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Poster: 249

Non-Genotoxic Anti-CD117 Transplant Conditioning in Infants with Newly Diagnosed Severe Combined Immune Deficiency

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Background

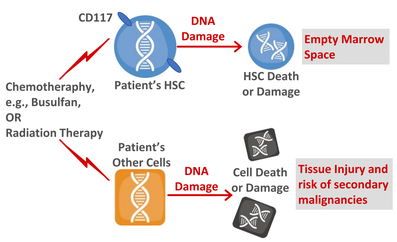
Successful hematopoietic cell transplantation (HCT) requires vacating recipient hematopoietic stem cell (HSC) niches to permit donor HSC engraftment. Currently, HCT relies on genotoxic modalities to achieve niche clearance. We have pursued a non-genotoxic approach to target and deplete HSC using humanized monoclonal antibody JSP191 that binds CD117 (c-Kit). JSP191 acts by inhibiting stem cell factor (SCF) binding to CD117 (c-Kit) present on HSC.

Based on safety and successful HSC engraftment in a Phase 1 trial in subjects with severe combined immunodeficiency (SCID), who underwent a second transplant because of HSC engraftment failure and poor immunity (PART A), the study of JSP191 (NCT#02963064) was expanded to include additional cohorts (PART B) of newly diagnosed infants with SCID.

This presentation focuses on the two infants in PART B.

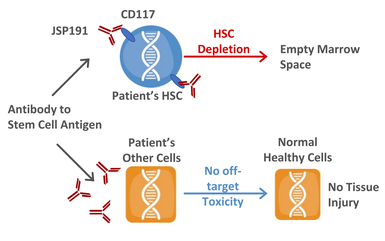
Toxic Conditioning Regimens is an Obstacle for Transplant: JSP191 is a Safer Alternative

Current Transplant Conditioning Removes HSCs Through Highly Toxic Regimens



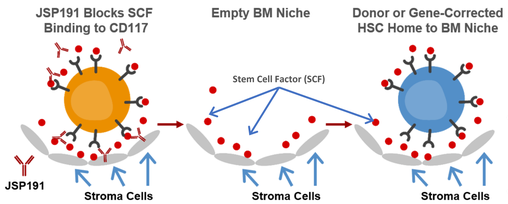
Marrow ablation by chemotherapy or radiation therapy causes cell damage or death to other patient cells

JSP191 Selectively Targets HSCs: An Alternative to Toxic Conditioning Regimens



Using an antibody to stem cell antigen will limit extramedullary tissue damage seen with conventional genotoxic conditioning

JSP191 Binds to CD117 on HSCs and Depletes HSCS



- Stem Cell Factor (SCF) / Stem Cell Factor Receptor (CD117) interaction required for stem cell survival
- JSP191 blocks SCF signaling leading to patient stem cell depletion from the bone marrow
- Allows for healthy donor stem cell engraftment

Clinical Study Design:
Evaluation of SCID patients in a re-transplant and first transplant setting

Key Inclusion Criteria	Dose Finding Cohorts	Status

PART A: SCID Re-Transplant population

- SCID defined by PIDTC
- Prior donor must be available
- Prior transplant ≥ 6 months
- Inadequate B cell engraftment
- Incomplete T cell reconstitution
- Clinical symptoms due to poor immune function

Cohort A1 0.1 mg/kg (n = 3) → Cohort A2 0.3 mg/kg (n = 4 of 6) → Cohort A3 1.0 mg/kg (n = 3)
Cohort A2 → Cohort A5 0.6 mg/kg (n = 1 of 6)

- No JSP191-related adverse events
- Outpatient conditioning
- 4 of 6 engraftment at 1yr
- OPEN TO ENROLLMENT

PART B: Newly Diagnosed SCID

- SCID defined by PIDTC
- No prior history of HCT
- Haploidentical or HLA matched donor

Cohort B2 0.3 mg/kg (n = 2 of 3) → Cohort B5 0.6 mg/kg (n = 0 of 3) → Cohort B3 1.0 mg/kg (n =0)

- No JSP191-related adverse events
- 1 of 2 infants with engraftment at 9 months
- OPEN TO ENROLLMENT

Subject Demographics

	Cohort B2: 0.3 mg/kg	
Subject ID	BABY #1 (0011)	BABY #2 (0015)
Genotype	IL2RG (NK-)	RAG2 (NK+)
Age at HCT	6 months	3 months
Donor	Paternal Haplo	Maternal Haplo
CD34+ cell dose	20x10^6 cells/kg	16.5x10^6 cells/kg
Maternal Engraftment	Yes	Yes
JSP191	Day -8	Day -6
ATG	Day -5, -4, -3 and -2	Day -5, -4, -3, and -2
Safety Signals	No Treatment related AEs No myelosuppression	No Treatment related AEs No myelosuppression
Status	On study >36 weeks Engraftment observed at week 4	Off study at 8 weeks No engraftment observed at week 8

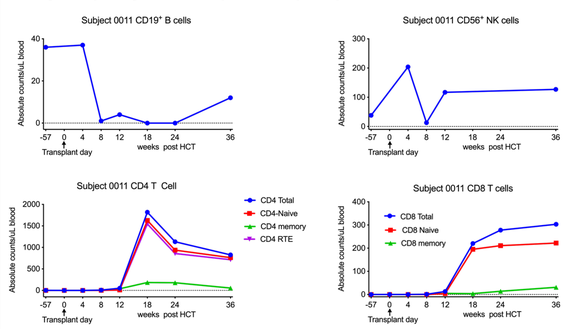
JSP191 is a well tolerated conditioning regimen

- **No transfusion reactions**
- **No treatment related toxicities**
- **No myelosuppression**

PART A subjects (re-transplant) may be discharged after 48 hours observation following JSP191 administration

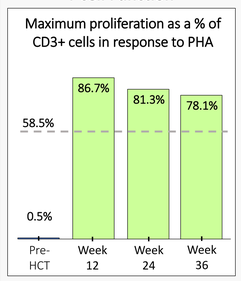
HCT conditioning with JSP191 alone enables engraftment, immune reconstitution, and function in newly diagnosed SCID patients

Baby #1 (Subject 0011) IL2RG (NK-)



T cell Function

Maximum proliferation as a % of CD3+ cells in response to PHA

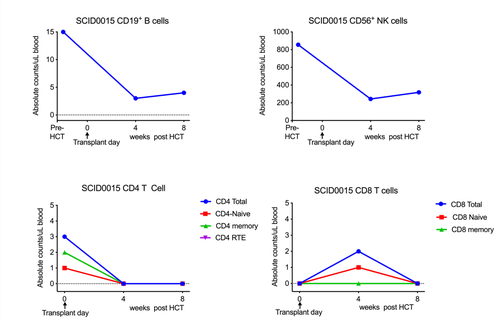


Normal T cell function associated with proliferation > 58.5%

Engraftment: Flow-sorted CD15+ Donor Myeloid Chimerism

Pre-HCT	Week 4	Week 8	Week 12	Week 18	Week 24	Week 36
0%	1%	8%	8%	5%	5%	QNS

Baby #2 (Subject 0015) RAG2 (NK+)



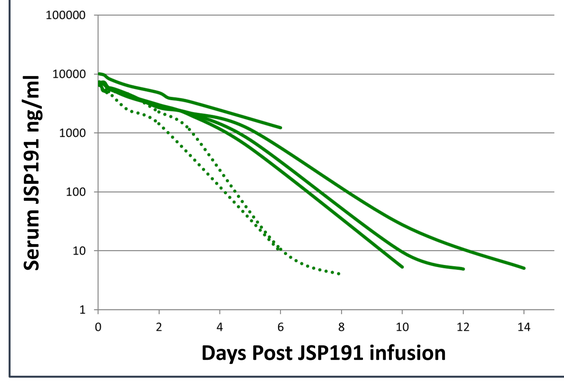
This patient had two SOC tests demonstrating low level maternal engraftment pre-HCT, suggesting host tolerance of maternal cells.

Post-HCT, SOC testing detected only host NK cells in the blood, and all maternal engraftment disappeared, remaining absent through Day +51.

It was clinically determined that the patient had lost tolerance to maternal cells and the patient likely experienced an NK-cell mediated rejection.

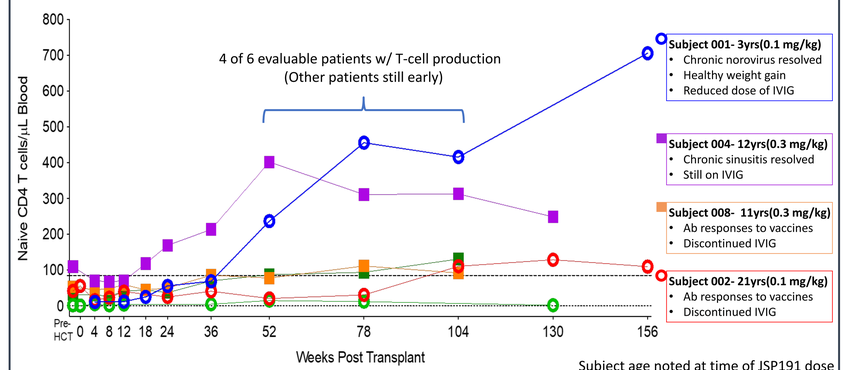
The clinical decision was made to proceed with a fully-conditioned HCT from the same donor.

JSP191 clearance in newly diagnosed (Cohort B2) and re-transplanted SCID subjects (Cohort A2)



Clearance of JSP191 was consistent and predictable in re-transplanted children and adults (ages 11, 12, 12, and 38 years old), and was faster in the newly diagnosed infants (6 and 3 months old).

Update on PART A subjects (re-transplant subjects)



Subject age noted at time of JSP191 dose
CD4+ Counts analyzed at local sites

Summary

- JSP191 is well tolerated as a single agent conditioning regimen for SCID patients undergoing their first HCT.
- JSP191 can create HSC niche space and has the potential to replace genotoxic conditioning.
- HSC engraftment in SCID patients is possible without myelosuppression.
- First SCID newborn patient achieved HSC engraftment following JSP191 conditioning as evidenced by sustained donor myeloid chimerism.
- SCID patients re-transplanted following single agent conditioning with JSP191 can achieve durable donor HSC engraftment, chimerism, and clinical benefit (resolution of chronic infections, independence from IVIG, or antibody response to vaccine challenge)
- This trial is open to enrollment for newly diagnosed and re-transplant patients with SCID

(NCT#02963064)

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