THE OHIO STATE UNIVERSITY
BIOMEDICAL SCIENCES
GRADUATE PROGRAM
AUTUMN 2012

[Houda Alachkar]
PhD Candidate

Novel Biological Insights and Therapeutic Approaches
in High-Risk Acute Myeloid Leukemia (AML):
“SPARC Contributes to Leukemia Growth and Aggressive Disease in
AML”

[November, 20th 2012]
BRT, Room 105
[8:30 AM]
VITA

[2001] ......................... [BS-Pharmacy] [Aleppo University]

[2005] ......................... [MS-Pharmacology&Toxicology] [Wright State University]

[2011] ......................... [PharmD] [Ohio Northern University]

[2008-present] .................. [PhD Candidate] [The Ohio State University]

COMMITTEE MEMBERS

Guido Marcucci, MD (Advisor)

Michael Caligiuri, MD

Danillo Perrotti, MD, PhD

Lai-Chu Wu, PhD

AWARDS AND HONORS

- Ray Travel Award, 2012 OSU, Columbus, OH
- 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.
- Finalist, Edward F. Hayes Graduate Research Forum, 2012 OSU, Columbus, OH.
- Finalist, Edward F. Hayes Graduate Research Forum, 2010 OSU, Columbus, OH

FUTURE PLANS

I am currently interviewing at several institutions for academic/research position in Clinical Pharmacology/Cancer therapeutics.
RECENT PUBLICATIONS


- Frasch HF, Barbero AM, **Alachkar H**, McDougal JN. Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutan Ocul Toxicol. 2007;26(2):147-60. PMID:17612981

ABSTRACT

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by clonal proliferation of myeloid progenitors with a reduced ability to differentiate into more mature functional blood cells. Consequently, an accumulation of leukemic cells (blasts) in bone marrow and blood occurs and leads to hematopoietic failure. Even with recent progress in understanding the biologic and genetic changes that underlie the disease, most patients with AML fail to achieve long-term survival. This highlights the need for novel therapeutic strategies that would improve outcome. Cytogenetic aberrations have long been shown to be the most important risk factor for predicting outcome in AML and have therefore been used to guide treatment. However, each cytogenetic risk group presents with molecular heterogeneity, which may explain different outcome among patients with similar chromosome aberrations. Cytogenetically normal AML (CN-AML) is the largest cytogenetic group (45% of AML) and the best molecularly characterized among both younger and older AML patients. Frequent genetic mutations with prognostic significance have been identified in CN-AML. Patients with FLT3 internal tandem duplication (ITD) or IDH2-R172 have been shown to have worse outcome, while patients with CEBPA or NPM1 mutations are commonly reported to have more favorable prognosis. The cytogenetic and molecular aberrations associated with AML influence the expression of downstream target genes that encode proteins involved in complex biologic networks supporting leukemogenesis. Therefore, microarray genome-wide gene-expression profiling and microRNA-expression profiling assays provide molecular insight into the underlying biology of the different disease subsets, offer diagnostic and prognostic information, and potentially reveal novel therapeutic targets. Our research focused on two major aims. Aim 1: identify novel therapeutic targets and prognostic markers employing genome-wide analyses of gene expression signatures in high risk AML patients. Aim 2: investigate novel therapeutic approaches directed toward previously identified molecular targets in high risk disease. Our work for aim 1 resulted in identifying SPARC as a novel molecular and therapeutic target in AML. We demonstrated a functional, mechanistic and clinical implication of SPARC in AML, revealing that high SPARC expression promoted growth advantage *in vitro*, aggressive disease *in vivo*, and
worse outcome in CN-AML patients. SPARC acts likely via activation of ILK/AKT/β-catenin pathways.

Our work for aim 2 focused on investigating the preclinical and pharmacological activity of the natural initiation of translation inhibitor, silvestrol in FLT3-ITD positive AML denoting a large proportion of high risk AML patients. We demonstrated that silvestrol had a potent in vitro and in vivo anti-leukemia activity in FLT3-ITD and FLT3 overexpressing AML cells. Silvestrol inhibited FLT3 mRNA translation resulting in FLT3 protein down-regulation and in turn inhibition of aberrant tyrosine kinase activity.

In conclusion, we identified an original molecular target with novel biological insights, and investigated innovative therapeutic approaches suitable for high risk subsets of AML. This research will significantly advance understanding of AML and open new avenues of treatment strategies, which will result in optimized patient care, and improved clinical outcome.

RECENT ABSTRACTS AND PRESENTATION


