

MikroRNA miR-155 a jeho role u lymfoproliferativních onemocnění.

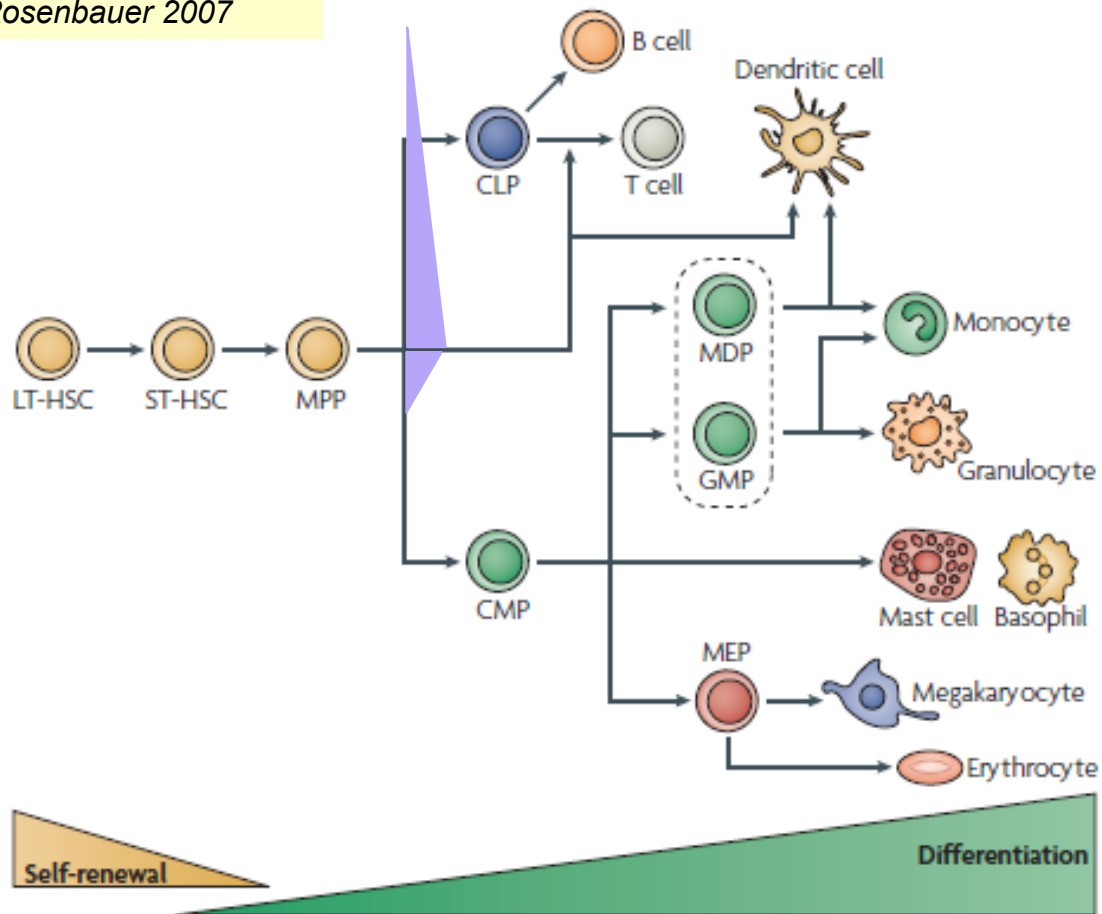
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Rosenbauer 2007



PU.1

ETS domain

GAGGAA

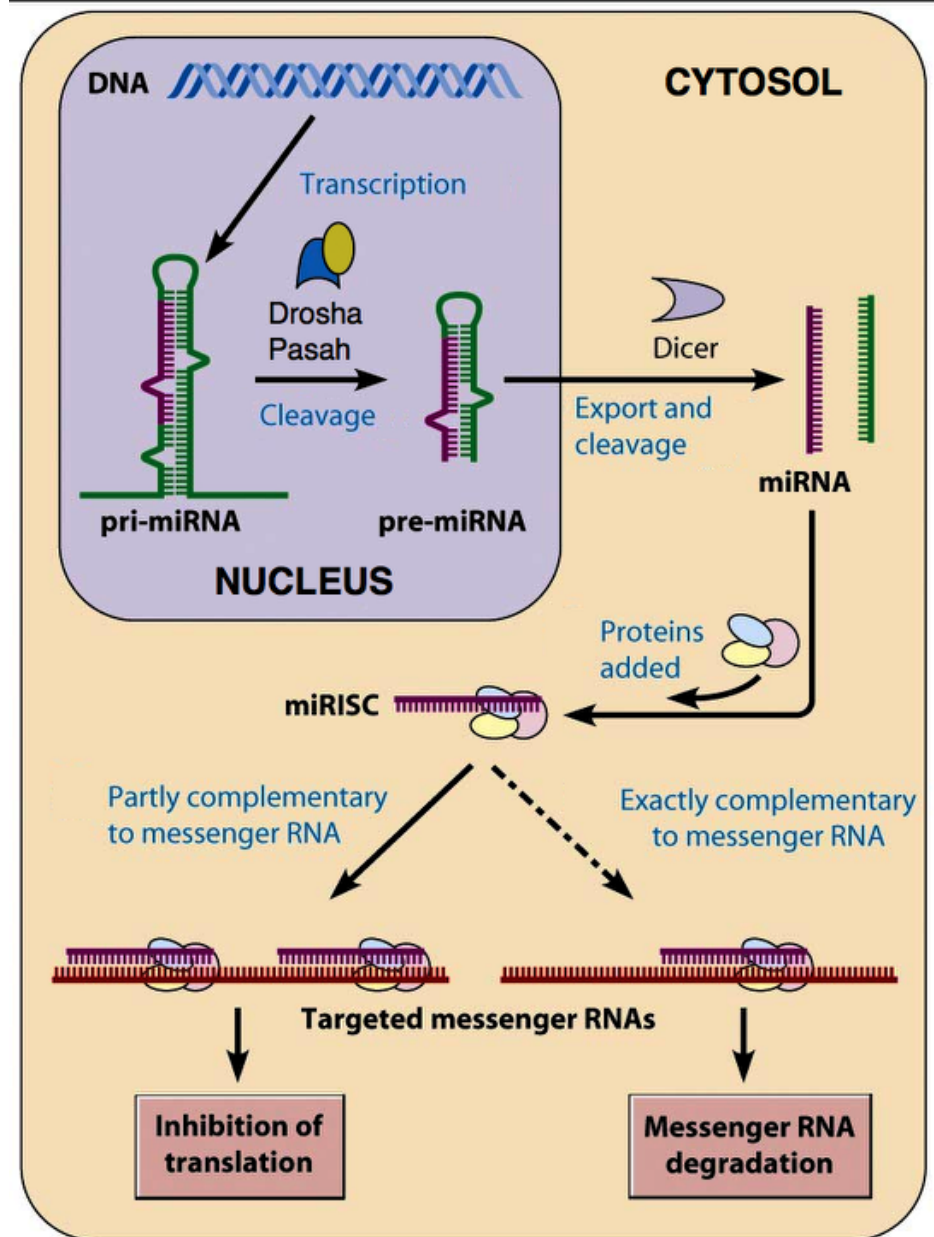
pancytopenie

GATA-1, Cebpa, Cbfb, c-Jun

mutace, snížená exprese

MikroRNA

- malé jednovláknové nekódující RNA (~22nt)
- zprostředkují vazbu komplexu RISC do 3'UTR cílové mRNA – dochází k represí translace nebo k degradaci mRNA
- regulace řady buněčných procesů
- změněná exprese byla zjištěna u různých chorob včetně solidních nádorů, leukemií a lymfomů (rev. in Dalmy 2008)

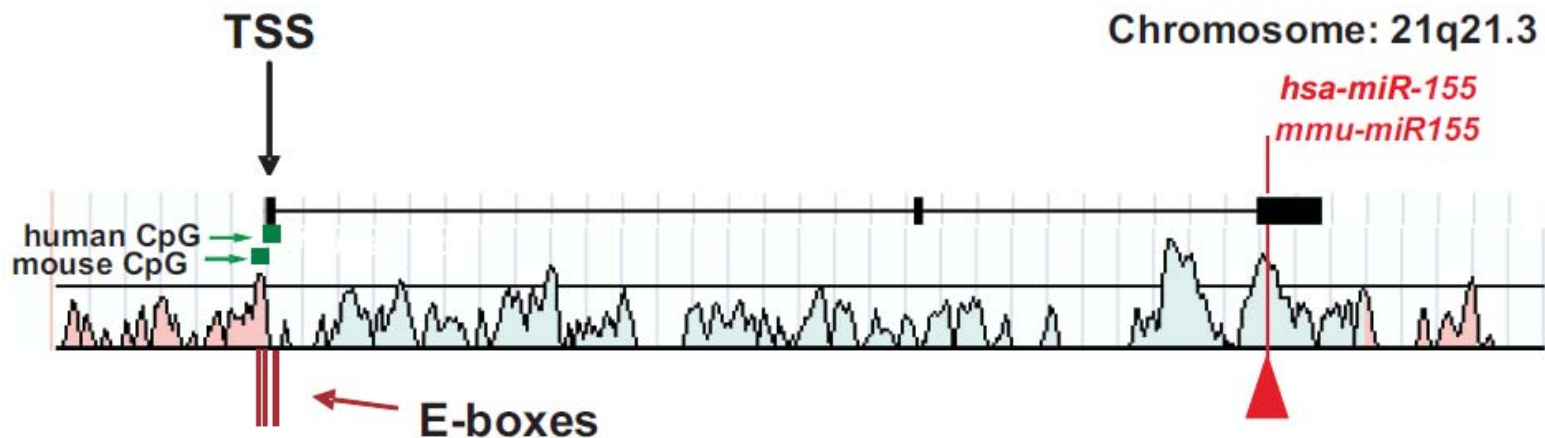


Lymfoproliferativní onemocnění

- nádory lymfocytů (především řady B) často začínající v lymfatických uzlinách
 - Hodgkinův lymfom
 - nehodgkinské lymfomy
 - agresivní – difuzní velkobuněčný B lymfom (DLBCL),
lymfom buněk plášťové zóny (MCL)
 - indolentní – folikulární lymfom (FL), lymfom marginální zóny (MZL), chronická lymfocytární leukémie resp. lymfom z malých lymfocytů (B-CLL/SLL)
- prognostika – věk, klinické stadium, LDH, „performance status“ a další podle typu lymfomu

miR-155

- *MIR155HG* (*bic*, B cell integration cluster) na chromozomu 21
exprese: hematopoetická tkáň (lymfocyty a makrofágy)
řízení germinální reakce, zánětlivé odpovědi, vývoje T lymfocytů (Thai 2007, He 2009, Rodriguez 2007, Vigorito 2007)
- zvýšení hladiny miR-155 postačuje k vyvolání lymfomu u myši (Costinean 2006)
- zvýšená hladina miR-155 u některých typů lymfoproliferací (van den Berg 2003, Kluiver 2005, Zhao 2010, Eis 2005)
- nedochází k cytogenetickým změnám v lokusu *MIR155HG* → úloha procesů na úrovni tvorby miR-155



miR-155 targets

Direct targets of miR-155.

Gene symbol	Full gene name	References
<i>Transcriptional regulatory genes</i>		
ARID2	AT rich interactive domain 2	[67]
BACH1	BTB and CNC homology 1, basic leucine zipper transcription factor1	[46,67]
C/EBP β	CCAAT/enhancer binding protein, beta	[46,67]
ETS1	v-ets erythroblastosis virus E26 oncogene homolog 1	[73]
HIF	Hypoxia-inducible factor 1	[46,67]
HIVEP2	Human immunodeficiency virus type I enhancer binding protein 2	[67]
MAF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian)	[28]
MEIS1	Meis homeobox 1	[73]
PUI1 (SPI1)	Spleen focus forming virus (SFPV) proviral integration oncogene spi1	[30,46,67]
SMAD5	SMAD family member 5	[67]
ZIC3	Zic family member 3	[67]
ZNF652	Zinc finger protein 652	[67]
<i>Protein receptors</i>		
AT1R	Angiotensin II receptor, type 1	[63,64]
CSF1R	Colony stimulating factor 1 receptor	[46]
<i>Kinases</i>		
IKK ϵ	Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase ϵ	[33]
MAP3K7IP2 (TAB2)	Mitogen-activated protein kinase kinase kinase 7 interacting protein 2	[74]
RIPK1	Receptor (TNFRSF)-interacting serine-threonine kinase 1	[33]
<i>Nuclear proteins</i>		
AID	Activation-induced cytidine deaminase	[31,32]
ARNTL	Aryl hydrocarbon receptor nuclear translocator-like	[46]
CUTL1 (CUX1)	Cut-like homeobox 1	[46]
JARID2	Jumonji, AT rich interactive domain 2	[46]
TP53INP1	Tumor protein p53 induced nuclear protein 1	[36]
<i>Binding proteins</i>		
FADD	Fas (TNFRSF6)-associated via death domain protein	[33]
PICALM	Phosphatidylinositol binding clathrin assembly protein	[46]
RHOA	Ras homolog gene family, member A	[75]
SLA	Scr-like-adaptor	[46]

Faraoni et al 2009

MYB

- E-box TF nezastupitelný pro vývoj B buněk ve stadiu pro-B (Fahl 2009)
- Inhibovaný transkripčně PU.1 v průběhu B-buněčné diferenciace (Lin 2008)
- 80 genových cílů (Lei 2004)
- Inhibitor diferenciace, stimuluje proliferaci, uplatňuje se v leukemogenezi (review Ramsay 2008).

hsa-miR-155/MYB Alignment	
3' uggGGAUAGUGC ¹ UAAUCGUAAU ⁵ 5' hsa-miR-155 1:5' -gaCAUUUCCAGAAAAGCAUU ³ Au 3' MYB	mirSVR score: -1.0548 PhastCons score: 0.7541

hsa-miR-155/MYB Alignment	
3' ugggggaUAGUGC ¹ UAAUCGUAAU ⁵ 5' hsa-miR-155 416:5' uuaaaaaAUCAGUAAAAGCAUU ³ Ac 3' MYB	mirSVR score: -1.0114 PhastCons score: 0.5950

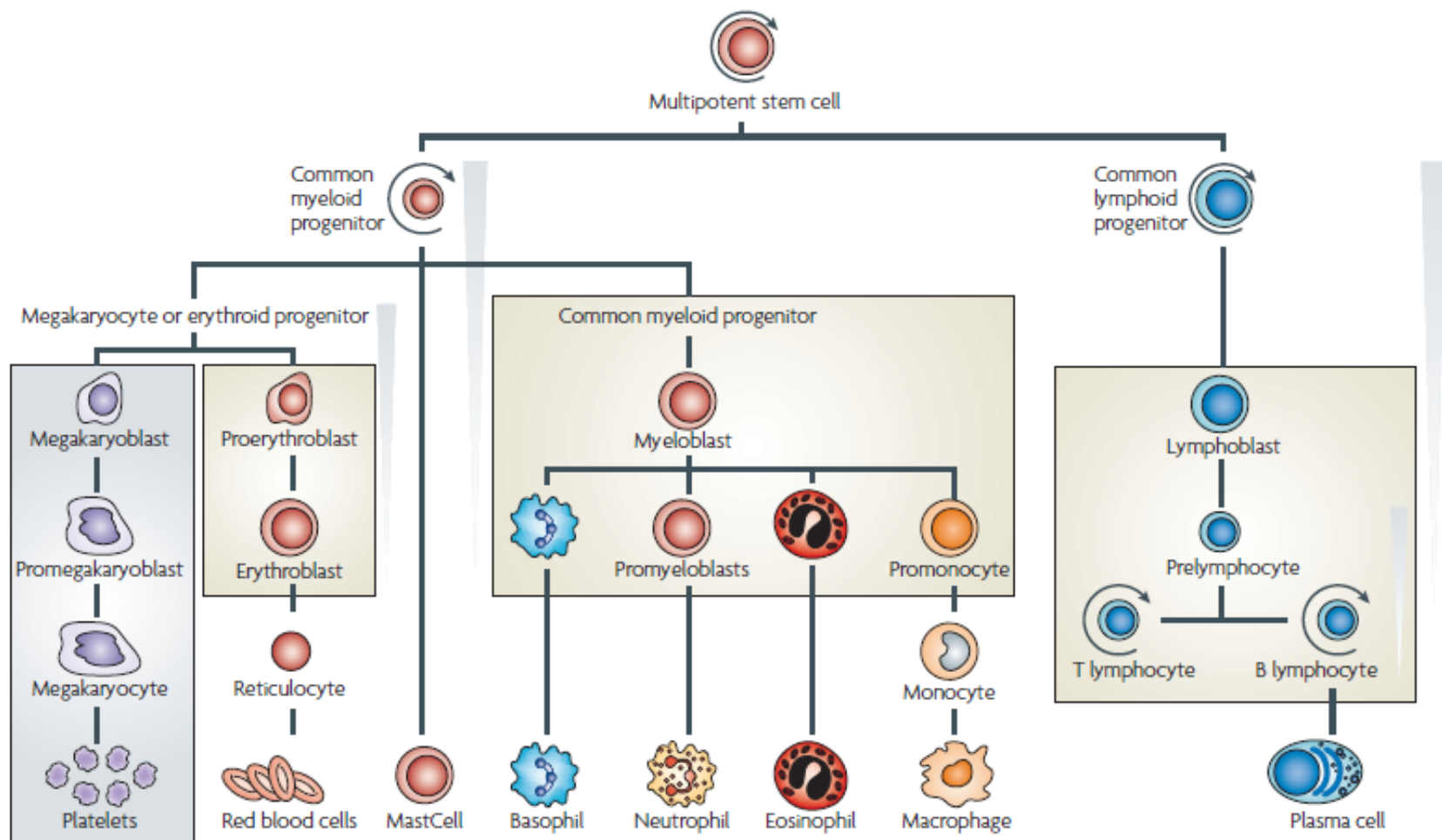


Figure 3 | **MYB is required for normal adult haematopoiesis.** The multiple lineages of the haematopoietic system are depicted. Circular arrows indicate that MYB is required for the self-renewal and expansion of these cell populations, and in the case of T and B cells MYB levels govern progressive differentiation steps. The relative levels and function of MYB protein are highest in the immature progenitors and these levels decline as cells commit to the various lineages that are indicated by grey wedges. When MYB overexpression occurs, differentiation is perturbed in cells demarcated by the beige boxes. The exception to this theme appears to be in the case of the megakaryocyte lineage (enclosed by a grey box) where the expansion of precursors and platelet numbers is favoured under circumstances in which MYB levels are reduced or MYB function is compromised. Finally, it seems that MYB is required for maintaining haematopoietic stem cell homeostasis, but how this is achieved is unclear.

Ramsay 2008

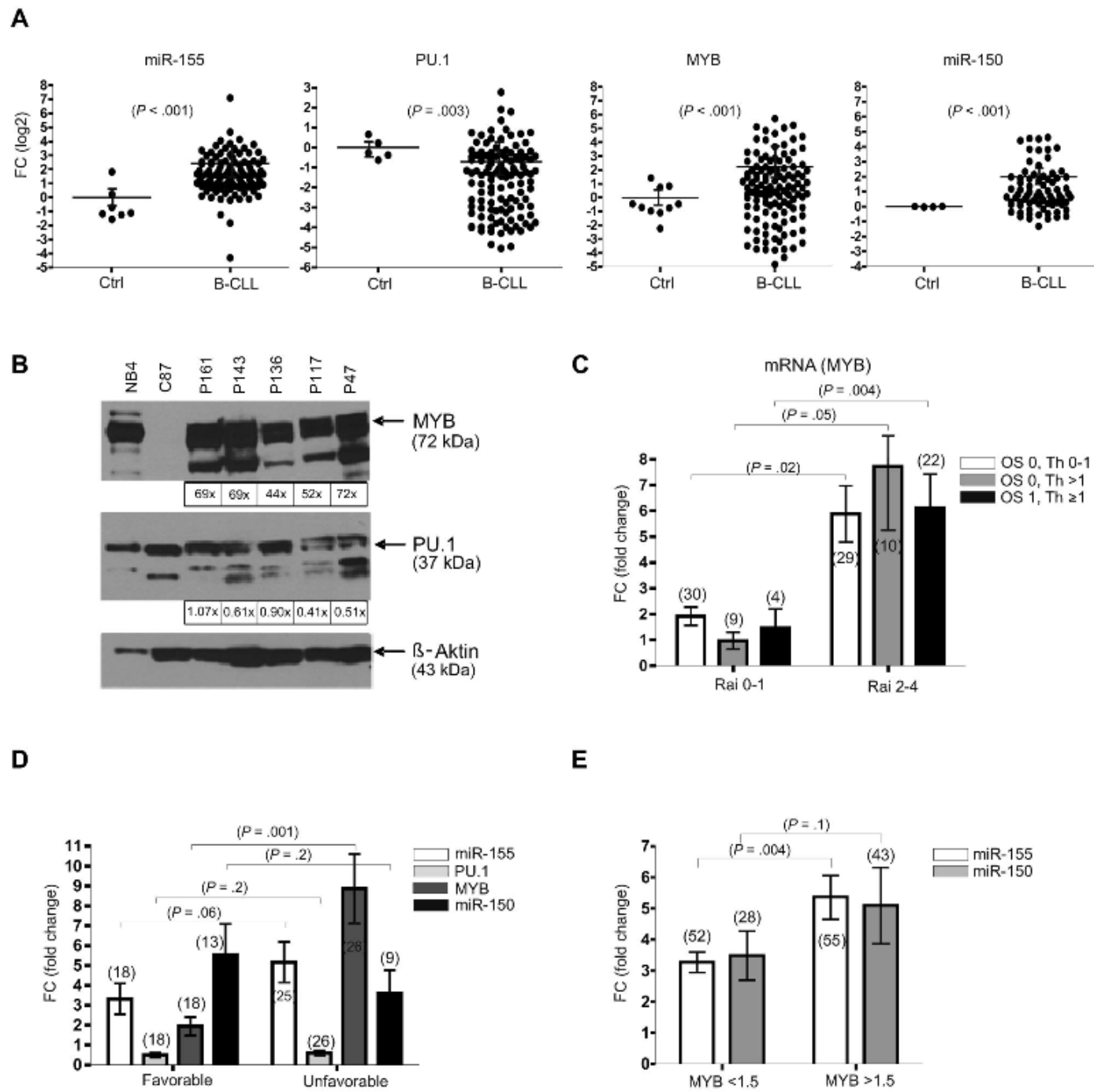


Fig 1

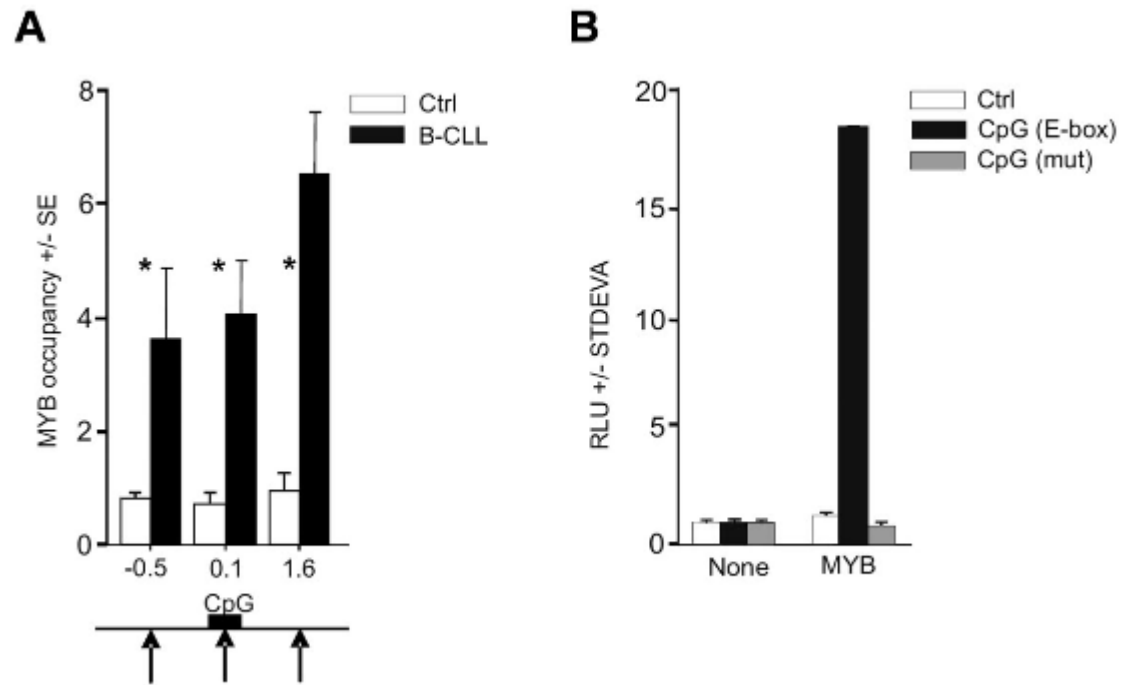


Fig 2

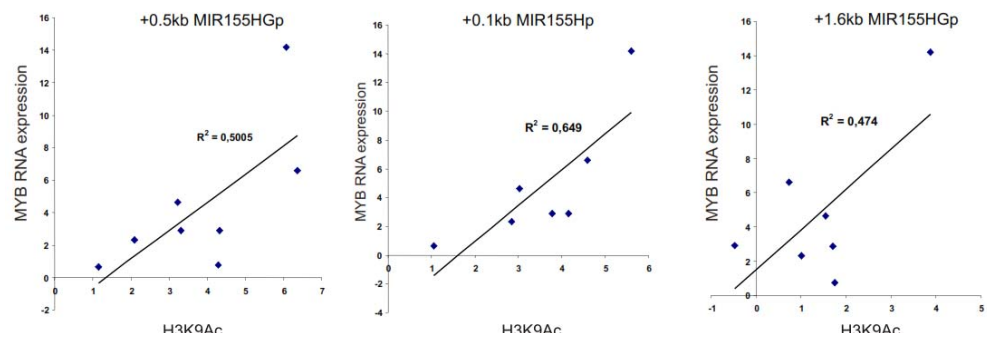
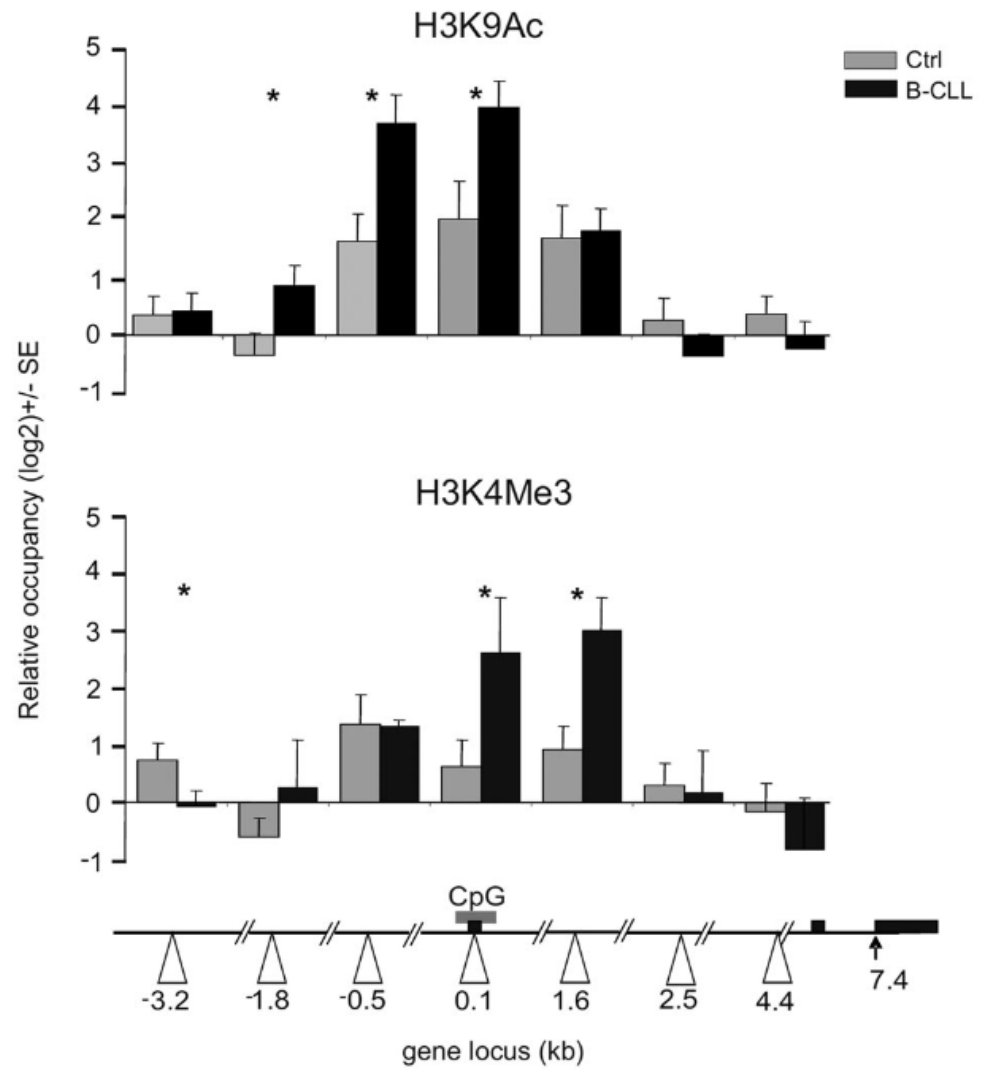


Fig 3

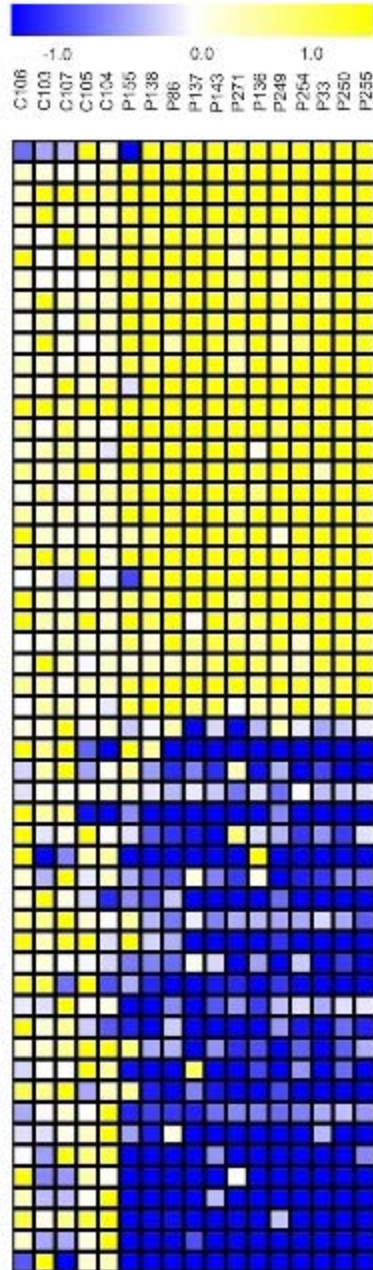
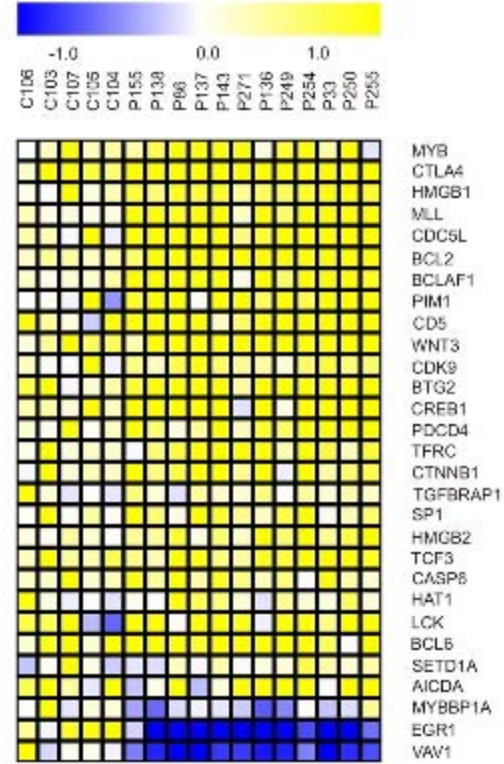
A**B**

Fig 4

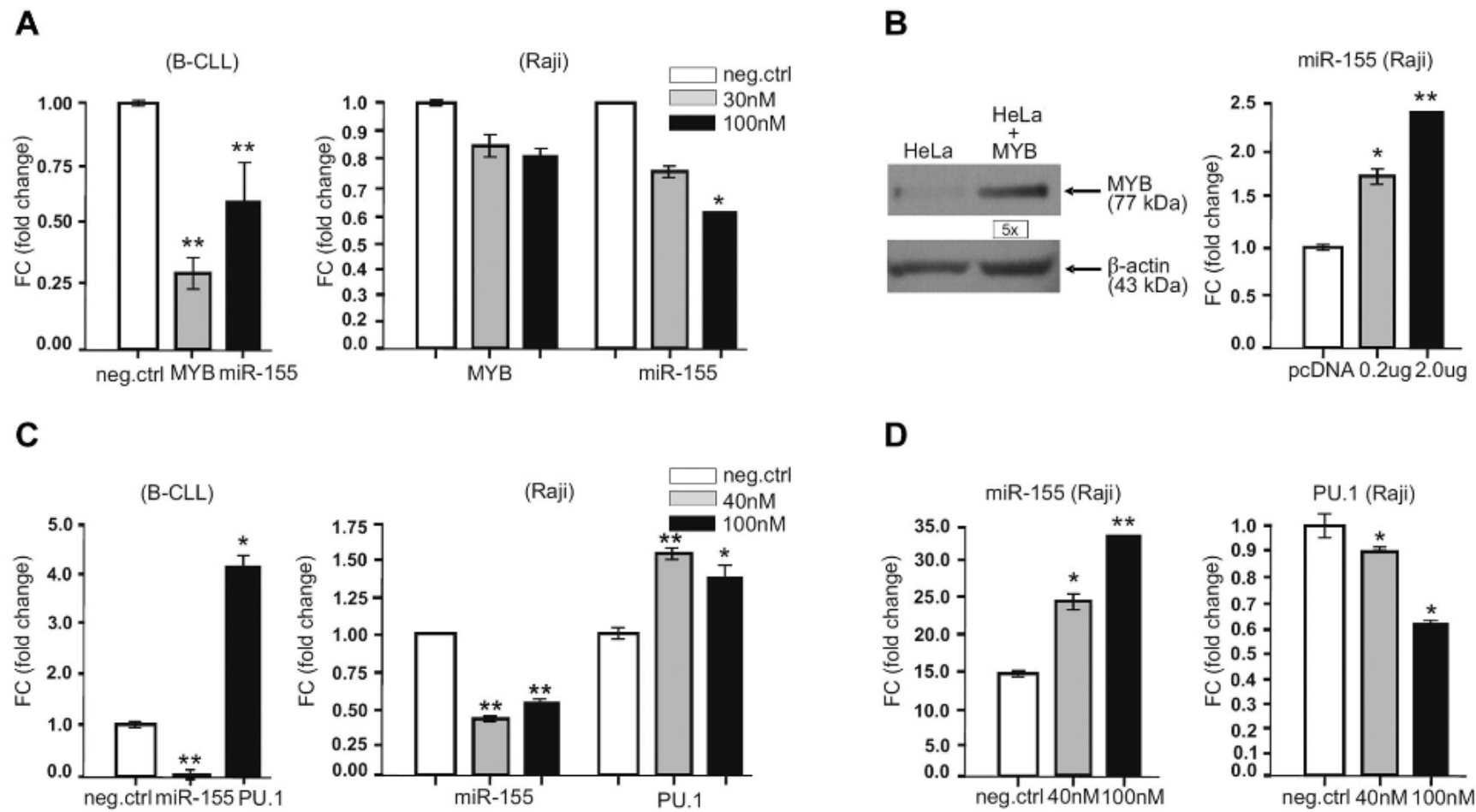
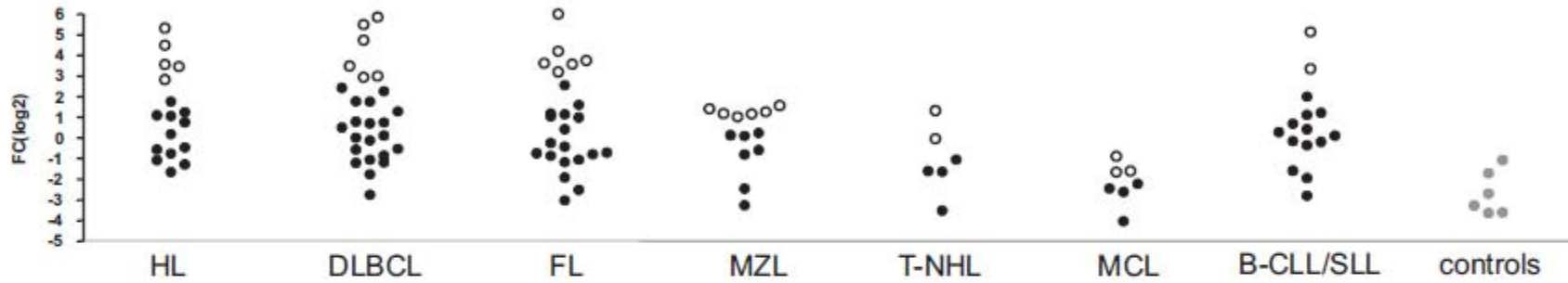
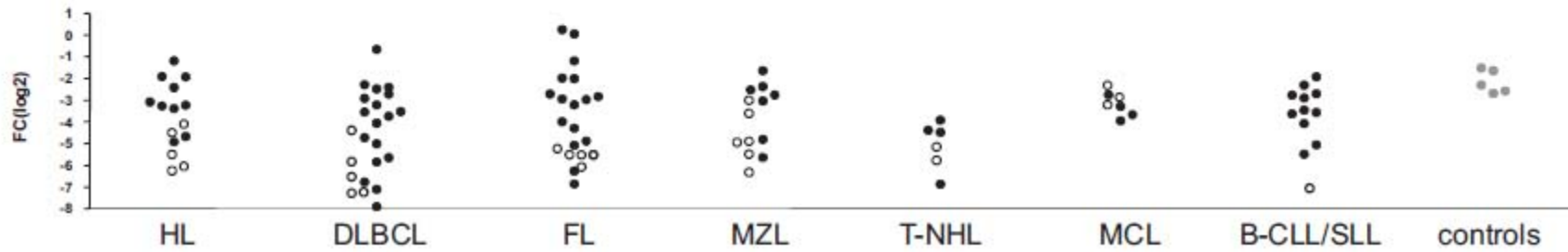


Fig 5

Relative expression of miR-155

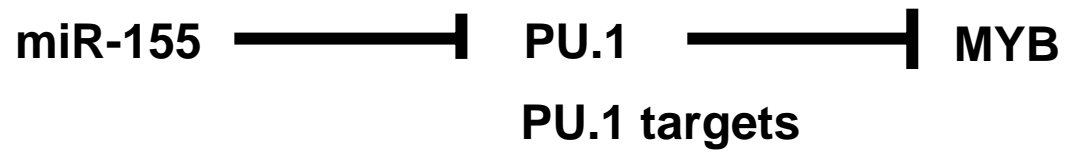


Relative expression of PU.1

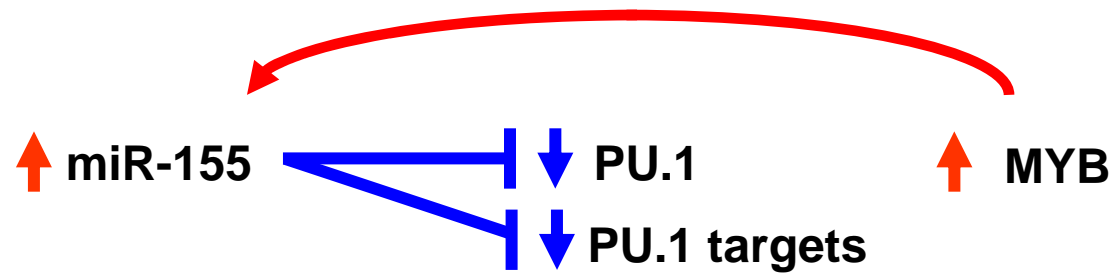


- miR-155 below average
- miR-155 over average

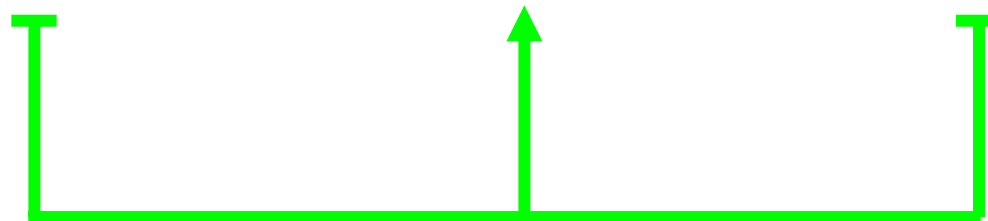
Homeostasis



CLL



Therapy



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blood

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MYB transcriptionally regulates the miR-155 host gene in chronic lymphocytic leukemia

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