Developing Molecularly Targeted Therapies for Basal Cell Carcinoma

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Disclosures

- Genentech, Inc
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  - Stock holder
Hedgehog Signaling Pathway

- Fundamental signal transduction pathway in embryogenesis
- Originally delineated in *Drosophila*
- Mutant fruit fly embryos covered with bristles (normally only in stripe on anterior segment)
- Vertebrate homologues (Sonic, Desert and Indian Hh)
- Mutations may lead to congenital anomalies and to human cancers
Hedgehog Signaling

- Via patched (PTCH) receptor on cell membrane
- In absence of Hh, patched represses smoothened (SMO) and inhibits activation of the pathway
Hedgehog Signaling

- Binding of Hh removes inhibition and activates pathway
- SMO acts downstream from PTCH and activates the GLI transcription factors when released from PTCH inhibition
Blocking of Hh Pathway

- In embryogenesis: holoprosencephaly – incomplete cleavage of forebrain, cyclopia, midline clefting of lip, palate, nose
- Caused by mutations of sonic Hh
Activation of Hh Pathway

Basal Cell Nevus Syndrome (BCNS)
- Autosomal dominant
- Multiple BCCs
- Also medulloblastoma, ovarian fibroma, fibrosarcoma, rhabdomyosarcoma, meningioma, cardiac fibroma
- Palmo-plantar pits, jaw cysts, characteristic facies, calcification of falx, bifid ribs, spina bifida occulta
Basal Cell Nevus Syndrome

- Positional cloning identified human homologue of *Drosophila* PTCH as a candidate gene
- PTCH functions in developing neural tube, pharyngeal pouches, limb buds and somites
- Screening identified spectrum of PTCH mutations in BCNS patients
Basal Cell Nevus Syndrome

- BCCs develop secondary to activation of target genes of Hh pathway in cells that have lost both normal copies of PTCH.
- Gene mapped to chromosome 9q22-31: deleted in high % of BCCs and other syndrome tumors.
Sporadic BCCs

- Majority show allelic loss for chromosome 9q22 and inactivating mutations of PTCH
- Activating mutations of SMO in 10-20% sporadic BCCs
- Suggests abnormal Hh signaling involved in most (all?) BCCs - high levels of Hh target genes such as GLI1
Mutations in PTCH or SMO Lead to BCC
Holoprosencephaly and cyclopia may be due to genetic defects (blocking of Hh pathway) or environmental effects.

Cyclopia in lambs found to be due to pregnant ewes ingesting corn lily in western USA.

Chemical identified: “cyclopamine” (also jervine).

No effect in adult sheep.

Effect due to inhibiting Hh.
If cyclopamine blocks Hh signaling, could it be used for treating BCCs?

To be effective, should block Hh pathway downstream of molecular defect

Cyclopamine shown to act downstream of PTCH and upstream of GLI

SMO probable site of action
Effects of Oncogenic Mutations Reversed by Cyclopamine

- Genetically engineered cells lacking functional copy of PTCH
- Addition of cyclopamine led to inhibition of Sonic Hh pathway by antagonizing SMO
- Cyclopamine inhibits Hh pathway by binding directly to SMO
- Cells stopped growing and malignant characteristics reversed
  - Taipale, Chen, Cooper et al, Nature, 2000;
  - Chen, Taipale, Cooper, Beachey, Genes Devel 2002
Small Molecule Inhibitors of Hh

- Small molecules identified that directly inhibits SMO activity
- Structurally distinct from cyclopamine
- “May represent promising step in pathway-specific cancer treatments”
Small Molecule Inhibitor

- Hh responsive reporter cell line developed and used in high-throughput screen against ~100,000 small synthetic molecules
- Aminoproline identified – potent inhibitor of Hh activity
- CUR 61414
- Strongly inhibited Hh signaling in cell lines with inactive PTCH
Small Molecule Inhibitor

- **In vitro** BCC model system using PTCH+/-LacZ heterozygous mice
- Shh addition led to activation of signaling pathway and histology showed large basaloid nests

Hh Antagonist Blocks Lesion Formation in LacZ Embryos

control

activated

activated + CUR61414

H&E + X-gal

CUR61414 Induces Selective Apoptosis in Adult Mouse BCC Lesions

Control

CUR61414

Topical Hedgehog Antagonist in BCC Study

Phase I study with 3 segments N=66

- Segment 1: Dose Escalation (n=28)
- Segment 2: MTD Expansion (n=14)
- Segment 3: PD Marker (GLI) (n=24)
halted enrollment in the BCC Phase I clinical trial, and have made a decision not to move forward with the molecule in its current formulation.

As previously announced, preliminary data revealed no significant safety concerns in four weeks of topical treatment. The clinical activity seen was far less than anticipated. The results showed that the formulation did not down-regulate the targeted pharmaco-dynamic marker in this tumor.
Conclusions

- It is difficult to translate science from the laboratory (bench or animal research) to the clinic.
- If GLI had been down-regulated and there was no clinical effect, then the science was incorrect.
- The molecule down-regulated GLI in the lab and in animal models but ……
- This molecule may not have been potent enough or it did not penetrate human skin/BCC lesions adequately to achieve a biologic and clinical effect.