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Feasibility of Serial Biopsies of Large Dysplastic Nevus as a Melanoma Chemoprevention Model

Christopher D. Lao¹, Timothy Johnson^{2,3}, Vernon K. Sondak^{8,9}, Lori Lowe^{2,4}, David S.L. Kim⁵, Lili Zhao⁶, Mark Naftanel², Stephen Olsen^{2,4}, and Dean E. Brenner^{1,10}

¹ Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI

² Department of Dermatology, University of Michigan Medical Center, Ann Arbor, MI

³ Department of Otolaryngology, University of Michigan Medical Center, Ann Arbor, MI

⁴ Department of Pathology, University of Michigan Medical Center, Ann Arbor, MI

⁵ Department of Dermatology, Marshall Clinic, Marshfield, WI

⁶ Department of Biostatistics, University of Michigan Medical Center, Ann Arbor, MI

⁸ Department of Cutaneous Oncology, Moffitt Cancer Center, University of South Florida College of Medicine, Tampa, FL

⁹ Departments of Oncologic Sciences and Surgery, University of South Florida College of Medicine, Tampa, FL

¹⁰ Department of Pharmacology, University of Michigan Medical Center, Ann Arbor, MI

To the editor

Few attempts have been made to study melanoma chemoprevention as a viable option in humans and currently no human model has been firmly established to study this approach.¹

² Large scale clinical trials will ultimately be required to prove efficacy of cancer chemopreventive agents, but the investment in such an endeavor is substantial. Establishment of a human model can result in the acquisition of data that supports testing only the most promising agents in large scale efficacy trials.

Identifying and targeting events in precancerous lesions, which allows interrogation of the process of carcinogenesis, remains the framework for early chemopreventive investigations.

³ Most melanomas arise from normal-appearing skin, but the large collections of melanocytes that reside in nevi and dysplastic nevi (DN) can include cells at risk for malignant degeneration. A pilot study was conducted to determine if (1) a clinical model using serial biopsies of DN represents an approach that can potentially exploit rapid (<4 weeks) biomarker modulation as an efficient way to test agents for melanoma chemoprevention and (2) to determine the feasibility of this approach, including effects of

Corresponding author: Christopher D. Lao, M.D., M.P.H., Division of Hematology-Oncology, Department of Internal Medicine, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0848; Tel: 734-615-4762; Fax: 734-936-4940; clao@umich.edu.

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serial biopsies on the same pigmented lesion. Following approval by the University of Michigan Institutional Review Board participants with a large dysplastic nevus ≥ 8 mm in diameter were recruited for enrollment. A 4 mm punch biopsy was obtained from one side of the DN at baseline, and four weeks later the remaining lesion was completely excised. The feasibility of recruitment to such a study design, variability of atypia within lesions, concordance between dermatopathologists, and effects of the biopsy on the grade of atypia were evaluated. No intervention was used in this pilot study. Thirty-eight potential participants were identified within the University of Michigan Health System from June 2008 to August 2009 (TABLE 1). Fifteen participants completed all planned study procedures for a recruitment rate of 47%. There was fair agreement between dermatopathologists on histologic atypia for baseline specimens (weighted kappa = 0.33, $p < 0.05$), but no agreement on histologic atypia for the excision specimens (weighted kappa = 0.02, $p > 0.05$). More importantly, however, there was no significant difference in histologic atypia when individual participants' baseline and excision specimens were directly compared ($p = 0.83$) (FIGURE 1). Thus, there was no evidence of worsening atypia or malignant progression induced by the biopsy, but having the same dermatopathologist read paired baseline and excision specimens will be essential.

Success of future investigations targeting DN for chemoprevention depends on the identification of critical genetic mutations, aberrant cell signaling or other molecular changes within those lesions. This will likely require studying this approach in only persons at the highest risk of developing melanoma. In this pilot study, 93% of participants had a personal or family history of melanoma. Evaluation of particular genetic and molecular events (e.g., activated NF- κ B, 12-LOX expression, and mutated BRAF) in these DN, benign nevi and normal skin is ongoing.^{4, 5} This pilot study provides preliminary data supporting a model to evaluate the chemoprevention of melanoma. The concordance of interpretation of cellular atypia between dermatopathologists is lacking; however, each individual dermatopathologist is internally consistent across multiple time points. The association of histologic atypia with critical molecular and genetic events must be explored further prior to determining the validity of this approach.

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Abbreviations

DN	Dysplastic nevi/nevus
NF-κB	Nuclear factor kappa B
12-LOX	12-Lipoxygenase

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Fig. 1. Compound dysplastic nevus (hematoxylin and eosin stain): baseline biopsy (A) and excision at week 4 (B) from the same participant. Non-uniform distribution of irregular, variably sized nests, with interreticular bridging (arrowheads); lateral extension beyond the focal dermal component (small arrowhead); random cytologic atypia (arrows), commensurate of a mildly atypical lesion without worsening of atypia at week 4.

Table 1

Demographics and Histopathologic Evaluations for the Study Population

Participant	Gender	Age (years)	Family history	Personal history	Pathology		
					Baseline (Punch biopsy)		Week Four (Complete excision)
					Nevus Type ¹	Atypia ²	Nevus Type ¹
1	Male	35	Yes	No	Compound	Absent-Slight	Compound
2	Male	59	Yes	Yes	Compound	Absent-Slight	Compound
3	Male	59	Yes	Yes	Compound	Slight	Compound/Junctional ³
4	Male	57	Yes	Yes	Junctional	Slight	Junctional
5	Male	45	Yes	Yes	Compound	Slight	Compound
6	Male	47	Yes	No	Compound	Slight-Moderate	Compound
7	Male	64	Yes	Yes	Compound	Slight	Compound
8	Male	68	Yes	Yes	Compound	Absent-Slight	Compound
9	Male	60	Yes	No	Compound	Slight	Compound
10	Male	59	No	Yes	Junctional	Slight-Moderate	Junctional
11	Female	52	No	Yes	Compound	Moderate	Compound
12	Male	53	Yes	Yes	Compound	Slight	Junctional
13	Female	21	Yes	No	Junctional	Slight-Moderate	Junctional
14	Female	58	Yes	No	Compound	Slight	Compound
15	Female	42	No	No	Compound	Absent	Compound

¹ Junctional nevus is a collection of nevomelanocytes in the epidermis; Compound nevus is a collection of nevomelanocytes in both the epidermis and dermis.

² Range of atypia reported between two independent dermatopathologists (absent, slight, moderate, severe)

³ One dermatopathologist read the excision biopsy as junctional nevus and the other read it as compound nevus