BIOGRAPHICAL SKETCH

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NAME: Crystal L. Mackall, M.D.

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POSITION TITLE: Ernest and Amelia Gallo Family Professor of Pediatrics and Medicine Stanford University

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 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 Medicine at Stanford University, the Founding Director of the Stanford Center for Cancer Cell Therapy, Associate Director of the Stanford Cancer Institute, Leader of the Cancer Immunotherapy Program and Director of the Parker Institute for Cancer Immunotherapy @ Stanford. During a 27-year tenure at NCI culminating as Chief of the Pediatric Oncology Branch and Head of the Immunology Section and since 2016 at Stanford, I've led an internationally recognized translational research program focused on immune-oncology. My work has advanced understanding of fundamental immunology and translated this understanding for the treatment of human disease with a major focus on children's cancers. I've 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 work is credited with identifying an essential role for the thymus in human T cell regeneration (NEJM 1995) and discovering IL-7 as the master regulator of T cell homeostasis (Blood 2001, J Exp Med 2008). My group was among the first to demonstrate impressive activity of CD19-CAR in pediatric leukemia (Lancet 2015), developed a CD22-CAR that is the only active salvage therapy for CAR19 resistant B cell malignancies (Nat Med 2018, J Clin Onc 2020, Blood 2021), demonstrated preclinical activity of GD2 targeting CARs for pediatric diffuse intrinsic pontine glioma (Nat Med 2018), demonstrated superiority of regional CNS delivery of CAR T cells for brain tumors (Nat Med 2020) and demonstrated impressive clinical activity of GD2-CAR T cells in this disease (NCT04196413), which is among the first to demonstrate significant and consistent activity of CAR T cells in solid cancers (Nature 2022). My group identified T cell exhaustion as a major feature CAR T cell potency (Nat Med 2015), created the first exhaustion-resistance (Nature 2019) and exhaustion-reversal platforms (Science 2021), developed a best-in-class regulatable "remote-controlled" CAR T cell platform (Cell, 2022) and discovered a role for mediator kinase in regulating T cell differentiation (Science 2022). I have received numerous awards, including election as a member of the National Academy of Medicine, a Fellow of the AACR Academy, and election to the American Association of Physicians and the American Society of Clinical Investigation. I received the Smalley Award for outstanding contributions to cancer immunotherapy from the Society for the Immunotherapy of Cancer, the AACR-St.Baldrick's Distinguished Achievement Award for Pediatric Cancer Research, and the Nobility in Science Award from the Sarcoma Foundation of America. I have founded 3 biotech companies to translate my discoveries. I have published over 250 manuscripts and my h-index in November 2022 according to google scholar is 96. I am Board Certified in Pediatrics, Pediatric Hematology-Oncology and Internal Medicine.

Ongoing and recently completed projects that I would like to highlight include:

1 R01 CA263500-01 Mackall, Monje (MPI) 07/01/2021 - 06/30/2026
National Institutes of Health
Developing Safe and Effective GD2-CAR T Cell Therapy for Diffuse Midline Gliomas
Major Goals: To test GD2-CAR therapies in diffuse midline gliomas and identify biomarkers of response.
Role: PI

CLIN2-12595 Mackall (PI) 6/1/2018-5/31/2022
California Institute for Regenerative Medicine
GD2-CAR T cells for Diffuse Midline Gliomas
Aim/Goal: This award funds a Phase I clinical trial of the CD19/22 CAR in Adults with Relapsed/Refractory B cell malignancies and conducts correlative studies to define the basis for resistance.
Role: PI

U54 CA232568-01 Mackall, Maris (MPI) 07/01/2018 - 06/30/2023
NIH/NCI
Discovery and Development of Optimal Immunotherapeutic Strategies for Childhood Cancers
Aim/Goal: This is a Multi-institutional Center grant to discover new immunotherapeutic strategies for childhood cancers as part of the Pediatric Immunotherapy Discovery and Development Network, Cancer Moonshot Program.
Role: PI

2UM1CA154967-07 (PI: Cheever, Ped CITN PI: Mackall) 9/01/2017 – 08/31/2022
NIH/NCI
Pediatric Cancer Immunotherapy Trials Network
Aim/Goal: I lead the multi-institutional clinical trial consortium that will undertake studies of immune based therapies for pediatric cancers.
Role: Inaugural Consortium Chair

SU2C-AACR-DT1113 Maris/Mackall (MPI) 12/01/2017 – 11/30/2021
St.Baldrick's Foundation/Lucile Packard Children's
Immunogenomics to Create New Therapies for High-Risk Childhood Cancers
Aim/Goal: Dr. Mackall serves as a Dream Team Co-Leader for this multi-institutional translational research project to use the power of cancer genomics to define and exploit immunotherapeutic targets in high-risk pediatric cancers. The project focuses on clinical trials and late IND-enabling preclinical studies and was awarded the 2021 AACR Team Science Award.
Role: Team Co-Leader

Parker Institute for Cancer Immunotherapy@Stanford (PI: Mackall) 09/01/2016 – 08/31/2022
The institute conducts fundamental and translational studies of cancer immunotherapy through collaborations within Stanford and at Parker Institute Centers throughout the US.
Role: Institute Director

Citations:

1. Labanieh L, Majzner RG, Klysz D, Sotillo E, Vilches-Moure JG, Pacheco KZ, Hui JH, Malipatlolla M, Xu P, Murty T, Theruvath J, Weber EW, Heitzeneder S, Parker KR, Satpathy AT, Lin MZ, Cochran JR, and **Mackall CL**, Enhanced safety and efficacy of protease-regulated CAR-T cell receptors (2022), Cell, Apr 20:S0092-8674(22)00391-9. doi: 10.1016/j.cell.2022.03.041. PMID: 35483375
2. Majzner RG*, Ramakrishna S*, Yeom K, Patel S, Chinnasamy H, Schultz L, Richards R, Barsan V, Mancusi R, Jiang L, Geraghty A, Good Z, Mochizuki A, Gillespie S, Toland AMS, Mahdi J, Reschke A, Nie E, Chau I, Rotiroti MC, Mount CM, Baggott C, Mavroukakis S, Egeler E, Moon J, Erickson C, Green S, Kunicki M, Fujimoto M, Ehlinger Z, Reynolds W, Kurra S, Warren KE, Prabhu S, Vogel H, Rasmussen L, Cornell TT, Partap S, Fisher P, Campen C, Filbin M, Grant G, Sahaf B, Kara L. Davis KL, Steven A. Feldman SA, **Mackall CL#**, Monje M#, GD2-CAR T-cell therapy for H3K27M-mutated diffuse midline gliomas (2022), Nature 603(7903):934-941, PMID: 35130560.
3. Heitzeneder S, Bosse KR, Zhongyu Z, Zhelev D, Dhingra S, Majzner RG, Sotillo E, Buongervino S, Xu P, Huang J, Salzer B, Delaidelli A, Hasselblatt M, Parker K, Anbunathan H, Alag A, Hwang J, Huang M, Klysz DD, Theruvath JL, Vilches J, Satpathy AS, Lehner M, Taschner-Mandl S, Dimitrov DS, Maris JM, **Mackall**

CL, GPC2-CAR T Cells Tuned for Low Antigen Density Mediate Potent Activity Against Neuroblastoma Without Toxicity (2022) Cancer Cell, Jan 10;40(1):53-69.e9. PMID: 34971569.

4. Weber EW, Parker KR, Sotillo E, Lynn RC, Anbunathan H, Lattin J, Good Z, Belk JA, Daniel B, Klysz D, Malipatlolla M, Xu P, Bashti M, Heitzeneder S, Labanieh L, Vandris P, Majzner RG, Qi Y, Sandor K, Chen LC, Gentles AJ, Wandless TJ, Satpathy AT, Chang HY, **Mackall CL** (2021), Transient rest restores functionality in exhausted CAR-T cells via epigenetic remodeling, Science. 372(6537):eaba1786. doi: 10.1126/science.aba1786. PMID: 33795428.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments (selected)

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, NCI
2008-2015	Chief, Pediatric Oncology Branch, NCI
2016-present	Endowed Professor, Pediatrics and Medicine, Stanford University
2016-present	Associate Director, Stanford Cancer Institute
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
2020-present	Co-Executive Director, Laboratory for Cell and Gene Medicine, Stanford University

Honors (selected)

1984-present	Alpha Omega Alpha Honorary Medical Society
2000	Distinguished Clinical Teaching Award, National Institutes of Health
2003, 10, 13	Director's Awards, National Cancer Institute
2012, 2021	Great Teacher Award Lecture, National Institutes of Health
2015	NIH G. Burroughs Mider Lecture, Honoring a Distinguished NIH Intramural Research Scientist
2018	Top 10 Clinical Research Award
2019	Lila and Murray Gruber Memorial Cancer Research Award and Lectureship, American Academy of Dermatology
2021	AACR-St. Baldrick's Foundation Award for Outstanding Achievement in Pediatric Cancer Research
2021	Pediatrics Oncology Award and Lecture, American Society of Clinical Oncology
2021	Team Science Award, AACR, St.Baldrick's-Su2C Pediatric Cancer Dream Team
2021	Richard V. Smalley Award and Lectureship, The Society for the Immunotherapy of Cancer's "most prestigious award to a clinician/scientist and luminary in the field who has significantly contributed to the advancement of cancer immunotherapy research"
2022	AACR Academy of Fellows
2022	Nobility in Science Award, Sarcoma Foundation of America

C. Contributions to Science

1. Development of Chimeric Antigen Receptor Therapies for B cell malignancies. My group was among the first to demonstrate the potency of CD19-CAR in pediatric B-ALL, and in response to toxicity observed in these early trials, I led consensus development of the first toxicity grading scale for cytokine release syndrome. Noting relapse with antigen negative leukemia, my group developed a novel CAR targeting CD22, another pan-B cell marker, and conducted first-in-human and first-in-child trials of the CD22-CAR for B-ALL, which demonstrated complete response rates of 70%. This agent has been awarded Breakthrough Therapy designation from the FDA. My group has also demonstrated that the CD22-CAR mediates potent activity in CAR19 refractory large B cell lymphoma refractory to CAR19 therapy.

a) Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, Fry RJ, Orentas R, Sabatino M, Shah NN, Steinberg SM, Stroncek D, Yuan C, Zhang L, Rosenberg SA, Wayne AS, **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. 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.

b) Fry TJ, Shah NN, Orentas RJ, Stetler-Stevenson M, Yuan CM, Ramakrishna S, Wolters P, Peron-Martin S, Delbrook C, Yates B, Shalabi H, Fountaine TJ, Shern JF, Majzner RG, Stroncek DF, Sabatino M, Feng Y, Dimitrov DS, Zhang L, Nguyen S, Qin H, Dropulic B, Lee DW, and **Mackall CL (2018)**. CD22-CAR T Cells Induce Remissions in CD19-CAR Naïve and Resistant B-ALL, 2018, Nature Med.

c) Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, Grupp SA, **Mackall CL**, **(2014)**. Current Concepts in the Diagnosis and Management of Cytokine Release Syndrome, 2014, Blood, 124:188-195.

d) [$]Spiegel JY, [$]Patel S, [$]Muffly L, Hossain N, Oak J, Baird JH, Frank M, Shiraz P, Sahaf B, Craig J, Iglesias M, Younes S, Natkunam Y, Ozawa MG, Yang E, Tamaresis J, Chinnasamy H, Ehlinger Z, Reynolds W, Lynn R, Arai S, Johnston L, Lowsky R, Majzner RG, Meyer E, Negrin RS, Rezvani AR, Sidana S, Shizuru J, Weng WK, Mullins C, Jacob A, Kirsch I, Schultz L, Ramakrishna S, Davis KL, Kong KA, Shah NN, Qin H, Fry T, *Feldman S, ***Mackall CL** (2021), *Miklos DB, Dual Targeting CD19/CD22 Chimeric Antigen Receptor T cells in Adults with Recurrent or Refractory B cell Malignancies, 2021, Nature Medicine, DOI: 10.1038/s41591-021-01436-0.

2. Defining Pathways of Resistance to CAR Based Therapies and Engineering Next Generation Therapeutics to Improve Efficacy. My lab discovered that CAR T cells are predisposed to exhaustion due to antigen independent tonic signaling, that exhaustion limits the efficacy of CAR T cells and that costimulatory signals play a central role in modulating exhaustion in human T cells. We discovered that an imbalance in AP-1/IRF transcription factors drives dysfunction in exhausted T cells, developed a novel platform for exhaustion resistance using c-Jun overexpression and have challenged the paradigm that exhaustion is an epigenetically fixed state by demonstrating that transient cessation of CAR signaling reverses exhaustion physiology and epigenetic changes induced by exhaustion. We also demonstrated that insufficient trafficking of CAR T cells in CNS tumors can be overcome by intracerebroventricular administration, paving the way for more effective application of CAR T cell therapeutics for the treatment of brain tumors.

a) Long A, Haso W.M., Shern J.F., Wanhainen K.M., Murgai M., Ingaramo M., Smith J.P., Walter A.J., Kohler M.E., Venkateshwara V.R., Kaplan R.N., Patterson G.H., Fry T.J., Orentas R.J., **Mackall C.L**., 4-1BB Costimulation Ameliorates T Cell Exhaustion Induced by Antigen Independent Signaling of Chimeric Antigen Receptors, Nat Med, 2015, 21:581-90.

b) Lynn RC, Weber EW, Gennert D, Sotillo E, Good Z, Anbunathan H, Jones R, Tieu V, DeBourcy C, Xu P, Majzner R, Satpathy AT, Quake SR, Chang H, **Mackall CL**, c-Jun Overexpressing CAR-T Cells are Exhaustion-Resistant and Mediate Enhanced Antitumor Activity, Nature, 2019, 576:293-300.

c) Theruvath J, Sotillo E, Mount CW, Graef CM, Delaidelli A, Heitzeneder S, Labanieh L, Majzner RG, Xu P, Mueller S, Yecies DW, Finetti MA, Williamson D, Johann PD, Kool M, Pfister S, Hasselblatt M, Frühwald MC, Mitra SS, Cheshier S, Sorensen PH, Monje M, **Mackall CL**, Locoregionally Administered B7-H3-targeting CAR T Cells Mediate Potent Antitumor Effects in Atypical Teratoid/Rhabdoid Tumor, Nat Med, 2020, 26:712-719.

d) Weber EW, Parker KR, Sotillo E, Lynn RC, Anbunathan H, Lattin J, Good Z, Belk JA, Daniel B, Klysz D, Malipatlolla M, Xu P, Bashti M, Heitzeneder S, Labanieh L, Vandris P, Majzner RG, Qi Y, Sandor K, Chen LC, Gentles AJ, Wandless TJ, Satpathy AT, Chang HY, **Mackall CL**, Transient “rest” induces functional reinvigoration and epigenetic remodeling in exhausted CAR-T cells, Science, 2021, 372(6537):eaba1786.

3. Development of Immunotherapeutics for Solid Pediatric Cancers

I led the first and only multicenter trial of nivolumab in pediatric cancer undertaken thus far, which demonstrated safety and activity in some pediatric lymphomas, but a lack of efficacy in sporadic pediatric solid tumors. I led the multicenter study of NY-ESO-1 engineered T cells for synovial sarcoma and demonstrated impressive polyclonal persistence of the engineered population. My group discovered that diffuse intrinsic pontine gliomas demonstrate dramatic overexpression of the GD2 ganglioside, that CARs targeting GD2 show potent activity in preclinical models and have moved this discovery forward to a first-in-child clinical trial.

a) D’Angelo SP, Melchiori L, Merchant MS, Bernstein D, Glod J, Grupp S, Tap WD, Chagin K, Binder-Scholl GK, Basu S, Lowther DE, Wang R, Bath N, Tipping A, Betts G, Ramachandran I, Navenot JM, Zhang H, Wells DK, van Winkle E, Kari G, Trivedi T, Holdich T, Pandite L, Amado R, **Mackall CL,** Antitumor activity associated with prolonged persistence of adoptively transferred NY-ESO-1c259 T cells in synovial sarcoma 2018, Cancer Discovery,2018,8:944-957.

b) Davis KL, Fox E, Reid JM, Kudgus RA, Liu X, Minard CG, Voss S, Berg SL, Weigel BJ, **Mackall CL**, A Phase I/II Trial of Nivolumab in Children and Young Adults with Relapsed/Refractory Solid Tumors: A Children’s Oncology Group Pediatric Early Phase Clinical Trial Network Study, ADVL1412, Lancet Oncology, 2020, 21:541-550.

c) Majzner RG*, Ramakrishna S*, Yeom K, Patel S, Chinnasamy H, Schultz L, Richards R, Barsan V,

Mancusi R, Jiang L, Geraghty A, Good Z, Mochizuki A, Gillespie S, Toland AMS, Mahdi J, Reschke A, Nie E, Chau I, Rotiroti MC, Mount CM, Baggott C, Mavroukakis S, Egeler E, Moon J, Erickson C, Green S, Kunicki M, Fujimoto M, Ehlinger Z, Reynolds W, Kurra S, Warren KE, Prabhu S, Vogel H, Rasmussen L, Cornell TT, Partap S, Fisher P, Campen C, Filbin M, Grant G, Sahaf B, Kara L. Davis KL, Steven A. Feldman SA, **Mackall CL#**, Monje M#, GD2-CAR T-cell therapy for H3K27M-mutated diffuse midline gliomas, Nature. 2022 Mar;603(7903):934-941. PMID: 35130560.

d) Heitzeneder S, Bosse KR, Zhongyu Z, Zhelev D, Dhingra S, Majzner RG, Sotillo E, Buongervino S, Xu P, Huang J, Salzer B, Delaidelli A, Hasselblatt M, Parker K, Anbunathan H, Alag A, Hwang J, Huang M, Klysz DD, Theruvath JL, Vilches J, Satpathy AS, Lehner M, Taschner-Mandl S, Dimitrov DS, Maris JM, **Mackall CL**, GPC2-CAR T Cells Tuned for Low Antigen Density Mediate Potent Activity Against Neuroblastoma Without Toxicity, Cancer Cell. 2022 Jan 10;40(1):53-69. PMID: 34971569.

4. IL-7 is the master regulator of T cell homeostasis and has potent immunorestorative properties. My work defined the fundamental biology of T cell homeostasis in humans and discovered that IL-7 is a master regulator of this system. This work served as the foundational science supporting the incorporating of lymphodepleting regimens into current adoptive cell therapy strategies.

a) Fry TJ, Connick E, Falloon J, Lederman MM, Liewehr DJ, Spritzler J, Steinberg SM, Wood LV, Yarchoan R, Zuckerman J, Landay A and **Mackall CL**. A potential role for IL-7 in T cell homeostasis. Blood, 2001; 97:2983-2990.

b) Melchionda F, Fry TJ, Milliron M, McKirdy, Tagaya Y, **Mackall CL**, Immunizing with IL7 Overcomes Immunodominance and Improves Survival of the Memory Cell Pool. Journal of Clinical Investigation, 2005, 115:1177-1187.

c) Zhang H, Chua K, Guimond M, Kapoor V, Brown MR, Fleisher TA, Long LM, Bernstein D, Hill BJ, Douek DC, Berzofsky JA, Carter CS, Read EJ, Helman LJ, and **Mackall CL**, Lymphopenia and IL2 Therapy Alter Homeostasis of $CD4^+CD25^+$ Regulatory T Cells. Nature Medicine, 2005, 11:1238-1243.

d) Sportès C, Hakim FT, Memon SA, Zhang H, Chua KS, Brown MR, Fleisher TA, Krumlauf MC, Babb RR, Chow CK, Fry TJ, Engels J, Buffet R, Morre M, Amato RJ, Venzon DJ, Korngold R, Pecora A, Gress RE, **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.

5. Thymic insufficiency is the fundamental factor limiting T cell regeneration in humans. My work delineated the primary pathways of immune reconstitution in humans, identified an essential role for thymopoiesis in human T cell immune restoration, and defined the factors limiting the efficiency of thymic-independent pathways of immune reconstitution. This work was completed while I was a fellow in Ron Gress' laboratory.

a) **Mackall CL**, Granger, L, Sheard MA, Cepeda R and Gress RE. CD45 isoform expression on thymic-derived versus thymic-independent progeny. Blood, 1993, 82:2585-2594.

b) **Mackall CL**, Fleisher TA, Brown MR, Andrich MP, Chen CC, Feuerstein IM, Horowitz ME, Magrath IT, Shad AT, Steinberg SM, Wexler LH and Gress R.E. Regeneration of T cells after chemotherapy. New England Journal of Medicine, 1995, 332:1652.

c) **Mackall CL**, et al. Thymic-independent T cell regeneration occurs via antigen-driven expansion of peripheral T cells resulting in a repertoire that is limited in diversity and prone to skewing. J Immunol, 1996, 156:4609-4616.

d) Hakim FT, Memon SA, Cepeda R, Jones EC, Chow CK, Kasten-Sportes C, Odom J, Vance BA, Christensen BL, **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/myncbi/1pU7A4uuqsfka/bibliography/public/