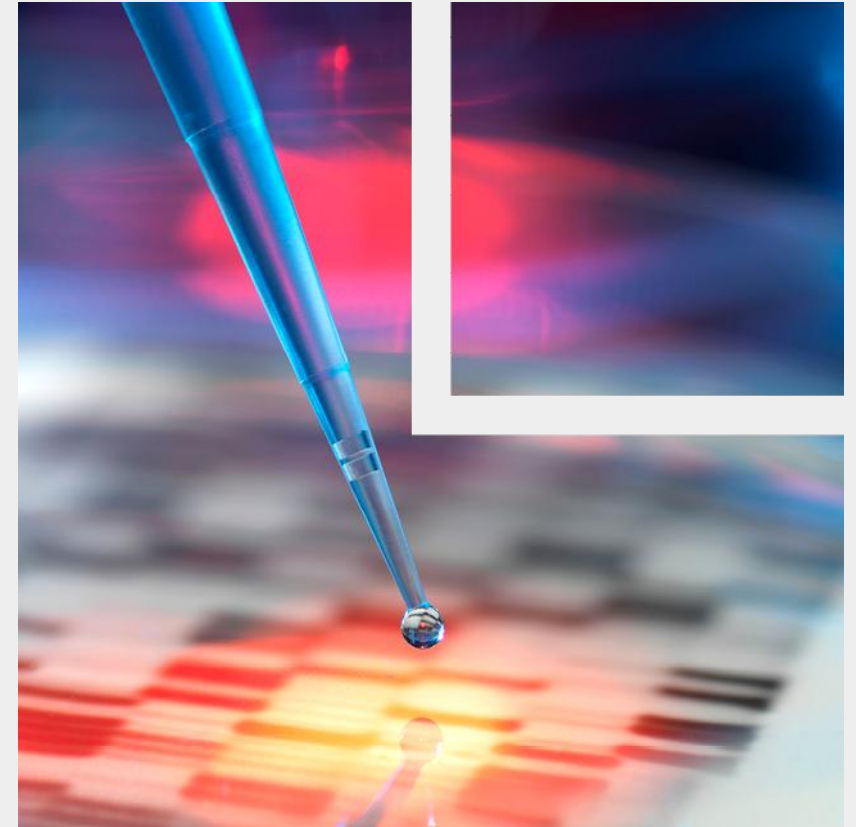


IP Portfolio for Cell Therapy Global Expansion

Ryan Hagglund

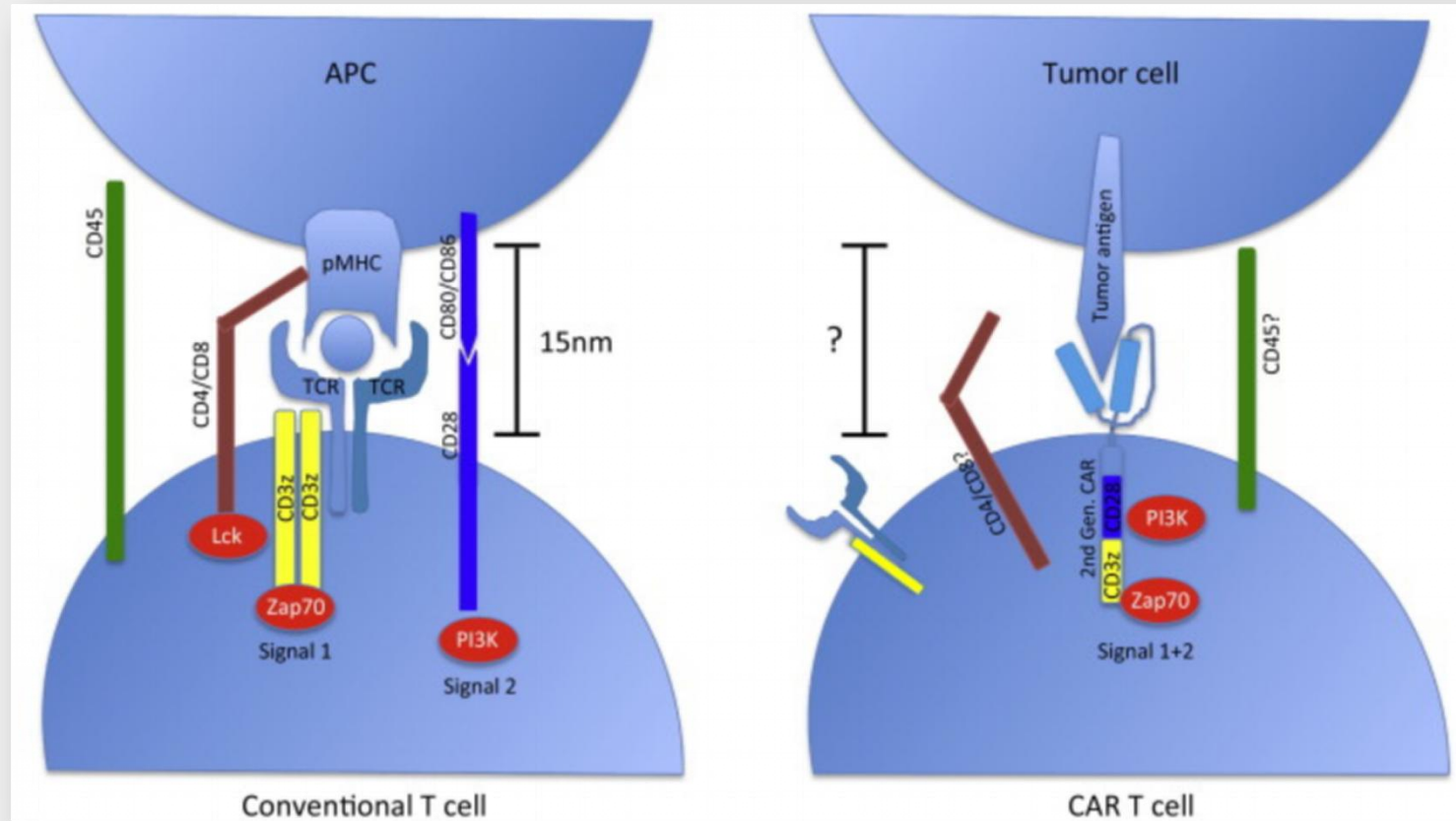
Partner (Patent Litigation and Counseling, New York)





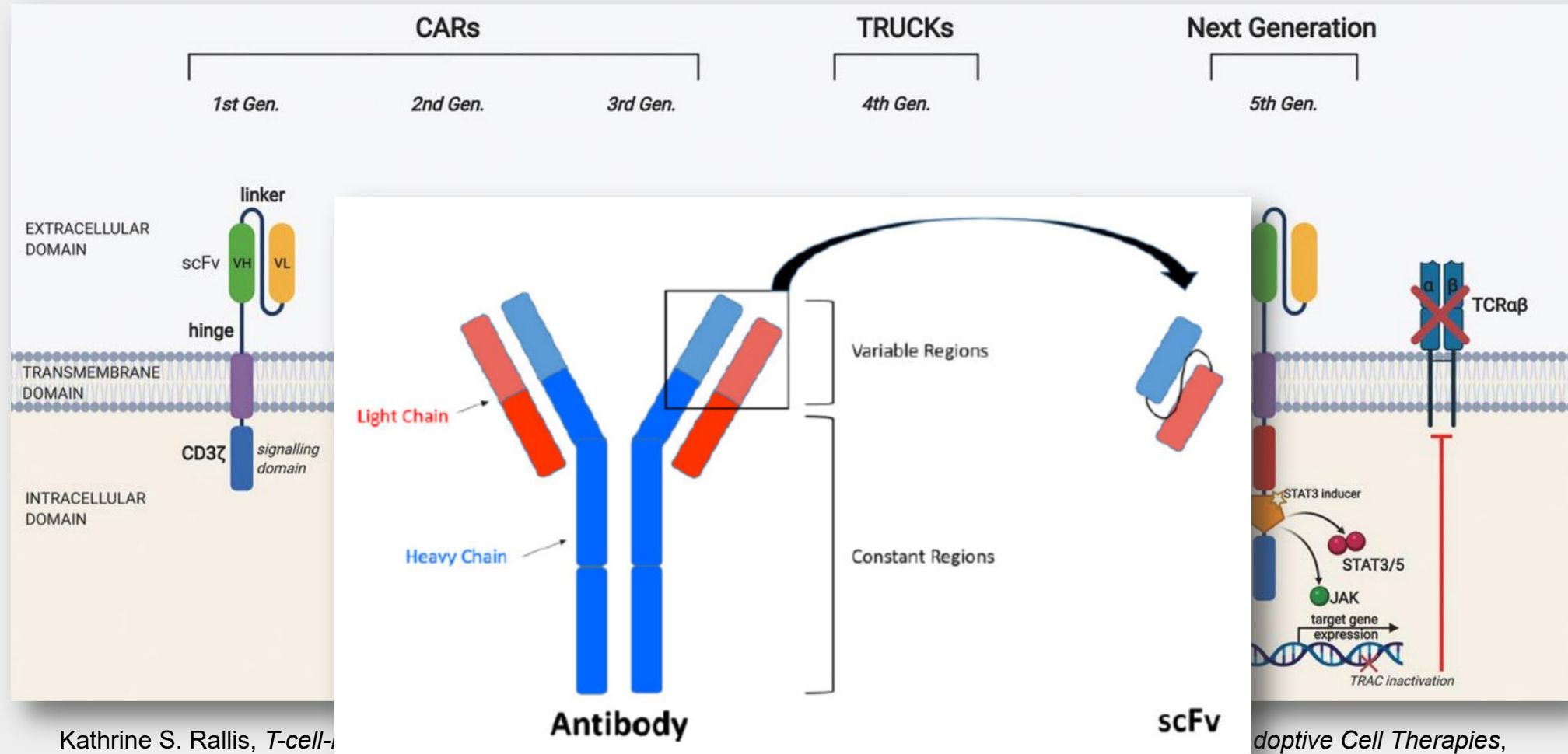
CAR-T Technology

Chimeric Antigen Receptor (CAR) T Cell Therapy



Shivani Srivastava & Stanley R. Riddell, *Engineering CAR-T cells: Design Concepts*, 36 Trends in Immunology P494 (2015).

CAR Structure and Development



Kathrine S. Rallis, *T-cell-*
41 Anticancer Res. 1141, 1147, fig. 3 (2021).

adoptive Cell Therapies,

Broad Range of CAR-T-Related Patents

- CAR
 - Bispecific tandem CAR (containing two scFvs)
- CAR components
 - Structures comprising specific signaling, co-stimulatory signaling, and/or transmembrane domains
 - Optimized signaling domains
- Nucleotides encoding the CAR (or components)
- Vectors comprising nucleotides encoding the CAR (or components) (e.g., lentiviral transduction vectors)
- Immune cells comprising the CAR
- Compositions comprising said immune cells
- Methods of treatment
- Methods of manufacture
 - Lentiviral transduction, gene editing, and transposon-based gene transfer methods
 - Advanced manufacturing processes, including resulting accelerated *ex vivo* expansion times
- Reagents for CAR-T-cell manufacture (e.g., gene editing components, transposon-based gene transfer components)
- Methods relating to *in vivo* CAR delivery using targeted vectors or lipid nanoparticles



United States CAR-T Patent Considerations

CAR-T Patentability in the United States

- Unlike China and Europe, express method of treatment claims are permitted in the U.S.
 - Example Claim: A method for treating disease X comprising administering compound Y to a patient in need thereof.
- Given the proliferation of patents and publications in the CAR-T space, prior art can be crowded, which can pose issues relating to nonobviousness.
 - Narrow claims to novel CAR sequences generally not susceptible to an obviousness challenge.
- The *written description* and *enablement* requirements of 35 U.S.C. § 112(a) significantly limit the breadth of claims to the CAR beyond those specific CARs actually disclosed in the specification.

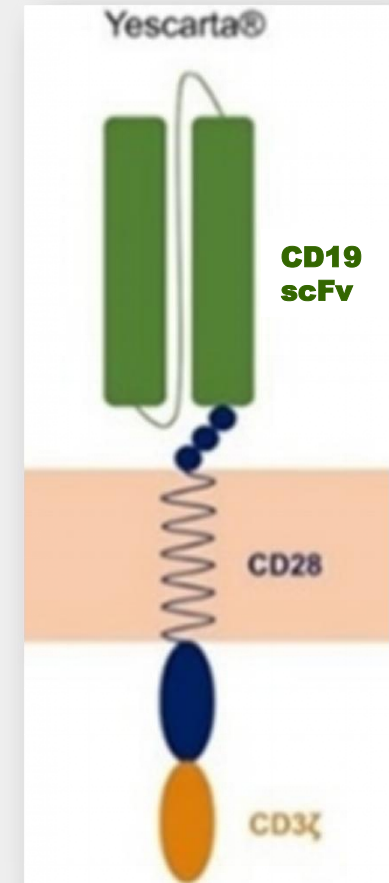
Written Description and Enablement

35 U.S.C. § 112(a)

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

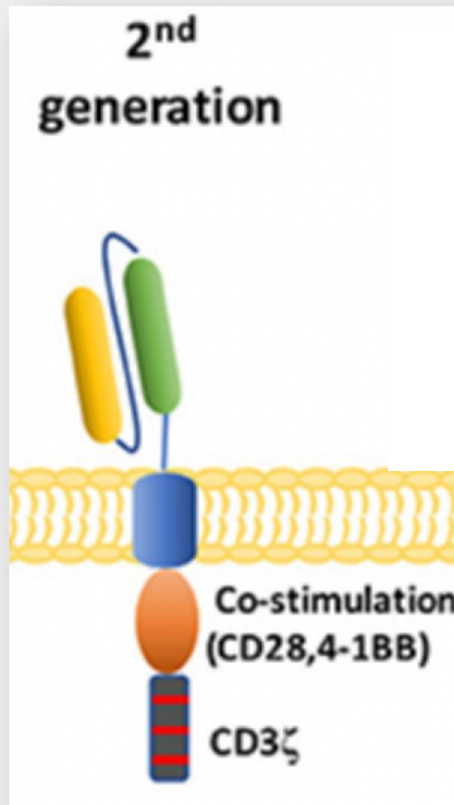
Written Description

Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021)



Written Description

Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021)



Lijun Zhou & Yu J. Cao, *Engineered T Cell Therapy for Cancer in the Clinic*, 10 *Frontiers in Immunology* 2250, at 4, fig. 2 (2019).

(12)	United States Patent Sadelain et al.	(10) Patent No.: US 7,446,190 B2 (45) Date of Patent: Nov. 4, 2008
(54)	NUCLEIC ACIDS ENCODING CHIMERIC T CELL RECEPTORS	Dranoff et al., Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity, Proc. Natl. Acad. Sci. USA, 1993, pp. 3539-3543.
(75)	Inventors: Michel Sadelain, New York, NY (US);	
(73)	Assignee:	
(*)	Notice of Allowance	
(21)	Application No.	
(22)	Filed:	
(65)	US 2008/0111444 A1	
(60)	Provisional Application No. 60/772,200	
(51)	Int. Cl. C07H 21/00	
(52)	U.S. Class. 435/254	
(58)	Field of Classification	
(56)	References Cited	
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	4,859,331	
	4,946,777	
	5,302,333	
	5,328,660	
	5,339,019	
	5,405,599	
	5,585,099	
	5,686,223	
	5,728,333	
	6,051,444	
	6,344,444	
	2003/007722	
	FOREIGN PATENT DOCUMENTS	
WO	WO/96/29421 A1	9/1996
WO		
WO		
	Chimeric T cell receptors (TCR) are provided that combine, in a single polypeptide chain, the intracellular domain of a TCR	
	5. The nucleic acid polymer encodes a chimeric T cell receptor, said chimeric T cell receptor comprising: (a) a zeta chain portion comprising a portion of human CD3 ζ chain, (b) a costimulatory signaling element, and (c) a binding element that binds to a selected target, wherein the binding element region comprises the amino acid sequence SEQ ID NO:6.	
	2. The nucleic acid polymer encodes a chimeric T cell receptor, said chimeric T cell receptor comprising: (a) a zeta chain portion comprising a portion of human CD3 ζ chain, (b) a costimulatory signaling element, and (c) a binding element that binds to a selected target, wherein the binding element region comprises the amino acid sequence SEQ ID NO:6.	
	3. The nucleic acid polymer encodes a chimeric T cell receptor, said chimeric T cell receptor comprising: (a) a zeta chain portion comprising a portion of human CD3 ζ chain, (b) a costimulatory signaling element, and (c) a binding element that binds to a selected target, wherein the binding element region comprises the amino acid sequence SEQ ID NO:6.	
	body is a single chain antibody	
	Kroczyk et al., Antigen-specific targeting of CD28-mediated T cell co-stimulation using chimeric single-chain antibody variable fragment-CD28 receptors, Eur. J. Immunol., 1996, pp. 2304-2309, vol. 26.	
	Anni et al., Three-Dimensional Structure of an Antigen-Antibody Complex at 2.8 Å Resolution, Science, 1986, pp. 747-753, vol. 233.	
	TCR's are able to provide both the activation and the co-stimulation signals from a single molecule to more effectively direct T-lymphocyte cytotoxicity against the selected target and T-lymphocyte proliferation.	
	13 Claims, 8 Drawing Sheets	

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

Written Description

Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021)

Disclosure of '180 Patent:

- Specification disclosed two scFvs by alphanumeric designation only as part of CAR working embodiments.
- SJ25C1 scFv binds CD19 (protein that appears on the surface of diffuse large B-cell lymphoma cells).
- J591 scFv binds PSMA (protein on the surface of prostate cancer cells).
- No amino acid sequence or additional details regarding any scFv disclosed.
- Prior art disclosed up to five CD19-specific scFvs.

Written Description

Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021)

Case Background:

- Kite knew that its collaborator, the National Cancer Institute, had obtained/copied the CAR structure from the inventor.
- After announcement of the collaboration and CAR publication, Memorial Sloan Kettering (the owner of the '190 patent) sought and received a CoC for the '190 patent to cover the CD28 region ACI/Kite was using.
- Kite aggressively sought a license from Sloan (telling Sloan it needed to license the '190 patent), but Sloan decided to grant an exclusive license to Juno, rejecting Kite's and other parties' requests to license the '190 patent
- Kite's design-around efforts failed.
- Juno and Sloan sued Kite for infringement of the '190 patent after the launch of YESCARTA® in the Central District of California in 2017.
- After a two-week jury trial, the '190 patent was found infringed and not invalid and the court awarded Kite over \$1.2 billion in damages as well as an ongoing running royalty of 27.6%.

Written Description

Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021)

Written Description of ScFv Claims:

- Federal Circuit reversed the jury verdict and damages award, finding the '190 patent invalid for lack of written description.
- Written description of a generic claim requires representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one can visualize or recognize its members.
- Disclosed no details about the two species beyond the alphanumeric designations J591 and SJ25C1 for a skilled artisan to determine how or whether they are representative of the entire claimed genus.
- Does not provide information sufficient to establish that a skilled artisan would understand how to identify the species of scFvs capable of binding to the limitless number of targets (known and unknown) as the claims require.
- Without more in the disclosure, such as the characteristics of the exemplary scFvs that allow them to bind to particular targets or nucleotide sequences, the mere fact that scFvs in general bind (or that how to make them was known) does not demonstrate that the inventors were in possession of representative species or the claimed invention.
- To satisfy the written description requirement, the inventors needed to convey that they possessed the claimed invention, which encompasses all scFvs, known and unknown, as part of the claimed CAR that bind to a selected target.
- Specification provides no means of distinguishing which scFvs will bind to which targets and thus that scFvs generally known insufficient to support claims requiring binding to a selected target.

Written Description

Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021)

Written Description of ScFv Claims:

- Court distinguished *Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005).
 - PTAB found claims directed to 1st generation CARs (e.g., scFv binding domain and signaling domain) invalid for want of written description because the specification did not disclose the sequences of the chimeric genes.
 - Prior art disclosed over 785 mouse antibody DNA light chains and 1,327 mouse antibody DNA heavy chains.
 - Specifications disclose specific examples and procedures for making.
 - Federal Circuit vacated and remanded, holding that the Board erred in imposing a per se rule requiring disclosure of the sequences of claimed chimeric genes when the sequences were known in the field.
 - Board did not separately analyze broad and narrower claims, and Federal Circuit instructed it to consider if there was adequate support for each claim separately in light of the specific examples and general teachings in the specifications and known science.
- Federal Circuit in *Juno* rejected the argument that *Capon* held that scFvs were well-known CAR components that did not need to be detailed in CAR patents' specification.
 - *Capon* did not hold the written description requirement met, but vacated the Board's decision for imposing too high a standard and remanded for the Board to consider the evidence and determine whether the specification adequately supported the claims at issue.
 - More known in the prior art in *Capon*, particularly when the inventors here used only two scFvs out of the vast number of possibilities.

Written Description

Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021)

Written Description of ScFv Claims:

- Specification also failed to disclose structural features supporting the genus.
- No details regarding the characteristics, sequences, or structures that would allow a person of ordinary skill in the art to determine which scFvs will bind to which target (or which ones would bind any target).
- Court founds that the patent claimed problem to be solved while claiming all solutions to it, covering any compound later actually invented and determined to fall within the claim's functional boundaries, which fails the written description requirement.
- Not cured because scFvs in general were well known or have same general structure.

Written Description

Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021)

Written Description of CD19 ScFv Claims:

- Diversity of the functional scFv genus, the unpredictability of an scFv's binding ability, and that the prior art had, at most, five CD19-specific scFvs as of the priority date are all relevant to the written description inquiry.
- Specification discloses no details about any CD19-specific scFv, such as an exemplary amino acid sequence, a shape, or general characteristics that would allow this target-specific scFv to bind.
 - Provides only an alphanumeric designation, SJ25C1, as the source for the CD19-specific scFv.
 - Provides no details about which scFvs bind to CD19 in a way that distinguishes them from scFvs that do not bind to CD19.
- Without more guidance, in a vast field of possible CD19-specific scFvs with so few of them known, the court found that no reasonable jury could find the inventors satisfied the written description requirement.
- That CARs were made with up to 30 CD19 scFvs after the priority date as of which written description is assessed is irrelevant.

Written Description

Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021)

Written Description of CD19 ScFv Claims:

- Rejected argument that the real invention was the CAR backbone, not scFvs since the claims were not so limited and also included the functional scFv for binding the target and the test is the same whether a claim element is essential or auxiliary to the invention.
- Evidence that no functional CD19 scFv that had not been shown to work as a part of the claimed CAR presupposes an scFv already known to be functional and does not support possession of the full scope of possible CD19-specific scFvs, particularly given the expansive genus and the small number of known CD19 scFv species at the time.

Written Description

Written Description Requirement Met—Representative Species

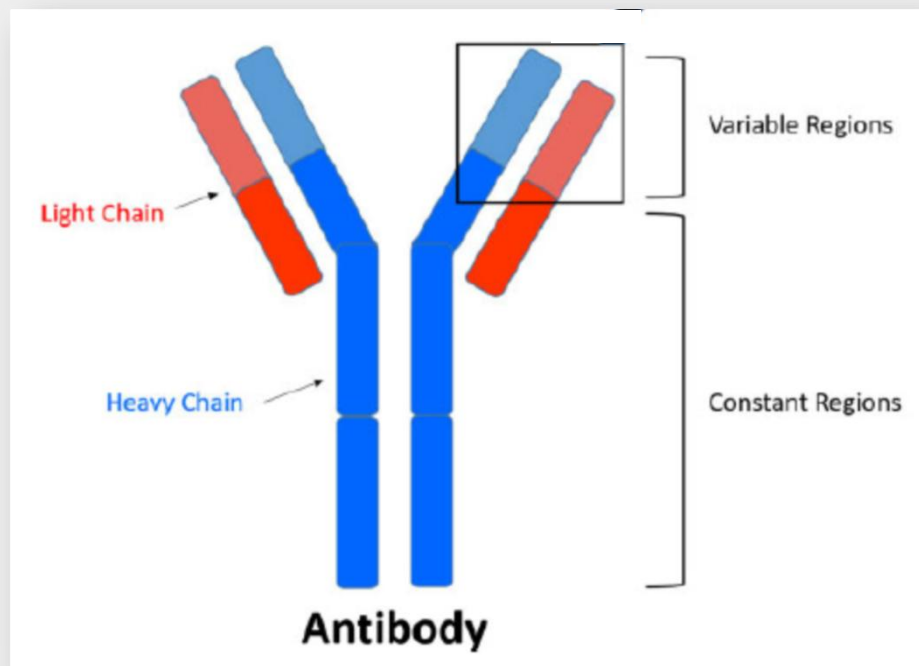
Amgen Inc. v. Sanofi, No. 14-1317, 2019 U.S. Dist. LEXIS 146305 (D. Del. Aug. 28, 2019):

- Claims directed toward antibodies that bind PCSK9 and block it from binding to the LDL receptor.
- Specification disclosed 26 working examples of antibodies that bind PCSK9 and block LDL receptor binding.
- District court held that substantial evidence supported jury finding of no invalidity for lack of written description with respect to disclosure of representative species.
- Substantial evidence of similarity in the three-dimensional structure of the antibodies disclosed in the patent and the accused competitor antibodies.
- Amino acid sequence differences between the competitor antibodies are not as extreme as in *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014).
 - 80% similarity between the disclosed antibodies and the competitor antibodies' amino acid sequences, and the disclosed antibodies cover more classes of antibodies than the patent disclosed in *Abbvie* (i.e., 8 families of binding/blocking antibodies).
- Substantial evidence of functional similarity as the disclosed antibodies blocked PCSK9 binding to LDL-R through a variety of binding interactions while binding to different residues across the sweet spot of PCSK9 that interacts with LDL-R.

Written Description

Written Description Requirement Met—Variable Regions Described

Daniel Kolker, USPTO, *Antibodies and the Written Description Requirement of 35 U.S.C.112(a)* (Sept. 17, 2020):

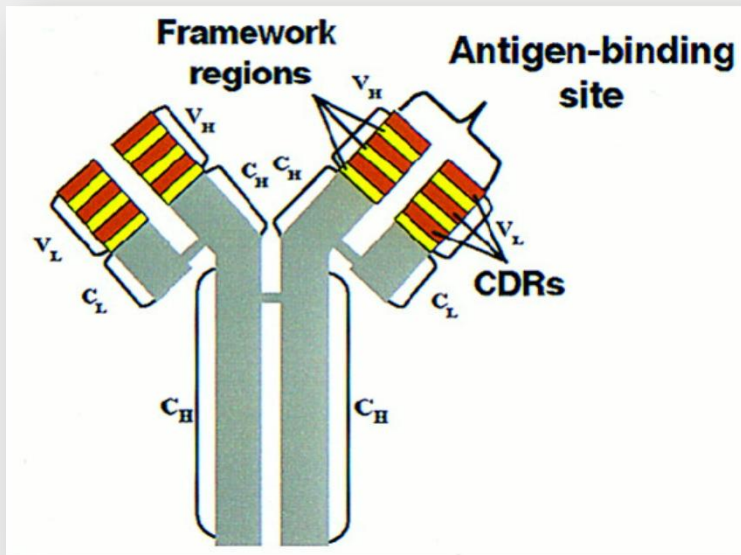


- Disclosure of one antibody containing the specified V_H and V_L sequences meets the written description requirement for claims defining antibody binding a certain antigen by V_H and V_L sequences.
- Function (antigen binding) correlated to structure/sequence (variable region sequences).
- Person of ordinary skill in the art can envision antibodies with different constant regions.

Written Description

Written Description Requirement Met—CDRs Described

Ex parte Grosmaire, No. 2017-006468, 2018 Pat. App. LEXIS 8348 (P.T.A.B. Oct. 12, 2018):



- Claims directed to humanized or chimeric antibodies, fragments, and immunoglobulin binding fusion proteins binding CD37 comprising heavy and light chains that respectively contain specific sequences for each of the 3 heavy chain CDRs and 4 heavy chain framework regions as well as specific sequences for each of the 3 light chain CDRs and 4 framework regions in order found to meet the written description requirement where several such binding proteins (humanized and nonhumanized) containing such sequences disclosed.
- Recitation of the CDR sequences and their positional information within the framework in conjunction with the characterized antigen to which the CDR sequences bind provides sufficient descriptive support for a genus of immunoglobulin binding proteins that contain these sequences as claimed.
 - Specification provides sufficient description of the amino acid residues necessary to interact with the binding protein (*i.e.*, the CDRs), the position of these critical residues in the structure of the binding protein framework, and the known antigen CD37.
 - Claimed proteins limited to those with immunoglobulin structure (which is known)
 - Humanized and chimeric immunoglobulins and that the CDRs can be placed on other frameworks are known.

Malik E. Juweid, *Radioimmunotherapy of B-Cell Non-Hodgkin's Lymphoma: From Clinical Trials to Clinical Practice*, 43 J. Nuclear Med. 1507, 1509 fig. 1 (2002).

Written Description

Written Description Requirement Met—Methods where all Antibodies to Target Work

Teva Pharms. Int'l GmbH v. Eli Lilly & Co., 172 F.4th 1367 (Fed. Cir. 2026):

- Court found claims to methods of using humanized antibodies to CGRP to treat headache met the written description requirement even though only one such antibody was disclosed because “a skilled artisan would have understood from the specification that all humanized anti-CGRP antagonist antibodies treat headache.”
- “[A]sserted claims are not to ‘methods of antagonizing CGRP using humanized antibodies that antagonize CGRP’; they are to methods of treating headache using such antibodies— something different from the function that characterizes these antibodies”, specifically, the use of a well-known genus (i.e., CGRP antibodies) used as part of a different invention (i.e., headache treatment).
- [A] reasonable jury could have found that a skilled artisan . . . would have understood that anti-CGRP antagonist antibodies were well known (and disclosed), that humanizing was routine (and disclosed), and that, insofar as treating headache is concerned, all humanized versions of such antibodies work.
 - “[A] reasonable jury could have found that a skilled artisan reading the specification would have understood that ‘anti-CGRP antagonist antibodies could bind to different regions of CGRP and still accomplish the claimed function of treating headache.’”
 - “[D]ifferences in binding regions among humanized anti-CGRP antagonist antibodies do not prevent those antibodies from performing in the claimed method of treating headache.”
- Specification therefore disclosed members of the genus that are sufficiently representative for purposes of the claimed invention.

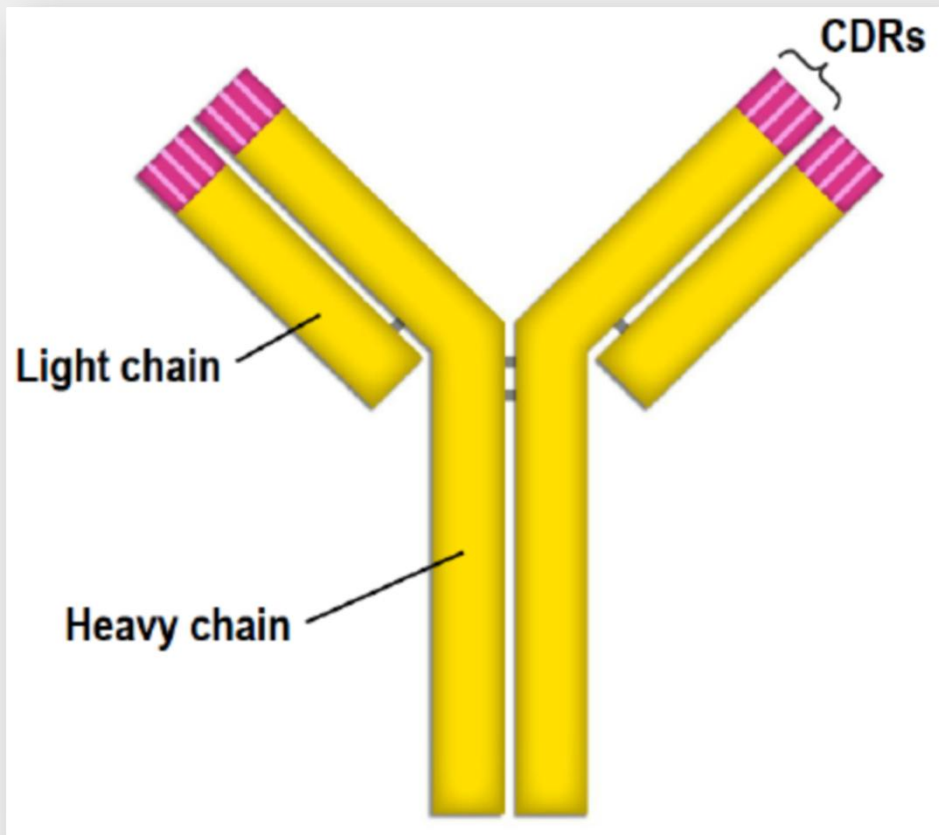
Written Description

Written Description in the CAR-T Context—Unpredictability of ScFvs in CAR-T Cells

- Unlike the method of treatment of headache in *Teva* in which any antibody to CGRP works, it is not the case that a CAR containing any scFv binding a given target, CAR-T cells incorporating such a CAR, or methods of treatment of cancer using such a CAR or CAR-T cells would work.
 - CARs containing some scFvs directed to a given target do not actually bind the target because of cell surface aggregation.
 - CARs containing some scFvs directed to a given target are rarely expressed.
 - Particular scFv directed to a given target incorporated into a CAR affects CAR expression efficiency and stability on T cells.
 - CAR-T cells with CARs with different scFvs binding the same antigen vary in metabolism, proliferation, and nutrient uptake.
Aliya Lakhani et al., *Extracellular Domains of CARs Reprogram T-Cell Metabolism without Antigen Stimulation*, 6 Nature Metabolism 1143 (2025); Chengcheng Zhang et al., *Screening and Characterization of the scFv for Chimeric Antigen Receptor T cells Targeting CEA-Positive Carcinoma*, 2023 Frontiers in Immunology 1182409; Kento Fujiwara et al., *Impact of ScFv Structure in Chimeric Antigen Receptor on Receptor Expression Efficiency and Antigen Recognition Properties*, 527 Biochemical & Biophysical Res. Commun. 350 (2020).
 - CARs with different scFvs have different cell phenotypes and functions.

- Thus, in contrast to the method claims in *Teva*, a claim directed to CAR-T cells incorporating a CAR containing any scFv binding a given target or method of treatment of cancer using such CAR or CAR-T cells would not meet the written description requirement because disclosure of a limited number of scFvs would not be representative of a genus covering all scFVs binding a target as it is not the case that incorporation of any scFv into the CAR works in CAR-T cells or methods of

***Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023)**

[illegible]

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, C718, 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%.

1. An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

2. The isolated monoclonal antibody of claim 1, wherein the isolated monoclonal antibody is a neutralizing antibody.

7. The isolated monoclonal antibody of claim 2, wherein the epitope is a functional epitope.

Enablement

Amgen Inc. v. Sanofi, 598 U.S. 594 (2023)

Disclosure:

- Specification identified the amino acid sequences of 26 antibodies meeting the claim requirements and disclosed three-dimensional structures of 2 of these 26 antibodies.
- Specification also disclosed 2 methods of making the claimed antibodies.
 - “Roadmap” directing scientists to: (1) generate a range of antibodies in the lab; (2) test those antibodies to determine whether any bind to PCSK9; (3) test those antibodies that bind to PCSK9 to determine whether any bind to the sweet spot as described in the claims; and (4) test those antibodies that bind to the sweet spot as described in the claims to determine whether any block PCSK9 from binding.
 - Conservative substitution requires scientists to: (1) start with an antibody known to perform the described functions; (2) replace select amino acids in the antibody with other amino acids known to have similar properties; and (3) test the resulting antibody to see if it also performs the described functions.

Enablement

Amgen Inc. v. Sanofi, 598 U.S. 594 (2023)

- “[A] specification may call for a reasonable amount of experimentation to make and use a patented invention[, and w]hat is reasonable in any case will depend on the nature of the invention and the underlying art.”
- “Amgen has failed to enable all that it has claimed, even allowing for a reasonable degree of experimentation.”
- Court found lack of enablement because Amgen attempted to “monopolize an entire class of things defined by their function—every antibody that both binds to particular areas of the sweet spot of PCSK9 and blocks PCSK9 from binding to LDL receptors [but] this class of antibodies does not include just the 26 . . . described by their amino acid sequences, but a ‘vast’ number of additional antibodies that [were] not.”
- The two approaches disclosed “amount to little more than two research assignments.”
 - While such approaches “might suffice to enable other claims in other patents—perhaps because . . . the inventor identifies a quality common to every functional embodiment, they do not here.”
 - Rather “[t]hey leave a scientist . . . forced to engage in ‘painstaking experimentation’ to see what works.”
- A specification that “offers persons skilled in the art little more than advice to engage in ‘trial and error’” is not sufficient for enablement.

Enablement

Amgen Principles Apply in the CAR-T Context

Ex parte O'Donoghue, No. 22-004500, 2023 Pat. App. LEXIS 3025 (P.T.A.B. Sept. 11, 2023):

- Relying on *Amgen*, the Board found that claims directed to CARs incorporating a modified α or β chain containing an scFv or single domain antibody directed to any target fused to a portion of the extracellular domain of either the TCR α or β chain without the variable region and a modified other of the α or β chains containing a portion of the extracellular domain of the other of the TCR α or β chain without the variable region were invalid for want of enablement.
- Claims are broader than those found invalid in *Amgen* inasmuch as they cover a genus of chimeric TCRs that bind to any part of any cell surface antigen and activate the immune cell when the chimeric TCR binds rather than binding a specific part of a specified single protein.
- Disclosure less than that found insufficient in *Amgen*—the specification only disclosed one chimeric TCR that binds to mesothelin, one scFv that binds mesothelin, and one nanobody that binds to GFP while 26 antibodies and the structures of two of them were disclosed in *Amgen*.
- Experimentation here is the same general research assignment proposed by the inventors in *Amgen* as it includes determination of the expressed chimeric TCR binds to the target antigen and activates the immune cell.
- As in *Amgen*, the specification leaves a scientist forced to engage in painstaking experimentation to see what works and thus provides inadequate guidance to enable a skilled person to make and use the invention without undue experimentation, as is required for enablement.

Enablement

Enablement Requirement Met—Methods where all Antibodies to Target Work

Teva Pharms. Int'l GmbH v. Eli Lilly & Co., 172 F.4th 1367 (Fed. Cir. 2026):

- Court found claims to methods of using humanized antibodies to CGRP to treat headache met the enablement requirement because it is undisputed that a reasonable jury could have found that all humanized anti-CGRP antagonist antibodies treat headache, thereby obviating any extensive screening to determine which ones do.
- Claims unlike the claims in *Amgen* and cases following it, because they do not claim humanized anti-CGRP antagonist antibodies themselves; instead, they claim only the use of such antibodies for the different, limited purpose of treating headache. In light of the well-known status of anti-CGRP antagonist antibodies and the routine nature of humanization, the more relevant "research assignment" in this case would have been determining which humanized anti-CGRP antagonist antibodies treat headache.
 - That assignment was completed inasmuch as specification disclosed that all such antibodies work for that purpose.
 - Humanizing well-known anti-CGRP antagonist antibodies would have been routine.
 - Undertaking to find or make all such humanized antibodies (not claimed here) would—in the context of these claims to a method in which they all work—be more akin to extra credit than a necessary research assignment left to others to complete.
 - Argument against enablement might be more persuasive if the asserted claims were to the genus of humanized anti-CGRP antagonist antibodies themselves and thus tracked those found invalid in *Amgen*.
- In contest, a claim directed to CAR-T cells incorporating a CAR containing any scFv binding a given target or method of treatment of cancer using such CAR or CAR-T cells would not meet the enablement requirement because trial and error experimentation would be required to determine which scFvs incorporated into the CAR actually worked in CAR-T cells or methods of treatment of cancer.

Potential Approach to Broad CAR Claims

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

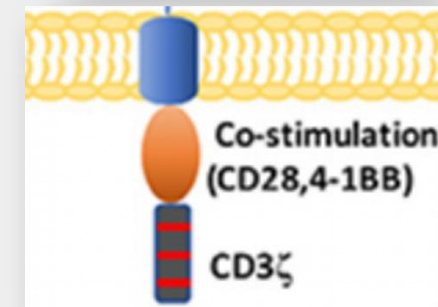
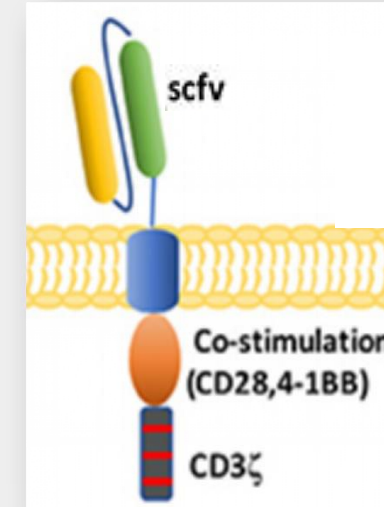
- (a) a zeta chain portion comprising the intracellular domain of human CD3 ζ chain,
- (b) a costimulatory signaling region, and
- (c) a binding element that specifically interacts with a selected target, wherein the costimulatory signaling region comprises the amino acid sequence encoded by SEQ ID NO:6.

Found invalid in *Juno*

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, and
- (b) a costimulatory signaling region,

Potentially Valid



Adapted from U.S. Patent No. 7,446,190; Lijun Zhou & Yu J. Cao, *Engineered T Cell Therapy for Cancer in the Clinic*, 10 *Frontiers in Immunology* 2250, at 4, fig. 2 (2019).

Potential Approach to Broad CAR Claims

***Teva Branded Pharm. Prods. R&D, Inc. v. Amneal Pharms. of N.Y., LLC*, 124 F.4th 898 (Fed. Cir. 2024):**

- Court noted in a hypothetical that a car incorporating an improved steering wheel would infringe a claim to an improved steering wheel that did not mention a car even though the steering wheel clearly is intended for use in a car.
- Court further explained that one could not argue that a patent claiming the improved steering wheel would need to describe and enable the car.
- If the reasoning in *Teva Branded* were to be extended to the CAR context, a claim to a CAR fragment encompassing all components except the scFv would be infringed by CARs containing the claimed components and any scFv.

Takeaways for U.S. Generic CAR Claims

- The number of embodiments disclosed in the specification must be commensurate with the magnitude of the claimed genus, particularly if the genus is to cover species that are not known in the prior art.
- If the disclosed embodiments are meant to be representative of members of the genus, then the disclosure should explicitly state that and explain why the disclosed species are representative of the members of the genus.
- The specification should provide guidance to a skilled artisan as to how to identify species that fall within the claimed functional genus.
- Sequences not always required, but disclosure of sequences weighs in favor of written description, even when they are in the prior art.
- Written description requirement more likely met when the specification provides “structural features common to the members of the genus” or explains the commonality between the members of the genus and why that commonality matters to the invention (e.g., is critical to carrying out the claimed function of biological compounds).
- Enablement requirement can be met for functionally defined claim if there is a quality common to every functional embodiment.



CAR-T Patent Considerations in China

Common Rejection Grounds for CAR-T Patent Application In China

While the **core patentability standards** remain novelty, inventiveness, and practical applicability (Article 22), we have seen **common rejection grounds** in patents that failed to pass examination or were invalidated in China:

Art. 25

Therapeutic method exclusion

No patent right shall be granted for, inter alias, methods for the diagnosis or treatment of diseases

Art. 26(4)

Written Support from Description

The claims shall be based on the description and shall define the scope of the patent protection sought for in a clear and concise manner.

Art. 22(3)

Lack of Inventive Step

Inventiveness means that, as compared with the prior art, the invention has prominent substantive features and represents an obvious progress, and that the utility model has substantive features and represents a progress.

Ground #1: Therapeutic Method Exclusion

Article 25:

“No patent right shall be granted for...methods for the diagnosis or treatment of diseases”

- Under **Article 25** of the Patent Law, claims directed to methods of medical treatment (e.g., “A method of treating cancer by administering CAR- T cells...”) are **not patentable** in China.
- Alternatively, Applicants must instead draft claims in the **Swiss- type format**, which frames the invention as a **use in preparing a medicament**, rather than the treatment itself.
- **Typical structure** for a CAR-T therapeutics claims – *“Use of X in the preparation of a medicament (or kit) for treating disease Y.”*
- Other viable claim strategies include: nucleic acid claims encoding the CAR construct, vector claims expressing the CAR sequence, CAR receptor or the engineered CAR- T cell *per se*, or methods of preparing CAR- T cells.

Ground #2:

Sufficiency of Disclosure

Article 26(3):

“The description shall contain a clear and comprehensive description of the invention or utility model so as to enable a person skilled in the relevant field of technology to carry it out; where necessary, drawings shall be attached to it.”

- Patent Law Article 26(4) requires claim to be supported by the **description**. Chinese patent claim amendments must strictly adhere to the original disclosure of the specification, requiring **precise and literal support**.
- The scope should be sufficiently supported by **working examples**, i.e. technical effects cannot be broadly generalized.

Ground #2:

Sufficiency of Disclosure

PATENT NO.

201680011435.3

PATENTEE

Icell Gene Therapeutics LLC

ORIGINAL CLAIMS

1–23 (granted)

OUTCOME

Partially invalidated

- Granted claims covered engineered T cells or NK cells targeting any of four pan-T-cell antigens (CD2, CD3, CD5, CD7), with the target gene knocked out to prevent self-targeting/fratricide.
- The Specification provided working data only for **CD5-CAR-T cells** (in vivo tumor burden reduction, survival extension) and CD3-CAR-NK cells; no data existed **for CD3-CAR-T cells or CD7-CAR-T cells specifically**.
- Invalidated all claims/claim portions reciting CD3-CAR-T and CD7-CAR-T cells for lack of support — data from one antigen/cell-type combination cannot support an unrelated combination given how differently T cells and NK cells behave.
- Patentee's post-filing supplemental data (Exhibits 14, 18, 19) was **rejected** as evidence — it reflected research done **AFTER** the filing date and could not retroactively establish what was enabled at filing.
- Claims are narrowed to CD5-CAR-T cells with experimental support

Ground #2:

Sufficiency of Disclosure

Other Examples:

Rejection for CN 202080091049.6

Applicant: Texas A&M University System

Title: Protease switches for dual target chimeric antigen receptor T cell therapy

Claim 1: Claims a chimeric antigen receptor containing common CAR-T domains, and a generalized HCV NS3 protease domain and cleavage site placement defined by functions.

Examiner's view: Only two constructs (NS3-T54A-CD19 and NS3-1CS-CD19) were tested; examiner held the specification could not teach a skilled person how to obtain other CARs with similar function.

Rejection for CN 202180046709.3

Applicant: University of Texas System

Title: Anti- CD79b Antibody & CAR

Claim 15: Sought protection for the use of anti- CD79b antibodies in treating “cancers expressing CD79b.”

Evidence in specification: Gene expression data (Oncomine) showed CD79b highly expressed in **ALL, CLL**, and confirmed in **four lymphoma subtypes** (Burkitt, DLBCL, follicular, mantle cell). Expression validated only in a limited set of B- cell lines.

Examiner's view: The claim was considered **overly broad**. Only four B- cell lymphoma subtypes were supported by experimental data. Although the specification listed a wider spectrum of “CD79b- expressing cancers,” efficacy beyond the validated lymphoma types remained **unproven and unpredictable**, making the claim insufficiently supported.

Ground #3:

Lack of Inventive Step

Article 22:

“Any invention or utility model for which a patent right is to be granted shall meet the requirements of novelty, inventiveness and practical use...Inventiveness means that, as compared with the prior art, the invention has prominent substantive features and represents an obvious progress, and that the utility model has substantive features and represents a progress.”

1

Identify closest prior art



2

Determine distinguishing features



3

Define the technical problem to be solved based on the distinguishing features



4

Ask: Whether the claimed invention is obvious to skilled artisan to solve the technical problem?

Obviousness may be rebutted by demonstrating:

- **Surprising technical effects** supported by experimental data (post-filing data admissible for overcoming obviousness rejections)
- **Overcoming established technical prejudice** within the field.
- **Solving a long- standing technical problem** that experts have sought to resolve but failed to achieve.
- **Evidence of reasonable commercial success** attributable to the inventive features of the claimed invention.

Ground #3:

Lack of Inventive Step

PATENT NO.

201680059597.4

APPLICANT

Viromed Co Ltd,
Bluebird Bio Inc

FILING DATE

30 August 2016

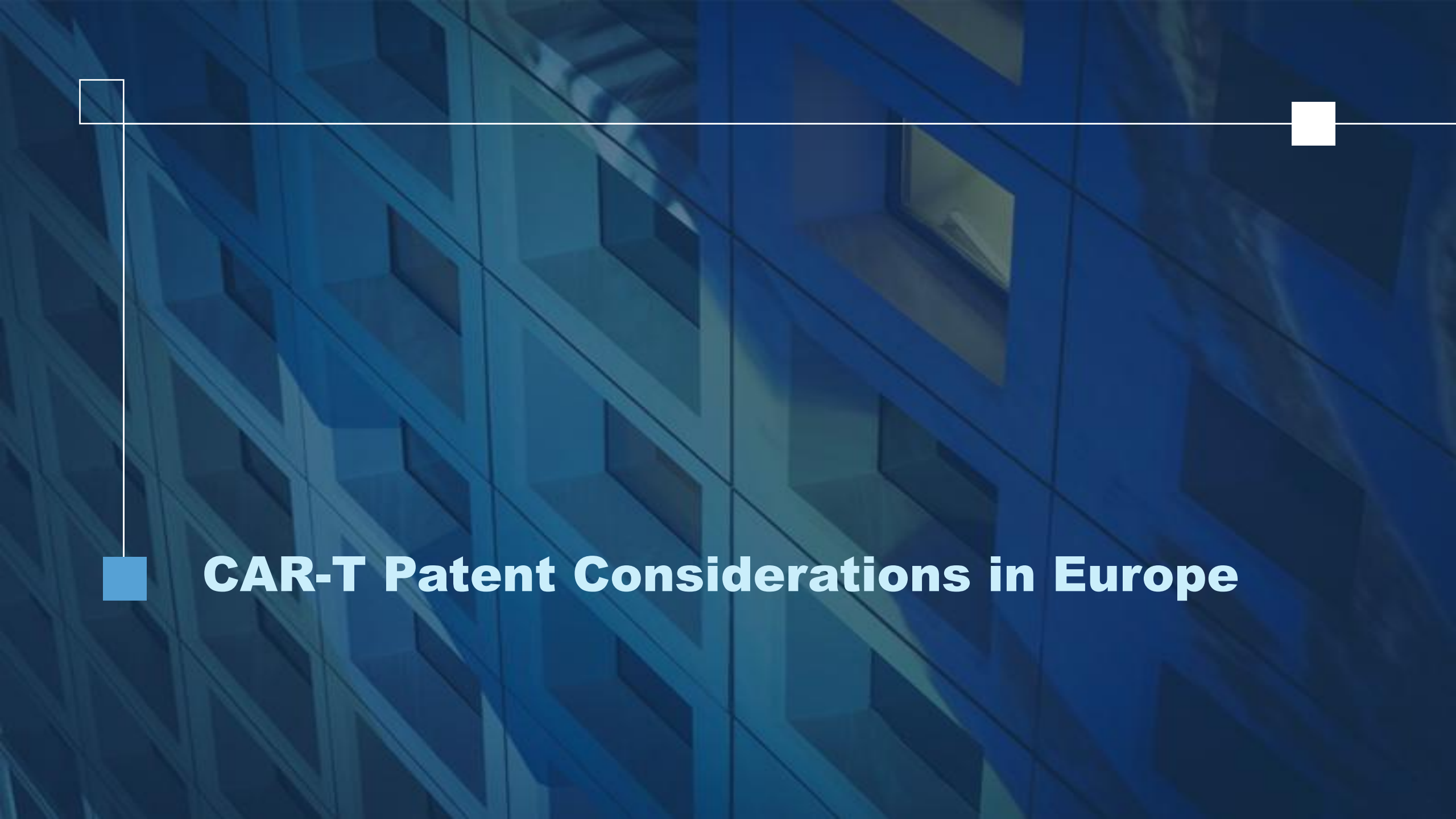
OUTCOME

Finally rejected

- Reference D1 disclosed the basic CAR scaffold (antigen-binding domain + costimulatory domain + CD3ζ) but not linked to an anti-STn antibody.
- Reference D2 disclosed anti-TAG-72 antibodies with CDR sequences matching the claimed anti-STn antibody, and separately taught that STn is a glycan expressed on TAG-72 across solid tumors.
- Applicant argued no motivation existed to combine the two references — Reference D1 never mentioned STn, and Reference D2 never discussed CARs.
- The technical problem identified is to providing a CAR specifically targeted to Sialyl Tn (STn) / TAG-72 antigen-expressing tumor cells. The Examiner concludes that reference D1 explicitly teaches targeting tumor-associated antigens with an scFv, and reference D2 provides the specific anti-STn scFv sequence, substituting reference D2's known antibody into reference D1's known CAR framework to solve this problem was deemed obvious with reasonably predictable technical results.
- Applicant failed to provide experimental data support for surprising technical effect.

CAR-T Takeaways for China

- **Literal support requirement:** Claims must have a **direct textual basis** in the specification from the outset and throughout prosecution. Beyond working examples, the claimed scope must be **explicitly and literally supported** in the description. Broad generalizations or scopes not fully covered risk rejection for lack of support.
- **Overcoming Obviousness Assertions with Comparative Data:** The formulation of the “technical problem to be solved” relies heavily **on the examiner's discretion**. It is usually challenging to overcome the general assertions by the examiner that a technical solution would be obvious to a person skilled in the art, unless with robust comparative data demonstrating an unexpected technical effect or superior performance. Whether an effect is deemed “surprising” must be scientifically grounded, but **ultimately depends on examiner discretion**.
- **Prepare sufficient data at filing:** Robust experimental evidence must be included in the **original application** to support the **intended and enforceable claim scope**. While post-filing data may be admitted to demonstrate **unexpected technical effects** or **superior performance** to rebut obviousness rejections, it generally cannot overcome sufficiency rejections under Article 26(4), in particular, evidence generated after the filing date cannot retroactively prove support.



CAR-T Patent Considerations in Europe

Treatment-Related Claims in Europe

- European Patent Convention *excludes from patentability methods for treating humans* by therapy but *does not prohibit patenting products for use* in such methods (Art. 53(c), 54(4), 54(5) EPC).
 - Example Claim: Compound Y for use in a method for treating disease X in a patient in need thereof comprising administering compound Y to the patient.
- Such purpose-limited product claims are construed to include the therapeutic effect as a functional technical feature and are therefore limited to achieving such an effect.
 - Method of treatment claims are not necessarily construed to require the claimed treatment to be effective, in which case the claims may encompass a method designed to treat, which may impact validity/patentability with respect to enablement, written description, and novelty. (*United Therapeutics Corp. v Liquidia Techs., Inc.*, 74 F.4th 1360, 1369-71 (Fed. Cir. 2023))

Definition of Antibodies in Europe

- Structure of antibody
 - Requires that all six CDR sequences are provided in the claim, or are defined as being part of larger defined variable region sequences unless evidence that a CDR does not bind the antigen
 - There must be a surprising effect compared to known antibodies for the same antigen, such as improved therapeutic activity; improved affinity; or reduced toxicity, immunogenicity, or cross-reactivity for inventive step.
 - Sequence/structure differences (or structural novelty/nonobviousness) not sufficient.
- Reference to target antigen
 - Unlike in the U.S., an antibody claim can also be directed towards the antigen that the antibody targets, but *only if the antigen is novel*.
 - Example Claim: An antibody specific for antigen X consisting of SEQ ID NO: Y
 - Antigen must be defined with no variability.
 - Negative features to exclude certain targets can also be included
 - Example Claim: Antibody binding to antigen X and not binding to antigen Y.

Guidelines for Examination in the European Patent Office §§ 6.1.1-6.1.2 (Apr. 2026).

Definition of Antibodies in Europe

- Target antigen and additional features
 - In addition to being functionally defined by their target antigen, antibodies can be further characterized by functional features defining their other properties, for example binding affinity, neutralizing properties, induction of apoptosis, internalization, and/or inhibition or activation of receptor
 - Can be claimed by reference to the epitope
 - Claims in terms of the ability to compete with antibody disclosed for the first time application.
 - If there is no indication to the contrary, it is to be assumed that a prior-art antibody binding the same target antigen will have the claimed functional properties, requiring the applicant/patent owner to show novelty
 - Specification must enable production of further antibodies having the claimed functional property without undue burden
 - Functional definition must allow the skilled person to easily and unambiguously verify whether they are working inside or outside the claim, and thus the claim should include relevant characteristics and how to determine and define the functional property.
- Functional and structural features
 - Can claim an antibody characterized by the sequences of both variable domains or CDRs with less than 100% sequence identity when combined with a clear functional feature.
- Production Process
 - Immunization protocol of an animal with a well-characterized antigen or specific cell line used to produce antibody
- Deposited hybridoma producing antibody

Guidelines for Examination in the European Patent Office §§ 6.1.3-6.1.6.

CAR-T Patent Disputes in Europe

CARsgen EP3445407 Opposition



Main Request Claim 1: A pharmaceutical composition comprising a therapeutically effective amount of anti-GPC3 chimeric antigen receptor (CAR) immunoresponsive cells for use in the treatment of a solid tumor that expresses GPC3 in a subject, wherein the treatment comprises administering to the subject the pharmaceutical composition after or concurrent with subjecting the subject to a lymphocyte reduction treatment, wherein the lymphocyte reduction treatment comprises administering cyclophosphamide and fludarabine to the subject and wherein the anti-GPC3 CAR immunoresponsive cells are T cells (anti-GPC3 CAR T cells).

- Sotio Biotech and Murgytroid, a Scotland-based European IP firm, filed oppositions to CARsGEN's EP '407 patent relating to a pharmaceutical composition comprising CAR-T cells directed to the GPC3 protein for use in treatment of solids tumors where the treatment also includes administration of cyclophosphamide and fludarabine.
- Opposition Division found Main Request not entitled to priority to an earlier Chinese application because it provides no basis for treatment of solid tumors expressing GPC3 (EP3445407, Grounds for Decision of Opposition Division (Mar. 26, 2025))
 - Solid tumors in general are not disclosed
 - Disclosure of tumors in general and specific solid tumors (e.g., hepatocellular carcinoma, and lung carcinoma) not sufficient.
 - GPC3 expressed on some, but not all solid tumor types, and normal tissues.
 - Statement in background section that “the inventors had devoted to develop the treatment of solid tumors by CAR-T cells for a long time not an implicit disclosure because the background section provides scientific background does not describe the invention.
 - Not general knowledge that all tumors expressing GPC3 are solid tumors.
- 2 clinical trial protocol references are prior art and render inventive step lacking.

CAR-T Patent Disputes in Europe

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Auxiliary Request No. 2 Claim 1: A pharmaceutical composition comprising a therapeutically effective amount of anti GPC3 chimeric antigen receptor (CAR) immunoresponsive cells for use in the treatment of a tumor that expresses GPC3 which is liver cancer, lung cancer, ovarian cancer, breast cancer, gastric cancer or thyroid cancer in a subject, wherein the treatment comprises administering to the subject the pharmaceutical composition after subjecting the subject to a lymphocyte reduction treatment, wherein the lymphocyte reduction treatment comprises administering cyclophosphamide and fludarabine to the subject and wherein the anti-GPC3 CAR immunoresponsive cells are T cells (anti-GPC3 CAR-T cells).

- Basis in the priority application for the specific types cancer of Auxiliary Request No 2. Claim 1 which are expressly mentioned in the priority document, so the clinical trial protocol references were not prior art.
- Opposition Division rejected inventive step and disclosure arguments with respect to Auxiliary Request No. 2.
- CARsgen and Sotio filed an appeal, but Sotio withdrew its appeal shortly thereafter
- Board of Appeal issued a communication indicating it was inclined to dismiss CARsgen's appeal one (T0726/25-3.3.04 (Mar. 12, 2026)), and CARsgen withdrew its appeal prior to the oral hearing.

CAR-T Patent Disputes in Europe

Collectis EP3126390 Appeal Case

- EPO Technical Board of Appeal No. T1502/22 (Apr. 25, 2024) rejected the opponent's appeal of the Opposition Division's maintenance of claims directed to engineered immune cells expressing a CD33-specific CAR comprising a CD33 binding domain containing VH and VL domains from a monoclonal antibody, a FcγRIIIα hinge domain, a CD8α transmembrane domain, and a cytoplasmic domain containing a CD3ζ signaling domain, and a 4-1BB co-stimulatory domain for use in therapy of enumerated types of leukemia and lymphoma.
- Objection against sufficiency of disclosure must be based on serious doubts substantiated by verifiable facts.
- Specification disclosed activation of CAR-T cells of the claims by CD33+ cells, which is evidence of therapeutic activity against cells expressing CD33 because the activity is conferred by the CAR.
 - Disclosed experimental results sufficient to create strong presumption that therapeutic effect can be achieved, which the opponent bears the burden of rebutting and proving insufficient disclosure.
- Opponent based argument on the fact that cell lines used in patent were derived from two cancer types, but no evidence that a skilled person would have doubted that the cancers recited in the claim could be treated with CD33 CAR-T cells or that any of those cancers do not express CD33.
- Specification indicated that CD33 expressed on myeloid cells but also on some lymphoid cells, rendering therapeutic effect credible.
- Rejected argument that claims also directed to cancers that did not express CD33 because known that action of CAR-T cells against cancer required binding a target on the cancer cells and thus it would be understood that therapeutic effect was only in CD33+ cells.
 - Supported by disclosure in specification that the CD33-specific CARs targeted CD33+ cancer cells with clinical advantage.

CAR-T Patent Disputes in Europe

Collectis EP3126390 Appeal Case

Takeaways:

- Disclosure of limited in vitro data may be sufficient for adequate disclosure if demonstrates clear mechanistic activity
- Medical use claims need not be explicitly limited to biomarker-positive patient populations.
- Demonstrating target engagement and downstream biological activity can establish therapeutic plausibility.

CAR-T Patent Disputes in Europe

Dartmouth College EP2297223 Case

- EPO Technical Board of Appeal No. T0203/22 (Mar. 24, 2024) rejected the opponent's appeal of the Opposition Division's maintenance of claims directed to CARs containing an antibody fragment binding B7-H6, a transmembrane domain, and intracellular TCR signaling domain and related composition and medical use claims as having an inventive step over prior art disclosing CAR-T cells targeting B7-H6 with a CAR containing the NKp30 extracellular domain instead of an antibody fragment
- Board found surprising technical effect rendering claimed CAR nonobvious
 - Significantly increased IFN- γ levels (Indicative of T-cell activation) in the presence of tumor cells expressing B7-H6 over prior art
 - Improved specificity evidenced by no reactivity against autologous dendritic cells in contest to NKp30-based CARs
 - Superior survival outcomes inasmuch as 90% of mice treated with claimed anti-B7H6 CAR-T cells survived 50 days post-tumor challenge compared to about 25% for mice treated with NKp30-based CAR-T cells
- Board reasoned that while tumor specific expression of B7-H6 and multiple ligand binding of NKp30 were known, "the skilled person would not have expected the improved IFN- γ production observed with anti-B7-H6 CAR T cells"
- Takeaways
 - Measurably improved performance parameters (e.g., enhanced T-cell activation and survival) can show nonobviousness even though general approach of antigen-specific targeting known
 - Comparative efficacy data critical for establishing nonobviousness
 - Specific quantitative improvement important to establish an inventive step

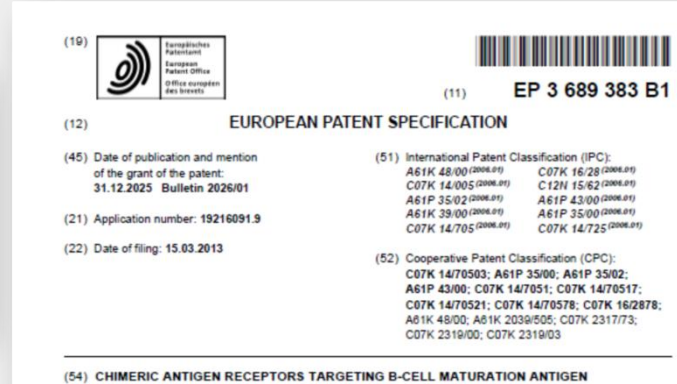
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CAR-T Patent Disputes in Europe

2seventy bio, Inc. v. Johnson & Johnson, No. UPC-CFI-0000029/2026 (Unified Patent Court)



1. A pharmaceutical composition comprising a population of T-cells that express a chimeric antigen receptor (CAR) for use in a method of treating multiple myeloma, wherein the CAR comprises an antigen recognition moiety and a T-cell activation moiety, and wherein the antigen recognition moiety is directed against B-cell Maturation Antigen (BCMA).



- Janssen and Legend's CAR-T product directed to the BCMA protein Carvykti® was approved by the FDA in February 2022 and the EMA in May 2022 for the treatment of multiple myeloma.
- European Patent No. EP3689383 broadly claiming CAR directed to BCMA issued on December 31, 2025
 - Owned by U.S. Dept. of Health & Human Services, and licensed to 2seventy bio, a BMS subsidiary.
- Opposition filed by Boult Wade Tennant LLP on same day
 - Opponent's facts and arguments due on Sept. 30
- 2seventy filed an infringement case against Janssen, its parent J&J, and Legend on January 5, 2026
 - Written phase filings are confidential, but defendants have filed counterclaim for revocation



Freedom-to-Operate Considerations

Examples of Foundational CAR-T Patents

Owner	Jurisdictions	Parent Patent Family	Scope of Claims	Expiry Year
University of Pennsylvania	US CN EP	US 9,499,629 CN103492406B EP 2649086	CAR-T constructs comprising 4-1BB/CD3-zeta CARs specifically directed against CD19 antigens on B-cells.	2031
US Department of Health and Human Services	US CN EP	US 10,287,350 CN106536564B EP 3149044	Specific CD19 CAR architectures.	2035
US Department of Health and Human Services	US EP	US 8,556,882 EP 2424887	Armored cytokine expression cassette.	2030
University Health Network	US EP	US 10,336,810 EP 3256496	Cytokine JAK-STAT3/5 signaling.	2036

CAR-T FTO Risks & Challenges

- **Crowded and fragmented landscape:** CAR- T therapies integrate numerous technical modules: scFv antibodies, hinge and transmembrane regions, co- stimulatory domains (e.g., 4- 1BB, CD28), viral vectors, gene- editing tools (CRISPR), and cell expansion processes. Even if one module is patented in- house, reliance on another party's protected technology (e.g., CD19 antibody sequence, lentiviral transduction method) may expose the product to infringement risk.
- **Litigation risk and precedent** In the U.S., *Juno v. Kite (Yescarta)* initially resulted in a damages award exceeding **USD 1.2 billion**. Although later overturned, the case underscores the extraordinary financial consequences of patent disputes in CAR- T.
- **Commercialization and investment requirements:** Discovering blocking patents late in clinical development or pre- launch can force costly route changes or licensing negotiations.

Questions ?

Ryan Hagglund
Partner (New York)

