



# Emerging Concepts in Targeted Therapy for Basal Cell Carcinoma: New Frontiers for Evidence-Based Practice

## OVERVIEW OF BASAL CELL CARCINOMA

Basal cell carcinoma (BCC) is the most commonly diagnosed human malignancy. It currently represents 70-80 percent of the approximately one million cases of non-melanoma skin cancer diagnosed annually in the United States alone.<sup>1</sup>

BCC can present as one of four subtypes: nodular, superficial, morpheaform, and micronodular.<sup>1</sup> The nodular subtype appears as the classically described “pearly papule” with telangiectasia and rolled borders. These lesions are often found on the head and neck. Superficial BCCs appear as erythematous patches and plaques, sometimes with erosion. Morpheaform, or infiltrative BCCs, appear as indurated plaques with poorly defined margins. Micronodular BCCs appear with intermediate characteristics between nodular and morpheaform subtypes, tumor extension of this subtype may be more difficult to detect on physical examination than nodular BCCs.<sup>2</sup> Due to their higher rates of recurrence and greater likelihood of positive margins on excisions, micronodular and morpheaform/infiltrating BCCs have been grouped by some experts as aggressive-subtype BCCs.<sup>3</sup> Overall, nodular and mixed subtypes are the most common lesions encountered.

The major risk factor for basal cell carcinoma appears to be early childhood sun exposure.<sup>4</sup> In addition, it has been suggested that intermittent periods of intense sun exposure confer greater risk than a stable, continuous level of exposure.<sup>5</sup> Other accepted risk factors are physical traits such as fair complexion, red or blond hair, and light eye color, along with prior exposure to ionizing radiation, arsenic, and psoralen/ultraviolet A therapy.<sup>1</sup>

Basal cell carcinoma does have the potential to metastasize, although the risk is low. The reported incidence of metastasis ranges from .0028% to 0.55%.<sup>6</sup> The most common sites of metastasis include regional lymph nodes (60%), lung (42%), bone (20%), and skin (10%).<sup>6</sup>

For localized disease, both simple excision and microscopically-controlled surgery (Mohs) can achieve impressively low long-term recurrence rates. A recent prospective cohort study conducted at UCSF evaluated 1,174 patients with 1,498 tumors treated with electrodesiccation with curettage, excision, and Mohs surgery with a median follow-up of 7.4 years.<sup>7</sup> The reported five-year recurrence rates for excision and Mohs were 3.5% and 2.1%, respectively. Similarly, local destruction with electrodesiccation performed reasonably well, with a 5-year recurrence rate of 4.9%.

There was likely to be selection bias involved with local destruction, however, as the tumors treated in this group were statistically less likely to be located on the H-zone of the face and were less likely to have aggressive tumor histology. These data have been generally supported by a randomized controlled trial in the Netherlands comparing Mohs vs. surgical excision.<sup>8</sup> In this study involving treatment of 408 primary BCC tumors and 204 recurrent BCC tumors, the reported 5-year recurrence rate for excision and Mohs was 4.1% and 2.5%, respectively. Interestingly, the authors observed no statistical difference between the two techniques in primary BCC lesions, although Mohs clearly proved superior in treatment of recurrent tumors. In addition to achieving excellent rates of local control, surgical modalities allow for diagnostic confirmation by histology and evaluation of tumor margins to ensure complete removal of the tumor. As a result, excision and Mohs are often the preferred approach for BCC.

Even with localized disease, however, a small percentage of BCC tumors are considered inappropriate for surgery. This can be due to reduced likelihood of cure due to the size of the tumors, unacceptable risk to important anatomical structures with surgery or radiation (such as the eyes and surrounding structures), cosmetic concerns regarding scarring, and also a history of repeated recurrences at the same site. Patients with the propensity to develop numerous BCC lesions per year, such as those with xeroderma pigmentosum or the basal cell nevus syndrome (BCNS, or Gorlin syndrome), may be especially poor candidates due to the high likelihood of numerous new lesions. Consequently, there has been significant interest in the development of non-surgical interventions for patients who fall into any of these categories.

## Current Non-Molecularly Targeted Therapies

The simplest non-surgical treatment for BCC is cryotherapy, which involves rapid application of liquid nitrogen to rapidly freeze BCC tumors. At least 2 freeze-thaw cycles are required. Cryotherapy has generally been reserved for small, well-defined tumors. The treatment is noted for post-treatment adverse effects such as erythema, blistering, hypopigmentation, hypertrophic scarring, and tissue distortion.<sup>9</sup> Given that cryotherapy also inflicts local tissue damage and potential scarring, this modality does not offer significant benefit over excision or Mohs.





# Targeting Angiogenesis in Basal Cell Carcinoma

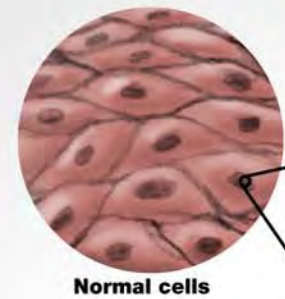
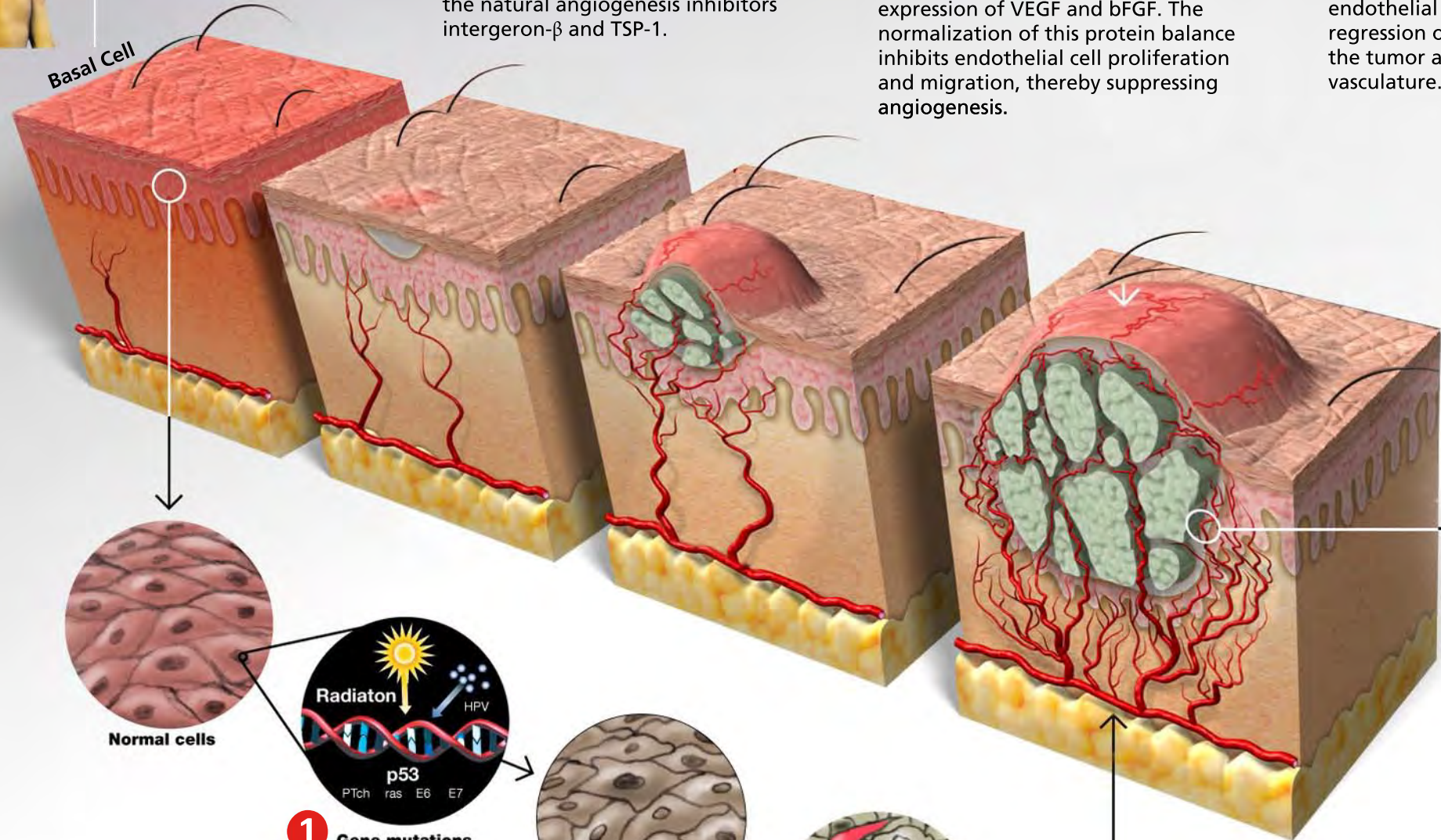
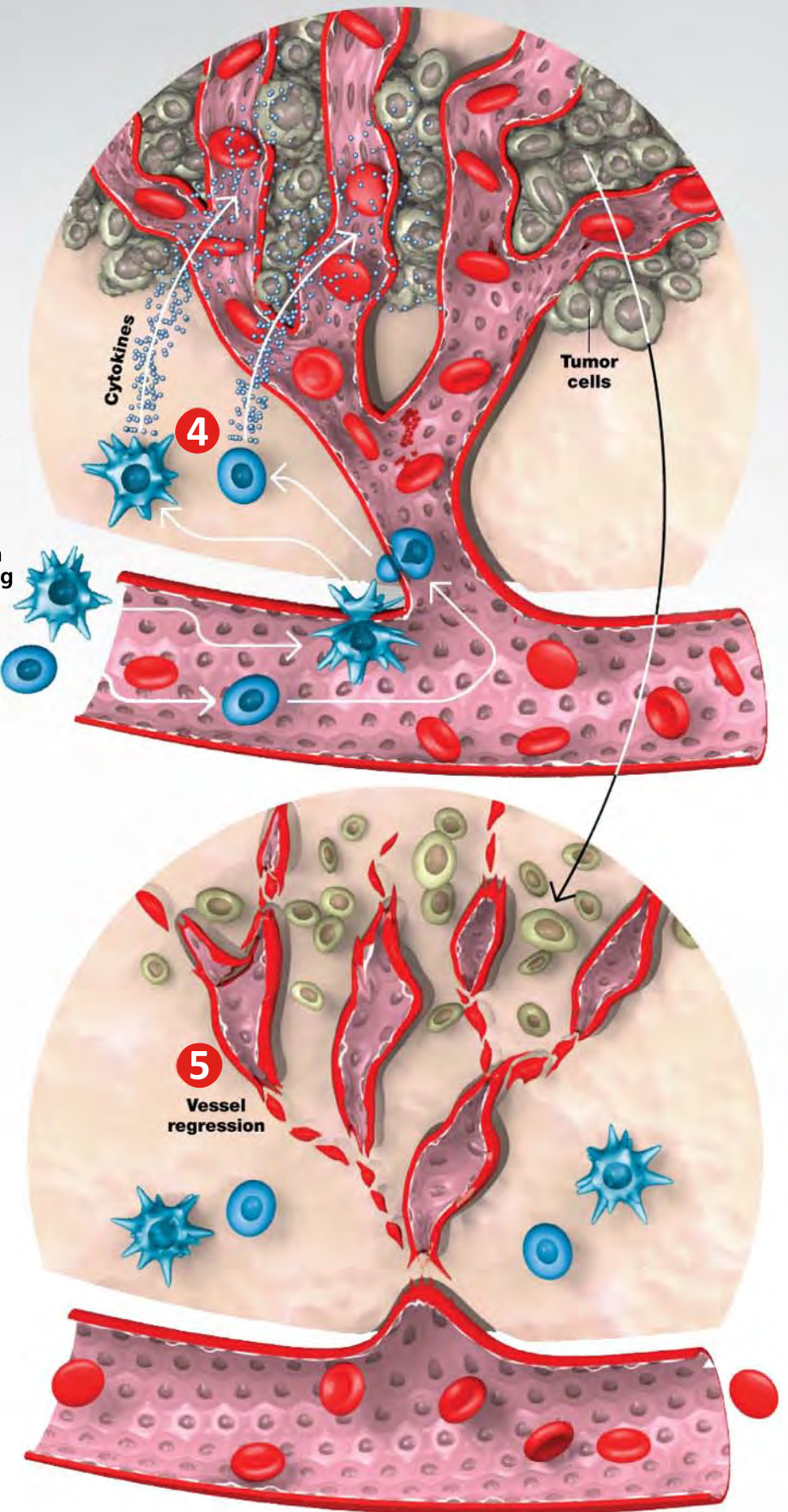
**1 Chronic UV Exposure** causes the accumulation of genetic damage in kerationocytes, resulting in clonal expansion of p53 mutant cells and eventual neoplastic transformation of the skin. The human papillomavirus (HPV) also induces these changes.

**2 Transformed lesions** must "switch" to an antiangiogenic phenotype in order to continue growing. Tumor cells produce high levels of endogenous angiogenic growth factors, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), while simultaneously suppressing the natural angiogenesis inhibitors intergeron- $\beta$  and TSP-1.

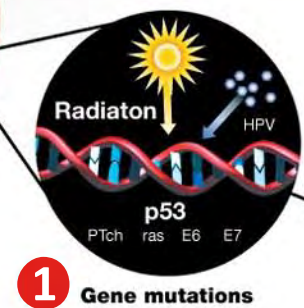
**3 Imiquimod** stimulates the production and recruitment of immune cells to the tumor site. It is used to treat superficial basal cell carcinoma.

**4 Immune cells** produce cytokines, including IL-10, IL-12, and IL-18, which upregulate IFN- $\beta$  and downregulate expression of VEGF and bFGF. The normalization of this protein balance inhibits endothelial cell proliferation and migration, thereby suppressing angiogenesis.

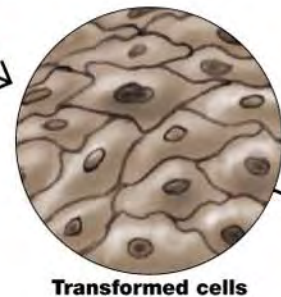
**5 The immunostimulatory** response also induces apoptosis of both tumor and endothelial cells, resulting in regression of both the tumor and its vasculature.



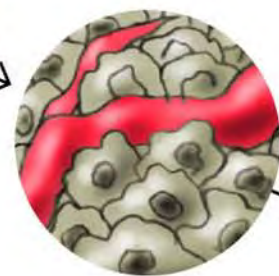
Normal cells



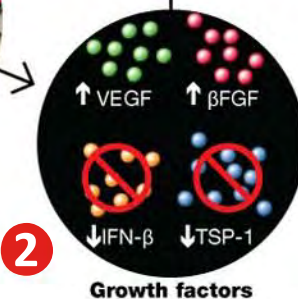
1 Gene mutations



Transformed cells



Tumor cells



2

Growth factors

Clonal expansion of p53 mutant cells  
Inhibition of DNA and cell cycle repair  
Angiogenesis and tumor growth



The chemotherapeutic agent 5-fluorouracil (5-FU) was the first FDA approved topical treatment for superficial BCC.<sup>10</sup> 5-FU enters cells and is modified into an end product that mimics a natural nucleotide. It then binds to and inhibits thymidylate synthase, thus preventing the conversion of deoxyuridine nucleotides to thymine. This halts DNA synthesis, causing reduced cell growth and cell death in fast-growing tumor cells. While 5-FU has poor absorption in normal tissue, skin at the site of the BCC lesion will demonstrate an inflammatory dermatitis that can involve erythema, burning, blistering, and erosion. In current clinical practice, 5-FU is often utilized to treat multiple BCCs in close proximity to each other, and has the added benefit of avoiding much of the scarring that results from excisional therapy. It appears to have good efficacy against superficial subtypes, with histologic cure rates on the order of 90% with twice daily application of 5% topical 5-FU for up to 12 weeks.<sup>11</sup> Nevertheless, 5-FU tends to have a high recurrence rate in nodular and high-risk BCCs. Indeed, past examination of surgically-excised BCCs that recurred following 5-FU treatment suggested that the therapy is ineffective at targeting deeper tumor tissue, resulting in poor control of non-superficial subtypes.<sup>12</sup> Thus, 5-FU should only be used in selected cases of superficial, low-risk lesions.

Photodynamic therapy (PDT) is FDA-approved only for the treatment of AK, but it is also commonly employed for nodular and superficial BCC lesions > 2 mm in thickness or treatment of multiple BCCs in close proximity.<sup>13</sup> The technique involves application of topical photosensitizers, most commonly 5-aminolevulinic acid (ALA) and methyl 5-aminolevulinate (MAL). These photosensitizers are then converted preferentially by tumor cells to the photosensitizer protoporphyrin IX. When exposed to light, protoporphyrin generates free radicals and reactive oxygen species that inflict localized tumor destruction. Recently, interest has shifted towards the use of MAL-PDT due to its superior penetration. Longer-term follow-up studies on the order of 2-5 years post-treatment have reported complete response rates of 78-92% for MAL-PDT, with the added benefit of minimal post-treatment scarring.<sup>14</sup> For nodular BCC, however, MAL-PDT results in a 60 month complete response rate of only 76%, compared to 96% with surgery. When utilized for larger lesions, such as nBCCs > 2mm in thickness, the technique generally requires concurrent debulking therapy with techniques such as curettage.

Radiotherapy is another option for locally advanced disease, which can include lesions >2 cm, are deeply invasive, and are otherwise not amenable to simple excision or Mohs.<sup>6</sup> In locally advanced disease, radiation therapy can achieve locoregional control of 86% at 4 years for appropriately selected candidates.<sup>6, 15</sup> Nevertheless, both short-term and long-term radiation toxicity can be damaging to sensitive anatomical structures, particularly within the face and neck. As a result, radiation is similar to surgery in that its application can be greatly limited by anatomical considerations.

While these modalities have provided additional options for management of BCC, most of these interventions are effective primarily for low-risk lesions. There is a continued need for effective treatment of locally advanced, metastatic, or genetic syndrome-driven BCC, particularly when surgery or radiation is not appropriate. The development of advanced, molecularly-targeted therapies has meant a significant expansion in the clinical armamentarium for advanced BCC in the past few years. We review here a number of pathways relevant to BCC pathogenesis and present new targeted modalities that take advantage of insights into these crucial molecular pathways for BCC tumorigenesis.

## MECHANISMS AND PATHWAYS OF BCC

### HH and WNT Signaling Pathway

Dysregulation of the hedgehog (HH) signaling pathway is key to both tumorigenesis and sustained proliferation of BCC. HH signaling is often found to be upregulated in sporadically occurring BCCs.<sup>16</sup> Laboratory studies have also demonstrated that HH signaling is required for BCC proliferation and survival. In animal models, abrogation of HH signaling via transgene inactivation results in tumor death and a halt to tumor proliferation.<sup>17</sup>

In normal human development, the HH signaling pathway is crucial for guiding the patterning of distal tissues. In adults, however, significant HH activity normally only persists in the hair, skin, and stem cells.<sup>13,18</sup> HH itself is a family of secreted signaling proteins with three mammalian isoforms: Sonic hedgehog (SHH), Desert hedgehog (DHH), and Indian hedgehog (IHH).<sup>3</sup> HH interacts with the extracellular receptor patched (PTCH1) (Figure 1). Upon binding, PTCH1 releases its inhibitory activity on the G-coupled receptor-like protein smoothened (SMO). SMO then transmits HH signaling downstream into the cytosol via a number of associated proteins, including suppressor of fused (SUFU). The ultimate downstream effect is activation of the GLI family of transcription factors.

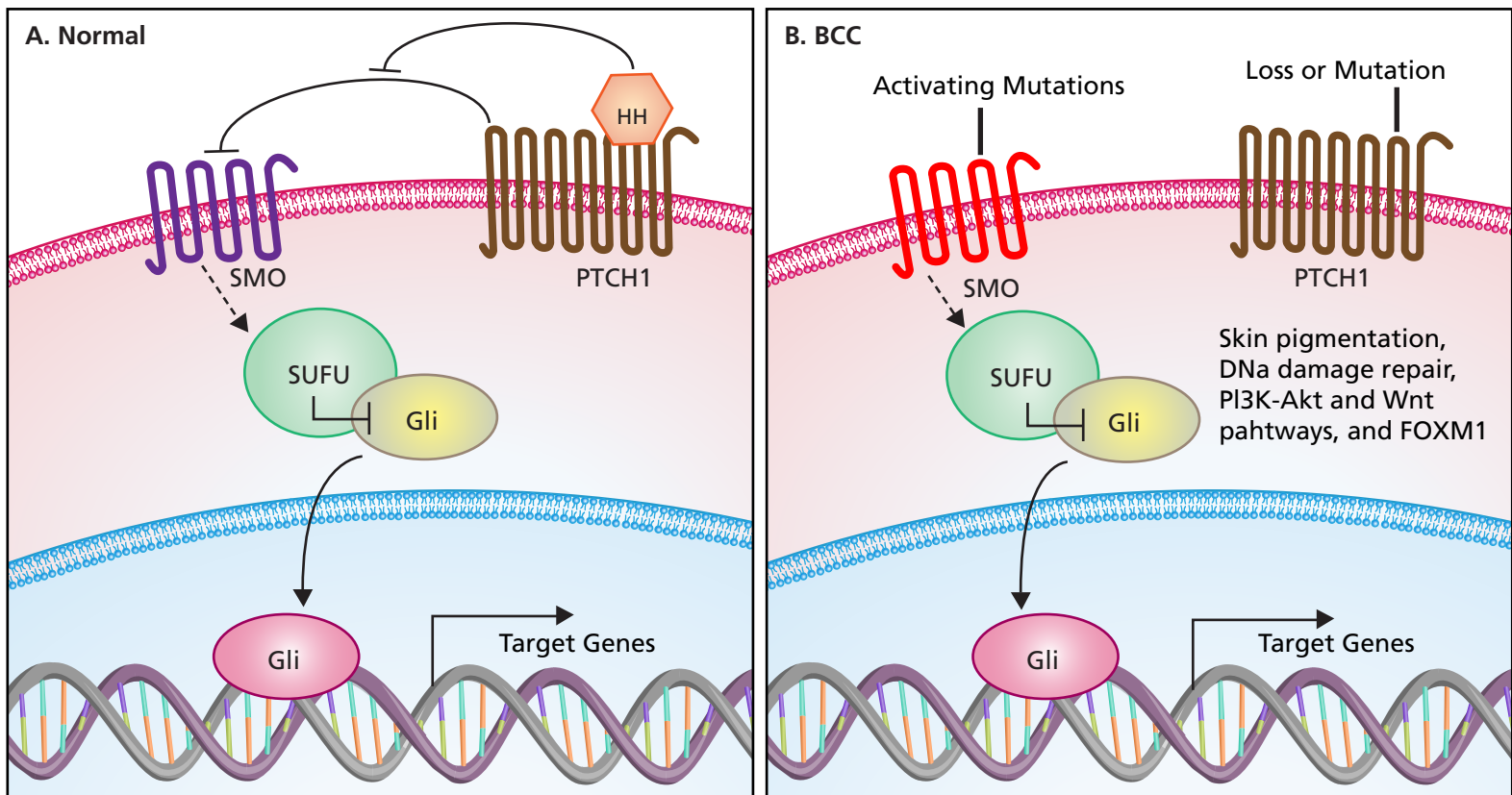
Dysregulation of any of the critical actors within the HH pathway is thought to predispose a patient to the development of BCC. One particularly instructive example involves the basal cell nevus syndrome (BCNS), also known as Gorlin syndrome. Patients with this condition can develop hundreds of BCC lesions over their lifetime due to a genetic defect in PTCH1. Because PTCH1 acts as a tumor suppressor gene, patients who inherit the defective gene are at higher risk of acquiring bi-allelic inactivation of PTCH1, leading to constitutive HH signaling and BCC lesion formation.<sup>16</sup>

SHH, the human isoform of HH, has also been shown to promote angiogenesis. Human-derived fibroblast cultures, which were developed to mimic tumor stroma, have been found to respond to SHH by producing pro-angiogenic paracrine signaling proteins VEGF-A, hepatocyte growth factor, and PDGF-C.<sup>19</sup> Antagonizing the SHH signaling pathway has been shown to reduce vascular density in tumor xenografts. Additional cells as diverse as bone marrow stem cells have also been shown to respond to SHH signaling by upregulating VEGF production.<sup>20</sup>

In recent years, activation of the HH pathway has also been shown to drive the wingless-related integration site (WNT) signaling pathway in BCC. WNT ligands are secreted glycoproteins that bind to the seven-transmembrane span Frizzled (FZ) receptor family.<sup>21</sup> There are a number of WNT pathways, with the canonical WNT pathway currently thought to be relevant to BCC (Figure 2). The ultimate result of activated WNT signaling is the accumulation of and translocation of the protein  $\beta$ -catenin into the cell nucleus, which then facilitates gene transcription. When the WNT pathway is not activated, cytoplasmic  $\beta$ -catenin is rapidly degraded by a protein complex involving casein kinase 1 (CK1), adenomatous polyposis coli (APC), glycogen synthase kinase 3 (GSK3) and Axin. Molecular analysis has shown that human BCC buds show high levels of cytoplasmic and nuclear  $\beta$ -catenin, which is highly

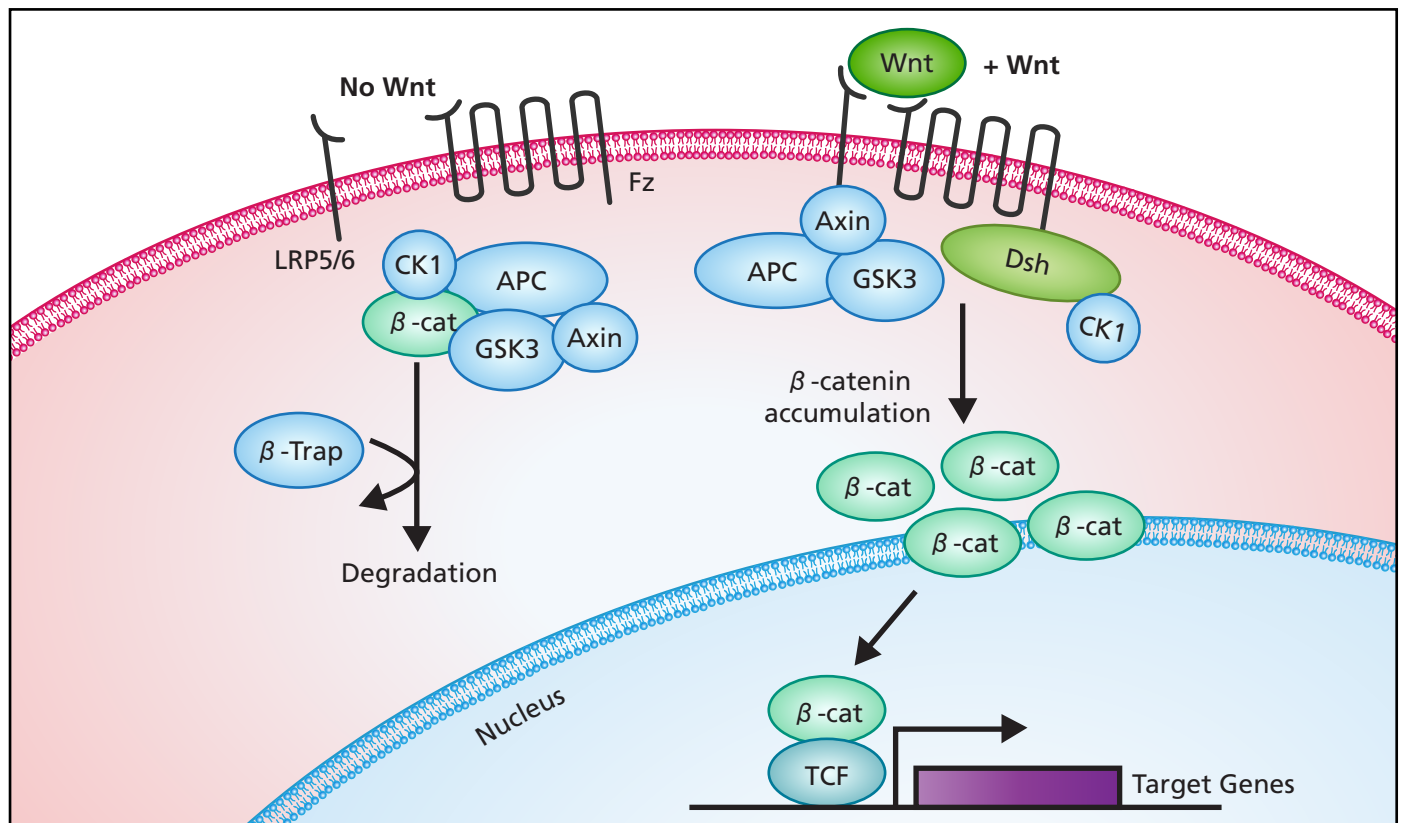


**FIGURE 1: Hedgehog Signaling in Basal Cell Carcinoma**



Original Reference: Nat Rev Cancer. 2008 Oct;8(10):743-54 PMID: 18813320

**FIGURE 2: Canonical Wnt Signaling Pathway**



Original reference: Organogenesis. 2008 Apr;4(2):68-75. PMID: 19279717

suggestive of unregulated WNT signaling.<sup>22</sup> In the same study, investigators utilized a mouse model of constitutively active HH signaling to show that ligand-driven WNT signaling is actually a requirement for HH-driven oncogenesis. While the mouse model normally developed epithelial buds and hamartomas mimicking the initial stages of BCC formation, overexpression of WNT pathway inhibitor Dkk1 in the animal model inhibited oncogenesis.

WNT signaling also plays an important role in promoting tumor angiogenesis, which becomes more crucial as a tumor grows in size. Endothelial cells express both WNT ligand and their receptor, frizzled (FZ).<sup>23</sup> Numerous WNT ligands have been shown to stimulate endothelial cell proliferation. In addition, WNT signaling by endothelial cells can mediate the NOTCH signaling system, promoting the development of aberrant vascular phenotypes.

## NOTCH Signaling Pathway

The NOTCH pathway plays an important role in promoting keratinocyte differentiation. NOTCH itself is a transmembrane protein that can interact with a variety of ligands. Upon binding, the intracellular portion of NOTCH is proteolytically cleaved, allowing the released portion to enter the cell nucleus to mediate gene transcription (Figure 3).<sup>24</sup> The intracellular portion itself is composed of a number of domains including nuclear localization signals (NLS) and a transactivation domain (TAD). Once released, the intracellular portion of NOTCH associates with a transcription factor, recombining binding protein suppressor of hairless (RBP-J), and activates it. RBP-J subsequently recruits co-activator Mastermind along with histone acetyltransferases to mediate gene transcription. NOTCH1 deficiency in the skin has been shown to result in increased WNT and HH signaling, along with development of tumors such as squamous cell carcinoma.<sup>25</sup> Indeed, in situ

hybridization experiments have shown that human BCC cells demonstrate weak or non-existent NOTCH signaling.<sup>26</sup>

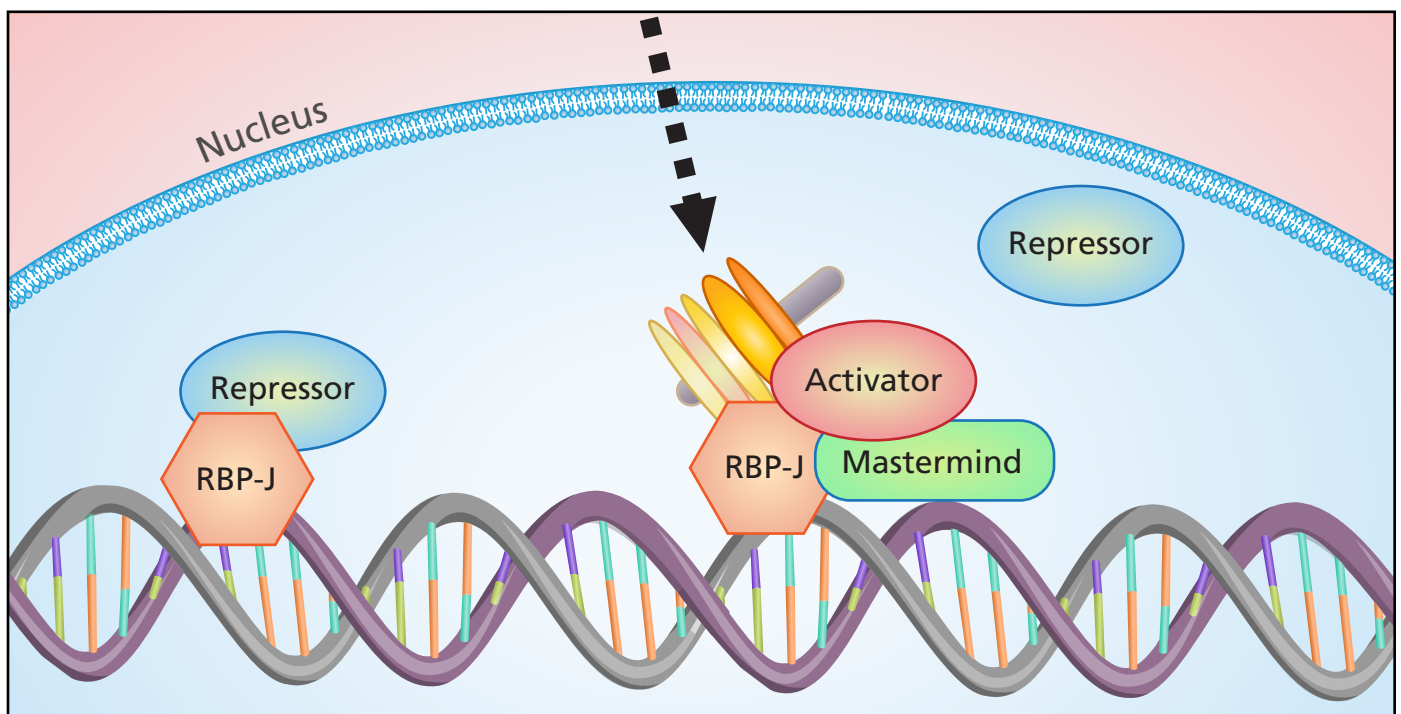
NOTCH's role as a cutaneous tumor suppressor has been demonstrated in animal models. Ablation of NOTCH1 in mouse skin tissue results in corneal hyperplasia and development of a variety of skin cancers after chemical insult.<sup>27</sup> These tumors include BCC and SCC. BCC-like tumors were also noted to develop spontaneously in Notch1 deficient mice. These mice were found to have upregulated Gli2 activity, which was suggestive of crosstalk between NOTCH and the HH pathway.

In tumor angiogenesis, NOTCH is activated in response to signaling from vascular endothelial growth factor (VEGF). NOTCH signaling activity results in mediation of VEGF and other pro-angiogenic signaling to restrict nascent blood vessels from branching.<sup>23</sup> Thus, NOTCH helps to form better perfused vessels. NOTCH signaling in new vessels has been shown to be dynamic over time, and its deficiency leads to more numerous, but poorly perfused vasculature. It is thought that this relative deficiency in NOTCH results in tumor hypoxia.

## TLR Signaling Pathway

Toll-like receptors (TLRs) are a family of proteins expressed in keratinocytes, Langerhans cells, macrophages, T and B cells, mast cells, endothelial cells, and fibroblasts that are classically thought to mediate innate immunity. There are currently 10 known human TLRs.<sup>28</sup> TLRs have garnered interest from an oncologic perspective as TLR agonists can enhance the activity of natural killer, tumor-reactive T cells, and other immune cells through upregulation of cytokines and chemokines. TLR activation has also been shown to result in alteration of the tumor microenvironment and inhibition of angiogenesis.<sup>29</sup>

**FIGURE 3: NOTCH Signaling Pathway**





## CLINICAL PROGRESS IN TARGETED THERAPY FOR BCC

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### SMO Inhibitors

In 2012, two landmark phase II studies were reported in the *New England Journal of Medicine* investigating the use of the first-in-class, small-molecule SMO inhibitor vismodegib (GDC-0449, Genentech) for treatment of advanced BCC (both metastatic and locally advanced) and for management of patients with basal cell nevus syndrome (BCNS). By targeting the HH pathway, it was hoped that these medications could lead to lesion resolution and prevent the development of new BCC lesions. Both studies met their primary endpoints in terms of anti-BCC efficacy, although the studies demonstrated a moderate toxicity profile for the medication.

Sekulic and coworkers evaluated the efficacy and safety profile of vismodegib in BCC patients who were inappropriate surgical candidates given the low likelihood of cure or potential disfigurement of surgery. Of the 104 patients enrolled in the non-randomized study, 33 had metastatic BCC, while 71 had locally-advanced disease. Patients received vismodegib 150 mg daily by mouth and were assessed periodically by both study investigators and independent assessors for a decrease of 30% or more in the externally visible or radiographic dimension of their tumors. Therapy was continued for the duration of the trial or until disease progression, which resulted in a median length of therapy of 10 months. In patients with metastatic disease, the study achieved an objective response rate of 30% as determined by independent reviewers. All of these patients experienced partial responses with a median duration of response of 7.6 months. An additional 64% of patient with metastatic disease experienced stable disease during the course of the study. Only a single patient experienced progression of metastatic disease while on therapy. Patients with locally advanced disease experienced greater benefit, with a 43% objective response rate. Impressively, 21% of the analyzed patients experienced complete resolution of their BCC lesion with no evidence of residual tumor in their post-therapy biopsy specimen. The majority of patients experienced tumor shrinkage. Vismodegib had a moderate toxicity profile, with almost half of patients reporting grade 1 muscle spasms and alopecia. Approximately one third of patients reported dysgeusia (taste disturbance), weight loss, and fatigue. The medication was discontinued in 12% of patients due to serious adverse events, and a quarter of the locally advanced treatment group elected to discontinue therapy although the reasons for doing so were not officially recorded. Finally, 7 patients expired during the trial, despite the fact that six of these individuals only had locally advanced disease. All of these patients had clinically significant risk factors and comorbidities, and thus the investigators were unable to determine a clear link between the study drug and their fatal adverse events.

As a result of the durable benefits observed in this trial, vismodegib received formal FDA approval for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery, or for patients who are not candidates for surgery or radiation.<sup>30</sup> Due to the high likelihood of fetal harm due to its anti-HH mechanism, usage of vismodegib requires warning for females of reproductive

age to utilize contraception during and after therapy, and for the use of barriers in males. The drug did not, however, receive a contraindication to use for pregnancy due to its labeled use for serious and life-threatening disease with limited alternative therapies.

In a second major trial, Tang and coworkers evaluated the anti-BCC efficacy of vismodegib in a randomized, double-blind, placebo-controlled study involving 41 patients with BCNS. Patients with BCNS can develop numerous new BCC lesions in a single year, and thus the investigators chose reduction in the incidence of new surgically-eligible BCC lesions as their primary endpoint. Notably, patients in the vismodegib treatment arm experienced a significantly reduced per-patient rate of new BCCs compared to the placebo group, with a mean of 2 vs. 29 new lesions per year, respectively. Patients also experienced a mean reduction in lesion size of 65%. In lesions that appeared clinically resolved, based on a clinical exam, only 17% of biopsied samples yielded residual tumor. Molecular studies further demonstrated reduced hedgehog signaling, with a 90% reduction in GLI1 messenger RNA present in BCC lesions biopsied following 1 month of therapy. No change in apoptosis markers was observed, however. Notably, therapy was significantly limited by adverse events. Similar to the Sekulic trial, patients routinely experienced grade 1 or 2 adverse events related to muscle cramps, dysgeusia, hair loss, and weight loss. This resulted in more than half (54%) of patients discontinuing therapy prior to completion of the trial. Only one of five eligible patients was able to tolerate 18 months of therapy. No deaths were observed in this study.

While the clinical role of vismodegib and other SMO inhibitors is still being defined, it is clear that targeted systemic therapy provides a welcomed therapeutic option for patients with advanced disease who are inappropriate candidates for surgery or radiotherapy for their BCC lesions. In addition, vismodegib is under investigation in at least one clinical trial as a neoadjuvant for shrinking BCC lesions to a size that is more amenable to Mohs (ClinicalTrials.gov identifier: NCT01631331). The goal is to reduce the morbidity of surgery for locally advanced lesions by sparing crucial structures, such as the eyelids, or by simply reducing the required volume of excision. A number of case reports have already surfaced regarding the successful use of vismodegib as a neoadjuvant or adjuvant therapy. In the ophthalmology literature, neoadjuvant use of vismodegib enabled resection of an orbital BCC without ocular destruction.<sup>31</sup> In another case, a patient with a BCC eroding through the calvarium and into the dural surface experienced significant tumor shrinkage with vismodegib, enabling surgical resection with reduced morbidity.<sup>32</sup> Vismodegib has also been used following a margin-positive BCC resection in a patient with an extensive tumor infiltrating the spinal processes of multiple vertebrae, allowing for more optimal radiation therapy.<sup>33</sup>

Vismodegib is also being actively investigated for use in other oncologic conditions where dysregulated hedgehog signaling has been identified, although results of the first few reported studies have been disappointing thus far. Vismodegib has been shown to have no added benefit when combined with existing standard of care chemotherapy regimens for metastatic colorectal cancer.<sup>34</sup> In patients with ovarian cancer in second or third complete remission, vismodegib failed to achieve the a priori declared degree of improvement in progression-free survival for treatment efficacy.<sup>35</sup> Additional clinical trials are currently underway investigating vismodegib's use in medulloblastoma (NCT01601184), refractory

pediatric pontine glioma (NCT01774253), high risk first remission or relapsed multiple myeloma (NCT01330173), refractory or relapsed B-cell lymphoma or chronic lymphocytic leukemia (NCT01944943), advanced or metastatic sarcoma (NCT0154452), pancreatic cancer (NCT01064622, NCT00878163), and extensive-stage small cell lung cancer (NCT00887159).

## Immune Response Modifiers

Imiquimod (imidazoquinoline 5% cream; Aldara), a Toll-like receptor-7 (TLR-7) agonist, was initially FDA approved for the treatment of external genital warts and actinic keratosis. In 2004, imiquimod was approved for the treatment of superficial BCC on the strength of two double-blind controlled studies, described below. Application of imiquimod results in local upregulation of the cytokines IFN- $\alpha$ , IFN- $\gamma$ , and interleukin-12 (IL-12). It is also known to promote both activation and migration of Langerhan's cells, which are bone-marrow derived antigen presenting cells present in the epidermis.<sup>36</sup> In addition to immune upregulation, many of these cytokines inhibit angiogenesis. This occurs through downregulated production of several pro-angiogenic growth factors and inducing endothelial cell apoptosis.<sup>37</sup> For example, IL-12 inhibits endothelial cell proliferation and capillary tube formation through upregulation of IFN- $\gamma$  and downregulation of VEGF and bFGF.

Studies have shown that topically-applied imiquimod causes BCC tumor cells to express lower levels of the apoptosis-related protein Bcl-2, thereby making them more susceptible to cell death.<sup>38</sup> Investigators have also observed massive peri- and intra-tumoral infiltration with macrophages during the inflammatory response that results during active treatment.

The efficacy of topical imiquimod for the treatment of superficial BCC was demonstrated through two identical, phase 3 randomized, vehicle controlled studies.<sup>39</sup> The studies, which involved a total of 724 patients, found that topical imiquimod 5% cream could achieve 75% clearance of superficial BCCs with 5X/week application frequency for six weeks. Daily dosing frequency was also investigated, although it showed no additional benefit in clearance rate. Clearance was assessed through a combination of clinical exam and pathologic examination at 12 weeks following the initiation of therapy. Interestingly, histologic clearance (89%) was higher than clinical clearance, suggesting that clinical examiners relying on physical examination alone may have been conservatively underestimating clearance.

Topical imiquimod was well tolerated, with only 4% of patients in the 5x/week dosing arm discontinuing therapy due to adverse events. The most commonly reported adverse events included erosion, erythema, and crusting of the treatment zones. Local skin reactions such as these were seen in 28% of patients in the 5x/week treatment arm. In general, patients who reported higher intensity of these adverse effects experienced greater benefit in terms of lesion clearance. From a clinical perspective, this highlighted the importance of preparing patients to expect localized skin reactions during active therapy, and further raised the possible use of the intensity of the local skin reaction as a surrogate marker for treatment efficacy.

Imiquimod appears to offer less benefit when used for non-superficial subtypes. A similar phase 3 study investigating the use

of topical imiquimod 5% cream for nodular BCC showed that 78% of the 90 evaluable patients experienced clinical clearance, which is similar to the results seen for superficial subtypes.<sup>40</sup> Nevertheless, only 64% of patients in the treatment arm experienced full histologic clearance, suggesting persistent disease that eluded visual diagnosis.

Imiquimod appears to achieve good sustained clearance for superficial BCC, with a reported 5-year sustained clinical cure rate of 84.5%, with 90.3% sustained histologic cure.<sup>41</sup> Results were notably worse in a trial that included a significant portion of nodular and infiltrating tumor subtypes.<sup>42</sup> The reported five-year sustained clearance rate of 66% in this trial serves to emphasize the reduced efficacy of imiquimod when used for non-superficial BCC subtypes.

In 2013, a well-designed, government-funded study in the Netherlands evaluated the comparative efficacies of imiquimod, 5-FU, and PDT for the treatment of superficial BCC.<sup>43</sup> In the multicenter, single blind, non-inferiority, randomized controlled trial, patients with localized superficial BCC were randomized to each of the three therapies, with approximately 200 patients in each group. Patients were followed at 3 and 12 months post-treatment, with the primary endpoint being percentage of patients demonstrating complete tumor clearance based on clinical exam. The PDT arm received two sessions of MAL-PDT with a 1-week interval, while the 5-FU group was instructed to apply 5-FU at a frequency of twice daily for 4 weeks. The imiquimod group applied the topical once daily, five times a week, for a total of six weeks. Imiquimod performed the best in this trial, with 83.4 percent of patients being tumor-free at both 3 and 12 months. The PDT and 5-FU groups achieved tumor-free percentages of 72.8% and 80.1%, respectively. Based on the non-inferiority analysis, imiquimod was shown to be superior to PDT, while 5-FU was found to be non-inferior. Thus, this particular trial is supportive of imiquimod as the preferred therapy for localized, superficial BCC. The study had a few notable weaknesses, namely its relatively short follow-up time of 1 year and the lack of evaluation for histologic clearance. Nevertheless, head-to-head comparative effectiveness studies for BCC are rare, making its insights useful for decision-making with regards to therapies for superficial BCC. Its results are also in agreement with a 2012 meta-analysis that pooled treatment efficacy results from 28 randomized and non-randomized studies evaluating non-invasive modalities for treatment of superficial BCC.<sup>44</sup> The authors reported a pooled, 12-week post-treatment complete response rate for imiquimod and PDT of 86.2% (95% confidence interval [CI] 82-90%) and 79.0% (95% CI 71-87%), respectively. Tumor-free survival at 1 year was 87.3% for imiquimod (95% CI 84-91%) and 84.0% (95% CI 78-90%) for PDT.

## Other Agents in Clinical Trials

Early phase clinical development is currently ongoing for a number of other SMO inhibitors for a number of oncologic indications. These include: LDE225 (Erismodegib), BMS-833923, TAK441, and LEQ506.<sup>45</sup> While the majority of these early stage trials have yet to be reported, LDE225 has shown some promising results with regard to anti-BCC efficacy.

LDE225 is a selective SMO inhibitor with oral bioavailability.<sup>46</sup> It is notable for showing potential as a topical formulation. Skvara

and coworkers found that topical LDE225 could induce regression of basaloid tumor nests in heterozygous PTCH1+/- mice.<sup>47</sup> In the same study, they reported a small vehicle-controlled human trial in 8 patients with BCNS. A total of 27 BCCs were treated with either 0.75% LDE225 cream twice daily or vehicle for a total of 4 weeks. Half the lesions received active treatment, and these were comprised of 8 nodular and 5 superficial BCC subtypes. The trial showed encouraging results, with 3 lesions demonstrating complete visible resolution and 9 showing a partial response, defined as visible reduction in size without complete resolution. Notably, patients in this topical trial did not experience any of the systemic toxicities associated with oral SMO inhibition such as hair loss, muscle cramps, weight loss, or dysgeusia. Patients also did not report any skin irritation. The authors noted that LDE225 serum levels were undetectable for these patients, and no serum, urine, or physical exam abnormalities were observed. While the trial's sample size was quite small, it is still notable for what appears to be an attractive toxicity profile with potentially significant clinical benefit.

## CURRENT CLINICAL CHALLENGES IN TARGETED THERAPY OF BCC

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### Resistance to SMO inhibition

The development of tumor resistance to SMO inhibitors such as vismodegib has been observed, although the exact incidence of this is still being determined. In a case series of 28 patients with metastatic or locally advanced BCC being treated with vismodegib, 21% of patients were found to have tumor regrowth following an initial response to therapy.<sup>48</sup> The patients who experienced tumor regrowth had tumors of all three major subtypes. Overall, the mean time to observed regrowth was 56.4 weeks. All of the patients with regrowth had locally advanced disease, although the authors noted that a longer study period may have been required to observe regrowth events involving their patients with metastatic disease.

At least one elucidated mechanism of resistance involves disruption of vismodegib's ability to bind to SMO. During the early development of vismodegib, a medulloblastoma patient with known PTCH mutation experienced progression of disease following an initial treatment from vismodegib.<sup>49</sup> A biopsy was obtained of the tumor, and molecular profiling revealed a single amino acid substitution that abrogated vismodegib's ability to bind SMO. The point mutation apparently had no effect on SMO's function itself, allowing it to continue to activate the HH signaling pathway. Indeed, further molecular studies have demonstrated that mutation of a conserved aspartic acid residue in the 473 position of SMO confers some degree of vismodegib resistance to all functional mutants.<sup>50</sup> Some of these mutations actually increased SMO's ability to activate HH signaling, suggesting potential pro-oncogenic resistance pathways.

Amplification of the GLI2 pathway is another potential resistance pattern that is particularly concerning as this downstream activity would bypass any inhibition of SMO or other upstream effectors. GLI2 amplification in tumors has been seen in both human

medulloblastoma and a mouse model of BCC.<sup>50</sup> Upregulation of the phosphatidylinositol 3-kinase (PI3K) pathway has also been implicated as another associated resistance pathway. In a transgenic mouse model of medulloblastoma, investigators found upregulated PI3K signaling in tumor allografts that had become resistant to the SMO inhibitor LDE225.<sup>51</sup> Interestingly, it was found that addition of the PI3K inhibitor NVP-BKM120 or the dual PI3K-mTOR inhibitor NVP-BEZ235 to anti-SMO therapy delayed the development of resistance.

Combined, these studies into SMO inhibitor resistance patterns have emphasized the importance of investigating a broader set of HH inhibitors, including downstream targets, in order to ensure continued efficacy against resistant tumors. In addition, animal data have raised the possibility that combination therapy targeting additional pathways, such as PI3K, may ultimately play a role in either delaying or overcoming resistance to anti-SMO monotherapy.

## FUTURE DIRECTIONS

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### An Evolving Clinical Understanding of Hedgehog Inhibition

The recent approval of vismodegib and the development of additional HH pathway inhibitors herald a new era of targeted therapy for the management of BCC. As the field develops greater experience with agents like vismodegib, the role of targeted systemic therapy will likely expand beyond its current role as an agent of last resort for controlling advanced BCC that is not amenable to surgery. Early case reports suggest potential roles for targeted therapy as a neoadjuvant or adjuvant to surgery or radiation, and the community awaits data from clinical trials investigating this possible application.

In addition, given the current moderate toxicity profile for vismodegib, further research into alternate dosing regimens and length of therapy is needed. This is particularly important if SMO inhibitors are to find a role in treating patients who do not have advanced disease, but rather suffer from a high burden of BCC. This includes patient populations with genetic syndromes like BCNS, or who have had extensive sun exposure. In these patients, significant adverse effects are less acceptable as the goal is to avoid the pain and disfigurement of repeated surgeries rather than to prevent mortality from metastatic disease. As such, it is quite telling that more than half of the patients in the BCNS vismodegib trial elected to stop therapy prior to completion of the trial, despite dramatic efficacy. It is possible that the current adverse effects will limit the role of the therapy beyond advanced BCC unless strategies can be developed to minimize the drug's toxicity. This could involve alternate dosing strategies, shorter courses or therapy, or potentially pharmacologic interventions that can minimize the cramping, dysgeusia, and fatigue patients currently experience.

The development of tumor resistance to SMO inhibition is concerning, but not altogether unexpected given past examples of acquired resistance to targeted therapy seen in other oncologic



conditions. A particularly instructive example is the case of imatinib, a highly effective targeted therapy used in the treatment of chronic myelogenous leukemia (CML). Imatinib was the first of a class of inhibitors targeting the BCR-ABL tyrosine kinase protein found in approximately 70% of CML patients.<sup>52</sup> Similar to vismodegib, acquired resistance quickly became a significant issue with imatinib therapy, and common mutations leading to tyrosine kinase resistance to inhibition were ultimately elucidated. With time, the CML community developed additional FDA-approved BCR-ABL inhibitors, dasatinib and nilotinib, for use as both second- and third-line therapies in patients who developed initial resistance. In addition, sophisticated molecular testing for identifying developed resistance and for determining initial susceptibility to tyrosine-kinase inhibitors evolved to guide clinicians in their choice of therapy. As the resistance patterns to SMO inhibitors in patients with BCC are better elucidated, it is likely that additional HH inhibitors will become necessary for patients who develop resistance. This highlights the importance of not only investigating the other candidate SMO inhibitors, but to also evaluate therapies focused on downstream targets in the HH pathway in order to ensure continued efficacy. In addition, animal data have raised the possibility that combination therapy targeting additional pathways, such as PI3K, may ultimately play a role in either delaying or overcoming resistance to anti-SMO monotherapy. These new research directions will likely require a significant amount of time, but will enable the BCC community to offer patients the promise of personalized, targeted therapy for advanced BCC.

## Cancer Prevention and Beyond

The possibility of a chemopreventive role for advanced therapies is also an intriguing application. In addition to causing tumor regression, the BCNS trial showed that vismodegib significantly reduced rates of BCC development in the trial population. Other high-risk patients besides those with genodermatoses may benefit from a chemopreventive strategy as well. These include patients with significant past sun exposure, transplant patients, and other immunosuppressed individuals.

Beyond the HH pathway, the cyclooxygenase 2 inhibitor (COX-2) pathway may be a viable potential target. In 2010, a double-blind, placebo-controlled randomized trial with 240 patients with extensive history of actinic keratosis evaluated the effect of the COX-2 inhibitor celecoxib versus placebo in preventing the development nonmelanoma skin cancer for a period of 9 months.<sup>53</sup> The investigators found that patients with celecoxib developed significantly fewer nonmelanoma skin cancers, including BCC, with only 0.14 cumulative tumors per patient versus 0.35 for the placebo arm. Patients in the celecoxib arm had a relative risk of only 0.40 versus placebo for the development of new BCC, suggesting that COX-2 inhibition could be an effective preventive strategy for high-risk patients.

In addition, a recent epidemiologic study raised the interesting possibility of using caffeine as a chemopreventive agent. Preclinical data have suggested that caffeine may act through the ataxia telangiectasia mutated and Rad3-related (ATR) protein to trigger pro-apoptotic signaling in cells that have suffered DNA damage from UV radiation.<sup>54</sup> As a result, investigators conducted a prospective cohort study using the large-sized Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) to evaluate the relationship between caffeine intake and development of nonmelanoma skin cancer. They found a statistically significant risk reduction in BCC development for participants with the highest quintile of caffeine consumption compared to those with the lowest (RR, 0.82 in women, 0.87 in men). Furthermore, the amount of caffeine consumed from other dietary sources such as tea, cola, and chocolate were also inversely associated with BCC risk. Combined with the promising chemopreventive effects of vismodegib, these studies suggest that it may be possible to tailor effective regimens to prevent tumor development in selected patient populations who are at high risk of BCC.

Finally, while the recent years have been remarkable for the validation of HH pathway inhibition as a paradigm for BCC therapy, other pathways such as WNT, NOTCH, PI3K, and TLR still offer the potential for new, effective interventions for BCC. Given the field's gradual evolution from simple chemotherapeutic approaches such as 5-FU to targeting TLR with imiquimod and HH with vismodegib, it is clear that targeted therapy is becoming a powerful new ally in the management of patients with BCC.

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## CME REQUIREMENTS

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## ACCREDITATION STATEMENT

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## RELEASE AND EXPIRATION

Date of original release: June 26, 2014

Date of expiration: June 25, 2015

CME Course Code: 2014BCC

## TARGET AUDIENCE

Practicing oncologists, dermatologists, and primary care physicians in the U.S., researchers and medical students

## HEALTHCARE GAP

Cancer of the skin (including melanoma and basal and squamous cell skin cancers) is by far the most common of all types of cancer. An estimated 3.5 million basal and squamous cell skin cancers are diagnosed each year (occurring in about 2.2 million Americans, as some people have more than one). Most of these are basal cell cancers.

The number of these cancers has been increasing for many years. This is probably due to a combination of better skin cancer detection, people getting more sun exposure, and people living longer. The overall lifetime risk for BCCs is estimated to be approximately 30%. The risk of development increases with age reaching its peak during sixth to eighth decades.

## PROGRAM LEARNING OBJECTIVES

At the completion of this activity, participants should be able to:

- Assess new data on novel agents and combination regimens for the management of non-melanoma skin cancer
- Describe recent clinical data evaluating signaling pathway inhibitors for the treatment of BCC
- Apply recent, practice-changing developments in the treatment of basal cell carcinoma to the management of patients with advanced or metastatic disease
- Manage adverse events and safety issues associated with the treatment of basal cell carcinoma
- Identify barriers to effective care of patients with BCC and identify strategies for overcoming those barriers

## ACTIVITY GOAL

This activity is designed to address the following ABMS / IOM competencies:

- Patient Care and Medical Knowledge

## METHOD OF PARTICIPATION

There are no fees for participating in and receiving credit for this online educational activity. The participant should, in order, read the objectives and faculty disclosures, review the educational content, answer the multiple-choice post-test and complete the evaluation. This program is available in PDF format accessible from the Angiogenesis Foundation's website (<http://www.angio.org>) in the CME section. A print version is also available; for more information contact [outreach@angio.org](mailto:outreach@angio.org). After reviewing the material, CME credits are available through the Angiogenesis Foundation's website (<http://www.cmeonline.org>) by selecting the name of the program (registration required). Course code: 2014BCC

## ACKNOWLEDGEMENT OF SUPPORT

This activity is supported by educational grants from Genentech.

## COURSE FACULTY

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William W. Li, M.D.

President,  
The Angiogenesis Foundation  
Editor-in-Chief

Disclosure: No relevant financial relationships to disclose.

## TOPICS AND EDUCATIONAL CONTENT

Emerging Concepts in Targeted Therapy for Basal Cell Carcinoma:

- Overview of Basal Cell Carcinoma
- Mechanisms and Pathways of BCC
- Clinical Progress in BCC for Targeted Therapy
- Current Clinical Challenges in Targeted Therapy of BCC
- Future Directions

## SYSTEM REQUIREMENTS

This educational program is available as a mobile application and a PDF file. The mobile application can be run on any iOS or Android device. To view and print PDF files, you must have Adobe Reader installed on your computer. Most computers already have this software installed. If yours does not, you can download Adobe Reader free from the Adobe Web site: <http://www.adobe.com>.

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