Integrating Cancer Molecular, Clinical, and Pathways Data with caBIG®
Molecular Medicine Tri-Conference
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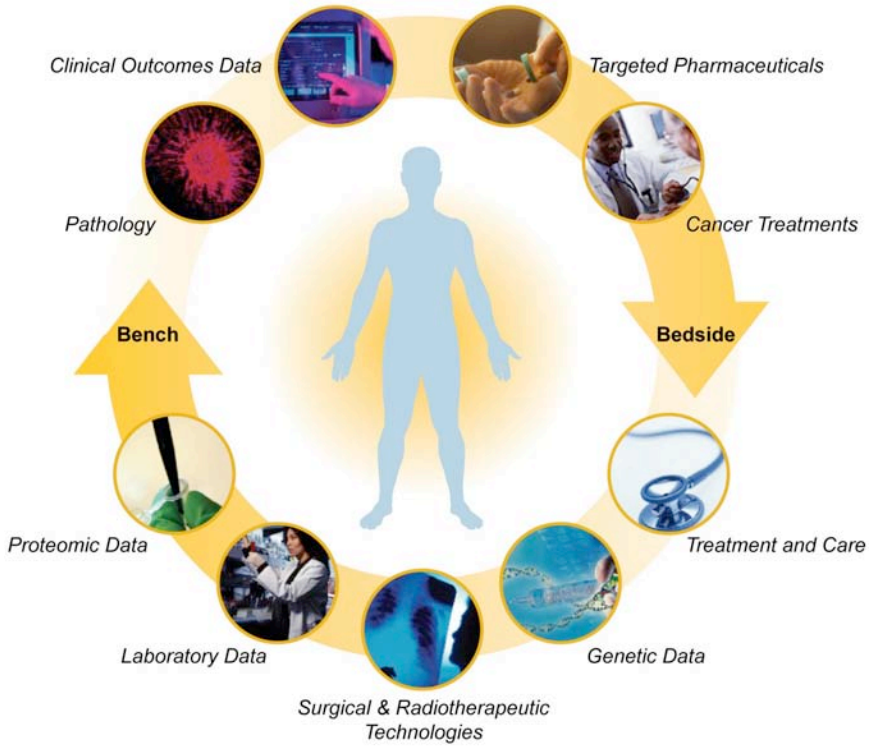
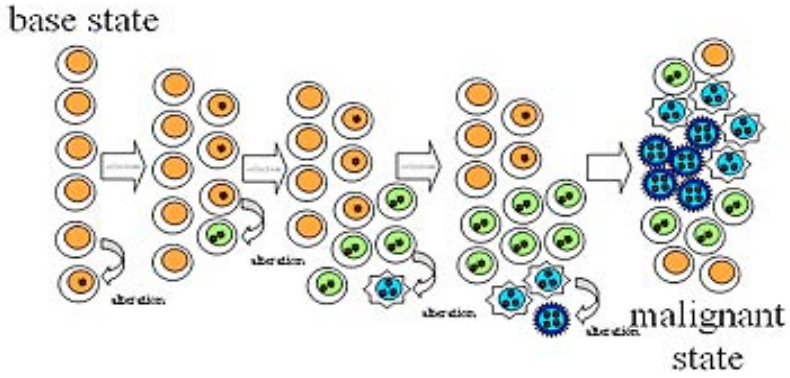
21st Century Biomedicine

- Personalized, Predictive, Preemptive, Participatory……
- Unifies clinical research, clinical care, and discovery (bench-bedside-bed) into a seamless continuum
- Results in improved clinical outcomes
- Accelerates the time from discovery to patient benefit
- Enables a health care system, not a disparate "sector"
- Empowers consumers in managing their health over a lifetime

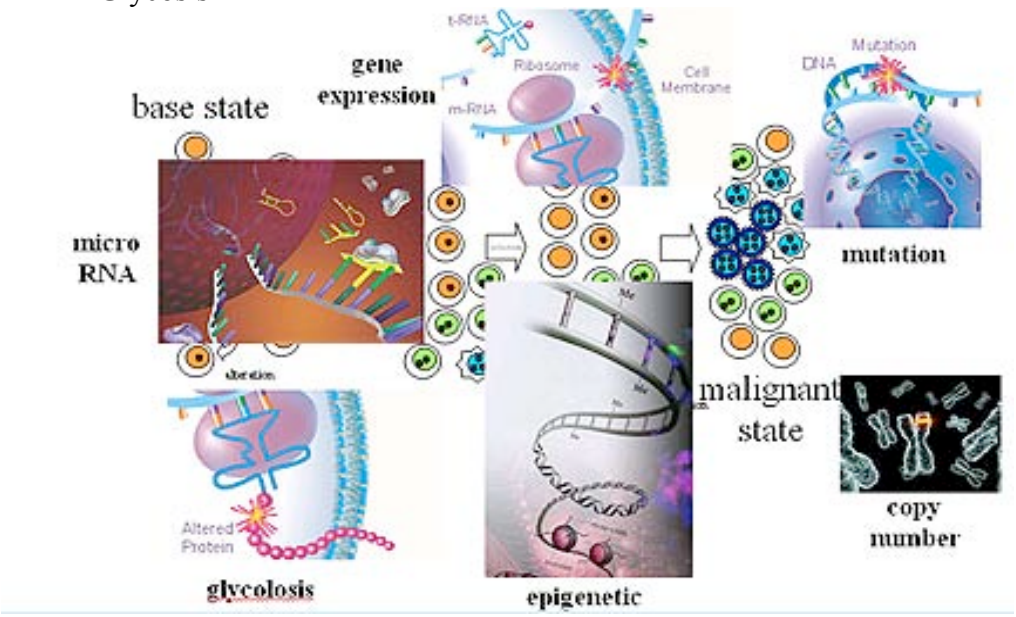


Cancer is a Complex Adaptive System



Cancer is a Complex Adaptive System

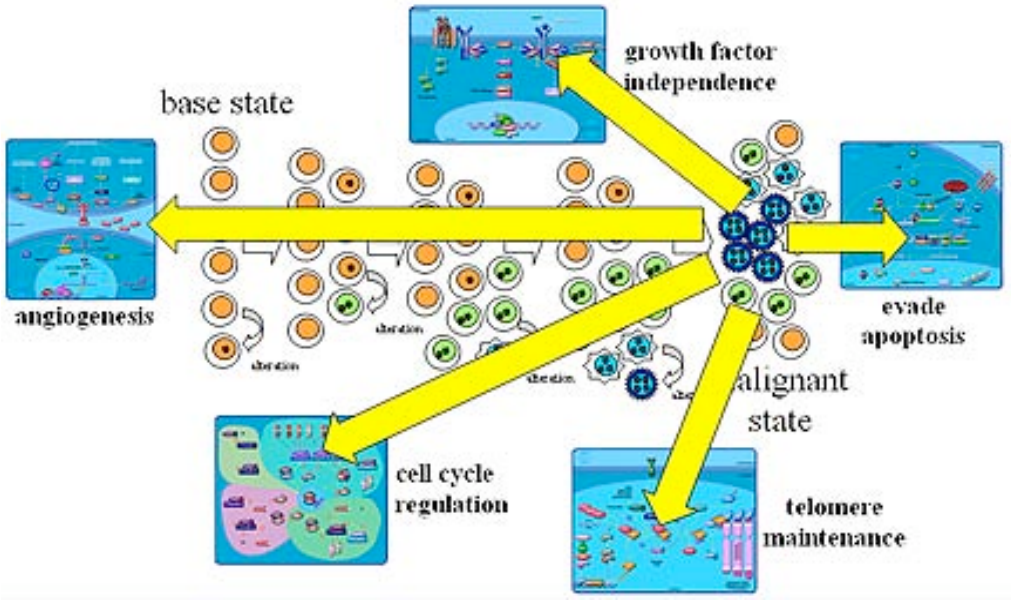
- Copy number
- Mutation
- Gene expression
- Epigenetic
- Micro RNA
- Glycosis



Cancer is a Complex Adaptive System

- Angiogenesis
- Cell cycle regulation
- Telomere maintenance
- Evade Apoptosis

Growth factor independence



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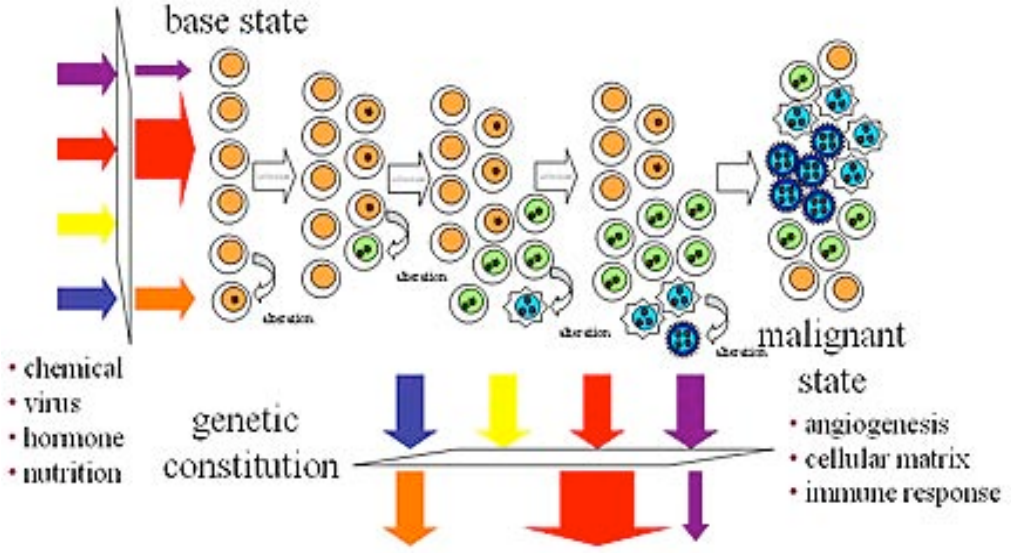
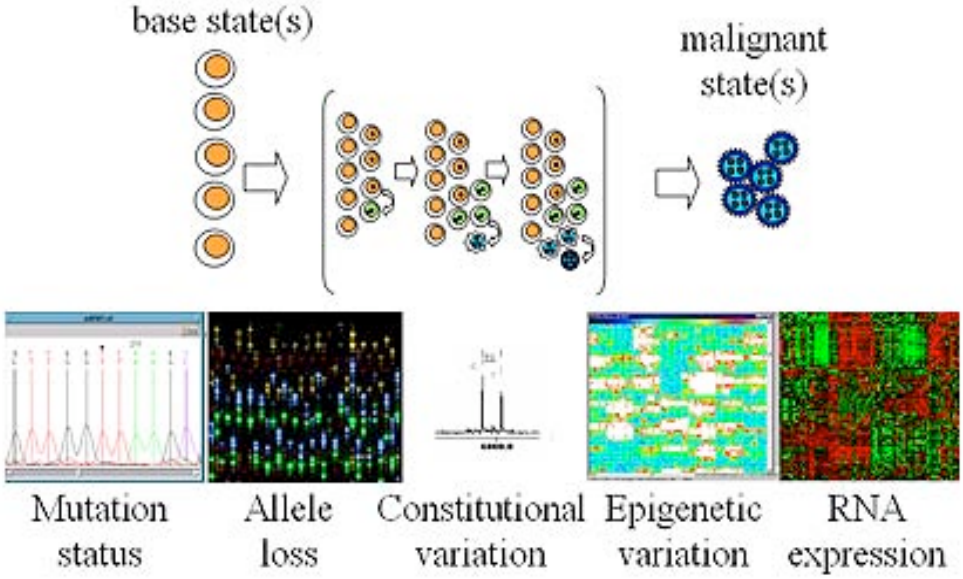


Multiple systems technologies are needed to triangulate molecular state of disease



Molecular Medicine as a Complex Continuum

- Clinical Research
- Imaging
- Molecular Biology
- Pathology

caBIG®:
Biomedical Information Highway

- The cancer Biomedical Informatics Grid® (caBIG®) is a virtual network of interconnected data, individuals, and organizations that redefines how research is conducted, care is provided, and patients/participants interact with the biomedical research enterprise.

The caBIG® Initiative

caBIG® empowers researchers to see the "BIG" picture by integrating increasingly complex layers of cancer biology, from gene to clinical phenotype, as a whole
Gene – Genome – Genomes – Pathways – Clinical Outcomes
All from their computer

caBIG® Capabilities Advance Discovery, Clinical Research, and Clinical Care

Clinical Research

- Track clinical trial registrations
- Facilitate automatic capture of clinical laboratory data
- Manage reports describing adverse events during clinical trials

Imaging

- Use NBIA repository for medical images including CAT scans and MRIs
- Visualize images using DICOM-compliant tools
- Annotated Images with distributed tools

Pathology

- Access library of well characterized and clinically annotated biospecimens
- Use tools to keep an inventory of a user's own samples
- Track storage, distribution, and quality assurance of specimens

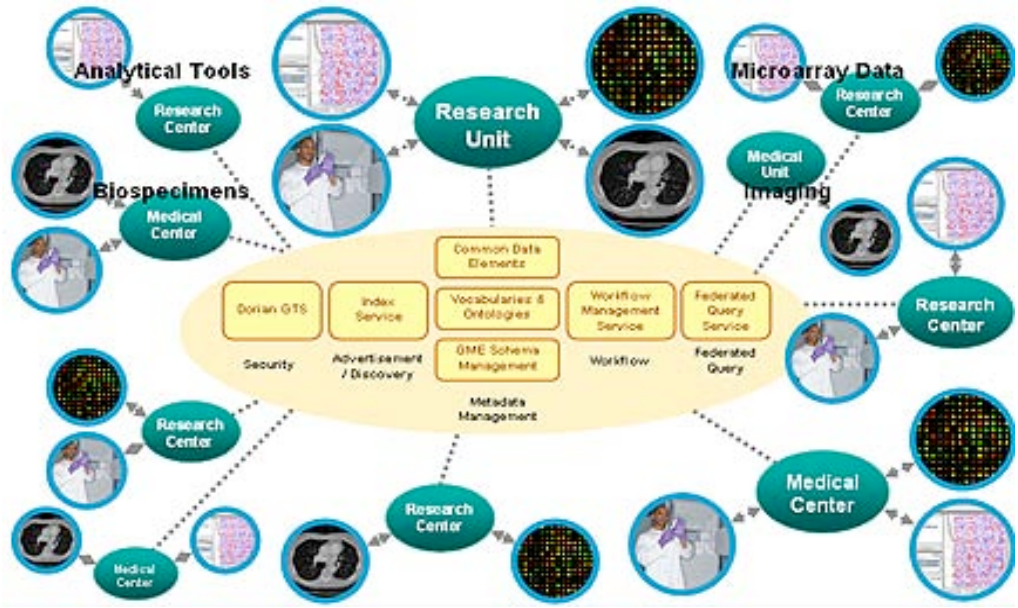
Discovery Research

- Combine proteomics, gene expression, and other basic research data
- Submit and annotate microarray data
- Integrate microarray data from multiple manufacturers and permit analysis and visualization of data

IT-enabled ecosystem

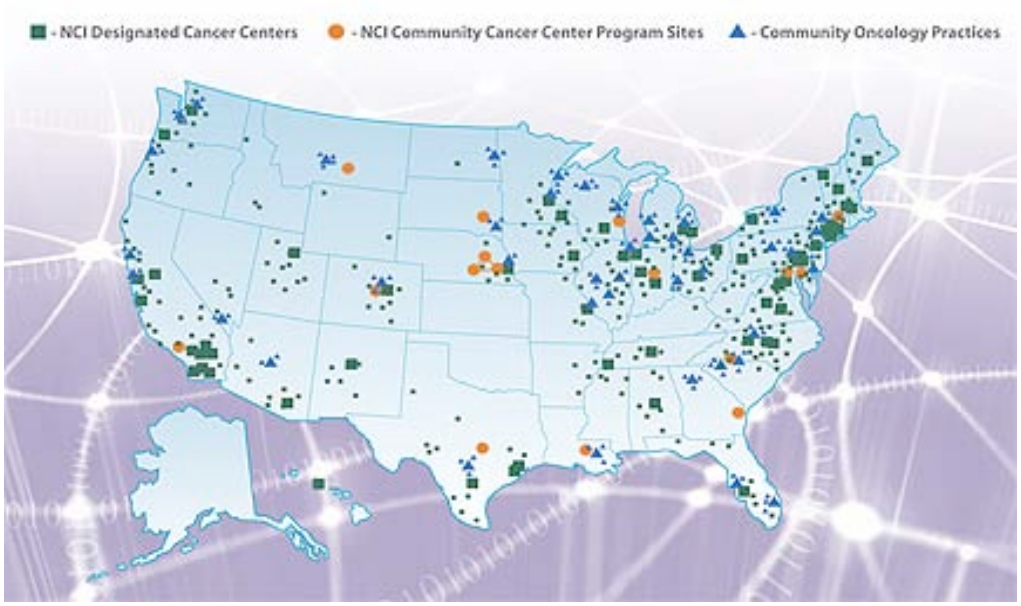
Analytical Tools, biospecimens, array data, imaging, research units/centers and medical units/centers all connect to:

- **Security:** Dorian GTS
- **Advertisement/Discovery:** Index Service
- **Metadata Management:** Common Data Elements, Vocabularies & Ontologies, GME Schema Management
- **Workflow:** Workflow Management Service
- **Federated Query:** Federated Query Service



IT-enabled ecosystem
Together creates the:
Biomedical Knowledge Cloud
Grid Services Infrastructure

caBIG® is Linking the Cancer Community



caBIG® is Establishing Global Connections

United States, Mexico, Chile, Uruguay, Argentina, Brazil, UK, Netherlands, Germany, Czech Republic, Finland, Jordan, India, China, Australia, New Zealand

caBIG®, the world's largest biomedical research "highway", connecting a growing number of people and organizations across the globe

***Case Study*:**
Hypothesis Generation Utilizing TCGA Resources

Connecting multiple sources, experiments, and data types

Three forms of cancer

- glioblastoma multiforme (brain)
- squamous carcinoma (lung)
- serous cystadenocarcinoma (ovarian)

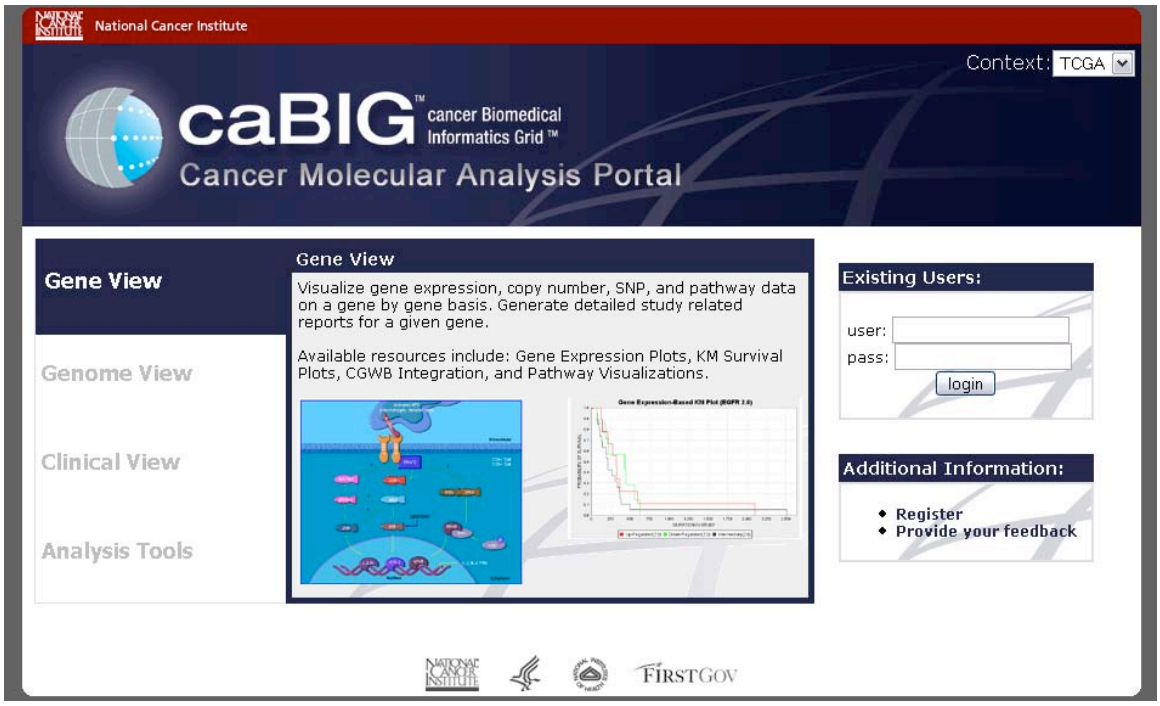
12 Organizations

- Biospecimen Core Resource
- 7 Cancer Genomic Characterization Centers
- 3 Genome Sequencing Centers
- Data Coordinating Center

Multiple data types

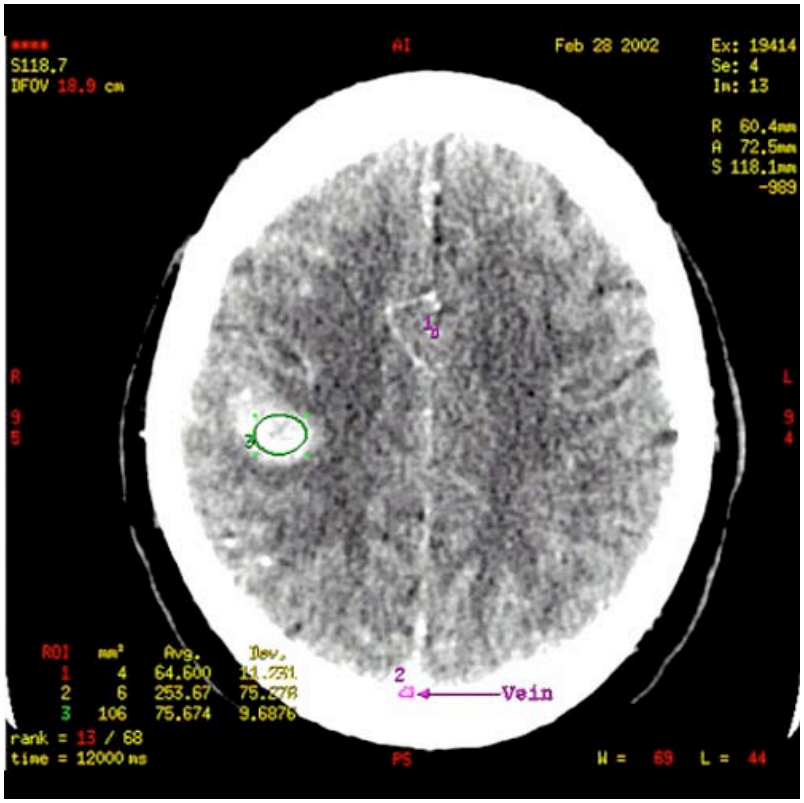
- Clinical diagnosis
- Treatment history
- Histologic diagnosis
- Pathologic status
- Tissue anatomic site
- Surgical history
- Gene expression
- Chromosomal copy number
- Loss of heterozygosity
- Methylation patterns
- miRNA expression
- DNA sequence

A Single Web-based Portal for all Analyses – http://cma.nci.nih.gov

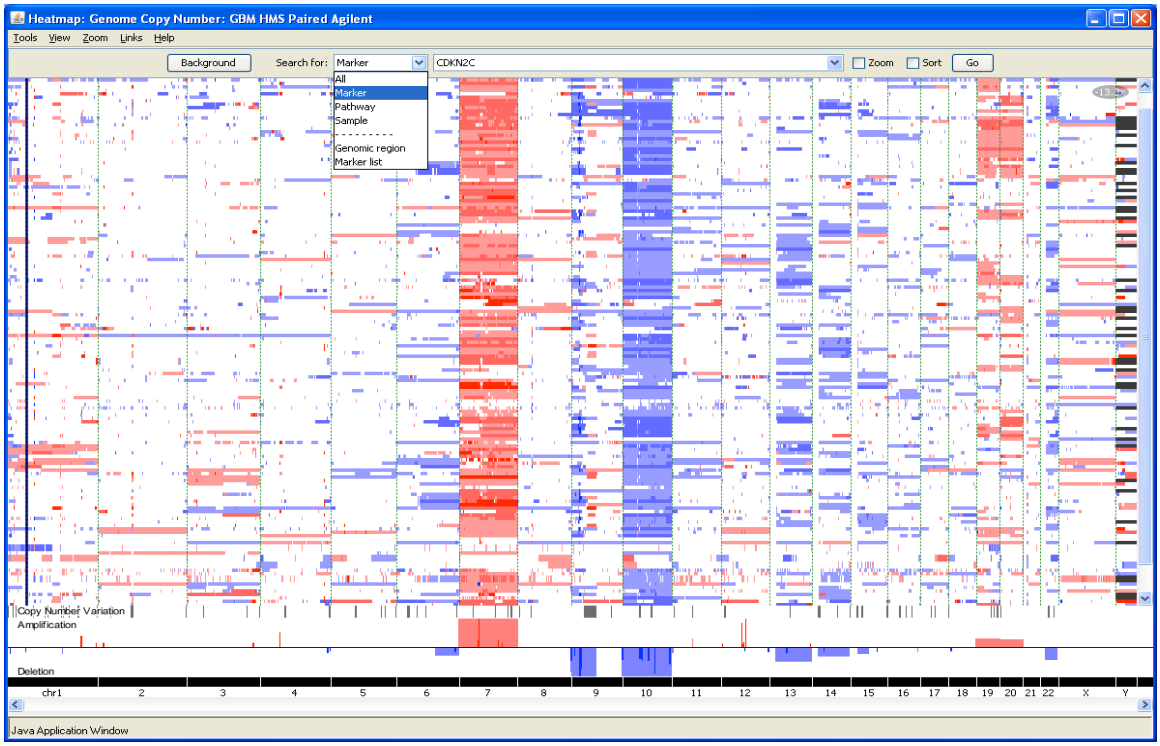


Glioblastoma Multiforme (GBM)

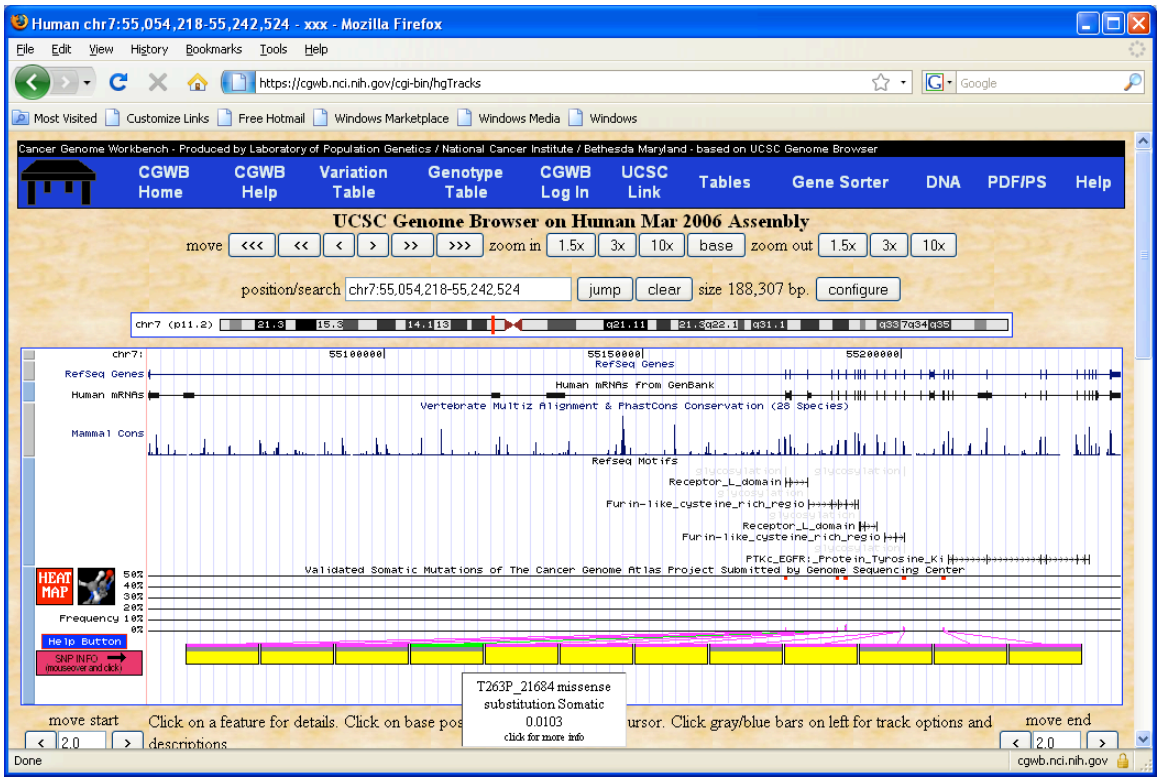
- GBM is the most common type of brain tumor. High grade gliomas are incurable and tumors expressing a mesenchymal phenotype are the most aggressive form



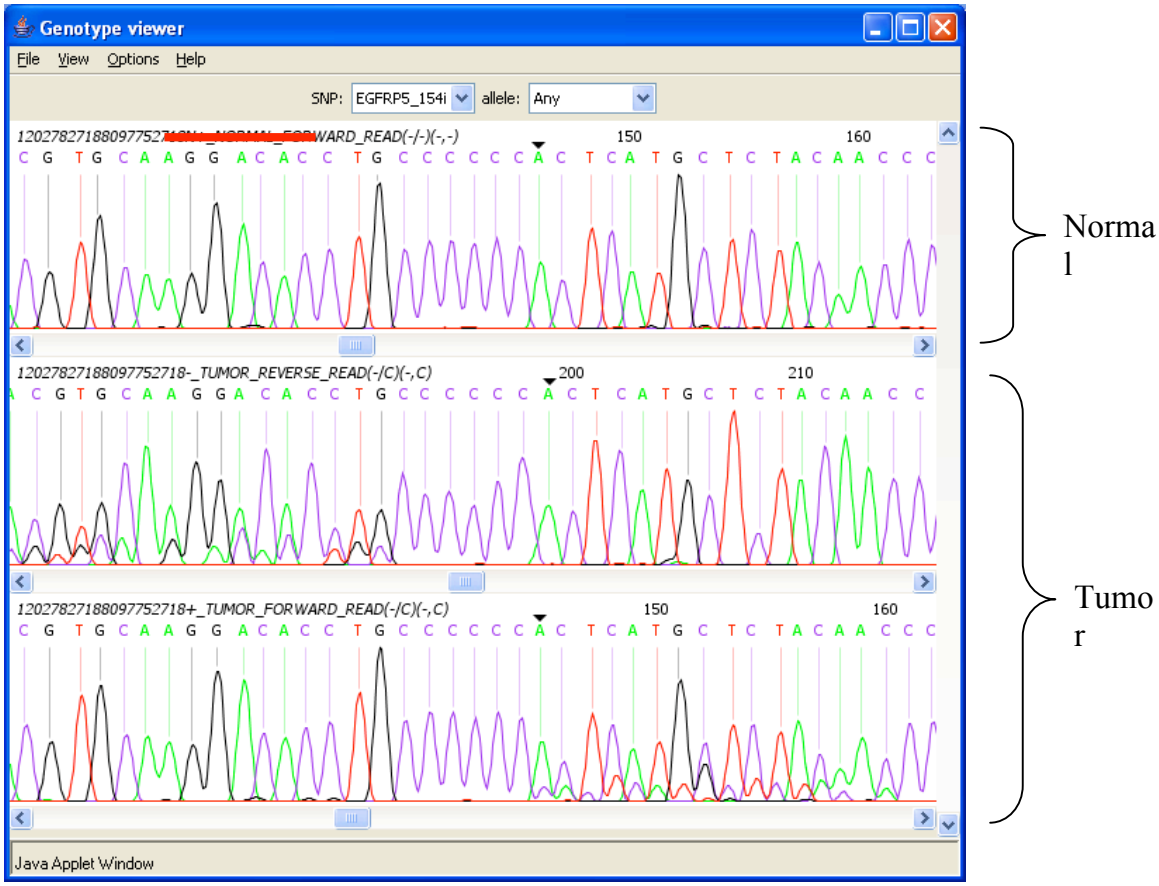
Chromosome 7 and EGFR Seen as Frequent Targets of Alteration in GBM
(glioblastoma multiforme)



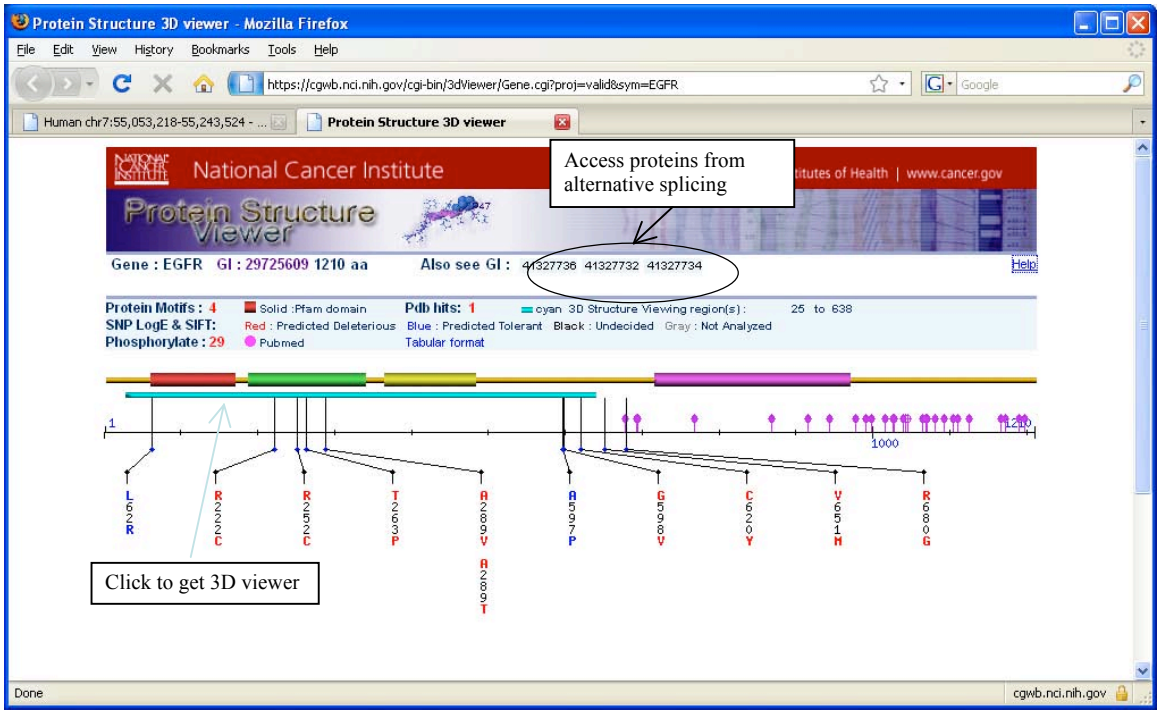
Summary View of EGFR Mutations Shows Clustering Around Extracellular Domain



Putative Somatic Mutations can be Manually Reviewed
e.g.: Frameshift Mutation in EGFR in Paired Tumor/Normal

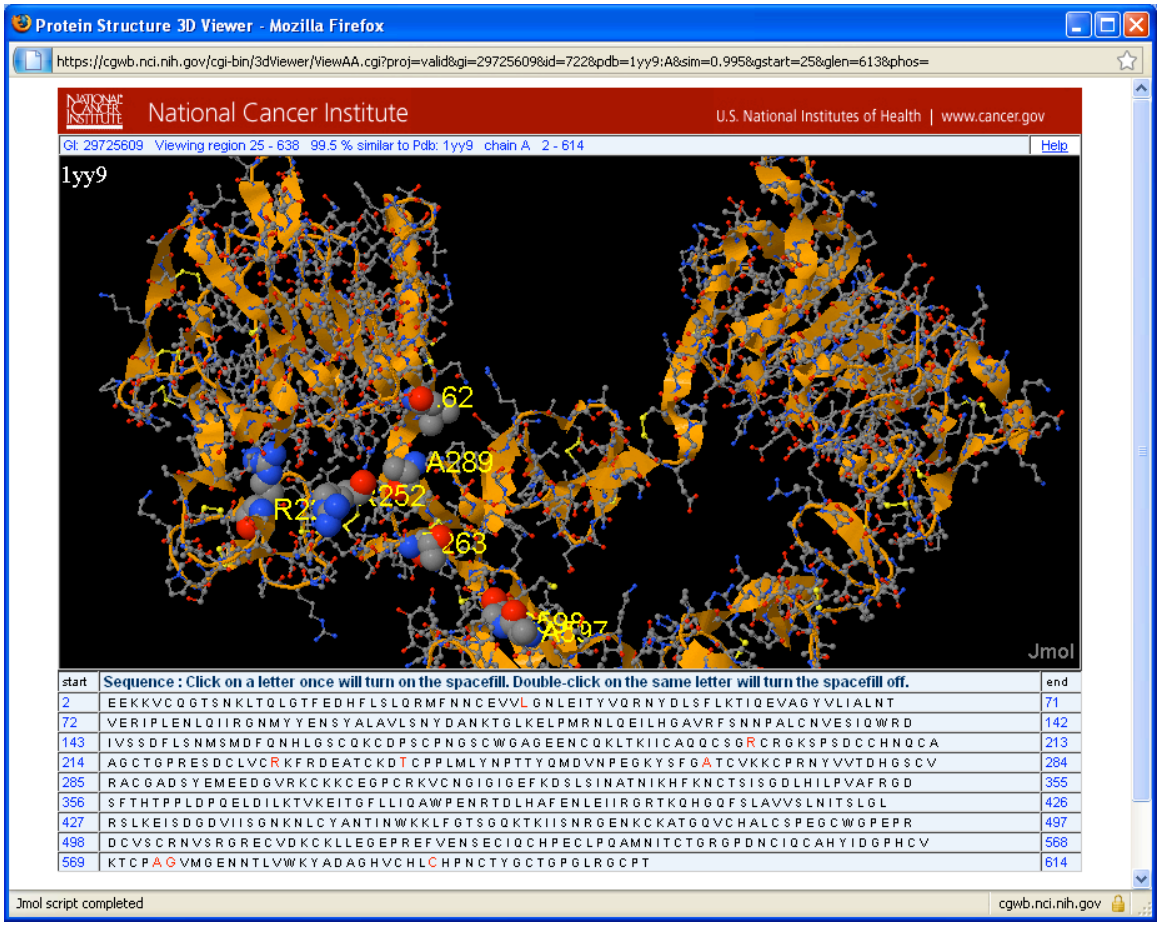


Protein Structure View of EGFR Mutations

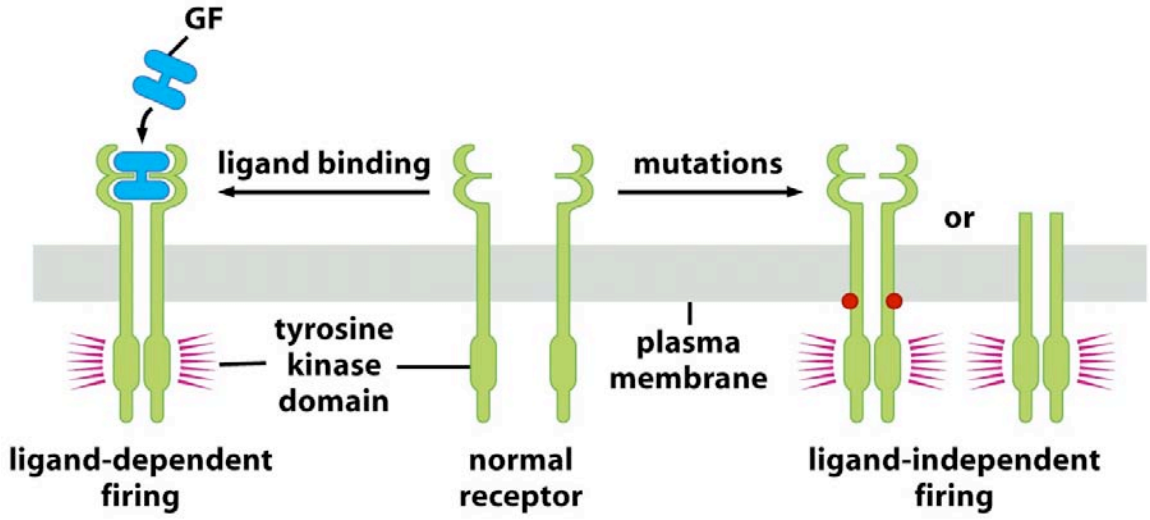


3D Structure Viewer

Big, highlighted atoms refer to the mutated amino acids. You can also click on the mutated amino acid to turn on or off a specific mutation

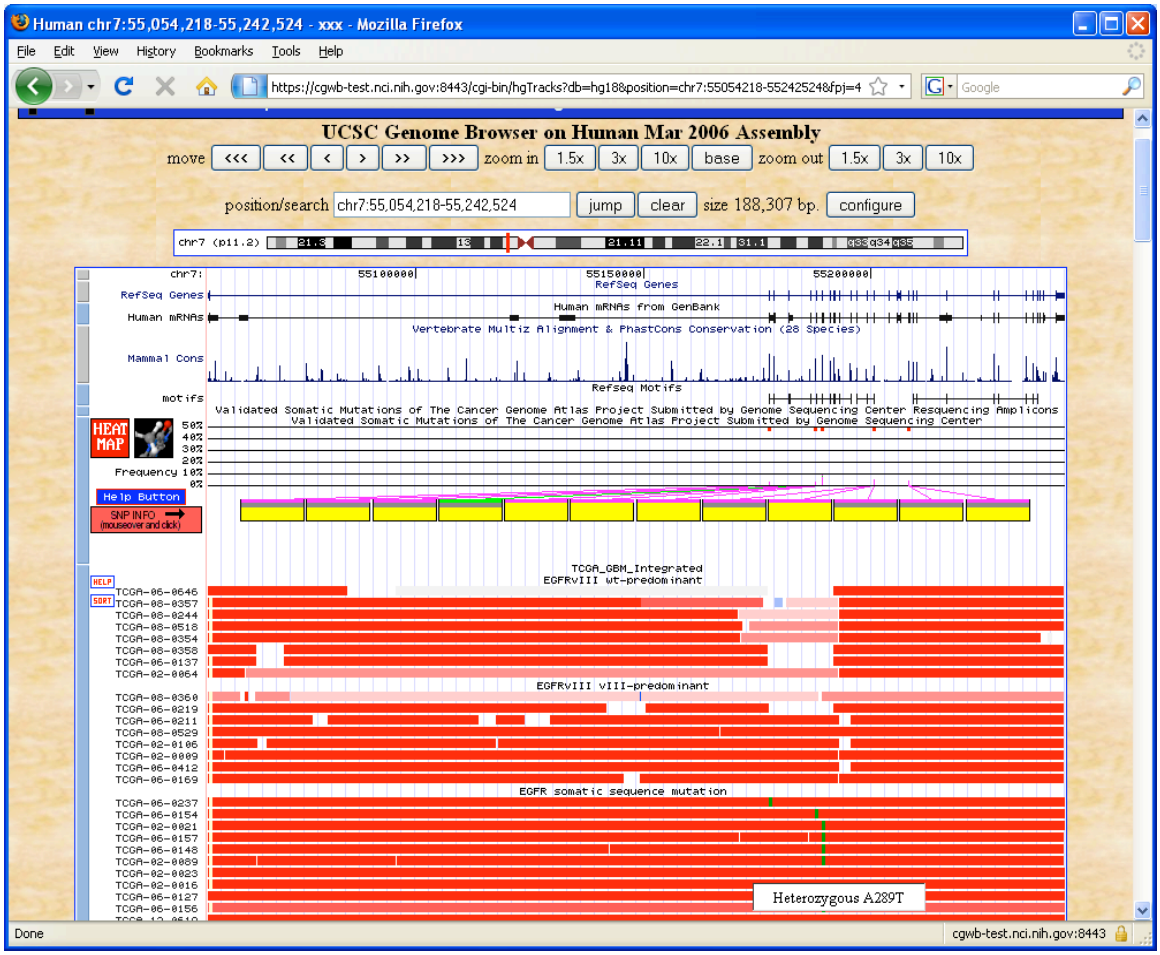


Constitutive Activation of EGFR Leads to Abnormal Growth

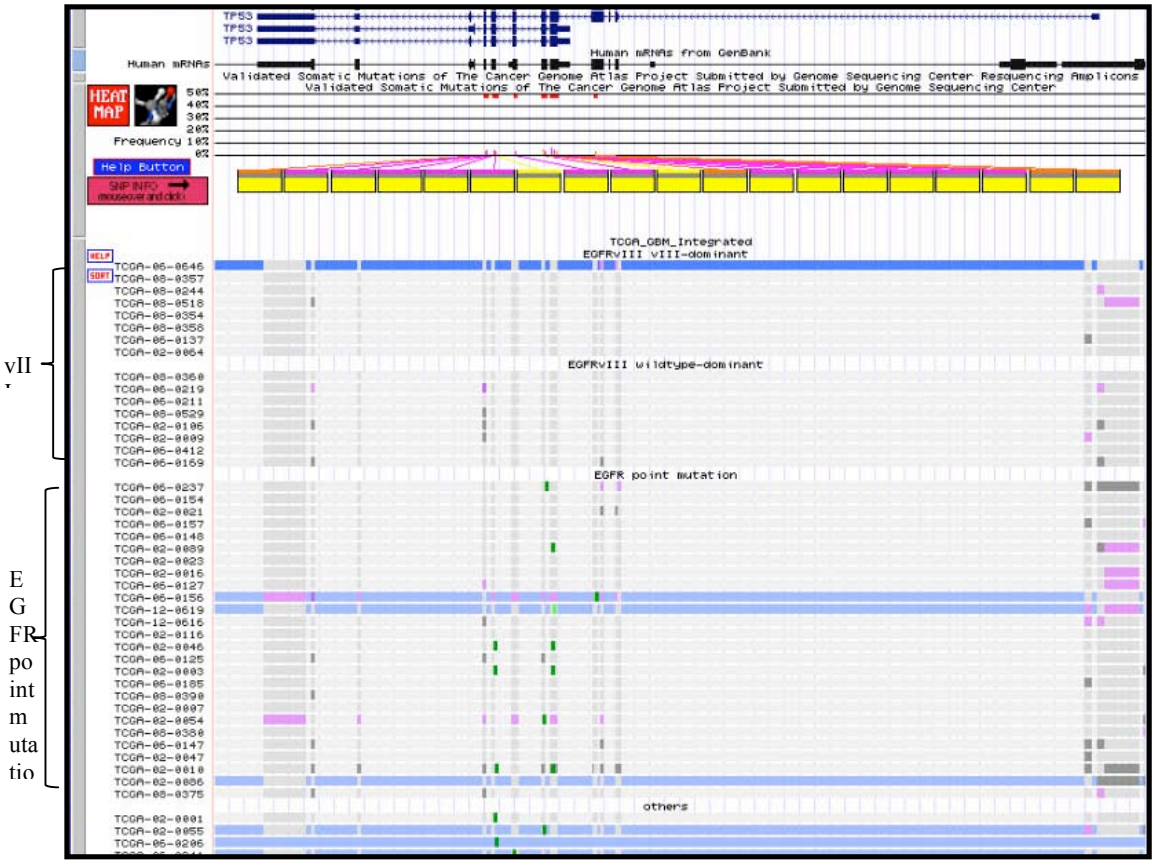


"EGFRvIII" mutation
Modified from The Biology of Cancer (© Garland Science 2007)

View EGFR vIII Patient Subgroups to find vIII Mutations Occurring in Amplified Samples and Exclusive with EGFR Point Mutations



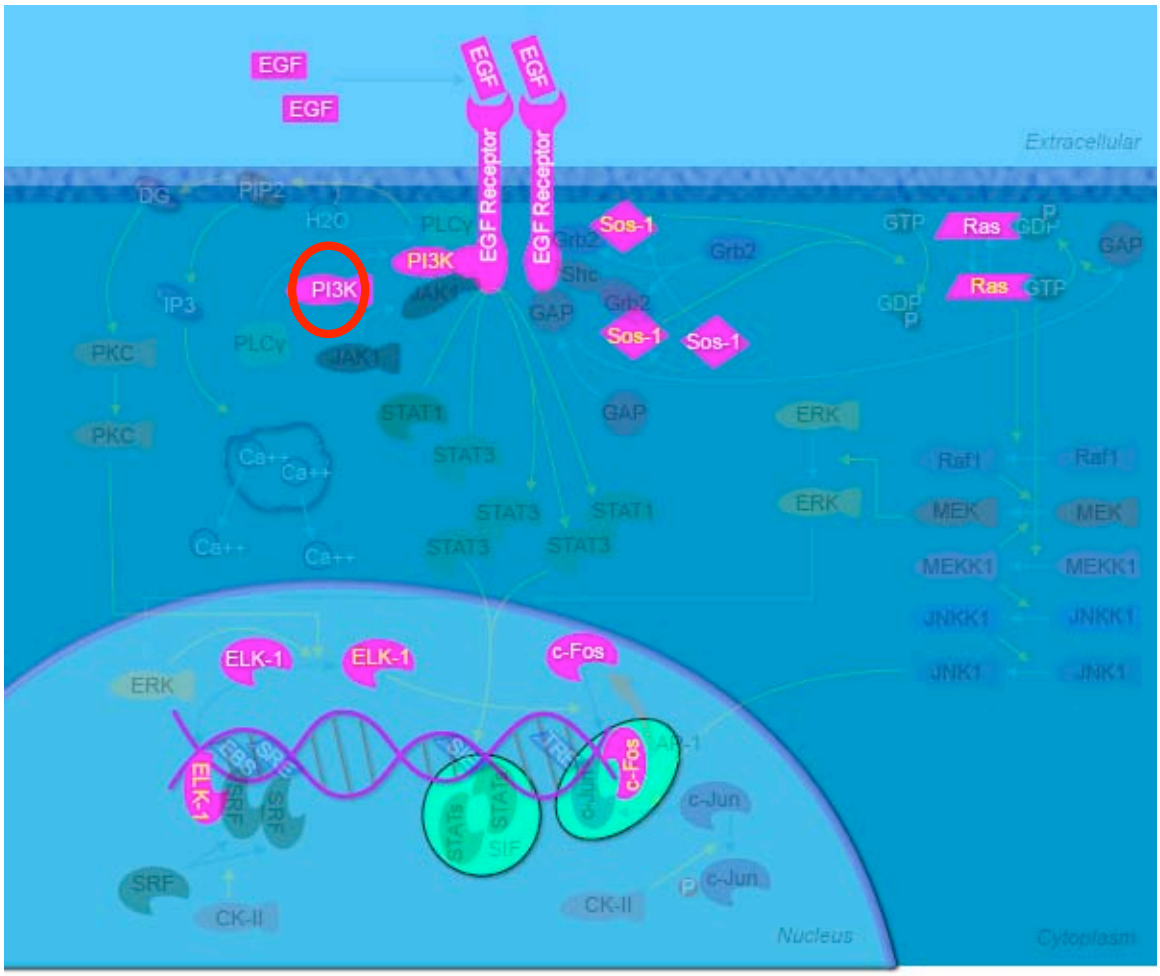
EGFR Mutation Subgroups Viewed at the TP53 Locus
No Mutation for EGFRvIII but 1/3 of EGFR Point Mutations have TP53 Mutations (p=0.036)



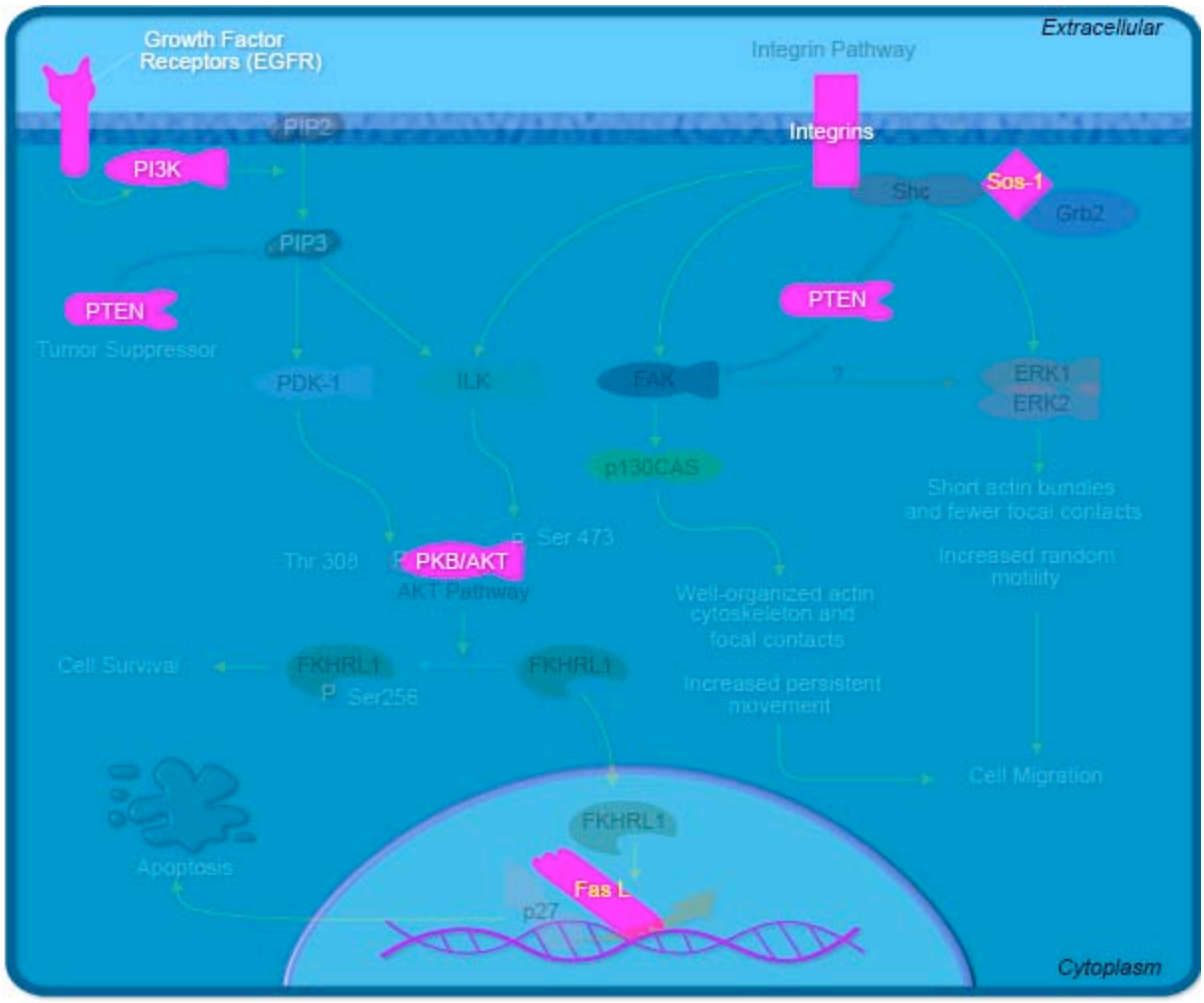
Mutations in EGFR vIII and TP53 May be Anti-Correlated

	EGFR amplification			No EGFR amplification		
	EGFR point mutation	EGFRvIII	No EGFR mutation	EGFR point mutation	EGFRvIII	No EGFR mutation
	18	12	37	7	0	79
TP53	5	0	4	3	0	35
Fraction	28%	0%	11%	43%	N/A	44%

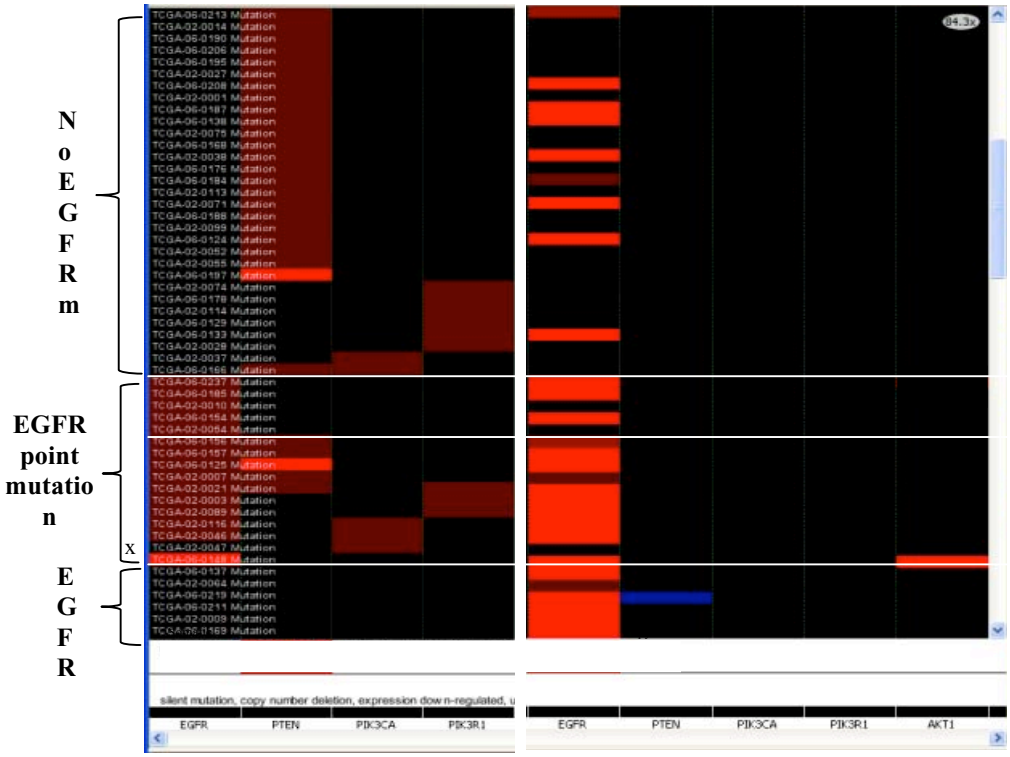
EGFR Pathway Mutation Profile Through CMA



Alterations in PI3K Pathway Through CMA



Somatic Mutations (L) and Copy Number (R) Shows Frequent Co-occurrence of EGFR Point Mutations with Other Genes in PI-3K Pathway but not the EGFR vIII Mutations



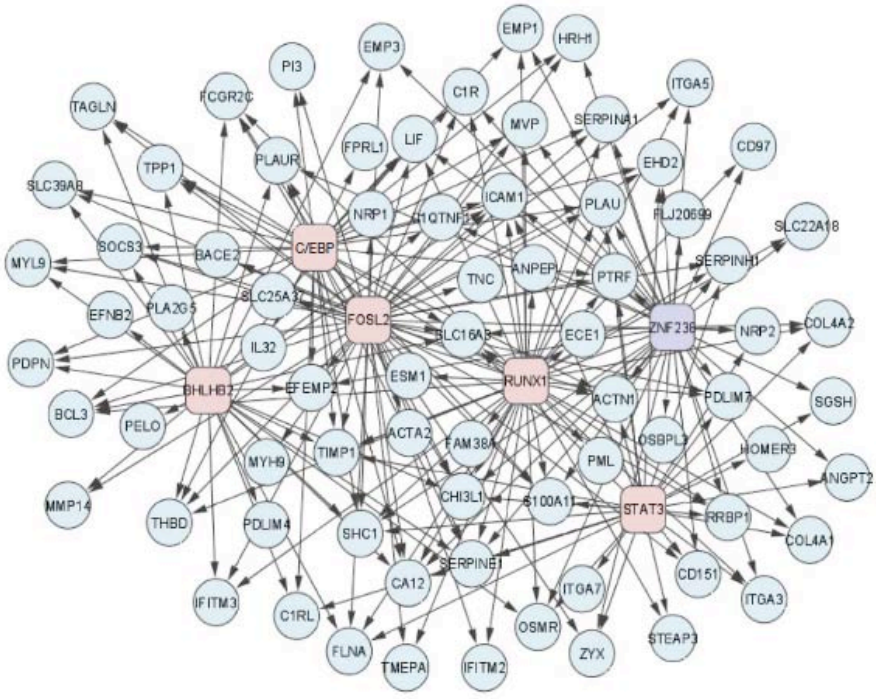
***In Silico* Hypotheses**

1) No P53 mutations were found in amplified samples with EGFRvIII while significant levels of P53 mutation were found in amplified samples with EGFR point mutations. Suggests alternative molecular etiologies.

1) EGFR point mutations co-exist with additional mutations in other genes involved in PI-3K pathway while EGFRvIII rarely have additional mutations in PI-3K pathway. This suggests the possibility of oncogene addiction in EGFRvIII tumors but not in tumors with EGFR point mutations even though both types of mutations target EGFR extracellular domains.

Case Study:
Identification of Transcriptional Networks in GBM

Identification of Transcriptional Networks in GBM

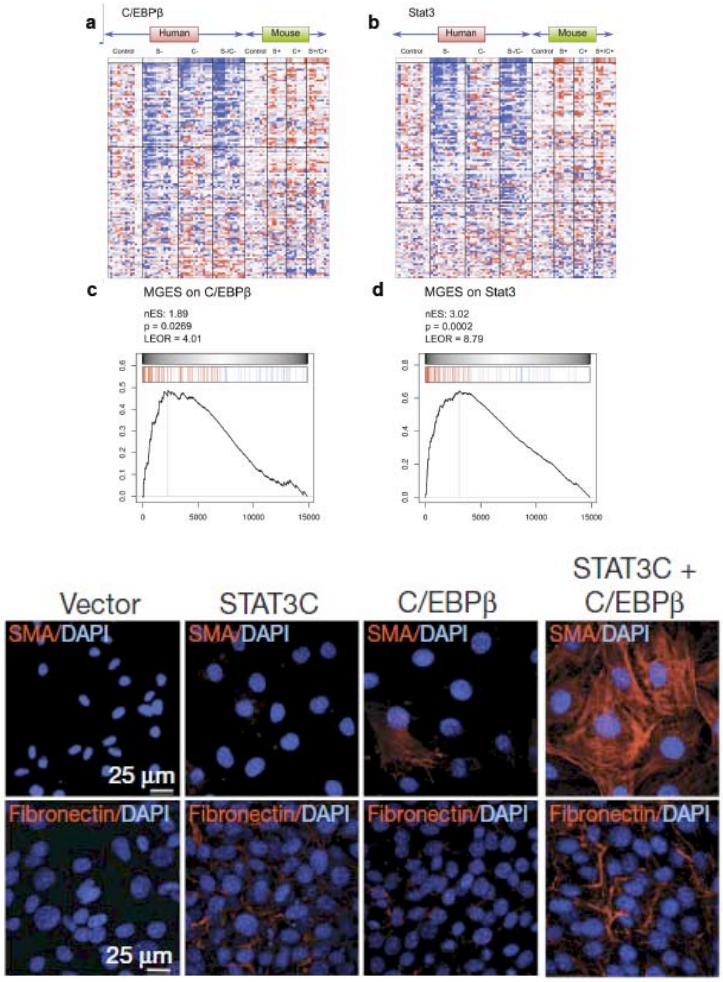


Carro, MS, et. al. The Transcriptional Network for Mesenchymal Transformation of Brain Tumors.
Nature 463:21, Jan 2010, 318-327.

- Gene expression profiles, comparative genomic hybridization, and copy number data collected by the TCGA program were subjected to integrated analysis
- More than 92K predicted glioma-specific transcriptional interactions were identified, 53 of which were specific to mesenchymal pathway genes

Identification of Transcriptional Networks in GBM

- Two genes, C/ERPβ and STAT3C, were specifically associated with activating genes in the mesenchymal pathway, with associated protein expression and phenotypic changes
- The group is part of the caBIG® *In Silico Research Centers* program from



Summary

- Effective translational research requires new ways to manage and integrate biomedical data and new ways to conduct collaborative research
- Interoperable IT frameworks enable the next wave of translational research
- Beginning in cancer, caBIG® is providing these interoperable IT frameworks that will lead to the development of a Learning Healthcare System

For more information, please visit:
http://caBIG.cancer.gov