

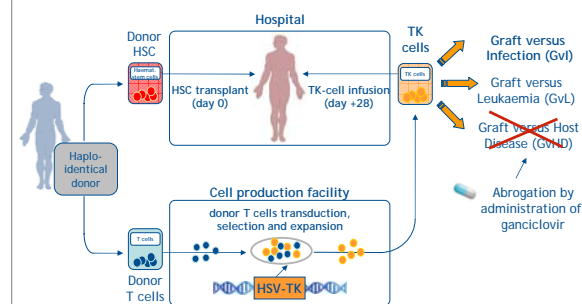
# Thymic renewal and anti-leukemic effect in adults after haploidentical transplantation and suicide gene therapy

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## Background

- Haematopoietic stem cell transplantation from partially HLA-matched family donors (haplo-HSCT) represents a promising therapy for high-risk leukaemia
- The infusion of donor T cells transduced with the HSV-TK suicide gene (TK cells) provides a rapid immune-reconstitution while controlling Graft-versus-Host-Disease (GvHD)
- Here we investigated the contribution of TK cells to post-transplantation thymic renewal and Graft-versus-Leukaemia (GvL) effect

Figure 1. TK cell therapy in haploidentical-HSCT

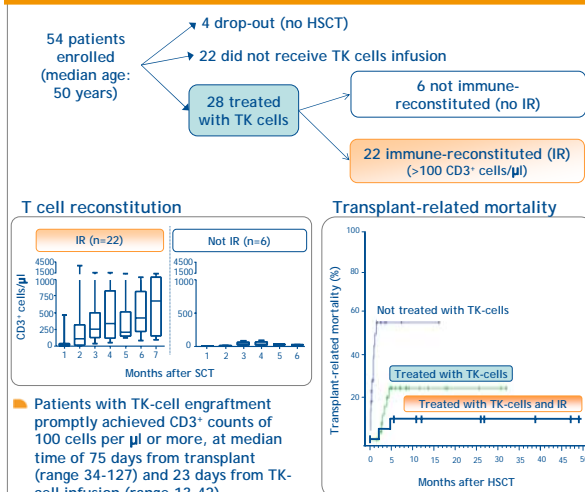


- Donor T cells transduced with the Herpes Simplex Virus Thymidine Kinase gene (TK cells) are selected and expanded *in vitro*
- After 20-40 days from haploidentical HSCT, TK-cells are infused into the patient

## Methods

- In a Phase II trial (TK007) of haplo-HSCT for high-risk leukaemia, 28 patients received TK cells (TK<sup>+</sup> donor T cells)
- In a selected subset of patients, thymic function was assessed by quantitation of CD31<sup>+</sup> in CD4<sup>+</sup> naive T cells, and was correlated with thymic volume, assessed by CT scans
- Alloreactivity against leukemic blasts was studied by MLC

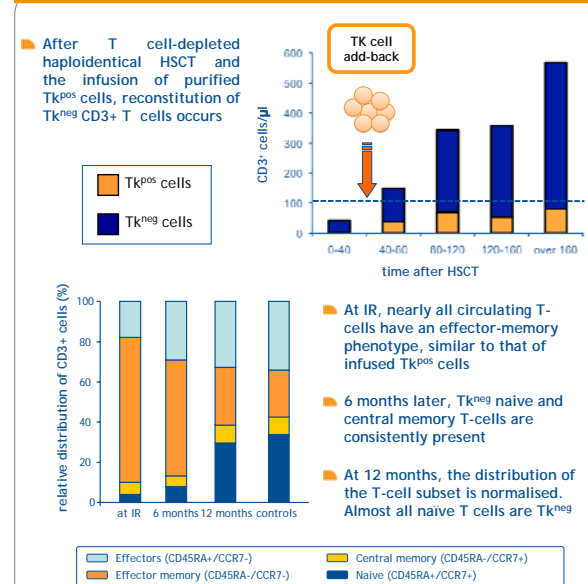
Figure 2. Phase II trial TK007: T cell reconstitution and transplant-related mortality



## Results

- Post-transplant recovery of TK-negative naive T cells occurred, reaching values comparable to controls in approximately one year
- After infusion of TK cells, almost all circulating CD4<sup>+</sup> naive T cells were CD31<sup>+</sup> Recent Thymic Emigrants, suggesting a direct role of the infused TK cells in promoting thymopoiesis. Accordingly, CT scans documented an increase of thymic volume
- TK cells displayed also a direct anti-leukemic effect, as demonstrated by their selective enrichment and functional activity against leukemic blasts
- Consistent with their *ex vivo* alloreactivity, in two of the treated patients TK cells drove *in vivo* selection of immuno-resistant leukemic variants with genomic loss of the mismatched HLA haplotype

Figure 3. Thymic contribution to T cell recovery after infusion of TK cells



- Naive TK<sup>neg</sup> cells reconstituting after HSCT and TK<sup>pos</sup> cell infusion express PECAM-1 (CD31), a hallmark marker of Recent Thymic Emigrants (RTEs). Accordingly, an increase in thymic volume could be documented by CT scans.

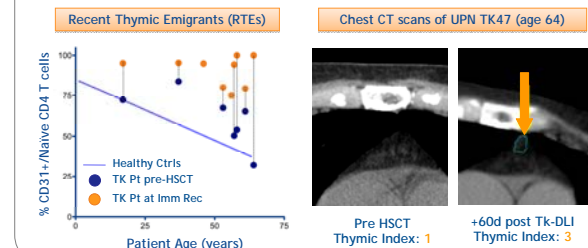


Figure 4. Protection against pathogens mediated by Tk<sup>neg</sup> cells

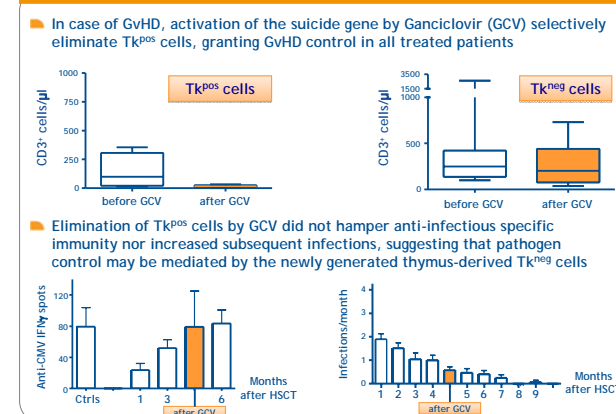
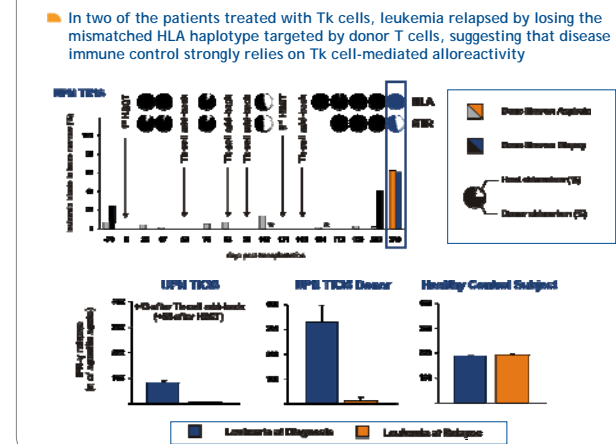
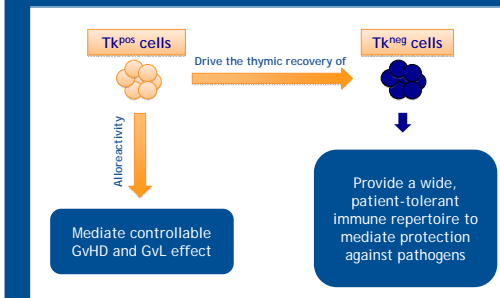


Figure 5. Leukemia control through alloreactivity mediated by TK<sup>pos</sup> cells



## CONCLUSIONS

- The infusion of genetically modified donor T cells prompts renewal of thymic activity, which contributes to recovery of a polyclonal T cell repertoire
- Contextually, TK cells also mediate a direct anti-leukemic effect



- TK cells activity in the context of haplo-HSCT is currently being assessed in a Phase III clinical trial (TK008)

## References

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## Acknowledgements

- Istituto San Raffaele: C. Soldati, S. Mastaglio, R. Greco
- MolMed: L. Callegaro, S. Colombi, A. Troysi, E. Lungagnani