Enkele nieuwe geneesmiddelen 2019

Prof. Koen Augustyns

Farmant, Antwerpen, 04/02/2020

Content

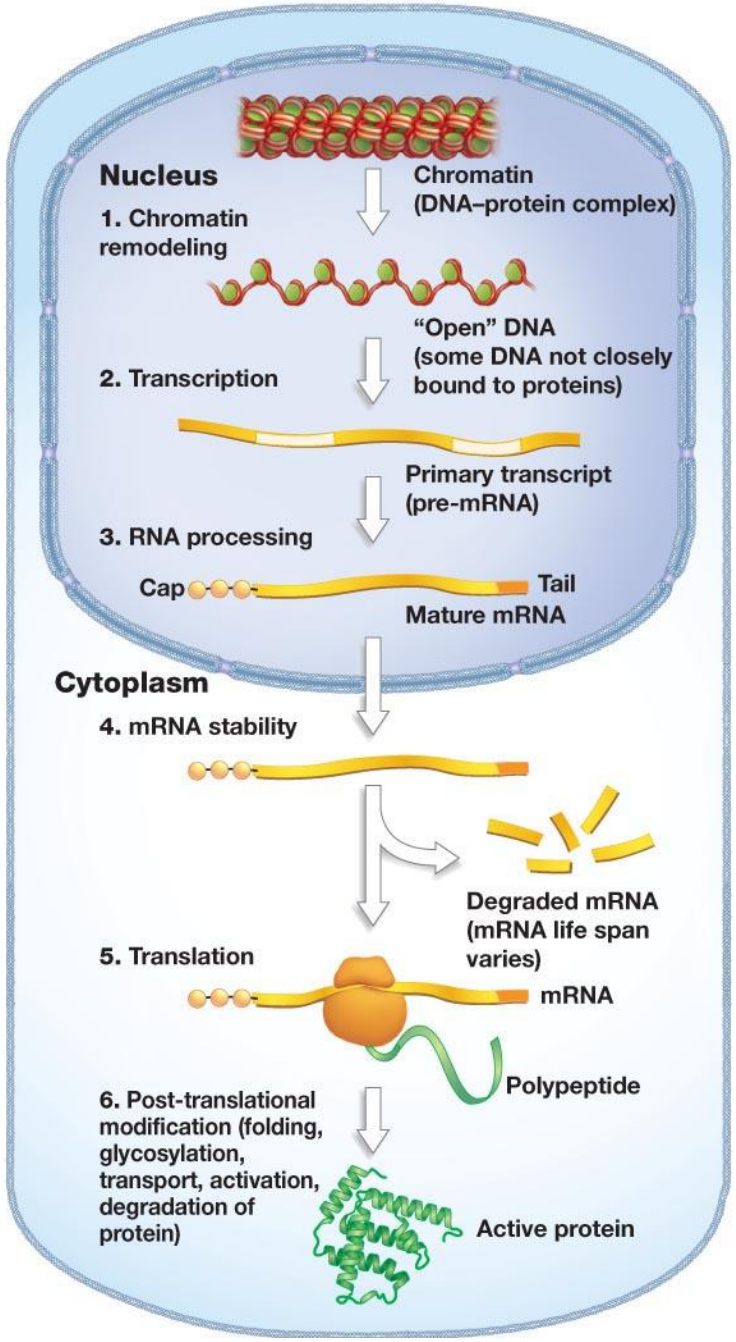
- **Zolgensma®** (onasemnogene abeparvovec) Novartis
  - Spinal muscular atrophy (SMA) FDA 24/05/2019
- **The cost of medicines**
- **Ozempic®** (Semaglutide) Novo Nordisk
  - Type 2 diabetes EMA 08/02/2018

Zolgensma

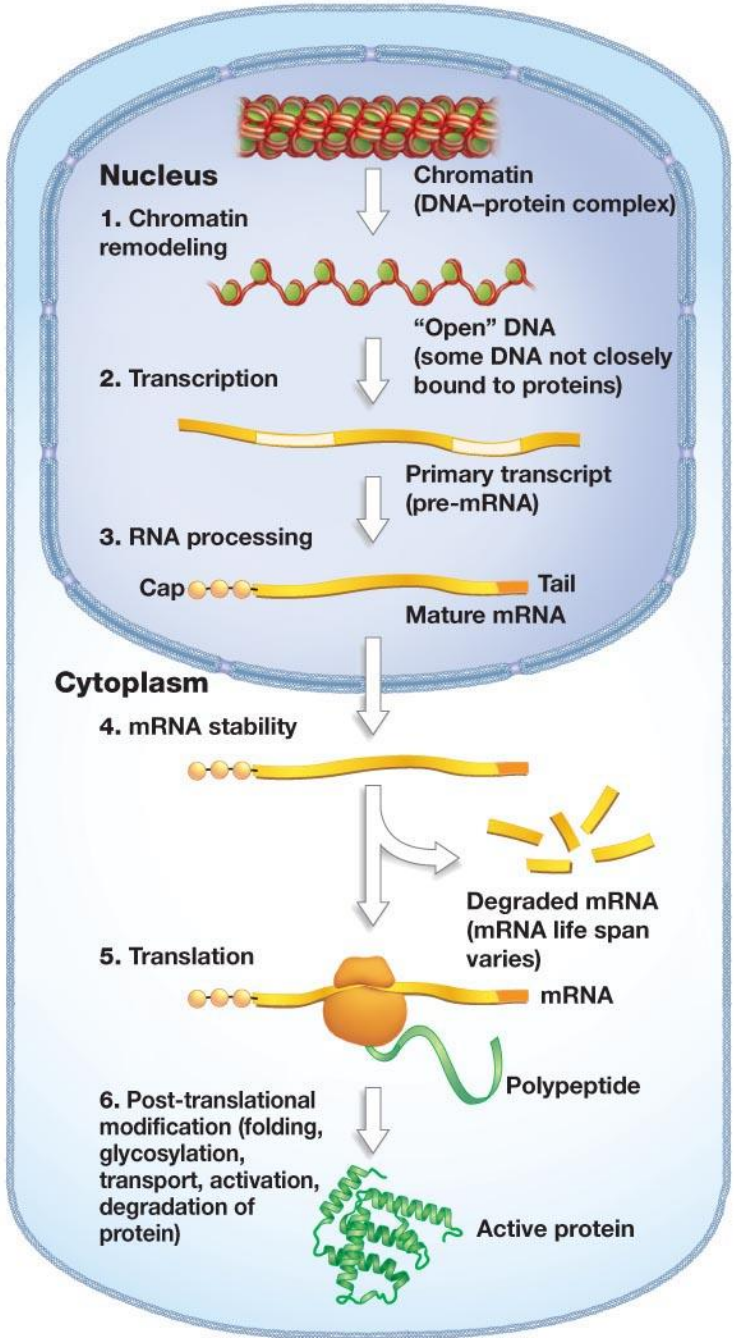
Introduction

Interfering with the genetic expression

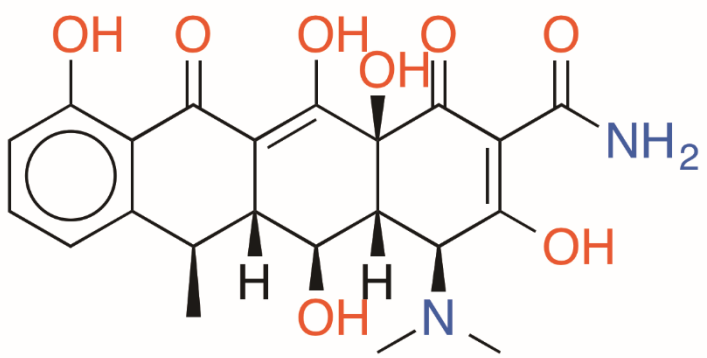
Almost all drugs work at the protein level:
Receptors - Enzymes



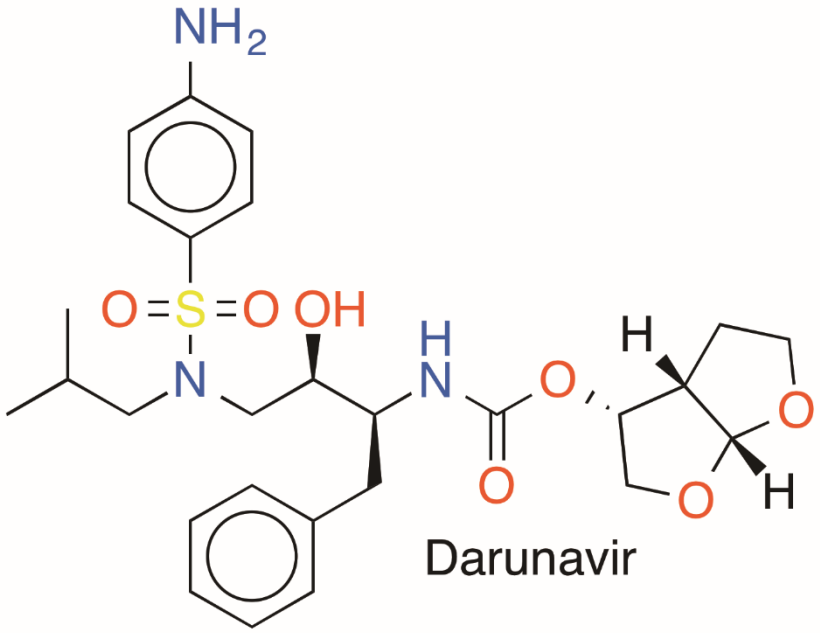
What about drugs acting at the level of translation?



Drugs acting at the level of translation



Doxycycline

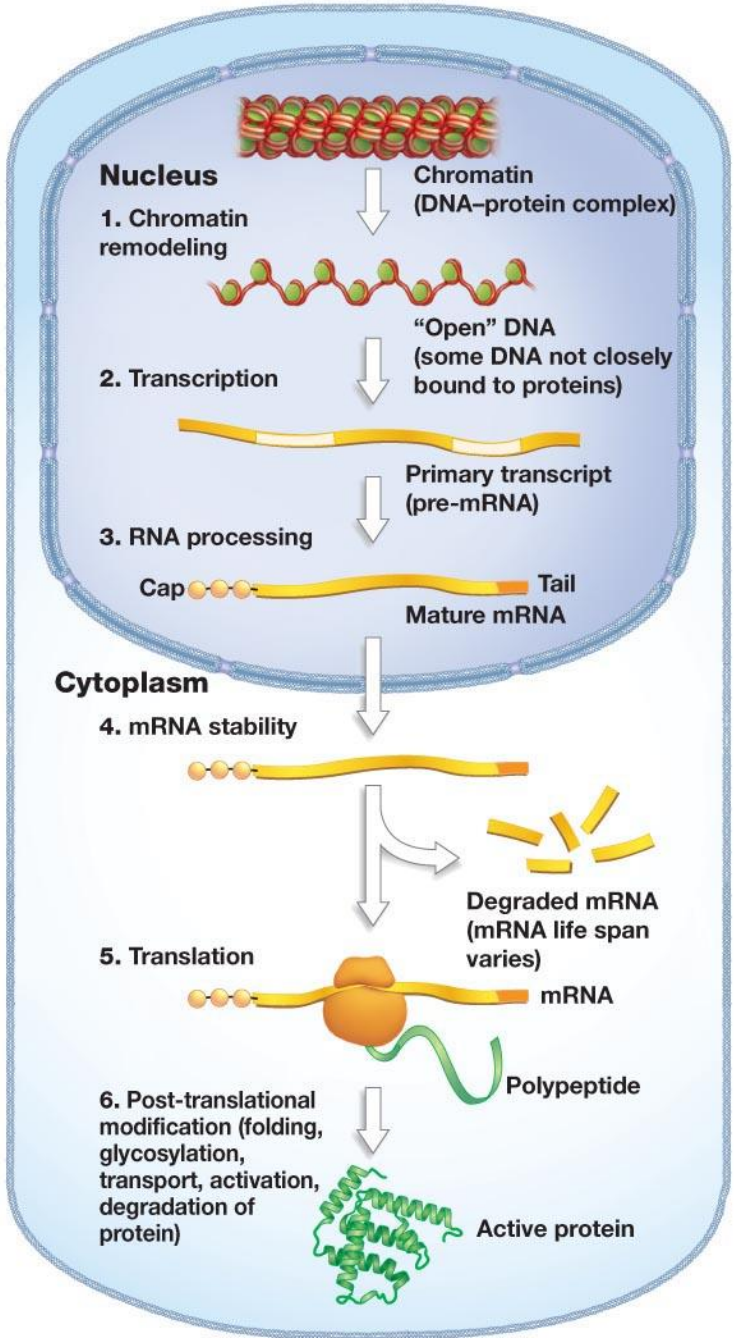


Darunavir

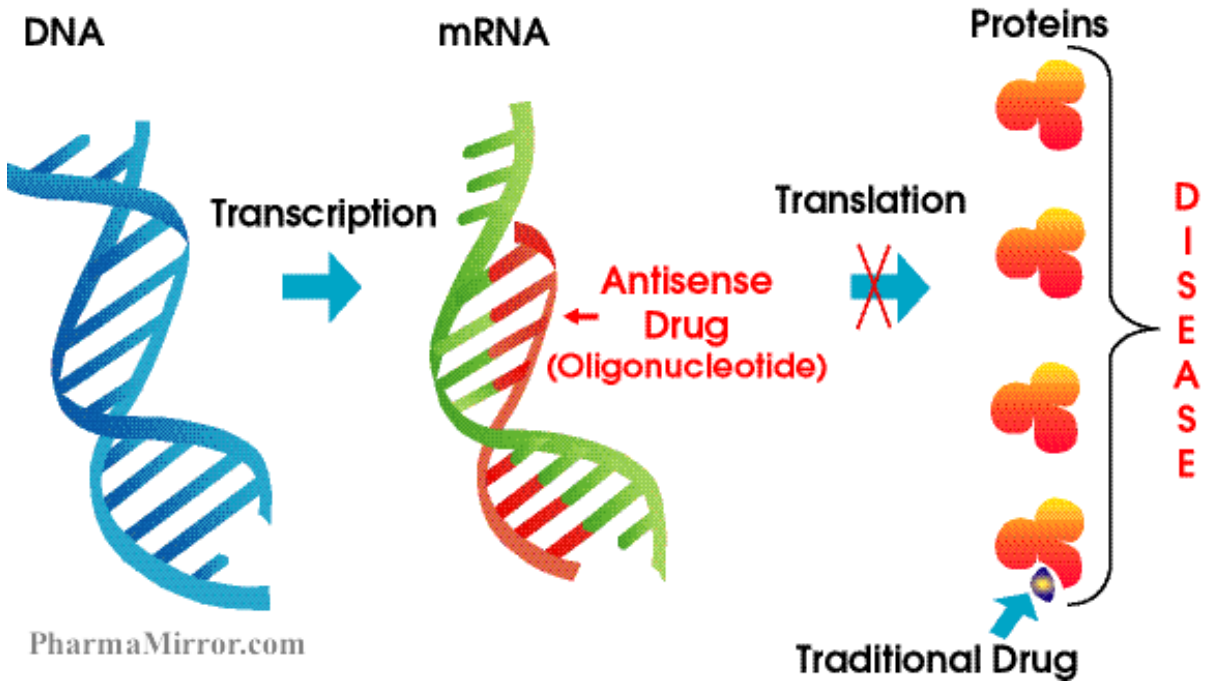
Inhibitor of bacterial protein biosynthesis by binding to bacterial ribosome

Inhibitor of HIV protease

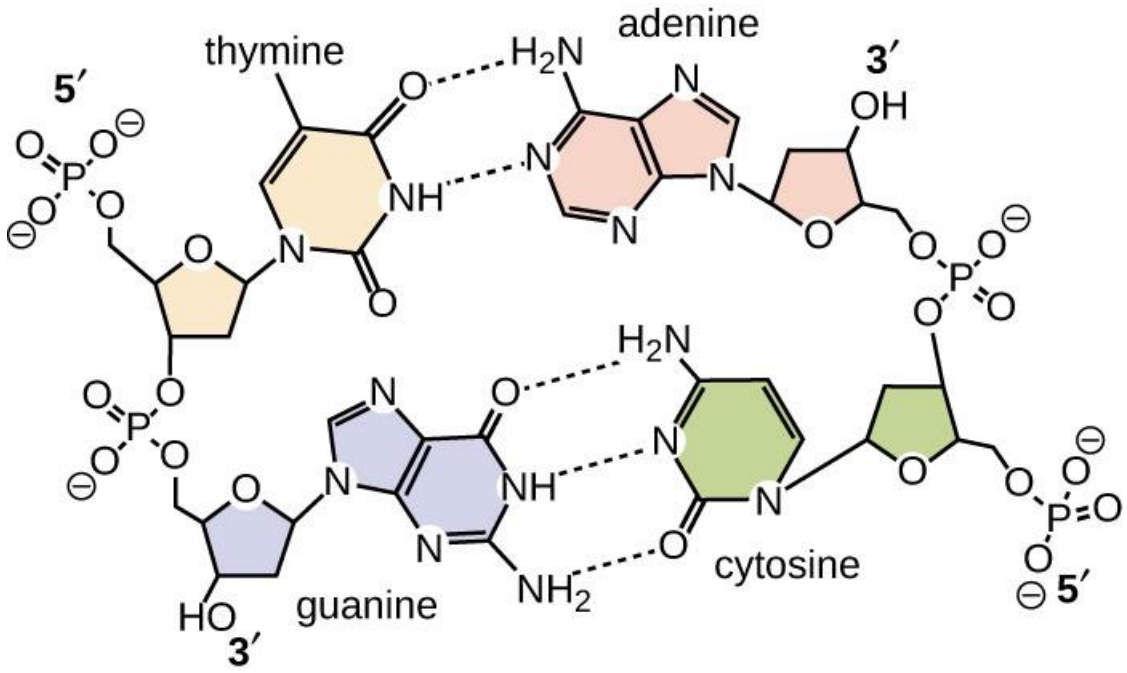
What about drugs acting at pre-mRNA or mRNA level?



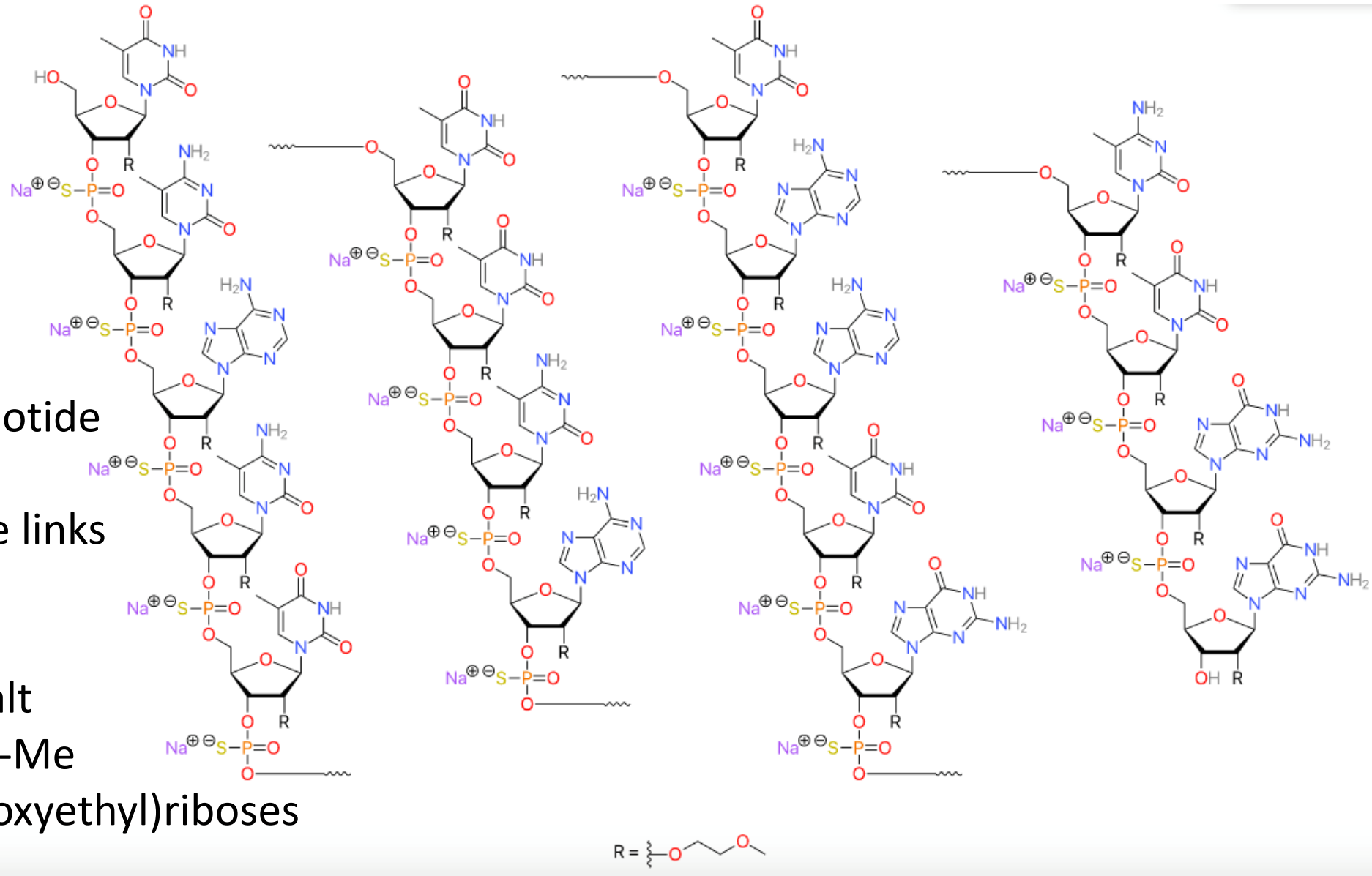
Drugs acting at pre-mRNA or mRNA level



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

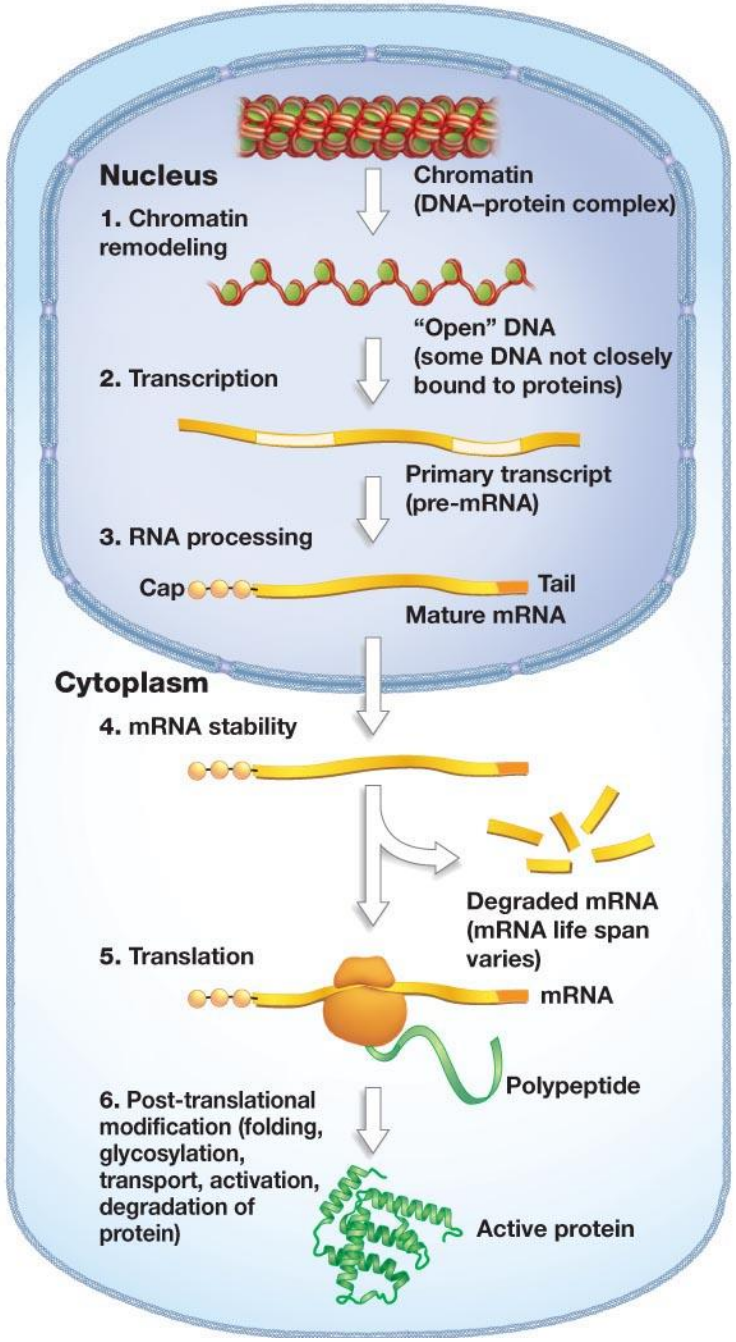


Spinraza® (Nusinersen) for spinal muscular atrophy



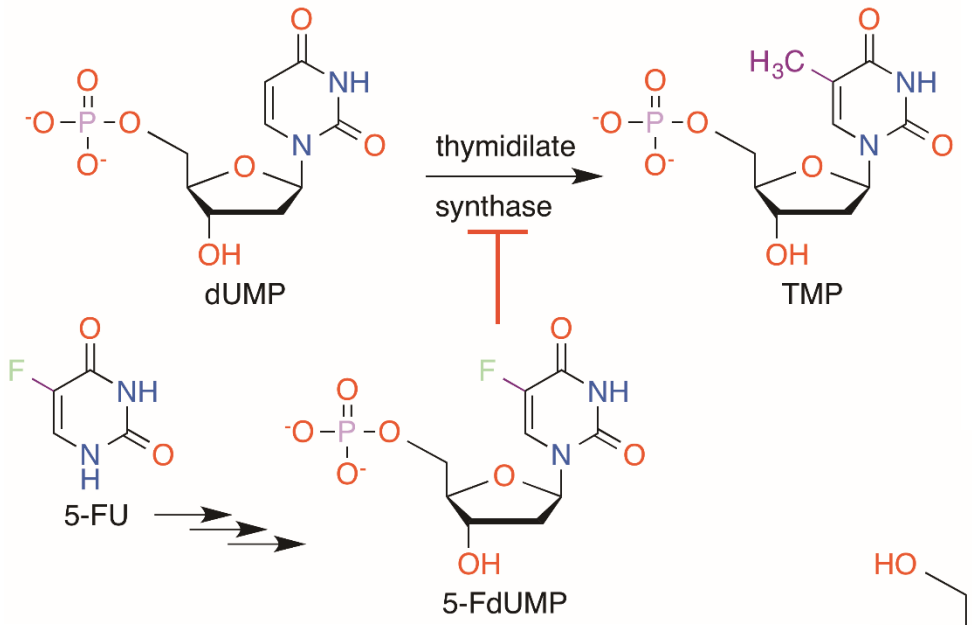
- Antisense oligonucleotide
- 18 nucleotides
- 17 phosphorothioate links
- 2^n diastereoisomers
  $= 2^{17} = 131072$
- Heptadecasodium salt
- All pyrimidines are 5-Me
- All are 2’-O-(2-methoxyethyl)riboses
- MW = 7501

What about drugs acting at DNA level?

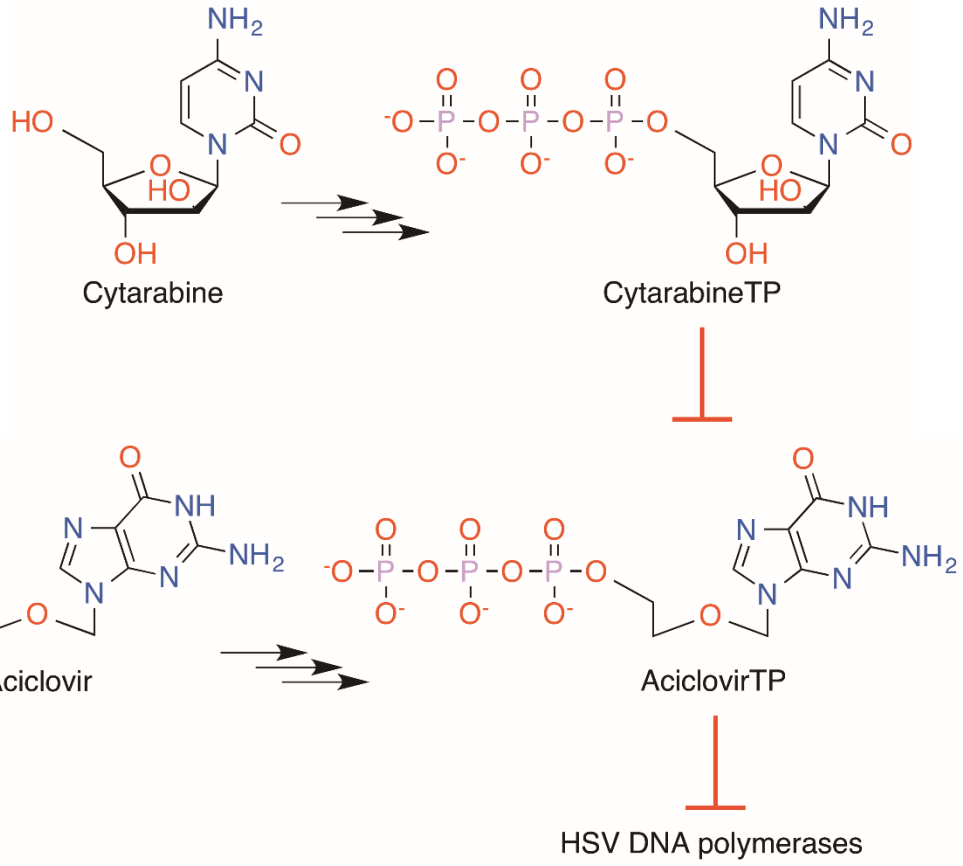


Drugs acting at DNA level

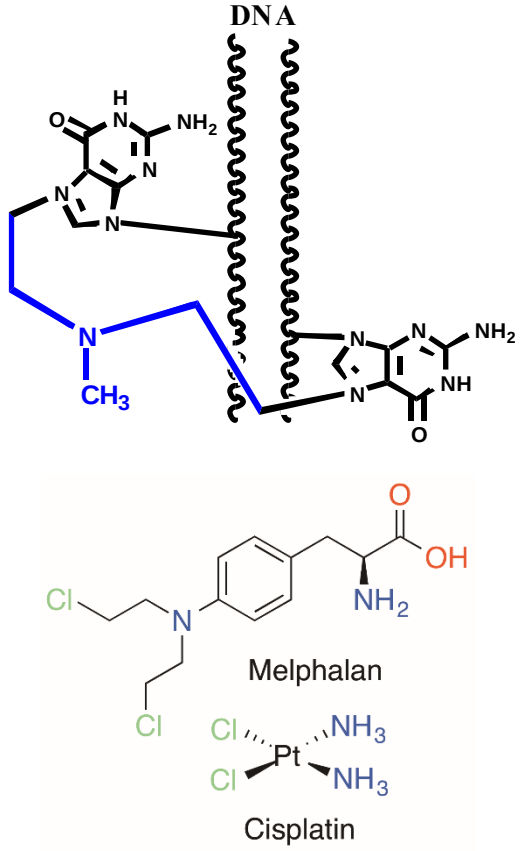
Synthesis of building blocks



Synthesis of DNA



DNA alkylation

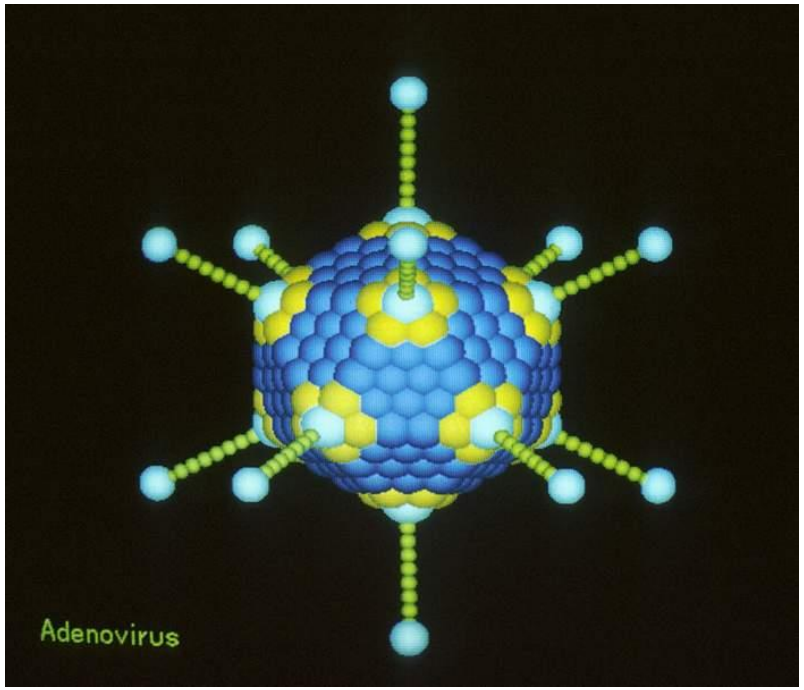


Drugs acting at DNA level

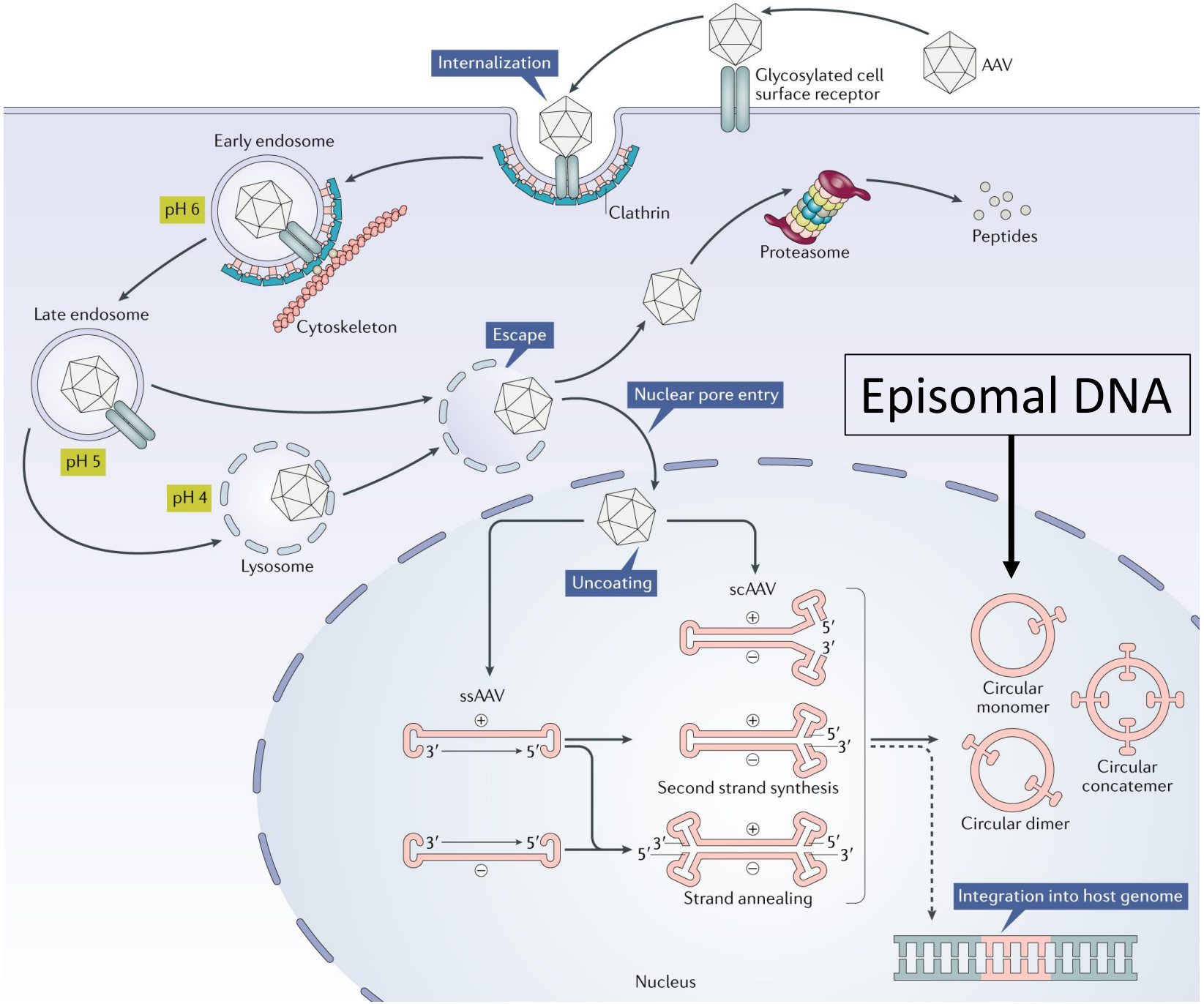
- Cytostatics in Oncology
  - Aselective interaction with DNA
  - Highly toxic
- Antiviral drugs
- Future?
  - Gene therapy
  - CRISPR/Cas

Gene therapy

- The therapeutic **delivery of nucleic acid** into a patient's cells as a drug to treat disease
- Adeno-associated virus (AAV) vectors are the leading platform
- AAV
  - Non-pathogenic member of the Parvoviridae
  - Single-stranded DNA
  - Icosahedral protein capsid
- Gene
  - Replacement: compensate for loss-of-function mutations
  - Silencing: tackle gain-of-toxicity mutations (RNAi)
  - Addition: e.g. to deliver therapeutic antibodies
  - Editing: repair mutations



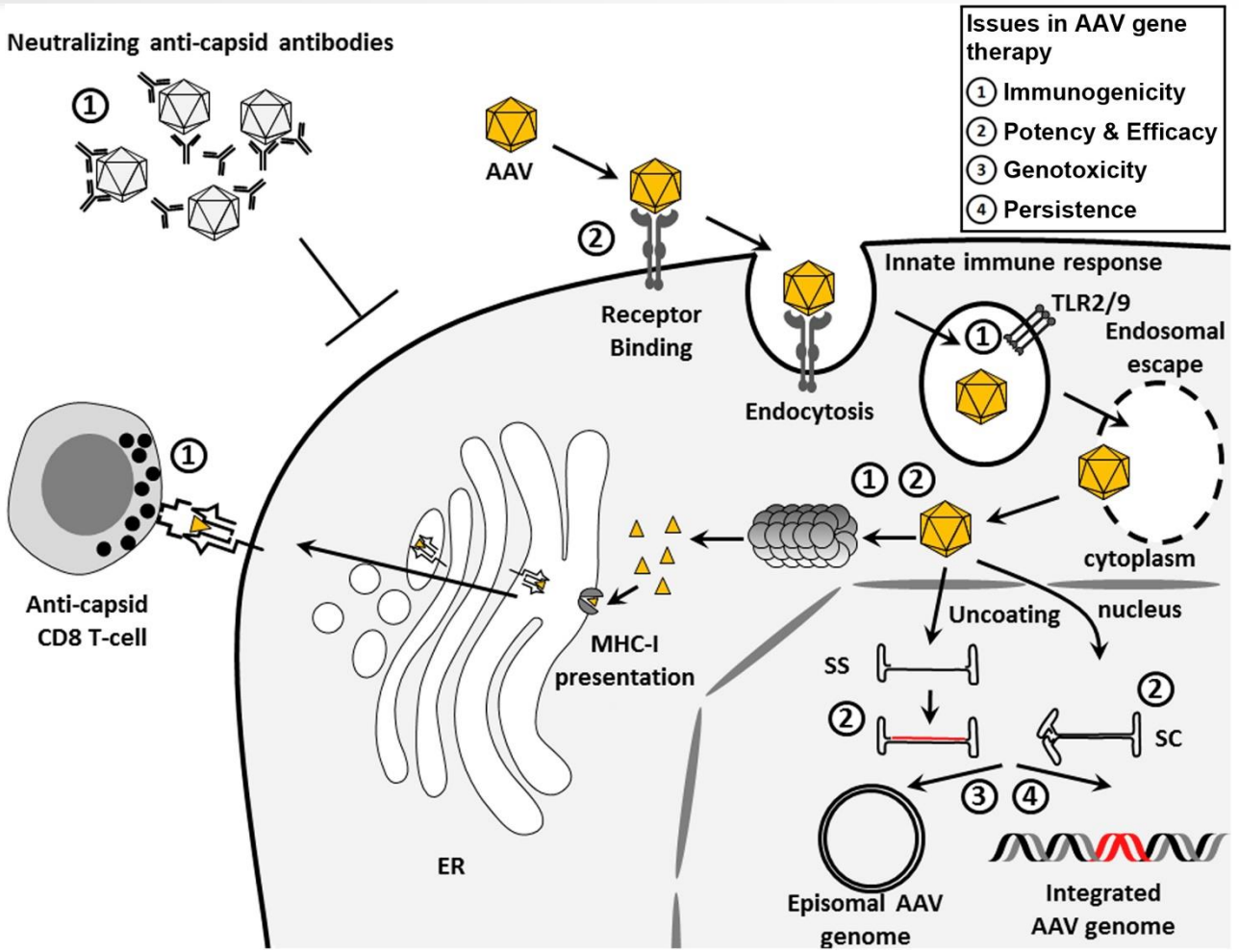
Recombinant AAV(rAAV) transduction pathway



Wang, D. et al.
Nature Reviews Drug Discovery
2019, 18, 358

Key challenges

- Large-scale vector manufacturing and cost
- Vector quality control
- Immunological barriers
  - NAbs from previous wtAAV infection
  - Immune response
- Efficacy
- Genotoxicity



Colella, P. et al. Molecular Therapy – Methods & Clinical Development, 2018, 8, 87

rAAV pipeline

- Glybera, EMA approved 2012, but stopped
  - Gene replacement, Lipoprotein lipase
- Luxturna, FDA approved 2017
  - Gene replacement, RPE65, to treat retinal dystrophy
- Zolgensma, FDA approved 2019
  - Gene replacement, SMN1, to treat spinal muscular atrophy
- Phase 3
  - Gene replacement, FVIII, Haemophilia A
  - Gene replacement, FIX, Haemophilia B

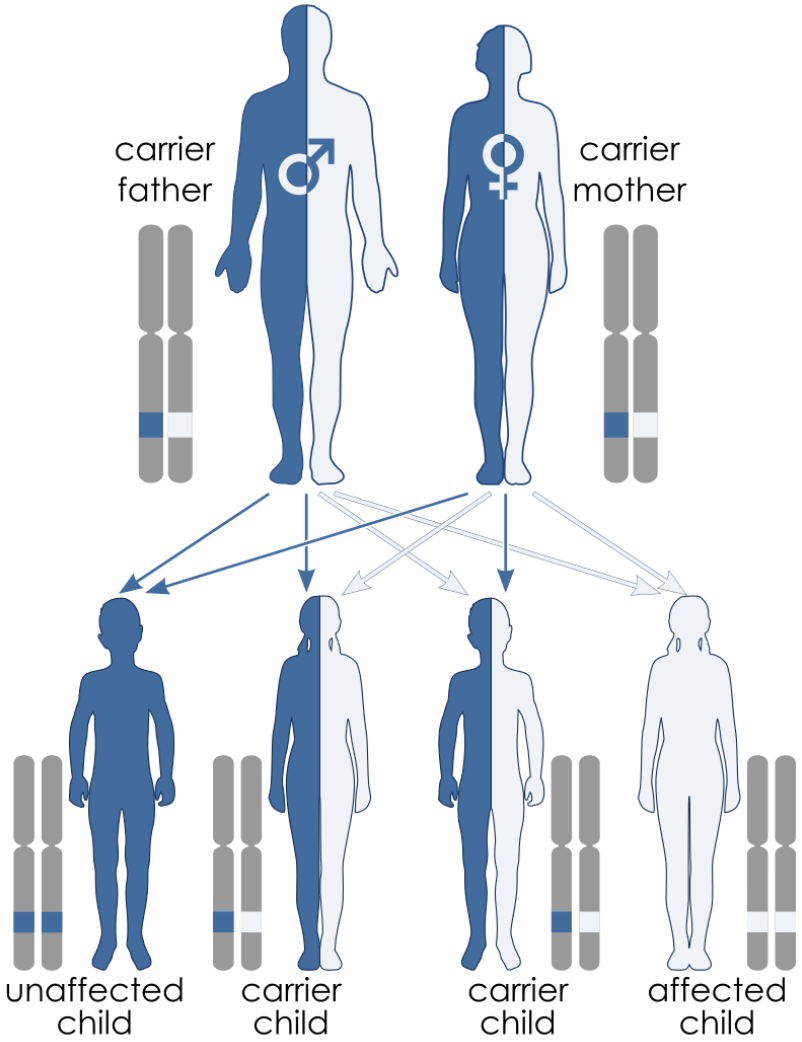
Content

- **Zolgensma®** (onasemnogene abeparvovec)
  - Spinal muscular atrophy (SMA)
- **The cost of medicines**
- **Ozempic®** (Semaglutide)
  - Type 2 diabetes

Spinal muscular atrophy (SMA)

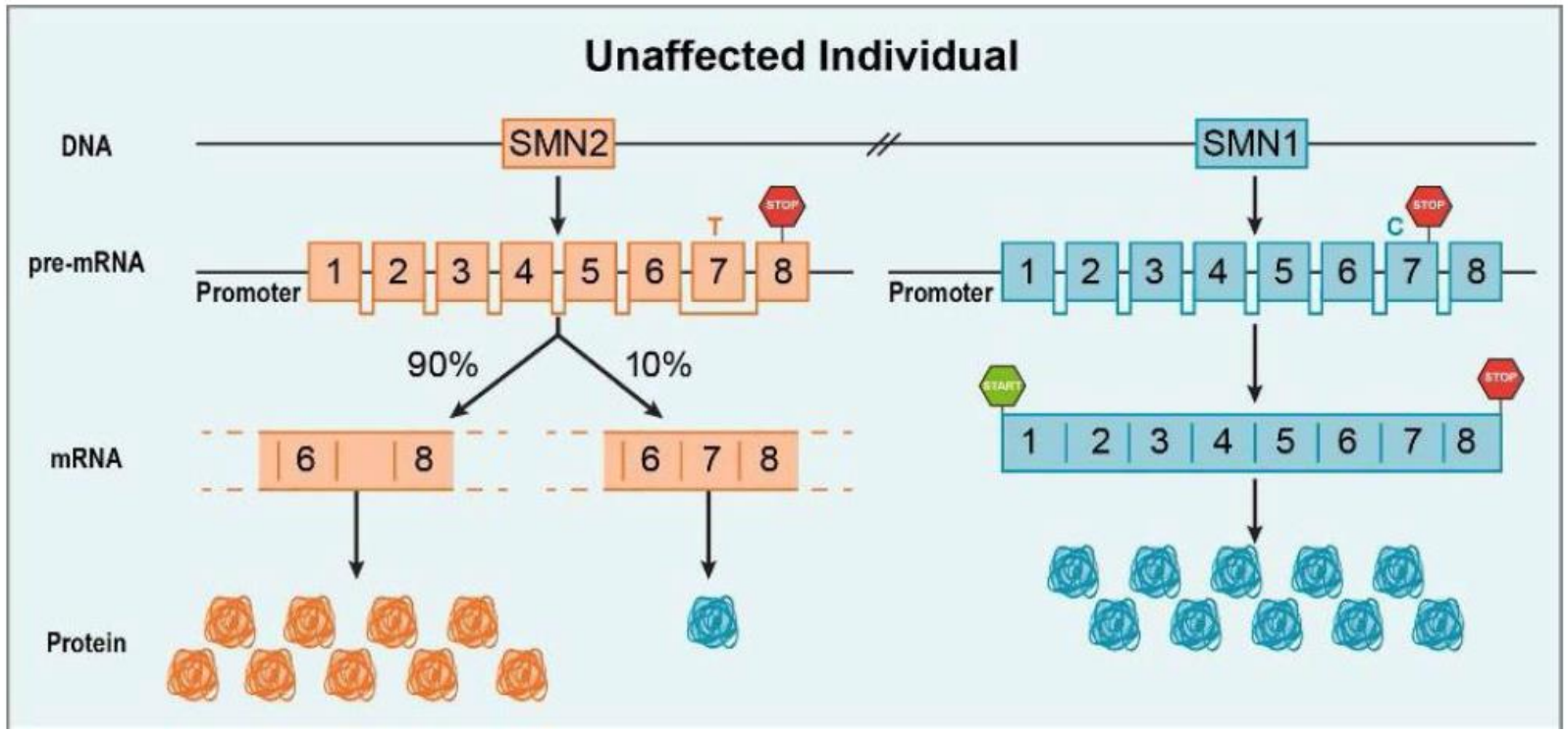
- SMA is **a rare genetic disease** characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in muscular atrophy
  - Progressive muscle wasting and mobility impairment
  - Proximal muscles (arm and leg) and respiratory muscles are affected first
- Genetic 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

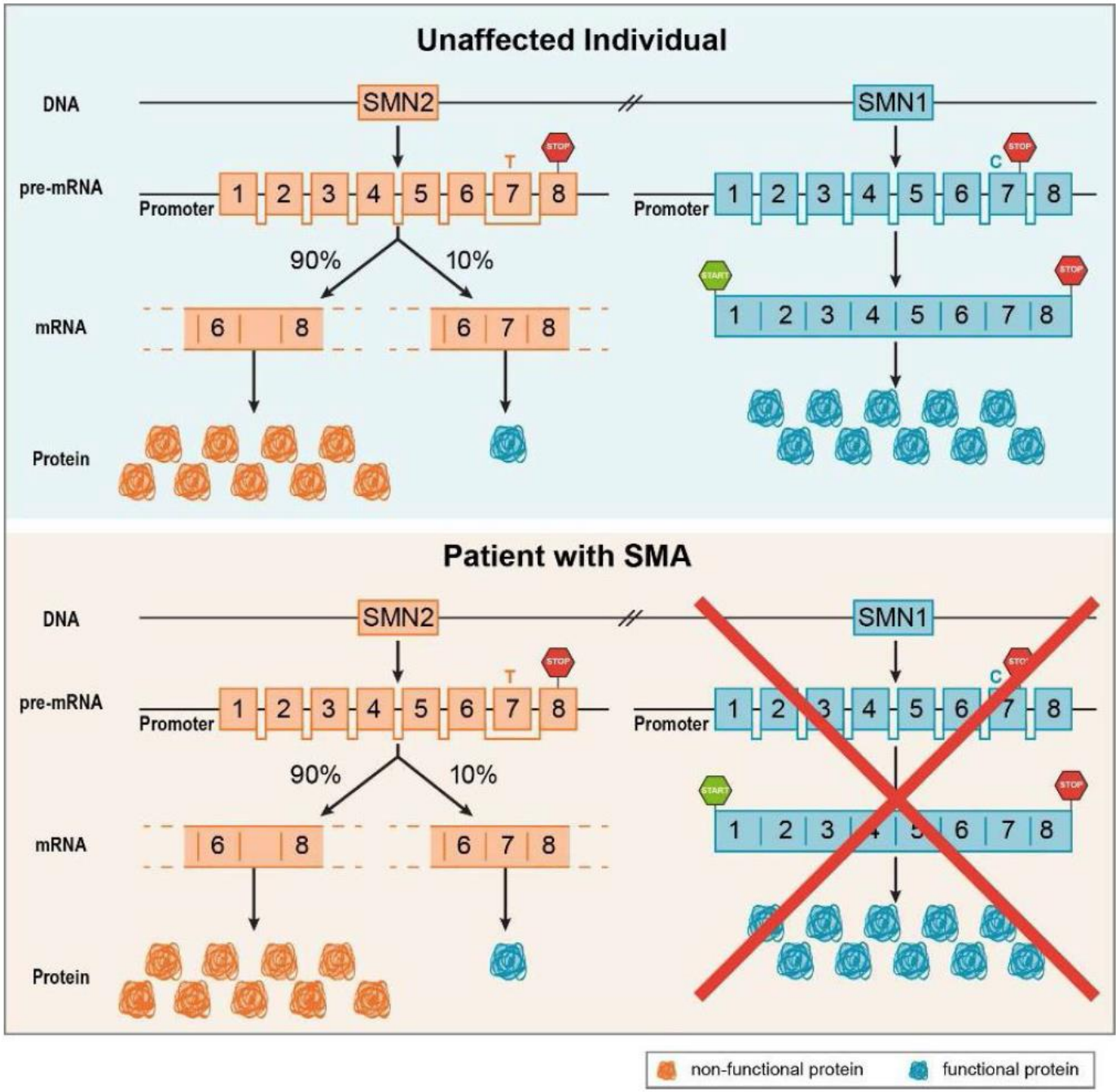
- **SMN1** results in functional SMN protein
- **SMN2** (5 to 11 nucleotides difference)
  - Can encode functional SMN with identical amino acid sequence
  - **BUT** a C-T substitution in **exon 7** favors skipping of that exon
  - mRNA lacking exon 7 leads to truncated, non-functional SMN protein

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)

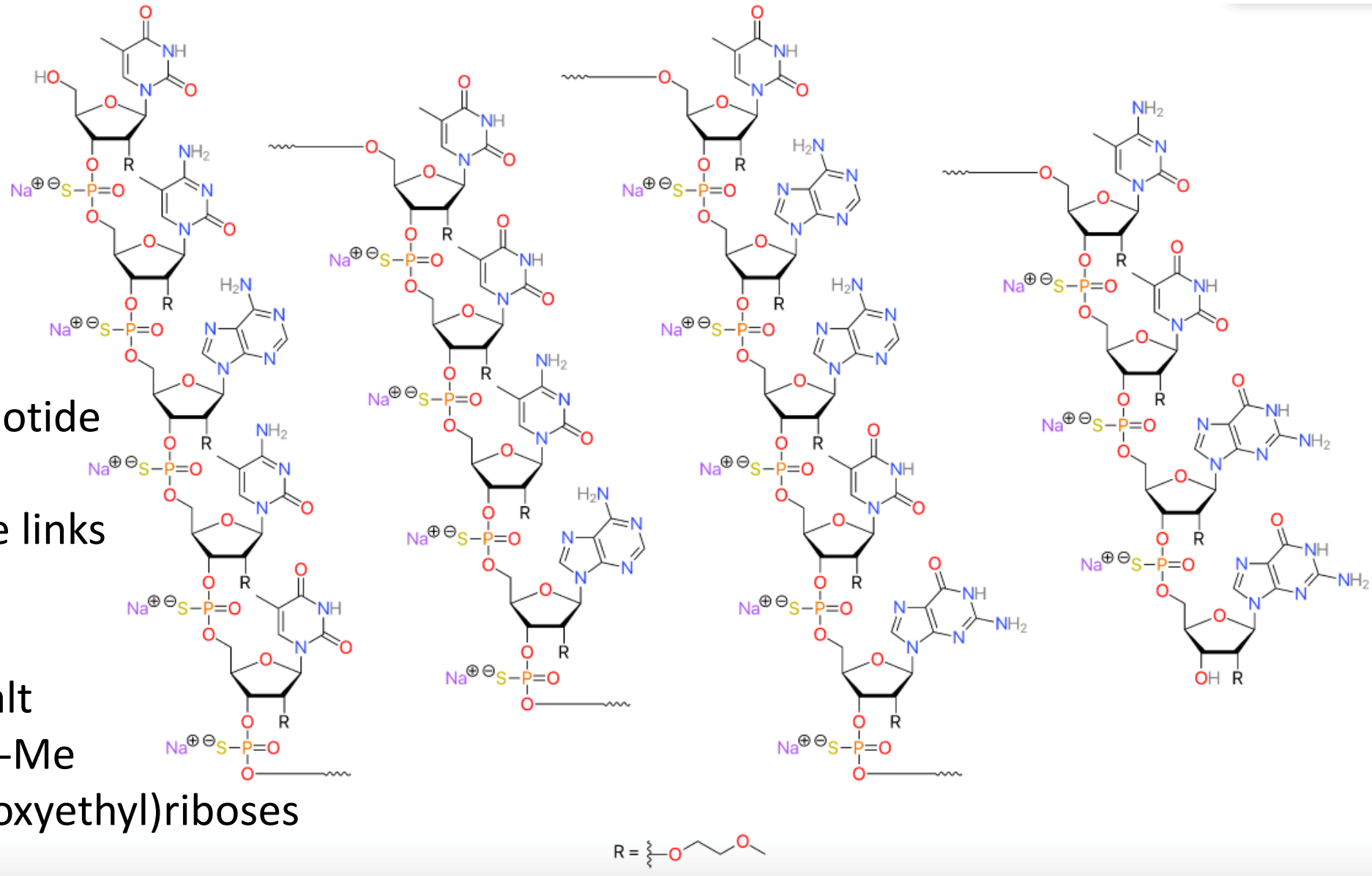
TYPE 3

- 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) for spinal muscular atrophy



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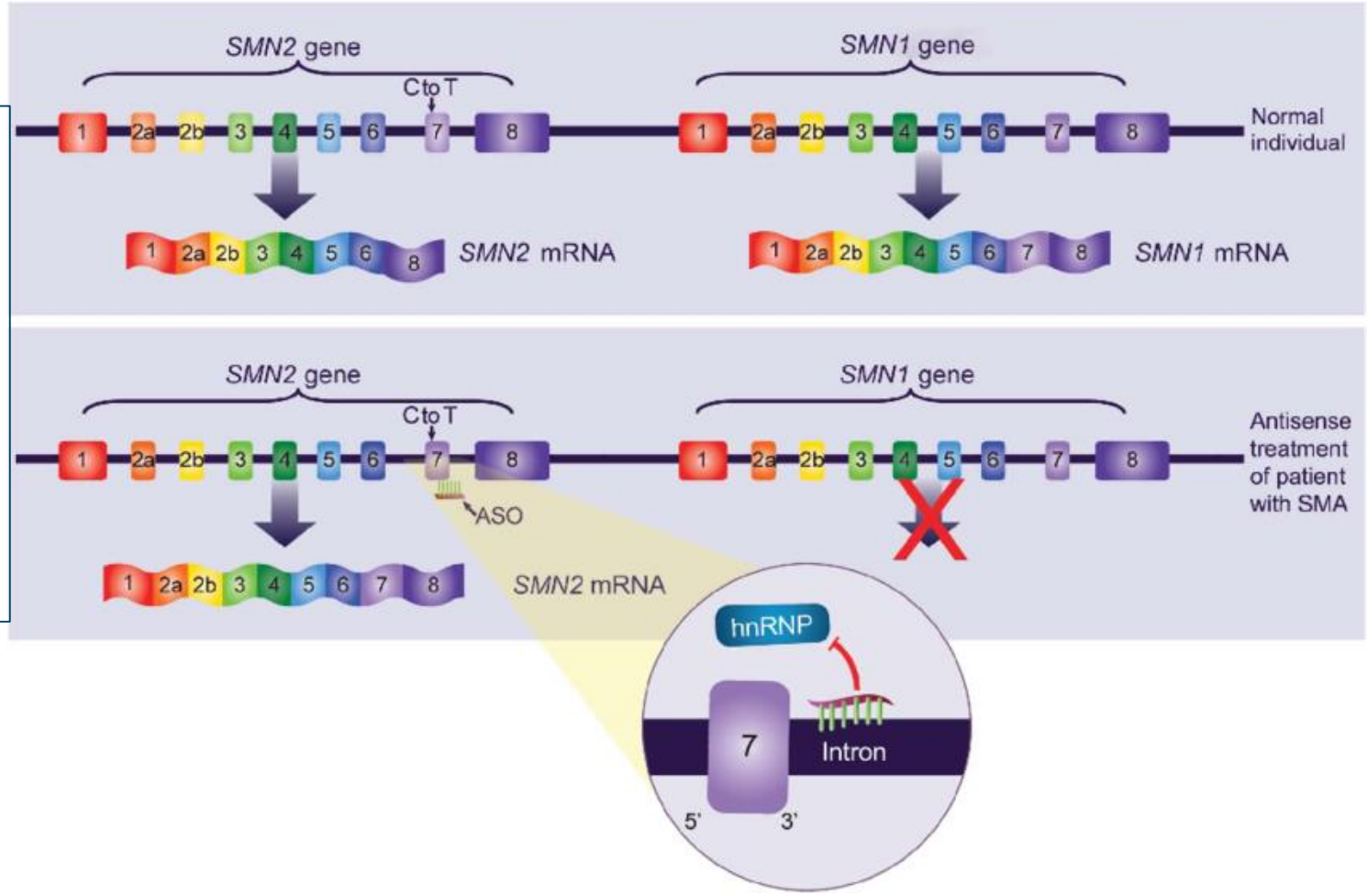
- Heptadecasodium salt
- All pyrimidines are 5-Me
- All are 2’-O-(2-methoxyethyl)riboses
- MW = 7501

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

Zolgensma® (onasemnogene abeparvovec)

- Pediatric patients less than 2 years of age
- Spinal muscular atrophy (SMA)
- bi-allelic mutations in the survival motor neuron 1 (SMN1) gene
- AAV9 with a fully functional copy of SMN1
- Only one injection needed
- No long term results yet
- Warning for severe liver injury
- Patients with preexisting immunity to AAV9 are excluded

Zolgensma®: ongoing phase 3 clinical trial data

- 21 patients
  - Mean age = 3.9 months
  - SMA before 6 months and 2 copies of SMN2 (type 1 SMA)
  - No AAV9 antibodies
  - A single dose via intravenous infusion
- Clinical endpoints
  - 19 were still alive

Endpoints	Phase 3 (N = 21)	Natural history control (N = 23)
Survival at 14 months of age	13 (67%) only 13 had reached the age of 14 months	25%
Sitting without support for > 30 seconds at 18 months	10 (47%)	0%

Content

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  - Spinal muscular atrophy (SMA)
- **The cost of medicines**
- **Ozempic®** (Semaglutide)
  - Type 2 diabetes

Waarom is het medicijn dat Pia's leven kan redden zo peperduur?

'Het voelt akelig als we we de waarde van een mensenleven in geld proberen uit te drukken'

'Ons systeem kan geen honderden Pia's aan'

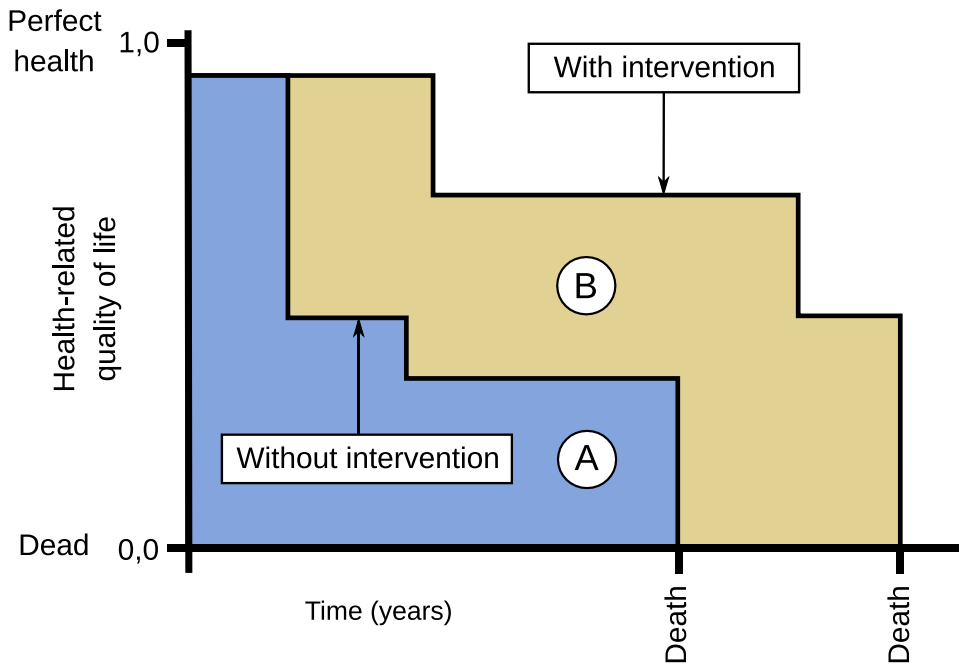
Ruim 970.000 sms'jes en meer dan 1,9 miljoen euro: geld om baby Pia te redden is binnen!

The prices for Zolgensma® and Spinraza®

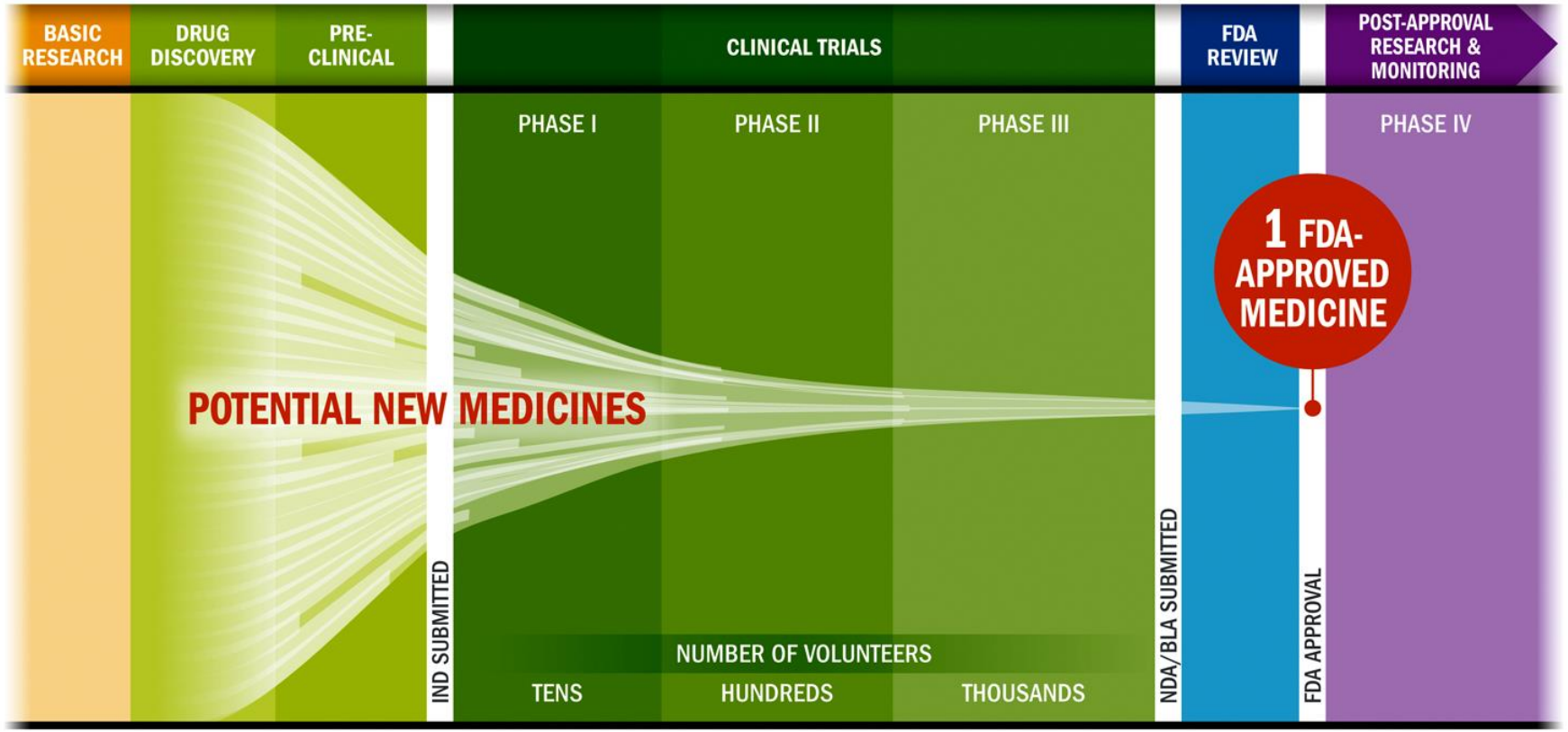
- Spinraza®
  - 88.3K EURO/year
  - First year: 529.8K EURO
  - Following years: 264.9K EURO
  - After 6 years: 1.85M EURO
- Zolgensma®
  - 1.9M EURO once
  - Novartis acquired AveXis for 7800M EURO in 2018

Factors determining the price of medicines

- Production costs
- Research and development costs
- Patent exclusivity (driver for innovation)
- Return on investment
- Market size, the blockbuster model
  - Cheap drugs for many patients
- Competition
- The Orphan Drug Act
  - For rare, deadly diseases
  - Longer patent protection, shorter approval, tax reduction
- What is the cost without intervention?
- Value-based pricing
  - Quality-adjusted life year (QALY)
  - 1 QALY = 1 year in perfect health
  - 1 QALY = 50K to 150 K USD, 40K Euro in Belgium ???
- Ethical and political considerations
  - Rule of rescue: for individuals in high need
  - Emotions, political suicide



Challenges in drug discovery & development



LONG

> 13 years

EFFICIENCY

COSTLY

> $ 2.6 billion

Factors driving R&D costs

1. Out-of-pocket costs
2. Success rates
3. Developments times
4. Cost of capital
   - 11%

R&D costs of the different phases

- Drug Discovery
  - Target-to-hit
    - 1M USD, 80%, 1 year
  - Hit-to-lead
    - 2.5M USD, 75%, 1.5 years
  - Lead optimization
    - 10M USD, 85%, 2 years
  - Preclinical
    - 5M USD, 69%, 1 year
- Drug Development
  - Phase 1
    - 15M USD, 54%, 1.5 years
  - Phase 2
    - 40M USD, 34%, 2.5 years
  - Phase 3
    - 150M USD, 70%, 2.5 years
  - Submission to launch
    - 40M USD, 91%, 1.5 years

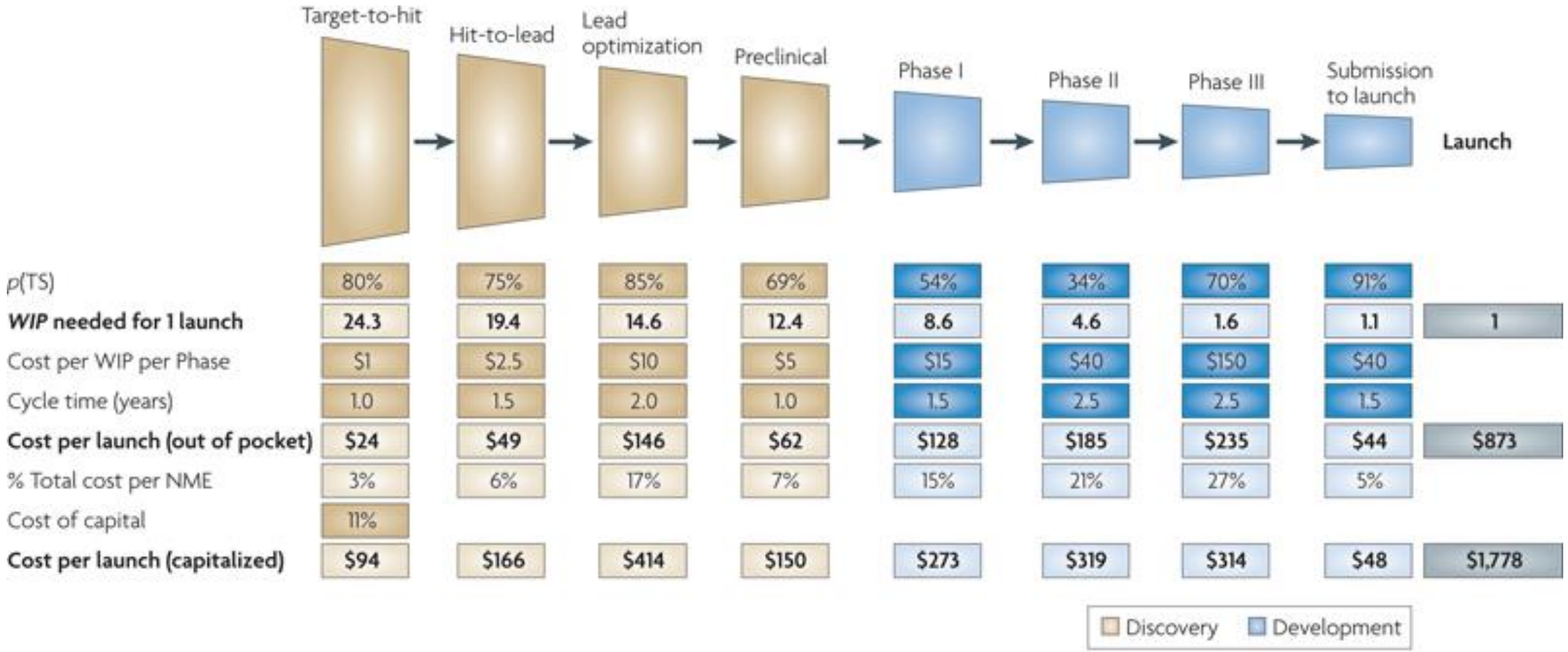
R&D costs of the different phases

- Global success rate
  - 4.12%
  - 24.3 projects need to be started to get 1 drug on the market
- Total development time
  - 5.5 years drug discovery
  - 8 years drug development
  - 13.5 years in total

How to calculate total costs?

- E.g. for target-to-hit
  - 1M USD cost per project
  - But 24.3 projects need to be started
  - So 24.3M USD out-of-pocket cost
- But cost of capital 11% per year for 13.5 years
  - So 94M USD capitalized cost
- Total costs
  - 873M USD out-of-pocket cost
  - 1778M USD capitalized cost
  - Currently estimated at **2600M USD** capitalized cost

R&D costs per approved NME

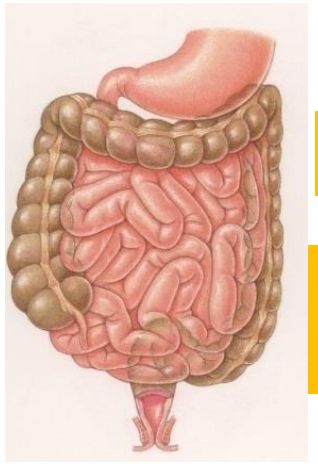


Paul, S.M. et al. Nature Reviews Drug Discovery, 2010, 9, 203

Introduction

Type 2 diabetes: physiology

Carbohydrates
Amino Acids
Fats



intestines

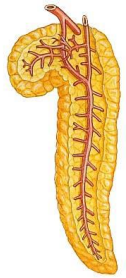
Glucose

Neurotransmission

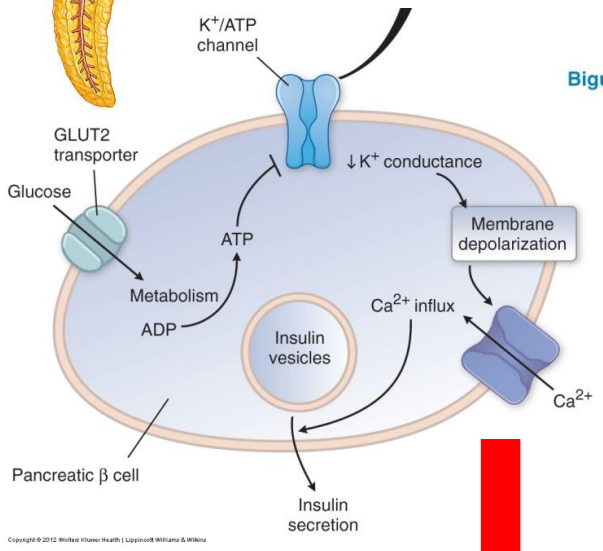
Incretin Hormones
GLP-1

enteroinsular axis

Less insulin



pancreas

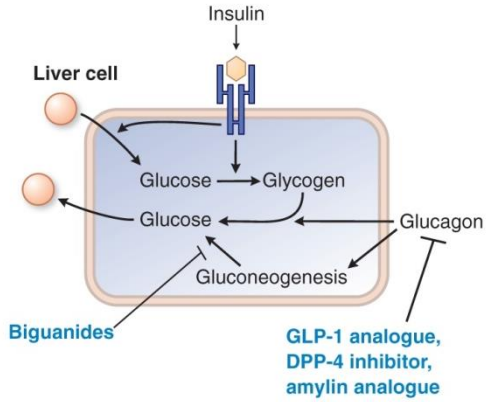


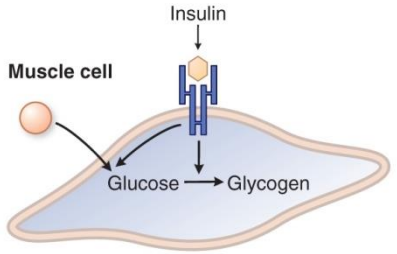
β-cell

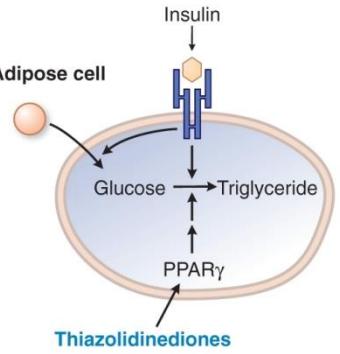
Insulin

Insulin resistance

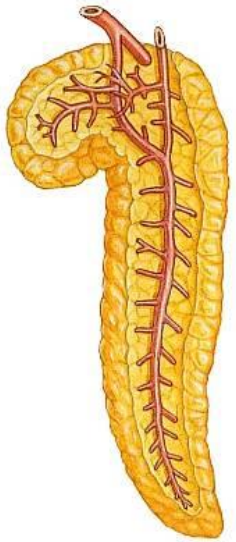
Peripheral tissues

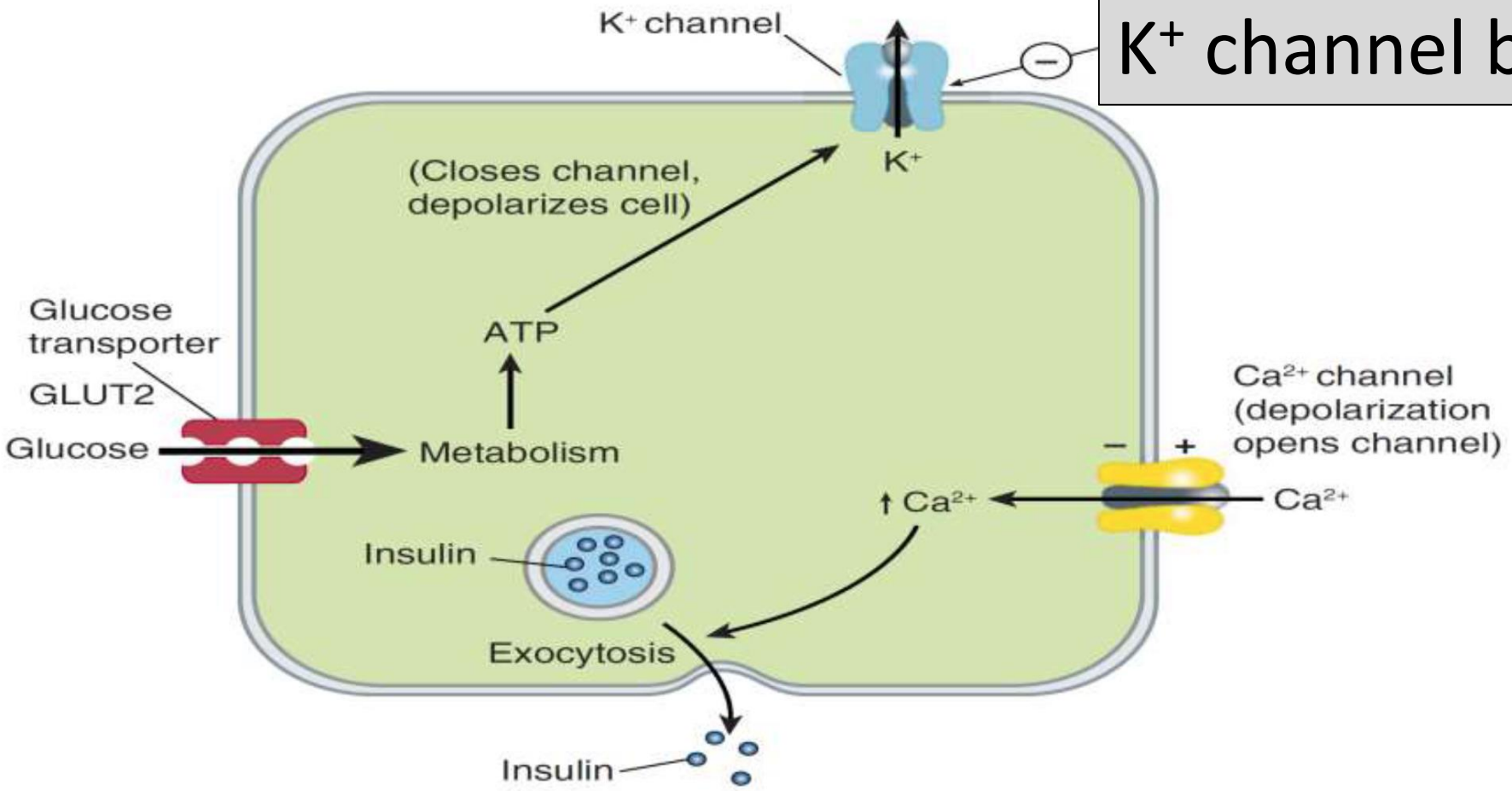






Target: ATP-sensitive K^+ ion channel

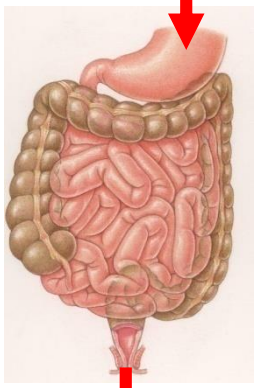




K^+ channel blockers

Targets: GLP-1 (glucose dependent) and DPP4

Meal



L-cells

Active GLP-1

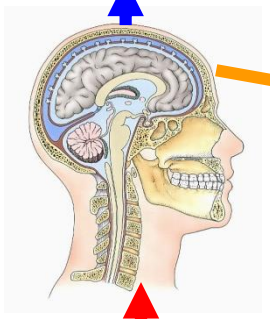
His — Ala — Glu

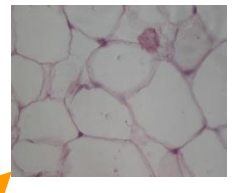
DPP4

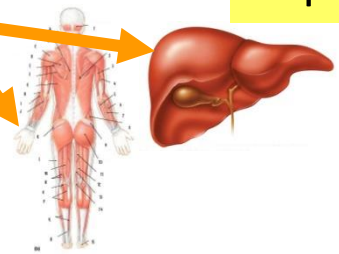
Glu

85% inactive GLP-1

↑ Satiety

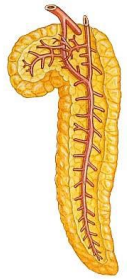




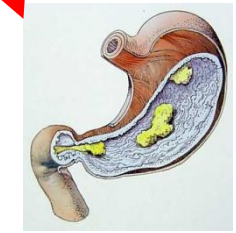


↑ Glucose uptake
↑ Glycogen synthesis
in peripheral tissues

Stable GLP-1
receptor agonists



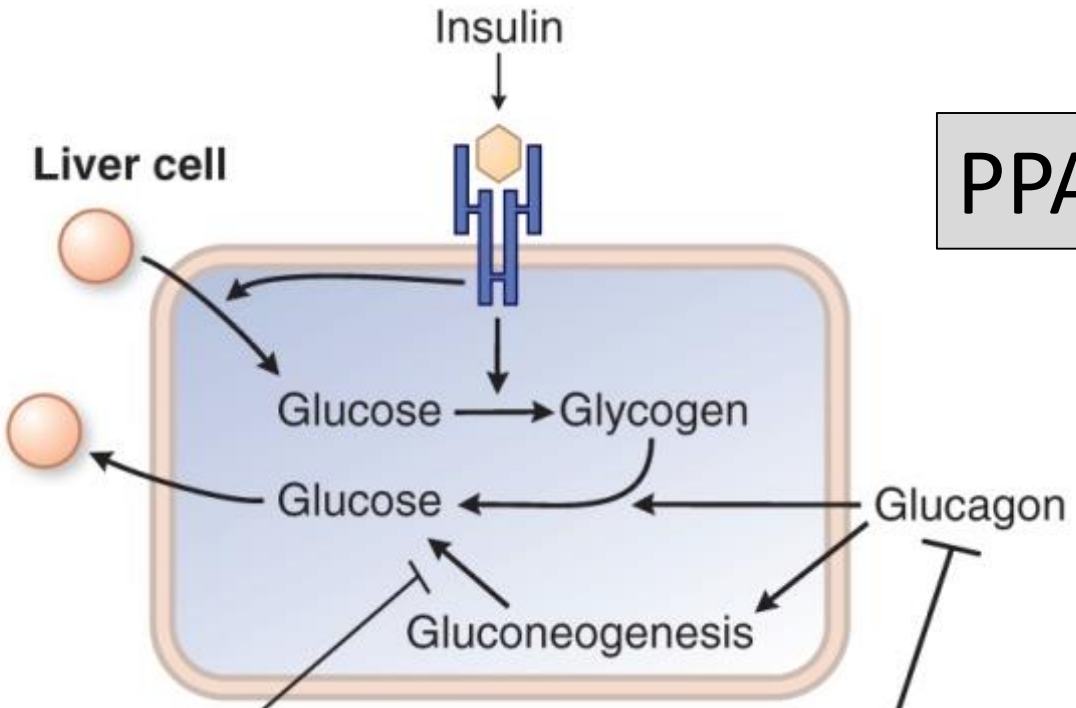
↑ Insulin secretion
↓ Glucagon secretion
↑ β-cell mass



↓ Gastric emptying

DPP4 inhibitors

Targets: insulin resistance in the liver

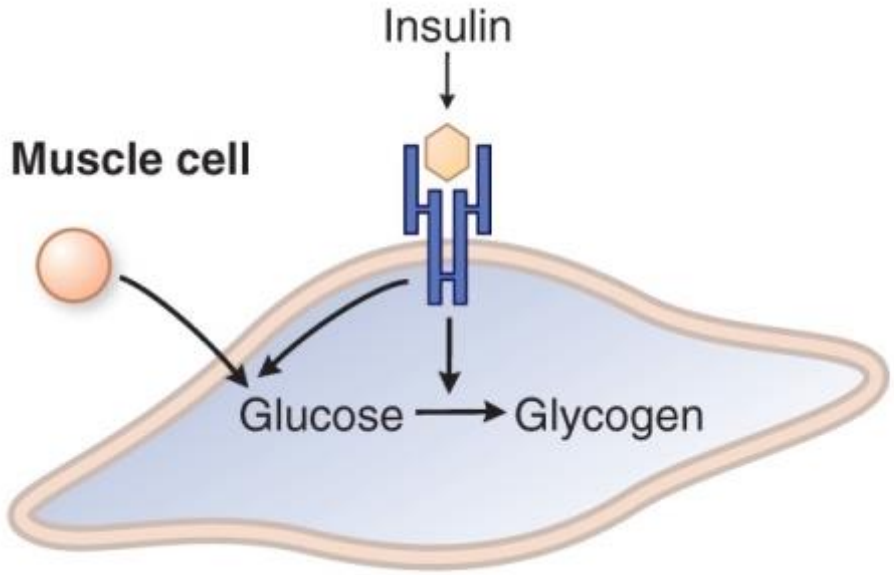


PPARγ agonists

metformin

Decreased glucagon secretion from pancreatic α-cells
GLP-1 RA and DPP4 inh

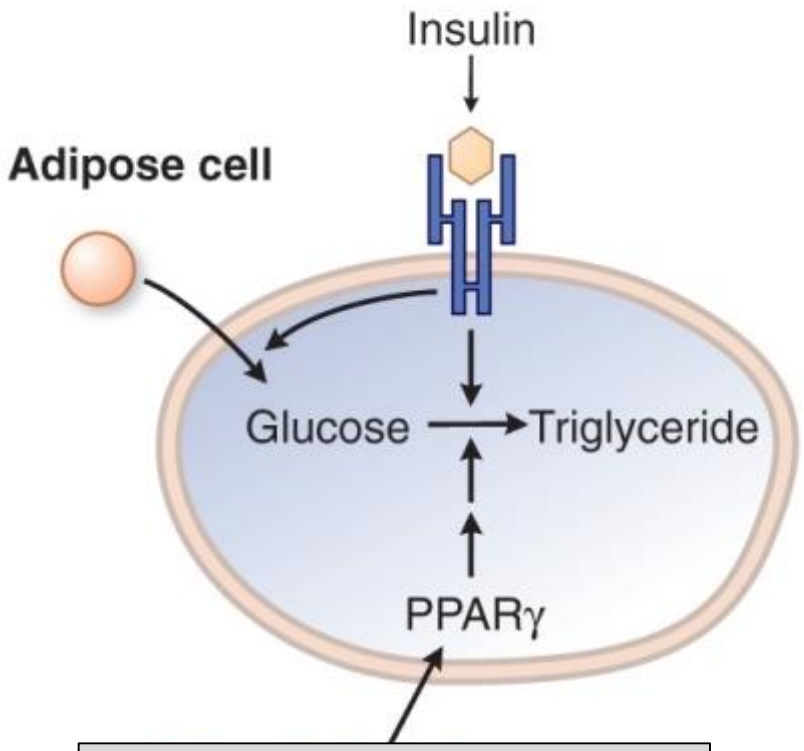
Target: insulin resistance in skeletal muscle



PPARγ agonists and metformin:

Increase glucose uptake

Target: insulin resistance in adipocytes

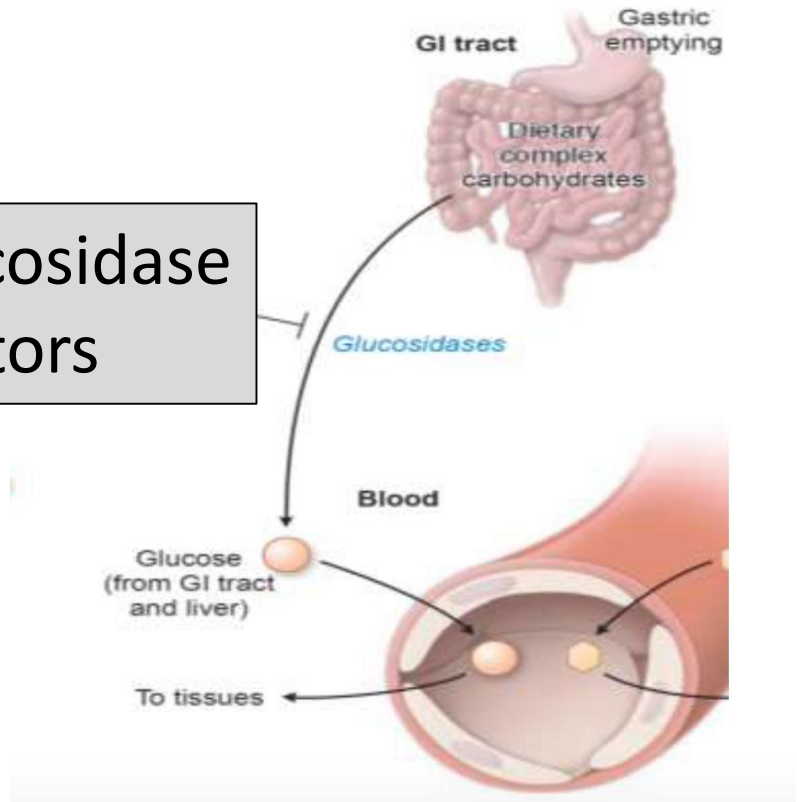


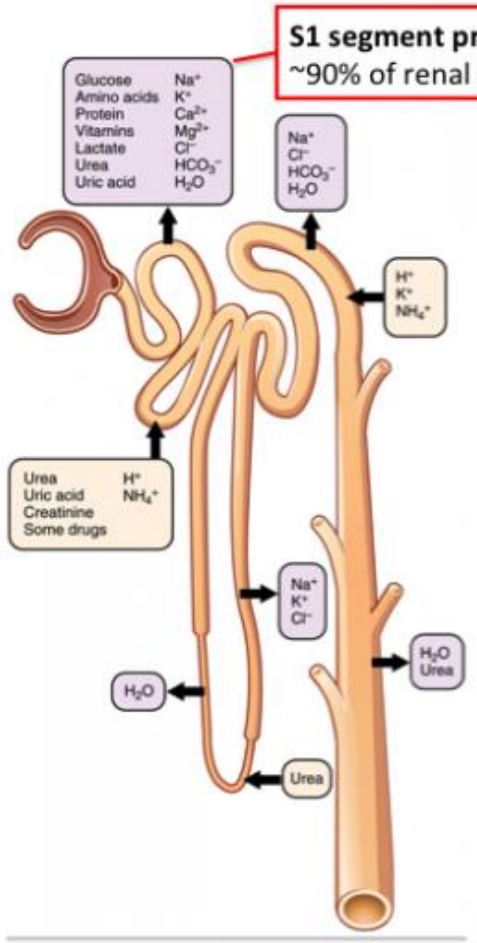
metformin:

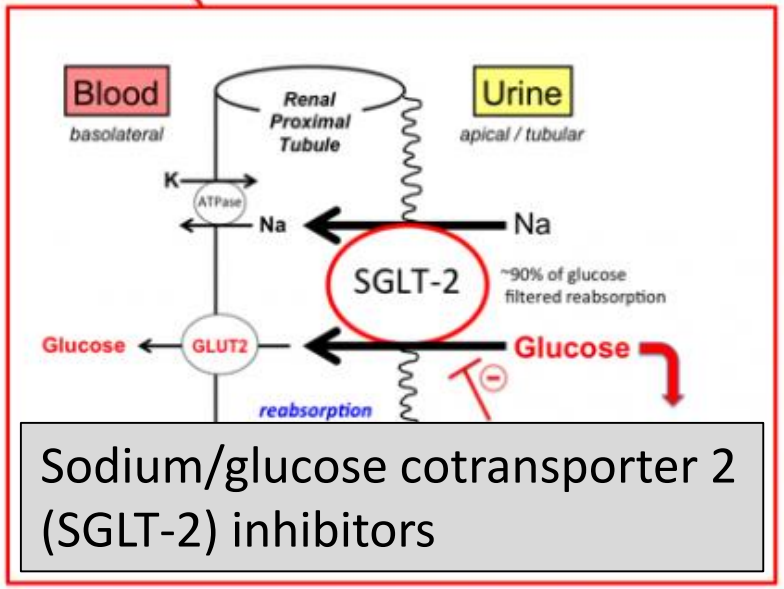
Increase glucose uptake

Targets: decrease glucose uptake and increase glucose excretion

α-glucosidase inhibitors

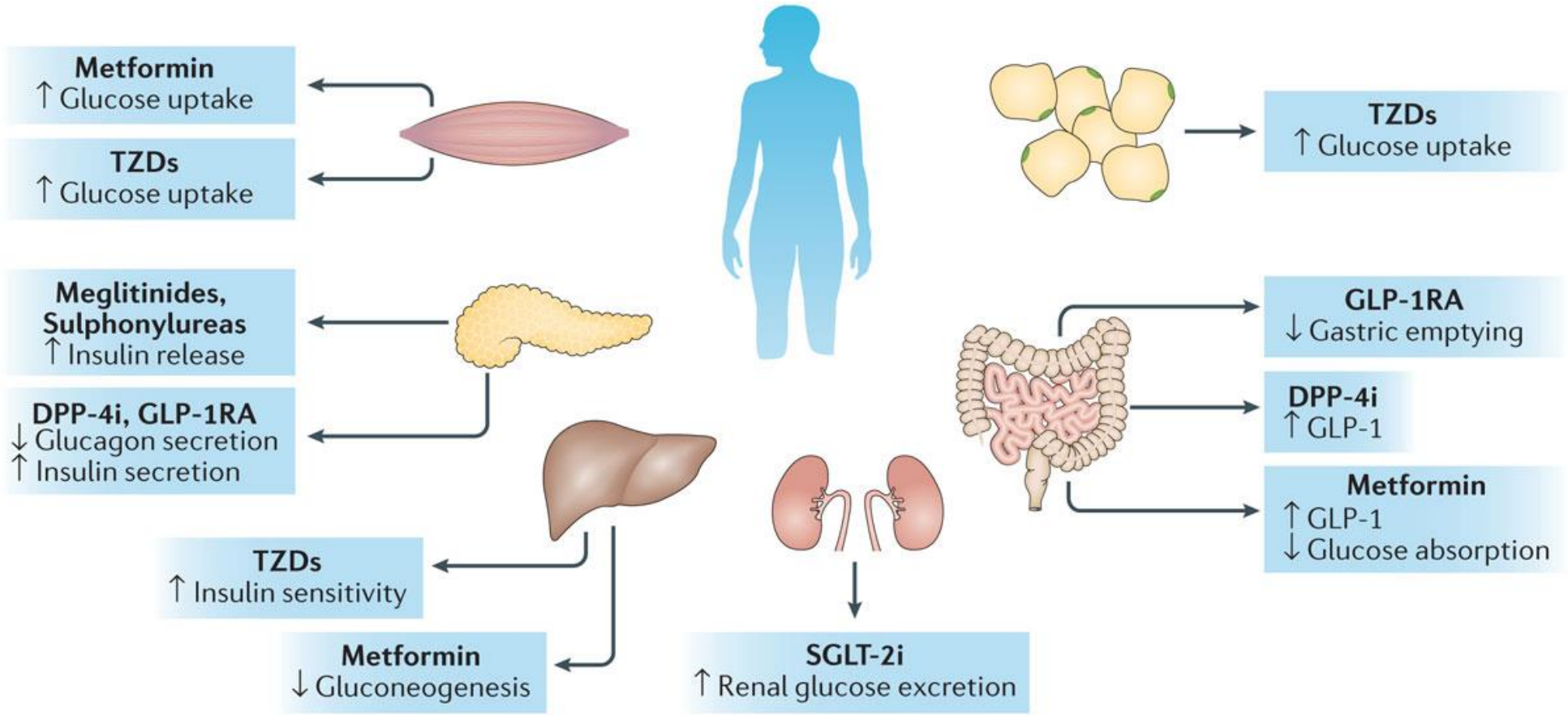






Sodium/glucose cotransporter 2 (SGLT-2) inhibitors

Targets: summary



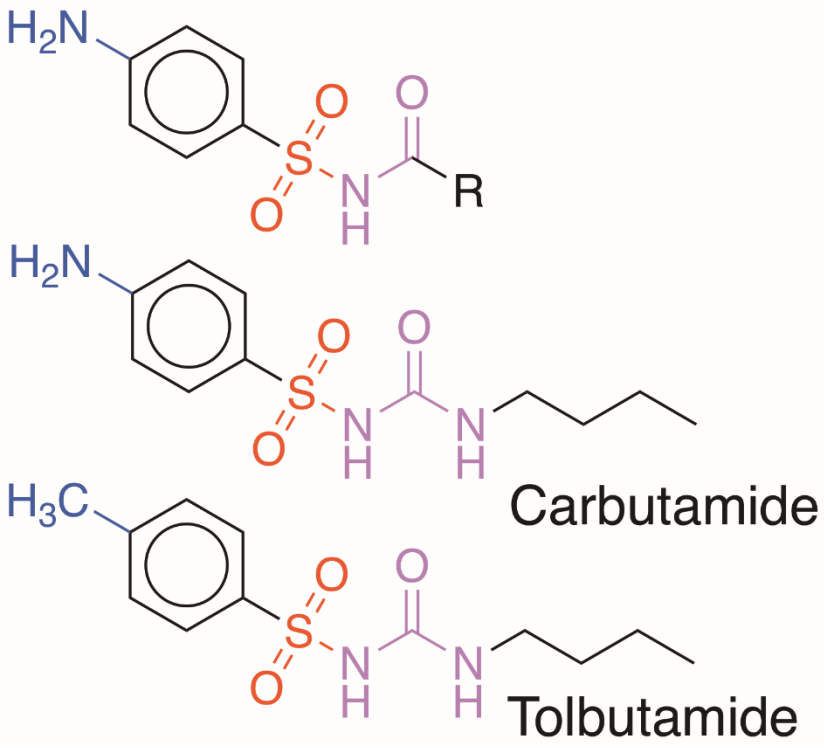
Nature Reviews | Endocrinology

Zhou. K. et al. Nat. Rev. Endocrinol. 2016, doi:10.1038/nrendo.2016.51

Classification of drugs

- Insulin deficiency
  - K^+ channel blockers: **sulfonylureas and glinides**
  - **Insulin** (exogenous)
- Insulin resistance
  - **Metformin**
  - PPARγ agonists: **glitazones**
- Decreased uptake, increased excretion
  - α-glucosidase inhibitors: **acarbose**
  - SGLT-2 inhibitors: **gliflozines**
- Incretins
  - GLP-1 receptor agonists: **incretin mimetics**
  - DPP4 inhibitors: **gliptins**

Sulfonylureas and glinides

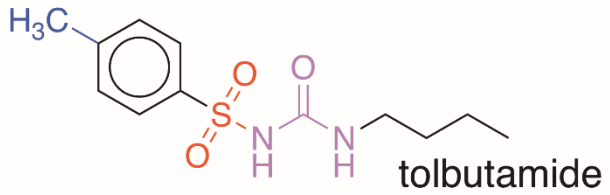


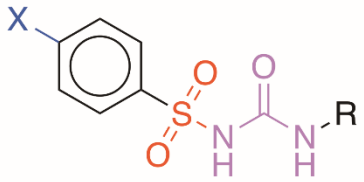
Antibacterial sulfonamides with hypoglycaemic adverse effects

Sulfonylureum: less antibacterial, stronger hypoglycaemic

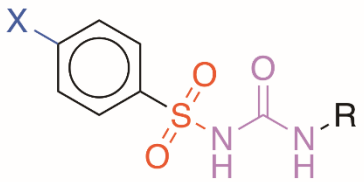
Desamino sulfonylureum: no antibacterial, still hypoglycaemic

Sulfonylureas and glinides

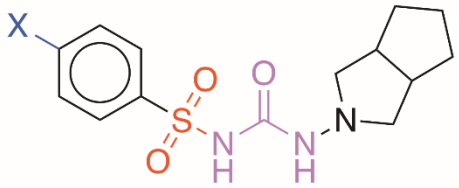




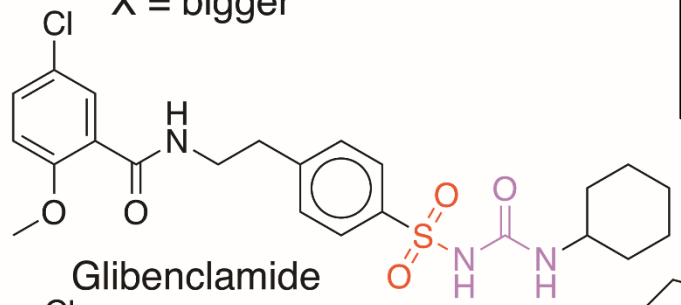
1st generation
X = H, CH_3, Cl, OCH_3



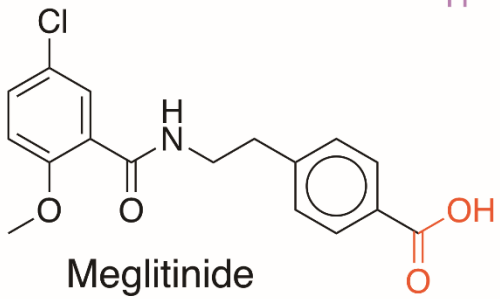
2nd generation
X = bigger



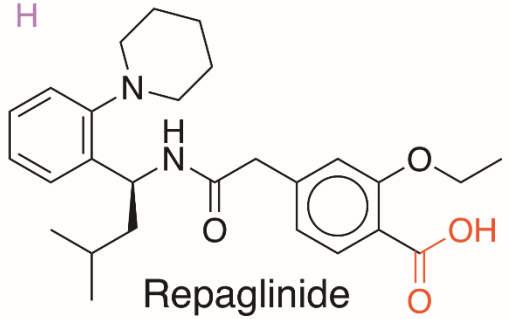
Gliclazide



Glibenclamide



Meglitinide



Repaglinide

Sulfonylureas

2nd generation more potent

1st : e.g. Gliclazide

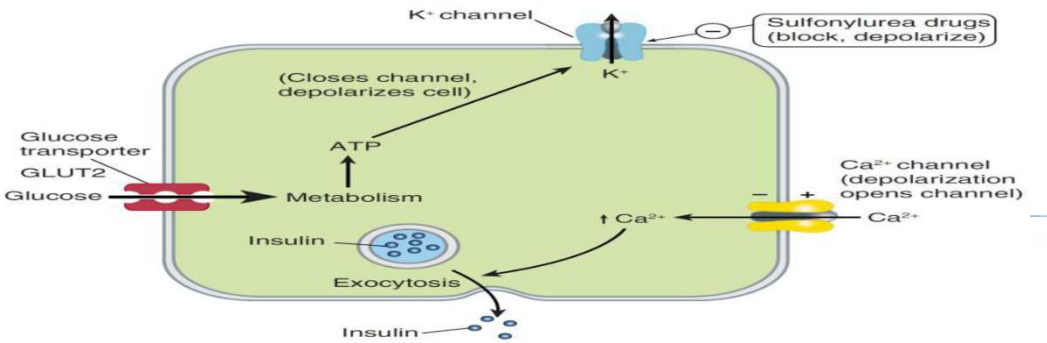
2nd : e.g. Glibenclamide

Glinides

Carboxylic acids

e.g. Repaglinide

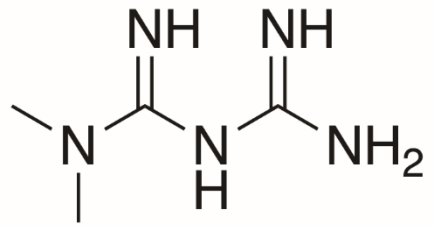
Sulfonylureas and glinides



- Together with metformin or if metformin is contra-indicated
- Risk of hypoglycaemia, certainly for longer acting
- Sulfonylureas
  - Longer acting
    - Glibenclamide (2nd): Daonil®
    - Glimepiride (2nd): Amarylle®
  - Shorter acting
    - Gliclazide (1st): Uni Diamicron®
    - Glipizide (2nd): Minidiab®
    - Gliquidon (2nd): Glurenorm®
  - Glinides
    - Repaglinide: NovoNorm® (rapid onset, short acting, postprandial glucose control)

Metformin (biguanide)

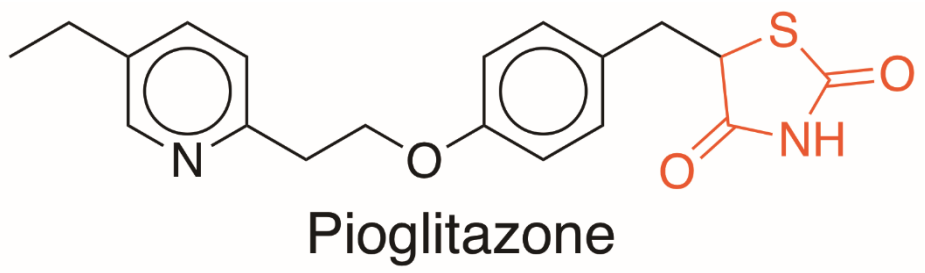
- First choice, combined with lifestyle management
- Glucophage®
- Improves insulin resistance, reduces gluconeogenesis
- No hypoglycaemia, no weight gain
- GI adverse effects
- Lactic acidosis (can be fatal)
  - Increased risk with dose, age, renal and liver insufficiency
  - Stop before surgery



Metformin

PPARγ agonists (glitazones, thiazolidinediones, TZDs)

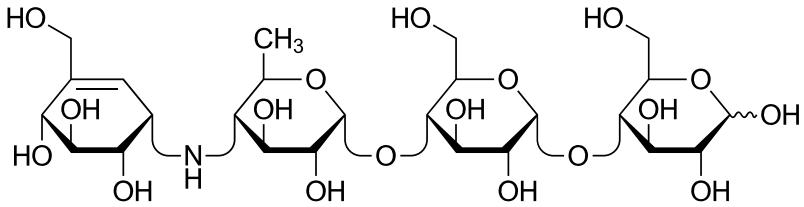
- Improve insulin resistance
- Pioglitazone, Actos®
- Limited use
- Hypoglycaemia, weight gain
- Sodium and fluid retention leading to heart failure
  - Increased with age, NSAID's, insulin
- Slightly increased risk for bladder cancer



Pioglitazone

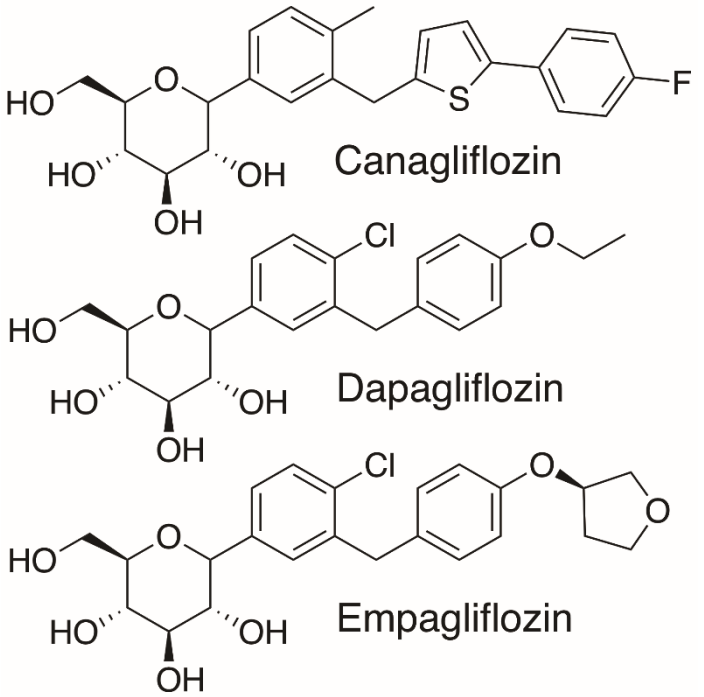
Acarbose

- Inhibits α-glucosidases needed to digest carbohydrates in small intestine leading to reduced absorption of carbohydrates and reduced postprandial hyperglycaemia
- Glucobay®
- Limited use
  - Limited effect. Always in combination with other antidiabetics.
  - Frequent GI adverse effects
- Hypoglycaemia induced by other antidiabetics can only be treated with oral glucose (e.g. druivensuiker)



Gliflozines

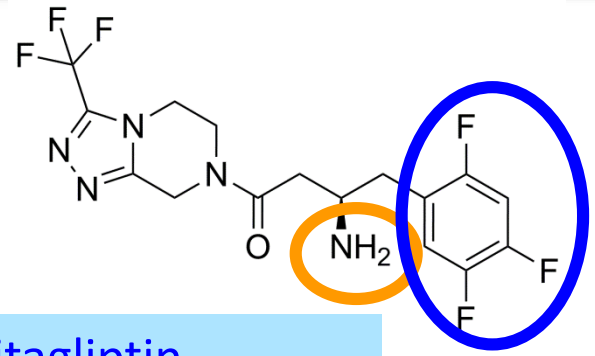
- Sodium/glucose cotransporter 2 (SGLT-2) inhibitors
  - Less glucose reabsorption in the kidney causing glucosuria
- Monotherapy or in combination
- No efficacy in case of renal insufficiency
- Low risk of hypoglycaemia, small weight loss
- Risk for dehydration, polyuria
  - Increased with age and diuretics (loop diuretics, thiazides)
- Canagliflozin: Invokana®
- Dapagliflozin: Forxiga®
- Empagliflozin: Jardiance®



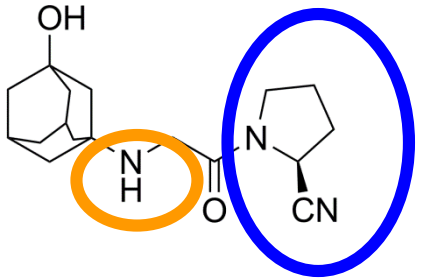
DPP4 inhibitors: gliptins

- DPP4 is a serine protease responsible for the inactivation of the incretin hormones (GLP-1 and GIP)
- Incretins are glucose-dependent
  - Low to no risk of hypoglycaemia
  - Can be considered for e.g. professional drivers
- Monotherapy or in combination
- Rare: pancreatitis

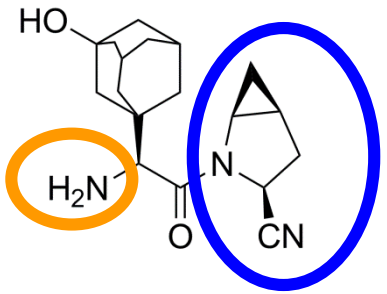
DPP4 inhibitors: gliptins



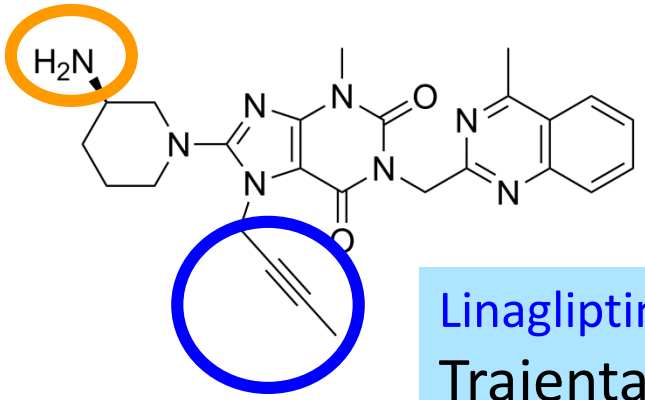
Sitagliptin
Januvia® (MSD)



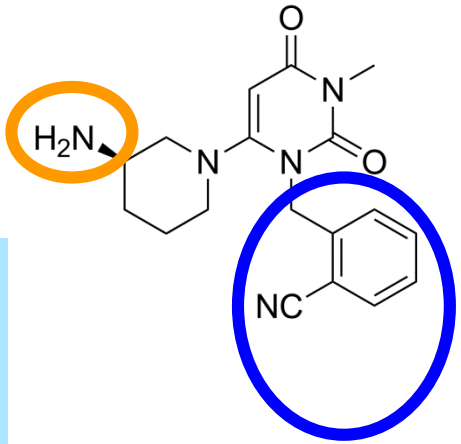
Vildagliptin
Galvus® (Novartis)



Saxagliptin
Onglyza® (AstraZeneca)



Linagliptin
Trajenta®
(Boehringer-Ingelheim)

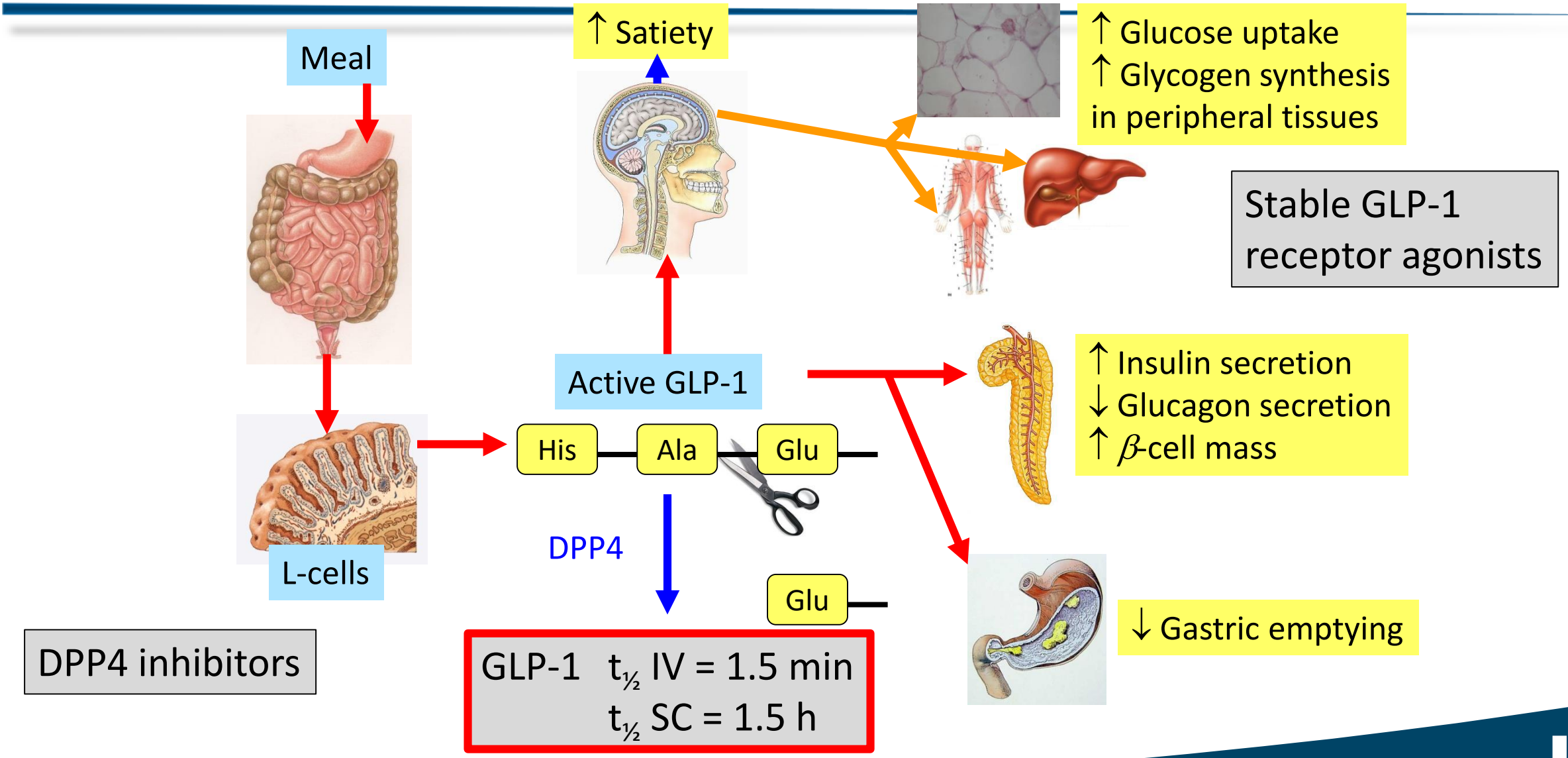


Alogliptin
Vipidia®
(Takeda)

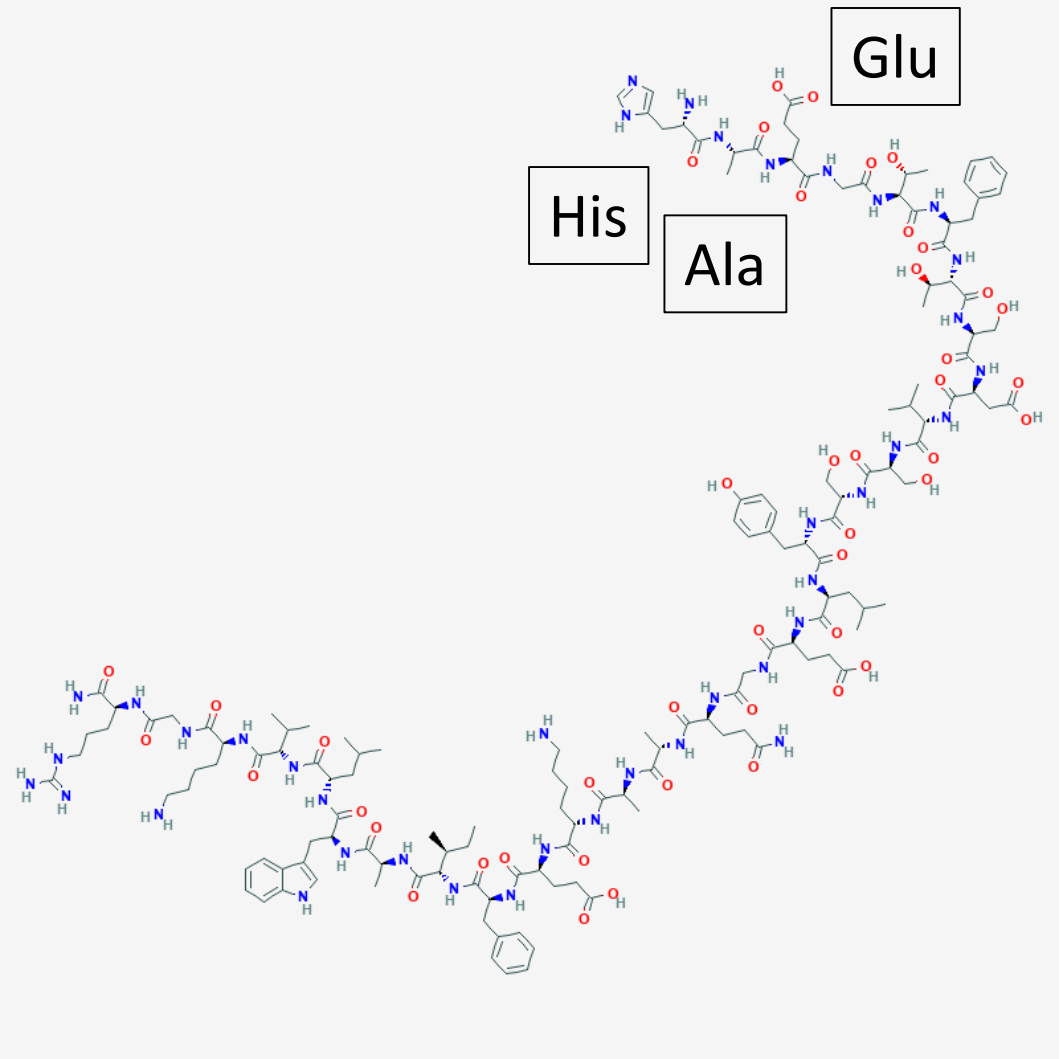
Content

- **Zolgensma®** (onasemnogene abeparvovec)
  - Spinal muscular atrophy (SMA)
- **The cost of medicines**
- **Ozempic®** (Semaglutide)
  - Type 2 diabetes

GLP-1 receptor agonists: incretin mimetics



GLP-1 structure



A peptide

31AA long

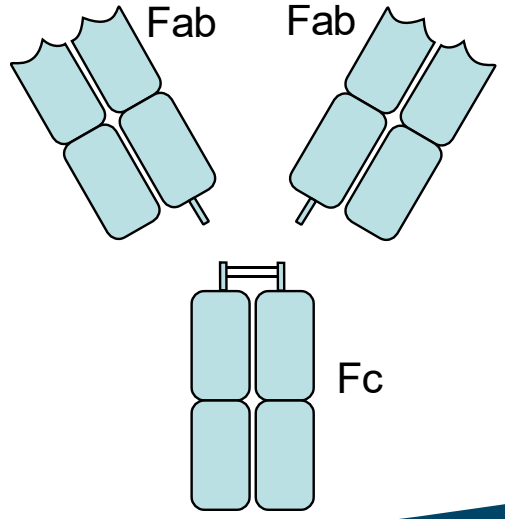
High MW

Low bioavailability

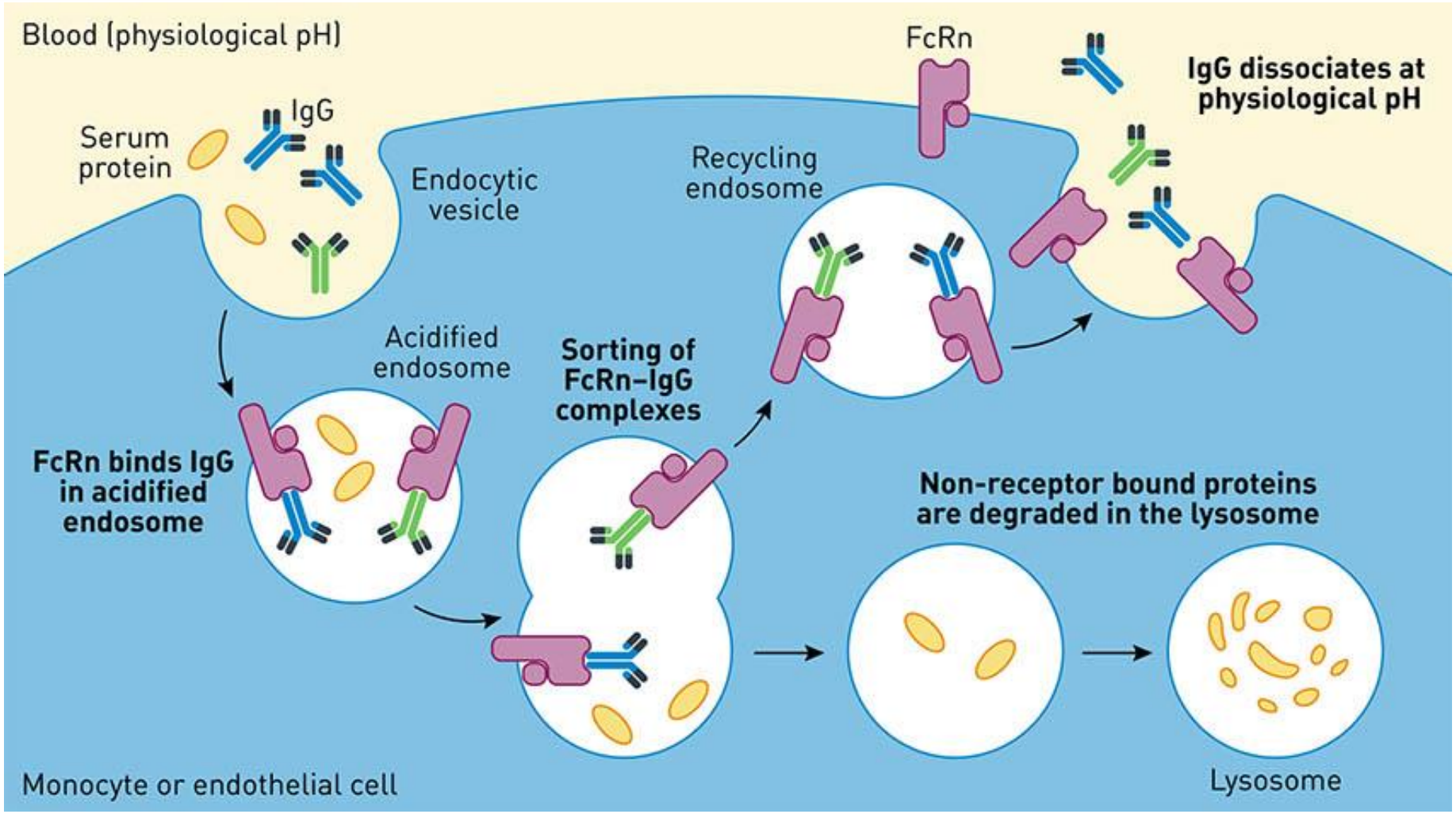
Short $t_{1/2}$

How to improve the pharmaceutical properties of peptide drugs?

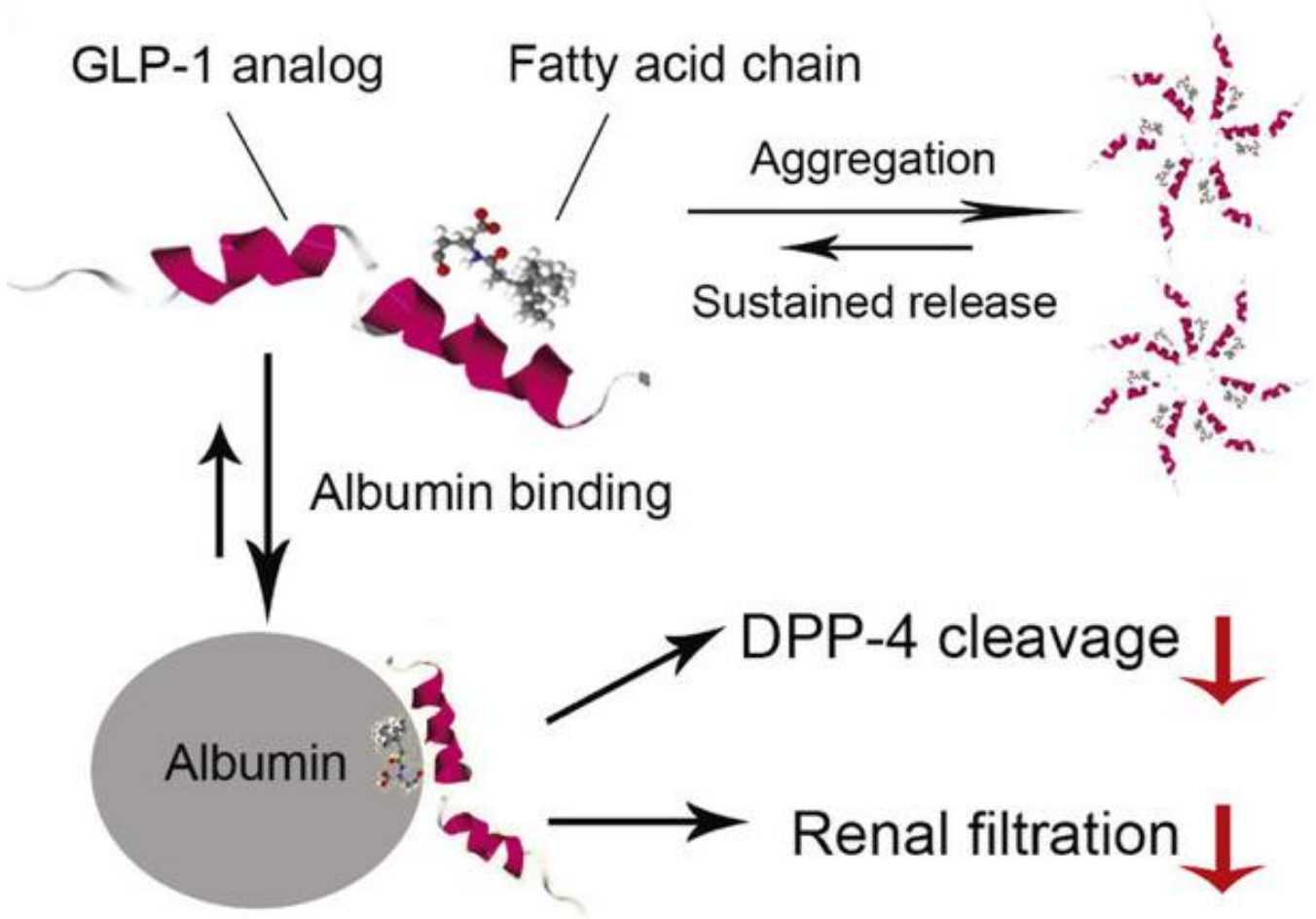
- Replace amino acids recognized by degrading proteases
- Use non-natural amino acids
- Replace amide bonds
- Conjugate to albumin or F_c-fragment of human IgG4
  - $t_{½}$ of albumin and IgG = 21 days



Neonatal Fc receptor (FcRn) recycling pathway of IgG
Similar for albumin



Reversible binding to albumin via a fatty acid side chain



Covalent binding to a IgG4 F_c-fragment

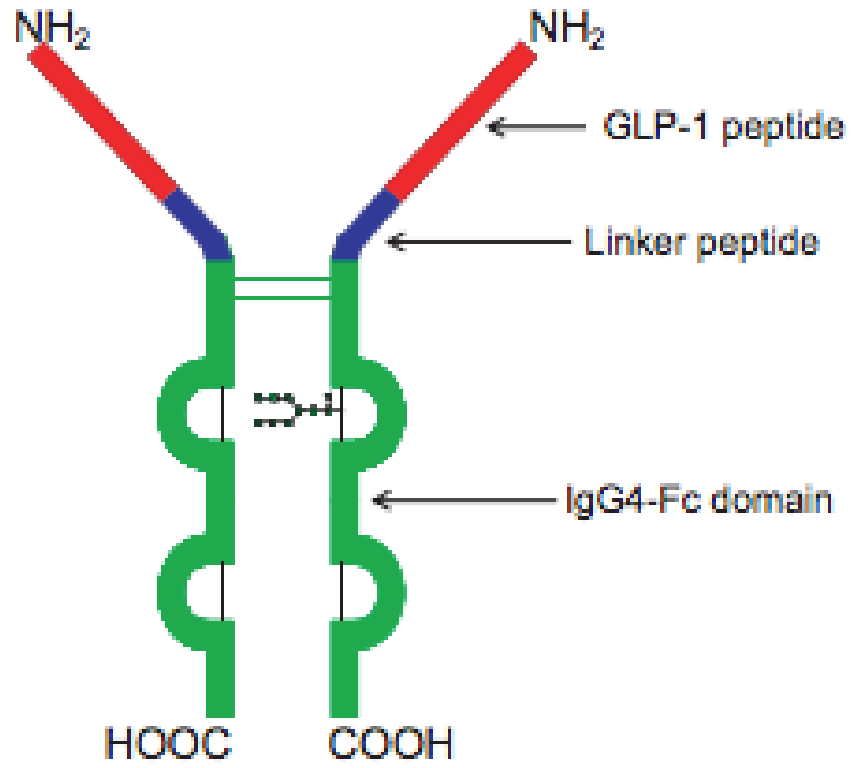
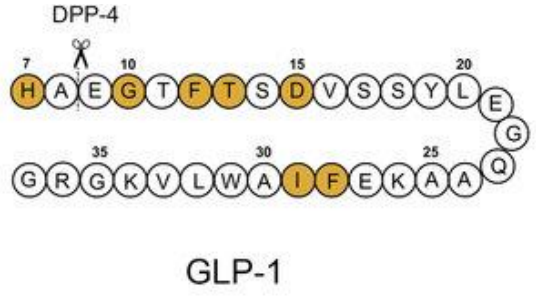


FIGURE 1 Dulaglutide structure of the molecule.

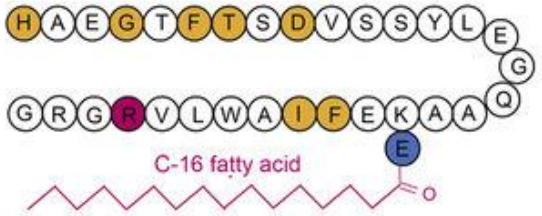
GLP-1
$t_{½}$ IV = 1.5 min
$t_{½}$ sc = 1.5 h




Exenatide

Byetta®
$t_{½}$ sc = 2.4 h
2 x day

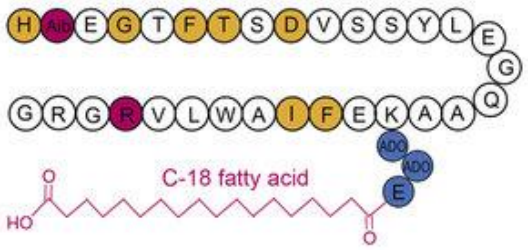
Victoza®
$t_{½}$ sc = 13-15 h
1 x day

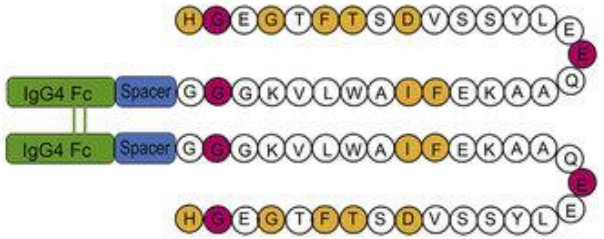



Lixisenatide

Lyxumia®
$t_{½}$ sc = 3 h
1 x day

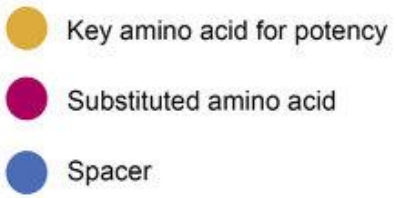
Ozempic®
$t_{½}$ sc = 165 h
1 x week





Trulicity®
$t_{½}$ sc = 24-72 h
1 x week

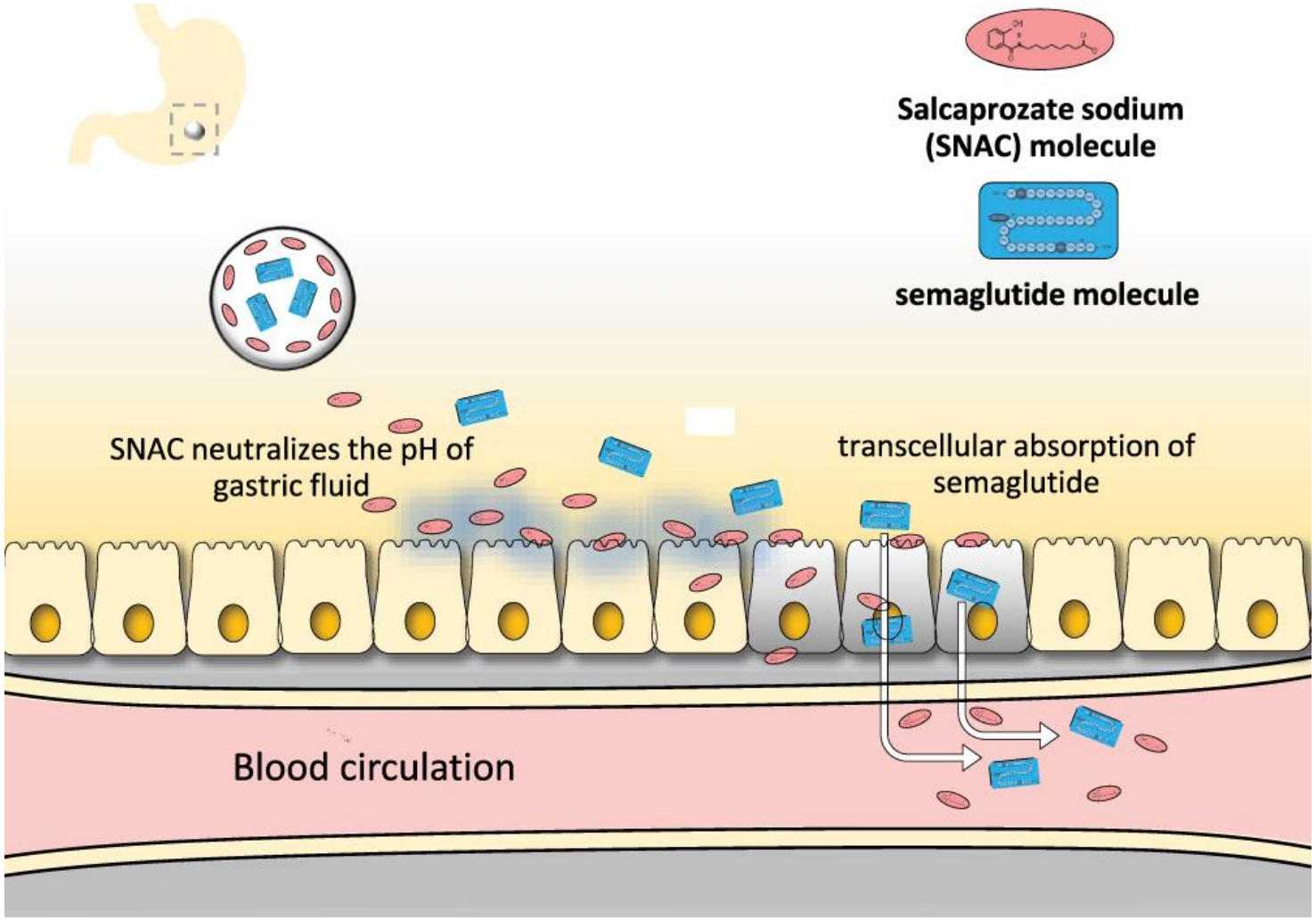
GLP-1 receptor agonists



GLP-receptor agonists: incretin mimetics

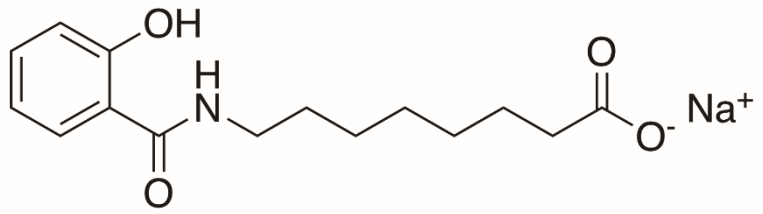
- Incretins work glucose-dependent
  - Low to no risk of hypoglycaemia
  - Can be considered for e.g. professional drivers
- Usually in combination with other antidiabetics
- Weight loss
- GI adverse effects
- Low risk of pancreatitis
- Slower gastric emptying might influence absorption of other medicines
- Subcutaneous injections

Rybelsus® - FDA 2019: oral tablets of semaglutide 1 x dag



Coformulation of semaglutide with Salcaprozate sodium (SNAC)

Allows transcellular absorption in the stomach



Salcaprozate sodium

DANK U