Personalized Cancer Medicine:
Individualized Care at a Population Scale

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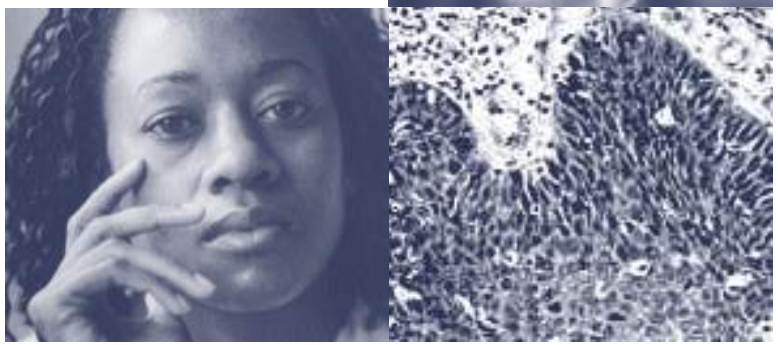
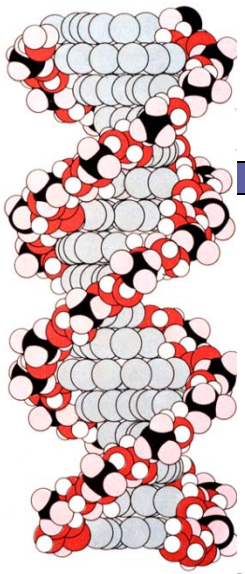
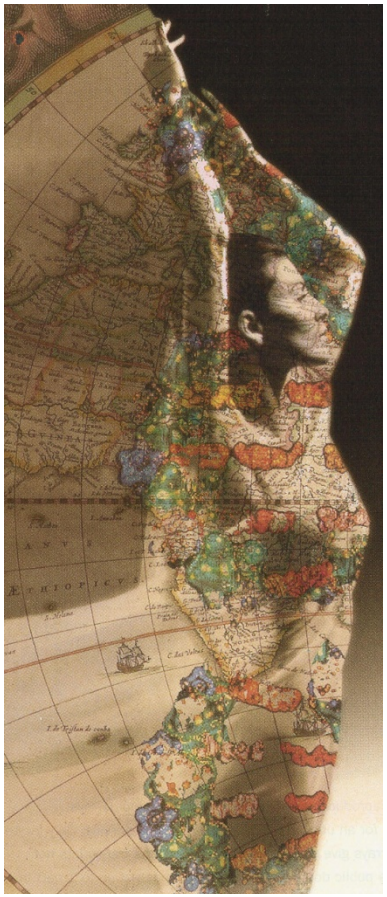
- **Cancer Medicine/Research in 2010**
- **Movement toward Individualization/Personalization of Cancer Care**
- **Genetic/Epigenetic Biomarkers as Drug Development and Resource Allocation Tools**





Mapping/Sequencing of the Human Genome

- Milestone in molecular biology
- Revolutionized cancer genetics and epidemiology
- New technologies for molecular profiling of cancer cells
- Unprecendented opportunities for the discovery of new approaches to cancer treatment and prevention
- Greatly augmented public expectations
- Potential to decrease healthcare costs through personalization of care



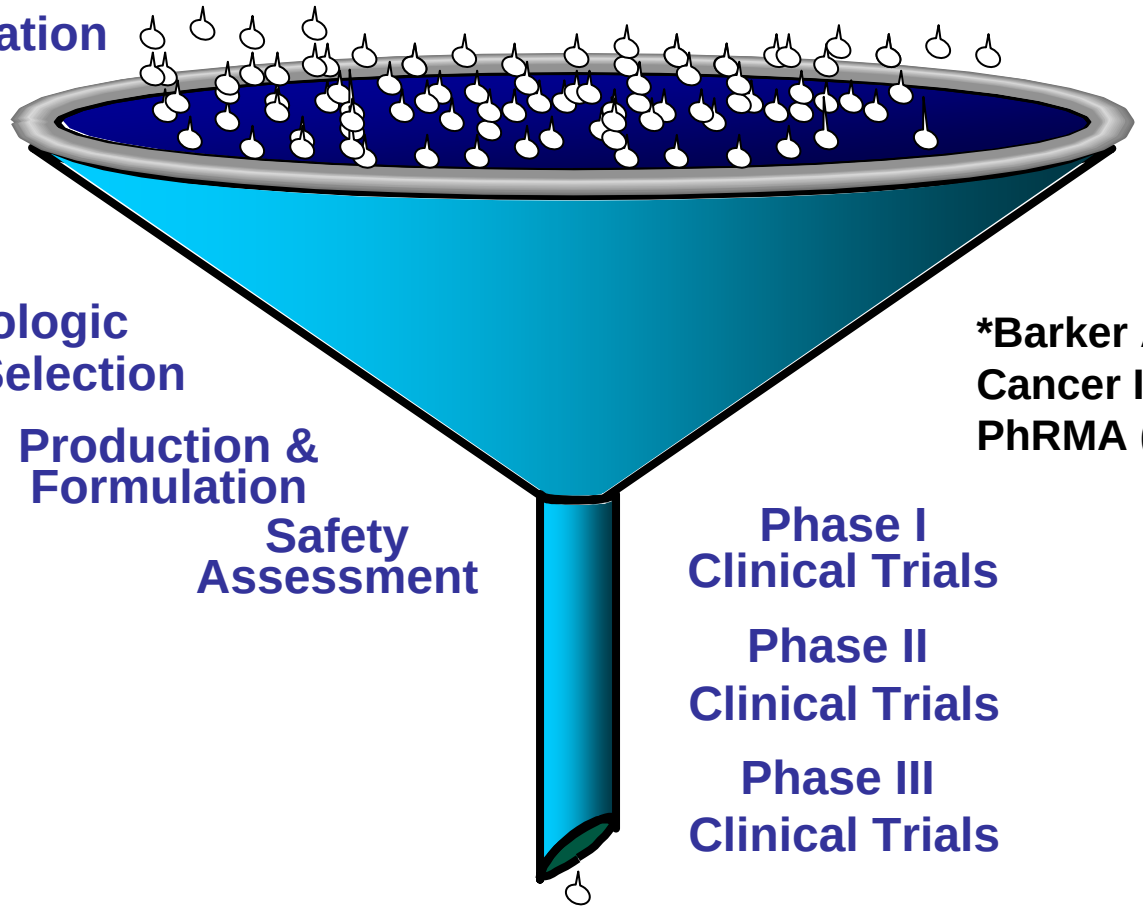
Transformation of Medicine by Translational Research*

20th century medicine	*21st century medicine*	*implications*
treat disease when symptoms arise and normal function is compromised	intervene before symptoms appear and preserve normal function	prevention of disease and preservation of health
morphological understanding of disease state	cellular/molecular understanding of evolving disease process	prediction of disease risk permitting less toxic and more effective intervention
high financial and disability costs	opportunity for improved efficacy and efficiency	personalization of risks and treatments; greater participation of patients in health care decision-making

*adapted from Hood L, von Eschenbach A, and Zerhouni E (2005-6)

Current Challenges of Drug Discovery and Development

Flow of Approved Products*



*Barker A, National Cancer Institute; PhRMA (www.phrma.org)

approval by U.S. Food and Drug Administration

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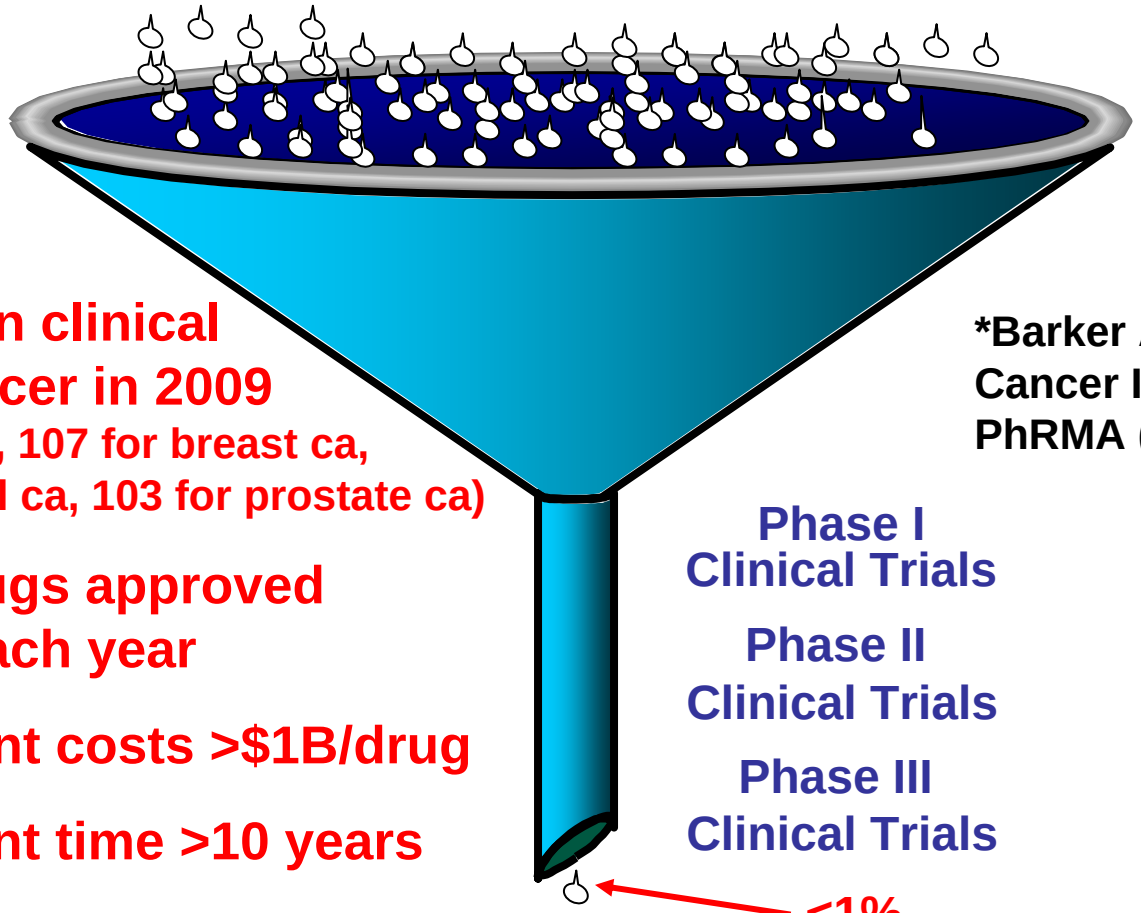
Current Challenges of Drug Discovery and Development

Flow of Approved Products*



- **861 drugs in clinical trials for cancer in 2009**
  (122 for lung ca, 107 for breast ca, 70 for colorectal ca, 103 for prostate ca)
- **1-2 new drugs approved for cancer each year**
- **development costs >$1B/drug**
- **development time >10 years**

Phase I Clinical Trials

Phase II Clinical Trials

Phase III Clinical Trials

<1%

approval by U.S. Food and Drug Administration

***Barker A, National Cancer Institute; PhRMA (www.phrma.org)**

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Historical Development Pathway for Anti-Cancer Drugs

Investigational New Drug (IND) application filed with Food and Drug Administration

Phase 1 (Toxicity) Testing

Goal is to determine the dose and dose-schedule for the drug

(MTD = maximally tolerated dose; DLT = dose-limiting toxicity)

Phase 2 (Efficacy) Testing

Goal is to estimate/define drug benefit

(Response rates: complete responses + partial responses)

Phase 3 (Comparative Efficacy)

Goal is to test patient benefit

FDA Approval/Labeling for Marketing

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New Development Pathway for Anti-Cancer Drugs

Investigational New Drug (IND) application filed with Food and Drug Administration

Phase 1/2 (Toxicity/Efficacy) Testing

Goals are: (i) to determine optimal biological dose (the dose that maximizes "on-target" effects while minimizing "off-target" effects, using molecular biomarker of pharmacodynamic action),

and (ii) to estimate drug benefit in setting with maximal chance of efficacy (using molecular biomarker of risk/for indication)

Phase 3 (Comparative Efficacy)

Goal is to test patient benefit

FDA Approval/Labeling for Marketing

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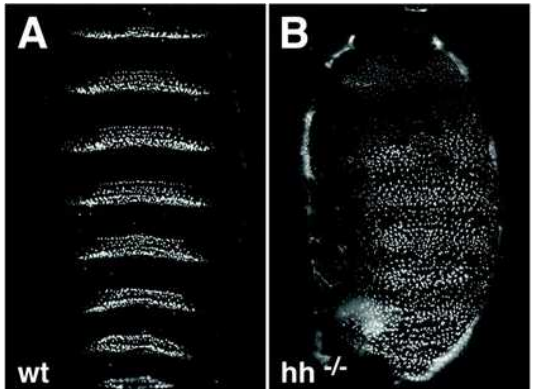
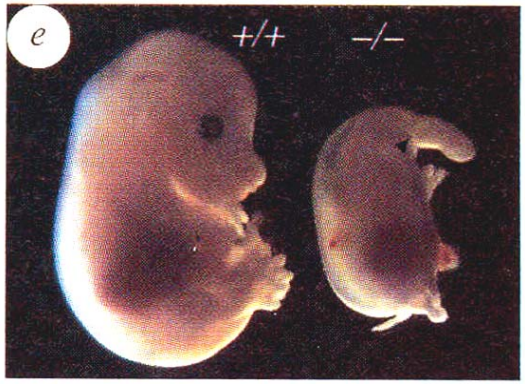
A New Cancer Therapeutic Lead from Basic Developmental Biology Research

***Drosophila Hh* mutant**



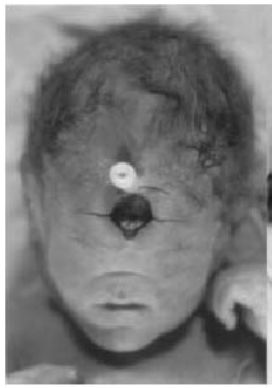
Nüsslein-Volhard C and Weischaus E. Nature *287:* 795-801 (1980)

mouse *Shh* mutant



Chiang C et al. Nature *383:* 407-13 (1996)

human *SHH* mutant

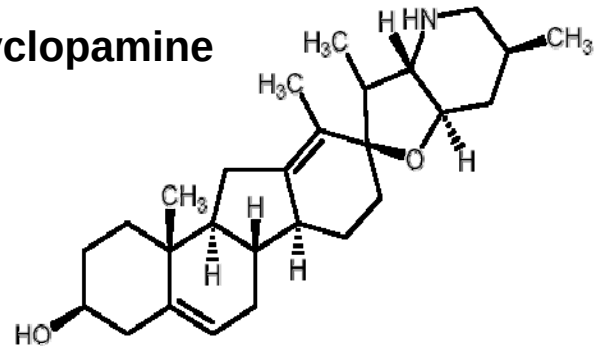


Roessler E et al. Nature Genet *14:* 357-60 (1996)

Veratrum californicum

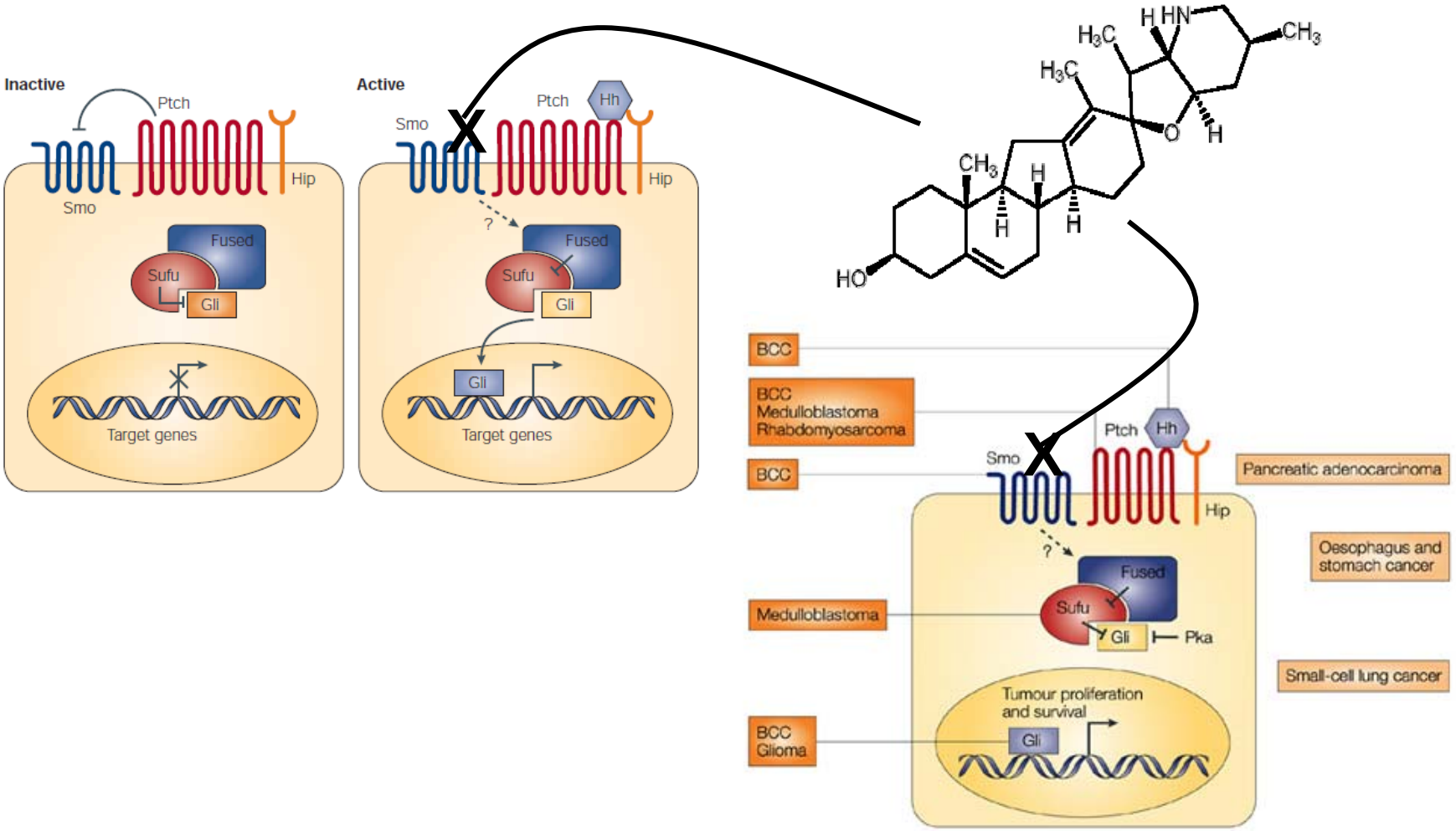
Binns W *et al.* Am J Vet Res *24:*1164-75 (1963)
Keeler RF and Binns W. Teratology *1:* 5-10 (1968)

cyclopamine



Cooper MK *et al.* Science *280:* 1603-7 (1998)

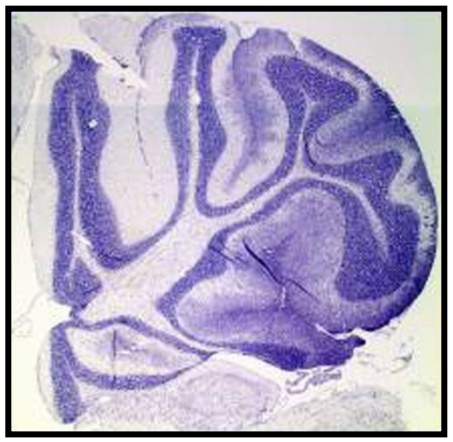
Corruption of the Hedgehog Signaling Pathway Leads to Cancer Development*



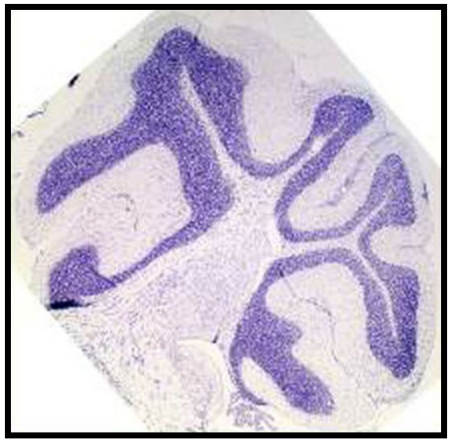
*Pasca di Magliano M and Hebrok M Nature Rev Cancer *3:* 903-11 (2003)

Hedgehog Signaling Antagonists Inhibit Growth of Medulloblastoma in *Ptch*$^{+/-}$*p53*$^{+/-}$ Mice*

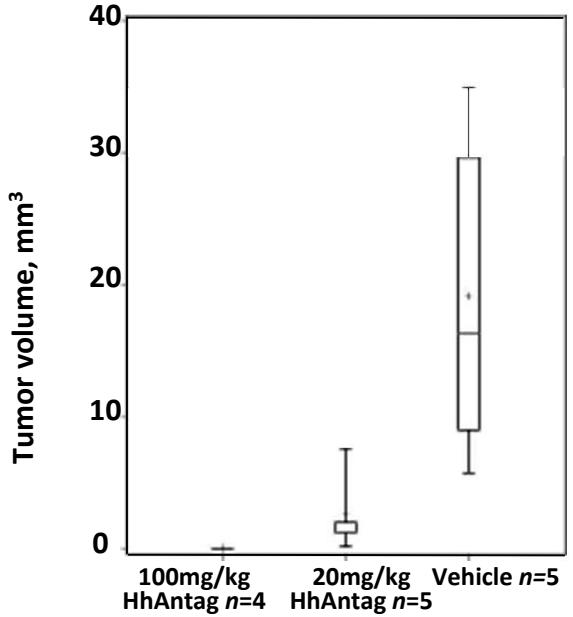
***Ptch*$^{+/-}$*p53*$^{-/-}$ mice treated twice daily for two weeks with Hedgehog antagonist**



untreated



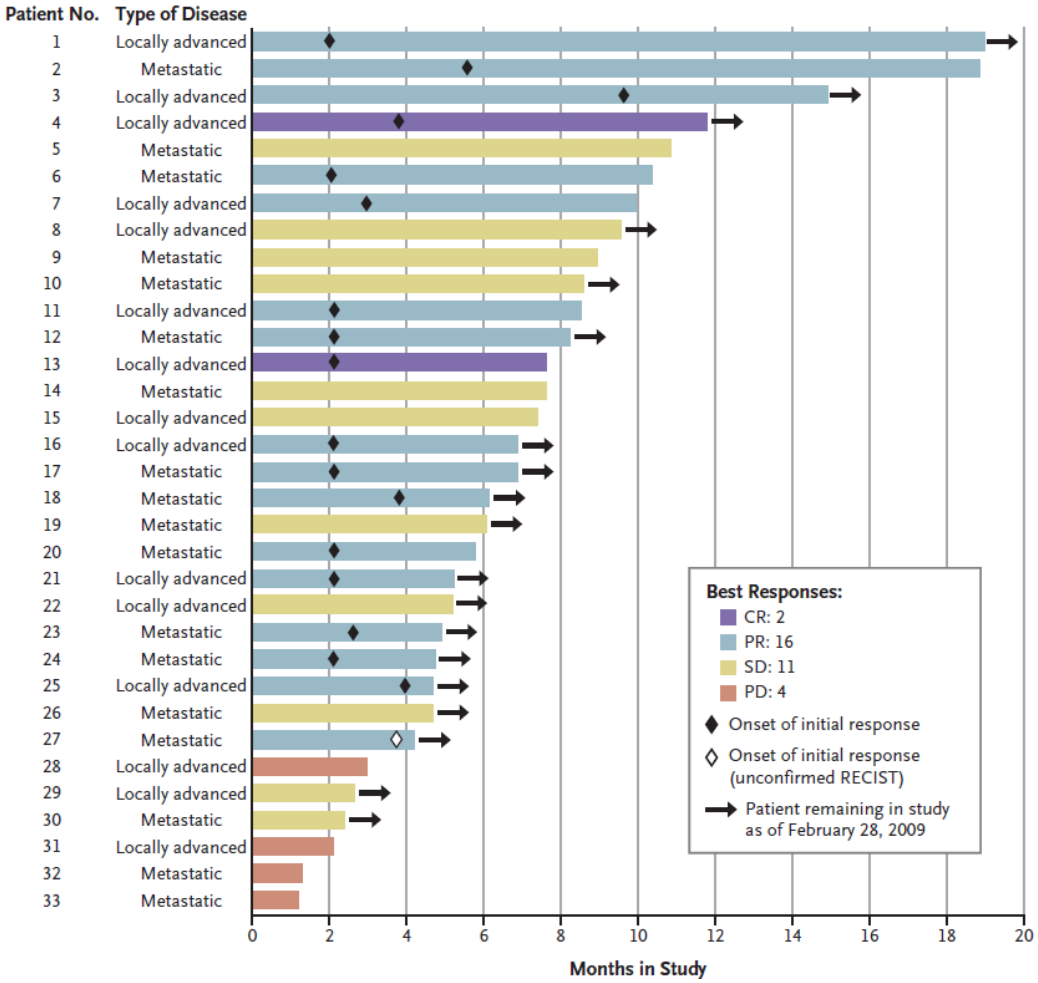
Hedgehog antagonist



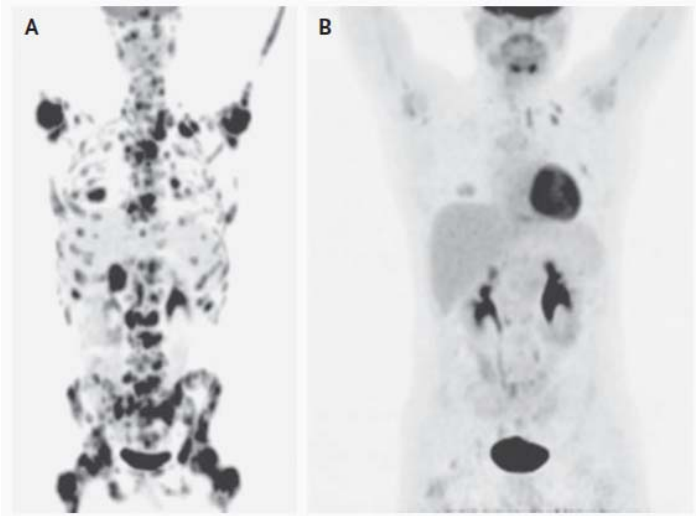
Romer et al., *Cancer Cell*, 2004

A Targeted Hedgehog Signaling Antagonist Exhibits Activity Against Tumors with *Patched* Mutations*

basal cell carcinoma



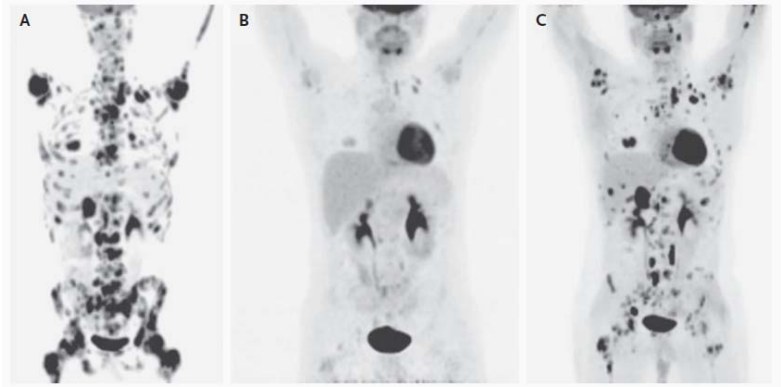
medulloblastoma



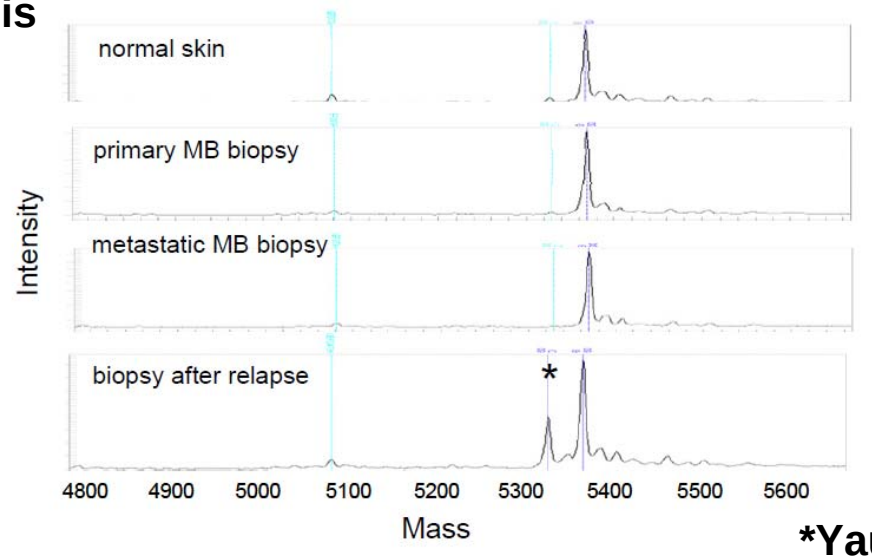
*Von Hoff DD *et al.* N Engl J Med 361: 1164-72 (2009); Rudin CM *et al.* N Engl J Med 361: 1173-8 (2009)

Resistance to Hedgehog Signaling Antagonist Exhibits Pathway Addiction via Acquired *SMO* Mutation*

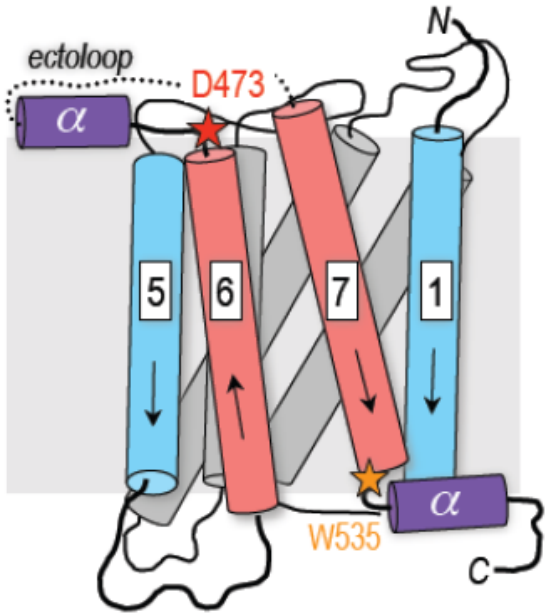
medulloblastoma **response** **progression /resistance**



***SMO* sequence analysis**



acquired *SMO* mutation D473M blocks drug binding



***Yauch RL *et al*. Science *326:* 572-4 (2009)**

Cancer Genetics and Epigenetics:
Individualized Cancer Care at a Population Scale
Key Points

- **Both Germline and Somatic Genetic/Epigenetic Information will Impact Cancer Risk Stratification, Screening, Early Detection, Diagnosis, Prevention, and Treatment**

- **Genetic/Epigenetic Biomarkers as New Tests that Improve Efficacy, Safety, and Cost-Effectiveness of Cancer Care**

Right Treatment

⇨ **Right Person**

Right Time

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