“Ocular Graft vs Host Disease: A dry eye condition that we know when it starts and we can prevent and better treat”

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Graft versus Host Disease
Ocular Manifestations:
Ocular Surface Dry Eye

Dry eye is the most frequent complication of GVHD (chronic), occurring in 40 to 76% of patients.

Approximately half the patients who undergo SCT develop dry eye 6 months later.

Severe dry eye resembling Sjögren syndrome progresses rapidly after the onset of symptoms in the majority of these patients.

The median time from transplantation to diagnosis of dry eye was 171 ± 59 days.

T Cell Replete Allogeneic HSCT

Donor T Cells

Donor Stem & Progenitor Cells

Peripheral Immune Dysregulation

Alloreactive (GVHD) T cells

Thymic Compartment Defective Selection

Auto-rx T

Target Organs

Auto-rx T
Similar to autoimmune diseases

- Primary biliary cirrhosis
- Sjogren's syndrome
- Lung-transplant-related bronchiolitis obliterans
- Systemic lupus erythematosus
- Lichen planus
- Scleroderma
- Fasciitis
- Primary biliary cirrhosis
Ocular Graft-versus-Host Disease

IS A DISEASE WHEN WE KNOW WHEN DRY EYE IS GOING TO START: AT TIME OF TRANPLANTATION.

WE CAN PREVENT IT AND USE IT TO UNDERSTAND Ocular Surface Inflammation
Why we need to know about Ocular Graft-versus-Host Disease?

• **Reason:**
Most common long-term complication of allogeneic hematopoietic cell infusion.

Eye manifestations can help guide systemic treatment. 60% of HSCT recipients will develop “ocular surface disease: dry eye and MGD”.

Eye manifestations significantly affect quality of life.
Murine Model of Ocular GVHD

- Major (MHC)-matched, minor antigen-mismatched induction of GVHD
- Clinically relevant

**Donor mouse strains:**
- C57BL/6 H2b

**Control group:**
- 5x10^6 donor TCD-BM

**GVHD group:**
- 5x10^6 donor TCD-BM
- 2.3 x10^6 CD4+/CD8+ T cells

10.5 Gy single dose
TBI conditioning 2 hr before BMT

Recipient mouse strain:
- C3H.SW H2b

* weekly evaluation

**In Vivo Ocular Surface Assessment post HSCT**

- **Tear Fluid Production**
  - C57BL/6 to C3H.SW
  - TCD-BM
  - BM + T cells

- **Ocular Surface Staining**
  - Fluorescein Staining score
  - p<0.0001

Evaluation of Conjunctival Goblet Cells at 6 weeks Post-HSCT

B6 --> C3H.SW BMT
Conjunctival Goblet cells at 6 weeks

Number of Cells
Lacrimal Gland Histology/IHC at 6 Weeks Post HSCT

Graph showing the number of cells for CD11b, Ly6G, CD4, and CD8 for TCD-BM and BM + T cells.
Role of CD4 vs CD8 T Cells in Ocular GVHD

Clinical Scoring

**Eyelid**

- BM only
- BM+ T cells
- BM + CD4 only
- BM+ CD8 only

**Cornea**

- BM only
- BM+ T cells
- BM + CD4 only
- BM+ CD8 only

Role of Donor T Cells in Ocular GVHD
Corneal Sensation

![Graph showing corneal sensation threshold over time for different groups: BM only, BM + CD8, BM + CD4, BM + CD4/CD8. The graph indicates statistical significance at certain time points marked by asterisks.](image)
Cytokine/Chemokine Assessment by qPCR in Corneal RNA at 6 Weeks Post HSCT

**A**

- **CXCL10**
  - BM + T cells
  - BM

- **CXCR3**
  - BM + T cells
  - BM

**B**

- **IFNγ**
  - BM + T cells
  - BM

- **TNFα**
  - BM + T cells
  - BM

- **IL-6**
  - BM + T cells
  - BM
Ocular GVHD in CXCR3-/- Mice
Corneal Sensation and Staining

Esthesiometry (corneal sensation)

Corneal Staining

Corneal sensitivity threshold vs. Day post-HSCT

Corneal Fluorescein Stain Green Pixel Intensity (MFI)

- BM only
- BM + T<sup>WT</sup>
- BM + T<sup>CXCR3-/-</sup>
Infiltration of Macrophage in Ocular GVHD
T Cell Replete Allogeneic HSCT

Donor T Cells

Donor Stem & Progenitor Cells

Peripheral Immune Dysregulation

Alloreactive (GVHD) T cells

Thymic Compartment Defective Selection

• Skin
• Liver
• GI

Auto-rx T

Macrophages

Ocular GVHD
• Corneal Nerve Damage Mediated by T cells
• Dry Eye and Keratopathy