CAR-T

Y OTROS MEDICAMENTOS DE TERAPIAS AVANZADAS

Legislación

Necesidades estructurales SF para gestión medicamentos terapias avanzadas

Requisitios manipulación muestras biológicas

Responsabilidad EECC

Atención Fca CART

Otros medicamentos de terapia avanzada

Antisentido

ORGANIZA

sefh Sociedad Española de Farmacia Hospitalaria

fefh Fundación Española de Farmacia Hospitalaria

JORNADA MEDICAMENTOS DE TERAPIAS AVANZADAS

FARMACOS ANTISENTIDO

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Hospital Universitari de Bellvitge

Tecnología antisentido : introducción

Tecnología innovadora para el abordaje terapéutico de diversas enfermedades, al manipular la expresión de ciertos genes (premio Nobel de Medicina 2006, Mello & Fire)

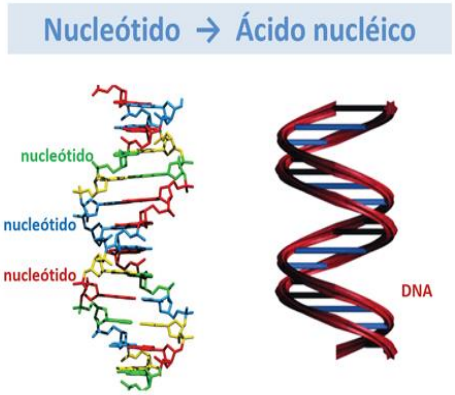
- Los fármacos antisentido son generalmente oligonucleótidos que se unen a proteínas o secuencias específicas de ácido ribonucleico (ARNm) y bloquean la formación o el funcionamiento de las proteínas causantes de la enfermedad.

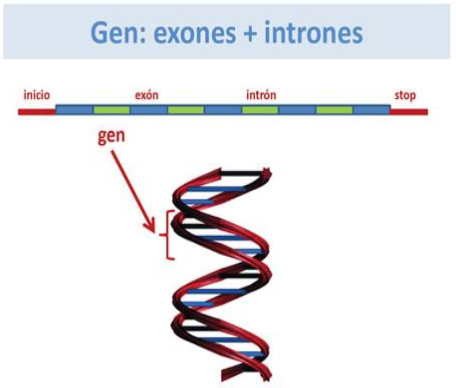
- Fármacos que ya se están utilizando en la práctica clínica:

Nusinersen (Spinraza®), autorizado para la atrofia muscular espinal.

Pegaptanib (Macugen®) ,autorizado para la degeneración macular neovascular (exudativa) asociada a la edad en adultos.

Algunos conceptos





DNA: ácido desoxiribonucleico (almacén genes)

RNA: ácido ribonucleico (copia el DNA para síntesi proteica; contiene Uracil)

Pre-mRNA: RNA mensajero con intrones (antes del splicing o procesamiento)

mRNA: RNA mensajero. Intermediaro entre el DNA (gen) y los tripletes aminoácidos (proteína)

ASO: ***antisense oligonucleotide*****,** oligonucleótido (12-15 nucleótidos) sintético, que se aparea a un mRNA concreto impidiendo que se forme proteína

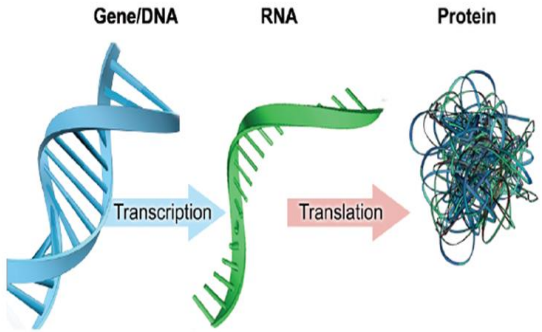
RNAi: RNA interferente. RNA no codificante (“egoísta”).

El dogma central de la biología: de DNA a RNA, y de RNA a proteína

Las secuencias del DNA se transcriben para formar el **RNA mensajero**(**mRNA**). A una determinada base púrica o pirimidínica del DNA le corresponde otra complementaria del RNA, de forma que se van disponiendo una a una formando una cadena a medida que “lee” el DNA.

De esta forma **el RNA contiene la información génica del DNA** necesaria para la formación de la proteína. Mediante una maquinaria celular posterior, la cadena de RNA da lugar a la formación de una cadena de aminoácidos, es decir, a una proteína.

En el proceso de formación del mRNA se eliminan los intrones del DNA, en un proceso de **empalmes** o ***splicing***, manteniéndose en el mRNA sólo la información de los **exones del DNA**, que codifican para la proteína.

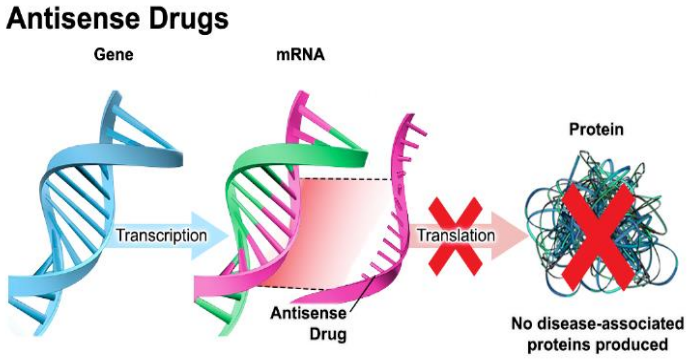


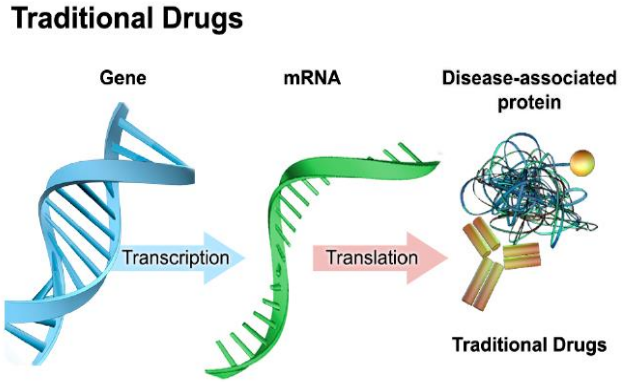
Silenciamiento génico por oligonucleótidos antisentido (ASO)

La **terapia antisentido** se basa en el uso de **oligonucleótidos** (pequeños fragmentos de ácido nucleico (13-25 nucleótidos), **antisentido**, complementarios para una secuencia específica de un gen, con objeto de unirse al mRNA del mismo y evitar así la producción de una proteína mutada.

¿Por qué se llaman oligonucleótidos antisentido?
Porque están diseñados para que sean **complementarios** a una secuencia específica de un gen, es decir, para que sean capaces de unirse a una determinada secuencia génica del RNA mensajero (mRNA), evitando con ello la producción de una **proteína anómala.**

Mecanismo de acción mas “preciso” que los fármacos *tradicionales*





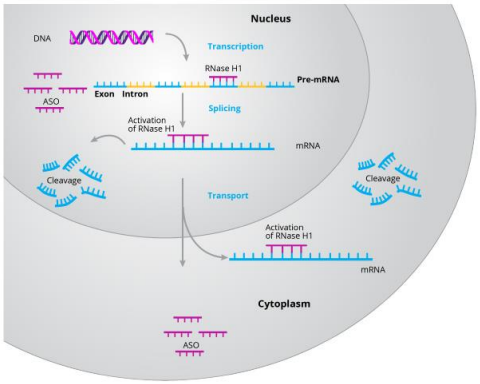
Goyal N, Narayanaswami P. Muscle Nerve. 2018;57(3):356-370.
Bennett CF, Swayze EE. Annu Rev Pharmacol Toxicol. 2010;50:259-93.
Ionis Pharmaceuticals. Basic Science. http://www.ionispharma.com/rd/ antisense-technology/discovery-platform/basic-science/. Accessed April 30, 2018.
Southwell AL, Skotte NH, Bennett CF, Hayden MR. Trends Mol Med. 2012;18(11):634-644.

Mecanismos principales de acción de los fármacos antisentido

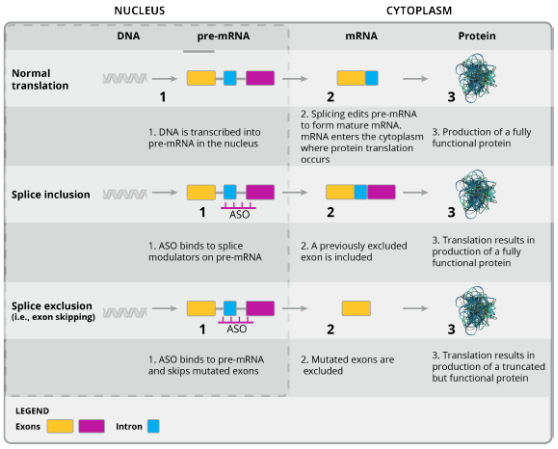
Vía la endonucleasa RNAse H1 (en el núcleo): el antisentido se une a un mRNA específico, esto recluta la enzima nuclear RNAsa H1, y el complejo ASO-mRNA diana es degradado.

Modificando el splicing (procesamiento): si un antisentido se une en una de las dianas de corte para el splicing, esta diana no puede ser reconocida, no se elimina el intron, y se produce una proteína defectuosa (no codificante).

RNA interferencia (citoplasma): se une a la secuencia específica de mRNA, una vez procesado en el citoplasma, y esto recluta un complejo enzimático que degrada el RNAi-mRNA, y por tanto la proteína final no se sintetiza. Éste mecanismo es utilizado por la célula para "silenciar" expression génica en las vías de señalización intracelulares.



Adapted from Goyal and Narayanaswami. *Muscle Nerve*. 2017;1-15.



Adapted from Goyal et al. *Trends Mol Med*. 2012;18(11):634-644.

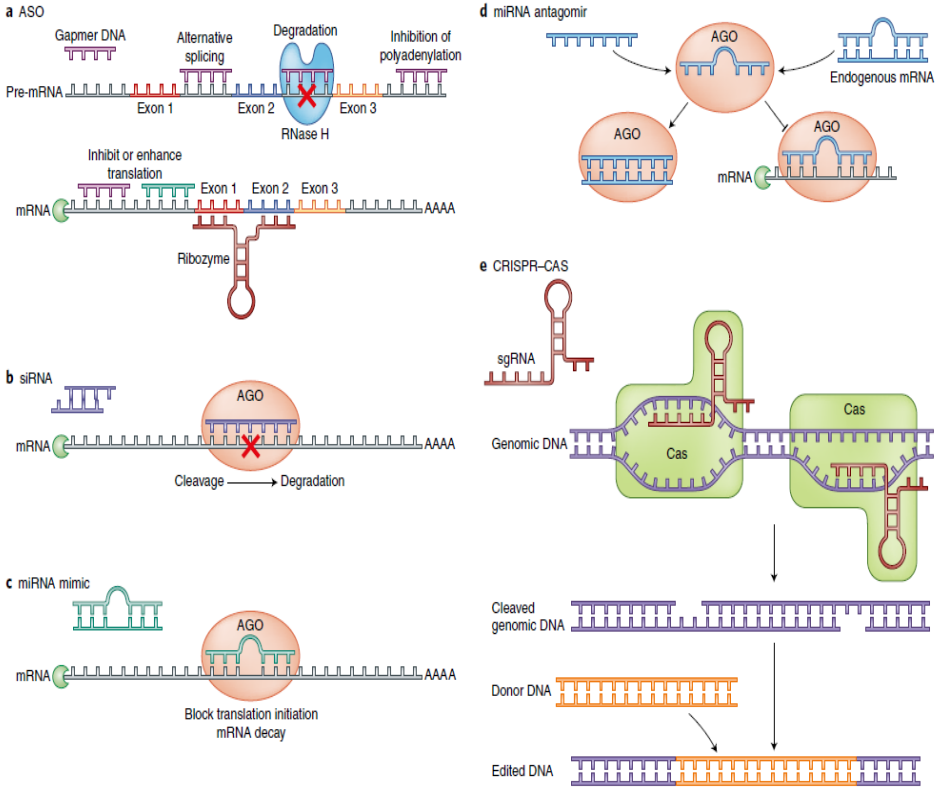
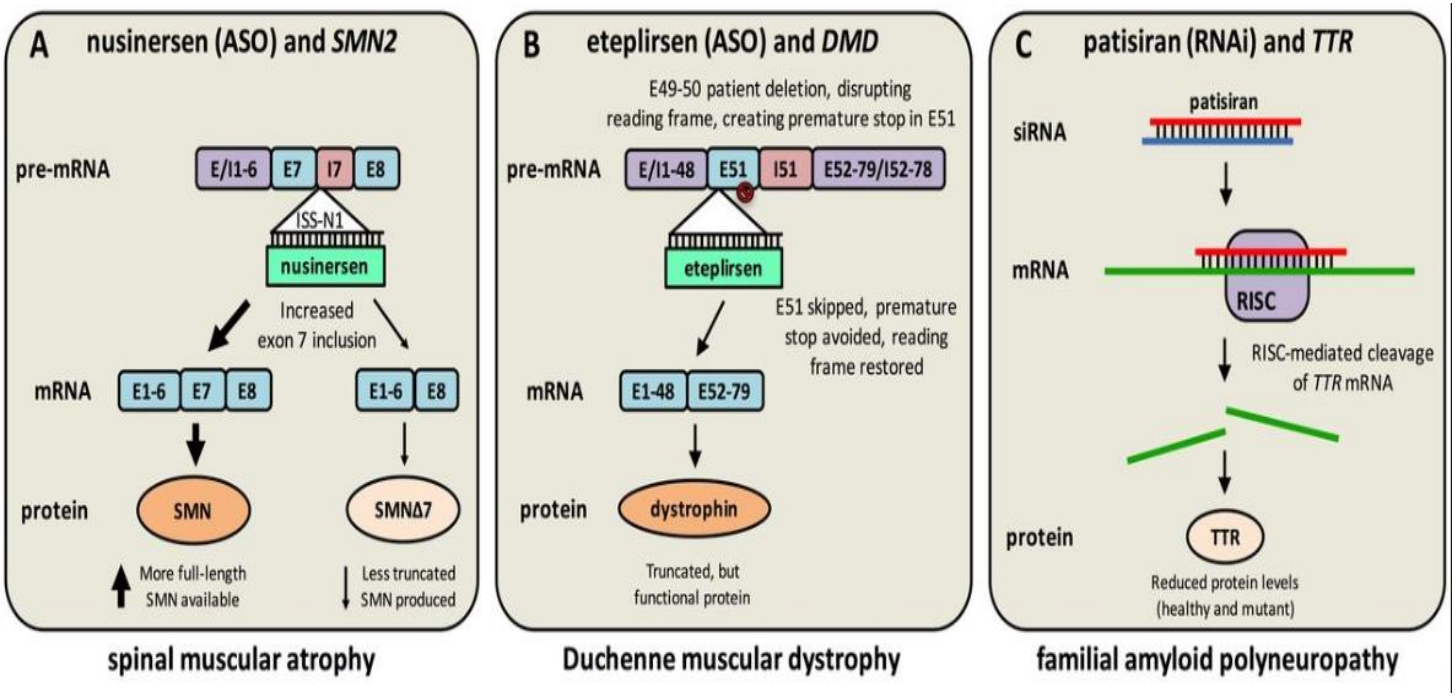


Fig. 1 | Antisense mechanisms of RNA-based drugs. Most RNA-based drugs take advantage of complementary base-pairing of RNA analogs. They are generally extensively modified to improve their resistance to RNases and innate immune sensors and to potentially increase binding affinity to their nucleic acid or protein targets, which mediate their intracellular activity. These drugs bind to complementary sequences in endogenous genomic DNA or its RNA transcripts. The major classes are ASOs (usually single-stranded with a central DNA gapmer region) (**a**), double-stranded siRNAs (**b**), miRNA mimics (**c**) or antagomirs (**d**) and, most recently, single guide RNAs (sgRNAs) for gene editing using CRISPR–Cas (**e**). Although the targets are depicted in the diagram as pre-mRNAs, mRNAs or genomic DNA, in principle, these strategies could also be used to target ncRNAs. Credit: Debbie Maizels/Springer Nature

Ejemplos de los 3 principales mecanismos de acción



Rossor AM, Reilly MM, Sleigh JN
Antisense oligonucleotides and other genetic therapies made simple
Practical Neurology 2018;18:126-131.

Específicos y con un amplio potencial

ASOs have several unique features that differentiate them from other classes of agents and make them ideal therapeutic options for development:

- Targeted approach – Many diseases are due to a dysfunction in the production of a specific protein. By targeting RNA, an ASO can directly target the disease-associated protein and affect pathways that are not treatable by traditional mechanisms.
- Specificity – RNA is universal and simple, and ASOs can bind their targets with great specificity. ASOs hybridize specifically to their target mRNA through Watson-Crick base-pair interactions without affecting other mRNAs, reducing the potential for off-target binding.
- Broad applicability – ASOs have been shown to accumulate in specific organs and tissues, including the liver, kidney, spleen, bone marrow, and fat cells. Because they work broadly throughout the body, ASOs can treat a wide variety of diseases and bring benefit to patients in need.
- Predictable safety profile – All ASOs share a common chemical structure, and the distribution and metabolism of antisense drugs are very similar from drug to drug. This results in a common side effect profile among ASOs.

Southwell AL, Skotte NH, Bennett CF, Hayden MR. Trends Mol Med. 2012;18(11):634-644.
Crooke ST. Nucleic Acid Ther. 2017;27(2):70-78.
Crooke ST, Witztum JL, Bennett CF, Baker BF. Cell Metab. 2018;27(4):714- 739.

Ensayos clínicos actuales con mecanismos“RNA”

Table 2 Current clinical trials involving RNA delivery *(Continued)*

IONIS-HTT Rx	ASO	Huntingtin	Naked (modified)	Intrathecal injection	Huntington's disease
IONIS ANGPTL3-LRx	ASO	ANGPTL3	Conjugate (GalNAc)	Subcutaneous injection	Elevated triglycerides/familial hypercholesterolemia
AZD9150	ASO	STAT3	Naked (modified)	Intravenous infusion	Solid cancer
QR-010	ASO	CFTR (causes base insertion)	Naked (modified)	Nebulization (inhaled)	Cystic fibrosis
SB012	ASO	GATA-3	Naked (modified)	Enema	Ulcerative colitis
AEG35156	ASO	XIAP	Naked (modified)	Intravenous infusion	Solid cancer
DS-5141b	ASO	Dystrophin (exon skipping)	Naked (modified)	Subcutaneous injection	Duchenne muscular dystrophy
AKCEA-APO(a)-LRx	ASO	ApoA	Conjugate (GalNAc)	Subcutaneous injection	Hyperlipoproteinemia(a)
Apatorsen (OGX-427)	ASO	Hsp27	Naked (modified)	Intravenous infusion	Solid cancer
IONIS-HBV Rx	ASO	HBV surface antigen	Naked (modified)	Subcutaneous injection	Hepatitis B infection
IONIS-GCGR Rx	ASO	GCGR	Naked (modified)	Subcutaneous injection	Type 2 diabetes
ASM8	ASO	CCR3, β-chain of IL-3, IL-5, and GM-CSF	Naked (modified)	Nebulization (inhaled)	Allergen-induced asthma
SB010	ASO	GATA-3	Naked (modified)	Nebulization (inhaled)	Asthma
SB011	ASO	GATA-3	Naked (modified)	Topical	Atopic dermatitis
G4460	ASO	C-myb	Naked (modified)	Intravenous infusion	Liquid cancer
Prexigebersen (BP1001)	ASO	Grb2	Lipid nanoparticle	Intravenous infusion	Myeloid leukemia
IONIS-FXI Rx	ASO	Factor XI	Naked (modified)	Subcutaneous injection	Clotting disorders
Aganirsen (GS-101)	ASO	IRS-1	Naked (modified)	Eye drops	Neovascular glaucoma
Eteplirsen (AVI-4658)	ASO	Dystrophin (exon skipping)	Naked (modified)	Intramuscular injection	Duchenne muscular dystrophy
Alicaforsen	ASO	ICAM-1	Naked (modified)	Enema	Pouchitis
Volanesorsen	ASO	ApoCII	Naked (modified)	Subcutaneous injection	Familial chylomicronemia syndrome Familial partial lipodystrophy
IONIS-TTR Rx	ASO	TTR	Naked (modified)	Subcutaneous injection	Familial amyloid polyneuropathy
Custirsen (OGX-011)	ASO	Clusterin	Naked (modified)	Intravenous infusion	Prostate cancer Non small cell lung cancer
Lipo-MERIT	mRNA	Tumor-associated antigens	mRNA–Lipoplex	Intravenous infusion	Melanoma
IVAC mutanome/warehouse	mRNA	Patient-specific tumor antigens	Naked mRNA	Intra-nodal	Triple negative breast cancer Melanoma
TNBC-MERIT	mRNA	Tumor-associated antigens	mRNA–Lipoplex	Intravenous infusion	Triple negative breast cancer
CV7201	mRNA	Rabies virus glycoprotein	Naked mRNA	Intramuscular injection	Rabies
CV8102	mRNA	RNA-based adjuvant	Naked mRNA	Intramuscular injection	RSV, HIV, rabies
mRNA-1851	mRNA	Hemagglutinin 7 (H7) protein	ND	Intramuscular injection	Influenza A

Medicamentos aprobados FDA/EMA

As of May 2019, five ASOs have received regulatory approval in the US and/or Europe

- Fomivirsen (VITRAVENE®, Ionis Pharmaceuticals) is a 1st generation ASO approved by the US FDA in 1998 and by the European Commission in 1999 for cytomegalovirus retinitis; it was administered acutely and non-systemically
- Mipomersen sodium (KYNAMRO®, Kastle Therapeutics) is a 2nd generation ASO approved by the US FDA in 2013 for the treatment of homozygous familial hypercholesterolemia; it is the first ASO administered systemically
- Nusinersen (SPINRAZA®, Biogen Inc.) is an ASO approved by the US FDA in 2016 and by the European Commission in 2017 for spinal muscular atrophy (SMA); it is administered intrathecally into the cerebrospinal fluid
- Inotersen (TEGSEDI™, Akcea Therapeutics) is a transthyretin-directed 2nd generation ASO approved by the European Commission in July 2018 and by the US FDA in October 2018. In the EU, it is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary ATTR amyloidosis
- Volanesorsen (WAYLIVRA™, Akcea Therapeutics) is an ASO approved by the European Commission in May 2019. It is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate

Un ejemplo : amiloidosis familiar transtiretina (hATTR) y *antisense* anti- TTR (inotersén, ASO)

Hereditary ATTR (hATTR) Amyloidosis

DESCRIPTION

Orphan multi-system disease caused by mutant transthyretin (TTR) amyloid deposits in nerves, heart, GI tract, and other tissues

Significant morbidity and fatal within **2-15** years from symptom onset

PATIENT POPULATION*

~50,000 worldwide

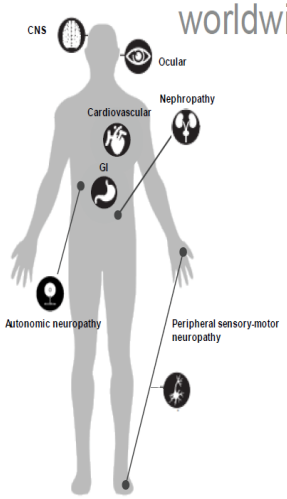


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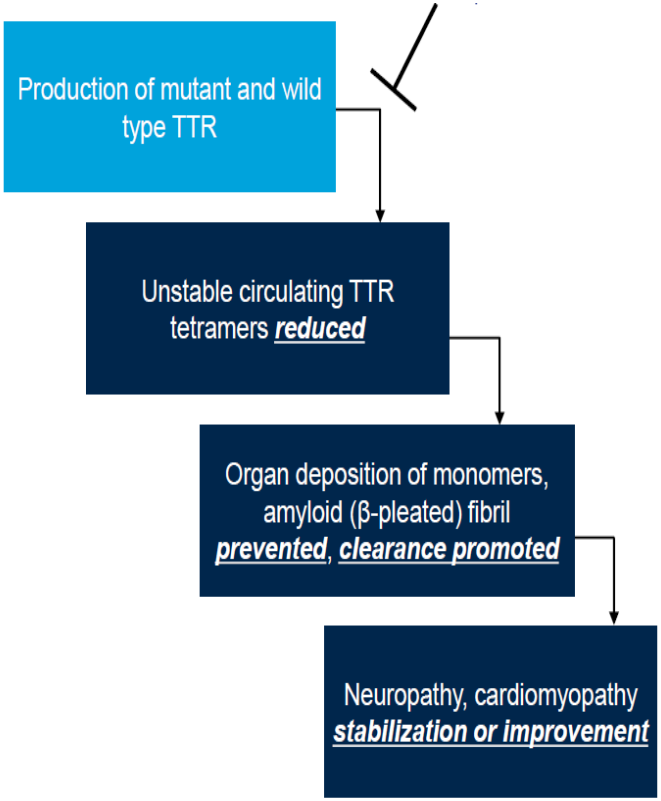
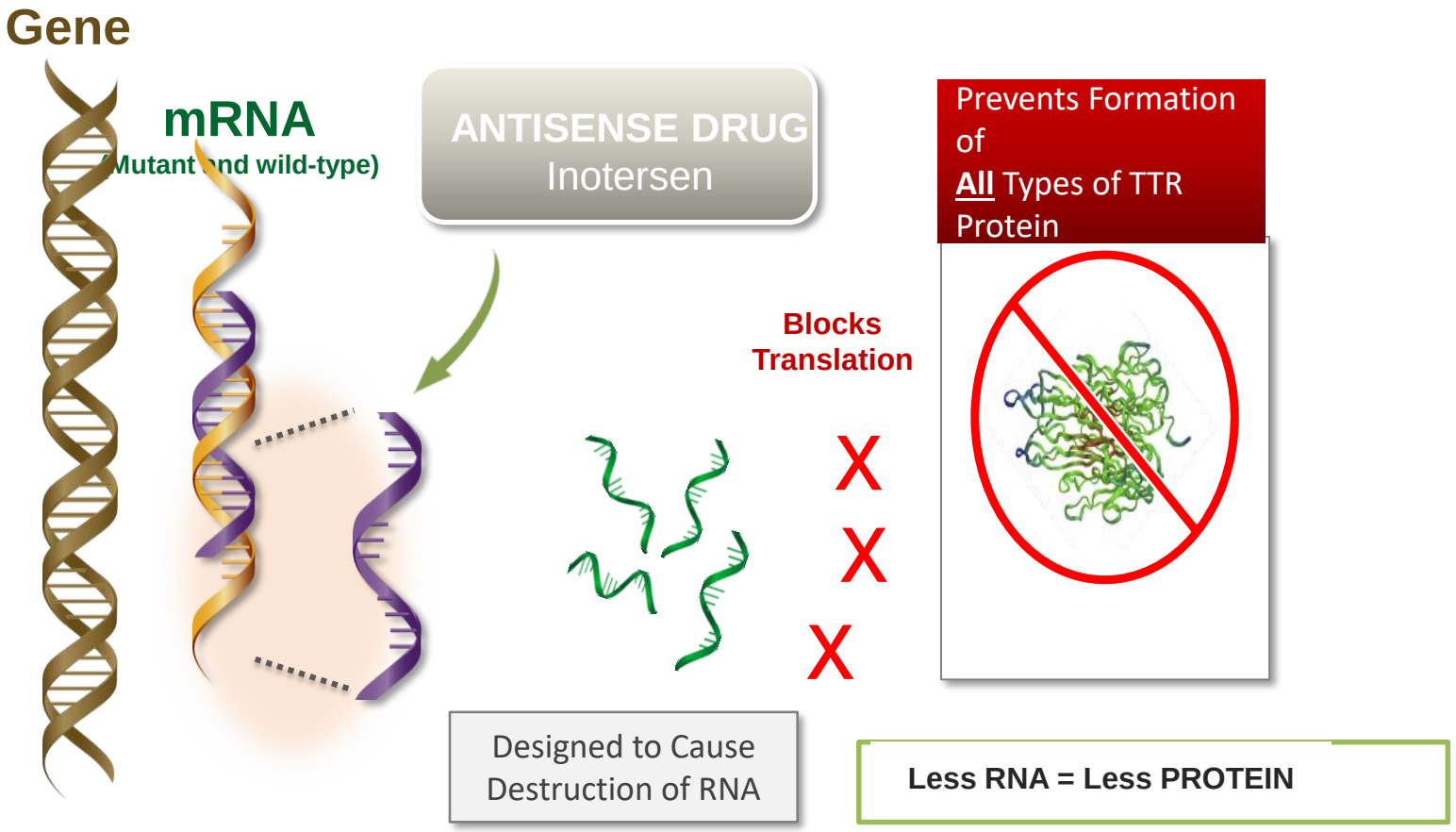
Image based on Conceicao *et al., J Peripher Nerv Syst*, 2016;21:5–9
*Ando *et al., Orphanet J Rare Dis*, 2013; Ruberg *et al., Circulation*, 2012

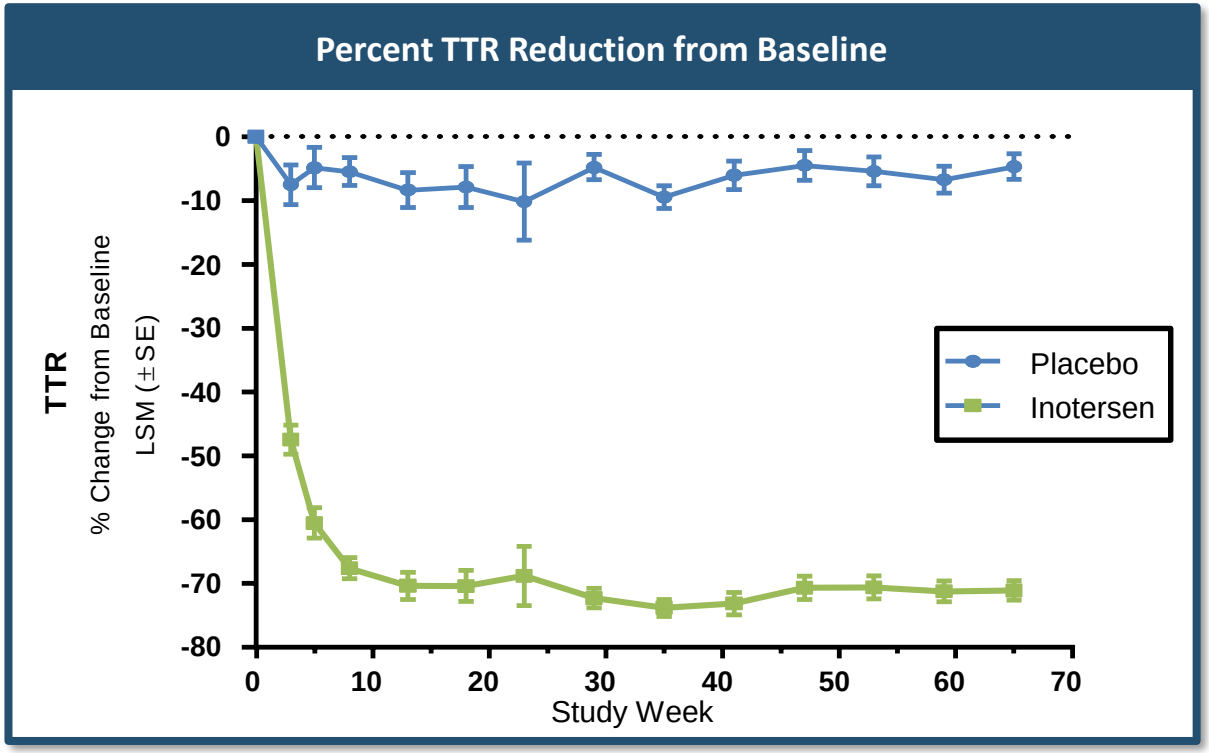
Posibles estrategias terapéuticas



El principio activo, inotersén, es un oligonucleótido antisentido que **inhibe la producción de TTR humana**. La unión selectiva del inotersén al ARN mensajero (ARNm) de la TTR provoca la degradación del ARNm de la TTR de tipo tanto mutante como salvaje.



Inotersen (ASO) Produced Robust and Sustained Lowering of TTR (protein) Levels in hATTR Patients



TTR Reduction (nadir) : -79% (median), -74% (mean)

Benson et al, NEJM 2018

Muchas gracias

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