Basal cell carcinoma (BCC) of the skin, the most common malignancy in individuals of mixed European descent, is increasing in incidence due to an aging population and sun exposure habits. The realization that aberrant activation of Hedgehog signaling is a pathognomonic feature of BCC development has opened the way for exciting progress toward understanding BCC biology and translation of this knowledge to the clinic. Genetic mouse models closely mimicking human BCCs have provided answers about the tumor cell of origin, and inhibition of Hedgehog signaling is emerging as a potentially useful targeted therapy for patients with advanced or multiple BCCs that have hitherto lacked effective treatment.

Introduction

Description of basal cell carcinoma. In 1827 Arthur Jacob termed the skin tumor that we now call basal cell carcinoma (BCC) “Ulcer rodens” (1). In 1900, Krompecher described BCC as a malignant, locally invasive, and destructive cancer and named it “Carcinoma epitheliale adenoïdes”; he then went on to pioneer the classification of skin tumors using histogenetic principles, three years later coining the term “Basalzellenkrebs” (2, 3), a term indicating that the tumor originated in the basal layer of the epidermis or hair follicle (HF). In contrast, in 1910, Mallory used the term “hair matrix tumor” to specify the follicular origin of BCC (4), illustrating the conflict of interest: The authors have declared that no conflict of interest exists.

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Basal cell carcinoma — molecular biology and potential new therapies

Maria Kasper, Viljar Jaks, Daniel Hohl, and Rune Toftgård

Karolinska Institutet, Center for Biosciences and Department of Biosciences and Nutrition, Novum, Huddinge, Sweden. Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia. University Hospital of Lausanne (CHUV), Department of Dermatology, Lausanne, Switzerland.

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Other genetic syndromes such as Bazex-Dupré-Christol syndrome (22), Rombo syndrome (23), cartilage-hair hypoplasia (CHH) (24), and xerodermia pigmentosa (XP) (25) are associated with a high risk for BCC (reviewed in ref. 26), illustrating the...
Involvement of additional genetic factors and pathways such as DNA repair (XP) and telomere maintenance (CHH).

Crosstalk between Hh and other molecular signaling pathways in BCC. The Wnt pathway has a well-established role in normal HF development and cycling, and both human and mouse BCCs have increased levels of β-catenin, a critical mediator of Wnt signaling (27, 28). In accordance with these observations, overexpression of the potent Wnt antagonist, Dkk1, in mouse epidermis resulted in the inhibition of benign Hh-driven hamartomas, showing that active Wnt signaling is required for their growth (29).

In line with its importance in epidermal development, the EGFR/MEK/ERK pathway has been shown to modulate GLI-dependent transcription in human keratinocytes (30) and to synergistically induce oncogenic transformation of human keratinocytes (31). Additionally, the tumor suppressor p53 may influence BCC development. The complete loss of p53 was shown to result in upregulated expression of the Hh pathway mediator smoothened (Smo) in the interfollicular epidermis (IFE) in mice, thereby making these keratinocytes receptive to BCC induction (32).

Finally, the correct cellular context is important for the persistent growth of BCCs, and epithelial-stromal interactions play a role in creating a favorable microenvironment. Stromal cells, isolated from human BCCs, express high levels of gremlin 1, which antagonizes the pro-differentiation factors BMP2 and BMP4, synthesized in the BCC tumor cells, thereby sustaining tumor growth (33).

Modeling the disease. Genetic mouse models represent a major advance in cancer research as they provide the possibility of studying tumors in the context of the entire organism. The study of BCC tumorigenesis in mice has been hindered by the inexplicable failure of mutagenic chemicals and UV or IR to induce BCCs (34). However, genetically engineered mouse models for BCC provide the option to investigate the molecular mechanisms of BCC formation and progression and the identification of the cells of origin. Due to the obligate dependency of BCCs on activated Hh signaling, all current BCC mouse models target different components of the Hh signal transduction pathway, and these are summarized in Tables 1 and 2. In this context it is important to note that tumors developing in the mouse may not always fully mimic human BCCs but represent various stages in a spectrum of benign to malignant Hh pathway–induced BCC-like tumors, likely reflecting a similar variation in humans, where benign hamartomas and BCCs appear to be driven by different levels of Hh pathway activation (35–38).

Cell of origin and morphological diversity of BCC. Stem and progenitor cells are thought to be the most probable sources of tumor initiation due to their longevity and ability to self-renew (39, 40). In the skin, several populations of cells with stem cell (SC) properties have been discovered; however, defined SC markers are, as yet, limited to the HF (Figure 3; reviewed in refs. 41, 42). A collection of recent publications describes the use of mouse genetics to identify BCC cells of origin using Cre-mediated cell-specific targeting, either by lineage tracing, which involves the genetic labeling of cells, or by the activation of oncogenic Hh signaling in distinct skin cell populations (Figure 3). The identification of tumor cells of origin and, equally importantly, cells that cannot initiate tumorigenesis, will make it possible to pinpoint molecular mechanisms that either predispose or protect a cell from oncogenic transformation.

In the first publication to address the cellular origin of BCC, Youssef et al. used mice conditionally expressing SmoM2 (43), a constitutively active variant of Smo (44). When SmoM2 expression was activated in different cell compartments in the epidermis,
including HF SCs (Table 2), only cells originating in the IFE and the upper infundibulum produced full-blown BCCs. Importantly, the IFE-derived tumors also exhibited an HF-like protein expression pattern, demonstrating that the biochemical and morphological characterization of tumor cells may be misleading when used to identify the cellular origin of cancers (29, 43).

These same mouse models (employing conditional expression of SmoM2 in K14- or K15-positive cells; Table 2) were used to study the effect of wound healing on BCC development (45). It was previously reported that active wound repair recruits HF cells for re-epithelialization (46–48). In K15-SmoM2 skin, which targets SmoM2 expression mostly to the HFs, the HFs exhibited only occasional basaloid lesions in the bulge and the hair germ (HG) (43, 49). Intriguingly, during wound healing, the HF SmoM2-expressing cells are mobilized to the IFE, where they drive BCC formation and form tumors (45). Why does SmoM2 induce tumors in the IFE upon wounding but not in the intact bulge or HG? One possible explanation is that the bulge microenvironment suppresses SmoM2-mediated oncogenesis, as Gli1 and Gli2 mRNAs, which encode Hh pathway effector proteins downstream of Smo, are upregulated in IFE-associated tumors but not in HFs (45).

Our group has also addressed the question of the BCC cell of origin and the effect of wounding on tumor growth (ref. 50 and Table 2). Overexpression of human GLI1 under the control of the K5 promoter resulted in BCC formation, preferentially in the IFE, but also in the HF. Lineage-tracing of Lgr5+ SCs, which give rise to the bulge and HG, showed that in this BCC model, HF- and IFE-associated lesions had distinct cells of origin, as no Lgr5+-labeled lesions were found in the IFE. However, Lgr5-labeled HF cells were able to give rise to BCCs in the IFE upon wounding, in line with the study by Wong et al. (45). In the Lgr5Cre-Ptch1fl/fl mouse model, Ptch1 deletion in Lgr5-expressing HF SCs resulted in the formation of locally restricted basaloid proliferations in the lower part of the HF. In wounded skin, Ptch1-deficient Lgr5+ cells were again recruited to the wound sites in the IFE, where they induced de novo basaloid lesions (50). Thus, the concept that wounding is an important factor in tumor development, postulated 150 years ago (52), also appears applicable to BCC development.

Despite similar molecular pathogenesis, a considerable morphological heterogeneity exists among BCCs (53). How do these morphological differences occur? By comparing two different BCC models, Grachtchouk et al. found that BKS-GLI2 mice (54) with strong Hh signaling developed full-featured BCCs, while the weaker Hh signal in ΔK5-SMO-M2 mice resulted in follicular hamartomas (35). Furthermore, a recent, more detailed study from the same group revealed that activated SmoA1 expression in the HF does not give rise to BCC-like lesions in the HF and that low levels of GLI2ΔN expression throughout the basal compartment do not lead to nodular BCCs in the HF (in contrast to the model with high GLI2ΔN expression), but to slow-growing basaloid follicular ham-
artomas resembling the tumors found in ΔBSM-O-M2 mice (ref. 37 and Table 2). These observations support the suggestion that, downstream of Pch1, the level of Hh pathway activation, rather than the exact molecular target, is crucial in determining the BCC subtype. It is worth noting that high levels of GLI2ΔN expression in the bulge and HG rapidly lead to nodular tumors, most likely initiated in the lower bulge and the HG (37), and the HG may also be the source for tumor-initiating cells in BCNS patients, providing compelling reasons to consider the HG as a potential tumor progenitor.

The influence of the hair cycle phase on BCC growth is also important, and the authors of three studies have presented direct evidence that BCC development occurs preferentially, but not exclusively, during anagen phase (37, 57, 58). One reason may be that cells located in the outer root sheath (ORS) of anagen HFs can give rise directly to nodular BCCs, supporting the idea that this compartment contains cells capable of transformation by oncogenic Hh signaling and, therefore, provides an expanded pool of potential tumor progenitors.

Together, the results obtained using mouse models to study BCC development have so far revealed that oncogenic Hh signaling can drive BCC-like tumor formation in several different epithelial progenitor populations in skin, although the morphology and the final outcome of BCC development are influenced by the cell of origin, the mutated Hh pathway member, and the strength of oncogenic Hh signaling.

### New therapies

Highly efficient treatment modalities such as surgery that aims at complete extirpation, radiotherapy, curettage, cryotherapy, photodynamic therapy, and topical applications of imiquimod or 5-fluorouracil are available and effective for the great majority of BCC patients (9, 59). However, the occurrence of locally aggressive and invasive tumors, a bleak prognosis upon metastatic spread, a significant rate of recurrence often associated with increased aggressiveness, as well as the multitude of tumors appearing in high-risk populations such as BCNS patients, provide compelling reasons to search for new preventive and therapeutic avenues (60).

### Hh signaling as a target for new BCC therapies

The first evidence that the Hh signaling pathway is sensitive to inhibition by small molecules stemmed from the observation of cyclopia in lambs, induced by the maternal ingestion of corn lilies (Veratrum californicum) (61), followed by the demonstration that the active compound, cyclopamine, inhibits Hh signaling (62) and binds to SMO (63). Initial studies showed that, in addition to Hh inhibition in various in vitro systems, the oral administration of cyclopamine reduced the growth and development of BCCs in Pch1−/− mice exposed to UV irradiation (64), and its topical application to human BCCs can induce regression (65).

New derivatives of cyclopamine with improved pharmaceutical properties are now in clinical trials (Table 3 and ref. 66). Excellent results were obtained with the orally administered SMO inhibitor GDC-0449 (vismodegib; Table 3) in a phase I trial of patients with locally advanced or metastatic BCC (67, 68). Phase II results...
<table>
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<th>Cell targeting alleles</th>
<th>Effector alleles</th>
<th>Additional alleles</th>
<th>Start of Hh pathway modulation</th>
<th>Additional treatment</th>
<th>Pathology</th>
<th>BCC localization</th>
<th>Ref.</th>
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<td>P21–P23</td>
<td>No</td>
<td>Rare hyper/dysplastic changes</td>
<td>HF</td>
<td>43</td>
</tr>
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<td>–</td>
<td>P21–P23</td>
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<td>Rare hyper/dysplastic changes</td>
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<td>Ptch1&lt;sup&gt;+/–&lt;/sup&gt;</td>
<td>R26-YFP</td>
<td>7.5 weeks</td>
<td>X-ray at 8 weeks</td>
<td>BCC</td>
<td>HF</td>
<td>32</td>
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<td>P53&lt;sup&gt;+/–&lt;/sup&gt;</td>
<td>7.5 weeks</td>
<td>X-ray at 8 weeks</td>
<td>BCC</td>
<td>HF (enhanced)</td>
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<td>R26-YFP</td>
<td>7.5 weeks</td>
<td>X-ray at 8 weeks</td>
<td>BCC</td>
<td>HF</td>
<td>32</td>
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<td>Ptch1&lt;sup&gt;+/–&lt;/sup&gt;</td>
<td>P53&lt;sup&gt;+/–&lt;/sup&gt;</td>
<td>7.5 weeks</td>
<td>X-ray at 8 weeks</td>
<td>BCC</td>
<td>IFE and HF</td>
<td>32</td>
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<td>K5I1TA (bovine)</td>
<td>TREGLI1 Tg</td>
<td>Lgr5-EGFP-IRESCreERT2/ R26-LacZ&lt;sup&gt;C&lt;/sup&gt;</td>
<td>P16&lt;sup&gt;D&lt;/sup&gt;</td>
<td>DOX off and full-thickness wound</td>
<td>Enhanced size of BCC-like lesions</td>
<td>IFE and HF</td>
<td>50</td>
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<td>Lgr5-EGFP-IRESCreERT2/ R26-LacZ&lt;sup&gt;C&lt;/sup&gt;</td>
<td>P16&lt;sup&gt;D&lt;/sup&gt;</td>
<td>DOX off and full-thickness wound</td>
<td>Enhanced size and number of BCC-like lesions</td>
<td>IFE and HF</td>
<td>50</td>
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<tr>
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<td>Ptch&lt;sup&gt;+/–&lt;/sup&gt;</td>
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<td>P18–P24</td>
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<td>Locally restricted BCC-like lesions</td>
<td>HF</td>
<td>50</td>
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<td>–</td>
<td>P18–P24</td>
<td>Full-thickness wound</td>
<td>Rare small basoloid proliferations</td>
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<td>Lgr5-EGFP-CreERT2</td>
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<td>R26-LacZ</td>
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<td>45</td>
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<td>R26-LacZ</td>
<td>P14–P20</td>
<td>Full-thickness wound</td>
<td>BCC (IFE), rare small basoloid proliferations (HF)</td>
<td>IFE and HF</td>
<td>45</td>
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<td>R26-LacZ</td>
<td>7.5 weeks</td>
<td>Full-thickness wound, 3 days&lt;sup&gt;f&lt;/sup&gt;</td>
<td>BCC (IFE), rare small basoloid proliferations (HF)</td>
<td>Not tumor promoting</td>
<td>HF</td>
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<td>R26-LacZ</td>
<td>7.5 weeks</td>
<td>Full-thickness wound, 5 weeks&lt;sup&gt;f&lt;/sup&gt;</td>
<td>BCC (IFE), rare small basoloid proliferations (HF)</td>
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<td>HF</td>
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<td>Anagen induction via HF depilation, 3 days&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>R26-LacZ</td>
<td>7.5 weeks</td>
<td>Full-thickness wound, 3 days&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Not tumor initiation promoting</td>
<td>IFE</td>
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<td>7 weeks</td>
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<td>HF and ORS</td>
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<td>High DOX dose</td>
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<td>HF</td>
<td>37</td>
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<td>High DOX dose and anagen</td>
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<td>High DOX dose</td>
<td>BCC (nodular; HF; superficial, IFE)</td>
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<td>R26-LSL-rtTA</td>
<td>7 weeks</td>
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<td>BCC (nodular; HF; superficial, IFE)</td>
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<td>High DOX dose</td>
<td>Modest hyperplasia</td>
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<td>37</td>
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SG, sebaceous gland. Preferential localization, when present, is indicated by bold font.<sup>f</sup> Fusion protein of mSmoM2 with YFP inserted into the Rosa26 locus.<sup>e</sup> Only used for lineage tracing and p53 alleles; Ptch1 heterozygous in all cells and all tissues. <sup>c</sup> Cre activated at P14. <sup>d</sup> Effective GLI1 protein expression: P28. <sup>e</sup> Time after SmoM2 induction.
using GDC-0449 in patients with locally advanced or metastatic BCC (69) and in BCNS patients with multiple BCCs (70) were so promising that the Data Safety Monitoring Board recommended ending the placebo arm of the BCNS study in light of the differences between the study arms. Importantly, no resistance has so far been reported. In addition, a phase I study of IPI-926 (Table 3) given orally to patients with advanced types of BCC also resulted in a positive response rate (71).

In the studies investigating systemic treatment with SMO inhibitors, a common set of adverse effects has been observed, including muscle spasms, loss of taste (dysgeusia), hair loss, fatigue, nausea, and hyponatremia. It is likely that hair loss and altered taste, at least, are related directly to SMO inhibition, since Hh signaling is known to be active in HFs and taste buds (72, 73). One way to avoid or reduce such effects might be to use these inhibitors topically, thus limiting systemic exposure. A small, short-term study in BCNS patients with nodular and superficial BCC, employing twice-daily topical treatments of the SMO inhibitor LDE225 for four weeks, resulted in a positive response, and BCC regression correlated with a decrease in Hh target gene expression in most treated tumors (74). No treatment-related side effects were noted, consistent with low levels of systemic exposure to the inhibitor.

A potential caveat associated with the use of Hh pathway antagonists for the treatment of BCC is the possibility that, while treatment may result in a dramatic reduction in tumor mass, a small number of residual cells that are relatively insensitive to Hh signal inhibition may persist so that treatment may not be curative. The existence of such a cell population has been shown both in a mouse BCC model (75) and in a clinical trial of the SMO inhibitor LDE225 (ref. 74 and Table 3).

Another concern is the development over time of resistance to SMO inhibitors used in treatment, which may or may not involve mechanisms similar to those that render certain BCCs refractory from the start. Medulloblastoma is another tumor type in which Hh signaling is frequently activated by mutations in PTCH1 or SMO, and the treatment of one patient with a medulloblastoma carrying PTCH1 mutations with GDC-0449 led to rapid but transient tumor regression (76). Subsequently, it was found that an amino acid substitution in SMO that had no effect on Hh signaling but disrupted the ability of GDC-0449 to bind SMO and suppress this pathway was the underlying cause of the relapse (77). Studies in animal models confirmed that the development of resistance can be caused by mutations in Smo as well as by the amplification of downstream genes such as Gli2 and cyclin D1 (78, 79).

Potential methods of overcoming such resistance involve the use of alternative SMO inhibitors (79) such as the FDA-approved antifungal drug itraconazole, which was recently found to inhibit Hh signaling by binding to SMO at a site different from cyclopamine and to delay BCC development in Pch1+/− mice (80). At present, itraconazole is being evaluated as a possible treatment for BCC.
Given the key role of primary cilia in the transduction of the Hh signal (Figure 2), inhibitors of ciliogenesis or ciliary function represent a further means of intervention in BCC tumorigenesis, and a small molecule blocking ciliogenesis has been identified as an Hh inhibitor (ref. 82 and Table 3). Again, the multiple cellular effects expected as a result of cilia disruption will place obstacles in the way of obtaining specificity.

**Table 3**

<table>
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<th>Agent/compound Target</th>
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<th>Study phase</th>
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<th>Reference</th>
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<td>LDE-225 SMO</td>
<td>Advanced solid tumors (BCC, medulloblastoma)</td>
<td>I</td>
<td>NCT01208831</td>
<td>–</td>
</tr>
<tr>
<td>LDE-225 SMO</td>
<td>Advanced solid tumors (BCC, medulloblastoma)</td>
<td>I</td>
<td>NCT00880308</td>
<td>–</td>
</tr>
<tr>
<td>LDE-225 SMO</td>
<td>Sporadic superficial and nodular BCC</td>
<td>II</td>
<td>NCT01033019</td>
<td>–</td>
</tr>
<tr>
<td>LDE-225 SMO</td>
<td>Locally advanced or metastatic BCC</td>
<td>II</td>
<td>NCT01327053</td>
<td>–</td>
</tr>
<tr>
<td>LDE-225 SMO</td>
<td>BCNS patients</td>
<td>II</td>
<td>NCT01350115</td>
<td>–</td>
</tr>
<tr>
<td>LDE-225 SMO</td>
<td>BCNS patients</td>
<td>Preclinical</td>
<td>–</td>
<td>74</td>
</tr>
<tr>
<td>Cur61414 SMO</td>
<td>UV-treated Pch1&lt;sup&gt;+/–&lt;/sup&gt; mice; Superficial and nodular BCC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Preclinical</td>
<td>–</td>
<td>98, 99</td>
</tr>
<tr>
<td>Cur61414 SMO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPI-926 SMO</td>
<td>BCC (including locally advanced or metastatic)</td>
<td>I</td>
<td>NCT00761696</td>
<td>71</td>
</tr>
<tr>
<td>BMS-833923 SMO</td>
<td>Advanced or metastatic BCC</td>
<td>I</td>
<td>NCT00670189</td>
<td>–</td>
</tr>
<tr>
<td>TAK-441 SMO</td>
<td>Advanced BCC</td>
<td>I</td>
<td>NCT01204073</td>
<td>–</td>
</tr>
<tr>
<td>Itraconazole SMO</td>
<td>BCC</td>
<td>II</td>
<td>NCT01108094</td>
<td>–</td>
</tr>
<tr>
<td><strong>Downstream Hh pathway inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GANT 58, GANT 61 GLI</td>
<td>NA</td>
<td>Preclinical</td>
<td>–</td>
<td>81</td>
</tr>
<tr>
<td>Arsenic trioxide GLI</td>
<td>NA</td>
<td>Preclinical</td>
<td>–</td>
<td>83, 84</td>
</tr>
<tr>
<td>HP11/2/3 GLI</td>
<td>NA</td>
<td>Preclinical</td>
<td>–</td>
<td>82</td>
</tr>
<tr>
<td>HPI4 Ciliogenesis</td>
<td>NA</td>
<td>Preclinical</td>
<td>–</td>
<td>82</td>
</tr>
<tr>
<td><strong>Other agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D3 SMO/cell proliferation</td>
<td>BCC</td>
<td>III</td>
<td>NCT01358045</td>
<td>–</td>
</tr>
<tr>
<td>Tazarotene RAR-β/RAR-γ</td>
<td>BCC on chest and back of BCNS patients</td>
<td>II</td>
<td>NCT00483065</td>
<td>–</td>
</tr>
<tr>
<td>Tazarotene RAR-β/RAR-γ</td>
<td>BCC on face of BCNS patients</td>
<td>II</td>
<td>NCT00489086</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup>Drug name vismodegib. <sup>b</sup>BCCs failed to show signs of clinical response or significant GLI1 target gene inhibition, likely due to inadequate drug absorption.

In a phase II trial (Table 3). Alternatively, blocking other signaling pathways in resistant tumors may be effective, and in preclinical studies of medulloblastomas, PI3K inhibition has emerged as a promising possibility (78, 79).

In situations in which Hh pathway activation occurs downstream of SMO, targeting the final effectors in the pathway, such as the GLI transcription factors, would be preferable. The potential viability of this strategy has been demonstrated by the identification of small molecule inhibitors acting at the level of GLI, or at alternative steps downstream, and independent of SMO (refs. 81, 82, and Table 3). Interestingly, in two studies it has been found that arsenic trioxide, in clinical use for the treatment of acute promyelocytic leukemia, can inhibit Hh signaling at the GLI protein level, although the exact mechanism remains controversial (83, 84). However, given the diverse set of targets for arsenic trioxide, it will be challenging to delineate critical targets in an in vivo setting, and existing side effects may limit its attractiveness as a treatment for BCC; curiously, arsenic exposure is also a known risk factor in BCC development (85).

Finally, topical treatment with the RARB/RARG-selective retinoid tazarotene has been shown to reduce the number and size of early BCC lesions in irradiated Pch1<sup>−/−</sup>/K14-CreERT2-p53<sup>−/−</sup> mice exposed to IR. Vitamin D3 has been shown to block Hh signaling in vitro and in murine BCCs in vivo, presumably at the level of SMO, in a manner independent of vitamin D receptor (VDR) activation (86, 87). The enhanced differentiation of keratinocytes induced via VDR activation is an additional and well-established effect of vitamin D3. A phase III trial combining topical vitamin D3 therapy and treatment with an anti-inflammatory agent in patients with nodular BCC has been initiated (Table 3).

To summarize, early clinical results targeting the Hh signaling pathway are very promising, especially in regard to BCC treatment and chemoprevention in BCNS patients and for the treatment of locally aggressive or metastatic BCC. However, we still do not have the answer to several important questions: (a) Will treatment truly result in the eradication of BCCs, or will dormant tumor cells remain? (b) What are the major resistance mechanisms in BCCs? (c) Why are a substantial fraction of BCCs refractory to treatment...
Perspectives
The great advances in our understanding of BCC biology, derived from deciphering its molecular genetics and from incisive studies using genetic mouse models that closely mimic the human disease, have been translated rapidly into new and promising targeted therapies. At the same time, it is important to realize that we are only just beginning to resolve the long-standing question about the BCC cell of origin. We know from studies in the mouse that SCs and progenitor cells present in the HF can serve as cells of origin, but that additional cells of origin must exist. The marked plasticity of skin epithelial stem cell populations, as revealed under tissue injury, provides an additional layer of complexity.

Another challenging question begging an answer is the nature of the genetic events that cooperate with an activated HH signaling pathway to determine BCC subtypes, ranging from the benign nodular and superficial forms to aggressive and, in rare cases, metastatic forms. Future studies will certainly provide answers to many of these questions, and it is to be hoped, moreover, that the lessons learned from treating BCC with HH pathway inhibitors will pave the way for progress in the treatment of other tumors that depend on the presence of active HH signaling.

Acknowledgments
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Address correspondence to: Rune Toftgård, Karolinska Institutet, Center for Biosciences and Department of Biosciences and Nutrition, Novum, SE-141 83 Huddinge, Sweden. Phone: 46.8.52481053; Fax: 46.8.6081501; E-mail: rune.toftgard@ki.se.
Patched1 interacts with cyclin B1 to regulate cell cycle progression. EMBO J. 2001;20(9):2214–2223.


