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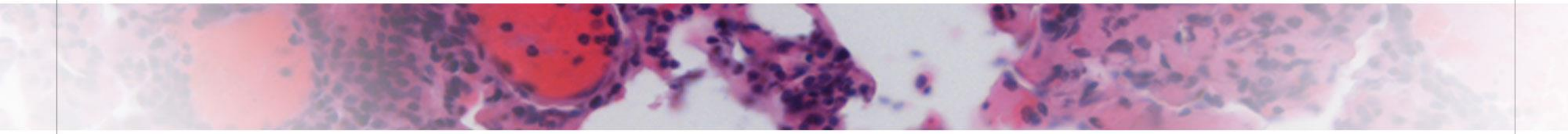

Gene Therapy for Fanconi Anemia (Group A): Preliminary Results of Ongoing RP-L102 Clinical Trials

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***authors contributed equally to this work**

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Disclosures

- Consultant: Beam Therapeutics, GV, Spotlight Therapeutics, Stemodontics
- Current Equity: Beam Therapeutics, Decibel Therapeutics, Editas Medicine, Global Blood Therapeutics, GV, Magenta Therapeutics, Spotlight Therapeutics, Stemodontics, Divested Equity in last 24 months: Forty Seven, Inc.
- Intellectual property rights: Gilead Sciences, Jasper Therapeutics, Magenta Therapeutics
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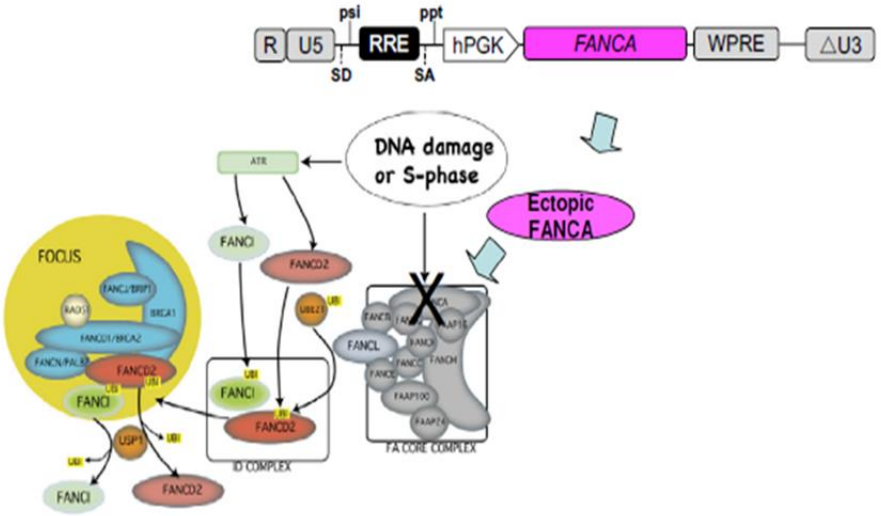
Introduction

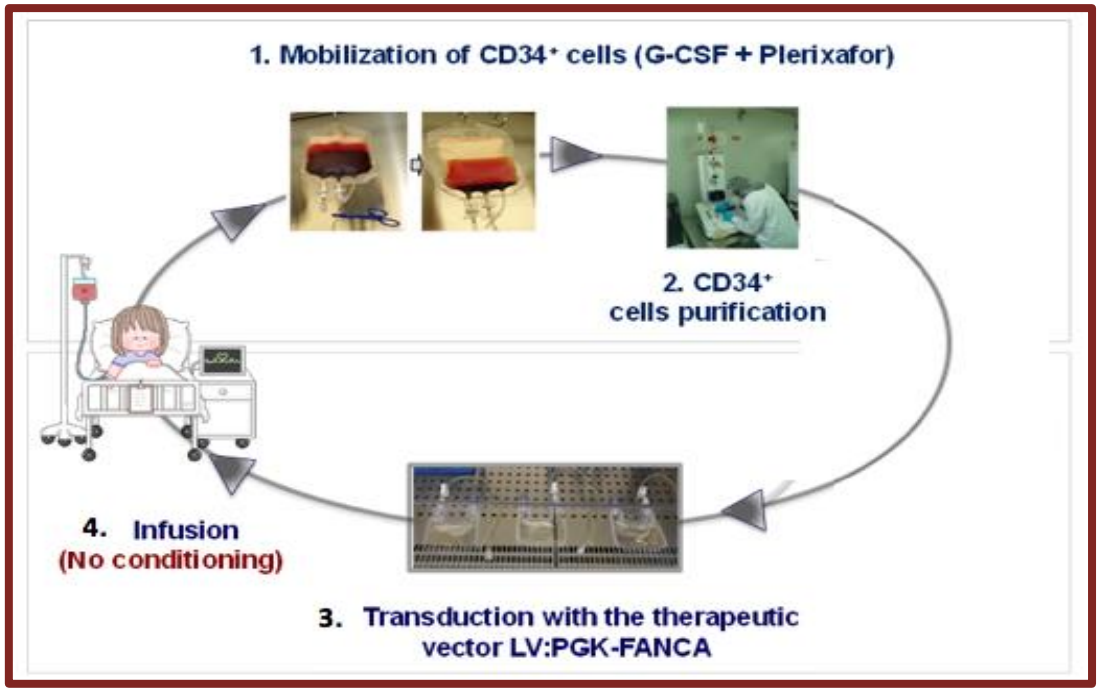
- Fanconi anemia (FA) is a rare inherited disorder of defective deoxyribonucleic acid (DNA) repair characterized by:
  - Progressive bone marrow failure (BMF); 80% of patients experience BMF within 1st decade of life
  - Predisposition to hematologic malignancies and solid tumors
  - Congenital abnormalities
- FA complementation group A (FA-A) accounts for 60–70% of FA
- Allogeneic hematopoietic stem cell transplant (HSCT) is frequently curative of FA-associated BMF, but utilization and efficacy are limited by:
  - Donor availability
  - Acute and chronic toxicities including graft-versus-host disease (GvHD)
  - Increased risk of subsequent solid tumors (particularly in patients with chronic GvHD)

RP-L102 Rationale and Study Design

- Insertion of a functional *FANCA* gene into autologous FA-A CD34+ cells confers resistance to DNA-damage & provides proliferative advantage to modified cells
- Enables engraftment in the absence of conditioning as demonstrated in FANCOLEN-I



Schematic of Product Manufacture and Treatment



Patients undergo hematopoietic stem cell (HSC) mobilization and collection, followed by CD34+ immunoselection, transduction, and subsequent infusion *without conditioning*.

Río P *et al*. Nat Med 2019; 25:1396-1401

Global RP-L102 Studies

Key Eligibility Criteria

Inclusion:

- FA complementation group A
- Minimum age: 1y
- *Maximum age: US Ph 1 (12y); US Ph 2 (none); EU Ph 2 (17y)*
- BM CD34+ cell concentration ≥30/µL (from aspirate)
- *US Ph 1 only : At least 1 hematologic parameter (Hb, ANC or Plt) below lower limit of normal*

Exclusion:

- Available & eligible HLA-identical sibling donor
- MDS or leukemia (including associated cytogenetic abnormalities)
- Mosaicism with stable/improved blood counts

Endpoints

Efficacy:

Engraftment: Peripheral blood (PB) and BM vector copy number (VCN)

Phenotypic correction: Increased resistance of BM and PB cells to DNA-damaging agents mitomycin-C (MMC) and diepoxybutane (DEB)

Clinical response: Prevention of BMF (stabilization or increase in PB counts)

Safety of RP-L102

Patient Demographics and Investigational Product Metrics

Subject #	Age at Enrollment (years)	Follow Up (months)	CD34+ Cells/kg	CFCs/kg	Mean VCN: Liquid Culture	Mean VCN: CFCs	Transduction Efficiency (%)	CFC Survival MMC 10nM (%)
1 (1001)	5	32	$2.0 \times 10^{5*}$	$5.2 \times 10^{4*}$	2.08	0.62	67	33
2 (1002)	6	18†	$3.7 \times 10^{5*}$	$5.0 \times 10^{4*}$	2.21	0.92**	72	47
3 (2004)	3	21	4.8×10^{5}	1.1×10^{5}	1.70	0.73	100	63
4 (2008)	2	15	3.2×10^{6}	2.8×10^{5}	1.65	1.56	97	63
5 (2009)	3	15	1.9×10^{6}	1.5×10^{5}	2.16	0.76	61	45
6 (2010)	3	15	$4.1 \times 10^{6*}$	n/a	0.62	n/a	n/a	n/a
7 (2011)	5	15	$2.8 \times 10^{6*}$	n/a	1.46	n/a	n/a	n/a
8 (2014)	6	12	$5.4 \times 10^{5*}$	$3.6 \times 10^{4*}$	3.68	pending	pending	31
9 (2016)	2	9	$3.0 \times 10^{5*}$	$2.5 \times 10^{4*}$	1.96	0.64	88	64
10 (2021)	2	0‡	$2.3 \times 10^{6*}$	pending	pending	pending	pending	pending

- **10 patients treated across 3 clinical sites**
- **All patients ≤6 years at enrollment**
- **8 patients have ≥12 months of follow-up; 1 patient (1002) withdrawn from the study at 18 months**

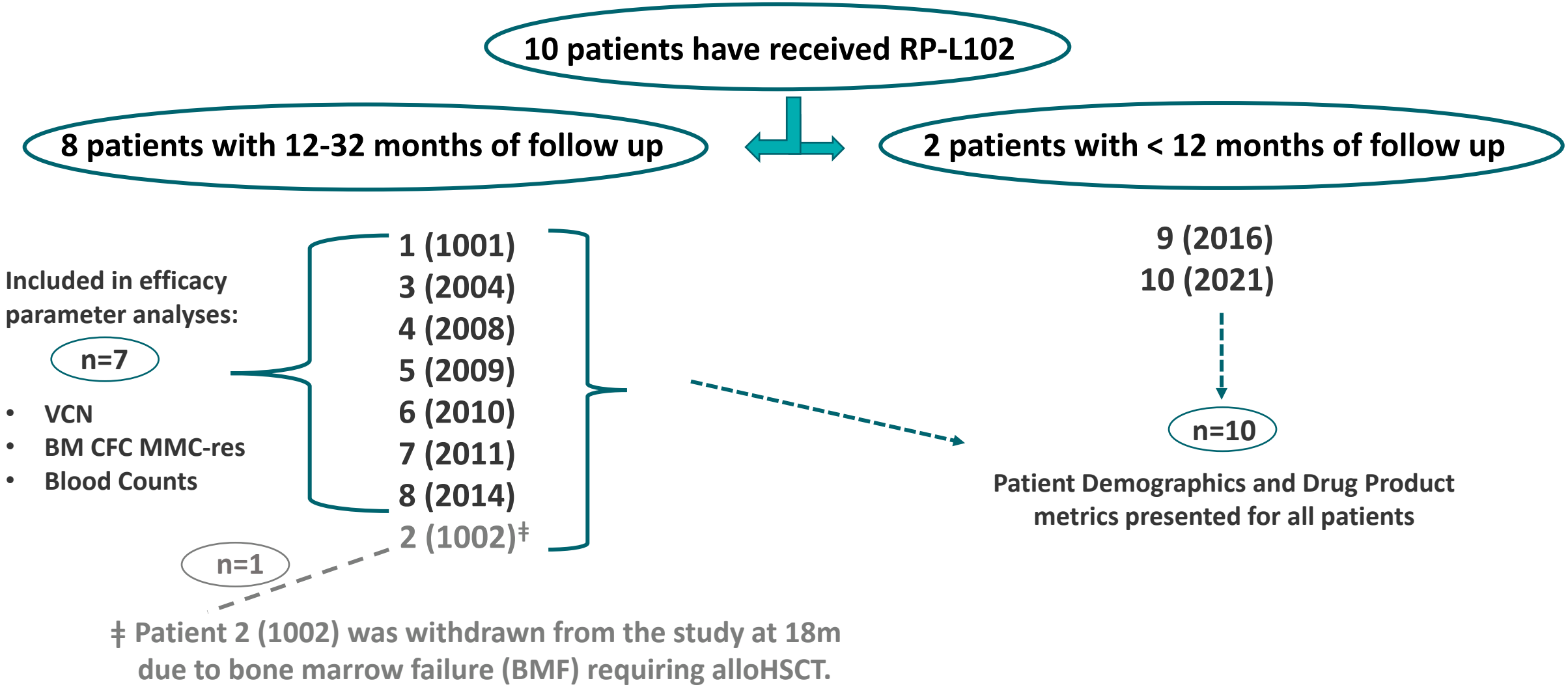
Mean values:

VCN (liq) 1.95
VCN (CFC) 0.87
TD efficiency 81%
CFC MMC-res 49%

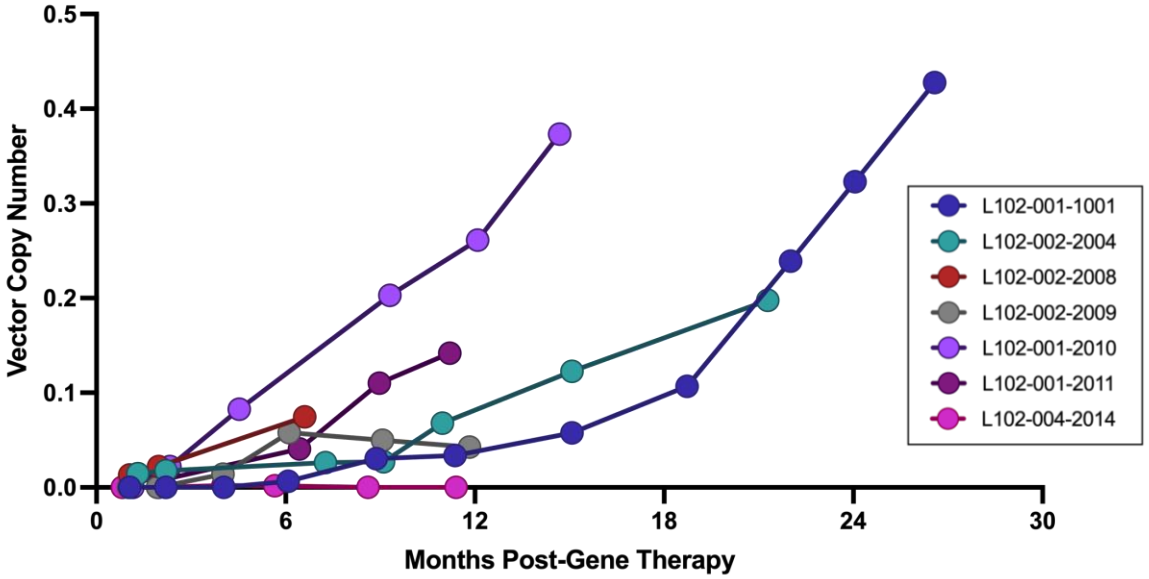
*Per NC200 automated count (results in ~50% lower count vs. manual count used in FANCOLEN-I)
**Mean CFC VCN was assessed from a cryopreserved drug product sample

† Subject withdrawn from the study at 18 months post-RP-L102 infusion; received successful allogeneic HSCT
‡ Subject recently received RP-L102 infusion as of October 2021

Current Status of Patients



RP-L102 Study Patients with ≥12 m Follow Up Demonstrate Evidence of Genetic and Phenotypic Correction



- **Sustained PB VCN seen in 6 of 7 enrolled patients with ≥ 12 months of follow up**
- **Concomitant BM CFC MMC resistance ≥ 10% of baseline values seen**

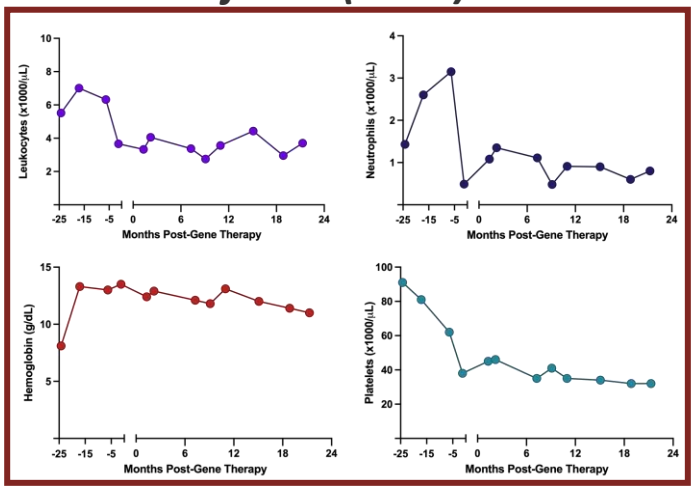
Efficacy in 5 of 12 patients (observed over 1–3 years post rx) required to reject null hypothesis.

Subject #	Bone Marrow Assessment Performed (months)	BM CFC MMC Resistance at 10 nM MMC (%)
1 (1001)	24	16†
3 (2004)	21	63
4 (2008)	12	21
5 (2009)	12	29
6 (2010)	12	42
7 (2011)	12	31
8 (2014)	12	0

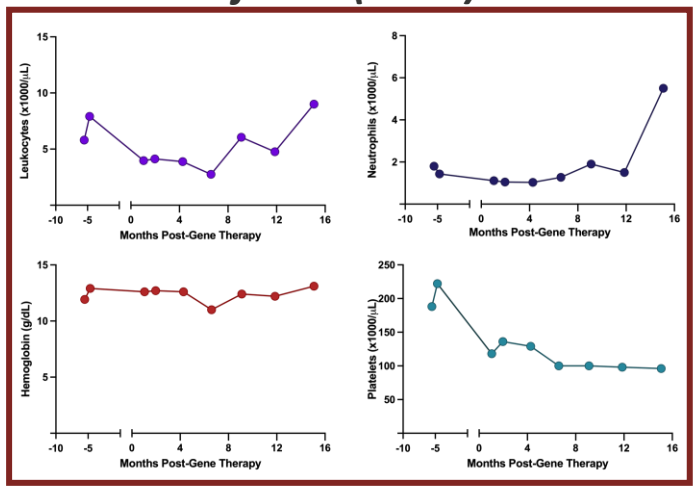
† Assessment was not performed at study's centralized laboratories

Blood Count Stabilization in at Least 5 Patients with BM CFC MMC Resistance ≥10%

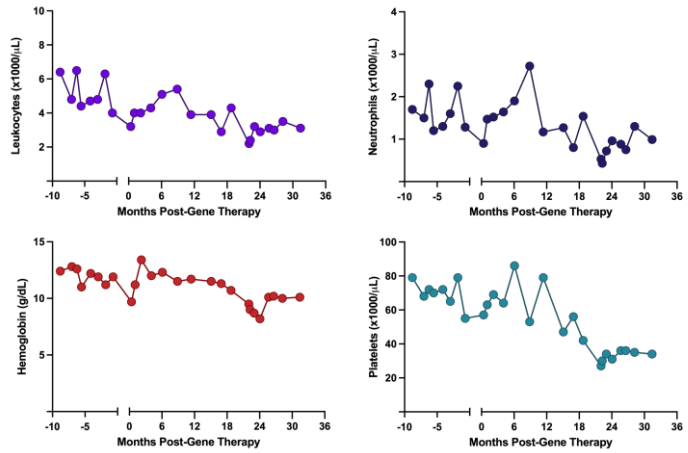
Subject 3 (2004)



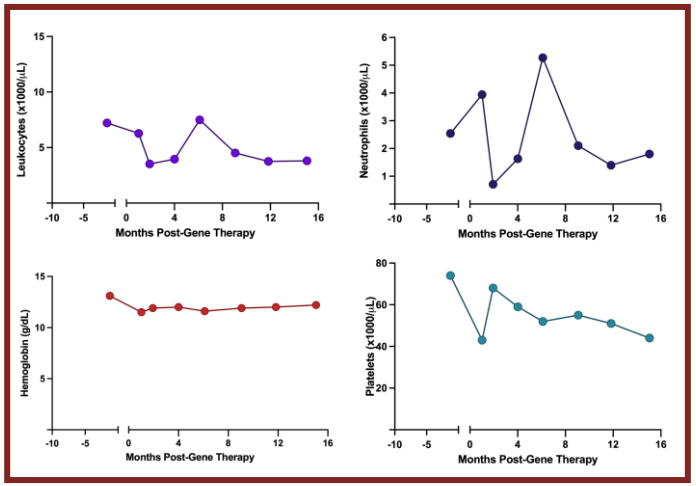
Subject 4 (2008)



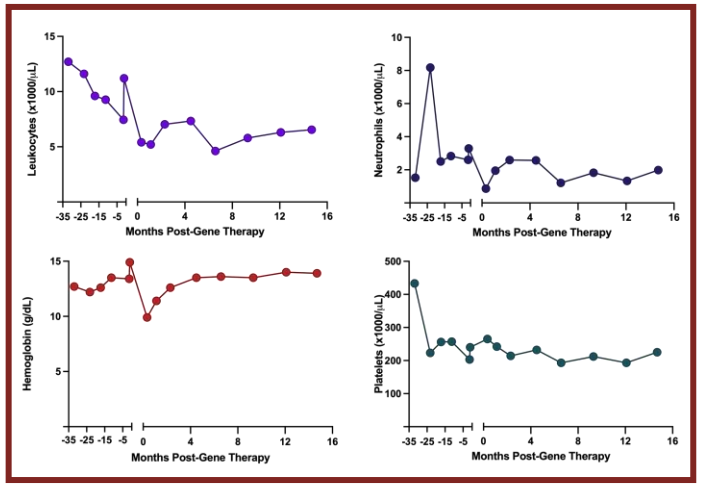
Subject 1 (1001)



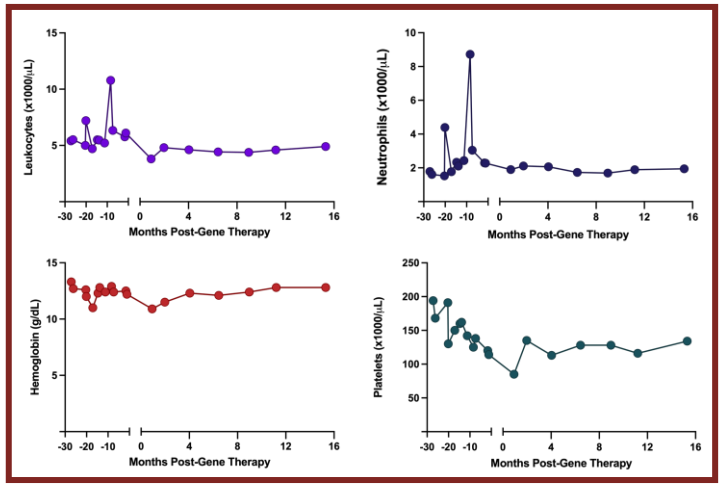
Subject 5 (2009)



Subject 6 (2010)



Subject 7 (2011)



- Blood count stabilization in 5/5 patients with BM CFC MMC Resistance ≥ 20%
- Patient 1 (1001; MMC-res 16%) had modest decline in blood counts with potential stabilization after ~21m;
  no transfusions have been required

Conclusions

- Of 10 patients treated to date:
  - 6 of 8 patients with ≥12m of follow-up display evidence of engraftment
    - 1 patient's course (1002) complicated by *Influenza B* infection & BMF; required BMT and engrafted without complications

- Increasing BM CFC MMC resistance seen in 6 patients*
  - Concomitant blood count stabilization

- Safety profile of RP-L102 appears favorable
  - Patients treated without conditioning
  - No signs of dysplasia or other concerning features
  - RP-L102 related SAEs: 1 infusion-related reaction (transient, Grade 2)

**** Efficacy in 5 of 12 subjects (observed over 1-3 years post rx) required to reject null hypothesis***

Acknowledgements

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