BIOGRAPHICAL SKETCH
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NAME: Crystal L. Mackall, M.D.

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

POSITION TITLE: Professor of Pediatrics and Medicine Stanford University

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Akron, Akron OH	B.S.	06/1980	Natural Sciences
Northeastern Ohio Univ Col of Med, Rootstown OH	M.D.	06/1984	Medicine
Akron General Med Center/ Children's Hospital of Akron, Akron OH		06/1988	Residency, Internal Medicine/Pediatrics
Pediatric Oncology Branch, National Cancer Institute, Bethesda MD		06/1992	Fellowship, Pediatric Hematology/Oncology
Experimental Immunology Branch, National Cancer Institute, Bethesda MD		06/1996	Postdoctoral Fellowship, Immunology

A. Personal Statement

I am the Ernest and Amelia Gallo Family Professor of Pediatrics and Internal Medicine at Stanford University. I serve as Founding Director of the Stanford Center for Cancer Cell Therapy, Associate Director of Stanford Cancer Institute, Leader of the Cancer Immunology and Immunotherapy Program and Director of the Parker Institute for Cancer Immunotherapy at Stanford. During my tenure as Head of the Immunology Section and Chief of the Pediatric Oncology Branch at the National Cancer Institute, I built an internationally recognized translational research program spanning basic studies of T cell homeostasis and tumor immunology, and clinical trials of immune based therapies for cancer. My work is credited with identifying an essential role for the thymus in human T cell regeneration and discovering IL-7 as the master regulator of T cell homeostasis. I have led numerous first-in-human and first-in-child clinical trials spanning dendritic cell vaccines, cytokines, and adoptive immunotherapy using NK cells and genetically modified T cells. My group was among the first to demonstrate impressive activity of CD19-CAR in pediatric leukemia (Lancet 2015), developed a novel, clinically active CD22-CAR for leukemia (Nat Med 2018), demonstrated preclinical efficacy of CARs for pediatric diffuse intrinsic pontine glioma (Nat Med 2018) and identified T cell exhaustion as a major feature limiting the activity of CAR T cells (Nat Med 2015). My work has both advanced understanding of fundamental immunology and has translated this understanding for the treatment of human disease. I has published over 185 manuscripts and serves in numerous national leadership positions, including Leader of the NCI Pediatric Cancer Immunotherapy Trials Network, and co-Leader of the St. Baldrick's-StandUp2Cancer Pediatric Dream Team. I is a member of the American Society of Clinical Investigation, American Academy of Physicians and have received numerous awards, including several NIH Director's award, the NIH Great Teachers Award and the NIH Distinguished Clinical Teacher Award. I am Board Certified in Pediatrics, Pediatric Hematology-Oncology and Internal Medicine.

B. Positions and Honors

Positions and Employment

1998-2003 Principal Investigator, Tenure Track, Pediatric Oncology Branch, NCI
2003-2015 Tenured Principal Investigator, Head Immunology Section, Pediatric Oncology Branch, NCI
2005-2008 Acting Chief, Pediatric Oncology Branch
2008-2015 Chief, Pediatric Oncology Branch
2016-present Professor, Pediatrics and Medicine, Stanford University
2016-present Associate Director, Stanford Cancer Institute

2016-present Leader, Cancer Immunology and Immunotherapy Program, Stanford University
2016-present Director, Parker Institute for Cancer Immunotherapy at Stanford School of Medicine
2017-present Founding Director, Center for Cancer Cell Therapy, Stanford University School of Medicine
2018-present Ernest and Amelia Gallo Family Professor of Pediatrics and Medicine, Stanford University

Honors and Awards (selected)

1984 Alpha Omega Alpha Honorary Medical Society
1997, 99, 00 Intramural Research Award, National Cancer Institute
2000 Distinguished Clinical Teacher Award, NIH
2000, 05 Bench-to-Bedside Research Award, NIH
2003 Mentor of Merit, NIH
2003 PHS Commendation Medal
2003, 10 NCI Director's Award
2004 Distinguished Alumni Award, NEOUCOM
2004 NIH Technology Transfer Award
2005 American Society of Clinical Investigation
2006-present Best Doctors in America
2007 NIH Merit Award
2012 Great Teacher Award, National Institutes of Health
2015 Association of American Physicians
2015 NIH G. Burroughs Mider Lecture for Distinguished NIH Intramural Research
2015 William Hathaway Visiting Professorship, Univ of Colorado
2016 Nitschke-Kaskake Viisting Professorship, Oklahoma City Children's Hospital
2017-present Chair, Pediatric Cancer Working Group, AACR
2017 Stephen Max Memorial Lecture, University of Maryland MSTP Program
2017 Warren Sutow Distinguished Lecture, MD Anderson Cancer Center

C. Contributions to Science

1. Enhancing the Efficacy and Safety of Chimeric Antigen Receptor Therapies. My group was among the first to demonstrate the remarkable potency of CD19-CAR in pediatric B-ALL and we developed a CAR targeting another pan-B cell marker CD22. I led clinical trials of CD19-CAR therapy for B-ALL at the NCI and led the work that resulted in the invention of CD22-CAR for B-ALL. I played a major role in directing the launch and execution of the first-in-human, first-in-child trial of CD22-CAR and led consensus development of what has become the gold standard toxicity grading scale for cytokine release syndrome. We have recently discovered that the GD2 ganglioside is highly overexpressed on H3K27M Diffuse Midline Gliomas, a devastating pediatric cancer for which no effective therapy exists and demonstrated that GD2-CAR T cells show impressive activity against this tumor in orthotopic xenograft models.

a) Fry TJ, Shah NN, Orentas RJ…..**Mackall CL**. CD22-CAR T Cells Induce Remissions in CD19-CAR Naïve and Resistant B-ALL, 2018, Nature Med.
b) Lee DW, Kochenderfer JN, Stetler-Stevenson M, … **Mackall CL**. T Cells Expressing CD19 Chimeric Antigen Receptors for Acute Lymphoblastic Leukemia in Children and Young Adults: A Phase I Dose-escalation Trial, 2015, Lancet, 385:517-528.
c) Lee DW….**Mackall CL**. Current Concepts in the Diagnosis and Management of Cytokine Release Syndrome, 2014, Blood, 124:188-195.
d) Mount C….**Mackall CL**. Potent antitumor efficacy of GD2-directed chimeric antigen receptor T cells in diffuse intrinsic pontine glioma, Nature Medicine, 2018.

2. Delineating Fundamental Principles that Govern Activity of Chimeric Antigen Receptor Based Therapies. My lab provided the seminal insight that costimulatory signals play a central role in modulating exhaustion in human T cells; 4-1BB provides anti-exhaustion signals whereas CD28 mediates pro-exhaustion signals, and this imparts an outsized impact on the persistence of CAR T cells. This work also identified antigen independent tonic signaling as a significant factor limiting the efficacy of CAR T cells. We further identified limiting antigen expression levels as a major cause of resistance to CAR based therapies and developed the first bispecific chimeric antigen receptor to enter the clinic.

a) Long A, Haso W.M., Shern J.F., … **Mackall CL**, 4-1BB Costimulation Ameliorate T Cell Exhaustion Induced by Antigen Independent Signaling of Chimeric Antigen Receptors, Nat Med, 2015, 21:581-90.

b) Walker AJ, Mazjner TG, Zhang L,…..**Mackall CL**, Tumor Antigen and Receptor Densities Regulate Efficacy of a Chimeric Antigen Receptor Targeting Anaplastic Lymphoma Kinase. Mol Ther, 2017.
c) Patent: Dual Specific Anti-CD22-Anti-CD19-Chimeric Antigen Receptors, US Patent Application No 62/135,442 filed March 29, 2015
d) Patent: M971 Chimeric Antigen Receptors, US Patent Application No. 61/717,960 filed Oct 24, 2012, Patent Pending: 61/717,960; E291-2012/0

3. IL-7 has potent immunorestorative properties and induces an anti-aging effect by broadening T cell repertoire diversity and diminishes regulatory T cells. I led first-in-human and first-in-child trials of this drug. Pharmacologic dosing of IL-7 safely and reversibly expands total body T cell numbers, induces anti-aging effects on the T cell repertoire, and diminishes the frequencies of regulatory T cells, without any clinical evidence for capillary leak syndrome. IL-7's properties render it a superior T cell growth support cytokine compared to interleukin-2.

a) Zhang H, Chua K, Guimond M, …. **Mackall CL**, Lymphopenia and IL2 Therapy Alter Homeostasis of $CD4^+CD25^+$ Regulatory T Cells. Nature Medicine, 2005, 11:1238-1243.
b) Sportès C, Hakim FT, Memon SA, …. **Mackall CL**. Administration of rhIL-7 in Humans Increases in vivo TCR Repertoire Diversity by Preferential Expansion of Naïve T-cell Subsets, 2008, Journal of Experimental Medicine, 205:1701-1714.
c) Sportès C, Babb RR, …., **Mackall CL** and Gress RE, Phase I study of recombinant human interleukin-7 administration in subjects with refractory malignancy, 2010, Clin Can Res, 16:727-735.
d) **Mackall CL**, Fry TJ, Gress RE. Harnessing the biology of IL-7 for therapeutic application, Nature Reviews Immunology, 2011, 11:330-342.

4. IL7 is the Master Regulator of T Cell Homeostasis This work demonstrated that lymphopenia induces elevations in IL-7 through diminished consumption and that increased IL-7 increases total body T cell numbers through enhanced homeostatic and cognate antigen driven expansion. It also demonstrated an important role for soluble interleukin-7 receptor in modulating peripheral T cell responses and in predisposing to autoimmunity. This novel paradigm provided the fundamental basis for incorporating lymphodepleting therapies into modern adoptive cell therapy protocols. This work was performed in my laboratory with myself providing the scientific oversight.

a) Fry TJ, Connick E, Falloon J, … **Mackall CL**. A potential role for IL-7 in T cell homeostasis. Blood, 2001; 97:2983-2990.
b) Melchionda F, Fry TJ, … **Mackall CL**, Immunizing with IL7 Overcomes Immunodominance and Improves Survival of the Memory Cell Pool. Journal of Clinical Investigation, 2005, 115:1177-1187.
c) Guimond MS, Veenstra RG, ….**Mackall CL**, IL-7 Signaling on IL-7R□DCs Regulates the Naïve CD4 Niche Controlling Homeostatic Peripheral Expansion, 2009, Nature Immunology, 10:149-157.
d) Lundstrom W, Highfill S, …. **Mackall CL**, Soluble *IL7Ra* Potentiates IL-7 Bioactivity and Promotes Autoimmunity, 2013, Proceedings of the National Academy of Sciences, 110:E1761-70.

5. Age associated thymic involution is the fundamental factor limiting regeneration of T cell populations. This work delineated the primary pathways of immune reconstitution in humans, identified an essential role for thymopoiesis in the restoration of human T cell immune restoration, and led to an understanding of the factors which limit the efficiency of thymic-independent pathways of immune reconstitution. It provided the foundation for the discovery that lymphodepleting therapies lead to alterations in immune physiology that support augmented T cell expansion, which provides the basis for incorporation of lymphodepleting therapie into the backbone of all effective adoptive cell therapies utilized today. This work was completed while I was a fellow in Ron Gress' laboratory.

a) **Mackall CL**, et al. CD45 isoform expression on thymic-derived versus thymic-independent progeny. Blood, 1993, 82:2585-2594.
b) **Mackall CL**, et al. N Engl J of Medicine, 1995, 332:143-149. Comment: Mackall CL, Steinberg SM, Gress RE. Regeneration of T cells after chemotherapy. New England Journal of Medicine, 1995, 332:1652.
c) **Mackall CL**, et al. J Immunol, 1996, 156:4609-4616.
d) Hakim FT, Memon SA, ….**Mackall CL**, Gress RE. Age Dependent Incidence, Time Course and Consequences of Thymic Renewal in Adults. Journal of Clinical Investigation, 2005, 115:930-939.

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/1pU7A4uuqsfka/bibliography/49606318/public/?sort=date&direction=descending

D. Research Support

ACTIVE

CLIN2-10846 (PI: Mackall) 9/1/2017-8/30/2020
California Institute for Regenerative Medicine
CD19/CD22 Bispecific CAR T cells for Adults with B Cell Malignancies

U54 CA232568 (MPI: Maris and Mackall) 7/1/2018-6/30/2023
NIH/NCI
Discovery and Development of Optimal Immunotherapeutic Strategies for Childhood Cancers

2UM1 CA154967-07 (PI: Cheever, PedCITN PI: Mackall) 10/1/17-9/30/21
NIH/NCI
Pediatric Cancer Immunotherapy Trials Network

P01 CA217959-01 (PI: Maris and Seeger, Mackall: Project Co-PI) 9/1/2017– 8/30/2022
New Therapeutics for High Risk Neuroblastoma

SU2C-AACR-DT1113 (MPI: Mackall and Maris) 7/1/13 – 9/30/21
St.Baldrick's Foundation/Lucilie Packard Children's
Immunogenomics to Create New Therapies for High-Risk Childhood Cancers

5P30CA124435 Mitchell (PI); Mackall (Program Leader) 6/4/2007 – 5/31/2021
NIH/NCI
Stanford Cancer Institute
I lead the SCI Cancer Immunology and Immunotherapy Program.

U24-CA224309-01 Macker (PI); Mackall (Co-I) 9/1/2017– 7/2/2022
NIH/NCI; (CIMACs) Cancer Immune Monitoring Center at Stanford
Role: AI

U01-FP00013560_SUB80_01 Adamson (PI); Mackall (Study Chair) 1/1/2016 – 12/31/2018
NIH/NCI
Children's Oncology Group Phase I Consortium
A Phase I Study of Nivolumab with or without Ipilimumab in Children with Refractory Cancer

Parker Institute for Cancer Immunotherapy (PICI), Mackall (Institute Director) 9/1/2016 – 8/31/2021
I direct the Parker Institute for Cancer Immunotherapy at the Stanford School of Medicine.

PICI Research Project Mackall (PI) 9/1/2016 – 8/31/2018
Addressing Target Antigen Heterogeneity to Enhance Efficacy of CAR T Cells Against Solid Tumors
The goal of this project is to optimize approaches to engineer multivalent and multi-specific chimeric antigen receptors to address antigen loss escape.

PICI Correlative Science Unit Mackall (PI) 9/1/2016 – 8/31/2020
The goal of this project is to provide infrastructure to conduct studies on clinical samples obtained as part of cancer immunotherapy trials at Stanford.

Obsidian Therapeutics Mackall (PI) 11/1/2017-11/1/2019
Assessment of in vitro and in vivo Activity of hDHFR/PDE5-Regulated CARs
This project will assess the effects of regulating CAR expression levels on functionality.

Alliance for Cancer Gene Therapy Mackall (PI) 9/1/2016 – 8/31/2019
GD2 Chimeric Antigen Receptor Therapy for Osteosarcoma

The goal of this project is to perform preclinical work and initiate a clinical trial of an optimized chimeric antigen receptor targeting GD2 in pediatric and young adult patients with osteosarcoma and neuroblastoma.

Ludwig Institute for Cancer Research Weissman (PI); Mackall (Project PI) 01/01/16-12/31/19
Reversing T Cell Exhaustion
The major goals of this project are to explore the biology of T cell exhaustion in the setting of a tonically signaling chimeric antigen receptor.

COMPLETED

NIH ZIA BC 011498 Mackall (PI) 07/01/97-12/31/15
Clinical Trials of Immunotherapies for Childhood Cancer
This project funded the clinical research efforts of the Mackall laboratory focused on the development of immunotherapies for childhood cancer.

NIH ZIA BC 011073 Mackall (PI) 07/01/97-12/31/15
Immunobiology and Immunotherapy of Pediatric Cancer
This project seeks to identify appropriate antigens for targeting pediatric tumors, investigate factors that limit the effectiveness of immune responses directed toward childhood cancer and create new therapeutics that can be translated to the clinic.

NIH ZIA BC 011069 Mackall (PI) 07/01/97-12/31/15
Biology and Therapy of Lymphopenia
The goals of this project are to address critical barriers to progress in the study of T cell homeostasis by improving understanding of the biology of T cell depletion and by developing new therapies to improve immune reconstitution or that could replicate the beneficial aspects of lymphopenia while avoiding long-term detrimental effects.

Bluebird Bio Mackall (PI) 11/1/2016 – 10/31/2017
Enhancing CAR Responses to Solid Tumors by Modulating Immunosuppression and Exhaustion
The goals of this project are to develop CAR expressing T cells which have been engineered to be unresponsive to TGFbeta and IL10 via megaTAL technology.

Emerson Collective Mackall (PI); 9/1/2016 – 8/31/2018
Identification of Exhaustion Checkpoints in CAR Expressing T Cells Using CRISPR/Cas9 Gene Disruption
The goal of this project is to use CRISPR to target candidate genes overexpressed in exhausted CAR expressing T cells to explore functional consequences of gene editing.

Stand Up to Cancer Mackall (PI) 7/1/2016 – 6/30/2018
Phil Sharpe Award for Scientific Collaboration
The goal of this project is to conduct correlative science on a clinical trial of nivolumab in children with biallelic mismatch repair deficiency.