CAN Treg PREVENT GVHD WITHOUT LOSING GVL?

NO
DO Tregs PREVENT GVHD AND PRESERVE GVL AFTER HLA-HAPLOIDENTICAL HCT?

Logistics enable donor Treg collection, but 30% of infusion is FoxP3-

TRM in 13/26 patients:
2 GVHD, 2 graft failures, 3 VOD, 8 infxns

With 50% TRM, how would we know?
Several studies confirm Treg permutation of GVHD with preservation of GVL effects

Most models of GVHD are CD4+-dependent, but GVL is largely CD8+-dependent

- GVL/GVHD separation often achieved in such models, rare translation to clinic

Not all leukemias are created equal

Treg preservation of GVL against A20 (leukemia cell-line), but loss of GVL against P815 (mastoma, lymphoma-like line)

Tumor burden, localization/sanctuary sites, growth rate, are all likely to be factors

GVHD PREVENTION: EXPERIMENTAL DATA

“Naturally occurring” Tregs infused with Tconv at 1:1 ratios [multiple donors needed]

Caveats:
- All experiments performed in young mice with intact thymi; amplification of Tregs potentially different in older hosts
- Only CD103+ Tregs improved chronic GVHD

GVHD PREVENTION: CLINICAL FEASIBILITY

Very large numbers needed: “Take a billion or so and call me in the morning”

“For most applications, Treg cells will require ex vivo expansion”

(FDA) considerations of expanded product: Sterility, Identity, Purity, Potency

Riley J et al, Immunity 2009
**EXPANDED Tregs: FEASIBILITY**

Sufficient Tregs from single donor very difficult

Three to six weeks needed for expansion

Unrelated donors rarely available in suitable timeframe

Inflammatory conditions early after HCT may impede Treg function

Delayed Treg infusion ineffective

Lewis et al, *PNAS* 2008
CD4+ CD25++ selection often used
CD25+ may contain many effector cells

100% FoxP3+ unlikely with current culture techniques

FoxP3+ lost with repetitive stimulation

EXPANDED Tregs: IDENTITY

Various Treg subsets: no unique surface markers

FoxP3+ population is heterogeneous

Most Treg expansion causes maturation: memory

Memory Tregs [CD45RA- FoxP3+] may revert to Tconvs

CD103+ Treg more effective in chronic GVHD

Komatsu et al, PNAS 2009
Zhao D et al, Blood 2008
EXPANDED Tregs: POTENCY

Poor understanding of regulation in vivo

Suppression of T-Cell proliferation
- Varies with assay:
  - Requirement for IL-2
  - Requirement for APCs

In vitro does not predict in vivo

EXPANDED Tregs: IMMUNOSUPPRESSION

Tregs require IL-2

Calcineurin inhibitors prevent IL-2 transcription
- Low dose IL-2 infusion may expand Tregs
- Usefulness of Tregs that need added IS very unclear

Lorn E et al, *BBMT* 2009
CAN Treg PREVENT GVHD WITHOUT LOSING GVL in 2011?

EXPERIMENTAL DATA: robust, encouraging

CLINICAL DATA:

Feasibility
Numbers: No
Timing: No
Purity: Maybe
Identity: Maybe
Potency: Unclear

CONCLUSION: NO