

## Beyond the Scalpel: Targeting Hedgehog in Skin Cancer Prevention

Perspective on Tang et al., p. 25

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### Abstract

This perspective places the article by Tang et al. in this issue of the journal (beginning on page 25) in the context of recent work defining the hedgehog signaling pathway as a central etiologic factor and as a therapeutic target in basal cell cancer. Tang et al. show that inhibition of cyclooxygenase activity, either genetically (in a relevant mouse model) or pharmacologically (in the mouse and in patients highly predisposed to develop basal cell skin cancers), may suppress basal cell carcinogenesis. This new study of cyclooxygenase inhibition, together with recent data on the efficacy of hedgehog pathway inhibition, offers new hope for patients at a high risk for basal cell cancer. *Cancer Prev Res*; 3(1); 1–3.

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### Epidemiology and Genetics of Basal Cell Skin Cancer

Basal cell carcinoma (BCC) of the skin is far and away the most common human malignancy, with an estimated incidence of 800,000 to 900,000 cases per year in the United States (1). Forty percent to 50% of Americans who live to age 65 years will develop a nonmelanoma skin cancer. The large majority of these cancers will be BCCs. Fortunately, in most instances, BCCs can be surgically cured. As these cancers typically arise on sun-exposed skin, these surgeries can be both debilitating and disfiguring. In addition, sporadic BCCs can recur and rarely can invade and metastasize. There are no therapies of proven benefit for unresectable BCC (2).

For individuals with basal cell nevus syndrome (Gorlin syndrome), BCCs are much more than a nuisance (3). Gorlin syndrome patients can develop hundreds or even thousands of BCCs, overwhelming the capacity for surgical removal and ultimately leading to development of fatal metastatic disease. A typical Gorlin syndrome patient presented to our medical oncology clinic last year complaining that her plastic surgeon spoke of “running out of skin” with which to continue trying to patch her up (more on her below).

BCCs show constitutive activation of the hedgehog signaling pathway, most commonly due to inactivating mutations in *PTCH1* (4). The hedgehog pathway is a central embryonic regulatory pathway implicated in cell fate

decisions in multiple aspects of fetal development (5). *PTCH1* encodes a cell surface receptor for the hedgehog ligands. In most adult tissues, *PTCH1* represses hedgehog signaling by inhibiting a second cell surface molecule, Smoothened (SMO), a key activator of hedgehog signaling. Gorlin syndrome patients carry germ-line heterozygous mutations in *PTCH1* and are highly predisposed to develop BCCs with loss or inactivation of the remaining wild-type allele (6, 7). Absence of functional *PTCH1* leaves SMO in a constitutively active state, leading to dysregulated hyperactivity of the hedgehog pathway. Until very recently, no specific inhibitors of the hedgehog pathway were available for clinical use.

### Cyclooxygenase and Basal Cell Carcinogenesis

Tang et al. (8) report an impressive series of studies of the importance of cyclooxygenase (COX) activity in the growth and development of BCC in both mice and humans. The prostaglandin metabolic pathways regulated by the COX-1 and COX-2 enzymes have been implicated in many carcinogenesis models, including the development of the less common type of nonmelanoma skin cancer, squamous cell carcinoma. The investigators hypothesized that COX inhibition might offer protection against basal cell carcinogenesis.

A murine model of Gorlin syndrome based on heterozygous *PTCH1* gene disruption provides an excellent phenocopy of the human disease, showing a markedly increased rate of BCC formation following UV or gamma radiation and an increased predilection for medulloblastoma, another hedgehog-related cancer that is increased in Gorlin syndrome patients. By crossing the *PTCH1*<sup>+/-</sup> mouse with COX-1- or COX-2-deficient mice, the investigators showed that loss of either COX enzyme resulted in a marked reduction in the resulting basal cell cancer burden, with the primary effect in both instances being on the size of the resulting tumors. The suppression in tumor burden

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could be reproduced (although somewhat less effectively) with either nonspecific or COX-2-specific pharmacologic COX inhibitors.

Perhaps the most remarkable part of the Tang report is the 3-year clinical study of the COX-2 inhibitor celecoxib in 60 patients with Gorlin syndrome and multiple active BCCs. Assembling this number of patients with a relatively rare genetic syndrome and enrolling them in a double-blind randomized investigational therapeutic protocol over a short period of time is no mean feat, and the authors are to be congratulated on this alone. Celecoxib significantly reduced the increase in clinically detectable BCCs in a prespecified cohort with fewer than 15 active BCC lesions at study entry and produced a trend toward disease amelioration in the cohort with 15 or more active lesions. Although the patient numbers are small and the trial was cut short by cardiac concerns related to COX-2 inhibitors (none observed in this study), these results plus the murine data support further study of targeted inhibition of COX activity as a potential means of inhibiting basal cell carcinogenesis.

Although encouraging, the findings of Tang et al. should be interpreted with caution. In each of their several murine experiments, the effect of genetic or pharmacologic COX inhibition on tumor burden was predominantly attributable to a decrease in tumor size, with a lesser, if any, effect in reducing tumor number. This result suggests that the primary effect of COX inhibition may be on proliferation rate rather than on malignant transformation per se. In this scenario, the reported minor decreases in tumor number could reflect maintenance of a small number of tumors at a size below clinical detection. These observations may be reminiscent of the differentiating effects of retinoids, which may suppress tumorigenesis, but in a transient and thus questionable manner (9).

### Hedgehog Pathway in BCC: A New Target for Chemopreventive Inhibition?

The pace of translation of research on the hedgehog signaling pathway has been remarkable. Work reported in 1980 involving the fruit fly *Drosophila* led to the first description of the hedgehog gene (10), so named because a loss of function mutation leads to failure to establish segment polarity in embryonic development, resulting in an ovoid embryo thought to resemble a hedgehog. Work over the next decade primarily focused on defining components of the hedgehog pathway in the fruit fly (reviewed in ref. 5). SMO was identified as a critical determinant of hedgehog signaling in 1996 (11). The initial descriptions of mutations in the *PTCH1* gene were reported in 1996 (BCC) and 1997 (medulloblastoma; refs. 7, 12). Naturally occurring and synthetic pharmacologic inhibitors of hedgehog signaling were first identified in 2000 (13). The initial results of clinical testing of an orally bioavailable hedgehog pathway inhibitor, including its evident activity against advanced and

metastatic BCC and medulloblastoma, were published in September 2009 (14, 15). These results have already triggered a series of phase II studies in medulloblastoma and other diseases, including a potential registration trial for this inhibitor in patients with locally advanced and metastatic BCC.<sup>1</sup>

Several hedgehog pathway inhibitors targeting the critical SMO cell surface signaling protein are now in early-phase clinical development. The first such trial to be reported involved the inhibitor GDC-0449 (14, 15). Remarkable for a first-in-human, first-in-class phase I clinical trial, GDC-0449 treatment resulted in major objective responses in about 50% of patients with locally advanced and metastatic BCC (15). Several of these responses have been prolonged, with BCC patients remaining on therapy with continued response beyond 20 months. The long-term durability of these responses remains to be determined; at least one mechanism of acquired clinical resistance—a secondary mutation in SMO that prevents drug binding—was defined recently (16). Several of the advanced BCC patients in this study are Gorlin syndrome patients.

As impressive as the clinical responses have been, an equally intriguing result has been the absence of new skin cancers in Gorlin syndrome patients in this study, as illustrated by the participating patient described earlier as “running out of skin” before joining the trial. Over the 5 years prior to initiation of GDC-0449 therapy (2003-2008), she underwent 22 surgeries on the face alone, and had over 100 skin lesions treated. Over the past 12 months of continuous daily GDC-0449 treatment, no new lesions have arisen. Four of nine selected target (measurable) BCCs are no longer evident, and each of the other five has diminished in size. Per defined clinical trial end points, the patient has an ongoing “partial response” based on the assessment of these nine target lesions. From the patient's perspective, however, by far the greatest relief has not been the diminution in these particular cancers, but rather the several months without any NEW skin cancers and with no indicated need for further surgical procedures. After years of a seemingly unending series of excisional biopsies and wide-margin lesion removals, the patient finally gets a break.

### Implications: New Opportunities for BCC Chemoprevention

The hedgehog signaling pathway normally controls key cell fate decisions of early progenitor cells in embryogenesis. The hedgehog pathway and other critical developmental pathways (controlled by factors such as Notch, Wnt, and BMP) also have been implicated in the maintenance, differentiation, and distribution of highly clonogenic progenitor cells (“tumor stem cells”) in cancer (5, 17). Led by Dr. Epstein, senior author of the present

<sup>1</sup> <http://www.clinicaltrials.gov/ct2/show/NCT00833417>

report by Tang et al. (8), a formal phase II study of GDC-0449 in patients with Gorlin syndrome was launched in August 2009 and is designed to assess not only the response of extant tumors but also the inhibition of new cancer formation.<sup>2</sup>

Hedgehog inhibitors and COX inhibitors may affect basal cell carcinogenesis by different, and complementary, mechanisms. One hypothesis suggested by the available data is that the hedgehog pathway has a fundamental role in malignant transformation and maintenance of tumor progenitor cells in basal cell carcinogenesis, whereas COX inhibitors preferentially interfere with a later proliferative phase of BCC growth. Combined targeting of multiple levels of carcinogenesis, using these orally bioavailable and relatively well-tolerated agents, may be a particularly effective chemopreventive strategy. The underlying mechanistic hypotheses are readily testable in the *PTCH1* heterozygous mouse model described by Tang et al.

Remarkable features of BCC include its exceptionally high prevalence and tendency to remain localized for a long time. BCC also is directly accessible, making it a particularly attractive target for topical delivery of therapeutic and chemopreventive agents. Systemic administration of either COX inhibitors or hedgehog inhibitors has an acceptable safety profile for patients with active cancers, but this may be less true in the context of disease prevention. A pilot study of topical administration of the first-generation hedgehog inhibitor Cur61414 was disappointing and was closed early. However, topical delivery

of both hedgehog inhibitors and COX inhibitors is feasible and represents an interesting and important area for future cancer prevention research.

The study of Tang et al. highlights the power of studying rare and highly disease-prone patient populations. Clinical trials of chemopreventive strategies in patients with rare genetic syndromes are feasible in the internet age, provide important biological insights, and have implications for cancer prevention in more broadly defined populations of lesser-risk individuals. Recent progress in understanding the biology of BCC has been rapidly translated into clinical trials involving Gorlin syndrome patients and the rare sporadic patients with advanced and metastatic BCC. These avenues of research herald new hope for developing effective treatment and prevention of this increasingly common and highly morbid disease.

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No potential conflicts of interest were disclosed.

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<sup>2</sup> <http://www.clinicaltrials.gov/ct2/show/NCT00957229>

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