The Human Genome: Similarities and Differences among Individuals

Human genome size:

♀ 3,117,838,593 base pairs (6 feet)

23 Chromosomes

19-20,000 protein-coding genes

Different individuals:

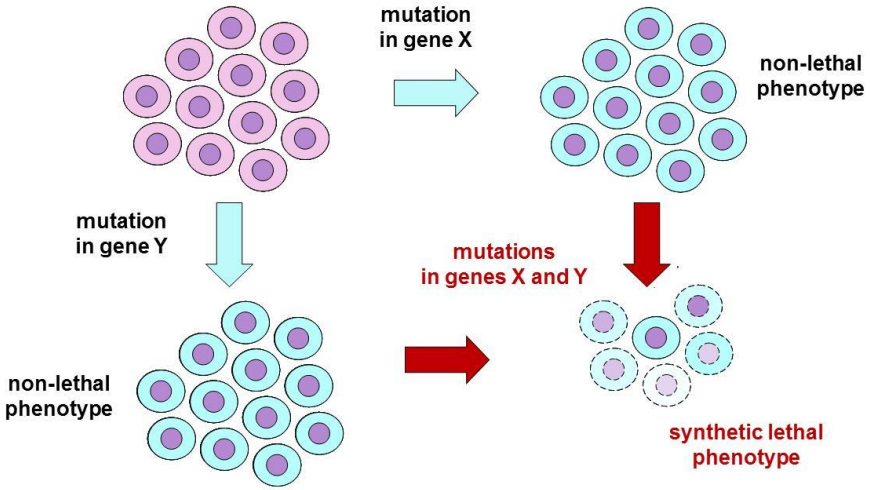
99.9% identical

1 in every 1000 base-pairs are different (>3,000,000 differences between Individuals)

Synthetic Lethality as a Paradigm for "Targeted" Therapy of Cancer

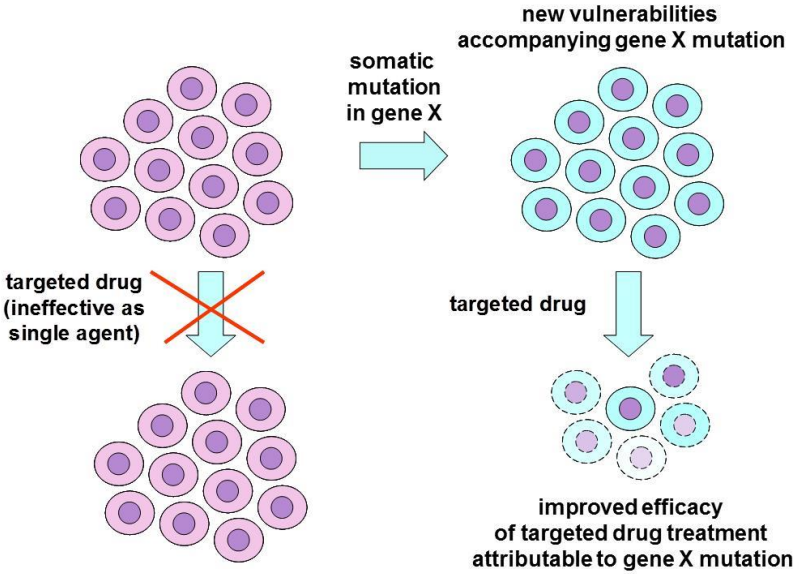
Synthetic Lethality:

Two otherwise non-lethal mutations confer a lethal phenotype in combination



Targeted Therapy:

Targeted drug, otherwise harmless, kills cancer cells with somatic mutation



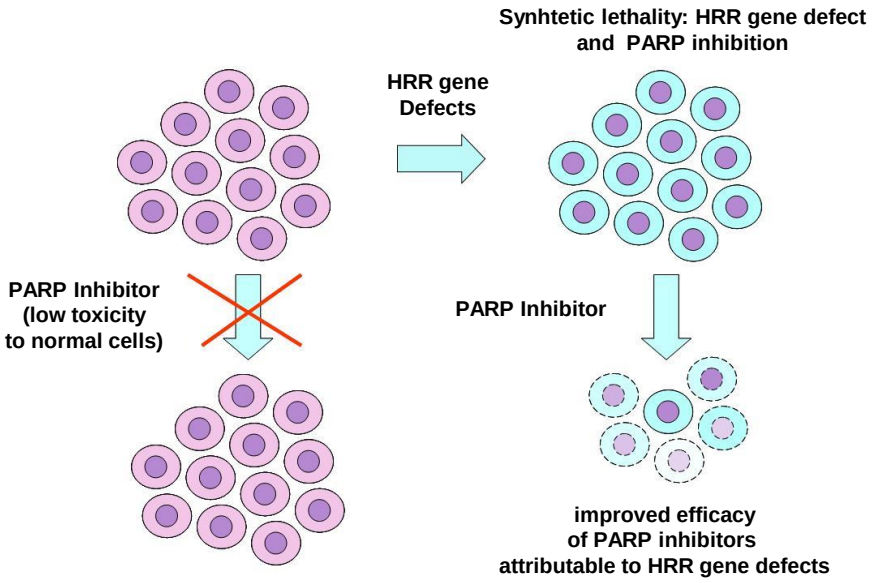
Somatic Gene Defects in Prostate Cancers*

	Genetic
Number of somatic alterations in each cancer case	Mutations: 3,866 (range 3,192-5,865) Rearrangements: 108 (range 13-43)
Number of alterations that are "drivers" versus "passengers"	20 (<1%)
Heterogeneity in somatic changes	Mutations: Cell-to-cell: High Lesion-to-lesion: High Case-to-case: High Other Defects: Cell-to-cell: High Lesion-to-lesion: High Case-to-case: High
Rate of accumulation in cancer cells	10^{-9}/cell each division or higher
Number of alterations that can be therapeutically targeted	1-3

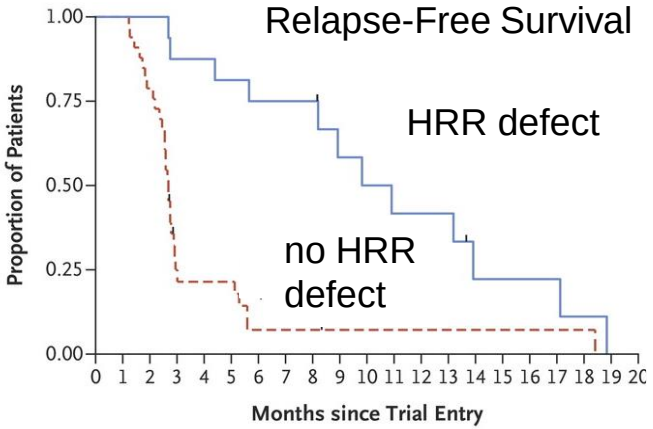
* Berger MF *et al.* Nature *470:* 214-20 (2011)

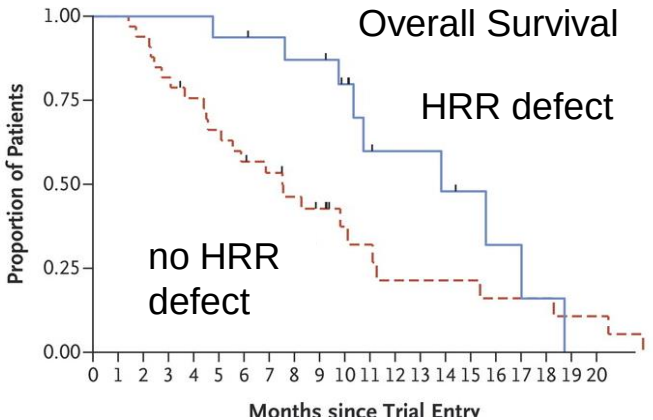
Defects in Homologous Recombination Repair Genes (*eg. BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *FANCA*) and Olaparib in Castration-Resistant Prostate Cancer

Homologous Recombination Repair (HRR) Gene Defects in Prostate Cancer and Vulnerability to Poly(ADP-ribose) polymerase (PARP) inhibitors



Olaparib and HRR Gene Defects





*Mateo J *et al.* N Engl J Med *373:* 1697-1708 (2015)

Somatic Gene Defects in Prostate Cancers*

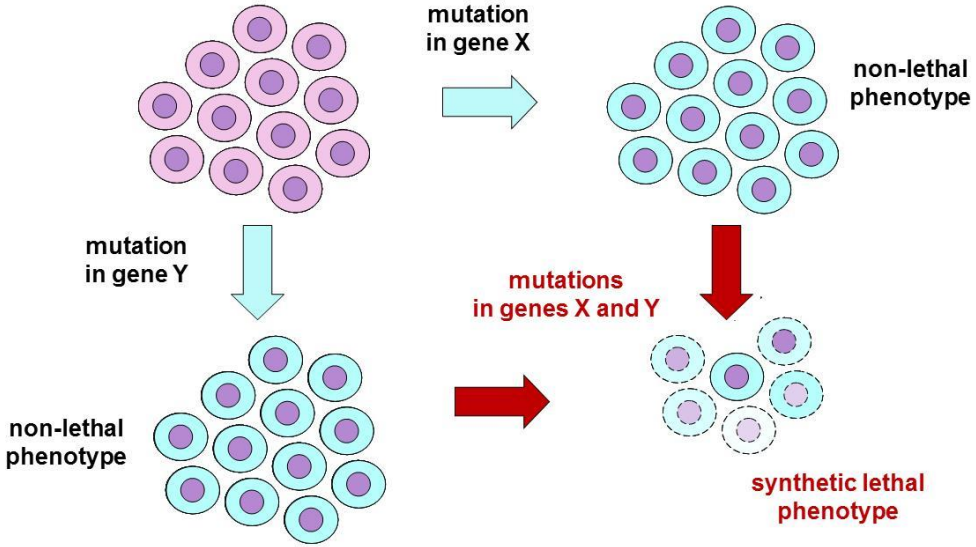
	Genetic	Epigenetic
Number of somatic alterations in each cancer case	Mutations: 3,866 (range 3,192-5,865) Rearrangements: 108 (range 13-43)	Hypermethylation: 5,408 regions
Number of alterations that are "drivers" versus "passengers"	20 (<1%)	Majority or all
Heterogeneity in somatic changes	Mutations: Cell-to-cell: High Lesion-to-lesion: High Case-to-case: High Other Defects: Cell-to-cell: High Lesion-to-lesion: High Case-to-case: High	Hypermethylation: Cell-to-cell: Low Lesion-to-lesion: Low Case-to-case: Medium Hypomethylation: Cell-to-cell: High Lesion-to-lesion: High Case-to-case: High
Rate of accumulation in cancer cells	10^{-9}/cell each division or higher	Unknown
Number of alterations that can be therapeutically targeted	1-3	Many if not all?

* Berger MF *et al.* Nature *470:* 214-20 (2011); Yegnasubramanian S *et al.* BMC Genomics *12:* 213 (2011)

Epigenetic Drugs Modulate Activities of Targeted Drugs to Create Induced Synthetic Lethality (ISLET) in Cancer Cells

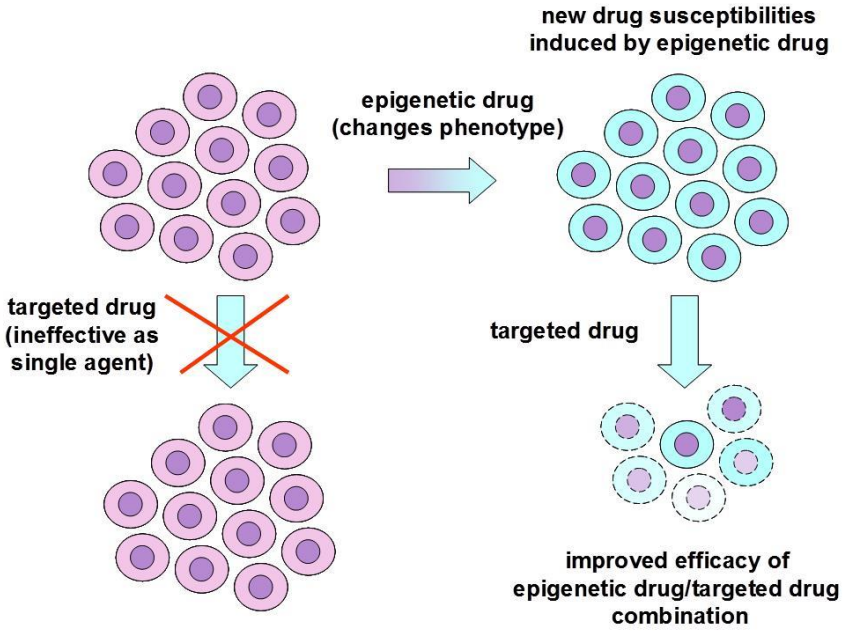
Synthetic Lethality:

Two otherwise non-lethal mutations confer a lethal phenotype in combination



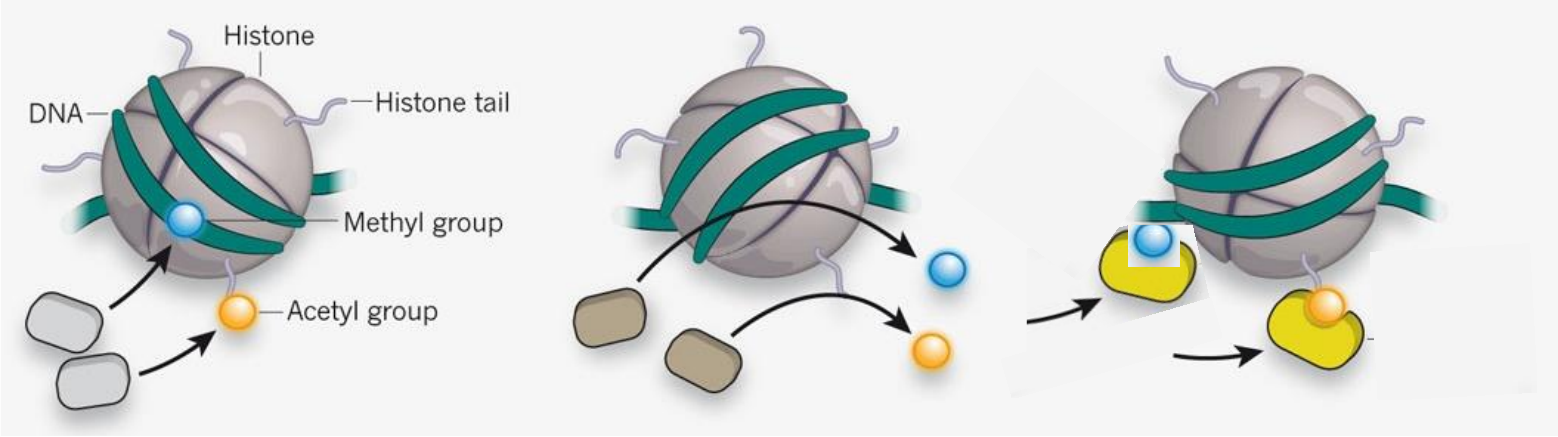
Epigenetic Therapy:

Epigenetic drug, generally harmless, sensitizes cancer cell to other agents



Epigenetic Regulators as Candidate Targets for Treatment of Prostate Cancer

Writers | Erasers | Readers



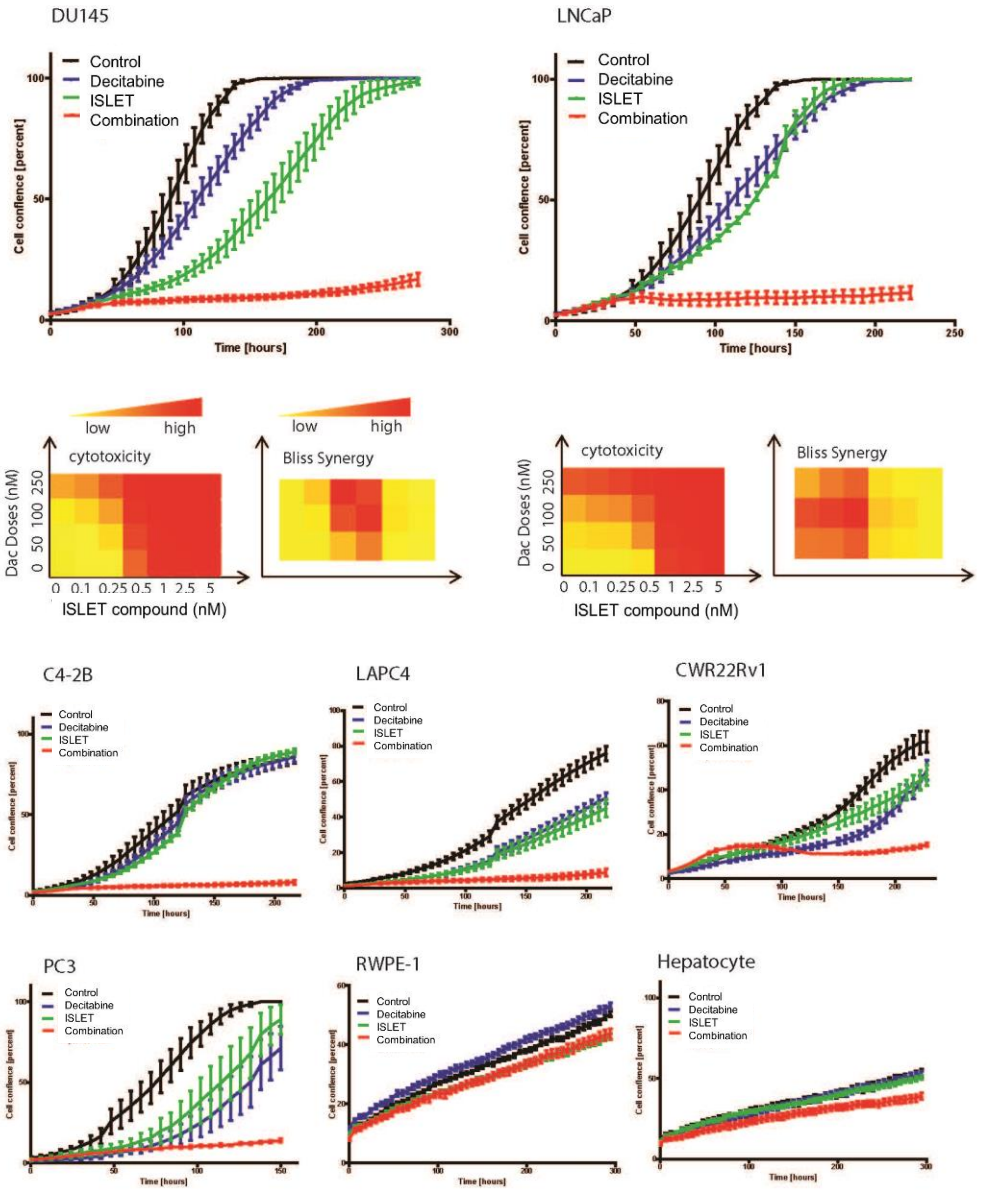
DNA Methyltransferases*
Histone methyltransferases
Histone acetyltransferases
Kinases
Ubiquitin conjugases/ligases

Tet proteins
Histone demethylases
Histone deacetylases*
Phosphatases
Ubiquitin proteases

^{5me}CpG binding domains
Chromodomains
Bromodomains
Tudor domains
PHD fingers/SRA (UHRF1)

*Molecular targets with Food and Drug Administration (FDA)-approved drugs

Therapeutic Index of ISLET Compound-Decitabine Combinations: Activity Against All Prostate Cancer Cell Lines but Not Against Normal Cells*



*Liu J *et al.* (2017)