

**Pharmacoepigeneretics:
an element of personalized
therapy?**

Che cos'è l'epigenetica?

(επί) epì = "sopra"

(γεννητικός) gennetikòs = "relativo all'eredità familiare"

Definita come lo studio dei meccanismi responsabili di cambiamenti ereditabili che influenzano il fenotipo (espressione genica) senza alterare il genotipo (sequenza del DNA).

Il termine risale al 1942 quando **C.H. Waddington** lo coniava per designare la branca della biologia che studia le interazioni causali fra i geni e il loro prodotto cellulare (fenotipo).



Che cos'è l'epigenetica?

Coniglio Himalayano

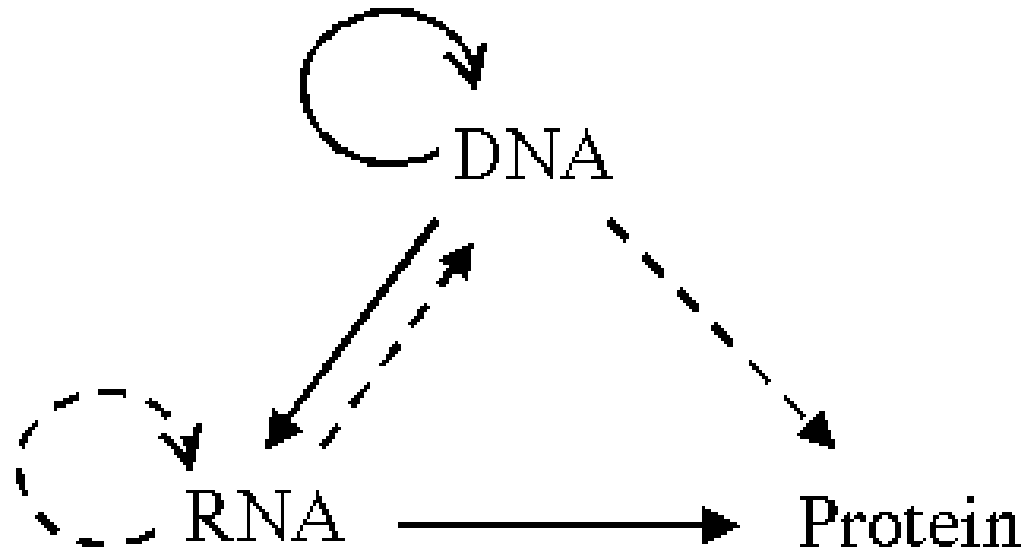


LA RIVOLUZIONE EPIGENETICA



Completion of the First draft of the Human Genome Project was announced on the 26th June 2000, jointly presented to the world by US President Bill Clinton and UK PM Tony Blair.

DOGMA DELLA BIOLOGIA MOLECOLARE



NATURE VOL. 227 AUGUST 8 1970

561

Central Dogma of Molecular Biology

by
FRANCIS CRICK
MRC Laboratory of Molecular Biology,
Hills Road,
Cambridge CB2 2QH

The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information. It states that such information cannot be transferred from protein to either protein or nucleic acid.

Pharmacoepigenetics

Epigenetic regulation of genes

ADME genes

- Drug response
- Adverse drug reactions
- Acquired drug resistance

Disease-related genes

- Disease diagnosis
- Disease prognosis
- Stratification of patients

Pharmacoepigenetic biomarkers
(invasive or circulating)

Increased efficacy of drug treatment

Epigenetic effects of drugs

Drugs
on market

Drugs of abuse

Epigenetics of
drug action

Epidrugs

Epigenetic editing

Correction of
epigenetic signatures

New paradigms for the drug treatment

EPIDRUGS

Type of enzyme	Drug	Target enzyme	Clinical application
DNMT inhibitors	5-Azacytidine (Vidaza)	DNMT1	Approved by the FDA in 2004 for treatment of myelodysplastic syndromes (MDS)
	5-Aza-2'-deoxycytidine (aza-dC, decitabine, Dacogen)	DNMT1	Approved by the FDA in 2006 for treatment of MDS Reversed platinum resistance in ovarian cancer when coadministered with carboplatin (Phase II trial)
	Hydralazine	DNMT1	Clinical benefit in cancer patients with refractory solid tumors when added to valproic acid (Phase II trial) Reversed imatinib resistance in patients with chronic myeloid leukemia when coadministered with magnesium valproate
HDAC inhibitors	Valproic acid	HDAC	Promising nontoxic and effective therapy for MDS in combination with hydralazine (Phase II trial ongoing) Under evaluation in metastatic cervical cancer in combination with hydralazine (Phase III trial ongoing) Combined with aza-dC for non-small-cell lung cancer (Phase I trial)
	Suberoylanilide hydroxamic acid (vorinostat, Zolinza)	HDAC	Approved by the FDA in 2006 for treatment of advanced cutaneous T-cell lymphoma Reversed hormone resistance in patients with ER ⁺ metastatic breast cancer, when coadministered with tamoxifen (Phase II trial)
	Romidepsin (depsipeptide, Istodax)	HDAC	Approved by the FDA in 2009 for treatment of advanced cutaneous T-cell lymphoma
	Sodium butyrate	HDAC	Induces antimicrobial peptide LL-37 in the rectum of shigellosis patients (Phase II trial)
	Panobinostat	HDAC	Promising results in monotherapy of heavily pretreated Hodgkin's lymphoma patients (Phase II trial) Recaptures responses in bortezomib-resistant multiple myeloma patients (Phase II trial)
	Entinostat	HDAC1, HDAC2	Improved survival in women with ER ⁺ advanced breast cancer when added to exemestane (Phase II trial)
	Mocetinostat	HDAC1, HDAC2	Promising effect in monotherapy of relapsed Hodgkin's lymphoma (Phase II trial)
	Selisistat	SIRT1	Under evaluation for treatment of Huntington's disease (Phase II trial ongoing)



EPIDRUGS

Epidrugs: targeting epigenetic marks in cancer treatment

- 1) Zolinza → DNMTi
- 2) Vidaza → HDACi
- 3) Ixodax → HDACi
- 4) Belodaq → HDACi
- 5) Farydak → DNMTi
- 6) Venclexta → HDACi

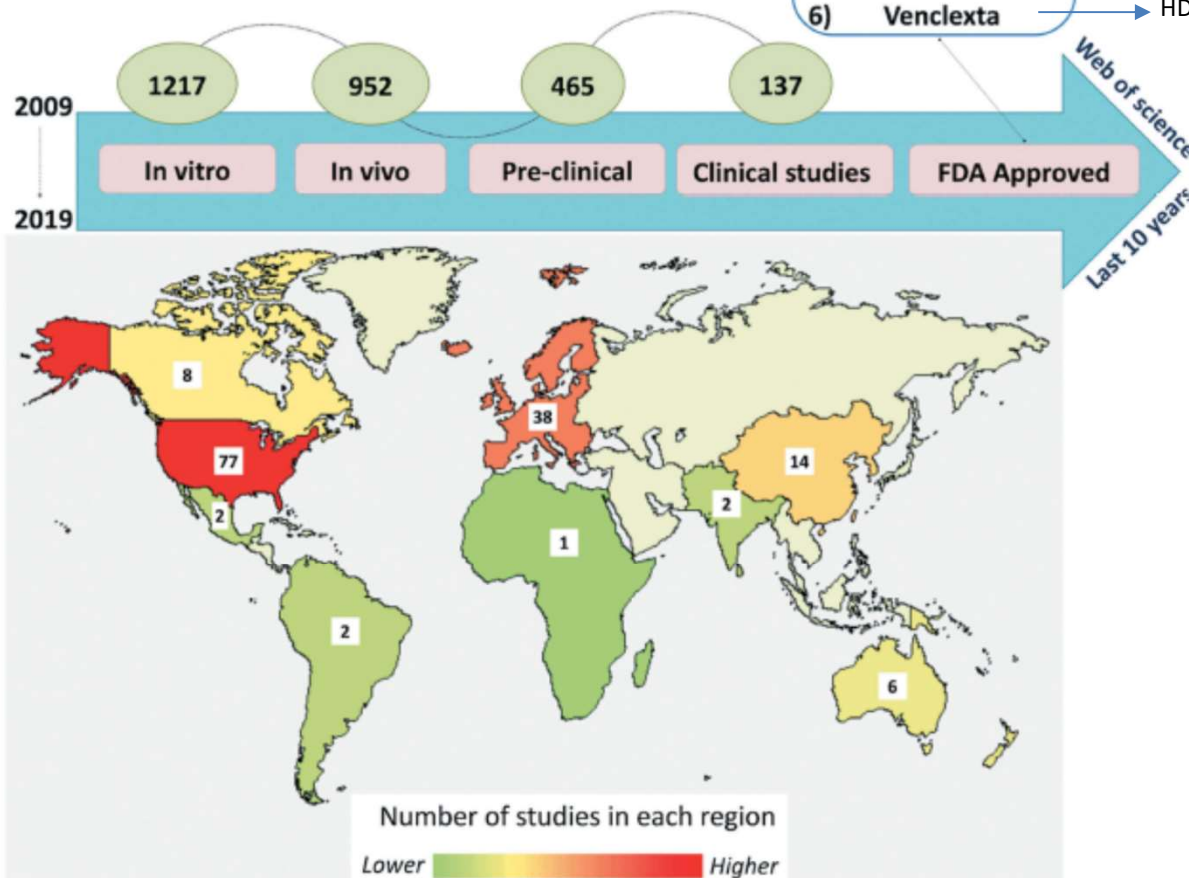


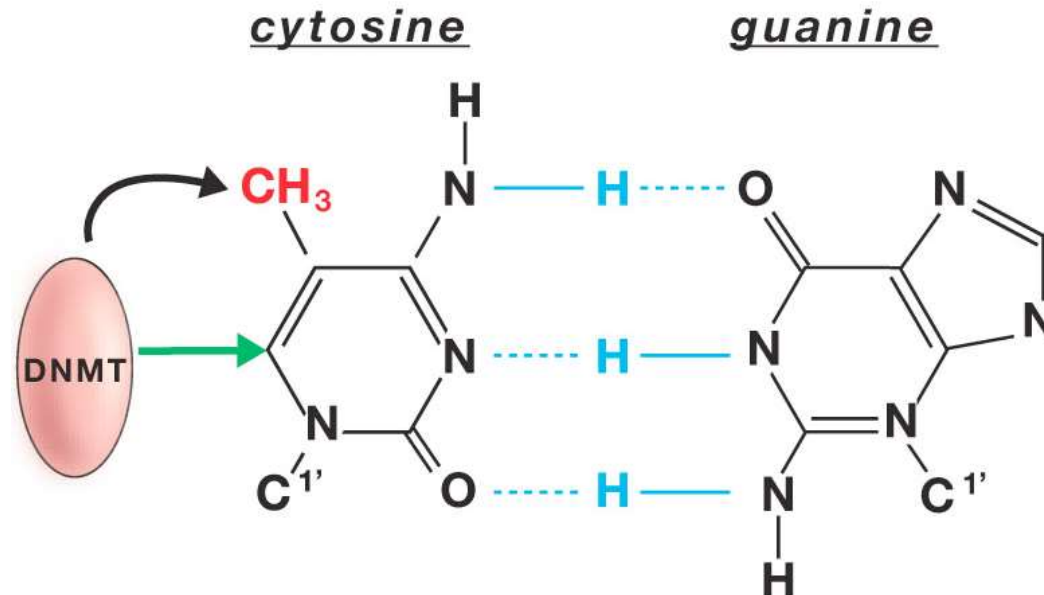
Figure 2. Progress of epigenetic drugs in different stages of pharmacological studies. The number of epigenetic studies from 2009 to 2019 according to 'web of science' database is shown according to each study phase: *in vitro* (1217) *in vivo* (952), preclinical (465) and clinical (137). The map represents the global distribution of clinical epigenetic drug studies according to clinical trial database (www.clinicaltrials.org, June, 2019), and the box show the exact number of studies.



I principali componenti del codice epigenetico:

- Metilazione del DNA
- Metilazione dell'RNA (N6-metiladenosina)
- Modificazione della cromatina (acetilazione e/o metilazione degli istoni)
- RNA non codificanti

METILAZIONE DEL DNA

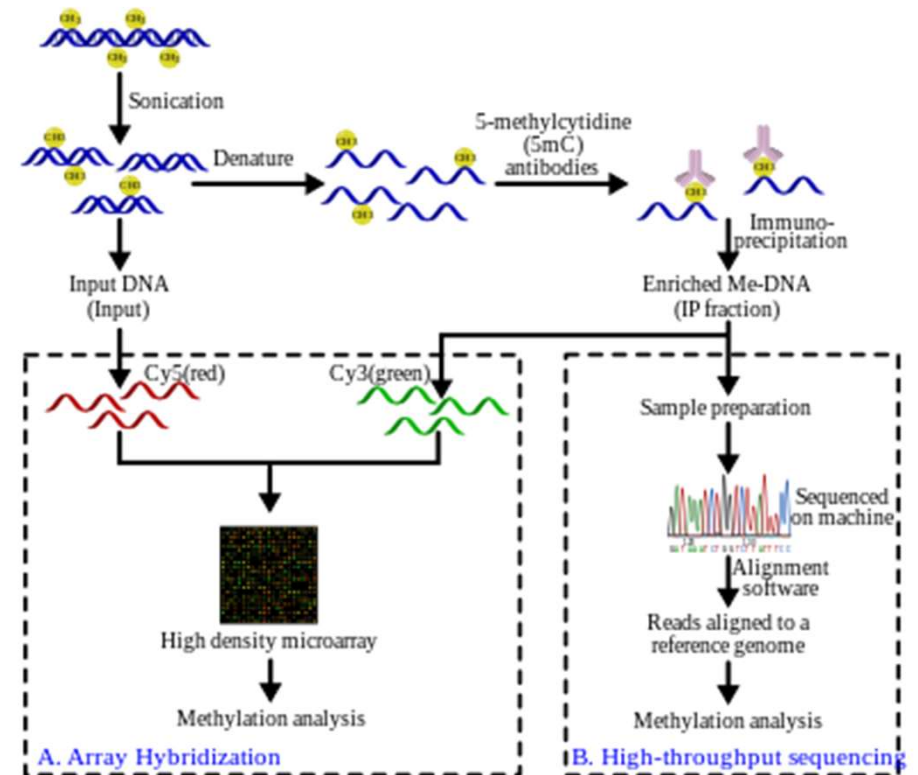
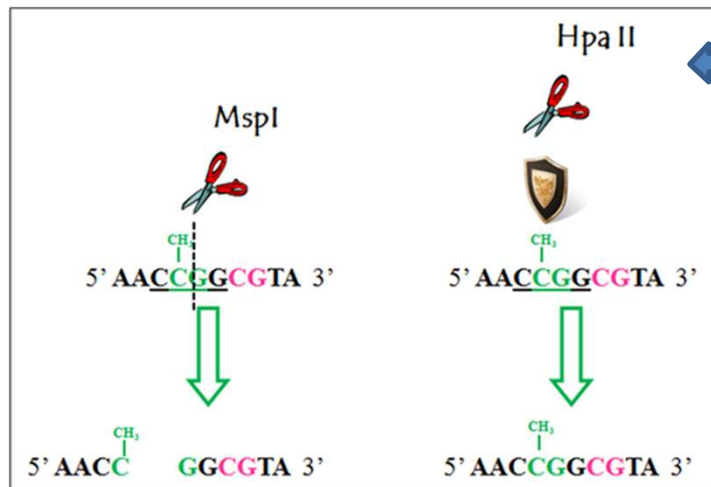


La citosina metilata NON esiste nel pool dei nucleotidi liberi presenti nella cellula!
E' una modificazione post-replicativa del genoma catalizzata da enzimi DNA-metil-transferasi.
Avviene a carico dei dinucleotidi CpG.



Techniques for profiling DNA methylation

- Digestione con endonucleasi



- Arricchimento per affinità

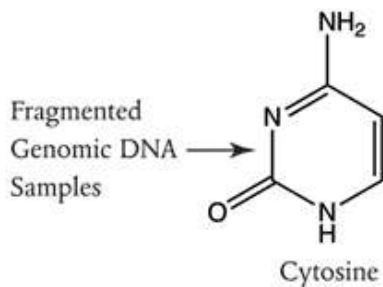
Techniques for profiling DNA methylation

- Trattamento con bisolfito

Step 1

Denaturation

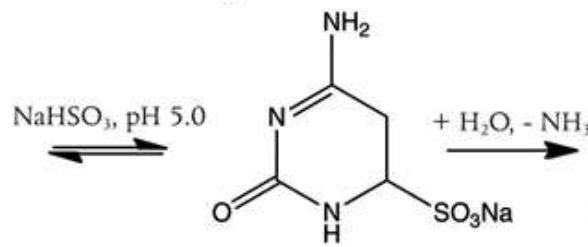
Incubation at 95°C
fragments genomic DNA



Step 2

Conversion

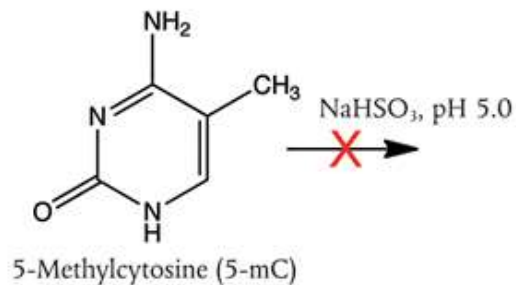
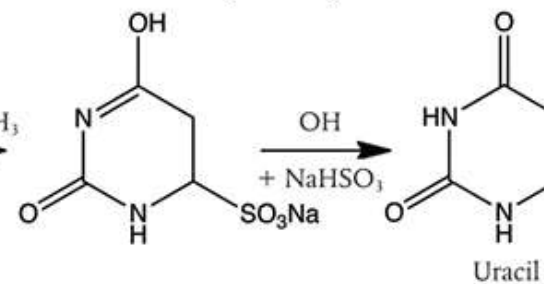
Incubation with sodium bisulfite
at 65°C and low pH (5-6)
deaminates cytosine residues
in fragmented DNA



Step 3


















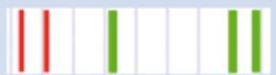
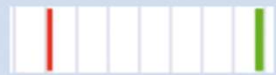


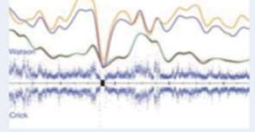
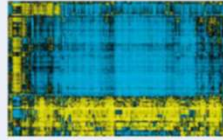
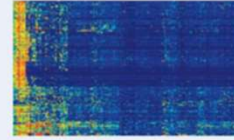
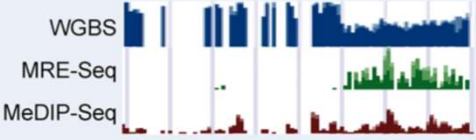
Desulphonation

Incubation at high pH
at room temperature for 15 min
removes the sulfite moiety,
generating uracil



5-mC and 5-hmC (not shown) are not susceptible
to bisulfite conversion and remain intact

High-throughput techniques for profiling DNA methylation

Widely used high throughput techniques	WGBS	RRBS	Illumina 27K/450K arrays	MeDIP-Seq	MRE-Seq
Full name	Whole-genome Bisulfite sequencing	Reduced representation bisulfite sequencing	Infinium HumanMethylation27/450 BeadChip arrays	Methylation dependent immuno precipitation sequencing	Methylation-sensitive restriction enzyme digestion sequencing
Pretreatment	Sodium bisulphite 	Enzyme digestion  <i>MspI</i> Sodium bisulphite 	Sodium bisulphite 	Affinity enrichment 	Enzyme digestion 
Detection method	Next-generation sequencing 	Next-generation sequencing 	BeadArray microarray 	Next-generation sequencing 	Next-generation sequencing 
Resolution	Single C sites 	Sparse single C sites 	Selected single CpG site 	Methylated Region 	Un-methylated Region 
Visualization					
Special application	Whole-genome cytosine methylation analysis at single-base resolution  Lister, R., et al., Nature, 2009. 462(7271)	Specific methylation analysis across a large number of cell lines  Varley, K.E., et al., Genome Res, 2013. 23(3)	Aberrant methylation analysis in a large number of cancer tissues  TCGA project. N Engl J Med, 2016. 374(2)	Combination Identification of intermediate methylation regions  Elliott, G., et al. Nat Commun, 2015. 6	

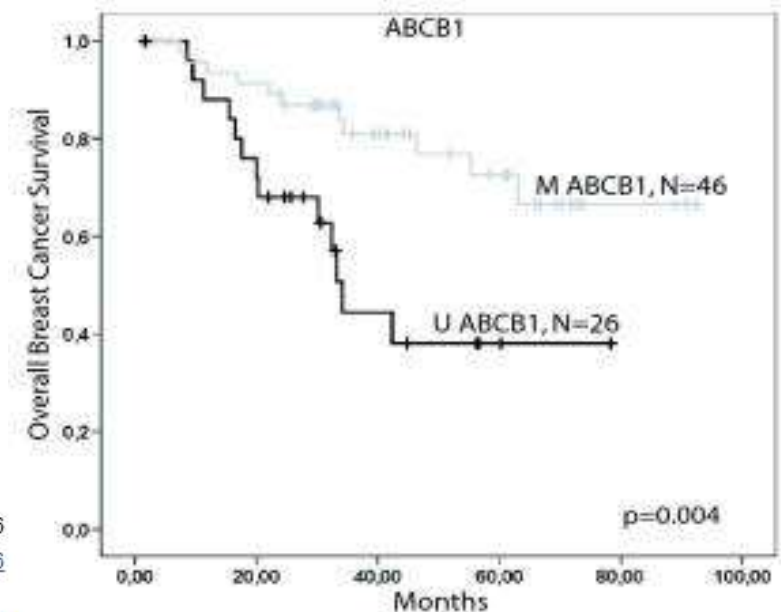
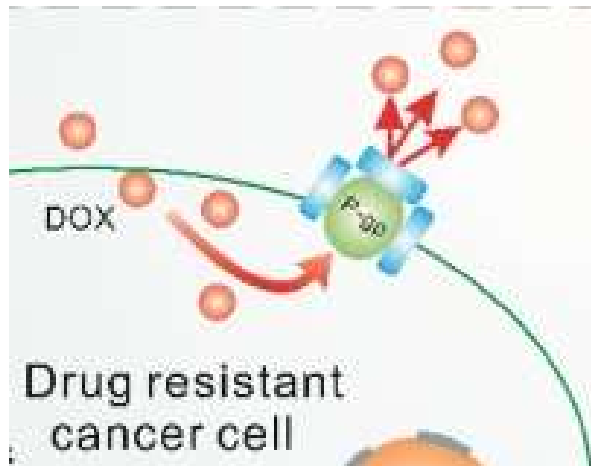
MARCATORI EPIGENETICI ASSOCIATI ALLA RISPOSTA DI ANTINEOPLASTICI

Table 1. Relevant examples of epigenetic biomarkers of drug responses

Drug	Gene	Function	Evidence for epigenetic regulation	Power
Anthracyclines	<i>ABCB1</i>	Transport	Promoter methylation correlated with survival in breast cancer patients and may be a marker for the efficacy of doxorubicin treatment	$n = 75, P = 0.004$ (validation cohort $n = 163$)
	<i>GSTP1</i>	Detoxification		
	<i>PTX2</i>	Cell proliferation		
Alkylating agents	<i>BRCA1</i>	DNA damage response	Promoter hypermethylation of <i>BRCA1</i> predicted enhanced sensitivity to platinum-derived drugs in cancer cell lines and xenografted tumors; it also predicted increased time to relapse ($P = 0.0087$) and survival ($P = 6.4 \times 10^{-7}$) in ovarian cancer patients under cisplatin treatment	$n = 30$
	<i>GPX3</i>	Detoxification of hydrogen peroxide	Loss of <i>GPX3</i> expression due to promoter hypermethylation correlated with resistance to cisplatin ($P = 0.014$) and with reduced disease-free survival ($P = 0.02$) in head and neck cancer patients	$n = 46$
	<i>MGMT</i> ^a	DNA repair	Promoter methylation of <i>MGMT</i> associated with improved overall survival (21.2 vs 14 months; HR 1.74, $P < 0.001$), progression-free survival (8.7 vs 5.7 months; HR 1.63, $P < 0.001$), and response ($P = 0.012$) in glioma patients treated with temozolomide	$n = 411$
	<i>PLK2</i>	Tumor suppression	Promoter methylation of <i>PLK2</i> associated with a higher risk of relapse in ovarian cancer patients	$n = 54, P = 0.003$
Fluoropyrimidines	<i>TFAP2E</i>	Transcriptional regulation	Hypermethylation of <i>TFAP2E</i> associated with clinical nonresponsiveness in colorectal cancer patients	$n = 220, P < 0.001$
DNMTi	<i>GSTP1</i>	Detoxification	DNA methylation of <i>GSTP1</i> correlated with efficiency of DNMTi therapy in prostate cancer cells	
Tyrosine kinase inhibitors	<i>OSCP1</i>	Transport	Patients with higher methylation of <i>OSCP1</i> were resistant to imatinib treatment	$n = 90, P = 0.0003$
	<i>SFRP5</i>	WNT signaling	DNA methylation of <i>SFRP5</i> correlates with lower progression-free survival rate in non-small-cell lung cancer patients in response to EGFR tyrosine-kinase inhibitors	$n = 155, P = 0.011$
Docetaxel	<i>RASSF1A</i>	Cell cycle, DNA repair	Promoter methylation of <i>RASSF1A</i> is associated with nonresponsiveness to docetaxel in breast cancer patients	$n = 45, P = 0.042$

MARCATORI EPIGENETICI ASSOCIATI ALLA RISPOSTA DI ANTRACICLINE

DNA methylation of the *ABCB1* CpG island is associated with response to doxorubicin treatment and overall survival in a doxorubicin-exposed cohort of primary breast cancers.



Mol Cancer. 2010; 9: 68.

Published online 2010 Mar 25. doi: [10.1186/1476-4598-9-68](https://doi.org/10.1186/1476-4598-9-68)

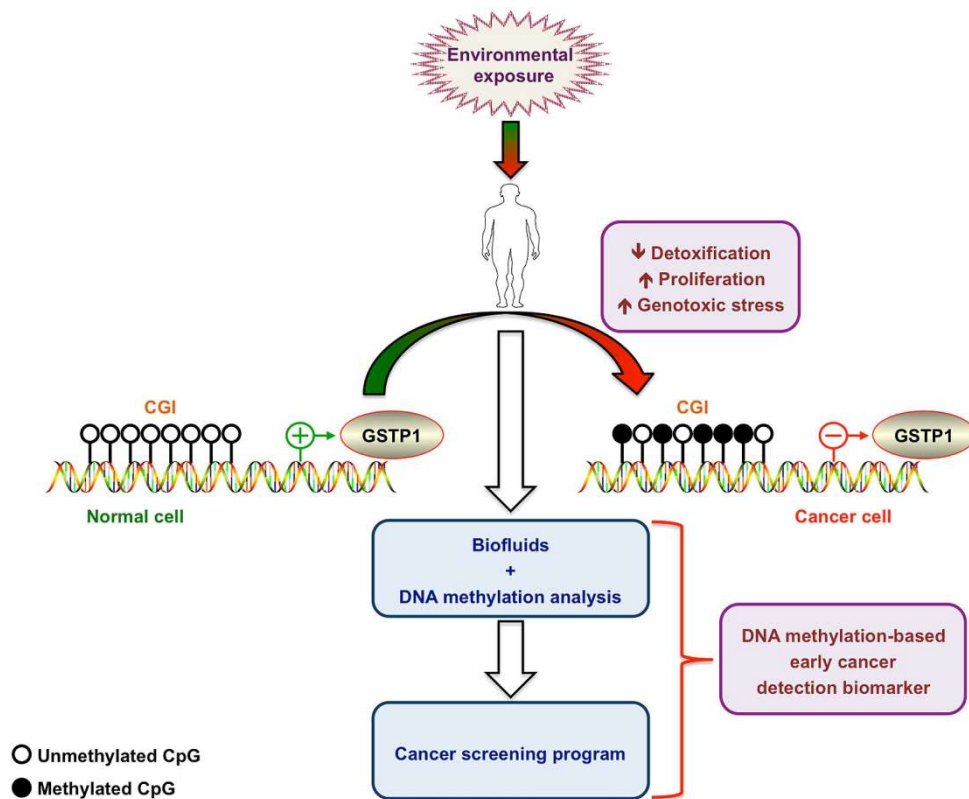
PMCID: PMC2861056

PMID: [20338046](https://pubmed.ncbi.nlm.nih.gov/20338046/)

DNA methylation profiling in doxorubicin treated primary locally advanced breast tumours identifies novel genes associated with survival and treatment response

Emelyne Dejeux,^{#1} Jo Anders Rønneberg,^{#2,3} Hiroko Solvang,^{3,4} Ida Bukholm,^{3,5} Stephanie Geisler,⁶ Turid Aas,⁷ Ivo G Gut,¹ Anne-Lise Børresen-Dale,^{2,3} Per Eystein Lønning,^{6,8} Vessela N Kristensen,^{2,3} and Jörg Tosi^{#1}

MARCATORI EPIGENETICI ASSOCIATI ALLA RISPOSTA DI ANTRACICLINE



DNA methylation of the *GSTP1* CpG island is associated with overall survival in a doxorubicin-exposed cohort of primary breast cancers.

Mol Cancer. 2010; 9: 68.

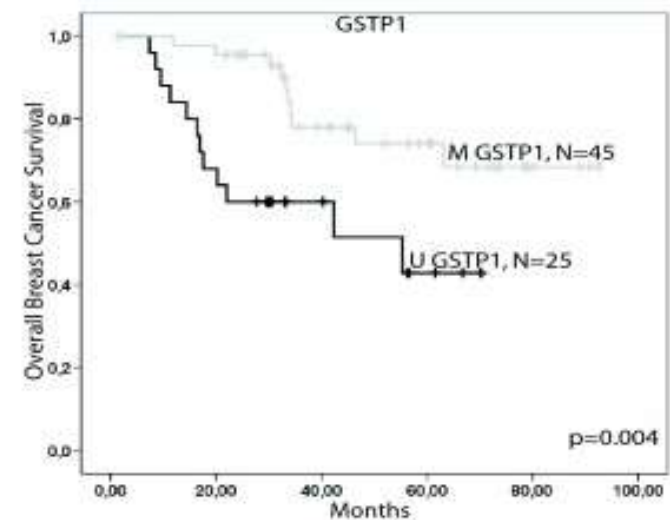
Published online 2010 Mar 25. doi: [10.1186/1476-4598-9-68]

PMCID: PMC2861056

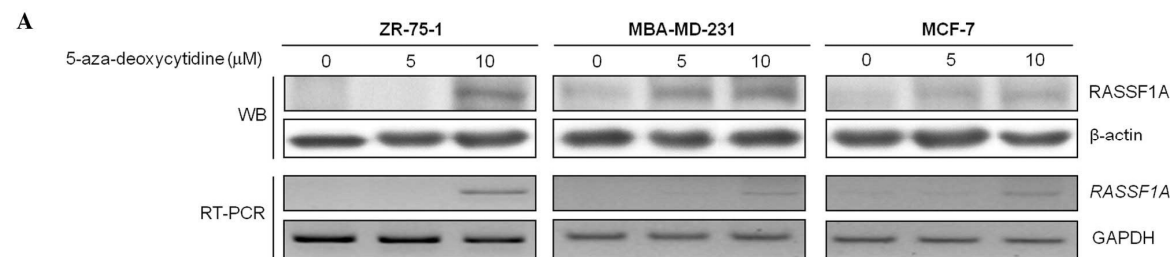
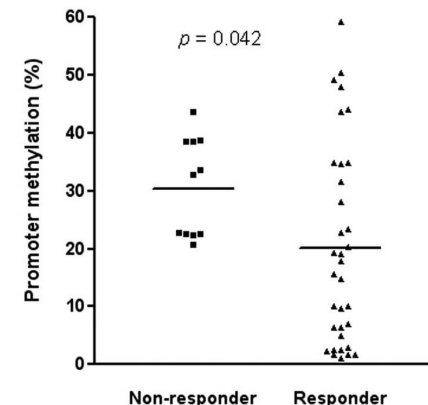
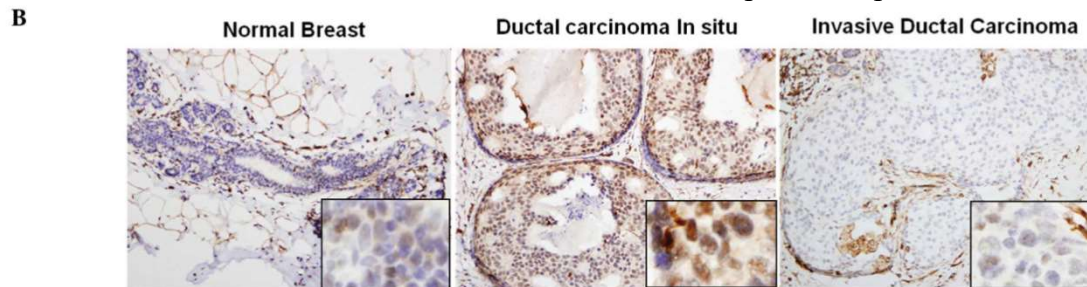
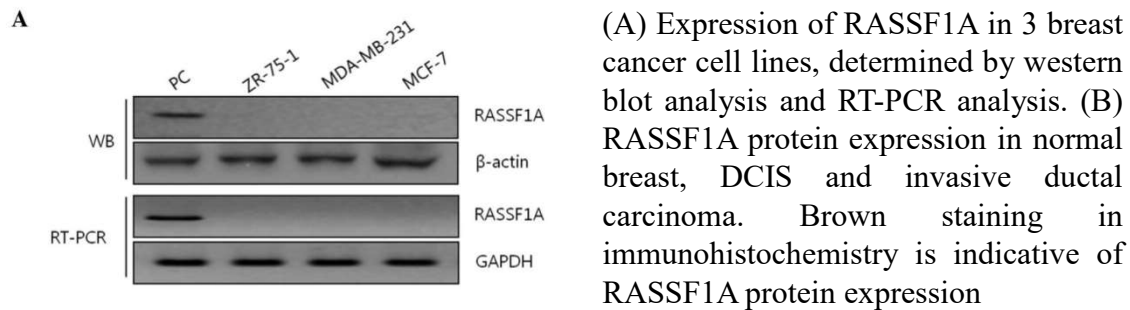
PMID: 20338046

DNA methylation profiling in doxorubicin treated primary locally advanced breast tumours identifies novel genes associated with survival and treatment response

Emelyne Deieux,^{#1} Jo Anders Rønneberg,^{#2,3} Hiroko Solvang,^{3,4} Ida Bukholm,^{3,5} Stephanie Geisler,⁶ Turid Aas,⁷ Ivo G Gut,¹ Anne-Lise Børresen-Dale,^{2,3} Per Eystein Lønning,^{6,8} Vessela N Kristensen,^{2,3} and Jörg Tost^{#1}



MARCATORI EPIGENETICI ASSOCIATI ALLA RISPOSTA DI DOCETAXEL



Re-expression of RASSF1A by treatment of 3 different breast cancer cell lines with 5-azadeoxycytidine. Western blot analysis and RT-PCR show that RASSF1A is re-expressed by treatment with increasing concentrations of 5-azadeoxycytidine

Int J Oncol. 2012 Aug;41(2):611-20. doi: 10.3892/ijo.2012.1470. Epub 2012 May 10.

Promoter methylation of RASSF1A modulates the effect of the microtubule-targeting agent docetaxel in breast cancer.

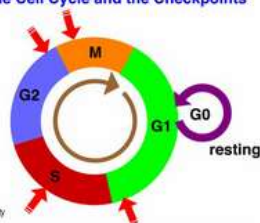
Gil EY¹, Jo UH, Jeong H, Whang YM, Woo OH, Cho KR, Seo JH, Kim A, Lee ES, Koh I, Kim YH, Park KH.

MARCATORI EPIGENETICI ASSOCIATI ALLA RISPOSTA DI AGENTI ALCHILANTI

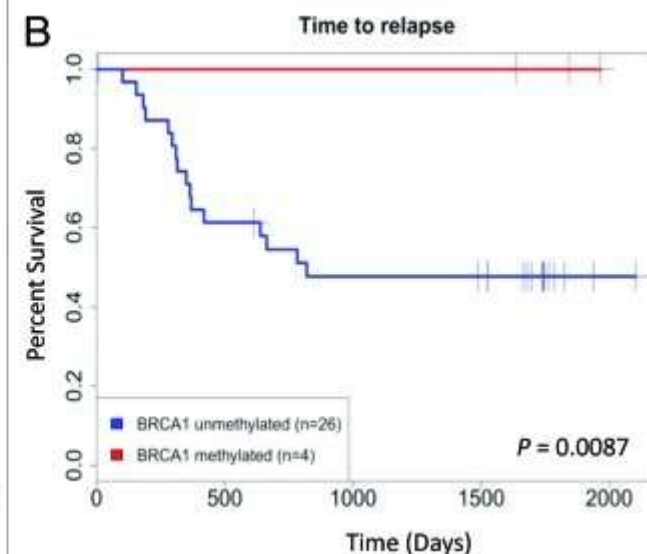
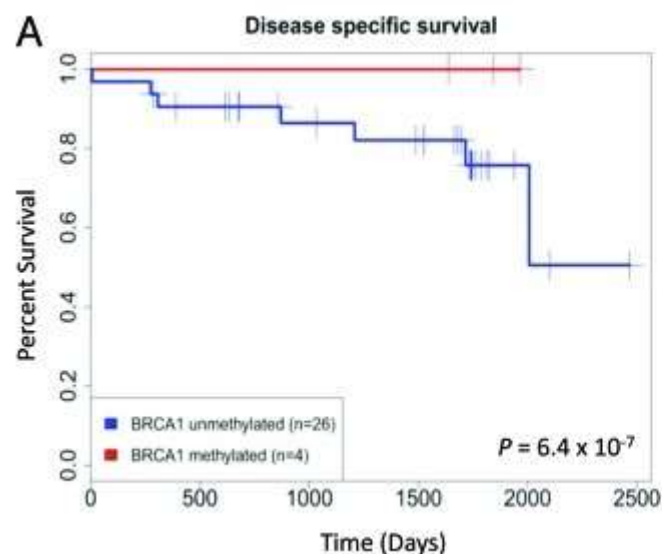
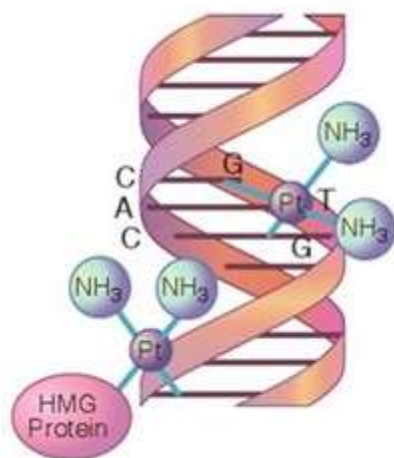
BRCA1 regulates the cell cycle in response to DNA damage

For example, BRCA1 represses transcription of Cyclin B, which is needed for entry into mitosis

The Cell Cycle and the Checkpoints



©(2006) Drexel University



BRCA1 hypermethylation proves to be a predictor of good response to chemotherapy with cisplatin in ovarian cancer patients. BRCA1 hypermethylation in patients with ovarian cancer is associated with longer time to relapse and improved disease-specific survival.

Epigenetics. 2012 Nov 1; 7(11): 1225–1229.
doi: [10.4161/epi.22561](https://doi.org/10.4161/epi.22561)

PMCID: [PMC3499323](https://pubmed.ncbi.nlm.nih.gov/3499323/)
PMID: [23069641](https://pubmed.ncbi.nlm.nih.gov/23069641/)

BRCA1 epigenetic inactivation predicts sensitivity to platinum-based chemotherapy in breast and ovarian cancer

Olafur A. Stefansson,¹ Alberto Villanueva,² August Vidal,³ Lola Martí,⁴ and Manel Esteller^{1, 5, 6,*}

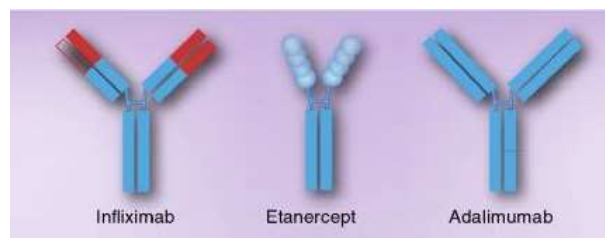
Pharmacogenetics of anti-TNF drugs in psoriasis

Variable	Number	Comparison	CpG site	CHR	Gene Name	CpG-site neighborhood	adj. p-value
Anti-TNF drug global response	70	ER (N=49)	cg18837178	5	NA	N_Shelf	0.003
		vs PR (N=21)	cg23132469	1	TAS1R2	Island	0.014
Adalimumab response	25	ER (N=21)	cg05221720	6	COL9A1	N_Shore	0.049
		vs PR (N=4)					
Etanercept response	27	ER (N=16)					
		vs PR (N=11)					
Infliximab response	18	ER (N=12)					
		vs PR (N=6)					
			CpG site	CHR	Gene Name	CpG-site neighborhood	adj. p-value
			cg09141835	5	CBFA2T3	NA	0.001
			cg23446055	16	PRELID2	NA	0.002
			cg03242666	17	PMP22	S_Shelf	0.026

Significant correlation between PASI at 6 months and DNA methylation values

Psoriasis Area and Severity Index (PASI)

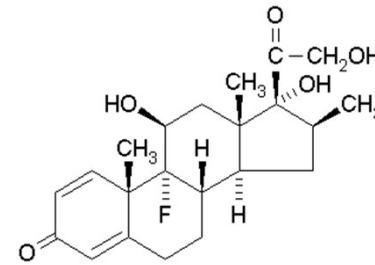
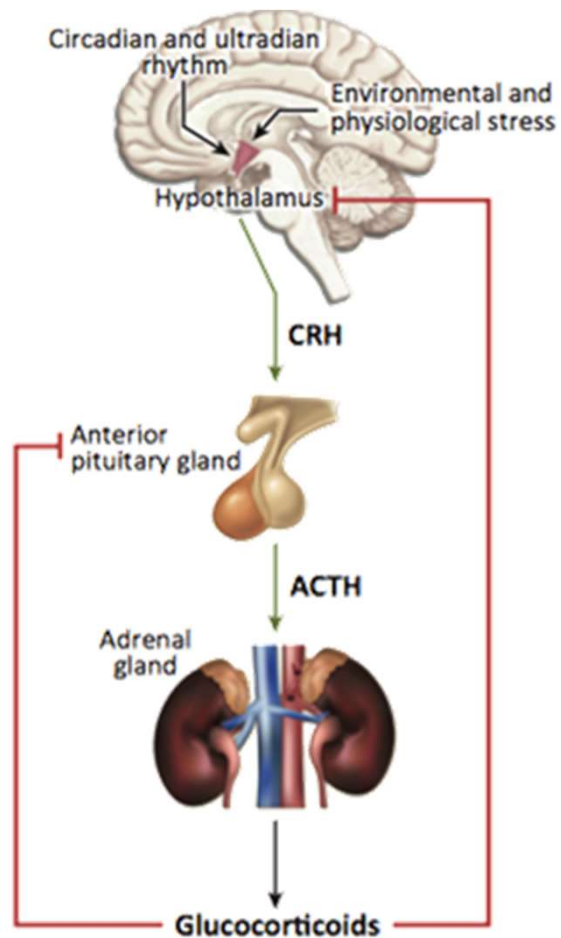
3 CpGs were hypermethylated in PR patients (N=4) with respect to ER patients to adalimumab (N=21)



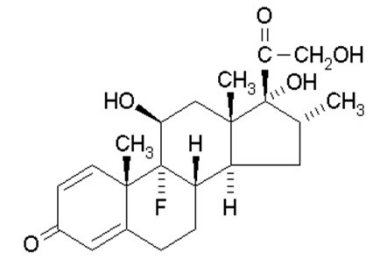
cg09141835 hypermethylated in patients with a poorer response to anti-TNF drugs.

cg23446055 and cg03242666 tend to be hypomethylated in patients with a poorer response to anti-TNF drugs.

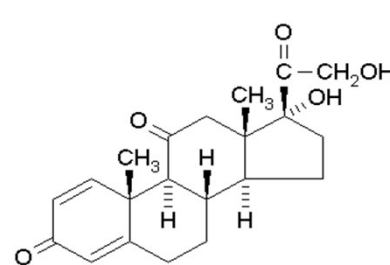
Pharmacogenetics of Glucocorticoids



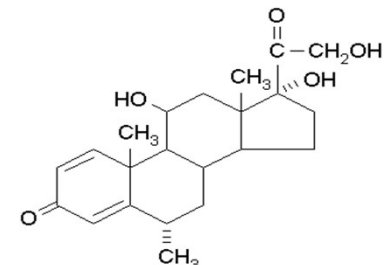
BETAMETHASONE



DEXAMETHASONE



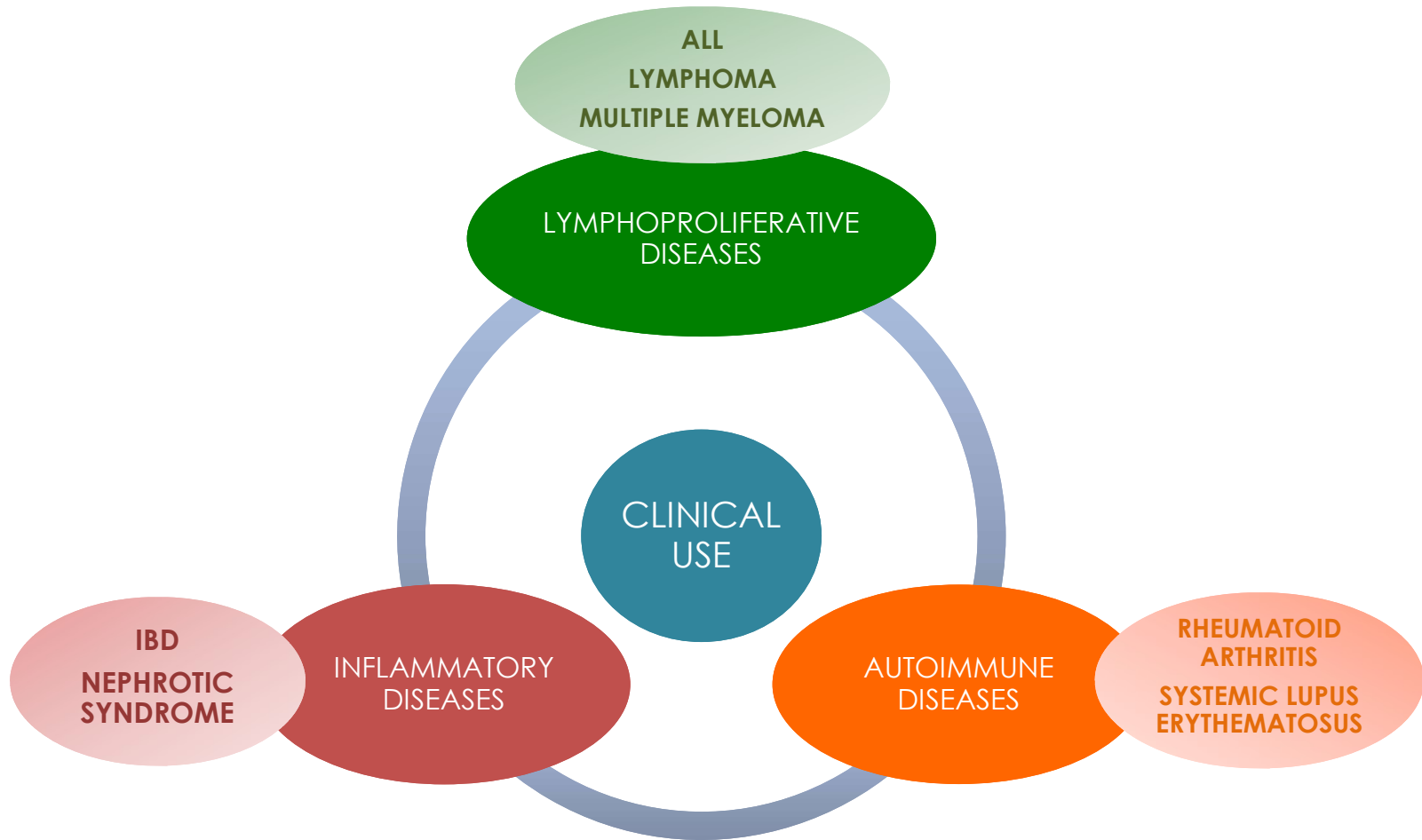
PREDNISONE

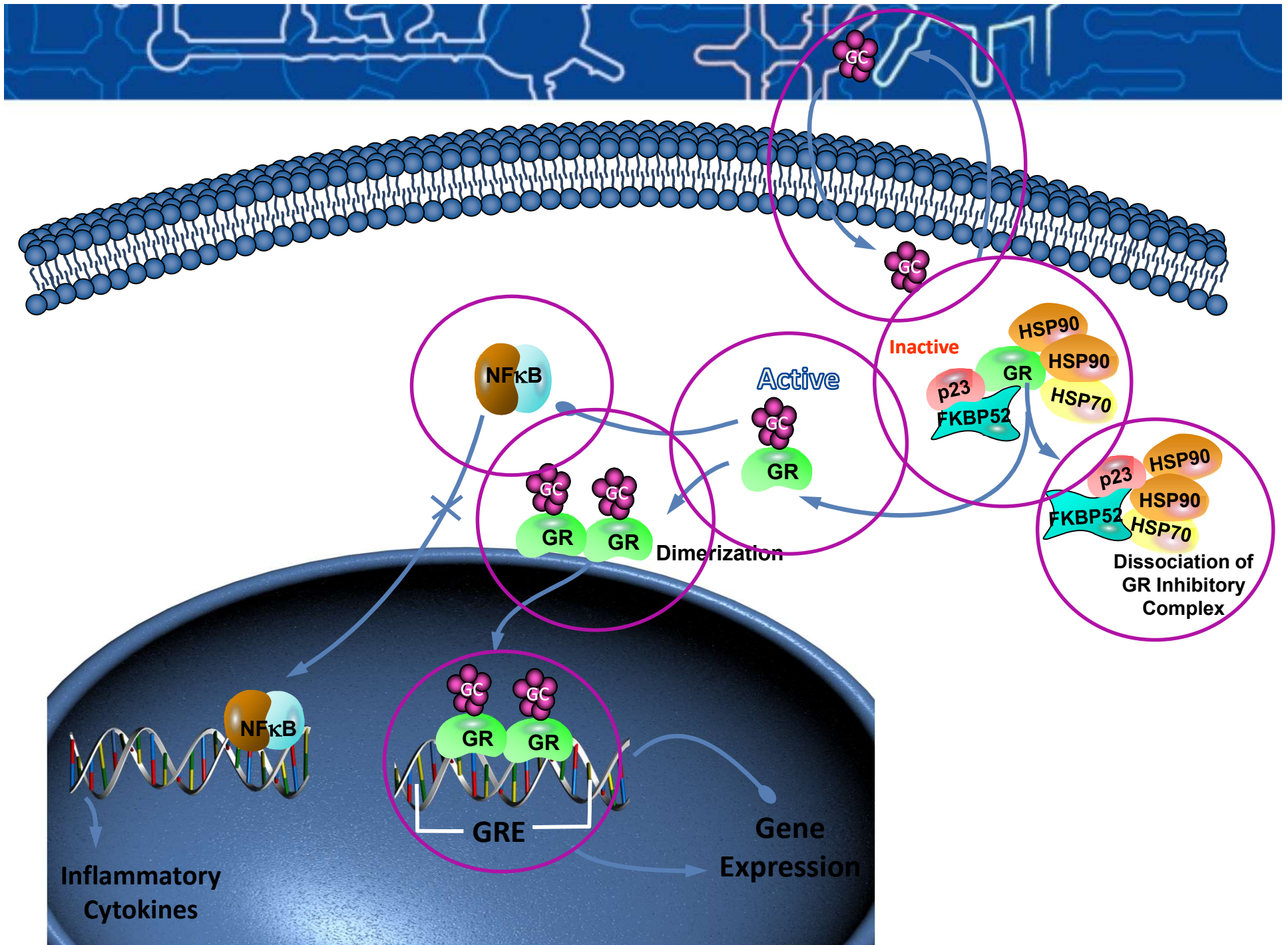


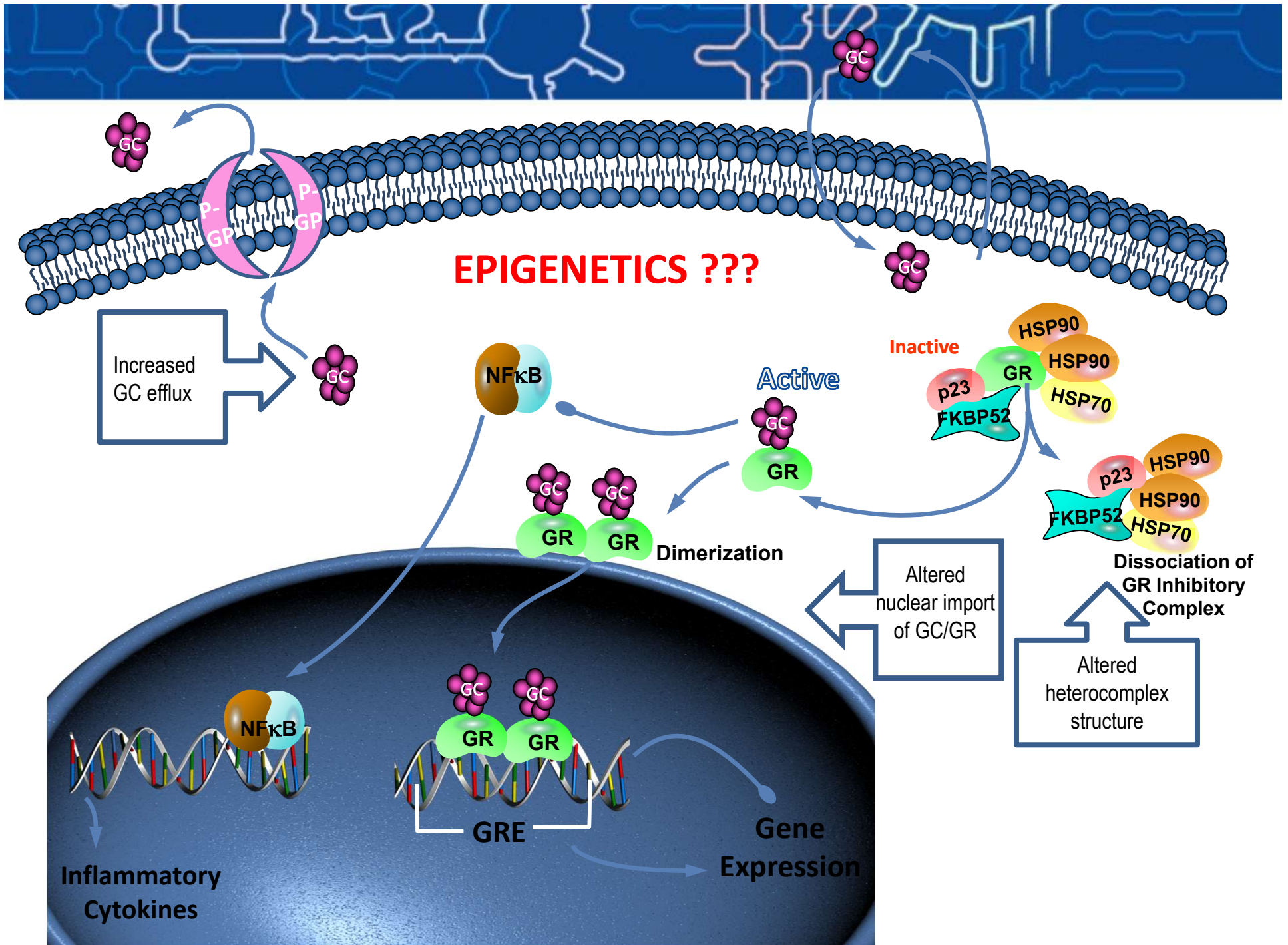
METHYLPREDNISOLONE

(Kadmiel & Cidlowski, 2013)

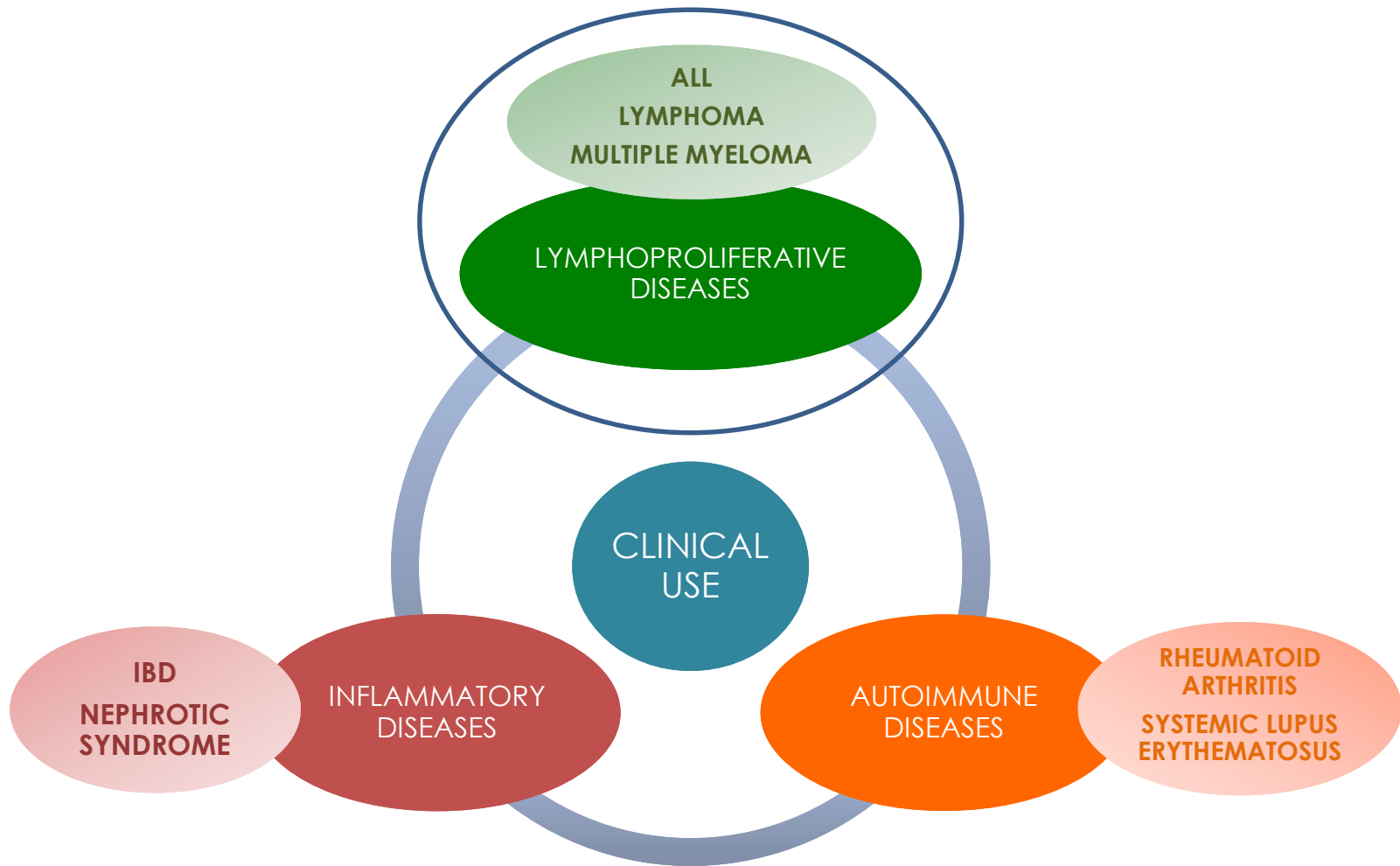
GLUCOCORTICOIDS





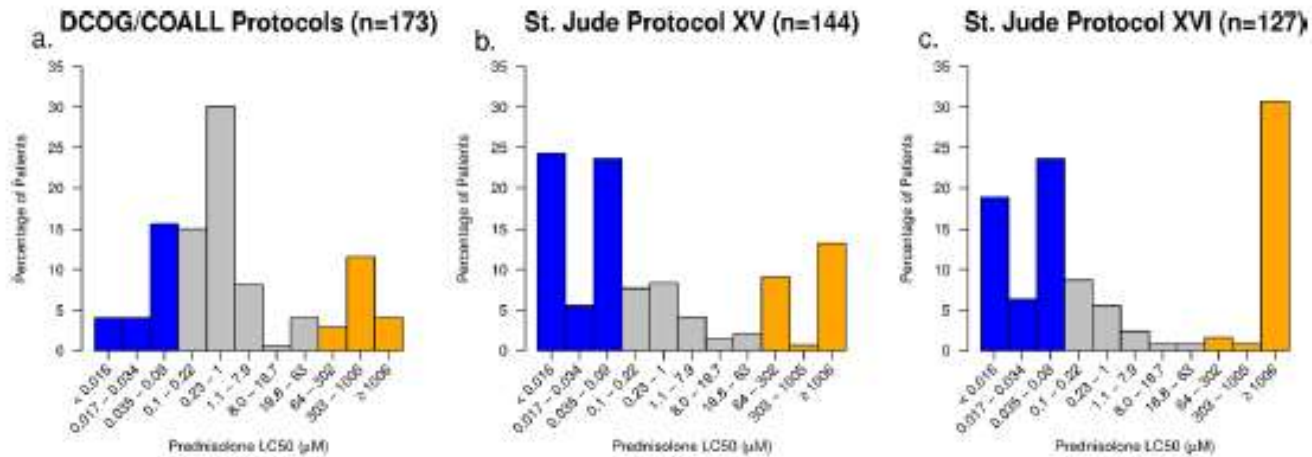


GLUCOCORTICOIDS



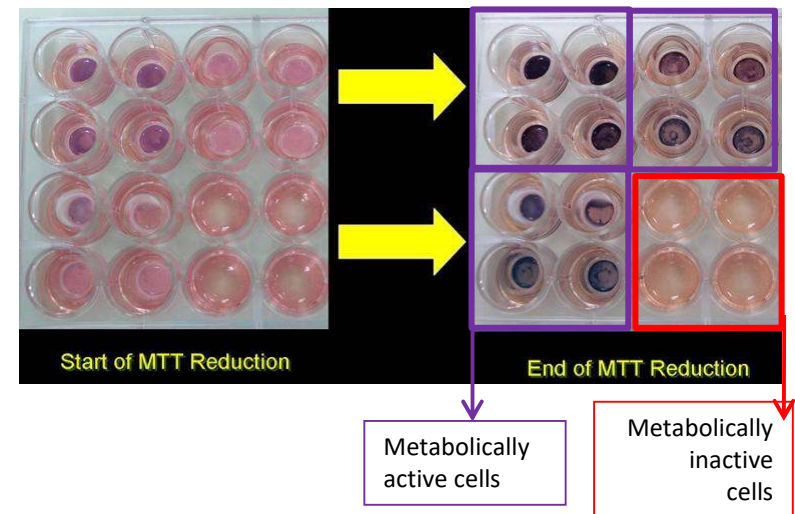
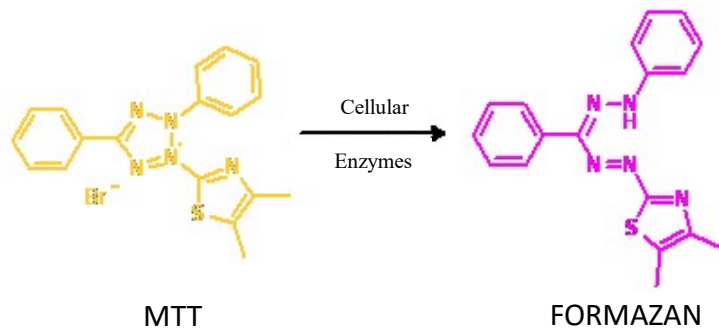
Epigenetic biomarkers associated with GCs response in ALL patients

Steven W. Paugh et al., Nat Genet. 2015

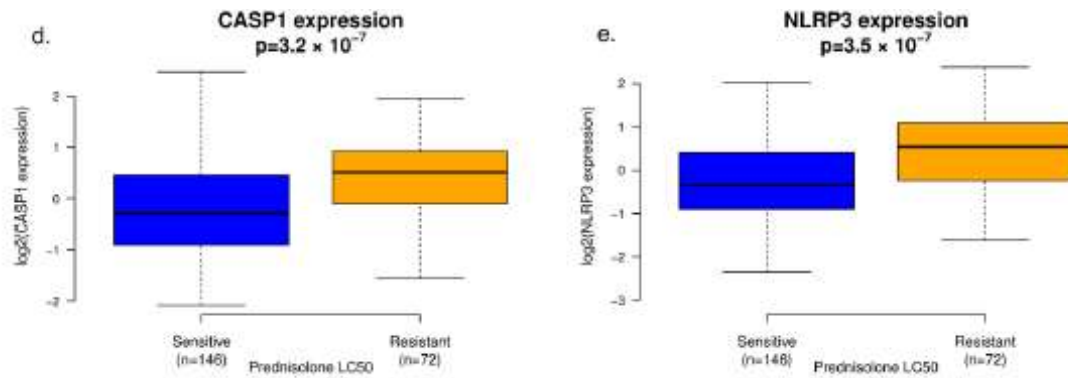


Primary leukemia cells were obtained from 444 patients (B and T cell leukemia) with newly diagnosed acute lymphoblastic leukemia and analyzed for their sensitivity to prednisolone using the MTT assay. Distributions of measured LC50 values are shown for the three independent cohorts of patients; sensitive and resistant leukemias are highlighted in blue and orange, respectively.

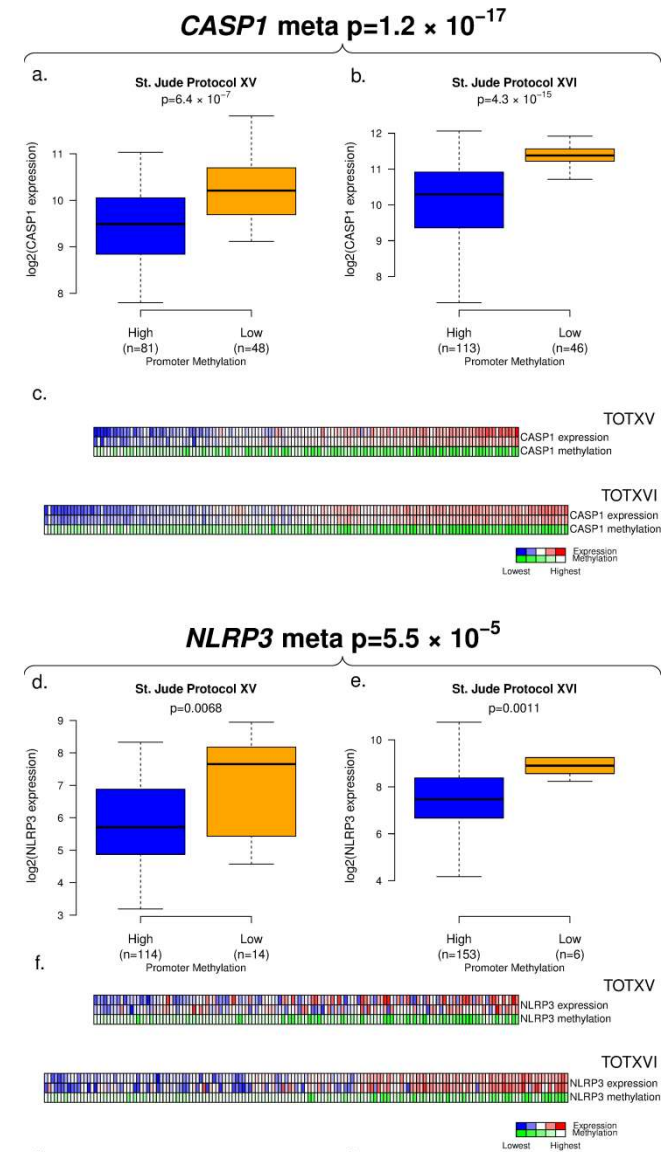
The MTT assay is a colorimetric test for measuring the activity of cellular enzymes:



Epigenetic biomarkers associated with GCs response in ALL patients

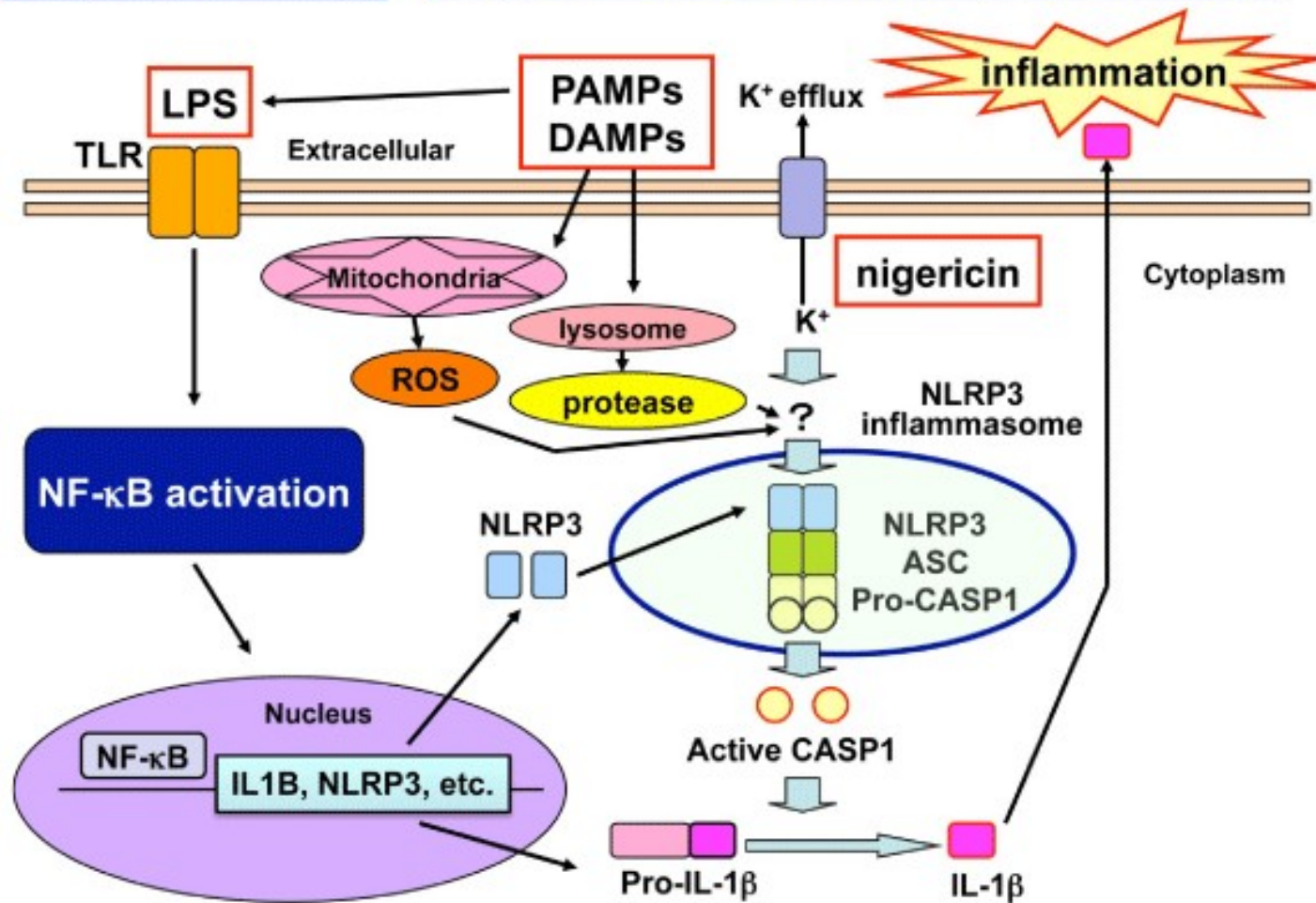


CASP1 (panel D) and *NLRP3* (panel E) expression was significantly higher in glucocorticoid resistant leukemia cells. DNA methylation analysis show significantly lower levels of *CASP1* and *NLRP3* methylation in leukemia cells with higher expression of *CASP1* and *NLRP3*.

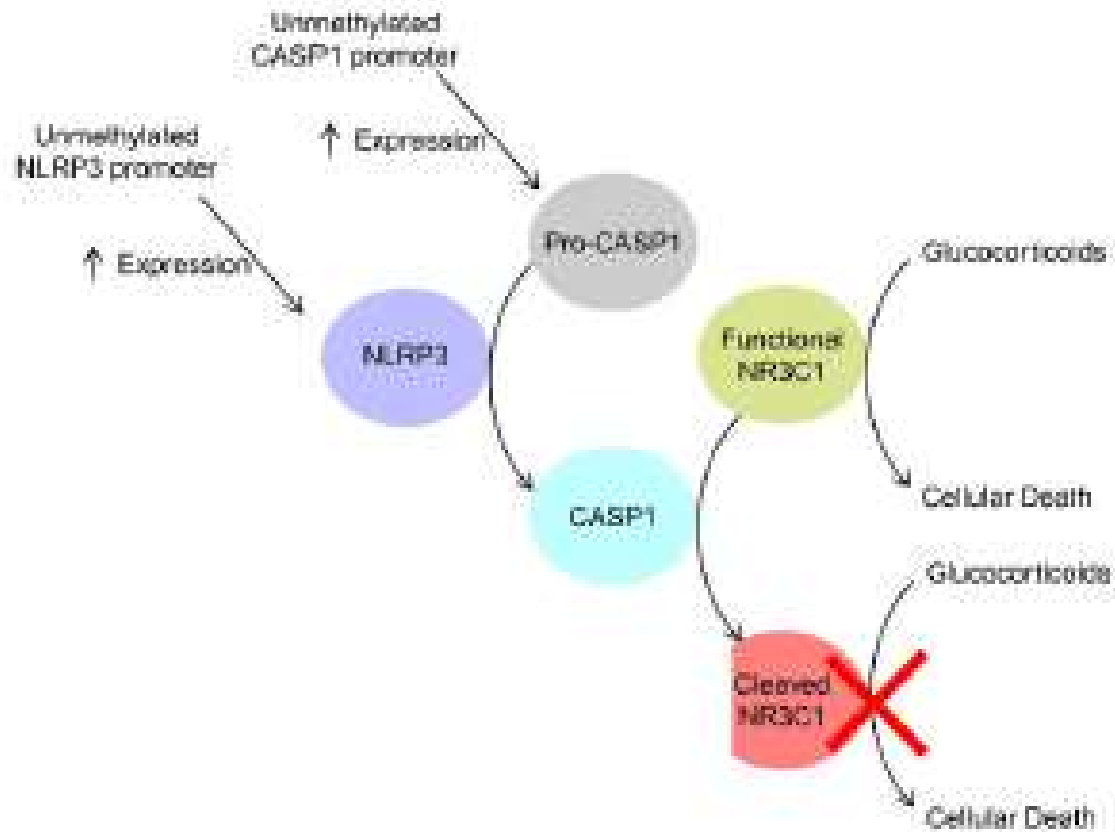


Signal 1: priming

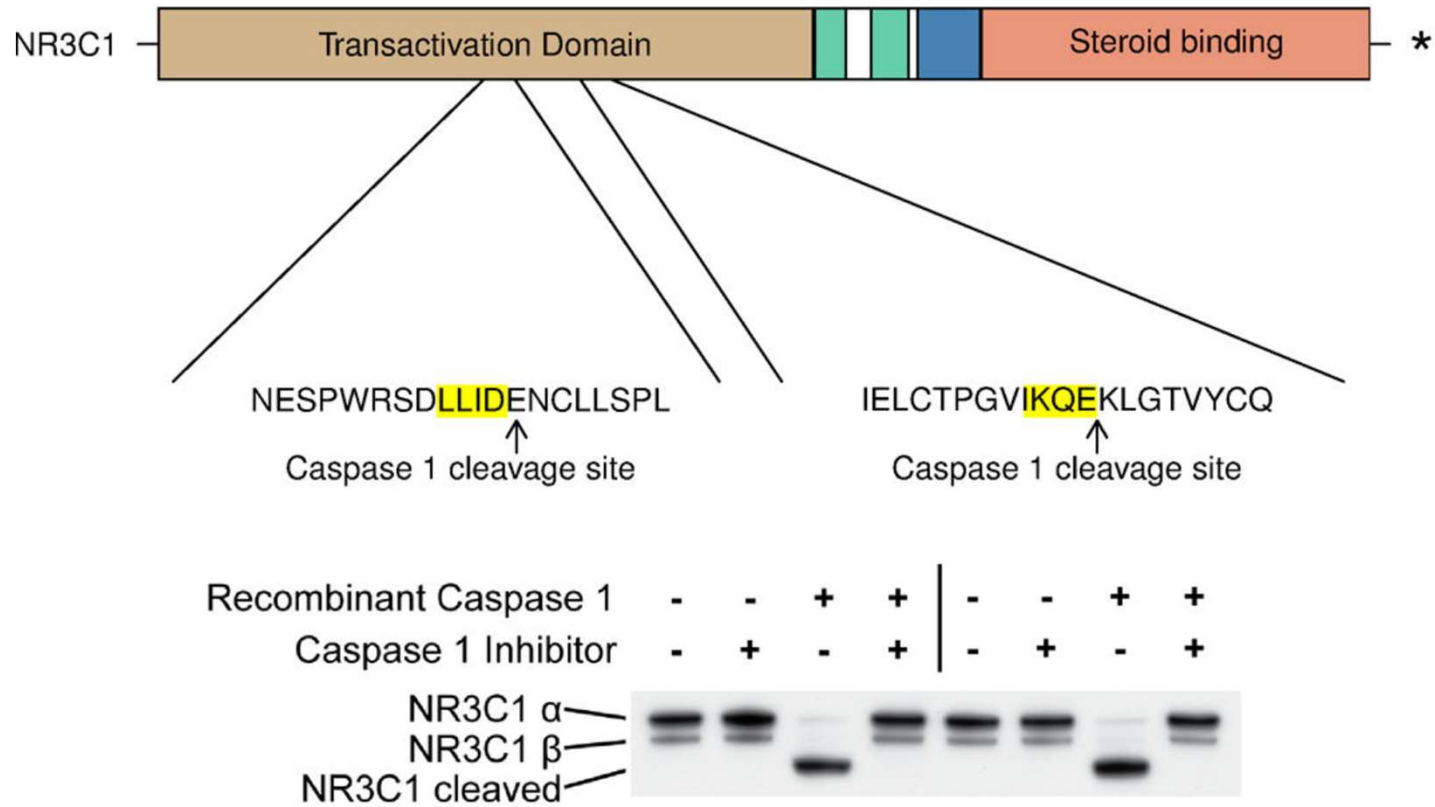
Signal 2: activation for complex formation



Epigenetic biomarkers associated with GCs response in ALL patients

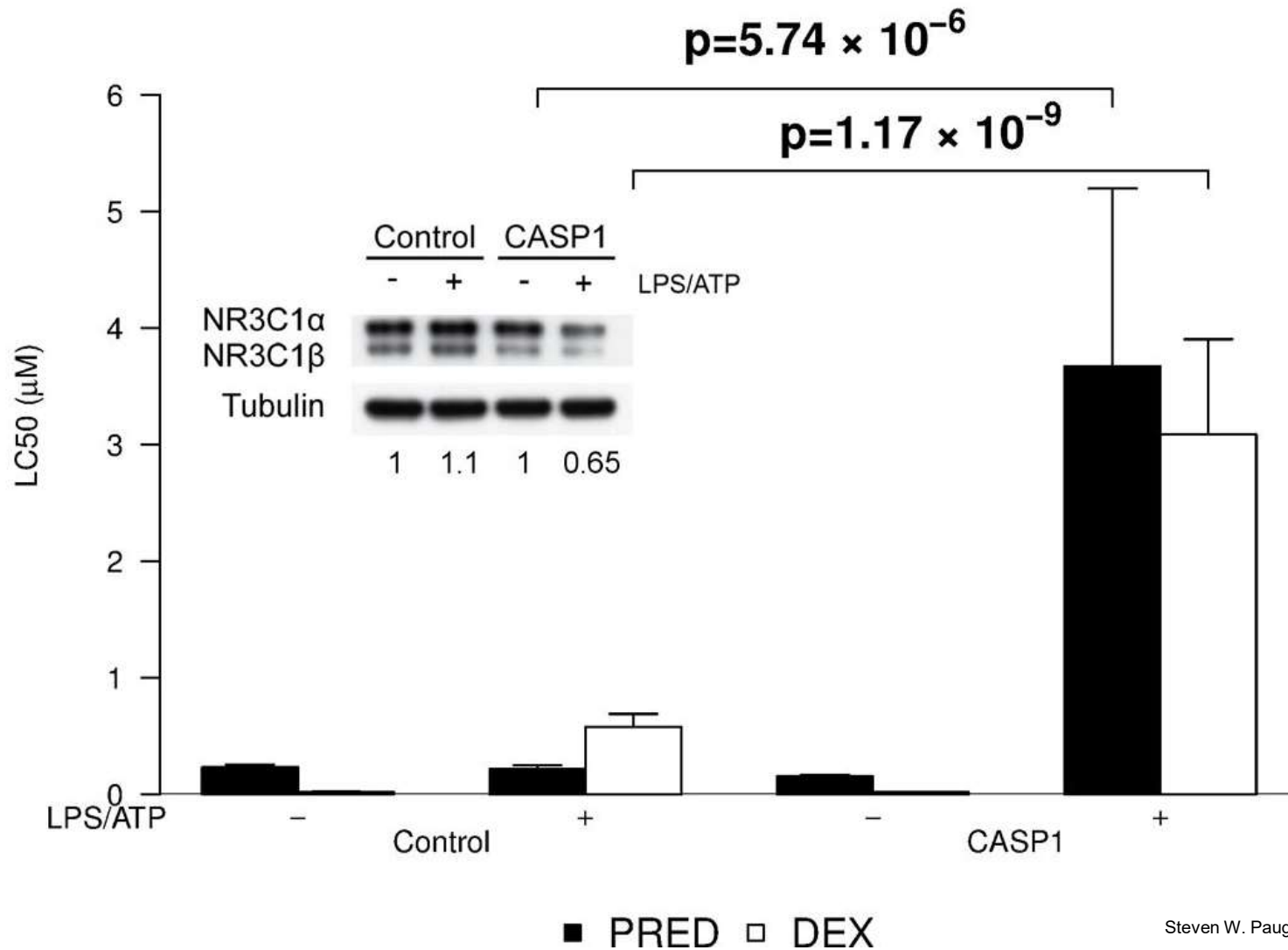


Epigenetic biomarkers associated with GCs response in ALL patients



Epigenetic biomarkers associated with GCs response in ALL patients

CASP1 increases resistance to glucocorticoids

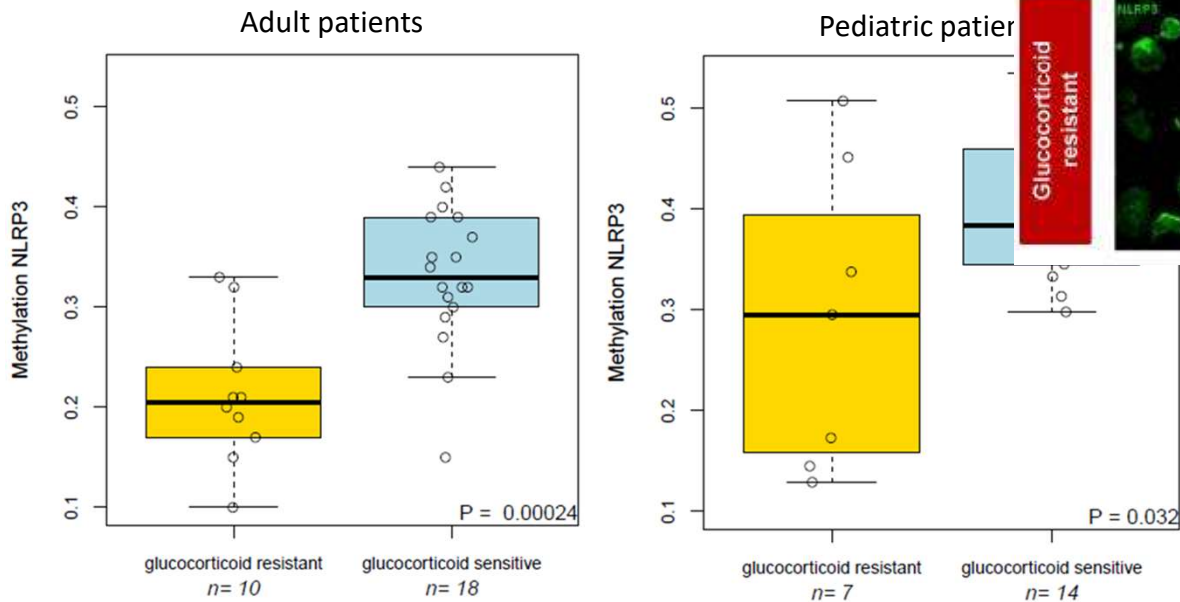
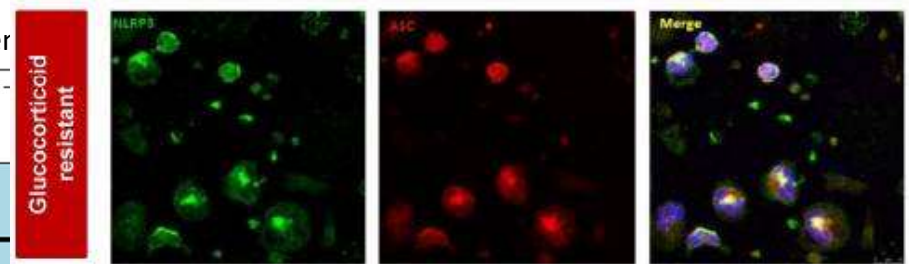
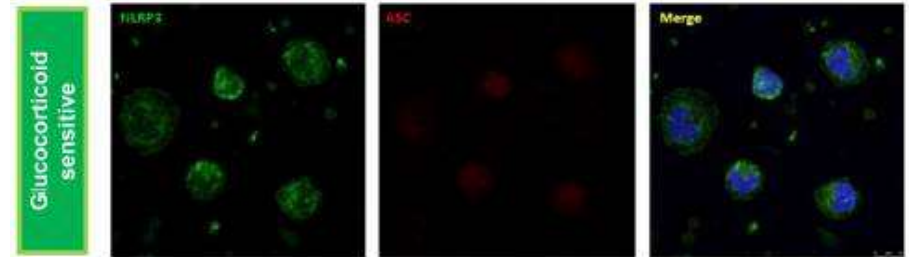


Epigenetic biomarkers associated with GCs response in INS patients

> Clin Transl Sci. 2020 Dec 31. doi: 10.1111/cts.12961. Online ahead of print.

Hypomethylation of NLRP3 gene promoter discriminates glucocorticoid-resistant from glucocorticoid-sensitive idiopathic nephrotic syndrome patients

Marianna Lucafò¹, Simona Granata², Erik J Bonten³, Robert McCorkle³, Gabriele Stocco⁴, Chiara Caletti², Davide Selvestrel⁴, Alessio Cozzarolo⁴, Chan Zou³, Eva Cuzzoni⁴, Andrea Pasini⁵, Giovanni Montini⁶, Giovanni Gambaro², Giuliana Decorti^{1,7}, William Evans³, Gianluigi Zaza²



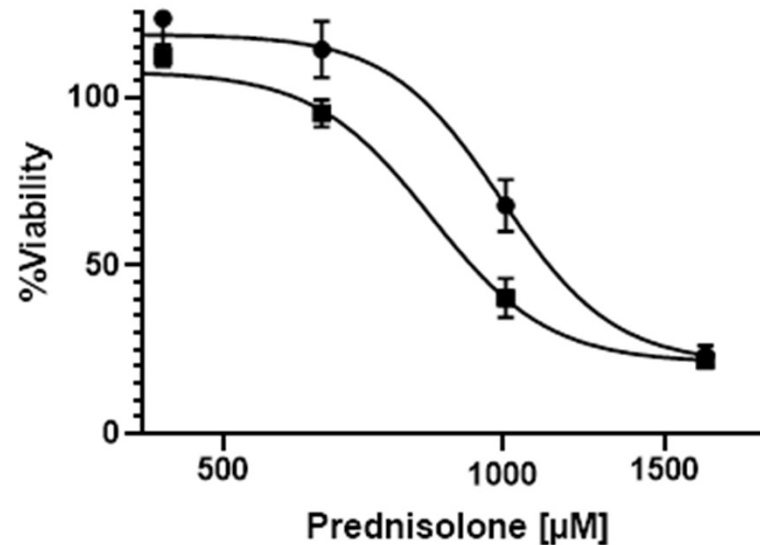
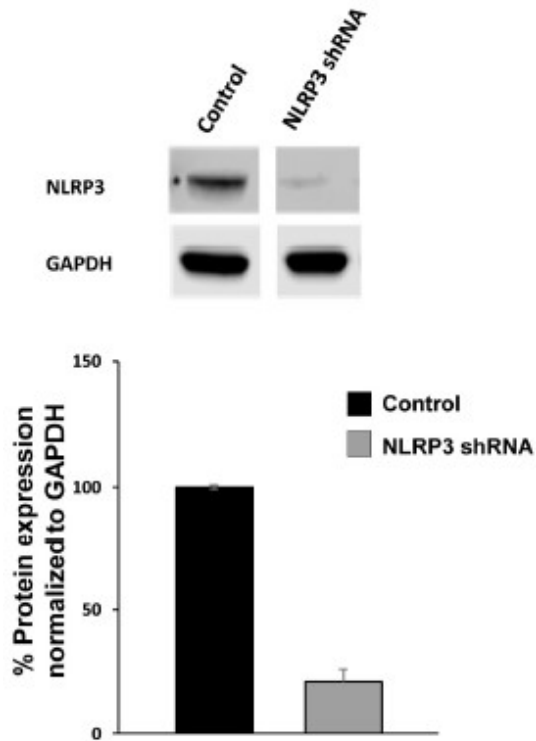
Confocal microscopy was used to confirm that NLRP3 was significantly more abundant in PBMC from GC-resistant compared to GC-sensitive patients.

NLRP3 promoter methylation resulted significantly reduced in GC-resistant compared to GC-sensitive in both adult ($p=0.00024$) and pediatric patients ($p=0.032$).

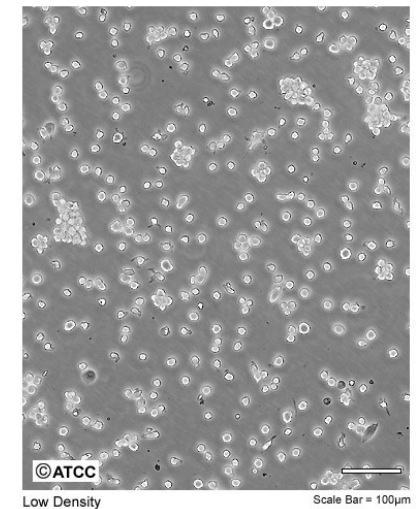
Epigenetic biomarkers associated with GCs response in INS patients

> Clin Transl Sci. 2020 Dec 31. doi: 10.1111/cts.12961. Online ahead of print.

Hypomethylation of NLRP3 gene promoter discriminates glucocorticoid-resistant from glucocorticoid-sensitive idiopathic nephrotic syndrome patients



ATCC Number: TIB-202
Designation: THP-1



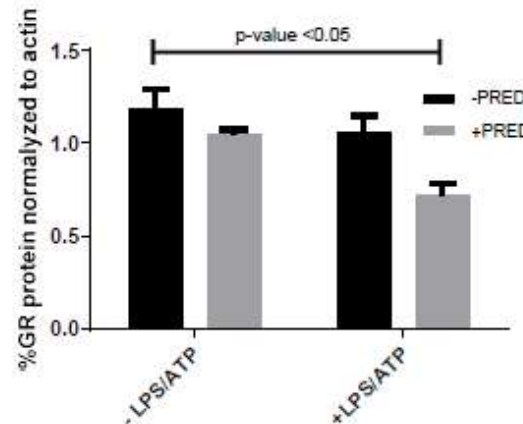
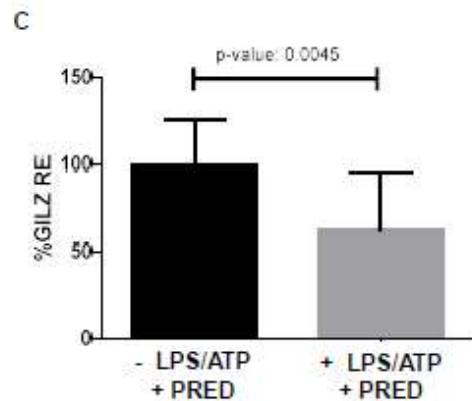
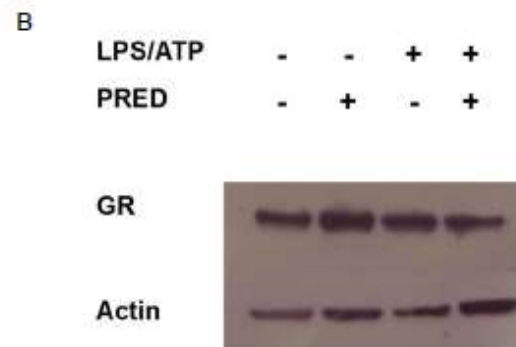
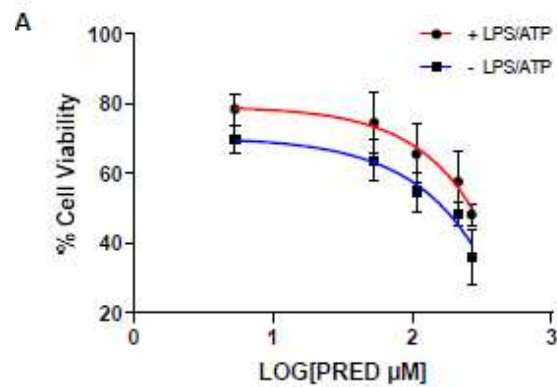
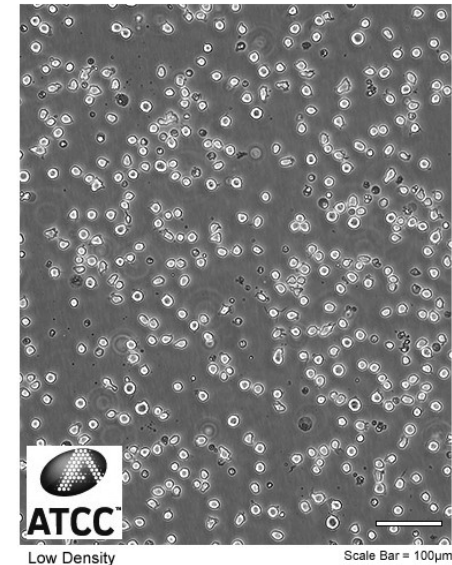
NLRP3 was knocked down in human THP-1 monocyte cells. The shRNAs targeting NLRP3 caused significant knockdown of the encoded protein (79.3%). The knockdown of NLRP3 significantly increased sensitivity to glucocorticoids ($p < 0.0001$), decreasing the PRED LC50 from 998.9 to 833 µM.

Epigenetic biomarkers associated with GCs response in INS patients

> Clin Transl Sci. 2020 Dec 31. doi: 10.1111/cts.12961. Online ahead of print.

Hypomethylation of NLRP3 gene promoter discriminates glucocorticoid-resistant from glucocorticoid-sensitive idiopathic nephrotic syndrome patients

ATCC Number: **CRL-1593.2™**
Designation: **U-937**

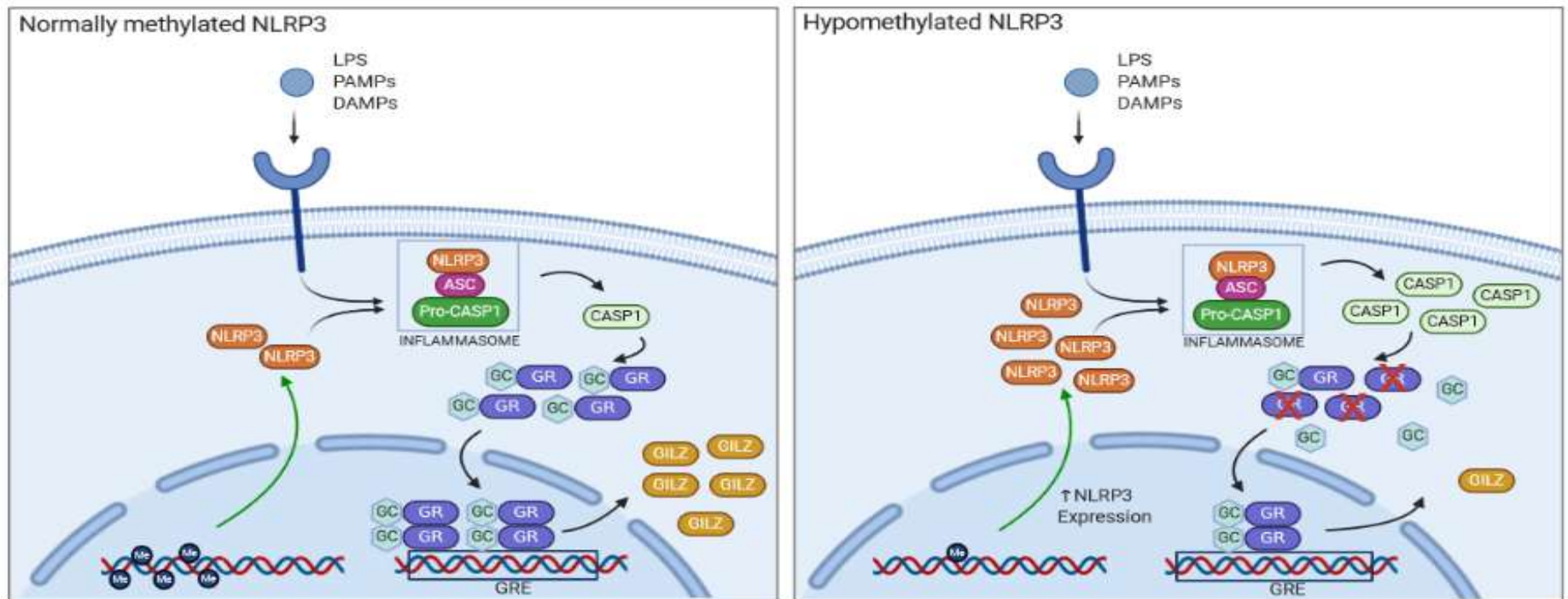


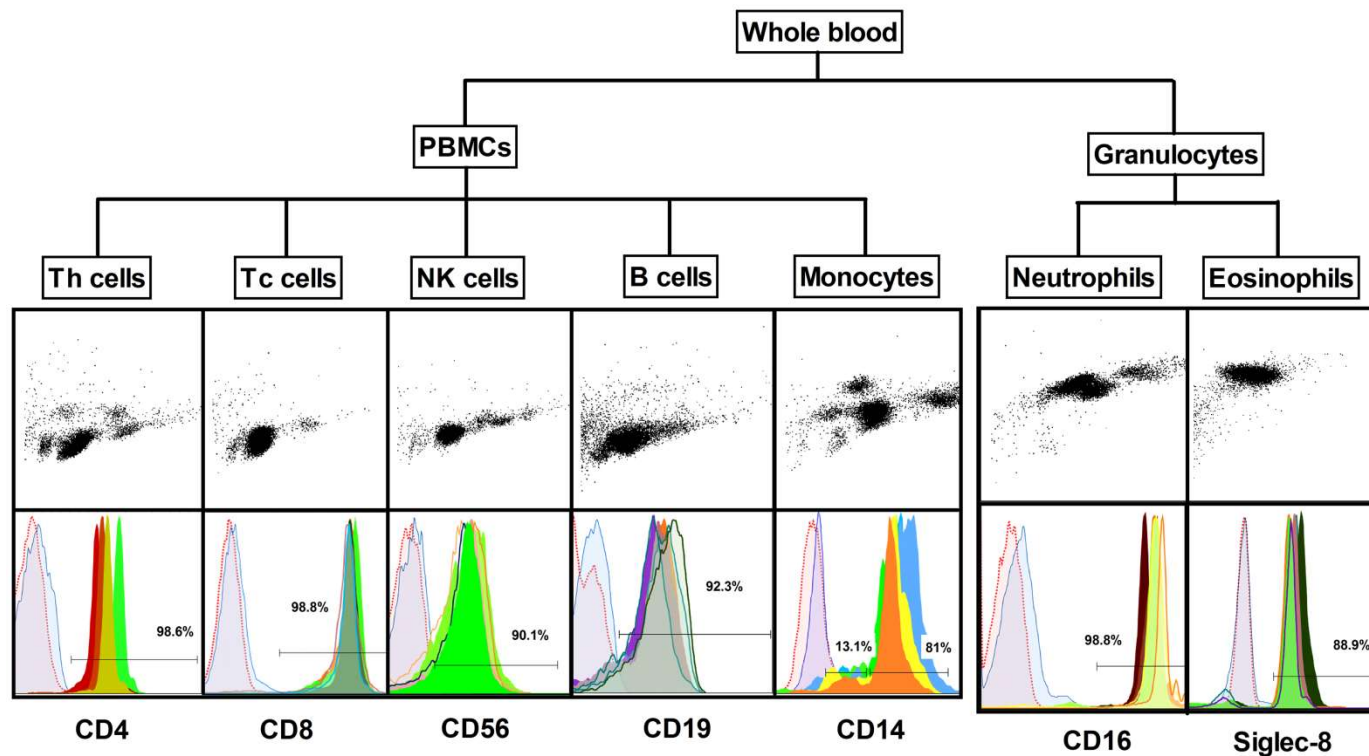
NLRP3 inflammasome activation significantly increased resistance to GC on U937 cells ($p=0.027$). Consistent with this finding, the levels of glucocorticoid receptor diminished significantly after the activation of the NLRP3 inflammasome ($p<0.05$). The ability of GC to induce GILZ expression was markedly lower after activation of the NLRP3 inflammasome compared to the cells without NLRP3 activation ($p=0.0045$), results consistent with reduced GC transcriptional effect after NLRP3 activation.

Epigenetic biomarkers associated with GCs response in INS patients

> Clin Transl Sci. 2020 Dec 31. doi: 10.1111/cts.12961. Online ahead of print.

Hypomethylation of NLRP3 gene promoter discriminates glucocorticoid-resistant from glucocorticoid-sensitive idiopathic nephrotic syndrome patients





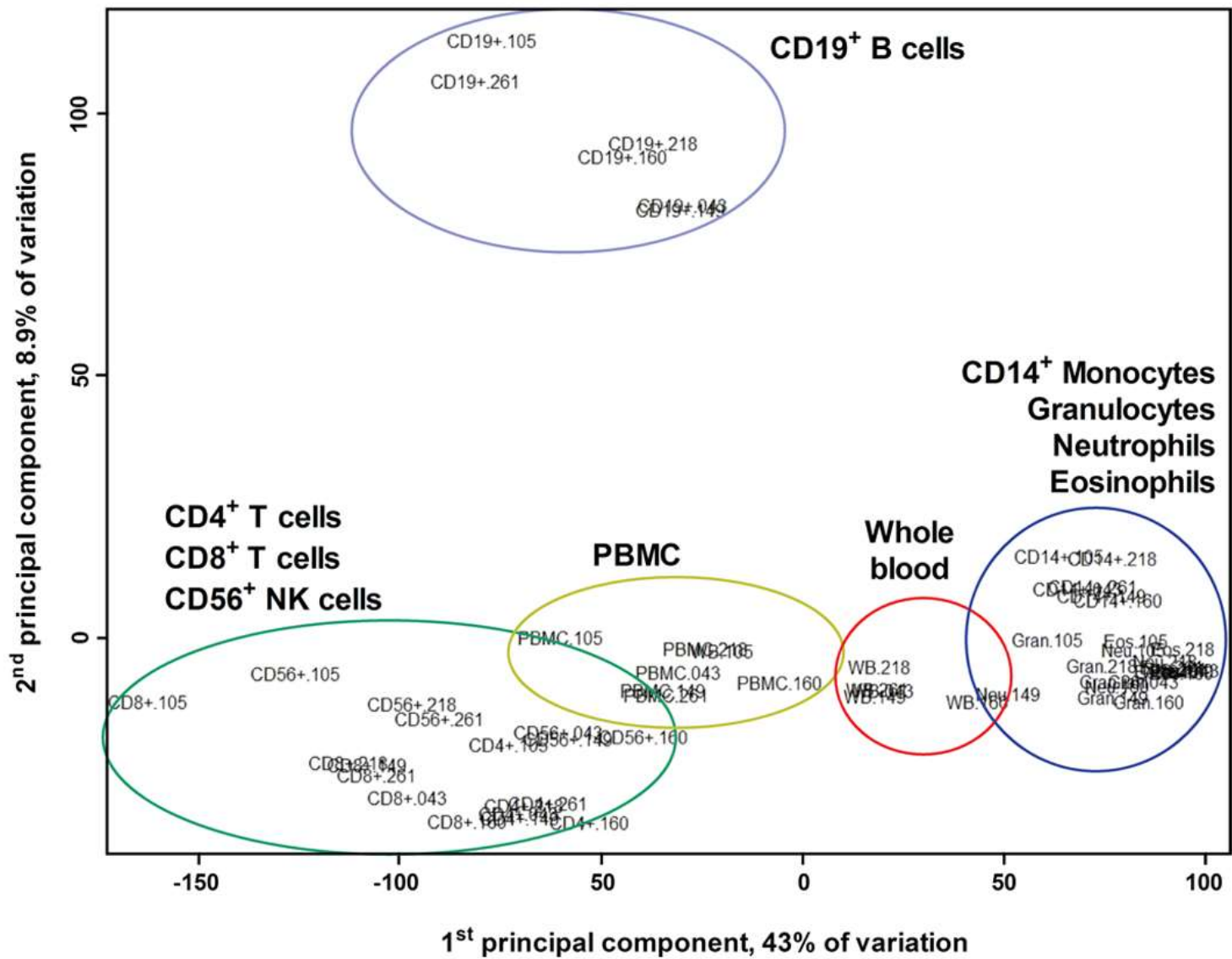
PLoS One. 2012;7(7):e41361. doi: 10.1371/journal.pone.0041361. Epub 2012 Jul 25.

Differential DNA methylation in purified human blood cells: implications for cell lineage and studies on disease susceptibility.

Reinius LE¹, Acevedo N, Joerink M, Pershagen G, Dahlén SE, Greco D, Söderhäll C, Schevnius A, Kere J.

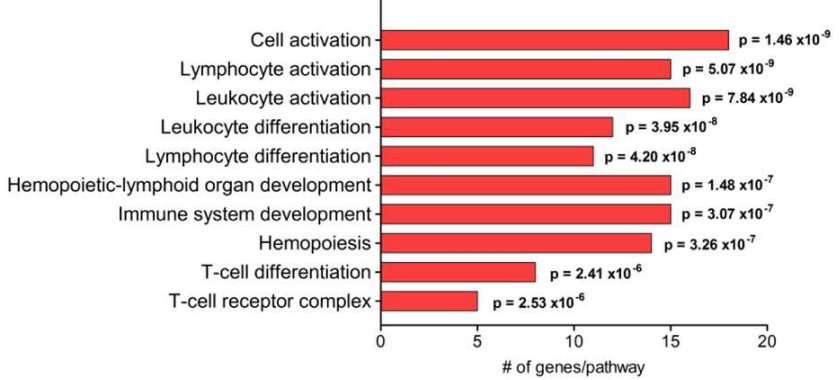


3

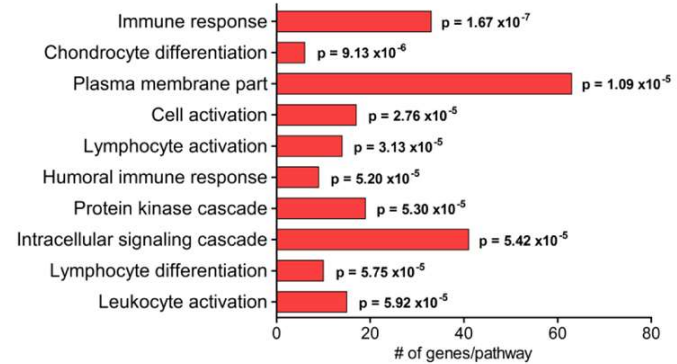




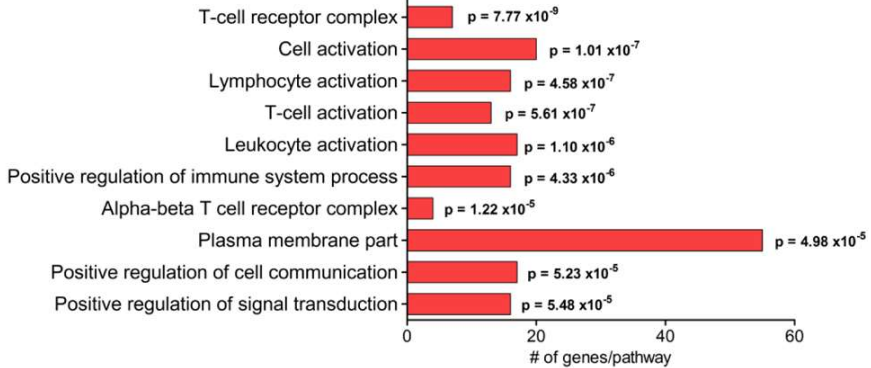
CD4⁺



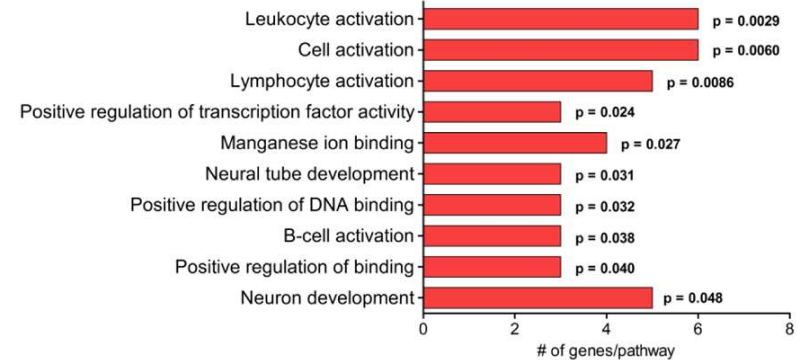
CD19⁺



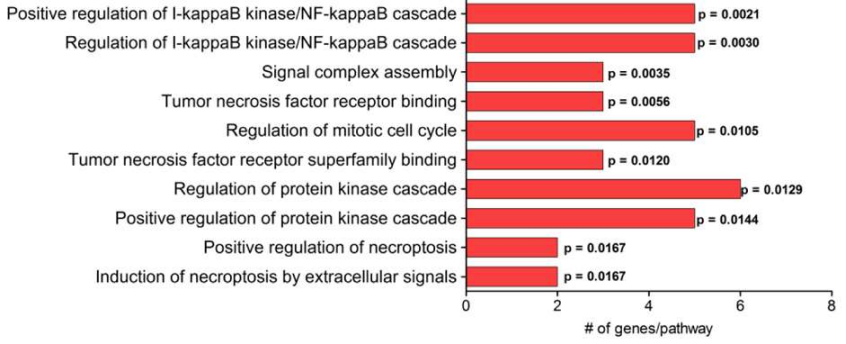
CD8⁺



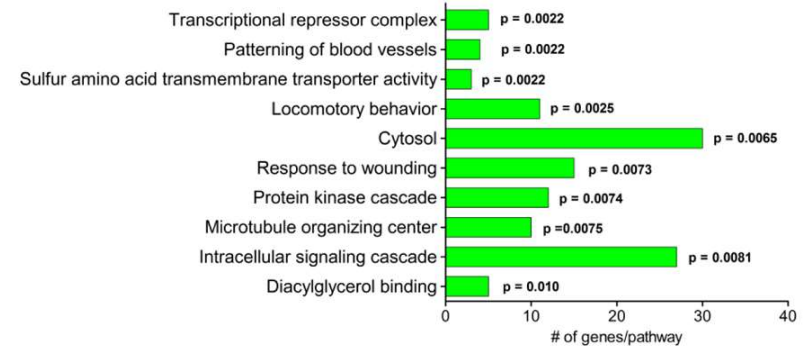
CD14⁺



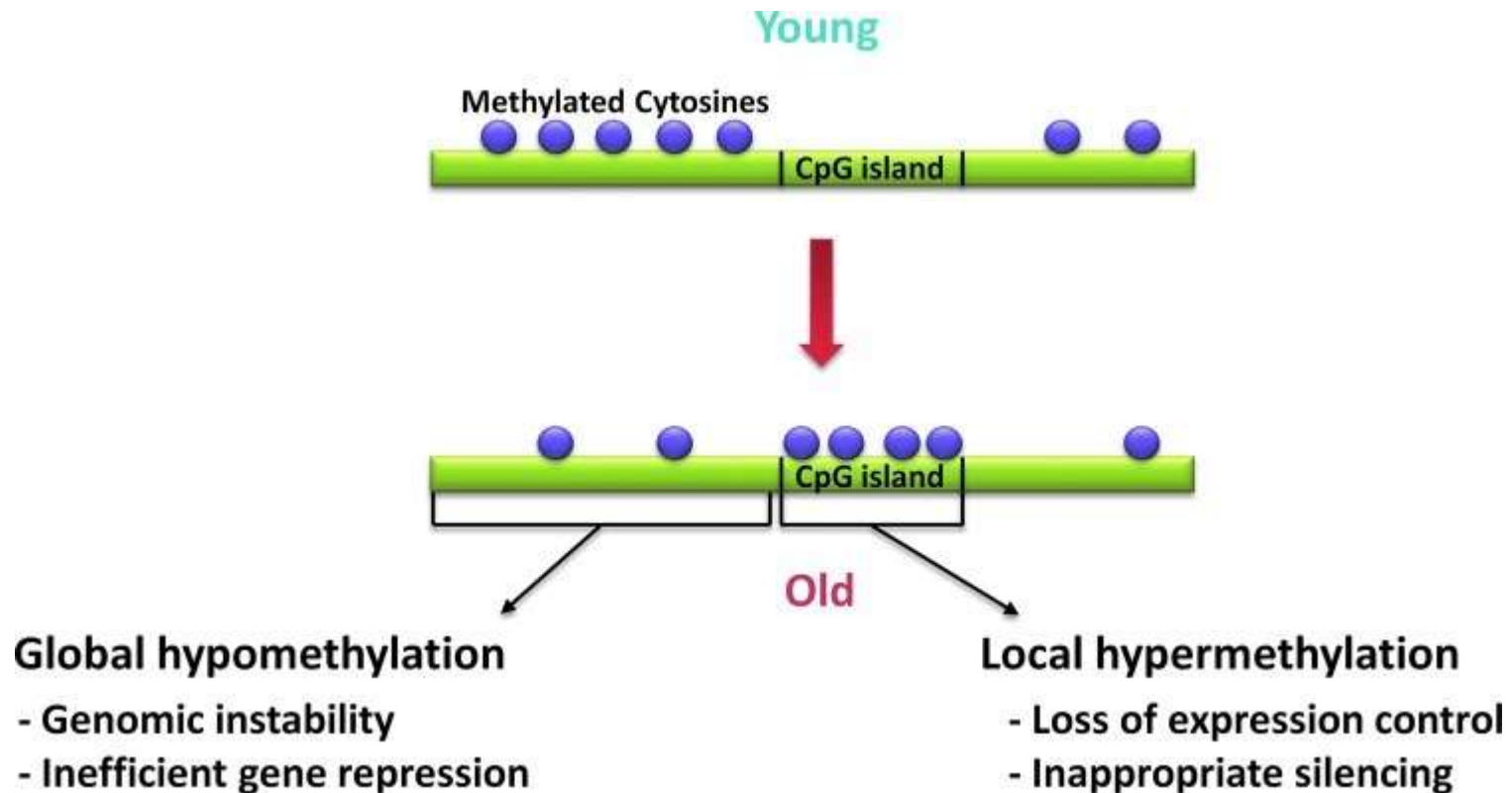
CD56⁺



Eosinophils

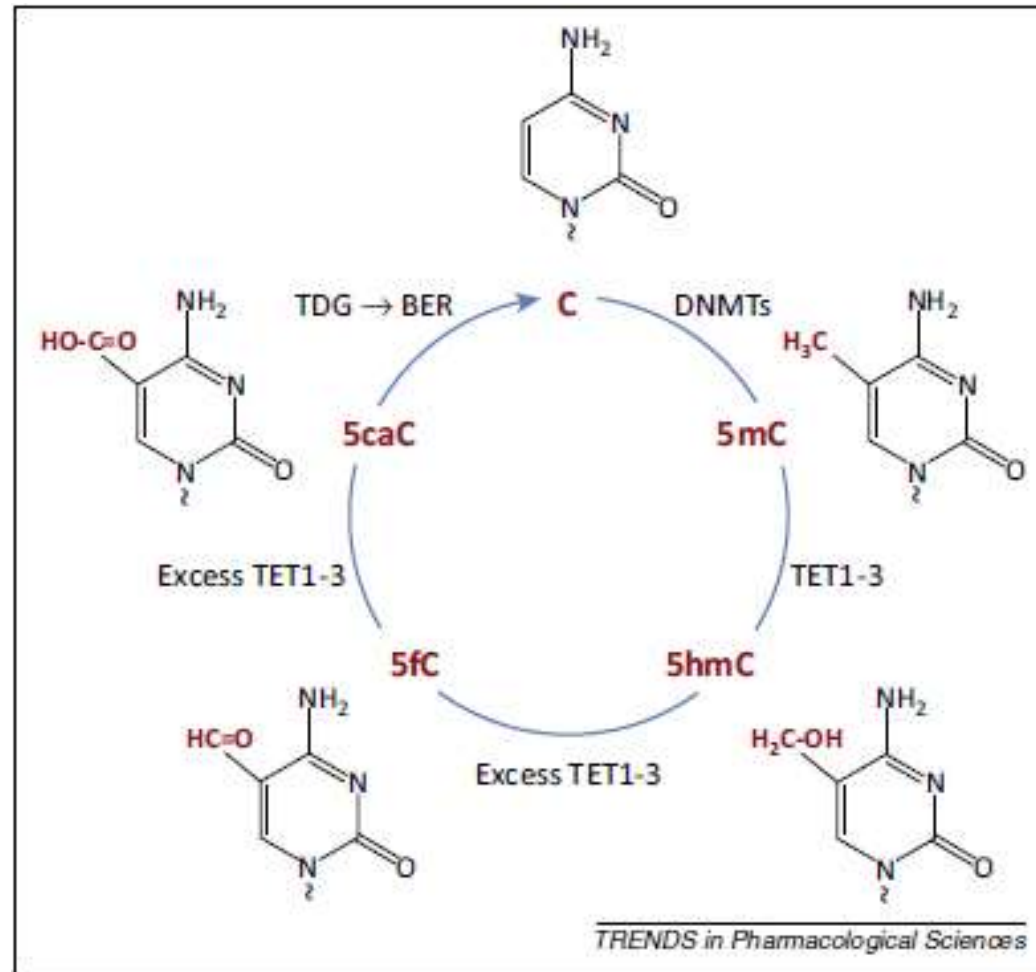


DNA methylation dynamics in aging

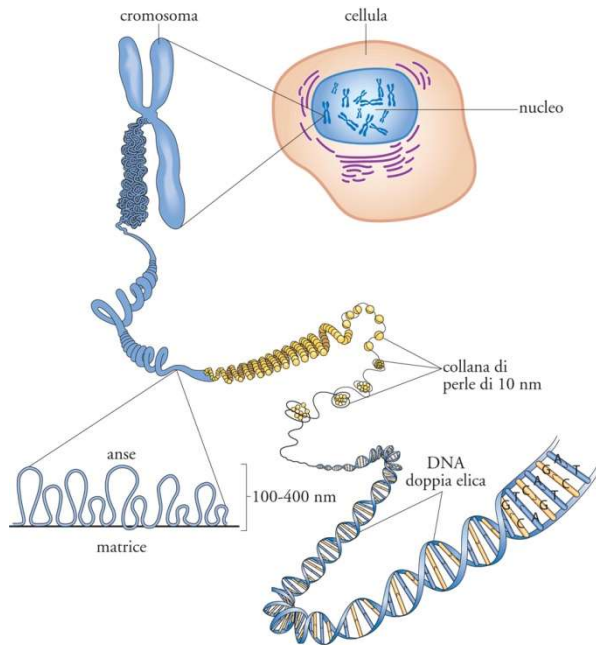


Schematic representation of the changes in the methylome during aging. Purple circles are indicative of methylated CpG dinucleotides. Aging is often marked by the establishment of global hypomethylation and regions of CpG island hypermethylation.

Cytosine modification cycle

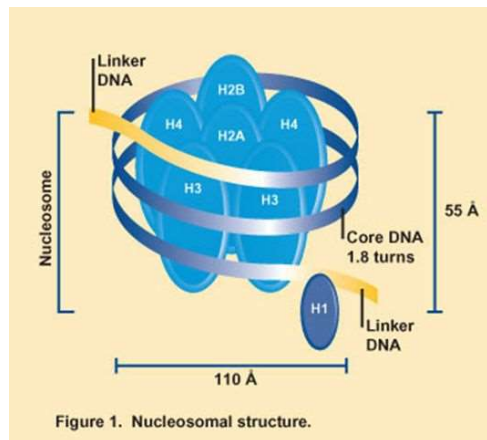
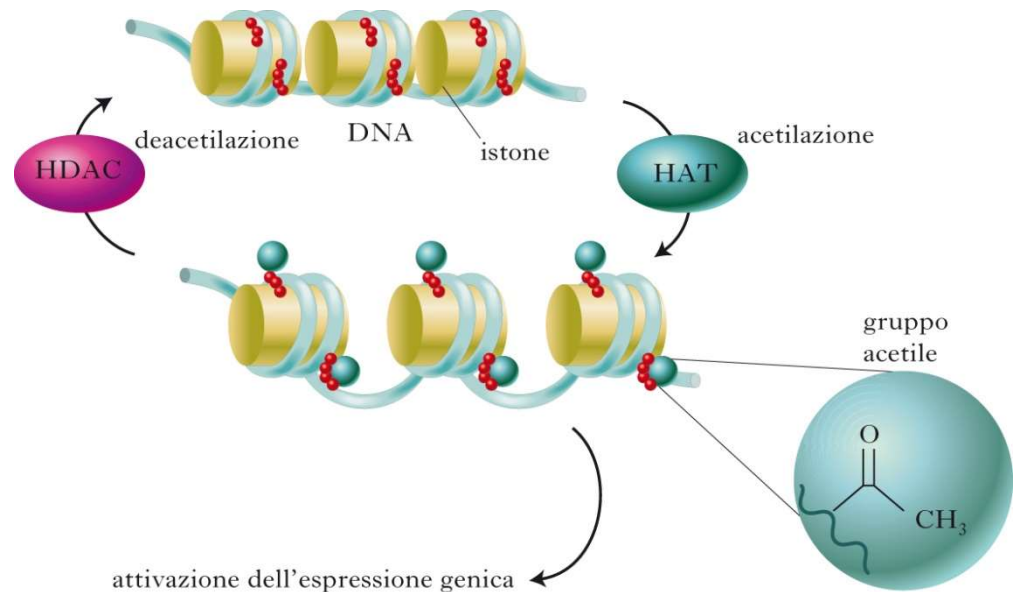


MODIFICAZIONE DELLA CROMATINA (acetilazione e/o metilazione degli istoni)



Modifiche covalenti a carico degli istoni

- Acetilazione (influenza la condensazione della cromatina), fosforilazione, monoubiquitinazione. Sono modifiche reversibili
- Metilazione; è parzialmente reversibile e pare ci sia corrispondenza tra metilazione degli istoni e del DNA

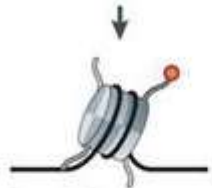


MODIFICAZIONI ISTONICHE: metodologie

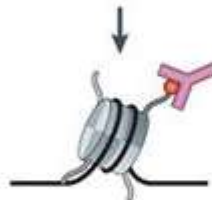
Histone modification ChIP-seq



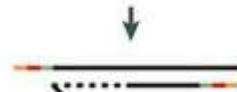
Crosslink proteins and DNA



Sample fragmentation
• MNase digestion



Immunoprecipitate and
then purify DNA



Amplify, if few cells
• Nano-ChIP-seq
• LinDA

•A library creation and sequencing

Histone ChIP-Seq:

- Reagente che instaura legami crociati proteine-DNA (formaldeide)
- Estrazione cromatina
- Rottura meccanica del DNA
- Uso di anticorpi contro istoni acetilati
- Rottura legami istoni-DNA
- Sequenziamento DNA: la sequenza rivela quali regioni del genoma erano associate a istoni acetilati

MARCATORI EPIGENETICI ASSOCIATI AI GENI ADME

Phase I enzymes	ADH1B ALDH1A2 ALDH1A3 CYP17A1 CYP26C1 CYP39A1 CYP3A5	CYP3A7 CYP7B1 DPYD FMO3 GPX1 GPX3 GPX7	ADH1C CYP19A1 CYP1A1 CYP1A2 CYP1B1 CYP24A1 CYP26A1	CYP27B1 CYP2A13 CYP2E1 CYP3A4 DHRS4L2 SULF1
	Phase II enzymes	GSTM1 GSTM5 SULT1A1 SULT1C2 UGT1A6 UGT2B15 UGT2B28	GSTA1 GSTA2 GSTT2 NNMT SULT2B1 UGT2B11 UGT2B7	GSTM2 GSTP1 NAT1 UGT1A1
Transporters	ABCB4 ABCC6 SLC22A18AS SLC22A1 SLC22A3 SLC22A6	SLC22A8 SLC26A4 SLC29A1 SLCO1B3 SLCO1C1 SLCSA5	ABCA1 ABCB1 ABCG2 SLC19A1 SLC22A2 SLC2A5	SLCSA8 SLCO2A1
	Modifiers	CAT HNF1A PXR RARβ	CFTR MPO PPARA PPARG SOD2 SOD3	

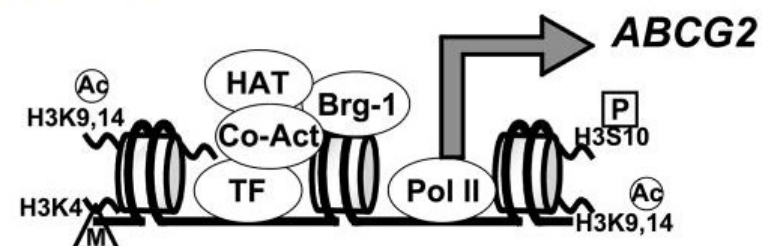
Green denotes genes regulated by DNA methylation; blue denotes genes modulated by histones modifications; orange denotes genes influenced by both mechanisms

TRENDS in Pharmacological Sciences

MARCATORI EPIGENETICI ASSOCIATI AI GENI ADME

Histone Modifications at the *ABCG2* Promoter following Treatment with Histone Deacetylase Inhibitor Mirror Those in Multidrug-Resistant Cells

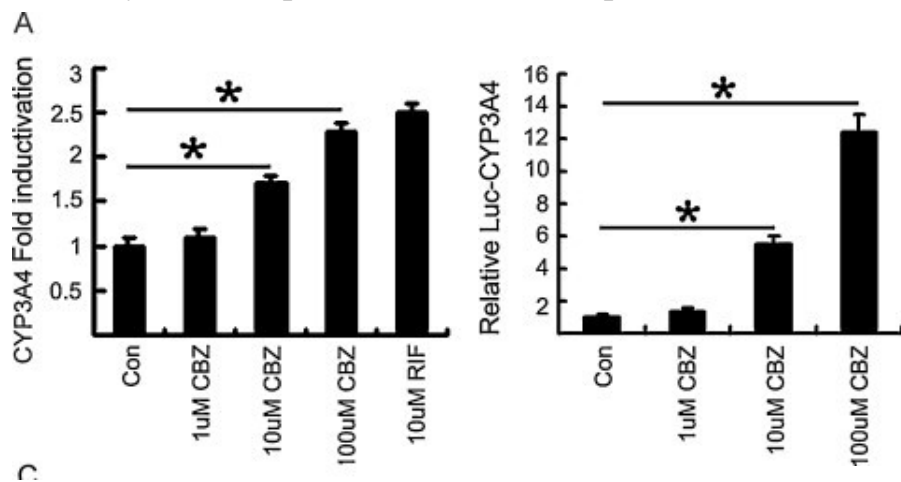
[Kenneth K.W. To](#), [Orsolva Polgar](#), [Lyn M. Huff](#), [Kuniaki Morisaki](#), and [Susan E. Bates](#)



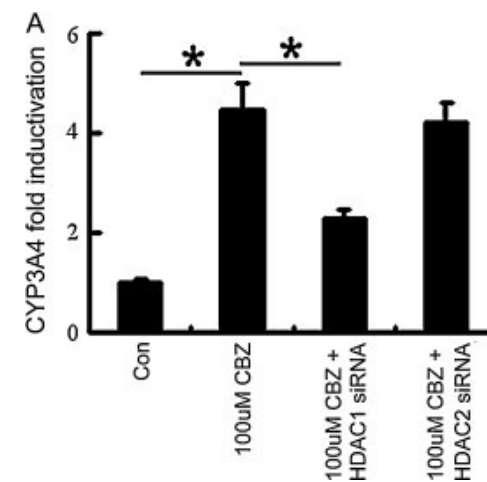
Histone deacetylase 1 is required for Carbamazepine-induced CYP3A4 expression

Yin Wu^{a,1}, Xiaopeng Shi^{a,1}, Yonghong Liu^b, Xianzhi Zhang^c, Jinwen Wang^a, Xiaoxing Luo^{d,**}, Aidong Wen^{a,*}

CBZ induced CYP3A4 expression. Real time results of CBZ-induced CYP3A4 in HepG2 cells. Luciferase reporter assay of the expression of CYP3A4 promoter in CBZ treated cells (C).



C



RNA non codificante

Non-coding RNA is an RNA that functions without being translated to a protein.

