Establishment of durable chimerism with minimal graft versus host disease in highly mismatched recipients receiving an investigational facilitated allo-HSCT

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Disclosures

- JL has received funding for research from Talaris Therapeutics, Inc.
Transplant, allogenic tolerance, and chimerism

• The risk of transplant rejection increases in donor-recipient pairs with greater HLA mismatch\(^1\)
• Facilitated allo-HSC transplantation therapy using FCR001 could prevent organ rejection without the morbidity and mortality that has been associated with the use of lifelong IS

HLA, human leukocyte antigen; HSC, hematopoietic stem cell; IS, immunosuppression.
Transplant, allogenic tolerance, and chimerism

- FCR001 is an investigational cell therapy derived from donor-mobilized peripheral blood cells, processed to contain an optimized number of HSCs, facilitating cells, and αβTCR+ T-cells that could induce chimerism and immune tolerance in highly HLA-mismatched donor-recipient pairs. Facilitating cells promote stem cell engraftment in unmatched recipients, prevent GvHD in mouse models, and induce antigen-specific T\textsubscript{reg} and B\textsubscript{reg}.

- We previously reported using FCR001 to induce kidney transplant tolerance by establishing durable whole blood and T-cell chimerism that allowed withdrawal of IS in 26 of 37 highly mismatched recipients of combined stem cell and living donor kidney transplant with a low risk of GvHD. 

\( B\textsubscript{reg} \) regulatory B cells; GvHD, graft versus host disease; HLA, human leukocyte antigen; HSC, hematopoietic stem cell; IS, immunosuppression; T\textsubscript{reg}, regulatory T cells.

Background and objective

- The Phase 2 study protocol included an analysis of HLA matching at HLA-A, -B and DR (limited to 6/6 only)
- The objective of this retrospective analysis was to evaluate the impact of varying degrees of bidirectional donor/recipient mismatching using high-resolution allele typing HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 on the ability to establish durable chimerism, allowing full IS withdrawal and the induction of transplant tolerance
- HLA typing was performed using sequence specific oligonucleotide probe hybridization or next-generation sequencing for HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1, DQB1, DPA1, and -DPB1. Results were analyzed using Fusion (One Lambda – California, USA) or NGSengine (GenDeX – Utrecht, NL), as appropriate

HLA, human leukocyte antigen; IS, immunosuppression.
The “Vein to Vein” process

- **FCR001 cryopreserved and sent to transplant center**
- **Donor’s cells processed to yield FCR001**

**3+ WEEKS PRIOR**
- GCSF mobilization and collection of donor stem and immune cells

**3+ WEEKS PRIOR**
- Donor’s cells processed to yield FCR001

**4 DAYS PRIOR**
- Recipient starts nonmyeloablative conditioning

**DAY 0**
- Kidney transplant

**NEXT 6 MONTHS**
- Frequent, routine monitoring

**+ 6-9 MONTHS**
- Potentially lowering doses of chronic immunosuppression*

**12 MONTHS & AFTER**
- Potentially free from all immunosuppression*

*Assuming no BPAR, stable kidney function, >50% donor T-cell chimerism, no GvHD. BPAR, biopsy-proven acute rejection; GCSF, granulocyte colony stimulating factor; GvHD, graft versus host disease.
Trial registration number:
NCT00498160

N = 37 LDKT patients 18–65 years of age Cross-match negative (donor-recipient)

Methylprednisolone 500 mg IV on Day 0; 250 mg Day 1 and 125 mg Day 2.

*Assuming no biopsy-proven acute rejection; stable kidney function; >50% donor chimerism; no GvHD.

**Methylprednisolone 500 mg IV on Day 0; 250 mg Day 1 and 125 mg Day 2.

cGy, centigray; Cy, cyclophosphamide; FLU, fludarabine; GvHD, graft versus host disease; IS, chronic immunosuppression; IV, intravenous; LDKT, living donor kidney transplant; Mesna, mercapto-ethyl sulfonate; TBI, total body irradiation.
Whole blood and T-cell chimerism measurements during year 1 and relationship with ability to withdraw from IS at 1-year posttransplant

Values are mean +/- standard error. N indicates the number of FCR001 treated patients weaned off IS at approximately 1-year post-transplant for whom % whole blood and T-cell donor chimerism were measured at that time point.

IS, immunosuppression.

• “Chimerism”
  — % of recipient’s T-cells that are donor-derived
  — Simple blood test, measured at multiple time points

• 26/27 patients (96%) who achieved chimerism at month 6 were able to be weaned off chronic IS

• Every patient weaned off chronic IS by month 12 has remained off chronic IS for full duration of follow-up
  — Median follow-up >6 years
  — Longest follow-up >11 years
Results – Degree of HLA mismatch

• High-resolution allele level typing was performed in 32 of the 37 subject pairs at HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 (12/12)
  — Three of the 32 subjects did not have sufficient DNA to test for locus DPB1 (10/10)
• All 32 recipients (age range 18–65 years) have reached at least 4.5 years of follow-up (median >6 years, maximum >12 years)
  — Two recipients were re-transplants
  — Of the 29 donor-recipient pairs with data from all 12 alleles:
    o 21 were mismatched between 6–12 alleles (6 related, 15 unrelated)
    o 8 were mismatched between 2 and 5 alleles (all related)
Bidirectional HLA mismatch and immunosuppression status

Degree of donor/recipient HLA mismatch by high-resolution typing

- LRD off IS
- LRD
- LURD off IS
- LURD

3 subject missing DP allele
1 LRD 6/10 Mismatch OFF IS
1 LRD 2/10 Mismatch OFF IS
1 LURD 10/10 Mismatch OFF IS
Donor chimerism achieved across HLA mismatch

- Despite the high degree of mismatch, 25 of 32 subjects achieved durable chimerism and full IS withdrawal (time off IS 3.5–11 years)
  - 12/25 off IS were from unrelated donor-recipient pairs with ≥8 HLA mismatches; the majority showed >95% donor whole blood/T-cell chimerism
  - Three have exhibited stable mixed chimerism ranging between 40%–60%
  - Durably chimeric patients retained chimerism after removal of IS, remain rejection-free without donor-specific antibodies, and have not resumed IS up to 12 years following transplant
- Of the subjects not off IS, 2 failed to engraft their cells; 4 lost chimerism by 4 months, and 1 developed GvHD
- Transiently chimeric subjects resumed endogenous hematopoiesis and are maintained on low-dose IS with stable renal function

GvHD, graft versus host disease; HLA, human leukocyte antigen; IS, immunosuppression.
Limited incidence of GvHD

- Two cases of GvHD, both in the setting of a female donor to an unrelated male recipient:
  - One Grade 2 lower GI acute GvHD that developed during conversion from tacrolimus to sirolimus and responded to steroids
    - This patient has developed moderate chronic GvHD of the skin. He is off IS with normal renal function
  - The second presented late following development of severe GI symptoms and manifested treatment-resistant lower GI GvHD with associated tissue-invasive cytomegalovirus colitis that proved fatal at 11 months posttransplant
  - An exclusion criterion for this donor-recipient pairing was added to the Phase 2 trial
Conclusions

• High levels of durable chimerism and tolerance with a low (5.5%) incidence of GvHD has been achieved in highly mismatched related and unrelated recipients of FCR001 + kidney transplant

• There was no correlation between the degree of HLA mismatch and any of durable chimerism, safety, or GvHD

GvHD, graft versus host disease; HLA, human leukocyte antigen.
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