BIOGRAPHICAL SKETCH

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NAME: Abdel-Wahab, Omar

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

POSITION TITLE: Associate Member, Human Oncology and Pathogenesis Program

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)	END DATE MM/YYYY	FIELD OF STUDY
Duke University	BS	05/2000	Biology
Duke University School of Medicine	MD	05/2004	

A. Personal Statement

The Abdel-Wahab lab is focused on understanding the functional implications of somatic mutations found in patients with hematopoietic malignancies with the hopes of improving our understanding of disease biology and develop novel therapies. Currently, we are centered on the role of mutations affecting the regulation of gene expression in hematologic malignancies. This includes mutations in RNA splicing factors (SRSF2, SF3B1, ZRSR2, and U2AF1) and epigenetic modifiers (including mutations in Polycomb-group proteins (EZH2, ASXL1, ASXL2, and BAP1) as well as proteins regulating DNA methylation). Finally, we are also interested in developing mechanism-based approaches to targeting genetic alterations across a variety of hematologic malignancies.

1. Inoue, D, Polaski, JT, Taylor, J, Castel, P, Chen, S, Kobayashi, S, Hogg, SJ, Hayashi, Y, Bello Pineda, JM, El Marabti, E, Erickson, C, Knorr, K, Fukumoto, M, Yamazaki, H, Tanaka, A, Fukui, C, Lu, SX, Durham, BH, Liu, B, Wang, E, Mehta, S, Zakheim, D, Garippa, R, Chew, G-L, McCormick, F, Bradley, RK, **Abdel-Wahab, O**. Minor intron retention drives clonal hematopoietic disorders and diverse cancer predisposition. Nature Genetics 2021 (in press)
2. Yoshimi A, Lin KT, Wiseman DH, Rahman MA, Pastore A, Wang B, Lee SC, Micol JB, Zhang XJ, de Botton S, Penard-Lacronique V, Stein EM, Cho H, Miles RE, Inoue D, Albrecht TR, Somervaille TCP, Batta K, Amaral F, Simeoni F, Wilks DP, Cargo C, Intlekofer AM, Levine RL, Dvinge H, Bradley RK, Wagner EJ, Krainer AR, **Abdel-Wahab O**. Coordinated alterations in RNA splicing and epigenetic regulation drive leukaemogenesis. Nature. 2019 Oct;574(7777):273-277. PubMed PMID: 31578525; PubMed Central PMCID: PMC6858560.
3. Lee SC, Dvinge H, Kim E, Cho H, Micol JB, Chung YR, Durham BH, Yoshimi A, Kim YJ, Thomas M, Lobry C, Chen CW, Pastore A, Taylor J, Wang X, Krivtsov A, Armstrong SA, Palacino J, Buonamici S, Smith PG, Bradley RK, **Abdel-Wahab O**. Modulation of splicing catalysis for therapeutic targeting of leukemia with mutations in genes encoding spliceosomal proteins. Nat Med. 2016 Jun;22(6):672-8. PubMed PMID: 27135740; PubMed Central PMCID: PMC4899191.
4. Kim E, Ilagan JO, Liang Y, Daubner GM, Lee SC, Ramakrishnan A, Li Y, Chung YR, Micol JB, Murphy ME, Cho H, Kim MK, Zebari AS, Aumann S, Park CY, Buonamici S, Smith PG, Deeg HJ, Lobry C, Aifantis I, Modis Y, Allain FH, Halene S, Bradley RK, **Abdel-Wahab O**. SRSF2 Mutations Contribute to Myelodysplasia by Mutant-Specific Effects on Exon Recognition. Cancer Cell. 2015 May 11;27(5):617-30. PubMed PMID: 25965569; PubMed Central PMCID: PMC4429920.

B. Positions and Honors

Positions and Employment

2004 - 2005 Intern, Dept. of Medicine, Massachusetts General Hospital, Boston, MA
2005 - 2007 Resident, Dept. of Medicine, Massachusetts General Hospital, Boston, MA
2007 - 2008 Fellow, Dept. of Medicine, Memorial Sloan Kettering Cancer Center (MSK), New, York NY

2008 - 2012	Postdoctoral Fellow, Human Oncology and Pathogenesis Program, MSK, New, York NY
2009 - 2011	Instructor, Leukemia Service, Dept. of Medicine, MSK, New, York NY
2011 - 2012	Assistant Member (non-tenure track), Leukemia Service, Dept. of Medicine, MSK, New, York NY
2012 -	Assistant Member (tenure track), Human Oncology and Pathogenesis Program, MSK, New, York NY
2016 -	Co-Director, Hematology/Medical Oncology Fellowship Program, MSK, New, York NY
2017 -	Associate Member, Human Oncology and Pathogenesis Program, MSK, New, York NY
2020 -	Director, MSK Center of Hematologic Malignancies, New, York NY

Honors

1999	Phi Beta Kappa, Duke University
2004	Alpha Omega Alpha, Duke University
2008	John Mendelsohn House-staff Teaching Award, Memorial Sloan Kettering Cancer Center
2008	Chief Fellow, Hematology/Oncology, Memorial Sloan Kettering Cancer Center
2009	Research Training Award for Fellows, American Society of Hematology (ASH)
2010	Fellow Scholar Award, ASH
2011	Fellow Scholar Award, Gabrielle's Angel Foundation
2012	Paul Sherlock House-staff Teaching Award, Memorial Sloan Kettering Cancer Center
2012	Josie Robertson Young Investigator Award, Memorial Sloan Kettering Cancer Center
2012	Post-doctoral Award in Bone Marrow Failure Research, U.S. Dept. of Defense
2013	Damon Runyon Clinical Investigator Award, Damon Runyon Foundation
2013	Junior Faculty Scholar Award, ASH
2014	V Scholar Award, V Foundation
2015	Leukemia & Lymphoma Society Clinical Scholar Award, Leukemia & Lymphoma Society
2015	Young Physician Scientist Award, American Society of Clinical Investigation (ASCI)
2015	Joanne Levy Memorial Award for Outstanding Achievement, ASH
2016	Pershing Square Sohn Prize for Young Investigators in Cancer Research, Pershing Square Sohn Cancer Research Alliance
2017	Seldin-Smith Award for Pioneering Research, ASCI
2018	Member, ASCI

C. Contribution to Science

1. **Identification that cancer-associated mutations in RNA splicing factors confer change-of-function and novel therapeutic vunerabilities.** Our group was the first to generate models of mutations in RNA splicing factors as found in patients with leukemias and solid tumors. In comparison to models with conditional deletion of the same factors we identified that cancer-associated mutations in SRSF2 confer an alteration of function, distinct from loss of function. We subsequently identified that cancer cells containing heterozygous point mutations in RNA splicing factors are genetically and pharmacologically dependent on otherwise wild-type RNA splicing catalysis. This has led to preclinical studies as well as early phase clinical trials testing the effects of drugs binding SF3B1, degrading RNA splicing factors, or altering post-translational modifications of splicing proteins as novel therapies for spliceosomal mutant leukemias.

    a. Fong JY, Pignata L, Goy PA, Kawabata KC, Lee SC, Koh CM, Musiani D, Massignani E, Kotini AG, Penson A, Wun CM, Shen Y, Schwarz M, Low DH, Rialdi A, Ki M, Wollmann H, Mzoughi S, Gay F, Thompson C, Hart T, Barbash O, Luciani GM, Szewczyk MM, Wouters BJ, Delwel R, Papapetrou EP, Barsyte-Lovejoy D, Arrowsmith CH, Minden MD, Jin J, Melnick A, Bonaldi T, **Abdel-Wahab O (co-corresponding),** Guccione E. Therapeutic Targeting of RNA Splicing Catalysis through Inhibition of Protein Arginine Methylation. Cancer Cell. 2019 Aug 12;36(2):194-209.e9. PubMed PMID: 31408619; PubMed Central PMCID: PMC7194031.

    b. Wang E, Lu SX, Pastore A, Chen X, Imig J, Chun-Wei Lee S, Hockemeyer K, Ghebrechristos YE, Yoshimi A, Inoue D, Ki M, Cho H, Bitner L, Kloetgen A, Lin KT, Uehara T, Owa T, Tibes R, Krainer AR,

Abdel-Wahab O (co-corresponding), Aifantis I. Targeting an RNA-Binding Protein Network in Acute Myeloid Leukemia. Cancer Cell. 2019 Mar 18;35(3):369-384.e7. PubMed PMID: 30799057; PubMed Central PMCID: PMC6424627.

c. Lee SC, Dvinge H, Kim E, Cho H, Micol JB, Chung YR, Durham BH, Yoshimi A, Kim YJ, Thomas M, Lobry C, Chen CW, Pastore A, Taylor J, Wang X, Krivtsov A, Armstrong SA, Palacino J, Buonamici S, Smith PG, Bradley RK (co-corresponding), **Abdel-Wahab O (co-corresponding).** Modulation of splicing catalysis for therapeutic targeting of leukemia with mutations in genes encoding spliceosomal proteins. Nat Med. 2016 Jun;22(6):672-8. PubMed PMID: 27135740; PubMed Central PMCID: PMC4899191.

d. Kim E, Ilagan JO, Liang Y, Daubner GM, Lee SC, Ramakrishnan A, Li Y, Chung YR, Micol JB, Murphy ME, Cho H, Kim MK, Zebari AS, Aumann S, Park CY, Buonamici S, Smith PG, Deeg HJ, Lobry C, Aifantis I, Modis Y, Allain FH, Halene S, Bradley RK (co-corresponding), **Abdel-Wahab O (co-corresponding).** SRSF2 Mutations Contribute to Myelodysplasia by Mutant-Specific Effects on Exon Recognition. Cancer Cell. 2015 May 11;27(5):617-30. PubMed PMID: 25965569; PubMed Central PMCID: PMC4429920.

2. **Discovery of the functional importance of mutations in epigenetic modifiers in myeloid leukemias and clonal hematopoiesis and the interplay of aberrant epigenetic modifications and RNA splicing in leukemias.** My postdoctoral work was focused on identification of the clinical and biological role of mutations in the epigenetic modifiers TET2 and ASXL1 in hematopoiesis. This led to the initial identification that TET2 and IDH1/2 mutations are mutually exclusive in leukemia and have overlapping functions and led to the discovery that IDH1/2 mutations result in hypermethylation of DNA by impairing the enzymatic function of TET2. Since then, we discovered that mutations in IDH2 frequently overlap with those in the RNA splicing factor SRSF2. Together, the two mutations result in malignant transformation. These data identify an important pathogenic role for cross talk between altered epigenetic state and splicing in leukemia, provide functional evidence that mutations in RNA splicing factors drive leukemia development, and uncover spliceosomal changes as a major mediator of IDH2-mutant leukemogenesis.

a. Inoue D, Chew GL, Liu B, Michel BC, Pangallo J, D'Avino AR, Hitchman T, North K, Lee SC, Bitner L, Block A, Moore AR, Yoshimi A, Escobar-Hoyos L, Cho H, Penson A, Lu SX, Taylor J, Chen Y, Kadoch C, **Abdel-Wahab O (co-corresponding)**, Bradley RK **(co-corresponding)**. Spliceosomal disruption of the non-canonical BAF complex in cancer. Nature. 2019 Oct;574(7778):432-436. PubMed PMID: 31597964; PubMed Central PMCID: PMC6858563.

b. **Abdel-Wahab O,** Gao J, Adli M, Dey A, Trimarchi T, Chung YR, Kuscu C, Hricik T, Ndiaye-Lobry D, Lafave LM, Koche R, Shih AH, Guryanova OA, Kim E, Li S, Pandey S, Shin JY, Telis L, Liu J, Bhatt PK, Monette S, Zhao X, Mason CE, Park CY, Bernstein BE, Aifantis I, Levine RL. Deletion of Asxl1 results in myelodysplasia and severe developmental defects in vivo. J Exp Med. 2013 Nov 18;210(12):2641-59. PubMed PMID: 24218140; PubMed Central PMCID: PMC3832937.

c. **Abdel-Wahab O,** Adli M, LaFave LM, Gao J, Hricik T, Shih AH, Pandey S, Patel JP, Chung YR, Koche R, Perna F, Zhao X, Taylor JE, Park CY, Carroll M, Melnick A, Nimer SD, Jaffe JD, Aifantis I, Bernstein BE, Levine RL. ASXL1 mutations promote myeloid transformation through loss of PRC2-mediated gene repression. Cancer Cell. 2012 Aug 14;22(2):180-93. PubMed PMID: 22897849; PubMed Central PMCID: PMC3422511.

d. **Abdel-Wahab O**, Mullally A, Hedvat C, Garcia-Manero G, Patel J, Wadleigh M, Malinge S, Yao J, Kilpivaara O, Bhat R, Huberman K, Thomas S, Dolgalev I, Heguy A, Paietta E, Le Beau MM, Beran M, Tallman MS, Ebert BL, Kantarjian HM, Stone RM, Gilliland DG, Crispino JD, Levine RL. Genetic characterization of TET1, TET2, and TET3 alterations in myeloid malignancies. Blood. 2009 Jul 2;114(1):144-7. PubMed PMID: 19420352; PubMed Central PMCID: PMC2710942.

3. **Identification of the clinical importance of mutational profiling to the clinical care of patients with hematologic malignancies.** My lab has been involved with identifying genetic alterations with clinical and/or prognostic significance in patients with a variety of hematologic malignancies including acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), hairy cell leukemia (HCL), and histiocytic neoplasms.

a. Durham BH, Lopez Rodrigo E, Picarsic J, Abramson D, Rotemberg V, De Munck S, Pannecoucke E, Lu SX, Pastore A, Yoshimi A, Mandelker D, Ceyhan-Birsoy O, Ulaner GA, Walsh M, Yabe M, Petrova-Drus K, Arcila ME, Ladanyi M, Solit DB, Berger MF, Hyman DM, Lacouture ME, Erickson C, Saganty R, Ki M, Dunkel IJ, Santa-María López V, Mora J, Haroche J, Emile JF, Decaux O, Geissmann F, Savvides SN, Drilon A, Diamond EL, **Abdel-Wahab O.** Activating mutations in CSF1R and additional receptor tyrosine kinases in histiocytic neoplasms. Nat Med. 2019 Dec;25(12):1839-1842. PubMed PMID: 31768065; PubMed Central PMCID: PMC6898787.

b. Diamond EL, Durham BH, Ulaner GA, Drill E, Buthorn J, Ki M, Bitner L, Cho H, Young RJ, Francis JH, Rampal R, Lacouture M, Brody LA, Ozkaya N, Dogan A, Rosen N, Iasonos A, **Abdel-Wahab O (co-corresponding),** Hyman DM. Efficacy of MEK inhibition in patients with histiocytic neoplasms. Nature. 2019 Mar;567(7749):521-524. PubMed PMID: 30867592; PubMed Central PMCID: PMC6438729.

c. Taylor J, Pavlick D, Yoshimi A, Marcelus C, Chung SS, Hechtman JF, Benayed R, Cocco E, Durham BH, Bitner L, Inoue D, Chung YR, Mullaney K, Watts JM, Diamond EL, Albacker LA, Mughal TI, Ebata K, Tuch BB, Ku N, Scaltriti M, Roshal M, Arcila M, Ali S, Hyman DM, Park JH, **Abdel-Wahab O.** Oncogenic TRK fusions are amenable to inhibition in hematologic malignancies. J Clin Invest. 2018 Aug 31;128(9):3819-3825. PubMed PMID: 29920189; PubMed Central PMCID: PMC6118587.

d. Diamond EL, Durham BH, Haroche J, Yao Z, Ma J, Parikh SA, Wang Z, Choi J, Kim E, Cohen-Aubart F, Lee SC, Gao Y, Micol JB, Campbell P, Walsh MP, Sylvester B, Dolgalev I, Aminova O, Heguy A, Zappile P, Nakitandwe J, Ganzel C, Dalton JD, Ellison DW, Estrada-Veras J, Lacouture M, Gahl WA, Stephens PJ, Miller VA, Ross JS, Ali SM, Briggs SR, Fasan O, Block J, Héritier S, Donadieu J, Solit DB, Hyman DM, Baselga J, Janku F, Taylor BS, Park CY, Amoura Z, Dogan A, Emile JF, Rosen N, Gruber TA, **Abdel-Wahab O.** Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms. Cancer Discov. 2016 Feb;6(2):154-65. PubMed PMID: 26566875; PubMed Central PMCID: PMC4744547.

4. **Identification of the cell-of-origin of chronic myeloid and lymphoid leukemias.** Our lab has worked to identify the cell-of-origin of rare and poorly understood forms of leukemias including chronic myelomonocytic leukemia (CMML), hairy cell leukemia (HCL), and the histiocytic neoplasms Erdheim-Chester Disease and Langerhans Cell Histiocytosis. In so doing, we have generated the first preclinical models of HCL and the first patient-derived xenografts of CMML, HCL, and histiocytoses.

   a. Mass E, Jacome-Galarza CE, Blank T, Lazarov T, Durham BH, Ozkaya N, Pastore A, Schwabenland M, Chung YR, Rosenblum MK, Prinz M, **Abdel-Wahab O (equal contributor),** Geissmann F (equal contributor). A somatic mutation in erythro-myeloid progenitors causes neurodegenerative disease. Nature. 2017 Sep 21;549(7672):389-393. PubMed PMID: 28854169; PubMed Central PMCID: PMC6047345.

   b. Yoshimi A, Balasis ME, Vedder A, Feldman K, Ma Y, Zhang H, Lee SC, Letson C, Niyongere S, Lu SX, Ball M, Taylor J, Zhang Q, Zhao Y, Youssef S, Chung YR, Zhang XJ, Durham BH, Yang W, List AF, Loh ML, Klimek V, Berger MF, Stieglitz E, Padron E, **Abdel-Wahab O.** Robust patient-derived xenografts of MDS/MPN overlap syndromes capture the unique characteristics of CMML and JMML. Blood. 2017 Jul 27;130(4):397-407. PubMed PMID: 28576879; PubMed Central PMCID: PMC5533204.

   c. Chung SS, Kim E, Park JH, Chung YR, Lito P, Teruya-Feldstein J, Hu W, Beguelin W, Monette S, Duy C, Rampal R, Telis L, Patel M, Kim MK, Huberman K, Bouvier N, Berger MF, Melnick AM, Rosen N, Tallman MS, Park CY, **Abdel-Wahab O.** Hematopoietic stem cell origin of BRAFV600E mutations in hairy cell leukemia. Sci Transl Med. 2014 May 28;6(238):238ra71. PubMed PMID: 24871132; PubMed Central PMCID: PMC4501573.

   d. Busque L, Patel JP, Figueroa ME, Vasanthakumar A, Provost S, Hamilou Z, Mollica L, Li J, Viale A, Heguy A, Hassimi M, Socci N, Bhatt PK, Gonen M, Mason CE, Melnick A, Godley LA, Brennan CW, **Abdel-Wahab O (equal contributor),** Levine RL (equal contributor). Recurrent somatic TET2 mutations in normal elderly individuals with clonal hematopoiesis. Nat Genet. 2012 Nov;44(11):1179-81. PubMed PMID: 23001125; PubMed Central PMCID: PMC3483435.

https://www.ncbi.nlm.nih.gov/myncbi/omar.abdel-wahab.1/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1 R01 CA251138-01, NCI — Abdel-Wahab, Omar (PI)
08/01/20-07/31/24
Interrogating the minor spliceosome to understand and treat leukemia

2 R01HL128239-06, NHLBI — Abdel-Wahab, Omar (MPI)
01/08/15-01/07/24
Genetic and molecular basis for SRSF2 mutations in myelodysplasia

1 R01 CA201247-01A1, NCI — Abdel-Wahab, Omar (PI)
04/01/16-03/31/21
Origins of BRAF-mutant hematologic malignancies and their therapeutic resistance

R01CA242020, NCI — Abdel-Wahab, Omar (PI)
06/01/20-05/31/25
Targeting an RNA Binding Protein Network in Acute Myeloid Leukemia

LLS 01, Leukemia and Lymphoma Society — Abdel-Wahab, Omar (PI)
10/01/17-09/30/22
LLS SCOR: Interventional Epigenetics in Myeloid Malignancies

W81XWH 18-1-0383, Dept. of Defense — Abdel-Wahab, Omar (PI)
08/15/18-08/14/21
Mechanistic and Therapeutic Implications of Spliceosomal Gene Mutations in ER+ Breast Cancer

1 R01 HL138090-01, NHLBI — Geissmann, Frederic (PI)
8/16/17 - 6/30/21
Lineages and pathophysiology of clonal histiocytic disorders

Completed Research Support

Dr. Abdel-Wahab has an extensive list of completed grants from both federal and non-federal sponsors.