



Priming of Type-1 EBV-specific CD8+ T cell from EBV⁻ pediatric HTx recipients for cellular immunotherapy for PTLT

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PTLD

- Life-threatening complication after SOTx
- Triggered by EBV infection in chronically IS recipients
- Highest incidence in pediatric SOTx patients (EBV⁺)
- Current treatments not always effective (25% refractory cases)



Goal of our study

- Adoptive immunotherapy with EBV-specific CTL for refractory PTLD in pediatric SOTx patients

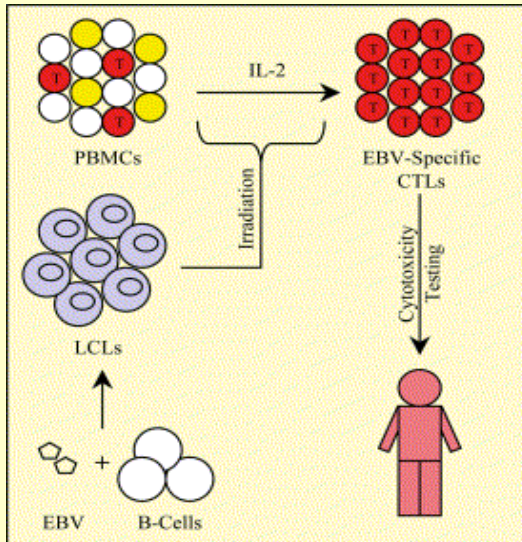


- Establish protocols for efficient priming of naïve T cells into EBV-specific Type-1 CTLs



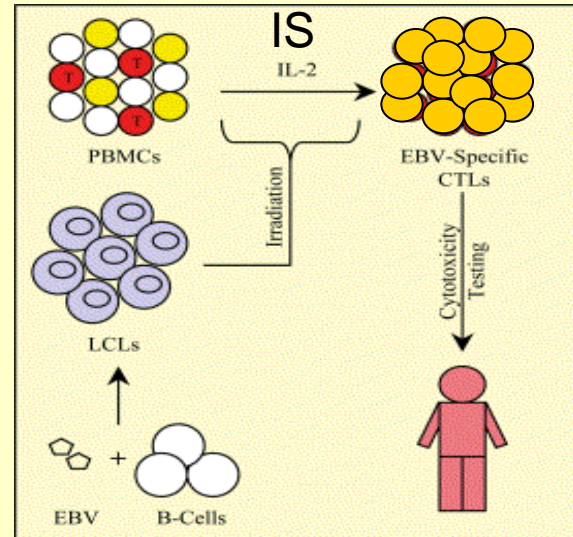
Adoptive immunotherapy with CTLs

- In BMTx successful



- PTLD are exclusively of donor origin mandating *ex vivo* generation of donor-derived EBV specific CTLs from healthy EBV positive subjects.

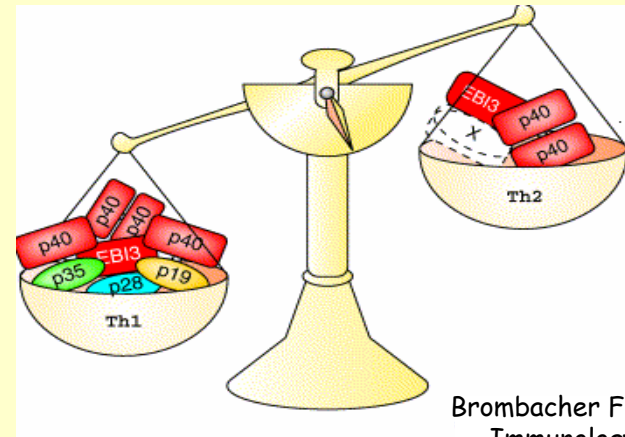
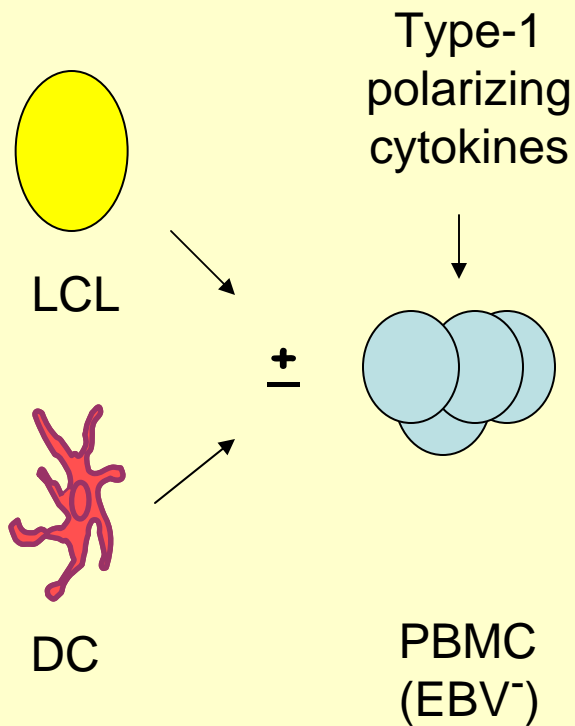
- In SOTx more challenging



- PTLD are exclusively of recipient origin (IS) mandating *ex vivo* generation of patient-derived EBV specific CTLs. EBV negative Tx patients very challenging

Burns, Blood reviews, 2004, 18(3):193-209

Hypothesis



Brombacher F, Trends in Immunology, 2003

Effective anti-EBV
Type-1 immunity



Our previous data:

LCL-based protocols

- not effective at priming Type-1 EBV-specific T cell responses in EBV⁻ adults or children
- effective only in the presence of IL-12p70

Metes D. et al., *Transplantation* 2000, 70(10): 1507-1515

DC-based protocols

- effective at priming Type-1 EBV-specific T cell responses in EBV⁻ healthy or SOTx adults

Popescu I. et al., *Amer J. of Transpl.* 2003, 3 (11) : 1369 -1377

Popescu I. et al., *Amer J. of Transpl.* 2007, 7(5):1215-1223

- effective for EBV⁺ pediatric SOTx patients
- **what about EBV⁻ pediatric SOTx patients?**



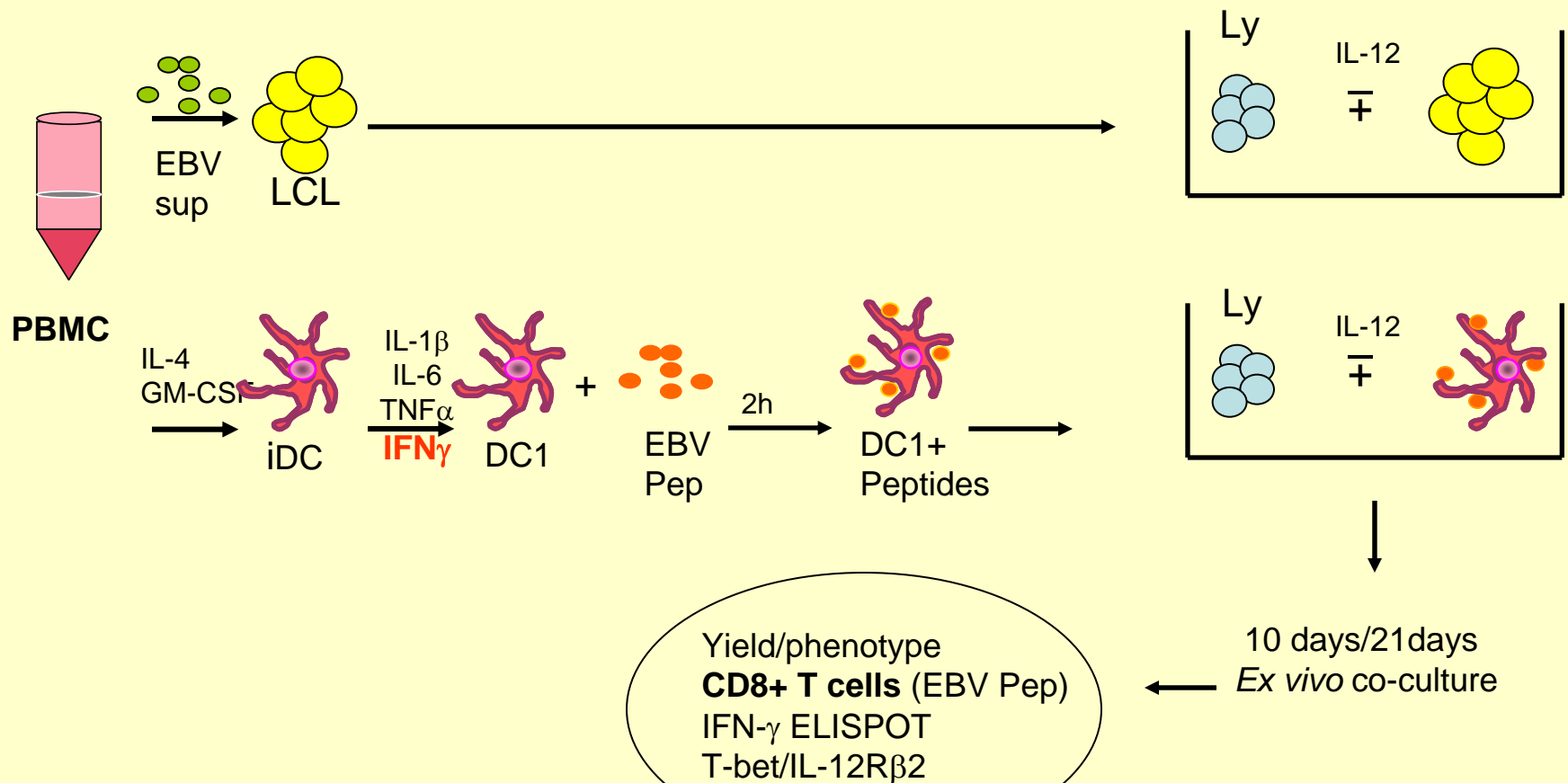
Patient Demographics

PEDIATRIC HTx PATIENTS*	PATIENTS	SEX	AGE	EBV STATUS Pre-Tx		EBV STATUS Post-Tx	
				Serology (VCA IgG)	PCR (EBV DNA)	Serology (VCA IgG)	PCR (EBV DNA)
EBV ⁻	n=4	1F / 3M	10.2 ± 6.2	Negative	Negative	Negative	Negative

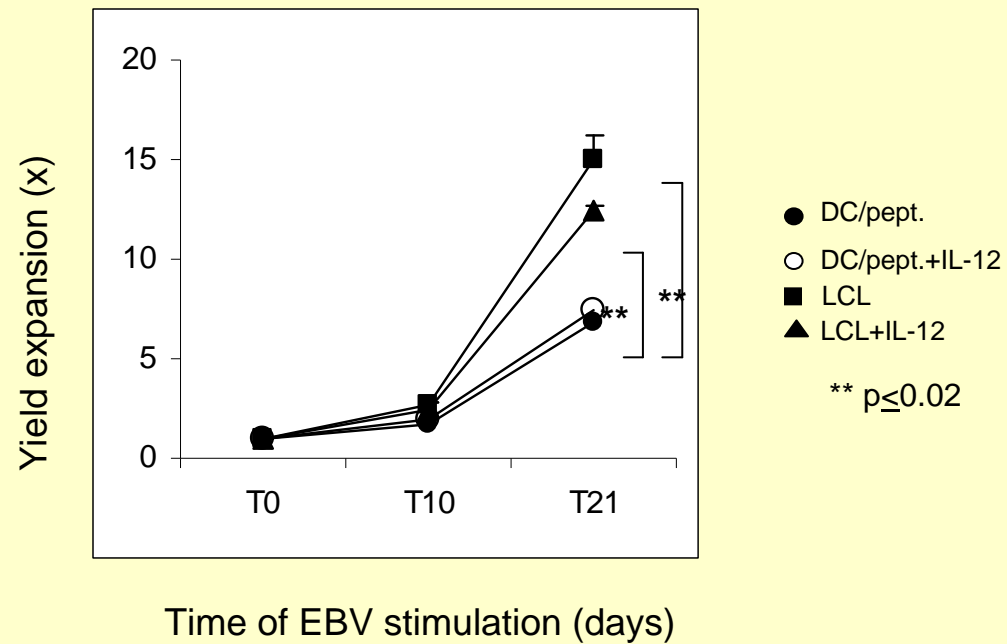
*All patients are HLA-A2 and are on Tacrolimus-based IS, with variable use of anti-proliferative agents and / or steroids.



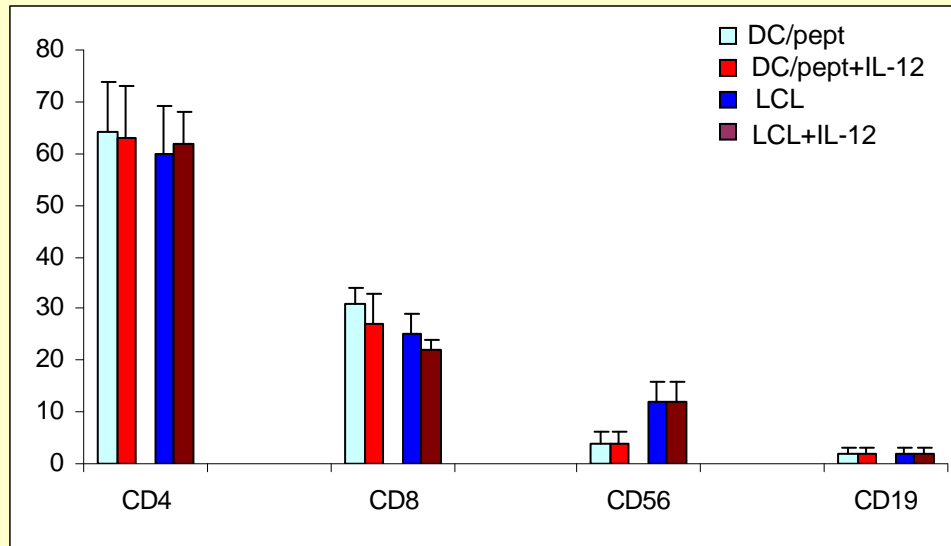
Methods



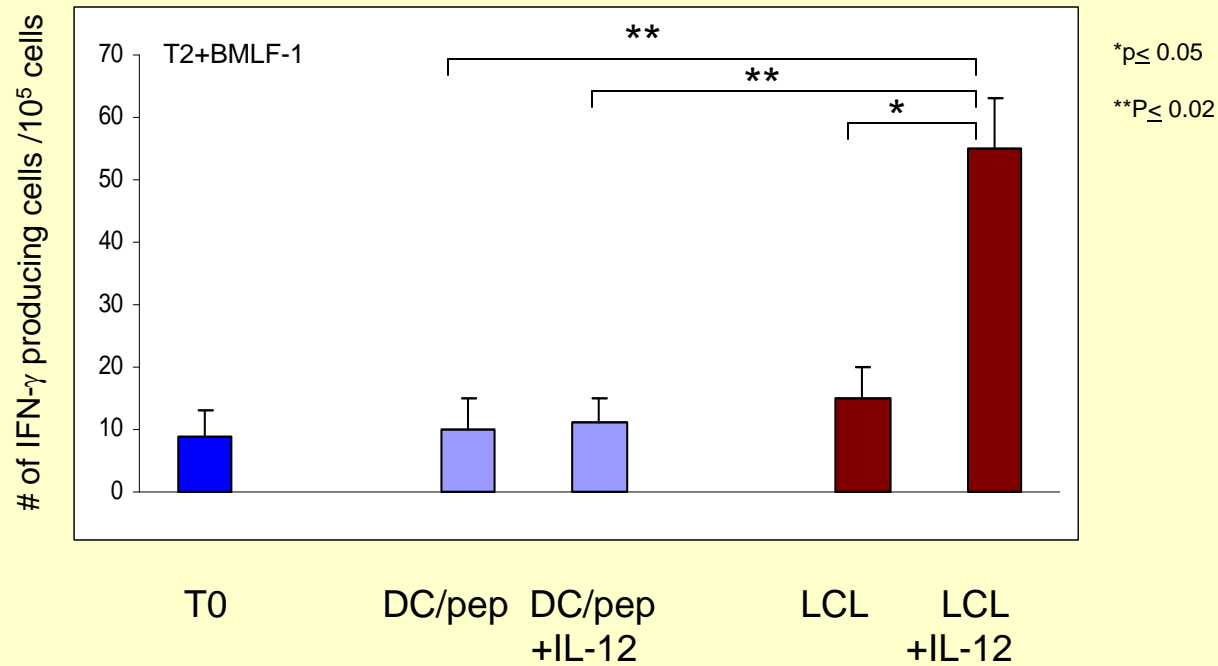
EBV-specific CTL yield after *in vitro* stimulation



Phenotype of *in vitro* generated CTLs



LCL can prime naïve CD8+ T cells into Type-1 EBV-specific CD8+ T cells only in the presence of exogenous IL-12p70



Cytokines that regulate Type-1 responses

