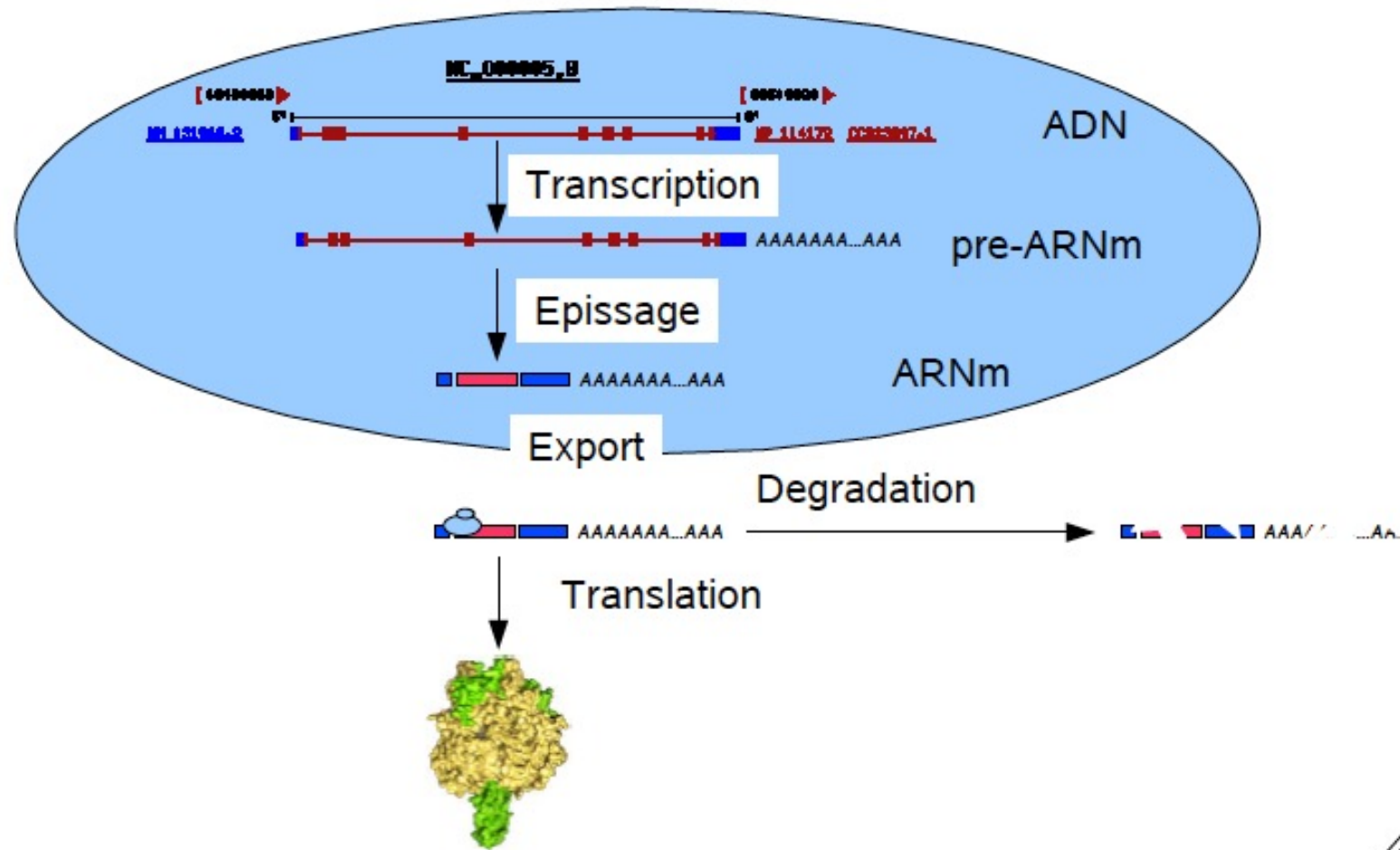
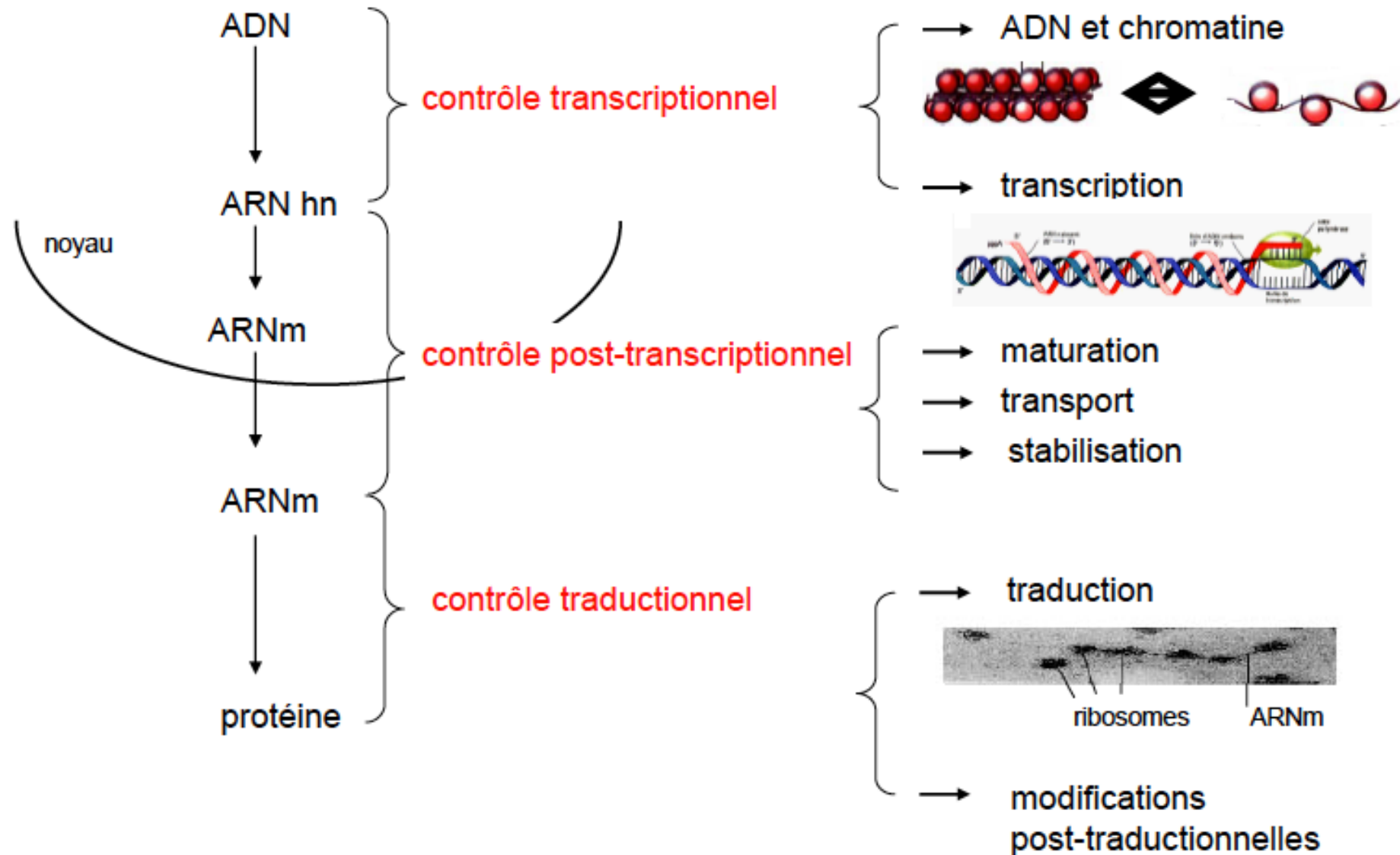
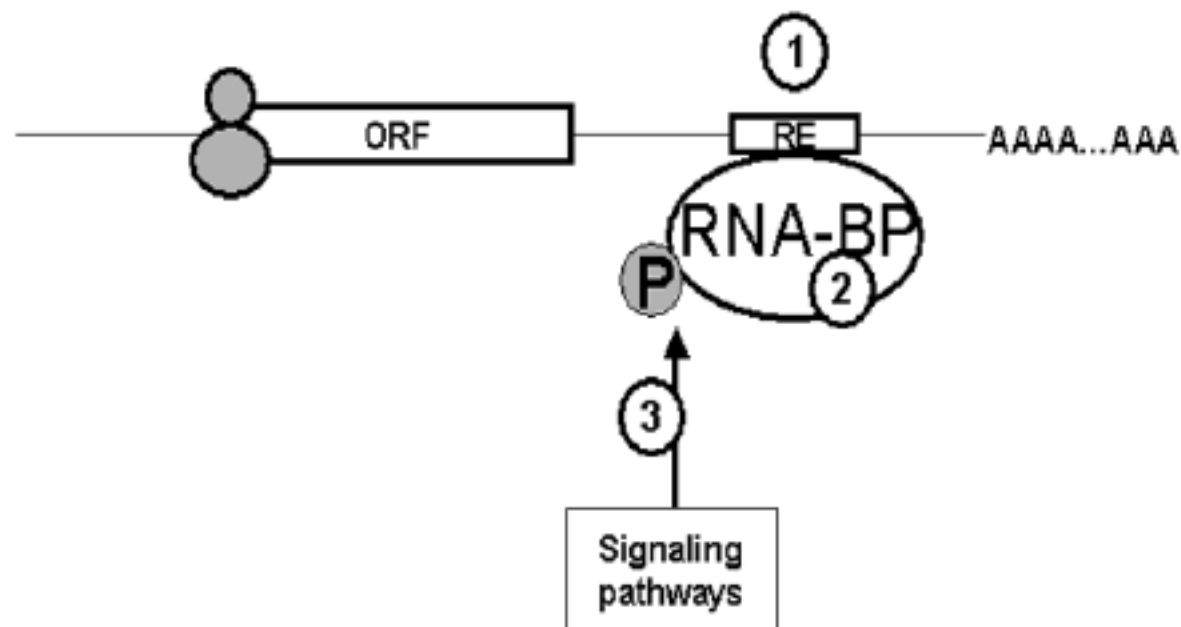


Du GENE à la PROTEINE

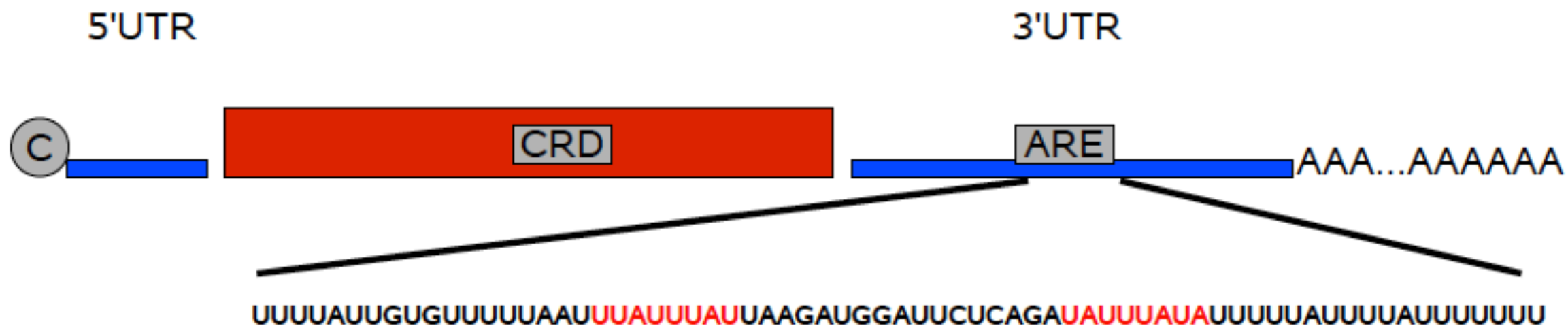


Niveaux de régulation de l'expression





- ① Alteration of regulatory elements by point mutations or deletions
- ② Alteration of the RNA Binding Protein
 - Mutations leading to a change in the affinity of the RNA-BP for its target
 - Titration of RNA-BP by overexpression of a target sequence
 - Over or underexpression of the RNA-BP
- ③ Alteration of signalling pathways
 - Change in the binding specificity of the RNA-BP via post-translational modifications
 - Change in the cofactors (or protein partners) interacting with the RNA-BP



1) l'AU-Rich Element :

- Les ARE sont présent dans de nombreux ARNm codant pour des Cytokines, Oncogènes ou Facteurs de croissances.
- Ce sont des plateformes de fixation pour des facteurs régulateurs (environ une dizaine différents sont connus).

Soit des protéines induisant la désadénylation puis dégradation de l'ARNm (AUF1, TTP,...)

Soit des protéines stabilisant l'ARNm (HuR).

Soit des protéines bloquant la traduction.

Ceci peut dépendre du type cellulaire ou des conditions physiologiques.

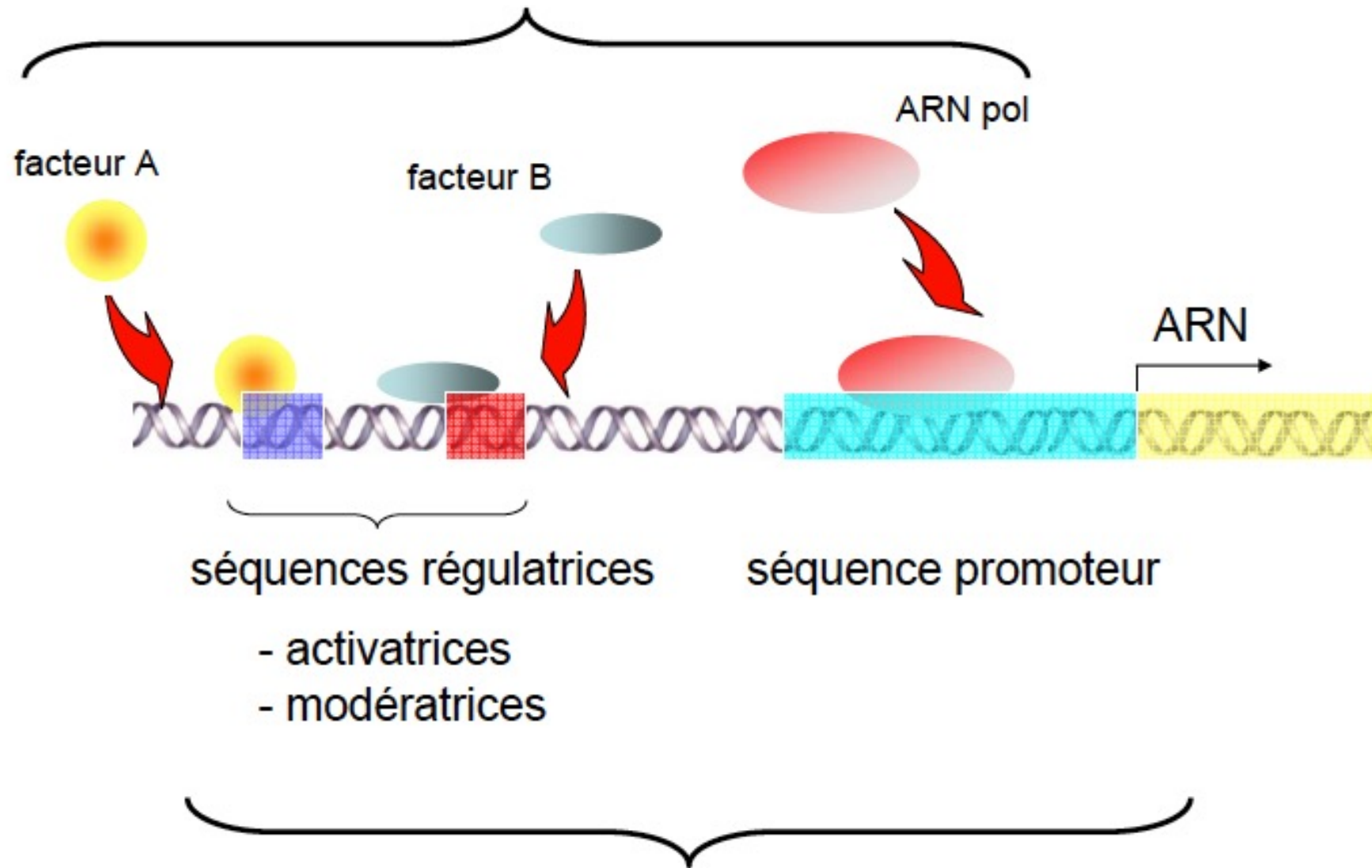
2) L'importance de l'ARE est démontré par a) sa délétion rend c-fos oncogénique et peut induire la transformation de fibroblastes (Meijlink et al.1985), b)Le pendant viral de c-fos (FBJ osteosarcoma virus) ne contient pas d'ARE et induit des tumeurs osseuses.

ARE-BP et leurs cibles

Table 2. Effect of ARE-BPs on the stability and translation of ARE-containing mRNAs

ARE-BPs	mRNA stability		Protein expression Translational efficiency		Abundance Up regulated	Down regulated
	Increase	Decrease	Increase	Decrease		
AUF1	e-myc (42) e-fos (42,67) PTH (56) GM-CSF (42) TNF-alpha (42)	e-myc (46) e-fos (53) p21 (48) Cyclin D1 (48) GM-CSF (53,54) IL-3 (55)				GM-CSF (55) IL-3 (55)
HuR	e-fos (59,63,67) MyoD (68) p21 (48,68,69) Cyclin A (70) Cyclin B1 (70) Cyclin D1 (48) NOS II/iNOS (64) GM-CSF (59) TNF-alpha (65,74,139) Cox-2 (71,139) IL-3 (55,66) VEGF (62) Myogenin (68) TNF-alpha (74) GLUT1 (72)		p53 (99,137)	TNF-alpha (139) Cox-2 (139)	p21 (69) Cyclin A (70) Cyclin B1 (70) NOS II/iNOS (64) GM-CSF (55) Cox-2 (71,173) IL-3 (55) VEGF (173) p53 (99,137)	TNF-alpha (139)
Hel-N1	GAP-43 (75-77)		NF-M (73) GLUT1 (72)		NF-M (73) GLUT1 (72) GAP-43 (75,76)	
HuD TTP		e-fos (90) GM-CSF (18, 81,83-85, 91) TNF-alpha (18,81,83-86,89,90) Cox-2 (87) IL-2 (82,90) IL-3 (18, 66, 83,84, 88) TNF-alpha (89,93) IL-3 (55,92,93)				GM-CSF (81) TNF-alpha (80) IL-2 (82) IL-3 (88)
BRF1						GM-CSF (55) IL-3 (55)
TIA-1				TNF-alpha (120) Cox-2 (121)		TNF-alpha (120) Cox-2 (121) NOS II/iNOS (102)
KSRP		e-fos (90,93) NOS II/iNOS (102) TNF-alpha (90,93) IL-2 (90,93) e-jun (93)				
CUG-BP2	Cox-2 (150)			Cox-2 (150)		Cox-2 (150)
Nucleolin	bcl-2 (175)					
TINO		bcl-2 (176)				
PAIP2	VEGF (177)				VEGF (177)	

facteurs de « trans » régulation



séquences régulatrices

- activatrices
- modératrices

séquence promoteur

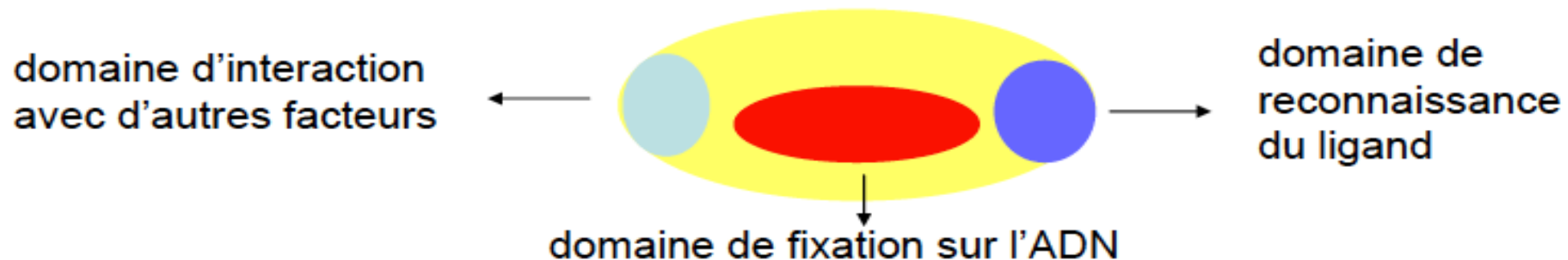
séquences de « cis » régulation

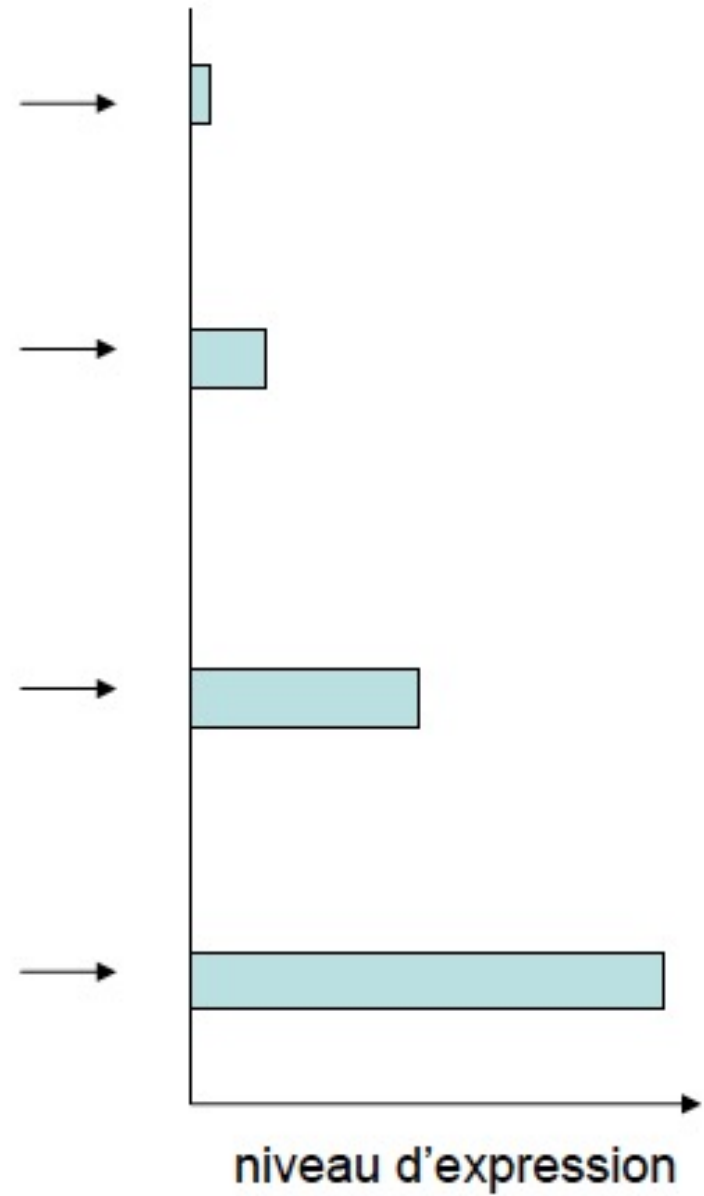
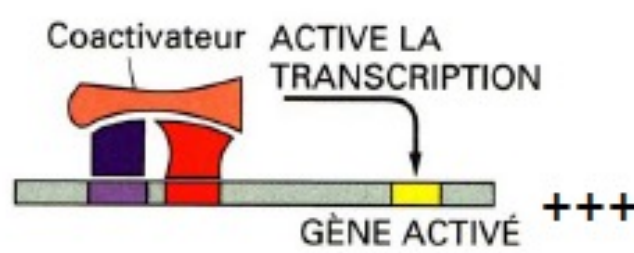
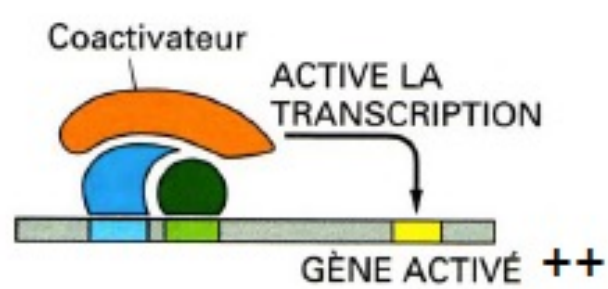
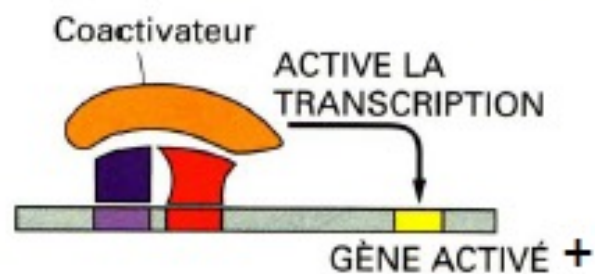
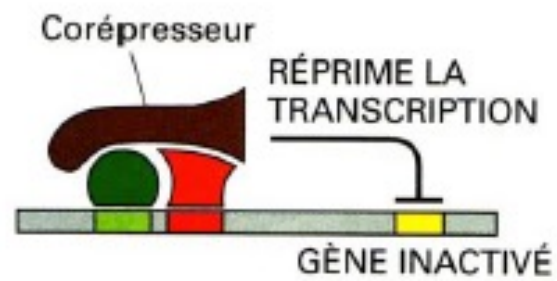
1. Séquences cis régulatrices

- promoteur : -1 à \approx -100 , motifs (CAAT, TATA...)
- séquences RE : GRE, CRE, IRE
- séquences activatrices ou modératrices :
 - localisation variable
 - nombreuses
- combinaisons

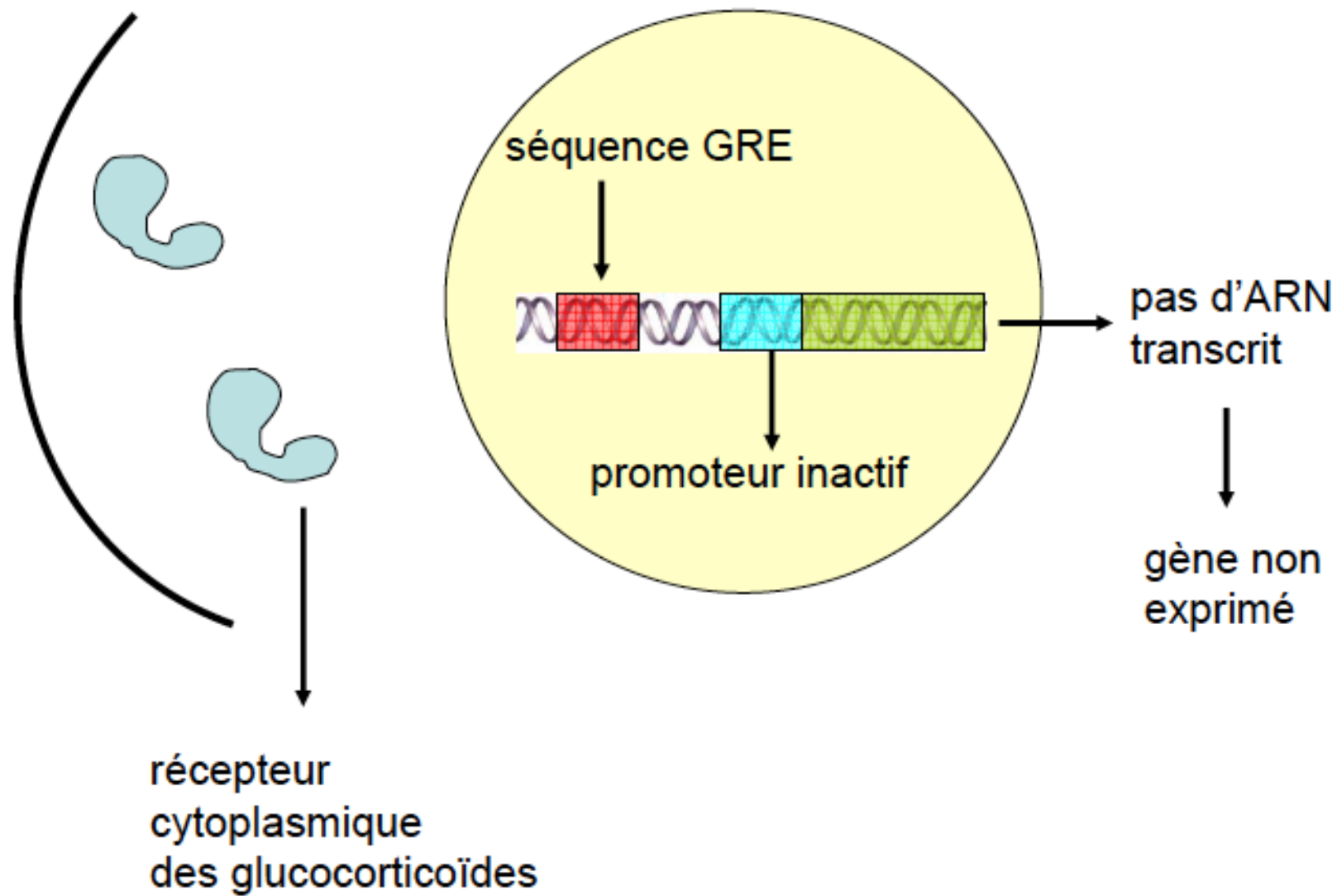
2. Protéines trans régulatrices

- facteurs de transcription
 - généraux
 - spécifiques (tissus, stade de développement)
 - inductibles (phosphorylation, protéolyse, ligands...)
- familles de protéines

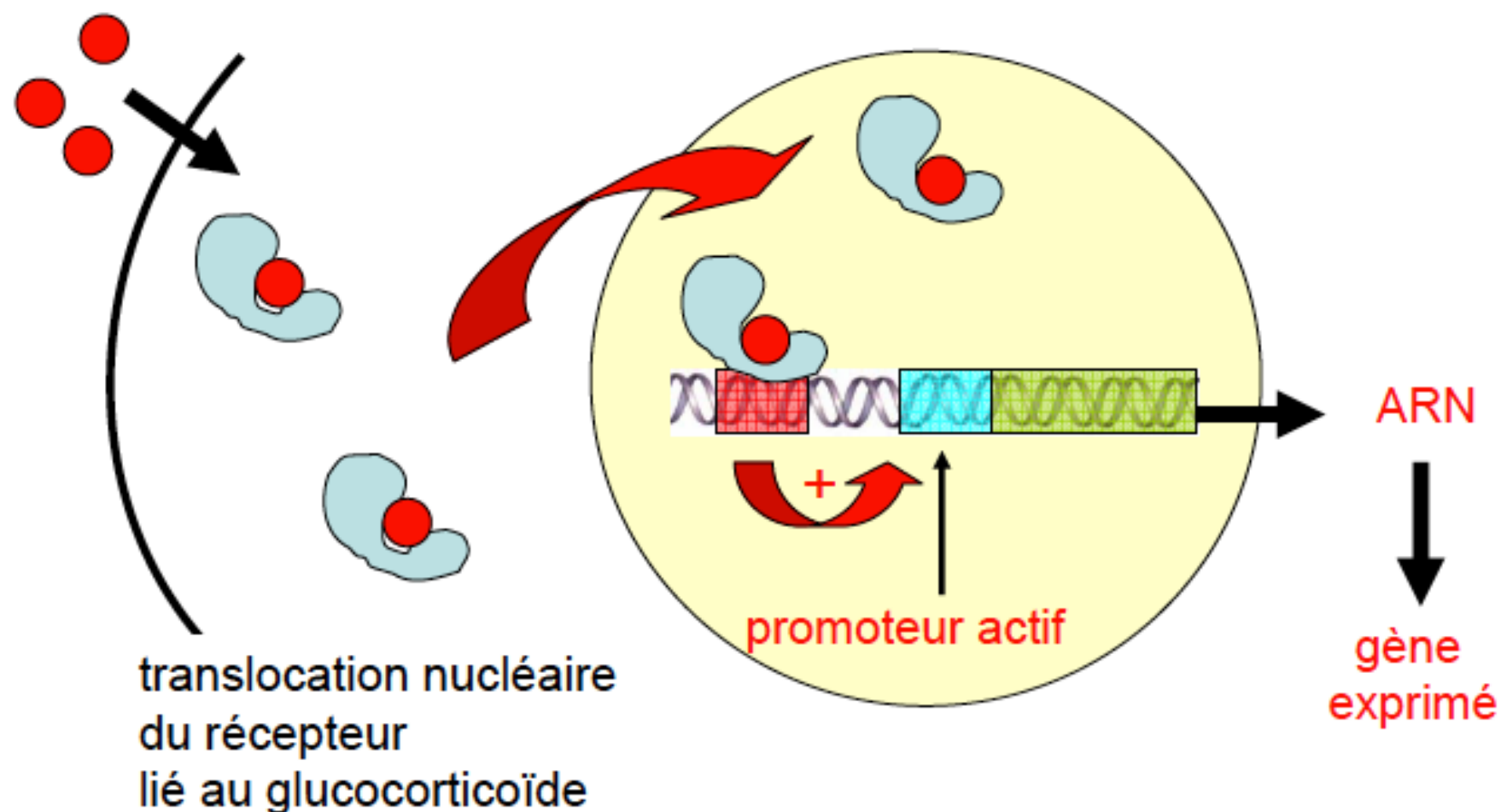


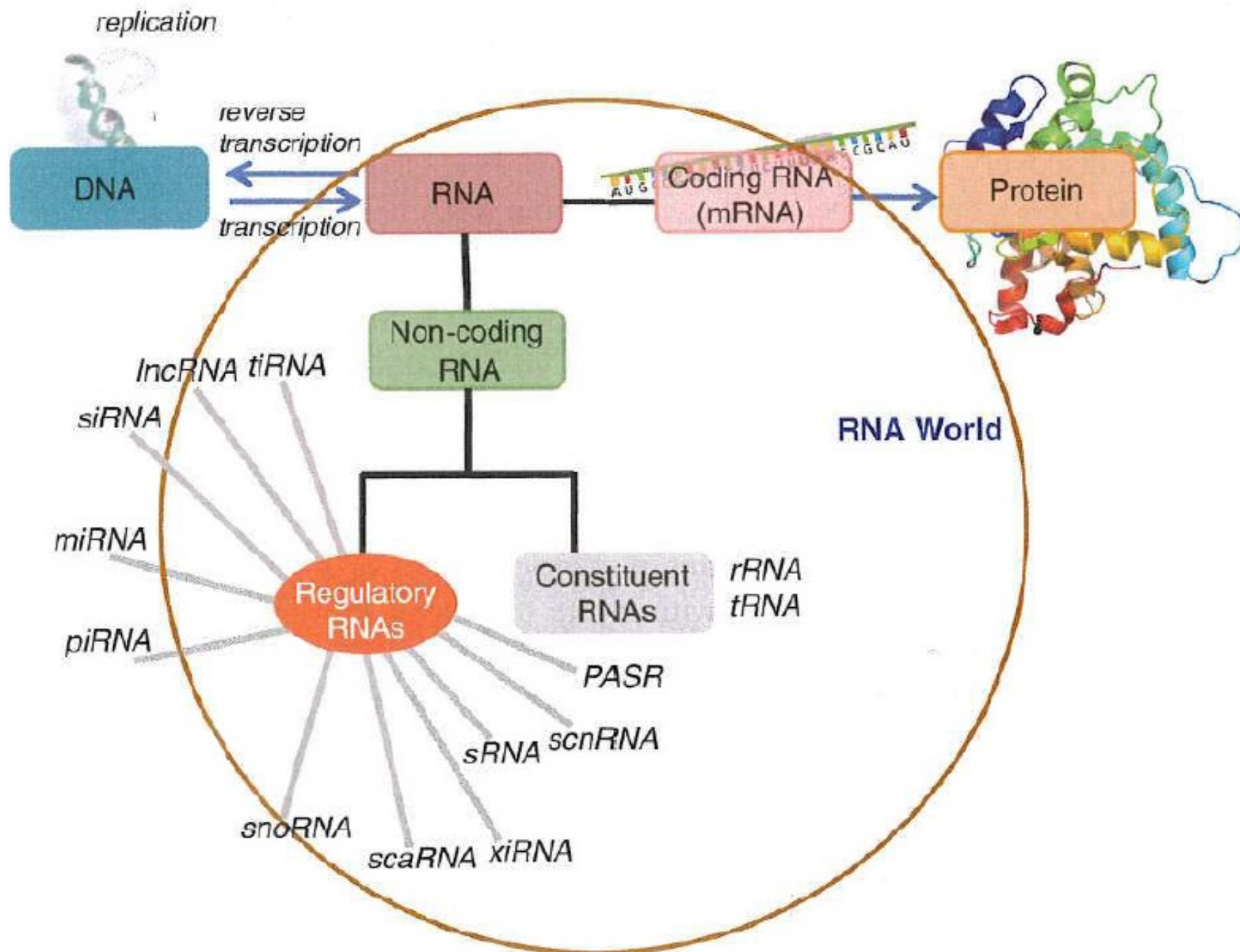


➔ exemple d'activation de la transcription de certains gènes par les hormones glucocorticoïdes

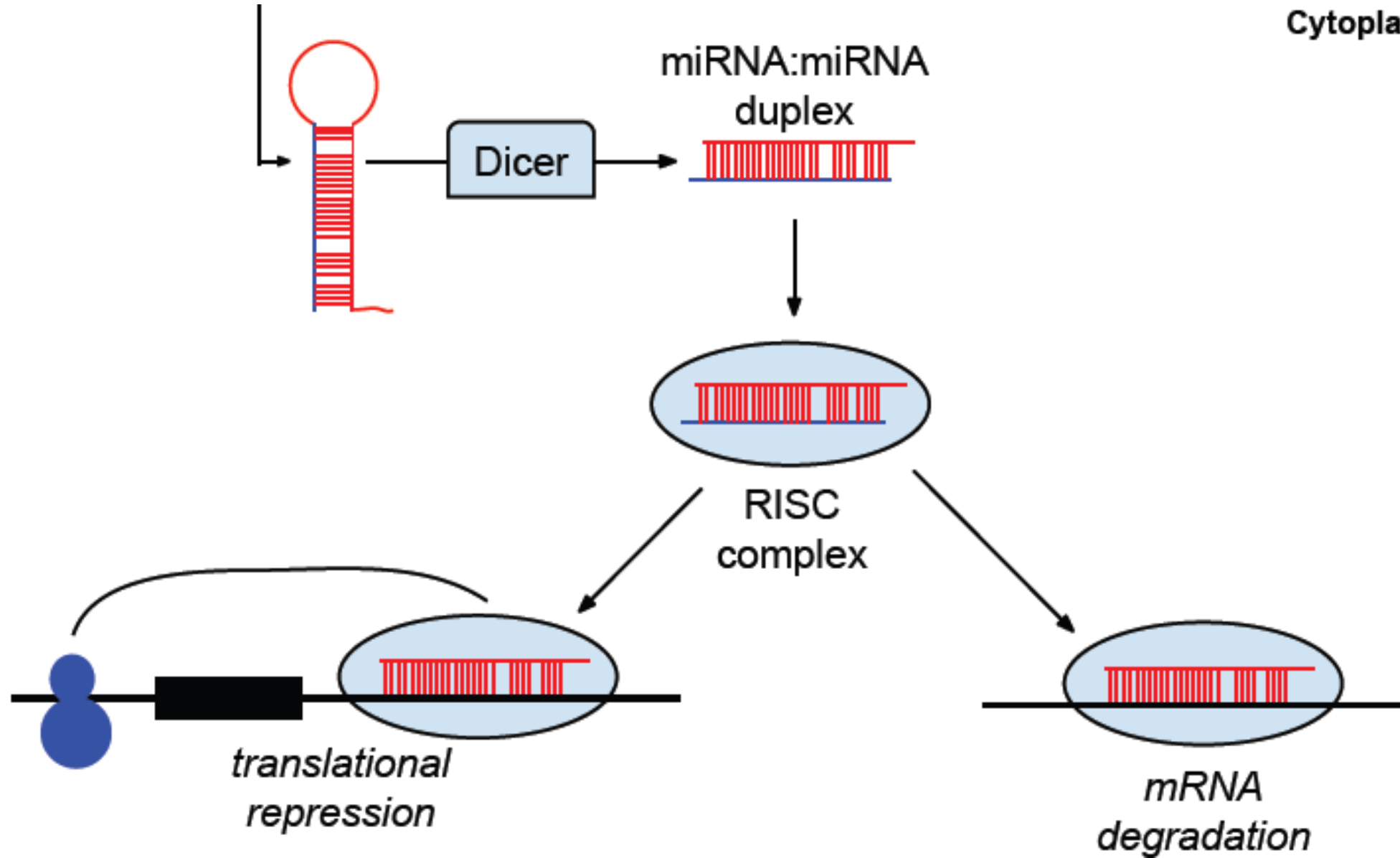


Situation en présence d'hormone glucocorticoïde





Cytoplasm



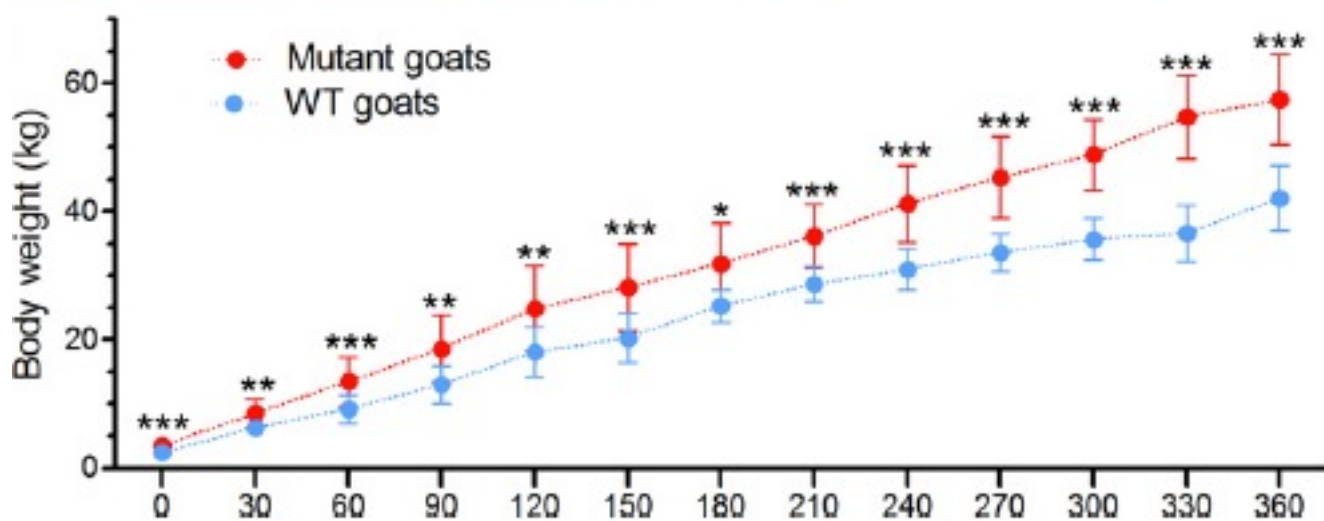
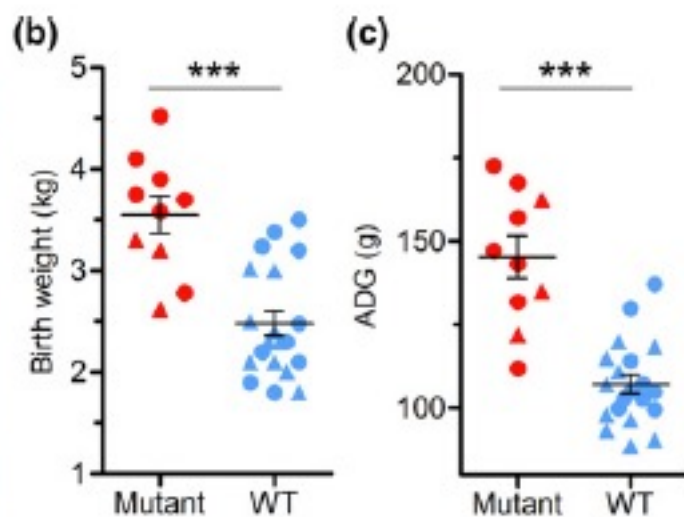
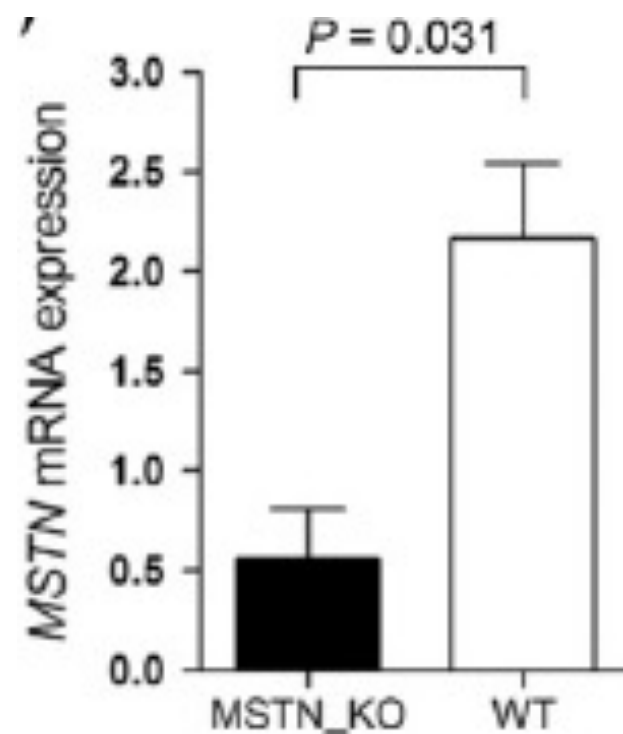
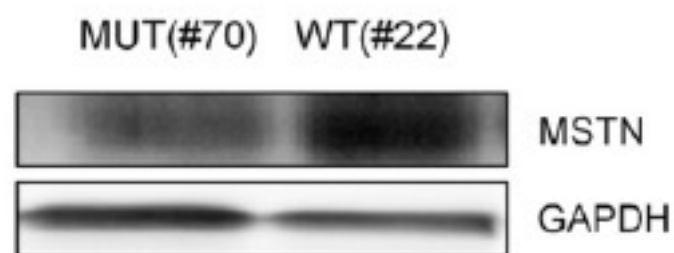
A mutation creating a potential illegitimate microRNA target site in the myostatin gene affects muscularity in sheep

nature
genetics



g+6723G-A
CAAATCTCAAC(A/G)TTCCAATA
Tex: 0.99 (084)
Ctrl: 0.01 (178)

CRISPR/Cas9-mediated *MSTN* disruption and heritable mutagenesis in goats causes increased body mass



microRNA.org - Targets and Expression

Predicted microRNA targets & target downregulation scores. Experimentally observed expression patterns.

August 2010 Release Last Update: 2010-11-01 [[release notes](#)]

target sites by: scores by:

Computational Biology Center:

[miRNA](#)[Target mRNA](#)[miRNA Expression](#)[Downloads](#)[FAQ](#)

You are currently searching:

· All Species

miRNA Stats:

· Homo sapiens: 1100
· Mus musculus: 717
· Rattus norvegicus: 387
· Drosophila melanogaster: 186
· Caenorhabditis elegans: 233

Target mRNA Search

Target mRNA:

Species:

All Species

Go

mirSVR predicted target site scoring method: [Comprehensive modeling of microRNA targets predicts functional non-conserved and non-canonical sites](#). Betel D, Koppal A, Agilus P, Sander C, Leslie C., *Genome Biology* 2010 11:R90

microRNA target predictions: [The microRNA.org resource: targets and expression](#). Betel D, Wilson M, Gabow A, Marks DS, Sander C., *Nucleic Acids Res.* 2008 Jan; 36(Database Issue): D149-53.

miRanda application: [Human MicroRNA targets](#). John B, Enright AJ, Aravin A, Tuschl T, Sander C, Marks DS., *PLoS Biol.* 2005 Jul;3(7):e264.

miRanda algorithm: [MicroRNA targets in Drosophila](#). Enright AJ, John B, Gaul U, Tuschl T, Sander C and Marks DS., *Genome Biology* (2003) 5;R1

mirnatargets@cbio.mskcc.org | [Computational Biology](#) | [Sander Lab](#) | [Marks Lab](#) | [Betel Lab](#) | [Leslie Lab](#)
Copyright © 2010 [Memorial Sloan-Kettering Cancer Center](#).

microRNA.org - Targets and Expression

Predicted microRNA targets & target downregulation scores. Experimentally observed expression patterns.

August 2010 Release Last Update: 2010-11-01 [[release notes](#)]

target sites by: scores by:

Computational Biology Center:



miRNA

Target mRNA

miRNA Expression

Downloads

FAQ

You are currently searching:

- Homo sapiens
- KHSRP
- NM_003685

miRNA Stats:

- Homo sapiens: 1100
- Mus musculus: 717
- Rattus norvegicus: 387
- Drosophila melanogaster: 186
- Caenorhabditis elegans: 233

Query Target Sites:**Displayed miRNAs ordered by sum of mirSVR scores:**

- hsa-miR-23a 1
- hsa-miR-23b 1
- hsa-miR-590-3p 277 311 681
- hsa-miR-27a 11
- hsa-miR-27b 11
- hsa-miR-300 684
- hsa-miR-495 817 962
- hsa-miR-149 218
- hsa-miR-181a 1
- hsa-miR-181b 1
- hsa-miR-181c 1
- hsa-miR-181d 1
- hsa-miR-340 822
- hsa-miR-129-5p 257 676
- hsa-miR-758 724
- hsa-miR-1 496

Display OptionsView target sites of conserved miRNAs with good mirSVR scores

Selected miRNAs:

You may add additional miRNAs to the box above.

hsa-miR-181a/KHSRP Alignment

```

3' ugaguggcugucgcaACUUACAa 5' hsa-miR-181a
      |||||
1:5' -----aucgaaUGAAUGUG 3' KHSRP

```

mirSVR score: -0.7788

PhastCons score: 0.6701

Mouseover a miRNA mature name to see the miRNA/KHSRP alignment.

KHSRP KH-type splicing regulatory proteinDisplay bases per row

```

          miR-23b
          miR-23a
          miR-181d
          miR-181c
          miR-181b          miR-27b
          miR-181a          miR-27a
1  AUCGAAUGAAUGUGAACUUCUUCUUCUGUGAAAAAUCUUUUUUUUUUUCCAUUUUGUUCUGUUUGGGGGCUUCUGU 75
76  UUUGUUUGGCGAGAGAGCGAUGGCUGCCGUGGGGAGUACUGGGGAGCCUCGCGGCAAGCAGGGUGGGGGGACU 150
151 UGGGGGCAUGCCGGGCCUCACUCUCUGCCUGUUCUGUGUCUCACAUGCUUUUUUCUUUCAAUUUGGGAUCCUU 225

```

miR-129-5p
miR-181



miRNA

Target mRNA

miRNA Expression

Downloads

FAQ

You are currently searching:

· Mus musculus

miRNA Stats:

- Homo sapiens: 1100
- Mus musculus: 717
- Rattus norvegicus: 387
- Drosophila melanogaster: 186
- Caenorhabditis elegans: 233

Tissue-based Search

mmu_Adipo-diff
mmu_Adipo-undiff
mmu_Alpha-pancreas-TC1
mmu_B-cell-K1-Tg-naive
mmu_B-cell-K2-Tg-anergic
mmu_B-cell-K4-WT
mmu_B-cell-spleen-IL4LPS24h
mmu_B-cell-spleen-IL4LPS48h
mmu_B-cell-spleen-IL4LPS72h
mmu_B-cell-spleen-IL4LPS8h
mmu_B-cell-spleen-unstim
mmu_B-lymphoma-A20_NP
mmu_B-lymphoma-A20_OP
mmu_B-lymphoma-S11
mmu_B-lymphoma-S11E
mmu_Beta-pancreas-MIN
mmu_Brain-FMR-KO
mmu_Brain-WT
mmu_Cerebellum
mmu_Colon
mmu_Cortex
mmu_DC-GCSF
mmu_DC-stim
mmu_DC-unstim
mmu_Embryo-E11
mmu_Embryo-E12
mmu_Embryonic-kidney
mmu_ESC-fem
mmu_ESC-WT-frac-21
mmu_Eye

Look up tissues

Process Data

172 human, 64 mouse and 16 rat small RNA libraries from major organs and cell types: [A mammalian microRNA expression atlas based on small RNA library sequencing.](#) Landgraf P, et al., *Cell* 2007 Jun 29;129(7):1401-14.

mirSVR predicted target site scoring method: [Comprehensive modeling of microRNA targets predicts functional non-conserved and non-canonical sites.](#) Betel D, Koppal A, Agius P, Sander C, Leslie C., *Genome Biology* 2010 11:R90

microRNA target predictions: [The microRNA.org resource: targets and expression.](#) Betel D, Willson M, Gabow A, Marks DS, Sander C., *Nucleic Acids Res.* 2008 Jan; 36(Database Issue): D149-53.

miRanda application: [Human MicroRNA targets.](#) John B, Enright AJ, Aravin A, Tuschl T, Sander C, Marks DS., *PLoS Biol.* 2005 Jul;3(7):e264.

Search for predicted microRNA targets in mammals

[\[Go to TargetScanMouse\]](#)

[\[Go to TargetScanWorm\]](#)

[\[Go to TargetScanFly\]](#)

[\[Go to TargetScanFish\]](#)

1. Select a species

Human

AND

2. Enter a human gene symbol (e.g. "Hmga2")
or an Ensembl gene (ENSG00000149948) or transcript (ENST00000403681) ID

AND/OR

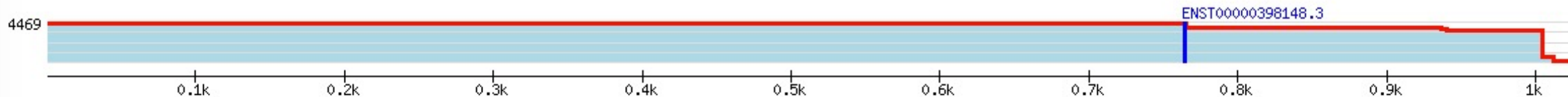
3. Do one of the following:

- Select a broadly conserved* microRNA family
- Select a conserved* microRNA family
- Select a poorly conserved but confidently annotated microRNA family
- Select another miRBase annotation

Note that most of these families are star miRNAs or RNA fragments misannotated as miRNAs.

- Enter a microRNA name (e.g. "miR-9-5p")

Human KHSRP ENST00000398148.3 3' UTR length: 1024



Conserved sites for miRNA families broadly conserved among vertebrates

miR-27-3p

miR-1-3p/206

- [\[Show poorly conserved sites for miRNA families conserved among vertebrates\]](#)
- [\[Show conserved sites for miRNA families conserved only among mammals\]](#)
- [\[Show poorly conserved sites for miRNA families conserved among mammals\]](#)
- [\[Show sites for poorly conserved but confidently annotated miRNA families\]](#)
- [\[Show sites for other miRBase annotations, most of which are miRNA* sequences or RNA fragments misannotated as miRNAs\]](#)

- [\[Download SVG image of miRNA sites\]](#)
- [\[View table of miRNA sites\]](#)
- [\[View human genome browser \(hg19\)\]](#)

[\[Show all species\]](#)

Key:

Sites with higher probability of preferential conservation

8mer 7mer-m8 7mer-A1 non-canonical

Sites with lower probability of preferential conservation

8mer 7mer-m8 7mer-A1 non-canonical

	1	10	20	30	40	50	60
Human	AUCGAAUGAAUGUGAA	---CUUCUUCAUCUGUGAAA	--A---AU---C---U---	UUUUUUU-UU---	CCAUUUU-GUUCUGUUUGGGGC	-----	-----
Chimp	AUCGAAUGAAUGUGAA	---CUUCUUCAUCUGUGAAA	--A---AU---C---UU---	UA-UUUUUUU-UU---	CCAUUUU-GUUCUGUUUGGGGC	-----	-----
Rhesus	AUCGAAUGAAUGUGAA	---CUUCUUCAUCUGUGAAA	--A---AU---C---UU---	UA-UUUUUUU-UU---	CCAUUUU-GUUCUGUUUGGGGC	-----	-----
Squirrel	AUCGAAUGAAUGUGAA	---CUUCUUCAUCUGUGAAA	--AA---UC---U---UUA---	UUUUUUUUUU-CU---	CCAUUUU-GUUCUGUUUGGGGC	-----	-----
Mouse	AGCAAUGGAUAUGAA	---CUUC---AUCUGUGAAA	--A-----UUUUUUUUUUUCU---	CCAUUUUUUUUCCAUUUUGGGGC	-----	-----	-----
Rat	AGCAAUGGAUAUGAA	---CUUC---AUCUGUGAAA	--A-----UUUUUUUUUCC-CU---	UCAUUUUUUUUCCAUUUUGGGGU	-----	-----	-----
Rabbit	-----	-----	-----	-----	-----	-----	-----
Pig	AUCGAAUGAAUGUGAA	---CUUCUUCAUCUGUGAAA	--A---UC---U---U---	UUUUU-UU---	CCAUUUU-GUUCUGUUUGGGGC	-----	-----
Cow	AUCGAAUGAAUGUGAA	---CUUCUUCAUCUGUGAAA	--A---UC---U---UU---	UUUUU-UU---	CCAUUUU-GUUCUGUUUGGGGC	-----	-----

Converging pathways involving microRNA-206 and the RNA-binding protein KSRP control post-transcriptionally utrophin A expression in skeletal muscle

Adel Amirouche^{1,2}, Helina Tadesse^{1,2}, Pedro Miura^{1,2}, Guy Bélanger^{1,2}, John A. Lunde^{1,2}, Jocelyn Côté^{1,2} and Bernard J. Jasmin^{1,2,*}

¹Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario K1H 8M5, Canada and

²Centre for Neuromuscular Disease, University of Ottawa, Ottawa, Ontario K1H 8M5, Canada

