# Enkele nieuwe geneesmiddelen 2018

Prof. Koen Augustyns

Farmant, Antwerpen, 17/12/2018

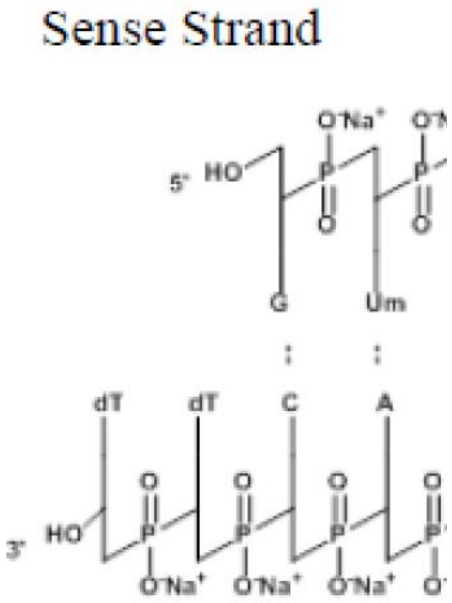
# Content

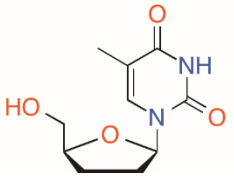
- **Tegsedi®** (Inotersen) and **Onpattro®** (Patisiran) Ionis and Alnylam
  - hereditary transthyretin amyloidosis — EMA 05/07/2018 and 26/08/2018
- **Spinraza®** (Nusinersen) — Biogen
  - Spinal muscular atrophy (SMA) — EMA 30/05/2017
- **Aimovig®** (Erenumab) — Novartis
  - Migraine — EMA 26/07/2018
- **Ibrance®** (Palbociclib) — Pfizer
  - Breast cancer — EMA 09/11/2016

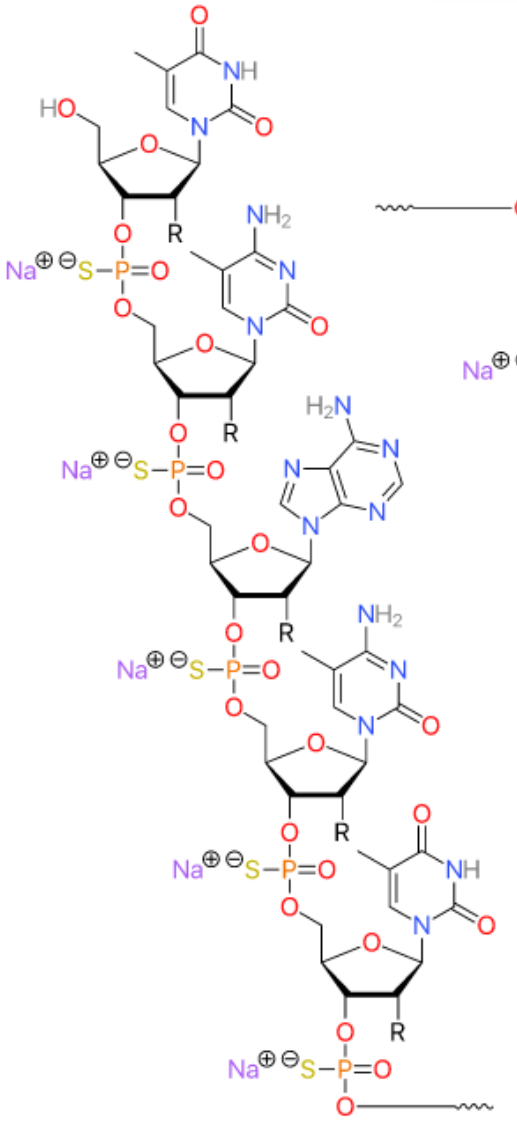
Tegsedi, Onpattro, Spinraza

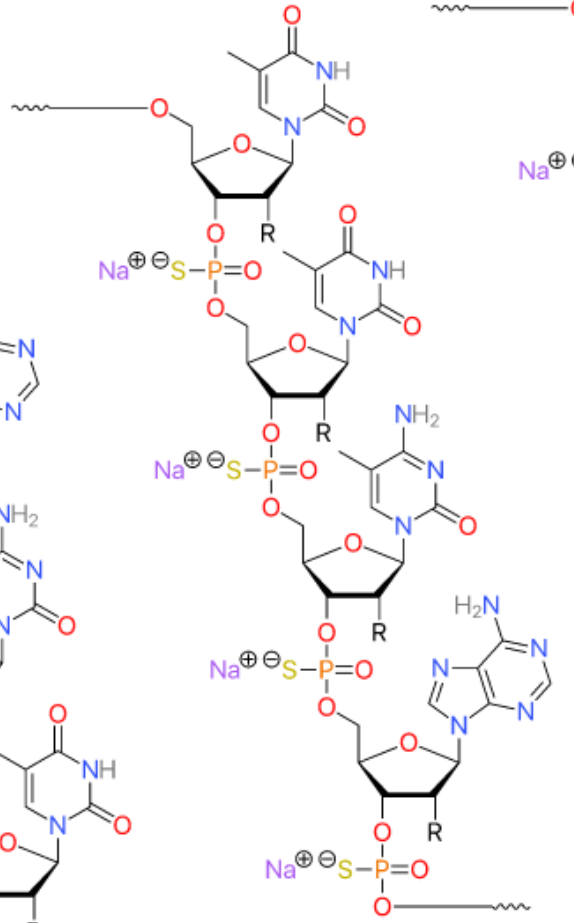
# Introduction

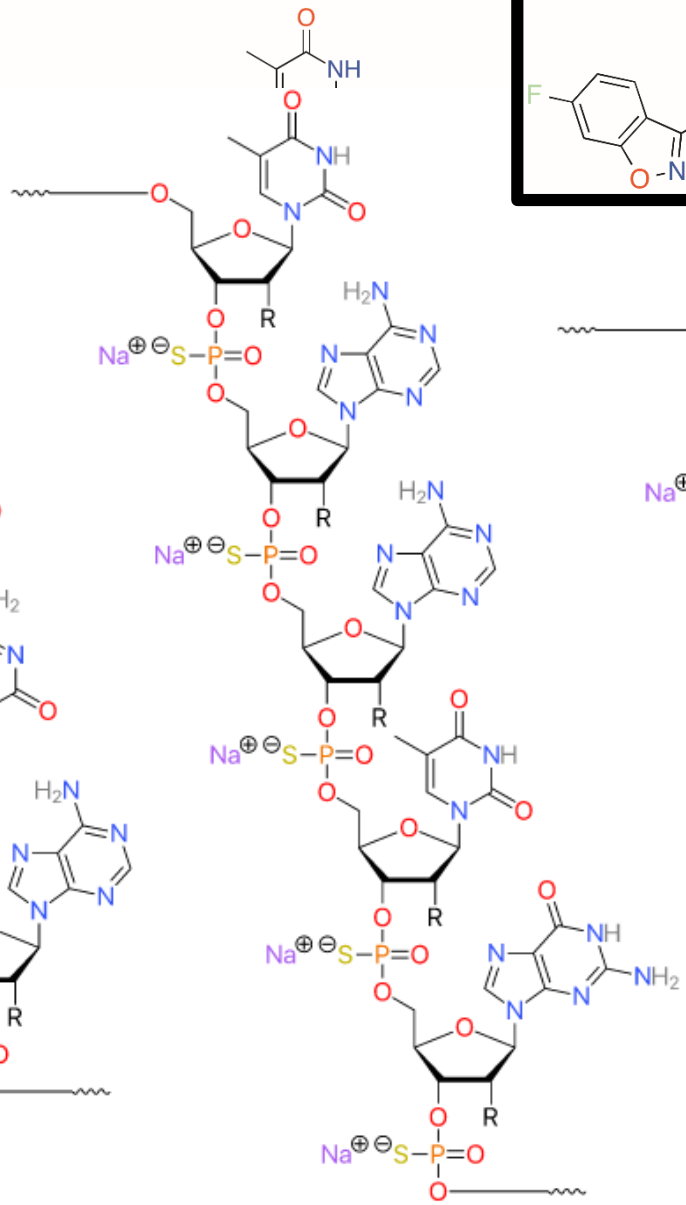
# Oligonucleotides as drugs

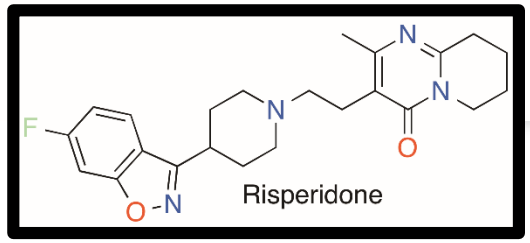


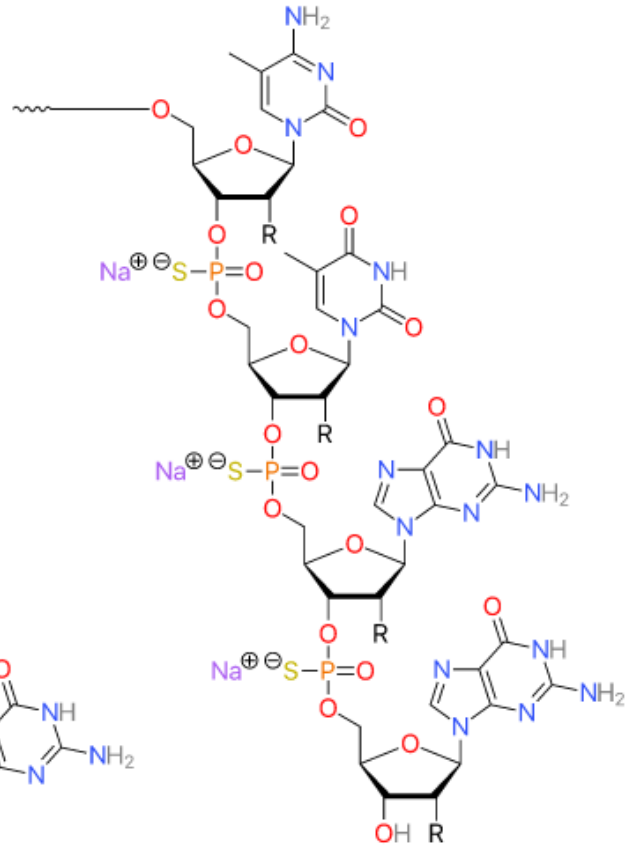



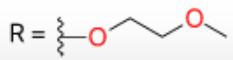






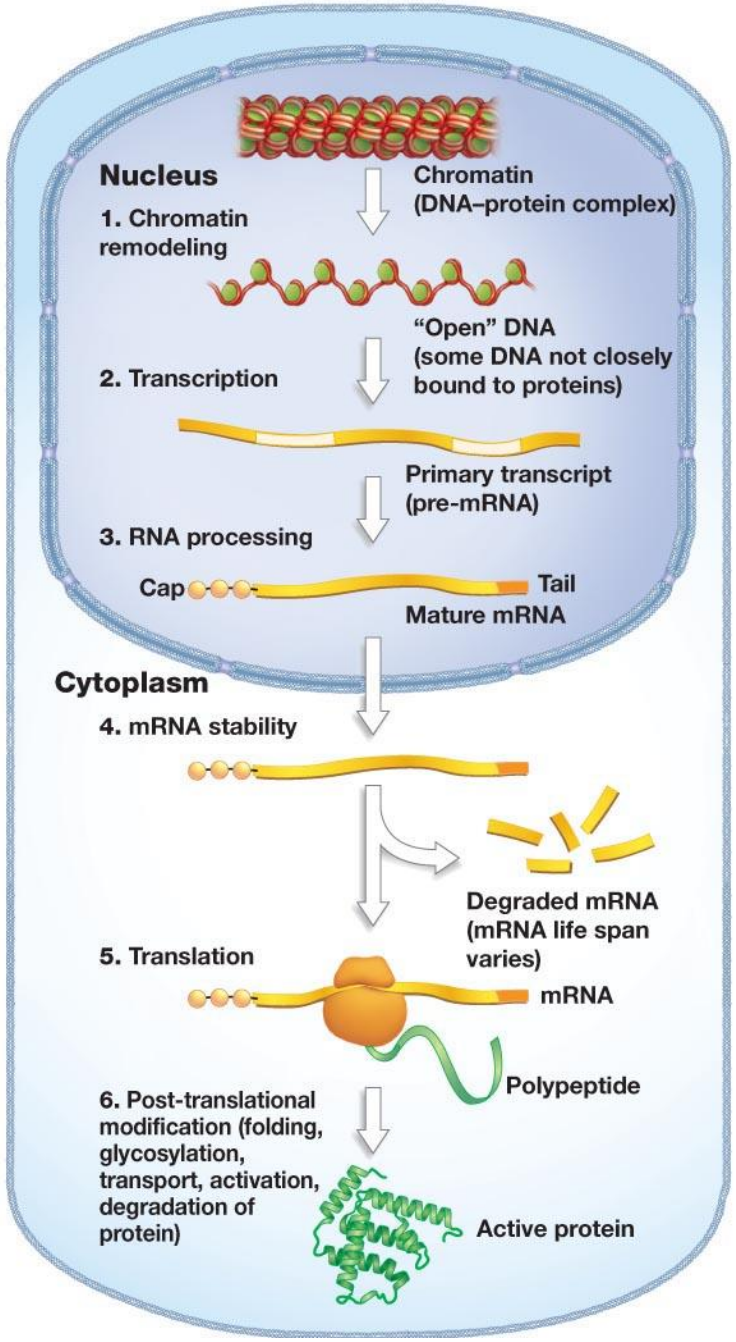


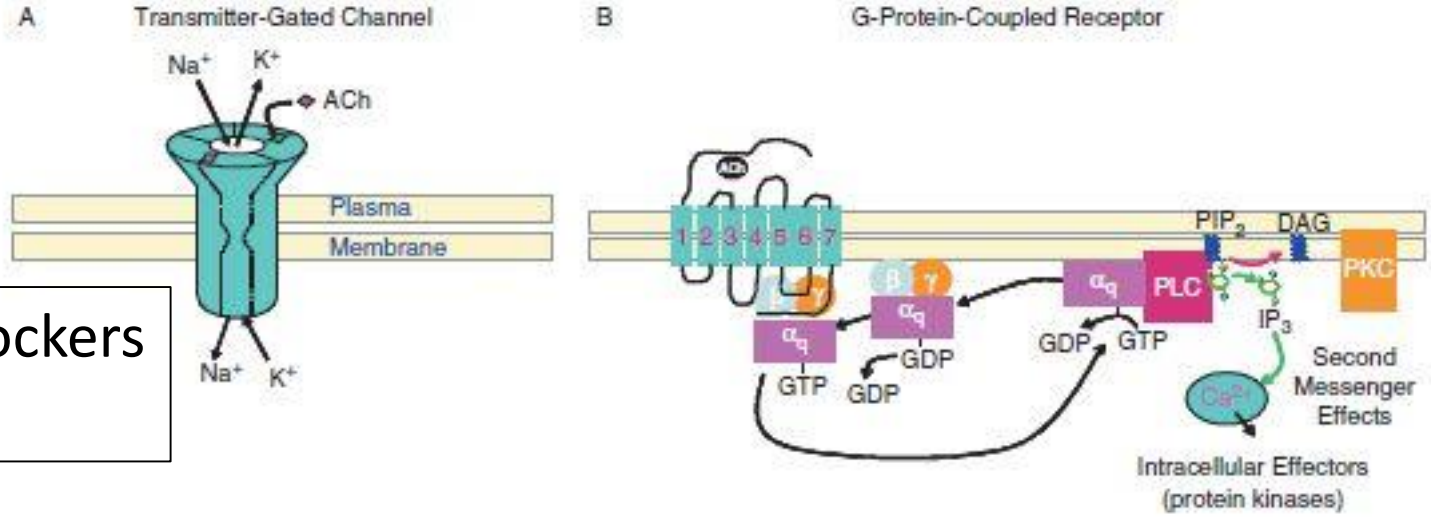


# Interfering with the genetic expression

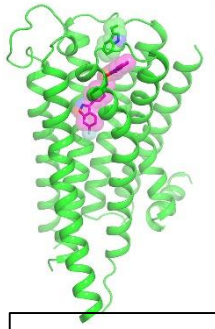
Almost all drugs work at the protein level:
Receptors - Enzymes



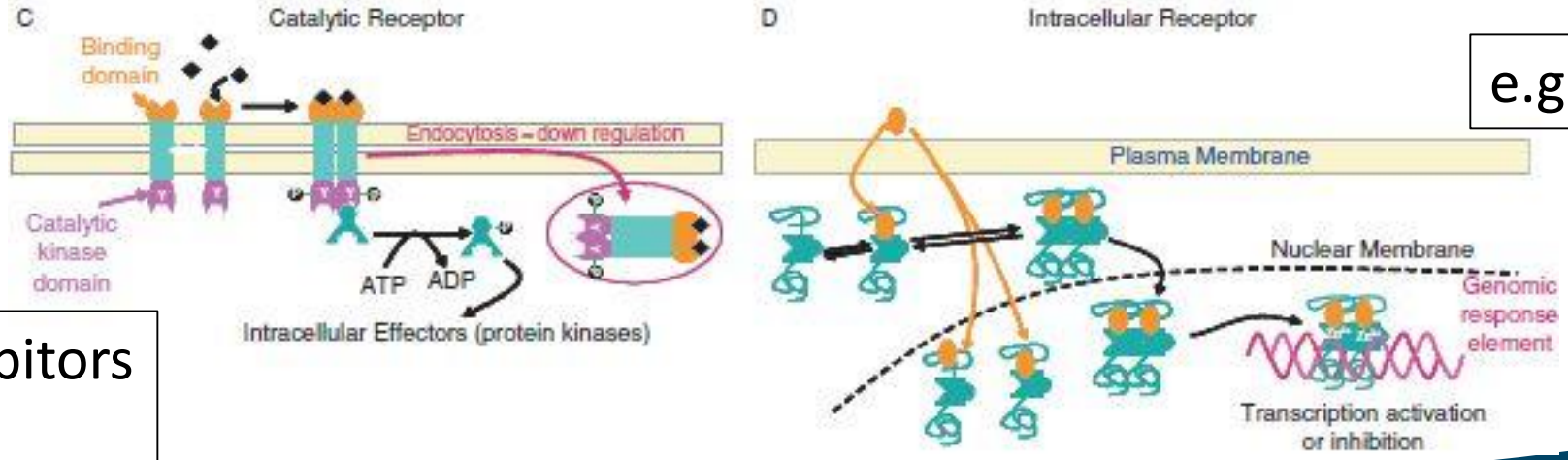
# Interfering with the genetic expression




e.g. Na-channel blockers as antiarrythmics



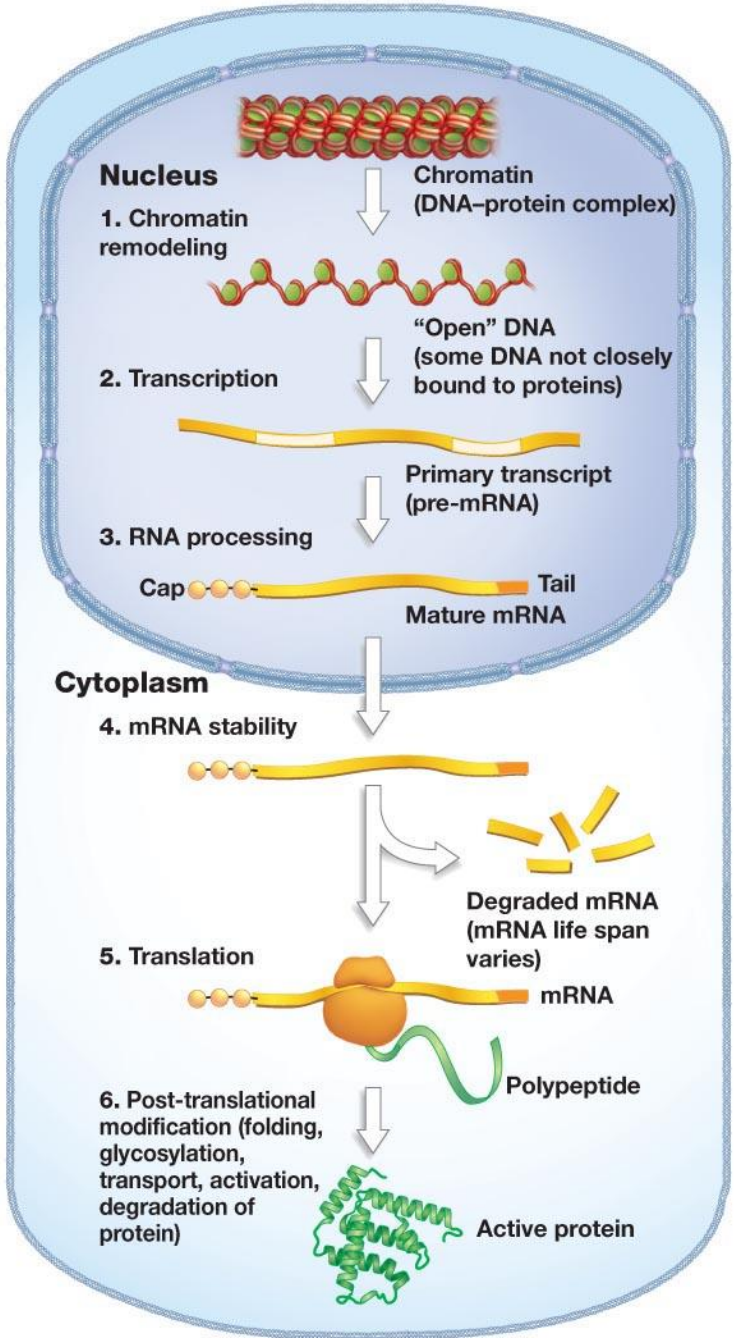
e.g. D2-antagonists as antipsychotics




e.g. Glucocorticoids

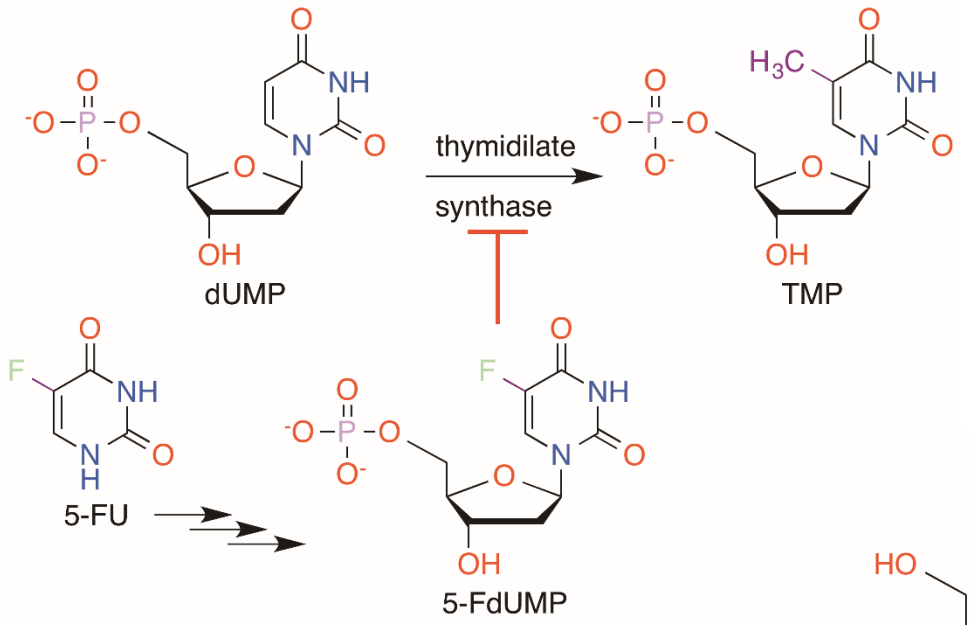
e.g. Kinase inhibitors in oncology

What about drugs acting at DNA level?

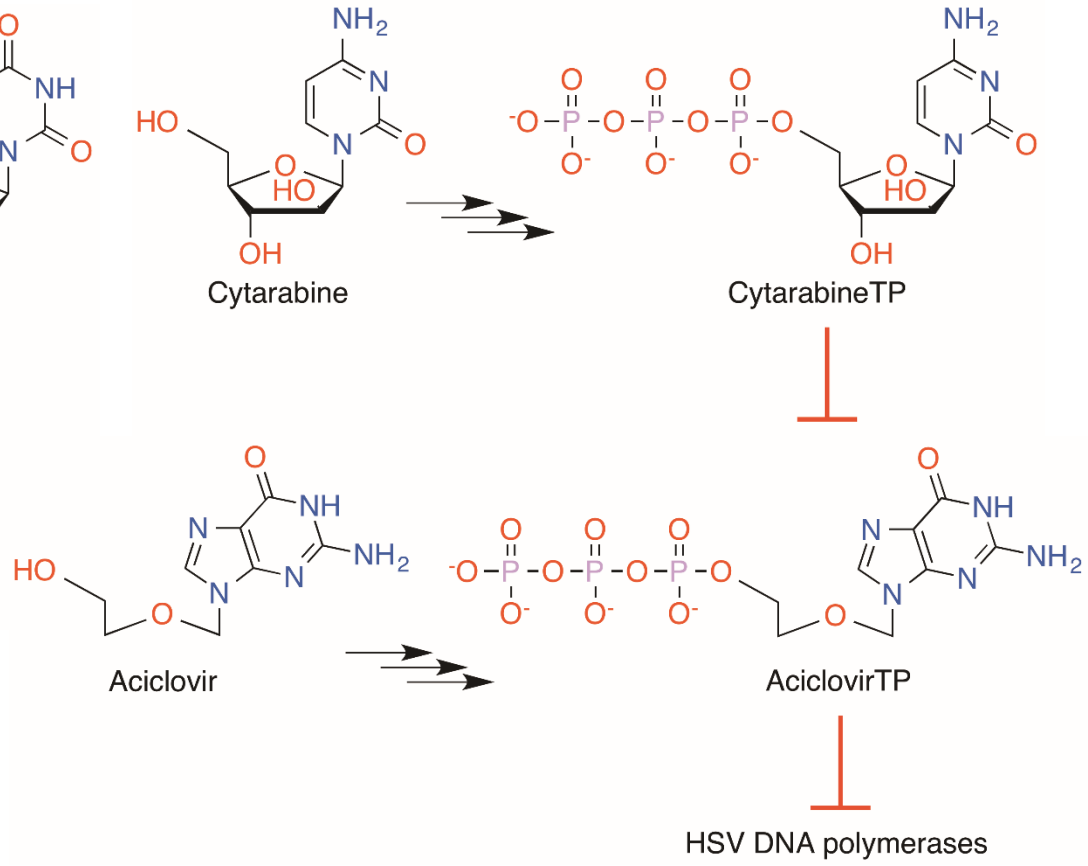


# Drugs acting at DNA level

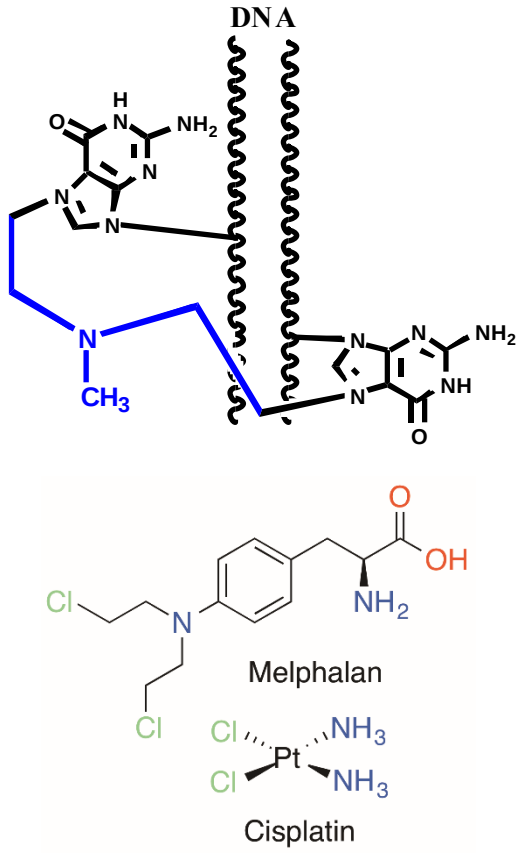
## Synthesis of building blocks




## Synthesis of DNA



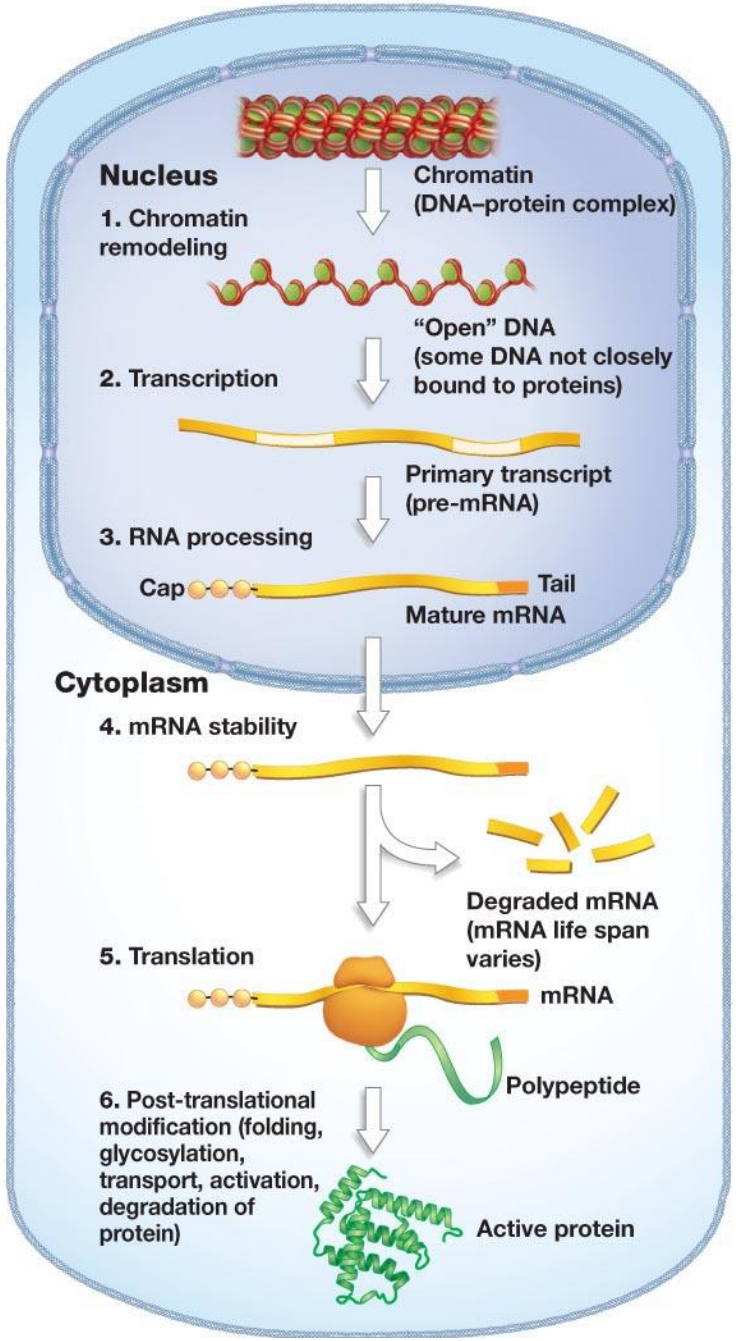

## DNA alkylation



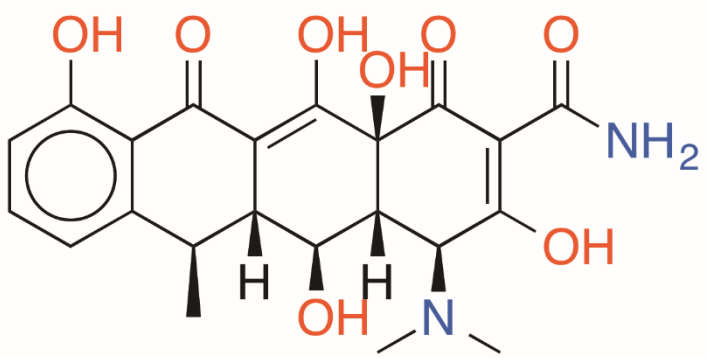
# Drugs acting at DNA level

- Cytostatics in Oncology
  - Aselective interaction with DNA
  - Highly toxic
- Antiviral drugs
- Future?
  - Selective gene editing
  - CRISPR/Cas

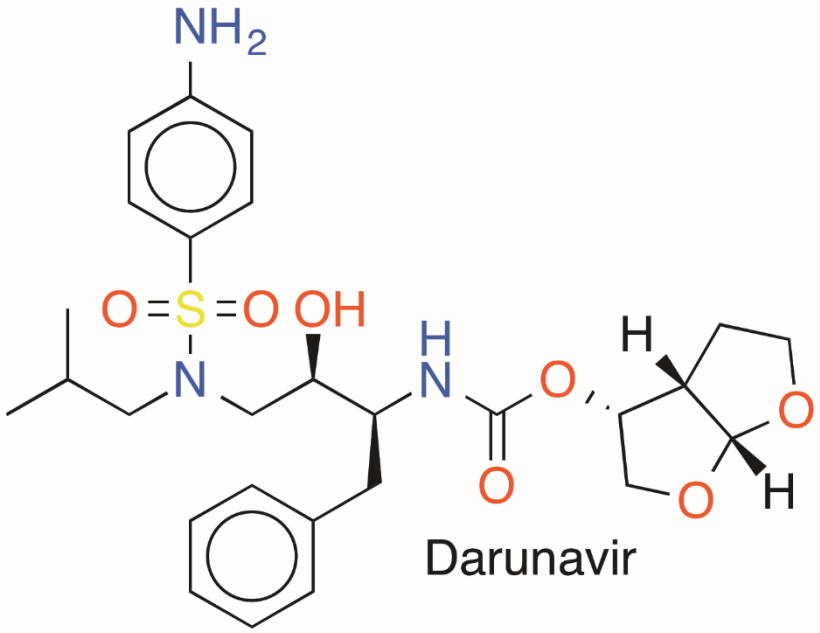
What about drugs acting at the level of translation?



# Drugs acting at the level of translation




Doxycycline

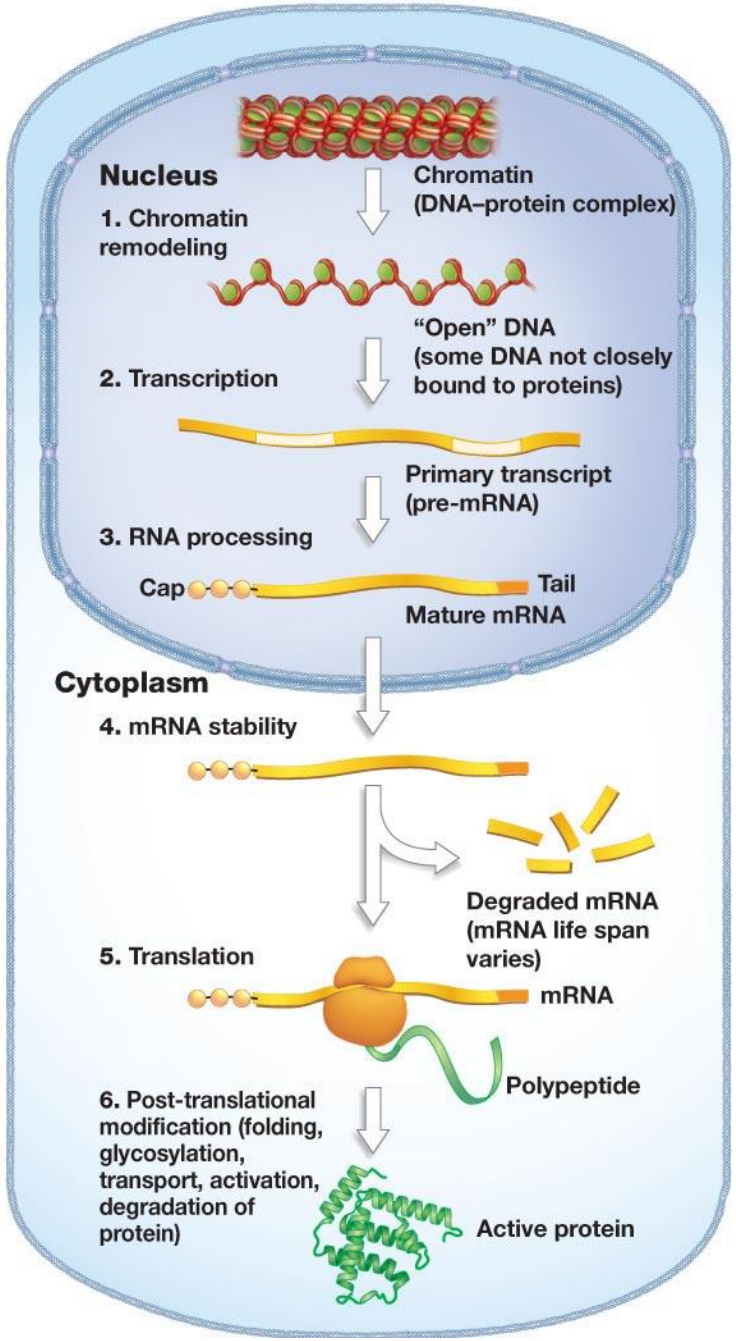



Darunavir

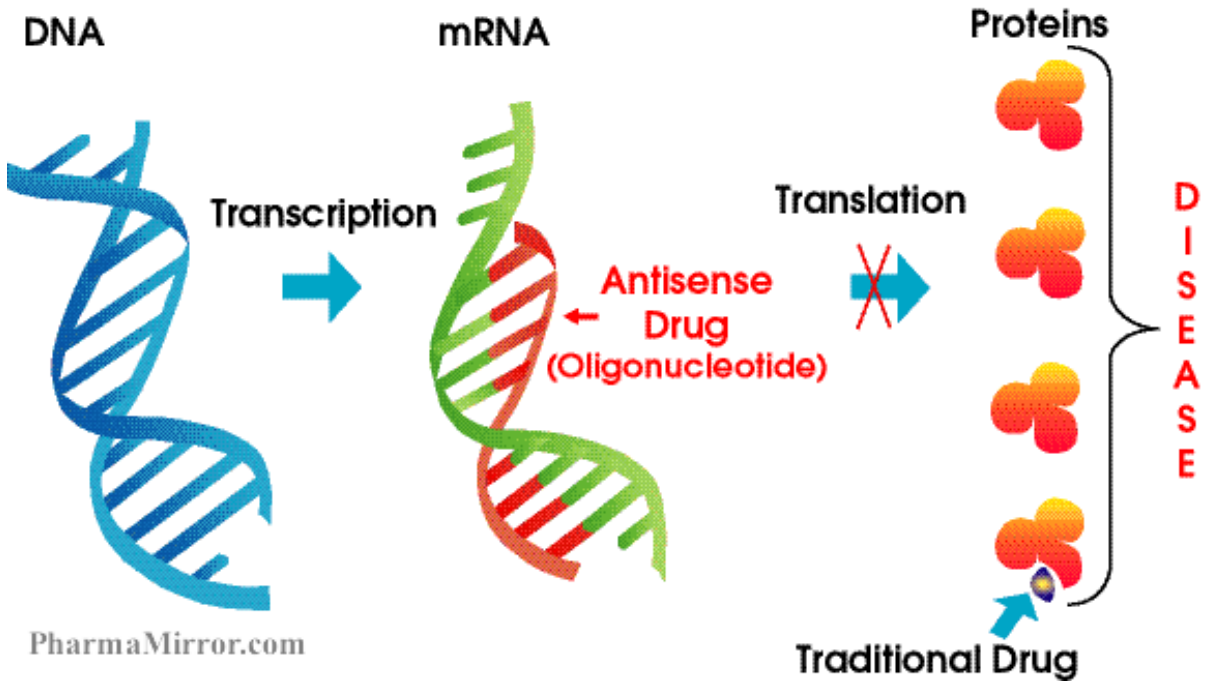
Inhibitor of bacterial protein biosynthesis by binding to bacterial ribosome

Inhibitor of HIV protease

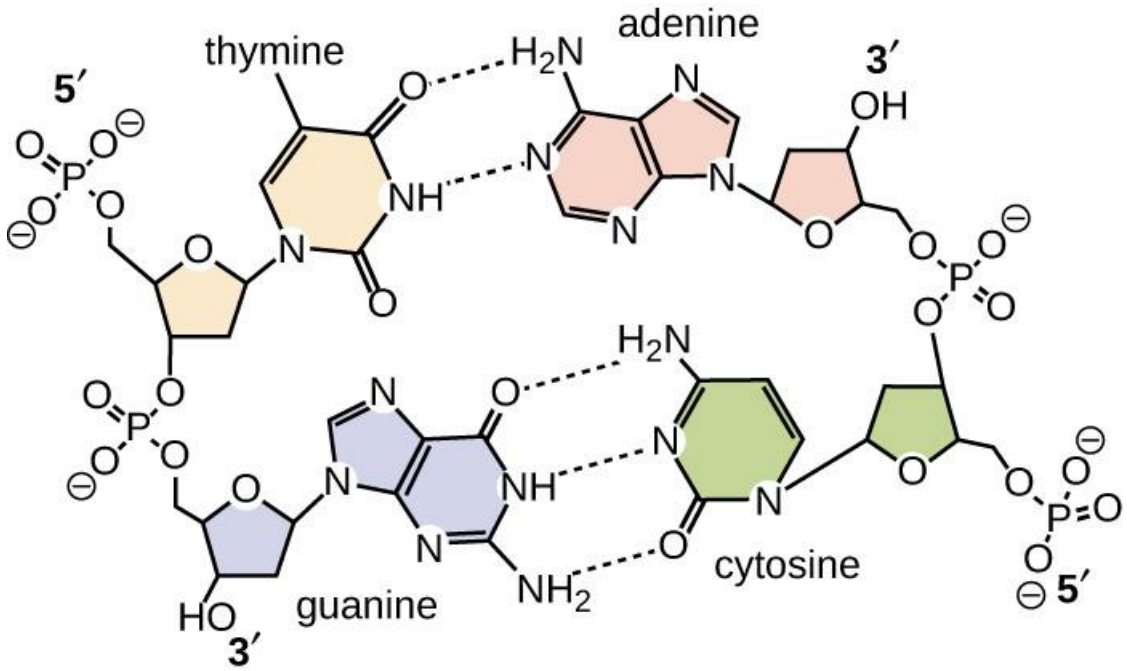
What about drugs acting at pre-mRNA or mRNA level?



# Drugs acting at pre-mRNA or mRNA level

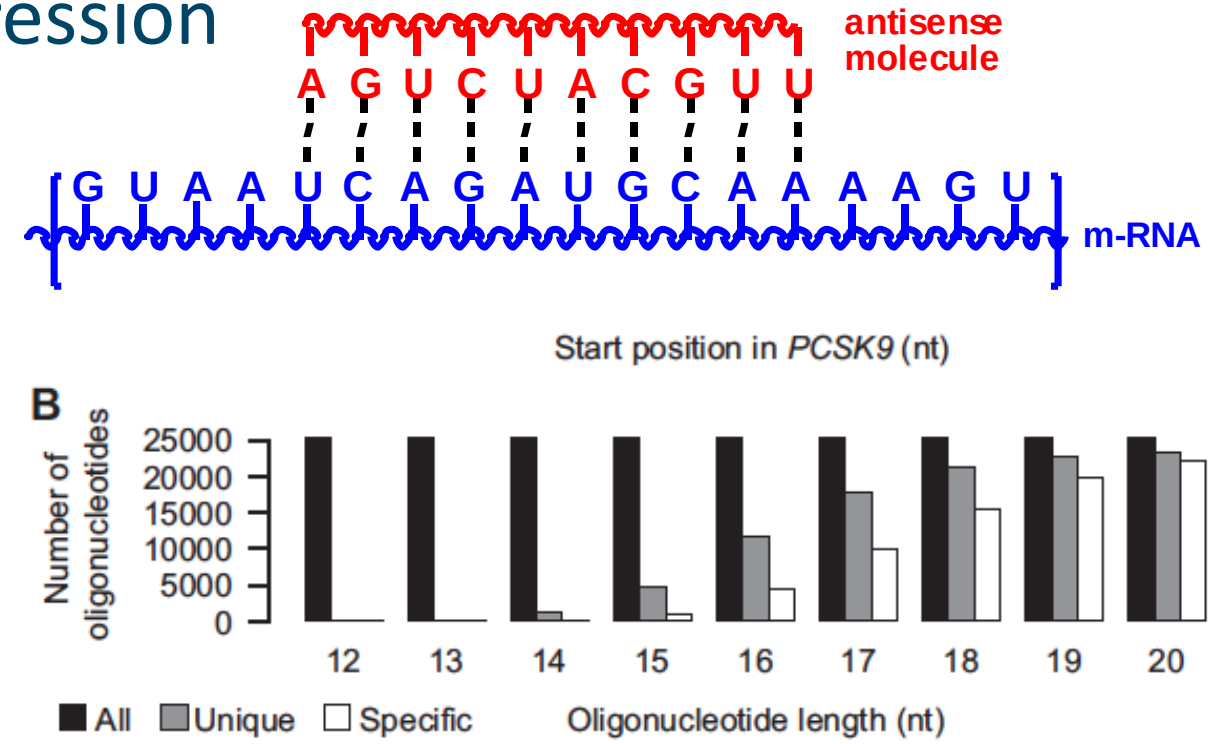



Highly specific interaction between RNA and oligonucleotide drug via Watson-Crick base pairs



# **Advantages** of oligonucleotide drugs

- Targets earlier in genetic expression
  - More powerful
- Design looks easy
- Unique sequence with 20 nucleotides or above
- Highly specific
  - Less side effects expected compared to small molecules
- Well suited for genetic diseases

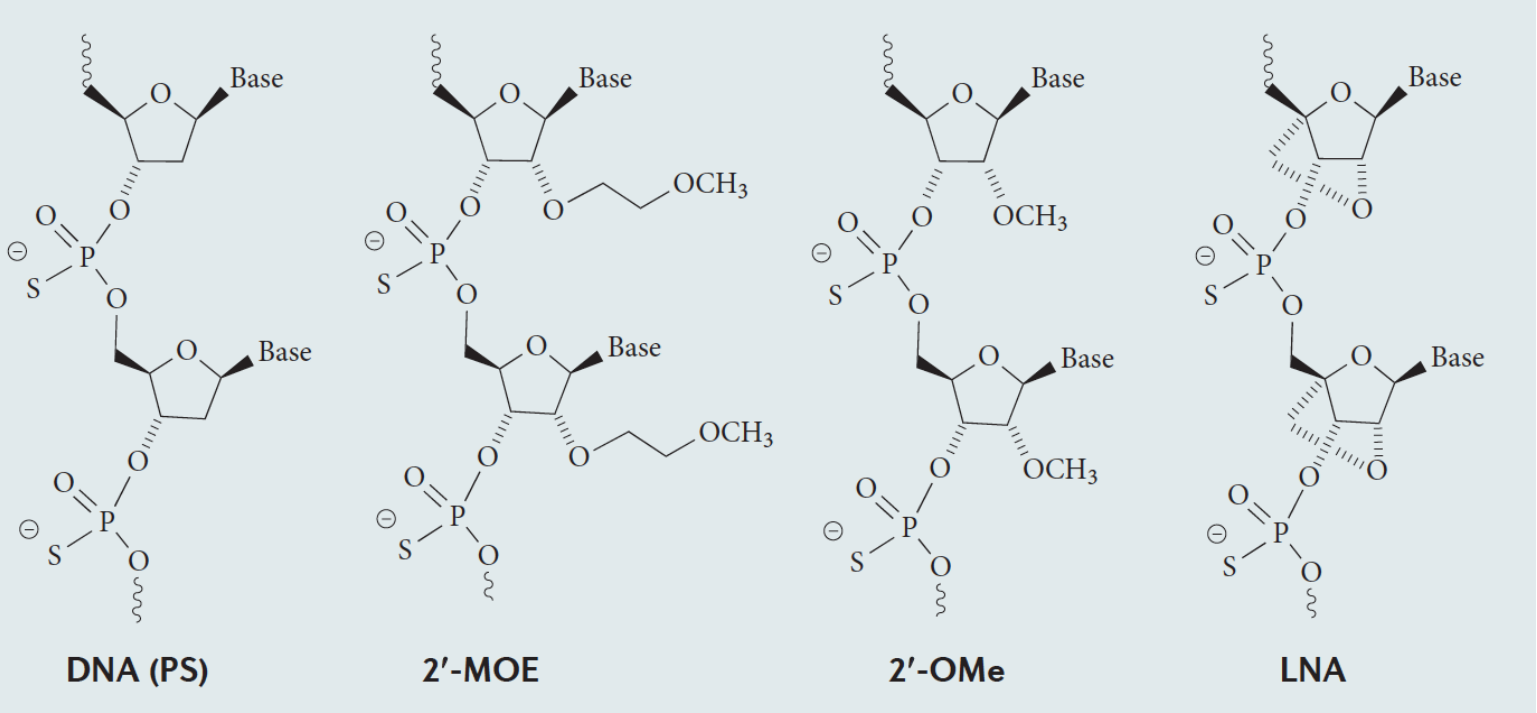



*Hagedorn, P et al. Nucleic Acids Res. 2017, 45, 2262*

# **Disadvantages** of oligonucleotide drugs

- Large molecules with multiple negative charges
- Poor membrane permeability
- Unstable in biological media
- Short half-life, poor pharmacokinetics
- Chemical modifications are required
- Only exposed regions of RNA can be targeted

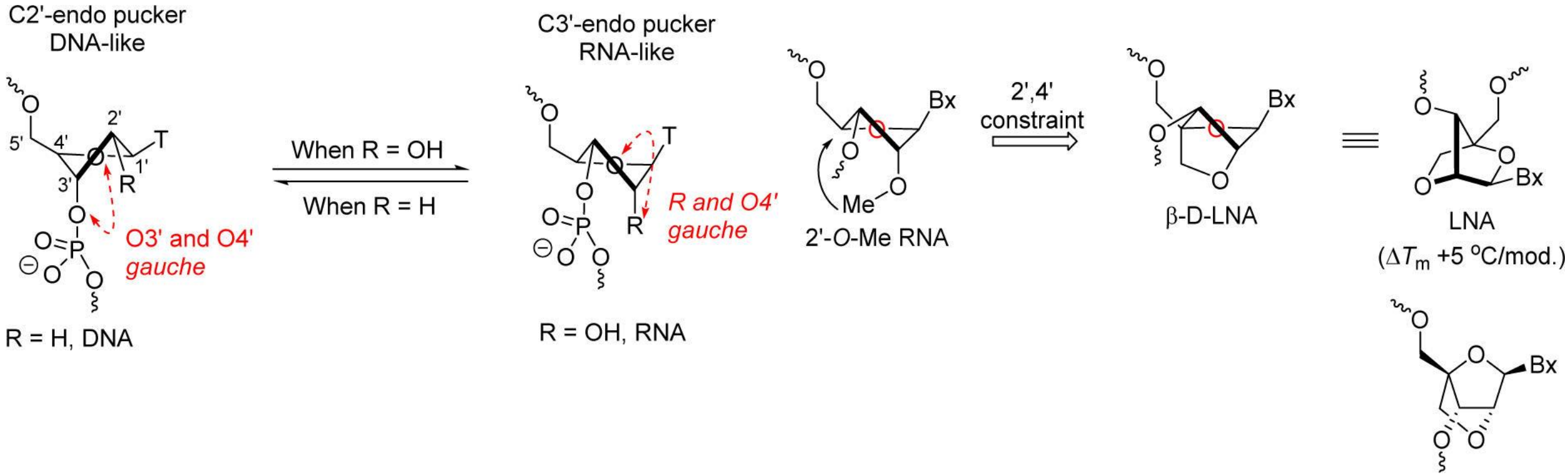
# The **medicinal chemistry** of oligonucleotide drugs




*Kole, R. et al.*
*Nature Rev. Drug Discov.*
*2012, 11, 125*

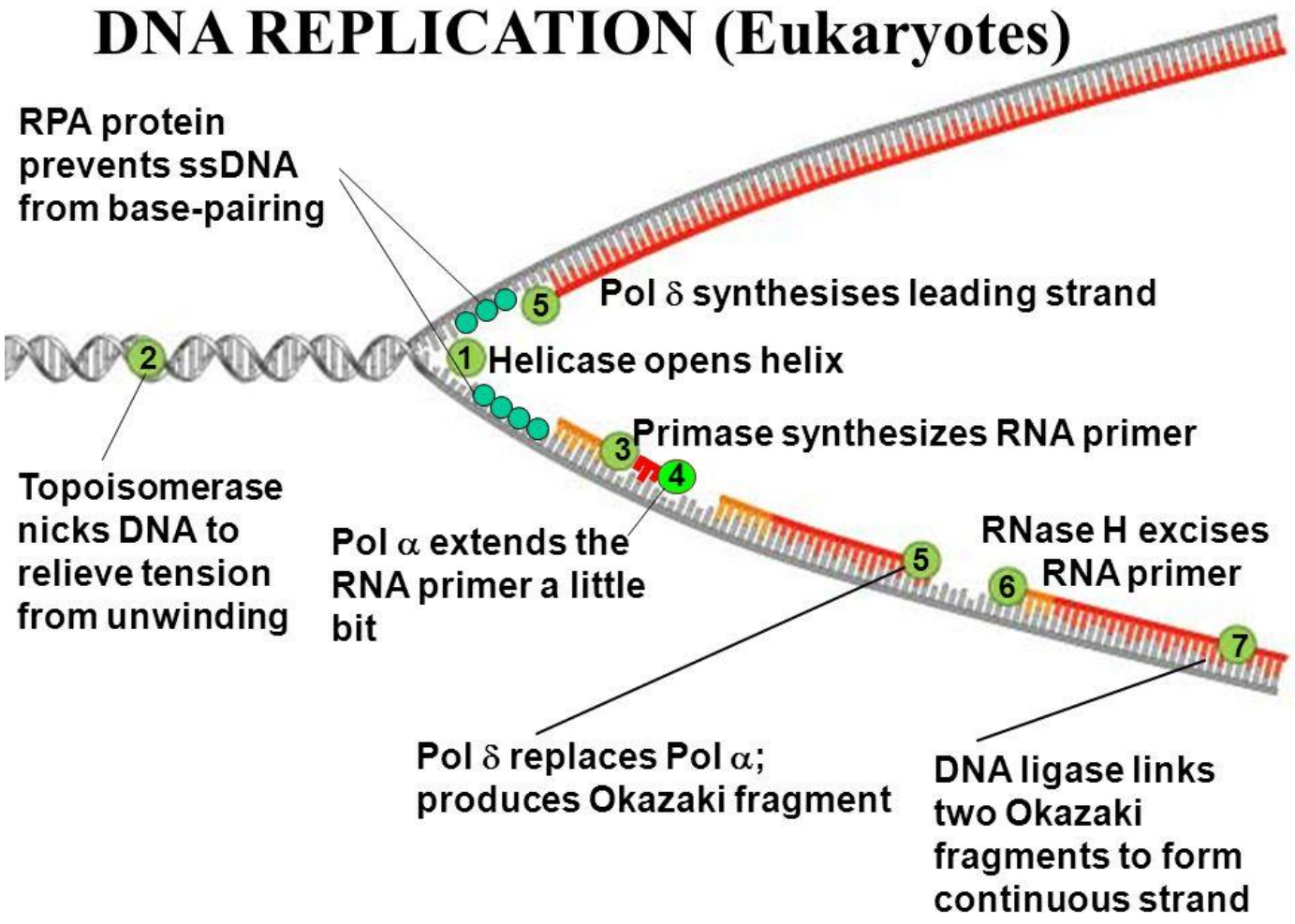
- Phosphorothioates increase stability
- 2’ O-modification furher increase stability and affinity for RNA
  - Duplex stability: RNA-RNA > RNA-DNA > DNA-DNA
  - LNA: conformational restriction to RNA conformation

# The **medicinal chemistry** of oligonucleotide drugs




*Wan, W. et al. J. Med. Chem. 2016, 59, 9645*

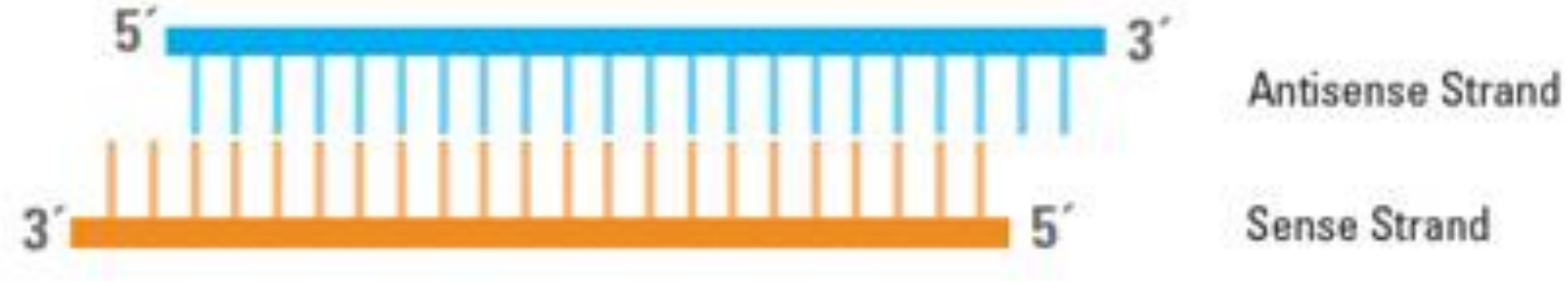
# RNase H



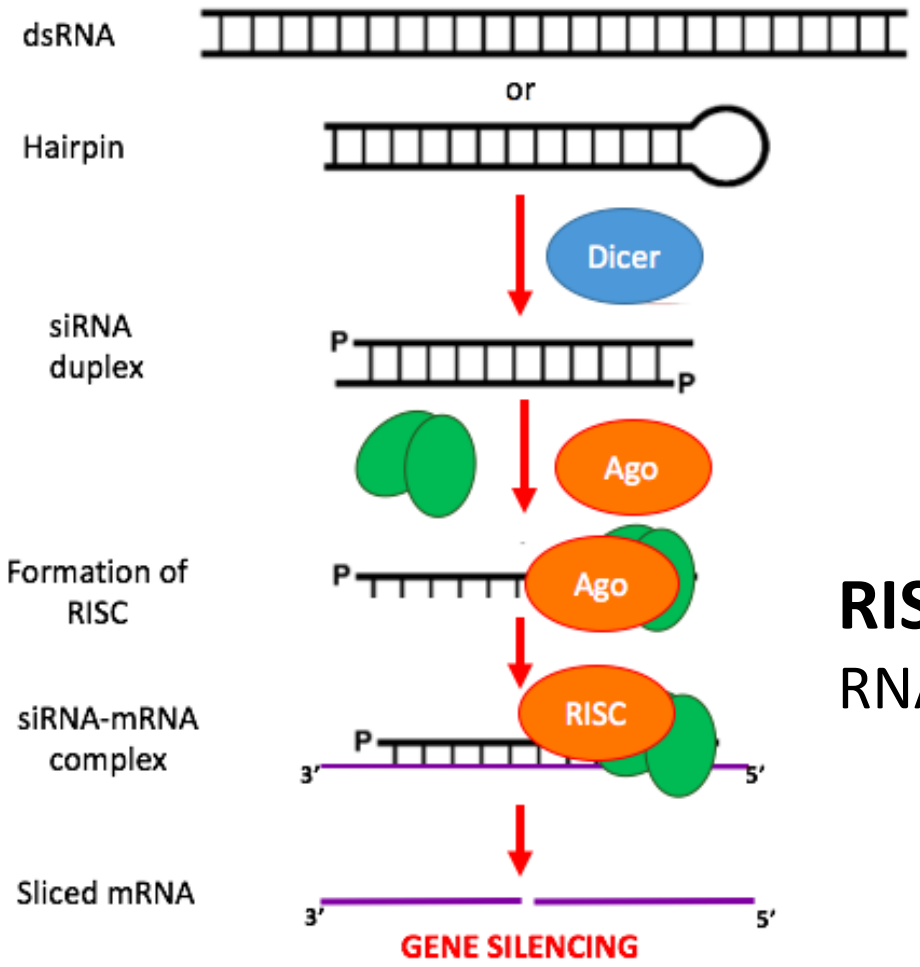

**RNase H degrades RNA** in a RNA-DNA duplex

# Nature developed a similar principle for gene silencing: siRNA

- siRNA = Small Interfering RNA
- Structure
  - Short double-stranded RNA
  - 20-24 basepairs long
  - Phosphorylated 5’ ends and hydroxylated 3’ ends with two overhanging nucleotides



# Mechanism of siRNA for gene silencing, also called RNA interference (RNAi)

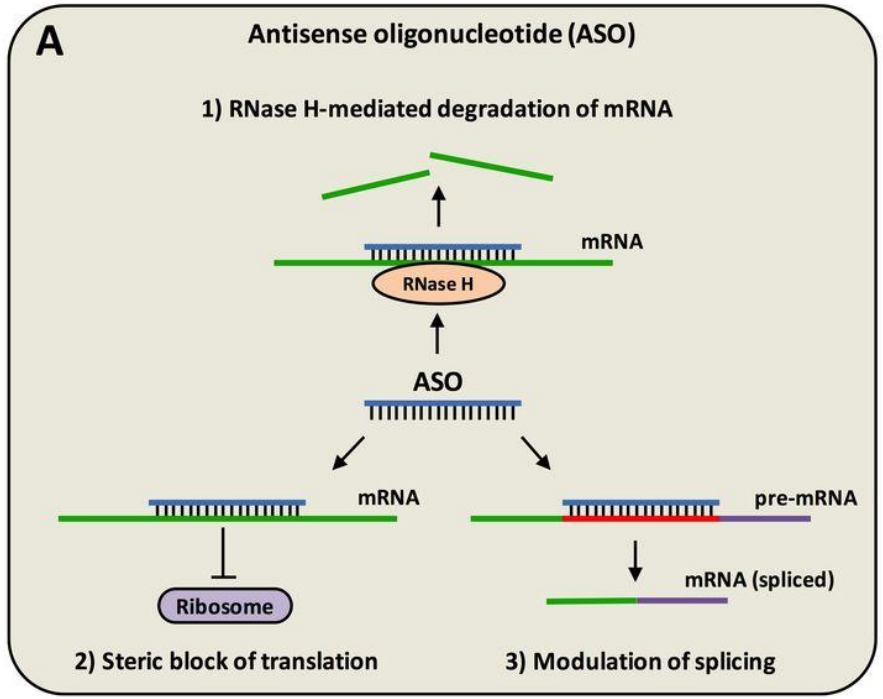


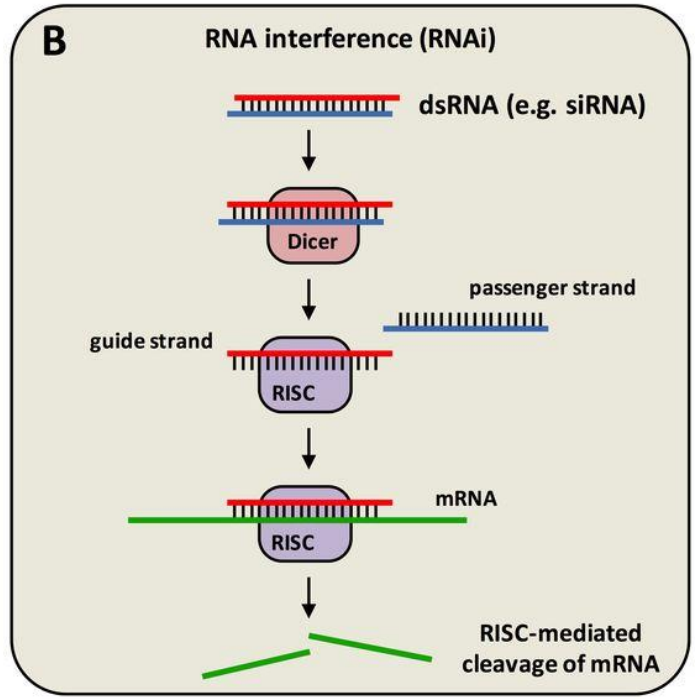

**RISC**

RNA-induced silencing complex

# Mechanism of action of therapeutic oligonucleotides

1. ASO for mRNA degradation via RNase H
2. siRNA for mRNA degradation
3. ASO that does not degrade mRNA
    1. Steric block of translation
    2. Splicing modulation



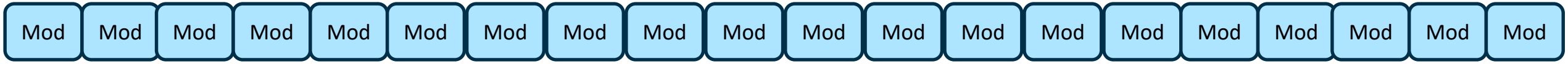
# Design of different therapeutic oligonucleotides

1. RNase H ASO's (contain a central DNA gap = gapmers)


   - All phosphorothioate, Mod = e.g. 2'-O-modified RNA

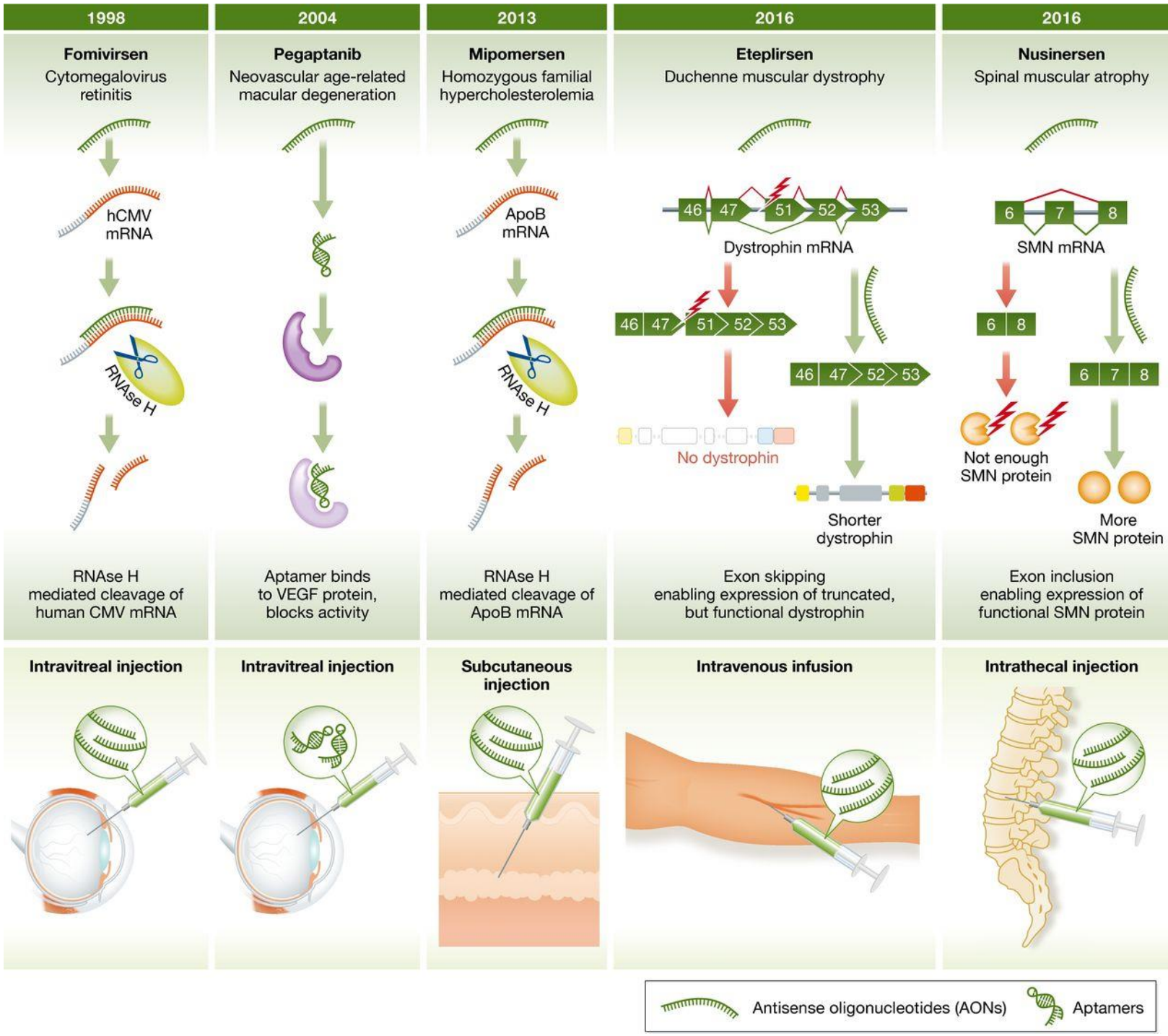
2. siRNA
   - RNA double helix is in itself more stable
   - One or two phosphorothioates or other modifications at 3' and 5' end

3. No mRNA degradation




   - Fully modified with phosphorothiate and e.g. 2'-O-modified RNA

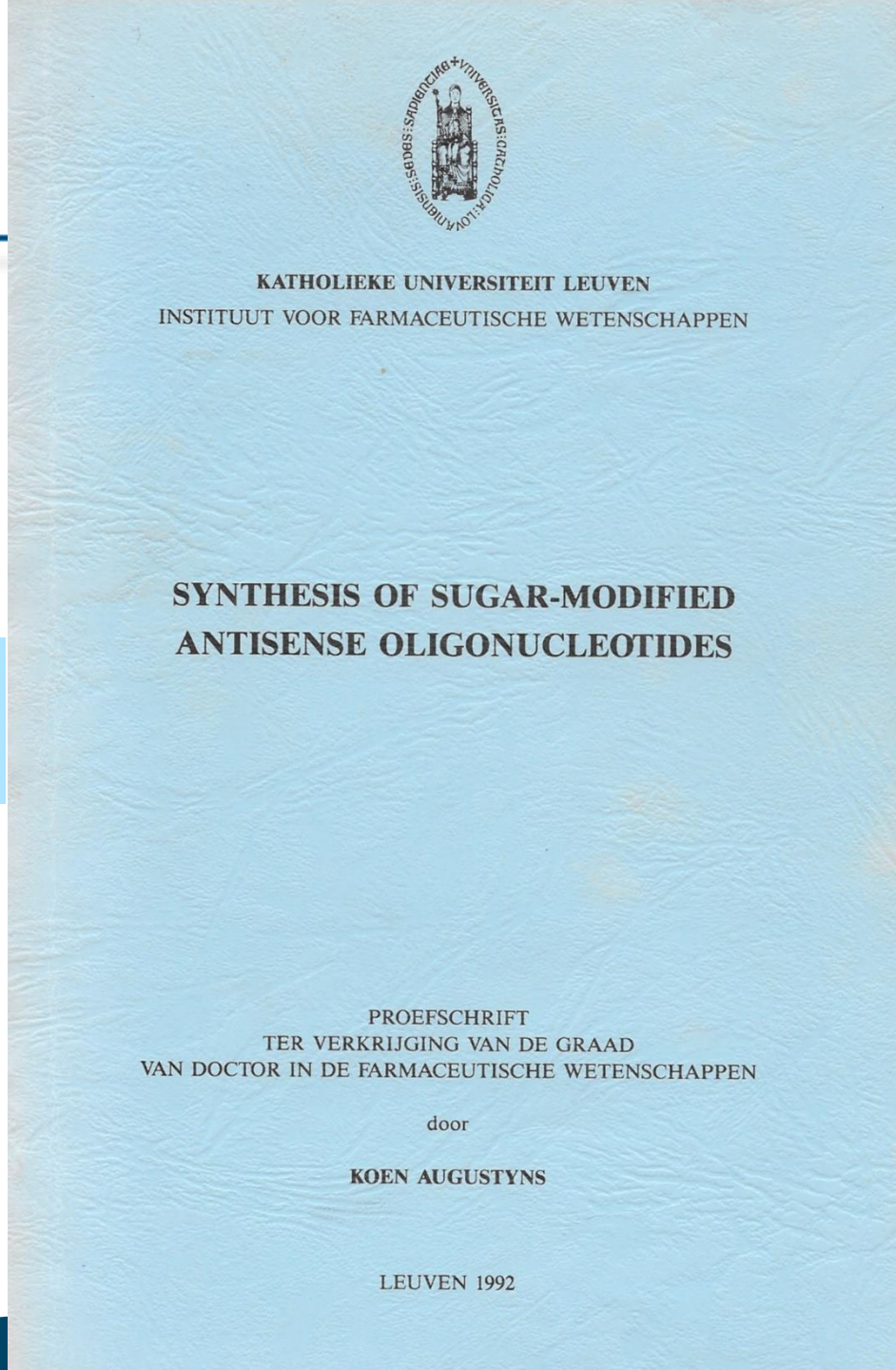
# Delivery is key



# Oligonucleotide drugs: history

- 1978: birth of antisense: a 13-mer DNA could block viral replication
- 1979: RNase H: site-specific cleavage of RNA with DNA
- 1984: automated DNA synthesis
- 1997: LNA synthesis
- 1998: Fomivirsen FDA approved for CMV retinitis
- 1998: discovery of siRNA
- 2001: siRNA oligonucleotides
- 2002: Fomivirsen withdrawn because of better HIV/AIDS drugs
- 2016: Nusinersen FDA approved

Synthesis of many ON analogues


KATHOLIEKE UNIVERSITEIT LEUVEN
INSTITUUT VOOR FARMACEUTISCHE WETENSCHAPPEN

SYNTHESIS OF SUGAR-MODIFIED ANTISENSE OLIGONUCLEOTIDES

PROEFSCHRIFT
TER VERKRIJGING VAN DE GRAAD
VAN DOCTOR IN DE FARMACEUTISCHE WETENSCHAPPEN

door

KOEN AUGUSTYNS

LEUVEN 1992

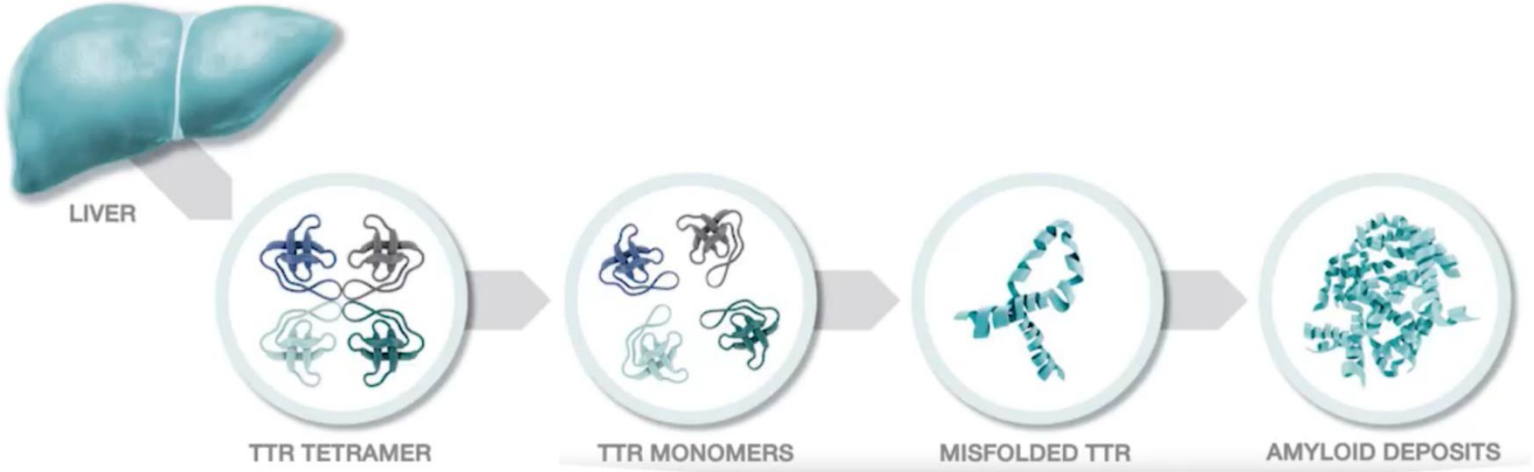
# Content

- **Tegsedi®** (Inotersen) and **Onpattro®** (Patisiran)
  - hereditary transthyretin amyloidosis
- **Spinraza®** (Nusinersen)
  - Spinal muscular atrophy (SMA)
- **Aimovig®** (Erenumab)
  - Migraine
- **Ibrance®** (Palbociclib)
  - Breast cancer

# hereditary transthyretin amyloidosis (hATTR)

**hATTR amyloidosis** is an inherited, rapidly progressive, debilitating, life-threatening disease caused by a mutation in the *TTR* gene, resulting in misfolded TTR proteins accumulating as amyloid deposits in the nerves, heart, and GI tract.[6,7]

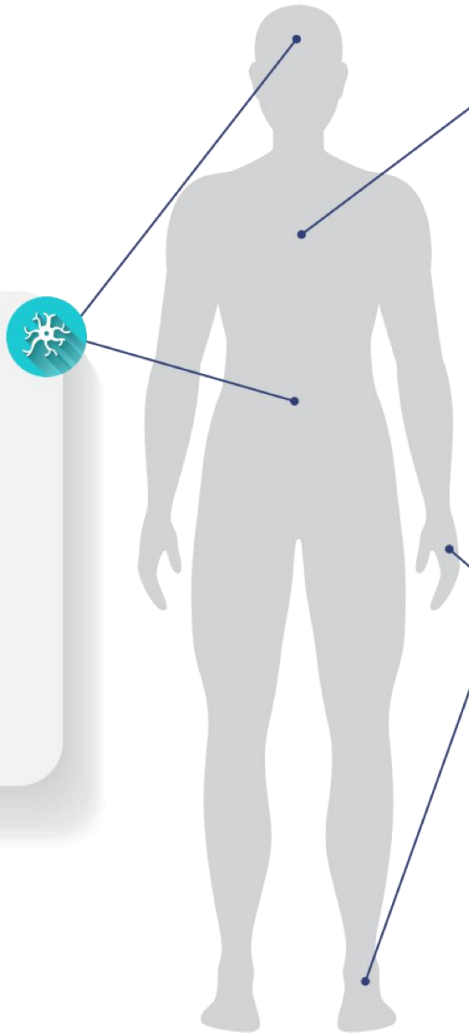
Polyneuropathy and cardiomyopathy




**Transthyretin**
**Trans**ports **thy**roxin (T4) and **retin**ol (Vit. A)

Mutations in TTR lead to unstable tetramers,
resulting in misfolded TTR monomers leading to amyloid deposits

# hereditary transthyretin amyloidosis (hATTR)



### Autonomic Dysfunction

Symptoms of autonomic dysfunction include:

- Urinary tract infections
- Excessive sweating
- Dizziness upon standing
- Sexual dysfunction
- Nausea and vomiting
- Diarrhea
- Severe constipation
- Unintentional weight loss

### Cardiomyopathy

Symptoms of cardiomyopathy include:

- Increasing fatigue
- Dizziness
- Shortness of breath
- Leg swelling (edema)
- Palpitations and abnormal heart rhythms (atrial fibrillation)
- Chest pain

### Polyneuropathy

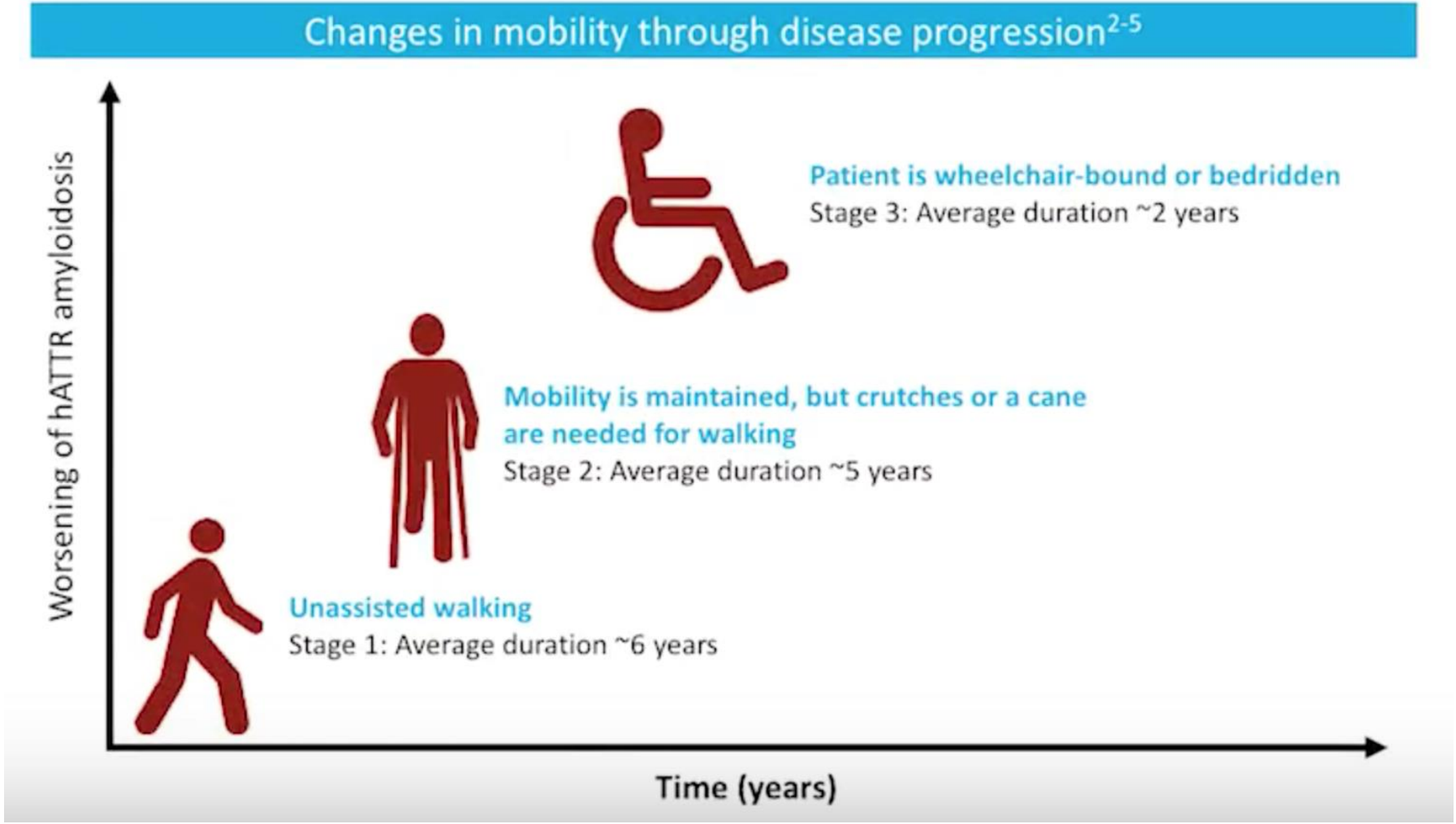
Peripheral neuropathy includes symptoms such as:

- Tingling
- Numbness
- Carpal tunnel syndrome
- Burning pain
- Loss of sensitivity to temperature
- Weakness

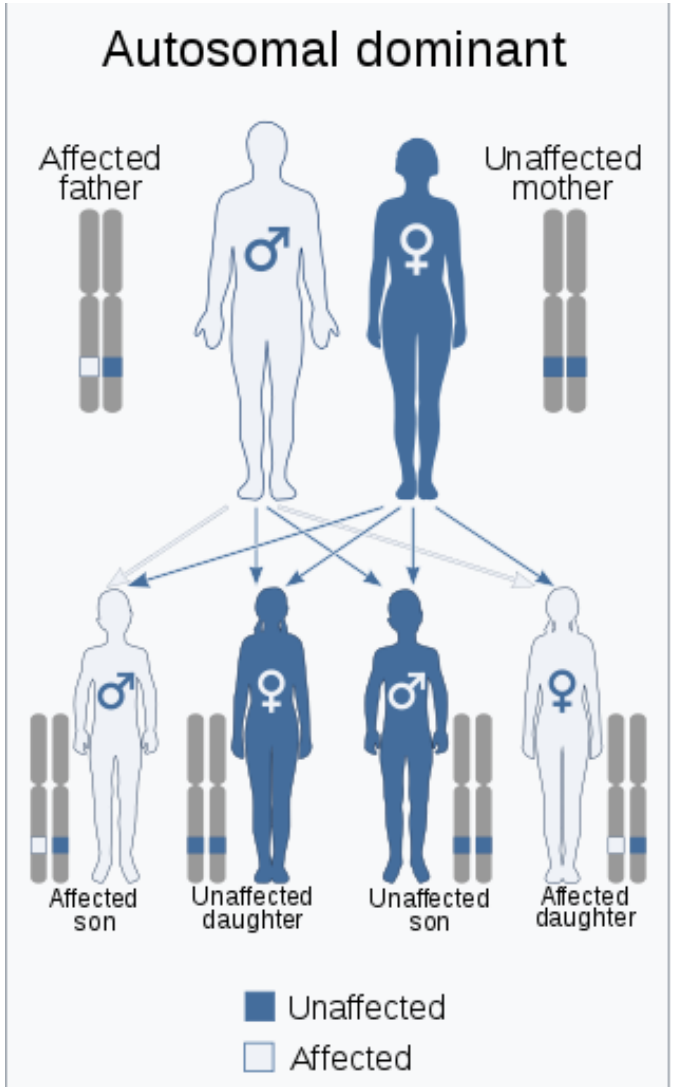
### Other Symptoms

- Glaucoma
- Blurred or spotty vision
- Abnormalities of the pupil or blood vessels on the white of the eye
- Detached retina
- Progressive dementia
- Headache
- Loss of movement control
- Seizures
- Weakness
- Stroke-like episodes
- Kidney dysfunction

# hereditary transthyretin amyloidosis (hATTR)
# Progress of polyneuropathy



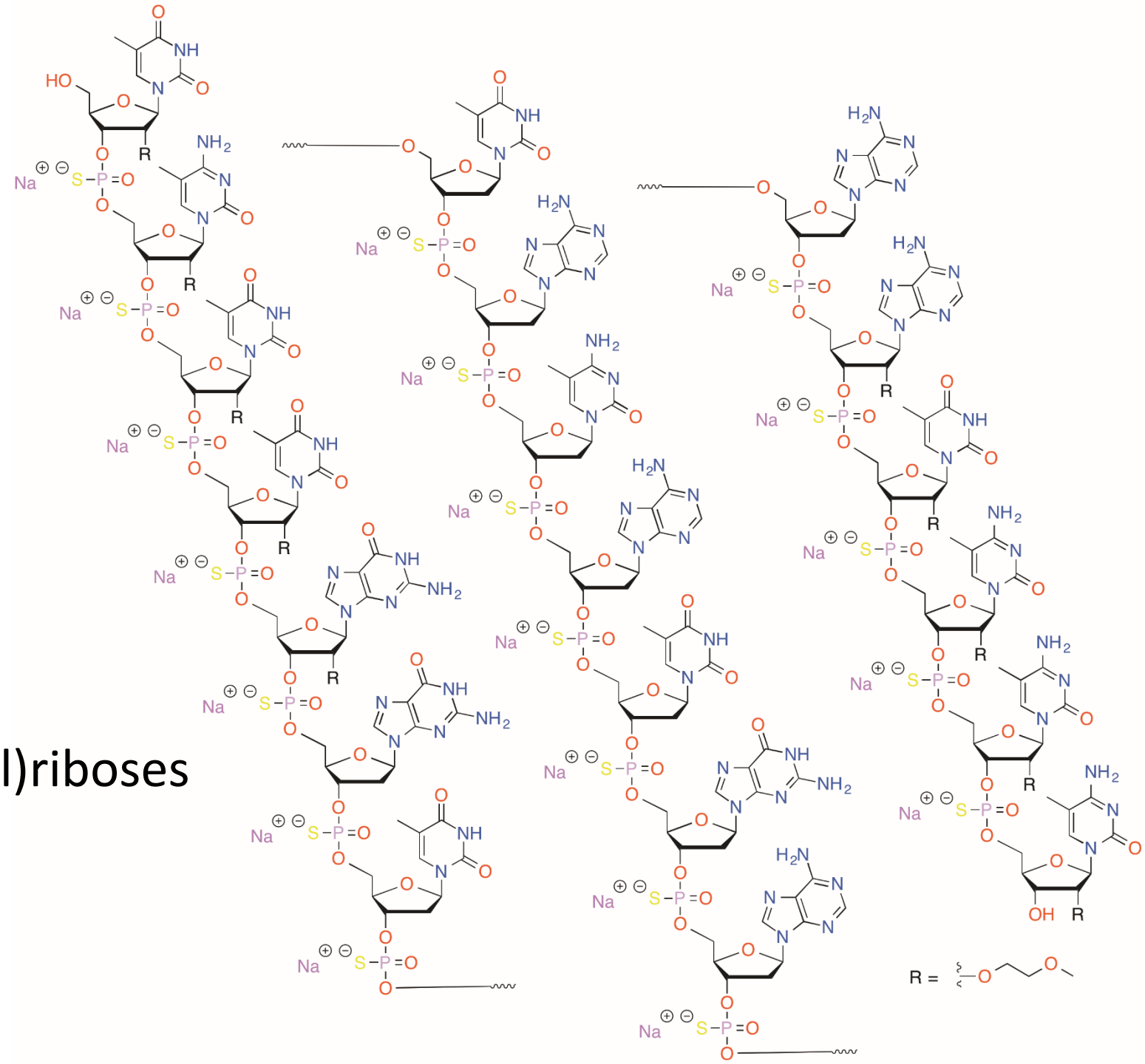
# hereditary transthyretin amyloidosis (hATTR)




- Very rare: 50,000 affected individuals worldwide
- Median age of onset = 39 years
- Can lead to mortality within 2 to 15 years

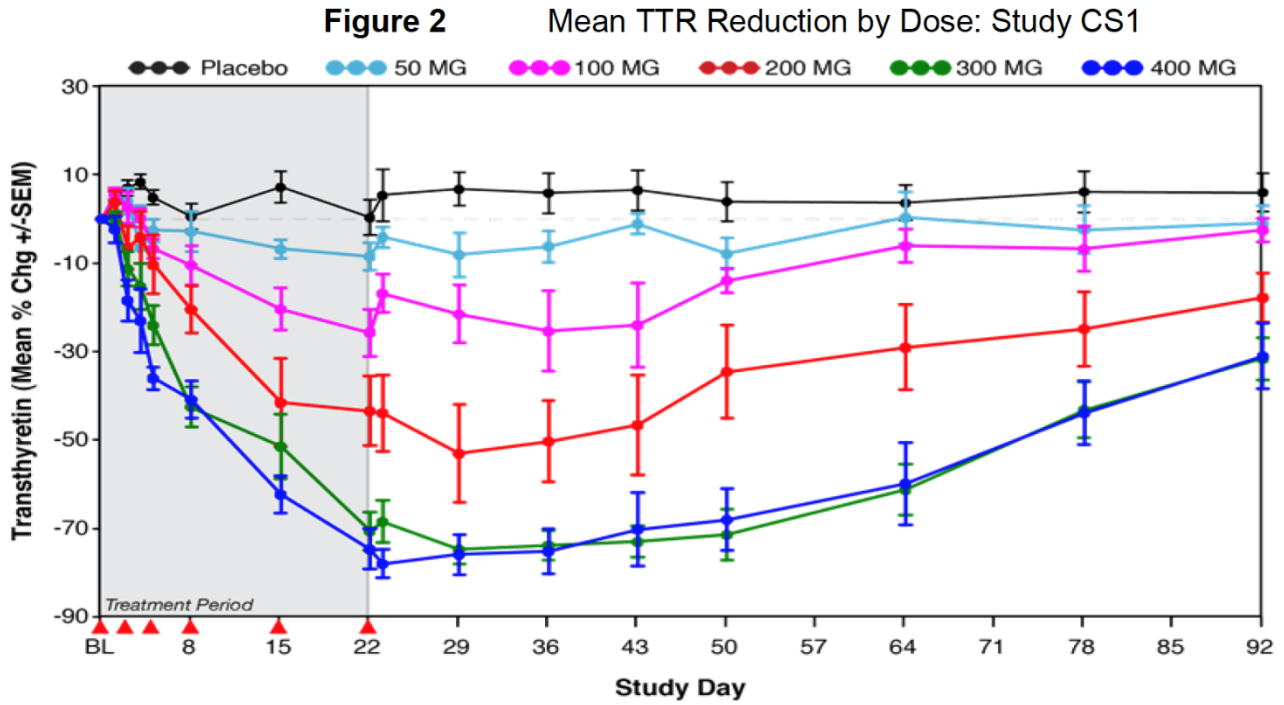
# Tegsedi® (Inotersen)

- Antisense oligonucleotide
- 20 nucleotides
- 19 phosphorothioate links
- $2^n$ diastereoisomers
  $= 2^{19} = 524288$
- Nonadecasodium salt
- All pyrimidines are 5-Me
- 2 x 5 2’-O-(2-methoxyethyl)riboses
- 10 2’-deoxyriboses



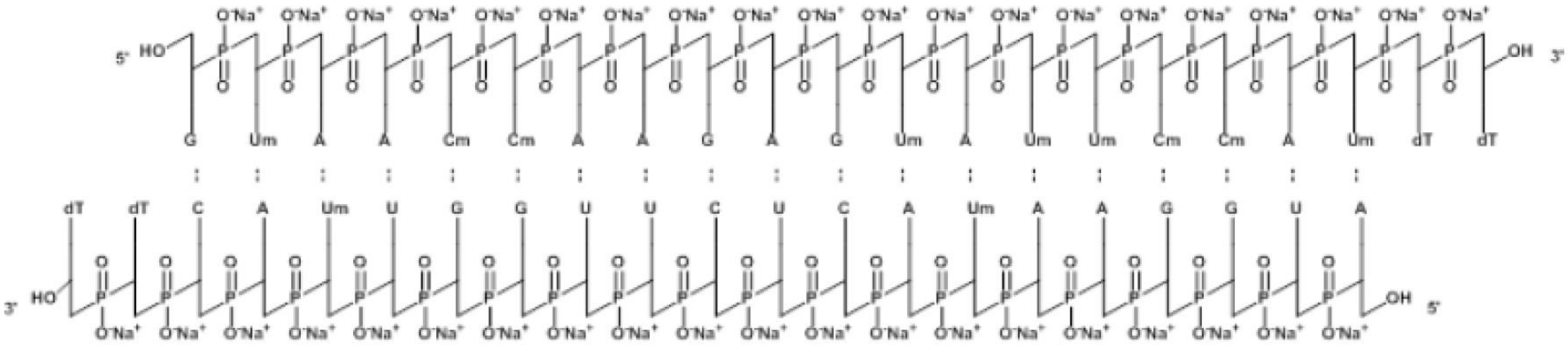
# Tegsedi® (Inotersen)

- RNase H antisense oligonucleotide
- Causes the degradation of both wild-type and mutant TTR mRNA
- Leads to lower TTR levels
- Clinical data
  - 284 mg injection under the skin once per week
  - Elimination $t_{½}$ = 2 to 4 weeks
  - 173 hATTR patients with stage 1 or 2 nerve damage
  - Significant reduction in nerve damage and improvement in quality of life over placebo
  - Side effect: low blood platelet counts



# **Onpattro®** (Patisiran)

Sense Strand



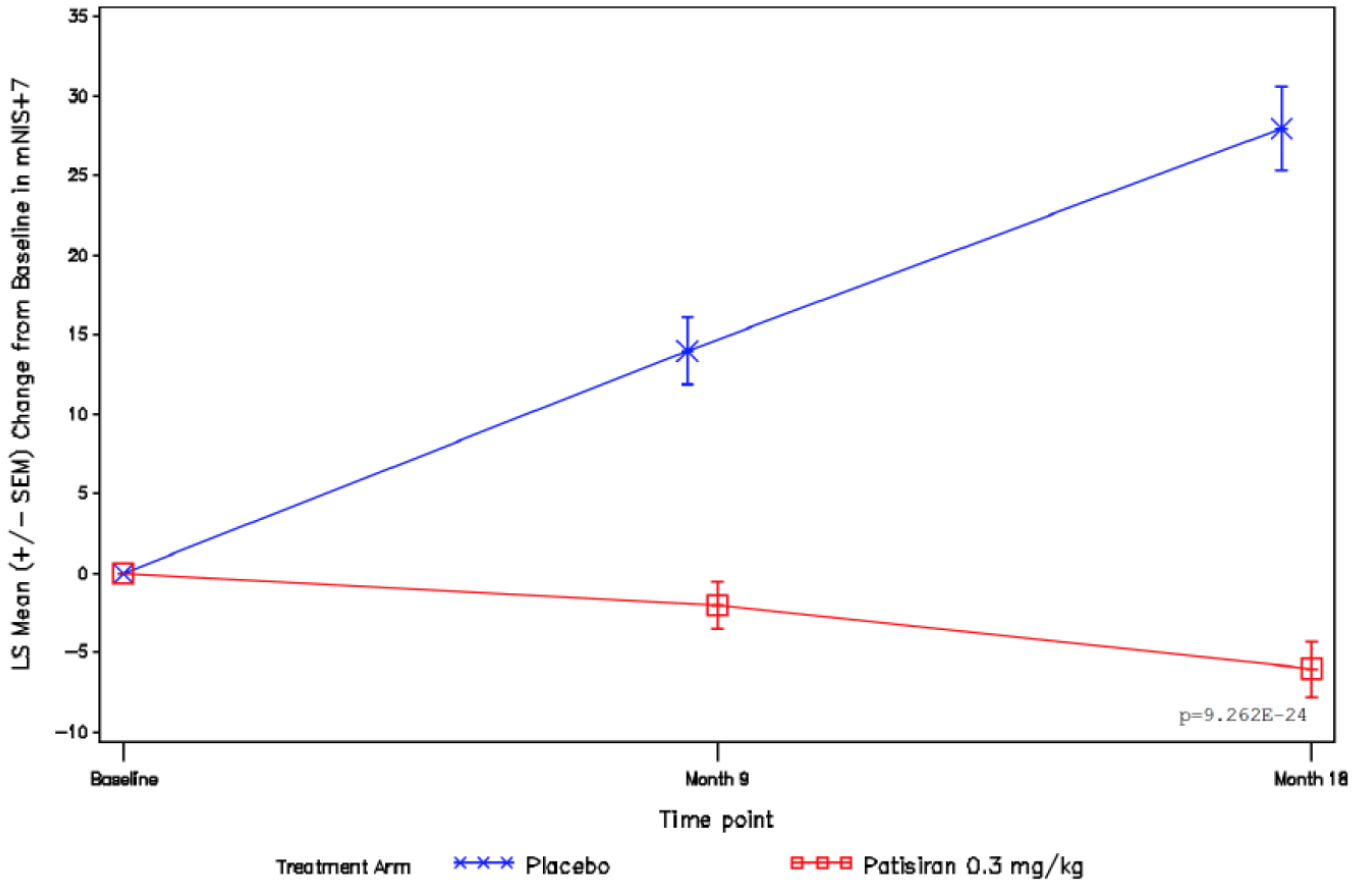

Antisense Strand

- Double stranded oligonucleotide
- Each 21 nucleotides
- 19 base pairs
- two 3’-terminal nucleotides unpaired
- Cm and Um are 2’-O-methylcytidine and 2’-O-methyluridine respectively
- dT is thymidine deoxyribose, all the others are ribonucleotides

# Onpattro® (Patisiran)

- siRNA
- Clinical data
  - Infusion of 300 microgram/kg once every 3 weeks
  - Elimination $t_{½}$ = 3.2 days
  - 225 hATTR patients with stage 1 or 2 nerve damage
  - Significant reduction in nerve damage over placebo
  - Take vitamin A supplements

Neurological impairment score



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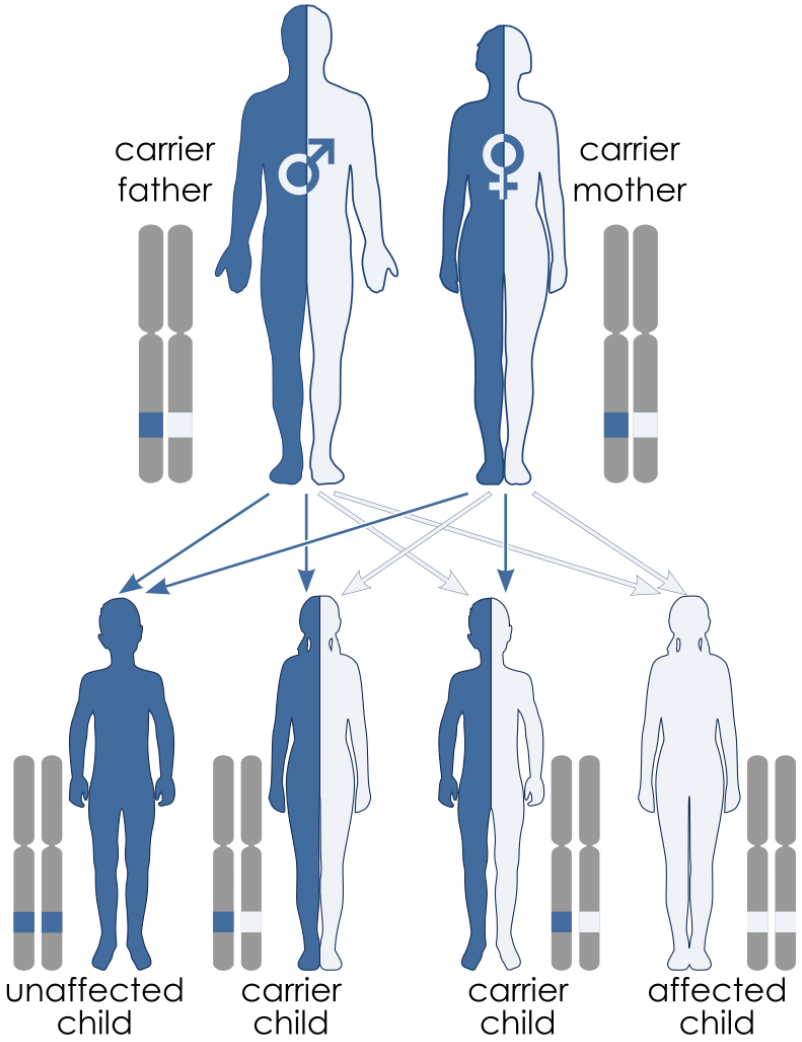
  - Breast cancer

# Spinal muscular atrophy (SMA)

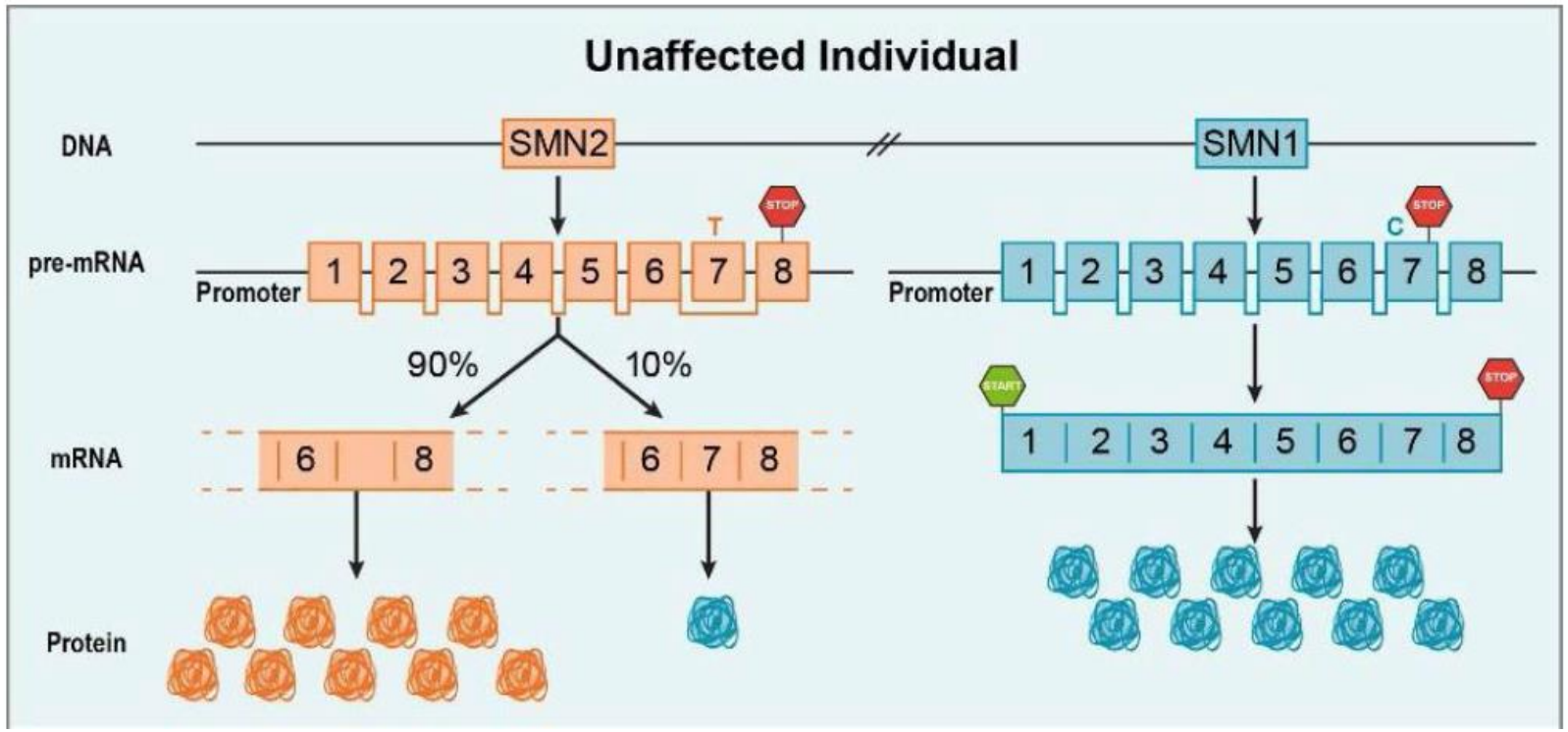
- SMA is **a rare genetic disease** characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in muscular atrophy
  - Progressive muscle wasting and mobility impairment
  - Proximal muscles (arm and leg) and respiratory muscles are affected first
- Genetic defect in the SMN1 gene
  - Encodes SMN protein (survival motor neuron)
  - Necessary for survival of motor neurons
  - Functions in transcriptional regulation and SMN deficiency results in widespread splicing defects

# SMA genetics: autosomal recessive




- global incidence of 8.5 to 10.3 per 100,000 live births
- most common genetic cause of infant mortality
- major cause of childhood morbidity due to muscle weakness.

# SMA genetics




Two nearly identical genes

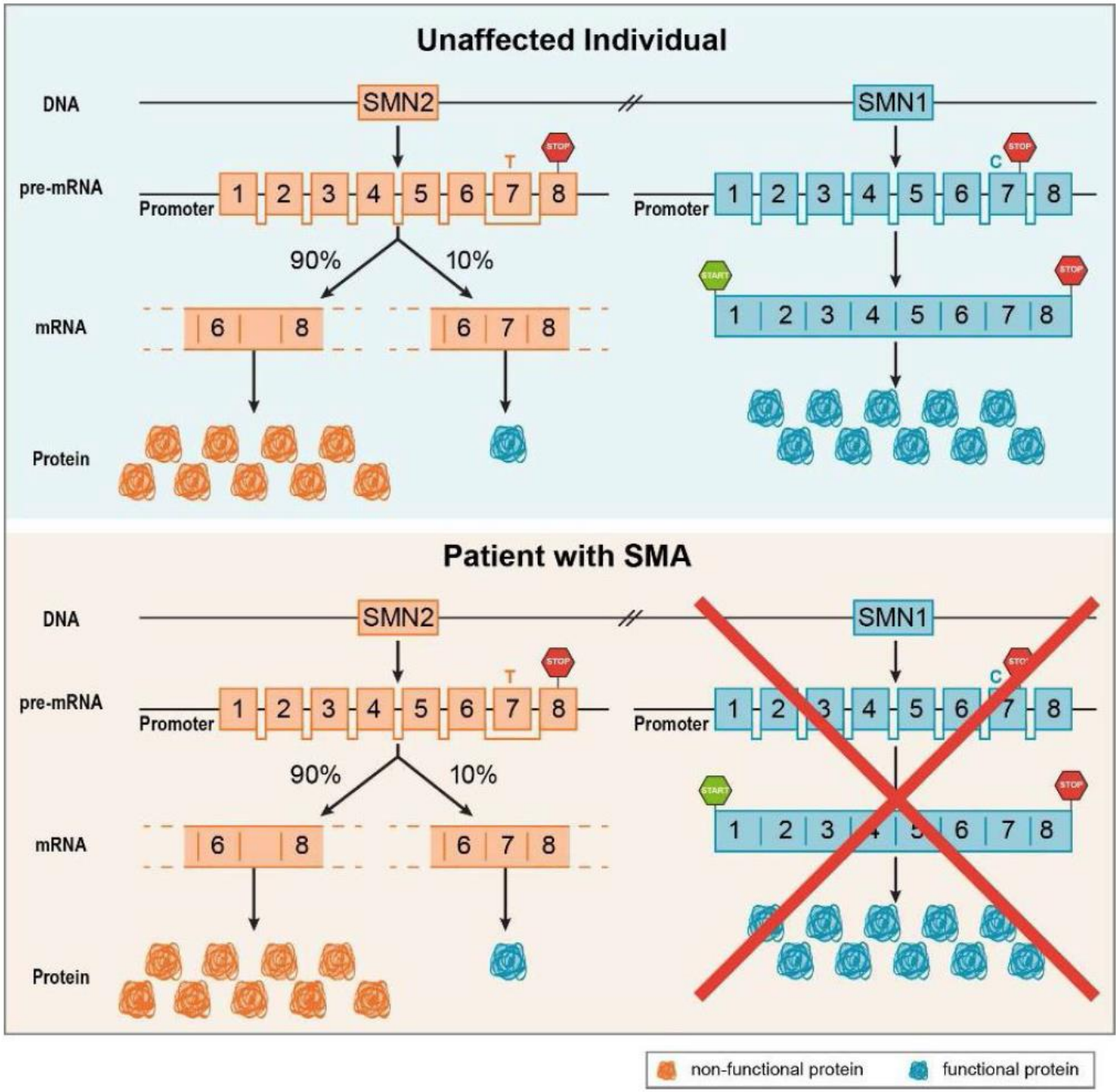
- **SMN1** results in functional SMN protein
- **SMN2** (5 to 11 nucleotides difference)
  - Can encode functional SMN with identical amino acid sequence
  - **BUT** a C-T substitution in **exon 7** favors skipping of that exon
  - mRNA lacking exon 7 leads to truncated, non-functional SMN protein

# SMA genetics

Deletions and mutations in SMN1 lead to seriously reduced levels of functional SMN

Humans have a variable number of copies of SMN2

- 0 to 8 copies
- Copy number is an important predictor of disease



# Spinal muscular atrophy (SMA)

- SMA has been categorized into **Types 0, 1, 2, 3, and 4** based on age of symptom onset and maximal achieved motor abilities.
- In general, symptom onset and severity of SMA correlate with SMN2 gene copy number in this genetic disorder
  - Type 0 1 copy of SMN2 rare prenatal SMA
  - Type 1 2 copies of SMN2 58%
  - Type 2 3 copies of SMN2 29%
  - Type 3 3-4 copies of SMN2 13%
  - Type 4 > 4 copies of SMN2 < 5% adult-onset SMA

# Spinal muscular atrophy (SMA): different types

**TYPE 0**

- Little or no movement before birth
- Severe weakness
- Respiratory failure a major problem
- Short life expectancy (usually less than 6 months)

**TYPE 1**

- Symptoms start within weeks of birth
- Poor head control
- Weak upper arms and thighs
- Abnormal breathing and difficulty feeding - risk of inhaling food
- Needs support to sit
- Short life expectancy (often less than 2 years)

**TYPE 2**

- Symptoms start at 7-18 months
- Twitching of upper arms and thighs
- Jaw weakness
- Sits independently, but not able to walk
- Shortened life expectancy (but more than 2 years)

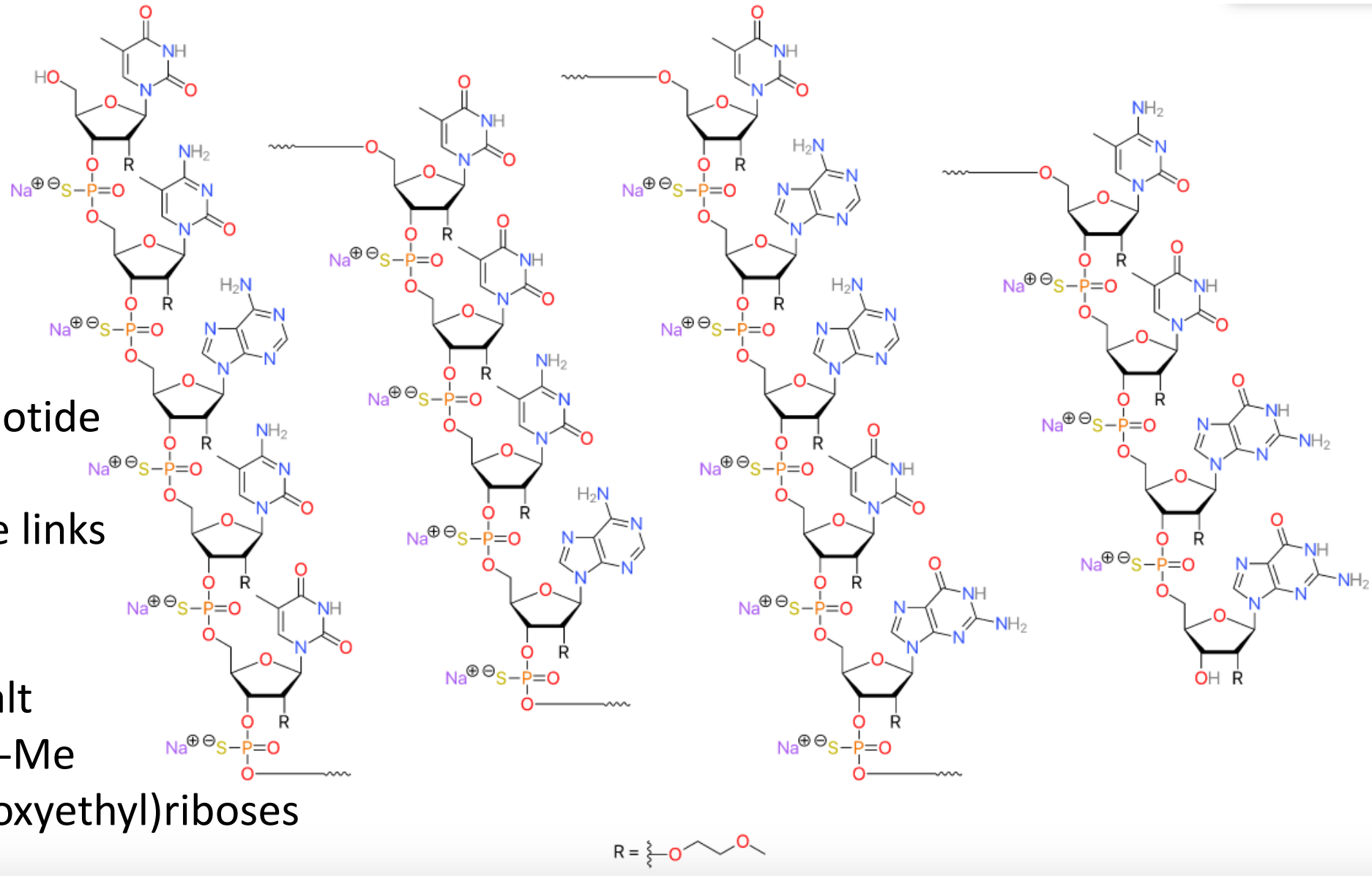
**TYPE 3**

- Symptoms start after 18 months
- Increasing weakness of upper legs
- Walks independently, but may lose ability over time
- At risk of obesity and osteoporosis
- Normal life expectancy

**TYPE 4**

- Symptoms typically start after 30 years of age
- Muscle weakness in upper arms and thighs
- Walks independently but ability may be affected later in life
- Normal life expectancy

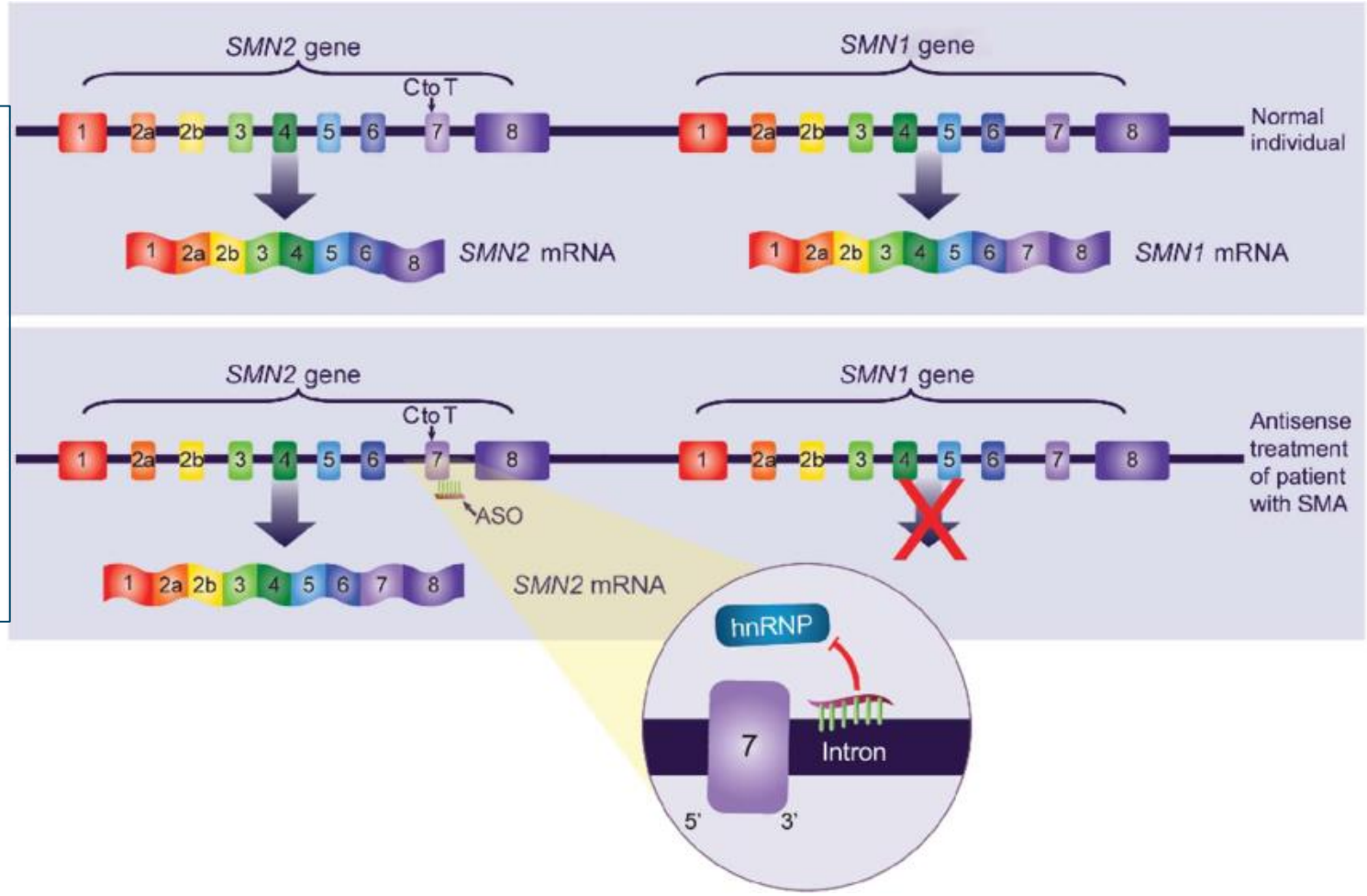
# Spinraza® (Nusinersen)



- Antisense oligonucleotide
- 18 nucleotides
- 17 phosphorothioate links
- $2^n$ diastereoisomers
  $= 2^{17} = 131072$
- Heptadecasodium salt
- All pyrimidines are 5-Me
- All are 2’-O-(2-methoxyethyl)riboses
- MW = 7501

# **Spinraza®** (Nusinersen): mechanism of action

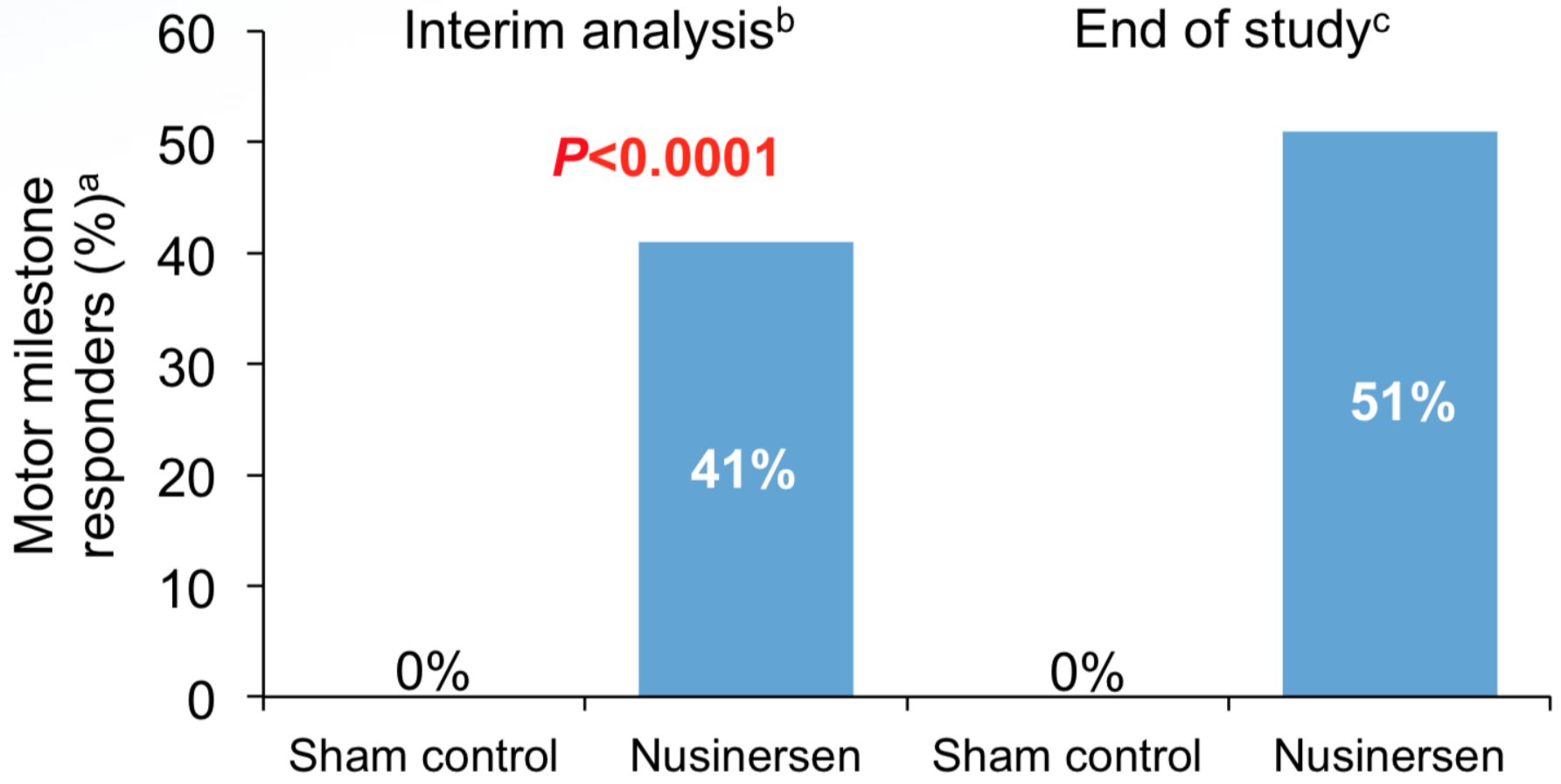
- ASO with no mRNA degradation
- Modulation of splicing at pre-mRNA of SMN2 gene
- ASO binds to intron 7 avoiding splicing factor hnRNP to bind
- Exon 7 is included leading to a functional protein



# **Spinraza®** (Nusinersen): clinical data

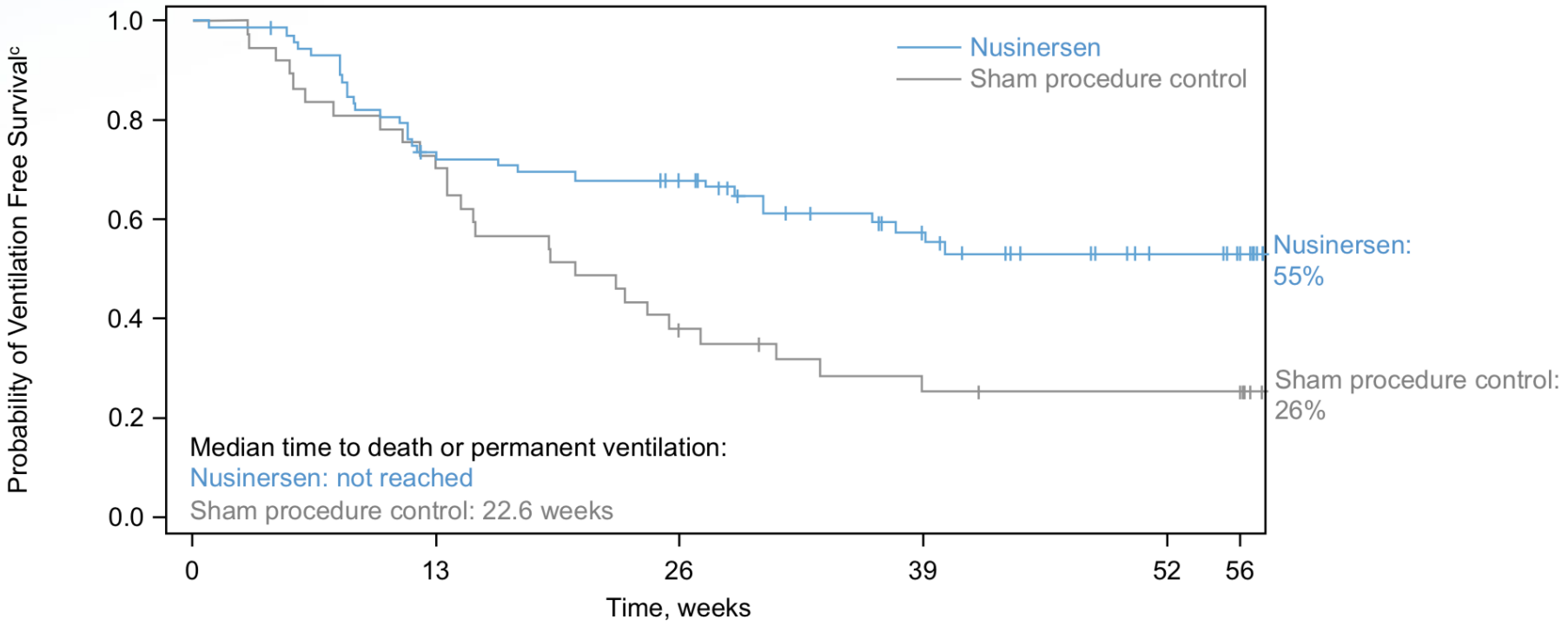
- Intrathecal injection of 12 mg
- Repeated after 2, 4 and 9 weeks and then every 4 months
- Terminal elimination $t_{½}$ in CSF = 135-177 days
- Most side effects related to injection directly into the spine
- Phase 3 infantile-onset
  - 121 babies, age of SMA onset < 6 months
    - Improved motor control and survival
- Phase 3 later-onset
  - Average age = 3 years
    - 57% showed improvement in movement over 26% improvement on placebo

# **Spinraza®** (Nusinersen): infantile-onset



# Spinraza® (Nusinersen): infantile-onset

| Outcome | Sham procedure control | Nusinersen |
|---|---|---|
| Death or permanent ventilation, n (%) | 28 (68%) | 31 (39%) |
| Alive and no permanent ventilation, n (%) | 13 (32%) | 49 (61%) |



# Content

- **Tegsedi®** (Inotersen) and **Onpattro®** (Patisiran)
  - hereditary transthyretin amyloidosis
- **Spinraza®** (Nusinersen)
  - Spinal muscular atrophy (SMA)
- **Aimovig®** (Erenumab)
  - Migraine
- **Ibrance®** (Palbociclib)
  - Breast cancer

# Migraine: symptoms and current drugs

- Severe headache pain
  - Unilateral
  - Throbbing
  - Exacerbation by physical activity
- Other symptoms
  - Nausea
  - Vomiting
  - Photophobia
  - Phonophobia
- Prevalence
  - 15% in Europe, Canada
  - 12% USA
- Huge societal and economic impact
  - UK: 25 million working/school days are lost each year

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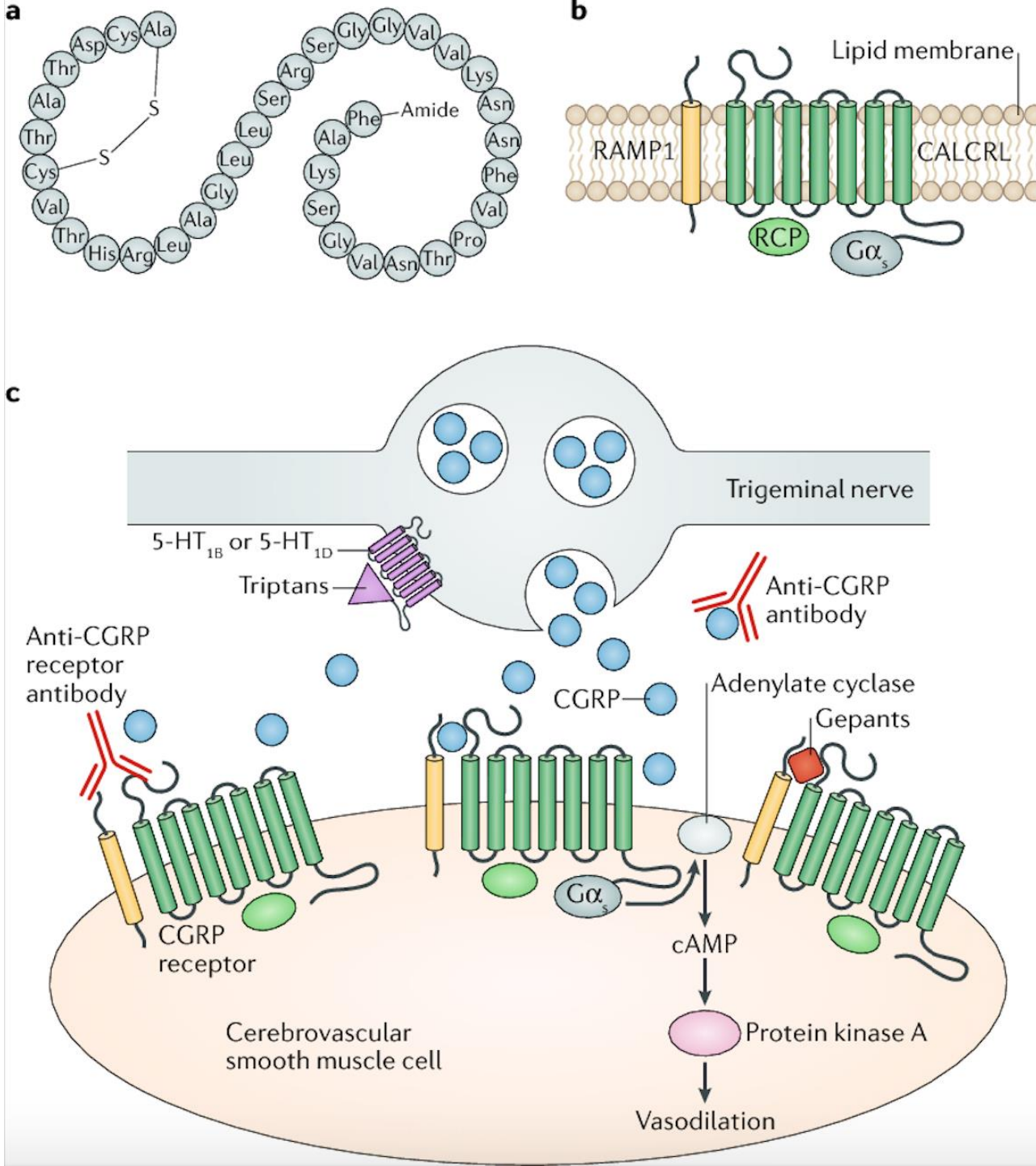
- Acute migraine
  1. Paracetamol, ASA
  2. NSAID
  3. Triptan (sumatriptan)
  4. Ergotamine ??
  5. Parenteral phenothiazines and glucocorticoids

  } gastroprokinetic: metoclopramide

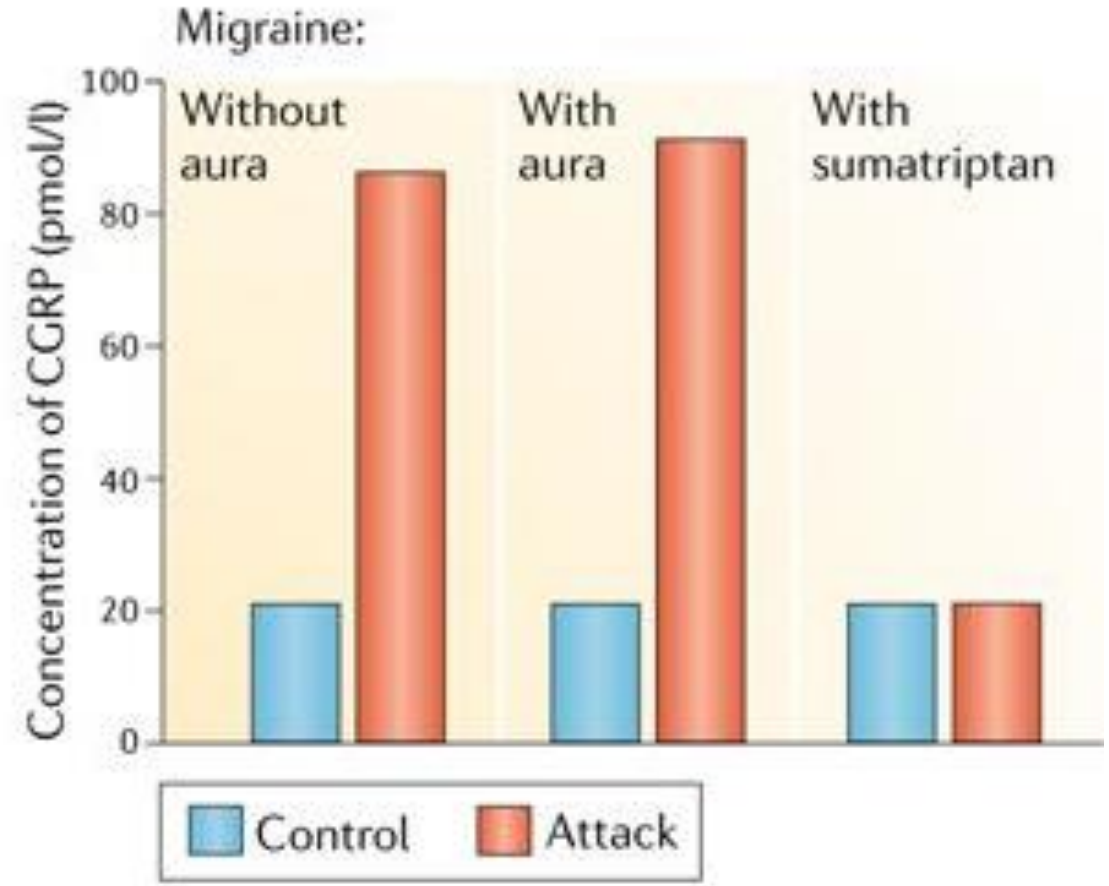
- Prophylactic
  1. Beta-blockers: propranolol, metaprolol
  2. Others
     - Anti-epileptics: sodium valproate, topiramate
     - Ca-antagonists: flunarizine
     - Antidepressant: amitryptilline

# Calcitonin-gene related peptide (CGRP)

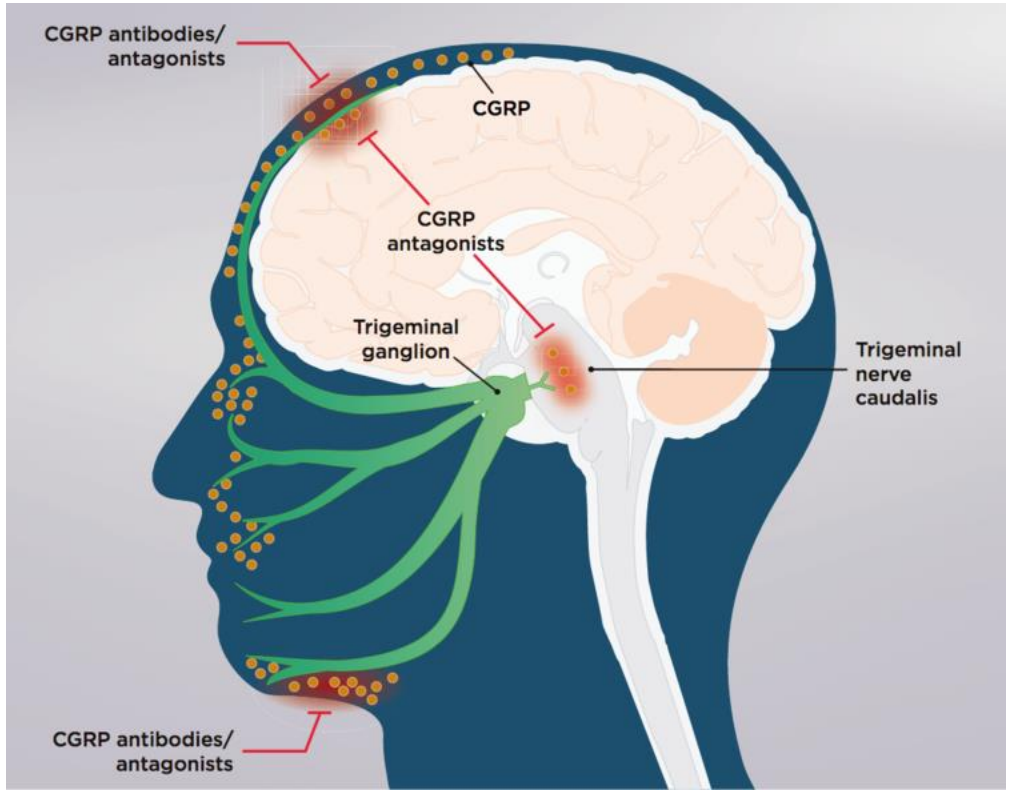
- A neuropeptide that binds to a GPCR
- Released from both peripheral and central neurons
- Vasodilator, nociception
- CGRP is **increased during acute migraine** attacks
- Is important in the trigeminal ganglion and the trigeminovascular reflex
- Potential drugs
  - CGRP receptor **antagonists**
  - **Antibodies** against CGRP or CGRP receptor
  - **Triptans** prevent the release of CGRP

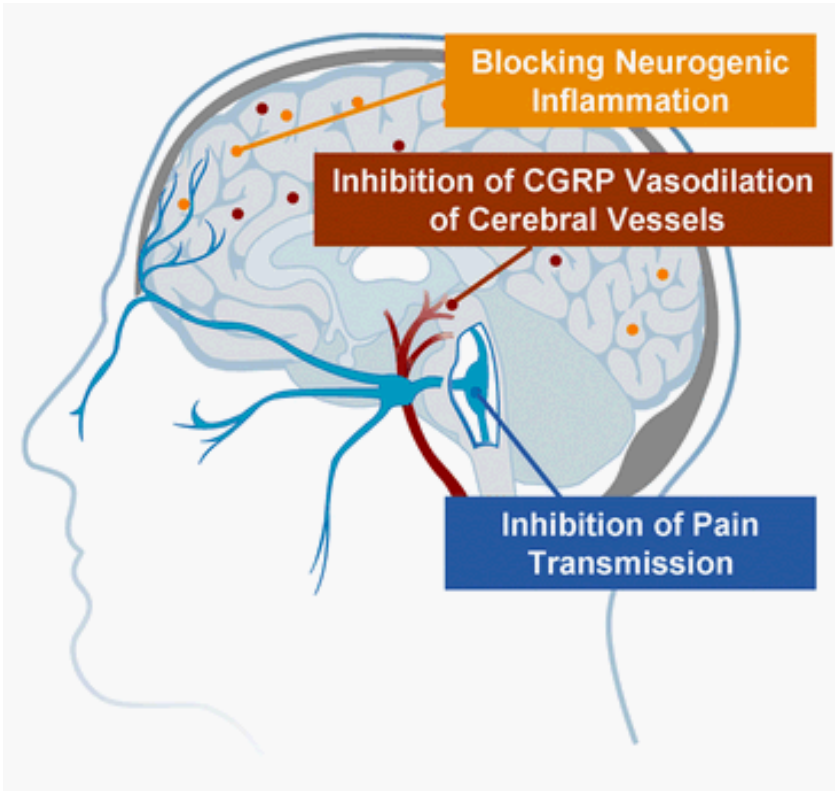


# CGRP levels


Migraine:
Without aura
With aura
With sumatriptan
Concentration of CGRP (pmol/l)
100
80
60
40
20
0
Control
Attack

# Role of CGRP in migraine pathophysiology



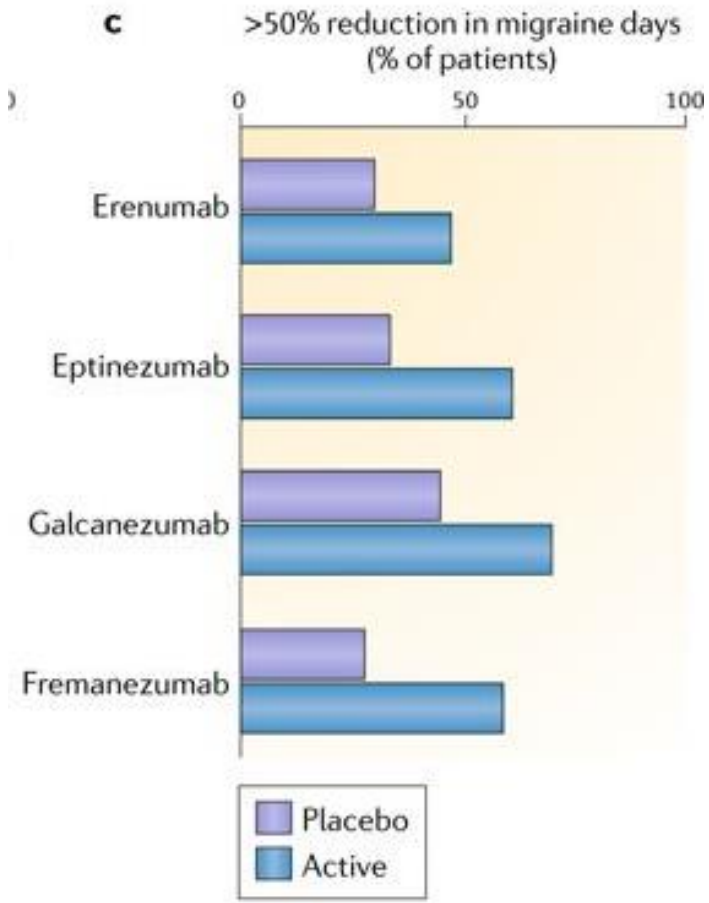

The trigeminal ganglion and dura are not behind the blood–brain barrier. Can be reached by antibodies

# Potential therapies influencing CGRP

- CGRP receptor antagonists
  - Can potentially cross the blood-brain barrier
  - E.g. ubrogepant in development for acute relief of migraine
- CGRP antibodies
  - E.g. eptinezumab, fremanezumab and galcanezumab for prevention of migraine
- CGRP receptor antibodies
  - Erenumab (Aimovig®) for prevention of migraine
  - First GPCR directed antibody

# **Aimovig®** (Erenumab)

- mAb targeting the CGRP receptor
- A single injection of 70 mg every 4 weeks
- Terminal $t_{½}$ = 28 days
- Efficacy
  - Phase 3 with 667 patients
    - 18 migraine days/month on average
    - 7 fewer days compared to 4 days with placebo
  - Phase 3 with 995 patients
    - 8 migraine days/month on average
    - 3-4 fewer days compared to 2 days with placebo



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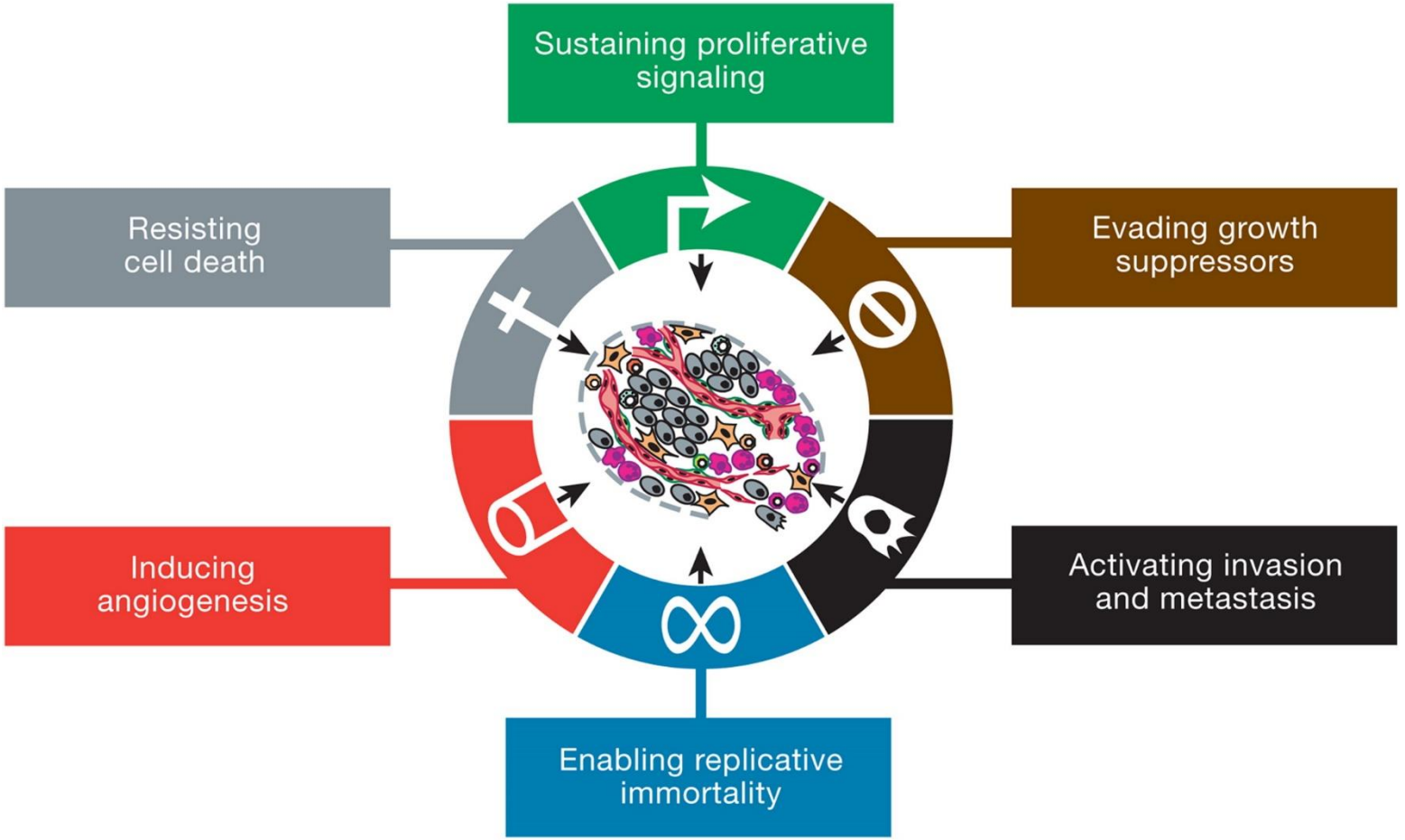
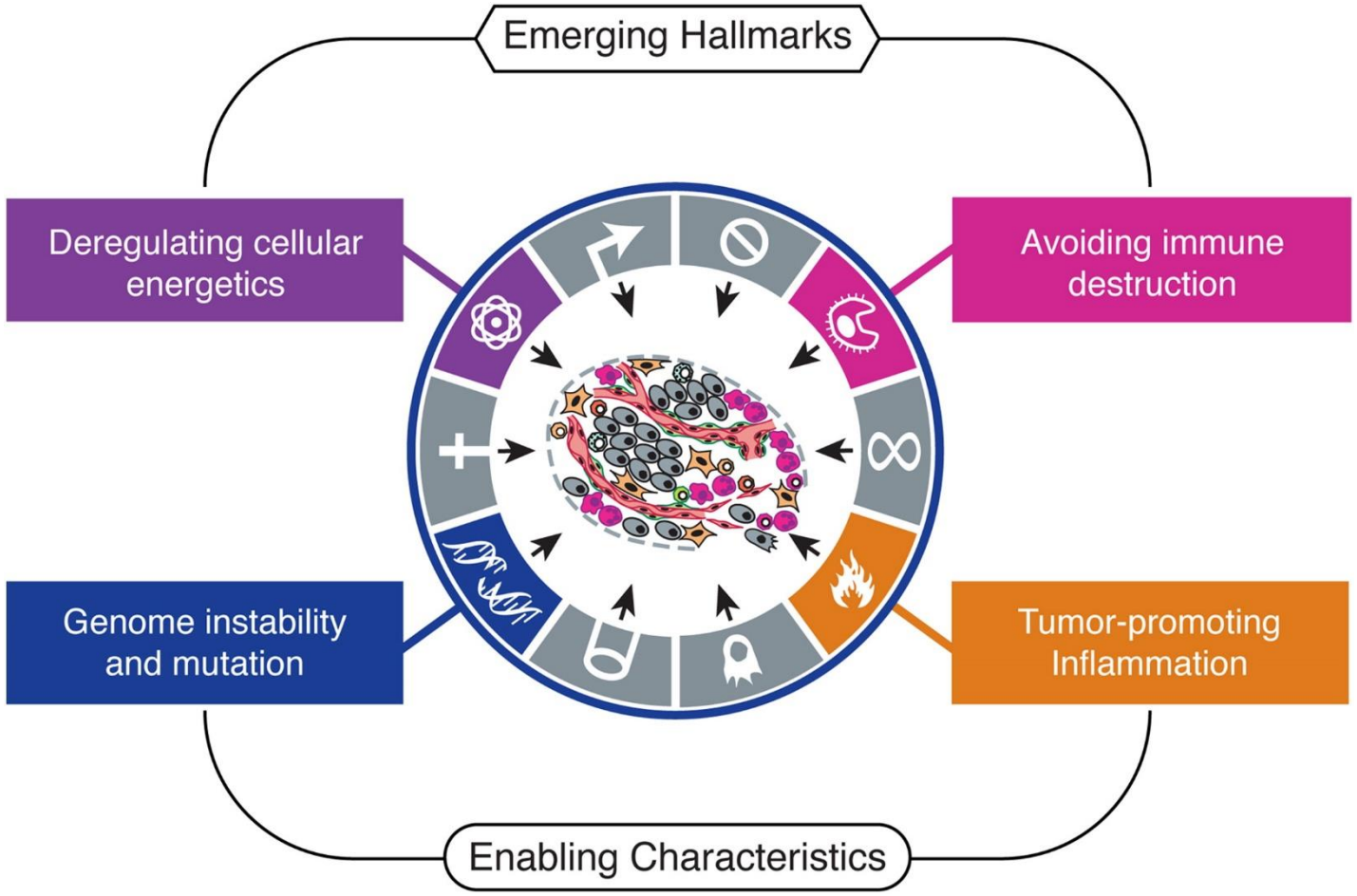
  - Breast cancer

# What are the hallmarks of cancer?

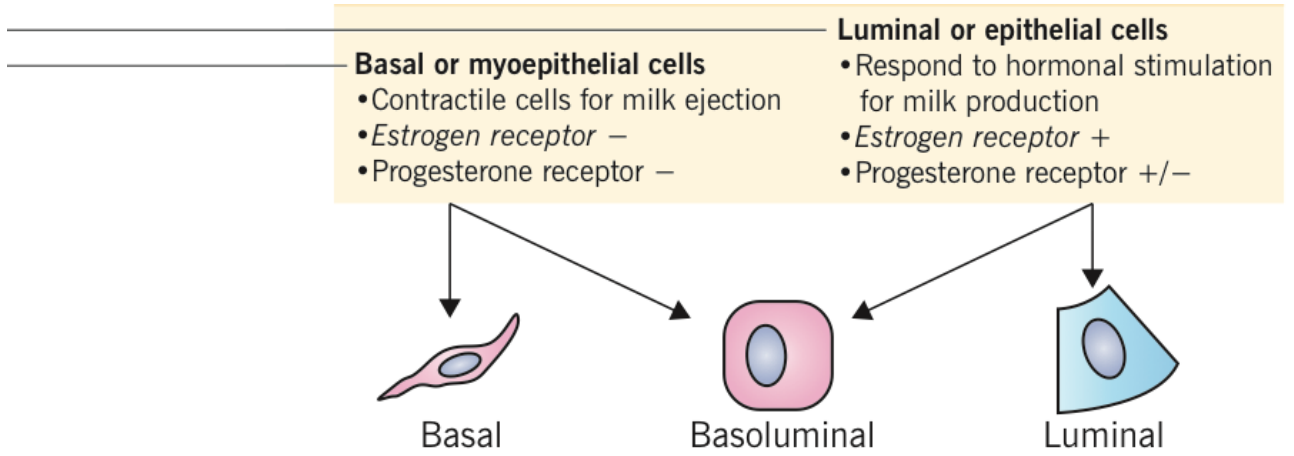


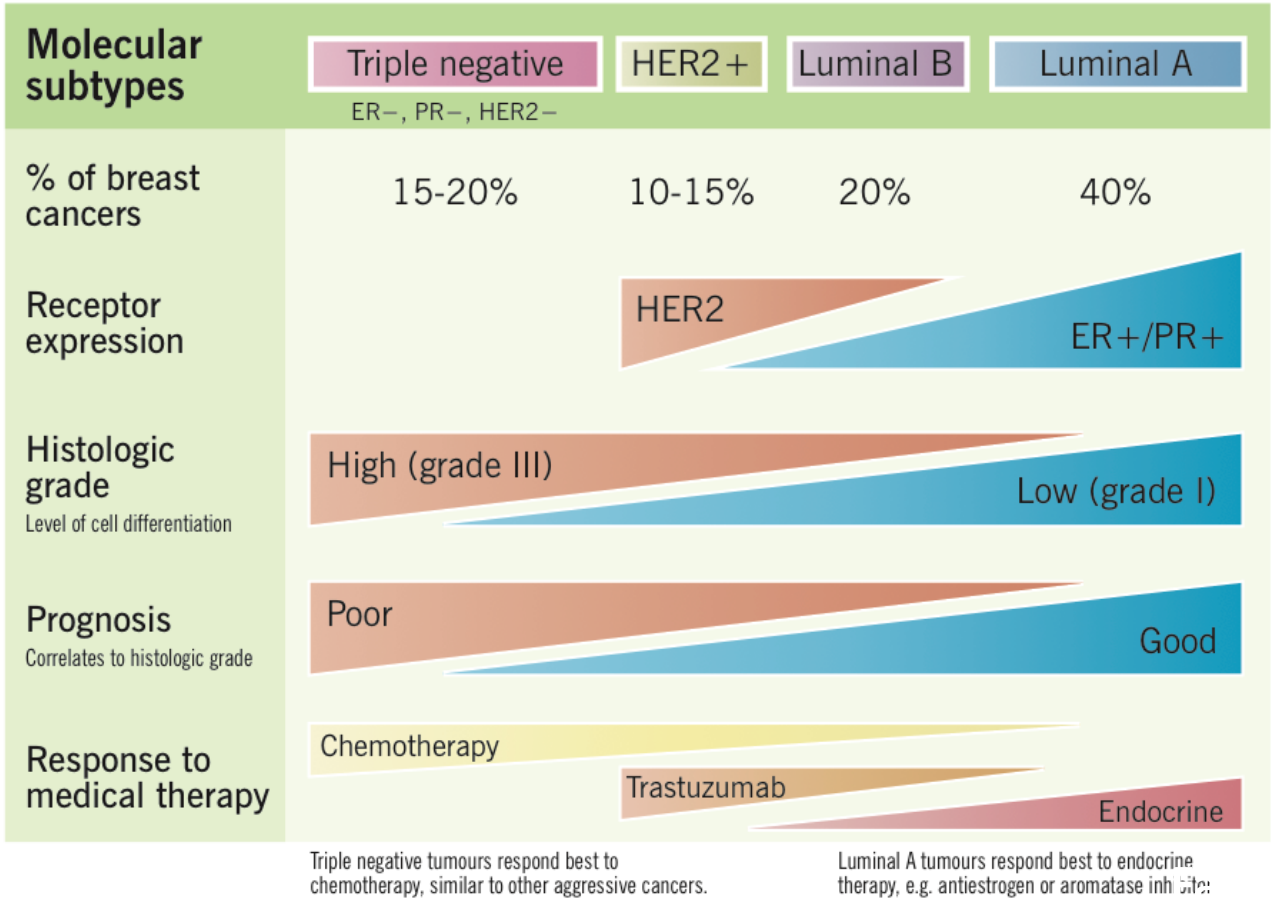

*Hanahan, D. et al. Cell, 2011, 144, 646*

# Emerging Hallmarks and new enabling characteristics



# Breast cancer



# Stop proliferation: chemotherapy for breast cancer

## Inhibitors of nucleotide biosynthesis

- 5-fluorouracil, capecitabine

## Inhibitors of DNA biosynthesis

- Gemcitabine, Anthracyclines (doxorubicin, epirubicin)

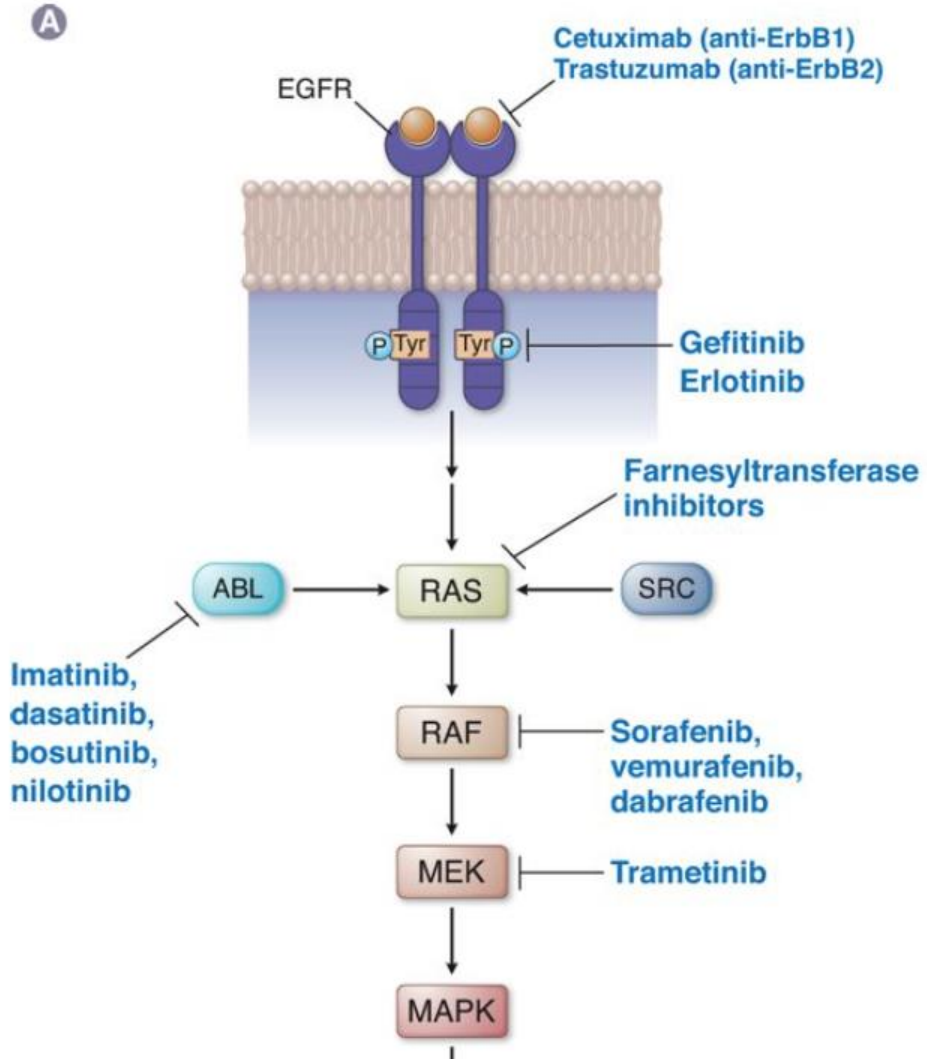
## Direct DNA binding and modification

- Cyclophosphamide, cisplatin, carboplatin

## Inhibition of microtubule polymerization or depolymerization

- Paclitaxel, docetaxel

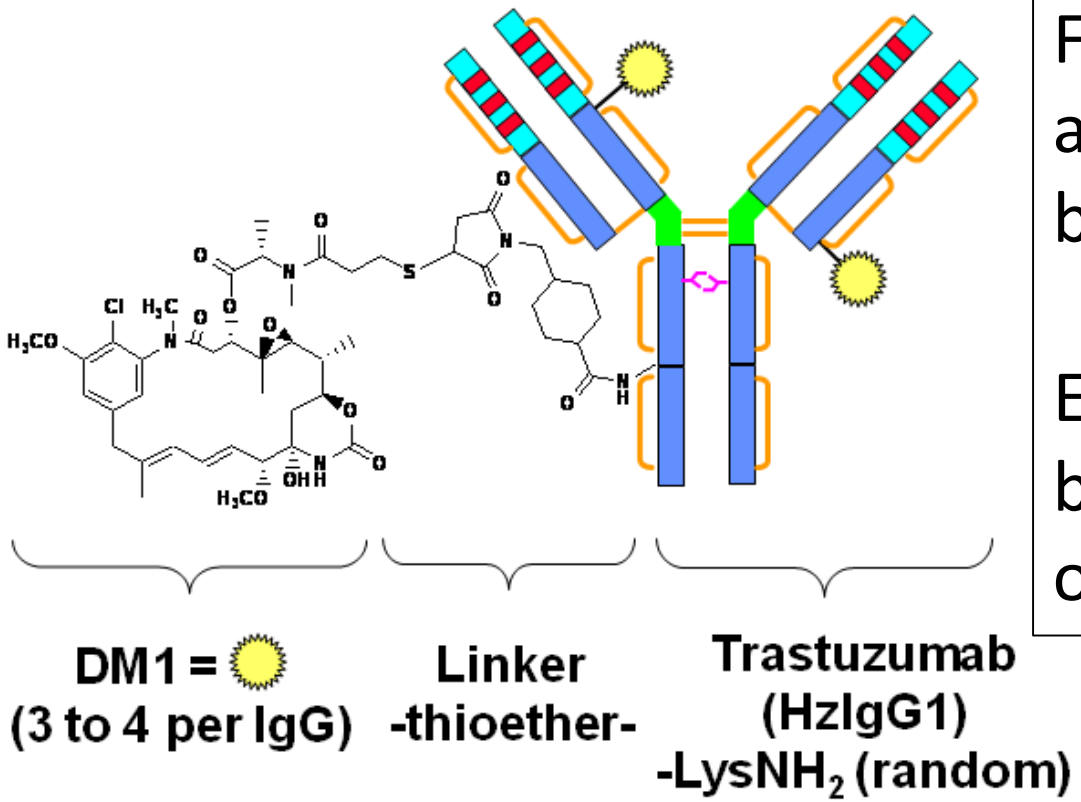
# Stop proliferation: Targeted drugs for breast cancer




- Monoclonal antibodies
  - Trastuzumab (Herceptin®)
- Tyrosine kinase inhibitors
  - Lapatinib (Tyverb®)

# Stop proliferation: antibody-drug conjugates

Trastuzumab emtansine (Kadcyla®, Roche, EMA 2013)




For HER-2 overexpressing advanced or metastatic breast cancer

Emtansine is a tubulin binder that blocks mitosis once in the cell

# Stop proliferation: Hormones in breast cancer

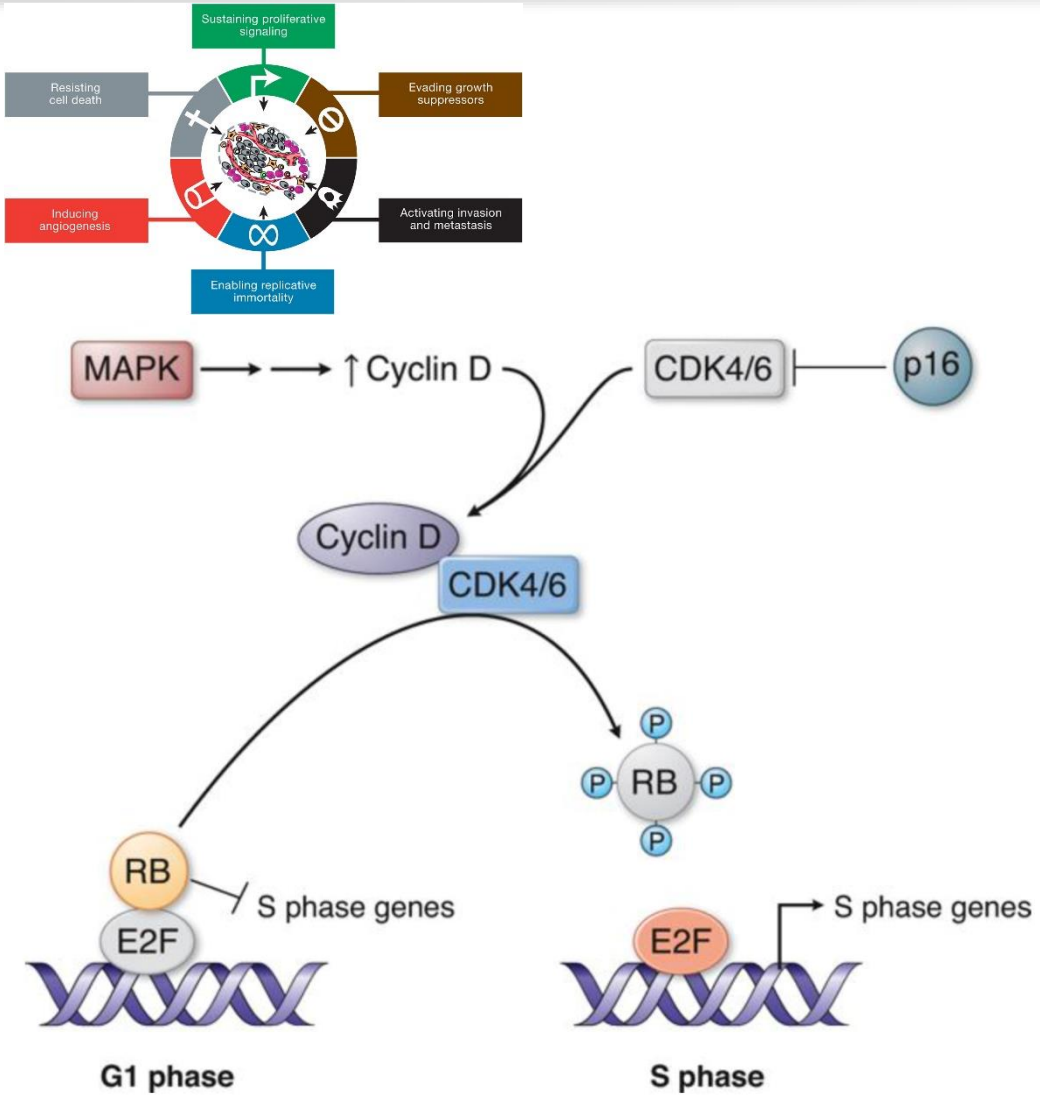
## Estrogen receptor

- Selective estrogen receptor modulator (SERM)
  - Tamoxifen
- Estrogen receptor antagonist
  - Fulvestrant (Faslodex®)

## Estrogen biosynthesis (aromatase inhibitors)

- Anastrozol, Letrozole, Exemestan

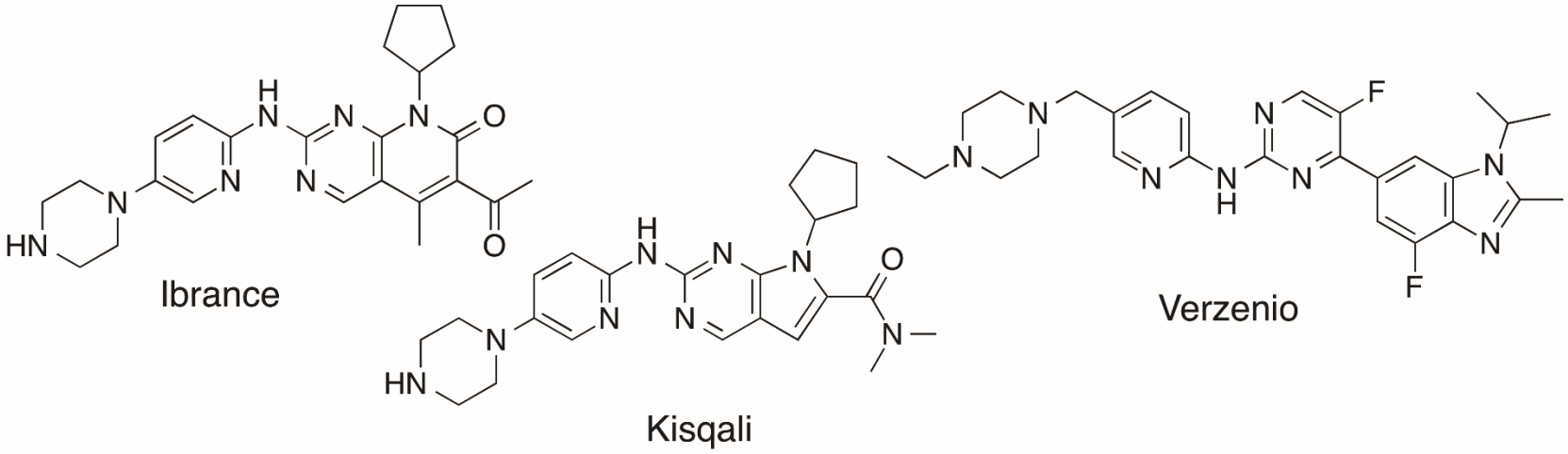
# 2. Evading growth suppressors




- Retionblastoma (RB) protein is a tumour suppressor
- Phosphorylated RB is inactive and allows cell cycle progression
- Inhibition of CDK4/6 will stop phosphorylation of RB and stops cell cycle progression

# The first CDK4/6 inhibitors recently entered the market

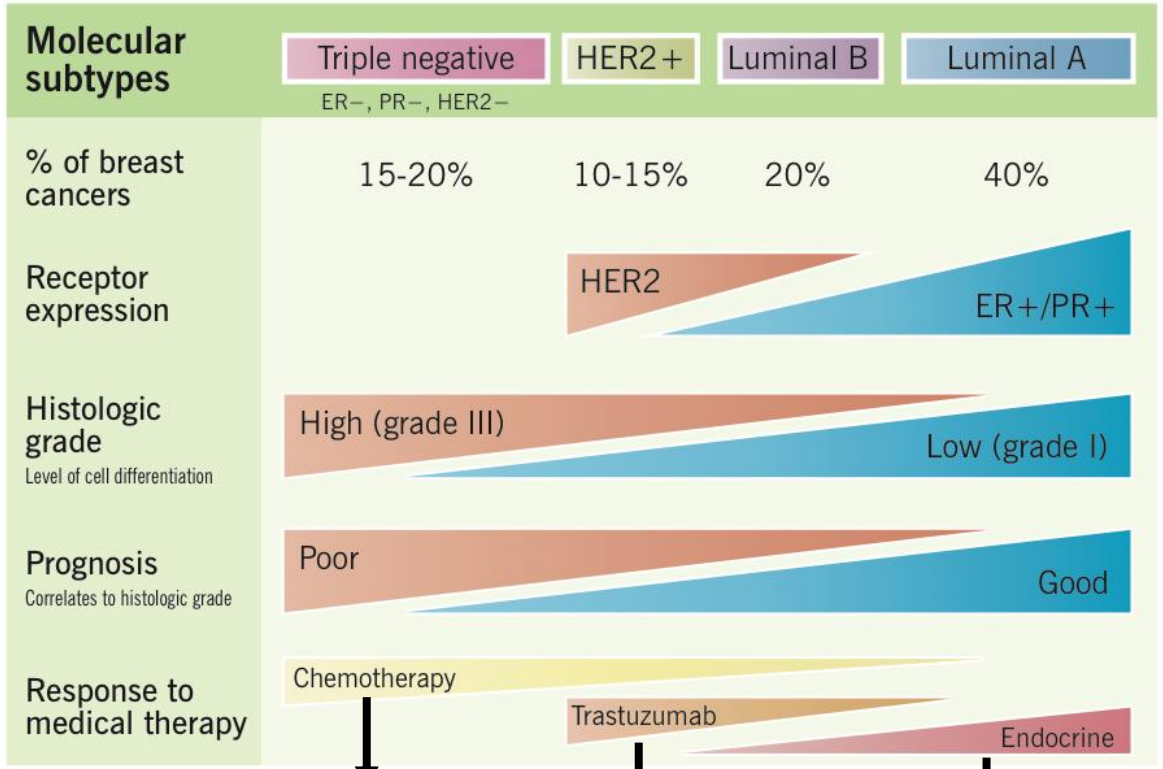
| MOA | Name | Active substance | Company | EMA | FDA |
|---|---|---|---|---|---|
| CDK4/6 | Ibrance | Palbociclib | Pfizer | 2016 | 2015 |
| CDK4/6 | Kisqali | Ribociclib | Novartis | 2017 | 2017 |
| CDK4/6 | Verzenio | Abemaciclib | Eli Lilly | - | 2017 |



# **Ibrance®** (Palbociclib)

- To treat locally advanced or metastatic breast cancer
  Hormone-positive, HER2-negative
  - Together with a aromatase inhibitor
  - Or together with fulvestrant in patients who have previously received a hormonal medicine
- 125 mg, once a day for 21 days, followed by a 7-day break
- Efficacy
  - Phase 3 with 521 women with metastatic breast cancer that got worse after receiving a hormonal medicine
    - Palbociclib + fulvestrant: 11.2 months PFS
    - Placebo + fulvestrant: 4.6 months PFS
  - Phase 3 with 666 postmenopausal women with breast cancer that started to spread and no previous treatment
    - Palbociclib + letrozole: 24.8 months PFS
    - Placebo + letrozole: 14.5 months PFS
- neutropenia, leucopenia, anaemia, tiredness and infections

# Options for breast cancer depending on the phenotype




Doxorubicin, Paclitaxel, 5-FU, cyclophosphamide, carboplatin, …

Herceptin®
Kadcyla®
Tyverb®

Tamoxifen
Fulvestrant
Letrozole
Palbociclib

BCRA gene mutation
PARP inhibitors
- Olaparib
- Talazoparib

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