Variable	Change from enrollment to visit with progressive impairment (N=237)					Change from enrollment to last visit without impairment (N=130)					p-value
	N	Median	Mean	Min	Max	N	Median	Mean	Min	Max	
MD 0-3*	233	0	-0.15	-3	2	128	0	-0.59	-3	1	<0.001
MD 0-10**	232	-1	-0.64	-8	6	128	-2	-1.98	-8	2	<0.001
PT 0-3*	179	0	-0.01	-2	2	59	-1	-0.58	-2	1	<0.001
PT 0-10**	176	0	-0.37	-7	6	63	-2	-1.62	-6	3	<0.001
FACT-BMT	180	-0.92	0	-44.67	54.67	60	13	15	-24.33	45.94	<0.001
Lee symptom summary	190	-0.27	-0.46	-45.22	33.57	63	-6.05	-7.59	-38.81	10.85	<0.001

FACT-BMT = functional assessment of cancer therapy, bone marrow transplant
*Clinician (MD) or Patient (PT)-rated overall chronic GVHD severity on a 0-3 scale (none, mild, moderate, severe)
**MD or PT-rated overall chronic GVHD severity on a 0-10 scale

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Cannabidiol for the Prevention of Graft-Versus-Host-Disease after Allogeneic Stem Cell Transplantation: Results of a Phase I/II Study

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Purpose: Graft-versus-host-disease (GVHD) affects more than 50% of transplanted patients and is a major obstacle to successful allogeneic stem cell transplantation (alloSCT). Cannabidiol (CBD), a non-psychotropic ingredient of Cannabis has been shown to exhibit potent anti-inflammatory properties in animal models of various autoimmune diseases like multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease and diabetes mellitus. We hypothesized that the addition of CBD to standard GVHD prophylaxis may decrease GVHD incidence and severity.

Patients and Methods: We conducted a prospective phase I/II study (NCT01385124). Patients were given oral CBD 300 mg/day from day -7 through day +30 plus standard GVHD immunoprophylaxis consisting of cyclosporine and methotrexate.

Results: Forty-eight consecutive adult patients undergoing alloSCT were enrolled. Thirty-eight patients (79%) had acute leukemia or MDS and 13 patients (27%) had progressive disease. Thirty-five patients (73%) were given a myeloablative conditioning. The donor was either an HLA identical sibling (n=28), a 10/10 matched unrelated donor (n=16) or a 1-antigen mismatched unrelated donor (n=4). Median follow-up was 16 (range, 7-23) months. There were no grade 3-4 toxicities attributed to CBD. The cumulative incidences of grade 2-4 and grade 3-4 acute GVHD by day 100 were 12% and 5%, respectively. None of the patients developed acute GVHD while consuming CBD. Compared to 101 historical control subjects given standard GVHD prophylaxis, the hazard ratio of developing grade 2-4 acute GVHD among subjects treated with CBD plus standard GVHD prophylaxis was 0.3 (95% CI: 0.2-0.6; p=0.0002). The cumulative incidence of moderate-to-severe chronic GVHD at 1 year was 20%. Relapse rate, non-relapse mortality and overall survival at 1 year were 41%, 11.1% and 68%, respectively.

Conclusions: The combination of CBD with standard GVHD prophylaxis is a safe and promising strategy to reduce the

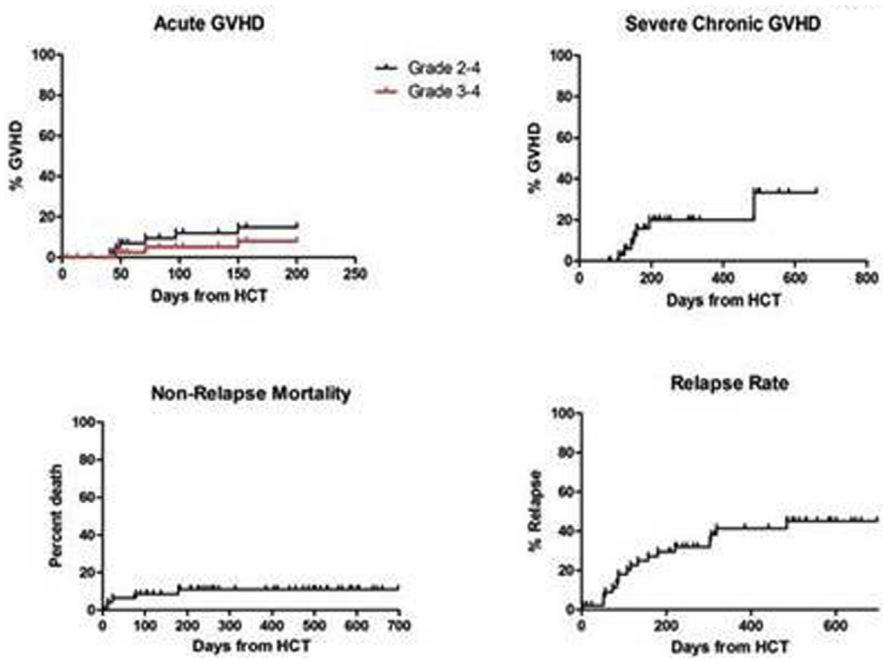

Figure 1.

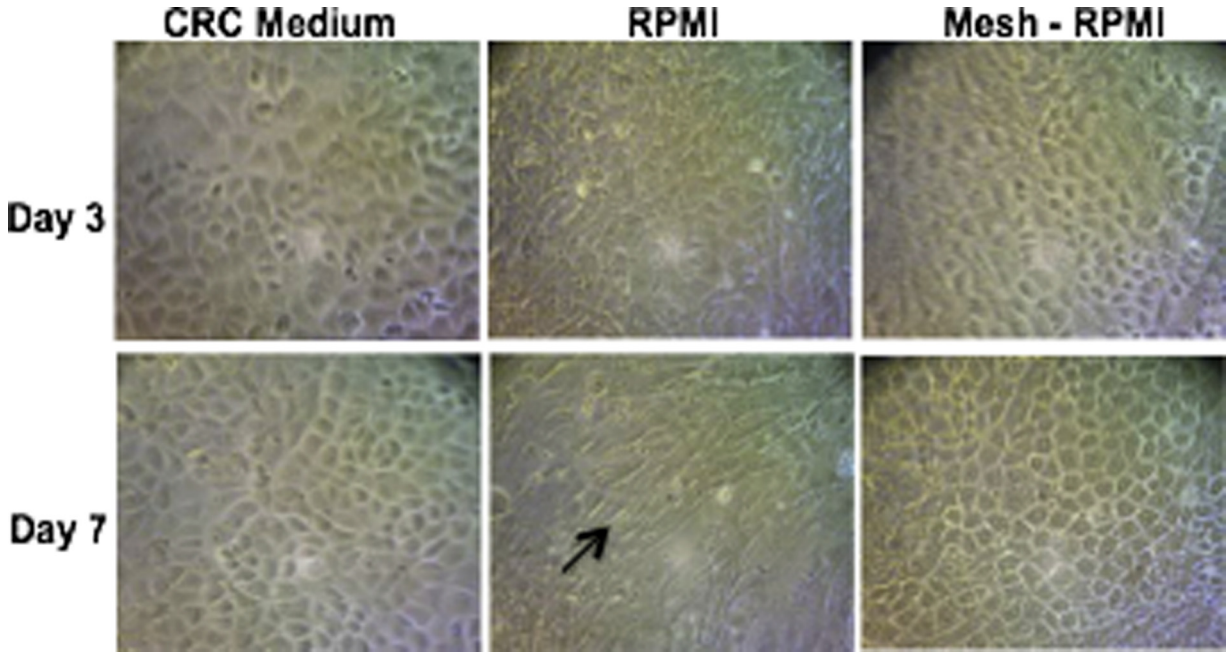

Figure 1. Morphology of m-CRIECs cultured in CRC medium, RPMI, and RPMI on nanofibrous mesh for 7 days to evaluate morphology and viability. Loss of cobble stone morphology (black arrow) was observed in cultures without nanofibrous mesh.

incidence of acute GVHD. A randomized double blind controlled study is warranted.

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Biomimetic Nanofibrous Mesh for Long-Term Preservation of Intestinal Epithelial Cells

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Gastrointestinal GVHD is a major complication of allogeneic blood and marrow transplantation. In vitro models for screening potential donor T cell reactivity to host intestinal epithelial cells (IEC) as a portent of GVHD have been hampered by difficulty in maintaining primary IEC cultures. To approach this problem, conditional reprogramming (CR) technology was combined with tissue-engineering scaffolds composed of biocompatible polycaprolactone (PCL)/collagen nanofibers to enable a long-term preservation of primary murine IECs. Conditioned medium (CM) used for CR contains the Rho-associated kinase inhibitor Y-27632, an anti-apoptotic agent that can render CRIEC unsuitable for cell damage assays indicative of GVHD. Thus, we sought to create an enabling biomimetic extracellular matrix (ECM) platform that could support viable and functional CR murine-IEC (m-CRIEC) in the absence of Y-27632.

Methods: Small intestine-derived IEC were plated on fibronectin-coated coverslips with CM+Y-27632. The m-CRIEC were removed from this media and seeded onto nanofibrous matrices in the presence of RPMI-1640 media. IEC normally reside on the thin fibrous basement membrane (BaMe) consisting of intermingled networks of laminins and type IV collagen, which provides cell anchoring and barrier functions. The BaMe interacts with cells through integrin receptors and other plasma membrane molecules, influencing cell phenotype and survival. Using electrospinning, BaMe-like fibrous meshes were prepared. Slow degradable PCL was used as the fiber matrix phase in which Type I collagen (representing ECM molecules) was dispersed.

Results: Flow cytometric analysis and microscopic inspection of m-CRIEC growing $\leq$ 7 days under CM+Y-27632-depleted conditions presented with comparable viability and phenotypic display to that of m-CRIEC growing in CM+Y-27632; however only cells placed on nanofibers maintained cobblestone morphology and integrity (Figure 1).

Conclusions: We have demonstrated that nanofibrous meshes can provide a physiologically relevant ECM-like microenvironment for the ex vivo maintenance of IEC. This biomimetic approach should prove particularly beneficial for the assessment of intestinal GVHD potential elicited by donor T cells.