Gene editing and the promises of genetic immunotherapy

Anne Galy, PhD

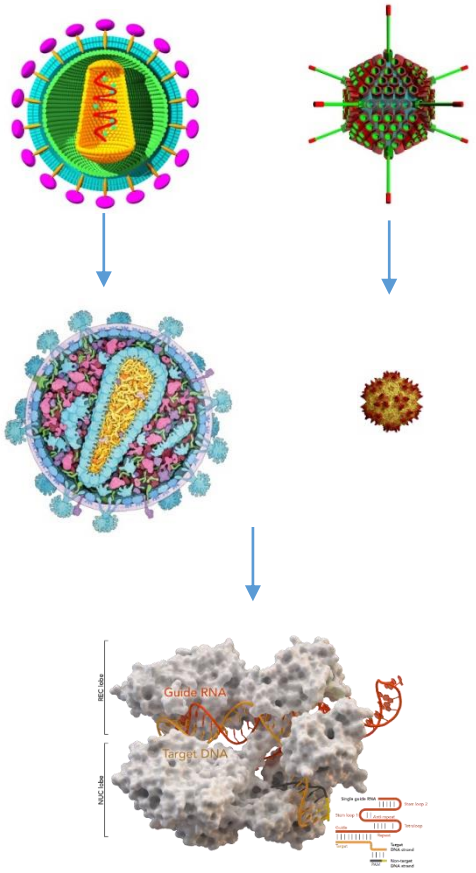
ART-TG, Inserm US35, Genopole Evry
Integrare research unit (UMR_S951), Genethon, Evry

Cent Gardes Conference: HIV Vaccines

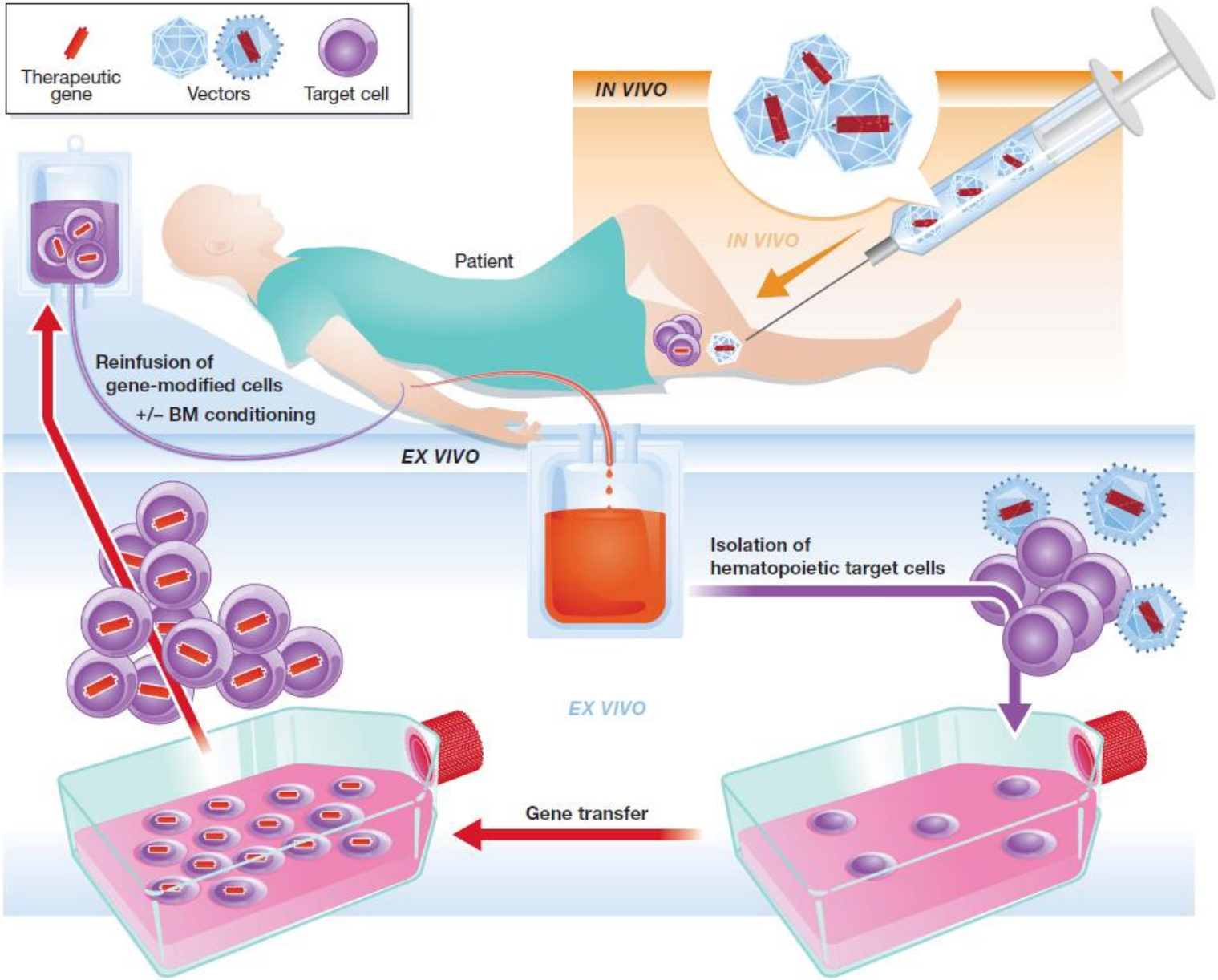
Les Pensières Center for Global Health
Veyrier du Lac - France

September 30th to October 2nd, 2019

Sept 30, 2019



Nishimasu et al. 2014



Kaufmann, Buening, Galy, Schambach, Grez, EMBO Mol Med 2013

Lentiviral gene therapy for X-CGD
Successful transduction of myeloid stem cells

Gene Therapy of Chronic Granulomatous Disease: The Engraftment Dilemma

Manuel Grez[1], Janine Reichenbach[2], Joachim Schwäble[1,3], Reinhard Seger[2], Mary C Dinauer[4–7] and Adrian J Thrasher[8,9]

Great Ormond Street Hospital for Children NHS Trust — Pr. Adrian Thrasher, Pr. H. Bobby Gaspar, LONDON

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS — Pr. Stéphane Blanche, Pr Marina Cavazzana, PARIS

Children's Hospital Boston — Pr. D.A. Williams, Dr. L. Wang, Dr. P. Newburger, BOSTON

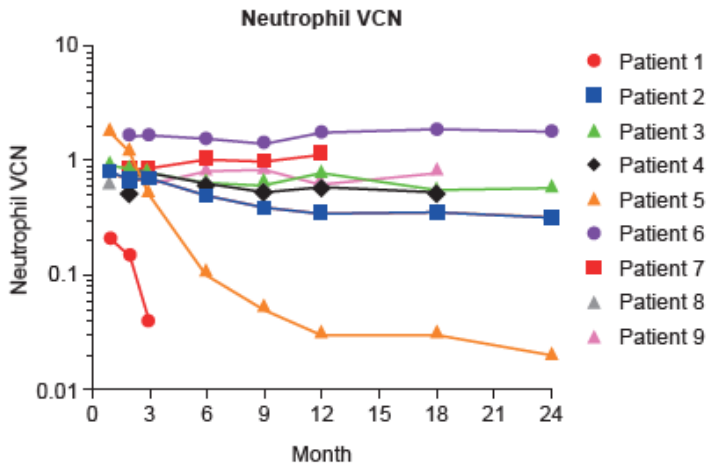
NIH National Institutes of Health — Dr. E. Kang, Dr. S.S. DeRavin, Dr. Harry Malech, BETHESDA

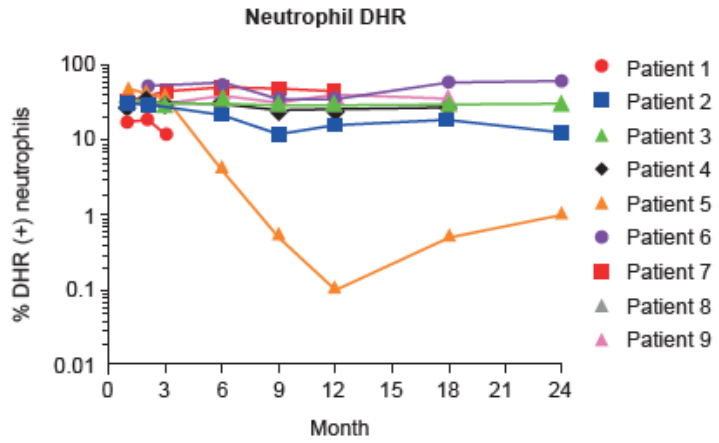
UCLA — Dr. C. Kuo, Pr. Don Kohn, LOS ANGELES

YPOSKESI · GENETHON CURE THROUGH INNOVATION PRIX GALIEN 2012 · net CGD · CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE CIRM

Brendel et al. Mol Ther 2018
Corre et al. Hum Gene Ther 2016

Orchard therapeutics





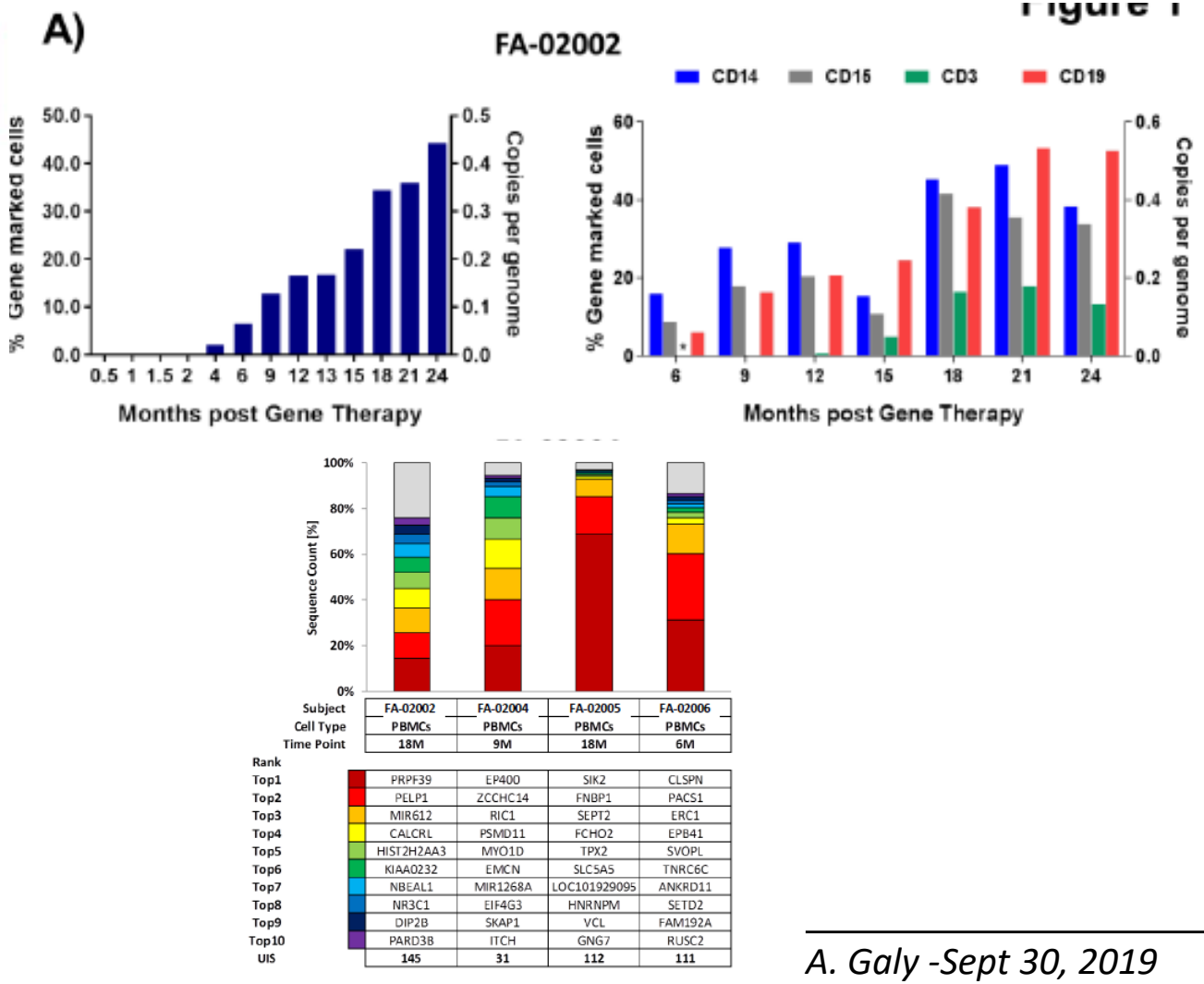
Kohn et al. ASH2018, ASGCT 2019, Submitted

Lentiviral gene therapy for Fanconi Anemia
Successful transduction of fragile polyclonal HSC

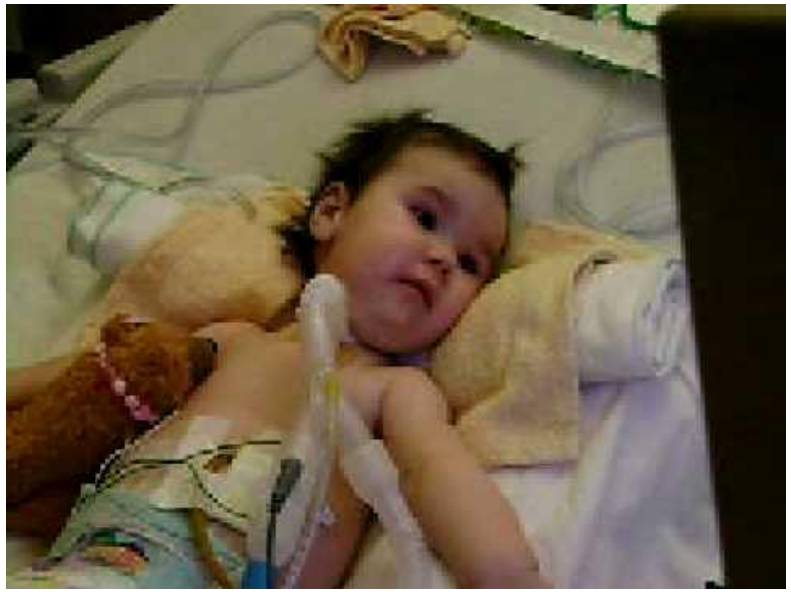
LETTERS
https://doi.org/10.1038/s41591-019-0550-z
nature medicine

Successful engraftment of gene-corrected hematopoietic stem cells in non-conditioned patients with Fanconi anemia

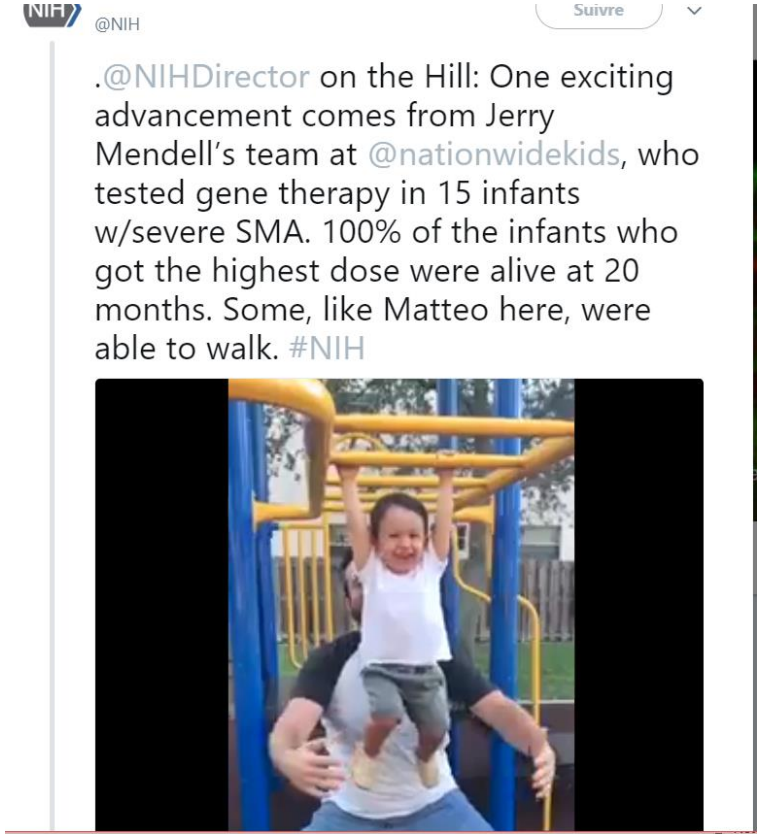
Paula Río[1,2,3], Susana Navarro[1,2,3], Wei Wang[4,5], Rebeca Sánchez-Domínguez[1,2,3], Roser M. Pujol[2,6,7,8], José C. Segovia[1,2,3], Massimo Bogliolo[2,6,7,8], Eva Merino[2,9], Ning Wu[4], Rocío Salgado[10], María L. Lamana[1,2,3], Rosa M. Yañez[1,2,3], José A. Casado[1,2,3], Yari Giménez[1,2,3], Francisco J. Román-Rodríguez[1,2,3], Lara Álvarez[1,2,3], Omaira Alberquilla[1,2,3], Anna Raimbault[11,12], Guillermo Guenechea[1,2,3], M. Luz Lozano[1,2,3], Laura Cerrato[1,2,3], Miriam Hernando[1,2,3], Eva Gálvez[2,9], Raquel Hladun[13,14], Irina Giralt[14], Jordi Barquinero[14], Anne Galy[15], Nagore García de Andoín[16], Ricardo López[17], Albert Catalá[2,18], Jonathan D. Schwartz[19], Jordi Surrallés[2,6,7,8], Jean Soulier[11,12], Manfred Schmidt[4,5], Cristina Díaz de Heredia[13,14], Julián Sevilla[2,9] and Juan A. Bueren[1,2,3]*



Spinal Muscular Atrophy Gene Therapy



scAAV9 gene transfer of SMN1 in SMA type 1
PI Jerry Mendell
Columbus Ohio – AveXis (Novartis)
A single IV injection
low dose cohort 6.7E+13 vg/Kg none walk.
Medium cohort 2E+14 vg/Kg all have reached development milestones



https://www.c-span.org/video/?c4745365/nih-pediatrics-success-story-gene-therapy&start=502

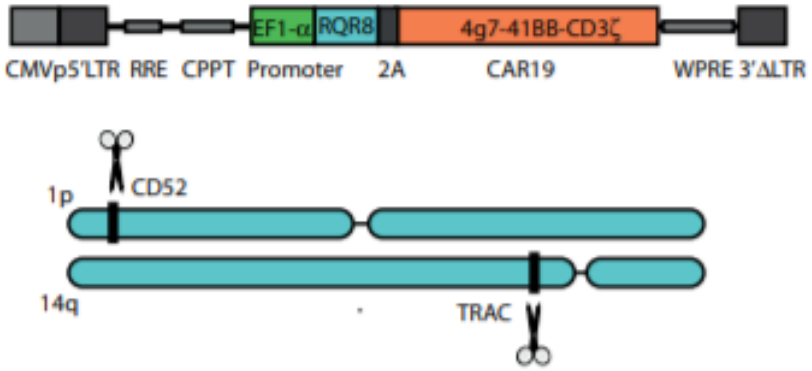
Gene editing in the clinic since 2017, actively in ex vivo

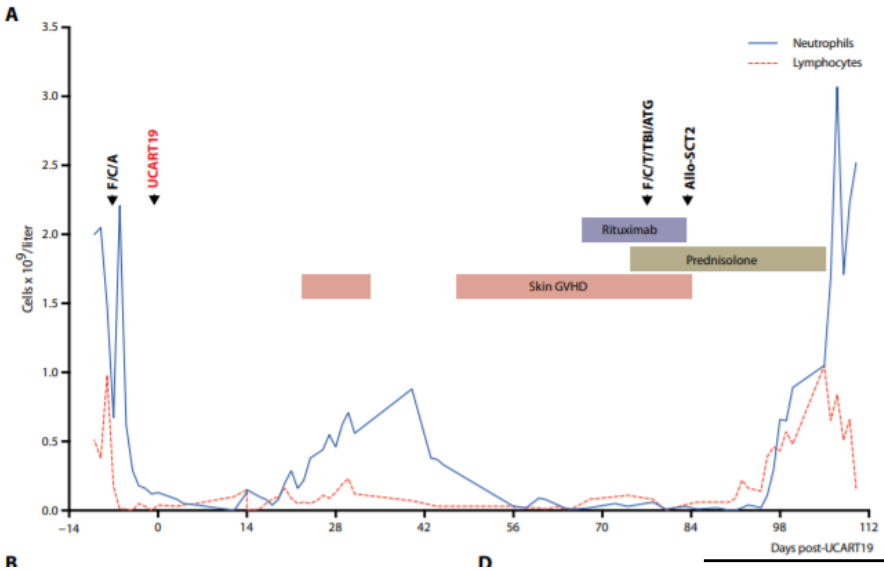
SCIENCE TRANSLATIONAL MEDICINE | REPORT

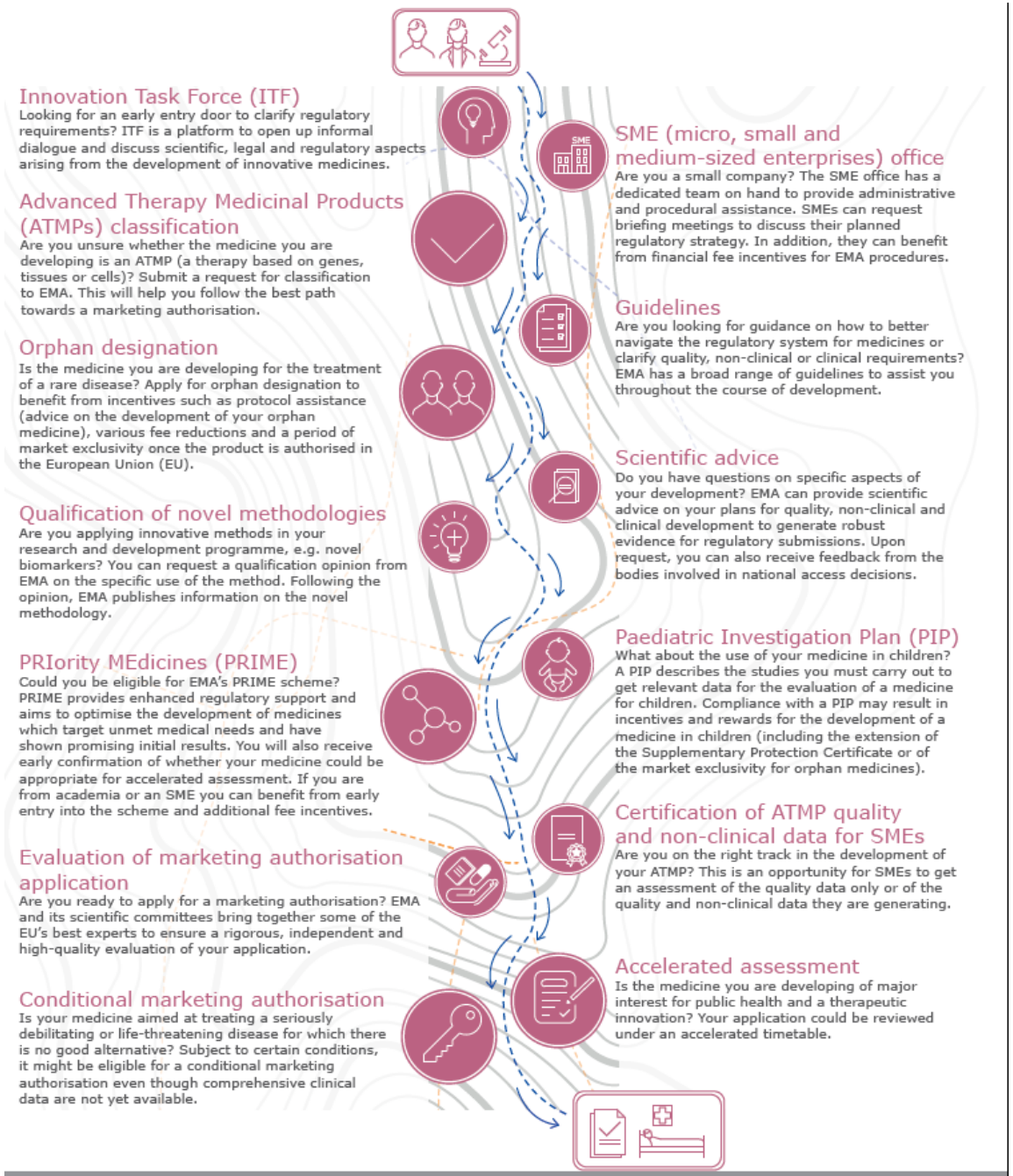
CANCER

Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells

Waseem Qasim,[1,2]* Hong Zhan,[1] Sujith Samarasinghe,[2] Stuart Adams,[2] Persis Amrolia,[1,2] Sian Stafford,[1] Katie Butler,[1] Christine Rivat,[1] Gary Wright,[2] Kathy Somana,[2] Sara Ghorashian,[1] Danielle Pinner,[2] Gul Ahsan,[2] Kimberly Gilmour,[2] Giovanna Lucchini,[2] Sarah Inglott,[2] William Mifsud,[2] Robert Chiesa,[2] Karl S. Peggs,[3] Lucas Chan,[4] Farzin Farzaneh,[4] Adrian J. Thrasher,[1] Ajay Vora,[5] Martin Pule,[3] Paul Veys[1]







Innovation Task Force (ITF)
Looking for an early entry door to clarify regulatory requirements? ITF is a platform to open up informal dialogue and discuss scientific, legal and regulatory aspects arising from the development of innovative medicines.

Advanced Therapy Medicinal Products (ATMPs) classification
Are you unsure whether the medicine you are developing is an ATMP (a therapy based on genes, tissues or cells)? Submit a request for classification to EMA. This will help you follow the best path towards a marketing authorisation.

Orphan designation
Is the medicine you are developing for the treatment of a rare disease? Apply for orphan designation to benefit from incentives such as protocol assistance (advice on the development of your orphan medicine), various fee reductions and a period of market exclusivity once the product is authorised in the European Union (EU).

Qualification of novel methodologies
Are you applying innovative methods in your research and development programme, e.g. novel biomarkers? You can request a qualification opinion from EMA on the specific use of the method. Following the opinion, EMA publishes information on the novel methodology.

PRIority MEdicines (PRIME)
Could you be eligible for EMA's PRIME scheme? PRIME provides enhanced regulatory support and aims to optimise the development of medicines which target unmet medical needs and have shown promising initial results. You will also receive early confirmation of whether your medicine could be appropriate for accelerated assessment. If you are from academia or an SME you can benefit from early entry into the scheme and additional fee incentives.

Evaluation of marketing authorisation application
Are you ready to apply for a marketing authorisation? EMA and its scientific committees bring together some of the EU's best experts to ensure a rigorous, independent and high-quality evaluation of your application.

Conditional marketing authorisation
Is your medicine aimed at treating a seriously debilitating or life-threatening disease for which there is no good alternative? Subject to certain conditions, it might be eligible for a conditional marketing authorisation even though comprehensive clinical data are not yet available.

SME (micro, small and medium-sized enterprises) office
Are you a small company? The SME office has a dedicated team on hand to provide administrative and procedural assistance. SMEs can request briefing meetings to discuss their planned regulatory strategy. In addition, they can benefit from financial fee incentives for EMA procedures.

Guidelines
Are you looking for guidance on how to better navigate the regulatory system for medicines or clarify quality, non-clinical or clinical requirements? EMA has a broad range of guidelines to assist you throughout the course of development.

Scientific advice
Do you have questions on specific aspects of your development? EMA can provide scientific advice on your plans for quality, non-clinical and clinical development to generate robust evidence for regulatory submissions. Upon request, you can also receive feedback from the bodies involved in national access decisions.

Paediatric Investigation Plan (PIP)
What about the use of your medicine in children? A PIP describes the studies you must carry out to get relevant data for the evaluation of a medicine for children. Compliance with a PIP may result in incentives and rewards for the development of a medicine in children (including the extension of the Supplementary Protection Certificate or of the market exclusivity for orphan medicines).

Certification of ATMP quality and non-clinical data for SMEs
Are you on the right track in the development of your ATMP? This is an opportunity for SMEs to get an assessment of the quality data only or of the quality and non-clinical data they are generating.

Accelerated assessment
Is the medicine you are developing of major interest for public health and a therapeutic innovation? Your application could be reviewed under an accelerated timetable.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

www.ema.europa.eu

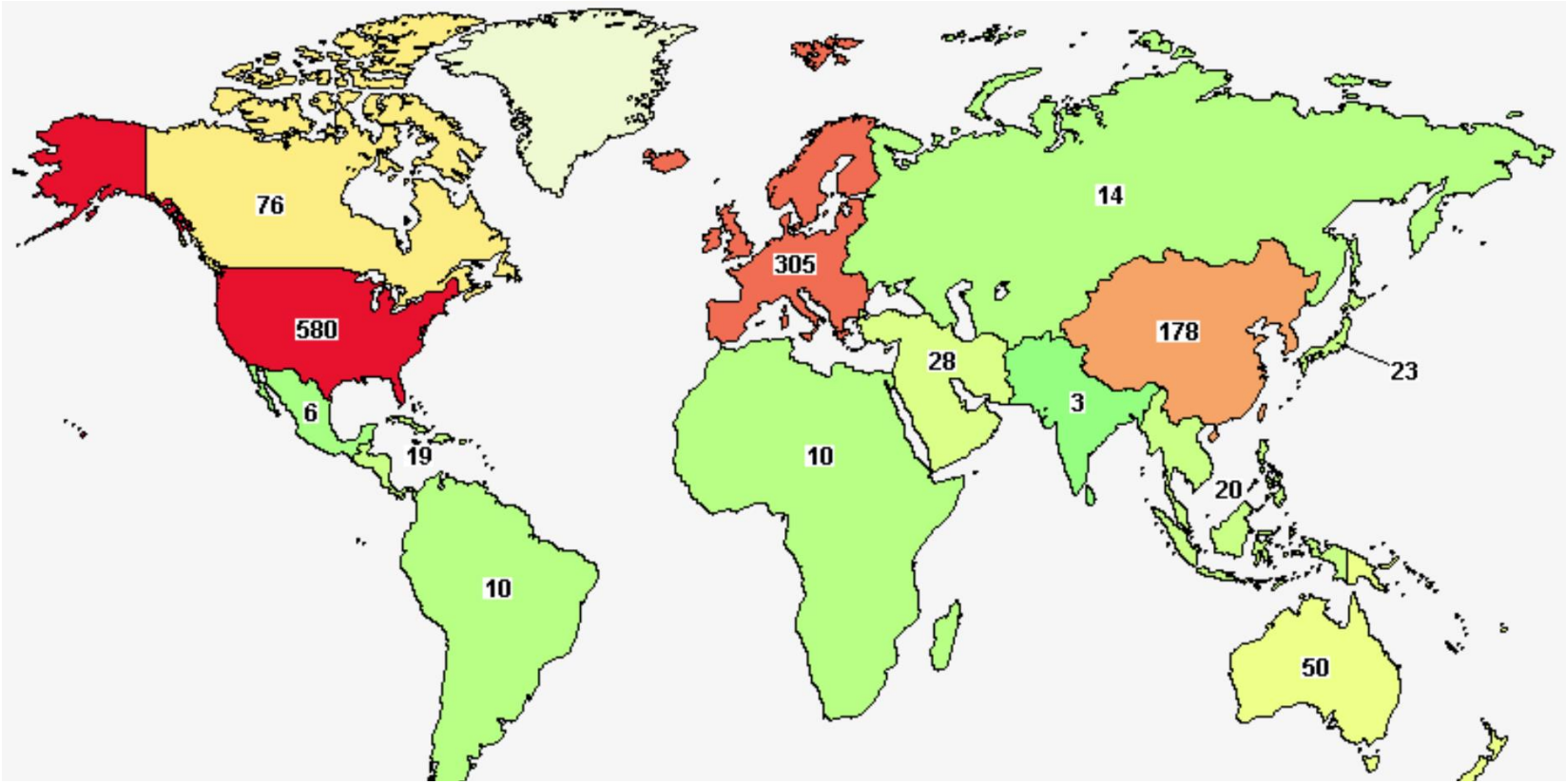
Now, 9 approved gene therapy drugs in Europe/US

Name of Drug	Type	Promoter	Date approved	Indication
Europe				
Glybera alipogene tiparvovec	rAAV1	UniQure Biopharma	25/10/2012 Withdrawn 2016	adults, deficit in lipoprotein lipase
Imlygic talimogene laherparepvec	live, attenuated herpes simplex virus expressing GM-CSF	Amgen Europe	16/12/2015	adults, non resectable melanoma
Strimvelis autologous CD34+	Autol CD34+ gRV (ADA cDNA)	Glaxo SmithKline	26/05/2016	patients ADA-SCID
Zalmoxis allogenic T cells	Allo T cells + gRV (HSVTK dNGFR)	MolMed SpA	18/08/2016	treatment GvHD
Yescarta axicabtagene ciloleucel	Autologous CD19CAR T cells (gRV) (CD28 CD3zeta)	Gilead Sciences SAS	23/08/2018	relapse or refractory B lymphoma
Luxturna voretigene neparvovec-rzyl	AAV2 – rpe65	Novartis	2018	biallelic *RPE65* mutation-associated retinal dystrophy
Zynteglo autologous CD34+	Autologous CD34 βA-T87Q-globin gene	BlueBirdBio	29/03/2019	patients >12 years transfusion-dependent beta thalassemia
Zolgensma	AAV9 SMN1	Avexis	ATU – France	SMA – type 1
USA				
Imlygic talimogene laherparepvec	live, attenuated herpes simplex virus expressing GM-CSF	Biovex Inc (Amgen)	27/10/2015	adults, non resectable melanoma relapse post surgery
Kymriah tisagenlecleucel	autologous CD19 CAR T cells (LV) (41BB CD3zeta)	Novartis	30/08/2017	adults, relapsed or refractory B ALL, relapsed or refractory B lymphoma
Yescarta axicabtagene ciloleucel	Autologous CD19CAR T cells (gRV) (CD28 CD3zeta)	Kite Pharma	18/10/2017	adults, relapsed or refractory B lymphoma
Luxturna voretigene neparvovec-rzyl	AAV2 – rpe65	Spark Therapeutics	19/12/2017	biallelic *RPE65* mutation-associated retinal dystrophy
Zolgensma onasemnogene abeparvovec-xioi	AAV9 SMN1	Avexis	2019	pediatric <2 years of age, SMA with bi-allelic mutations in the *SMN1* gene.
China				
Gencidine	Adenovirus 5 p53 (replication incompetent)	SiBiono GeneTech	2003	Head & Neck SCC
Oncorine	Replication competent Ad5 E1bE3del replicates & kills p53-deficient cells	Shanghai Sunway Biotech Co. Ltd.	2005	Nasopharyngeal carcinoma combined with chemotherapy

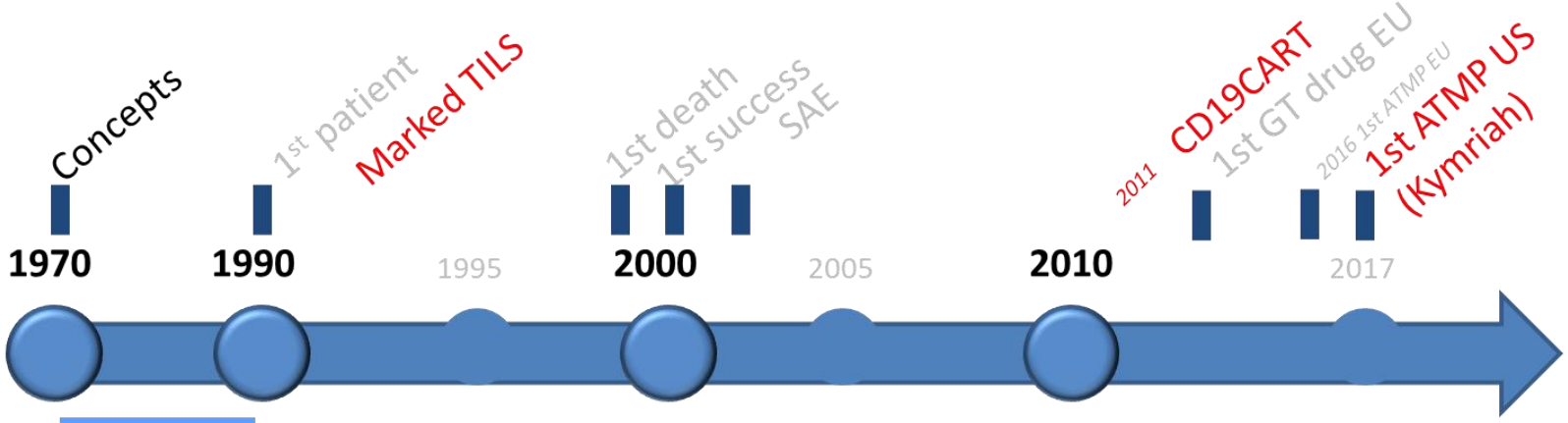
Ongoing gene therapy trials in 2019 in hematology indications

Company	Product	Vector	Indication	Clinical Stage	Expected Reporting Date
bluebird bio	Lentiglobin	Gene therapy	Transfusion dependent beta-thalassemia	MAA filing	Submitted MAA in 2H 2018; response expected 2019
BioMarin	Valoctocogene roxaparvovec	Gene therapy	Hemophilia A	Ph III	Increase in enrollment to 130 participants anticipated by 1Q 2019
Pfizer	Fidanacogene elaparvovec	Gene therapy	Hemophilia B	Ph III	Initiated trial July 2018
uniQure	AMT-061	Gene Therapy	Hemophilia B	Confirmation study	Topline data from dose confirmation study expected Q4 2018; dosing of patients expected to start early 2019
Sangamo	SB-525	Gene Therapy	Hemophilia A	Ph I/II	Positive preliminary data reported in August 2018
Sangamo	SB-FIX	Genome Editing	Hemophilia B	Ph I/II	UK clinical sites to be set up 2018; currently screening patients in US
CRISPR Tx/Vertex	CTX001	Autologous gene-edited hematopoietic stem cell therapy	Transfusion dependent β-thalassemia & sickle cell disease	Ph I/II	Expected to initiate in 2h 2018
Spark Therapeutics	SPK-8011	AAV-vector gene therapy	Hemophilia A	Ph I/II	plan to initiate a Phase 3 run-in study in Q4 2018
Bioverativ	BIVV003	Gene-edited cell therapy	Sickle cell disease	Pre-Ph I	Received IND approval in May 2018; expected to open clinical sites later this year

Currently about 1000 ongoing gene therapy trials
(clinicaltrials.gov)



25 years to develop CAR-T cells



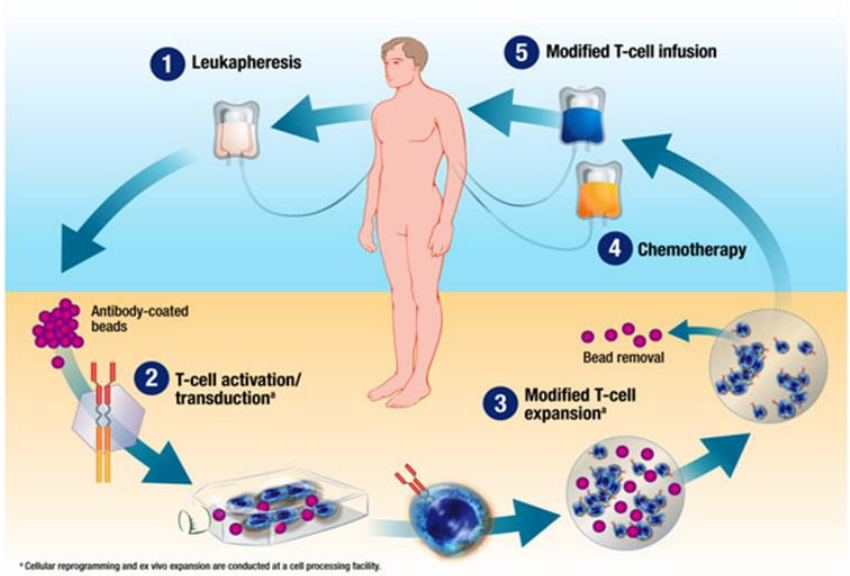
Genetics

Recombinant DNA technology

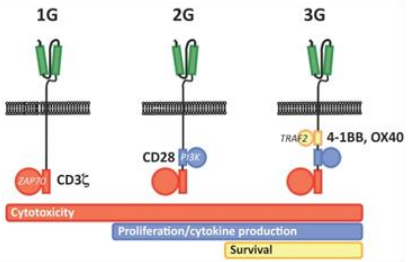
DNA sequencing

Virology

Cell culture



Adapté de Sagar B. Kudchodkar and Marcela V. Maus onclive 2014



2 approved products

Aderse events

Many trials

Hundreds of patients

A driving force

HIV gene therapy

About 10 ongoing gene therapy trials (clinicaltrials.gov)

HSC

CCR5 shRNA/TRIM5alpha/TAR decoy-transduced autologous CD34 during HSCT for lymphoma (UCSD, UCSF, MSKCC)

Cal-1 (LVsh5/C46) drug product (StLouis, Paris)

Multiplex shRNA anti HIV (Shangai)

CCR5 deletion by CRISPR during HSCT for malignancy (Beijing and affiliated hospitals)

T

CD4 CAR+CCR5 ZFN T-cells (Upenn)

Vac

DNA vaccine + IL12 (UCLA, SF)

Ab

AAV8-VRC07 IM (NIH)

Molecular Therapy
Methods & Clinical Development
Original Article

VIP

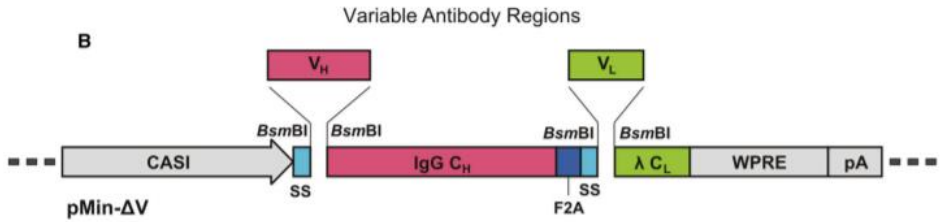
AAV-Mediated Expression of Broadly Neutralizing and Vaccine-like Antibodies Targeting the HIV-1 Envelope V2 Region

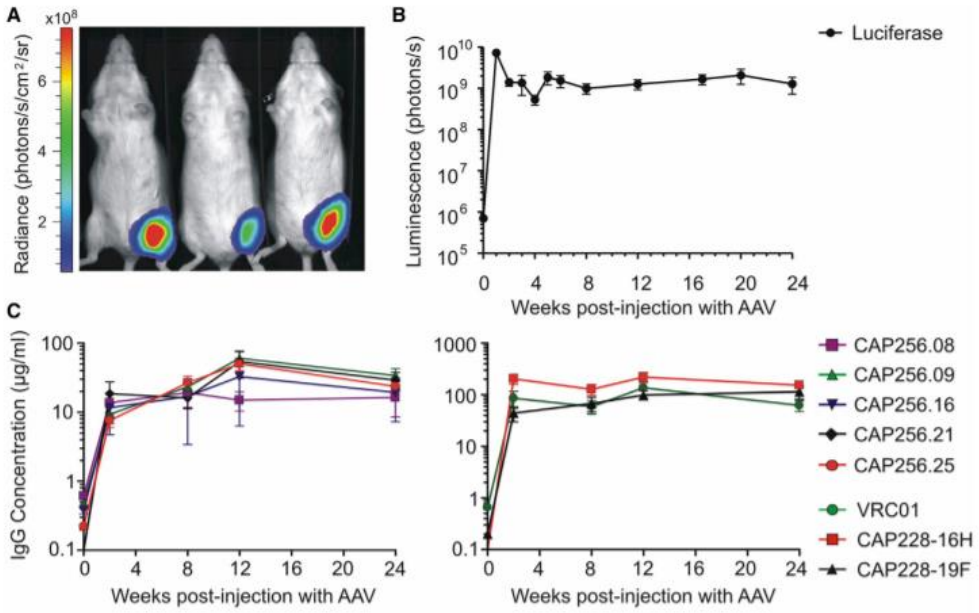
Fiona T. van den Berg,[1,2,8] Nigel A. Makoah,[3,4,8] Stuart A. Ali,[2] Tristan A. Scott,[1,2] Rutendo E. Mapengo,[3] Lorraine Z. Mutsvunguma,[2] Nonhlanhla N. Mkhize,[3] Bronwen E. Lambson,[3] Prudence D. Kgagudi,[3] Carol Crowther,[3] Salim S. Abdool Karim,[5,6] Alejandro B. Balazs,[7] Marc S. Weinberg,[1,2] Abdullah Ely,[1] Patrick B. Arbuthnot,[1] and Lynn Morris[3,4,5]

A

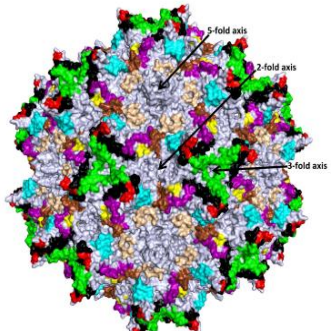
Antibody	Envelope Target	Heavy Chain	Light Chain	Neutralization		Ref.
				Breadth (%)	Potency (IC_{50}, μg/ml)	
CAP256-VRC26.08	V2 apex	VH3-30	VL1-51	46*, 67**	0.08*, 0.15**	12, 56
CAP256-VRC26.09				46*	0.02*	
CAP256-VRC26.16				28*	0.67*	
CAP256-VRC26.21				13*	0.58*	
CAP256-VRC26.25				63*, 72**	0.003*, 0.002**	
CAP228-16H	V2 linear	VH5-51	VL3-21	-	-	38
CAP228-19F				-	-	
VRC01	CD4bs	VH1-02	VK3-11	91*, 84**	0.39*, 0.75**	12, 40, 56
PGT121	V3 glycan	VH4-59	VL3-21	70*, 68**	0.03*, 0.71**	13, 56

B





Apparent limitations rAAV vectored immunoprophylaxis



Yu-Shan Tseng and Mavis Agbandje-McKenna

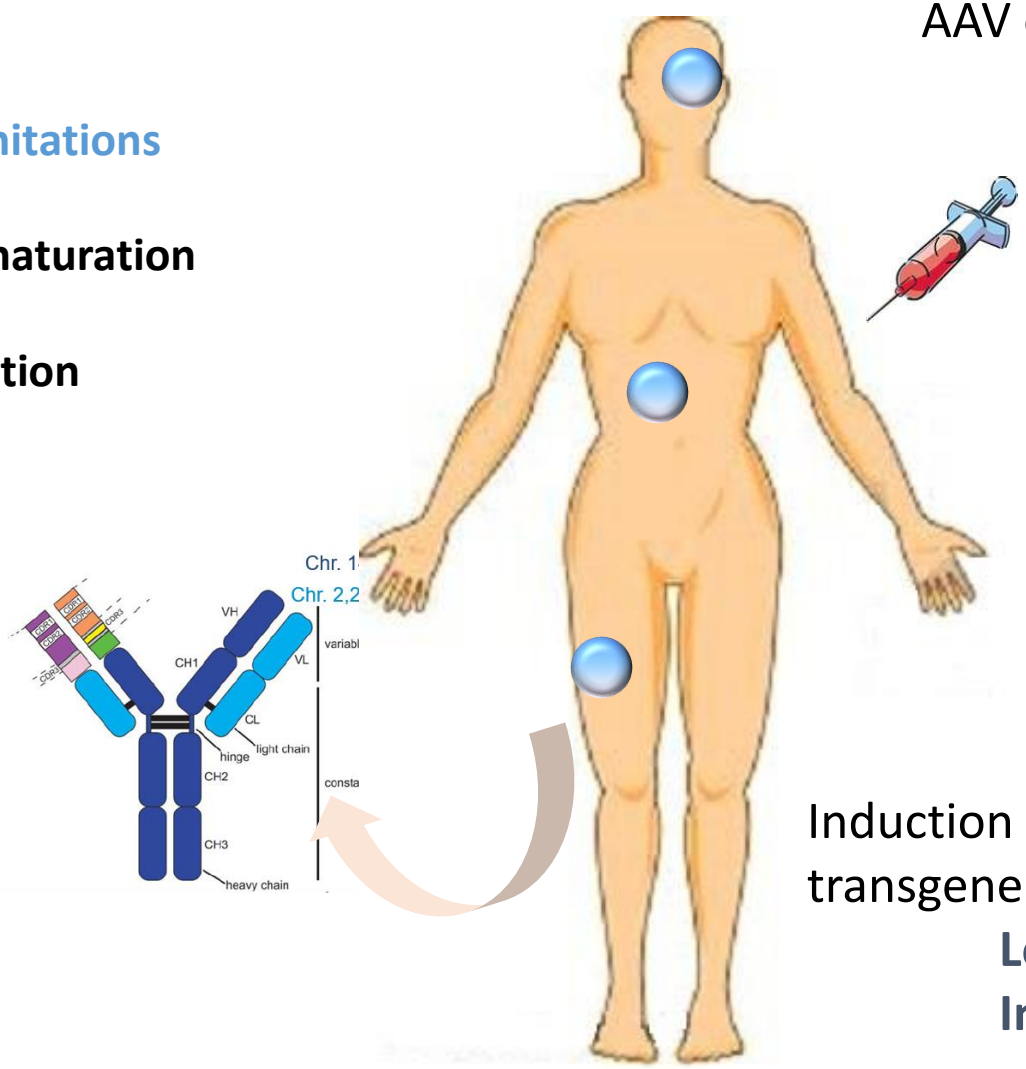
Frontiers in Immunology, 2014

AAV VIP limitations

Lack of Ig maturation

Ig glycosylation

Active [C]



AAV capsid seropositivity nAbs

Ineligible persons

Induction of antibodies and T cell responses to capsid

Toxicity

(Loss of therapeutic efficacy)

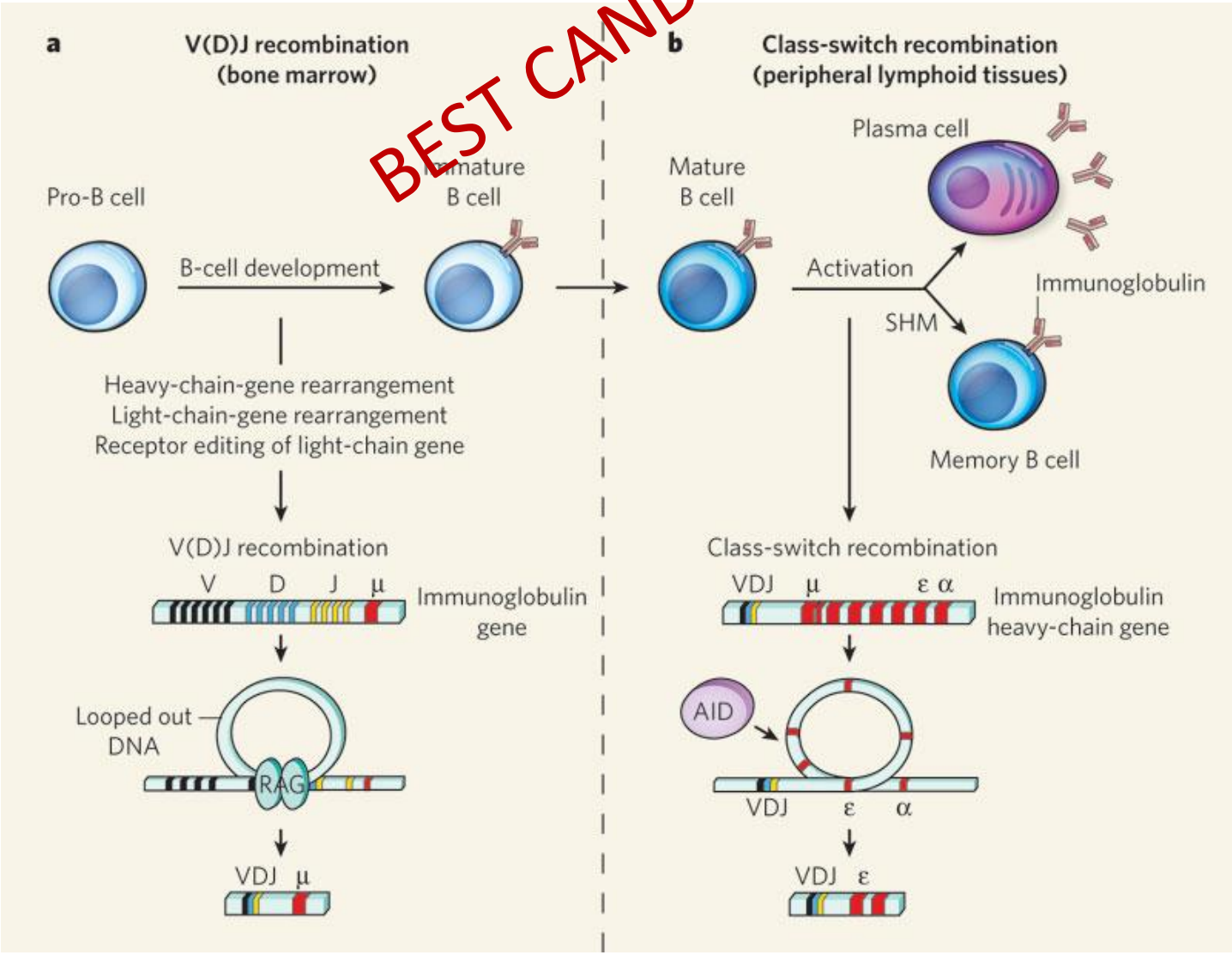
Prevents redosing

Induction of T cells and antibodies against the transgene product and gene-modified cells

Loss of therapeutic efficacy

Inflammation/Toxicity

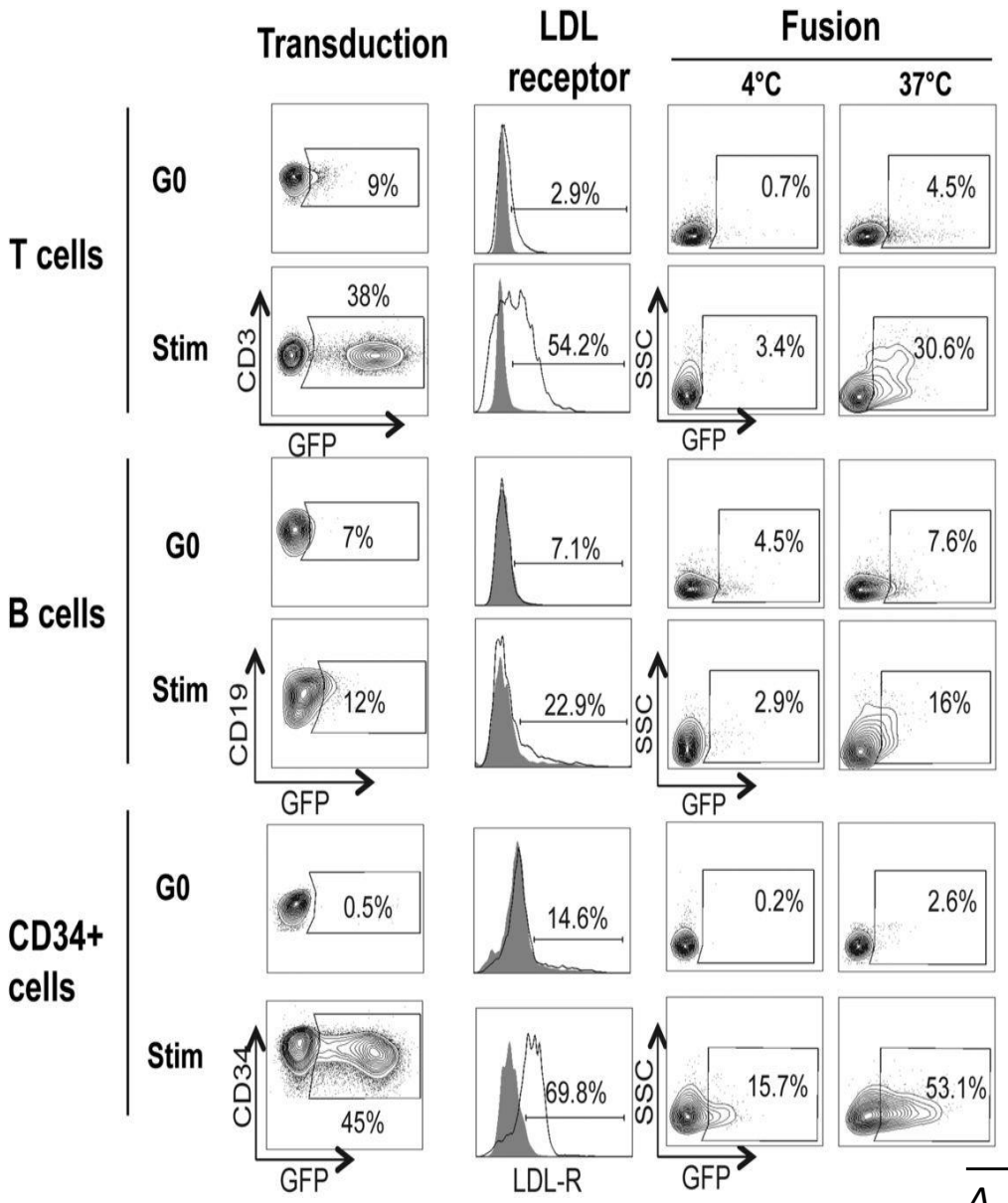
BEST CANDIDATE

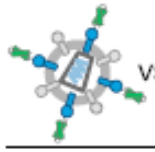


Gene transfer in B cells

Limitations

Human B cells remain difficult to transduce
(Amirache et al, Blood, 2014)



Vector	Envelope proteins	Degree of retargeting	Targeted receptors	
			Lymphocytes	Other cells
 VSV-LV	VSV G	Preferential retargeting	CD30[60]	EGFR[60]
 tVSV-LV	Truncated VSV G, non-viral membrane anchor	Preferential retargeting	None	Unknown human APC epitope[61]
 VSV-MLV-LV	VSV G, MLV Env	Preferential retargeting	CD3[89] IL7R[61]	CD117[104] CD110[104]
 SINV-LV	SINV E1, 2	Full retargeting Off-target: 1 - 10% (estimated from Fig. 5 in[89])	CD19[70] CD4[68] CD3[90] BCR/Ig[106]	DC-SIGN[107] CD34[108] CD117[109] P-glycoprotein[63] Mucin 4[110]
 MV-LV	MV H, F	Full retargeting Off-target: 1 - 5% (estimated from Fig. 4, 5 in[84])	CD20[85] CD19[58] CD30[74] CD8[55] CD4[56]	CD133[111,112] CD105[111] IL3R[113] Her2/neu[78]
 MV-D-LV	MV H, F non-viral membrane anchor	Full retargeting Off-target: < 1% (estimated from Fig. 6 in[88])	None	Her2/neu[69]
 TPMV-LV	TPMV H, F	Full retargeting Off-target: 1 - 5% (estimated from Fig. 3 in[85])	CD20[85]	None
 NiV-LV	NiV G, F	Full retargeting Off-target: < 1% (estimated from Fig. 3,7 in [65])	CD20[65] CD8[66,98]	EpCAM[66] Her2/neu[66] GluA4[66] CD117[66]

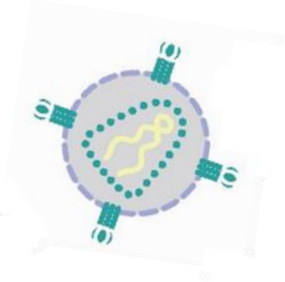
Molecular Therapy
Methods & Clinical Development
Review

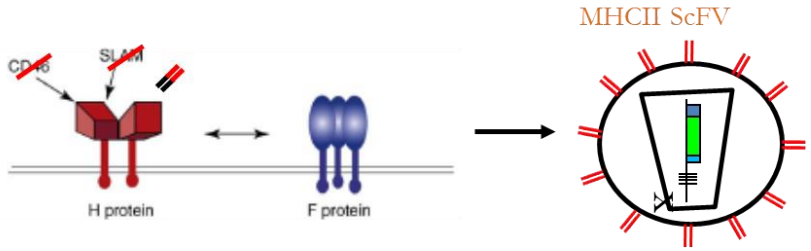
Surface-Engineered Lentiviral Vectors for Selective Gene Transfer into Subtypes of Lymphocytes

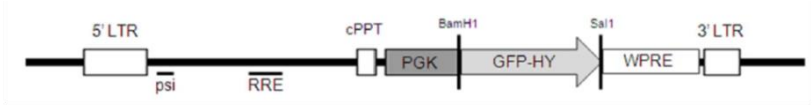
Annika M. Frank[1] and Christian J. Buchholz[1,2]

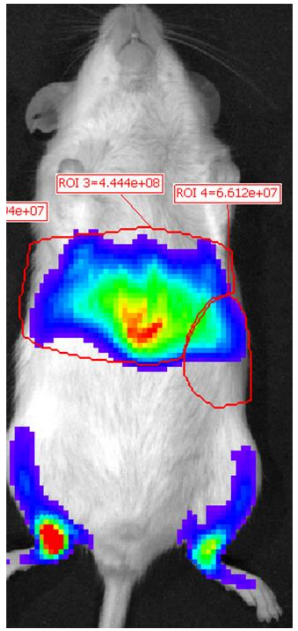
March 2019

Lentiviral pseudotyping and immunization

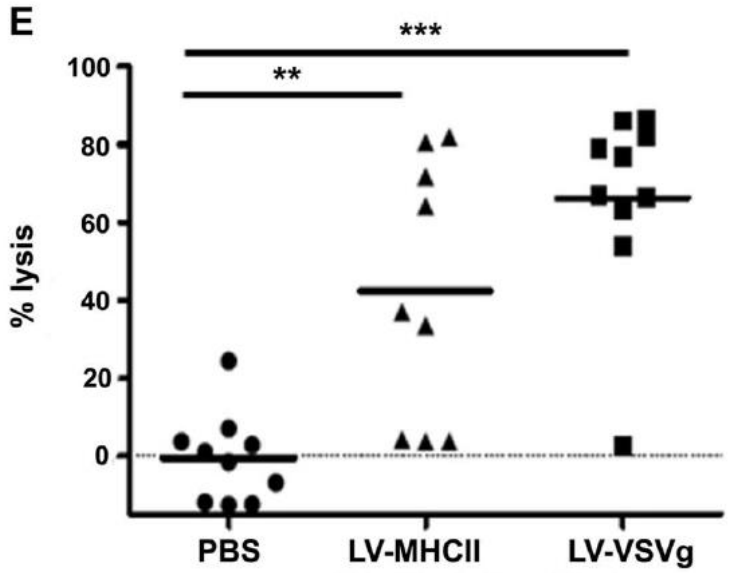




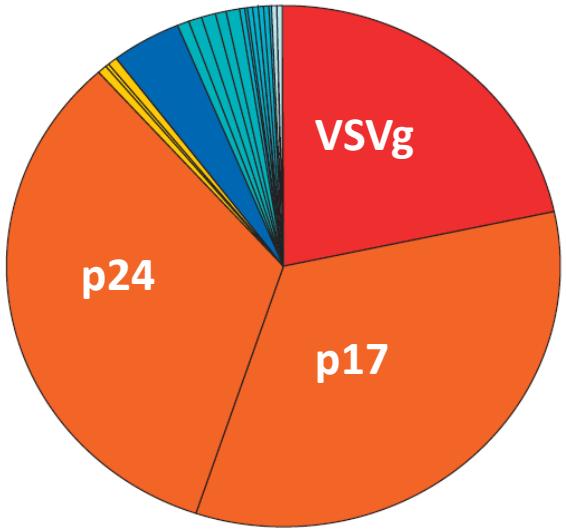




D16 post-injection
VSVg-LV-Luc2
5^{E}+05 IG/mL I.V.

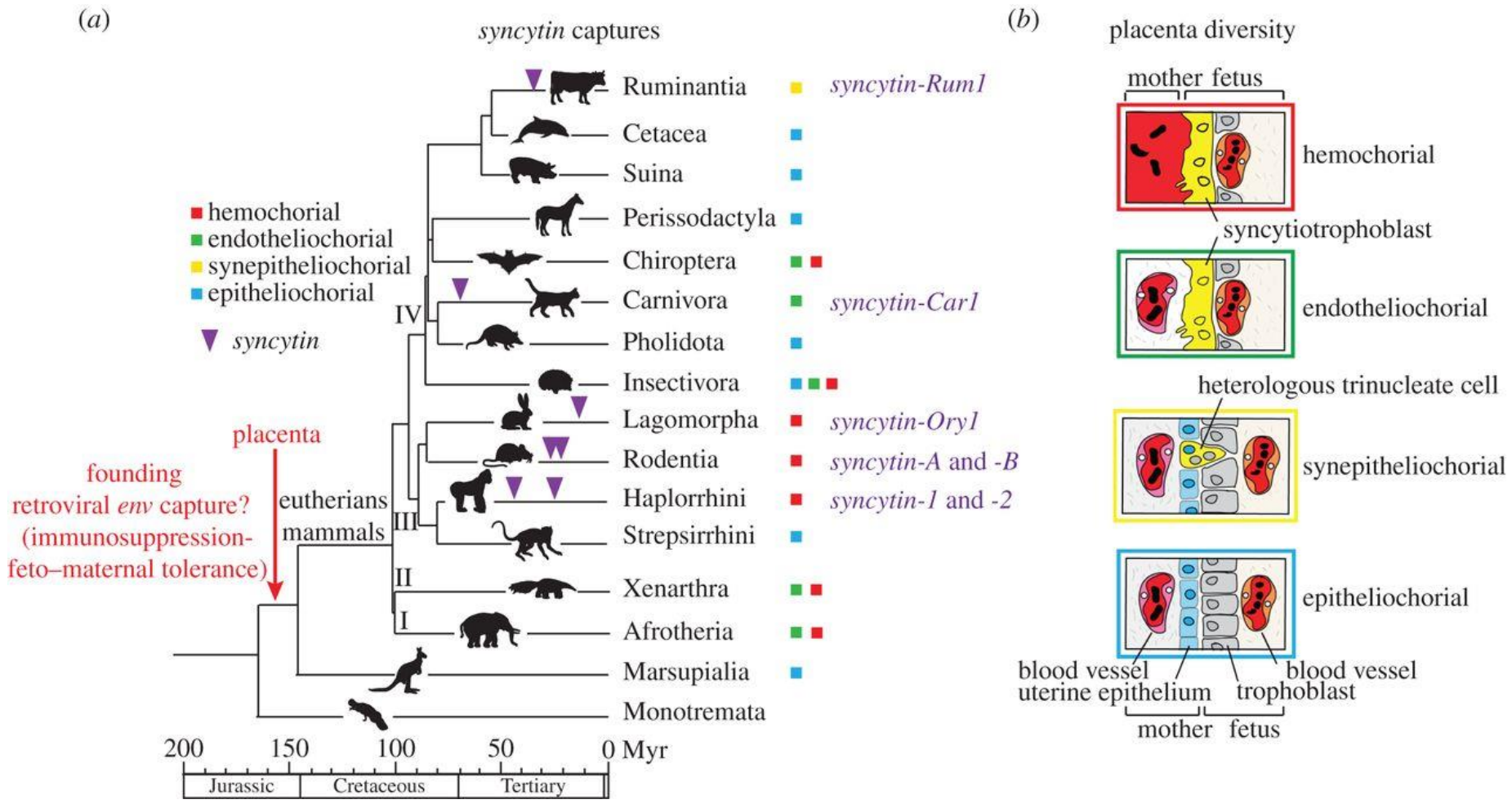


Ciré et al. PlosOne 2014



Denard et al. Proteomics 2009

Syncytins, *env* genes exapted for placentation



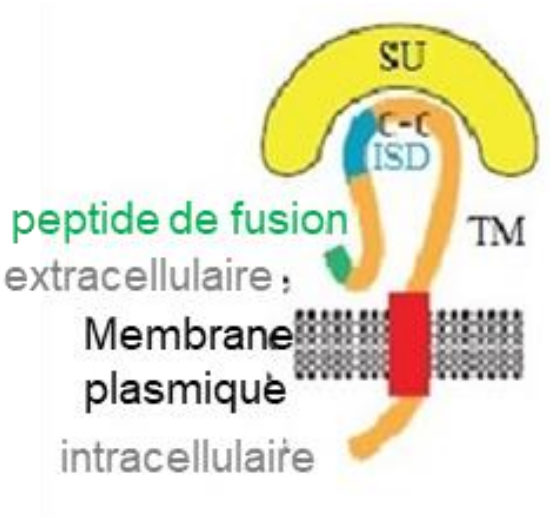
Lavialle et al. Physiological Transactions of the Royal Society, 2013

Human and murine syncytins

Typical retroviral envelope structures

Fusogenic properties

Involved in biological membrane fusion processes (placentation, skeletal mmlmuscle regeneration, osteoclast differentiation

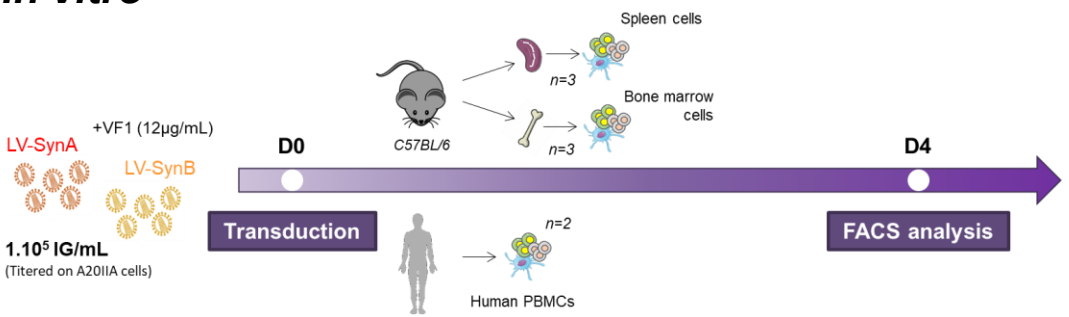


D'après Rawn et al. 2008 et Esnault et al. 2013

	Hu Syn1	Hu Syn2	Mu SynA	Mu SynB
Receptors	ASCT1/2	MSFD2a	GPI anchored protein Ly6e	Not determined yet

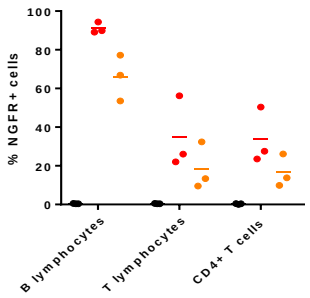
Blaise et al, PNAS 2003; Potgens et al, Histo and CellBio, 2004; Cheynet et al, J.Virol,2005; Esnault et al, PlosGenetics 2013; Lokossou et al, Viruses, 2014 Bacquin et al, J.Virol,2017

In vitro



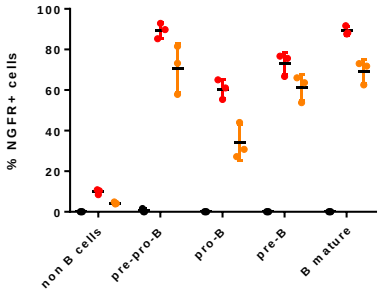
Cells were transduced with 1x10e5 IG/mL of LV-SynA or LV-SynB in presence of VF1 (12µg/mL). The transgene ΔNGFR expression was measured by FACS 4 days post-transduction. Murine cells were cultured in RPMI medium + 10% FCS + 1% glutamine + 50µM β-mercaptoethanol. Human cells were cultured in X-Vivo medium + 10% FCS + 1% glutamine + 2µg/mL CD40L + 50ng/mL IL-21.

Mouse spleen



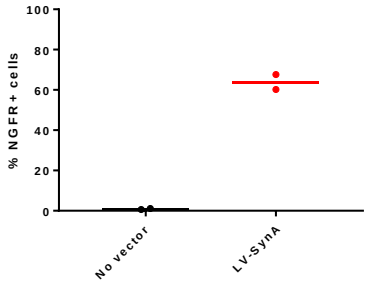
B cells : 7AAD-CD19+B220+CD3-
T cells : 7AAD-CD19-B220-CD3+
CD4+ T cells : 7AAD-CD19-B220-CD3+CD4+

Mouse bone marrow



Non B cells : 7AAD-CD19-B220-
Pre-pro-B : 7AAD- CD19- B220+ ckit- CD43+ CD24-
Pro-B : 7AAD- CD19+ B220+ ckit- CD43+ CD24-
Pre-B : 7AAD- CD19+ B220+ ckit- CD43low CD24+
Mature B : 7AAD- CD19+ B220+ ckit- CD43- CD24-

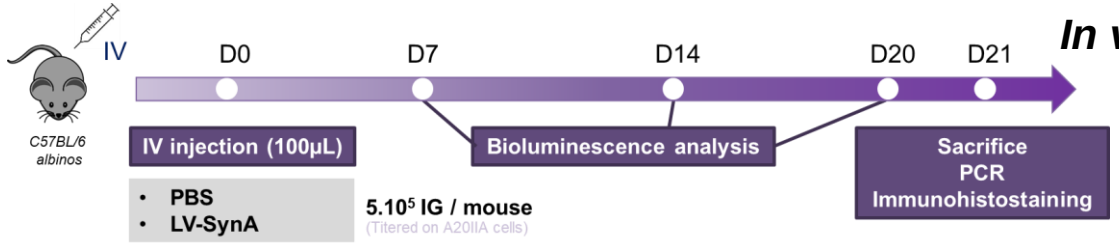
Human PBMC

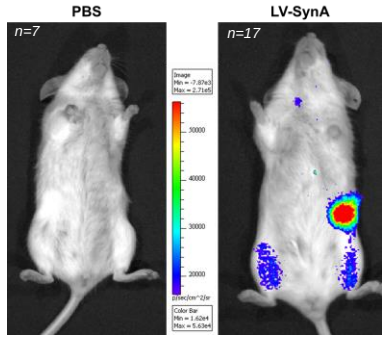


B cells : 7AAD-CD19+CD20+

LV-SynA & LV-SynB vectors allows an efficient transduction of murine mature and immature primary B cells
LV-SynA vectors transduced human primary B cells

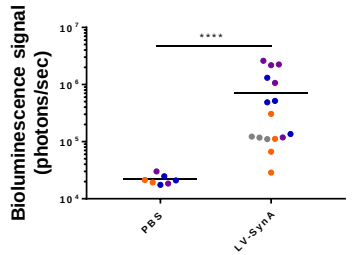
In vivo



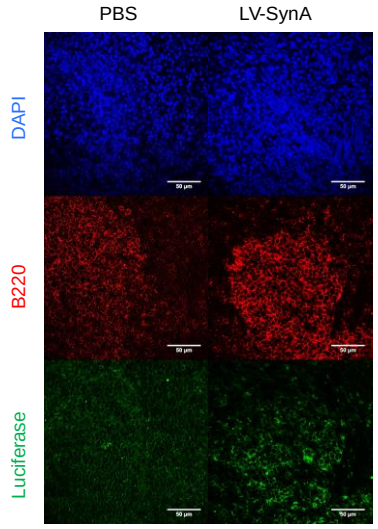


Bioluminescence analysis

Day 20 post-injection (spleen)



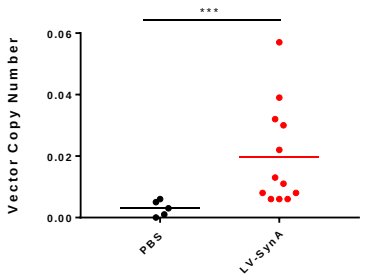
Immunohistostaining



4µm sections of spleen are blocked with PBS-BSA 5% during 30min and stained with anti-B220 (1/20) and anti-luciferase (1/50) for 2h, then with a goat anti-rat-Alexa594 (1/1000) for 1h30 and with a donkey anti-goat-Alexa488 (1/1000) for 1h30.

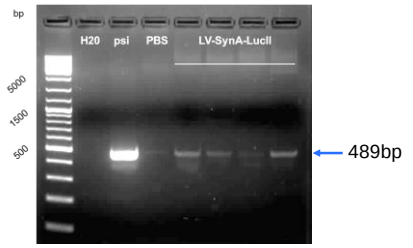
Vector integration analysis

Total spleen



A qPCR on WPRE sequence is performed on total spleen cells gDNA at 21 days post-injection. Statistics were done using Kruskall-Wallis test.

FACS-purified B cells



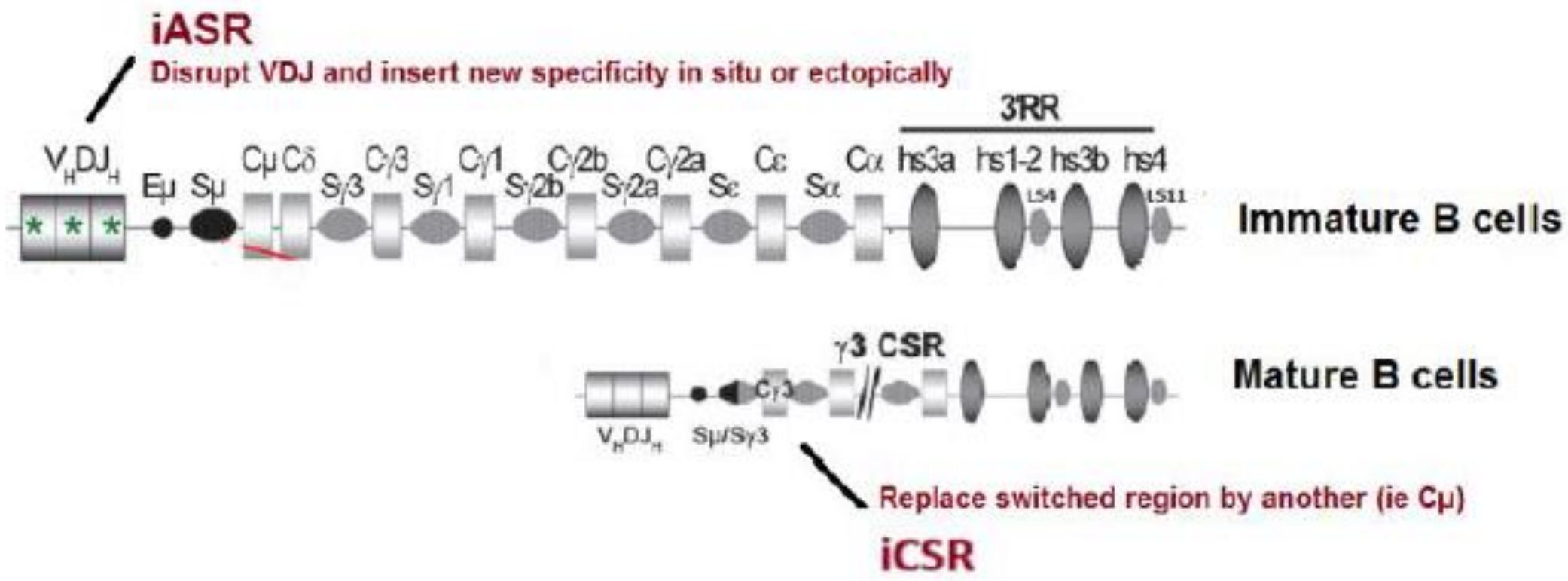
Spleen B cells from are sorted by FACS at 21 days post-injection, they are 7AAD-CD19+B220+CD3-. A PCR on PSI sequence is performed on B cells gDNA.

Spleen B lymphocytes are efficiently transduced after a single intravenous administration of LV-SynA in mice

SYNB project: CRISPR-mediated Ig gene editing in B cells for immunotherapy

Induced antigenic specificity replacement Induced class switch replacement

ANR-AAPG. A. Galy, M. Cogné, G. Semana



Therapeutic potential of anti-HIV bnAbs

LETTER

doi:10.1038/nature14411

Viraemia suppressed in HIV-1–infected humans by broadly neutralizing antibody 3BNC117

Marina Caskey[1]*, Florian Klein[1]*, Julio C. C. Lorenzi[1], Michael S. Seaman[2], Anthony P. West Jr[3], Noreen Buckley[1], Gisela Kremer[4,5], Lilian Nogueira[1], Malte Braunschweig[1,6], Johannes F. Scheid[1], Joshua A. Horwitz[1], Irina Shimeliovich[1], Sivan Ben-Avraham[1], Maggi Witmer-Pack[1], Martin Platten[4,7], Clara Lehmann[4,7], Leah A. Burke[1,8], Thomas Hawthorne[9], Robert J. Gorelick[10], Bruce D. Walker[11], Tibor Keler[9], Roy M. Gulick[8], Gerd Fätkenheuer[4,7], Sarah J. Schlesinger[1] & Michel C. Nussenzweig[1,12]

HIV-1 immunotherapy with a combination of first generation monoclonal antibodies was largely ineffective in pre-clinical and clinical settings and was therefore abandoned[1–3]. However, recently developed single-cell-based antibody cloning methods have uncovered a new generation of far more potent broadly neutralizing antibodies to HIV-1 (refs 4, 5). These antibodies can prevent infec-

half-maximal inhibitory concentration (IC_{50}) of 0.08 μg ml^{-1} (Extended Data Fig. 1)[11]. 12 uninfected and 17 HIV-1-infected individuals (Table 1) were administered a single intravenous dose of 1, 3, 10 or 30 mg kg^{-1} of 3BNC117 (Extended Data Table 1a). 3BNC117 serum concentrations, plasma HIV-1 viral loads (VL), $CD4^+$ and $CD8^+$ T-cell counts, and safety were monitored closely (Fig. 1a, Extended Data Figs 2, 3, and

HIV-1 ANTIBODIES

HIV-1 therapy with monoclonal antibody 3BNC117 elicits host immune responses against HIV-1

Till Schoofs,[1]* Florian Klein,[1,2,3]* Malte Braunschweig,[1,4]* Edward F. Kreider,[5] Anna Feldmann,[6] Lilian Nogueira,[1] Thiago Oliveira,[1] Julio C. C. Lorenzi,[1] Erica H. Parrish,[5] Gerald H. Learn,[5] Anthony P. West Jr.,[7] Pamela J. Bjorkman,[7] Sarah J. Schlesinger,[1] Michael S. Seaman,[8] Julie Czartoski,[9] M. Juliana McElrath,[9] Nico Pfeifer,[6] Beatrice H. Hahn,[5] Marina Caskey,[1] Michel C. Nussenzweig[1,10]†

LETTER

doi:10.1038/nature18929

HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption

Johannes F. Scheid[1,2]*, Joshua A. Horwitz[1]*, Yotam Bar-On[1], Edward F. Kreider[3], Ching-Lan Lu[1], Julio C. C. Lorenzi[1], Anna Feldmann[4], Malte Braunschweig[1], Lilian Nogueira[1], Thiago Oliveira[1], Irina Shimeliovich[1], Roshni Patel[1], Leah Burke[5], Yehuda Z. Cohen[1], Sonya Hadrigan[1], Allison Settler[1], Maggi Witmer-Pack[1], Anthony P. West Jr[6], Boris Juelg[7], Tibor Keler[8], Thomas Hawthorne[8], Barry Zingman[9], Roy M. Gulick[5], Nico Pfeifer[4], Gerald H. Learn[3], Michael S. Seaman[10], Pamela J. Bjorkman[6], Florian Klein[1,11,12], Sarah J. Schlesinger[1], Bruce D. Walker[7,13], Beatrice H. Hahn[3], Michel C. Nussenzweig[1,14] & Marina Caskey[1]

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JEM Journal of Experimental Medicine

ARTICLE

Relationship between latent and rebound viruses in a clinical trial of anti-HIV-1 antibody 3BNC117

Yehuda Z. Cohen[1]*, Julio C.C. Lorenzi[1]*, Lisa Krassnig[1], John P. Barton[2], Leah Burke[3], Joy Pai[1], Ching-Lan Lu[1], Pilar Mendoza[1], Thiago Y. Oliveira[1], Christopher Sleckman[1], Katrina Millard[1], Allison L. Butler[1], Juan P. Dizon[1], Shiraz A. Belblidia[1], Maggi Witmer-Pack[1], Irina Shimeliovich[1], Roy M. Gulick[3], Michael S. Seaman[4], Mila Jankovic[1], Marina Caskey[1**], and Michel C. Nussenzweig[1,5**]

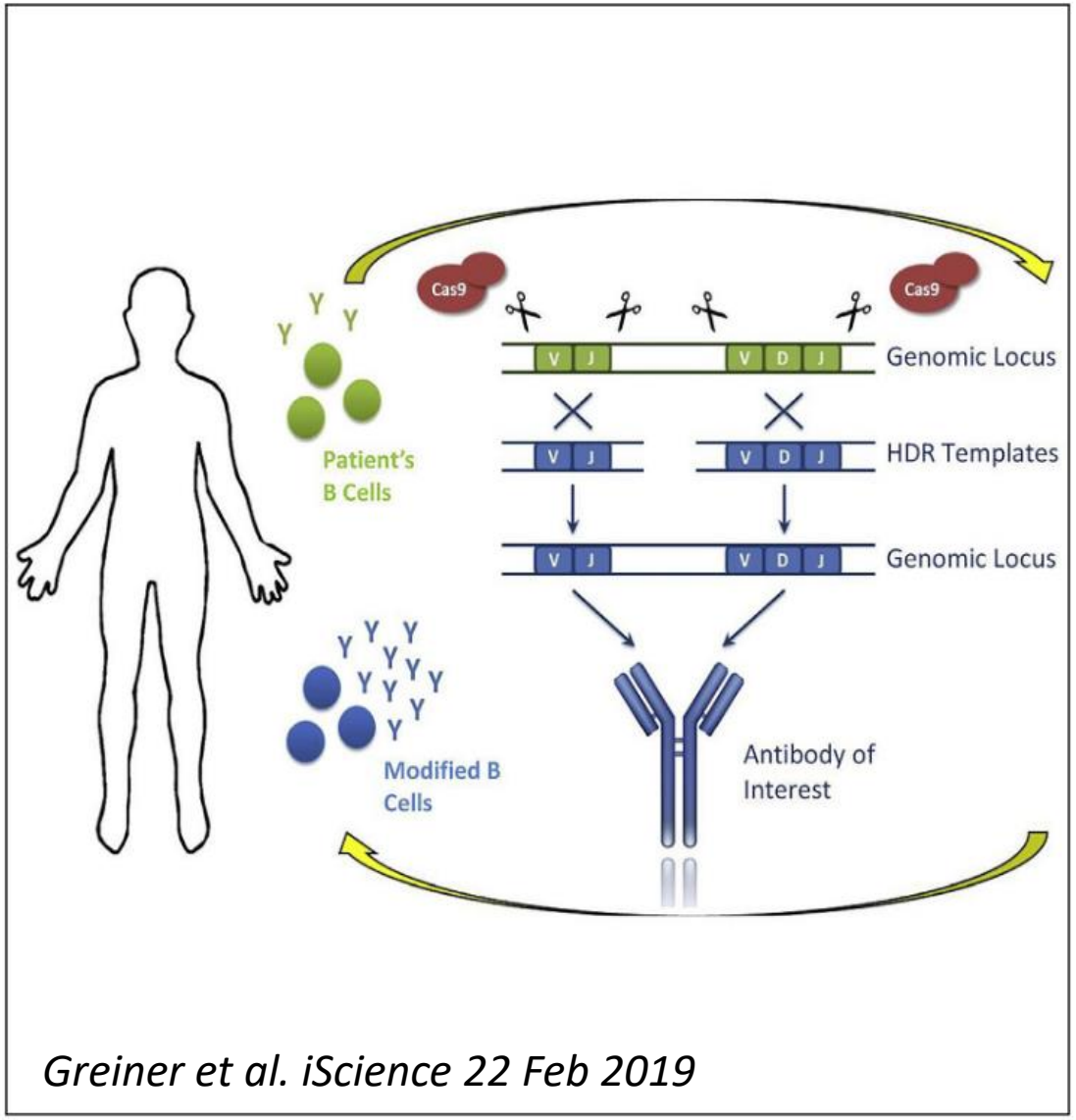
.....

Collaboration VRI
Y. Lévy
G.Pantaleo
C. Fenwick

HIVbnAbs

Lentiviral bnAb gene transfer

Ig gene editing for bNab specificity replacement



Greiner et al. iScience 22 Feb 2019

eLIFE elifesciences.org SHORT REPORT

Reprogramming the antigen specificity of B cells using genome-editing technologies

James E Voss[1,2,3†*], Alicia Gonzalez-Martin[4†*], Raiees Andrabi[1,2,3†], Roberta P Fuller[1,2,3‡], Ben Murrell[5,6‡], Laura E McCoy[7‡], Katelyn Porter[1,2,3‡], Deli Huang[1], Wenjuan Li[1], Devin Sok[1,2,3], Khoa Le[1,2,3], Bryan Briney[1,2,3], Morgan Chateau[8], Geoffrey Rogers[8], Lars Hangartner[1], Ann J Feeney[1], David Nemazee[1], Paula Cannon[8], Dennis R Burton[1,2,3,9*]

Published: 17 January 2019

Published Online: 11 April, 2019 | Supp Info: http://doi.org/10.1084/jem.20190287
Downloaded from jem.rupress.org on June 6, 2019

JEM Journal of Experimental Medicine

TECHNICAL ADVANCES AND RESOURCES

HIV-specific humoral immune responses by CRISPR/Cas9-edited B cells

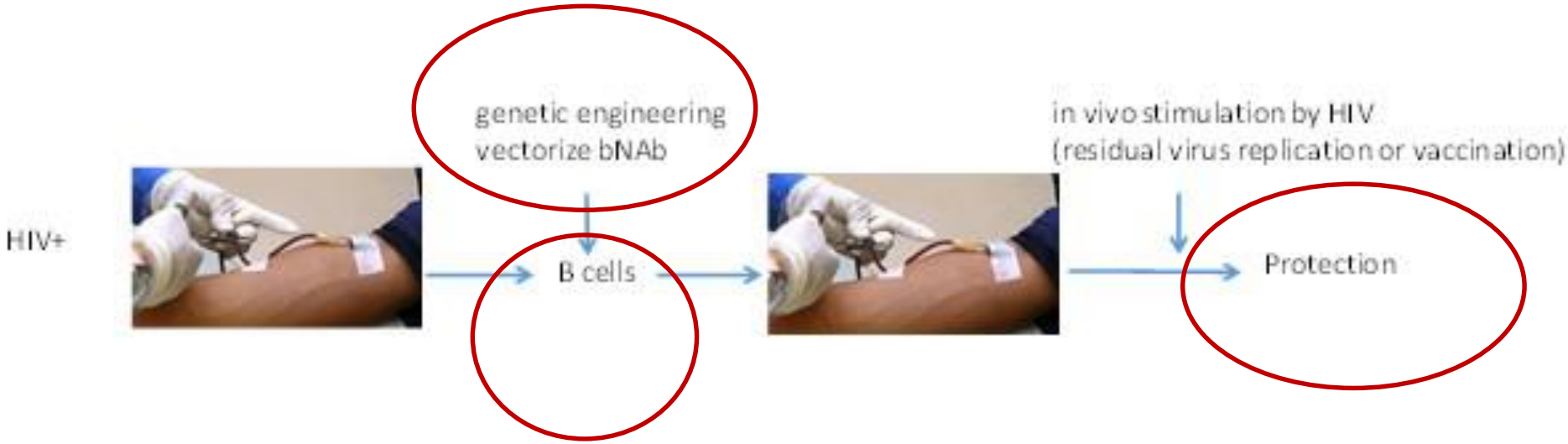
Harald Hartweger[1], Andrew T. McGuire[2,3], Marcel Horning[1], Justin J. Taylor[2,3,4], Pia Dosenovic[1], Daniel Yost[1], Anna Gazumyan[1], Michael S. Seaman[5], Leonidas Stamatatos[2,3], Mila Jankovic[1], and Michel C. Nussenzweig[1,6]

bioRxiv preprint first posted online Feb. 6, 2019; doi: http://dx.doi.org/10.1101/541979.

B cells engineered to express pathogen-specific antibodies using CRISPR/Cas9 protect against infection.

Howell F. Moffett[1], Carson K. Harms[1], Kristin S. Fitzpatrick[1], Marti R. Tooley[1], Jim Boonyaratankornkit[1], Justin J. Taylor[1,2,3*]

[1]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N. Seattle, WA 98109, USA



Technology

Preclinical models

Translation capacity

Inserm

La science pour la santé
From science to health

© Inserm/Patrick Delapierre/U949 Biologie et pharmacologie des plaquettes sanguines

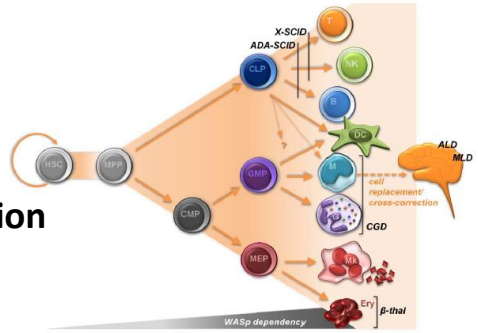
Accélérateur de Recherches Technologiques en Thérapie Génomique

Accelerator of Technological Research in Genomic Therapy

A. Galy, PhD. Inserm

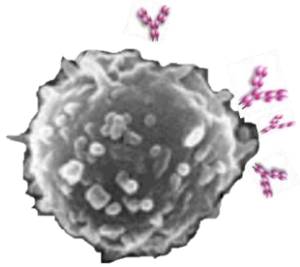
Platform of genomic engineering for immunotherapy

HSC Gene Correction

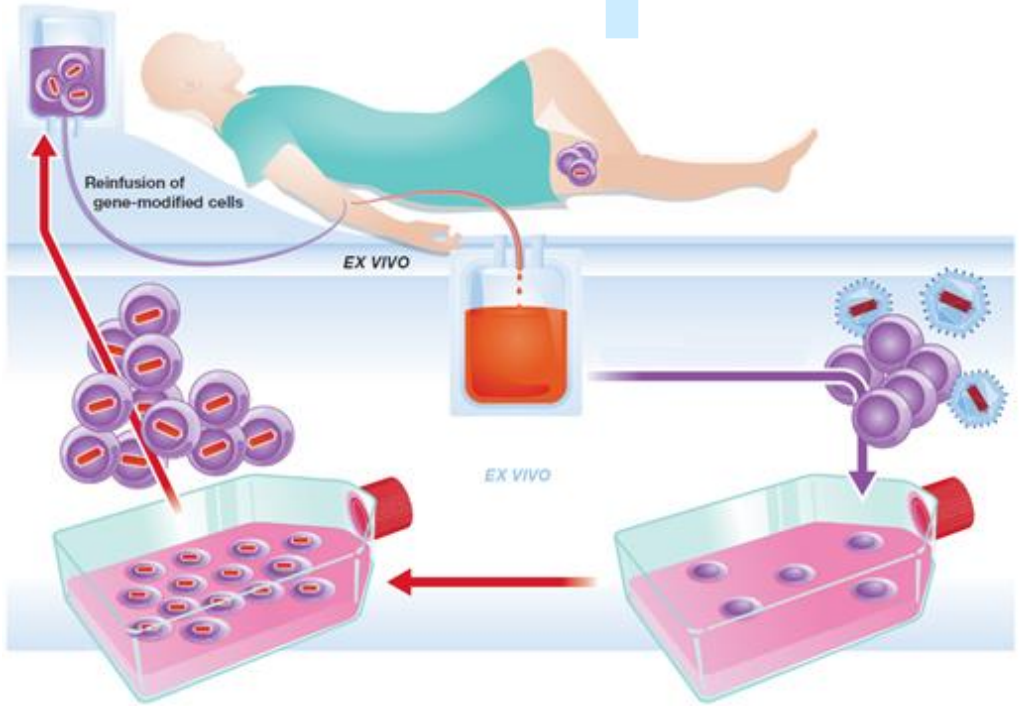


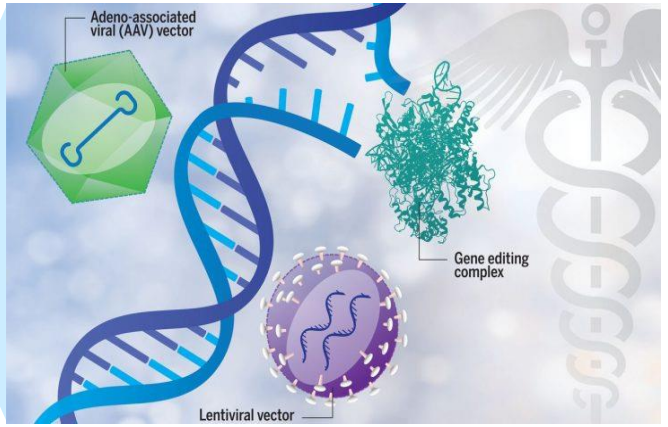
CAR T-cells

Antibody-Reprogrammed B cells



Rare genetic diseases
Cancer
Infectious diseases

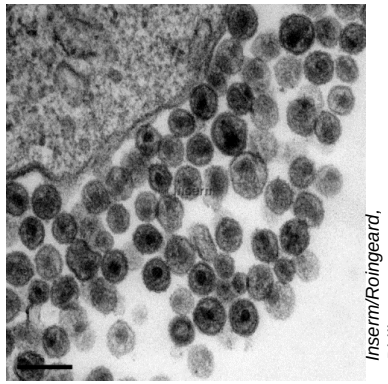




Product development, Bioproduction and Controls

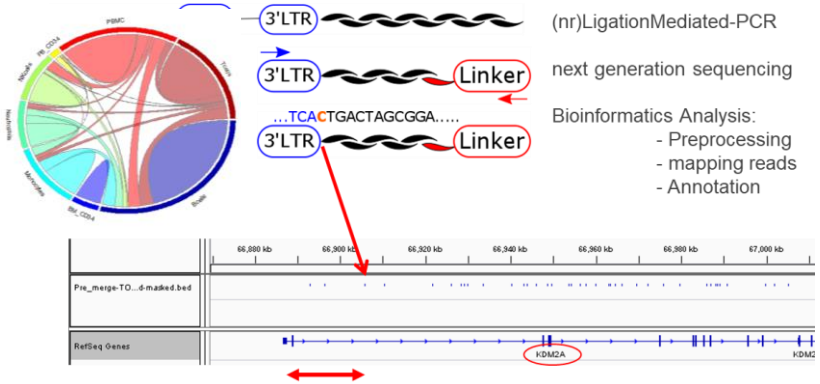
ART-TG Technologies

rHIV-1 vectors



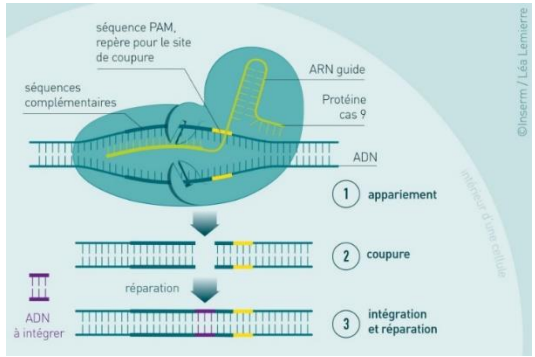
Inserm/Roingeard, Philippe

Production (LV/IDLV)
Purification
Controls



Cell Processing ie CB

CRISPR



Patents

Patent N° EP16194180.2
TatBeclin transduction enhancer
Patent N° EP16305466.1
Novel lentiviral vector pseudotypes …..

Genetic modification

ATx

MaxCyte®

Hilma Af Klint (1908)

Guggenheim, NYC, March 2019

A vision of Gene Editing and the Promises of Genetic Immunotherapy

Thanks to.....

IMBI– Genethon UMR 951

Youna Coquin,
Maxime Ferrand,
Sophie Frin
Khalil Seye

ART-TG Clémence Fournier
Antoine Biek
N'deye Diouf

SYN-B consortium

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VRI

Yves Lévy, Gepi Pantaleo, Craig Fenwick, Mireille Centlivre