD30, CD44v6, Wue-1,
형질 세포 항원(Plasma Cell Antigen)(WO 01/47953 참조), 막-결합(membrane-bound) IgE, 층막 콘도리인
황산염 프로테오글리칸(MCSP), STEAP, 메소텔린(mesothelin), 전립선 증기세포 항원 (PSCA), stn (시알릴화
(sialylated) Tn 항원), FAP (상유아세포(fibroblast) 환성화 항원), EGFRv111, Igα, Igβ, MT-MMPs, 코라 항
원(Cora antigen), EphA2, L6 및 CO-29를 포함한다.

본 발명의 CD3 특이적 결합 구조체의 Ig-유래의 제2 도메인은 EpCAM, CCR5, CD19, HER-2, HER-2 neu, HER-3,
HER-4, EGFR, PSMA, CEA, MUC-1 (뮤신), MUC2, MUC3, MUC4, MUC5ac, MUC5b, MUC7, Lewis-Y, CD20, CD23,
CD30, 강글리오시드(ganglioside) GD3, 9-0-아세틸-GD3, GM2, 글로보(Globo) H, 뷰로실(fucosyl) GM1, 폐리 SA, GD2, 카르보안화이드라세 IA (MB/CA IA)X, CD44v6, 소닉 헨도호그(Sonic Hedgehog) (Shh), Wue-1, 형
질 세포 항원, (막-결합) IgE, 층막 콘도리인 황산염 프로테오글리كان(MCSP), STEAP, 메소텔린(mesothelin), 전립선 증기세포 항원 (PSCA), stn (시알릴화 (sialylated) Tn 항원), FAP (상유아세포(fibroblast) 환성화 항원), EGFRv111, Igα, Igβ, MT-MMPs, 코라 항
원(Cora antigen), EphA2, L6 및 CO-29를 포함한다.

여기서 제공된 구조체들은 의학적 세팅에 특히 유용하다. 예를 들면, 종양성 질환 및/또는 림프종, 바람직하게
는 비(非)-호지킨 B-세포 림프종은 인간 CD3 및 CD20 (CD3xCD20 또는 CD20xCD3)에 대해 지시된 본 발명의 탈면
역화된(이중특이적) 구조체로 치료할 수 있다. 자가면역 질환은 인간 CD3 및 CD20 (CD3xCD20 또는 CD20xCD3)
에 대해 지시된 본 발명의 탈면역화된(이중특이적) 구조체로 치료할 수 있다. 유합항체의 관점에서, 이는 역
용성 질환은 인간의 CD3 및 CCR5 (CD3xCD5 또는 CCR5xCD3)에 대해 지시된 본 발명의 탈면역화된 (이중특이적)
구조체로 치료할 수 있다. 여기서 정의되고 TNF-
알파 전구체에 대해 지식되고/결합하는 제2 Ig-유래의 도메인을 포함하는 탈면역화된 CD3 특이적 결합 구조체
는 또한 양성성 질환의 치료 및/또는 예방에 유용할 수 있다. 여기서 제공된 EpCAM, CD19, HER-2, HER-2 neu, HER-
3, HER-4, EGFR, PSMA, CEA, MUC-1 (뮤신), MUC2, MUC3, MUC4, MUC5ac, MUC5b, MUC7, Lewis-Y, CD20, CD23,
CD30, CD44v6, Wue-1, 형질 세포 항원 (WO 01/47953 참조), (막-결합) IgE, 층막 콘도리인 황산염 프로테오
글리칸(MCSP), STEAP, 메소텔린, 전립선 증기세포 항원 (PSCA), stn (sialylated Tn antigen), FAP (fibroblast activation antigen), EGFRv111, Igα, Igβ, MT-MMPs, 코라 항원, EphA2, L6 및 CO-29에 대해 지
시되고/에 결합하고/와 상호작용하는 제2의, Ig-유래의 도메인을 포함하는 CD3 구조체는 특히 유용하다.
전립선암, 두경부암, 피부암(흑색종), 예를 들어 난소암, 자궁내막암, 자궁경부암 및 신장암과 같은 비뇨-생식 기관의 암, 폐암, 위암, 소장암, 간암, 췌장암, 신암 및 갑상선암과 같은 종양성 질환, 또는 혈액암, 신경교종(gliomas), 육종 또는 골육종과 같은 기타 종양성 질환의 의학적 시술에 유용할 수 있다. CD3 결합 구조체의 주의는 또한 미세 잔류 질환(minimal residual disease), 바람직하게는 초기 고형 암, 진행된 고형 암 및 전이성 고형 암에 대해 지시된다.

또한 첨부한 실시예에서 나타낸 바와 같이, 본 발명의 특히 바람직한 CD3 특이적 결합 구조체는 T-세포 에피토프를 생성하는 감소된 성향을 갖는 전술한 제1 도메인 및 EpCAM에 대해 특이성을 갖는 항원-상호작용 부위를 포함하는 제2의, Ig-유래의 도메인을 포함한다.


가장 바람직한 구체예에서, EpCAM에 대해 지시되고/결합하는 제2 Ig-유래의 도메인을 포함하는 본 발명의 CD3 특이적 결합 구조체는 다음과 그로으로부터 선택되는 아미노산 서열을 포함한다:


(b) 서열번호: 30, 32, 34, 36, 38, 48, 54, 57, 60, 62, 64, 66, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322 및 324의 어느 하나의 아미노산 서열; 

(c) 상기 (b)의 뉴클레오티드 서열에 대한 유전자 코드(genetic code)의 결과로서 축퇴하는(degenerate) 핵산 서열에 의해 인코딩된 아미노산 서열. 

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따라서, 본 발명은, 특히 바람직한 구체예에서 T-세포 에피토프를 생성하는 감소된 성향을 갖는 CD3 결합/상호작용 부분("항-CD3") 및 EpCam과 특이적으로 상호작용/결합하는("항-EpCam") 추가적인 단일 셋 부분(일반 품종의 도메인)을 포함하는 특이적 CD3 구조체를 제공한다. 다음의 표 1A, 1B, 2A, 2B, 3A, 3B, 4A, 4B, 5A 및 5B는 상기 CD3 및 EpCam 결합 구조체의 바람직한 구성(configuration)에 관한 것이다.

EpCam 3-1, EpCam 3-5, EpCam 4-1, EpCam 4-7 및 EpCam 5-10은 WO99/25818에서 기술된_antibody_interceptor 시스템에 의해 분리된 CD3 및 EpCam에 대한 특이적 단일 셋 형제에 관한 것이다.


만일 단백질 모듈 A가 VII 형제 도메인인 경우, 단백질 모듈 C는 VL 단백질 도메인이며, 그 역도 성립한다. 만일 단백질 모듈 E가 VII 형제 도메인인 경우, 단백질 모듈 G는 VL 단백질 도메인이며, 그 역도 성립한다.

인간 CD3 항체에 대해 특이성을 가지는 항체의 탈면역화된 VII 도메인은 서열번호: 74 또는 76에 나열된 서열들에서 선택될 수 있다. 인간 CD3 항체에 대해 특이성을 가지는 항체의 탈면역화된 VII 도메인은 서열번호: 78, 80 또는 82에 나열된 서열들에서 선택될 수 있다. 인간 EpCam 3-1, 3-5, 4-1, 4-7 및 5-10 항체의 VII 형제 도메인은 각각, 서열번호: 137, 141, 145, 149 및 133에 나열된 것이다. 인간 EpCam 3-1, 3-5, 4-1, 4-7 및 5-10 항체의 VL 형제 도메인은 각각, 서열번호: 139, 143, 147, 151 및 135에 나열된 것이다.


만일 단백질 모듈 A가 VII 형제 도메인을 인코딩하는 경우, 핵산 모듈 C는 VL 단백질 도메인을 인코드하며, 그 역도 성립한다. 만일 단백질 모듈 E가 VII 형제 도메인을 인코딩하는 경우, 핵산 모듈 G는 VL 단백질 도메인을 인코드하며, 그 역도 성립한다.

3-5, 4-1, 4-7 및 5-10 항체의 VH 단백질 도메인을 인코드하는 핵산 분자는 각각 서열번호: 136, 140, 144, 148 및 132에 제시된 것이다. 인간 EpCAM 3-1, 3-5, 4-1, 4-7 및 5-10 항체의 VL 단백질 도메인을 인코드하는 핵산 분자는, 각각 서열번호: 138, 142, 146, 150 및 134에 제시된 것이다.


핵산 모듈 A-B-C의 조합 및 핵산 모듈 E-F-G의 조합은 각각 인간 CD3 항원 또는 EpCAM 항원 중 어느 하나에 대해 특이성을 가지는 항체의 하나의 scFv 단편을 구성한다. 만약 A 및 C 모듈이 CD3 결합 시열을 포함하면, 핵산 모듈 A-B-C 및 E-F-G의 각 그룹은 서열번호 175에 제시된 뉴클레오티드 시열을 가지는, 핵산 모듈 D를 통해서 서로 연결된다. 만약 A 및 C 모듈이 EpCAM 결합 시열을 포함하면, 핵산 모듈 A-B-C 및 E-F-G의 각 그룹은 서열번호 173에 제시된 뉴클레오티드 시열을 가지는, 핵산 모듈 D를 통해서 서로 연결된다. 그러나, 전술한 바와 같이, 서열번호 175 내의 서열을 인코드하는 추가적인 코돈이 클로닝 목적으로 삽입될 수 있다. 당업자는 서열번호 173으로 나타낸 뉴클레오티드 시열의 5' 말단에 세린을 인코드하는 코돈이 없이 VL 비도미노드 도메인을, 후속하는 V 도메인과 직접 연결할 수 있다. 핵산 모듈 D는 핵산 모듈 C의 3'-말단을 핵산 모듈 E의 5'-말단과 연결하는 기능을 한다.

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표 2B  단일체 항-EPICAM-3-5 가변 영역을 포함하는 탈면역화된 항-인간 CD3 구조체 : 뉴클레오티드 서열

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표 3A  단일체 항-EpCAM 4-1 가변 영역을 포함하는 탈면역화된 항-인간 CD3 구조체 : 애니노산 서열

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따라서, 본 발명은 또한 하기 (a)부터 (d)로 이루어지는 그룹으로부터 선택되는, 인간 CD3에 특이적으로 결합
하고 T-세포 에피토프를 생성하는 감소된 경향을 갖는 제1 도메인; 및 EpCAM에 대해 지시되는/EpCAM에 결합할 수 있는, Ig-유래의 제2 도메인을 포함하는 CD3 특이적 결합 구조체를 제공한다:


(c) 상기 (b)의 뉴클레오티드 서열에 대한 유전자 코드의 결과로 축퇴하는 핵산 서열에 의해 인코딩되는 아미노산 서열;


본원에서 사용된 바와 같은 "하이브리드화(hybridizing)"이란 용어는, 본원에서 정의된 탈면역화된 구조체를 인코드하는 폴리뉴클레오티드/핵산 서열을 뜻한다. 그러므로 상기 폴리뉴클레오티드는 RNA 또는 DNA 준비시 각기, 노던 또는 써던 블롯 분석에서 탐침으로서 유용할 수 있고, 또는 그들의 각각의 크기에 따라 PCR 분석에서 올리고뉴클레오티드 프라이머로서 사용될 수 있다. 바람직하게는, 상기 하이브리드화 폴리뉴클레오티드는 길이가 적어도 10, 더 바람직하게는 적어도 15 또는 그 이상의 뉴클레오티드를 포함하고, 탐침으로 사용될 본 발명의 하이브리드화 폴리뉴클레오티드는 길이가 적어도 100, 더 바람직하게는 적어도 200 또는 가장 바람직하게는 적어도 500 뉴클레오티드를 포함한다.


"엄격한 하이브리드화 조건"은, 즉, 50% 포름아마이드, 5x SSC (750 mM NaCl, 75 mM 구연산 나트륨), 50mM 스리온 포스페이트(pH 7.6), 5x 멘하르트 용액, 10% 백스탄 석회석, 및 20㎍/ml 의 변성되고 전단된 연어 정액 DNA를 함유하는 용액 중 42℃에서 하룻밤 인큐베이션(incubation)한 다음 약 65℃에서 0.1 x SSC 중에서 필터를 세척하는 것을 나타낸다. 또한 더 낮은 엄격 하이브리드화 조건에서 본 발명의 폴리뉴클레오티드에 하이브리드화하는 핵산 분자가 고안되었다. 하이브리드화 및 선풍 검출의 엄격함의 변화는 포름아마이드 농도 (포름아마이드의 더 낮은 백분율은 저하된 엄격함을 야기한다); 하이브리드화 및 선풍 검출의 엄격함의 변화는 포름아마이드 농도 (포름아마이드의 더 낮은 백분율은 저하된 엄격함을 야기한다); 엄격한 하이브리드화 조건에서 본 발명의 폴리뉴클레오티드 또는 그들의 일부는 하이브리드화할 수 있는 폴리뉴클레오티드이다.

SDS, 30% 포름아마이드, 100㎍/ml 연어 정액 물로기 DNA를 포함하는 용액 중에 37℃에서 하룻밤 인큐베이션한 다음, 약 50℃에서 1 x SSPE, 0.1% SDS로 세척을 포함한다. 그 외에, 훨씬 낮은 엄격함을 달성하기 위하여, 엄격한 하이브리드화 후에 수행되는 세척은 더 높은 엄 농도 (예, 5x SSC)에서 행할 수 있다. 상기 조건에서 변이온은 하이브리드화 실험에서 배경을 억제하지 않아야 한다: 엄격한 하이브리드화 조건에서 본 발명의 폴리뉴클레오티드 또는 그들의 일부는 하이브리드화할 수 있는 폴리뉴클레오티드이다.
여 상술한 하이브리드화 조건의 변형을 필요로 할 수 있다.

기술된 핵산 분자는 예를 들어 DNA, cDNA, RNA 또는 합성으로 생성된 DNA 또는 RNA, 또는 단독으로 또는 조합으로 이들 폴리뉴클레오티드의 어느 것을 포함하는 재조합적으로 생산되는 키메라 핵산 분자일 수 있다.

본 발명에 제공된 탐면역화된 CDR 및 EpCAM 결합 구조체는 의학적 세팅에, 예를 들면 종양질환, 특히 유방암, 대장암, 침윤성 암, 피부암 (흑색종) 등 다양한 암종의 치료, 대장암, 전립선암, 피부암 (흑색종), 비뇨생식기의 암, 약물 투여 담소암, 자궁내막암, 자궁경부암 및 신장암, 패혈, 암암, 장암, 소장암, 줄기세포암, 호르몬암, 신장암의 치료, 그리고 감상선암의 예방, 치료 및/또는 개선에 특히 유용하다. 특히, CD3 및 EpCAM에 결합하는 탐면역화된 구조체는 상피암, 바람직하게는 상피암의 치료와 개선에 사용될 수 있다.

여기에 기술된 CD3 특이적 결합 구조체의 보다 특히 바람직한 구체예에서, 상기 구조체는, CCR5에 특이성을 갖는 항원-항체작용 부위를 포함하는 제2 Ig-유래의 도메인을 포함한다.

케모카인(chemokine) 수용체 CCR5는 전염증성(proinflammatory) 케모카인들인 RANTES, MIP1-α, MIP1-β 및 MCP-2 이 결합하는, G 단백질이 결합하 G 단백질이 결합한 7개의 막횡단 도메인 수용체의 큰 패밀리의 구성원이다. 케모카인은 백혈구의 혈관 밖으로 유출을 유도하기 위해 그리고 그들은 손상 밖으로 향하게 하기 위해, 부착 분자(adhesion molecule)와 협력하여 작용한다. CCR5는 단핵세포 및 T-세포의 소수에서 발현되고, 또한 HIV-감염 경로의 초기에 우세한 M-항성 (M-tropic) HIV-1 스테로이드(strain)에 대한 주요 공동-수용체이다.

(infiltrating) T-세포에서 뿐 아니라 병원작용 환자의 면역학적 차원에서 우월하게 발현된다는 것이 보여졌다. T-세포를 제거하면, 이 자가면역질환의 T-세포 팔(arm)을 차단할 것이다.

[0101]
CCR3 및 CCR5의 높은 발현은 또한 호전된 환자의 말초혈액에서 우하여 발현된 T 세포 및 B 세포에서 발견되었다.

[0102]
당뇨병 타입 I은 T-세포 매개의 자가면역 질환으로 간주된다. CCR5 수용체의 유효성의 상승에 대한 허혈으로서 사용할 수 있다. 따라서, T-세포의 경우에서도, 본 발명의 적극적도의 도메인을 포함하는 이중특이적 구조체에 관한 것으로, 여기서 제1 도메인은 인간 CD3에 특이성을 제공하고 T-세포 에피포트를 생성하는 감소된 영향을 가지며, 이에 의해 상기 Ig-유래의 제2 도메인 (인간) CCR5에 특이적인 항체로부터 유래되는 것이다. 가장 바람직하게는, 그러한 구조체는 본원에 정의된 바와 같은 단일 체 scFv이다.

[0103]

[0104]

[0105]
갖는 단백질 모듈 D 을 통해 서로 연결된다. 또다른 링커 서열번호: 175 가 또한 VL 도메인을 뒤이은 V 도메인 (클로닝 목적으로 사용한 세린 잔기를 인코딩하는 추가의 코돈을 포함)과 접합시키는 데 사용될 수 있다.

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바람직하게는 상기 구조체는 하기 그룹으로부터 선택되는 아미노산 서열을 포함한다:

(a) 서열번호: 206, 208, 210, 212, 214 또는 216 중 어느 하나의 아미노산 서열;
(b) 서열번호: 205, 207, 209, 211, 213 또는 215 중 어느 하나의 핵산 서열에 의해 인코드되는 아미노산 서열; 및
(c) 상기 (b)의 뉴클레오티드 서열에 대한 유전자 코드의 결과로서 축퇴하는 핵산 서열에 의해 인코드되는 아미노산 서열; 및
(d) 엄격한 하이브리드화 조건하에 상기 (b)에 정의한 바와 같은 핵산 서열의 상보적 가닥으로 하이브리드화하는 핵산 서열에 의해 인코드되는 아미노산 서열.

CCR5 및 CD3 결합 구조체 서열번호: 206, 208, 210은 표 6의 구조체 5를 나타내고 서열번호: 212, 214 및 216은 구조체 13을 나타내며, 3개의 상이한 VL 영역 (VL1 (서열번호:78), VL2 (서열번호:80), 또는 VL3 (서열번호:82))을 갖는다.

본 발명은 또한, 인간 CD3에 특이적으로 결합하고 T 세포 에피포트를 생성하는 감소된 경향을 갖는 제1 도메인 및 상기 (b)에 정의된 핵산 서열, 즉 서열번호: 205, 207, 209, 211, 213 또는 215의 어느 하나의 핵산 서열의 상보적 가닥을 엄격한 하이브리드화 조건 하에서 하이브리드화하는 핵산 서열에 의해 인코드되는 아미노산 서열을 포함하는 CCR5에 대해 지시하고(CCR5에 결합할 수 있는 Ig-유래의 제2 도메인을 포함하는 CD3 특이적 결합 등록특허 10-1229731)
구조체를 제공한다. 용어 "하이브리드화" 및 "엄격한 조건"은 상기에 기술되었다. 상응하는 정의들 및 구체에는 필요한 변경을 가하여 본원에 적용한다.

여기에 제공된 탈면역화된 CD3 및 CCR5 결합 구조체는 바이러스성 질환, 특히 HIV 감염 및 AIDS, 또는 자가면역 질환 및/또는 류마티스성 관절염과 같은 염증성 질환의 의료적 시술에 특히 유용하다.

또다른 구체예에서, 본 발명은 상기 정의된 CD3 특이적 결합 구조체를 제공하는데, 본 발명의 구조체의 Ig-유래의 제2 도메인은 CD19에 특이성을 갖는 항체-상호작용 부위를 포함한다.


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</table>
더 바람직한 구체예에서, 본 발명은 상기 기술된 것과 같은 CD3-결합 도메인을 포함하는 탈면역화된 CD3-특이적 결합 구조체, 및 CD19, 바람직하게는 인간 CD19에 특이적으로 결합/상호작용하는 제2, Ig-유래의 도메인을 포함하는 탈면역화된 CD3-특이적 결합 구조체를 제공하는데, 이때 상기 CD3-특이적 결합 구조체는 하기 그룹으로부터 선택되는 아미노산 서열을 포함한다:


(c) 상기 (b)의 뉴클레오티드 서열에 대한 유전자 코드의 결과로 축퇴하는 핵산 서열에 의해 인코딩된 아미노산 서열; 및

(d) 엄격한 하이브리드화 조건에서 상기 (b)에 정의된 핵산 서열의 상보적 가닥과 하이브리드화된 핵산 서열에 의해 인코딩된 아미노산 서열.
등록특허 10-1229731
[0128]

본 발명에 따른 바람직한 CD19 및 CD3 결합 구조체는 표 7의 구조체 5를 나타내는 서열번호:190, 192, 194 및
구조체 13를 나타내는 서열번호:196, 198 및 200이고, 3개의 상이한 VL 영역 (VL1 (서열번호:78), VL2 (서열번
호:80), 또는 VL3 (서열번호:82))를 갖는 것이다.

[0129]

본 발명은 또한 인간 CD3에 특이적으로 결합하고 T-세포 에피토프를 생성하는 경향이 감소된 제1 도메인; 및 엄
격한 하이브리드화 조건 하에서 상기 (b)에 정의된 핵산 서열, 즉 서열번호:

189, 191, 193, 195, 197, 199,

366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404,
406 또는 408의 어느 하나의 핵산 서열의 상보적 가닥과 하이브리드화하는 핵산 서열에 의해 인코드되는 아미노
산 서열을 포함하는, CD19에 대해 지시된/CD19에 결합할 수 있는, Ig-유래의 제2 도메인을 포함하는 CD3 특이적
결합 구조체를 제공한다. 용어 "하이브리드화" 및 "엄격한 조건"은 상기에 기술되었다. 상응하는 정의들 및 구
체예는 필요한 변경을 가하여 본원에 적용한다.
[0130]

여기에 제공된 탈면역화된 CD3 및 CD19 결합 구조체는 증식성 질환, 종양성 질환, 염증성 질환, 면역학적 장애,
자가면역 질환, 감염성 질환, 바이러스 질환, 알레르기 반응, 기생충 반응, 이식대숙주병, 숙주대이식병 또는
B-세포 악성종양, 특히 B 세포 비-호지킨 림프종, 호지킨 림프종 또는 B 세포 백혈병 (예를들면, B 세포 급성
림프성 백혈병 (B-ALL), (예를 들면, 털세포 림프종) B 세포 전구체 급성 림프성 백혈병 (pre-B-ALL), B 세포
만성 림프성 백혈병 (B-CLL)) 백혈병의 예방, 치료 및 개선에 특히 유용하다.

[0131]

추가의 구체예에서, 본 발명은 인간 CD3에 특이적으로 결합하고 T-세포 에피토프를 생성하는 경향이 감소된 제1
도메인; 및 Ig-유래의 제2 도메인을 포함하고 CD20에 대해 특이성을 갖는 항원-상호작용 부위를 포함하는 CD3
특이적 결합 구조체에 관한 것이다.

[0132]

CD20 는 B-림프구에 존재하는 세포 표면 단백질들 중의 하나이다. CD20 항원은 90%를 초과하는 B-세포 비-호지
킨 림프종 (NHL)에서의 것들을 포함하여, 정상 및 악성 예비-B 및 성숙한 B 림프구에서 발견된다. 항원은 조혈
줄기 세포, 활성화된 B 림프구 (형질 세포(plasma cells)) 및 정상 조직에는 없다. 대부분이 뮤린(murine) 기원
인 여러 항체들이 기술되어 왔다: 1F5 (Press 등, 1987, Blood 69/2, 584-591), 2B8 / C2B8, 2H7, 1H4 (Liu
등, 1987, J Immunol 139, 3521-3526; Anderson 등, 1998, 미국 특허 번호 5,736,137; Haisma 등, 1998,

[0133]

CD20는 캐리어 단백질에 연결된 scFv를 인코드하는 DNA로 예방접종하는 것을 사용하는 형질 세포 악성종양의 치
료를 위한 면역요법적 전략에 기술되어 왔고 (Treon 등, 2000, Semin Oncol 27(5), 598) 면역요법적 치료에서
CD20 항체 (IDEC-C2B8)의 사용이 비-호지킨 B-세포 림프종의 치료에 효과적인 것으로 보여져 왔다. CD20 항체는
비-호지킨 림프종에서 효능 및 참을수 있음(tolerability)이 증명되었고, 이전에 치료받지 않은 또는 재발된/고
질의(refractory) 무통성 비-호지킨림프종 각각에서 73% 및 48%의 반응률을 달성하였다 (Montserrat, 2003,
Semin Oncol 30(1suppl2), 34-39). 게다가, CD20 항체는 재발 또는 발전된 단계의 B-세포 신생물(neoplasms)을
약 50%의 효능으로 치료하는데 널리 사용되어 왔다.

[0134]

본 발명의 특히 바람직한 구체예에서, CD3-특이적 결합 구조체가 제공되고, 이는 CD3에 대해 지시되는/CD3에 결
합하는/CD3와 상호작용하는, 탈면역화된 도메인 및 CD20에 특이적으로 결합/CD20와 상호작용 하는 제2 Ig-유래
의 도메인을 포함한다. 그러한 구조체는 표 8A 및 8B에 나타난다. 표 8A 및 8B의 모듈 A-G 은 표 1-5에 대해 상
기 언급된 바와 같이 정의될 수 있다. 인간 CD3 항원에 대해 특이성을 갖는 항체의 탈면역화된 VH 도메인들은,
서열번호: 74 또는 76에 기술된 바와 같은 서열들로부터 선택될 수 있다. 인간 CD3 항원에 대해 특이성을 갖는
항체의 탈면역화된 VL 도메인들은, 서열번호: 78, 80 또는 82에 기술된 바와 같은 서열들로부터 선택될 수
있다. 인간 CD20 항체의 VH 단백질 도메인은 서열번호: 170 에 기술된 것과 같다. 인간 CD20 항체의 VL 단백질
도메인은 서열번호: 172에 기술된 것과 같다. 모듈 쌍 A/C 또는 E/G 의 어느 하나가, 인간 CD3 항원에 대해 특
이성을 갖는 항체로부터의 탈면역화된 VH/VL 또는 VL/VH 단백질 도메인들의 쌍이면, 단백질 모듈 B 또는 F 각각
은, 서열번호: 3에 기술된 바와 같은 아미노산 서열을 갖는다. 모듈 쌍 A/C 또는 E/G 의 어느 하나가, CD20 항
원에 대해 특이성을 갖는 항체로부터의 VH/VL 또는 VL/VH 의 쌍이면, 단백질 모듈 B 또는 F 각각은, 서열번호:
168에 기술된 바와 같은 아미노산 서열을 갖는다. 단백질 모듈 A-B-C 및 E-F-G 의 각각의 그룹은, 서열번호:
174에 기술된 바와 같은 서열을 갖는 단백질 모듈 D 을 통해 서로 연결된다. 그렇지만, 상기 언급된 바와 같이,
추가의 세린이 VL 및 뒤이은 V 도메인 사이에 클로닝 목적을 위해 도입될 수 있다 (서열번호:176에 기술된 것과
같은 링커).

[0135]

인간 CD3 항원에 대해 특이성을 갖는 항체의 탈면역화된 VH 도메인들을 인코드하는 핵산 분자들이, 서열번호:

- 36 -



표 8A

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<tr>
<th>서지</th>
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<td>C</td>
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<tr>
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<td>B</td>
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표 8B

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</tbody>
</table>

[0137]

더 바람직하게는, 본 발명의 탈면역화된 CD3 및 CD20 결합 구조체는 하기 그룹으로부터 선택되는 아미노산 서열을 포함한다:

(a) 서열번호: 218, 220, 222, 224, 226, 또는 228 중 어느 하나의 아미노산 서열;

(b) 서열번호: 217, 219, 221, 223, 225 또는 227 중 어느 하나의 핵산 서열에 의해 인코드되는 아미노산 서열 및

(c) 상기 (b)의 뉴클레오티드 서열에 대한 유전자 코드의 결과로서 축퇴하는 핵산 서열에 의해 인코드되는 아미노산 서열 및

(d) 엄격한 하이브리드화 조건하에 상기 (b)에 정의한 바와 같은 핵산 서열의 상보적 가닥과 하이브리드화되는 핵산 서열에 의해 인코드되는 아미노산 서열.

[0138]

[0139]

[0140]

[0141]

[0142]

본 발명은 또한, 인간 CD3에 특이적으로 결합하고 T 세포 에피토프를 생성하는 감소된 경향을 갖는 제1 도메인 및 엄격 하이브리드화 조건에서 상기 (b)에 정의된 핵산 서열, 즉 서열번호: 217, 219, 221, 223, 225 또는 227의 어느 하나의 핵산 서열의 상보적 가닥과 하이브리드화하는 핵산 서열에 의해 인코드되는 아미노산 서열을 포함하는 CD20에 대해 지식되는/CD20에 결합할 수 있는 Ig-유래의 제2 도메인을 포함하는 CD3 특이적 결합 구조체를 제공한다. 용어 "하이브리드화" 및 "엄격한 조건"은 상기의 기술하였다. 상용하는 정의들 및 구체에서는 필요
한 변경을 가하여 본원에 적용한다.

여기에 기술된 탈면역화된 CD3 및 CD20 결합 구조체는 B-세포 관련 장애의 치료, 예방 및/또는 개선, 바람직하게는 혈-호지킨 림프종의 치료에의 용도가 예정될 수 있다.

본 발명은 또한 본 발명의 CD3 특이적 결합 분자를 인코드하는 핵산 서열을 제공한다.


계다가, 추가의 목적의 위해, 핵산 분자들은 예를 들면, 티오에스테르 결합 및/또는 뉴글리세오이드 유사체를 포함할 수 있다는 것을 예정할 수 있다. 상기 변경은 세포내의 앤도- 및/또는 엑소뉴클레아제에 대한 핵산 분자의 안정화에 유효할 수 있다. 상기 핵산 분자들은, 세포내에서 상기 핵산 분자의 전사를 가능하게 해주는 키메라 유전자를 포함하는 적절한 백테리에 의해 전사될 수 있다. 이 점에서, 그러한 풀리뉴클레오티드는 "유전자 표적화" 또는 "유전자 요법적" 수법을 통해 사용할 수 있는 것으로 또한 예상된다. 또 하나의 구체예에서는 상기 핵산 분자가 표적화된다. 핵산의 검출법은 예를 들면, 세포 및/또는 노던 블로팅(blotting), PCR 또는 프라이머 신장(primer extension)으로 당해 분야에 잘 알려져 있다. 이 구체예에는 유전자 요법 수법 중에 상술한 핵산분자의 성공적인 도입을 입증하는 스크리닝 방법에 유효할 수 있다.

상기 핵산 분자(들)은, 전술한 핵산 분자의 어느 것을 단독으로 또는 조합으로 포함하는, 제조목적으로 생성된 키메라 핵산분자일 수 있다. 바람직하게는, 상기 핵산분자는 백테리의 일부이다.

따라서 본 발명은 본 발명에서 기술된 핵산분자를 포함하는 백테리에 관한 것이다.


바람직하게는 상기 백테리가 여기에 정의된 이중특이적 단일 세 항체 구조체를 인코드하는 상기 핵산 서열에 작동적으로 연결된 조절서열이 있다. 이러한 조절서열은, 전사의 시작과 중간, 전사의 종료, 전사 후의 이동지를 포함한다.

상기 백테리는 여기에 기술된 이중특이성 단일 세 항체 구조체를 인코드하는 핵산분자를 포함하는 백테리의 경우로 예정된다.

용어 "조절서열"은 관리되는(ligated) 코딩 서열의 발현을 수행하는데 필요한 DNA 서열을 말한다. 상기 컨드트 서열의 성질은 숙주 유기체에 따라 다르다. 원핵생물에서, 컨드트 서열은 일반적으로 프로모터, 리보좀 결합 부위 및 터미네이터(terminator)를 포함한다. 전사생물에서는 일반적으로 컨드트 서열은 프로모터, 터미네이터 및 일부의 경우에 인렌서, 전사활성화인자(transactivator) 또는 전사 인자를 포함한다. 상기 용어 "컨드트 서열"은 활성화자(트랜스점극자)를 포함하는 것으로 의도되며, 또한 추가의 유리한 성분들을 포함할 수 있다.

용어 "작동적으로 연결된(operably linked)"은 전술한 성분들이 그들의 의도한 방식으로 기능하도록 하는 관계에 있는 별개의 분리를 나타낸다. 코딩서열에 "작동적으로 연결된" 컨드트 서열은 코딩서열의 발현이 컨드트 서
열과 양립가능한 조건하에 달성되는 방식으로 라이게이트된다. 컨트롤시열이 프로모터인 경우에, 이중-가닥 핵산이 바람직하게 사용되는 것은 당업자에게 자명하다.

따라서 기술된 벡터는 바람직하게는 발현 벡터이다. "발현 벡터"는 선택된 수주를 형질전환시키기 위해 사용할 수 있는 구조이며 또한 선택된 수주에서 코딩 시열의 발현을 제공한다. 발현 벡터는 예를 들면 클로닝 벡터, 이원 벡터(binary vector) 또는 통합 벡터(integrating vector)일 수 있다. 발현은 바람직하게는 해독가능한 mRNA로의 핵산분자의 전사를 포함한다. 원핵 및/또는 전핵 세포에서 발현을 보장하는 조절 요소는 당해 기술자들에게 잘 알려져 있다. 전후 세포의 경우에 이들은 보통 전사의 개시를 보장하는 프로모터 및 선택적으로 전사의 종료 및 전사의 안정화를 보장하는 폴리-A 신호를 포함한다. 원핵 수주세포에서 발현을 허용하는 가능한 조절 요소는 E. coli에서 P, lac, trp 또는 tac 포모터를 포함하며 또한 전핵 수주세포에서 발현을 허용하는 조절요소는 예로 AOX1 또는 GAL1 프로모터 또는 포유동물 및 기타 동물세포에서 CMV-, SV40-, RSV-프로모터 (다우스 개종 비아이어, CMV-언덴서, SV40-언덴서 또는 로보만 인트로다.)

전사는 개시에 관여하는 요소 외에도, 이러한 조절 요소는 또한 전사 종결 신호, 예를 들어 SV40-폴리-A 부위 또는 tk-폴리-A 부위, 폴리뉴클레오티드의 하류(downstream)를 포함할 수 있다. 또한, 사용된 발현 시스템에 따라, 폴리펩티드를 세포 구조로 향하게 하거나 또는 이를 배체 내에 분비할 수 있는 리더 시열(leader sequence)은 기술된 핵산 시열의 코딩 시열에 첨가할 수 있으며 또한 당해 분야에 잘 알려져 있다: 예를 들어 첨부된 실시예 1 참조. 리더 시열(들)은, 바람직하게는 세포질 공간(periplasmic space) 또는 세포의 배체 내로, 해독된 단백질 또는 그의 일부의 분비를 시각할 수 있는 리더 시열은, 해독, 개시 및 종결 시열과 함께 적절한 상으로 조합된다. 일부, 이중기원 시열(heterologous sequence)은 원하는 특성, 예를 들면 클로닝 제조할 생명의 안정화 또는 단순화된 정제를 부여하는 N-말단 식별(identification) 펩티드를 포함할 수 있다: 참조, 예를 들어 첨부된 실시예.

바람직하게는, 발현 컨트롤 서열은 전핵 수주 세포를 형질전환 또는 트랜스펙트할 수 있는 벡터에서 전핵 프로모터 시스템일 것이나, 원핵 수주에 대한 컨트롤 시열이 또한 사용될 수 있다. 벡터가 적절한 수주내로 편입되면, 수주는 폴리펩티드 시열의 높은 수준 발현에 적합한 조건하에 유지되며 또한 본 발명의 폴리펩티드의 수집 및 정제가 되게 될 수 있다: 참조, 예를 들어 첨부된 실시예.


상기에 따라, 본 발명은 여기에 정의된 이중특이적 단일 쇄 항체 구조체의 폴리펩티드 서열을 인코드하는 핵산분자를 포함하는 유전공학에서 통상적으로 사용되는 벡터, 특히 플라스미드, 코스미드, 바이러스 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리오파지를 얻는 방법에 관한 것이다. 바람직하게는, 상기 벡터는 발현 벡터 및 또는 유전자 전달 또는 표적화 벡터이다. 헤트로바이러스, 백시나 바이러스, 아데노바이러스, 아데노바이러스 또는 바이러스성 및 박테리ophon 과정(electroporation)은 다음 세포를 직접적으로 사용하는 방법도 있다. 본 발명의 핵산분자는 빠르고, 실험적인 공정에 따라 그 특성을 보다 잘 감지할 수 있다. 본 발명은 여기에 기술된 벡터로 형질전환 또는 트랜스젝션 숙주를 제공한다. 상기 숙주는 상술한 벡터의 하나 이상 또는 상술한 핵산 분자의 하나 이상을 숙주내로 도입하여 생길 수 있다. 숙주 내에 상기 하나 이상의 벡터 또는 하나 이상의 핵산 분자와 결합된 유전자들의 발현을 매개할 수 있다. 숙주 내에 도입되는 상술한 핵산 분자 또는 벡터는 숙주의 게놈내에 통합(integrate)되거나 또는 염색체외(extrachromosomally) 유지될 수 있다. 숙주는 원핵 또는 단핵 세포일 수 있다. 용어 "원핵생물"은 본 발명의 단핵질의 발현을 위한 DNA 또는 RNA 분자로 형질전환 또는 트랜스젝션을 할 수 있는 모든 세균을 포함하는 것을 의미한다. 원핵 숙주는 그람 양성은 물론 그람 음성균, 예를 들어 E.
coli, S. typhimurium, Serratia marcescens 및 Bacillus subtilis를 포함할 수 있다. 용어 "진핵생물"은 효모, 고등 식물, 곤충 및 바람직하게는 포유동물 세포를 포함하는 것을 의미한다. 재조합 생산 절차에서 사용된 숙주에 따라, 본 발명의 폴리뉴클레오티드에 의해 인코드된 단백질은 글리코실화 되거나 또는 비-글리코실화 될 수 있다. 특히 바람직한 것은 본 발명의 폴리펩티드의 코딩 서열을 함유하는 바이러스 또는 플라스미드의 사용이며, 또한 여기에 C-말단 His-tag 또는 C-말단 FLAG-tag가 유전적으로 융합된 다. 바람직하게는 성기 FLAG-tag의 길이는 약 4 내지 8개 아미노산, 가장 바람직하게는 8개 아미노산이다. 상술한 플러그레피프법 분리(preparative chromatographic separations), 및 면역학적 분리 예를 들어 첨부된 실시예에 기술된 바와 같이 본 발명의 폴리펩티드의 태그에 대해 지시하는 모노클로날 또는 폴리클로날 항체의 사용을 수반할 수 있다. 바람직하게는, 상기 수용체는 세균, 곤충, 진균, 식물 또는 동물 세포이다. 

기술된 숙주에는 포유동물 세포, 더욱 바람직하게는 인간 세포 또는 인간 세포주인 것이 특별히 예견된다. 특히 바람직한 수용체는 CHO 세포, COS세포, SP2/0 또는 NS/0같은 곡주 세포주를 포함한다. 첨부된 실시예에 설명된 바와 같이 특별한 수용체로서 CHO 세포이다. 

또 하나의 구체예에서, 본 발명은 상기 기술된 CD3 특이적 구조체의 제조방법에 관한 것이다. 상기 방법은 상기 구조체를 발현시킨다. 여러 조건에서 본 발명의 세포 및/또는 숙주를 배양하고 상기 세포 또는 상기 배양 배지로부터 발현된 방법은 당해 분야에 공지되어 있다 (Sambrook, loc cit). 바람직하게는, 상기 수용체는 세균, 곤충, 진균, 식물 또는 동물 세포이다. 

형질전환된 숙주는 발효조에서 성장하고 최적 세포성장을 달성하기 위해 당해 분야에 공지된 기술에 따라 배양될 수 있다. 이어서 본 발명의 폴리펩티드는 성장 배지, 세포 용해질, 또는 세포막 분획으로부터 분리할 수 있다. 예를 들어 본 발명의 미생물로 발현된 폴리펩티드의 분리 및 정제는 임의의 기존의 수단을 동일에 비 크로마토그래피법 분리(preparative chromatographic separations), 및 면역학적 분리 예를 들어 첨부된 실시예에 기술된 바와 같이 또는 본 발명의 폴리펩티드의 테그에 대해 지시하는 모노클로날 또는 폴리클로날 항체의 사용을 수반할 수 있다. 또한 본 발명은, 여기 정의된 (인간) CD3-특이적 결합 구조체 또는 상기 기술된 공정으로 생성된 (인간) CD3-특이적 결합 구조체, 본 발명의 핵산 분자, 본 발명의 백터 또는 숙주를 포함하는 조성물을 제공한다. 상기 조성물은, 임의로, 또한 면역 작동 세포(immune effector cell)에 대한 활성화 신호를 제공할 수 있는 단백질성 화합물(proteinasaceous compound)을 포함할 수 있다. 가장 바람직하게는, 상기 조성물은 약학 조성물이고, 임의로, 적합한 담체, 안정화제 및/또는 부형제를 포함한다. 본 발명에 따라, 용어 "약학 조성물"은 환자, 바람직하게는 인간 환자에게 투여하기 위한 조성물에 관한 것이다. 바람직한 구체예에서, 약학 조성물은 비경구, 경피성, 관강내(intraluminal), 동맥내(intra arterial), 정맥내(intravenous) 투여를 위한 또는 조직 또는 중앙내에 직접 주사에 의한 조성물을 포함한다. 특히 상기 약학 조성물은 주입 또는 주사를 통해 환자에게 투여될 것이 예견된다. 적절한 진핵생물의 투여는 상이한 방법으로, 예를 들어 경구, 경피, 피하, 근육내, 국소 또는 피내 투여에 의해 수행할 수 있다. 본 발명의 약학 조성물은 약제학적으로 허용되는 담체를 추가로 포함할 수 있다. 적절한 약제학적 담체의 예는 당 업계에 잘 알려져 있으며 또한 인산염 완충 용액, 물, 유화액, 액을 들어 오일/물 유화액, 다양한 유형의 습윤제, 멸균액 등을 포함한다. 이러한 유한체를 포함하는 조성물은 잘 공지된 통상의 방법으로 제조할 수 있다. 이들 약학 조성물은 대상에게 적절한 용량으로 투여할 수 있다. 용량 요법은 주치의 및 임상 요소에 의해 결정할 수 있다. 의약 기술에서 잘 알려진 바와 같이, 임의의 한 환자를 위한 용량은 환자 크기, 체표면적, 나이, 투여할 특정 화합물, 성, 투여 시간 및 경로, 일반적 건강, 및 동시에 투여되는 다른 약물 등을 포함한 많은 인자에 따라 달라진다. 일반적으로, 약학 조성물의 정규적인 투어로서의 용량은 하루에 1㎍ 내지 5g유니트의 범위 내에 있어야 한다. 그러나로 임의 주입에 대한 다양한 용량은 시간당 최고량을 제시하는 0.01㎍ 내지 2 mgr, 바람직하게는 0.01㎍ 내지 2 mgr, 더욱 바람직하게는 0.01㎍ 내지 200㎍, 아울러 더 바람직하게는 0.01㎍ 내지 50㎍ 및 가장 바람직하게는 0.01㎍ 내지 10㎍ 단위의 범위일 수 있다. 특히 바람직한 용량은 아래에 기술된다. 경과는 주기적인 평가에 의해 모니터 될 수 있다. 용량은 발효에 의한 DNA의 정맥내 투여의 바람직한 투여량은 대략 10⁶ 내지 10²개 카피의 DNA 분자이다. 본 발명의 조성물은 국소적으로 또는 전신적으로 투여할 수 있다. 투여는 일반적으로 바 경구로, 예를 들어 정맥내로일 것이며, DNA는 또한 예를 들어 내부 또는 외부 표적부위로 비올리스틱 전달 (biolistic delivery)에 의해 또는 동맥 내외의 어느 부위로 카테터(catheter)에 의해 표적 부위에 직접적으로 투여할 수 있다. 비경구 투여용 제제는 멸균된 수성 또는 비수성 용액, 혈액액, 그리고 단백질성 화합물의 유합체를 포함한다. 비수성 용액의 예는 프로필렌 글리콜, 폴리에틸렌 글리콜, 식물성 오일을 들어 물리바이오, 및 주사 가능한 유기 에
스테르 예를 들어 에틸 올리에이트이다. 수성 담체는 염수 및 완충 매체를 포함하는, 물, 알코올/수성 용액, 유화 액 또는 혼합액을 포함한다. 비경구 비히클(vehicle)은 염화 나트륨 용액, 링거 덱스트로스,&w0; 데크스트로스 및 양화 나트륨, 유산을 가한 액체(lactated Ringer's) 또는 고정유(fixed oil)를 포함한다. 본 발명의 약학 조성물은 혈청 알부민 또는 면역글로불린과 같은 단백질성이 용액, 바람직하게는 인간 기원의 것을 포함할 수 있다. 본 발명의 약학 조성물은, 단백질성 이중 특이적 단일 체 항체 구조체 또는 이를 인코드하는 핵산 분자가 또는 벡터(본 발명에서 기술된 바와 같이) 이외에도, 약학 조성물의 의도한 용도에 따라 생물학적 활성계를 추가로 포함할 수 있을 것이다. 이러한 작용제(agent)는 단계에서 알려진, 약물, 세포증식 억제제(cytostatical)로 작용하는 약물, 고요산 혈증을 예방하는 약물, 면역반응을 억제하는 약물(예, 코르티코스테로이드) 순환계에 작용하는 약물 또는 T 세포 공-자극성(co-stimulatory) 분자 또는 사이토카인(cytokine) 등의 작용제일 수 있다.

본 발명의 조성물(들)의 투여를 위한 가능한 장호는 종양성 질환 특히 상피 암/암종 예를 들어 유방암, 대장암, 전립선암, 흉부암, 피부암(촉형증), 비뇨생식기관암, 악, 악으로 낙소암, 자궁내막 악, 자궁경부 악 및 신장 악, 패암, 위암, 소장 악, 큰장, 신장암, 쓰개낭암 악, 쓰개관 악, 신장암, 청과 악, 및 감상선 악 또는 혈액암, 신경증, 육중 또는 골육중과 같은 다른 종양성 질환이다. 본 발명의 조성물의 투여는 특히 최소 접촉 접합 바람직하게 초기 고형 악을, 진행된 고형 악 또는 전이성 고형 악에 대해 지시되며, 이것은 단일 세포의 생존에 의해 아기약성의 국소적 및 비-국소적 계획을 특징으로 한다.

본 발명은 또한, 세포 증식 또는 세포 자극을 위해, 다른 화합물들, 예를 들어 면역 작동 세포에 대해 활성화 신호를 제공할 수 있는 분자등과의 공동 투여 프로토콜이 예견될 수 있다. 상기 분자는 예를 들어 T 세포의 추가적 1차 활성화 신호 (예를 들면, 추가의 공동작용 분자: B7-패밀리, Ox40L, 4.1BBL의 분자), 또는 추가의 사이토카인: 인터루킨 (예, IL-2), 또는 NGK-2D 결합 화합물(engaging compound)일 수 있다.

상기 기술된 본 발명의 조성물은 또한 임의로 검출을 위한 수단 및 방법을 포함하는 진단 조성물일 수 있다.

여기에 제공된 CD3-특이적 구조체는 또한 액체상에서 또는 고체상 담체에 결합되어 사용될 수 있는 면역측정법에서 사용하기에 적합하다. 본 발명의 폴리펩티드를 사용할 수 있는 면역측정법의 예에는 직접 또는 간접 포맷의 경쟁적 또는 비경쟁적 면역측정법이다. 그러한 면역측정법의 예는 효소연관면역흡착법(enzyme linked immunoabsorbent assay) (ELISA), 효소면역측정법(enzyme immunoassay) (EIA), 방사선면역측정법 (radioimmunoassay) (RIA), 샌드위치 면역계량 검사(immunometric assay) 및 웨스턴 블롯 측정법이 있다.

본 발명의 CD3 특이적 결합 구조체는 많은 상이한 담체에 결합될 수 있고, 상기 폴리펩티드에 특이적으로 결합하는 세포를 분리하는 데 사용될 수 있다. 잘 알려진 담체의 예로는 유리, 폴리스티렌, 폴리염화비닐, 폴리프로판, 폴리에틸렌, 폴리카보네이트, 덱스트란, 나일론, 아밀로스, 천연 및 변형 셀룰로오스, 폴리아크릴아미드, 아가로오스 및 자철광(magnetite)을 포함한다. 담체의 속성은 가용성 또는 불용성을 가할 수 있다. 본 발명의 목적을 위한 비드(beads)일 수 있다.

본 발명은, 또한, 표지의 많은 상이한 표지 및 방법이 있다. 본 발명에 사용될 수 있는 표지 유형의 예는, 효소, 방사성 동위원소, 콜로이드 금속, 형광 화합물, 화학발광 화합물, 샌드위치 면역계량검사(immunometric assay)) 및 웨스턴 블롯 측정법이 있다.

당업자의 발달에 알려진 표지의 많은 상이한 표지 및 방법이 있다. 본 발명에 사용될 수 있는 표지 유형의 예는, 효소, 방사성 동위원소, 콜로이드 금속, 형광 화합물, 화학발광 화합물 및 생물발광 화합물은 포함한다. 또한 상기 설명된 구체예를 참조.

본 발명의 가장 바람직한 구체예에서, 약학 조성물의 제조를 위한 본 발명의 CD3 특이적 결합 분자, 본 발명의 벡터 또는 숙주의 사용이 예견된다. 상기 약학 조성물은 종양성 질환, 종양성 질환, 염증성 질환, 면역학적 장애, 자가면역 질환, 감염성 질환, 바이러스 질환, 알레르기 반응, 기생충 반응, 신생대속주병 및 숙주대이식병의 예방, 치료 또는 개선에 사용될 수 있다.


본 발명은 또한 예방, 치료 또는 개선이 필요한 대상에게 본 발명의 (이중특이적) CD3 특이적 결합 분자 또는 여기에 기술된 공정에 의해 생산된 (이중특이적) CD3 특이적 결합 분자, 본 발명의 핵산 분자, 벡터 또는 숙주의 투여를 포함하는, 증식성 질환, 종양성 질환, 염증성 질환, 면역학적 장애, 자가면역 질환, 감염성 질환, 바이러스 질환, 알레르기 반응, 기생충 반응, 이식대숙주병 또는 숙주대이식병의 예방, 치료 또는 개선을 위한 방법에 관한 것이다. 상기 대상은 바람직하게는 인간이다.

예방, 치료 또는 개선을 위한 방법은 또한, 추가로, 면역 작동 세포에 활성화 신호를 공급할 수 있는 단백질성 화합물의 투여를 포함한다. 상기 단백질성 화합물은 본 발명의 CD3 결합 분자, 핵산 분자, 벡터 또는 숙주와 동시적으로 또는 비-동시적으로 투여될 수 있다. 단백질성 화합물은, 특히, 추가의 공동작용성 분자: B7 패밀리, Ox40L, 4.1 BBL의 분자들), 또는 추가의 사이토카인: 인터루킨 (예를 들면, IL-2) 또는 NKG-2D 결합화합물로 이루어진 그룹으로부터 선택될 수 있다.

마지막으로, 본 발명은 본 발명의 CD3 특이적 결합 분자, 핵산 분자, 벡터 또는 숙주를 포함하는 키트를 제공한다.

상기 키트는 본 발명의 약학 조성물의 제조에 특히 유용하고, 특히, 주사 또는 주입에 유용한 용기(container)로 이루어질 수 있다. 유리하게는, 본 발명의 키트는, 임의로 (a) 의료 또는 과학 목적의 수행에 필요한 완충액, 저장 용액 및/또는 나머지 시약 또는 물질을 더 포함한다. 또한, 본 발명의 키트의 일부는 바이어리(vial) 또는 병(bottle)에 개별적으로, 또는 용기의 조합으로 또는 다중용기 유니트에 포장될 수 있다. 본 발명의 키트는 특히 본 발명의 방법을 수행하기 위해 유리하게 사용될 수 있고, 예를 들면, 연구 도구 또는 의료 도구들 사이에 일부와 같은 여권에 언급된 다양한 용어로 사용될 수 있다. 상기 키트의 제조는 바람직하게는 당업자에 알려진 표준 절차를 따른다.


실시예

하기 실시예에는 본 발명을 설명한다:


실시예 1. 탈면역화된 항-CD3 구조체의 클로닝 및 발현


실시예 2. 단백질의 단일쇄 항-인간 CD3 항체가 인간에서의 감소된 면역원성을 나타내기 위해 설계되었다. 상이한 탈면역화된 항-인간 CD3 항체는 서로 결합된 4개의 상이한 VH 영역 (VH2 (서열번호: 69, 70), VH3 (서열번호: 71, 72), VH5 (서열번호: 73, 74) 및 VH7 (서열번호: 75, 76)) 및 3개의 상이한 VL 영역 (VL1 (서열번호: 77, 78), VL2 영역(서열번호: 79, 80) 및 VL3 (서열번호: 81, 82))의 12개의 조합을 포함한다. 상기 언급된 VH 및 VL 영역의 아미노산 및 핵산 서열은 도 3-6에 나타난다. 설명된 것처럼, 탈면역화된 항-CD3 단일체 항체는 이중특이적 생물학을 협상하기 위해 항-CD19 단일체 항체 또는 항-EpCAM 단일체 항체와 결합되었다.


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1.1 단일쇄 항체를 인코드하는 cDNA의 이동

탈면역화된, 항-CD3 단일쇄 항체를 인코드하는 DNA는 여기에서 항-CD3 카세트로서 언급된다. 이 항-CD3 카세트는 SGGGGS 링커 (서열번호: 176), 항-CD3 VH 영역 (서열번호: 110), 14 아미노산 GS 링커 (VEGGSGGSSGGGSGGYD 링커 (서열번호: 68)), 및 항-CD3 VL 쇄 영역 (서열번호: 112)으로 이루어지고, 6 히스티딘 잔기가 뒤를 이한다. 상기 언급된 DNA는 벡터 p-PCR-Script-Amp SK+ (Stratagene)의 Srf1 부위에 클로닝되었다. 항-CD3 카세트의 DNA 및 아미노산 서열은 서열번호: 1, 서열번호: 2 및 도 1에 나타낸다.

1.2 면역원성 T 세포 에피토프에 대한 서열의 컴퓨터 분석 및 탈면역화된 단일쇄 항체 서열의 디자인

항-CD3 카세트의 아미노산 서열 (서열번호: 2)이, WO 98/52976에 기술된 방법으로 가능한 T 세포 에피토프를 확인하기 위해 펩티드 쓰레딩(threading) 프로그램에 의해 분석되었다. 서열번호: 3 은 탈면역화된 링커 서열을 나타내고 서열번호: 68은 원래의 링커 서열을 나타낸다.

1.3 탈면역화된 단일쇄 항체 서열의 구축

항-CD3 카세트의 탈면역화된 판(versions)은 오버래핑 PCR 재조합 방법에 의해 구축되었다. pPCR-S-Amp SK+ 벡터의 항-CD3 카세트 (서열번호: 1, 2)는 필요한 탈면역화된 서열의 돌연변이 유발(mutagenesis)을 위한 주형으로 사용되었다. 돌연변이 유발성 프라이머 쌍의 세트는 변형된 영역을 포함하여 합성되었다. 4개의 상이한 VH 및 3개의 상이한 VL 영역을 포함하는 탈면역화된 서열이 생성되었는데, 벡터 pPCR-S-Amp SK+ 에 Not I 이어서 Hind III 단편으로서 클로닝되었고, 전체의 DNA 서열은 정확한 것으로 확인되었다. 4 개의 상이한 VH 및 3 개의 상이한 VL 영역이 모든 조합 (총 12)로, PCR에 의해 또는 VH 영역의 3’말단에 도입된 독특한 BstE II 부위를 사용하여 결합되었다. 각각의 조합의 전체의 DNA 서열은 정확한 것으로 확인되었다. 상이한 탈면역화된 VH 영역 (서열번호: 70, 72, 74 및 76) 및 VL 영역 (서열번호: 78, 80 및 82)이, 항-CD3 구조체의 상응하는 본래의 탈면역화 되지 않은 서열 (VH:서열번호: 110; VL:서열번호: 112)과 함께 표 9에 요약되었다.

표 9.

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1.4 탈면역화된 단일쇄 항체 유전자 발현 벡터로의 이동
탈면역화된 항-CD3 카세트는 pPCR-S-Amp-SK+ 로부터 BspE I 및 Sal I 으로 절단되었고 VL_{CD19}-VH_{CD3}-VL_{CD3}을 포함하는 발현 벡터 pEF 로 클로닝되었다. pEF-DHFR 벡터의 CD3 부분은 각각의 탈면역화된 항-CD3 카세트로 BspE I 부위 내지 Sal I 부위까지 대체되고, 하기 12 구조체가 그 결과이다:

- pEF 항-CD19x항-CD3 (VH2/VL1) (서열번호: 177, 178)
- pEF 항-CD19x항-CD3 (VH2/VL2) (서열번호: 179, 180)
- pEF 항-CD19x항-CD3 (VH2/VL3) (서열번호: 181, 182)
- pEF 항-CD19x항-CD3 (VH3/VL1) (서열번호: 183, 184)
- pEF 항-CD19x항-CD3 (VH3/VL2) (서열번호: 185, 186)
- pEF 항-CD19x항-CD3 (VH3/VL3) (서열번호: 187, 188)
- pEF 항-CD19x항-CD3 (VH5/VL1) (서열번호: 189, 190)
- pEF 항-CD19x항-CD3 (VH5/VL2) (서열번호: 191, 192)
- pEF 항-CD19x항-CD3 (VH5/VL3) (서열번호: 193, 194)
- pEF 항-CD19x항-CD3 (VH7/VL1) (서열번호: 195, 196)
- pEF 항-CD19x항-CD3 (VH7/VL2) (서열번호: 197, 198)

상기 구조체는 또한 단백질 분비를 가능하게 하기 위해 뮤린 IgG 중쇄 리더(leader)를 포함한다. 발현 벡터의 탈면역화된 항-CD3 카세트의 DNA 서열은 서열 프라이머 (서열번호: 28 및 29)를 사용하여 확인되었다. pEF 벡터 내에서 BspE I 부위 내지 Sal I 부위까지의 12개의 탈면역화된 항-CD3 카세트의 DNA 및 아미노산 서열은 서열번호: 177-200에 나타낸다.

1.5 항체 구조체의 생산
상기 벡터의 대장균 K12로의 형질전환 후에, 상이한 발현 벡터의 트랜스펙션-등급 DNA 가 제조되었다. 분비된 단백질은 CHO-dhfr- 세포에서 생산되었다. 일시적인(transient) 생산을 위해, 세포 배양 상황이 트랜스펙션 후에 2일간 수확되었다. 안정한 트랜스펙션 세포를 생성하기 위해, 세포들은 트랜스펙션 후에 2일간 선택 배지에 두었다. 5번의 계대(passage) 후에, 안정한 폴(pool)이 얻어졌다. 이어서, 단일 클론이 한계회식법으로 확 인되었다. 경제 과정을 촉진하기 위해, 세포는 무혈청 배지에 적응되었다. 항체 구조체는 약 II.의 상장적으로부터 제거되었다.

생산 수준은 ELISA로 테스트되었다. 항-CD19 및 탈면역화된 항-CD3 구조체를 포함하는 상이한 구조체 사이에서 분비된 항체 수준에서의 어떠한 주요 차이도 관찰되지 않았다.

실시예 2: 결합 측정법
탈면역화된 구조체의 CD3 및 CD19 에의 결합 효능을 분석하기 위해, FACS-기반의 측정법이 수행되었다. 처음에는, 조(crude) 상청액이 CD3-풍부화된 PBMCs 또는 CD19-양성 NALM-6 세포에 대한 결합에 대해 테스트되었다. 세포는 최적화된 상장액과 함께 8℃에서 30분간 인큐베이트되었다. 두 번의 세척 단계 직후, 세포는 동일한 조건에서 항-His 항체 (Qiagen)로 표지되었다. 추가의 세척 단계 후에, 구조체의 결합이 FITC-접합된 양(sheep) 항-마우스 항체 (Sigma)로 검출되었다. 세포는 FACS Calibur 세포계수기 (B&D)로 분석되었다. 대조군으로서 항-CD19x항-CD3의 상장액 및 GFP-트랜스펙트된 세포가 포함되었다. CD3 및 2차 항체는 응성 대조군으로서 사용되었고 그것의 평균 형광 강도는 약 3.5 (MFI ca. 3.5)를 보였다. 항-CD3 (VH5/VL1) (서열번호: 190), 항-CD3

이 실험에서, 모든 측정된 구조체의 MFI가 적어도 80이었고, 음성대조군의 평균형광강도는 약 3(MFI ca. 3)이었다.

FACS-기반의 결합 측정법은 또한 CD19에 대해 수행되었다. 이 실험에서 CD19 및 2차 항체는 음성대조군이었다. 이 실험에서, 모든 측정된 구조체의 MFI가 적어도 80이었고, 음성대조군의 평균형광강도는 약 3(MFI ca. 3)이었다.

FACS-기반의 결합 측정법은 또한 CD19에 대해 수행되었다. 이 실험에서 CD19 및 2차 항체는 음성대조군이었다. 이 실험에서, 모든 측정된 구조체의 MFI가 적어도 80이었고, 음성대조군의 평균형광강도는 약 3(MFI ca. 3)이었다.

실시예 3. 높은 결합친화도를 보이는 변이체의 발현 및 정제


탈면역화된 항-CD3 부분을 포함하는 이중특이적 단일쇄 구조체를 정제하기 위해, CHO-CD19 세포를 수확하기 전 7일간 HiClone CHO 변형된 DMEM 배지로 회전병에서 키웠다. 세포는 원심분리에 의해 분리하였으며, 발현된 단백질의 포함하는 상황은 -20℃에서 보관되었다.

Akta FPLC System (Pharmacia) 및 Unicorn Software (Pharmacia)를 사용하여 HiTrap 컬럼을 사용하여 IMAC이 수행되었다. 컬럼은 완충액 A2 (20 mM NaP pH 7.5, 0.4 M NaCl)로 평형화되어 대조적으로 작용하는 MEP Hypercel 배지에 부착되었다. 500ml의 세포배양 상층액을 10ml의 용액으로 침입하여 제거하였고, 결합된 단백질은 100% 완충액 B1 (20 mM 아세테이트 pH 3.5) 으로 용출되었다. 용출된 단백질 분획은 추가의 정제를 위해 풀링하였다.

제작자의 프로토콜에 따라 NiSO$_4$가 로드된 Histrap 컬럼 (Pharmacia)를 사용하여 IMAC이 수행되었다. 컬럼은 완충액 A2 (20 mM NaP pH 7.5, 0.4 M NaCl)로 평형화되었고, 그 샘플은 완충액 A2로 2:1로 회색하여 pH 7을 얻었다. 그 샘플을 1ml 분의 용액으로 컬럼 (2ml)에 적용하였고, 그 컬럼은 완충액 A2로 세척되어 결합되지 않은 샘플을 제거하였다. 결합된 단백질은 완충액 B2 (20 mM NaP pH 7.5, 0.4 M NaCl, 0.5 M 이미다졸)의 단계 그래디언트를 사용하여 용출되었다. 단계 1: 10 컬럼 부피의 20% 완충액 B2; 단계 2: 10 컬럼 부피의 100% 완충액 B2. 용출된 단백질 분획은 추가의 정제를 위해 풀링하였다.

[0307] 케이크가 크로마토그래피가 PBS (Gibco)로 평형화된 Sephadex S200 HiPrep 컬럼 (Pharmacia)에서 수행되었다.
용출된 단백질 샘플은 (유속 1ml/분)은 검출을 위해 SDS-Page 및 웨스턴 블롯을 행하였다 (도 11). 결과는 이전 에 분자량 결정을 위해 보정되었다 (분자량 마커 카드, Sigma MW GF-200).

항-CD19x항-CD3 단백질의 탈면역화된 변이체는 소수성 전화 유도 크로마토그래피 (HCIC) (도 8), 고정된 금속 친화성 크로마토그래피 (IMAC) (도 9) 및 젤 여과 (도 10)를 포함하는 3단계 정제 방법으로 분리되었다. 이중특 이적 구조체는 PBS 내의 젤여과에 의해 측정된 바와 같은 음성 조건하에서 52 kDa의 분자량을 가졌다.

정제된 이중특이적 단백질은 미리 만들어진 4-12% Bis Tris 젤 (Invitrogen)을 사용하여 원활 조건하에서 SDS-PAGE로 분석되었다. 생물 준비 및 적용은 제작자의 프로토콜을 따랐다. 분자량은 MultiMark 단백질 표준 (Invitrogen)으로 결정되었다. 젤은 콜로이드성 쿠마시 (Invitrogen 프로토콜)로 염색되었다. 분리된 단백질의 순도는 >95% (도 11a) 이었고 분자 크기는 52 kDa이었다.

항-CD19x항-CD3 단백질의 탈면역화된 변이체는 웨스턴 블롯에 의해 특이적으로 검출되었다. 웨스턴 블롯은 Optitran BA-S83막 및 Invitrogen Blot Module로 제작자의 프로토콜에 따라 수행되었다. 사용된 항체는 Penta His (Quiagen) 및 알칼리 포스파타아제(AP) (Sigma)로 표지된 염소-항-마우스-Ig였고, 염색 용액은 BCIP/NBT액체 (Sigma)이었다. 주요 신호는 SDS-PAGE에서 52kD의 주 밴드에 상응하는 것으로 보여졌다 (도 11b).

단백질 농도는 단백질 측정법 염료 (MicroBCA® Pierce) 및 IgG (Biorad)를 표준 단백질로 사용하여 측정되었다. 정제된 단백질 변이체의 최종 수율이 표 10에 요약되었는데, 모든 구조체가 높은 생산성을 보여주었으며 항-CD3 (VH5/VL1) (시열번호:190)을 갖는 구조체가 924.8㎍의 매우 좋은 수율을 보여준다.

### 표 10

<table>
<thead>
<tr>
<th>탈면역화된 항-CD19-항-CD3 구조체의 단백질 수율</th>
</tr>
</thead>
<tbody>
<tr>
<td>탈면역화된 CD3 구조체</td>
</tr>
<tr>
<td>CD19x항 CD3 (VH5/VL1) (시열번호:190)</td>
</tr>
<tr>
<td>CD19x항 CD3 (VH5/VL2) (시열번호:192)</td>
</tr>
<tr>
<td>CD19x항 CD3 (VH5/VL3) (시열번호:194)</td>
</tr>
<tr>
<td>CD19x항 CD3 (VH7/VL1) (시열번호:196)</td>
</tr>
<tr>
<td>CD19x항 CD3 (VH7/VL2) (시열번호:198)</td>
</tr>
<tr>
<td>CD19x항 CD3 (VH7/VL3) (시열번호:200)</td>
</tr>
</tbody>
</table>

CD19x항-CD3 (VH5/ VL2) 및 CD19x항-CD3(VH7/VL2) 구조체의 생산성은 상용하는 탈면역화 되지 않은 구조체와 비교되었다. 그 결과는 표 11에 나타났다.

### 표 11

<table>
<thead>
<tr>
<th>상용하는 탈면역화 되지 않은 구조체와 비교된 탈면역화된 이중특이적 구조체의 수율</th>
</tr>
</thead>
<tbody>
<tr>
<td>구조체</td>
</tr>
<tr>
<td>CD19x항-CD3</td>
</tr>
<tr>
<td>CD19x항CD3 (VH5/VL2)</td>
</tr>
<tr>
<td>CD19x항CD3 (VH7/VL2)</td>
</tr>
</tbody>
</table>

표 11은 탈면역화된 CD3 결합 도메인을 포함하는 이중특이적 구조체가 상용하는 탈면역화 되지 않은 구조체보다 월등히 높은 (적어도 3배) 생산성을 갖는다는 것을 명확하게 증명한다.

실시예 4. 항-CD3 구조체의 FACS 기반의 결합 측정법

항-CD19 및 항-CD3를 포함하는 선택된 정제된 항체 구조체의 결합은 다양한 농도에서 실시에 2에 상기 기술된

모든 항체 구조체가 CD19에 높은 효능으로 결합했고 MFI가 약 200이었으며, 한편 탈면역화 되지 않은 항-<br>CD19x항-CD3 구조체 (서열번호:204)는 80 MFI를 보였다. 상이한 구조체들에 대해 테스트된 농도에서 CD19 결합<br>에 대한 차이가 발견되지 않았다 (도 12B).

실시예 5. 세포독성 측정법

항-CD19x항-CD3는 CD19-양성 표적 세포에 대한 T세포 의존성 세포독성을 매개한다. 이것은 항-CD19x항-CD3의<br>생물학적 효능(potency)의 결정을 위해 시험관 내에서 분석되었다.

이러한 목적을 위해, 형광 표지된 CD19-양성 NALM-6 표적 세포가, 항-CD19x항-CD3의 존재하에서 작동 세포로서<br>임의의 기증자의 분리된 PBMC 또는 CD15 T세포 (표준화된 T세포주)와 함께 인큐베이트되었다. 습윤화된 인큐베이터에서 37℃에서 4시간 동안의 인큐베이션 후에, 표적세포로부터 상청액으로의 형광염료의 방출량을 측정하는 데 사용된다. 항-CD19x항-CD3이 없이 인큐베이트된 표적 세포 및 인큐베이트 마지막에 사포닌 첨가에 의해 완전히 용해된 표적 세포는 각각 음성 및 양성 대조군으로 작용한다. 특정 항-CD19x항-CD3 농도에서 매개된 특정 세포독성은 하기 식으로부터 계산될 수 있다:

특정세포독성(%) =

\[
\frac{RFU( samp)-평균RFU( 대조군)}{평균RFU( 완전 용해)-평균RFU( 대조군)} \times 100
\]

응량 반응(dose response)이, EC50 수치를 결정하기 위해, 0.4 pg/ml 항-CD19x항-CD3 로부터 100 ng/ml 항-<br>CD19x항-CD3 까지 분석되었다. 비록 EC50 수치가 항-CD19x항-CD3의 생물학적 효능을 기술하지만, 절대 수치는<br>작동 세포의 공급원에 따라 상당히 달라질 것이다. 그래서 상대 효능은 하기 식에 기반하여 항-CD19x항-CD3 기준<br>물질에 비교하여 계산된다:

상대 효능 = \frac{EC50 samp}{EC50 참조}

항-CD19 및 탈면역화된 항-CD3를 포함하는 구조체의 세포독성 활성은 도 13에 나타난다. 정제된 탈면역화 되지<br>않은 항-CD19x항-CD3은 대조군으로 사용되었다. 탈면역화된 구조체의 EC50 수치는 21.9-81.6 pg/ml의 범위이었고, 반면 탈면역화되지 않은 항-CD19x항-CD3 구조체의 EC50 수치는 22.7 pg/ml이었다. 그래서, 모든 탈면역화된 구조체는 탈면역화 되지 않은 분자에 걸쳐도 한반 EC50 수치를 나타냈다.

실시예 6. T세포 증식 측정법

20명의 건강한 기증자가 HLA-DR 타이핑 기반의 T세포 증식정법에서 스캔을 위해 선정되었다 (표 12). 이것<br>은 T세포 증식정법에서 세계 인구에서 발현되는 DR 대립유전자(allele)의 80% 초과에 대해 패턴의 스크린을 가능하게 한다.

표 12
탈면역화된 및 탈면역화 되지 않은 항-CD3 scAb로부터 얻은 펩티드의 면역원성을 테스트하기 위해 사용된 20 명의 건강한 기증자의 HLA DR 일배체형(haplotypes).

<table>
<thead>
<tr>
<th>HLA DR 동종이인자형(Allotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 DRB1<em>07, DRB1</em>15, DRB4*01, DRB5</td>
</tr>
<tr>
<td>2 DRB1<em>03, DRB1</em>04, DRB3, DRB4*01</td>
</tr>
<tr>
<td>3 DRB1<em>04, DRB1</em>07 및 DRB4*01</td>
</tr>
<tr>
<td>4 DRB1<em>07, DRB1</em>11, DRB4*01</td>
</tr>
<tr>
<td>5 DRB1<em>04, DRB1</em>07, DRB4*01</td>
</tr>
<tr>
<td>6 DRB1<em>01, DRB1</em>04, DRB4*01</td>
</tr>
<tr>
<td>7 DRB1<em>03, DRB1</em>07, DRB3, DRB4*01</td>
</tr>
<tr>
<td>8 DRB1<em>07, DRB1</em>11, DRB3, DRB4*01</td>
</tr>
<tr>
<td>9 DRB1<em>12, DRB1</em>15, DRB3, DRB5</td>
</tr>
<tr>
<td>10 DRB1<em>01, DRB1</em>09, DRB4*01</td>
</tr>
<tr>
<td>11 DRB1<em>03, DRB1</em>15, DRB3, DRB5</td>
</tr>
<tr>
<td>12 DRB1<em>10, DRB1</em>13, DRB3</td>
</tr>
<tr>
<td>13 DRB1<em>03, DRB1</em>15, DRB3, DRB5</td>
</tr>
<tr>
<td>14 DRB1<em>04, DRB1</em>15, DRB4*01, DRB5</td>
</tr>
<tr>
<td>15 DRB1<em>04, DRB1</em>13, DRB3, DRB4*01</td>
</tr>
<tr>
<td>16 DRB1<em>01, DRB1</em>13, DRB3</td>
</tr>
<tr>
<td>17 DRB1<em>01, DRB1</em>04, DRB4*01</td>
</tr>
<tr>
<td>18 DRB1<em>07, DRB1</em>13, DRB3, DRB4*01</td>
</tr>
<tr>
<td>19 DRB1<em>07, DRB1</em>16, DRB3, DRB4*01</td>
</tr>
<tr>
<td>20 DRB1<em>04, DRB1</em>15, DRB4*01, DRB5</td>
</tr>
</tbody>
</table>

6.1 T-세포 증식 측정법

펩티드는 Pepscan (네덜란드)로부터 90% 이상의 순도로 얻었다. 20 명의 선택된 건강한 기증자 (표 12)로부터의 말초혈액 단핵세포 (PBMC)가 1 및 5μM의 3배수 웰에서 개별 펩티드를 스캔하는데 사용되었다. 두 개의 양성 대조군 펩티드 (C32 및 C49) 및 열쇠구멍삿갓조개해모시아닌(keyhole limpet hemocyanin) (KLH) 이 측정법에 포함되었다. 세포와 펩티드의 인큐베이션 7일 후에, T 세포 증식을 평가하기 위해, 1μCi/웰의 3H-티미드를 사용하였다. 이들 데이터는 하기 자극 지수로 표현된다:

$$\text{자극지수} = \frac{\text{테스트 펩티드의 CPM}}{\text{처리되지 않은 대조군의 CPM}}$$

T 세포 에피토프는 2 보다 큰 자극 지수 (SI)를 가진 펩티드로서 정의된다.

두개의 독립적인 실행으로부터의 결과는 탈면역화되지 않은 항-CD3 서열 내의 22 개의 MHC 결합 펩티드 중의 5개가 인간의 T 세포 증식을 유도하는 능력이 있다는 것을 나타낸다 (SI > 2). 이와는 대조적으로, 상응하는 탈면역화된 분자들은 어느것도 T 세포 증식을 유도하지 않았다. 표 13은 T 세포 증식 측정법 결과를 요약하였는데, 두개의 독립적인 실행의 평균 SI 수치를 보여 준다.

데이터는 또한 농도 의존적 효과를 보여주는데, 이에 의해 각각의 탈면역화되지 않은 결합 분자들은 사용된 두개의 농도 (1μM 또는 5μM)에서의 어떤 하나에서만 SI > 2를 나타내었다. 높은 농도에서는 높은 반응의 차이가, 개별 펩티드들이 T 세포의 증식을 유도하는 최적의 농도를 가질 것이라는 사실에 의해 설명된다. 만약 이 농도를 넘어서면, 증식이 감소할 수 있다 (높은 농도는 세포 증식에 억제 효과를 가질 수 있다). 이것은, 농도에 따라서의 반응의 차이가 더 낮은 농도에서 발견되고, 더 높은 농도에서 발견되지 않는지를 설명해 준다. 경험적으로, 경도의 농도에서, T 세포 에피토프를 포함하고 있다면, T 세포 증식은 사용한 하나 또는 두개의 농도에서 발견될 것이다. 이들 데이터는 탈면역화가 성공적으로 T 세포 에피토프를 항-CD3 (VH5/VL2) (서열번호: 19) 및 항-CD3 (VH7/VL2) (서열번호: 25)로부터 제거했다는 것을 증명하였다. 탈면역화되지 않은 항-CD3 서열로부터의 약 75%의 MHC 결합 펩티드들이 T 세포 증식을 유도하지 않았다는 사실은 인간 면역 시스템의 이들 펩티드들에 대한 내성(tolerance) 또는 인간 T 세포 렘버토리(repertoire)가 이들 특정 펩티드들을 인식할 수 없음을 의해 설명된다.
표 13
양성 (SI>2) 마우스 펩티드 및 상응하는 탈면역화된 펩티드의 비교 데이터의 요약

<table>
<thead>
<tr>
<th>펩티드</th>
<th>동종이인자형</th>
<th>농도 (μM)</th>
<th>평균 SI</th>
<th>평균 SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-20</td>
<td>5</td>
<td>5</td>
<td>2.51</td>
<td>0.77</td>
</tr>
<tr>
<td>74-86</td>
<td>5</td>
<td>1</td>
<td>2.52</td>
<td>0.97</td>
</tr>
<tr>
<td>90-102</td>
<td>5</td>
<td>5</td>
<td>2.21</td>
<td>0.56</td>
</tr>
<tr>
<td>90-102</td>
<td>6</td>
<td>5</td>
<td>2.24</td>
<td>0.90</td>
</tr>
<tr>
<td>90-102</td>
<td>11</td>
<td>5</td>
<td>2.23</td>
<td>0.83</td>
</tr>
<tr>
<td>162-174</td>
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<td>3.82</td>
<td>0.78</td>
</tr>
<tr>
<td>216-230</td>
<td>10</td>
<td>1</td>
<td>2.12</td>
<td>1.03</td>
</tr>
</tbody>
</table>

실시예 7. 항-CD3 (VH5), 항-CD3 (VH7), 항-CD3 (VH2) 및 항-CD3 (VH3)의 탈면역화 되지 않은 항-CD3 VH 와의 상동성 정렬

탈면역화 되지 않은 CD3 항체의 가변 중(heavy) 영역, VH5 (서열번호:74), VH7 (서열번호:76), VH2 (서열번호:70) 및 VH3 (서열번호:72)가 Vector NTI Advance (Informax, Inc., USA)사의 AlingnX 프로그램을 사용하여 정렬되었다. 사용된 Clustal W 알고리듬은 Nucleic Acid Research, 22 (22): 4673-4860, 1994에 기술되어 있다. 상기 정렬은 도 14에 나타났다. 상기 정렬로부터 CDR1에 대한 높은reno 종은 결합을 보이는 가변 영역 VH5 및 VH7는 골격 1에서 CDR1로의 전이영역에 서열 ASGYTF를 갖는다. 또한, 결합을 보이지 않는 VH 영역 (VH2 (서열번호:70) 및 VH3 (서열번호:72))는 골격 1에서 CDR1로의 전이(transition)에 서열 ASGYTA를 포함한다. 따라서, T 세포 에피토프를 생성시키는 감소된 경향을 갖고 CD3에 결합하는 구조체를 얻기 위해, 상기 구조체는 골격 1에서 CDR1로의 전이(transition)에 서열 ASGYTF를 포함해야 한다. 높은reno 종이 연금된 서열 ASGYTF를 포함하고 CD3에 결합하고 T 세포 에피토프를 생성하는 감소된 경향을 보이는 가변 중 영역이 좋은 결합을 보였다.

실시예 8. 탈면역화된 항-CD3 및 항-EpCAM 을 포함하는 구조체의 클로닝

본 발명의 탈면역화된 항-CD3 폴리펩티드를 다신 포적을 갖는 가능적 구조체의 일부가 될 수 있다는 것을 입증하기 위해, 탈면역화된 항-CD3 (VH5/VL2) (서열번호:19) 및 상이한 항-EpCAM 단일쇄 항체(3-1 (서열번호:137, 139), 3-5 (서열번호:141, 143), 4-1 (서열번호:145, 147), 4-7 (서열번호:149, 151), 5-10 (서열번호:133, 135))를 포함하는 다수의 이중특이적 구조체가 생성되었다.

8.1 탈면역화된 항-CD3 부분 (서열번호: 30, 31, 32, 33, 34, 35, 36, 37, 38 및 39)을 포함하는 C-말단 EpCAM-바인더의 클로닝

8.1.1 항-CD19x항-CD3 (VH5/VL2) 구조체 (서열번호:192)로부터 탈면역화된 항-CD3의 증폭

N-말단의 탈면역화된 항-CD3(VH5/VL2)는, 탈면역화된 (CD19 x 항-CD3 (VH5/VL2) (서열번호:192)를 주형으로 사용하고 하기 브라이머를 사용하는 PCR에 의해 얻어졌다: (D1 CD3 5-2 VH BarGl
AGGTGTACACTCCGACGTCCAACTGGTGCAGTCAG (서열번호: 40), DI CD3 5-2 VL BspE I AATCCGGATTTGATCTCCACCTTGGTCCCG (서열번호: 41).

8.1.2. VH

상기 언급된, 탈면역화된 항-CD3를 포함하는 PCR 생산물이 제한효소 BsrG I 및 BspE I 으로 절단되었고 뒤이어서 불루스크립트 KS 벡터 (Stratagene, La Jolla, CA) 에 클로닝되었는데, 이는 핵생물의 분비 신호(리더 펩티드)의 암모산 서열을 EcoRI/BsrGI-단편으로 포함한다. 이 구조체를 EcoRI 및 BspE I로 절단한 후에 이로 인한 각각의 리더 펩티드를 갖는 항-CD3 scFv를 포함하는 DNA 단편이, pEF-DHFR- 벡터내에 C-말단 위치에 항EpCAM scFv 3-1, 4-7, 또는 5-10을 포함하여 C-terminal을 확장한 플라스미드에 클로닝되었다. 서열분석 (sequencing)에 의해 이중특이적 단일체에 대한 서열을 확인한 후에 (Sequiserve, Vaterstetten), 진핵 발현을 위해 상기 플라스미드는 DHFR 결합 CHO 세포들에 트랜스페스트되었다. DHFR 결합 CHO 세포들에서의 진핵 단백질 발현은 Kaufmann R.J. (1990) Methods Enzymol. 185, 537-566에 기술된 바에 따라 수행하였다.

8.1.3. VL

15 아미노산 표준 링커 (서열번호: 168)를 포함하는 VL-VH 배향의 항-EpCAM 4-7이 PCR에 의해 얻어졌다. 4-7 VH 영역 및 4-7 VL 영역은 하기 프라이머들에 의해 별개로 증폭되었다: (4-7 VL: 4-7 VL BspE I FOR CTGAAATCCGGAGGTGGTGGATCCGAGCTCGTGATGACCCAGACTCC  (서열번호: 117), 4-7 VL GS15 REV GGAGCCGGCGCCGCAAAACCCACCTTTGATCTCAAGTGGTCCCGCC (서열번호: 118); 4-7 VH: 4-7 VH GS15 FOR GGCGGCGGCGCTCCGGTGGTGGTTCTGAGGTGCAGCTGCTCGAGC  (서열번호: 42), 4-7 VH Sal I REV TTTTATGTCGACCTAAATGATGTGAT-GAGGAGGACGTGAGCGTTGG (서열번호: 43)). 뒤이은 응합 PCR 동안 PCR 생산물에 도입된 오버랩핑 상보적 서열이 사용되어 15-아미노산 (G(S)3) (단일-문자 아미노산 코드) 링커 (표준 링커) (서열번호: 168)의 코딩 서열을 형성하였다. 이 중폭 단계는 프라이어 렉 4-7 VL BspE I FOR 및 4-7 VH Sal I REV (서열번호 42 및 43) 로 수행되었다.

15 아미노산 표준 ((G(S)3)3) 링커를 포함하는 VL-VH 배향의 항-EpCAM 5-10 이 PCR에 의해 얻어졌다. 5-10 VH 영역 및 5-10 VL 영역은 하기 프라이머에 의해 별개로 증폭되었다: (5-10 VL: 5-10 VL BspE I FOR CTGAAATCCGGAGGTGGTGGATCCGAGCTCGTGATGACACAGTCTCCAT  (서열번호: 44), 5-10 VL GS15 REV GGAGCCGGCGCCGCAAAACCCACCTTTGATCTCAAGTGGTCCCGCC (서열번호: 45); 5-10 VH: 5-10 VH GS15 FOR GGCGGCGGCGCTCCGGTGGTGGTTCTGAGGTGCAGCTGCTCGAGC  (서열번호: 46), 5-10 VH SalI REV TTTTATGTCGACCTAAATGATGTGAT-GAGGAGGACGTGAGCGTTGG (서열번호: 47)). 뒤이은 응합 PCR 동안 PCR 생산물에 도입된 오버랩핑 상보적 서열이 사용되어 15-아미노산 (G(S)3) (단일-문자 아미노산 코드) 링커 (표준 링커) (서열번호: 168)의 코딩 서열을 형성하였다. 이 중폭 단계는 프라이어 렉 5-10 VL BspE I FOR 및 5-10 VH SalI REV 로 수행되었다.


8.1.4. 탈면역화된 항-CD3x항-EpCAM 구조체의 EpCAM 및 CD3로의 결합

N-말단 배향에서 항-CD3 부분을 갖는 이중특이적 단일체 분자의 EpCAM 및 CD3로의 결합은 FACS 분석에 의해 확인되었다. 이 목적을 위해, EpCAM 양성 인간 위암 세포주 Kato III (ATCC HTB-103)가 사용되었다. 항-CD3 부분의 결합은 주르카트 세포 (ATCC TIB 152)에서 측정되었다. 세포는 공급자의 권고에 따라 배양되었고, 2% FCS (태아 송아지 혈청)이 첨가된 50㎕ PBS에서 200000 개의 세포
가 10㎍/㎖의 구조체와 함께 배양되었다. 구조체의 결합은 2% FCS가 첨가된 PBS에서 2㎍/ml의 항-His 항체 (Penta-His 항체, Qiagen, Hilden, FRG에서 구입)로 검출되었다. 두번째 단계로, 2% FCS가 첨가된 50㎕의 PBS 내에 1:100으로 희석된, 멜초 항-마우스 IgG로부터 유래된, R-피코에리트린-접합(R-Phycoerythrin-conjugated) 친화성 정제된 F(ab')2이 사용되었다 (Dianova, Hamburg, FRG에서 구입). 샘플은 FACSscan (BD biosciences, Heidelberg, FRG)로 측정되었다.

FACS 분석의 결과는 도 15에 나타낸다. 탈면역화된 항-CD3 부분을 포함하는 모든 구조체는, EpCAM 양성 카토II 세포 상에서 탈면역화 되지 않은 항-EpCAM (M79)x항-CD3 이중특이적 단일체 항체 보다 더욱 강한 결합을 나타내었다.

8.2 탈면역화된 항-CD3 부분을 포함하는 N-말단 EpCAM 바인더의 클로닝

8.2.1 항-EpCAM x 항-CD3 구조체의 클로닝

8.2.1.1 탈면역화된 3-1x항-CD3 (VH5/VL2) 구조체의 클로닝(서열번호:48, 49):

탈면역화된 구조체 3-1x항-CD3 (VH5/VL2) (서열번호: 48)는 탈면역화되지 않은 구조체 항-EpCAM (3-1)x항-CD3로부터 유래되었다. 항-EpCAM 항체 3-1이 VH 및 VL 영역은 서열번호:137 및 139에 나타내었다. 플라스미드 pEF-DHFR-3-1x 항-CD3 및 pEF 항-CD3 (VH5/VL2) (서열번호:192)는, 벡터 및 인서트 항-CD3 (VH5/VL2) 삽입체를 각각 분리하기 위해 BspEI 및 SalI (Biolabs)으로 소화되었다. BspEI-SalI-소화된 벡터를 탈인산화되고 0.7% 아가로스겔에서 정제되었다. 인서트는 1.5% 아가로스겔에서 정제되었다.

정제된 단편 (BspEI-SalI)은 이어서 pEF-DHFR 벡터의 상위에서 클로닝되었다. 최종 3-1x항-CD3 (VH5/VL2) 구조체 (서열번호:48, 49)는 제한 효소 및 전체 인서트의 DNA 서열분석에 의해 확인되었다.

탈면역화 되지 않은 3-1x항-CD3 구조체의 클로닝:

3-1x항-CD3 (VH5/VL2) 구조체의 클로닝을 위해, 상호하는 탈면역화 되지 않은 구조체가 하기와 같이 생성되었다.

VH-VL 배향에서의 C-말단 3-1이 탈면역화 되지 않은 3-1 x 항-CD3 분자의 구축을 위해 PCR에 의해 얻어졌다. 3-1 VH-VL 을 두 부분으로 포함하는 단편 I 및 II가 각각 프라이머 삽 me 91a (서열번호: 53) /me 90 (서열번호: 52) 및 me 83 (서열번호: 50) /me 84 (서열번호: 51)를 사용하여 PCR에 의해 증폭되었다. 핫 스타트 PCR (Hot Start PCR)이 Roche Diagnostics사의 Expand High Fidelity System을 사용하여 수행되었다. 20 주기 (94℃/30초; 60℃/1분; 72℃/1분)가 증폭을 위해 사용되었고, 이어서 72℃에서 3분 동안의 1 주기가 수행되었다.

PCR 단편 I 및 II는 1.5% 아가로스겔 전기영동을 행하였다. 단편은 혼합되어 (각각 1 ng) 전체 3-1을 포함하는 단편 111이 항-CD3 구축을 위한 PCR에 의해 얻어졌다. 3-1 항-EpCAM 양성 보고서에 서열번호:75과 79의 100bp를 사용하여 PCR에 의해 증폭되었다. 핫 스타트 PCR (Hot Start PCR)이 Roche Diagnostics사의 Expand High Fidelity System을 사용하여 수행되었다. 20 주기 (94℃/30초; 60℃/1분; 72℃/1분)가 증폭을 위해 사용되었고, 이어서 72℃에서 3분 동안의 1 주기가 수행되었다.

사용된 프라이머의 서열은 다음과 같다:

Me 83: 5'-GGT TCT GGC GGC GGC GGC GGC TCC GGT GGT GGT GGT GGT GGT TCT GAG GTG CAG CTG CTC GA CAG TCT G -3' (서열번호: 50)

Me 84: 5'- GTG CTC CGG AGG AGA AGA CGG TGA CGG TGG TCC CTT GGC CCC AG -3' (서열번호: 51)

Me 90: 5'- CGG GAG CCG CCG CCG CCA CAA CCA CCC CCA CCT TTG ATC TCA AGC TTG GTC CC -3' (서열번호: 52)

Me 91a: 5'- GGA TGGA TGGA CTG CAG GGT GAG CAT GAC CCA GTC CTC ATC TTA GTC TGCC AG -3' (서열번호: 53)

8.2.1.2 탈면역화된 3-5x항-CD3 (VH5/VL2) 구조체의 클로닝 (서열번호:54, 55):

VH-VL 배향에서 C-말단 3-5는 3-5 x항-CD3 분자의 구축을 위한 PCR에 의해 얻어졌다. 항-EpCAM 항체 3-5의
VH 및 VL 영역은 서열번호: 141 및 143에 나타낸다. 플라스미드 pEF-DHFR-3-5x항-CD3 및 pEF 항-CD3 (VH5/VL2) (서열번호: 192)은 인서트 (3-5) 및 벡터 각각의 분리를 위해 EcoRI 및 BspEI (Biolabs)에 의해 소화되었다. 탈인산화된 벡터 (EcoRI 및 BspEI 소화한) 및 인서트는 아가로스겔-전기영동에 의해 정제되었다.

정제된 단편 (EcoRI-BspEI)은 pEF-DHFR 벡터의 상응하는 부위에 클로닝되었다. 최종 3-5x항-CD3 (VH5/VL2) (서열번호: 54) 구조체는 제한 소화에 의해 확인되었다.

탈면역화 되지 않은 3-5x항-CD3 구조체의 클로닝:
3-5x항-CD3 (VH5/VL2) 구조체의 클로닝을 위해, 상응하는 탈면역화 되지 않은 구조체가 하기와 같이 생성되었다.
3-5을 두 부분으로 포함하는 단편 I 및 II는 3-1x항-CD3에 대해 기술된 조건에 따라 각각 프라이머 쌍 me 81 (서열번호: 56) / me 90 (서열번호: 52) 및 me 83 (서열번호: 50) / me 84 (서열번호: 51)을 사용하여 PCR에 의해 증폭되었다. PCR 단편 I 및 II의 결과는 아가로스겔 단편으로, 전체 3-5를 포함하는 단편 III의 증폭을 위해 프라이머 쌍 me 81 (서열번호: 56) 및 me 84 (서열번호: 51)로 제조되었다. PCR은 상기 기술된 바와 같이 수행되었다. 단편 III는 아가로스겔에서 정제되었고 BssHII 및 BspEI (Biolabs)로 소화되고, 정제되고, 이어서 pEF-DHFR 클로닝 벡터의 상응하는 부위에 클로닝되었다. 클로닝된 영역은 제한효과 및 DNA-서열분석에 의해 확인되었다.

Me81 프라이머의 서열(서열번호: 56):
Me 81: 5'- GGA TGC GCG CGA GCT CGT GAT GAC ACA GTCTCC ATC CTC C -3'

8.2.1.3 탈면역화된 4x1x항-CD3 (VH5/VL2) 구조체의 클로닝 (서열번호: 57, 58):
VH-VL 배향에서 C-말단 4-1은, 4x1x항-CD3 분자의 구축을 위해 PCR에 의해 얻어졌다. 항-EpCAM 항체 4-1의 VH 및 VL 영역은 서열번호: 145 및 147에 나타낸다. 플라스미드 pEF-DHFR-4x1x항-CD3 및 pEF 항-CD3 (VH5/VL2) (서열번호: 192)는, 삽입체 (4-1) 및 벡터 각각의 분리를 위해 EcoRI 및 BspEI (Biolabs)에 의해 소화되었다. 탈인산화된 벡터 (EcoRI 및 BspEI로 절단된) 및 인서트는 아가로스겔-전기영동에 의해 정제되었다.

정제된 단편 (EcoRI-BspEI)은 뒤이어서 벡터의 상응하는 부위에 클로닝되었다. 최종 구조체 4x1x항-CD3 (VH5/VL2) (서열번호: 57)은 제한 소화에 의해 확인되었다.

탈면역화 되지 않은 4x1x항-CD3 구조체의 클로닝:
4x1x항-CD3 (VH5/VL2) 구조체의 클로닝을 위해, 상응하는 탈면역화 되지 않은 구조체가 하기와 같이 생성되었다.
4-1을 두 부분으로 포함하는 단편 I 및 II 가, 상기 기술된 조건에 따라 각각 프라이머 쌍 me 91a (서열번호: 53) / me 90 (서열번호: 452) 및 me 83 (서열번호: 50) / me 84 (서열번호: 51)로 기술된 조건에 의해 증폭되었다. PCR 단편 I 및 II의 결과는 아가로스겔 단편으로, 전체 4-1을 포함하는 단편 III의 증폭을 위해 프라이머 쌍 me 92a (서열번호: 59) 및 me 84 (서열번호: 51)로 제조되었다. PCR은 상기 기술된 바와 같이 수행되었으나, 다만 어닐링은 68℃에서 수행되었다. 단편 III는 아가로스겔에서 정제되었고, BsrGI 및 BspEI (Biolabs)으로 소화되었고, 정제되고, 이어서 pEF-DHFR-항 EpCAM (M79) X 항-CD3 클로닝 벡터 구조체의 상응하는 부위에 클로닝되었다. 클로닝된 영역은 제한 효과 및 DNA-서열분석에 의해 확인되었다.

Me92a 프라이머의 서열 (서열번호: 59):
Me 92a: 5'- GGA TTG TAC A CTCC GA GCT CGT GAT GAC ACA GTCTCC ATC CTC C -3'

8.1.2.4 탈면역화된 4x7x항-CD3 (VH5/VL2) 구조체의 클로닝 (서열번호: 60, 61):
VH-VL 배향에서 C-말단 4-7는, 4x7x항-CD3의 구축을 위해 PCR에 의해 얻어졌다. 항-EpCAM 항체 4-7의 VH 및 VL 영역은 서열번호: 149 및 151에 나타난다. 플라스미드 pEF-DHFR-4x7x항-CD3 및 pEF 항-CD3 (VH5/VL2) (서열번호: 192)는, 삽입체 (4-7) 및 벡터 각각의 분리를 위해 EcoRI 및 BspEI (Biolabs)에 의해 소화되었다. 탈인산화된 벡터 (EcoRI 및 BspEI로 절단된) 및 인서트는 아가로스겔-전기영동에 의해 정제되었다.

정제된 단편 (EcoRI-BspEI)은 뒤이어서 벡터의 상응하는 부위에 클로닝되었다. 최종 구조체 4x7x항-CD3 (VH5/VL2) (서열번호: 57)은 제한 소화에 의해 확인되었다.

Me92a 프라이머의 서열 (서열번호: 59):
Me 92a: 5'- GGA TTG TAC A CTCC GA GCT CGT GAT GAC ACA GTCTCC ATC C TC -3'
호:192)는 인서트 (4-7) 및 벡터 각각의 분리를 위해 EcoRI 및 BspEI (Biolabs)로 절단되었다. 탈인산화된 벡터 (EcoRI 및 BspEI로 소화됨) 및 인서트는 아가로스겔-전기영동에 의해 정제되었다.

정제된 단편 (EcoRI-BspEI로 절단됨) 및 인서트는 아가로스겔-전기영동에 의해 정제되었다. 최종 구조체 4-7x항-CD3 (서열번호:60)는 제한 소화에 의해 확인되었다.

탈면역화 되지 않은 구조체 4-7x항-CD3의 클로닝:
4-7x항-CD3 (VH5/VL2) 구조체의 클로닝을 위해, 상응하는 탈면역화 되지 않은 구조체가 하기와 같이 생성되었다.

4-7를 두 부분으로 포함하는 단편 I 및 II 가, 각각 상기 언급된 조건으로 각각 프라이머 쌍 me 81 (서열번호:56) / me 90 (서열번호:52) 및 me 83 (서열번호:50) / me 84 (서열번호:51)를 사용하여 PCR에 의해 증폭되었다.

정제된 단편 (EcoRI-BspEI로 절단됨) 및 인서트는 아가로스겔-전기영동에 의해 정제되었다. 최종 구조체 4-7x항-CD3 (서열번호:60)는 제한 소화 및 DNA 서열분석으로 확인되었다.

8.1.2.5 탈면역화된 5-10x항-CD3 (VH5/VL2) 구조체의 클로닝 (서열번호: 62, 63):

VH-VL 배향에서 C-말단 5-10은 5-10 x항-CD3 분자의 구축을 위해 PCR 에 의해 얻어졌다. 항-EpCAM 항체 5-10의 VH 및 VL 영역은 서열번호:133 및 135에 나타난다. 플라스미드 pEF-DHFR-5-10x항-CD3 및 pEF-항-CD3 (서열번호:192)는, 인서트 (5-10) 및 벡터 각각의 분리를 위해 EcoRI 및 BspEI (Biolabs)로 소화되었다. 탈인산화된 벡터 (EcoRI 및 BspEI로 절단됨) 및 인서트는 아가로스겔-전기영동에 의해 정제되었다.

정제된 단편 (EcoRI-BspEI로 절단됨)은 위어서 pEF-DHFR 클로닝 벡터의 상응하는 부위에 클로닝되었다. 클로닝된 영역은 제한 소화 및 DNA 서열분석으로 확인되었다.

8.2.2 N-말단 위치에서 항-EpCAM을 갖는 항 EpCAMx탈면역화된-항-CD3 분자들의 발현:
DHFR 유전자 결핍된 CHO-세포는 10% 태아 송아지 혈청 (Life Technologies, 65℃ 에서 30 분동안 열 불활성화) 및 HT (하이포잔틴 및 티미딘; Life Technologies)를 보충한 알파 MEM 배지 (Life Technologies, cat.no: 32561)에서 유지되었다. 그 세포는 pEF-DHFR-3-1x항-CD3 (서열번호: 48), 및 pEF-DHFR-5-10x항-CD3 (서열번호:62)로 Lipofectamine 2000 kit® (Invitrogen)을 사용하여 제조사에 의해 제공된 제작자 의 설명서에 의해 트랜스펙트되었다. 48시간 후에, 선택 배지 (열 불활성된 10% 투석된 태아 송아지 혈청 (Life Technologies)을 포함하는 알파 MEM 배지)에서 선택을 수행하였다. 3-4주 후, 세포 배양 상정액이 수집되었고, 4 등록특허 10-1229731 - 55 -
℃에서 10 분간 300g 에서 원심분리하여 세포 및 세포 찌꺼기를 제거하였다. 이중특이적 항체를 포함하는 상청액은 추가적 분석까지 -20℃ 에서 보관하였다.

8.2.3 이중특이적 항-EpCAMx항-CD3 변이체의 결합 분석:

(CD3 결합을 위한) 250000 쥬르카트 세포 및 (EpCAM 결합을 위한) 카토 세포가 독립적으로 이중특이적 구조체 (pEF-DHFR-3-1x항-CD3 (VH5/VL2) (각각 Nr.50, 서열번호: 48) 및 pEF-DHFR-5-10x항-CD3 (VH5/VL2) (Nr.54) (서열번호:62)를 포함하는 세포 배양 상청액 (50 μl)을 함께 45 분동안 4℃에서 배양하였다. 그후에, 세포는 FACS 완충액(1% 태아 송아지 혈청 (FCS) 및 0.05% 소디움 아자이드(sodium azide)를 포함하는 인산염-완충된 식염수)으로 두번 세척되었고, 마우스 항-His 항체 (Dianova, DIA910)과 함께 60 분동안 4℃에서 인큐베이트되었다. 세척단계는 상기와 같이 수행되었다.

세포는 최종적으로 염소 항-마우스 Ig-PITC-접합된 항체 (BD 550003) 또는 PE와 접합된 항-마우스 IgG (Sigma, P8547)과 함께 세척되었다. 세척 단계 후에, FACS Calibur (BD&D)를 이용하여 10,000 번의 경우가 분석되었다. 결합 측정의 결과는 도 16에 나타났다. 구조체 3-1x항-CD3 (VH5/VL2) (서열번호:49) 및 5-10x항-CD3 (서열번호:63)는 극도로 나타났지만 카토 세포에서 CD3에, 그리고 쥬르카트 세포에서 CD19에 강한 결합을 보였다.

실시예 8.3. 탈면역화된 항-CD3 부분을 갖는 이중특이적 항 EpCAM 구조체의 정제

탈면역화된 항-CD3 영역 및 EpCAM-특이적 영역을 포함하는 구조체는 고정된 금속 친화성 크로마토그래피 (IMAC) 및 겔 여과를 포함하는 두 단계 정제에 의해 정제되었다. 금속 친화성 크로마토그래피 (IMAC) 및 겔 여과는 실시예 3.2에 설명된 바와 같이 수행되었다.

추가의 고 해상도 양이온교환크로마토그래피가 MiniS 컬럼 (Amersham)에서 수행되었고, 20mM MES 버퍼 pH 5.5로 평형화되었다. 샘플은 동일한 완충액을 사용하여 컬럼에 로딩하기 전에 1:3으로 희석하였다. 결합된 단백질은 평형 완충액에서 1M NaCl의 0-30% 용량구배 그래디언트로 용출되었다. 용출된 단백질 분획은 생활성 측정법에서 테스트되었다. 표 14는 정제된 탈면역화된 EpCAM 구조체의 수율을 보여준다. 모든 구조체는 효율적으로 생산될 수 있다. 높은수도 구조체 5-10x항-CD3 (VH5/VL2) (서열번호:63)는 2200 μg/1 라는 극히 좋은 수율을 가졌다.

<table>
<thead>
<tr>
<th>구조체</th>
<th>단량체의 수율 [배양 리터당 정제된 단백질μg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>항-CD3 (VH5/VL2)x4-7 (서열번호:33)</td>
<td>112.5</td>
</tr>
<tr>
<td>3-1x항-CD3 (VH5/VL2) (서열번호:49)</td>
<td>87.5</td>
</tr>
<tr>
<td>항-CD3 (VH5/VL2)x3-1 (서열번호:31)</td>
<td>442.5</td>
</tr>
<tr>
<td>5-10x항-CD3 (VH5/VL2) (서열번호:63)</td>
<td>2200</td>
</tr>
<tr>
<td>항-CD 3 (VH5/VL2)x5-10 (서열번호:37)</td>
<td>80</td>
</tr>
</tbody>
</table>

실시예 8.4 탈면역화된 항-CD3 부분을 갖는 이중특이적 항-EpCAM 구조체의 세포독성 측정법

본 발명의 이중특이적 항체는 보편적 생활성을 확인하기 위해, FACs 기반의 측정법이 수행되었다. CHO 세포가 사포세포 부착 분자 (EpCAM)로 트랜스펙트되었다. 이 트랜스펙트된 세포 클론은 CHO-EpCAM 이라고 불리는데, 이 실험을 위해 사용되었다.

세포 독성 테스트를 위해, CHO-EpCam (1.5x103)-awaited 세포는 혈청이 없도록 PBS로 두 번 세척하였고, 제작자의 설명에 따라 PKH26 염료(Sigma-Aldrich 사)와 인큐베이트되었다. 염색후에, 세포는 RPMI/10% FCS로 두 번 세척되었다.

세포는 계수되었고, CB15 적응 세포와 섞어졌다. CD4-양성 T 세포 클론 CB15은 독일의 Erlangen/Nueonnberg 대학 의 피크셔 박사(Dr. Fickenscher)에 의해 제공되었다. 세포는 공급자의 권고에 따라서 배양되었다. 결과물은 세
포 현탁액은 ml 당 400,000 표적 및 2 x 10^6 작동 세포를 포함하였다. 96렬 둥근 바닥 플레이트의 햄 당 혼합
물 50 μl가 사용되었다.

항체는 요구되는 농도로 RPMI/10% FCS에서 희석되었고, 이 용액의 50μl가 세포 현탁액에 첨가되었다. 표준 반
응은 16시간 동안 37℃/5% CO2에서 인큐베이트되었다. 프로피디움 아이오다이드가 최종농도 1 μg/ml로 첨가
되었다. 10분의 실온에서의 인큐베이션 후 세포는 FACS에 의해 분석되었다. 표적 세포의 양성 확인을 위해
PKH26 혈청이 사용되었다. 세포독성은 모든 표적 세포들에 대한 PI 양성의 비율로 측정되었다.

S자형 용량 반응 곡선(sigmoidal dose response curves)은 전형적으로 Prism Software (GraphPad Software
사, 샌디에이고, 미국)에 의해 측정된 바와 같이 R2 값 >0.97 이었다. 세포 독성 측정법의 결과는 도 17 및 18에
나타낸다.

실시예 8.5. CHO 세포에서 EpCAM 결합 부분 및 탈면역화된 CD3 결합 부분을 포함하는 이중특이적 분자들의 생산
성의 비교

탈면역화된 구조체의 생산성을 측정하기 위해 단백질 L ELISA 이 수행되었다. 생산성 데이터는 배치 배양으로부
坦 계산되었다.

8.5.1 세포 배양

탈면역화된 (CHO-DHFR-) 및 탈면역화 되지 않은 (CHO-DHFR 또는 CHO-K1)를 생산하는 CHO 세포주는, 37℃ 및 5%
CO2의 CO2 배양기 내에서, HyQ PF CHO LS 배지 + 4 mM L-글루타민 에서 배양되었다. 세포수 및 생존능은 트리
판 물질을 사용하여 측정되었다. 세포 밀도는 1-2 x 10^5 세포/ml로 세팅되었다.

세포는 스피너 플라스크(spinner flasks)로 옮겨졌고 그래서 교반되는 배양의 조건으로 조정되었다. 작동 변수
세팅은 CO2 배양기 내에 가스를 처리하며 80 rpm, 37℃ 및 5% CO2 이었다. 배양 부피는 100-500 ml-범위였고, 접종시의 세포 밀도는 1-2 x 10^5 세포/ml 이었다. T-플라스크에서의 하위배양(subcultivation)에서는, 배양들은
원심분리되고 각각의 계대에서 신선한 미리-따뜻하게 한 배지에 재현탁되었다. 세포 밀도는 1-2 x 10^5 세포/ml
로 세팅되었다.

생산성 데이터 (표 15)의 분석을 위해, 세포는 최장 14일까지 어떠한 배지의 첨가 또는 교환없이 배양되었다.
세포수 및 생존능은 매일 트리판 튜브로 양성 염색을 사용하여 측정되었다. 상청액에서의 생산물 농도는 단백질 L
ELISA에 의해 분석되었다.

8.5.2 단백질 L ELISA

이중특이적 분자들의 정량적 결합이 r단백질 L-코팅된 마이크로타이터 플레이트로 수행되었다. r단백질 L 은 캠플
토스트렙토코커스 마그너스(Peptostreptococcus magnus)에 의해 생산되는 면역글로불린-결합 단백질 L의 재조합
체 형태이다. 그것은 네 개의 결합 도메인이 있고 경쇄(κ)를 통해 면역글로불린에 결합한다. 각각 모(parent)
항체의 두 개의 상이한 경쇄들로부터의 가변 도메인을 포함하는 이중특이적 분자들은 또한 r단백질 L에 의해 결
합된다.

마이크로타이터 플레이트는 하루방동한 2-8℃에서 PBS 완충액 (2 μg r단백질 L/mL PBS 완충액) 내에서 r단백질
L로 코팅되었다. 캠플에 이어서, 혼합 부피의 나머지는 브로팅 완충액 (PBS 완충액 내의 2% BSA)으로 브로팅된다. 그
후, 플레이트는 방동되고 ≤18℃에서 보관된다. 사용하기 전에, 그 플레이트는 해동되고 세척 완충액 (PBS
완충액 내의 0.05% 트윈 20)으로 세척되어 코딩 용액 및 브로팅 완충액의 혼합물을 제거한다.

PBS 내의 1% BSA + 0.01% 트윈 20 (회색 완충액) 내의 세포 없는 세포 배양 상청액의 계단 희석이
분석되었다. 이중특이적 항-EpCAM(M79)x항-CD3 가 비교 희석액으로 양성 대조군으로 사용되었다.

인큐베이션은 하루방동한 2-8℃에서 수행되었다.
세척 후에, 토끼 항-마우스 IgG (희석 완충액에서 1:5,000)가 첨가되었고 60분간 실온에서 항온 보관되었다. 세척 후에, 알칼리 포스파타아제로 표지된 염소 항-토끼-IgG 가 첨가되었다 (희석 완충액에서 1:1,000; 실온에서 60 분). pNPP 기질 용액이 첨가되었고, 반응은 3 M NaOH의 첨가로 중지되었다. 흡광도는 ELISA 판독기로 405 nm (참조 필터 492 nm)에서 측정되었다.

표 15
탈면역화된 항-EpCAM 구조체의 생산성

<table>
<thead>
<tr>
<th>구조체</th>
<th>M79x항-항-CD3</th>
<th>5-10x항-CD3 (VH5/VL2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>기본 세포주</td>
<td>CHO-K1</td>
<td>CHO-dhfr-</td>
</tr>
<tr>
<td>비(Specific) 생산성</td>
<td>하루당 0.2-0.6 pg/세포</td>
<td>하루당 1-3 pg/세포</td>
</tr>
<tr>
<td>최대 세포 밀도</td>
<td>3x10⁶ c/ml</td>
<td>1.2-1.8x10⁶ c/ml</td>
</tr>
<tr>
<td>배가시간</td>
<td>17-20 h</td>
<td>25-30 h</td>
</tr>
</tbody>
</table>

그래서, 본 발명의 5-10x항-CD3 (VH5/VL2) 구조체는, 종래 기술 이중특이적 탈면역화 되지않은 EpCAM 및 CD3 결합 항체보다 훨씬 더 높은 비 생산성 (specific productivity) (적어도 5배 이상 높음) 을 보인다.

도면의 간단한 설명
도 1. 탈면역화 되지않은 항-CD3 카세트의 DNA 및 아미노산 서열들 (서열번호: 1 및 2).
도 2.
A) 중쇄 VH2 (서열번호:70), VH3 (서열번호:72), VH5 (서열번호:74) 및 경쇄 VL1 (서열번호:78), VL2 (서열번호:80) 및 VL3 (서열번호:82) 각각의 아미노산 서열,
B) 중쇄 VH2 (서열번호:69), VH3 (서열번호:71), VH5 (서열번호:73) 및 경쇄 VL1 (서열번호:77), VL2 (서열번호:79) 및 VL3 (서열번호:81) 각각의 뉴클레오티드 서열,
C) 탈면역화 되지않은 항-CD3 의 중쇄 (각각, 서열번호:84, 90, 96), VH2 (각각, 서열번호:86, 94, 96), VH3 (각각, 서열번호:86, 94, 96), VH5 (각각, 서열번호:88, 92, 96) 및 VH7 (각각, 서열번호:88, 90, 96) 및 탈면역화 되지않은 항-CD3 의 경쇄 (각각, 서열번호:98, 102, 104), VL1 (각각, 서열번호:100, 102, 104), VL2 (각각, 서열번호:100, 102, 104) 및 VL3 (각각, 서열번호:98, 102, 104) 의 CDR 1, 2 및 3의 아미노산 서열, 및
D) 탈면역화 되지않은 항-CD3 의 중쇄 (각각, 서열번호:83, 89, 95), VH2 (각각, 서열번호:85, 93, 95), VH3 (각각, 서열번호:85, 93, 95), VH5 (각각, 서열번호:87, 91, 95) 및 VH7 (각각, 서열번호:87, 89, 95) 및 탈면역화 되지않은 항-CD3 의 경쇄 (각각, 서열번호:97, 101, 103), VL1 (각각, 서열번호:99, 101, 103), VL2 (각각, 서열번호:99, 101, 103) 및 VL3 (각각, 서열번호:97, 101, 103) 의 CDRs 1, 2 및 3의 뉴클레오티드 서열.

도 3.
A) 항-CD3 (VH2/VL1)의 뉴클레오티드 서열 (서열번호:4)
B) 항-CD3 (VH2/VL1)의 아미노산 서열 (서열번호:5)
C) 항-CD3 (VH2/VL2)의 뉴클레오티드 서열 (서열번호:6)
D) 항-CD3 (VH2/VL2)의 아미노산 서열 (서열번호:7)
E) 항-CD3 (VH2/VL3)의 뉴클레오티드 서열 (서열번호:8)
F) 항-CD3 (VH2/VL3)의 아미노산 서열 (서열번호:9).
도 4.
A) 항-CD3 (VH3/VL1)의 뉴클레오티드 서열 (서열번호:10)
B) 항-CD3 (VH3/VL1)의 아미노산 서열 (서열번호:11)
C) 항-CD3 (VH3/VL2)의 뉴클레오티드 서열 (서열번호:12)
D) 항-CD3 (VH3/VL2)의 아미노산 서열 (서열번호:13)
E) 항-CD3 (VH3/VL3)의 뉴클레오티드 서열 (서열번호:14)
F) 항-CD3 (VH3/VL3)의 아미노산 서열 (서열번호:15).

도 5.
A) 항-CD3 (VH5/VL1)의 뉴클레오티드 서열 (서열번호:16)
B) 항-CD3 (VH5/VL1)의 아미노산 서열 (서열번호:17)
C) 항-CD3 (VH5/VL2)의 뉴클레오티드 서열 (서열번호:18)
D) 항-CD3 (VH5/VL2)의 아미노산 서열 (서열번호:19)
E) 항-CD3 (VH5/VL3)의 뉴클레오티드 서열 (서열번호:20)
F) 항-CD3 (VH5/VL3)의 아미노산 서열 (서열번호:21).

도 6.
A) 항-CD3 (VH7/VL1)의 뉴클레오티드 서열 (서열번호:22)
B) 항-CD3 (VH7/VL1)의 아미노산 서열 (서열번호:23)
C) 항-CD3 (VH7/VL2)의 뉴클레오티드 서열 (서열번호:24)
D) 항-CD3 (VH7/VL2)의 아미노산 서열 (서열번호:25)
E) 항-CD3 (VH7/VL3)의 뉴클레오티드 서열 (서열번호:26)
F) 항-CD3 (VH7/VL3)의 아미노산 서열 (서열번호:27).

도 7. 상이한 탈면역화된 항-CD3 부분:

도 8: 280 nm 에서의 HCIC 컬럼으로부터의 항-CD19x항-CD3 단백질 분획의 탈면역화된 변이체의 대표적인 용출 패턴. 700 ml 에서의 주요 단계를 보여주는 바닥선은, 20 mM 아세테이트, pH 3.5를 포함하는 용출 완충액의 이론적 그래디언트를 나타낸다. 280 nm에서의 높은 흡착은 컬럼 흐름-통과(flow-through)에서의 비-결합 단백질에 기인하였다. 810.98 ml에서의 화살표는 용출된 탈면역화된 항-CD3 분획을 나타낸다.

도 9: 280 nm에서의 Ni-킬레이팅 His Trap 컬럼으로부터의 항-CD19x항-CD3 단백질 분획의 탈면역화된 변이체
의 대표적인 용출 패턴. 85 ml 에서의 제 1단계 및 90ml 에서의 제2 주요 단계를 보여주는 바닥선은, 용출 완충액의 이론적 그래디언트를 나타낸다 (점선). 93.16 ml 에서의 화살표는 해당하고 단면액화된 항CD19 x 항CD3 구조체를 포함하는 단백질 분획을 나타낸다.

도 10: 세파덱스 S200 져여과 컬럼으로부터의 대표적인 단백질 용출 패턴. 분획은 0~130 ml 정체시간에 수집되었다. 80.44 ml 에서의 단백질 피크는 약 52 kD 의 분자량에 해당하고 단면액화된 항CD19 x 항CD3 구조체를 포함한다.

도 11: 

도 12: 상이한 탈면역화된 항-CD3 부분:

도 13: 상이한 탈면역화된 항-CD3 부분: 
(A) 항-CD3 (VH5/VL1) (서열번호:190), 항-CD3 (VH7/VL1) (서열번호:196), 항-CD3 (VH7/VL2) (서열번호:198) 및 항-CD3 (VH7/VL3) (서열번호:200),

도 14: 탈면역화 되지 않은 CD3 항체의 가변 중(heavy) 영역, VH5 (서열번호:74), VH7 (서열번호:76), VH2 (서열번호:70) 및 VH3 (서열번호:72)의 서열 배열. FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4, CDR4가 박스로 표시되었다. 정렬은 벡터 NTI Advance (Informax 사, 미국) 사의 AlingnX 프로그램을 사용하여 수행되었다.

도 15: CD3-양성 주르카트 및 EpCAM-양성 카토 III 세포에서, FACS-기반의 측정법으로,

상이한 탈면역화된 항-CD3 부분:

(A) 항-CD3 (VH5/VL2)x5-10 (서열번호:37),

(B) 탈면역화된 항-CD3 (VH5/VL2)x4-7 (서열번호:33),

(C) 탈면역화된 항-CD3 (VH5/VL2)x3-1 (서열번호:31),

(D) 탈면역화된 항-CD3 (VH5/VL2)x4-7 (VL-VH) (서열번호:35) 및 등록특허 10-1229731
탈면역화된 항-CD3 (VH5/VL2)x5-10 (VL-VH) (서열번호:39),

올 갖는 이중특이적 항 EpCAM 구조체의 결합 분석.


도 16. CD3-양성 자르크트 세포에서 및 EpCAM-양성 카토 세포에서,

FACS 기반 측정법으로,

상이한 탈면역화된 변-CD3 부분:

(A) 3-1x항-CD3 (VH5/VL2) (서열번호:49) 및

(B) 5-10x항-CD3 (VH5/VL2) (서열번호:63)

를 갖는 이중특이적 항 EpCAM 구조체의 결합 분석.

오른쪽으로의 변위는 결합을 나타낸다.

도 17. 상응하는 탈면역화 되지 않은 구조체에 비교한,

N-말단 위치에서 탈면역화된 항-CD3 부분 (디(di) 항-CD3), 항-CD3 (VH5/VL2)x3-1 (서열번호:31), 항-CD3 (VH5/VL2)x5-10 (서열번호:37) 및 항-CD3 (VH5/VL2)x4-7 (서열번호:33)을 갖는 EpCAM 구조체의 세포독성 측정법.

CB15 T 세포 클론 및 CHO-EpCAM 세포는 5:1 의 E:T 비율로 사용되었다. CHO-EpCAM 세포는 PKH26 염료로 염색되었고, 세포는 FACS 분석으로 이중특이적 단일쇄 항체 인큐베이션 후에 계수되었다.

도 18. 상응하는 탈면역화 되지 않은 야생형 구조체에 비교한.

C-말단 위치에 탈면역화된 항-CD3 부분 3-1x항-CD3 (VH5/VL2) (서열번호:49) 및 5-10x항-CD3 (VH5/VL2) (서열번호:63)을 갖는 EpCAM 구조체의 세포독성 측정법. 세포독성 측정법은 도 17과 동일하게 수행되었다.
항-CD3 WT
GATATCAAACTGCAGCAGTCAGGGGCTGAACCTGCAAGACCTGGGGCCTCACTGGAAGATGTCCT
GCAAGACTTCTGGCTACCCTTTTACTAGGTAACAGAGTGCAGCTGGTAAAACAGAGGCCCTGGACA
GGGCTGGGATGGATTGGAATACATTATTACATCTAGCGTTTTACTTATTACATGATCGARTATC
AAGGACAGGGCCACATTGACTAAGAACAATCTCTCCAGCAGCGCTACTGACAGTCGAGCGCC
TGACCATCTGAGACTCTGCAGCTATTACTGTGCAAGATTATTATGATGATCATATACATTGCGT
CTACTGGGGAAGCGAAGGCCTCTCACTCGATCTCCTCGAAGCTGGAAGTGGGAGTTGCTG
TGGAAAGTGAGGTCCAGGTGAGTTCGACAGACATTCTAGCTGACCAGACTCCTCCAGCAATCATGCTCG
CATCTCCAGGGGAGAGTTACCATAGCTCGAGGCGAGCGTCAGTGTAGTTACATGAACTG
GTACCAAGCAGAAGTCAAGGACCTCCCTCCCCAAAGATGGAATTATGACACATCACAAGTAGGCTTCT
GGAGTCCTTTATCGCTTCACTGCGAGTGCTGGCTGGGACTCTACGTCTCATAACAGACGCA
TGGAGGCTGAAGATGCTGAGCTCCACTTATTTACGTGCAAACAGTGGAGTGAATACCCGCTACGTTGG
TGCTGGGACCAGCTGGAGCTGAAA

AA 시열
DILKLQGSAGELARPGASVKSCKTSGYTFTRTYMHWKVQRPGQGLEWIGYINPSRGYTNYNQKF
KDKALTLDSSSLAYQMSLTLTSEDSAVYCHARYYDDHYCLDYWGQTTLTVSSVGGGSGS
GSGGGGYVDDIQLTLQSPAIMASPSGEKVTMCASSSVSYMNWYQQKSGTSPKRWYDTSKVAS
GVPRFSGSGSGTGYSLTISSMAEADAYYQCQQWSSNPLTFGAGTKLELK
도면24계속

<table>
<thead>
<tr>
<th>VL1</th>
<th>VL2</th>
<th>VL3</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIOQTSPSSLSVGRVTITCRASQSVSVSYMYWQQKQPKGKPWRWYTDT</td>
<td>DIOQTSPSSLSVGRVTITCRASQSVSVSYMYWQQKQPKGKPWRWYTDT</td>
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**vH CDR1**
Wt 항-CD3 GYTFTRYTMH
VH2, 3 GYATATRYTMH
VH5, 7 GYTFTRYTMH

**vH CDR2**
WT 항-CD3,
VH7 YINPSRGTYTNQNFKD
VH5 YINPSRGTYNAYDSDKLG
VH2, 3 YINPSRGTYNAYQKLDYG

**vH CDR3**
WT 항-CD3,
VH2, 3, 5, 7 YYDDHYCLDY

**vK CDR1**
WT 항-CD3,
VL3 RASSVSsymn
VL1, 2 RASQVSsymn

**vK CDR2**
WT 항-CD3,
VL1, 2, 3 DTSKVAS

**vK CDR3**
WT 항-CD3,
VL1, 2, 3 QWSSNPLT
도면2D

**vH CDR1**
- **WT** 항-CD3: GGCTACACCTTTACTAGGTACACGATG CAC
- **VH2, 3** : GGCTACACCGCTACTAGGTACACGATG CAC
- **VH5, 7** : GGCTACACCTTTACTAGGTACACGATG CAC

**vH CDR2**
- **WT** 항-CD3, VH7 : TACATTAATCTAGGCCGTGTTTATCT AATTACAATCAGAAGTTCAAGGAC
- **VH5** : TACATTAATCTAGGCCGTGTTTATCT AATTACGCAGACAGCGTCAAGGAC
- **VH2, 3** : TACATTAATCTAGGCCGTGTTTATCT AATTACGCACAGAGTTGACGGGC

**VH CDR3**
- **WT** 항-CD3, VH2, 3, VH5, 7 : TATTATGATGATCATATTACTGCCTT GACTAC
도면 2D계속

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도면 3

A) 항 - CD3 (VH2/VL1)
GAGTCCAACCTGTCAGTCAGGGGCTGAAGTTGAAGAAAAAC
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CGGCTACTAGAGCAGTAGCAGGCTGATTGCCAGCCAGCT
GGACAGCTGAGCTGGAATGAGCTGATACATTATGCTG
CGAAGATATTATGATATGATATTACTGCGCTTGACTACTG
GCCAAGGCACCACGGCTCACGCTGCTCTCGAGCGAAGGTACT
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GACATTCAGATGACCCAGTCTCCATCTAGCCTGCTGCAT
CTGTCGGGACCGTGCACCACATCATGCCAGACCCAGTCAA
ACTGTAAGTTAGCTGAACTCGTGACACGAGAAGCCGGCGAA
GCCACCCAAAGATGGATTATGACACATCCAAGTTGCTT
CTGGAGTCCTGCGCTCGCTCAGTGGCACTGGTCTGGACC
GACTACTCTCTCAACTACACGTGGCTGAGCTGAC
GCCACCTTATTACTGCCAAGCAGTGGAGATGTAACCCGCTCA
CGTTCCGGTGCAGGCCAGAAGTTGGAGATCAAA

B) 항 - CD3 (VH2/VL1)
DVQLVQSGAEVKPGASVKVSVCKASGYATTRYTMHWVRQAP
GQGLEWGYINPSRGFYNTYAQLQGRVTMTDTSTSTAYME
LSSLREDTATYYCARYYDDHYCLDYWQGGTVTVVSSGEQT
STGGSSGGSGGGGADDIOMTQPSPLASVGRVTVTICRASQ
SVSYMNWYQQKPGKAPKRWIDTSTKVASVGPARFSGSGST
DYSMTINSLEAEDAATYYCQWSSNPLTFGGGTKVEIK
도면3계속1

C) 항 -CD3 (VH2/VL2)
GACGTCCACTGTGGTCAGTCAGGGGCTGAGTGAATGAAA-
AACCTGGGGCCTCAGTGAAAGGTGTCCCTG-
CAAGGGCTTCTGGCTACACCCTGCTACTAGGTAAGAGATG-
CAGCTGGTAAGCCAGGCAACTGGGACAGGTGATGATGGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATGATGGATGATG
도면3계속2

E) 항 -CD3 (VH2/VL3)
GACGTCCAACACCCCTGGGCTCACAGGGGGCTGAAGTGAGAAACCTGGGGCTGCTACACCCGGTATCGATCGAT
CAGGGTTTCTTTTACCGTACCCCGCTCTATAGTGAGGTAC
CAGTGTTGCTGTGGAGACAGGCTGCAACCTAACCTACTGTGCAA
GATATTATGATGATCATTACTGCTTGGACTACTGGGCC
CAAGCCACAGGCTACCCGCTTCCCTCCAGGGCAAGGTAC
TAGTACTGGGGTCTGGGTGAAGTGAGGTCCAGTGCAGCAGCA
GACAGCATTGATCGACCAGCTCTCCAGCAACTCTGTCTCT
GTCGCTCGGGAGCTGGTGCCACCTCGACCTTGCAAGCGAC
CAGTTCAGTGTAAAGTACATGGAAGCAGCACGAAGGCCGGCCACCCCGCCAAAGATGGATTATGACAC
CATCCAAAGTGGCTTCTGGAGTCCCTCTGCTGCTTCAGTGCC
AGTGGGTCCTGGGACCCGACTACTCTCTCCTCAACATCAA
CAGCTGTGAGGCTGAAAGTGGCTCACTTACCTACCTGCAA
CAGTGGAATAGTACCCGGCTCAGTCTCGGTGGCCGGGAC
CAAGGTGGAGATCAA

F) 항 -CD3 (VH2/VL3)
DVQLVQSGAEVKPGASVKVSCKASGYTATRYYTMHWVR
QAPCQGLEWGYINPSRGTYNY
AQKQLQGRVTMTTSTSTAYMEILSSLRSEDTATYCA
RYYDDHYCLDYWGQTTVTVSSGESELSTSGSGGSGGSGGADD
IVLTQSPATISLSFGERATLTCRASSSVMNYQPKFG
KAPKRWWYDSKSVASGVPARFSGSGTDSLTLINSLEAE
DAATYYCQWSSNPLTFGGGGTKVEIK
도면4

A) 항-CD3 (VH3/VL1)
GACGTCCAACCTGTGGTCAGTCAGGGGCTGAAATGAAAAAACC
TGCGGCTCTAGTGAGGTGTGGTCCCTGCAAGGCTTCTGGCTACA
CCGCTACTAGGTACACGATCGACTGGTAAGGCAGGACCT
GGACAGGTCTGGGAATGGGGATTGGGATACATTAATCCTTAGCC
TGTTTATACTAATTACGCACAGAAGTTGGCAGGGCGCGCTCA
CAATGACTACAGACACACTTCCACCCACACAGCAGCTACTGCAA
ATGAAACAGCCTGAAACTGAGGAACACTGCAGTCCTATTACTG
TGCAAGATATTGATATGATCATATTAGCTGGCTTGGACTACTGCG
GCCAAGGCAACCGGTCACCGGTCTCCTCAGGCGGAAAGTACT
AGTACTGGTCTCGTGGGAAAGTGAGGTTACGAGTTGAGACAGA
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CTGTCGAGGGGACCTGTCCACCATCACCTGAGAGCAGATCAA
AGTGAAGTTACATGAACTGTAGGTACACGAGAGCCGGCAA
GGCACCAAAAGATGGATTTAGATCAACATCAAGAAGTGGCT
CTGGAGTCCCTGCTCCTCGCTAGTGGCAGGGTCTGGGACC
GACTACTCTCTCATCACAATCAACAGCTTTGAGAGTGAATGTC
TGCCACCTTATTACCTGCAACAGTGAGTAGTACCGCTGACA
CGTCCGGTGCGGGGAGACAGTGGAGATCAA

B) 항-CD3 (VH3/VL1)
DVQLVQSGAEVKPKPGASVKEKSCKASGYATTRYTMLWVR-
QAPGGQLEWGYINPSGRTYNY-
AQKLGQGRVTMTTDTSTSTAYLQMNSLKTEDTAVYYCARDD-
HYCDWGGTGTGVSSGEGTSTGSGSGLGSGGADDIQTQSP
SSLSAVGDRVTITCRASQSVSYMNWYQQKPQ-
KAPKRWIYDTSKVASGVPRFSGSGTGDSLTINSLEAE-
DAATYYCQQWSSNPLTFGGGTKVEIK
도면4계속1

C) 항-CD3 (VH3/VL2)

GACGTCCAATCGGTGAGTCAGGGGCTGAAGTGAAAAACCT
TGCGCTCTAATGAAGTGTCTGCTGCAAGCTTCTGCTACA
CCGCTACTAGTACCACTGCGTGGGTAAAGCAGGCACCT
GGACGAGGGCTCTGGAATGGAGAAGATACATAATTCCTAGCG
TGCTTATTTACTATTACCAGCAGAGGCTGAGGGCGCGTCA
CAATGACACTAGCAGACATTTCCACCAGCAACAGGCTACCTGCAAA
ATGAACAGCCTGAAAAACTGAGGACACTGCAGTCTATTAGTGC
TGCAAGATATATTATGACATCATTACTGCTTTGACTACTGGG
GCCAACGCCACCCACGGTCACCGTCTCTCCACGGCAAGGTACT
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CTCCAGGGAGGGTGCCACCTGAGCTGACAGGCCAGTCAAA
AGTGAAGTTACATGAACCTGGTACCACGCAAGGCGGGGCAAA
GGACCAAAAAGATGGATTTATGACACATCCAAATGGCTT
CTGGAAGCTCCCTGCGTTCACTGAGCACGATGGTCTGGGACC
GACTACTCTCTACAAATCAGAGCTTTGGAGGCTGAAGATGC
TGCCACCTATTACTGCCAACAGTGGAGTAGTAAACCCGCTAC
CGTTCGCTGGCCGGACAAAGGTGGAGATCAAA

D) 항-CD3 (VH3/VL2)

DVQLVQGAEVKPGASVKVSCKASGYTATRYTMHWVRQAP
GQGLEWIGYINPRGTYNAQKLGQRTMTDDSTTSTAYLQ
MNSLKTEDTAYVYIRYDDHYLDYWGGQTTVTVSSGEGT
STGSASSSGSSGSGADDHVIQTSPATLSLPSGERALTSCRASQ
SVSYMNWYQQKPGKAPKRVIYDTSKVASGVARFSGSGSGT
DYSIINSLEAEAATYYCQQVSNPLTFGGGTKVEIK
도면4계속 2

E) 항 -CD3 (VH3/VL3)
GACGTCCAACCTGGTGCACTCGGGCTGAAATGGAAGAAACCTGGGGGCTCAGTGAAGGTGCTCCTG-
CAAGGCTTCCTGGCTACACCCGCTACTAGTGCAAGATGCATG-
CACTGGTAAGGCAAGGACACTGCTGGATGGAATGGAT
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ACTGTCTCTGCTGTCAGGAACTGCTGGGCTGGAGAGGCGAGGAG-
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TCCAGGGGAGCCTGACCCCTGACCTGCAGGCGAGGCAGTT-
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CAAGGACACCCAAAGATGGATTATGACACACTCCA-
AAACTGCTCTGGAGTCCTGCCTCGTTCGTGGCAGGATGGG
TCCTGGGAGCAGCATCTCTCTCCAAATACAACAGCTTG-
GAGGCTGAAGATGCTGCCACTTATTACTGCCAACAGTG-
GAGTAGGAACCCTCGCTACGTTCGATGGCCGGGACCAAGGTGG-
GAGATCAA

F) 항 -CD3 (VH3/VL3)
DVQLVQSGAEVKPGASVKVSCKASGYTATRYMHWVR-
QAPGQGLEWYGYYINPSRGTYNY-
AQKLQQRVTMDTSTSTSTAYLMNLKTEDTAVYYCA-
RYYDDHYCLDYGQGTGTVTSSGEGTSTGSGSGGGSGGADD
IVLTQSPATLSLSPERATLTCRASSSVYMNWAYQKPG-
KAPKRWIYDSKVASVGPRFSGSGLTGDSLTINSLEAE-
DAATYCYQWSSNPLTFGGGKVEIK
A) CD3 ( VH5/VL1 )
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GGCACCACAAAGATGGATTTATGACACATCCAAAGTGGCTT
CTGGGATCCCTGTCCCGCTCGTCCACTAGGGAGCTGGTGGGACC
GACTACTCTCTCACAATCAACAGCTTGGAGCTGAAGATGC
TGCCACATTTATTACTGGCAACAGTGAGTGAACCCGCTCA
CGTTCGGTCGGCGGGCAACAGTGGAGATCCAA

B) CD3 ( VH5/VL1 )
DVQLVQSGAEVKPGASVKVSCKASGYTFTRTYMHWRQAP
GGQGLEWIGYINPSRGYTNQNASVKGRFTITIDKSTAYME
LSSLRSEDTATYYCARYDHYCLUDTYWGQTTVTGVSSEGTS
STGGSGSGSSGSGADDIQMTQSPSSLASVGDRTITCRASQ
SVSYMNWYQPKPGAKPKRVIYDTSKVASGVPARFSGSGSGT
DYSLTNSLEAEDAAATYYCQQWSSNPLTFGGGTKVEIK
도면5계속1

C) 항 - CD3 (VH5/VL2)
GACGTCCAACGTCGAGTTCAGGAAGCTGAAATGAAAAACC
TGGGGCCTCAGTGAAGGTGCTCTGCAAAGCTCTGCTACA
CCTTTACTAGGACAGCTACGAGTGACTGGGTAAGGCGAGCCT
GGACAGGGTCCTGGAGATTGGATATACATTACTCTAGCCG
TGGTTATACTAAATTACGCAGACAGCCTCAAGGGCCGCTTCA
CAATACCTACAGACAATACTCAGAGACACAGCTAATGAGA
CTGACGACGCTGCTCTGAGGACACTGCAACCTATTACTG
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CTCCAGGGAGGCGTGGCACCCTGTAGCTGACAGCAGCAGTCAA
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CTGGAGTCTCTGCTCCAGTGCCAGTGCTGGGCAGGACC
GACTACTCTCCTCAATCACAACGCTTTGAGGCTGAAGATGC
TGCCACTATTACTGCCACAGTGGAGTAGTAACCGCCTCA
CTTCCGTGGCAGGGCCAGGACAGGTGGAGATCAAA

D) 항 - CD3 (VH5/VL2)
DVQLVQSGAEVKPGASVQKSCKASGRGVTFSKTVWMHWVRQAP
GQGLEWIGYINPSRNYADSGVKGRFTITTDKSTSTAYME
LSLRLSDETATYCYCARYYDDHHCNYCLIDYWGQGTVTVSSGEGT
STGRSGSGSGGSGSADDIYLTQSPATLSLSPGERATLSCRASQ
SVSVMNYQQKPQKKAPRNYDALTSKVASGVPARFSGSGST
DYSLTLNSLEAEDAAATYYCQQQWSSNPLTFGGTKVEIK
도면5계속2

E) 항 -CD3 (VH5/VL3)

GACGTCCAATCTGGAAGCTCAAGGCTGAAGTGAAA-
AACCTGGGCTACGTGAAAGGGTGCTTCTGCTGAG-
CAAGGCCTACTATCCACTTTAGGACTACGAT-GC-
CACTGGTAAGCACGACCTGAAGATGGATGAT-
TGATACATTAATCTCCTGCGGTGTCTAATTGCA-
CAGACAGCCGCTCAAGGCGGCCCTCTCAATCAGCA-
AATCCACCGACAGCCTACATGGAACTGAG-
CAGCCTGCTTCTGTGAGCACGTGCAACCTAAAATGTGCAA-
GATATTATGATGATCATTACTGCTTTGACTACTGGGCC-
CAAGGCACACGCTACCGGCTCCTCCTCACGGCGAGGTAC-
TAGTACTGGTTTCTGTGGAAGTAGGTGGATCAGGTCAGG-
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CTGCTTCCAGGGAGCGTGCCACCCTGACCCCTGACAGC-
CAGTTCAAGTGTAAGTTACATGAACTGCTACCTGACCAGCA-
GAAGCCGGCAAGGCACCCCAAAAGATGGATTTTAGACA-
CATCCAAAGTGGCTTCTGGAGTCCTGCTCTCAGTTGGCC-
AGTGGCTTTGAGCCACAGACTACTCTCTCCACAAATCAA-
CAGCTTGAGCTGAGATCGCTGCCAATTTACTGC-
CAACAGTTGAGTAGTAACCAGCTACGTTGGTGGCGG-
GACCAAGTTGGAGATCAGA

F) 항 -CD3 (VH5/VL3)

DVQLVQSGAEVKPGASVVKVSCKASGYTFTRYTMHWVR-
QAPQQGLEWIGYINPSRGYNY-
ADSVKGRFTITTDKSTAYMELSSLRSEDATYYCA-
RYYDDHYCLDYWQGTTTVSSGEGTSTGGSGGSGGADD-
IVLQQPSATLSSLPSGERATLTCRSSSSVSYNYWQKPG-
KAPKRWYDTSVAVSVPARFSGSSTGTDSLTSLEAE-
DAATYYCQQWSSNPFTGGTVEIK
도면6

A) 항-CD3 (VH7/VL1)
GACGTCCAACCTGCTCAGTGCCGGGTGCTGAGGTGAAAGTGAAAAACC
TGGGGGCTCAGTGCCGGGTGCTGAGGTGAAAGTGAAAAACC
CCTTACTAGTTACAGTGCCGGGTGCTGAGGTGAAAGTGAAAAACC
GGACAGGTTGCTGGAAGGTGACTGAGGTGAAAGTGAAAAACC
CTGACGAGCTGTTCTGAGCGACGTGCTACTGCTATTTCG
TGCAAGATATTATGATGATCATTACTTCCTTGACTACTGG
GCAAGGCAACCAGGTCTCCCGCTCTCCAGCGAGATC
AGTACTGTTCTGTTGGAAGTGGAAGTTACGGGAGACAGA
CGACATTTCCAGTGACCAGTCTCCATCTAGCTGCTGTCTGCA
CTGTCGGCGCGCTGTCACCATCAGCTGACAGCACAGC
AGTGTAGTTACATGACACCTGATTACAGCAGAAGCAGGGCAA
GGCACCCCAAGAGATGGATATATAGACACTCAAAGATGCGT
CTGAGTCCTGCTCCGGCTACGTGAGGTGCTCGGACC
GACTACTCTCTCCACATACAAGCTTGGAGGTGCTGAGATGC
TTCCACATTATTACTGCCAACCAGTGGAATGATACCCGCCTCA
CGTCCGTCGGCGCGCCAAAGGCGGTGAGACAGAC

B) 항-CD3 (VH7/VL1)
DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVR-
QPQGQLEWGYINPSRGYT-
YNQKFKDRVTITDKSTSTAYMELSSLRSEDTAVVYCA-
RYYDDHYCLDVWQGTTVTVSSGEGSTGSGSGSGSSGAD
IQMTQSPSSLASGDRVTITCRASIQQSYMNYQQKPG-
KAPKRWYDTSKVASGVPARFSGSGLDSDLINSLEAE-
DDATYYCQWSSNPLTFGGGTKVEIK
C) 항-CD3 (VH7/VL2)
GACGTCCAACCTGATGCAGTCAAGGCTGAAGTGGAAGAAGGACCCCT
TGGGGCCCTCAGTGAGGTTGGCTCTGCAAGGCTTCTGCTACA
CCTTTACTAGTGACACGATGCATCGGTAGGTGAAGCCAGCCACCT
GACAGGATCCGATGAGGATCTTCTGATACATAATCCTAGACG
TGGTTTATACTTTAATCAACTACAGAAGTTCAAGGACCAGGTCA
CAACACATACAGACAAATCCACACAGCAGCCCTACATGGA
CTGAGCGAGCTGCGTCTGAGAGACACTGCAGTCTATTCTG
TGCAAGATATATTATGATCATTACTGCCTTGACTACTGGG
GCCAAGGCACCACGGTCACCCTCCTCAGGGCAAGGTACT
AGTACTGTTCTGGTGAAGTTGGAGTCCAGTGAGACAGA
CGACACTGTACTGACCCAGCTCCTCCAGCAACTCTCTGCTCTG
CTCCAGGGGAGGCTGACCCCTGAGCTGAGGACACTCAA
AGTGAAGTACATGAACCTGGATACAGCAGAAGCCGGCA
AGCACCCCAAAGATGGATTTATGACCAATCCCAAGTTGCTT
CTGGAGTCCCTGCTCAGTTGAGTGGGCTGCTGGAGCC
GACTACTCTCTCACAATCAACAGCTTGGAGGCTGAGATGC
TCCCAAGTTACTCTGCAACAGTAGTGAGTAGCTCCGCCTCA
CGTCCGGTGCCGGGACAAAGGTGGAGATCAA

D) 항-CD3 (VH7/VL2)
DVQLVQSGAEVKPGASVKSQASGLFHYTFRYTMHWRQAPGQGLEWIGYINPSGYT-
NYQKFKDRVTITDKSTAYMELSSRSEDATYYCA-RYDDHYCLVYWGQTTVTVSGGEGTSTGSGGSGGSGGAADD
IVLTQSPATLSDLPSGERATLSCRAASQSVSYMNWYQQKPG-KAPKRWYIDTSKVASSVGFRFSGSGTDYSLTINSLEAE-DAAAYYCQQWSSNPLTFGGGTKVEIK
도면6계속2

E) 항-CD3 (VH7/VL3)
GACGTCCAACCTGGTGCACTCGAGGGCTGAGTGAA---
AACCTGGGCTCAGTGAAAGGTGTCCTG--
CAAGGGCTCTGGCTACACCTTTACTAGGTACGATG--
CAGCTGGTGAAAGGCACGCCTGGACAGGGCTGGAT---
TGAGTACATTATATCTCTACGGGATGTAACTACTAA---
CAGAAGTCTCAAGGCAGCCCTGACCACTACAGACAC---
AATCCACACGAGCAAGGCTACATAGGAACTGAG---

F) 항-CD3 (VH7/VL3)
DVQLVQSGAEVKPGASVKVSCKASGYTFTRYTMHWVR-
QAPGQGLEWIGYINPSRGY--
NYQKFKDRTVTITDKSTSTAYMELLRS EXTAVYYCA-
RYYDHCLDYWQGVTFTVVSSTGSGGSSSGGSGADD-
IVLQSPATLSPSGERATLTCRASSVSYMNQYQKPG-
KAPKRWIYDTSKVAGVPARFSGSGSGETYDSTLTINSLEAE-
DAATYYCQWSSNPLTFFGGGTKVEIK
도면8
도면10
도면11

A)

B)
본 도면은 CD3에의 결합 실험 1과 실험 2에 대한 MFI 값을 비교한 그래프를 보여줍니다. 실험 1에서는 VL1, VL2, VL3의 비교가 이루어지며, 실험 2에서는 동일한 시나리오가 반영되었습니다. 실험에 사용된 항체는 CD19, CD3, CD3(VH5/VL1), CD3(VH7/VL1-3), EpCAM (M79)를 포함했습니다. 각 항체의 농도는 [1 μg/ml]와 [5 μg/ml]로 설정되었습니다.
도면15B

항CD3(VH5/VL2) x 4-7 (서열 식별 번호: 33)

주로카드, CD3

항EpCAM(M79) x 항CD3  항CD3(VH5/VL2) x 4-7

카토 III, EpCAM
도면15C

항CD3(VH5/VL2) x 3-1 (서열 식별 번호:31)

\[ \text{류르카트, CD3} \]

\[ \text{카토 III, EpCAM} \]
도면15D

항CD3(VH5/ VL2) x 4-7 VL-VH
(서열 식별 번호 : 35)

주로카트 CD3

항CD3(VH5/ VL2) x 4-7 VL-VH

카토 III, EpCAM
도면16B 
등록특허 10-1229731

CD3 결합 (주로카트 세포)  
EpCAM 결합 (카토 세포)

5-10 x 항CD3(VH5/VL2)

5-10 x 항CD3(VH5/VL2)

(서열 식별 번호: 63)
<110> Micromet AG

<120> Multispecific deimmunized CD3 binders

<130> G 2728 PCT

<160> 409

<170> PatentIn version 3.1

<210> 1

<211> 729

<212> DNA

<213> artificial sequence

<220>

<223> wt Anti-CD3 cassette

<400> 1

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tcctgcaaga cttctggcta cacctttact aggtacacga tgcactgggt aaaacagagg    120
cctggacagg gtctgggaatgt gagttgatac ataatccta gcctggtaga tactaattac 180
<210> 2

<211> 243

<212> PRT

<213> artificial sequence

<220>

<223> wt Anti-CD3 cassette

<400> 2

Asp Ile Lys Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
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Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Arg Tyr
Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
Met Gln Leu Ser Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
Thr Thr Leu Thr Val Ser Ser Ser Val Glu Gly Ser Gly Ser Gly Ser Gly
Pro Ala Ile Met Ser Ala Ser Pro Gly Gln Val Thr Met Thr Cys
Arg Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Ser
Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
Gly Val Pro Tyr Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser
Leu Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu
Glu Leu Lys

<210>  3
<211>  18
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<213> artificial sequence
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<223> deimmunized linker
<400>  3
Gly Glu Gly Thr Ser Thr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly
Ala Asp

<210>  4
<211>  729
<212> DNA
<213> artificial sequence
VH2/VL1

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cctgggacagg gctctgaatg gattggatac attaattccta ggcgtctgta tactaattac 180
gcacagaagt tgccagggcg tgcaccaatg actacagaca ctteccacag cacacgctac 240
atggaacetga gcagccctcg ttctgaccag actgcaccct attaactgtge aagatattat 300
gatgactctg actgccttga ctactggtggt gcaggttcag acggtcagca ccacatctccag 360
gaaggtacta gtactgtccgt tggggaaggt ggaggttcag gtggagcaga cgacatccag 420
atgacccagt ctctcatctg cctgtcagtg tctgtggggt acggtcgtae catcaactgc 480
agagccagt ttaactgaag ttaaataggt gttacagca ccagcccccc caagggaccc 540
aaaagatgga tttatgacac atccaaagtg gcttctggag tccctgctcg cttcagtggc 600
agatggttgg ggacccagct cctctcata atcaacagct tggggtcctg ctagttgtgc 660
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gagatcaaa 729

PRT

artificial sequence
<220>

<223> VH2/ VL1

<400> 5

Asp Val Gln Leu Val Gln Ser Gly Ala G1u Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr
20                  25                  30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35                  40                  45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu
50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85                  90                  95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100                 105                 110

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
115                 120                 125

Gly Ser Gly Ser Gly Gly Ala Asp I1e G1n Met Thr Gln Ser
130                 135                 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Val Thr I1e Thr Cys
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<td>230</td>
<td>235</td>
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**<210> 6**

**<211> 729**

**<212> DNA**

**<213> artificial sequence**

**<220>**

**<223> VH2/VL2**

**<400> 6**

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cctggacagg gtctggaatg gattggatac attaatccta gccgtggtta tactaattac 180
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gcacagaagt tgcaaggccc gcgctcaaaatg actacagaca cttccaccag cacagcctac 240
atggaactga gcagcctgcg ttctgaggac actgcaacct attactgtgc aagatattat 300
gatgatcatt actgccttgca ctacttgagcc caaggtacca cagtcacagt ctcctcaggc 360
gaaggtacta gtactgtgct tggtggnagt ggaggttcag gtggagcaca cgacatgtga 420
cgtaccagt ccctagcaac tctgctcttg tctccagggt aagcgtgccac cctgagctgc 480
agagccagtc aaagtgaag ttatagtaag ttcctgaccg tggagtccag gaagccggtg caaggeacce 540
aaaagatggaa ttattgacac atccaaagtg gcttcggagt tctctgctcg ctctcaagtg 600
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gagatcaaa 729

<210>  7
<211>  243
<212> PRT
<213> artificial sequence

<220>
<223> VH2/VL2

<400> 7

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1      5     10      15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
115 120 125

Gly Ser Gly Gly Ser Gly Gly Ala Asp Ile Val Leu Thr Gln Ser
130 135 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145 150 155 160

Arg Ala Ser Gin Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195 200 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val

Glu Ile Lys

<210> 8

<211> 729

<212> DNA

<213> artificial sequence

<220>

<223> VH2/VL3

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cctggacagg gcctgctcta gattggatac attaatccta gccgtggtta tataattac 180
gcagacgaatgc gtcgatgctg cctcaccag cacagctac 240
atggaactga gcagcctgcg ttctgaggac actgcaacct attactgtgc aagatattat 300
gatgatcatt actgctgtga ctaactgggge caagccacca cggtcaccgt ctctccaggc 360
gaatgataatt aactggtcct ggtggaagt gtgaacggtc aacgcctgtctgcttcaggg 420
tgcacaggt ctcagcacaac tcttctcag tctccaggg gaeatggeca cctgacctggc 480
agagccagtt caaggtgaag ttggaacagc agaagccagg cacagcctac 540
aaaagatgga ttatgacac atccaaagtg gcttctggag tccctgctcg cttcagtggc 600
agtgggtctg ggaccgacta ctctctcaca atcaacagct tggaggctga agatgctgcc 660
acttattaact gcacacagtg agatntaac ccgctcaagt tcggtggcgg gaccaaggtg 720
gagatcaaa 729

<210> 9

<211> 243

<212> PRT

<213> artificial sequence

<220>

<223> VH2VL3

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr
20                  25                  30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35                  40                  45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu
50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85  90  95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
115 120 125

Gly Ser Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser
130 135 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys
145 150 155 160

Arg Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195 200 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225 230 235 240

Glu Ile Lys

<210> 10
<211> 729

<212> DNA

<213> artificial sequence

<220>

<223> VH3/VL1

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cctggacagg tgcagggcag gttgctgata agtagttcata aagcagtct attataattac 180
cacacagagt tgtcagggcc gcgtaacatg actacaaca ccctcaccag cacagctac 240
cctgcaaatga acagctggaa aactgagggac aagtccagct ataagttcag aagatattat 300
gatgatcatt actgecttga ctaactggggc caagcaccac cggtcaccgt ctcctcagcc 360
gagagtacta gtaactgggtc tggtagaatg ggaagtctccg gttgacagca gcacatcag 420
tagacctgg cttcatctag cctcttgca cctctggggt accgtgtcag catcaacgtg 480
agacccagtc ccagccagtc cctcttgca cctctggggt accgtgtcag ccaacatcag 540
aaaagggtgt gtaataaacc atcaaggtgc gttctgtcag tctctcagct atcctggtgc 600
aggtgggttg ggaccgacta ccctctcaca atcaacagct tggagggcag agatctgcc 660
acttattact gccaagagtg gattagtaac ccctctcaca atcaacagct tggagggcag gaccaaggtg 720

gagatcaaaa 729
artificial sequence

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Pro Gly Ala

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr

Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys

Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Gln Met Thr Gln Ser
130 135 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Val Thr Ile Thr Cys
145 150 155 160

Arg Ala Ser Gin Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195 200 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225 230 235 240

Glu Ile Lys

<210> 12

<211> 729

<212> DNA

<213> artificial sequence
VIII/VL2

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120
cctggacagg gttctgaatg gatttcgta atcatctctg gctgtttta tactaaat
180
gcacagaagt tgcagggcgg cgtcaacatg actacagaca ctctccacag cacaacctac
240
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300
gatgtcatct agtggcctga ctactggggc caagccacca ccgtagcctt ctctcaggc
360
gaaggtctga gtacctggttc tgtgtaaggt ggagggcaggt gttggcaca cagacatgtga
420
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480
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600
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660
actattact gcacacgtgt gaggtagtaac ecgetcagct tggggtgccg gaccaagtgt
720
gagatcaaa
729

13

243

PRT

artificial sequence
Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr 20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile 35 40 45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu 50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr 65 70 75 80

Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly 100 105 110

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Gly Ser Gly 115 120 125

Gly Ser Gly Gly Gly Gly Ala Asp Ile Val Leu Thr Gln Ser 130 135 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys 145 150 155 160

Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180  185  190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195  200  205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210  215  220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225  230  235  240

Glu Ile Lys

<210> 14

<211> 729

<212> DNA

<213> artificial sequence

<220>

<223> VH3/VL3

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cctggacagg gtctggaatg gattggatac attaatccta gccgtggtta tactaattac    180
gcacagaagt tgcagggccg cgtcacaatg actacagaca ctteaccag cacagctac    240
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aaaagatgga tttatgacac atccaaagtg gcttctggag tccctgctcg cttcagtggc 600
agtgggtetg ggacagacag eetctetcaga atcaacagct tggagggtga agagtctgcc 660
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<210>  15

<211>  243

<212>  PRT

<213>  artificial sequence

<220>

<223>  VH3/VL3

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Asp Val Gln Leu Val Gln Ser Gly Ala Gln Val Lys Lys Pro Gly Ala
1      5       10       15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35        40        45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu
50        55        60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65        70        75        80

Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85        90        95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100       105       110

Thr Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
115       120       125

Gly Ser Gly Gly Ser Gly Gly Ala Asp Ile Val Leu Thr Gln Ser
130       135       140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys
145       150       155       160

Arg Ala Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165       170       175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180       185       190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195       200       205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys

- 120 -
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val

Glu Ile Lys

<210> 16

<211> 729

<212> DNA

<213> artificial sequence

<220>

<223> VH5/VL1

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cctggcagcg gtcggggata gattggtgata ataaatccta gcaatggta tactaattac  180
gcagacacgg tcaaggcccc etctcaacte actacacaca aatccaccag cacagctac  240
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<213>  artificial sequence

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Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser

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Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
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Pro Ala Thr Leu Ser Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys
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Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser

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Lys Asp Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
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Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Ser Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr

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Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly

Gly Ser Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys

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Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser

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Glu Ile Lys

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DNA

artificial sequence

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artificial sequence

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Pro Gly Ala
1               5                   10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20                  25                  30
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
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Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser

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Sequencing primer

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DNA artificial sequence

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- 138 -
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<210>  31

<211>  491

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD3 VH5/VL2 x 3-1 VHVL

<400>  31

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala 1  5  10  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr 20  25  30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Glu Trp Ile 35  40  45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val 50  55  60

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr 65  70  75  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85                  90                  95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100                 105                 110

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser
130                 135                 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Arg Ala Ser Gin Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165                 170                 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180                 185                 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195                 200                 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210                 215                 220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225                 230                 235                 240

Glu Ile Lys Ser Gly Gly Gly Ser Gly Val Gln Leu Leu Glu Gln
245                 250                 255

Ser Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys
260                 265                 270

Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr Trp Leu Gly Trp Val Lys
Gln Arg Pro Gly His Gly Leu Glu Trp Ile Gly Asp Leu Phe Pro Gly
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Ser Gly Asn Thr His Tyr Asn Glu Arg Phe Arg Gly Lys Ala Thr Leu
305 310 315 320
Thr Ala Asp Lys Ser Ser Thr Ala Phe Met Glu Leu Ser Ser Leu
325 330 335
Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Leu Arg Asn Trp
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355 360 365
Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
370 375 380
Glu Leu Val Met Thr Gln Ser Pro Ser Tyr Leu Ala Ala Ser Pro Gly
385 390 395 400
Glu Thr Ile Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Tyr
405 410 415
Leu Ala Trp Tyr Gln Glu Gly Pro Gly Lys Thr Asn Lys Leu Leu Ile
420 425 430
Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ser Arg Phe Ser Gly
435 440 445
Ser Gly Ser Gly Thr Asp Thr Leu Thr Ile Ser Ser Leu Glu Pro
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Glu Asp Phe Ala Met Tyr Tyr Cys Gin Gin His Asn Glu Tyr Pro Tyr

- 142 -
Thr  Phe  Gly  Gly  Gly  Thr  Lys  Leu  Glu  Ile  Lys

<210>  32

<211>  1500

<212>  DNA

<213>  artificial sequence

<220>

<223>  anti-CD3 VH5/VL2 x 4-7 VHVL

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720
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"<211> 500
"<212> PRT
"<213> artificial sequence
anti-CD3 VH5/VL2 x 4-7 VHVL

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1      5     10      15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20     25     30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35     40     45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
50     55     60

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
65     70     75     80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85     90     95

Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100   105    110

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
115   120    125

Gly Ser Gly Ser Gly Gly Ala Asp Ile Val Leu Thr Gln Ser
130   135    140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145   150    155    160
Arg Ala Ser Gin Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro

165                 170                 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser

180                 185                 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser

195                 200                 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Cys

210                 215                 220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val

225                 230                 235                 240

Glu Ile Lys Ser Gly Gly Gly Ser Gly Ser Glu Val Gln Leu Leu Glu Gin

245                 250                 255

Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys

260                 265                 270

Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys

275                 280                 285

Gln Arg Pro Gly Gln Val Leu Glu Trp Ile Gly Gln Val Tyr Pro Arg

290                 295                 300

Ile Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu

305                 310                 315                 320

Thr Ala Asp Lys Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu

325                 330                 335

Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr

340                 345                 350

Asp Thr Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr

- 146 -
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405 410 415
Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys
420 425 430
Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe
435 440 445
Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
450 455 460
Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe
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Cys Ser Gln Ser Thr His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys
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Leu Glu Ile Lys
500

<210>  34

<211>  1500

<212>  DNA

<213>  artificial sequence
<220>

<223> anti-CD3 VH5/VL2 x 4-7 VLVH

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cgtgacagtc tcaaggggctc ctccacattc actacagaca aatccaccag cacagctac     180
atggaactga gcaagctctgct ttactgagga cagttcaacct attactgtgc aagatattt     240
gatgatcatct actctctgga caagggcactc eggtaacgct ccctctacagcc cggtaagc     300
胃gagctact a tgtgtgggtc gaggcttgcag gggaggtgca cagctggttc agacatgtga     360
cggacagcgc tcgacgcgac tctctgtctg tcctcagggg agctgtgccac cctgacggtg     420
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- 148 -
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<210> 35
<211> 500
<212> PRT
<213> artificial sequence

<220>
<223> anti-CD3 VH5/VL2 x 4-7 VLH

<400> 35

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1       5       10       15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20      25       30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val

Lys Gly Arg Phe Thr Ile Thr Asp Lys Ser Thr Ser Thr Ala Tyr

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly

Thr Thr Val Thr Val Ser Gly Glu Gly Thr Ser Gly Ser Gly

Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys

Arg Ala Ser Gin Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
Glu Ile Lys Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr

Pro Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys

Arg Ser Ser Gin Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His

Trp Tyr Leu Gin Lys Pro Gin Gin Ser Pro Lys Leu Leu Ile Tyr Lys

Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly

Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp

Leu Gly Val Tyr Phe Cys Ser Gin Ser Thr His Val Pro Tyr Thr Phe

Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly

Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser

Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys

Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys Gin

Arg Pro Gly Gin Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile
Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
435 440 445

Ala Asp Lys Ser Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu Thr
450 455 460

Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr Asp
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Thr Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr Val
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Thr Val Ser Ser
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<210> 36

<211> 1491

<212> DNA

<213> artificial sequence

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<223> anti-CD3 VH5/VL2 x 5-10 VHVL

<400> 36

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<210> 37

<211> 497

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD3 VH5/VL2 x 5-10 VHVL

<400> 37

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1      5      10        15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20     25     30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35     40     45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
50     55     60

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
65     70     75        80

Met Glu Leu Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85     90     95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly

- 154 -
Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly 115 120 125
Gly Ser Gly Gly Ser Gly Gly Ala Asp Ile Val Leu Thr Gln Ser 130 135 140
Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys 145 150 155 160
Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro 165 170 175
Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser 180 185 190
Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser 195 200 205
Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys 210 215 220
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val 225 230 235 240
Glu Ile Lys Ser Gly Gly Gly Gly Ser Gly Val Gln Leu Leu Glu Gln 245 250 255
Ser Gly Ala Glu Leu Val Arg Pro Gly Thr Ser Val Lys Ile Ser Cys 260 265 270
Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr Trp Leu Gly Trp Val Lys 275 280 285
Gln Arg Pro Gly His Gly Leu Glu Trp Ile Gly Asp Ile Phe Pro Gly
Ser Gly Asn Ile His Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu
Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
Thr Phe Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Leu Arg Asn Trp
Asp Glu Pro Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
Glu Leu Val Met Thr Gln Ser Pro Ser Ser Leu Thr Val Thr Ala Gly
Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
Ile Ser Ser Val Gln Ala Glu Leu Ala Val Tyr Tyr Cys Gln Asn
Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile
Lys

<210>  38

<211>  1491

<212>  DNA

<213>  artificial sequence

<220>

<223>  anti-CD3 VH5/VL2 x 5-10 VLVI

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<210> 39
<211> 497
<212> PRT
<213> artificial sequence
anti-CD3 VH5/VL2 x 5-10 VLVH

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala

1  5  10  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr

20  25  30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Glu Trp Ile

35  40  45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val

50  55  60

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr

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Leu Phe Pro Gly Ser Gly Asn Thr His Tyr Asn Glu Arg Phe Arg Gly
180 185 190

Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Phe Met Gin
195 200 205

Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg
215 220

Leu Arg Asn Trp Asp Glu Ala Met Asp Tyr Trp Gly Gin Gly Thr Thr
225 230 235 240

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp Val Gln Leu Val Gin
245 250 255

Ser Gly Ala Glu Val Lys Pro Gly Ala Ser Val Lys Val Ser Cys
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Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg
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Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
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Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile
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Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu
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340 345 350
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His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
370     375     380
Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Gly Ser Gly Gly Ala Asp
385     390     395     400
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
405     410     415
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Met
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Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
435     440     445
Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
450     455     460
Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
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<212> DNA

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DNA artificial sequence

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3-5(VL-VH)xanti-CD3 (VH(5)-VL(2))
atgggatgga gctgtatcat cctcttcttg gtagcaacag ctacaggtgt acactccgcg
cgcgagctcg tgatgaccca gactccactc tccctgcctg tcagtcttgg agatcaagcc

DNA artificial sequence
etcattcatt gcagacctt tcagagctt gttccagaaaactggaacactcttaatcattcat 180

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<220>

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Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln
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Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln
50   55   60

Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg
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Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr

Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln Ala Pro Gly Gln

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr

Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp

Tyr Trp Gly Gin Gly Thr Val Thr Val Ser Ser Gly Gly Gly Thr

Ser Thr Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile

Val Leu Thr Gin Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg

Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp

Tyr Gin Gin Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr
Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser
Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala
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<210> 56
<211> 40
<212> DNA
<213> artificial sequence
<220>
<223> 4-1(VL-VH)xanti-CD3(VH(5)-VL(2))

<400> 57
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agttcagatg cagtcagag tctgttaaac agtggaatga aaaagaacta ctgtacctg 180
taccagcag aaccaggcca gctctctaaa ctgtgtctag caggagagaa ggtcactatg 240
tcgggattc etgatcgct tccagggcgat ggtetgagaa cagattteac ttcacctatc 300
agcagttgc aggctgaaga tctgactggt ttttacctcgt tagttatccg 360
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<211> 515

<212> PRT

<213> artificial sequence

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Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu  
35                  40                  45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys  
50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu  
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe  
85                  90                  95

Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr  
100                 105                 110

Cys Gln Asn Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys  
115                 120                 125

Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly  
130                 135                 140

Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val  
145                 150                 155                 160

Arg Pro Gly Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala  
165                 170                 175

Phe Thr Asn Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly  
180                 185                 190

Leu Glu Trp Val Gly Asp Ile Phe Pro Gly Ser Gly Asn Ala His Tyr  
195                 200                 205

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser  
210                 215                 220
Tyr Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
  225  230  235  240

Val Tyr Phe Cys Ala Arg Leu Arg Asn Trp Asp Glu Ala Met Asp Tyr
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Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser
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Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
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Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Glu Trp Ile
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Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
  325  330  335

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
  355  360  365

Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
  370  375  380

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
  385  390  395  400

Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Glu Ser
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- 180 -
Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
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Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
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Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
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Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
465 470 475 480

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
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Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln
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Lys Pro Gly Gin Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg
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Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
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225                 230                 235                 240

Val Tyr Phe Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr
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Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser
260                 265                 270

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
275                 280                 285

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
290                 295                 300

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
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Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
325                 330                 335

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
355                 360                 365

Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
370                 375                 380

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
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Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser
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등록특허 10-1229731
Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
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Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
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Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
450  455  460

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
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Leu Thr Ile Asn Ser Leu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
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Glu Ile Lys
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<212> PRT

<213> artificial sequence

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<223> VH5/VL2x3-5

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
   20     25      30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
  35     40      45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
  50     55      60

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
115 120 125

Gly Ser Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser
130 135 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145 150 155 160

Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195 200 205

Leu Thr Ile Asn Ser Leu Ala Glu Ala Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ser Gly Gly Gly Ser Gln Val Gln Leu Leu Gly Glu
245 250 255

Ser Gly Ala Glu Leu Val Arg Pro Gly Thr Ser Val Lys Leu Ser Cys
Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Gly Leu Ser Trp Val Lys
275 280 285

Gln Arg Thr Gly Gin Gly Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg
290 295 300

Ile Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu
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Thr Ala Asp Lys Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu
325 330 335

Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr
340 345 350

Gly Ser Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr
355 360 365

Val Thr Val Ser Ser Gly Gly Gly Gly Gly Gly Gly Gly Ser Gly
370 375 380

Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr Pro Leu Ser Leu Pro
385 390 395 400

Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
405 410 415

Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys
420 425 430

Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe
435 440 445

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe
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Cys Ser Gln Ser Thr His Val Pro Tyr Phe Gly Gly Gly Thr Lys
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Leu Glu Ile Lys
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<210> 66
going to a line break

<211> 1491
going to a line break

<212> DNA

<213> artificial sequence

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<223> VH5/VL2x4-1

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gcagacagcg tcaagggccg cttcacaatc actacagaca aatccaccag cacagctac    240
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artificial sequence

VH5/VL2x4-1

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
115 120 125
Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser
130     135     140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145     150     155     160

Arg Ala Ser Gin Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165     170     175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180     185     190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195     200     205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210     215     220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225     230     235     240

Glu Ile Lys Ser Gly Gly Gly Ser Gly Val Gln Leu Leu Glu Gln
245     250     255

Ser Gly Ala Glu Leu Val Arg Pro Gly Thr Ser Val Lys Ile Ser Cys
260     265     270

Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr Trp Leu Gly Trp Val Lys
275     280     285

Gln Arg Pro Gly His Gly Leu Glu Trp Val Gly Asp Ile Phe Pro Gly
290     295     300

Ser Gly Asn Ala His Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu
305     310     315     320

Thr Ala Asp Lys Ser Ser Tyr Thr Thr Met Gin Leu Ser Ser Leu

Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Leu Arg Asn Trp
  340 345 350

Asp Glu Ala Met Asp Tyr Trp Gly Gln Gly Thr Val Thr Val Ser
  355 360 365

  370 375 380

Glu Leu Val Met Thr Gln Ser Pro Ser Ser Leu Ser Val Ser Ala Gly
  385 390 395 400

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
  405 410 415

Gly Asn Gln Lys Asn Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln
  420 425 430

Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu Ser Gly Val
  435 440 445

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
  450 455 460

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn
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Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
  485 490 495

Lys

<210> 68
artificial sequence

non-deimmunized linker sequence

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Val Asp

dNA

artificial sequence

anti-CD3 VH2

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<211> 119
<212> PRT
<213> artificial sequence

<220>
<223> anti-CD3 VH2

<400> 70

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr
20        25       30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35        40       45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu
50       55       60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65       70       75     80
Met Glu Leu Ser Ser Leu Arg Ser Glu Thr Ala Thr Tyr Tyr Cys
85                  90                  95

Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100                 105                 110

Thr Thr Val Thr Val Ser Ser
115

\text{\textless 210\textgreater} 71

\text{\textless 211\textgreater} 357

\text{\textless 212\textgreater} DNA

\text{\textless 213\textgreater} artificial sequence

\text{\textless 220\textgreater}

\text{\textless 223\textgreater} anti-CD3 VH3

\text{\textless 400\textgreater} 71

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cctggacagg tgcttggaatg gattggatac attaatccta gccgtggtta tactaattac    180
gcacagaagt tgccagggcg cgtcacaatg actacagaca ctteccacag cacagctac    240
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<213> artificial sequence

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<223> anti-CD3 VH3

<400> 72

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser
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<211> 357

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<223> anti-CD3 VH5

<400> 73
gacgtcaac tggtagcgc aagggctaaga gtaaaaaaact cgggctcct actggagttg 60
tcctgcaagg cttctggcta cacctttact aggtacagca tgcactgggt aaggcaggca 120
cctggacagg gcttggaagt gattggatac attaaatccta gcctgggta tactaattac 180
gcagacacgg tcaaggcgc ggctcaaatc actacagaca aatccacag cacagctac 240
atggcaactga gcagcctgcg ttctgaggac actgcaacct attactgtgc aagatattat 300
gatgatcatt actgcccttgaga tactgggac caagggcaaca gcgtcacgct ctcctca 357

<210> 74

<211> 119

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD3 VH5
Asp Val Gln Leu Val Gln Ser Gly Ala Val Lys Lys Pro Gly Ala
1               5                   10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20                  25                  30
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35                  40                  45
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
50                  55                  60
Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85                  90                 95
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100                 105                 110
Thr Thr Val Thr Val Ser Ser
115

<210>  75

<211>  357

<212> DNA

<213> artificial sequence
<223> anti-CD3 VH7

<400> 75

gacctcaac tgggtcagtc aggggctgaa gtgaaaaac ctgggccctc agtgaaggtg     60
tctgcaagg cttctgcttc caggtaacga tgcactgggt aagggcagcc

120
cctgacggc gtctggaatg gattggatac ataaacctga gctacctgta taactatcac

180
aatcagaagt tcaaggacgc gccacaaac aactagaca catacactct aatcagctccacac

240
atggaactga gcagcctgcg ttctgaggac actgcagtct attactgtgc aagatattata

300
gatgatcatt actgctttga cnttgccggc cagggccacca cggtacccgt ctcctca

357

<210> 76

<211> 119

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD3 VH7

<400> 76

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1     5     10     15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20    25    30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35    40    45
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50                  55                  60
Lys Asp Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85                  90                  95
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100                 105                 110
Thr Thr Val Thr Val Ser Ser
115

<210>  77

<211>  318

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD3 VL1

<400>  77
gacattcaga tgaccagtct ccactctgctg tgcgtctcat ctgtgcggga ccgtgtcacc  60
atcacctgcag gagccagctc aagtgtaagt tacatgaact ggtaccagca gaagccgggc 120
aaggcaccca aaagatggat ttatgacaca tccaaagtgg cttctggagt ccctgctcgc 180
ttcagttggca gttgggtgg gaccgactac tctctcacaa tcaacagctt ggaggctgaa 240
gatgtgcca cttattaac gccagagtgg agtgaacc cgtcagtt cggcgccg

accaaggtgg agatcaaa

<210> 78
<211> 106
<212> PRT
<213> artificial sequence

<220>
<223> anti-CD3 VL1

<400> 78

Asp Ile Gln Met Thr Gln Ser Pro Ser Leu Ser Ala Ser Val Gly
1    5       10       15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Tyr Met
20   25     30

Asp Trp Tyr Gin Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
35   40     45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50   55     60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
65   70     75     80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
85   90     95
Phe Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 79

<211> 318

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD3 VL2

<400> 79
gacattgtaa tgacccagtc tccagcaact ctgtctctgt ctccagggga gcgtgccacc 60
ctgagctgca gagccagtca aagtgtaagt tacatgaact ggtaccagca gaagccgggc 120
aagcaccca aaagatggat ttatgacaca tccaaagtgg cttctggagt ccctgctcgc 180
ttcagtggca gtgggtctgg gaccgactac tctctcacaa tcaacagctt ggaggctgaa 240
gatgctgcca cttattactg ccaacagtgg agtagtaacc cgctcacgtt cggtggcggg 300
accaaggtgg agatcaa

318

<210> 80

<211> 106

<212> PRT

<213> artificial sequence
anti-CD3 VL2

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Met
20                  25                  30

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
35                  40                  45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50                  55                  60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Gln Gln Tyr Ser Ser Asn Pro Leu Thr
85                  90                  95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100                 105

<210> 81

<211> 318

<212> DNA

<213> artificial sequence
<223> anti-CD3 VL3

<400> 81
gacattgtac tgcaccgaact ctgctctctg ctccagggga gcgtgccacc 60
etgacctgca gacccagttc aagtgaagt ttagtttaa ggtaccagca gaagccgggc 120
aagggcaccc aagagatggat ttatgaca aactgtaagta ggtaccagca gaagccgggc 180
ttcggtgca cggagctgga gacccagcag tctctgtaagc cctctgctcgc 240
gatgctgcca cttattactg ccaacagtgg aggatca            300
accacagttg agataca                        318

<210> 82

<211> 106

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD3 VL3

<400> 82

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5  10  15

Glu Arg Ala Thr Leu Thr Cys Arg Ala Ser Ser Val Ser Tyr Met
20  25  30

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
35  40  45
Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

<210> 83

<211> 30

<212> DNA

<213> artificial sequence

<220>

<223> vH CDR1 anti-CD3 wt

<400> 83
ggtacacct ttactaggta cagatgcac

<210> 84

<211> 10

<212> PRT

<213> artificial sequence
vH CDR1 anti-CD3 wt

Gly Tyr Thr Phe Thr Arg Tyr Thr Met His
1  5  10

vH CDR1 VH2,3

ggetacaccg ctactaggta cacagtgac
30

DNA

artificial sequence

vH CDR1 VH2,3

PRT

artificial sequence
Gly Tyr Thr Ala Thr Arg Tyr Thr Met His
1               5                   10

DNA
artificial sequence

vH CDR1 VH5,7

Gly Tyr Thr Phe Thr Arg Tyr Thr Met His
1               5                   10
DNA

artificial sequence

vH CDR2 wt anti-CD3 VH7

tacattaat ccagggcagttataatc tacaagagaga c

PRT

artificial sequence

vH CDR2 wt anti-CD3 VH7

Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys
1 5 10 15

Asp
DNA artificial sequence

vH CDR2 VH5

tacattaatc ctagccgtgg ttatactaat tacgcagaca gcgtcaaggg c

Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys

Gly

- 217 -
DNA artificial sequence

vH CDR2 VH2,3

tacattaatc ctagccgtgg ttatactaat tacgcacaga agttgcaggg c 51

PRT artificial sequence

vH CDR2 VH2,3

Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu Gln 1 5 10 15

Gly

DNA
artificial sequence

tattatgatg atcattactg ccttgactac

DNA
vK CDR1 wt anti-CD3 VL3

agagccagtc aaagtgtaag ttacatgaac

Arg Ala Ser Ser Ser Val Ser Tyr Met Asn
1 5 10

DNA

vK CDR1 VL 1,2

agagccagt c aaagtgaag ttacatgaac
<210> 100

<211> 10

<212> PRT

<213> artificial sequence

<220>

<223> vK CDR1 VL 1-2

<400> 100

Arg Ala Ser Gln Ser Val Ser Tyr Met Asn
1     5     10

<210> 101

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> vK CDR2 wt anti-CD3 VL1-3

<400> 101

gacacatcca aagtggcttc t
                      21

<210> 102

<211> 7
<212> PRT

<213> artificial sequence

<220>

<223> vK CDR2 wt anti-CD3 VL1-3

<400> 102

Asp Thr Ser Lys Val Ala Ser
1               5

<210> 103

<211> 27

<212> DNA

<213> artificial sequence

<220>

<223> vK CDR3 wt anti-CD3 VL1-3

<400> 103
caacagtga gtagtaaccg gctacgcg 27

<210> 104

<211> 9

<212> PRT

<213> artificial sequence
vK CDR3 wt anti-CD3 VL1-3

Gln Gln Trp Ser Ser Asn Pro Leu Thr

1 5

vH anti-CD3 with the mutations of cys->ser

DNA

artificial sequence

gatatcaaac tgcagcagtc aggggctgaa ctggcaagac ctggggcctc agtgaagatg

tcctgcaaga cttctggcta cacctttact aggtacacga tgcactgggt aaaacagagg
cctggacagg gtctggaatg gattggatac attaatccta gccgtggtta tactaattac
aatcagaagt tcaaggacaa ggcacatgg actacagaca aatctecag cacagectac
atgcaactga gcagcctgac atctgaggac tctgcagtct attactgtgc aagatattat
gatgatcatt actcccttga ctacctggge caaggeacca etetcacagt etcetca

104
105
357
DNA

artificial sequence
artificial sequence

VH anti-CD3 with the mutations of cys -> ser

Asp Ile Lys Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30

Thr Met His Trp Val Lys Gln Gly Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115
DNA artificial sequence

vH CDR3 anti-CD3 with the mutation cys-> ser

tattatgatg atcattactc ccttgactac

PRT artificial sequence

vH CDR3 anti-CD3 with the mutation cys-> ser

Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr
1 5 10
<213> artificial sequence

<220>

<223> wild type anti-CD3 VH

<400> 109
gatatcaac tgccacgtc aggggtgaa ctggcaagac ctgggcccct agtgaagatg 60

tcttgcaaga cttctgctca cacctttact aggtacacga tgcactggtt aaaaacaggg 120
cctggacagg gttggttagt gattggatac attaatccta gccgtggtta tactaattac 180
aatttgaagt tcaaggacaa ggccacattg actacagaca aatctccag cacagctgca 240
atggcaacttg gcagctgctg acctgaggac tctgcagtct attactgtgc aagatattat 300
gatgatcatt actgcccctg ctaactgggca cagggcacca ctctgacagt cttcctca 357

<210> 110

<211> 119

<212> PRT

<213> artificial sequence

<220>

<223> wild type anti-CD3 VH

<400> 110

Asp Ile Lys Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1      5      10      15

- 226 -
Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Arg Tyr
20                  25                  30

Thr Met His Trp Val Lys Gln Arg Pro Gly Gly Leu Glu Trp Ile
35                  40                  45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50                  55                  60

Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85                  90                  95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100                 105                 110

Thr Thr Leu Thr Val Ser Ser
115

<210>  111

<211>  318

<212> DNA

<213> artificial sequence

<220>

<223> wild type anti-CD3 VK

<400> 111
gacattcagc tgacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc     60
atgacctgca gagccagttc aagtgtaagt tacatgaact ggtaccagca gaagtcaggc 120
acctccccca aaagatggat ttatgacaca tccaaagtgg cttctggagt cccttatcgc 180
ttcagtggca gtgggtctgg gacctcatac tctctecaa tacagcagcat ggaggtgaa 240
gatgetgcca cttattaagt ccaacagtgg agtagtaacc gctcaagt gggtgctggg 300
accaagctgg agctgaaa 318

<210> 112
<211> 106
<212> PRT
<213> artificial sequence

<220>
<223> wild type anti-CD3 VK

<400> 112

Asp Ile Gln Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly 1 5 10 15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met 20 25 30

Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr 35 40 45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Tyr Arg Phe Ser Gly Ser 50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys

<210> 113

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> CD19 VH

<400> 113
caggtgcagc tgcagcagtc tggggctgag ctggtgaggc ctgggtcctc agtgaagatt
tcctgcaagg cttctggcta tgcattcagt agctactgga tgaactgggt gaagcagagg
cctggacagg gtcttgagtg gattggacag atttggcctg gagatggtga tactaactac
aatggaaagt tcaaggttaa agccaccttg actgcagacg aatcctccag cacagcctac
atgcaactca gcagcctagc atctgaggac tctgcggtct atttctgtgc aagacgggag
actacgacgg taggccgtta ttactatgct atggactact ggggccaagg gaccacggtc
accgtctcct cc

<210> 114
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
1       5       10       15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
20      25      30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45

Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
50      55      60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr
65      70      75      80

Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys
85      90      95

Ala Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp
100     105     110

Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115     120

<211>  124

<212>  PRT

<213>  artificial sequence
DNA artificial sequence

CD19 VL

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atctcctgca aggccagcca aagtgttgat tatgatggtg atagttattt gaactggtac
ciaacagattc caggacagcc acccaaactc ctcatctatg atgcatccaa tctagtttct
gggatcccac ccaggtttag tggcagtggtg tctgggacag acttcaccct caacatccat
ccctggagga aggtggttag tgcacccat acctgtcage aagaagtctga ggatccgtgg
acgttcggtg gagggaccaa gctcgagatc aaa
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Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20                  25                  30

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35                  40                  45

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80

Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85                  90                  95

Glu Asp Pro Trp Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys
100                 105                 110

<210> 117

<211> 47

<212> DNA

<213> artificial sequence
ctgaaatccg gaggtggtgg atccgagctc gtgatgaccc agactcc

118

<210> 118

<211> 52

<212> DNA

<213> artificial sequence

<220>

<223> 4-7 VL GS15 REV

<400> 118

ggagccgccg ccgccagaac caccaccace tttgatctca agcttggtcc cc

52

<210> 119

<211> 10

<212> PRT

<213> artificial sequence

<220>

<223> CDRH3 M1 mutant

<400> 119

His Tyr Asp Asp His Tyr Cys Leu Asp Tyr

1 5 10

<210> 120
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<th>Start</th>
<th>End</th>
<th>Sequence</th>
<th>Description</th>
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<td>5</td>
<td>Tyr Ser Asp Asp His Tyr Cys Leu Asp Tyr</td>
<td>CDRH3 M4 mutant</td>
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<tr>
<td>1</td>
<td>5</td>
<td>Tyr Tyr Asp Ala His Tyr Cys Leu Asp Tyr</td>
<td>CDRH3 M7 mutant</td>
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artificial sequence

CDRH3 M9 mutant

122

Tyr Tyr Asp Asp Gln Tyr Cys Leu Asp Tyr
1 5 10

CDRH3 M10 mutant

123

Tyr Tyr Asp Asp Pro Tyr Cys Leu Asp Tyr
1 5 10

artificial sequence
CDRH3 M11 mutant

Tyr Phe Asn Asp His Tyr Cys Leu Asp Tyr
1               5                   10

CDRH3 M13 mutant

Tyr Tyr Asn Asp Gln Tyr Cys Leu Asp Tyr
1               5                   10

CDRH3 M20 mutant

Tyr His Asp Asp Pro Tyr Cys Leu Asp Tyr
CDRH3 M76 mutant

Tyr Tyr Asp Asp Asn Tyr Cys Leu Asp Tyr
1  5  10

CCR5 Heavy chain

cagctggagc agtctggacc tgaactgaag aagcctggag agacagtcac gatctcctgc 60
aaggtttaa aagttatggg ctgtgataac acctccactg gagagcccaac atattctgat 180
gacttcaagg gacggtttgc cttcttttg gaaacgtctg ccagcactgc ctatttgcgg
atcaacaacc tcaaaaatga ggacatggct aaatacttct gtgccagagg tggtccttac
gtaaaggtg ctttgacta ctgggtcaaa ggaacctcag tcacgctc eetc

<210> 129
<211> 118
<212> PRT
<213> artificial sequence

<220>
<223> CCR5 Heavy chain

<400> 129

Gln Leu Glu Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val
1               5                   10                  15
Thr Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Lys Phe Gly Met
20                  25                  30

Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly Trp
35                  40                  45

Ile His Thr Ser Thr Gly Glu Pro Thr Tyr Ser Asp Asp Phe Lys Gly
50                  55                  60

Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Arg
65                  70                  75                  80

Ile Asn Asn Leu Lys Asn Glu Asp Met Ala Lys Tyr Phe Cys Ala Arg
Gly Gly Pro Tyr Val Arg Gly Ala Leu Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Ser Val Thr Val Ser Ser
115

<210> 130

<211> 333

<212> DNA

<213> artificial sequence

<220>

<223> CCR5 Light chain

<400> 130
gacattatcc tgatccaatc tccacctct tgtgccgtgt ctctagggca gagggccacc
60
atctcctgca gaaccagcga aaatgttgac ggatacggca ttagttttat aaactggtac
120
caacagaagc caggacagcc acccaaactc ctcatctatg ctgcatccca ccaaggatcc
180
ggggactgtg ccagattttg tgtccgtttt tgcagcagc acttcgaag ttcgcgccat
240
ceccggactt ggaggtggact tttgggacag acttcagcct caacatgcct
300
cctttggagg aggatgatac tgcaatgtat ttctgtcacc aaagtaagaa ggttccgtgg
333
acgttggtg gagggccacc gttgaaatc aaaa

<210> 131

<211> 111
artificial sequence

CCR5 Light chain

Asp Ile Ile Leu Ile Gln Ser Pro Pro Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15

Gln Arg Ala Thr Ile Ser Cys Arg Thr Ser Glu Asn Val Asp Gly Tyr
20                  25                  30

Gly Ile Ser Phe Ile Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35                  40                  45

Lys Leu Leu Ile Tyr Ala Ala Ser His Gln Gly Ser Gly Val Pro Ala
50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His
65                  70                  75                  80

Pro Leu Glu Glu Asp Thr Ala Met Tyr Phe Cys His Gln Ser Lys
85                  90                  95

Lys Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100                 105                 110

DNA
artificial sequence

EpCAM5-10 heavy chain

```
gaggtgcagc tgctcgagca gtctggagct gagctggtaa ggcctgggac ttcagtgaag
atatcctgca aggcttctgg atacgccttc actaactact ggctaggttg ggtaaagcag
aggcctggac atggacttga gtggattgga gatattttcc ctggaagtgg taatatccac
tacaatgaga agttcaaggg caaagccaca ctgactgcag acaaatcttc gagcacagcc
tatatgcagc tcagtagcct gacatttgag gactctgctg tctatttctg tgcaagactg
aggaactggg acgagcctat ggctacttcag ctgactcagc gcctcgcctgc gctcctca
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PRT

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Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1           5           10           15
Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
35  40  45

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
50  55  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Ala
65  70  75  80

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
85  90  95

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gin
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 134

<211> 339

<212> DNA

<213> artificial sequence

<220>

<223> EpCAM5-10 light chain

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5' - gagctcgtga tgacacagtc tccatcctcc ctgactgtga cagcaggaga gaaggtcact - 60

5' - atgagctgca agtccagtca gagtctgtta aacagtggaa atcaaaagaa ctacttgacc - 120

- 242 -
tggtaccagc agaaaccagg gcagcctcct aaactgttga tctactgggc atccactagg 180
gaatctgggg tccctgatcg cttcacaggc agtggatctg gaacagattt cactctcacc 240
atcagcagtg tgcaggtga agacctggca gtttattact gtcagaatga ttatagttat 300
cgctcaacgt tctgtgcttg gaccnaagtt gagateaaa 339

135 135 135 135

<210> 135

<211> 113

<212> PRT

<213> artificial sequence

<220>

<223> EpCAM 5-10 light chain

<400> 135

Glu Leu Val Met Thr Gln Ser Pro Ser Ser Leu Thr Val Thr Ala Gly 1 5 10 15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser 20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gin 35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val 50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr 65 70 75 80
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136

DNA

artificial sequence

EpCAM 3-1 VII

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- 244 -
PRT

artificial sequence

EpCAM 3-1 VH

EpCAM 3-1 VH

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Phe Arg Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Ala
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
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Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
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Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
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EpCAM 4-1 VH

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Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr

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Ile Gly Glu Val Tyr Pro Arg Ile Gly Asn Ala Tyr Tyr Asn Glu Lys 50 55 60
Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala 65 70 75 80
Ser Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe
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Cys Ala Arg Arg Gly Ser Tyr Asp Thr Asn Tyr Asp Trp Tyr Phe Asp
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Val Trp Gly Gin Gly Thr Val Thr Val Ser Ser
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<213> artificial sequence

<220>

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tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc    240
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<212> PRT

<213> artificial sequence

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<223> VH7 Framework 1

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Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1    5    10    15

Ser Val Lys Val Ser Cys Lys Ala Ser
20   25
VH2 Framework 1

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser
20 25

VH3 Framework 1

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser
20                  25

<210> 156
<211> 15
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<213> artificial sequence

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Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
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<210> 157
<211> 15
<212> PRT
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<220>
<223> VH7 Framework 2

<400> 157

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
artificial sequence

VH2 Framework 2

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile
Asn Pro Ser Arg Gly Tyr

VH3 Framework 2

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile
Asn Pro Ser Arg Gly Tyr

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<212> PRT

<213> artificial sequence

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<223> VH5 Framework 3

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Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
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<210> 161

<211> 32

<212> PRT

<213> artificial sequence

<220>

<223> VH7 Framework 3
Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu
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Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
  20      25      30

PRT

artificial sequence

VH2 Framework 3

Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Met Glu
  1       5       10       15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
  20      25      30

PRT

artificial sequence
<220>

<223> VH3 Framework 3

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Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Leu Gln
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<210> 164

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<212> PRT

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<223> VH7 Framework 4

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<223> VH2 Framework 4

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1 5 10 15
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tcttgcaagg cttctgctta cacatttacc agttacaata tgcactgggt aaagcagaca
ectggacagg gcctggaatg gattggagct atttatccag gaaatggtga taaccttac
aatcagaagt tcaaagccaa ggccacattg actgcagaca aatcctccag cacaacctac
atgcagctca gcagtctgac atctgaggac tctgcggtct attactgtgc aagatcgcac
tacgtagta actagtaga ctactttgac tactggggcc aaggcacact agtcacagtc
tcgaca

Gln Val Gln Leu Arg Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1       5       10      15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20      25      30
Asn Met His Trp Val Lys Gln Thr Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85                  90                  95

Ala Arg Ser His Tyr Gly Ser Asn Tyr Val Asp Tyr Phe Asp Tyr Trp
100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Thr
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<210>  171

<211>  318

<212> DNA

<213> artificial sequence

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<223> CD20VL

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tcctccccca aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgctcgc    180
ttcagtggtca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa    240

등록특허 10-1229731
gatgtgcca cttattcgtg ccatcagttt agtagtaacc cgctcacgtt cggtgcctgg

acaaaggtgg aaataaaa

172

106

PRT

artificial sequence

CD20VL

172

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1    5    10    15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Leu Ser Phe Met
20   25   30

His Trp Tyr Gin Gin Lys Pro Gly Ser Pro Lys Pro Trp Ile Tyr
35   40   45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50   55   60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65   70   75   80

Asp Ala Ala Thr Tyr Phe Cys His Gln Trp Ser Ser Asn Pro Leu Thr
85   90   95
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<210> 173

<211> 15

<212> DNA

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<223> GGGGS linker

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ggagtggtg gatcc 15

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<223> GGGGS linker

<400> 174

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DNA artificial sequence

SGGGGS linker

tccggaggtg gtggatcc

PRT artificial sequence

SGGGGS linker

Ser Gly Gly Gly Gly Ser

DNA artificial sequence
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<223> antiCD19xantiCD3 VH2VL1

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caacagatc caggacagcc accnaacte ctcactctat atgcatecaa tctagtltctt 180

gggatccac ccaggtttag tcggagttgg gctgggccag acctcaccct caacaatcct 240

cctgtggaga aagttggagtc tgcaacctat cactgaccgg aaagttactga ggatccgtgg 300

agctctgttg gaggaccaaa gctcgagatc aaagttgttg gtgttcttg cggccggccg 360

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gggtctctcg tgaagatttc ctgcaaggct tctggctatg catttaagtag ctactggatg 480

aactgggtga aqcgagggcc tggacagggt ctgtgaagtt tcggacagat ttgcctggga 540

gatgggtgata ctactacaa tggaaaaagtt aaggtaaag ccactcagct gcacagaaaa 600

tctcagcga caccctacat gcacatcagc aqcgacctgct ctggactcct tcgggtctat 660

tcctgtgcgg gacgggagac tagcagagta ggcctttatt actaatctat ggactctgg 720

ggccaaggg ccagggcagc cgctctcctc gacgagttgg gctcgagcct ccaactggtgt 780

cagtcaggg ctagttgac aaaaactttgg gctcaagtga aggtgttcct caagttttcct 840

ggcctccagag ctactaggat cagcagccag tggtaaaggc agggcctggg cagaggtctg 900

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등록특허 10-1229731

- 272 -
<210> 178
<211> 498
<212> PRT
<213> artificial sequence

Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
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Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35                  40                  45

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80

Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85                  90                  95

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100                 105                 110

115                 120                 125

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
130                 135                 140

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
145                 150                 155                 160

Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gin
165                 170                 175

Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
180                 185                 190

Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Thr Ala Tyr Met Gin
195                 200                 205

Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg
Arg Glu Thr Thr Val Gly Arg Tyr Tyr Ala Met Asp Tyr Trp
225 225 230 235 240

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Asp
245 250 255

Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser
260 265 270

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr Thr
275 280 285

Met His Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Ile Gly
290 295 300

Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu Gln
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Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Met
325 330 335

Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Cys Ala
340 345 350

Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Glu Gly Thr
355 360 365

Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Gly
370 375 380

Ser Gly Gly Ser Gly Gly Ala Asp Ile Gln Met Thr Gln Ser Pro
385 390 395 400

Ser Ser Leu Ser Ala Ser Val Gly Arg Val Thr Ile Thr Cys Arg
405 410 415
Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly 420 425 430

Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly 435 440 445

Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu 450 455 460

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Ile Lys

<210> 179

<211> 1527

<212> DNA

<213> artificial sequence

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caccactcattagagatctgctac 1527

<210> 180

<211> 498

<212> PRT

<213> artificial sequence

<220>

<223> antiCD19antiCD3 VH2VL2

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Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20                  25                  30

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35                 40                   45

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His

- 278 -
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85  90  95

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Leu Glu Ile Lys Gly
100 105 110

115 120 125

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
130 135 140

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
145 150 155 160

Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln
165 170 175

Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
180 185 190

Lys Ala Thr Leu Thr Ala Asp Ser Ser Thr Ala Tyr Met Gln
195 200 205

Leu Ser Ser Leu Ala Ser Glu Ser Ser Thr Ala Tyr Cys Ala Arg
210 215 220

Arg Glu Thr Thr Val Gly Arg Tyr Tyr Ala Met Asp Tyr Trp
225 230 235 240

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp
245 250 255

Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser
Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr Thr
275 280 285

Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly
290 295 300

Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu Gln
305 310 315 320

Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Met
325 330 335

Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Cys Ala
340 345 350

Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr
355 360 365

Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Gly
370 375 380

Ser Gly Gly Ser Gly Gly Ala Asp Ile Val Leu Thr Gln Ser Pro
385 390 395 400

Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg
405 410 415

Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly
420 425 430

Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Lys Val Ala Ser Gly
435 440 445

Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu
Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gin

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Ile Lys

<210> 181

<211> 1527

<212> DNA

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caacagattc caggacagcc acccaaactc ctcatctatg atgcatccaa tctagtttct 180
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<td>26-30</td>
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165  170  175
Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
180  185  190
Lys Ala Thr Leu Thr Ala Asp Ser Ser Ser Thr Ala Tyr Met Gln
195  200  205
Leu Ser Ser Leu Ala Ser Glu Ser Ala Val Tyr Phe Cys Ala Arg
210  215  220
Arg Glu Thr Thr Val Gly Arg Tyr Tyr Ala Met Asp Tyr Trp
225  230  235  240
Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp
245  250  255
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Pro Gly Ala Ser
260  265  270
Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Thr Arg Tyr Thr
275  280  285
Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly
290  295  300
Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu Gin

등록특허 10-1229731
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Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Cys Ala
340 345 350

Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr
355 360 365

Thr Val Thr Val Ser Ser Gly Gly Thr Ser Thr Gly Ser Gly Gly
370 375 380

Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser Pro
385 390 395 400

Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys Arg
405 410 415

Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly
420 425 430

Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly
435 440 445

Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu
450 455 460

Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Cys Gln
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Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu
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Ile Lys
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<211> 1527

<212> DNA

<213> artificial sequence

<220>

<223> antiCD19xantiCD3 VH3VL1

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cacaagatc caggacagcc acccaacact tcaatcttag atgcatccaa tctagtltct 180
gggateccac ccaggtttag tggcagtggg tctgggacag actctacect caacatccat 240
cctgtggaga aggtaggtgc tgaacctat cactgtcage aaaaatcgtaa ggtatccggtg 300
acgttcgtgg gaggaccaaa gctcgagatc aaggtggttg gttggtcgtg cggcgggccc 360
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aactggttga aacacagggc tggcgagggg aitgagttgg tggagccagc ttggcccctg 540
gtggattcata ctaactacaag cggggtaggt guggtaaaag ccacactgac tgcagacgaa 600
ttcctccagca cagctctacg gcagctctcgc gctctacggt ctagaggact gtcggtctat 660
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 등록특허 10-1229731

<210>  184
<211>  498
<212>  PRT
<213>  artificial sequence
<223>  ant iCD19xant iCD3 VH3VL1

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Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35                  40                  45

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80

Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85                  90                  95

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100                 105                 110

115                 120                 125

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
130                 135                 140

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
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Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln
165                 170                 175

- 288 -
Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly

Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Thr Ala Tyr Met Gln

Leu Ser Ser Leu Ala Ser Glu Ser Ala Val Tyr Phe Cys Ala Arg

Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp

Gly Gln Gly Thr Thr Val Th Val Ser Ser Gly Gly Gly Gly Ser Asp

Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser

Val Lys Val Ser Cys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr Thr

Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly

Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu Gln

Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Leu

Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Cys Ala

Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr
Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
370 375 380
Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Gln Met Thr Gln Ser Pro
385 390 395 400
Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
405 410 415
Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly
420 425 430
Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly
435 440 445
Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu
450 455 460
Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gin
465 470 475 480
Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu
485 490 495
Ile Lys

<210> 185
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caacagttc  caggacagcc  acccaaaetc  ecatetctg  atgcatccaa  tctagttctt   180
ggatcccaa  ccaggttttag  tggcngtggg  tctgggacag  acitteeccct  caacatccat  240
cctgtggaga  aggtggatgc  tgcaacctat  cactgtcage  aagahtactga  ggateccctgg  300
acgtggtgag  gagggaccaaa  gcteagagtc  aaaggttggg  tgggtctcttg  ggcggccgac  360
tccggtgtgg  gtggttctca  ggtgcaetgt  cagcaglctg  ggggctagctg  gtggaggcct   420
ggttccagc  tgaagatlttc  etgcaaggtt  tctggetatg  catcagagtcttgagggt  480
aactggttaa  agcagagccc  tggacaggg  ctggagtgga  tggacatag  tggccctgga  540
gatggctgta  cttaactaca  tggaaagtgc  aaggttaaaag  ccactctgac  tgcagacga  600
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ggccaggag  ccaggtctac  cgtlctctgc  ggaggtgggt  gctcagaagct  ccaactggtt  780
cagtcaggag  ctgaaagtgaa  aaaaactctgg  gctctgtgga  aggtgtctct  cagctctctc  840
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gaaggtaatg  gatcaattaa  tcctgccggt  ggattacta  attacgccaa  gagaagttgag  960
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<210>  186

<211>  498

<212> PRT

<213> artificial sequence

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<223> antiCD19xantiCD3 VH3VL2

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Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35                  40                  45

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80

Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85                  90                  95

Glu Asp Pro Trp Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys Gly
100                 105                 110

115                 120                 125

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
130                 135                 140

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
145                 150                 155                 160

Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln
165                 170                 175

Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
180                 185                 190

Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Thr Ala Tyr Met Gln
195                 200                 205

Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg
210                 215                 220
Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp
225 230 235 240

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp
245 250 255

Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser
260 265 270

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ala Thr Arg Tyr Thr
275 280 285

Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly
290 295 300

Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Gln Lys Leu Gin
305 310 315 320

Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Leu
325 330 335

Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Cys Ala
340 345 350

Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr
355 360 365

Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Gly
370 375 380

Ser Gly Gly Ser Gly Gly Ala Asp Ile Val Leu Thr Gln Ser Pro
385 390 395 400

Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg
405 410 415

Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly

- 294 -
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Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu 450 455 460
Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Cys Gln 465 470 475 480
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Ile Lys

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caacagattc caggacagcc accaaactc ctcatctatg atgcatccaa tctagtttct    180
gggatccca ccaggttag tggcgtggg tctgggacag acttacctt caacatccat 240

- 295 -
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aactgggtga acgcagagcc tggacagggg cttgaagtgg gttgacagat ttcgcttca
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- <210> 188
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Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35                  40                  45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50                  55                  60
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Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
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Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Leu

Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Ala

Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr

Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Gly

Ser Gly Gly Ser Gly Gly Ala Asp Ile Val Leu Thr Gln Ser Pro

Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys Arg

Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly

Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly

Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu

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Ile Lys

<210> 189
<211> 1527
<212> DNA
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gggateccac ccagtttag tggcagttgg tctgggacag acttcaccc caacatccat 240
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<210> 190

<211> 498
PRT

artificial sequence

antiCD19xantiCD3 VH5VL1

190

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Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro

35  40  45

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro

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Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His

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Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr

85  90  95

Glu Asp Pro Trp Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys Gly

100  105  110


115  120  125

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Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Thr Ala Tyr Met Gin
Leu Ser Ser Leu Ala Ser Glu Ser Ser Ala Val Tyr Phe Cys Ala Arg
Arg Glu Thr Thr Val Gly Arg Tyr Tyr Ala Met Asp Tyr Trp
Gly Gin Gly Thr Thr Val Thr Val Ser Ser Gly Gin Gin Gin Ser Asp
Val Gin Leu Val Gin Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser
Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr
Met His Trp Val Arg Gin Ala Pro Gly Gin Gin Leu Glu Trp Ile Gin
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Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr Met
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Val Pro Ala Arg Phe Ser Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu
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Ile Lys

<210>  191
artificial sequence

antiCD19xantiCD3 VH5VL2

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  50                  55                  60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
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Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
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Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
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Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly

Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu

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Ile Lys

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등록특허 10-1229731
Ile Lys

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<211> 1527
<212> DNA
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<212> DNA
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Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
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Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
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Glu Asp Pro Trp Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys Gly
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115                 120                 125

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Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
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Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met Gin

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Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser
Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr
Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly
Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys
Asp Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met
Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr
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Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly

Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly

Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu

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Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
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Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
 50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65                  70                  75                  80

Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
 85                  90                  95

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Met His Trp Val Lys Gin Gin Arg Pro Gin Gin Gly Leu Glu Trp 1le Gly

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Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr

Thr Leu Thr Val Ser Ser Val Glu Gly Ser Gly Ser Gly Ser Gly

Ser Gly Gly Gly Val Asp Asp Ile Gln Leu Thr Gln Ser Pro

Ala Ile Met Ser Ala Ser Pro Gly Lys Val Thr Met Thr Cys Arg

Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Ser Gly

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- 333 -
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<211>  1476

<212> DNA

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Lys Leu Leu Ile Tyr Ala Ala Ser His Gln Gly Ser Gly Val Pro Ala
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Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His
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Pro Leu Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys His Gln Ser Lys
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Lys Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
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115                 120                 125

Glu Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val Thr Ile
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Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Lys Phe Gly Met Asn Trp
145                 150                 155                 160

- 336 -
Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Thr Met Gly Trp Ile His
Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Thr Met Gly Trp Ile His
Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Thr Met Gly Trp Ile His

Thr Ser Thr Gly Glu Pro Thr Tyr Ser Asp Asp Phe Lys Gly Arg Phe
Thr Ser Thr Gly Glu Pro Thr Tyr Ser Asp Asp Phe Lys Gly Arg Phe
Thr Ser Thr Gly Glu Pro Thr Tyr Ser Asp Asp Phe Lys Gly Arg Phe

Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Arg Ile Asn
Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Arg Ile Asn
Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Arg Ile Asn

Asn Leu Lys Asn Glu Asp Met Ala Lys Tyr Phe Cys Ala Arg Gly Gly
Asn Leu Lys Asn Glu Asp Met Ala Lys Tyr Phe Cys Ala Arg Gly Gly
Asn Leu Lys Asn Glu Asp Met Ala Lys Tyr Phe Cys Ala Arg Gly Gly

Pro Tyr Val Arg Gly Ala Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val
Pro Tyr Val Arg Gly Ala Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val
Pro Tyr Val Arg Gly Ala Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val

Thr Val Ser Ser Gly Gly Gly Gly Ser Asp Val Gln Leu Val Gln Ser
Thr Val Ser Ser Gly Gly Gly Gly Ser Asp Val Gln Leu Val Gln Ser
Thr Val Ser Ser Gly Gly Gly Gly Ser Asp Val Gln Leu Val Gln Ser

Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys
Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys
Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys

Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Thr Val Arg Gin
Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Thr Val Arg Gin
Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Thr Val Arg Gin

Ala Pro Gly Gin Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg
Ala Pro Gly Gin Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg
Ala Pro Gly Gin Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg

Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Thr
Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Thr
Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Thr

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Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg
Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg

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Ser Glu Asp Thr Ala Thr Tyr Cys Ala Arg Tyr Tyr Asp Asp His
Ser Glu Asp Thr Ala Thr Tyr Cys Ala Arg Tyr Tyr Asp Asp His

Tyr Cys Leu Asp Tyr Trp Gly Gin Gly Thr Thr Val Thr Val Ser Ser
Tyr Cys Leu Asp Tyr Trp Gly Gin Gly Thr Thr Val Thr Val Ser Ser
Tyr Cys Leu Asp Tyr Trp Gly Gin Gly Thr Thr Val Thr Val Ser Ser
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Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp
420 425 430
Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser
435 440 445
Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu
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Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro
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Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
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Gly Ile Ser Phe Ile Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35  40  45
Lys Leu Leu Ile Tyr Ala Ala Ser His Gln Gly Ser Gly Val Pro Ala
50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His
65                  70                  75                  80

Pro Leu Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys His Gln Ser Lys
85                  90                  95

Lys Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100                 105                 110

115                 120                 125

Glu Gln Ser Gly Pro Glu Leu Lys Pro Gly Glu Thr Val Thr Ile
130                 135                 140

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Lys Phe Gly Met Asn Trp
145                 150                 155                 160

Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly Trp Ile His
165                 170                 175

Thr Ser Thr Gly Glu Pro Thr Tyr Ser Asp Asp Phe Lys Gly Arg Phe
180                 185                 190

Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Arg Ile Asn
195                 200                 205

Asn Leu Lys Asn Glu Asp Met Ala Lys Tyr Phe Cys Ala Arg Gly Gly
210                 215                 220

Pro Tyr Val Arg Gly Ala Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val
225                 230                 235                 240

Thr Val Ser Ser Gly Gly Gly Ser Asp Val Gln Leu Val Gly Ser
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Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln

Ala Pro Gly Gin Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg

Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Thr

Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg

Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His

Tyr Cys Leu Asp Tyr Trp Gly Glu Gly Thr Thr Val Thr Val Ser Ser

Gly Glu Gly Thr Ser Thr Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly

Ala Asp Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser

Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser

Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp

Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser
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Pro Gly Glu Arg Ala Thr Leu Thr Cys Arg Ala Ser Ser Ser Val Ser
Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp
Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser
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artificial sequence

CCR5xanti-CD3 VH7VL1

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Pro Leu Glu Glu Asp Thr Ala Met Tyr Phe Cys His Gln Ser Lys

Lys Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly


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Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Lys Phe Gly Met Asn Trp

Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly Trp Ile His

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- 355 -
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DNA artificial sequence

CCR5xanti-CD3 VI7VL3

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Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His  
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<210> 217

<211> 1473

<212> DNA

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<210> 218

<211> 491

<212> PRT

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Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
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Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
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Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly
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Thr Pro Gly Gin Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn
165 170 175

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Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly

Glu Gly Thr Ser Thr Gly Ser Gly Gly Ser Gly Ser Gly Gly Ser Gly Ala

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Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Tyr

Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile

Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly

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<211> 1473

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<223> CD20xanti-CD3 VH5VL2

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catatctgttg gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa
gatgcctgca cttatcttc gcctcagtttg agtagtaacc egctcaacggg cgttgtcggg
acaaggtgg aaataaaagg tggtggtggt tctggcggcg gcggctccgg tggtggtggt
ttcaggtgc aacctggcga gctggtgttc gacctggcag agcctggggc ttcaggtgaag
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acacgtggag gaggcctggg aatggattgg ctttggtgga agcctggggc ctcaggttgaag
acaatacaga agttaaagg caagggcaca tggactgcag acaatacctc cagcacagcc
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tacattcaca agttaaagg caagggcaca tggactgcag acaatacctc cagcacagcc
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d등록특허 10-1229731
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agcttggagg ctgaagatgc tgccacttat tactgccaac agtggagtag taacccgctc

acgttcggtg gcgggaccaa ggtggagatc aaa

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1      5      10      15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Leu Ser Phe Met
20     25     30
His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35                  40                  45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Phe Cys His Gln Trp Ser Ser Asn Pro Leu Thr
85                  90                  95

Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly
100                 105                 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Arg Gln Pro
115                 120                 125

Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
130                 135                 140

 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp Val Lys Gln
145                 150                 155                 160

Thr Pro Gly Gin Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn
165                 170                 175

Gly Asp Thr Ser Tyr Asn Gin Lys Phe Lys Gly Lys Ala Thr Leu Thr
180                 185                 190

 Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gin Leu Ser Ser Leu Thr
195                 200                 205

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser His Tyr Gly Ser
210                 215                 220
Asn Tyr Val Asp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr  
225  230  235  240

Val Ser Thr Gly Gly Gly Gly Ser Asp Val Gln Leu Val Gln Ser Gly  
245  250  255

Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala  
260  265  270

Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln Ala  
275  280  285

Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly  
290  295  300

Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Thr Thr  
305  310  315  320

Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser  
325  330  335

Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Asp Asp His Tyr  
340  345  350

Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly  
355  360  365

Glu Gly Thr Ser Thr Gly Ser Gly Gly Ser Gly Gly Ser Gly Ala  
370  375  380

Asp Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro  
385  390  395  400

Gly Glu Arg Ala Thr Leu Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr  
405  410  415

- 374 -
Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile
420                 425                 430

Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly
435                 440                 445

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala
450                 455                 460

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu
465                 470                 475                 480

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
485                 490

<210> 223

<211> 1473

<212> DNA

<213> artificial sequence

<220>

<223> CD20xanti-CD3 VH7VL1

<400> 223
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tctccccca aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgctcgc    180
ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa    240

ttcagtgcca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa    300

ttcagtgcca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa    360

ttcagtgcca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa    420

ttcagtgcca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa    480

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ttcagtgcca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa    600

ttcagtgcca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa    660

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ttcagtgcca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa    1260

ttcagtgcca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa    1320

등록특허 10-1229731
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acacetggac aggectggga atgacattgga gctattttct caggaatgg tgaacttcc 480
tacaatcaga agtccaaggg caagggcaca ttgactgcaag acaaaactte cagcagcagc 540
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cagatgcaact ggtagaaggca ggcaactctgg gacagcattt gatggatggtt atacatgaat 840
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gacaaateca ccaacgacagc tcatatggaat ctgactgacg ggcagacctgca 960
gTcagtttact gtgcaagata ttaagctctg gctactctgg gggcgaaggg 1020
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gaggattcctg cgacgttctgc cggcagagct acacctctct cacaatcaac 1320
gagttggagg ctgaagatgc tgccacttat tactgccaac agtggagtag taaccccgttc 1380
- 376 -
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<210> 224

<211> 491

<212> PRT

<213> artificial sequence

<220>

<223> CD20xanti-CD3 VH7VL1

<400> 224

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
 1    5     10     15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Leu Ser Phe Met
 20   25    30

His Trp Tyr Gin Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
 35   40    45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
 50   55    60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
 65   70    75    80

Asp Ala Ala Thr Tyr Phe Cys His Gln Trp Ser Ser Asn Pro Leu Thr
 85   90    95

Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly

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Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Val Lys Met Ser Cys Lys

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp Val Lys Gln

Thr Pro Gly Gin Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn

Gly Asp Thr Ser Tyr Asn Gin Lys Phe Lys Gly Lys Ala Thr Leu Thr

Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser His Tyr Gly Ser

Asn Tyr Val Asp Tyr Phe Asp Tyr Trp Gly Gin Gly Thr Leu Val Thr

Val Ser Thr Gly Gly Gly Gly Ser Asp Val Gin Leu Val Gin Ser Gly

Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala

Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gin Ala

Pro Gly Gin Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly

등록특허 10-1229731
Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Ile Thr Thr
Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser
Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr
Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly
Glu Gly Thr Ser Thr Gly Ser Gly Ser Gly Gly Ser Gly Gly Ala
Asp Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Tyr
Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile
Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala
Glu Asp Ala Ala Thr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu
Thr Phe Gly Gly Thr Lys Val Glu Ile Lys
<210> 225

<211> 1473

<212> DNA

<213> artificial sequence

<220>

<223> CD20xanti-CD3 VH7VL2

<400> 225
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tctceccca aaccctgagat tcatgcacac tccaaacctg cttctggagt cctgtcgcg 180
ttcagttgcc atgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa 240
gatgtccca cttaatttctg cactcagttg agtagtaacc cgcctacgtt cgggtctgg 300
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tctcgaggtg aacgtgcggca gctctggggt gacgttggta agcctggggc ctcagttgaa 420
atgttcctcag aggctttctg ctacactttg atagggtgga cacagtttac atatgcatcg ggttaagg 480
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ttttcatcaga acggacagc caagccccag tctgctgcag acaaatccct cggcagcagc 600
tatttgcagct ctcgcaattg ctcagcttgg gacttgggct gctttactgg gagaagactc 660
cactcgggtat aactcacaat gactactggt gactctggtg gccagccag cacactgca 720
gtctgacag gaggtgcttg atccgaagtc caactggttg agtcaggccc tgaagtgaaa 780

aaacctgggg cctcagtgaa ggtgtcctgc aaggcttctg gctacacctt tactaggtac 840

acgagctcgttg ttatactaa ttacatggg ggttcaaggg acctgtcag t aga gtcgacga 900

gacataat ccgcacacag ctacatggg ggtgcagacca tgcgttctga ggacactgca 960

gettattact gtcaagata ttagtagat cattactgce ttagactctg gggcaaggg 1020

accacggtca cgcgtctctc aggcgaaggt aagctatagt gttctggttg aagtggaggt 1140

tcaggtggag cagacagcat tggactgac acgtctctca cagctcagc caactctgtc tetgtcttca 1200

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caggagaagc ccggcagagc acccaaaaga tggatattag acacattcag ccgggctccct 1320

ggaggctcttg ctcggctcag tggcagtggg ttctgtgactg cacacatatc cacaatcaca 1380

agcttgggagctgaagatgctgcatcactgtagagta gaacccgctc 1440

acgttgcggct gccgacacag ggtgagctgg 1473

<210> 226

<211> 491

<212> PRT

<213> artificial sequence

<220>

<223> CD20xanti-CD3 VH7VL2

등록특허 10-1229731
Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1               5                   10                  15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Leu Ser Phe Met
20                  25                  30

His Trp Tyr Gin Gin Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35                  40                  45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Phe Cys His Gln Trp Ser Ser Asn Pro Leu Thr
85                  90                  95

Phe Gly Ala Gly Thr Val Glu Ile Lys Gly Gly Gly Gly Ser Gly
100                 105                 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Arg Gln Pro
115                 120                 125

Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
130                 135                 140

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp Val Lys Gin
145                 150                 155                 160

Thr Pro Gly Gin Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn
165                 170                 175

Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr

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180                 185                 190
Ala Asp Lys Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr
195                 200                 205
Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser His Tyr Gly Ser
210                 215                 220
Asn Tyr Val Asp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240
Val Ser Thr Gly Gly Gly Gly Ser Asp Val Gln Leu Val Gln Ser Gly
245                 250                 255
Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala
260                 265                 270
Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln Ala
275                 280                 285
Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly
290                 295                 300
Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Ile Thr Thr
305                 310                 315                 320
Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser
325                 330                 335
Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr
340                 345                 350
Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly
355                 360                 365
Glu Gly Thr Ser Thr Gly Ser Gly Ser Gly Gly Ser Gly Gly Ala
Asp Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr
Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile
Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala
Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu
Thr Phe Gly Gly Thr Lys Val Glu Ile Lys

<210> 227
<211> 1473
<212> DNA
<213> artificial sequence
<220>
<223> CD20xanti-CD3 VH7VL3
<400> 227
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120
tctcccccct aacccctggttt tatgcccaca tccaaacttg gttttggagt cctgcgctgc
180
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tcctccccca aaccctggaa agtttaaagt ttcatgcact ggtaccagca gaagccagga
240
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360
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tcctccccca aaccctggaa agtttaaagt ttcatgcact ggtaccagca gaagccagga
420
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440
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tcctccccca aaccctggaa agtttaaagt ttcatgcact ggtaccagca gaagccagga
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560
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620
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680
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ggaagtccctg etcgcttcag tggcngtggg tcgggaccg actactctct cacaatcaac

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acgttecggt gcgggaccaa ggtggagct aaaa

<210>  228

<211>  491

<212> PRT

<213> artificial sequence

<220>

<223> CD20xanti-CD3 VH7VL3

<400> 228

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1  5  10  15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Leu Ser Phe Met
20  25  30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35  40  45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50  55  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu

- 386 -
Asp Ala Ala Thr Tyr Phe Cys His Gln Trp Ser Ser Asn Pro Leu Thr

Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Arg Gln Pro

Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp Val Lys Gin

Thr Pro Gly Gin Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn

Gly Asp Thr Ser Tyr Asn Gin Lys Phe Lys Gly Lys Ala Thr Leu Thr

Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gin Leu Ser Ser Leu Thr

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser His Tyr Gly Ser

Asn Tyr Val Asp Tyr Phe Asp Tyr Trp Gin Gly Thr Leu Val Thr

Val Ser Thr Gin Gly Gly Ser Asp Val Gin Leu Val Gin Ser Gly

Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala
Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln Ala

Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly

Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Ile Thr Thr

Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr

Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly

Glu Gly Thr Ser Thr Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala

Asp Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro

Gly Glu Arg Ala Thr Leu Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr

Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile

Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala
Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

<210> 229

<211> 25

<212> PRT

<213> artificial sequence

<220>

<223> non-deimmunized anti-CD3 Framework 1

<400> 229

Asp Ile Lys Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala

Ser Val Lys Met Ser Cys Lys Thr Ser

<210> 230

<211> 15

<212> PRT

<213> artificial sequence
<220>

<223> non-deimmunized anti-CD3 Framework 2

<400> 230

Trp Val Lys Gin Arg Pro Gly Gin Gly Leu Glu Trp Ile Gly Tyr
1  5  10  15

<210> 231

<211> 32

<212> PRT

<213> artificial sequence

<220>

<223> non-deimmunized anti-CD3 Framework 3

<400> 231

Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Thr Ala Tyr Met Gin
1  5  10  15

Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 232

<211> 11

<212> PRT

<213> artificial sequence
non-deimmunized anti-CD3 Framework 4

Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
1       5       10

artificial sequence

Sequence motif

artificial sequence
Met Glu Leu Ser

Ile Thr Thr Asp Lys

DNA

artificial sequence

5-10xVH5VL1 LHHL

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등록특허 10-1229731

- 393 -
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<210> 237

<211> 496

<212> PRT

<213> artificial sequence

5-10xVH5VL1 LHHL

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35  40  45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50  55  60
Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn
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Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile
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115                 120                 125

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Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
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Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
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Phe Lys Gly Ala Thr Leu Thr Ala Asp Ser Ser Ser Thr Ala
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Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
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Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gin
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Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Asp Val Gin
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Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg

Phe Thr Ile Thr Thr Asp Ser Thr Ser Thr Ala Tyr Met Glu Leu

Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Cys Ala Arg Tyr

Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val

Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Ser Gly

Gly Ser Gly Gly Ala Asp Asp Ile Gln Met Thr Gln Ser Pro Ser Ser

Leu Ser Ala Ser Val Gly Arg Val Thr Ile Thr Cys Arg Ala Ser

Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala

Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile
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<210> 238
<211> 1491
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tacaatgaga atgtcaaggg caaagccaca ctgactgcag acaaatcttc gagcacagcc    240
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aggaactggg acgagcctat ggactactgg ggccaaggga ccacggtcac cgtctcctca    360
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cgtctcctat cctccctgac tgtgacagca ggagagaagg tcactatgag ctgcaagtcc    480
agtcagagtc tgttaaacag tggaaatcaa aagaactact tgacctggta ccagcagaaa    540
ccagggcage ctcttaaa tacttgatetac tgggatcaca ctgggaact tgggtctcct 600
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gctgagatcc tggcagttga aatgattata gtattcagt caagttgcgt 720
gctgggacca agcttgagat caaatccgga ggtggtggag cggctgacca actggtgcag 780
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<210> 239

<211> 497

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<213> artificial sequence

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<223> 5-10xVH5VL1 HLHL

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180 185 190
Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser
195 200 205
Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu
210 215 220
Ala Val Tyr Tyr Cys Gln Asn Asp Tyr Ser Tyr Pro Leu Thr Phe Gly
225 230 235 240
Ala Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser Asp Val
245 250 255
Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val
260 265 270
Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met
275 280 285
His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
290 295 300
Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly
305 310 315 320
Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu
325 330 335

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Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
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Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr
355          360          365
Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Gly Ser
370          375          380
Gly Gly Ser Gly Gly Ala Asp Asp Ile Gln Met Thr Gln Ser Pro Ser
385          390          395          400
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
405          410          415
Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys
420          425          430
Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val
435          440          445
Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
450          455          460
Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
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<210> 240

<211> 1488
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<210> 241
<211> 496
<212> PRT
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Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser

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Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr

Ile Ser Ser Val Gin Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gin Asn

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile


Glu Val Gin Leu Leu Glu Gin Ser Gly Ala Glu Leu Val Arg Pro Gly

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn

Tyr Trp Leu Gly Trp Val Lys Gin Arg Pro Gly His Gly Leu Glu Trp

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Ser Ser Ser Thr Ala

Tyr Met Gin Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gin  
Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Asp Ile Gin  
Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val  
Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr  
Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser  
Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly  
Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala  
Thr Tyr Tyr Cys Gin Gin Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly  
Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr Gly Ser Gly  
Gly Ser Gly Ser Gly Gly Ala Asp Asp Val Glu Val Leu Val Gin Ser  
Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys  
Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gin  
- 405 -
Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg
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Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Thr
435                 440                 445

Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg
450                 455                 460

Ser Glu Asp Thr Ala Thr Tyr Cys Ala Arg Tyr Tyr Asp Asp His
465                 470                 475                 480

Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
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<210> 242

<211> 1491

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aggcctggac atggacttga gtggattgga gatattttcc ctggaagtgg taatatccac 180
tacaatgaga agttcaaggg caaagccaca ctgactgcag acaaatcttc gagcacagcc 240

- 406 -
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<210> 243

<211> 497

<212> PRT

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<223> 5-10xVL1VH5 HLLH

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20     25     30

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
35     40     45

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
50     55     60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65     70     75   80

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
85     90     95

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gin

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Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr Gly Ser
Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu Val Gln
Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys
Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg
Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile
Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu
Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp
His Tyr Cys Leu Asp Tyr Trp Gln Gly Thr Thr Val Thr Val Ser
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<211> 1491

<212> DNA

<213> artificial sequence

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tacaatgaga agtcgaaggg caaagccaca ctgacactag acaaatcttc gagcagcagc  240
tatatgacag gccttgcctg gacgctgtgc cttctgctg tctatttctg tgcagactgc  300
gttgccgtgc gtcgatgctc gcctttctgg ttcggactag gcgcagcagc ccctgaactgc  360
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<210> 245

<211> 497

<212> PRT

<213> artificial sequence
Glu Val Glu Leu Leu Glu Glu Ser Gly Ala Glu Leu Val Arg Pro Gly
1  5  10  15

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
20  25  30

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
35  40  45

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
50  55  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65  70  75  80

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
85  90  95

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Ser Glu Leu Val Met Thr Gln Ser Pro Ser
130 135 140

Ser Leu Thr Val Thr Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser
145 150 155 160
Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Thr Trp  
165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala  
180                 185                 190

Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser  
195                 200                 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu  
210                 215                 220

Ala Val Tyr Tyr Cys Gln Asn Tyr Ser Tyr Pro Leu Thr Phe Gly  
225                 230                 235                 240

Ala Gly Thr Lys Leu Gln Pro Ser Gly Gly Gly Ser Asp Val  
245                 250                 255

Gln Leu Val Gln Ser Gly Ala Glu Val Lys Pro Gly Ala Ser Val  
260                 265                 270

Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met  
275                 280                 285

His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr  
290                 295                 300

Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly  
305                 310                 315                 320

Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu  
325                 330                 335

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Cys Ala Arg  
340                 345                 350

Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr
Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Gly Ser
370 375 380
Gly Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser Pro Ala
385 390 395 400
Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
405 410 415
Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys
420 425 430
Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val
435 440 445
Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
450 455 460
Ile Asn Ser Leu Glu Ala Glu Ala Ala Thr Tyr Cys Gln Gln
465 470 475 480
Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
485 490 495
Lys

<210> 246

<211> 1488

<212> DNA

<213> artificial sequence
<220>
<223> 5-10xVL2VH5 LILII

<400> 246
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tgtatcc aggaaaccaggg gcacccctcct aatactgtga tctactggge atccacttgg 180
gatcttgaggg tctctgatcg ttccacaggc agtggatctg gaacaggttt cactctcacc 240

atcagcagtgt tcaggttga agacctggca gtttattact gtccagaatt tttatattta 300
cggctcagtt tcgggctgtaa gcacacactg ttggcactg  360
ggggctggcct gccggctctg ctcagtcgtg ggtggatgggc cagctgctcg agcagttgctg 420
gtaagggctt ggtcctcgct cgcctgagtaa ctggccagct ctactctcacc 480
tacttctag ggctggttaaa gcagagggctt ggacatggac ttgagtggat tggagatatt 540

ttccctggaa gttggttaat ccaactataa gagaaagttc aagggcact gccacactggtct 600
gcagacaat ctggacaccc atccatatgt gatgctgctt gcctacactg tggaactctcg 660
gccggctggcct gccggctctg ctcagtcgtg ggtggatgggc cagctgctcg agcagttgctg 720

gggaacacgg tcacgcgtctc ccgggctgatg gttggatgctt cagattgttct gcacactgct 780
cagcagcagc tggccacccc tgcggcagcg ctggccagct ctaactgcaag ccagcagctg 840

agttgaagt ataggcaagt gttgagccag aagcgggcga aagccacccaa aagatgggtatt 900
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gaaggtacta gta tgtggttc tgt gaaagt ggagt ttcag tgt gac gaca ga gtcgtaag 1140
cagtggagt caggggctga agg aaaa ca cgtgggctc cagt gaagaggt tcgt gcaag 1200
gcttggtt acacetttac tagtatcag atgc actggg taaggcagc ac tgtgacag 1260
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gtc gaa ggttccaat cactcacagc aataccacca gcacagecta catgggaatg 1380
agtgtgagtg gtctgcacca cact gnaacc tattactgtg caagatat gat gatcat 1440
tactgcttg actactgggg ccaaggcacc a ggtgaccc tctctca 1488

<210> 247

<211> 496

<212> PRT

<213> artificial sequence

<220>

<223> 5-10xVL2VH5 LILIL

<400> 247

Glu Leu Val Met Thr Gln Ser Pro Ser Ser Leu Thr Val Thr Ala Gly
1      5      10      15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20     25     30

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Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile


Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Ser Ser Ser Thr Ala

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
  225           230           235           240

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp Ile Val
  245           250           255

Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala
  260           265           270

Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr
  275           280           285

Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser
  290           295           300

Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
  305           310           315           320

Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala
  325           330           335

Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly
  340           345           350

Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr Gly Ser Gly
  355           360           365

Gly Ser Gly Ser Gly Gly Ala Asp Asp Val Gln Leu Val Gln Ser
  370           375           380

Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys
  385           390           395           400

Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln
  405           410           415

Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg
Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Thr
Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg
Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His
Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Val Thr Val Ser Ser

<210> 248

<211> 1491

<212> DNA

<213> artificial sequence

<220>

<223> 5-10xVL2VH5 HLLH

<400> 248
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aggcctggac atggacttga gtggattgga gatattttcc ctggaagtgg taatatccac    180
tacaatgaga agttcaaggg caaagccaca ctgactgcag acaaatcttc gagcacagcc    240
tatatgcagc tcagtagcct gacatttgag gactctgctg tctatttctg tgcaagactg    300
aggaactggg acgagcctat ggactactgg ggccaaggga ccacggtcac cgtctcctca 360
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cagtctccat cctccctgac tgtgacagca ggagagaagg tcactatgag etgcaagtcc 480
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ceagggcage ctcctaaact tgtgatctac tgggcatcca ctagggaatc tggggtccct 600
gategtcct caggeagttg atetggaaca gatgcaacte tcacacetg cagtgtgcag 660
gtaagacg tggcgtltta ttaactgtct aatgattata gttatcegt caagttcgtg 720
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tcctcaggca ctctgtctct gtcctcccaag gcacggtgeca cccatgacct cagagccagt 840
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caggagtcgg cccggcctcc aaccacggtc aacgtctact atgtgctgctgact 1491

- 422 -
115 120 125

Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Ser Pro Ser
130 135 140

Ser Leu Thr Val Thr Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser
145 150 155 160

Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Thr Trp
165 170 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala
180 185 190

Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser
195 200 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu
210 215 220

Ala Val Tyr Tyr Cys Gln Asn Asp Tyr Ser Tyr Pro Leu Thr Phe Gly
225 230 235 240

Ala Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser Asp Ile
245 250 255

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
260 265 270

Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp
275 280 285

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr
290 295 300
Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser
305                 310                 315                 320

Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala
325                 330                 335

Ala Thr Tyr Ty r Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly
340                 345                 350

Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr Gly Ser
355                 360                 365

Gly Gly Ser Gly Gly Ser Gly Ala Asp Asp Val Gln Leu Val Gln
370                 375                 380

Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys
385                 390                 395                 400

Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg
405                 410                 415

Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
420                 425                 430

Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile
435                 440                 445

Thr Thr Asp Lys Ser Thr Ser Thr Al a Tyr Met Glu Leu Ser Ser Leu
450                 455                 460

Arg Ser Glu Asp Thr Ala Thr Tyr Cys Ala Arg Tyr Tyr Asp Asp
465                 470                 475                 480

His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
485                 490                 495
Ser

<210> 250

<211> 1488

<212> DNA

<213> artificial sequence

<220>

<223> 5-10 VH5VL3 LJHL

<400> 250
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tggtaccagc agaaccagg gcagctcctct cactggttga aacagtggaa atcaaaagaa ctacttgacc 180
gaatctggttcctgatctgact gacagagaga gaaagctactctacttgacc 240
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gaatctggttcctgatctgact gacagagaga gaaagctactctacttgacc 420
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agtatagtcacc gcgtcagcgg gtaaaaatcc gacaagagca gaaaggtgtaa 1488

<210> 251

<211> 496

<212> PRT

<213> artificial sequence
Glu Leu Val Met Thr Glu Ser Pro Ser Ser Leu Thr Val Thr Ala Gly
1  5  10  15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Asn Ser
20  25  30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35  40  45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50  55  60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65  70  75  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn
85  90  95

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile
100 105 110

115 120 125

Glu Val Gln Leu Leu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
130 135 140

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
145 150 155 160

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
165 170 175
Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys 180 185 190

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Ser Ser Ser Thr Ala 195 200 205

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe 210 215 220

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gin 225 230 235 240

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp Val Gin 245 250 255

Leu Val Gln Ser Gly Ala Glu Val Lys Lys Ser Gly Ala Ser Val Lys 260 265 270

Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His 275 280 285

Trp Val Arg Gin Ala Pro Gly Gin Gly Leu Glu Trp Ile Gly Tyr Ile 290 295 300

Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg 305 310 315 320

Phe Thr Ile Thr Thr Asp Ser Thr Ser Thr Ala Tyr Met Glu Leu 325 330 335

Ser Ser Leu Arg Ser Glu Asp Thr Ala Tyr Tyr Cys Ala Arg Tyr 340 345 350

Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gin Gly Thr Thr Val 355 360 365
Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Gly Ser Gly
370                 375                 380

Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Glu Ser Pro Ala Thr
385                 390                 395                 400

Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys Arg Ala Ser
405                 410                 415

Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala
420                 425                 430

Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro
435                 440                 445

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile
450                 455                 460

Asn Ser Leu Glu Ala Glu Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
465                 470                 475                 480

Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
485                 490                 495

<210> 252

<211> 1491

<212> DNA

<213> artificial sequence

<220>

<223> 5-10VH5VL3 HLHIL
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tactctctca caateaaacag ctggaggtg ccagatgtct ccaacca aagcgccag 1440
tggagtagta accegctcac gttggtgcgg ggaccaagg tggagataa a 1491

<210> 253

<211> 497

<212> PRT

<213> artificial sequence

<220>

<223> 5-10VH5VL3 HLHL

<400> 253

Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1  5  10  15

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
20  25  30

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
35  40  45

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
50  55  60
Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala 
65                  70                  75                  80

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe 
85                  90                  95

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln 
100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly 
115                 120                 125

Gly Ser Gly Gly Gly Ser Glu Leu Val Met Thr Gln Ser Pro Ser 
130                 135                 140

Ser Leu Thr Val Thr Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser 
145                 150                 155                 160

Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Thr Trp 
165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala 
180                 185                 190

Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser 
195                 200                 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu 
210                 215                 220

Ala Val Tyr Tyr Cys Gln Asn Asp Tyr Ser Tyr Pro Leu Thr Phe Gly 
225                 230                 235                 240

Ala Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser Asp Val 
245                 250                 255
Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val
260                 265                 270

Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met
275                 280                 285

His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
290                 295                 300

Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly
305                 310                 315                 320

Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu
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<212> DNA

<213> artificial sequence

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<223> 5-10VL3VH5 LILH

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- 434 -
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- 435 -
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Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln

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Gly Ser Gly Gly Gly Ser Glu Leu Val Met Thr Gln Ser Pro Ser

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Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Thr Trp

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala

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Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val 50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
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Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala
Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro
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Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr

Ile Ser Ser Val Gin Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gin Asn

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile


Glu Val Gin Leu Leu Glu Gin Ser Gly Gin Ala Glu Leu Val Arg Pro Gly

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn

Tyr Trp Leu Gly Trp Val Lys Gin Arg Pro Gly His Gly Leu Glu Trp

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys

Phe Lys Gly Ala Thr Leu Thr Ala Asp Ser Ser Ser Thr Ala

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Ala Val Tyr Tyr Cys Gln Asn Asp Tyr Ser Tyr Pro Leu Thr Phe Gly
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Ala Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser Asp Ile
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- 469 -
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Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met

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Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg

Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr

Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Gly Ser

Gly Gly Ser Gly Ala Asp Ile Val Leu Thr Gln Ser Pro Ala

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala

Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Gly Pro Gly Lys

 Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val
Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr

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등록특허 10-1229731

- 472 -
artificial sequence

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Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
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Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
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- 475 -
DNA artificial sequence

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Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Ala
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Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
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Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gin
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165                 170                 175

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195                 200                 205
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260                 265                 270
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275                 280                 285
Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr
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325                 330                 335
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Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr Gly Ser
355                 360                 365
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370                 375                 380
Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys
Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg
Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Ile
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<211> 1488

<212> DNA

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   35     40     45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
   50     55     60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn
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Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile
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115 120 125

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Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
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Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
165 170 175

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
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Phe Lys Gly Ala Thr Leu Thr Ala Asp Ser Ser Ser Thr Ala
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Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
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Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg 305 310 315 320

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Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro 435 440 445

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Ala Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser Asp Val
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Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val
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Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp
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Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu
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등록특허 10-1229731

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Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Ser
370                 375                 380

Gly Gly Ser Gly Gly Ala Asp Ile Val Leu Thr Gln Ser Pro Ala
385                 390                 395                 400

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys Arg Ala
405                 410                 415

Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys
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Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val
435                 440                 445

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
450                 455                 460

Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
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Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gln Thr Lys Val Glu Ile
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Lys

<210> 278

<211> 1488
DESCRIPTIVE INFORMATION

DNA

artificial sequence

5'-VL3WH LHLH

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480

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Phe  Lys  Gly  Ala  Thr  Leu  Thr  Ala  Asp  Ser  Ser  Ser  Thr  Ala
Tyr  Met  Gln  Leu  Ser  Ser  Leu  Thr  Phe  Glu  Asp  Ser  Ala  Val  Tyr  Phe
Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gin
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Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala
Thr Leu Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr
Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser
Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala
Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly
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<223>  5-10/VL3W7 HLLLH

<400>  280
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aggcctggac atggacttga gtggattgga gatattttcc ctggaagtgg taatatccac 180
tacaatgaga agttcaaggg caaagccaca ctgactgcag acaaatcttc gagcacagcc 240

- 494 -
tatatgcage tcagtagcct gacatttgag gactctgctg tctatttctg tgcaagactg 300
aggaactggg acgagcttat ggacactctgg gcaccaaggga ccaacgttcac egtdtctca 360
gtgtgtgttg ttcttgccgg cgccgctgcgg ggttgtgttg gttctgagct cgtgatgaca 420
cagtdtctcat cctctctgac tggacactga ggagagaagg tcaactatgag ctgcaagtcc 480
agtcagagtc tgttaacacag tggaaatcag tgaaccttgta ccaacaggaa 540
cacggcagc etcetaaact gtggatctae tgggcatcna etagggaate tggggttctct 600
gatgcgtca cagcgatggg atcttggaaca gattlcactc tcaccatcaag cagtgtgcag 660
getgaagaccc tggcagtitta ttactgtcag atattgtata gttatcgct caagttgatt 720
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ggcagggagct acctctctca ccaacacage ttggagggct aagatctgctc cactttataa 1020
tgccaacaggt ggagttgatt caacgtcggc ataggagttc cgggtcggag caagctgcgc 1080
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cacaatggcc aacgctcgtgc gtagagttaaaccttggtg cagcgggttc aaccttggtg 1200
aaggttttctg gtttaaactt ttaagctata gctgagcagg ggtggtggct ggcaggtgcg 1260
ctgagctttc atctttcata ctctgcgaag ggtgttcttt gacagcttgct cgggatcag 1320
aagttttaacg ttcctctctat ggtttaactta ctagttgatt cgggatcag cgggatcag 1380
ttgagcgctt gccttgcttc gggactagtctg tctatttctg tgtgaagactg 1440
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<210> 281

<211> 497

<212> PRT

<213> artificial sequence

<220>

<223> 5-10/VL3VH7 IIII

<400> 281

Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
  1       5       10       15

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
  20      25      30

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
  35      40      45

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
  50      55      60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
  65      70      75      80

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
  85      90      95

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gin
Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Ser Pro Ser
Ser Leu Thr Val Thr Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser
Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Thr Trp
Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala
Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser
Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu
Ala Val Tyr Tyr Cys Gln Asn Asp Tyr Ser Tyr Pro Leu Thr Phe Gly
Ala Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser Asp Ile
Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
Ala Thr Leu Thr Cys Arg Ala Ser Ser Val Ser Tyr Met Asn Trp
Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr
Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser
Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala
Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly
Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr Gly Ser
Gly Gly Ser Gly Ser Gly Gly Ala Asp Asp Val Gln Leu Val Gln
Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys
Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg
Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Ile
Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu
Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp
His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
Ser

<210> 282

<211> 1497

<212> DNA

<213> artificial sequence

<220>

<223> VL1/VH5x4-7 LHHL

<400> 282
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aaggcaccca aaagatggat ttatgacaca tccaaagtgg cttetggagt cctctgctgc 180
ttcagtgccag ttgggttggg gacgctgactac tctctcagacatgctcgtgaa 240
gatgetgccag cttaattaatg ccaacagtgg agtagtaacc cggctcagtt cgggtgcggg 300
accaagttgg agatcaaaaaa cgaagttact atagtaacc cggtgctggag tggaggttca 360
accaagttgg agatcaaaaaa cgaagttact atagtaacc cggtgctggag tggaggttca 420
ttcagtgccag ttgggttggg gacgctgactac tctctcagacatgctcgtgaa 480
gatgetgccag cttaattaatg ccaacagtgg agtagtaacc cggctcagtt cgggtgcggg 540
accaagttgg agatcaaaaaa cgaagttact atagtaacc cggtgctggag tggaggttca 600
tataaatt aagcagcaaca cgtnaagggc cggctcagtt ccaactacag ccatacag ccatacag 660
agcacagcct acatggaact gacgagcttg cgttctgagg acactgcaac ctattaactgt 660
gcaagatatt atgalgatca ttaactgacct gactaetgppp gccaaggcac cagcttcacc 720
gttccctcg gaggttggtt cttccgatt tgcaagctgt ctggactgtc ctteacaacac 780
gcgttgtcgt gaagctgtcc ttgaagtgagt tggagaggtt 840
tatgttaaa gctggttga gacgactgct ggcaagaggt tggagacgca 900
tatcttagaa ttgtaaatge ttactacaat gagaagttca aaggaaggct cacaetgact 960
gcagacaaat ccctcaagcc agcactccatg gagcactgact cctgcctgtc 1020
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agtctgggac aagggaccac gagctgacct gcggtctatt tctgtgcaag acggggatcc tacgactagtc actacgactg 1140
gttcctgag atgagaggtt ttgaagtcgg acggggttatgc atgacccaga ctccactctc 1200
gatctttgg cccagctgcc cagcctgacct gcggtctatt tctgtgcaag acggggatcc 1260
ttaaaagttt ccaaccgatt ttctggggtc ccagacaggt tcagtggcag tggatcaggg 1320
acagatttta cactcaagat cagcagagtg gaggctgagg gctttgtaac gatcaaa 1380
Asp  Ile  Gln  Met  Thr  Gln  Ser  Pro  Ser  Ser  Leu  Ser  Ala  Ser  Val  Gly  
   1                              5                              10                 15
Asp  Arg  Val  Thr  Ile  Thr  Cys  Arg  Ala  Ser  Gln  Ser  Val  Ser  Tyr  Met  
   20                             25                             30
Asn  Trp  Tyr  Gln  Gln  Lys  Pro  Gly  Lys  Ala  Pro  Lys  Arg  Trp  Ile  Tyr  
   35                             40                             45
Asp  Thr  Ser  Lys  Val  Ala  Ser  Gly  Val  Pro  Ala  Arg  Phe  Ser  Gly  Ser  
   50                             55                             60
Gly  Ser  Gly  Thr  Asp  Tyr  Ser  Leu  Thr  Ile  Asn  Ser  Leu  Glu  Ala  Glu  
   65                             70                             75                 80
Asp  Ala  Ala  Thr  Tyr  Tyr  Cys  Gln  Gln  Trp  Ser  Ser  Asn  Pro  Leu  Thr  
   85                             90                             95
Phe  Gly  Gly  Thr  Lys  Val  Glu  Ile  Lys  Gly  Glu  Gly  Thr  Ser  Thr  
  100                            105                            110
Gly  Ser  Gly  Ser  Gly  Ser  Gly  Ser  Gly  Ala  Asp  Asp  Val  Gln  Leu  
  115                            120                            125
Val  Gln  Ser  Gly  Ala  Glu  Val  Lys  Lys  Pro  Gly  Ala  Ser  Val  Lys  Val  
  130                            135                            140
Ser  Cys  Lys  Ala  Ser  Gly  Tyr  Thr  Phe  Thr  Arg  Tyr  Thr  Met  His  Trp  
  145                            150                            155                 160
Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn
           165                   170                   175

Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe
           180                   185                   190

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
           195                   200                   205

Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr
           210                   215                   220

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Val Thr
           225                   230                   235                   240

Val Ser Ser Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser
           245                   250                   255

Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys
           260                   265                   270

Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys Gln
           275                   280                   285

Arg Pro Gly Gin Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile
           290                   295                   300

Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
           305                   310                   315                   320

Ala Asp Lys Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu Thr
           325                   330                   335

Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr Asp
           340                   345                   350

Thr Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gin Gly Thr Thr Val

- 502 -
Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
370 375 380
355
360
365
Gly Gly Ser Glu Leu Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val
385 390 395 400
Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
405 410 415
Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro
420 425 430
Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser
435 440 445
430
425
420
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495
490
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465
455
450
440
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430
425
420
415
410
405
400
395
390
385
380
375
370
Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
450 455 460
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460
455
450
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430
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375
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284
1500
DNA
artificial sequence
<220>

<223> VH5/VL1x4-7 HLHL

<400>  284
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cctggacaggg ctcttggaatg gatgggtac attaactcata gcctgtggtta taataattac 180
gcagacagcg tcaagggcgg cttcacaatc actacagaca aatccaccag cacagcctac 240

ctgggaacctga gcagcttgcc ctcttgaggac actgcaacct attactgtgc aagatattat 300
gatgatcatt actgctttga ctacttgggg caagcaccg caagcaccg etctgttgcc 360
gagagtcagct gtagtgaggt ggaagttgac agggcaggca cgacaticag 420

tggacacagt etctactetac egctgtcaca ctcttcggg accgtgtaac catcacttcg 480

gagagcagt aaagtgaag ttacatgaac tggtaccagc agaagccggg caaggcacc 540

aaaagatgga tttatgacae atccaagatg getttcgggag tccccgtcctg etctgatg 600

agttcgggctg ggacccgacta etctctcaca atcaacagct tggagctcga agatgctgc 660

aacttctact gccacacgtg gagaagatca cgctctcagt tctttggcgg gaccaagatg 720

gagatcaaat cggagggctg tggatcgcag ttgagctctgac aagccagttg 780

cctggcaggg ctctgggttc aagttgagctg tctctgcagct ctctcgcagct caccttcaca 840

aactatggtt taagctggtg gaacagcagg cctggcagg tctctgagtg gatttgagag 900

gtttatcacta gaatggtgtaa tctgttcata aatgagagaat tcaagggcga gccacaacgt 960

actgcagaca aatctgcttc cacagctgcc agagataac gcagcttgcc ctcttgaggc 1020

- 504 -
tctgcggtct atttctgtgc aagacgggga tcctacgata ctaactacga ctggtacttc 1080
gatgtctggg gcacaagggac cacgtcacc gtctctccag gtggttgtgg ttctggcggc 1140
gccggtctcg gtgggtggtgg ttctgagctc gtgatgaccc agactccact ctcctgtcct 1200
gtcagtcttg gagatcaagc ctccatctct tgcagatcta gtcagacgct tgtacacagt 1260
aatggaaca cctatttaca ttggtaetg cagaagccag gccagtcetc aaagctcctg 1320
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gggacagatt tcacactcaag tacagcaga gttgaggctg aggtctgggg agtttaatttc 1440
tgcetctaaa gtacacatgt tccgtacacg ttcggagggg ggaccaagct tgagatcaaa 1500

<210> 285

<211> 500

<212> PRT

<213> artificial sequence

<220>

<223> VH5/VL1x4-7 HILIL

<400> 285

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1       5       10       15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20      25      30

- 505 -
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35  40  45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
50  55  60

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
65  70  75  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85  90  95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser Gly Gly Thr Ser Thr Gly Ser Gly
115 120 125

Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Gln Met Thr Gln Ser
130 135 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145 150 155 160

Arg Ala Ser Gin Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195 200 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210 215 220
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gin
245 250 255

Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys
260 265 270

Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys
275 280 285

Gln Arg Pro Gly Gln Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg
290 295 300

Ile Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu
305 310 315 320

Thr Ala Asp Lys Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu
325 330 335

Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr
340 345 350

Asp Thr Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr
355 360 365

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
370 375 380

Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr Pro Leu Ser Leu Pro
385 390 395 400

Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gin Ser
405 410 415

Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gin Lys
Pro Gly Gin Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe
420  425  430

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
435  440  445

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe
450  455  460

Cys Ser Gin Ser Thr His Val Pro Tyr Phe Gly Gly Gly Thr Lys
465  470  475  480

Leu Glu Ile Lys
485  490  495  500

<210> 286

<211> 1497

<212> DNA

<213> artificial sequence

<220>

<223> VL1/VH5x4-7 LILII

<400> 286
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aaggcaccca aaagatggat ttatgacaca tccaaagtgg cttctggagt ccctgctcgc 180
ttcagtgcca gttggtctgg gaccgactac tctctcacaa tcaacagctt ggaggctgaa 240
gatgcctgccca ttatatactg ccaacagtgg agttagtaacc cgtcaccgtt cggtaggcggg

accaaggctg agatacaaggg cgaaggtacct ctggtggaag tggaggttca

ggtggagcag acagcgttcca actgtggccag tcagggcttg aagtggaaaaa acctgggccc

tcagtgaagg tgtctgcaaa ggtttctgge tacacettta ctaggatcag cagtcatcgg

gtaaggcagg cactgggaca cggctggga aaggggtttg acattaatc ctagcctgtt

tatactaatt acgcagacag ctggcaaggg cgttccaca ctactacaga caaatccacc

agcagatcct acatcggact cagcgagcttg cgttctgagg acacgcacac ctatattgct

gcaagatact atgatgataca ttaatgtcct gactactggg gccaagcacc caggttcacc

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gtcgtagctct gagatcaacge ctctcctcct tgcagatcaga ctcagagctct ctcagctct

aatggaaaca cctatttaca tttctatttc gtcagagctct gtcagagctt ctgcaaggct

tctggctaca ccttcacaaa ctatggatct ttcgggggtt gatacaagtc aagggcaagg

ggcagatctt tcccacaactg gatcagcaca gggcagagct cggtagctgg agtttatttc

tgctctcaaa gtaacctgact tgtacagctg cggcagctcc ggtcaggctc gtagatcagc
<210> 287

<211> 499

<212> PRT

<213> artificial sequence

<220>

<223> VL1/VH5x4-7 LHHL

<400> 287

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ser Tyr Met
20                  25                  30

Asn Trp Tyr Gin Gin Lys Pro Gly Lys Ala Pro Lys Arg Thr Ile Tyr
35                  40                  45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50                  55                  60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gin Gin Trp Ser Ser Asn Pro Leu Thr
85                  90                  95

Phe Gly Gly Gin Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr
Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp

Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Ile Gly Tyr Ile Asn

Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser

Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Cys Ala Arg Tyr Tyr

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Val Thr

Val Ser Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr Pro

Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg

Ser Ser Gln Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp

Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val
Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
305 310 315 320
Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu
325 330 335
Gly Val Tyr Phe Cys Ser Gln Ser Thr His Val Pro Tyr Thr Phe Gly
340 345 350
Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly
355 360 365
Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser Gly
370 375 380
Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala
385 390 395 400
Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys Gln Arg
405 410 415
Pro Gly Gln Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile Gly
420 425 430
Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala
435 440 445
Asp Lys Ser Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu Thr Ser
450 455 460
Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr Asp Thr
465 470 475 480
Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr Val Thr
485 490 495
Val Ser Ser

<210>  288
<211>  1500
<212>  DNA
<213>  artificial sequence

<220>
<223> VH5/VLx4-7 HLLH

<400>  288
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cctggacagg gtcctgaatg gattggatac attaatccta gccgtggtta tactaattac 180
gcagacacgc tcaagggcgg ctccacacte actacagaca aatccaccag cacagcctac 240
atggaactga gcagcctgcg ttctgaggac actgcaacct attactgtgc aagatattat 300
gatgatcatt actgccttga ctctgggggc caaggcaccc cggtcaccgt ctccttcaggc 360
gaggtacta gtcttggttc tggtaagaat ggaagtttccag gtggagcaga cgacattcag 420
atgacccagt ctccatcctag cctgtctgca tctgtcgggg accgtgtcac catcacctgc 480
agagccagtc aaagtgtaag ttacatgaac tggtaccagc agaagccggg caaggcaccc 540
aaaagatgga tttatgcac atccnaagtg gctcttgag tcctgtgcg cttcagtgcc 600
agtgggtctg ggaccgacta ctctctcaca atcaacagct tggaggctga agatgctgcc
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agatcaaat ccggaggtgg tggatccgag ctcgtgatga cccagactcc actctccctg
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agtaatggaa acacetaatt acatgtgtac ctgcagaagc caggccagtc tccaaagctc
tgatctaca aagtttccaa ccgattttct ggggtcccag acaggttcag tggcagtgga
tcagggacag atttcacact caagatcagc agagtgaggag ctgaggatct ggggttat

ttetgetetc aaagtaacaca tgttccgtac acgttcggag gggggcacaag acctgagct
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tctgtgact ctggagcgtag cggagcagg cggccgacaag gggggtgcag tggccagtg
ctggagctga gctggcgagg cctggggctt cagtgaagct gtcctgcaag
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<210> 289

<211> 500

<212> PRT

<213> artificial sequence
VH5/VLx4-7 HLLH

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Thr Met His Trp Val Arg Glu Ala Pro Gly Gln Gly Leu Glu Trp Ile
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
Thr Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
Gly Ser Gly Ser Gly Ser Gly Ala Asp Ile Gln Met Thr Gln Ser
Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
Arg Ala Ser Gin Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195 200 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Cys
210 215 220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ser Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr
245 250 255

Pro Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys
260 265 270

Arg Ser Ser Gin Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His
275 280 285

Trp Tyr Leu Gin Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys
290 295 300

Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
305 310 315 320

Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp
325 330 335

Leu Gly Val Tyr Phe Cys Ser Gin Ser Thr His Val Pro Tyr Thr Phe
340 345 350

Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly

- 516 -
Gly Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser

Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys

Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys Gln

Arg Pro Gly Gln Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile

Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr

Ala Asp Lys Ser Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu Thr

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<211>  1497

<212>  DNA

<213> artificial sequence
<220>

<223> VL2/VH5x4-7 LIHL

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180
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240
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300
accaagggcggatcaaaaggggggtcaggaact cgtactggtt tetteccggag tggagggta
360
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420
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480
gtaagccag cactggaca ggtctctgaaa tggatttgggt tctggcagac gagaataactg
540
tatatagat acgccagcacag caaagggggtt ctcctacagtc caaacctcacc
600
agccagcctt atcaagtgaagact gagcagccgt cggcgggtcactgcagagac atgcaaccc
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720
gctctctgagc gggagccgaggtcctgtggtct cctctctgtgg tggcagggtc cttgttggc
780
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<210> 291
<211> 499
<212> PRT
<213> artificial sequence

<220>
<223> VL2/VH5x4-7 LHHL

<400> 291

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Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Met
20  25  30

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
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Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr
Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu
Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val
Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp
Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ille Gly Tyr 1le Asn
Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe
Thr Ille Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr
Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
Val Ser Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser
Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys
Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys Gln
Arg Pro Gly Gln Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile
Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
Ala Asp Lys Ser Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu Thr
Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr Asp
Thr Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr Val
Gly Gly Ser Glu Leu Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val
Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro
Gly  Gln  Ser  Pro  Lys  Leu  Leu  Ile  Tyr  Lys  Val  Ser  Asn  Arg  Phe  Ser
435  440  445

Gly  Val  Pro  Asp  Arg  Phe  Ser  Gly  Ser  Gly  Ser  Gly  Thr  Asp  Phe  Thr
450  455  460

Leu  Lys  Ile  Ser  Arg  Val  Glu  Ala  Glu  Asp  Leu  Gly  Val  Tyr  Phe  Cys
465  470  475  480

Ser  Gln  Ser  Thr  His  Val  Pro  Tyr  Thr  Phe  Gly  Gly  Gly  Thr  Lys  Leu
485  490  495

Glu  Ile  Lys

<210>  292

<211>  1497

<212>  DNA

<213>  artificial sequence

<220>

<223>  VL2/VH5x4-7 LILII

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aaggcaccca  aaagatggat  ttatgacaca  tccaaagtgg  cttctggagt  ccctgctcgc 180
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tcgtgagaag tgtcctgcaa ggtctggaag tggaggttca tggatggtt gctggggtt 480
gtaaggcagg cacctgacac ggtctggaag tggatggtt gctggggtt 540
tatactatac acgcagcagc cgttcagtt cgttcagtt cgttcagtt 600
agcagcagc cgttcagtt cgttcagtt cgttcagtt cgttcagtt 660
tatactatac acgcagcagc cgttcagtt cgttcagtt cgttcagtt 720
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gtcctcg gaaagttggtc acgcagcagc cgttcagtt cgttcagtt 840
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<210>  293

<211>  499

<212>  PRT

<213>  artificial sequence

<220>

<223>  VL2/VH5x4-7 LILIL

<400>  293

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20                  25                  30

Asn Trp Tyr Gin Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp 1le Tyr
35                  40                  45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50                  55                  60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr 1le Asn Ser Leu Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
85                  90                  95

Phe Gly Gly Gly Thr Lys Val Glu 1le Lys Gly Glu Gly Thr Ser Thr
Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu
100 105 110

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val
115 120 125

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn
130 135 140

Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe
145 150 155 160

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
165 170 175

Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Cys Ala Arg Tyr Tyr
180 185 190

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Val Thr
195 200 205

Val Ser Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr Pro
210 215 220

Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg
225 230 235 240

Ser Ser Gln Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp
245 250 255

Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val
260 265 270
Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
305 310 315 320

Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu
325 330 335

Gly Val Tyr Phe Cys Ser Gln Ser Thr His Val Pro Tyr Thr Phe Gly
340 345 350

Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly
355 360 365

Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser Gly
370 375 380

Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala
385 390 395 400

Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys Gln Arg
405 410 415

Pro Gly Gln Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile Gly
420 425 430

Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala
435 440 445

Asp Lys Ser Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu Thr Ser
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Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr Asp Thr
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Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr Val Thr
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<210> 294

<211> 1497

<212> DNA

<213> artificial sequence

<220>

<223> VL3VH5x4-7 LHHL

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aaggcaccca aaagatggat ttatgacaca tccaaagttg ettetggaat ccttctegc 180
rtcagttgca gtgggtettgg gacccaactae tetctacaa aaccaaggtt ggaggtgaa 240
gatgetgcca eettattactg ecaacagtgg agtagtatacc cgetcaagtct eggtggeggg 300
accaagttgg agaataaaag cgaagttact agtactgttt etggttgaag tggagttcag 360
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gtaagggcg caagtggacat ggtctggaa tggattggat acattaatcc tagccgtggt 540
tataactatt acgccacagc egtenagggc egtttacaaa tcactacaga caaatccacc 600
agcacagcct acatggaact gacgagcctg cgttctgagg acactgcaac ctattactgt
660
gcaagatatt atgalatca ttactgcttt gactaetggg gccaaggcac cacaagtgcc 720
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780
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840	
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900
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1260
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1320	
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1380
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1497

<210>  295

<211>  499

<212> PRT

<213> artificial sequence
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295

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Glu Arg Ala Thr Leu Thr Cys Arg Ala Ser Ser Val Ser Tyr Met
20  25  30

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
35  40  45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50  55  60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
65  70  75  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
85  90  95

Phe Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr
100 105 110

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ala Asp Asp Val Glu Leu
115 120 125

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val
130 135 140

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp
145 150 155 160
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Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn
165                 170                 175

Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe
180                 185                 190

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
195                 200                 205

Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr
210                 215                 220

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Val Thr
225                 230                 235                 240

Val Ser Ser Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser
245                 250                 255

Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys
260                 265                 270

Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys Glu
275                 280                 285

Arg Pro Gly Gin Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile
290                 295                 300

Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
305                 310                 315                 320

Ala Asp Lys Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu Thr
325                 330                 335

Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr Asp
340                 345                 350

Thr Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr Val
- 530 -
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370                 375                 380
355                 360                 365
Gly Gly Ser Glu Leu Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val
385                 390                 395                 400
Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
405                 410                 415
Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro
420                 425                 430
Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser
435                 440                 445
Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
450                 455                 460
Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
465                 470                 475                 480
Ser Gln Ser Thr His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu
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Glu Ile Lys

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<211> 1503

<212> DNA

<213> artificial sequence
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<223> VH5VL3x4-7 HLHL

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cctggacagg gttctgaatg gattggatac alttactca gecggtgtta tataaattac 180
gcagacagcg tcaaggcccg tttcacaact actacagaca aatccacccag cacagcatc 240
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gatgatcatct actgcttcca ctacttgggg ccagccacca cggtcacccgt ctctcaggc 360
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1200
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1260
aatgaaacca ctatttaca ttggtacttg cagaagccag ggcagctcct aaagctcctg
1320
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1380
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1500
cat
1503

<210> 297

<211> 500

<212> PRT

<213> artificial sequence

<220>

<223> VH5VL3x4-7 HLHL

<400> 297

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr

- 533 -
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly

Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys

Arg Ala Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
Glu Ile Lys Ser Gly Gly Gly Ser Gly Val Gln Leu Leu Gly Gln
Ser Gly Ala Gly Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys
Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys
Gln Arg Pro Gly Gin Val Leu Glu Trp Ile Gly Gln Val Tyr Pro Arg
Ile Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu
Thr Ala Asp Lys Ser Ser Ser Thr Ala Ser Met Gin Leu Arg Ser Leu
Thr Ser Gln Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr
Asp Thr Asn Tyr Asp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
Gly Gly Gly Ser Gin Leu Val Met Thr Gin Thr Pro Leu Ser Leu Pro
Val Ser Leu Gln Asp Gin Ala Ser Ile Ser Cys Arg Ser Ser Gin Ser
Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys
420                 425                 430
Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe
435                 440                 445
Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
450                 455                 460
Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe
465                 470                 475                 480
Cys Ser Gln Ser Thr His Val Pro Tyr Lys Thr Phe Gly Gly Gly Thr Lys
485                 490                 495

Leu Glu Ile Lys
500

<210> 298

<211> 1497

<212> DNA

<213> artificial sequence

<220>

<223> VL3VH5x4-7 LHLH

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<213> artificial sequence

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Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr
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Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu
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Ser Cys Lys Ala Ser Gly Thr Phe Thr Arg Tyr Thr Met His Trp
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Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe
180 185 190

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
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Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr
210 215 220

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
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Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg
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- 539 -
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Gly Val Tyr Phe Cys Ser Gln Ser Thr His Val Pro Tyr Thr Phe Gly

Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly

Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser Gly

Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala

Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys Gln Arg

Pro Gly Gln Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile Gly

Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala

Asp Lys Ser Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu Thr Ser

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<210>  301

<211>  500

<212> PRT
artificial sequence

VH5VL3x4-7 HILIH

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Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly

Thr Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly

Gly Ser Gly Ser Gly Gly Ala Asp Ile Val Leu Thr Gln Ser
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Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
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Arg Pro Gly Gin Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile

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Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr

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Ala Asp Lys Ser Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu Thr

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Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr Asp

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artificial sequence

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<210> 303

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<212> PRT

<213> artificial sequence

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<223> VL1VH7x4-7 LHHL

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Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser

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Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr

Phe Gly Gly Gly Thr Val Glu Ile Lys Gly Glu Gly Thr Ser Thr

Gly Ser Gly Ser Gly Gly Ser Gly Ser Gly Ala Asp Asp Val Gln Leu

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn

Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val

Thr Ile Thr Thr Asp Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser

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Glu Ile Lys

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<211> 1500

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<213> artificial sequence

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<211>  500

<212> PRT

<213> artificial sequence

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<400>  305

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Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe 50                  55                  60

Lys Asp Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr 65                  70                  75                  80

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Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
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Glu Ile Lys Ser Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln
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Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr

Asp Thr Asn Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr Pro Leu Ser Leu Pro

Val Ser Leu Gly Asp Gin Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser

Leu Val His Ser Asn Gin Thr Tyr Leu His Trp Tyr Leu Gln Lys

Pro Gly Gin Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe

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<210> 306

<211> 1497

<212> DNA

<213> artificial sequence

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<223> VL1-VH7x4-7 LHLH

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Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr

Val Ser Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr Pro

Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg

Ser Ser Gln Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp

Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val

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Gly Val Tyr Phe Cys Ser Gln Ser Thr His Val Pro Tyr Thr Phe Gly
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr

-561-
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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
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Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
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Glu Ile Lys Ser Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr
Pro Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys
Arg Ser Ser Gln Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His
Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys
Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp
Leu Gly Val Tyr Phe Cys Ser Gln Ser Thr His Val Pro Tyr Thr Phe
Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly
Gly Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser
Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys
Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys Gin

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450 455 460
Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr Asp
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<211> 1497
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35                  40                  45

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Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp
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Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn
165 170 175

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Ser Leu Gly Asp Gin Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro
Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser
Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
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Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile 35 40 45
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe 50 55 60
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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

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Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly

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Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser

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Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys

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Arg Ala Ser Gin Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro

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Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser

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Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser

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Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys

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Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val

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Glu Ile Lys Ser Gly Gly Gly Gly Ser Leu Val Met Thr Gln Thr

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Pro Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys

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Arg Ser Ser Gin Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His
Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys
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305 310 315 320

Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp
325 330 335

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370 375 380

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385 390 395 400

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405 410 415

Arg Pro Gly Gln Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile
420 425 430

Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
435 440 445

Ala Asp Lys Ser Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu Thr
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| Asp | Ile | Val | Leu | Thr | Gln | Ser | Pro | Ala | Thr | Leu | Ser | Leu | Ser | Pro | Gly |   1 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Glu | Arg | Ala | Thr | Leu | Thr | Cys | Arg | Ala | Ser | Ser | Ser | Val | Ser | Tyr | Met |   20|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Asn | Trp | Tyr | Gin | Gin | Lys | Pro | Gly | Lys | Ala | Pro | Lys | Arg | Trp | Ile | Tyr |   35|     |     |     |     |     |     |     |     |     |     |     |     |     |     |
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Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr
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Ala Ser Gly Tyr Thr Phe Thr Tyr Gly Leu Ser Trp Val Lys Gin
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Arg Pro Gly Gin Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile
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Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
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Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
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Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
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Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
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Glu Ile Lys Ser Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln
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Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys
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Lys Ala Ser Gly Tyr Thr Thr Asn Tyr Gly Leu Ser Trp Val Lys
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<211>  499

<212>  PRT

<213>  artificial sequence

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<223>  VL3VH7x4-7 LILJH

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| His | Val | Pro |
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| Ser | Thr | Ala |

| 540 | 545 | 550 |
| Glu | Asp | Ser |
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| Ala | Val | Tyr |
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Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys

Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Leu Ser Trp Val Lys Gln

Arg Pro Gly Gin Val Leu Glu Trp Ile Gly Glu Val Tyr Pro Arg Ile

Gly Asn Ala Tyr Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr

Ala Asp Lys Ser Ser Ser Thr Ala Ser Met Glu Leu Arg Ser Leu Thr

Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Gly Ser Tyr Asp

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Thr Val Ser Ser
DNA

artificial sequence

VL1VH5xCD19 LHHL

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Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp
Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn
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Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly  
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Asn Ile His Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gin  
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Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu  
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Ile Lys

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<211> 1497

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90
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Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
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265
270

Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gin
- 609 -
Arg Pro Gly Gin Gly Leu Glu Trp Ile Gly Gin Ile Trp Pro Gly Asp

Gly Asp Thr Asn Tyr Asn Gin Lys Phe Lys Gin Gin Lys Gin Gin Gly Gin Gin Lys Gin Gin Thr Gin Thr

Ala Gin Gin Ser Gin Ser Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin

Ser Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin

Val Gin Arg Tyr Tyr Tyr Ala Met Gin Asp Tyr Trp Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin

Val Thr Val Ser Ser Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin

Gly Gin Gin Gin Ser Gin Ile Gin Gin Thr Gin Gin Ser Pro Ala Ser Gin Lea

Val Ser Leu Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin

Val Gin Gin Gin Gib Gin Gin Gib Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin

Gly Gin Pro Pro Lys Leu Leu Ile Tyr Gin Gin Gin Gin Gin Gin Ile Pro

Gly Ile Pro Pro Arg Phe Ser Gin Ser Gin Ser Gin Thr Asp Phe Thr

Leu Gin Ile Gin His Pro Val Gin Gin Lys Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin
Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu

Glu Ile Lys

<210> 330
<211> 1494
<212> DNA
<213> artificial sequence

<220>
<223> VL1VH5xCD19 LHLH

<400> 330
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aaggcaccca aaagatggat ttatgacaca tccaaagtgg cctcttgagtt cccctctgac
240
ttcagtggca gtgggtcttg gaccgaact accttcacaa tcaacagtt ggagctgaa
gatgtggcca cttaccagtc gaagaagttg agtaaagtttt ggtggcaggag ccgggggtcc
420
tcagtgaagg tgtcctgcaa ggcttctggc tacaccttta ctaggtacac gatgcactgg
gtaaggcagg cacctggaca gggtctggaa tggattggat acattaatcc tagccgtggt
540
d등록특허 10-1229731
등록특허 10-1229731

tatactaat acgcaagacg cgctcaaggg gegecacaac ttaactacaga caaatccacc 600
agcagacgct acatggaact gacgagcttg gttctctagg acactgcaac ctattactgt 660
gcaagatatt atgatgatca ttaactacgtg gactactggg gccaaggcac caagtcacc 720
gtcctcctgg ggggtctctgg atccgatatc cagctgacce agtctctcgc ttcttggtct 780
gtctcttag gcagagggge cccatctcgc tgcgaaggcc gccaagctgt tgattatgat 840
ggtgatgtt atttgaaact gcacccgacg acctccggac gccaacccaa actctcactc 900
tatgtatcct ccaattctgt tttctgggac ccacccaggt ttaagctgag tgggtctggg 960
acagacacac ccctcacaat ccactctgtg gagaaagttg atgetgcaac ctatactgt 1020
cagcaagta ctgaagacgc gtggagcttc ggggagggga ccaactcaca gataaaggt 1080
gttgtggtt ctgtctgccg gggcacaggt gttgtggtt ctcaggtgca ggtgacagcag 1140
tctgggcttg agctggtggag gcttggttt ctcaggtgca ggtgacagcag 1200
tatggtacaa gtagctactg gatgaactgg gtgaagcaga ggcctggaca gggtcttgag 1260
tggattggaa cgactgacacg caaatctcgc acacagacct acatgcact cagcagcctc 1320
aagcactc tggataacag gcacccgacg actctcgcgc ggaagctggg atggctgcag 1380
gcagagggct actctcggtt ctagcttggt gcaagacggc agacctacag ggtctgcggt 1440
tatggtactg ctatggacta ctgagccgca gggaccaagg tcaacttcct cccc 1494

<210> 331

<211> 498

<212> PRT

- 612 -
<213> artificial sequence

<220>

<223> VL1VH5xCD19 LHLH

<400> 331

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Tyr Met  
20                  25                  30

Asn Trp Tyr Gin Gin Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr  
35                  40                  45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser  
50                  55                  60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu  
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gin Gin Trp Ser Ser Asn Pro Leu Thr  
85                  90                  95

Phe Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr  
100                 105                 110

Gly Ser Gly Ser Gly Gly Ser Gly Ala Asp Asp Val Gln Leu  
115                 120                 125

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val  
130                 135                 140
Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp  
145 150 155 160

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn  
165 170 175

Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe  
180 185 190

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser  
195 200 205

Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr  
210 215 220

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr  
225 230 235 240

Val Ser Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro  
245 250 255

Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys  
260 265 270

Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp Tyr  
275 280 285

Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser  
290 295 300

Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly  
305 310 315 320

Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala  
325 330 335

- 614 -
Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly
340 345 350

Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly
355 360 365

Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
370 375 380

Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
385 390 395 400

Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
405 410 415

Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr
420 425 430

Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu
435 440 445

Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp
450 455 460

Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Val Gly Arg
465 470 475 480

Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val
485 490 495

Ser Ser

<210> 332

<211> 1497
DNA

artificial sequence

VH5VL1xCD19 HLLH

332
gacgtccaac tggtgcagtc aggggctgaa gtgaaaaaac ctggggcctc agtgaaggtg  60
tcctgcaagg cttctggcta cacctttact aggtacacga tgcactgggt aaggcaggca 120
cctggacagg gtctggaatg gatgggatac attaattccta gecgtggtta tactaattac 180
gcagacagcg tcaagggccg cttcacaatc actacagaca aatccaccag cacagcctac 240
atggaaatga gcagcctgcg ttctgaggac actgcaacct attaattgge aagatattat 300
gatgtcatl actgccttgta etctttgggg caagccacca cgttacgctg ctcetcaggc 360
gaaggtacta gtactgttct ttggtggaaa ggaggttcag gtggagcaga cgacatccag 420
atgacgccgt ctcactctag cctgtgctca cttctggggg acctggttcac catcacctgc 480
agagccagc tcaaatgtaa ttctacgaaac ttggtaccag tcagcatccg caaagccccc 540
aaaagatgga tttatgcaac atcccaagtg ctctctggag tccctgctcg cttcagtggc 600
agtagcttc gacctggact ctctctccag atccacagct tggacgtaga agagctgccc 660
actattattc gcacaactgt gcgttagaaac ctctctcagt ttgggtgggg gaccaaggtg 720
gatgtcttc tagggctag gcacactaca ctctctggag tccatcagtt gttggattat 780
gacgatcagc ttgatcgcgg tggatggatt atccatcagtc cggagcaggc caagccaaaag 840
ctttttttcg ccggaggtgg tggatggatt atccatcagtc cggagcaggc caagccaaaag 900
atctatgaag cactcaaatct agttttctggg atcccacccga gtttagtgg cagttgggct
960
ggacagact tcacccctca acactcactct gtggagaagg tggatgctgc cagttgtcag
1020
tgtcagcaaa gtactgaggag tcgctggagc cggccctgct gcaggctgc cctcctgct
1080
ggatgtgttg cttctgccgg cgccgctctg cttccggcttg ttctctggt gcagctgcag
1140
cagcttgccg cttgctgctgc gagccctggg tctctcgatg agagtttctgc caagttgtc
1200
gcatagcact tccatagacag caggtggagt cggatgcacgg cagctgcag ccgctgctgc
1260
ggatgtgttg gacagatttg gcctgagatgt ggtgataacta actacacttg gaagtttcag
1320
gtagttttgc atctgactgc ggtctatttc tgtgcaagac gggagactac gacggtaggc
1380
tactagcgagactgcctggatttctgctgagcttttc gggagactac gacggtaggc
1440
cgtattctg atctgagct gctactgagct gctactgagct gctactgagct gctactgagct
1497

<210> 333

<211> 499

<212> PRT

<213> artificial sequence

<220>

<223> VH5VL1xCD19 HLLH

<400> 333

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1  5  10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly

Gly Ser Gly Ser Gly Ser Gly Ala Asp Ile Gln Met Thr Gln Ser

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys

Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ser Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser
245 250 255

Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys
260 265 270

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Ser Ser Tyr Leu Asn Trp
275 280 285

Tyr Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Ile Tyr Asp Ala
290 295 300

Ser Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser
305 310 315 320

Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala
325 330 335

Ala Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly
340 345 350

Gly Gly Thr Lys Leu Gln Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly
355 360 365

Gly Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala
370 375 380

Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser
385 390 395 400

Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro
405 410 415

등록특허 10-1229731

- 619 -
Gly Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp 420 425 430

Thr Asn Tyr Asn Gly Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp 435 440 445

Glu Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu 450 455 460

Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Val Gly 465 470 475 480

Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr 485 490 495

Val Ser Ser

<210> 334

<211> 1494

<212> DNA

<213> artificial sequence

<220>

<223> VL2/VH5xCD19 LHHL

<400> 334
gacctgtac tgcccttc tccagcaacct ctgtctctgt ctccagggga gcgtgccacc gtagctgga ggctctctct 60
gtagctgga gagccggtc aagttaagt tacatgaaact ggtaccgca gaagccgggc 120

- 620 -
aaggcaccca aaagatggat ttatgacaca tccaaagtgg cttctggagt ccctgctcgc
 180
ttcagtggca gttgggtctgg gaccgactac tctctcacaa tcaacagctt ggaggctgaa
 240
gatgtgcca ctattactgt ccaacagtgg agtagtaacc cgctcaagtt cgttgccgg
 300
accaaggtgg agataaagg cgaaggtact agtactggtt ctggtggaag tggaggttca
 360
agtcagcagc tgcctgcaa ggccttggag catctgacgg cagctcagag tggacagtgg
 420
tcagtaagg tgcctgcaa ggccttggag catctgacgg cagctcagag tggacagtgg
 480
glaaagccag cacttggaca ggccttggag catctgacgg cagctcagag tggacagtgg
 540
tatactaaatt acgcagacag cgcctgacgg cagctcagag tggacagtgg cagctcagag
 600
agcacagect acatggaact gacgagcctg egttctgagg acactgcaac atattattg
 660
gcaagataatt atgatgatca tcacagcttt ggccttggag tggacagtgg cagctcagag
 720
gtctctcgt ggtggtcttg actcctcctgg agatgatgg cgggctggtt cgcctgacgg
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 840
tgtgataagg tggcttcttg cgctcagctt gcacggagct gtcctgagct tcggcttcta
 900
gactgttctc gcctgctgcag ggtgcttctg cgcctgacgg cgcctgacgg cgcctgacgg
 960
gagggacgcc aagggacgcc aagggacgcc aagggacgcc aagggacgcc aagggacgcc
1020
gtctctcct cgctctctcg ccctcctcct ccctcctcct ccctcctcct ccctcctcct
1080
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1260
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gatgcateca atctagt ttc tggatccca cccagttta gtcgatgg gg tctgggaca 1380

gacttcaccc tcaacatcca tcctgtggag aaggtggatg ctgcaaccta tcactgtcag 1440
caaagtactg agagtcggtg gacgttgggt ggagggacca agctcgagat caaa 1494

<210> 335

<211> 498

<212> PRT

<213> artificial sequence

<220>

<223> VL2/VH5xCD19 LHHL

<400> 335

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly 1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Met 20                  25                  30

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr 35                  40                  45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser 50                  55                  60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu 65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr  
85          90          95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr  
100         105         110

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ala Asp Asp Val Gln Leu  
115         120         125

Val Glu Ser Gly Ala Glu Val Lys Pro Gly Ala Ser Val Lys Val  
130         135         140

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp  
145         150         155         160

Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Ile Gly Tyr Ile Asn  
165         170         175

Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe  
180         185         190

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser  
195         200         205

Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr  
210         215         220

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Glu Gly Thr THR Val Thr  
225         230         235         240

Val Ser Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly  
245         250         255

Ala Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala  
260         265         270

Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Glu Arg  
- 623 -
Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly

Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala

Asp Glu Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser

Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr Val

Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly

Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser Leu Ala Val

Ser Leu Gly Gin Arg Ala Thr Ile Ser Cys Lys Ala Ser Gin Ser Val

Asp Tyr Asp Gly Asp Tyr Leu Asn Trp Tyr Gin Gin Ile Pro Gly

Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly

Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu

Asn Ile His Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gin
Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly Thr Lys Leu Glu
485 490 495

Ile Lys

<210> 336
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tctgcaagg ctcttgctca cacctttact aggtacacgt gcctaggtgt aaggcagcca
120
cctggacagg gtctggagtg gatttggata attaatctct acgctaggtg taactattac
180
gcagacacgg tcaagggcgg ctctacaatc actacagaca aatccaccaag cacagccctc
240
atggaactga gcagcctgcg ttctgaggac actgcaacct attactgtgc aagatattat
300
gatgatcatt actgccttga ctctggggc caaggcacca cggtcaccgt ctcctcaggc
360
gagagccagtc aaagtgtaag ttacatgaac tggtaccagc agaagccggg caaggcacc
420
agagccagtc aaagtgtaag ttacatgaac tggtaccagc agaagccggg caaggcacc
aaagaagagga ttataagcag atccaaagtt gtcttggag tccctgctcg ettcagtgcc
agttggcttg ggacccgaet ataatacaat atcaacacgt tggaggctga agatgtgc
acattatact gcccaacagt gaggtaaag ccgcttctgc tggaggcctg acaggtgtgc
gatgggtctg ggaccgacta ctctctcaca atcaacagct tggaggctga agatgctg
agtgggtctg ggaccgacta ctctctcaca atcaacagct tggaggctga agatgctg
acttattact gccaacagtg gagtagtaac ccgctcagct tcggtggcgg gaccaaggtg
gagatcaaat ccggaggtgg tggatcccag gtgcagcgtg agcagtctgg ggctgagctg
gttgaggctg ggtcctcagt gaagatttcc tgcaaggctt ctgctcattg attcagtgac
tactggatga acitggtgaa gcagagacct ggacagggct ttcagcagt tggacagatt
tggcctagg atgtgtgatac taactacaat ggaaagttca aggttaaagc cactctgacg
gacagaagat cctccagcac agcttaccatg caactcagca gcttgacata tcgagactct
gcggttatt tgttgtgcaag acgggagaat acgacgcttag gcggattttat ctagcttag
gactctggtc gcccaagggac caagtctcag gttctctcag gttgtggtgg ttcctggg
gccgctccgg gttgtggtgg gttctctcag cactctcag gttctgtgctt cactctgct
gttcctctag gcagagggg gcaccatctcc tgcaaggcca gccaaagtgt tgattatgat
ggtgatagtt atttgaactg gtaccaacag attccaggac acgcacccaa acatctcactc
ttagcatc ccaatctagt ttctgggatc ccacccaggt ttactggcag tggctctggg
acagacttca cctccacagt ccatctcttg gagaagttgg atgttgcaac ctatcactgt
cagcaagatg tatgagcttc gttggagggc ccaagctcga gatcaaa

<210> 337

<211> 499

<212> PRT
artificial sequence

VH5VL2xCD19 iliHil

337

Asp Val Gln Leu Val Gln Ser Gly Ala Gln Val Lys Lys Pro Gly Ala
1  5  10  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20  25  30

Thr Met His Trp Val Arg Gln Ala Pro Gly Glu Gln Gly Leu Glu Trp Ile
35  40  45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
50  55  60

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
65  70  75  80

Met Glu Leu Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85  90  95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
115 120 125

Gly Ser Gly Ser Gly Gly Ala Asp Ile Val Leu Thr Gln Ser
130 135 140
Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145 150 155 160

Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195 200 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser
245 250 255

Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys
260 265 270

Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln
275 280 285

Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp
290 295 300

Gly Asp Thr Asn Tyr Asn Gln Phe Lys Gly Lys Ala Thr Leu Thr
305 310 315 320

Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala
325 330 335
Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr
340                 345                 350

Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
355                 360                 365

Val Thr Val Ser Ser Gly Gly Gly Gly Gly Gly Gly Ser Gly Thr Thr
370                 375                 380

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser Leu Ala
385                 390                 395                 400

Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser
405                 410                 415

Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro
420                 425                 430

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser
435                 440                 445

Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
450                 455                 460

Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys
465                 470                 475                 480

Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
485                 490                 495

Glu Ile Lys

<210> 338

<211> 1494
DNA

artificial sequence

VL2/VH5xCD19

338

gacattgtac tgacccagtc tccagcaact cttctctctgt ctccagggga gcgtgccacc 60
ctgagctgca gacccagtca aagtgtaaag ttaatcatca ggtaccagca gaaggcgacc 120
aaagcaccac aaagatggat ttatgacaca tccaaagttg cttctggagt ccctgctcgc 180
ttcagttgca gttgtttcgg gaccgactac tctctcacaa tcaacagtt ggagctgaa 240
gatgtgcgca cttattaact ggcaacagtgg acagtaattc cgetcagtt cgtggtgcggg 300
accaaggtgg gACKAAAGGG ATAGATAGTC GGTGGCAGTG CCAGTTGGGA 360
accaagggg cgacgtcagc actcctgagag tggggctgag ggctggctgct gctggctggg 420
tcagttgaaag ttcctgaaag agtacacctt ttaggtctcc gatactgtcc gatactgtcc 480
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Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1  5  10  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Met
Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr

Phe Gly Gly Gly Thr Val Glu Ile Lys Gly Glu Gly Thr Ser Thr

Gly Ser Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn

Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe

Thr Ile Thr Thr Asp Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser

Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr
Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
Val Ser Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro
Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys
Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp Tyr
Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser
Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly
Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala
Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly
Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly
Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly

등록특허 10-1229731
Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr
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Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu
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Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp
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Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gin Gly Thr Thr Val Thr Val
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<211>  1497

<212> DNA

<213> artificial sequence

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<223> VH5VL2xCD19 HLLH

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<210> 341

<211> 499

<212> PRT

<213> artificial sequence

<220>

<223> VH5VL2xCD19 IIIII

<400> 341

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Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile 35          40                    45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val 50          55          60

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr 65          70          75          80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85                  90                  95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
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Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
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Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser
130                 135                 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Arg Ala Ser Gin Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165                 170                 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180                 185                 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195                 200                 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210                 215                 220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225                 230                 235                 240

Glu Ile Lys Ser Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser
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Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys
260                 265                 270

Lys Ala Ser Gin Ser Val Asp Tyr Asp Gly Ser Tyr Leu Asn Trp
Tyr Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala

Ser Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser

Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala

Ala Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly

Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly

Gly Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala

Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser

Gly Tyr Ala Phe Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro

Gly Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp

Thr Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp

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<211> 1494
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<212> DNA

<213> artificial sequence
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<220>

<223>  VL3VH5xCD19 LHHL

<400>  343

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Asn Trp Tyr Gin Gin Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr 35                  40                  45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser 50                  55                  60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu 65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gin Gin Trp Ser Ser Asn Pro Leu Thr 85                  90                  95

Phe Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr 100                 105                 110

Gly Ser Gly Gin Ser Gly Ser Gly Gly Ala Asp Asp Val Gln Leu 115                 120                 125

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val 130                 135                 140

등록특허 10-1229731
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Val  Arg  Gln  Ala  Pro  Gly  Glu  Glu  Leu  Glu  Trp  Ile  Gly  Tyr  Ile  Asn
165  170  175

Pro  Ser  Arg  Gly  Tyr  Thr  Asn  Tyr  Ala  Asp  Ser  Val  Lys  Gly  Arg  Phe
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Thr  Ile  Thr  Thr  Asp  Ser  Thr  Ser  Thr  Ala  Tyr  Met  Glu  Leu  Ser
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Ser  Leu  Arg  Ser  Glu  Asp  Thr  Ala  Thr  Tyr  Tyr  Cys  Ala  Arg  Tyr  Tyr
210  215  220

Asp  Asp  His  Tyr  Cys  Leu  Asp  Tyr  Trp  Gly  Gln  Gly  Thr  Thr  Val  Thr
225  230  235  240

Val  Ser  Ser  Gly  Gly  Gly  Gly  Ser  Gln  Val  Gln  Glu  Leu  Gln  Gln  Ser  Gly
245  250  255

 Ala  Glu  Leu  Val  Arg  Pro  Gly  Ser  Ser  Val  Lys  Ile  Ser  Cys  Lys  Ala
260  265  270

Ser  Gly  Tyr  Ala  Phe  Ser  Ser  Tyr  Trp  Met  Asn  Trp  Val  Lys  Gln  Arg
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Gly Arg Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val
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Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly
  370     375     380

Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser Leu Ala Val
  385     390     395     400

Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val
  405     410     415

Asp Tyr Asp Gly Asp Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly
  420     425     430

Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly
  435     440     445

Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
  450     455     460

Asn Ile His Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln
  465     470     475     480

Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu
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Ile Lys

<210> 344

<211> 1497
DNA

artificial sequence

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr

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Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly

Gly Ser Gly Ser Gly Gln Ala Asp Ser Ile Val Leu Thr Gln Ser

Pro Ala Thr Leu Ser Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys

Arg Ala Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
Glu Ile Lys Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser
Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys
Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln
Arg Pro Gly Gin Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp
Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr
Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala
Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr
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- Glu Ile Lys

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- <211> 1494
- <212> DNA
- <213> artificial sequence

- <220>
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<212> PRT

<213> artificial sequence

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<223> VL3VH5xCD19 LHLH

<400> 347

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20                  25                  30

Asn Trp Tyr Gln Gln Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
35                  40                  45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50                  55                  60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
85  90  95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr
100 105 110

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu
115 120 125

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val
130 135 140

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp
145 150 155 160

Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Ile Gly Tyr Ile Asn
165 170 175

Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe
180 185 190

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
195 200 205

Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Cys Ala Arg Tyr Tyr
210 215 220

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
225 230 235 240

Val Ser Ser Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro
245 250 255

Ala Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Ser Cys Lys
260 265 270

Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Thr Tyr

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Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser
290 295 300

Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly
305 310 315 320

Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala
325 330 335

Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly
340 345 350

Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly Gly Gly Gly
355 360 365

Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
370 375 380

Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
385 390 395 400

Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
405 410 415

Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr
420 425 430

Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu
435 440 445

Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Gly Asp
450 455 460

Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Val Gly Arg

동록특허 10-1229731
Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val

Ser Ser

<210> 348

<211> 1497

<212> DNA

<213> artificial sequence

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<223> VH5VL3xCD19 HLLHI

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cctggacagg gttgggaattg gattggatac attaatccta ggcgtgggta tactaattac    180
gcagacagcg tcaagggcgg cttcacaate actacagaca aatccaccag cacagctac    240
atggcaactga gcagcctgcg ttctgaggac actgcaacct attactgtgc aagatattat    300
gatgatcatt actgcccgtc ccctgggctt tcttgaggac actgcaacct attactgtgc aagatattat    360
gatgatcatt actgcccgtc ccctgggctt tcttgaggac actgcaacct attactgtgc aagatattat    420
gaggttacta gtactggttc tgggtgaagt ggaaggcttc gttggacaga cagactgtgta    480
tggagccggt ccctgggctt tcttgaggac actgcaacct attactgtgc aagatattat    540

- 653 -
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<210> 349
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<212> PRT
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165 170 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195 200 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser
245 250 255

Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys
260 265 270

Lys Ala Ser Gin Gin Ser Gin Ser Val Gin Tyr Gin Ser Gin Ser Gin Gin
275 280 285

Tyr Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala
290 295 300

Ser Asn Leu Val Ser Gin Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser
305 310 315 320

Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala
325 330 335
Ala Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly
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  350

Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly
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  365

Gly Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala
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  375
  380

Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser
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  400

Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro
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  410
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Gly Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp
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  425
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Thr Asn Tyr Asn Gly Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp
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  445

Glu Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu
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Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr Val Gly
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Arg Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
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Val Ser Ser

<210> 350

<211> 1494
DNA

artificial sequence

VL1VH7xCD19 LHHL

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<210> 351
<211> 498
<212> PRT
<213> artificial sequence

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Tyr Met
Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr

Phe Gly Gly Gly Thr Val Glu Ile Lys Gly Gly Gly Thr Ser Thr

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn

Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val

Thr Ile Thr Thr Asp Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser

Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr
Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
Val Ser Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly
Ala Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala
Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg
Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly
Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala
Asp Glu Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser
Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr Val
Gly Arg Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val
Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser Leu Ala Val
Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val
Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly
420 425 430

Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly
435 440 445

Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
450 455 460

Asn Ile His Pro Val Glu Val Asp Ala Ala Thr Tyr His Cys Gin
465 470 475 480

Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu
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Ile Lys

<210>  352
<211>  1497
<212>  DNA
<213>  artificial sequence

<220>
<223>  VH7VL1xCD19 HLHL

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agtggtgctg ggaccgacta ctctcagctc atcagaccgcttgagcgtgta atgggtgttc 660
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<210> 353

<211> 499

<212> PRT

<213> artificial sequence

<220>

<223> VH7VL.1xCD19 HILH

<400> 353

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Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile 35 40 45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe 50 55 60

Lys Asp Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr 65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
115 120 125

Gly Ser Gly Ser Gly Gly Ala Asp Asp Ile Gln Met Thr Gln Ser
130 135 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145 150 155 160

Arg Ala Ser Gin Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195 200 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ser Gly Gly Gly Gly Ser Gin Val Gin Leu Gin Gln Ser
245 250 255

Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys
260 265 270

Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gin
Arg Pro Gly Gin Gly Leu Glu Trp Ile Gly Gin Ile Trp Pro Gly Asp

Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr

Ala Asp Gin Ser Ser Thr Ala Tyr Met Gin Leu Ser Ser Leu Ala

Ser Gin Asp Ser Ala Val Tyr Phe Cys Ala Arg Gin Thr Thr Thr

Val Gin Arg Tyr Tyr Tyr Ala Met Gin Asp Tyr Trp Gin Gin Gin Gin Gin Gin Gin

Val Thr Val Ser Ser Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin

Gly Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin

Val Ser Leu Gin Gin Gin Arg Gin Ala Thr Ile Ser Cys Lys Ala Ser Gin Ser

Val Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin

Val Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin

Gly Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin

Leu Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin
Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
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490
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Glu Ile Lys

<210> 354

<211> 1494

<212> DNA

<213> artificial sequence

<220>

<223> VL1V1H7xCD19 LHLH

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aaggcaccca aaagatggat ttatgacaca tccaaagtgg cttctggagt ccctgctcgc  180
ttcagtggca gtgggtcttg gacctgactac tctctcacaa tcaacagctt ggaggctgaa  240
gatgctgcca cttattactg ccaacagtgg agtagtaacc cgctcacgtt cggtggcggg  300
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<210> 355

<211> 498

<212> PRT
artificial sequence

VL1VH7xCD19 LHLH

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20                  25                  30

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35                  40                  45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50                  55                  60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gin Gin Trp Ser Ser Asn Pro Leu Thr
85                  90                  95

Phe Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr
100                 105                 110

Gly Ser Gly Ser Gly Ser Gly Ala Asp Asp Val Gin Leu
115                 120                 125

Val Gin Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val
130                 135                 140
Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp
145       150       155       160

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn
165       170       175

Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val
180       185       190

Thr Ile Thr Thr Asp Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
195       200       205

Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Cys Ala Arg Tyr Tyr
210       215       220

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
225       230       235       240

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Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys
260       265       270

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275       280       285

Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Ile Tyr Asp Ala Ser
290       295       300

Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly
305       310       315       320

Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala
325       330       335
Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly
  340                 345                 350

Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly Gly Gly
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Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
  370                 375                 380

Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
  385                 390                 395                 400

Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
  405                 410                 415

Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr
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Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu
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Ser Ser

<210>  356

<211>  1497

등록특허 10-1229731
DNA

artificial sequence

VH7VL1xCD19 HLLH

356

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1497

<210> 357

<211> 499

<212> PRT

<213> artificial sequence

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<223> VH7VL1xCD19 HLLH

<400> 357

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Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
Lys Asp Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
Thr Thr Val Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
Gly Ser Gly Ser Gly Gly Ala Asp Ile Gln Met Thr Gln Ser
Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
Glu Ile Lys Ser Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser
Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys
Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Ser Ser Tyr Leu Asn Trp
Tyr Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Ile Tyr Asp Ala
Ser Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser
Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala
Gly Gly Thr Lys Leu Gln Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly
Gly Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala
Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser
Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro
Gly Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp  
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435                 440                 445
Glu Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu  
450                 455                 460
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465                 470                 475                 480
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<211> 1494
<212> DNA
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1494

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<211> 498

<212> PRT

<213> artificial sequence

<220> 

<223> VL2VH7xCD19 LJHL

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Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr  
35                  40                  45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser  
50                  55                  60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu  
65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr 85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr 100 105 110

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu 115 120 125

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val 130 135 140

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp 145 150 155 160

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn 165 170 175

Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val 180 185 190

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser 195 200 205

Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr 210 215 220

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr 225 230 235 240

Val Ser Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly 245 250 255

Ala Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala 260 265 270

Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg

등록특허 10-1229731
Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly 
Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala 
Glu Asp Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser 
Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr Val 
Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val 
Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly 
Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser Leu Ala Val 
Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val 
Asp Tyr Asp Gly Asp Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly 
Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly 
Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu 
Asn Ile His Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gin 

- 680 -
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Ile Lys

<210> 360
<211> 1497
<212> DNA
<213> artificial sequence

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등록특허 10-1229731
<213> artificial sequence

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20                  25                  30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35                  40                  45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50                  55                  60

Lys Asp Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85                  90                  95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100                 105                 110

Thr Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
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Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser
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Val Asp Tyr Asp Gly Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro
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Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser
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Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
  450                 455                 460

Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys
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Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
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Glu Ile Lys

<210>  362

<211>  1494
<212> DNA

<213> artificial sequence

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<223> VL2VHxCD19 LHLH

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<211> 498

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<220>

<223> VL2VH7xCD19 LHLH

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Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Met
Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr

Phe Gly Gly Gly Thr Val Glu Ile Lys Gly Glu Gly Thr Ser Thr

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn

Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val

Thr Ile Thr Thr Asp Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser

Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr

- 688 -
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Val Ser Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro
Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys
Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp Tyr
Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser
Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly
Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala
Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly
Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly
Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr
420 425 430

Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu
435 440 445

Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp
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<210> 364

<211> 1497

<212> DNA

<213> artificial sequence

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Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser

Gly Tyr Ala Phe Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro

Gly Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp

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Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
Glu Ile Lys Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser
Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys
Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gin
Arg Pro Gly Gin Gly Leu Glu Trp Ile Gly Gin Ile Trp Pro Gly Asp
Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr
Ala Asp Glu Ser Ser Thr Ala Tyr Met Gin Leu Ser Ser Leu Ala
Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr
Val Gly Arg Tyr Tyr Ala Met Asp Tyr Trp Gly Gin Gly Thr Thr
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
Gly Gly Ser Asp Ile Gin Leu Thr Gin Ser Pro Ala Ser Leu Ala
Val Ser Leu Gly Gin Arg Ala Thr Ile Ser Cys Lys Ala Ser Gin Ser
Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro  
420                 425                 430

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser  
435                 440                 445

Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr  
450                 455                 460

Leu Asn Ile His Pro Val Gln Val Asp Ala Ala Thr Tyr His Cys  
465                 470                 475                 480

Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu  
485                 490                 495

Glu Ile Lys

<210> 370

<211> 1494

<212> DNA

<213> artificial sequence

<220>

<223> VL3VH7xCD19 LHLH

<400> 370

gactttgtaac cgtactgtc ctcagcaact cttgtcttgt ctccagggga gcgtgccacc  60
cgtctgctc ctgacctgca gacattgtac tgacccagtc tccagcaact ctgtctctgt ctccagggga gcgtgccacc 120
aaggcaccca aaagatggat ttatgacaca tccaaagtgg cttctggagt ccctgctcgc 180
 ttcagtggca gttgggtcgg gacgcaacct ctcctcaaca tcaacaggtt ggaggtcaga 240
gatgtgcca ctttggcttc caacagtttg agtagtaacc cgctcaagtt cgtgtgcccgg 300
accaagggtgg agataacaacc cgaaggtact catctgtgtg aagtgaaaaa acctgggccc 360
gttggaacag acagcttcda acttgggctg tcaagggttc aalggaacaaa acctgggccc 420
tcagtgaagg tcgtctgcca aacctttgge tacacelttta etaggtacac gatgcacactg 480
glaagggcagg cacttggaca ggtgtggga aaagttggaat acaatataacct cagccggttt 540
tatactaat açaacgagac gcacggtacac tcacaagcag tggacttgag gcacggtcacc 600
agcacagcct acatggaact gagcagcctg cgttctgagg acactgcagt ctattactgtt 660
agaatagtta atgtgatca ctactgcttt gacaaggtgg ggcaccagaacctt ctgggtaccc 720
gttctctcg gagttgtgtgg atccgtatate cagctgaccc agtctcaagc ttctttggct 780
ggtgatagt ttattgaaact gcacaagcc aacaatacag agcgcctcgtt agtcggtcgg 840
tatgagcag ttcacactg ttcacgact acaaatcaca cagcgtcacc ttcaccagct 900
acagacttc acaatcactg ttcacatttt gagaaggtgg atgctgcaac ctatcactgt 960
cagcaaaatgcaggcagttc ggtggagggc caccatctcc tcacgccgtag aatctgcaagc 1020
acagacttc acaatcactg ttcacatttt gagaaggtgg atgctgcaac ctatcactgt 1080
ggtgatagt ttattgaaact gcacaagcc aacaatacag agcgcctcgtt agtcggtcgg 1140
ttgggggtcgc atcggggtag gtggggtggg ctcaggtgca gctgcagcag 1200
ttgcattca gtactaagct gagtaactgg gtgaactgta ggcctgcagc ggctcggagc 1260
ttgattccac agatittggcc tgagatggt gataacactg acaatgggaa aatgcaaggtt 1320
aaagccactc tgactgcaga cgaatcctcc agcacagcct acatgcaact cagcagccta 1380

gcatctgagg actctgcggt ctatttctgt gcaagacggg agactacgac ggtaggccgt 1440
tattactatg ctatggacta ctggggccaa gggaccacgg tcaccgtctc ctcc 1494

<210> 371

<211> 498

<212> PRT

<213> artificial sequence

<220>

<223> VL3VH7xCD19 LHLH

<400> 371

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
20                  25                  30

Asn Trp Tyr Gln Gln Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
35                  40                  45

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50                  55                  60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr
100 105 110

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu
115 120 125

Val Gln Ser Gly Ala Glu Val Lys Pro Gly Ala Ser Val Lys Val
130 135 140

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp
145 150 155 160

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn
165 170 175

Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val
180 185 190

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
195 200 205

Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr
210 215 220

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
225 230 235 240

Val Ser Ser Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro
245 250 255

Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys
260 265 270

Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp Tyr

--- 707 ---
Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser
Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly
Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala
Thr Tyr His Cys Gln Gln Thr Glu Asp Pro Trp Thr Phe Gly Gly
Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly Gly Gly
Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr
Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu
Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp
Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Val Gly Arg
465 470 475 480
Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val
485 490 495
Ser Ser

<210> 372
<211> 1497
<212> DNA
<213> artificial sequence

<220>
<223> VH7V3xCD19 HLLH

<400> 372
gacgtccac tggtgcagtc aggggctgaa gtgaaaaaac ctggggcctc agtgaaggtg     60
tctgcaagg cttctgcta cacctttact aggtacacga tgcactgggt aaggcaggca 120
cctggacagg gtetggaaatg gattggatac attaatccta gcccgtggtta tactaattac 180
aatcagaagt tcaaggacgc cgteacaate actacagaca aatccaccag cacagctac 240
atggaactga gcagcctgcg ttctgaggac actgcagtct attactgtgc aagatattat 300
gatgatcatt actgacctga ctactggtggtg gagtcagctac cacagtgcagcctgaccc 360
gagtaactga gtactggttc tggtggaagt ggaggttcag gtggagcaga cgacattgta 420
cctggacagg ctggacggcg ccgacggag cgtagtcagc actgcacctg acacgtgcctg 480
agagccagtt caagtgtaag ttacatgaac tggtaccagc agaagccggg caaggccccc 540
aaaagatgga tttatgacac atccaaagtg gcttctggag tccctgctcg cttcagtggc
agtgggtctg ggaccgacta ctctctcaca atcaacagct tggaggctga agatgctgcc
acttattact gccaacagtg gatgtagtaac cagcacaagtc ccaacaaaggg ccctggat
gacaccagag gccaccacc tctgcaaggg ccagccaaaaggg ccctggat
gattatgatg catcatactt agtttctggg ccaccagacc ggctgtgtcc tggaggtcgc
actgctgctt atggatgtgg gttctgcaaggg ccctggat
<210> 373
<211> 499
<212> PRT
artificial sequence

VH7VL3xCD19 HLLH

373

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20  25  30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35  40  45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50  55  60

Lys Asp Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
65  70  75  80

Met Glu Leu Ser Ser Leu Ser Leu Ser Ser Gln Ala Val Tyr Tyr Cys
85  90  95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105  110

Thr Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
115 120 125

Gly Ser Gly Ser Gly Gly Gly Ala Asp Ile Val Leu Thr Gln Ser
130 135 140
Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys
145 150 155 160

Arg Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
195 200 205

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser
245 250 255

Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys
260 265 270

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp
275 280 285

Tyr Gln Ile Pro Gly Gln Pro Pro Lys Leu Ile Tyr Asp Ala
290 295 300

Ser Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser
305 310 315 320

Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala
325 330 335

- 712 -
Ala Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly
340                 345                 350

Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly Gly
355                 360                 365

Gly Ser Gly Gly Gly Ser Gly Val Glu Gly Leu Gly Gly Ser Gly Ala
370                 375                 380

Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ile Ser
385                 390                 395                 400

Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Glu Arg Pro
405                 410                 415

Gly Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp
420                 425                 430

Thr Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp
435                 440                 445

Glu Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu
450                 455                 460

Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr Val Gly
465                 470                 475                 480

Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
485                 490                 495

Val Ser Ser

<210> 374

<211> 1497
DNA

artificial sequence

CD19xVH5/VL1 HLHL

374

caggtgcaee tgcagcagtc tgggtgctag etggtgagge etgggtctc agtgaagatt tcctgcaagg cttctggcta tgcattcagt agctactgga tgaactgggt gaagcagagg cctggacagg gtcttgagtg gattggacag atttggcttg gagatggtga tactaactac aatggaaagt tccaggttaa agccactctg actgcagacg aatcctccag cacagctac atgcaactca gcagcctagc atctgaggac tctgcggtct atttctgtgc aagacgggag actacgacgg taggccgtaa ttactatgct atggactact ggggccaagg gaccacggtc accgtctcct ccgggtggtgg tggttctggc ggcggcggct ccggtggtgg tggttctgat atccagctga cccagttcct ccagccaaag tgttgattat gatggtgata gttatttgtg ccagggtaa ggcaggcacc tggacagggt cagattcag gacagccace caaatctctc atctatgatg catccaatct agtttctggg atcccaccca ggttagtgg cagtggtgct gggacagact tcaccctcaa catccatcct gttggagaag tggatgcgtc aacactac tgcagcagaa tgaactggga tccgtggacg ttccggtggag ggaccaagct cgagatcaaa tccggaggtg gtggatccga cgtccaactg gtggagaagg tggatgcgtc aaacttauac tgcagcagaa tgaactggga tccgtggacg ttccggtggag ggaccaagct cgagatcaaa tccggaggtg gtggatccga cgtccaactg gtggagaagg tggatgcgtc aaacttauac tgcagcagaa tgaactggga tccgtggacg ttccggtggag ggaccaagct cgagatcaaa tccggaggtg gtggatccga cgtccaactg gtggagaagg tggatgcgtc aaacttauac tgcagcagaa tgaactggga tccgtggacg ttccggtggag ggaccaagct cgagatcaaa tccggaggtg gtggatccga cgtccaactg

- 714 -
ctggaatgga ttggatacat taatcctagc cgtggttata ctaattacgc agacagcgtc
960
aagggccgct tcacaatc ac tacagaca aa tccaccagca cagcctacat ggaactgagc
1020
agcttggtt ac gtagggc ca aagccacag gcctacgtct cctcaggcga aggtactagt
1080
tgcttgact ac tgggcca aaggcagaca gggacctgct tgggtctggg ccgactact
1140
tgtctgcate tgtctgggga cgtgttcacca tcacctgcag agccagtcaa agtgtaagtt
1200
acatgaactg gt ggatttgc atacagcag gacgggca aagcgggca tagatggatt
tatgacact ccaggtggge tctgggagte cctgctcgct gatcaaa gatcaaa
ttattactgc caacagtgga gtagtaaccc gctcacgttc ggtggcggga ccaaggtgga
cacagtggga gtagtaaccc gctcacgttc ggtggcggga ccaaggtgga
cacagtggga gtagtaaccc gctcacgttc ggtggcggga ccaaggtgga
cacagtggga gtagtaaccc gctcacgttc ggtggcggga ccaaggtgga
cacagtggga gtagtaaccc gctcacgttc ggtggcggga ccaaggtgga

<210>  375

<211>  499

<212>  PRT

<213>  artificial sequence

<220>

<223>  CD19xVH5VL1 HLHL

<400>  375

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
1  5  10  15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr

- 715 -
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr
Met Gln Leu Ser Ser Leu Ala Ser Glu Ser Ala Val Tyr Phe Cys
Ala Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp
Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
Ser Gly Gly Gly Ser Gly Gly Gly Gly Gly Asp Ile Gln Leu Thr
Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile
Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu
Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr
Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser
Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val
Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr
210 215 220

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
225 230 235 240

Asp Val Gln Leu Val Gln Ser Gly Ala Val Lys Lys Pro Gly Ala
245 250 255

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
260 265 270

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
275 280 285

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
290 295 300

Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
305 310 315 320

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Cys
325 330 335

Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
340 345 350

Thr Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
355 360 365

Gly Ser Gly Ser Gly Gly Ala Asp Ile Gln Met Thr Gln Ser
370 375 380

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
385 390 395 400

- 717 -
Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
420 425 430

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
435 440 445

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
450 455 460

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Cys
465 470 475 480

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
485 490 495

Glu Ile Lys

<210> 376

<211> 1494

<212> DNA

<213> artificial sequence

<220>

<223> CD19xVL1VH5 LHLH

<400> 376
gatatccagc tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

agctcgtca aaggccagca aagtgtgtgat tatgatggtg atatgtgatt gaactggtaca 120
caacagatc caggacagcc acccaaaact ctcatctctg atgcatccaa tctagtttct 180
gggateccac ccaggttagt tagcagtgtag ctcagacag acttcacct caacatccat 240
cctgtggaga aggtgagatgc tgcacatct cactgtcagc aaaggttggg tgggttcctg cggccgccgc 360
ttcgctgttgac gtgttctca cggacagct cagcaacgtc gggetgagct gggtagggttct 420
ggctctcag tgaaggttctg tctgcctagc cattcagatg etactgtgagt 480
aactgggtga agcagagggc tggacaggt tggatgtaga tggacagat tggcccttga 540
gatggtgata etactacaag tggaaatgtc aaggttaaaag ccaectgtac tgcagacaa 600
tctcctagca ccacagtctag cgtactcatc ctggtaccgc tgggtctgtat 660
tctgtgcac aaccccgttg actacgtaga ggccggtatt actatcgtat ggacctgtgg 720
ggccacggga ccacggctcg cgctccctcc ggagctggtg gatccgctca tcaagatgcc 780
cgctctcag ctgtctgtgc tgcacgagtc gggaacctgc tcaccaacac etgcagacagcc 840
agtaaatagc taagttcatc gcaactgttc cagcaggaag cgggcaaggg acccaaaaga 900
tggtttagc acacatacaac acctggctct ctcagtacct cgcagcagcct 960
tcctgaggcc actactctct cacatcaacc agettggagg ctgaagatgc tgccacatct 1020
tactgcaac aagtgagagt tagaacgggct acgtttctgtag cgggacacca ggtggagatc 1080
aagggcgaag gcaggacagtg ctggttttggt ggaaggtggag gttcaggtgg agcagacgac 1140
gtcgaactgg tggcagctat cggccagcct gcgggctcag tgaaggttgg gaaagtaccc 1200
tgcaaggtt tagttcttagc cattcagatg acctggtaag gcagacaccct 1260
ggcaggggtc tggataagc tagataactc agtgcattcc gttgatttaca taattacgca 1320
gacagcgtca agggccgctt cacaatcact acagacaaat ccaccagcac agcctacatg  1380
gaactgagca gcgtgcgttc tgaggacact gcaacctatt actgtgcaag atattatgat  1440
gatcattaact gcetgacta ctggtggccaa ggaccaecgg tcaecgtetc ctca  1494

<210>  377

<211>  498

<212> PRT

<213> artificial sequence

<220>

<223> CD19xVL1VH5 LHLH

<400>  377

Asp Ile Gln Leu Thr Gln Ser Ala Ser Leu Ala Val Ser Leu Gly  
1               5                   10                  15

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
20                  25                  30

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro  
35                  40                  45

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro  
50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His  
65                  70                  75                  80

등록특허 10-1229731
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85  90  95

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Leu Glu Ile Lys Gly
100 105 110

115 120 125

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
130 135 140

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
145 150 155 160

Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gin
165 170 175

Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
180 185 190

Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Thr Ala Tyr Met Gin
195 200 205

Leu Ser Ser Leu Ala Ser Glu Ser Ser Thr Ala Tyr Met Gin
210 215 220

Arg Glu Thr Thr Val Gly Arg Tyr Tyr Ala Met Asp Tyr Trp
225 230 235 240

Gly Gin Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp
245 250 255

Ile Gin Met Thr Gin Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
260 265 270

Arg Val Thr Ile Thr Cys Arg Ala Ser Gin Ser Val Ser Tyr Met Asn
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp
275 280 285

Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly
290 295 300

Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp
305 310 315 320

Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe
325 330 335

Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Thr Ser Thr Gly
340 345 350

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu Val
355 360 365

Gln Ser Gly Ala Glu Val Lys Pro Gly Ala Ser Val Lys Val Ser
370 375 380

Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val
385 390 395 400

Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro
405 410 415

Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr
420 425 430

Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser
435 440 445

Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr Asp
Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val

Ser Ser

<210> 378

<211> 1497

<212> DNA

<213> artificial sequence

<220>

<223> CD19xVL1VH5 IIIII

<400> 378
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tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa    120
cctggacagg gtctggagtg gattggcacg atttggcctg gagatgggtga tactaactac   180
aatggaaagt tcaagggtaa agccactctg actgcagacg aatcctccag cacagcctac   240
atgcaactca gcagcctagc atctgaggac tctgcggtct atttctgtgc aagacgggag   300
actacgacgg taggccccga tccatctgtg atggactact ggggccaagg gaccacggtc   360
accgtctcct ccggtgggtg tggtttcatg ggggceggct ccggtgggtg tggtttctgat   420
atccagctga cccagtctcc agcttctttg gctgtgtctc tagggcagag ggccaccatc   480
tcctgcaagg ccagccaaag tgttgattat gatggtgata gtattttgaa etggttacaa   540
cagattccag gacagccace caaacteetc atctatgatg catccaatct agtttctggg 600
ateccaccca gtttaagtgg cagtgggtct gggacagact tcacccctaa catcctcctc 660
gtggagaagg tggatgetgc aacctatcac tgtcagc aaaatctgagga tcggtttggc 720
ttcggtggag gggccacctg cggagtttgg cggagagttg gttgctccga cttcagatg 780
acccagcetakgactgtgtgctcgtgagggace gtgctcaccat cactgcgaga 840
gccagtcaaa gtgaagtta catgtaaacttg taccagcaga agccgggccaa ggcacccaa 900
agaggtgttt atggacacact caagatgggtc tctggagtcct gtctgctctc cagtggcagt 960
pggctgtggga cggactaectc tetccactc aacagctgg aggtgaaaga tctggtcact 1020	tatctgccc aacagtggag tagtaacccg etcagcttgg cttgagggccc caagggaggg 1080
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CD19xVH5VL2 HLHL

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Gln Ser Gly Ala Glu Val Lys Pro Gly Ala Ser Val Lys Val Ser

Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val

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Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr

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atgcacaactc gaagactccg atgcaccgcc actgtcgtact atttcggtct attttgctgct
agacggagc actacgacgg taggccaagg atggactact ggggccaagg gaccacggtc
accgtctcct ccgggtggtgg tggttctggc ggcggcggct ccggtggtgg tggttctgat
atccagctga cccagtctcc agcttctttg gctgtgtctc tagggcagag ggccaccatc
tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa
<211> 1497
<212> DNA
<213> artificial sequence

<220>
<223> CD19xVL2VH5 HLLH

<400> 384
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tcctgcaagg cttctggcta tgcattcagt agctactgga tgaactgggt gaagcagagg
cctggacagg gtcttgagtg gattggacag atttggcctg gagatggtga tactaactac
aatggaaagt tcaaggatg aagcactctg actgcagacg aatcctccag cacagctac
atgcacaactc gaagactccg atgcaccgcc actgtcgtact atttcggtct attttgctgct
agacggagc actacgacgg taggccaagg atggactact ggggccaagg gaccacggtc
accgtctcct ccgggtggtgg tggttctggc ggcggcggct ccggtggtgg tggttctgat
atccagctga cccagtctcc agcttctttg gctgtgtctc tagggcagag ggccaccatc
tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa
cagattccag gacagccacc caaactcetc atctatgatg catccaatct agtttctggg     600
atcccaccca ggttagtggc cagttccgct tggacagact tcaacctcaaa catccatcct    660
gtggagaagg tggatgcact gcacctcgcg ctgcagcgtta gaactgagga tccgtggacg    720
ttcggtgga ggcacaagct cggatcggg tccggagggt gcgttagcgg agcttctagt    780
acccgctgct cagcaactct gtctctgtct ccaaggggac agtgccaccc gacctgcaga   840
gccagtcaaa gtgaagttta catgcaaccttg taccacagta acgcgggcaaa ggcaccccaa 900
agatggtatctcgagatcgact cgggccagct cgtggccgag ctcgtggtct cagtgggagt 960
ggtttgggaa cccactctct ctcacacttc acacagcttg aagcttgaga tgcgtgccact 1020
ttaactgcct aacagttggag tagtccccgt ctcagcgctg gttggccgcc caaggtggag 1080
atcaagggc aagagtatag tgrcctgcct cttgagcccc gagttccgct tggagcagac 1140
gaacggctc tggcgactgc aggggttct gcgtgaaac actggtggtct actggtgatgc 1200
tgtgtgaagg ctctggcctg cggagtctat ctgctctgtg cggagtcggg ttaaggtggc 1260
gcgacagg acggccctgg cttgacaact ctgcagaacc cattgtctcg ctcgctgctg 1320
gagagctgg cggccactgc atggatcgag gcacgagatc ccctggagag cggcgagcct 1380
atggaactca ggctgacccc ttcctggctg ctcctgttct ctgcaacctgc agagttctat 1440
gatgatcatt actgcctgcttc actggtgagc ctcggagcaag cggcagcgct ctcgctgct 1497

<210> 385

<211> 499

<212> PRT
<213>  artificial sequence

<220>

<223>  CD19xVL2VH5 IIIII

<400>  385

Gln Val Gln Leu Gln Gln Ser Gly Ala Gln Leu Val Arg Pro Gly Ser
1       5       10     15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
20      25      30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45

Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
50      55      60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr
65      70      75     80

Met Gln Leu Ser Leu Ala Ser Gly Asp Ser Ala Val Tyr Phe Cys
85      90     95

Ala Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp
100     105    110

Tyr Trp Gly Gin Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
115     120    125

Ser Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Gln Leu Thr
130     135    140
Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Il e 145 150 155 160

Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu 165 170 175

Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr 180 185 190

Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser 195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val 210 215 220

Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr 225 230 235 240

Phe Gly Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser 245 250 255

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly 260 265 270

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Met 275 280 285

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr 290 295 300

Asp Thr Ser Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser 305 310 315 320

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu 325 330 335
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
340 345 350

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Thr Ser Thr
355 360 365

Gly Ser Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu
370 375 380

Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val
385 390 395 400

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp
405 410 415

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn
420 425 430

Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe
435 440 445

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
450 455 460

Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Cys Ala Arg Tyr Tyr
465 470 475 480

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
485 490 495

Val Ser Ser

<210> 386

<211> 1497
<212> DNA

<213> artificial sequence

<220>

<223> CD19xVH5VL3 IIIH

<400> 386
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tctgtcaagg ettctggtca tgcattcagt actcttgga tgaattccgag gaagcagagg 120
cctggacagg gctggacagt gattggcagct atttggccct gcagattcacta tactaactac 180
aatggaaagt tcaaggtcag actgacagag aatttctccag cacagctac 240
atgcaactca gcagctcagc atctgaggac ttcggcgtct atttctgtgc aagacgggag 300
actagcagg taggcctgta ttactatgtc atggactact gggcccaagg gaccacggtc 360
acggtgtctc cgggtgtgag tgggcttctg cgggctcgtg cgggtggttgc gggctggggg 420
atcagctgac ccagctcctc agctctttct ggtctctgag cggcagagag ggccacagtc 480
tctgcagag cagcccaagattgctttgctaatggtacaa gaagcagctggg 540
cagatcctag gacagccacc caaactctct atcttatagct gattttggg gtgtcactg 600
ateccacca gtttagatgg cagttggctc ggccagactc tccctctcag cctccctctct 660
gttgagcag gctggactgc acactgcaaat tgctactggag ctggagtctt 720
tggtggtgac ggacagagct gggatccctca tctcagggat gcctgcaggg 780
gtgctgtcag ggtgtggtgc gatttctgcc cgggtattag cggagtctc gggattgggtc 840
tctggctcaca ctcttactag gtacagcagct gattttccag ggcacggcact cgggcttggt 900
ctggaatgga ttgatacat taatcttagc cgtggttata ctaattacgc agacagcgtc
960
aagggccgct tcacaatc ac tacagacaaa tccaccagca cagctctacat ggaactgagc
1020
agcctgcgt etggaagacac tgcaacctat tactgtgcaa gatattatga tgatcattac
1080
tgcetgtact acctgaggtc gaagcccaag gttcactgtct cctcaggcga aggtactagt
1140
actggttctg gtggaagtgg aggttcaggt ggagcagacg acattgtact gacccagtct
1200
cagcaactc tgccttgagtc ccagggggag cgtgccaccc tgacctgcag agccagttca
1260
agtgtaagtt atctgacttg gtaccacgag aagccaccca aagatggatt
1320
tatgacacat ccaaggtggc ttctggagtc cctgctcggc tcagtggcag tgggtctggg
1380
acgctact cgcctcagat ccaagtgaa gaagccctta ctgatgtcgc ccaaggtgga gatcaaa
1440
caacagtgga gtgaggtc gc cggg gga cggg gga cggg gga gatcaaa
1497

<210>  387
<211>  499
<212>  PRT
<213>  artificial sequence

<220>
<223>  CD19xVH5VL3 HLHL

<400>  387

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
1      5     10     15

Ser Val Lys 11e Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile

Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe

Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr

Met Gln Leu Ser Ser Leu Ala Ser Glu Ser Ala Val Tyr Phe Cys

Ala Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp

Tyr Trp Gly Gln Gly Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr

Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile

Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu

Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr

Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Arg Phe Ser Gly Ser

Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val
Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
Asp Val Gln Leu Val Gln Ser Gly Ala Val Lys Lys Pro Gly Ala
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val
Lys Gly Arg Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Cys
Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
Thr Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
Gly Ser Gly Gly Ser Gly Ala Asp Ile Val Leu Thr Gln Ser
Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys
Arg Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro  
420                 425                 430
Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser  
435                 440                 445
Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser  
450                 455                 460
Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys  
465                 470                 475                 480
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val  
485                 490                 495
Glu Ile Lys

<210> 388
<211> 1494
<212> DNA
<213> artificial sequence

<220>
<223> CD19xVL3WH LHLH

<400> 388
gatatccagc tgaccagtct tccagttct ttggtgtgt ctctaggcca gagggccacc 60

atctctgca aagccagcca aagttggat tatgatttg atagtttat tacgaacttgta 120
caacagatc caggacagcc acccaacct ctcatctatg atgcatccaa tctagtttct 180
gggateccac ccaaggtttag tggcagtggg tctgggacag acttacccct caacatccat 240
cctgtggaga aggtggatgc tgcgaacctat cactgtcage aaagtactgta ggatecggtgg 300
acgttgggtg gaggacccaa gctgagacte aaaggtgatttg gggtttcct ggcccgccgc 360
tccgtgggtg gttggtctca ggtgcagctt gaggagcttg ggtgcggctt 420
gggttcctag tgaagatttc ctgcaaggct tctggctatg cattcagtag ctactggatg 480
aactgggtga agccagagcc tggagacaggt cttgagtgga tggacagatf tggccttga 540
gatggtgata ctaactacaa tggagagctc aagggtaaag ccaccctgac tgcagagac 600
tctcagcac gacctcactg ccaactcactc agctgactctt gtcgagactc tgcggtctat 660
ttcctgtcga gacgggagac tacgacggta ggccgttatt actatgctat ggactactgg 720
ggccaagggg ccaacggtcc acgtcctctcc ggaggtggtg gatccgacat tgtactgacc 780
cagtctcag caactctgac tctctctca gggagcgttg ccaccctgac ctgcaagacct 840
agttcagtgc ctaacttagt cacaactcag acgttgacagat gggtgagatc acggcggc 900
tggatllatg acacatcagac agtggctctct ggtccctgct ctggccttac ctttactagg 960
tctgggccgc actactctct cacatcacaag cagttgggc gggtgagatcg gggtgctcct 1020
tactgccac agttggactt taacccgcct acgttgggtg gcggcagcc cattgggatcg 1080
aaagccgaagtac tcaagtactg ggttgcttg ggacggatgg gttggctcc gacagacgc 1140
gtccactgg tcgcagtcaggg gctgagttg caaaaaccct ggccctcagt gaaggtgtcc 1200
tgcagcttc ctctactgac ttcactagtc aagtggtaag gcaccaacctgg 1260
ggagcgggtc tggagatc tggatacatt actctagacc gttgccatac tataagcggctt 1320
<210> 389

<211> 498

<212> PRT

<213> artificial sequence

<220>

<223> CD19xVL3VH5 LHLH

<400> 389

Asp Ile Gln Leu Thr Gln Ser Ala Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20                  25                  30

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35                  40                  45

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85 90 95

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Leu Glu Ile Lys Gly
100 105 110

115 120 125

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
130 135 140

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
145 150 155 160

Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gin
165 170 175

Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
180 185 190

Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Thr Ala Tyr Met Gin
195 200 205

Leu Ser Ser Leu Ala Ser Glu Ser Ser Thr Ala Tyr Met Gin
210 215 220

Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp
225 230 235 240

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp
245 250 255

Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu
260 265 270

Arg Ala Thr Leu Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met Asn

- 749 -
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp
275 280 285

Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly
290 295 300

Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly
305 310 315 320

Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Gly Ala Glu Asp
325 330 335

Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr Gly
350 355 360 365

Gly Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu Val
370 375 380

Gln Ser Gly Ala Glu Val Lys Pro Gly Ala Ser Val Lys Val Ser
385 390 395 400

Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val
405 410 415

Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro
420 425 430

Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr
435 440 445

Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser
450 455 460

Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr Asp

- 750 -
Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val

Ser Ser

<210> 390
<211> 1497
<212> DNA
<213> artificial sequence

<220>
<223> CD19xVL3VH5 HLLH

<400> 390
caggtgcagc tgcagcagtc tggggctgag ctggtgaggc ctgggtcctc agtgaagatt tcttgcaagg ctcttgccta tgcattcagt agcacttgga tgaactgggt gaagcagagg tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa tcctgcaagg ccagccaaag tgttgattat gatggtgata gttatttgaa ctggtaccaa
cagattccag gacagccacc caaacteetc atctatgatg catecaatct agtttcgagg
600
ateccaccaa gttttagtggt cagtttggtct ggcacagaaact tcaacectcaaa catecaaccect
660
gtggagaagg tggagctgac aacctatcawe tgcacagcctat cactgagga tggagagggagc
720
ttgcgggag ggccacacaat ccagatcact cccggaatggt gggatcctgca catcgtgtctg
780
accagtttc cagcacaatct gctctgtctg ccaggggagc gttgcaaccct gacctgcaaga
840
gccagtgcaaa gttgaagttc agcacttcag gtcaccggcag aag cacccaaa
gcaccagaagcttgctctg gttgagacctct gcctcagctct ttagttcatt ggcacccaaa
900
agatggtatt atgcacatc cagcagttgcg ttcgctgctg cctctggtgcg tgggatcagtgc
960
ggtctgagaa ccaactactct ttcaccaacttc acaacgcttgg aggetgaaga tggcacaact
1020
tttactgcc aacagttggag tagtaaccgg etcaagggctg gtcggtggac caaaggggag
1080
atcacaagggc aaggtactag taccgtctgct gttgaagttc aggcttcagg tggagcacac
1140
gacgttccaac tggtcagttc aggggctagtg atggaaaaac ctgggctggc acegtaagatgg
1200
tctgcagaa ggctgactctc cctcaagct cctgcaaggct ccgataagttc gtcggtggac caaaggggag
1260
gcagacactg tcaaggctag ettcacaatct actacaagct cctggttaagta tactatttac
1320
aggtgtagtc attccagtcg tggag aggaggttcgag ggtaccaggtt actgtgcgatgtgagct
1380
agtgaatgta gcagcag tttgatgtctgaggtg tggagaggtgc ggtacctgatgtgagct
1440
gatgatcatt actgtggaga caggggacc caaggtcaggct ccctca
1497

<210> 391
<211> 499
<212> PRT

- 752 -
<213> artificial sequence

<220>

<223> CD19xVL3WH IIIHH

<400> 391

Gln Val Gln Leu Gln Gln Ser Gly Ala Gln Leu Val Arg Pro Gly Ser
  1   5      10     15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
  20     25    30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
  35     40    45

Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
  50     55    60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr
  65     70    75     80

Met Gln Leu Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys
  85     90    95

Ala Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp
 100    105   110

Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
 115    120   125

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr
 130    135   140
Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile
145                 150                 155                 160

Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu
165                 170                 175

Asn Trp Tyr Gin Gin Ile Pro Gly Gin Pro Pro Lys Leu Leu Ile Tyr
180                 185                 190

Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser
195                 200                 205

Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val
210                 215                 220

Asp Ala Ala Thr Tyr His Cys Gin Gin Ser Thr Glu Asp Pro Trp Thr
225                 230                 235                 240

Phe Gly Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245                 250                 255

Asp Ile Val Leu Thr Gin Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
260                 265                 270

Glu Arg Ala Thr Leu Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
275                 280                 285

Asn Trp Tyr Gin Gin Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
290                 295                 300

Asp Thr Ser Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
305                 310                 315                 320

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
325                 330                 335
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
340 345 350

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr
355 360 365

Gly Ser Gly Ser Gly Ser Gly Ser Gly Gly Gly Ala Asp Asp Val Gln Leu
370 375 380

Val Gln Ser Gly Ala Glu Val Lys Gly Ala Ser Val Lys Val
385 390 395 400

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp
405 410 415

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr 11e Asn
420 425 430

Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe
435 440 445

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
450 455 460

Ser Leu Arg Ser Gln Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr Tyr
465 470 475 480

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
485 490 495

Val Ser Ser

<210> 392

<211> 1497
<212> DNA

<213> artificial sequence

<220>

<223> CD19xVH7VL1 HJHL

<400> 392
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<210> 393

<211> 499

<212> PRT

<213> artificial sequence

<220>

<223> CD19xVH7VL1 HLHL

<400> 393

Gln Val Gln Leu Gln Gln Gly Ala Glu Leu Val Arg Pro Gly Ser 1 5 10 15

Ser Val Lys 11e Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35                  40                  45

Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Ala Ser Glu Ser Ala Val Tyr Phe Cys
85                  90                  95

Ala Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp
100                 105                 110

Tyr Trp Gly Gln Gly Thr Thr Val Gly Thr Val Ser Ser Gly Gly Gly
115                 120                 125

Ser Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Gln Leu Thr
130                 135                 140

Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile
145                 150                 155                 160

Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu
165                 170                 175

Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr
180                 185                 190

Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser
195                 200                 205

Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val

- 758 -
Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
Asp Val Gln Leu Val Gln Ser Gly Ala Val Lys Lys Pro Gly Ala
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
Lys Asp Arg Val Thr Ile Thr Thr Asp Ser Thr Ser Thr Ala Tyr
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
Thr Thr Val Thr Val Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly
Gly Ser Gly Ser Gly Gly Ala Asp Asp Ile Gln Met Thr Gln Ser
Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
Arg Ala Ser Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
420 425 430

Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
435 440 445

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
450 455 460

Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Cys
465 470 475 480

Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
485 490 495

Glu Ile Lys

<210> 394

<211> 1494

<212> DNA

<213> artificial sequence

<220>

<223> CD19xVL1VH7 LHLH

<400> 394

gatatccagc tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atetctgca aggccagcca aagtgtgtat tatgatggtg atagttattt gaactgtgatc 120

- 760 -
caacagatc caggacagcc acceaaaactc etcatetatg atgcatec caaactatc...
cagaagttca aggaccgct cacaatcact acagacaat ccaccagcac agctacatg 1380
gaactgagca gcctgcgttc tgaggacact gcagtctatt actgtgcaag atattatgat 1440
gatcattaact gcctgacta etggggccaa ggcaccacgg tcaccgtctc ctca 1494

<210> 395

<211> 498

<212> PRT

<213> artificial sequence

<220>

<223> CD19xVL1VH7 LHLH

<400> 395

Asp Ile Gln Leu Thr Gln Ser Ala Ser Leu Ala Val Ser Leu Gly 1               5                   10                  15

Gln Arg Ala Thr 1le Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp 20                  25                  30

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro 35                  40                  45

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly 1le Pro Pro 50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn 1le His 65                  70                  75                  80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
  85                  90                  95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Leu Glu Ile Lys Gly
  100                 105                 110
  115                 120                 125
Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
  130                 135                 140
Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
  145                 150                 155                 160
Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln
  165                 170                 175
Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
  180                 185                 190
Lys Ala Thr Leu Thr Ala Asp Ser Ser Ser Thr Ala Tyr Met Gln
  195                 200                 205
Leu Ser Ser Leu Ala Ser Glu Ser Ser Thr Ala Tyr Met Gln
  210                 215                 220
Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp
  225                 230                 235                 240
Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp
  245                 250                 255
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
  260                 265                 270
Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Tyr Met Asn

등록특허 10-1229731
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp
Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly
Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp
Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe
Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr Gly
Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu Val
Gln Ser Gly Ala Glu Val Lys Pro Gly Ala Ser Val Lys Val Ser
Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val
Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro
Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr
Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser
Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp
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<210> 396

<211> 1497

<212> DNA

<213> artificial sequence

<220>

<223> CD19xVL1VH7 HLLLH

<400> 396
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cctggacagg gtcttgagtg gattggacag atttgccccg gagatgggta tactaactac  180
aatggaatt tcaagggtaa agccactctg actgcagacg aatcctccag cacagcctac  240
atgcaactca gcagctagc atctgaggac tctgcggtct atttctgtgc aagacgggag  300
actacgacgg tagccgta ttacttctgt atggactact ggccccaaaag gaccacggtc  360
accgtctcct ccggtggtgg tcgggtggtg ccggtggtggtc ggcggcggct ccggtggtgg tcgggtggtga  420
atccagctga cccagtctcc agcttctttg gctgtgtctc tagggcagag ggccaccatc  480
tcctgcaagg ccagccaaaag tggattttat gattttgaga gttattttgaaa cttgtaccag  540
artificial sequence

CD19xVL1VH7 IIIII

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
1      5      10     15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
20     25     30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35     40     45

Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
50     55     60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr
65     70     75     80

Met Gln Leu Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys
85     90     95

Ala Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp
100   105    110

Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
115   120    125

Ser Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Gln Leu Thr
130   135    140
Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile
145  150  155  160

Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu
165  170  175

Asn Trp Tyr Gin Gin Ile Pro Gly Gin Pro Pro Lys Leu Leu Ile Tyr
180  185  190

Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser
195  200  205

Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val
210  215  220

Asp Ala Ala Thr Tyr His Cys Gin Gin Ser Thr Glu Asp Pro Thr Thr
225  230  235  240

Phe Gly Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
245  250  255

Asp Ile Gin Met Thr Gin Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
260  265  270

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gin Ser Val Ser Tyr Met
275  280  285

Asn Trp Tyr Gin Gin Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
290  295  300

Asp Thr Ser Lys Val Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
305  310  315  320

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asn Ser Leu Glu Ala Glu
325  330  335

등록특허 10-1229731
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
340 345 350

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Thr Ser Thr
355 360 365

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Asp Asp Val Gln Leu
370 375 380

Val Gln Ser Gly Ala Glu Val Lys Pro Gly Ala Ser Val Lys Val
385 390 395 400

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp
405 410 415

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn
420 425 430

Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val
435 440 445

Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
450 455 460

Ser Leu Arg Ser Gln Asp Thr Ala Val Tyr Cys Ala Arg Tyr Tyr
465 470 475 480

Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
485 490 495

Val Ser Ser

<210> 398

<211> 1497
<212> DNA

<213> artificial sequence

<220>

<223> CD19xVH7VL2 IIIIL

<400> 398
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tcttgaaggg ettttgctca tgctactcag agatcactgga tgaactctggg gaagacaggg 120
cctggcagagg gttctgagtg gattggacag atttggcctg gagatggtgc tactaactac 180
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tcttgaaggg cagctaccaag tggctgttat gatggtgata gttatgtaa etggcactaa 540
cagatcactc caacgctetc acatctatag catccacatct agtttcgggg 600
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gtgcgagagc gggtagaagc gaaaaaactc ggggcttcag tggagctctc gttcagagct 840
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aaggaccgcg tecaaatc ac tacagacaaa tccaccagca cagcctacat ggaactgagc
agcttgcgtt ctgaggacac tgcagtctat tactgtgcaa gatattatga tgatcattac
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<210> 399
<211> 499
<212> PRT
<213> artificial sequence

<220>
<223> CD19xVH7VL2 HLHL

<400> 399

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
1      5     10     15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile

Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe

Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr

Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys

Ala Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp

Tyr Trp Gly Gln Gly Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr

Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr 1le

Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu

Asn Trp Tyr Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu 1le Tyr

Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser

Gly Ser Gly Thr Asp Phe Thr Leu Asn 1le His Pro Val Glu Lys Val
Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr  
225                 230                 235                 240
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser  
245                 250                 255
Asp Val Gln Leu Val Gln Ser Gly Ala Val Lys Lys Pro Gly Ala  
260                 265                 270
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr  
275                 280                 285
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile  
290                 295                 300
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe  
305                 310                 315                 320
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Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys  
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Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser
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165                 170                 175

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195                 200                 205

Leu Ser Ser Leu Ala Ser Glu Ser Ser Thr Ala Tyr Met Gln
210                 215                 220

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Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe
Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Glu Gly Thr Ser Thr Gly
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Gln Ser Gly Ala Glu Val Lys Pro Gly Ala Ser Val Lys Val Ser
Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val
Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro
Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Arg Val Thr
Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser
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Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
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Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe

Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr

Met Gln Leu Ser Ser Leu Ala Ser Glu Ser Ala Val Tyr Phe Cys

Ala Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp

Tyr Trp Gly Gin Gly Thr Thr Thr Val Thr Val Ser Ser Gly Gin Gly Gly

Ser Gly Gin Gly Ser Gly Gin Gly Gin Ser Gin Asp Ile Gin Leu Thr

Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gin Arg Ala Thr Ile

Ser Cys Lys Ala Ser Gin Ser Val Asp Tyr Gin Gin Gin Gin Gin Ser

Asn Trp Tyr Gin Gin Ile Pro Gin Gin Pro Gin Pro Lys Leu Leu Ile Tyr

Asp Ala Ser Gin Leu Val Ser Gly Ile Pro Gin Pro Gin Pro Gin Pro Gin

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Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
Asp Val Gln Leu Val Gln Ser Gly Ala Val Lys Lys Pro Gly Ala
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gly Lys Phe
Lys Asp Arg Val Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
Ala Arg Tyr Tyr Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
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Gly Ser Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser
Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Thr Cys
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Glu Ile Lys

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Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
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Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
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Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly 
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Ala Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp  
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Asp Ala Ala Thr Tyr His Cys Gin Gin Ser Thr Glu Asp Pro Trp Thr
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Phe Gly Gly Thr Lys Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser
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Glu Arg Ala Thr Leu Thr Cys Arg Ala Ser Ser Val Ser Tyr Met
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Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Val
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Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser
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Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
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Val Ser Ser