Implementation of the Hospital Exemption in the EU and its role in boosting innovation and patient access to innovative therapies

HaDEA 2022 P3 08

Implementing FWC HaDEA 2022/OP/0012 EU4Health

21 November 2024

Implementation of Hospital Exemption in Europe and its role in boosting innovation and patient access to innovative therapies

DG SANTE & HaDEA

Brussels Nov 21, 2024

ATMPs development in hospitals

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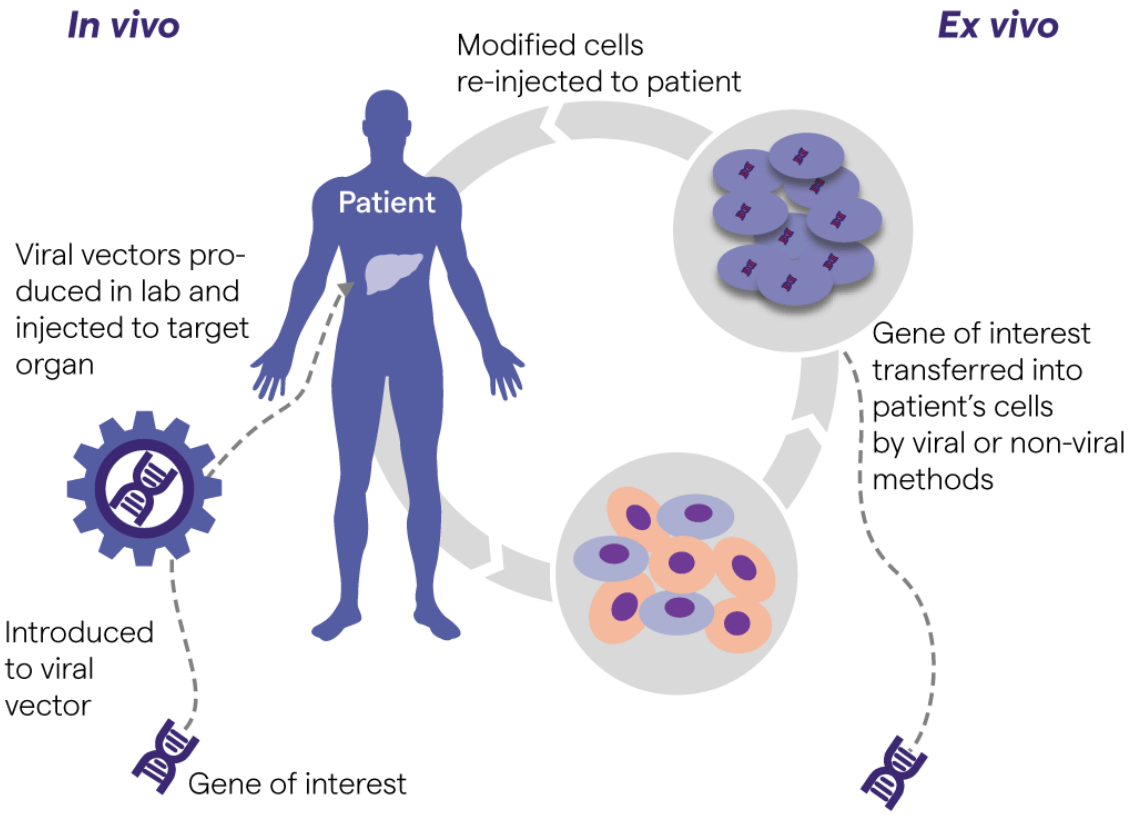
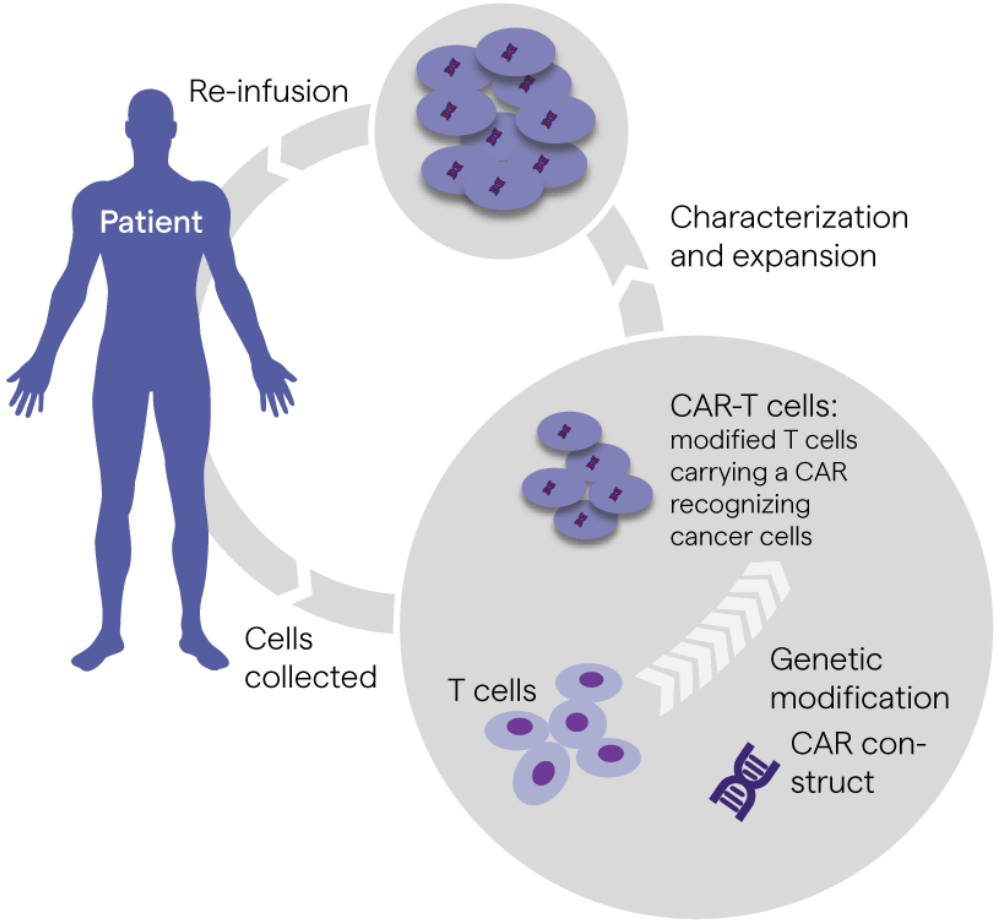
Director, Gene and Cell Therapy Center,
Hematology-BMT Unit
G.Papanikolaou Hospital
EMA-COMP member

Redifining the pharmaceutical model : personalized therapies and "living drugs"

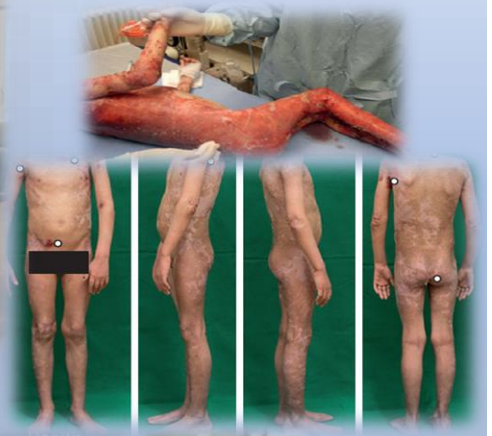
Gene therapy



Cell therapy



Success stories of gene/cell therapies



- X-SCID (*Science, 2000*)
- **ADA-SCID** (*Science 2002, New England J Medicine, 20*)
- Wiscott-Aldrich Syndrome (*New Eng J Medicine 2010, Science 2013*)
- **Adrenoleukodystrophy** (*Science 2009, New Engl J ne, 2017*)
- **Metachromatic leukodystrophy** (*Science*)
- **Congenital amaurosis Leber** (*New England J Medicine, 2009 and 2015*)
- Age-related macular degeneration (*Lancet 2015*)
- **Hemophilia A and B** (*New England J Medicine, 2011, 2017, 2020*)
- **Sickle Cell Disease** (*New Engl J Medicine, 2017 and 2024*)
- **Thalassemia** (*New Eng J Medicine 2018 and 2024, Lancet 20*)
- **Spinal Muscular Atrophy** (*New Engl J Medicine*)
- Junctional Epidermolysis Bullosa (*Nature 2017*)
- X-linked CGD (*Nat Med 2020*)
- **CAR T cells:Diffuse large B-cell lymphoma** (*ng J Medicine 2017, 2019*)
- **CAR T cells: B-cell lymphoblastic leukemia** (*New Eng J Medicine 2018*)
- **CAR T cells: Multiple Myeloma** *(New Eng J Med 2023)*
- CAR T cells: Autoimmune diseases *(New Eng J Med 202 and 2023)*

Approved gene/cell therapies and pricing

• Strimvelis for ADA-SCID	600.000 €
• Kymriah (CAR T) for ALL, DLBCL	475.000$
• Yescarta (CAR T) for DLBCL	373.000$
• Carvykti (CAR T) for Multiple Myeloma	465.000$
• Luxturna for congenital blindness (Leber)	850.000$
• Zolgensma for spinal muscular atrophy	2.125.000$
• Libmeldy for metachromatic leucodystrophy	3.400.000$
• Zynteglo for β-thalassemia	2.800.000$
• Hemgenix for hemophilia B	3.500.000$
• Roctavian for Hemophilia A	2.900.000$
• Casgevy for β-thalassemia and SCD	2.200.000$
• Amtavgi for advanced melanoma	515.000$

- Burdensome prices and demand to be paid upfront
- Outcome-based models of reimbursement

New Era - New Challenges in Disease Treatment

Availability

Limited manufacturing capacity, specialized infrastructure requirements, complexity of manufacturing

Accessibility

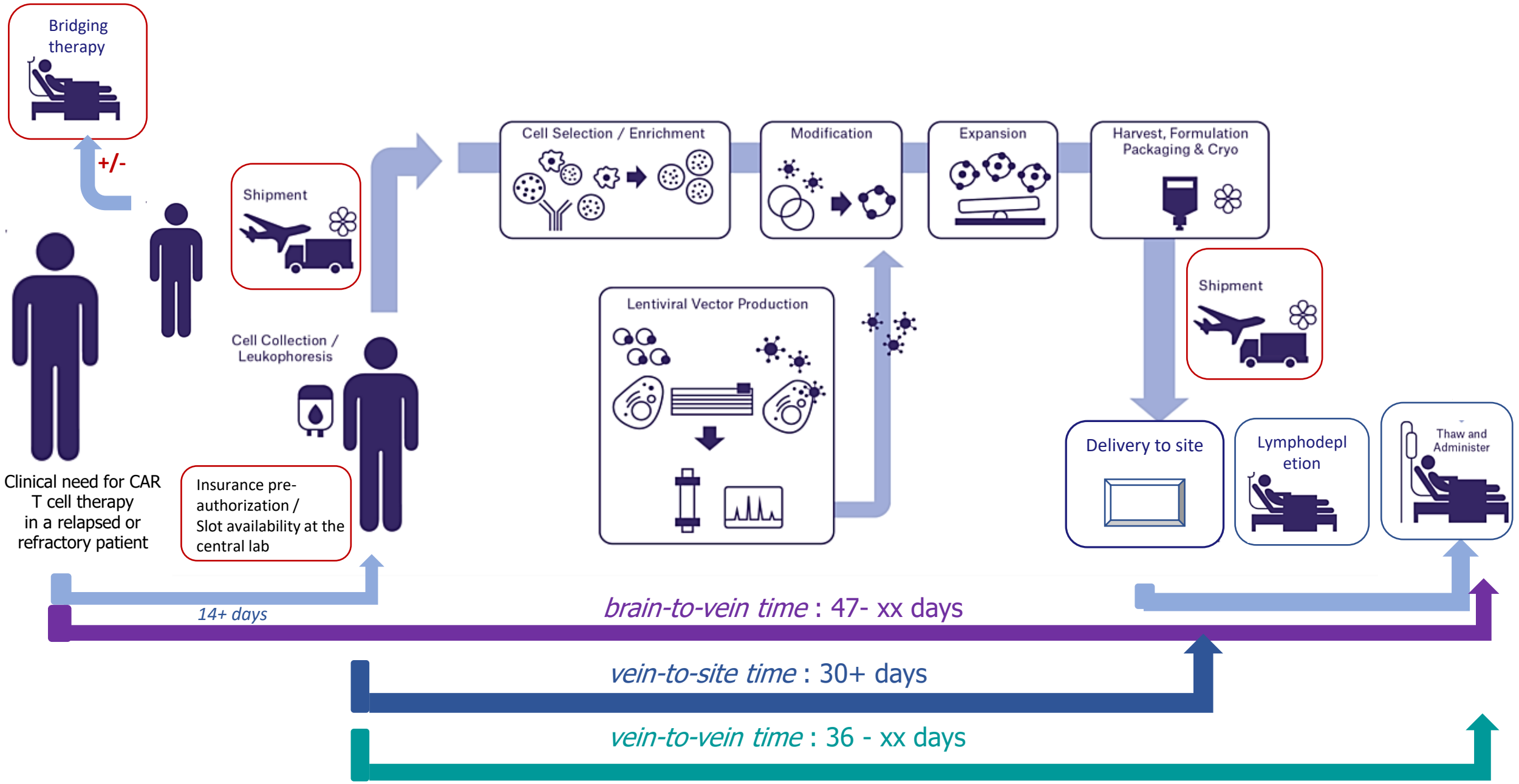
Complex logistics, geographic disparities, need for highly specialized healthcare facilities

Affordability

High costs often place patients and healthcare systems out of reach, straining financial sustainability

- *Delayed or denied access to life-saving treatments*
- *Inequality in healthcare*

The complex logistics of centralized CAR T cell manufacturing



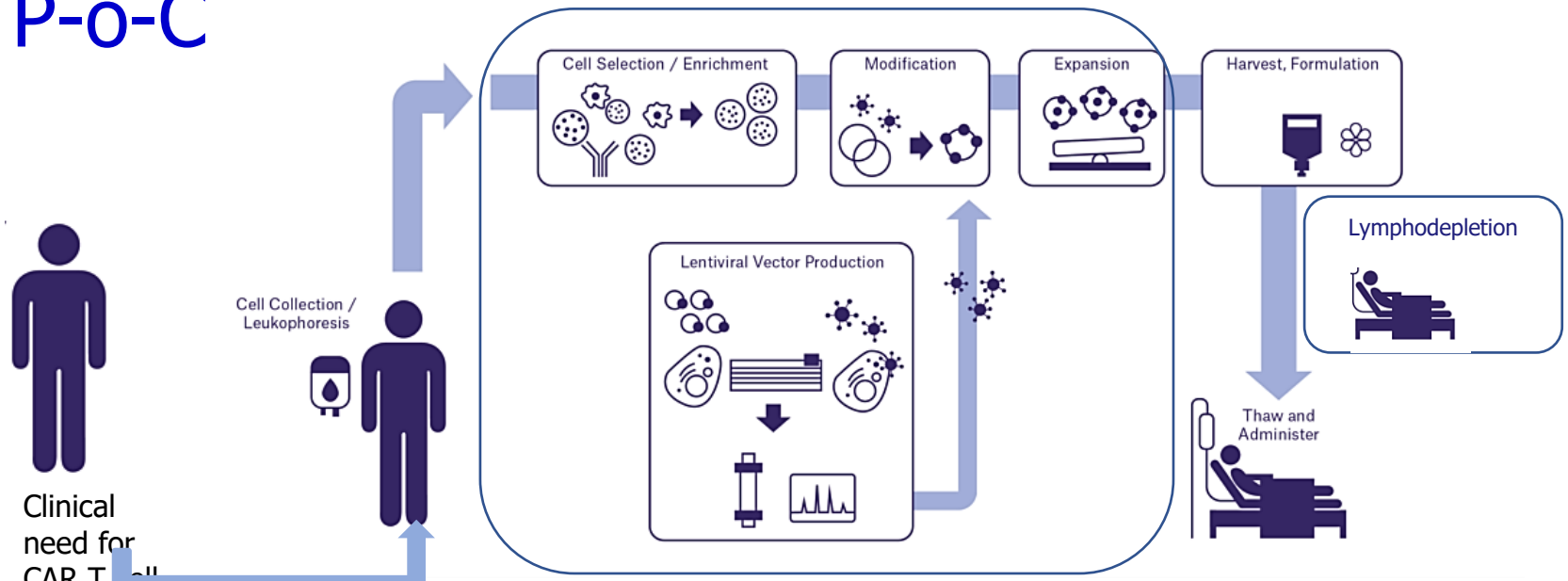
European ATMP regulation EC1394/2007 (Article 28)

Hospital Exemption enables manufacturing of ATMPs outside the standard centralized marketing authorization common pathway

- *"ATMP is prepared **on a non-routine basis according to specific quality standards**, and used within the same Member State in a hospital **under the exclusive professional responsibility of a medical practitioner,** in order to comply with an individual medical prescription for a custom-made product for an individual patient"*
- *"Manufacturing of these products shall be **authorized by the competent authority of the Member State.** Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards at Community level in respect of ATMPs for which authorization is required are pursuant to Regulation"*

Improving the "3 A" health pillars: Point-of-Care CAR T cell manufacturing and Hospital Exemption

P-o-C



- Availability
- Accessibility
- Affordability

HE

Manufacturing w/o the need of traditional regulatory approvals
Overcoming production delays, geographic limitations, and high costs

The paradigm of Spain : ARI-0001, Point-of-Care CAR T cells

February 2021: **ARI-0001,** an anti-CD19 CAR against B-cell malignancies, received authorisation from the Spanish Agency of Medicines **under 'hospital exemption'** for the treatment of adult patients with relapsed/refractory acute lymphoblastic leukaemia

An important landmark : the 1st CAR to have been developed from bench to bedside in the EU and the 1st to receive the authorisation outside the centralized marketing authorization pathway, proving that local academic institutions could successfully develop, manufacture, and deliver cutting-edge therapies at a competitive cost compared to commercial alternatives.

The hospital exemption pathway for the approval of advanced therapy medicinal products: an underused opportunity? The case of the CAR-T ARI-0001

Bone Marrow Transplantation (2022) 57:156 – 159

Esteve Trias[1]✉, Manel Juan[1,2], Alvaro Urbano-Ispizua[3] and Gonzalo Calvo[1,4]

Molecular Therapy
Original Article

CART19-BE-01: A Multicenter Trial of ARI-0001 Cell Therapy in Patients with CD19+ Relapsed/Refractory Malignancies

DOI: 10.1111/bjh.19170
BJHaem
ORIGINAL PAPER
Haematological Malignancy - Clinical

The academic point-of-care anti-CD19 chimeric antigen receptor T-cell product varnimcabtagene autoleucel (ARI-0001 cells) shows efficacy and safety in the treatment of relapsed/refractory B-cell non-Hodgkin lymphoma

The Greek (non-) paradigm : ATMPs development w/o HE

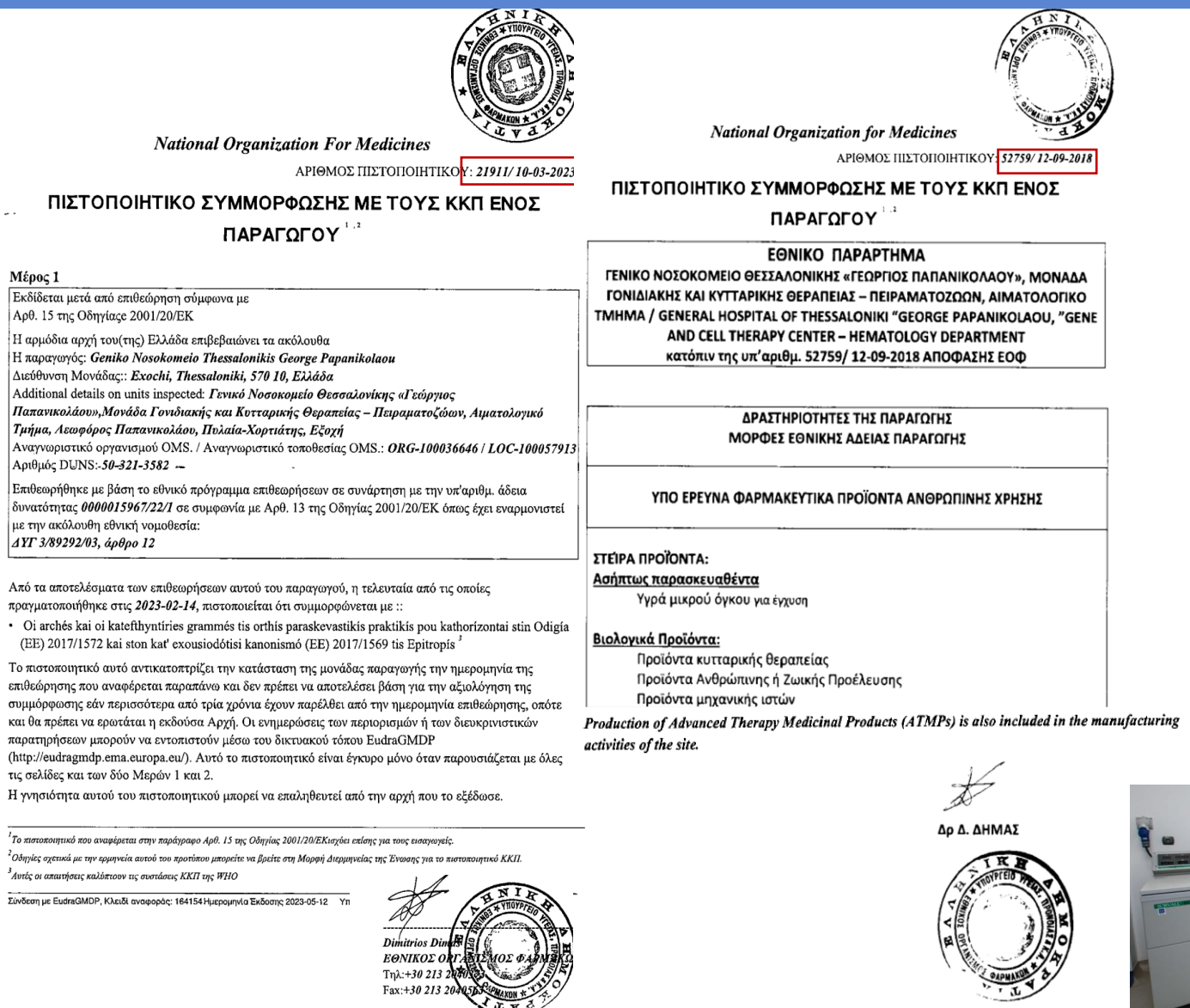
Greece has not implemented HE into its national regulatory framework

As a result, all ATMPs intended for clinical use must undergo centralized approval via the EMA, even for small-scale or non-commercial academic developments.

- Increased Regulatory Hurdles
- Limited development restricted to Early-Stage Clinical Trials
- Barriers to Patient Access

ATMPs development in Greece

2018 – 2021 : GMP accreditation and initiation of the first clinical trials with multi-virus-specific T-cells in Greece



National Organization For Medicines

ΑΡΙΘΜΟΣ ΠΙΣΤΟΠΟΙΗΤΙΚΟΥ: *21911/ 10-03-2023*

ΠΙΣΤΟΠΟΙΗΤΙΚΟ ΣΥΜΜΟΡΦΩΣΗΣ ΜΕ ΤΟΥΣ ΚΚΠ ΕΝΟΣ ΠΑΡΑΓΩΓΟΥ [1,2]

Μέρος 1

Εκδίδεται μετά από επιθεώρηση σύμφωνα με
Αρθ. 15 της Οδηγίας 2001/20/ΕΚ

Η αρμόδια αρχή του(της) Ελλάδα επιβεβαιώνει τα ακόλουθα
Η παραγωγός: ***Geniko Nosokomeio Thessalonikis George Papanikolaou***
Διεύθυνση Μονάδας:: ***Exochi, Thessaloniki, 570 10, Ελλάδα***
Additional details on units inspected: ***Γενικό Νοσοκομείο Θεσσαλονίκης «Γεώργιος Παπανικολάου»,Μονάδα Γονιδιακής και Κυτταρικής Θεραπείας – Πειραματοζώων, Αιματολογικό Τμήμα, Λεωφόρος Παπανικολάου, Πυλαία-Χορτιάτης, Εξοχή***
Αναγνωριστικό οργανισμού OMS. / Αναγνωριστικό τοποθεσίας OMS.: ***ORG-100036646 / LOC-100057913***
Αριθμός DUNS:.***50-321-3582***

Επιθεωρήθηκε με βάση το εθνικό πρόγραμμα επιθεωρήσεων σε συνάρτηση με την υπ'αριθμ. άδεια δυνατότητας ***0000015967/22/1*** σε συμφωνία με Αρθ. 13 της Οδηγίας 2001/20/ΕΚ όπως έχει εναρμονιστεί με την ακόλουθη εθνική νομοθεσία:
ΔΥΓ 3/89292/03, άρθρο 12

Από τα αποτελέσματα των επιθεωρήσεων αυτού του παραγωγού, η τελευταία από τις οποίες πραγματοποιήθηκε στις ***2023-02-14***, πιστοποιείται ότι συμμορφώνεται με ::

- Οι archés kai oi katefthyntíries grammés tis orthis paraskevastikís praktikís pou kathorízontai stin Odigía (ΕΕ) 2017/1572 kai ston kat' exousiodótisi kanonismó (ΕΕ) 2017/1569 tis Epitropís [3]

Το πιστοποιητικό αυτό αντικατοπτρίζει την κατάσταση της μονάδας παραγωγής την ημερομηνία της επιθεώρησης που αναφέρεται παραπάνω και δεν πρέπει να αποτελέσει βάση για την αξιολόγηση της συμμόρφωσης εάν περισσότερα από τρία χρόνια έχουν παρέλθει από την ημερομηνία επιθεώρησης, οπότε και θα πρέπει να ερωτάται η εκδούσα Αρχή. Οι ενημερώσεις των περιορισμών ή των διευκρινιστικών παρατηρήσεων μπορούν να εντοπιστούν μέσω του δικτυακού τόπου EudraGMDP (http://eudragmdp.ema.europa.eu/). Αυτό το πιστοποιητικό είναι έγκυρο μόνο όταν παρουσιάζεται με όλες τις σελίδες και των δύο Μερών 1 και 2.
Η γνησιότητα αυτού του πιστοποιητικού μπορεί να επαληθευτεί από την αρχή που το εξέδωσε.

[1] *Το πιστοποιητικό που αναφέρεται στην παράγραφο Αρθ. 15 της Οδηγίας 2001/20/ΕΚισχύει επίσης για τους εισαγωγείς.*
[2] *Οδηγίες σχετικά με την ερμηνεία αυτού του προτύπου μπορείτε να βρείτε στη Μορφή Διερμηνείας της Ένωσης για το πιστοποιητικό ΚΚΠ.*
[3] *Αυτές οι απαιτήσεις καλύπτουν τις συστάσεις ΚΚΠ της WHO*

Σύνδεση με EudraGMDP, Κλειδί αναφοράς: 164154 Ημερομηνία Έκδοσης 2023-05-12 Υπ

Dimitrios Dimas
ΕΘΝΙΚΟΣ ΟΡΓΑΝΙΣΜΟΣ ΦΑΡΜΑΚΩΝ
Τηλ.:*+30 213 2040*
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National Organization for Medicines

ΑΡΙΘΜΟΣ ΠΙΣΤΟΠΟΙΗΤΙΚΟΥ: *52759/ 12-09-2018*

ΠΙΣΤΟΠΟΙΗΤΙΚΟ ΣΥΜΜΟΡΦΩΣΗΣ ΜΕ ΤΟΥΣ ΚΚΠ ΕΝΟΣ ΠΑΡΑΓΩΓΟΥ [1,2]

ΕΘΝΙΚΟ ΠΑΡΑΡΤΗΜΑ
ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ «ΓΕΩΡΓΙΟΣ ΠΑΠΑΝΙΚΟΛΑΟΥ», ΜΟΝΑΔΑ ΓΟΝΙΔΙΑΚΗΣ ΚΑΙ ΚΥΤΤΑΡΙΚΗΣ ΘΕΡΑΠΕΙΑΣ – ΠΕΙΡΑΜΑΤΟΖΩΩΝ, ΑΙΜΑΤΟΛΟΓΙΚΟ ΤΜΗΜΑ / GENERAL HOSPITAL OF THESSALONIKI "GEORGE PAPANIKOLAOU, "GENE AND CELL THERAPY CENTER – HEMATOLOGY DEPARTMENT
κατόπιν της υπ'αριθμ. 52759/ 12-09-2018 ΑΠΟΦΑΣΗΣ ΕΟΦ

ΔΡΑΣΤΗΡΙΟΤΗΤΕΣ ΤΗΣ ΠΑΡΑΓΩΓΗΣ
ΜΟΡΦΕΣ ΕΘΝΙΚΗΣ ΑΔΕΙΑΣ ΠΑΡΑΓΩΓΗΣ

ΥΠΟ ΕΡΕΥΝΑ ΦΑΡΜΑΚΕΥΤΙΚΑ ΠΡΟΪΟΝΤΑ ΑΝΘΡΩΠΙΝΗΣ ΧΡΗΣΗΣ

ΣΤΕΙΡΑ ΠΡΟΪΟΝΤΑ:
Ασήπτως παρασκευαθέντα
Υγρά μικρού όγκου για έγχυση

Βιολογικά Προϊόντα:
Προϊόντα κυτταρικής θεραπείας
Προϊόντα Ανθρώπινης ή Ζωικής Προέλευσης
Προϊόντα μηχανικής ιστών

Production of Advanced Therapy Medicinal Products (ATMPs) is also included in the manufacturing activities of the site.

Δρ Δ. ΔΗΜΑΣ

Tri-VSTs (2019) :
Rapidly produced multivirus-specific T cells for the management of viral infections from CMV, EBV and BKV, post allogeneic hematopoietic cell transplantation

EudraCT #: 2014-004817-98

Penta-STs (2021) :
Donor-derived pentavalent T cells *(CMV, EBV, BKV, ADV & Aspergillus fumigatus)* for opportunistic infections post haploidentical transplantation

EudraCT: 2020-004725-23

Adoptive immunotherapy with virus-specific T cells

Seropositive SCT donor

1

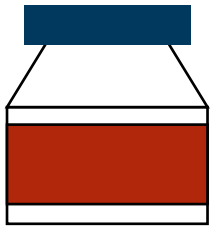
20-30ml blood

Peripheral blood mononuclear cells (PBMCs)

Stimulation with immunogenic peptides of viral Ags

EBV – EBNA1, LMP2, BZLF1
CMV – IE1, pp65
BKV – LT, VP1
Asp – Crf1, Gel1, SHMT
AdV – Hexon, Penton

2

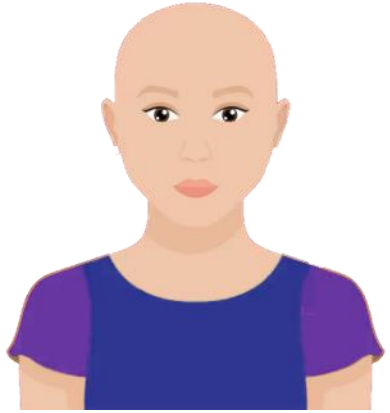


pathogen-specific T cells

3

Infusion

SCT patient



Preclinical proof-of-concept

Bone Marrow Transplantation
https://doi.org/10.1038/s41409-019-0501-9

ARTICLE

Clinical-scale production of *Aspergillus*-specific T cells for the treatment of invasive aspergillosis in the immunocompromised host

Anastasia Papadopoulou[1] · Maria Alvanou[1,2] · Kiriakos Koukoulias[1,2] · Evangelia Athanasiou[1] · Andriana Lazaridou[1] · Nikolaos Savvopoulos[1,2] · Panayotis Kaloyannidis[3] · Anthi-Marina Markantonatou[4] · Timoleon-Achilleas Vyzantiadis[4] · Minas Yiangou[2] · Achilles Anagnostopoulos[1] · Evangelia Yannaki[1,5]

"Cerberus" T Cells: A Glucocorticoid-Resistant, Multi-Pathogen Specific T Cell Product to Fight Infections in Severely Immunocompromised Patients

frontiers in Immunology

ORIGINAL RESEARCH
published: 18 January 2021
doi: 10.3389/fimmu.2020.608701

Kiriakos Koukoulias[1,2†], Penelope-Georgia Papayanni[1,2†], Aphrodite Georgakopoulou[1,2], Maria Alvanou[1,3], Stamatia Laidou[4], Anastasios Kouimtzidis[1,2], Chrysoula Pantazi[1], Glykeria Gkoliou[4], Timoleon-Achilleas Vyzantiadis[5], Alexandros Spyridonidis[3], Antonios Makris[4], Anastasia Chatzidimitriou[4], Nikoletta Psatha[6], Achilles Anagnostopoulos[1], Evangelia Yannaki[1,7‡] and Anastasia Papadopoulou[1*‡]*

Bone Marrow Transplantation (2021) 56:1445–1448
https://doi.org/10.1038/s41409-020-01210-9

CORRESPONDENCE

Multipathogen-specific T cells against viral and fungal infections

Anastasia Papadopoulou[1] · Kiriakos Koukoulias[1,2] · Maria Alvanou[1] · Anastasios Kouimtzidis[1,2] · Evangelia Athanasiou[1] · Nikolaos Savvopoulos[1,2] · Anthi-Marina Markantonatou[3] · Eleni Siotou[1] · Timoleon-Achilleas Vyzantiadis[3] · Achilles Anagnostopoulos[1] · Evangelia Yannaki[1,4]

bjh research paper

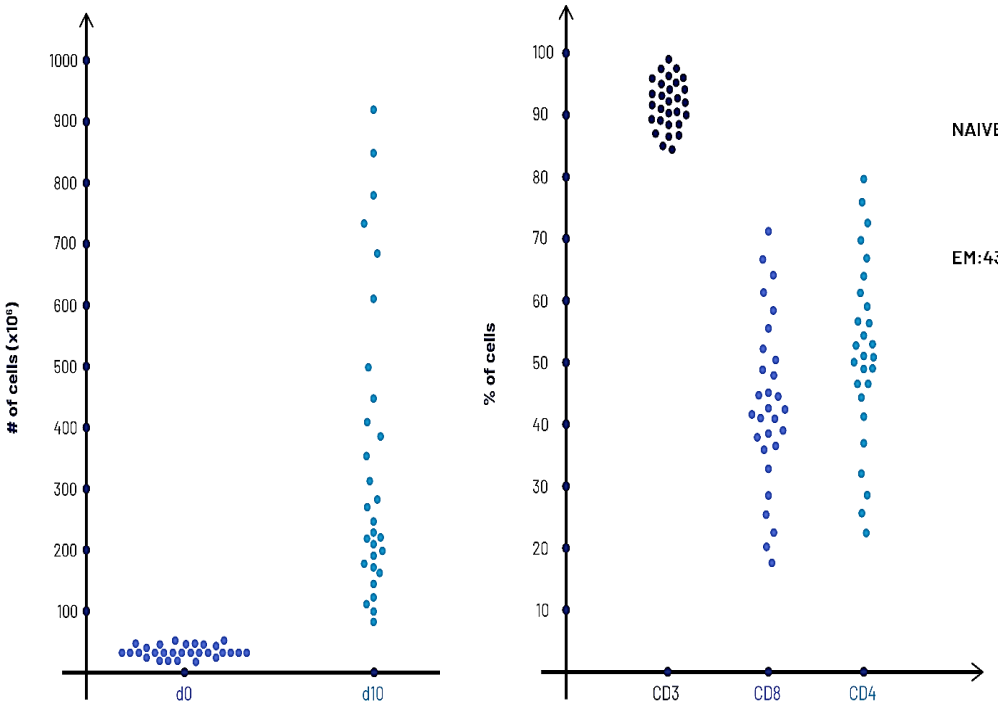
Non-transplantable cord blood units as a source for adoptive immunotherapy of leukaemia and a paradigm of circular economy in medicine

Kiriakos Koukoulias,[1,2,*]
Anastasia Papadopoulou,[1,*]
Anastasios Kouimtzidis,[1,2]
Penelope-Georgia Papayanni,[1,2]
Andri Papaloizou,[3]
Damianos Sotiropoulos,[1]
Minas Yiangou,[2] Paul Costeas,[3]
Achilles Anagnostopoulos,[1]
Evangelia Yannaki[1] and
Panayotis Kaloyannidis[4]

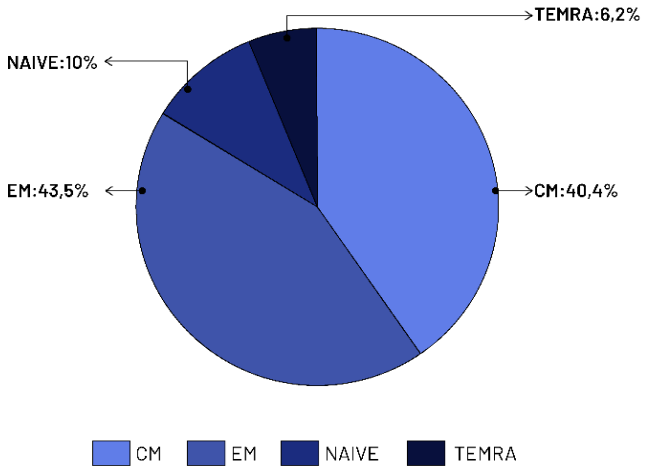
Clinical cell product characteristics

- Mean 7-fold cell expansion over baseline - Mean 222±30 x 10^6 cells in total (dose 20X10^6/m^2)

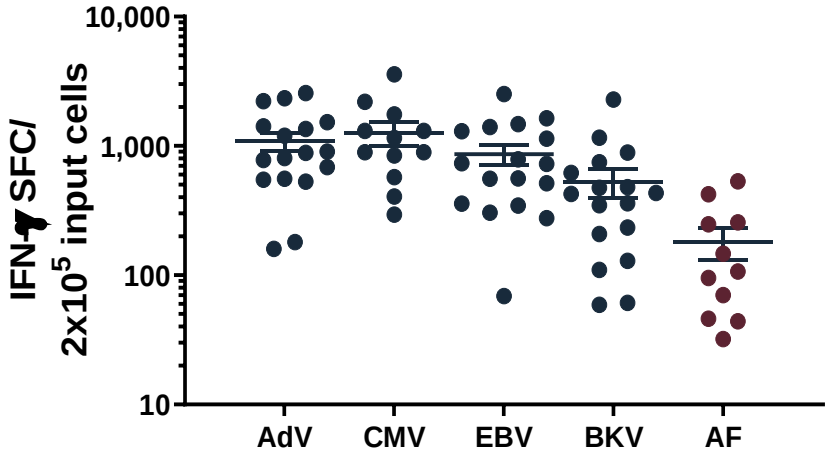
Expansion



Immunophenotype

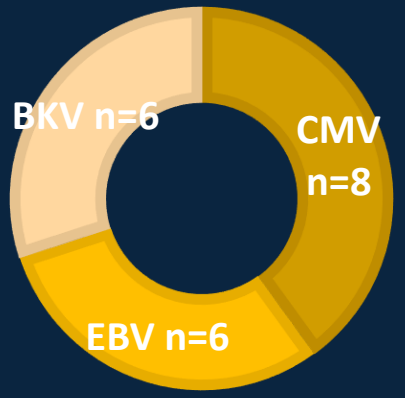


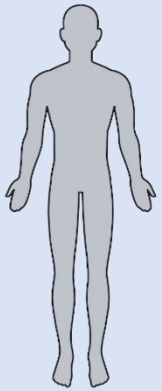
Specificity



Single pathogen infection

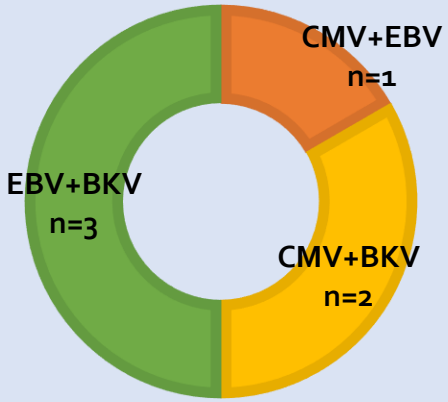
N=20



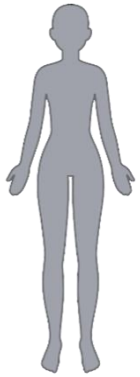


N=6

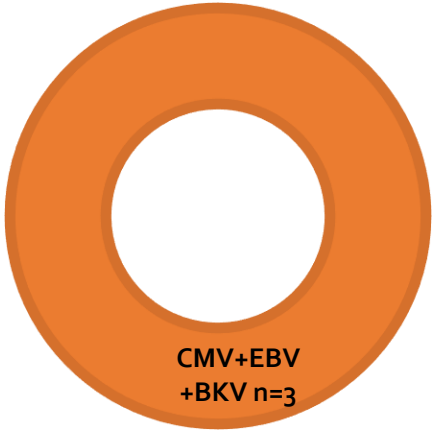
Double pathogen infection



Triple pathogen infection



N=3

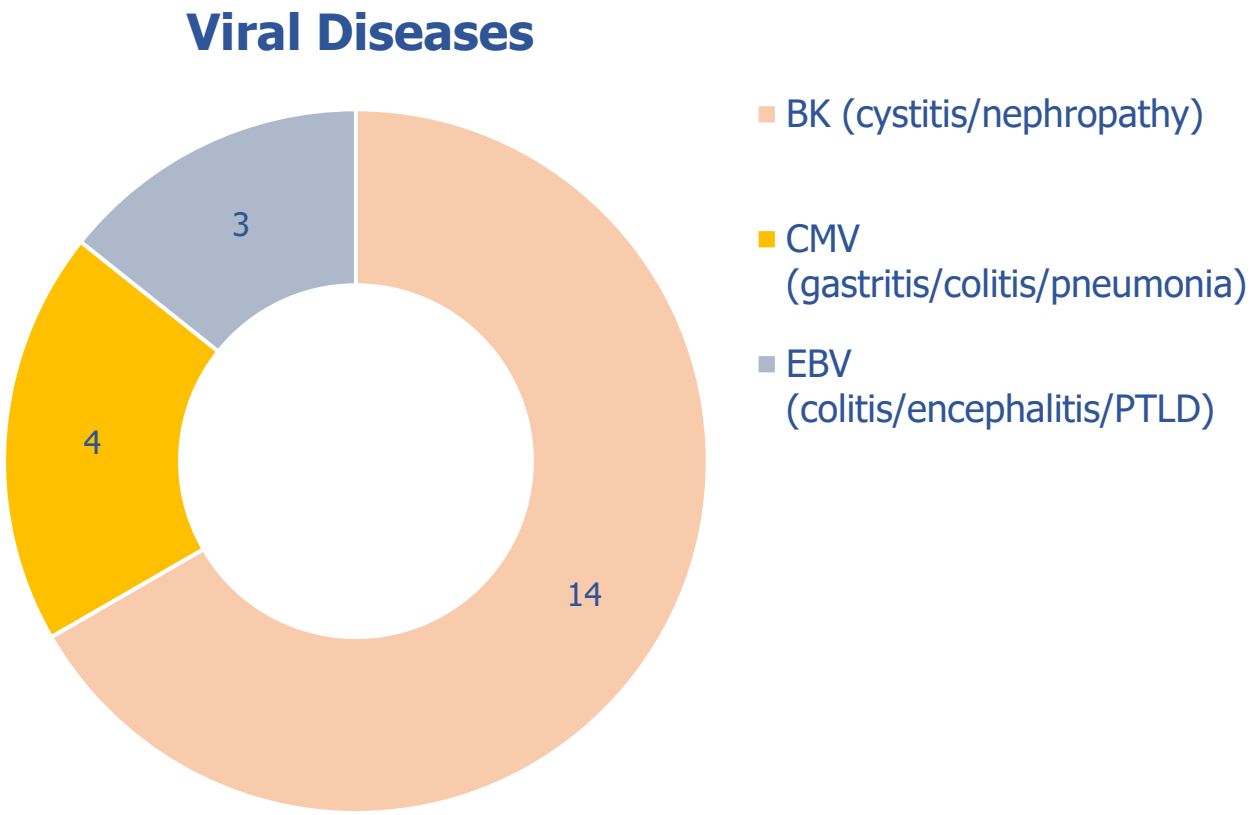


Safety

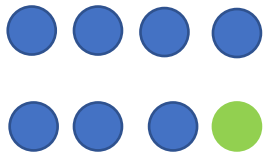
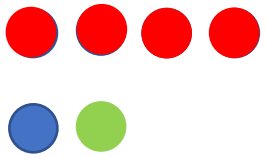
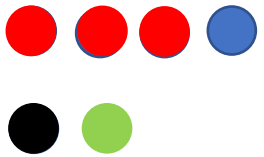
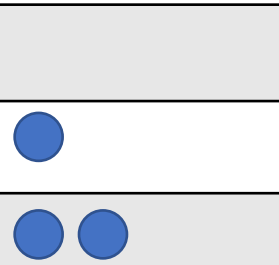
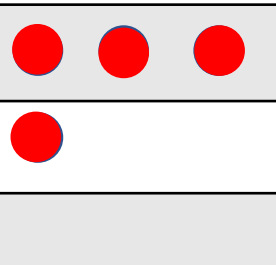
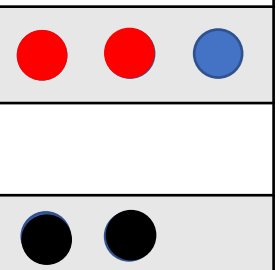
- Multivalent specific-T cell infusion was safe
- Serious infusion-related reactions were not encountered
- No product-related GvHD occurrence / exacerbation

Primary infections

- 29 patients received pSTs for 41 infections in total
- at median 70 days post transplant:
  - **21 viral diseases**
  - **20 viremias/virurias**



Clinical Responses

Patients	1ST Infection		
	CMV	EBV	BKV
1 virus (20 pts)			
2 viruses (6 pts)			
3 viruses (3 pts)			

ORR 97.5%

CR: 35(85.4%) PR: 5(12.2%) NR: 1(2.4%)

- 16/41 infections resolved without (9) or with only a short course (7) of antiviral drug treatment
- 3 BK infections refractory to cidofovir completely resolved post infusion

Complete response

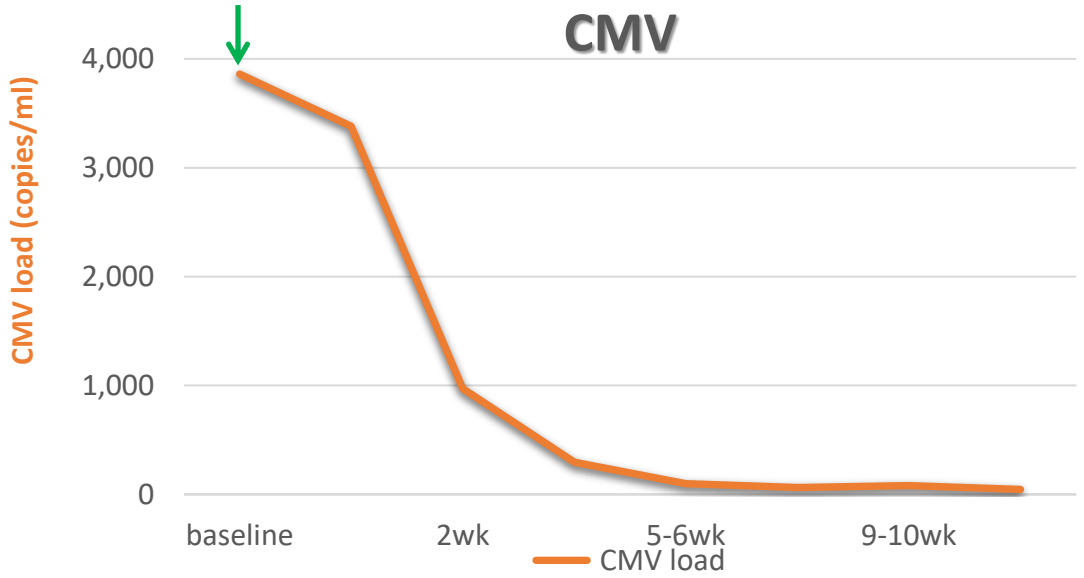
Partial response

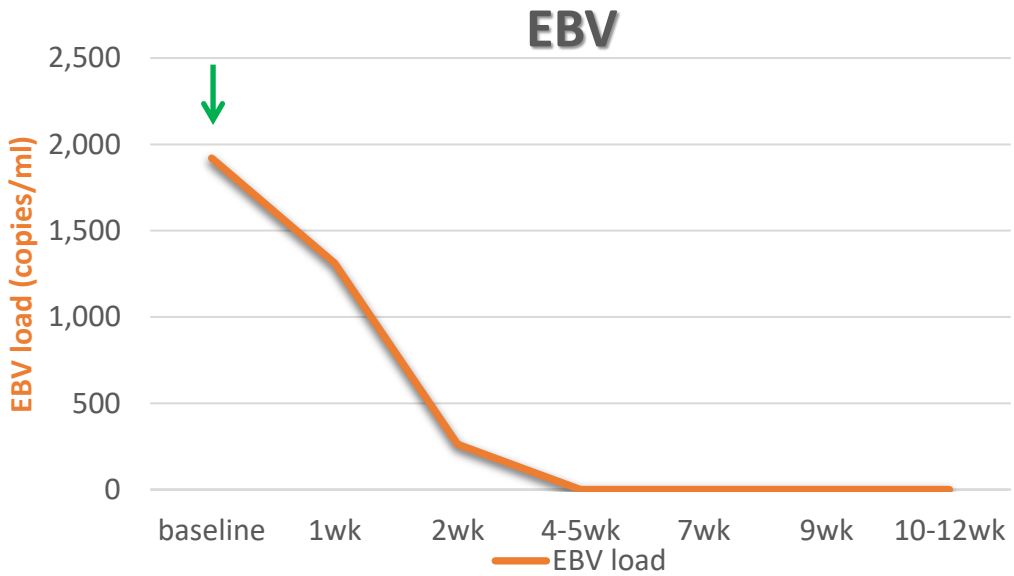
No response

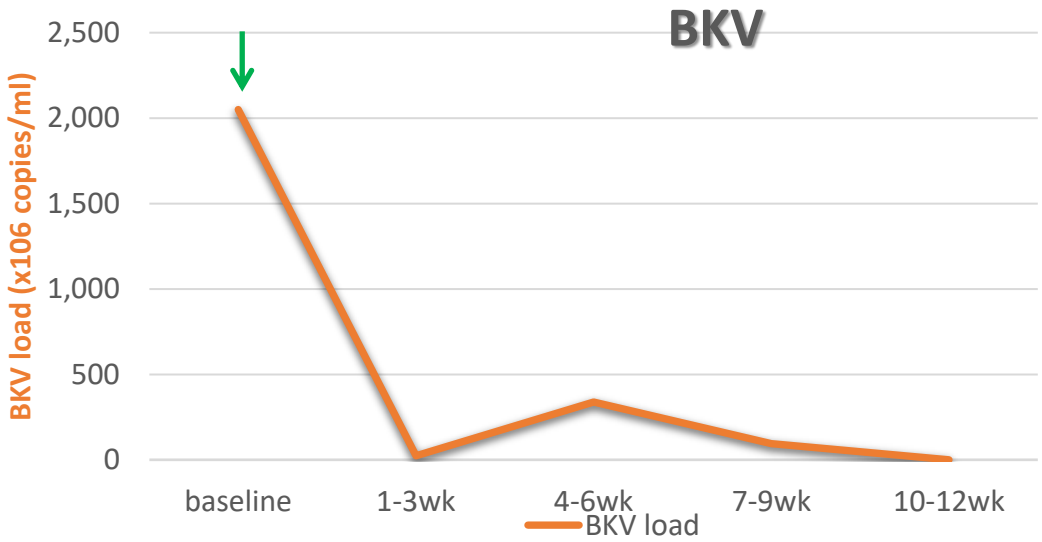
No/limited antiviral drug treatment

Refractory to antiviral drug treatment

Viral load kinetics

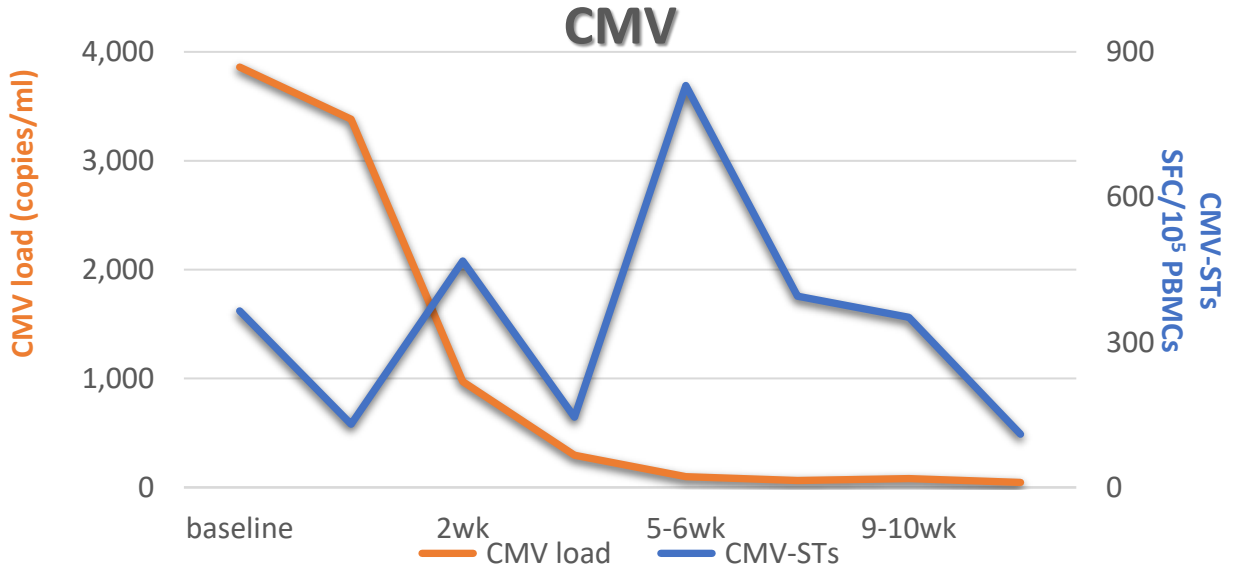


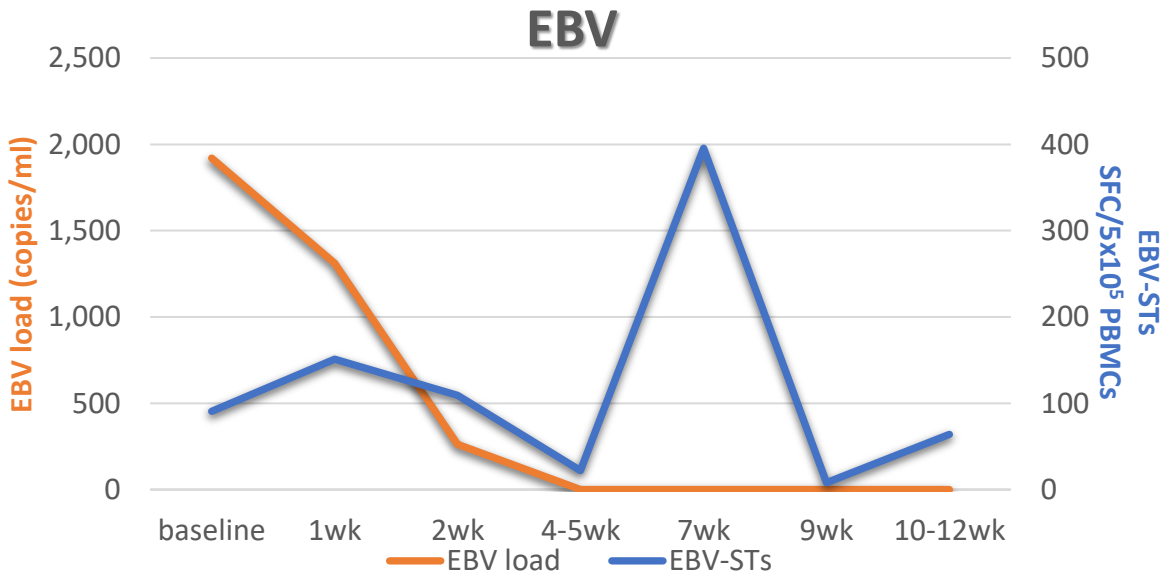


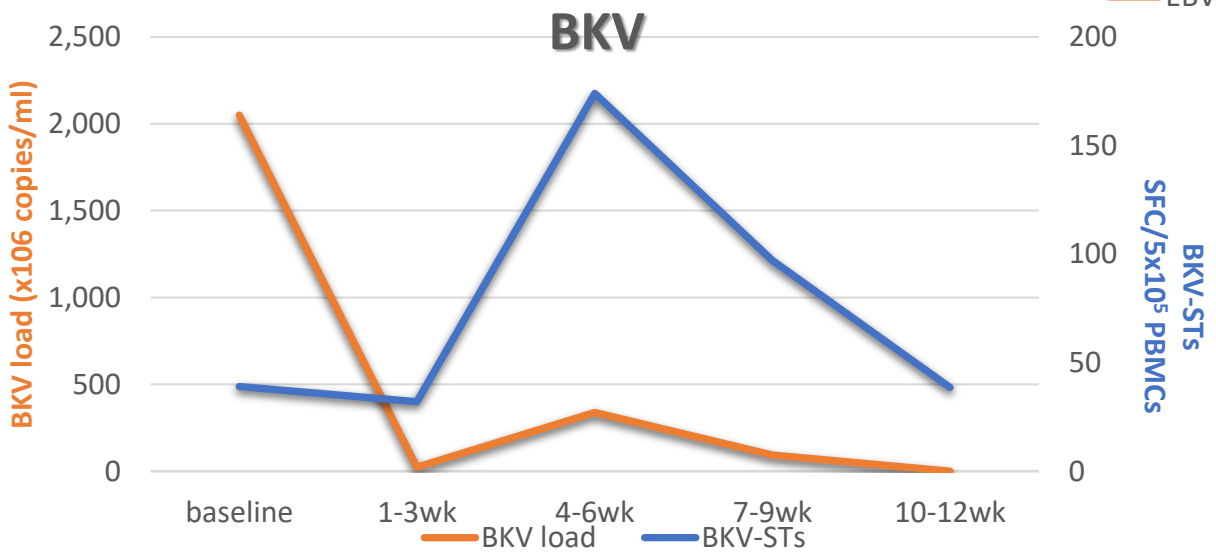


Clinical and viral load responses occurred at median 3 weeks post infusion

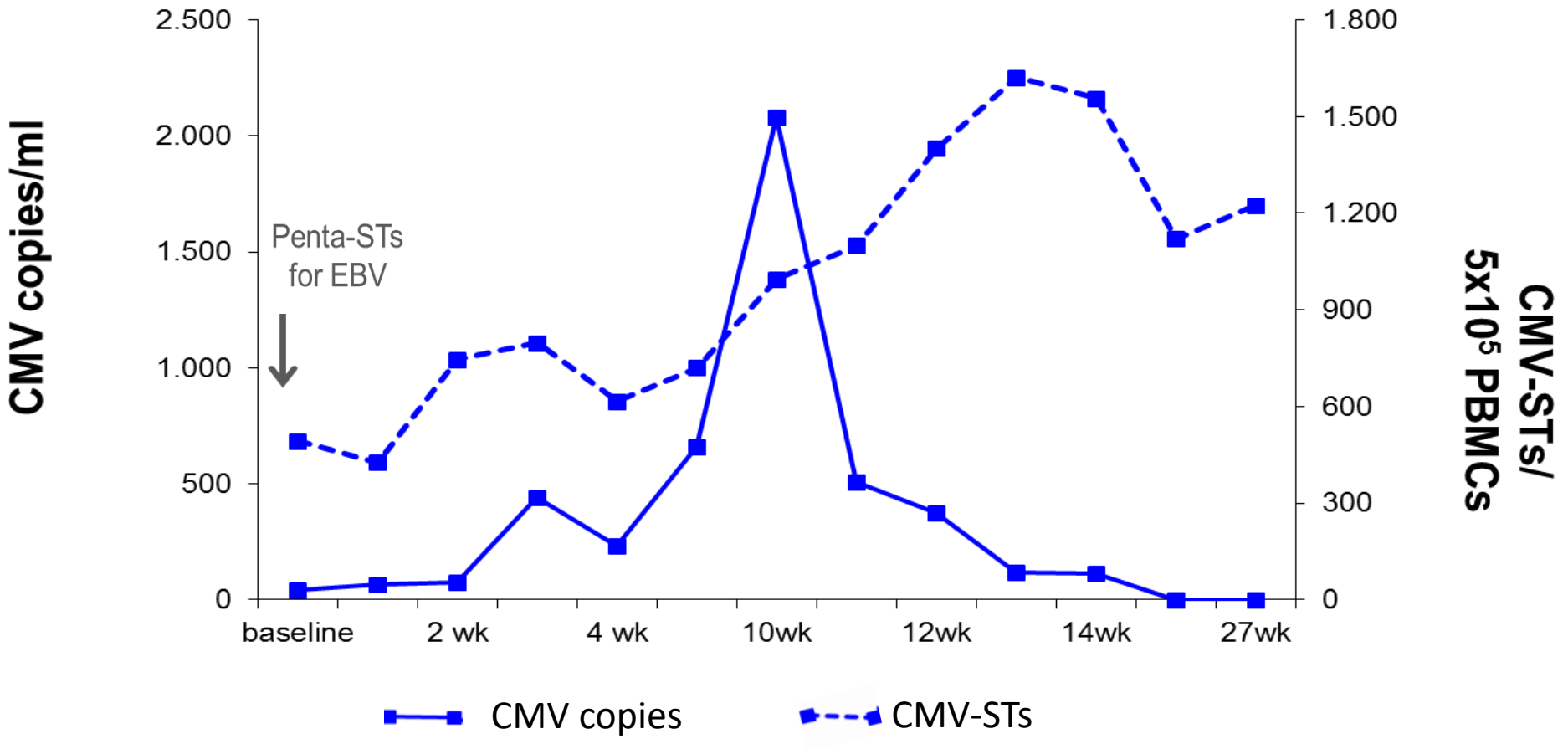
Viral load kinetics inversely correlated with virus-specific Ts expansion



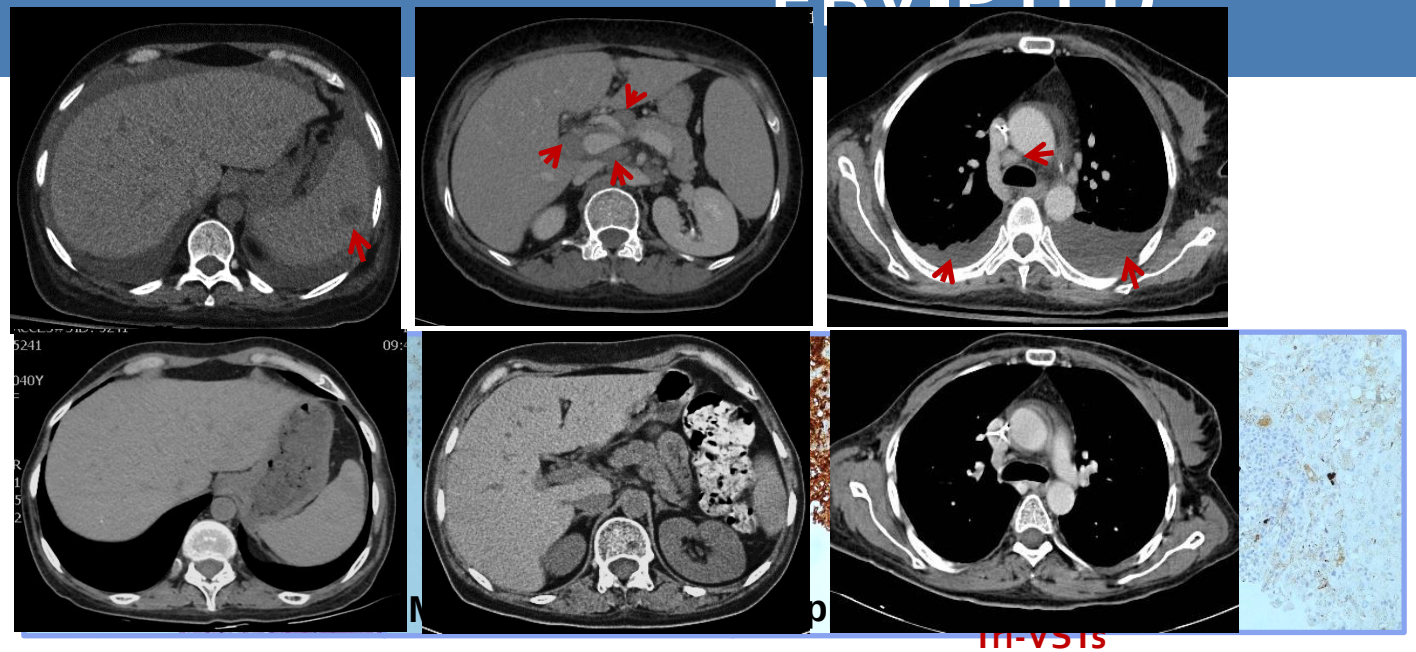


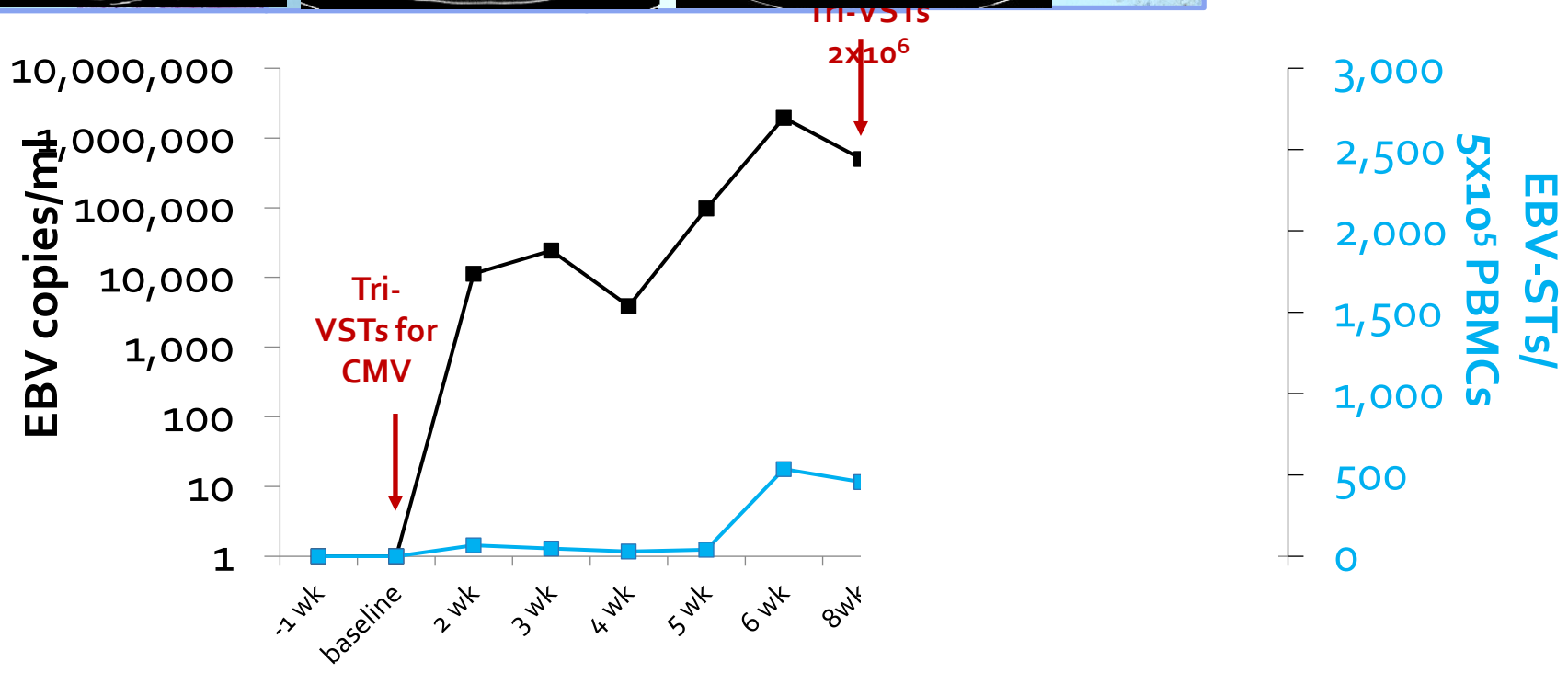


Living drugs : long-lasting protection



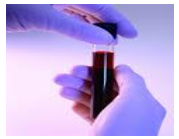
EBV-PTLD



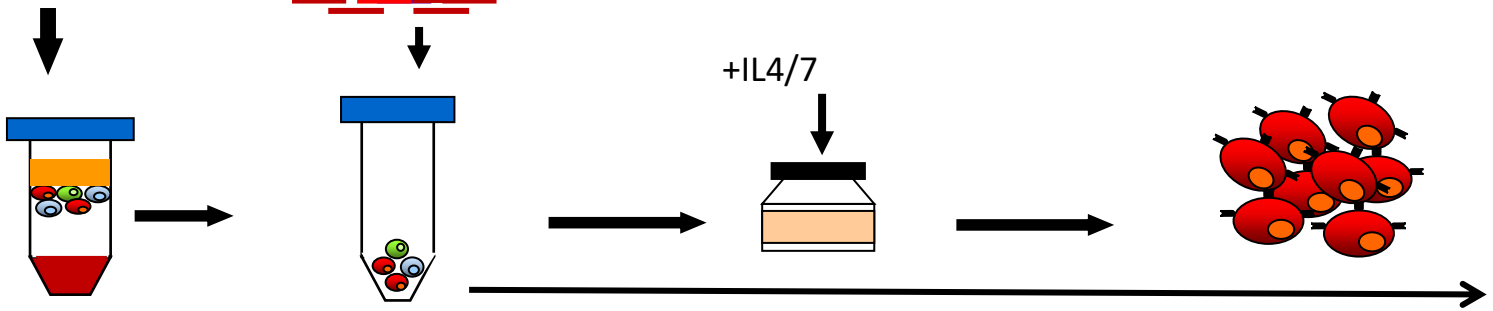

Tri-VSTs 2x10^6
10,000,000
1,000,000
100,000
10,000
1,000
100
10
1
EBV copies/mL
Tri-VSTs for CMV
-1 wk
baseline
2 wk
3 wk
4 wk
5 wk
6 wk
8wk
3,000
2,500
2,000
1,500
1,000
500
0
EBV-STs/ 5x10^5 PBMCs

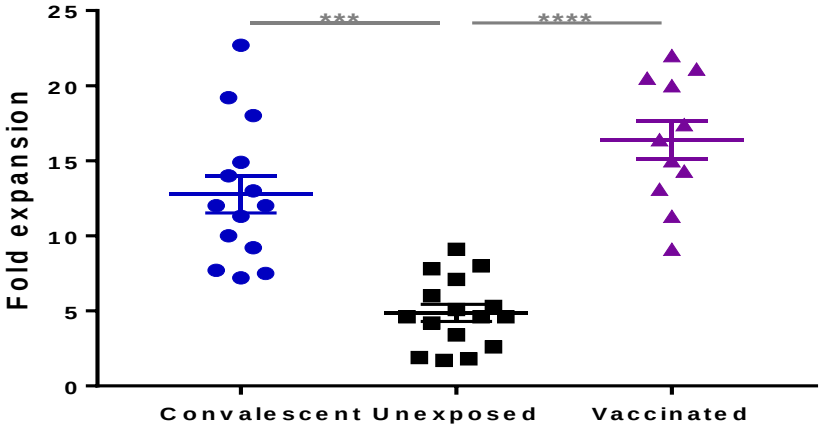
Virus-specific T-cells outside the transplantation setting: SARS-COV-2-specific T cells for severe COVID-19

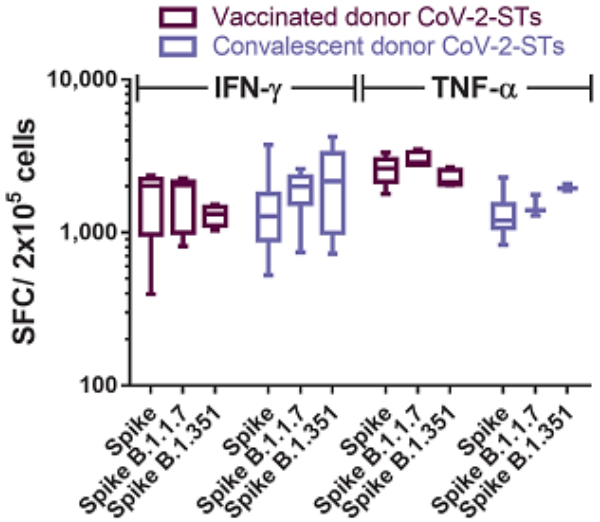
CoV-2-ST generation: proof of concept

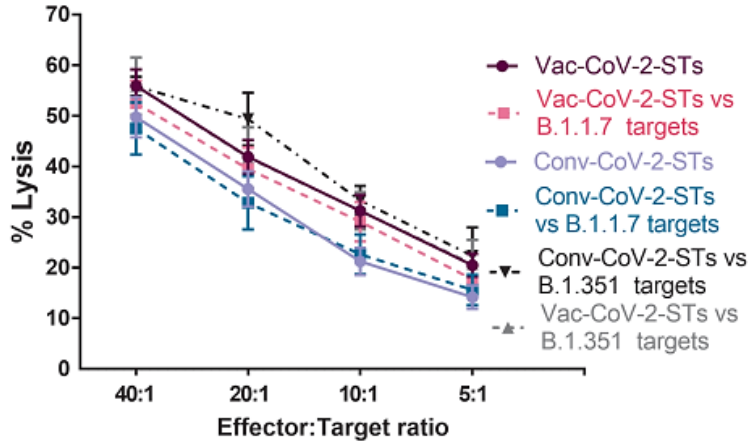


CoV-2 pepmixes (Membrane, Spike & NCAP)









Clinical Infectious Diseases

MAJOR ARTICLE

Vaccinated and Convalescent Donor–Derived Severe Acute Respiratory Syndrome Coronavirus 2–Specific T Cells as Adoptive Immunotherapy for High-Risk Coronavirus Disease 2019 Patients

Penelope-Georgia Papayanni,[1,2] Dimitrios Chasiotis,[1,2] Kiriakos Koukoulias,[1,2] Aphrodite Georgakopoulou,[1,2] Anastasia Iatrou,[3] Eleni Gavriilaki,[1] Chrysavgi Giannaki,[4] Militsa Bitzani,[4] Eleni Geka,[5] Polychronis Tasioudis,[5] Diamantis Chloros,[6] Asimina Fylaktou,[7] Ioannis Kioumis,[8] Maria Triantafyllidou,[1] Sotiria Dimou-Besikli,[1] Georgios Karavalakis,[1] Afroditi K. Boutou,[6] Eleni Siotou,[1] Achilles Anagnostopoulos,[1] Anastasia Papadopoulou,[1,a] and Evangelia Yannaki[1,9,a]

Coronavirus-2-specific T cells (CoV-2-STs) against delta variant COVID-19

nature medicine

Article https://doi.org/10.1038/s41591-023-02480-8

SARS-CoV-2-specific T cell therapy for severe COVID-19: a randomized phase 1/2 trial

Anastasia Papadopoulou[1], George Karavalakis[1,17], Efthymia Papadopoulou[2,17], Aliki Xochelli[3], Zoi Bousiou[1], Anastasios Vogiatzoglou[2], Penelope-Georgia Papayanni[1,4], Aphrodite Georgakopoulou[1,4], Maria Giannaki[1], Fani Stavridou[1], Ioanna Vallianou[1], Maria Kammenou[1], Evangelia Varsamoudi[1], Vasiliki Papadimitriou[1], Chrysavgi Giannaki[5], Maria Sileli[6], Zoi Stergiouda[7], Garyfallia Stefanou[8], Georgia Kourlaba[9], George Gounelas[8], Maria Triantafyllidou[1], Eleni Siotou[1], Antonia Karaglani[10], Eleni Zotou[1,4], Georgia Chatzika[3], Anna Boukla[3], Apostolia Papalexandri[1], Maria-Georgia Koutra[1], Dimitra Apostolou[11] ✉, Georgia Pitsiou[11], Petros Morfesis[12], Michalis Doumas[13], Theodoros Karampatakis[14], Nikolaos Kapravelos[6], Militsa Bitzani[5], Maria Theodorakopoulou[15], Eva Serasli[2], Grigorios Georgolopoulos[1], Ioanna Sakellari[1], Asimina Fylaktou[3], Stavros Tryfon[2], Achilles Anagnostopoulos[1] & Evangelia Yannaki[1,16] ✉

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✉e-mail: apostoloud8@gmail.com; eyannaki@u.washington.edu

I) Assess the **feasibility** of creating a bank of immediately available off-the-shelf SARS-CoV-2-specific T cells (CoV-2-STs) from convalescent donors

II) Assess the **safety and efficacy** of adoptive transfer of CoV-2-STs as treatment for high-risk, hospitalized COVID-19 pts in a randomized, phase I/II trial during Delta variant predominance

GREECE **2021**

George Papanikolaou Hospital

EudraCT: 2021-001022-22

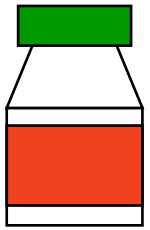
COV-2-ST cell bank for "off-the-shelf" anti-SARS-CoV-2 cells from convalescent donors

N=30 donors, selected to express the most common HLAs in the Greek population

~45ml blood

HLA
A2, 24;
DRB1*1, 15

CoV-2-STs



CoV-2 specificity
DRB1*1

A23, A30; **DRB1*1**, 8

A1, A24; **DRB1*1**, 3

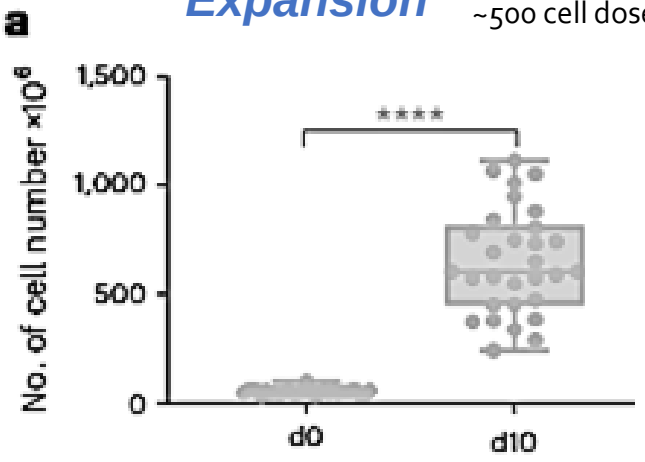
A1, A2; **DRB1*1**, 15

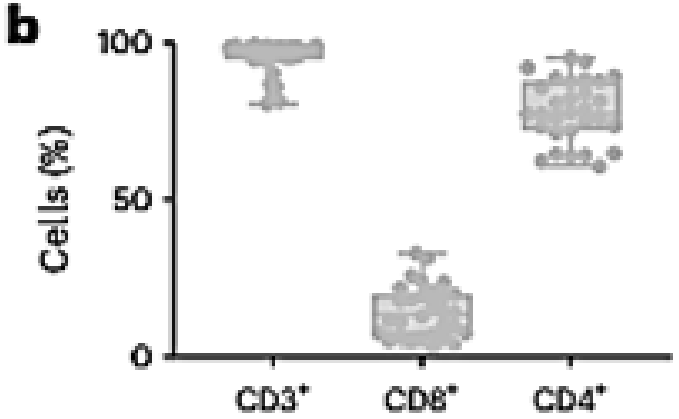
CoV-2-STs expansion & phenotype

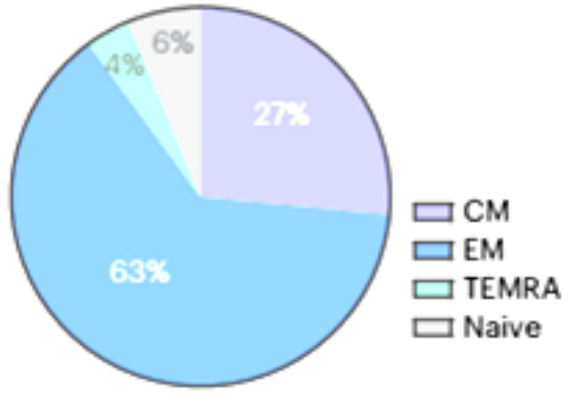
Expansion

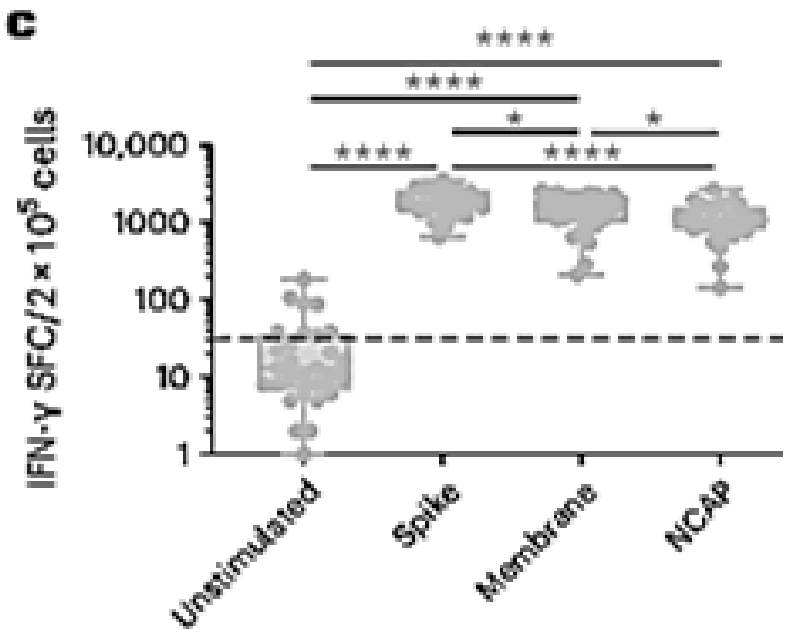
30 products
~500 cell doses in total

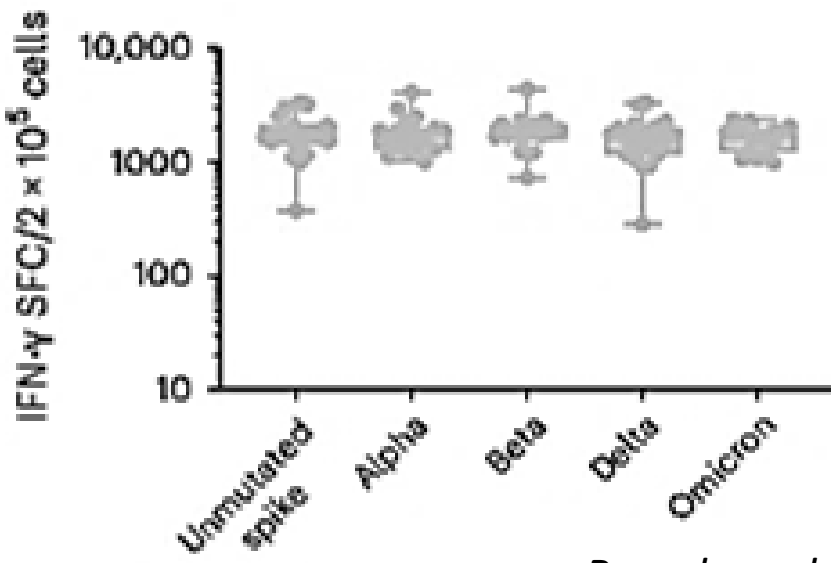
Phenotype











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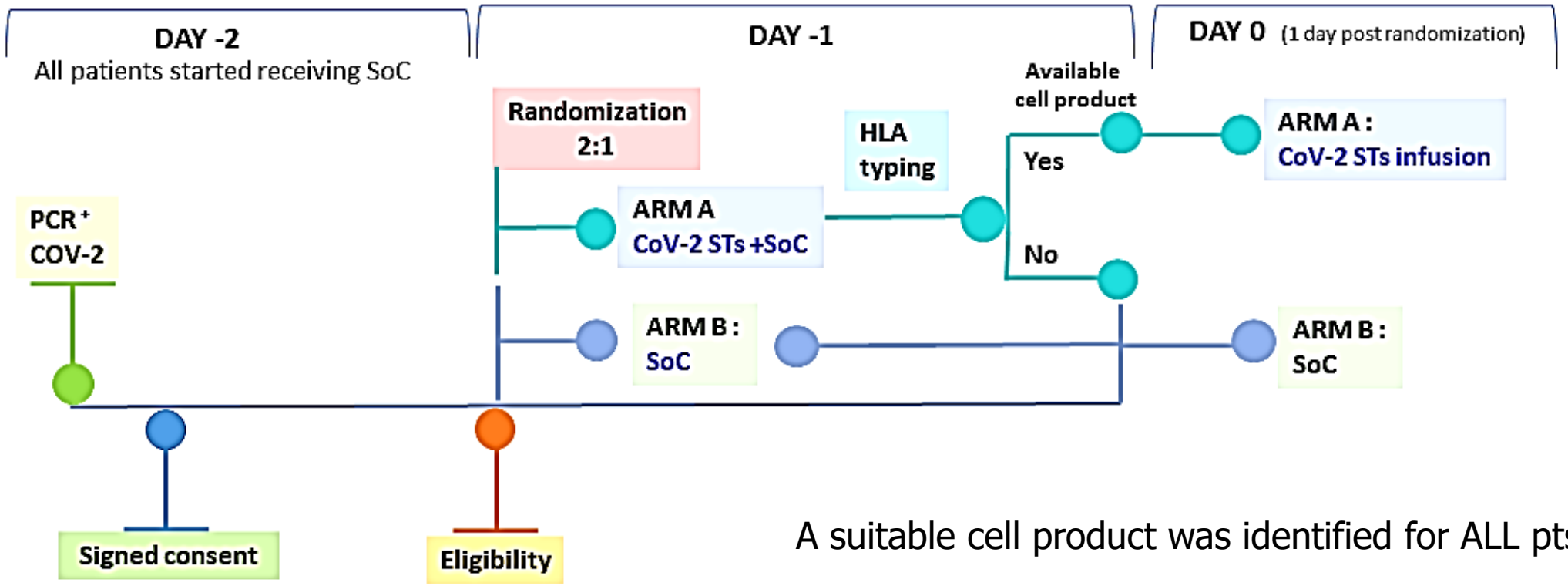
Phase II study design

Inclusion criteria

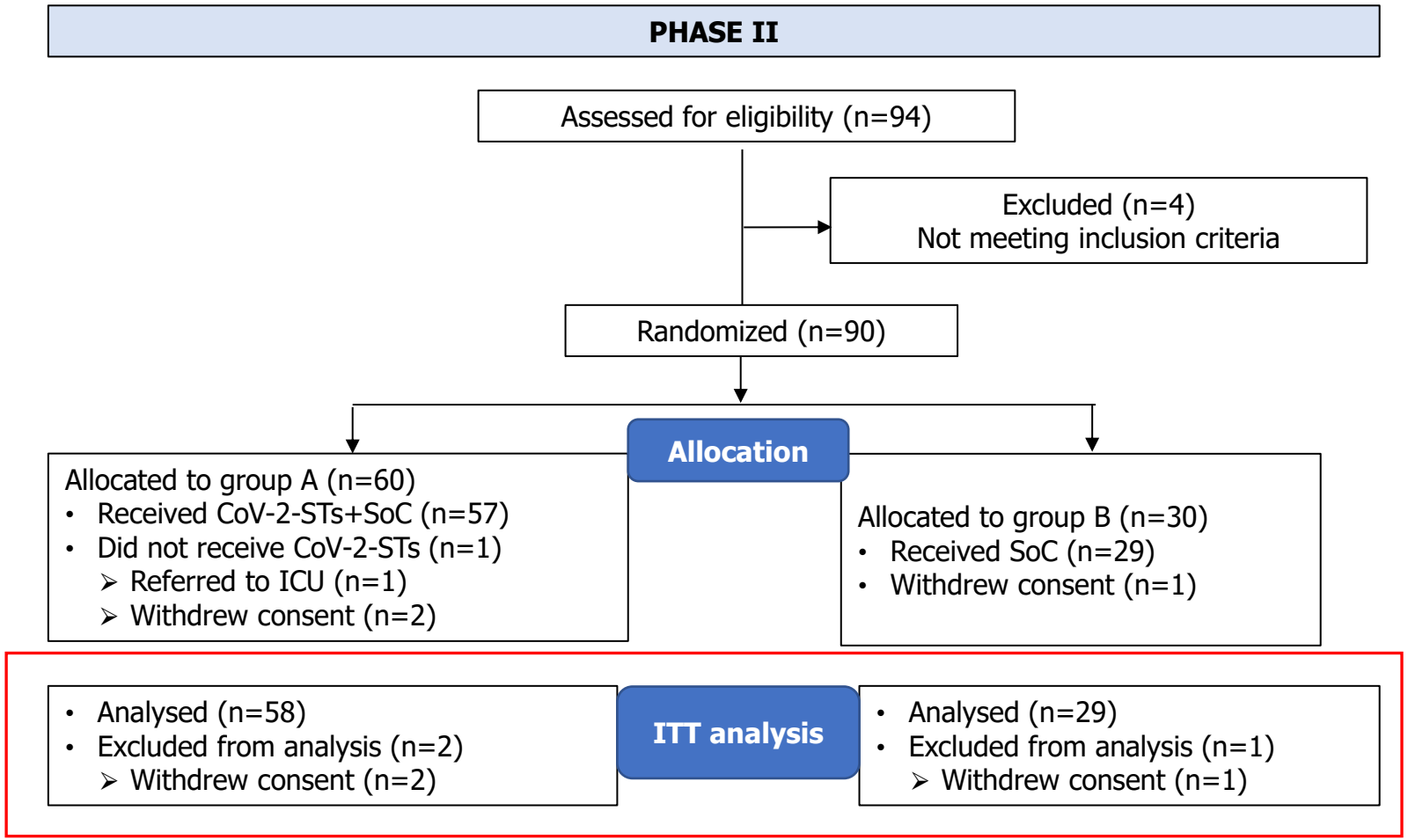
Hospitalized COVID-19 pts	Pneumonia
Within 6 days from the symptoms onset	Lymphopenia (CD3+≤650/µl)
At least 1 elevated inflammatory biomarker *(D-dimers >2, ferritin >1000, CRP >3X, LDH*	



A suitable cell product was identified for ALL pts

Standard of care (SoC): *O_2, heparin, dexamethasone (6mg/day), remdesevir, antibiotics, hydration*

Phase II results



Median age : 57yrs
>50% had at least 2 comorbidities

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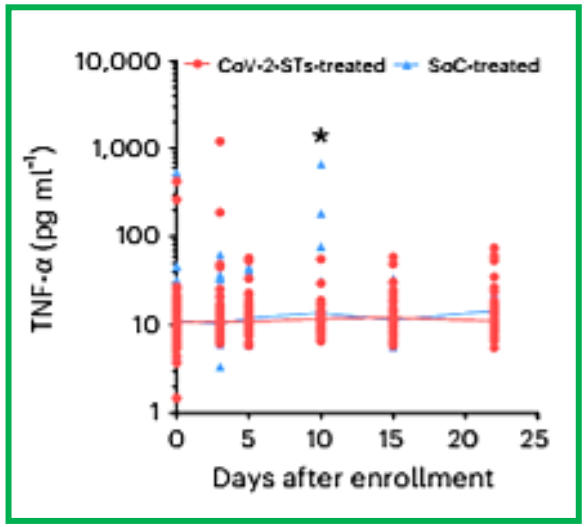
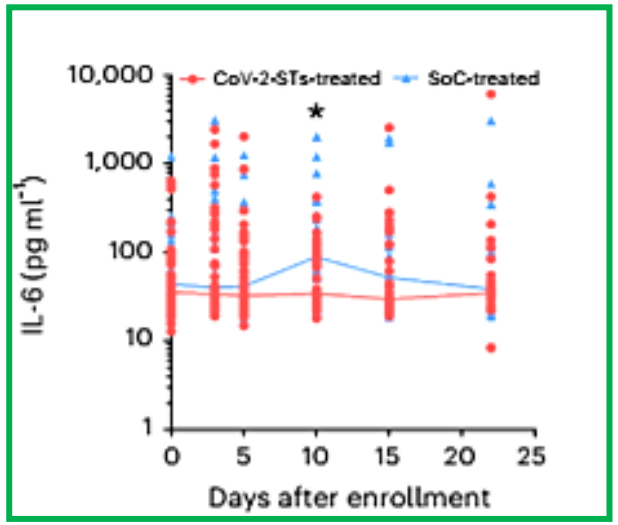
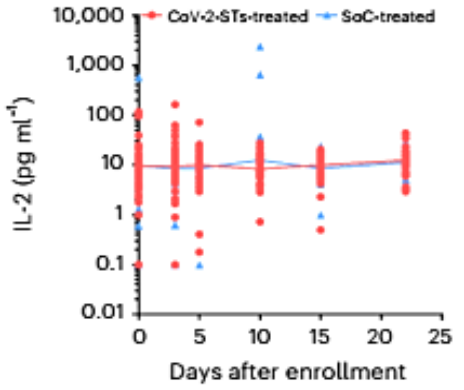
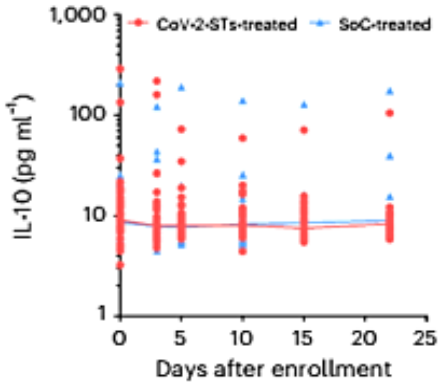
Clinical safety

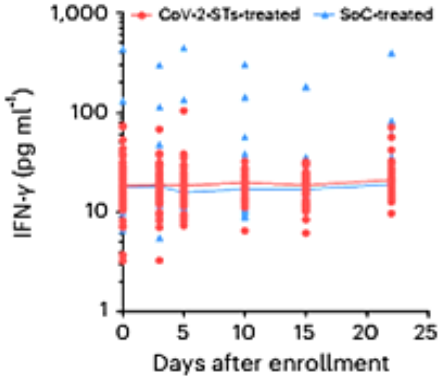
- No infusion-related adverse events
- No GvHD
- Cytokines did not reach levels reported in pts with CAR T cell-induced CRS











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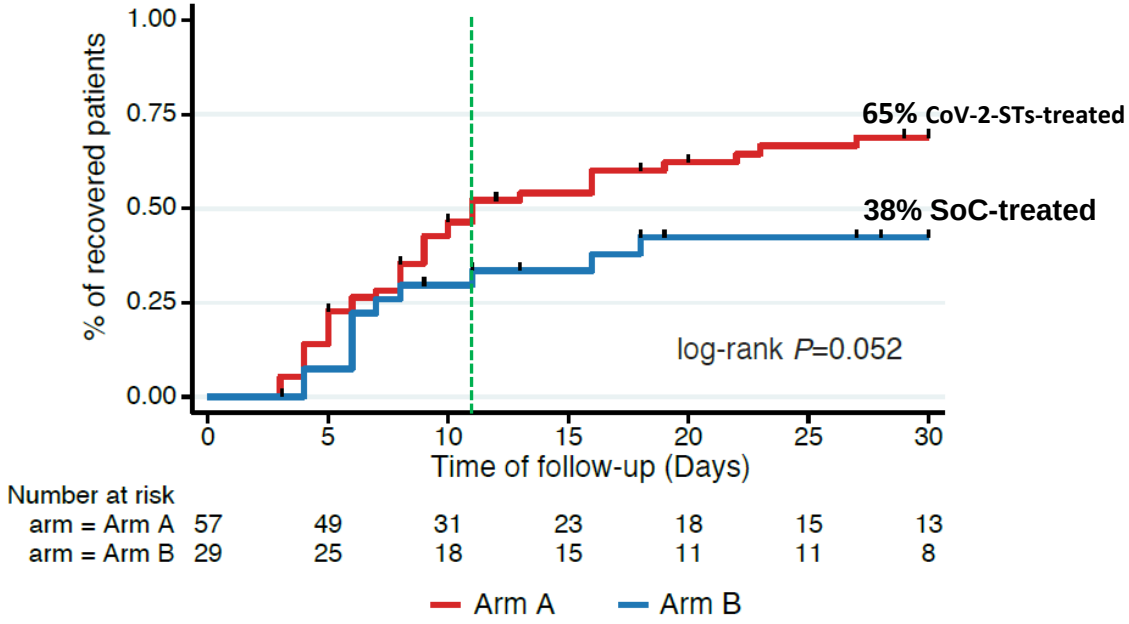
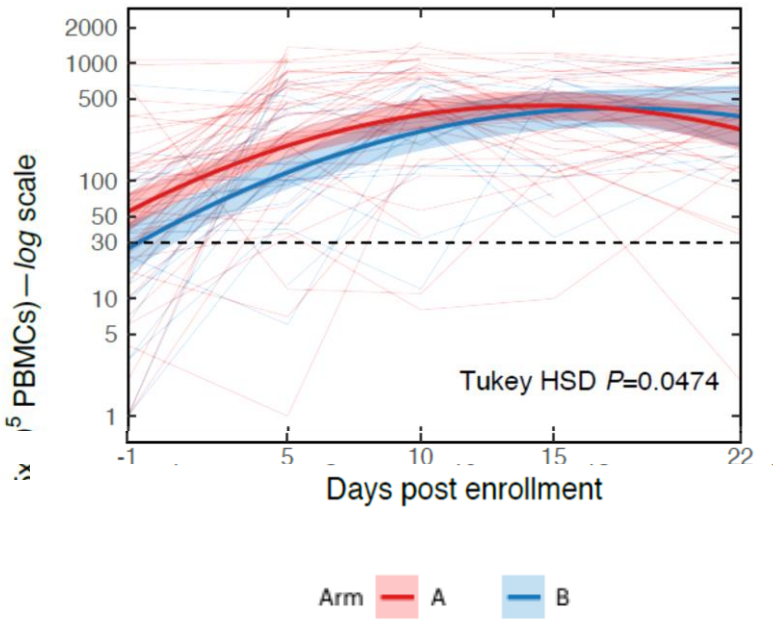
Primary efficacy outcomes: time to recovery/recovery by day 30 and expansion of SARS-COV-2 T cells

WHO 8point ordinal scale

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8





- % Recovered pts : 65% in the CoV-2-ST arm *vs* 38% in the control arm (p=0.017)
- Median time to recovery : 11 d for CoV-2-ST-treated patients, not reached (NR) for SoC-treated patients (*P* = 0.052)
- Rate Ratio for Recovery : 1.71 (95% CI 1.03–2.83; *P* = 0.036)

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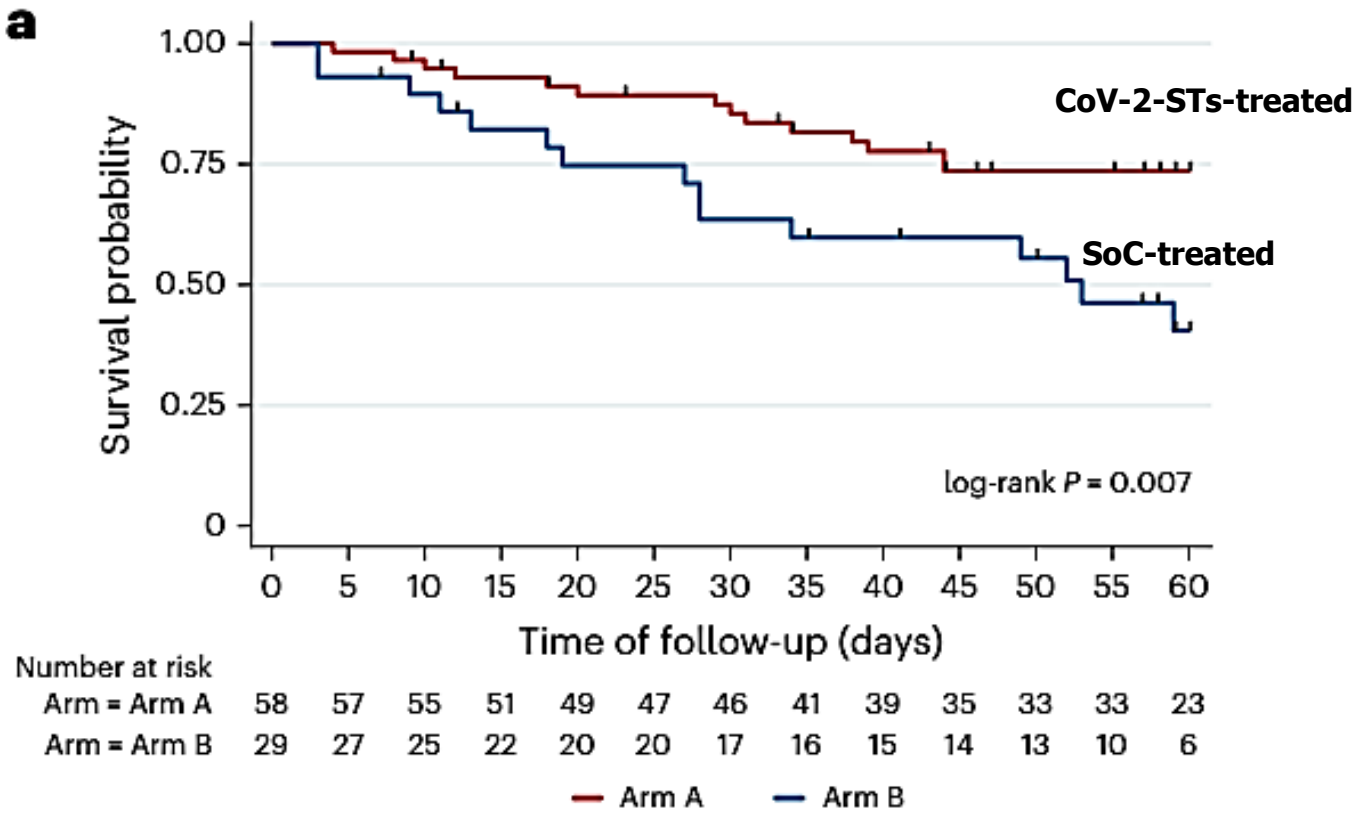
Key secondary endpoint: Survival



Day 60 CoV-2-ST+SoC vs SoC arm:

- Median time to death: NR and 53 days respectively ($P = 0.007$)
- 53% lower mortality risk (24.1% versus 51.7%), risk ratio (RR) 0.47; 95% CI 0.26–0.83; $P = 0.01$
- HR (95% CI) 0.38 (0.18–0.79), $P = 0.009$

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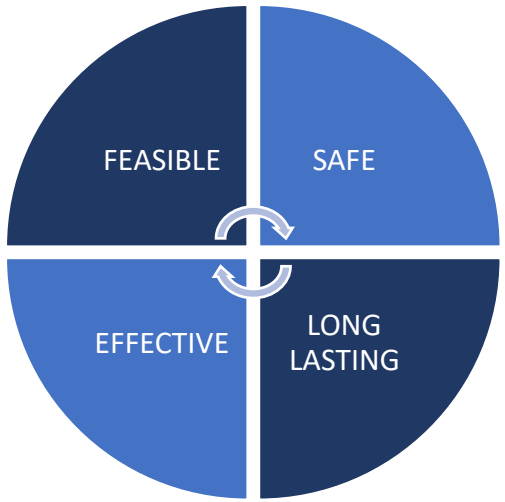
Conclusions

Multivalent pathogen-specific T-cell therapy

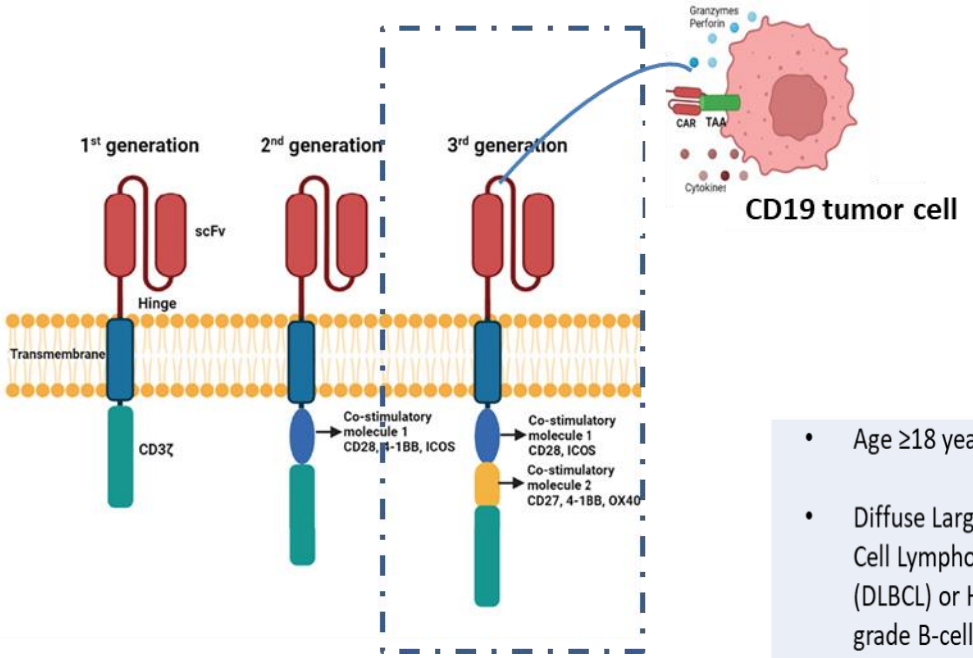


Off-the-shelf immunotherapy with CoV-2-STs

- should be considered as a safe & effective approach for severe COVID-19
- may serve as a platform for future pandemic threats…

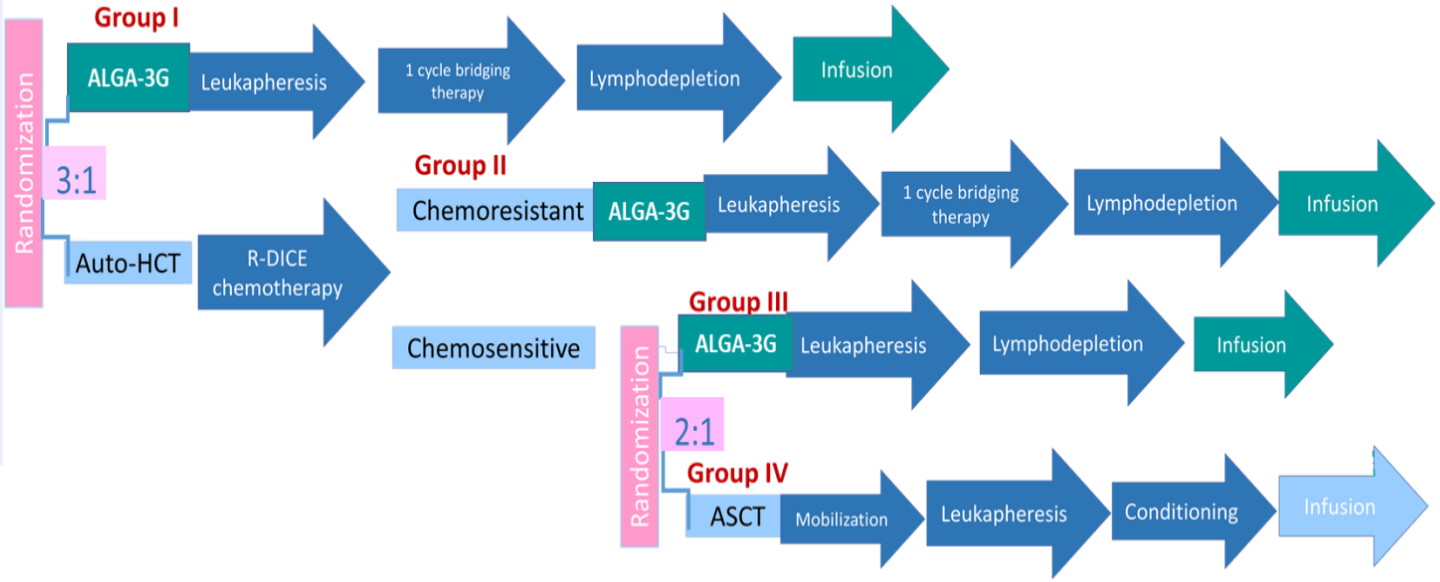
In the absence of a Hospital Exemption and following two study extensions, clinical production has been halted, resulting in several hundred doses of unused T cell products

Point-of-Care (PoC) CAR T cell development for R/R high-grade lymphoma : a phI/II clinical study



RV-SFG.CD19.CD28.4-1BBzeta 3rd generation CAR

- Age ≥18 years
- Diffuse Large B Cell Lymphoma (DLBCL) or High grade B-cell lymphoma (HGBCL)
- Relapsed or refractory disease after 1 line of systemic therapy



Submission to EOF is expected in early 2025 and trial initiation in the summer of 2025

Hospital Exemption vs Centralized Marketing Authorization : competitive or complementary?

HE and CMA : complimentary approaches

- Bridge to Market Authorization
- Addressing Unmet Needs
- Innovation Support
- Prompt Access During Centralized Manufacturing Saturation

The triple A-dilemma

"**A**vailability", "**A**ccessibility" ,"**A**ffordability"

ATMPs have the potential to transform our entire approach to disease treatment, but only if they can be accessed by the patients who will benefit from them

Hospital Exemption : can bridge the gap between innovation and access, ensuring that the life-changing potential of ATMPs directly benefits the patients who need them most.

Comunidad de Madrid | CONSEJERÍA DE SANIDAD

National Legislation Provisions- Spain

Raquel San José Rodríguez, PhD
Advanced Therapies Unit (UTA), Healhcare Office of Madrid
21 November 2024

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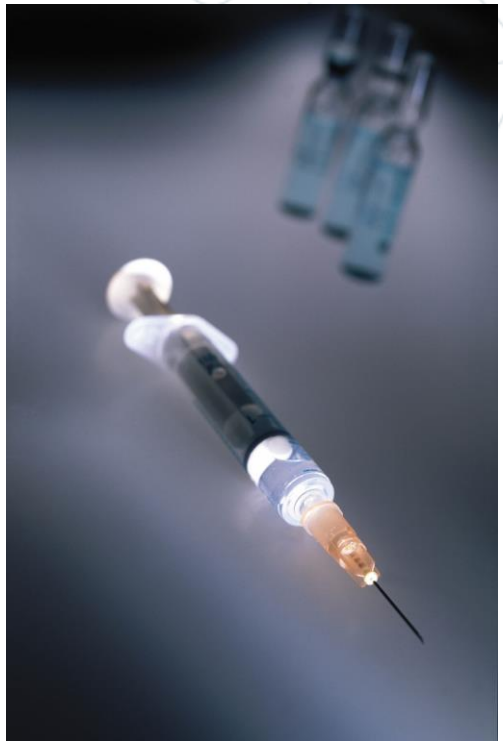
National Legislation Provisions- Spain

- HE clause
- HE clause regulation in Spain
- A case of HE in Spain
- HE challenges
- Conclusions

HE CLAUSE

Established in the European ATMP regulation **EC1394/2007 (Article 28)** with the following conditions:

- prepared on a **non-routine basis**
- according to **specific quality standards**
- used **within the same Member State**
- in a **hospital** under the **exclusive professional responsibility** of a medical practitioner
- in order to comply with an **individual medical prescription** for a **custom-made product** for an **individual patient**



"Manufacturing of these products shall be **authorised by the competent authority** of the Member State. Member States shall ensure that national **traceability** and **pharmacovigilance requirements** as well as the **specific quality standards** referred to in this paragraph are **equivalent** to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required (…)".

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HE CLAUSE REGULATION IN SPAIN

BOLETÍN OFICIAL DEL ESTADO
Núm. 144 Sábado 14 de junio de 2014 Sec. I. Pág. 45068

I. DISPOSICIONES GENERALES

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

6277 Real Decreto 477/2014, de 13 de junio, por el que se regula la autorización de medicamentos de terapia avanzada de fabricación no industrial.

This Royal Decree regulates the conditions for the **authorization** of ATMPs under the HE in Spain, and also the **follow-up requirements** of this authorization under the HE clause.

Competent Authority: **AEMPS**

HE CLAUSE REGULATION IN SPAIN

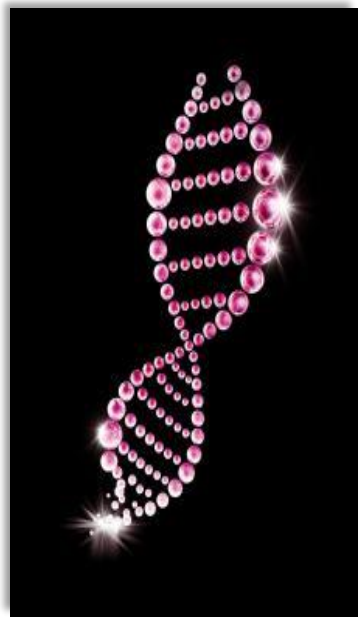
HE AUTHORIZATION

- **Medicinal products**: ATMPs as defined by Regulation EC 1394/2007

- **Holder of the authorization:** The **applicant** must be the manager-director of the **hospital institution** where the product is used. He will also act as product responsable, even if the AH is the Hospital Institution.

- **Requirements for MP to be authorized through HE clause**:

  - Pharmaceutical, pre-clinical and clinical tests results.
  - Quality dossier.
  - Pharmacovigilance system and risk management plan.
  - GMP compliance (manufacturing can take place in a location different from the Holder of the HA Authorization-legal agreements).
  - Product identification: product and authorization holder name.
  - Information requirements for patients.



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HE CLAUSE REGULATION IN SPAIN

Initial **validity** of the authorization: **three years**; it can be renewed periodically for five years, when **pharmacovigilance** and **annual report** requirements are fulfilled.

HE AUTHORIZATION FOLLOW-UP

Traceability

- Data that supports product traceability for 30 years after product expiry date

Pharmacovigilance

- Hospital institution - name of the responsable person (AEMPS, CCAA)
- System in place to compile, process and assess all suspected AR
- Periodic safety reports
- Risk management plan

Annual report

- Number of units and batches manufactured
- Production events

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HE CLAUSE REGULATION IN SPAIN

Nombre	Titular de la autorización de uso	Fecha autorización de uso	Ficha técnica	Prospecto	Material de prevención de riesgos
NC1 – Suspensión celular en plasma autólogo 100-300×10^6 células, jeringa precargada	Hospital Universitario Puerta de Hierro Majadahonda	29-01-2019	Ficha técnica	Prospecto	
ARI-0001 Dispersión para perfusión que contiene 0,1-1×10^6 células/kg	Hospital Clínic de Barcelona	01-02-2021	Ficha técnica	Prospecto	
CEMTROCELL 50.000 células/microlitro – Suspención para implantación	Clínica Cemtro S.A.	31-10-2023	Ficha técnica	Prospecto	
Piel humana obtenida por ingeniería de tejidos 1,0-1,5 x 10^6 / 1,5-3,0 x 10^6 células / lámina apósito impregnado	Hospital Universitario Virgen del Rocio – Sevilla	06-06-2024	Ficha técnica	Prospecto	
ARI0002H 13,5-720 X 10^e6 Células dispersión para perfusión	Hospital Clínic de Barcelona	08-08-2024	Ficha técnica	Prospecto	

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HE CLAUSE REGULATION IN SPAIN

Basic research

"in vitro" tests
API?
Excipients?
Manufacturing process?

Pre-clinical research

Animal models

Clinical studies

Clinical trials (IMPD)

GMPs

HE APPLICATION

CTD + Risk management plan submission

Authorization procedure (AEMPS)

Follow-up

NC1, A CASE OF HE IN SPAIN

2000-2006

Basic research

"in vitro" tests
API
Excipients
Manufacturing process

2000-2010

Pre-clinical research

Animal models
Toxicity
Distribution
Mechanism of action
Efficacy

2013-2019

Clinical studies

Clinical trials (IMPD)

GMPs (2012)

HE APPLICATION

CTD + Risk management plan submission **Nov 2017**

Authorization January **2019**

Follow-up

NC1, A CASE OF HE IN SPAIN

NC1, developed and manufactured by the Puerta de Hierro- Majadahonda Hospital, in the Autonomous Region of Madrid, became the "**first advanced therapy of public ownership**" in Spain, and so the inclusion of an autologous mesenchymal stem cell product manufactured under HE in the **Spanish National Health System service portfolio**, in September 2019.

The **official price** per patient was set for the drug in October 2019.

NC1 is available for all eligible Spanish NHS patients, and it can only be administered by Puerta de Hierro-Majadahonda Hospital…

How to manage?

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NC1, A CASE OF HE IN SPAIN

The Healthcare Office (*Consejería de Sanidad*) of the Region of Madrid established a regional strategy for a **comprehensive management of ATMP** so-called the *Estrategia Regional de Terapias Avanzadas* (ERTA), with the goal to grant equitable patients' access to these therapies.

In the frame of the ERTA, a **Management Plan for each ATMP** (MPATMP) is elaborated with a multidisciplinary approach, in collaboration with clinical experts from Madrid's Net of Advanced Therapies and the coordination of the Advanced Therapies Unit (UTA).

In this case, the **joint effort** between Puerta de Hierro-Majadahonda Hospital, and the Advanced Therapies Unit of the Healthcare Office, lead to NC1 Management Plan.

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SaludMadrid Hospital Universitario Puerta de Hierro Majadahonda

Comunidad de Madrid
CONSEJERÍA DE SANIDAD

NC1, A CASE OF HE IN SPAIN

Centralized Coordination via UTA
Mixed Follow-up Commission NC1

Treatment Center

Patients´Road Map and Treatment application form

Patients´Register **Database**

HE Authorization

Assessment of the Selection Comitee for every application (guarantees equitative treatment access)

Dynamic Dashboard

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HE CHALLENGES

Academic development/HE:

- Specific relevant know-how in regulatory science (STARs Program)
- Fundings
- ATMP Clinical Trials
- Personnel qualification and training
- Co-existance investigation-NHS

EU level

- Improvement **of harmonization in aspects as pre-clinical and clinical data requirements.**
- Promotion of the **transparency** around products licensed under HE, their intended patient populations as well as the extent to which they are used.

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CONCLUSIONS

- HE development of ATMPs is a **need** – **challenges** to face

- **Coordination** and appropiate definition of competences are essential for a suitable implementation of HE regulation and the integration in NHS

- Granting equitable patients' access to these therapies can only be achieved through an adequate **organization of the stakeholders** and the **transparency** of processes

- **HE** is an **essential element** in transferring new ATMPs to patients who need them, specially in case of products with no commercial interests and rare diseases.

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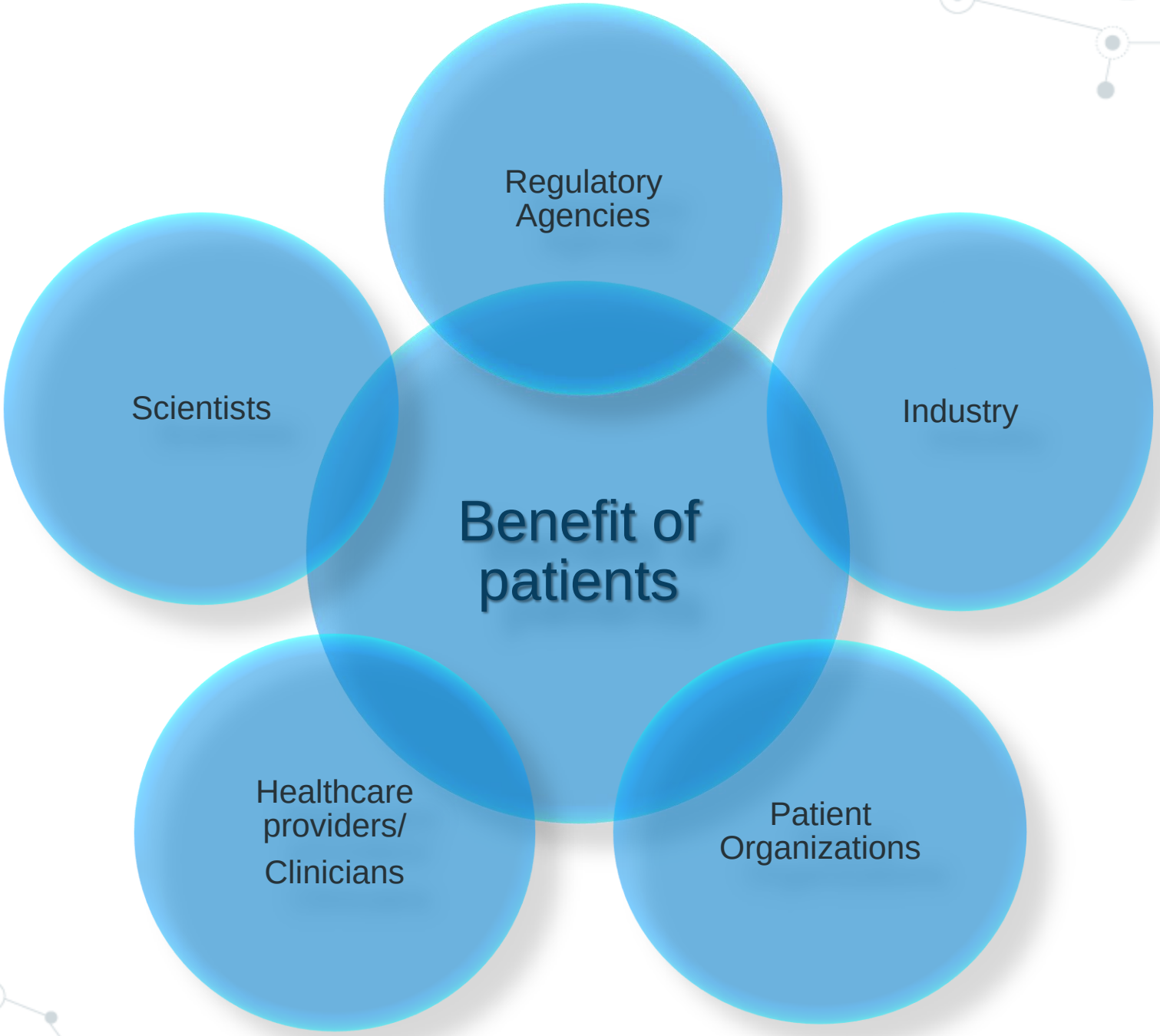

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Thank you very much for your attention

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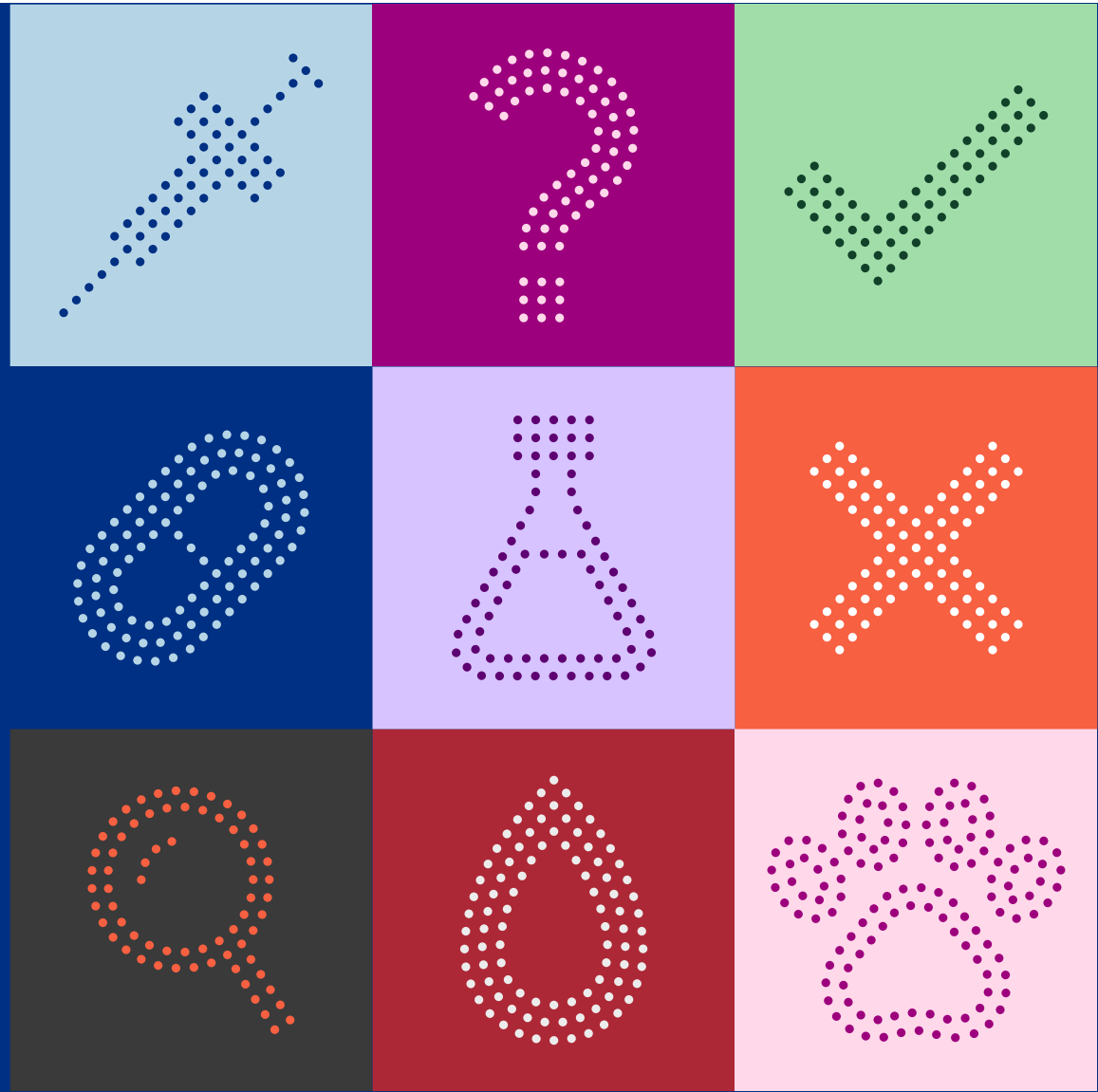
RAVIMIAMET

Hospital exemption in Estonia



Triin Suvi
State Agency of Medicines
Estonia

21.11.2024

Current situation

- Hospital exemption is regulated since January 2022 (Medicinal Products Act)
- ‘Hospital exemption’ means the making and use of a custom-made advanced therapy medicinal product (hereinafter hospital-exemption medicinal product) in Estonia on non-routine basis for an individual patient in a hospital and under the professional responsibility of a medical specialist.
- A hospital exemption authorisation is valid for up to two years or for the treatment of up to ten patients.

  The State Agency of Medicines may renew the validity of a hospital exemption authorisation by up to two years where the hospital-exemption medicinal product is ready for the treatment of up to ten patients

The maker of a hospital-exemption medicinal product may be:

- a central hospital, regional hospital or specialised hospital within the limits of the health care services provided by it;
- a research and development institution or a company connected therewith;
- person holding the right to handle cells or tissues or an undertaking holding a medicinal product manufacturing authorisation.

The user of a hospital-exemption medicinal product may, within the limits of its specialty, be a central hospital, regional hospital or specialised hospital that provides an intensive care or emergency care service.

Hospital exemption authorisation may be applied for, provided that application of the authorisation meets all of the following criteria:

- no authorised advanced therapy medicinal product is available or marketed for the same therapeutic indication and the same patient group;
- there is no clinical trial for the same therapeutic indication and the same patient group in the European Union or the patient has not been included in the trial;
- there is no similar hospital-exemption medicinal product in Estonia for the same therapeutic indication and the same patient group;
- existing therapies have been exhausted and using the medicinal product for the treatment of an individual patient is medically justified;
- there is sufficient research data on the medicinal product, which allow for assuming that the benefits of the medicinal product outweigh possible risks related to using the medicinal product;
- the custom-made medicinal product is made in Estonia on non-routine basis for an individual patient in a hospital and under the professional responsibility of a medical specialist;
- the making of the medicinal product complies with the good manufacturing practice of advanced therapy medicinal products;
- pharmacovigilance and the traceability of the medicinal product meet the requirements established for hospital-exemption medicinal products.

Problems

RAVIMIAMET

- There are hospitals/companies who do not want to apply for marketing authorisation in the future. Therefore hospital exemption is not worth the investment if they can only treat 10 patients.
- There may be ATMP-s with marketing authorisation in EU, but they are not available to the patients in Estonia. Manufacturers are not willing to come to our market because of the size of the population. Therefore medicines are actually not available for the patient.
- Using limitation „ the same therapeutic indication and the same patient group“ rules out too many potential medications.

Change proposals

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Hospital exemption authorisation may be applied for, provided that application of the authorisation meets all of the following criteria:

- no **similar authorised advanced therapy medicinal product** is available or **sufficiently marketed in Estonia**;
- there is no clinical trial with the **similar advanced therapy medicinal product in Estonia** or the patient has not been included in the trial;
- existing therapies have been exhausted **or** using the medicinal product for the treatment of an individual patient is medically **favourable**
- In case authorization ends, licence holder must compile and submit a plan for the further efficacy monitoring until the end of the monitoring period of the patients. They have to submit the data collected at the end of monitoring period.
- ~~there is no similar hospital-exemption medicinal product in Estonia for the same therapeutic indication and the same patient group.~~

Change proposals

RAVIMIAMET

- A hospital exemption authorisation is valid for up to two years.
- **Authorisation can be extended for up to five years** if the quality of the medicinal product is ensured, the risk-benefit ratio remains favourable and the requirements for the making and use of the medicinal product have been met. **Hospital exemption authorization may be extended repeatedly.**

Authorisation will not be extended when upper requirements are not met and if **similar authorised advanced therapy medicinal product has become sufficiently available in Estonia**

Change proposals

RAVIMIAMET

The holder of a hospital exemption authorisation:

- submits in every **twelve** months after the issue of the authorisation the data regarding the making and using of the hospital-exemption medicinal product;
- submits in every **twelve** months after the issue of the authorisation a list of the adverse reactions in using the hospital-exemption medicinal product along with a description of the adverse reactions and an assessment of a link between the adverse reaction and the medicinal product;

RAVIMIAMET

Thank you!

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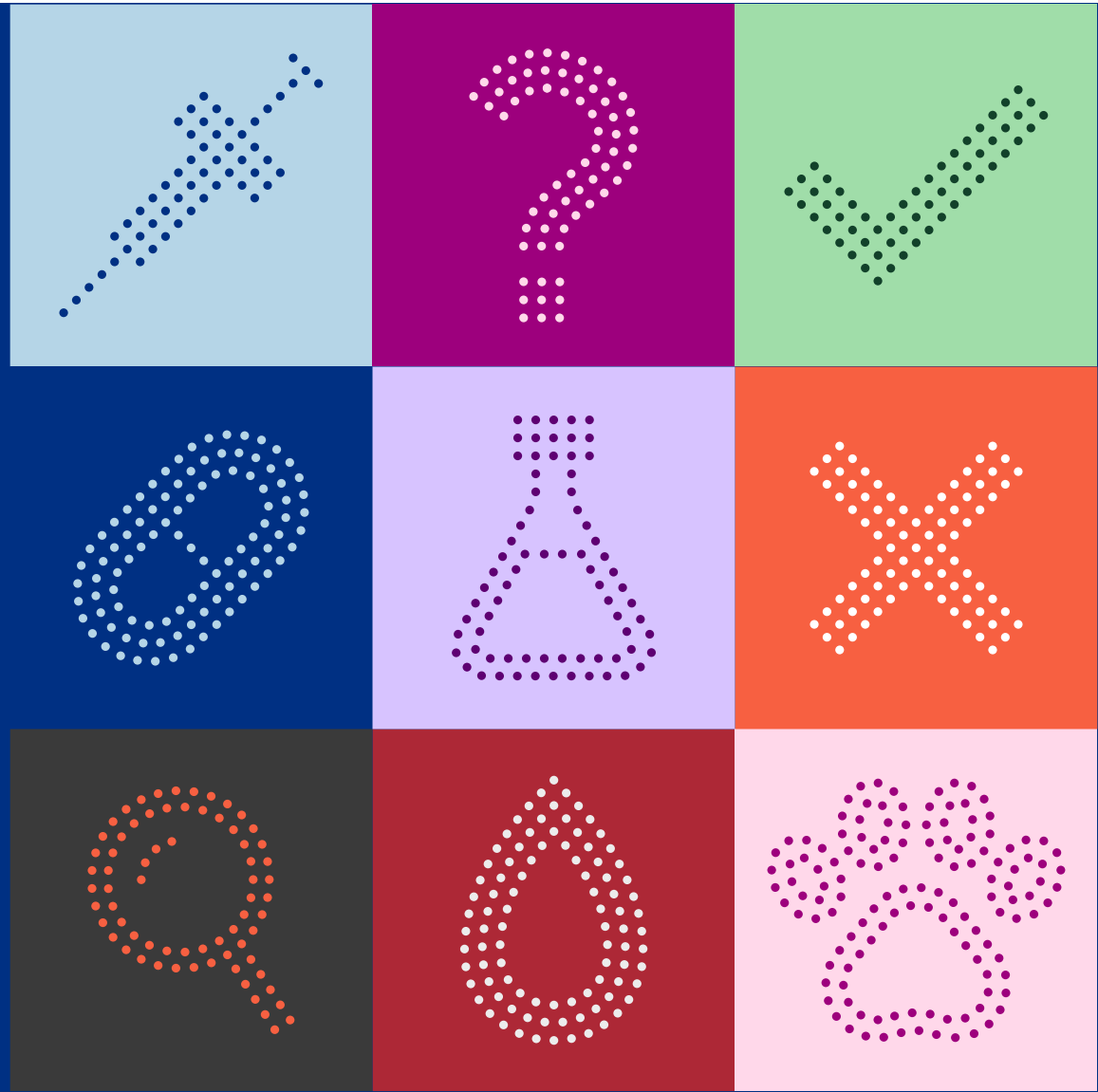


Experiences in the Netherlands with Hospital Exemptions (HEs) of ATMPs

Dr. Babs O. Fabriek
Sr. Clinical assessor Medicines Evaluation Board

Organisations involved in the Hospital exemption procedure:

- Health and Youth Care Inspectorate
- Medicines Evaluation Board (**MEB**)
- National Institute for Public Health and the Environment

Key principles in NL

- Prepared under specific quality standards
  -> compliance with GMP for ATMP requirement
- 'Non-routine' manufacturing
  -> prepared specific for one patient (autologous or allogeneic) on a small scale
  -> quantitative approach (in principle for max. 10 pts/yr)
- Unmet medical need
  -> No access to alternative treatment options (registered product or in clinical trial)
- (Some) evidence of a therapeutic effect and acceptable safety.
- Use in hospital—but applicant can be hospital or company.
- Under the exclusive responsibility of a medical practitioner.
- HE is valid for 1 year, extension possible.
- Reimbursement not available

Application/Reporting

Application:

- Pre- application meeting optional
- Mandate of Health Inspectorate, partially outsourced to MEB.
- Time of assessment app. 6 weeks, Qs can be raised.

Reporting:

- Report/Overview: number of treated patients, manufacturing specifications, efficacy results and side effects.
- When?
  - after approval period or maximum number of treatments.
  - at time of request for extension with 1 year.
  - at end of HE.

Status

- 2010-2024: 23 initial applications, 4-6 applications and/or renewals per year
- Most of the requests were awarded (>80%)
- HE granted for 1-50 patients
- Broad scope of indications: oncology, transplant setting, and debilitating diseases
- Applicants: mainly academia, only 2 companies.
- Type of ATMPs: sCTMP (majority) and TEP- autologous and allogenic

Unmet medical need – how is it defined in practice?

- Limited treatment options
  - Either authorised or unauthorised
  - Based on short response to prior treatments, foreseen that patient(s) will not respond; want to have alternative available

- Prognosis:
  - Life-threatening acute disease
  - Survival
  - Comorbidities of patients not eligible for standard additional treatment options

Clinical trails?

- HE vs possible clinical trial, examples:
  - HE as bridge until (new) clinical trial is open for respective indication
  - Strict inclusion criteria of current clinical trial(s) for respective indication
  - No clinical trial possible for current indication because of disease rarity
  - HE as bridge until marketing authorisation: offer ATMP outside of study context to patients

Thus far, **no product related safety signals have been** registered

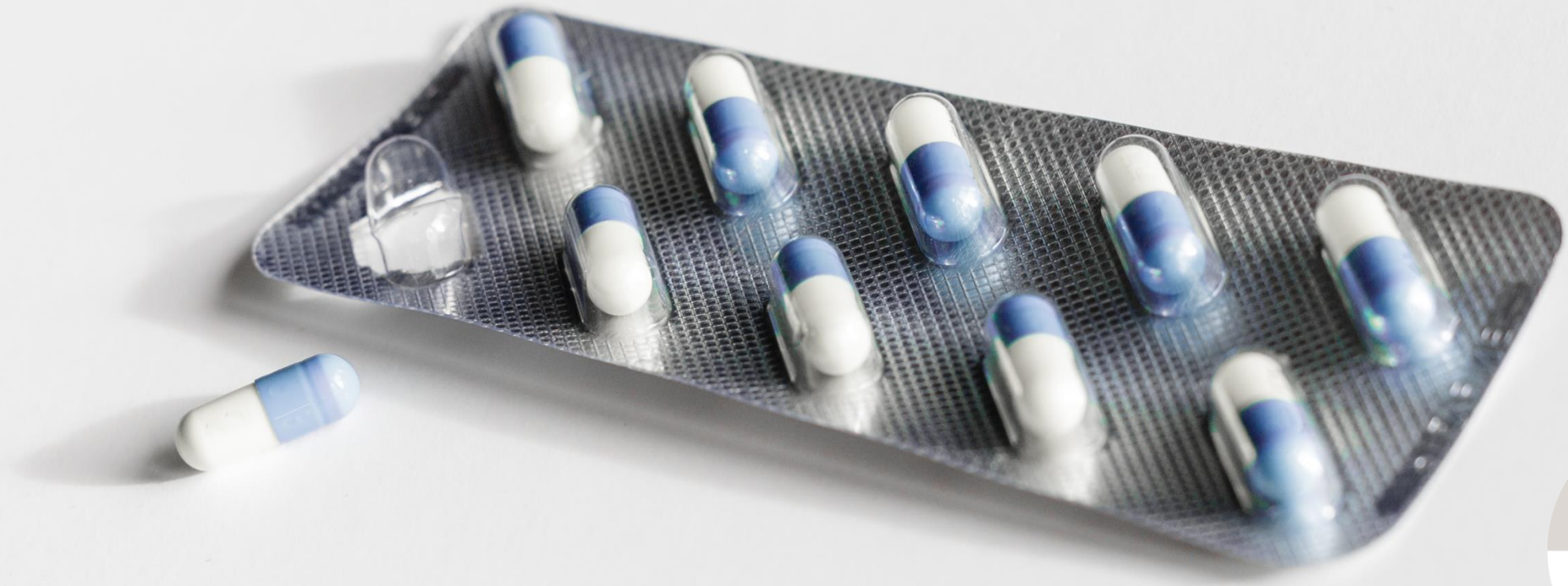
- Diversity in quality and detail in **yearly reporting**.
- Meaningful **assessment of safety (and efficacy)** of treatment under HE remains **challenging**.
- **Low patient numbers** preclude strong conclusions.
- Scientific uncertainty vs patient access!

Conclusions and challenges

- Size of the HE population (non-routine?)
- Is a clinical trial really not possible?
- Definition of unmet medical need?
- Comprehensiveness of the yearly reporting
- Call for transparency for patients and developers → 2025 publication

CBG MEB

MEDICINES EVALUATION BOARD



GOOD MEDICINES USED BETTER

bo.fabriek@cbg-meb.nl

2009- National implementation of legislation:

The Dutch Medicines Act (Geneesmiddelenwet) states in §40.3d and §40.8 that it is allowed to provide unlicensed ATMPs, under the approval of the IGJ, according to a **prescription** for a made-to-order medicine used on a **non-routine basis** for a particular patient on a hospital basis according to specific **quality standards** and **within the same Member State under the exclusive professional responsibility of a physician**.

Available at: https://wetten.overheid.nl/BWBR0021505/2022-01-31

Agence nationale de sécurité du médicament et des produits de santé

Implementation of the Hospital Exemption in the EU

Presentation of French Legislation Provisions

Manon THAMIN - ANSM
Regulatory assessor pharmacist
21 novembre 202

Hospital Exemption Scope Article 3.7 of Directive 2001/83/EC

- **Excluded Products from the scope of Regulation (EC) No. 1394/2007 concerning ATMPs falls under "Hospital Exemption" (regulated by Member States, referred to as MTI PP in France):**

for ATMPs that are:

- Prepared on an non-routine basis, according to specific quality standards,
- Used within the same Member State,
- Administered in a hospital,
- Under the exclusive professional responsibility of a physician,
- To comply with an individual medical prescription,
- Custom made for an individual, specific patient.

Hospital exemption : requirements

- The production of these products must be authorised by the competent authority of the Member State (ANSM in France).
- Member States ensure that national requirements for traceability and pharmacovigilance are equivalent to those at the EU level for authorised ATMPs as specified under Regulation (EC) No. 726/2004 of the European Parliament and Council.
- Specific quality standards equivalent to community-level standards for ATMPs.

General framework in France

- **The EU regulation allows Member States to establish their own regulations.**

  - Law No. 2011-302 of March 22, 2011: Adaptations of national law to EU regulations regarding health, labor, and electronic communications.
  - Decree No. 2012-1236 of November 6, 2012: Pertains to advanced therapy medicinal products.
  - Ordinance of February 4, 2013: Sets the content requirements for initial, renewal, or modification authorisations for ATMPs prepared occasionally and the establishments or organisations that prepare these products.
  - Law No. 2016-41 of January 26, 2016: Modernisation of the healthcare system – Article 155 IV (MTI PP import/export in the context of interventional research).
  - Decree No. 2016-1536 of November 15, 2016: Pertains to ATMPs (including MTI PP traceability).
  - Law No. 2021-1017 of August 2, 2021: Related to bioethics (Article 36 II) – MTI PP in the context of the same medical intervention.
  - Decree No. 2022-193 of February 16, 2022: Concerns perioperative ATMPs prepared occasionally.

Definition of MTI PP (Advanced Therapy Medicinal Products prepared occasionally):

- **Article L. 5121-1 17° of the Public Health Code:**

  - An ATMP
  - manufactured in France
  - following specific quality standards,
  - used in a hospital in France,
  - under the responsibility of a physician,
  - **to execute a specific medical prescription, designed for an individual, specific patient.**

Manufacturing process

- **Authorisation is granted by ANSM to establishments or organisation :**
  - Private pharmaceutical establishments (L. 5124-1).
  - Public establishments (excluding hospitals) or non-profit organisations that may create pharmaceutical establishments within their organisation (L. 5124-9-1).
  - Hospitals and specific organisations: EFS, CTSA, EPST, Foundations, associations (L4211-9-1).
- Activities may include **preparation, storage, distribution**, or **dispensing** of MTI PP, and **import** and **export** activities only for clinical trials (modified by article L. 4211-9-1 and Decree No. 2016-1536 of November 15, 2016).
- **Inspections conducted by ANSM.**
- **GMP specific for MTIPP which are similar to UE GMP for ATMPs (Part IV)**
- **New provision**: Preparation, distribution, and administration of MTI PP within hospitals in the context of the same medical intervention as the tissue or autologous cell collection involved (II of article L.4211-9-1).

Responsabilities

- The responsible person ensures compliance with regulations concerning the quality and safety of MTI PP.
- Site activity manager oversees compliance with Good Manufacturing Practices (GMP) specific to ATMPs.
- Role of Pharmacy Units in hospitals : they are authorised by regional health agencies for appropriate conditioning of the product (Articles R. 5126-9 and R. 5126-25 of Decree No. 2019-489 of May 21, 2019).

MTI PP authorisation

- **In France, regulation requires an authorisation for medicinal product**
- **Authorisation request must be submitted to ANSM by authorised establishments or organisations only.**
- **Dossier content as per Article R. 5121-210 of the Public Health Code:**
  - General information,
  - Quality data,
  - Safety data (e.g., viral safety),
  - Non-clinical data,
  - Clinical data.
  - Clinical studies may be exempted if justified by specific conditions, such as the absence of alternative treatments at the time of the request and if the treatment presents the only chance to avoid a fatal outcome in the short term.
  - Safety and efficacy monitoring plan (Risk Management Plan).

- **Modifications impacting MTI PP Quality/Safety/Efficacy require express authorisation from ANSM; other modifications may proceed under implicit authorisation (declarative).**

Authorised MTI PP examples

- **Autologous mesenchymal stromal cell concentrate amplified in vitro** (4 patients a year)**,**
  - Radiation skin burns, severe thermal skin burns

- **Allogeneic anti-Adenovirus T lymphocytes (10 to 15),**
  - Alternative treatment of adenoviruses occurring after allogeneic Hematopoietic Stem Cell transplantation

- **Autologous epidermal layer (5 to 10),**
  - Complement to autologous skin grafting for the recovery of severe burns

- **Autologous concentrated bone marrow for orthopaedic use (100),**
  - Early epiphyseal aseptic osteonecrosis

Authorised MTI PP examples

- **Allogeneic anti-Cytomegalovirus T lymphocytes (10 to 15),**
  - Alternative treatment of adenoviruses occurring after allogeneic Hematopoietic Stem Cell transplantation
- **Allogeneic anti-Epstein Barr T lymphocytes (10 to 15),**
  - Alternative treatment of adenoviruses occurring after allogeneic Hematopoietic Stem Cell transplantation
- **Allogeneic human mesenchymal stromal cells (MSC) derived from adipose tissue,**
  - Graft-versus-host disease
- **Allogeneic epidermal layer**
  - Recovery of severe burns

New provision : Peri-Operative autologous MTI PP:

- Article 36 II of Law No. 2021-1017 of August 2, 2021 (bioethics law).
- Modifies article L.4211-9-1 of the Public Health Code: adds a provision for the preparation, distribution, and administration of an MTI PP within hospitals as part of the same medical intervention as the tissue or autologous cell collection involved.
- Preparation and distribution must be conducted **under the responsibility of an establishment duly authorised to prepare a MTI-PP**.
- MTI PP must comply with **GMP standards** and be supported by a written contract with the establishment performing the **preparation** and **distribution**.
- ANSM verifies the necessity for the patient of an administration within the same medical intervention.

Peri-Operative autologous MTI PP :Decree n° 2022-193

MTIPP Concerned:

- Autologous,
- Including combined innovative therapy medicinal products,
- And not subject to substantial manipulation: this therefore excludes gene therapy medicinal products, as they are substantially manipulated.

All steps from collection to administration are carried out within a single medical intervention and in the same room.

- Written Contract/Document: a written contract or document must be concluded in advance by the authorised establishment or organisation with the hospitals that performs the preparation and distribution of the MTIPP.

- PR (Responsible Person) : extended responsibilities: additionally tasked with ensuring compliance with peri-operative MTIPP provisions, particularly ensuring that the hospitals meets its obligations regarding the preparation and distribution of peri-operative MTIPP.

Peri-Operative autologous MTI PP : Decree n° 2022-193

- Authorisation Request for the establishment :
  - Name of the healthcare facility,
  - Floor plan of the room where peri-operative activities are conducted,
  - Description of equipment and materials used,
  - List and qualifications of personnel,
  - Written contract/document,
  - List of procedures.
- ANSM authorisation includes a statement about conducting, within a single medical intervention, the collection of autologous tissues or cells, preparation, distribution, and administration of the MTIPP.
- Specific Provisions for modifications of the initial authorisation, Activity Report
- MTIPP Authorisation Request: elements aimed at establishing the necessity and safety of administering this medicinal product within the same medical intervention, specifically:
  - Clinical benefit for the patient,
  - Control of risks associated with the preparation.

Conclusion :

- **High standards** for hospital exemption in France
- Is there a need for more **harmonisation** between EU Member States on Hospital exemption **?**
- Article 2 of the Commission's proposal for the revision of the directive 2001/83/EC

Thank you for your attention!

Implementation of the Hospital Exemption in the EU and its role in boosting innovation and patient access to innovative therapies

The San Raffaele Telethon Institute for Gene Therapy of Milan experience

November 21st, 2024

Maria Pia Cicalese, MD PhD

San Raffaele Telethon Institute for Gene Therapy (SR-Tiget)

Pediatric Immunohematology

Bone Marrow Transplantation Unit

San Raffaele Scientific Institute, Milan, Italy

DISCLOSURE/STATEMENTS

The San Raffaele Telethon Institute for Gene Therapy (**SR-TIGET**) is a joint venture between Fondazione Telethon and Ospedale San Raffaele (OSR).

Gene therapy for ADA-SCID was developed at SR-TIGET, licensed to GSK in 2010 assigned to Orchard Therapeutics in 2018.

Strimvelis received marketing authorization in the EU in 2016, which was transferred to Fondazione Telethon in 2023 and is not approved in the US.

Libmeldy received marketing authorization in the EU in 2020 and as Lenmeldy in 2024 in the US.

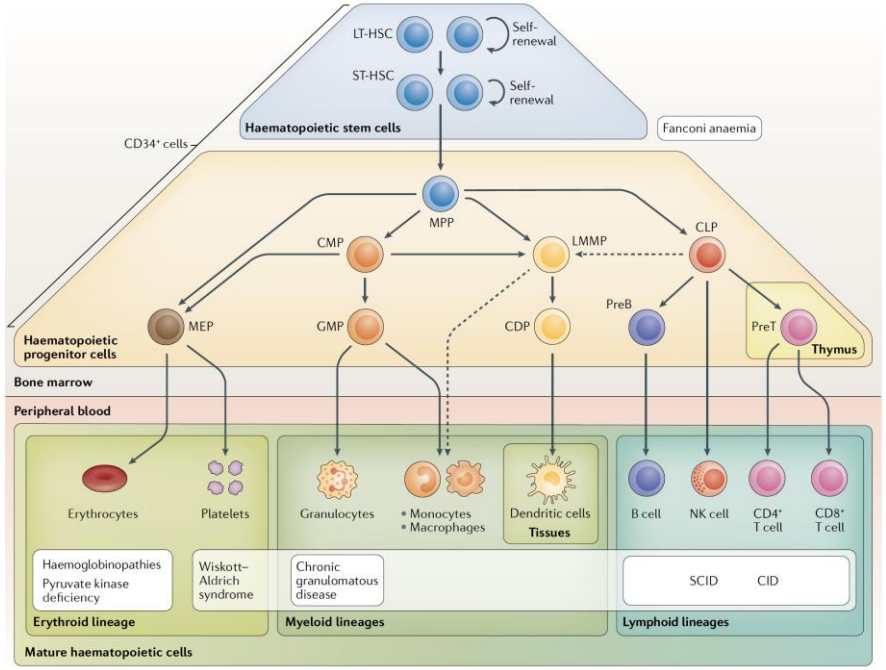
Lentiviral vector-based gene therapy for Wiskott-Aldrich Syndrome (WAS), Metachromatic Leukodystrophy (MLD), beta thalassemia (BTHAL) and Mucopolysaccharidosis I (MPSI) developed at SR-TIGET were licensed to Orchard Therapeutics in 2018 and 2019.
MP Cicalese is an investigator of the above clinical trials and is the PI of the Strimvelis Registry, RIS and RMMs studies.

Gene therapies for WAS, BTHAL, MPSI are still in development, they are not approved for use in patients outside of clinical trial or pre-approved compassionate use.

HSPC gene therapy for inborn errors

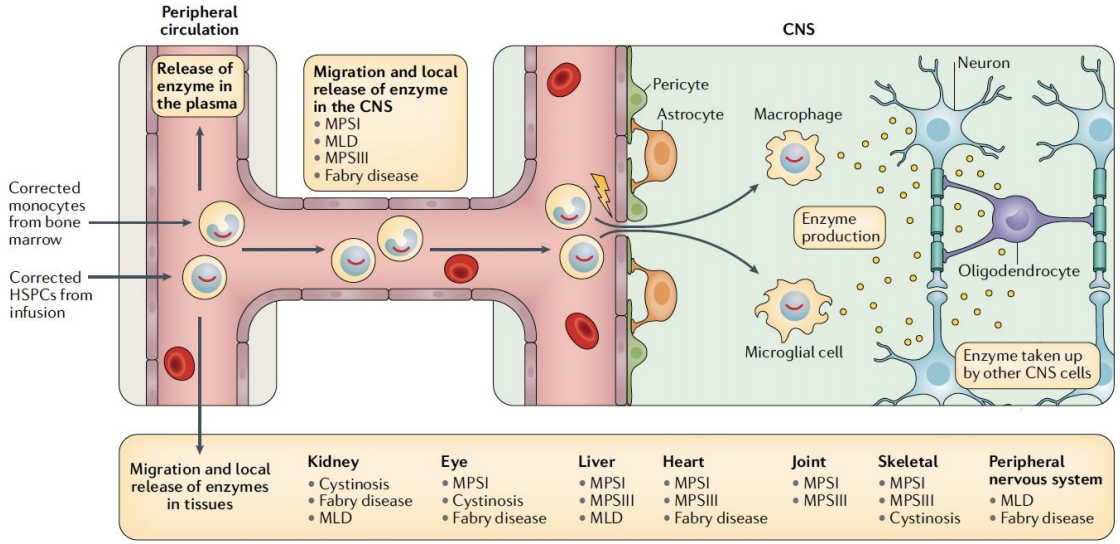
Immune and blood cell disorders

- Replacement of diseased cells



Metabolic disorders

- Replacement of diseased cells (*ie* microglia)
- Systemic and local (hyper) production and cross correction of non hematopoietic tissue (CNS, PNS, visceral, skeletal)



Ferrari, Thrasher, Aiuti Nat Rev Gen 2020

SCID and other immunodeficiencies

ADA-SCID (gRV) (EMA)
WAS
SCID-X1
ADA-SCID (LV)
RAG-1 def
ARTEMIS

CGD (gp91phox & p47)
Leukocyte adesion deficiency
Osteopetrosis

RBC disorders/BM failure

Beta thalassemia and SCD (LV)* (FDA)
SCD and Bthal (editing) (FDA & EMA)
Fanconi Anemia

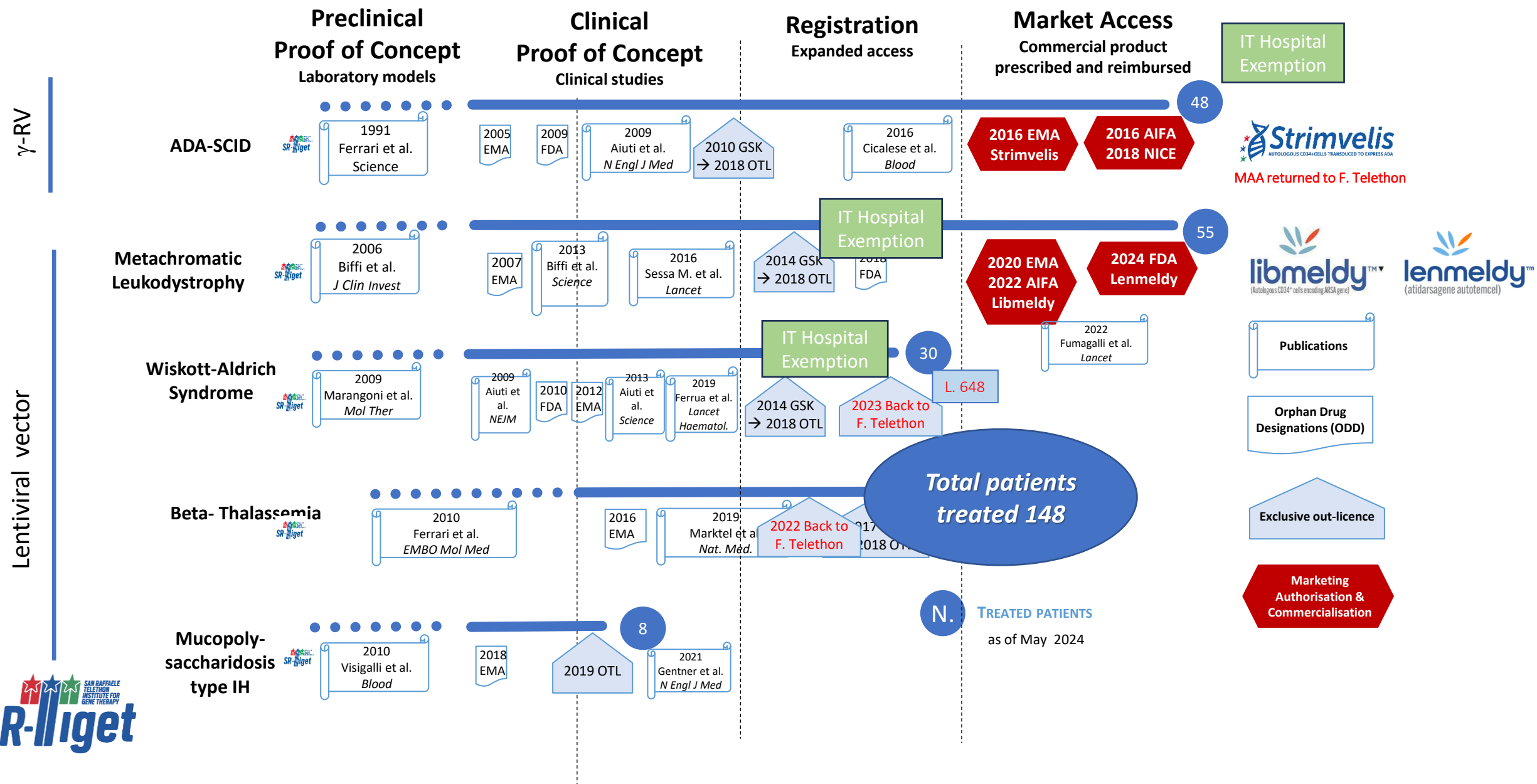
Piruvate Kinase deficiency

Metabolic disorders

MLD (EMA, FDA)
X-ALD (FDA)
MPSIH
MPSII, MPSIIIA
Gaucher Type 1 and 3
Fabry Disease
Cystinosis

*withdrawn

SR-Tiget HSPC Gene Therapy Experience



Case study I Gene therapy for ADA-SCID

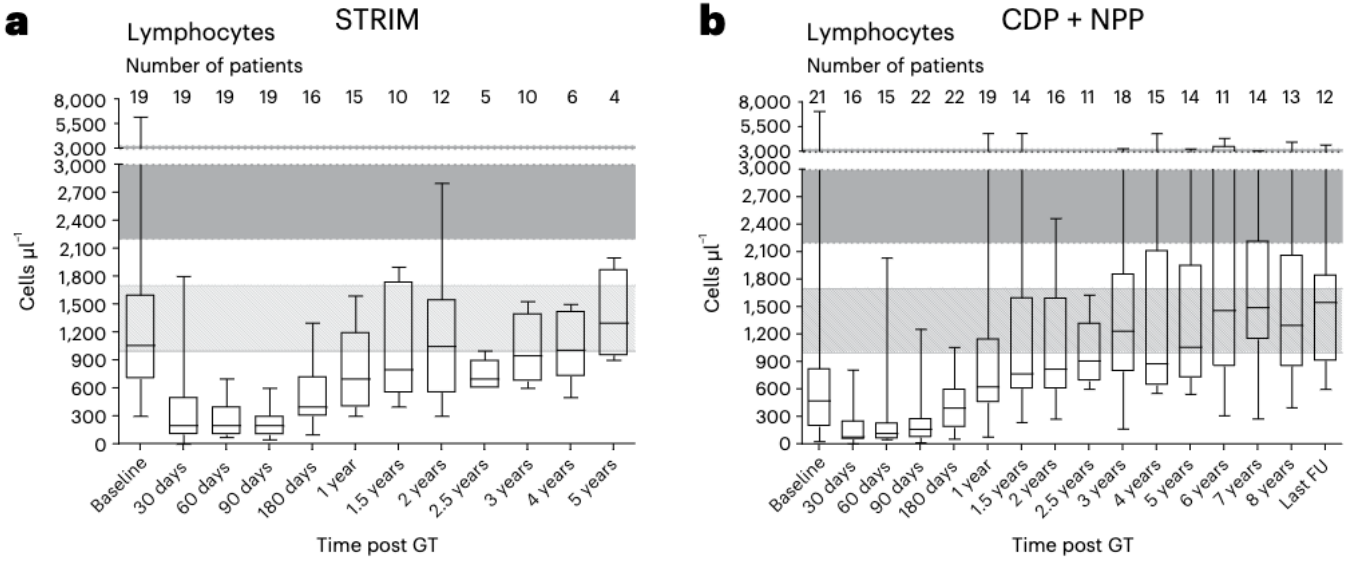
nature medicine

Article https://doi.org/10.1038/s41591-023-02789-4

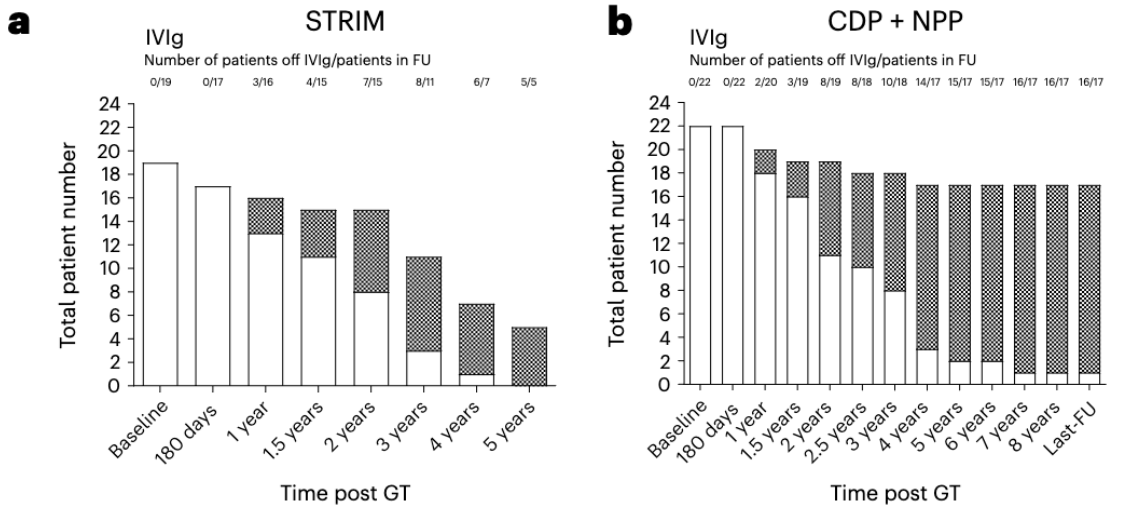
Long-term and real-world safety and efficacy of retroviral gene therapy for adenosine deaminase deficiency

Maddalena Migliavacca[1,2], Federica Barzaghi[1,2], Claudia Fossati[1], Paola M. V. Rancoita[3], Michela Gabaldo[4], Francesca Dionisio[1], Stefania Giannelli[1], Federica Andrea Salerio[1], Francesca Ferrua[1,2], Francesca Tucci[1,2], Valeria Calbi[1,2], Vera Gallo[1,2], Salvatore Recupero[1,2], Giulia Consiglieri[1,2], Roberta Pajno[1,2], Maria Sambuco[1,2], Alessio Priolo[1,2], Chiara Ferri[5], Vittoria Garella[5], Ilaria Monti[1], Paolo Silvani[6], Silvia Darin[1], Miriam Casiraghi[1], Ambra Corti[1], Stefano Zancan[4], Margherita Levi[4], Daniela Cesana[1], Filippo Carlucci[7], Anna Pituch-Noworolska[8], Dalia AbdElaziz[9], Ulrich Baumann[10], Andrea Finocchi[11,12], Caterina Cancrini[11,12], Saverio Ladogana[13], Andrea Meinhardt[14], Isabelle Meyts[15], Davide Montin[16,17], Lucia Dora Notarangelo[18], Fulvio Porta[19], Marlène Pasquet[20], Carsten Speckmann[21,22], Polina Stepensky[23], Alberto Tommasini[24], Marco Rabusin[24], Zeynep Karakas[25], Miguel Galicchio[26], Lucia Leonardi[27], Marzia Duse[27], Sukru Nail Guner[28], Clelia Di Serio[3,29], Fabio Ciceri[1,5,30], Maria Ester Bernardo[1,2,5], Alessandro Aiuti[1,2,5] ✉ & Maria Pia Cicalese[1,2,5]

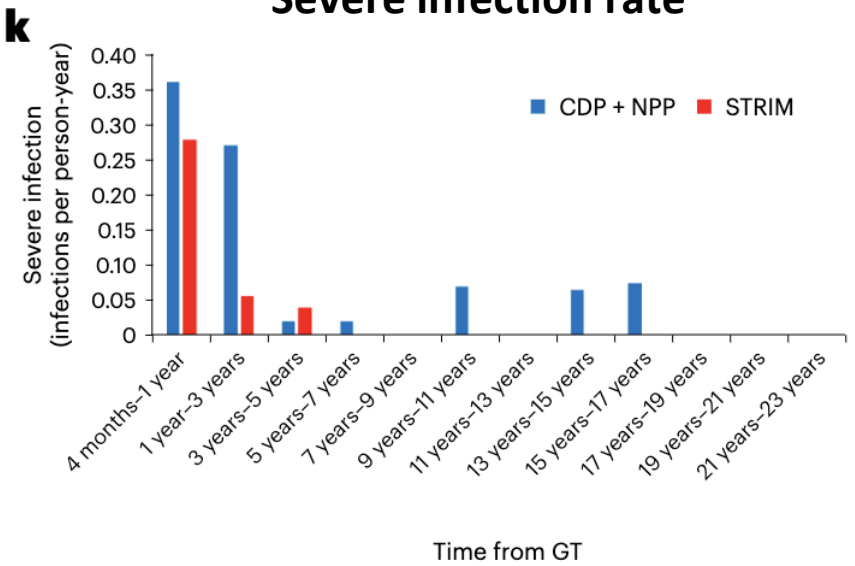
Lymphocyte counts



Ig discontinuation



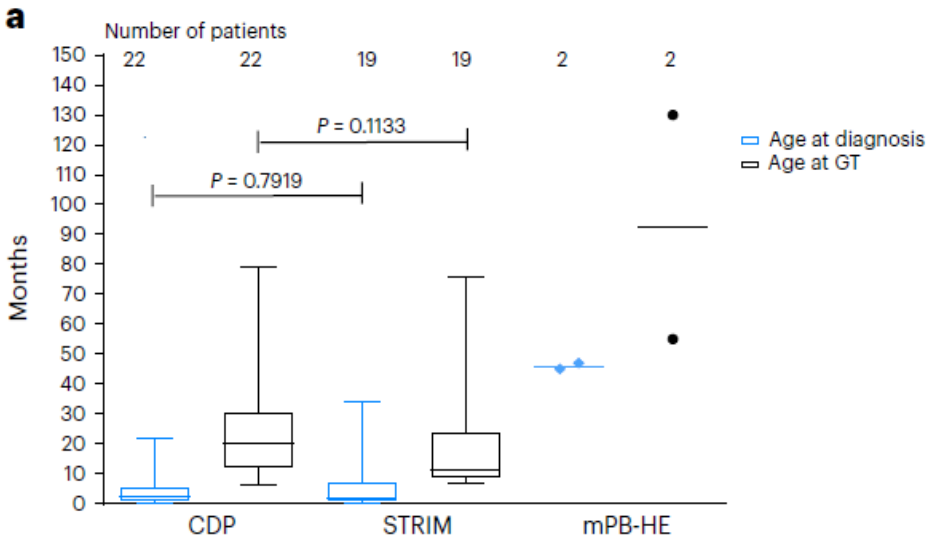
Severe infection rate

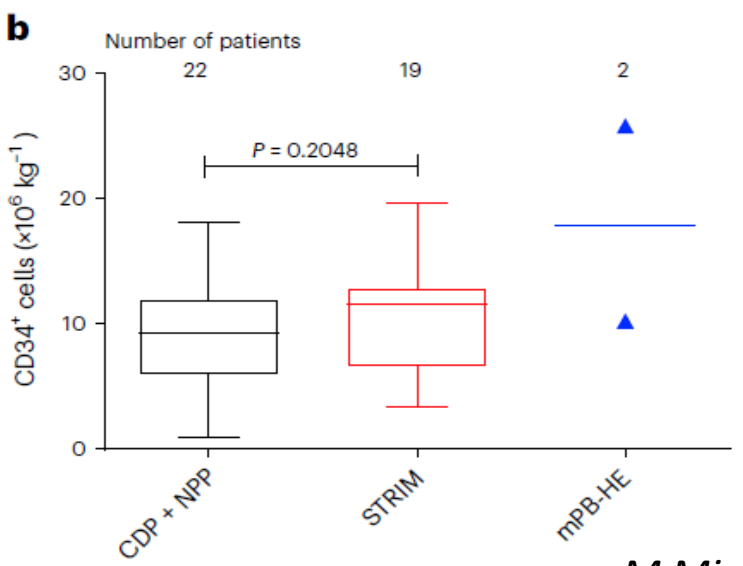


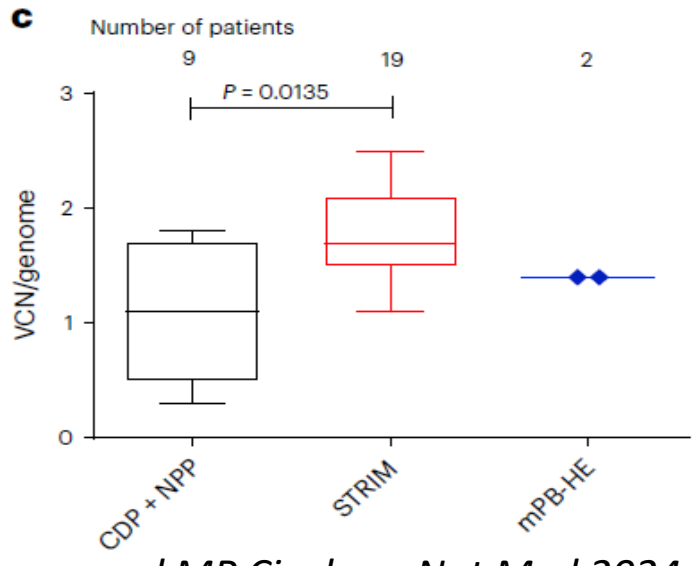
MP Cicalese
M Migliavacca

Gene therapy prepared on non-routine basis from mobilized peripheral blood for patient with ADA-SCID (STRIMHE)

- Strimvelis® is a medicinal product approved in the EU based on an autologous CD34+ bone marrow (BM) cells transduced with retroviral vector encoding for ADA, indicated for the treatment of ADA SCID in patients with no suitable human leukocyte antigen (HLA)-matched related stem cell donor.
- **Strimvelis-like DP** (Investigational Medicinal Product) is intended to be used for ADA-SCID patient who are **not eligible to receive Strimvelis** because they are **unable to donate a sufficient amount of BM CD34+ cells** due to low BM stem cell content or unfeasibility to conduct a BM harvest.
- Strimvelis-like DP will be prepared on a **non-routine basis** according to the same manufacturing procedures and by the same contract manufacturing organization (CMO) of Strimvelis, but the starting material will consist of **mPB CD34+ cells** instead of BM CD34+ cells.

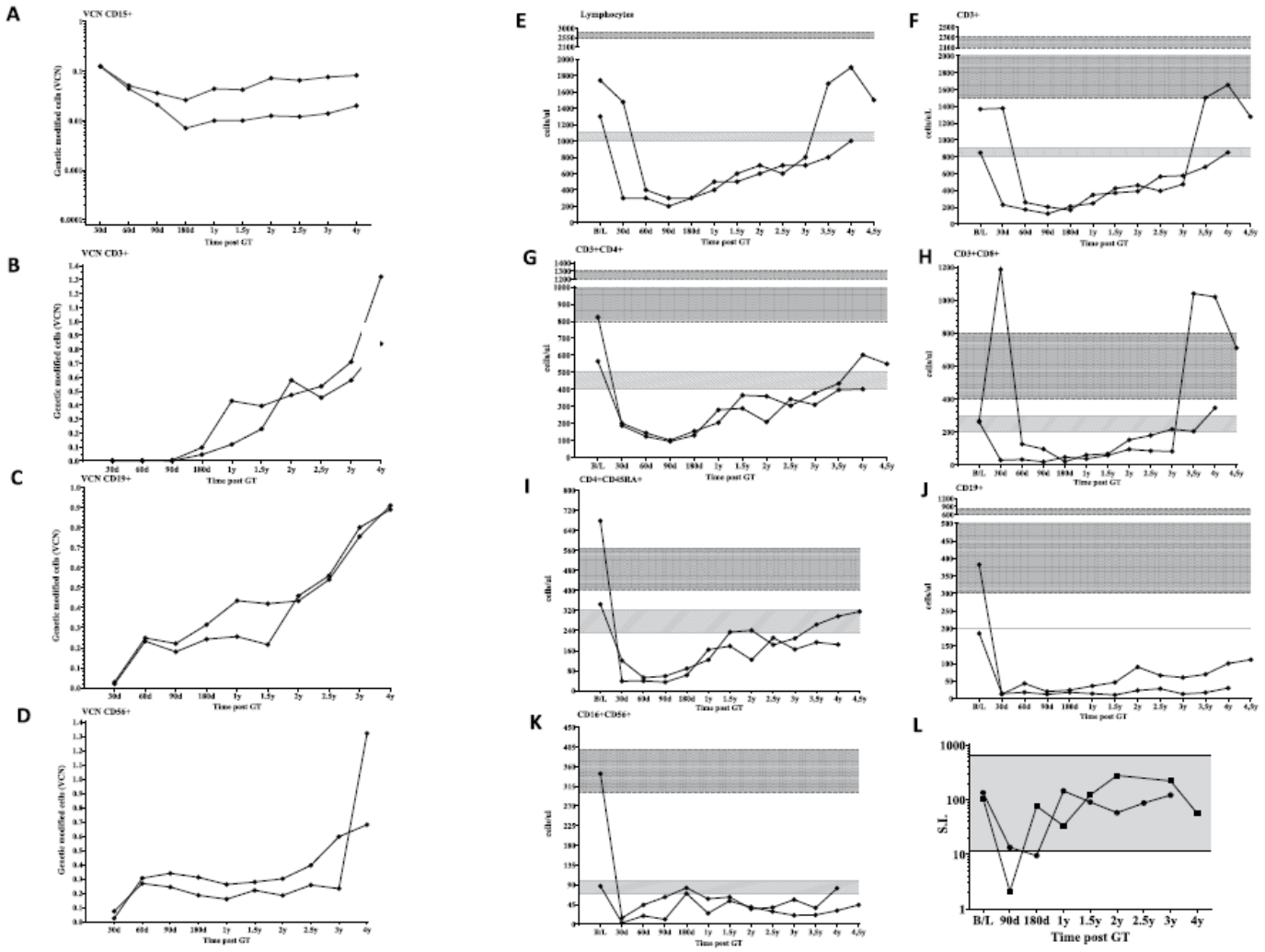


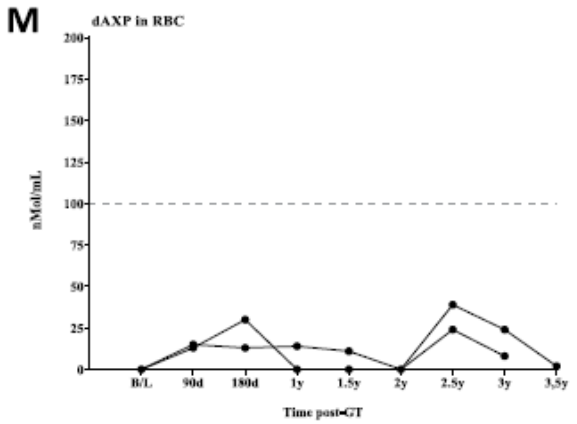


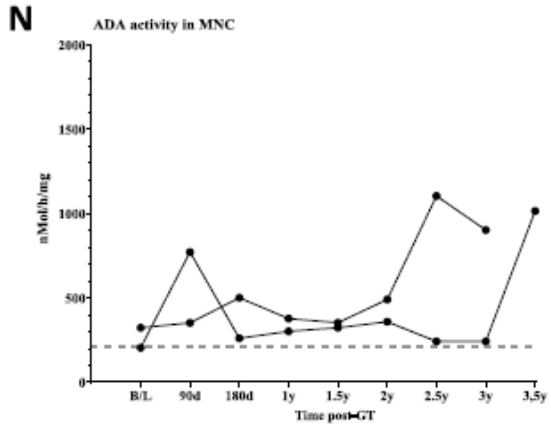


M Migliavacca…and MP Cicalese, Nat Med 2024

Engraftment of gene corrected cells, immune reconstitution and metabolic correction in STRIMHE patients.







-3 patients have been treated at the time of the survey (as of June 2024), data not shown for patient 3.

M Migliavacca…and MP Cicalese, Nat Med 2024

Now Fondazione Telethon is:

*The **first charity** in the world holding the manufacturing and distribution rights of an approved ATMP*

*A **sustainable** model of market access for these advanced therapies for rare and ultra-rare diseases*

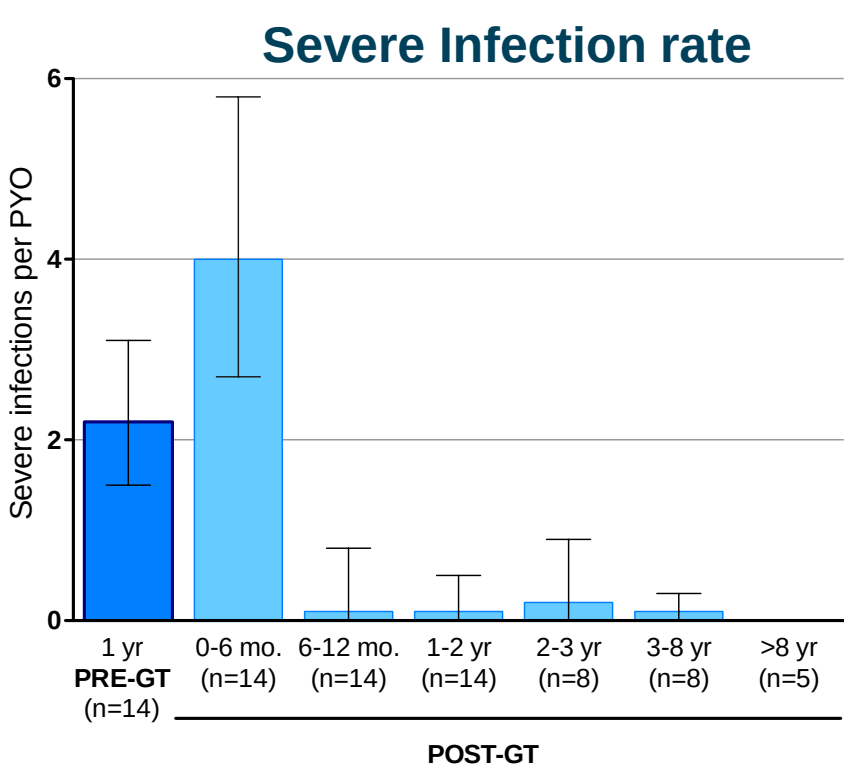
***An alternative to industry** when there is no other way to ensure that a drug remains available to patients*

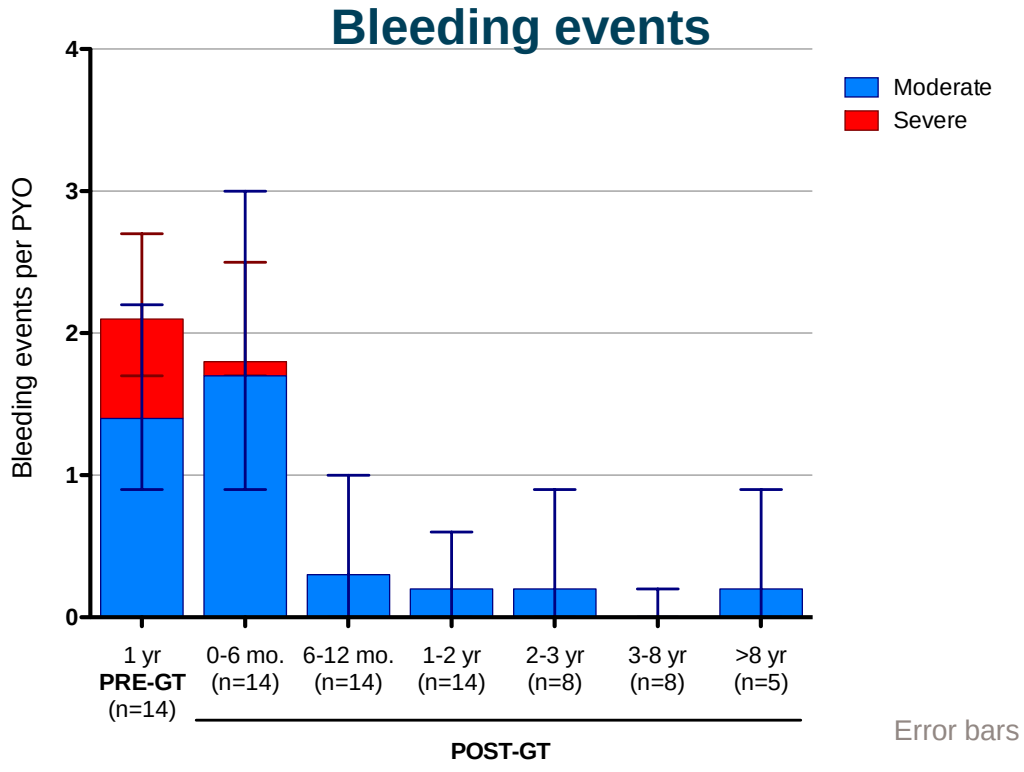
To pursue these goals, Fondazione Telethon made a courageous choice, to remain true to its mission.

Case study I Gene therapy for ADA-SCID

- 19 patients treated with g-RV gene therapy since Strimvelis availability on the market (Nov 2016):
- Limited shelf life as fresh product, with single center of administration at San Raffaele Hospital, Milan, Italy
- 8 patients from EU countries, 5 from non-EU countries treated with approved product (Migliavacca et al. Nat Med 2024)
- S2 Form" route (Regulation 883/04 and Regulation 987/09) for EU patients was somehow successful but
- response of countries and time to access were variable
- Overall 19 pts initially referred not treated as not eligible, or due to lack of funding or other treatment choice
- Changing from fresh formulation to cryopreserved or expanding region would require high investment difficult to recover
- EMA does not offer automatic discount on maintenance (or variation) fees

Case study II. Gene therapy for Wiskott-Aldrich Syndrome





Error bars indicate the 95% CI

F. Ferrua et al. unpublished,
presented at ESID & ESGCT 2022

Case study II. Gene therapy for Wiskott-Aldrich Syndrome

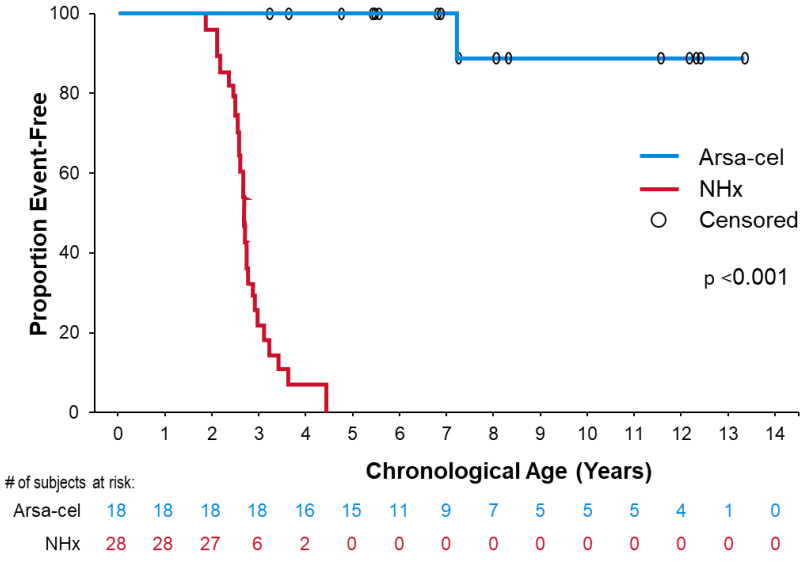
- Phase I/II clinical trial started in 2010
- 28 patients treated (27 alive) as part of clinical trial & early access program with TELETHON003
- Immune reconstitution, discontinuation of Ig and protection from infections
- Improvement in autoimmunity, eczema, quality of life
- Improvement in platelet count/functions –> protections from bleedings
- No gene therapy related AE or clonal expansion
- 3 patients treated under HE as a bridge between phase I/II trial completed enrollment and start of phase III study
- Cryopreserved product with similar safety and efficacy profile result than fresh (phase III study Ferrua et al., ESID 2024)

Case study III Gene therapy for MLD

Pre-Symptomatic Late Infantile (PSLI)

Severe Motor Impairment Free Survival (sMFS)

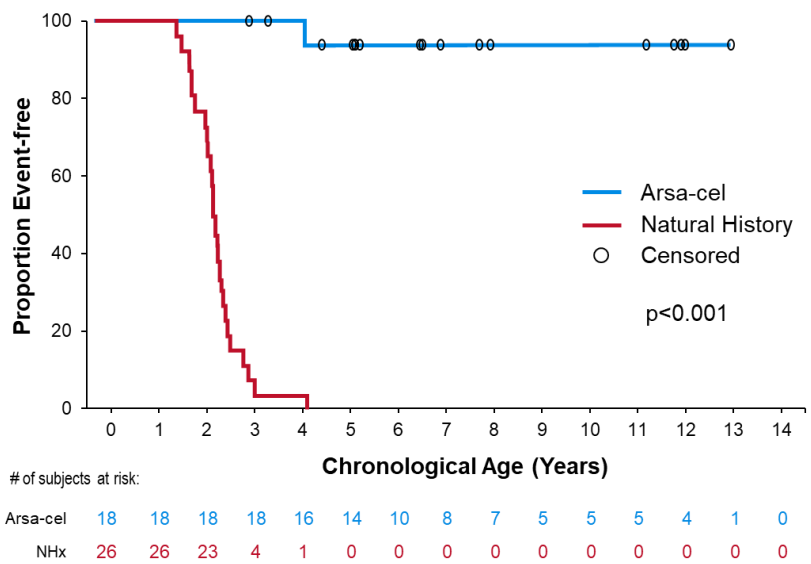
Interval from birth to first occurrence GMFC-MLD ≥ 5 (no locomotion and unable to sit) or death



# of subjects at risk:															
Arsa-cel	18	18	18	18	16	15	11	9	7	5	5	5	4	1	0
NHx	28	28	27	6	2	0	0	0	0	0	0	0	0	0	0

Motor Impairment Free Survival (MFS)

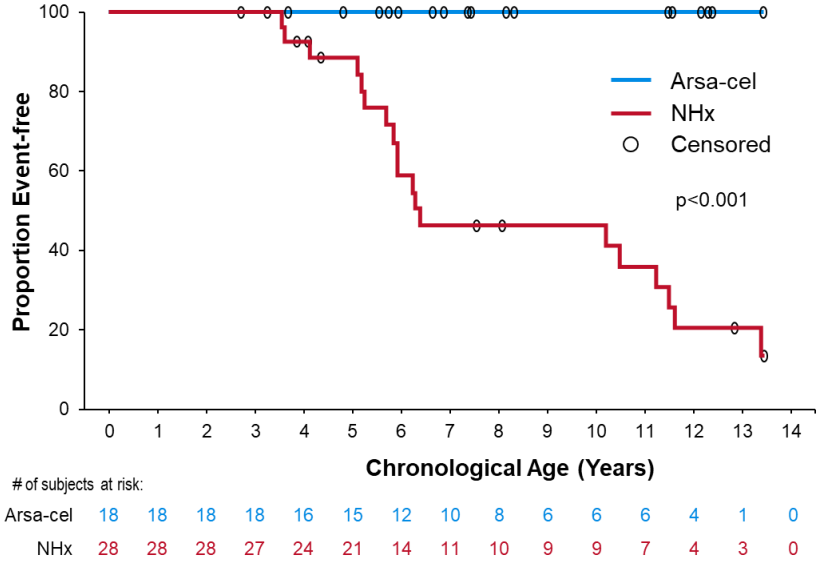
Interval from birth to first occurrence of GMFC-MLD ≥ 3* (unable to walk with or without support) or death



# of subjects at risk:															
Arsa-cel	18	18	18	18	16	14	10	8	7	5	5	5	4	1	0
NHx	26	26	23	4	1	0	0	0	0	0	0	0	0	0	0

Overall Survival (OS)

Interval from birth to death from any cause



# of subjects at risk:															
Arsa-cel	18	18	18	18	16	15	12	10	8	6	6	6	4	1	0
NHx	28	28	28	27	24	21	14	11	10	9	9	7	4	3	0

Arsa-cel treated PSLI patients exhibit a clinically meaningful improvement in sMFS, MFS, and OS as compared to LI NHx patients.

LI NHx patients experience rapid loss of motor function and ultimately death.

If no event is recorded, subject is censored at the last GMFC assessment (SMFS; MFS) or the last contact date (OS)
*GMFC-MLD ≥ 3 maintained at all subsequent assessments

Case study III. Gene therapy for MLD

- Phase I/II clinical trial started in 2010 with fresh DP, phase III started with cryopreserved product in 2017
- 3 patients treated under HE as a bridge between phase I/II trial completed enrollment and start of phase III study

- With extended follow-up (median 6.76 yrs, max 12.19 yrs) arsa-cel treatment:
  -Preserves motor, cognitive, and speech abilities in treated early-onset MLD patients as compared to NHx
  -Continues to show a favorable benefit-risk profile and long-term durability of treatment effect

- Newborn screening pilot projects started in some countries to treat patients

Effective therapies are not reaching patients in need for non-medical reasons

DIVE BRIEF

Orchard abandons promising gene therapy for rare immune disorder

Published June 3, 2021

By Kristin Jensen

HOME • NEWS AND TRENDS

Bluebird Bio Withdrawal Raises Gene Therapy Doubts in Europe

BY ANITA CHAKRAVERTY
MAY 4, 2021 · 5 MINUTES

Last month, the US firm bluebird bio abandoned the sale of its gene therapy Zynteglo in Germany after a pricing dispute with health authorities — a blow that could have repercussions for the rollout of other gene therapies in Europe.

Check for updates

comment

Ensuring a future for gene therapy for rare diseases

Hematopoietic stem-cell gene therapy has proven to be an effective treatment for several primary immunodeficiencies, and yet companies in this space are withdrawing from the EU market. Technological and regulatory innovations and a change to cost–benefit models are needed so that rare disease patients can receive these life-saving medicines.

Alessandro Aiuti, Francesca Pasinelli and Luigi Naldini

Science & Society

TRANSPARENT PROCESS · OPEN ACCESS · EMBO reports

Cost and availability of novel cell and gene therapies

Can we avoid a catastrophic second valley of death?

Michele De Luca[1,*] & Giulio Cossu[2,3,**]

The Economist

Menu

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My Economist

By Invitation | Pharmaceutical innovation

What good are whizzy new drugs if the world can't afford them?

Bringing gene therapies and obesity drugs to the masses will require financial innovation too, says Steven Pearson

nature medicine

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nature › nature medicine › correspondence › article

Correspondence | Published: 13 February 2023

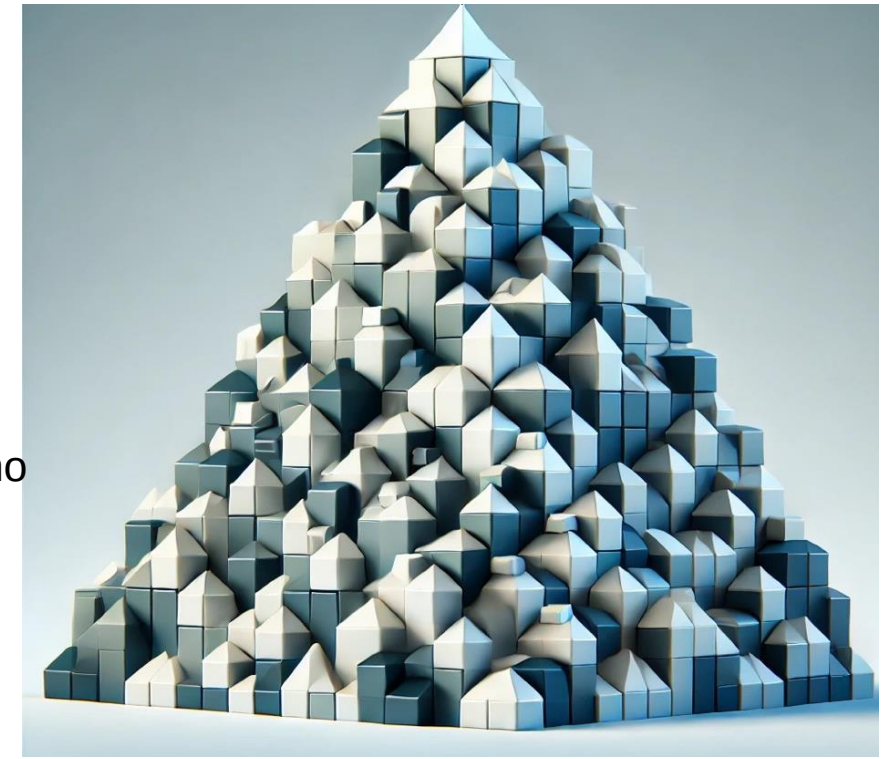
Access to gene therapy for rare diseases when commercialization is not fit for purpose

Thomas Fox, Juan Bueren, Fabio Candotti, Alain Fischer, Alessandro Aiuti, Arjan Lankester, The AGORA Initiative & Claire Booth

Critical issues in development and accessibilities of GTMP

CMC Development & Manufacturing

-Complex manufacturing, extensive control and testing
-High costs for product development and standardisation
-Changes and adaptation over the whole product lifecycle
-Scalability (autologous: low volume/no economy of scale), reproducibility (intrinsic cells variability)
-Limited capacity and flexibility of manufacturing slots vs clinical need
- Complex supply chain requiring hospital qualification and maintenance



Market Access

-Cost-benefit analyses (value of “once and done” treatment by HTA)
- High upfront cost with potential lifelong benefit
-Fragmented pricing and reimbursement processes in the EU
-Access to treatment for some EU countries

Clinical Development & Regulatory

-Ultra-rare diseases (sample size, trial design, comparator, ethical considerations)
-Long term follow up to evaluate GT safety and persistent effect
-High investment with elevated upfront costs while high uncertainty at the time of launch
-Challenging evaluation for cell-based autologous personalised medicine
-Disalignment between regulatory requirements in development phase among different geografic jurisdictions, and lack of mutual recognition

Prioritising Patients

Relevant measures of benefit
Collection of real-world evidence
Facilitate cross-border mobility

Sustainability

Supra-national funding
Increased incentives for rare diseases
Non-profit provision
Spreading reimbursements over years

Manufacture

Innovations in optimizing process
Minimal batch testing
Non-profit vector and
cell production

Cross-border collaboration

Health Economics

Appropriate health cost analyses
Information sharing between HTA bodies
Standardised reimbursement

Harmonised regulation

Harmonised regulatory requirements
Platform-based approvals
Transnational recognition of
approvals

Delivery Infrastructure

Networks of expert centres
Knowledge transfer
Apheresis services
GMP Pharmacy

Aiuti, Booth Human Gene Ther 2023

Some actions supporting academic development of ATMPs

- **National initiatives to support** academic development and manufacturing
  - UK government → Cell and Gene Therapy Catapult
  - Italy (Next Generation EU): National Center For R&D for Gene Therapy and medicines with mRNA tecnhology
- **EU funding** initiatives (ie JOIN4ATMP) for European University Hospital (EUHA)
- **Not-for-profit** for production and distribution of registered medicinal products (Fondazione Telethon) complementing the private sector when a for-profit model is not sustainable
- **«Agora» European academic initiative** on rare diseases
- **EMA ATMP pilot** for academia and non profit developers (4 products included in 2024)
- **FDA pilot program** to explore the possibility of concurrent collaborative review of new gene therapy applications (Gene Therapies Global Pilot (CoGenT))
- **FDA Operation Warp Speed** for rare diseases

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M. Levi (care coordinator)
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S. El Hossary, G. Tomaselli
M. Levi

Sr-TIGET Good Clinical Lab. Practice

(AIFA autocertified)
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C. Sartirana F. Salerio
S. Miglietta

M Gabaldo

All patients and families

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Orchard Therapeutics

FONDAZIONE Telethon

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S. Benvenuti

JOIN 4 ATMP

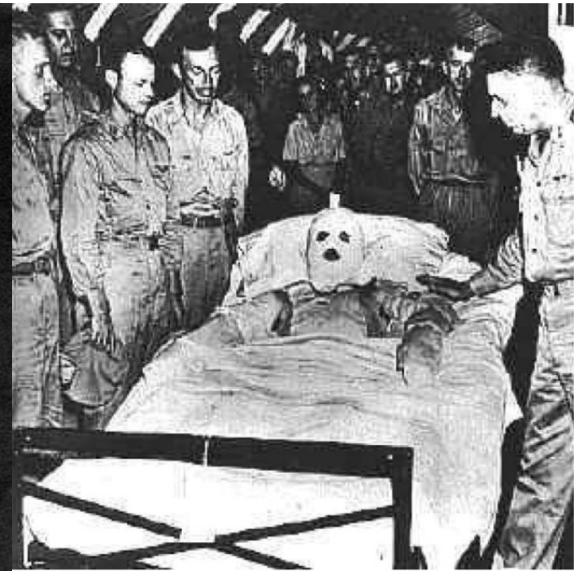
AKADEMISKA SJUKHUSET

Autologous keratinocytes for treatment of severe burns in Sweden

Alexandra Karström, Uppsala University Hospital, Sweden

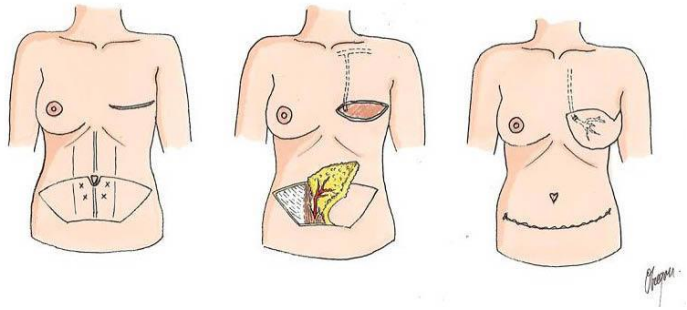
Plastic Surgery and Maxillofacial surgery

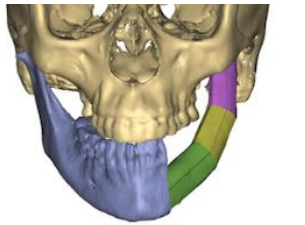


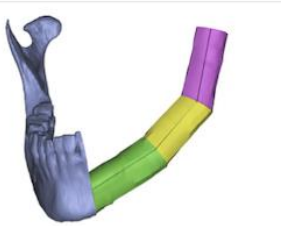


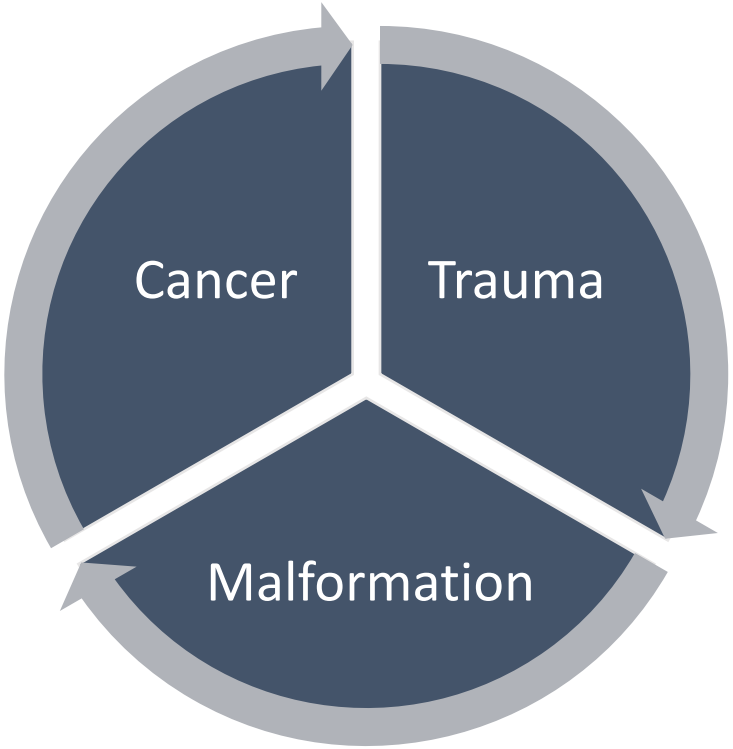
A medical speciality developed in times of war…….

Restoration of form and function - Highly specialized plastic surgery/oral surgery

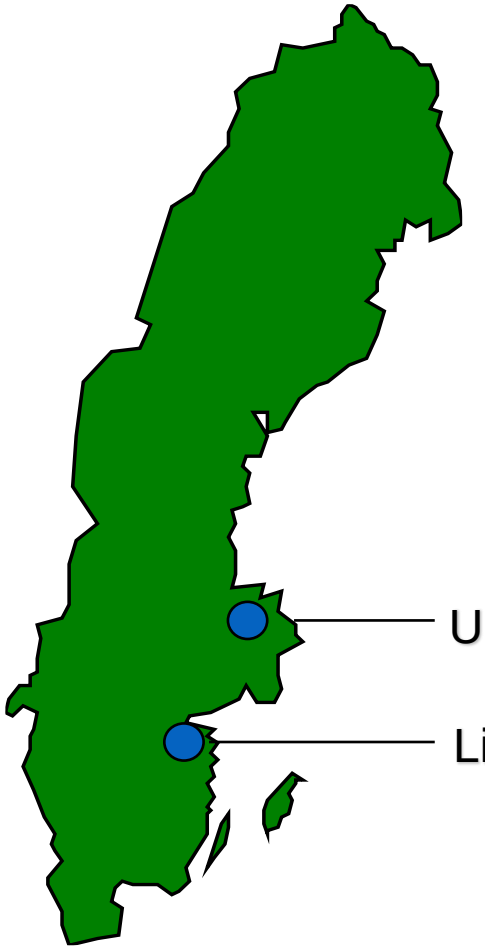








Burn Care in Sweden - National specialized medical care

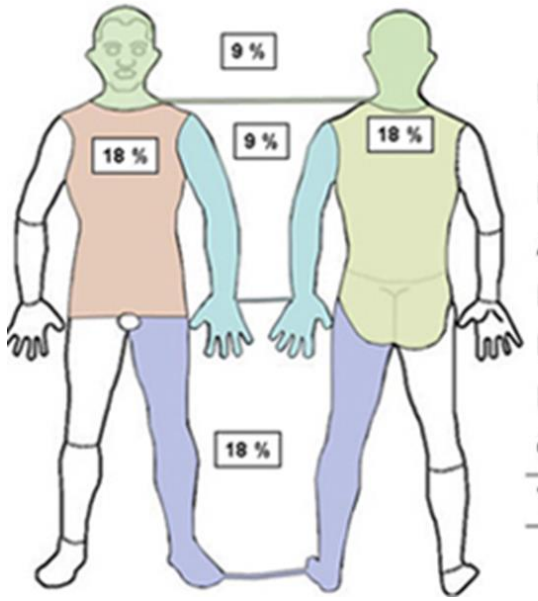


Number of patients with burns annually:

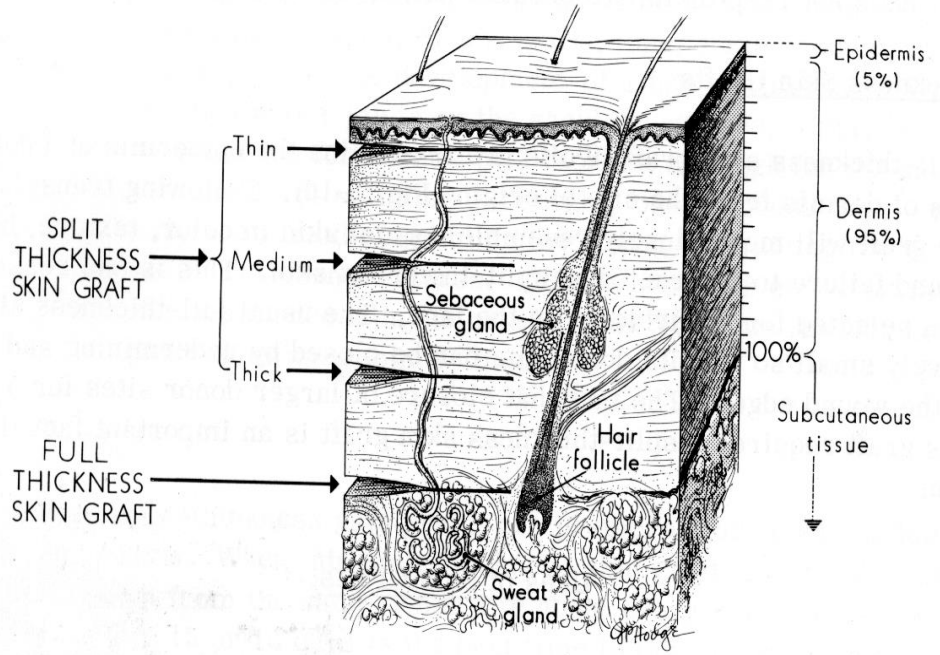
- 36 000 in total
- 1 300 require hospitalisation
- 500 treated according to National specialized care

Key factors in a burn….

- Depth of burn injury
- Extent of the burn
- Cause of the burn
  - Flame
  - Electricity (including lightning)
  - Chemical
  - Scald
- Inhalation injury
- Any other injuries
- Any other medical conditions



Head - neck	9%
Left arm	9%
Right arm	9%
Anterior trunk	18%
Posterior trunk	18%
Left leg	18%
Right leg	18%
Genitals	1%
Total	100%



Different factors for today's improved survival rate

- Early excision (start 24-48 hours) regardless extent of burn

- Other factors:
  - Antibiotics,
  - Intensive care
  - Nutrional care
  - Etc.

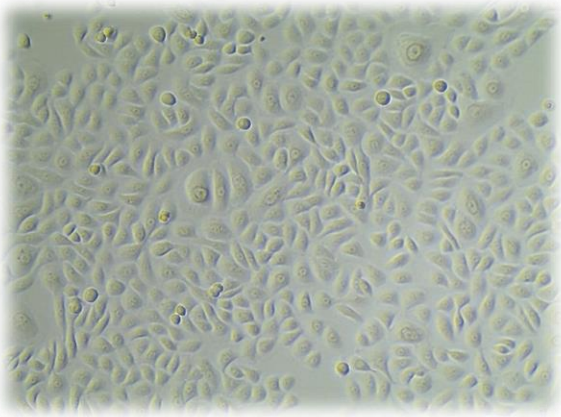
Background – 1794 and 1914

1794

- Bunger performs first successful human skin autograft
- Reverdin performs first allograft using pinch grafting to demonstrate rapid healing of granulating wounds

1914

- Kreibich was the first person to cultivate keratinocytes in vitro



Background - 1975

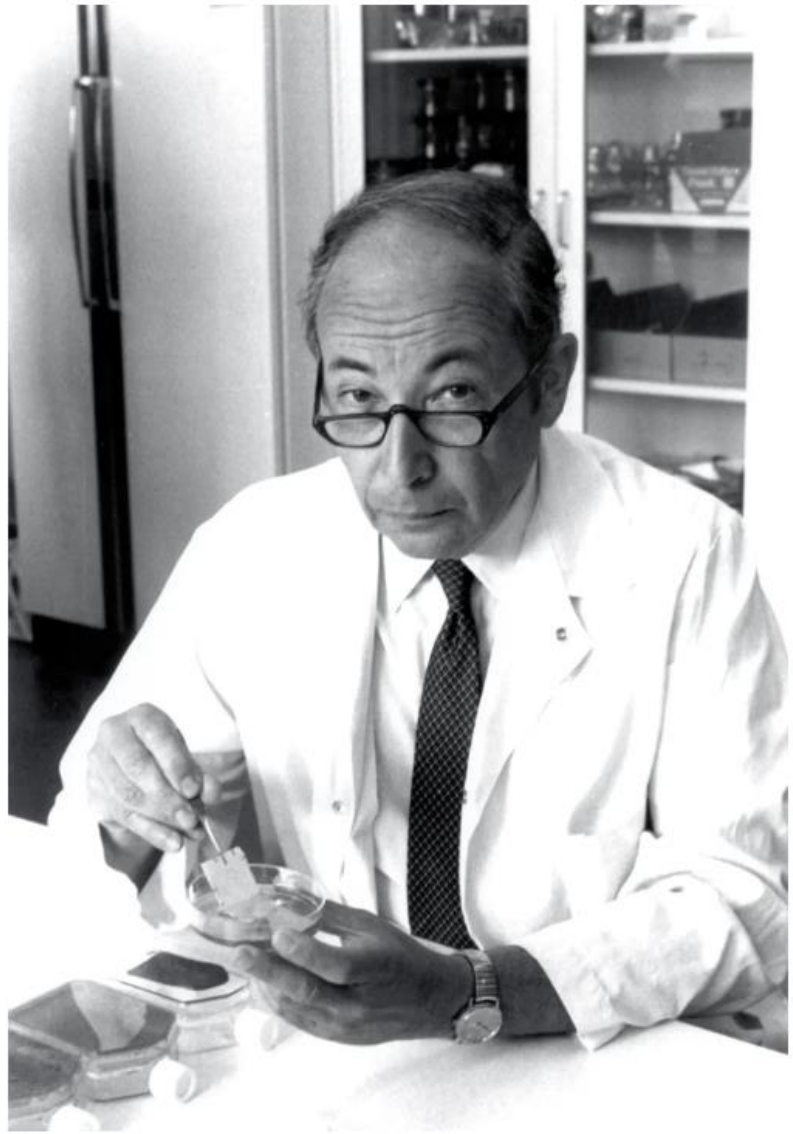
Rheinwald and Green developed the method of culturing human keratinocytes in viable epithelial sheets.

Serial Cultivation of Strains of Human Epidermal Keratinocytes: the Formation of Keratinizing Colonies from Single Cells

James G. Rheinwald and Howard Green
Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Formation of a Keratinizing Epithelium in Culture by a Cloned Cell Line Derived from a Teratoma

James G. Rheinwald and Howard Green
Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139



Background - 1981

Cultured epithelial sheets used for the first time in burn care

MEDICAL INTELLIGENCE

PERMANENT COVERAGE OF LARGE BURN WOUNDS WITH AUTOLOGOUS CULTURED HUMAN EPITHELIUM

G. Gregory Gallico, III, M.D.,
Nicholas E. O'Connor, M.D.,
Carolyn C. Compton, M.D.,
Olaniyi Kehinde, B.A., and Howard Green, M.D.

THE LANCET

Volume 317, Issue 8211, 10 January 1981, Pages 75-78

GRAFTING OF BURNS WITI
EPITHELIUM PREPARED FR
AUTOLOGOUS EPIDERMAL

NicholasE. O'Connor [a], JohnB. Mulliken [a], Susan Banks-Sch
Howard Green [b]

Burned boy home after hospital stay

CASPER — One of two Casper boys who was severely burned in a flash fire last summer is back home after 10 months in a Boston hospital.

Jamie Selby, 6, was released from the Shriners Burn Institute three weeks ago, according to Dr. Salvatore Russo. His older brother Glen, 7, will remain at the hospital for several more months to undergo additional skin grafts, Russo said.

The two Selby boys suffered severe burns over most of their bodies last July 1. They and a third boy, 6-year-old Ricky Parras, were burned while attempting to remove paint thinner from themselves in an unoccupied house in Casper.

Parras died in a Denver hospital two days after the accident. The Selby boys were flown to Boston on July 7.

Both boys are due for more plastic surgery, Russo said. Glen is "still a pretty sick kid," he said, but both "have done very well, considering."

Regulatory journey in Sweden

From 1980s

From 2009

From 2017

Therapy developed by research

Cell and tissue law

ATMP and the regulatory framework for medicines

National Board of Social Affairs and Health

Health and Social Care Inspectorate (IVO)

Swedish Medical Product Agency (MPA)

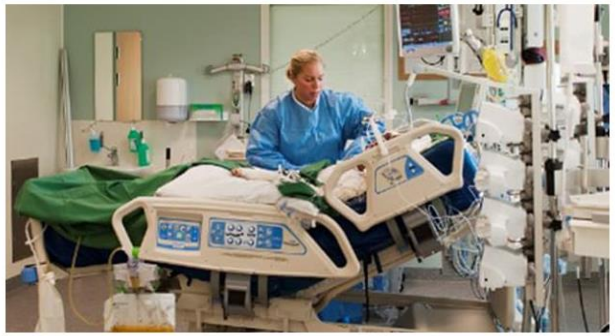
Hospital Exemption

Culturing of keratinocytes – Sweden

AKADEMISKA SJUKHUSET

Akademiska får odla fram hud för transplantation av svårt brännskadade

Pressmeddelande · Nov 23, 2017 10:21 CET



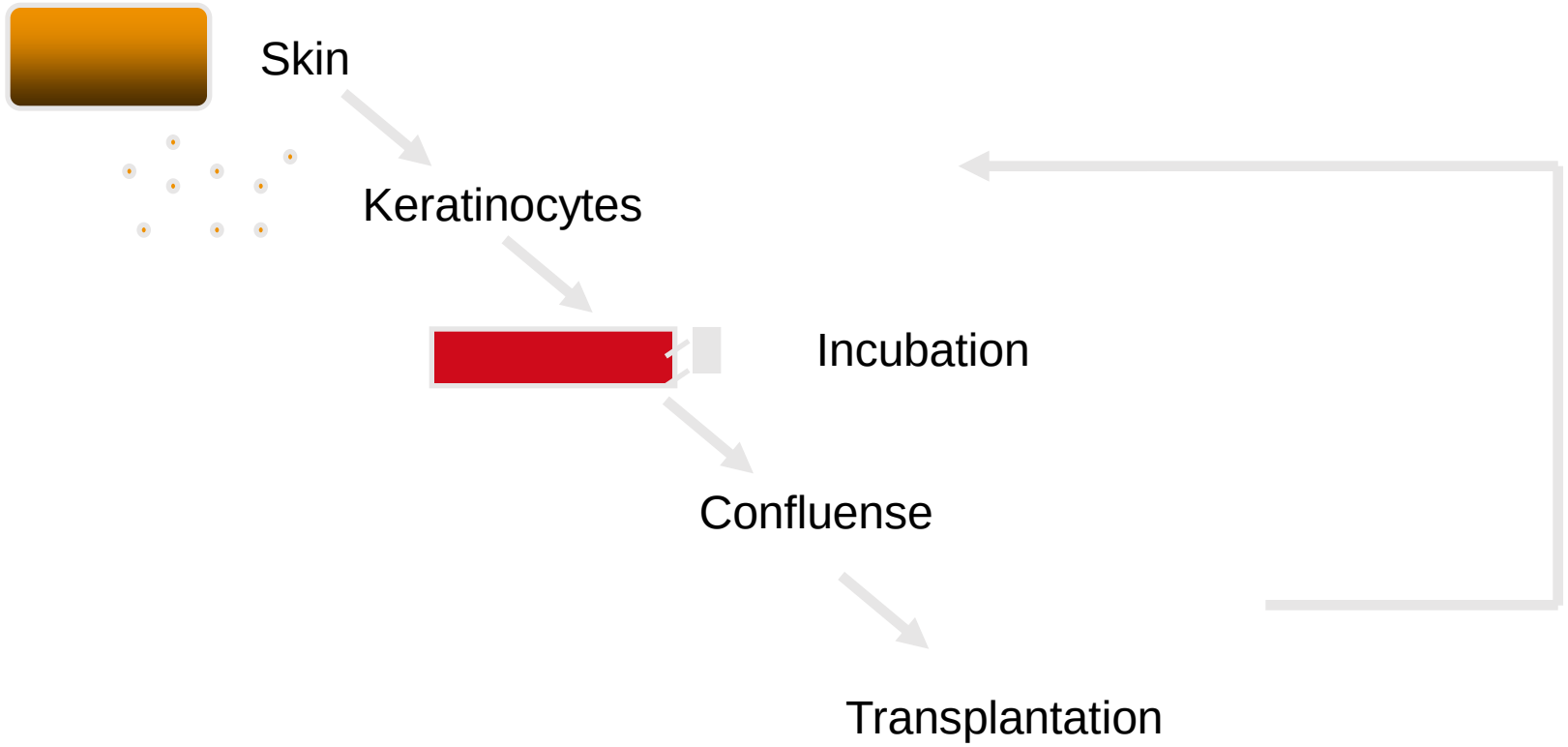
Som första sjukhus i Sverige har Akademiska fått tillstånd av Läkemedelsverket att odla fram hud för transplantation vid svåra brännskador.

Som första sjukhus i Sverige har Akademiska fått tillstånd av Läkemedelsverket att odla fram hud för transplantation vid svåra brännskador. Målgruppen är patienter med mycket stora hudförluster där kvarvarande frisk hud inte räcker för gängse behandling.

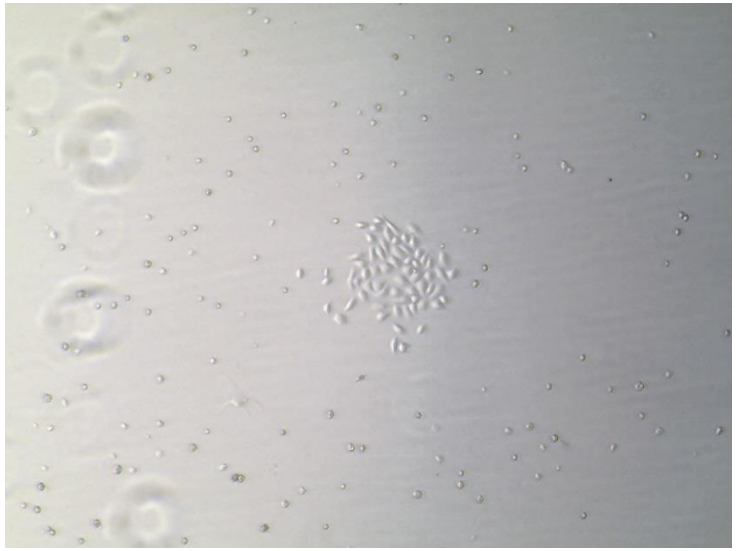
- Manufacturing license by the Medical Agency, received November 2017
- Hospital exemption
- Uppsala University hospital as only hospital in Sweden

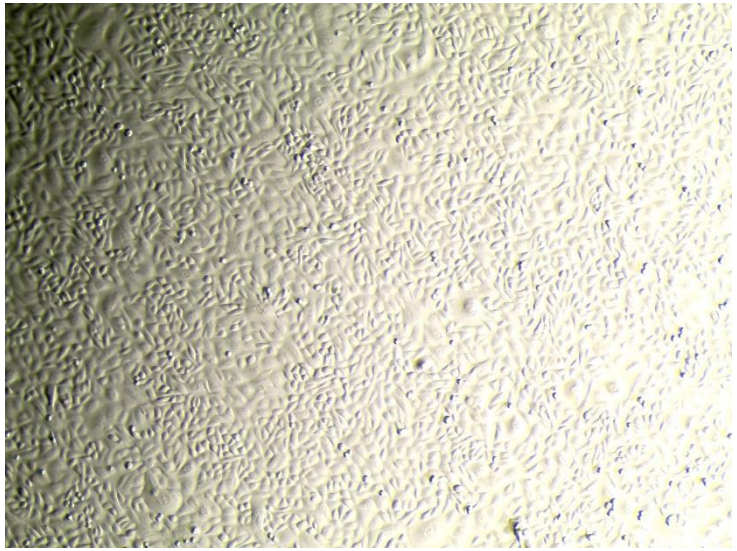
Culturing of keratinocytes

- When there is a lack of own healthy skin, ‘always’ for injuries covering over 50% burned body surface



Keratinocyte culture – in pictures





Application methodology – Past and present

Clinical results….

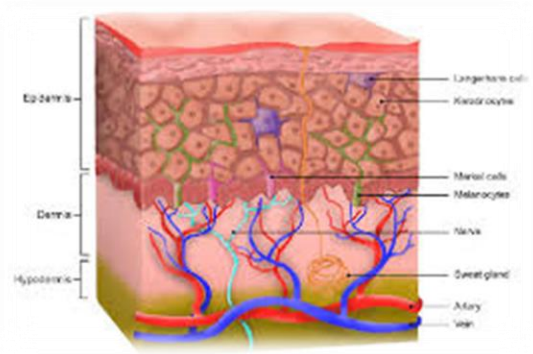
- CEA take varies - 15 to 85%
- Higher take with dermal elements present in wound (eg partial-thickness wounds)
- Take dependent on the nature of the wound bed
  - Chronic granulating wounds 15% take
  - Freshly excised or early granulating wounds 28–47% take
  - Wounds dressed with cadaveric skin before grafting 45–75% take

What is going on today?

- Treatment of patients with severe burns
- Quality assurance and development
- European joint initiative on cultured keratinocytes initiated in spring 2023
- Revision of the Medical Products Agency's regulations for the hospital exemption is ongoing

What happens tomorrow?

- Cultivation of allogeneic keratinocytes for wound healing in a clinical trial is a next step for the future....
- Possibility to automate the production process
- Construction of a skin substitute (permanent)



Conclusion

- Established at Uppsala University Hospital since late 1980s
- Burn Care is National Specialised Medical Care in Sweden
- Autologous cultured keratinocytes is part of a life saving treatment
- Last resort for burns >50%
- Manufacturing license within the provision of the hospital exemption
- European joint initiative on cultured keratinocytes, initiated in spring 2023

Questions?

Thanks!

Alexandra Karström

Head of Tissue Establishment, Qualified person

Assisting head of Department of Plastic and Maxillofacial surgery

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Hospital exemption: an academic experience

Julio Delgado, MD, PhD
Oncoimmunotherapy Unit, Hospital Clinic de Barcelona
FRCB-IDIBAPS, University of Barcelona

Conflicts of interest

- None from pharmaceutical companies
- Principal investigator in the first clinical trial (CART19-BE-01) evaluating the role of varnimcabtagene autoleucel (ARI-0001 cells) in patients with B-cell malignancies

The emergence of commercial CART-cell products

Parliamentary question - E-000739/2021
European Parliament

Availability of CAR-T cell therapy in the European Union

5.2.2021

Question for written answer E-000739/2021
to the Commission
Rule 138
Liudas Mažylis (PPE)

Chimeric antigen receptor (CAR) T-cell therapy is a well-established breakthrough treatment in oncology that is personalised for each patient. Unfortunately, its price is particularly high and can reach up to EUR 500 000 per person. Lithuania is one of the countries in which Novartis and Thermo Fisher Scientific are involved in this therapy, but this modern treatment method is inaccessible not only in Lithuania, but also in some other Member States.

1. What approach to funding should be followed in order to expand cell therapy (CAR-T) to the largest possible number of cancer patients?
2. What should the Commission do – and what assurances can it make – to ensure that modern but expensive treatments are equally accessible to citizens of all Member States and become common practice in all Member States? Will the new Europe's Beating Cancer Plan address the issue of access to modern cancer treatments?
3. With regard to the new EU approach to health policy (European Health Union), are there any plans to address existing inequalities in treatment (between Member States, different age groups, etc.)? How will the EU4Health programme ensure the transparency of data and processes in the development and/or sale of medicines and medical devices?

Features | April 29, 2022

Access to CAR-T therapies in Central and Eastern Europe in "catch-up" mode compared to the West

Although some countries are moving ahead, the use of CAR-T therapies in the region remains uneven.

Comment | November 21, 2022

Manufacturing challenges set back development progress of cell therapies in oncology

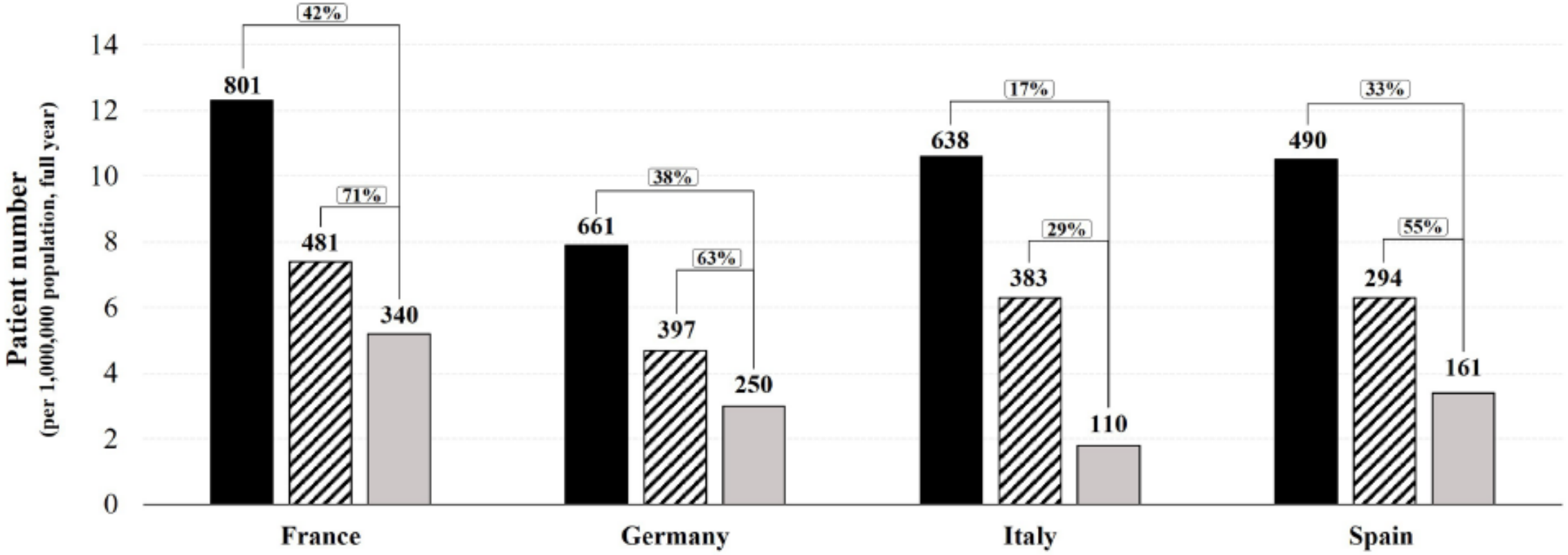
GlobalData Healthcare

EU member state	Tisagenlecleucel			Axicabtagene ciloleucel			Brexucabtagene autoleucel		Lisocabtagene maraleucel		Idecabtagene vicleucel		Ciltacabtagene autoleucel	
	DLBCL 3rd line	ALL ≤25 yr	FL 3rd line	DLBCL 3rd line	DLBCL 2nd line	FL 4th line	MCL 3rd line	ALL >25 yr	DLBCL 3rd line	DLBCL 2nd line	MM 4th line	MM 3rd line	MM 4th line	MM 2nd line
Germany														
Austria														
France														
Italy														
Czech Republic														
Greece														
Finland														
Greece														
Spain														
Luxembourg*														
Belgium														
Slovakia														
Portugal														
Poland														
Sweden														
Netherlands**														
Ireland														
Slovenia														
Romania														
Croatia														
Denmark														
Hungary														
Malta***														
Bulgaria														
Estonia														
Lithuania														
Latvia														
Cyprus														

*In Luxembourg, patients may be referred to neighbour countries (e.g. Germany and Belgium) and the cost reimbursed by the Luxembourgish Government.
**In The Netherlands, there are four different indicactions currently under evaluation (in yellow)
***In Malta, CAR T cells are not available, but patients may be referred to the United Kingdom and the cost reimbursed by the Maltese Government if the product is recommended by the National Institute for Health and Care Excellence (NICE).

May 2024

Patient access to therapy in Germany, France, Italy and Spain



Canales et al. Front Med 2023

ATMPs legal framework

ATMPs are under EU regulation that states that their authorisation **must follow** the centralised procedure.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

However, the regulation itself establishes a **hospital exemption (HE).**

European Regulation EC 1394/2007, directive 2001/83/EC and EC 723/2004

HE: legal framework

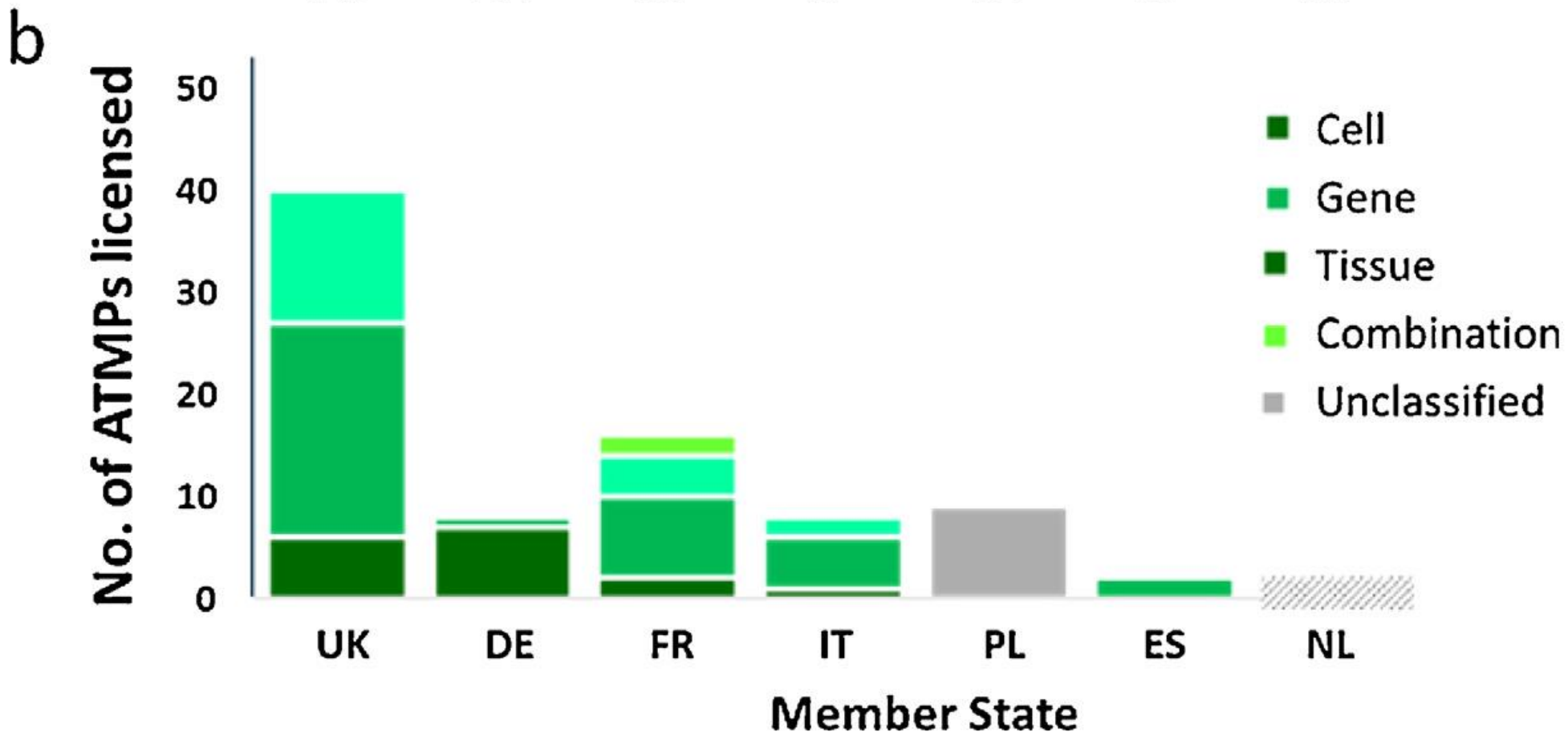
- ATMPs prepared occasionally in a **hospital** and under the professional responsibility of a registered **physician** to comply with an individual optional prescription of a custom-made product intended for a **single patient**
- Manufacture must be authorised by the national competent authority (NCA)
- ATMPs entirely prepared in **non-profit** institutions linked to the National Health System
- Medicines in clinical investigation phase or medicines that the NCA considers that satisfy the guarantees of **quality, safety, efficacy, identification and information**

European Regulation EC 1394/2007, directive 2001/83/EC and EC 723/2004

What is the difference?

CENTRALISED PROCEDURE	HOSPITAL EXEMPTION
EMA administrative procedure	NCA procedure
Approval valid for all EU at the same time	Approval valid only for requesting hospital(s)
EMA eCTD submission	National CTD submission
Industrially manufactured	Non industrially manufactured: • Individual patients treated in authorised hospital • Manufacturing is carried out in authorised sites
Commercial authorisation	Non-for-profit

HE approvals in EU



Hills A. et al. 2020

HE authorization clause - SPAIN

RD 477/2014 AUTHORISATION OF ATMPs OF NON-INDUSTRIAL MANUFACTURE

- It allows the use of ATMPs under the conditions specified in the same authorization. Guarantees that the medicinal product satisfies the required quality, safety, efficacy, identification and information standards

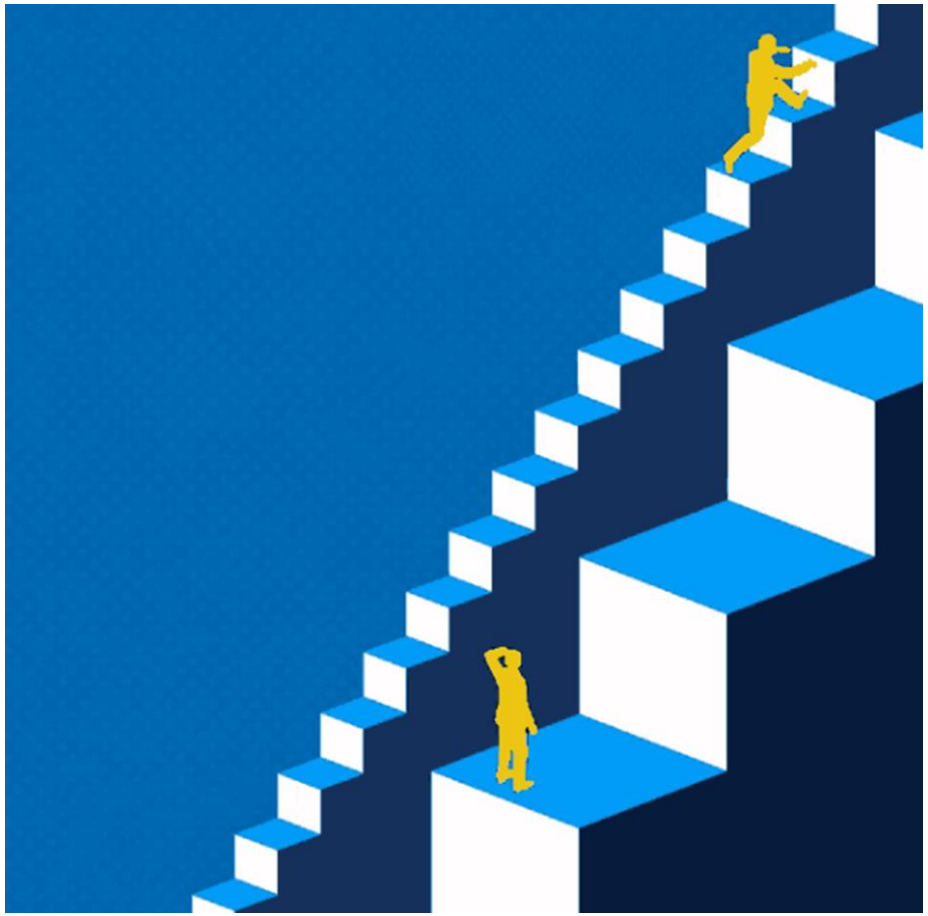
- The authorisation of use may contain elements of cross-compliance which oblige the holder to submit additional data

HE follows strict standards of traceability, pharmacovigilance, and quality

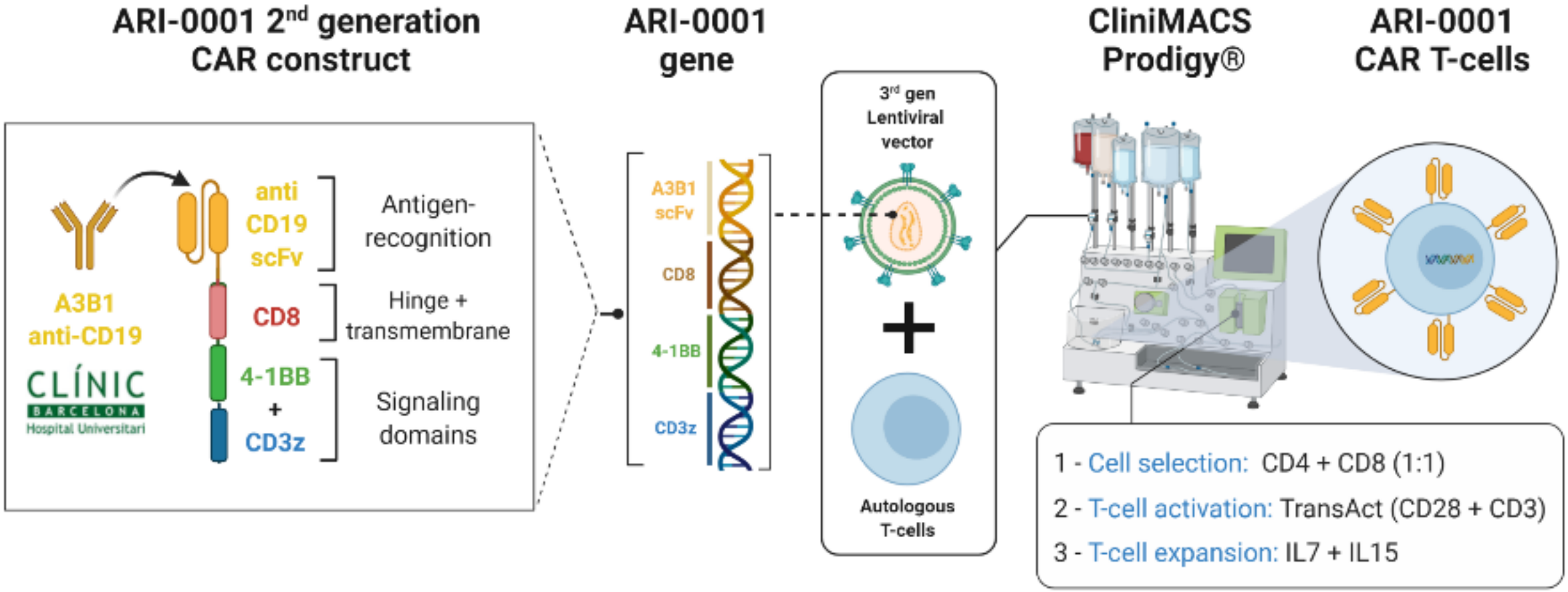
Spanish Royal Decree 477/2014 complements EC 1394/2007, directive 2001/83/EC and EC 723/2004

HE: an opportunity for academia

- HE allows for the use of ATMPs under special conditions
- HE is only applicable to individual patients treated in the hospital setting and it is limited to EU member states
- HE is only granted by the NCA to the academic centre that developed the ATMP



ARI-0001 cells (varnimcabtagene autoleucel [var-cel])



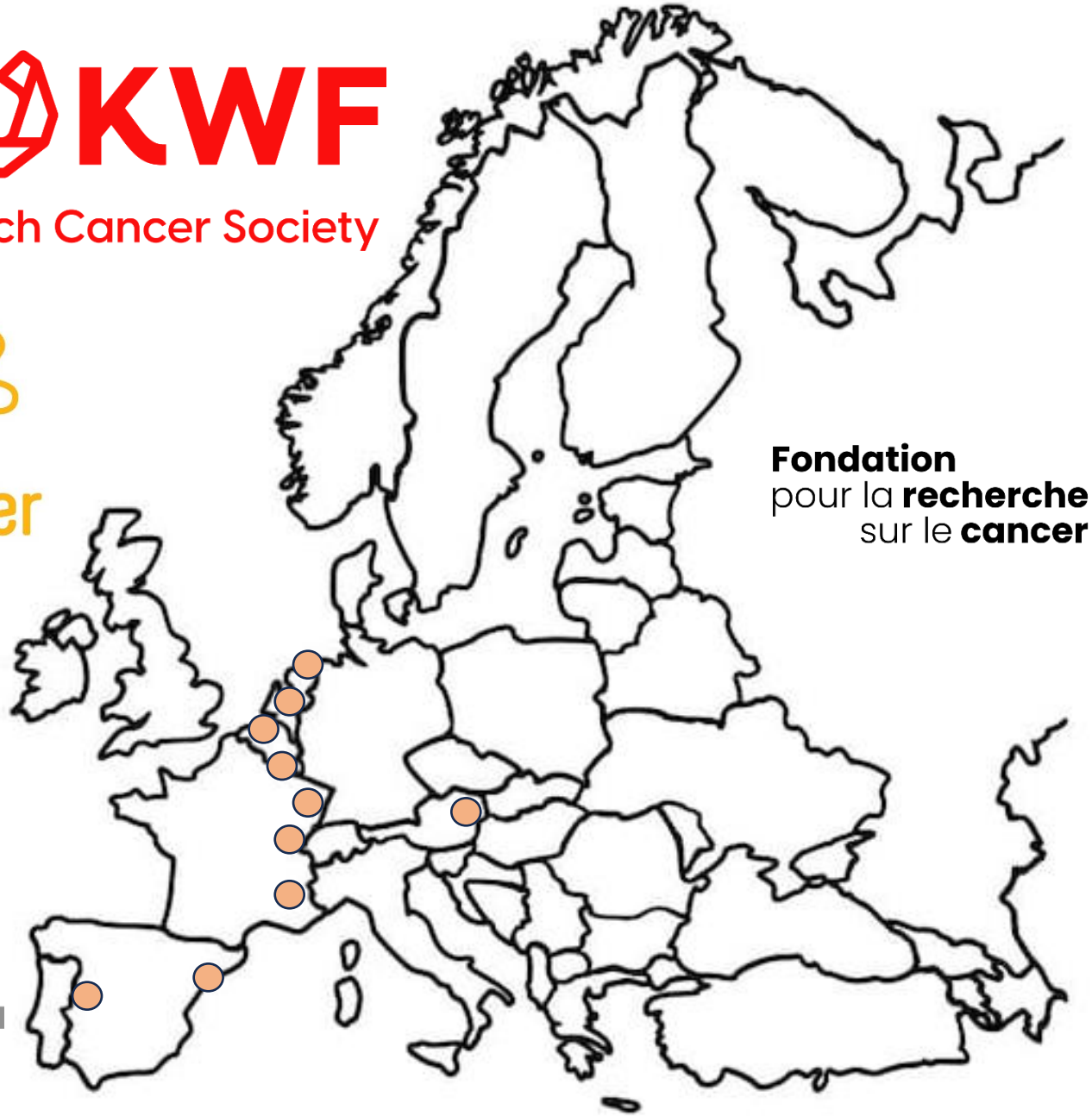
ARI-0001: Updated development status

- Registration dossier submitted to the AEMPS in FEB2020 (HE) → ARI-0001 cells (var-cel) approved for patients older than 25 years of age with R/R ALL (FEB2021). Based on 38 pts treated in the CART19-BE-01
- Price & reimbursement agreed with Ministry of Health in JUN2021 → €89,270
- PRIME designation in OCT2021 (first academic product to achieve it)
- Inclusion in EMA's pilot programme of enhanced support to academic ATMP developers in SEP2022 (first product included in the programme)
- First EMA's Scientific Advice completed in DEC2022, follow-up in APR2024. Paediatric Investigation Plan agreed in MAY2023
- Pivotal CART19-BE-02 trial in 12 Spanish centres (adult R/R ALL indication) → finished recruitment in AUG2023 → currently preparing CSR
- Pivotal CART19-BE-03Ped trial in 4 Spanish centres (paediatric R/R ALL) → currently ongoing
- Confirmatory CART19-EU-04 trial in 10 EU centres (5 different EU member states) → funding obtained, currently in preparation

Clínic Barcelona | Universitat de Barcelona

KWF
Dutch Cancer Society

Kom op tegen Kanker



Fondation pour la **recherche** sur le **cancer**

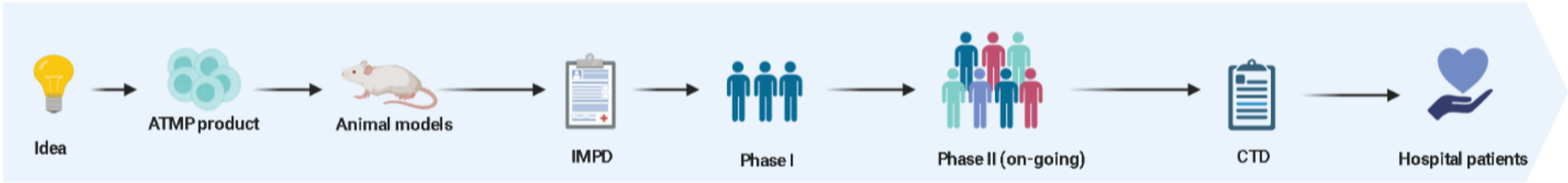
fundación científica
asociación española
contra el cáncer

How did we get HE approval?

Basic research & Non-clinical development

Clinical development

Post-HE approval



National regulatory requirements

Investigational Medicinal Product Dossier (IMPD)

Common Technical Dossier (CTD)

Olesti E. et al. under preparation

Key regulatory requirement: IMPD

1

QUALITY

To guarantee that the ATMP product is manufactured under quality standards.

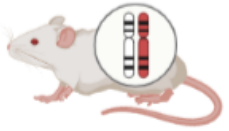
- Product development according to: Pharmacopoeia and EMA/ICH guidelines.
- Definition of the in-process controls and product specifications with scientific justification.
- Evaluation of the quality controls in all batches analysed.

2

NON-CLINICAL

To evaluate the pharmacology, pharmacokinetics and toxicology of the drug product.

- Exploraotry studies, GLP assays and longer toxicological assays during clinical studies.
- Evaluation of safety and efficacy of the product in: in vitro, in vivo and in silico models.
- Experiments must be considered for each application product.



3

HUMAN EXPERIENCE DATA

To identify the previous clinical experience data with the product.

- Compendium of all the clinical data of the product that is available and evaluation of initial results of efficacy and safety.
- In case of first-in-humans, report efficacy and safety of comparable products with similar indications.

4

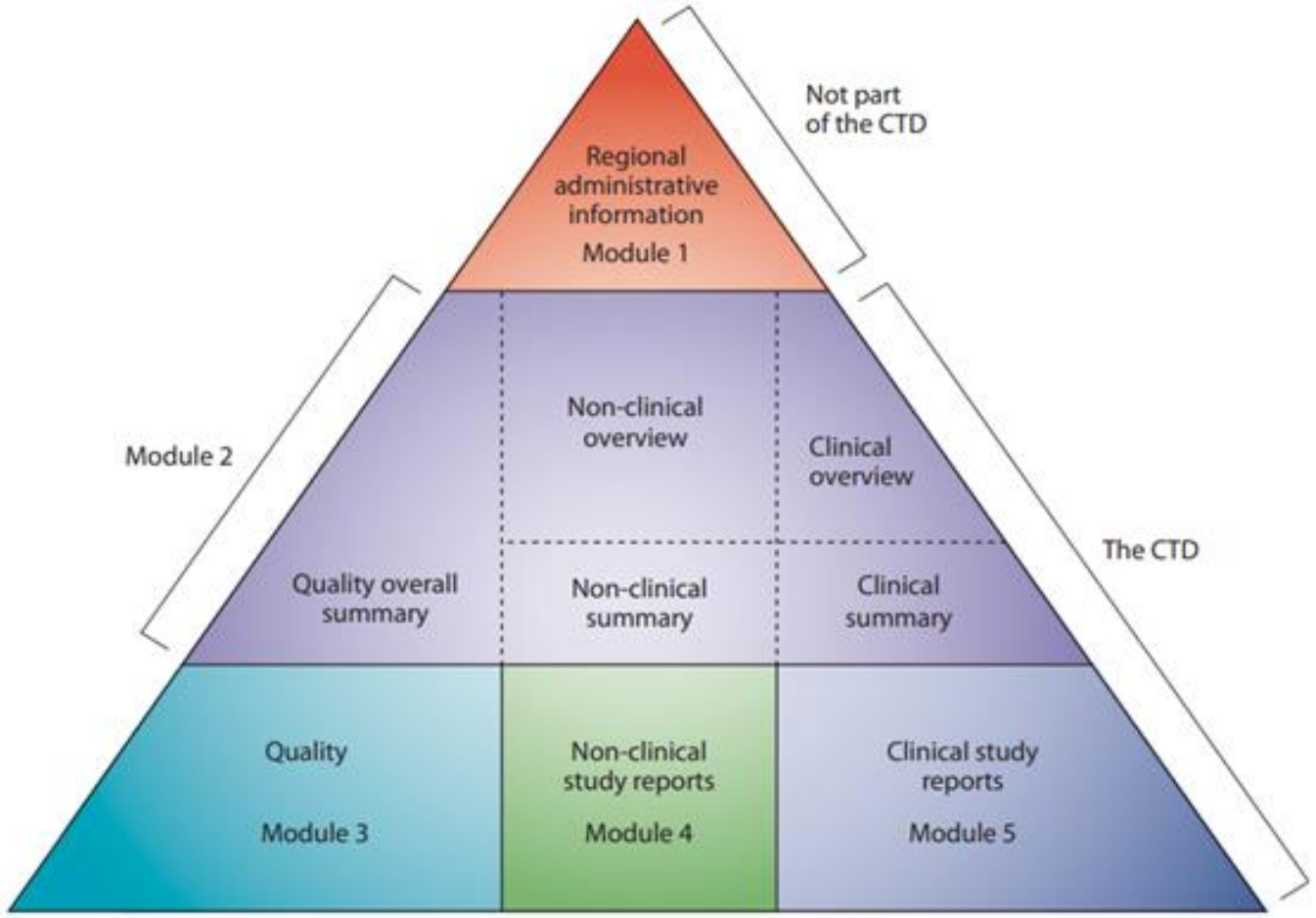
OVERALL RISK & BENEFIT ASSESMENT

To guarantee that the the risk of product adminitration is inferior to the potential benefit.

- Assessment of the product related potential risk (simiilar products) and identification of potential measures for risk minimization.
- Analysis of the potential therapeutic advances of the product and patient's clinical benefits.

Olesti E. et al. under preparation

National common technical dossier (CTD)



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Pharmacovigilance

- Constant interaction with the NCA (AEMPS) to report severe adverse effects
- Submission of PBRER (periodic benefit-risk evaluation report) after 6 months of authorisation of use → and then repeatedly
- Constant up-date of the Risk Management Plan
- Design of a long-term follow-up study: **Safety CAR-T**

Close pharmacovigilance of ARI-0001 in all possible administration regimes:

- Hospital Exemption
- Compassionate use programmes
- Clinical trials (CART19-BE-01, CART19-BE-02, CART19-BE-03Ped)

What was our experience with HE (ARI-0001)?

Strict (and lengthy!) evaluation by the Spanish Medicines Agency:

- Nonclinical
- Quality
- Clinical

Approval limited to patients with R/R ALL **older than 25 years**

No need for:

- Paediatric investigation plan
- Non-similarity evaluation
- Fees

Is Hospital Exemption an Alternative or a Bridge to European Medicines Agency for Developing Academic Chimeric Antigen Receptor T-Cell in Europe? Our Experience with ARI-0001

Manel Juan,[1–5,*,i] Julio Delgado,[3–6] Gonzalo Calvo,[2–4,7] Esteve Trias,[2,4] and Álvaro Urbano-Ispizua[3–6,*]

[1]Inmunology Service; [2]Advanced Therapies Unit; [3]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS); [4]Hospital Clínic de Barcelona; [5]Universitat de Barcelona; [6]Hematology Service; and [7]Clinic Pharmacology, Barcelona, Spain.
[i]ORCID ID (https://orcid.org/0000-0002-3064-1648).

Nombre	Titular de la autorización de uso	Fecha autorización de uso	Ficha técnica	Prospecto	Material de prevención de riesgos
NC1 – Suspensión celular en plasma autólogo 100-300×10^6 células, jeringa precargada	Hospital Universitario Puerta de Hierro Majadahonda	29-01-2019	Ficha técnica	Prospecto	
ARI-0001 Dispersión para perfusión que contiene 0,1-1×10^6 células/kg	Hospital Clínic de Barcelona	01-02-2021	Ficha técnica	Prospecto	
CEMTROCELL 50.000 células/microlitro – Suspención para implantación	Clínica Cemtro S.A.	31-10-2023	Ficha técnica	Prospecto	
Piel humana obtenida por ingeniería de tejidos 1,0-1,5 x 10^6 / 1,5-3,0 x 10^6 células / lámina apósito impregnado	Hospital Universitario Virgen del Rocio – Sevilla	06-06-2024	Ficha técnica	Prospecto	
ARI0002H 13,5-720 X 10^e6 Células dispersión para perfusión	Hospital Clínic de Barcelona	08-08-2024	Ficha técnica	Prospecto	

What was our experience with ARI0002h?

- Even lengthier evaluation by the Spanish Medicines Agency (2.5 years)
- More prevalent disease (R/R multiple myeloma)
- One commercial CART-cell product became available (reimbursed) during evaluation → AEMPS reasoned that this would not suffice to cover the entire Spanish population
- Price & reimbursement not agreed yet

How should we continue (EMA-wise)?

- PRIME designation impossible (difficult to justify unmet medical need with two commercial products approved) → First SA with EMA completed (€30K)
- Only possibility for approval would be a 200 pt randomised trial (€30-50M??)

Conclusions

HE legislation has allowed the development of a CAR T cell therapy under an academic hospital setting, warranting the standards of safety and efficacy required for commercial CARTs

Investing in human and logistic resources is essential for success, and therefore unequivocal institutional commitment is needed to undertake these complex projects

HE is a great opportunity to develop ATMPs in the EU academic environment

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Javier López
J.M. García-Gala
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J.M. Ribera

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Mireia Bachiller
Laura Palau
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Judit Pich
Gemma Domènech
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María Calvo

Susana Rives
Anna Alonso
Iolanda Jordan
Montse Torrebadell
Mireia Camós

Valentín Ortiz
Núria Martínez
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Mercedes Montoro
Pilar Ayora
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Gerardo Rodríguez
Aina Oliver-Caldes

Esteve Trias
Cristina Bernadó
Sílvia Cufí

Pedro Castro
Yolanda Blanco
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Xavier Setoaín
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Víctor Albarrán

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Mireia Uribe
Bea Martín

Miquel Lozano
Joan Cid
Paola Charry

Dolors Colomer
Neus Villamor
Elías Campo
Mònica Garcia
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Noelia Mateo
Rosa García
Marc Roda
Antoni Castells
Pep Canals

Collecting data: The EBMT Patient registry

Ana Alarcón Tomás, Hospital Universitario Puerta de Hierro Madrid, Spain

on behalf of the EBMT

Agenda

The EBMT Patient Registry

Who we are

Fast facts

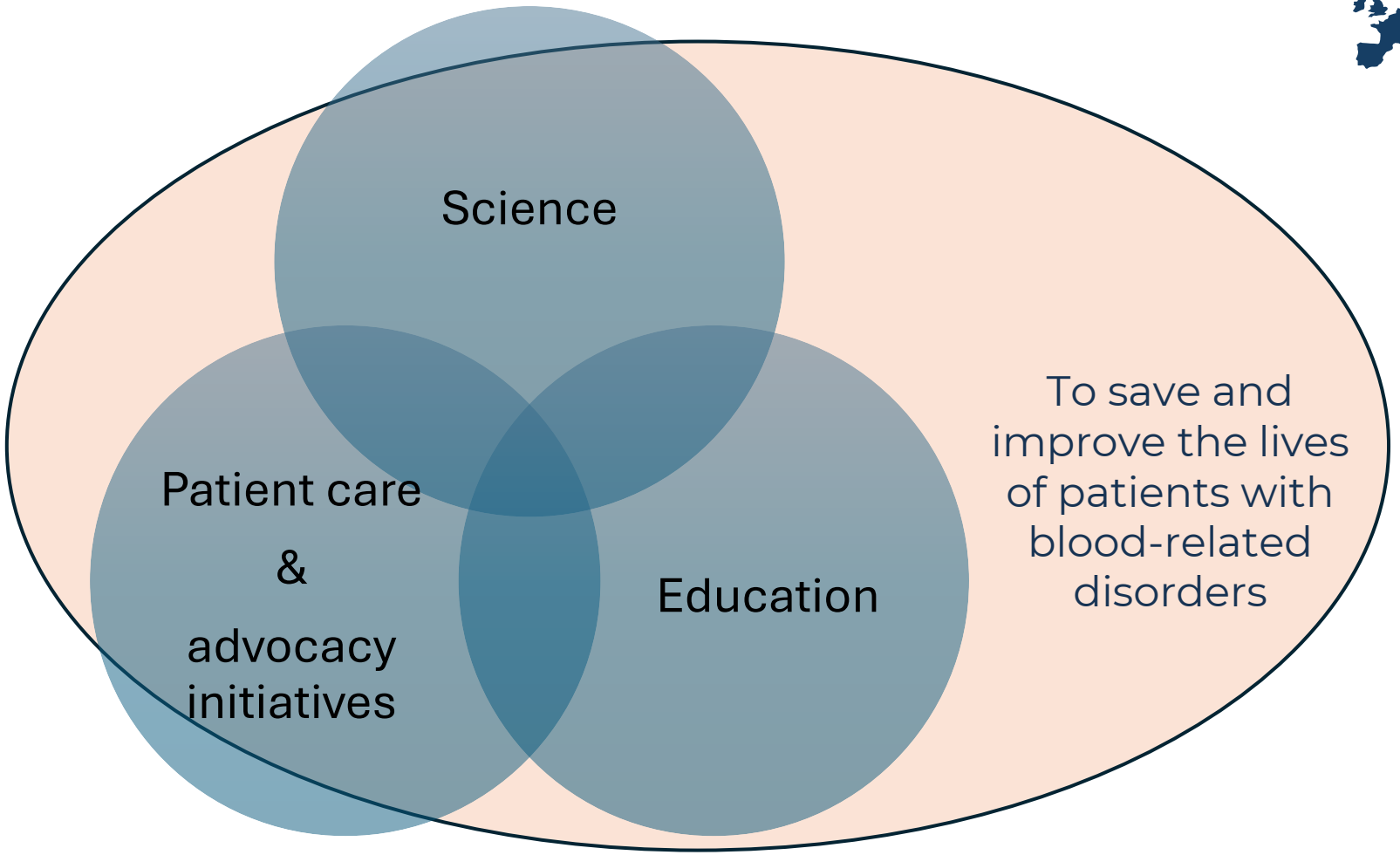
How it works

Challenges in data collection and how to avoid them

HE Data

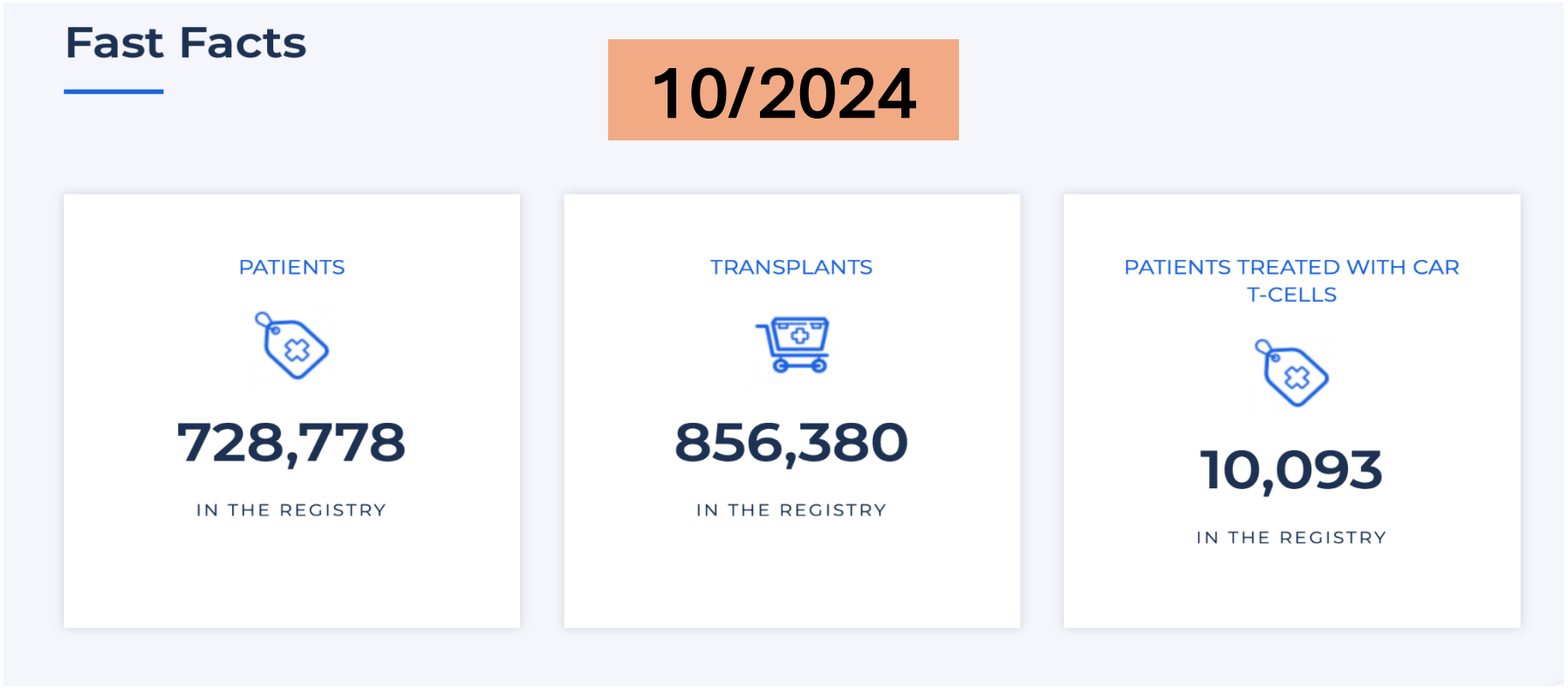
The EBMT : Who we are

Established in 1974
>500 Centers
>70 Countries



We are a community of healthcare professionals focused on innovation, research and the advancement of cellular and stem cell-based therapies

The EBMT Patient Registry: Fast facts

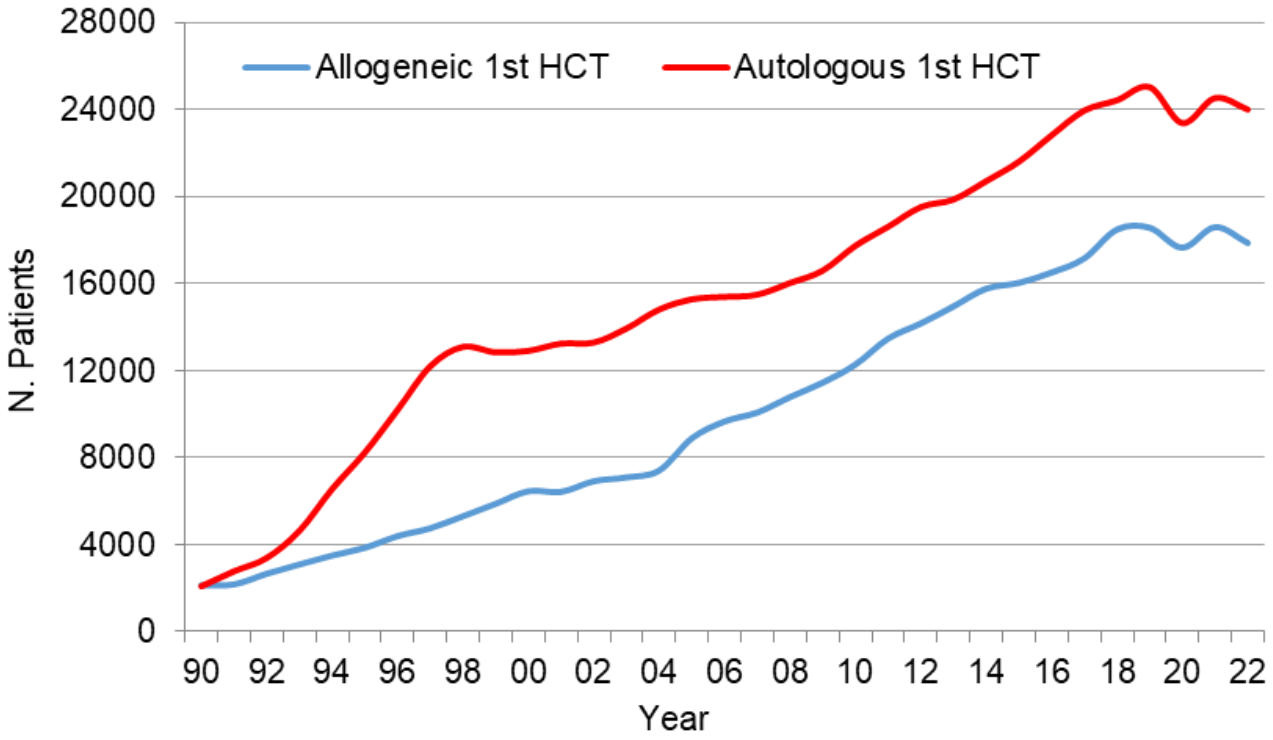


500 centers
70 countries

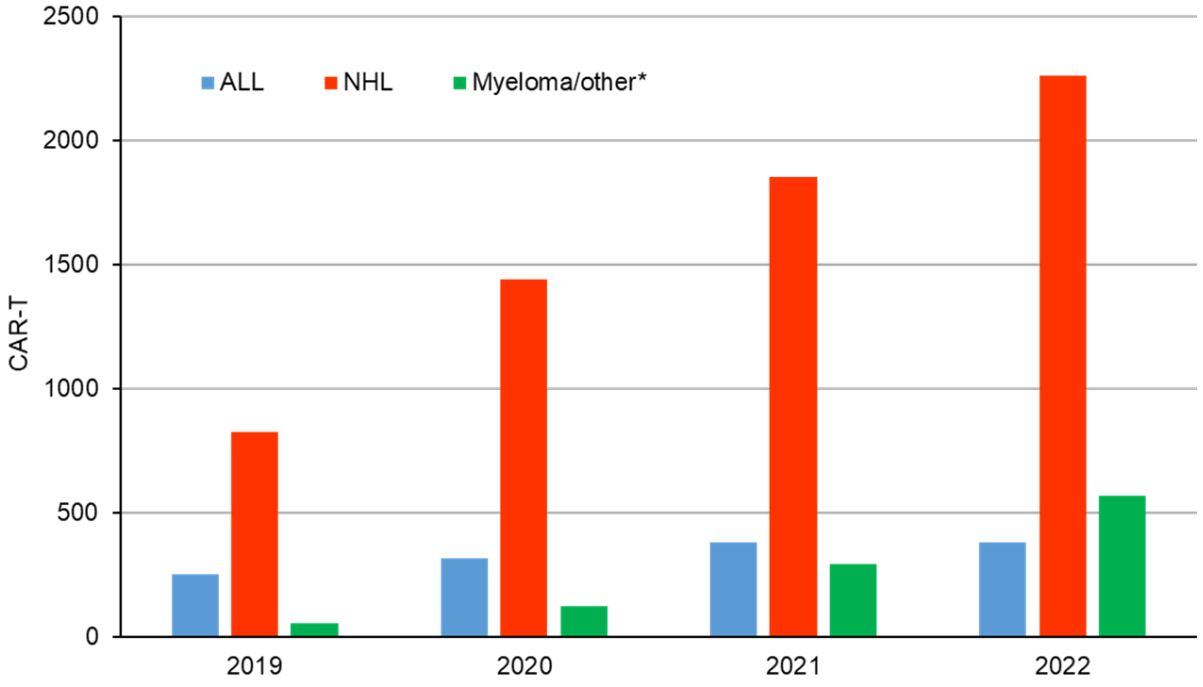
2023. New EBMT Registry platform.
European Transplant and Cellular Therapy Online Registry (EuroTraCTOR):The objective of the project is to design, develop and implement a new EBMT registry to improve the processes of collecting and using data across EU health systems.

The EBMT Patient Registry. Ebmt.org

The EBMT Patient Registry: activity

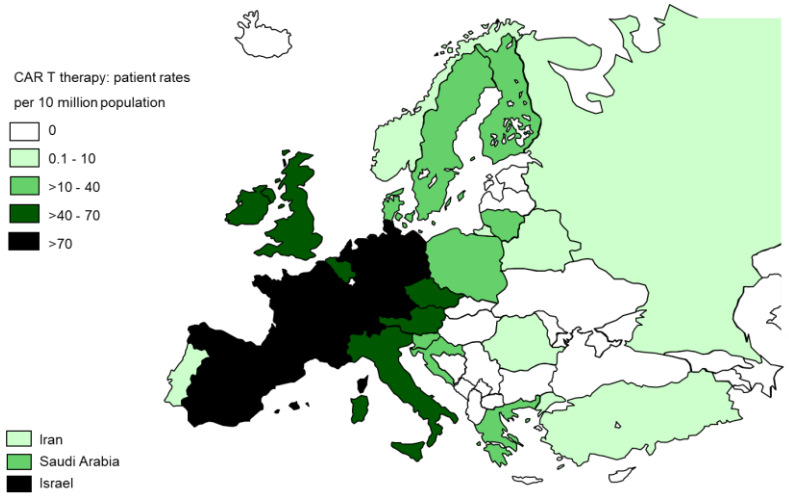


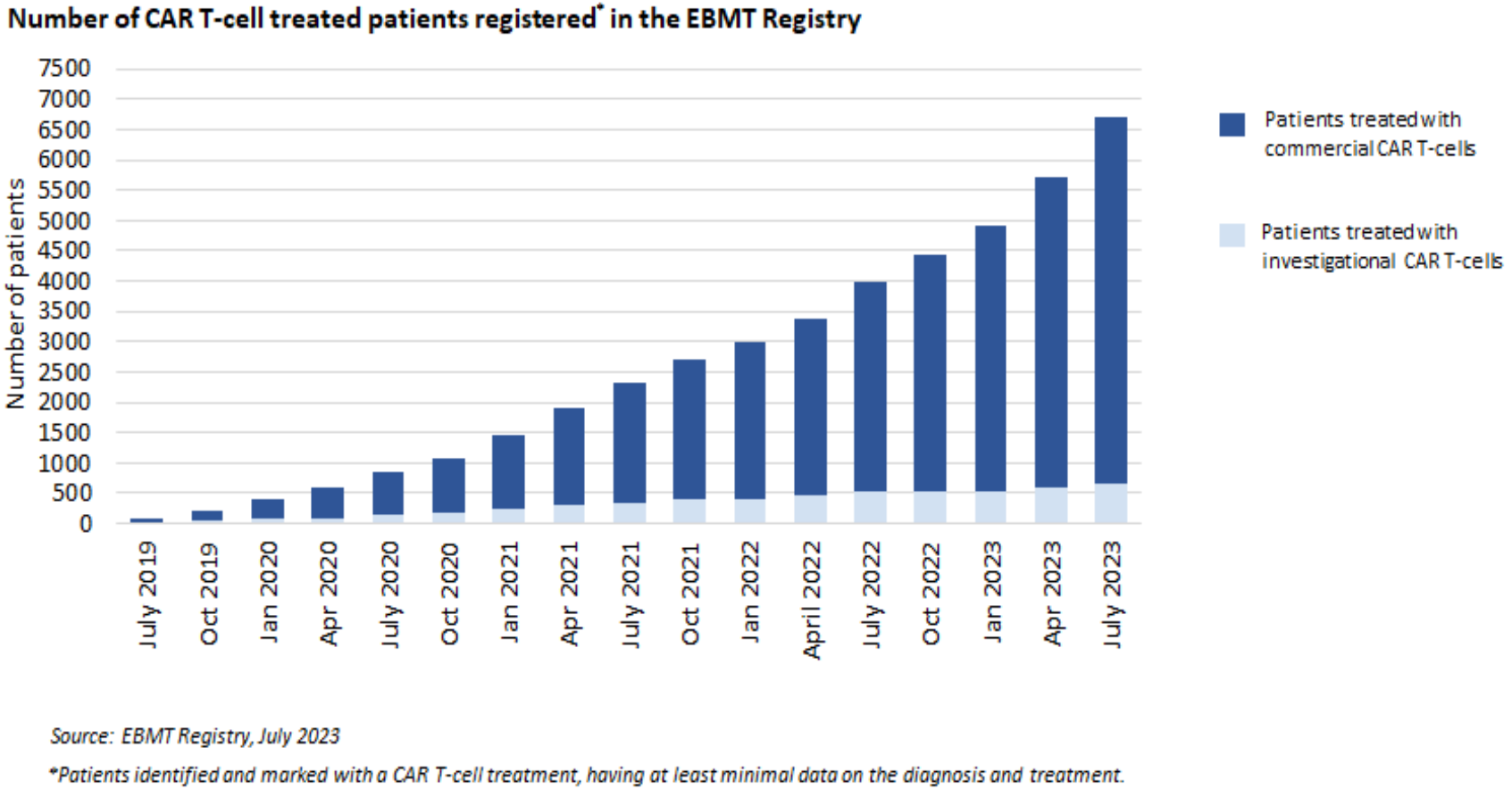
CAR T activity from 2019-2022



Activity survey Office in Basel and Leiden

CAR-T per 10 million population in 2022





Source: EBMT Registry, July 2023

**Patients identified and marked with a CAR T-cell treatment, having at least minimal data on the diagnosis and treatment.*

Activity survey Office in Basel and Leiden

Cellular therapies in Europe 2022

Number of patients	CAR-T		MSC		NK cells		Selected/expanded T cells or CIK		Regulatory T cells (TREGS)		Genetically modified T cells		Dendritic cells		Expanded CD34+ cells		Genetically modified CD34+ cells		Other		Total	
	Allo	**Auto**	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	allo	auto
GvHD			273	1			1		30										13		317	1
Graft enhancement			30				16								12			2	111	50	169	52
Autoimmune dis.		**9**	11	3											5				4		20	12
Genetic disease																4	3	19	3		6	23
Infection			1	8			116	46	4		7	2							6	1	134	57
Malignancy - ALL	**44**	**336**			19		18	9				4		4	1				14		96	353
Malignancy - HL/NHL	**1**	**2258**			4	2	23				1		1						1	8	31	2268
Malignancy - myeloma	**3**	**467**			7							6							3	12		485
Malignancy - other indication	**4**	**83**	15	13	15	3	41	17				19		20				4	35	23	110	182
Total	**52**	**3153**	**330**	**25**	**45**	**5**	**215**	**72**	**34**	**0**	**8**	**31**	**1**	**24**	**18**	**4**	**3**	**25**	**190**	**94**	**896**	**3433**

DLI for graft enhancement/failure	804
DLI for residual disease	393
DLI for relapse	1294
DLI per protocol	363
Total	2854

Activity survey Office in Basel and Leiden

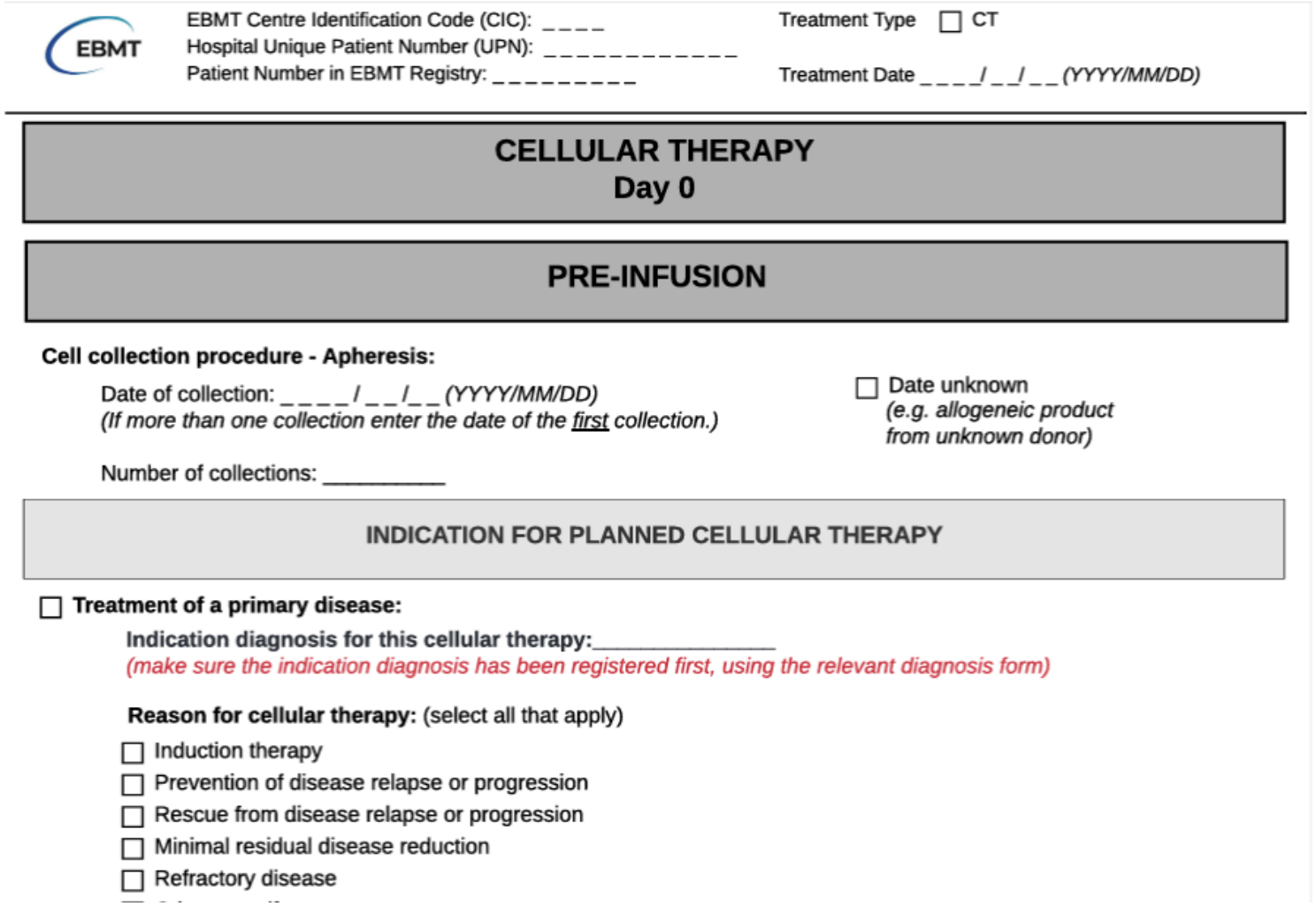
The Registry: How it works

EBMT Registry

Data Collection Forms (DCFs).

It contains:

- Patients' clinical data, including aspects of the diagnosis and disease
- first-line treatments
- HCT or cell-therapy-associated procedures, transplant type, donor type, stem cell source, complications and outcome.
- Patients are followed up indefinitely.



EBMT Centre Identification Code (CIC): ____
Hospital Unique Patient Number (UPN): _____
Patient Number in EBMT Registry: _____

Treatment Type ☐ CT
Treatment Date ____/__/__ (YYYY/MM/DD)

CELLULAR THERAPY
Day 0

PRE-INFUSION

Cell collection procedure - Apheresis:

Date of collection: ____/__/__ (YYYY/MM/DD)
(If more than one collection enter the date of the first collection.)

☐ Date unknown
(e.g. allogeneic product from unknown donor)

Number of collections: _____

INDICATION FOR PLANNED CELLULAR THERAPY

☐ **Treatment of a primary disease:**

Indication diagnosis for this cellular therapy:_____
(make sure the indication diagnosis has been registered first, using the relevant diagnosis form)

Reason for cellular therapy: (select all that apply)

☐ Induction therapy
☐ Prevention of disease relapse or progression
☐ Rescue from disease relapse or progression
☐ Minimal residual disease reduction
☐ Refractory disease

EBMT web page

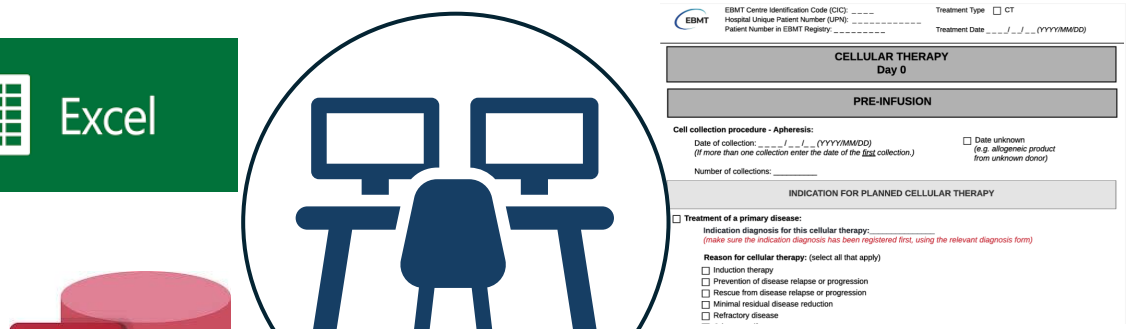
Challenges in Data collection

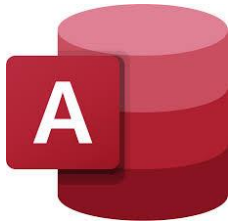
Expectation

Reality

REDCap
Research Electronic Data Capture

Excel





Redundancy

Burden

Challenges in Data collection. Keep the *"quid pro quo"*

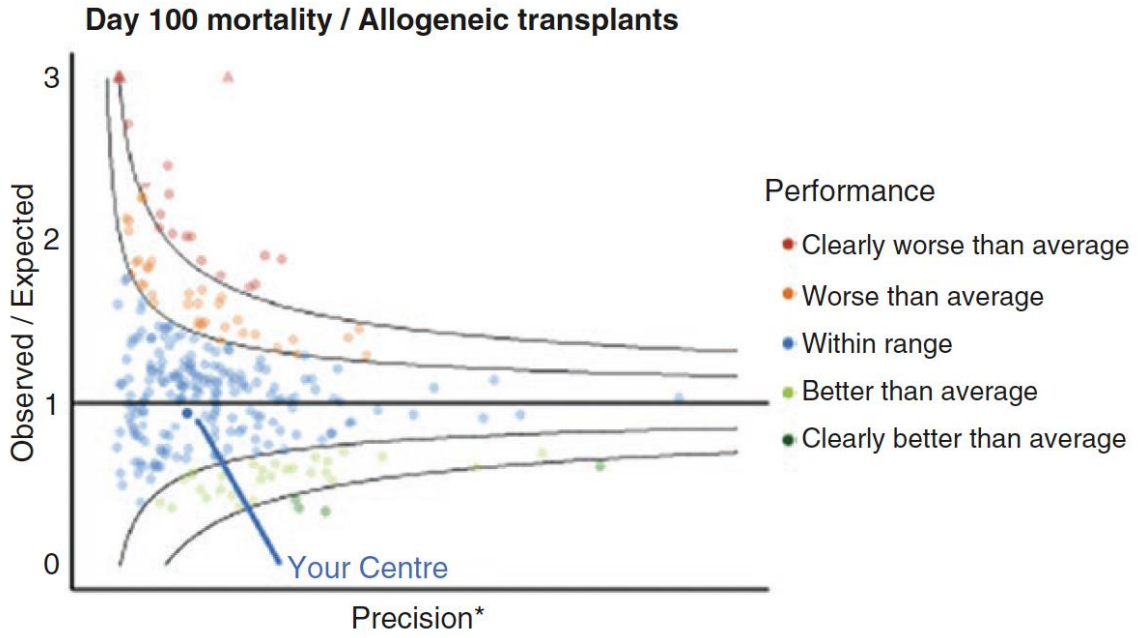
"In order to retain full EBMT membership status, they must report all consecutive HCTs each year."

Data Sharing

Access to EBMT Registry to retrieve data with statistical overviews
Working parties.

EBMT and Education

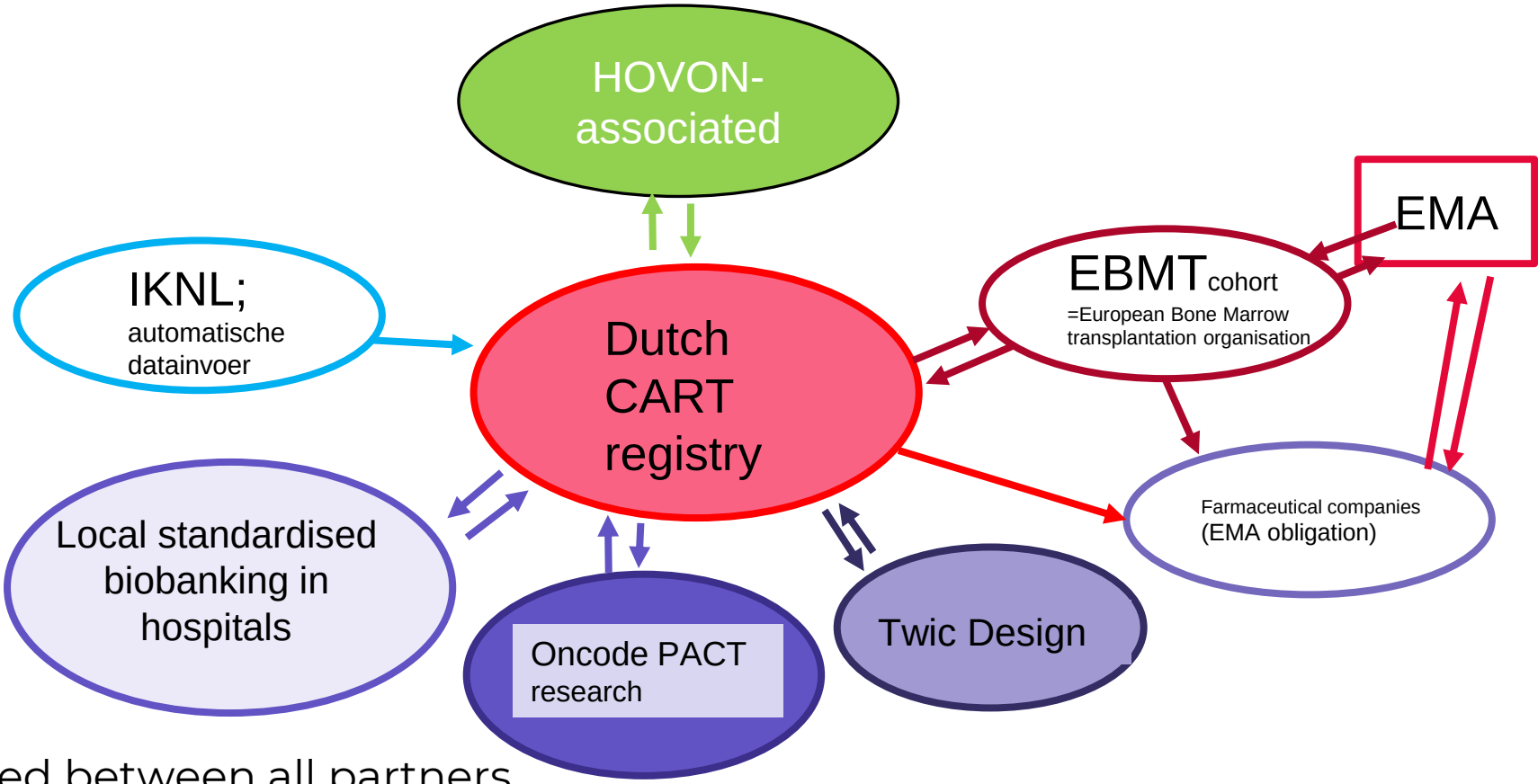
JACIE Accreditation fees.



R. Saccardi et al. EBMT Handbook 2022. . Figure from Kyrus

Future directions: How to simplify transfer data from the hospital to a registry

Linking National Registries electronically to the EBMT Registry Funded project by Dutch Authorities Oncode Accelerator



10/2024 NDA has been signed between all partners

https://www.oncodeaccelerator.nl

Shared by Dr. Jurgen Kuball.

Hospital exemption data from the EBMT

EBMT Centre Identification Code (CIC): _____
Hospital Unique Patient Number (UPN): _____
Patient Number in EBMT Registry: _____

Treatment Type ☐ CT

Treatment Date ____/__/__ *(YYYY/MM/DD)*

BASIC INFORMATION ON THE PLANNED CELLULAR THERAPY

Clinical setting:
(check only one)

☐ As per marketing approval / Standard of care / Institutional guidelines

☐ Hospital exemption

☐ Compassionate use / Accelerated access

☐ Investigational drug product (IDP)/ Clinical trial

Phase: ☐ 1 ☐ 1/2 ☐ 2 ☐ 2/3 ☐ 3

Blind trial: ☐ No ☐ Yes

Randomised trial: ☐ No ☐ Yes

EudraCT number: _____

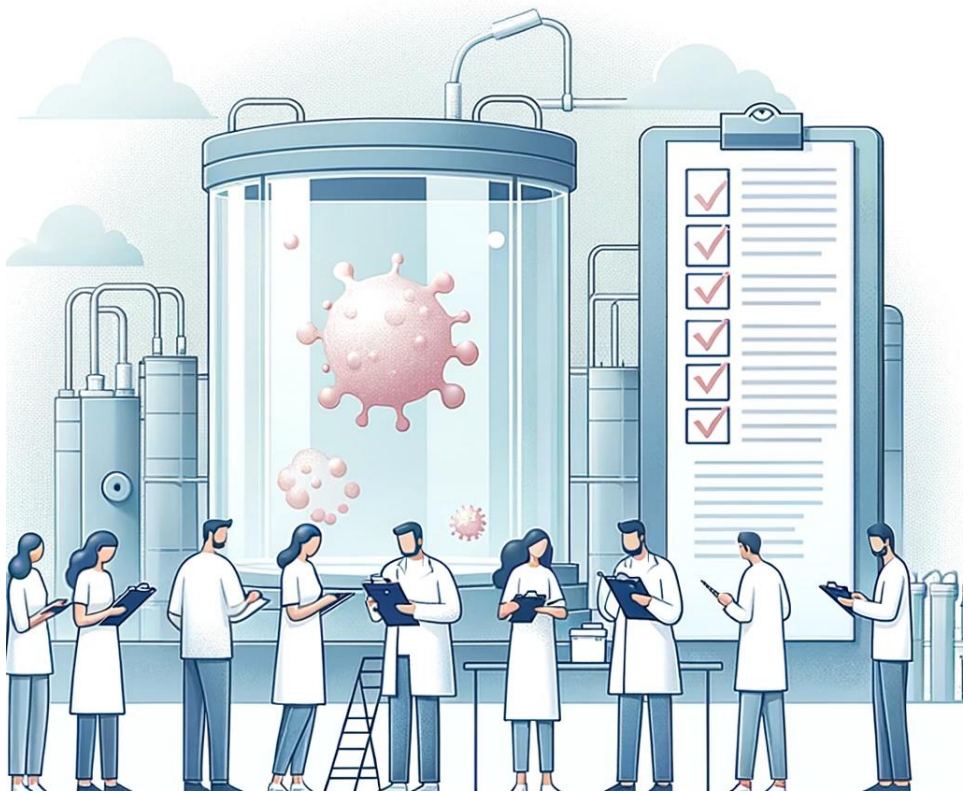
USA NCT number: _____

UMIN CT number: _____

Data shared by The office of EBMT Registry.

Hospital exemption data from the EBMT

Survey on the organization and techniques of ATMP facilities in Europe



10/2024 analysis of survey started

Jurgen **Kuball**

Trudy **Straetemans**

Michael **Hudecek**

Annalisa **Ruggeri**

Ruud **Das**

Data shared by Dr. Jurgen Juball.

EBMT & stakeholders

EBMT is collaborating with different Marketing Authorisation Holders (MAH) on the conduct of **EMA-endorsed Post Authorisation studies**.

Manufacturer	Product	Enrolment period	Contracted indications	Enrolment (target)	No patients included (% accrual)
Kite	Yescarta	2020-2023	DLBCL+PMBCL	**Closed**	1471 (100%)
Novartis	Kymriah	2020-2023	ALL+DLBCL	**Closed**	800 (100%)
Celgene-BMS	Abecma	2021-	MM	300	174 (58%)
Celgene-BMS	Breyanzi	2022-	DLBCL+PMBCL+FL	200	26 (13 %)
Kite	Tecartus	2023-	MCL	300	151 (50%)

1st PASS interim report as oral at ASH, 2nd submitted to CART25

Data shared by Dr. Jurgen Juball.

EBMT & HE

Thank you!

Ana Alarcón Tomás on behalf the EBMT

EMA
EUROPEAN MEDICINES AGENCY

Supporting academic developers of ATMPs

European regulatory tools

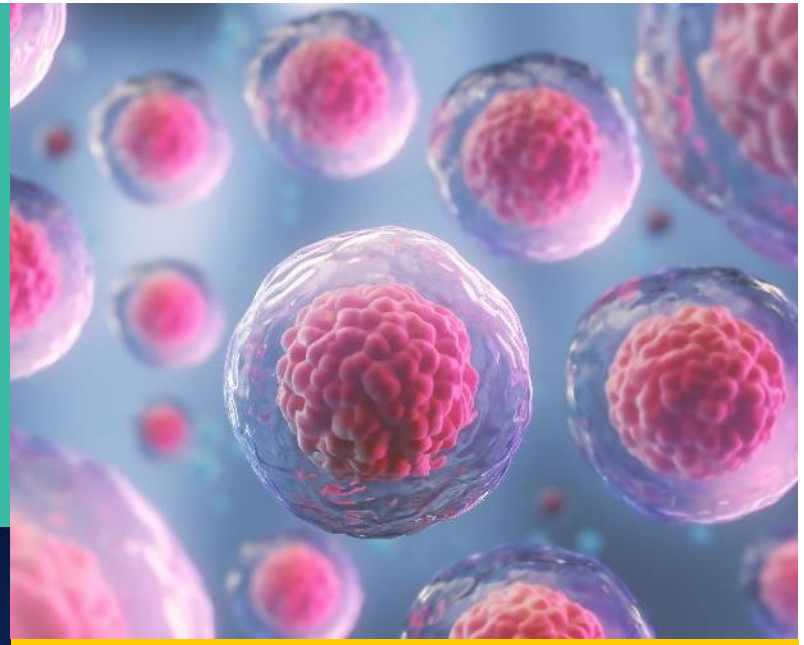
Caroline Pothet
Head of advanced therapies and haemato-oncology

I do not have any conflict of interests.

AT (Medicine) P

EU patients are entitled to good quality medicines that are **safe and effective medicines** …

NB: 2020 CAT warning against **unproven cell-based therapies**.



Science

Academia **= Driver for innovation**

About 25% of approved ATMPs originated in an academic environment (…) - yet only 1 non-profit MAH so far.

Health

Framework and standards apply

Pharmaceutical legislation, scientific guidelines (GMP, GCP,…), “Lex specialis”, GMP for ATMPs,…

Commitment towards advanced therapies

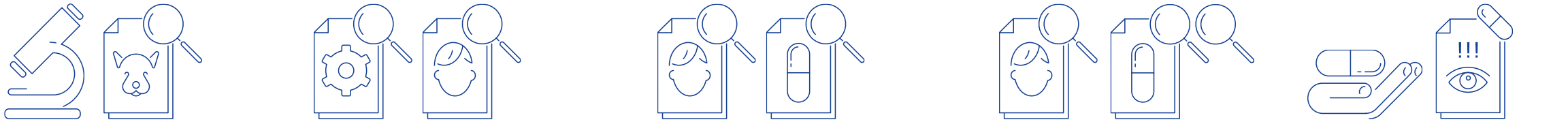
Support translation of advanced therapy medicinal products (ATMPs) into patient treatments	▸ Identify therapies that address unmet medical need; ▸ Provide assistance with early planning, method development and clinical evaluation; ▸ Address the challenges of decentralised ATMP manufacturing and delivery locations; ▸ Support evidence generation, pertinent to downstream decision-makers;
Support translation of advanced therapy medicinal products (ATMPs) into patient treatments	▸ Evaluate and improve interactions relevant to ATMPs with European institutions (research, financial and environmental); ▸ Raise global awareness of ATMPs to maximise knowledge sharing, promote data collection; ▸ Engage with other international regulatory agencies to foster global convergence of requirements for ATMPs.

Network strategy to 2028 : Seizing opportunities in a changing medicines landscape – Consultation open!
Supporting academic developers of ATMPs

Engagement with academia

- **Framework for collaboration with academia since 2017.**
  - Promote and further develop regulatory support for translating academic research into novel methodologies and medicines
  - Ensure best scientific expertise and research is available
  - Collaborate on areas of research on regulatory science
- **Dedicated entry point for Academia:** Academia@ema.europa.eu
- **Financial incentives**
- **Dedicated support tools**
  - e.g. ATMP support pilot, multi-national clinical trials, CTIS

Key support tools for academia



Early Research → **Non-clinical and First in Man** → **Clinical exploratory** → **Clinical confirmatory**

- **Authorisation**
- **Access decision**
- **Post-licensing evidence**

ITF/Academia briefing

Scientific Advice/Protocol Assistance

PRIME + Academic support pilot

ATMP classification

Orphan Drug Designation

Paediatric Investigation Plan (stepwise PIP)

Quality Innovation Group

CTIS helpdesk + ACT-EU initiatives (map and consolidated advice)

Supporting academic developers of ATMPs

EU-IN = EU Innovation Network

Innovation task force

To apply for an ITF briefing meeting, complete the **request form** below and email it to: itfsecretariat@ema.europa.eu

Innovation Task Force (ITF)

EUROPEAN MEDICINES AGENCY

Multidisciplinary platform

for preparatory dialogue and orientation on

innovative methods, technologies and medicines

- Support **innovative** drug development
- **Early informal** dialogue with opinion leaders (can be requested at any stage)
- 1,5-hour discussion – Free of charge
- Brainstorming "style" focusing on areas without/with limited guidance
- First step to engage is submit completed 3-page template

EMA
EUROPEAN MEDICINES AGENCY

Scientific advice & PRIME

Scientific advice and protocol assistance | European Medicines Agency (EMA)

PRIME: priority medicines | European Medicines Agency (EMA)

Scientific Advice & Protocol Assistance

EUROPEAN MEDICINES AGENCY

- Scientific advice (SA) is about advising developers on the best way to **generate robust evidence** (methods & study designs)
- SA for ATMPs is provided by the Scientific Advice Working Party (SAWP) supported by the Committee of Advanced Therapies (CAT) and Working Parties (e.g. BWP)
- SA can be provided on **any scientific question** (quality, non-clinical and clinical) at **any timepoint** of the development
- Possibility of *parallel consultation* (EMA/HTA bodies) and *parallel SA* with FDA (USA) or *qualification of novel methodology*

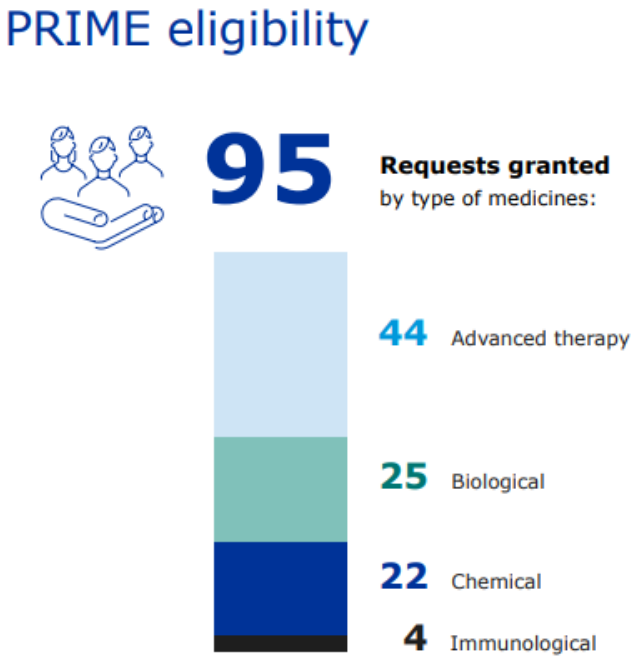
Special fee incentives:

- Protocol assistance **free-of-charge** to SMEs & academic developers
- SA free-of-charge to academic-owned **PRIME** and **ATMP PILOT** products
- Starting Jan-25, SA free-of-charge to academic-developed products

PRIME scheme (PRiority MEdicines)

EUROPEAN MEDICINES AGENCY

- Medicines under development (not yet authorized)
- Targeting conditions with an unmet medical need
- Require preliminary clinical evidence (proof of concept), exceptionall proof of principle
- Many intended for rare diseases and/or **ATMPs**



Key benefits:

- **Early assessment team** appointment
- **"Kick-off" meeting** with multidisciplinary expertise from EU network
- Scientific advice at key development milestones
- Potential to be eligible for **accelerated assessment**
- **Submission readiness meeting**

PRIME@ema.europa.eu

Academic support pilot for academic developers

EUROPEAN MEDICINES AGENCY

- ATMP support pilot for **academic** developers **launched Sep-22** with first product/applicant (ARI-0001; Hospital Clinic Barcelona)
  - EMA pilot offers enhanced support to academic and non-profit developers of advanced therapy medicinal products | European Medicines Agency (europa.eu)
- In line with framework of collaboration with academia : payment of fees identified by academia as a key hurdle.
- 2 new products selected in 2024
  - **TregTacRes**, modified (tacrolimus resistant) T regulatory cells, developed by Berlin Center for Advanced Therapies (BeCAT) as adjunctive therapy after living donor kidney/solid organ transplantation.
  - **Telethon003**, autologous CD34+ cells transfected with a lentiviral vector (containing the human WAS cDNA), developed by Fondazione Telethon (Italy) for Wiskott Aldrich Syndrome.

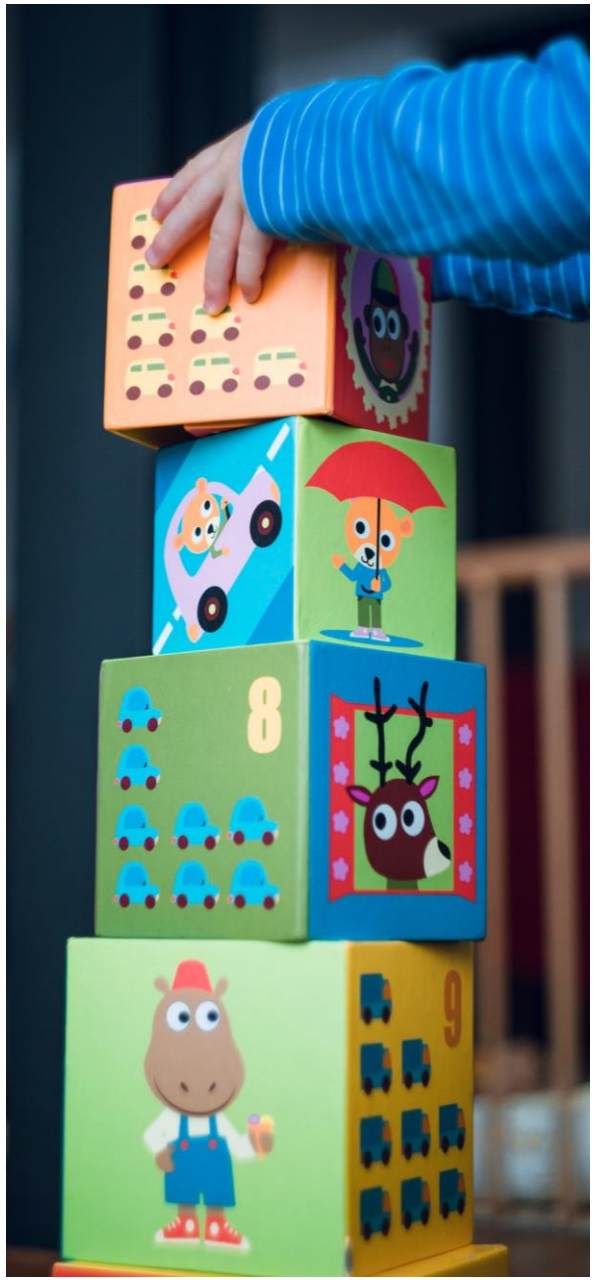
→ *In kind* regulatory support and fee incentives

Stepwise PIP (since 2023)

- Initial contact via AskEMA
- Allocation of a paediatric officer with expertise in the area
- (Informal) teleconference to discuss suitability

Reasons for applying

- Challenges with development in ultra-rare conditions for dose finding and endpoints.
- Lack of relevant animal model, no established PD markers or endpoints
- Condition in children different to adults, no proof of concept in humans yet.
- Rare, life-threatening disease, recently identified in children with no approved medicine or regulatory guidance, validated endpoints.



Requests

14 expr. of interest

7 qualify for pilot
5 under discussion
2 rejected

5 sPIPs applications submitted

Steps

- PDCO decides on D30 if application appropriate for sPIP pilot
- Advice provided during pre-submission meeting on suitability for sPIP pilot

Reasons for potential rejection

- Ongoing PIP
- Previous PIP for the same active
- After the pre-submission meeting it became clear how the development programme could be defined

EMA aims to analyse pilot results when 8 sPIP opinions adopted

Oncology

Metabolic diseases

Cardiology

Neurology

Respiratory diseases

Immunology

ACT-EU initiatives

Consolidated advice on clinical trials - European Union

Support for non-commercial sponsors - European Union

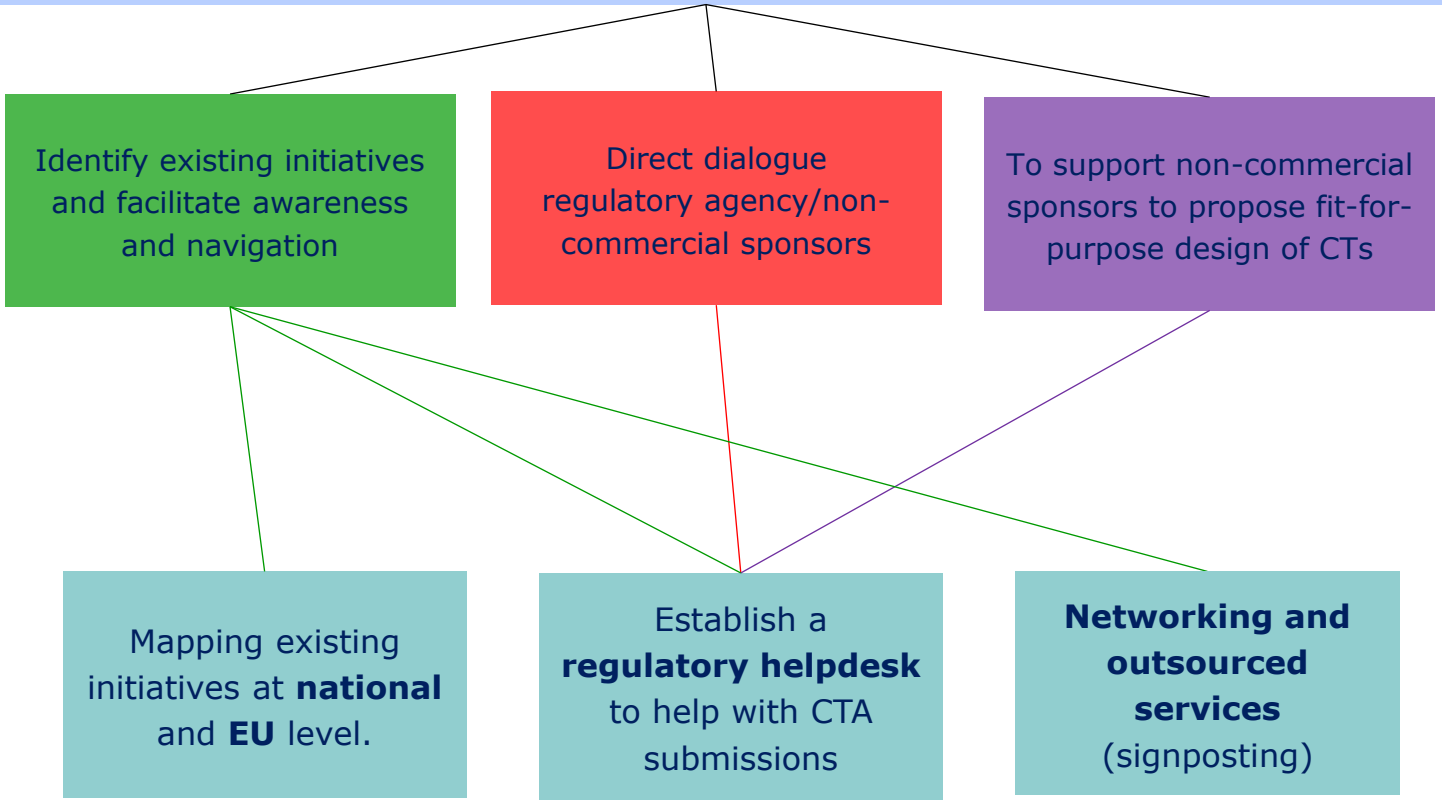
ACT EU Vision

Better, faster, optimised clinical trials

Mission

To make (multinational) CTs for non-commercial sponsors more accessible, economically advantageous and impactful

Objectives = to solve problems identified



Map of national initiatives supporting noncommercial sponsors

The ACT EU initiative aims to **identify gaps, issues and bottlenecks** (regulatory, resourcing, operational) that present challenges for non-commercial sponsors in the conduct of multinational clinical trials.

The programme intends to **propose pragmatic and harmonised solutions to support non-commercial sponsors** setting up and conducting multi-national clinical trials across the European Union / European Economic Area.

Map of national support initiatives

The Clinical Trials Regulation aims to create a more favourable environment for the conduct of clinical research in the EU.

With input from the Clinical Trials Coordination Group (CTCG), ACT EU has identified initiatives available in each EU Member State to support non-commercial sponsors at national, EU or global level.

National initiatives for non-commercial sponsors

- Webpage live since **July 2024**
- Updates dependant on MSs' input

Webpage populated with other initiatives useful for non-commercial sponsors and academia conducting CTs in the EU:

a. Network
b. Infrastructure
c. Database
d. …

National initiatives for non-commercial sponsors - European Union

Pre-CTA and SAWP-CTCG consolidated advice

The Accelerating Clinical Trials in the EU (ACT EU) launched **two advice pilots**

The pilots
- enhance the **coordination within the EMRN**
- to offer applicants **harmonised advice** on
- how to improve the quality of their applications for **clinical trial application** and **marketing authorisation**.

I Pilot: SAWP-CTCG

II Pilot: Pre-CTA Advice

Context:
Up to date **mapped information on current voluntary advice procedures** available from EU regulators on Medicines for human use

Pilots started officially on **June 10th**

Supported by training Webinars
for Applicants (recorded)
for Assessors
Published Guidance documents on ACT EU website

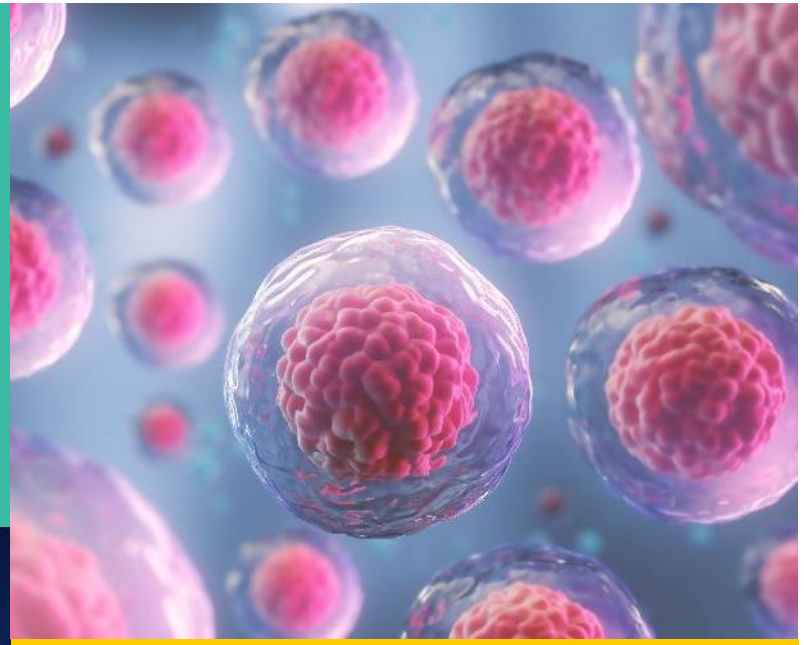
List of MS participating in the pilot projects:
Member States participating in ACT EU pilots on consolidated advice (europa.eu)

Supporting academic developers of ATMPs

Consolidated advice on clinical trials - European Union

AT (Medicine) P

Various tools available and regularly introduced based on your feedback : Make full use of it!



Science

Academia = Driver for innovation

We are committed to innovation via **(early) engagement and multistakeholder platforms**

Health

We are aware of the challenges faced by the sector and **committed to tackle them together along the future pharmaceutical legislation**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Find out more on **ema.europa.eu**

[Advanced therapy medicinal products: Overview | European Medicines Agency (EMA)]

Supporting academic developers of ATMPs and competitiveness of the EU biotech sector

In-depth product specification and therapy response monitoring to support clinical development of CGTs

Hans-Dieter Volk

Professor (em) of Clinical Immunology and Regeneration

Institute of Medical Immunology and BCRT

Charité Universitätsmedizin Berlin

&

CSO

Checkimmune GmbH

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

CheckImmune
ADDED-VALUE FOR YOUR CLINICAL DEVELOPMENT

Supporting academic developers of ATMPs – Why ?

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CGTs: a breakthrough innovation promises to cure chronic diseases (RESTORE Health)

KeyTasks: To further increase efficacy and open up new clinical applications and **quickly bring progress to benefit of patients**

Drivers: **Academic developers**, especially since big pharma and VCs are showing less and less interest in effective **autologous** CGT products and in less common indications

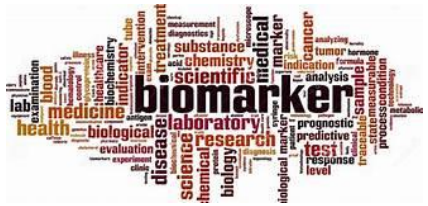
⇒ **Numerous arising challenges that require support to overcome**

Challenges: - Robust and cost-effective manufacturing
- Safety and efficacy of genetic manipulation (part. multiplex editing)
- Patient-to-patient and lot-to-lot variability of CGT products
- Interpatient variability in therapy response
  => adverse effects, immunogenicity, PK, PD, responder/non-responder, sustainability

Usefullness of biomarker analyses

⇒ ***In depth* CGT product specification** from source to final product

⇒ **Therapy response monitoring:** safety, PK/PD, MoA, stratifiers



Analysis of Identity, Phenotype and Functionality of CGT Products

⇒ Starting material

⇒ in-process controls

⇒ **Release Tests of Final Product**

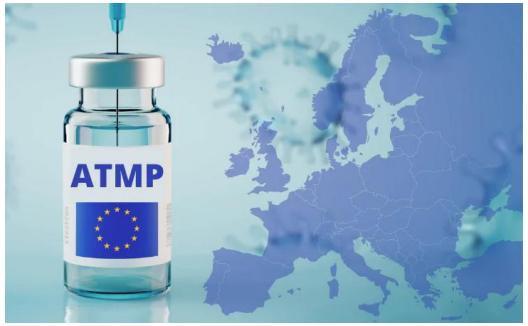
Standard / Product-related tests

⇒ Comparator Product

⇒ *Reference Product*

⇒ *Product-to-Product Variability*

⇒ *Prediction Safety/Efficacy*



According to EU guidelines GMP for ATMP

⇒ Decision-making data (validated assays)

⇒ Exploratory data (qualified/validated assays)

Innovative, product-specific and reliable assays with maximum information gain

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN CheckImmune ADDED-VALUE FOR YOUR CLINICAL DEVELOPMENT

Monitoring the Therapy Response of Patients receiving Investigational Medicinal or Marketing Authorised CGT Products (real life data)

⇒ Safety Parameter
⇒ Pharmakokinetics (PK)
⇒ Pharmacodynamics (PD)
⇒ Mode-of-Action (MoA)
⇒ Surrogate Endpoint Markers
⇒ Stratification of Patient Groups

GOOD CLINICAL LABORATORY PRATICE
GCLP
COMPLIANT

GCLP
(Good Clinical & Laboratory Practice)

⇒ Decision-making markers (validated assays)
⇒ Exploratory markers (qualified/validated assays)

Innovative, study-specific and reliable Assays with maximum information gain

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CheckImmune
ADDED-VALUE FOR YOUR CLINICAL DEVELOPMENT

Innovation, Flexibility & and Quality

	INNOVATION	FLEXIBILITY	QUALIY ASSURANCE
Academic Research Labs	+	+	-
GMP core units	-/+	-	+
Routine Medical Labs	-/+	-	+

Product Specification & Therapy Response Monitoring

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CheckImmune
ADDED-VALUE FOR YOUR CLINICAL DEVELOPMENT

Innovation, Flexibility & and Quality

	INNOVATION	FLEXIBILITY	QUALIY ASSURANCE
Academic Research Labs	+	+	-
GMP core units	-/+	-	+
Routine Medical Labs	-/+	-	+
Specialised Accredited Labs	+	+	+

Need for Specialised Labs that combine Innovation, Flexibility & Quality Assurance

Academic Accredited Core Lab Unit

Charité spin-off company

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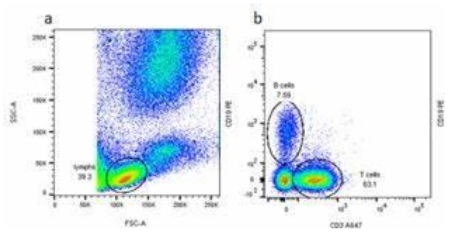
ADDED-VALUE FOR YOUR CLINICAL DEVELOPMENT

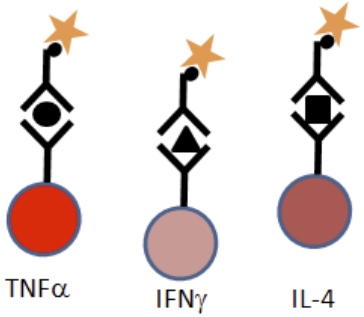
How ?

Multiple Cutting-Edge Test Platforms

Multiparameter flow cytometry

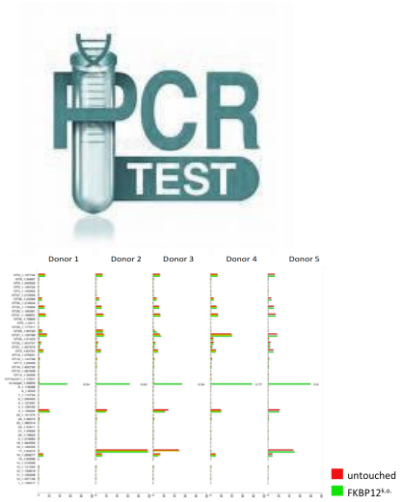


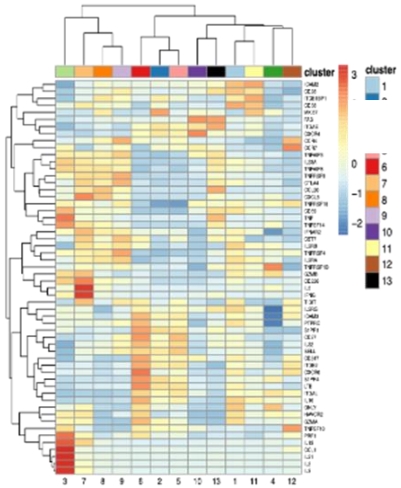
Multiplex-Ligand Assays



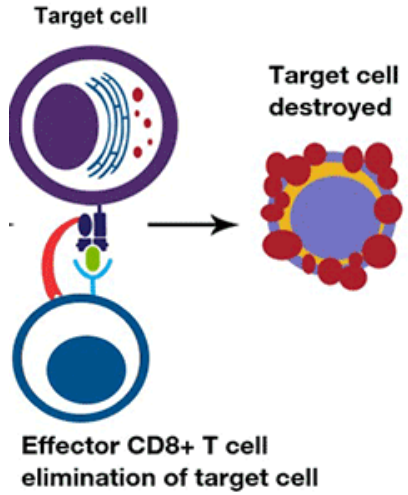
Molecular Analyses

- bulk level: PCR, Epigenetics, DNA/RNAseq
- single cell level: CITEseqTCRseqATACseq)





Functional Assays



How to come to decision-making assays with high informative resolution ?

Complex assays are not easy to standardize

Challenge of Multicenter Studies

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CheckImmune
ADDED-VALUE FOR YOUR CLINICAL DEVELOPMENT

How ?

How to deliver robust biomarker data from multicenter clinical trials ?

⇒ Multicentric analyses in regional labs

Quality, Comparability

⇒ Decentral test execution up to intermediate stage

Quality, Comparability

⇒ **Centralized test execution**

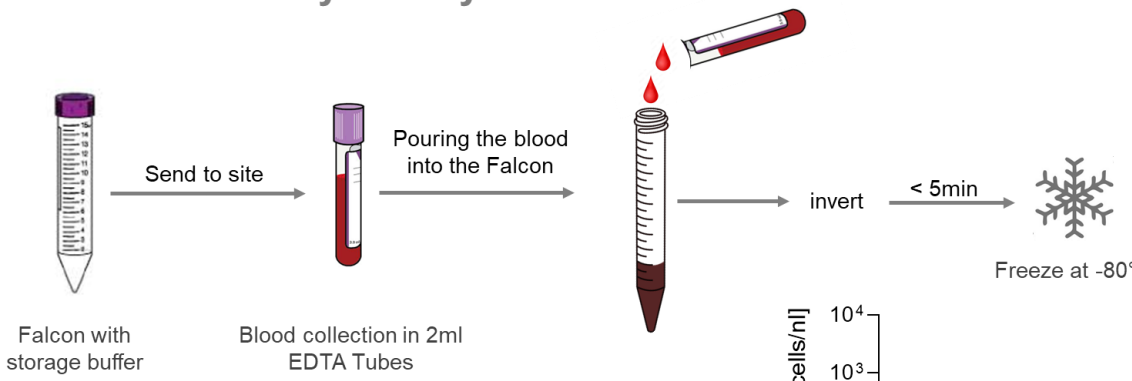
Preanalytic Issues

Use of Stabilized Blood

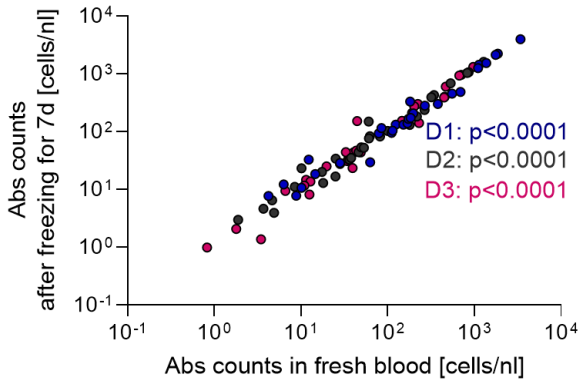
Novel successful method for conservation of blood for **flowcytometric, functional and multiomics single cell analyses**

=> Minimised decentral handling required

Methods: Flow cytometry with stabilized blood



- ✓ Validation of stabilized blood up to six month
- ✓ Easy handling and suitable for multi center studies
- ✓ Reliable results for activation marker pSTAT5



1. **Therapy Response to 1st-gen Treg cell therapy (FiH phase 1/2a)**

2. Following the Fate of Rare Cells, e.g. gene-modified CAR-T cell products

3. Multiomics Single Cell Analysis of Gene-edited Treg cell IMP

4. Comparability Analysis of CAR-T IMP by Multiplex-Spectralcytometry

Therapy Response Monitoring **Treg FiH phase 1/2a Study**

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

CheckImmune
ADDED-VALUE FOR YOUR CLINICAL DEVELOPMENT

Case:
Impact of IMP (Treg cells) on Kidney Transplant Recipients
>250 Read-outs
Multiple Technologies

Challenges:

Establishing numerous validated assays on different platforms

PK, Safety, PD/MoA, Stratification => 1.5 years preparation
(start in late preclinical phase)

Monitoring Response to the IND

GCLP COMPLIANT

Validated Tests at multiple Platforms

Multiparameter flow cytometry

Molecular Analyses (bulk level)

Multiplex-Ligand Assays (cytokines)

Functional Assays

Some major **questions** addressed by the immune monitoring program:
- What is the fate of Treg ? (PK)
- Do we see signs of cytokine release or Treg instability (Safety)
- Do we see signs of overimmunosuppression ? (Safety)
- Why is tapering of immunosuppression in the majority of Treg patients feasible ? (PD/MoA)
- What distinguishes the patients in whom the minimization of immunosuppression was successful from the two patients in whom it failed? (Stratification)

Therapy Response Monitoring Treg FiH phase 1/2a Study

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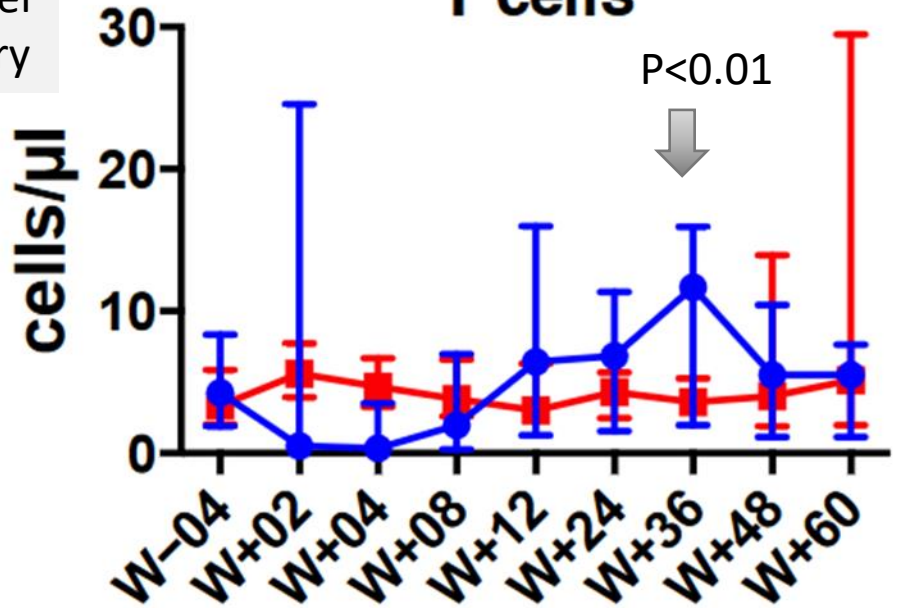
Question: Why is tapering of immunosuppression (IS) feasible in most Treg patients (PD/MoA) ?

Long-lasting inhibition of T-cell activation
(and NK-cell differentiation, higher Treg/Teff ratio)
Treg effectively prevent T-cell activation (tapering IS feasible)
Patients with failure of IS minimization developed activated Teff

activated CD8+ T cells: $CD25^{+}CD127^{high}CD8^{+}$ T cells

Multiparameter flow cytometry



Blue: standard-of-care (triple drug)

Red: Treg group (stepwise weaning IS to low-dose Tac monotherapy wk48)

thebmj Roemhild-A et al. BMJ 2020

THE LANCET Sawitzki et al. Lancet 2020

1. Therapy Response to 1st-gen Treg cell therapy (FiH phase 1/2a)

2. **Following the Fate of Rare Cells, e.g. gene-modified CAR-T cell products**

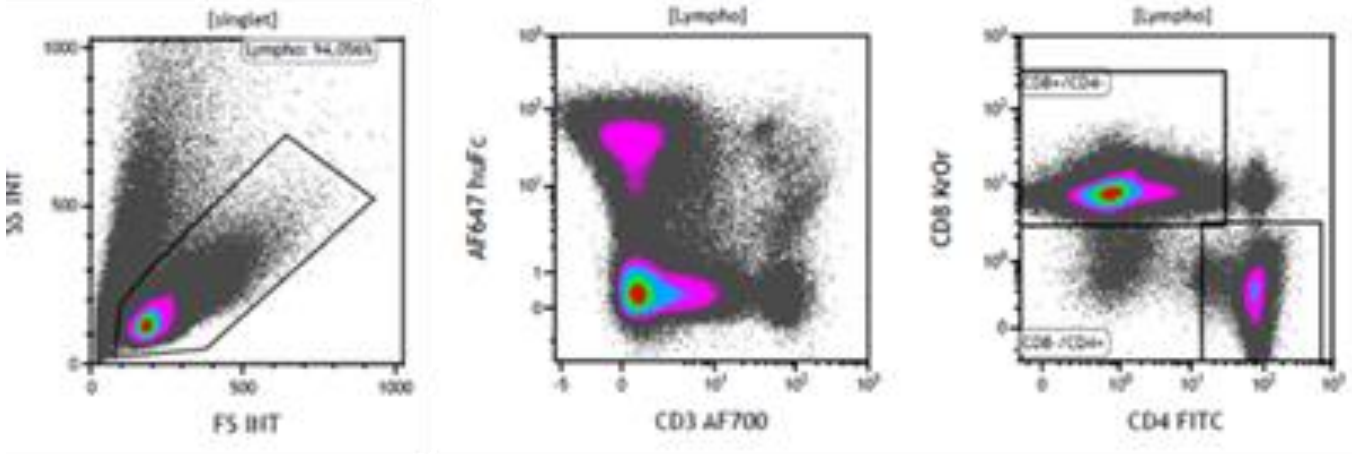
3. Multiomics Single Cell Analysis of Gene-edited Treg cell IMP

4. Comparability Analysis of CAR-T IMP by Multiplex-Spectralcytometry

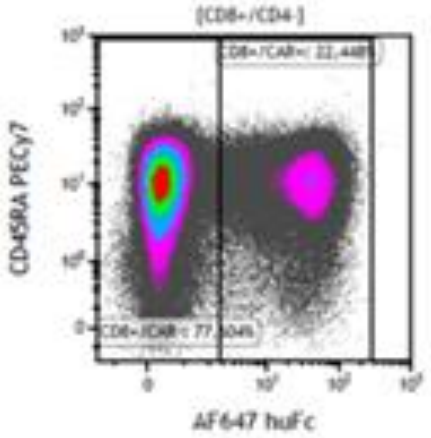
Case – Fate of CD19 CAR-T cells following Therapy

Gating Strategy (13-Parameter Flowcytometry)

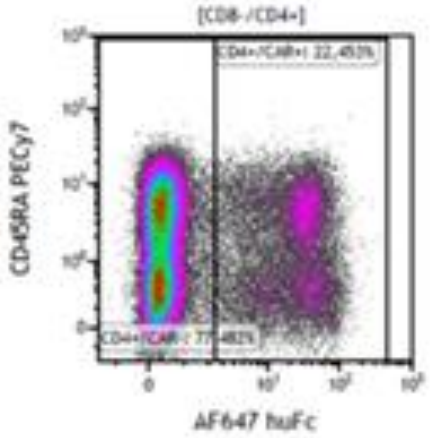
CD19 CAR-T cell product



22% CAR+CD4+

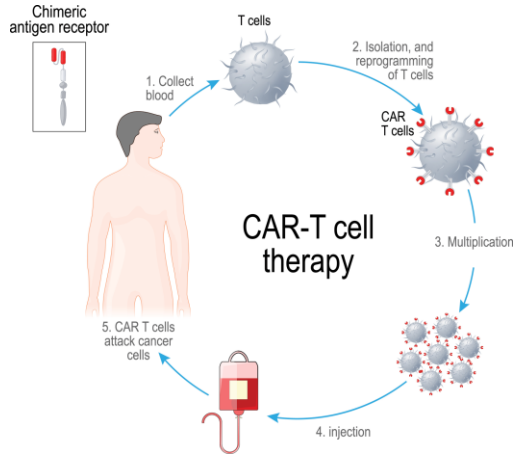


22% CAR+ CD8+



CAR

CAR



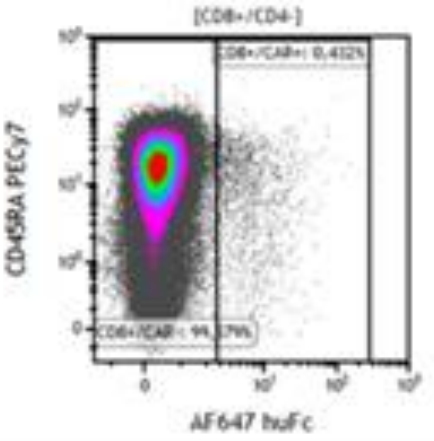
d13 post-Infusion

(*ex vivo*)

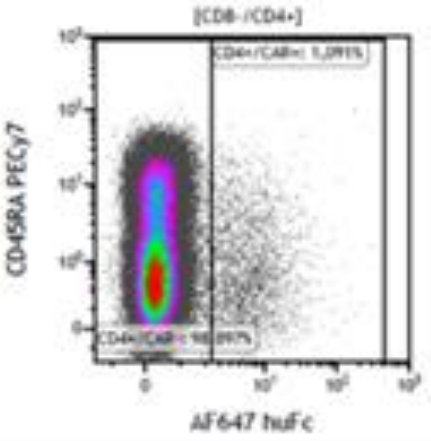
CAR-T detectable but CD8+ CAR-T show low early memory level

(less sustainable)

0.4% CAR+CD4+



1.1% CAR+ CD8+



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IMP Specification – Multiomics-scAnalysis of next-gen Treg

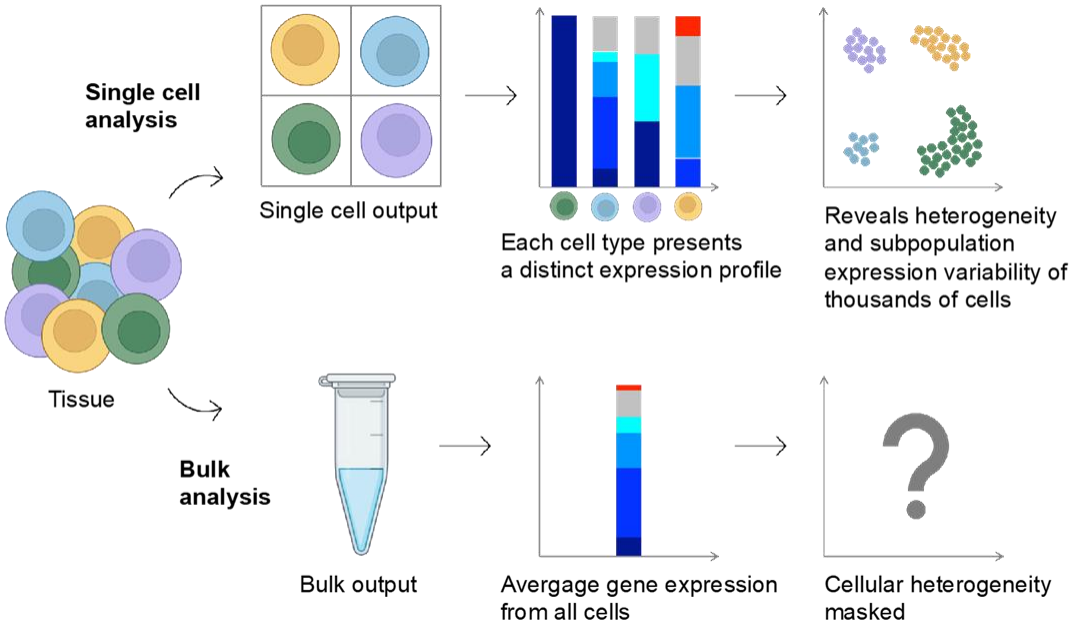
Treg IMP analysis and therapy response monitoring

Numerous Read-outs

Multiomics scAnalyses

Challenge:

Multiomics single cell (sc) Analysis Platform –
From an exploratory research tool to a qualified/validated test platform



Tasks:

- establishment and qualification of workflow and equipment (10X)
- multiomics (surface markers + RNAprofile + TCR profile)
  => enhanced information and cross-validation
- internal controls for QA and to allow compensation of run-to-run variations
- bioinformatic pipeline

IMP Specification – Multiomics-scAnalysis of next-gen Treg

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Multiomics scAnalyses

Breakthrough:

Multiomics single cell (sc) Analysis Platform - From an exploratory research tool to a qualified/validated test platform

GCLP conform qualification/validation of complex multiomics sc-analysis is feasible

Individual adaption to the cell type addressed

GCLP COMPLIANT

3,402 genes (RNAseq)

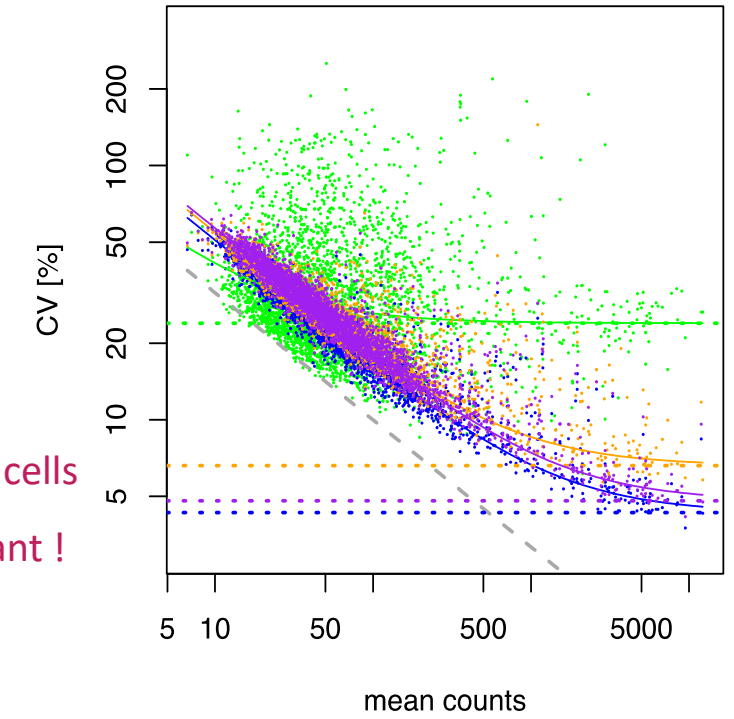
Validation of multiomics single cell analysis (CITEseqRNAseq)

→ inter-assay CV by accounting for 11 cell types × 3 donors × 3 operators → qualified !

→ donor-biological CV by accounting for 11 cell types × 3 operators → qualified !

→ inter-operator CV by accounting for 11 cell types × 3 donors → qualified !

→ total variation of cell „frequencies“ mainly explained by Poisson effects and blood donor → enrich target cells if low abundant !



IMP Specification – Multiomics-scAnalysis of next-gen Treg

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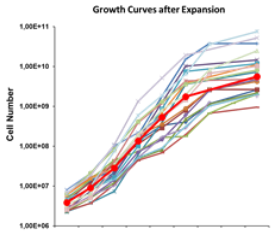
Are the FKBP-12 gene-edited and then expanded cells functional Treg cells ?

Treg sort

Gene Editing



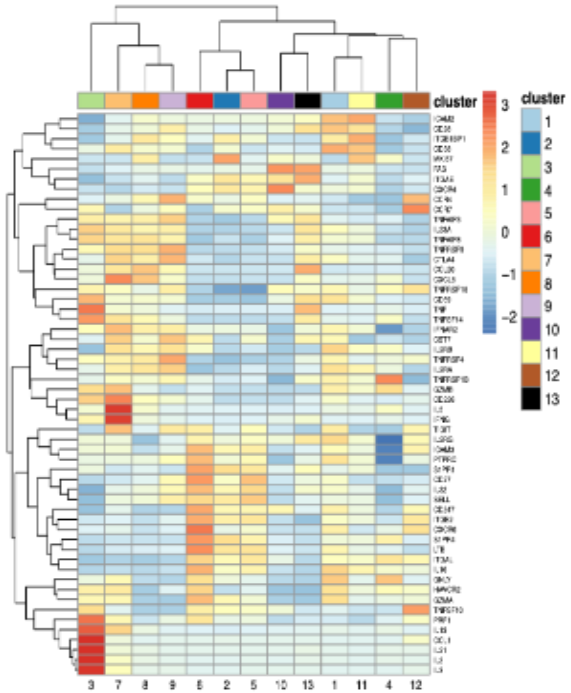
T reg expansion

Treg product specification

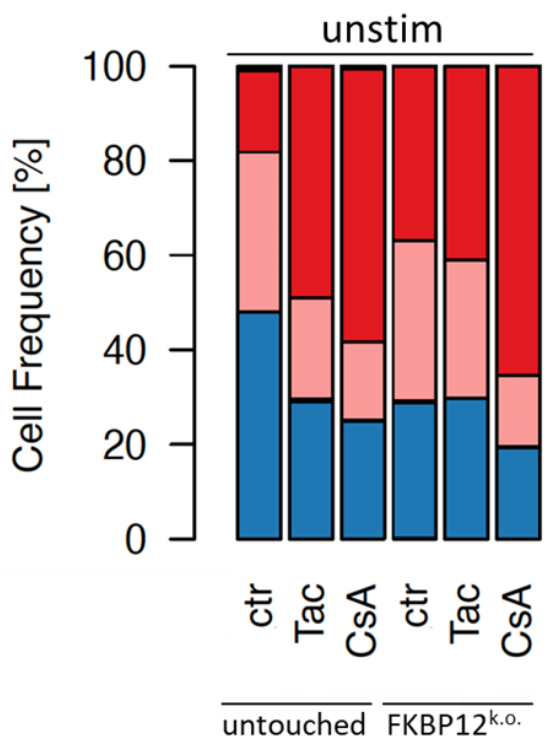
- Phenotype (Flowcytometry & Epigenetics) > 90% purity Treg < 0.1 % CD8+, NK, B, >80% TSDR demethylated
- CNI resistance (Growth and Function) Tac resistant but sensitive to CSA (rescue option)
- Safety of gene editing (Clonal Outgrowth, Karyotype, Off-target Analyses) no safety issues
- Suppressive Function (Inhibition of non-Treg cells) more CTLA4, suppression of proliferation
- Proteomics (High Resolution Mass Spectrometry) target (FKBP12) low, hints for fitness of Treg
- Transcriptome Analysis on single cell level (scRNAseq) confirming Treg state and superiority to Tac

IMP Specification – Multiomics-scAnalysis of next-gen Treg

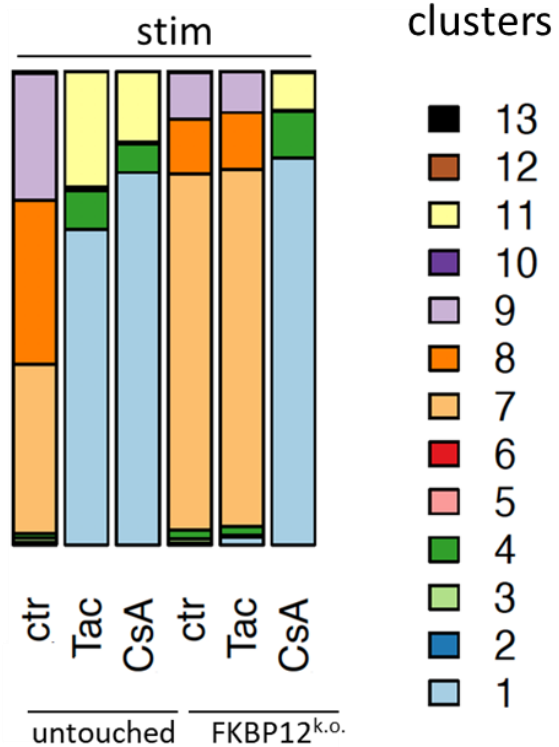
High efficient gene editing FKBP12 KO induces Tacrolimus resistance without impact on yield, purity and function



13 clusters of CD4+



Culture for 7 days in presence of Tac (6ng/ml) or CsA (125ng/ml)



FKBP12k.o. Treg :
- no major differences to untouched Treg even after exposure to CNIs

Stimulated FKBP12k.o. Treg :
- w/o CNI comparable
- Tac inhibits Control but not Tacres
- CsA inhibits the both Treg (rescue)

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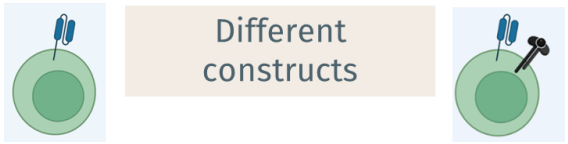
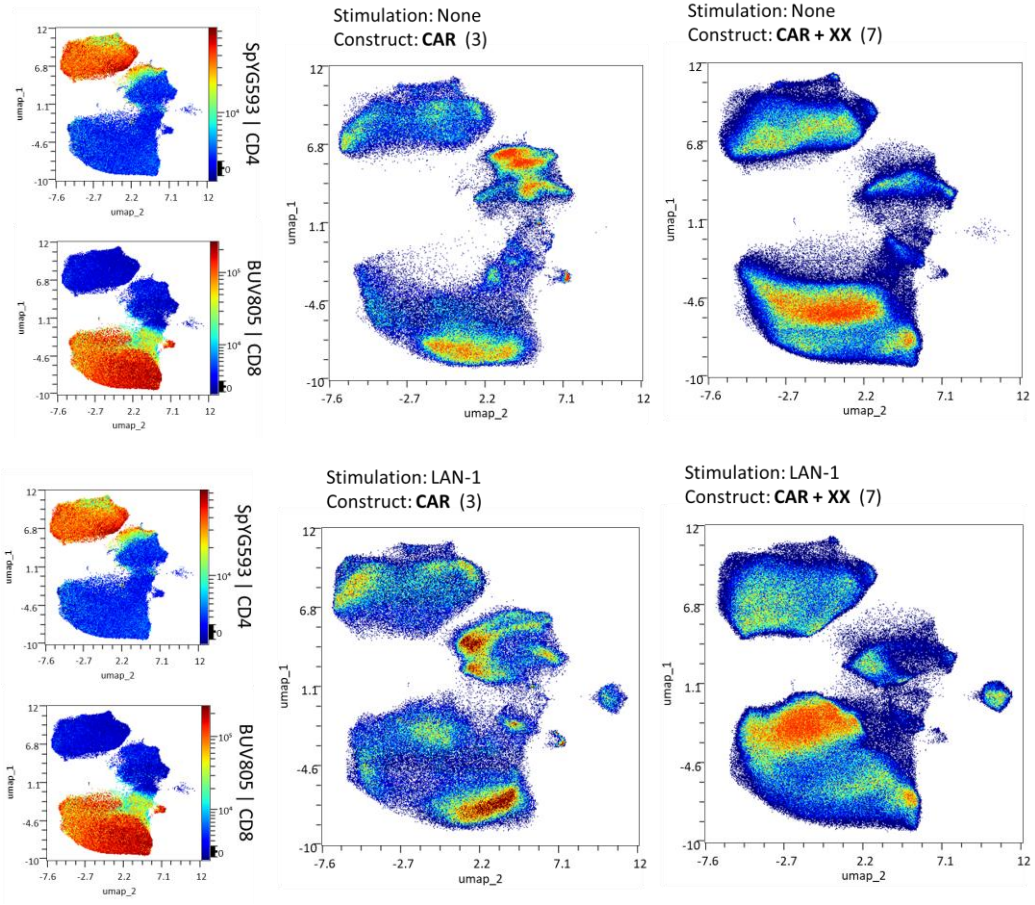
Comparability Analysis – Spectralflow of two CAR-T IMPs

Response: (+)/- ++/+





Spectralflow allows deep analysis within hours

	Feasibility as GMP release criteria	Representative	Panel complexity
Conventional Flow Cytometry	✓	✓	✗
Single cell sequencing	~	✓	✓
Spectral Flow Cytometry	✓	✓	✓

The next gen CAR-T product shows enhanced therapy response

⇒ predictable in the spectralflow product analysis

Conclusions

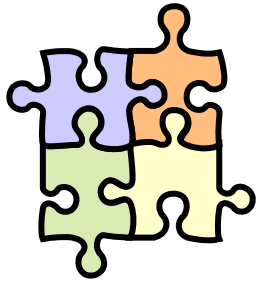
- Complex biomarker analyses for deep product specification and therapy response monitoring support clinical development and “real world” pot-approval studies of CGT products

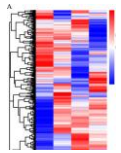
- Different test platforms required for addressing all questions of interest

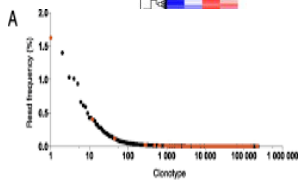
- Qualification / Validation of complex assays - required for therapy monitoring- is challenging but feasible

- Specialised lab required that combine innovation, flexibility and quality assurance (accredited academic core units / spin-off companies, like CheckImmune)

Acknowledgment







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Physicians & Nurses

Patients


THANK
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GRACIAS
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