

# Exceptions for inventions involving the treatment of humans

James Love, KEI

AIFA Workshop on CAR-T in operation: Challenges and Perspectives

Rome, Italy  
24 January 2019

# TRIPS

## Article 27: Patentable Subject Matter

3. Members may also exclude from patentability:

(a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals;

# Trade agreements typically have provisions on exceptions methods of treatment from patentability

Canada – Korea ([article 16.12](#))

China – Korea ([article 15.15](#))

Colombia – EFTA ([article 6.9](#))

EU - CARIFORUM ([article 148](#))

Japan – Switzerland ([article 117](#))

Korea – Australia ([article 13.8](#))

Korea – Viet Nam ([article 12.7](#))

NAFTA 1992 ([article 1709](#))

Peru – EFTA ([article 6.9](#))

Switzerland – China ([article 11.8](#))

USA – Australia ([article 17.9](#))

USA – Bahrain ([article 14.8](#))

USA – Jordan ([article 4.18](#))

USA – Oman ([article 15.8](#))

CRISPR

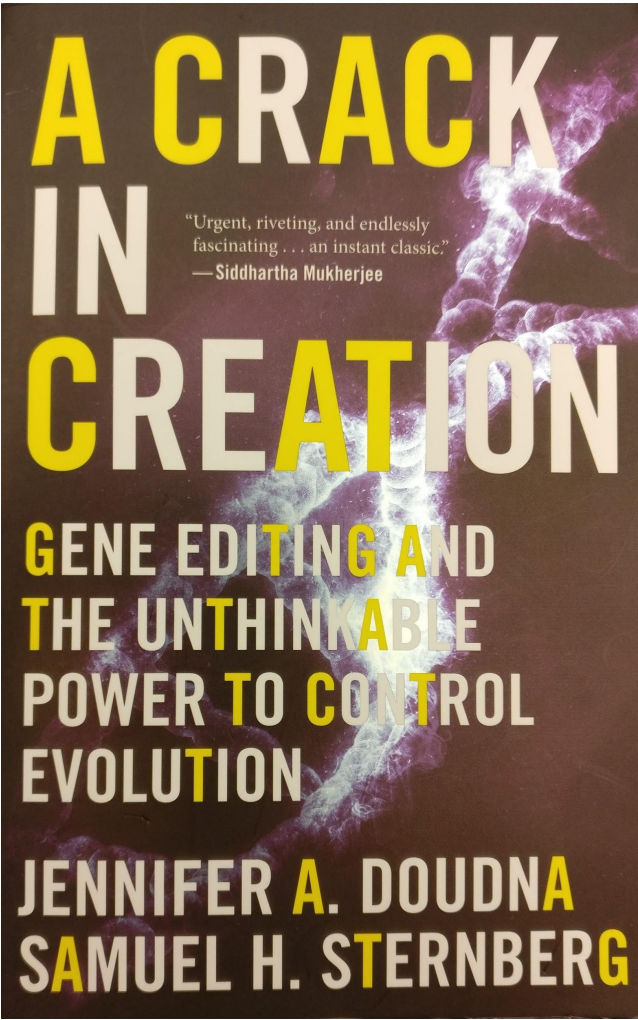
## Q: What is “CRISPR”?

A: “CRISPR” (pronounced “crisper”) stands for Clustered Regularly Interspaced Short Palindromic Repeats, which are the hallmark of a bacterial defense system that forms the basis for CRISPR-Cas9 genome editing technology. In the field of genome engineering, the term “CRISPR” or “CRISPR-Cas9” is often used loosely to refer to the various CRISPR-Cas9 and -CPF1, (and other) systems that can be programmed to target specific stretches of genetic code and to edit DNA at precise locations, as well as for other purposes, such as for new diagnostic tools. With these systems, researchers can permanently modify genes in living cells and organisms and, in the future, may make it possible to correct mutations at precise locations in the human genome in order to treat genetic causes of disease. Other systems are now available, such as CRISPR-Cas13’s, that target RNA provide alternate avenues for use, and with unique characteristics that have been leveraged for sensitive diagnostic tools, such as SHERLOCK.

1. Number of USPTO  
Patent applications  
with term CRISPR

2. Applications that  
declare U.S.  
government funding  
or are assigned to  
the United States

Year	Applications	Applications with GOVT or AN/"United States"	USG Funding declared
2000-2005	0		
2006	1	0	0%
2007	0		
2008	2	0	
2009	0		
2010	13	2	15%
2011	16	2	13%
2012	4	1	25%
2013	16	2	13%
2014	111	48	43%
2015	229	63	28%
2016	533	166	31%
2017	864	200	23%
2018:11	1380	321	23%



# A CRACK IN CREATION

"Urgent, riveting, and endlessly  
fascinating . . . an instant classic."

—Siddhartha Mukherjee

GENE EDITING AND  
THE UNTHINKABLE  
POWER TO CONTROL  
EVOLUTION

JENNIFER A. DOUDNA  
SAMUEL H. STERNBERG

To treat many diseases, though, CRISPR offers the potential to edit and repair mutated genes directly in human patients. So far we've gotten only a glimpse of its capabilities, but what we've seen in the past few years is exhilarating. In laboratory-grown human cells, this new gene-editing technology was used to correct the mutations responsible for cystic fibrosis, sickle cell disease, some forms of blindness, and severe combined immunodeficiency, among many other disorders. CRISPR enables scientists to accomplish such feats by finding and fixing single incorrect letters of DNA out of the 3.2 billion letters that make up the human genome, but it can be used to perform even more complex modifications. Researchers have corrected the DNA mistakes that cause Duchenne muscular dystrophy by snipping out only the damaged region of the mutated gene, leaving the rest intact. In the case of hemophilia A, researchers have harnessed CRISPR to precisely rearrange over half a million letters of DNA that are inverted in the genomes of affected patients. CRISPR might even be used to treat HIV/AIDS, either by cutting the virus's DNA out of a patient's infected cells or by editing the patient's DNA so that the cells avoid infection altogether.

# Despite CRISPR baby controversy, Harvard University will begin gene-editing sperm

Even as a furious debate broke out in China over gene-edited babies, some scientists in the US are also hoping to improve tomorrow's children.

by Antonio Regalado   November 29, 2018

**I**n the wild uproar around an experiment in China that claimed to have created twin girls whose genes were altered to protect them from HIV, there's something worth knowing—research to improve the next generation of humans is happening in the US, too.

In fact, it's about to happen at Harvard University.

At the school's [Stem Cell Institute](#), IVF doctor and scientist Werner Neuhausser says he plans to begin using CRISPR, the gene-editing tool, to change the DNA code inside sperm cells. The objective: to show whether it is possible to create IVF babies with a greatly reduced risk of Alzheimer's disease later in life.

ClinicalTrials.Gov

24 Studies found for: crispr

# Luxturna (voretigene neparvovec-rzyl)

First Gene Therapy for an inherited form of childhood blindness. The a gene therapy can restore vision in people with a specific genetic mutation that causes progressive vision loss.

It was developed by Spark Therapeutics and Children's Hospital of Philadelphia

Licensed to Novartis.

Luxturna has a list price of \$850,000, or \$425,000 per eye

# Search Orphan Drug Designations and Approvals

[FDA Home](#) [Developing Products for Rare Diseases & Conditions](#)

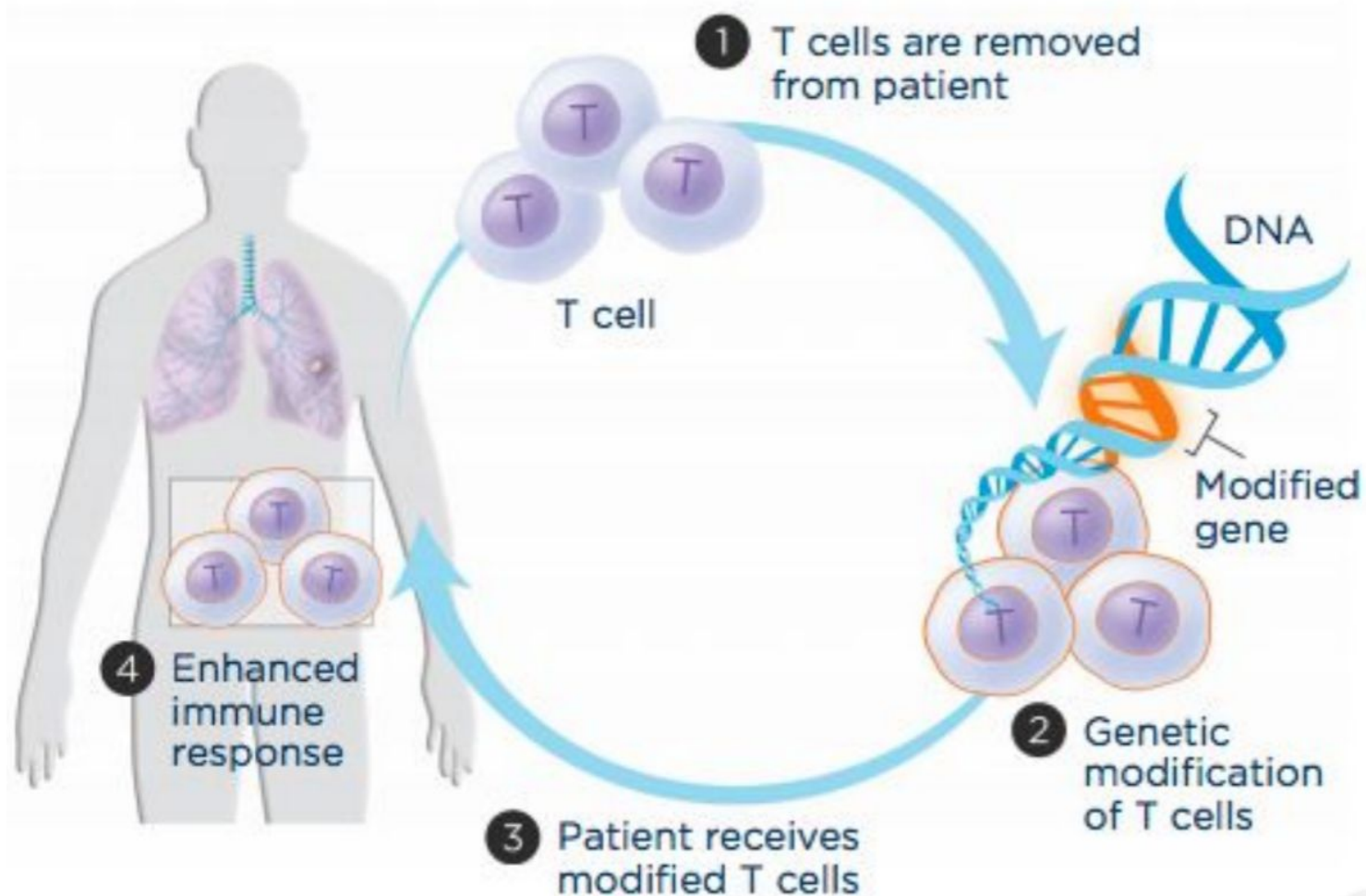
<b>Generic Name:</b>	voretigene neparvovec-rzyl
<b>Trade Name:</b>	Luxturna
<b>Date Designated:</b>	03/18/2015
<b>Orphan Designation:</b>	Treatment of inherited retinal dystrophy due to biallelic RPE65 gene mutations
<b>Orphan Designation Status:</b>	Designated/Approved
<b>Marketing Approval Date:</b>	12/19/2017
<b>Approved Labeled Indication:</b>	an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells determined by a treating physician
<b>Exclusivity End Date:</b>	12/19/2024
<b>Sponsor:</b>	Spark Therapeutics, Inc. 3737 Market Street Suite 1300 Philadelphia, Pennsylvania 19104 USA  <i>The sponsor address listed is the last reported by the sponsor to OOPD.</i>

CAR T

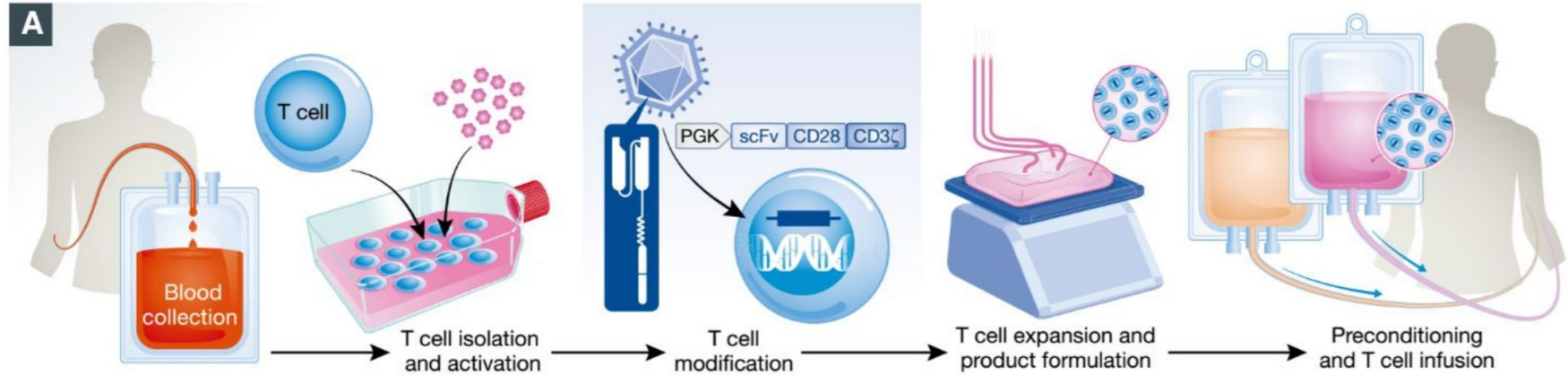
## Chimeric Antigen Receptor Therapy

The concept of generating chimeric T-cell receptors to target and fight cancerous cells was first described over 28 years ago by Gross *et al.* in a paper entitled “Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity”. A chimeric molecule is a molecule made up of components from different sources. T-cells are a subtype of immune cells that can seek out a threat, with their antibody like receptors, and eliminate it. Scientist today can engineer these t-cell receptors into chimeric antigen receptors that will specifically target tumor cells and kill them.

Ultimately, the best outcome would be for the patient to develop lifelong immunological memory (since a subset of CAR T-cells could become memory T-cells) and therefore the ability to mount a persistent antitumor response. However, the immune system is a tightly regulated by intricate networks of signaling molecules. Scientists must determine the proper ligands or receptors to target that would minimise fatal reactions such as severe cytokine release syndrome.



# CAR T manufacturing and Treatment



Hartmann et al, 2017

▲  
...  
**CRISPR**

# Kymriah (tisagenlecleucel), August 2017

FDA [describes](#) Kymriah as “a genetically-modified autologous T-cell immunotherapy. Each dose of Kymriah is a customized treatment created using an individual patient’s own T-cells, a type of white blood cell known as a lymphocyte. The patient’s T-cells are collected and sent to a manufacturing center where they are genetically modified to include a new gene that contains a specific protein (a chimeric antigen receptor or CAR) that directs the T-cells to target and kill leukemia cells that have a specific antigen (CD19) on the surface. Once the cells are modified, they are infused back into the patient to kill the cancer cells.”

- Indication: certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL).
- Company: Novartis, based upon collaboration with the University of Pennsylvania.
- Cost: \$475,000, plus unknown additional costs, subject to rebates when patients fail after 30 days
- The safety and efficacy of Kymriah were demonstrated in one multicenter clinical trial of 63 pediatric and young adult patients
- Orphan designation: January 31, 2014

# Yescarta (axicabtagene ciloleucel), October 2017

FDA [describes](#) Yescarta as “a customized treatment created using a patient’s own immune system to help fight the lymphoma. The patient’s T-cells, a type of white blood cell, are collected and genetically modified to include a new gene that targets and kills the lymphoma cells. Once the cells are modified, they are infused back into the patient.”

- Indication: certain types of large B-cell lymphoma
- Company: Gilead, having acquired Kite Pharma, and licenses from NIH and other parties.
- Cost, \$373,000, rebates when patients fail, plus unknown costs of care.
- The safety and efficacy of Yescarta were established in a multicenter clinical trial of more than 100 adults with refractory or relapsed large B-cell lymphoma
- Orphan designation: March 27, 2014.

# Search Orphan Drug Designations and Approvals

[FDA Home](#) [Developing Products for Rare Diseases & Conditions](#)

<b>Generic Name:</b>	(tisagenlecleucel) Autologous T Cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19
<b>Trade Name:</b>	Kymriah (Tisagenlecleucel)
<b>Date Designated:</b>	01/31/2014
<b>Orphan Designation:</b>	For the treatment of Acute Lymphoblastic Leukemia
<b>Orphan Designation Status:</b>	Designated/Approved
<b>Marketing Approval Date:</b>	08/30/2017
<b>Approved Labeled Indication:</b>	Treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
<b>Exclusivity End Date:</b>	08/30/2024
<b>Sponsor:</b>	Novartis Pharmaceuticals Corporation One Health Plaza East Hanover, New Jersey 07936 USA  <i>The sponsor address listed is the last reported by the sponsor to OOPD.</i>

# Search Orphan Drug Designations and Approvals

[FDA Home](#) [Developing Products for Rare Diseases & Conditions](#)

<b>Generic Name:</b>	axicabtagene ciloleucel
<b>Trade Name:</b>	Yescarta
<b>Date Designated:</b>	03/27/2014
<b>Orphan Designation:</b>	Treatment of diffuse large B-cell lymphoma.
<b>Orphan Designation Status:</b>	Designated/Approved
<b>Marketing Approval Date:</b>	10/18/2017
<b>Approved Labeled Indication:</b>	Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
<b>Exclusivity End Date:</b>	TBD
<b>Sponsor:</b>	Kite Pharma, Inc. 2225 Colorado Avenue Santa Monica, California 90404 USA  <i>The sponsor address listed is the last reported by the sponsor to OOPD.</i>

# Product or procedure?

Current CAR T therapies involves the modification of your own cells.

Physicians working with trained technical staff can perform the procedures and culture the T cells.

Some medical practices could develop the capacity to providing existing CAR T treatments in house.

# Juno's patent portfolio

As of December 31, 2016, our owned and licensed patent portfolio consists of approximately 31 licensed U.S. issued patents, approximately 37 licensed U.S. pending patent applications, approximately 41 owned U.S. issued patents, and approximately 48 owned U.S. pending patent applications covering certain of our proprietary technology, inventions, and improvements and our most advanced product candidates . . .

as well as approximately five owned patents issued in jurisdictions outside the United States, approximately 81 licensed patents issued in jurisdictions outside of the United States, approximately 268 licensed patent applications pending in jurisdictions outside of the United States . . . and approximately 128 owned patent applications pending in jurisdictions outside of the United States . . .

*Source: 10-K report, filed March 1, 2017*

# Juno describing its patent claims

Patents and patent applications include claims directed to:

1. proprietary CARs, T cell receptors and antibodies;
2. proprietary CAR constructs, including those with customized spacer domains for improved tumor recognition;
3. engineered transgenes for T cell selection, identification, and in vivo ablation;
4. proprietary gene transfer vectors;
5. reversible reagents for cell selection, expansion and engineering;
6. systems, assays, and processes for generating, evaluating, and manufacturing cells and compositions for adoptive immunotherapy;
7. adoptive immunotherapy using defined T cell compositions;
8. multispecific cellular therapy approaches, including bispecific CARs, cells and compositions;
9. formulations, dosages, and treatment methods for adoptive immunotherapy, including those for predicting risk of and reducing toxicity associated with adoptive immunotherapy;
10. approaches for improving exposure to therapeutic cell product and promoting resistance to factors of tumor microenvironments;
11. diagnostic and prognostic methods and compositions;
12. libraries and high throughput methods for the discovery of antigen-binding molecules and targets; and
13. compositions, combinations, and treatment methods related to the modulation of adenosine and/or adenosine receptors.

. . . we intend to pursue, when possible, composition, method of use, dosing and formulation patent protection. We may also pursue patent protection with respect to manufacturing and drug development processes and technology.

## CAR patents granted by USPTO, 2013 to 2018

2013: 4 patents.

2014: 10 patents.

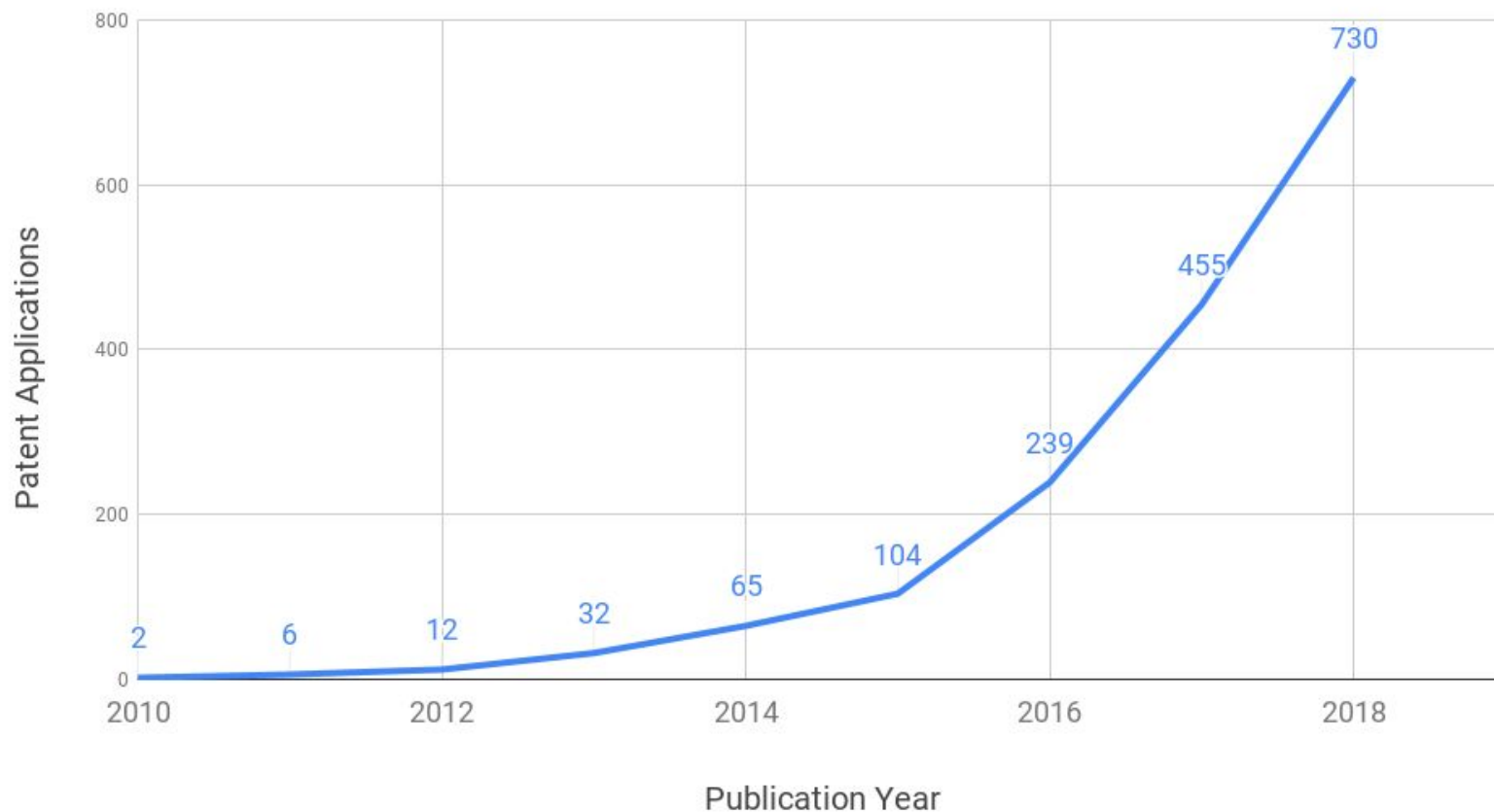
2015: 27 patents.

2016: 64 patents.

2017: 117 patents.

2018: 195 patents.

## U.S. Patent Applications that mention "chimeric antigen receptor" by publication year



1. Number of USPTO Patent applications with term "chimeric antigen receptor"
2. Applications that declare U.S. government funding or are assigned to the United States

Year	Patent Applications	with US Gov funding or US gov assignment		
2018	730	125	17%	
2017	455	75	16%	
2016	239	54	23%	
2015	104	33	32%	
2014	65	16	25%	
2013	32	16	50%	
2012	12	7	58%	
2011	6	5	83%	
2010	2	2	100%	

ClinialTrials.Gov

344 Studies found for: "**chimeric  
antigen receptor**"

(15 added in last month)

# National Exceptions

# Many countries copy the TRIPS language for national exceptions

“The following may not be patented: (...) methods of diagnosis or surgery or therapy for the treatment of persons or animals.”

Examples, Costa Rica, Ecuador, Egypt, Guatemala

# Several countries narrow the exception

## Chile

The following shall not be considered inventions and will be excluded from the protection provided by this law: (...) d) The methods of surgical or therapeutic treatment of the body human or animal, as well as diagnostic methods applied to the human or animal body, except the products destined to put in practice one of these methods.”

## Germany

“Patents are not granted for (...) A method for surgical or therapeutic treatment of the human or animal body and diagnostic procedures performed on the human or animal body. This does not apply to products, in particular to substances or mixtures of substances, for use in one of the above-mentioned processes.”

## Malaysia

the following shall not be patentable: (...) methods for the treatment of human or animal body by surgery or therapy, and diagnostic methods practised on the human or animal body: Provided that this paragraph shall not apply to products used in any such methods.”

## United States

35 USC §287. Limitation on damages and other remedies; marking and notice

(c)(1) With respect to a medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b) of this title, the provisions of sections 281, 283, 284, and 285 of this title shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity.

. . .

(A) the term “medical activity” means the performance of a medical or surgical procedure on a body, but shall not include (i) the use of a patented machine, manufacture, or composition of matter in violation of such patent, (ii) the practice of a patented use of a composition of matter in violation of such patent, or (iii) the practice of a process in violation of a biotechnology patent.

## Italy

4. Patents may not be granted for the following:

a) methods for surgical or therapeutic treatment of the human or animal bodies and diagnostic methods applied to human or animal bodies; . . .

5. The provision of paragraph 4 does not apply to microbiological processes and products obtained through such processes, or to the products, and in particular substances or compositions, for the use of one of the specified methods.

# The European Patent Convention

## Article 53 Exceptions to patentability

European patents shall not be granted in respect of:

(c) methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.

The EPO Board of Appeals has defined the term “medical treatment” in the context of article 53(c) as “any non-insignificant intentional physical or psychic intervention performed directly or indirectly by one human being - who need not necessarily be a medical practitioner - on another (or, by analogy, on animals) using means or methods of medical science.”

A 1994 Decision by the Board of Appeal for the European Patent Organization found that the exclusion was “based on social-ethical and public health considerations”.

2.4 It is generally accepted that the exclusions from patentability under Article 52(4) are based on social-ethical and public health considerations. The intent underlying this Article is to ensure that nobody who wants to use the methods specified in this Article as part of the medical treatment of humans or animals should be prevented from this by patents.

T 0024/91 (Cornea) of 5.5.1994

To fall within the exclusion provided under the EPC article 53(c), the method of treatment must be “practised on the human or animal body.”

EPC article 53(c) “does not require a specific type and intensity of interaction with the human or animal body.”

A method claim falls under the prohibition if it includes at least one feature defining a physical activity or action that constitutes a method step for treatment of the human or animal body by surgery or therapy.

According to the EPO Boards of Appeals and November 2018 edition of the EPO Guidelines for Examination, Part G, Chapter II, Section 4.2.1.

- “[...] the surgical or therapeutic nature of a method claim can perfectly be established by a single method step [...].”

Claims that disclose methods carried out fully *in vitro*, without requiring that at least one of the steps is practiced on the human or animal body, do not fall within the article 53(c) exception.

# EPO Guidelines

## 4.2.1 Limitations of exception under Art. 53(c)

- Treatment of body tissues or fluids after they have been removed from the human or animal body, or diagnostic methods applied thereon, are not excluded from patentability as long as these tissues or fluids are not returned to the same body.
- Whether or not a method is excluded from patentability under **Art. 53(c)** cannot depend on the person carrying it out (see **G 1/04** and **G 1/07**, Reasons 3.4.1).
- A method claim is not allowable under **Art. 53(c)** if it includes at least one feature defining a physical activity or action that constitutes a method step for treatment of the human or animal body by surgery or therapy. In that case, whether or not the claim includes or consists of features directed to a technical operation performed on a technical object is legally irrelevant to the application of **Art. 53(c)** (see **G 1/07**, Reasons 3.2.5).

# Policy questions

## 1. Legal

- a. Is CAR T a product or a service or procedure?

## 2. Normative

- a. Should patents be enforced against a medical practitioner who can cure or prevent a disease?
- b. If patents are not available for services by a medical practitioner, what are alternative incentives for innovation?\*
- c. How do we address patent thickets?

\* Alternatives to the Patent System that are used to Support R&D Efforts, Including both Push and Pull Mechanisms, with a Special Focus on Innovation-Inducement Prizes and Open Source Development Models, commissioned by the Secretariat, [CDIP/14/INF/12](#), September 19, 2014

# Policy options

1. Declare that autologous CAR T therapies are medical procedures, and not products
2. Challenge the granting of patents or specific patent claims at the national level, on the grounds the national exception provides for an exception
3. Propose alternative reward systems to address innovation incentive objectives.
4. Consider reforms of national law or EPO or EU policies