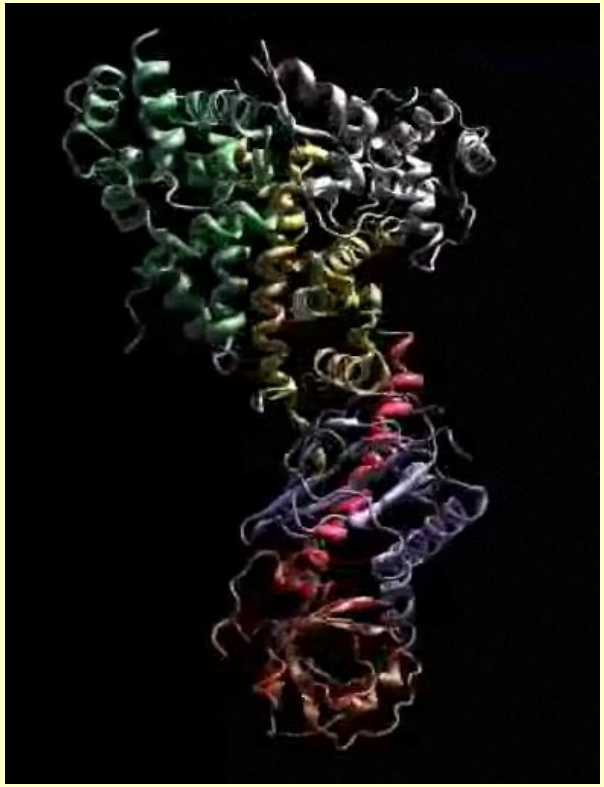
# Genomics, Bioinformatics & Medicine

http://biochem158.stanford.edu/

## miRNA Regulatory Networks

http://biochem158.stanford.edu/Gene%20Expression.html



Doug Brutlag
Professor Emeritus of Biochemistry & Medicine
Stanford University School of Medicine

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# Gene Regulatory Mechanisms

- Transcriptional Mechanisms
  - Type of promoters & RNA polymerase
  - 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
  - Histone acetylation
  - DNA methylation

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# The ENCODE Project

http://www.nature.com/news/encode-the-human-encyclopaedia-1.11312

- 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.

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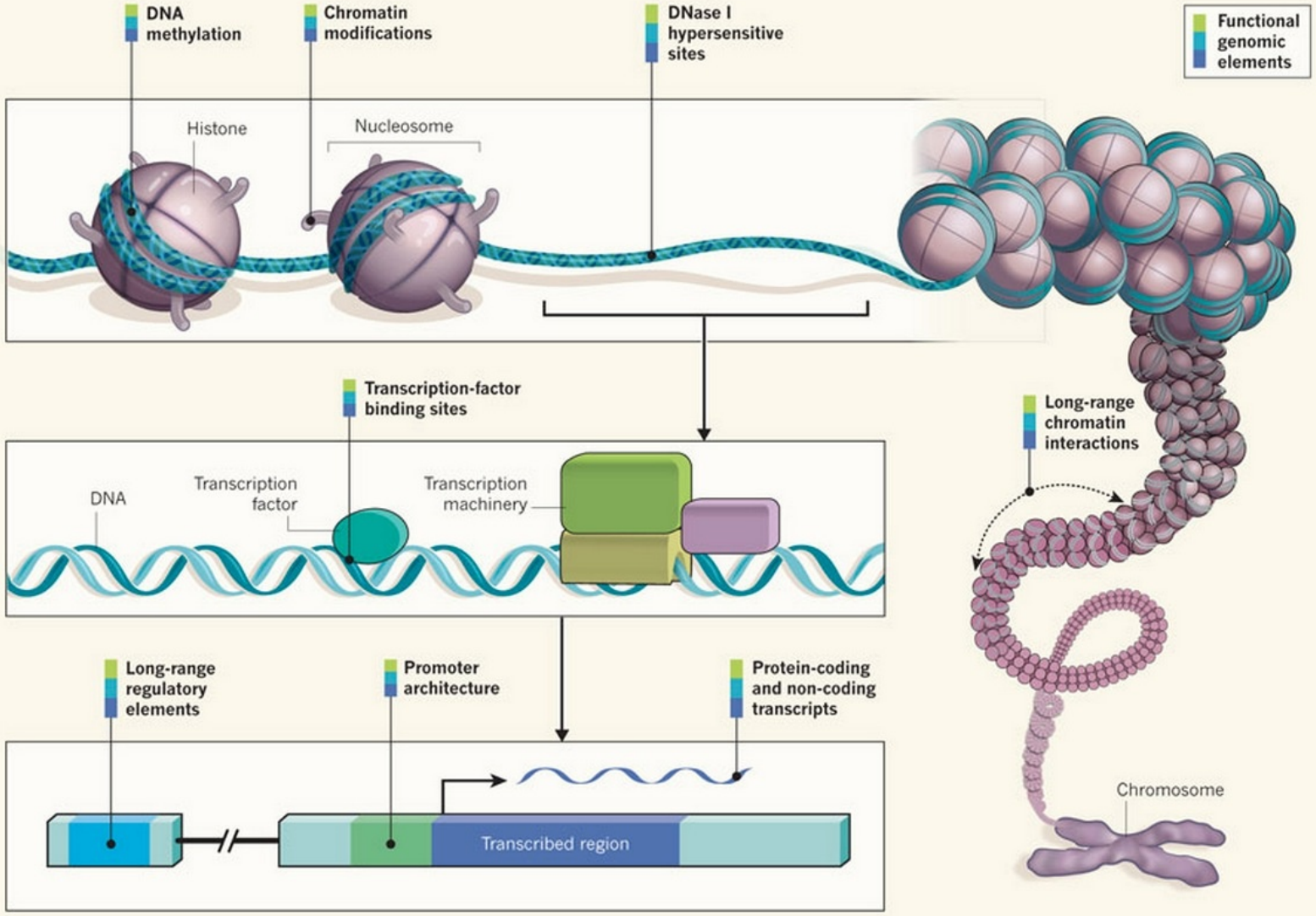
# ENCODE Explained

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

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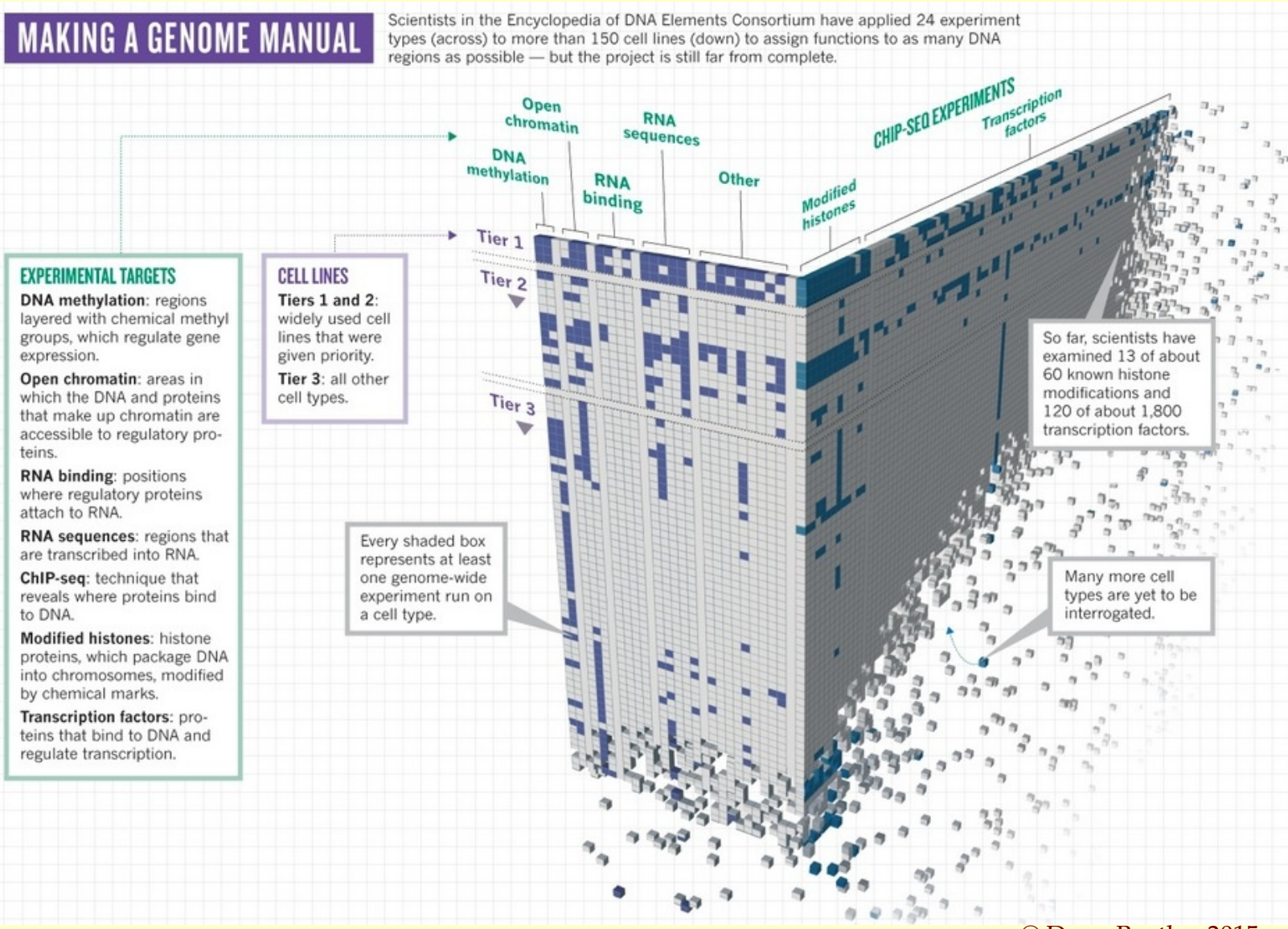
# Making a Genome Manual

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

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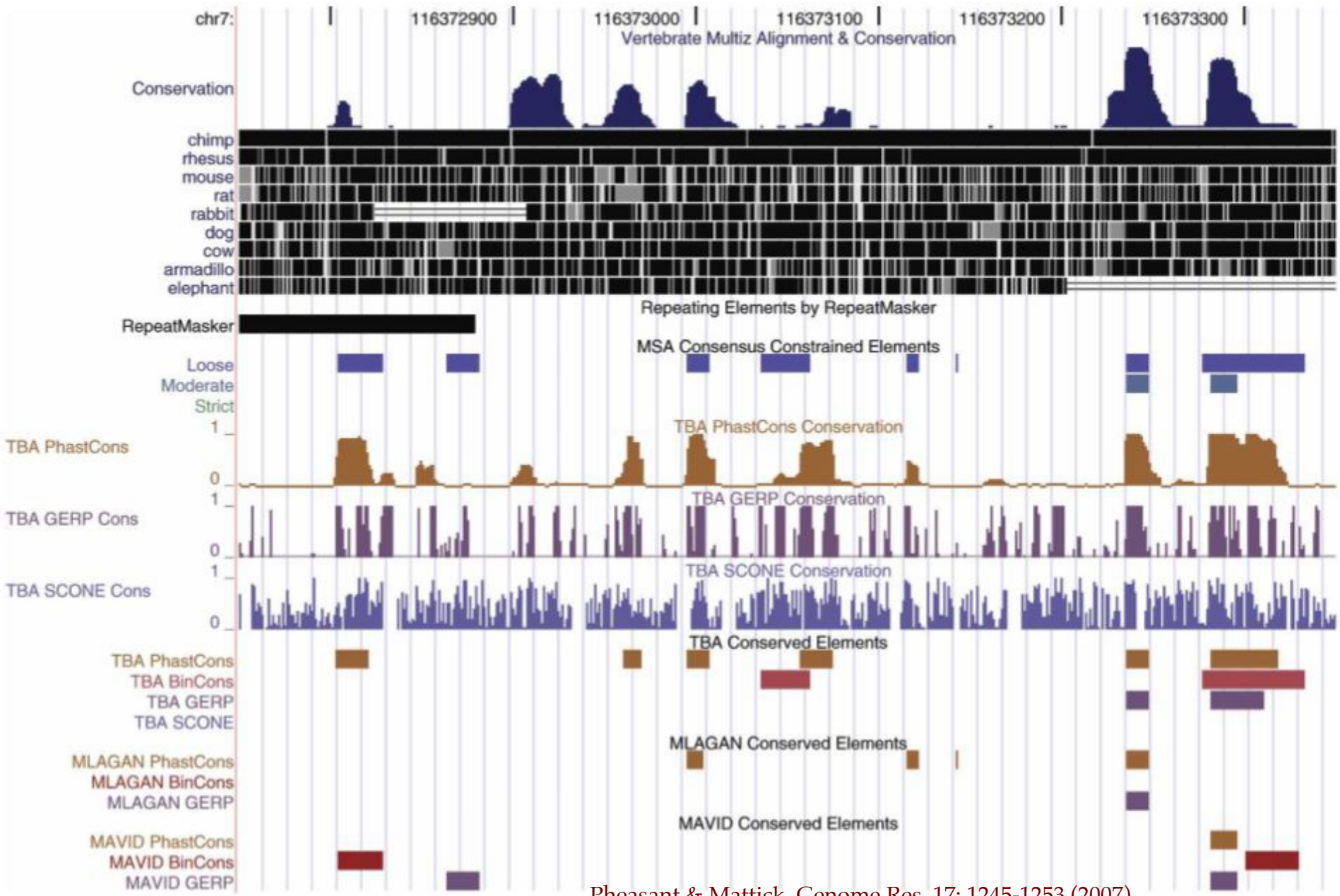
# Conserved Regions in CFTR Intron




Pheasant & Mattick, Genome Res. 17: 1245-1253 (2007)

# Epigenome Roadmap

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

## Epigenome Roadmap

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Advanced search

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Welcome to the Epigenome Roadmap! Here, we have collected research papers describing the main findings of the NIH Roadmap Epigenomics Program, the aim of which was to systematically characterize epigenomic landscapes in primary human tissues and cells. The papers are complemented by eight threads each of which highlights a topic that runs through more than one paper. Threads are designed to help you explore the wealth of information collectively published across several Nature Publishing Group journals. Each thread consists of relevant paragraphs, figures and tables from across the papers, united around a specific theme.

We invite you to explore the research content, the News & Views, the video and other associated material.

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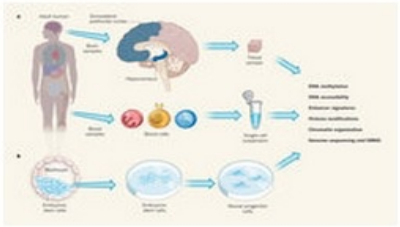
### News and Multimedia

Nature News | Editorial

**Beyond the genome**



Nature | News and Views

**Epigenomics: Roadmap for regulation**

Nature News | News

**Epigenome: The symphony in your cells**

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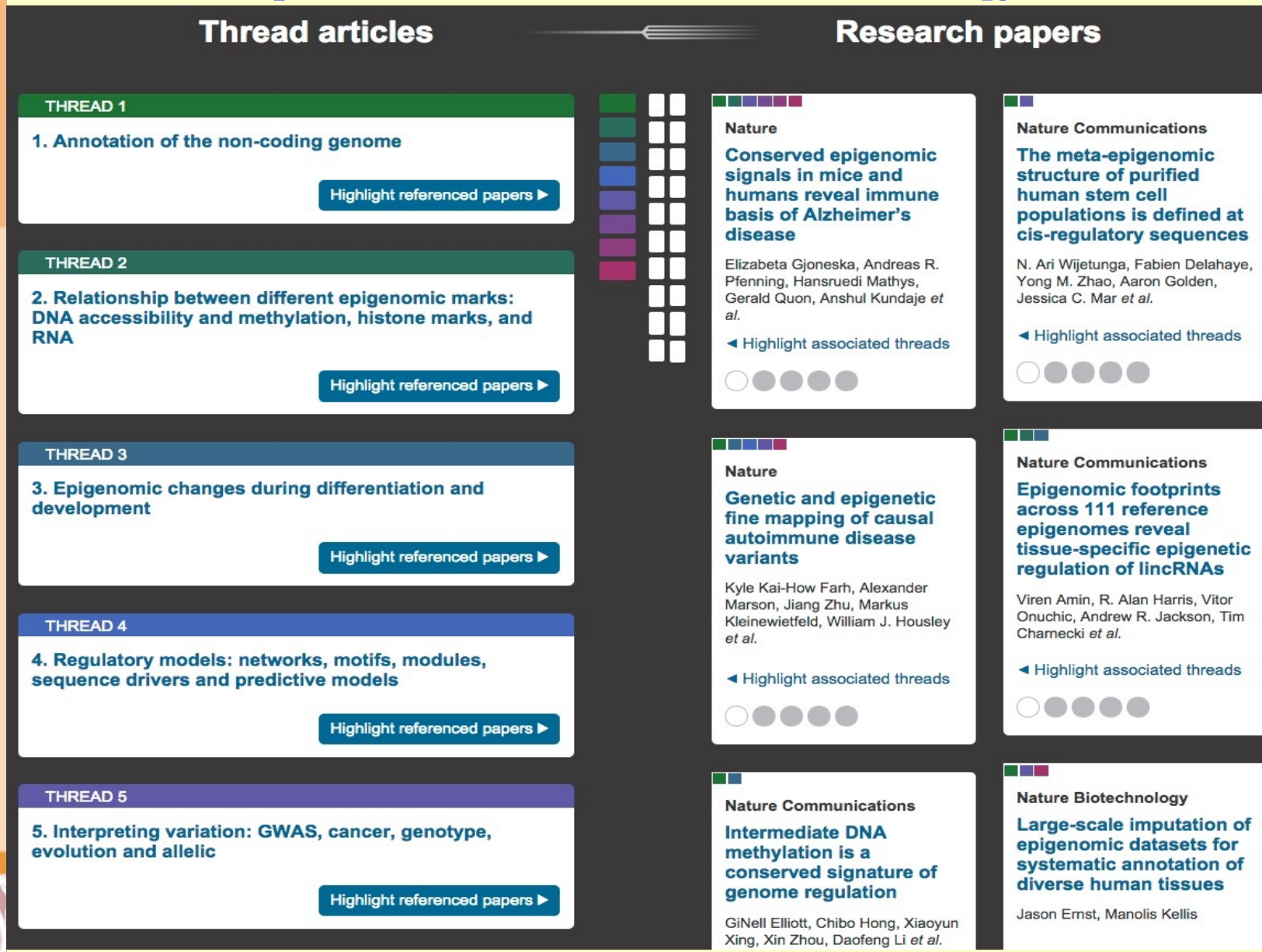
# Epigenome Roadmap

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

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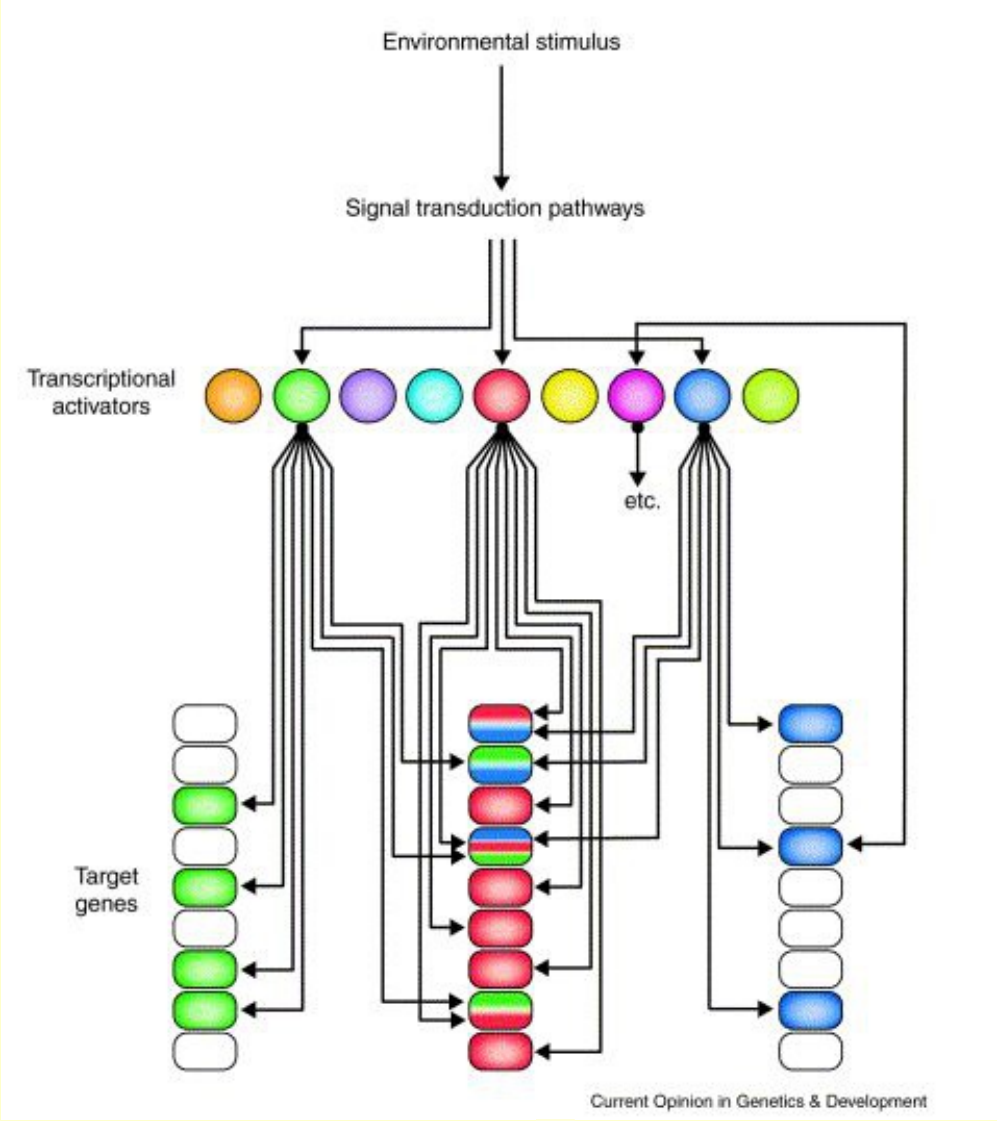
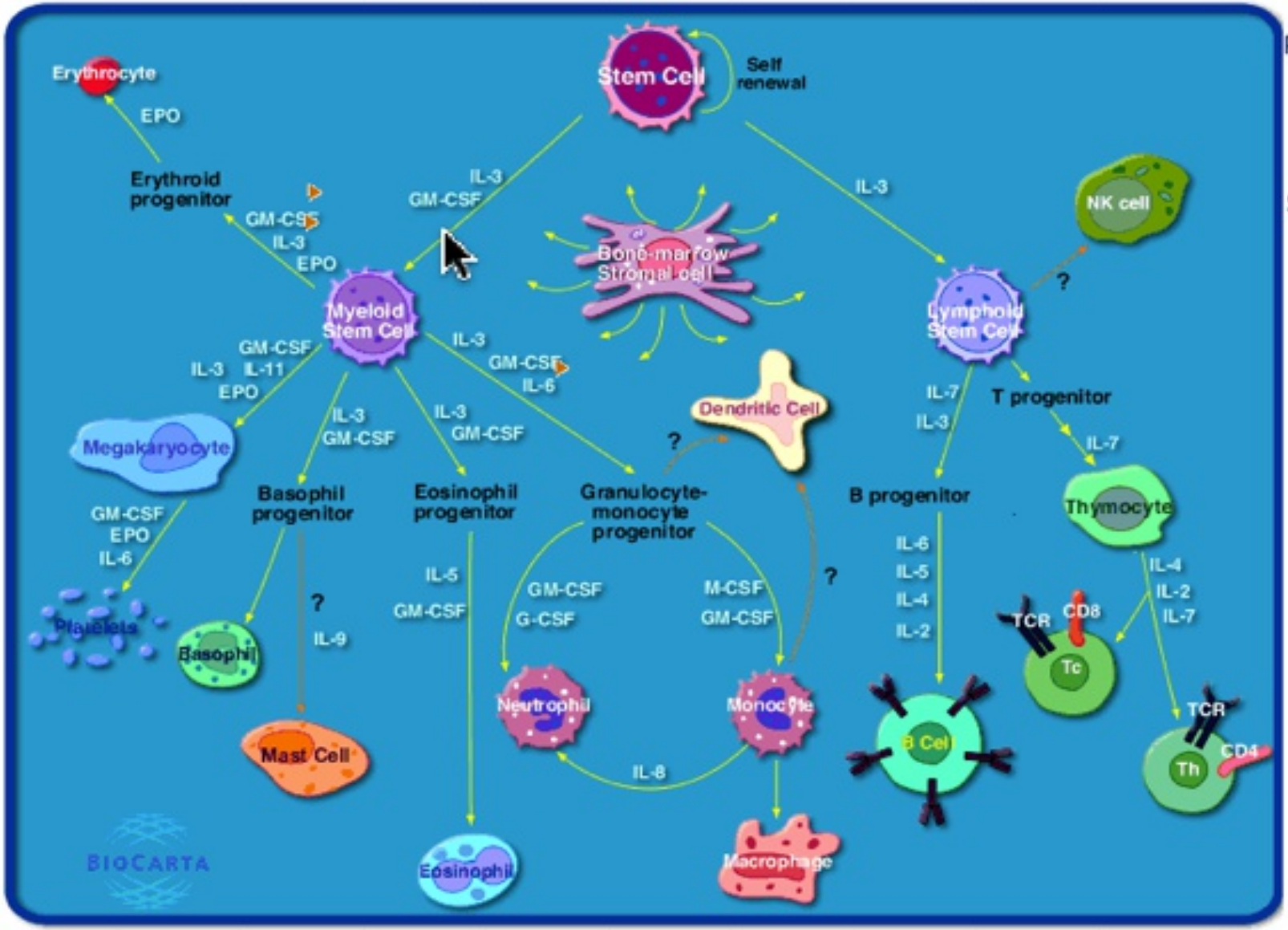
# Gene Expression Regulatory Network




Current Opinion in Genetics & Development

# Hematopoiesis

http://www.biocarta.com/pathfiles/h_stemPathway.asp

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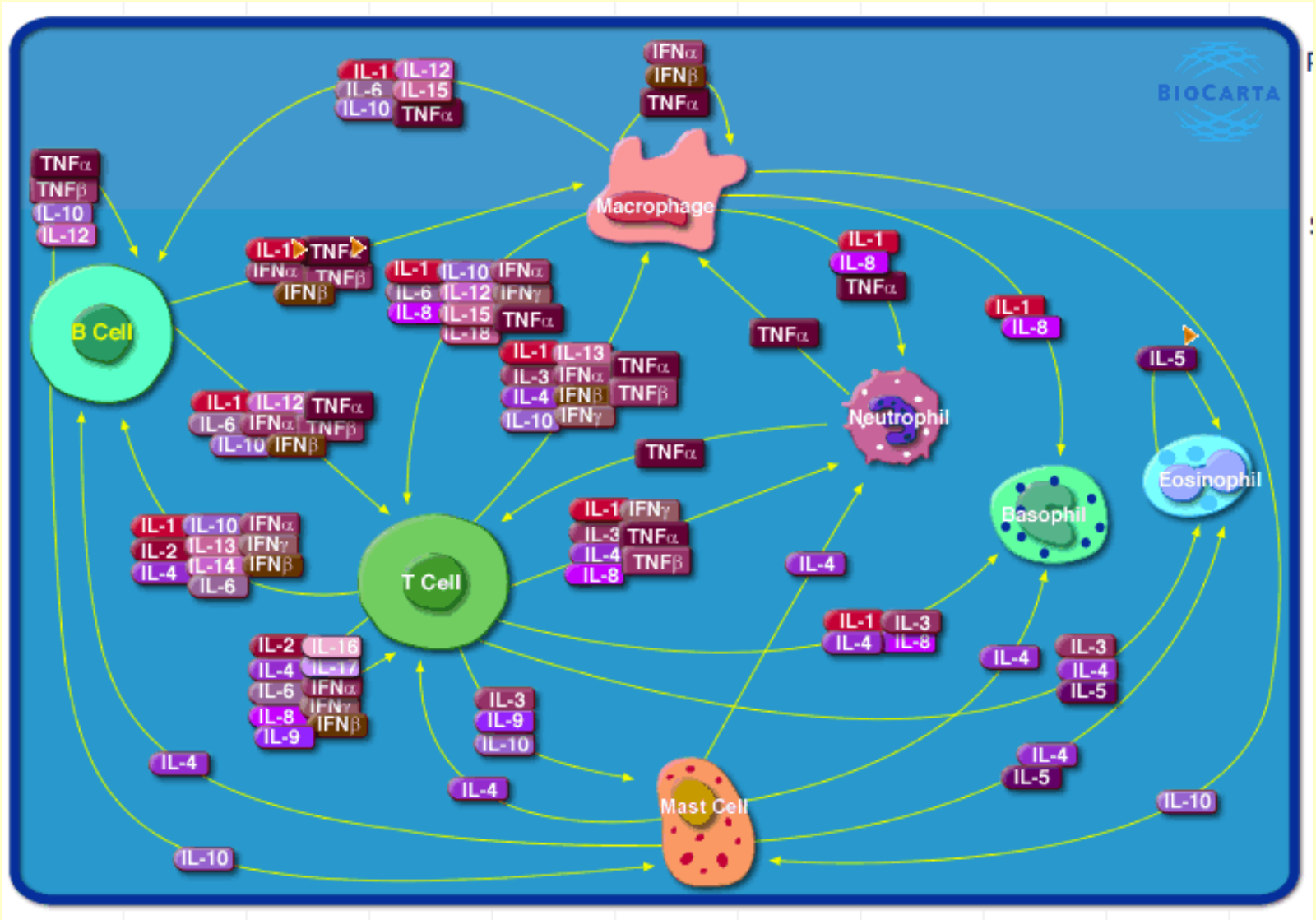
# Cytokine Network

http://www.biocarta.com/pathfiles/h_cytokinePathway.asp

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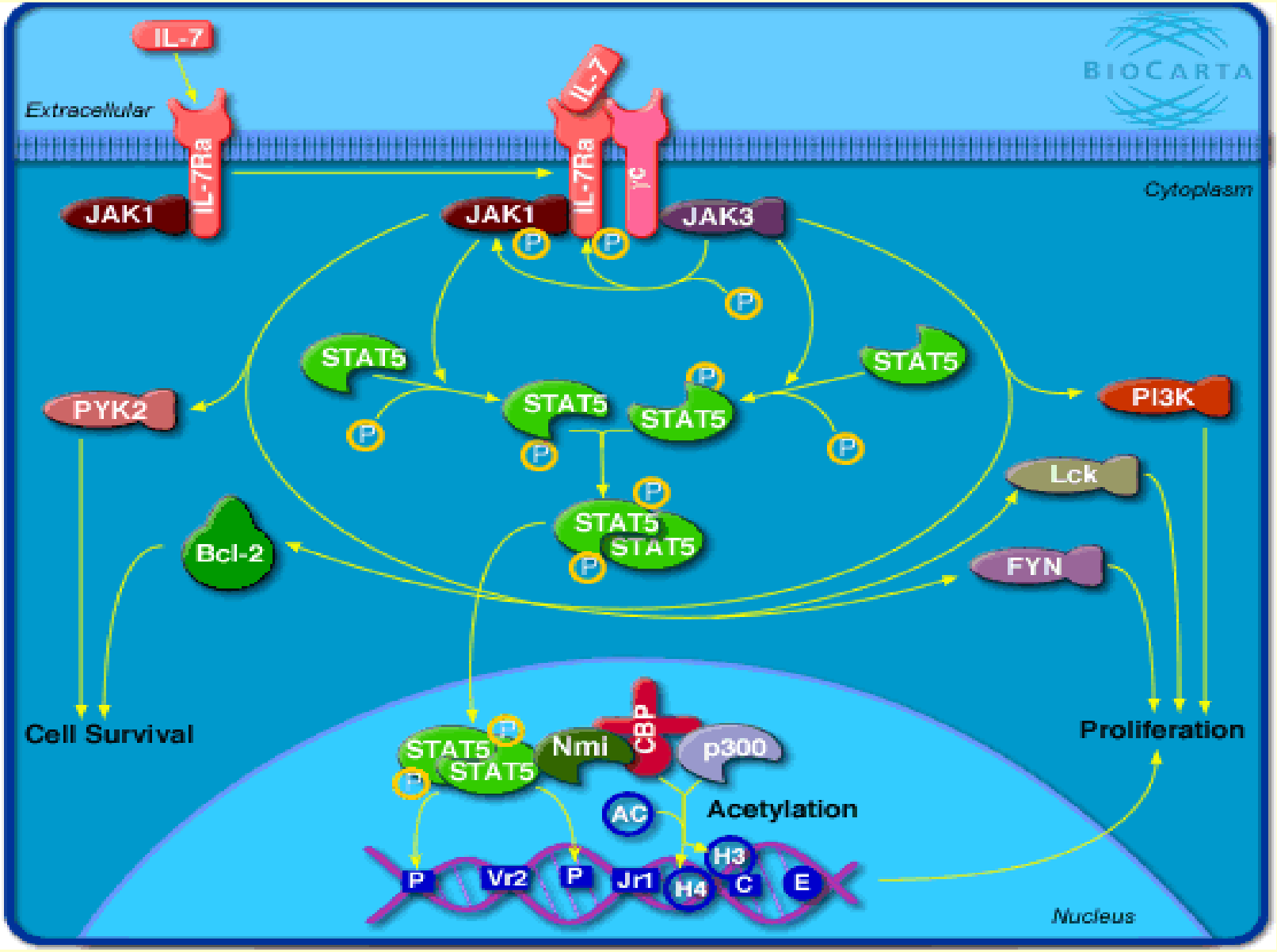
# IL7 Regulatory Pathway

http://www.biocarta.com/pathfiles/h_il7Pathway.asp/

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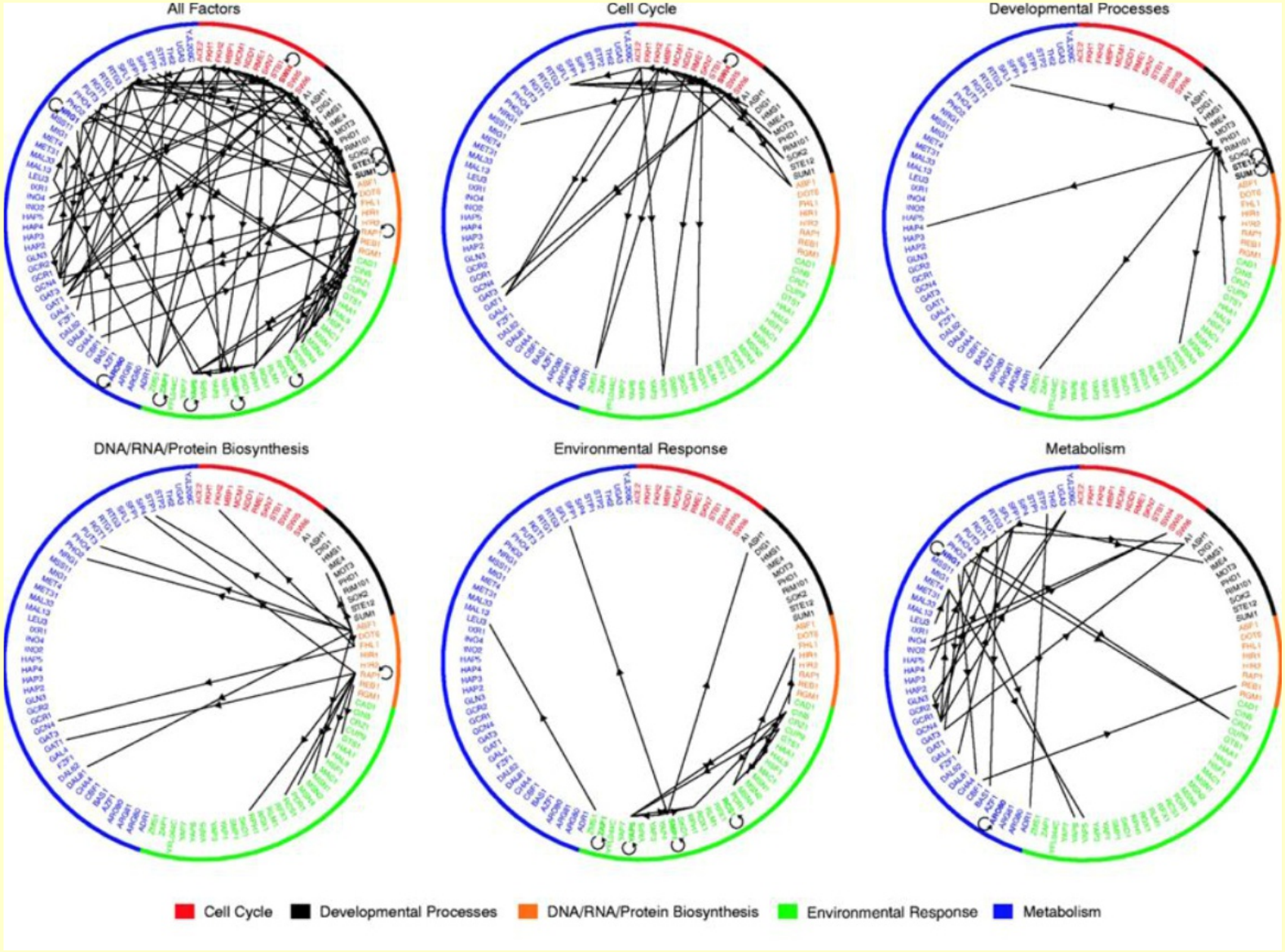
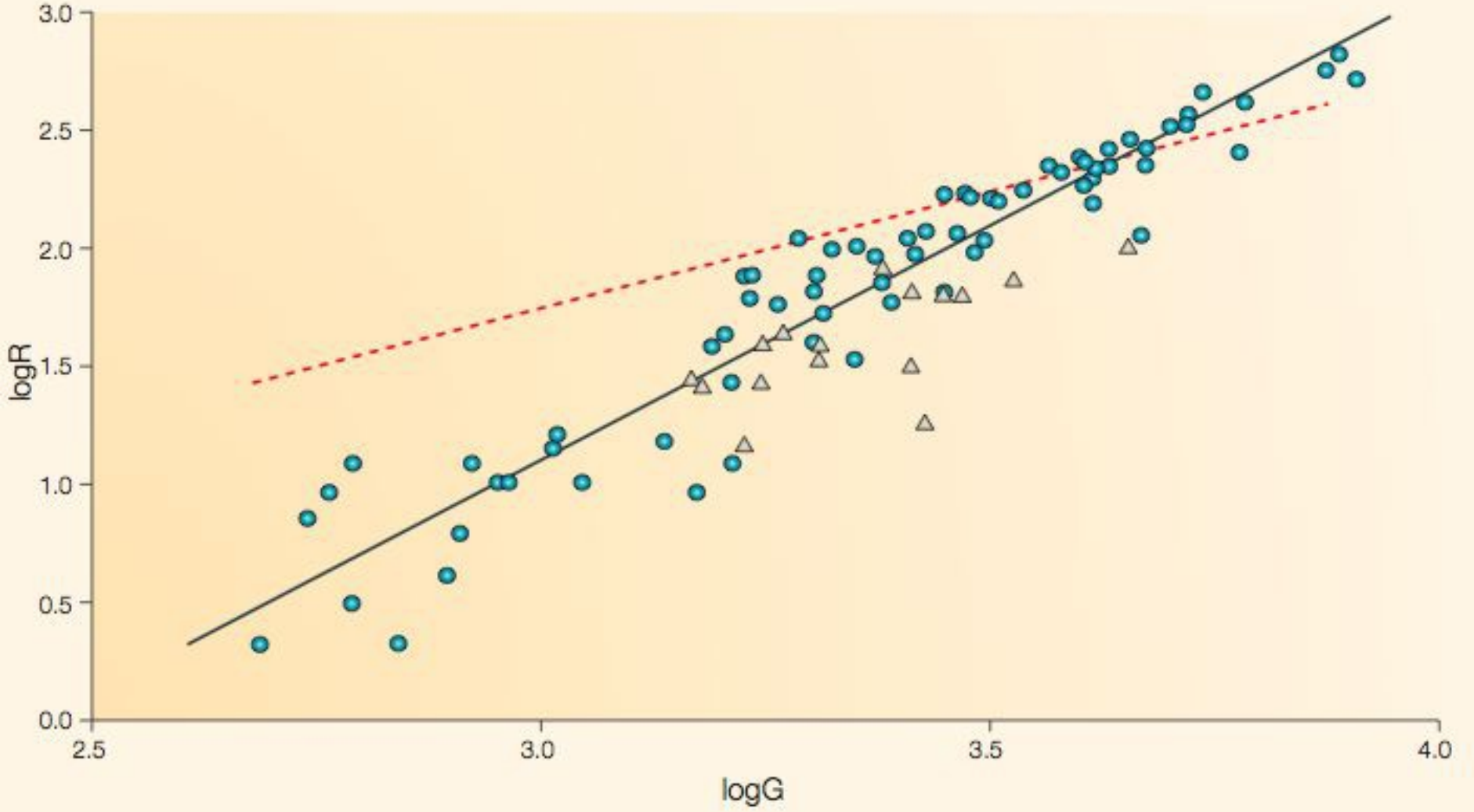
# Yeast Transcription Factors



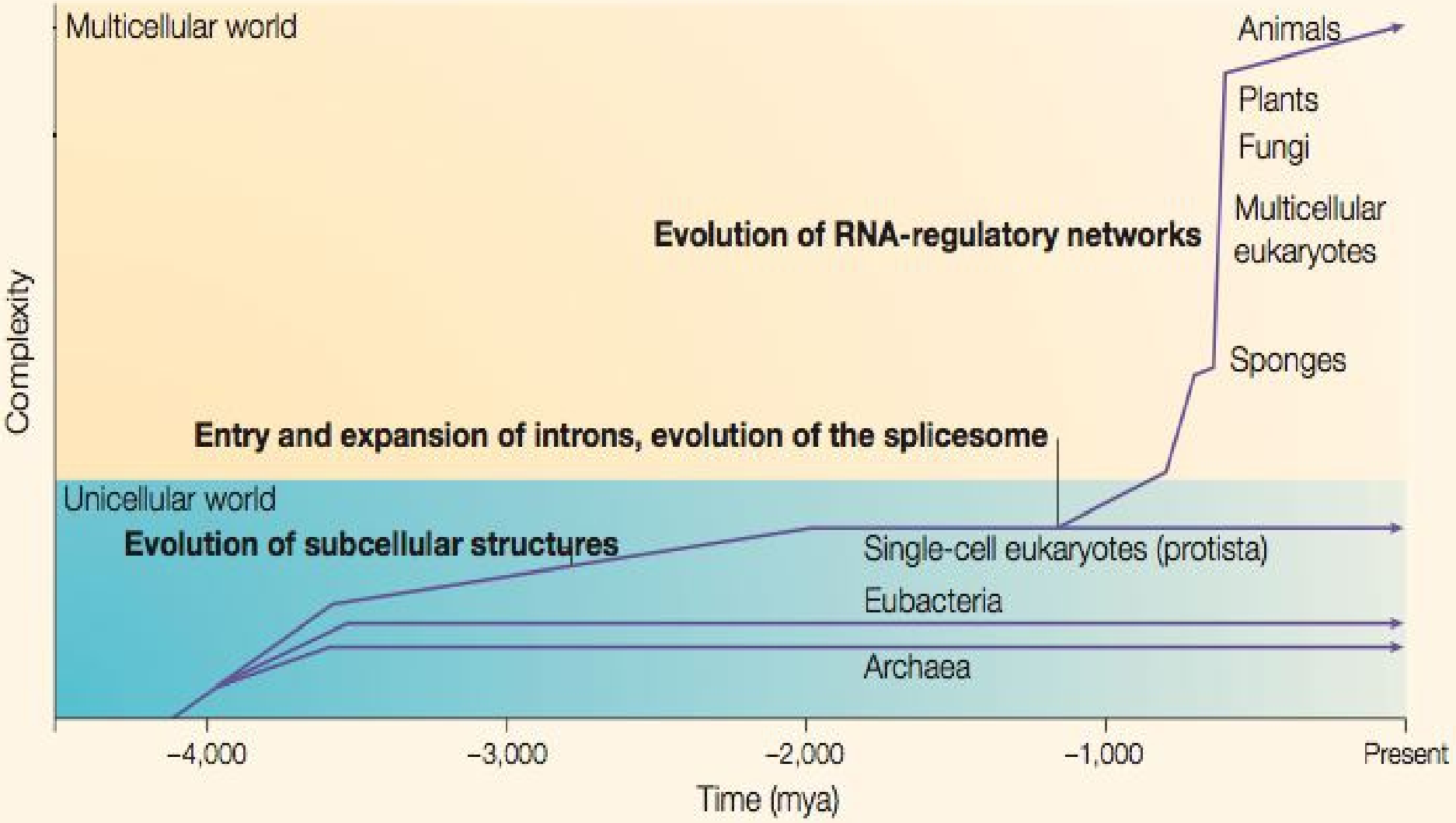

Lee et al. Science 298, 799-804 (2002)

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



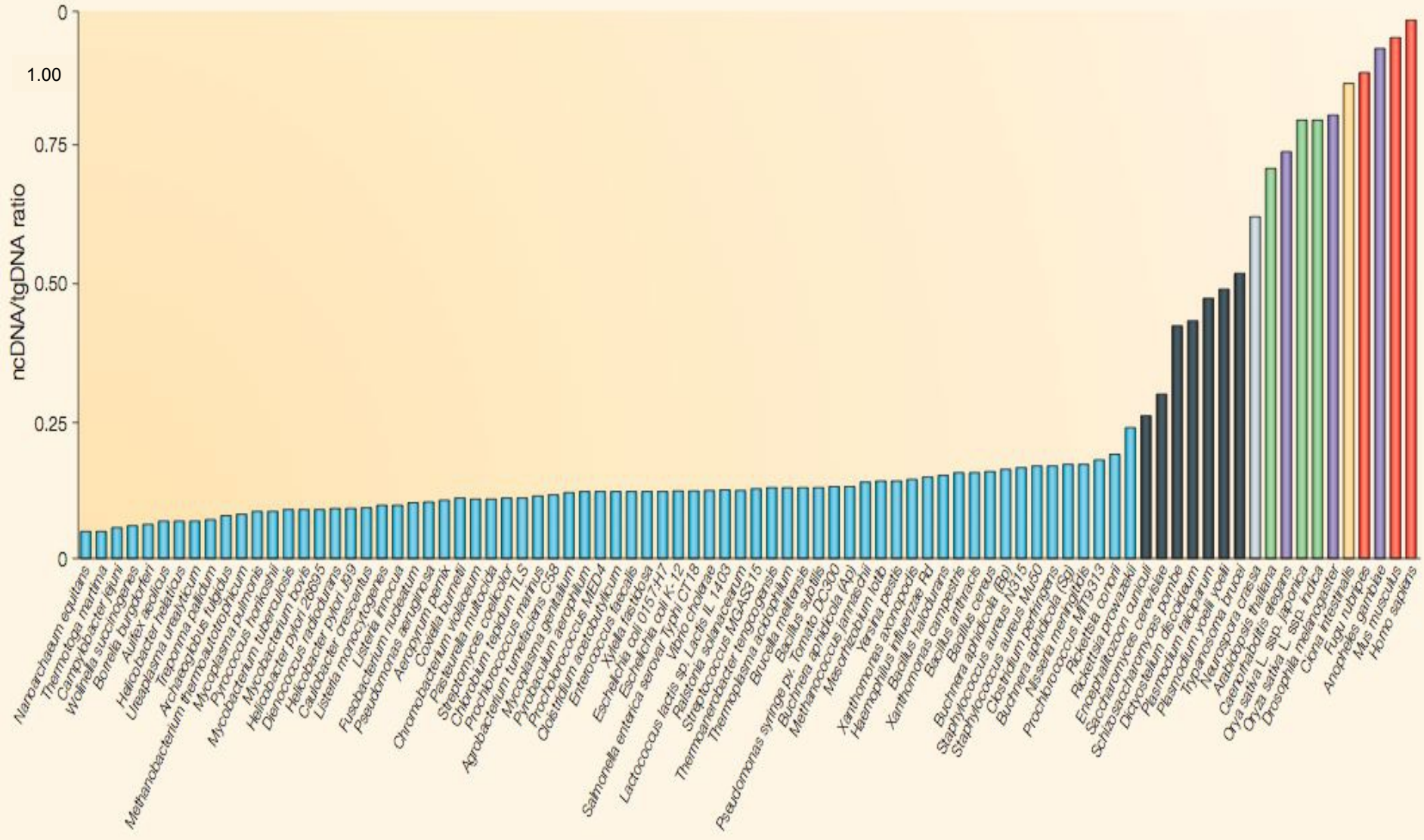

Mattick (2004) Nature Reviews Genetics 5: 316-323.

# A Simplified History of Life on Earth



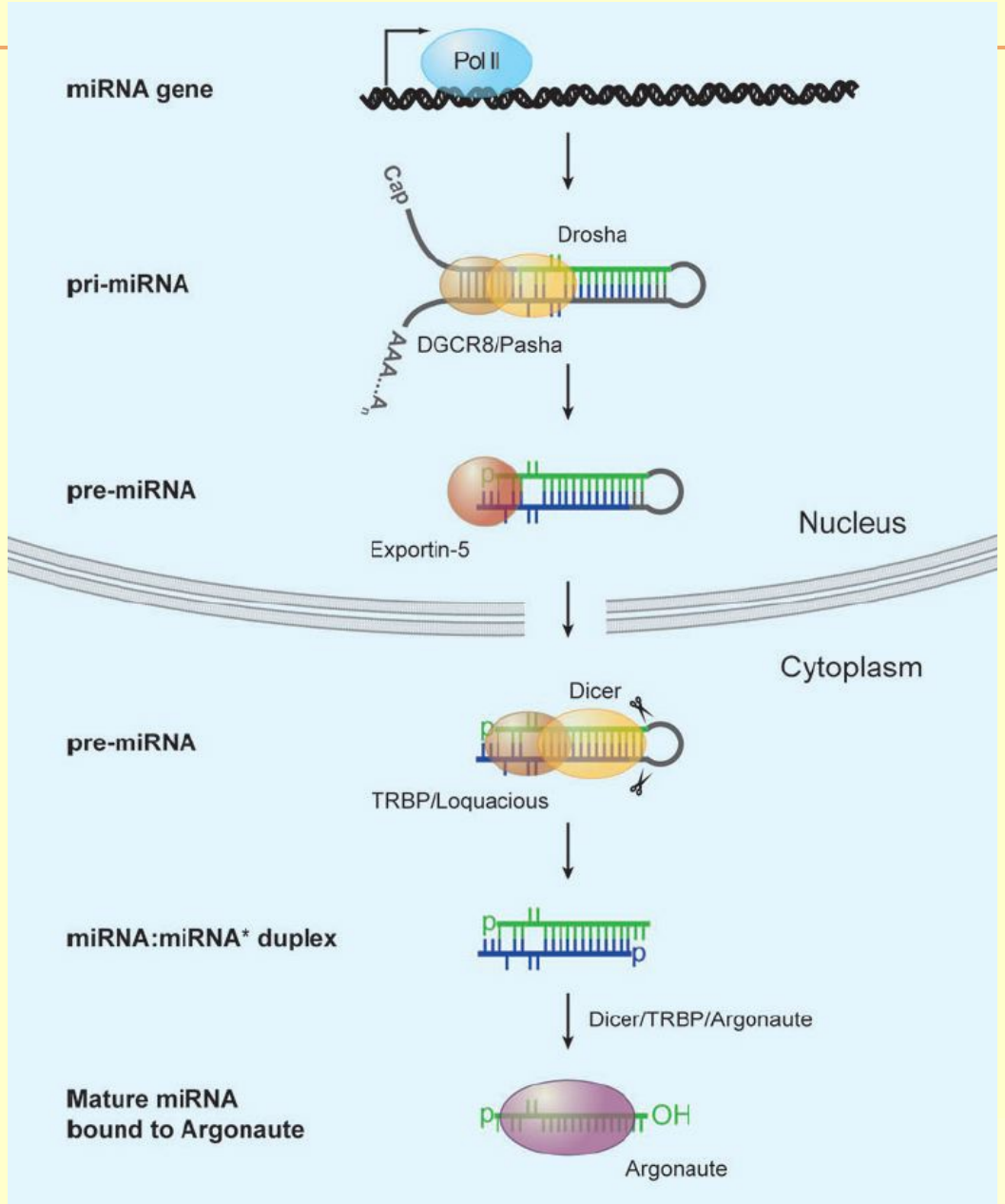

Mattick (2004) Nature Reviews Genetics 5: 316-323.

# Fraction of Non-Protein-Coding DNA During Evolution

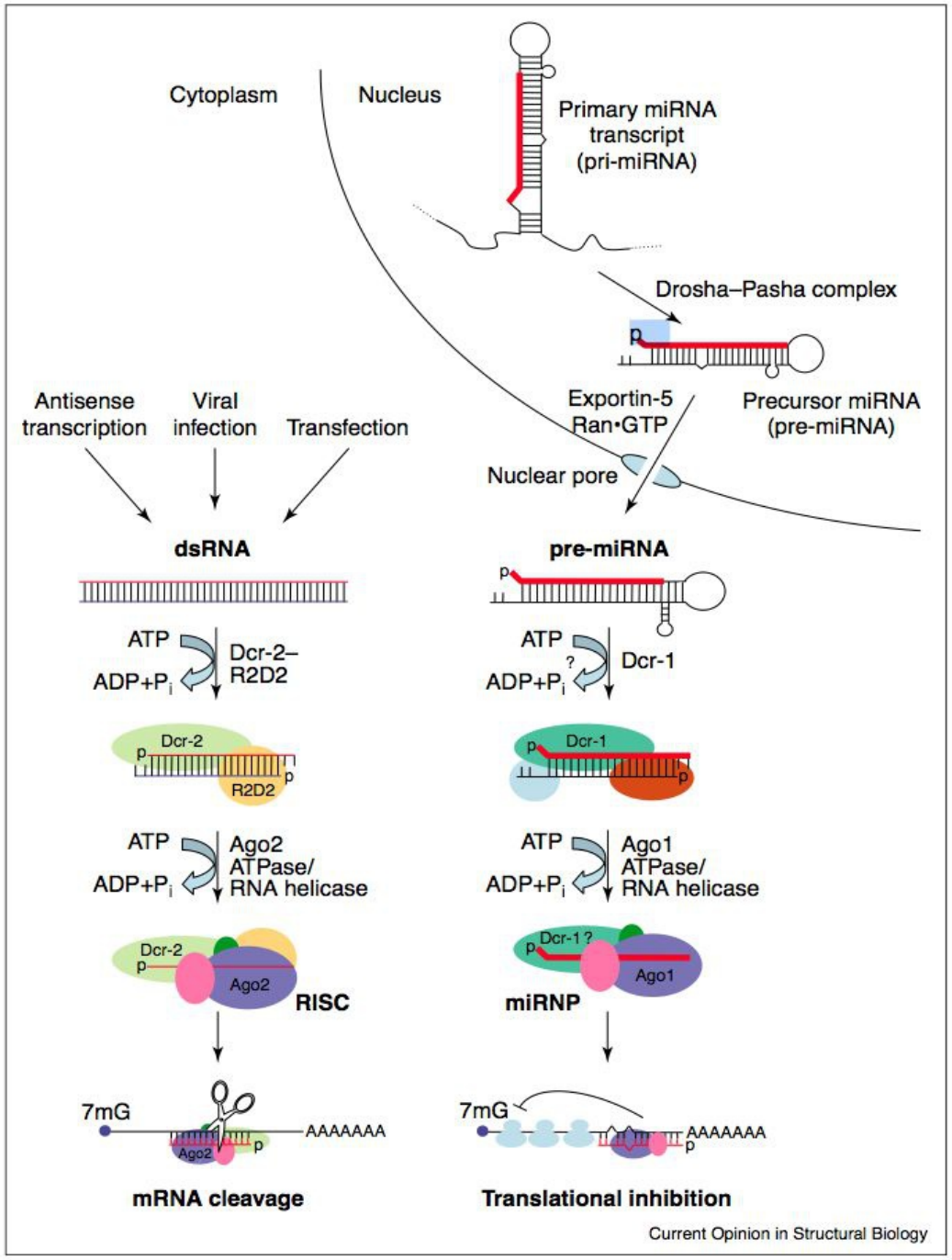



Mattick (2004) Nature Reviews Genetics 5: 316-323.

# microRNA Biogenesis




Annu. Rev. Cell Dev. Biol. 2007.23:175-205



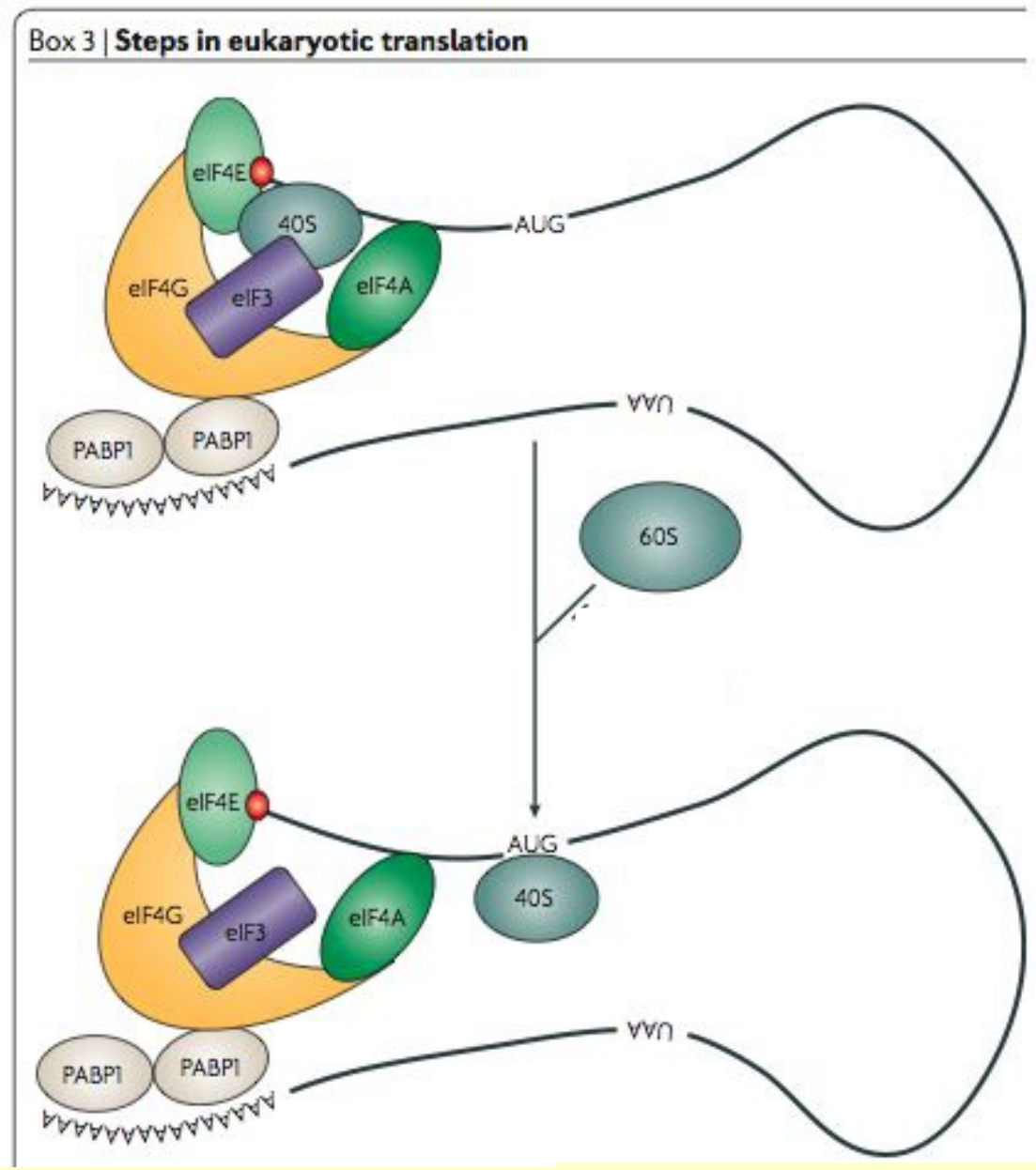

siRNA(or RNAi) mediated degradation of mRNA

versus

miRNA mediated inhibition of mRNA translation

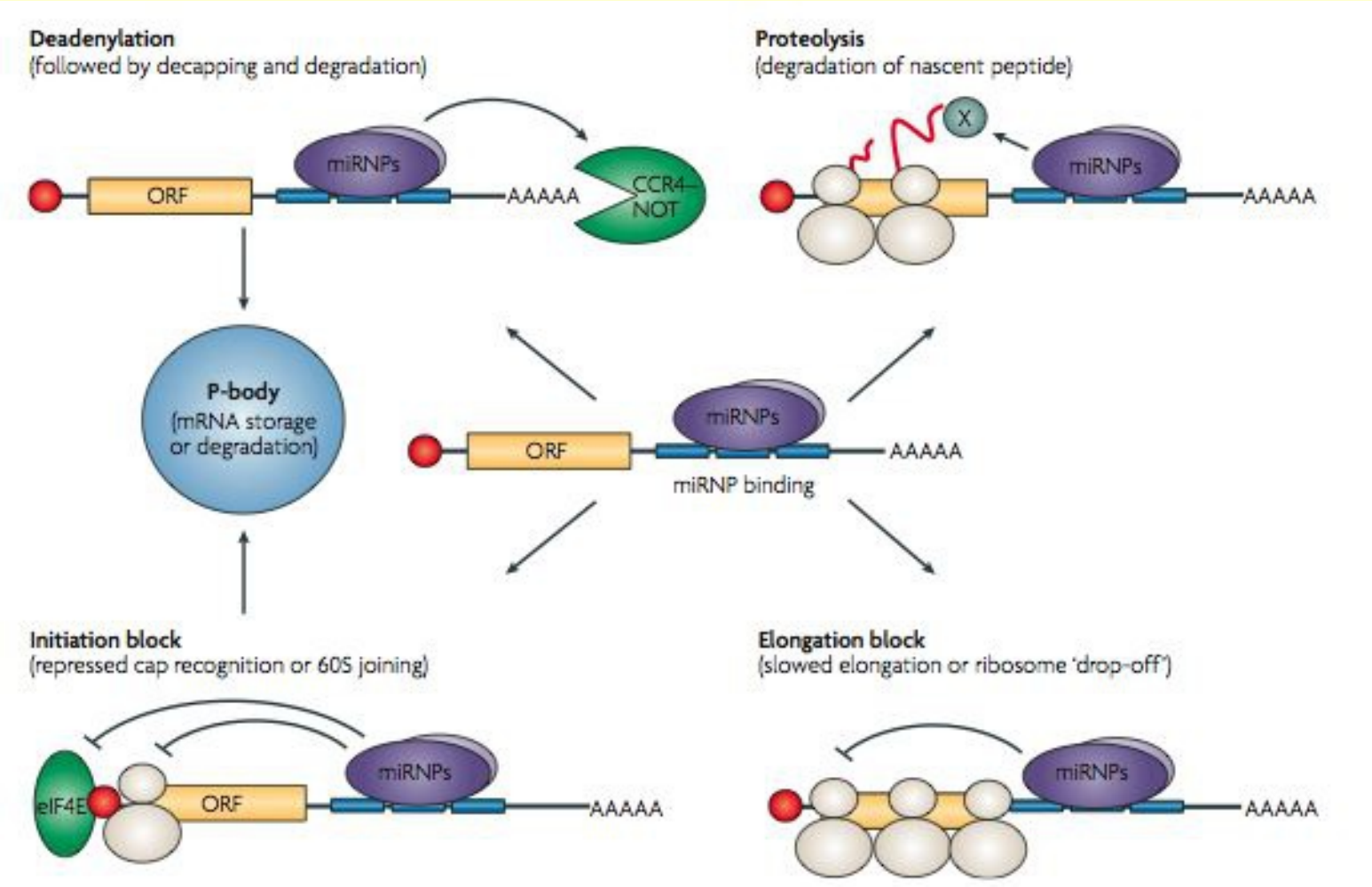
Filipowicz, Curr. Op. Structural Biology 15: 331-341 (2005)

# Initiation of Translation



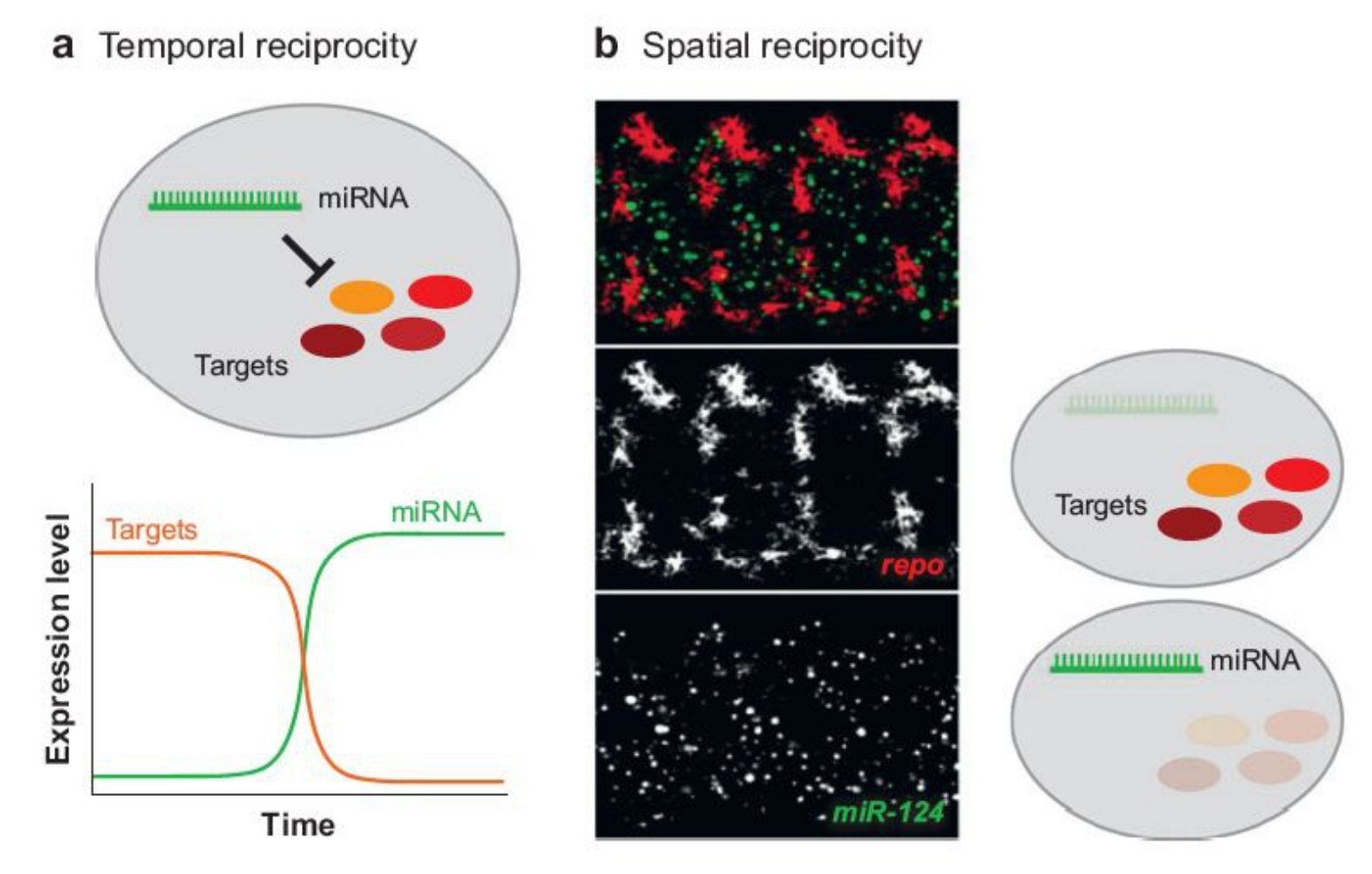

Filipowicz (2008) Nature Review Genetics 9:102-112.

# Mechanisms of Translational Regulation by miRNP Complexes



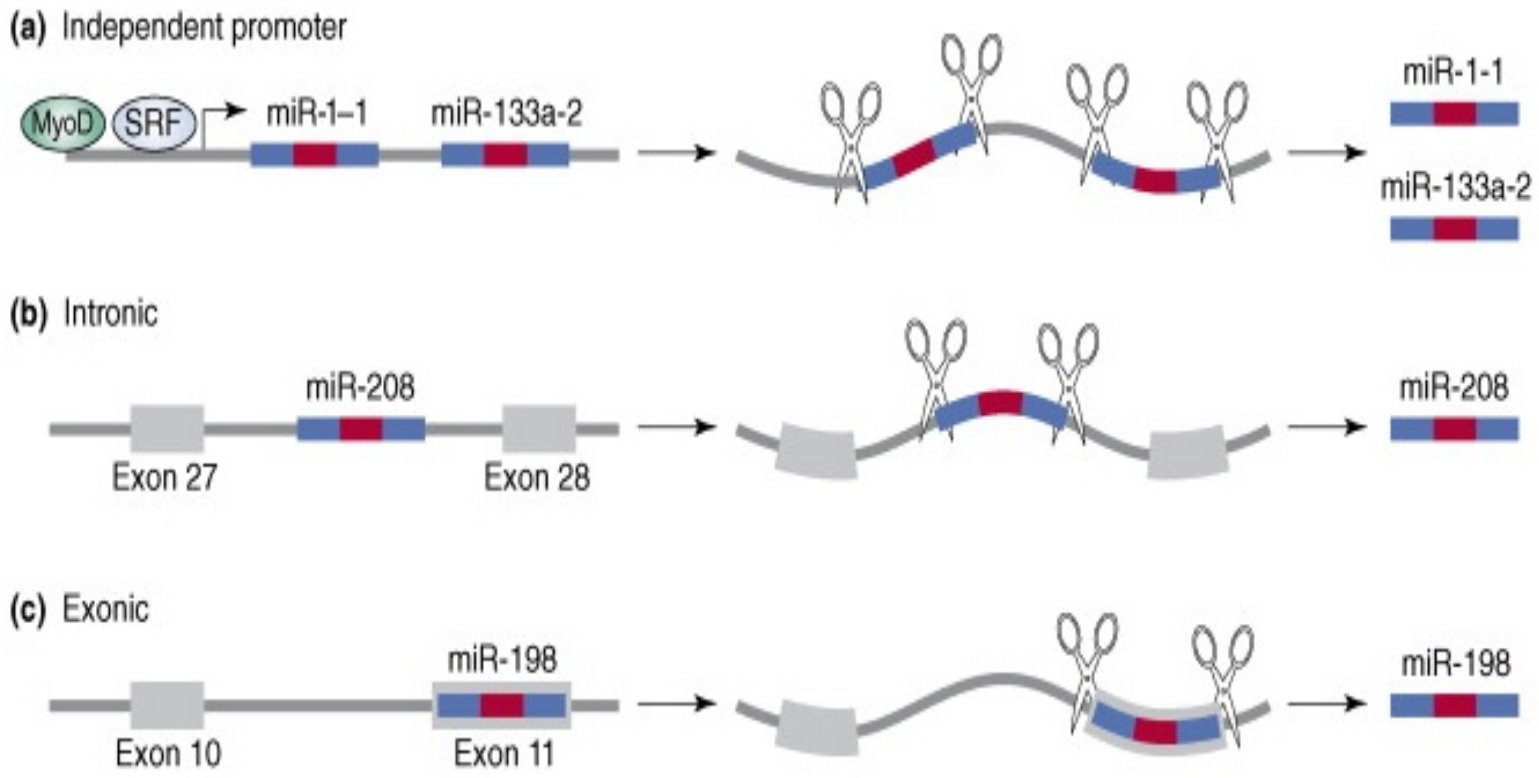

Filipowicz (2008) Nature Review Genetics 9:102-112.

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




Annu. Rev. Cell Dev. Biol. 2007.23:175-205

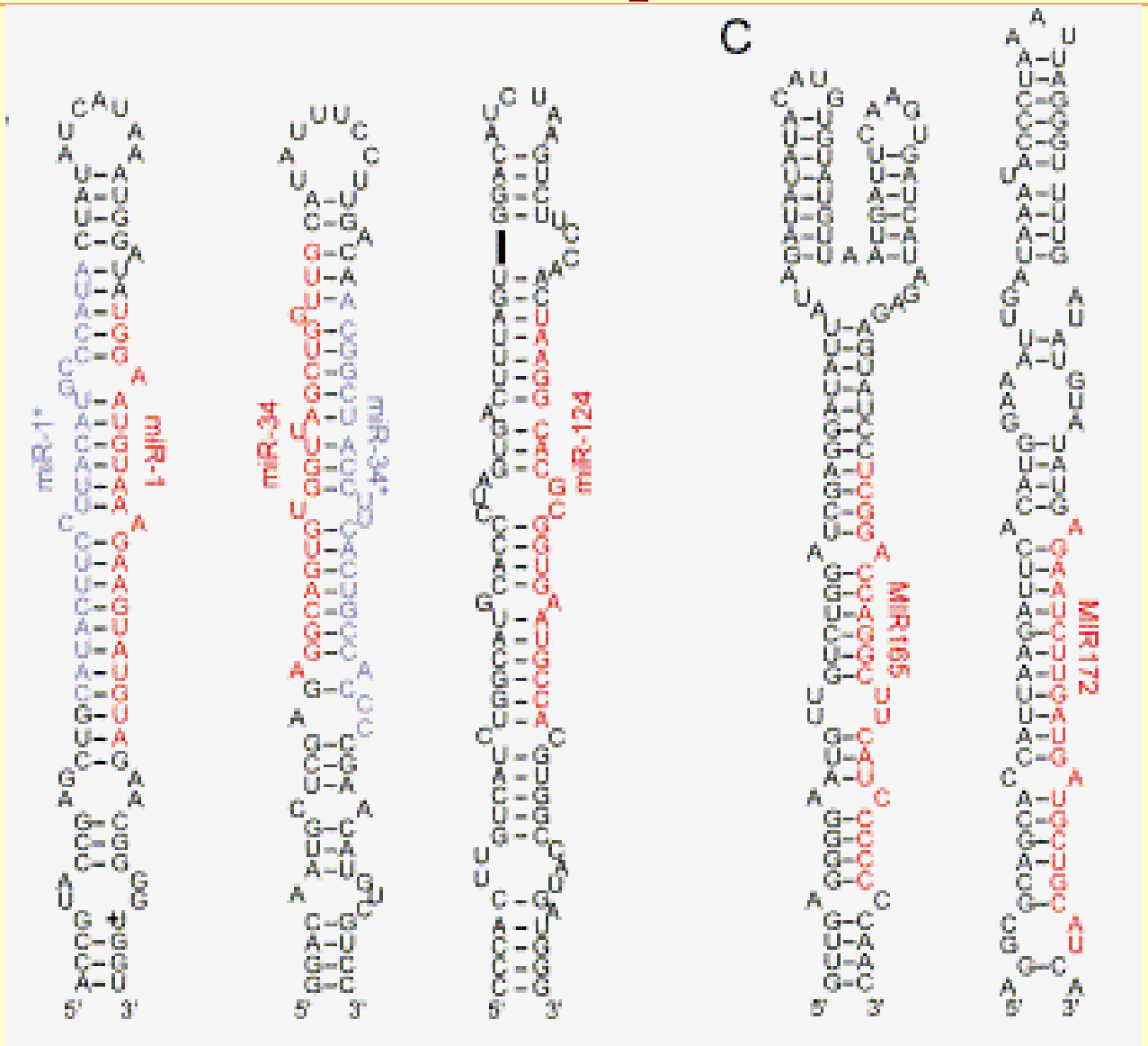
# Genomic Organization of miRNA Genes



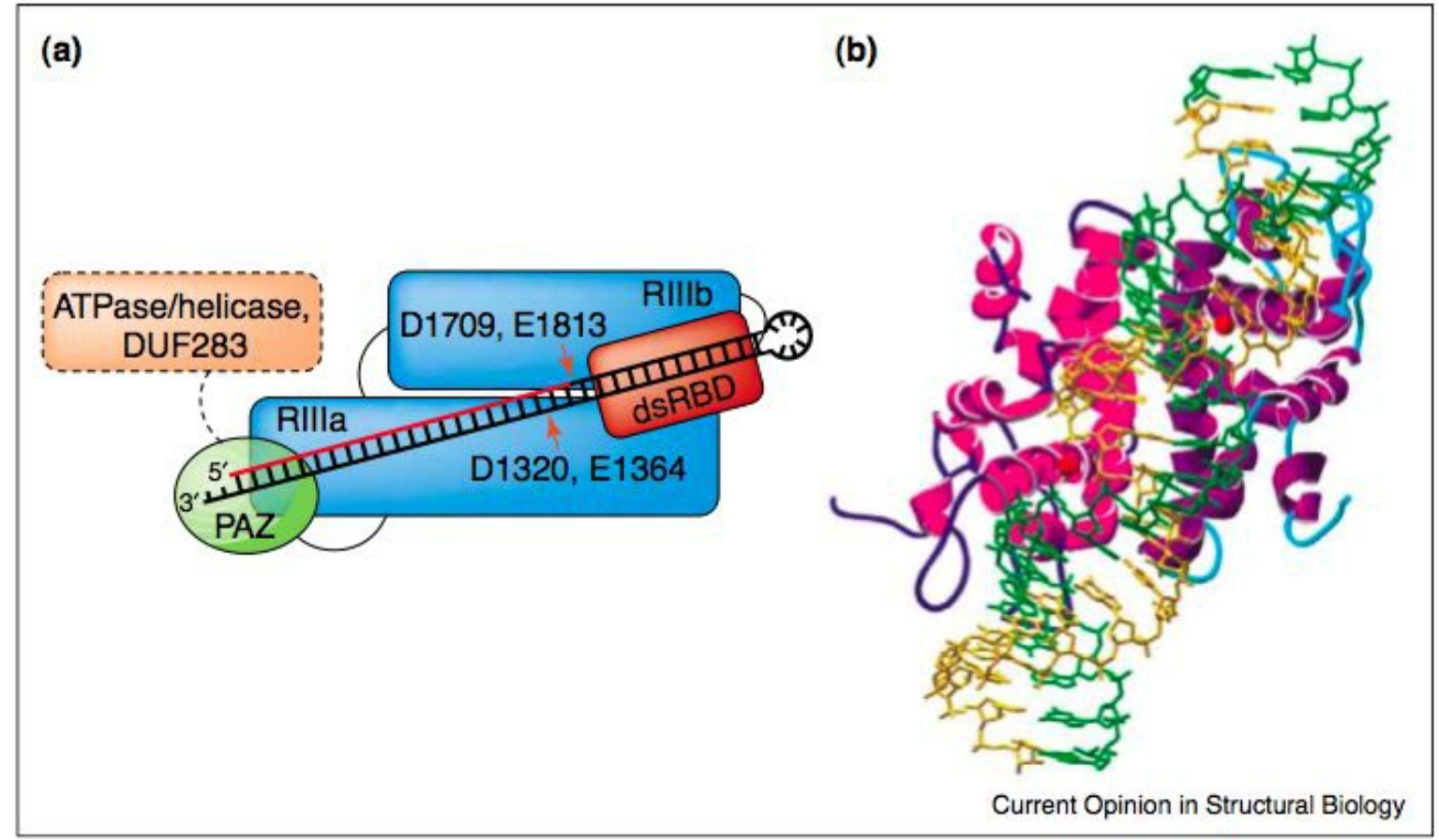

- Intronic miRNAs often in antisense direction, made from own promoter
- Exonic miRNAs - non-coding (or in alternatively spliced exons)

Zhao Y, Srivastava D, TIBS 32:189,2007

# Precursor miRNA Products Form Stem Loop Structures



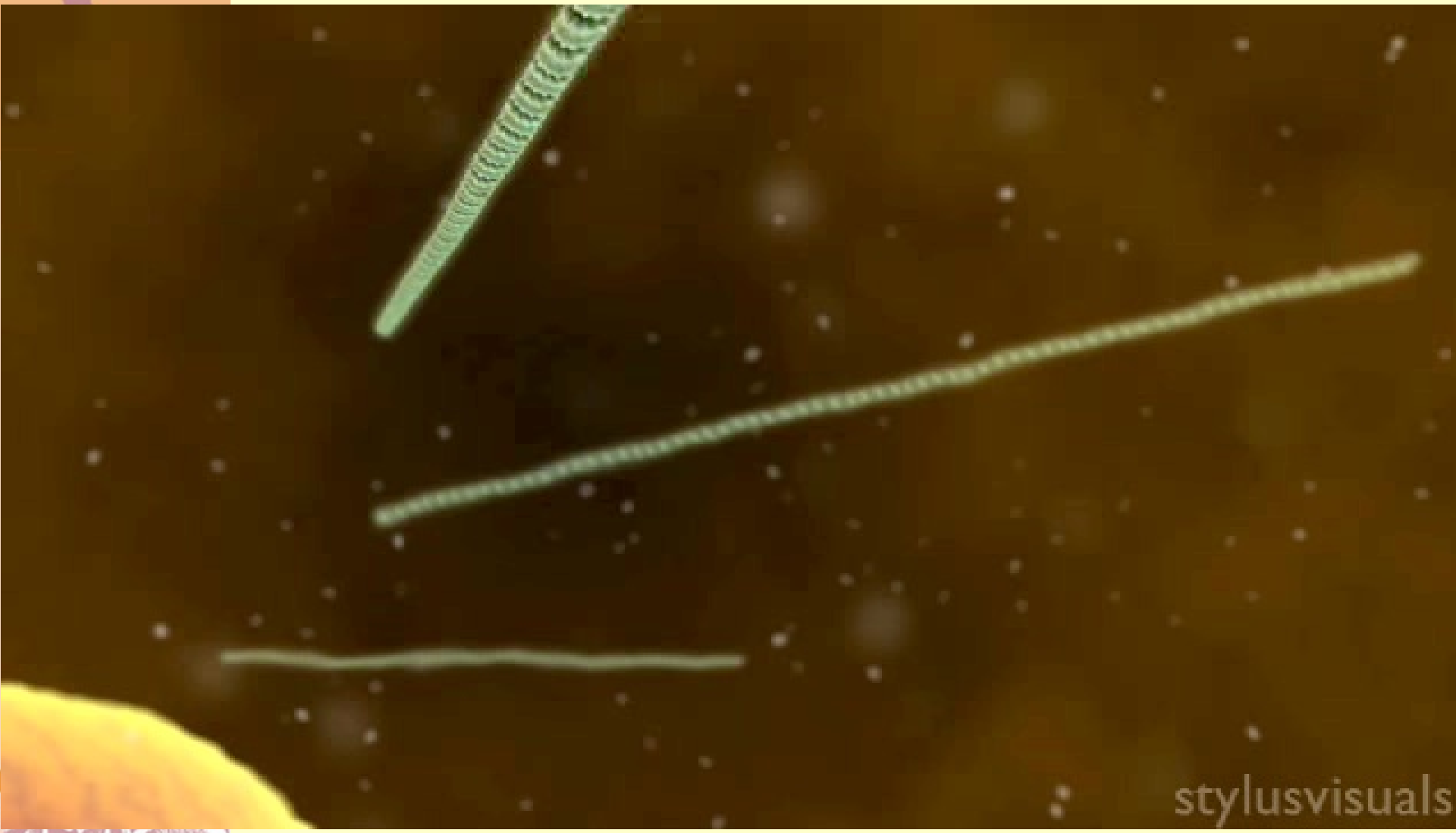
# Dicer Structure & Function




Filipowicz, Curr. Op. Structural Biology 15: 331-341 (2005)

# Dicer Structure & Function

http://www.moma.org/

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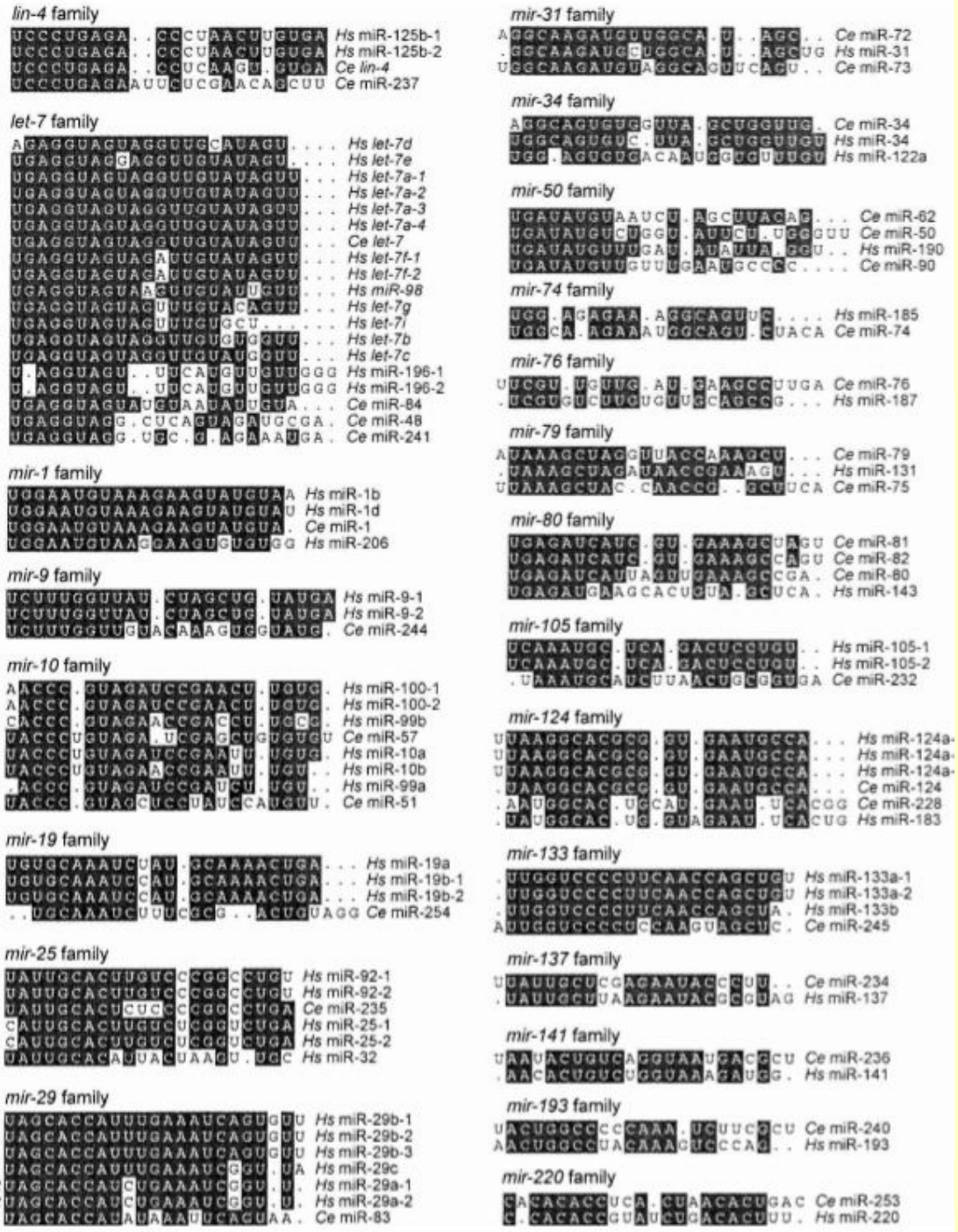
# Homology Between *C. elegans* and *Homo sapiens* miRNAs




Lim (2003) Genes & Dev. 17: 991-1

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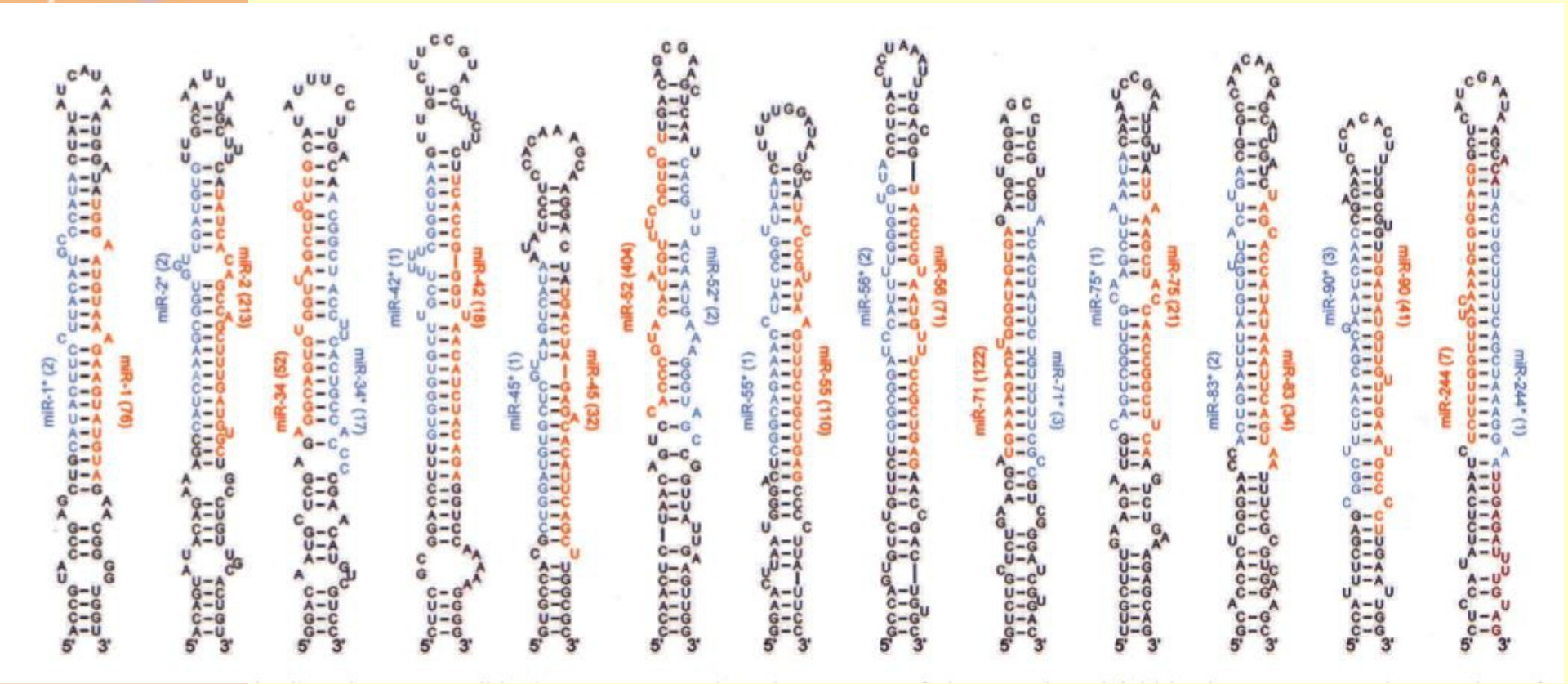
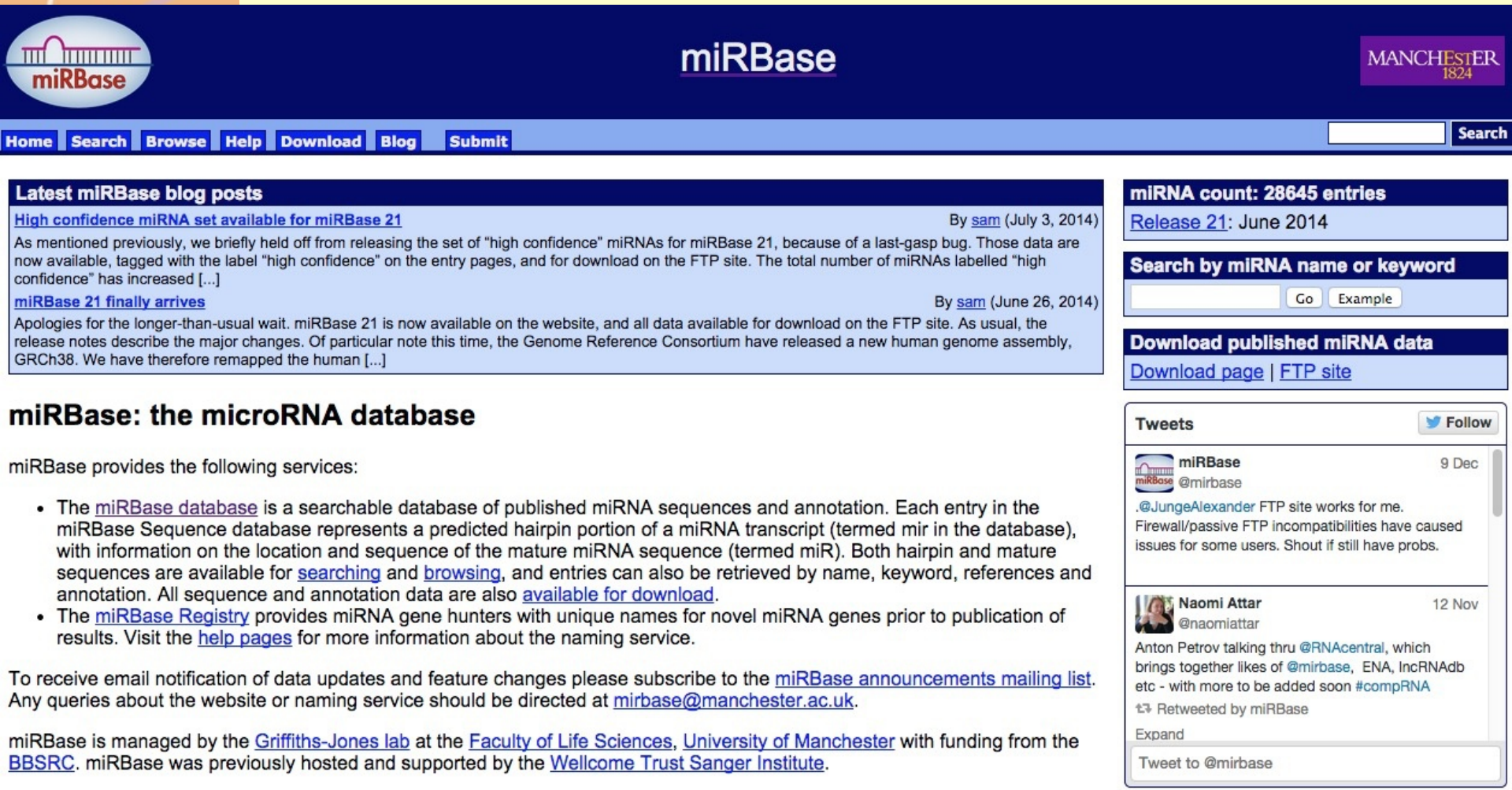
# Predicted miRNA Precursors



# miRBase

http://www.mirbase.org/




Kozomara and Griffiths-Jones. miRBase: integrating microRNA annotation and deep-sequencing data. Nucleic Acids Res. (2010) Vol 39, pages D152-D157.

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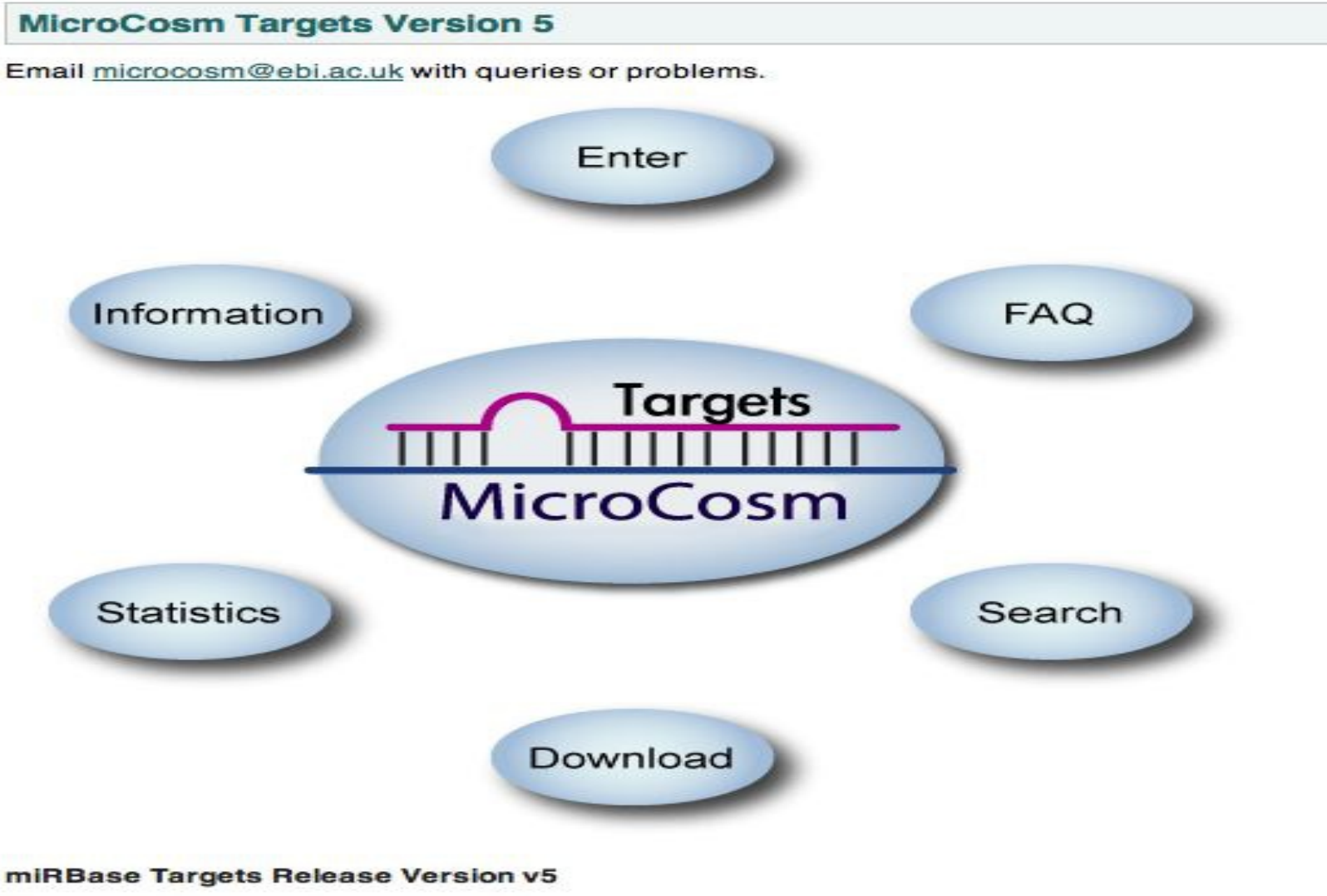
# miRBase::MicroCosm miRNA Targets

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

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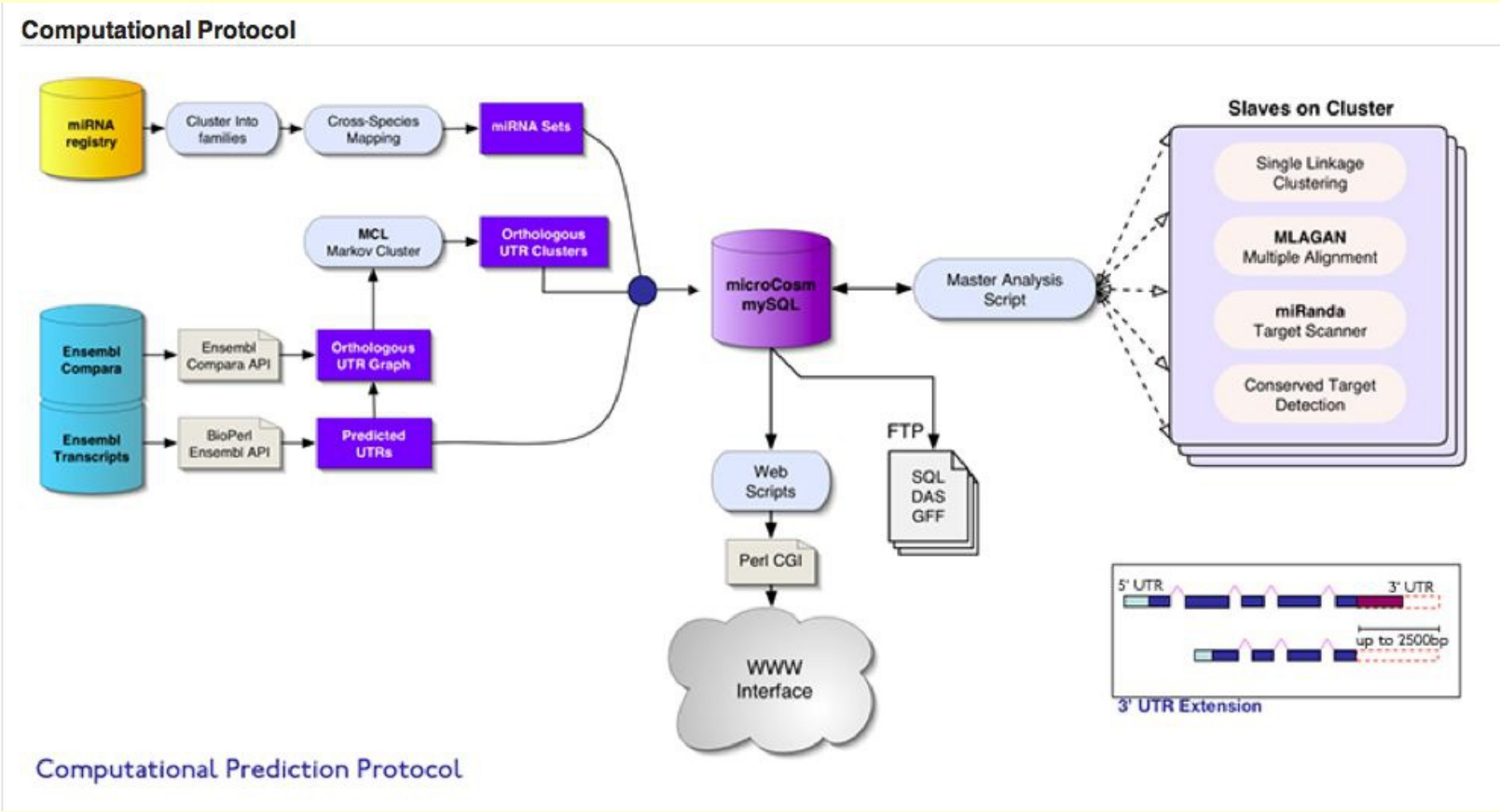
# MicroCosm miRNA Targets Prediction

http://www.ebi.ac.uk/enright-srv/microcosm/htdocs/targets/v5/info.html




Griffiths-Jones S., Saini HK., van Dongen S., Enright AJ. (2008) miRBase: tool for microRNA genomics. Nucleic Acids Res 36(Database issue): D154-8

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# Human miRNAs (March 4, 2014)

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

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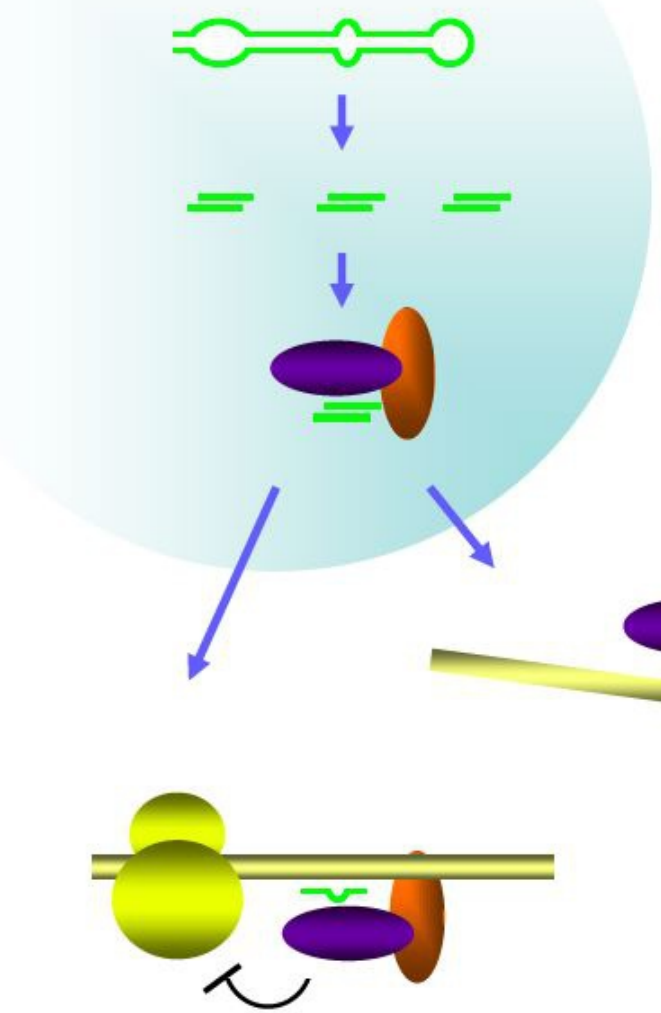
- miRNAs can have multiple targets
- Target mRNAs can have multiple miRNA binding sites

miRBase @ http://www.mirbase.org/
MicroCosm @http://www.ebi.ac.uk/enright-srv/microcosm

# Thousands of microRNAs act in multiple biological events



Developmental timing

Differentiation

Aging

Apoptosis

Metabolism

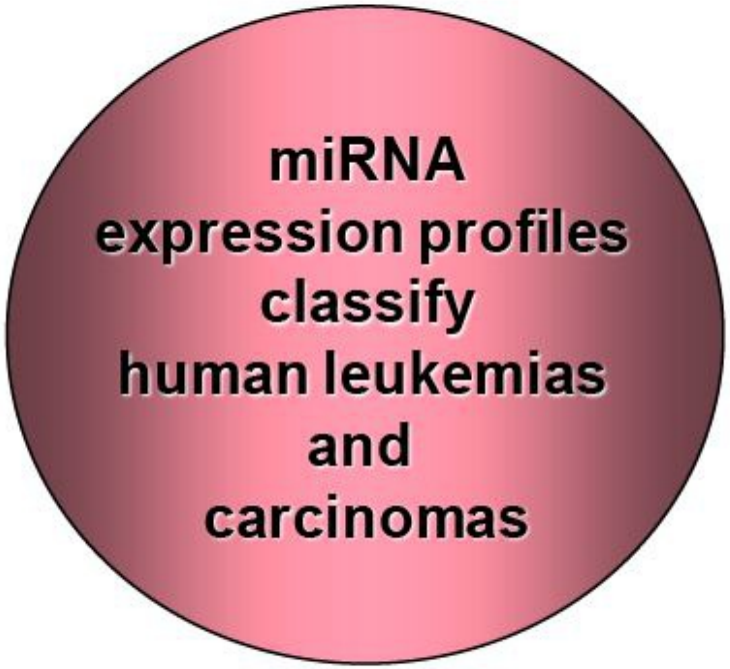
Cancer

…

Cell fate/differentiation, Cell cycle…

© Frank Slack frank.slack@yale.edu

# 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)

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# miRNAs Involved in Human Cancer

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

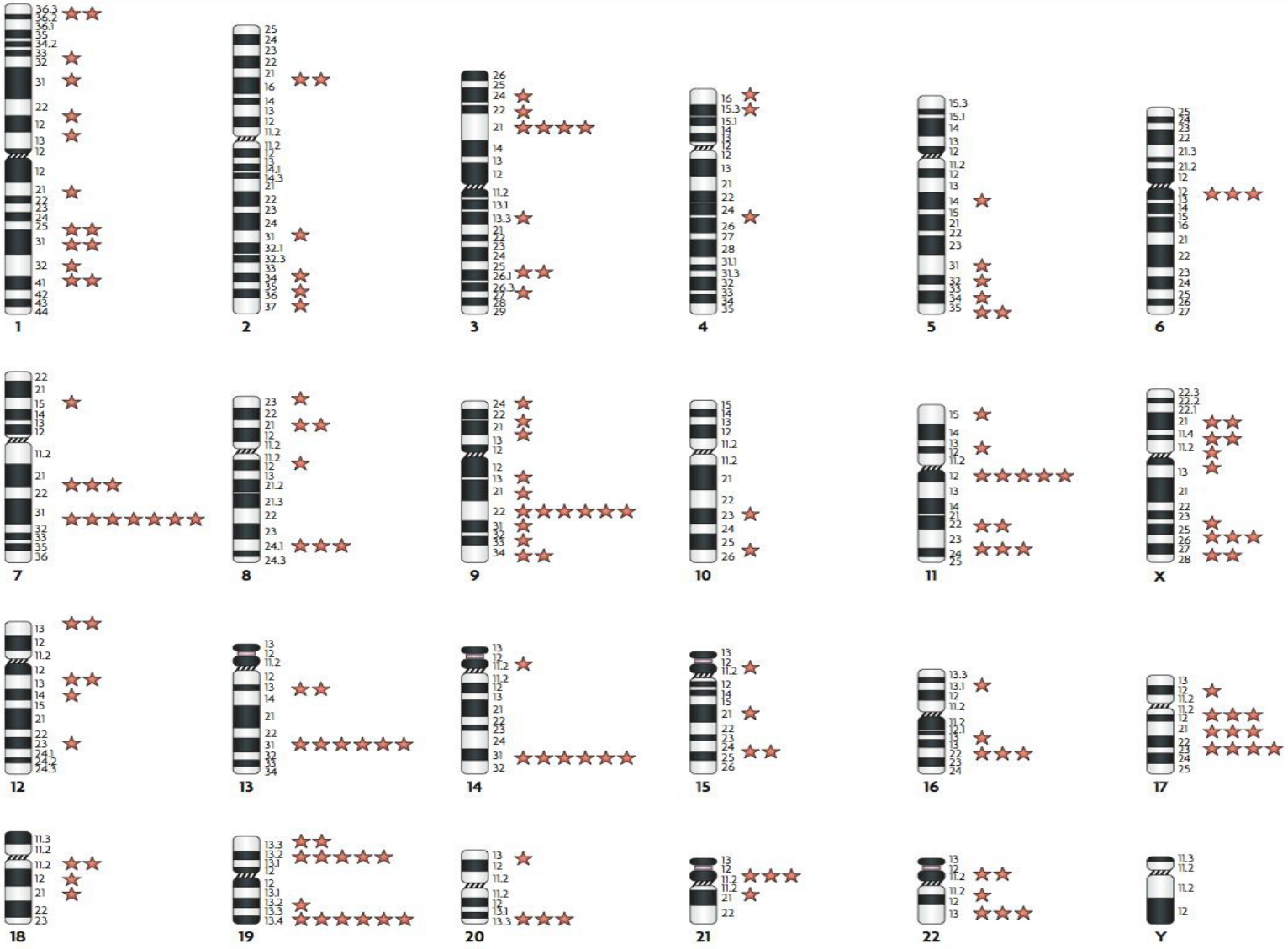
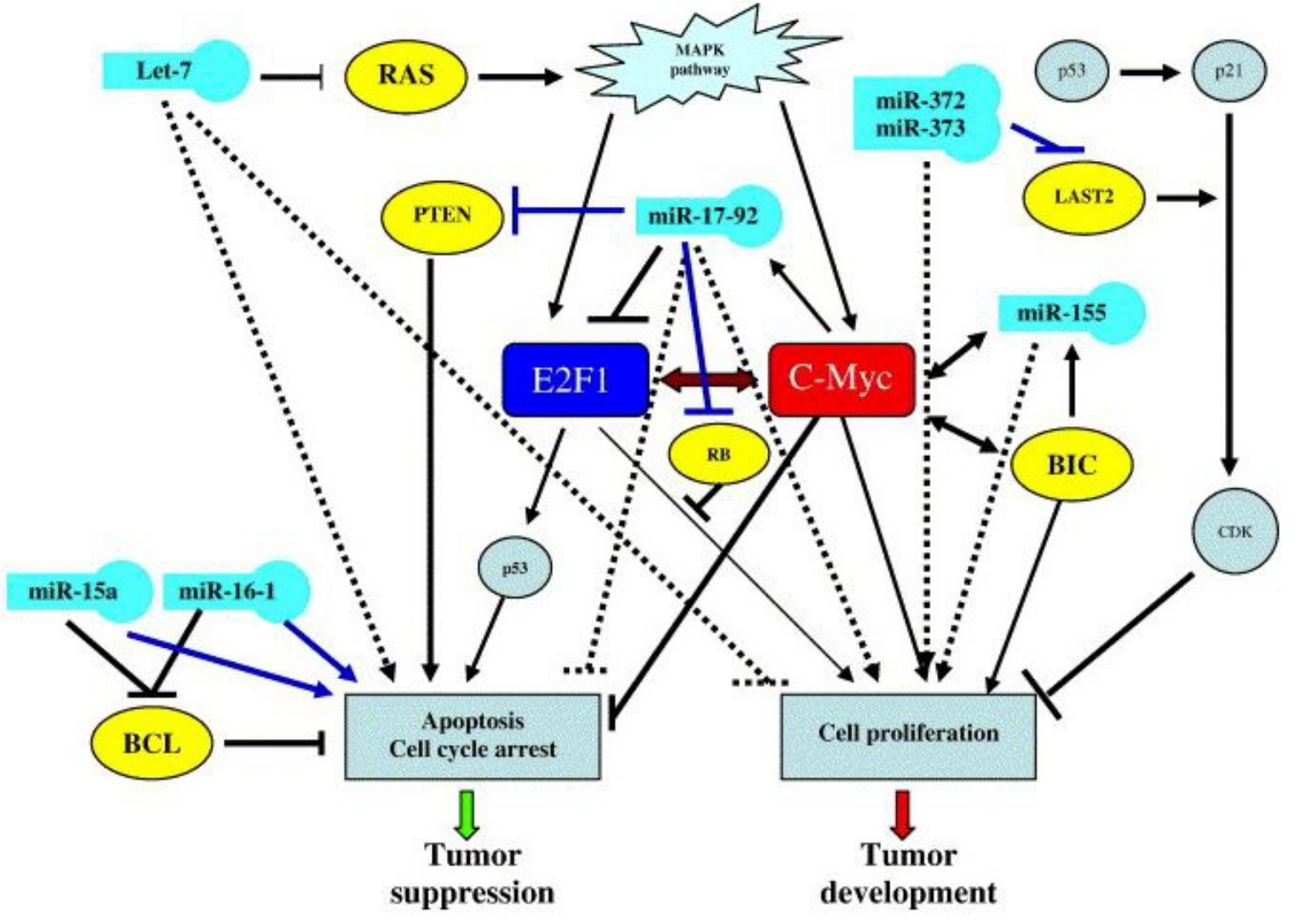



Figure 1 | **MicroRNA genes map to chromosomal regions that are involved in alterations in human cancer.**

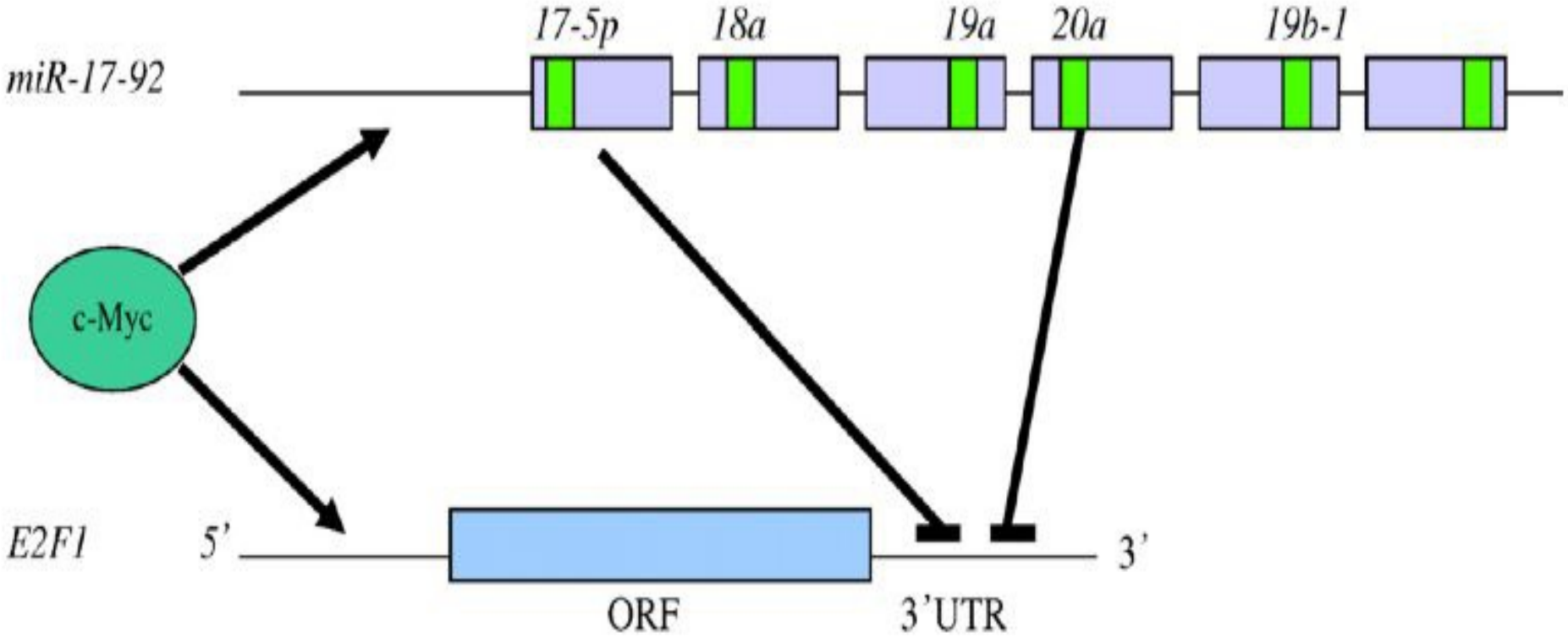
Croce Nat Rev Genet. 2009 Oct;10(10):704-14

# miRNAs as Oncogenes and Tumor Supressors
## Zhang et al Dev Biol. 2007 Feb 1;302(1):1-12



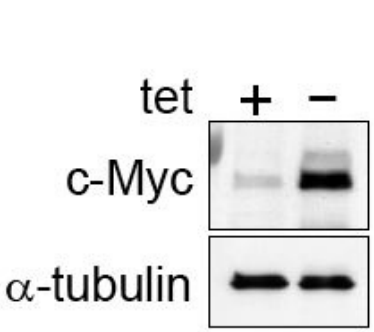

Zhang et al Dev Biol. 2007 Feb 1;302(1):1-12

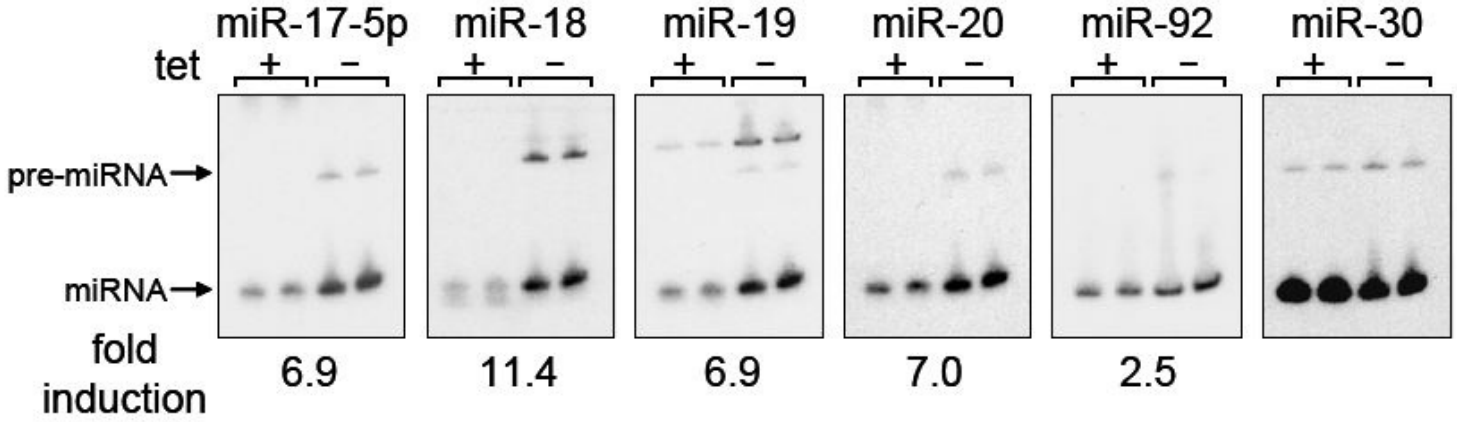
# cMyc & miRNAs Regulate E2F1 Cell Cycle TF
## Zhang et al Dev Biol. 2007 Feb 1;302(1):1-12




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

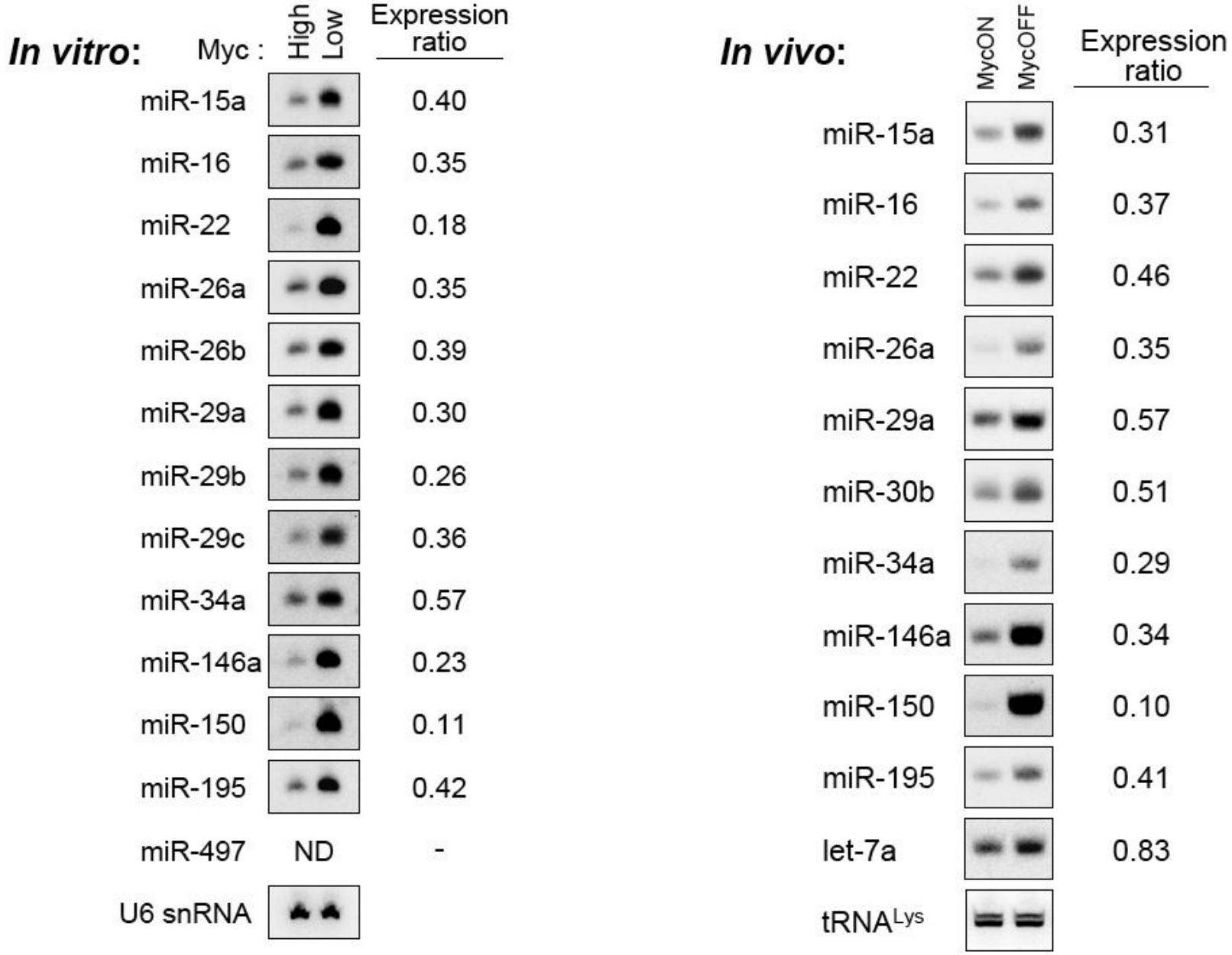
# The miR-17-92 cluster is activated by Myc




O'Donnell et al. Nature 2005 435, 839-843

# Myc represses the expression of many miRNAs




Chang *et al. Nature Genetics*, 2008

© George Calin

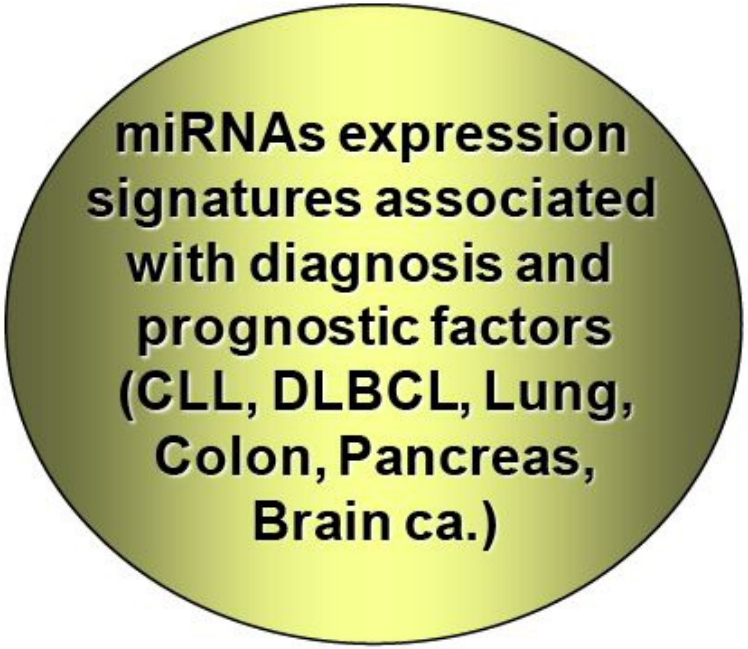
# miRNA Oncogenes or Tumor Suppressor Genes (Croce Nat Rev Genet. 2009 Oct;10(10):704-14.)

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 |
|---|---|---|---|---|---|
| *miR-15a* and *miR-16-1* | 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 |
| *let-7* (*a*, *b*, *c*, *d*, *e*, *f*, *g* and *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 |
| *miR-29* (*a*, *b* and *c*) | Loss in aggressive CLL, AML (11q23), MDS lung and breast cancers and cholangocarcinoma | Induces apoptosis and inhibits tumorigenicity. Reactivates silenced tumour suppressor genes | TCL1, MCL1 and DNMTs | TS | 30,64, 71,72 |
| *miR-34* | Loss in pancreatic, colon, breast and liver cancers | Induces apoptosis | CDK4, CDK6, cyclin E2, EZF3 and MET | TS | 56–58 |
| *miR-145* | Loss in breast cancer | Inhibits proliferation and induces apoptosis of breast cancer cells | ERG | TS | 31 |
| *miR-221* and *miR-222* | Loss in erythroblastic leukaemia | Inhibits proliferation in erythroblasts | KIT | TS | 30 |
| *miR-221* and *miR-222* | 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 |
| *miR-155* | 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 |
| *miR-17–92* 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 |
| *miR-21* | 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 |
| *miR-372* and *miR-373* | 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*




(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)

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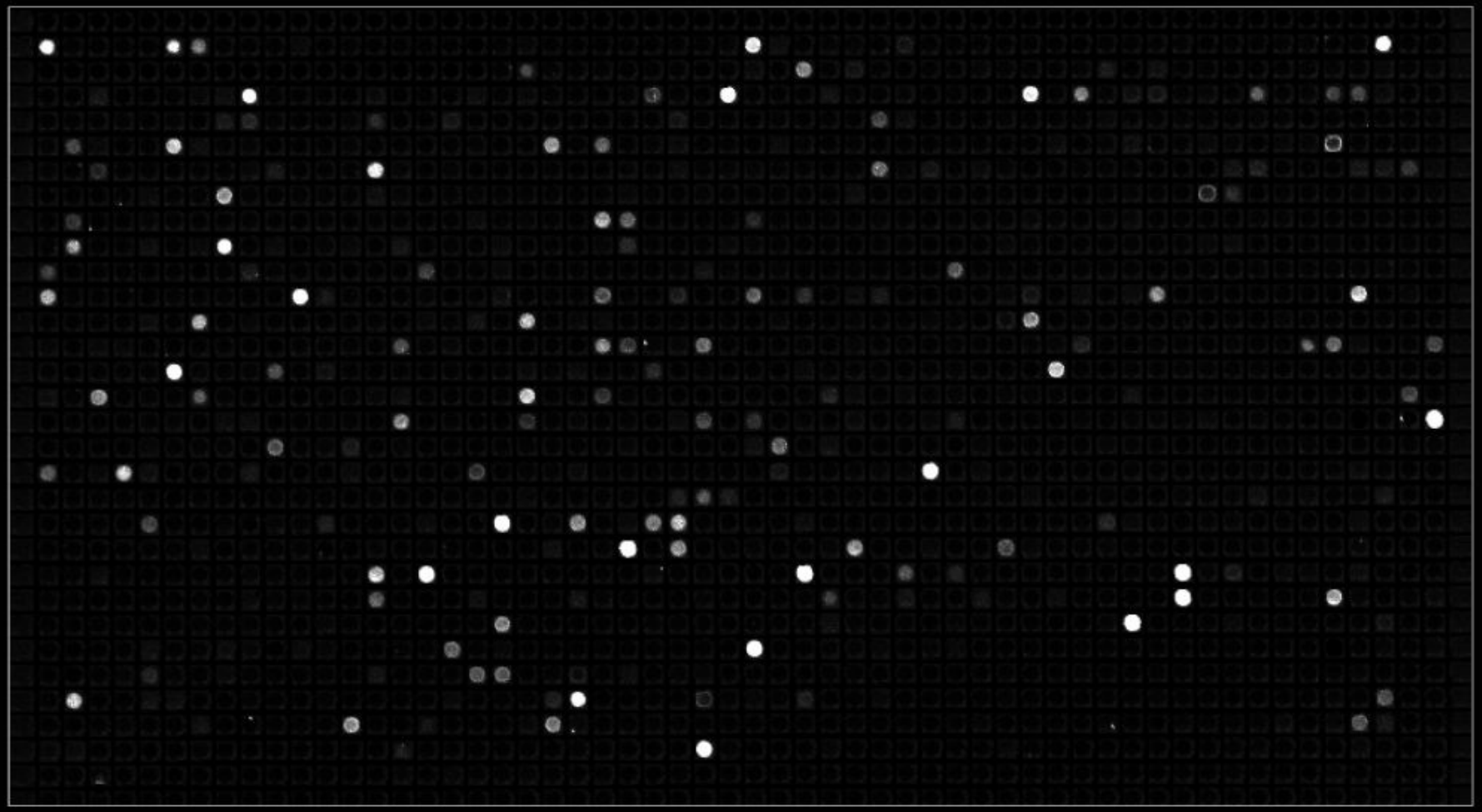
# Profiling miRNA expression using custom microarrays



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# miRNAs and Cancer – A Summary

- miRNAs control cell cycle, cell differentiation and apoptosis by regulating oncogenes and tumor supressor 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.

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# Important Micro RNA Web Sites

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

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