BIOGRAPHICAL SKETCH

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NAME: Armstrong, Scott Allen

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

POSITION TITLE: Chair, Department of Pediatric 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
University of Oklahoma- Norman, OK	B.S.	05/89	Chemistry
University of Texas Southwestern Medical School-Dallas, TX	M.D.	06/96	Medicine
University of Texas Southwestern Medical School-Dallas, TX	Ph.D.	06/96	Cellular and Molecular Biology

A. Personal Statement:

I am the Chair of the Department of Pediatric Oncology at Dana- Farber Cancer Institute, and a pediatric oncologist. I direct a 20-member lab that is studying normal and leukemia stem cell biology. My lab uses genomic/epigenomic and biochemical approaches to characterize genetically engineered mouse models and human leukemias to assess the role of specific genes and pathways in normal and malignant self-renewal with a focus on chromatin-based mechanisms. Our recent work on small molecule DOT1L and Menin inhibitors as potential therapeutics in *MLL*-rearranged and *NPM1* mutant leukemias has led to the development of clinical trials in children and adults.

B. Positions and Honors:

1996-1998 Intern and Resident in Pediatrics, Boston Combined Residency Program in Pediatrics, Children's Hospital, Boston, MA
1996-2001 Clinical Fellow in Pediatrics, Harvard Medical School, Boston, MA
1998-2001 Clinical Fellowship in Pediatric Hematology and Oncology, Children's Hospital and Dana Farber Cancer Institute, Boston, MA
1999 American Society of Hematology Fellow Scholar Award
1999-2003 Postdoctoral research with Dr. Stanley Korsmeyer, Department of Cancer Immunology and AIDS, Dana Farber Cancer Institute, Boston MA
2001-2003 Instructor in Pediatrics, Harvard Medical School, Dana Farber Cancer Institute, Boston, MA
2001-2012 Staff Physician, Children's Hospital and Dana Farber Cancer Institute, Boston, MA
2002 Claire W. and Richard P. Morse Research Award, Dana Farber Cancer Institute
2003 Damon Runyon-Eli Lilly Clinical Investigator Award
2003-2009 Assistant Professor of Pediatrics, Harvard Medical School, Children's Hospital, Dana Farber Cancer Institute, Boston MA
2006 Claudia Adams Barr Program in Cancer Research Scholar, Dana-Farber Cancer Institute, Boston, MA
2006 Wilson S. Stone Memorial Award, Univ. of Texas M.D. Anderson Cancer Center, Houston, TX
2008 Mary Ellen Avery Investigator, Children's Hospital Boston, MA
2008 Sir William Osler Award for Clinician-Scientists, Interurban Clinical Club
2008-2012 Director of Translational Research in Pediatric Cancer and Blood Diseases, Children's Hospital and Dana Farber Cancer Institute.
2009-2012 Associate Professor of Pediatrics, Harvard Medical School, Children's Hospital, Dana Farber Cancer Institute, Boston MA

2009 McCulloch and Till Award, International Society of Experimental Hematology (ISEH)
2010 Elected Member of the American Society of Clinical Investigation
2011 Paul Marks Prize for Cancer Research, Memorial Sloan Kettering Cancer Center
2012 E. Mead Johnson Award for Research in Pediatrics
2012-2016 Vice Chair for Research, Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY
2012-2016 Member, Cancer Biology and Genetics Program, Memorial Sloan Kettering Cancer Center, New York, NY
2012-2016 Director, Center for Leukemia Research, Memorial Sloan Kettering Cancer Center, New York, NY
2014 Frank A. Oski Award, American Society of Pediatric Hematology/Oncology
2014- Elected Member of the Association of American Physicians (AAP)
2014 William Dameshek Prize, American Society of Hematology (ASH)
2016- Chair, Department of Pediatric Oncology, Dana-Farber Cancer Institute
2016- Associate Chief, Division of Hematology-Oncology, Boston Children's Hospital
2016- David G. Nathan Professor of Pediatrics, Harvard Medical School
2017- Elected Member of the National Academy of Medicine
2019 Tobias Award, International Society for Stem Cell Research (ISSCR)

C. Contribution to Science:

1. My lab has used genomic approaches to characterize childhood acute lymphoblastic leukemias (ALL) with a goal of developing a better understanding of leukemogenesis and developing new therapeutic approaches. Initially we used microarray-based gene expression analysis to show that the presence of a chromosomal translocation specifies a unique gene expression profile which defines a subset of poor prognosis ALL. This was the first study to show that microarray-based classification could distinguish subsets of leukemias. We have subsequently used gene expression-based approaches to guide development of novel therapeutic combinations like glucocorticoids and mTOR inhibitors, which are now in clinical trials. Finally, we have shown that mutation of genes that control epigenetic processes are gained in ALL samples from patients that have relapsed. These studies have had a direct impact on our understanding of the biology of ALL and therapeutic intervention

    a. Armstrong, S.A., Staunton, J.E., Silverman, L.B., Pieters, R., den Boer, M.L., Minden, M.D., Sallan, S.E., Lander, E.S., Golub, T.R. Korsmeyer, S.J.: MLL translocations specify a distinct gene expression profile, distinguishing a unique leukemia. Nature Genetics. 2002 Jan;30(1):41-7. PMID: 11731795.
    b. Wei, G., Twomey, D., Lamb, J., Agarwal, J., Stam, R., Opferman, J. T., Sallan, S.E., den Boer, M.L., Pieters, R., Golub, T.R., Armstrong, S.A.: Gene expression-based chemical genomics identifies rapamycin as a modulator of MCL1 and glucocorticoid resistance. Cancer Cell. 2006: 10, 331-42.
    c. Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, Wrobel MJ, Lerner J, Brunet JP, Subramanian A, Ross KN, Reich M, Hieronymus H, Wei G, Armstrong SA, Haggarty SJ, Clemons PA, Wei R, Carr SA, Lander ES, Golub TR. The Connectivity Map: using gene-expression signatures to connect small molecules, genes and disease. Science. 2006: 313, 1929-35.
    d. Mar B, Bullinger L, McClean K, Grauman P, Harris M, Stevenson K, Neuberg D, Sinha A, Sallan S, Silverman L, Kung A, Nigro L, Ebert B, Armstrong SA. Mutations in epigenetic regulators including SETD2 are gained during relapse in paediatric acute lymphoblastic leukaemia. Nature Communications. 2014 Mar 24; 5:3469. PMCID: PMC4016990

2. I also have an interest in the mechanisms that control leukemic self-renewal and how self-renewal of cancer cells is related to normal stem cell biology. We have used genome-scale approaches to characterize the role of specific genes in mouse hematopoietic cells and mouse models of leukemia. We have shown that myeloid leukemia stem cells (LSC) are often most similar to committed myeloid progenitors that inappropriately express stem cell programs and have defined the role for the Wnt/b-catenin pathway in myeloid leukemias. Most recently we have shown that novel chromatin associated proteins control leukemia gene expression and that some of the most common mutant alleles found in leukemia induce self-renewal in myeloid progenitors. This provides further evidence that progression to leukemia is driven by self-renewal in myeloid progenitors. These studies have helped define the identity of cancer stem cells and mechanisms of self-renewal in leukemia.

a. Krivtsov AV, Twomey D, Feng Z, Stubbs MC, Wang Y, Faber J, Levine JE, Wang J, Hahn WC, Gilliland DG, Golub TR, Armstrong SA. Transformation from committed progenitor to leukaemia stem cell initiated by MLL AF-9. Nature. 2006: 442, 818-22.
b. Wang Y, Krivtsov AV, Sinha AU, North TE, Goessling W, Feng Z, Zon LI, Armstrong SA. The Wnt/beta-catenin pathway is required for the development of leukemia stem cells in AML. Science. 2010 Mar 26;327(5973):1650-3. PMCID: PMC3084586
c. Wan L, Wen H, Li Y, Lyu J, Hoshii T, Joseph J, Wang X, Loh Y, Erb M, Souza A, Bradner J, Shen L, Li W, Li H, Allis D, Armstrong SA, Shi X. ENL links histone acetylation to oncogenic gene expression in AML. Nature 2017 Mar 9;543(7644):265-269. PMCID: PMC5372383
d. Uckelmann HJ, Kim SM, Wong EM, Hatton C, Giovinazzo H, Gadrey JY, Krivtsov AV, Rücker FG, Döhner K, McGeehan GM, Levine RL, Bullinger L, Vassiliou GS, Armstrong SA. Therapeutic targeting of preleukemia cells in a mouse model of NPM1 mutant acute myeloid leukemia. Science. 2020 Jan 31;367(6477):586-590. PMID: 32001657

3. My interest in the mechanisms of transformation of MLL-fusion proteins led us to chromatin-based complexes and histone modifications as central for the development of MLL-rearranged leukemias and for the maintenance of leukemogenic gene expression more broadly. We identified the histone 3 lysine 79 (H3K79) methyltransferase, DOT1L as critical for the control of leukemogenic Hox gene expression in multiple subtypes of leukemia. We have also contributed to the development of new small molecule DOT1L inhibitors that are the first histone methyltransferase inhibitors to be tested in humans. Recently, we have expanded our focus to a number of different chromatin-based complexes as critical for the maintenance of gene expression in leukemia and developed additional small molecule inhibitors.

   a. Krivtsov AV, Feng Z, Lemieux ME, Faber J, Vempati S, Sinha AU, Xia X, Jesneck J, Bracken AP, Silverman LB, Kutok JL, Kung AL, Armstrong SA. H3K79 methylation profiles define murine and human MLL-AF4 leukemias. Cancer Cell. 2008 Nov 4; 15(5):355-68.
   b. Bernt KM, Zhu N, Sinha AU, Vempati S, Faber J, Krivtsov AV, Feng Z, Punt N, Daigle A, Bullinger L, Pollock RM, Richon VM, Kung AL, Armstrong SA. MLL-rearranged Leukemia is Dependent on Aberrant H3K79 Methylation by DOT1L. Cancer Cell 2011, Jul 12;20(1)66-78. PMCID: PMC3329803
   c. Xu H, Valerio DG, Eisold ME, Sinha A, Koche RP, Hu W, Chen CW, Chu SH, Brien GL, Park CY, Hsieh JJ, Ernst P, Armstrong SA. NUP98 Fusion Proteins Interact with the NSL and MLL1 Complexes to Drive Leukemogenesis. Cancer Cell. 2016 Dec 12;30(6):863-878. PMCID: PMC5501282
   d. Hoshii T, Cifani P, Feng Z, Huang CH, Koche R, Chen CW, Delaney CD, Lowe SW, Kentsis A, Armstrong SA. A Non-catalytic Function of SETD1A Regulates Cyclin K and the DNA Damage Response. Cell. 2018 Feb 22;172(5):1007-1021. PMCID: PMC6052445

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/scott.armstrong.1/bibliography/45168405/public/?sort=date&direction=ascending

D. Research Support:

Ongoing Support:

5R01 CA176745-08 Armstrong/Qi (PI) 6/18/2018 - 5/31/2023
NCI
T*argeting DOT1L for degradatiopen in MLL-rearranged Leukemia*
The major goals of this renewal application are to understand the biological underpinnings of DOT1L inhibitor resistance and develop a novel class of small molecule DOT1L degraders to overcome resistance.

1U54 CA231637-01 Stegmaier/Armstrong (PI) 9/10/2018 - 6/30/2023
NCI
The Center for Therapeutic Targeting of EWS-oncoproteins

The primary scientific focus of this Center is to understand the molecular underpinnings of EWS-ETS driven Ewing sarcoma and to investigate novel treatments and therapeutic mechanisms to improve outcomes for pediatric patients with this disease. This Center brings together outstanding basic cancer biologists, chemists, computational biologists, and translational researchers as well as five pediatric oncologists to perform research that will identify new targets and develop new therapies, thus developing the fundamental preclinical knowledge and tools to more effectively treat this devastating disease.

1U54 CA243124-01 Mullighan (PI) 8/1/2019 - 7/31/2024
NCI
Experimental and preclinical modeling of NUP98-rearranged acute leukemias: Project 2
This project will focus on defining the critical dependencies created by NUP98-fusion oncoproteins and how NUP98-fusion oncoproteins influence gene expression to perturb normal cellular programs. Role: Project Co-Lead.

5R01 CA204639-05 Allis et al (MPI) 5/23/2016 - 2/28/2022
NCI *(NCE)*
Functional and Mechanistic Study of Histone Crotonylation in Hematological Malignancies
The general objective of this research is to understand the fundamental role and mechanism of histone lysine crotonylation in the regulation of transcription in physiological and pathological conditions. The Armstrong lab will focus on Aim 3, to define the genome-wide consequences histone lysine crotonylation has on chromatin landscape and gene expression in normal and transformed cells and examine the functional importance of these modifications in leukemias via cell based assays and mouse models.

5P50 CA206963-04 Ebert (PI) 9/19/2017 - 7/31/2022
NIH / NCI
SPORE in Myeloid Malignancies: Project 1
The major goals of this project are to characterize newly developed MLL1-Menin inhibitors and work to bring one of these small molecules to clinical assessment.

2P01 CA066996-21 Ebert (PI) 5/1/2020 – 4/30/2025
NCI
Development of Novel Therapeutic Strategies in Human Leukemias
Project 3: Biology and therapeutic targeting of zinc finger transcription factors in AML
The immediate objective of this research is to functionally characterize the role of ZnF transcription factors in AML, leveraging a highly collaborative Program of Investigators in chemical biology, structural biology, leukemia biology, cancer modeling, and epigenome science. The long-term goal is to increase AML cure rates by targeting gene regulatory pathways.

Consortium Grant Roberts et al (MPI) 12/1/2017 - 11/30/2022
St. Jude Children's Research Hospital
Chromatin Regulation in Pediatric Cancer
The goal of this consortium is to advance understanding of epigenetic regulation of transcription and development in contexts directly relevant to the most problematic subtypes of childhood cancer. The Collaborative brings together six investigators who are leaders in their fields of investigations, ranging from basic chromatin biology, epigenetic and transcriptional regulation, epigenomics, and modeling of pediatric cancer.

TRP #6607-20 Armstrong (PI) 7/1/2019 – 6/30/2022
LLS
Selective BRD4 degradation in pediatric leukemia
The major goal of this project is to chemically optimize our BRD4-degrader and evaluate its mechanisms and anti-cancer effects in models of leukemia to determine if it is a novel therapeutic for the treatment of pediatric acute leukemia.

Development Seed Grant Kuroda/Armstrong (PI) 4/1/2019 – 3/31/2021
Harvard Medical School

Dynamic transitions in cell type-specific transcriptional programming
The major goal of this collaboration is to investigate the molecular interactions that govern cell-type specific transitions in transcriptional programs.

Completed Support (last 3 years):

Individual Award Armstrong — Armstrong (PI) — 12/17/2019- 12/16/2020
Curing Kids' Cancer
Therapeutic targeting of IKZF1/IKAROS to improve clinical outcomes in MLL-rearranged AML

1R01 CA204915-01S1 — Stegmaier/Sweet-Cordero (MPI) — 1/1/2017 - 11/30/2020
NIH
Dissecting the Pathogenesis of Ewing Sarcoma with Integrative Genomics (Administrative Supplement)

2017 Innovation Grant — Armstrong (PI) — 10/1/2017 - 9/30/2019
Alex's Lemonade Stand Foundation
Targeting BRD9 in Sarcoma

Research Award — Armstrong (PI) — 12/1/2016 - 11/30/2018
Cookies for Kids' Cancer
New Combination Therapies for MLL-rearranged Acute Lymphoblastic Leukemia