BIOGRAPHICAL SKETCH

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NAME: Alachkar, Houda

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

POSITION TITLE: Assistant Professor, USC School of Pharmacy, University of Southern California

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
Aleppo University Pharmacy School, Aleppo	BS	07/2002	Pharmacy
Wright State University, Dayton, OH	MS	04/2005	Pharmacology & Toxicology
Ohio Northern University, Ada, OH	PharmD	12/2011	Pharmacy
Ohio State University, Columbus, OH	PhD	12/2012	Biomedical Sciences/Pharmacology
University of Chicago, Chicago, IL	NA	NA	Clinical pharmacology and pharmacogenomics

A. Personal Statement

One of my most distinguishing characteristics is my unique mix of work and educational background. I have several years of experience in pharmacy practice in addition to my extensive academic training under the mentorship of some of the most renowned scientists in the world in the field of pharmacogenomics and cancer therapeutics. I believe my excellent knowledge and experience in molecular and clinical pharmacology and basic research combined with my leadership skills had shaped my research career as an independent young investigator.

My current research in cancer therapeutics focuses on investigating and developing novel therapeutic approaches in acute myeloid leukemia aiming to improve the dismal outcome of patients with this disease. I have a broad knowledge and research experience in basic and translational investigation of novel therapeutic agents for acute myeloid leukemia (AML). I have explored several investigational drugs in the last 6 years; such as small molecule kinase inhibitors (TOPK inhibitor, MELK inhibitor), natural compounds (Silvestrol) proteasome inhibitor (Bortezomib) and P53 antisense (Cenersen). The findings of my research made important contributions to the field of preclinical development of novel therapeutic approaches in AML. The research I performed has resulted in numerous abstracts presented in several national scientific meetings such as: The American Association of Cancer Research (AACR) Annual Meeting, The American Society of Hematology (ASH) Annual Meeting, AAPS National Biotechnology Conference and received several awards. I have published several articles in high impact journals.

B. Positions and Honors

Positions and Employment

2008-2012 Graduate Res. Associate, Biomedical Sciences, Ohio State University, Columbus, OH
2013-2015 Clinical Pharmacology Fellow, CCPP, University of Chicago, Chicago, IL
2015-2015 Assistant Professor, University of Chicago, Chicago, IL
2015- Assistant Professor, University of Southern California, Ca

Other Experience and Professional Memberships

2010-2014 Associate Member, American Association of Cancer Research (AACR)

2013-2014 Member, American Society for Clinical Pharmacology and Therapeutics (ASCPT)
2013-pres Licensed Registered Pharmacist in Illinois
2004-pres Licensed Registered Pharmacist in Ohio

Honors

2015 The University of Chicago, Janet D. Rowley Research Day Best abstract
2014 The Clinical Pharmacology and Pharmacogenomics Featured Fellow.
2014 The University of Chicago BSD Postdoctoral Association Travel Award.
2014 AACR Scholar-in-Training Award.
2012 Ray Travel Award, 2012 OSU, Columbus, OH
2012 The American Society of Hematology (ASH) 53rd Abstract Achievement Award.
2012 Finalist, the Biomedical Sciences Graduate Program's Travel Award Abstract Competition, 2012. OSU, Columbus, OH.
2012 Finalist, Edward F. Hayes Graduate Research Forum, OSU, Columbus, OH
2010 Finalist, Edward F. Hayes Graduate Research Forum, OSU, Columbus, OH

C. Contribution to Science

1. My earlier work published in the Journal of Clinical Investigation (PMID: 24590286), highlighted the role of SPARC in Acute Myeloid Leukemia (AML) and identified it as a novel prognostic marker and a therapeutic target in this disease. I found that SPARC overexpression is associated with adverse outcome in Cytogenetic Normal (CN-) AML patients. I also reported that SPARC overexpression was mediated by the SP1/NF-κB transactivation complex, and results in promoting aggressive leukemia growth in leukemia cells and in murine models of AML. Furthermore, I described the mechanism by which SPARC mediates leukemia growth by demonstrating that secreted SPARC activated the integrin-linked kinase/AKT (ILK/AKT) pathway, likely via integrin interaction, and subsequent β-catenin signaling, which is involved in leukemia cell self-renewal. The Pharmacologic inhibition of the SP1/NF-κB complex resulted in SPARC downregulation and leukemia growth inhibition.

- **Alachkar H**, Santhanam R, Maharry K, Metzeler KH, Huang X, Kohlschmidt J, Mendler JH, Benito JM, Hickey C, Neviani P, Dorrance AM, Anghelina M, Khalife J, Tarighat SS, Volinia S, Whitman SP, Paschka P, Hoellerbauer P, Wu YZ, Han L, Bolon BN, Blum W, Mrózek K, Carroll AJ, Perrotti D, Andreeff M, Caligiuri MA, Konopleva M, Garzon R, Bloomfield CD, Marcucci G. SPARC promotes leukemic cell growth and predicts acute myeloid leukemia outcome. ***J Clin Invest***. 2014 Mar 3. PMID: 24590286.

2. I contributed significantly to the study published in the Science Translational Medicine journal (PMID: 25338756), in which we developed and investigated a potent TOPK inhibitor, OTS964 which inhibits TOPK kinase activity with high affinity and selectivity. This inhibitor causes a cytokinesis defect and the subsequent apoptosis of cancer cells in vitro as well as in xenograft models of human lung cancer. Although administration of the free compound induced hematopoietic adverse reactions (leukocytopenia associated with thrombocytosis), the drug delivered in a liposomal formulation effectively caused complete regression of transplanted tumors without showing any adverse reactions in mice. Our results suggested that the inhibition of TOPK activity is a viable therapeutic option for the treatment of various human cancers with upregulated TOPK.

- Matsuo Y, Park J, Miyamoto T, Yamamoto S, Hisada S, **Alachkar H**, and Nakamura Y. Complete tumor regression of xenograft model of human cancers with TOPK inhibitor in liposomal formulation. ***Science Translational Medicine***. 2014 Oct 22. PMID: 25338756

3. I am also the lead author on a study that investigated the role of MELK in AML published in Oncotarget (PMID: 25365263). This study shows that MELK is frequently upregulated in AML with complex karyotypes and is associated with worse clinical outcome. MELK knockdown resulted in growth inhibition and apoptosis of

leukemic cells. Hence, we investigated the potent anti-leukemia activity of OTS167, a small molecule MELK kinase inhibitor, in AML, and found that the compound induced cell differentiation and apoptosis as well as decreased migration of AML cells. MELK expression was positively correlated with the expression of FOXM1 as well as its downstream target genes. Furthermore, MELK inhibition resulted in downregulation of FOXM1 activity and the expression of its downstream targets. Taken together, and given that OTS167 is undergoing a phase I clinical trial in solid cancer, my works give the rational for further preclinical and clinical evaluation of this compound as a novel targeted therapy for AML patients.

- **Alachkar H**, Mutonga M, Metzeler KH, Fulton N, Malnassy G, Herold T, Hiddermann W, Matsuo Y, Stock W, Nakamura Y. Preclinical efficacy of Maternal Embryonic Leucine-zipper Kinase (MELK) Inhibition in Acute Myeloid Leukemia. ***Oncotarget***. 2014 Oct 28. PMID:25365263

4. My yet unpublished ongoing work on investigating the activity of TOPK in AML with FLT3-ITD has provided the rationale for the first in human clinical trial for TOPK inhibitor in AML. In addition it helped expanding the research funds for our labs by obtaining a V Foundation grant. Gain-of-function mutations of FLT3 (*FLT3*-ITD), comprises up to 30% of CN-AML in all age groups and is associated with adverse prognosis with current chemotherapeutic approaches. Current FLT3 Kinase inhibitors have been tested extensively, but have not yet resulted in a survival benefit and novel therapies are eagerly awaited. My previous work demonstrated that TOPK, is expressed in AML, but not normal CD34+ cells and that TOPK knockdown decreased cell viability. Treatment of AML cells with TOPK inhibitor (OTS514) resulted in a dose-dependent decrease in cell viability, particularly in *FLT3*-mutated cells including blasts obtained from patients relapsed after FLT3-inhibitor treatment. Using an MV4-11-engrafted mouse model, we found that OTS514 treated mice survived significantly longer than vehicle-treated mice. Thus, OTS514 preferential activity in FLT3-ITD mutated AML represents a novel targeted therapy for this adverse risk subset of AML. Importantly, we found that OTS514 downregulated FLT3 expression in both transcriptional and protein levels and decreased CEBPA phosphorylation. This suggests that TOPK inhibitor acts in a mechanism that is totally different from that of FLT3 kinase inhibitors currently in clinical development.

5. I have also explored several investigational drugs in the last 6 years; such as natural compounds (Silvestrol) and P53 antisense (Cenersen). The findings of my research made important contributions to the field of preclinical development of novel therapeutic approaches in AML.

- **Alachkar H**, Santhanam R, Harb JG, Lucas DM, Oaks JJ, Hickey CJ, Pan L, Kinghorn AD, Caligiuri MA, Perrotti D, Byrd JC, Garzon R, Grever MR, Marcucci G. Silvestrol Exhibits Significant In vivo and In vitro Antileukemic Activities and Inhibits FLT3 and miR-155 Expression in Acute Myeloid Leukemia. ***Journal of Hematology and Oncology*** 2013 Mar. PMID:23497456
- **Alachkar H**, Xie Z, Marcucci G, Chan KK. Determination of cellular uptake and intracellular levels of Cenersen (Aezea(®), EL625), a p53 antisense oligonucleotide in acute myeloid leukemia cells. J ***Pharm Biomed Anal.*** 2012 Dec;71:228-32. doi: 10.1016/j.jpba.2012.08.011. Epub,2012Aug19.PMID:22944355

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1TkXbbb9m6f5g/bibliography/46549112/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research

V Foundation **(Stock)** 09/01/14-08/31/17
TOPK (T-LAK cell-originated protein kinase): A new target for FLT3 mutated AML
To define the mechanism by which a TOPK inhibitor treatment results in preferential anti-leukemia activity in FLT3-ITD positive AML.
Role: Study and experimental design, oversee and perform experiments and data analysis.

CTSA-ITM Core Subsidies funding 05/2015-05/2016
National Center for Advancing Translational Sciences of the NIH through Grant # UL1 TR000430.

Complete Research

The University of Chicago Cancer Research Foundation 04/2013 - 04/2015
Women's Board and Division of Biological Science