UNIVERSITY of VIRGINIA HEALTH SYSTEM

DEPARTMENT of BIOCHEMISTRY
and MOLECULAR GENETICS
School of Medicine

September 29, 2005

Yves Brun
Systems Biology/Microbiology Faculty Search
Department of Biology
Indiana University
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1001 E 3rd Street
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Dear Systems Biology/Microbiology Faculty Search Committee,

In response to a recent job advertisement in the Journal of *Science*, I would like to be considered for a tenure-track Assistant/Associate Professor position at your institution. Enclosed please find my CV, a research and teaching statement, and copies of three publications. I have arranged four letters to be directly sent to you.

I am currently an Associate Professor of Research of Biochemistry and Molecular Genetics at University of Virginia School of Medicine. My primary research interests are in the molecular mechanism of the tumor suppressor function of breast cancer susceptibility gene *BRCA1*. My laboratory currently focuses on how BRCA1 in transcriptional regulation contributes to its role in breast cancer suppression.

Please let me know if there is any more information I can provide regarding my application. Thank you for your consideration.

Sincerely,

Yanfen Hu

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RESEARCH STATEMENT

Breast cancer is the most common malignancy among women in the Western world. Between 5 to 10% of breast cancer cases are hereditary, the majority of which are caused by germline mutations in the breast cancer susceptibility gene *BRCA1* or *BRCA2*. In addition, germline mutations in these two genes also lead to increased risk of hereditary ovarian cancer. **The long-term objective of my research is to elucidate the underlying mechanism by which the BRCA genes suppress development of breast and ovarian cancers in women.** The ongoing research in my laboratory has been focused on addressing two conundrums regarding BRCA1 functions: 1) Why do mutations in *BRCA1* specifically lead to breast and ovarian cancer in women (gender- and tissue-specificity)? 2) Why are somatic mutations of *BRCA1* are rarely found in sporadic breast cancers?

A wealth of information regarding BRCA1 functions has been accumulated since cloning of the *BRCA1* gene in 1994. BRCA1 has been mainly implicated in two cellular functions: DNA repair and transcriptional regulation. The function of BRCA1 in DNA damage response provides a reasonable molecular explanation for its role as a tumor suppressor. Compromised functions of BRCA1 in DNA repair and checkpoint most likely contribute in a significant manner to cancer susceptibility. However, maintenance of genetic stability alone cannot easily explain why loss of BRCA1 function would increase cancer risks in such a gender and tissue-specific manner, as DNA repair is fundamental and universally important to all cell types in both genders. My earlier work on BRCA1's potential to remodel chromatin (Hu et al., 1999 Genes & Dev.) and the interaction of BRCA1 with a family of site-specific transcription factors, AP-1/Jun (Hu & Li, 2002 Genes & Dev.), supports a role of BRCA1 in transcriptional regulation. It is conceivable that BRCA1 may modulate tissue-specific gene expression critical to cancer development in breast and ovary.

I. Role of BRCA1 in Estrogen Biosynthesis

Based on scientific reasoning and available literature, I proposed several years ago that BRCA1 might down-regulate the estrogen biosynthesis by negatively regulating the expression of aromatase, the rate-limiting enzyme in estrogen biosynthesis. The expression of aromatase and hence the production of estrogen is highly tissue specific. Importantly, estrogen plays a significant role in the development and progression of breast cancer, and aromatase is a clinically proven target for breast cancer treatment. Several pieces of important data from my research support this hypothesis (Hu et al., 2005 Oncogene). First, there is an inverse correlation between BRCA1 level and aromatase expression. Second, knockdown of BRCA1 by siRNA specifically leads to elevation of aromatase expression. Third, preliminary studies using chromatin immunoprecipitation (ChIP) show that BRCA1 is physically associated with the aromatase promoter. Interestingly, we demonstrate that Jun proteins specifically down-regulate aromatase promoter activity (Ghosh et al., 2005 Oncogene). Thus, BRCA1-mediated modulation of aromatase expression may rationalize the tissue-specific tumor suppressor function of BRCA1.

To more rigorously test the hypothesis, we have launched additional studies in both tissue culture and animal models in the following three directions:

1. *In-depth mechanistic studies at the molecular and cellular levels.* Specifically, we will elucidate the mechanism by which BRCA1 is recruited to the tissue-specific promoter of the aromatase gene and the impact of BRCA1 on aromatase promoter activity.
2. *Genetic studies in mouse models.* In collaboration with mouse geneticists Drs. Chuxia Deng at NIH and Louis Dubeau at University of Southern California, we will determine the effect of mouse Brca1 on aromatase expression, circulating estrogen levels, and estrogen-dependent growth in reproductive tissues.
3. *Cancer biology studies with clinical samples.* We have an ongoing collaboration with Dr. Andy Godwin at Fox Chase Cancer Center to examine the aromatase expression in ovaries obtained from women carrying wild type or mutant *BRCA1/BRCA2* gene.

The potential link between BRCA1 and aromatase expression represents a conceptual advance in understanding the tumor suppressor function of BRCA1. Given that aromatase inhibitors have become one of the most effective drugs in breast cancer treatment, our research will have profound impact on familial breast/ovarian cancer research and prevention. An RO1 application based on this project was regarded highly innovative and ranked 15.6% after first submission (Feb. 2005).

II. The Potential Role of BARD1 and BRCA2 in Hormone Metabolism

We are also exploring the potential involvement of BARD1 and BRCA2 in aromatase expression. BARD1 is a BRCA1-associated protein and the BRCA1/BARD1 complex displays an E3 ubiquitin ligase activity. It is believed that BRCA1 exists mainly as a heterodimer with BARD1. Interestingly, knockdown of BARD1 has a similar profound effect on aromatase expression (Hu et al., 2005 Oncogene). While BRCA2 does not share sequence homology with BRCA1, it displays cellular functions and genetic phenotypes similar to those of BRCA1, suggesting that BRCA2 and BRCA1 may function in the same pathway that contributes to breast cancer development.

We propose:

1. To investigate whether BRCA1 and BARD1 regulate aromatase expression as a complex and what role BRCA1/BARD1 E3 ubiquitin ligase might play in this function.
2. We have an ongoing collaboration with Dr. Magoffin/Dr. Geller's laboratory at Cedars-Sinai Medical Center to examine potential involvement of BRCA1 and BRCA2 in regulation of hormone metabolism.

This project will reveal significant insights on specific functions of BRCA1, BRCA2 and BARD1 in hormone regulation and breast/ovarian cancer development. A DOD grant application based on this project is currently under review.

TEACHING STATEMENT

My teaching interest is primarily on gene expression and cancer research, however, I am open to other teaching subjects.