

BIOGRAPHICAL SKETCH

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NAME Cleary, Michael L	POSITION TITLE Professor of Pathology and Pediatrics		
eRA COMMONS USER NAME (credential, e.g., agency login) cleary.michael			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
College of Wooster, Wooster, OH	B.A.	1974	Chemistry
University of South Carolina, Columbia, SC	M.S.	1976	Chemistry
University of Cincinnati, Cincinnati, OH	M.D.	1981	Medicine
Stanford University, Stanford, CA		1981-1983	Pathology Resident
Stanford University, Stanford, CA		1983-1986	Postdoctoral Fellow

A. Personal Statement

Our laboratory studies the molecular pathogenesis of cancer, particularly hematologic malignancies, with a specific focus on hematopoietic stem/progenitor cells and their conversion into cancer stem cells. We have discovered several genes that are damaged by chromosomal translocations in human leukemias. We are currently investigating their normal functions and contributions to cancer employing a variety of experimental approaches that include biochemical techniques, in vitro cellular transformation assays, as well as genetic analyses using mouse models. These efforts have defined a major pathway in leukemogenesis that critically depends on Hox and TALE class homeodomain proteins, and their immediate upstream transcriptional regulators (e.g. MLL). However, less is known about the downstream effectors in this critical pathway in normal and neoplastic blood cell development. We possess the experimental tools and scientific expertise in cancer biology and hematopoiesis to further investigate this pathway to advance the novel preliminary studies described in the current application implicating a unique new function for a known enzyme.

B. Positions and Honors

Positions and Employment

1981-1983	Intern and Resident, Department of Pathology, Stanford University School of Medicine
1983-1986	Postdoctoral Scholar, Department of Pathology, Stanford University School of Medicine
1986-1991	Assistant Professor of Pathology, Stanford University School of Medicine
1991-1999	Associate Professor of Pathology, Stanford University School of Medicine
1999-	Professor of Pathology, Stanford University School of Medicine
2002-	Professor of Pediatrics, Stanford University School of Medicine

Other Experience and Professional Memberships

2000-2003	Board of Scientific Counselors, National Cancer Institute
2001-	Associate Chair for Experimental Pathology, Department of Pathology, Stanford University
2002-	Director, Division of Pediatric Cancer Biology, Department of Pediatrics, Stanford University
2005-	Associate Director for Basic Science, Stanford Cancer Center
2005-	Co-leader, Cancer Biology Program, Stanford Cancer Center
2009-	Institute of Medicine

Honors

1983-1985	Fellow of the Jane Coffin Childs Memorial Fund for Medical Research
1985-1991	Scholar of the Lucille P. Markey Charitable Trust
1987, 1988	Robert W. Cahill Faculty Prize in Cancer Research, Stanford University
1991-1996	Scholar of the Leukemia Society of America
1996	Warner-Lambert Parke-Davis Award of the American Society of Investigative Pathology

1999-2007 MERIT Award, NCI/NIH (CA42971)

C. Selected Peer-reviewed Publications (Selected from 175 peer-reviewed publications)

Most relevant to the current application

1. Smith KS, Chanda S, Lingbeek M, Ross DT, Botstein D, Brown PO, van Lohuizen M, **Cleary ML**. Bmi-1 regulation of INK4A-ARF is a downstream requirement for transformation of hematopoietic progenitors by E2a-Pbx1. *Mol Cell* 12:393-400, 2003.
2. Yokoyama A, Wang Z, Wysocka J, Sanyal M, Aufiero DJ, Kitabayashi I, Herr W, **Cleary ML**. Leukemia proto-oncoprotein MLL forms a SET1-like histone methyltransferase complex with menin to regulate Hox gene expression. *Mol Cell Biol* 24:5639-5649, 2004.
3. Brendolan A, Ferretti E, Salsi V, Moses K, Quaggin S, Blasi F, **Cleary ML**, Selleri L. A Pbx1-dependent genetic and transcriptional network regulates spleen ontogeny. *Development* 132:3113-3126, 2005.
4. Yokoyama A, Somervaille CP, Smith KS, Rozenblatt-Rosen O, Meyerson M, **Cleary ML**. The menin tumor suppressor protein is an essential oncogenic cofactor for MLL-associated leukemogenesis. *Cell* 123:207-218, 2005.
5. Somervaille TCP, **Cleary ML**. Identification and characterization of leukemia stem cells in murine MLL-AF9 acute myeloid leukemia. *Cancer Cell* 10:257-268, 2006.
6. Sanyal M, Tung JW, Karsunky H, Zeng H, Selleri L, Weissman IL, Herzenberg LA, **Cleary ML**. B cell development fails in the absence of the Pbx1 proto-oncogene. *Blood* 109:4191-4199, 2007.
7. Wong P, Iwasaki M, Somervaille TCP, So ECW, **Cleary ML**. Meis1 is an essential and rate-limiting regulator of MLL leukemia stem cell potential. *Genes & Dev*. 21:2762-2774, 2007.
8. Yokoyama A, **Cleary ML**. Menin critically links MLL proteins with LEDGF on cancer-associated target genes. *Cancer Cell* 14:36-46, 2008. PMC2692591
9. Wang Z, Smith KS, Murphy M, Piloto O, Somervaille TCP, **Cleary ML**. Glycogen synthase kinase-3 in MLL leukemia maintenance and targeted therapy. *Nature* 455:1205-1209, 2008.
10. Ficara F, Murphy MJ, Lin M, **Cleary ML**. Pbx1 regulates self-renewal of long-term hematopoietic stem cells by maintaining their quiescence. *Cell Stem Cell* 2:484-496, 2008.
11. Stankunas K, Shang C, Twu KY, Kao S-C, Jenkins NA, Copeland NG, Sanyal M, Selleri L, **Cleary ML**, Chang C-P. 2008. Pbx/Meis deficiencies demonstrate multi-genetic origins of congenital heart disease. *Circ Res* 103:702-709, 2008.
12. Chang C-P, Stankunas K, Shang C, Kao S-C, Twu KY, **Cleary ML**. Pbx1 functions in distinct regulatory networks to pattern the great arteries and cardiac outflow tract. *Development* 135:3577-3586, 2008.
13. Somervaille TCP, Matheny CJ, Spencer GJ, Masayuki I, Rinn JL, Witten DM, Chang HY, Shurtleff SA, Downing JR, **Cleary ML**. Hierarchical maintenance of MLL myeloid leukemia stem cells employs a transcriptional program shared with embryonic rather than adult stem cells. *Cell Stem Cell* 4:129-140, 2009.
14. Yokoyama A, Lin M, Naresh A, Kitabayashi I, **Cleary ML**. A higher-order complex containing AF4 and ENL family proteins with P-TEFb facilitates oncogenic and physiologic MLL-dependent transcription. *Cancer Cell* 17:1-15, 2010.
15. Wang Z, Iwasaki M, Ficara F, Lin C, Matheny C, Wong SHK, Smith KS, **Cleary ML**. GSK-3 promotes conditional association of CREB and its coactivators with MEIS1 to facilitate HOX-mediated transcription and oncogenesis. *Cancer Cell* 17:597-608, 2010.
16. Chang P-Y, Hom RA, Musselman CA, Zhu L, Kuo A, Gozani O, Kutateladze TG, **Cleary ML**. Binding of the MLL PHD3 finger to histone H3K4me3 is required for MLL-dependent gene transcription. *J Mol Biol* 400:137-144, 2010.
17. Hom RA, Chang P-Y, Roy S, Musselman C, Glass K, Selezneva A, Gozani O, Ismagilov R, **Cleary ML**, Kutateladze TG. Molecular mechanism of MLL PHD3 and RNA recognition by the Cyp33 RRM domain. *J Mol Biol* 145-154, 2010.

D. Research Support

Ongoing Research Support

1 R01 CA 116606-06 Cleary (PI)

06/04/10-04/30/15

NIH/NCI

Molecular Targeting of MLL and Associated Factors

Determine the requirements for menin and other MLL-associated factors in leukemogenesis and establish the feasibility of targeting their molecular interactions as a therapeutic strategy. Define the pathogenic roles of AF4 macromolecular complex components in MLL-mediated leukemogenesis.

No overlap.

Role: PI

Specialized Center of Research Mitchell (PI)

10/1/08-9/30/13

Leukemia & Lymphoma Society

Molecular and Cellular Characterization of Myelodysplastic Syndromes

Project 4: MEIS/HOX-dependent pathways in the pathogenesis and progression of MDS (Cleary)

The objectives of Project 4 are to characterize the role of MEIS/HOX-dependent pathways in the pathogenesis of MDS using mouse xenograft models.

No overlap.

Role: Project 4 Leader

3 P30 CA 124435-02S1

06/01/10-05/31/15

NIH/NCI

Stanford Cancer Center Mitchell (PI)

Role: Associate Director for Basic Science and Program 1 Co-Leader
