Julie M. Wells

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Research Summary:

I began graduate school with an interest in mammalian DNA replication and choose to study in the laboratory of Dr. Nicholas Heintz. During the course of my studies, I performed *in vivo* footprinting analysis of the *dhfr* promoter and discovered that the footprint encompassing the overlapping E2F binding sites was cell cycle regulated. I spent the remainder of my graduate career characterizing the various E2F protein complexes, which bound to the *dhfr* promoter. After graduation, I welcomed the opportunity to join Dr. Peggy Farnham's laboratory at the University of Wisconsin-Madison where I worked on adapting formaldehyde crosslinking and immunoprecipitation (ChIP) to study protein-DNA interactions in mammalian cells. While in Dr. Farnham's lab, I used ChIP to study cell cycle regulated binding of various E2F complexes to the promoters of several genes, to study histone acetylation, to identify novel transcription factor binding sites and to compare transcription factor binding between tumors and corresponding non-neoplastic tissue. I then used a combination of ChIPs and CpG microarrays to examine *in vivo* interactions between E2F1, NBS1 and pRB at multiple loci in synchronized cells. I completed a second post-doctoral fellowship in the laboratory of Dr. Daniel Haber's laboratory at Massachusetts General Hospital. While in Dr. Haber's laboratory, I used ChIP-cloning to identify DNA binding sites of the poorly characterized Wilms tumor associated WT1(+KTS) protein and I was involved in the discovery of WTX, a gene that is commonly mutated in Wilm's tumor. I am currently a Research Scientist at The Jackson Laboratory where I am studying the role of microRNAs in progression of pulmonary adenocarcinoma.

Research Interests:

During the course of my graduate and post-doctoral studies, I have become very interested in understanding the links between development and carcinogenesis. Specifically, I want to know how mutations or other molecular changes in proteins or non-coding RNAs contribute to disease. At present, I am studying expression of mRNAs and non-coding microRNAs during normal mouse lung development and disease. I am

also developing new techniques for identifying the targets of microRNAs in both normal lung tissue and in lung tumors, using both mouse models and human samples.

Formal Education:

University of Vermont Burlington, VT 1990-1996
PhD Cell & Molecular Biology

University of Wisconsin Madison, WI 1986-1990
BS Molecular Biology

Academic Training:

2010-present Research Scientist, The Jackson Laboratory
Advisor: Dr. Carol Bult
Project: Molecular genetic analysis of lung development, lung cancer and disease

2008-2010 Assistant Research Scientist, The Jackson Laboratory
Advistor: Dr. Carol Bult
Project: Molecular genetic analysis of lung development, lung cancer and disease

2002-2008 Post-doctoral Fellow, Department of Molecular Genetics, Massachusetts General Hospital Cancer Center
Advisor: Dr. Daniel Haber
Project: Identification and characterization of WT1 (+KTS) target genes.

2001-2002 Scientist, McArdle Laboratory, University of Wisconsin-Madison Medical School
Advisor: Dr. Peggy J. Farnham
Project: Identification of cellular target genes of E2F1, NBS1 and pRb during S phase.

1996-2001 Post-doctoral Fellow, McArdle Laboratory, University of Wisconsin-Madison Medical School
Advisor: Dr. Peggy J. Farnham
Project: Regulation of cellular target genes by different subsets of E2F proteins in cultured cells, tissues and tumors.

1990-1996 Graduate Research Assistant, Department of Pathology, University of Vermont School of Medicine
Advisor: Dr. Nicholas H. Heintz
Project: Regulation of *dhfr* expression in Chinese hamster ovary (CHO) cells during the cell cycle.

1988-1990 Research Assistant, Department of Veterinary Science, University of Wisconsin-Madison

Advisor: Dr. Geoffrey Letchworth
Project: Epitope mapping on glycoprotein 4 of bovine herpes virus (BVH).

Awards:

2004 Tosteson Postdoctoral Fellowship, Massachusetts General Hospital

2000 AFLAC Travel Award recipient to attend AACR special conference, Genetic and Functional Consequences of Cell Cycle Alteration in Cancer

1996-2001 Post-doctoral Fellowship, Department of Oncology, University of Wisconsin-Madison Medical School

1996 NIH Travel grant award recipient to attend Keystone Symposia on The Cell Cycle

1991-1996 Environmental Pathology Fellowship, Department of Pathology, University of Vermont School of Medicine

1990-1991 Research Fellowship, University of Vermont Graduate College

Techniques:

Mammalian cell culture, formaldehyde crosslinking and immunoprecipitation (ChIP), ChIP-cloning, ChIP-ChIP, shRNA, siRNA, Lentiviral vectors, cell synchronization, mouse husbandry, DNA assays, DNA and RNA isolation, gel electrophoresis, dideoxy DNA sequencing, dye-termination sequencing, Maxam-Gilbert DNA sequencing, PCR, primer extension, cloning DNase I footprinting, $KMnO_4$ footprinting, gel mobility shift assays, western, northern and Southern blot analysis, solid phase peptide synthesis, polyclonal antibody production, RIA and ELISA analysis, Mouse husbandry, tail tipping, mouse lung isolation

Teaching and Supervising Experience:

5/13-8/13 Mentored Megan Taylor, a participant in The Jackson Laboratory's Summer Student Internship program. Megan's project was titled "RIP Analysis of Human Pulmonary Adenocarcinomas".

1/09-5/09 Mentored Patrick Breen, a participant in The Jackson Laboratory's High School Internship program. Patrick's project was titled "Using PCR to Genotype Mice".

1/02-9/02 Mentored Meredith Cechvala's undergraduate research project to characterize S phase cellular targets of pRb. Meredith received a Hilldale Undergraduate Research Fellowship for her project proposal.

6/98-7/99 Mentored Eric Maliborski's undergraduate Senior Honors Thesis titled "Cloning and Characterization of Cellular Targets of E2F-2 and E2F-4". Eric won the Mark Mensink Award for his proposal.

6/98-8/98 Mentored LaNissa A. Brown, a participant in the Center for Biology Education Summer Research program for minority students.

Publications:

M. Longoni , F.A. High, M.K. Russell, A. Kashani, Tracy A.A., Coletti C.M., R. Hila, A. Shamia, **J. Wells**, K.G. Ackerman, J.M. Wilson, C.J. Bult, C. Lee, K. Lage, B.R. Pober and P.K. Donahoe (2014). Molecular pathogenesis of congenital diaphragmatic hernia revealed by exome sequencing, developmental data, and bioinformatics. Proc Natl Acad Sci U S A 111(34):12450-5.

M.K. Russell, M. Longoni, **J. Wells**, F.I. Maalouf, A.A. Tracy, M. Loscertales, K.G. Ackerman, B.R. Pober, K. Lage, C.J. Bult and P.K. Donahoe (2012). Congenital Diaphragmatic Hernia Candidate Genes Derived from Embryonic Transcriptomes. Proc Natl Acad Sci U S A 109(8): 2978-83.

J. Wells, M.N. Rivera, W.J. Kim, K. Starbuck and D.A. Haber (2010). The Predominant WT1 Isoform (WT1) Encodes a DNA-Binding Protein Targeting the Planar Cell Polarity Gene Scribble in Renal Podocytes. *Mol Cancer Res* 8(7):975-85.

M.N. Rivera, W.J. Kim, **J. Wells**, A. Stone, A. Burger and D.A. Haber (2009). The Tumor Suppressor WTX Shuttles to the Nucleus and Modulates WT1 Activity. Proc Natl Acad Sci 106(20): 8338-8343.

M.N. Rivera, W.J. Kim, **J. Wells**, D.R. Driscoll, B.W. Brannigan, M. Han, J.C. Kim, A.P. Feinberg, W.I. Gerald, S.O. Vargas, L. Chin, A.J. Iafrate, D.W. Bell and D.A. Haber (2007). An X Chromosome gene, WTX, is Commonly Inactivated in Wilms Tumor. *Science* 315(5812) 642-645.

G.A. Smolen, M.T. Vassileva**, J. Wells**, M.J. Matunis and D.A. Haber (2004). SUMO-1 Modification of the Wilm's Tumor Suppressor WT1. *Cancer Research* 64 7846-7851.

J. Wells, P.S. Yan, M.M. Cechvala, T. Huang and P.J. Farnham (2003). Identification of Novel pRb Binding Sites Using CpG microarrays Suggests that E2F Recruits pRb to Specific Genomic Sites During S Phase. *Oncogene*, 22 1445-1460.

J. Wells and P.J. Farnham (2002). Characterizing Transcription Factor Binding Sites Using Formaldehyde Crosslinking and Immunoprecipitation *Methods*, 26 48-56.

J. Wells*, C.R. Graveel*, S.M. Bartley, S.J. Madore and P.J. Farnham (2002). The Identification of E2F1-Specific Target Genes *Proc. Natl. Acad. Sci.*, 99(6) 3890-3895.

R.S. Maser, O. Mirzoeva, **J. Wells**, H. Olivares, B. Williams, R. Zinkel, P.J. Farnham and J.H.J. Petrini (2001). The Mre11 Complex and DNA Replication: Linkage to E2F and Sites of DNA Synthesis *Mol. Cell. Biol.* 21(17) 6006-6016.

T. Albert, **J. Wells**, J.O. Funk, A. Pullner, E.-E. Raschke, G. Stelzer, M. Meisterernst, P.J. Farnham and D. Eick (2001). Chromatin Remodeling and Acetylation of the Dual c-myc promoters P1/P2 are Hierarchically Regulated by Separate Elements. *J. Biol. Chem.* 276(23) 20482-20490.

J. Wells, K.E. Boyd, C.J. Fry, S.M. Bartley and P. J. Farnham (2000). Target Gene Specificity of E2F and Pocket Protein Family Members in Living Cells. *Mol. Cell. Biol.* 20(16) 5797-5807.

K.E. Boyd, **J. Wells**, J. Gutman, S.M. Bartley and P.J. Farnham (1999). c-Myc Target Gene Specificity is Determined by a Post-DNA Binding Mechanism. *Proc. Natl. Acad. Sci.* (95) 13887-13892.

J. Wells, S. Illenye, J. Magee and N.H. Heintz (1997). Accumulation of E2F-4/DP-1 DNA Binding Complexes Correlates with Induction of *dhfr* Gene Expression During the G_1 to S Phase Transition. *J. Biol. Chem.* 272(7) .

J. Wells, P.G. Held, S. Illenye and N.H. Heintz (1996). Protein-DNA Interactions at the Major and Minor Promoters of the Divergently Transcribed *dhfr* and *rep3* Genes During the Chinese Hamster Ovary Cell Cycle *Mol. Cell. Biol.* 16(2) 634-647.

Oral Presentations:

J. Wells, Z. M. Diaz, C.A. D'Cunha and P.J. Farnham (1999). Cloning Target Genes of Oncogenic Transcription Factors Using Formaldehyde Crosslinking. Symposium on Genetics, Genomics and Molecules.

J. Wells, K.E. Boyd, C.J. Fry and P.J. Farnham (1998). Transcriptional Activation and Repression are Mediated by Different Subsets of E2F. Cold Spring Harbor Symposium on Cancer Genetics and Tumor Suppressor Genes abs. #215.

J. Wells, P. Held, and N.H. Heintz (1994). Cell-cycle Regulated Interactions of E2F with the *dhfr* Gene Promoter Third McGill Conference on Regulation of Eukaryotic DNA Replication abs. #54.

Funding:
Ongoing Research Support

5 R21 CA155164-02 Wells (PI)
01/14/11-12/31/14

NIH/NCI
Development of a Genome-wide Unbiased Screen for Identifying miRNA Target Genes
The primary goal of this study is to develop a genomewide screen to identify the transcriptional (mRNA) targets of microRNAs in normal biology and disease states.
Role: Principal Investigator

5 P01 HD068250-02 Donahoe (PI)
07/01/11-06/30/16
NIH/NICHD
Expressed CDH Genes can be Prioritized then Functionally Validated in Animal Models and iPS Cells
The goal of this program project component is to experimentally validate genes that are predicted to be involved in diaphragm defects using knockout mice.
Role: Consortium Investigator

MCF JMW-02 Wells (PI)
07/01/14-06/30/15
Maine Cancer Foundation
Characterization of Circulating MicroRNAs Involved in Lung Cancer Metastasis
The goal of this pilot project proposal is to use a patient derived xenograft (PDX) mouse model of lung cancer to identify which microRNAs (miRNAs) are circulating within the bloodstream, which miRNAs are retained with the primary tumors and the origin (tumor or host) of those miRNAs.
Role: Principal Investigator

Completed Research Support

MCF JRW-01 Wells (PI)
07/01/10-06/01/12
Maine Cancer Foundation
MicroRNA Expression During Lung Tumor Progression
The goal of this research is to identify changes in genome-wide expression of miRNAs and mRNAs that are characteristic of the progression from early-stage to late-stage pulmonary adenocarcinomas using RNA immunoprecipitation followed by high-throughput sequencing (RIP-SEQ).
Role: Principal Investigator

12-80-34-WELL Wells (PI)
07/01/12-06/30/13
American Association for Cancer Research
Detecting Changes in Circulating MicroRNAs During Lung Cancer Progression

Specific Aim 1: Measure circulating microRNAs present in the serum samples from two mouse models of pulmonary adenocarcinoma. 1) Collect blood samples from six different populations of mice Kras G12D uninfected, Kras G12D infected with adenovirus, Kras G12D infected with adenovirus Cre , KrasG12D;Trp53 tm1Brn/J , , KrasG12D;Trp53 tm1Brn/J infected with adenovirus, and , KrasG12D;Trp53 tm1Brn/J infected with adenovirus Cre every two weeks, beginning before infection and ending at 16 weeks after infection. 2) Isolate RNA from serum fractions of collected blood samples. 3) Count miRNAs present in each serum sample using Nanostring . Specific Aim 2: Determine if changes in microRNA expression profiles in the blood correlate with changes in lung tumors. 1) Results of specific Aim 1 will be compared to results obtained from analysis of microRNA expression in lung tumors (R21 grant) to determine how quickly changes in microRNA expression profiles in tumors and serum samples become detectable and how long these changes remain detectable. 2) The identity of aberrantly expressed microRNAs in tumors and serum will be compared to determine the degree of similarity between the two pools of microRNAs.
Role: Principal Investigator

References:

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