Early Patent on Cancer Therapy CAR-T Invalidated for Lack of Written Description

JUNO THERAPEUTICS, INC., SLOAN KETTERING INSTITUTE FOR CANCER RESEARCH

v.

KITE PHARMA, INC.

By: Estella M. Gustilo

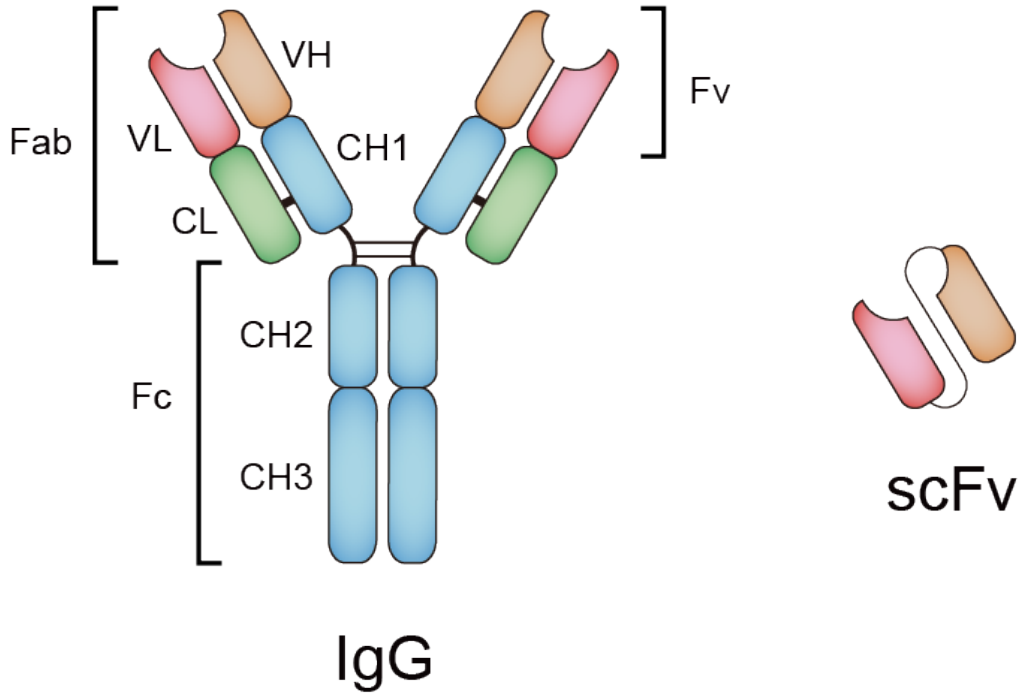
September 15, 2021

August 26, 2021

- CAFC reverses $1.2 billion jury verdict for Juno Therapeutics (Bristol Myers Squibb) and Sloan Kettering in favor of Kite Pharma (Gilead Sciences).
- Result of Kite's appeal questioning the validity of Juno's 7,446,190 patent.
- "Substantial evidence does not support the jury's verdict in Juno's favor on the issue of written description. For the claimed functional scFv genus, the '190 patent does not disclose representative species or common structural features to allow a person of ordinary skill in the art to distinguish between scFvs that achieve the claimed function and those that do not. Accordingly, we reverse." – Chief Judge Moore
- The latest of several patents involving antibodies that have been invalidated.

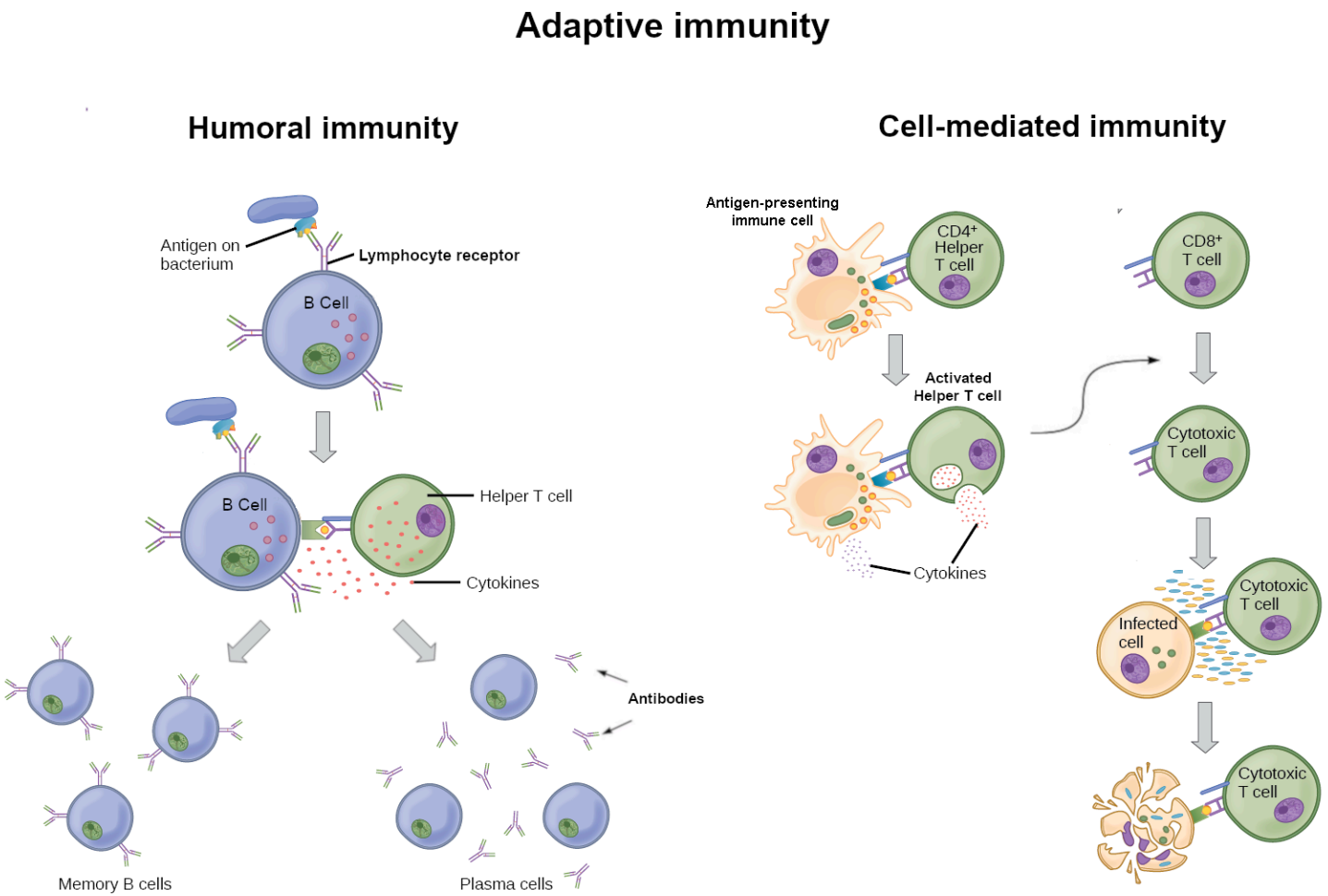
Single chain variable fragment (scFv)

- Fusion protein of the variable region of an antibody
- Came about in the late 1980's
- Significant part of the Juno's CAR-T patent '190



https://www.creativebiolabs.net/scfv-fragment-antibodies_25.htm

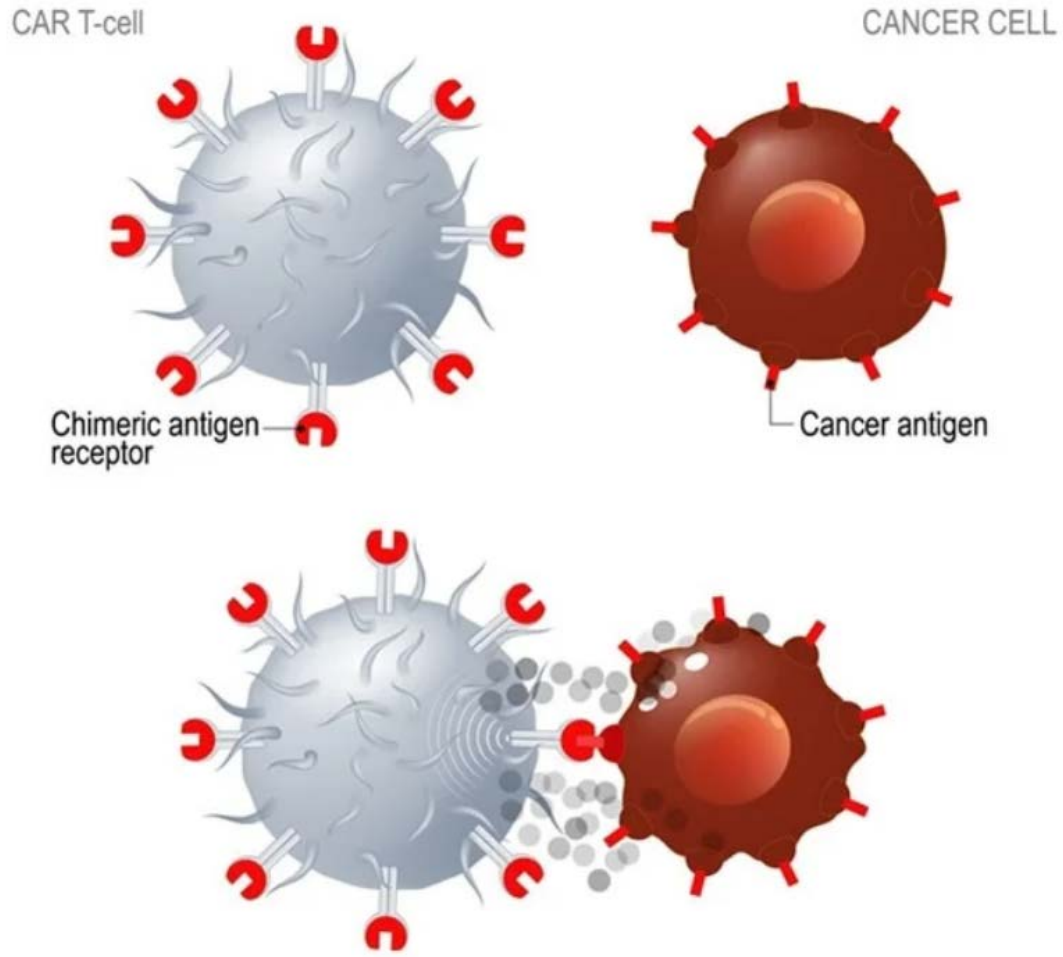
The Immune Response



https://neurohacker.com/how-the-gut-microbiota-influences-our-immune-system

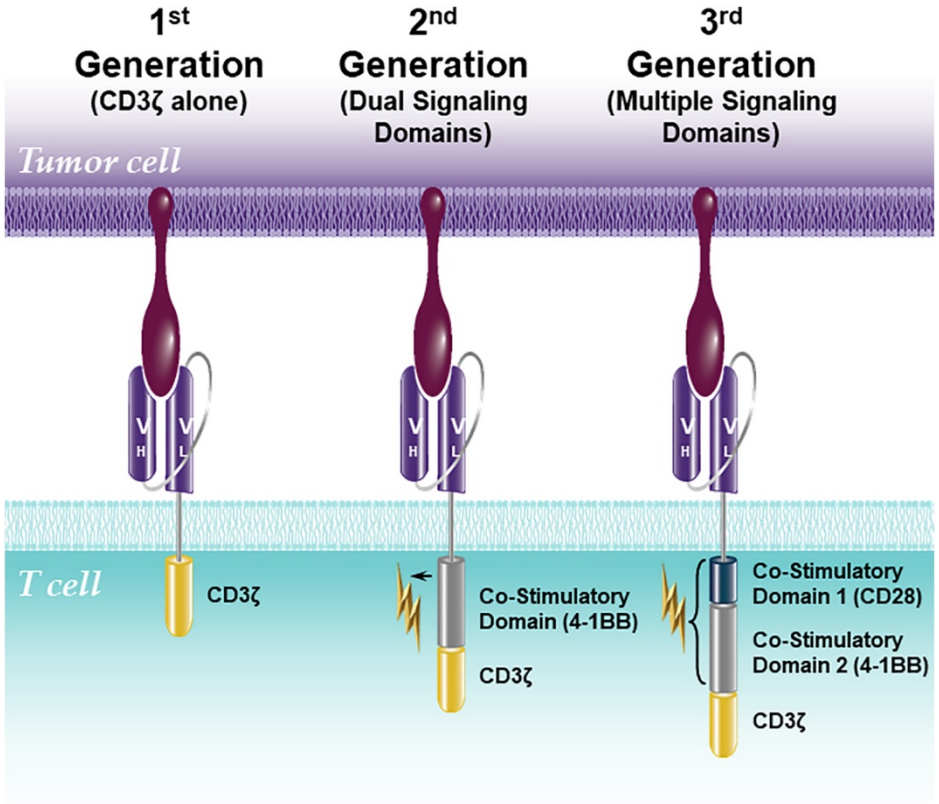
Chimeric Antigen Receptor T-cell (CAR-T) Technology

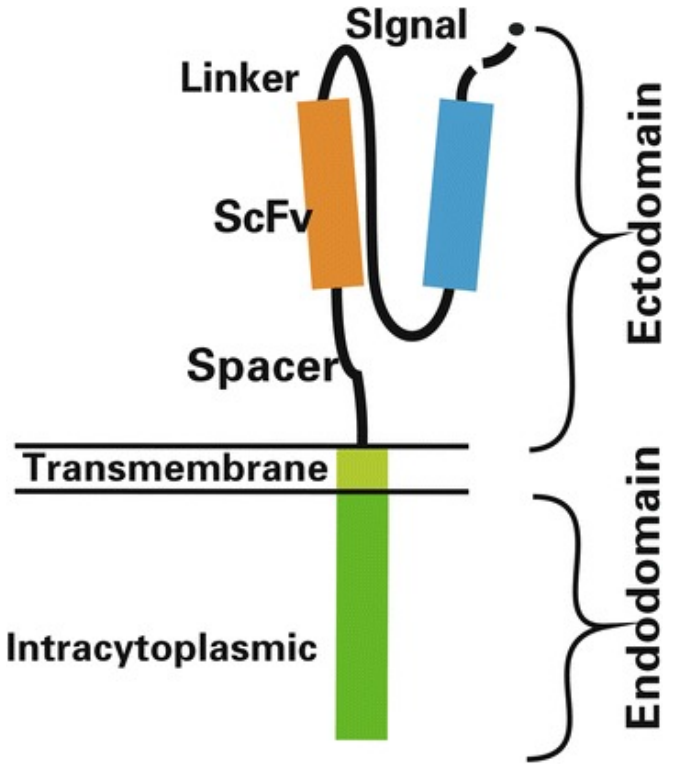
- T-cells genetically engineered to destroy cancer cells
- 1987: chimeric receptor composed of antibody and regions of T-cell receptor in Japan.
- 1989: similar type CAR-T in Israel
- By the 1990s, CARs resemble modern CAR with scFvs
- Inventor of ‘190 patent, Dr. Sadelain, pioneered working model.



Designua/Shutterstock; https://www.news-medical.net/health/CAR-T-Cell-Toxicity-and-Safety-Profiles.aspx

CARs



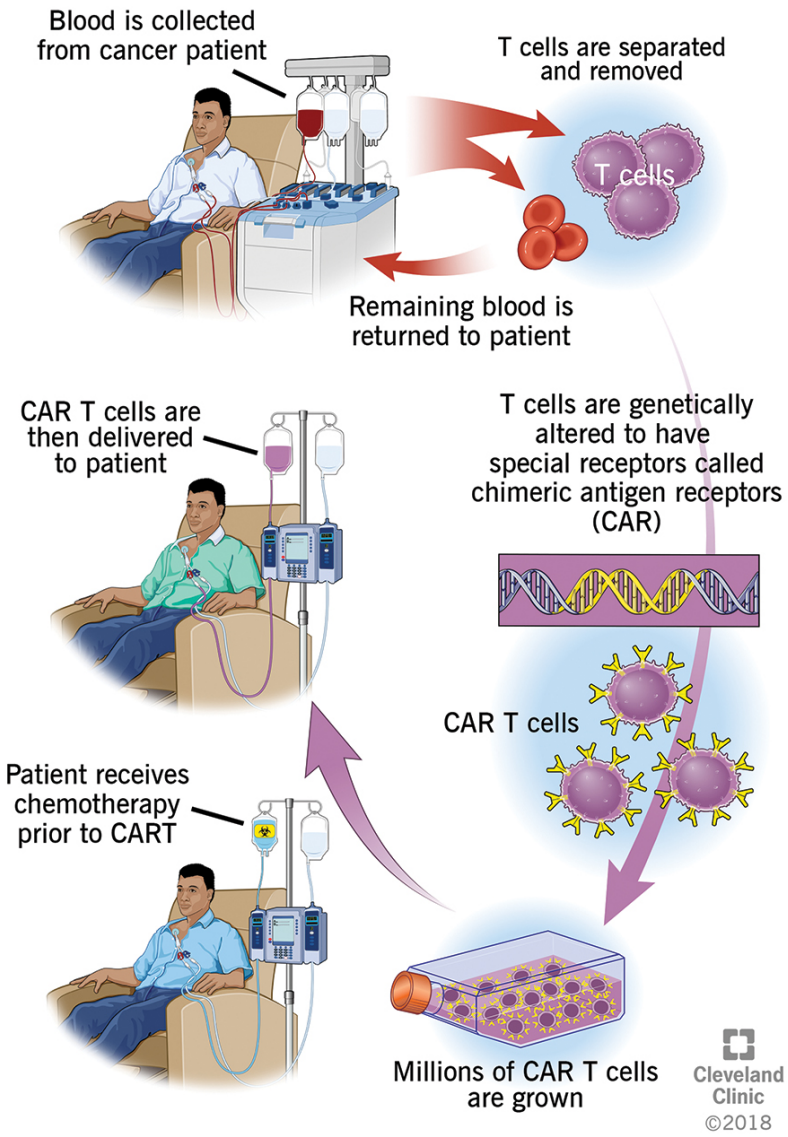


American Journal of Hematology, Volume: 94, Issue: S1, Pages: S3-S9, First published: 25 January 2019, DOI: (10.1002/ajh.25418)

Zhang C, Liu J, Zhong JF, Zhang X. Biomark Res. 2017 Jun 24;5:22. doi: 10.1186/s40364-017-0102-y. eCollection 2017.

CAR-T Therapy

- Gene Therapy
- Immunotherapy
- May cure cancer
- Very expensive
- Main problems involve Cytokine Release Syndrome and Neurotoxicity – can be deadly
- May be tailored for other diseases



https://my.clevelandclinic.org/health/treatments/17726-car-t-cell-therapy

Company	Generic Name	Drug Name	Disease Treated	Antigen recognized by scFv	Signaling Domain	FDA Approval Date
Novartis	tisagenlecleucel	Kymriah	B-cell acute lymphoblastic leukemia (ALL); Diffuse Large B-cell lymphoma (DLBCL)	CD19	41BB - CD3ζ	08/30/2017
Kite Pharma (Gilead)	axicabtagene ciloleucel	Yescarta	Diffuse Large B-cell lymphoma (DLBCL); Follicular lymphoma	CD19	CD28 - CD3ζ	10/18/2017
Kite Pharma (Gilead)	brexucabtagene autoleucel	Tecartus	Mantle Cell Lymphoma (MCL)	CD19	CD28 - CD3ζ	07/24/2020
Juno (BMS)	lisocabtagene maraleucel	Breyanzi	Diffuse Large B-cell lymphoma (DLBCL)	CD19	41BB - CD3ζ	02/05/2021
Bluebird Bio (BMS)	idecabtagene vicleucel	Abecma	Multiple myeloma	BCMA	41BB - CD3ζ	03/26/2021

Adapted from en.wikipedia.org/wiki/Chimeric_antigen_receptor_T_cell

bskb

US 7,446,190 B2 Patent, Nov. 4, 2008

(12) **United States Patent**
Sadelain et al.

(54) **NUCLEIC ACIDS ENCODING CHIMERIC T CELL RECEPTORS**

(75) Inventors: **Michel Sadelain**, New York, NY (US); **Renier Brentjens**, Maplewood, NJ (US); **John Maher**, Surrey (GB)

(73) Assignee: **Sloan-Kettering Institute for Cancer Research**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 458 days.

(21) Appl. No.: **10/448,256**

(22) Filed: **May 28, 2003**

(65) **Prior Publication Data**

US 2004/0043401 A1 Mar. 4, 2004

Related U.S. Application Data

(60) Provisional application No. 60/383,872, filed on May 28, 2002.

Claims (13)

1. A nucleic acid polymer encoding a chimeric T cell receptor, said chimeric T cell receptor comprising (a) a zeta chain portion comprising the intracellular domain of human CD3 ζ chain, (b) a costimulatory signaling region, and
(c) a binding element that specifically interacts with a selected target, wherein the costimulatory signaling region comprises the amino acid sequence encoded by SEQ ID NO:6.

2. The nucleic acid polymer of claim 1, wherein the binding element is an antibody.

3. The nucleic acid polymer of claim 2, wherein the antibody is a single chain antibody.

4. The nucleic acid polymer of claim 3, wherein the single chain antibody binds to prostate specific membrane antigen.

5. The nucleic acid polymer of claim 3, wherein the single chain antibody binds to CD19.

6. The nucleic acid polymer of claim 3, wherein the encoded T cell receptor comprises binding element-costimulatory signaling region-zeta chain portion in that order.

7. The nucleic acid polymer of claim 1, wherein the zeta chain portion comprises the sequence obtained by amplification of human zeta chain DNA with the primers of SEQ ID Nos 1 and 2.

8. The nucleic acid polymer of claim 7, wherein the binding element is an antibody.

9. The nucleic acid polymer of claim 8, wherein the antibody is a single chain antibody.

10. The nucleic acid polymer of claim 9, wherein the single chain antibody binds to prostate specific membrane antigen.

11. The nucleic acid polymer of claim 9, wherein the single chain antibody binds to CD19.

12. The nucleic acid polymer of claim 9, wherein the encoded T cell receptor comprises binding element-costimulatory signaling region-zeta chain portion in that order.

13. The nucleic acid polymer of claim 1, wherein the encoded T cell receptor comprises binding element-signaling region-zeta chain portion in that order.

History of Juno v. Kite

- December 16, 2016: PTAB upholds patent 7,446,190 after challenge from Kite on obviousness.
- October 18, 2017: FDA approves Kite's Yescarta.
- October 18, 2017: Juno sues Kite for infringing on patent 7,446,190
- December 13, 2019: Jury awards Juno about three-quarters of a billion dollars
- April 8, 2020: Judge increases damages to $1.2 billion dollars
- August 26, 2021: CAFC reverses; invalidates Juno's patent

bskb

Juno v. Kite 2019 Jury Trial

- At the Central District Court of California
- 8 days
- 22 witnesses
- Jury sided with Juno
- Awarded the plaintiffs over $778 million for Kite's infringing sales of Yescarta, enhanced damages of over $389 million for Kite's willful infringement, and an ongoing royalty of 27.6% on Yescarta revenues through patent expiration.
- The court denied Kite's post-trial motions to overturn the jury verdict and to obtain a new trial.

Prosecution of Patent Application

- Priority: 2002
- Non-Final Rejection, February 3, 2006: 112, first paragraph
- Argument: Capon v. Eshhar v. Dudas, 2005: sequences do not need to be disclosed
- RCE
- Patent Issued on 2008
- Certificate of Correction, 2013
- Patent expires Aug. 28, 2024

bskb

United States Court of Appeals for the Federal Circuit

JUNO THERAPEUTICS, INC., SLOAN KETTERING INSTITUTE FOR CANCER RESEARCH,
Plaintiffs-Appellees

v.

KITE PHARMA, INC.,
Defendant-Appellant

2020-1758

Appeal from the United States District Court for the Central District of California in No. 2:17-cv-07639-PSG-KS, Judge Philip S. Gutierrez.

Decided: August 26, 2021

MORGAN CHU, Irell & Manella LLP, Los Angeles, CA, argued for plaintiffs-appellees. Also represented by ALAN J. HEINRICH, ELIZABETH C. TUAN; GREGORY A. CASTANIAS, JENNIFER L. SWIZE, Jones Day, Washington, DC; LISA LYNN FURBY, Chicago, IL; ANDREA WEISS JEFFRIES, Los Angeles, CA; MATTHEW J. RUBENSTEIN, Minneapolis, MN.

E. JOSHUA ROSENKRANZ, Orrick, Herrington & Sutcliffe LLP, New York, NY, argued for defendant-appellant. Also represented by MELANIE L. BOSTWICK, ROBBIE MANHAS, JEREMY PETERMAN, Washington, DC; GEOFFREY DONOVAN BIEGLER, Fish & Richardson, San Diego, CA; TED G. DANE, PETER GRATZINGER, ADAM R. LAWTON, GARTH VINCENT, JEFFREY I. WEINBERGER, Munger, Tolles & Olson LLP, Los Angeles, CA.

Before MOORE, *Chief Judge*, PROST and O'MALLEY, *Circuit Judges*.

E. Joshua Rosenkranz Representing Kite

- “Juno achieved this massive $1.2 billion dollar verdict for a combination of securing a patent that awarded it vastly more than it described or taught,
- Impermissibly expanding a claim four and a half years after issuance, and
- It damages opinion that was manipulated to yield results that were many multiples of any reference likeness that Juno’s own expert described as comparable.”
- Focus on 112, then damages, then certificate of correction.

Rosencranz on the Validity of ‘190 Patent

- Structural limitations in the narrowest claim describe a genus of millions of billions of potential candidates
- The patent does not disclose the structure of the one CD19-specific scFv.
- vast majority of cancer cells have no known antigens at the time
- Binding is highly unpredictable
- 6 months to a year to make scFv
- Certificate of correction is invalid because it corrects sequence to remove one amino acid, broadening the scope

35 U.S. Code § 112 - Specification

- (a) In General.— The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.
- (b) Conclusion.— The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.
- (c) Form.— A claim may be written in independent or, if the nature of the case admits, in dependent or multiple dependent form.
- (d) Reference in Dependent Forms.— Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.
- (e) Reference in Multiple Dependent Form.— A claim in multiple dependent form shall contain a reference, in the alternative only, to more than one claim previously set forth and then specify a further limitation of the subject matter claimed. A multiple dependent claim shall not serve as a basis for any other multiple dependent claim. A multiple dependent claim shall be construed to incorporate by reference all the limitations of the particular claim in relation to which it is being considered.
- (f) Element in Claim for a Combination.— An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

(July 19, 1952, ch. 950, 66 Stat. 798; Pub. L. 89–83, § 9, July 24, 1965, 79 Stat. 261; Pub. L. 94–131, § 7, Nov. 14, 1975, 89 Stat. 691; Pub. L. 112–29, § 4(c), Sept. 16, 2011, 125 Stat. 296.)

bskb

US7446190 Claims

The invention claimed is:

1. A nucleic acid polymer encoding a chimeric T cell receptor, said chimeric T cell receptor comprising

(a) a zeta chain portion comprising the intracellular domain of human CD3 ζ chain,

(b) a costimulatory signaling region, and

(c) a binding element that specifically interacts with a selected target, wherein the costimulatory signaling region comprises the amino acid sequence encoded by SEQ ID NO:6.

2. The nucleic acid polymer of claim **1**, wherein the binding element is an antibody.

3. The nucleic acid polymer of claim **2**, wherein the antibody is a single chain antibody.

4. The nucleic acid polymer of claim **3**, wherein the single chain antibody binds to prostate specific membrane antigen.

5. The nucleic acid polymer of claim **3**, wherein the single chain antibody binds to CD19.

6. The nucleic acid polymer of claim **3**, wherein the encoded T cell receptor comprises binding element-costimulatory signaling region-zeta chain portion in that order.

7. The nucleic acid polymer of claim **1**, wherein the zeta chain portion comprises the sequence obtained by amplification of human zeta chain DNA with the primers of SEQ ID Nos 1 and 2.

8. The nucleic acid polymer of claim **7**, wherein the binding element is an antibody.

9. The nucleic acid polymer of claim **8**, wherein the antibody is a single chain antibody.

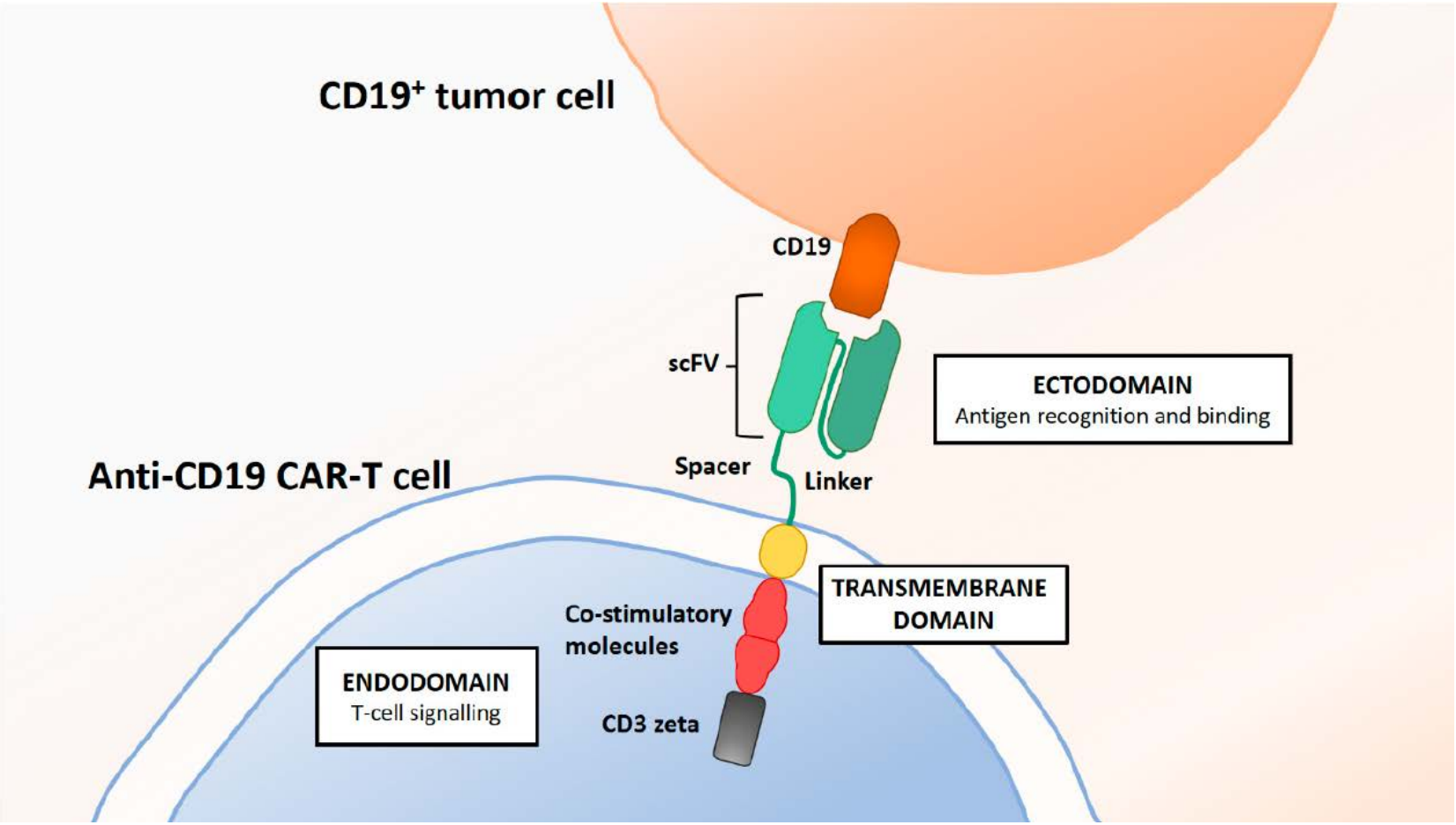
10. The nucleic acid polymer of claim **9**, wherein the single chain antibody binds to prostate specific membrane antigen.

11. The nucleic acid polymer of claim **9**, wherein the single chain antibody binds to CD19.

12. The nucleic acid polymer of claim **9**, wherein the encoded T cell receptor comprises binding element-costimulatory signaling region-zeta chain portion in that order.

13. The nucleic acid polymer of claim **1**, wherein the encoded T cell receptor comprises binding element-signaling region-zeta chain portion in that order.

* * * * *



Britten et al., Cells 2019

Morgan Chu for Juno

- Judge talks about testimony from expert witness Brocker that a lab dishwasher was able to make a scFv.
- Judge: “Why were you all not able to implement it?”
- Chu replies that there were competing projects at Juno.
- Chu describes scFvs as “fasteners” and have been around 15 years when the patent was filed.
- Judge: “The problem is you haven’t defined or given any sort of roadmap for how you would identify *which* scFv might work with *which* antigen. There are many of each. Your patent is like saying people knew about antibiotics and people knew there were bacteria out there. What people didn’t know is what antibiotic work with what bacteria. Your patent seems like it gave sort of an idea but not clear guidance on how to solve the problem.”

Specification (col. 4, lines 52-col. 5, lines 1-5)

The binding elements used in the invention are suitably antibodies that recognize a selected target. For convenience, the antibody used as the binding element is preferably a single chain antibody (scFv). Single chain antibodies may be cloned from the V region genes of a hybridoma specific for a desired target. The production of such hybridomas has become routine, and the procedure will not be repeated here. A technique which can be used for cloning the variable region heavy chain (V-H-) and variable region light chain (V-L-) has been described in Orlandi et al., Proc. Natl. Acad. Sci. (USA) 86: 3833-3837 (1989). Briefly, mRNA is isolated from the hybridoma cell line, and reverse transcribed into complementary DNA (cDNA), for example using a reverse transcriptase polymerase chain reaction (RT-PCR) kit. Sequence-specific primers corresponding to the sequence of the V-H- and V-L-genes are used. Sequence analysis of the cloned products and comparison to the known sequence for the V-H- and V-L-genes can be used to show that the cloned V-H-gene matched expectations. The V-H- and V-L-genes are then attached together, for example using an oligonucleotide encoding a (gly-ser-2-)-5-linker.

Chu on why scFvs were fully described

- Antibody and the antigen CD 19 was disclosed.
- There were two representative examples in the specification: scFvs for CD19 and PMSA antigens.
- Chu states that in Capon v. Eshhar (Fed. Cir. 2005), sequences do not need to be disclosed.
- Col. 11, lines 12-22

Example 7 To construct a CD19-specific scFv, we cloned the heavy (VH) and light (VL) chain variable regions from hybridoma cell line SJ25C1 derived cDNA by the polymerase chain reaction (PCR) using degenerate primers described by Orlandi et. al.[43] and fused these coding regions with a DNA fragment encoding for a $(Gly3Ser)_4$ spacer region. We ligated a costimulatory signaling element from human CD28, including transmembrane and extracellular portions SEQ ID NO: 6) to the 3' end of the resulting scFv and the cytoplasmic domain of the human-ζ SEQ ID NO: 3) to the 3' end of the CD28 portion to form fusion gene 19-28z.

Were the scFvs enabled?

- Chu: all scFvs have a common structure.
- Judge: “If I go to a car dealership and I tell my children to pick up the car, and the car dealership has a lot of a thousand cars, and I say ah well mine is the car with four wheels. Every car has a common structure of four wheels. I haven’t helped my children identify which car to drive off the lot.”
- Chu: “If you have an antigen, you can make an scFv.”

Capon v. Eshhar v. Dudas, August 12, 2005

- Capon and Eshhar were involved in a patent interference proceeding.
- USPTO's Board of Patent Appeals and Interferences held that neither party met the written description requirement.
- Appealed to the CAFC
- Invention: chimeric DNA encoding an scFv
- "In summary, the Board erred in ruling that '112 imposes a *per se* rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence is already known in the field. However, the Board did not explore the support for each of the claims of both parties, in view of the specific examples and general teachings in the specifications and the known science, with application of precedent guiding review of the scope of claims." – Circuit Judge Newman
- Juno used this verdict to argue its case.

Ariad Pharmaceuticals et al. v. Eli Lilly and Company, 598 F.3d 1336 (Fed. Cir. 2010)

- US6410516B1: Nuclear factors associated with transcriptional regulation
- Specifically, NF-kB, the gene encoding NF-kB, IkB and the gene encoding IkB and uses therefor.
- Licensed to Ariad from MIT, Harvard, and Whitehead Institute
- Ariad: Eli Lilly's Evista® (treats osteoporosis/prevents breast cancer) and Xigirs® (treats sepsis) infringe on the patent
- Eli Lilly ordered to pay approx. $65 million to Ariad.
- Eli Lilly appealed to CAFC.
- "We now reaffirm that § 112, first paragraph, contains a written description requirement separate from enablement, and we again reverse the district court's denial of JMOL and hold the asserted claims of the '516 patent invalid for failure to meet the statutory written description requirement." – Circuit Judge Lourie

bskb

Amgen v. Sanofi, Feb. 11, 2021

- Amgen's patents '165 and '741: antibodies lower LDL levels by binding to the PCSK9 protein and blocks it from binding to LDL receptors.
- twenty-six antibodies were disclosed – fully described
- Representative claims:

1. An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

19. The isolated monoclonal antibody of claim 1 wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3.

29. A pharmaceutical composition comprising an isolated monoclonal antibody, wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO: 3 and blocks the binding of PCSK9 to LDLR by at least 80%.

- Judgement: claims are invalid for lack of enablement.
- Kite uses this verdict to argue its case.

bskb

Prior Art on anti-CD19 scFvs

ANTI-CD19 scFvs

A:

	FR1	CDR1	FR2	CDR2	FR3
B43	**QVQLLESG**AELVRPGSSVKISCKASGYAFS	SYWMN	WVKQRPGQGLEWIG	QIWPGDGDTNYNGKFKG	KATLTADESSSTAYMQLSSLRSEDSA
25C1	----------	-----	----------	--Y----------	Q------K----------G-T-----
BLY3	----------A----------	-S---	----------	R-Y----------E	A------K----------T-V---

	CDR3	FR4
B43	VYSCAR RETTTVGRYYYAMDY	**WGQGTTVT**
25C1	------ KTISS-VDF-F --	--------
BLY3	------ S-YW -N- W----	--------

B:

	FR1	CDR1	FR2	CDR2	FR3
B43	**ELVLTQSP**ASLAVSLGQRATISC	KASQSVDYDGDSYLN	WYQQIPGQPPKLLIY	DASNLVS	GIPPRFSGSGSGTDFTLNIHPVEKVDAATYHC
25C1	--------KFMST-V-D-VSVT-	----N-GTNVA	----K---S--P---	S-TYRN-	-V-D--T----------T-TN-QSK-L-D-FY
BLY3	----------	R------NY-I-FM-	-F--K----------	A---QG-	-V-A----------S-----M-ED-T-M-FC

	CDR3	FR4
B43	QQSTED PWT	FGG**GTKLEIKRRS**
25C1	FCQYNRY-Y-	S----------
BLY3	---K-V -R-	----------

Fig. 3. Amino acid sequence alignment of the variable heavy (*A*) and light (*B*) chain regions from the three different hybridomas: B43, 25C1, and BLY3. Sequence differences are as indicated. The predicted protein sequences from the primers used for PCR are shown in bold type.

Bejcek et al. Cancer Research, 55, 2346-2351, 1995

Prior Art on anti-CD19 scFvs

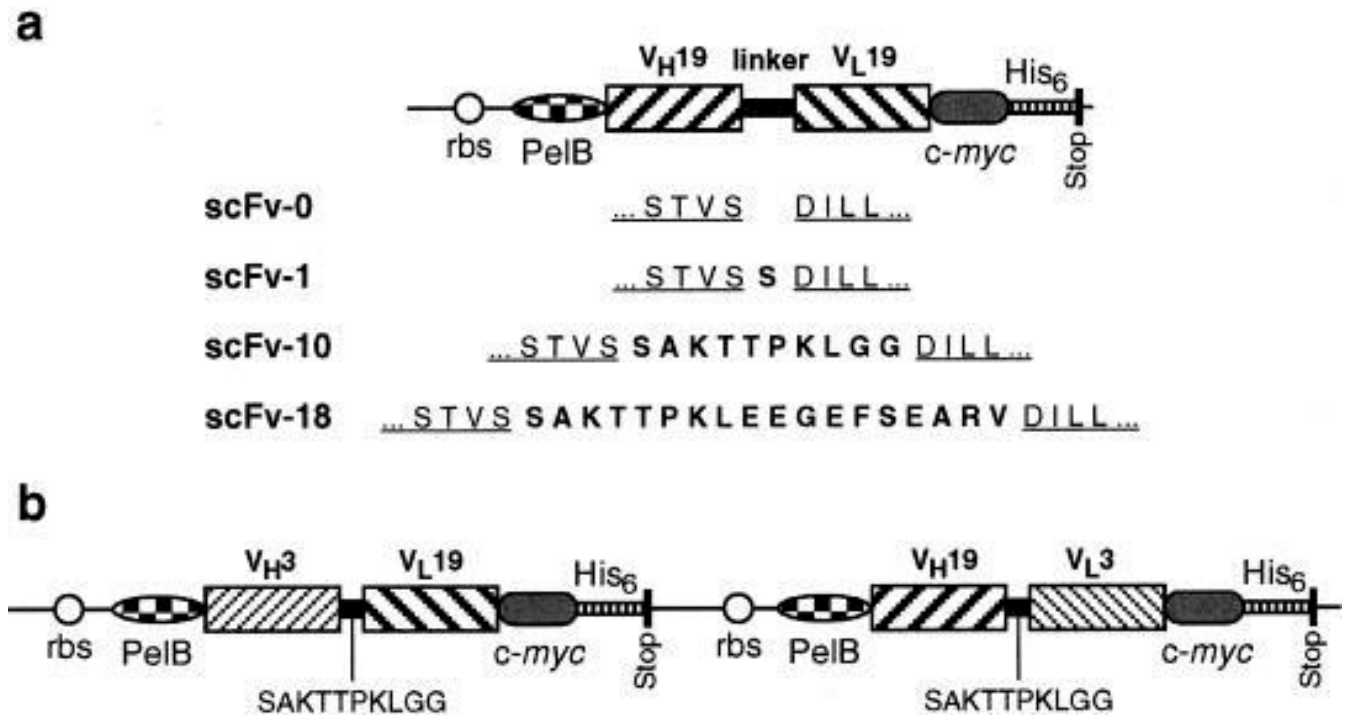
Rapid detection of recombinant antibody fragments directed against cell-surface antigens by flow cytometry

S M Kipriyanov, O A Kupriyanova, M Little, G Moldenhauer
J Immunol Methods. 1996 Sep 13;196(1):51-62. doi: 10.1016/0022-1759(96)00115-9.

Abstract
Cloning the correct genes coding for antibody variable domains (especially VL kappa) from hybridomas is often complicated by the presence of several immunoglobulin transcripts, some of them arising from the myeloma cell line. Indeed, four different VL genes were obtained after the amplification of immunoglobulin genes by PCR from the hybridoma HD37, which produces an antibody against the human CD19 B cell differentiation antigen. Most of the variants (eight out of 15) were derived from the kappa chain of the myeloma MOPC-21. For the rapid functional evaluation of recombinant antibody fragments against cell surface antigens, we established an efficient expression and detection system. First, deleted and mutated genes were eliminated by a colony screening procedure. Bacteria from picked colonies were then induced and grown in the presence of 0.4 M sucrose to increase the accumulation of soluble scFv in the periplasm (5-10 micrograms per ml of bacterial shake-tube culture). Finally, the cell-specific binding of scFv in crude periplasmic extracts was detected by flow cytometry. This procedure facilitated the efficient cloning of a functional anti-CD19 VH/VL combination from the hybridoma cDNA.

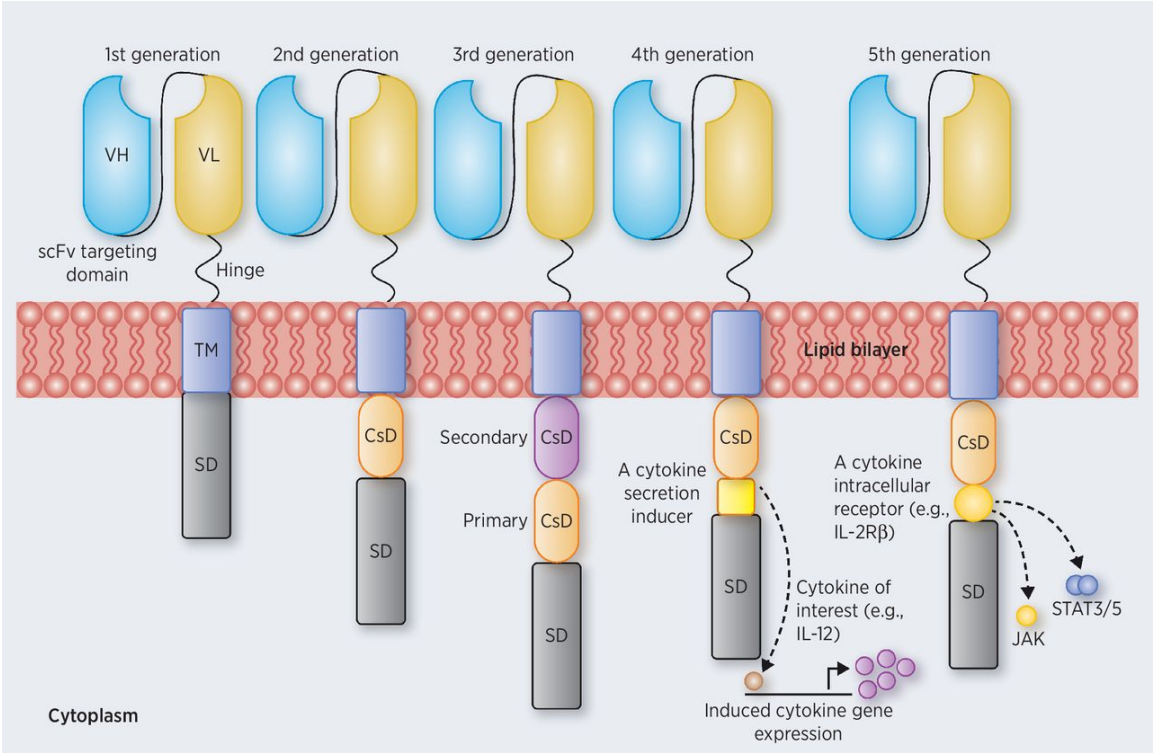
bskb

Di-, tri- and tetrameric single chain Fv antibody fragments against human CD19: effect of valency on cell binding



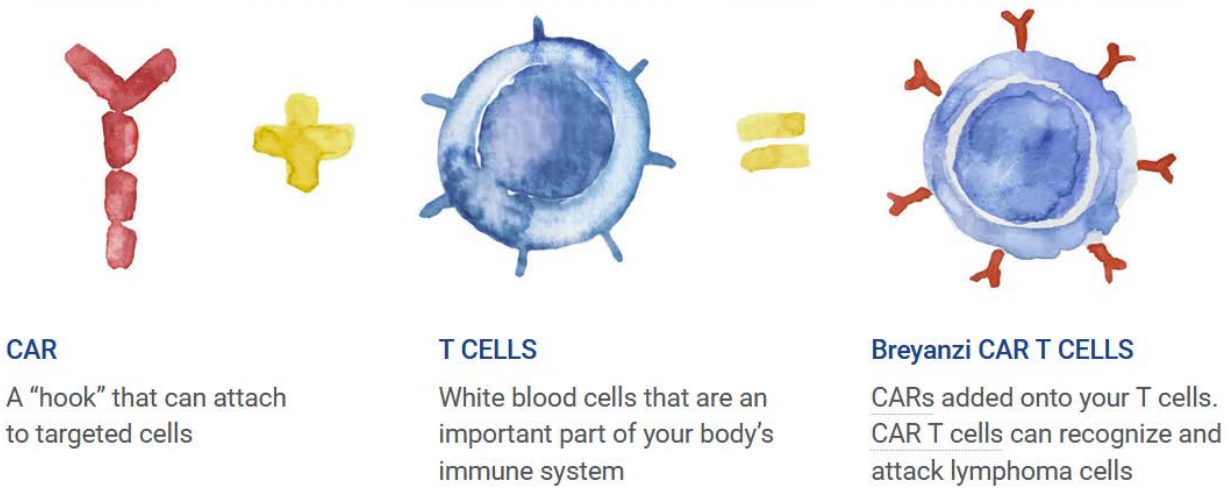
FEBS Letters, Volume: 453, Issue: 1-2, Pages: 164-168, First published: 17 June 1999, DOI: (10.1016/S0014-5793(99)00713-9)

Evolution of CARs



Kozani PS et al. Mol Cancer Ther. 2021 Jul;20(7):1223-1233

Breyanzi: Juno's Car-T therapy



CAR

A "hook" that can attach to targeted cells

T CELLS

White blood cells that are an important part of your body's immune system

Breyanzi CAR T CELLS

CARs added onto your T cells. CAR T cells can recognize and attack lymphoma cells

https://www.breyanzi.com/how-it-works/

Approved by FDA on 2021

Recent Antibody Rulings

Patents ruled invalid:

- Amgen v. Sanofi (Feb. 2021)

"*Amgen and its amici argue that our decisions on enablement (just as it was once argued with respect to written description) threaten innovation and will "devastate" the incentives to invest in drug discovery. It seems to them that the sky is falling. But enablement is part of our law, and for good reason.*" – Judges Lourie, Prost, and Hughes, June 21, 2021

- Teva v. Eli Lilly (migraine treatment, Aug. 16, 2021)
- Juno v. Kite (Aug. 26, 2021)

bskb