Skin Cancer: Biology & Therapy

Arianna L. Kim Ph.D.

Department of Dermatology
Annual Incidence and Death from Skin Cancer in the US

- BCC: 700,000 cases
- SCC: 60,000 cases
- Melanoma: 6,000 cases
- Merkel Cell Carcinoma: 250 cases

Incidence:
- BCC: 2,800,000 cases
- SCC: 80,000 cases
- Melanoma: 6,000 cases
- Merkel Cell Carcinoma: 250 cases

Death:
UV Radiation is the Primary Risk Factor

Mutagenic photoproducts

Mutations, Cancer

UV Radiation

Thymine

Cytosine

Cyclobutane Dimer

[6,4]-Photoproduct

UVB

UVA
Melanoma Incidence is Highest in Countries Populated by Fair-Skinned Persons Living in High-UV Environments

United States incidence map
The highest rates of melanoma in the United States occur in the northwest and southeast states, reflecting the higher proportion of the population who are of non-Hispanic white ethnicity in those states.

Cases per 100,000 people per year
- 22.9–34.1
- 20.5–22.8
- 18.5–20.4
- 9.0–18.4
- No data

Europe incidence map
Switzerland has the highest incidence of melanoma in Europe, with 25.8 cases per 100,000 people per year. Southern European populations have the lowest burden of melanoma. The incidence is highest in Northern Europe, particularly in Nordic countries.

Cases per 100,000 people per year
- 16.9+
- 13.1–16.8
- 7.7–13
- 5.3–7.6
- <5.3

South Africa has the highest incidence on the African continent, with 4.5 cases per 100,000 people per year.

The highest incidence rates are found in New Zealand and Australia. The highest recorded incidence is in Queensland, Australia: 56 cases per 100,000 per year for men, and 41 cases per 100,000 per year for women.
OF NEARLY 9.5 MILLION TOTAL PROCEDURES IN 2014

the top medically necessary and cosmetic procedures* performed are:

SKIN CANCER TREATMENTS
3.08 million total procedures
2.8 million non-melanomas
206,000 melanomas

LASER/LIGHT/ENERGY-BASED
2.06 million total procedures

WRINKLE-RELAXING INJECTIONS
(Injectable Neuromodulators)
1.74 million total procedures
Nearly 1.2 million Botox
Nearly 382,000 Dysport
Nearly 175,000 Xeomin

BODY SCULPTING
208,000 total procedures
33,000 tumescent liposuction
79,000 cryolipolysis “fat-freezing”
14,600 laserlipolysis
49,600 radiofrequency
32,000 non-invasive treatment of fat and cellulite

SOFT-TISSUE FILLERS
1.01 million total procedures

LASIC HAIR REMOVAL
633,000 total procedures

CHEMICAL PEELS
564,000 total procedures

VEIN TREATMENT/SCLORETHERAPY
163,000 total procedures

HAIR TRANSPLANTS
4,600 total procedures

*Source: American Society for Dermatologic Surgery (ASDS) Survey on Dermatologic Procedures.

Note: Data were collected for the 2014 experience and generalized to represent all ASDS members.
Sun scare

RATE OF SKIN MELANOMAS IN YOUNG PEOPLE HAS INCREASED DRAMATICALLY, STUDY FINDS

By Megan Niccoli, Post-Crescent staff writer

Young women are eight times more likely to develop skin cancer today than they were 40 years ago — and young men are four times as likely to battle the disease, according to a study by Mayo Clinic researchers.

See CANCER, Page A-4
### Excess Health Risks Associated with Ultraviolet (UV) Exposure, by Type of Skin Cancer and Type of UV Exposure

<table>
<thead>
<tr>
<th>Exposure (No. of Studies)</th>
<th>Excess Risk (95% CI)</th>
<th>Comparison Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MELANOMA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun exposure&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sun exposure (N = 28)</td>
<td>34% (2, 77)</td>
<td>N/A</td>
</tr>
<tr>
<td>Intermittent sun exposure (N = 34)</td>
<td>61% (31, 99)</td>
<td>N/A</td>
</tr>
<tr>
<td>Chronic sun exposure (N = 40)</td>
<td>-5% (-13, 4)</td>
<td>N/A</td>
</tr>
<tr>
<td>Sunburn&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunburn in childhood (N = 27)</td>
<td>91% (59, 130)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Sunburn in adolescence (N = 13)</td>
<td>63% (42, 86)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Sunburn in adulthood (N = 13)</td>
<td>44% (27, 63)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Sunburn in past 5–10 years (N = 5)</td>
<td>62% (-1, 165)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Ever sunburned in lifetime (N = 28)</td>
<td>59% (37, 83)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Indoor tanning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever indoor tanned (N = 27)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>20% (8, 34)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Ever indoor tanned (N = 8; U.S. studies only)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>23% (3, 47)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Ever indoor tanned (N = 10; studies from year 2000 onward)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>22% (3, 45)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Indoor tanned before age 35 years (N = 13)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>59% (36, 85)</td>
<td>Ever before age 35 vs never before age 35</td>
</tr>
<tr>
<td>Frequent indoor tanning (N = 15)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>42% (15, 74)</td>
<td>Frequent vs infrequent/never</td>
</tr>
<tr>
<td>Relative risk for each indoor tanning per year (N = 4)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>2% (0, 4)</td>
<td>N/A</td>
</tr>
<tr>
<td>&gt;10 lifetime tanning sessions (N = 10)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>34% (5, 71)</td>
<td>&gt;10 lifetime tanning sessions vs never</td>
</tr>
<tr>
<td>Indoor tanned &gt;1 year (N = 3)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>61% (-2, 167)</td>
<td>Indoor tanned &gt;1 year vs never</td>
</tr>
<tr>
<td><strong>BASAL CELL CARCINOMA&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever indoor tanned (N = 10)</td>
<td>29% (8, 53)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Frequent indoor tanning (N = 4)</td>
<td>50% (-19, 177)</td>
<td>Frequent vs infrequent/never</td>
</tr>
<tr>
<td>Indoor tanned before age 25 years (N = 3)</td>
<td>40% (29, 52)</td>
<td>Ever before age 25 vs never before age 25</td>
</tr>
<tr>
<td><strong>SQUAMOUS CELL CARCINOMA&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever indoor tanned (N = 10)</td>
<td>67% (29, 117)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Indoor tanned before age 25 years (N = 2)</td>
<td>102% (-30, 486)</td>
<td>Ever before age 25 vs never before age 25</td>
</tr>
</tbody>
</table>
Causes and Risk Factors

- **Ultraviolet (UV) radiation** (sun, tanning bed)
- Pigmentary characteristics
- Other environmental factors
  - Petroleum byproducts (e.g., asphalt, tar, soot, and paraffin), organophosphate compounds, and arsenic are all occupational exposures associated with cutaneous non-melanoma cancers.
  - The populations in Bangladesh, Taiwan, and many other locations have high levels of skin cancer, both melanoma and non-melanoma, associated with elevated levels of arsenic in the drinking water.
- Immunosuppression
  - Among solid-organ transplant recipients (OTRs), the risk of SCC is 65 - 250X higher, and the risk of BCC is 10X higher than in the general population. Melanoma is 1.6 - 2.5x more common among OTRs.
- Family history/Previous personal history
- Other radiation exposure
  - Exposure to therapeutic radiation (e.g., psoralen and UVA (PUVA)) > a three-fold to six-fold increase in SCC.
- Current or previous cigarette smoking
  - a 1.5-fold to 2-fold increase in SCC risk
- Nevi
Cell Types of the Epidermis

Non-melanoma skin cancer
Langerhans cell histiocytosis (benign)
Langerhans cell sarcoma
Merkel cell carcinoma
Melanoma

(a) Four principal cell types in epidermis

Figure 05.03 Tortora - PAP 12/e
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Multistage Skin Carcinogenesis

Initiation
Carcinogen/UV

Irreversible genetic mutation in stem cell/progenitor cell

Promotion
tumor promoter/UV

Clonal expansion of initiated cells within generalized hyperplasia

Outgrowth of pre-malignant tumors = papillomas

Progression

Malignant conversion to invasive carcinoma

metastasis

<table>
<thead>
<tr>
<th>Cells of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>DMBA-TPA induced papilloma</td>
</tr>
<tr>
<td>KRas$^{G12D}$ induced papilloma</td>
</tr>
<tr>
<td>KRas$^{G12D}$/p53 cKO induced SCC</td>
</tr>
</tbody>
</table>
Squamous Cell Carcinoma (SCC)

- 250,000 new cases, ~2,500 deaths.

Source: Pathology of the skin with clinical correlation, 2005
Probability that Human Cutaneous Neoplastic Lesions will Progress to Invasive Carcinoma

Mouse

Normal skin
Hyperplastic epidermis
Papilloma
SCC

Human

Normal skin + UV
AK/SCCIS
SCC
Metastatic SCC

Regression

< 1% (Pt w/ # ≤ 5)
20% (Pt w/ # ≥ 20)
26% in 1 yr
< 1%
0.5% - 3.3%

A Clinical, Histologic, and Molecular Comparison of AKs, cSCC, and Metastatic cSCC

**Clinical description**

- **Normal skin**
- **AK**: Scaly skin colored/pink macule or papule
- **cSCC**: Persistent firm or scaly papule or red nodule which may spontaneously bleed
- **Metastatic cSCC**: Multiple nodular lesions in skin or internal organs

**Histopathology**

- **Normal skin**
- **AK**: Well-defined stratum basalis, spinosum, and granulosum with orthokeratotic scale
- **cSCC**: Enlarged, atypical keratinocytes confined to the epidermis with parakeratotic scale
- **Metastatic cSCC**: Enlarged, atypical keratinocytes in the dermis, lymph nodes, or internal organs, typically with no epidermal connection

**Histological description**

- **Normal skin**
- **AK**: Increased signaling (activation, overexpression, or amplification)
  - ras, Fyn/SFKs, bcl-2
- **cSCC**: ras, Fyn/SFKs, c-myc, PI3K/Akt, p16 LOH
- **Metastatic cSCC**: In addition to cSCC alterations: VEGF (ras), MMP2, MMP7, MMP12 (ras)

- **Normal skin**
- **AK**: Decreased signaling (deactivation, transcriptional or translational repression, or gene deletion)
  - p53, Srcasm
- **cSCC**: p53, Ssrcasm, Notch (p53), PKC δ, E-cadherin
- **Metastatic cSCC**: In addition to cSCC alterations: E-cadherin, P-cadherin

**Genomic changes**

- **Normal skin**
- **AK**: Genomic instability with few chromosomal alterations
- **cSCC**: Increased genomic instability resulting in chromosomal translocations, isochromosomes, gene deletions, and amplifications
- **Metastatic cSCC**: In addition to cSCC alterations: VEGF (ras), MMP2, MMP7, MMP12 (ras)
Key Signaling Pathways Involved in the Formation of cSCC

In K14-Fyn Y528F mice:
- Lesions resembling AKs and SCCs
- Akt/mTOR
- MEK/ERK
- STAT3

Substrate/negative regulator of Fyn
- Inhibits KC proliferation
- Promotes differentiation

UVB → EGFR → Fyn → Ras → Akt → MEK → ERK → c-Jun

p53 → Bax, Bak → APAF-1 → Apoptosis/Senescence
BAD → Bcl-2, Bcl-XL → Survival

Ras → Raf → MEK → ERK → c-Jun, p21

Cytosol → Nucleus

p53 → c-Jun, p21 → Cyclin D1
## Drugs Approved for SCC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target/Action</th>
<th>Actinic keratoses</th>
<th>sSCC</th>
<th>BD</th>
<th>Invasive SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-fluorouracil*</td>
<td>Incorporates into DNA and/or RNA</td>
<td>🟢</td>
<td>🟢</td>
<td>🟢</td>
<td>?</td>
</tr>
<tr>
<td>imiquimod</td>
<td>Stimulates the immune system/produces interferon</td>
<td>🟢</td>
<td>🟢</td>
<td>🟢</td>
<td>✔</td>
</tr>
<tr>
<td>Picato (ingenol mebutate)</td>
<td>A protein kinase C inhibitor</td>
<td></td>
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<tr>
<td></td>
<td>Induces necrosis and inflammatory response</td>
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<tr>
<td></td>
<td>The first topical therapy for AK</td>
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</tbody>
</table>

* viable tumor remained in the deeper dermis

❓ Maybe effective
✔️ FDA-approved
✔️ Being tested
Potential Pathways that May be Targeted by Small Molecules to Treat AKs and cSCCs
Hereditary Syndromes Associated with SCC

- **Xeroderma pigmentosum (XP):** A hereditary disorder of nucleotide excision repair that results in cutaneous malignancies in the first decade of life.

  - **↑ sensitivity to sunlight**
  - **↑ NMSC 150-fold**

### Table: Hereditary Syndromes Associated with SCC

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene(s)</th>
<th>Clinical Testing Availability</th>
<th>Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xeroderma pigmentosum (XP)</td>
<td>XPA (OMIM), XPF/ERCC3 (OMIM), XPC (OMIM), XPD/ERCC2 (OMIM), XPE/ERCC4 (OMIM), XPF/ERCC3 (OMIM)</td>
<td>XPA, XPC</td>
<td>Nucleotide excision repair</td>
</tr>
<tr>
<td>Xeroderma pigmentosum variant</td>
<td>POLH/XPFV (OMIM)</td>
<td>No</td>
<td>Error-prone polymerase</td>
</tr>
<tr>
<td>Multiple self-healing squamous</td>
<td>TGFBRI (OMIM)</td>
<td>No</td>
<td>Growth factor signaling</td>
</tr>
<tr>
<td>epithelioma (Ferguson-Smith</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(OMIM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oculocutaneous albinism (type IA</td>
<td>TYR (OMIM), OCA2 (OMIM), SLC4A2/MATP1/OCAS (OMIM), TYRP1 (OMIM)</td>
<td>TYR, OCA2, TYRP1</td>
<td>Melanin synthesis</td>
</tr>
<tr>
<td>IA/OMIM), type IB (OMIM), type II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II/OMIM), and type IV/OMIM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hermansky-Pudlak syndrome (OMIM)</td>
<td>HPS1 (OMIM), HPS3 (OMIM), HPS4 (OMIM), HPS6 (OMIM), HPS7/DTNB1 (OMIM), HPS/BLCC1S3 (OMIM)</td>
<td>HPS1, HPS3, HPS4, HPS7</td>
<td>Melanosomal and lysosomal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>storage</td>
</tr>
<tr>
<td>Fanconi anemia (OMIM)</td>
<td>FANCA (OMIM), FANCB (OMIM), FANCC (OMIM), FANCD1/BRCA2 (OMIM), FANCD2 (OMIM), FANCE (OMIM), FANCF (OMIM), FANCG/XRCC9 (OMIM), FANCI (OMIM), FANCJ (OMIM), FANCB (OMIM), FANCL (OMIM), FANCM (OMIM), FANCN/PALB2 (OMIM)</td>
<td>Chromosomal breakage testing, BRIP1, FANCA, FANCC, FANCJ, FANC, FANCF, FANCG, PALB2</td>
<td>DNA repair</td>
</tr>
<tr>
<td>Dyskeratosis congenita (OMIM)</td>
<td>DKC1 (OMIM), TERC (OMIM), TINF2 (OMIM), NHP2/NOLA2 (OMIM), NOP10/NOLA3 (OMIM), TERT (OMIM), WRAP53 (OMIM), C16orf57 (OMIM), RTE1 (OMIM)</td>
<td>DKC1, TERC, TINF2, NHP2, NOP10, TERT</td>
<td>Telomere maintenance and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>trafficking</td>
</tr>
<tr>
<td>Rothmund-Thomson syndrome (OMIM)</td>
<td>RECOL4 (OMIM), C16orf57 (OMIM)</td>
<td>RECOL4</td>
<td>Chromosomal stability</td>
</tr>
<tr>
<td>Bloom syndrome (OMIM)</td>
<td>BLM/RECOL3 (OMIM)</td>
<td>Sister chromatid exchange, BLM</td>
<td>Chromosomal stability</td>
</tr>
<tr>
<td>Werner syndrome (OMIM)</td>
<td>WRN/RECOL2 (OMIM)</td>
<td>No</td>
<td>Chromosomal stability</td>
</tr>
</tbody>
</table>

*For more information on genetic testing laboratories, refer to the NIH Genetic Testing Registry.*
Knockdown of XPC Results in Epithelial Hyperplasia

Day 15

shCtrl    shXPC1    pt XPC KC

H&E

K14

K167
XPC Knockdown Induces SCC Formation

**Graph:**
- X-axis: Days after injection (0, 30, 60, 90, 120, 150, 180)
- Y-axis: Tumor size (mm$^3$) (0, 10, 20, 30, 40, 50, 60)
- Legend:
  - shCtrl
  - (shXPC+shAKT1)
  - (shXPC1+shNOX)
  - (shXPC+shNOX1)
  - shXPC1
  - shXPC2
  - XPC-KC

**Images:**
- **shXPC:**
  - Tissue section showing cellular structures
- **shXPC+NOX1:**
  - Tissue section showing cellular structures

**Caption:**
XPC Knockdown Induces SCC Formation. The graph shows the progression of tumor size over time for various conditions, indicating a significant increase in tumor size upon XPC knockdown. The images compare tissue sections of normal tissue (shCtrl) and tissue sections showing SCC formation upon XPC knockdown (shXPC) and with additional knockdown of NOX1 (shXPC+NOX1).
Basal Cell Carcinoma (BCC)

- The most common type of skin cancer, accounts for about 90% of the skin cancers.
- **Almost never metastasizes** or crosses the basement membrane, so is almost never fatal.
- **It is the most easily cured**: surgical removal, no chemotherapy or radiation usually needed.
- Extensive morbidity through local invasion and tissue destruction.
- Recurrence is common.
The Sonic Hedgehog (SHH) Pathway

- cell fate, growth, and differentiation

- embryonic development and adult tissue homeostasis (left-right body asymmetry and limb patterning, eye, brain, and central nervous system development)

Wild-Type

Shh -
Dysregulation of Hh Signaling Drives BCC Development

INHIBITION

ACTIVATION
The Cellular Origin of BCCs

The IFE (interfollicular epidermis) origin of SmoM2-induced basal cell carcinoma in mouse-tail epidermis
Phenotypes of BCC subtypes are regulated by not only the cell of origin but also the tissue context and the level of oncogenic signaling.

From a subset of stem cells in the lower bulge and secondary hair germ compartment.

Requires high-level signaling in the interfollicular epidermis.

A. Nodular BCC

B. Nodular BCC histology

C. Superficial BCC

D. Superficial BCC histology

E. Sclerosing BCC

F. Sclerosing BCC histology
Basal Cell Nevus Syndrome (BCNS)

- Inherit one mutated copy of the *patched* (*PTCH*) gene.
- *PTCH* haploinsufficiency is responsible for the developmental abnormalities associated with BCNS.
- Tumors in BCNS individuals likely to arise with inactivation of the remaining *PTCH* allele.
Vismodegib Reduces Tumor Burden in BCNS

IPI-926 (saridegib)
Vismodegib (Erivedge)
BMS-833923 (XL139)
LDE-225
NVP-LEQ506 (Smo D473H)

Adverse Events in Vismodegib-Treated Subjects

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>GDC-0449 (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste loss</td>
<td>83</td>
<td>8</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>70</td>
<td>8</td>
</tr>
<tr>
<td>Hair loss</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>Dropped out due to AEs</td>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>

- **Tumor recurrence**
- **The adverse events** associated with treatment led to discontinuation in over half of treated patients.
- **Acquired resistance**: the first documented mechanism of clinical acquired resistance to vismodegib is a secondary mutation in the extracellular domain of SMO, D473H, which prevents vismodegib binding.
Suppressor of fused (SUFU) negatively regulates the Hh pathway by binding and sequestering GLI transcription factors in the cytoplasm. SMO inhibits SUFU.

*Suppressor of fused (SUFU) negatively regulates the Hh pathway by binding and sequestering GLI transcription factors in the cytoplasm. SMO inhibits SUFU.*
SMO Variants Explain Both Intrinsic and Acquired Drug Resistance

Baseline Histopathology 21 months 30 months

Sensitive Resistant

SMO Inhibitor

Wild Type Constitutively Active Active
Inhibited Tumor Growth Tumor Growth

Resistance-associated mutations

Cancer Cell. 2015 Mar 9;27(3):342-53
Hh Pathway Modulators with Different Mechanisms of Action

<table>
<thead>
<tr>
<th>Hh pathway modulator</th>
<th>Mechanism of action</th>
<th>Comment</th>
<th>Status b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upstream of or at SMO</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMANT</td>
<td>Inhibits cilia accumulation, distinct binding mode on SMO</td>
<td>Weak competition with cyclopamine; active on SMO M2</td>
<td>Research</td>
</tr>
<tr>
<td>CA1 and CA2</td>
<td>Inhibit cilia biogenesis, do not bind SMO</td>
<td></td>
<td>Research</td>
</tr>
<tr>
<td>Glucocorticoids a, class I (FA and TA)</td>
<td>Induce SMO accumulation in cilia</td>
<td>Compete with cyclopamine; enhance Hh pathway activation; interfere with action of SMO inhibitors</td>
<td>Research (in clinical use for other indications)</td>
</tr>
<tr>
<td>Glucocorticoids a, class II (Bud and Cic)</td>
<td>Inhibit cilia accumulation of SMO</td>
<td>Do not compete with cyclopamine; active on resistant mutation D473H and SMO M2</td>
<td>Research (in clinical use for other indications)</td>
</tr>
<tr>
<td>Itraconazole a</td>
<td>Prevents cilia translocation of SMO</td>
<td>Does not compete with cyclopamine; active on resistant mutation D473H but not SMO M2</td>
<td>In clinical evaluation for Hh-driven cancers; phase 2 study in chemotherapy-naive metastatic castration-resistant prostate cancer: 24-week PFS, 48% (600 mg dose, n = 29), 11.8% (200 mg dose, n = 17); median PFS, 35.9 weeks (600 mg dose) compared to 11.9 weeks (200 mg dose)</td>
</tr>
<tr>
<td><strong>ALLO1 and ALLO2</strong></td>
<td>Distinct binding mode on SMO</td>
<td>Active on D473H (ALLO1 and ALLO2) and SMO M2 (ALLO1)</td>
<td>Research</td>
</tr>
<tr>
<td>Compound 5</td>
<td>Binds SMO and inhibits ciliary translocation</td>
<td>Active on D473H, inhibits in vivo growth of vismodegib-resistant tumors</td>
<td>Research</td>
</tr>
<tr>
<td>Robotnikinin</td>
<td>Binds to SHH and blocks pathway activity</td>
<td>Different MOA than SMO inhibitors</td>
<td>Research</td>
</tr>
<tr>
<td>RU-SKI</td>
<td>Inhibits Hh acyltransferase</td>
<td>Interferes with SHH palmitoylation and blocks SHH signaling</td>
<td>Research</td>
</tr>
<tr>
<td>Hh-specific monoclonal antibody SE1</td>
<td>Blocks binding of Hh ligands to PTCH1</td>
<td>Used widely to demonstrate Hh dependency in tumor models</td>
<td>Research</td>
</tr>
<tr>
<td><strong>Downstream of SMO</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GANTS8 and GANT61</td>
<td>Block GLI1- and GLI2-mediated reporter activity; GANT61 interferes with DNA binding of GLI1</td>
<td></td>
<td>Research</td>
</tr>
<tr>
<td>HPI 1–4</td>
<td>Act at or downstream of SULF2; modulate GLI1 processing, activation and or trafficking</td>
<td></td>
<td>Research</td>
</tr>
<tr>
<td>Arsenics a</td>
<td>Act at level of GLI</td>
<td>Two proposed mechanisms: inhibition of Hh-induced ciliary accumulation of GLI2 or direct binding and inhibition of GLI1 independent of primary cilia</td>
<td>Research (in clinical use for other indications; <a href="http://www.fdaapproveddrugs.us/trisenox.htm">www.fdaapproveddrugs.us/trisenox.htm</a>)</td>
</tr>
<tr>
<td>Myristoylated aPKC peptide inhibitor (PSI)</td>
<td>Inhibits the phosphorylation and activation of GLI1 by aPKC-</td>
<td>Inhibits growth of SMO inhibitor–resistant mouse BCC lines</td>
<td>Research</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>Inhibits TNF-α–induced and mTOR-S6K–mediated phosphorylation and activation of GLI1 in EAC lines</td>
<td></td>
<td>Research</td>
</tr>
</tbody>
</table>

*High dose needed to achieve efficacious plasma levels.  bStatus in regard to Hh-driven cancers. Bud, budesonide; Cic, ciclesonide; FA, fluocinolone acetonide; MOA, mechanism of action; PFS, prostate-specific antigen progression-free survival; TA, triamcinolone acetonide.
Tumor Types with Evidence of Crosstalk Between Hh and Other Signaling Pathways

ESOPHAGEAL
PI3K/AKT/mTOR

MELANOMA
RAS/RAF/MEK/ERK
PI3K/AKT/mTOR

BCC
EGFR/RAS/RAF/MEK/ERK

BREAST
PI3K/AKT/mTOR
NOTCH

GASTRIC
RAS/RAF/MEK/ERK
PI3K/AKT/mTOR

PROSTATE
EGFR
RAS/RAF/MEK/ERK
PI3K/AKT/mTOR
NOTCH

OVARIAN
NOTCH

Glioma
EGFR
RAS/RAF/MEK/ERK
PI3K/AKT/mTOR
NOTCH

MB
EGFR
PI3K/mTOR

HNSCC
EGFR

NSCLC
EGFR

PANCREATIC
EGFR
RAS/RAF/MEK/ERK
PI3K/AKT/mTOR
NOTCH

CHOLANGIO-CARCINOMA
RAS/RAF/MEK/ERK
Hh Pathway Crosstalk with Other Signaling Pathways

Cancer Research Reviews

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Cancer Res 2014;74:4967-4975
Melanomas often resemble moles; some develop from moles. The majority of melanomas are black or brown, but they can also be skin-colored, pink, red, purple, blue or white (not uniform in color).
Molecular Changes in the Progression of Melanoma

The tumor-constraining CDKN2A (tumor suppressors, p16INK4a and p14ARF) network

The growth-promoting Ras signaling network
A Stepwise Decrease in CDKN2A and p16 at the Transition to Melanoma

RAS-RAF-MAPK Cascade: a Major Stimulus of Melanocytic Proliferation

- Exposure to extracellular ligands
  - Activation of RTKs and the recruitment of adaptor protein complexes (GRB2-SOS) to the plasma membrane
  - The exchange of GDP for GTP by RAS, resulting in RAS activation
  - RAF activation (conformational changes, phosphorylation and dimerization)
  - MEK activation
  - ERK activation

- Regulation of cell cycle progression and proliferation.
- ERK directly phosphorylates and inactivates upstream signaling intermediates (direct negative feedback, solid lines).
- ERK regulates SPRY and DUSPs, inhibitors (dotted lines).
- SPRY impedes signaling by disrupting the GRB2-SOS interaction; DUSPs are ERK-specific phosphatases.
BRAF is the Single Most Commonly Mutated Gene in Melanoma

» ARAF, CRAF, and BRAF serine/threonine protein kinase; BRAF has the highest basal kinase.

» About 90% of the reported changes occur at a single codon in the BRAF kinase domain (Threonine1799Alanine, Valine600Glutamic acid). BRAF$^{V600E}$ can gain 500-fold increased activation.

» BRAF$^{V600E}$ is prevalent in benign nevi supporting a role for BRAF activation in melanocytic proliferation, but not full transformation.

» The full oncogenic potential of BRAF appears to be dictated by the presence or absence of other genetic constraints (inactivation of p16INK4a/p14ARF, or p53, or activation of PIK3CA).
Unclear Carcinogenic Mechanism Underlying the BRAFV600E Mutation

The T>A transversion is not a classic UVB signature change and many internal malignancies harbor the identical BRAF alteration, thus UV radiation is clearly not essential for c.T1799 mutagenesis.

It has been suggested that UVB-induced cyclobutane pyrimidine dimer formation at the neighboring position (c.1800–1801) may promote subsequent BRAF mutations at the 1799 position.
Hyperactivated ERK signaling results in increased proliferation and evasion of apoptosis.

ERK-dependent negative feedback suppresses RTK-mediated signaling, resulting in low amounts of active GTP-bound RAS.

In this state, BRAF V600E signals as a functional monomer.
Clinical Efficacy of PLX4032 (Vemurafenib), a BRAF Inhibitor

The recommended phase 2 dose: 960 mg twice daily

Clinical endpoint: progression-free survival (%)

Chapman et al, NEJM 2011; Flaherty et al, NEJM 2010
ODDP 2014, Amsterdam (Alain van Gool)
Clinical Effects of PLX4032 (Vemurafenib)

Before Rx

PLX4032-15 wks

Strong initial effects

PLX4032-23 wks

Drug resistance

Tumor recurrence

The tumor was refractory to several therapeutic regimens.
Mechanisms of Resistance to BRAF Inhibitors

- BRAFV600 alternate splicing and gene amplification; CRAF overexpression; AKT, PI3K mutations…

Oncogene (2014) 33, 1–9
Uveal
GNAQ 32%
G11 45%

Face/Scalp
NRAS 15%
BRAF 28%

Trunk/Legs
NRAS 18%
BRAF 57%

ACRAL
C-KIT 5-10%
NRAS 25%
BRAF 10%

Mucosal
NRAS 15%
C-KIT 10-20 %

GNAQ, guanine nucleotide binding protein, q polypeptide
G11, guanine nucleotide-binding protein subunit alpha 11

N Eng J Med 2010, 363
J Clin Oncol 2006
BJ Derm 2011, 164
A. Daud, UCSF
Targeting Melanoma Signaling Networks

I. The growth-promoting Ras signaling network

- Zelboraf (vemurafenib; BRAF^{V600E})
- Tafinlar (dabrafenib; BRAF/CRAF)
- Cotelllic (cobimetinib; BRAF^{V600E} or V600K)

II. The tumor-constraining CDKN2A network

III. PI3K-AKT cascade: promoter of melanoma progression

Mekinist (trametinib; MEK1/2)
Waking up the Body’s Defences

Tumour cells can inhibit the body’s immune response by binding to proteins, such as PD-1, on the surface of T cells. Antibody therapies that block this binding re activates the immune response.

T-cell Activity ↓

T-cell Activity ↑
T Cell Targets for Immunoregulatory Antibody Therapy

Keytruda (pembrolizumab; PD-1 antibody)

Yervoy (ipilimumab; CTLA-4 antibody)

Opdivo (nivolumab; PD-1 antibody)
The number of approved agents more than tripled in the past 3 years.
Age-adjusted Melanoma Incidence and Death Rates (actual and projected, by sex, 1975-2020)

The Surgeon General’s Call to Action to Prevent Skin Cancer
Sun Protection Strategies

- Wear Protective Clothing
- Wear a Hat and Sunglasses
- Seek Shade
- Avoid Times of Peak Sunlight
- Use Sunscreen
- Avoid Indoor Tanning and Sunbathing

UV Exposure is a Major Cause of Skin Cancer—and the Most Preventable!

For the most up-to-date information on approved sunscreen ingredients, visit the FDA website at <www.fda.gov>.