

**BIMM 143**  
**Cancer Genomics & Immunoinformatics**  
**Lecture 18**  
**Barry Grant**  
UC San Diego  
<http://thegrantlab.org/bimm143>

## What is Cancer?

“Cancer is a name given to a collection of related diseases, where some of the body’s cells begin to divide without stopping and spread into surrounding tissue”

Source: <https://www.cancer.gov>

NIH-NCI

## Today's Menu

### Cancer Genomics

Brief review of cancer fundamentals,  
What is cancer and what causes it?

### Mining Cancer Genomic Data

**Hands-on analysis** to identify genomic changes in different cancers and identify new targets for therapy

### Cancer Immunotherapy

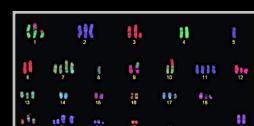
**Hands-on analysis** to design personalized cancer vaccines and harness the patient's own immune system to fight cancer

## Cancer is a disease of the Genome

- Caused by changes to genes that control the way our cells function, especially how they **grow and divide**.
- A major challenge in treating cancer is that every tumor is different: Each person's cancer has a unique combination of genetic changes (both “driver” & “passenger”).
- As the cancer continues to grow, additional changes will occur.



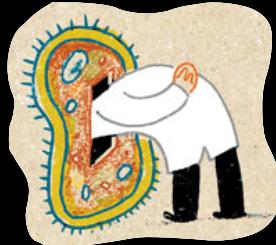
Healthy 46 chromosomes



Example cancer 59 chromosomes

## Goals of Cancer Genome Research

- Identify changes in the genomes of tumors that drive cancer progression
- Identify new targets for therapy
- Select drugs based on the genomics of the tumor
- Provide early cancer detection and treatment response monitoring
- Utilize cancer specific mutations to derive neoantigen immunotherapy approaches



## Finding Cancer Drivers



## Motivation for adopting a genomics approach...

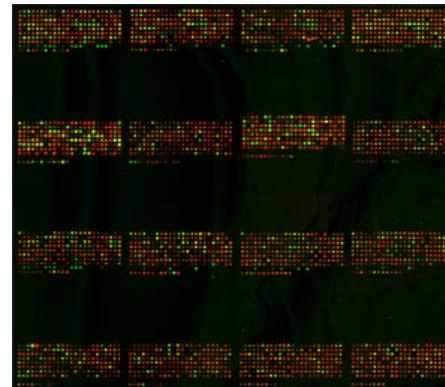
- Cancer is caused by mutations to specific genes
- Knowing which genes and proteins enables the development of **targeted treatments**
- 1st major Goal:  
**Define ALL cancer genes!**

AGCT → AGAT



## Use A Cancer Genomics Approach

### Arrays

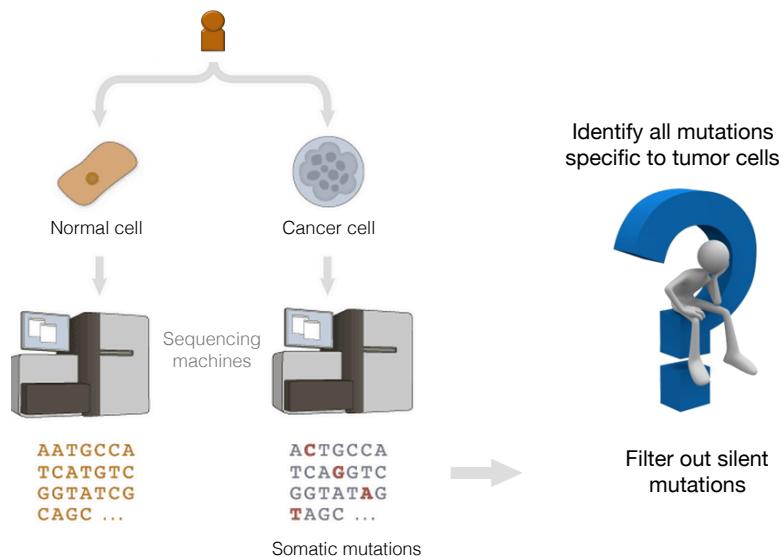


### Parallel Sequencing

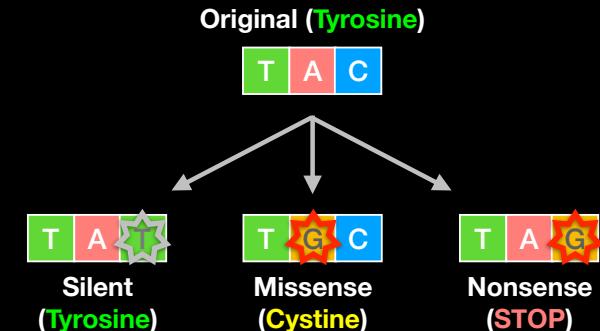


ACT CAGCCCAGGGAGGTTGAAGGACGTCTTCCCAGGGGCCGGTAGA  
AGC GCA GT CGGGGACGGGGATGAGCTCAGGGGCTCTAGAAAGATGTA  
GCTGGGACCTCGGGAAAGCCCTGGCCTCAGGTAGTCAGGAGACCTACT  
CAGGGTCGGGCTTGGGGAGGGAGGGAGGGCGGGGGAGGCAGCAGCAGGG  
GAC TGGACACTGGGAAGGGCTGGGAGCAGACGACCCGACCCCTAGAA  
GGTGGGGTGGGGAGAGCATGTGGACTAGGAGCTAACGCACAGCAGGACCC  
CAACGAGTTGTCACGTCAATTATCGAGCACCTACTGGGTGCCCCAGTG  
TCC TLAGATCTCCAATCTGGAGACGACGGGCAGCGACACGGTAGCTAG  
CGTCTGAT TGAGAACACTTAAATGAGACTGAATTAGCTCTATAATGAA  
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GCCGACCTGGGGATGGGAATAAGAAAGACGAGGGGGATTAAATAG  
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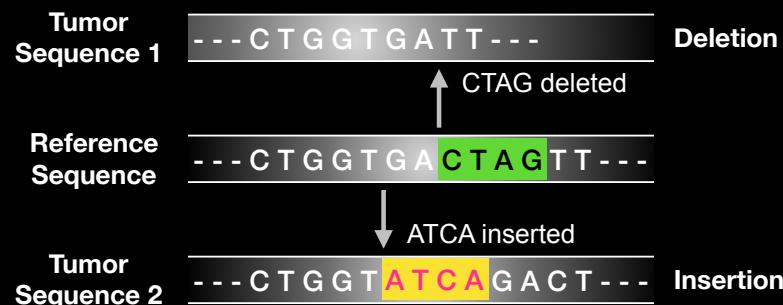
### Finding Cancer Associated Mutations



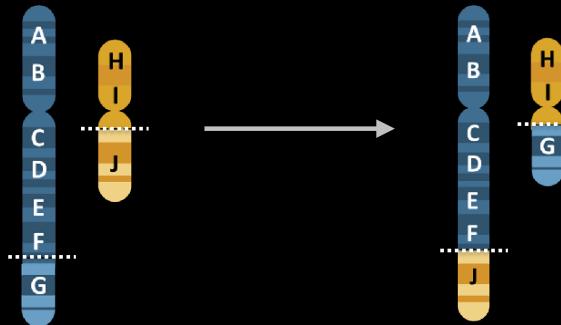
### Mutations detected: Point mutations



### Mutations detected: Indels



### Mutations detected: Translocations



# What can go wrong in cancer genomes?

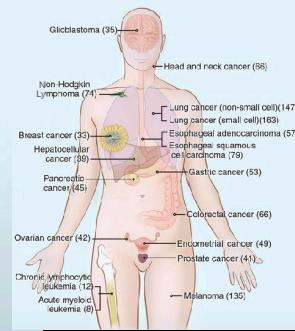
Type of change	Some common technology to study changes
DNA mutations	WGS, WXS
DNA structural variations	WGS
Copy number variation (CNV)	CGH array, SNP array, WGS
DNA methylation	Methylation array, RRBS, WGBS
mRNA expression changes	mRNA expression array, RNA-seq
miRNA expression changes	miRNA expression array, miRNA-seq
Protein expression	Protein arrays, mass spectrometry

WGS = whole genome sequencing, WXS = whole exome sequencing

RRBS = reduced representation bisulfite sequencing, WGBS = whole genome bisulfite sequencing

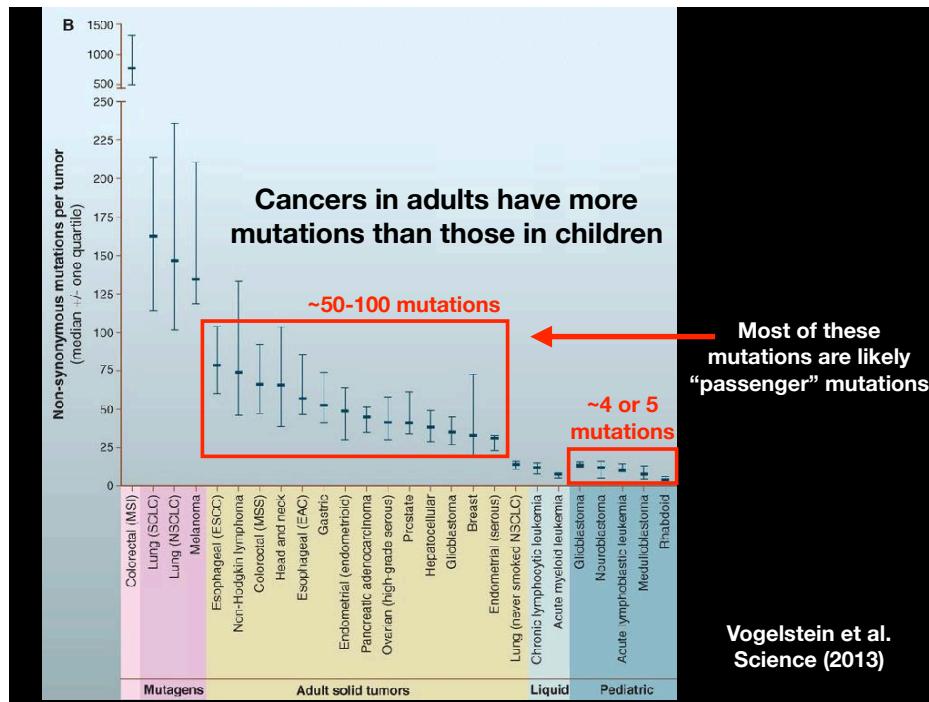
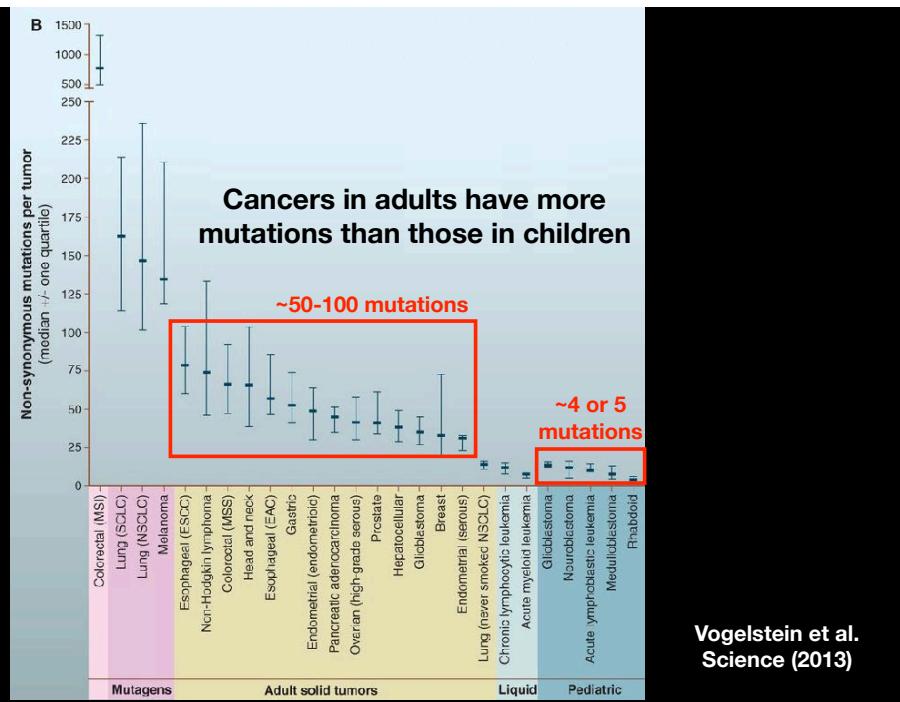
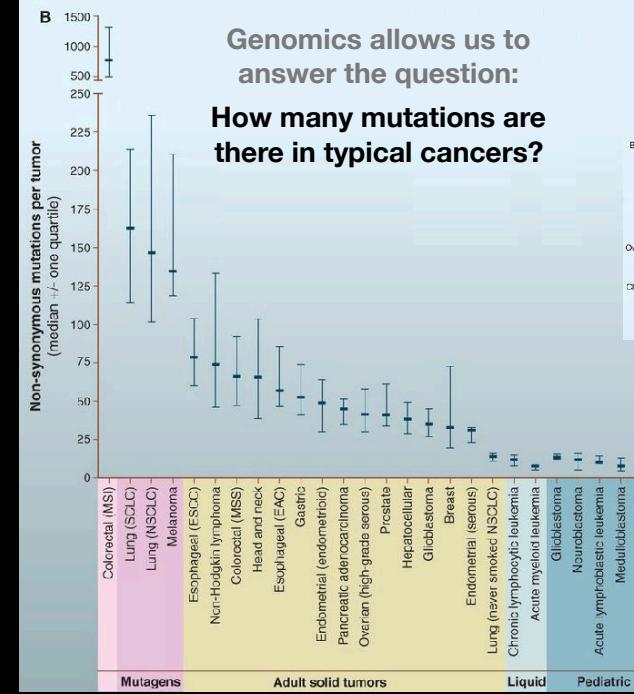
Genomics allows us to answer the question:

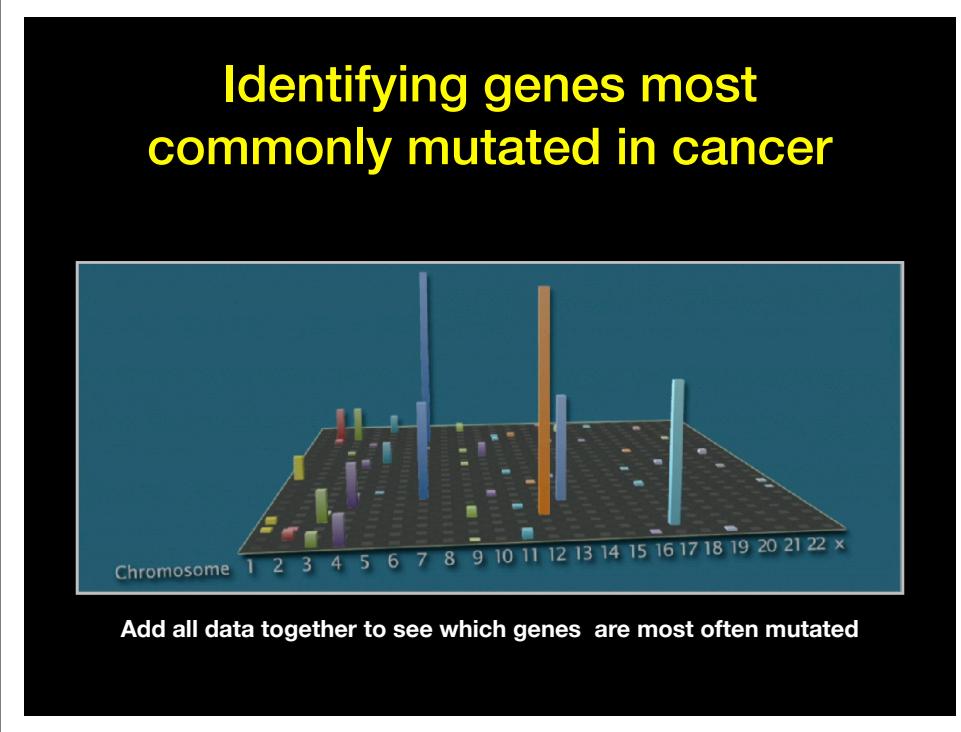
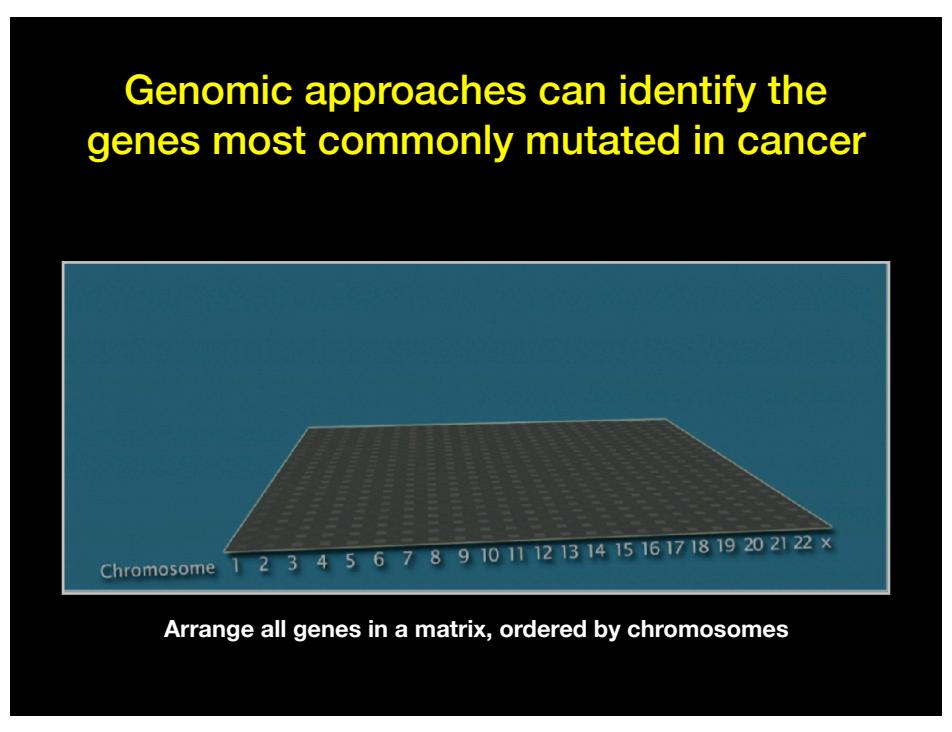
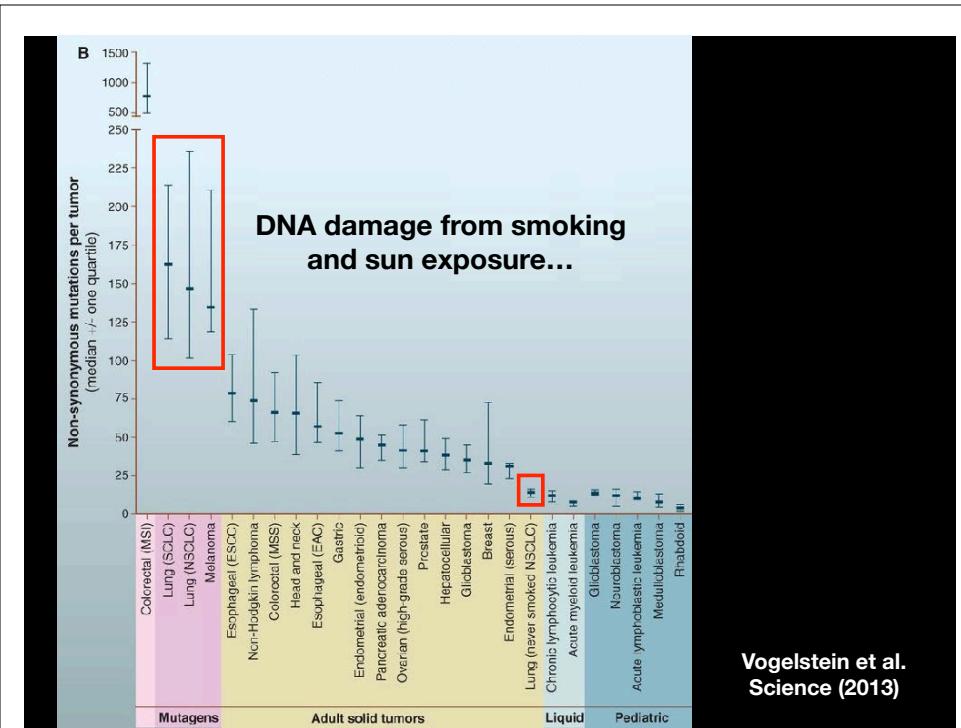
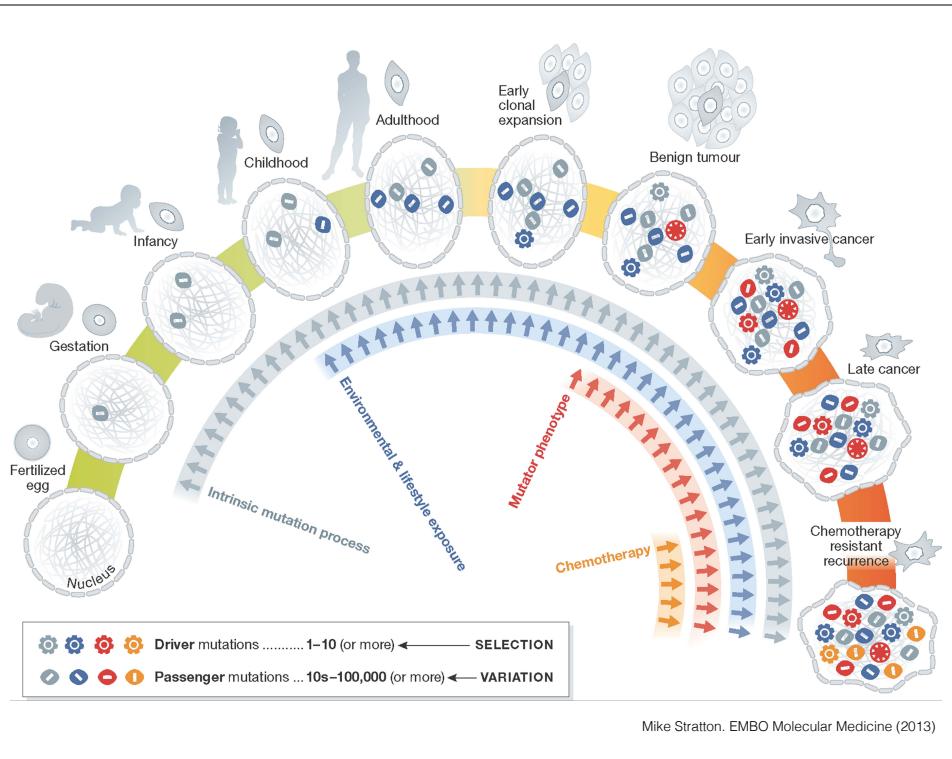
How many mutations are there in typical cancers?



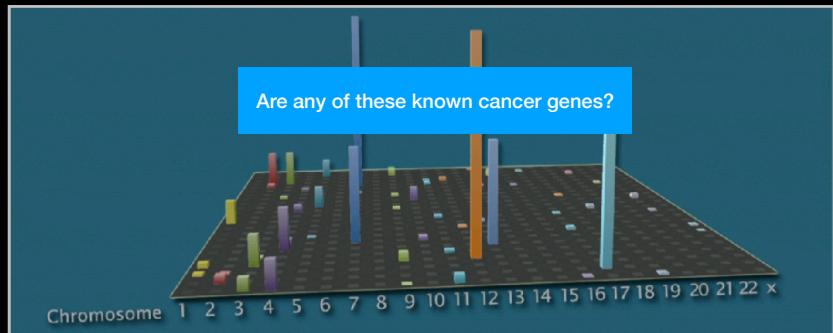
Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

Vogelstein et al.  
Science (2013)

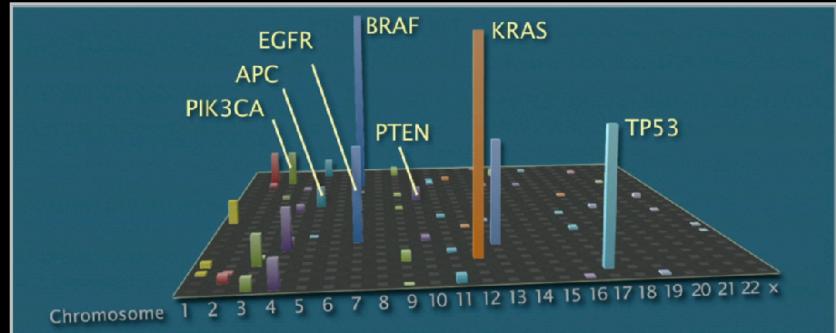




## Identifying genes most commonly mutated in cancer



## Identifying genes most commonly mutated in cancer



## Three Main Types of Cancer Genes:

- **Oncogenes**, such as **Ras**, normally function to accelerate cell division and growth. They can be mutated to act like stuck gas pedals.
- **Tumor suppressor genes**, such as **p53** normal act like breaks. Mutations can cause these breaks to fail.
- **DNA repair genes**, such as **BRCA1 & 2**, normally function to fix minor damage to DNA when it replicates. When these genes are mutated, DNA damage can accumulate and lead to cancer.

## Functions of the 140 cancer genes

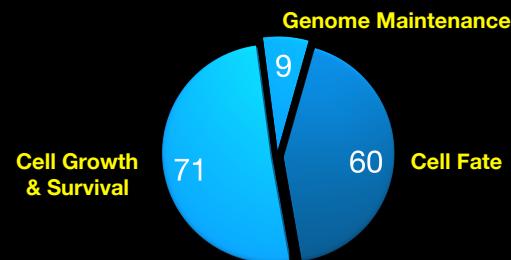
Current genomics approaches have identified ~140 cancer genes. Of which there are:

- ~60 **Oncogenes** (normally stimulate growth)
- ~80 **Suppressor genes** (normally inhibit growth)

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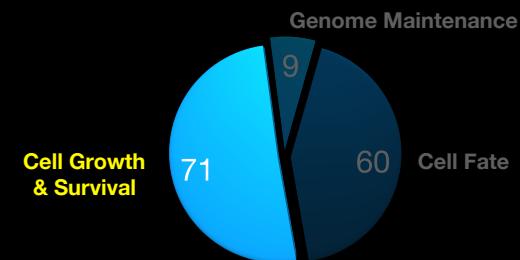
Three main categories



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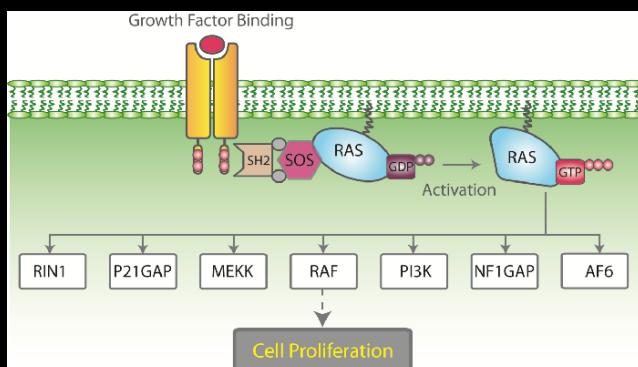
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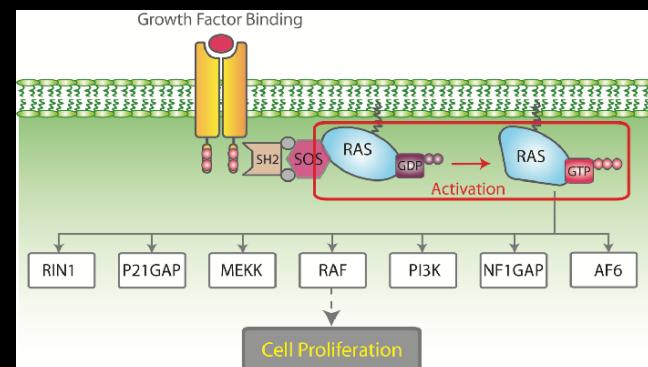
## Cell growth and survival genes

Many participate in signaling pathways that promote cell proliferation  
(E.G. EGFR, Ras, BRAF, MEK etc.)

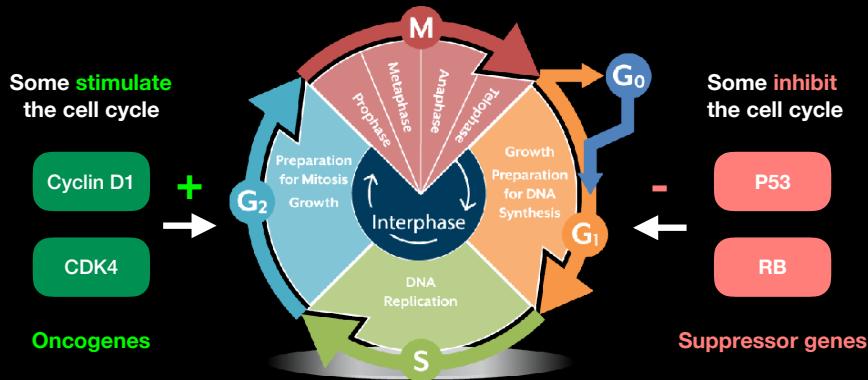


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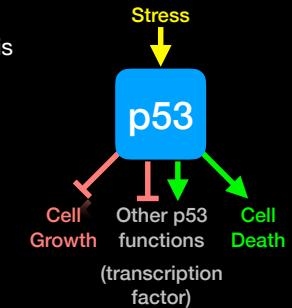
## Regulators of Cell Cycle and Cell Death



## p53 Regulates Cell Division

Probably the most famous cancer gene that is mutated in about half of all tumors. Often called the '*guardian of the genome*'

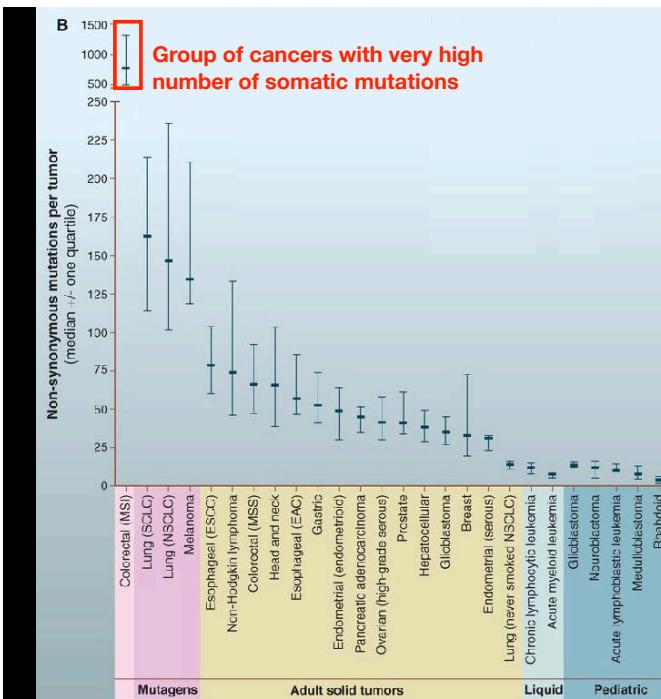
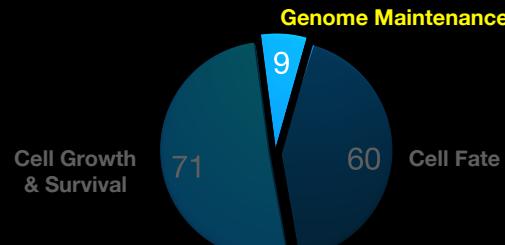
- p53 normally shuts down cell division when a cell is stressed (e.g. by DNA damage)
- When DNA is damaged, p53 activates genes that stop cell growth or trigger the cell to die.
- Thus, p53 guards against changes to cells that might lead to tumor formation.
- It appears necessary to inactivate p53 to develop many forms of cancer.



## Functions of the 140 cancer genes

Current genomics approaches have identified ~140 cancer genes. Of which there are:

Three main categories



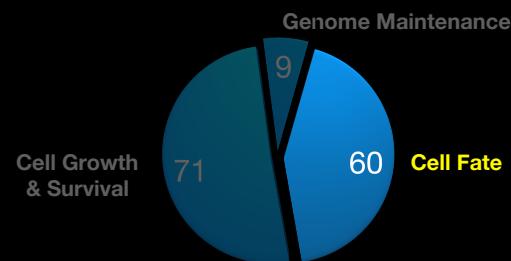
Linked to mutations in DNA repair genes.

Vogelstein et al.  
Science (2013)

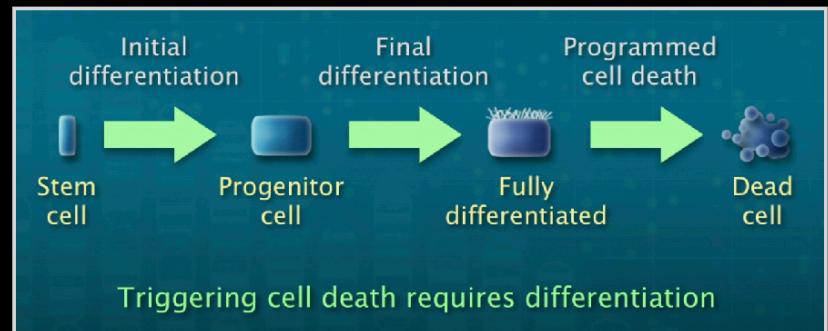
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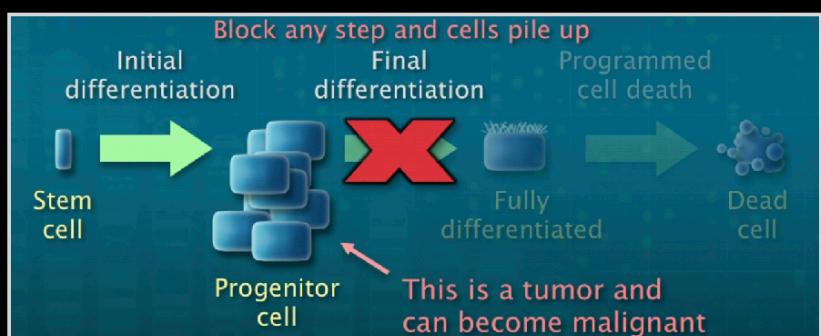
Three main categories



## How Can Mutations in Cell Fate Genes Cause Cancer?



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Disrupting the normal processes of differentiation and maturation of the intestinal epithelial cells can lead to cancer.



Clevers Lab|Digizyme

[http://molecularmovies.com/movies/kellermcgill\\_clonalconveyorbelt.mov](http://molecularmovies.com/movies/kellermcgill_clonalconveyorbelt.mov)

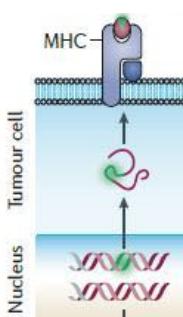
# Hands-on time!

[https://bioboot.github.io/bimm143\\_W18/lectures/#18](https://bioboot.github.io/bimm143_W18/lectures/#18)

**Part 1 Only Please**

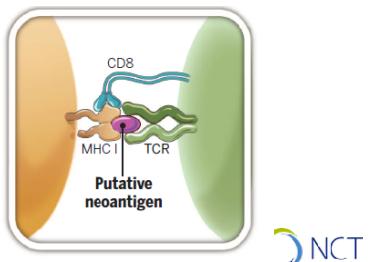
## Neoepitopes (Neoantigens)

- Cancers genomes accumulate mutations
- Mutations in coding regions are translated in mutated protein sequences
- Mutated peptides can be presented as epitopes on MHC to T cells



**Neoepitopes** are presumably recognized by tumor-infiltrating lymphocytes (**TILs**)

**Neoepitopes** are highly tumor-specific!

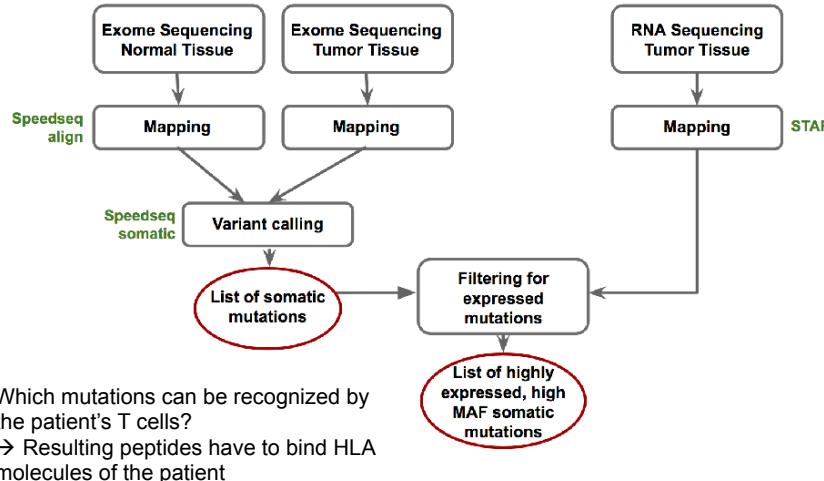


# Cancer Immunotherapy

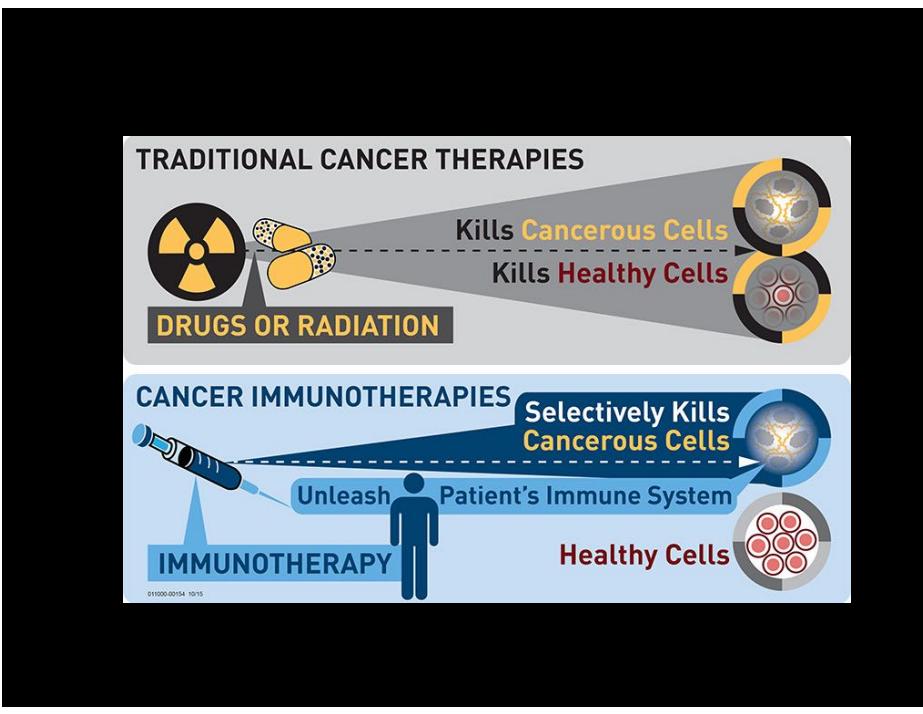
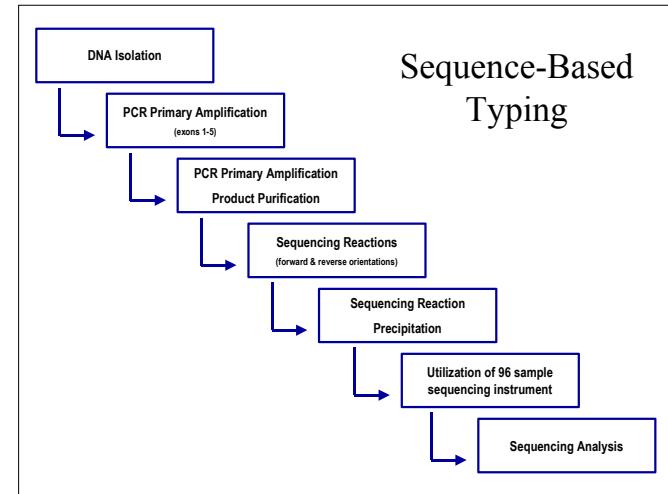
## Cancer Immunotherapy

- Vaccination: Introduce or boost an immune response against a specific target (antigen)
- Cancer cells contain non-self antigens that *could* be recognized by T cells, but presence of cancer means this mechanism has failed, typically by the tumor suppressing immune responses
- Checkpoint blockade treatments: Block immune suppressive mechanisms to boost T cell immune responses against cancer cells.
- Problem: Checkpoint blockade is unspecific, and will also boost unwanted autoimmune responses
- Personalized Cancer Immunotherapy: Boost anti-tumor response with vaccine containing peptides corresponding to cancer mutations that can be recognized by T cells.  
→ How can such a vaccine be designed?

## DNA and RNA sequencing identifies tumor specific somatic mutations



## HLA Typing: Targeted sequencing of HLA locus



## Hands-on time!

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**Part 2**