



# XVIII IPOPI GLOBAL PATIENTS' MEETING

an **IPOPI** event

16-19 OCTOBER 2024  
MARSEILLE, FRANCE

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## “Adult perspective” in Session 11: Outlook on new and innovative therapies

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# Disclosures

I have the following real or perceived conflicts of interest that relate to this presentation:

<b>Affiliation / Financial interest</b>	<b>Commercial company</b>
Grants:	Grifols, CSL Behring, Takeda, Binding-Site
Speaking and Consultancy fees:	Grifols, CSL Behring, Takeda, Biotest and Octapharma
Participation in a company sponsored bureau:	NA
Stock shareholder:	NA
Spouse / partner:	NA
Other support / potential conflict of interest:	None

# Towards Precision Medicine

**Vaccines**  
**Antimicrobial Ab**  
**Antibiotics**  
**Gammaglobulin**  
**Adoptive transfer of  
virus-specific T cells**

**Preventive**

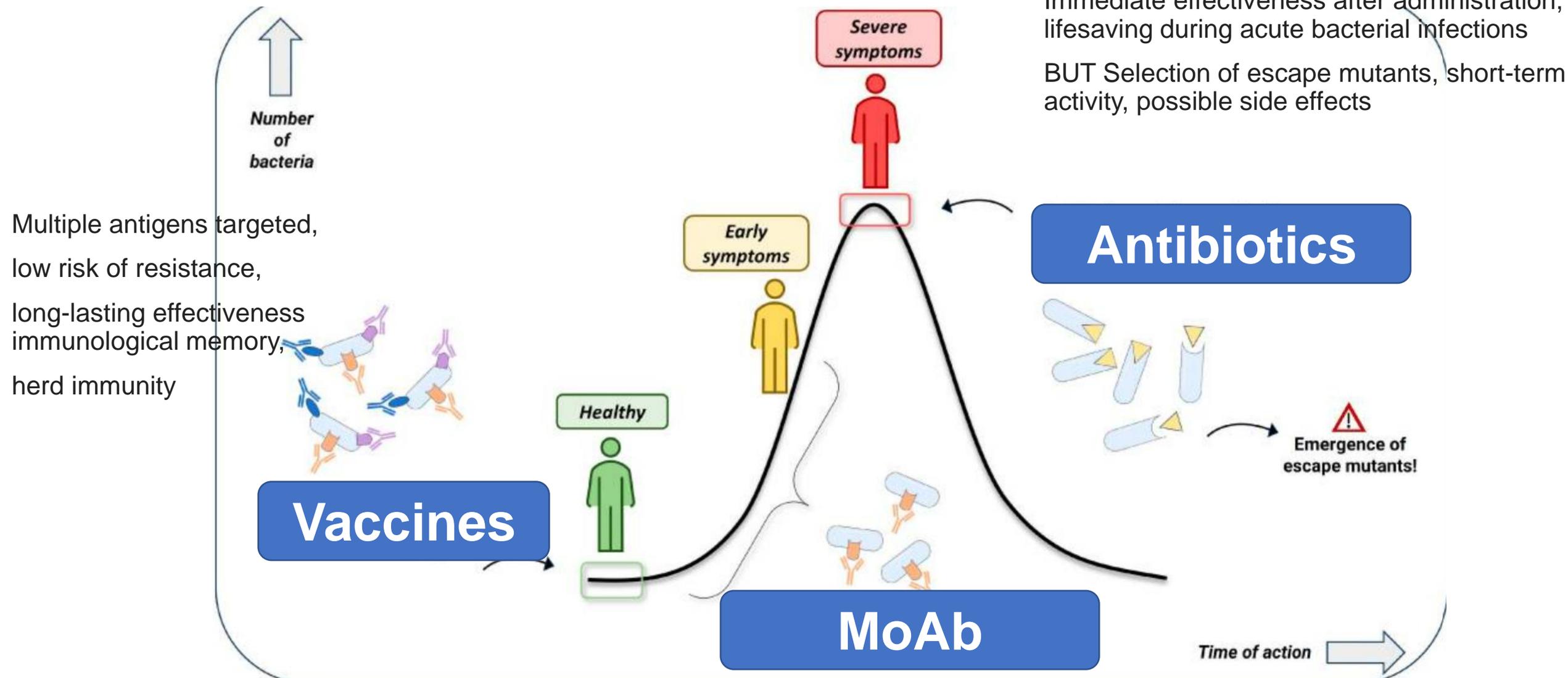
**Immunosuppressors**  
**Small molecule  
inhibitors**  
**Fusion proteins**  
**Biologics**

**Immunomodulatory**

**BMT**  
**Gene therapy**

**Curative**

# Prevention of Infections



Safety, high target-specificity, less susceptible to resistance mechanisms, longer half-lives (~21 days for IgG) compared to antibiotics

BUT expensive, need of cocktails, limitation of penetrance due to biofilm

# New Vaccines

**Innovative technologies to accelerate the development of vaccines against AMR pathogens.**

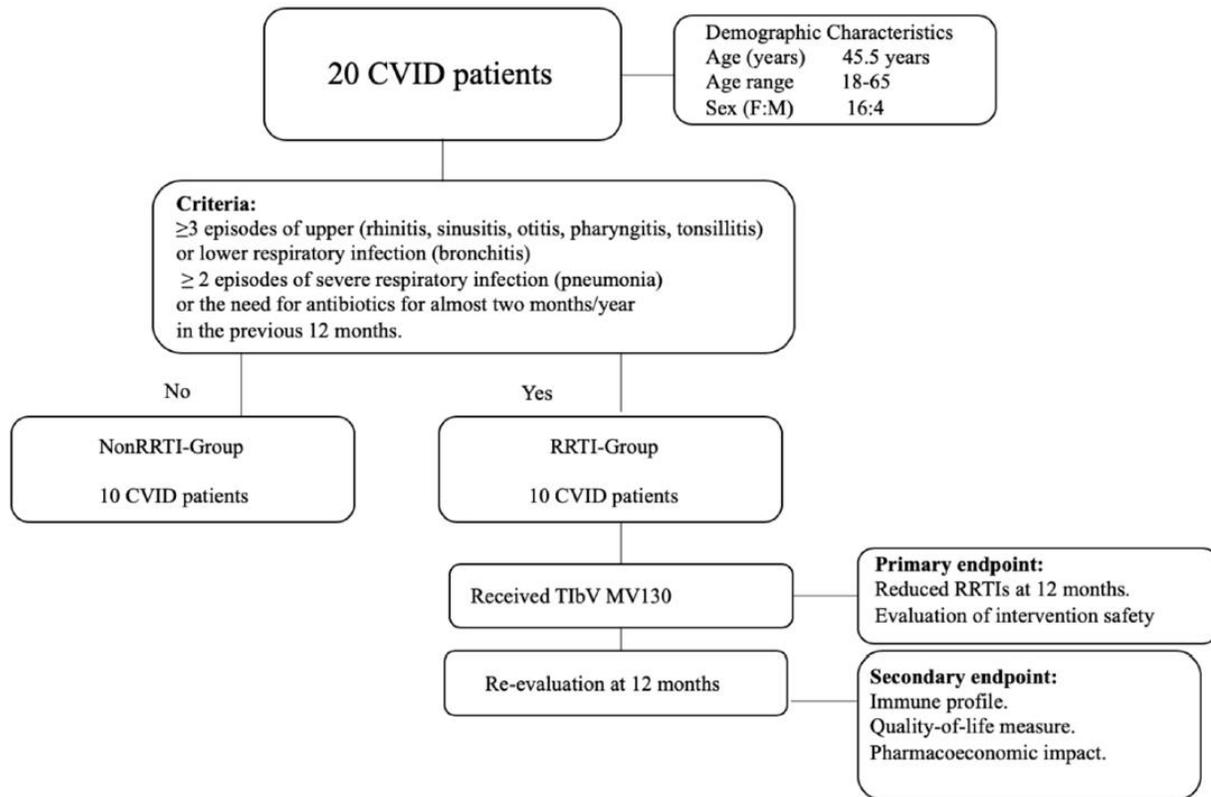
- Glycoconjugation
- Bioconjugation
- Multiple Antigen-Presenting System (MAPS)
- Reverse vaccinology
- Structural vaccinology
- Nanoparticle vaccines
- Generalized modules for membrane antigens (GMMAs)
- RNA-based vaccines
- Adjuvants

**Trained immunity based vaccines: MV130 or MV140**



Article

# Trained Immunity Based-Vaccines as a Prophylactic Strategy in Common Variable Immunodeficiency. A Proof of Concept Study



Daily for 3 months

- *Staphylococcus spp.*,
- *S. pneumoniae*,
- *K. pneumoniae*,
- *M. catarrhalis*,
- *H. influenzae*)



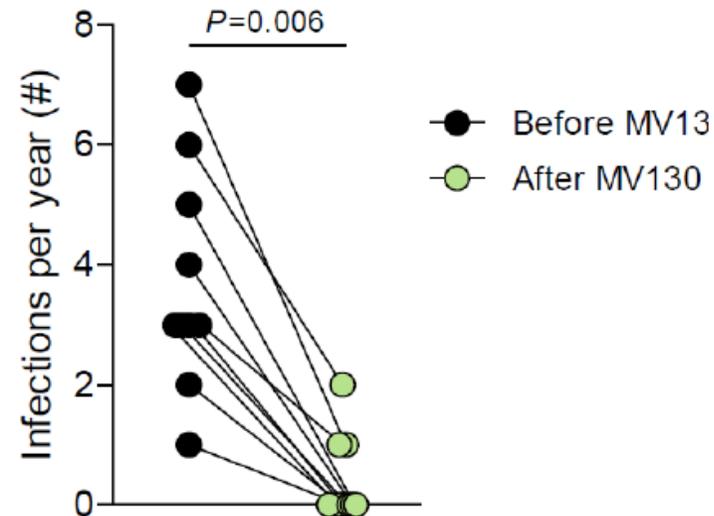
# MV130 significantly reduces the incidence of respiratory infections

## Respiratory tract infections

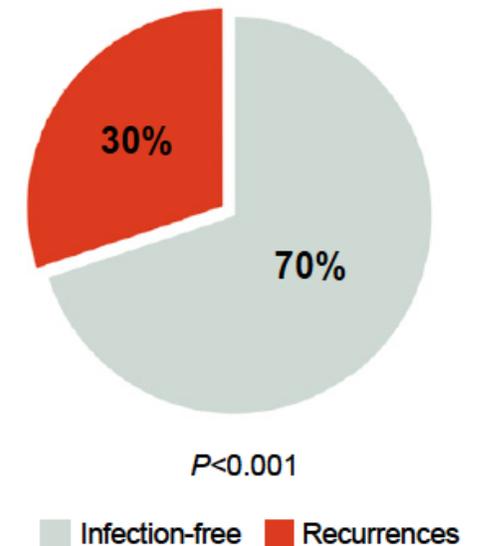
A

Subjects	Episodes before MV130	Episodes after MV130
#1	3	0
#2	3	0
#3	1	0
#4	7	1
#5	4	0
#6	3	0
#7	2	0
#8	5	0
#9	6	2
#10	3	1

B

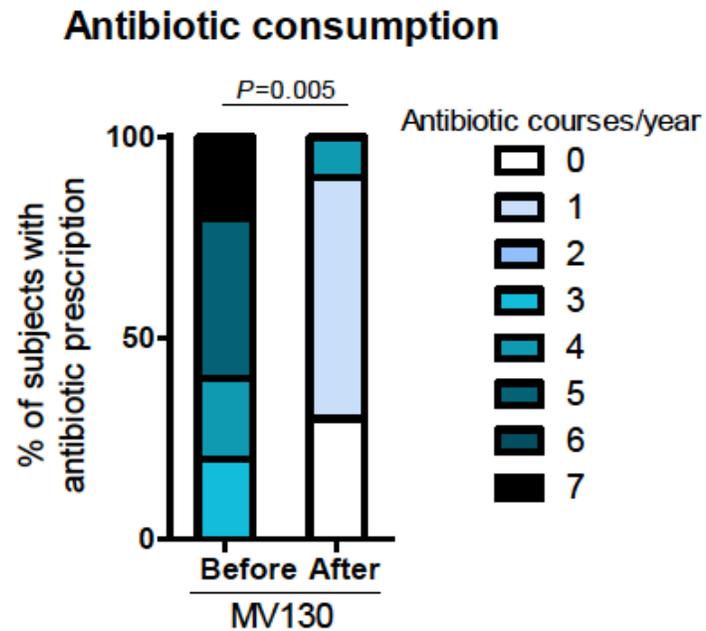


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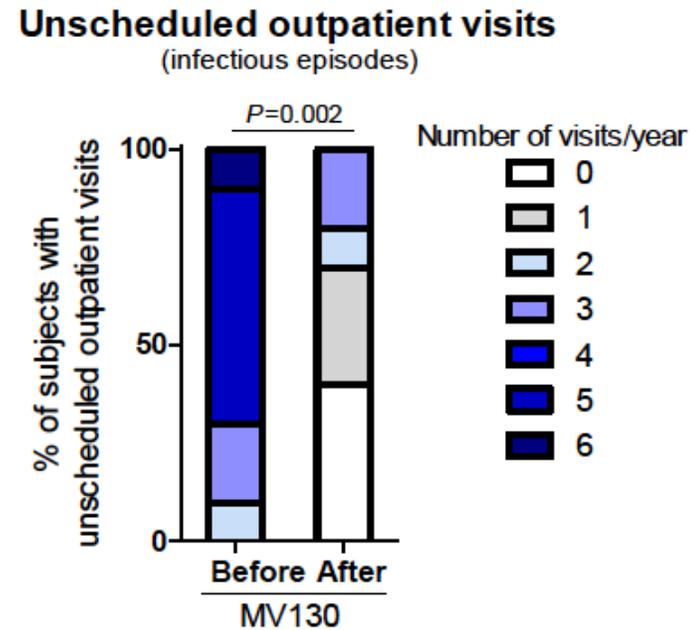


# Prophylaxis with MV130 significantly decreases the rate of healthcare resources consumption and work absenteeism

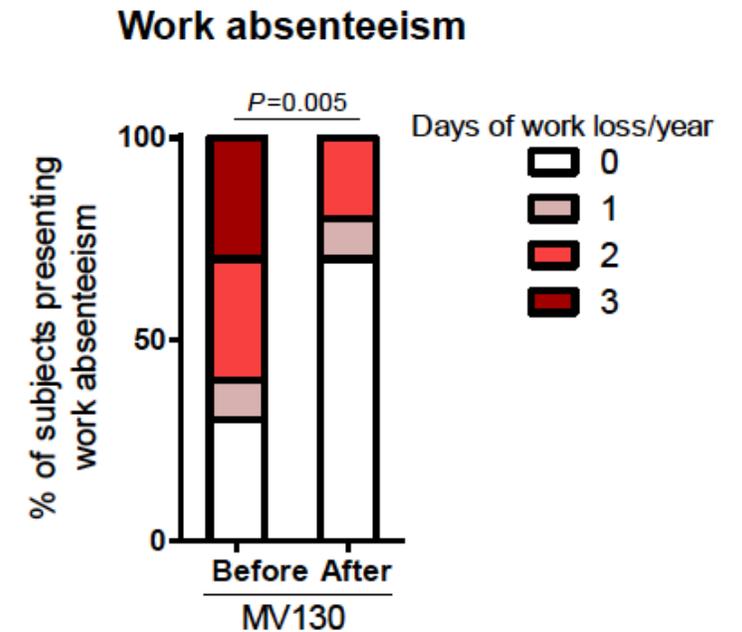
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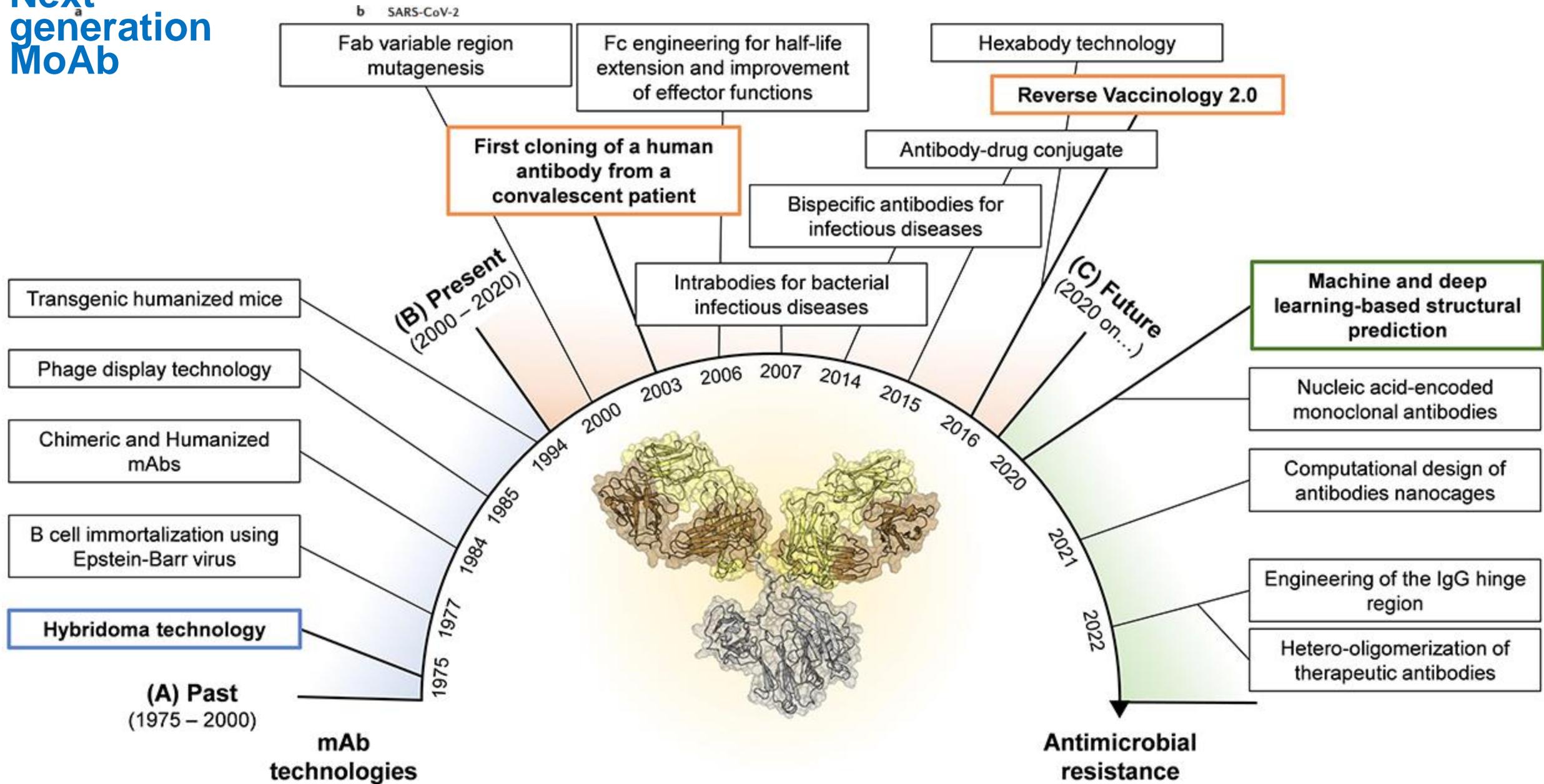
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# MV130 reduced health economic expenses

Condition	Average # of Episodes before TibV MV130	Average # of Episodes after TibV MV130	Cost per Patient per Episode/ Day €	Annual Cost per Patient before TibV MV130 €	Annual Cost per Patient after TibV MV130 €	Annual Savings per Patient with TibV MV130 €
# of RRTIs	3.7	0.4	1656	6127	662	5464
# of physician/hospital/ ER visits	4.4	1.1	1288	5667	1416	4250
# Days Hospitalizations for RRTIs	7	3	792	5546	2377	3169
Cycles of antibiotics	4.8	1	259	1243	259	984
School/work days missed (Absenteeism)	1.6	0.5	14	22.4	7	15
Total per patient Annual cost TibV				18,606	4722	13,884
MV130 prophylaxis					190	13,694

# Next generation MoAb



Bacterial species	Drug	Type	Target	Phase	Clinical trial ID
Bacillus anthracis	Obiltoximab	Humanized IgG1	Protective antigen (toxin)	IV	NCT03088111
	Thravixa	Human IgG1		I	NCT01202695
	Valortim	Human IgG1		I	NCT00964561
	Raxibacumab	Human IgG1		IV	NCT02016963
Clostridium botulinum	XOMA 3ab	Mix of 3 humanized IgG1	Botulinum neurotoxin type B (toxin)	I	NCT01357213
	NTM-1632	Mix of 3 humanized IgG1		I	NCT02779140
Clostridium difficile	Actoxumab	Human IgG1	<i>C. difficile</i> toxin A (toxin)	III	NCT01241552
	Bezlotoxumab	Human IgG1	<i>C. difficile</i> toxin B (toxin)	III	NCT05304715
Escherichia coli	Edobacumab	Mouse IgM	LPS lipid A	III	/
	Nebacumab	Human IgM		III	/
	MAB-T88	Human IgM		III	/
STEC*	Shiga toxin MAbs, $\alpha$ Stx1 & 2	Mix of 2 humanized IgG1	<i>E. coli</i> Stx1 & Stx2	II	NCT01252199
Pseudomonas aeruginosa	Aerucin	Human IgG1	<i>P. aeruginosa</i> alginate	II	NCT02486770
	Panobacumab	Human IgM	<i>P. aeruginosa</i> LPS O11	II	NCT00851435
	KB001	Human PEGylated Fab	<i>P. aeruginosa</i> PcrV	II	NCT01695343
	MEDI3902	Bispecific human IgG1	<i>P. aeruginosa</i> PcrV and Psl	II	NCT02255760
Staphylococcus aureus	Salvecin, AR-301	Human IgG1	<i>S. aureus</i> alpha-hemolysin	II	NCT03816956
	ASN100	Mix of 2 human IgG1	Bi-component toxins & alpha-hemolysin	II	NCT02940626
	Tefibazumab	Humanized IgG1	<i>S. aureus</i> ClfA	II	NCT00198289
	MEDI4893	Human IgG1 modified	<i>S. aureus</i> alpha-hemolysin	II	NCT02296320
	514G3	Human IgG3	<i>S. aureus</i> protein A	II	NCT02357966
	Pagibaximab	Chimeric IgG1	Lipoteichoic acid	II	NCT00646399
	Aurograb	scFv	GrfA (lipoprotein)	III	NCT00217841
Multiple species	F598	Human IgG1	Poly-N-acetylglucosamine	II	NCT03222401

\*STEC, Shiga toxin-producing Escherichia coli.

# Viral-Specific T Cells

VST against viral infections including CMV, EBV, and adenovirus and used in various clinical trials in stem cell transplant patients both the pre- and post-transplant period.

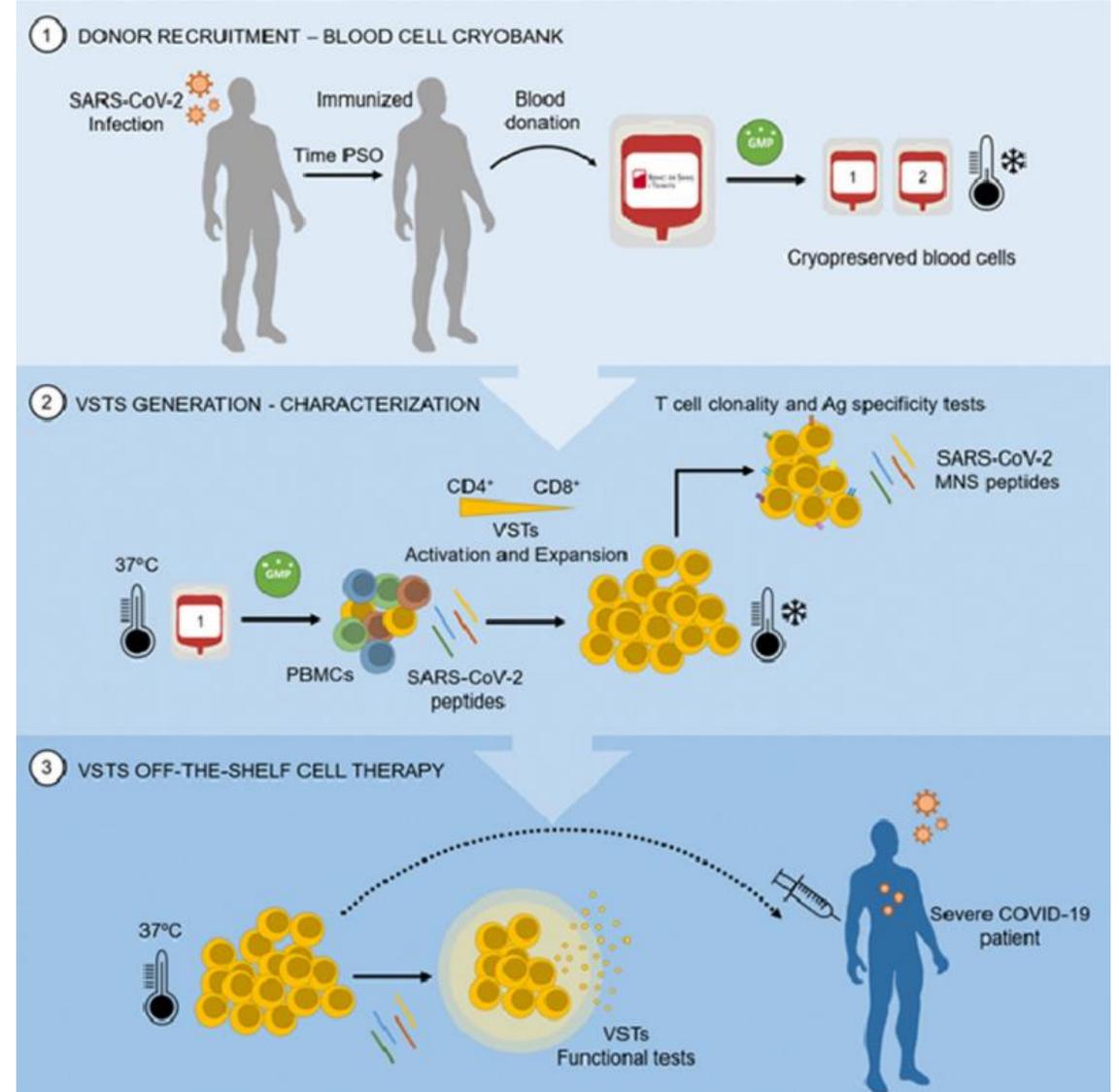
These cell products are derived from stem cell donors or third party partially HLA matched donors as “of the shelf” therapy. Recent trials show success rates from 75 to 92%

## VST banking

Promising role in SCID patients, HIGM, CID, HLH, LAD, GATA2, CGD, CTPS1 deficiency, WAS, NK cell defect, SCAEBV, and XLP requiring transplant.

Peptide libraries representing multiple viral antigens were used to induce rapid expansion of VST targeting a wide range of viral targets in less than 2 week

In phase I studies, VST appear to be safe, well-tolerated, and rarely induce graft versus host disease or cytokine release syndrome



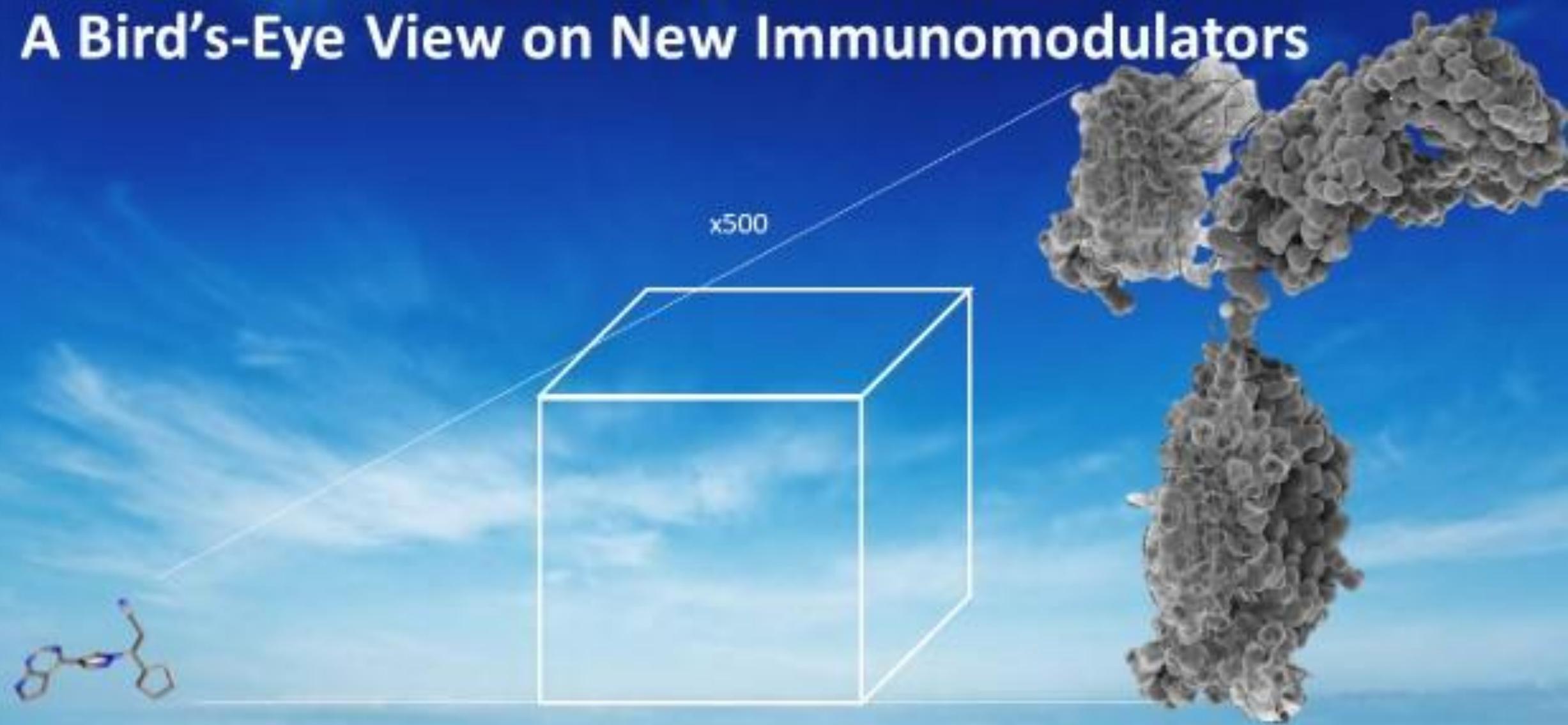
# IgA & IgM products

Product	Description	Features	Use in humans?
<b>Pentaglobin</b>	IgA + IgM containing Ig preparation from Cohn Fraction III, (72% IgG, <b>12% IgM</b> , and <b>16% IgA</b> ) for IV use	<ul style="list-style-type: none"> <li>-Decreased aggregation</li> <li>-Effective reduction of endotoxin</li> <li>-Greater opsonic activity against <i>P.aeruginosa</i>, <i>S.aureus</i>, <i>E. coli</i> than conventional IVIG</li> </ul>	Has been used in the treatment of persistent gastroenteric <i>C. jejuni</i> in 2 patients with hypogammaglobulinemia
<b>Trimodulin</b>	IgA and IgM containing Ig with 23% IgM and 21% IgA	-10-fold increase in opsonization of <i>E. coli</i> compared to pentaglobin	Phase II trial, which included 160 patients with severe community-acquired pneumonia
<b>IgAbulin</b>	IgA-enriched IgG preparation	-Might provide enhanced bacterial clearance and prevention of infection at mucosal surfaces	When administered <b>orally</b> : <ul style="list-style-type: none"> <li>-Prevented necrotizing enterocolitis in babies with low birth weight</li> <li>-Successfully treated children with chronic diarrhea</li> </ul>

# Advances in Immunoglobulin Therapy

- Administration of Ig products via inhalation: nebulized immunoglobulins delivered directly to rats' and non-human primates' airways ([Vonaburg 2019](#)), which are currently under phase I clinical evaluation.
- Hyperimmune globulins (hlg): high titers of pathogen-specific antibodies can significantly reduce the risk or severity of a specific infection, which is particularly relevant in the context of emerging infectious diseases warranting a rapid, targeted approach ([Pati 2023](#)).
- Development of polyclonal recombinant hlg products ([Keating Nat Biotechnol 2021](#)), as well as monoclonal recombinant therapeutic antibodies derived from human antibody repertoires.
- Recombinant production would help address not only the limitation of plasma availability and secured supply, but it would also provide a highly consistent and reproducible product that can be modified for increased efficacy and specificity ([Basu 2019](#)).

# A Bird's-Eye View on New Immunomodulators



Ruxolitinib (DB08877)  
MW: 306.4 g/mol

Infliximab (DB00065)  
MW: 144,190.3 g/mol

# Targeted treatment options are growing<sup>1</sup>

Condition	Gene	Targeted therapy <sup>2</sup>
<i>STAT1</i> GOF	<i>STAT1</i>	Ruxolitinib (JAK1/2 inhibitor), Tofacitinib (Jak1/3)
<i>STAT3</i> GOF	<i>STAT3</i>	Tocilizumab (IL-6 receptor blocker), siltuximab (IL-6 blocker), ruxolitinib (JAK1/2 inhibitor), Tofacitinib (Jak1/3)
<i>SOCS1</i> haploinsufficiency	<i>SOCS1</i>	Tofacitinib, Baricitinib (JAK1/2 inhibitors) <sup>3</sup>
<i>LRBA</i> deficiency	<i>LRBA</i>	Abatacept, Belatacept
<i>CTLA4</i> haploinsufficiency	<i>CTLA4</i>	Abatacept, Belatacept
<i>XIAP</i> and <i>NLRC4</i>	<i>BIRC4</i> , <i>NLRC4</i>	IL-18 binding protein
Primary HLH	<i>PRF</i> , <i>UNC13 D</i> , <i>STX11</i> , <i>STXBP2</i>	Emapalumab (IFN $\gamma$ blocking antibody), ruxolitinib (JAK1/2 inhibitor), Alemtuzumab
APDS	PI3K $\delta$ , PI3KR1	Leniolisib, nemiralisib
GLILD		Rituximab
Cryopyrin-associated periodic fever syndromes		Anti-IL-1 $\alpha$ (Anakinra, Rilonacept)

[Delmonte O Front Ped 2019. Pérez E. Clin Rev Allergy Immuno 2023](#)

**Abbrev:** CTLA4: cytotoxic T-lymphocyte-associated protein 4; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; IFN: interferon; IL: interleukin; JAK: Janus kinase; LRBA: lipopolysaccharide-responsive and beige-like anchor protein; NLRC4: NLR family CARD domain-containing protein 4; SOCS1: suppressor of cytokine signalling 1; STAT: signal transducer and activator of transcription; XIAP: X-linked inhibitor of apoptosis protein. **References:** 1. Ballou M, Leiding JW. *Clin Rev Allergy Immunol*. 2021. Chandrakasan S. *Pediatr Blood Cancer*. 2019. Hadjadj J. *Front Immunol*. 2021: 12(717388).

# Hematopoietic Stem Cell Transplant in adolescent and adults

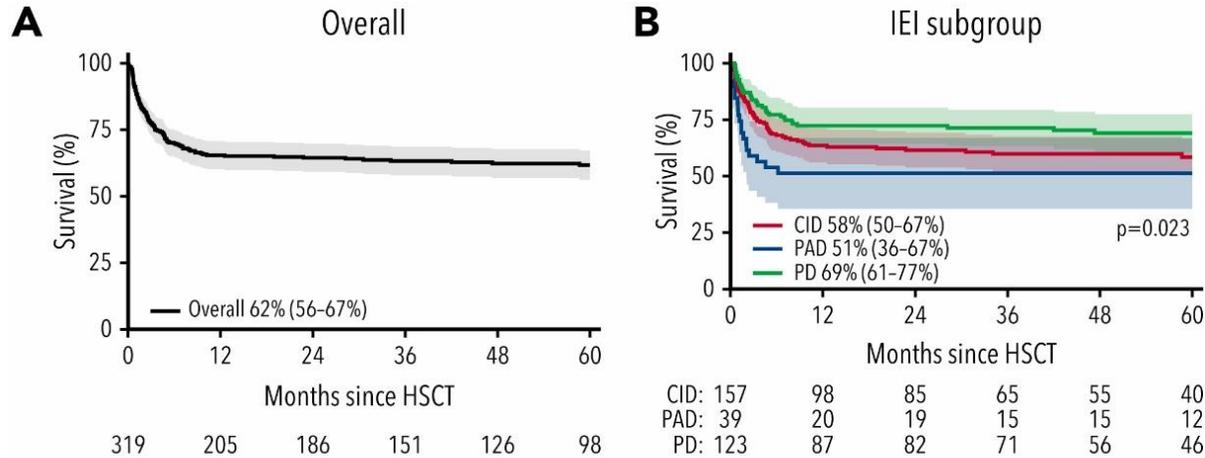
- Knowledge of an underlying genetic diagnosis improves outcome of HSCT
- HSCT at a younger age before organ impairment improves outcome of HSCT
- Determining which patients to offer HSCT to is challenging: specific biologic therapies are effective for some diseases and can be used as a bridge to HSCT to improve outcome
- Long-term outcome studies are required to compare conservative management, targeted therapy and HSCT outcomes

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<b>Role of HSCT</b>	<b>Immune deficiency</b>
Curative	SCID, CID, CGD, DOCK8, DOCK2, IPEX, WAS, WIP, ARPC1B, CD40L, XLP1, XLP2, APDS, MHC class II, AD HIGE, CTLA4 haploinsufficiency, LRBA, HLH 1–5, GATA2, RAB27A, LAD1, RD
Partially curative	CHH, PGM3, STAT-1 and STAT-3 GOF, SCN, ADA2, C1Q, CD25, IL-10 & IL-10R deficiency, dsDNA break repair disorders
Controversial	CVID, Agammaglobulinemia, other complement deficiencies, DGS, IKBA deficiency, NEMO

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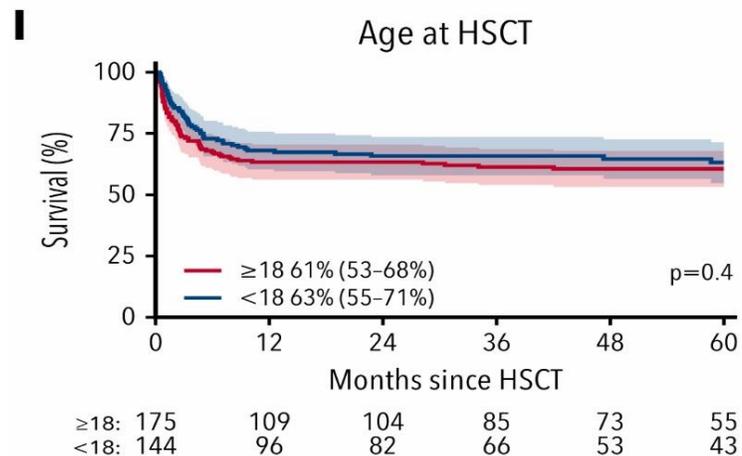
# Hematopoietic Stem Cell Transplant



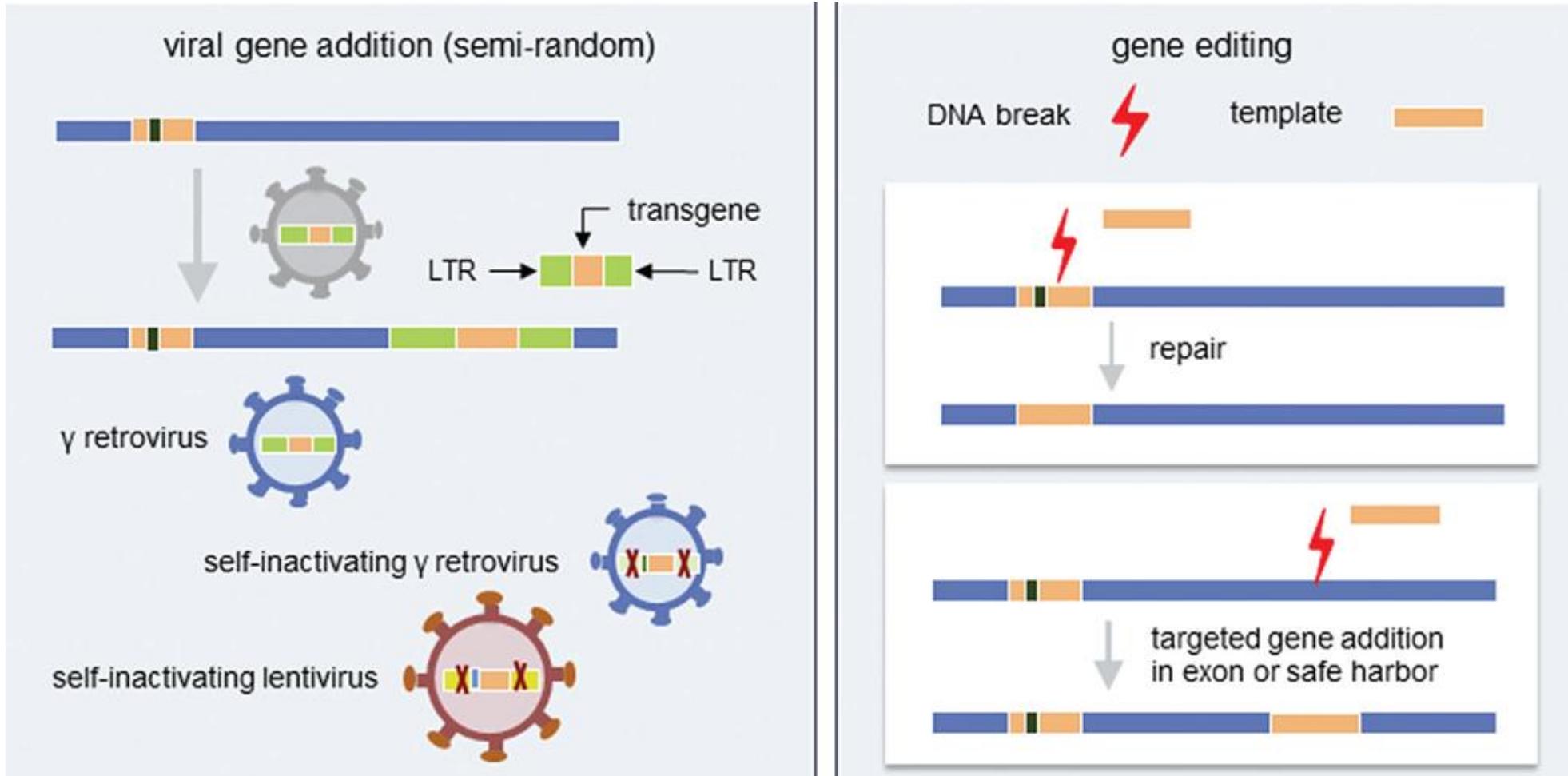
Outcomes following HSCT for the largest cohort to date of IEI patients aged 15 years or more at transplant.

IEI-related factors that adversely affected outcomes were bronchiectasis, prior splenectomy, hepatic comorbidity, and cumulative number of IEI-related complications at HSCT

“Our data strongly support the notion that HSCT should be considered for adult patients prior to development of significant end organ complications”



# Gene therapy



Aiuti A, Roncarolo MG (2009) Hematology Am Soc Hematol Educ Program 682–9. Booth C, et al (2011) Curr Opin Pediatr. Booth C, (2019). Hum Mol Genet. Bloomer H, (2020) Mol Ther. De Ravin SS, Brault J (2019) Emerg Top Life Sci 3(3):277–287. Houghton BC, Booth C (2021) Hemasphere Kohn DB, Kuo CY (2017). J Allergy Clin Immunol Zhang ZY, Thrasher AJ, Zhang F (2020). Genes Dis. Ferrua F, Aiuti A (2017). Hum Gene Ther Fischer A, Hacein-Bey-Abina S (2020). J Exp Med 217(2). Cavazzana M, et al(2019) Nat Rev Drug Discov

# Gene therapies using viral gene addition

Disease name	Gene	Vector	Status	Ref/trial
ADA-SCID	ADA	gRV	Commercial product in Europe (strimvelis)	[14]
	ADA	LV	Compassionate use (GOSH)/Human trial (UCLA/NIH)	[79 <sup>***</sup> ]
X-SCID	IL2RG	SIN gRV	Human trial completed	[37]
	IL2RG	LV	Human trial GOSH/BCH/UCL open	[82,83] NCT03311503, NCT03601286
	IL2RG	LV	Human trial UCSF/St Jude/Seattle/NIH Suspended	NCT01306019 NCT01512888
Artemis SCID	DCLRE1C	LV	Human trial UCSF Open	[86 <sup>***</sup> ] NCT03538899
	DCLRE1C	LV	Human trial Paris Necker hospital Open	NCT05071222
RAG1 SCID	RAG1	LV	Human trial Open LUMC	NCT04797260 [125]
RAG2 SCID	RAG2	LV	Mice	[126,127] (manuscript in preparation)
WAS	WAS	LV	Human trial completed	[90,91,92 <sup>*</sup> ]
X-CGD	CYBB	LV	Human trial (UCLA and UCL/GOSH) Open	[96] NCT01855685 NCT02234934
Autosomal recessive CGD	NCF1	LV	Human trial at GOSH, starting soon at NIH	NCT05207657
LAD1	ITGB2	LV	Human trial (UCLA, HIUNI, GOSH) Open	NCT03812263 [106]
IPEX	FOXP3	LV in T cells	Ongoing Human trial (Stanford)	NCT05241444 [110,111]
fHLH	PRF1	gRV in T cells	Mice	[128]
	PRF1	LV	Mice	[129]
	UNC13D	LV	Mice (Stanford)	[130–133]
XIAP	XIAP	LV	Mice	[134]
XLP1	SAP	LV	Mice	[135]
	SAP	gRV in T cells	Mice	[136]
XLA	BTK	LV	Mice	[137,138]
Reticular dysgenesis	AK2	LV	In vitro	[139]

# Take Home Messages

Early diagnosis and treatment is a major goal and has prognostic implications

Advances in vaccines, monoclonal antibodies for prevention

Innovation in immunoglobulins and high-specific Ig

Advances in immunomodulatory small molecules and biologics: targeted therapy and personalized medicine

Advances in Gene therapy

Improvements in Stem cell transplantation

# Thank you!

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