126. Magnitude and Dynamics of the T-Cell Response to SARS-CoV-2 Infection and Vaccination

Thomas M. Snyder, PhD[1]; Rachel M. Gittelman, PhD[1]; Mark Klinger, PhD[1]; Damon H. May, PhD[1]; Edward J. Osborne, PhD[2]; Ruth Taniguchi, PhD[1]; H. Jabran Zahid, PhD[3]; Rebecca Elyanow, PhD[1]; Sudeb C. Dalai, MD, PhD[4]; Ian M. Kaplan, PhD[1]; Jennifer N. Dines, MD[1]; Matthew T. Noakes, PhD[1]; Ravi Pandya, PhD[3]; Lance Baldo, MD[1]; Simona Semprini, PhD[5]; Claudio Cerchione, MD, PhD[6]; Fabio Nicolini, PhD[7]; Massimiliano Mazza, PhD[7]; Ottavia M. Delmonte, MD[8]; Kerry Dobbs, MS[8]; Rocio Laguna-Goya, PhD[9]; Gonzalo Carreño-Tarragona, MD, PhD[10]; Santiago Barrio, PhD[10]; Luisa Imberti, MD[11]; Alessandra Sottini, BS[11]; Eugenia Quiros-Roldan, MD, PhD[11]; Camillo Rossi, MD, PhD[11]; Andrea Biondi, PhD[12]; Laura Rachele Bettini, MS[13]; Mariella D'Angio, MD, PhD[12]; Paolo Bonfanti, PhD[14]; Miranda F. Tompkins, PhD[15]; Camille Alba, PhD[15]; Clifton Dalgard, PhD[15]; Vittorio Sambri, MD, PhD[5]; Giovanni Martinelli, MD, PhD[6]; Jason D. Goldman, MD, MPH[16]; James R. Heath, PhD[17]; Helen C. Su, MD, PhD[8]; Luigi D. Notarangelo, MD[18]; Estela Paz-Artal, MD, PhD[9]; Joaquin Martinez-Lopez, MD, PhD[10]; Jonathan M. Carlson, PhD[3]; Harlan S. Robins, PhD[1]; [1]Adaptive Biotechnologies, Seattle, Washington; [2]Adaptive BIotechnologies, Seattle, Washington; [3]Microsoft Research, Redmond, Washington; [4]Adaptive Biotechnologies and Stanford University School of Medicine, Seattle, Washington; [5]Unit of Microbiology - The Great Romagna Hub Laboratory, Pievesestina ITALY and DIMES, University of Bologna, Bologna, Emilia-Romagna, Italy; [6]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Medola, Lombardia, Italy; [7]Immunotherapy, Cell Therapy and Biobank (ITCB), Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Medola, Lombardia, Italy; [8]Immune Deficiency Genetics Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; [9]Department of Immunology, Hospital 12 de Octubre, i+12, Madrid, Madrid, Spain; [10]Hematology Department, Hospital 12 de Octubre, i+12, CNIO, Complutense University, Madrid, Madrid, Spain; [11]Laboratorio CREA, Department of Infectious and Tropical Diseases, and Medical Officer, ASST Spedali Civili di Brescia and University of Brescia, Brescia, Lombardia, Italy; [12]Department of Pediatrics and Centro Tettamanti-European Reference Network PaedCan, EuroBloodNet, MetabERN-University of Milano-Bicocca-Fondazione MBBM-Ospedale San Gerardo, Monza, Lombardia, Italy; [13]Department of Pediatrics and Centro Tettamanti-European Reference Network PaedCan, EuroBloodNet, MetabERN-University of Milano-Bicocca-Fondazione MBBM-Ospedale San Gerardo, Monza, Lombardia, Italy; [14]Department of Infectious Diseases, University of Milano-Bicocca-Ospedale San Gerardo, Monza, Lombardia, Italy; [15]The American Genome Center, Uniformed Services University of the Health Sciences, Bethesda, Maryland; [16]Swedish Medical Center, Seattle, WA, USA, and Division of Allergy and Infectious Diseases, University of Washington, Seattle, Washington; [17]Institute for Systems Biology, Seattle, WA, USA, Seattle, Washington; [18]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD

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Background. T cells are central to the early identification and clearance of viral infections and support antibody generation by B cells, making them desirable for assessing the immune response to SARS-CoV-2 infection and vaccines. We combined 2 high-throughput immune profiling methods to create a quantitative picture of the SARS-CoV-2 T-cell response that is highly sensitive, durable, diagnostic, and discriminatory between natural infection and vaccination.

Methods. We deeply characterized 116 convalescent COVID-19 subjects by experimentally mapping CD8 and CD4 T-cell responses via antigen stimulation to 545 Human Leukocyte Antigen (HLA) class I and 284 class II viral peptides. We also performed T-cell receptor (TCR) repertoire sequencing on 1815 samples from 1521 PCR-confirmed SARS-CoV-2 cases and 3500 controls to identify shared public TCRs from SARS-CoV-2-associated CD8 and CD4 T cells. Combining these approaches with additional samples from vaccinated individuals, we characterized the response to natural infection as well as vaccination by separating responses to spike protein from other viral targets.

Results. We find that T-cell responses are often driven by a few immunodominant, HLA-restricted epitopes. As expected, the SARS-CoV-2 T-cell response peaks about 1-2 weeks after infection and is detectable at least several months after recovery. Applying these data, we trained a classifier to diagnose past SARS-CoV-2 infection based solely on TCR sequencing from blood samples and observed, at 99.8% specificity, high sensitivity soon after diagnosis (Day 3–7 = 85.1%; Day 8–14 = 94.8%) that persists after recovery (Day 29+/convalescent = 95.4%). Finally, by evaluating TCRs binding epitopes targeting all non-spike SARS-CoV-2 proteins, we were able to separate natural infection from vaccination with > 99% specificity.

Conclusion. TCR repertoire sequencing from whole blood reliably measures the adaptive immune response to SARS-CoV-2 soon after viral antigenic exposure (before antibodies are typically detectable) as well as at later time points, and distinguishes post-infection vs. vaccine immune responses with high specificity. This approach to characterizing the cellular immune response has applications in clinical diagnostics as well as vaccine development and monitoring.

127. Development of a Kinetic ELISA (kELISA) and Reactive B-cell Frequency (RBF) Assay to Detect Respiratory Syncytial Virus (RSV) Pre-Fusion F Protein-Specific Immune Responses in Infants

Stephanie L. Rolsma, MD, PhD[1]; Sandy M. Yoder, BS[1]; Rachel S. Nargi, Bachelor of Science[1]; Eric Brady, BS[1]; Natalia Jimenez-Truque, MSCI, PhD[1]; Isaac Thomsen, MD, MSCI[1]; Marissa Thompson, B.S.[2]; Robert H. Carnahan, PhD[1]; Rachel E. Sutton, n/a[1]; Erica Armstrong, BS[3]; Len Dally, M.Sc[4]; James E. Crowe, Jr., MD[1]; Kathryn M. Edwards, MD[1]; Buddy Creech, MD, MPH[5]; [1]Vanderbilt University Medical Center, Nashville, TN; [2]The Emmes Company, LLC, Rockville, Maryland; [3]VUMC, Antioch, Tennessee; [4]The Emmes Company, Rockville, Maryland; [5]Vanderbilt University School of Medicine, Nashville, TN

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Background. RSV is a major cause of pediatric respiratory disease. Antibodies to the prefusion conformation of the RSV fusion (pre-F) protein are needed for virus neutralization.

Methods. We measured RSV-specific responses in two groups of children < 3 years of age; subjects with laboratory-confirmed RSV (RSV-infected) or infants born in the period May to September and enrolled prior to their first RSV season (RSV-uninfected). RSV-infected infants had blood samples obtained at 1, 6, 9, and 12 months after infection. RSV-uninfected infants had blood samples obtained at enrollment, at the end of their first RSV season, and 6 months later. A kELISA to measure RSV pre-F-specific antibodies and an RBF assay to identify RSV F-specific B cells were developed.

Results. 102 subjects were enrolled; 11 were excluded due to missed visits or withdrawal. Of the 65 subjects in the **RSV-uninfected** group, all were kELISA positive at enrollment, consistent with maternal antibody transfer. 53 subjects had sufficient samples for analysis at multiple time points; 29 became seronegative and 24 remained seropositive. In the seronegative group, the kELISA value decreased rapidly to < 0.25 by 6 months after the RSV season in 27/29 (93%), (Figure 1a). In the persistently seropositive group, all 24 subjects maintained a positive kELISA value, with some developing higher values over time, consistent with asymptomatic infection (Figure 1b). An RBF assay was used to determine whether antibodies were due to persistent maternal antibodies or endogenous production (Figure 2). In the seronegative group, 24/29 (80%) had a negative RBF; in the seropositive group, 23/24 (96%) had a positive RBF during follow-up.

There were 26 subjects in the **RSV-infected** group; 22 had sufficient samples for analysis at multiple time points. All were seropositive by kELISA at one month post-infection with variable kELISA values during follow-up (Figure 3). 17/22 (77%) had a positive RBF, although 4 of the subjects without a positive RBF had indeterminate results at ≥ 1 visit.
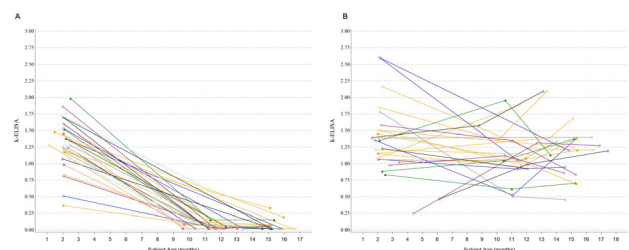

Figure 1. kELISA values of baseline RSV-negative subjects, by subject age at time of sample. Panel A: Subjects classified as seronegative (n=29). Panel B: Subjects without known RSV classified as persistently seropositive (n=24).