RNA: The Quiet Revolution

Jeffrey S. Deitch, PhD
Drexel University College of Medicine
ALS Hope Foundation
Philadelphia, PA

Therapeutic Revolutions

Gene Therapy

Therapeutic Revolutions

Gene Therapy

Stem Cells

Therapeutic Revolutions

Gene Therapy

Stem Cells

RNA Interference

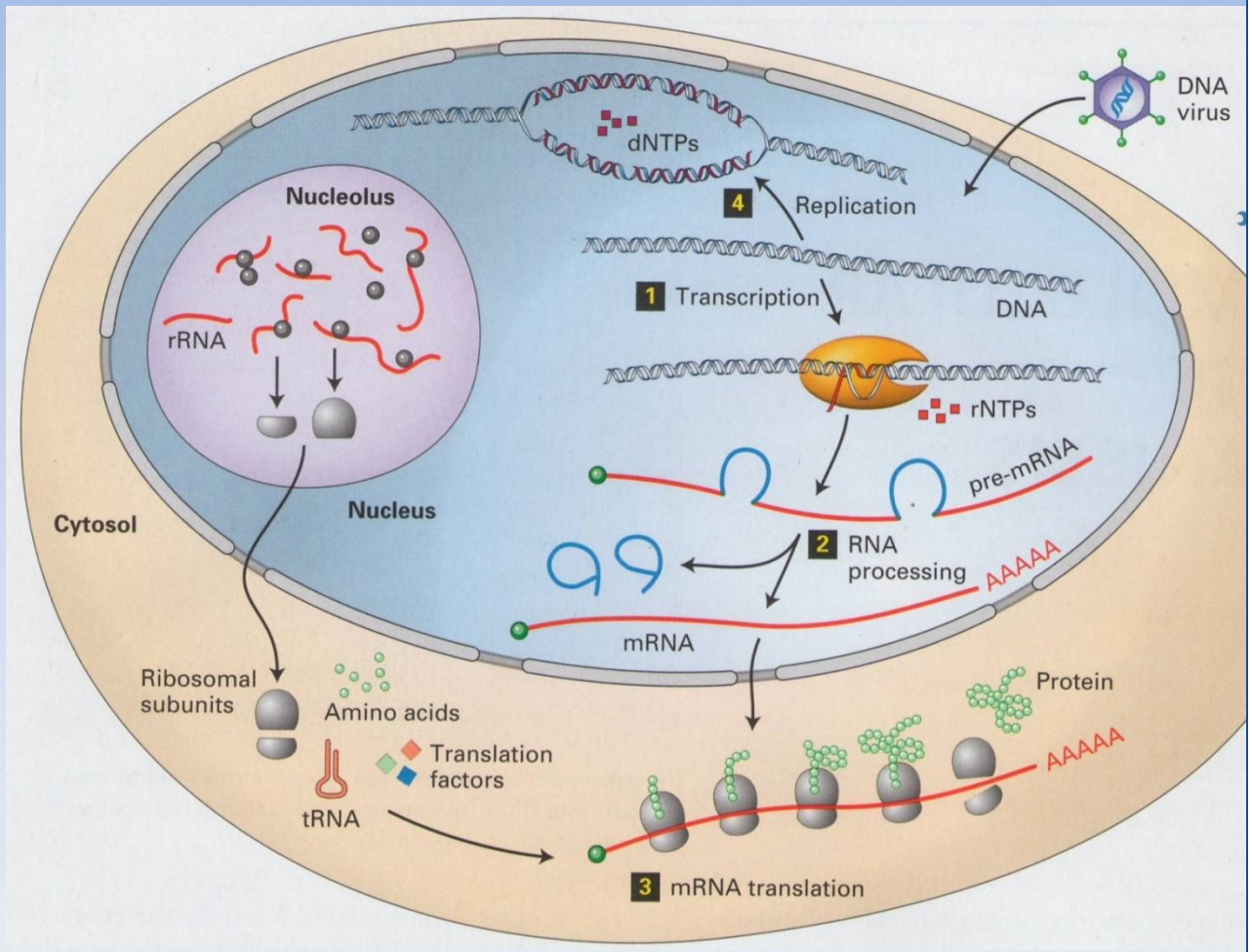
Therapeutic Revolutions

Gene Therapy

Stem Cells

RNA Interference – What?

Transcription of DNA to RNA
Translation of RNA to Protein



TACCAACTACACACTG
ATGGTTGATGTGTGAC

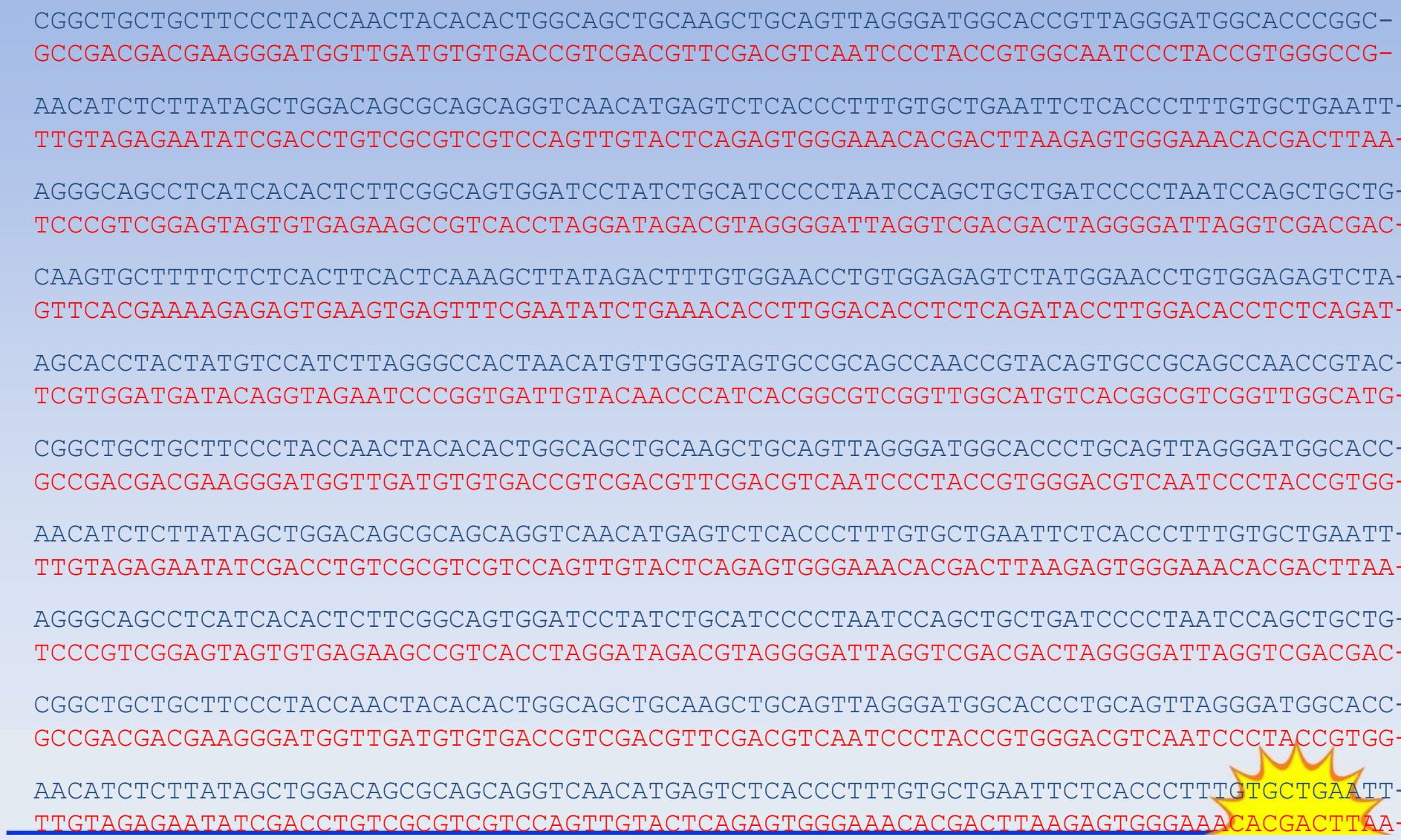
Template strand:
TACCAACTACACACTG

Antisense strand :
ATGGTTGATGTGTGAC

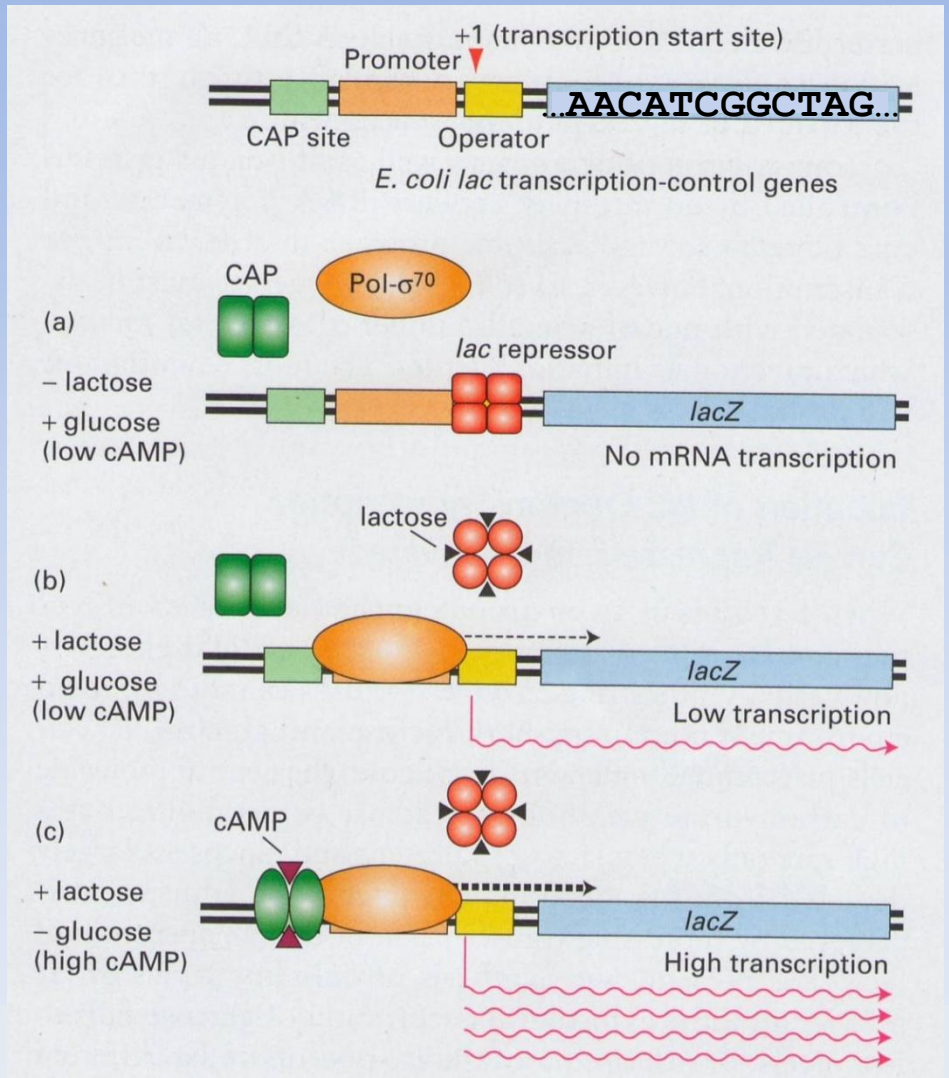
TACCAACTACACACTG
AUGGUUGAUGUGUGAC

mRNA:
AUGGUUGAUGUGUGAC

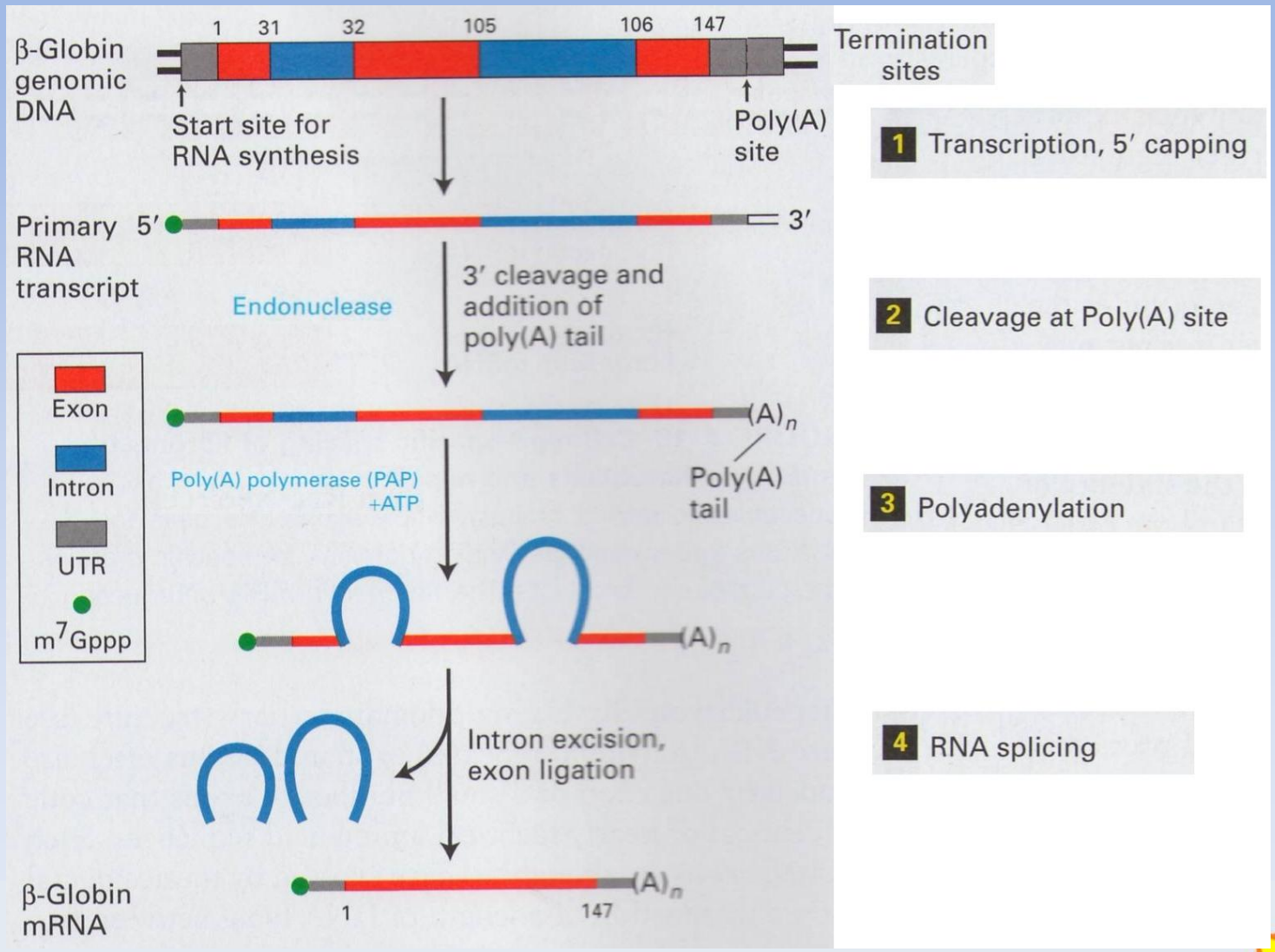
Here's our strand of DNA



Transcription Regulation



Transcription – A Closer Look



Alternative Splicing

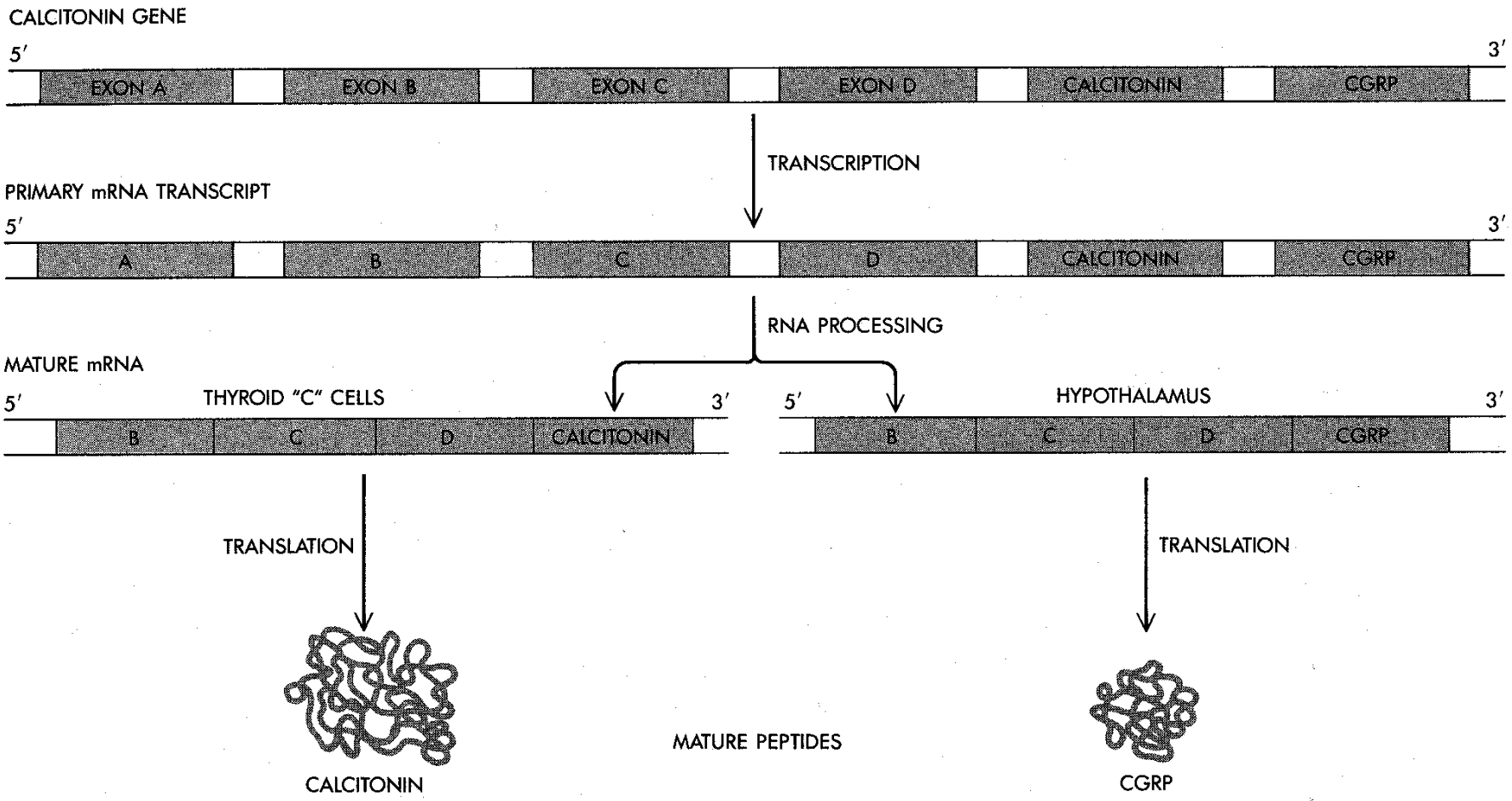
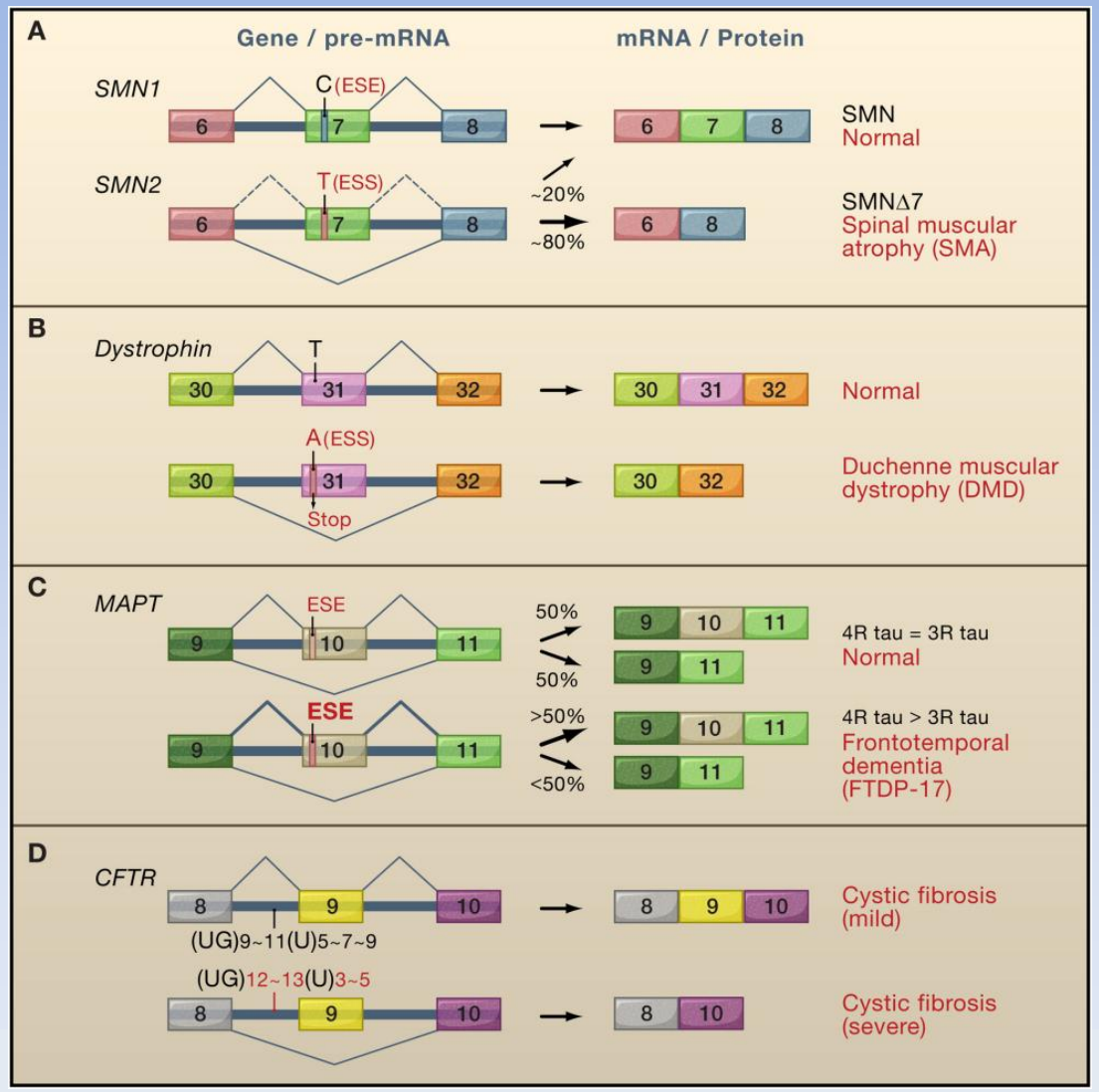
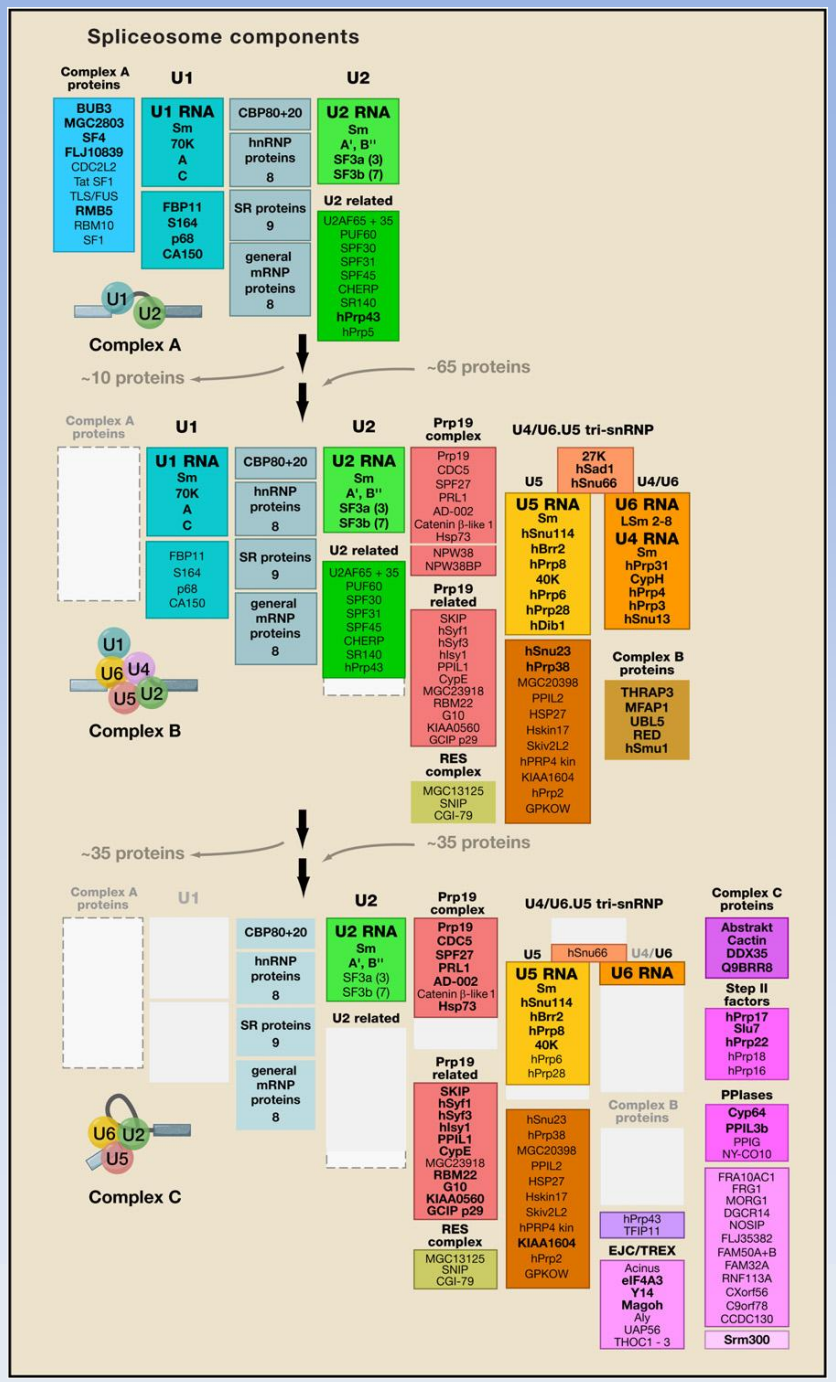


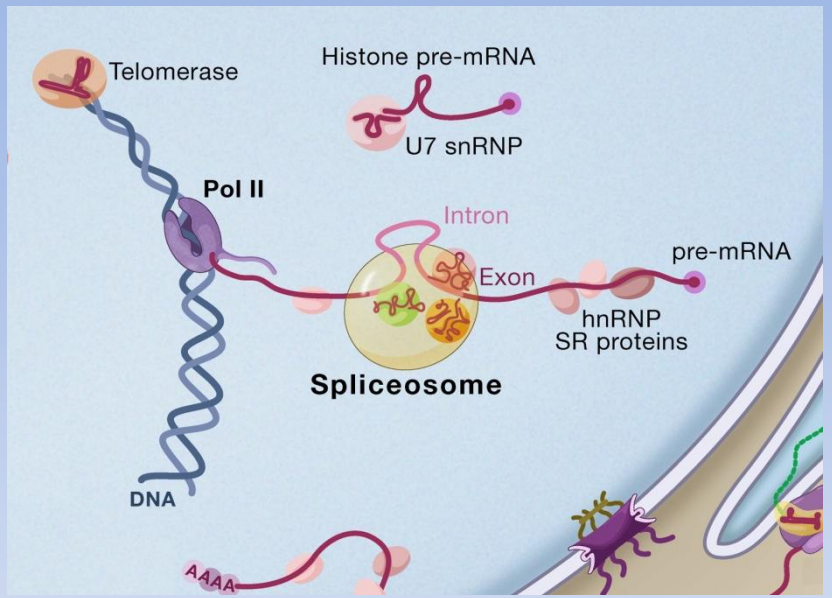
Figure 7-8
The calcitonin gene generates primary mRNA transcript that is spliced to produce two different forms of mature mRNA—that coding for calcitonin, which is produced primarily in the thyroid gland, and that coding for calcitonin-gene-related product (CGRP), which is produced mainly in the hypothalamus.

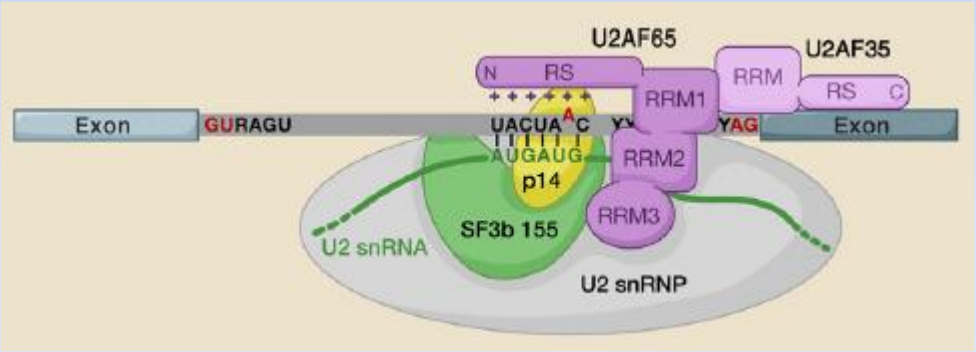
Alternative Splicing in Disease



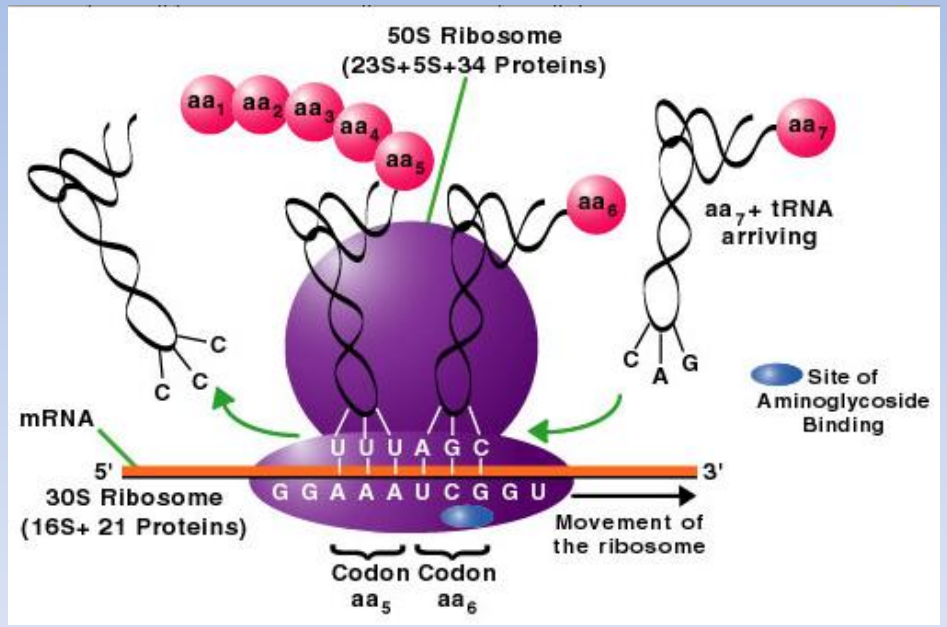
The Spliceosome

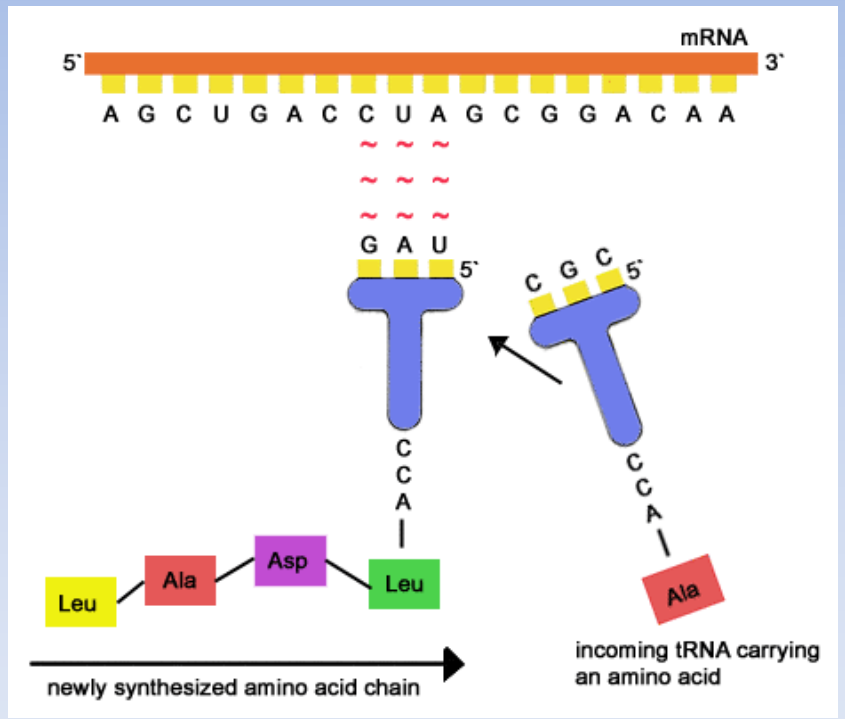




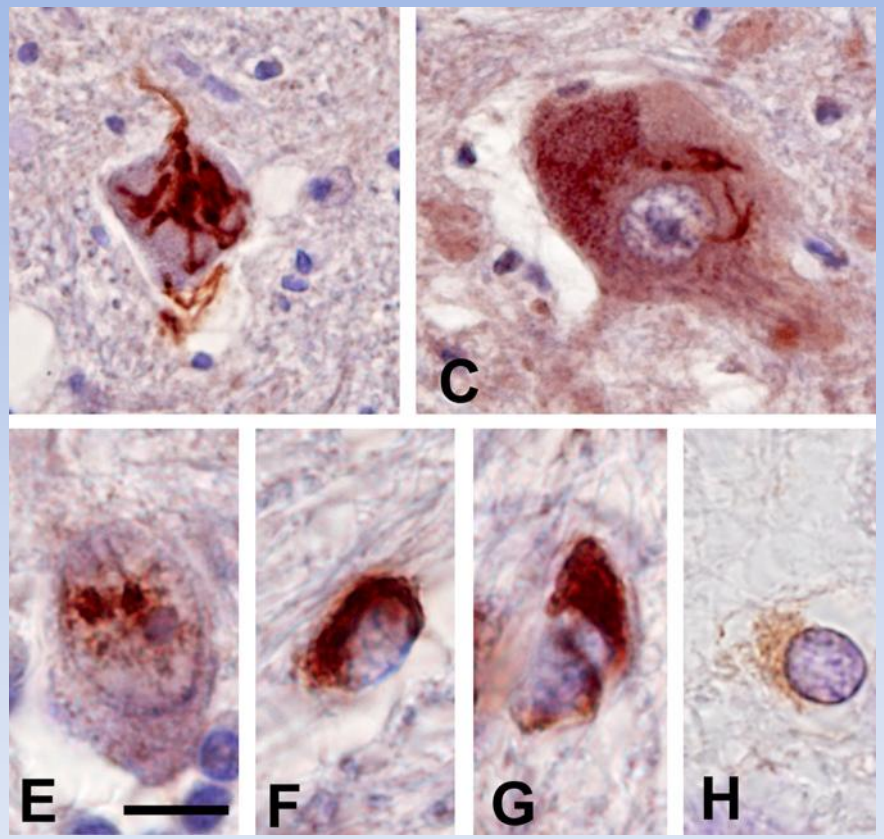


mRNA is translated into protein in the ribosome via t-RNA - Briefly

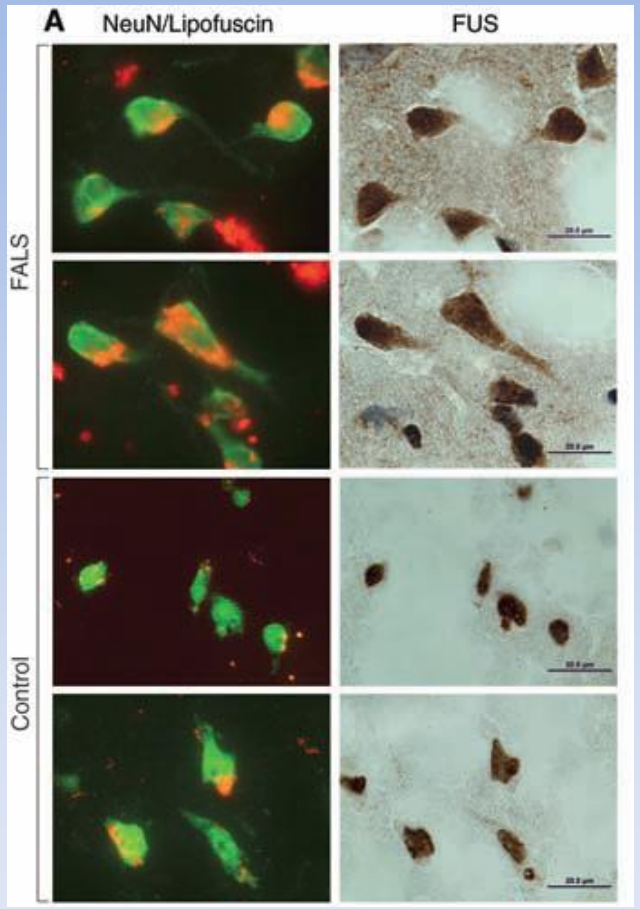




TDP-43 and FUS are RNA-binding proteins involved in ALS

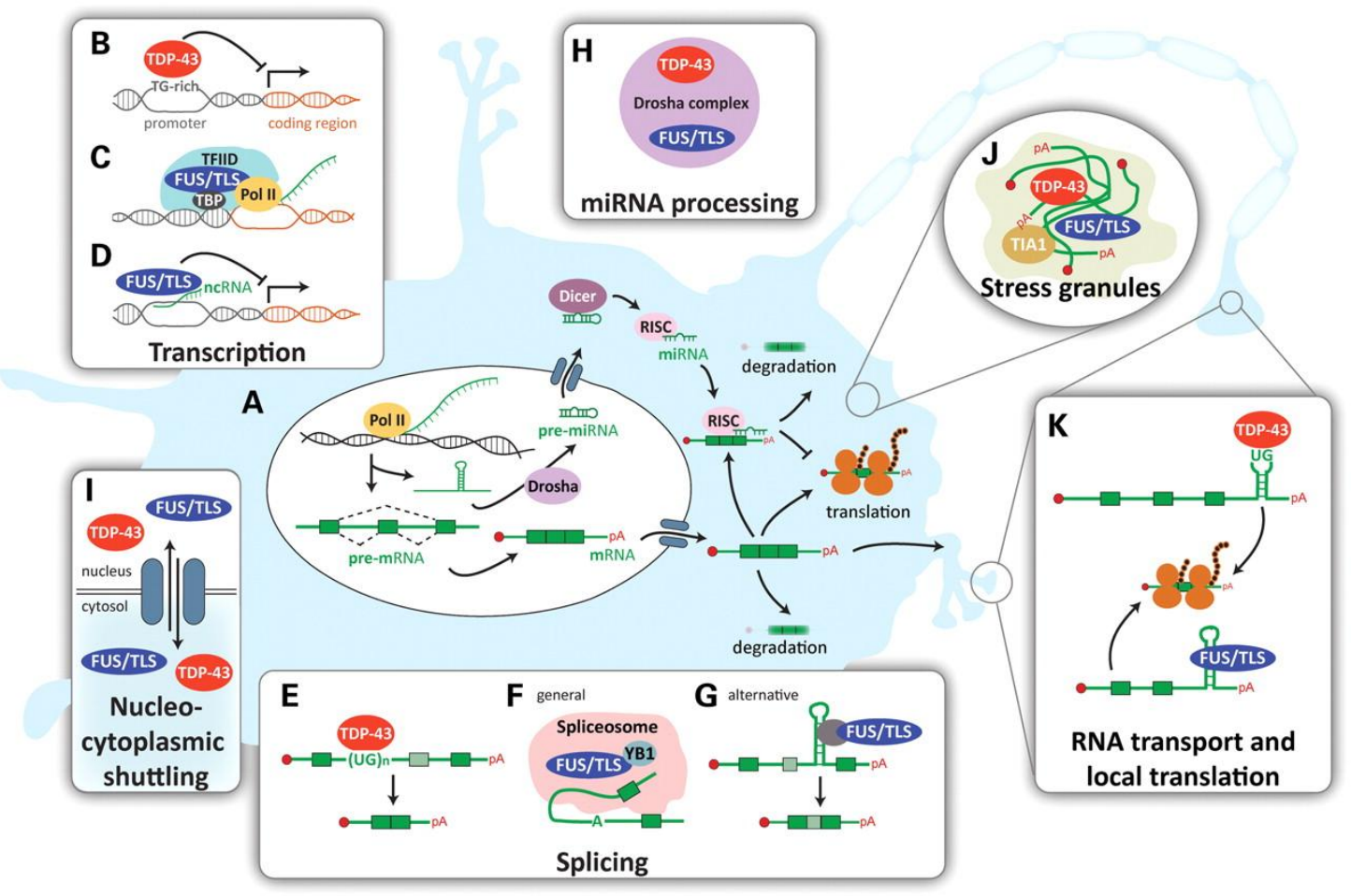


T. Arai et al. / Biochemical and Biophysical Research Communications 351 (2006) 602–611



Kwiatkowski, Jr., *et al. (2009) Science 323, 1205*

Proposed physiological roles of TDP-43 and FUS/TLS.



Lagier-Tourenne C et al. Hum. Mol. Genet. 2010;19:R46-R64

Diseases Associated with Mutations in RNA Processing

Table 1. *Trans*-Acting Mutations Affecting RNA-Dependent Functions that Cause Disease

Disease	Gene/Mutation	Function
Prader Willi syndrome	*SNORD116*	ribosome biogenesis
Spinal muscular atrophy (SMA)	*SMN2*	splicing
Dyskeratosis congenita (X-linked)	*DKC1*	telomerase/translation
Dyskeratosis congenita (autosomal dominant)	*TERC*	telomerase
Dyskeratosis congenita (autosomal dominant)	*TERT*	telomerase
Diamond-Blackfan anemia	*RPS19*, *RPS24*	ribosome biogenesis
Shwachman-Diamond syndrome	*SBDS*	ribosome biogenesis
Treacher-Collins syndrome	*TCOF1*	ribosome biogenesis
Prostate cancer	*SNHG5*	ribosome biogenesis
Myotonic dystrophy, type 1 (DM1)	*DMPK* (RNA gain of function)	protein kinase
Myotonic dystrophy, type 2 (DM2)	*ZNF9* (RNA gain of function)	RNA binding
Spinocerebellar ataxia 8 (SCA8)	*ATXN8/ATXN8OS* (RNA gain of function)	unknown/noncoding RNA
Huntington's disease-like 2 (HDL2)	*JPH3* (RNA gain of function)	ion channel function
Fragile X-associated tremor ataxia syndrome (FXTAS)	*FMR1* (RNA gain of function)	translation/mRNA localization
Fragile X syndrome	*FMR1*	translation/mRNA localization
X-linked mental retardation	*UPF3B*	translation/nonsense-mediated decay
Oculopharyngeal muscular dystrophy (OPMD)	*PABPN1*	3′ end formation
Human pigmentary genodermatosis	*DSRAD*	editing
Retinitis pigmentosa	*PRPF31*	splicing
Retinitis pigmentosa	*PRPF8*	splicing
Retinitis pigmentosa	*HPRP3*	splicing

Table 1. *Trans*-Acting Mutations Affecting RNA-Dependent Functions that Cause Disease

Disease	Gene/Mutation	Function
Retinitis pigmentosa	*PAP1*	splicing
Cartilage-hair hypoplasia (recessive)	*RMRP*	splicing
Autism	7q22-q33 locus breakpoint	noncoding RNA
Beckwith-Wiedemann syndrome (BWS)	*H19*	noncoding RNA
Charcot-Marie-Tooth (CMT) Disease	*GRS*	translation
Charcot-Marie-Tooth (CMT) Disease	*YRS*	translation
Amyotrophic lateral sclerosis (ALS)	*TARDBP*	splicing, transcription
Leukoencephalopathy with vanishing white matter	*EIF2B1*	translation
Wolcott-Rallison syndrome	*EIF2AK3*	translation (protease)
Mitochondrial myopathy and sideroblastic anemia (MLASA)	*PUS1*	translation
Encephalomyopathy and hypertrophic cardiomyopathy	*TSFM*	translation (mitochondrial)
Hereditary spastic paraplegia	*SPG7*	ribosome biogenesis
Leukoencephalopathy	*DARS2*	translation (mitochondrial)
Susceptibility to diabetes mellitus	*LARS2*	translation (mitochondrial)
Deafness	*MTRNR1*	ribosome biogenesis (mitochondrial)
MELAS syndrome, deafness	*MTRNR2*	ribosome biogenesis (mitochondrial)
Cancer	*SFRS1*	splicing, translation, export
Cancer	*RBM5*	splicing
Multiple disorders	mitochondrial tRNA mutations	translation (mitochondrial)
Cancer	*miR-17-92* cluster	RNA interference
Cancer	*miR-372*, *miR-373*	RNA interference

Coming up at the Symposium

JOINT OPENING SESSION

C1 NEW PERSPECTIVE ON AMYOTROPHIC LATERAL SCLEROSIS AS TDP-43 PROTEINOPATHIES

LEE V M-Y

Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, PA, United States

SESSION 4A

C24 TDP-43 MUTANT TRANSGENIC MICE DEVELOP BIOCHEMICAL AND PATHOLOGICAL FEATURES OF AMYOTROPHIC LATERAL SCLEROSIS AND FRONTOTEMPORAL LOBAR DEMENTIA

SWARUP V, PHANEUF D, BAREIL C, JULIEN J-P

Centre de Recherche du CHUQ, Department of Neuroscience and Psychiatry, University Laval, Quebec, QC, Canada

SESSION 11A

C82 NOVEL RNA BINDING PROTEINS IN ALS

GITLER AD

Department of Cell and Developmental Biology, University of Pennsylvania School of Medicine, Philadelphia, PA, United States

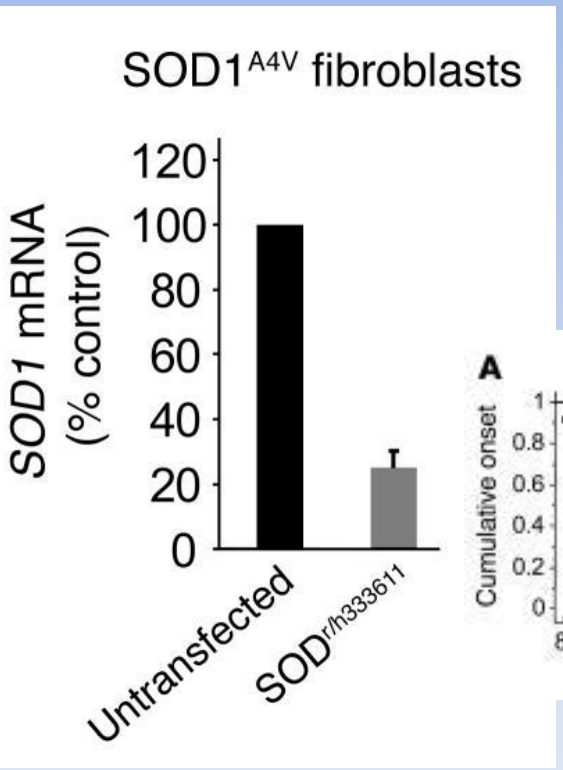
2

Saturday 11 December 2010

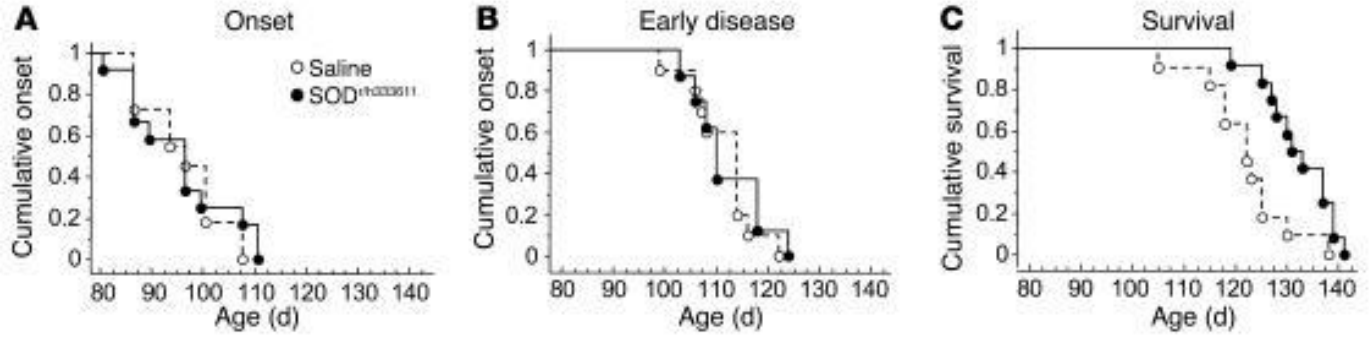
SESSION 2A **RNA Biology in ALS**

10.30 – 11.00	Using embryonic stem cells to study motor neuron/glia interactions in ALS – **T Maniatis (USA)**
11.00 – 11.15	Role of RNA processing in the pathogenesis of ALS – **C Lagier-Tourenne (USA)**
11.15 – 11.30	Genetic and biochemical analysis of TDP-43 proteinopathy – **R Tibbetts (USA)**
11.30 – 11.45	Characterizing the role of TDP-43 in ALS – **B Freibaum (USA)**
11.45 – 12.00	RNA targets of TDP-43 identified using UV-CLIP are deregulated in ALS – **J Robertson (Canada)**
12.00 – 12.15	Increasing autophagy rescues neurodegeneration in flies lacking Adar RNA editing – **S Paro (UK)**
12.15 – 12.30	miRNA dysregulation in human sporadic ALS – **T Möller (USA)**

RNA in ALS:
Antisense mutant SOD1

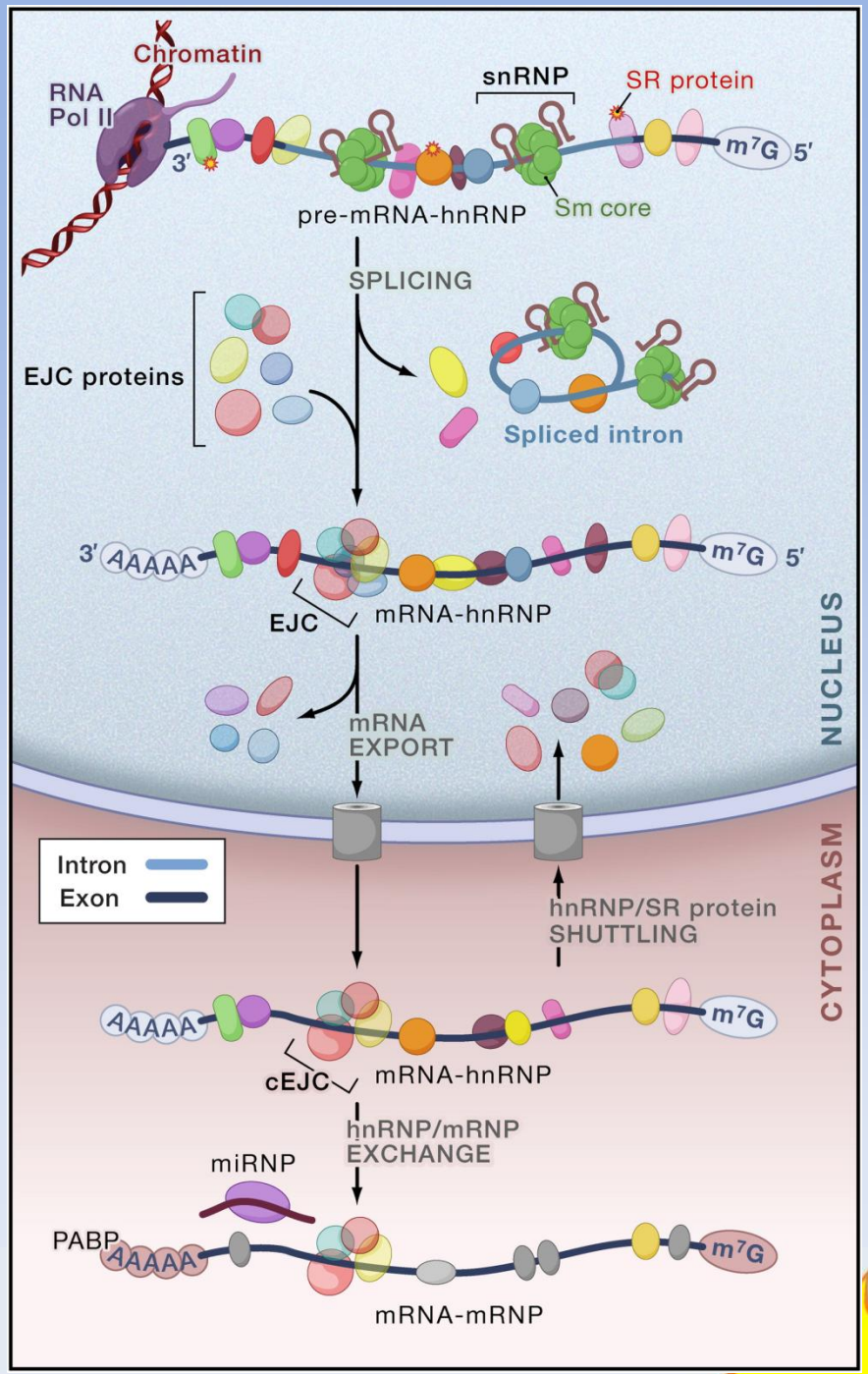


AUGUCCAUCUUA
AGCUCGUGGAUGAUACAGGUAGAAUCCCGGUGAU...

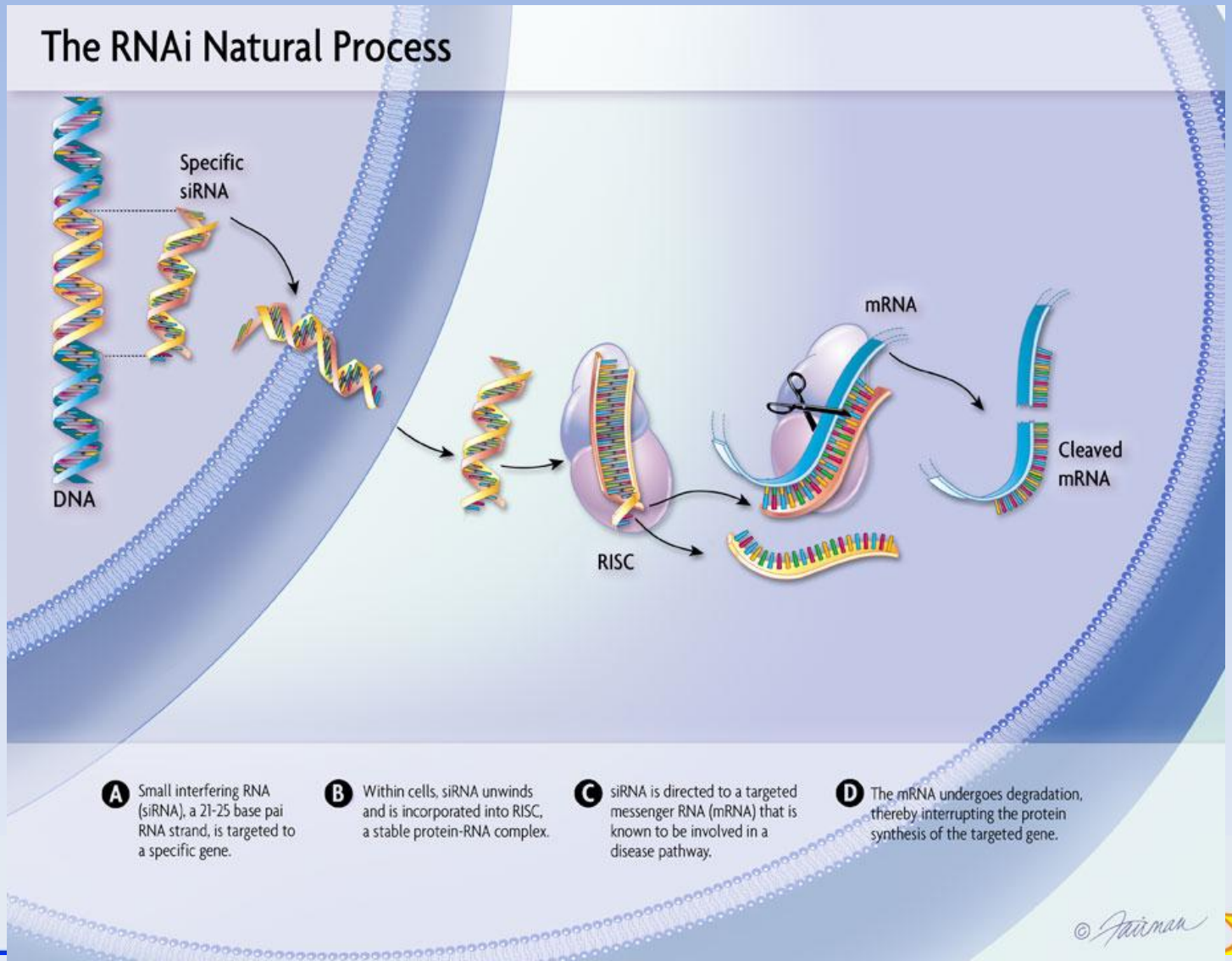


Source: Smith, et al. J Clin Invest. 2006 August 1;116(8):2290-2296

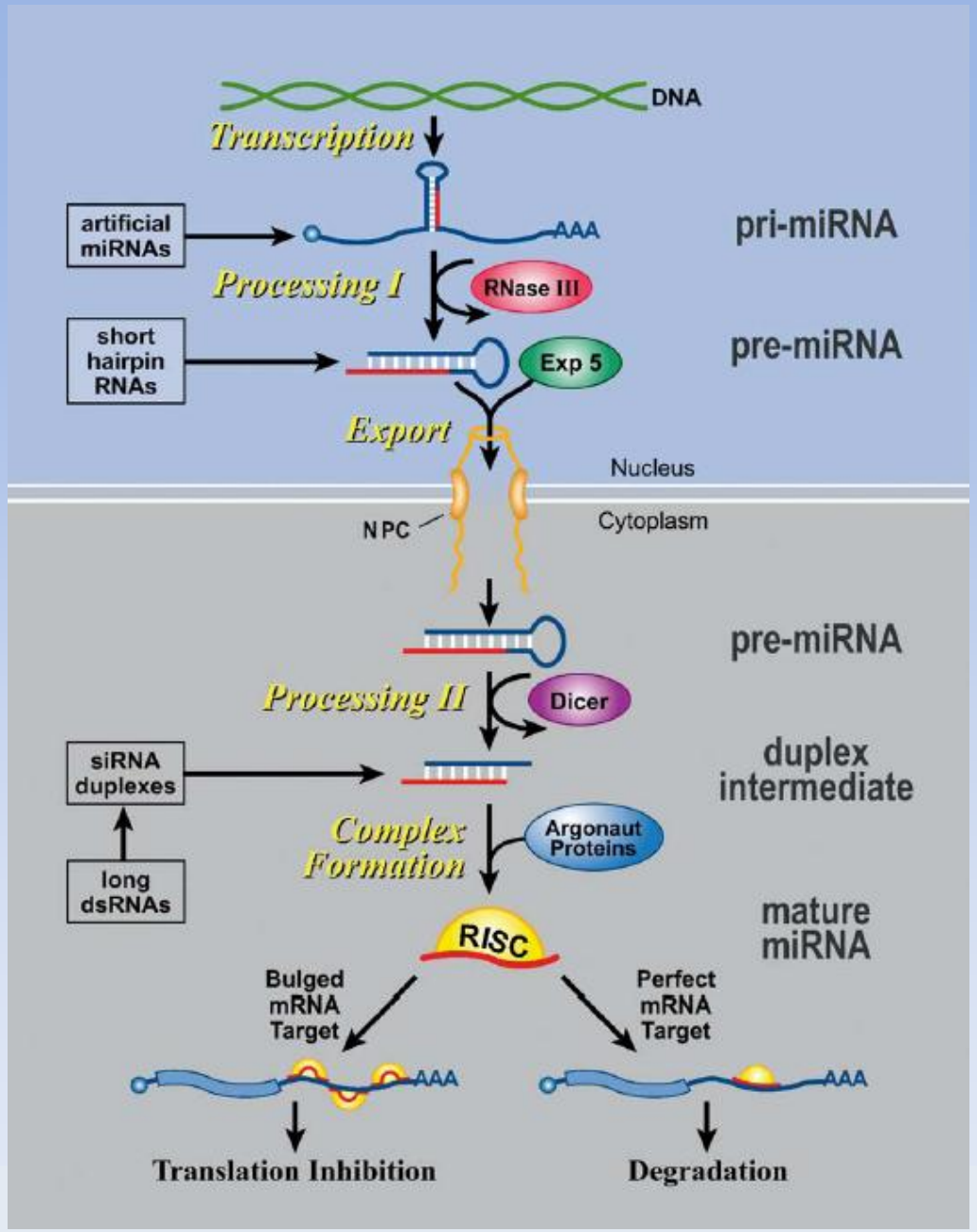
snRNAs, shRNAs miRNAs involved in mRNA processing



small interfering RNA (siRNA)

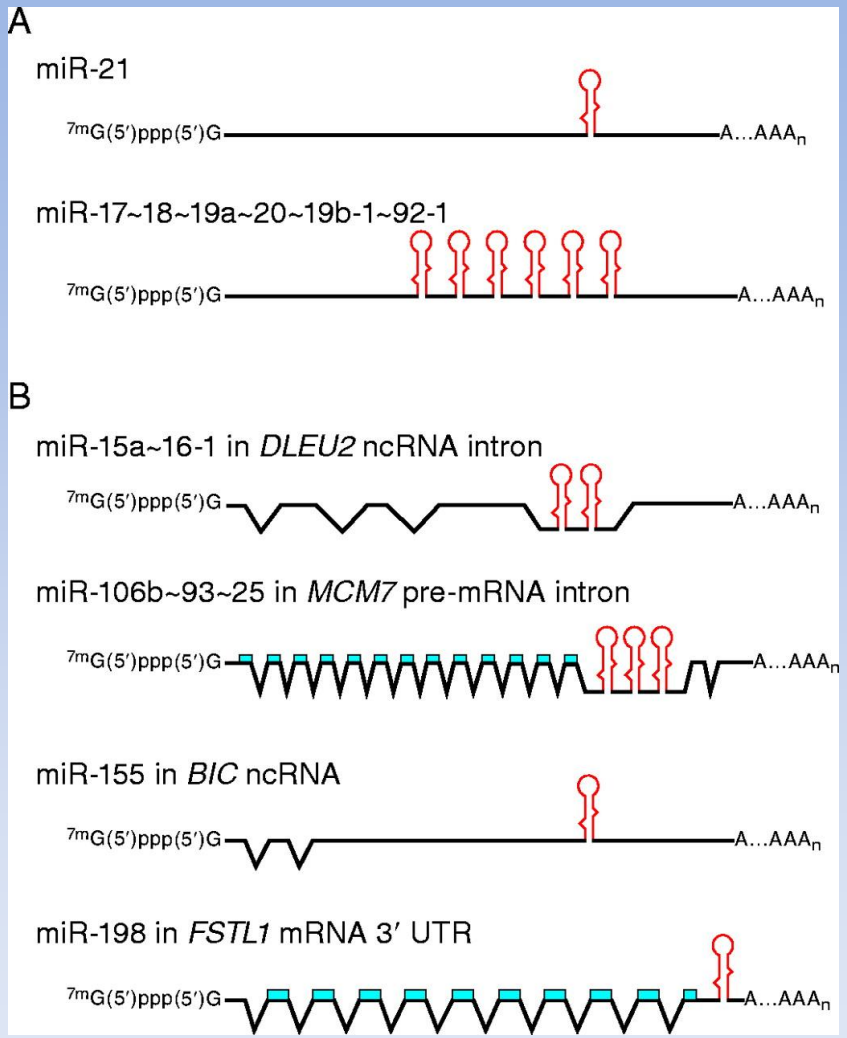


miRNA biogenesis and action



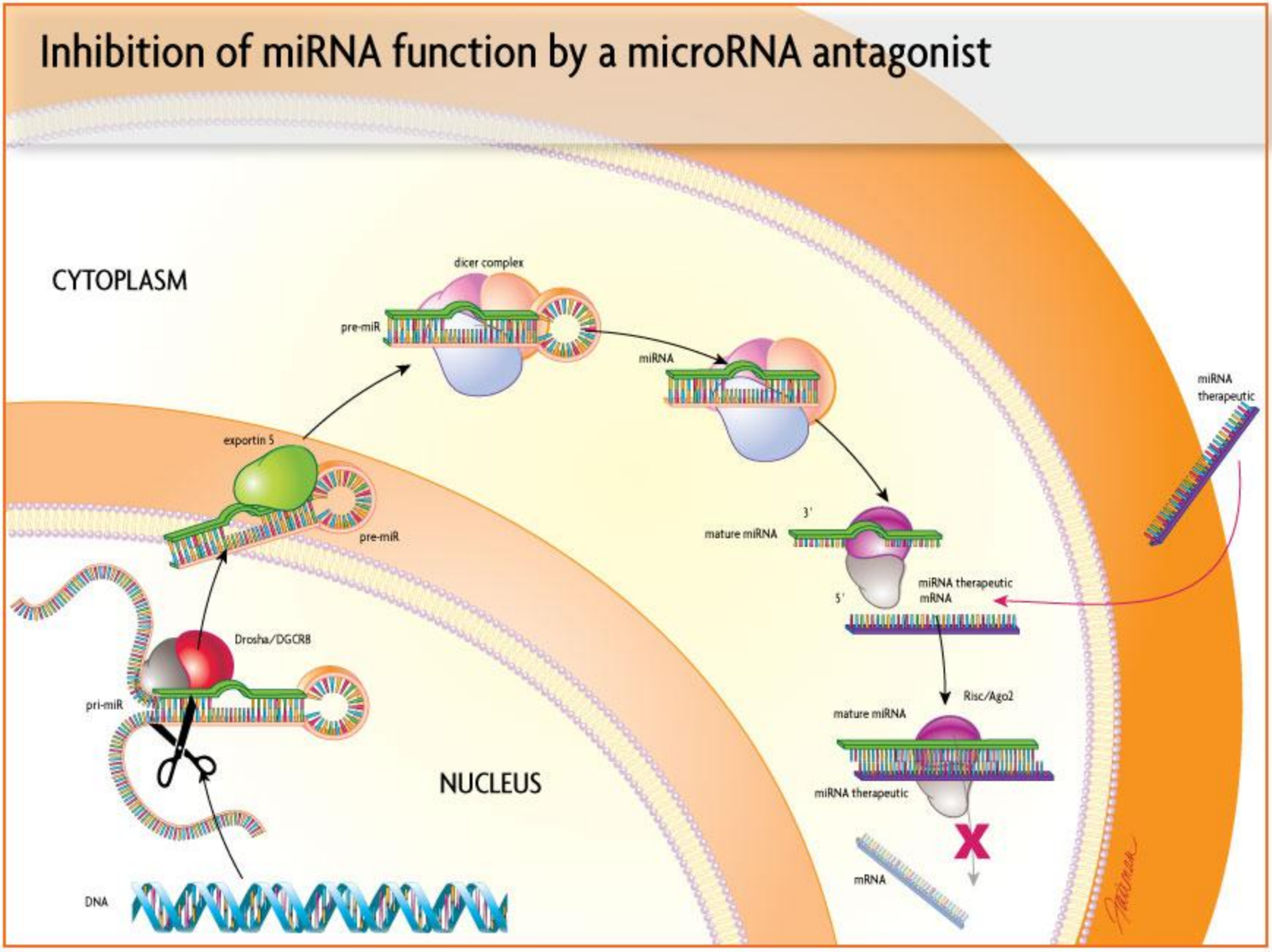
Cooper et al 09 Cell 136:777-793

The structure of human pri-miRNAs

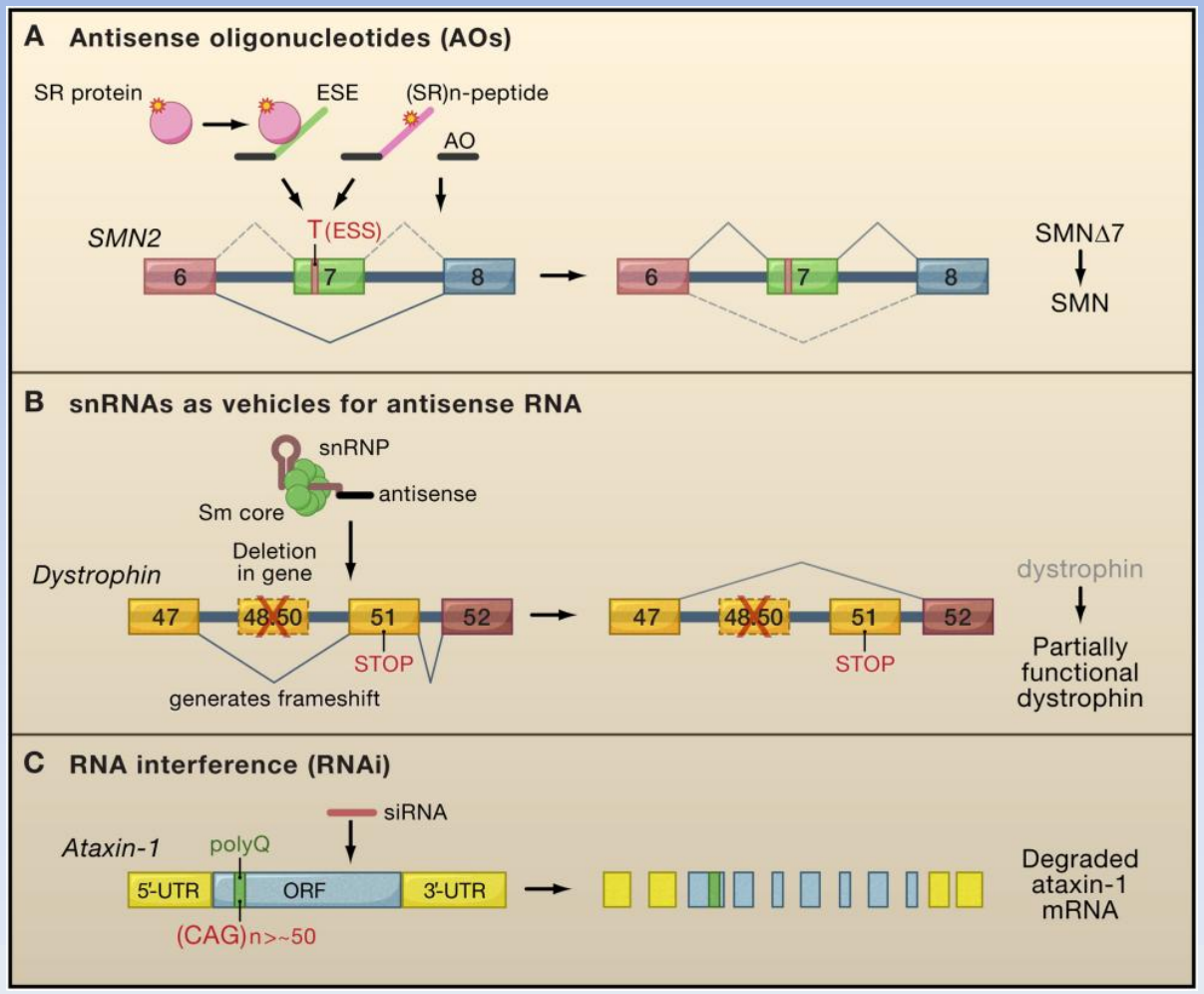


Du T , Zamore P D Development 2005;132:4645-4652

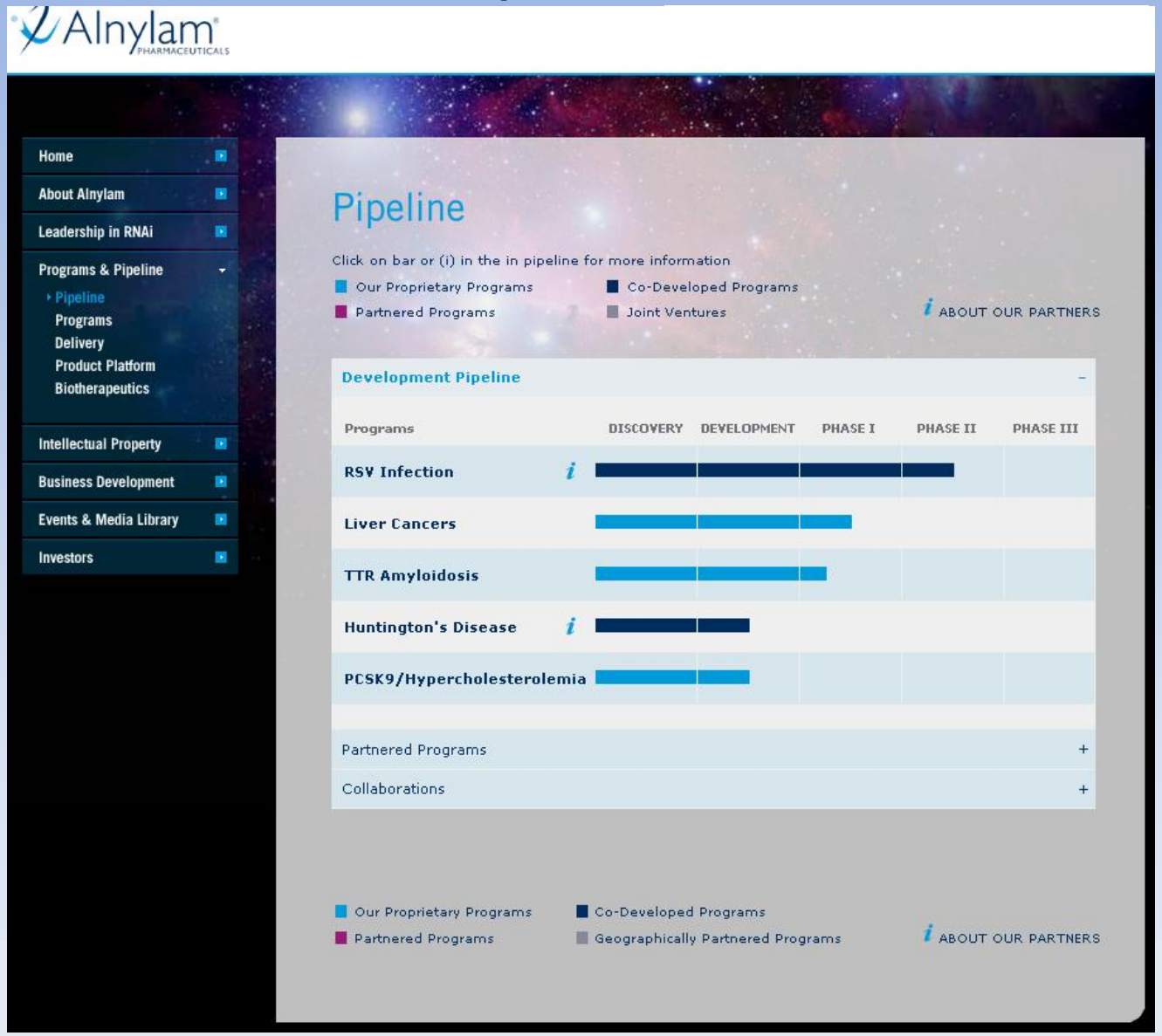
Inhibition of miRNA function by a microRNA antagonist



Therapeutics that alter RNA processing



Pipeline


Alnylam
PHARMACEUTICALS
Home
About Alnylam
Leadership in RNAi
Programs & Pipeline
Pipeline
Programs
Delivery
Product Platform
Biotherapeutics
Intellectual Property
Business Development
Events & Media Library
Investors
Pipeline
Click on bar or (i) in the in pipeline for more information
Our Proprietary Programs
Co-Developed Programs
Partnered Programs
Joint Ventures
ABOUT OUR PARTNERS
Development Pipeline
Programs
DISCOVERY
DEVELOPMENT
PHASE I
PHASE II
PHASE III
RSV Infection
Liver Cancers
TTR Amyloidosis
Huntington's Disease
PCSK9/Hypercholesterolemia
Partnered Programs
Collaborations
Our Proprietary Programs
Co-Developed Programs
Partnered Programs
Geographically Partnered Programs
ABOUT OUR PARTNERS

Pipeline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Hypercholesterolemia
TTR Amyloidosis
Huntington's Disease
Pre-clinical Programs
Delivery
Product Platform
Biotherapeutics
Intellectual Property
Business Development
Events & Media Library
Investors
Huntington's Disease
ALN-HTT: Huntington's Disease
ALN-HTT, an RNAi therapeutic for the treatment of Huntington's disease, is designed to silence the huntingtin gene, which is the cause of Huntington's when expressed as a toxic mutated protein.
In pre-clinical studies, ALN-HTT was well tolerated following administration to the brain and was shown to silence the huntingtin gene. Silencing the huntingtin gene also translated into a therapeutic effect in animal models, including improvement in motor behavior, which is a hallmark of this debilitating and fatal disease. The RNAi therapeutic reduced expression of mutant huntingtin in the brain and sustained a benefit in motor behavior for at least one week. In preliminary studies, the RNAi therapeutic was found to be well tolerated in the brain after direct CNS administration.
ALN-HTT is being developed in collaboration with Medtronic and CHDI Foundation. ALN-HTT is being developed for delivery to the central nervous system (CNS) using an implantable infusion system developed by Medtronic. CHDI is a not-for-profit virtual biotech company that is exclusively dedicated to rapidly discovering and developing therapies that slow the progression of Huntington's disease.
Learn More
Keystone Symposium: RNA Silencing
Therapeutic silencing of mutant huntingtin with siRNA attenuates striatal and cortical neuropathology and behavioral deficits
DiFiglia M et al.
Effective RNAi-mediated gene silencing without interruption of the endogenous microRNA pathway
John et al.

Pipeline

α-Synuclein Suppression by Targeted Small Interfering RNA in the Primate Substantia Nigra

Alison L. McCormack[1,2], Sally K. Mak[3], Jaimie M. Henderson[4], David Bumcrot[5], Matthew J. Farrer[6], Donato A. Di Monte[1,2]*

PLoS One. 2010; 5(8): e12122.

A randomized, double-blind, placebo-controlled study of an RNAi-based therapy directed against respiratory syncytial virus

John DeVincenzo[a,1], Robert Lambkin-Williams[b], Tom Wilkinson[c], Jeffrey Cehelsky[d], Sara Nochur[d], Edward Walsh[e], Rachel Meyers[d], Jared Gollob[d], and Akshay Vaishnaw[d]

www.pnas.org/cgi/doi/10.1073/pnas.0912186107

ISIS PHARMACEUTICALS

- ABOUT ISIS
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- DRUGS IN DEVELOPMENT
  - Therapeutic Areas
  - Current Advances
  - Patients
  - Partner News
- INVESTORS & MEDIA
- STRATEGIC ALLIANCES

Pipeline

Drug	Target	Partner	Preclinical	Phase I	Phase II	Phase III	Approved
CARDIOVASCULAR							
Mipomersen	apoB-100	Genzyme					
ISIS-CRP$_{Rx}$	CRP	-					
BMS-PCSK9$_{Rx}$	PCSK9	Bristol-Myers Squibb					
ISIS-FXI$_{Rx}$	Factor XI	-					
ISIS-APOCIII$_{Rx}$	ApoCIII	-					
METABOLIC							
ISIS 113715	PTP-1B	-					
ISIS-SGLT2$_{Rx}$	SGLT2	-					
ISIS-GCGR$_{Rx}$	GCGR	-					
ISIS-GCCR$_{Rx}$	GCCR	-					
CANCER							
OGX-011/TV-1011	clusterin	Teva/OncoGenex					
LY2181308	survivin	Lilly					
ISIS-EIF4E$_{Rx}$	eIF-4E	-					
OGX-427	Hsp27	OncoGenex					
NEURODEGENERATIVE / SEVERE AND RARE							
ISIS-SOD1$_{Rx}$	SOD1	ALSA, MDA					
ISIS-SMN$_{Rx}$	SMN2	-					
ISIS-GSK1$_{Rx}$	Severe and Rare Disease	GSK					
INFLAMMATION AND OTHER							
Vitravene	CMV	Novartis					
Alicaforsen	ICAM-1	Atlantic					
ACHN-490	Aminoglycoside	Achaogen					
ATL1102	VLA-4	Antisense					
EXC 001	CTGF	Excaliard					
iCo-007	C-raf kinase	iCo					
ATL1103	GHr	Antisense					

Regulus

Current R&D Portfolio

Multiple Emerging Clinical Candidates

RX CATEGORY		LEAD TARGETS
HCV	Developing HCV therapies. Seminal paper published demonstrating ability to block specific microRNAs.	gsk miR-122
FIBROSIS	Multiple collaboration targets with demonstrated therapeutic activity	sanofi aventis
ONCOLOGY	Novel therapeutic approach to target tumors	miR-34, others
IMMUNO-INFLAMMATORY	Multiple targets for immune-related diseases	gsk
METABOLIC DISEASE	Glucose lowering and improving insulin resistance for diabetes	Let-7, others

MACUGEN7 (Pegaptanib Sodium Inj.)

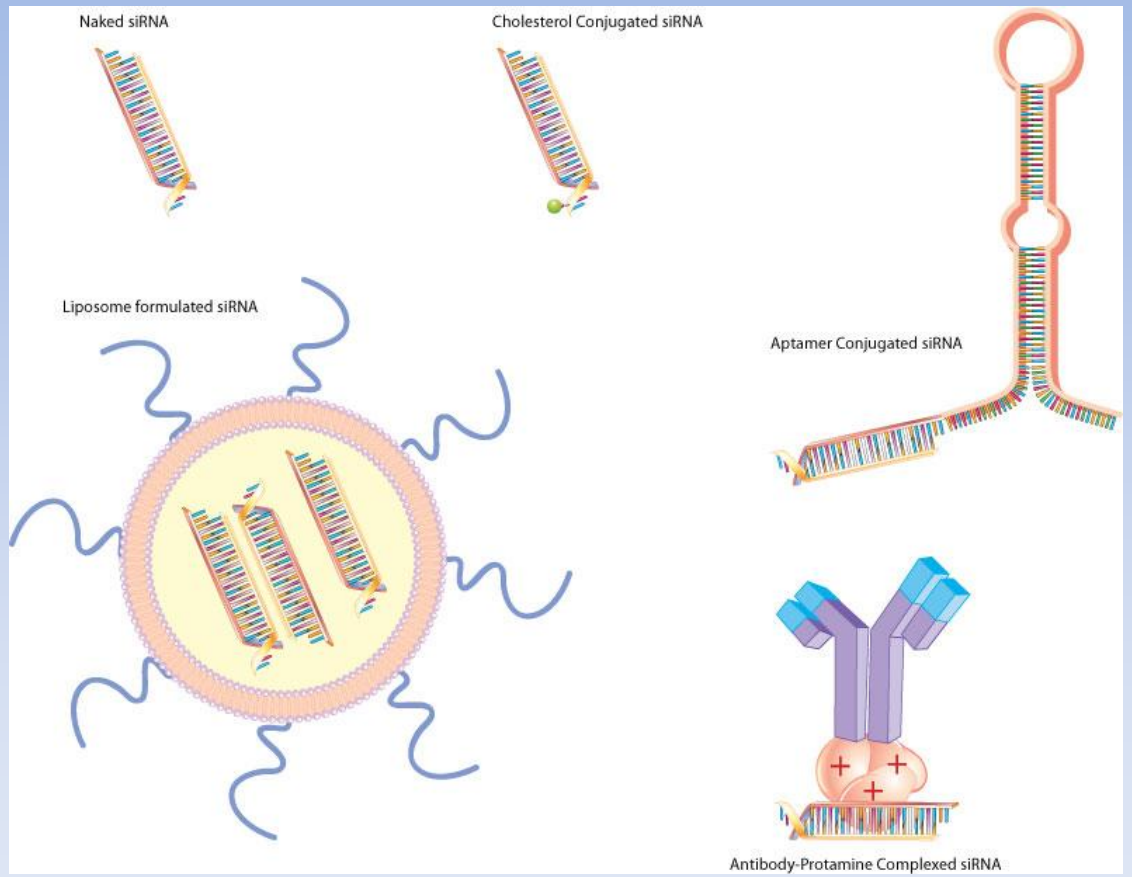
For wet age-related macular degeneration (AMD)

2'-F-pyrimidine RNA oligonucleotide ligands (aptamers) to human VEGF165

GACGAUGCGGUAGGAAGAAUUGGAAGCGC(U-2′OH); t22.29-OMe4,

Eyetech, Inc.

How to Deliver RNA molecules to the Nervous System?



SESSION 6A

C36 PLASTIC VIRUSES: ENGINEERING NANOPARTICLES FOR TARGETING THE CENTRAL NERVOUS SYSTEM

BATTAGLIA G

The Krebs Institute, Department of Biomedical Science, University of Sheffield, Sheffield, United Kingdom

siRNA or miRNA in ALS Studies

SESSION 3A

C16 RNA PROBLEMS AND SOLUTIONS: LESSONS FROM MYOTONIC DYSTROPHY

THORNTON C

University of Rochester, Rochester, NY, United States

E-mail address for correspondence: Charles_Thornton@urmc.rochester.edu

No abstract available.

C17 THE ROLE OF RNA SPLICING IN SPINAL MUSCULAR ATROPHY

PELLIZZONI L

Department of Pathology and Cell Biology, Columbia University, New York, NY, United States, Center for Motor Neuron Biology and Disease, Columbia University, New York, NY, United States

P29 DIFFERENTIAL EXPRESSION AND ALTERNATIVE SPLICING OF GENES IN THE LUMBAR SPINAL CORD OF SOD1-G93A TRANSGENIC MICE

GUO Y, CHEN H, HU M, ZHANG K, WANG Q, LI Z, LI C

P76 THE BH3-ONLY PROTEIN BIM: POSSIBLE LINK BETWEEN ER STRESS AND APOPTOSIS IN CELLULAR MODEL OF ALS

SOO KY[1,2], FARG M[1], WALKER A[1,3], HORNE M[3,4], NAGLEY P[2], ATKIN J[1,3]

P81 NFL MICRORNA EXPRESSION PROFILE IN SPORADIC ALS

STRONG M[1,2], HE Z[1], CAMPOUS D[1]

P92 CLOSE ASSOCIATION OF TDP-43 PATHOLOGY WITH LOSS OF RNA EDITING ENZYME ADAR2 IN MOTOR NEURONS IN SPORADIC ALS

AIZAWA H[2], SAWADA J[2], HIDEYAMA T[1], YAMASHITA T[1], KWAK S[1]

RNA: The Quiet Revolution

Jeffrey S. Deitch, PhD
Drexel University College of Medicine
ALS Hope Foundation
Philadelphia, PA

END

isis pharmaceuticals

RNase H

The antisense mechanism that has been the main focus of our research is RNase H. This cellular enzyme is activated when antisense drugs bind to their target RNA and form a duplex. Upon activation, RNase H seeks out and destroys the target mRNA, inhibiting a cell's production of a specific protein.

We have cloned and characterized human RNase H and have effectively used that information to optimize the design of many of our antisense drugs. We will continue to advance our understanding of antisense mechanisms, including RNase H, in order to improve the pharmaceutical properties of our drugs.

In addition to our RNase H expertise, we are the leaders in understanding and exploiting all antisense mechanisms, including the RNAi mechanism.

RNAi

RNAi is an antisense mechanism that involves using small interfering RNA, or siRNA, to target an mRNA sequence.

We design antisense drugs to control splicing to make one protein versus another. In December 2009, we advanced the first antisense drug, ISIS-SMNRx, to enter our development pipeline that modulates splicing. ISIS-SMNRx is designed to treat the splicing disease, SMA, which is a neuromuscular disorder and the leading genetic cause of infant mortality. The discovery of ISIS-SMNRx resulted from a joint research collaboration between scientists at Isis and Cold Spring Harbor. In earlier published research, we and our collaborators at Cold Spring Harbor demonstrated the feasibility of using our antisense technology to control splicing for the treatment of SMA.

MicroRNA

MicroRNAs are small naturally occurring RNA molecules that are created inside cells. There are many different types of RNA that exist within the body, including mRNA. MicroRNAs are important because they appear to have critical functions in controlling processes or pathways of gene expression.

There are nearly 700 microRNAs that have been identified in the human genome, and these are believed to regulate the expression of approximately one-third of all human genes. Targeting microRNA to inhibit disease-causing pathways is an exciting development in RNA-based therapeutics.

To fully exploit the therapeutic opportunities of targeting microRNAs, we and Alnylam jointly established Regulus as a company focused on the discovery, development, and commercialization of microRNA-based therapeutics.

Vitravene®

Vitravene, approved by the FDA in 1998, is an antisense drug that we discovered and developed, to treat cytomegalovirus, or CMV retinitis in AIDS patients. Novartis Ophthalmics AG, our worldwide distribution partner for this drug, launched Vitravene in November 1998. New anti-HIV drugs, particularly protease inhibitors and combination treatment regimens, have prolonged survival in HIV-infected individuals. This has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections, including CMV retinitis. As a result, Novartis no longer markets Vitravene. Vitravene demonstrates our ability to meet FDA and European regulatory requirements for safety and efficacy, and for the commercial manufacture of antisense drugs.

isis

ISIS-SOD1$_{Rx}$

ISIS-SOD1$_{Rx}$ is an antisense drug that targets superoxide dismutase, or SOD1, a molecule associated with an inherited, aggressive form of ALS. The FDA granted ISIS-SOD1$_{Rx}$ Orphan Drug designation for the treatment of ALS. Because antisense drugs do not cross the blood-brain barrier, a small pump administers the drug directly into the CNS infusing the drug into the cerebral spinal fluid. Clinicians call this type of administration intrathecal infusion.

Researchers reported in the Journal of Clinical Investigation that treatment with ISIS-SOD1$_{Rx}$ prolonged life in rats that showed many symptoms of ALS. By delivering our drug directly to the fluid that circulates within the CNS, we and our collaborators lowered production of the mutant protein in neurons and surrounding cells.

The ALS Association and the Muscular Dystrophy Association are providing funding for ISIS-SOD1$_{Rx}$. Additionally, as part of our alliance with Genzyme, Genzyme has a right of first negotiation to license ISIS-SOD1$_{Rx}$ from us. We are evaluating ISIS-SOD1$_{Rx}$ in a Phase 1 study in patients with the familial form of ALS.

ISIS-SMN$_{Rx}$

ISIS-SMN$_{Rx}$ is an antisense drug designed to treat SMA, a neuromuscular disorder and the leading genetic cause of infant mortality. The incidence of SMA is 1 in 6,000 to 10,000 births, and most infants born with the most severe form of SMA, Type 1, die within two years according to the National Institutes of Health's National Institute of Neurological Disorders and Stroke. A genetic deletion of the survival motor neuron 1, or SMN1, gene is responsible for SMA. ISIS-SMN$_{Rx}$ increases the production of the protein SMN by modulating the splicing of a closely related pre-mRNA, SMN2. Normal motor function is associated with normal levels of SMN. By altering splicing to produce SMN, ISIS-SMN$_{Rx}$ may compensate for the underlying genetic defect.

In 2008, we and researchers from Cold Spring Harbor published data that demonstrated the feasibility of using our antisense technology to control splicing. Our collaborative work with Cold Spring Harbor led to the discovery of ISIS-SMN$_{Rx}$. Our SMA program is part of our collaboration in neurodegenerative disease with Genzyme, pursuant to which Genzyme has a right of first negotiation to license ISIS-SMN$_{Rx}$ from us.

ISIS-GSK1$_{Rx}$

ISIS-GSK1$_{Rx}$ is an antisense drug designed to treat an undisclosed serious and rare disease. ISIS-GSK1$_{Rx}$ is the first drug to enter development under the recently announced partnership with GSK. We receive milestone payments from GSK as ISIS-GSK1$_{Rx}$ advances in development, and we are responsible for development of the drug up to Phase 2 proof-of-concept, at which time GSK has the option to license ISIS-GSK1$_{Rx}$ from us.

Genetic Code

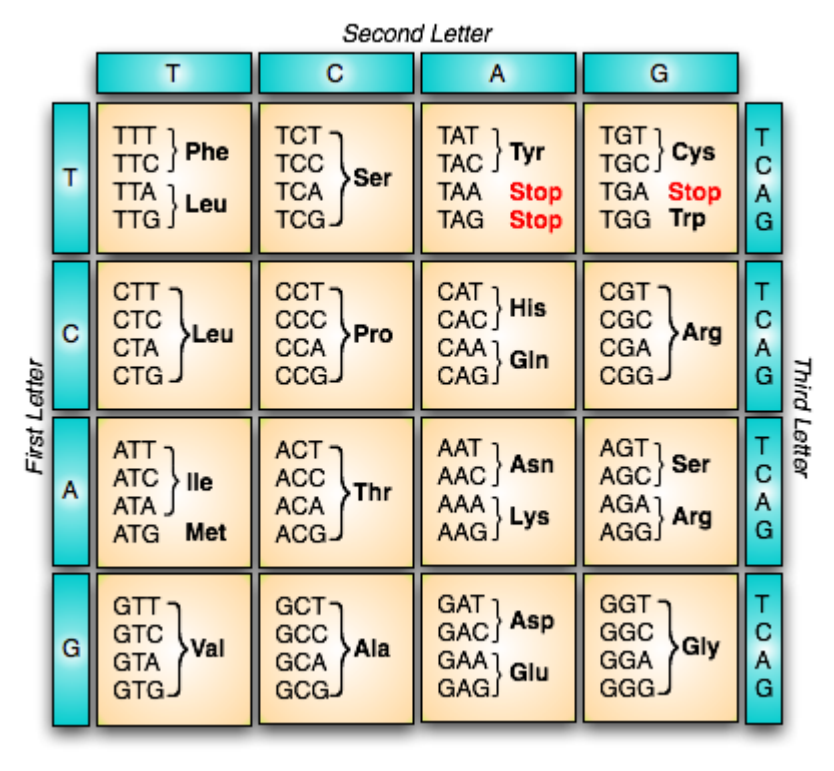
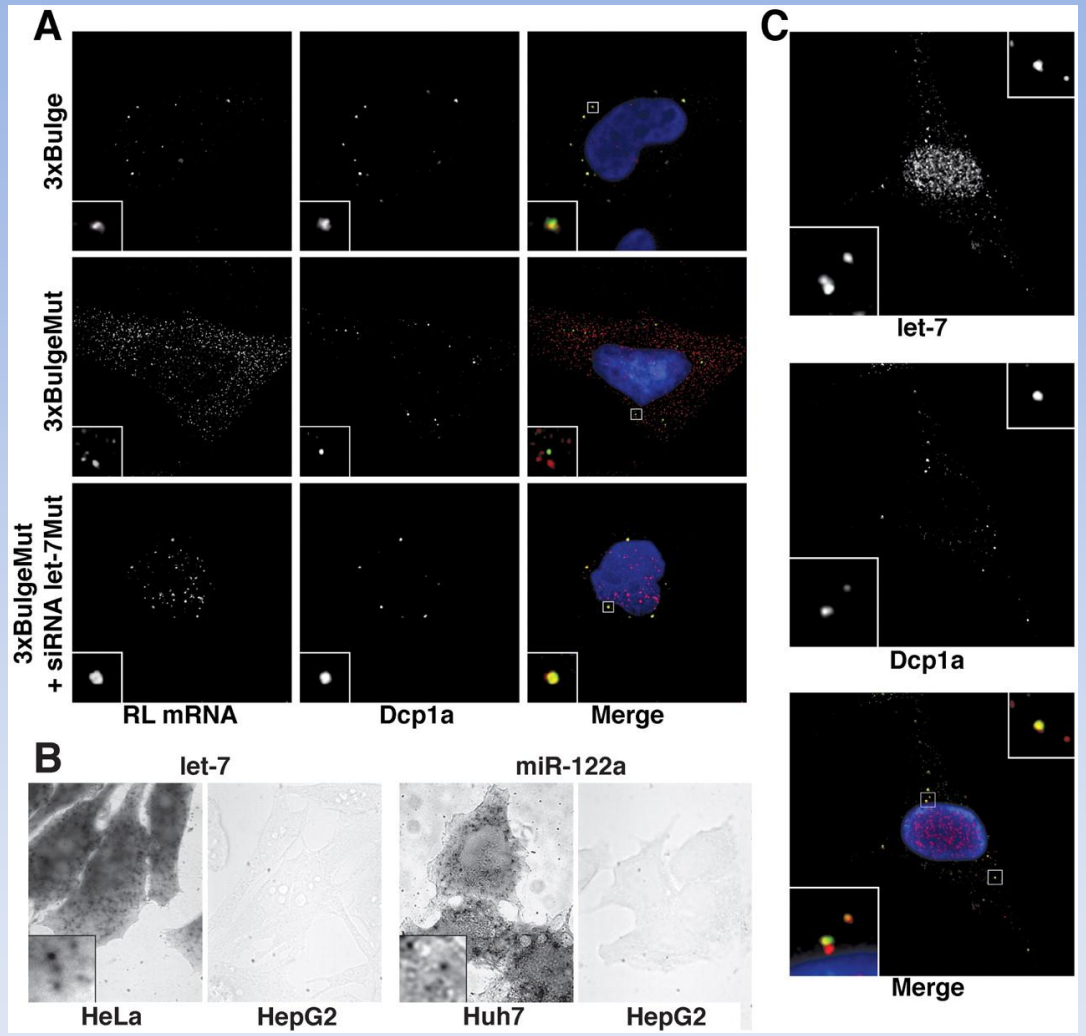
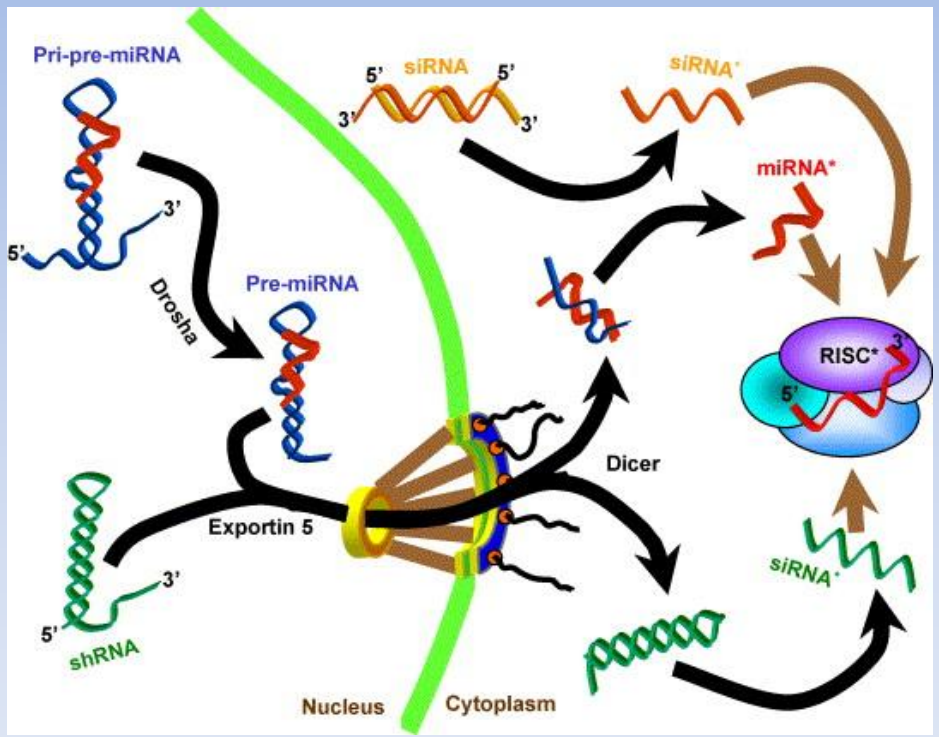
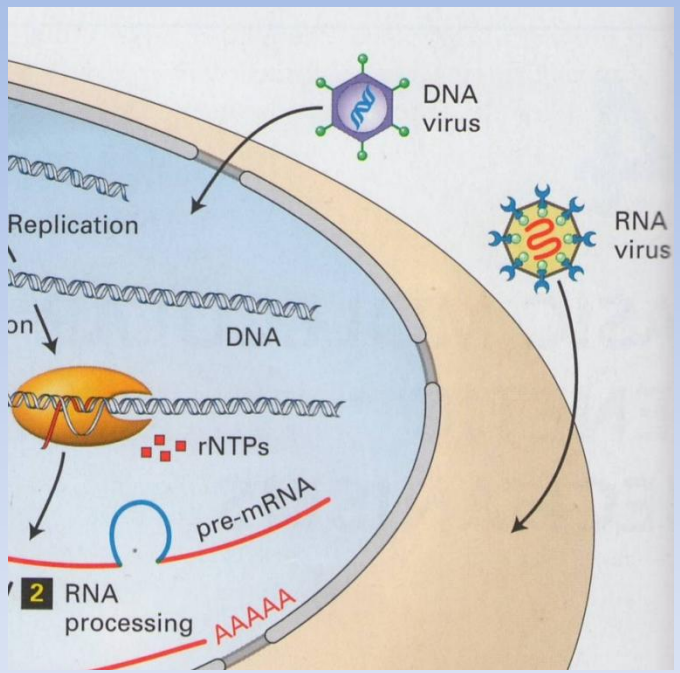


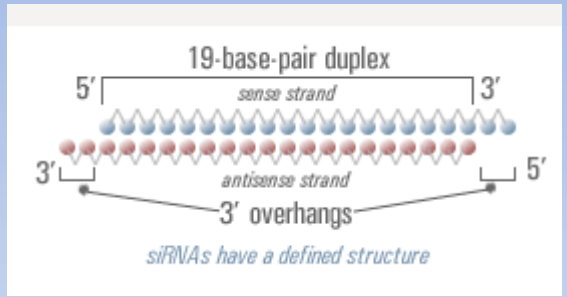
Fig. 3. Localization of translationally repressed mRNA and miRNAs to discrete foci adjacent to or overlapping with PBs.



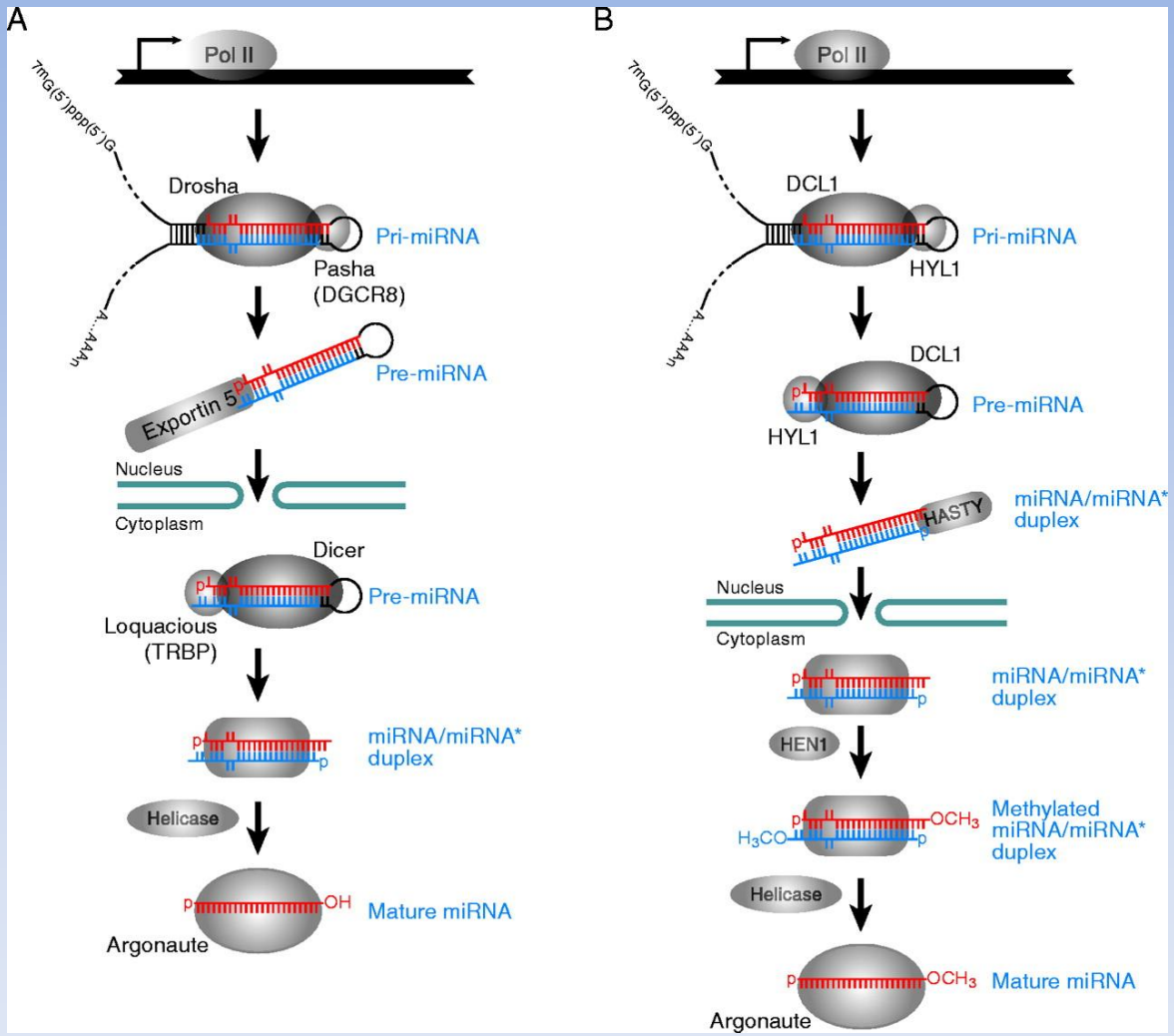
R S Pillai et al. Science 2005;309:1573-1576


Pri-pre-miRNA
5'
3'
Drosha
Pre-miRNA
5'
siRNA
5'
3'
3'
siRNA*
miRNA*
RISC*
3'
5'
Dicer
Exportin 5
5'
3'
shRNA
siRNA*
Nucleus
Cytoplasm


DNA
virus
RNA
virus
Replication
DNA
rNTPs
pre-mRNA
2 RNA
processing
AAAAA

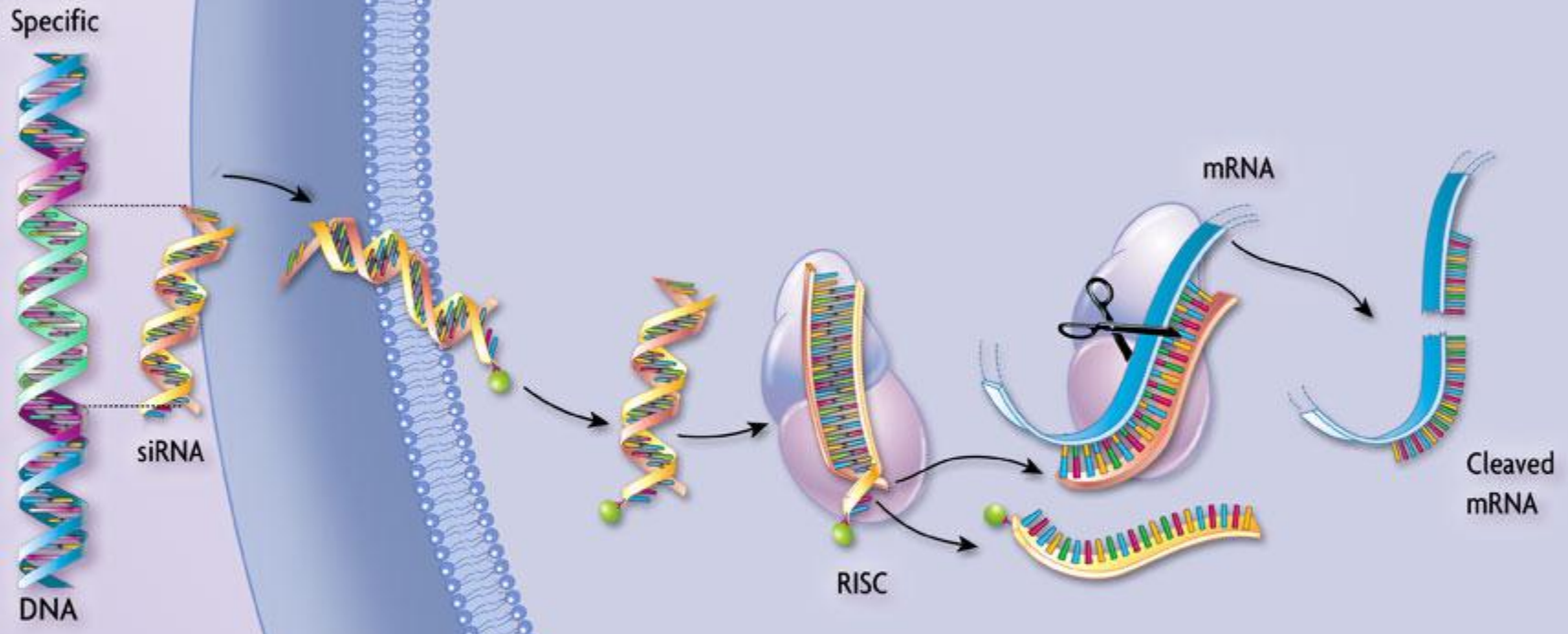

19-base-pair duplex
5′
3′
sense strand
3′
5′
antisense strand
3′ overhangs
siRNAs have a defined structure

The miRNA biogenesis pathway.



Du T , Zamore P D Development 2005;132:4645-4652

The RNAi Therapeutic Mechanism



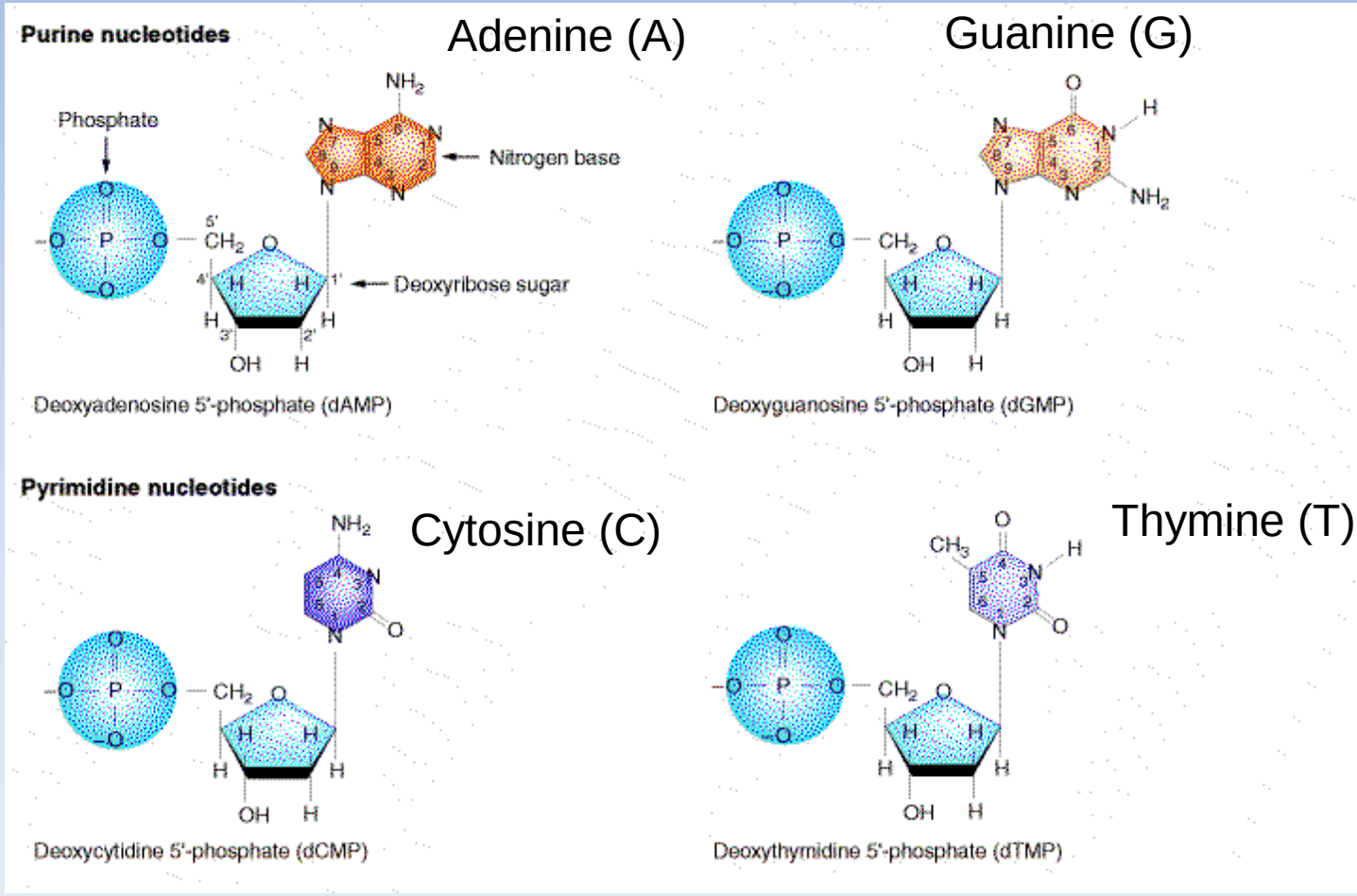
A Short interfering RNA (siRNA) designed to correspond to gene target

B siRNA synthesized with drug-like properties: stability and conjugation for delivery

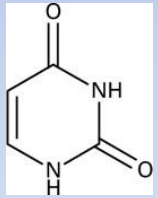
C Modified siRNAs penetrate the cell membrane and harness the RNAi mechanism for gene silencing

D Gene silencing achieves a therapeutic effect

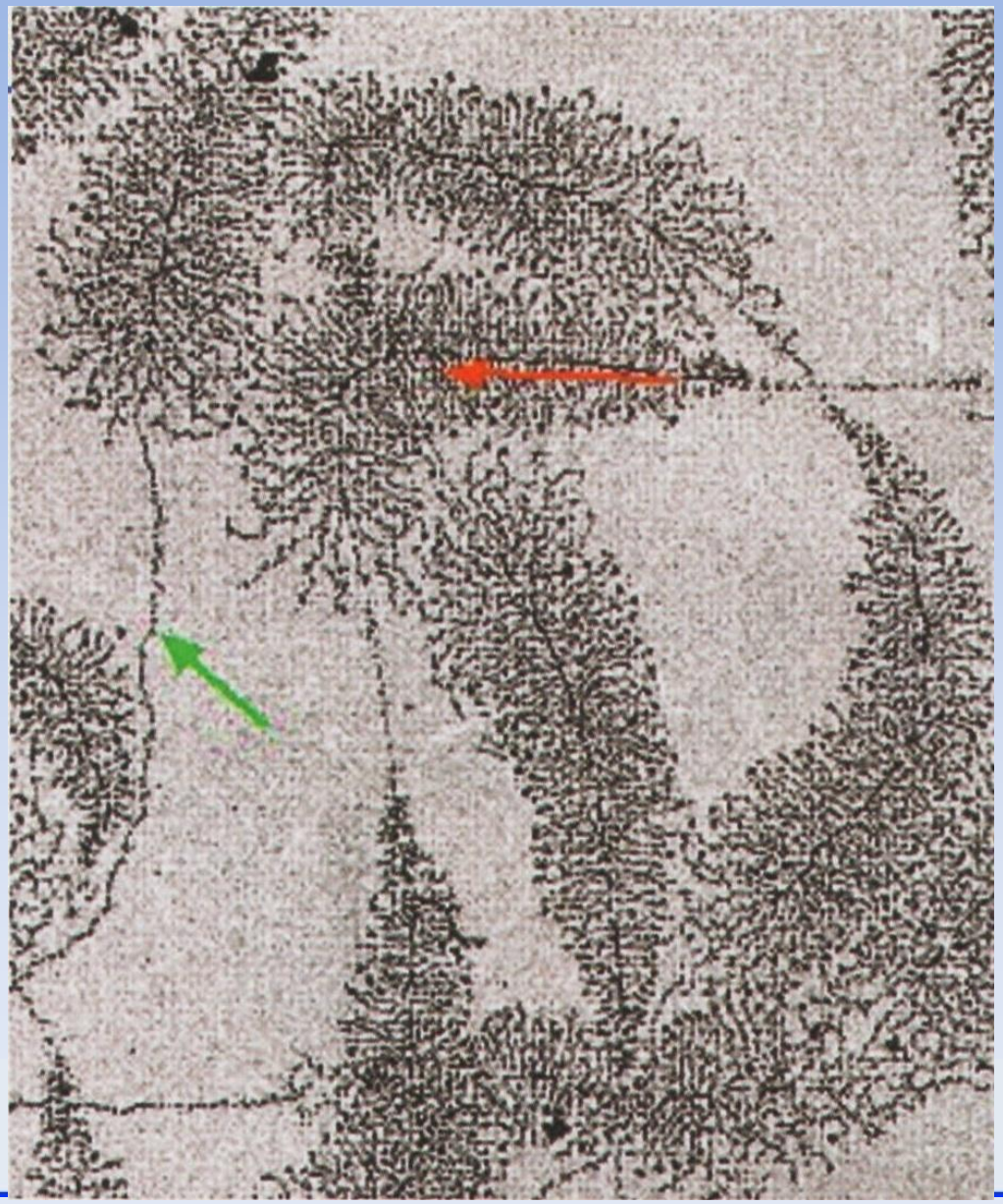
DNA (DeoxyRiboNucleic Acid) and RNA (RiboNucleic Acid) are composed of the following:



Uracil (U)



Transcription – A Closer Look

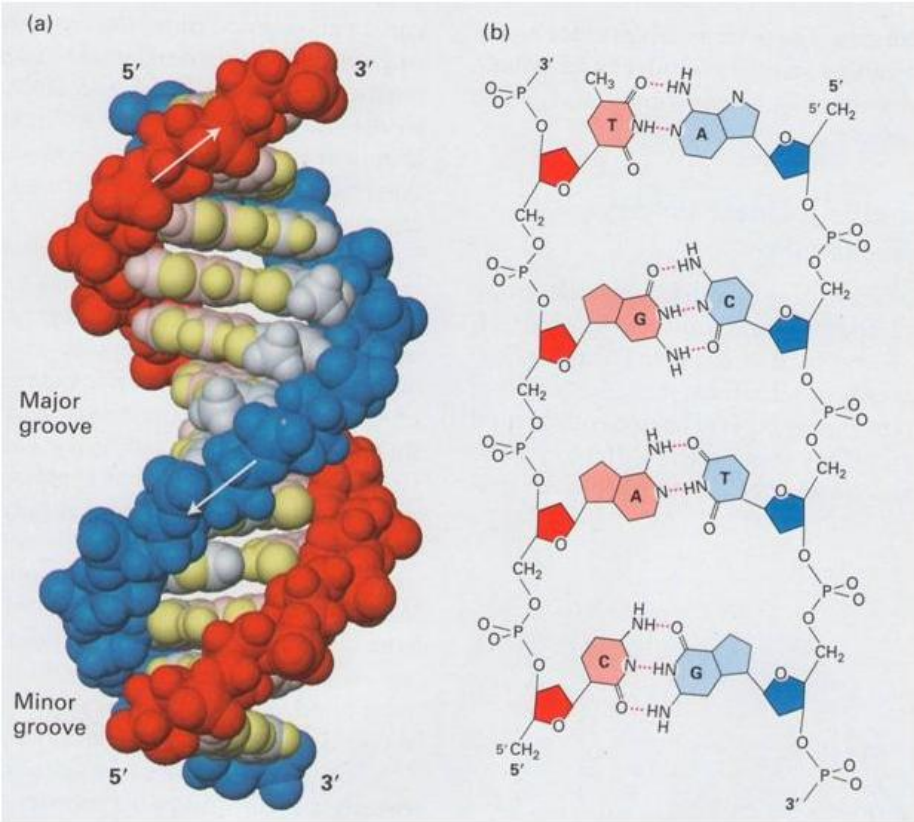


In DNA, the As, Gs, Cs & Ts form two intertwined and bound long strands (Double Helix)

G ↔ C

A ↔ T (DNA)

A ↔ U (RNA)



CGGCTGCTGCTTCCCTACCAACTACACACTG-
GCCGACGACGAAGGGATGGTTGATGTGTGAC-

GCAGCTGCAAGCTGCAGTTAGGGATGGCACC-
CGTCGACGTTCGACGTCAATCCCTACCGTGG-

AACATCTCTTATAGCTGGACAGCGCAGCAGG-
TTGTAGAGAATATCGACCTGTCGCGTCGTCC-

AGGGCAGCCTCATCACACTCTTCGGCAGTGG-
TCCCGTCGGAGTAGTGTGAGAAGCCGTCACC-

CAAGTGCTTTTCTCTCACTTCACTCAAAGCT-
GTTCACGAAAAGAGAGTGAAGTGAGTTTCGA-

AGCACCTACTATGTCCATCTTAGGGCCACTA-
TCGTGGATGATACAGGTAGAATCCCGGTGAT-

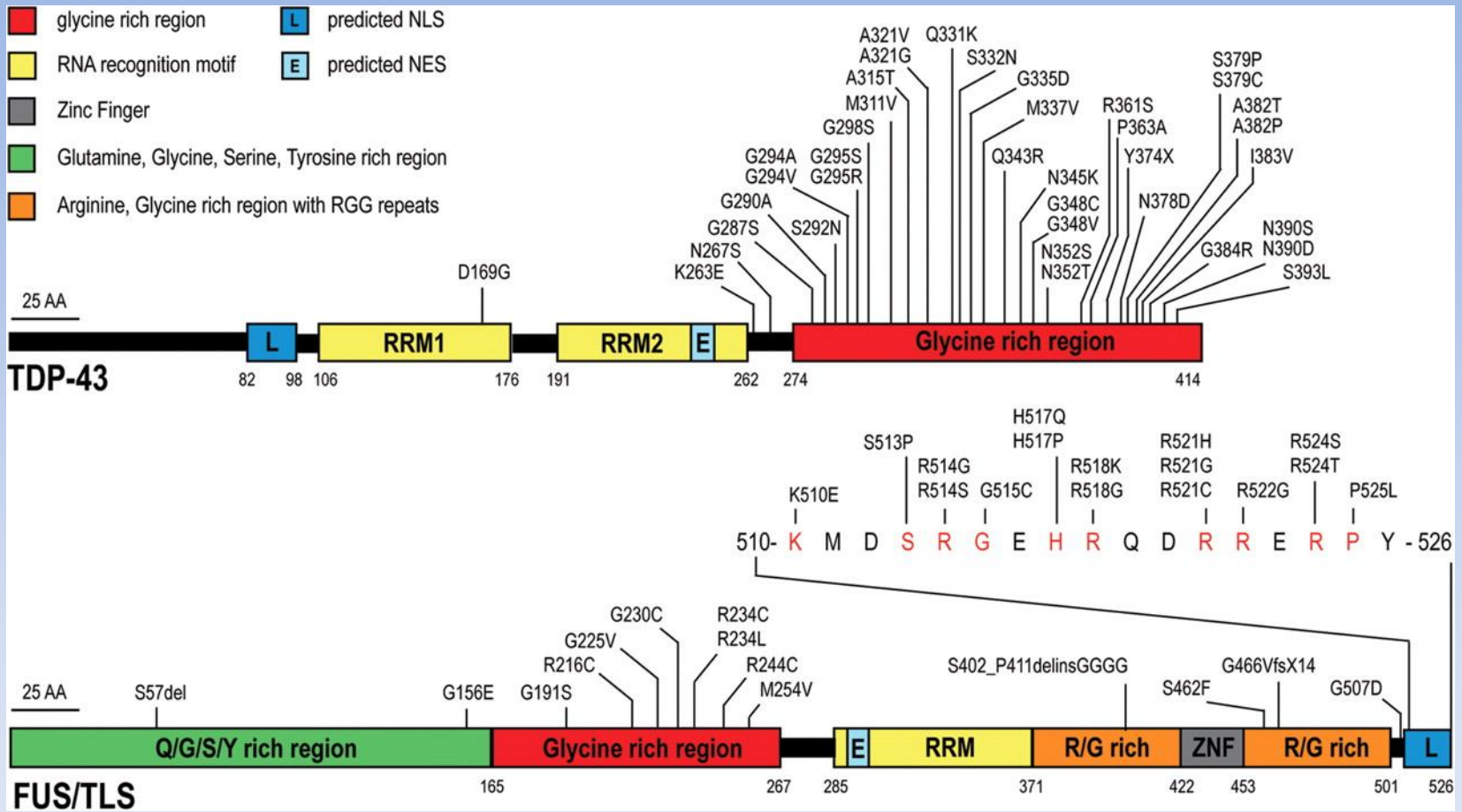
ACATGTTGGGTAGTGCCGCAGCCAACCGTAC-
TGTACAACCCATCACGGCGTCGGTTGGCATG-

TATAGACTTTGTGGAACCTGTGGAGAGTCTA-
ATATCTGAAACACCTTGGACACCTCTCAGAT-

ATCCTATCTGCATCCCCTAATCCAGCTGCTG-
TAGGATAGACGTAGGGGATTAGGTCGACGAC-

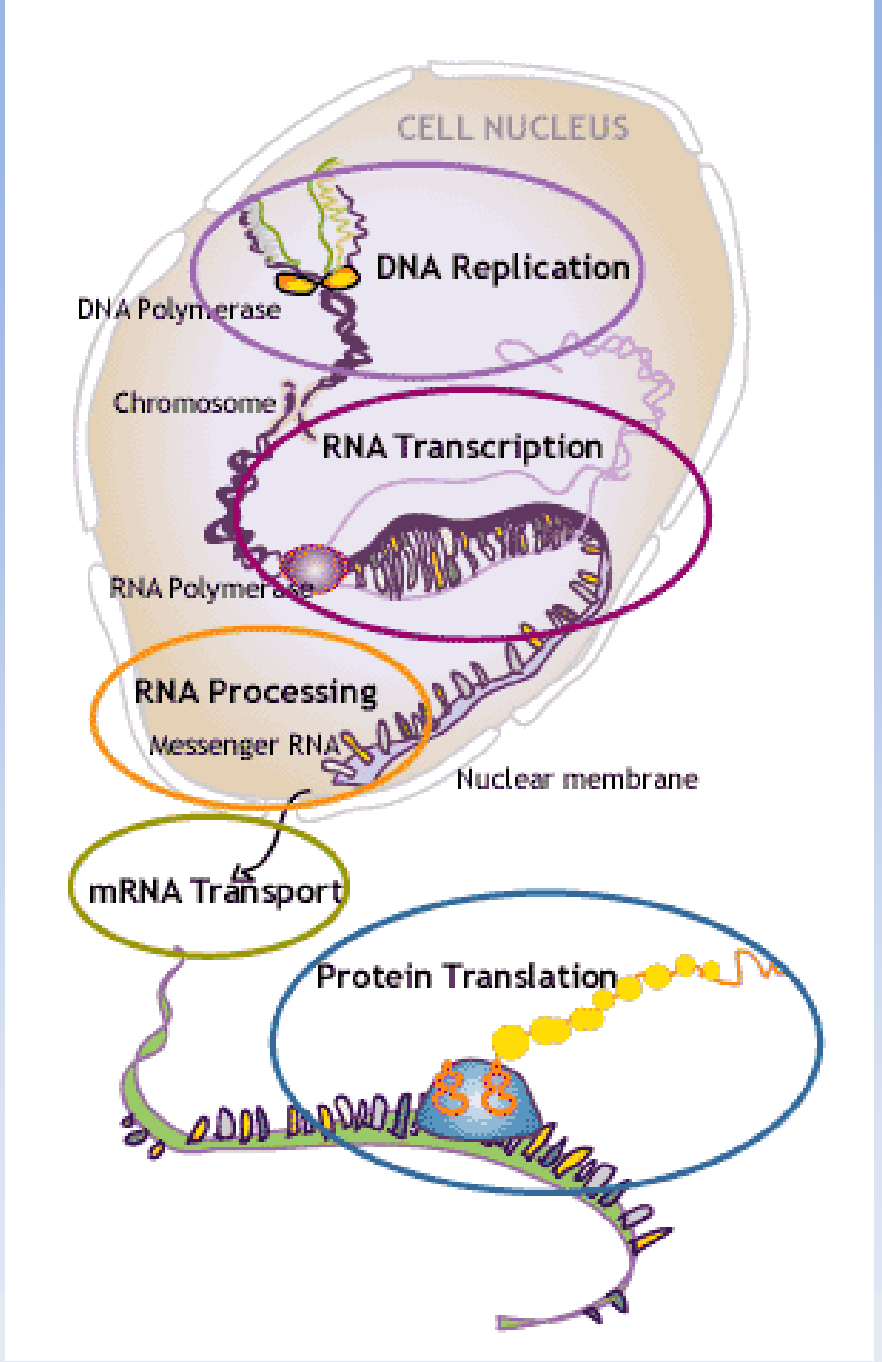
TCAACATGAGTCTCACCCTTTGTGCTGAATT-
AGTTGTACTCAGAGTGGGAAACACGACTTAA-

TDP-43 and FUS/TLS mutations in ALS and FTLD patients.



Lagier-Tourenne C et al. Hum. Mol. Genet. 2010;19:R46-R64

Human Molecular Genetics



Source: http://nobelprize.org/educational/medicine/dna/index.html

Biogenesis of microRNAs