Epigenetics: What is it and how it effects our health?

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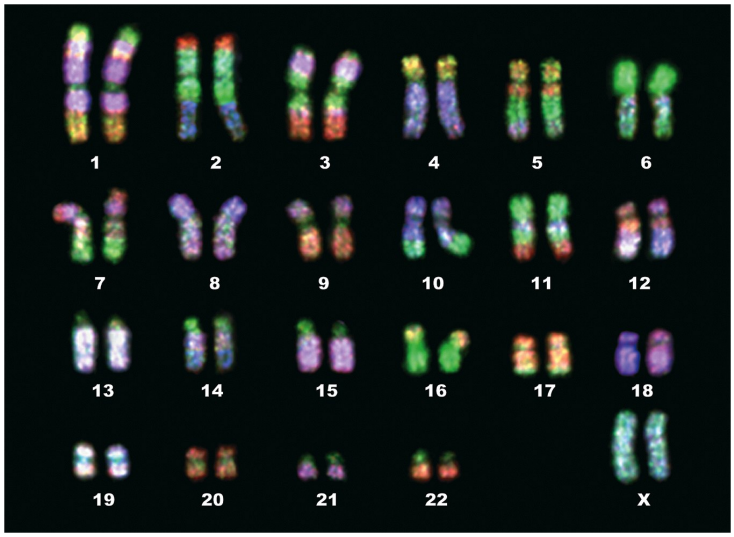
Overview

- Basic Background
- Epigenetics in general
- Epigenetics in cancer
- Epigenetics in Lymphoma
- Clinical Trials targeting Epigenetic proteins in Lymphoma

First, Some Basics

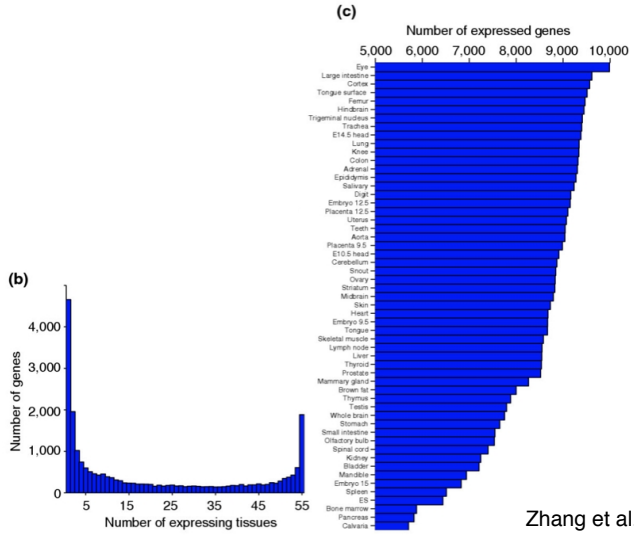
- DNA -> RNA -> Protein
- We have 23 sets of chromosomes, making 46 total.
- Most of the chromosomal DNA does not make DNA but much of it is not junk.
- Rather, much of the non-protein coding DNA regulates the expression of the protein-coding DNA.

Our DNA encodes all the proteins required for the >240 different cell types of our body



Spectral Karyotyping of Human Chromosomes

The ~20,000 genes encoding proteins are differentially expressed in each tissue and cell type, defining their function

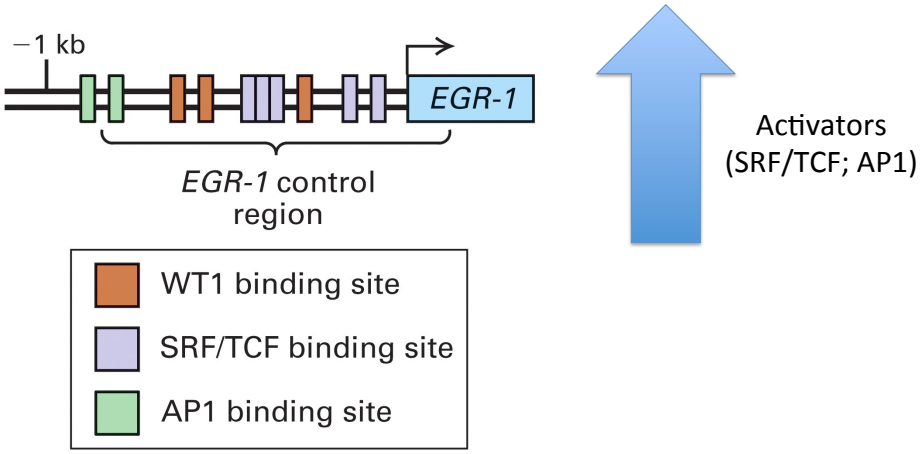


Zhang et al., J. Biol. 2004

Controlling the Combinatorial Code leading to differential gene expression

- Transcription Factors regulate the expression of genes
- Epigenetic marks regulate the accessibility of transcription factors to the DNA

Transcription factors work in a combinatorial fashion: promoters have both transcription activator (e.g., SRF/TCF & AP1) and repressor (e.g., WT1) sites



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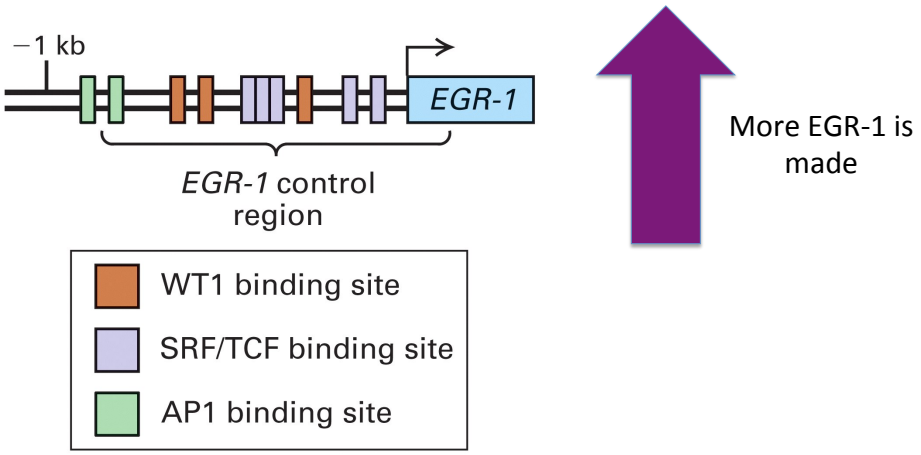

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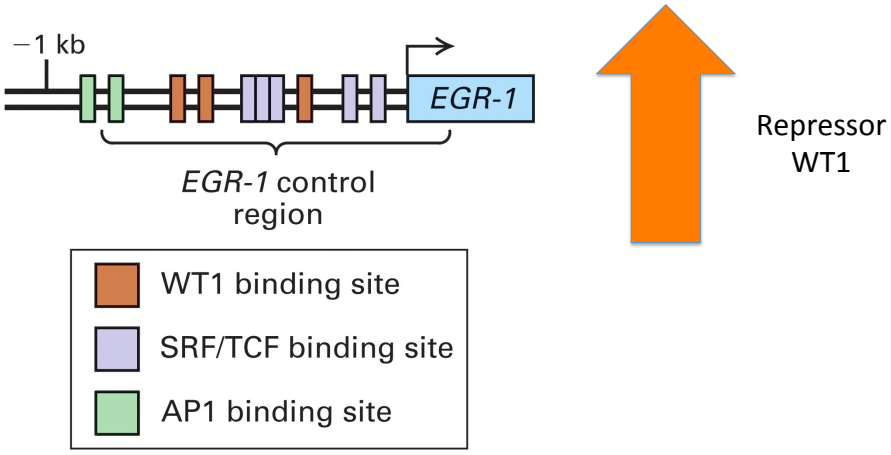

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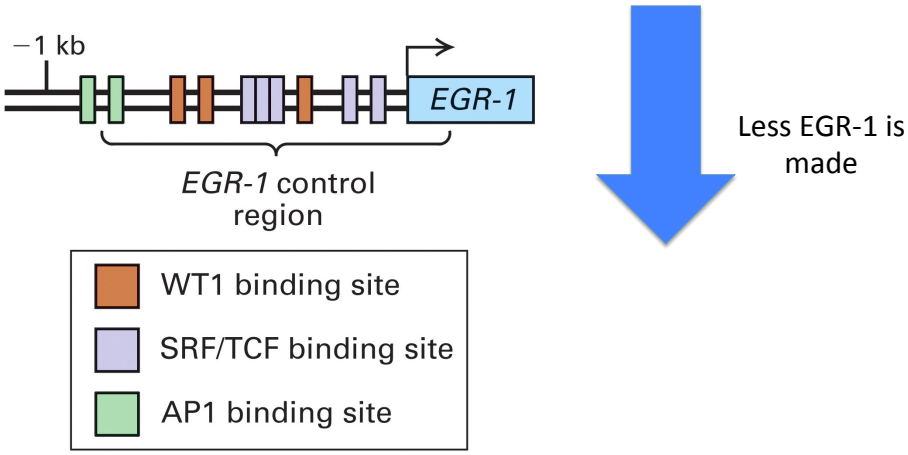
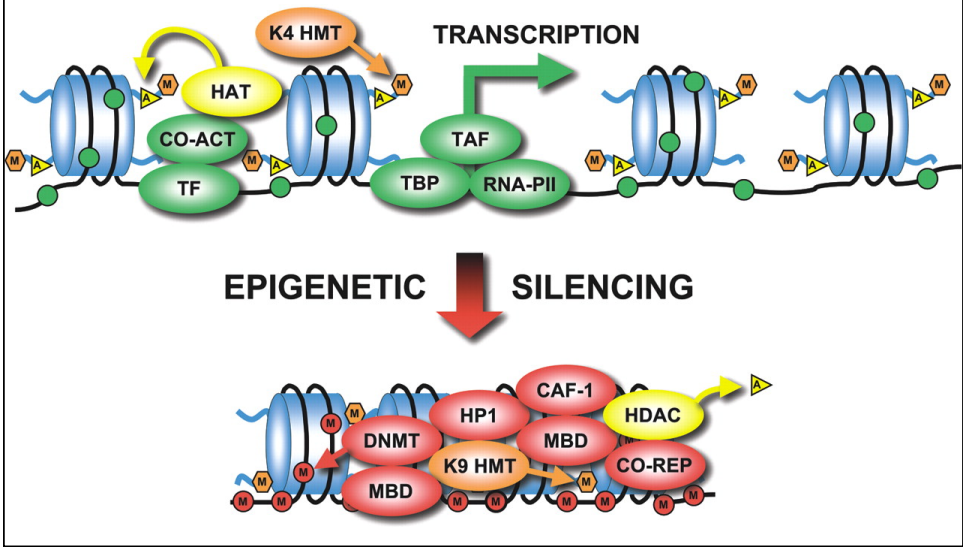
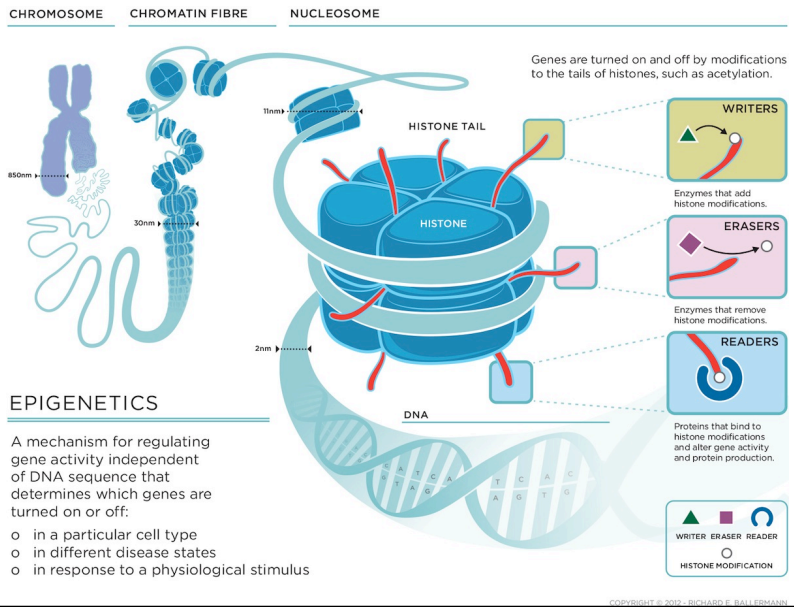


Epigenetic modifications to genes controls the accessibility of transcription factor to the gene



The Epigenetics of Identical Twins

Readers, Writers & Erasers



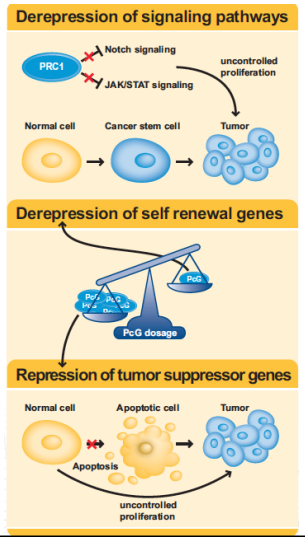
Epigenetics in Cancer

- Example: Breast Cancer
- Breast Cancer Susceptibility genes BRCA1 & BRCA2
- If a woman has a family history of breast cancer, then one copy of BRCA1 or BRCA2 mutations are inherited
- Breast cancer arises when the second copy is either mutated or epigenetically silenced.

Epigenetic proteins: a double edged sword

- Epigenetic proteins can be oncogenes (increased expression induces cancer)
- or tumor suppressors (lack of expression permits cancer development)
- Why? Because they regulate both tumor suppressors and oncogenes.

Epigenetics in Cancer: Role of the Polycomb Complex



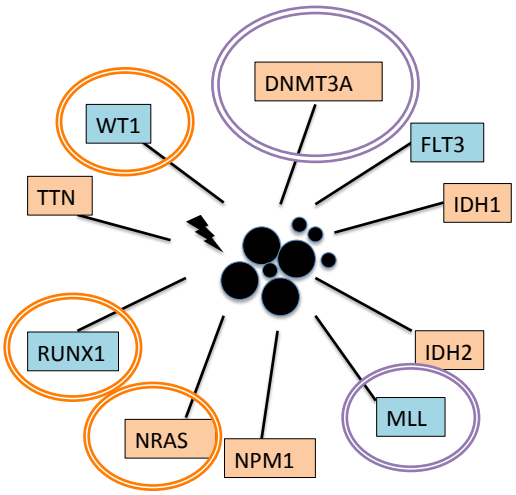
Epigenome modulators are already in the Clinic: Azacitidine & Decitabine are used in Myelodysplatic Syndrome

CLINICAL TRIAL	YEAR	DRUG
CALGB -9221	2002	Azacitidine
D-007	2006	Decitabine
ICD03-180	2007	Decitabine
AZA-001	2009	Azacitidine
US Oncology	2009	Azacitidine
ADOPT	2009	Decitabine
EORTC 06011	2011	Decitabine

Patients treated with hypo-methylating drugs show

- Higher complete remission (CR)
- Lower drug resistance
- Lower relapse rate.
- Low cytotoxicity

Most common Mutations in Acute Myeloid Leukemia



Epigenetic proteins

Transcription Factors

Exome Sequencing

Whole Genome Sequencing

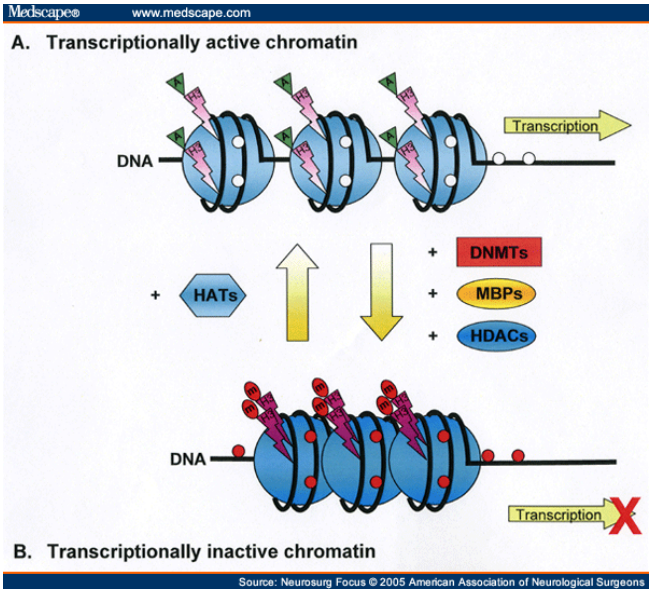
Common Mutations in Lymphoma

- Many different mutations depending on the type of Lymphoma
- T Cell Acute Lymphocytic Leukemias T-ALL and ETP-ALL commonly have loss of function mutations (i.e., inactivating mutations) in epigenetic regulators
- Diffuse Large B Cell Lymphoma (DLBCL) commonly has activating mutations in EZH2 but inactivating mutations in MLL2 or MLL3

T Cell Acute Lymphocytic Leukemias - 1

- Common Mutations in the DNA methyltransferase (DNMT3A) which modifies DNA directly, turning off gene expression.
- Thus, an inactivating mutation of DNMT3A will enable genes that are supposed to be OFF to be ON

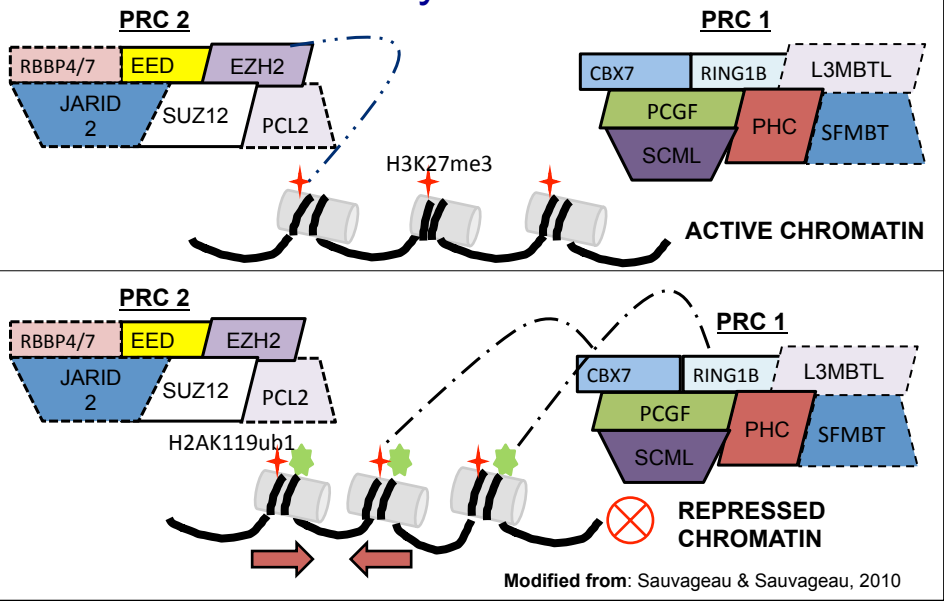
DNA Methylation turns off genes



T Cell Acute Lymphocytic Leukemias - 21

- Other common mutations are inactivating mutations in Histone Methylation genes which turn OFF gene expression
- These mutations are often in the PRC2 complex (EZH2, SUZ12, EED) or SETD2.

Two Polycomb Repressive Complexes with different enzymatic functions.



Modified from: Sauvageau & Sauvageau, 2010

Diffuse Large B Cell Lymphoma (DLBCL) & Follicular Lymphomas

- Most DLBCL patients have activating mutations in EZH2, meaning that the activity of EZH2 is very high and many genes are turned OFF that should be ON.
- Some patients have inactivating mutations in MLL2 or MLL3. These Epigenetic Proteins normally Turn genes ON. Thus, inactivating mutations leads to genes being OFF that should be ON.

Mutations in EZH2

DISORDER ([ref])	Number of mutations identified (per domain)						
GCB cell Lymphoma[37]							4
MDS/MPN[45]				8		3	14
T-ALL[43]				1	1	2	

Clinical Trials using Inhibitors of Epigenetic proteins

- At least 45 clinical trials have been performed using inhibitors of epigenetic proteins in cancer
- 4 clinical trials in lymphoma

Clinical Trial using E7438, an inhibitor of EZH2

- ClinicalTrials.gov Identifier: NCT01897571
- Currently recruiting patients in France
- Sponsor is by the companies that developed the drug and testing it: Eisai Limited & Epizyme, Inc.
- Indication: Diffuse Large B Cell Lymphoma or Grade 3 follicular lymphomas
- Phase 1/2: Toxicity & Efficacy
- Establish the maximum tolerated dose, pharmacokinetics (how the drug is processed by the body)
- Is it efficacious at the maximum tolerated dose?

Vidaza and Vorinostat in patients with relapsed or refractory DLBCL

- ClinicalTrials.gov Identifier: NCT01120834
- Phase 1/2: Toxicity & Efficacy
- VIDAZA demethylates DNA leading to the turning ON of genes (not specific)
- Vorinostat inhibits an enzyme (HDAC) that modifies DNA to turn OFF genes.
- Thus, Vorinostat will turn ON genes in a general fashion (not specific).
- Sponsored by Cornell (New York) and Celgene and Merck (companies that make the drugs)

Valproic Acid Treatment for refractory Non-Hodgkin Lymphoma, Hodgkin Lymphoma, CLL

- ClinicalTrials.gov Identifier: NCT01016990
- Valproic acid inhibits an enzyme (HDAC) that modifies DNA to turn OFF genes.
- Thus, Valproic acid will turn ON genes in a general fashion (not specific).
- Slowly recruiting in Puerto Rico

VIDAZA with chemotherapy for children with ALL or AML

- ClinicalTrials.gov Identifier: NCT01861002
- Phase 1: Safety only
- VIDAZA demethylates DNA leading to the turning ON of genes (not specific)
- Sponsored by Therapeutic Advances in Childhood Leukemia Consortium, Children's Hospital in Los Angeles

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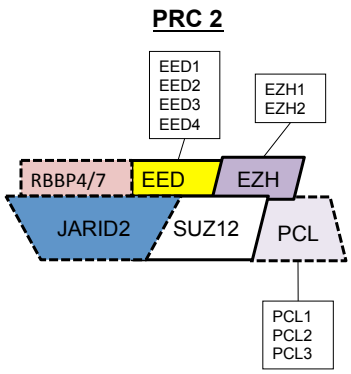

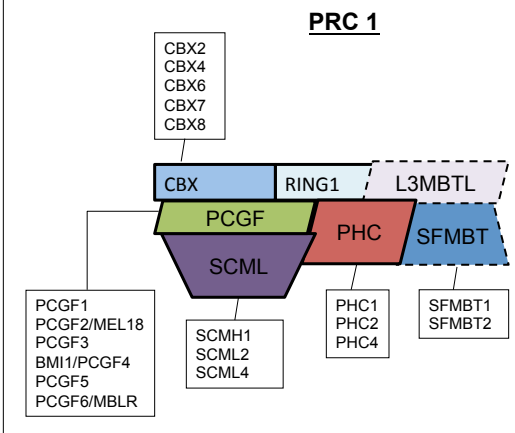

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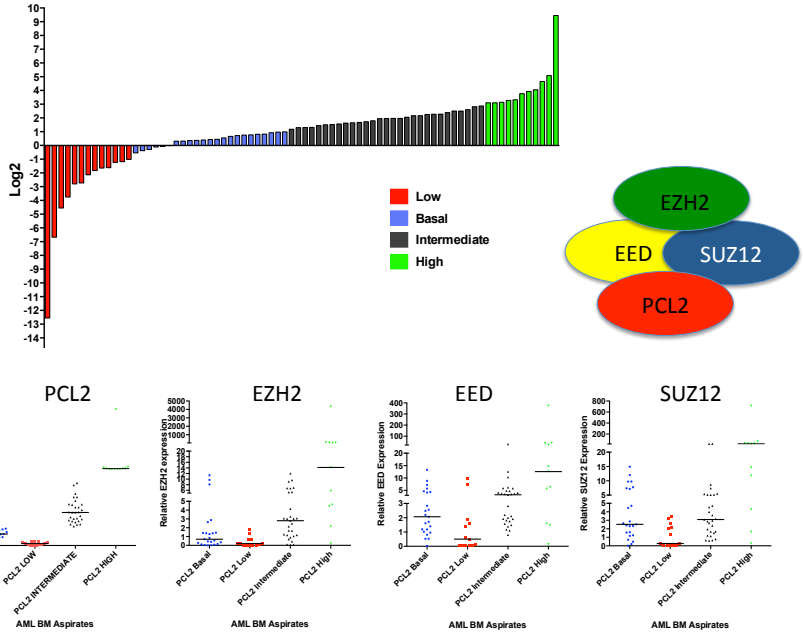
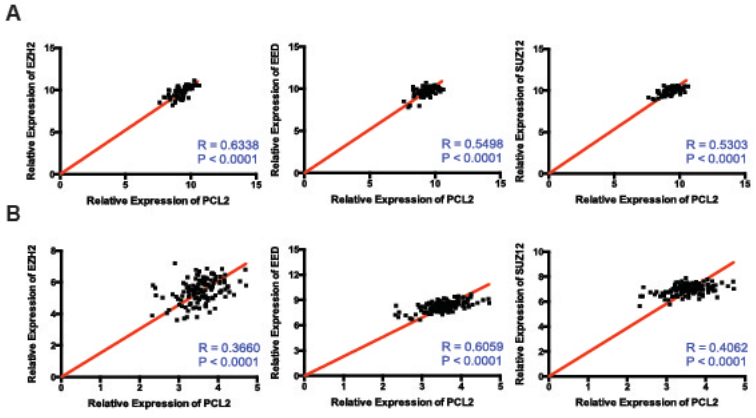
PCL2-PRC2 are misregulated in ~70% of the AML cases



Most Lymphoma patients have over-expression of EZH2 and PCL2



These patients could be candidates for treatment with the EZH2 inhibitor or a new drug directed at PCL2.