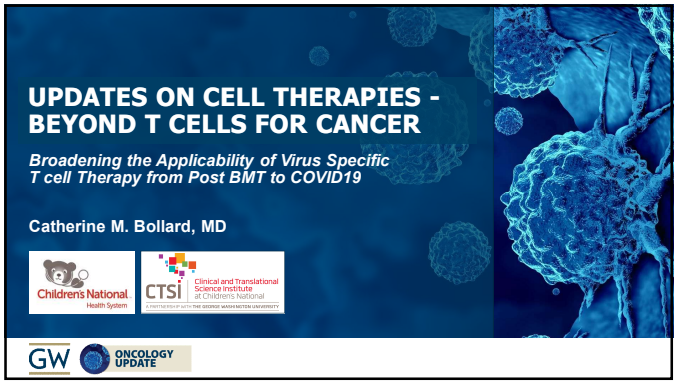


Disclosures

Catherine Bollard, MD, FRACP, FRCPA

- **Advisory Board:** Cellectis, BMS (ad hoc)
- **Co-Founder:** Mana Therapeutics, Catamaran Bio
- **Board Member:** Cabaletta Bio
- **Stock:** Repertoire Immune Medicines, Neximmune
- **DSMB:** SOBI

GW ONCOLOGY UPDATE 2

Limitations of Current Antiviral Therapy

Antiviral drugs not 100% effective

Antiviral drugs are not available for all viruses

Cost $$$

Side Effects ++ (Renal and Bone Marrow Toxicity)

GW ONCOLOGY UPDATE 3

Rationale for antiviral T cell therapy after BMT

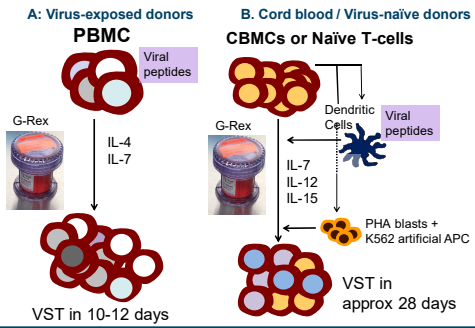
- T cell immunity is the guardian against reactivation
- Virus specific T cells frequency ↓ Viremia ↑
- Improved technology makes VST clinically feasibility

GW ONCOLOGY UPDATE 4

Hematopoietic Stem Cell Transplantation and Virus Infection

- High incidence of viral infections (not just single viruses EBV or CMV) post-transplant
- **Highest incidence when donor seronegative (i.e. cord blood)**

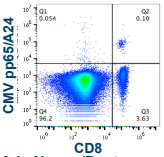
GW ONCOLOGY UPDATE 5

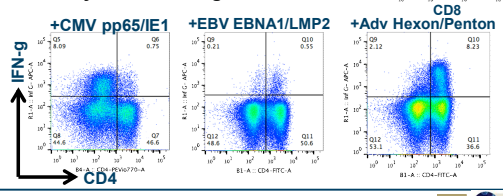


GW ONCOLOGY UPDATE

Measuring VST specificity- CMV/EBV/Adenovirus

- MHC Multimer staining
- Intracellular cytokine staining





GW ONCOLOGY UPDATE 7

Are Donor-derived Virus-specific T-cells safe?

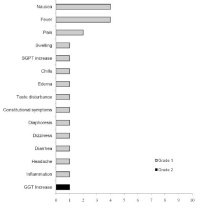
GW ONCOLOGY UPDATE 8

VSTs have Minimal Related Toxicity

- Cruz et al: 381 T-cell infusions in 180 patients reviewed
  - No 3-4 grade reactions
  - 24 minor events in 21 infusions
    - N/V, fever most common

Source	Donor/Recipient Matching	# of Patients	Acute GvHD
PB	Haplo	14	None
	MUD	6	1 Grade I
	MRD	10	1 Grade I
CB	CBT: 5/6	6	None
	CBT: 6/6	4	None

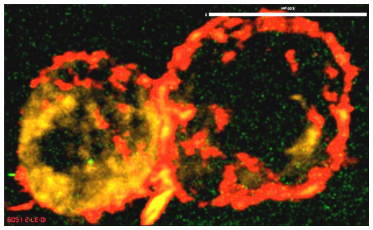
Adverse Reactions post-VST infusion



Melenhorst et al, *Blood* 2010
Cruz et al, *Cytotherapy* 2010.

GW ONCOLOGY UPDATE 9

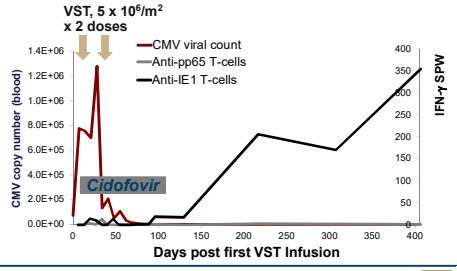
Are Virus-specific T cells efficacious?



GW ONCOLOGY UPDATE 10

PB-derived VST control CMV Infection

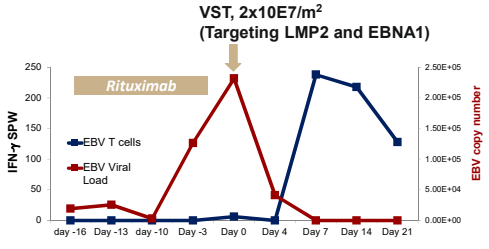
CNMC P1: Resolution of CMV after T-cell therapy in SCID patient



GW ONCOLOGY UPDATE 11

PB-derived VST restore EBV immunity

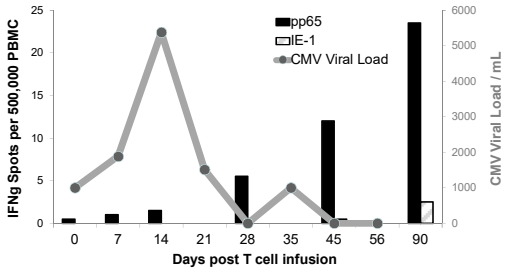
CNMC P8: EBV in a WAS patient 1 month post-MUD HSCT



Unpublished, Mike Keller

GW ONCOLOGY UPDATE 12

CB- VST restore immunity to CMV

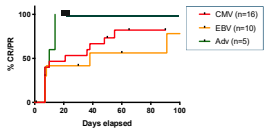


Abraham et al. *Blood Advances* 2019

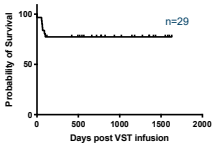
GW ONCOLOGY UPDATE 13

VSTs have Antiviral Activity In vivo

Antiviral Responses: CMV/EBV/Adv VSTs



Survival post Donor-Derived VST Infusion



- No high grade GVHD
  - 3/29 with grade I-II aGVHD
  - 4/29 with cGVHD
- OS at 12 months: 24/29 (83%)

GW ONCOLOGY UPDATE 14

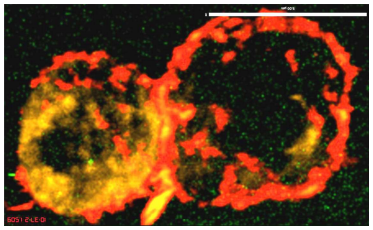
Overall Efficacy of Donor-derived VSTs

Prophylaxis: prevention	**>90%**
Treatment: Overall response	**81 - 94%**

Bollard and Heslop, *Blood* 2016,
Keller and Bollard, *Blood* 2020

GW ONCOLOGY UPDATE 15

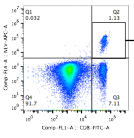
Do Virus-specific T cells persist?



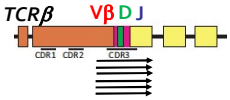
GW ONCOLOGY UPDATE 16

TCRb sequencing allows VST tracking

NLV: CMV pp65/A02

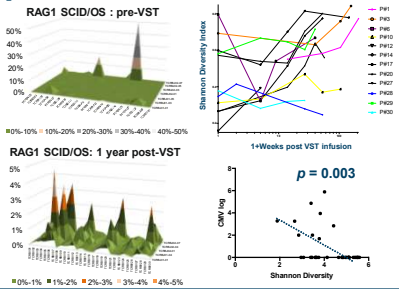


TCRβ sequencing of sorted cells



GW ONCOLOGY UPDATE 17

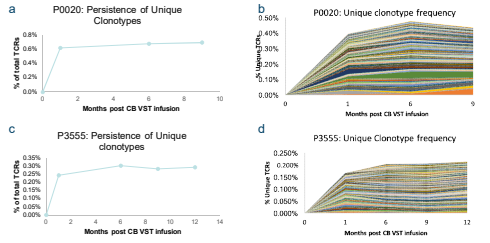
TCRb repertoire correlates with CMV control



Keller et al *BJH* 2019

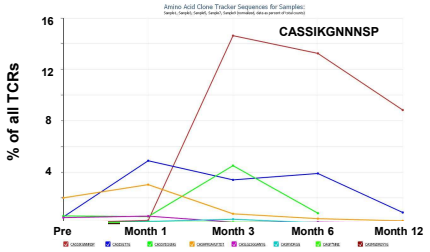
GW ONCOLOGY UPDATE 18

Infused CB-derived VST Clones Persist and Expand *in vivo*



Abraham et al, *Blood Advances* 2019

Infused CB-derived VST Clones Persist and Expand *in vivo*

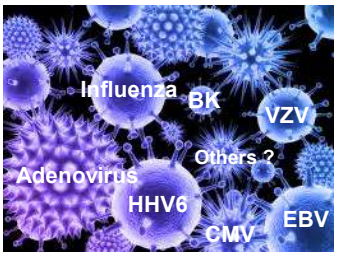


Hanley et al, *Science Translational Medicine* 2015

Summary: CB and PB Multivirus-specific T cells are Protective and Efficacious in vivo

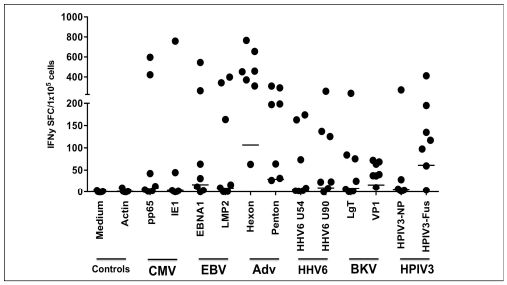
- We can now expand multi virus -specific T cells from TWO donor sources: cord blood and peripheral blood
- Safe to infuse to patients (minimal toxicity)
- Persistence of virus-specific T cells in presence of antigen
- Regardless of source of virus-specific T cells (naïve/memory), both populations appear protective

Targeting Multiple Viruses in a Single T cell Product – pepmix strategy



GW ONCOLOGY UPDATE 22

Expanding to 6 virus products- NATS

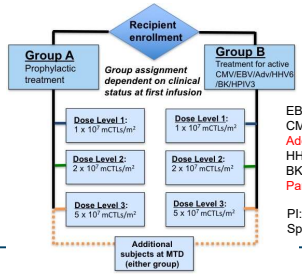


McLaughlin et al, *Cytotherapy* 2017

GW ONCOLOGY UPDATE 23

Can Target up to Six Viruses in Single Product

Novel Antigens Targeted by *ex vivo* Expanded T-Lymphocytes following Hematopoietic Stem Cell Transplantation (NATS)



EBV
CMV
Adenovirus
HHV6
BKV
Parainfluenza 3

PI: Mike Keller
Sponsor: Cath Bollard

GW ONCOLOGY UPDATE 24

Donor-derived Virus specific T cells are Safe and Effective and Persist in vivo

Prophylaxis: prevention	**>90%**
Treatment: Overall response	**81 - 94%**

Persistence of virus-specific T cells in presence of antigen for at least 12 months

(Keller et al, BJH 2019)

Incl. Cord Blood derived VSTs

(Hanley et al, STM 2013, Abraham et al, Blood Advances 2019)

Bollard and Heslop, Blood 2016, Keller and Bollard, Blood 2020

GW ONCOLOGY UPDATE 25

What if the donor not available?

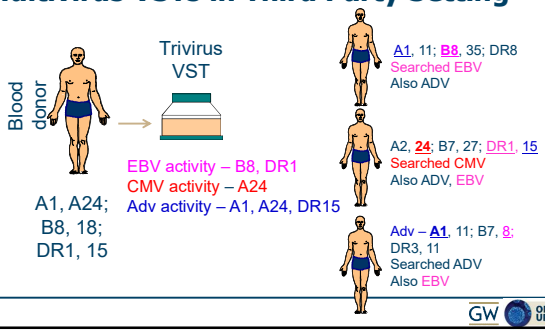
GW ONCOLOGY UPDATE 26

Third-party VST treatment

Utilizing a third party VST bank could bypass the need for an available donor, and eliminates the wait for T cell production.

GW ONCOLOGY UPDATE

Multivirus VSTs in Third Party Setting



Selection of Best EBV/LMP-specific T Cell Product for Infusion

Patient

A	B	C	DRB 1
24	40	03	11
01	39	07	04

Product 1

A	B	C	DRB 1
24	40	03	11
03	07	07	16

5/8 HLA Match

Product 2

A	B	C	DRB 1
24	40	03	04
26	39	07	14

6/8 HLA Match

Selection of Best EBV/LMP-specific T Cell Product for Infusion

Patient

A	B	C	DRB 1
24	40	03	11
01	39	07	04

Product 1

A	B	C	DRB 1
24	40	03	11
03	07	07	16

LMP Activity through 3/8 shared alleles

Product 2

A	B	C	DRB 1
24	40	03	04
26	39	07	14

LMP Activity through 1/8 shared alleles

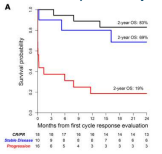
Prior Studies of Third-Party VST Support Safety

Study	Target	n	Serious adverse events	Clinical Results
Haque, 2007	EBV	33	None	• 52% CR/ PR
Barker, 2010; Doubrovina, 2012	EBV	5	None	• 4 / 5 CR's
Leen, 2013	CMV, EBV, Adv	50	8 cases GvHD (2 *de novo*)	• 74% CR/PR
Tzannou, 2017	CMV, EBV, Adv, BK, HHV6	38	2 cases of *de novo* GVHD (gr I)	• 92% CR/PR
Withers, 2017	CMV, EBV, Adv	30	2 cases of de novo GVHD	• 93% CR/PR
Prockop, JCI, 2020	EBV post SOT/BMT	46	None	68% CR/PR (BMT) 54% CR/PR (SOT)

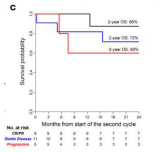
GW ONCOLOGY UPDATE 31

Large third party EST bank is safe and feasible (MSKCC Experience)

Survival based on response to 1st cycle



Survival based on response after all cycles

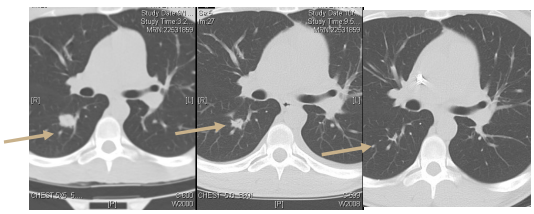


Cohort	N	First cycle CR + PR	Ultimate CR + PR
HSCT	33	45%	68%
SOT	13	23%	54%

Prockop et al, *JCI* 2020

GW ONCOLOGY UPDATE 32

CD20 Negative EBV-LPD Complicating Double UCB Transplantation for Aplastic Anemia – Response to Trivirus Third Party VSTs

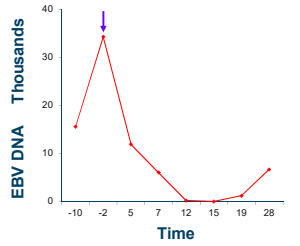


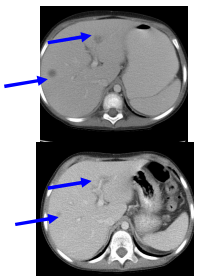
Sept 2008 Oct 2008 Jan 2009

Leen et al, *Blood* 2013

GW ONCOLOGY UPDATE 33

Clinical Response in Patient with EBV+ PTLD Post BMT



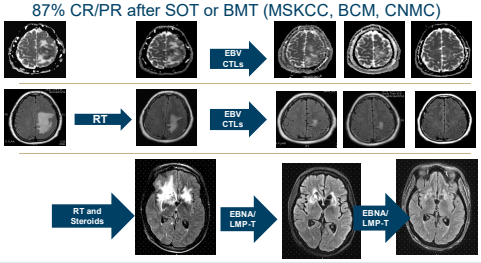


Leen et al, *Blood* 2013

GW ONCOLOGY UPDATE 34

CNS Disease Successfully Treated with 3rd party EBV-directed T cells

87% CR/PR after SOT or BMT (MSKCC, BCM, CNMC)

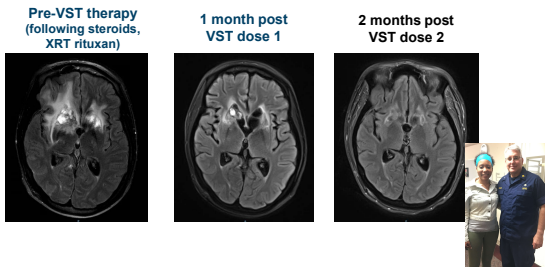


Prockop et al, *JCI* 2020
Bollard et al, *ASH* 2017 Keller et al, *ESID* 2017

Pakakasama S et al, *Transplantation*. 2004

GW ONCOLOGY UPDATE 35

Third party VSTs provide rescue therapy



Mike Keller, unpublished

GW ONCOLOGY UPDATE 36

ANHL1522: *A Pilot Study of Rituximab (RTX) and Third Party Latent Membrane Protein (LMP)-specific Cytotoxic T-Lymphocytes (LMP-TC, IND # 17068) in Pediatric Solid Organ Recipients (SOT) with EBV-Positive CD20-Positive Post-Transplant Lymphoproliferative Disease (PTLD)*

Study Co-Chairs: Birte Wistinghausen, MD
Catherine Bollard, MD

Version date: January 11, 2017

CHILDREN'S ONCOLOGY GROUP

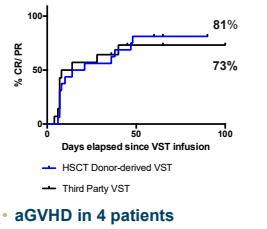
The world's childhood cancer experts

Developed from a LCTC consortium with Cairo/Bollard sponsored by St Baldricks

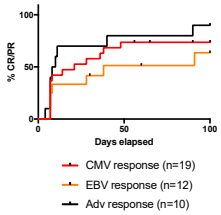
GW ONCOLOGY UPDATE

Overall efficacy of Third Party VSTs at CNH

Donor-derived versus Third party VST



VST responses by virus



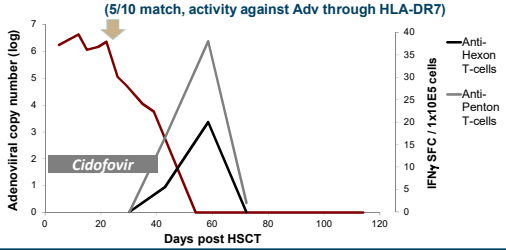
- aGVHD in 4 patients
  - Predominantly grade I-II and transient

GW ONCOLOGY UPDATE

Third party VSTs provide rescue therapy

- 4 year old IL-10R deficient patient, s/p MMRD HSCT

Third-party VST
(5/10 match, activity against Adv through HLA-DR7)



Mike Keller, unpublished

GW ONCOLOGY UPDATE

39

Extending Third-party VST therapy

- Antiviral Cellular Therapy for Enhancing T-cell Reconstitution Before or After Hematopoietic Stem Cell Transplantation (ACES)

Arm A

Viral infections following Stem Cell Transplantation

Arm B

Viral infections in PID patients *before* Transplantation

Banked, partially HLA matched VSTs

pediatric blood & marrow transplant consortium

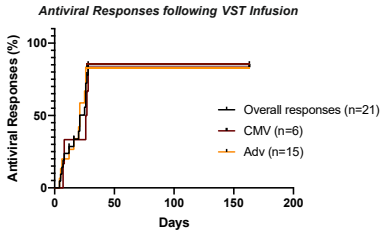
Primary Immune Deficiency Treatment Consortium

Children's Hospital LOS ANGELES

GW ONCOLOGY UPDATE 40

Antiviral Cellular Therapy for Enhancing T-cell Reconstitution Before or After HSCT (ACES), PBMTC SUP1701

- 21 evaluable patients
  - CMV: 5/6 responders
    - 2 NE
  - Adv: 11/15 responders



GW ONCOLOGY UPDATE 41

Conclusions - Third Party VSTs

- Low attributable toxicity
- Third party virus specific T cells (VSTs) effective in clearing viral disease
- T cell expansion seen in approx. 50% of responders
  Leen et al. *Blood 2013*/Naik et al, *JACI 2016*
- May require several infusions to sustain benefit – don't persist long term

GW ONCOLOGY UPDATE 42

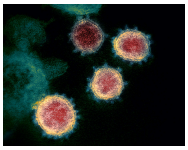
VSTs Can Target Multiple (? Any) Viruses/ Pathogens after BMT!

- **HIV** *(Ren et al, JCI 2020, Patel et al, Mol Ther Meth 2019,Patel et al, Mol Ther 2018, Patel et al BBMT 2016, Lam et al, Mol Ther 2015)* - *4 clinical trials*
- **EBV+ Lymphoma**
  (McLaughlin et al, Blood 2018, Bollard et al, JCO 2018)- 1 clinical trial
- **Pre-clinical targets**
  - **Norovirus** *(Hanajiri et al, JID 2019)- 1 clinical trial*
  - **Zika Virus** *(Hanajiri et al, Cytotherapy, 2019)*
  - **Mycobacteria** *(Patel et al, Frontiers Immunology, 2019)*
  - **Fungal** *(Castillo et al, Molecular Therapy - Methods & Clinical Development. 2018)*
  - **HPV** *(McCormack et al Cytotherapy 2018)*

McLaughlin et al, Cytotherapy 2017

GW ONCOLOGY UPDATE 43

Developing T cell therapies for SARS CoV-2



Mike Keller and Team COVID

GW ONCOLOGY UPDATE

The Journal of Clinical Investigation CLINICAL MEDICINE

Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation

Gunjan L. Shah,[1,2] Susan DeWolf,[1] Yeon Joo Lee,[3,4] Roni Tamari,[1,2] Parastoo B. Dahi,[1,2] Jessica A. Lavery,[4] Josel Ruiz,[1] Sean M. Devlin,[4] Christina Cho,[1,2] Jonathan U. Peled,[1,3] Ioannis Politikos,[1,2] Michael Scordo,[1,2] N. Esther Babady,[5] Tania Jain,[1] Santosha Vardhana,[3,6] Anthony Daniyan,[2,7] Craig S. Sauter,[1,2] Juliet N. Barker,[1,2] Sergio A. Giralt,[1,2] Cheryl Goss,[8] Peter Maslak,[9] Tobias M. Hohl,[2,5] Mini Kamboj,[2,5] Lakshmi Ramanathan,[8] Marcel R.M. van den Brink,[1,2] Esperanza Papadopoulos,[1,2] Genovefa Papanicolaou,[2,5] and Miguel-Angel Perales[1,2]

[1]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA. [2]Department of Medicine, Weill Cornell Medical College, New York, New York, USA. [3]Infectious Disease Service, Department of Medicine, [4]Department of Epidemiology and Biostatistics, [5]Clinical Microbiology Service, Department of Laboratory Medicine, [6]Lymphoma Service and [7]Leukemia Service, Department of Medicine, and [8]Stem Cell Service Medicine Service, [9]Cellular Immunology Laboratory, and [10]Clinical Chemistry Service, Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA.

Gunjan Shah

Susan DeWolf

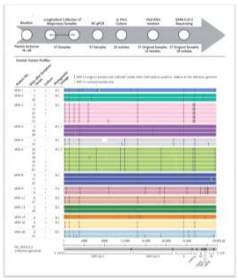
Miguel Perales

@DrMiguelPerales **Shah, DeWolf et al, *JCI* 2020**

GW ONCOLOGY UPDATE 45

Prolonged shedding of viable SARS Cov-2 can be seen post HCT

- >20 days in three patients
- Longest up to day 61
- Early post HCT/CAR-T (<6 mo)
- No evidence of reinfection
- Secondary cases not assessed



@DrMiguelPerales

Aydillo, ... Kamboj, *NEJM* 2020

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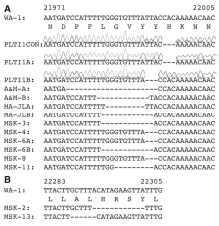
Deletions in SARS-CoV-2 spike arise during long-term persistent infections in immunosuppressed patients



@DrMiguelPerales

McCarthy KR et al, *bioRxiv* 2020.11.19.389916

GW ONCOLOGY UPDATE 47

Can SARS-CoV-2-specific T-cell Therapies be Developed to protect BMT patients?

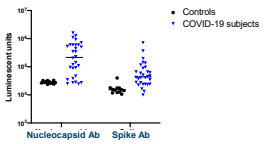
GW ONCOLOGY UPDATE 48

Developing a SARS-CoV-2 T cell Therapeutic from Convalescent Donors

Subject Demographics

Description	Value
Median age in years (range)	34.5 (20-69)
Male gender	21 (46%)
Disease Severity	
Mild	38 (83%)
Moderate	3 (7%)
Severe	1 (2%)
Asymptomatic	4 (9%)
Symptoms	
Fever	24 (52%)
Respiratory symptoms	38 (83%)
GI symptoms	9 (20%)
Fatigue	15 (33%)
Anosmia	20 (44%)
Median length of symptoms, days (range)	12 (0-30)
Need for Hospitalization	2 (4%)

SARS-CoV-2 Antibody Responses (n=46)



Collaboration with Jeff Cohen (NIAID LID), Peter Burbelo (NIDCR)
Keller et al, *Blood* 2020

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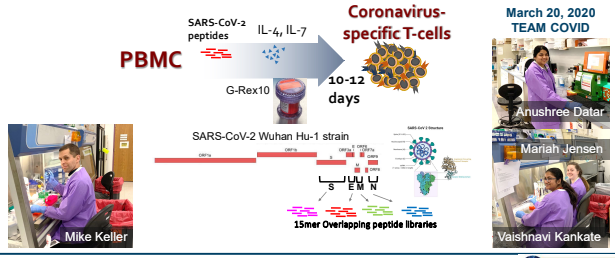
Generation of Coronavirus-Specific T-cells Using GMP Compliant Methodologies



March 20, 2020
TEAM COVID

Keller et al, *Blood*. 2020 Dec 17;136(25):2905-17

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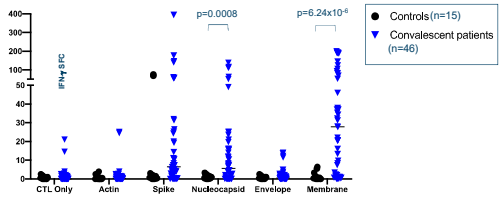
Convalescent Donors Recognize Multiple SARS-CoV-2 Structural Proteins

T-cell Specificity by ELISpot (day 10 post expansion)



Keller et al, *Blood*. 2020 Dec 17;136(25):2905-17

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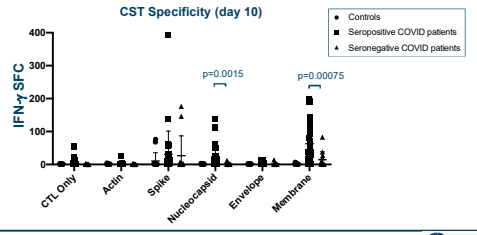
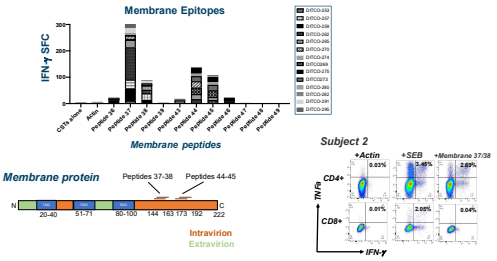
Seropositive Virus Exposed Donors Recognize a Broader Range of Viral Proteins Compared with Seronegative Exposed Donors



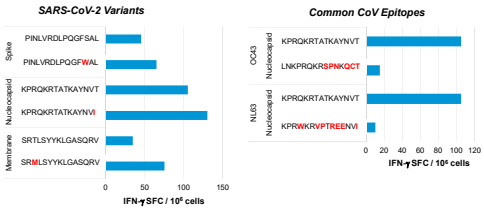
Keller et al, *Blood*. 2020 Dec 17;136(25):2905-17

Multiple Donors Recognize Epitopes Predominantly within a Conserved Region of Membrane Protein



Keller et al, *Blood*. 2020 Dec 17;136(25):2905-17

SARS-CoV-2 Epitopes Cross-React with Described Variants But not Seasonal CoV



Keller et al, *Blood*. 2020 Dec 17;136(25):2905-17

Can Vaccinated, SARS-Cov2 Unexposed Donors be used to Manufacture SARS-CoV2-specific T cells and are they Cross Reactive?

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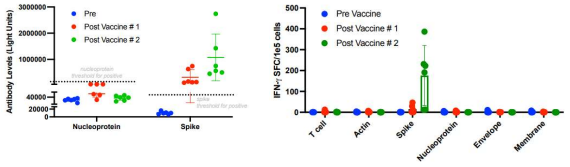
Vaccinated Donors Elicit Spike specific T cell responses in addition to Spike specific Ab Responses



Paper available as PrePrint in:
https://www.researchsquare.com/article/rs-403449/v1
Cruz et al, *Cytotherapy*, in press

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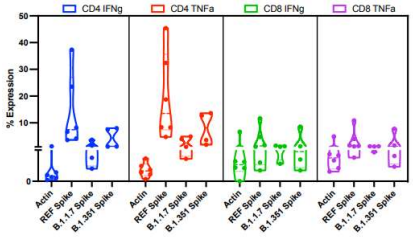
Vaccinated Donor-Derived T cells exhibit cross-reactivity against B.1.1.7 and B.1.351 variants



Paper available as PrePrint in: https://www.researchsquare.com/article/rs-403449/v1

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Moving SARS-CoV2 T cell Therapies to the Clinic

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New Clinical Trial

- "T-cell Therapy Opposing Novel Coronavirus Infection in Immunocompromised Patients (TONI)" IND 27588
- Post BMT Patients only (prophylaxis)
- Potential concerns treating patients with active infection?

GW ONCOLOGY UPDATE 59

Conclusions - VSTs

- Low attributable toxicity
- Donor-derived and Third party virus specific T cells (VSTs) effective in clearing viral disease (approx 80% efficacy)
- Can broaden applicability to multiple (?any) viruses

GW ONCOLOGY UPDATE 60

So…Why are VSTs Not More Widely Used?

Misconceptions regarding:

- Boutique therapy restricted to specialized centers and no randomized trials?
- No licensed product?
- Cost?

So…Why are CMV T cells/VSTs Not More Widely Used?

Misconceptions regarding:

- Boutique therapy restricted to specialized centers and no randomized trials? - Cooperative Group Protocols (COG ANHL1522, PBMTC ACES, BMT-CTN)
- No licensed product?- Orphan Drug Status and Pharma involvement- Atara, Allovir both have phase III trials
- Cost….?

Manufacturing Costs Of 6 Virus VST Production Including CMV VSTs

Cost Item	
GMP facility	$2,280
Trained technician	$1,000
VST manufacture	$3,076
Release testing	$1,651
TOTAL	$8,007

Standard Treatment Charges
Rituximab for EBV-PTLD $9,000-$11,000
Ganciclovir for CMV $15,000

Commercially viable
(Cellmedica, Atara, Allovir, Miltenyi)

Drugs versus VSTs → PRO VSTs!?

	Drugs	VSTs
Toxicity	Frequent	Low
Response Rates	Highly variable depending on virus	Response rates 90% in donor-specific setting
Prolonged Protection	No	Yes
1 agent for multiple viruses	Rarely	Yes
Economically Justifiable	Sometimes	Yes

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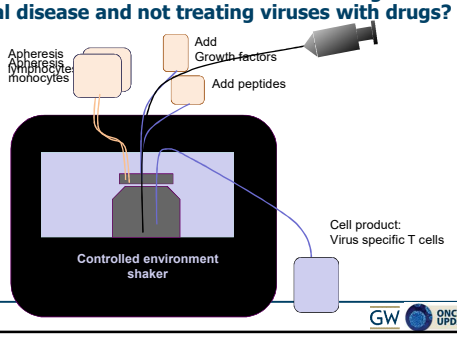
"GMP in a Box" Future for commercial VSTs? Using VSTs to prevent viral disease and not treating viruses with drugs?



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