BIOGRAPHICAL SKETCH

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NAME: Grupp, Stephan

eRA COMMONS USER NAME (credential, e.g., agency login): sgrupp

POSITION TITLE: Professor of Pediatrics (Penn) and Section Chief, Cell Therapy and Transplant (CHOP)

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Cincinnati, Cincinnati, OH	BS	06/1981	Biology
University of Cincinnati, Cincinnati, OH	PhD	06/1985	Immunology
University of Cincinnati, Cincinnati, OH	MD	06/1987	Medicine
Children's Hospital, Boston, MA	Resident	06/1989	Pediatrics
Dana Farber Cancer Institute and Children's Hospital, Boston, MA	Fellow	06/1992	Pediatric Heme/Onc
Brigham and Women's Hospital, Boston, MA	Research Fellow	06/1995	Immunology

A. PERSONAL STATEMENT

I have extensive experience in the development and preclinical testing of engineered cell therapies and signal transduction inhibitors in leukemia, in pediatric immunotherapy trials using both, and in the manufacture and use of cellular therapeutics in preclinical, GMP, and clinical trial settings. I currently lead most of the CTL019 (CD19 CAR) clinical trials at CHOP, in the US, and globally. Our group at U Penn and CHOP has led the field of highly active CAR T cell therapy, and CTL019 is on track for FDA submission within the year. Over the last 10 years, the P01 team has built a one of the most capable cell therapy groups in the world at CHOP and Penn, which can implement cell therapy trials with GMP cell manufacturing (Penn CVPF), regulatory support, and clinical implementation. My basic science research group currently consists of 1 graduate student, 2 postdoctoral fellows, 6 fellow/instructor trainees now at the Assistant Professor level, and 12 research assistants. I am committed to improving outcomes for children who undergo hematopoietic cell transplantation and changing the standard of care.

1. Milone, M, Fish J, Carpenito C, Carroll R, Binder G, Teachey DT, Samanta M, Lakhal M, Danet-Desnoyers G, Gloss B Campana D, Riley J, **Grupp SA**, June CH. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased anti-leukemic efficacy in vivo. *Mol Ther* 2009; 17:1453-64. PMC2805264.
2. Kalos M, Levine BL, Porter DL, Katz S, **Grupp SA**, Bagg A, June CH. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. *Sci Transl Med* 2011; 3: 95ra73. PMC3393096.
3. DW Lee, BD Santomasso, FL Locke, A Ghobadi, CJ Turtle, JN Brudno, MV Maus, JH Park, E Mead, S Pavletic, WY Go, L Eldjerou, RA Gardner, N Frey, KJ Curran, K Peggs, M Pasquini, JF DiPersio, RM van den Brink, KV Komanduri **SA Grupp***, SS Neelapu*. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. BBMT 2019, 25:625-638

B. POSITIONS AND HONORS

Positions and Employment

1978-1981 Research Assistant Marine Biological Laboratory, Woods Hole, MA
1981 Research Assistant, NINCDS, National Institutes of Health, Bethesda, MD
1992-1995 Instructor in Pediatrics, Harvard Medical School, Boston, MA
1992-1995 Assistant in Medicine, Children's Hospital and Dana Farber Cancer Institute, Boston, MA
1996-2006 Assistant Professor of Pediatrics, University of Pennsylvania
1999-2010 Director, Stem Cell Biology, Division of Oncology, Children's Hospital of Philadelphia
2001- Medical Director, Stem Cell Laboratory
2002-2017 Deputy Chair, IACUC
2006-2011 Associate Professor of Pediatrics, University of Pennsylvania
2007-2015 Chair, Children's Oncology Group Stem Cell Transplant Committee
2008- Director of Translational Research, Center for Childhood Cancer Research, CHOP
2008-2016 Fellowship Director, Pediatric Hematology-Oncology, CHOP
2011- Professor of Pediatrics, University of Pennsylvania
2015- Director, Cancer Immunotherapy Frontier Program, CHOP
2017 Section Chief, Cellular Therapy and Transplant, CHOP

Awards/Honors

1981 *Magna cum Laude* in Biology, Univ. of Cincinnati
1987 Bogen Award for Outstanding Medical Student Research, Univ. Cincinnati College of Medicine
1992-1995 Special Fellowship, Leukemia Society of America
1993-1996 Potter Fellow
1996 NIH FIRST Award
1999 Sanford Young Investigator
2002 Research Recognition Award, Leukemia and Lymphoma Society
2007 Lifetime Achievement Award, Eagles Fly for Leukemia
2014 Pennsylvania Bio Patient Impact Award
2014 Clinical Research Forum Top 10 Clinical Research US Achievement Award
2014 CRF Herbert Pardes First Place Achievement Award
2014 van Bekkum Award, European Society for Bone Marrow Transplantation
2014 Audrey Evans Service Award, Ronald McDonald House Charities
2015 Oski Lectureship and Award, American Society of Pediatric Hematology/Oncology
2015 Fred Saunders Lectureship and Award Canadian Blood and Marrow Transplant Society
2016 Philadelphia Scientist of the Year, Philly Geek Awards, Technical.ly
2018 Philadelphia Citizen Diplomat Award
2018 William Osler Patient Oriented Research Award
2019 Daniel Drake Medal, University of Cincinnati College of Medicine
2019 Elected to National Academy of Medicine

C. CONTRIBUTIONS TO SCIENCE

The primary focus of my lab's work is the development of targeted and cell therapies and studies ALL and T cell biology. Our group has leveraged studies using primary human ALL xenografts into treatments tested in a number of clinical trials, including national phase 3 randomized and FDA registration trials. In addition, as the Director of the Cancer Immunotherapy Frontier Program and the Section chief of Cell Therapy and Transplant, I oversee research into clinical use of CAR T cells and hematopoietic stem cells.

1. **CAR T cell studies**. Most relevant to this grant, our group has been working with Dr. Carl June and the Penn Translational Research Program on chimeric antigen receptor (CAR)-based engineered T cell therapies. One target is CD19 in ALL, where we have developed CTL019) in an ongoing basic and translational collaboration with the June group. The pediatric data on the ALL trials have been spectacular, leading to 3 NEJM publications and international publicity for the work. CTL019 for pediatric ALL was the 1st CART approved by the FDA, as well as the 1st gene therapy approved in the US, and I led the study steering committees for the global registration trials for CTL019 for ALL.

a. **Grupp SA**, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, Teachey DT, Levine BL, June CH. Induction of complete remissions of ALL by chimeric antigen receptor-expressing T cells. ***N Engl J Med*** 2013; 368:1509-18. PMC4058440.
b. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, Chew A, Gonzalez VE, Zheng Z Lacey SF, Levine BL, Mahnke YD, Melenhorst JJ, Rheingold SR, Shen A, Teachey DT, June CH, Porter DL, **Grupp SA**. Sustained remissions with chimeric antigen receptor T cells for leukemia. ***N Engl J Med*** 2014; 371:1507-17. PMC4267531.
c. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, Bader P, Verneris MR, Stefanski HE, Myers GD, Qayed M, De Moerloose B, Hiramatsu H, Schlis K, Davis KL, Martin PL, Nemecek ER, Yanik GA, Peters C, Baruchel A, Boissel N, Mechinaud F, Balduzzi A, Krueger J, June CH, Levine BL, Wood P, Taran T, Leung M, Mueller KT, Zhang Y, Sen K, Lebwohl D, Pulsipher MA, **Grupp SA**. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. ***N Engl J Med*** 2018; 378:439-448. PMC5996391.

In addition to the clinical trial results with CTL019 in ALL, we have done pioneering work in cytokine release syndrome (CRS). We discovered the link between CRS and macrophage activation syndrome and uncovered the key role that IL-6 plays in the development of severe CRS. Our observation that IL-6 blockade can reverse CRS has transformed the field of highly active cell therapy.

d. Kadauke, S, RM Myers, Y Li, R Aplenc, D Baniewicz, DM Barrett, AB Leahy, C Callahan, JG Dolan, JC Fitzgerald, W Gladney, SF Lacey, H Liu, SL Maude, R McGuire, LS Motley, DT Teachey, G Wertheim, L Wray, AM DiNofia, **SA Grupp**. Risk-Adapted Preemptive Tocilizumab to Prevent Severe Cytokine Release Syndrome after CTL019 for Pediatric B-Cell Acute Lymphoblastic Leukemia: A Prospective Clinical Trial. J Clin Oncol 2021 DOI: 10.1200/JCO.20.02477 PMID:33417474

2. **Signal transduction studies in ALL**. We have demonstrated the importance of the mTOR pathway in B cell cancer and demonstrated that mTOR inhibitors are effective agents against ALL as well as lymphoproliferative disorders (see below). IL-7 and a related molecule called TSLP reverse the effect of mTOR inhibitors on pre-B ALL cells, demonstrating the importance of TSLPR in ALL prior to the work we have participated in defining CRLF (TSLPR) overexpression as a risk factor in ALL. We have recently extended these studies into the JAK2-STAT pathway, which has also led to clinical trials.

a. Brown VI, Fang J, Alcorn K, Barr R, Kim JM, **Grupp SA**. The mTOR inhibitor rapamycin is active against B-precursor leukemia and reveals a role for IL-7 mediated signaling. ***Proc Natl Acad Sci USA*** 2003; 100:15113-15118. PMC299917.
b. Teachey DT, Sheen C, Hall J, Ryan T, Brown VI, Fish J, Reid GSD, Seif AE, Carroll M, **Grupp SA**. mTOR inhibitors are synergistic with methotrexate: an effective combination to treat acute lymphoblastic leukemia. ***Blood*** 2008; 112:2020-3. PMC2518903.
c. Maude SL, Tasian SK, Vincent T, Hall J, Sheen C, Roberts KG, Seif AE, Barrett DM, Chen I, Collins JR, Mullighan CG, Hunger SP, Harvey RC, Willman CL, Fridman JS, Loh ML, ***Grupp SA**, *DT Teachey. Targeting JAK1/2 and mTOR in murine xenograft models of Ph-like acute lymphoblastic leukemia (ALL). ***Blood*** 2012; 120:3510-8 (* denotes equal contribution). PMC3482861.
d. Maude, SL, Dolai S, Delgado-Martin C, Vincent TL, Robbins A, Selvanathan A, Ryan T, Hall J, Wood AC, Tasian SK, Hunger SP, Loh ML, Mullighan CG, Wood BL, Hermiston ML, **Grupp SA**, Lock RB, Teachey DT. Efficacy of JAK/STAT pathway inhibition in murine xenograft models of early T-cell precursor (ETP) acute lymphoblastic leukemia. ***Blood*** 2015; 125:1759-67. PMC4357583.

3. **mTOR inhibitor trials in ALL and transplant**. These mTOR pathway findings have had direct translational significance in ALL, leading to Phase I, II, and III (COG ASCT0431 and CTN 0401). These studies have also shown the importance of the GVL effect in ALL (long debated) and demonstrated the power of next-gen sequencing to detect clinically relevant MRD in the transplant setting.

a. Pulsipher MA, Wall DA, Grimley M, Goyal RK, Boucher KM, Hankins P, **Grupp SA**, Bunin NJ. A phase I/II study of the safety and efficacy of the addition of sirolimus to tacrolimus/methotrexate graft versus host disease prophylaxis after allogeneic hematopoietic cell transplantation in pediatric ALL. ***Br J Haematol*** 2009; 147:691-9. PMC2888481.
b. Cutler C, Logan B, Nakamura R, Johnston L, Choi S, Porter D, Hogan WJ, Pasquini M, MacMillan ML, Hsu J, Waller EK, **Grupp SA**, McCarthy P, Wu J, Hu ZH, Carter SL, Horowitz MM, Antin JH. Tacrolimus/sirolimus versus tacrolimus/methotrexate as GVHD prophylaxis after matched, related

donor allogeneic hematopoietic cell transplantation. ***Blood*** 2014; 124:1372-7. PMC4141519.

c. Pulsipher MA, Langholz B, Wall DA, Schultz KR, Bunin N, Carroll WL, Raetz E, Gardner S, Gastier-Foster JM, Howrie D, Goyal RK, Douglas JG, Borowitz M, Barnes Y, Teachey DT, Taylor C, **Grupp SA**. The addition of sirolimus to tacrolimus/methotrexate GVHD prophylaxis in children with ALL: a phase 3 children's oncology group/pediatric blood and marrow transplant consortium trial. ***Blood*** 2014; 123: 2017-2025. PMC3968388.

d. Pulsipher MA, Carlson C, Langholz B, Wall DA, Schultz KR, Bunin N, Kirsch I, Gastier-Foster JM, Borowitz M, Desmarais C, Williamson D, Kalos M, **Grupp SA**. IgH-V(D)J NGS-MRD measurement pre- and early post-allotransplant defines very low- and very high-risk ALL patients. ***Blood*** 2015; 125:3501-8. PMC4447864.

4. **Autoimmune lymphoproliferative syndrome (ALPS)**. In addition to ALL, we have worked with ALPS patients and animal models. ALPS combines lymphoproliferation with life-threatening autoimmunity. We have shown that the autoimmune disorder Evans Syndrome is very often actually ALPS. Leveraging our ALL work, we have also shown the power of mTOR inhibition in ALPS, and out recently published pilot trial of sirolimus in ALPS supports the first-line use of this drug in ALPS.

   a. Teachey DT, Manno C, Axsom K, Andrews T, Choi J, Greenbaum B, McMann J, Sullivan K, Travis S, **Grupp SA**. Unmasking Evans syndrome: T cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). ***Blood*** 2005; 105:2443-48. PMID: 15542578.
   b. Teachey DT, Obzut DA, Axsom J, Choi JK, Hall J, Manno C, Maris JM, Rhodin N, Sullivan K, Brown VI, **Grupp SA**. Rapamycin improves lymphoproliferative disease in autoimmune lymphoproliferative syndrome (ALPS). ***Blood*** 2006; 108:1965-1971. PMC1895548.
   c. Teachey DT, Greiner R, Seif A, Attiyeh E, Bleesing J, Choi J, Manno C, Rappaport E, Schwabe D, Sheen C, Sullivan KE, Zhuang H, Wechsler DS, **Grupp SA**. 2009. Treatment with sirolimus results in complete responses in patients with autoimmune lymphoproliferative syndrome. ***Br J Haematol*** 2009; 145:101-6. PMC2819393.
   d. Seif AE, **Grupp SA**, Teachey DT. Identifying autoimmune lymphoproliferative syndrome (ALPS) in children with Evans syndrome: a multi-institutional study. ***Blood*** 2010; 115:2142-5. PMID: 20068224.

5. **CD34 selection, and stem cell transplant in neuroblastoma**. As part of my role as Medical Director of the Stem Cell lab at CHOP and Transplant Discipline Chair for COG, we have performed trials to improve outcome in neuroblastoma (NBL), a disease that has <15% long-term survival with chemo and ~35% with single autologous stem cell transplant. I developed the tandem transplant approach at CHOP, we piloted it in COG and then designed a COG national phase III trial now published in JAMA.

   a. **Grupp SA**, Stern JW, Bunin N, Nancarrow C, Ross AA, Mogul M, Adams R, Grier HE, Gorlin JB, Shamberger R, Marcus K, Neuberg D, Weinstein HJ, Diller L. Tandem high dose therapy in rapid sequence for children with high-risk neuroblastoma. ***J Clin Oncol*** 2000; 18:2567-2575. PMID: 10893288.
   b. George RE, Shuli L, Medeiros-Nancarrow C, Neuberg D, Marcus K, Shamberger RC, Pulsipher M, **Grupp SA**, Diller L. High risk neuroblastoma treated with tandem autologous peripheral blood stem cell-supported transplant: long-term survival update. ***J Clin Oncol*** 2006; 24:2891-2896. PMID: 16782928.
   c. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, Smith M, Anderson B, Villablanca JG, Matthay KK, Shimada H, **Grupp SA**, Seeger R, Reynolds CP, Buxton A, Reisfeld RA, Gillies SD, Cohn SL, Maris JM, Sondel PM. Anti-GD2 antibody with GM-CSF, IL2 and isotretinoin for neuroblastoma: a children's oncology group (COG) phase III study. ***N Engl J Med*** 2010; 363:1324-34. PMC3086629.
   d. Park JR, Kreissman SG, London WB, Naranjo A, Cohn SL, Hogarty MD, Tenney SC, Haas-Kogan D, Shaw PJ, Kraveka JM, Roberts SS, Geiger JD, Doski JJ, Voss SD, Maris JM, **Grupp SA**, Diller L. Effect of tandem autologous stem cell transplant vs single transplant on event-free survival in patients with high-risk neuroblastoma: a randomized clinical trial. ***JAMA*** 2019; 322: 746-755. PMC6714031.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41154484/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

ONGOING RESEARCH SUPPORT

First CHOP Frontier Program Children's Hospital of Philadelphia Grupp (PI) 07/15/15-06/30/21
CHOP Cancer Immunotherapy Program
The goal of this project is to advance the use of CAR and TCR engineered T cell therapy.
Role: PI

NCI P30 CA016520-43 Vonderheide (PI) 12/01/20-11/30/25
Abramson Cancer Center Support Grant
This Center grant supports the cancer research mission of the Abramson Cancer Center of the University of Pennsylvania. Dr. Grupp is the Co-Leader of the Pediatric Oncology Program at the Abramson Cancer Center.
Role: PI, pediatric program

NCI UE5 (Hexner/Manhoff/Grupp MPIs) 04/01/2020-03/31/2023 1.20 calendar
NIH/NCI $39,832 (CHOP subcontract)
The cell and gene therapy toolkit for junior faculty

NIH 5P01CA214278-02 June (PI) 07/01/17-06/30/22
Enhancing Chimeric Antigen Receptor T-Cell Therapies for Hematologic Malignancies: Beyond CART19
The goal of this project to conduct studies to uncover mechanisms of CTL019 resistance in ALL, determine mechanisms of resistance to CART T cell therapy in CLL, and perform pilot clinical trials designed to address the limitations of CAR T cell therapy in CLL and ALL, and CD19-negative escape in ALL.
Role: PI, Project 1

SU2C-St. Baldrick's Dream Team Grant St. Baldrick's Maris (PI) 12/01/17–11/30/21
Immunogenomics to Create New Therapies for Pediatric Cancers
The goal of this multi-institutional translational research project to use the power of cancer genomics to define and exploit immunotherapeutic targets in high-risk pediatric cancers.
Role: Co-Investigator

NIH/NCI 1U01CA232563-01 Thomas-Tikhonenko/Barash (PI) 09/14/18-06/30/23
Cassette exons in neoplastic pro-B cells: implications for immunotherapy
This multi-PI grant investigates the impact of alternative splicing on immunotherapy.
Role: Co-Investigator

NIH/NCI 1U01CA232361-01A1 Grupp (PI) 09/04/19-07/31/24
Defining and overcoming intrinsic T cell dysfunction to enable pediatric immunotherapy
The goal of this project is to manipulate metabolic pathways and restore mitochondrial respiratory capacity to T cells from pediatric cancer patients. This will enable the high level of proliferative capacity required for effective CAR therapy.

LLS SCOR Leukemia and Lymphoma Society June (PI) 10/01/19-09/30/24
"Pan-heme" CAR: Anti-CD38 CAR T cells for myeloid, lymphoid and plasma cell malignancies
The overall goal of this SCOR multi-project grant is to focus on the development of CD38 as a single effective approach for the treatment pediatric acute myeloid leukemia (AML), T-cell acute lymphoid leukemia (T-ALL) and multiple myeloma (MM).
Role: Co-Investigator