A Phase 1/2 Study of Lentiviral-mediated Ex-vivo Gene Therapy for Pediatric Patients with Severe Leukocyte Adhesion Deficiency-I (LAD-I): Interim Results

Abstract ID **987691**

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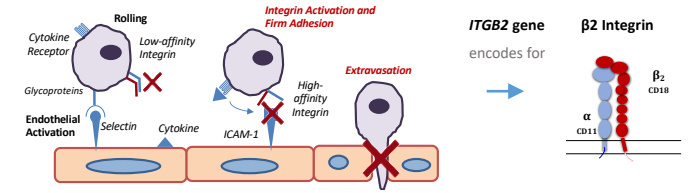
Leukocyte Adhesion Deficiency I (LAD-I)

- *ITGB2* encodes for the CD18 component of the beta-2-integrin receptor
- *ITGB2* mutations prevent functional expression of CD11/CD18 heterodimers on leukocyte cell surfaces essential for cell adhesion and subsequent migration
- Severe LAD-I is characterized by recurring and fatal infections due to inability of leukocytes to leave bloodstream and extravasate to sites of infection
- Current Treatment Option: Allogeneic HSCT (limited by availability of suitable donor, high incidence of GvHD and infections).



LAD-I Disease Spectrum

Moderate: 2-30% CD18+ PMN

Severe: <2% CD18+ PMN

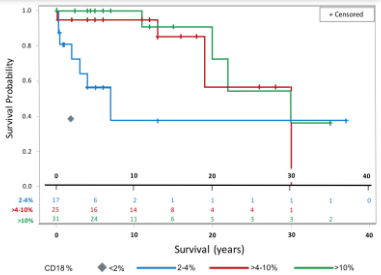
PMN = polymorphonuclear leukocytes

LAD-I Clinical Prognosis

Patients suffer from recurrent infections; fatal in majority

- 60-75% of pts with severe LAD-I die **prior to age 2**
- >50% of pts with moderate LAD-I die **before age 40**

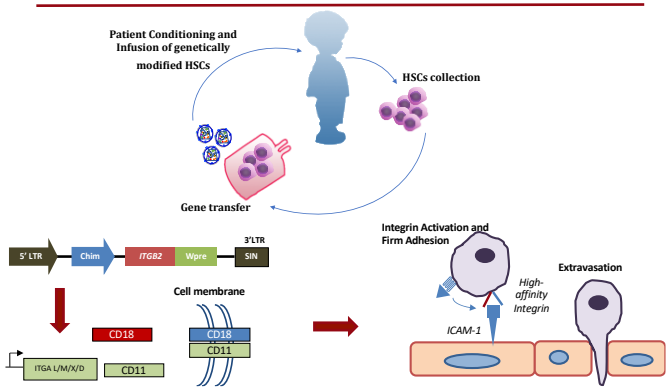
LAD-I Patients not receiving allogeneic HSCT



◆ 39% survival to age 2 years for 66 evaluable patients with severe LAD-I not receiving HSCT

Almarza E et al. J Allergy Clin Immunol Pract. 2018

Gene Therapy for LAD-I



RP-L201 Clinical Trial

Non-Randomized Global Phase 1/2 Study

Phase	N (Planned)	N (Treated)
1	2	2
2	7	5

Data from first 4 treated patients with follow-up reported

Primary Endpoints

Phase 1:

- Safety and preliminary efficacy

Phase 2:

- Survival: proportion of patients alive at age 2 and at least 1-year post infusion (& not requiring alloHSCT)
- Safety

Secondary Endpoints

- % of pts w/neutrophil CD18 expression at least 10% of normal
- % of pts w/neutrophil VCN of at least 0.1 copies/cell at 6m post-rx
- Incidence and severity of infections
- Improvement/normalization of neutrophilia
- Resolution (partial or complete) of underlying skin rash or periodontal abnormalities

Demographic and Cell Product Characteristics

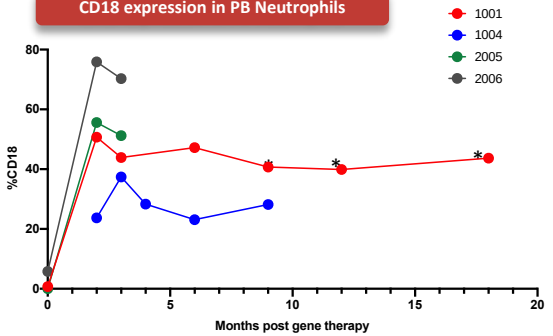
Patient	Gender	Age at enrollment	Drug Product VCN	CD34+ Cell Dose
L201-003-1001	F	9 yrs.	3.8	4.2 x 10^6 cells/kg
L201-003-1004	F	3 yrs.	2.5	2.8 x 10^6 cells/kg
L201-003-2005	F	2 yrs.	1.8	6.5 x 10^6 cells/kg
L201-003-2006	M	7 mo.	2.9	4.3 x 10^6 cells/kg

Conclusions

- Four severe LAD-I patients have been successfully infused with RP-L201
- Safety profile of RP-L201 appears favorable:
  Infusion well tolerated; no drug product-related SAEs or severe AEs
- Preliminary efficacy evident in 4 of 4 patients, including 2 patients with ≥ 6-months of follow-up
- Patient L201-003-1001 with durable CD18+ PMN expression ~40% at 18-months and PB VCN of 1.2 at 12-months post-infusion and resolution of pre-existing skin lesions
- Patient L201-003-1004 with CD18+ PMN expression at 28% 9-months post-treatment and early PB VCN trajectory similar to that of first patient

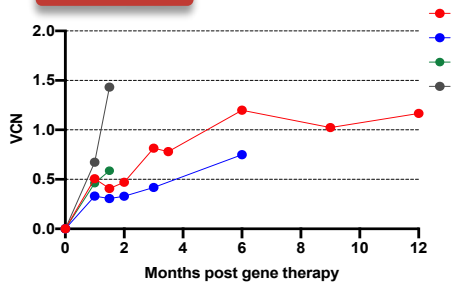
Clinical Results

CD18 expression in PB Neutrophils



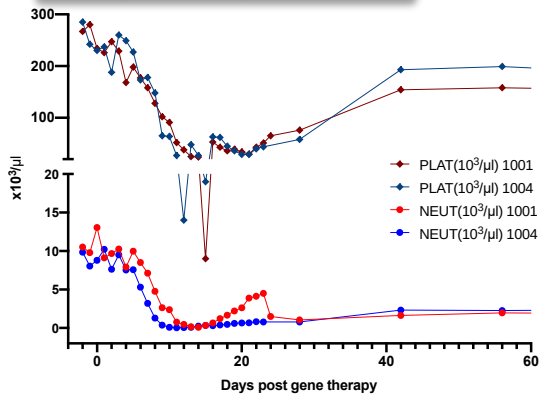
* Shipping delays (2° to COVID pandemic) may cause under-representation of results
Dim/weak CD18 expression reported at baseline for pt 1004 in ~60% of cells

VCN in PBMCs



PBMC: peripheral blood mononuclear cell

Hematopoietic Recovery : Initial 2 Patients

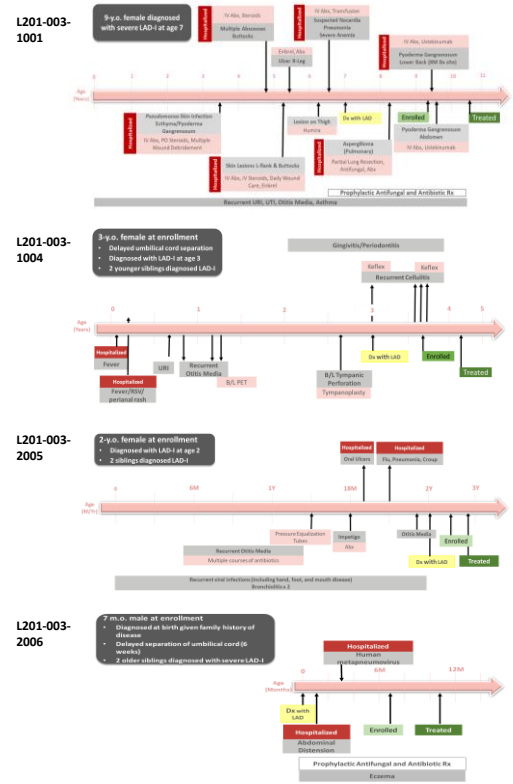


Improvements in Skin Lesions (Patient L201-003-1001)

Baseline (pre-treatment) | 3-months (post-treatment) | 6-months (post-treatment) | 12-months (post-treatment)

Pre-Treatment Medical History

Patients have had an extensive history of severe and/or persistent infections including infections requiring surgical, antibiotic & anti-inflammatory therapy. No severe infections have been reported in any patient following hematopoietic reconstitution.



Pre-study patient records collected by UCLA Mattel Children's Hospital