ACADÉMIE NATIONALE DE PHARMACIE

Séance Académique du 6 décembre 2017

Salle des Actes - Faculté de Pharmacie de Paris

Les micro-ARN : de leur rôle en tant que régulateurs cellulaires à leur utilisation comme biomarqueurs et cibles ou agents thérapeutiques

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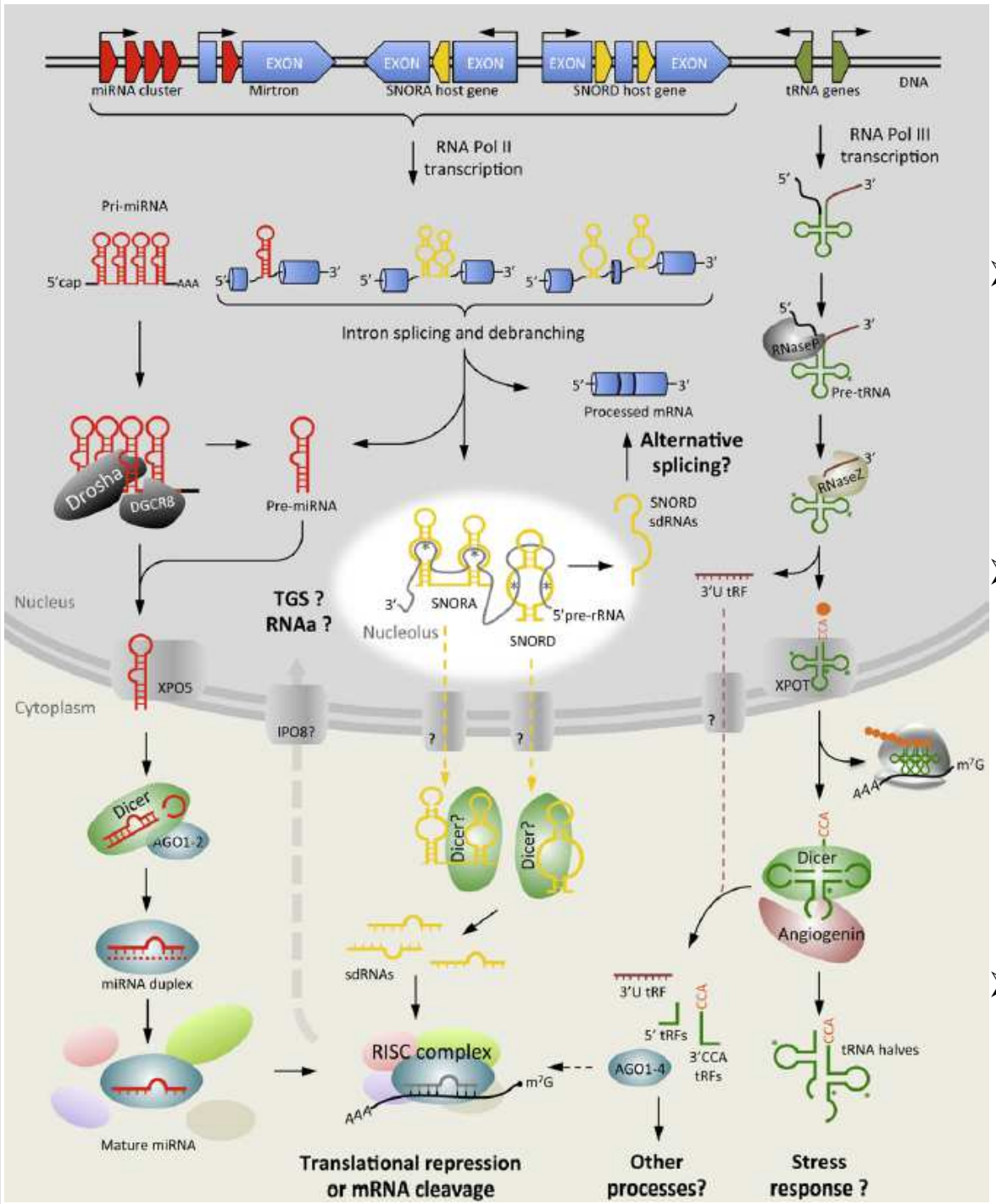
- Unité de Technologies Chimiques et Biologiques pour la Santé - Faculté de Pharmacie - Université Paris Descartes - Chimie ParisTech - UMR 8258 CNRS - UMR-S 1022 INSERM

Je n'ai pas de lien d'intérêt à déclarer dans le cadre de cette présentation



Short / Small non-coding RNAs (sncRNA ≤ 200 nt)

Cross-talk between the pathways of biogenesis and function of miRNAs, snoRNAs, tRNAs, sdRNAs and tRFs.

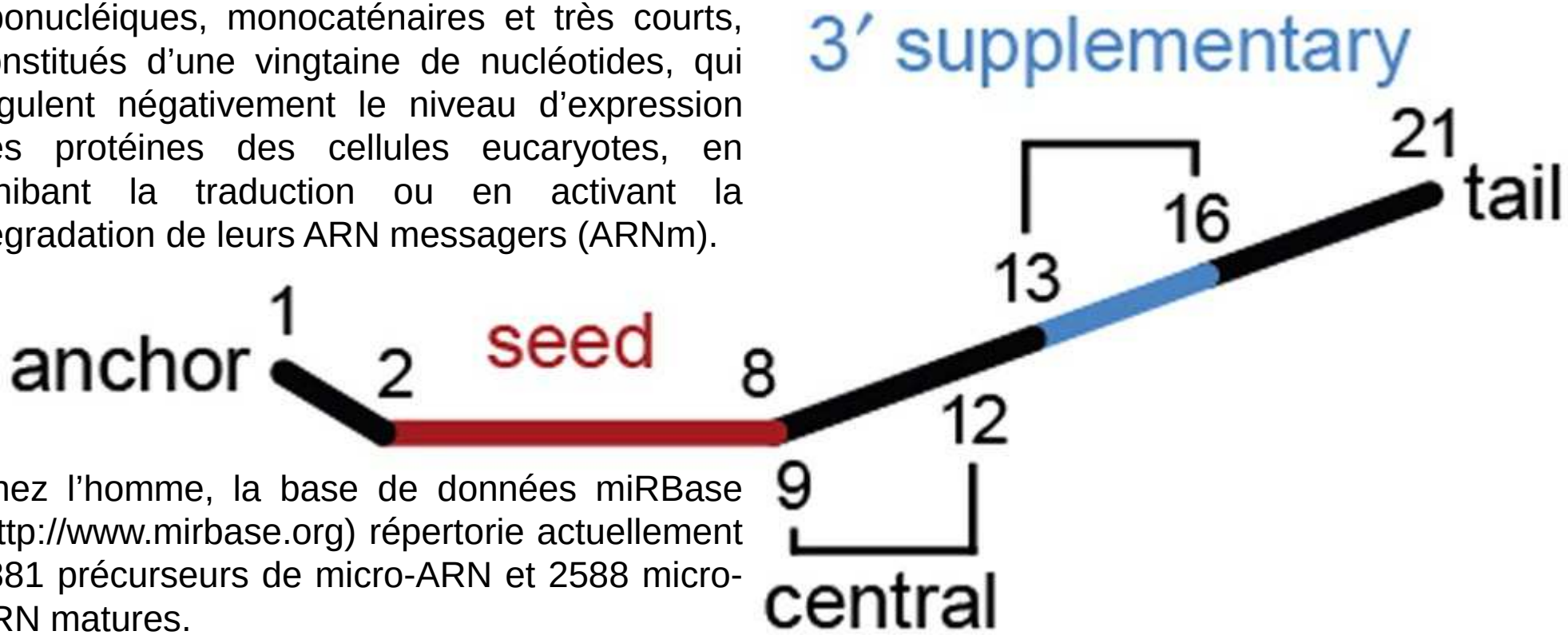
- **sncRNAs with well-known functions**
  - tRNAs (transfer RNAs) ~ 76-90 nt
  - srRNA (small ribosomal RNAs: 5S rRNA, 5.8S rRNA) ~ 120-160 nt
  - snRNAs (small nuclear RNAs) ~ 100-190 nt
  - snoRNAs (small nucleolar RNAs) ~ 60-140 nt
- **sncRNAs for RNA interference (RNAi) or RNA silencing** (short ssRNA from 20 to 30 nt)
  - siRNAs (small or short interfering RNAs): from the processing of dsRNAs
  - miRNAs (microRNAs): from gene transcription by RNA Pol II
  - piRNAs (Piwi-interacting RNAs): originally called rasiRNAs (repeat-associated siRNAs)
- **New classes of sncRNAs**
  - tsRNAs (tRNA-derived small RNAs)
  - sdRNAs (snoRNA-derived RNAs)
  - …

- **2013-Martens-Uzunova_ES-Beyond miRNA-Novel RNAs derived from sncRNA & their implication in cancer-Cancer Lett**

Les micro-ARN: biogenèse et mécanismes d’action moléculaires

The primary structure of miRNAs and siRNAs

Les micro-ARN (miRNA) sont des acides ribonucléiques, monocaténaires et très courts, constitués d'une vingtaine de nucléotides, qui régulent négativement le niveau d'expression des protéines des cellules eucaryotes, en inhibant la traduction ou en activant la dégradation de leurs ARN messagers (ARNm).



Chez l'homme, la base de données miRBase (http://www.mirbase.org) répertorie actuellement 1881 précurseurs de micro-ARN et 2588 micro-ARN matures.

- 2012-Concepcion-The miR-17-92 family of miRNA clusters in development & disease-Cancer J
- 2012-Wee-Argonaute divides its RNA guide into domains with distinct functions & RNA-binding properties-Cell

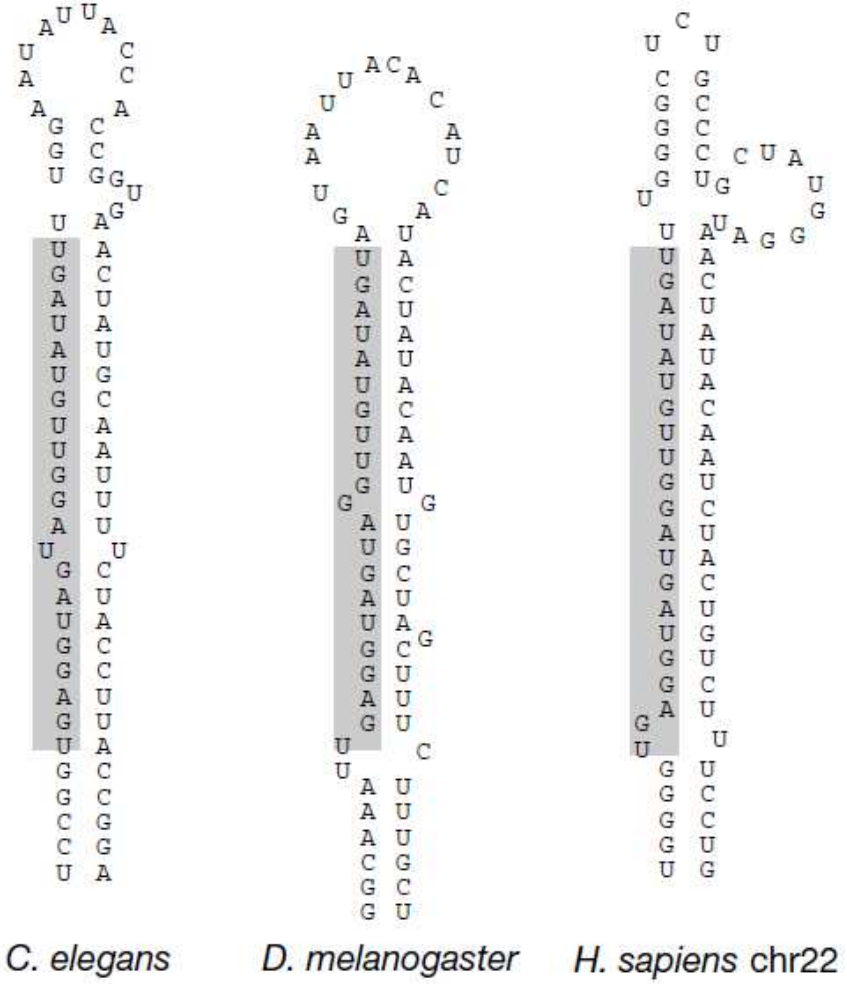
Quelques étapes clés dans la découverte des micro-ARN (1)

Le premier microRNA, dénommé lin-4, fut découvert en 1993 chez Caenorhabditis elegans (C. elegans) par les équipes de Victor Ambros et de Gary Ruvkun, grâce à l'identification d'une mutation de type « perte de fonction » qui entrainait des anomalies du développement chez le nématode.

La découverte de lin-4 a été un temps considérée comme une « singularité » dans la génétique des nématodes jusqu'à la mise en évidence par l'équipe de Gary Ruvkun, en 2000, soit sept ans plus tard, d'un deuxième microRNA, appelé let-7, jouant à nouveau un rôle régulateur dans le développement de C. elegans.

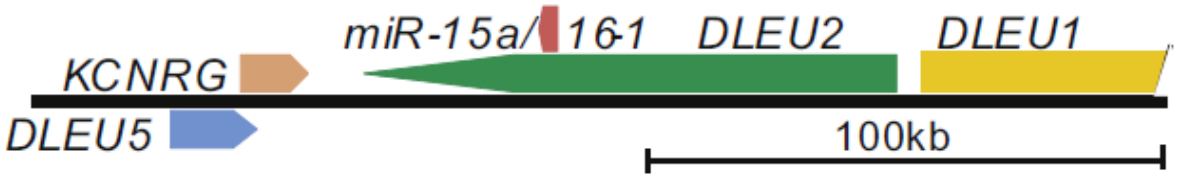
- Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993; 75(5): 843-854.
- Wightman B, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell. 1993; 75(5): 855-862.
- Reinhart BJ, Slack FJ, Basson M, Pasquinelli AE, Bettinger JC, Rougvie AE, Horvitz HR, Ruvkun G. The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans. Nature. 2000; 403(6772): 901-906.

Quelques étapes clés dans la découverte des micro-ARN (2)



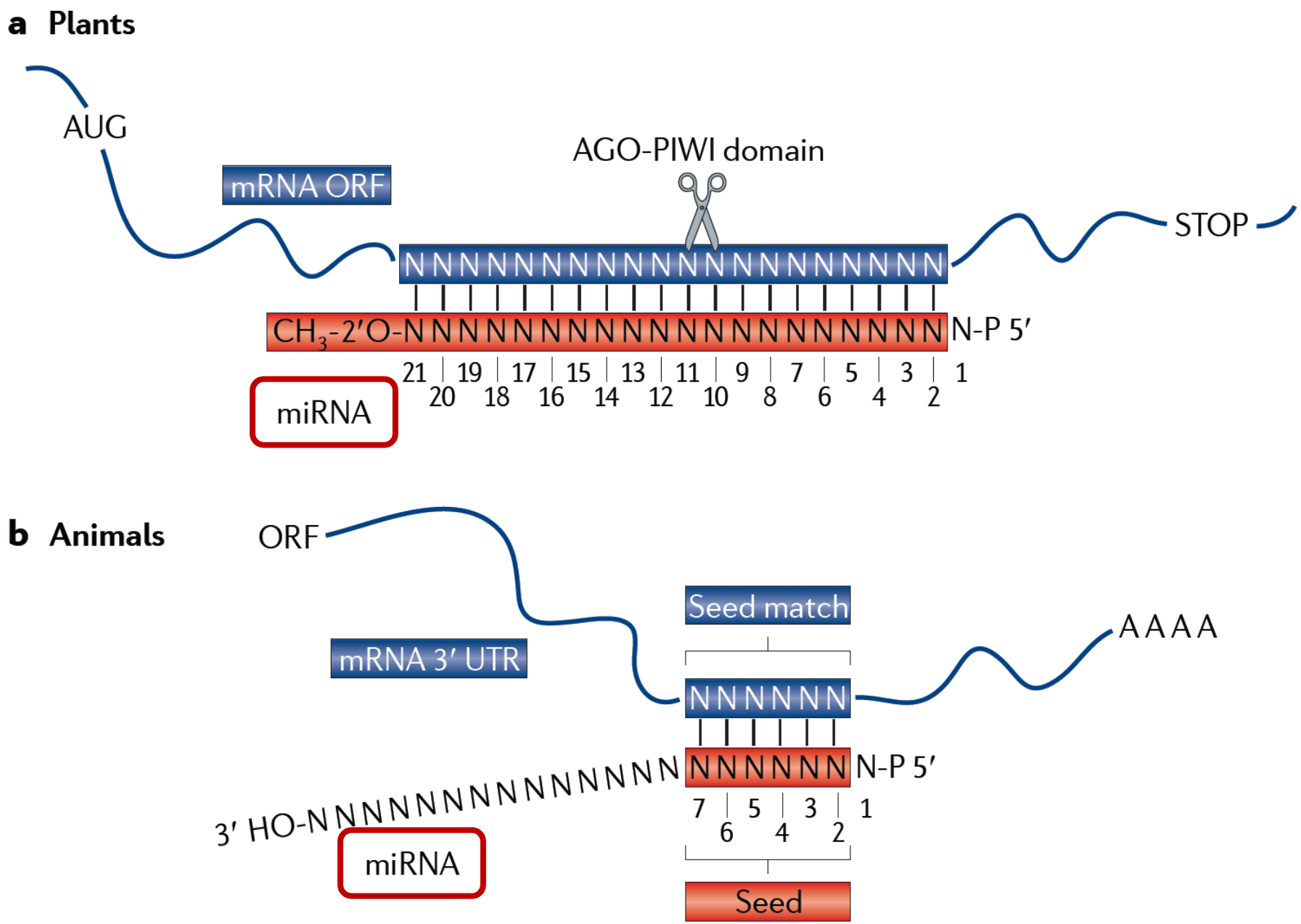
Plusieurs études ont ensuite montré que let-7 se retrouvait non seulement chez C. elegans mais aussi chez d'autres espèces telles que Drosophila melanogaster ainsi que chez les mammifères (l'homme inclus), avec une structure quasiment identique dans la plupart des cas.

Et c'est alors que, dès 2002, paraît la première étude rapportant une relation entre la dérégulation des microRNA et une pathologie humaine, en l'occurrence un cancer, avec la découverte par l'équipe de Carlo Maria Croce de l'implication de la délétion de deux gènes de microRNA dans de nombreux cas de leucémies lymphoïdes chroniques.



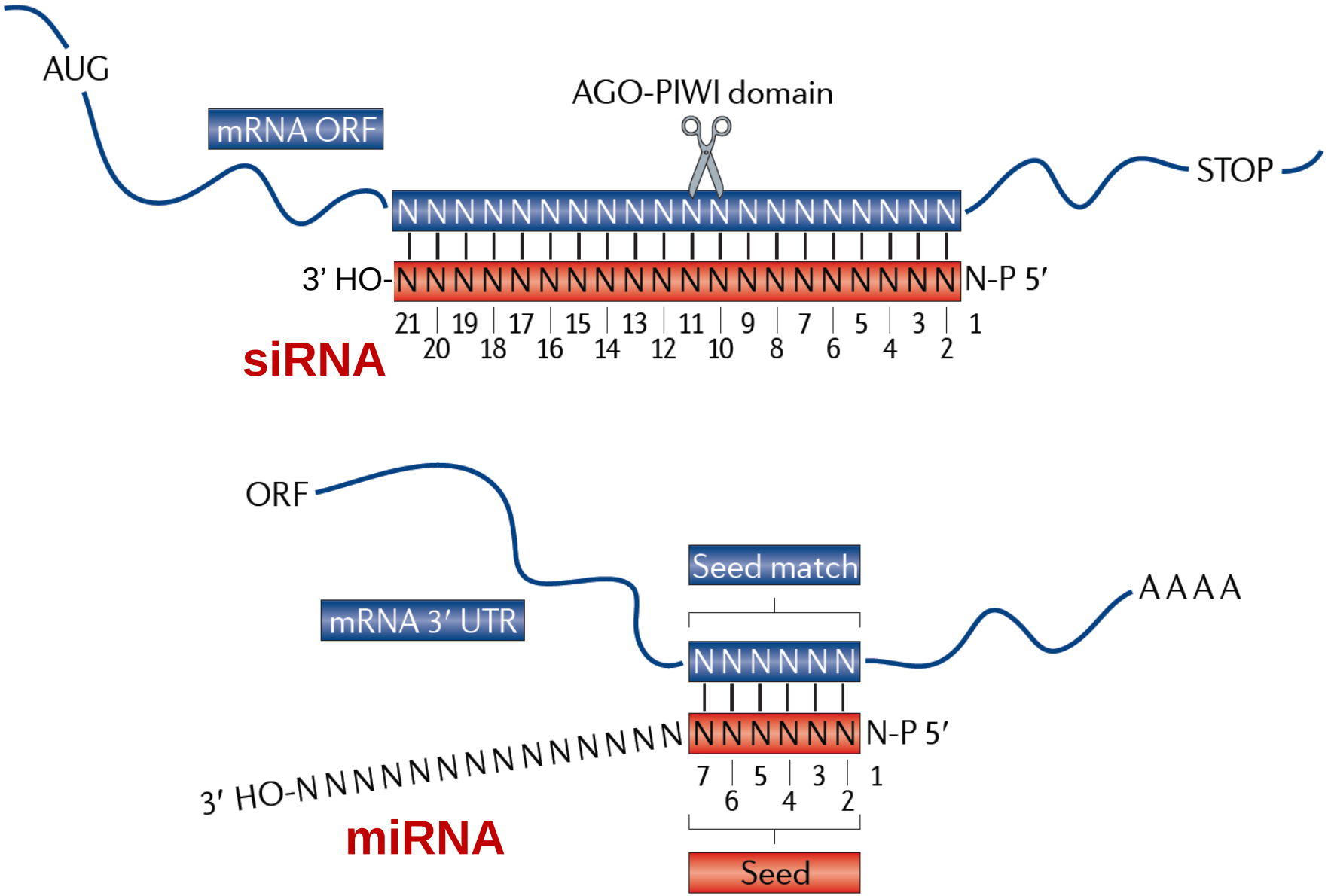
- Pasquinelli AE, Reinhart BJ, Slack F, Martindale MQ, Kuroda MI, Maller B, Hayward DC, Ball EE, Degnan B, Müller P, Spring J, Srinivasan A, Fishman M, Finnerty J, Corbo J, Levine M, Leahy P, Davidson E, Ruvkun G. Conservation of the sequence and temporal expression of let-7 heterochronic regulatory RNA. Nature. 2000; 408(6808): 86–89.
- Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Aldler H, Rattan S, Keating M, Rai K, Rassenti L, Kipps T, Negrini M, Bullrich F, Croce CM. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci U S A. 2002; 99(24): 15524-15529.

miRNA -> RNA-target recognition in plants and animals



- 2011-Huntzinger-Gene silencing by miRNAs-Contributions of translational repression & mRNA decay-Nat Rev Genet

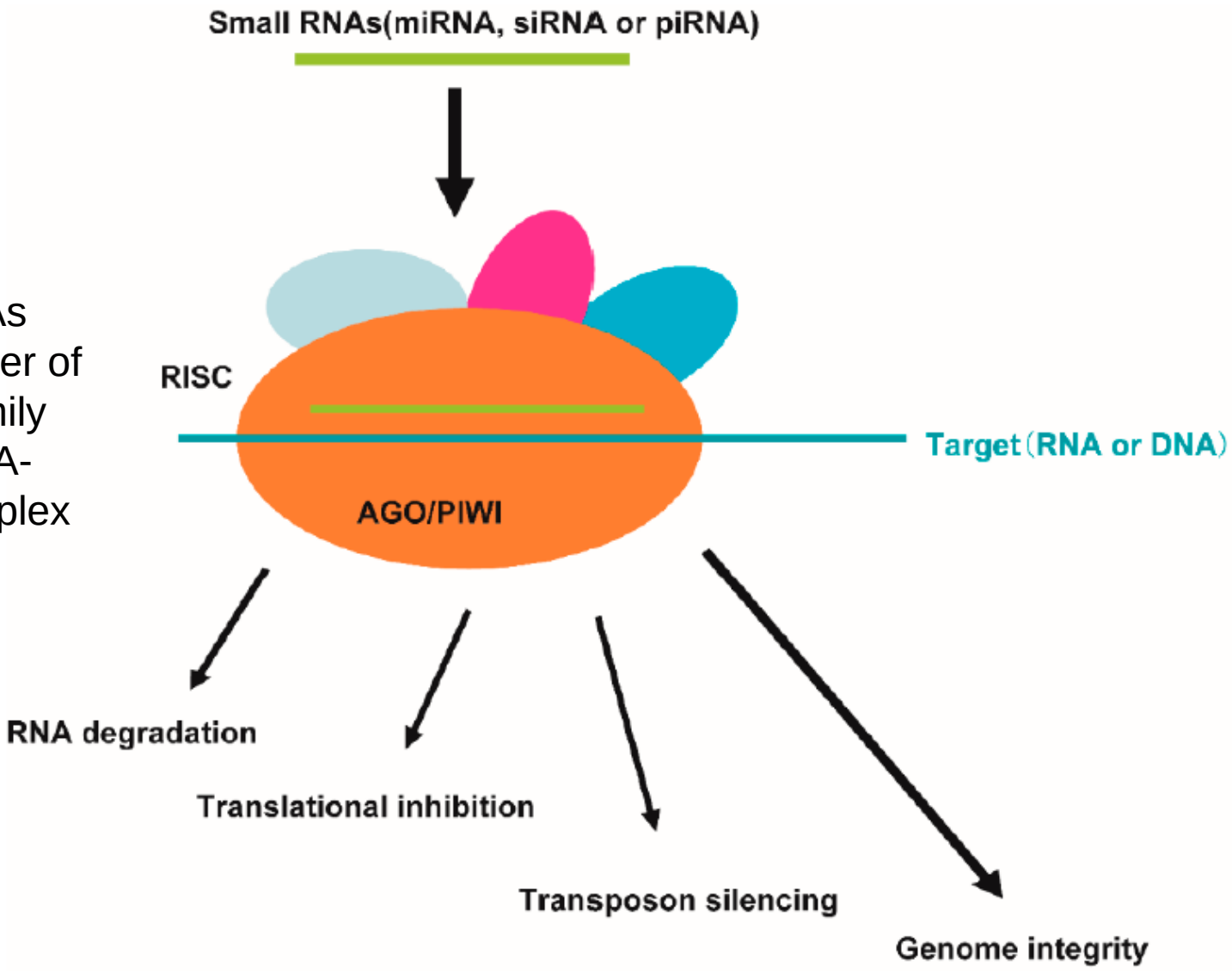
siRNA and miRNA -> RNA-target recognition in animals



- 2011-Huntzinger-Gene silencing by miRNAs-Contributions of translational repression & mRNA decay-Nat Rev Genet

Small silencing RNAs cannot work alone

Small silencing RNAs assemble with a member of Argonaute / PIWI family proteins into the RNA-induced silencing complex (RISC)

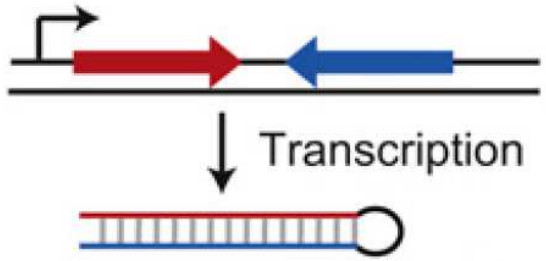


- Small RNAs must form effector ribonucleoprotein complexes known as RNA-induced silencing complexes (RISCs) to exert their function.
- Small RNAs guide RISCs to their targets in a sequence-specific manner.

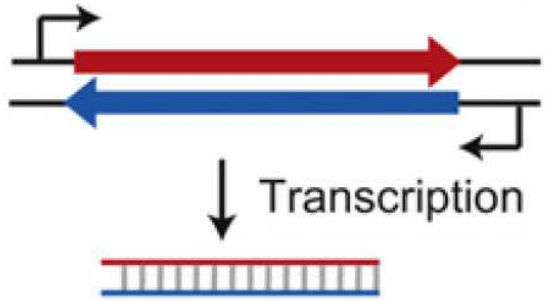
- 2016-Zhai_L-Argonaute & Argonaute-bound small RNAs in stem cells-Int J Mol Sci

Origins of siRNAs

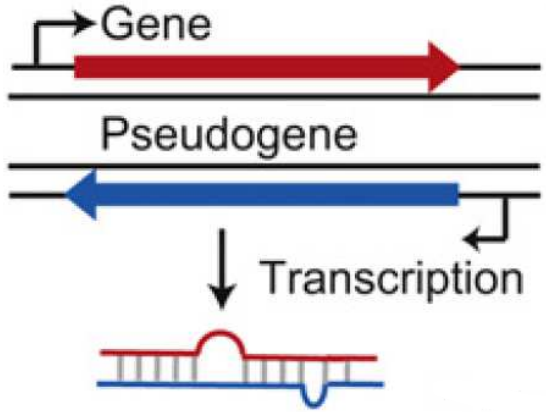
i) Hairpin derived endo-siRNA locus, inverted repeat



ii) cis-nat siRNA



iii) trans-nat siRNA



Transcripts that are able to form double-stranded RNA or long stem-loop structures serve as endogenous (endo-siRNA) or exogenous (exo-siRNA) siRNA precursors.

Endo-siRNAs can originate from RNA transcripts with extensive hairpin structures, from convergent transcription units or from the annealing of sense and antisense RNAs from unlinked loci.

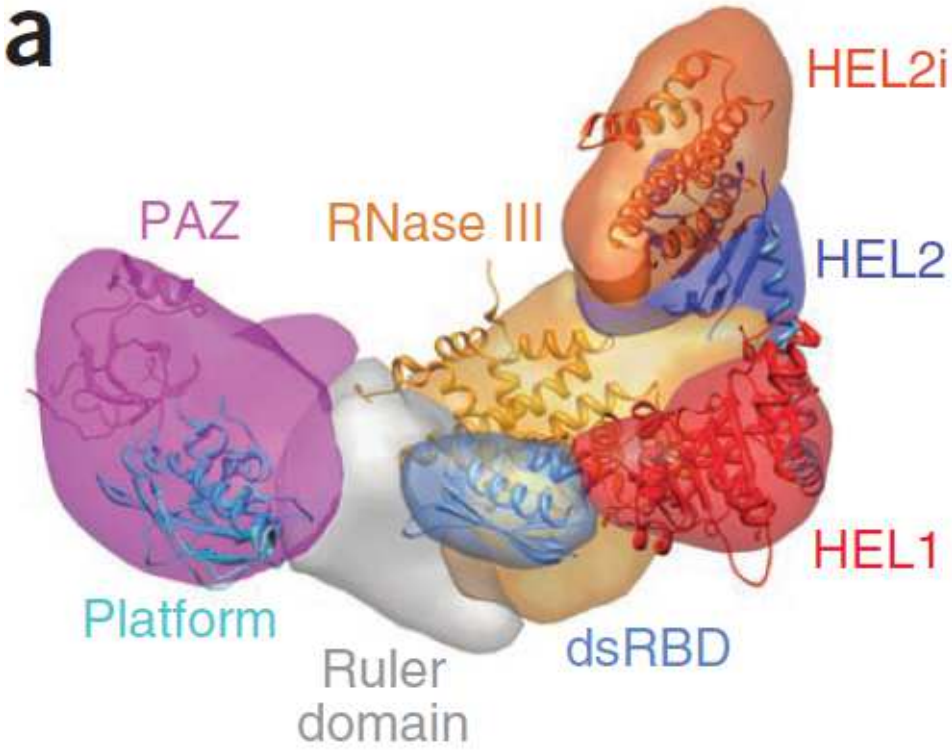
Exo-siRNAs may derive from viral replication intermediates or experimental introduction of long dsRNAs.

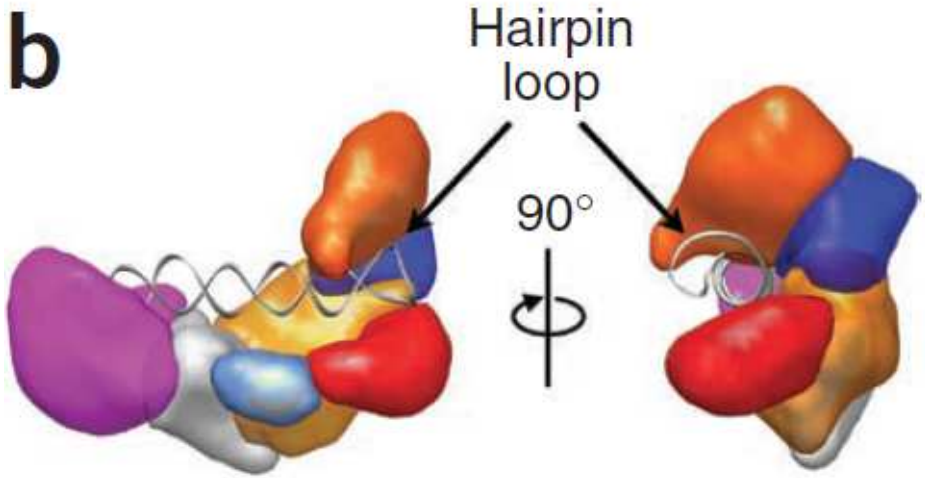
Small interfering RNAs (siRNAs) vary in their biogenesis mechanisms, but can be approximately divided into two classes, depending on whether they require RNA-dependent RNA polymerases (RdRPs) for their production.

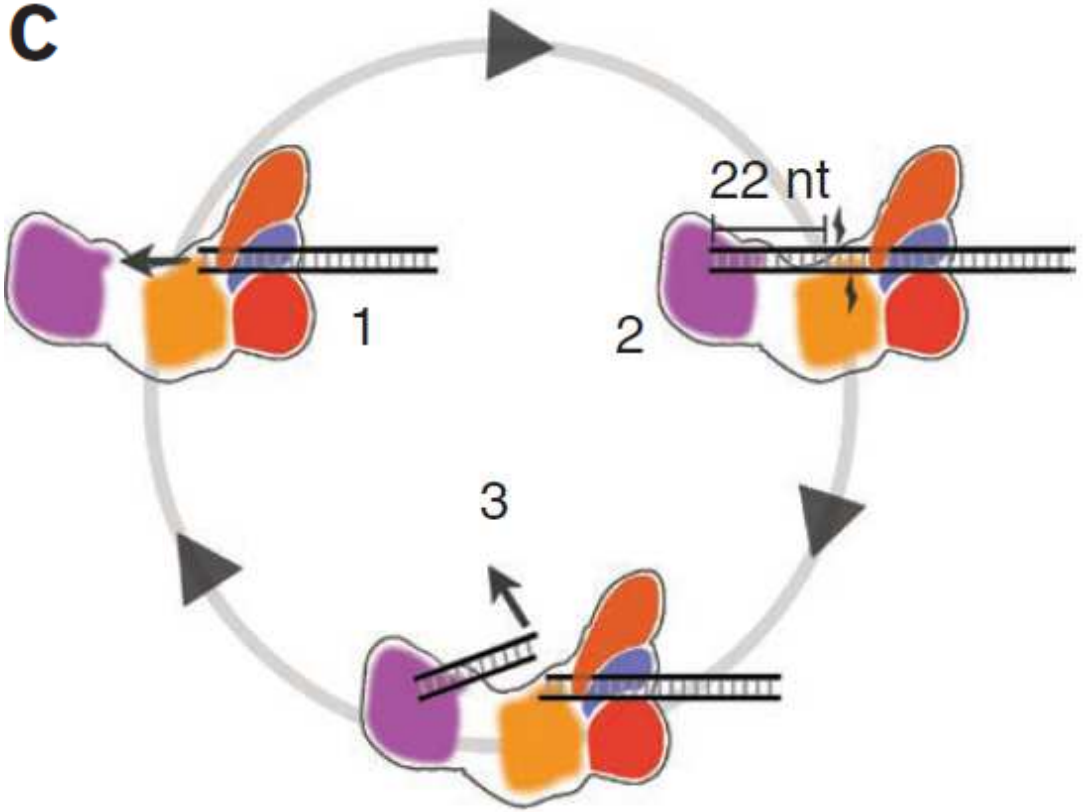
In contrast to mammals and flies, worms and plants produce numerous endo-siRNAs using biogenesis mechanisms that depend on the action of RdRPs.

- **2011-Röther_S-Small RNAs derived from longer non-coding RNAs-Biochimie**

The cytoplasmic enzyme Dicer is central to the production of siRNAs and miRNAs





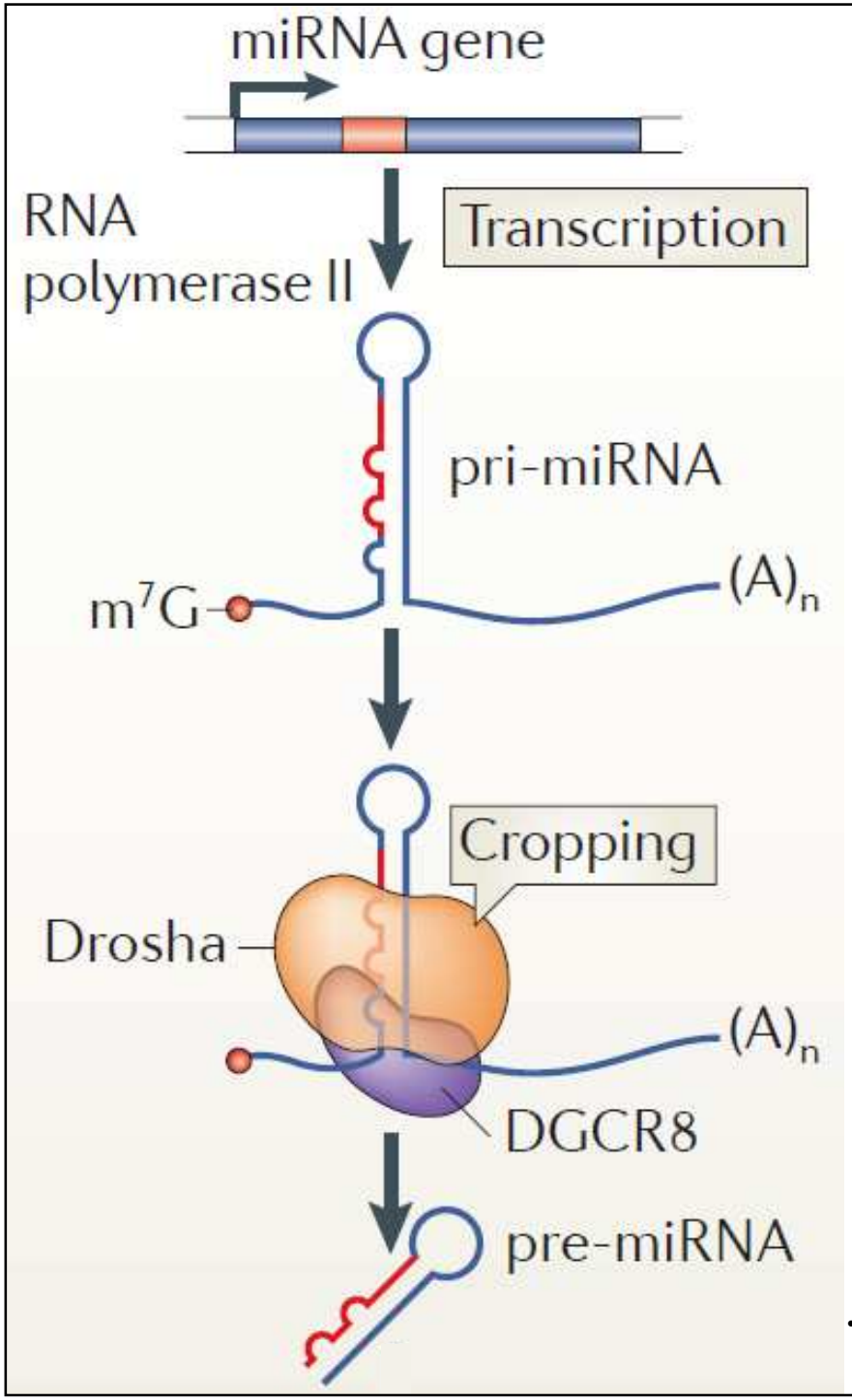


(a) Segmented map of human Dicer with crystal structures of homologous domains docked.
(b) Model for pre-miRNA recognition. A pre-miRNA hairpin is modeled into the proposed binding channel of Dicer, with the stem-loop fit in the RNA-binding cleft of the helicase.
(c) Schematic for processive dicing. The helicase translocates dsRNA into the nuclease core (1). The PAZ domain (purple) recognizes the dsRNA end, positioning RNase III (orange) for cleavage (2). The siRNA product is released while the dsRNA substrate remains bound to the helicase (3).

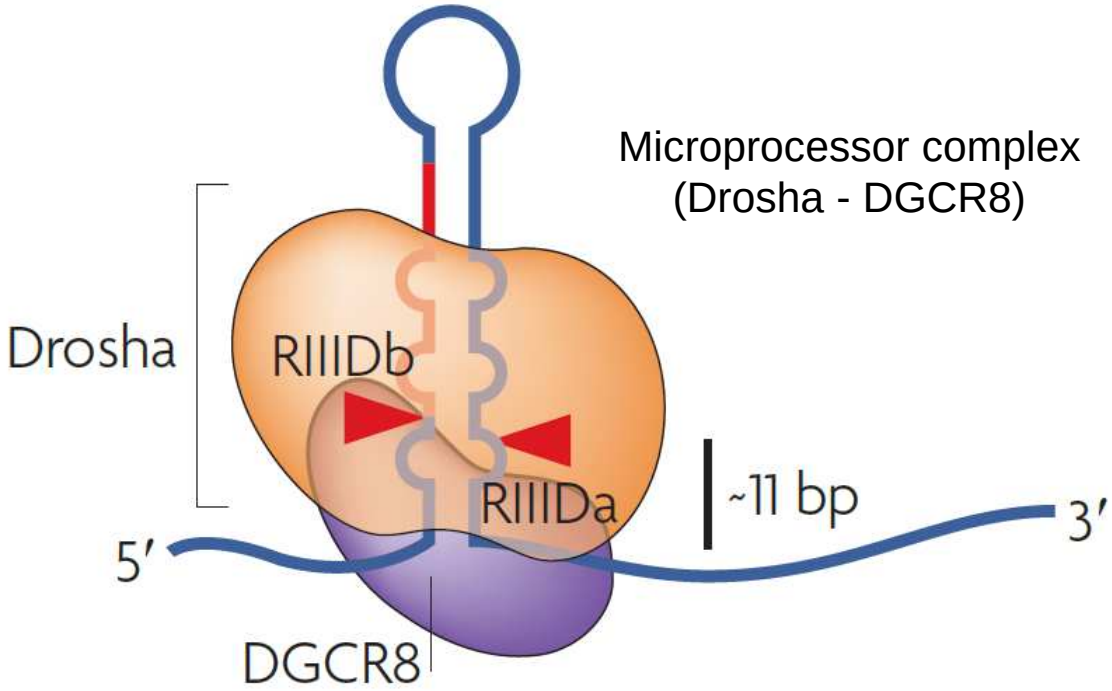
- **2012-Lau_PW-The molecular architecture of human Dicer-Nat Struct Mol Biol**

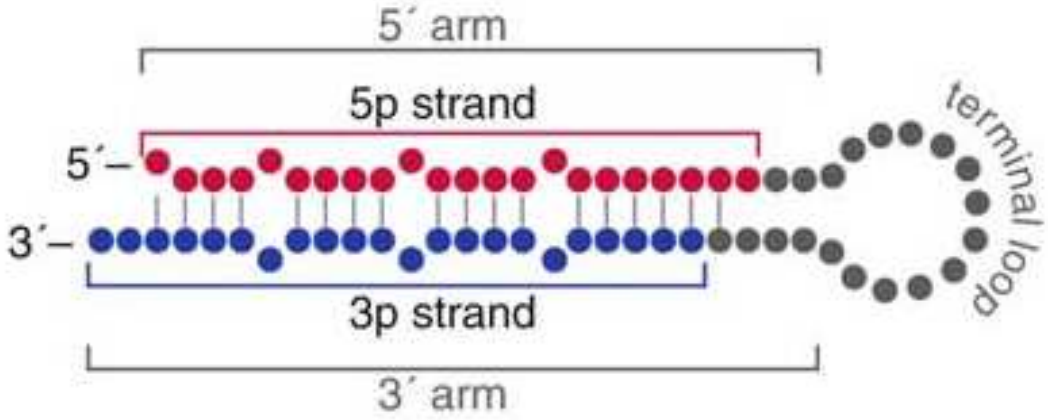
Origins of miRNAs (1)

Transcription of pri-miRNA and Drosha-mediated pre-miRNA biogenesis



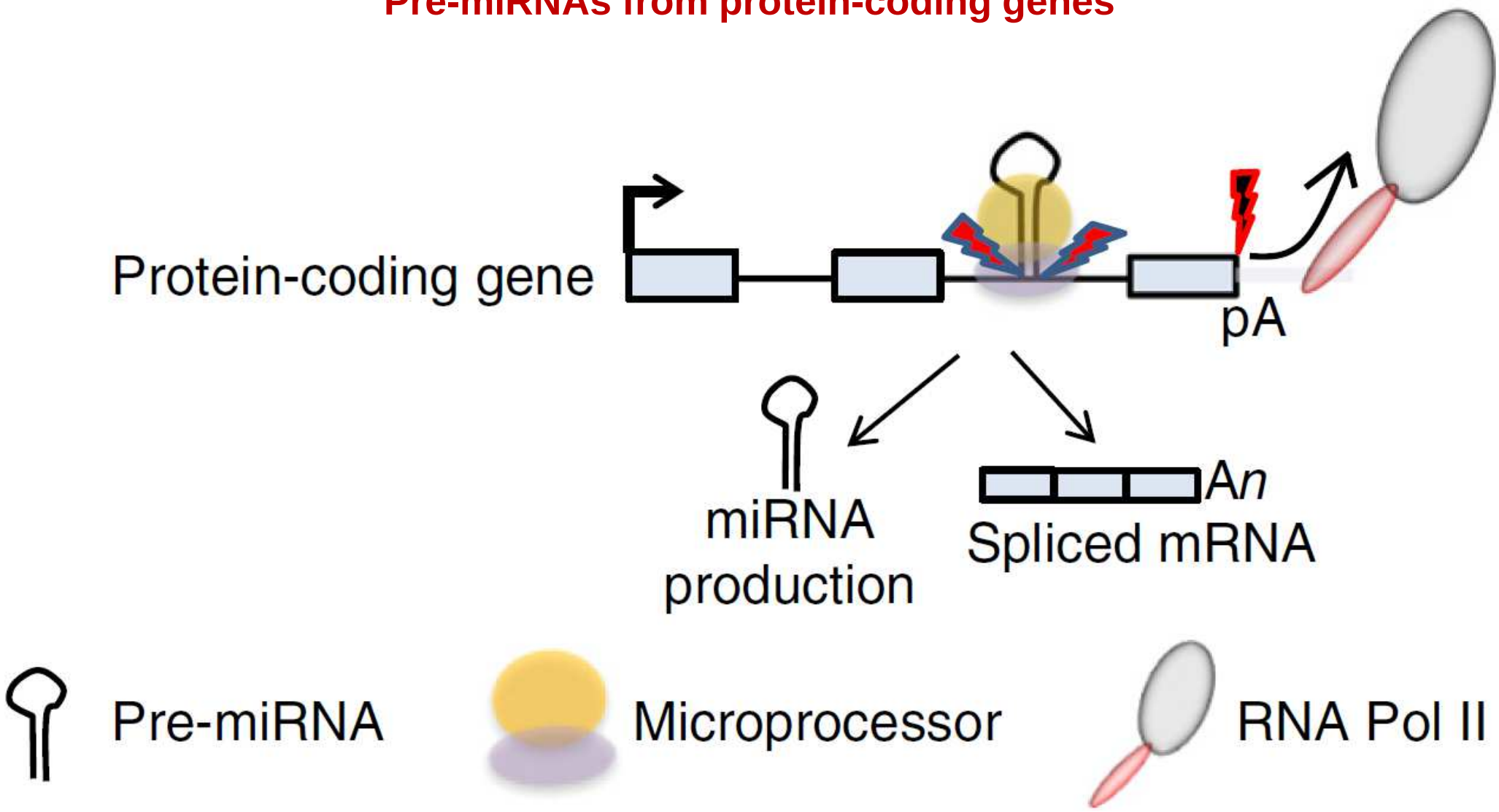
Microprocessor complex (Drosha - DGCR8)





- **2011-Siomi_MC-PIWI-interacting small RNAs-The vanguard of genome defence-Nat Rev Mol Cell Biol**
- **2010-Kawamata_T-Making RISC-TIBS**
- **2009-Kim_VN-Biogenesis of small RNAs in animals-Nat Rev Mol Cell Biol**

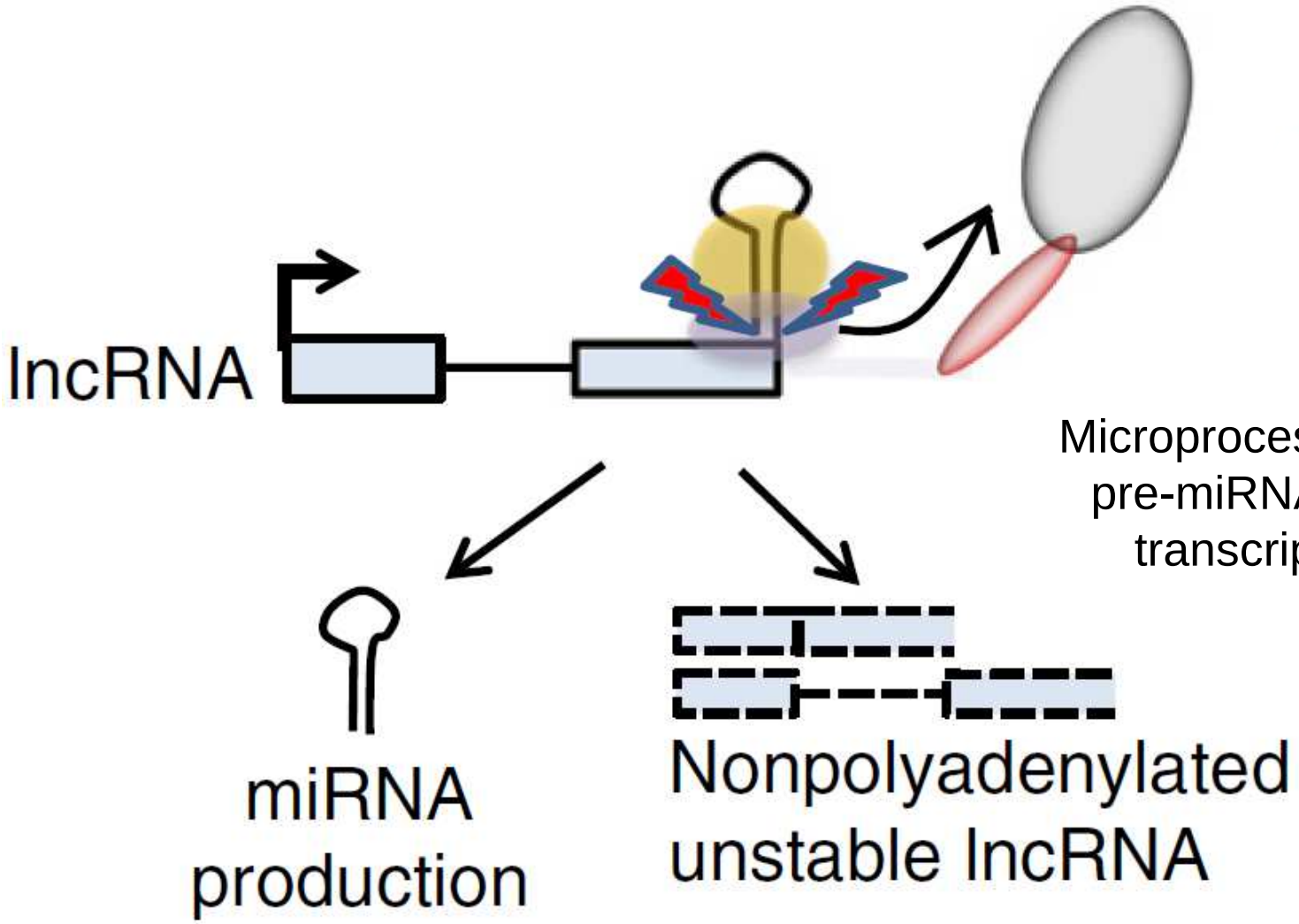
Pre-miRNAs from protein-coding genes



Most miRNAs derive from introns of protein-coding transcripts, for which cotranscriptional Microprocessor cleavage does not inhibit splicing, thus allowing coexpression of miRNA and mRNA from the same host transcript. In contrast, Drosha processing of a pre-miRNA located in a protein-coding-gene exon can inhibit production of the spliced host mRNA. CPA: cleavage and polyadenylation complex.

- **2015-Dhir_A-Microprocessor mediates transcriptional termination of lncRNA transcripts hosting miRNAs-Nat Struct Mol Biol**

Pre-miRNAs from long non-coding RNA genes

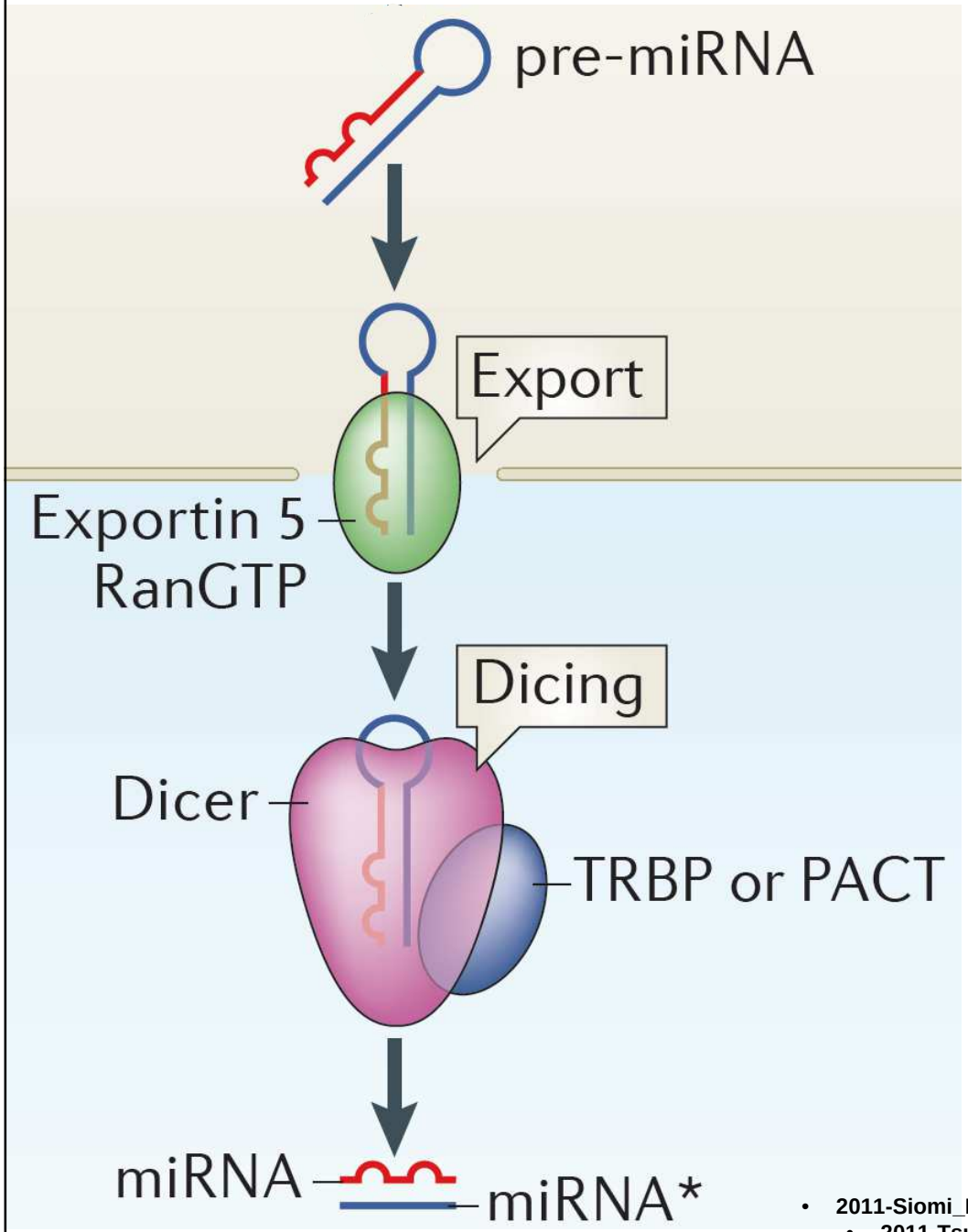


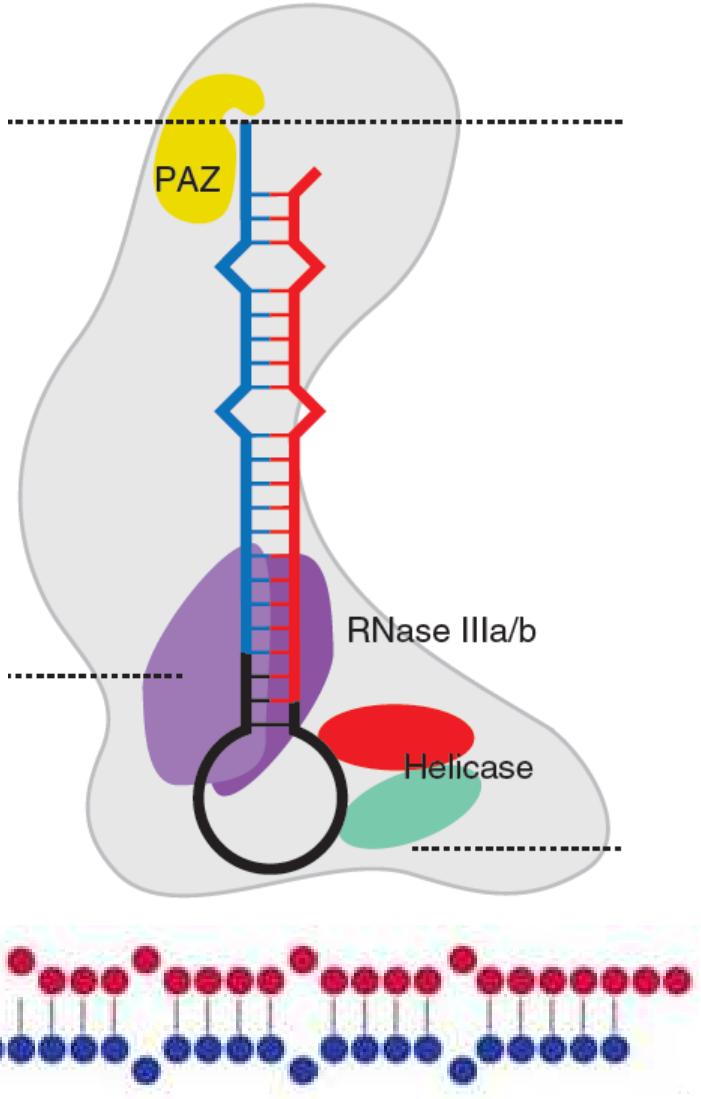
Microprocessor (Drosha-DGCR8) mediates transcriptional termination of most long noncoding RNA transcripts hosting miRNAs. Microprocessor-driven transcriptional termination occurs on lncRNA genes with either intronic or exonic miRNAs.

- **2015-Dhir_A-Microprocessor mediates transcriptional termination of lncRNA transcripts hosting miRNAs-Nat Struct Mol Biol**

Origins of miRNAs (2)

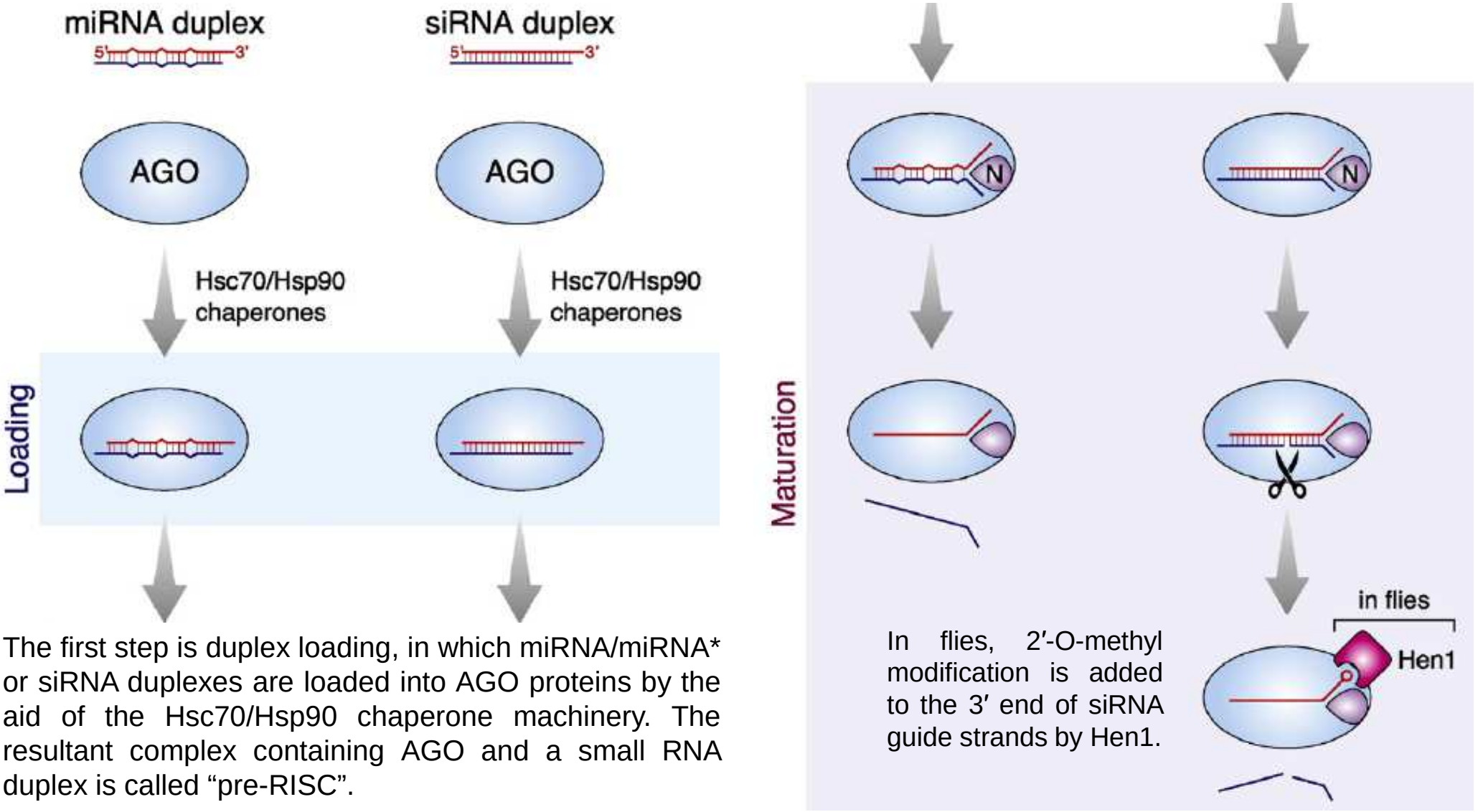
Pre-miRNA export into the cytoplasm and Dicer-mediated processing





- 2011-Siomi_MC-PIWI-interacting small RNAs-The vanguard of genome defence-Nat Rev Mol Cell Biol
- 2011-Tsutsumi_A-Recognition of the pre-miRNA structure by DM Dicer-1-Nat Struct Mol Biol
- 2010-Kawamata_T-Making RISC-TIBS

RISC assembly is divided into two major steps: loading and maturation



The first step is duplex loading, in which miRNA/miRNA* or siRNA duplexes are loaded into AGO proteins by the aid of the Hsc70/Hsp90 chaperone machinery. The resultant complex containing AGO and a small RNA duplex is called “pre-RISC”.

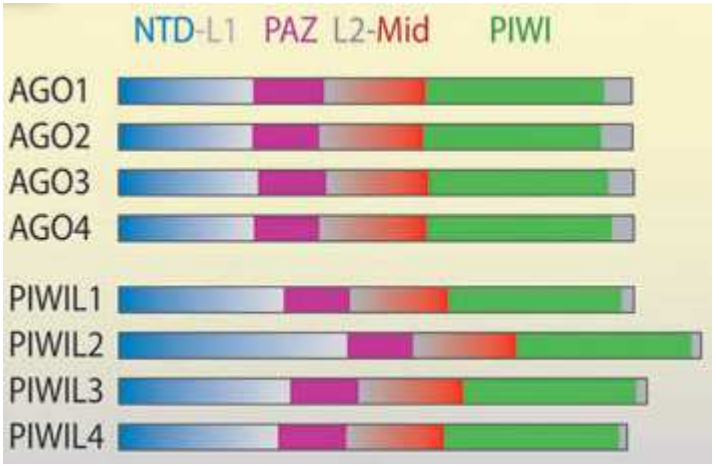
In flies, 2′-O-methyl modification is added to the 3′ end of siRNA guide strands by Hen1.

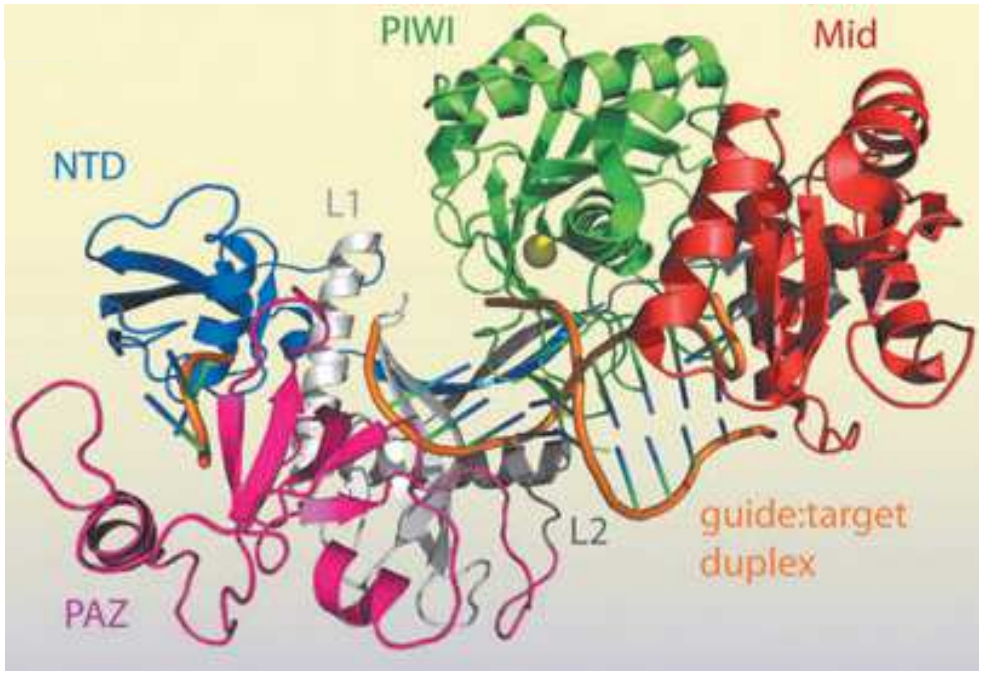
RISC maturation is initiated by wedging, in which the N domain of Ago subfamily proteins pries open base pairs at the 3′ end of the guide strand (paired with the 5′ end of passenger strand). Maturation is completed by passenger ejection, in which passenger strands are ejected from AGO proteins. Passenger ejection of miRNA/miRNA* duplexes and siRNA duplexes occurs in slicer-independent and slicer-dependent manners, respectively.

- **2016-Kobayashi_H-RISC assembly-Coordination between small RNAs & Argonaute proteins-BBA**

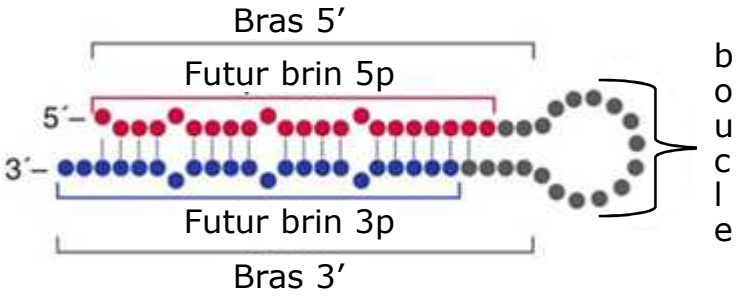
Les protéines de la famille Argonaute / PIWI

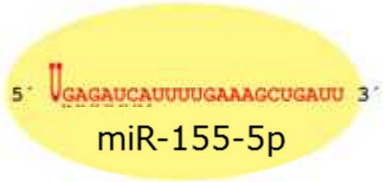
Entre les deux brins, lequel sera conservé et lequel sera éliminé ?

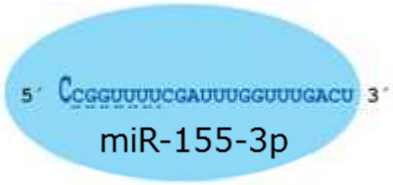


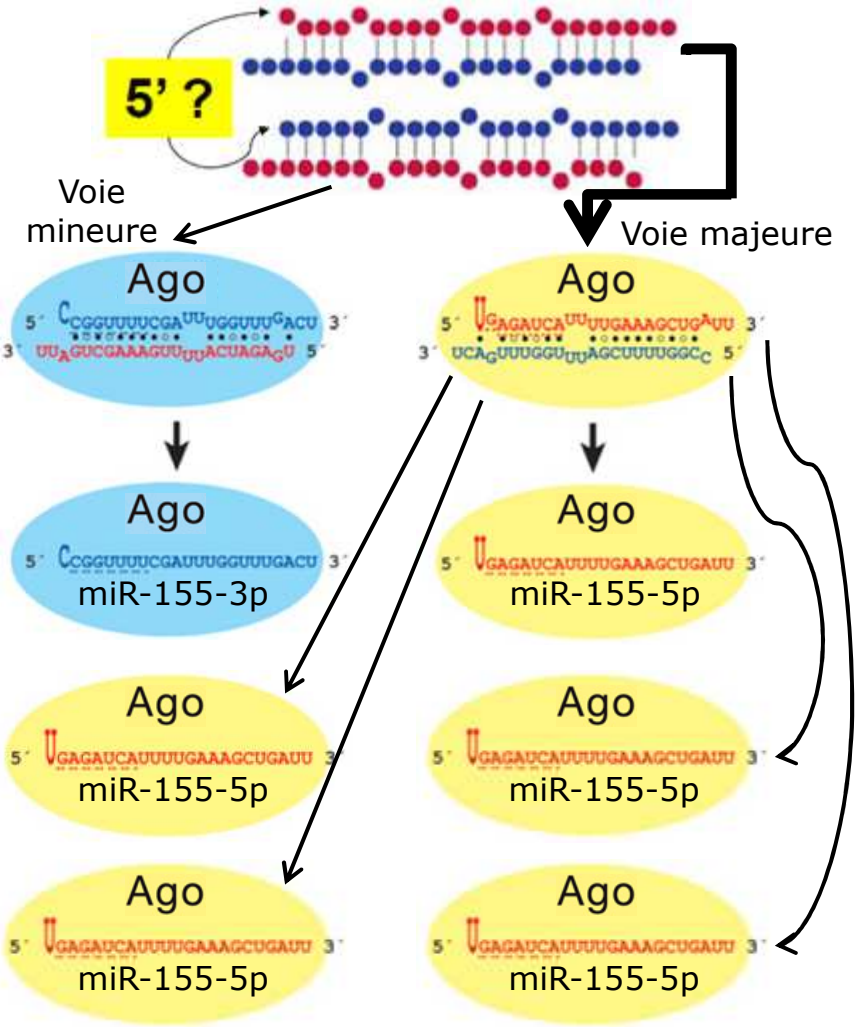


Exemple du pré-miRNA mir-155



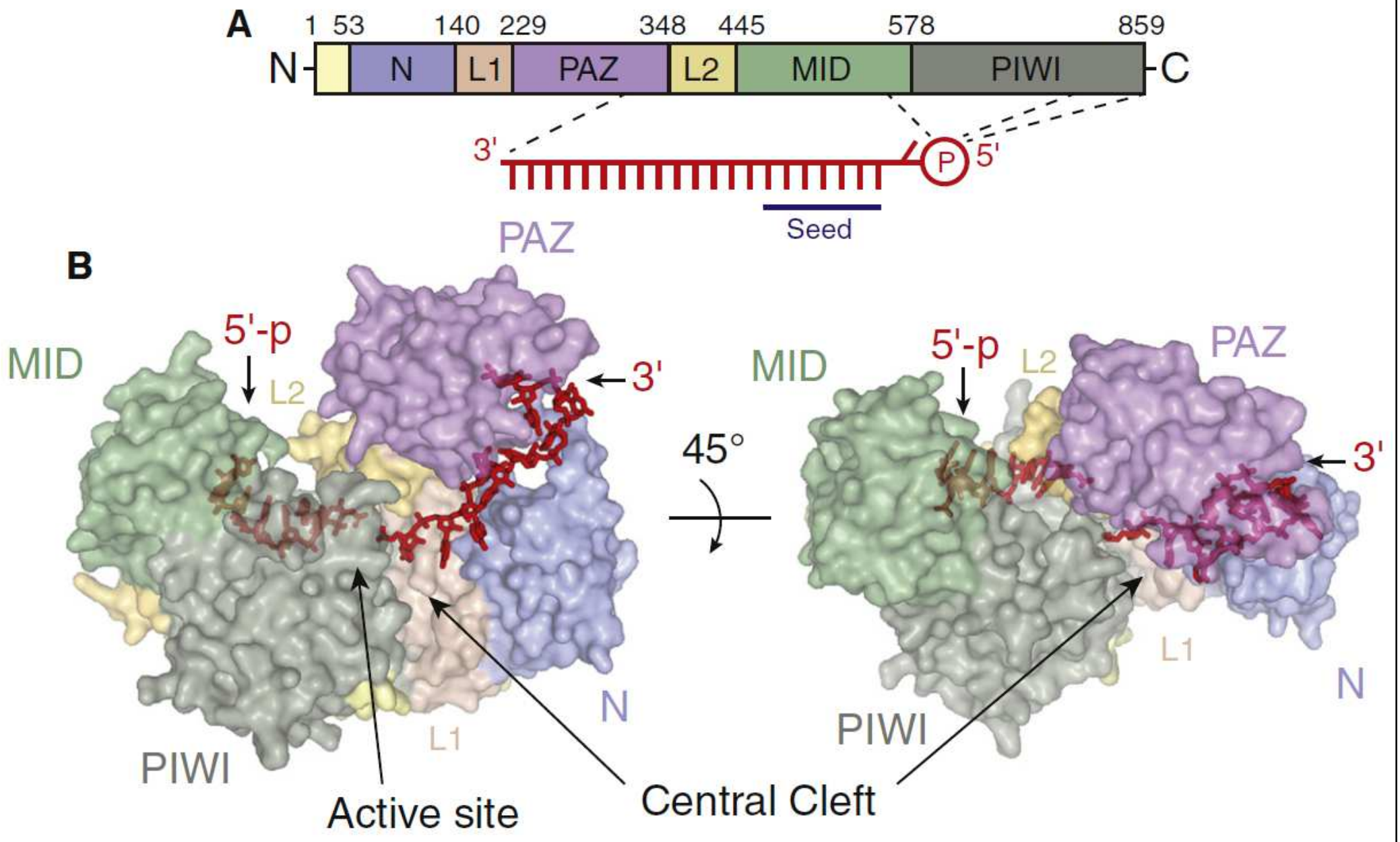






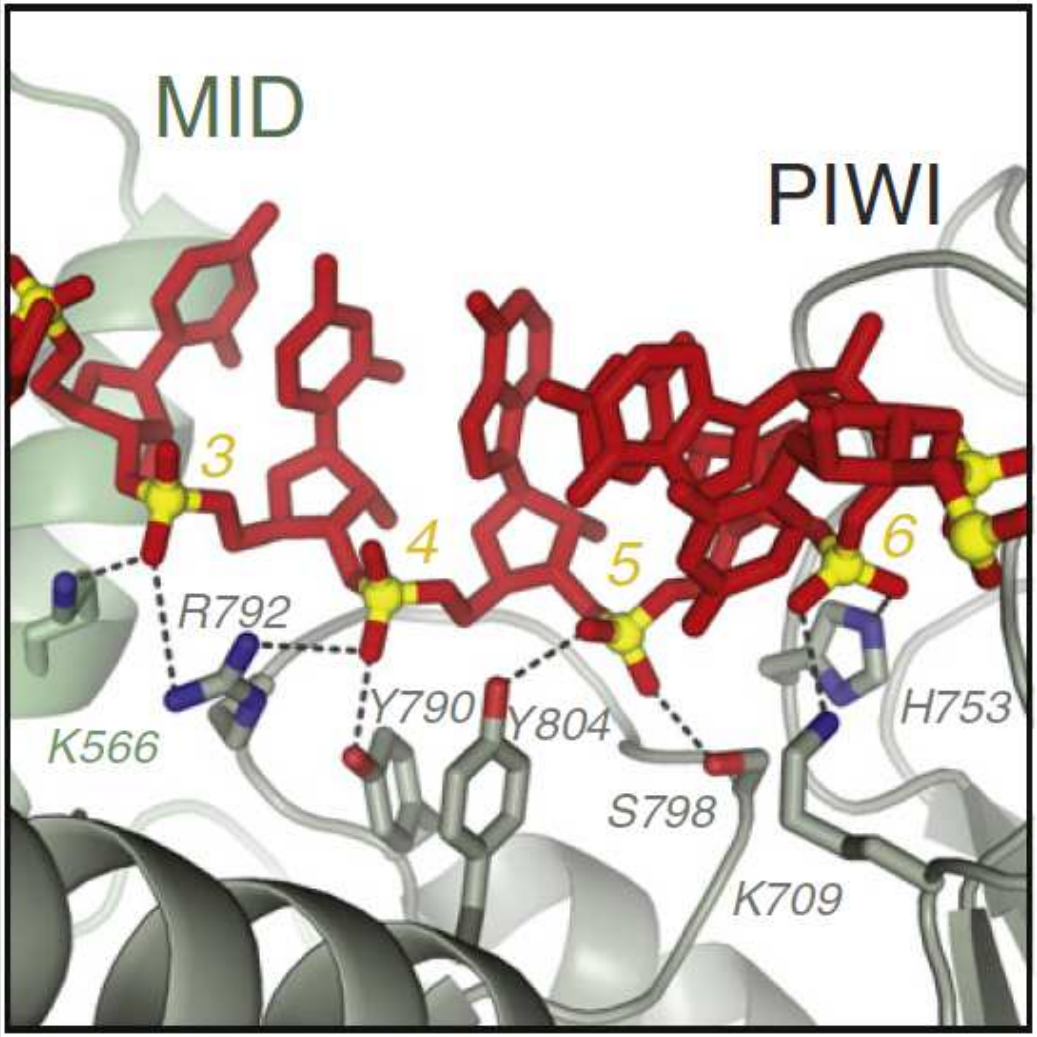
- 2017-Zendjabil_M-Les microRNA comme biomarqueurs-Quelles perspectives-CR Biol
- 2010-Ghildiyal_M-Sorting of Drosophila small silencing RNAs partitions miRNA* strands into the RNA interference pathway-RNA

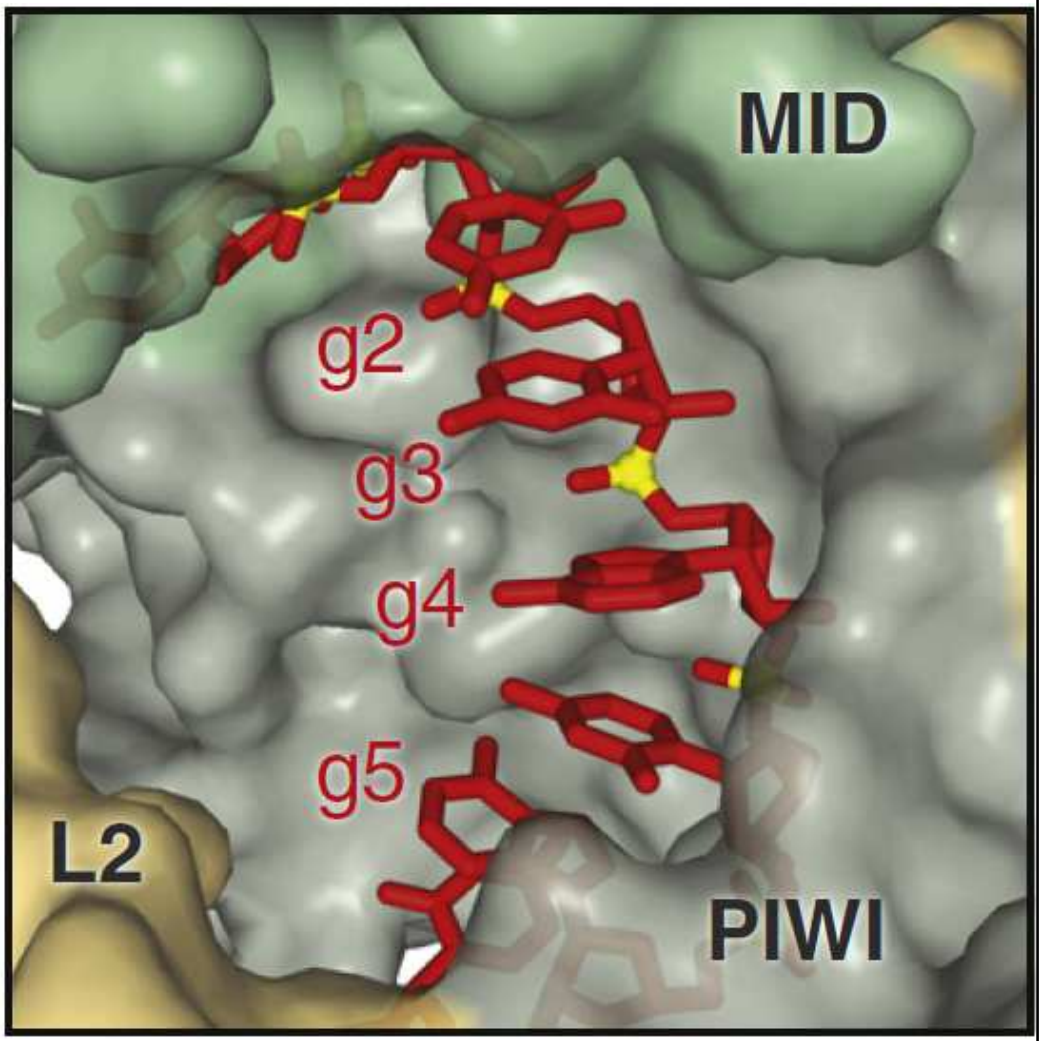
The architecture of human Argonaute-2



- 2017-Sheu-Gruttadauria_J-Structural foundations of RNA silencing by AGO-JMB

Close-up view of the seed region of human Argonaute-2



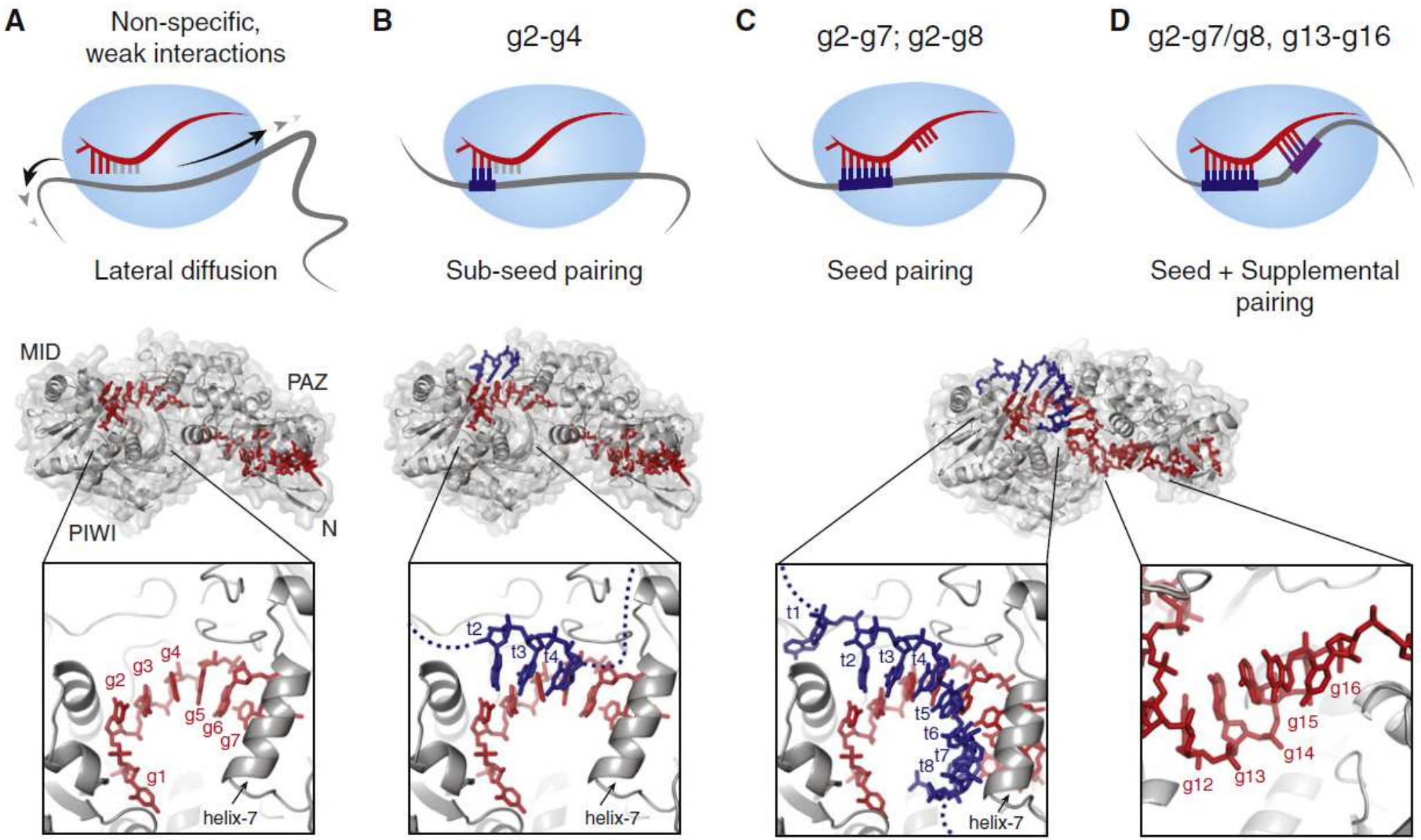


In keeping with the notion that Argonaute can bind guide RNAs of any sequence, almost all interactions with the protein are mediated through the RNA sugar-phosphate backbone.

Surface representation of Ago2 reveals that only guide nucleotides g2–g4 are fully available for initiating interactions with target RNAs.

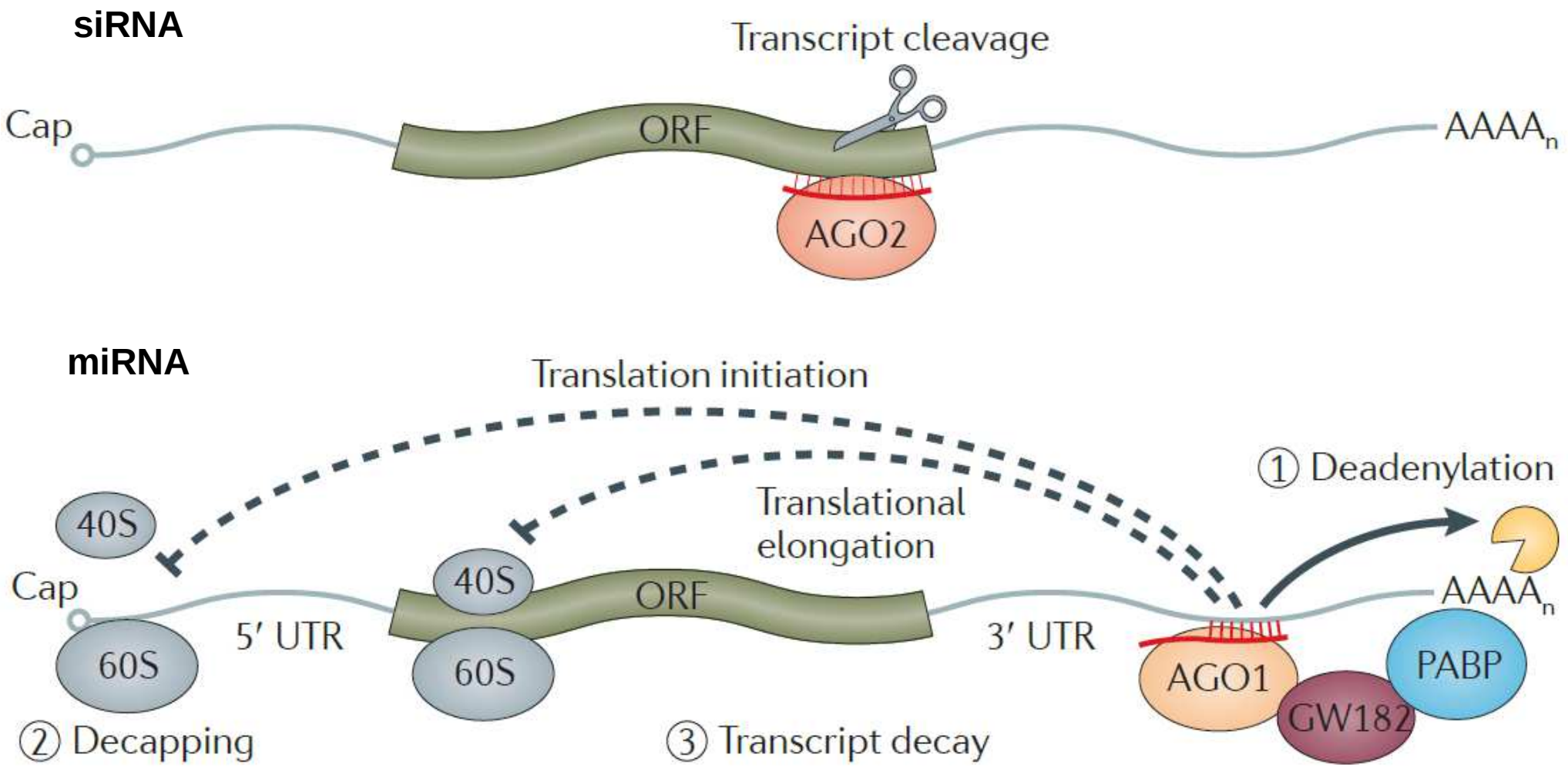
- **2017-Sheu-Gruttadauria_J-Structural foundations of RNA silencing by AGO-JMB**

Model for Argonaute targeting



- 2017-Sheu-Gruttadauria_J-Structural foundations of RNA silencing by AGO-JMB

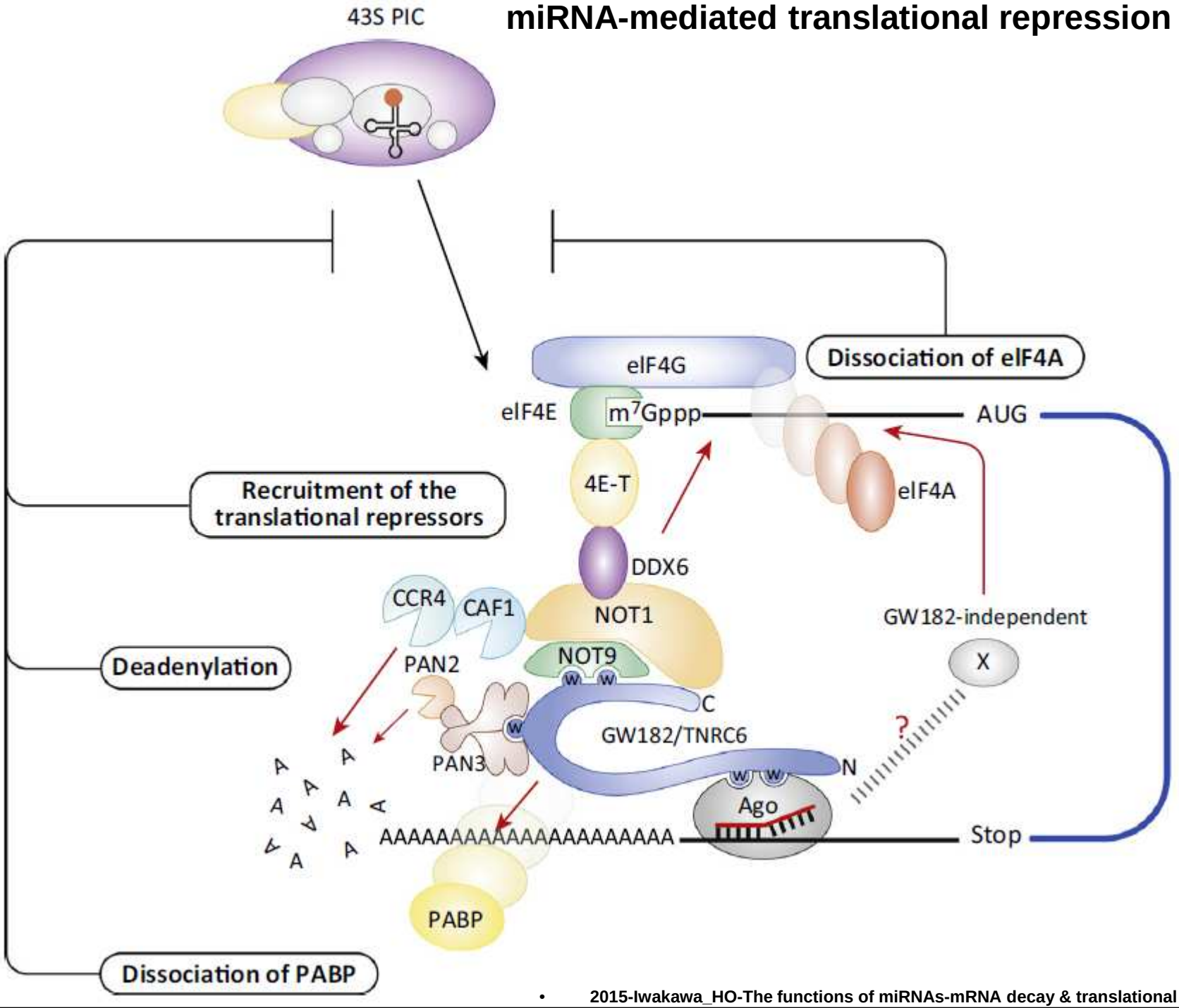
Mechanisms of post-transcriptional regulation by small RNAs



- **Les miRNA sont des régulateurs post-transcriptionnels de l'expression génique (action répressive)**
- **Leur rôle s'exerce dans tous les domaines de la vie**
  - Ils régulent les mécanismes de développement et de différenciation, les processus physiologiques visant à maintenir l'homéostasie cellulaire…

- **2011-Czech-Small RNA sorting-Matchmaking for Argonautes-Nat Rev Genet**

miRNA-mediated translational repression in animals



- 2015-Iwakawa_HO-The functions of miRNAs-mRNA decay & translational repression-TICB

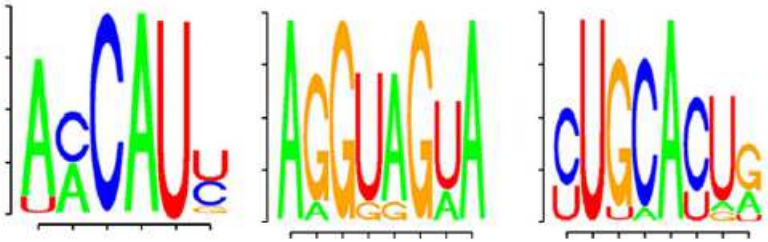
La sécrétion des miRNA par les exosomes : un nouveau mode de communication intercellulaire

CLmiRNA: miR-17

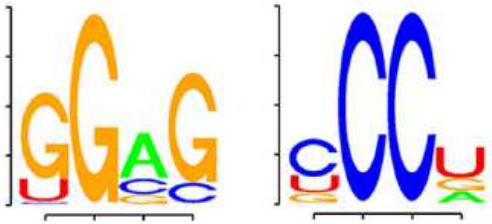
CAAAGUGCUUACAGUGCAGGUAG CLmotif

EXOmiRNA: miR-601

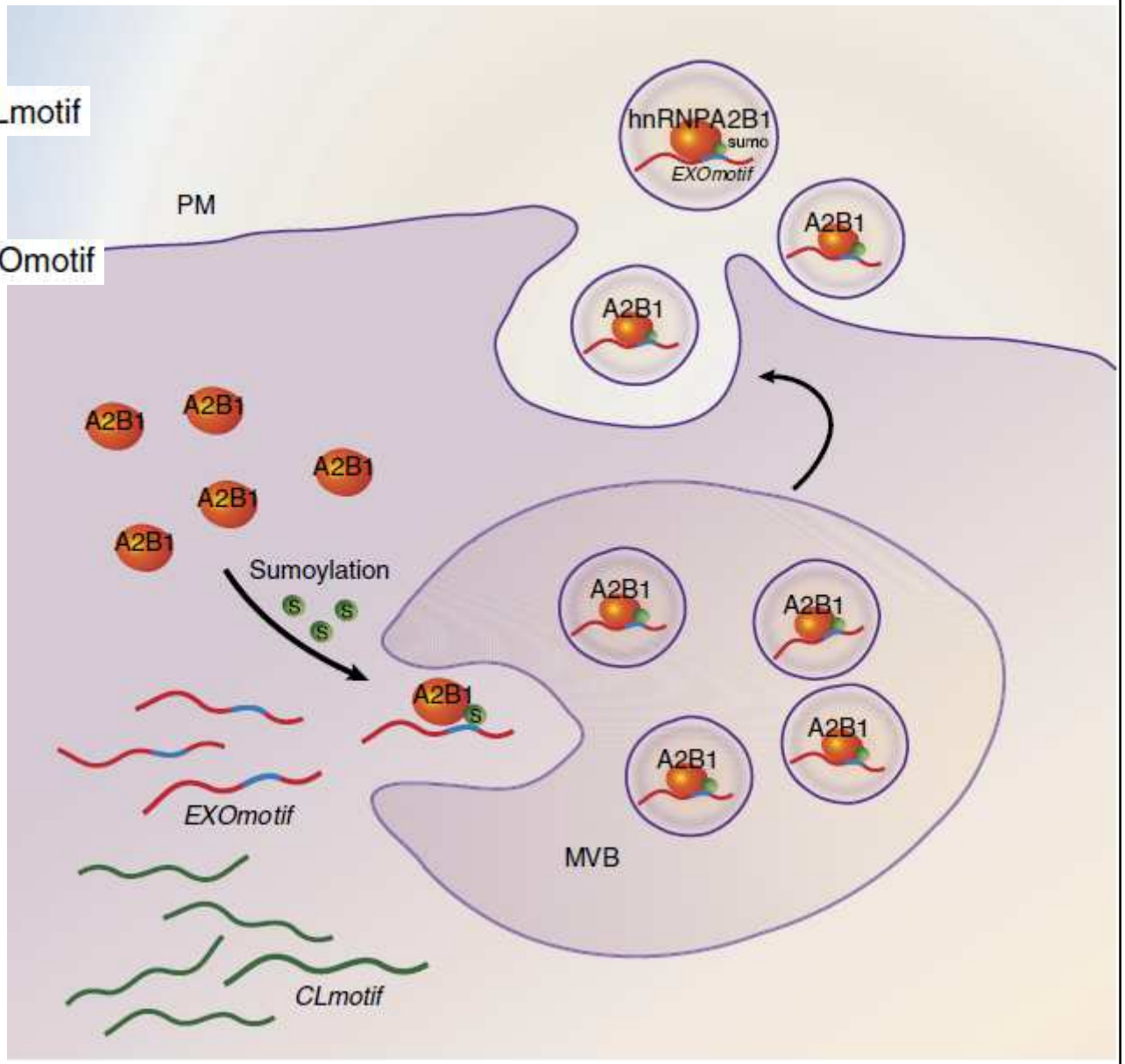
UGGUCUAGGAUUGUUGGAGGAG EXOmotif



CL-MOTIFS



EXO-MOTIFS

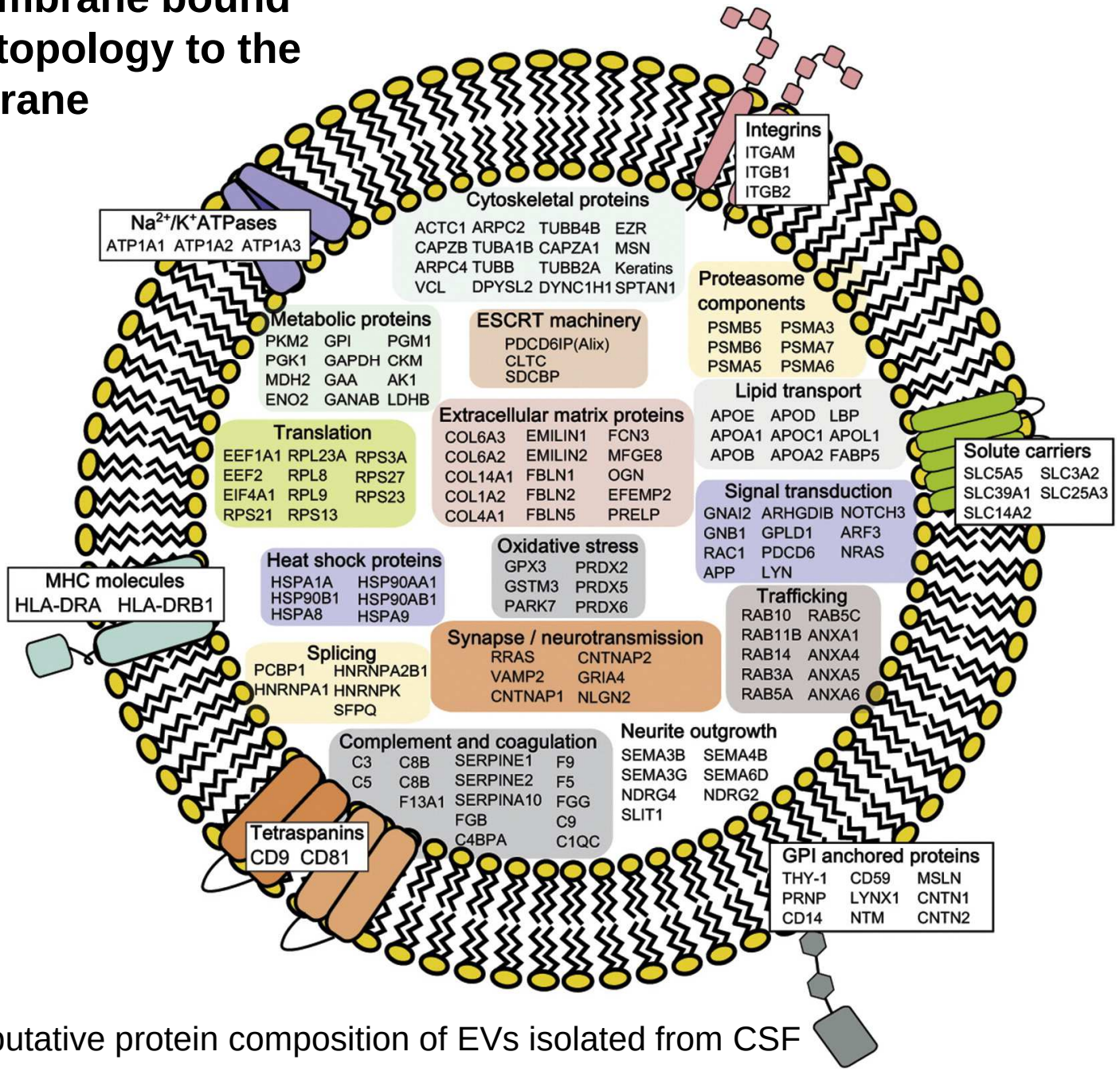


Proposed mechanism of the sorting of miRNA into exosomes through binding to hnRNPA2B1

- **2013-Villarroya-Beltri-Sumoylated hnRNPA2B1 controls the sorting of miRNAs into exosomes through binding to specific motifs-Nat Commun**

Exosomes are small membrane bound vesicles sharing similar topology to the plasma membrane

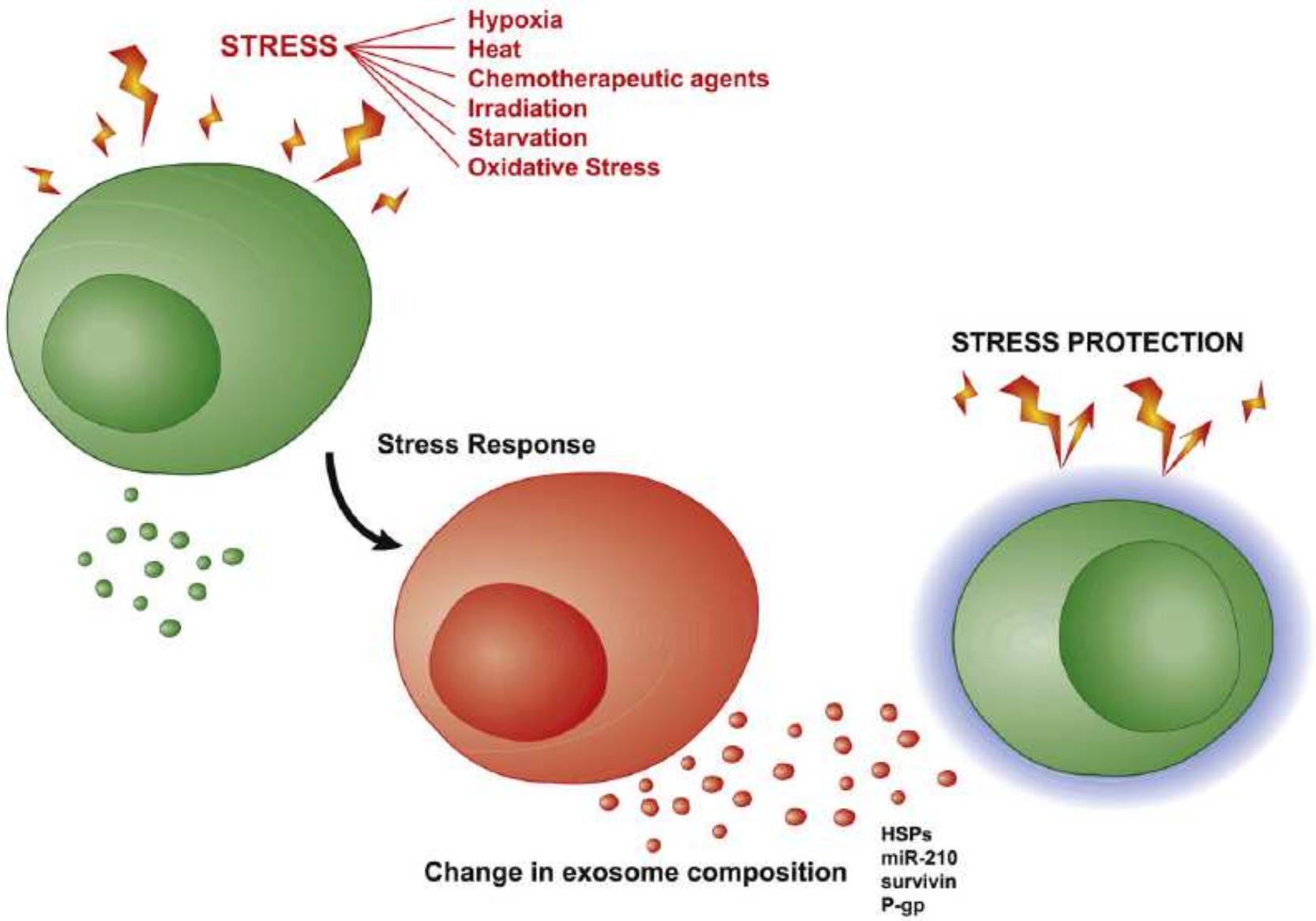
Exosomes contain specific repertoires of proteins, RNAs and lipids



Scheme of the putative protein composition of EVs isolated from CSF

- **2014-Chiasserini-Proteomic analysis of CSF EVs-A comprehensive dataset-J Proteomics**

Changes in exosomal RNA and protein composition can influence the response of distant cells



The stress-induced changes in exosomal RNA and protein composition can influence the response of distant cells to stress by providing protective signals (surveillance, drug resistance, etc.).

- **2014-Villarroya-Beltri_C-Sorting it out-Regulation of exosome loading-Semin Cancer Biol**

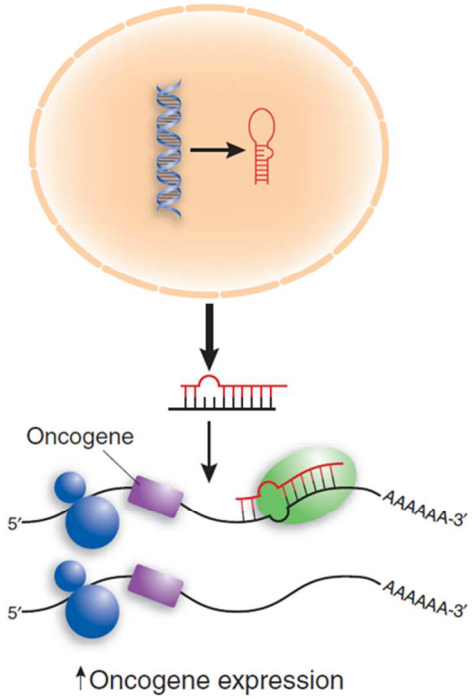
Utilisation des micro-ARN comme biomarqueurs

Les miRNA peuvent-ils être des biomarqueurs en pathologie ?

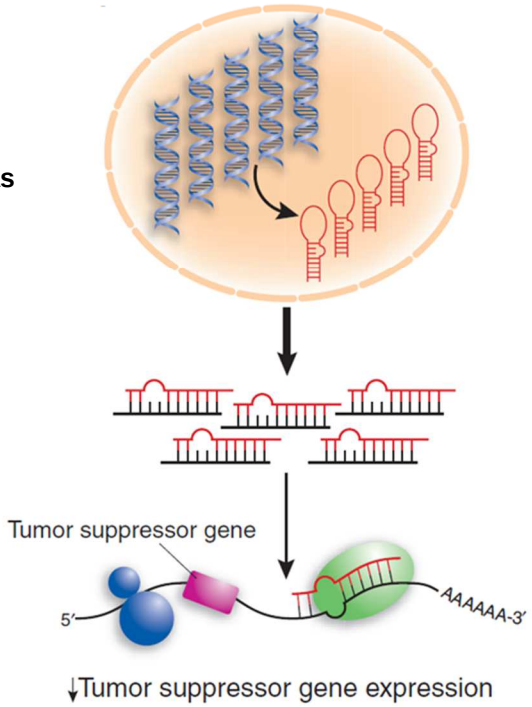
- **Oui, car dans de nombreuses maladies ces régulateurs sont eux-mêmes dérégulés:** leur expression peut être augmentée ou diminuée dans les cancers,

microRNA suppresseurs de tumeurs :
sous-exprimés par inhibition ou dérégulation de leur transcription, hyperméthylation ou délétion du locus chromosomique.

microRNA oncogènes :
sur-exprimés par activation ou dérégulation de leur transcription, hypométhylation ou amplification du locus chromosomique.



2005-Caldas_C-Sizing up miRNAs as cancer genes-Nat Med



ARN messager cible :
ARNm des oncogènes

-> augmentation de l'expression des oncogènes

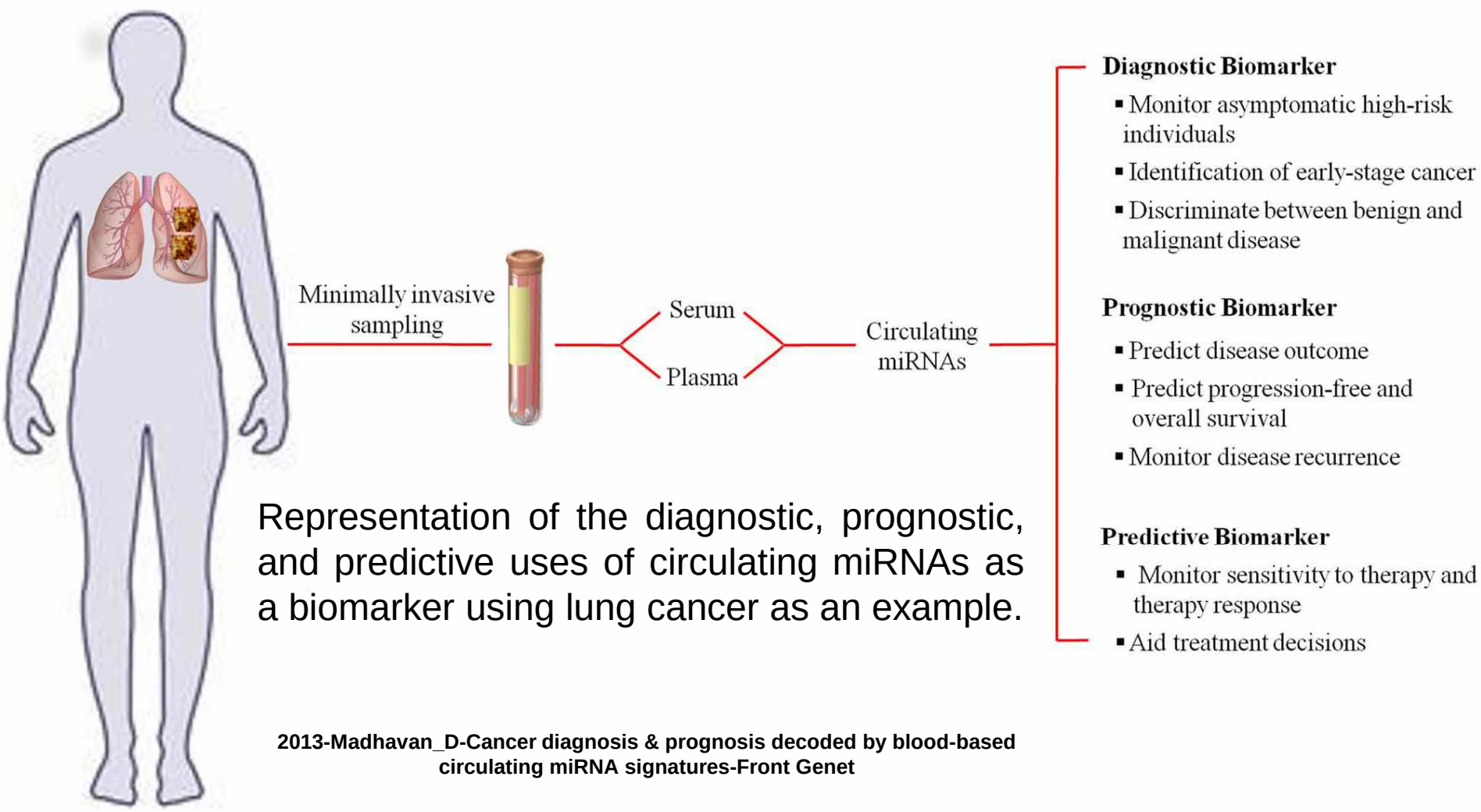
ARN messager cible :
ARNm des gènes suppresseurs de tumeur

-> diminution de l'expression des gènes suppresseurs de tumeur

… ainsi que dans les infections virales, l'inflammation, les maladies métaboliques, les pathologies dégénératives…

Peut-on étudier les miRNA dans les liquides circulants ?

- **Effectivement la question se pose car s'ils peuvent être des biomarqueurs tissulaires il faut expliquer comment on peut les retrouver dans le sang par exemple:**



Representation of the diagnostic, prognostic, and predictive uses of circulating miRNAs as a biomarker using lung cancer as an example.

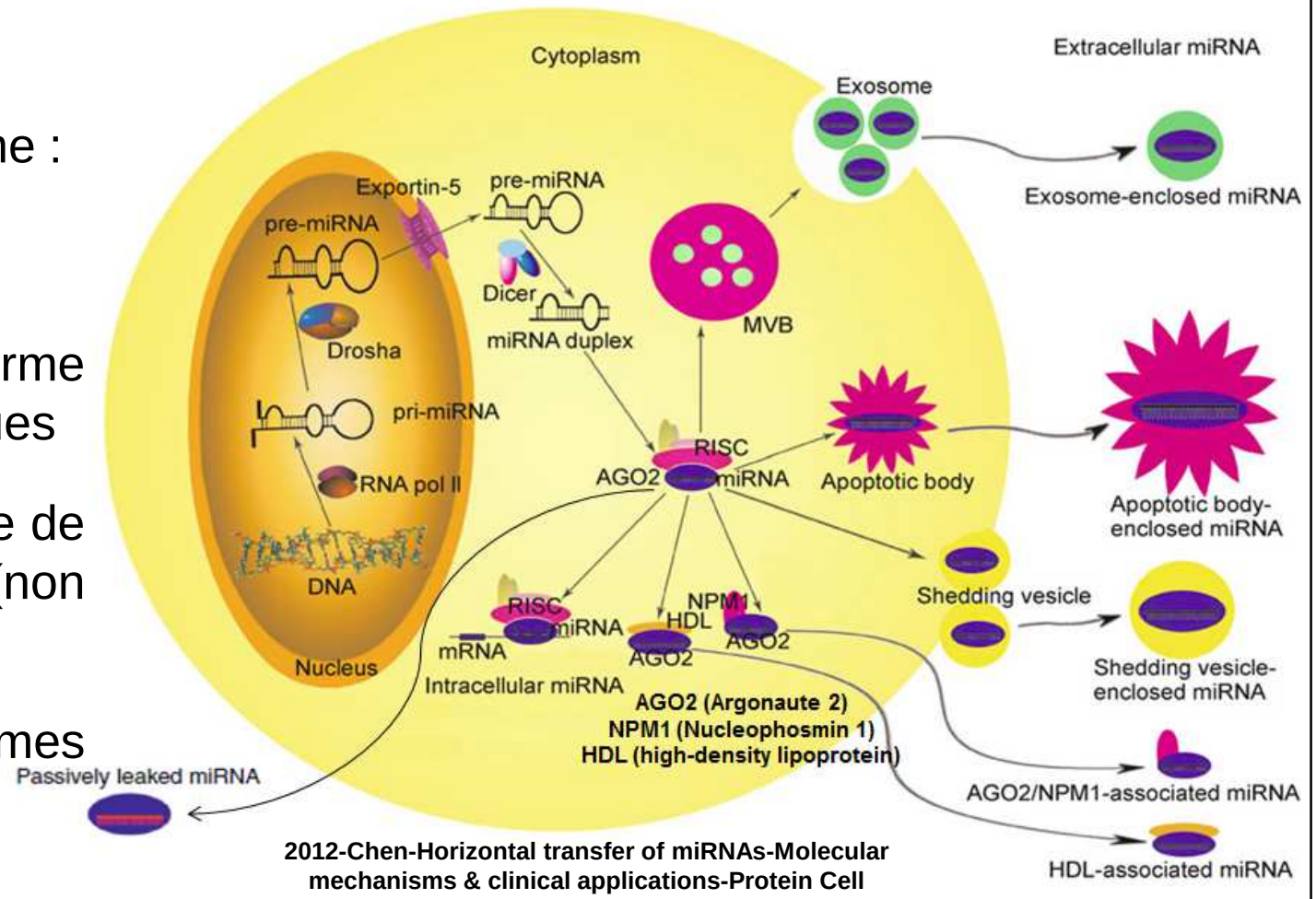
2013-Madhavan_D-Cancer diagnosis & prognosis decoded by blood-based circulating miRNA signatures-Front Genet

- **Mais représentent-t-ils la biologie tumorale ?**

Pourquoi et sous quelles formes les miRNA sont-ils présents dans les milieux extracellulaires et circulants ?

- **Les cellules tumorales ainsi que les cellules non tumorales libèrent des miRNA dans les milieux extracellulaires et cette production peut se faire sous plusieurs formes**

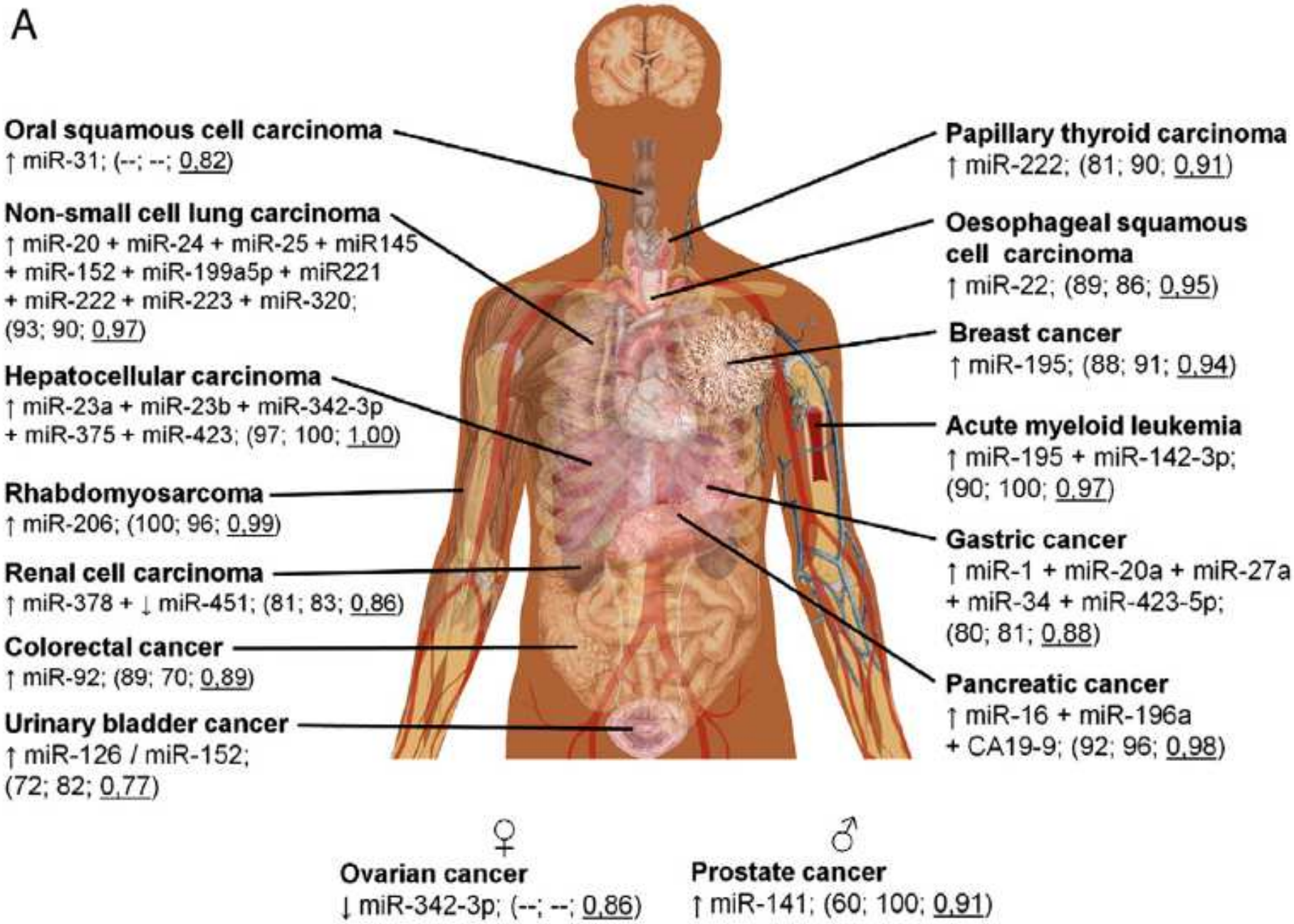
- Par sécrétion sous forme :
  - d'exosomes
  - de microvésicules
- Par apoptose sous forme de vésicules apoptotiques
- Par nécrose sous forme de complexes libres (non vésiculaires)
- Par d'autres mécanismes également



2012-Chen-Horizontal transfer of miRNAs-Molecular mechanisms & clinical applications-Protein Cell

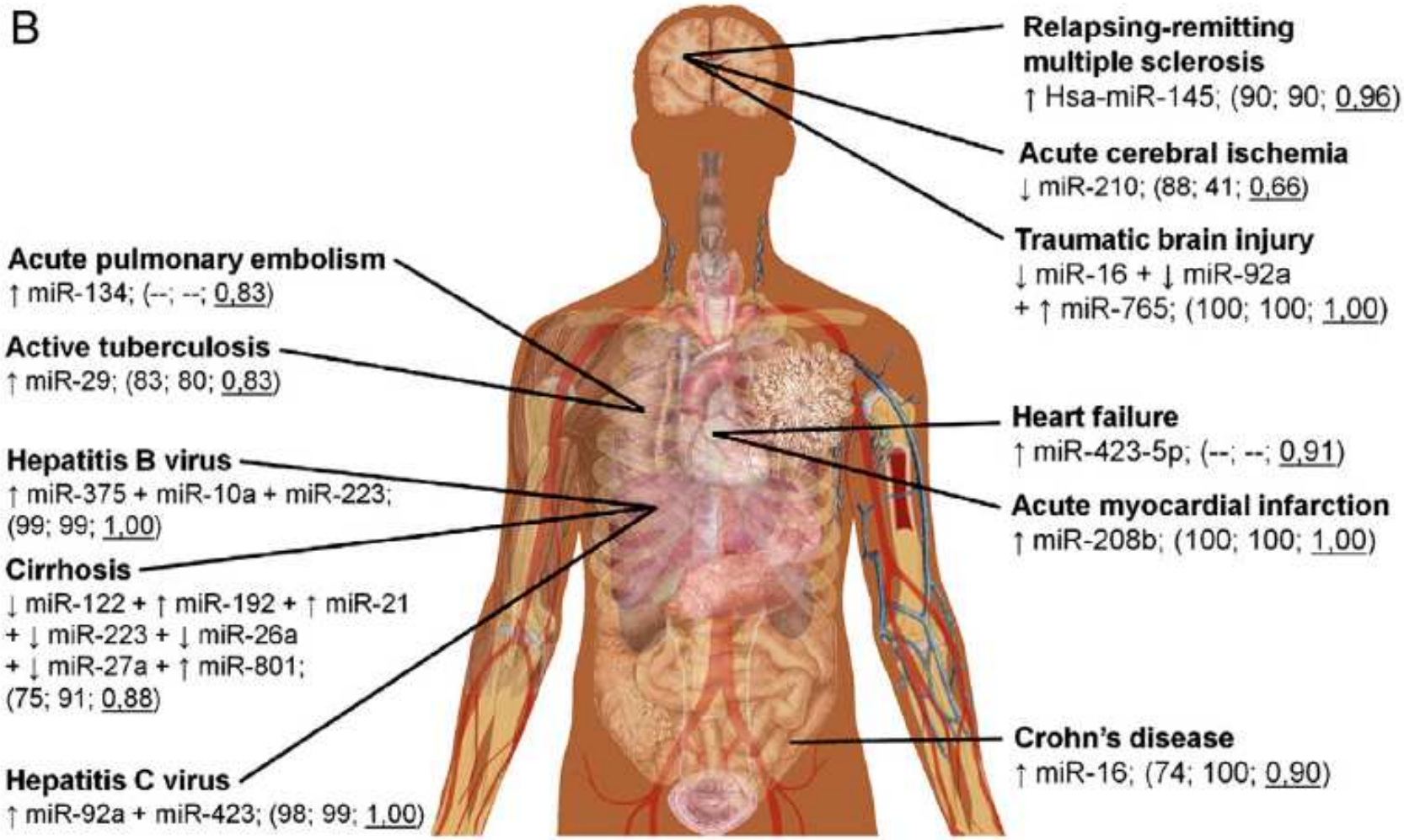
- **Les miRNA passent ensuite des milieux extracellulaires vers la circulation générale (ce phénomène est complexe en ce qui concerne le SNC)**

Circulating miRNAs in different types of cancer (sensitivity (%), specificity (%) and AUC)



- 2013-De Guire-Circulating miRNAs as sensitive & specific biomarkers for the diagnosis & monitoring of human diseases-Clin Biochem

Circulating miRNAs in non-oncological diseases (sensitivity (%), specificity (%) and AUC)

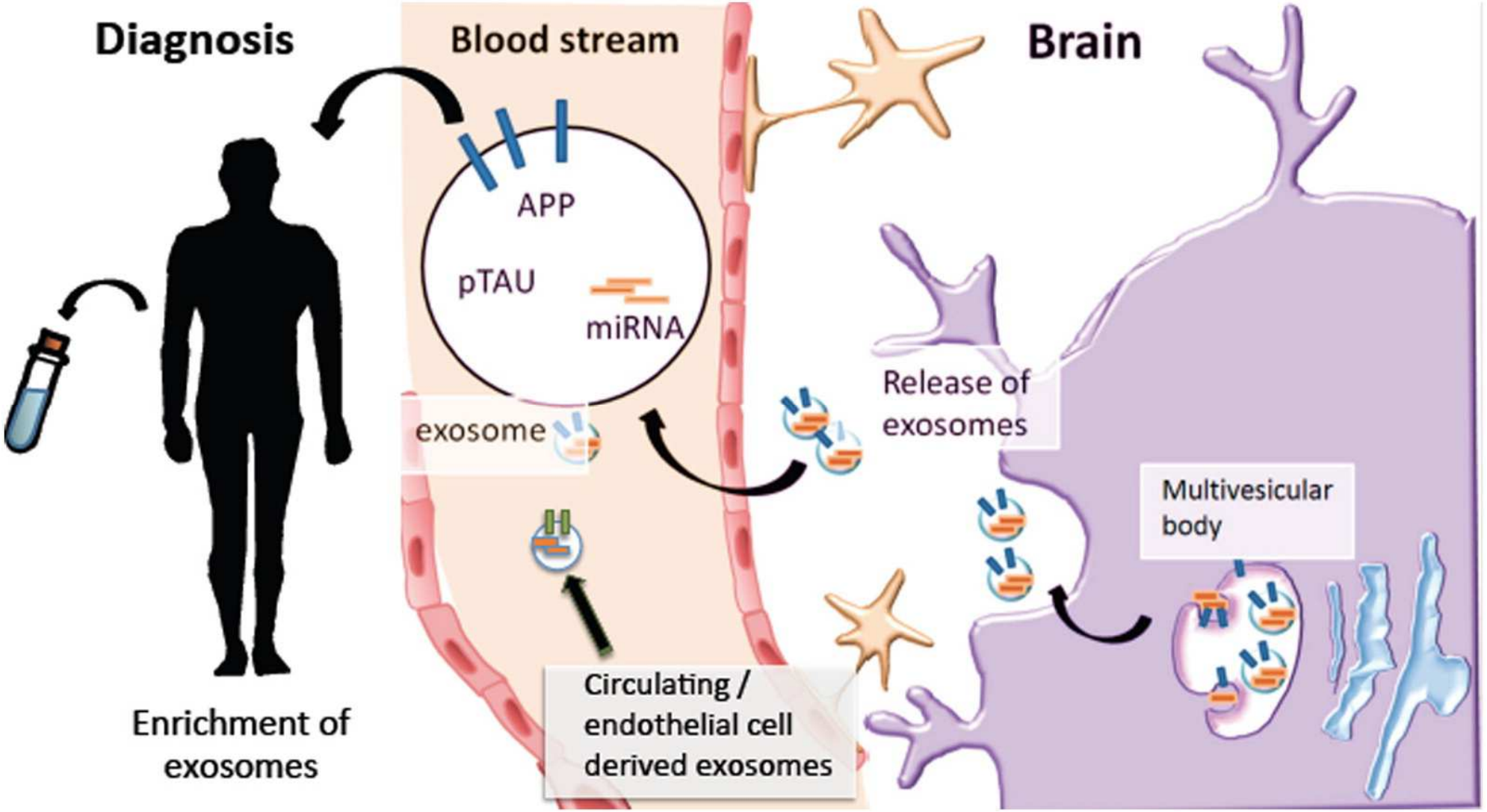


Sepsis
↓ miR-223; (80; 100; 0,86)

Hand-foot-and-mouth disease
↑ miR-148a + miR-143 + miR-324-3p + miR-628-3p + miR-140-5p + miR-362-3p; (97; 93; 0,99)

- **2013-De Guire-Circulating miRNAs as sensitive & specific biomarkers for the diagnosis & monitoring of human diseases-Clin Biochem**

Brain-derived exosomes can be drained into the blood and then can be traced to their origin as they express surface markers related to their cellular origin



Exosomes hold potential as diagnostic markers. Exosomes can be released from virtually all cell types. Exosomes released by brain cells are able to cross the BBB and can be detected in the blood stream. Similarly, endothelial and peripheral cells secrete exosomes into the circulation. Exosomes can be enriched from blood samples and used for detection of various proteins and nucleic acids. Exosomal membrane markers can be potentially used to identify their cellular origin.

- **2016-Kanninen_KM-Exosomes as new diagnostic tools in CNS diseases-BBA-ip**

Utilisation des micro-ARN comme cibles ou agents thérapeutiques

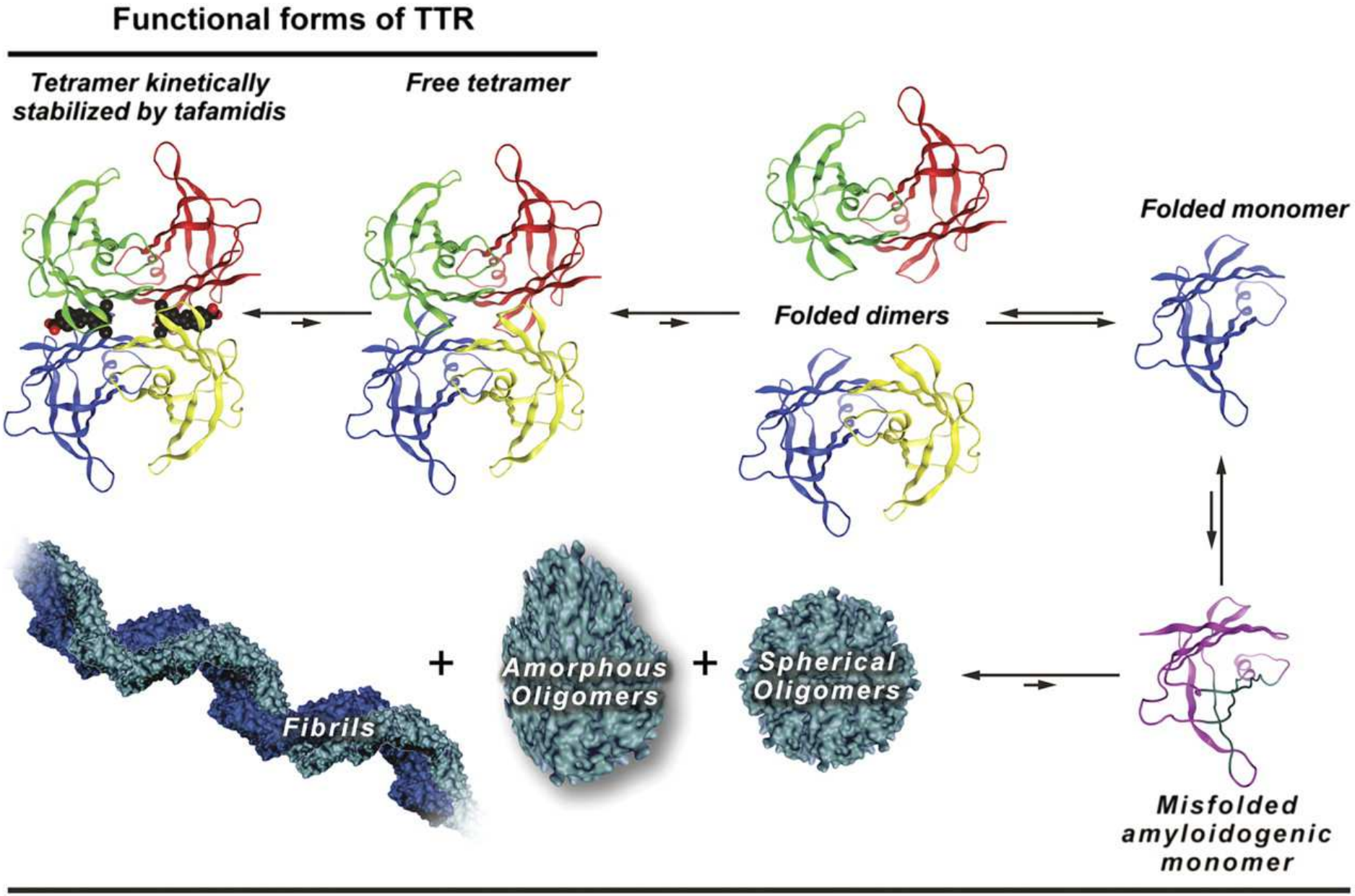
Synthetic RNAi-based drugs in phase 2–3 clinical trials

Drug	Target *(cell role)*	Chemistry / formulation	Route	Disease	Phase	Status/completion	Company/ collaborator
PF-04523655 (PF-655)	RTP801 / *(hypoxia-inducible)*	Naked siRNA, *O*-methylated	IVT	AMD, DME	II	Completed/2013	Quark / Pfizer
QPI-1002*[1] (I5NP)	p53 *(apoptotic)*	Naked siRNA, *O*-methylated	IV	AKI DGF	II III	Recruiting / 2018*[2] Recruiting / 2019*[2]	Quark
QPI-1007	CASP2 *(apoptotic)*	Naked siRNA, *O*-methylated; changes in sense strand	IVT	NAION Glaucoma	II / III II	Recruiting / 2019*[2] Completed / 2015	Quark
TKM-080301 (TKM-PLK1)	PLK1 *(kinase)*	siRNA / SNALP	IV	Solid tumors, HCC, NET, ACC, lymphoma	I / II	Completed / 2015	Arbutus
Atu027	PKN3 *(kinase)*	siRNA / LIPOPLEX	IV	Pancreatic cancer	I / II	Completed / 2016	Silence / Granzer, FGK
SYL040012 (Bamosiran)	ADRB2 *(β2 receptor)*	Naked siRNA	Eye drops	Ocular hypertension, glaucoma	II	Completed / 2013; 2016	Sylentis
SYL1001	TRPV1 *(nociceptor)*	Naked siRNA	Eye drops	Ocular pain in Dry Eye Syndrome	II	Completed / 2016	Sylentis
Patisiran (ALN-TTR02)	TTR *(amyloidogenic)*	siRNA / Lipid partide, ApoE	IV	TTR-mediated Amyloidosis	III	Active / 2017*[2]	Alnylam
siG12D-LODER	KRAS *(oncogene, GTPase)*	siRNA / Miniature PLGA device	Intra-tumoral	Pancreatic cancer*[3]	II	Active, not yet recruiting / 2020*[2]	Silenseed
Miravirsen	miR-122 *(microRNA)*	AntimiR, antisense oligodeoxynucleotide, LNA, PS	SC	Hepatitis C infection	II	Complete / 2011	Santaris

IV intravenous injection; IVT intravitreal injection; LNA locked nucleic acid; PS phosphorothioated; SC subcutaneous injection; SNALP stable-nucleic-acid-lipid particles; *2- estimated completion data; *3- siG12D-LODERs combined with chemotherapy treatment (Gemcitabine + nab-Paclitaxel).

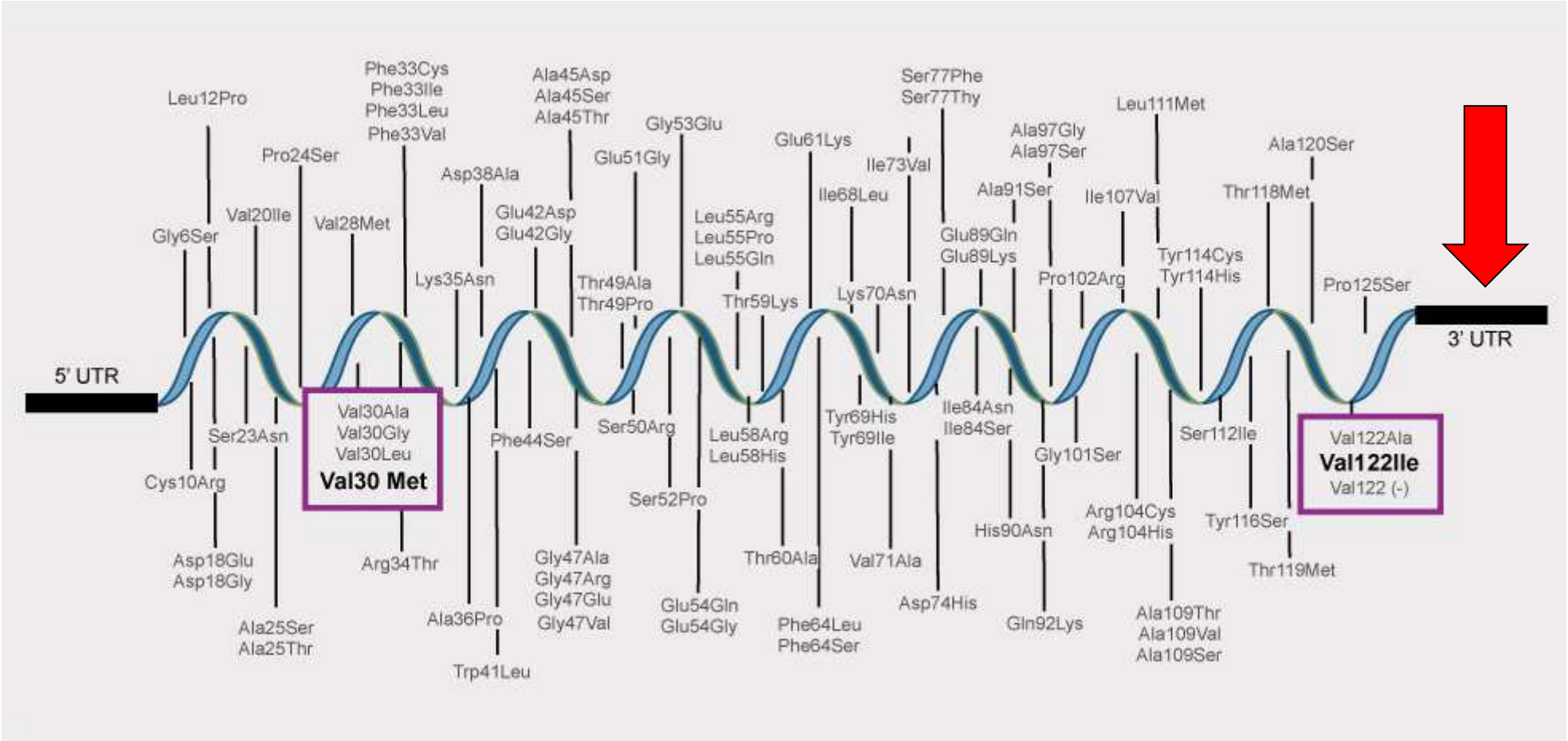
- **2017-Titze-de-Almeida_R-The race of 10 synthetic RNAi-based drugs to the pharmaceutical market-Pharm Res**

Transthyretin-mediated amyloidosis



- 2012-Bulawa-Tafamidis, a potent & selective transthyretin kinetic stabilizer that inhibits the amyloid cascade-PNAS

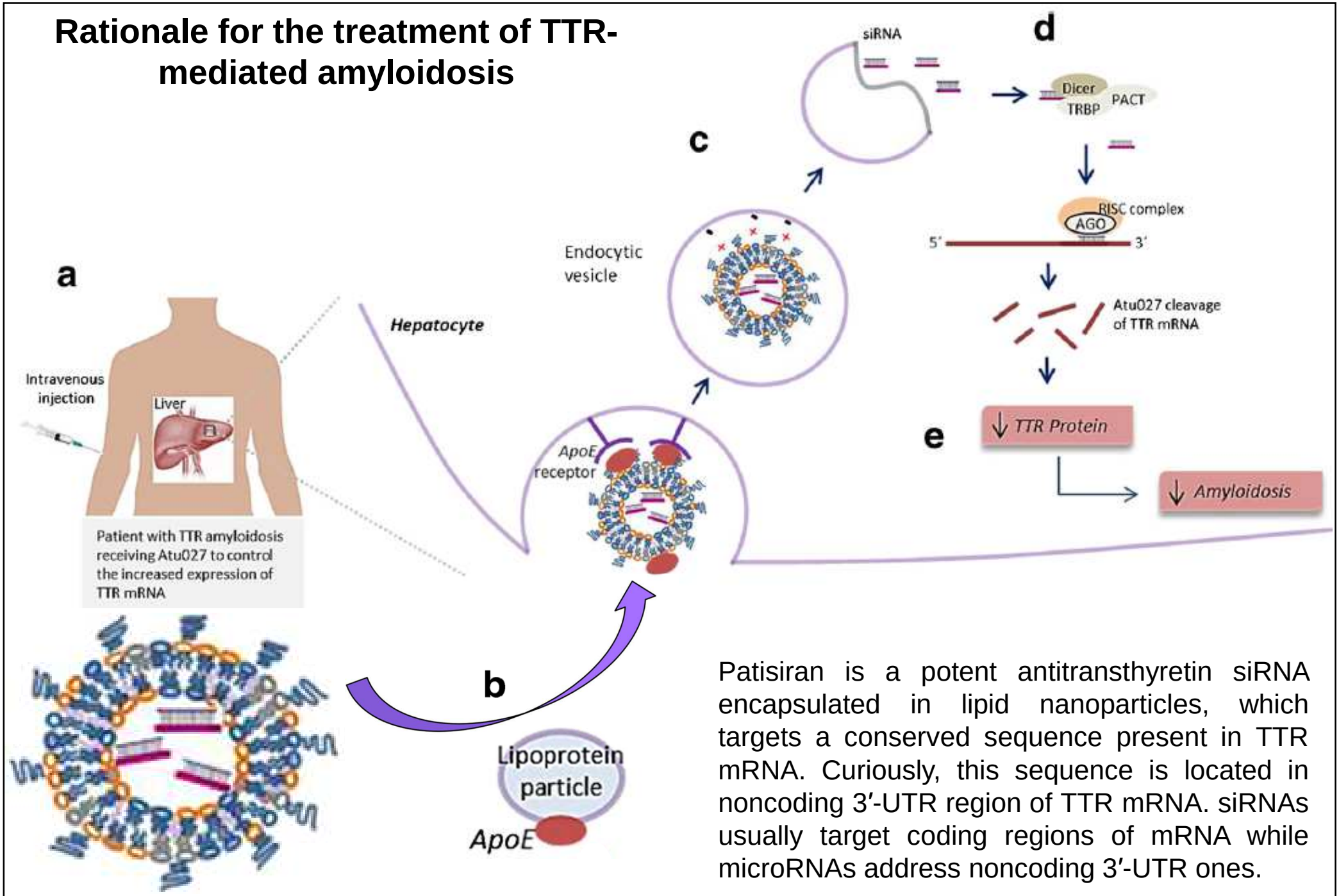
More than 100 genetic variants of the gene encoding transthyretin (TTR) are associated with autosomal dominant forms of the disease, known as familial amyloidotic polyneuropathy and familial amyloidotic cardiomyopathy



Maladie systémique caractérisée par une atteinte du système nerveux (polyneuropathie périphérique), des reins, des yeux et du cœur (cardiomyopathie).

- **http://www.alnylam.com**

Rationale for the treatment of TTR-mediated amyloidosis



Patisiran is a potent antitransthyretin siRNA encapsulated in lipid nanoparticles, which targets a conserved sequence present in TTR mRNA. Curiously, this sequence is located in noncoding 3′-UTR region of TTR mRNA. siRNAs usually target coding regions of mRNA while microRNAs address noncoding 3′-UTR ones.

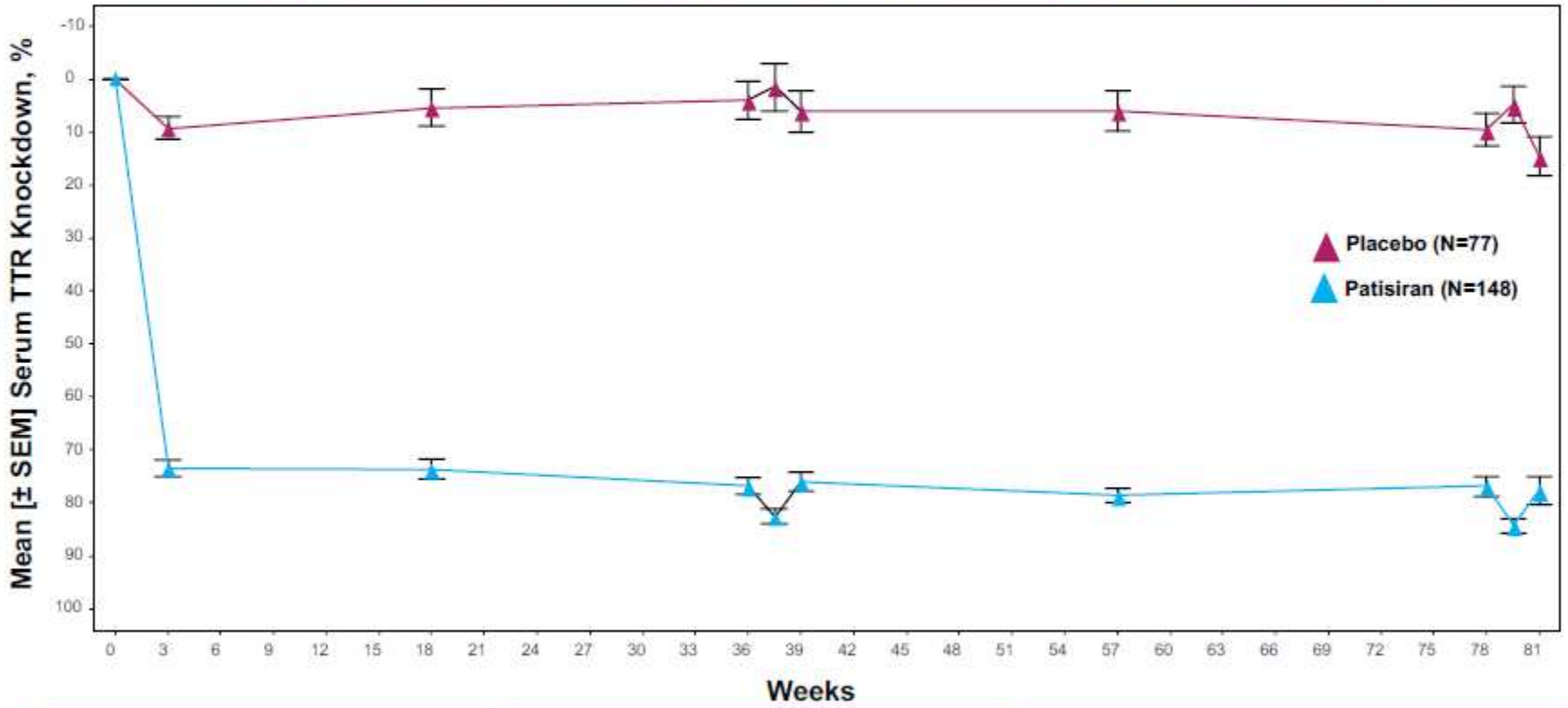
- 2017-Titze-de-Almeida_R-The race of 10 synthetic RNAi-based drugs to the pharmaceutical market-Pharm Res

Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy: Results from the Phase 3 APOLLO Study

Patisiran Phase 3 APOLLO Study Results

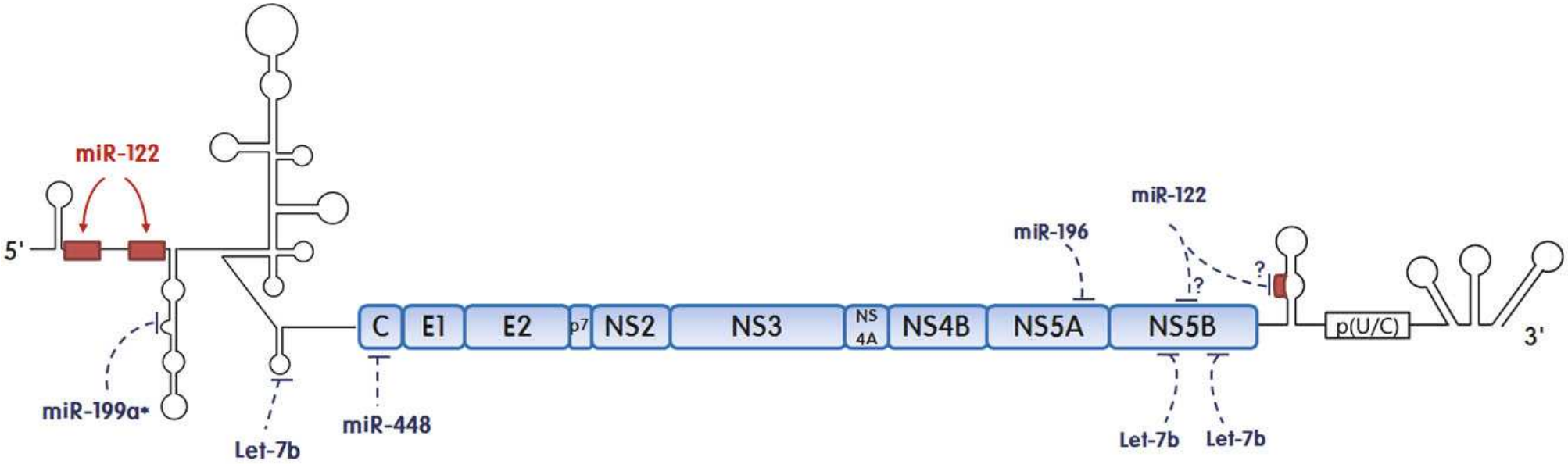
Serum TTR Reduction

87.8% mean max serum TTR reduction from baseline for patisiran over 18 months



TTR Change	Change from baseline at 9 months		Change from baseline at 18 months	
	Placebo (N=77)	Patisiran (N=148)	Placebo (N=77)	Patisiran (N=148)
Mean (SEM) Serum TTR Knockdown	1.5% (4.47)	82.6% (1.36)	4.8% (3.38)	84.3% (1.48)

Silencing of microRNAs in vivo with “antagomirs”: the example of Miravirsen



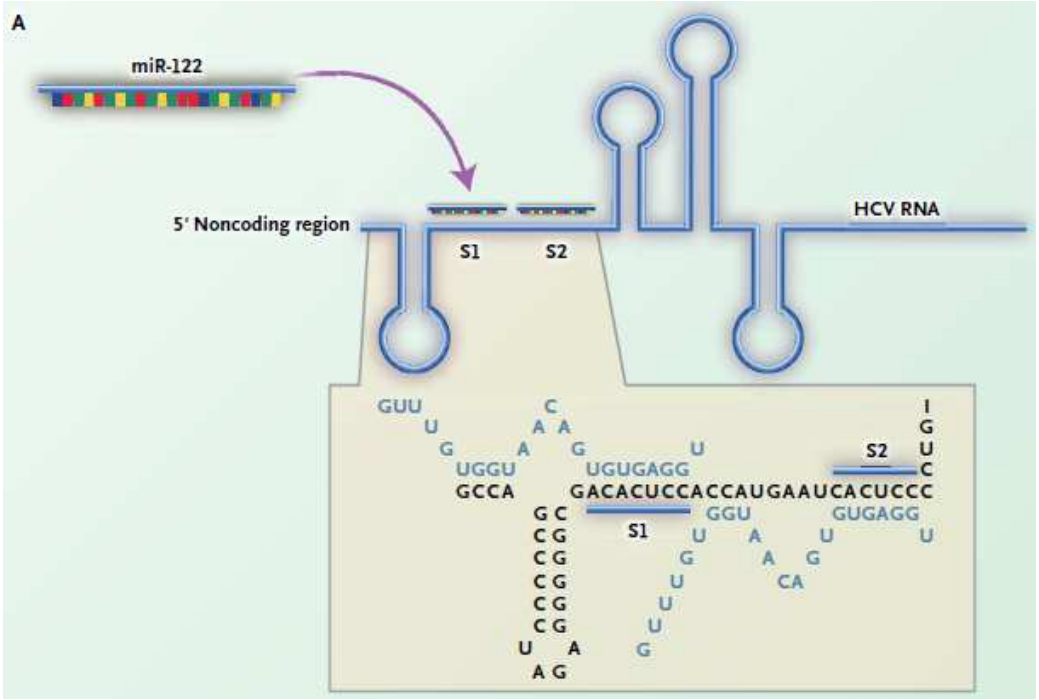
miR-122 is essential for HCV replication through direct interaction with HCV RNA genome

miRNAs positively regulating HCV replication are indicated in red. Inhibitory miRNAs are indicated in blue.

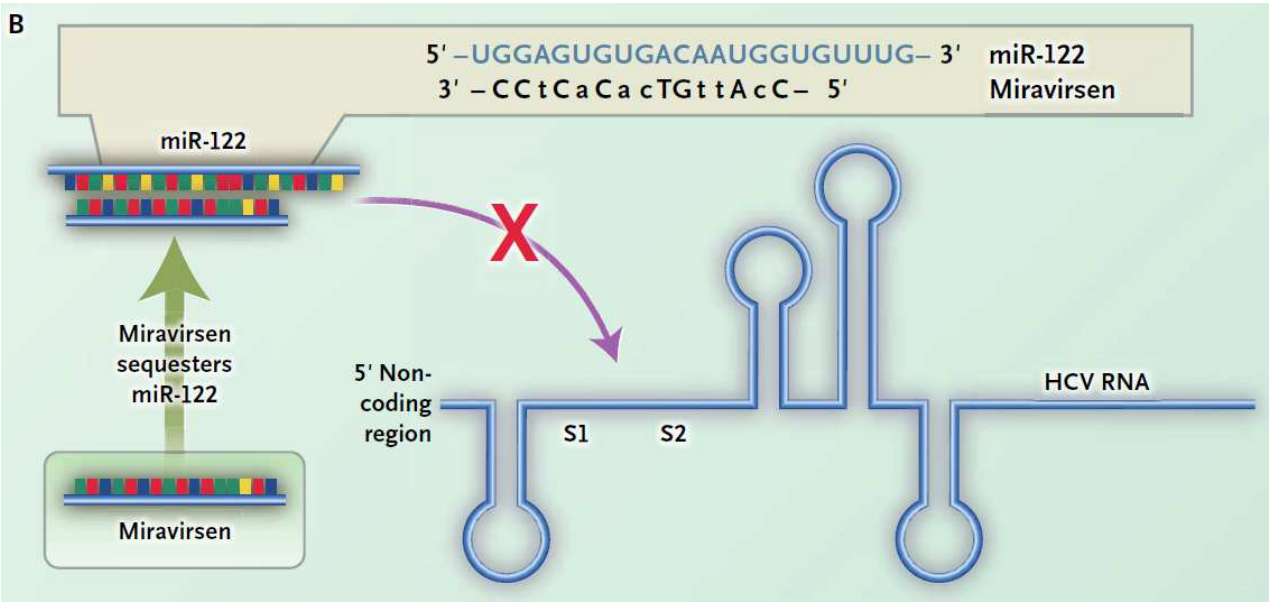
Miravirsen is a 15-base oligonucleotide, locked nucleic acid (LNA) modified, phosphorothioated, and complementary to 5′ region of mature miR-122. Regarding structure, miravirsen is a single stranded antisense DNA oligo, containing chemical modifications for stability and specificity.

- **2014-Lee_CH-The role of miRNAs in HCV replication & related liver diseases-J Microbiol**

Mechanism of action of Miravirsen



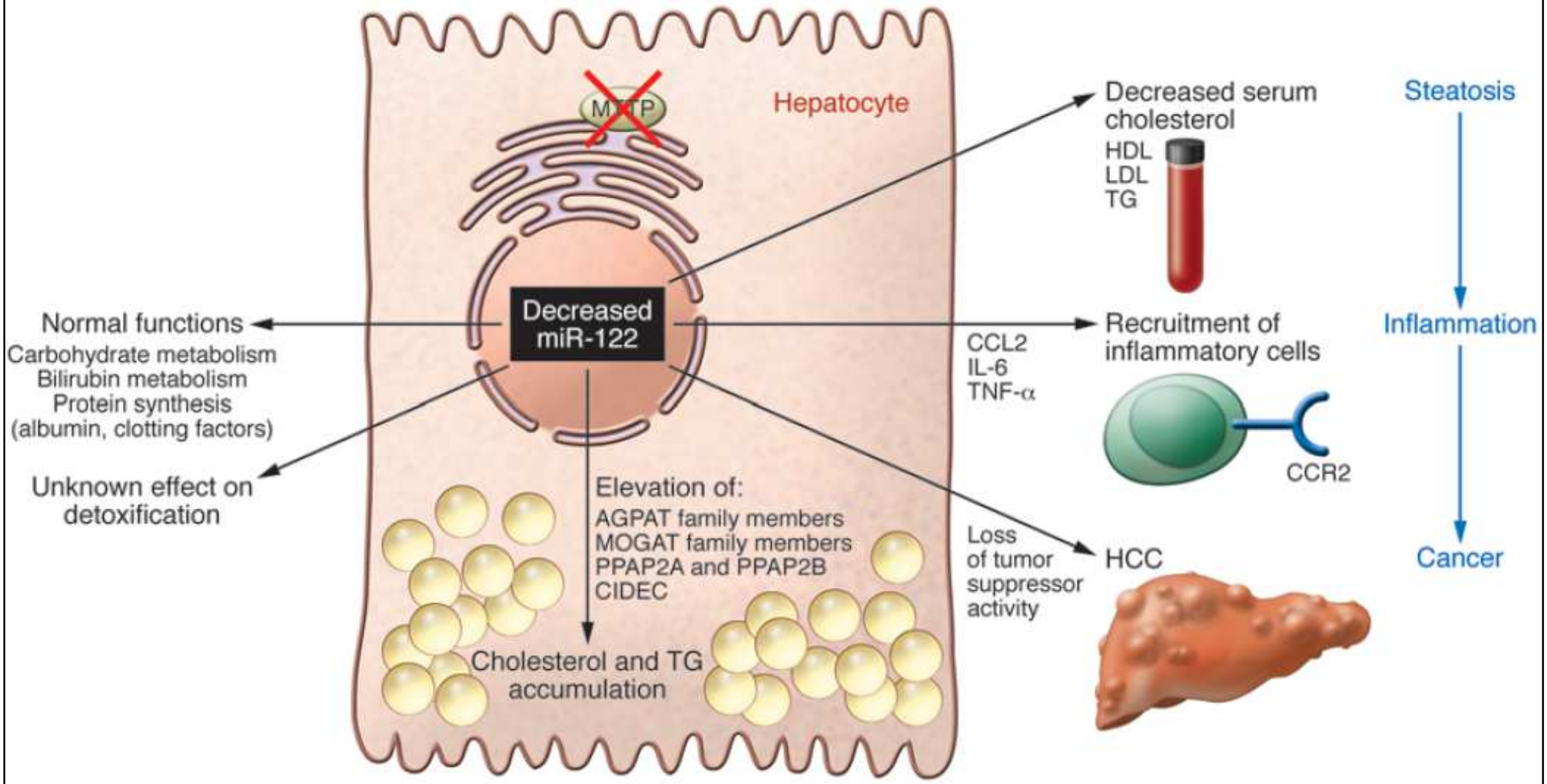
In Panel A, miR-122 binds to two closely spaced target sites (S1 and S2) in the 5′ noncoding region of the HCV genome and thereby promotes the propagation of HCV RNA.



In Panel B, miravirsen, a locked nucleic acid–modified antisense oligonucleotide, sequesters mature miR-122 in a highly stable heteroduplex, which results in the functional inhibition of miR-122.

- **2013-Janssen-Treatment of HCV infection by targeting miRNA-NEJM**

Overview of the consequences of miR-122 loss on hepatocyte function



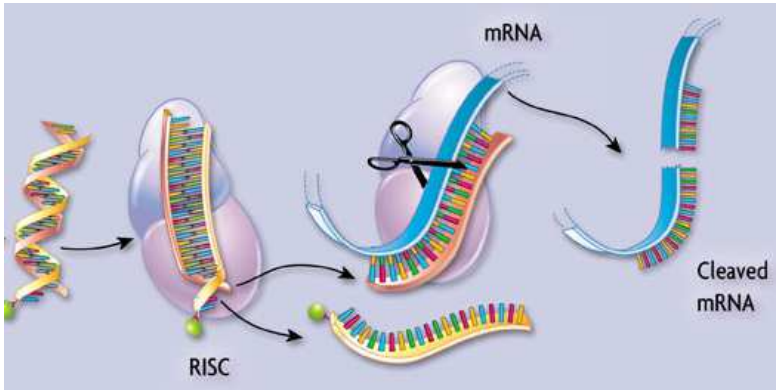
The normal functions of the hepatocyte include carbohydrate and lipid metabolism, bilirubin excretion, and detoxification of endogenous compounds and xenobiotics. Loss of miR-122 results in increased lipid synthesis and decreased lipid export, but other hepatocyte functions are unaltered. Loss of miR-122 also led to increased inflammation and fibrosis, and eventually the development of HCC, suggesting the miR-122 plays a tumor-suppressive role.

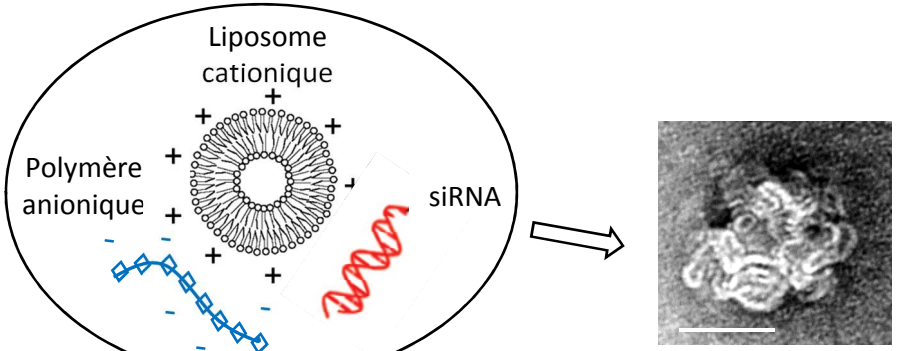
- **2012-Wen-miR-122 regulates hepatic lipid metabolism & tumor suppression-JCI**

Vectorisation de petits ARN interférents

Unité de Technologies Chimiques
et Biologiques pour la Santé
UMR 8258 CNRS - U1022 Inserm
Daniel Scherman

Equipe 3. Thérapie Génique, Pharmacologie
Génétique et Moléculaire
Virginie Escriou





- Nanoparticules formées par auto-assemblage de lipides et de polymères pour la vectorisation de siRNA (extinction de gène)
- Efficacité thérapeutique dans de nombreux domaines
  - Polyarthrite rhumatoïde (GILZ, hnRNPA2/B1)
  - Ostéolyse péri prosthétique (RANK)
  - Hépatite B (gènes viraux)
- Etude de fonction de gène
  - (Prickle – embryon de poulet – lésions tube neural)

Brevet : FR 0950336 (2013) - EP2389158 (2014) – PCT USA (2016)
9 publications (2012-2017) dont 2 JCR, 1 PNAS, 2 A&R