MIT MANAGEMENT SLOAN SCHOOL

The Human Cost And The Economic Burden: How Immunogenicity Affects Patients And The Economic Burden On The Healthcare System

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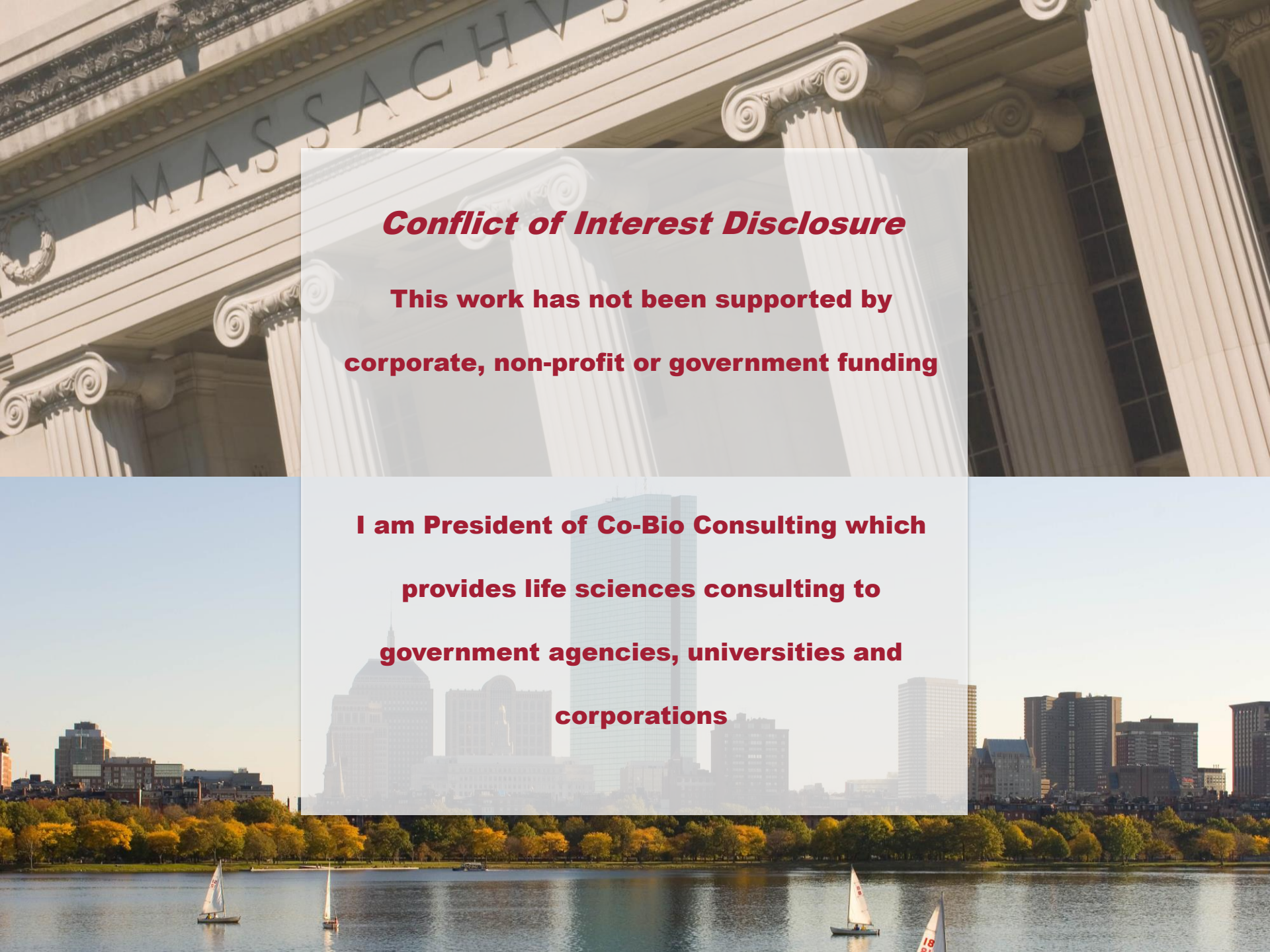
October 4, 2018



Conflict of Interest Disclosure

This work has not been supported by corporate, non-profit or government funding

I am President of Co-Bio Consulting which provides life sciences consulting to government agencies, universities and corporations

DIRECTIONAL COMMENTS NOT DEMONSTRATED FINDINGS

Scope
mABs, protein replacement, gene and cellular therapy but not classic vaccines

Limited health economics research on immunogenicity impacts

Will suggest effects via examples

WHY DO WE CARE? IMMUNOGENICITY HAS DIRECT AND INDIRECT ECONOMIC IMPACT

Costs of production, including R&D costs

Market size and demand

Uncertainty regarding product performance

Competition which affects price equilibrium

Products available, which affects market sizes and competition

IMMUNOGENICITY AFFECTS HUMANS AND THE SYSTEM DIFFERENTLY

Human Cost

Little financial impact
Due to deductible caps

Limits treatment options
- No treatment
- Treatments become ineffective

Adverse event suffering

Delays -> Harms

Healthcare System Burden

Developers
- More activities and so cost
- Lowers success rates
- Limits patients

Leads to
- Smaller markets
- Fewer products
- Less competition

Payers
- Adverse event cost
- Resistance management cost
- Fewer patients on new therapies
- Less bargaining power
- Ambiguous total spending outcome

Public Health
- Lower health status
- Ambiguous total financial value

THE IMMUNOGENICITY ECONOMIC MECHANISMS OF ACTION

01 Higher Treatment Costs

- *ADA in Protein Therapeutics*
- *Gene Therapy AEs*

02 Patient Options

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- *Time Cost for Variable Immune Response*

03 Development Costs

- *Higher Costs, Longer Time*
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04 Biosimilar Competition

ANTI-DRUG ANTIBODY COSTS

Protein Replacement Therapy

Hemophilia

Gaucher's disease

Fabry disease

20-30% of hemophilia patients develop inhibitors in their lifetimes

Berntorp E. et al. "Inhibitor treatment in haemophilias A and B: summary statement for the 2006 international consensus conference," *Haemophilila*. 2006; 12 (Suppl. 6), 1-7.

Factor inhibitors alter treatment

- **Increased dosing**
- **Bypass Therapy**
- **ITI (Immune Tolerance Induction) treatment**

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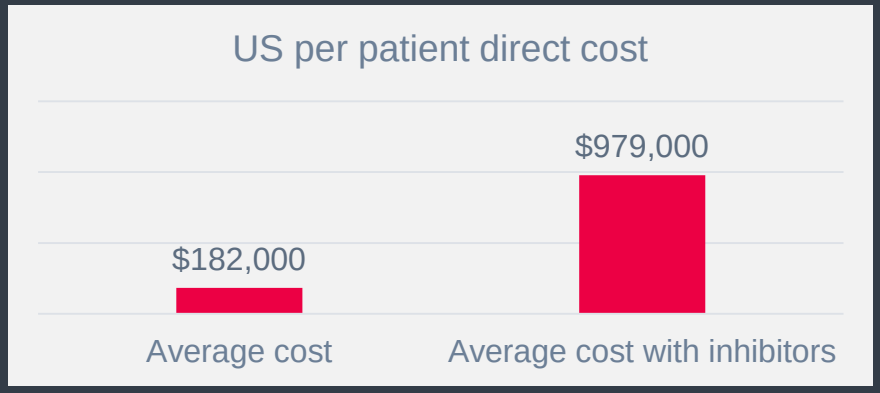


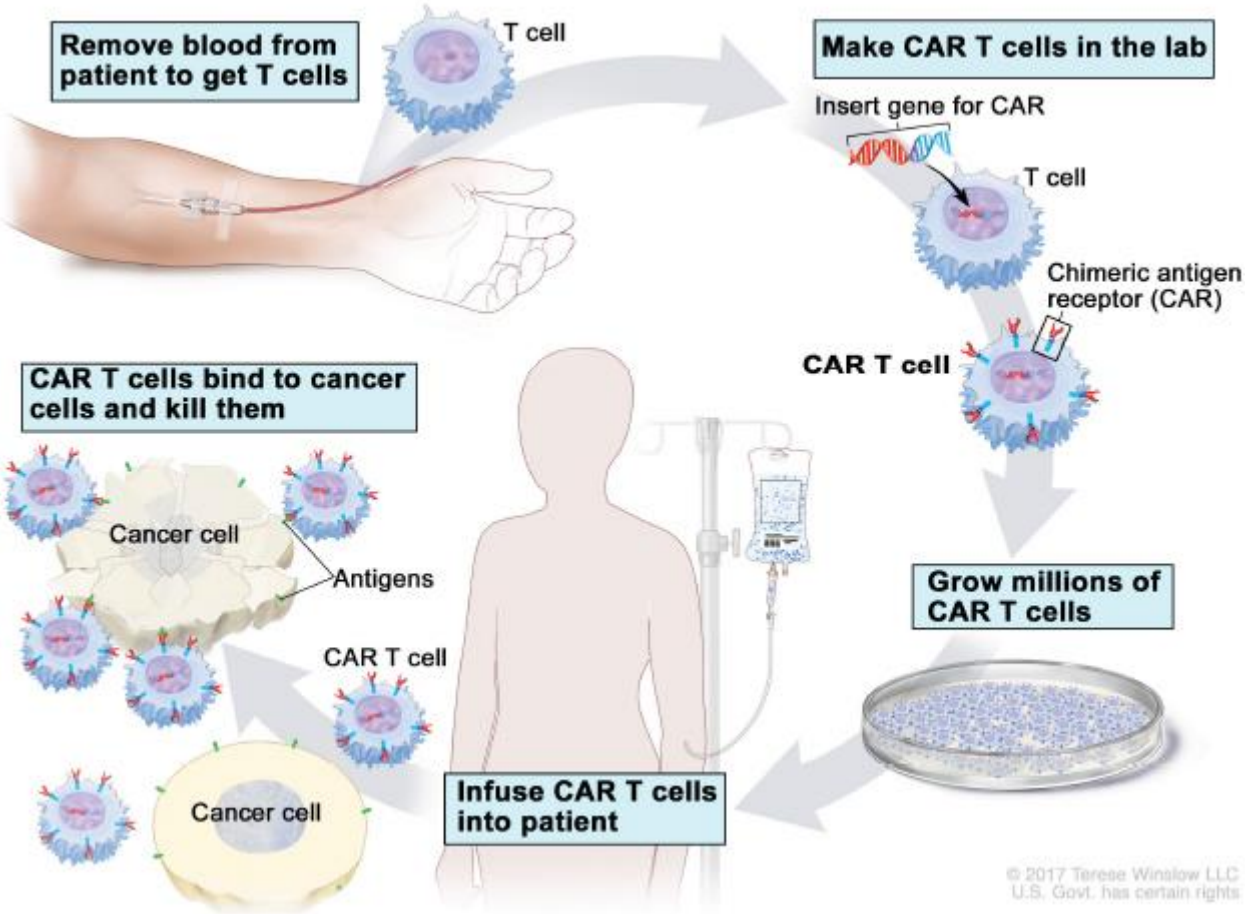
Zhou, Zheng-Yi, et al. "Burden of illness: direct and indirect costs among persons with hemophilia A in the United States." *Journal of medical economics* 18.6 (2015): 457-465.

And so costs increase

Factor inhibitors alter treatment

For 1,500 (~8%) of US hemophiliacs

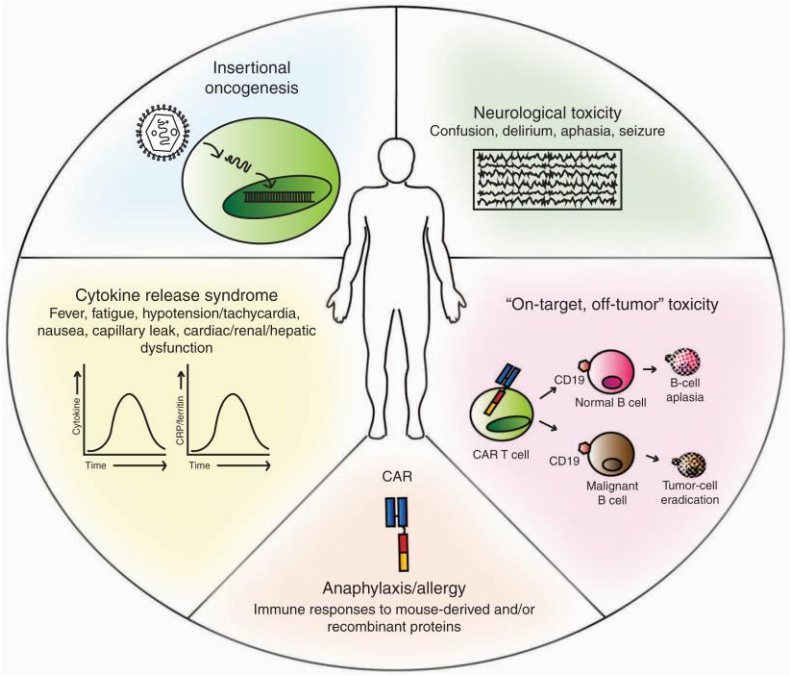
CAR-T CELLULAR THERAPY



How It Works. The above image illustrates the process of making CAR T cells for each individual patient from collecting the patient's T cells from their blood, shipping the cells to the laboratory for modification and manufacturing, to infusing the engineered CAR-containing T cells into the patient. © 2017 Terese Winslow LLC. U.S. Govt. has certain rights
http://www.ascopost.com/issues/may-25-2018/weighing-the-cost-and-value-of-car-t-cell-therapy/

CAR-T IMMUNOGENICITY ADVERSE EVENTS

Cytokine release syndrome (CRS), neurologic toxicity, "on target/off tumor" recognition, and anaphylaxis occur.



Bonifant, Challice L., et al. "Toxicity and management in CAR T-cell therapy." *Molecular Therapy-Oncolytics* 3 (2016). https://www.sciencedirect.com/science/article/pii/S2372770516300353

Patients will incur on average $30,000 to $36,000 in additional costs due to CRS. Patients who present with severe CRS may pay up to $56,000 more.

Hernandez I, et al. *JAMA Oncol.* 2018;doi:10.1001/jamaoncol.2018.0977.

1/3 to 1/2 of CAR-T patients go to Intensive care from CRS

CAR-T IMMUNOGENICITY AEs ADD 5-10% TO TOTAL COST OF CARE

Table 4.7. Base-Case Discounted Lifetime Costs from Model

	B-ALL		B-cell Lymphoma	
Cost Category	**Tisagenlecleucel**	**Clofarabine**	**Axicabtagene Ciloleucel**	**Chemotherapy**
CAR-T Treatment Costs	$405,490	$0	$438,284	$0
Chemotherapy Treatment Costs	$15,309	$163,686	$0	$40,142
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Base-case payment for tisagenlecleucel assumes payment only for responders at 1 month. Base-case payment for axicabtagene ciloleucel assumes payment at infusion

*For inpatient administered therapies, costs associated with adverse events only included costs associated with adverse events that were expected to increase the length of stay (cytokine release syndrome) or extend beyond discharge (B cell aplasia).

B-ALL: B-cell acute lymphoblastic leukemia, SCT: stem cell transplant

Source: ICER's final report on the comparative clinical effectiveness and value of tisagenlecleucel (KymriahTM, Novartis) and axicabtagene ciloleucel (YescartaTM, Kite Pharma/Gilead), including key policy recommendations. https://icer-review.org/material/car-t-final-report/

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IMMUNE RESPONSES TO rAAV VECTORS

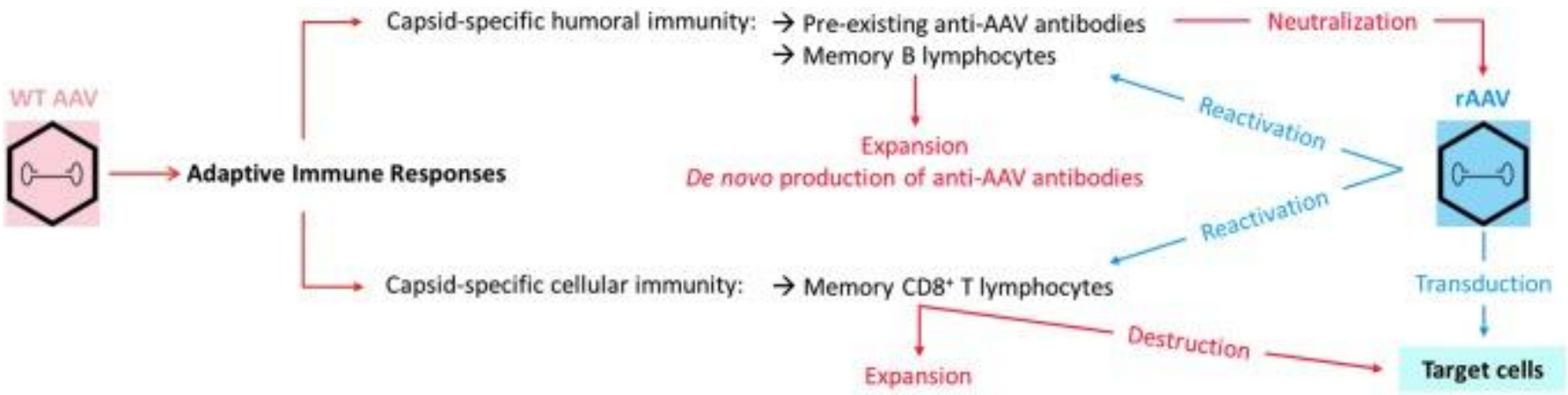


Figure 1. Initiation and reactivation of adaptive immune responses to adeno-associated virus (AAV). During natural infection with wild-type (WT) AAV, capsid-specific adaptive immune responses can be triggered, with the development of anti-AAV antibodies and the establishment of a pool of long-lasting capsid-reactive memory B and T lymphocytes. Upon *in vivo* administration of recombinant AAV (rAAV) vectors, pre-existing anti-AAV antibodies can neutralize vector particles, while memory lymphocytes can be reactivated and expanded, leading to the *de novo* production of anti-AAV antibodies or, potentially, to the destruction of transduced cells presenting capsid-derived antigens.
Vandamme, Céline, Oumeya Adjali, and Federico Mingozzi. "Unraveling the complex story of immune responses to AAV vectors trial after trial." Human gene therapy 28.11 (2017): 1061-1074.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5649404/

COST AND BURDEN OF IMMUNOGENICITY ON VECTOR-BASED THERAPY

Too soon for empirical evidence, but concern applies to all *in vivo* vector-based approaches

E. Dolgin. Early clinical data raise bar for hemophila gene Therapies. *Nature Biotechnology 34, 999-1001 (2016)*

	Company	Product	Vector	Therapeutic gene	Manufacturing platform	Year in which first patients dosed in phase 1/2 trial
Hemophilia B	Shire	BAX 335	**AAV8**	Padua mutant factor IX	HEK293 cells	2013
	Spark Therapeutics/Pfizer	SPK-9001	**Engineered AAV**	Padua mutant factor IX	HEK293 cells	2015
	uniQure	AMT-060	**AAV5**	Wild-type factor IX	Baculovirus	2015
	Dimension Therapeutics	DTX101	**AAVrh10**	Wild-type factor IX	HEK293 cells	2016
	Sangamo Biosciences	SB-FIX	**AAV6**	Zinc-finger-nuclease-mediated integration of wild-type factor IX into the albumin locus in hepatocytes	Baculovirus	Expected 2016
	Freeline Therapeutics	FLT-180	**Engineered AAV**	Undisclosed	HEK293 cells	Expected 2017
	Bioverativ	Undisclosed	**Lentivirus**	Padua mutant factor IX	HEK293 cells	Expected 2018
Hemophilia A	BioMarin	BMN 270	**AAV5**	B-domain deleted factor VIII	Baculovirus	2015
	Spark Therapeutics	SPK-8011	**Engineered AAV**	B-domain deleted factor VIII	HEK293 cells	Expected 2016
	Dimension Therapeutics/Bayer	DTX-201	**Undisclosed**	B-domain deleted factor VIII	HeLa cells	Expected 2017
	Shire	BAX-888	**AAV8**	B-domain deleted factor VIII	HEK293 cells	Expected 2017
	Sangamo Biosciences	SB-525	**AAV6**	B-domain deleted factor VIII	Baculovirus	Expected 2017

AAV THERAPY ACCESS LIMITED BY IMMUNOGENICITY

- **Immunogenicity Clinical trial exclusion criteria**
- ***Active inhibitors as measured by AAV transduction inhibition & AAV total antibodies***
- ***Hepatitis B or Hepatitis C positive***
- ***HIV positive***

- **Estimated 40-50% of potential patients excluded**

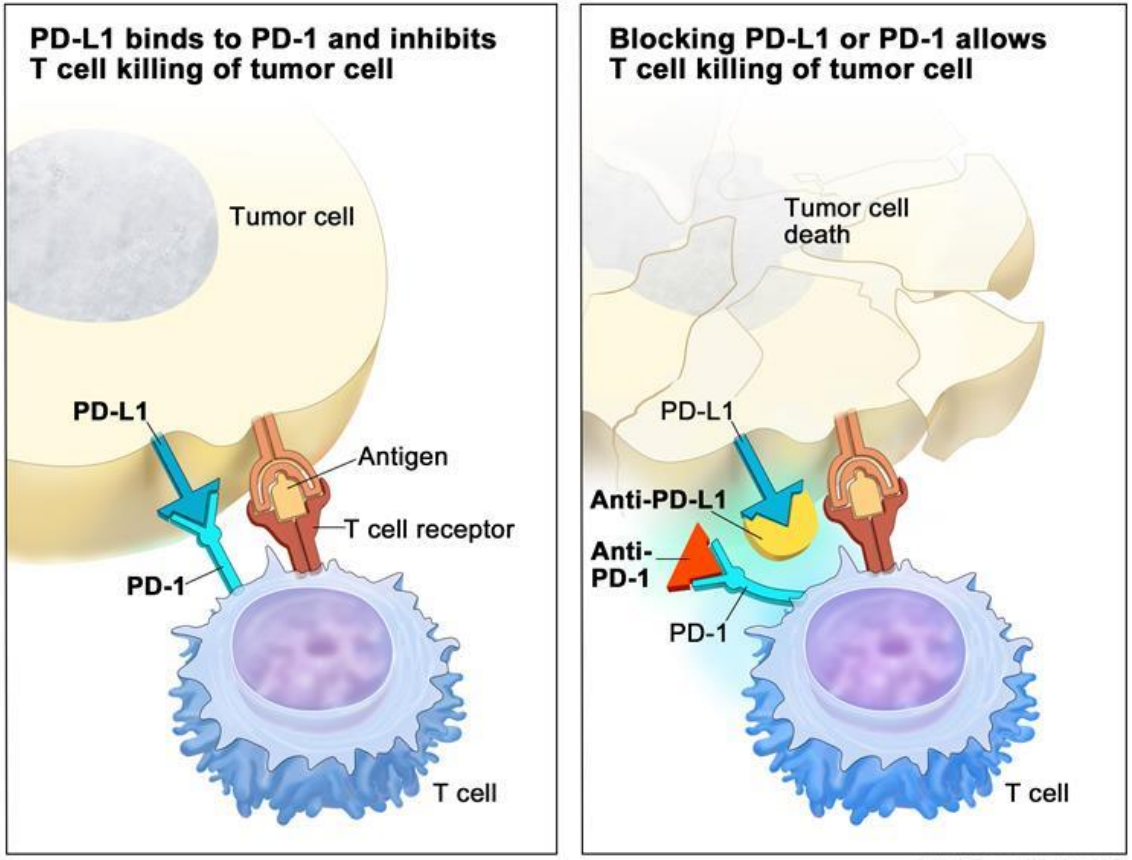
Falese, Lillian, et al. "Strategy to detect pre-existing immunity to AAV gene therapy." *Gene therapy* 24.12 (2017): 768.
George, Lindsey A. "Hemophilia gene therapy comes of age." *Blood advances* 1.26 (2017): 2591-2599.

- **PLUS: CD8+ T cell-mediated cytotoxic immune response to transduced cells presenting AAV capsid antigens AND/OR ADAs to the transgene product may also occur.**

- **May mean patients have only have 1 (or no) chance at gene therapy depending on AAV vectors employed, cross reactivity and wild-type inhibitor status**

- **Resulting sub-populations further fragment the market, reduce competition and reduce incentives for more entrants**

CHECKPOINT INHIBITOR LACK OF IMMUNE RESPONSE COSTS TIME



NCI Dictionary of Cancer Terms
https://www.cancer.gov/images/cdr/live/CDR774646-750.jpg

LACK OF IMMUNE RESPONSE COSTS PATIENTS TIME, HARM AND HOPE

Tremelimumab OR varies by Cancer Type

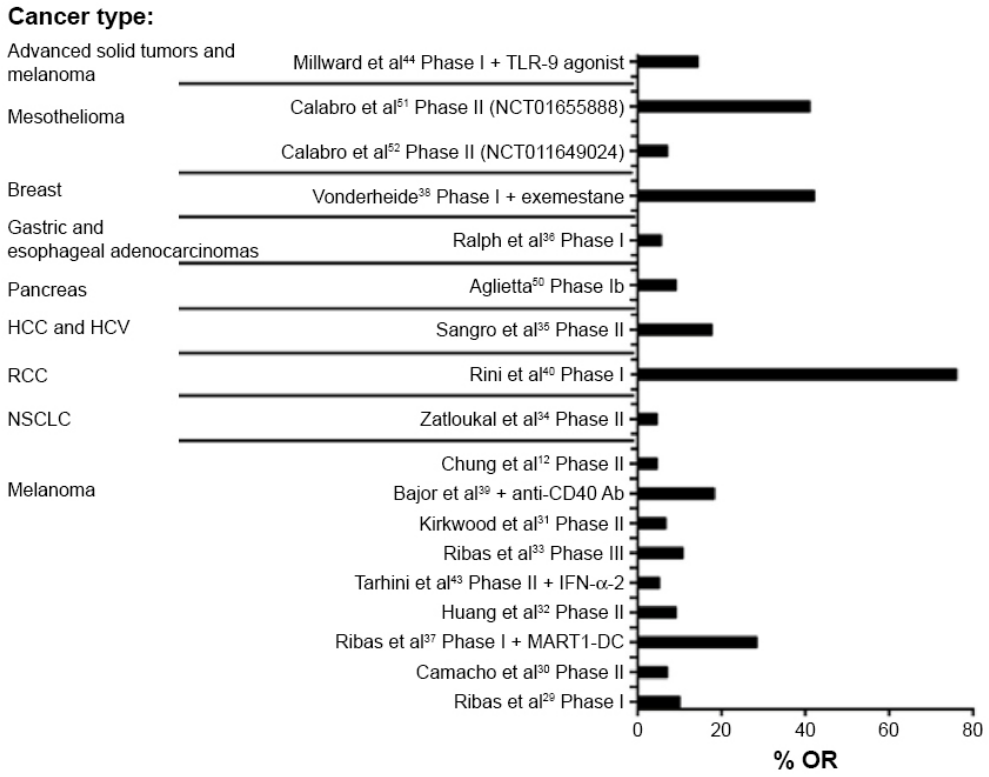


Figure 2 Overall objective response rate or overall response (OR) to treatment with tremelimumab in different cancer types.
Notes: Clinical benefit expressed as overall objective response or overall response (OR) of all the tremelimumab clinical trials. The percentage of OR is expressed on *X*-axis; and all the tremelimumab clinical trials that presented a clinical response are represented on the *Y*-axis. The high percentage of OR is due to the low number of patients normally enrolled on those Phase I clinical trials.
Abbreviations: DC, dendritic cell; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN-α-2, interferon-α-2; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; TLR-9, Toll-like receptor-9; MART-1, melanoma antigen recognized by T-cells.

Comin-Anduix, Begoña, Helena Escuin-Ordinas, and Francisco Javier Ibarrondo. "Tremelimumab: research and clinical development." *OncoTargets and therapy* 9 (2016): 1767.

BIOMARKERS HELP, BUT LARGE GAPS & ECONOMIC LOSSES REMAIN

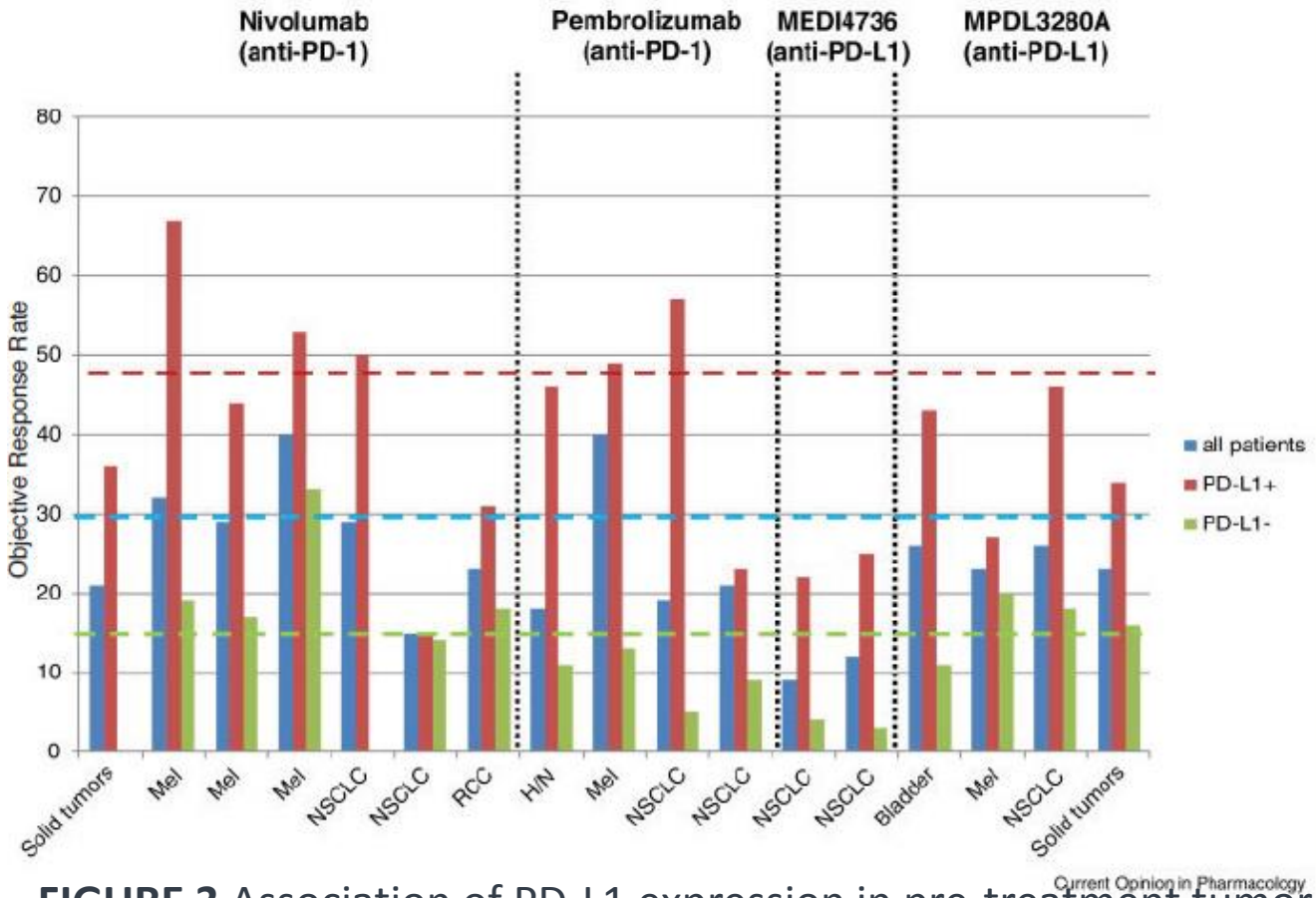


FIGURE 3 Association of PD-L1 expression in pre-treatment tumor specimens with objective response to anti-PD-1/PD-L1 therapy.

Sunshine, J., and J. M. Taube. 2015. PD-1/PD-L1 inhibitors. *Current Opinion in Pharmacology* 23:32-38.

TIME DELAYS REDUCE OPTIONS & INCREASE COSTS

"…it may take weeks or even months for a measurable response from your immune system"

OncoLink (Penn Medicine): All about Immunotherapy https://www.oncolink.org/cancer-treatment/immunotherapy/all-about-immunotherapy

Patient costs and healthcare burden of mis-control of immunogenicity poorly studied but keenly felt.

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LOWER SUCCESS RATES

ADAs causing project cancellations

Pratt, Kathleen P. "Engineering less immunogenic and antigenic FVIII proteins." *Cellular immunology* 301 (2016): 12-17.

- **PEGylated recombinant thrombopoeitin (TPO) molecule administered to healthy volunteers and patients elicited ADAs in several individuals that bound to their endogenous TPO, resulting in prolonged thrombocytopenia**

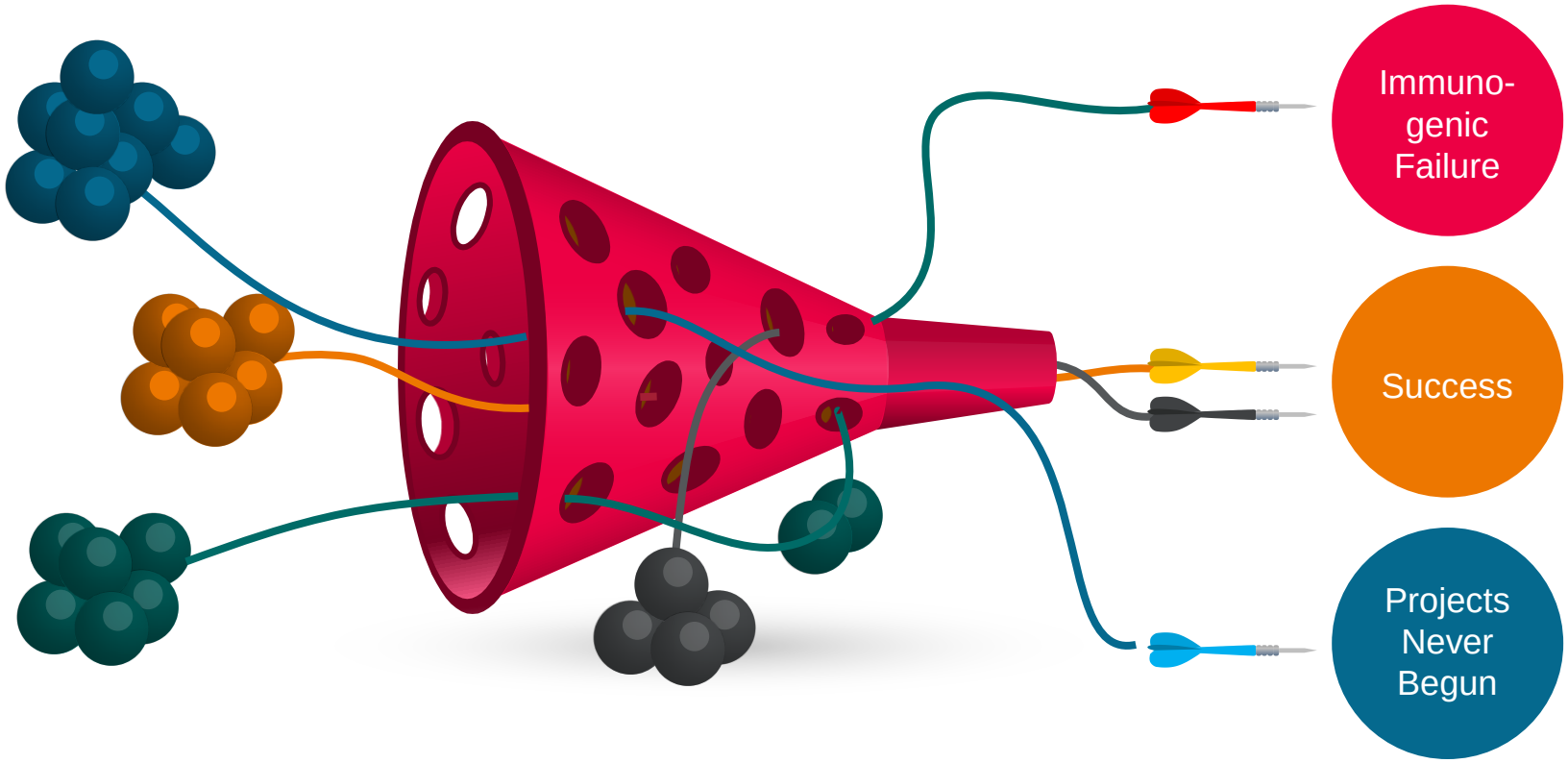
  Li J, Yang C, Xia Y, Bertino A, Glaspy J, et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood. 2001; 98:3241–3248. [PubMed: 11719360]

- **ADAs developed in 11% of hemophilia patients receiving a recombinant factor VIIa, vatreptacog alfa, during phase III confirmatory testing. Only 3 amino acid substitutions**

  -Mahlangu JN, Weldingh KN, Lentz SR, Kaicker S, Karim FA, et al. Changes in the amino acid sequence of the rFVIIa analog, vatreptacog alfa, are associated with clinical immunogenicity. J. Thromb. Haemost. in press.
  -Lentz SR, Ehrenforth S, Karim FA, Matsushita T, Weldingh KN, et al. Recombinant factor VIIa analog in the management of hemophilia with inhibitors: results from a multicenter, randomized, controlled trial of vatreptacog alfa. J. Thromb. Haemost. 2014; 12:1244–1253. [PubMed: 24931322]

- **Evidence remains anecdotal rather than systematic but immunogenicity appears to contribute to failures and perhaps to the number of project initiated**

IMMUNOGENICITY CONTRIBUTES TO DIRECT FAILURES AND TO CHANCES NOT TAKEN



Likely result is both higher costs and lower competition

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IMMUNOGENICITY CONCERNS CONTRIBUTE TO BIOSIMILAR ECONOMICS

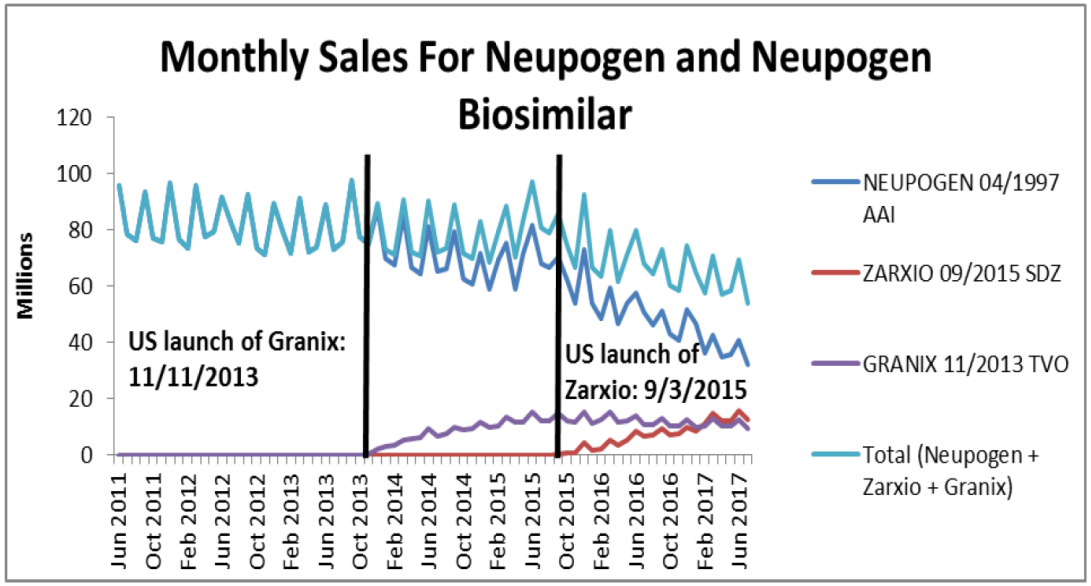
Immunogenicity contributes to clinical trial requirements raising costs. Pfizer claims:

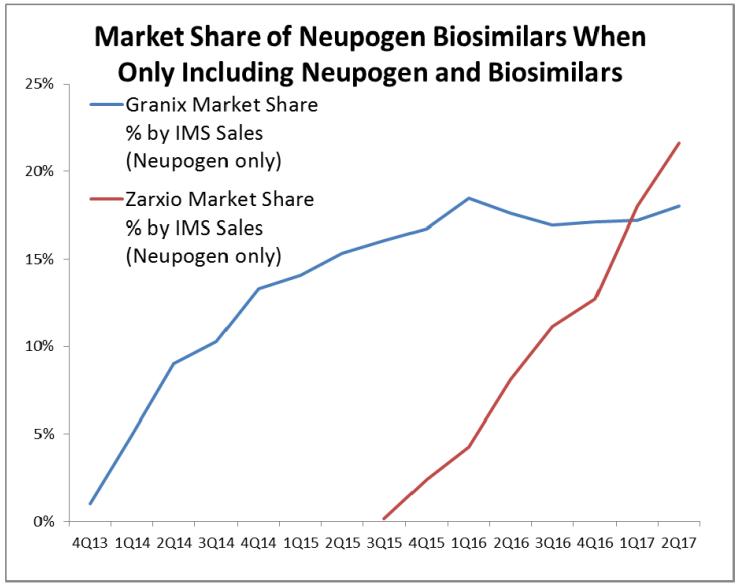
- >$100M biosimilar development cost over 5-9 years
- $1-2M small-molecule generic development cost
  https://www.pfizerbiosimilars.com/biosimilars-development

These higher costs in turn limit the potential maximum biosimilar discount and market shares

No biosimilar has yet achieved interchangeability designation in the US, a status which requires extensive direct and implicit immunogenicity clinical evidence.

BIOSIMILAR ADOPTION SLOW IN US





Light blue line showing total sales (Neupogen + Granix +Zarxio) partially overlaps with dark blue line showing Neupogen sales alone

Source: IMS Health, IMS National Sales Perspectives™, 06/2011-07/2017
Source of Market Share Calculations: Evercore ISI Research September 7, 2017

EU BIOSIMILAR ADOPTION ALSO SLOW

Table 3 Biosimilar Standard Unit Share of the Molecular Entity									
	France	**Germany**	**Italy**	**Spain**	**UK**	**Belgium**	**Finland**	**Norway**	**Sweden**
Somatropin									
2007	1%	1%	1%	0%	0%	0%	0%	0%	0%
2008	5%	2%	2%	0%	0%	0%	0%	0%	0%
2009	7%	2%	3%	1%	0%	5%	0%	0%	3%
2010	9%	3%	4%	1%	1%	6%	0%	0%	7%
2011	10%	4%	4%	2%	1%	7%	5%	0%	7%
2012	11%	5%	4%	3%	1%	7%	5%	0%	8%
Erythropoietin alpha & zeta									
2007	0%	2%	0%	0%	0%	0%	0%	0%	0%
2008	0%	41%	0%	0%	0%	0%	0%	0%	1%
2009	4%	58%	0%	3%	3%	0%	0%	0%	19%
2010	9%	64%	5%	19%	7%	0%	100%	0%	49%
2011	11%	69%	13%	31%	10%	0%	100%	100%	62%
2012	16%	68%	21%	39%	7%	0%	100%	100%	70%
G-CSF (filgrastim)									
2007	0%	0%	0%	0%	0%	0%	0%	0%	0%
2008	0%	0%	0%	0%	1%	0%	0%	0%	0%
2009	6%	8%	1%	9%	20%	0%	0%	25%	5%
2010	26%	15%	9%	23%	53%	0%	15%	0%	40%
2011	35%	23%	36%	33%	71%	0%	33%	0%	70%
2012	48%	27%	60%	51%	81%	0%	65%	20%	86%

Berndt ER, Trusheim MR. Biosimilar and Biobetter Scenarios for the US and Europe: What Should We Expect?", Chapter 15 in Biobetters: Protein Engineering to Approach the Curative, Amy Rosenberg and Barthelemy Demeule Editors. AAPS Advances in the Pharmaceuticals Sciences Series 19. Springer AAPSPress New York, 2015.

IMMUNOGENICITY CONCERNS CONTRIBUTE TO LIMITED US BIOSIMILAR COMPETITION

"The biosimilar penetration, particularly [sic] that of Inflectra, is 56 percent in Europe. In the US, our share is 6 percent, so there is something wrong with that," Pfizer COO Albert Bourla said in a response to a question on the company's stance on FDA's recent move to stimulate biosimilar uptake and development. *The Investor, May 2 2018*
http://www.theinvestor.co.kr/view.php?ud=20180502000769

Immunogenicity contributes to more stringent FDA guidance compared to EU rules. Specifically, "EMA does not regulate interchangeability, switching and substitution of a reference medicine by its biosimilar." *Biosimilars in the EU: Information guide for healthcare professionals*
https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf

EXAMPLES ILLUSTRATE BOTH INDIRECT AND INDIRECT ECONOMIC IMPACTS

Costs of production, including R&D costs

Market size and demand

Uncertainty regarding product performance

Competition which affects price equilibrium

Products available, which affects market sizes and competition

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BACK-UP

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Table 4 Annualized total costs by inhibitor status (€; Euros)

	Total cost	*P*-value
With inhibitor ($n=5$)	134,032	0.030
Without inhibitor ($n=98$)	40,318	

P value was computed using the Mann-Whitney U test

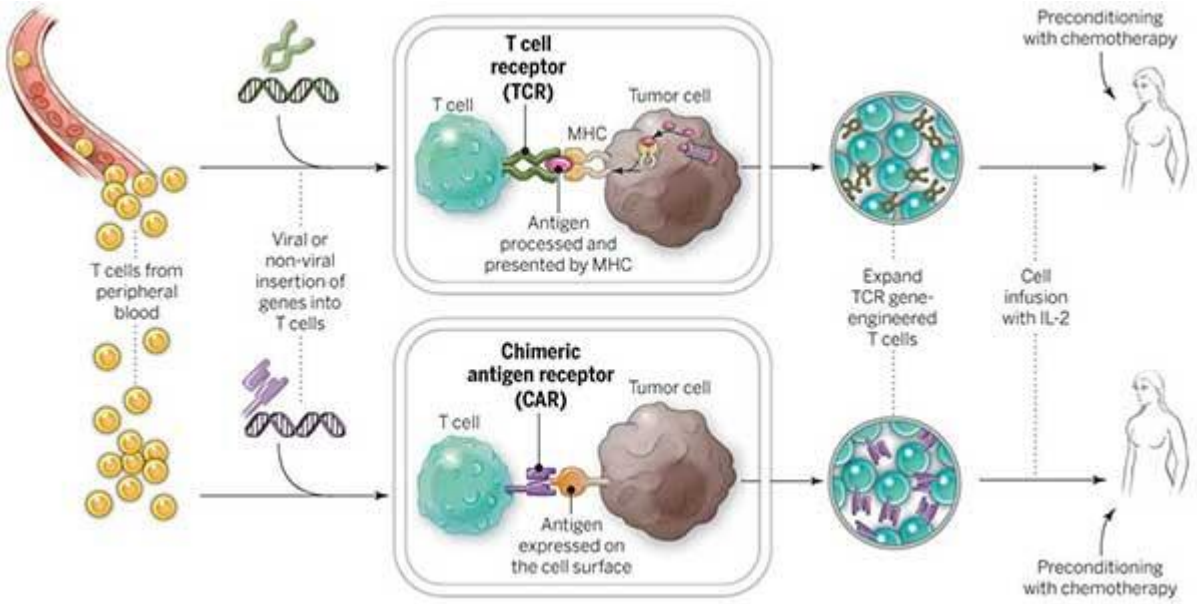
Rocha, Patrícia, et al. "Costs and utilization of treatment in patients with hemophilia." *BMC health services research* 15.1 (2015): 484.

And so costs increase

For 1,500 (~8%) of US hemophiliacs

CAR-T CELLULAR THERAPY

Harnessing immune cells to treat cancers



CAR T cells and TCR T cells are engineered to produce special receptors on their surfaces. They are then expanded in the laboratory and returned to the patient.
Credit: National Cancer Institute
https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

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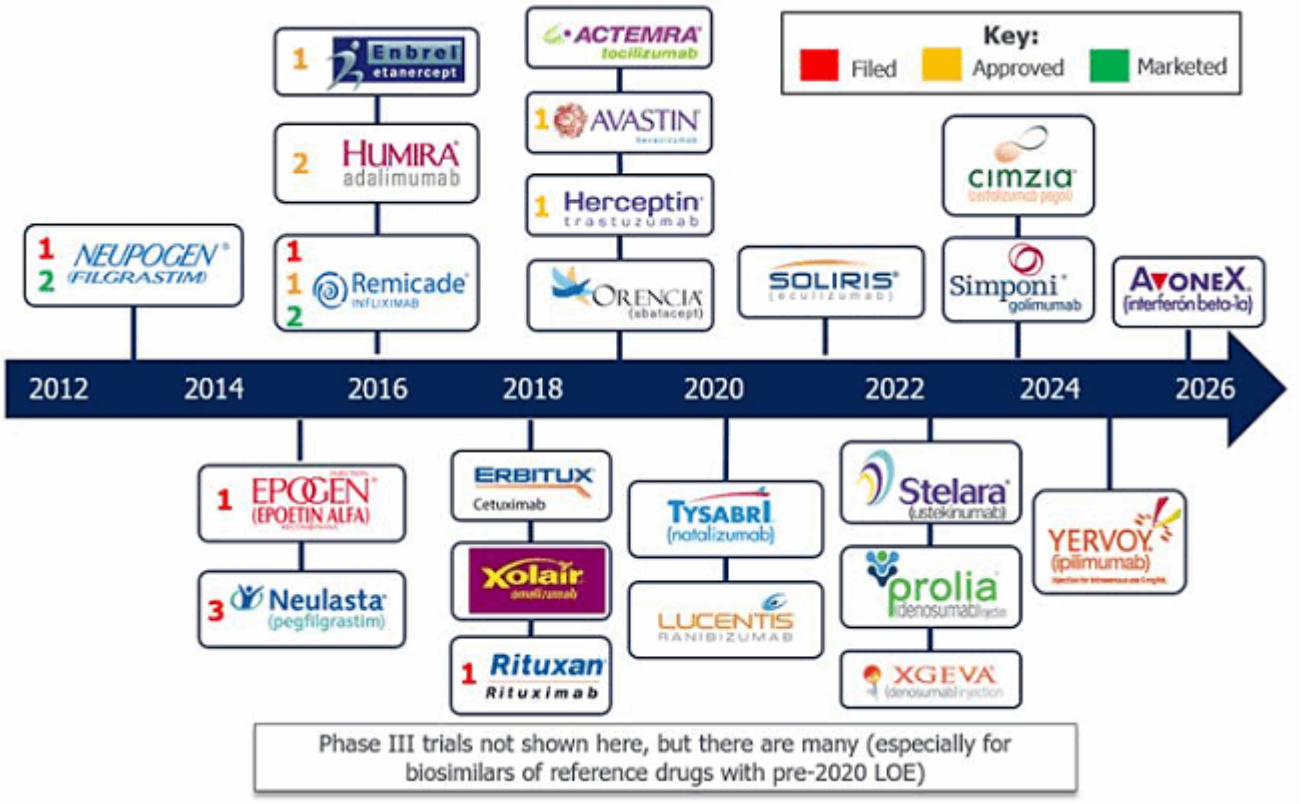
Figure 1: *Loss of exclusivity (LOE) and biosimilar entry timeline — LOE is approaching for many biologics, priming the market for more biosimilar entry.*



Source: C. Danosi et al. Why so Slow? Demystifying the barriers to U.S. Biosimilar Adoption. *Biosimilar Development* December 19, 2017. https://www.biosimilardevelopment.com/doc/why-so-slow-demystifying-the-barriers-to-u-s-biosimilar-adoption-0001

CAR-T IMMUNOGENICITY ADVERSE EVENTS

Cytokine release syndrome, neurologic toxicity, “on target/off tumor” recognition, and anaphylaxis occur.

Human Cost

Little incremental financial due to out-of-pocket caps

~1/3-1/2 go to intensive care for CRS

Healthcare System Burden

Developers

- **More activities**
- **Lower success**
- **Limited patient pools**

Leads to

- **Smaller markerts**
- **Fewer products**
- **Less competition**

Payers

- **Higher prices**
- **Lower patients on new therapies**
- **Ambiguous outcome**

COST AND BURDEN OF IMMUNOGENICITY ON VECTOR-BASED THERAPY

Too soon for empirical evidence, but concern applies to all *in vivo* vector-based approaches

Gene therapy for hemophilia A

Company	Product	Development phase	Vector
BioMarin	BMN 270	Phase III	AAV 5
Spark Therapeutics	SPK-8011	Phase I / II	AAV-LK03
Sangamo Biosciences	SB-525	Phase I / II	AAV 2/6
Shire	SHP654	Phase I / II	rAAV 8
uniQure	Undisclosed	Preclinical	
Bioverativ / Sanofi	Undisclosed	Discovery	

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Gene therapy for hemophilia B

Company	Product	Development phase	
uniQure	AMT-061	Phase III	AAV 5
Spark Therapeutics / Pfizer	SPK-9001	Phase I / II	rAAV 8 Spark100
Sangamo Biosciences	SB-FIX	Phase I / II	rAAV 6
Freeline Therapeutics	FLT-180	Phase I / II	
Bioverativ / Sanofi	Undisclosed	Discovery	

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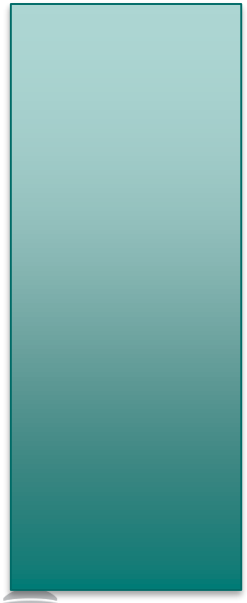
GENE THERAPY VECTOR SUB-POPULATIONS MAY REDUCE COMPETITION

All patients



Inhibitor Status

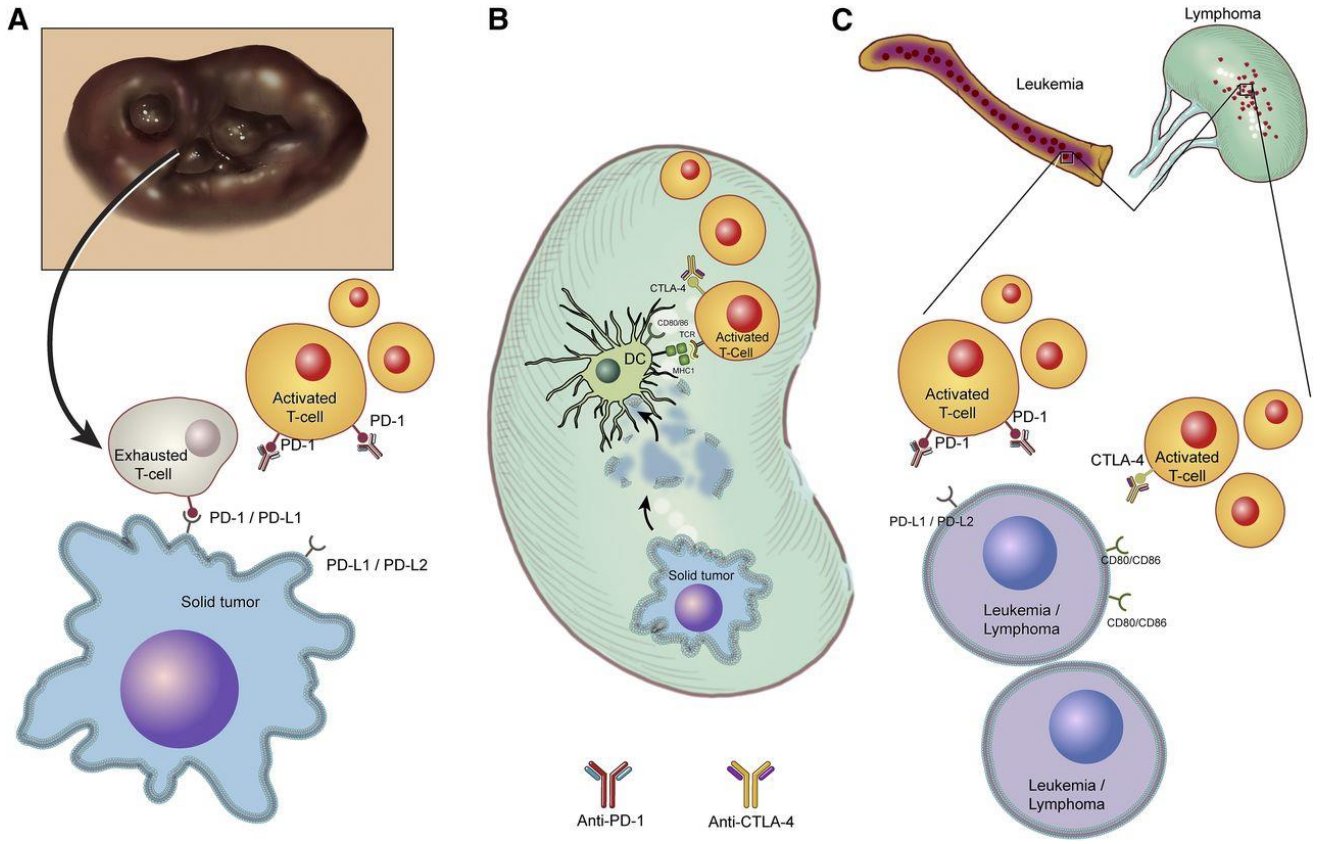
- AAV5
- AAV 2 /6
- AAV 8
- AAV 5

AE profile (1st, 2nd Gen)

Many needed Niches, few products in each

CHECKPOINT INHIBITORS INDUCE IMMUNE RESPONSE TO ATTACK CANCERS

Malignant hematologic cells express ligand for CTLA-4 and PD-1 and are therefore direct targets for immune checkpoint blockade.



Gheath Alatrash et al. Pharmacol Rev 2016;68:1014-1025

ASPET PHARMACOLOGICAL REVIEWS