Personalized Therapeutics for the Treatment of Hematological Malignancies

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Creating a 3D microfluidic platform to preserve the bone marrow tumor niche in multiple myeloma
Multiple Myeloma (MM)

- Uncontrollable clonal proliferation and accumulation of plasma cells in the bone marrow (BM)

- Incidence of 1 to 4 per 100,000 people per year (globally) - Marc Raab & Ken Anderson, Lancet, 2009

- Second most common hematological malignancy in the U.S.

- No cure due to drug resistance and relapse

- No in vitro models with clinical relevance
Complexity of the Tumor Niche

- Feedback loop
- Increased OCL formation and activity
- Decreased OSB proliferation and activity

Multiple Myeloma Cells

- T cell
- Hematopoietic stem cells
- Tumor growth factor
- RANKL
- TNF-α
- MIP-1α
- IL-6
- IL-3
- Sclerostin
- DKK1

Osteoblasts

- Stromal Cells
- Osteoclasts
- RANKL

Bone Marrow

Endosteal Layer

Bone
Ex vivo expansion of primary MM cells has been hindered because of a lack of an in vitro system capable of recapitulating the BM/MM niche—Critical for personalized medicine

Microfluidic 3D bone tissue model for high-throughput evaluation of wound-healing and infection-preventing biomaterials

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Patient BM Biopsy

Patient-Specific Microfluidic 3D Tissue Model

CFSE labeling

BM Mononuclear Cells (BMMC)

Frozen Samples

21-Day Culture (1 mL serum/week)

4-Day Ossified Tissue Grown from OSB (hFOB 1.19)

Semi-permeable barrier

BMMC Cells Seeding (~2X10^4 cells/chamber)

Time-Lapsed Microscopy

Flow Cytometry Characterization Of OSB matrix
BMMC and MM Cell Division Occurs Mostly within 7 Days

A cell loses ½ CFSE intensity with each division

• BMMC and MM cells divided 1 to 5 Times.
• Day 21 expansion was not statistically different to that of day 7.

From a clinical perspective, the use of an “off-the-shelf” microfluidic tissue culture technology

- Maximizes sample use
- Facilitates the evaluation of new therapeutics for the treatment of MM
- In line with personalized treatment designs
- **BEST** expansion is within 7 days of cultures which is an advantage for clinical use.
Students & Collaborators

• Wenting Zhang, Stevens
• Dr. Woo Y. Lee, Stevens Institute of Technology
• David Siegel, MD., JTCC, HackensackUMC
• Prof. Peter Tolias, Stevens
Tailoring T cell Responses
In the allo-HCT setting
Allo-HCT to treat hematological malignancies
**Long-term goal:** Identification, separation and administration of tumor reactive T cells to allow for the beneficial GVT effects of the transplant with minimization of GVHD.

**Approach:** Use TCR Vβ CDR3-size spectratyping to identify populations of alloreactive and tumor-reactive T cells in murine models of allo-HCT.

**Results:** Allogeneic transplants using tumor-reactive, but not overtly alloreactive, Vβ families demonstrated significant GVT effects with concomitant amelioration of GVHD.

Fanning SL, Zilberberg J, Stein J, Vazzana K, Berger SA, Korngold R, Friedman TM.
In Vitro Culture System to Predict GVL and GVHD Clinical Responses

Donor anti-tumor

Donor anti-host

Patient Post-transplant

CDR3-size Spectratyping

TCR sequencing (ImmunoSEQ analysis) to identify TCR clones


ImmunoSEQ Analysis of GVT CD8 vs. GVH CD8 TCR Clones
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