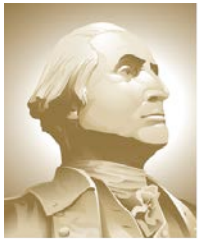
Broadening The Applicability of Virus specific T cell Therapy From Post BMT To COVID19

Catherine M. Bollard, MD



THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

Children's National Health System

CTSI Clinical and Translational Science Institute at Children's National
A PARTNERSHIP WITH THE GEORGE WASHINGTON UNIVERSITY

Disclosures

Catherine Bollard, M.D., FRACP, FRCPA.

Advisory Board: Cellectis, BMS (ad hoc)

Co-Founder: Mana Therapeutics, Catamaran Bio

Board Member: Cabaletta Bio

Stock: Repertoire Immune Medicines, Neximmune

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

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

Prophylaxis/ prevention — **>90%**

Treatment: Overall response — **81 - 94%**

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

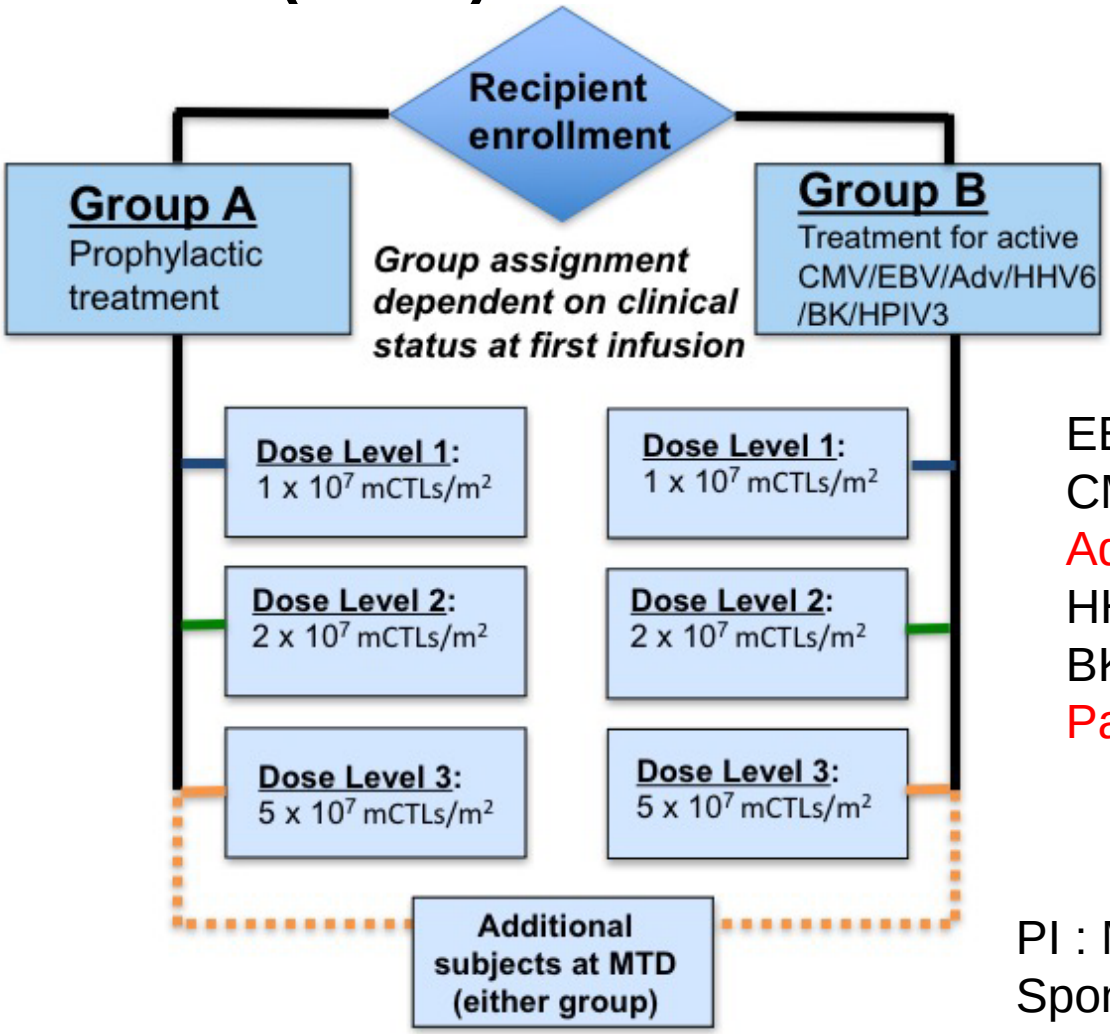
(Keller et al, BJH 2019)

Incl. Cord Blood derived VSTs

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

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

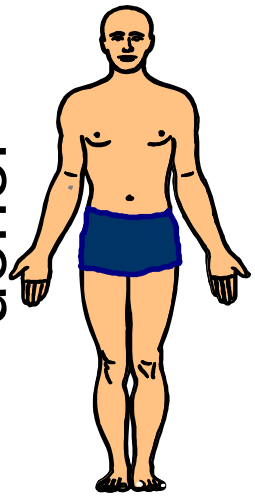
What if the donor not available?

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.

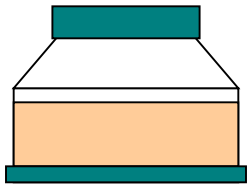
Multivirus VSTs in Third Party Setting

Blood donor

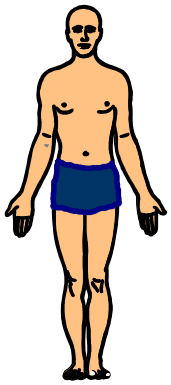


A1, A24;
B8, 18;
DR1, 15

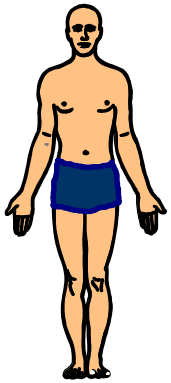
Trivirus VST



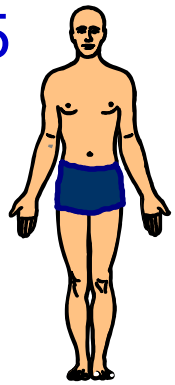
EBV activity – B8, DR1
CMV activity – A24
Adv activity – A1, A24, DR15



A1, 11; **B8**, 35; DR8
Searched EBV
Also ADV



A2, **24**; B7, 27; DR1, 15
Searched CMV
Also ADV, EBV



Adv – **A1**, 11; B7, 8; DR3, 11
Searched ADV
Also EBV

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)

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

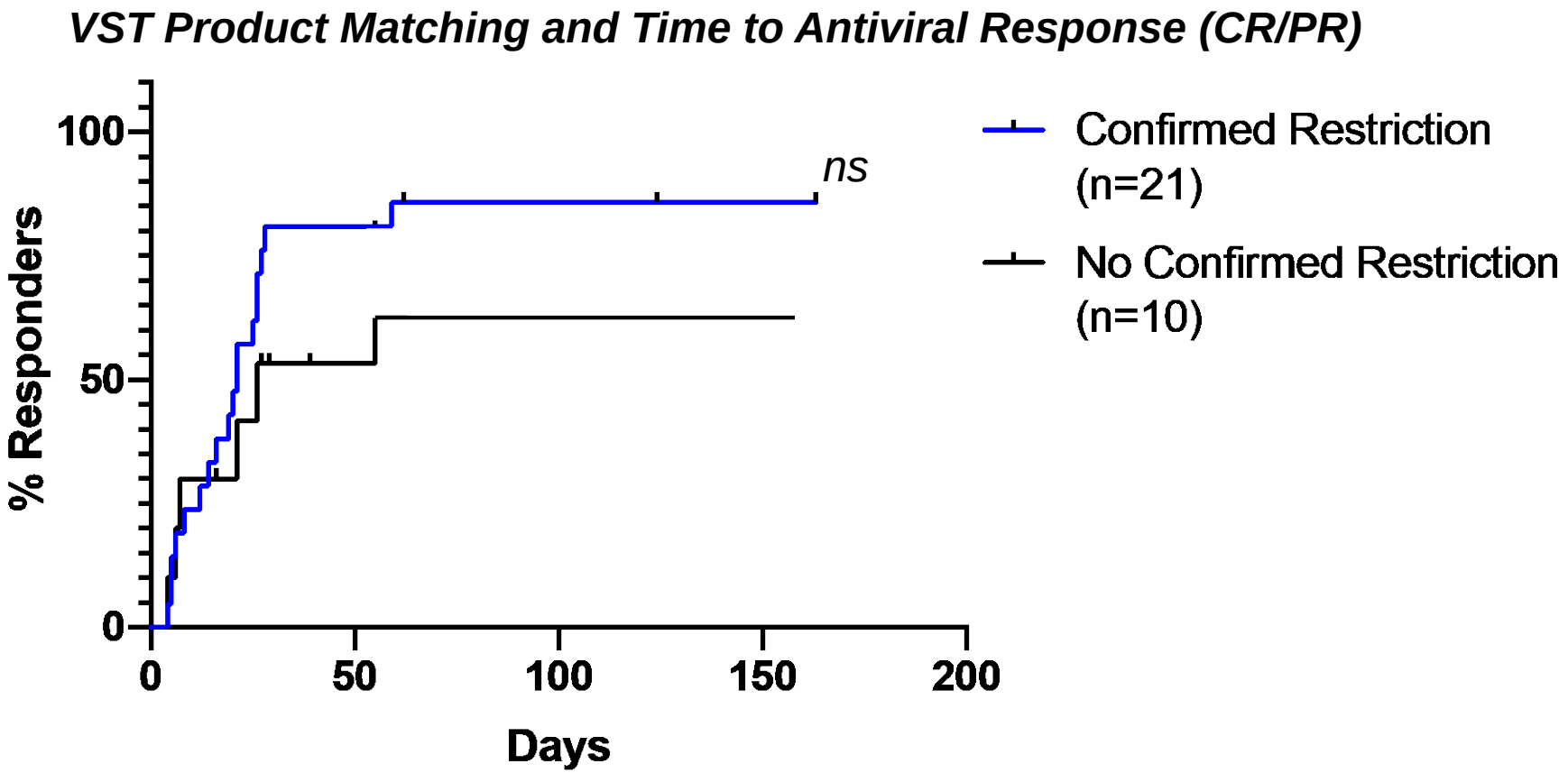
Banked, partially HLA matched VSTs

pediatric blood & marrow transplant consortium

Primary Immune Deficiency Treatment Consortium

Children's Hospital LOS ANGELES

Clinical Responses are More Likely with Confirmation of Shared Antiviral HLA Restriction



Conclusions - Third Party VSTs

- Low attributable toxicity
- Third party virus specific T cells (VSTs) effective in clearing viral disease (approx 75%)

  Leen et al. Blood 2013/Naik et al, JACI 2016
- T cell expansion seen in approx. 50% of responders
- May require several infusions to sustain benefit – don't persist long term
- Gene editing opportunities to give in setting of GVHD ***(Menger et al, Blood 2015)***

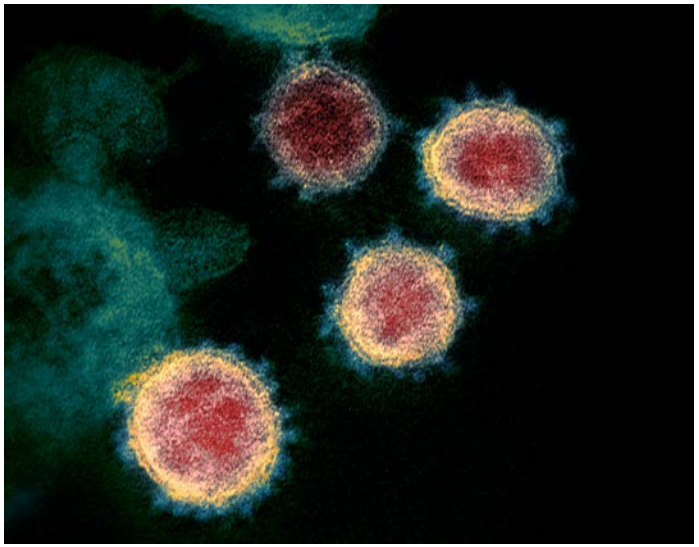
VSTs Can Target Multiple (? Any) Viruses/ Pathogens after BMT!

- **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)*

Developing T cell therapies for SARS CoV-2

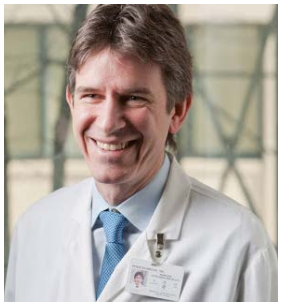


Mike Keller and
Team COVID

Gunjan Shah

Susan DeWolf

Miguel Perales



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,[2,3] 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,[1,2] Ioannis Politikos,[1,2] Michael Scordo,[1,2] N. Esther Babady,[5] Tania Jain,[1] Santosha Vardhana,[2,6] 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,[2,3] Mini Kamboj,[2,3] Lakshmi Ramanathan,[10] Marcel R.M. van den Brink,[1,2] Esperanza Papadopoulos,[1,2] Genovefa Papanicolaou,[2,3] and Miguel-Angel Perales[1,2]

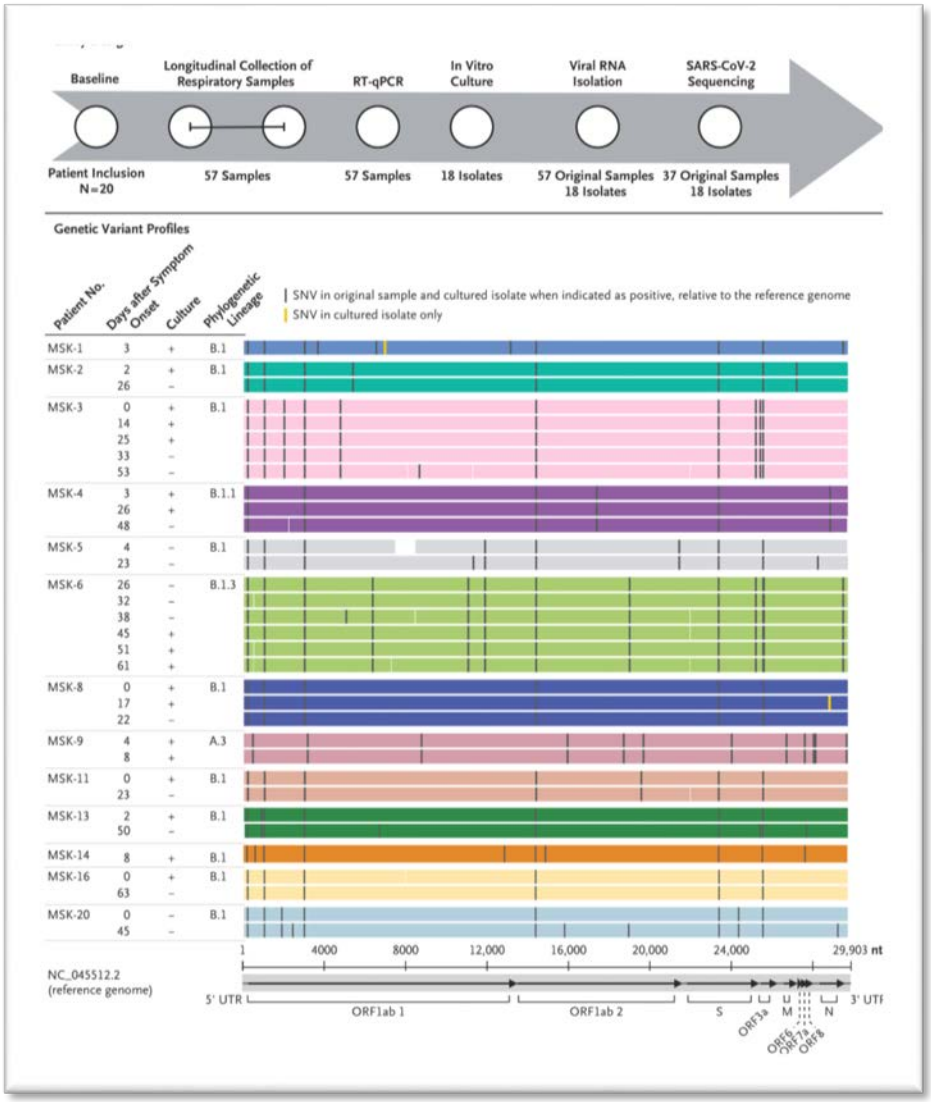
[1]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA. [2]Department of Medicine, Weill Cornell Medical College, New York, New York, USA. [3]Infectious Disease Service, Department of Medicine; [4]Department of Epidemiology and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

@DrMiguelPerales

Shah, DeWolf et al, JCI 2020

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



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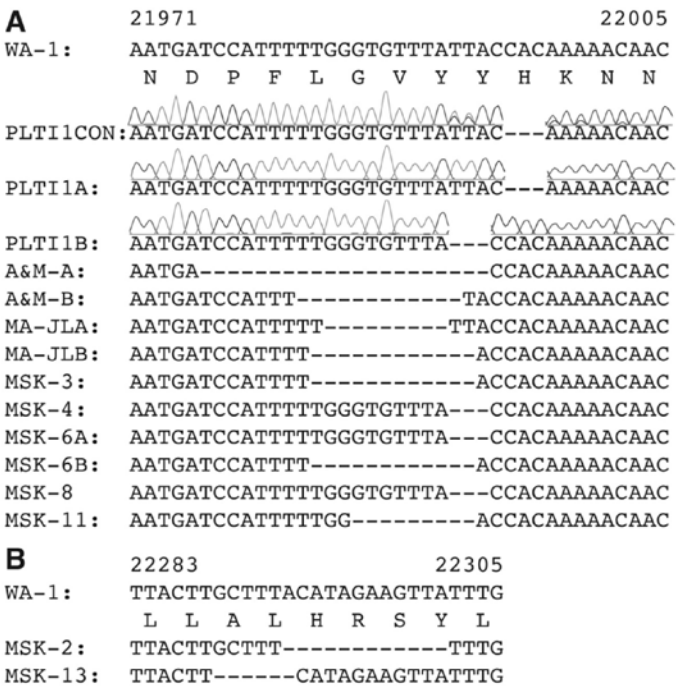
Aydillo, …. Kamboj, NEJM 2020

Icahn School of Medicine at Mount Sinai

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



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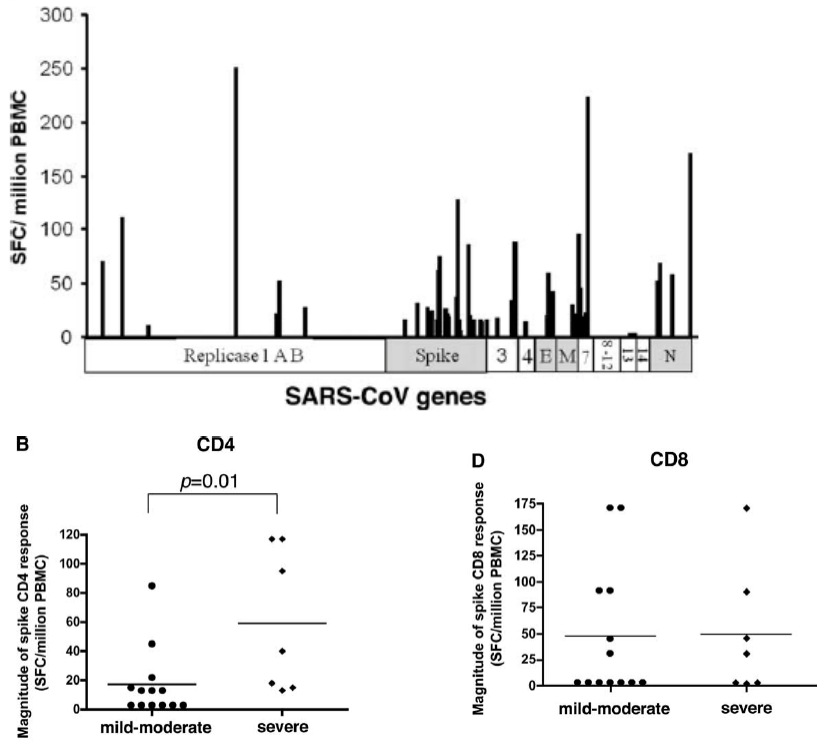
McCarthy KR et al, bioRxiv 2020.11.19.389916

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

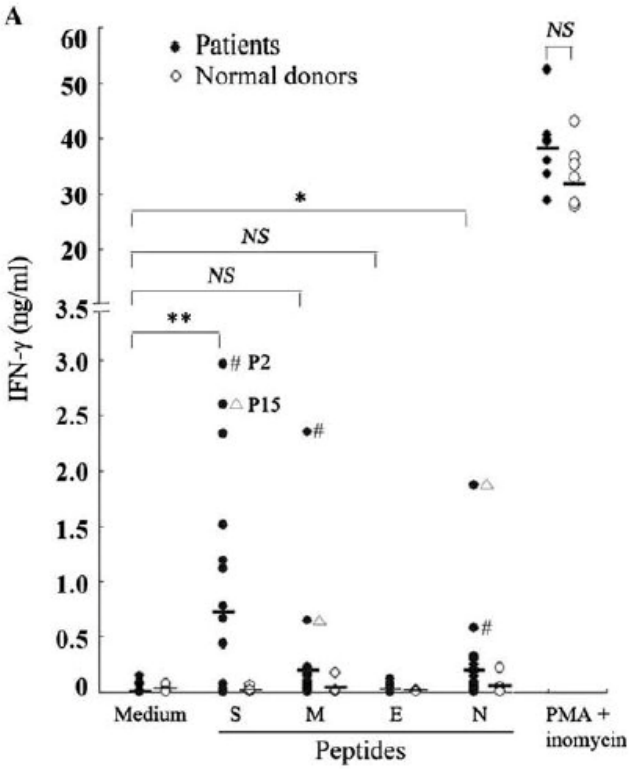
2003/2004: SARS-CoV Generated Lasting T-cell Responses

T-cell responses 1 year post SARS-CoV Infection



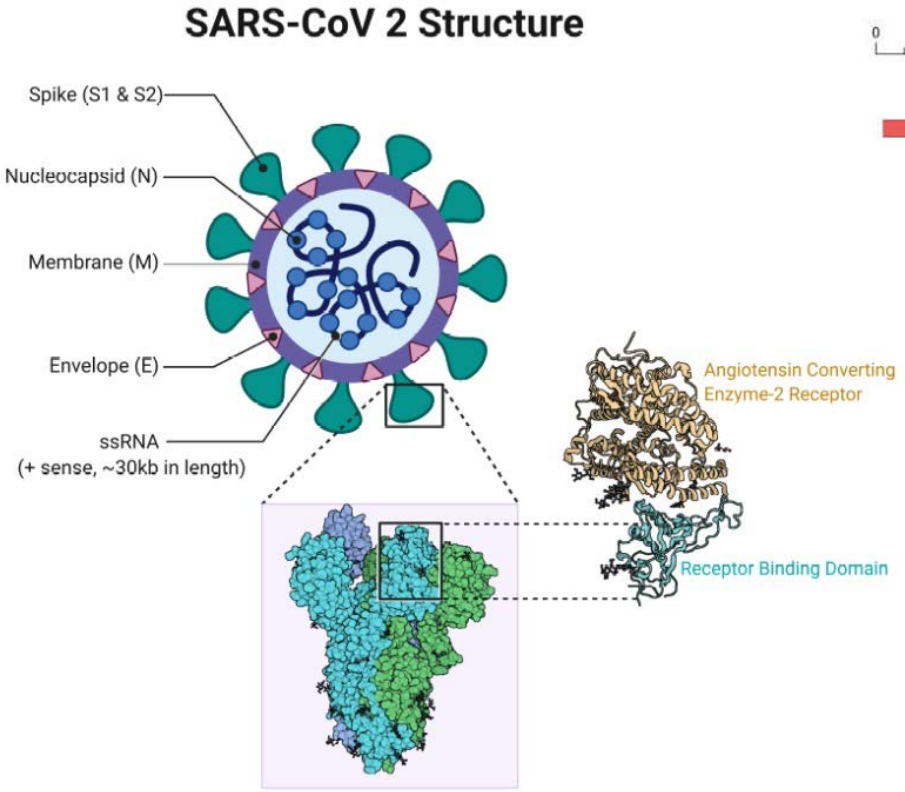
Li *et al. J Immuno* 2008

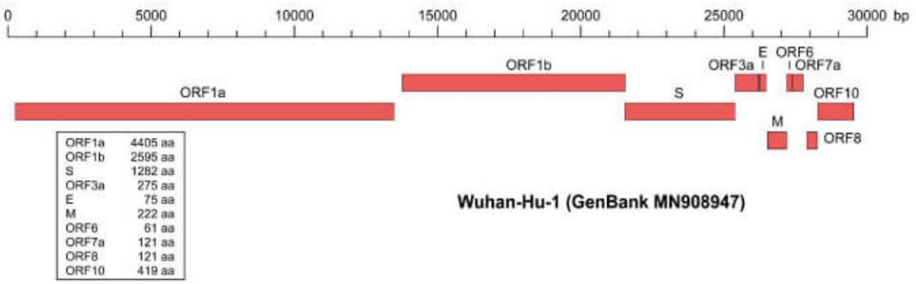
T-cell Responses 4 years post SARS-CoV

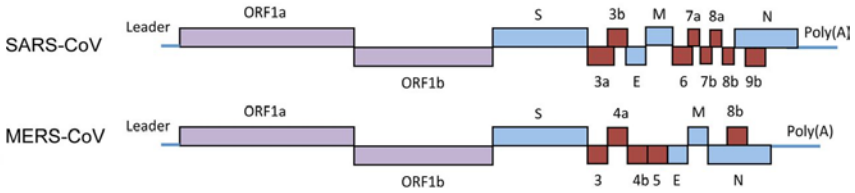


Fan *et al. Arch Virol* 2009

Structure & Genome of SARS COV-2





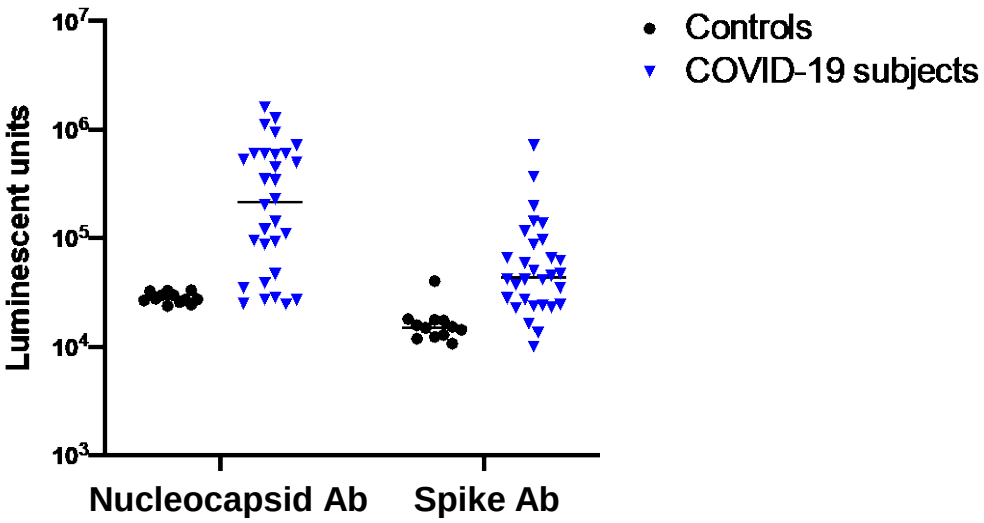


Developing a SARS-CoV-2 T cell Therapeutic from Convalescent Donors

Subject Demographics

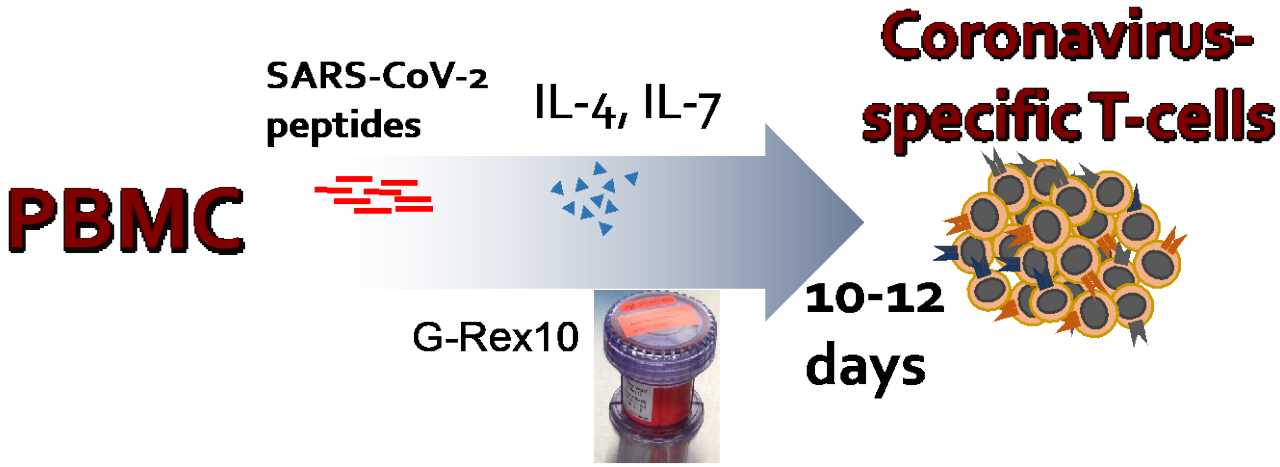
Description	Value
Median age in years (range)	34.5 (20-69)
Male gender	21 (46%)
Disease Severity	
Mild	38 (83%)
Moderate	3 (7%)
Severe	1 (2%)
Asymptomatic	4 (9%)
Symptoms	
Fever	24 (52%)
Respiratory symptoms	38 (83%)
GI symptoms	9 (20%)
Fatigue	15 (33%)
Anosmia	20 (44%)
Median length of symptoms, days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

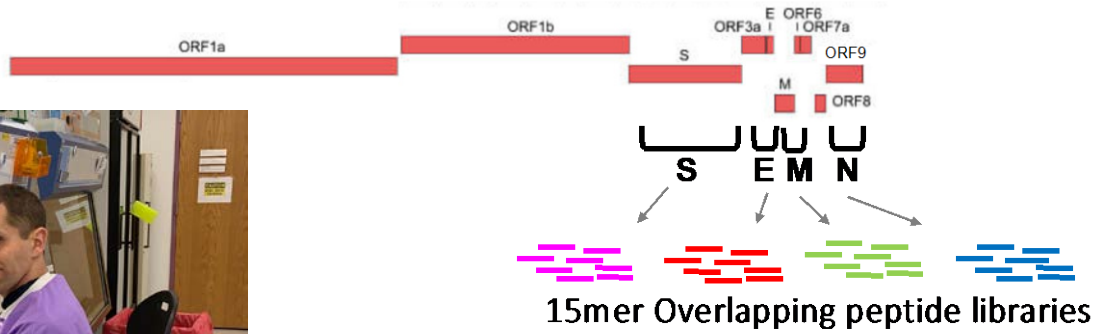
SARS-CoV-2 Antibody Responses (n=46)



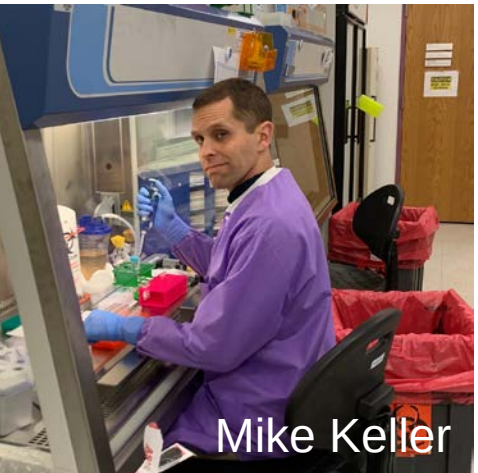
Collaboration with Jeff Cohen (NIAID LID), Peter Burbelo (NIDCR)
Keller et al, Blood 2020

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



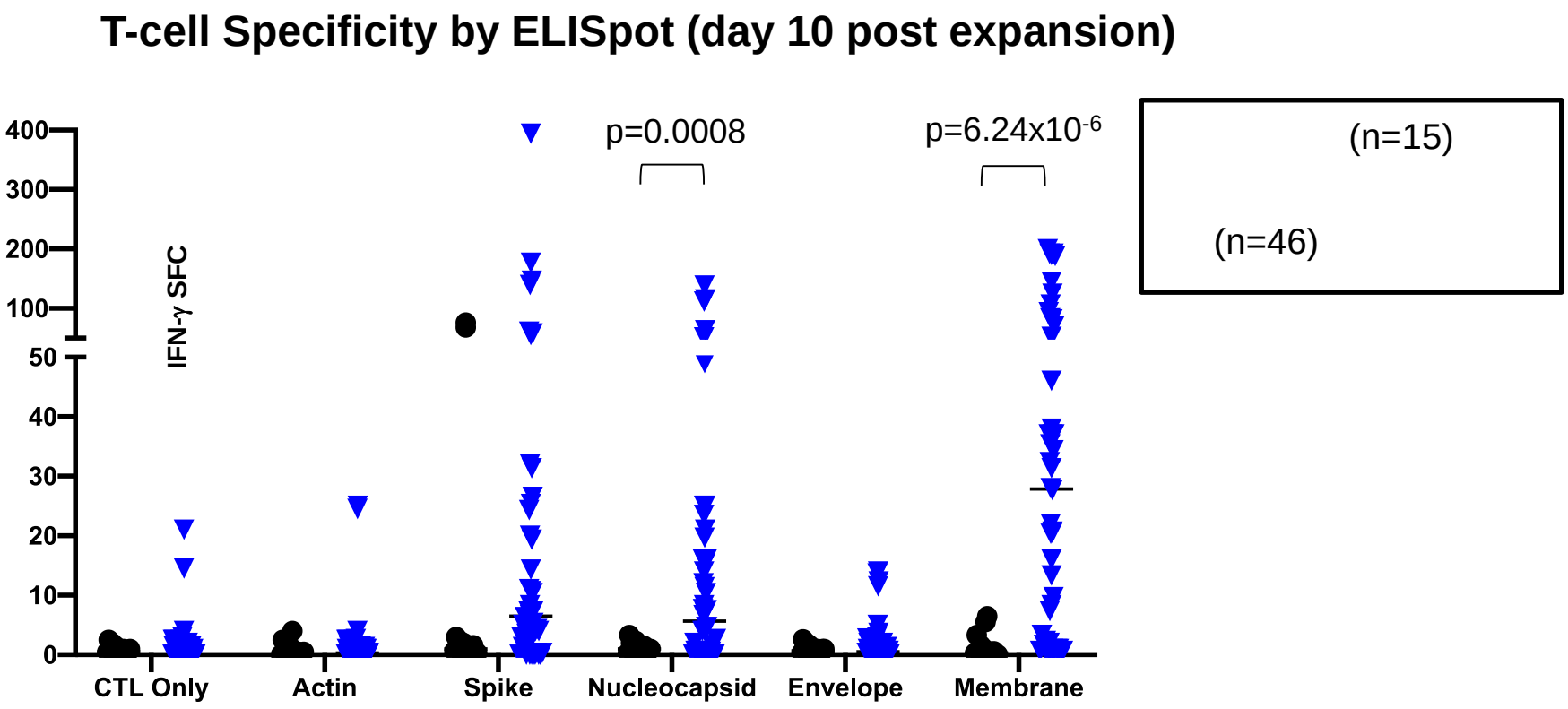


March 20, 2020
TEAM COVID



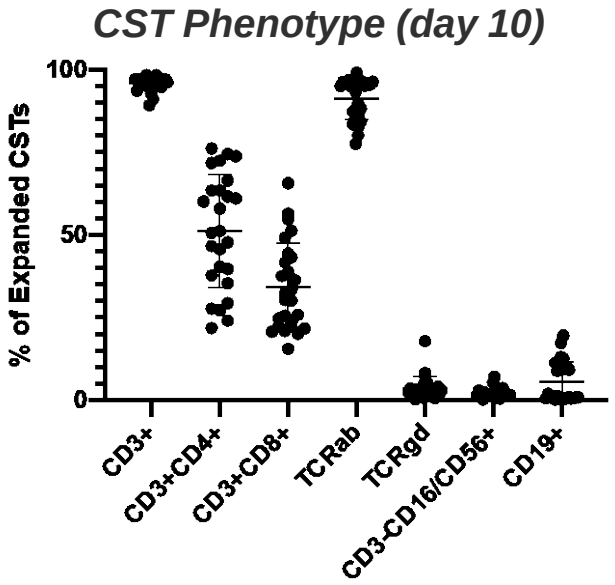
Keller et al, Blood. 2020 Dec 17;136(25):2905-17

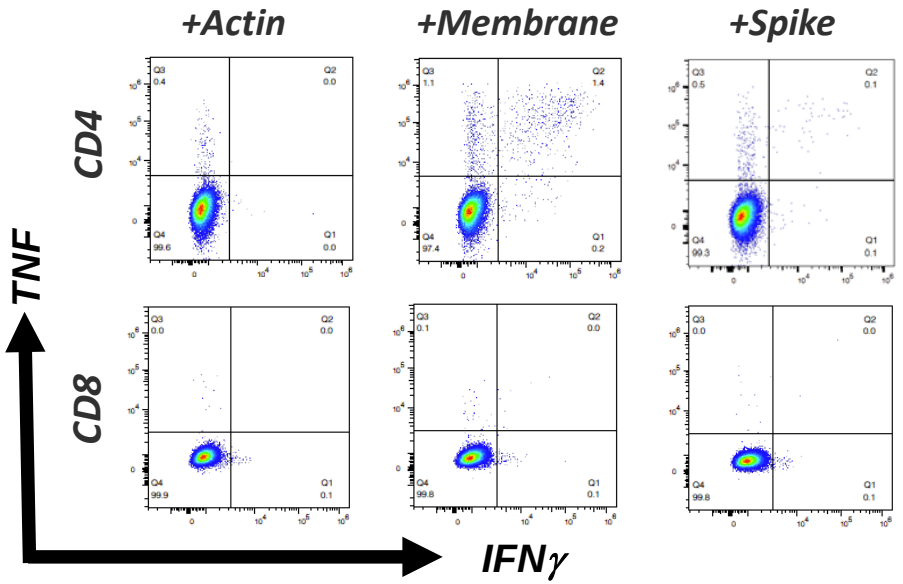
Convalescent Donors Recognize Multiple SARS-CoV-2 Structural Proteins

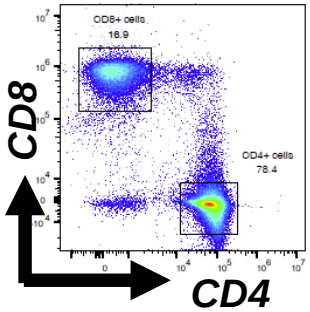


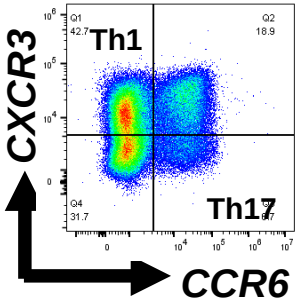
Keller et al, Blood. 2020 Dec 17;136(25):2905-17

Similar to Adenovirus, Norovirus, Parainfluenza virus specific T cell Responses – SARS-COV-2 T-cells are Predominantly Th1 CD4+





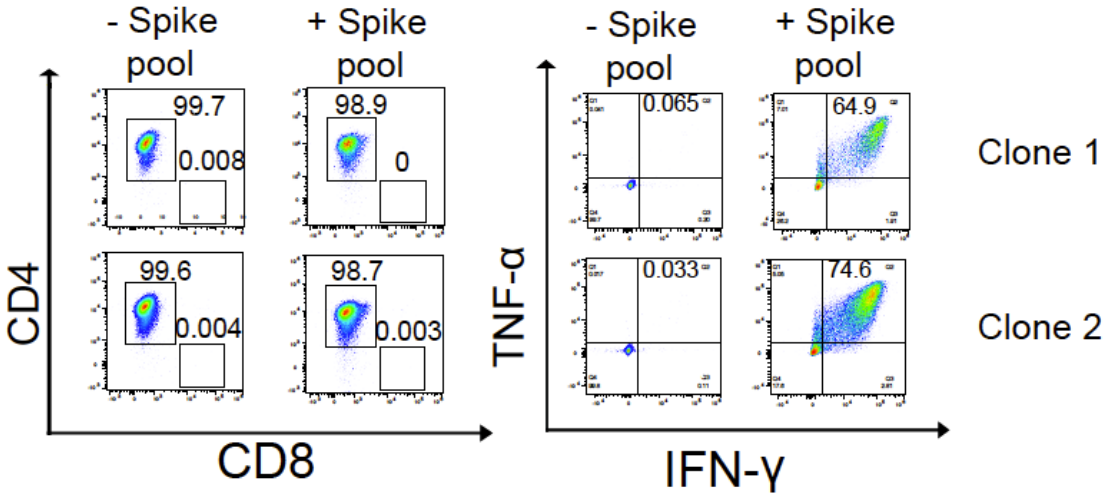




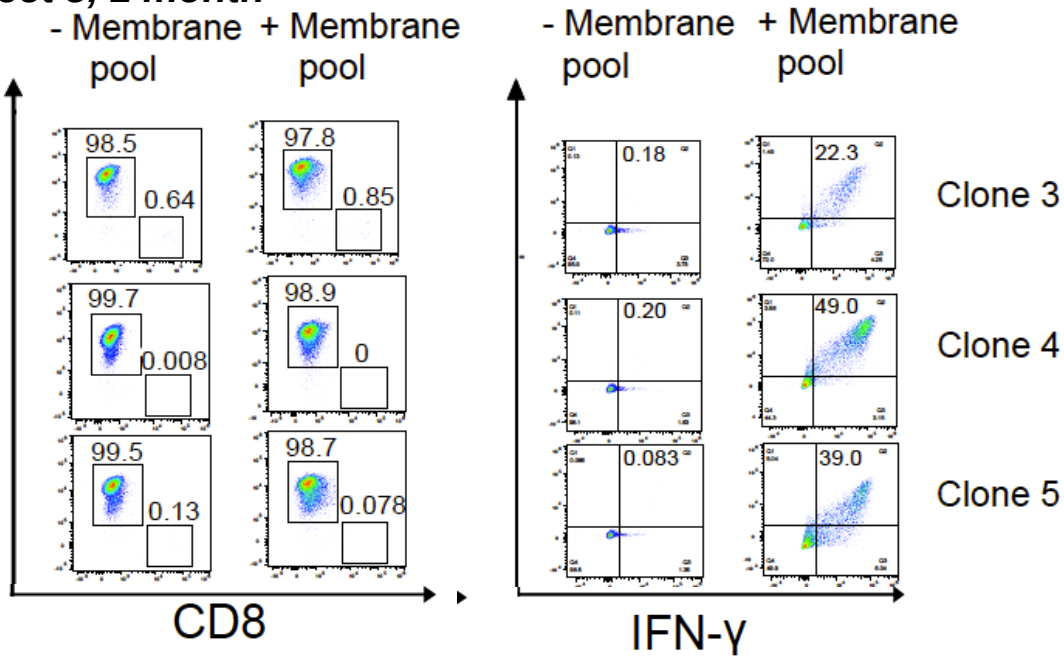
Leen et al. J Virol. 2008 Jan;82(1):546-54 (Adenovirus)
Hanajiri et al. J Infect Dis. 2020 Feb 3;221(4):578-88 (Norovirus)
Harris et al. Front Immunol. 2020 Oct 5;11:575977 (Parainfluenza)
Keller et al, Blood. 2020 Dec 17;136(25):2905-17 (SARS-CoV2)

SARS-CoV2 specific T cell clones expanded from Bulk CSTs are also Predominantly CD4+

Subject 4, 1 month

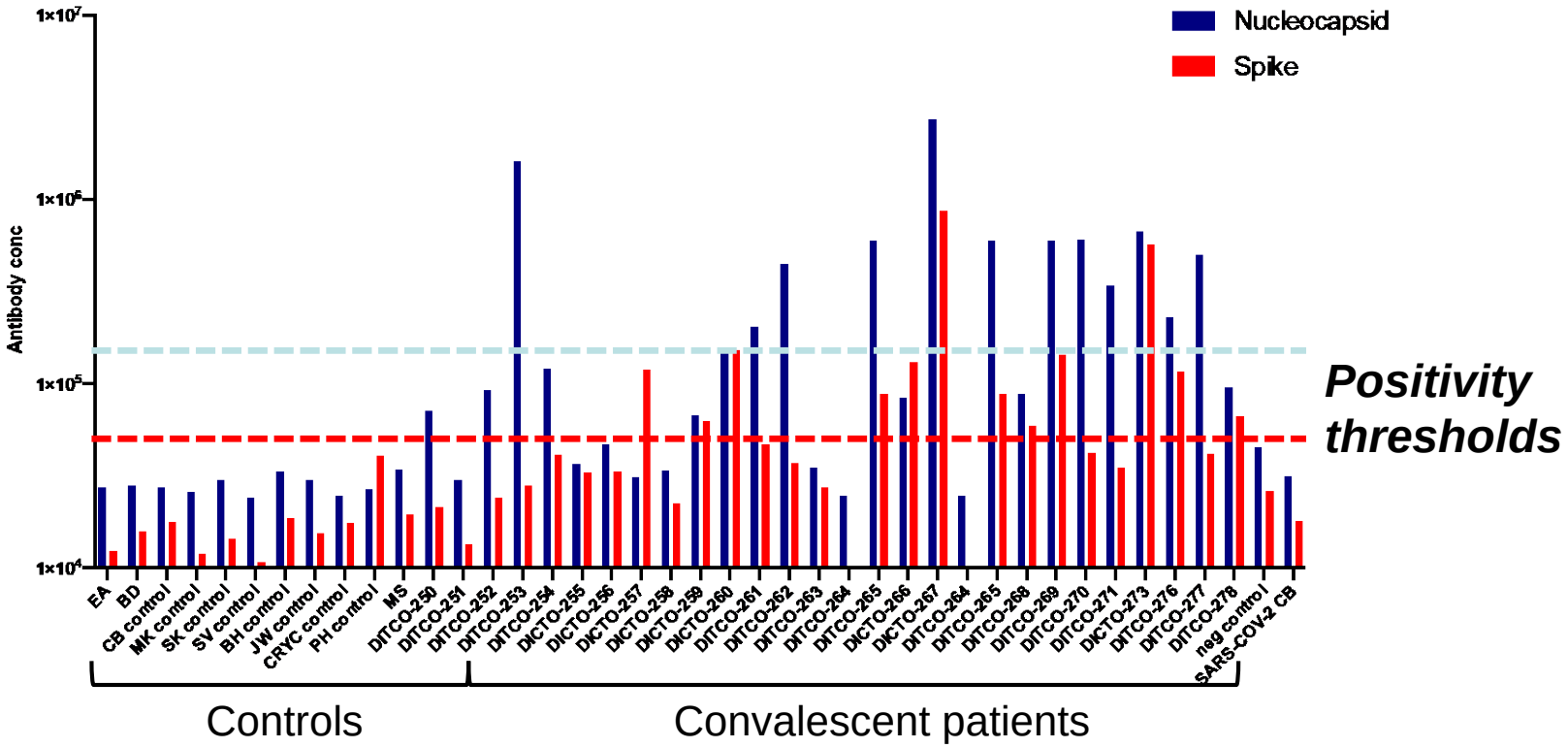


Subject 5, 1 month



Brad Jones,
Eva Stephenson
Cornell University

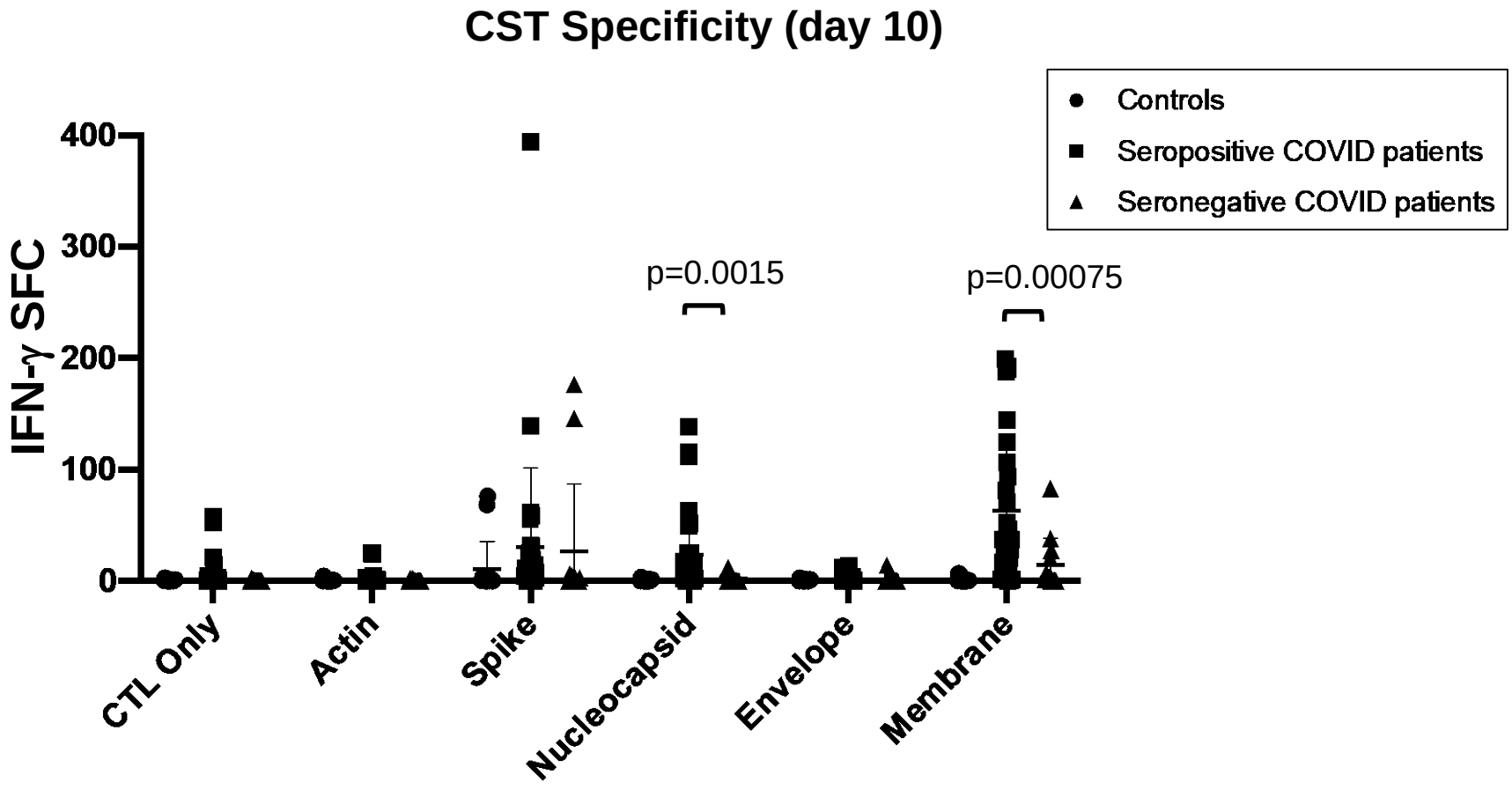
Most but not all convalescent patients have Antibodies to Spike and Nucleocapsid



Collaboration with Jeff Cohen NIAID

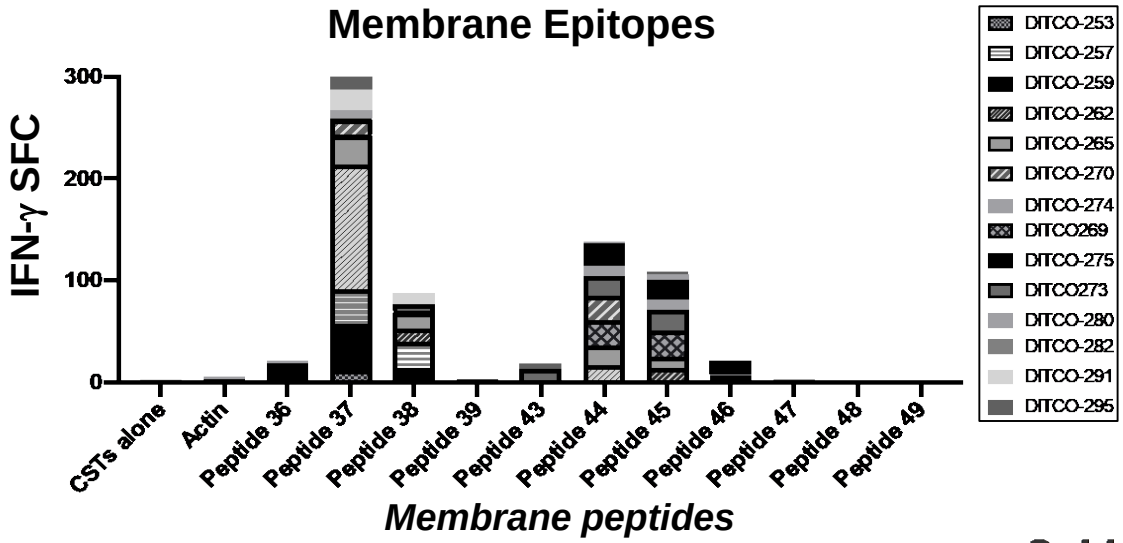
Keller et al, Blood. 2020 Dec 17;136(25):2905-17

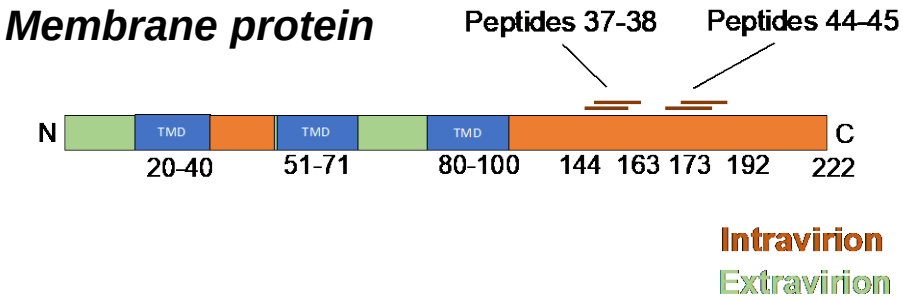
Seropositive Virus Exposed Donors Recognize a Broader Range of Viral Proteins Compared with Seronegative Exposed Donors

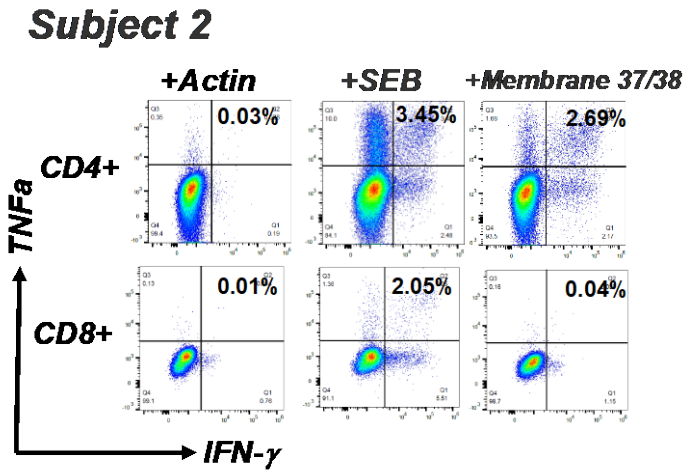


Keller et al, Blood. 2020 Dec 17;136(25):2905-17

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

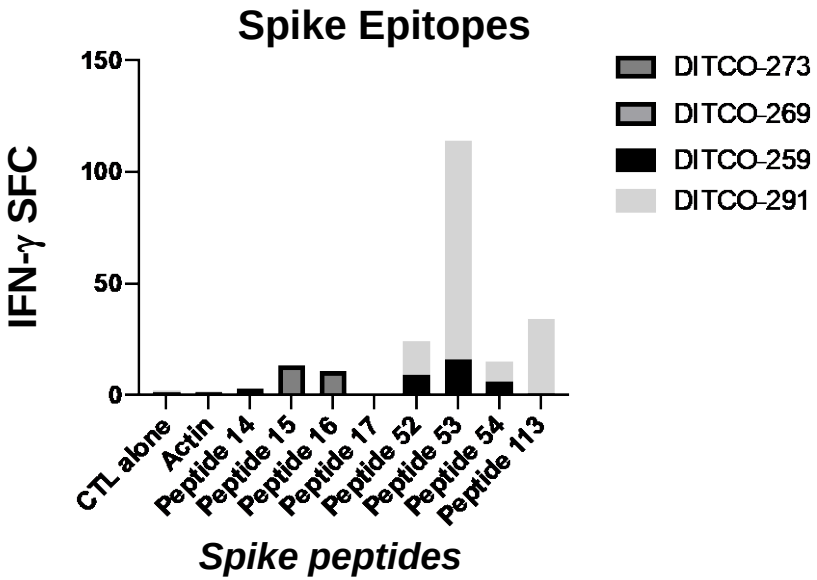


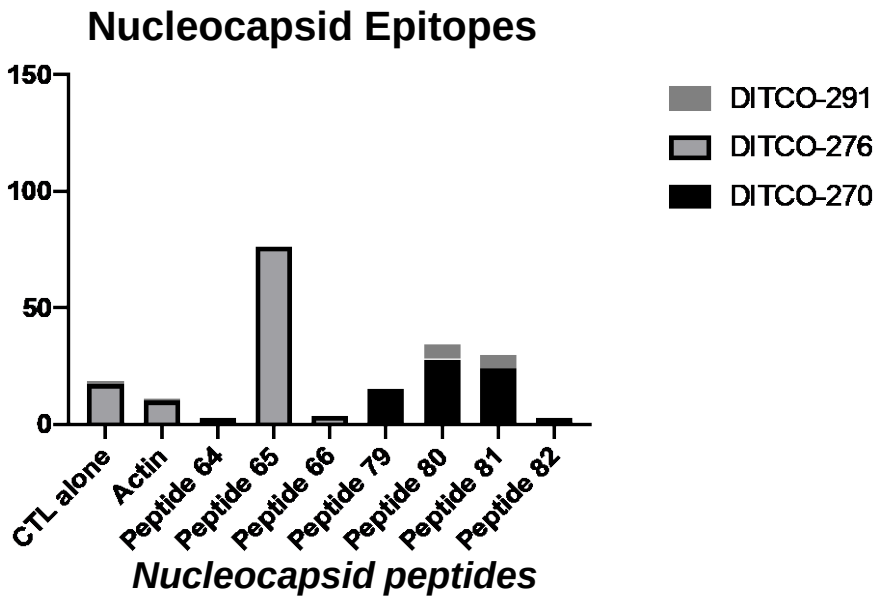


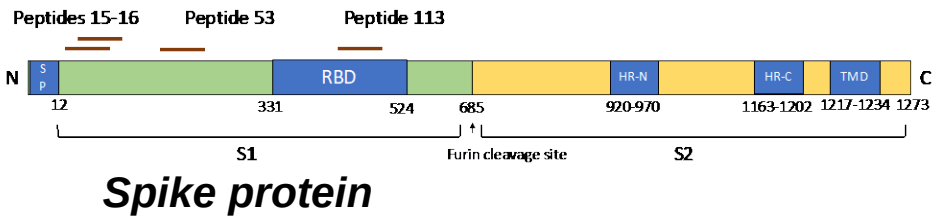


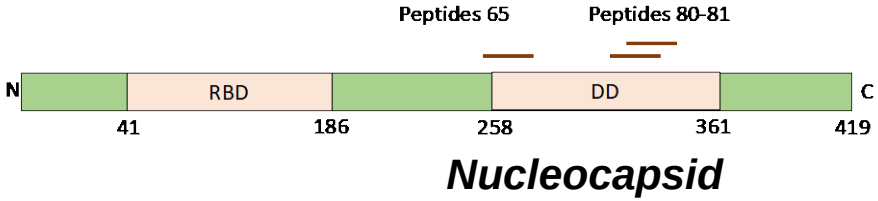
Keller et al, Blood. 2020 Dec 17;136(25):2905-17

Less Donors Recognize Epitopes within Spike and Nucleocapsid



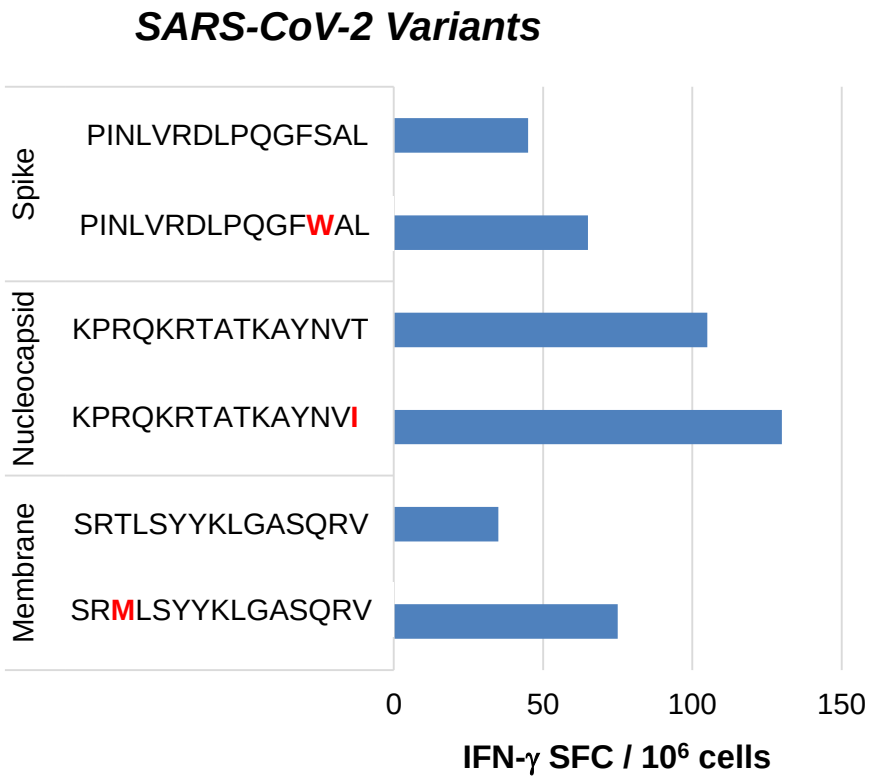


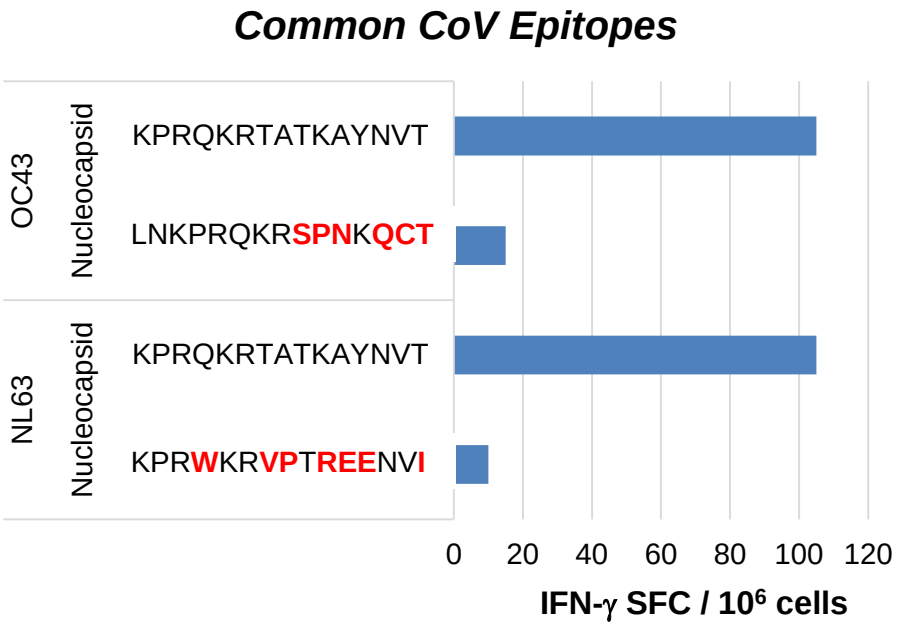




Keller et al, Blood. 2020 Dec 17;136(25):2905-17

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

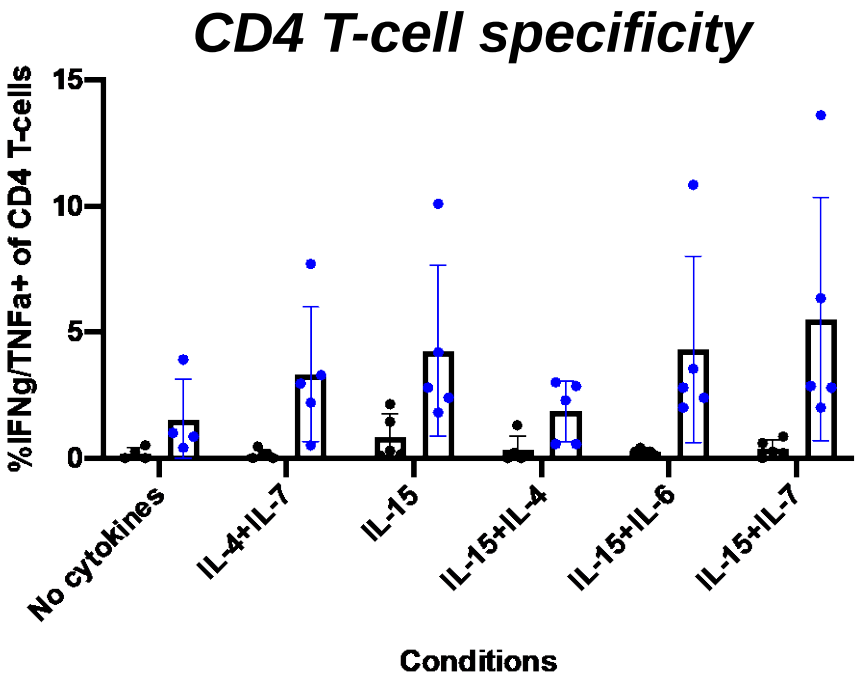


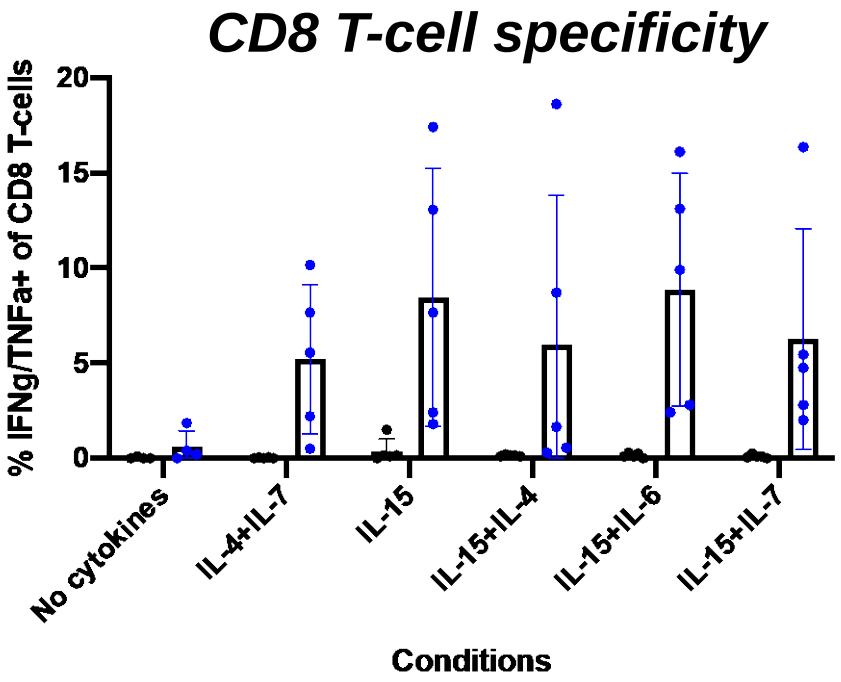


Keller et al, Blood. 2020 Dec 17;136(25):2905-17

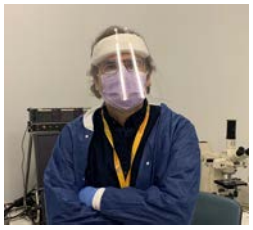
Moving SARS-CoV2 T cell Therapies to the Clinic

Improving Product Potency- IL15 Appears to Enhance CST Specificity



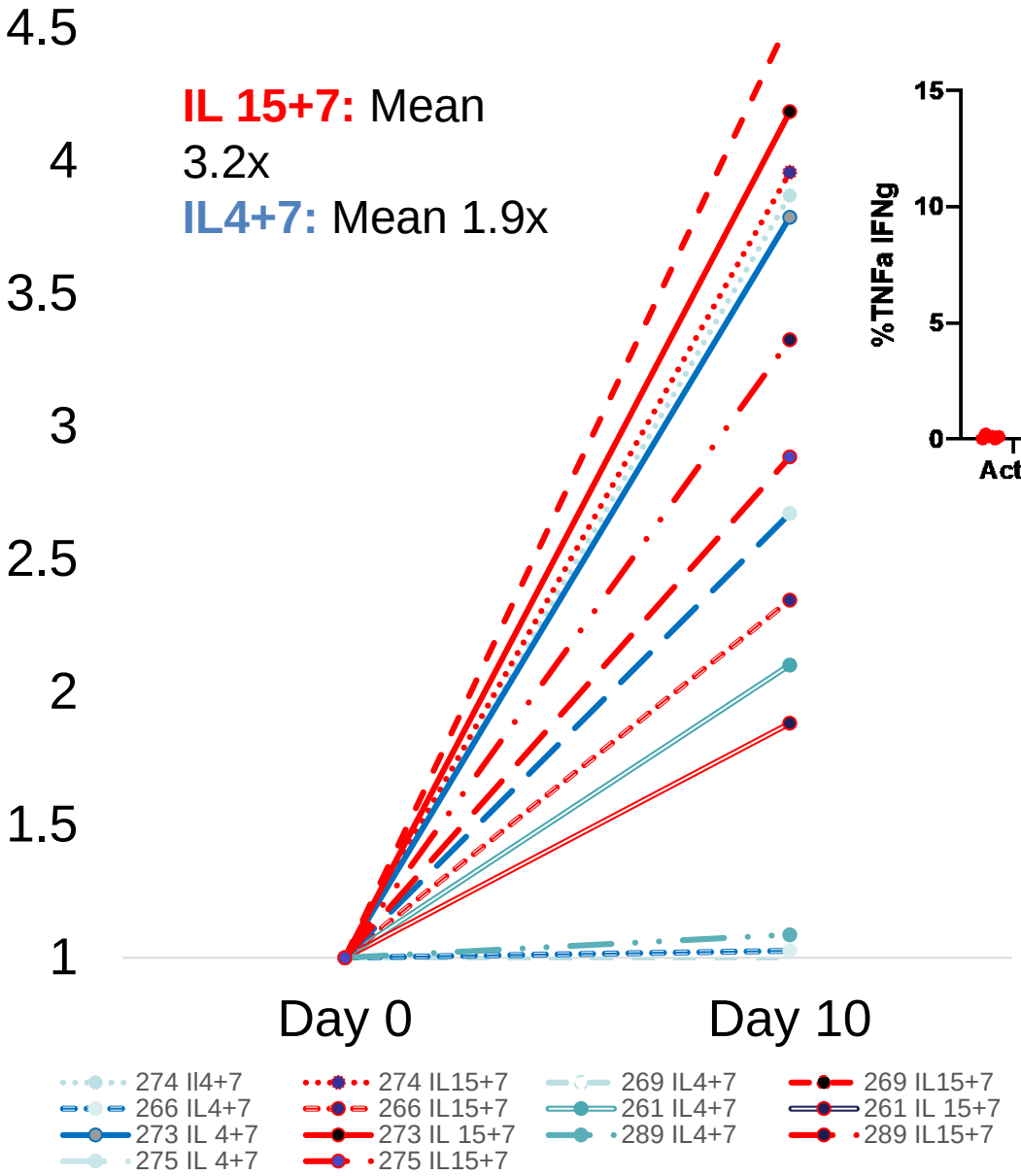


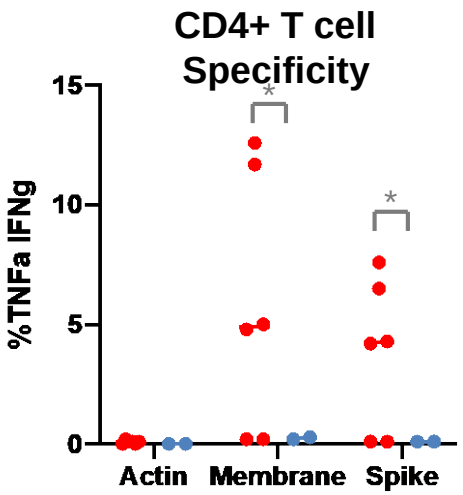
- Actin
- SARS-CoV-2 pepmixes

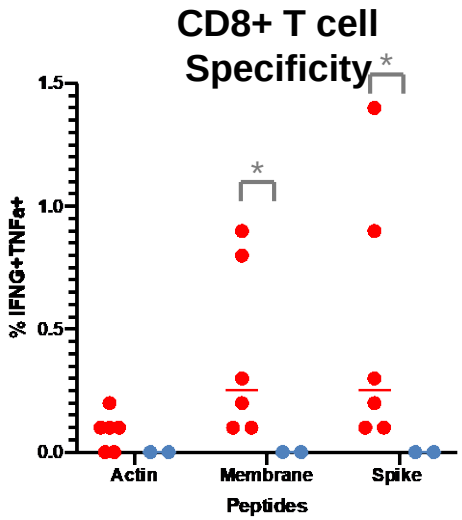


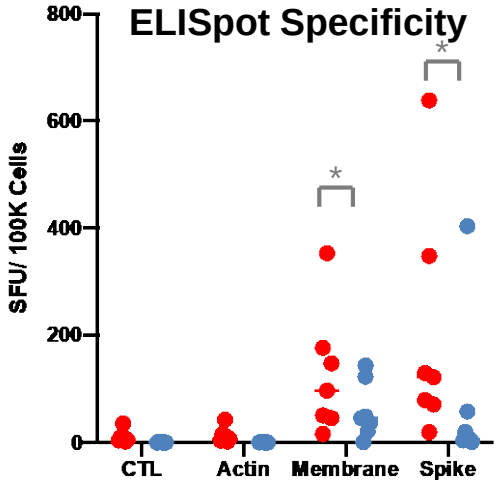
Chris Lazarski
Jessica Durkee Shock
Mariah Jensen Wachspress

IL15+7 Optimized Cytokine Cocktail Over IL4+7 Especially for CD8+ CSTs





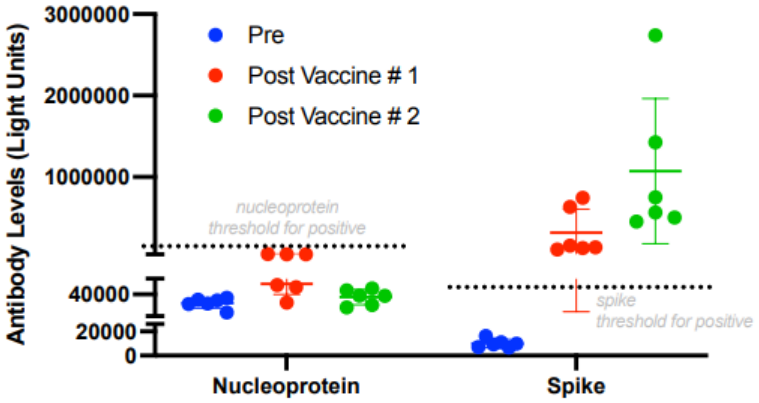


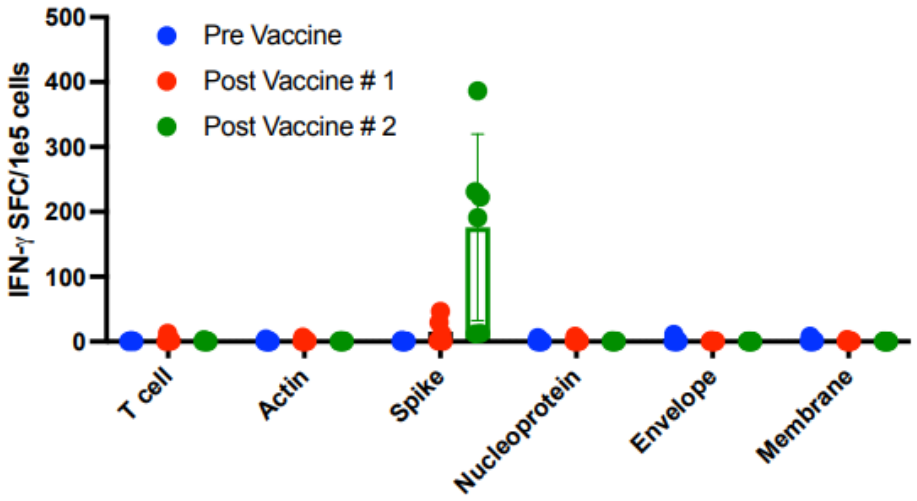


IL 4+7
IL 15+7

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

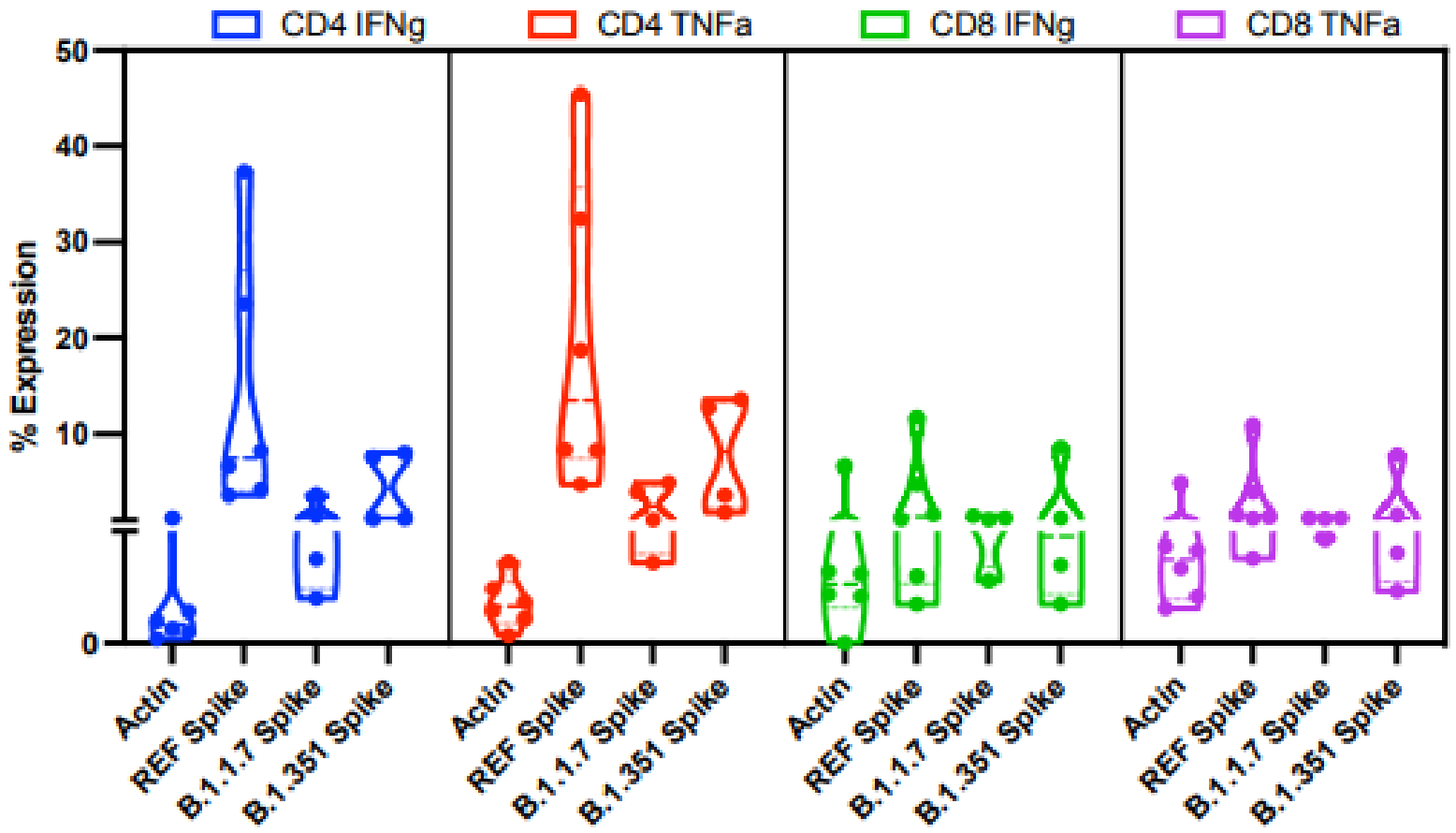
Vaccinated Donors Elicit Spike specific T cell responses in addition to Spike specific Ab Responses





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

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

Immunotherapy for COVID-19

- **Reports to date:**
  - Gladstone D *et al. Annals IM*:
    - 2 patients with ARDS treated with cord blood derived T-regulatory cells

Table 1. Laboratory Values: Patient 1

Characteristic	Day of Hospitalization				
	Day 12	Day 13*	Day 15	Day 17*	Day 22
CB Treg infusion	–	Infusion 1	–	Infusion 2	–
IL-6, *pg/mL*	23 239	–	13 517	–	3981
Lactate, *mmol/L*	–	2.7	1.5	–	
C-reactive protein, *mg/L*	–	124	67	55	14
Ferritin, *μg/L*	–	1963	1119	–	626
Aspartate aminotransferase, *U/L*	180	137	95	–	53
IL-12, *pg/mL*	–	5.7	3.7	–	<0.1
IFNγ, *pg/mL*	–	80.0	13.7	–	3.8
IL-8, *pg/mL*	–	17.5	34.7	–	12.3
MCP-1, *pg/mL*	–	>750	>750	–	329.4
MCP-4, *pg/mL*	–	192.0	377.5	–	88.9
TNFα, *pg/mL*	–	13.0	10.9	–	3.1

CB Treg – cord blood regulatory T cell; IFNγ – interferon-γ; IL – interleukin; MCP – monocyte chemoattractant protein; TNFα – tumor necrosis factor-α.
* Laboratory values collected before the infusion.

- **Phase I studies:**
  - **Regulatory T-cell therapy for COVID-19:** 1 developing study
  - **SARS-CoV-2 T-cell therapy**: 1 recruiting, 1 closed, 2 developing studies
  - **MSCs for COVID-19**: 2 recruiting, 2 developing studies
  - **NK cell therapy for COVID-19**: 2 recruiting studies

Conclusions

- Multiple CD4-restricted (and rarer CD8-restricted) epitopes are recognized by convalescent donors
- **Responses are predominantly membrane specific**
- **Seroconversion seems to correlate with the breadth of T cell responses**

- It is possible to expand SARS-CoV-2 specific T-cells from recovered ***and*** vaccinated donors, which may have clinical applicability for the treatment of BMT patients

- Clinical data using SARS-CoV2 specific T cells pending

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