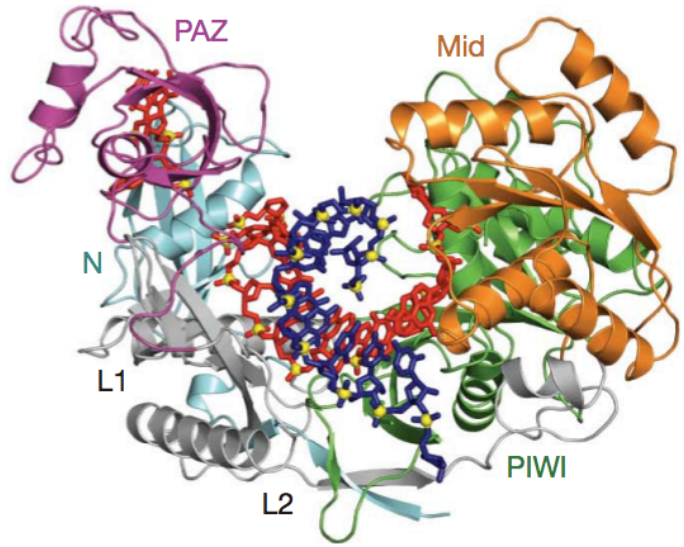
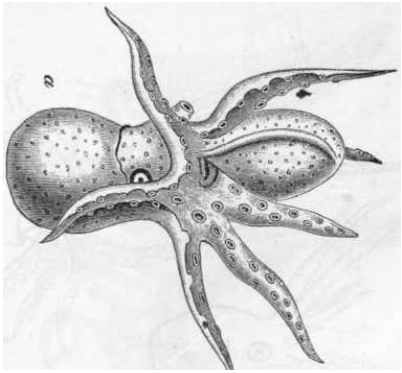
Piwi-Interacting RNAs

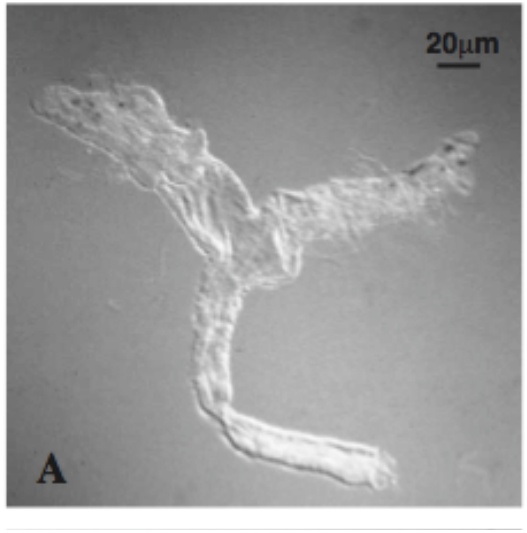


Molly Thomas
5/6/2009

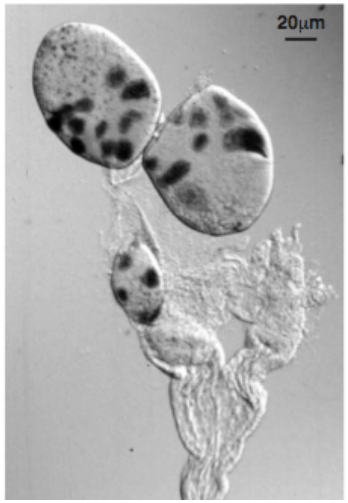
Piwi Discovery

- PIWI: **P**-element-**I**nduced **WI**mpy testes
- Comprises the Piwi clade of Argonaute proteins

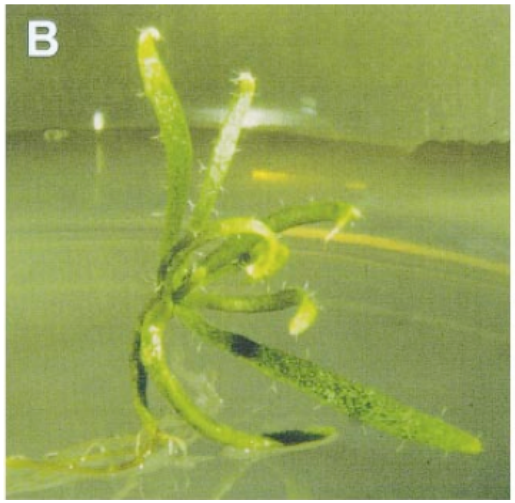




WT



Piwi$^{-/-}$



Ago$^{-/-}$

Lin et al, *Development*, 1997

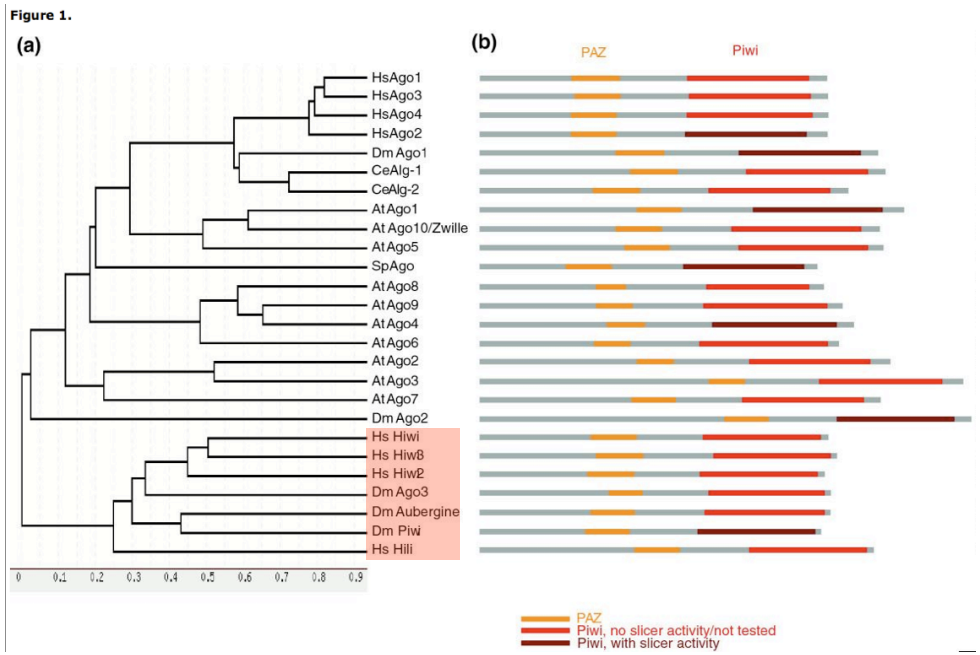
Bohmert et al, *EMBO Journal*, 1998

Piwi Discovery

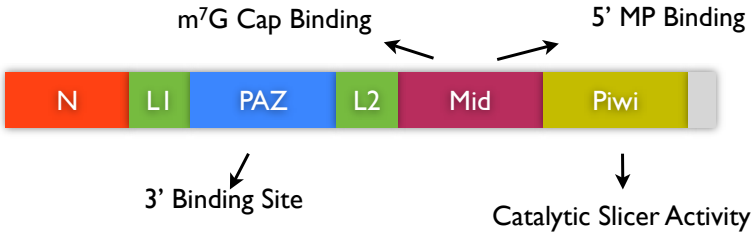
- PIWI: **P**-element-**I**nduced **WI**mpy testes
- Comprises the Piwi clade of Argonaute proteins

Ago

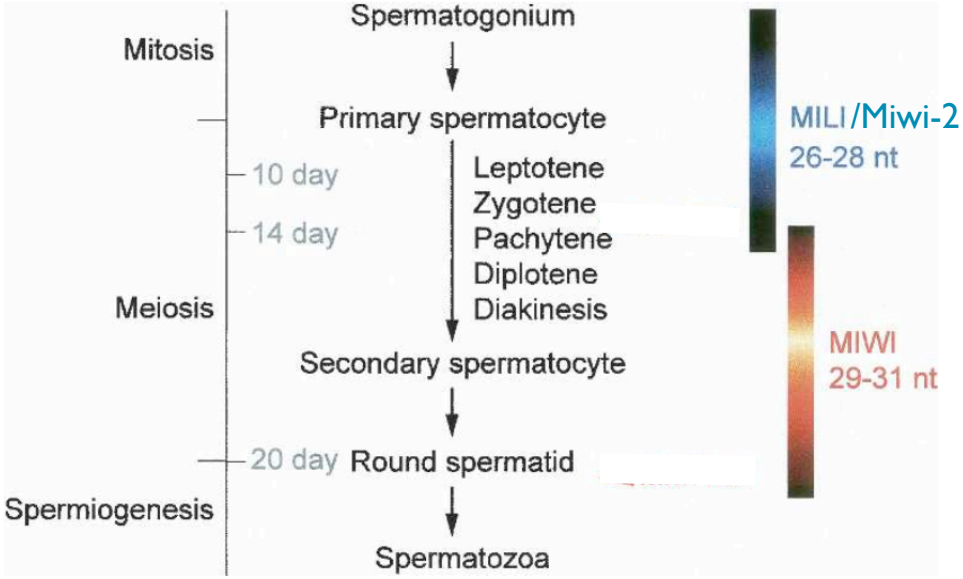
Piwi



Meister and Höck, *Genome Biol*, 2008



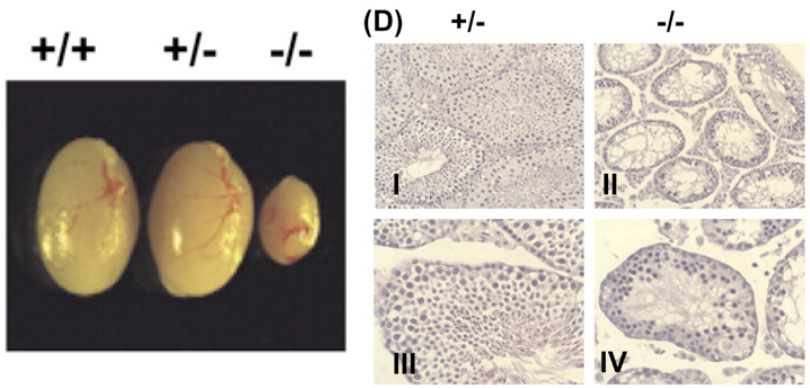
Loss of Murine Piwi Homologues Leads to Spermatogenic Arrest



Narry Kim, *Genes and Development*, 2006

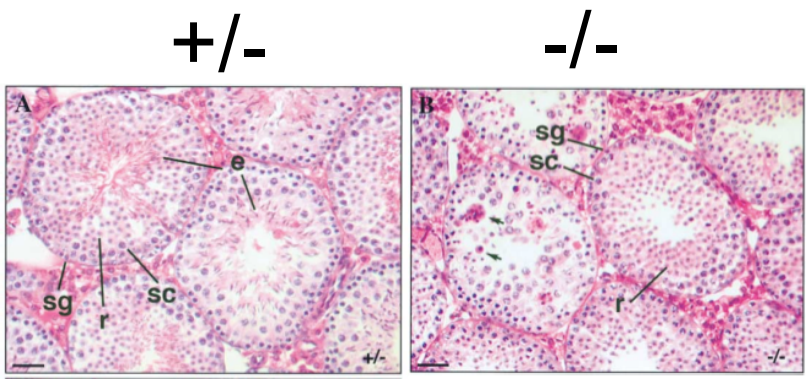
Loss of Murine Piwi Homologues Leads to Spermatogenic Arrest

Mili

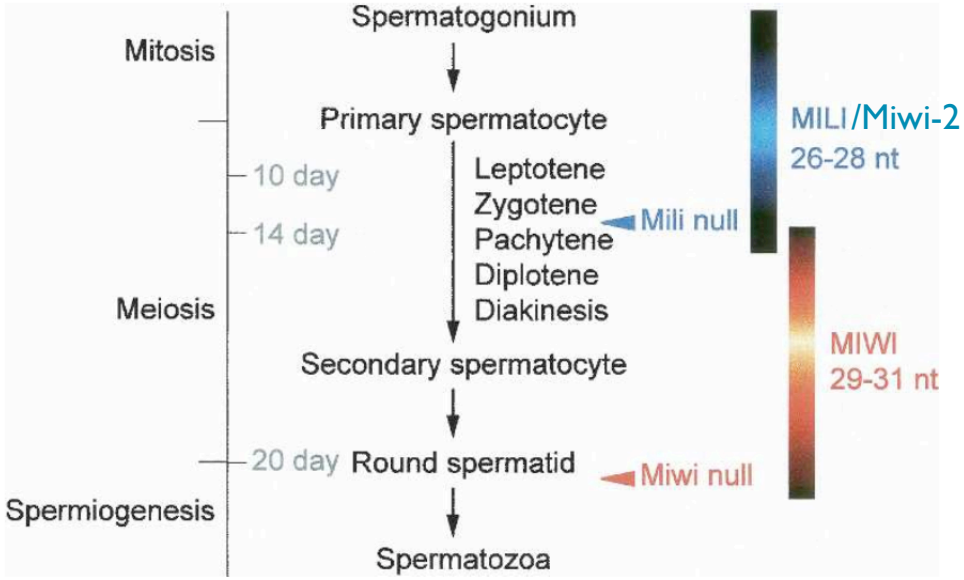


Kuramochi-Miyagawa, *Development*, 2004

Miwi

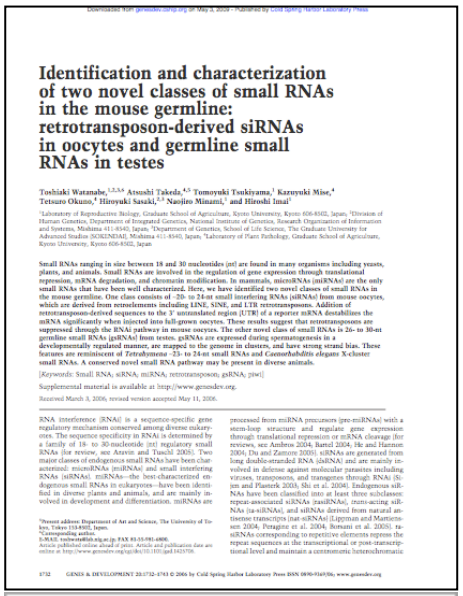


Deng and Lin, *Dev Cell*, 2002



Narry Kim, *Genes and Development*, 2006

piRNA Discovery



Identification and characterization of two novel classes of small RNAs in the mouse germline: retrotransposon-derived siRNAs in oocytes and germline small RNAs in testes

Toshiaki Watanabe, Atsushi Takeda, Tomoyuki Tsukiyama, Kazuyuki Mise, Tetsuro Okuno, Hiroyuki Sasaki, Naojiro Minami, and Hiroshi Imai

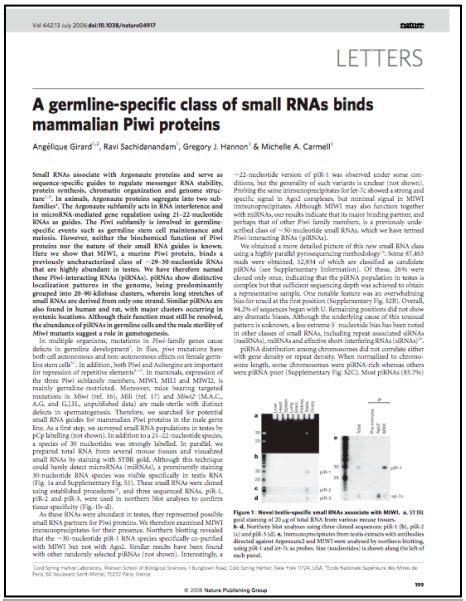
Watanabe et al, *Genes and Development*, 2006

RESEARCH COMMUNICATION

A novel class of small RNAs in mouse spermatogenic cells

Shane T. Grivna, Eugin Beyret, Zhong Wang, and Haifan Lin

Grivna et al, *Genes and Development*, 2006

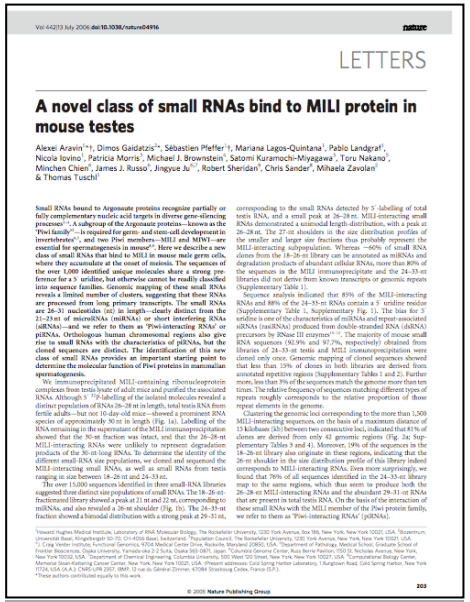


LETTERS

A germline-specific class of small RNAs binds mammalian Piwi proteins

Angélique Girard, Ravi Sachidanandam, Gregory J. Hannon & Michelle A. Carmell

Girard et al, *Nature*, 2006



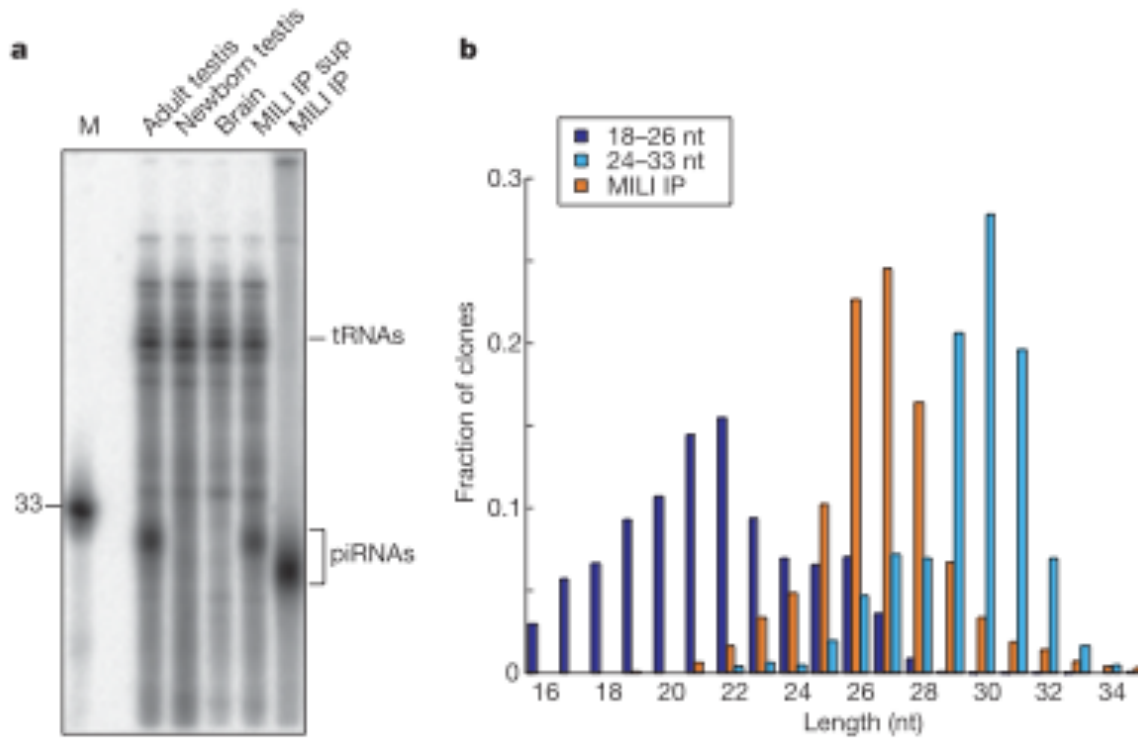
LETTERS

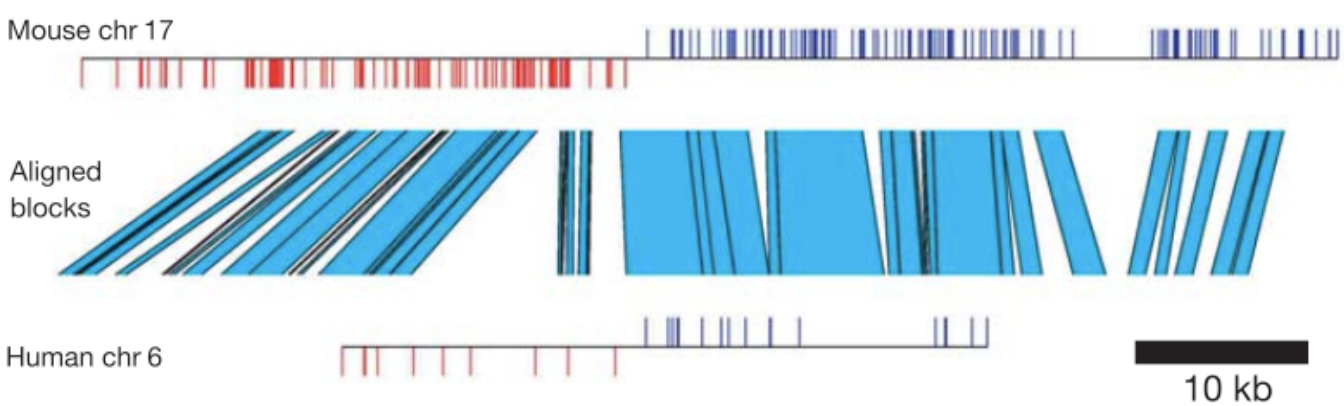
A novel class of small RNAs bind to MILI protein in mouse testes

Alexei Aravin, Dimos Gaidatzis, Sébastien Pfeffer, Mariana Lagos-Quintana, Pablo Landgraf, Nicola Iovino, Patricia Morris, Michael J. Brownstein, Satomi Kuramochi-Miyagawa, Toru Nakano, Minchen Chien, James J. Russo, Jingyue Ju, Robert Sheridan, Chris Sander, Mihaela Zavolan & Thomas Tuschl

Aravan et al, *Nature*, 2006

piRNA Discovery

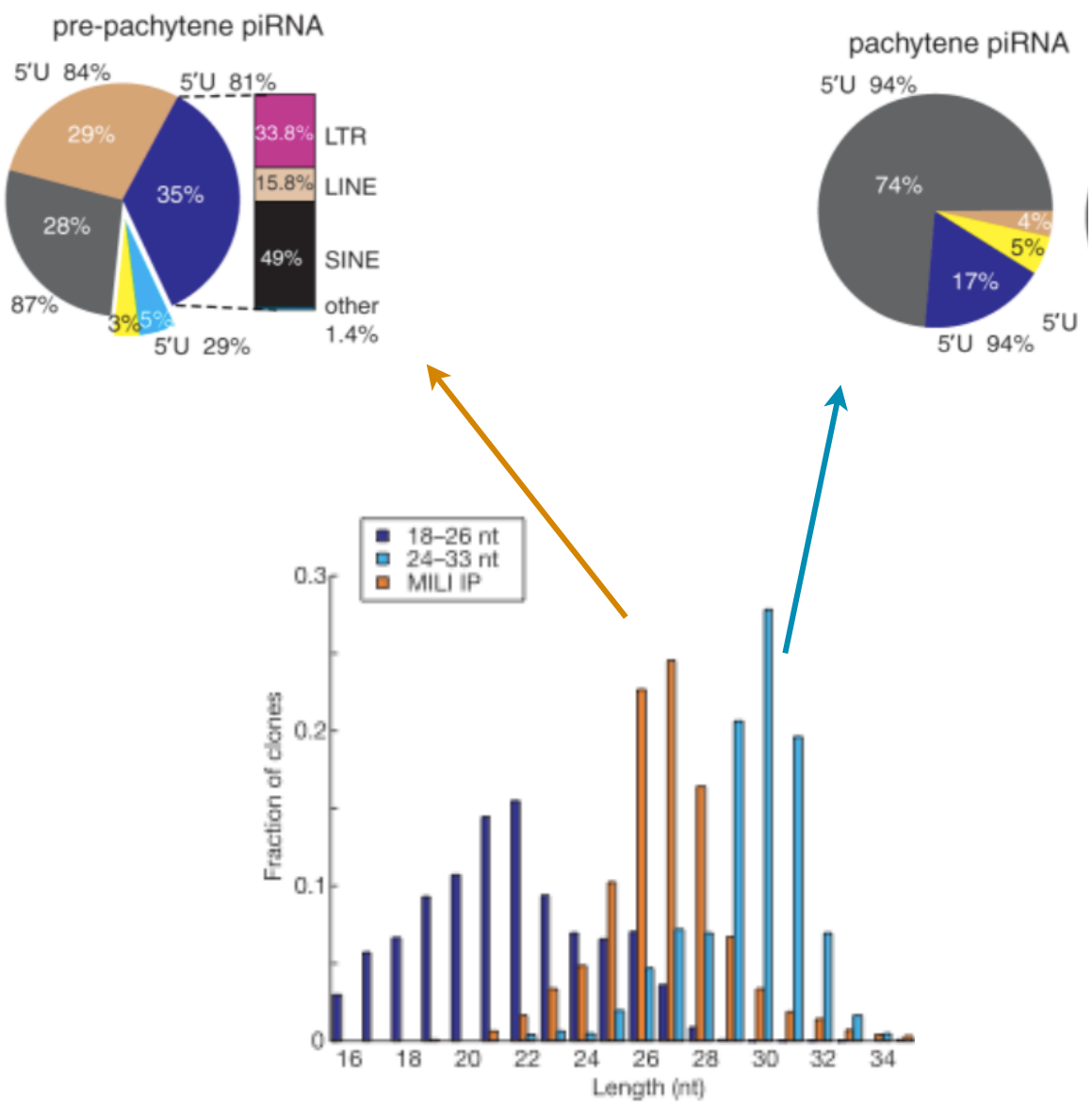




Highly conserved strand bias

Aravan et al, *Nature*, 2006

2 piRNA Populations in Mammals??



- transposons
- no annotation
- gene
- rRNA
- other ncRNAs

Aravan et al, *Nature*, 2006
Aravan et al, *Science*, 2007

Pre-pachytene piRNA

mmu_piR_036492

Hen1

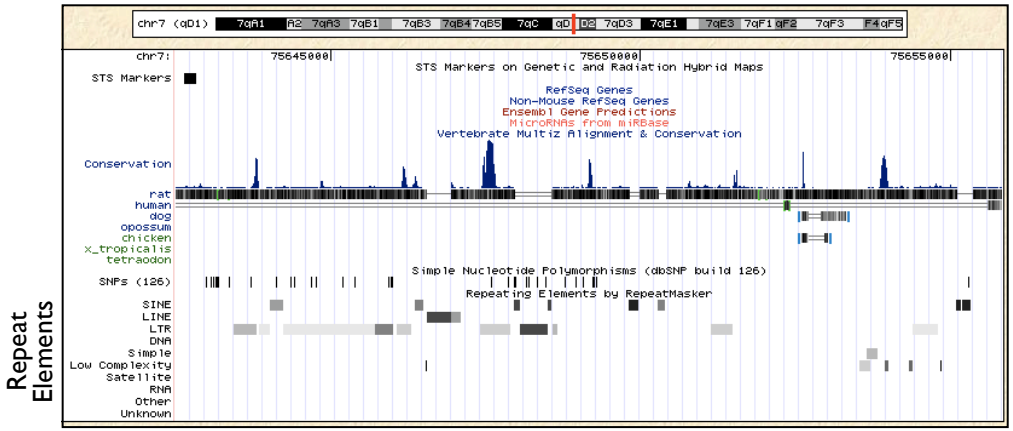
Reverse Complement

5'-MP-UGUUGUUCCACCUAUAGGGUUGCAGAU-2'-O-Me

5'U

A at position 10

Chromosome 7 Pre-pachytene Cluster



↓

Mili, Miwi-2
(26-28 bp)

Pachytene piRNA

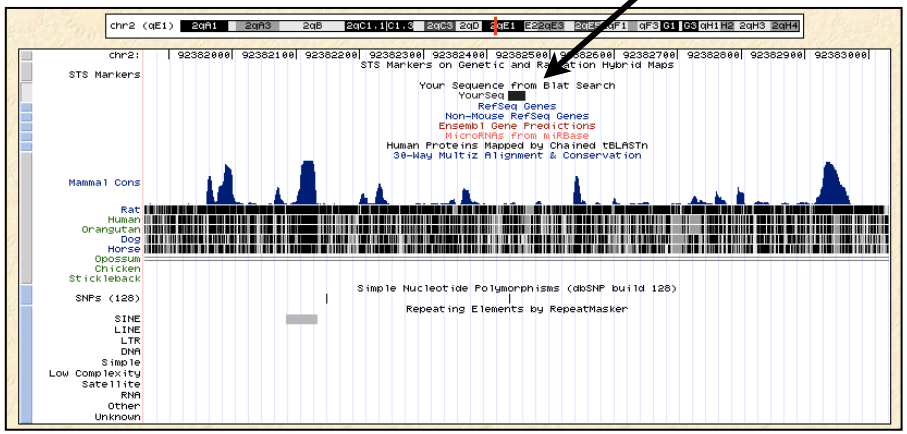
mmu_piR_000001

Hen1

5'-MP-UAGCAGUGAGGUCAAGGAAGAGGAAGC-2'-O-Me

5'U

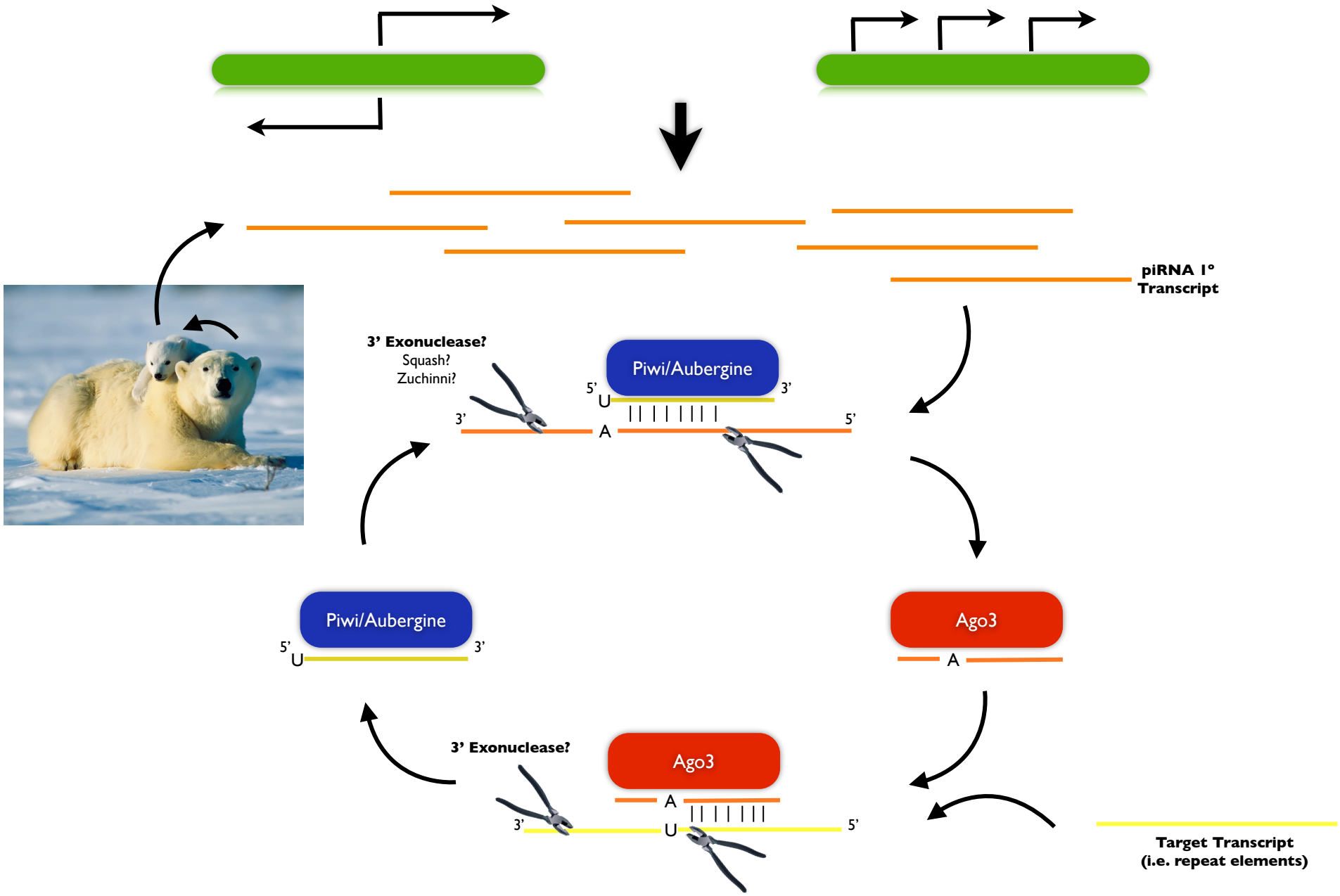
piR-1



↓

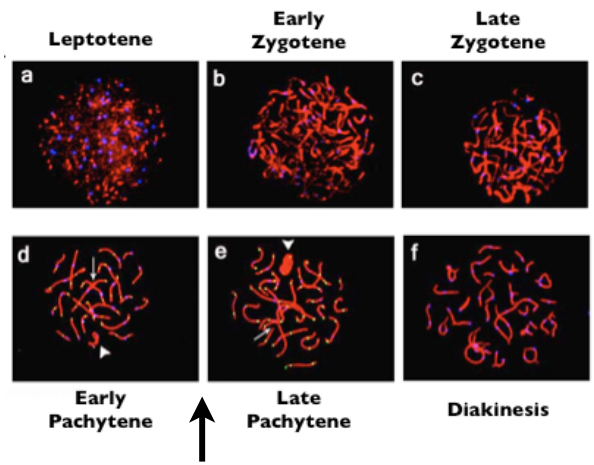
Miwi
(29-31)

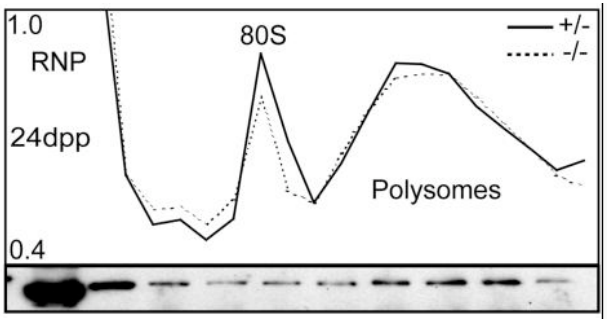
Ping-Pong Model of (Pre-Pachytene) piRNA Biogenesis



piRNA Functions and Mechanisms

- **Pre-pachytene**: Silence Transposable Elements
  - Miwi-2 and Mili
  - IAP, LINE, SINE, LTR
  - May require Piwi binding to heterochromatin (i.e. via HP1a)
- **Pachytene**: unknown
  - Miwi associates with polysome fractions
  - Miwi can bind translationally-inactive mRNAs

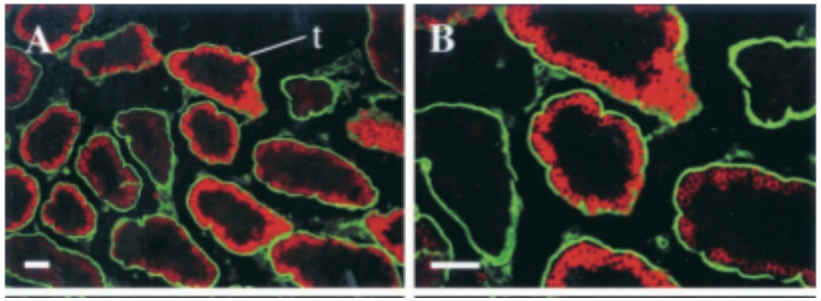


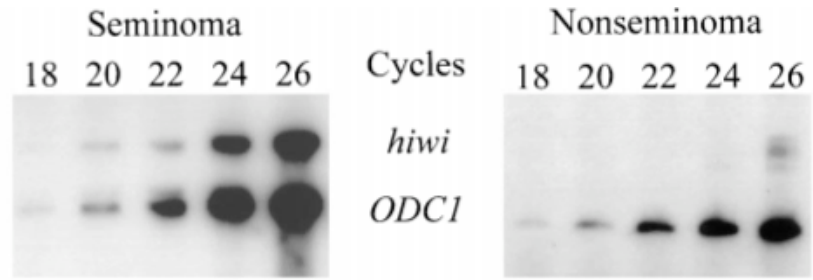


Grivna et al, *PNAS*, 2006

A Role for piRNAs in Human Disease?

- Hiwi is overexpressed in testicular seminomas



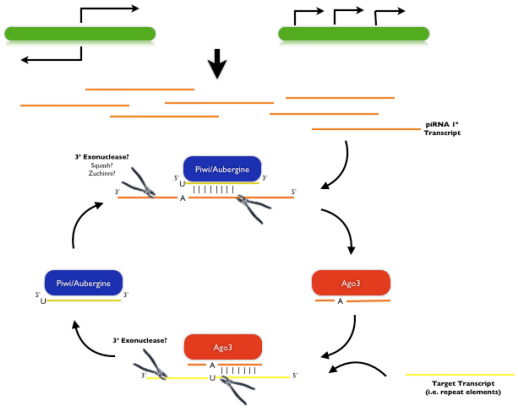


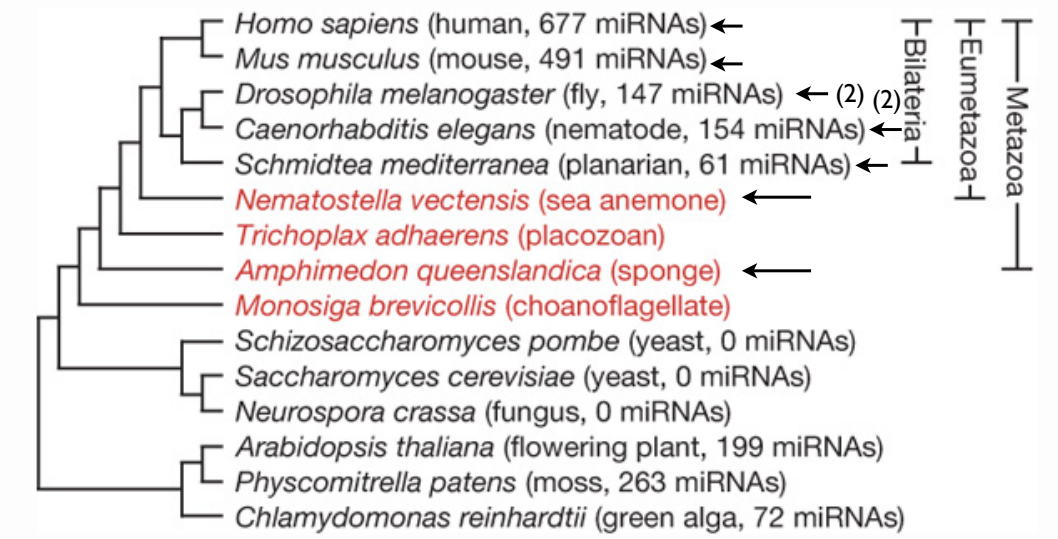
Qiao et al, *Oncogene*, 2002

- Expression of Hiwi in gastric and pancreatic cancers is positively correlated with cell proliferation

Type 1 (Pachytene) and Type 2 (pre-pachytene) piRNAs are Well-Conserved in Early Metazoans

Species	Ago	Piwi	Dicer	Drosha	Pasha	Hen1
Homo sapiens	4	4	1	1	1	1
Drosophila melanogaster	2	3	2	1	1	1
Caenorhabditis elegans[*]	5	3	1	1	1	1
Nematostella vectensis[†]	3	3	2	1	1	1
Trichoplax adhaerens[†]	1	0[‡]	5	1	0[§]	0[‡]
Amphimedon queenslandica[†]	2	3	4	1	1	2
Monosiga brevicollis	0[‡]	0[‡]	0[‡]	0	0	0[‡]
Saccharomyces cerevisiae	0[‡]	0[‡]	0[‡]	0	0	0[‡]
Schizosaccharomyces pombe[‖]	1	0[‡]	1	0	0	0[‡]
Arabidopsis thaliana	10	0[‡]	4	0	0	2
Physcomitrella patens	6	0[‡]	5	0	0	1
Chlamydomonas reinhardtii	2	0[‡]	3	0	0	1

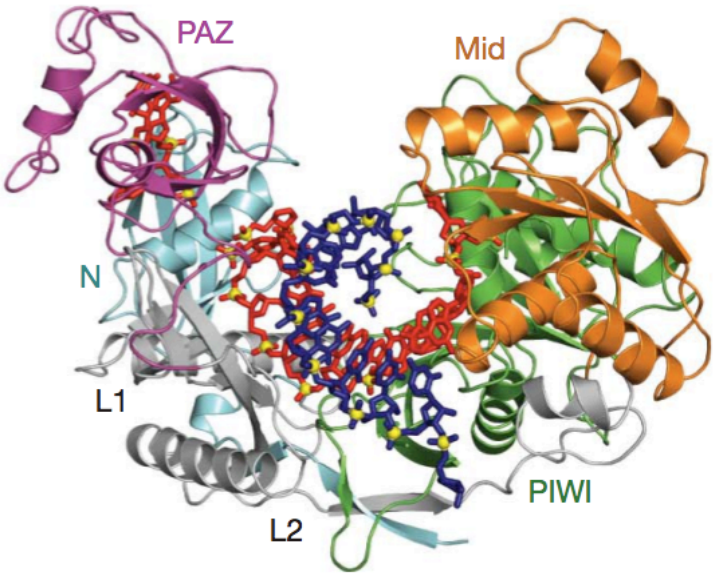




Nematostella

Amphimedon

Grimson et al, *Nature*, 2008

Conclusions

- piRNAs are a class of 24-30 nt small RNAs that associate with PIWI proteins
- piRNAs are expressed predominantly in the male germline
- They are transcribed from conserved clusters into long single-stranded precursors
- There are at least 2 major types of piRNAs:
    - **Type 1** (pachytene): no known function
    - **Type 2** (pre-pachytene): protect genome from transposable elements