
**Division of
Hematology/Oncology
Department of Medicine
Northwestern University
Feinberg School of
Medicine**

Alex C. Minella, M.D.
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**NORTHWESTERN
UNIVERSITY**

December 5, 2008

Sue Anne Tae
Northwestern University Feinberg School of Medicine
Ward Building, Room 1-003
Chicago, IL 60611

Dear Ms. Tae,

Attached please find materials supporting my application to join the medical student Summer Research and Research Thesis Programs as a faculty mentor, including an updated C.v., research summary, and description of possible student research projects. I am on the faculty of the department of Medicine in the division of hematology/oncology at Northwestern. I am also part of the Northwestern IGP in the Cancer Biology group and a full member of the Robert H. Lurie Comprehensive Cancer Center, with affiliations in the Cancer Cell Biology and Breast Cancer Programs.

My work focuses on the study of the mammalian cell cycle in normal and cancer cells. I believe that my research program will be of significant interest to students interested in gaining skills and knowledge applicable to studies of basic mechanisms of tumorigenesis. Additionally, students will have the opportunity, if desired, to participate in research involving mouse models of human cancer.

In my laboratory, students can expect regular interactions with and close supervision by me. I will have a vested interest in any student's success, and mentorship of graduate and medical students is a priority. Above all, I aim to preserve a collaborative, cooperative environment in which students, technicians, and post-docs learn and practice meticulous, safe, and ethical research methods.

I hope you will find this background information useful. Please feel free to contact me regarding other questions relating to this application.

Sincerely,

A handwritten signature in black ink, appearing to read "Alex Minella".

Alex Minella

Curriculum vitae

Alexander C. Minella, M.D.

Assistant Professor
Northwestern University Feinberg School of Medicine
Department of Medicine, Hematology/Oncology Division
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(312) 503-1679 • a-minella@northwestern.edu

EDUCATION

<i>Date degree awarded</i>	<i>Institution</i>	<i>Degree</i>	<i>Discipline</i>
May 1998	Vanderbilt University School of Medicine	M.D.	medicine
May 1993	Yale University	B.S.	molecular biophysics and biochemistry

GRADUATE MEDICAL EDUCATION

<i>Dates</i>	<i>Institution</i>	<i>Specialty</i>
July 2000-June 2004	University of Washington and Fred Hutchinson Cancer Research Center	medical oncology
July 1998-June 2000	University of Washington School of Medicine	internal medicine

POSTDOCTORAL RESEARCH TRAINING

<i>Dates</i>	<i>Institution</i>	<i>Field of Research</i>
July 2001-June 2007	Fred Hutchinson Cancer Research Center	cell cycle regulation

BOARD CERTIFICATION and MEDICAL LICENSURE

Medical License Illinois (active)
Board certified in internal medicine and medical oncology (valid through 2014)

FACULTY APPOINTMENTS

<i>Dates</i>	<i>Title</i>	<i>Institution</i>	<i>Department</i>
September 2007 -	Assistant Professor	Northwestern Feinberg School of Medicine	Medicine (heme/onc)

HOSPITAL APPOINTMENTS

<i>Dates</i>	<i>Title</i>	<i>Hospital</i>
September 2007 -	Consultant,attending physician	Northwestern Memorial Hospital
July 2004-August 2007	Attending staff	University of Washington Med. Ctr.

COMMITTEE SERVICE

July 2006-June 2007

University of Washington School of Medicine Admissions

PEER REVIEW ACTIVITIES (2008-9)

Ad hoc Reviewer for:
Cancer Research

AWARDS, HONORS, DISTINCTIONS

<i>Date</i>	<i>Name of award</i>
2008	American Society of Hematology Junior Faculty Scholar
2008	Leukemia Research Foundation New Investigator Award
2007	Schweppe Foundation Career Development Award
2005	AACR-Bristol Myers Squibb Scholar-in-Training Award
2003	National Cancer Institute Research Career Award (K08)
1993	United States Fulbright Scholarship

PROFESSIONAL SOCIETY MEMBERSHIPS

Active Member, American Association for Cancer Research (AACR)

TEACHING

Rotation graduate student and summer undergraduate student teaching - laboratory

University of Washington and Northwestern University
Department of Medicine housestaff teaching – inpatient oncology service

Course developer and lecturer for hematology/oncology fellows – UW didactic series;
lecture title “Molecular Biology in Clinical Oncology”

RESEARCH GRANTS

Active:

NCI K22 CA130984	(P.I. Minella, A)	9/1/08-8/30/11	\$141,860/yr
NCI Career Transition Award The role of cyclin E deregulation in breast tumorigenesis			

Schweppe Foundation	(P.I. Minella, A)	4/1/08-3/30/10	\$50,000/yr
Career Development Award Developing in vivo models of cyclin E-associated breast cancer			

Leukemia Research Foundation	(P.I. Minella, A)	7/1/08-6/30/09	\$100,000
New Investigator Award Deregulated cyclin E in the pathogenesis of hematologic cancers			

Pending:

American Society of Hematology	(P.I. Minella, A)	7/1/09-6/30/11	\$75,000/yr
Junior Faculty Scholars Award Deregulated cyclin E in the pathogenesis of myelodysplasia and leukemia			

Completed:

NCI K08 CA101800 (P.I. Minella, A) 7/1/03-6/30/08
Mentored Clinical Scientist Career Award
Mechanisms of cyclin E associated tumorigenesis

BIBLIOGRAPHY

Original, peer-reviewed research articles:

Minella AC, Loeb KR, Knecht A, Welcker M, Varnum-Finney B, Bernstein ID, Roberts JM, and Clurman BE. Cyclin E phosphorylation regulates cell proliferation in hematopoietic and epithelial lineages in vivo. *Genes and Development* 2008; 22: 1677-89.

Minella AC, Grim JE, Welcker M, and Clurman BE. Fbw7 and p53 cooperatively restrain cyclin E-associated genome instability. *Oncogene* 2007; 26: 6948-53.

Minella AC, Welcker M, and Clurman BE. Ras activity regulates cyclin E degradation by the Fbw7 pathway. *Proceedings of the National Academy of Sciences* 2005; 102: 9649-54.

Minella AC, Swanger J, Bryant E, Welcker M, Hwang HC, and Clurman BE. p53 and p21 form an inducible barrier that protects cells against cyclin E-cdk2 deregulation. *Current Biology* 2002; 12: 1817-1827.

Ross TM, Narayan M, Fang ZY, Minella AC, and Green PL. Human T-cell leukemia virus type 2 Tax mutants that selectively abrogate NFkB or CREB/ATF activation fail to transform primary human T-cells. *Journal of Virology* 2000; 74: 2655-2662.

Ross TM, Minella AC, Fang ZY, Pettiford SM, Green PL. Mutational analysis of human T-cell leukemia virus type-2 Tax. *Journal of Virology* 1997; 71: 8912-8917.

Invited Reviews:

Minella AC and Clurman BE. Mechanisms of tumor suppression by the SCF^{Fbw7}. *Cell Cycle* 2005; 4: 1356-9.

Book Chapter:

Green PL, Ross TM, Anderson M, and Minella AC. The role of the tax gene in human T-cell leukemia virus type 2-mediated transformation of human T-lymphocytes. In *Molecular Pathogenesis of HTLV: A Current Perspective*. Semmes OJ and Hammariskjold ML (eds), Vandermere Press (USA), 1998; 71-77.

Research Description

The overall goal of the work performed in my laboratory is to define how cancer cells exploit mechanisms that regulate normal cell division in order to survive and proliferate. Normal cell cycle phase transitions are carefully regulated by multiple, partially redundant mechanisms; however, loss of function of several key tumor suppressor pathways that regulate cell cycle progression occurs in virtually all cancer cells. Among these pathways are those controlled by the Retinoblastoma (Rb) and p53 tumor suppressor proteins. The Rb pathway controls cell cycle progression from G1-to-S phases. Negative regulators of this pathway include the INK4 and Cip/Kip proteins; positive regulators include the cyclins and cyclin-dependent kinases (Cdks). p53 is a master regulator of multiple cell cycle checkpoints and cell survival, and it is activated by post-translational modifications in response to DNA damage.

Cyclin E, which positively regulates S-phase entry, is a major focus of our studies. It is frequently over-expressed in cancer cells (often via impaired degradation caused by loss-of-function mutations in the E3 ubiquitin ligase protein, Fbw7), and cyclin E over-expression may promote further acquisition of malignant properties due to production of genome instability. Cyclin E-associated genome instability is dependent on loss of p53, which is able to inhibit cyclin E/Cdk2 activity via the induction of p21^{Cip1}. Despite its link to genome instability, how cyclin E overexpression promotes cancer remains unclear. Does cyclin E overexpression in cancer cells signify particular biological properties or does it more often only indicate loss of Rb pathway control? Is p53-loss absolutely required for deregulated cyclin E to promote tumors? What are other collaborating events in cyclin E-associated tumorigenesis? These are key questions we are addressing in my laboratory.

In addition to its role in promoting genome instability, we have found that cyclin E, when deregulated, is able to promote cellular hyper-proliferation in vivo. Specific cell lineages seem to be especially vulnerable to the consequences of deregulated cyclin E activity. Using a novel mouse knockin model to study the physiologic consequences of impaired Fbw7-mediated cyclin E degradation, we found that deregulated cyclin E produces multiple abnormalities in erythroid progenitors, including greatly increased proliferation, impaired maturation, increased apoptosis, and dysplastic morphologies. We see similar evidence of increased proliferation, counter-balanced by increased apoptosis, in mammary epithelial cells as well. In ongoing studies, we are elucidating the basis of this cell-type specificity in the physiologic responses to deregulated cyclin E. In addition to cancer models we are developing, we are also elucidating the mechanisms by which increased cyclin E activity promotes defective erythroid maturation in vivo. A long-term goal of our research is to determine whether these mechanisms are involved in the pathogenesis of human hematopoietic diseases, such as myelodysplasia and leukemia.

References:

Minella AC, Loeb KR, Knecht A, Welcker M, Varnum-Finney B, Bernstein ID, Roberts JM, and Clurman BE. Cyclin E phosphorylation regulates cell proliferation in hematopoietic and epithelial lineages in vivo. *Genes and Development* 2008; 22: 1677-89.

Minella AC, Grim JE, Welcker M, and Clurman BE. Fbw7 and p53 cooperatively restrain cyclin E-associated genome instability. *Oncogene* 2007; 26: 6948-53.

Minella AC, Welcker M, and Clurman BE. Ras activity regulates cyclin E degradation by the Fbw7 pathway. *Proceedings of the National Academy of Sciences* 2005; 102: 9649-54.

Minella AC, Swanger J, Bryant E, Welcker M, Hwang HC, and Clurman BE. p53 and p21 form an inducible barrier that protects cells against cyclin E-cdk2 deregulation. *Current Biology* 2002; 12: 1817-1827.

Potential Student Projects

1) Cyclin E deregulation and CDK inhibitor-loss in mammary epithelial cultures. Both cyclin E overexpression and loss of the CDK inhibitor p27 are found in poor prognosis breast cancers, but it is not known how these events contribute to tumorigenesis. We found that overexpression of cyclin E and shRNA-mediated depletion of p27^{Kip1} cooperate to produce hyper-proliferative acinar structures in mammary epithelial cells grown in three-dimensional basement membrane cultures. With normal p27 expression, deregulated cyclin E alone produces few proliferative acini but primarily causes arrested morphogenesis of the 3D structures. In ongoing studies, we are trying to identify the molecular mechanisms that underlie these morphologic phenotypes. In this project, the student will utilize a number of complementary cell imaging methodologies, including fluorescence and transmission electron microscopy.

2) Cancer-associated micro-RNAs. Aberrant expression of micro-RNAs is frequently found in human cancers, and some of these cancer-associated micro-RNAs may act to deregulate normal cell cycle control mechanisms. We are in the process of investigating several micro-RNAs that may target G1/S regulatory pathways and how, when overexpressed, these may promote cellular hyperproliferation and transformation. We are utilizing multiple experimental systems, including three-dimensional mammary epithelial cultures, to query how deregulated expression of cancer-associated micro-RNAs may be oncogenic in vivo.

3) Synthetic lethality screens in cells before and after cooperating oncogene activation in “real time.” Synthetic lethality screens have found that cancer cells containing mutations in specific tumor suppressors or oncogenes are vulnerable to subsequent genetic manipulations that would not produce significant consequences in normal cells. It is unknown whether synthetic lethal phenotypes can be reversed by the acquisition of new oncogenic mutations or whether these new mutations predispose to different synthetic lethal interactions. This question is highly relevant to cancer therapeutics. We will model this question by selectively activating particular oncogenes in cells that have defined mutations in tumor suppressor pathways. The student will help the principal investigator establish this screen using reagents already available in the lab and then will implement it making use of the Northwestern University high-throughput screening shared resource.

4) The role of deregulated cyclin E activity in impaired erythroid maturation. Using a novel knockin mouse model, I found that deregulated cyclin E activity results in a massive expansion of early erythroid progenitors in bone marrow and spleen. Surprisingly, there is a concomitant reduction in the absolute numbers of mature erythroids, suggesting a significant impairment of erythroid maturation. The basis for this is currently unknown. A number of experiments are planned to elucidate the mechanism whereby cyclin E deregulation impairs red cell maturation, including analyzing gene expression changes in erythroid progenitors, studying apoptosis associated with deregulated cyclin E activity in hematopoietic cells, and investigating how cyclin E deregulation may contribute to human myelodysplastic syndromes.