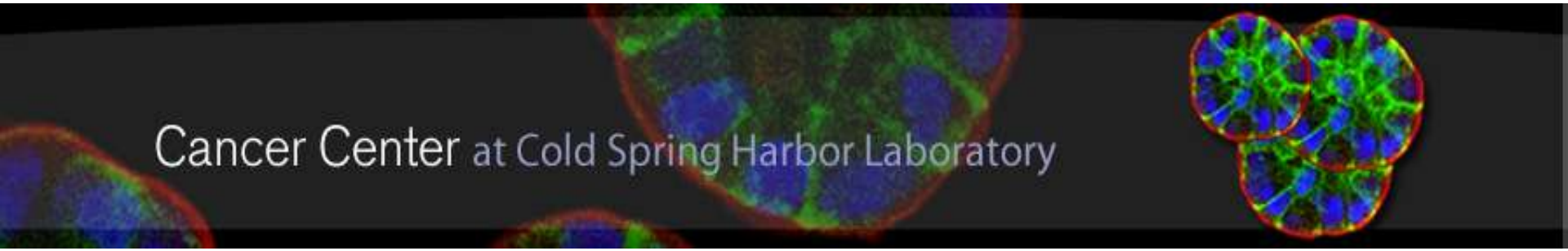



# MAY 2010 – MAY 2011

CSH Cold Spring Harbor Laboratory

# May 2010 to May 2011 - A year of key achievements in cancer research at CSHL

**Acute myeloid leukemia**: p53, self-renewal and cancer stem cells

**Lung cancer**: IL-6 and resistance to targeted therapy

**Skin cancer**: Stem cell origins and genetics of malignancy

**Liver cancer**: Molecular target for therapy and biomarker of response

**Breast cancer**: - New genomic method to track tumor evolution and metastasis
- Epigenetic profiling to predict risk of relapse

**Mosaic mice, RNAi sensor assays and accelerated discovery**

# JULY '10

Using their cutting-edge "mosaic" mouse models to study aggressive cancers such as **leukemia**, **Scott Lowe and colleagues** found that the loss of the master tumor suppressor gene p53—a frequent occurrence in cancer patients—facilitates the production of so-called "cancer stem cells." These cells have higher leukemia-initiating potential and are considered to be more resistant to therapy.

The scientists are now using their models in preclinical studies to test new drugs and drug combinations.

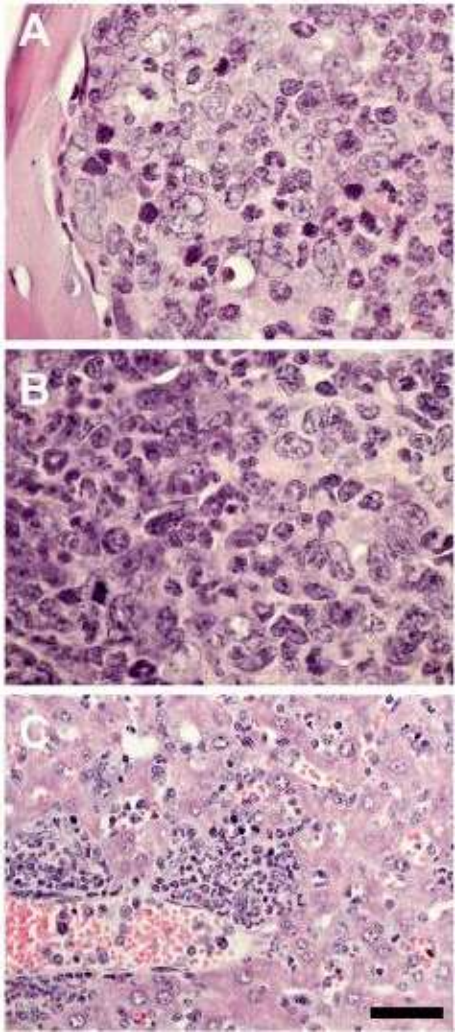



**Image**: Myeloid progenitor cells that become leukemia-initiating cells in bone (A), spleen (B), and liver (C).

**Links**: Paper in *Genes and Development*; *News release.*

# AUG '10

The targeted drug Tarceva has proven to be effective in **non-small cell lung cancer** patients who harbor cancer-causing mutations in a gene called EGFR. But a majority of these responders eventually develop resistance and succumb to the disease.

**RaffaellaSordella's group** found that resistance to Tarceva develops because of increased secretion of IL-6, a protein that mediates inflammation. Testing of a new treatment strategy based on these results is now under way.

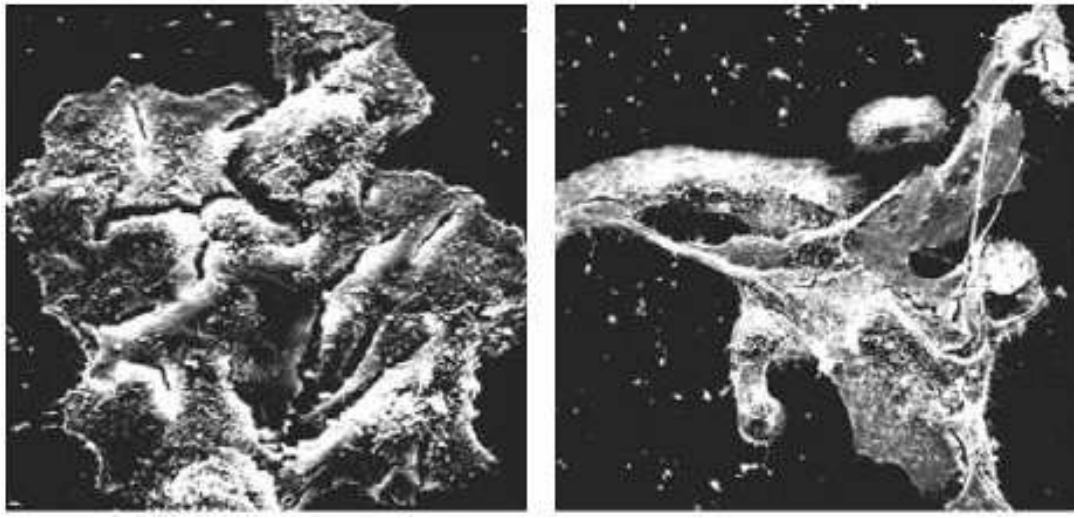


**Image**: Cells that become resistant to Tarceva develop an increased metastatic potential and features resembling cells that make up loose connective tissue (mesenchyme).

**Links**: Paper in the *Proceedings of the National Academy of Sciences*; *News release*

# DEC '10

Based on patterns of gene expression**, breast cancer** can be molecularly classified into 5 subtypes, with one subtype, Luminal A, having better prognosis than non-luminal subtypes. A multi-institutional collaboration including CSHL's**Jim Hicks** and colleagues discovered that patterns of DNA methylation—a chemical modification of DNA that can alter gene expression—also help to predict outcome.

The collaborators have compiled a list of genes whose methylation status correlate significantly with the likelihood of relapse, thus creating the possibility of identifying prognostic biomarkers as well as new molecular targets for therapy in the future.

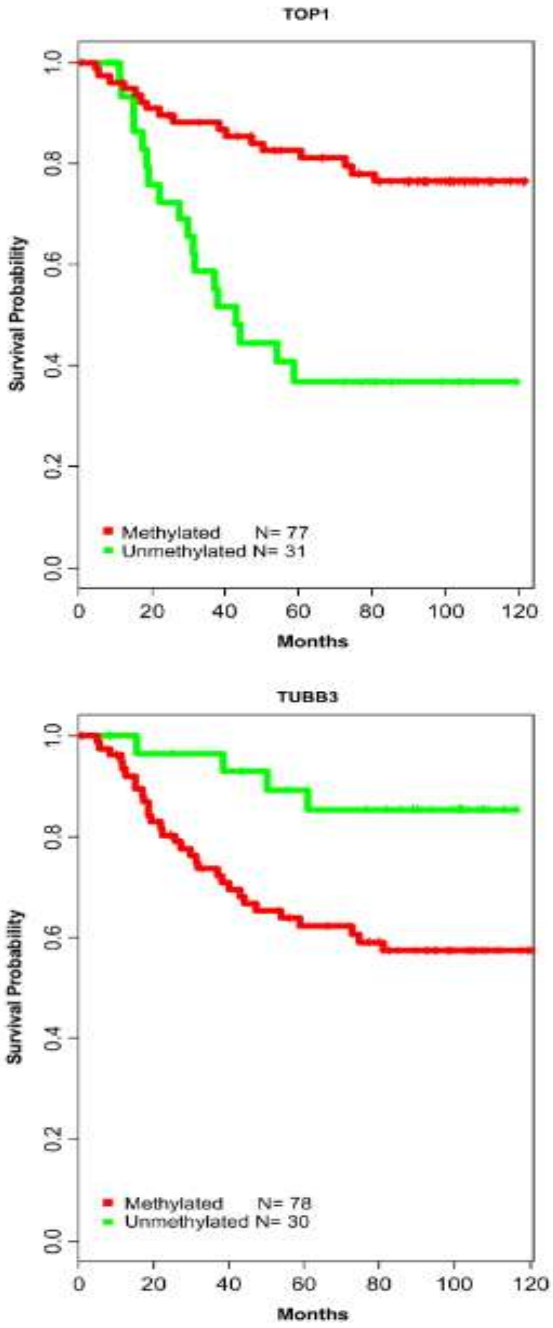
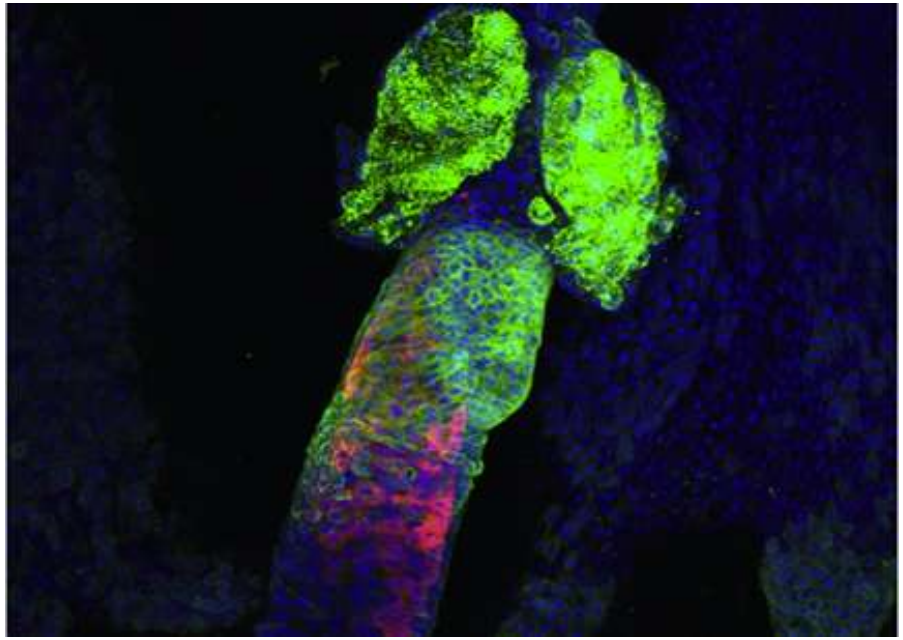



**Image**: Two genes whose methylation status (red=methylation; green=no methylation) can predict the risk of relapse.

**Links**: Paper in Molecular Oncology

# FEB ‘11



**AleaMills’s**group identified the stem cell origin of **skin cancer,** showing that a version of the p63 protein that is already being used as a pathological marker in the clinic to distinguish between cancer subtypes is responsible for maintaining carcinoma-promoting stem cells. The work suggests that when differentiated cells –which are more mature than stem cells—accumulate genetic lesions that make them more stem-like, they tend to promote cancer.

**Image**: The oncogeneRas and the p63 isoform ΔNp63α cause keratin 15-expressing stem cells (red) but not other stem cells in the skin such as the nestin-producing stem cells (green) to eventually transform into carcinoma cells.

**Links**: Paper in*Cell Stem Cell*; *News release.*

# MAR '11

**Scott Powers and his collaborators** identified a strategy for targeted molecular therapy in **liver cancer**, which currently has limited treatment options and one of the worst one-year survival rates of any cancer type. Their work uncovered a gene that can be targeted with a therapeutic monoclonal antibody and a clear strategy for identifying patients who might benefit from this antibody treatment.

**Links**: Paper in the *Cancer Cell*; *News release*.

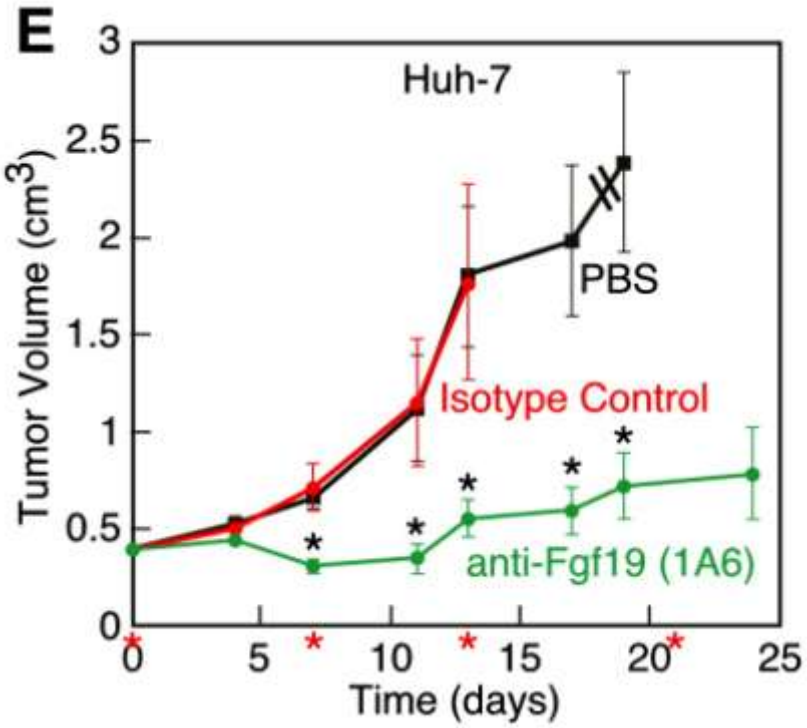



**Image**: Treatment with a monoclonal antibody that shuts off the activity of FGF19 protein dramatically decreases tumor growth in mice

# MAR ‘11

Scientists in **Mike Wigler’s**group developed a powerful new technique called single nucleus sequencing to analyze the genome of individual cells and understand how tumors—a genetically heterogenous mix of cells—evolve.

The scientists used this method to track the sequence of genetic changes in two **breast carcinomas** and found that the tumors showed not gradual, but “punctuated, clonal” expansions. Such details of a tumor’s evolutionary history could be invaluable in determining treatment strategies.

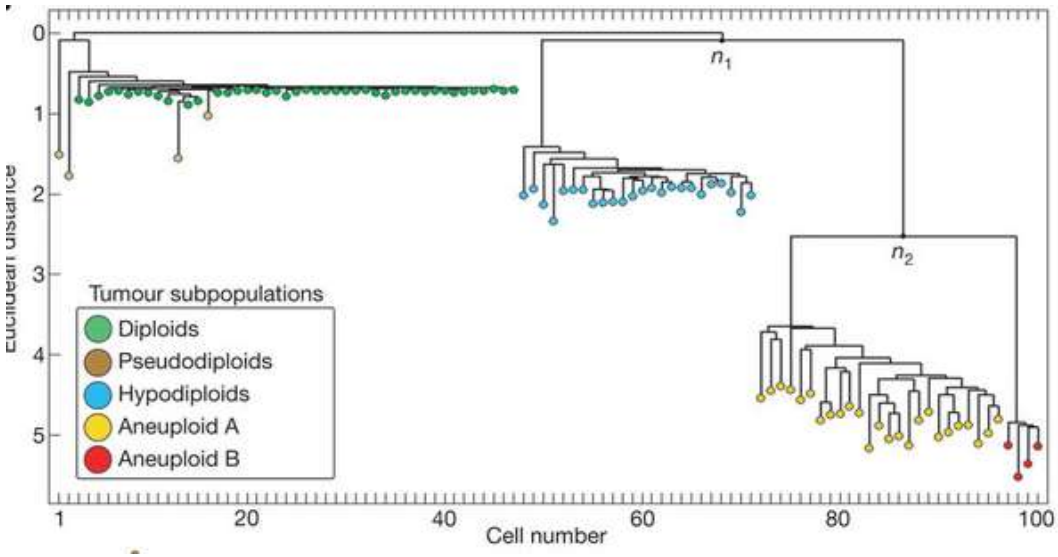



**Image**: Analysis of 100 individual cells teased out of 6 different areas of a single breast carcinoma shows four major branches of evolution occurring within.

**Links**: Paper in *Nature*; *News release*

# APR '11

Led by Scott Lowe, CSHL scientists have developed powerful "mosaic" mouse models of human cancer that can be generated in a fraction of the time and cost needed to produce traditional mouse models. A collaborative effort among several CSHL groups, this approach–which employs RNAi tools developed by Greg Hannon's lab—makes it possible to speedily and comprehensively model cancer's genetic diversity, or heterogeneity, characterize cancer-related genes and evaluate drug targets.

In April, the team reported their development of technology platforms to identify the most potent triggers for RNAi; and a rapid, scalable way of generating mice in which RNAi can be turned on or off conditionally. Using this system, they perfected a non-lethal way of switching off essential genes before the change kills the animals.

**Images**: Clockwise: Scott Lowe, Greg Hannon, Bruce Stillman, RaffaellaSordella.
**Links**: Papers in *Molecular Cell*, *Cell* and *PNAS*.
*News release #1*; *news release #2*