

# Genomics & Medicine

<http://biochem118.stanford.edu/>

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## miRNA Regulatory Networks



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Biochemistry & Medicine  
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# Gene Regulatory Mechanisms

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- Transcriptional Mechanisms
  - Type of promoters & RNA polymerases
  - Control of Transcription
  - Transcription Factors and TFBS
- RNA processing
  - 5' Capping & 3' poly-adenylation
  - RNA degradation rates
  - Splicing and Alternative Splicing
- Translational Mechanisms
  - Micro RNAs (miRNAs) control translation & degradation of mRNAs
  - Silencer RNAs (siRNAs or RNAi) catalyze degradation of mRNA
- Epigenetic Mechanisms
  - Chromatin remodeling in active and inactive regions
  - Histone acetylation, phosphorylation and methylation
  - DNA methylation in inactive regions

# The ENCODE Project

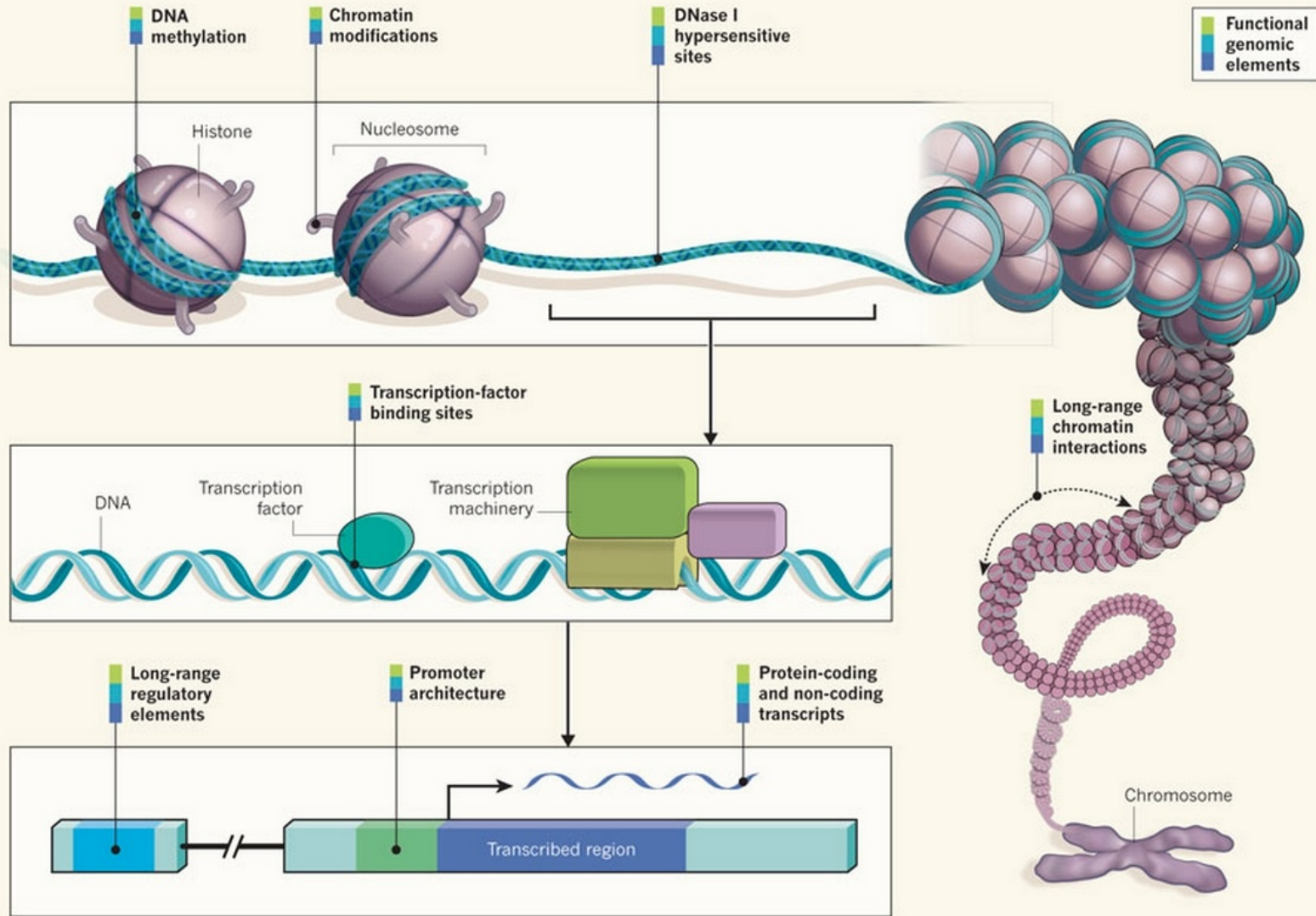
<http://www.genome.gov/encode/>



- The ENCODE Project searches the human genome for:
  - Transcribed regions
  - Conserved regions
  - Transcription factor genes
  - Transcription factor and other protein binding sites
  - DNA methylated regions
  - Regions with “open” chromatin
  - lncRNA coding regions
  - Regions associated with modified histones (Chip-CHIP)
  - Regions associated with disease (GWAS)
- So far these functional or conserved regions comprise 80% of the human genome.

# ENCODE Explained

<http://www.nature.com/nature/journal/v489/n7414/full/489052a.html>

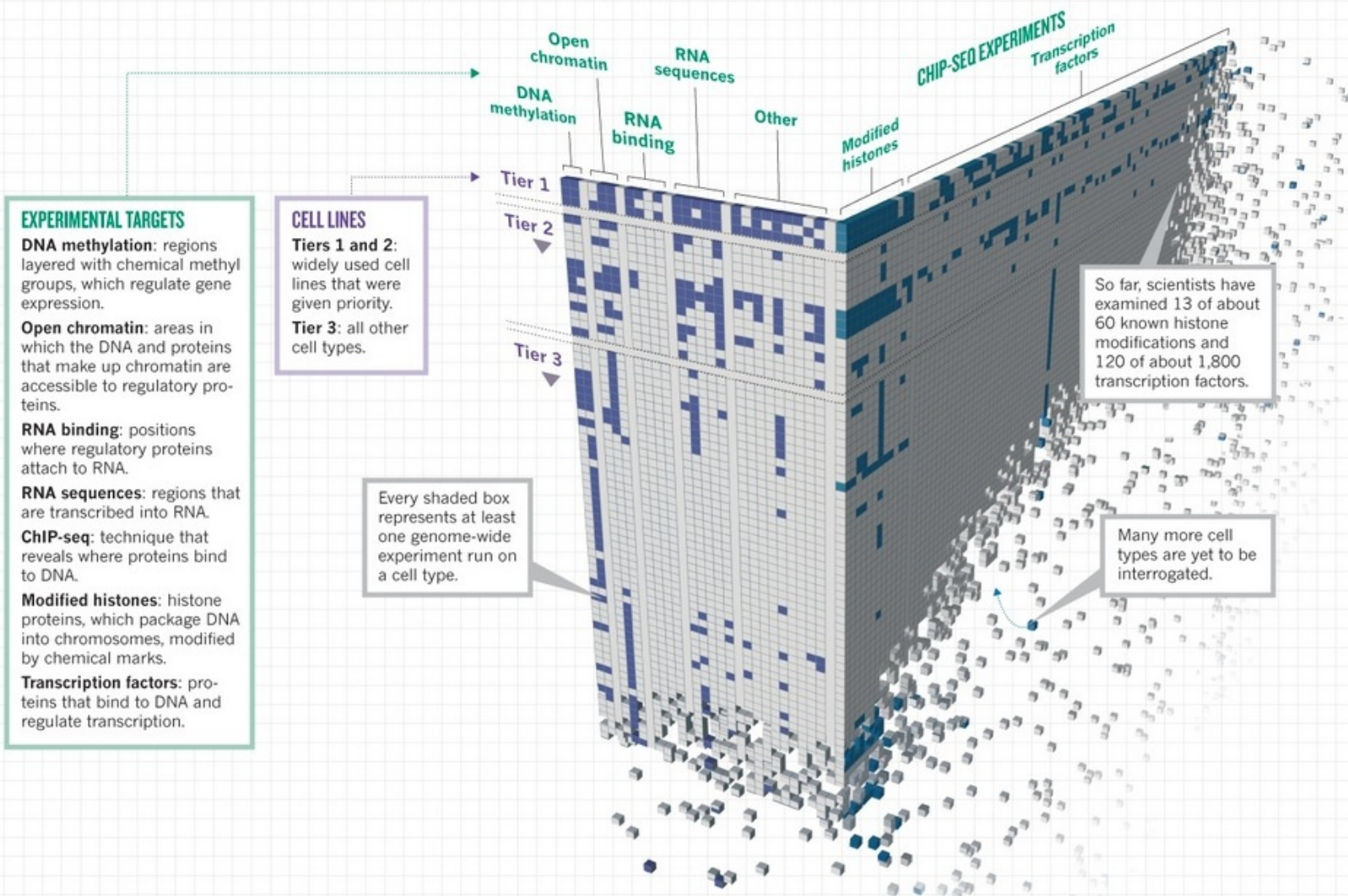


# Making a Genome Manual

<http://www.nature.com/news/encode-the-human-encyclopaedia-1.11312#/manual>

## MAKING A GENOME MANUAL

Scientists in the Encyclopedia of DNA Elements Consortium have applied 24 experiment types (across) to more than 150 cell lines (down) to assign functions to as many DNA regions as possible — but the project is still far from complete.

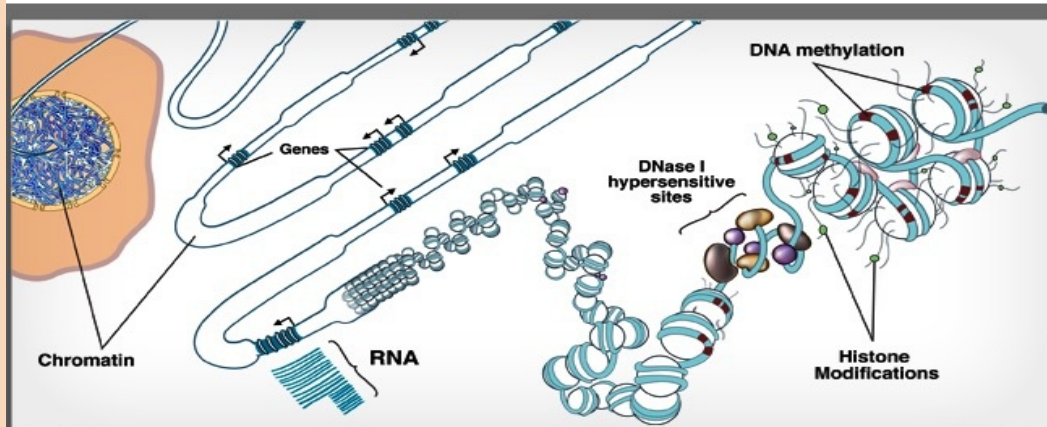


# Epigenome Roadmap

<http://www.roadmapepigenomics.org/>

HOME PARTICIPANTS BROWSE DATA PROTOCOLS COMPLETE EPIGENOMES TOOLS PUBLICATIONS

OVERVIEW PROJECT DATA MAPPING CENTERS PROTOCOLS & STANDARDS PUBLICATIONS



## NIH Roadmap Epigenomics Mapping Consortium

The NIH Roadmap Epigenomics Mapping Consortium was launched with the goal of producing a public resource of human epigenomic data to catalyze basic biology and disease-oriented research. The Consortium leverages experimental pipelines built around next-generation sequencing technologies to map DNA methylation, histone modifications, chromatin accessibility and small RNA transcripts in stem cells and primary ex vivo tissues selected to represent the normal counterparts of tissues and organ systems frequently involved in human disease. The Consortium expects to deliver a collection of normal epigenomes that will provide a framework or reference for comparison and integration within a broad array of future studies. The Consortium also aims to close the gap between data generation and its public dissemination by rapid release of raw sequence data, profiles of epigenomics features and higher-level integrated maps to the scientific community. The Consortium is also committed to the development, standardization and dissemination of protocols, reagents and analytical tools to enable the research community to utilize, integrate and expand upon this body of data.

### INTEGRATIVE ANALYSIS of 111 REFERENCE HUMAN EPIGENOMES

The infographic displays a human figure with various tissues and cell types highlighted. A list of tissues and cell types includes: Brain (Angular gyrus, Anterior caudate, Cingulate gyrus, Hippocampus middle, Inferior temporal lobe, Substantia nigra, Dorsolateral Prefrontal Cortex), Blood (Brain cells (CD14+), T Cells (CD4+, CD8+, CD8+), B-lymphocytes (CD19+), NK Cells (CD56+)), Stomach mucosa, Sigmoid colon, Ovary, and Colon. Other tissues shown include Thymus, Heart, Aorta, Lung, and Placenta. A 'VIEW DATA' button is located at the bottom.

### VIEW/DOWNLOAD QUICK LINKS

**Genome Browsers**

- <http://genomebrowser.wustl.edu/>
- <http://epigenomegateway.wustl.edu/>

**Data Repositories**

- [NCBI Epigenomics Gateway](#)
- [Epigenome Atlas](#)

### NEWS

**18 FEB** [NIH-supported researchers map epigenome of more than 100 tissue and cell types](#)

**4 SEP** [IHEC data portal online](#)

# Epigenome Roadmap

<http://www.nature.com/collections/vbqgtr>

## Thread articles

## Research papers

### THREAD 1

#### 1. Annotation of the non-coding genome

[Highlight referenced papers ▶](#)

### THREAD 2

#### 2. Relationship between different epigenomic marks: DNA accessibility and methylation, histone marks, and RNA

[Highlight referenced papers ▶](#)

### THREAD 3

#### 3. Epigenomic changes during differentiation and development

[Highlight referenced papers ▶](#)

### THREAD 4

#### 4. Regulatory models: networks, motifs, modules, sequence drivers and predictive models

[Highlight referenced papers ▶](#)

### THREAD 5

#### 5. Interpreting variation: GWAS, cancer, genotype, evolution and allelic

[Highlight referenced papers ▶](#)



Nature

#### Conserved epigenomic signals in mice and humans reveal immune basis of Alzheimer's disease

Elizabeta Gjoneska, Andreas R. Pfening, Hansruedi Mathys, Gerald Quon, Anshul Kundaje *et al.*

[◀ Highlight associated threads](#)



Nature Communications

#### The meta-epigenomic structure of purified human stem cell populations is defined at cis-regulatory sequences

N. Ari Wijetunga, Fabien Delahaye, Yong M. Zhao, Aaron Golden, Jessica C. Mar *et al.*

[◀ Highlight associated threads](#)



Nature

#### Genetic and epigenetic fine mapping of causal autoimmune disease variants

Kyle Kai-How Farh, Alexander Marson, Jiang Zhu, Markus Kleinewietfeld, William J. Housley *et al.*

[◀ Highlight associated threads](#)



Nature Communications

#### Epigenomic footprints across 111 reference epigenomes reveal tissue-specific epigenetic regulation of lincRNAs

Viren Amin, R. Alan Harris, Vitor Onuchic, Andrew R. Jackson, Tim Charnock *et al.*

[◀ Highlight associated threads](#)



Nature Communications

#### Intermediate DNA methylation is a conserved signature of genome regulation

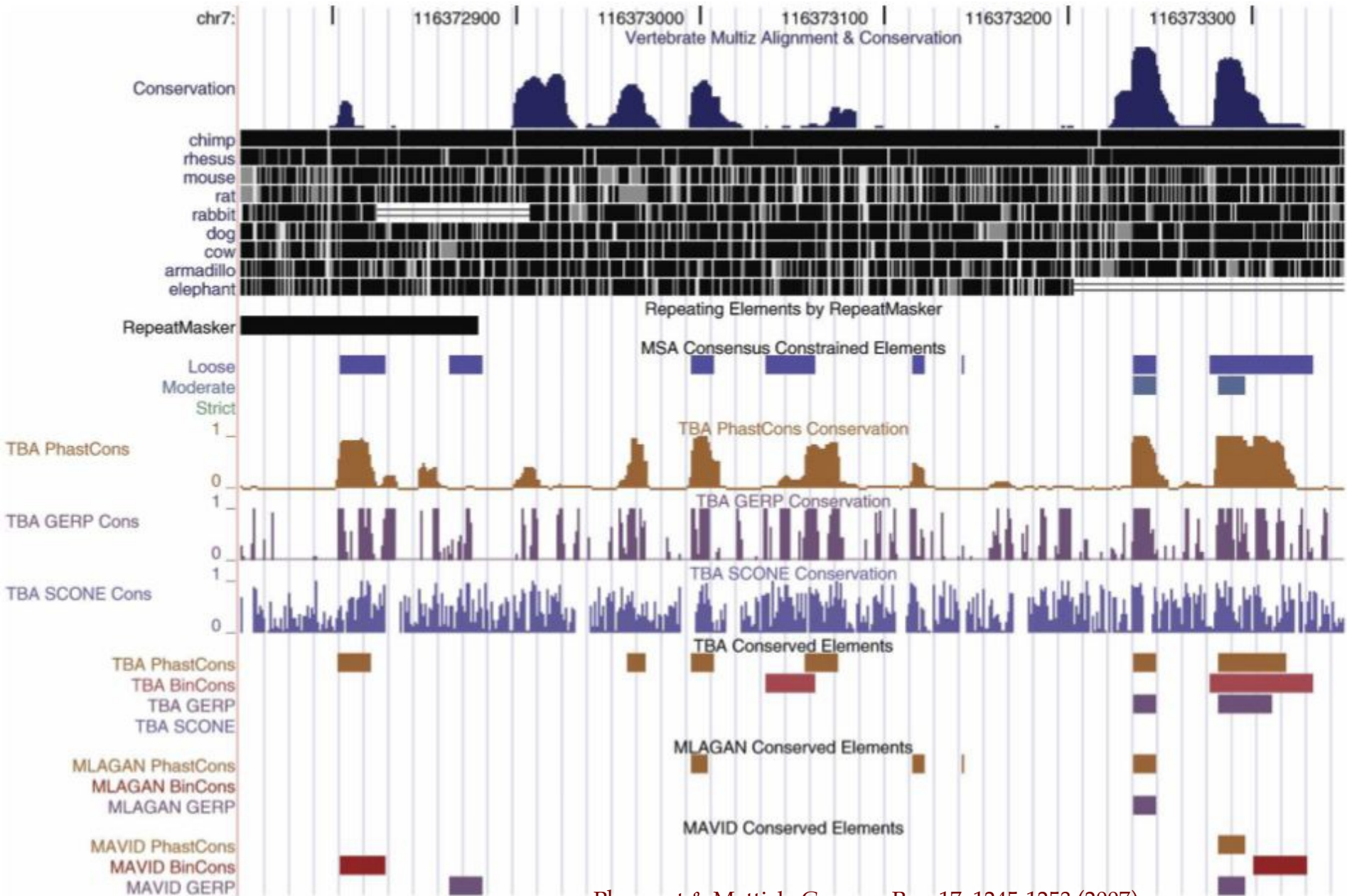
GiNell Elliott, Chibo Hong, Xiaoyun Xing, Xin Zhou, Daofeng Li *et al.*

Nature Biotechnology

#### Large-scale imputation of epigenomic datasets for systematic annotation of diverse human tissues

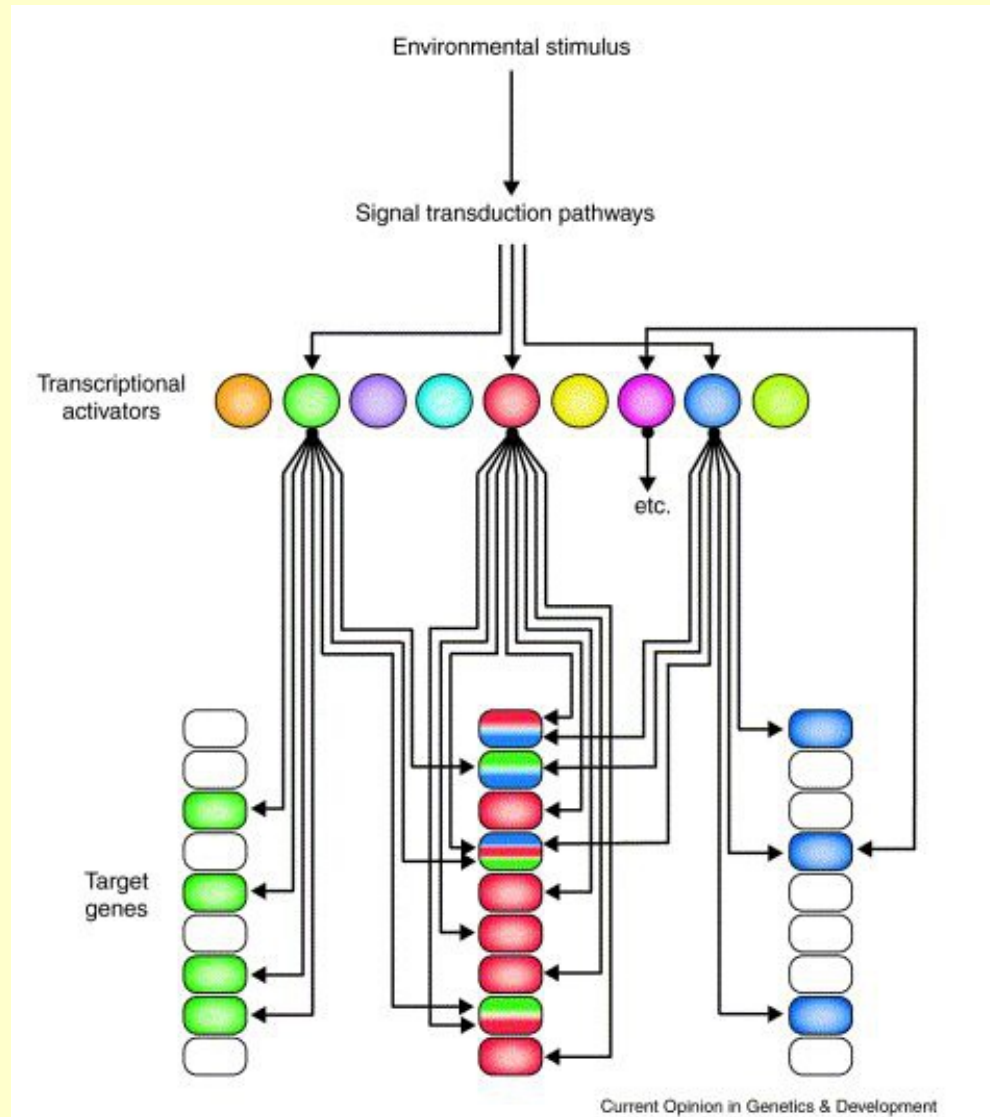
Jason Ernst, Manolis Kellis

# Conserved Regions in CFTR Intron

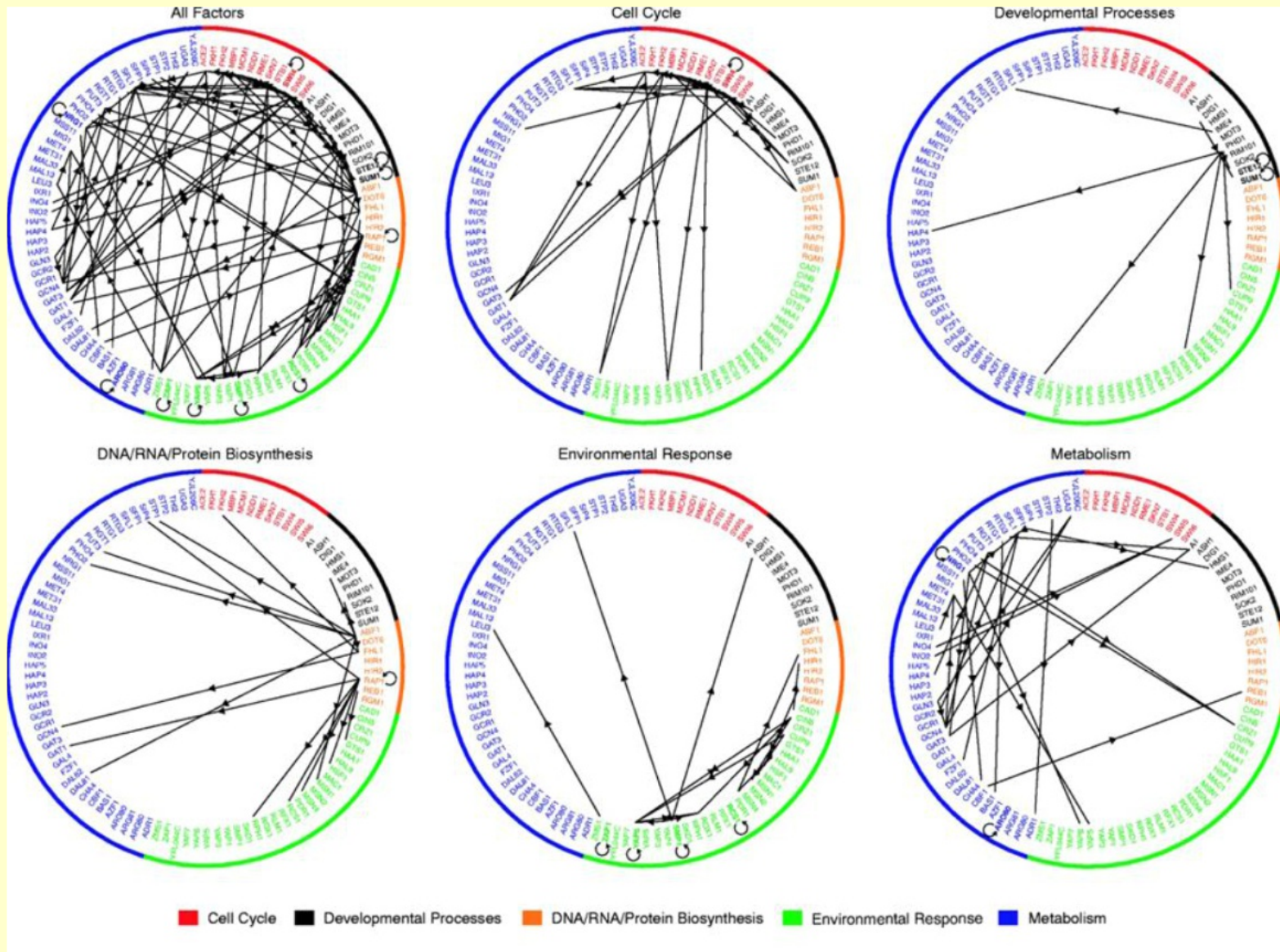




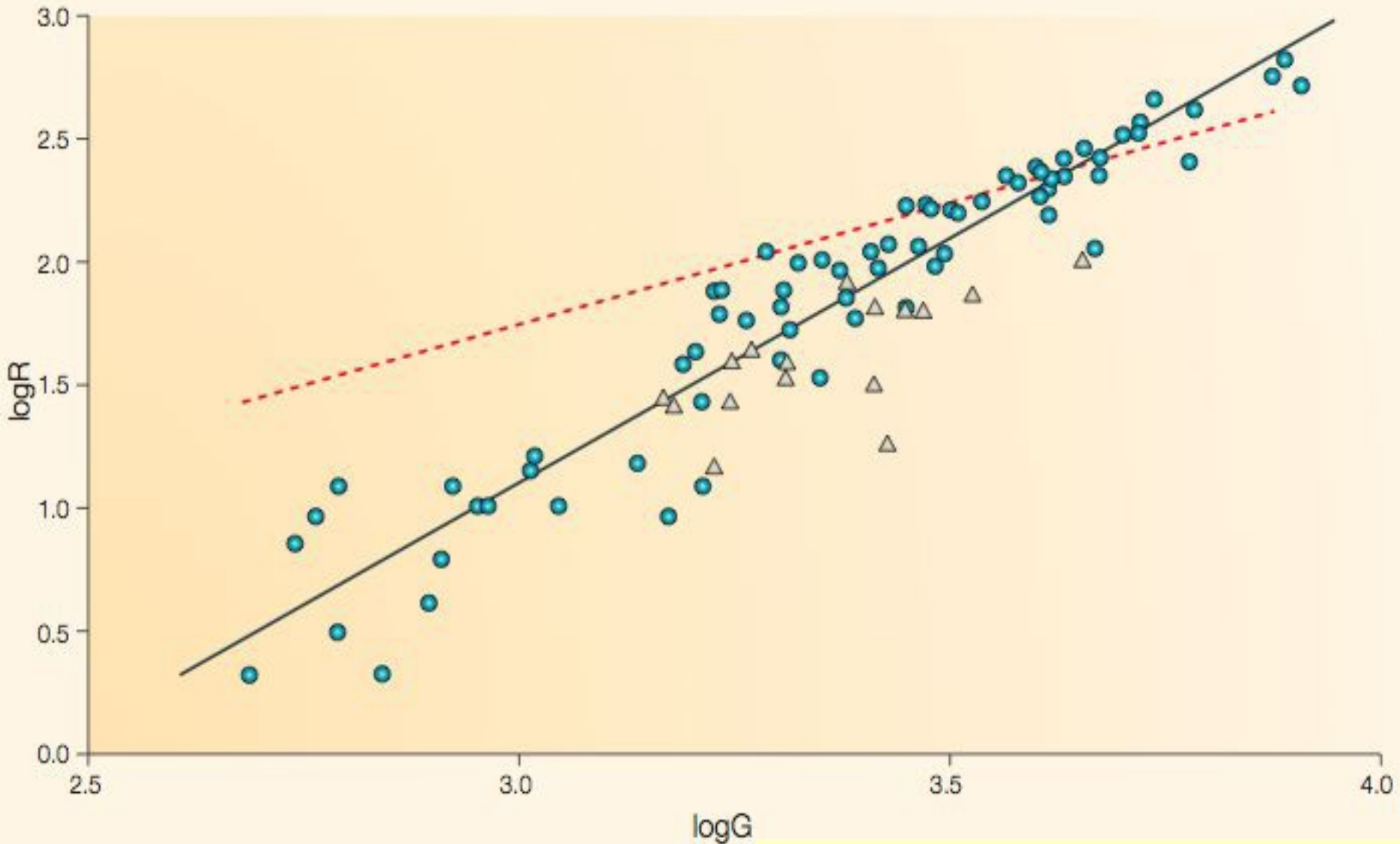
# Gene Expression Regulatory Network



# Yeast Regulatory Motifs

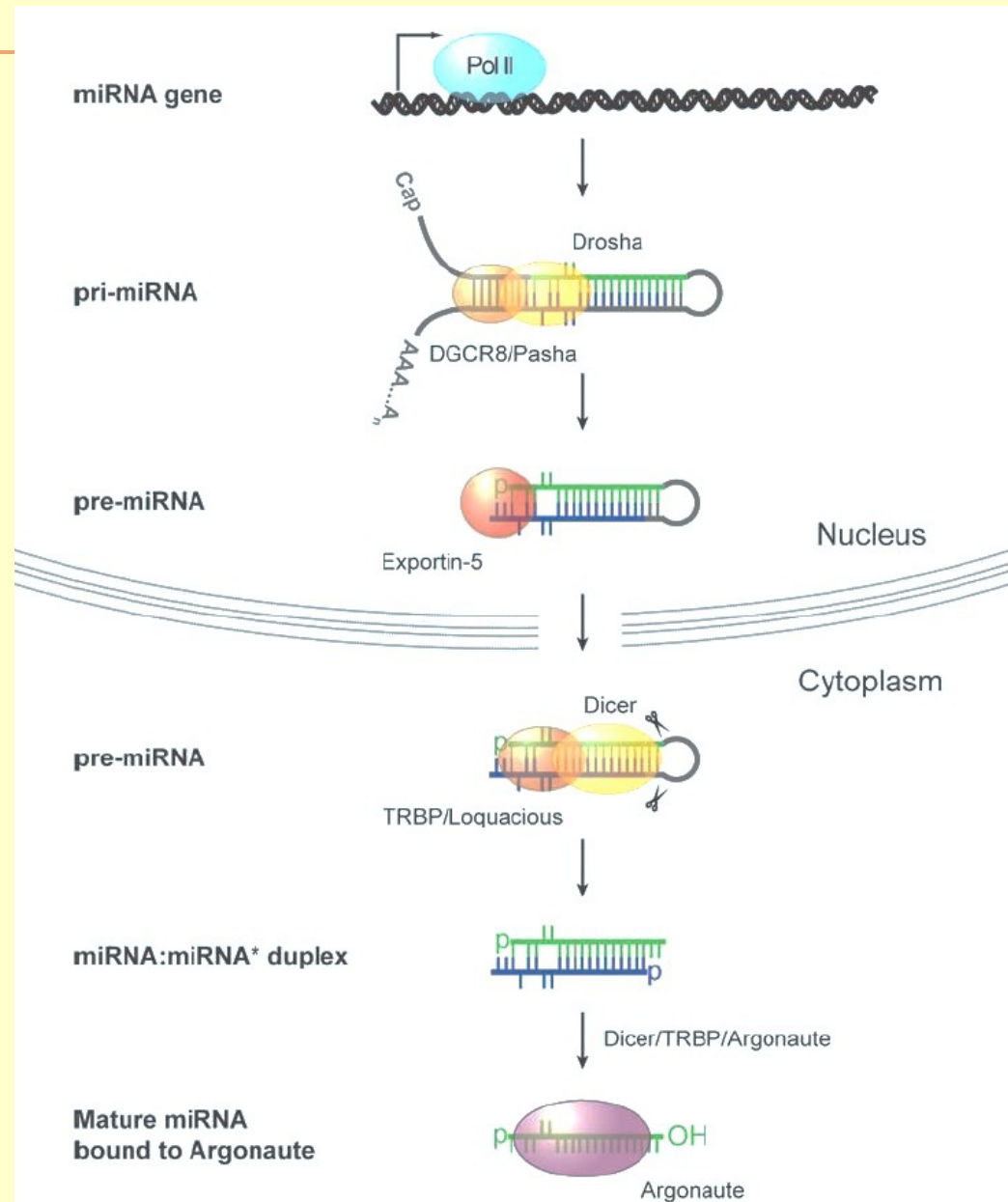


# Prokaryotic Regulatory Genes Grow as the Square of the Total Number of Genes

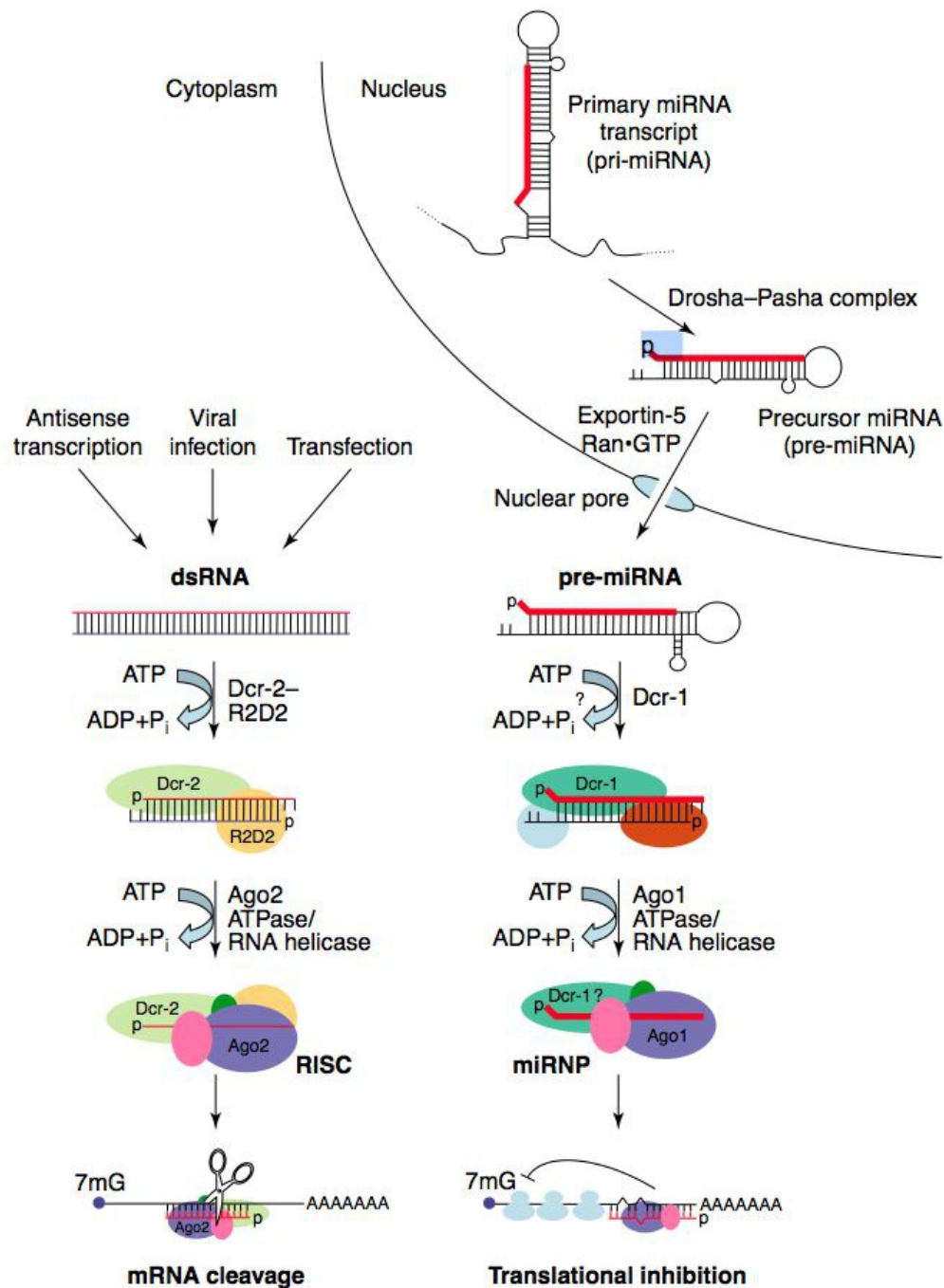




# microRNA Biogenesis



# siRNA mediated degradation of mRNA & miRNA mediated inhibition of mRNA translation



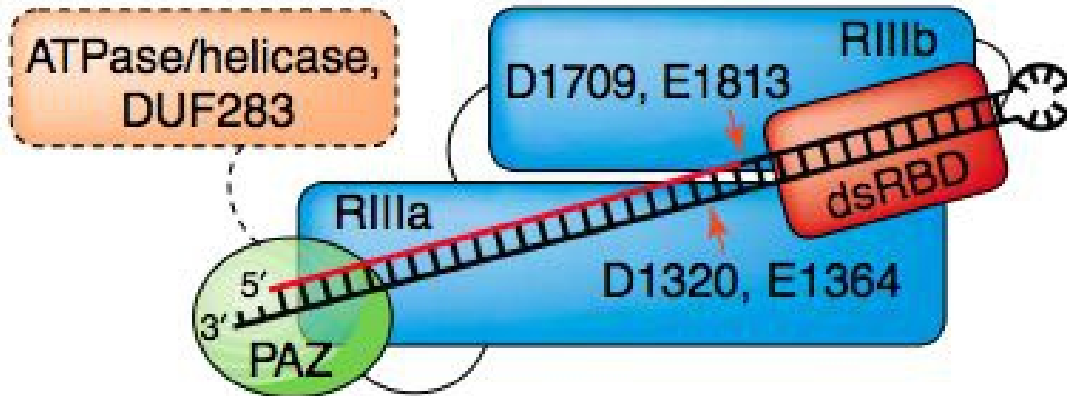
Current Opinion in Structural Biology



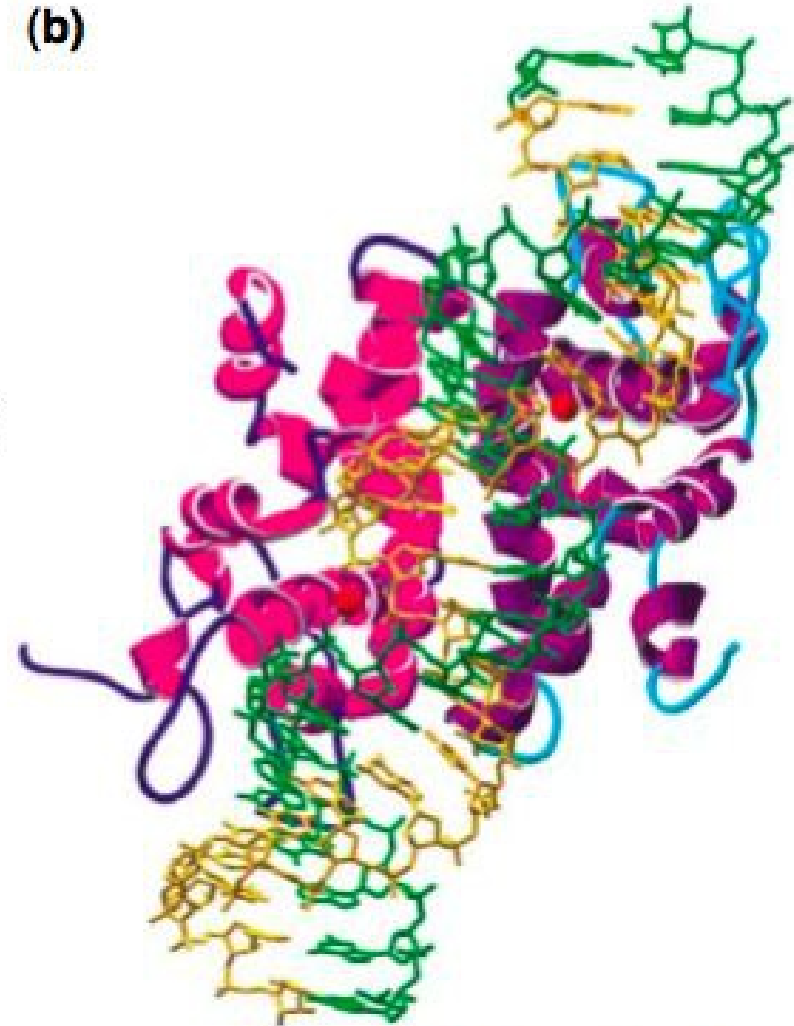
stylusvisuals

# Dicer Structure & Function

(a)



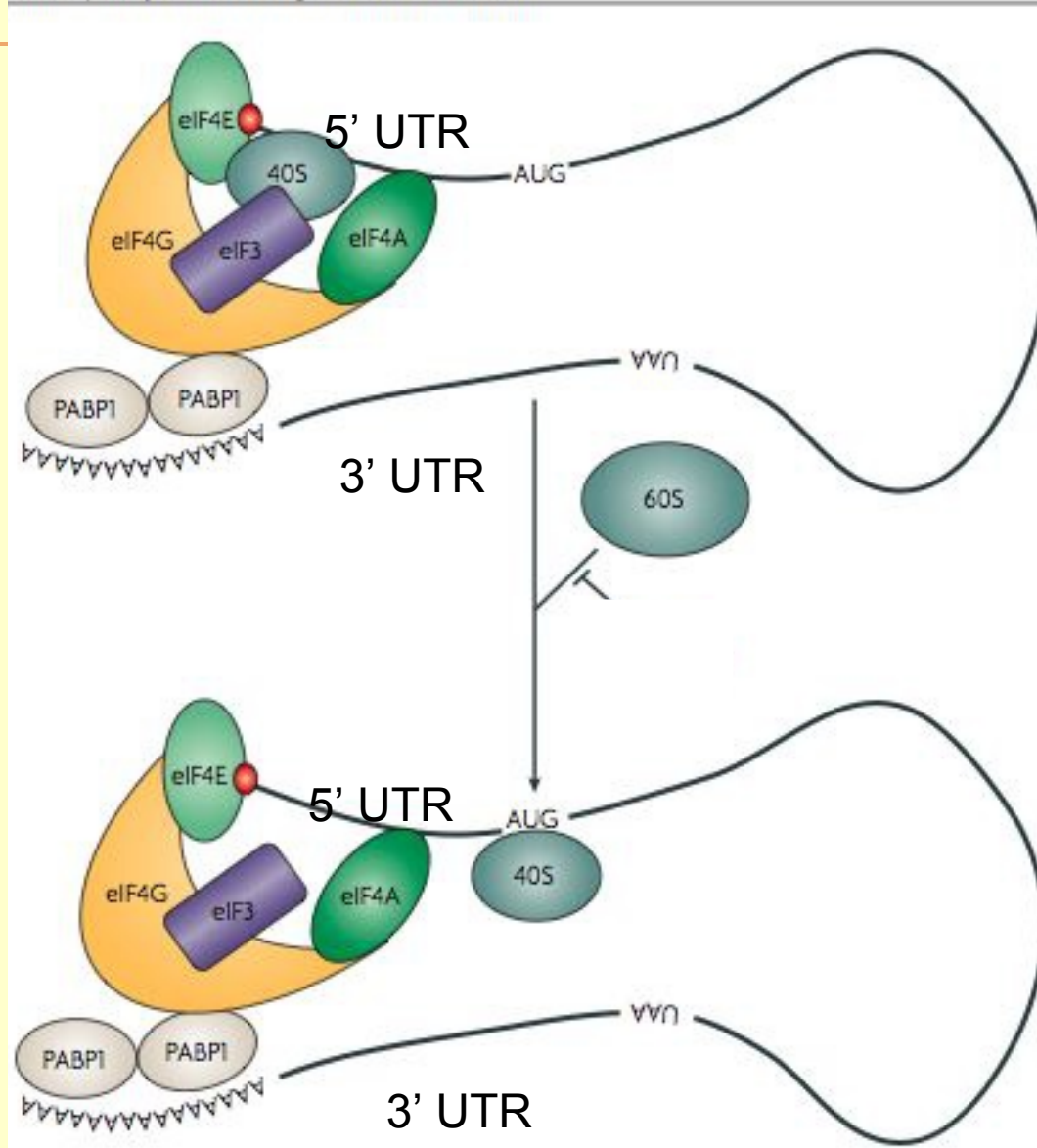
(b)



Current Opinion in Structural Biology

# Initiation of Translation

Box 3 | Steps in eukaryotic translation

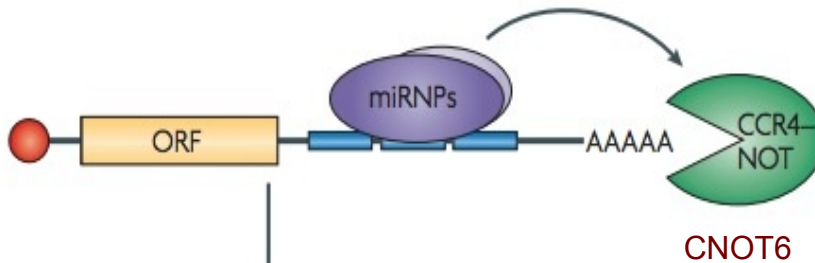




# Mechanisms of Translational Regulation by miRNP Complexes

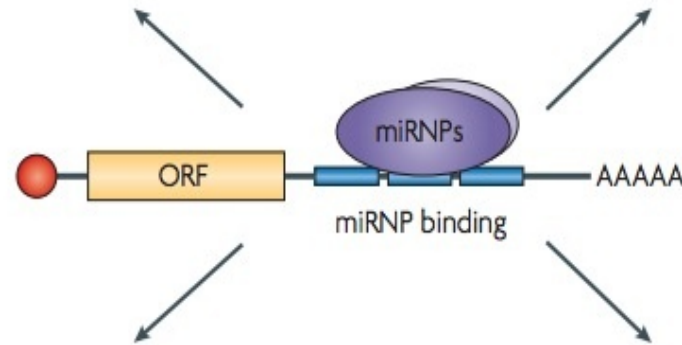
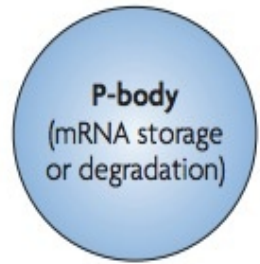
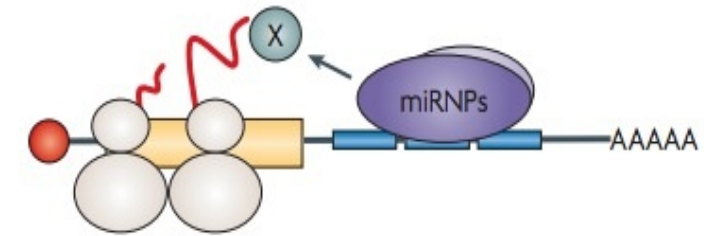
## Deadenylation

(followed by decapping and degradation)



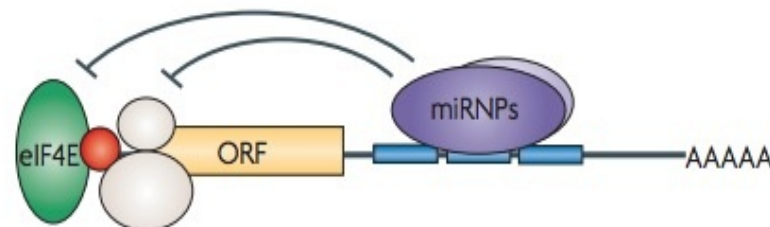
## Proteolysis

(degradation of nascent peptide)



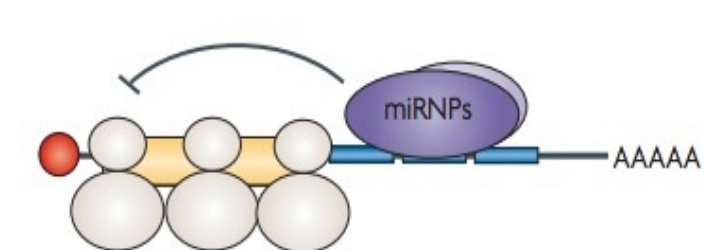
## Initiation block

(repressed cap recognition or 60S joining)



## Elongation block

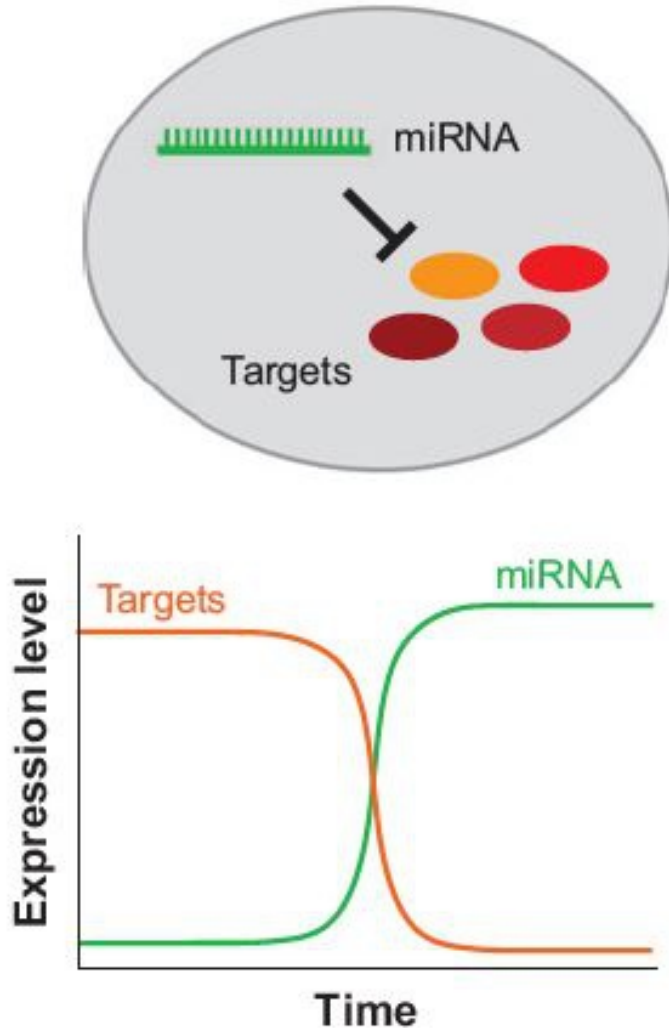
(slowed elongation or ribosome 'drop-off')



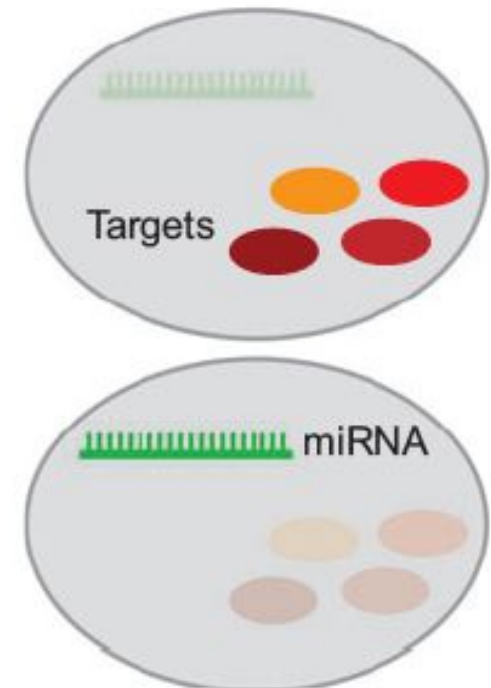
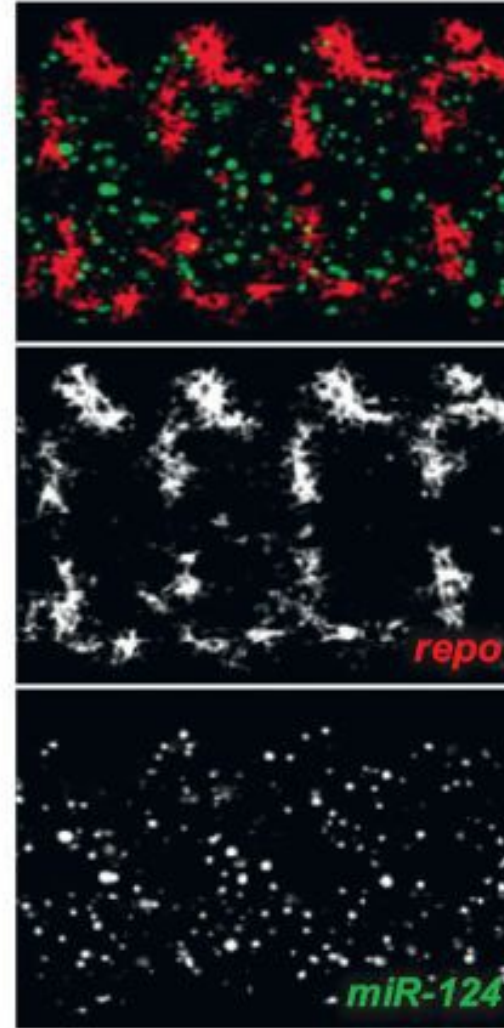
# miRNA Expression Results in Temporal and Spatial Reciprocity with Target Expression

Annu. Rev. Cell Dev. Biol. 2007

**a** Temporal reciprocity

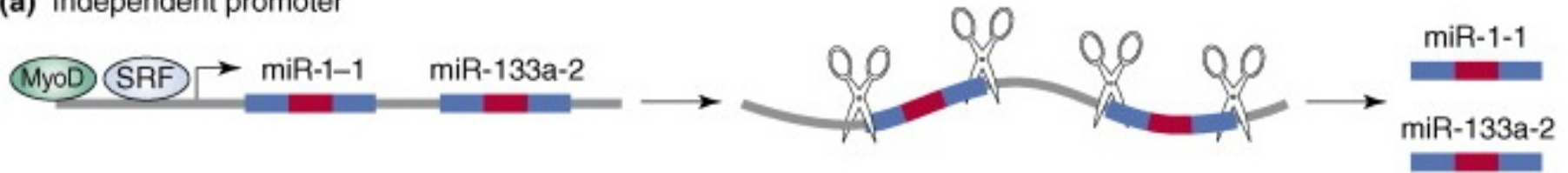


**b** Spatial reciprocity



# Genomic Organization of miRNA Genes

(a) Independent promoter



(b) Intronic



(c) Exonic



- Intronic miRNAs often in antisense direction, made from own promoter

- Exonic miRNAs - non-coding (or in alternatively spliced exons)

# Homology Between *C. elegans* and *Homo sapiens* miRNAs

## lin-4 family

```
UCCUGAGA . . . CCUAACUUGUGA Hs miR-125b-1
UCCUGAGA . . . CCUAACUUGUGA Hs miR-125b-2
UCCUGAGA . . . CCUAACUUGUGA Ce lin-4
UCCUGAGA AUUCUGAACAGCUU Ce miR-237
```

## let-7 family

```
AGAGGUAGUAGGUUGCAUAGU . . . Hs let-7d
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7e
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7a-1
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7a-2
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7a-3
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7a-4
UGAGGUAGUAGGUUGUUAUAGU . . . Ce let-7
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7f-1
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7f-2
UGAGGUAGUAGGUUGUUAUAGU . . . Hs miR-98
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7g
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7i
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7b
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7c
UAGGUAGU . . . UUCAUUGUUGGG Hs miR-196-1
UAGGUAGU . . . UUCAUUGUUGGG Hs miR-196-2
UGAGGUAGUAGGUUGUUAUAGU . . . Ce miR-84
UGAGGUAGG . . . CUCAGUAGUUGCA Ce miR-48
UGAGGUAGG . . . UGC . . . AGAAAUUGA Ce miR-241
```

## mir-1 family

```
UGGAAUGUAAAAGAAUGUA A Hs miR-1b
UGGAAUGUAAAAGAAUGUA U Hs miR-1d
UGGAAUGUAAAAGAAUGUA . . . Ce miR-1
UGGAAUGUAAAAGAAUGUA . . . Hs miR-206
```

## mir-9 family

```
UCUUUGGUUAA . . . CUGGUG . . . UAUGA Hs miR-9-1
UCUUUGGUUAA . . . CUGGUG . . . UAUGA Hs miR-9-2
UCUUUGGUUAA . . . CUGGUG . . . UAUGA Ce miR-244
```

## mir-10 family

```
AACCC . . . GUAGAUCGAAACU . . . UUGG . . . Hs miR-100-1
AACCC . . . GUAGAUCGAAACU . . . UUGG . . . Hs miR-100-2
CAACC . . . GUAGAUCGAAACU . . . UUGG . . . Hs miR-99b
UACCCUGUAGA . . . UCGAGCUGUGUGU Ce miR-57
UACCCUGUAGA . . . UCGAGCUGUGUGU Hs miR-10a
UACCCUGUAGA . . . UCGAGCUGUGUGU Hs miR-10b
AACCC . . . GUAGAUCGAAACU . . . UUGG . . . Hs miR-99a
UACCC . . . GUAGAUCGAAACU . . . UUGG . . . Ce miR-51
```

## mir-19 family

```
UGUGCAAUUC . . . UAU . . . GCAAAACUGA . . . Hs miR-19a
UGUGCAAUUC . . . UAU . . . GCAAAACUGA . . . Hs miR-19b-1
UGUGCAAUUC . . . UAU . . . GCAAAACUGA . . . Hs miR-19b-2
. . . UGCAAUUC . . . UAU . . . GCAAAACUGA . . . Ce miR-254
```

## mir-25 family

```
UAUUGCACUUGUC . . . CGGC . . . CUGU Hs miR-92-1
UAUUGCACUUGUC . . . CGGC . . . CUGU Hs miR-92-2
UAUUGCACUUGUC . . . CGGC . . . CUGU Ce miR-235
CAUUGCACUUGUC . . . CGGC . . . CUGU Hs miR-25-1
CAUUGCACUUGUC . . . CGGC . . . CUGU Hs miR-25-2
UAUUGCACUUGUC . . . CGGC . . . CUGU Hs miR-32
```

## mir-29 family

```
. . . UAGCACC AUUUGAAAUCAGUGUU Hs miR-29b-1
. . . UAGCACC AUUUGAAAUCAGUGUU Hs miR-29b-2
. . . UAGCACC AUUUGAAAUCAGUGUU Hs miR-29b-3
. . . UAGCACC AUUUGAAAUCAGUGUU Hs miR-29c
. . . UAGCACC AUUUGAAAUCAGUGUU Hs miR-29a-1
. . . UAGCACC AUUUGAAAUCAGUGUU Hs miR-29a-2
. . . UAGCACC AUUUGAAAUCAGUGUU Ce miR-83
```

## mir-31 family

```
AGGCAAGAUGUUGGCA . . . U . . . AGC . . . Ce miR-72
. . . GGCAGAUGUUGGCA . . . U . . . AGCUG Hs miR-31
UGGCAAGAUGUUGGCA . . . U . . . AGC . . . Ce miR-73
```

## mir-34 family

```
AGGCAGUGUGUUA . . . GCUGGUUG . . . Ce miR-34
UGGCAGUGUGUUA . . . GCUGGUUGU Hs miR-34
UGG . . . AGUCUC . . . ACAAU . . . GGUUGUUGU Hs miR-122a
```

## mir-50 family

```
UGAUUUGUAAUUC . . . AGCUUACAG . . . Ce miR-62
UGAUUUGUAAUUC . . . AGCUUACAGU Hs miR-50
UGAUUUGUAAUUC . . . AGCUUACAGU Hs miR-190
UGAUUUGUAAUUC . . . AGCUUACAGU Ce miR-90
```

## mir-74 family

```
UGG . . . AGAGAA . . . AGGCAGUUC . . . Hs miR-185
UGGC . . . AGAAAU . . . AGGCAGU . . . CUACA Ce miR-74
```

## mir-76 family

```
UCCGU . . . UGUUG . . . AU . . . GAAGCCUUGA Ce miR-76
UCCGU . . . UGUUG . . . AU . . . GAAGCCUUGA Hs miR-187
```

## mir-79 family

```
A . . . AAAAGCUAGC . . . U . . . ACCAAAGCU . . . Ce miR-79
. . . AAAAGCUAGC . . . U . . . ACCAAAGCU . . . Hs miR-131
U . . . AAAAGCUAGC . . . U . . . ACCAAAGCU . . . Ce miR-75
```

## mir-80 family

```
UGAGAUCATC . . . GU . . . GAAAGCCUAGU Ce miR-81
UGAGAUCATC . . . GU . . . GAAAGCCUAGU Ce miR-82
UGAGAUCATC . . . GU . . . GAAAGCCUAGU Ce miR-80
UGAGAUCATC . . . GU . . . GAAAGCCUAGU Hs miR-143
```

## mir-105 family

```
UCAAAUUC . . . UCA . . . GACUCCUUGU . . . Hs miR-105-1
UCAAAUUC . . . UCA . . . GACUCCUUGU . . . Hs miR-105-2
. . . UAAAUUC . . . UCA . . . GACUCCUUGU . . . Ce miR-232
```

## mir-124 family

```
U . . . AAAGGCACGG . . . GU . . . GAAUGCCA . . . Hs miR-124a
U . . . AAAGGCACGG . . . GU . . . GAAUGCCA . . . Hs miR-124a
U . . . AAAGGCACGG . . . GU . . . GAAUGCCA . . . Hs miR-124a
. . . AAAGGCACGG . . . GU . . . GAAUGCCA . . . Ce miR-124
. . . AAAGGCAC . . . UGCAU . . . GAAU . . . UCA . . . CGG Ce miR-228
. . . AAAGGCAC . . . UG . . . GAAU . . . UCA . . . CUG Hs miR-183
```

## mir-133 family

```
. . . UUGGUCCCCU . . . UCA . . . ACCAGCUGU Hs miR-133a-1
. . . UUGGUCCCCU . . . UCA . . . ACCAGCUGU Hs miR-133a-2
. . . UUGGUCCCCU . . . UCA . . . ACCAGCUGU Hs miR-133b
A . . . UUGGUCCCCU . . . UCA . . . ACCAGCUGU Ce miR-245
```

## mir-137 family

```
U . . . AAUUGCU . . . CG . . . AGAAUAC . . . CCUU . . . Ce miR-234
. . . AAUUGCU . . . CG . . . AGAAUAC . . . CCUU . . . Hs miR-137
```

## mir-141 family

```
U . . . AAUACUGUC . . . AGGUAAU . . . GAC . . . CCU Ce miR-236
. . . AAUACUGUC . . . AGGUAAU . . . GAC . . . CCU Hs miR-141
```

## mir-193 family

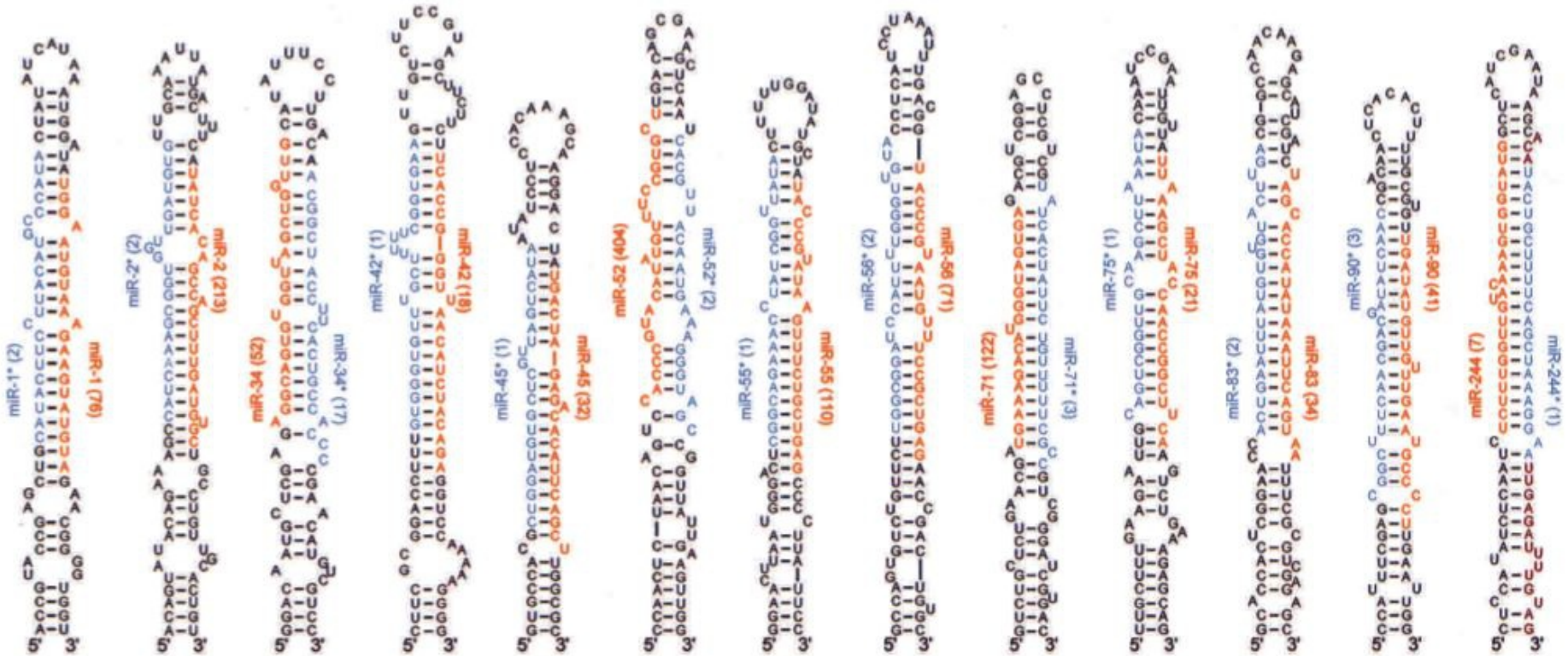
```
U . . . ACUGGCC . . . CC . . . AAA . . . UC . . . UUC . . . CCU Ce miR-240
A . . . ACUGGCC . . . CC . . . AAA . . . UC . . . UUC . . . CCU Hs miR-193
```

## mir-220 family

```
. . . CACACAC . . . UCA . . . CU . . . AACACU . . . GAC Ce miR-253
. . . CACACAC . . . UCA . . . CU . . . AACACU . . . GAC Hs miR-220
```



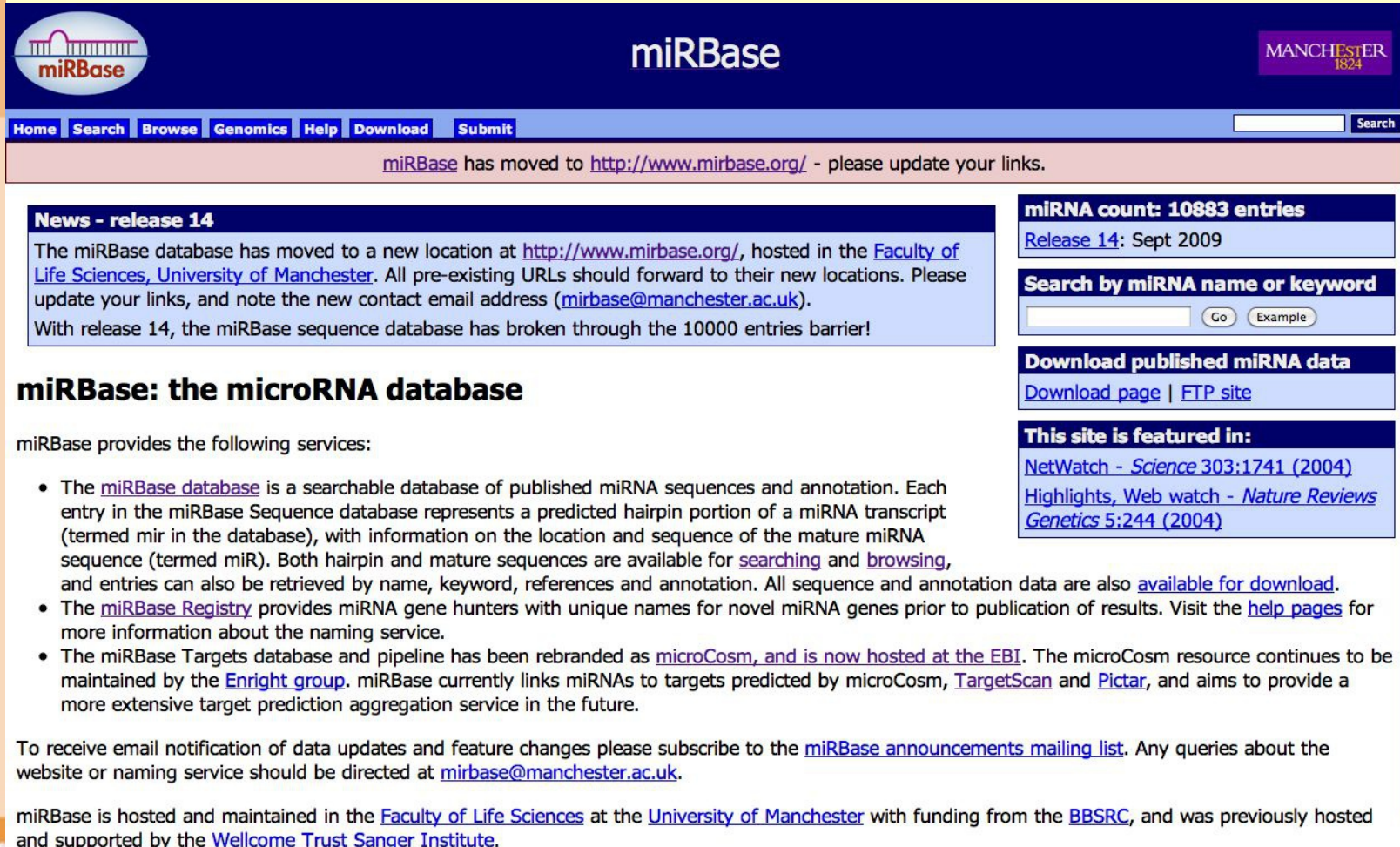

# Predicted miRNA Precursors





# miRBase

<http://www.mirbase.org/>



**miRBase**

MANCHESTER 1824

Home Search Browse Genomics Help Download Submit

miRBase has moved to <http://www.mirbase.org/> - please update your links.

**News - release 14**

The miRBase database has moved to a new location at <http://www.mirbase.org/>, hosted in the [Faculty of Life Sciences, University of Manchester](#). All pre-existing URLs should forward to their new locations. Please update your links, and note the new contact email address ([mirbase@manchester.ac.uk](mailto:mirbase@manchester.ac.uk)).

With release 14, the miRBase sequence database has broken through the 10000 entries barrier!

**miRBase: the microRNA database**

miRBase provides the following services:

- The [miRBase database](#) is a searchable database of published miRNA sequences and annotation. Each entry in the miRBase Sequence database represents a predicted hairpin portion of a miRNA transcript (termed mir in the database), with information on the location and sequence of the mature miRNA sequence (termed miR). Both hairpin and mature sequences are available for [searching](#) and [browsing](#), and entries can also be retrieved by name, keyword, references and annotation. All sequence and annotation data are also [available for download](#).
- The [miRBase Registry](#) provides miRNA gene hunters with unique names for novel miRNA genes prior to publication of results. Visit the [help pages](#) for more information about the naming service.
- The miRBase Targets database and pipeline has been rebranded as [microCosm](#), and is now hosted at the [EBI](#). The microCosm resource continues to be maintained by the [Enright group](#). miRBase currently links miRNAs to targets predicted by microCosm, [TargetScan](#) and [Pictar](#), and aims to provide a more extensive target prediction aggregation service in the future.

To receive email notification of data updates and feature changes please subscribe to the [miRBase announcements mailing list](#). Any queries about the website or naming service should be directed at [mirbase@manchester.ac.uk](mailto:mirbase@manchester.ac.uk).

miRBase is hosted and maintained in the [Faculty of Life Sciences](#) at the [University of Manchester](#) with funding from the [BBSRC](#), and was previously hosted and supported by the [Wellcome Trust Sanger Institute](#).

**miRNA count: 10883 entries**

Release 14: Sept 2009

**Search by miRNA name or keyword**

**Download published miRNA data**

[Download page](#) | [FTP site](#)

**This site is featured in:**

[NetWatch - Science 303:1741 \(2004\)](#)  
[Highlights, Web watch - Nature Reviews Genetics 5:244 \(2004\)](#)

# miRBase::MicroCosm miRNA Targets

<http://www.ebi.ac.uk/enright-srv/microcosm/htdocs/targets/v5/#>



**MicroCosm Targets Version 5**

Email [microcosm@ebi.ac.uk](mailto:microcosm@ebi.ac.uk) with queries or problems.

The navigation menu consists of a central oval containing a diagram of a miRNA-microcosm interaction. The diagram shows a pink miRNA hairpin structure above a blue horizontal line representing the microcosm. The word "Targets" is written above the miRNA, and "MicroCosm" is written below the blue line. Surrounding this central oval are six other blue ovals, each containing a navigation link: "Enter" (top), "Information" (top-left), "FAQ" (top-right), "Statistics" (bottom-left), "Search" (bottom-right), and "Download" (bottom).

miRBase Targets Release Version v5

# Human miRNAs (March 4, 2014)

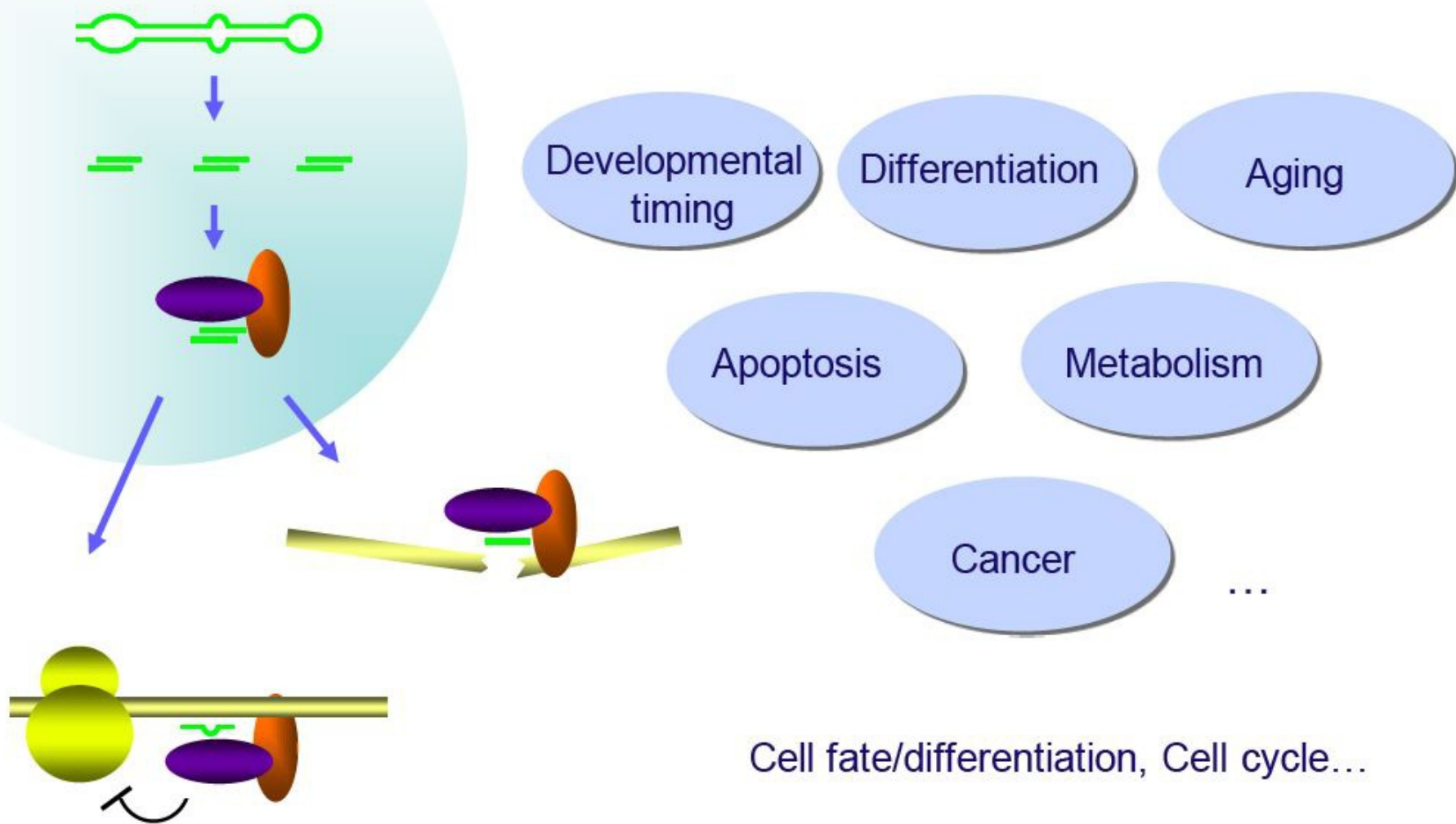
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- Total number of miRNAs known 24,521
  - Number human miRNAs identified 2,652
  - Number of human mRNA targets 34,788
- 

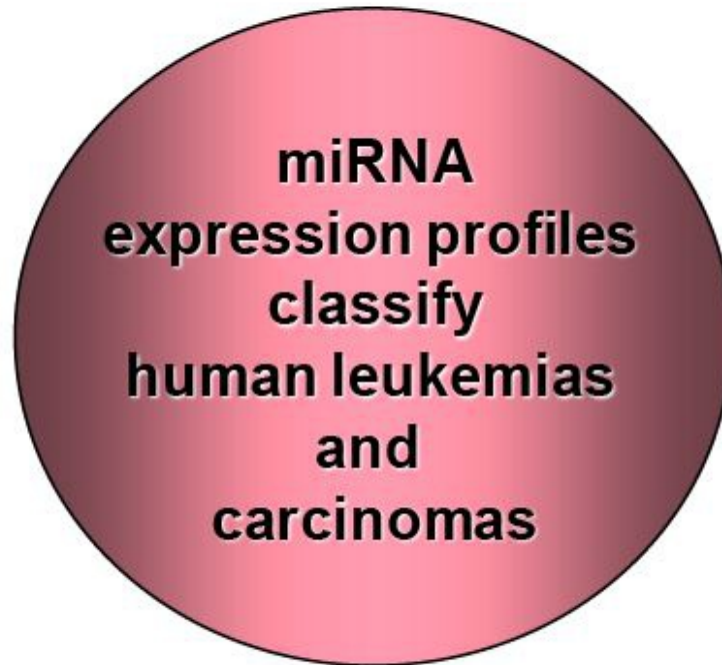
- miRNAs can have multiple targets
- Target mRNAs can have multiple miRNA binding sites



# Thousands of microRNAs act in multiple biological events



***ALTERATIONS OF MICRORNAS ARE FOUND IN EVERY  
TYPE OF HUMAN CANCER***



(Calin et al, PNAS 2002; Lu et al, Nature, 2005; Volinia & Calin et al, PNAS 2006; Landgraf et al, Cell 2007)

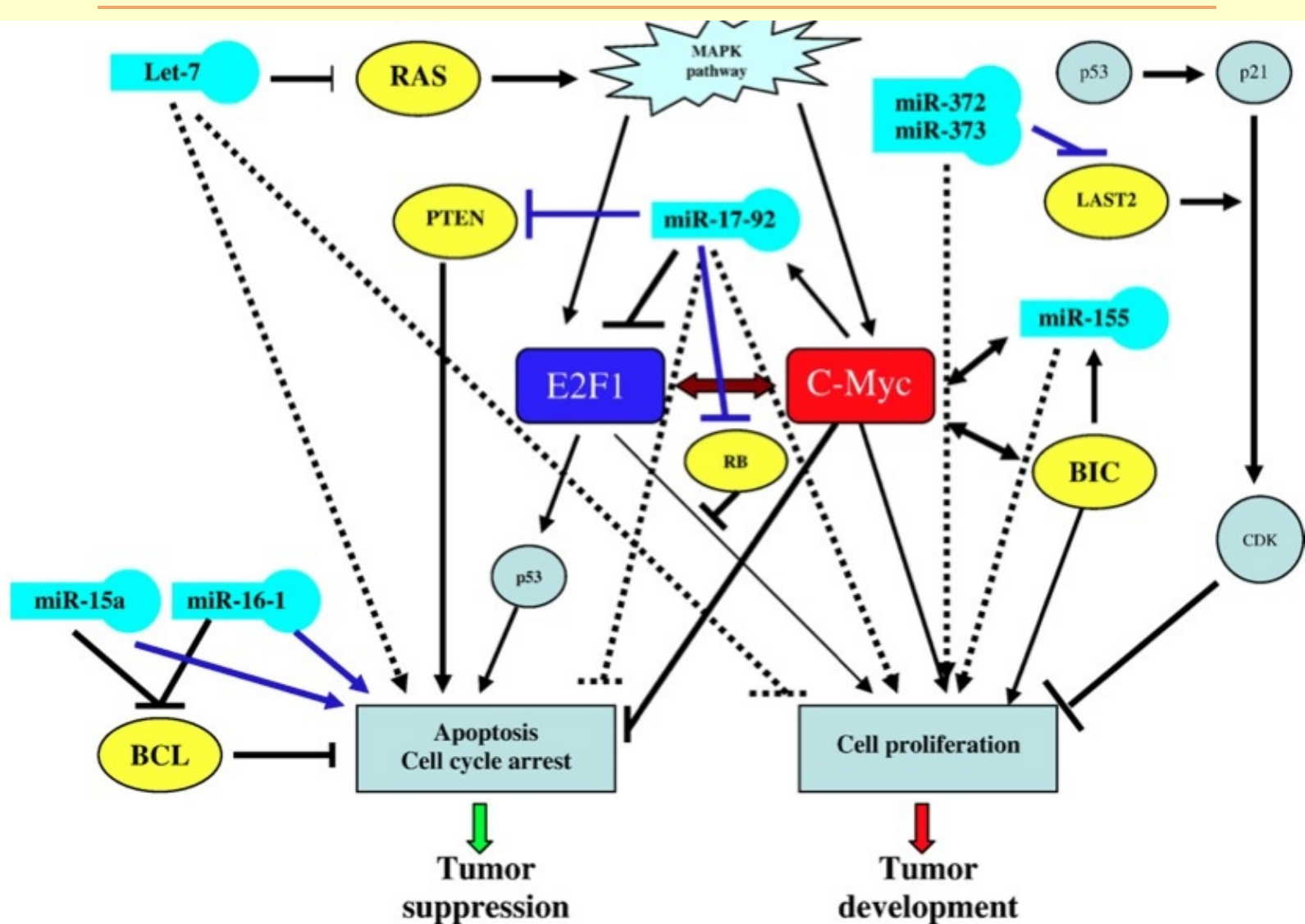
# miRNAs Involved in Human Cancer

(Croce Nat Rev Genet. 2009 Oct;10(10):704-14.)



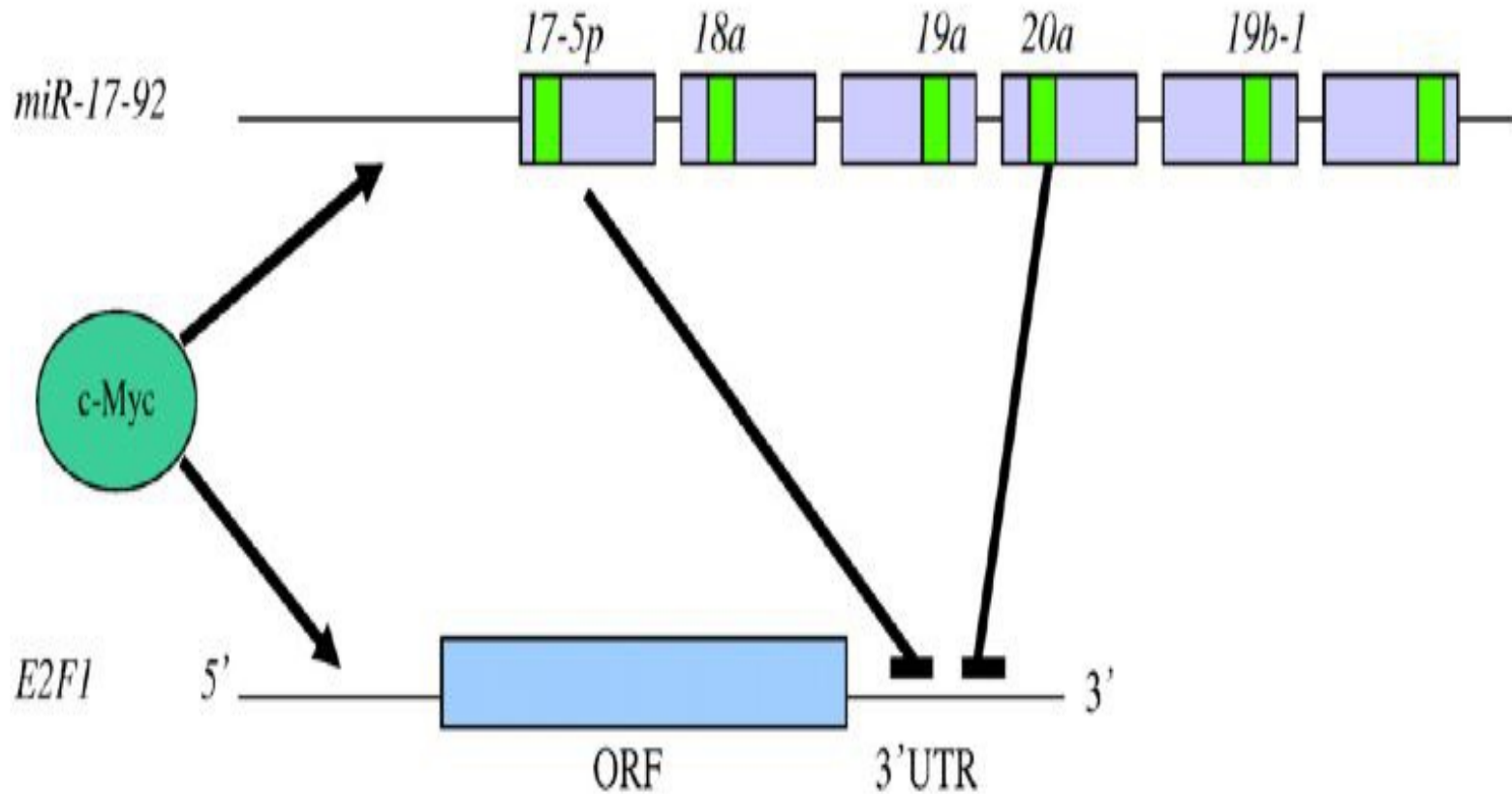
# miRNAs as Oncogenes and Tumor Suppressors

Zhang et al Dev Biol. 2007 Feb 1;302(1):1-12

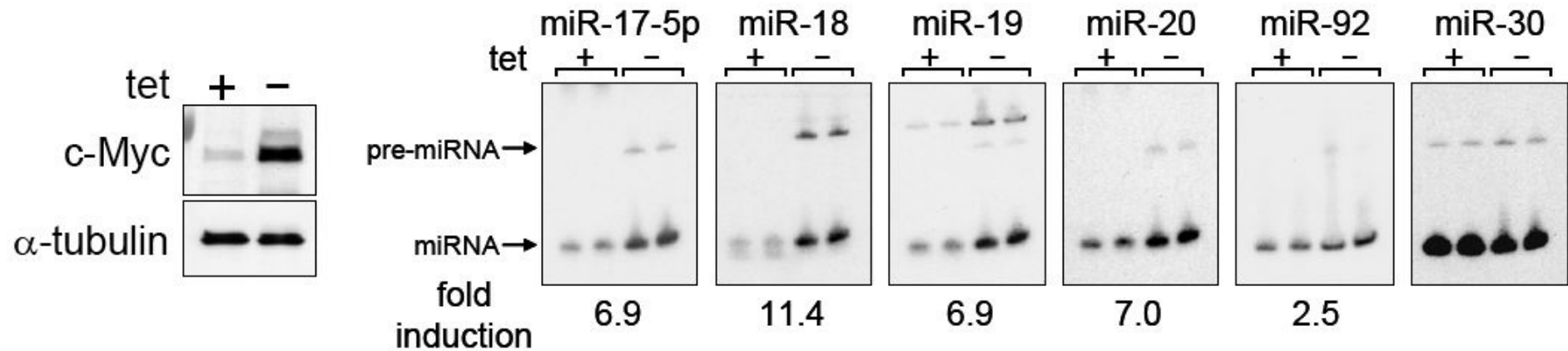
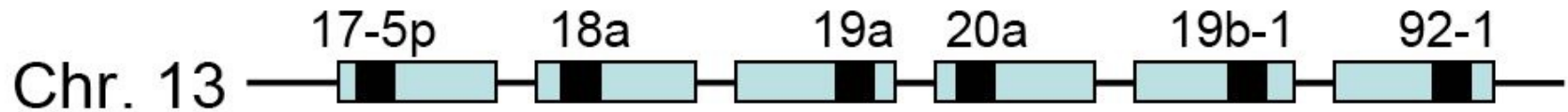


# cMyc & miRNAs Regulate E2F1 Cell Cycle TF

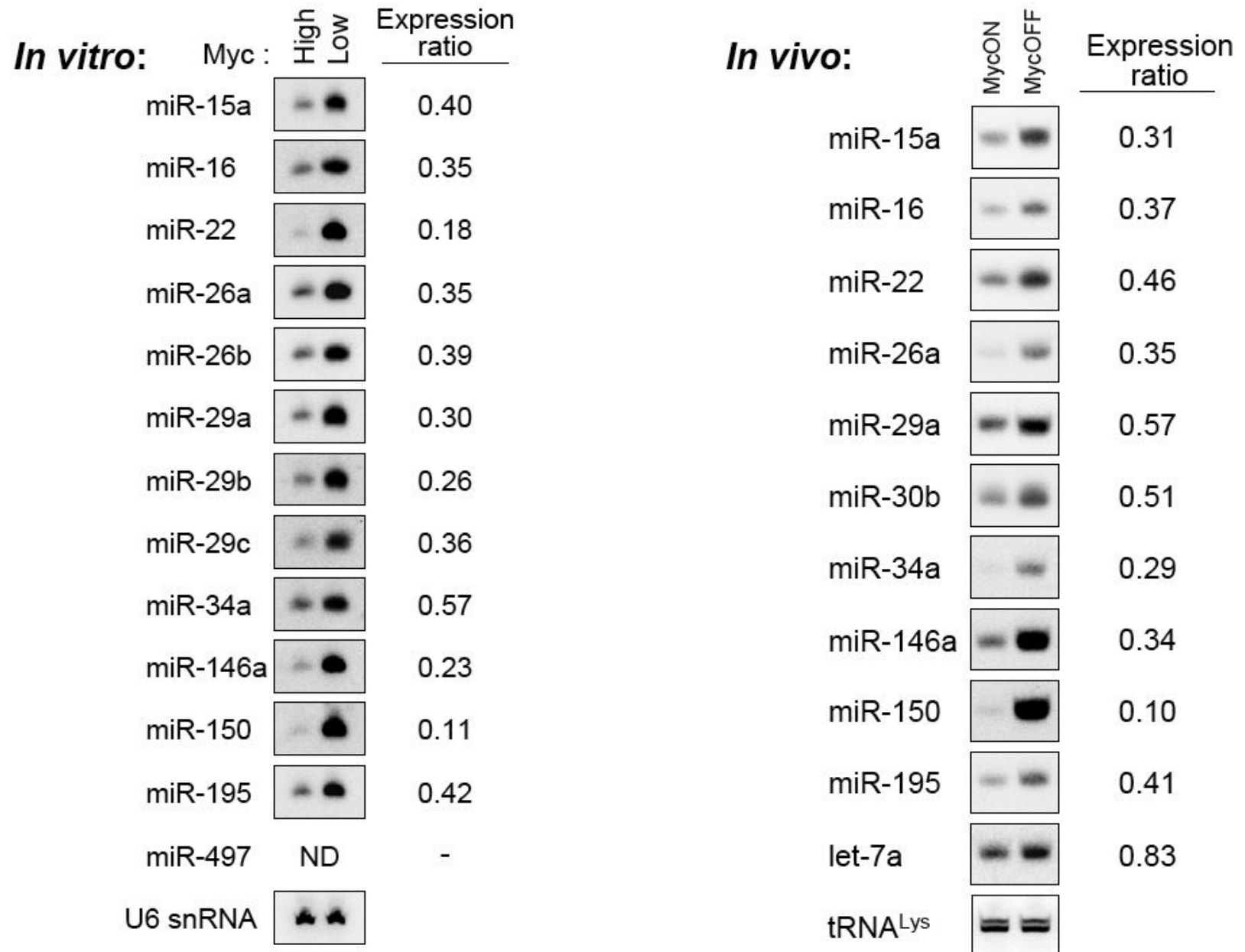
Zhang et al Dev Biol. 2007 Feb 1;302(1):1-12



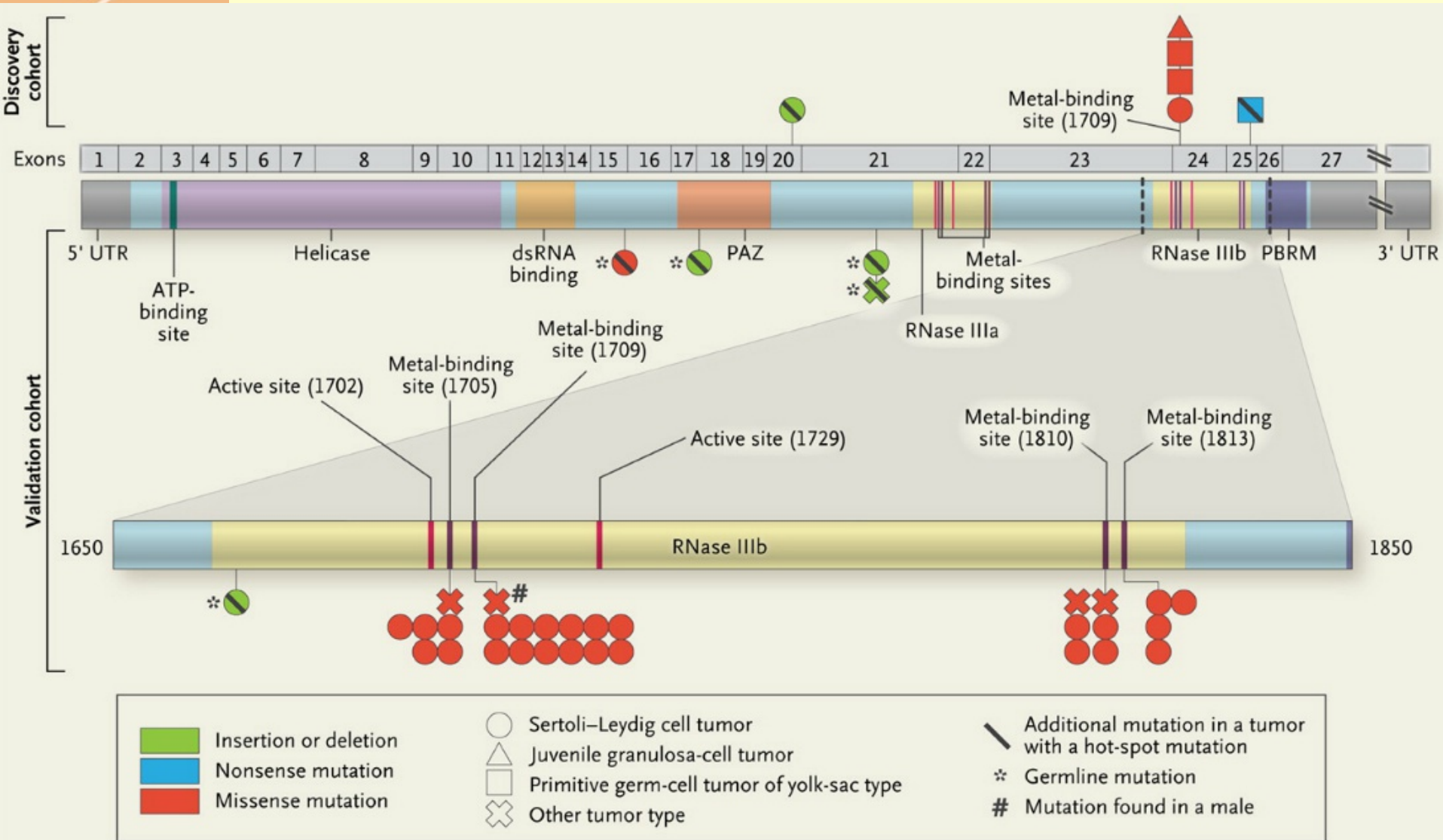
# The miR-17-92 cluster is activated by Myc



# Myc represses the expression of many miRNAs



# DICER1 mutations in cancers





# miRNA Oncogenes or Tumor Suppressor Genes (Croce Nat Rev Genet. 2009 Oct;10(10):704-14.)

Table 1 | **MicroRNAs that function as oncogenes or tumour suppressor genes in human cancers**

MicroRNA	Dysregulation	Function	Validated targets	Oncogene (ONC) or tumour suppressor (TS)	Refs
<i>miR-15a</i> and <i>miR-16-1</i>	Loss in CLL, prostate cancer and multiple myeloma	Induces apoptosis and inhibits tumorigenesis	BCL2, WT1, RAB9B and MAGE83	TS	15,20,23, 30,52,69
<i>let-7 (a, b, c, d, e, f, g and i)</i>	Loss in lung and breast cancer and in various solid and haematopoietic malignancies	Induces apoptosis and inhibits tumorigenesis	RAS, MYC and HMGA2	TS	22,26, 42,70
<i>miR-29 (a, b and c)</i>	Loss in aggressive CLL, AML (11q23), MDS lung and breast cancers and cholangiocarcinoma	Induces apoptosis and inhibits tumorigenicity. Reactivates silenced tumour suppressor genes	TCL1, MCL1 and DNMTs	TS	30,64, 71,72
<i>miR-34</i>	Loss in pancreatic, colon, breast and liver cancers	Induces apoptosis	CDK4, CDK6, cyclin E2, EZF3 and MET	TS	56–58
<i>miR-145</i>	Loss in breast cancer	Inhibits proliferation and induces apoptosis of breast cancer cells	ERG	TS	31
<i>miR-221</i> and <i>miR-222</i>	Loss in erythroblastic leukaemia	Inhibits proliferation in erythroblasts	KIT	TS	30
<i>miR-221</i> and <i>miR-222</i>	Overexpression in aggressive CLL, thyroid carcinoma and hepatocellular carcinoma	Promotes cell proliferation and inhibits apoptosis in various solid malignancies	p27, p57, PTEN and TIMP3	ONC	43,51,73
<i>miR-155</i>	Upregulated in aggressive CLL, Burkitt's lymphoma and lung, breast and colon cancers	Induces cell proliferation and leukaemia or lymphoma in mice	MAF and SHIP1	ONC	32–34, 36,37
<i>miR-17–92</i> cluster	Upregulated in lymphomas and in breast, lung, colon, stomach and pancreatic cancers	Induces proliferation	E2F1, BIM and PTEN	ONC	19,34,35, 40,41
<i>miR-21</i>	Upregulated in glioblastomas, AML (11q23), aggressive CLL and breast, colon, pancreatic, lung, prostate, liver and stomach cancers	Inhibits apoptosis and increases tumorigenicity	PTEN, PDCD4, TPM1 and TIMP3	ONC	31,37–39, 44–50
<i>miR-372</i> and <i>miR-373</i>	Upregulated in testicular tumours	Promotes tumorigenicity in cooperation with RAS	LATS2	ONC	74

AML, acute myeloid leukaemia; BCL2, B cell leukaemia/lymphoma 2; BIM, Bcl2-interacting mediator of cell death; CLL, chronic lymphocytic leukaemia; DNMT, DNA methyltransferase; HMGA2, high mobility group AT-hook 2; LATS2, large tumour suppressor homologue 2; MCL1, myeloid cell leukaemia sequence 1; MDS, myelodysplastic syndrome; PDCD4, programmed cell death 4; PTEN, phosphatase and tensin homologue; SHIP1, SH2 domain-containing inositol-5'-phosphatase 1; TCL1, T cell lymphoma breakpoint 1; TIMP3, tissue inhibitor of metalloproteinases 3; TPM1, tropomyosin 1; WT1, Wilms tumour 1.

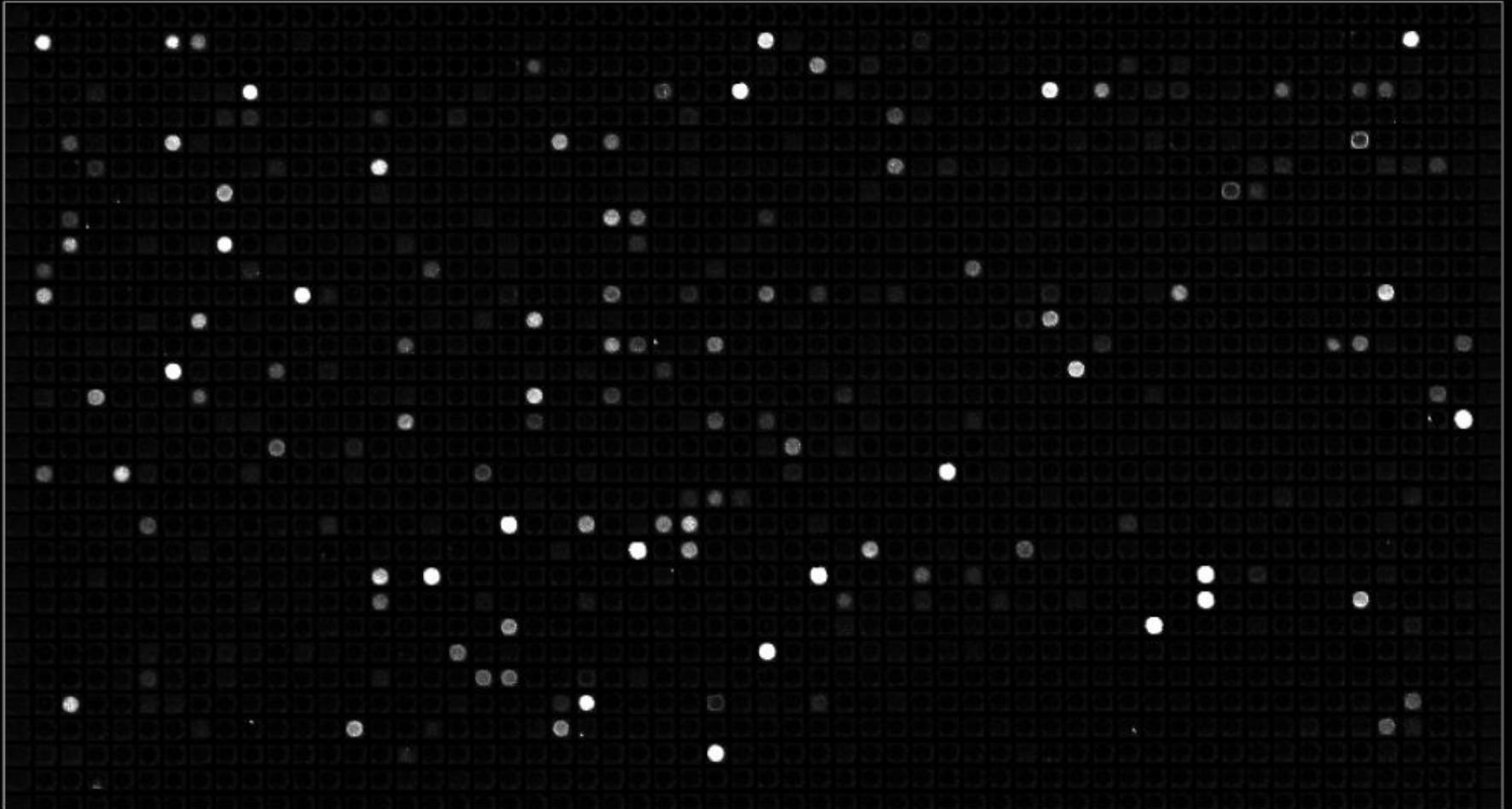
# ***MIRNA PROFILING AS A NEW DIAGNOSTIC & PROGNOSTIC TOOL FOR CANCER PATIENTS***



**miRNAs expression  
signatures associated  
with diagnosis and  
prognostic factors  
(CLL, DLBCL, Lung,  
Colon, Pancreas,  
Brain ca.)**

(Michael et al, Molec Cancer Res 2003; Lu et al, Nature, 2005; Eis et al, PNAS, 2005  
Lui et al, Cancer Res 2007, Bloomston et al, JAMA 2007; Mi et al, PNAS, 2007; Garzon et al, Blood in press 2008)

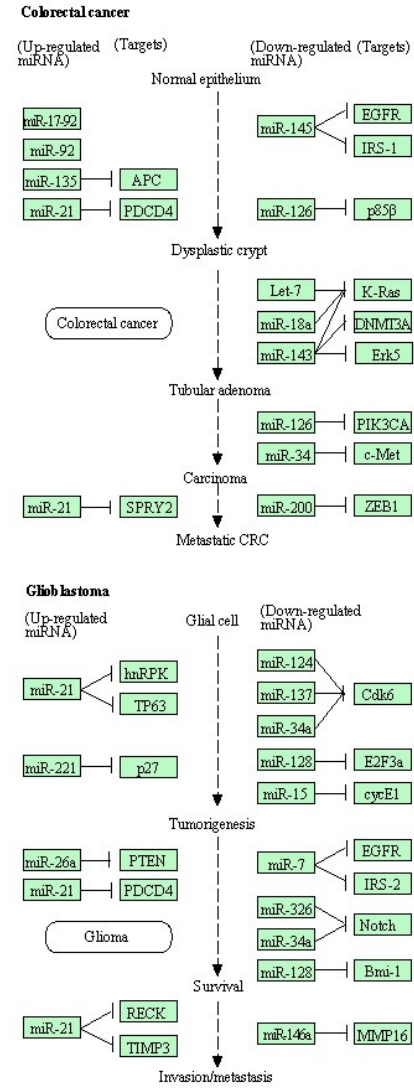
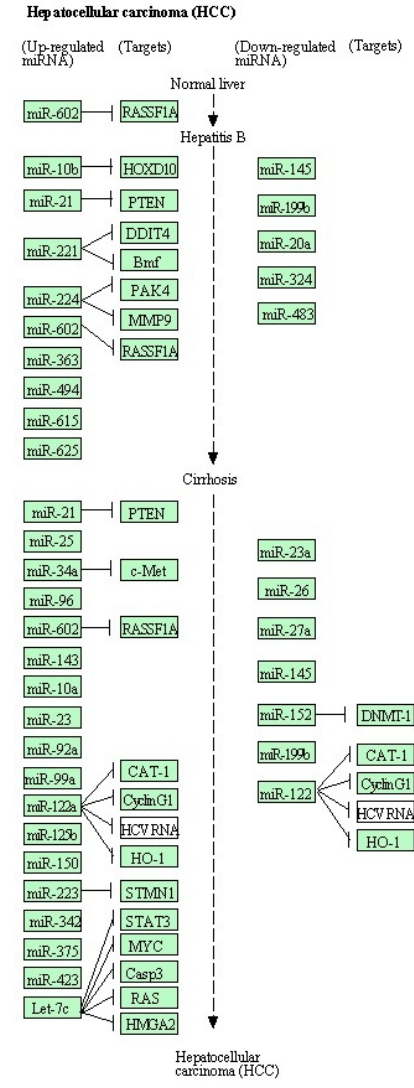
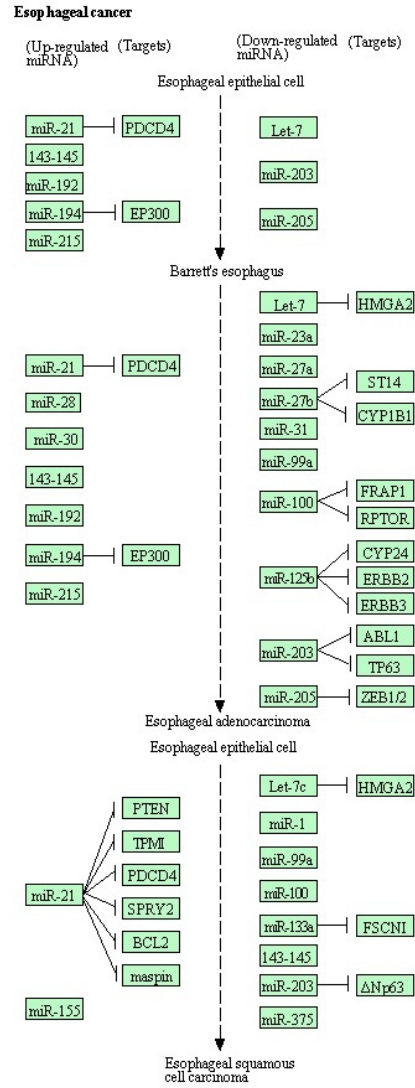
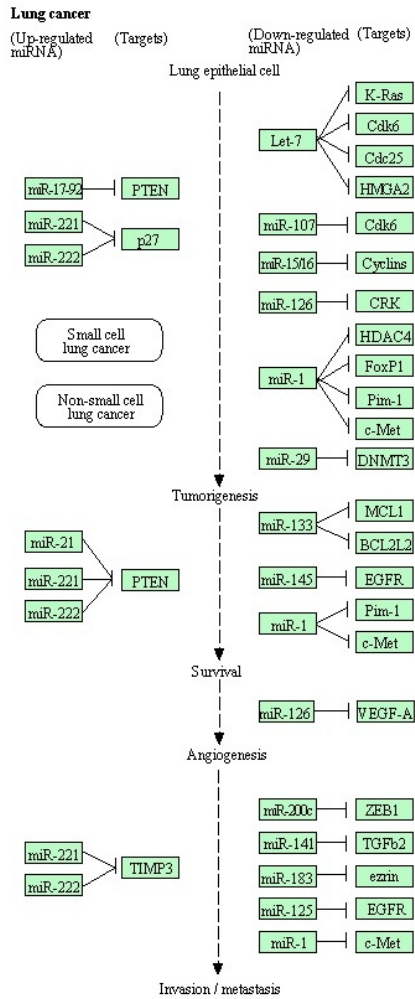
# Profiling miRNA expression using custom microarrays



# miRNAs in Cancer

<http://www.kegg.jp/pathway/hsa05206>

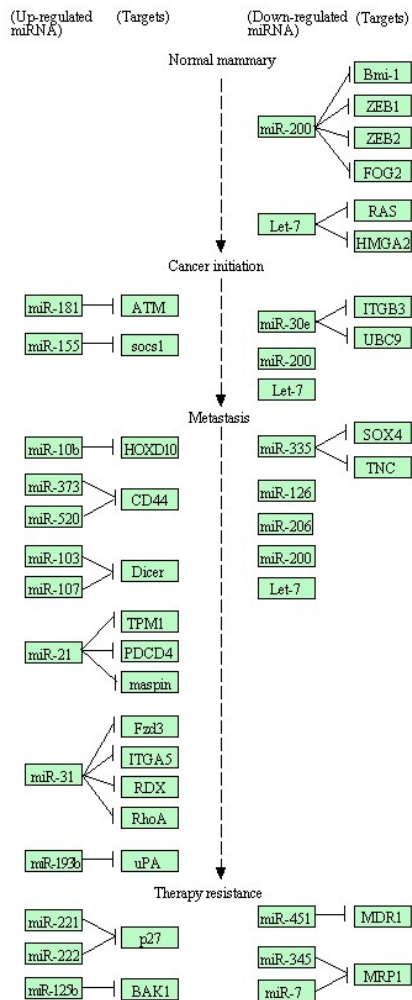
## MicroRNAs IN CANCER



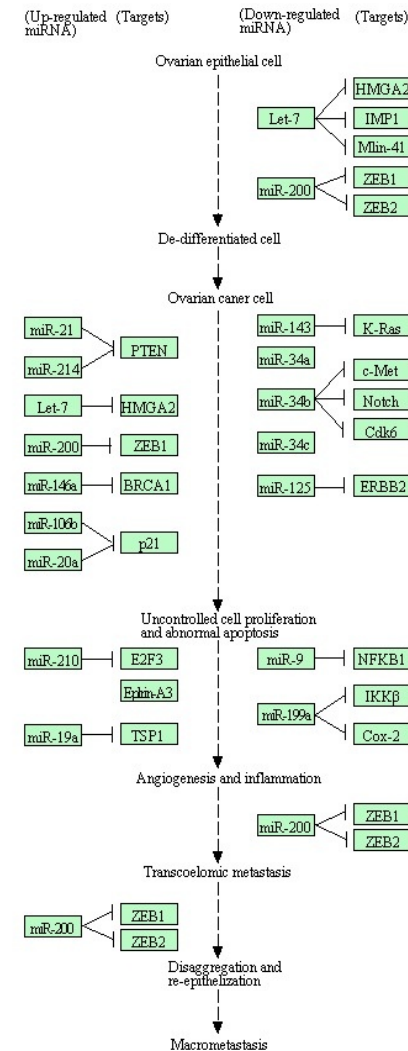
# miRNAs in Cancer

<http://www.kegg.jp/pathway/hsa05206>

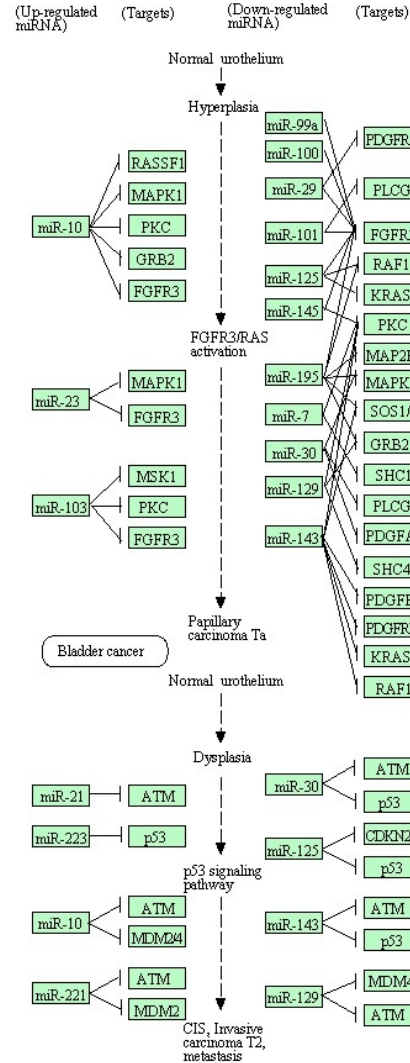
## Breast cancer



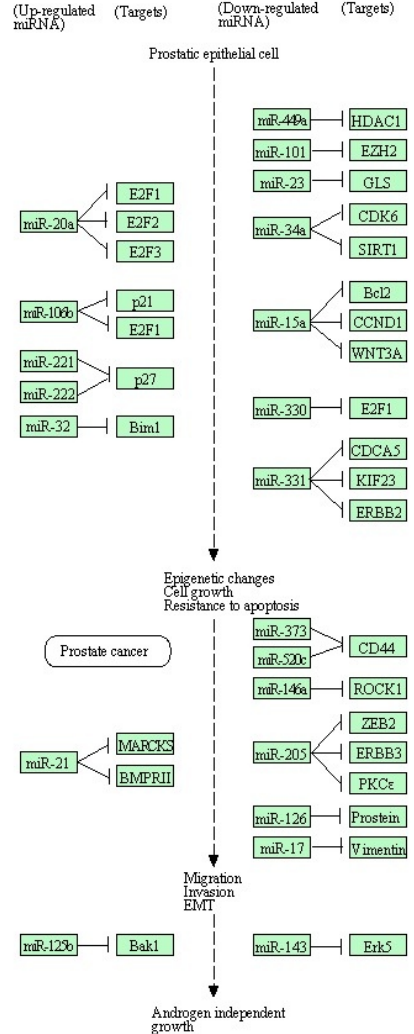
## Epithelial ovarian cancer



## Bladder cancer



## Prostate cancer



# miRNAs and Cancer – A Summary

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- miRNAs control cell cycle, cell differentiation and apoptosis by regulating oncogenes and tumor suppressor genes
- •miRNAs are misexpressed in cancer and are therefore excellent diagnostic / prognostic markers in cancer
- •Some miRNAs e.g. *mir-155*, can cause cancer and oncogenic miRNAs may be therapeutic targets in cancer
- •Other miRNAs like *let-7*, may prevent cancer and may be therapeutic molecules themselves.
- •MicroRNAs could augment current cancer therapies.

# References

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- Role of miRNAs in Cancer and Apoptosis [Lynan-Lennon Biol Rev Camb Philos Soc. 2009 Feb;84\(1\):55-71](#)
- Causes and consequences of microRNA dysregulation in cancer [Croce Nat Rev Genet. 2009 Oct;10\(10\):704-14.](#)
- miRNAs as oncogenes and tumor suppressors. [Zhang Dev Biol. 2007 Feb 1;302\(1\):1-1](#)
- Transcriptional regulatory networks in *Saccharomyces cerevisiae*. [Lee Science. 2002 Oct 25;298\(5594\):799-804.](#)
- RNA regulation: a new genetics? [Mattick Nat Rev Genet. 2004 Apr;5\(4\):316-23.](#)
- microRNA functions. [Bushati Annu Rev Cell Dev Biol. 2007;23:175-205.](#)
- Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? [Filiowicz Nat Rev Genet. 2008 Feb;9\(2\):102-14.](#)
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- The microRNAs of *Caenorhabditis elegans*. [Lim Genes Dev. 2003 Apr 15;17\(8\):991-1008.](#)
- A three-dimensional view of the molecular machinery of RNA interference. [Jinek Nature. 2009 Jan 22;457\(7228\):405-12.](#)
- miRNAs and Cancer AAAI Science Webinars February 20 with George Calin, Brank Slack and Scott Hammond
- Short RNAs repress translation after initiation in mammalian cells. [Petersen Mol Cell. 2006 Feb 17;21\(4\):533-42.](#)
- Raising the estimate of functional human sequence. [Pheasant Genome Res. 2007 Sep;17\(9\):1245-53.](#)
- A developmental view of microRNA function. [Zhao Trends Biochem Sci. 2007 Apr;32\(4\):189-97.](#)
- c-Myc-regulated microRNAs modulate E2F1 expression [O'Donnell Nature. 2005 Jun 9;435\(7043\):839-43.](#)

# Important Micro RNA Web Sites

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- miRBase: <http://www.mirbase.org/>
- MicroCosm: <http://www.ebi.ac.uk/enright-srv/microcosm/>
- miRNAMiner: <http://groups.csail.mit.edu/pag/mirnaminer>
- miRNAviewer: <http://people.csail.mit.edu/akiezun/miRviewer>
- Patrocles: <http://www.patrocles.org/>
- TargetRank: <http://hollywood.mit.edu/targetrank>
- TargetScanS: <http://www.targetscan.org/>



# miRNA Dysregulation in Cancer

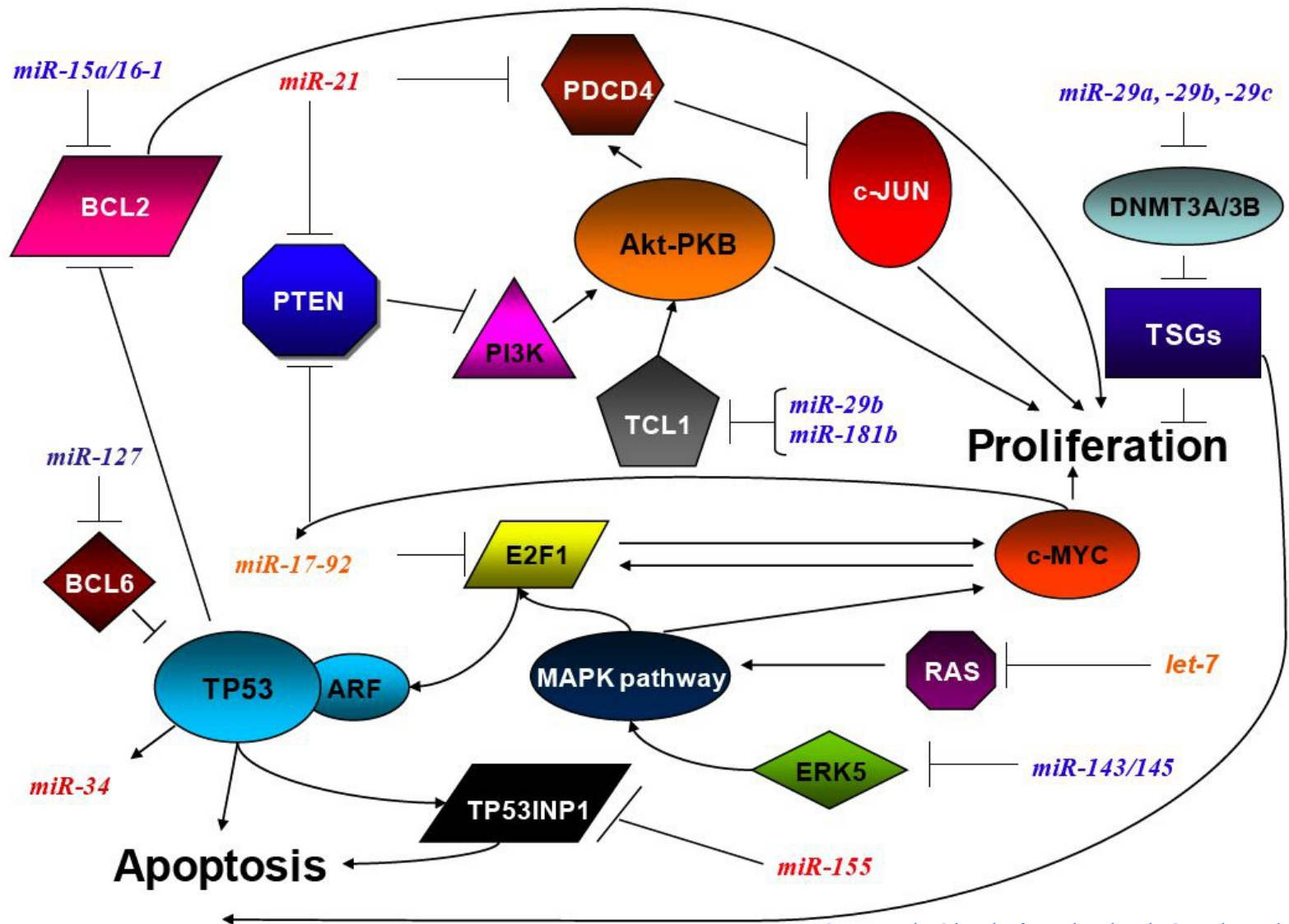
Croce Nat Rev Genet. 2009 Oct;10(10):704-14.

Table 2 | **Consequences of microRNA dysregulation in human cancers**

MicroRNA dysregulation	Targets	Consequences
MicroRNA overexpression	Tumour suppressors	Downregulation of tumour suppressors — for example, PTEN, p22, p57, TIMP3 and PDCD4
MicroRNA loss	Oncogenes	Upregulation of oncogenes — for example, <i>BCL2</i> , <i>MCL1</i> , <i>RAS</i> , <i>HMGA2</i> , <i>MYC</i> and <i>MET</i>
MicroRNA loss	DNA methyltransferases	Downregulation of tumour suppressors — for example, p16, FHIT and WWOX
MicroRNA loss	Chromatin silencers	Downregulation of tumour suppressors

*BCL2*, B cell leukaemia/lymphoma 2; FHIT, fragile histidine triad protein; *HMGA2*, high mobility group AT-hook 2; *MCL1*, myeloid cell leukaemia sequence 1; PDCD4, programmed cell death 4; PTEN, phosphatase and tensin homologue; TIMP3, tissue inhibitor of metalloproteinases 3; WWOX, WW domain-containing oxidoreductase.

# Micro RNAs Regulate Cell Growth and Death

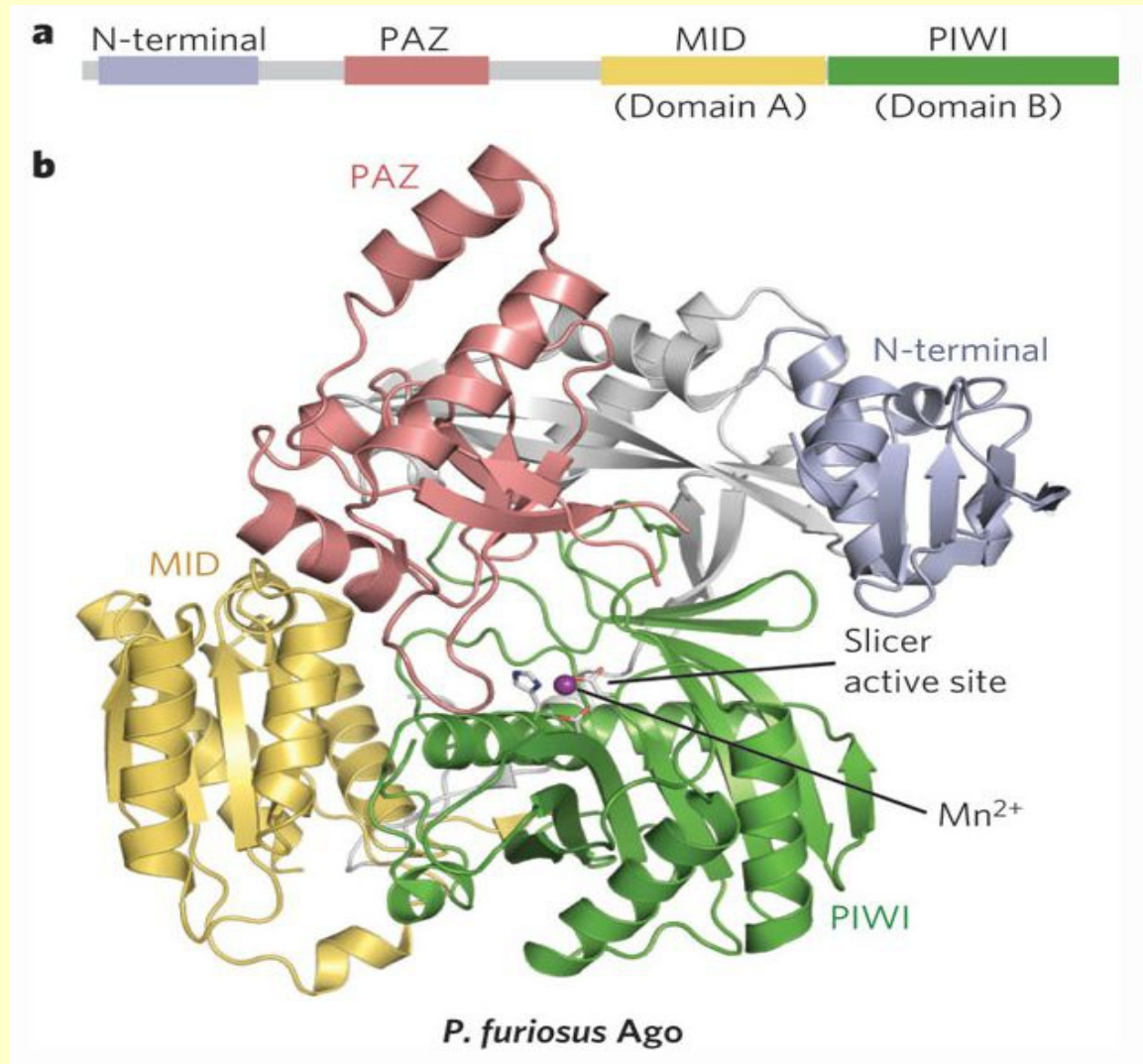


# MicroRNAs Commonly Associated with Human Cancer

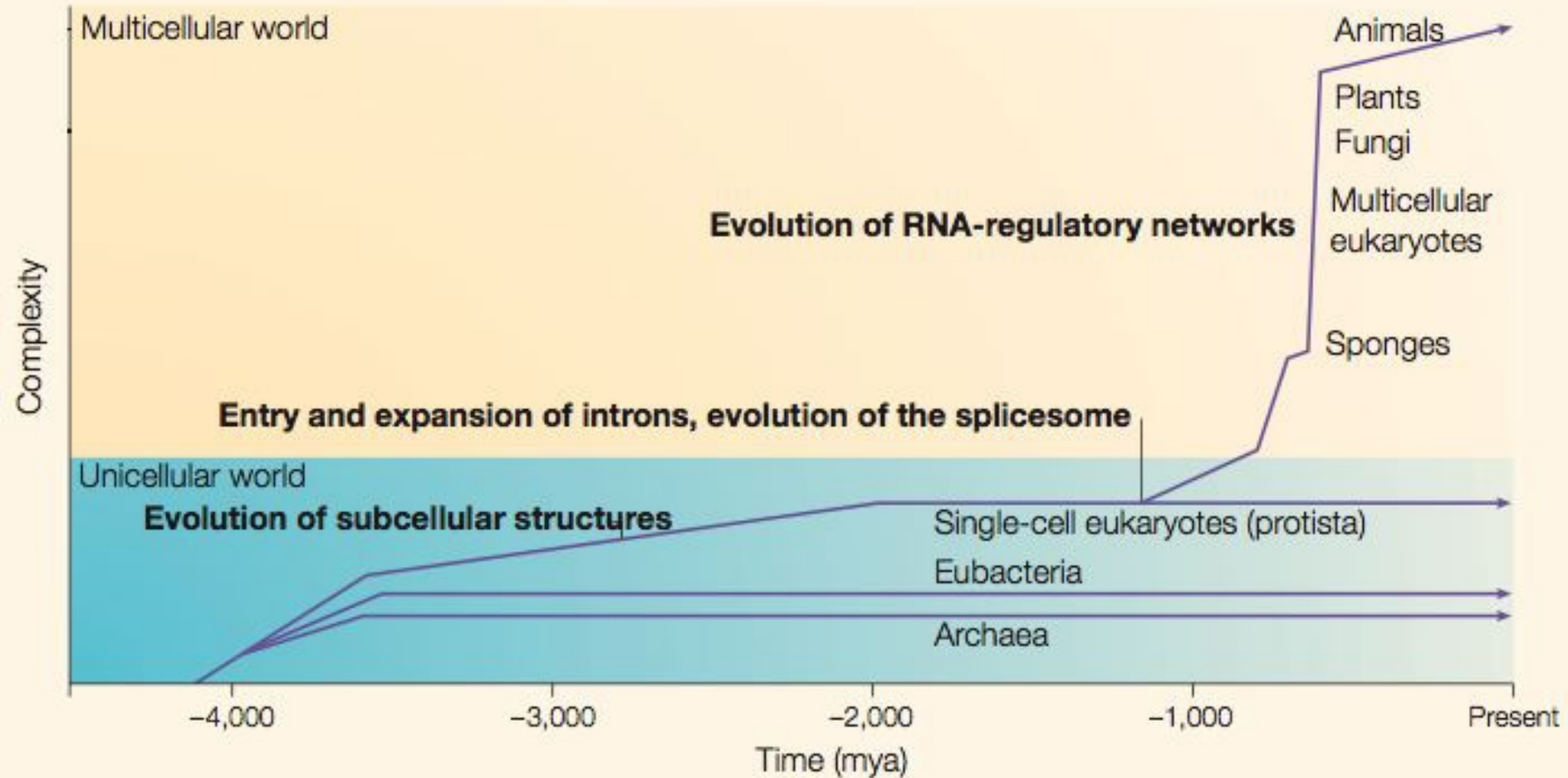
miRNA	Gene Loci	Cancer association	Function*	References
<b>miR15, miR-16</b>	chromosome 13q14	Frequently deleted/downregulated in B-cell chronic lymphocytic leukemia. Negatively regulates the anti-apoptotic gene, BCL2.	TS	Calin, 2002 Cimmino, 2005
<b>miR-143, miR-145</b>	chromosome 5q3233	Decreased abundance in colorectal cancer. Down-regulated in breast, prostate, cervical, and lymphoid cancer celllines. miR-145 decreased in breast cancer.	TS	Michael, 2003 Iorio, 2005
<b>miR-21</b>	chromosome 17q23.2	Antiapoptotic factor. Upregulated in glioblastomas and breast cancer.	OG	Chan, 2005 Ciafre, 2005 Iorio, 2005
<i>let-7</i>	multiple loci	Negatively regulates the Ras oncogene. Directs cell proliferation, differentiation. Decreased abundance in lung cancer.	TS	Johnson, 2005 Takamizawa, 2004
<b>miR-142</b>	chromosome 17q22	t(8,17) translocation that places the MYC oncogene downstream of the <i>mir-142</i> hairpin resulting in an aggressive B cell leukemia due to MYC over-expression.	N/A	Lagos-Quintana, 2002
<b>BIC/miR-155</b>	chromosome 21q21	Upregulated in pediatric Burkitt's lymphomas, Hodgkins, primary mediastinal and diffuse large B cell lymphomas. Upregulated in human breast cancer.	OG	Eis, 2005 Kluiver, 2005 van den Berg, 2003 Metzler, 2003 Iorio, 2005
<b>miR-17-19b cluster</b>	chromosome 13q3132	Upregulated by the c-Myc oncogene Negatively modulates E2F1 oncogene.  Loss-of-heterozygosity of cluster in hepatocellular carcinoma. Over-expressed in B cell lymphomas.	TS/ OG	He, 2005 O'Donnell, 2005

\*Abbreviations: TS, tumor-suppressor gene; OG oncogene; N/A, not applicable

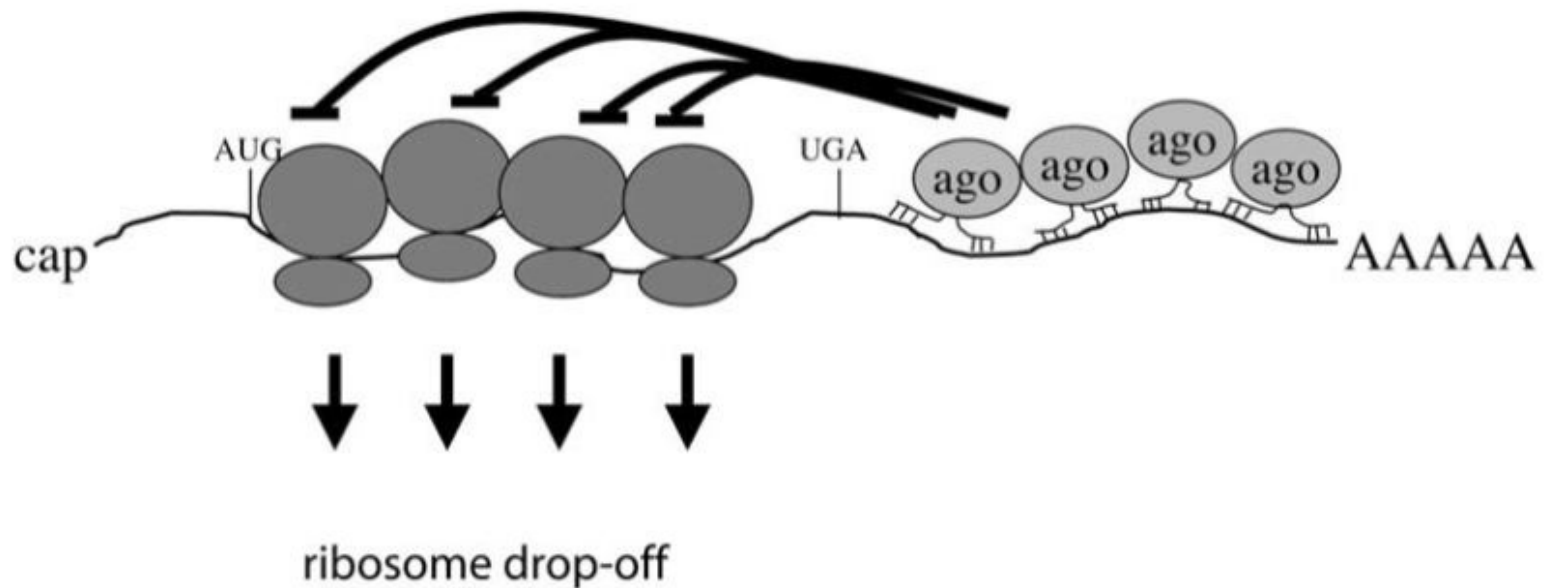
# Argonaute Structure and Function



# A Simplified History of Life on Earth



# miRNAs Inhibit Translation by Inducing Ribosome Drop-Off



# The miR-17-92 cluster accelerates Myc-induced lymphomagenesis

