



Updated Results of a European Gene Therapy Trial in Fanconi Anemia Patients, Subtype A

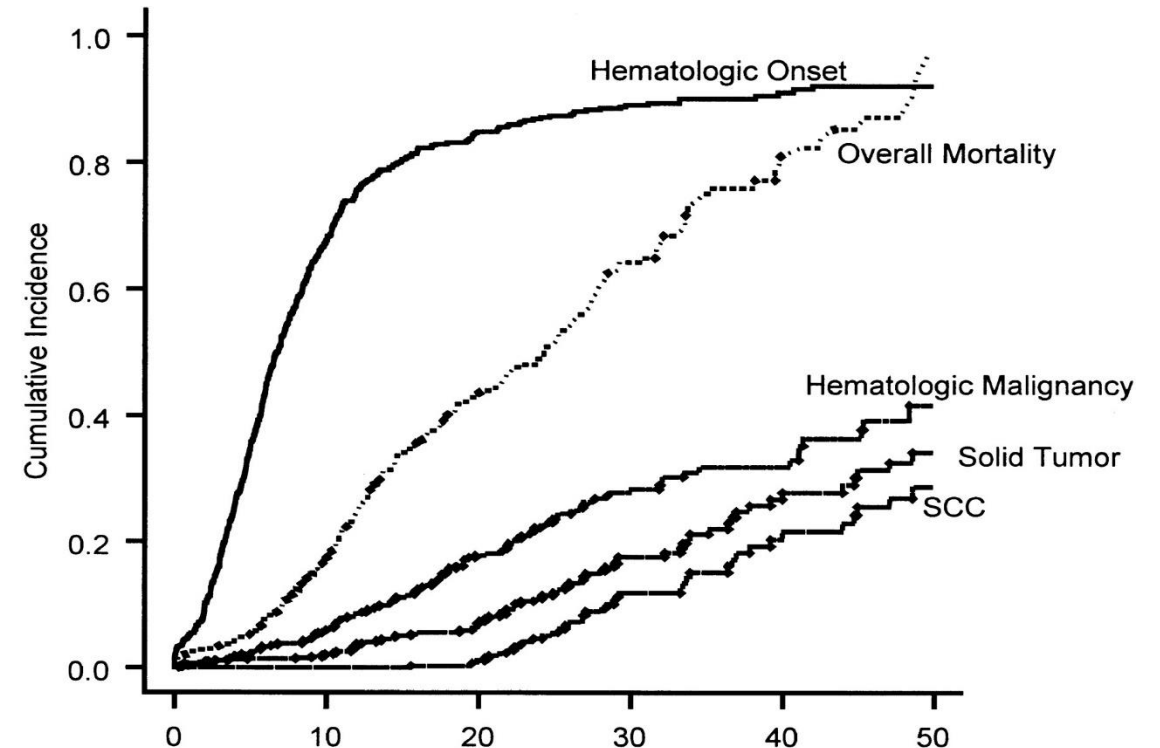
Juan A. Bueren

23rd ASGCT Annual Meeting, May 12th, 2020

Molecular and Clinical Aspects of Fanconi Anemia



- Genetic inherited disorder
- Rare disease 1-3 per million
- **Mutations in FA/BRCA Pathway**
 - 22 genes described (*FANCA* - *FANCW*)
 - Resolution of DNA interstrand-crosslinks
 - Genetic instability and cytotoxicity
- **Congenital abnormalities**
- **Bone marrow failure**
- **Cancer predisposition**
 - Myelodysplastic syndromes/AML
 - Solid tumors (HNSCC)

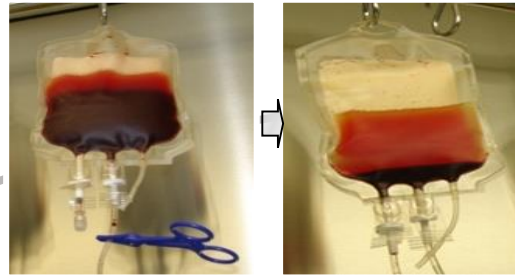


Kutler et al, Blood 101:1249, 2003

Gene Therapy Trial for FA-A Patients

1. Mobilization of CD34⁺ cells: 2-3 x (G-CSF+Plerixafor)

(9/11 Pts)



CD34⁺ cell
purification

(F: 3 Pts)



2. ± Cryopreservation

(C: 5 Pts)

(F+C: 1 Pt)

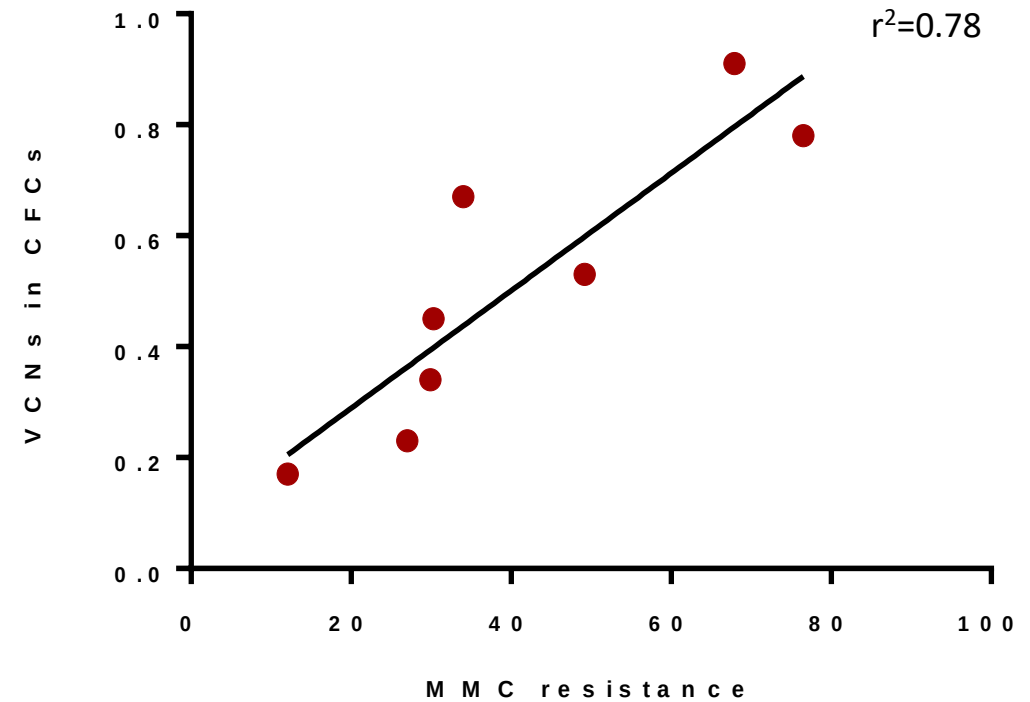
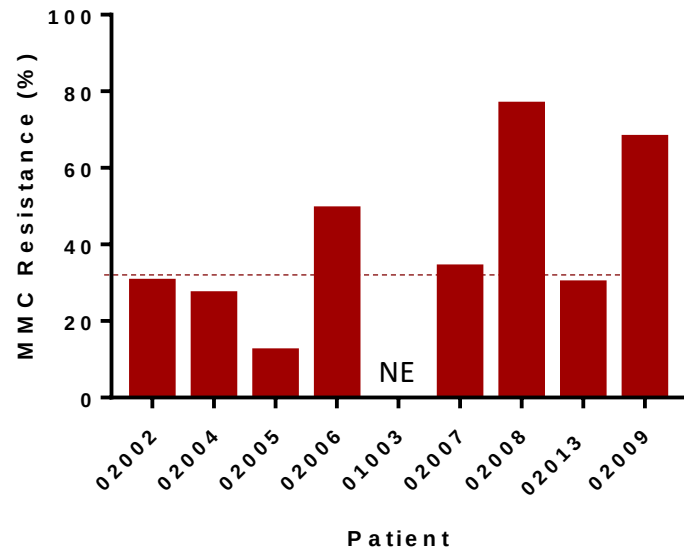
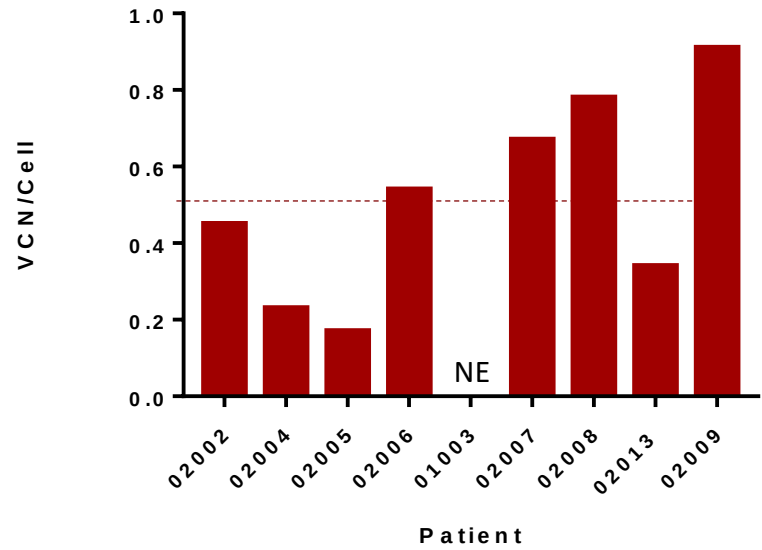


5. Infusion (No conditioning)



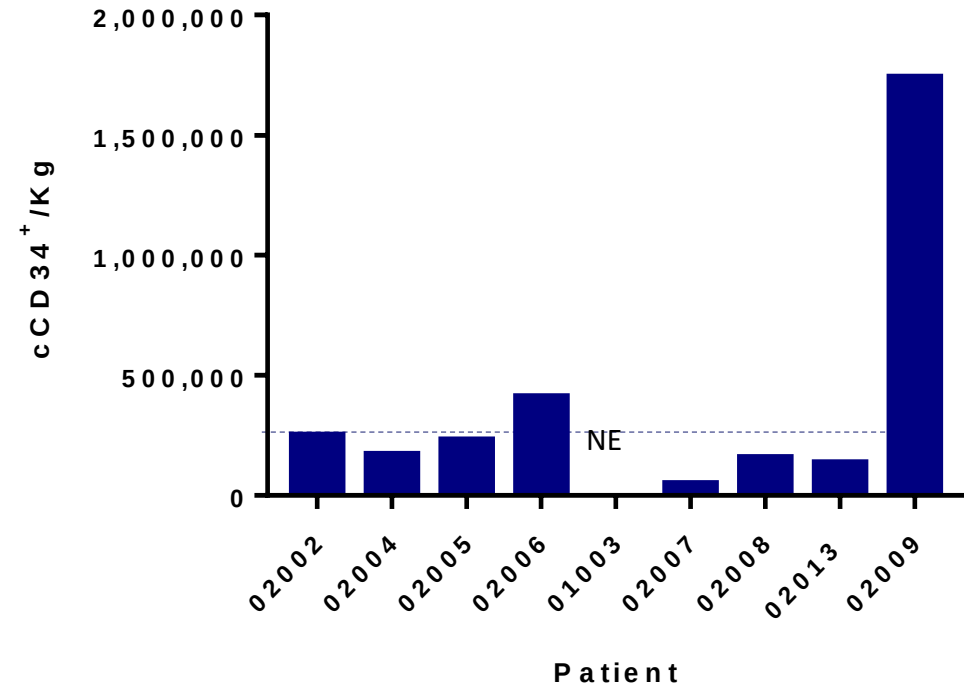
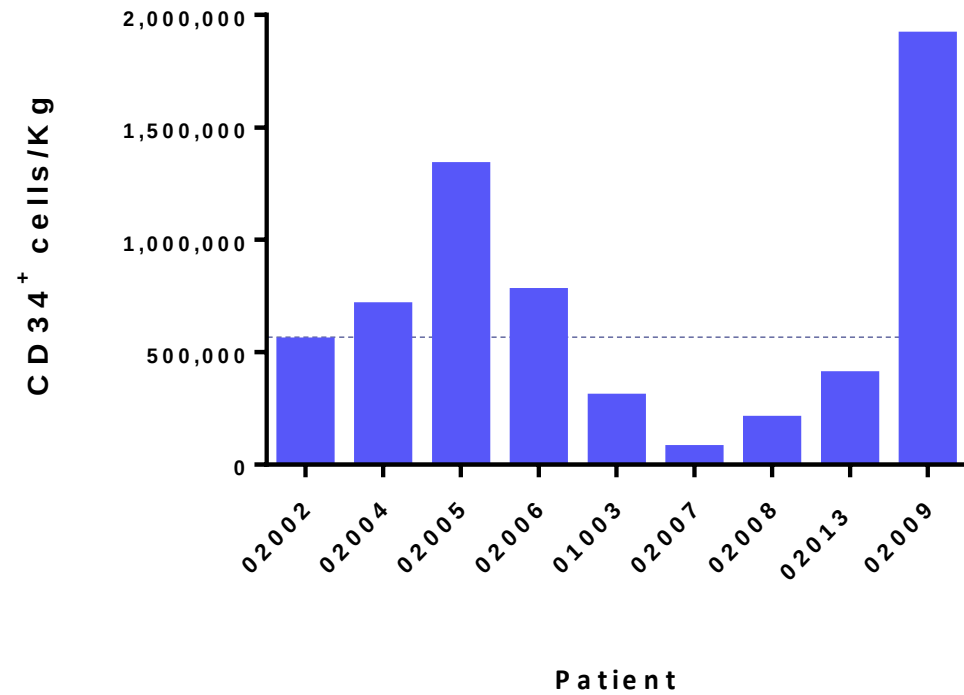
4. Transduction (24h)

FANCOLEN-I: Manufacturing Products



MMC-resistance at 10nM except for patient 02006 which was 3nM

Infused Number of CD34⁺ Cells

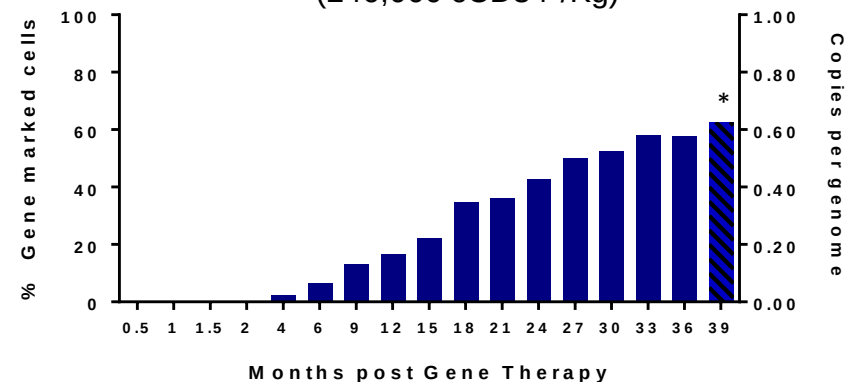


***Review of Patients with a Follow-up of
12-36 months Post-infusion***

Progressive Engraftment of Gene-marked Cells in PB

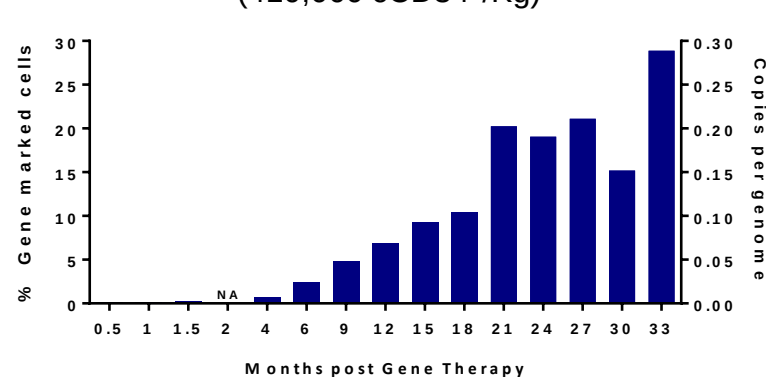
02002 (Cryo)

(246,000 cCD34⁺/Kg)



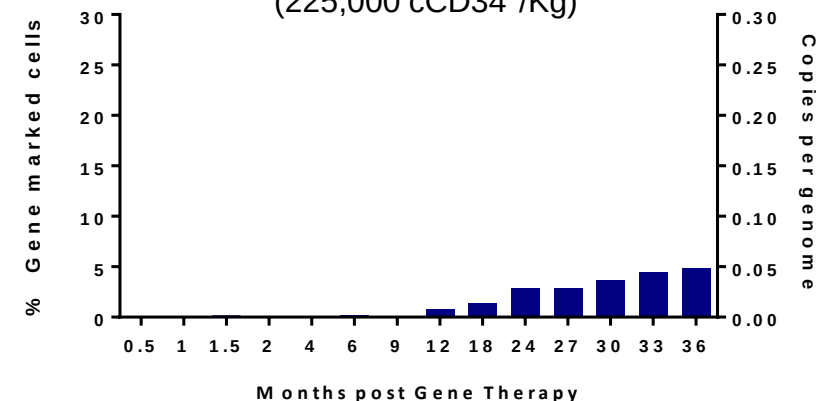
02006 (Fresh)

(410,000 cCD34⁺/Kg)



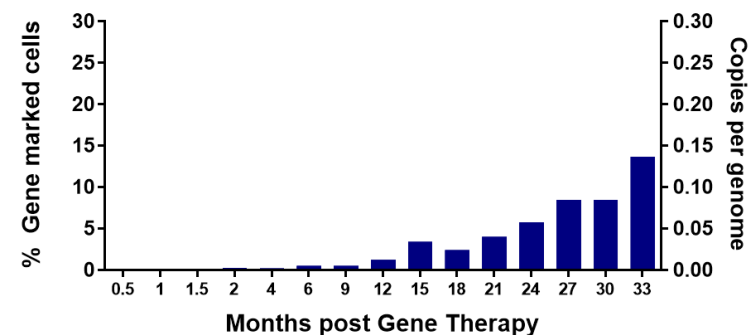
02005 (Fresh)

(225,000 cCD34⁺/Kg)



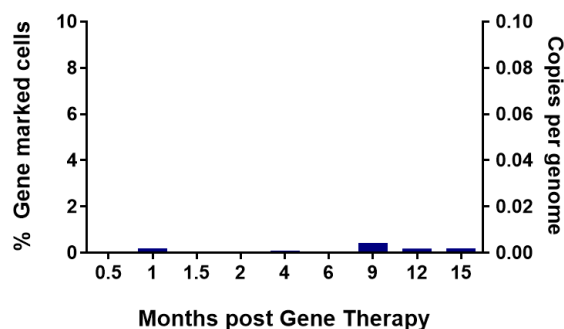
02004 (Cryo)

(163,000 cCD34⁺/Kg)



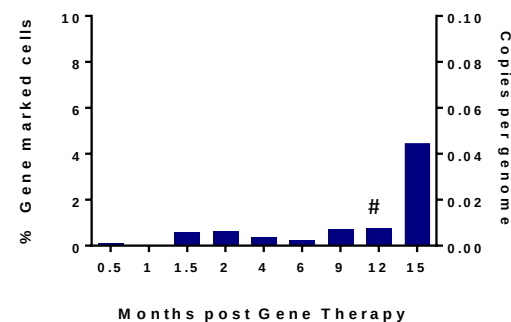
02007 (Cryo)

(48,600 cCD34⁺/Kg)



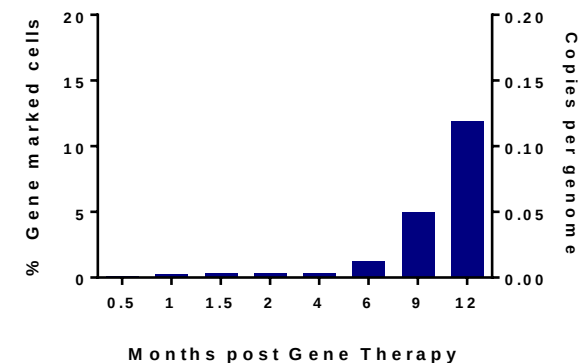
02008 (Fresh)

(157,000 cCD34⁺/Kg)



02013 (Cryo)

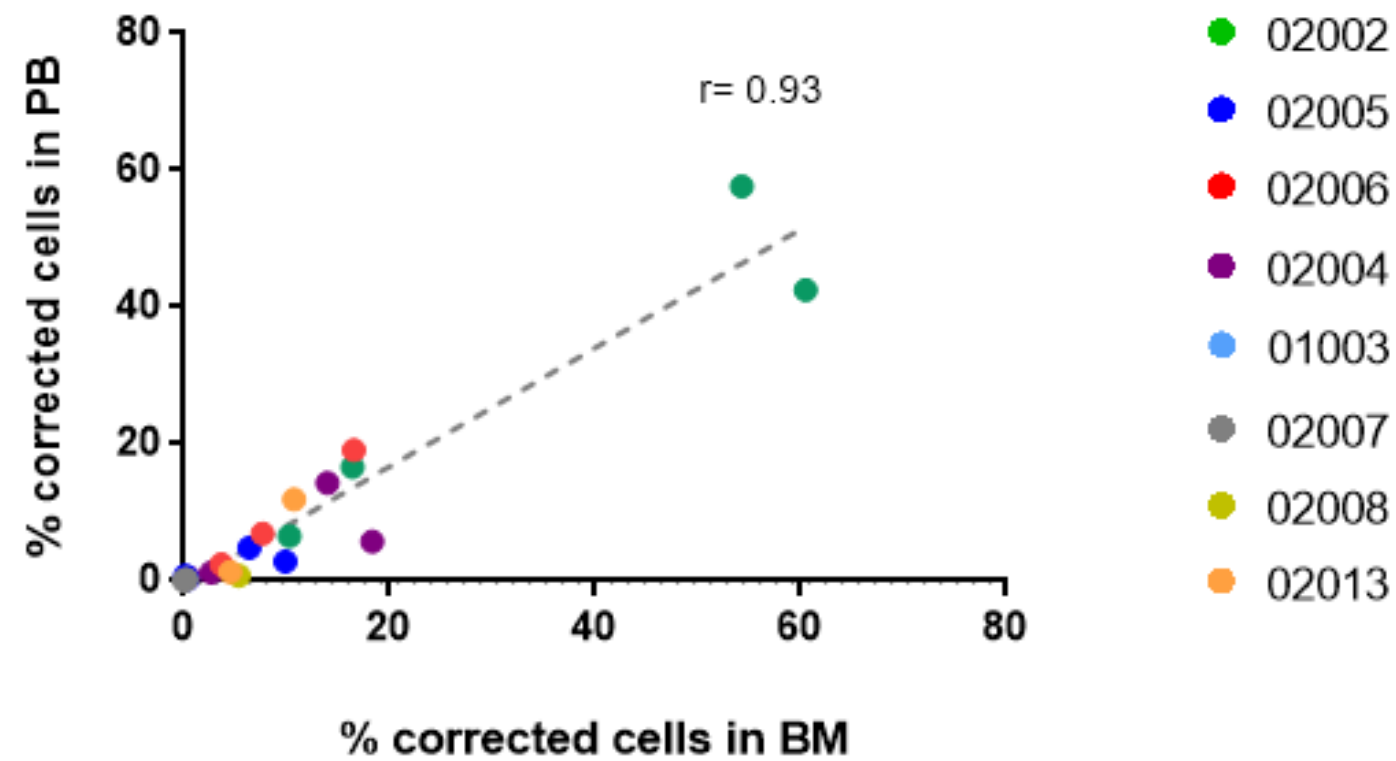
(135,000 cCD34⁺/Kg)



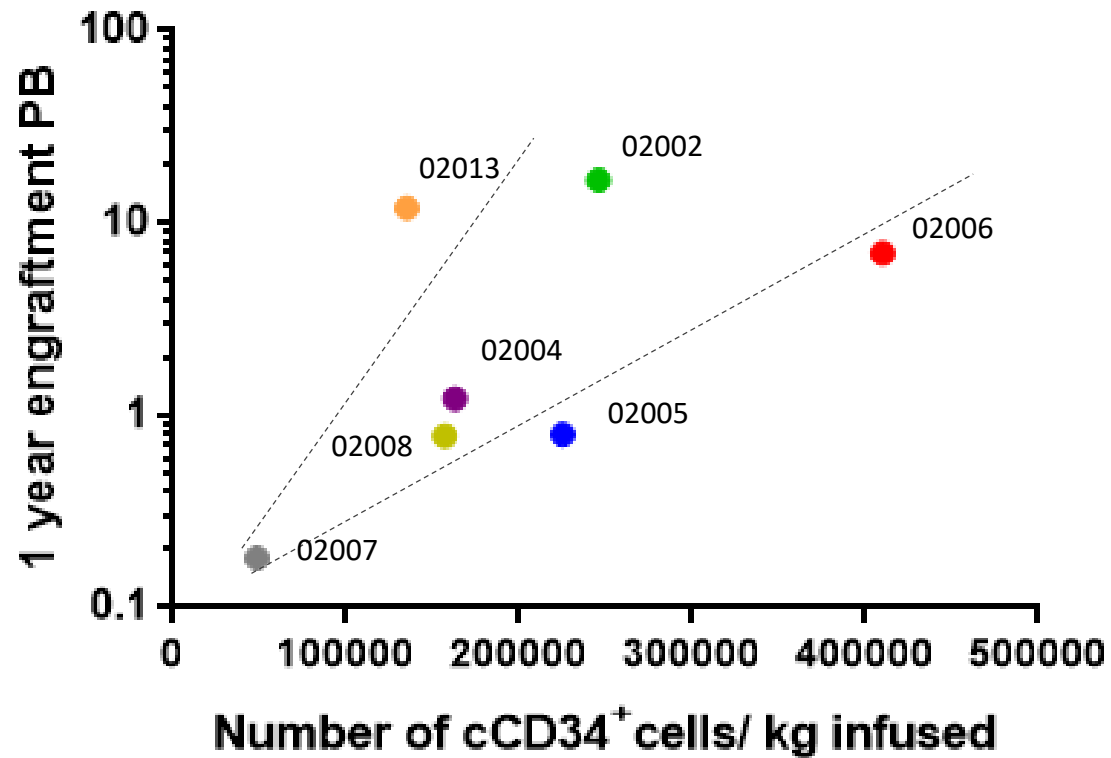
* This point requires additional validation as the long-term follow-up study is activated

This data point has been partially validated secondary to Covid-19 related limitations

Correlation Between the Proportion of Marked Cells in PB and BM



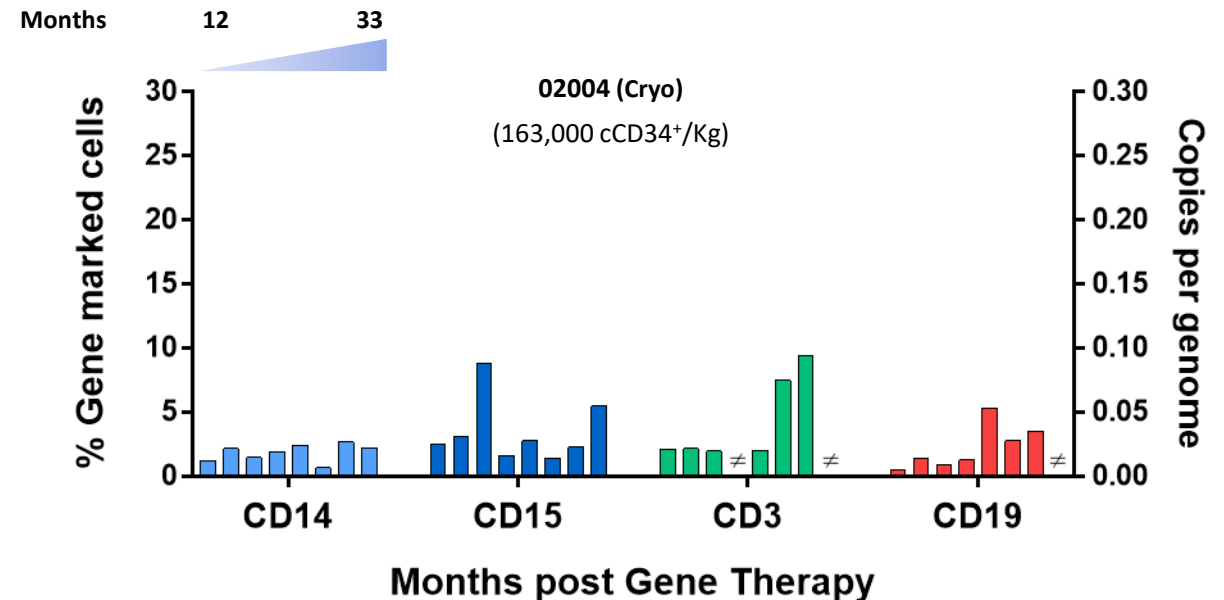
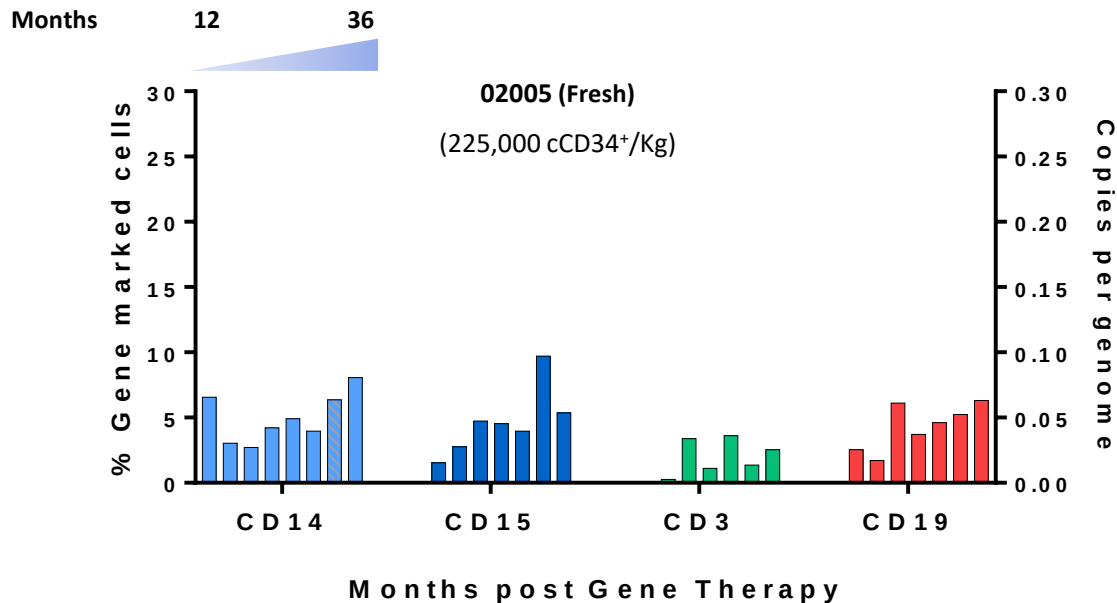
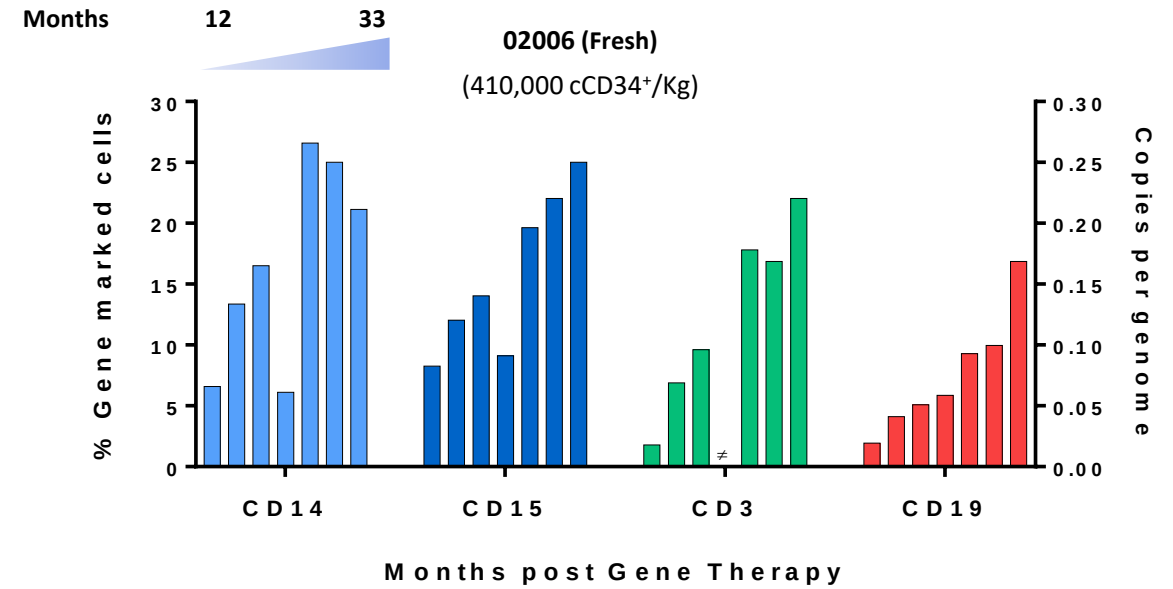
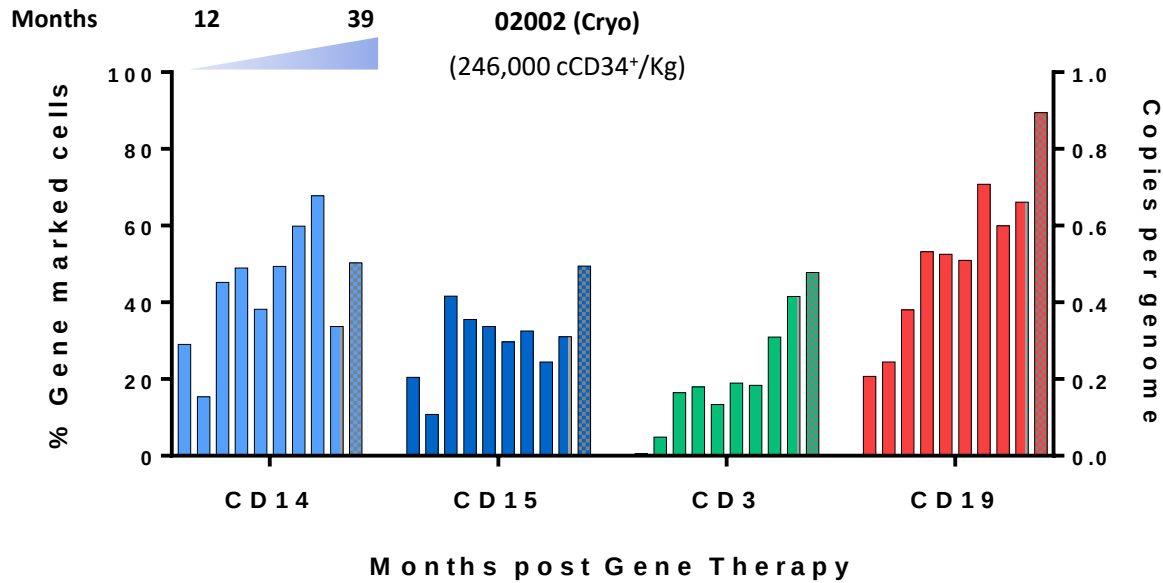
Dose-dependent Engraftment of Gene Marked Cells in PB at 1 year Post Gene Therapy



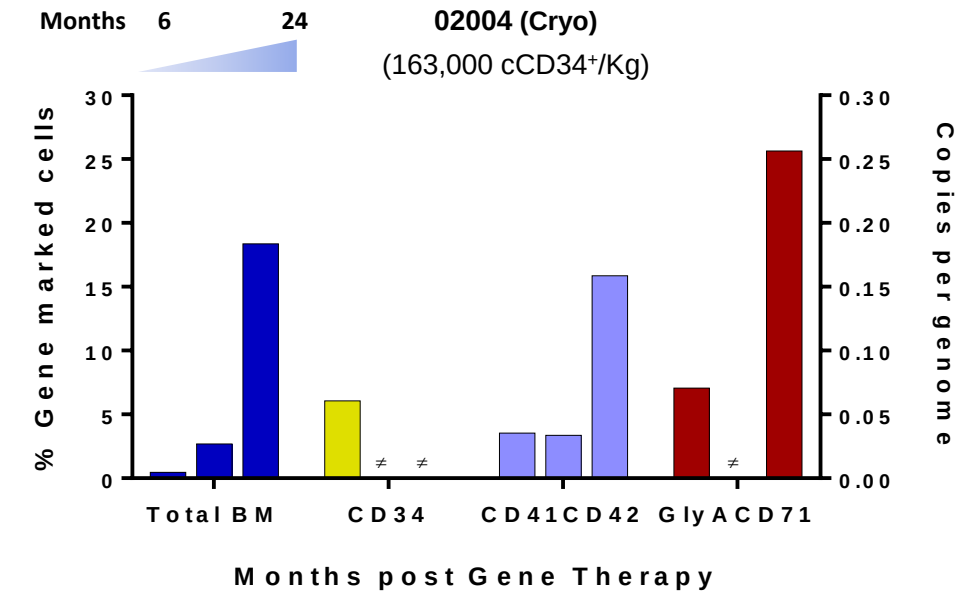
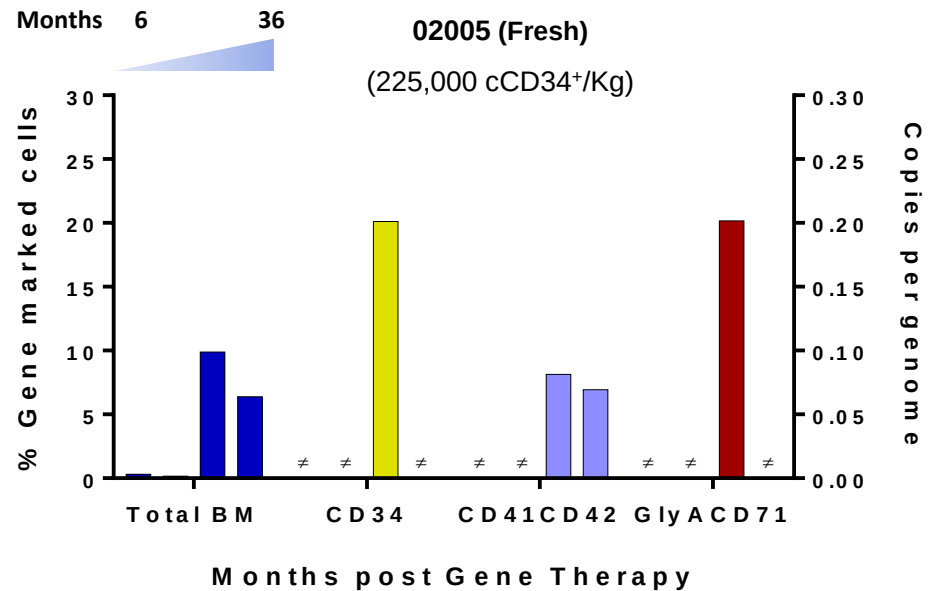
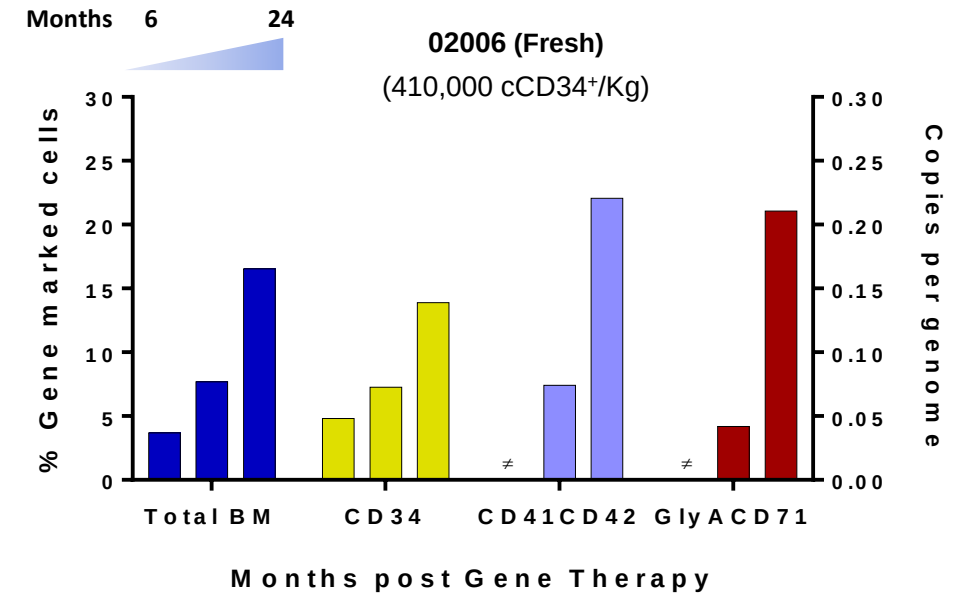
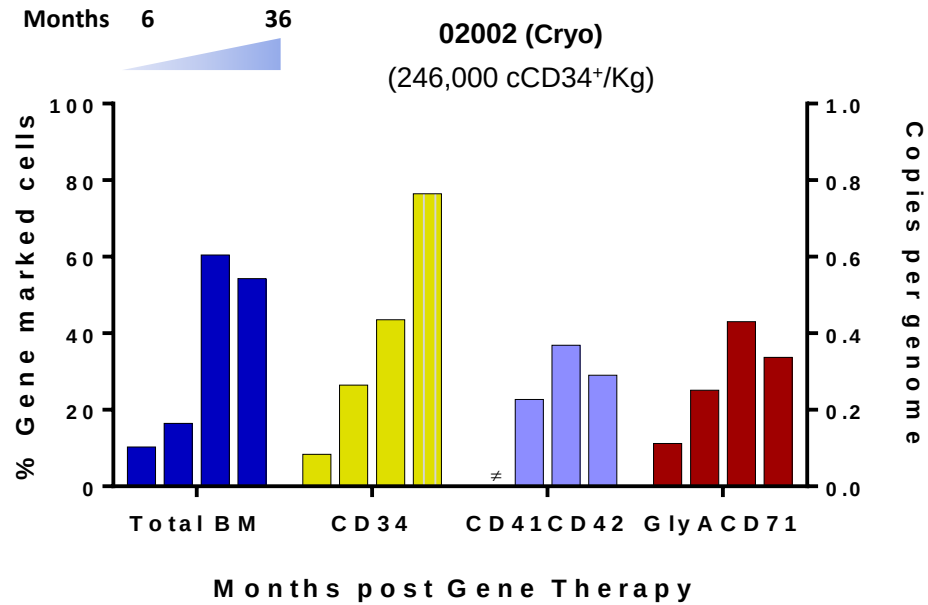
Patient 01003 not shown as did not meet the release criteria

Patient 02009 not shown because follow-up < 12 months

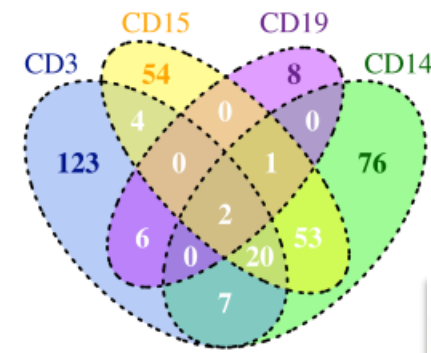
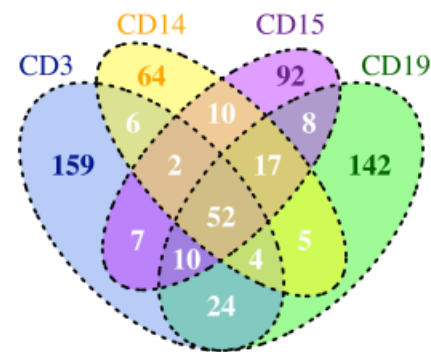
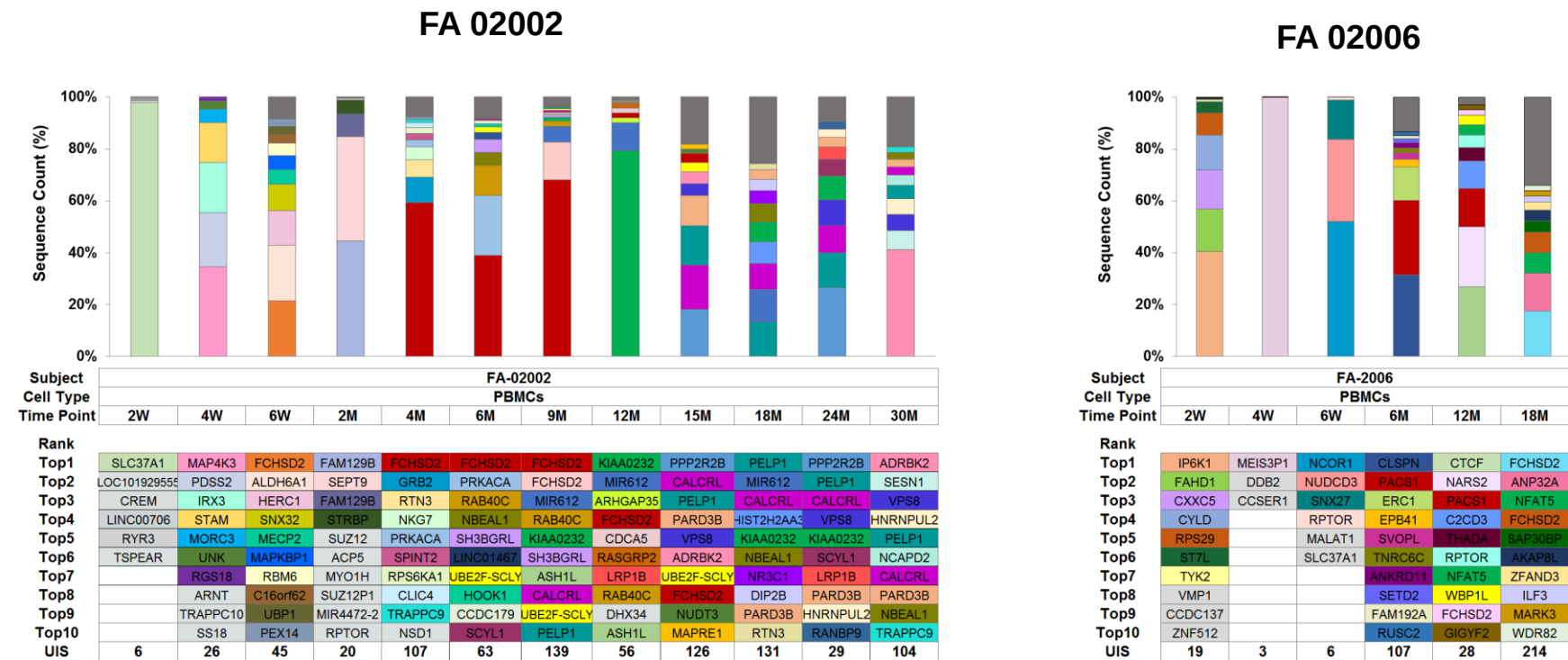
Progressive Increase of Gene-marked Subpopulations in PB



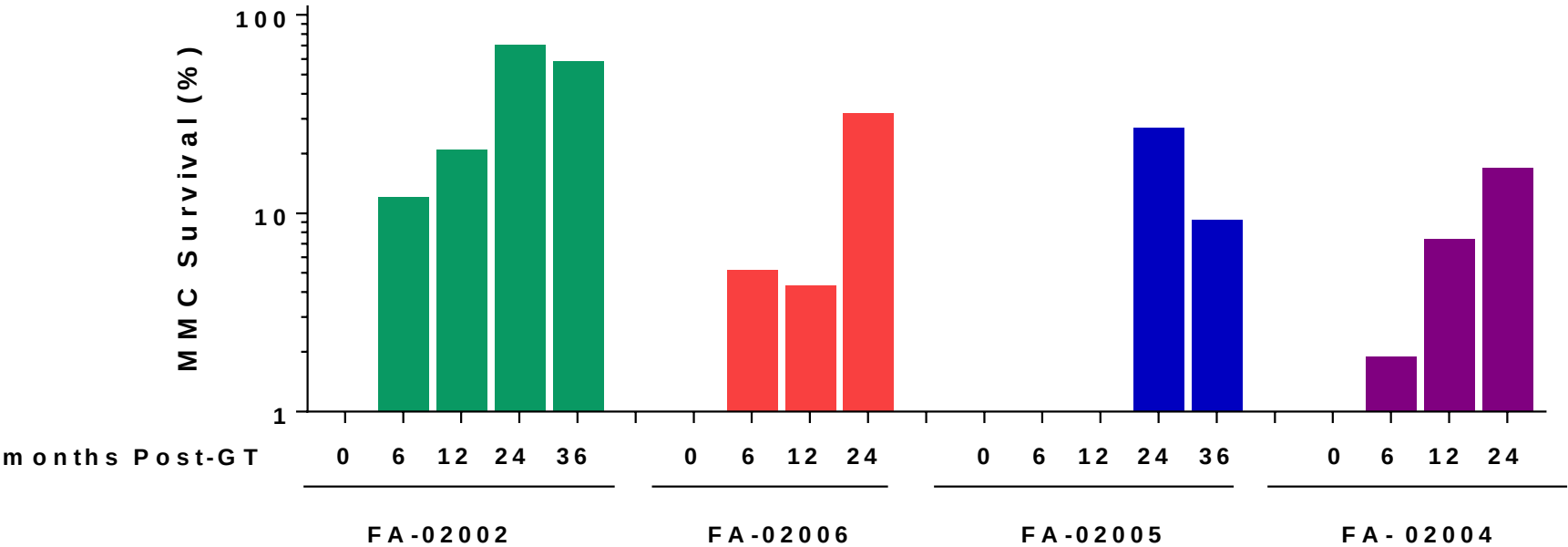
Progressive increase of gene-marked subpopulations in BM



Clonal Repopulation Analysis in Patients FA-02002 and FA-02006: Evidence of repopulation by Multipotent HSCs

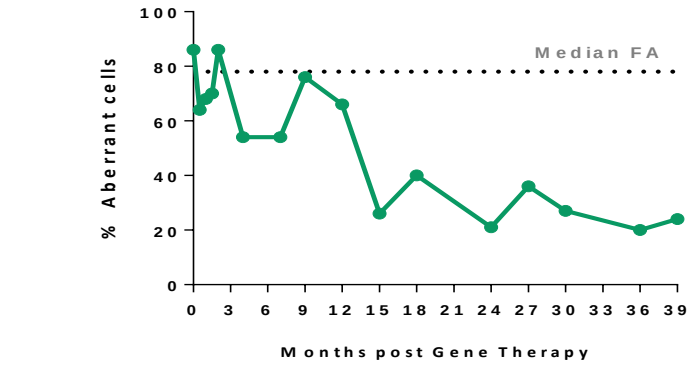


Progressive Phenotypic correction of BM CFCs (MMC-Resistance)

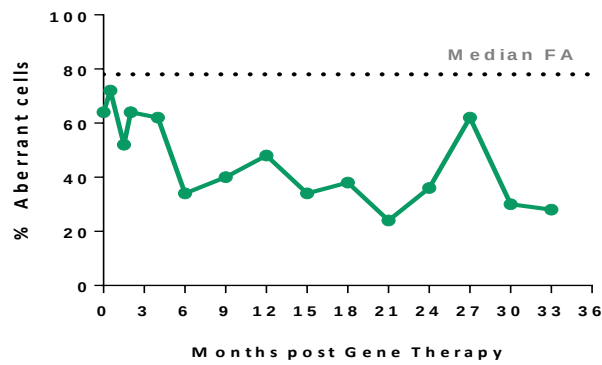


Progressive Phenotypic correction of PB T Cells (DEB-Induced Chr. Instability)

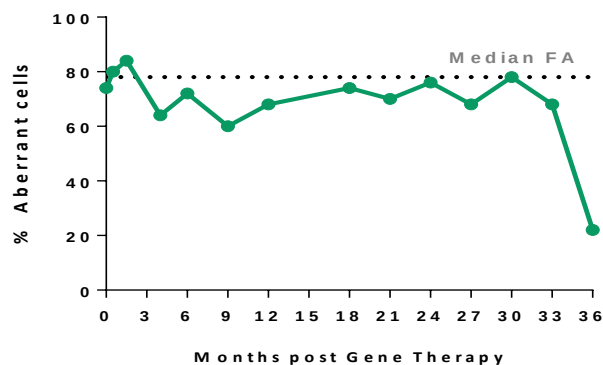
FA-02002



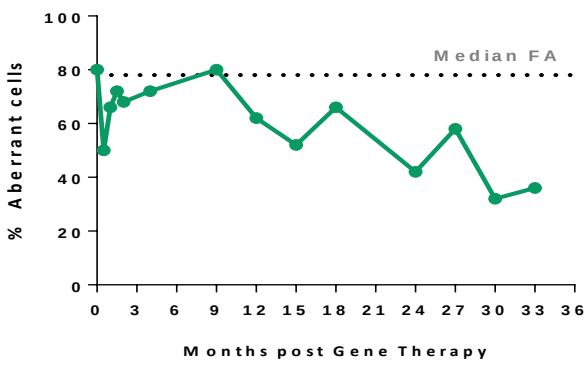
FA-02006



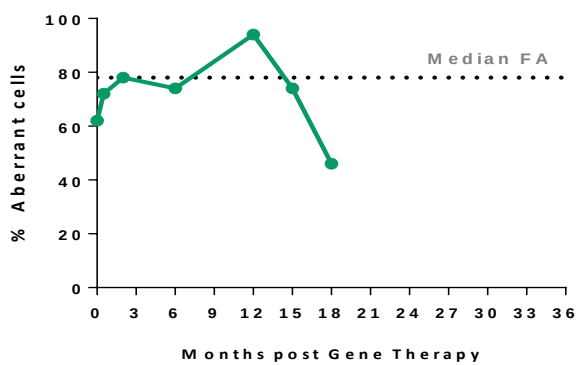
FA-02005



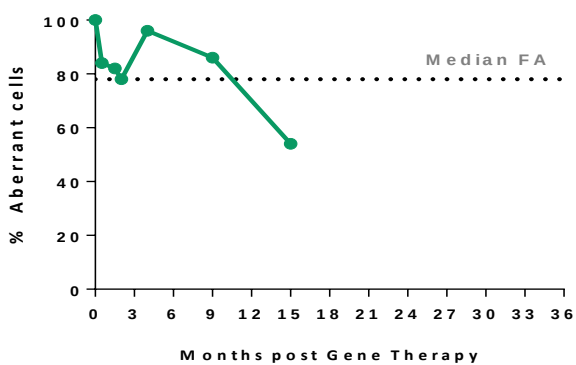
FA-02004



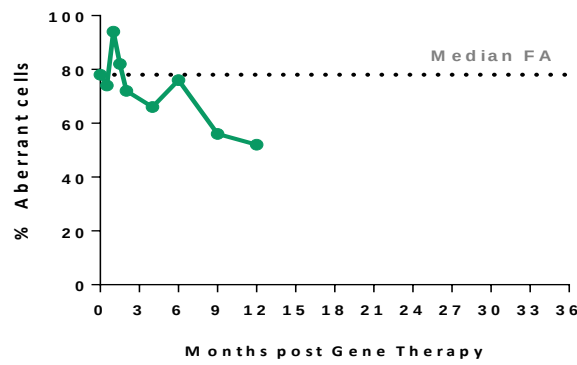
FA-02007



FA-02008

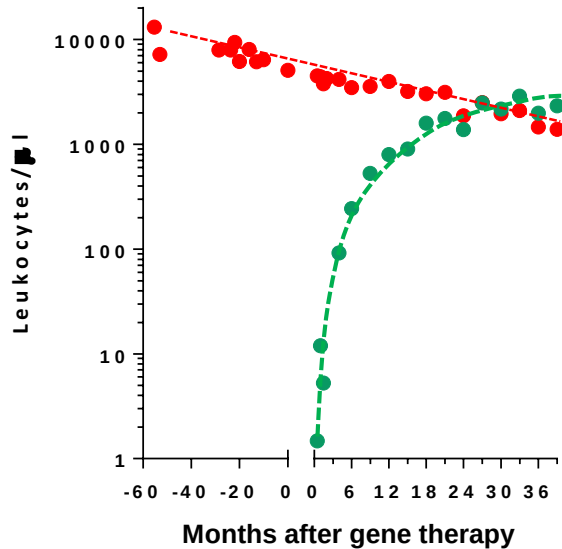


FA-02013

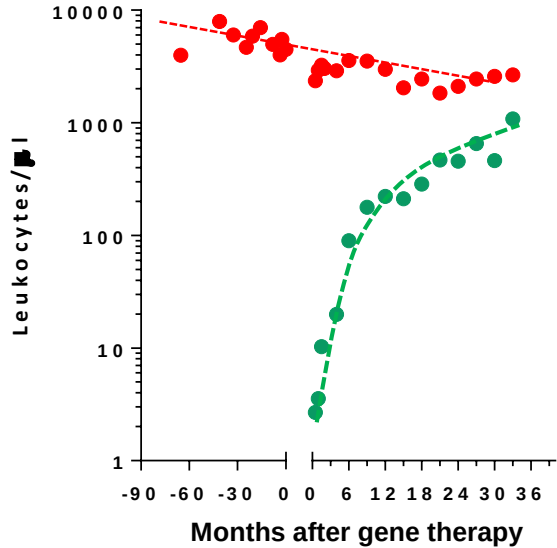


Kinetics of corrected and uncorrected PB leukocytes prior to and after Gene Therapy

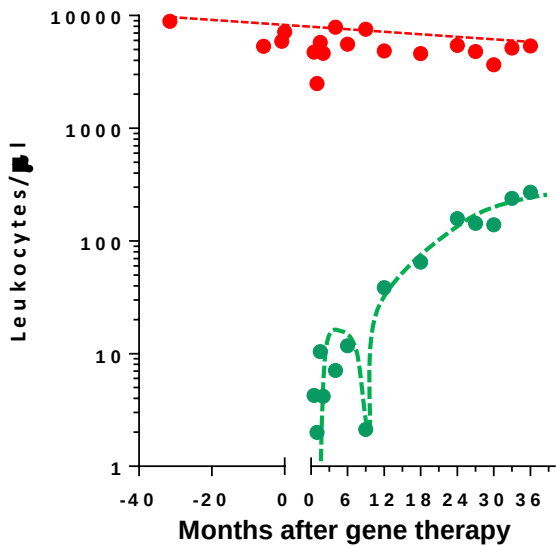
02002



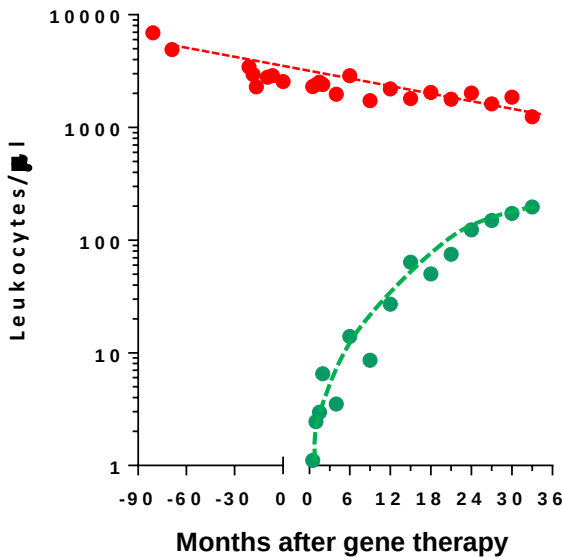
02006



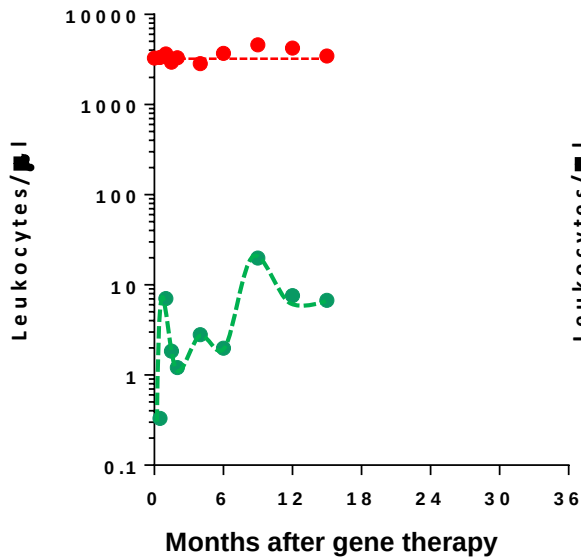
02005



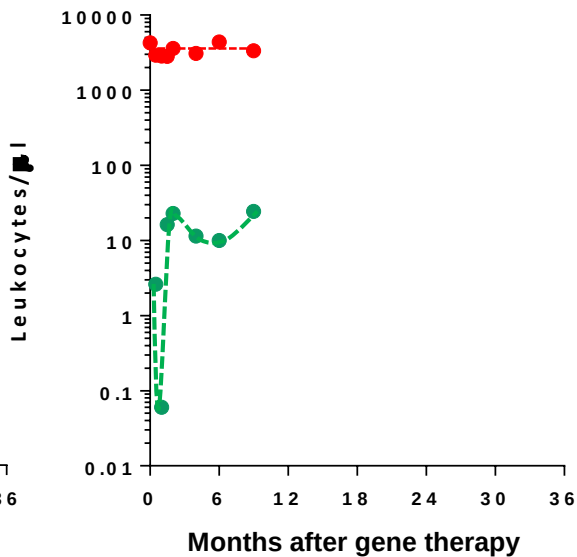
02004



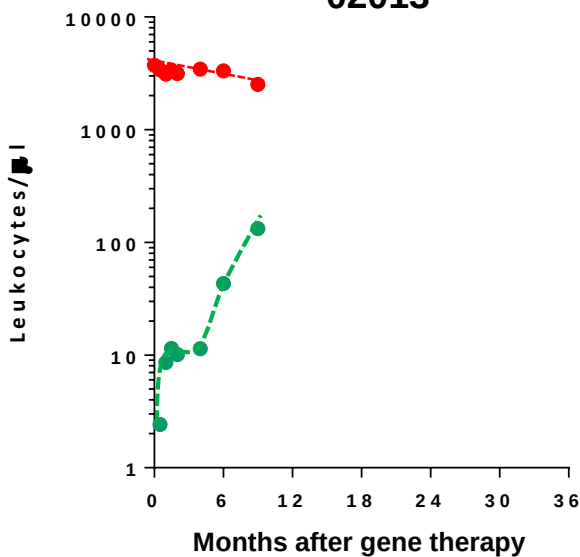
02007



02008

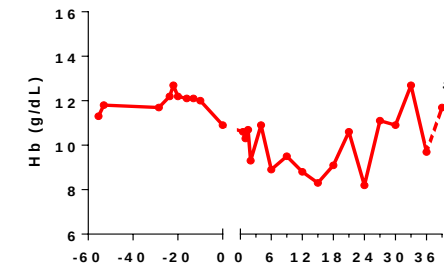
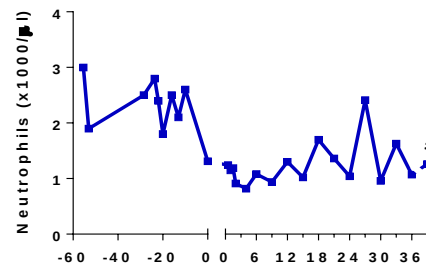
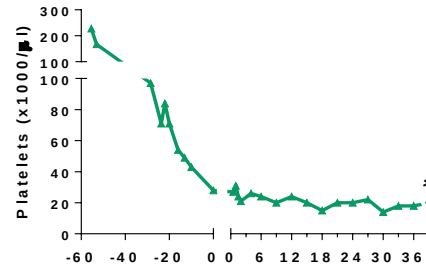


02013

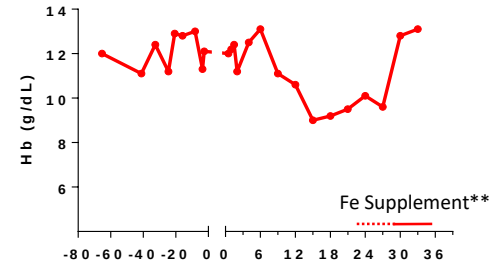
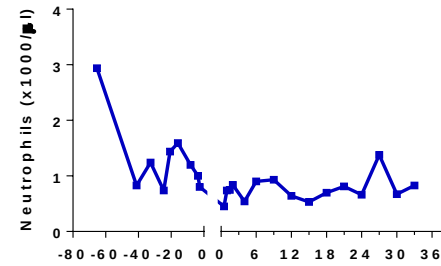
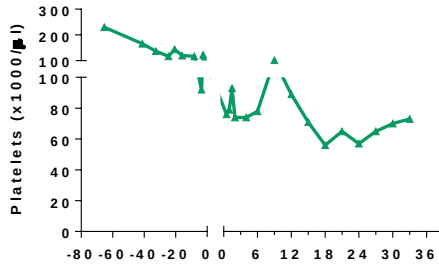


PB Cell Counts in FA Patients prior to and after Gene Therapy

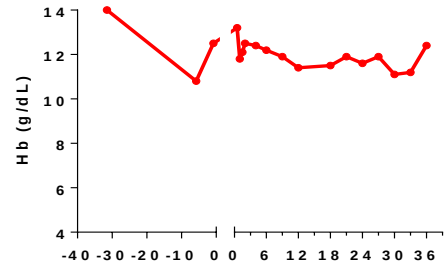
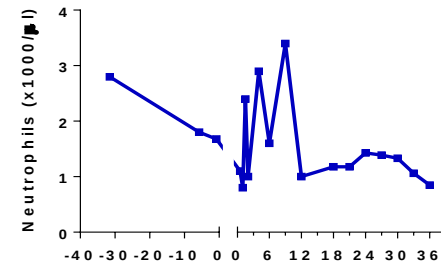
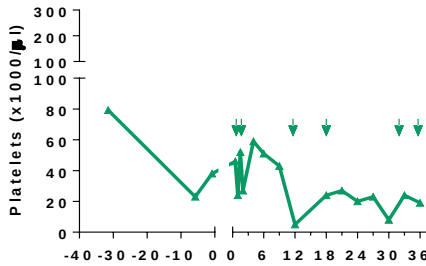
02002 (Cryo)
(246,000 cCD34⁺/Kg)



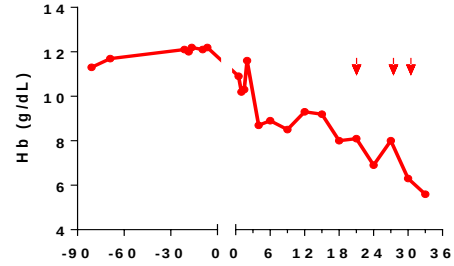
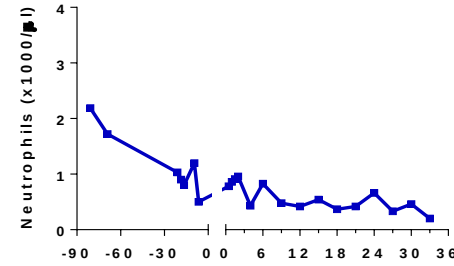
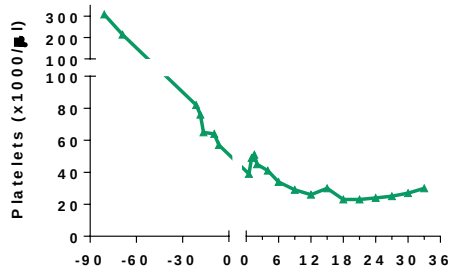
02006 (Fresh)
(410,000 cCD34⁺/Kg)



02005 (Fresh)
(225,000 cCD34⁺/Kg)



02004 (Cryo)
(163,000 cCD34⁺/Kg)



Months after gene therapy

Months after gene therapy

Months after gene therapy

* These particular data points require additional validation as the long-term follow-up study is activated

** Iron supplement is not likely to enable Hb increase in the absence of viable and productive HSPCs

Conclusions

- ❑ No SAEs associated with the gene correction of FA HSPCs
- ❑ Infusion of corrected CD34⁺ cells in non-conditioned FA patients:
 - ✓ Progressive repopulation advantage of gene-corrected HSPCs at 1-3 years post-infusion (6/6 patients infused with >100,000 cCD34⁺ cells/kg)
 - ✓ Oligoclonal reconstitution and gene correction of multipotent HSCs
 - ✓ Progressive phenotypic correction of BM progenitors and PB T cells
 - ✓ At 1-3 years post-infusion, stabilization in PBC counts or overall increase in the erythroid lineage (two patients infused with the highest doses of corrected CD34⁺ cells)

Open questions

- Additional product metrics that may be predictive of engraftment/phenotypic reversal, including cCFCs/kg, CD34⁺CD38⁻/kg, other.
- Fate of uncorrected BM cells?
- Management of transfusion-dependent patients with progressive engraftment of cHSCs?

FANCOLEN II



Ongoing Global Phase 2 Registrational Program Trial in the USA and Europe

AIM:

- ☐ **Treatment of patients in earlier stages of the BMF**
- ☐ **Infusion of higher numbers of corrected HSCs:**
 - ✓ ***CD34⁺ cell collection from patients with higher HSC numbers***
 - ✓ ***Modified Immunoselection (Higher yields of CD34⁺ cells)***
 - ✓ ***No cryopreservation***
 - ✓ ***Improved transduction of HSCs (transduction enhancers)***

Acknowledgments



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Miriam Hernando

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Marina Cavazzana



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Alan Lamproye

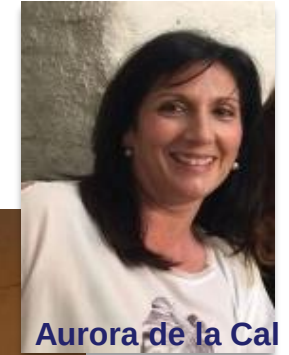


Sol Ruíz



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Acknowledgments



Aurora de la Cal



Patients and Families



Fundación
Anemia de Fanconi

Thank you!!!