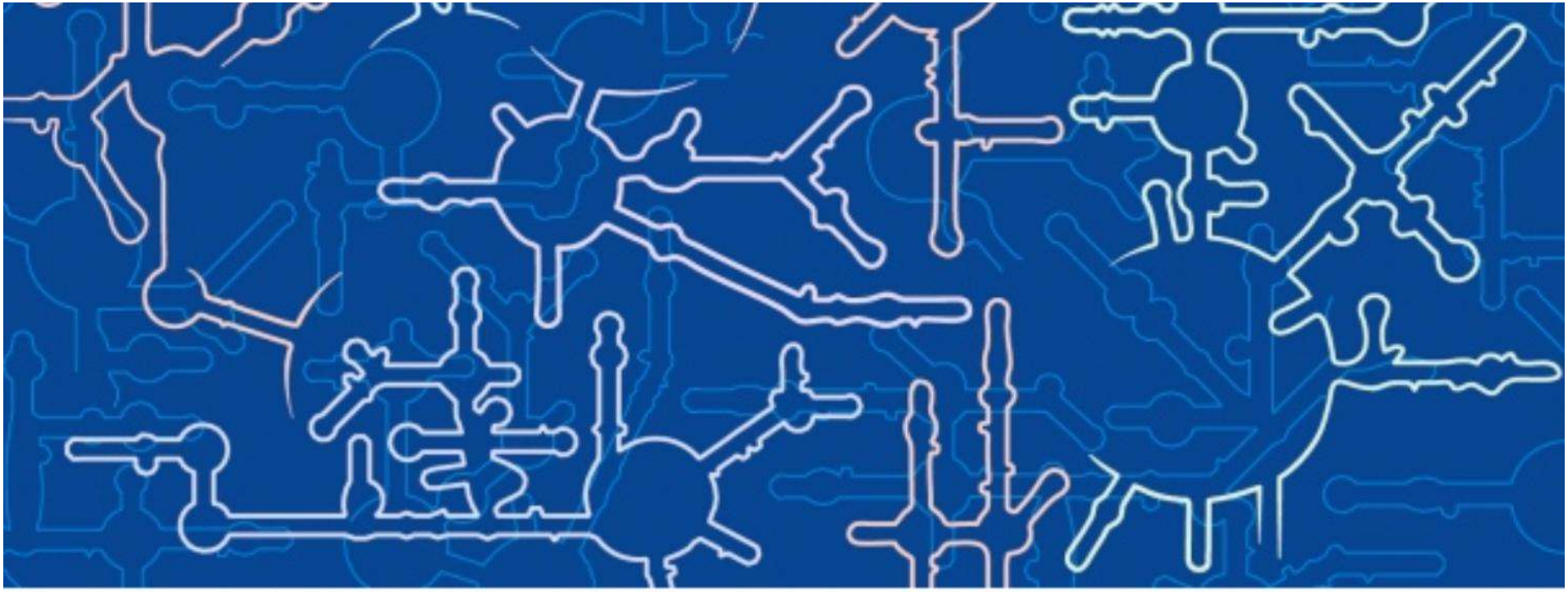
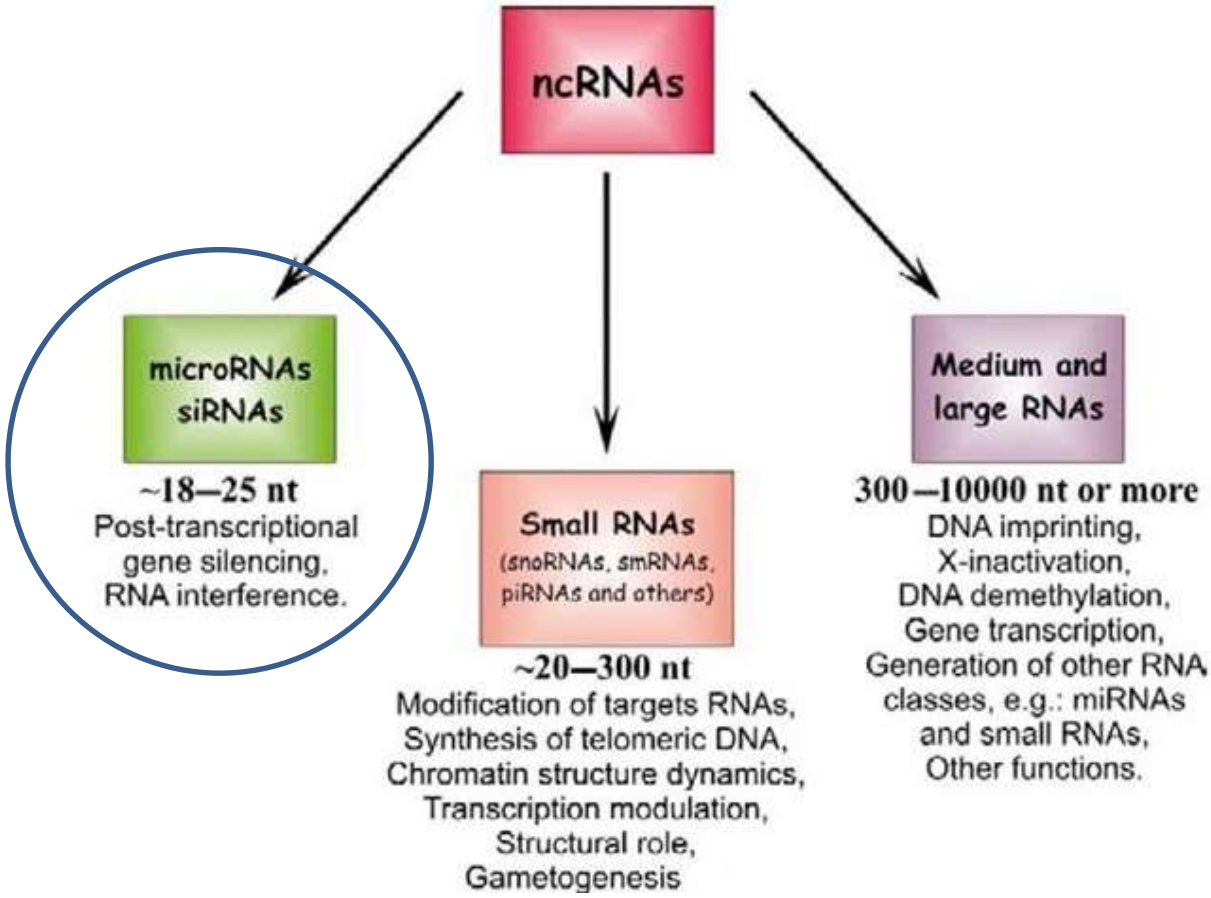


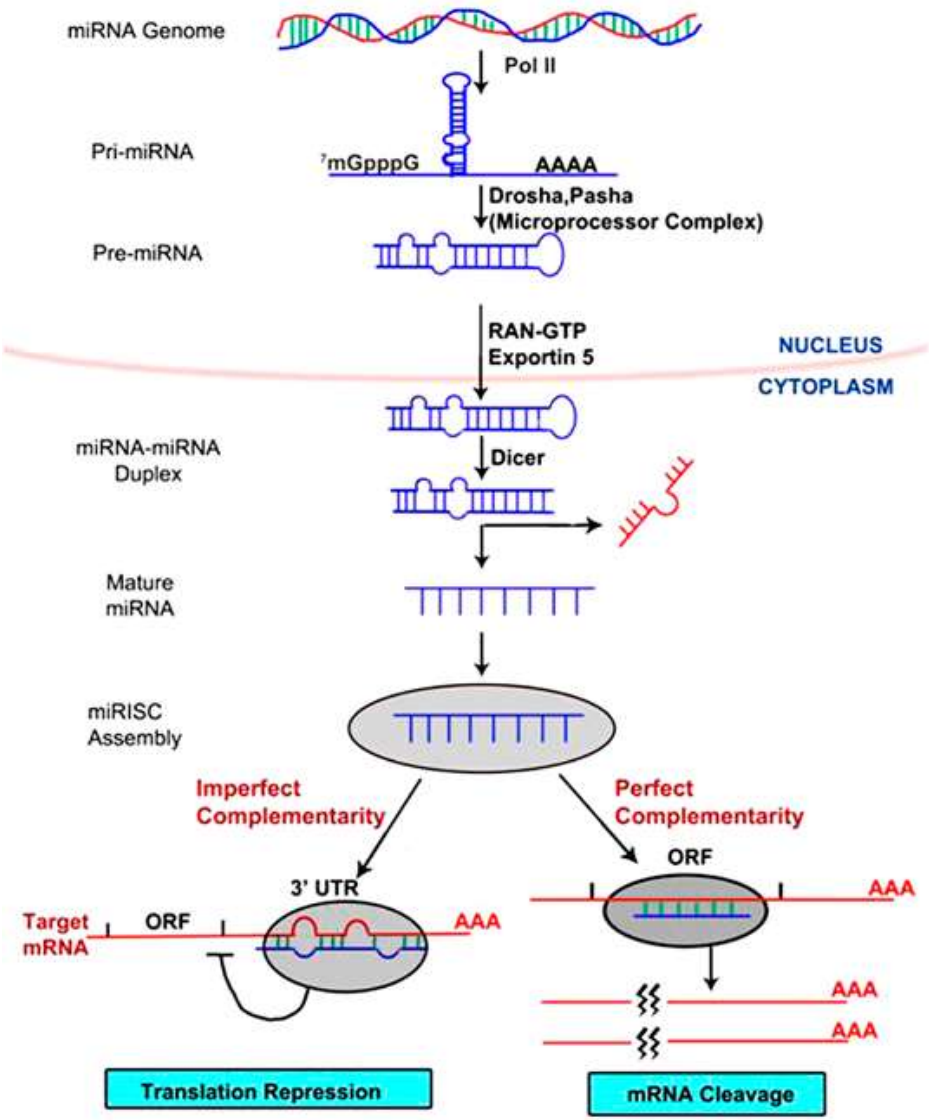
Pharmacoepigenetics: an element of personalized therapy?

RNA non codificante

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

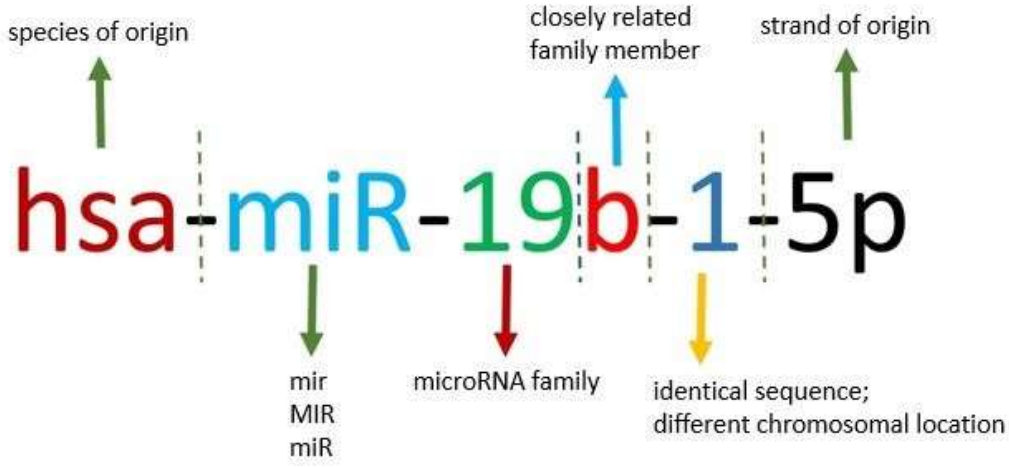


micro-RNA



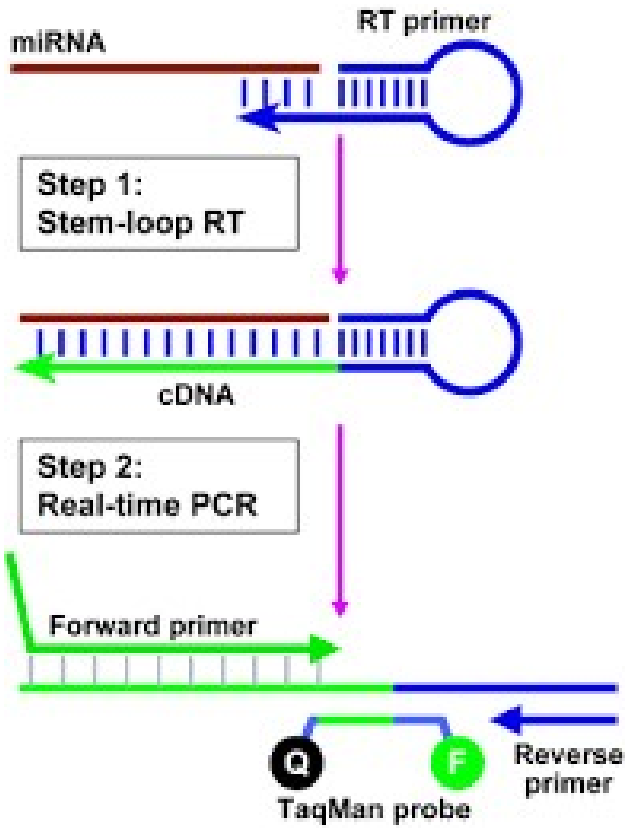
Cancer Gene Therapy (2008) 15, 341–355

Nomenclature of microRNA



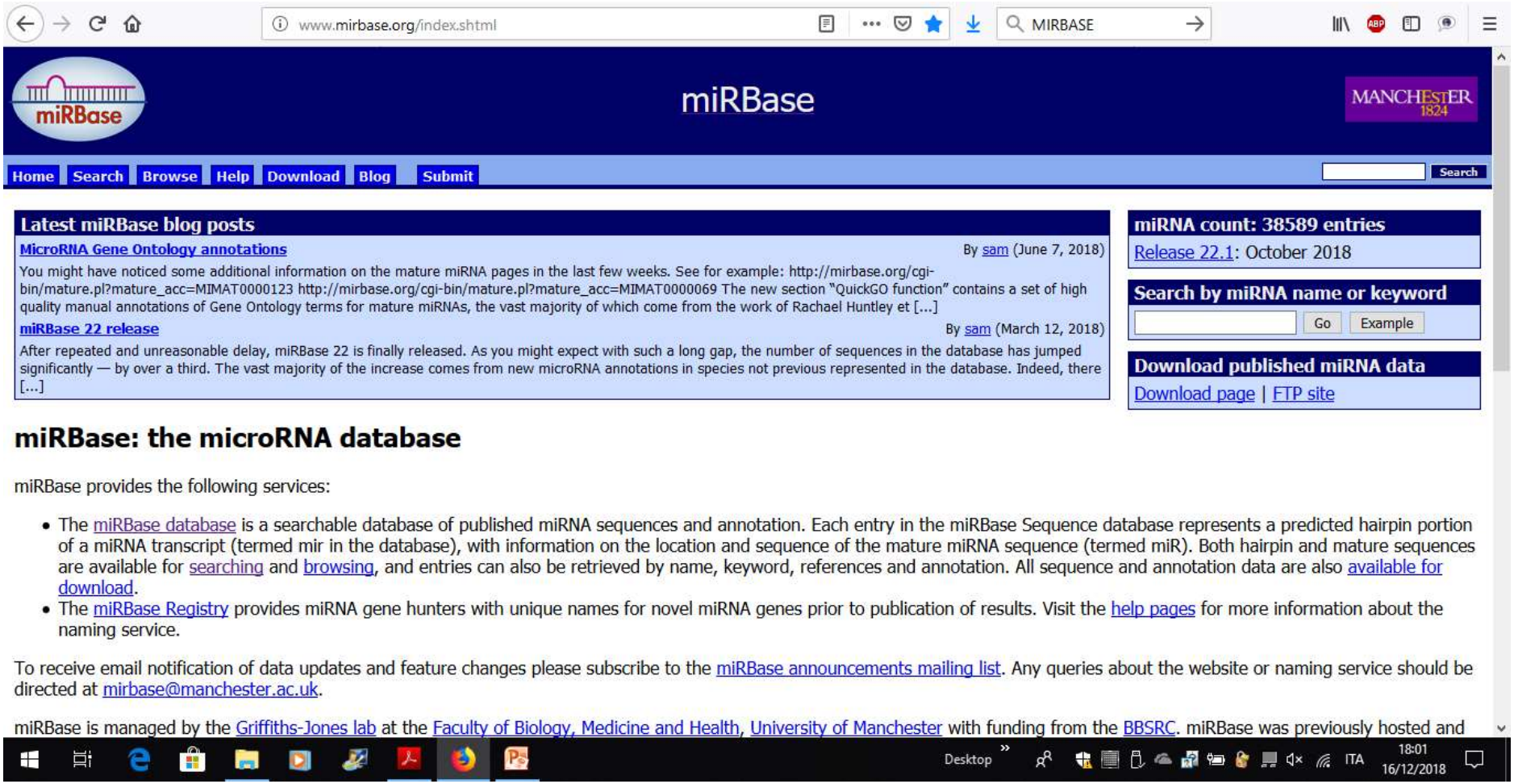
- According to standard nomenclature system, name of any MicroRNA is written as mir-123.
- miR = MicroRNA (mature form).
- mir = Precursor MicroRNA.
- Number indicates order of discovery.
- Annotated with an additional lower case letter e.g.- miR-123a & miR-123b, if deference in only one or two nucleotides.

microRNA detection methods

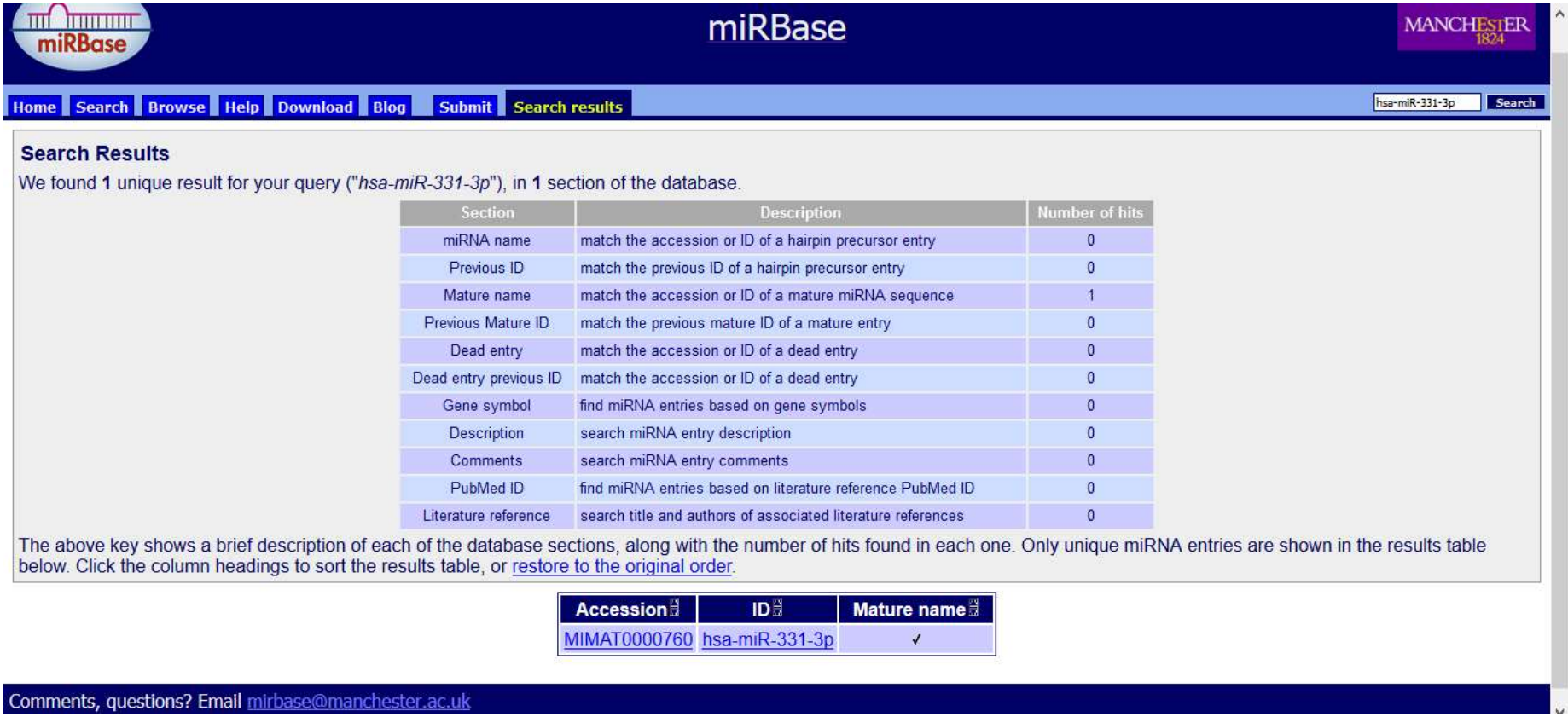


- qRT-PCR;
- TaqMan miRNA array;
- Microarray;
- NGS.

microRNA database
http://www.mirbase.org/



microRNA database
http://www.mirbase.org/



microRNA database
http://www.mirbase.org/

microRNA database
http://mirdb.org/

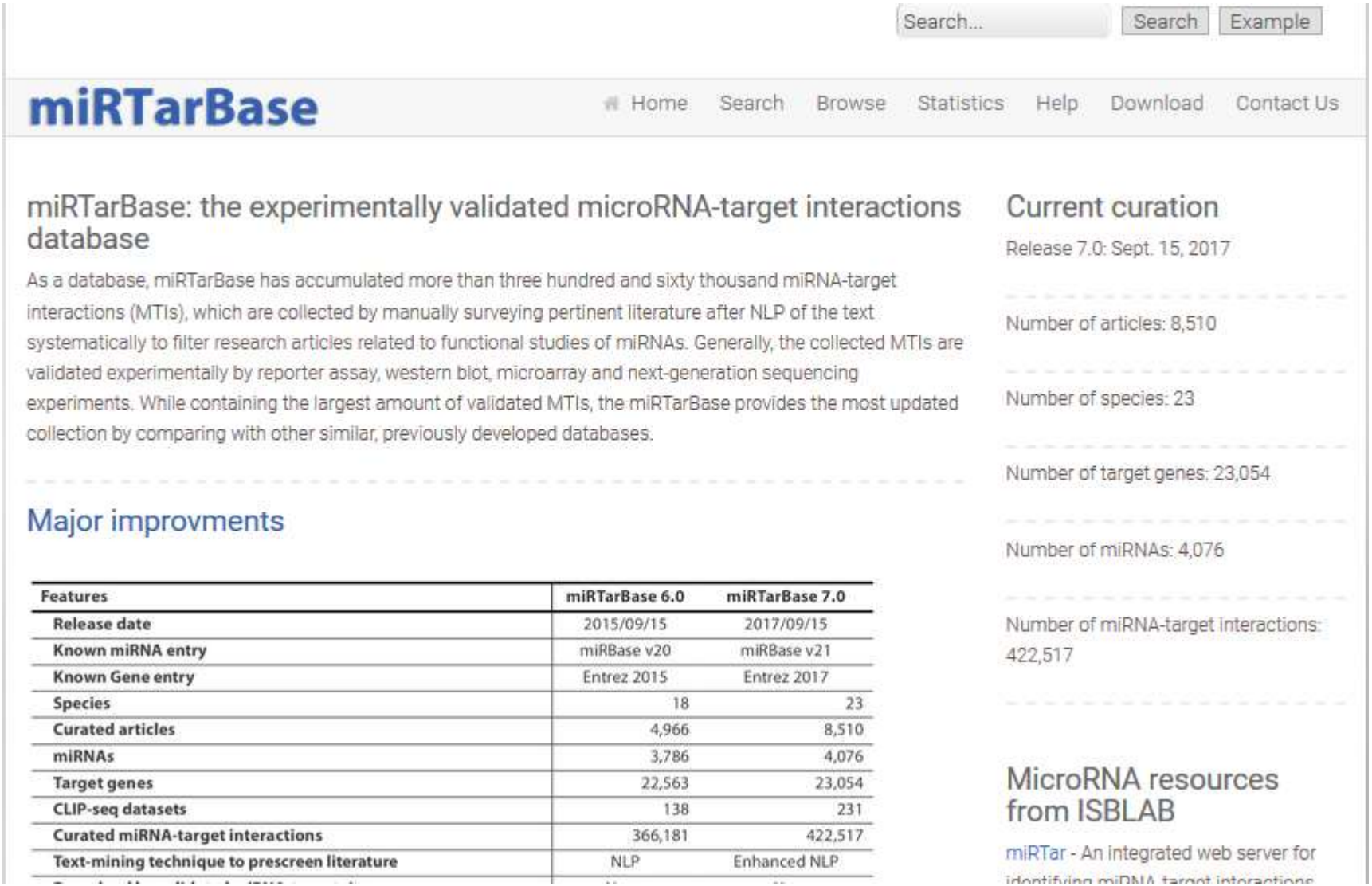
microRNA database
http://mirdb.org/

miRDB

There are 411 predicted targets for hsa-miR-331-3p in miRDB.

Target Detail	Target Rank	Target Score	miRNA Name	Gene Symbol	Gene Description
Details	1	99	hsa-miR-331-3p	NRP2	neuropilin 2
Details	2	96	hsa-miR-331-3p	PTPN2	protein tyrosine phosphatase, non-receptor type 2
Details	3	96	hsa-miR-331-3p	ZBTB2	zinc finger and BTB domain containing 2
Details	4	96	hsa-miR-331-3p	PHLPP1	PH domain and leucine rich repeat protein phosphatase 1
Details	5	94	hsa-miR-331-3p	CPSF2	cleavage and polyadenylation specific factor 2
Details	6	94	hsa-miR-331-3p	ZNF652	zinc finger protein 652
Details	7	93	hsa-miR-331-3p	DCLRE1B	DNA cross-link repair 1B
Details	8	93	hsa-miR-331-3p	TSPAN18	tetraspanin 18
Details	9	92	hsa-miR-331-3p	SLAMF9	SLAM family member 9
Details	10	92	hsa-miR-331-3p	SEMA7A	semaphorin 7A (John Milton Hagen blood group)
Details	11	92	hsa-miR-331-3p	BAIAP2	BAI1 associated protein 2
Details	12	91	hsa-miR-331-3p	CNTNAP4	contactin associated protein like 4
Details	13	90	hsa-miR-331-3p	FBLN7	fibulin 7
Details	14	90	hsa-miR-331-3p	CDC42EP4	CDC42 effector protein 4
Details	15	90	hsa-miR-331-3p	ARHGEF37	Rho guanine nucleotide exchange factor 37
Details	16	90	hsa-miR-331-3p	XPO7	exportin 7
Details	17	88	hsa-miR-331-3p	DUSP5	dual specificity phosphatase 5
Details	18	88	hsa-miR-331-3p	APBA1	amyloid beta precursor protein binding family A member 1
Details	19	88	hsa-miR-331-3p	UBL3	ubiquitin like 3
Details	20	87	hsa-miR-331-3p	TGFBR1	transforming growth factor beta receptor 1
Details	21	87	hsa-miR-331-3p	ZMYM4	zinc finger MYM-type containing 4
Details	22	87	hsa-miR-331-3p	SARM1	sterile alpha and TIR motif containing 1

microRNA database
http://mirtarbase.mbc.nctu.edu.tw/php/index.php



Search... Search Example

miRTarBase

Home Search Browse Statistics Help Download Contact Us

miRTarBase: the experimentally validated microRNA-target interactions database

As a database, miRTarBase has accumulated more than three hundred and sixty thousand miRNA-target interactions (MTIs), which are collected by manually surveying pertinent literature after NLP of the text systematically to filter research articles related to functional studies of miRNAs. Generally, the collected MTIs are validated experimentally by reporter assay, western blot, microarray and next-generation sequencing experiments. While containing the largest amount of validated MTIs, the miRTarBase provides the most updated collection by comparing with other similar, previously developed databases.

Major improvments

Features	miRTarBase 6.0	miRTarBase 7.0
Release date	2015/09/15	2017/09/15
Known miRNA entry	miRBase v20	miRBase v21
Known Gene entry	Entrez 2015	Entrez 2017
Species	18	23
Curated articles	4,966	8,510
miRNAs	3,786	4,076
Target genes	22,563	23,054
CLIP-seq datasets	138	231
Curated miRNA-target interactions	366,181	422,517
Text-mining technique to prescreen literature	NLP	Enhanced NLP

Current curation

Release 7.0: Sept. 15, 2017

Number of articles: 8,510

Number of species: 23

Number of target genes: 23,054

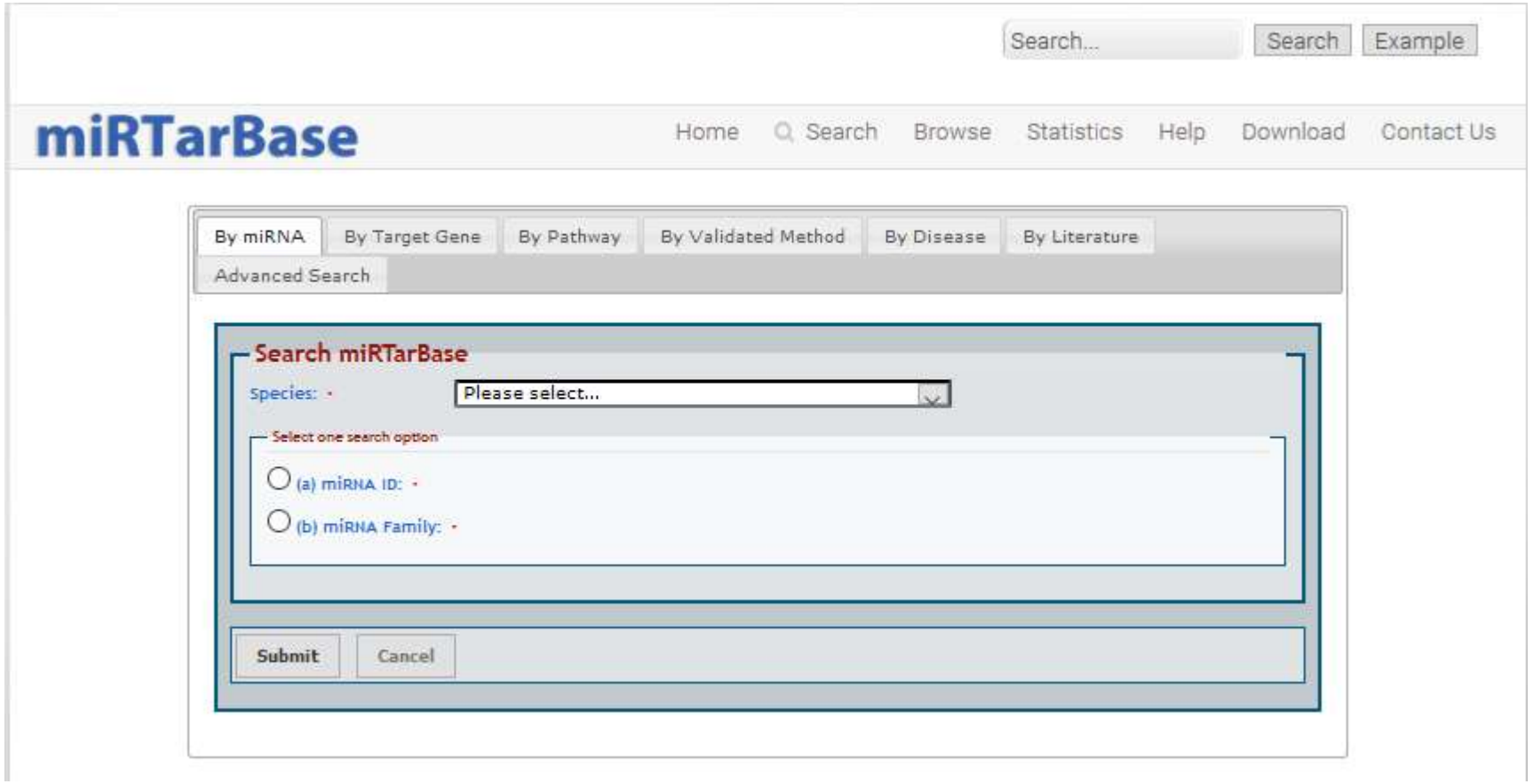
Number of miRNAs: 4,076

Number of miRNA-target interactions: 422,517

MicroRNA resources from ISBLAB

miRTar - An integrated web server for

microRNA database
http://mirtarbase.mbc.nctu.edu.tw/php/index.php



microRNA database
http://mirtarbase.mbc.nctu.edu.tw/php/index.php

miRTarBase Home Search Browse Statistics Help Download Contact Us

Page of 15 ‹ Prev 1 2 ... 15 Next ›

Pulsed stable isotope labeling by amino acids in cell culture (pSILAC)

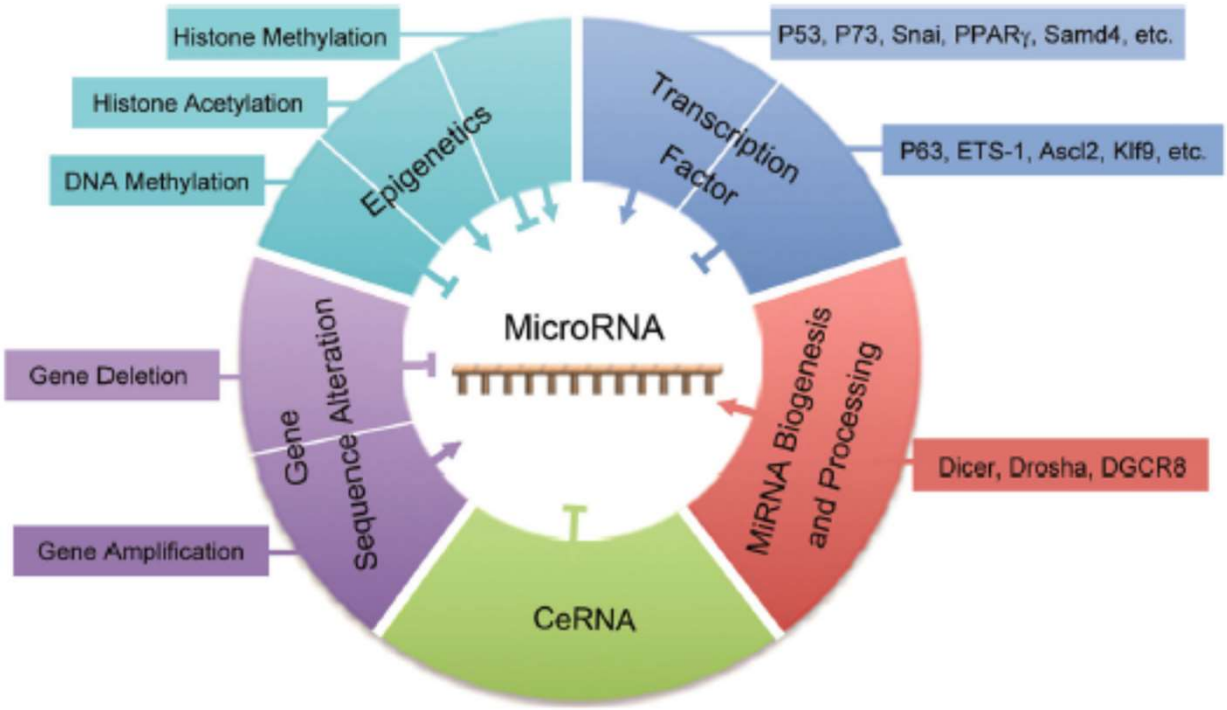
ID	Species (miRNA)	Species (Target)	miRNA	Target	Validation methods: Strong evidence: Reporter assay	Strong evidence: Western blot	Strong evidence: qPCR	Less strong evidence: Microarray	Less strong evidence: NGS	Less strong evidence: pSILAC	Less strong evidence: Other	Sum	# of papers
MIRT002222	Rattus norvegicus	Rattus norvegicus	rno-miR-331-3p	Fgf16				✔			✔	2	1
MIRT005805	Homo sapiens	Homo sapiens	hsa-miR-331-3p	ERBB2	✔	✔	✔	✔			✔	5	5
MIRT006364	Homo sapiens	Homo sapiens	hsa-miR-331-3p	FHIT	✔							1	1
MIRT006506	Homo sapiens	Homo sapiens	hsa-miR-331-3p	E2F1	✔	✔						2	1
MIRT006887	Homo sapiens	Homo sapiens	hsa-miR-331-3p	DOHH	✔	✔	✔		✔			4	2
MIRT019230	Homo sapiens	Homo sapiens	hsa-miR-331-3p	WDR60					✔			1	1
MIRT019231	Homo sapiens	Homo sapiens	hsa-miR-331-3p	RNF7					✔			1	1
MIRT019232	Homo sapiens	Homo sapiens	hsa-miR-331-3p	ARL8A					✔			1	1

MicroRNAs in the Control of Drug Metabolism and Transport

Some P450 drug-metabolizing enzymes and ABC transporters shown to be targeted by noncoding miRNAs

		MicroRNA	Reference
Enzymes	CYP1B1	miR-27b	Tsuchiya et al., 2006
	CYP2E1	miR-378	Mohri et al., 2010
	CYP3A4	miR-27b, mmu-miR-298	Pan et al., 2009a
Transporters	ABCB1	miR-451	Kovalchuk et al., 2008
		miR-27a	Zhu et al., 2008
	ABCG2	miR-520h	Liao et al., 2008; Wang et al., 2010; Li et al., 2011
		miR-519c	To et al., 2008; To et al., 2009; Li et al., 2011
		miR-328	Pan et al., 2009b; Li et al., 2011
	ABCC1	miR-134	Guo et al., 2010
		miR-326	Liang et al., 2010
		miR-199a, miR-199b, miR-296	Borel et al., 2012
		miR-1291	Pan et al., 2013
	ABCC2	miR-379	Haenisch et al., 2011
	ABCC3	miR-9-3p	Jeon et al., 2011
	ABCC4	miR-125a, miR-125b	Borel et al., 2012
	ABCC5	miR-101, miR-125a, Let-7a	Borel et al., 2012
		miR-128	Zhu et al., 2011
	ABCC6	miR-9-3p	Jeon et al., 2011

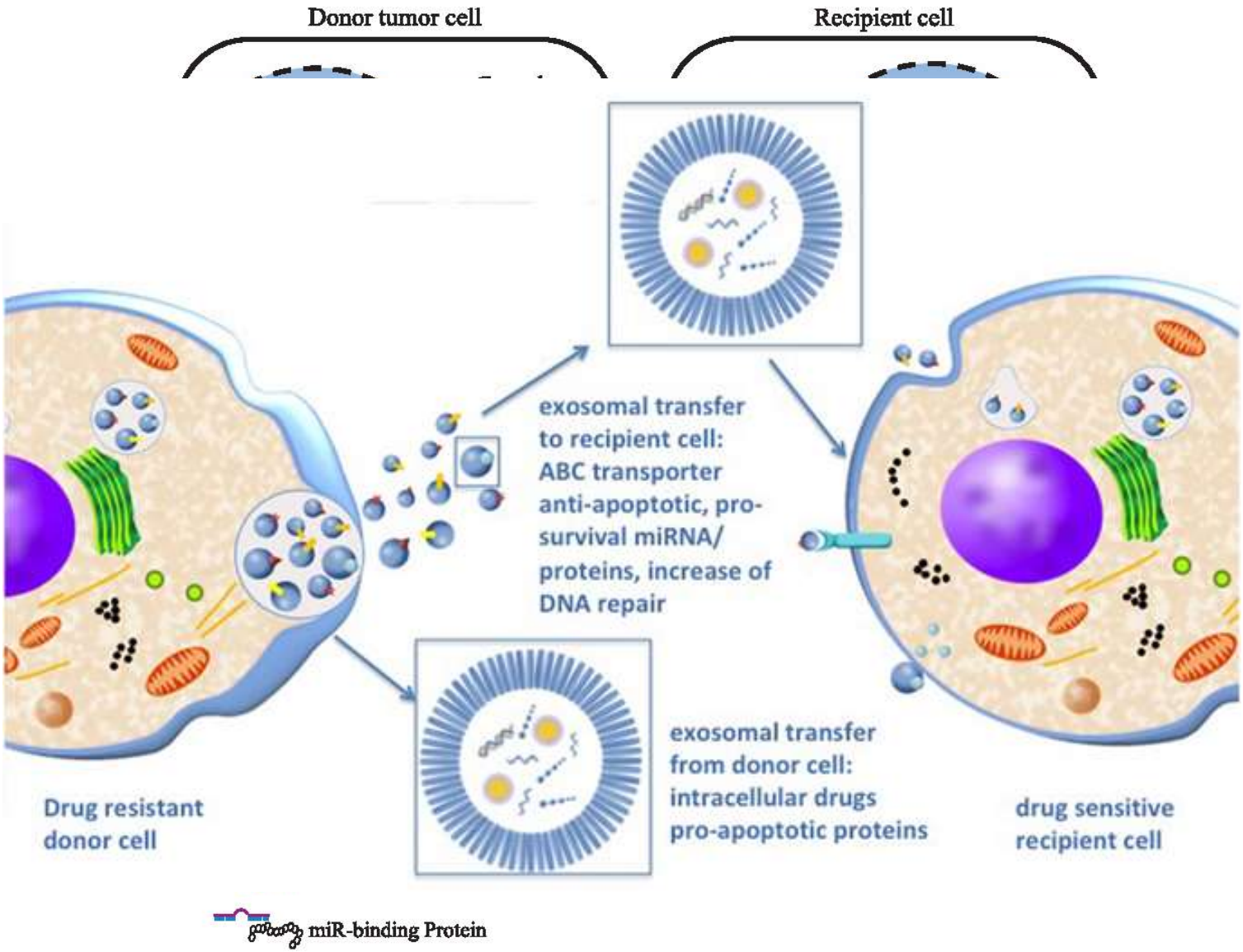
Deregulated expression of microRNAs



The mechanisms of deregulated expression of microRNAs. Different mechanisms can promote or/and inhibit the expression of miRNA

Si *et al. Clinical Epigenetics* (2019) 11:25
https://doi.org/10.1186/s13148-018-0587-8

Exosomes-derived microRNA and drug resistance



Circulating microRNA

cerebrospinal fluid

PCNSL miR-19, miR-21, miR-92a [33]

Glioblastoma miR-21 [34]

pleural effusion

Lung cancer miR-198 [35]

Lung cancer miR-22, miR-134, miR-185 [36]

Malignant pleural mesothelioma let-7a, miR-125a-5p, miR-320, miR-484 [37]

ascites

Ovarian cancer miR-21, miR-23b, miR-29a [38]

Serosa-invasive gastric cancer miR-21, miR-1225-5p [39]

vaginal discharge

Cervical cancer miR-21, miR-146a [40]

urine

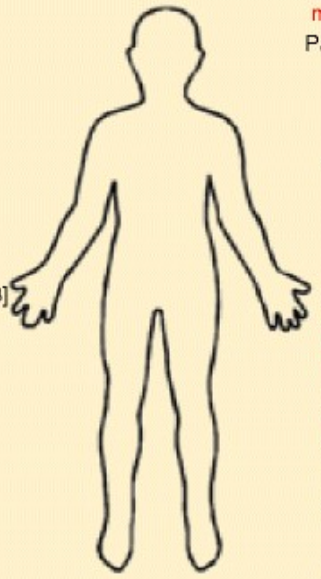
Ovarian cancer miR-30-5p [41]

Bladder cancer miR-106b [42]

Bladder cancer miR-99a, miR-125b [43]

Bladder cancer miR-155, miR-21, miR-125b, miR-451 [44]

Prostate cancer miR-484, miR-1825 [45]



saliva

Oral cancer miR-125a, miR-200a [46]

Esophageal cancer miR-10b-3p, miR-21, miR-144, miR-451 [47]

Pancreatic cancer miR-940, miR-3679-5p [48]

breast milk

miR-335-3p, miR-26a-2-3p, miR-181d [49]

blood (serum/plasma)

Ovarian cancer miR-21, miR-141, miR-200a, miR-200b, miR-200c, miR-203, miR-205, miR-214 [50]

Gastric cancer miR-1, miR-20a, miR-27a, miR-34, miR-423-5p [51]

Malignant melanoma miR-221 [52]

Cervical cancer miR-218 [53]

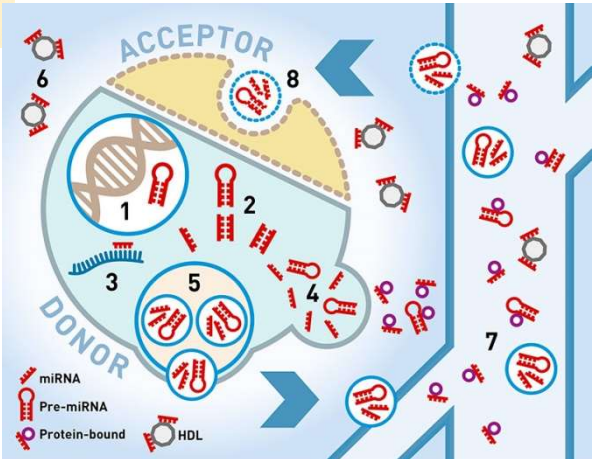
Thyroid cancer let-7e, miR-151-5p, and miR-222 [54]

Renal cell cancer miR-378, miR-451 [55]

Colorectal cancer miR-7, miR-93, miR-409-3p [56]

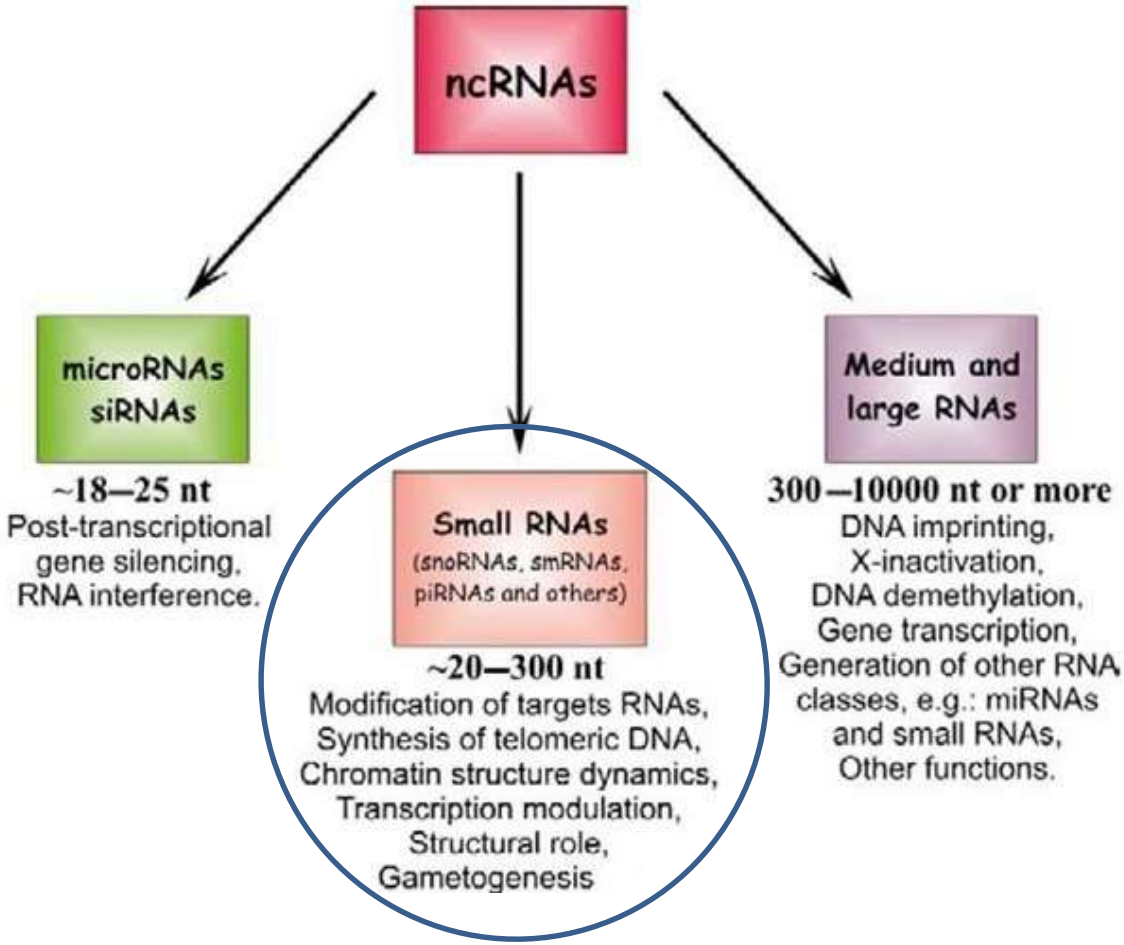
Breast cancer miR-148-3p, miR-652-3p [57]

NSCLC miR-21, miR-148a, miR-148b, miR-152 [58]



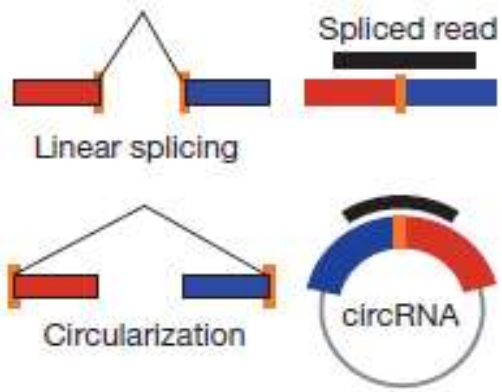
RNA non codificante

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

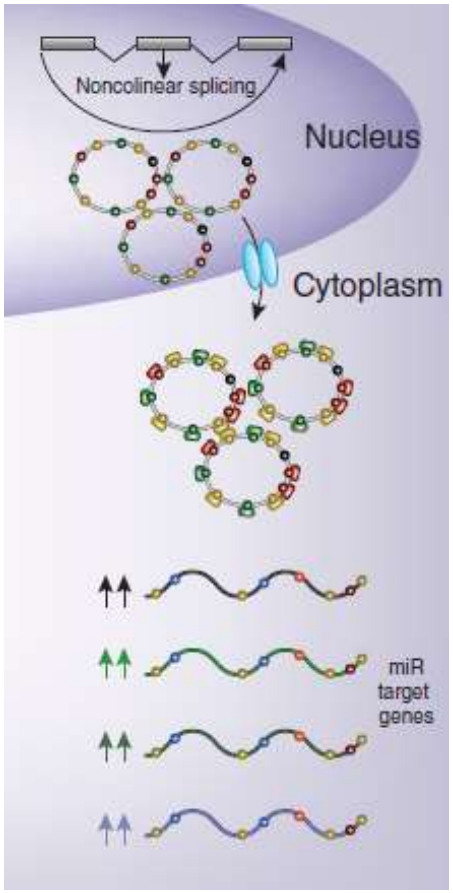


circRNAs

- Covalently circularized RNA loops
- Stable in cells and long in half-lives
- Multiple miRNA binding sites as miRNA sponges



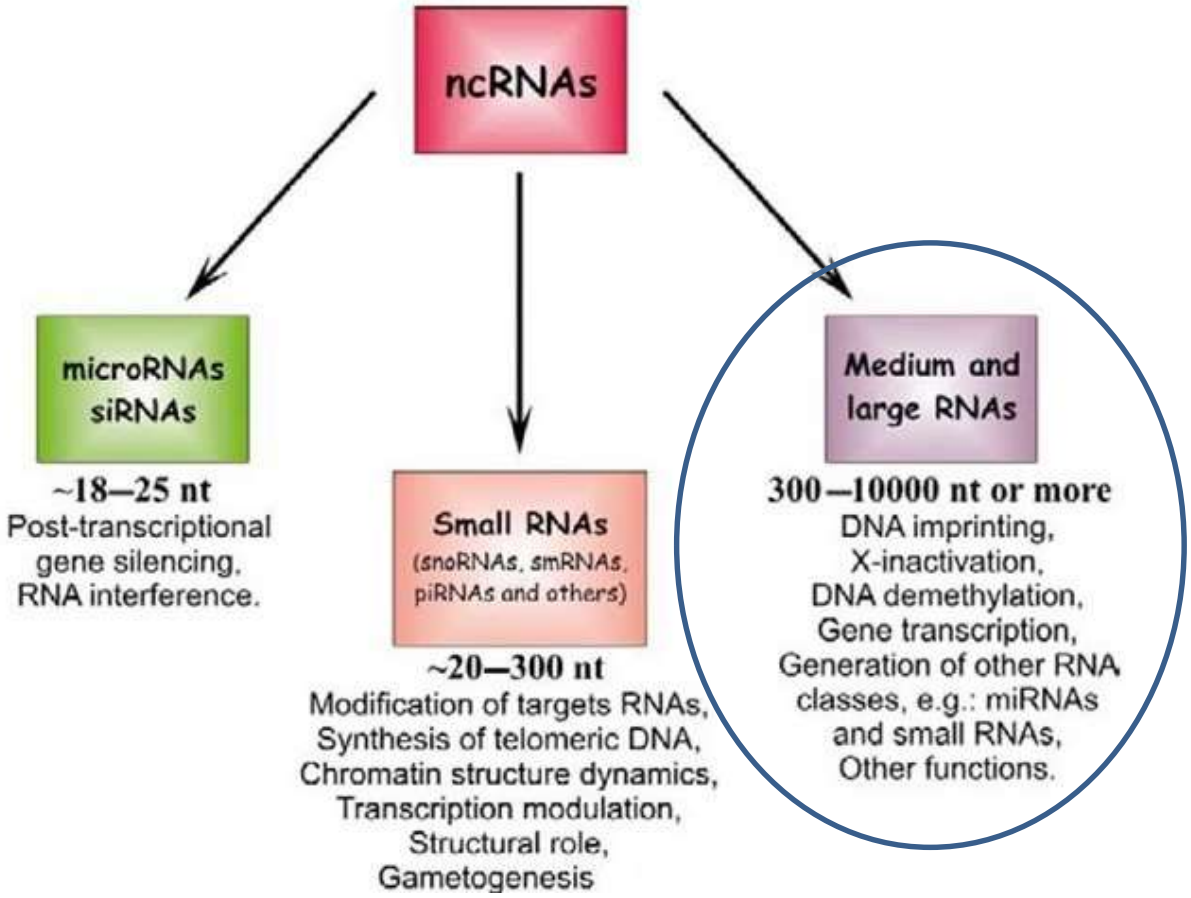
Nature (2013) 495, 333–343



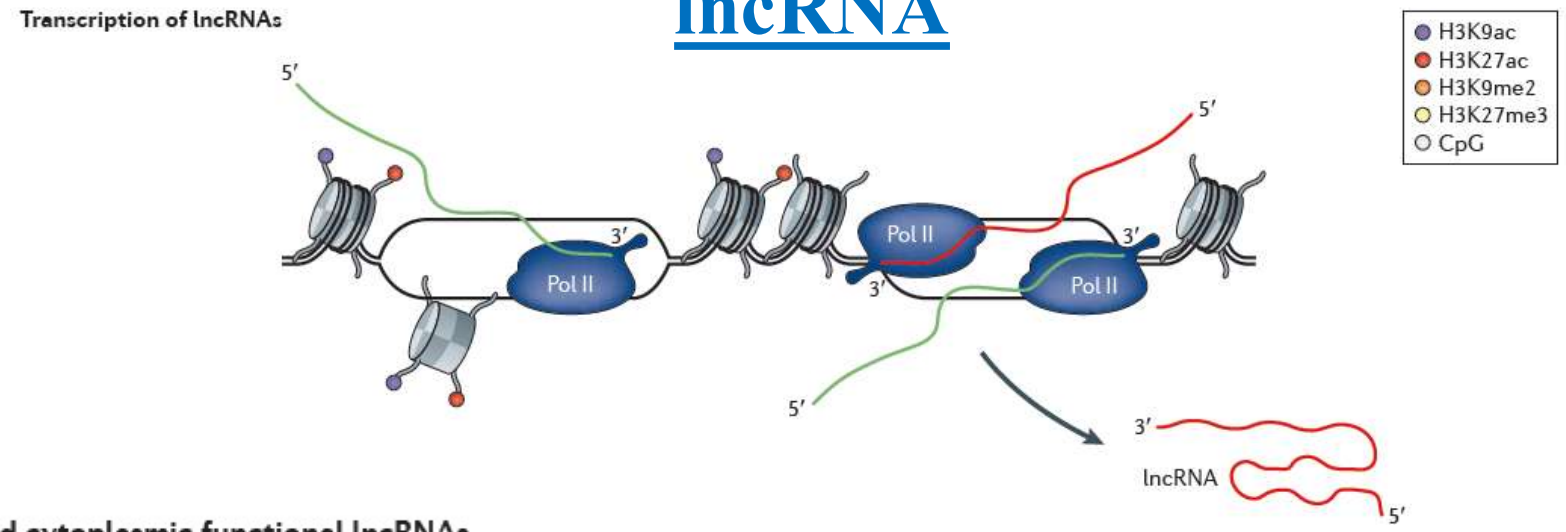
Nature Structural & Molecular Biology (2013), 20:5, 541-3

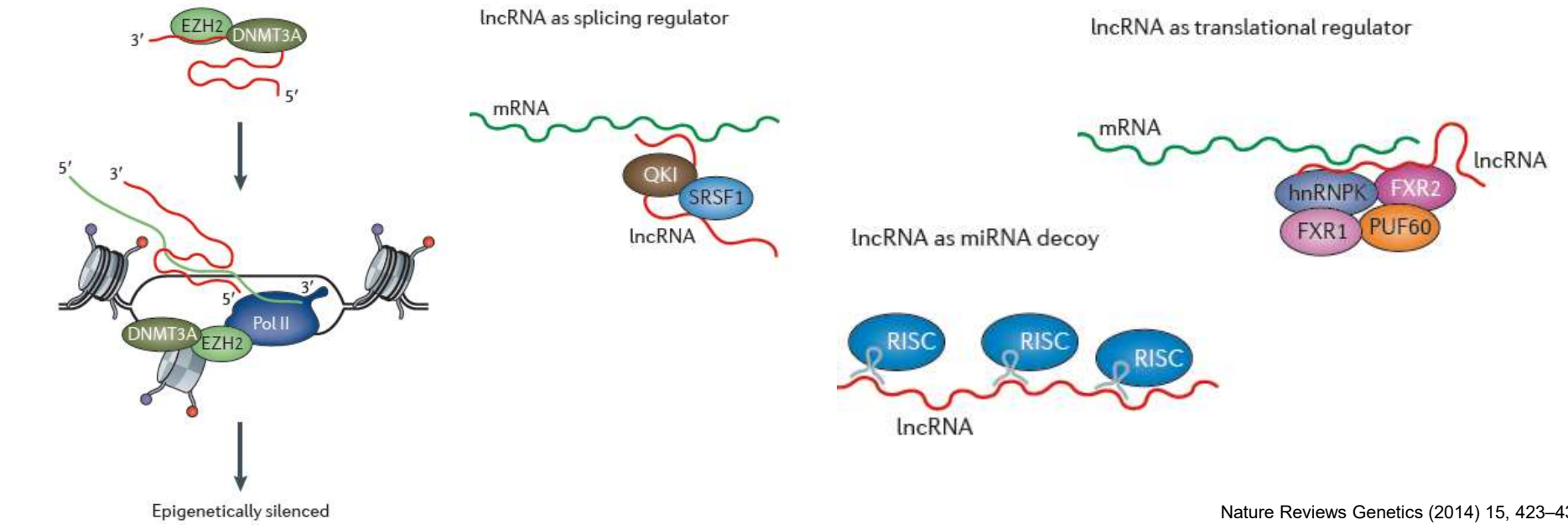
What is non-coding RNA ?

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



lncRNA





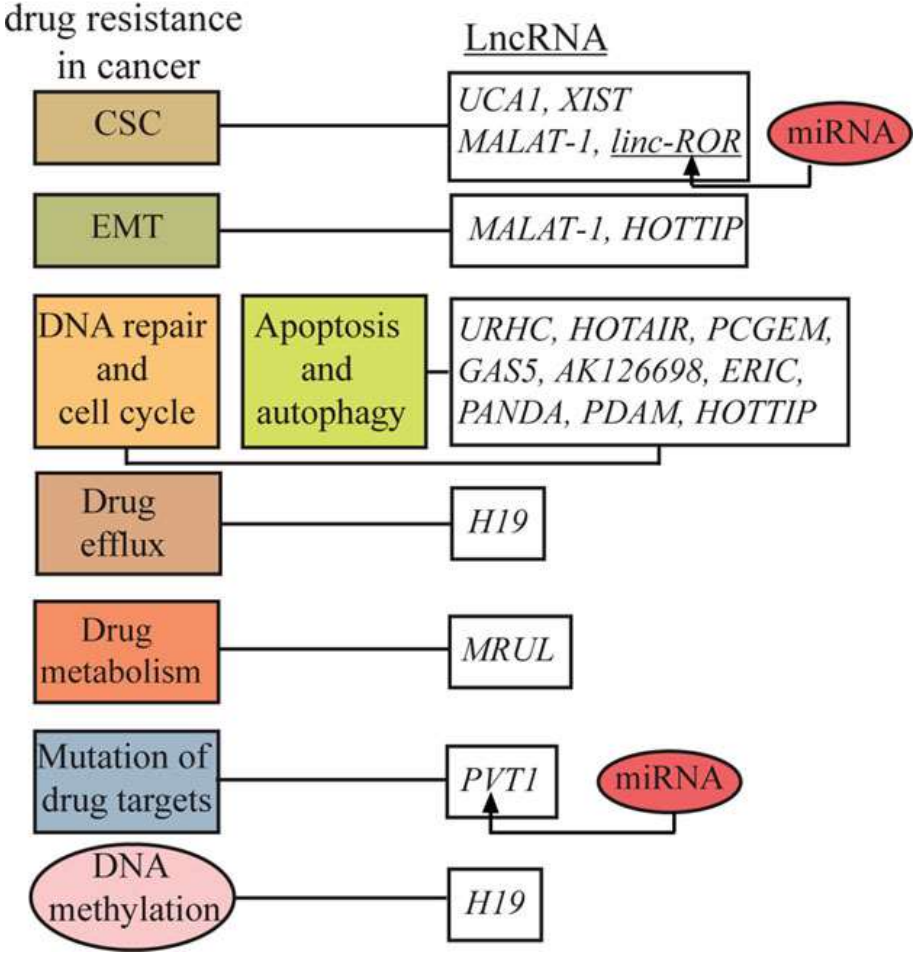
Nature Reviews Genetics (2014) 15, 423–437

lncRNA

LncRNAs and drugs affecting their expression in cancers

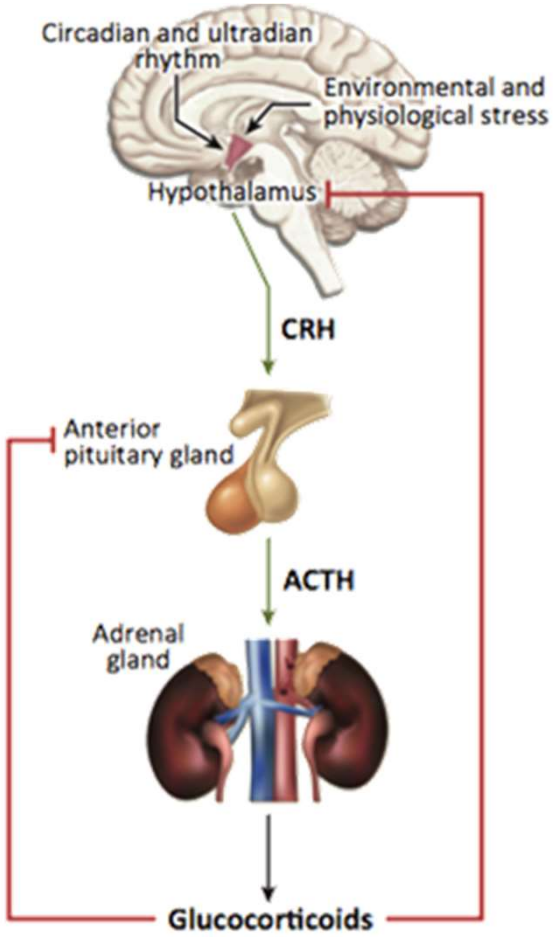
LncRNA	Cancer	Drug
UCA1	Bladder	?
Linc-ROR	Hepatocellular carcinoma	Sorafenib and doxorubicin
XIST	Ovarian, breast	Cisplatin, abexinostat
MALAT-1	Pancreas	Gemcitabine
URHC	Hepatocellular carcinoma	PD98059
HOTAIR	Lung	Cisplatin
PCGEM1	Prostate	Doxorubicin
GAS5	Lung	Gefitinib
AK126698	Lung	Cisplatin
ERIC	Bone osteosarcoma	Etoposide
PANDA	Breast	Doxorubicin
PDAM	Oligodendroglial	Cisplatin
HOTTIP	Pancreas	Gemcitabine
rRNA		Mitoxantrone
H19	Hepatocellular carcinoma cells	Paclitaxel, doxorubicin, etoposide, and vincristine
MRUL	Gastric	Doxorubicin and vincristine
ARA	Breast, hepatocellular carcinoma cells	Doxorubicin
PVT1	Pancreas, gastric cancer	Gemcitabine, paclitaxel
BCAR4	Breast	Tamoxifen

Cancer Stem Cells (CSC)
Epithelial to mesenchymal transitions (EMT)

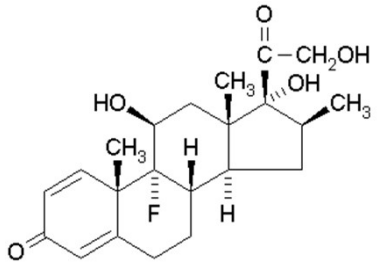


Urothelial Carcinoma-Associated 1 (UCA1)
Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT-1)

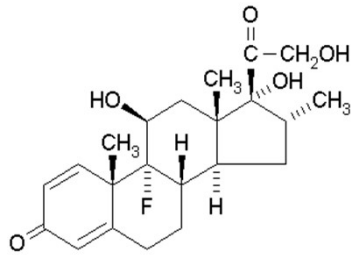
Pharmacoepigenetics of Glucocorticoids



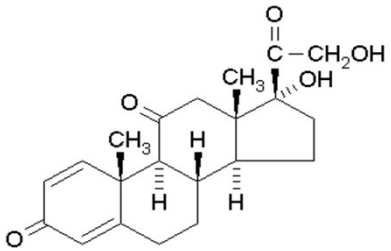
(Kadmiel & Cidlowski, 2013)



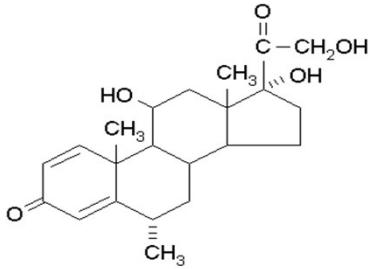
BETAMETHASONE



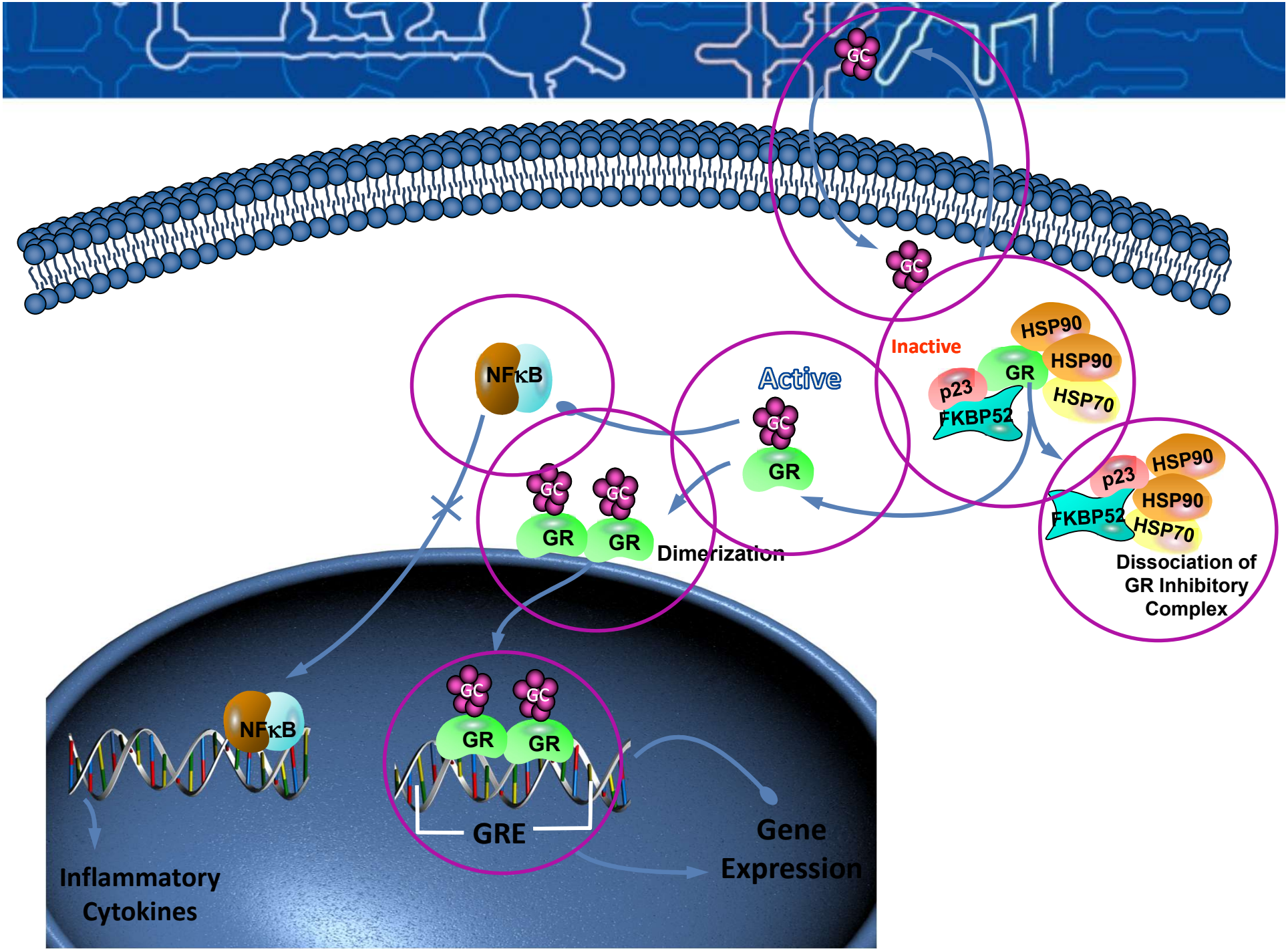
DEXAMETHASONE



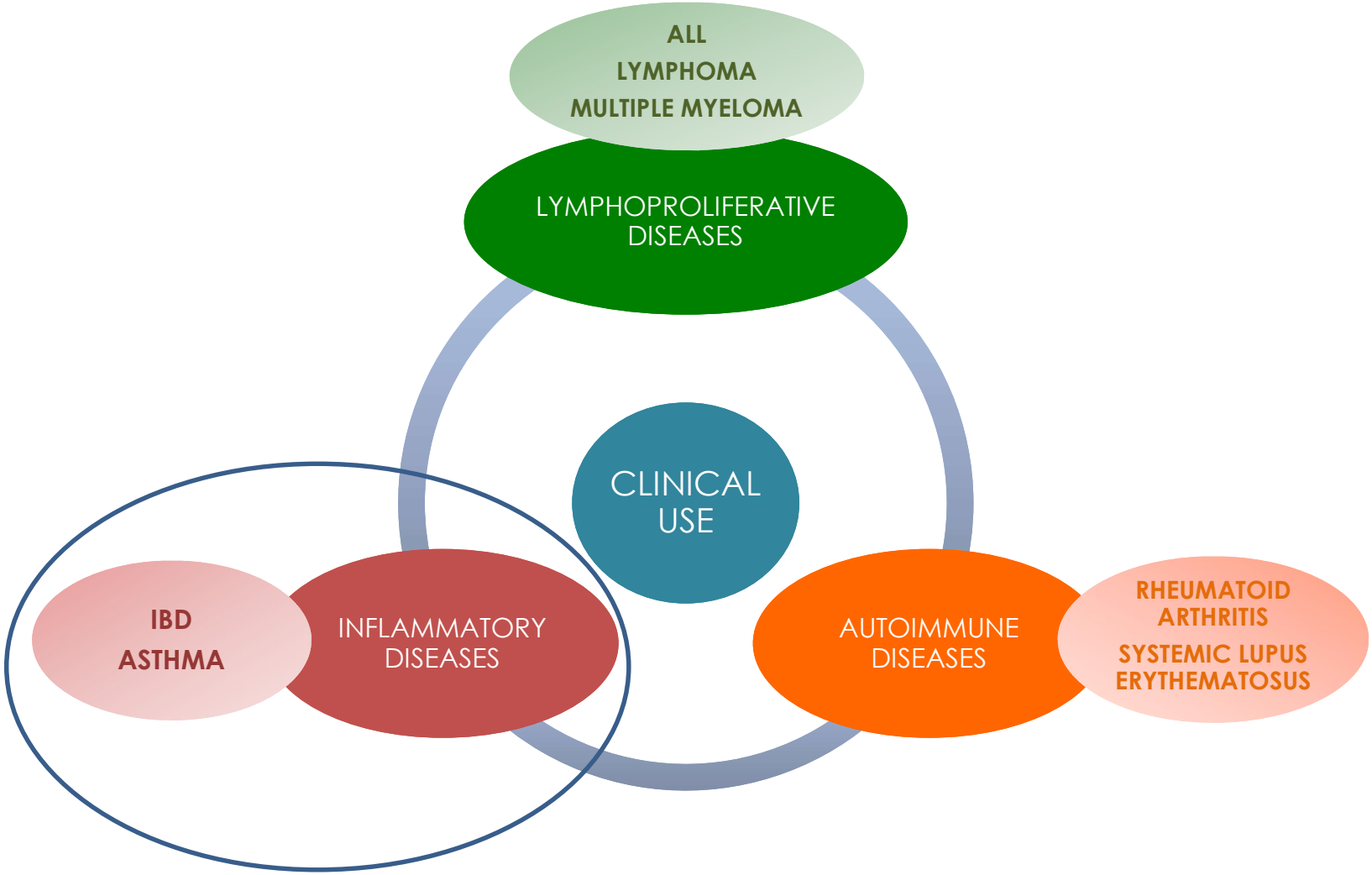
PREDNISONE



METHYLPREDNISOLONE

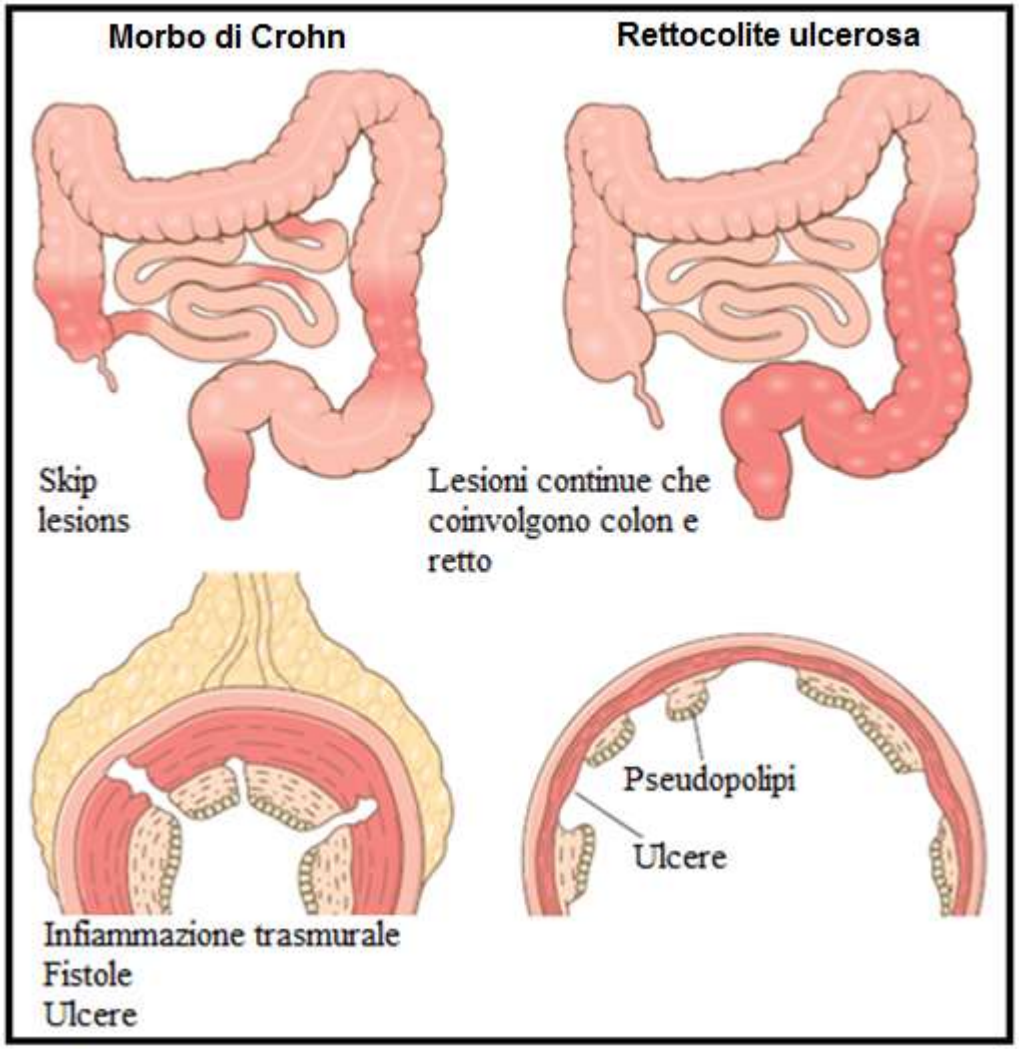

GC
GC
NFκB
Active
GC
GR
Inactive
HSP90
HSP90
GR
p23
FKBP52
HSP70
GC
GC
GR
GR
Dimerization
p23
HSP90
FKBP52
HSP90
HSP70
Dissociation of
GR Inhibitory
Complex
NFκB
GC
GC
GR
GR
GRE
Gene
Expression
Inflammatory
Cytokines

GLUCOCORTICOIDS



IBD

- **Infiammaz** **e**
- Due princi
- **Morbo di C**
- **Rettocolite**



EPIGENETIC PREDICTORS OF GLUCOCORTICOID RESPONSE IN CHILDREN WITH IBD

The research project was supported by Italian Ministry of Health, No. 44/GR-2010-2300447

DIAGNOSIS (T0)

30 DAYS OF TREATMENT WITH GC (T4)

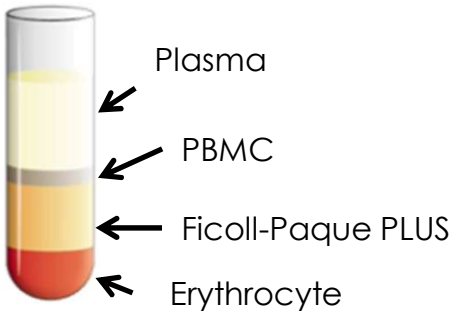
AFTER 1 YEAR

Correlation
between miRNAs expression and the clinical response to GC therapy

IRCCS materno infantile
Burlo Garofolo

University of Padua
CRIBI Genomics

CANDIDATE PREDICTORS OF GLUCOCORTICOID RESPONSE IN CHILDREN WITH IBD



Article

High-Throughput Sequencing of microRNAs in Glucocorticoid Sensitive Paediatric Inflammatory Bowel Disease Patients

Sara De Iudicibus [1,†], Marianna Lucafò [2,†], Nicola Vitulo [3], Stefano Martelossi [1], Rosanna Zimbello [4], Fabio De Pascale [4], Claudio Forcato [4], Samuele Naviglio [5], Alessia Di Silvestre [5], Marco Gerdol [6], Gabriele Stocco [6], Giorgio Valle [4], Alessandro Ventura [1,2], Matteo Bramuzzo [1,*] and Giuliana Decorti [1,2]

T4 vs T0

Table 1. Differentially expressed miRNAs.

Upregulated miRNAs	FC	FDR Corrected *P*-Value	Downregulated miRNAs	FC	FDR Corrected *p*-Value
hsa-miR-451a * [13]	4.16	1.66×10^{-6}			
hsa-miR-144-3p * [14,15]	4.44	1.04×10^{-5}			
hsa-miR-96-5p * [13,14]	2.96	6.38×10^{-3}			
hsa-miR-29b-3p * [13]	2.89	0.026			
hsa-miR-142-3p * [14]	2.21	0.026			
hsa-miR-873-5p	3.36	0.026			
hsa-miR-29c-3p * [16,17]	3.37	0.037			
hsa-miR-29a-3p * [13]	2.72	0.041	hsa-miR-7109-3p	−4.62	0.044
hsa-miR-363-3p	2.31	0.041	hsa-miR-654-5p	−2.27	0.049
hsa-miR-141-3p	2.59	0.041			
hsa-miR-548ak	3.11	0.042			
hsa-let-7g-3p* [18]	2.44	0.042			
hsa-miR-4772-5p	2.70	0.047			
hsa-miR-106a-3p	3.52	0.047			
hsa-miR-31-3p	3.36	0.049			
hsa-miR-146b-5p * [19]	2.27	0.049			

Fold changes (FC) for each miRNA regulated by glucocorticoids (GCs); * Linked to GC regulation in the literature. FDR, False Discovery Rate.

EPIGENETIC PREDICTORS OF GLUCOCORTICOID RESPONSE IN CHILDREN WITH IBD

Validation of Selected Differentially Expressed miRNAs by qRT-PCR

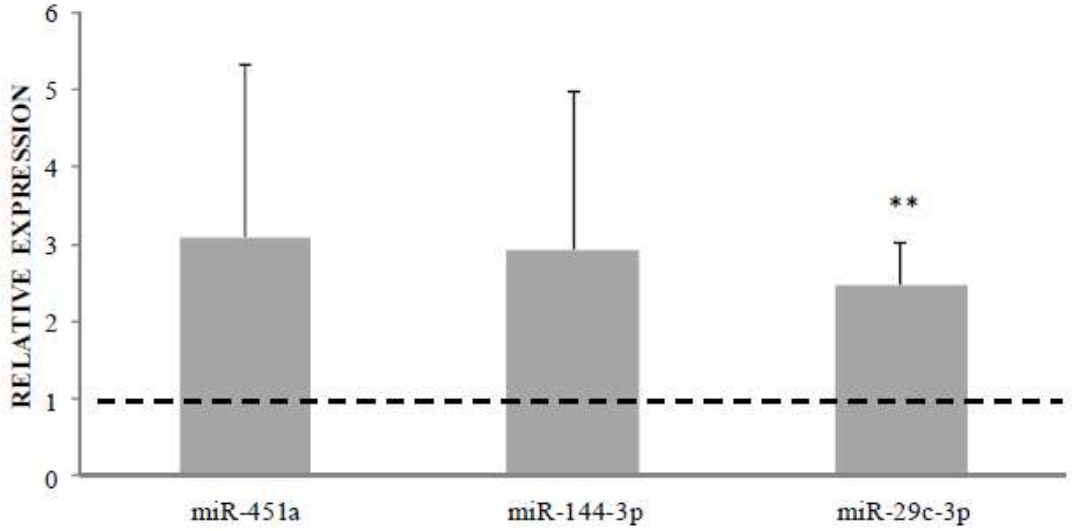


Figure 2. Relative expression of miR-451a, miR-144-3p, and miR-29c-3p (calculated as $2^{-\Delta\Delta Ct}$ T4 vs. T0). Values > 1 (dotted line) indicate upregulation, values < 1 indicate downregulation. Parametric *t*-test ΔC_t T0 vs. T4, ** $p < 0.01$.

Table 2. Glucocorticoid responsive element (GRE) sites predicted on miRNA promoter regions.

miRNA	pGRE	Start	End	Strand	Chrom	Expression
hsa-miR-363	GTGATAATGTGTGCTT	133303695	133303710	–	chrX	Up
hsa-miR-96	AGGACAAAGAGTCCTC	129416083	129416098	–	chr7	Up
hsa-miR-142	CTCACCTTCAGTTCTG	58331606	58331621	+	Chr17	Up
hsa-miR-142	CTGTCAGTCTGTCCTC	58332656	58332671	–	Chr17	Up

GC-sensitive miRNAs presenting positive GREs (pGRE).

CANDIDATE PREDICTORS OF GLUCOCORTICOID RESPONSE IN CHILDREN WITH IBD

T0 PRvsPS			
UP	**FC**	**DOWN**	**FC**
hsa-miR-1180-3p	7,96	hsa-miR-100-5p	43,95
hsa-miR-3591-3p	11,2	hsa-miR-1227-5p	2093,27
		hsa-miR-1255a	45,07
		hsa-miR-1271-5p	17,98
		hsa-miR-24-2-5p	15
		hsa-miR-25-5p	19,44
		hsa-miR-3065-5p	22,25
		hsa-miR-31-3p	25,65
		hsa-miR-3196	38,62
		hsa-miR-3656	19,63
		hsa-miR-3960	150,33
		hsa-miR-4443	47,81
		hsa-miR-4772-3p	20,55
		hsa-miR-5586-3p	17,04
		hsa-miR-6075	4465,59
		hsa-miR-6087	25,93
		hsa-miR-618	26,38
		hsa-miR-876-5p	19,32

POTENZIALI PREDITTORI

SCIENTIFIC REPORTS

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MiR-1180 promotes apoptotic resistance to human hepatocellular carcinoma via activation of NF-κB signaling pathway

Guosheng Tan[1,*], Linwei Wu[2,*], Jinfu Tan[3], Bing Zhang[4], William Chi-shing Tai[5,6], Shiqiu Xiong[7], Wei Chen[1], Jianyong Yang[1] & Heping Li[1,8]

T4 PRvsPS			
UP	**FC**	**DOWN**	**FC**
hsa-miR-1180-3p	6,48	hsa-miR-1197	10,19
hsa-miR-4732-5p	5	hsa-miR-1227-5p	434,07
		hsa-miR-154-3p	10,26
		hsa-miR-4443	64,78
		hsa-miR-4523	11,82
		hsa-miR-6075	1561,21
		hsa-miR-6087	20,31
		hsa-miR-876-5p	25,93

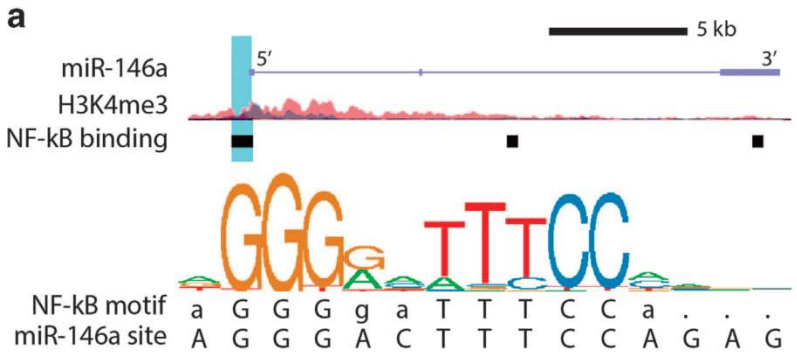
CANDIDATE PREDICTORS OF GLUCOCORTICOID RESPONSE IN CHILDREN WITH IBD

Clin Transl Gastroenterol. 2016 Sep 15;7(9):e192. doi: 10.1038/ctg.2016.49.

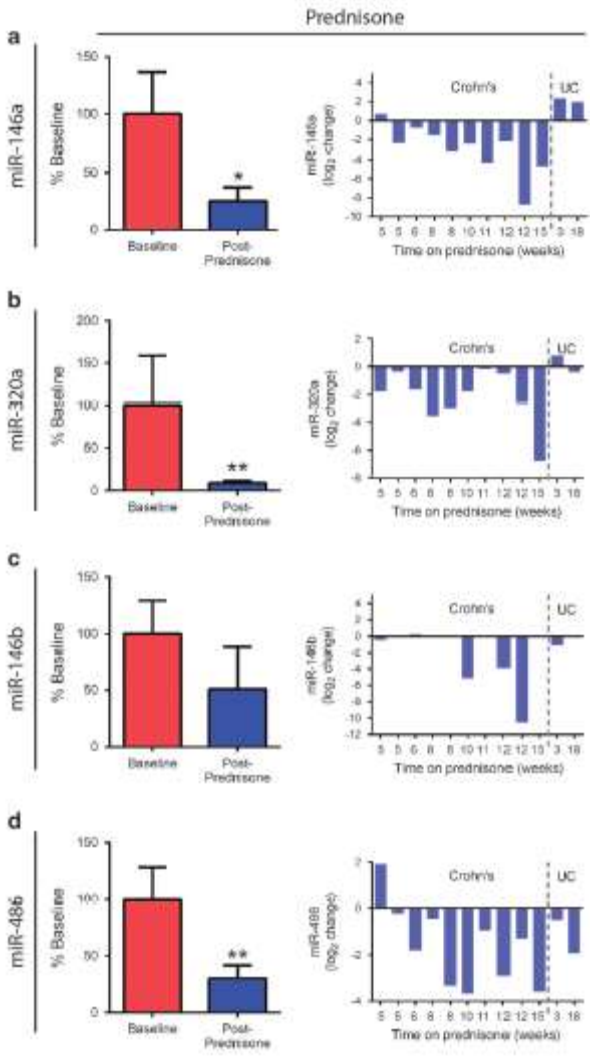
Identification of Pathway-Specific Serum Biomarkers of Response to Glucocorticoid and Infliximab Treatment in Children with Inflammatory Bowel Disease.

Heier CR[1], Fiorillo AA[1], Chaisson E[2], Gordish-Dressman H[1,3], Hathout Y[1,3], Damsker JM[1,4], Hoffman EP[1,3,4], Conklin LS[1,2].

Bioinformatic analysis of gene regulation pathways



Molecular marker	Expression Regulated by	Source	Drug changed	Up or Down
miR-146a	NF-κB	Wang 2012	Both	Down
miR-146b	NF-κB	Wang 2012	Both	Down
miR-320a	NF-κB and GR	Wang 2012	Both	Down
miR-486	GR	Wang 2012	Prednisone	Down



DIFFERENTIAL EXPRESSION OF miRNAs IN RAPAMYCIN-INDUCED REVERSION OF GC RESISTANCE

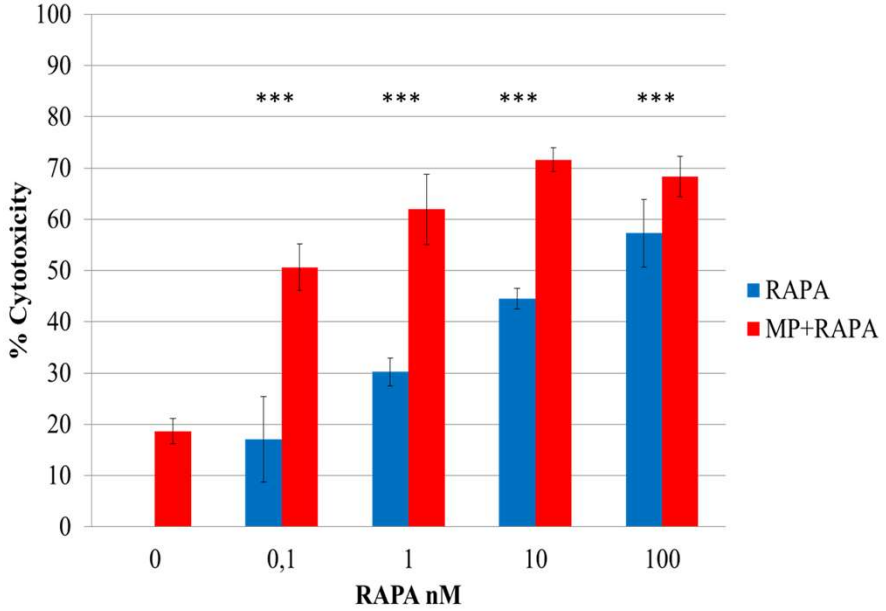


Fig. 1 Cells were exposed for 72 h to MP at 20 μg/ml and/or different concentrations of RAPA, and cell proliferation was evaluated by MTT assay. Two-way ANOVA (P<0.0001) and Bonferroni post-test *** p-value<0.001.

Cancer Chemotherapy and Pharmacology (2020) 86:361–374
https://doi.org/10.1007/s00280-020-04122-z

ORIGINAL ARTICLE

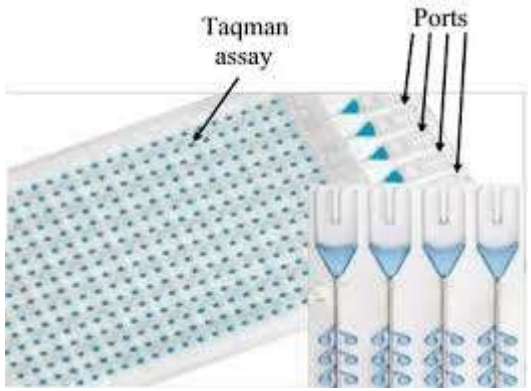
miR-331-3p is involved in glucocorticoid resistance reversion by rapamycin through suppression of the MAPK signaling pathway

Marianna Lucafò[1] · Daria Sicari[2,3] · Andrea Chicco[4] · Debora Curci[5] · Arianna Bellazzo[6] · Alessia Di Silvestre[5] · Chiara Pegolo[6] · Robert Autry[7] · Erika Cecchin[8] · Sara De Iudicibus[1] · Licio Collavin[6] · William Evans[7] · Giuliana Decorti[1,4] · Gabriele Stocco[6]

DIFFERENTIAL EXPRESSION OF miRNAs IN RAPAMYCIN-INDUCED REVERSION OF GC RESISTANCE

Differentially expressed miRNAs.

The expression analysis identified 70, 99 and 96 miRNAs that were differentially expressed after treatment with MP, RAPA and MP+RAPA, respectively.



TaqMan® Array MicroRNA Cards

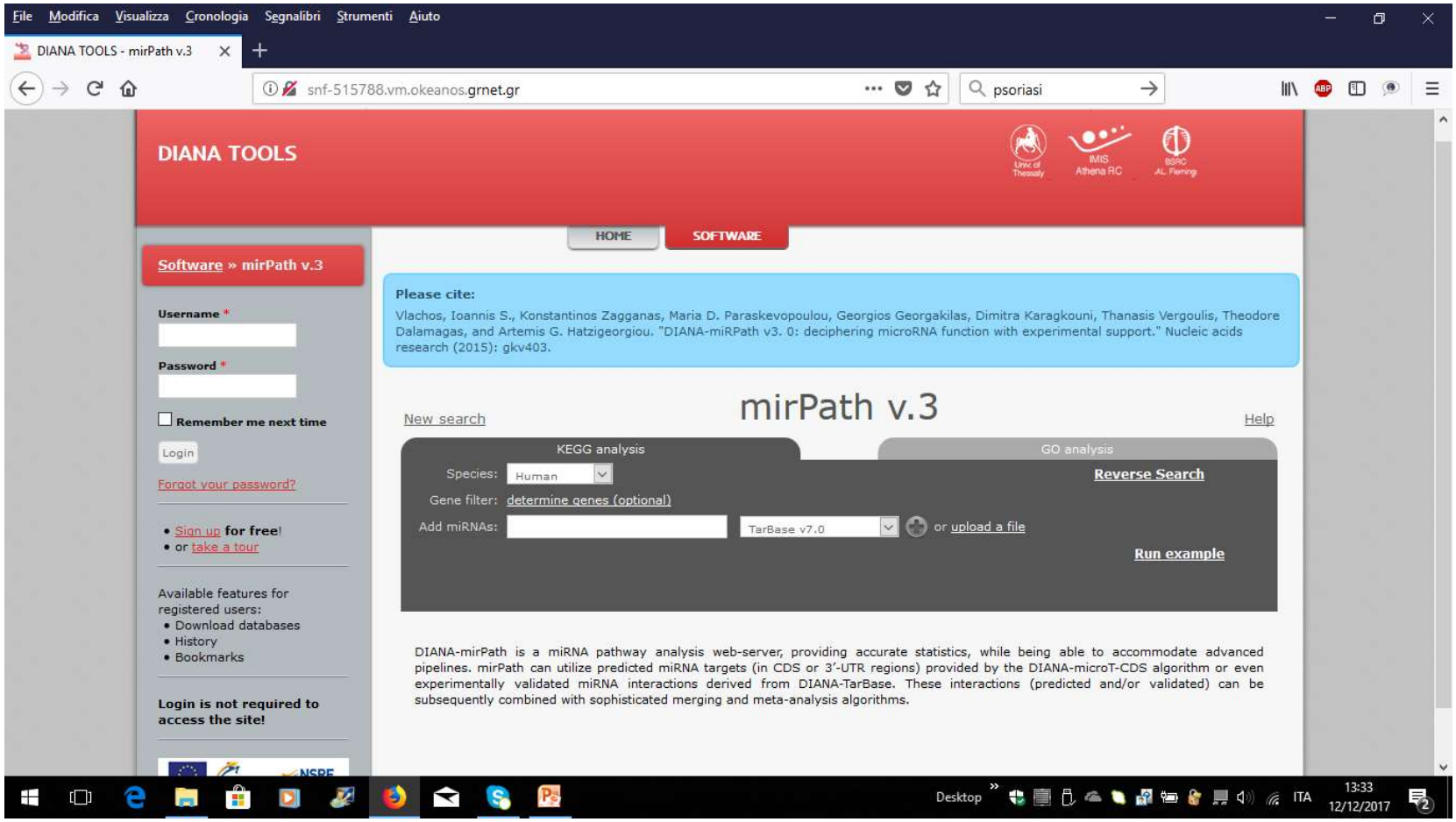
miRNA up e downregolati selettivamente dai diversi trattamenti farmacologici

	UP	DOWN
MP	hsa-miR-200b-3p	hsa-miR-181c-5p hsa-miR-192-5p hsa-miR-324-3p hsa-miR-361-5p hsa-miR-455-5p hsa-miR-576-3p
RAPA	hsa-miR-140-3p hsa-miR-26b-5p hsa-miR-28-5p hsa-miR-324-5p hsa-miR-454-3p	hsa-miR-142-5p hsa-miR-365a-3p hsa-miR-455-3p hsa-miR-501-5p
MP+RAPA	hsa-miR-30b-5p hsa-miR-30c-5p hsa-miR-331-3p hsa-miR-345-5p hsa-miR-744-5p	hsa-miR-19a-3p hsa-miR-886-3p hsa-miR-886-5p

DIFFERENTIAL EXPRESSION OF miRNAs IN RAPAMYCIN-INDUCED REVERSION OF GC RESISTANCE

DIANA miRPath v.2.0: investigating the combinatorial effect of microRNAs in pathways

http://snf-515788.vm.okeanos.grnet.gr/



DIFFERENTIAL EXPRESSION OF miRNAs IN RAPAMYCIN-INDUCED REVERSION OF GC RESISTANCE

UPREGULATED miRNAs

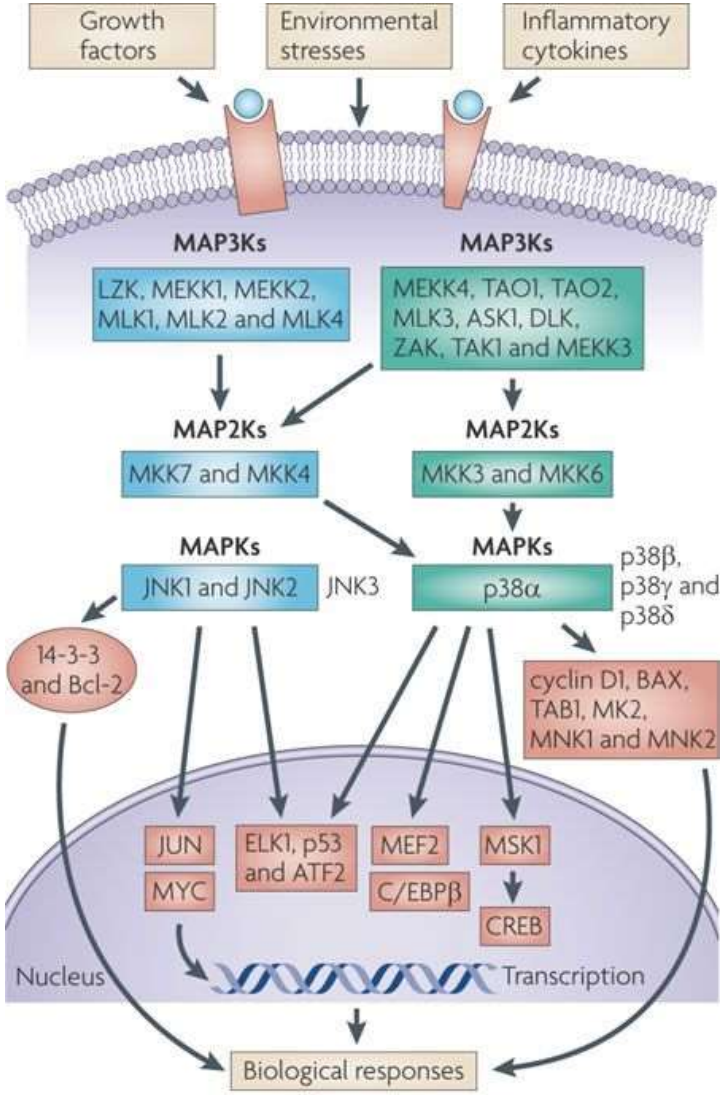
Pathways	MP			RAPA			MP+RAPA		
	p-Value	*Gene*	*miRNA*	*p-Value*	*Gene*	*miRNA*	*p-Value*	*Gene*	*miRNA*
ECM-receptor interaction	5.067 e-27	26	14	1.611 e-27	30	20	1.674 e-21	36	21
Biotin metabolism	7.131 e-5	2	2	0.0009	2	3	0.002	2	3
Vitamin B6 metabolism	0.00057	4	4	0.0294	3	3	0.0416	3	4
PI3K-Akt signaling pathway	0.00687	96	29	0.0009	124	44	0.0025	130	48
p53 signaling pathway	0.0086	24	18	0.0071	30	27	0.00271	33	31
Protein digestion and absorption	0.02	31	15	-	-	-	-	-	-
Ras signaling pathway	0.0201	64	26	0.003	85	39	0.027	83	42
Glycosaminoglycan biosynthesis	0.025	6	5	-		-	0.0065	11	11
Tight junction	0.028	41	21	-	-	-	-	-	-
Estrogen signaling pathway	0.0291	29	16	-	-	-	-	-	-
Neurotrophin signaling pathway	0.042	36	22	0.0294	47	31	0.0053	53	34
Fatty acid biosynthesis	-	-	-	1.898 e-13	4	4	3.734 e-12	4	5
Prion diseases	-	-	-	5.169	9	12	-	-	-
Bacterial invasion of epithelial cells	-	-	-	0.0052	34	28	-	-	-
Ubiquitin mediated proteolysis	-	-	-	0.0071	55	33	0.0146	57	37
MAPK signaling pathway	-	-	-	-	-	-	0.00576	98	41
Proteoglycans in cancer	0.019	74	39	-	-	-	-	-	-

DOWNREGULATED miRNAs

Pathways	MP			RAPA			MP+RAPA		
	p-Value	*Gene*	*miRNA*	*p-Value*	*Gene*	*miRNA*	*p-Value*	*Gene*	*miRNA*
Fatty acid biosynthesis	3.31 e-26	4	3	1.123 e-23	3	2	7.532 e-21	3	1
Fatty acid metabolism	2.069 e-8	11	9	0.00064	9	8	0.007	9	6
Proteoglycans in cancer	3.569 e-5	40	16	0.00074	37	20	0.0019	35	15
Thyroid hormone signaling pathway	0.0015	20	15	-	-	-	-	-	-
Path regulat pluripot of stem cells	0.005	30	15	0.03099	30	20	-	-	-
Thyroid hormone synthesis	0.0075	12	8	-	-	-	-	-	-
Glycosphingolipid biosynthesis	0.0106	5	3	0.0248	6	7	-	-	-
N-Glycan biosynthesis	0.0314	10	9	0.0248	12	9	0.03	10	8
PI3K-Akt signaling pathway	-	-	-	0.0248	67	22	-	-	-
Acute myeloid leukemia	-	-	-	0.0309	15	14	-	-	-
ErbB signaling pathway	-	-	-	-	-	-	0.014	22	14

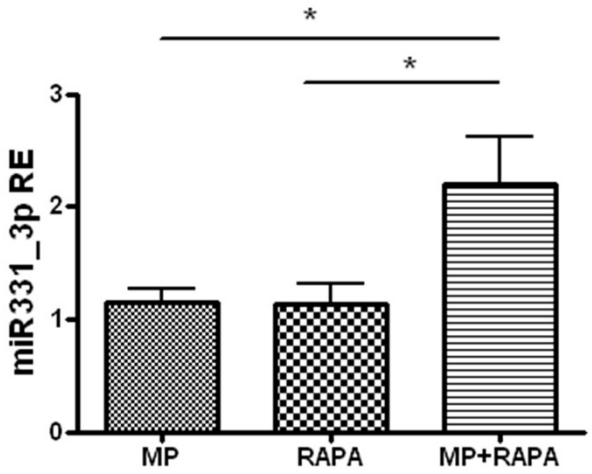
miR-331-3p

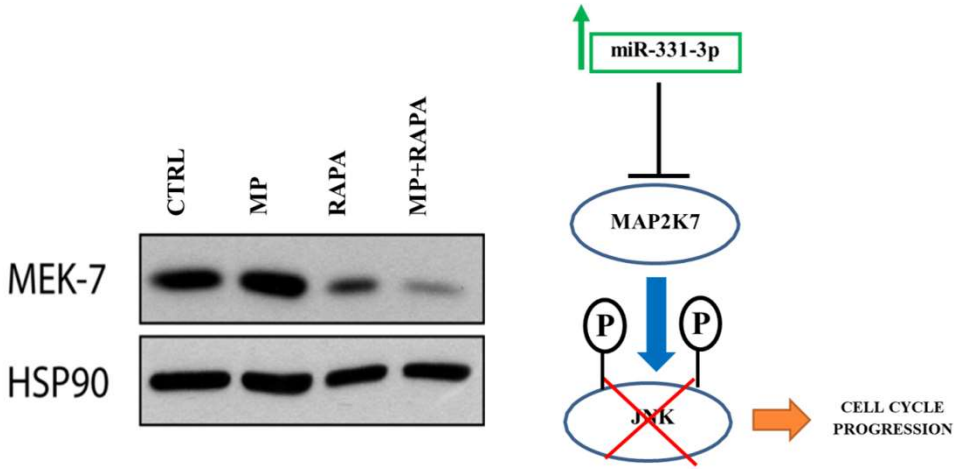
DIFFERENTIAL EXPRESSION OF miRNAs IN RAPAMYCIN-INDUCED REVERSION OF GC RESISTANCE



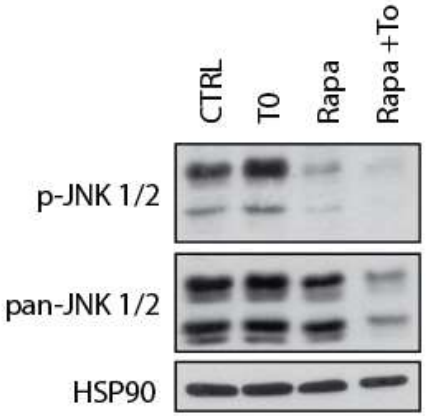
Nature Reviews | Cancer

DIFFERENTIAL EXPRESSION OF miRNAs IN RAPAMYCIN-INDUCED REVERSION OF GC RESISTANCE

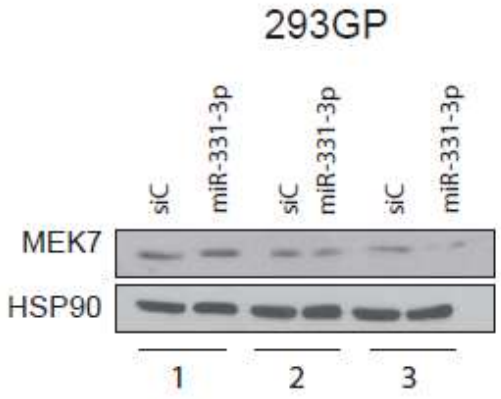


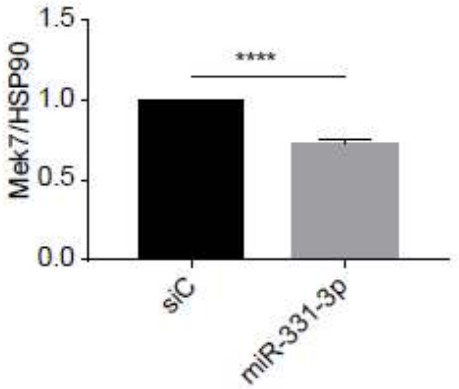


Validation of MAP2K7 as a target of miR-331-3p

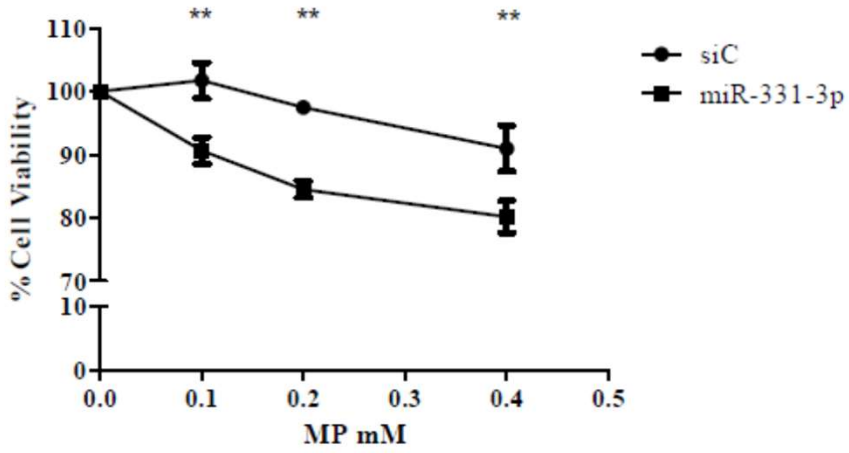


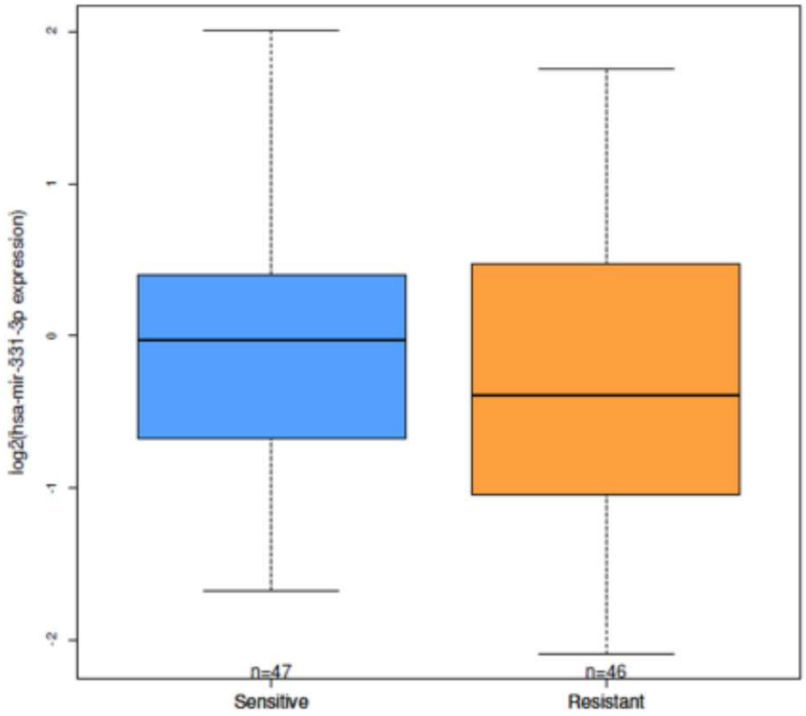
GC resistance reversion by RAPA through suppression of the JNK protein



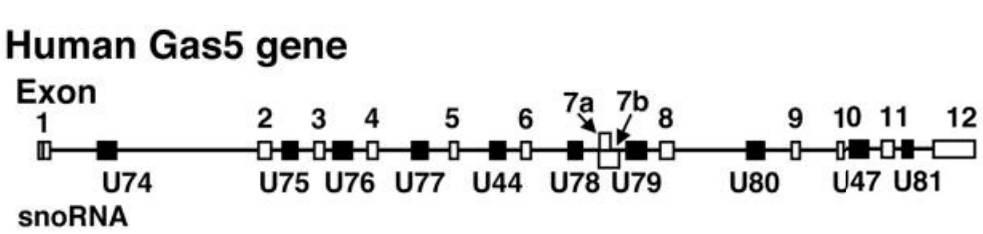


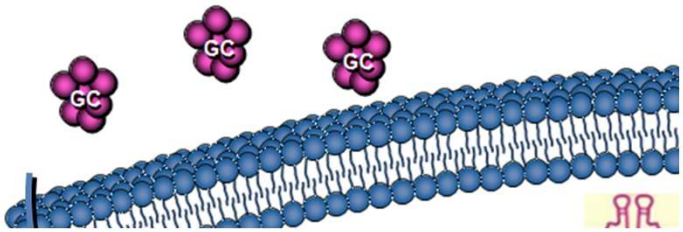
DIFFERENTIAL EXPRESSION OF miRNAs IN RAPAMYCIN-INDUCED REVERSION OF GC RESISTANCE

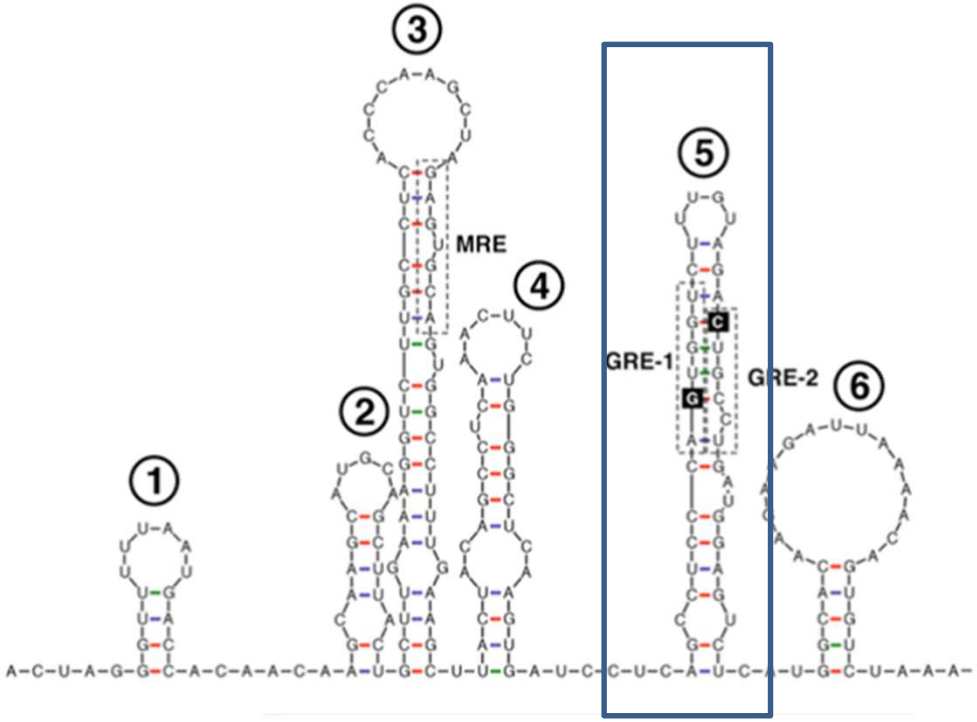




Growth arrest-specific 5 (GAS5)



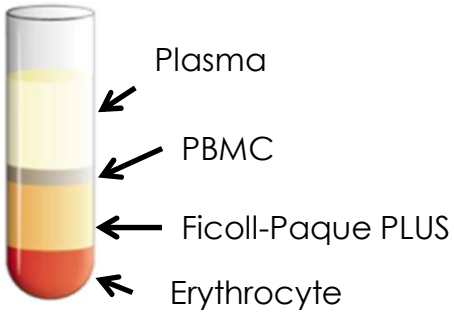




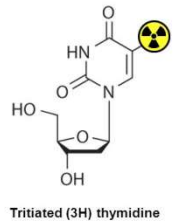
(Kino et al., Sci Signal. 2010)

ROLE OF GAS5 IN GC RESPONSE

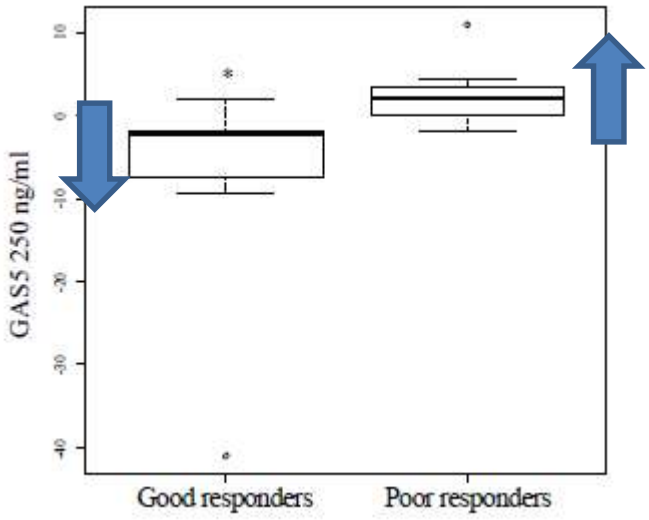
Samples from blood donors



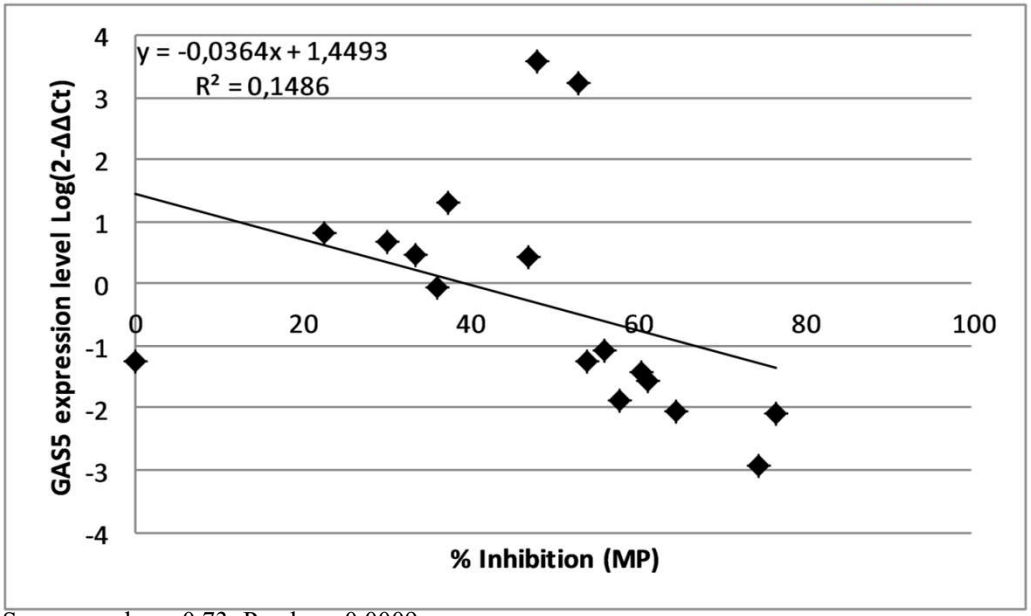
Pharmacodynamic test: inhibition of in vitro proliferation by the test of incorporation of [^{3}H]-thymidine.



Tritiated (3H) thymidine

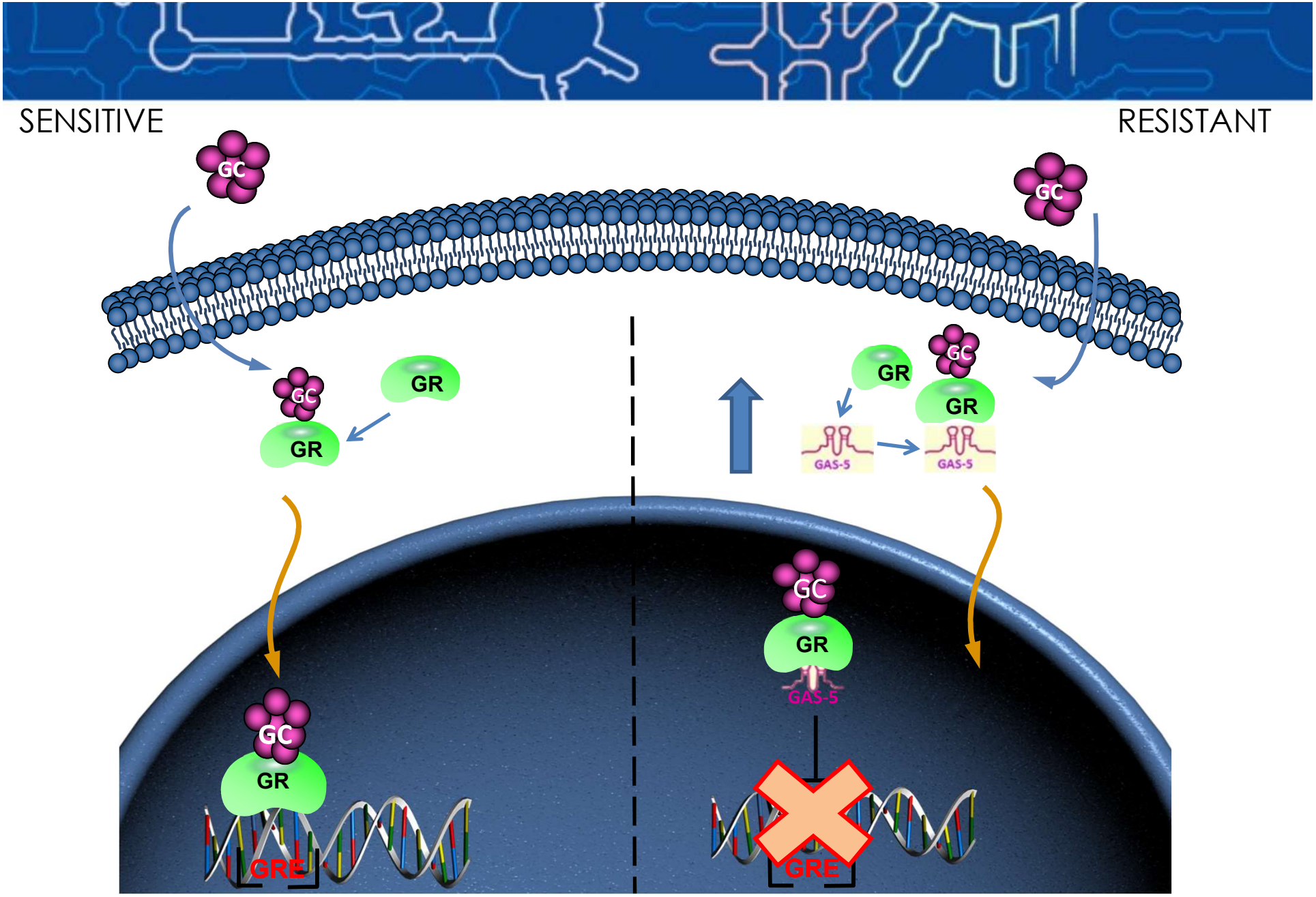


Lucafò M. et al., *Curr Mol Med* **2015**

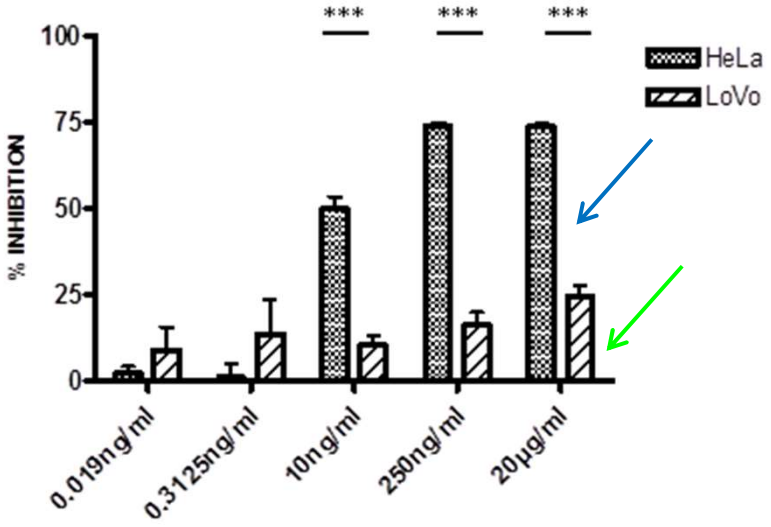


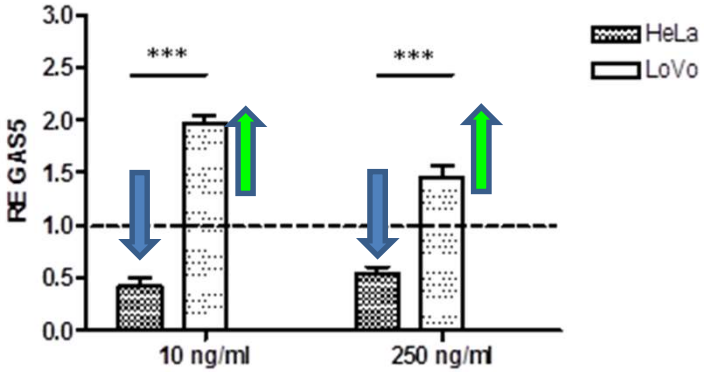
Spearman rho= -0,73; P value= 0.0009

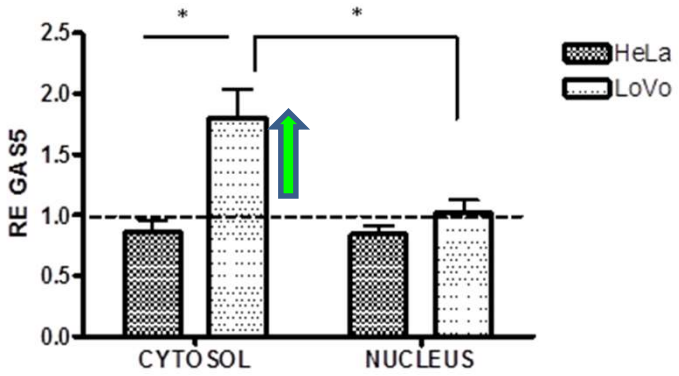
Lucafò M. et al., *Clin and Exp Pharm and Phys* **2016**

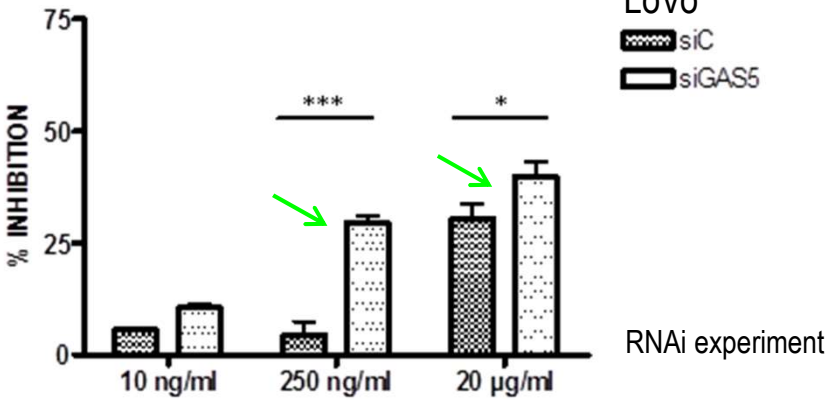

SENSITIVE
RESISTANT
GC
GR
GC
GR
GC
GR
GR
GAS-5
GAS-5
GC
GR
GAS-5
GC
GR
GRE
GRE

ROLE OF GAS5 IN GC RESPONSE







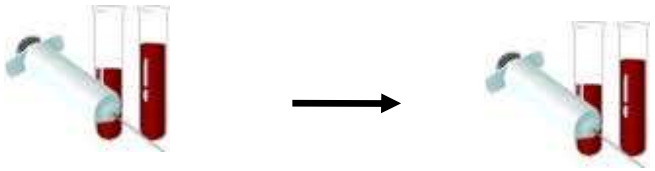


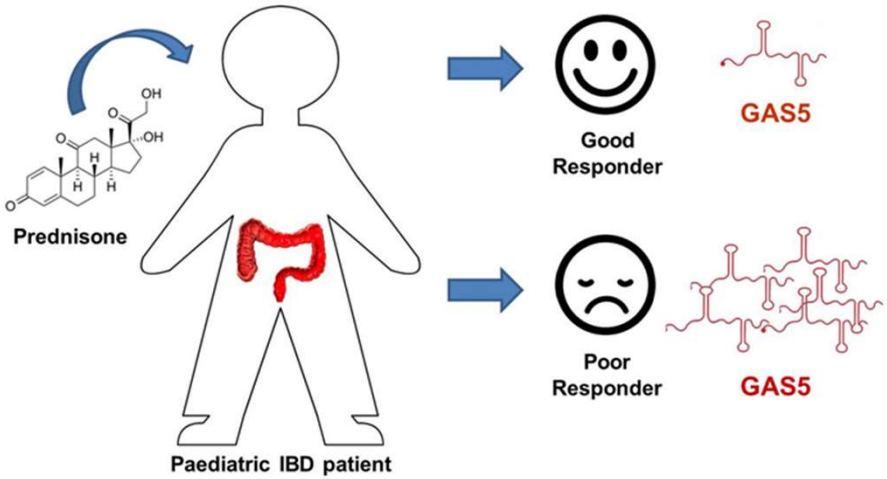
RNAi experiment

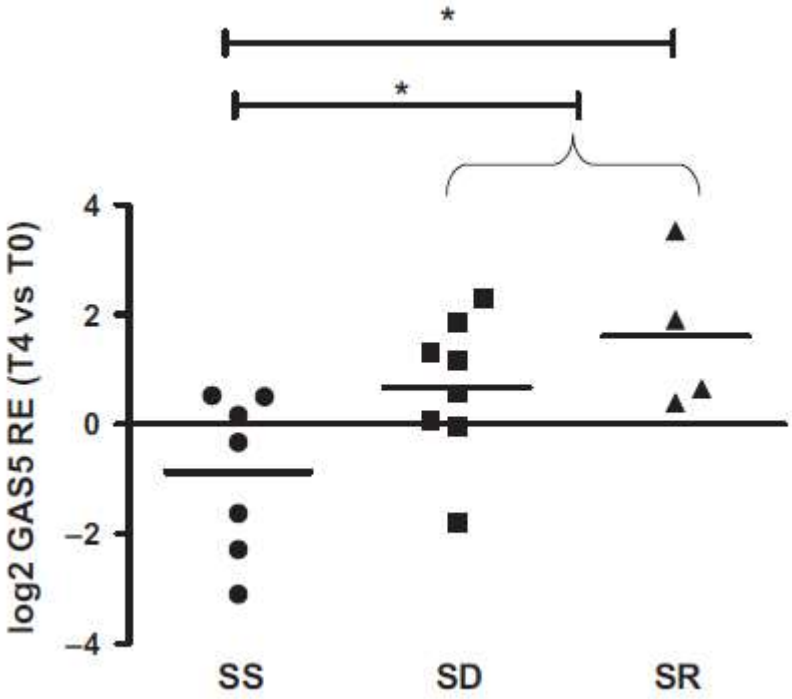
ROLE OF GAS5 IN GC RESPONSE IN CHILDREN WITH IBD

DIAGNOSIS (T0)

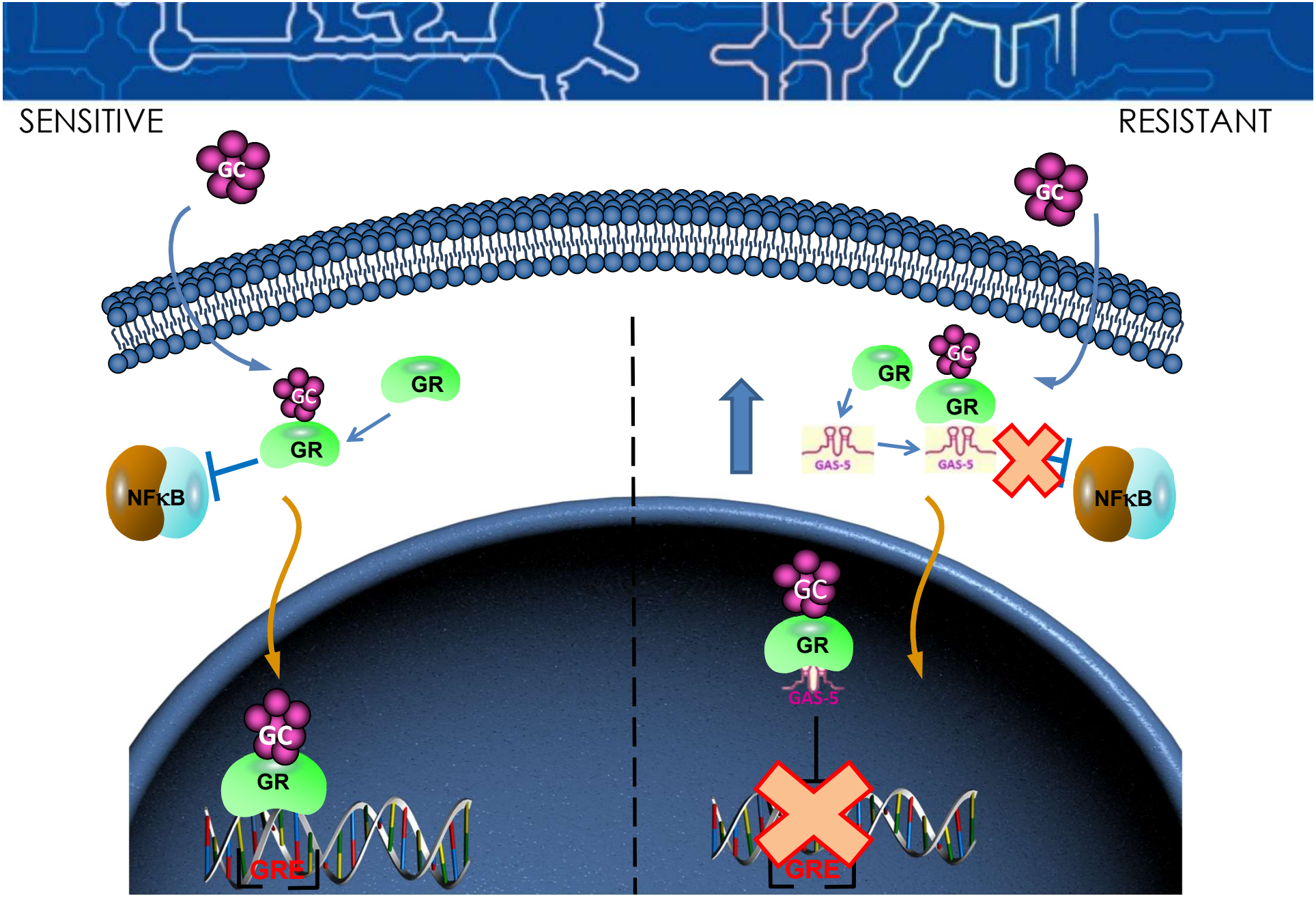
30 DAYS OF TREATMENT WITH GC (T4)



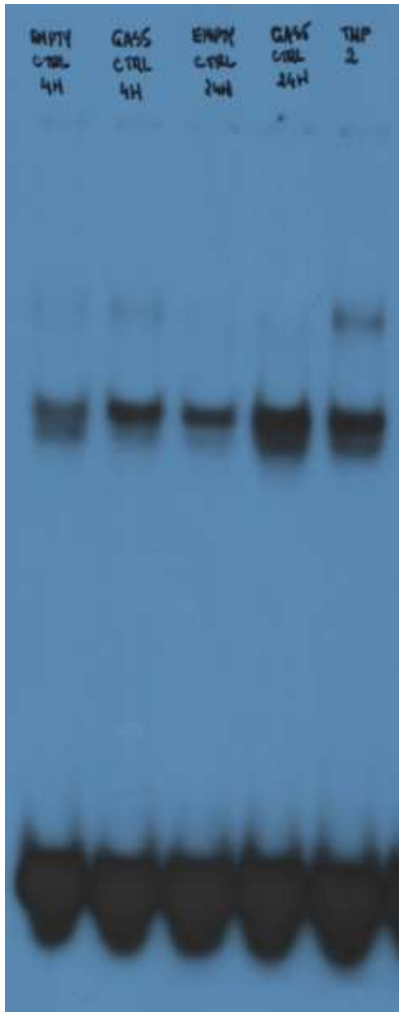


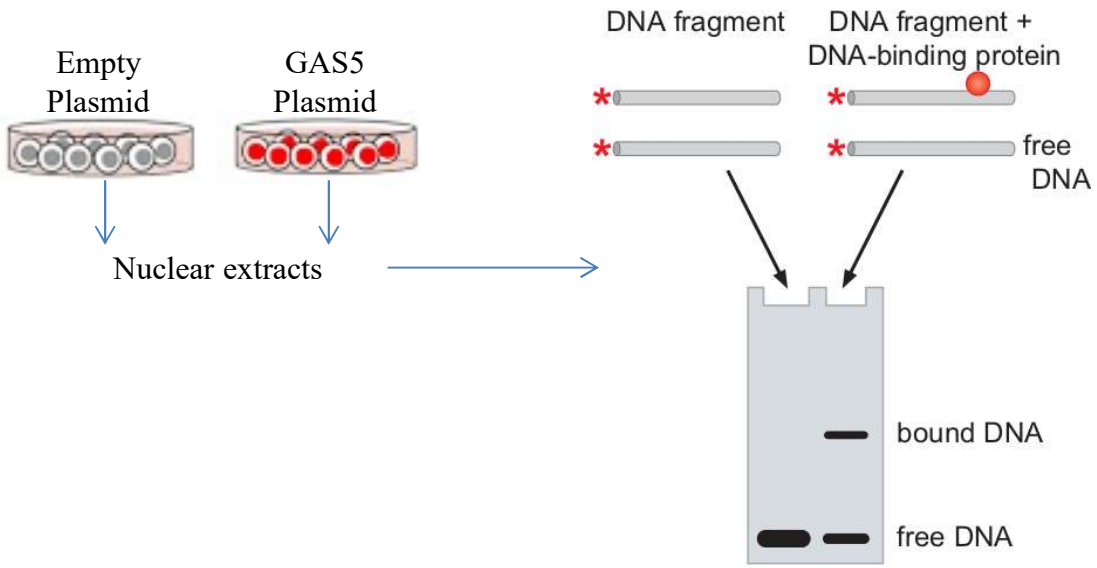


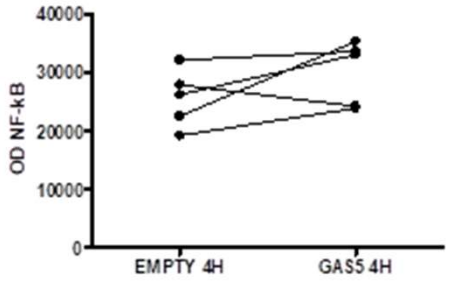
Lucafò M. et al., *Basic & Clinical Pharmacology & Toxicology* **2017**

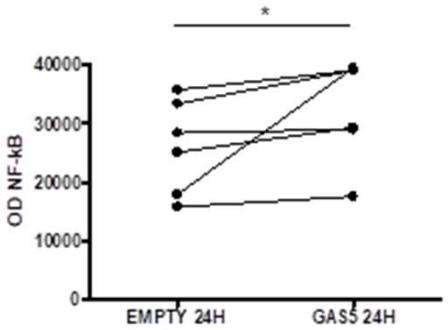

SENSITIVE
RESISTANT
GC
GR
NFκB
GAS-5
GRE

ROLE OF GAS5 on NF-kB activity by EMSA



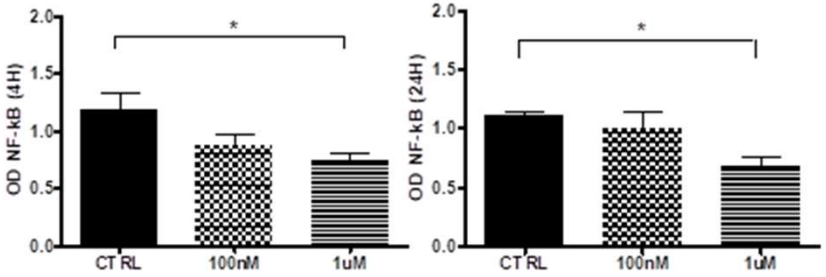


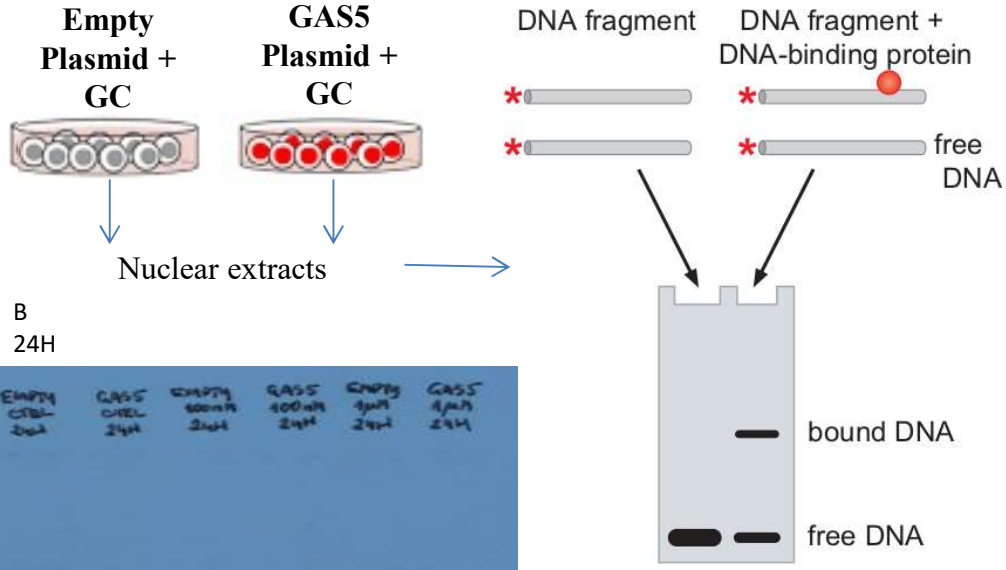




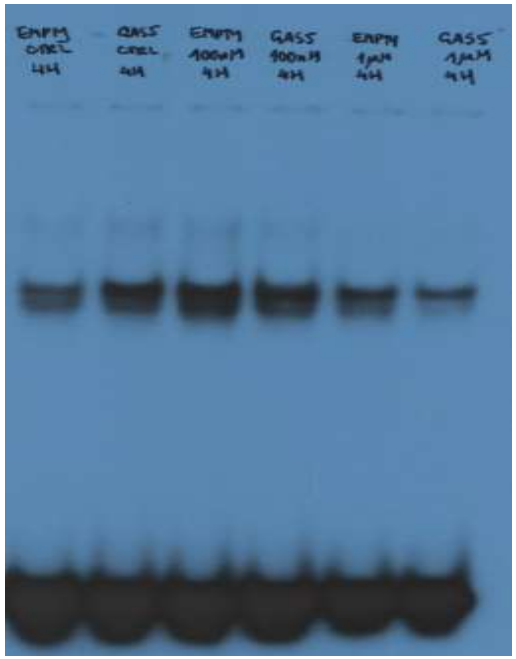
NF-kB EMSA analyses in HeLa cells transfected with empty pcDNA3.1 (EMPTY CTRL) and pcDNA3.1_GAS5 (GAS5 CTRL), after 4 (lanes 1, 2) and 24 h (lanes 3, 4) from transfection or treated with TNF-α (lane 5).

ROLE OF GAS5 on NF-kB activity by EMSA

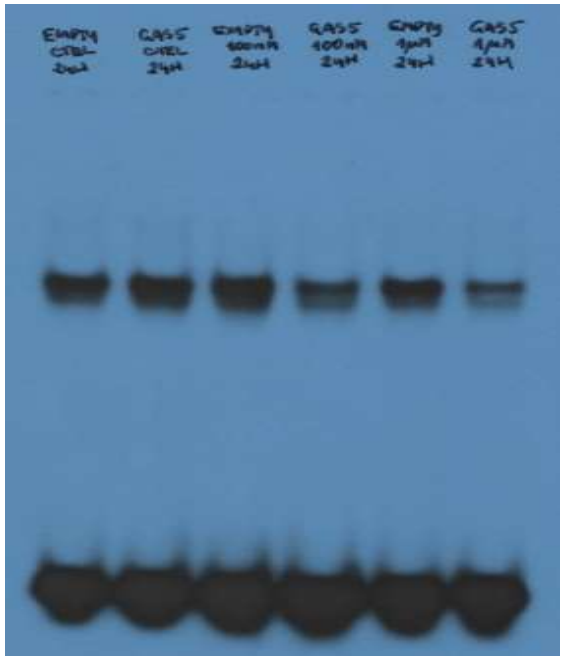




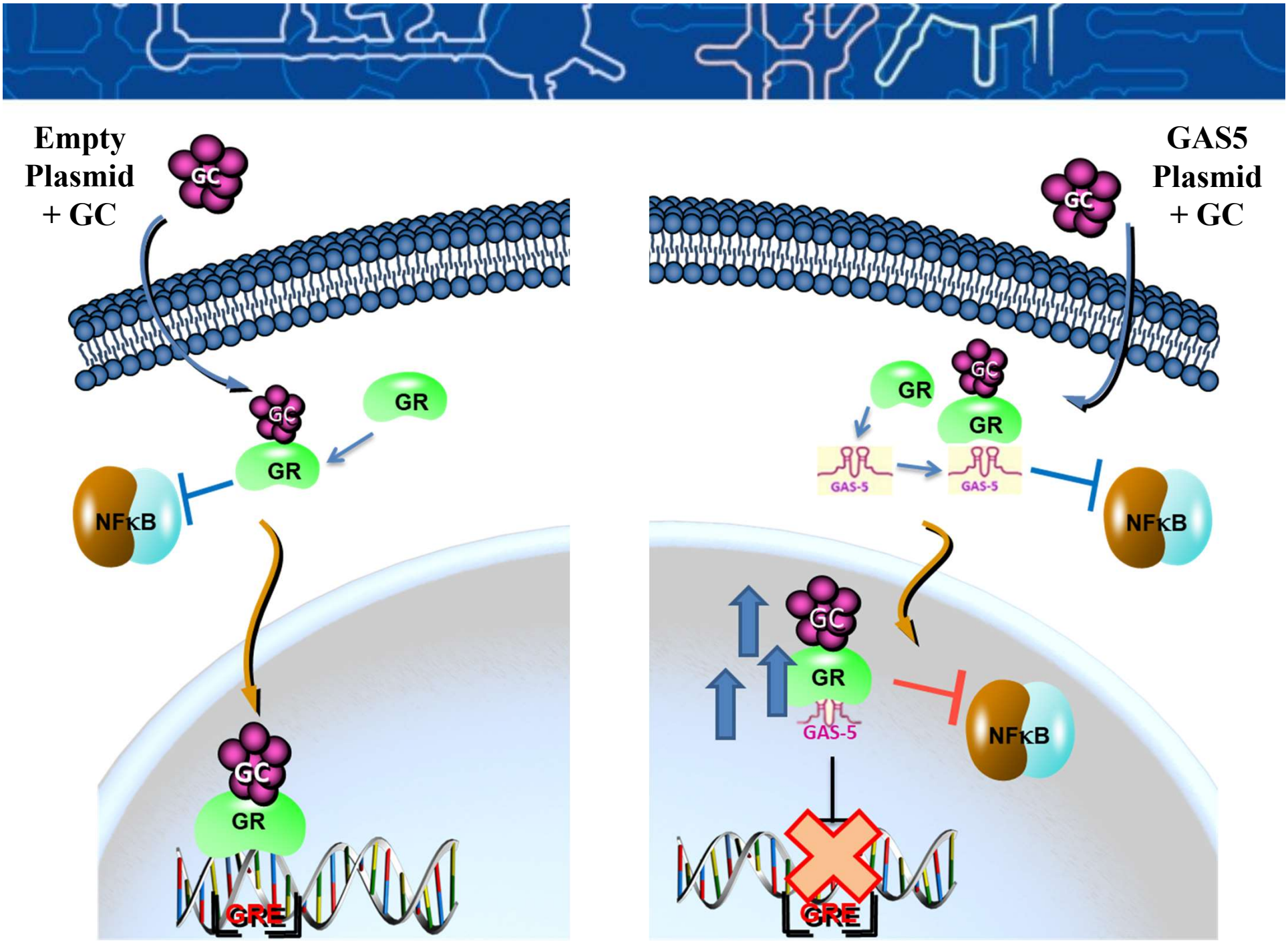
A
4H



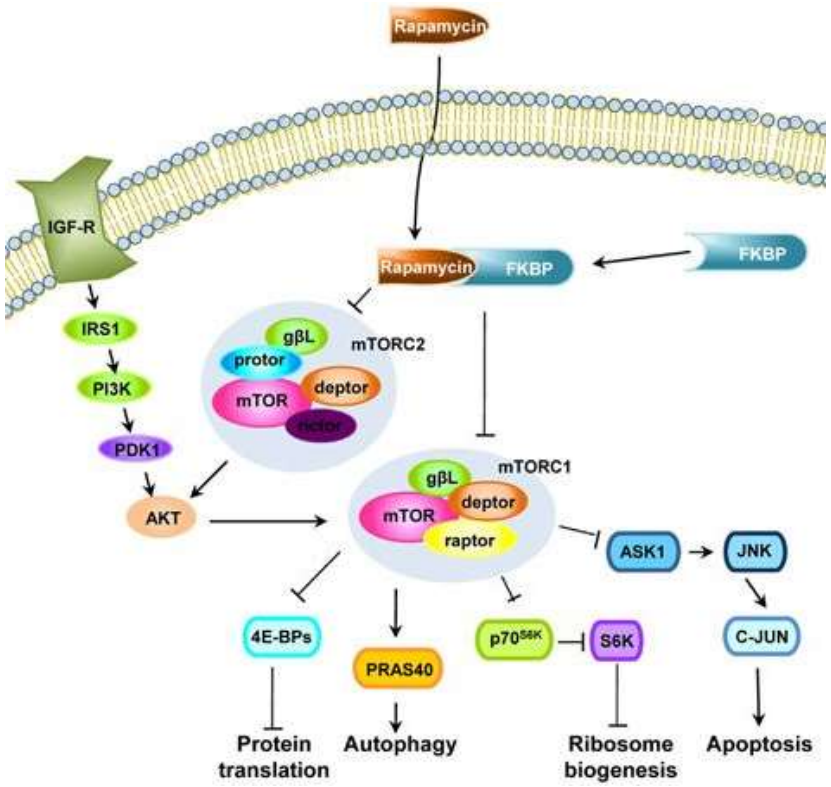
B
24H



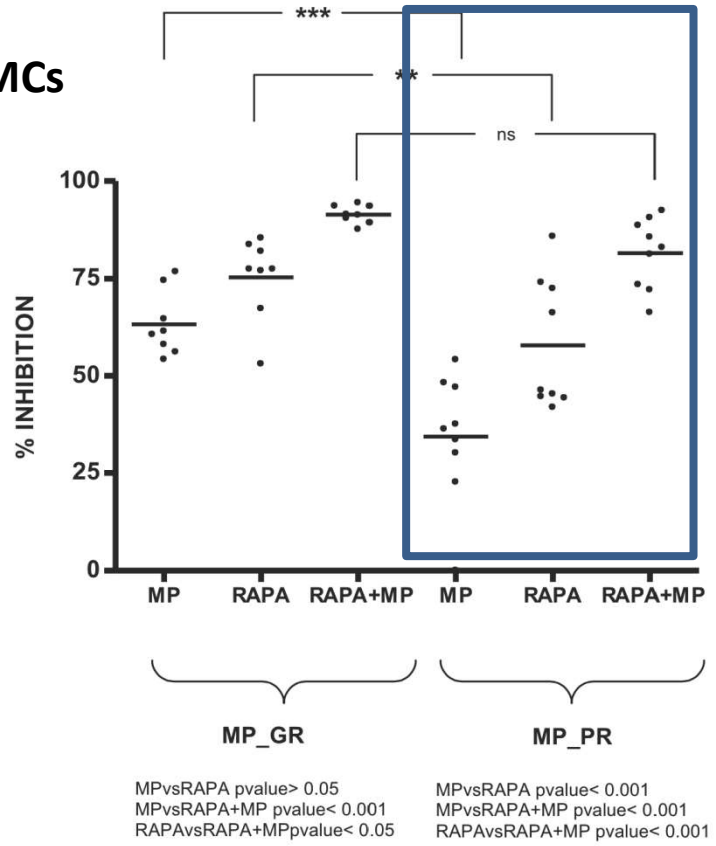
NF-kB EMSA analyses in HeLa cells transfected with empty pcDNA3.1 (EMPTY) and pcDNA3.1_GAS5 (GAS5), treated with DEXA 100 nM (lanes A and B 3, 4) and 1 µM (lanes A and B 5, 6) and untreated (CTRL; lanes A and B 1, 2) after 4 (A) or 24 h (B).


Empty
Plasmid
+ GC
GC
GR
GC
GR
NFκB
GC
GR
GRE
GAS5
Plasmid
+ GC
GC
GR
GR
GAS-5
GAS-5
NFκB
GC
GR
GAS-5
NFκB
GRE

DIFFERENTIAL EXPRESSION OF GAS5 IN RAPAMYCIN-INDUCED REVERSION OF GC RESISTANCE



PBMCs



Lucafò M. et al., *Clin and Exp Pharm and Phys* **2016**