## BIOGRAPHICAL SKETCH

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NAME: D'Andrea, Alan D.

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

POSITION TITLE: Professor, Radiation Oncology

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 |
|---|---|---|---|
| Harvard University, Cambridge, MA | A.B. | 06/1978 | Biology |
| Harvard Medical School, Boston, MA | M.D. | 06/1983 | Medicine |
| Children's Hospital of Philadelphia, PA | Residency | 07/86 | Pediatrics |
| Whitehead Institute, Cambridge, MA | Postdoctoral Fellow | 06/90 | Fellowship |

**A**. **Personal statement.**

Twenty-five years ago, Dr. D'Andrea began to study the molecular pathogenesis of Fanconi Anemia (FA), a human genetic disease characterized by bone marrow failure, leukemia susceptibility, and cellular hypersensitivity to DNA crosslinking agents. Dr. D'Andrea's laboratory contributed significantly to the elucidation of a new DNA repair pathway, the FA/BRCA pathway, and demonstrated that one of the FA genes (FANCD1) is identical to the breast cancer gene, BRCA2. A critical event in the FA pathway is the monoubiquitination of the FANCD2 protein. Interestingly, somatic disruption of genes in the FA/BRCA pathway account for the chromosome instability and drug sensitivity of many solid tumors in the general (non-FA) population.


1. Howlett NG, Taniguchi T, Olson S, Cox B, Waisfisz Q, de Die-Smulders C, Persky N, Grompe M, Joenje H, Pals G, Ikeda H, Fox EA, D'Andrea AD. Biallelic inactivation of BRCA2 in Fanconi Anemia. Science 297:606-609, 2002.
2. Taniguchi T, Tischkowitz M, Ameziane N, Hodgson SV, Mathew CG, Joenje H, Mok SC, D'Andrea AD. Disruption of the Fanconi Anemia/BRCA pathway in cisplatin-sensitive ovarian tumors. Nature Medicine 9:568-74, 2003
3. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. Cancer Discov. 2015 Nov;5(11):1137-54. PMCID: PMC4631624
4. Hill SJ, Decker B, Roberts EA, Horowitz NS, Muto MG, Worley MJ, Feltmate CM, Nucci MR, Swisher EM, Nguyen H, Yang C, Morizane R, Kochupurakkal BS, Do KT, Konstantinopoulos PA, Liu JF, Bonventre JV, Matulonis UA, Shapiro GI, Berkowitz RS, Crum CP, D'Andrea AD. Prediction of DNA Repair Inhibitor Response in Short Term Patient-Derived Ovarian Cancer Organoids. Cancer Discov. 2018. Epub 2018/09/15. doi: 10.1158/2159-8290.CD-18-0474. PMCID:PMC6365285 [Available on 2019-11-01]


**B**. **Positions and Honors.**

**Positions.**

1977-78 Research Associate, Laboratory of Dr. William Haseltine, Dana-Farber Cancer Institute, Boston, MA. Project: DNA damage and repair.

1980-83 Research Associate, Laboratory of Dr. Samuel Latt, Children's Hospital, Boston, MA.
Project: DNA replication kinetics.
1983-86 Resident in Pediatrics, Children's Hospital of Philadelphia
1986-87 Fellow in Medicine, (Hematology/Oncology), Children's Hospital, Boston
1987-91 Postdoctoral Fellow, Laboratory of Dr. Harvey Lodish, Whitehead Institute, Cambridge, MA.
Project: Molecular cloning of the Erythropoietin Receptor.
1991-95 Assistant Professor of Pediatrics, Harvard Medical School
1995-00 Associate Professor of Pediatrics, Harvard Medical School
2000- Professor of Pediatrics, Harvard Medical School, Dana-Farber Cancer Institute
2003-17 Chief, Division of Genomic Stability and DNA Repair, Dana-Farber Cancer Institute
2003- The Fuller-American Cancer Society Professor, Harvard Medical School, Department of Radiation Oncology and Pediatrics
2013- Director: Center for DNA Damage and Repair, Dana-Farber Cancer Institute
2017- Director: Susan F. Smith Center for Women's Cancers, Dana-Farber Cancer Institute

**Other Experience and Professional Memberships**

1998-02 Member: NIH Hematology 2 Study Section
2003-08 Senior Editor: Molecular Cellular Biology
2004 Editorial Board: Blood Journal
2004 Leukemia and Lymphoma Society (LLS) Scientific Advisory Board
2005 Editorial Board: Journal of Clinical Investigation
2006 Editorial Board: Cancer Research
2012-14 Chairman, NIH Molecular and Cellular Hematology Study Section
2013- External Advisor, Vanderbilt University Cancer Center
2013- Member, Joint Scientific Advisory Committee, AACR Stand Up To Cancer/St. Baldrick's Foundation
2013- Chairman, LLS Career Development (CDP) Review Committee
2013- Member, LLS Medical and Scientific Advisory Board
2013- Associate Member, Broad Institute
2013- External Advisor, Abramson Family Cancer Institute, University of Pennsylvania
2014- Member, External Advisory Board, Malignant Hematopoiesis Program, Mt. Sinai School of Medicine
2014- Member, NCI Board of Scientific Counselors for Basic Sciences
2015- Leader: SU2C-AACR Ovarian Cancer Dream Team, DNA Repair Therapies for Ovarian Cancer

**Honors and Awards:**

1987 NIH/NHLBI Physician Scientist Award (K08)
1990 March of Dimes Basil O'Connor Scholar Award
1990 Lucille Markey Scholar Award
1995 Elected Member, American Society of Clinical Investigators (ASCI)
1997 The American Academy of Pediatrics Award for Excellence in Pediatric Research
2000 Stohlman Scholar, The Leukemia & Lymphoma Society
2000 Doris Duke Distinguished Clinical Scientist Award
2000 The Ted Williams Senior Investigatorship, Dana-Farber Cancer Institute
2001 E. Mead Johnson Award, Society for Pediatric Research
2003 Award of Merit, The Fanconi Research Fund
2003 Award of Merit, The German Fanconi Anemia Research Fund
2003 Elected Member, American Association of Physicians (AAP)
2004 Merit Award, National Institutes of Health
2004 Speaker, Presidential Symposium, ASH
2005 Keynote Address, MD-PhD Retreat, University of Pennsylvania
2006 The Wilkinson Memorial Lecture, British Society of Hematology
2007 The Abelson Lecture, University of Washington, Seattle, WA.
2008 Chairman, NCI Workshop on DNA Repair and Cancer Therapy
2009 Chairman, Mammalian DNA Repair Gordon Research Conference
2009 Merit Award, National Institutes of Health, NHLBI
2009 Brian P. O'Dell Memorial Research Award, LLS
2010 Keynote Address, International Workshop on Radiation Damage to DNA

2011 Speaker, Presidential Symposium, ASH
2012 AACR G.H.A. Clowes Memorial Award
2012 Fellow, American Association for the Advancement of Science (AAAS)
2014 Plenary Basic Science Speaker, San Antonio Breast Cancer Symposium (SABCS)
2017 Member, National Academy of Medicine (NAM)
2018 Ernest Beutler Lecture and Prize, American Society of Hematology (ASH)

**C. Contribution to Science**

1. I have a longstanding interest in hematopoiesis. I cloned the EPO-Receptor as a postdoctoral fellow in Harvey Lodish's laboratory and continued my EPO-Receptor and Cytokinesis Receptor research as a faculty member at the Dana-Farber Cancer Institute. As a hematopoiesis expert, I was invited to chair hematopoiesis study sections at the National Institutes of Health and the Leukemia and Lymphoma Society.
   a. D'Andrea AD, Lodish HF, Wong GG. Expression cloning of the murine erythropoietin receptor. Cell 57:277-285, 1989.
   b. D'Andrea AD, Fasman GD, Lodish HF. Erythropoietin receptor and interleukin-2 receptor beta chain: a new receptor family. Cell 58:1023, 1989.
   c. D'Andrea AD, Cytokine receptors in congenital hematopoietic Disease. N Engl J Med 330:839-846, 1994.
   d. Zhang H, Kozono DE, O'Connor KW, Vidal-Cardenas S, Rousseau A, Hamilton A, Moreau L, Gaudiano EF, Greenberger J, Bagby G, Soulier J, Grompe M, Parmar K, D'Andrea AD. TGF-β Inhibition Rescues Hematopoietic Stem Cell Defects and Bone Marrow Failure in Fanconi Anemia. Cell Stem Cell, 2016 May 5;18(5):668-81. PMCID: PMC4860147

2. In addition to these contributions, I contributed significantly to elucidating the role of protein ubiquitination and deubiquitination in the process of DNA repair. Since these early reports from my laboratory, it has become clear that protein ubiquitination is a critical regulating mechanism in DNA repair.
   a. Huang TT, Nijman S, Mirchandani K, Galardy P, Cohn M, Haas W, Gygi S, Ploegh H, Bernards R, D'Andrea AD. Regulation of Monoubiquitinated PCNA by DUB Autocleavage. Nature Cell Biology 8: 341-347, 2006.
   b. Cohn MA, Kowal P, Yang K, Haas W, Huang T, Gygi SP, D'Andrea AD. A UAF1-containing multisubunit protein complex regulates the Fanconi Anemia Pathway. MolCell 28:786-797, 2007.
   c. Kee, Y., Kim, J. M. & D'Andrea, A. D. Regulated degradation of FANCM in the Fanconi anemia pathway during mitosis. Genes Dev 23, 555-560 (2009). PMCID: PMC2658523
   d. Li H, Lim KS, Kim H, Hinds TR, Jo U, Mao H, Weller CE, Sun J, Chatterjee C, D'Andrea AD, Zheng N. Allosteric Activation of Ubiquitin-Specific Proteases by β-Propeller Proteins UAF1 and WDR20. Mol Cell. 2016 Jul 21;63(2):249-260. PMCID: PMC4958508

3. My laboratory uses the underlying principles of DNA repair biology to predict the drug sensitivity of human leukemias and solid tumors. We have identified DNA repair abnormalities which underlie the cisplatin and PARP inhibitor sensitivities of various solid tumors, including breast and ovarian cancers.
   a. D'Andrea AD. The Fanconi Anemia and Breast Cancer Susceptibility Pathways. 2010 N Engl J Med 362: 1909-1919. PMC3069698
   b. Ceccaldi R, Liu J, Amunugama R, Hajdu I, Primack B, Petalcorin MIR, O'Connor KW, Konstantinopoulos PA, Elledge SJ, Boulton SJ, Yusufzai T, D'Andrea AD. Homologous recombination (HR)-deficient tumors are hyper-dependent on POLQ-mediated repair. Nature. 2015 Feb 12;518(7538):258-62. PMCID: PMC4631624
   c. Kim J, Mouw KW, Polak P, Braunstein LZ, Kamburov A, Kwiatkowski DJ, Rosenberg JE, Van Allen EA, D'Andrea AD, Getz G. Somatic ERCC2 Mutations Are Associated with a Distinct Genomic Signature in Urothelial Tumors. Nat Genet. 2016 Jun;48(6):600-6. PMCID: PMC4936490
   d. Rondinelli B, Gogola E, Yücel H, Duarte AA, van de Ven M, van der Sluijs R, Konstantinopoulos PA, Jonkers J, Ceccaldi R, Rottenberg S, D'Andrea AD. EZH2 promotes degradation of stalled replication forks by recruiting MUS81 through histone H3 trimethylation. Nat Cell Biol. 2017 Oct 16. doi: 10.1038/ncb3626

Complete list of Published Work
http://www.ncbi.nlm.nih.gov/pubmed?term=D'Andrea%20AD%5BAuthor%5D

**D. Research Support.**
**Ongoing Research Support**

5R01HL52725-25 (PI: D'Andrea) 04/15/15 – 03/31/20* NCE
NIH/NHLBI
*Molecular Pathogenesis of Fanconi Anemia*
This study investigates the molecular pathogenesis of Fanconi Anemia using the recently cloned human Fanconi Anemia Complementation Group C (FACC) cDNA and a newly developed antiserum against the FACC polypeptide.

Breast Cancer Research Foundation (D'Andrea) 10/1/11-9/30/19
*Extending the use of PARP Inhibitors for Triple Negative Breast Cancer Therapy*
Goals/Aims: To determine whether the combination of Velcade plus ABT-888 has enhanced cytotoxic activity for TNBC cell lines *in vitro*, compared to each agent alone; To generate colonies of mice bearing human TNBC orthotopic implants (derived from TNBC cell lines or from TNBC patient biopsies) and to treat these mice with the combination of Velcade plus ABT-888. As a subaim, we will examine the tumors dissected from these mice with numerous pharmacodynamic markers (i.e., immunohistochemistry for pBRCA1, FANCD2-Ub, and RAD51).

5P01HL048546-23 (PI: Grompe)
*Pathophysiology and Treatment of Fanconi/Project 2 and Core* 9/1/16-5/31/21
NIH
The major goals of this study are 1) determine the mechanism by which TGF-β inhibitors promote FA cellular growth and regulate DNA repair, 2) to determine whether inhibition of TGF-β pathway rescues hematopoietic defects in FA mouse models, and 3) to determine whether inhibition of TGF-β pathway rescues hematopoietic defects in primary bone marrow cells from FA patients.
Role: Project PI

Breast Cancer Research Program: Breakthrough Award (PI: D'Andrea)
DOD 9/1/16-8/31/19
*BC151331P1 Dissecting the mechanisms of drug resistance in BRCA ½ mutant breast cancers*
The major goal of this study is to identify novel molecular mechanisms of PARPi resistance in *BRCA1/2*-mutated breast cancer.

Stand Up to Cancer (PI: D'Andrea) 7/1/16-6/30/20*NCE
SU2C-AACR-DT16-15/Supplement
*DNA Repair Therapies for Ovarian Cancer*
Major goals of this study are to collect and distribute tumor samples, and blood samples, from TNBC (Triple Negative Breast Cancer) and HGSOC (High Grade Serous Ovarian Cancer) patients enrolled in this joint Tesaro/Merck/SU2C clinical trial and to complete the indicated biomarker studies, from multiple industry-sponsored and academic laboratories, and to analyze the collected data.
Role: PI

Richard & Susan Smith Family Foundation (PI: D'Andrea) 9/1/17-8/31/19
*Ovarian Tumor Living Biobank*
Major goals are to establish the Susan F. Smith Center Living Biobank of recurrent and primary ovarian tumors at Dana-Farber, and to disseminate the knowledge gained from the initiative to investigators with specialties that span multiple cancer types.
Role: PI
Overlap: None

SU2C/Lustgarten Foundation (PI: D'Andrea) 11/1/18/-12/31/19

*Exploiting DNA Repair Gene Mutations in Pancreatic Cancer*
Major goal of this study is to identify the most potent combinatorial strategy, along with predictive biomarkers, that will inform the design of a clinical trial for PDAC patients.
Role: PI

Bridge Project (PI: D'Andrea) 3/1/19-2/28/21
*Nanoparticle-mediated Drug Delivery to Ovarian Cancer Organoid Cultures*
Major goal of this study is to understand; 1) the mechanisms that lead to HGSC sensitivity and resistance to various immune and DNA damage repair therapies and 2) what the best method of delivering specific therapies for these defects is.
Role: PI

NIH 1P01CA228696-01A1 (PI: Kantoff) 7/1/19-6/30/24
Project 3: Functional Evaluation and Interpretation of DDR Variants in Prostate Cancer
Major goal of this proposal is to determine whether specific DNA repair gene mutations in prostate cancers are deleterious and vulnerable to targeted therapy.
Role: Project Leader

DF/HCC SPORE in Gastrointestinal Cancer 7/1/19-6/30/24
P50CA127003 (Bass/El-Bardeesy) Project 3
Major goal of this proposal is to define optimal strategies for identifying PDAC patients with DDR deficiency and to conduct innovative PARP inhibitor treatment trials to improve care for these patients.
Role: Co-Project Leader

SU2C Phillip A. Sharp Innovation in Collaboration Award (D'Andrea/Cubillos-Ruiz) 6/1/19-5/31/2021
*Resistance to PARP inhibitor plus anti-PD1 therapy driven by ER stress and bioactive lipids in ovarian cancer*
Major goals of this proposal are to evaluate the status of LPA/PERK-controlled signatures in responder vs. non-responder patients, and to determine whether inhibition of LPA-PERK sensitizes OC to Niraparib and Pembrolizumab.
Role: Co-PI

Basser Initiative at Gray Foundation, Team Science Grants (PI: Sung) 7/1/19-6/30/23
*Dissection of BRCA-mediated Tumor Suppression Pathways*
Major goals of this study are to evaluate the PARPi and platinum-resistant mechanisms, and to determine their impact on patient drug response.
Role: Specific 4 Project Leader

P50CA168504-06A1 (Winer) 7/01/19 – 06/30/24
NIH/NCI
Dana-Farber/ Harvard Cancer Center SPORE in Breast Cancer – Developmental Research Program
The overall goal of the Developmental Research Program (DRP) is to advance high quality, novel, early-phase research, to foster new ideas in breast cancer research and to move research projects from a pilot stage to a level where external funding for more mature research is possible. A secondary goal of the DRP is to create opportunities for the career development of junior faculty or senior investigators who are interested in transitioning into breast cancer research. The DRP will be co-led by Alan D'Andrea, MD and Nikhil Wagle, MD. They will work with a standing committee made up of SPORE and DF/HCC investigators to review applications.
Role: Co-Director, DRP