Supplemental Appendix

Table of Contents

1.0 Supplemental Methods

1.1 Exclusion Criteria

Eleven patients were excluded due to lack of development of CRS and one for early death. Of the 53 patients remaining an additional five were excluded due to lack of laboratory measurements collected in these patients for the coagulopathy parameters of fibrinogen, ferritin, D-dimer and PTT. These five were among the earliest to be treated in the trial and had no manifestations of bleeding.

Patients 4, 15, 19, 41, 42, 44, 45, and 57 were excluded from D28 bone marrow evaluation as they did not have a complete response.

1.2 Toxicity Evaluations

1.2.1 Systematic Neurotoxicity Evaluations

Specific neurotoxicity symptoms were included and attributed to CAR therapy if they were new or worsening from baseline and occurred in patients with CRS and evidence of CAR T cell expansion. Symptoms were reconciled with recently published ICANS grading, and excluded generalized symptoms of fever, pain, headaches, anxiety, tremor, dizziness, and dysgeusia to keep consistent with ICANS symptoms, however hallucinations and intracranial hemorrhage were included as neurotoxicity symptoms.

1.3 Correlative Studies

1.3.1 Ang-1 and Ang-2 Analysis

Just prior to assay, all plasma samples were spun on microfuge (max. speed, 1 min). The sensitivity limits (sample dilution-adjusted) were 313 and 469 pg/mL, for Plasma Ang-1 and -2. VEGF-A was performed using U-PLEX MSD assay (cat. no. K151UVK-2; Meso Scale Diagnostics, Rockville, MD) with dilution-adjusted sensitivity limit of 0.5 pg/mL. All three measured analytes were performed in duplicate and evaluated simultaneously to avoid intra- and inter-assay variations. Samples were analyzed upon QC technical controls passing requirements in each experimental set.

1.3.2 Platelet Granularity

Peripheral blood films spread on glass slides were examined by manual examination under the optical microscope. Peripheral smears were prepared from fresh whole blood samples obtained by venipuncture in K2 EDTA lavender top vacutainers, kept for less than 8 hours at room temperature from time of collection. The slides were stained with Wright-Giemsa using the Midas stainer or Protocol Wright-Giemsa on the Sysmex SP10 (Sysmex XN3000).

Slides were reviewed at the following time point: pre-treatment (Day -3); D0, D7, D14, D21. Estimation of platelet number and assessment of platelet morphology were done in the body of the film (avoiding edges) using 50X and 100X objectives under oil immersion. Platelets

were counted in 10 consecutive fields of the slide using a 100X oil immersion, in areas with no clumping. The average number of platelets per field was multiplied by 15,000 to get an estimate of platelet count/mm^3.

The presence of platelet granules was assessed semi-quantitatively after examining 12 peripheral blood films of normal patients and the presence of hypogranularity was defined as ≥ 10% of platelets per HPF. Twenty platelets were counted per each high-power field. A patient was considered to have worsening hypogranularity if the HPF had a hypogranular count ≥ (25)% and above (or a change from baseline).

The specimen was mixed on a rotator for at least 3 minutes, inverted manually at least 15 times or automatically mixed by the Sysmex SP10. Conventional wedge smears (push smears) were made by placing 1 drop of well-mixed blood about 3/4 " from the end of the slide.

The quality of the smear was evaluated for sufficient length (greater than half the length of the unfrosted portion of the slide), evenness, consistent staining of the smear and a smooth spread with a gradual transition from a thick to a thin area that terminated in a feathered edge without streaks, holes or tails. Stain quality was satisfactory if staining was consistent, imparting the characteristic cytoplasmic color differences and distinct nuclear chromatic patterns of the whole spectrum of blood cells. In well-stained smears and under normal conditions, platelets appear violet to purple.

1.3.3 CD22 Expression in the CNS

Single-cell RNA sequencing data for human developmental brain generated by the Kriegstein lab (10x droplet-based data) was downloaded from BICCN (https://knowledge.brain-map.org/data/E3TEC0QYTQLI9M78VF0/summary). Single-nucleus RNA-sequencing data for adult human brain that was sort-enriched for NeuN+ nuclei (SMART-seq data) was downloaded from the Allen Brain Map (https://portal.brain-map.org/atlases-and-data/rnaseq/human-multiple-cortical-areas-smart-seq). Bulk RNA-sequencing data of human brain was downloaded from the Allen Brainspan (http://www.brainspan.org/rnaseq/search/index.html). Full methods regarding the generation of each dataset can be found on the respective link.

Data was downloaded as processed counts for each cell and processed using Scanpy v1.6 with standard workflows. Briefly, cells were first filtered to remove low-quality cells, removing cells with fewer than 250 genes detected, fewer than 500 counts, and/or greater than 25%

mitochondrial reads. Counts were depth-normalized per-cell to 10,000 reads, then log transformed. The top 2000 highly variable genes were identified and used as input for downstream processing. Data was scaled, and PCA, the neighborhood graph, and UMAP was performed using default settings. Data was clustered using the Leiden algorithm. The indicated marker genes for each plot are shown, and the color of each cell indicates the log-transformed, depth-normalized counts per cell.

2.0 Supplemental Results

2.1 Subjects and Toxicity

2.1.1 Subject Characteristics and CAR response

Forty-three of 53 subjects had minimal residual disease negative complete remission across 3 different dose levels. Patient's received CAR T-cells at doses ranging from 0.3 x 10^6 to 3 x 10^6 transduced CAR-T cells/kg. Thirty (56.6%) patients received 0.3 x 10^6 transduced CAR T-cells/kg, 21 (39.6%) received 1 x 10^6 transduced CAR-T cells/kg and 2 (3.8%) received 3 x 10^6 transduced CAR-T cells/kg.

2.1.2 Laboratory Manifestations

There were no substantial differences in the observed baseline levels of proteins C (n=26), protein S (n=26), Factor VIII (n=23), antithrombin III (n=27), vWF antigen (n=26), and vWF activity (n=27) between the two groups.

When examining peak levels, no statistically significant differences were found for proteins C (n=23), protein S (n=23), or Factor VIII (n=21), antithrombin III (n=24), vWF antigen (n=24), and vWF activity (n=25) either.

2.1.3 TMA Patient Descriptions

Patient 27:

13-year-old male with relapsed/refractory ALL who received CD22 CAR T-cells on 6/9/2017. By day +32, he was noted to have hemolysis on lab evaluations as well as significant hypertension requiring multiple antihypertensive agents including a nicardipine drip. His sc5b9 peaked at greater than 2070 (normal <244 units). Eculizumab started on day +35 with dosing up

to every 4 days to achieve an eculizumab level >100. Hemolysis and hypertension improved with eculizumab therapy. He achieved a sustained sc5b9 <244 on day +81. He was slowly tapered off eculizumab and received his last dose on day +101. Symptoms of concurrent neurotoxicity included agitation, dizziness, paresthesia, and nystagmus.

Patient 51:

26-year-old male with high-risk, relapsed/refractory ALL who received CD22 CAR T-cells on 7/18/2018. By day +8 he was noted to have anemia with hyperbilirubinemia, thrombocytopenia and acute kidney injury (AKI). His AKI progressed to anuria necessitating continuous veno-venous hemofiltration (CVVH) by day +10. He was subsequently transitioned to hemodialysis on day +14. His sc5b9 peaked >1770 and he started eculizumab on day +16. His renal function continued to improve and his sc5b9 decreased. He required only 3 doses of eculizumab with the last dose on day +23. Symptoms of concurrent neurotoxicity included nystagmus and hallucinations.

Patient 63:

4-year-old male with relapsed/refractory ALL who received CD22 CAR T-cells on 4/3/2019. By day +17 he was noted to have increasing thrombocytopenia with rare schistocytes on peripheral blood smear and hypertension. His kidney function remained stable and transaminases were improving in the setting of treatment for hemophagocytic lymphohistiocytosis. He was noted to have an elevated sC5b9 level and eculizumab was started. Dosing frequency was based on maintenance of eculizumab level >100 with doses up to every 4 days. His sC5b9 improved after 3 doses and he continued treatment until approximately day +42. Symptoms of concurrent neurotoxicity included agitation, confusion, nystagmus and intracranial hemorrhage—which was believed to be due in part to concurrent B. cereus bacteremia and has been recently reported.[1]

2.1.3 Bone Marrow Evaluations

Of the 43 patients evaluable for bone marrow recovery, 40 had available laboratory data on CAR expansion at D28 bone marrow evaluation (patient 31, 50 and 63 not reported). Patient 31 also did not have a marrow that was adequate for evaluation and was excluded from analysis

of bone marrow cellularity and trilineage hematopoiesis. Absolute neutrophil counts were not reported for patients 16 and 63.

Patients were also stratified based on the presence or absence of HLH. Patient with HLH had higher CAR expansion (median, 62.0 vs. 35.5%, p=0.048) and lower absolute neutrophil counts (median, 200 vs. 960 cells/mcL, p=0.0032). Additionally, those with HLH had lower platelet counts after 28 days than those without HLH (median, 25 vs. 58 K/uL, p=0.031). Median day 28 bone marrow cellularity did not differ by the presence of HLH (median, 22.5 vs. 30.0, p=0.41).

28 (65%) patients had grade 3-4 neutropenia (ANC <1000 cells/mcL). 19 patients received GCSF within +/-7 days of their D28 bone marrow evaluation. Twenty-eight (65%) patients had grade 3-4 thrombocytopenia (platelet count <50,000/mm^3) or had received a platelet transfusion in the past seven days.

3.0 Supplemental Tables

Supplemental Table 1. HLH Definition

*Criteria used for identification of carHLH**	*Clinical or laboratory manifestations*
Major Criteria (Must have both)	Patient had CRS
	Ferritin ≥ 100,000*
Minor Criteria (Must have at least 2 criteria)	Hepatic transaminase levels ≥ grade 3 or bilirubin ≥ grade 3
	Pulmonary manifestations ≥ grade 3 (e.g., edema or hypoxia)
	Renal insufficiency ≥ grade 3
	Coagulopathy
	Evidence for hemophagocytosis on a bone marrow evaluation
Other laboratory or clinical manifestations that were monitored	Hypertriglyceridemia
	Cytopenias
*Specific to this specific CAR T-cell construct	

Supplemental Table 2. Coagulopathy Score

Coagulation Parameter	**Score (≥5=Coagulopathy)**
Bleeding	0=No bleeding 1= Bleeding
D-dimer	0=No increase (<0.5) 1=Slight increase (>0.5-5) 2= Moderate increase (>5-20) 3= Strong increase (>20)
Prothrombin Time	0= <3 seconds prolonged from ULN 1= 3 to 6 seconds prolonged from ULN 2= >6 seconds prolonged from ULN

Fibrinogen (nadir)	0= ≥100 mg/dL 1= <100 mg/dL
*modified from DIC score of Toh et al[4] in which the presence or absence of bleeding was substituted for thrombocytopenia, which was present in nearly all subjects and did not discriminate between those who bled or did not. **Abbreviation**: **ULN**, upper limit of normal	

Supplemental Table 3. Platelet Analysis Definitions

	Condition
Present	There must be ≥ 10% of platelets in a HPF for hypogranularity to be present
Baseline hypogranularity	Defined as ≥10% hypogranular cells
Worsening	Defined as hypogranular count ≥ 25% and above (or change from baseline)

Supplemental Table 4. Neurotoxicity Manifestations

Dose Level (DL)	**Subject**	**Agitation (grade)**	**Confusion (grade)**	**Dysphasia (grade)**	**Dizziness (grade)**	**Paresthesia (grade)**	**Nystagmus (grade)**	**Hallucination (grade)**	**ICH (grade)**
DL1	3	1							
	4		1	1					
DL2	9							1	
	15							2	
	18		1						
	19				1				
DL3	10							1	
DL2 TCS	27	1			1	1	2		
	31							1	
	33				1				
	42				1				
	45					1			

DL1 TCS	47	1						1	
	48	1	1		1				
	50	2							
	51						2	1	
	54		1						
	57	1							
	63	3	2				2		4
58 patients infused, 19 patients had 1 or more reported neuro symptom. Only those symptoms that were possibly or probably related to research/IND where captured; All patients who had neuro AE captured had CRS. Grading is per CTCAE V4.0 as defined in the protocol. T cell selected (TCS). Data is previously published in Shah NN, et al. (PMID: 32286905)									

Supplemental Table 5. Characteristics of Bleeding in Coagulopathy Cohort

ID	Year	Dose Level	CAR response	Max CRS	Day of CRS Start	HLH (Y/N)	Day of HLH Start	NTX (Y/N)	Bleeding Score (0-7)	Coagulopathy (Y/N)	Characteristic of Bleeding (CTCAE grade)	Day Bleeding Started	Atypical HUS (Y/N)
9	2015	$1x10^6$	MRD neg CR	2	7	N	N/A	Y	5	Y	No clinically relevant bleeding	N/A	N
16	2016	$1x10^6$	MRD pos CR	3	9	Y	22	N	7	Y	Epistaxis (1), bleeding from IV lines (1)	16	N
21	2016	$1x10^6$	MRD pos CR	2	7	Y	9	N	5	Y	Epistaxis (3), oozing at central line site (1)	8	N
27	2017	$1x10^6$ TCS	MRD neg CR	1	8	Y	12	Y	6	Y	Epistaxis (2), hematuria (1), gum bleeding (1), possible DAH (2)	16	Y
31	2017	$1x10^6$ TCS	MRD neg CR	2	7	Y	10	Y	5	Y	Bruising (1) and mild oral bleeding (1)	18	N
32	2017	$1x10^6$ TCS	MRD neg CR	3	4	Y	7	N	5	Y	Epistaxis (2), gum and lip bleeding (1), hematuria (1), subconjunctival hemorrhage (1)	10	N

33	2017	$1x10^6$ TCS	MRD neg CR	1	6	Y	10	N	5	Y	Epistaxis (2), PICC site bleeding (2)	12	N
35	2017	$1x10^6$	MRD pos CR	2	7	Y	18	N	6	Y	Epistaxis (1), hematuria (1), bone marrow site bleeding (1)	26	N
41	2017	$3x10^5$ TCS	SD	1	10	Y	16	N	5	Y	No clinically relevant bleeding	N/A	N
48	2018	$3x10^5$ TCS	MRD neg CR	4	6	N	N/A	Y	3	N	Epistaxis (1)	9	N
50	2018	$3x10^5$ TCS	MRD neg CR	2	7	Y	14	Y	3	N	bruising/petechia (1), hematuria (1)	12	N
51	2018	$3x10^5$ TCS	MRD neg CR	3	5	Y	9	Y	7	Y	Epistaxis (1), bleeding from dialysis catheter (1),	10	Y
54	2018	$3x10^5$ TCS	MRD neg CR	2	5	Y	26	Y	3	N	bruising from injections (1)	31	N
56	2018	$3x10^5$ TCS	MRD neg CR	2	7	Y	15	N	2	N	Epistaxis (1), bruising (1), mild gum bleeding (1)	5	N
57	2018	$3x10^5$ TCS	PD	2	8	Y	15	Y	2	N	Bruising (1), hematoma from injections (1)	15	N
63	2019	$3x10^5$ TCS	MRD neg CR	2	7	Y	10	Y	6	Y	Petechiae (1), ICH with concurrent B. 5cereus infection (4)	14	N
67	2019	$3x10^5$ TCS	MRD neg CR	2	5	Y	14	N	3	N	Epistaxis (1), blood-tinged emesis (1)	5	N
69	2019	$3x10^5$ TCS	MRD neg CR	2	11	N	N/A	Y	2	N	Conjunctival hemorrhage (1)	14	N

Abbreviations: **MRD neg CR**, minimal residual disease negative complete response; **MRD pos CR,** minimal residual disease positive complete response; **SD**, stable disease; **PD**, progressive disease. **TCS**, T-cell selection; **CRS**, cytokine release syndrome; **HLH**, hemophagocytic lymphohistiocytosis; **NTX**, neurotoxicity; **PT**, prothrombin time; **IV**, intravenous; **DAH**, diffuse alveolar hemorrhage; **PICC**, peripherally inserted central catheter; **HUS**, hemolytic uremic syndrome; **ICH**, intracranial hemorrhage.

Supplemental Table 6. Thromboelastography Parameters in Five Coagulopathic Patients

Subject	Time Point	R-Time (minutes)	Theta Angle (degrees)	Maximum Amplitude (mm)	EPL (%)	LY30 (%)
31	5/17/2017	12.5 (N)	27.7 (N)	26* (N)	0 (N)	0 (N)
		6.8 (K)	26.1* (K)	23.6* (K)	0 (K)	0 (K)

32	5/22/2017	6.9 (N)	27.6 (N)	33.7* (N)	0 (N)	0 (N)
		5.8 (K)	40.7* (K)	30.9* (K)	0 (K)	0 (K)
33	6/7/2017	12.8 (N)	18.9* (N)	24.9* (N)	0 (N)	0 (N)
		7.7 (K)	25.2* (K)	22.2* (K)	0 (K)	0 (K)
27B**	6/21/2017	7.4 (N)	40.3 (N)	32.2* (N)	0 (N)	0 (N)
		4.5 (K)	40.6* (K)	27.9* (K)	0 (K)	0 (K)
35	9/7/2017	21.2 (N)	28.0 (N)	40.2* (N)	0 (N)	0 (N)
		9.6 (K)	21.3* (K)	36.5* (K)	0 (K)	0 (K)

* = Abnormal
** = Second CAR T-cell treatment

Supplemental Table 7: Endothelial Activation Studies

Test	Median value at Baseline (range)		(p)	Median value at peak (range)		(p)	Relative change from baseline to peak (range)		(p)	Normal values
	No Coagulopathy	**Coagulopathy**		**No Coagulopathy**	**Coagulopathy**		**No Coagulopathy**	**Coagulopathy**		
Thrombo-modulin	3964 (2034-5095)	3193 (1798-5507)	0.28	4158 (2004-9985)	6411 (2712-13047)	0.15	1.133 (0.782-2.459)	1.508 (1.212-3.825)	**0.0076**	2385-5308 pg/mL
Tissue factor	212.5 (65-623)	230 (105-397)	0.91	212.5 (94-576)	351 (263-542)	**0.0035**	1.08 (0.15-4.00)	1.58 (1.06-2.62)	**0.033**	No range
Prothrombin F1+2	366.5 (190-1616)	424.0 (168-2106)	0.62	1247 (587-10625)	6648 (686-20131)	**0.033**	3.94 (0.36-20.32)	11.64 (2.73-52.98)	**0.047**	69-229 pmol/L
sE-selectin	31.6 (4.3-77.3)	13.1 (4.5-56.9)	0.12	35.8 (8.2-80.8)	33.3 (19.6-68.3)	0.68	1.30 (0.53-2.99)	2.63 (0.59-7.34)	0.12	13-51.3 ng/mL
sP-selectin	26.7 (5.1-49.0)	17.1 (8.4-35.2)	**0.047**	31.5 (19.9-53.4)	51.4 (23.7-101.0)	0.089	1.38 (0.56-4.86)	3.15 (1.02-6.92)	**0.018**	6-39 ng/mL
s-ICAM-1	338.5 (179-755)	446 (263-507)	0.66	696.5 (373-2520)	1338 (626-4222)	0.089	1.85 (1.23-14.08)	3.12 (1.57-9.47)	**0.028**	100-307 ng/mL
s-VCAM-1	1094 (554-2359)	1334 (515-3006)	0.25	2064 (1331-7779)	4833 (2701-5766)	**0.039**	2.52 (1.01-6.04)	3.73 (1.61-6.75)	0.28	341-897 ng/mL

Thrombomodulin (TM): An integral membrane protein expressed on the surface of endothelial cell that serves as a cofactor for thrombin. The thrombomodulin-thrombin complex caused inactivation of the coagulant activity of thrombin and activation of protein C, thereby causing an anticoagulation effect.[5] Plasma levels of thrombomodulin can be used as a molecular marker for endothelial cell injury.[6] Additionally, levels are found to decrease in the presence of inflammatory cytokines.[7]

Tissue Factor (TF): A transmembrane receptor for Factor VII/VIIa that plays a role in the clotting cascade. Upon endothelial damage TF is able to interact with Factor VII/VIIa and initiate the clotting cascade.[8]

F1+2: Prothrombin fragment 1+2 are part of the amino-terminus end of prothrombin and are cleaved when prothrombin is converted to thrombin by the prothrombinase complex.[9] Levels are found to be elevated in patients with thrombosis and is used as a marker to assess for patients who are in a hypercoagulable state.[10]

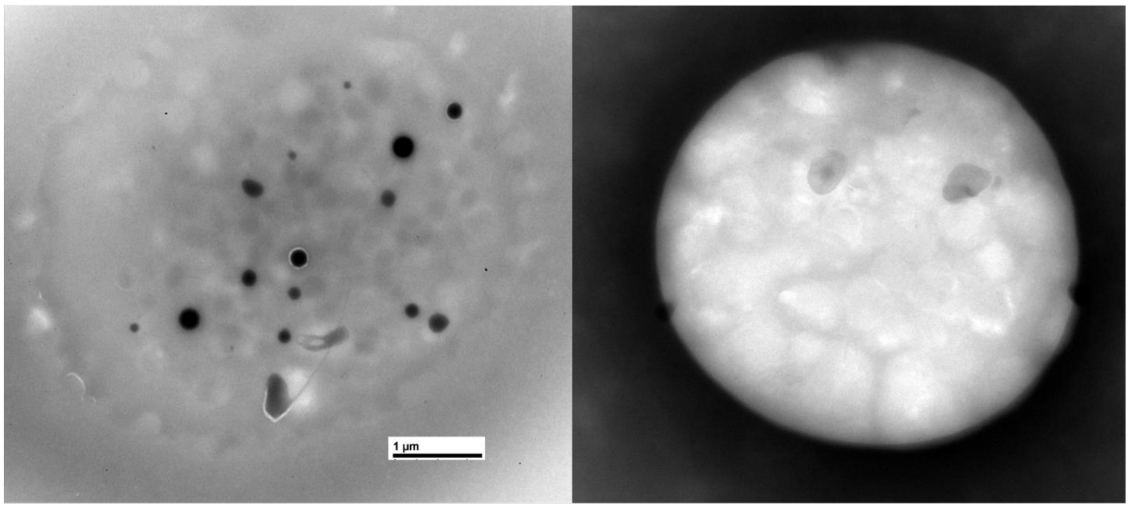
sE-selectin: Cell adhesion molecule expressed on endothelial cells. It is activated in states of inflammation by cytokines and aids in the recruitment of various cell types to sites of inflammation.

sP-selectin: Stored in Weibel-Palade bodies of endothelial cells and alpha-granules of platelets. It is released from these granules to the surface of endothelial cells in states of inflammation and plays a role in the recruitment of leukocytes to locations of injury and inflammation.

s-ICAM-1: An intercellular adhesion molecule that aids in the adhesion and transmigration of leukocytes across the endothelium to aid in the inflammatory response and is upregulated when endothelial cells are activated by cytokines.[11]

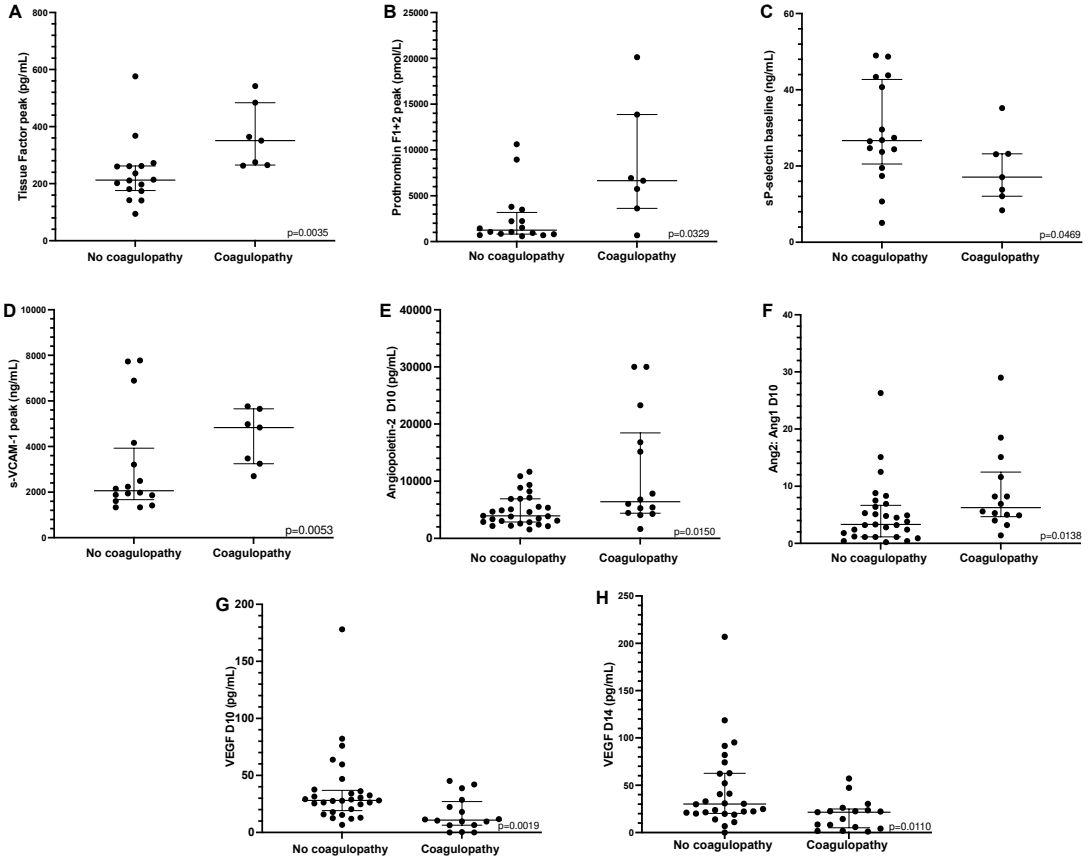
s-VCAM-1: Vascular cellular adhesion molecule that is expressed on blood vessels after stimulation by various cytokines. Their role is to aid the in leukocyte-endothelial cell adhesion and in signal transduction.

4.0 Supplemental Figures



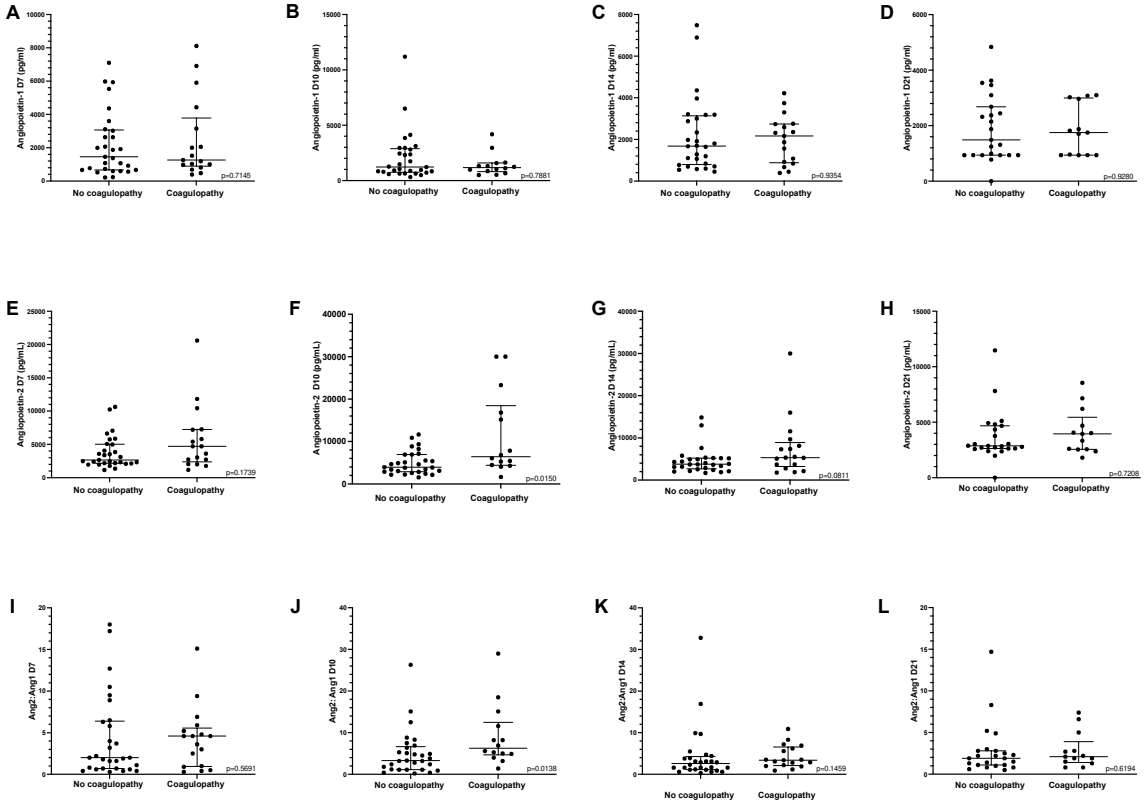
Supplemental Figure 1: Platelet Degranulation

Electron Microscopy of a normal platelet (left) and a degranulated platelet (right) from a patient with coagulopathy.



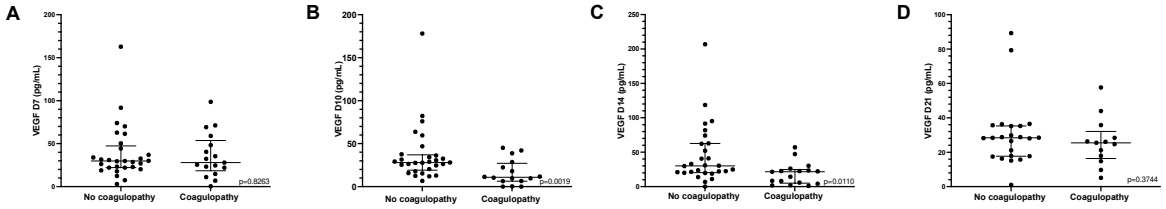
Supplemental Figure 2: Endothelial and Coagulation Markers in Patients Without and With Coagulopathy

Comparison between those without coagulopathy and those with coagulopathy. (A) Tissue factor peak; (B) prothrombin fragments, F1+F2, peak; (C) sP-selectin baseline; (D) s-VCAM-1 peak; (E) Angiopoietin-2 Day 10; (F) Ang2:ang1 Day 10; (G)VEGF Day 10; (H) VEGF Day 14.



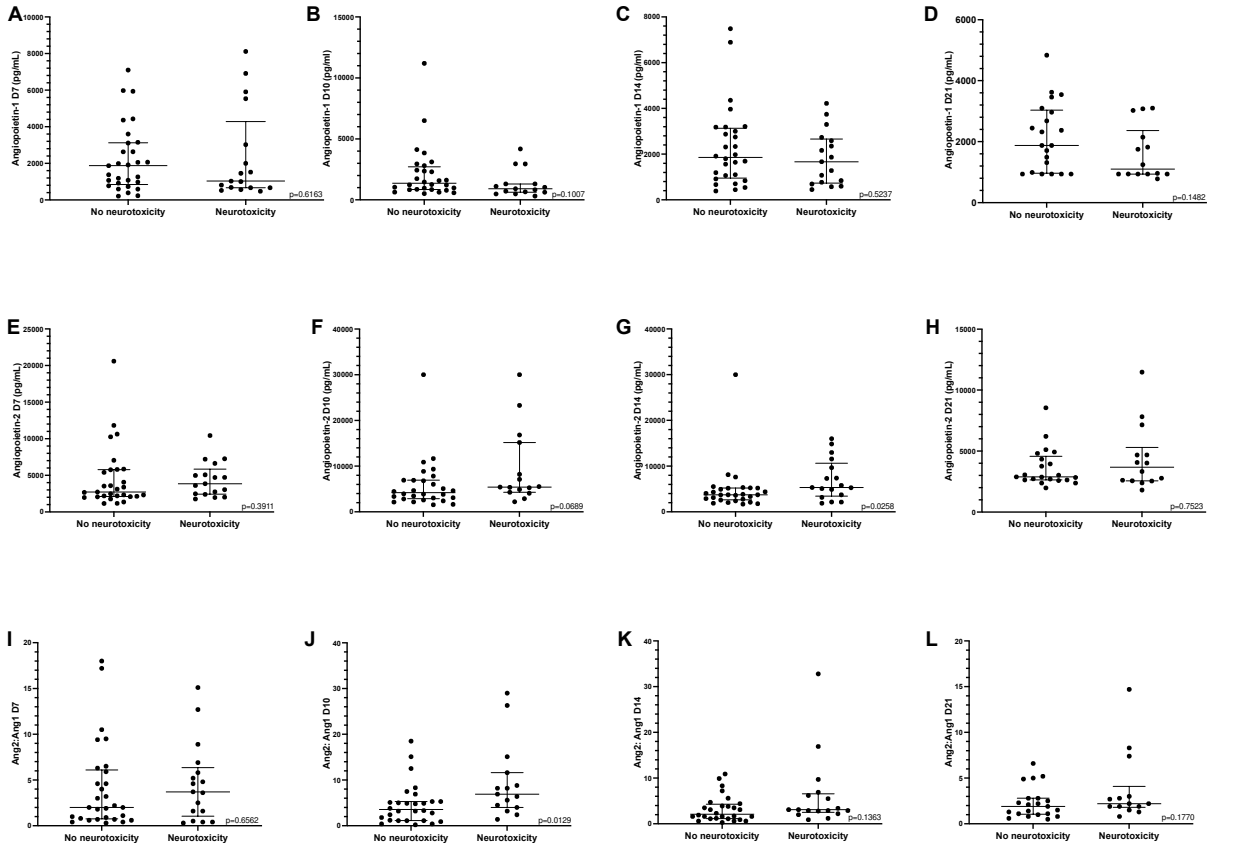
Supplemental Figure 3: Angiopoietin Levels in Patients Without and With Coagulopathy

Comparison of angiopoietin (Ang) levels between those without coagulopathy and those with coagulopathy on D7, 10, 14, and 21 post CAR T-cell infusion. (A) Ang1 day 7; (B) Ang1 day 10 (C) Ang1 day 14; (D) Ang1 day 21; (E) Ang2 day 7; (F) Ang2 day 10; (G) Ang2 day 14; (H) Ang2 day 21; (I) Ang2:Ang1 day 7; (J) Ang2:Ang1 day 10; (K) Ang2:Ang1 day 14; (L) Ang2:Ang1 day 21.



Supplemental Figure 4: VEGF Levels in Patients Without and With Coagulopathy

Comparison of vascular endothelial growth factor (VEGF) levels between those without coagulopathy and those with coagulopathy on D7, 10, 14, and 21 post CAR T-cell infusion. (A) VEGF day 7; (B) VEGF day 10 (C) VEGF day 14; (D) VEGF day 21.



Supplemental Figure 5: Angiopoietin Levels in Patients Without and With Neurotoxicity

Comparison of angiopoietin (Ang) levels between those without neurotoxicity and those with neurotoxicity on D7, 10, 14, and 21 post CAR T-cell infusion. A. Ang1 day 7; B. Ang1 day 10 C. Ang1 day 14; D: Ang1 day 21; E: Ang2 day 7; F: Ang2 day 10; G: Ang2 day 14; H: Ang2 day 21; I: Ang2:Ang1 day 7; J: Ang2:Ang1 day 10; K: Ang2:Ang1 day 14; L: Ang2:Ang1 day 21

References:

1. Masih KE, Ligon JA, Yates B, et al. Consequences of hemophagocytic lymphohistiocytosis-like cytokine release syndrome toxicities and concurrent bacteremia. *Pediatr Blood Cancer*. 2021;68(10):e29247.
2. Luft T, Benner A, Jodele S, et al. EASIX in patients with acute graft-versus-host disease: a retrospective cohort analysis. *Lancet Haematol*. 2017;4(9):e414-e423.
3. Luft T, Benner A, Terzer T, et al. EASIX and mortality after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2020;55(3):553-561.
4. Toh CH, Alhamdi Y, Abrams ST. Current Pathological and Laboratory Considerations in the Diagnosis of Disseminated Intravascular Coagulation. *Ann Lab Med*. 2016;36(6):505-512.
5. Esmon NL, Carroll RC, Esmon CT. Thrombomodulin blocks the ability of thrombin to activate platelets. *J Biol Chem*. 1983;258(20):12238-12242.
6. Boffa MC, Karmochkine M. Thrombomodulin: an overview and potential implications in vascular disorders. *Lupus*. 1998;7 Suppl 2:S120-125.
7. Conway EM, Rosenberg RD. Tumor necrosis factor suppresses transcription of the thrombomodulin gene in endothelial cells. *Molecular and Cellular Biology*. 1988;8(12):5588-5592.
8. Grover SP, Mackman N. Tissue Factor. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2018;38(4):709-725.
9. Aronson DL, Stevan L, Ball AP, Franza BR, Jr., Finlayson JS. Generation of the combined prothrombin activation peptide (F1-2) during the clotting of blood and plasma. *J Clin Invest*. 1977;60(6):1410-1418.
10. Ota S, Wada H, Abe Y, et al. Elevated Levels of Prothrombin Fragment 1 + 2 Indicate High Risk of Thrombosis. *Clinical and Applied Thrombosis/Hemostasis*. 2008;14(3):279-285.
11. Kjaergaard AG, Dige A, Nielsen JS, Tønnesen E, Krog J. The use of the soluble adhesion molecules sE-selectin, sICAM-1, sVCAM-1, sPECAM-1 and their ligands CD11a and CD49d as diagnostic and prognostic biomarkers in septic and critically ill non-septic ICU patients. *Apmis*. 2016;124(10):846-855.