BIOGRAPHICAL SKETCH

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NAME: Ronald A. DePinho, MD

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

POSITION TITLE: Professor and Past President, MD Anderson Cancer Center, University of Texas, USA

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
Fordham College, Bronx, NY	B.S.	06/1977	Biology
Albert Einstein College of Medicine, Bronx, NY	M.D.	06/1981	Medicine
Harvard University, Cambridge, MA	MS(hon)	1998	
Hofstra University, New York, NY	PhD (hon)	2017	

A. Personal Statement

Our basic and translational research program focuses on pathways and processes governing aging and age-related disorders, particularly cancer. Our experimental approach is built upon the use of unbiased computational analyses of multi-dimensional datasets, genetically engineered mouse models, and human-mouse comparisons on the molecular, cellular and physiological levels. Through MD Anderson's Institute for Applied Cancer Science, we strive to drive basic discoveries to therapeutic and diagnostic endpoints in a systematic action-oriented culture. Our activities have focused on (i) defining the role of telomeres in governing cancer genome alterations, epithelial carcinogenesis, aging and degenerative disorders (both acquired and inherited); (ii) utilizing genetically engineered mouse (GEM) models to study human cancers with an emphasis on comparative oncogenomics and proteomics to discover and ultimately validate new genes for enlistment into drug discovery, early detection or prognostic biomarkers; here, there is a focus on colorectal, pancreatic, and prostate cancers; and (iii) elucidating pathways that orchestrate aging and age-related disorders with the goal of therapeutically manipulating such pathways to attenuate the incidence of age-associated diseases such as cancer and neurodegeneration. Our mission is to convert basic knowledge into clinical endpoints that will impact on patient outcomes in meaningful ways.

Over my career I have mentored many successful graduate and postgraduate trainees, totaling 12+ graduate students and >40 postdoctoral fellows – the majority of whom now hold independent positions in academic institutions and in industry. A partial list of their current affiliations includes NYU Medical Center, Massachusetts General Hospital, Stanford University, Yale, Dana-Farber Cancer Institute, University of North Carolina, UT Southwestern, Baylor College of Medicine, Cornell University, MD Anderson Cancer Center, amongst others. Proudly, nearly all of my trainees have published papers from their laboratories in top journals, have secured federal support for their programs, and have received tenure or major leadership positions in the cancer field at their institutions, including cancer center directorships and departmental chairs.

Several key foundational papers from my laboratory include:

a. Maser RS, Choudhury B, Campbell PJ, Feng B, Wong KK, Protopopov A, O'Neil J, Gutierrez A, Ivanova E, Perna I, Lin E, Mani V, Jiang S, McNamara K, Zaghlul S, Edkins S, Stevens C, Brennan C, Martin ES, Wiedemeyer R, Kabbarah O, Nogueira C, Histen G, Aster J, Mansour M, Duke V, Foroni L, Fielding AK,

Goldstone AH, Rowe JM, Wang YA, Look AT, Stratton MR, Chin L, Futreal PA, DePinho RA (2007) Chromosomally unstable mouse tumours have genomic alterations similar to diverse human cancers. ***Nature***, 447(7147): 966-971. PMCID: PMC2714968

b. Chin L, Tam A, Pomerantz J, Wong M, Holash J, Bardeesy N, Shen Q, O'Hagan R, Pantginis J, Zhou H, Horner JW 2nd, Cordon-Cardo C, Yancopoulos GD, DePinho RA (1999) Essential role for oncogenic Ras in tumour maintenance. ***Nature***, 400(6743): 468-472.

c. Lee HW, Blasco MA, Gottlieb GJ, Horner JW 2nd, Greider CW, DePinho RA (1998) Essential role of mouse telomerase in highly proliferative organs. ***Nature***, 392(6676): 569-574.

d. Serrano M, Lee H, Chin L, Cordon-Cardo C, Beach D, DePinho RA (1996) Role of the INK4a locus in tumor suppression and cell mortality. ***Cell***, 85(1): 27-37.

B. Positions and Honors

Positions and Employment

1984-1988	Postdoctoral Fellow: 1) Dr. Matthew Scharff, Cell Biology, AECOM; 2) Dr. Frederick Alt, Biochemistry and Biophysics, College of Physicians and Surgeons of Columbia University
1988-1993	Assistant Professor, Microbiology, Immunology and of Medicine, AECOM
1988-1997	Attending Physician, Bronx Jacobi Hospital, AECOM
1993-1997	Associate Professor, Microbiology, Immunology and of Medicine, AECOM
1997-1998	Professor, Microbiology, Immunology and of Medicine, AECOM
1998-2011	Professor, Medicine (Genetics), DFCI, Harvard Medical School
2004-2011	Director, Belfer Institute for Applied Cancer Science, Dana-Farber Cancer Institute
2011-2017	President, University of Texas MD Anderson Cancer Center
2011-	Professor, Cancer Biology, MD Anderson Cancer Center, University of Texas

Other Experience and Professional Memberships

1988-1998	Scientific Director and Founder, Transgenic Mouse and Gene Targeting Facilities, AECOM
1991-1997	Organizer and Director, NCI-Sponsored Mouse Developmental Genetics Course, AECOM
1998-2008	American Cancer Society Research Professor
1998-2011	Scientific Director, Transgenic and Gene Targeting, DFCI
1999-2004	Scientific Director, Mouse Specialized Services, DF/HCC
2002-2004	Co-Chair, Gastrointestinal Cancer Program, DF/HCC
2002	Co-Organizer, Keystone Conference: Genomics and Genetics of Senescence and Cancer
2002	Co-Organizer, Cold Spring Harbor Laboratories Molecular Genetics of Aging
2003	Co-Organizer, Lustgarten Foundation Pancreatic Cancer
2003	Co-Organizer, AACR Conference on Mouse Models of Cancer
2006	Co-Organizer, AACR Conference on Mouse Models of Cancer
2007	Chair, AACR Centennial Anniversary Annual Meeting
2007-2010	Chair, Section 2 (Basic Sciences), Institute of Medicine Membership Committee

Advisory Boards

Scientific Advisory Board: Sidney Kimmel Foundation; Past Editorial Boards: Cancer Cell; Cancer Discovery; Genes & Development; Mechanisms of Ageing and Development; Aging; International Journal of Oncology; Neoplasia; Molecular Cancer Research; Oncotarget; EBioMedicine, Cell Press and Lancet.

Honors (partial list)

1990: Feinberg Sr. Faculty Scholar in Cancer Research. **1991**: American Heart Association Established Investigator Award. **1993**: Melini Award for Excellence in Biomedical Research. **1995**: Irma T. Hirschl Career Scientist Award. **1998**: American Cancer Society Research Professorship. **2000**: Kirsch Investigator Award. **2002**: American Society for Clinical Investigation Award (now Korsmeyer award). **2003**: AACR-G.H.A. Clowes Memorial Award; The Ellison Medical Foundation Senior Scholar in Aging Award. **2004**: Albert Einstein College of Medicine Distinguished Alumnus Award; American Cancer Society Edith A. Pistorino Research Professorship; Elected Member, Institute of Medicine of the National Academies**. 2007:** Harvey Society Lecture; Biomedicum Helsinki Medal and Lecture. **2009:** Albert Szent-Györgyi Prize. **2010:** American Academy of Arts and Sciences. **2012:** Member, National Academy of Sciences; American Italian Cancer Foundation, Prize for Scientific Excellence in Medicine. **2014:** Fellow, American Association of the Advancement of Science. **2015:** Fellow, American Association for Cancer Research. **2017:** Brien McMahon Award for Distinguished Public Service; Ellis

Island Medal of Honor; Foreign Member, Royal Academy of Science, Portugal; Member, Science Committee, Science and Faith Foundation – STOQ, Vatican. Numerous Keynotes Speeches and Named Lectureships.

C. Contributions to Science

1. *Role of telomeres in cancer and aging*. My research program established pathogenic links between telomere dysfunction and age related disorders and chronic degenerative diseases. We defined the major principles of how telomeres underlie the intimate link between advancing age and cancer and how telomere dysfunction drives epithelial cancers and contributes to genome instability. We also demonstrated that telomeres play central roles in premature aging conditions as well as somatically acquired degenerative diseases such as liver cirrhosis. Our recent work has defined a core pathway of aging providing the first unified view of how genotoxic stress, ROS and mitochondrial dysfunction are directly linked to drive the aging process. Through inducible telomerase models, my lab provided the first genetic evidence that reactivation of telomerase is required for tumor progression and that aging phenotypes can be reversed through reactivation of telomerase late in life.
   a. Colla S, Ong DS, Ogoti Y, Marchesini M, Mistry NA, Clise-Dwyer K, Ang SA, Storti P, Viale A, Giuliani N, Ruisaard K, Ganan Gomez I, Bristow CA, Estecio M, Weksberg DC, Ho YW, Hu B, Genovese G, Pettazzoni P, Multani AS, Jiang S, Hua S, Ryan MC, Carugo A, Nezi L, Wei Y, Yang H, D'Anca M, Zhang L, Gaddis S, Gong T, Horner JW, Heffernan TP, Jones P, Cooper LJ, Liang H, Kantarjian H, Wang YA, Chin L, Bueso-Ramos C, Garcia-Manero G, DePinho RA (2015) Telomere dysfunction drives aberrant hematopoietic differentiation and myelodysplastic syndrome. ***Cancer Cell***, 27(5): 644-57. PMCID: PMC4596059.
   b. Jaskelioff M, Muller FL, Paik JH, Thomas E, Jiang S, Adams AC, Sahin E, Kost-Alimova M, Protopopov A, Cadiñanos J, Horner JW, Maratos-Flier E, Depinho RA (2011) Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. ***Nature***, 469(7328): 102-106. PMCID: PMC3057569.
   c. Sahin E, Colla S, Liesa M, Moslehi J, Müller FL, Guo M, Cooper M, Kotton D, Fabian AJ, Walkey C, Maser RS, Tonon G, Foerster F, Xiong R, Wang YA, Shukla SA, Jaskelioff M, Martin ES, Heffernan TP, Protopopov A, Ivanova E, Mahoney JE, Kost-Alimova M, Perry SR, Bronson R, Liao R, Mulligan R, Shirihai OS, Chin L, DePinho RA (2011) Telomere dysfunction induces metabolic and mitochondrial compromise. ***Nature***, 470(7334): 359-365. PMCID: PMC3741661.
   d. Artandi SE, Chang S, Lee SL, Alson S, Gottlieb GJ, Chin L, DePinho RA (2000) Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. ***Nature***, 406(6796): 641-645.

2. *Mouse models of human cancer*. The challenge of cancer's genomic and biological complexity prompted my longstanding commitment to develop highly refined genetically engineered mouse models of cancer and to help the community develop and use such models through my efforts establishing the first NCI-supported shared transgenic facility, co-organizing the first meeting for mouse models of cancer, and establishing an NCI-sponsored training course. Through our animal modeling efforts, we validated (in collaboration with Beach) Ink4a/ARF as a tumor suppressor *in vivo*. We also established some of the first germline GEM models for melanoma and glioblastoma and subsequently generated more refined mouse models for many different cancer types including prostate, myeloma, pancreas, and colon cancer, among others. Our team championed the use of inducible cancer models for the study of host-tumor interactions and the validation of cancer targets. Through this system, we demonstrated the concept of tumor maintenance and showed that extinction of RAS in melanoma would lead to regression of fully established tumors. We also established the concept of collateral lethality and the power of comparative oncogenomics to discover novel therapeutic targets for cancer.
   a. Boutin AT, Liao WT, Wang M, Hwang SS, Karpinets TV, Cheung H, Chu GC, Jiang S, Hu J, Chang K, Vilar E, Song X, Zhang J, Kopetz S, Futreal A, Wang YA, Kwong LN, DePinho RA (2017) Oncogenic Kras drives invasion and maintains metastases in colorectal cancer. ***Genes Dev***, 31(4): 370-382. PMCID: PMC5358757.
   b. Hu J, Hwang SS, Liesa M, Gan B, Sahin E, Jaskelioff M, Ding Z, Ying H, Boutin AT, Zhang H, Johnson S, Ivanova E, Kost-Alimova M, Protopopov A, Wang YA, Shirihai OS, Chin L, DePinho RA (2012) Antitelomerase therapy provokes ALT and mitochondrial adaptive mechanisms in cancer. ***Cell***, 148(4): 651-663. PMCID: PMC3286017.

c. Aguirre AJ, Bardeesy N, Sinha M, Lopez L, Tuveson DA, Horner J, Redston MS, DePinho RA (2003) Activated Kras and Ink4a/Arf deficiency cooperate to produce metastatic pancreatic ductal adenocarcinoma. ***Genes Dev***, 17(24): 3112-3126.

3. *Deep genetic and biologic understanding of highly lethal cancers*. Beyond the production and in-depth characterization of our various mouse models, our work has emphasized exploiting these models to address major translational issues in cancer medicine. For example, our group (and Michael Bishop) demonstrated that extinction of an oncogene (RAS in melanoma) would lead to regression of fully established tumors and he established the first second site suppression screen in mammalian cells to discover RAS-equivalent druggable elements via proviral insertion and cDNA complementation. These concepts have impacted cancer drug development efforts by enabling context-specific genetic screens (resistance mechanisms), validating cancer targets and guiding drug response biomarkers. In GBM work, we dissected the basis for cooperation of the two most common mutations in the human disease by showing that Pten and p53 converge on Myc biology in cancer stem cell renewal and differentiation. Our GBM studies led to the discovery that all cancer cells express multiple activated RTKs, providing rationale for novel cancer therapies via co-extinction, and to identification of drivers of GBM stem cell differentiation and invasion. Our use of cancers of the telomerase KO mouse in comparative oncogenomics efforts led to the discovery of many new cancer genes and loci and established that mouse and human cells target many of the same loci in carcinogenesis. Our use of unbiased computational analyses of multi-dimensional datasets has identified collateral lethality genes and established the concept of "synthetic essentiality" as a framework for identifying new cancer vulnerabilities.
   a. Dey P, Baddour J, Muller F, Wu CC, Wang H, Liao WT, Lan Z, Chen A, Gutschner T, Kang Y, Fleming J, Satani N, Zhao D, Achreja A, Yang L, Lee J, Chang E, Genovese G, Viale A, Ying H, Draetta G, Maitra A, Wang YA, Nagrath D, DePinho RA (2017) Genomic deletion of malic enzyme 2 confers collateral lethality in pancreatic cancer. ***Nature***, 542(7639): 119-123. PMCID: PMC5398413.
   b. Zhao D, Lu X, Wang G, Lan Z, Liao W, Li J, Liang X, Chen JR, Shah S, Shang X, Tang M, Deng P, Dey P, Chakravarti D, Chen P, Spring DJ, Navone NM, Troncoso P, Zhang J, Wang YA, DePinho RA. (2017) Synthetic essentiality of chromatin remodelling factor CHD1 in PTEN-deficient cancer. ***Nature***, 542(7642): 484-488. PMCID: PMC5448706.
   c. Hu B, Wang Q, Wang YA, Hua S, Sauvé CG, Ong D, Lan ZD, Chang Q, Ho YW, Monasterio MM, Lu X, Zhong Y, Zhang J, Deng P, Tan Z, Wang G, Liao WT, Corley LJ, Yan H, Zhang J, You Y, Liu N, Cai L, Finocchiaro G, Phillips JJ, Berger MS, Spring DJ, Hu J, Sulman EP, Fuller GN, Chin L, Verhaak RG, DePinho RA (2016) Epigenetic Activation of WNT5A Drives Glioblastoma Stem Cell Differentiation and Invasive Growth. ***Cell***, 167(5): 1281-1295. PMCID: PMC5320931.
   d. Zheng H, Ying H, Yan H, Kimmelman AC, Hiller DJ, Chen AJ, Perry SR, Tonon G, Chu GC, Ding Z, Stommel JM, Dunn KL, Wiedemeyer R, You MJ, Brennan C, Wang YA, Ligon KL, Wong WH, Chin L, DePinho RA (2008) p53 and Pten control neural and glioma stem/progenitor cell renewal and differentiation. ***Nature***, 455(7216): 1129-1133. PMCID: PMC4051433.

4. *Translational science to guide detection and treatment of common cancers.* In a series of translational studies (with Dr. Sam Hanash), we used our PDAC model and comparative proteomics to discover a 5-marker panel capable of identifying pancreas cancer patients with occult disease over one year before onset of symptoms. More recently, we developed the first mouse model of metastatic prostate cancer made possible through an unbiased computational and genetic analysis of pathways constraining progression. This model and comparative oncogenomics enabled the identification of the first marker panel capable of stratifying men into high and low risk, illustrating our use of mouse models in translational research. Specifically, using an integrated approach, we discovered prostate cancer biomarkers for lethality prediction that enable improved management of the most common cancer in men. In a GBM study, we used the reality that homozygous deletion of tumor-suppressor genes in cancer often encompass neighboring genes to propose that homozygous deletions in such passenger genes could expose cancer-specific therapeutic vulnerabilities (termed "collateral lethality") when the gene is part of a gene family. Thus, we identified co-deletion of ENO1 in 1p36 locus-deleted GBM, and demonstrated that inhibition of ENO2 selectively inhibits growth. The principle of collateral lethality should be applicable to other passenger-deleted genes and provide an effective treatment strategy for cancers containing such deletion events.
   a. Ding Z, Wu CJ, Jaskelioff M, Ivanova E, Kost-Alimova M, Protopopov A, Chu GC, Wang G, Lu X, Labrot ES, Hu J, Wang W, Xiao Y, Zhang H, Zhang J, Zhang J, Gan B, Perry SR, Jiang S, Li L, Horner JW,

Wang YA, Chin L, DePinho RA (2012) Telomerase reactivation following telomere dysfunction yields murine prostate tumors with bone metastases. ***Cell***, 148(5): 896-907. PMCID: PMC3629723.

b. Muller FL, Colla S, Aquilanti E, Manzo VE, Genovese G, Lee J, Eisenson D, Narurkar R, Deng P, Nezi L, Lee MA, Hu B, Hu J, Sahin E, Ong D, Fletcher-Sananikone E, Ho D, Kwong L, Brennan C, Wang YA, Chin L, DePinho RA (2012) Passenger deletions generate therapeutic vulnerabilities in cancer. ***Nature***, 488(7411): 337-342. PMCID: PMC3712624.

c. Ding Z, Wu CJ, Chu GC, Xiao Y, Ho D, Zhang J, Perry SR, Labrot ES, Wu X, Lis R, Hoshida Y, Hiller D, Hu B, Jiang S, Zheng H, Stegh AH, Scott KL, Signoretti S, Bardeesy N, Wang YA, Hill DE, Golub TR, Stampfer MJ, Wong WH, Loda M, Mucci L, Chin L, DePinho RA (2011) SMAD4-dependent barrier constrains prostate cancer growth and metastatic progression. ***Nature***, 470(7333): 269-273. PMCID: PMC3753179.

d. Faca VM, Song KS, Wang H, Zhang Q, Krasnoselsky AL, Newcomb LF, Plentz RR, Gurumurthy S, Redston MS, Pitteri SJ, Pereira-Faca SR, Ireton RC, Katayama H, Glukhova V, Phanstiel D, Brenner DE, Anderson MA, Misek D, Scholler N, Urban ND, Barnett MJ, Edelstein C, Goodman GE, Thornquist MD, McIntosh MW, DePinho RA, Bardeesy N, Hanash SM (2008) A mouse to human search for plasma proteome changes associated with pancreatic tumor development. ***PLoS Med***, 5(6): e123. PMCID: PMC2504036.

D. Research Support

Ongoing Research Support

R01 CA225955 **DePinho (PI)** 04/01/18-03/31/23
National Institutes of Health
Exploring Collateral Lethality for Development of Cancer Therapeutics
In this project, we propose to validate ME3 as a therapeutic target *in vitro* and in preclinical animal models and to identify potential therapeutic compounds targeting ME3.

R01 CA231360 **DePinho (PI)** 09/01/18-08/31/23
National Institutes of Health
Genetics and Biology of Metastatic Colorectal Cancer
The goal of this proposal is to dissect the mechanistic actions of Kras* and its circuitry in controlling CRC immune biology with the goal of illuminating effective therapeutic strategies for testing in CRC patients.

P01 CA117969 **DePinho (PI)** 04/15/06-03/31/21
National Institutes of Health
Genetics and Biology of Pancreatic Ductal Adenocarcinoma
The goal of this P01 is to further elucidate the genetics and biology of disease progression and maintenance to a level that will guide the rational development of effective targeted agents, alone and in combination.

R01 CA084628 **DePinho (PI)** 01/01/15-12/31/19
National Institutes of Health
Telomerase in Development, Senescence and Neoplasia
To define the molecular circuitry of the telomere checkpoint response that constrains the progression tumor progression.

Prostate Cancer Moon Shot **DePinho (PI)** 09/01/18-08/31/19
MD Anderson Cancer Center
Targeting the PTEN synthetic essential chromatin remodeling factor CHD1 (Synthetic Essential)
The overall goal of the project is to further validate CHD1 as a target for Prostate cancer and identify additional CL and SE targets for prostate cancer

PFC Challenge Grant **DePinho (PI)** 12/31/17-12/31/19
Prostate Cancer Foundation
Synthetic essential approach to identify novel therapeutic targets for prostate cancer
This project's goal is to elucidate the role of CHD1 as a potential therapeutic target and explore additional novel SE targets for prostate cancer.