

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

# 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

## Towards personalized cancer treatments

Recap on how the immune system normally detects cancer cells and how we can predict mutations that can be recognized by T cells

## Cancer Immunoinformatics

**Hands-on analysis** to design personalized cancer vaccines

# 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>

It is estimated that cancer will strike 40% of people at some point in their lifetime with frequently devastating effects.

# 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”

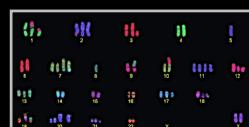
Source: <https://www.cancer.gov>

## 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.



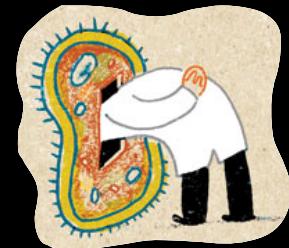
Healthy 46 chromosomes



Example cancer 59 chromosomes

## Goals of Cancer Genome Research

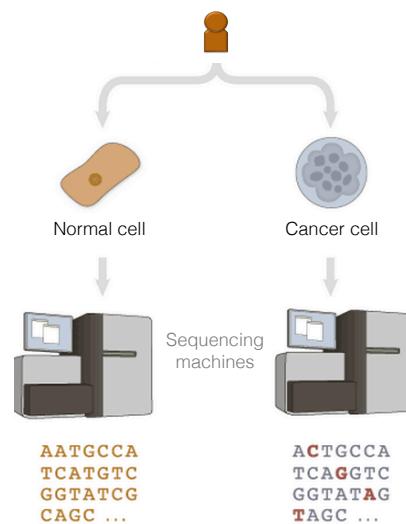
- Identify changes in the genomes of tumors that drive cancer progression
- Identify new targets for therapy
- Select drugs based on the genomics of the tumor
- Provide early cancer detection and treatment response monitoring
- Utilize cancer specific mutations to derive neoantigen immunotherapy approaches



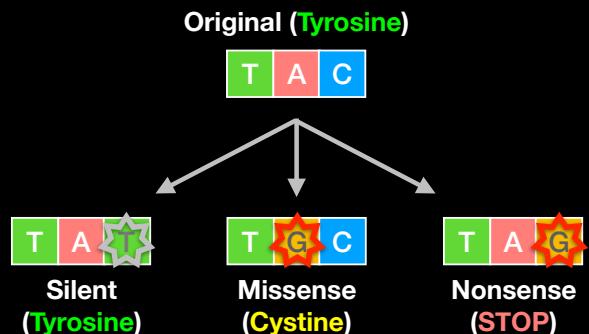
## Finding Cancer Drivers



## Finding Cancer Associated Mutations



## Mutations detected: Point mutations



## Mutations detected: Indels

Reference Sequence: - - C T G G T G A C T A G T T - -

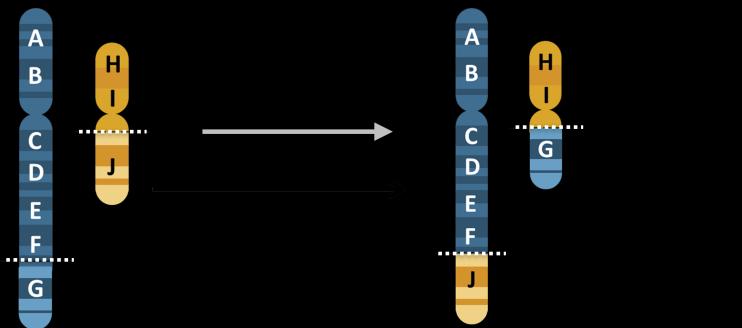
## Mutations detected: Indels

Tumor Sequence 1: - - C T G G T G A T T - -  
                            ↑ CTAG deleted  
Reference Sequence: - - C T G G T G A C T A G T T - -

## Mutations detected: Indels

Tumor Sequence 1: - - C T G G T G A T T - -  
                            ↑ CTAG deleted  
Reference Sequence: - - C T G G T G A C T A G T T - -  
Tumor Sequence 2: - - C T G G T A T C A G A C T - -  
                            ↓ ATCA inserted  
                            Insertion

# Mutations detected: Translocations



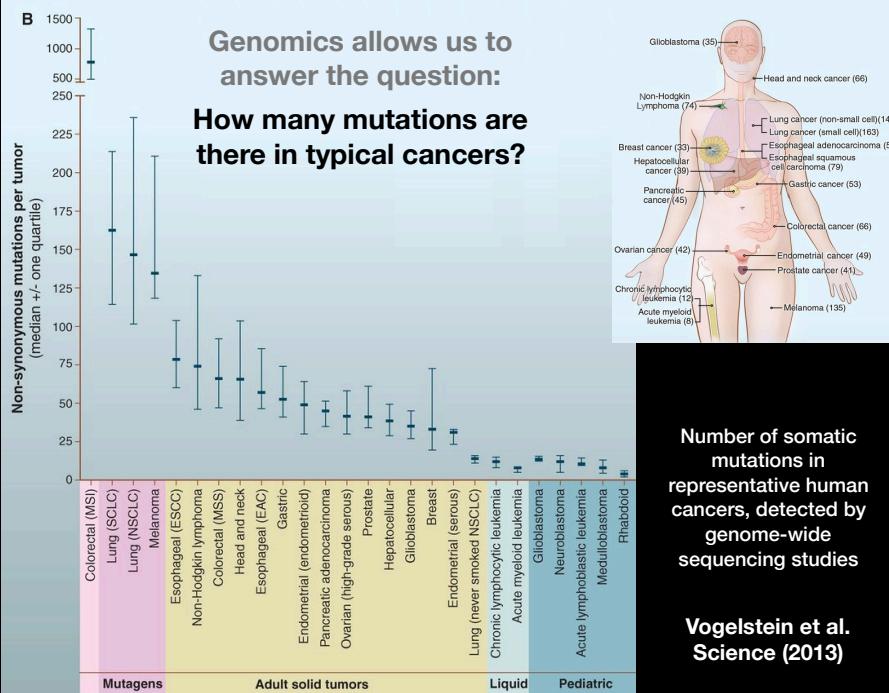
## What can go wrong in cancer genomes?

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

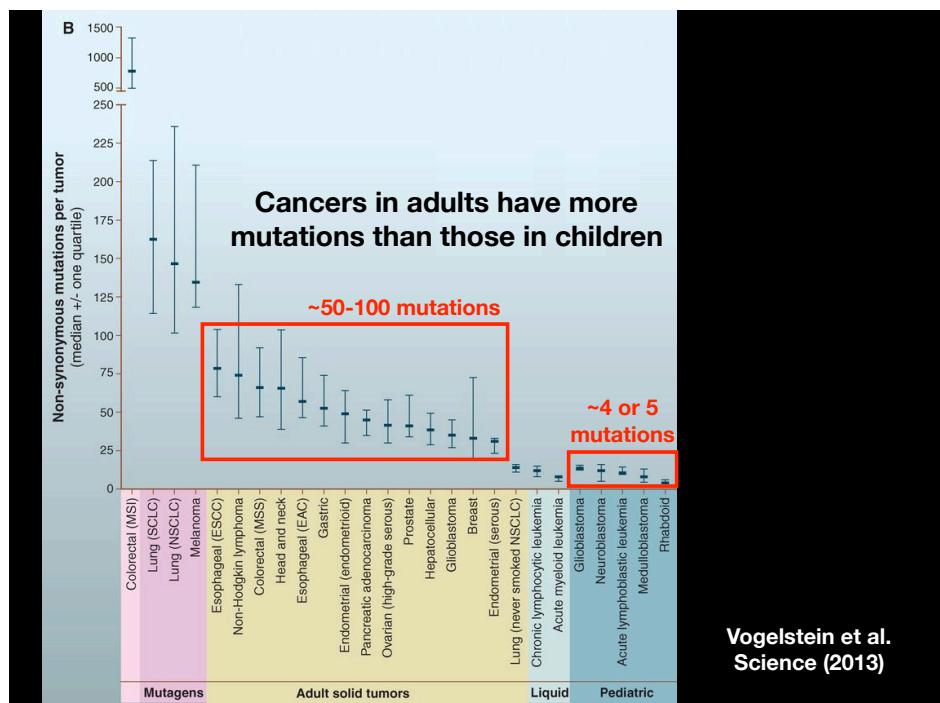
WGS = whole genome sequencing, WXS = whole exome sequencing

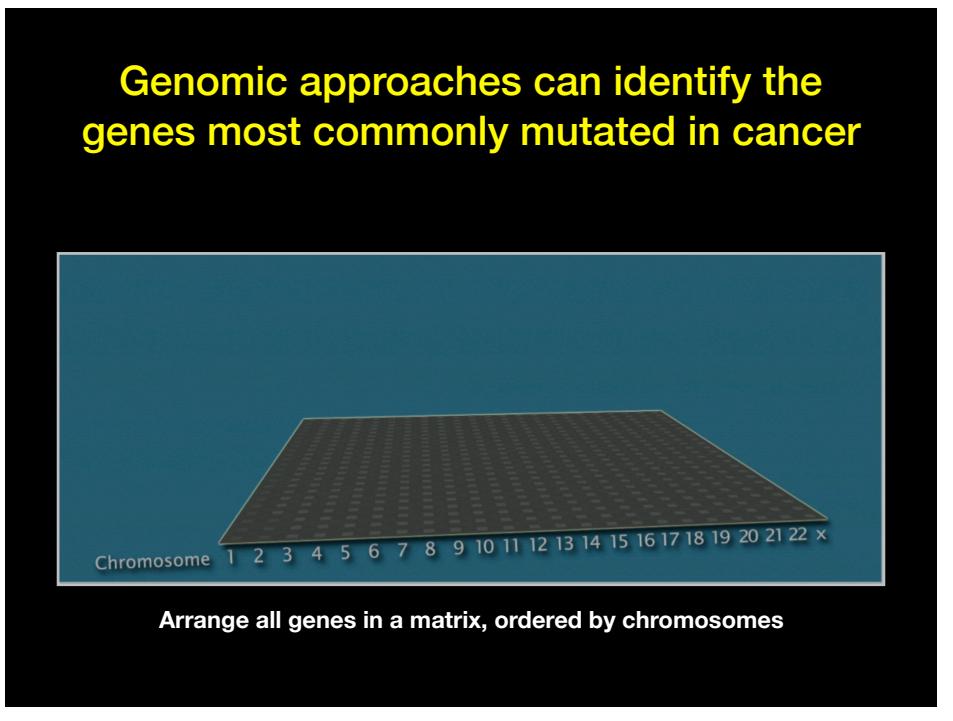
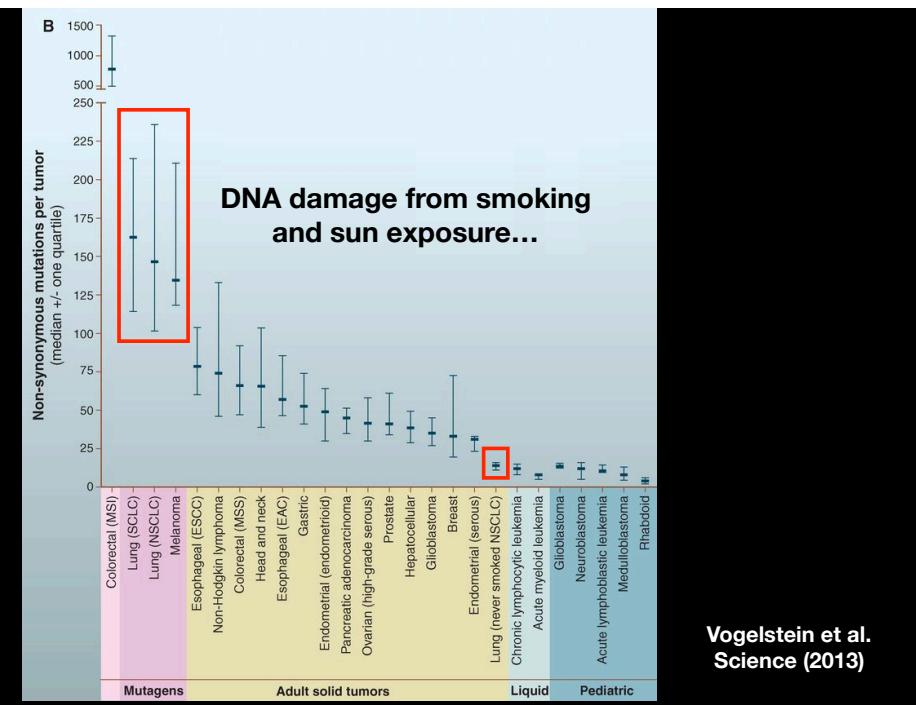
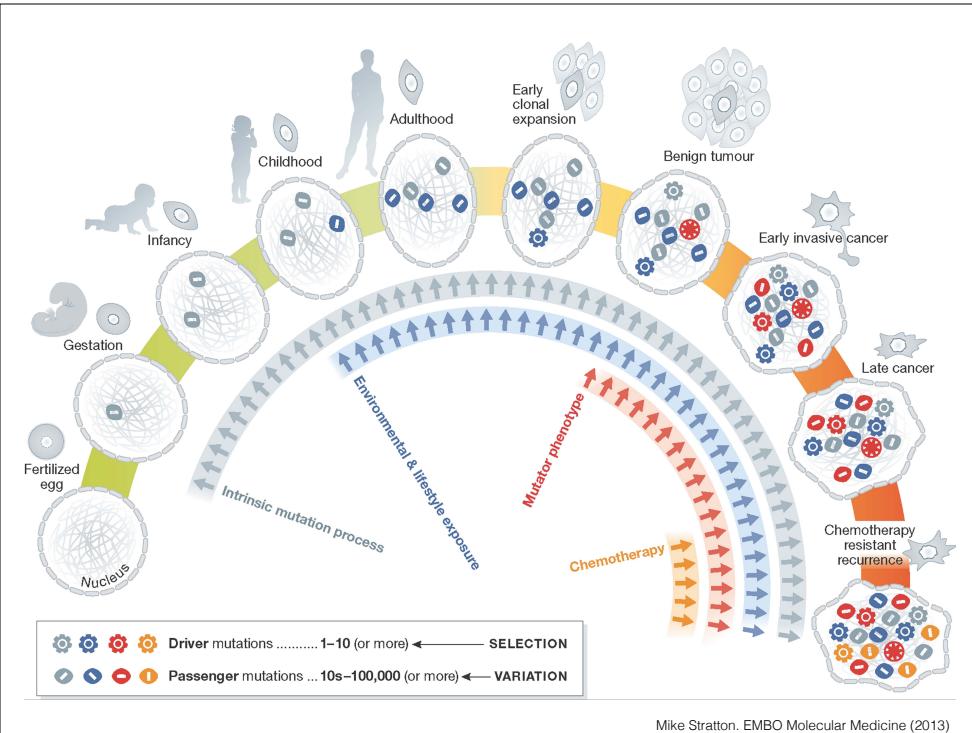
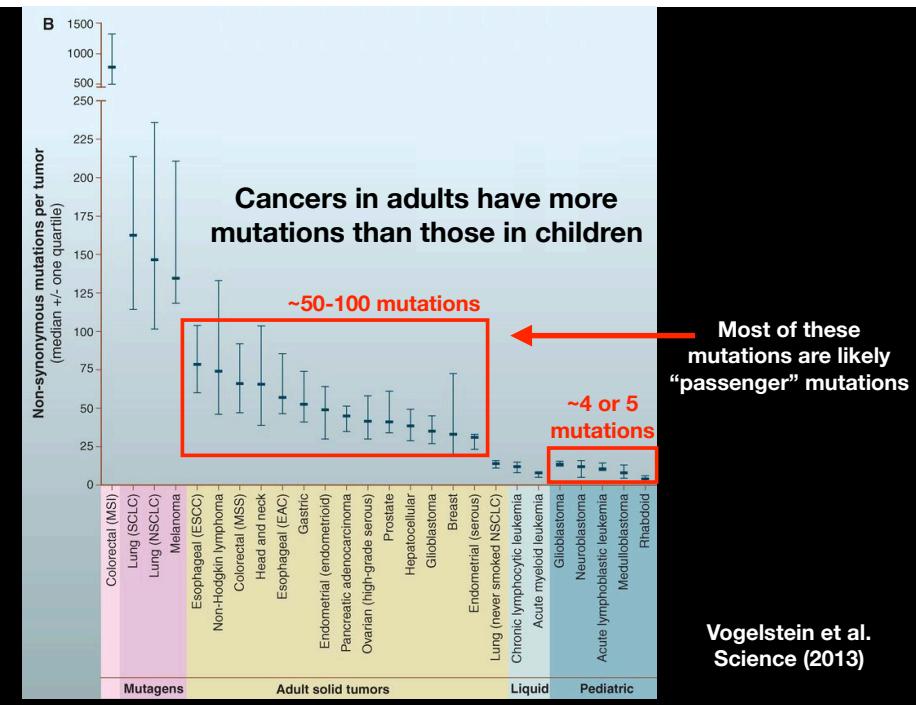
RRBS = reduced representation bisulfite sequencing, WGBS = whole genome bisulfite sequencing

Genomics allows us to answer the question:  
How many mutations are there in typical cancers?

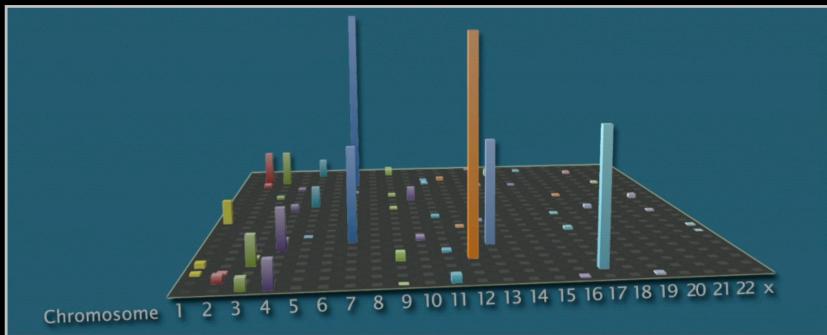


Cancers in adults have more mutations than those in children

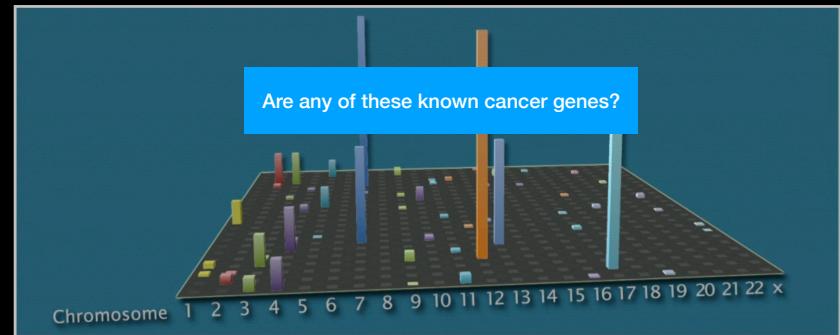




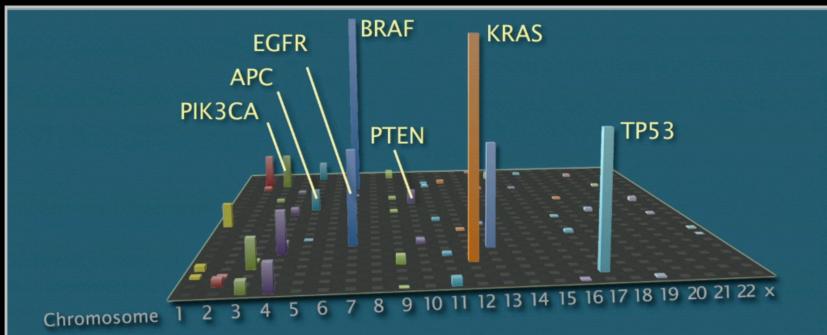
## Identifying genes most commonly mutated in cancer



## Identifying genes most commonly mutated in cancer



## Identifying genes most commonly mutated in cancer

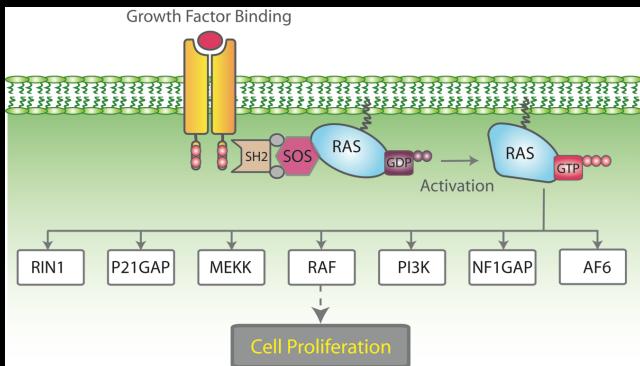


## Three Main Types of Cancer Genes:

- **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.

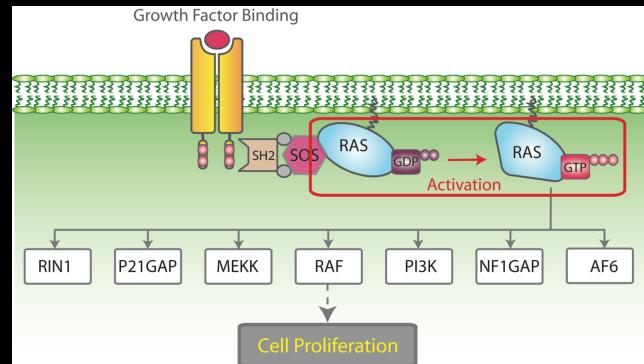
## Cell growth and survival genes

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

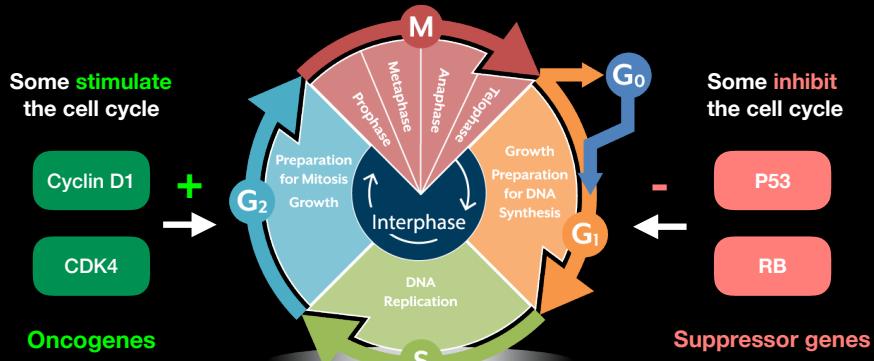


## Cell growth and survival genes

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



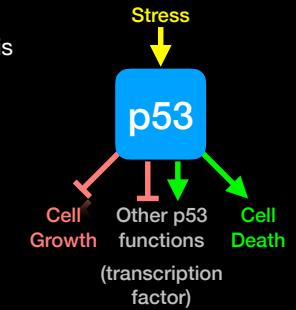
## Regulators of Cell Cycle and Cell Death



## 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.



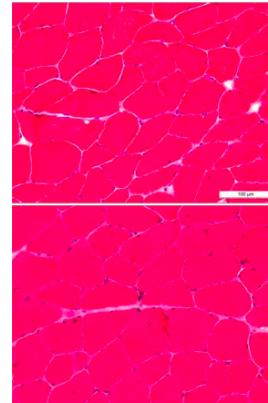
Do it Yourself!

# Hands-on time!

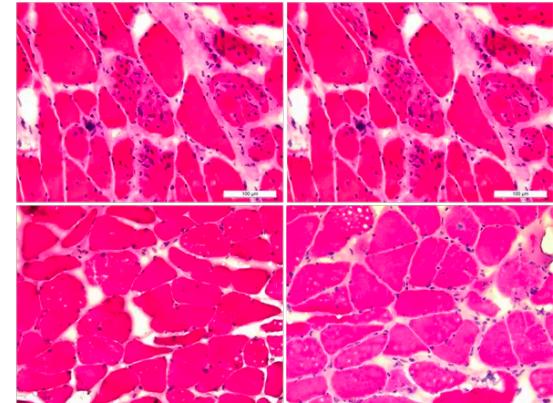
[https://bioboot.github.io/bimm143\\_W19/lectures/#17](https://bioboot.github.io/bimm143_W19/lectures/#17)

**Part 1 Only Please**

## Control



## Pancreatic Cancer



Representative H&E micrographs of rectus abdominis biopsies are displayed for two patients without cancer (left) and four patients with pancreatic cancer (right)

# Today's Menu

Next Up:

## 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

## Towards personalized cancer treatments

Recap on how the immune system normally detects cancer cells and how we can predict mutations that can be recognized by T cells

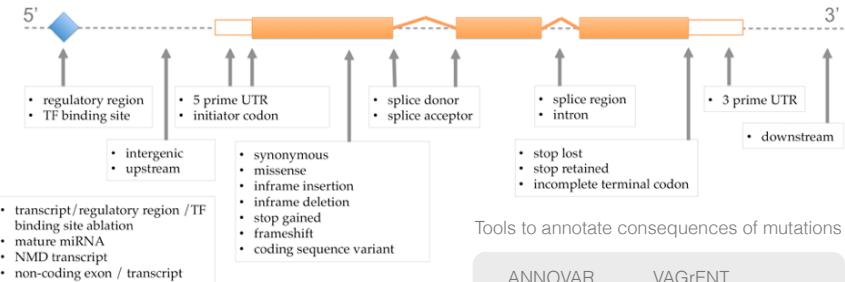
## Cancer Immunoinformatics

**Hands-on analysis** to design personalized cancer vaccines

## 1. Predict consequences of mutations

ACTGCCTACGTCTCACCGTCGACTTCAATCGCTTAACCGTACTCCCATGCTACTGCATCTCGGGTTAACTC  
GACGTTTTTTCATGCATGTGCACCCCAATATATATGCAACTTTGTGCACCTCTGTCACCGCGAGTTGCA  
CTGTCGCCCCCTGTGCATGTGCACTGTCTTCGCTGACTGCCTACGTCACCGTCGACTCAAATCGTT  
AACCGTACTCCCATGCTACTGCATCTCGGGTTAACCGTACGAGTTTGCACTGTCATGTGCAACCCAATATA  
TGCAACTTTGTGCACCTCTGTACCGCGAGTTGGCACTGTCGCCCTGTGTGCATGTGCACTGTCTCTCGA

Map mutations into genome annotations to predict its possible effect

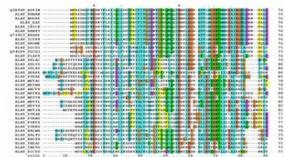


## 2. Assess the functional impact of nsSNVs

nsSNVs = non-synonymous Single Nucleotide Variant (missense)

ATC GAA GCA CGT  
Met Glu Ala Gly

ATC GAC GCA CGT  
Met **Asp** Ala Gly



Computational methods to assess the functional impact of nsSNVs

MutationTaster	LogRe	MutPred	SNPs&GO
CanPredict	Condel	CHASM	SNPeffect
SIFT	PolyPhen2	MutationAssessor	PMut

## 3. Identify cancer drivers from somatic mutations



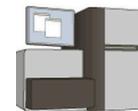
Patient cohort



Normal cell



Cancer cell



Sequencing machines



A**T**ATGCCA  
TC**A**TGTC  
GGT**A**TCG  
CAGC ...

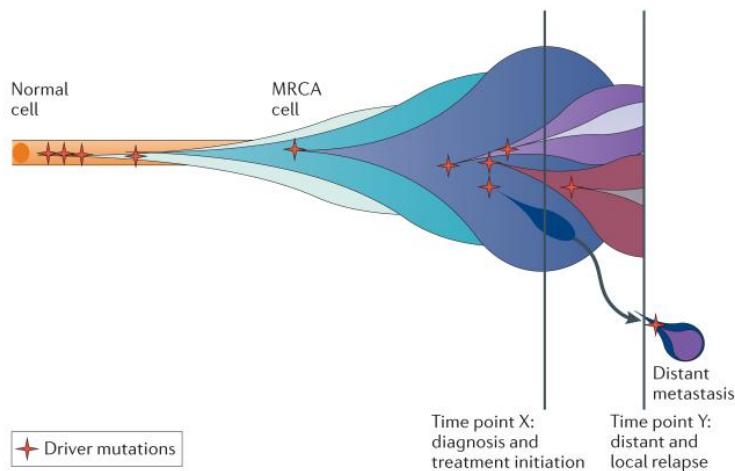
Somatic mutations



Which mutations are cancer drivers?

Find signals of selection across tumors

## Cancer is an evolutionary process



Yates and Campbell et al, Nat Rev Genet 2012

## How to differentiate drivers from passengers?

```
ACTGCCTACGCTCACCGTCGACTTCAAATCGCTTAACCGTACTCCCATGCTACTGC
ATCTCGGGTTAACCGACGTTTTTCATGCATGTGTCACCCCAATATATATGCAACT
TTGTGCACCTCTGTACCGCGAGTTGGCAGTGTGCCCCCTGTGTCATGTGCACT
CTCTCGCTGCACTGCCAACGCTACGTCTACCGTCGACTCAATCTAACCGTACTCCC
ATGCTACTGCACTCGGGTTAACCGACGTTTTGCATGCATGTGTCACCCCAATA
TATGCAACTTTTGTCACCTCTGTACCGCGAGTTGGCAGTGTGCCCCCTGTGCA
TGTGCACTGTCTTCGAGTTTGCATGCATGTGCACTGTGACCTCTGTACGTCT
```

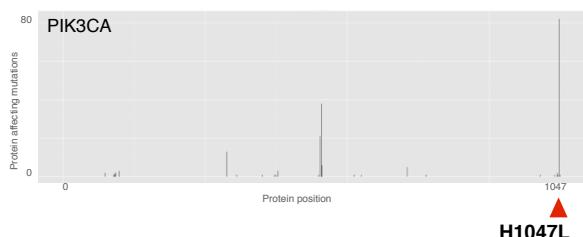
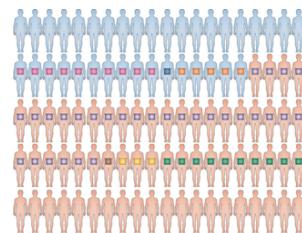


## How to differentiate drivers from passengers?

ACTG**C**CTACGTCTACCGTCGACTTCAAATCG**C**TTAACCCGACTCCCAGTGCAGTGC  
ATCTCGGGTTAACTCGACGTTTCATGCATGTGCAACCCAAATATATATGCA**A**CTT  
TTGTCACCTCTGTCACGCCAGTTGGCAGTGTGCACTGTCGCCCTGTGCAATGTGCACTGT  
CTC**T**CGCTGCACTGCCTACCGTCAACCGTCAACT**C**TTAACCCGACTCCC  
ATGCTACTGCACTCGGGTTAACTCGACGTTTG**C**ATGCATGTGCAACCCAAATA  
TATGCA**A**CTTTGTCACCTCTGTCACGCCAGTTGGCACTGTGCAACCTGTGCA  
TGTGCACTGTCT**T**CGAGTTTG**C**ATGCATGTGCACTGTGCAACCTGTGCA



Find signals of positive selection across tumour re-sequenced genomes

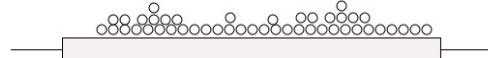


PIK3CA is recurrently mutated in the same residue in breast tumours

## Signals of positive selection

Recurrence

**MuSiC-SMG / MutSigCV**

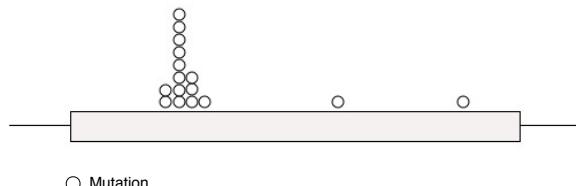


○ Mutation

Identify genes mutated more frequently than background mutation rate

Mutation clustering

**OncodriveCLUST**



○ Mutation

<http://www.intogen.org/mutations/analysis>

### IntOGen Mutations Analysis

Download

To interpret catalogs of cancer somatic mutations.

#### Cohort analysis

Use this if you have a list of somatic mutations for a cohort of tumors and want to identify driver mutations, genes and pathways.

View an example

Analyse your data

#### Single tumor analysis

Use this if you have a list of somatic mutations for a single tumor and want to rank them based on their implication in cancer development.

View an example

Analyse your data