Drug Delivery Systems: From Small Molecules to Gene Therapies

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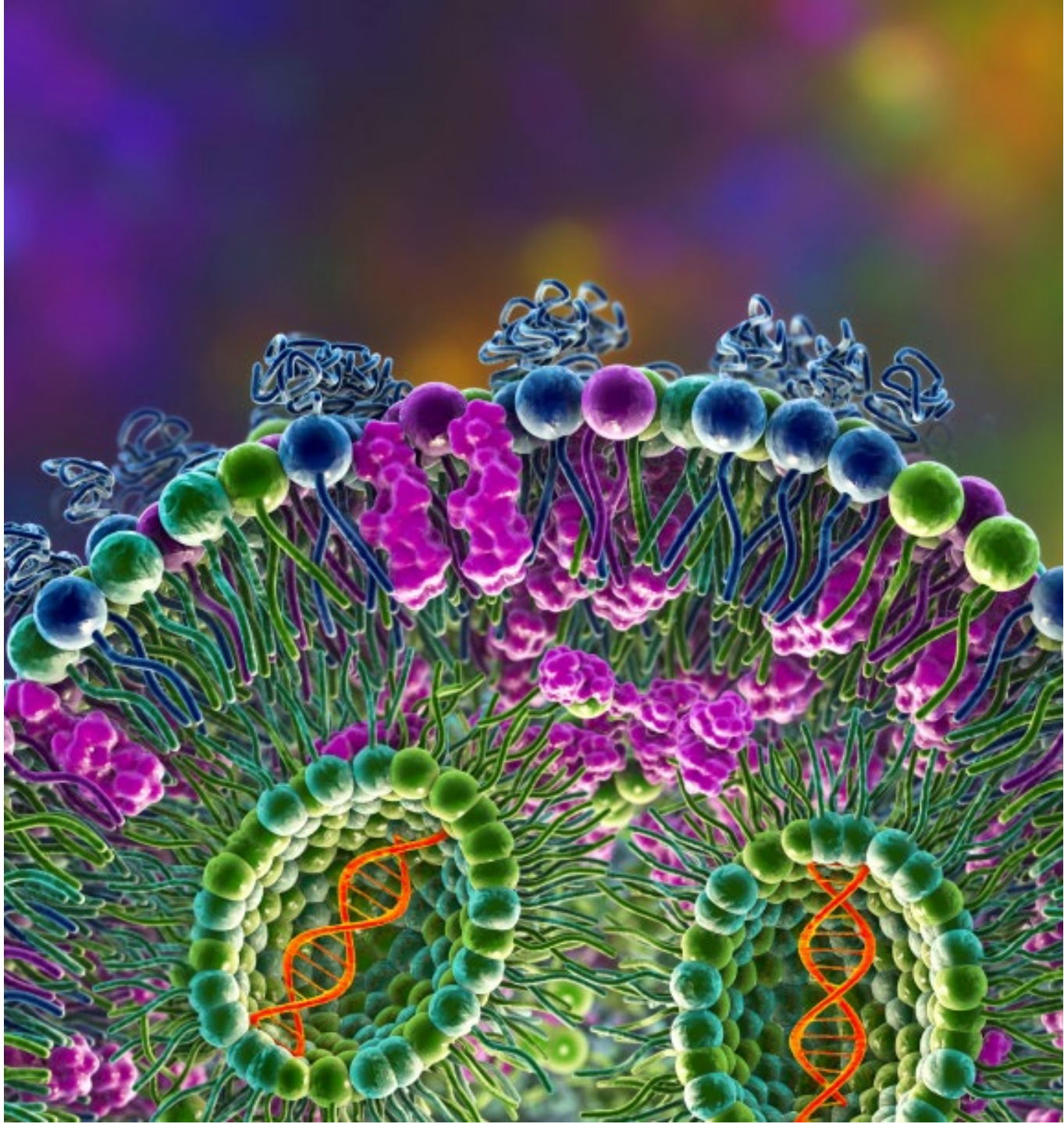
Cancer Engineering, October 14th, 2025

Memorial Sloan Kettering Cancer Center



Course Outline & Objectives

1. Introduce drug delivery systems (DDSs) and their role in optimizing therapies.
2. Explore the distinct needs of small-molecule drugs vs. macromolecules
3. Highlight cutting-edge advancements, including gene therapy
4. Identify key factors influencing the choice of DDS.

1.Introduction

Why we need drug delivery systems

Why we need drug delivery systems

QUIZ

- **Improve Therapeutic Efficacy:**

Ensure drugs reach their intended target in optimal concentrations.

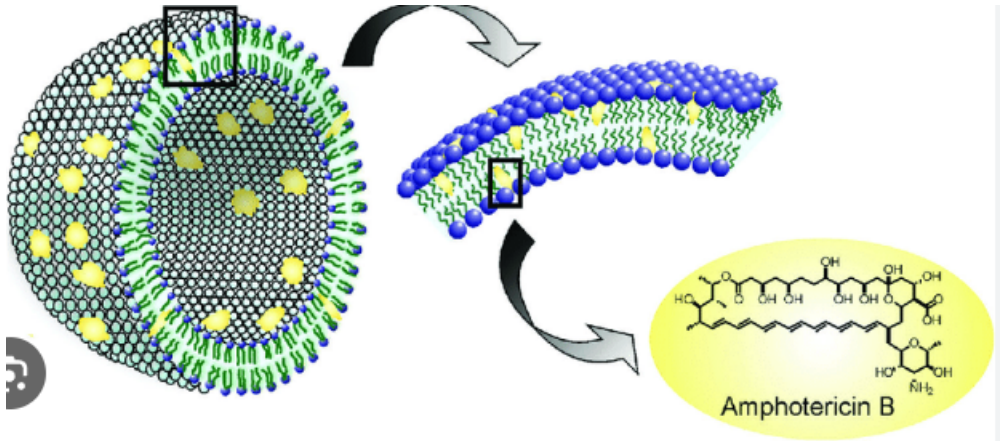
- **Minimize Side Effects:**
Reduce off-target exposure and toxicity.

- **Enhance Patient Compliance:**
Simplify dosing regimens and improve adherence.

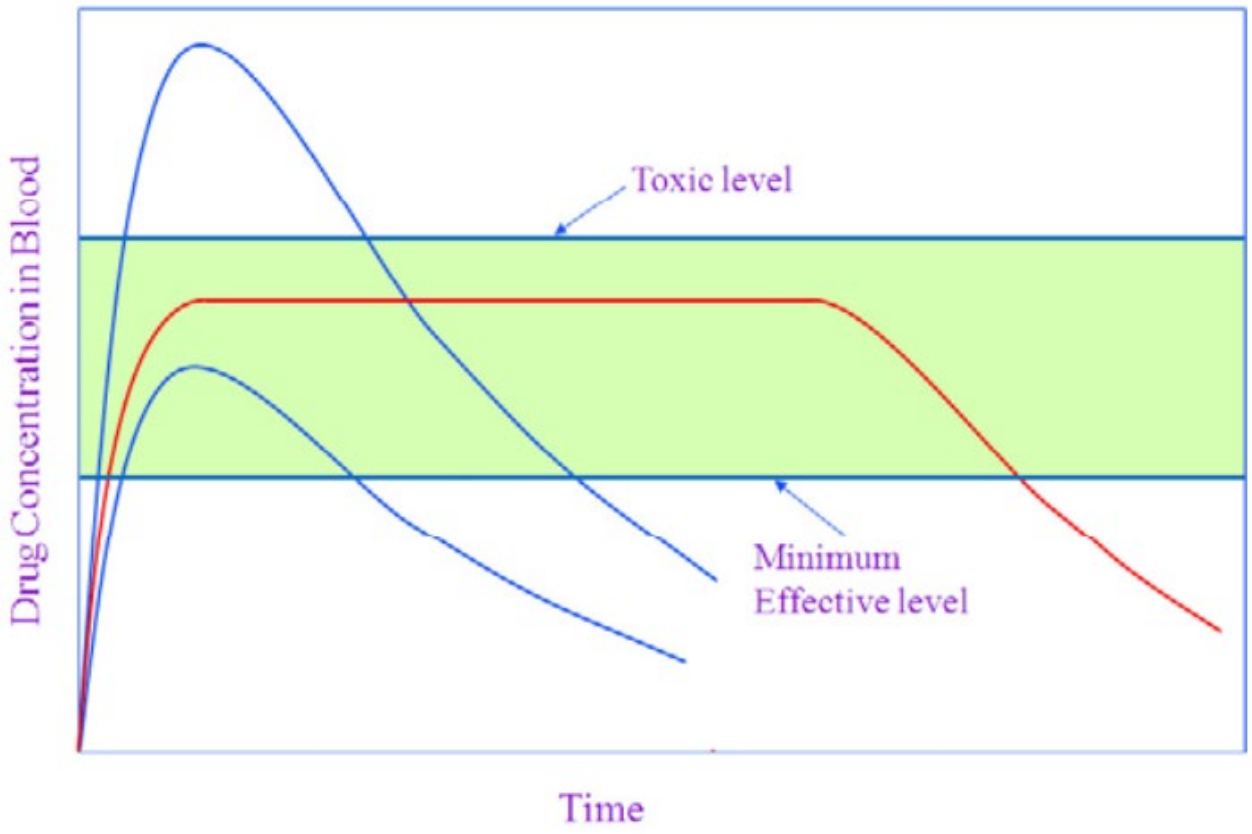
- **Control Drug Release:**
Enable sustained or controlled drug release over time.

- **Overcome Delivery Barriers:**
Facilitate drug transport across biological barriers (e.g., blood-brain barrier).

Example on image:
• Ambisome (Liposomal Amphotericin B): Reduces nephrotoxicity.



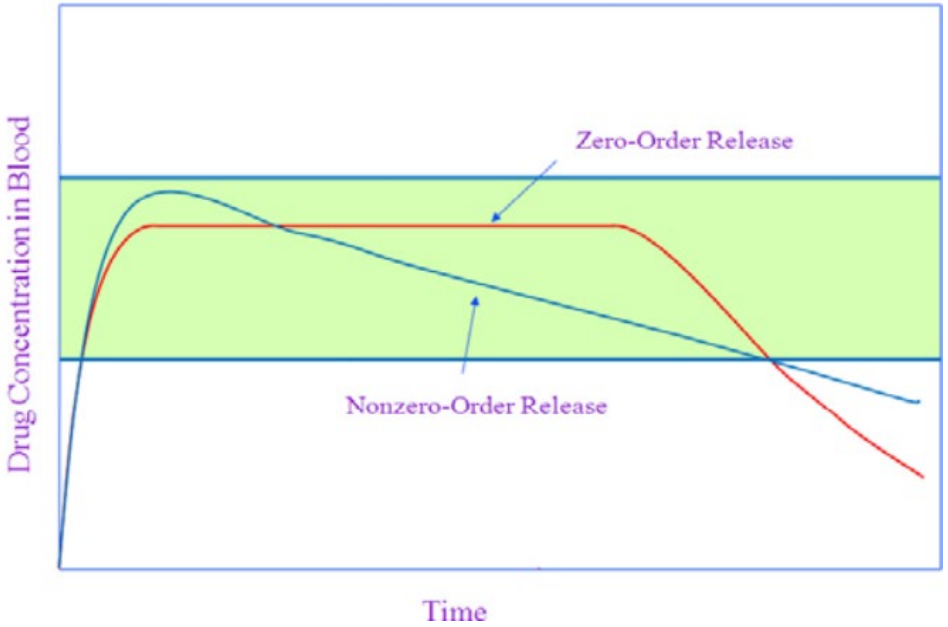
Why do we need *controlled* drug delivery systems



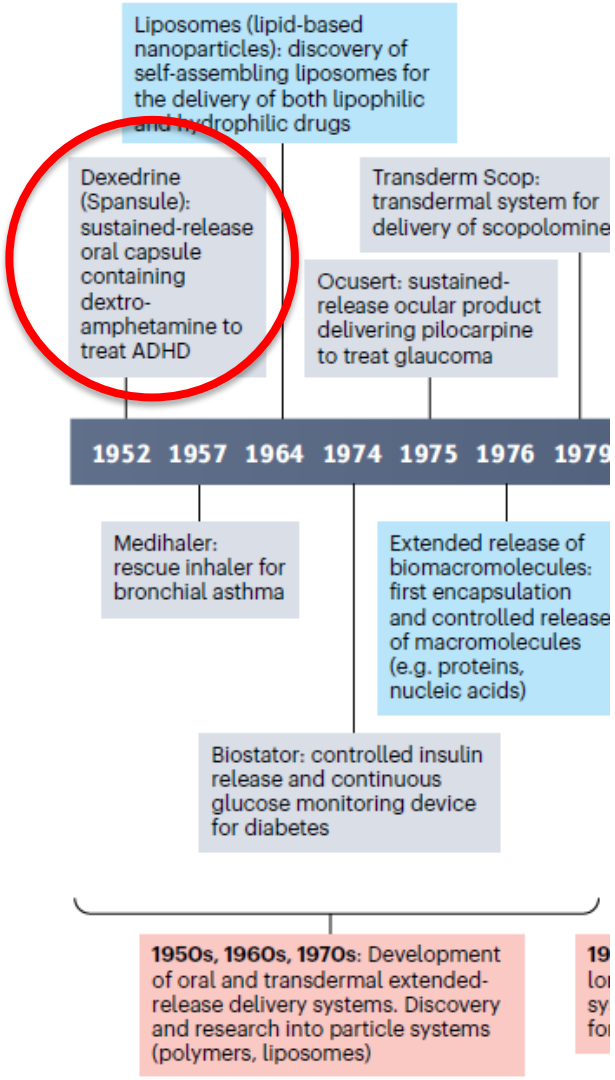
Conventional dosage forms:
The drug amount & duration of action

Controlled release DDS:
The drug amount & duration of action +
Release kinetics

Zero-Order vs. Nonzero-Order Systems



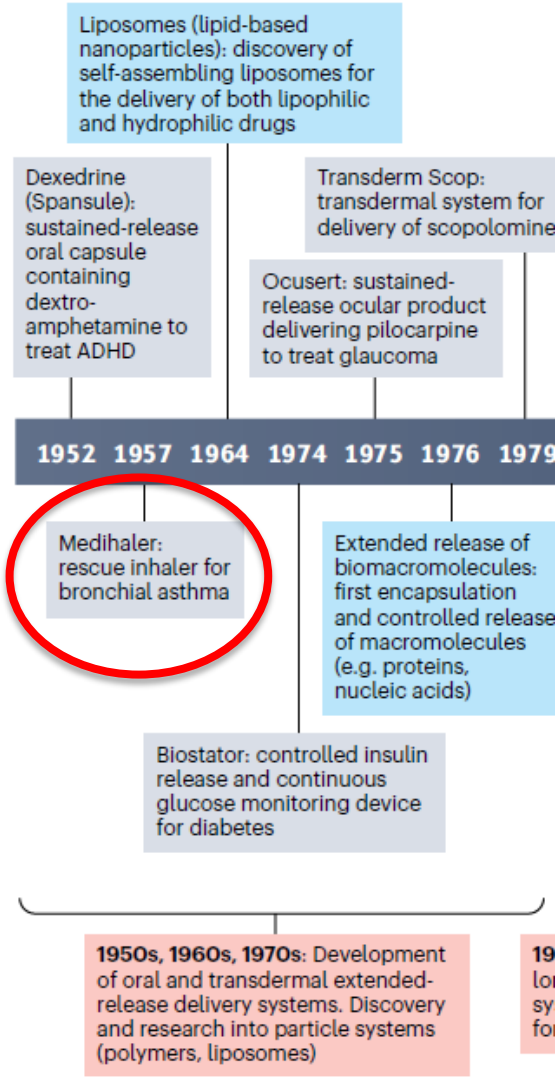
History and Evolution of Drug Delivery Systems



Resaid® (phenylpropanolamine & chlorpheniramine)
Green, red, and white spherical beads within a capsule. Each color of beads represents a different coating level. Some beads release the drug immediately. Some beads release after a short while, some after a longer while.

Baryakova et al. *Nat Rev Drug Discov 2023*

History and Evolution of Drug Delivery Systems



Baryakova et al. *Nat Rev Drug Discov 2023*

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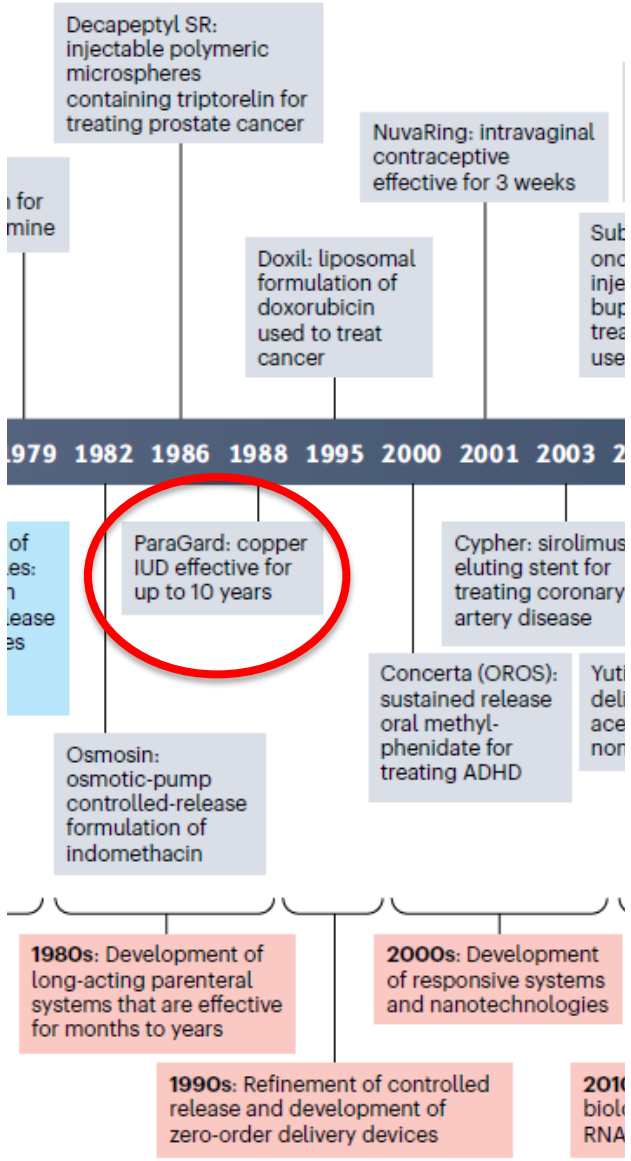

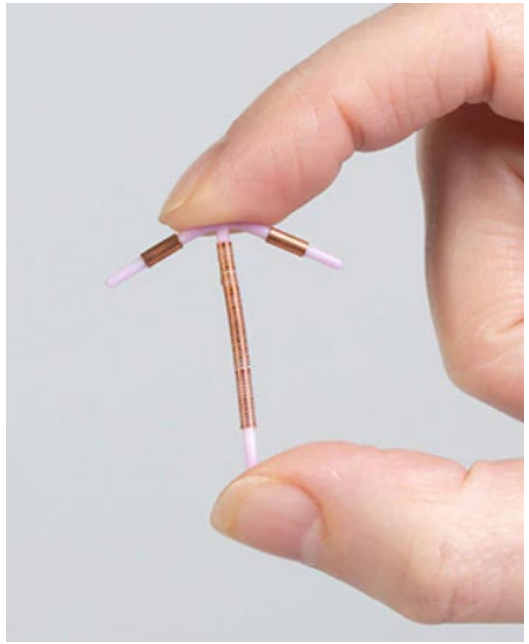

Baryakova et al. *Nat Rev Drug Discov 2023*

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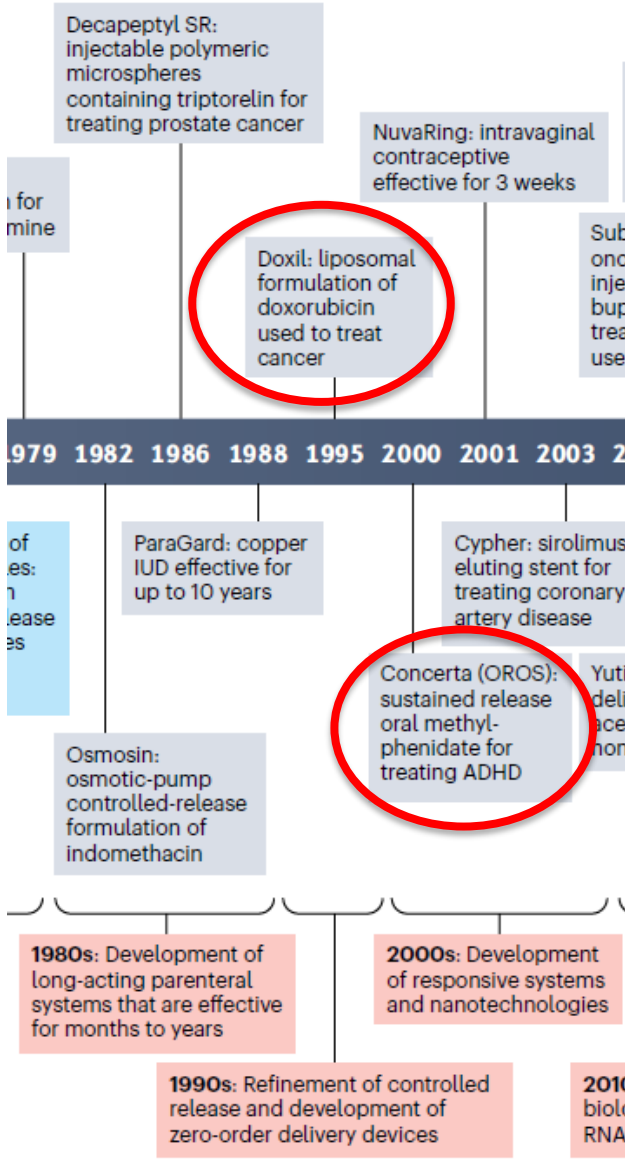

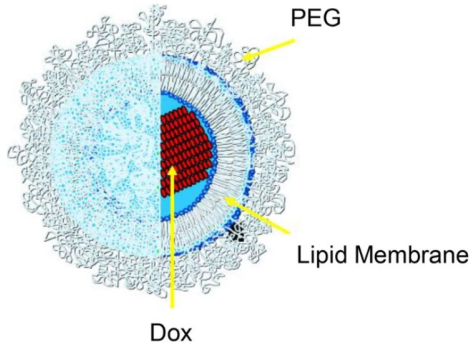

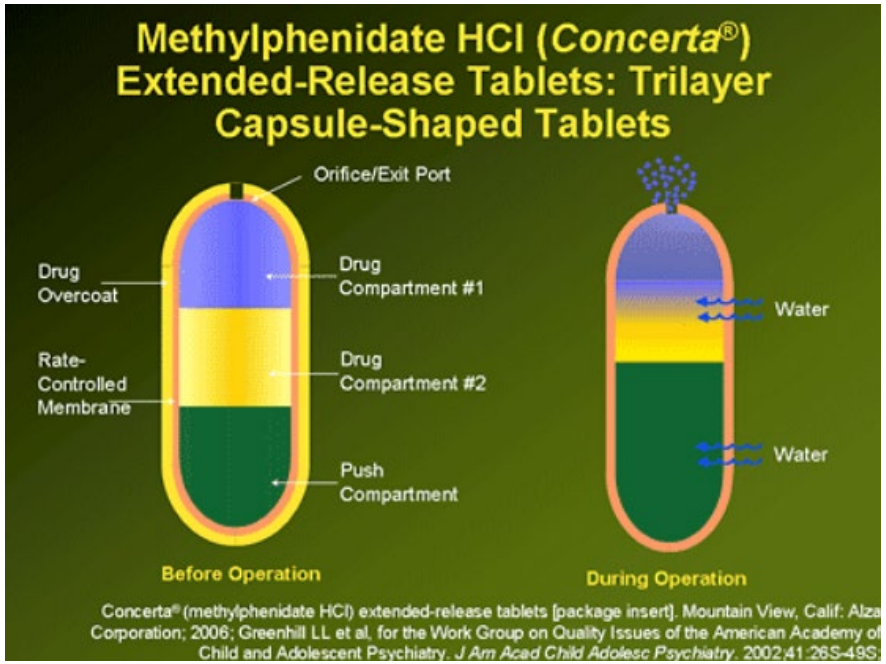

Baryakova et al. *Nat Rev Drug Discov 2023*

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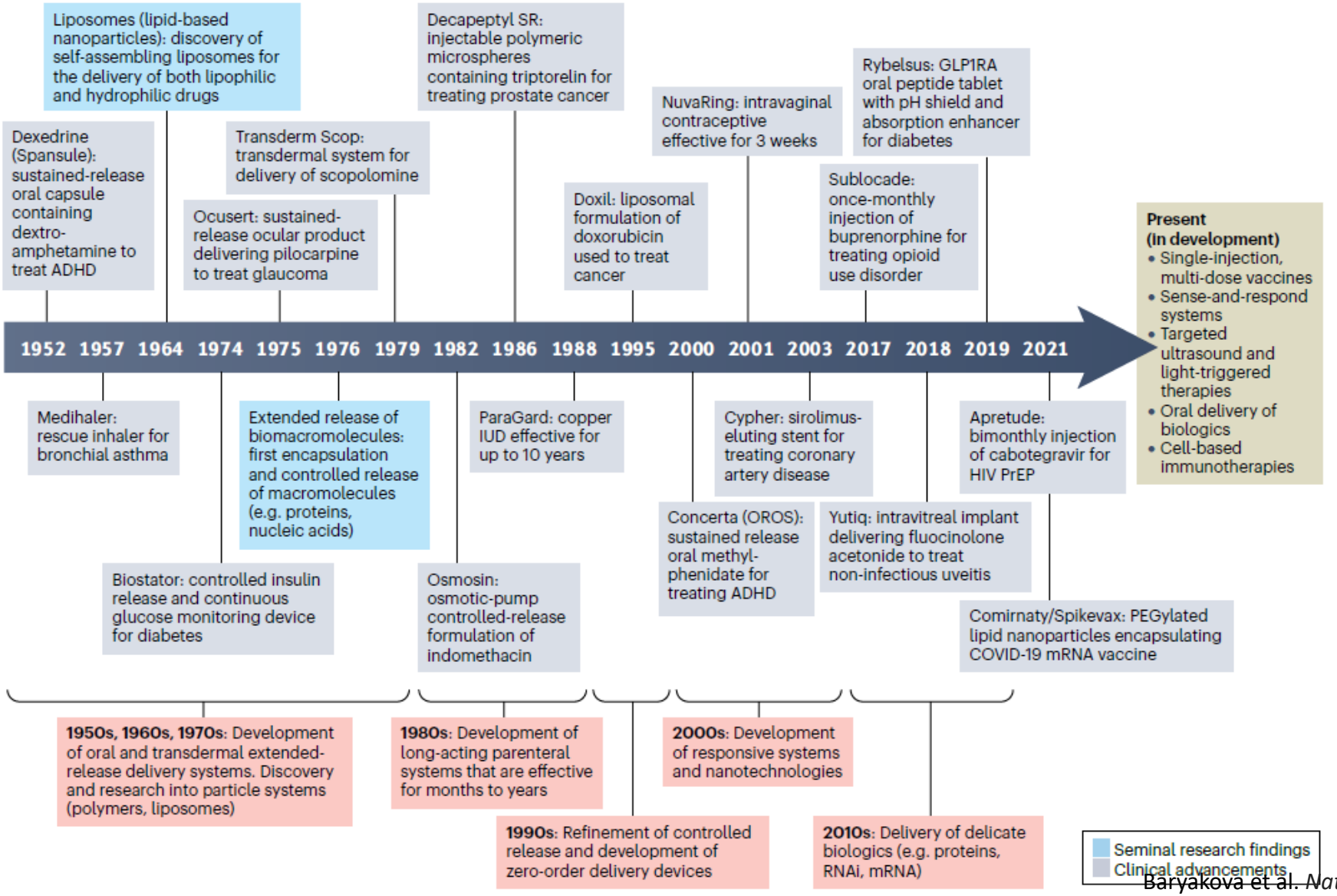
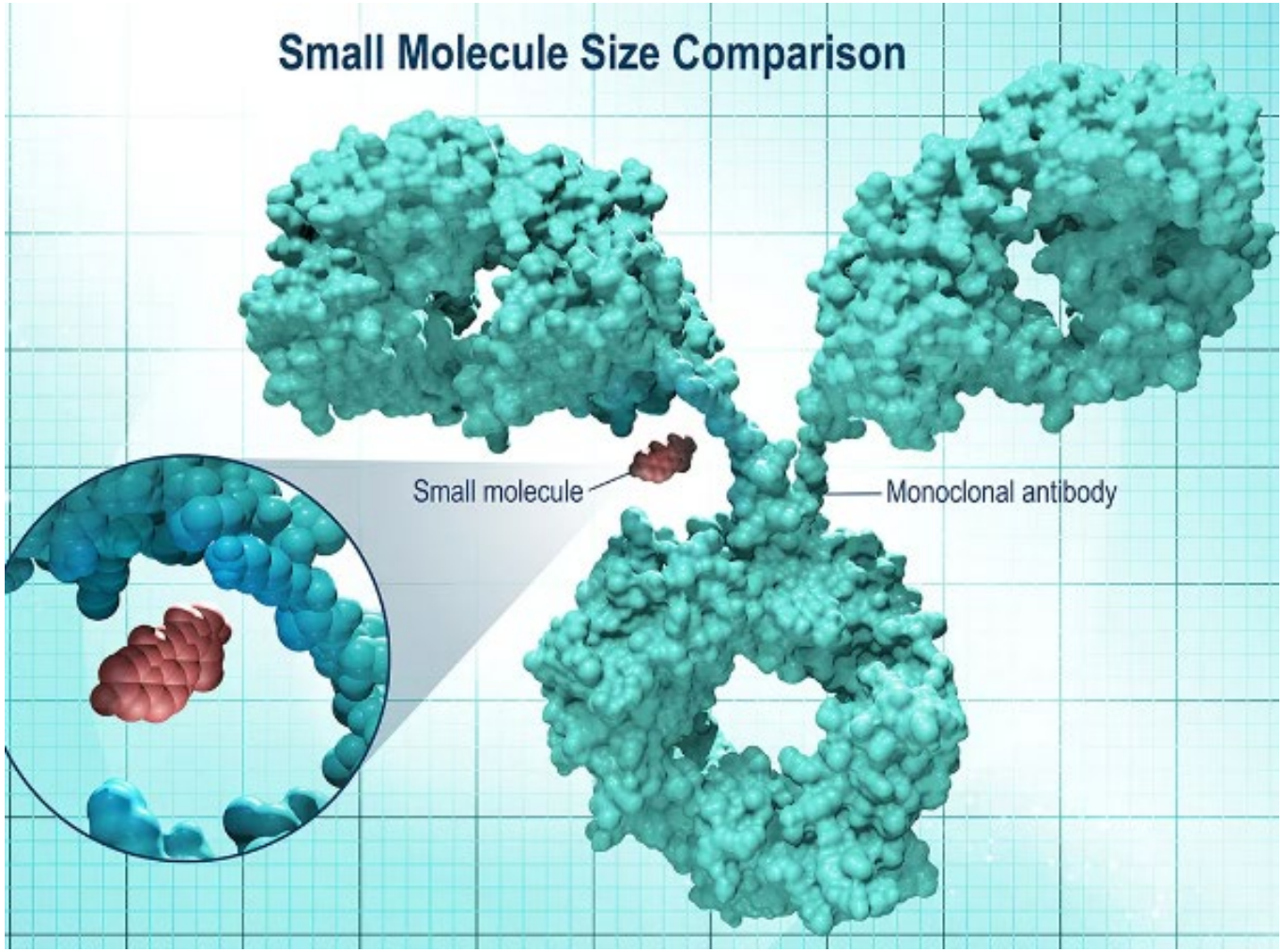


Baryakova et al. *Nat Rev Drug Discov 2023*


2. Small Molecule Delivery

Introduction to Small Molecules and Challenges

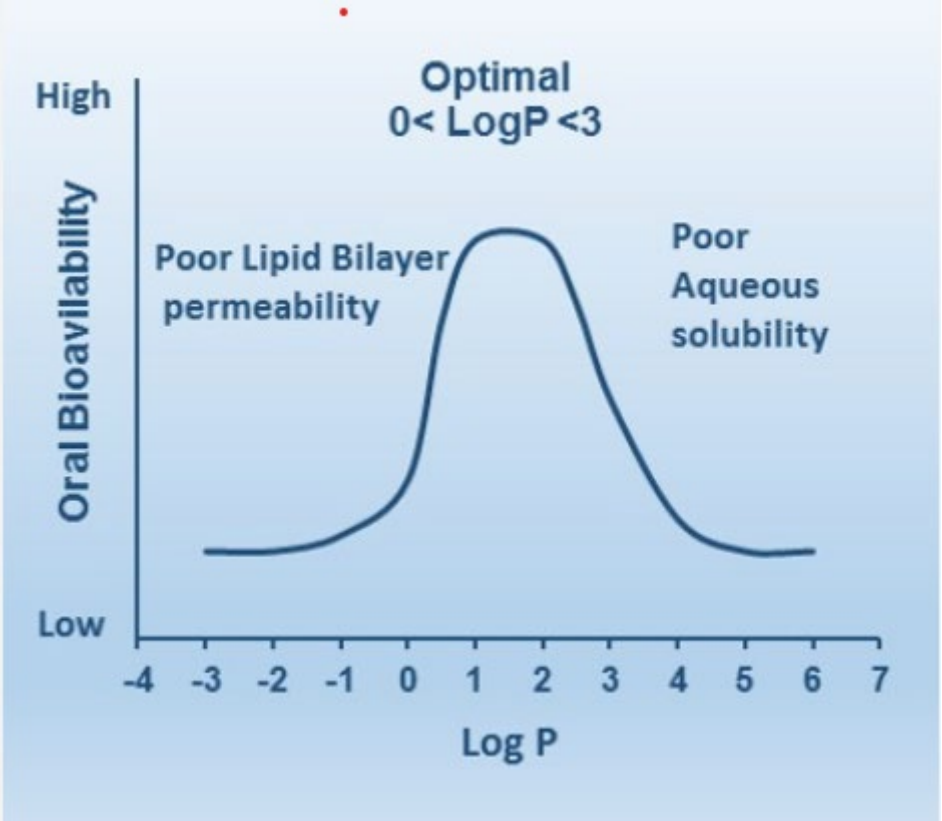
Small molecules ≤ 1000 Daltons



Introduction to Small Molecules and Challenges

Challenges in Small Molecule Delivery:

- Poor Solubility / Low Permeability



- Rapid Metabolism: Requires frequent dosing (first-pass liver metabolism).
- Short Half-Life: Limits therapeutic effect, reduces compliance.
- Toxicity: Off-target effects can cause side effects.

Available DDS Systems for Small Molecules

Examples of DDSs:

- Oral Systems: Tablets, capsules, prodrugs.
- Injectable Systems: IV, SC formulations.
- Transdermal Systems: Gels, patches.
- Inhalation Systems: Aerosols, inhalers.

Mechanisms of release and examples of common drug delivery systems

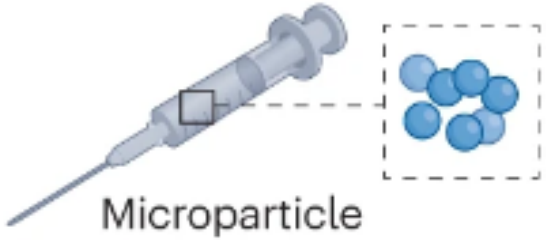
Dexedrine

Dextroamphetamine, ADHD

a **Reservoir-based system**

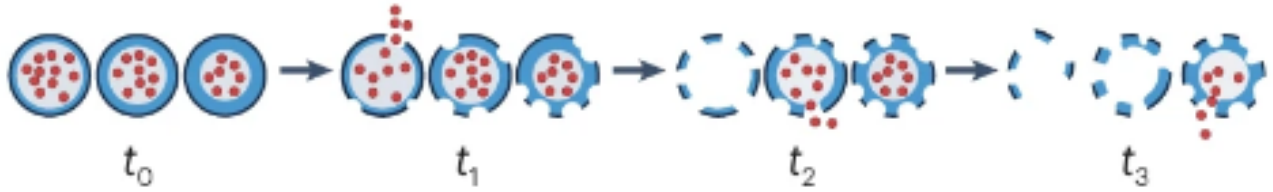
Examples

Extended-release pill



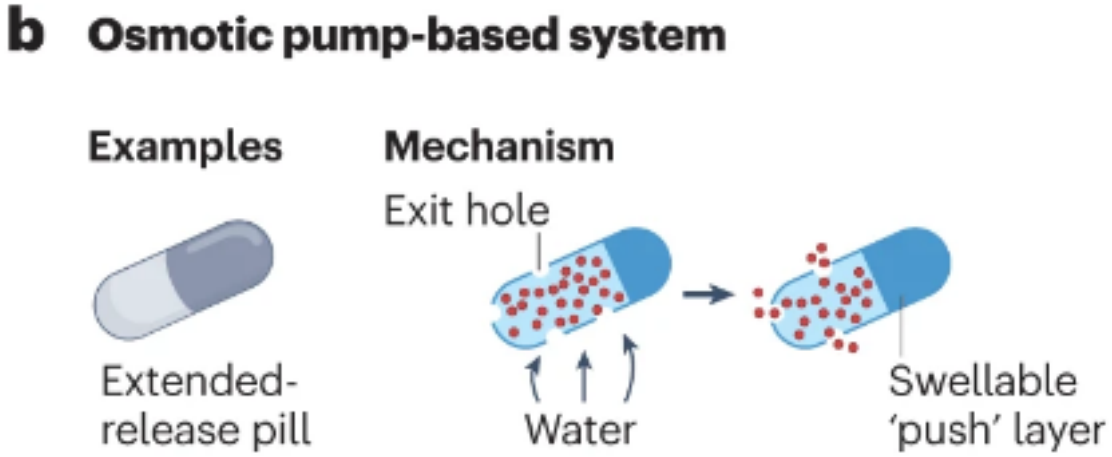
Microparticle depot

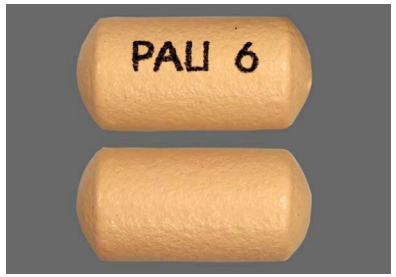
Mechanism



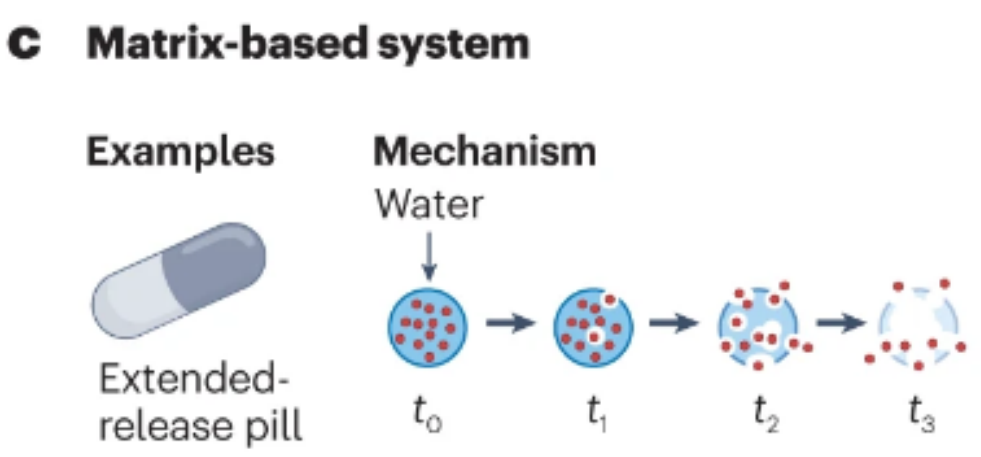
Oral capsule or suspension

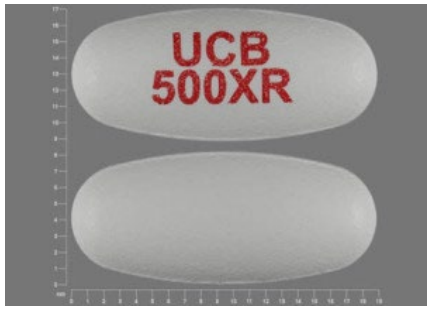
Mechanisms of release and examples of common drug delivery systems





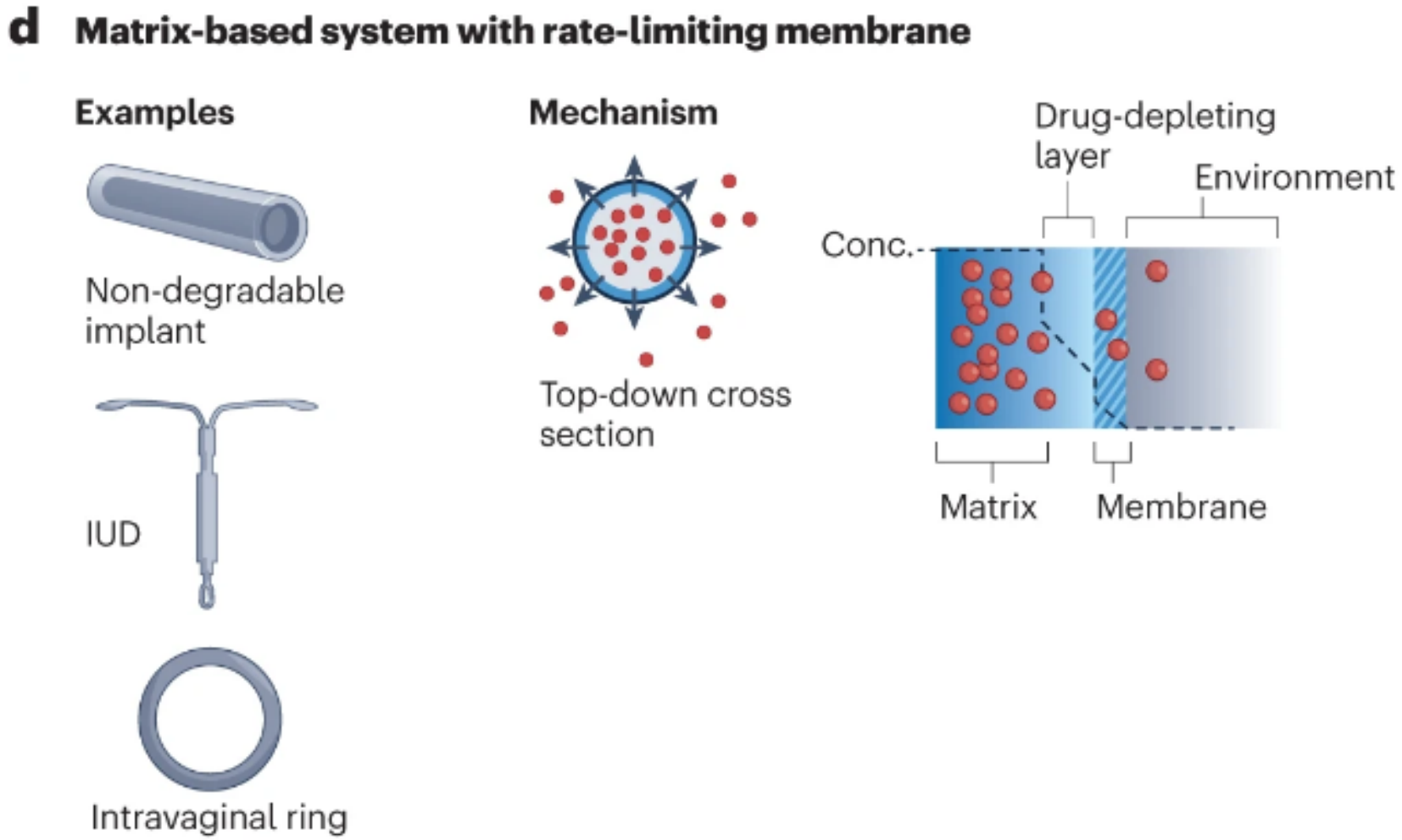
Invega, paliperidone, schizophrenia





Keppra XR, levetiracetam, epilepsy

Mechanisms of release and examples of common drug delivery systems



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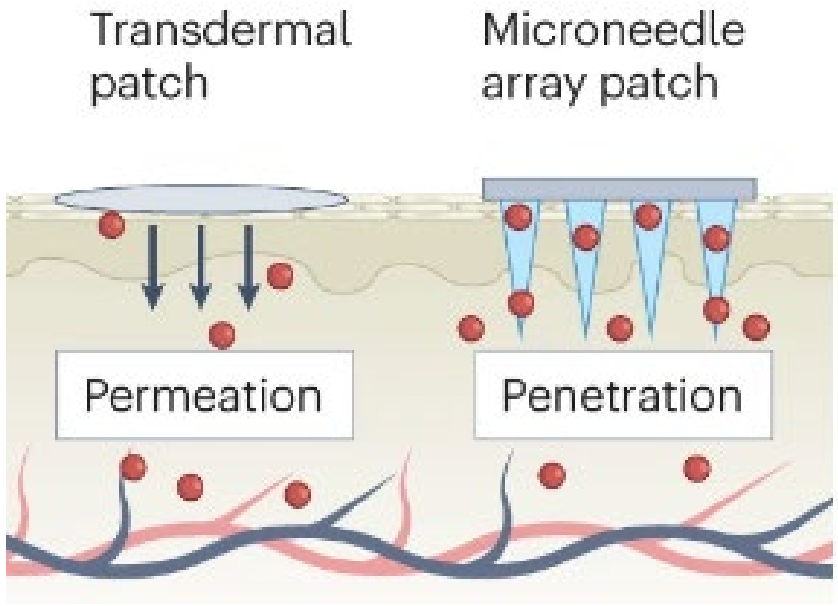
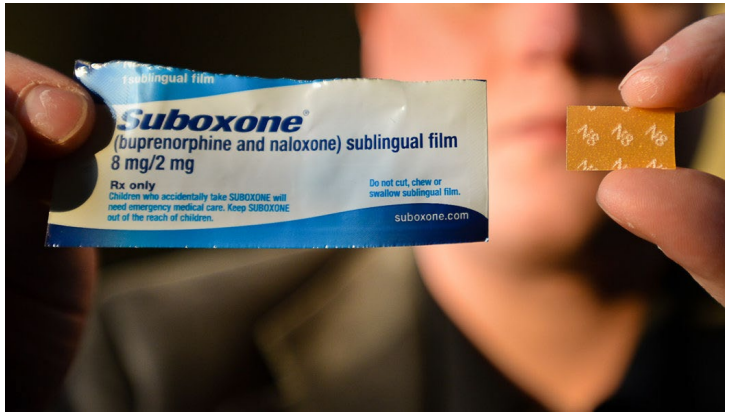
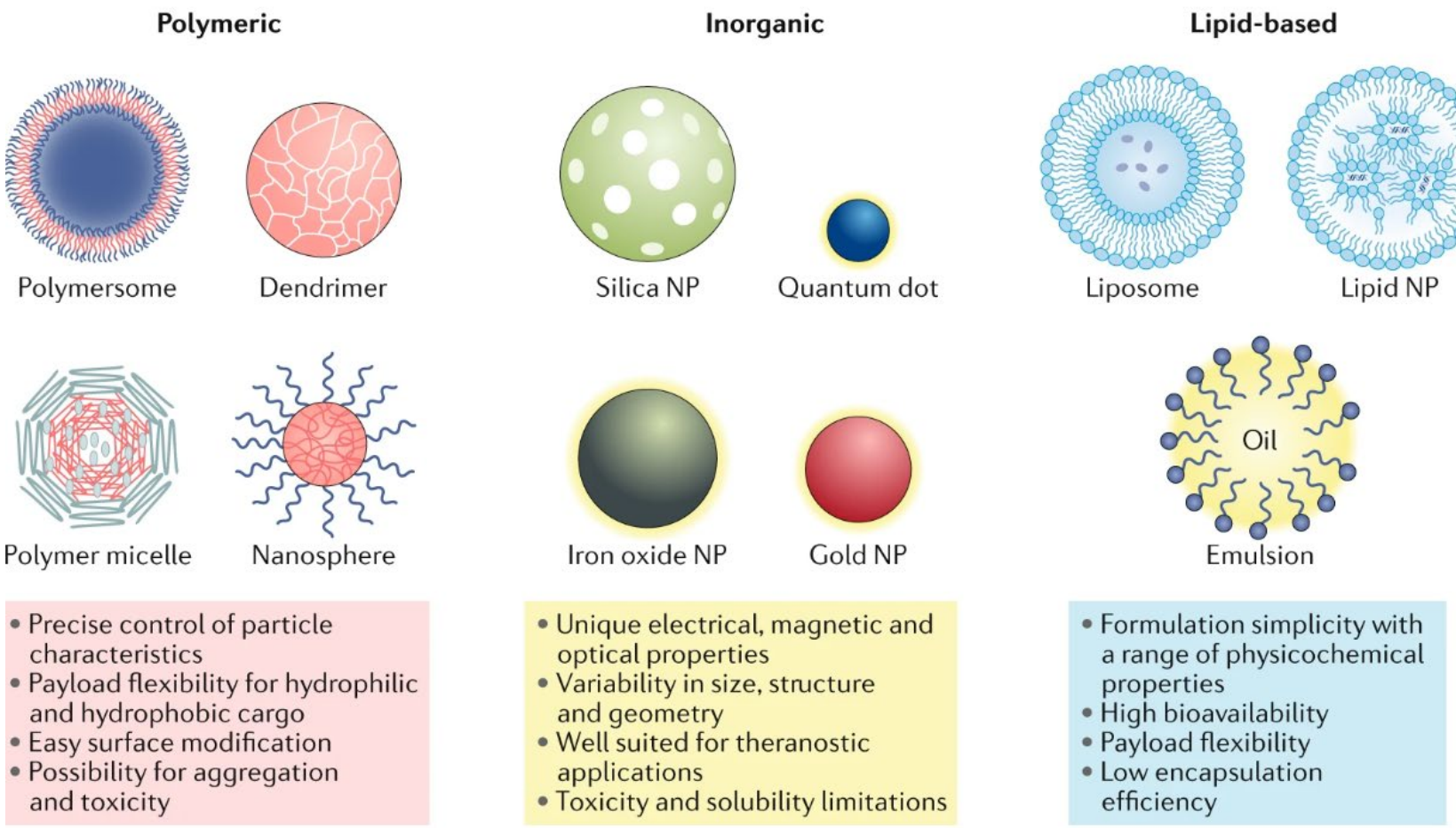




Buprenorphine, opioid addiction sublingually or buccally

Fluzone (flu vaccine)

Nanoparticle drug delivery systems



NPs have the potential to improve the **stability** and **solubility** of encapsulated cargos, promote **transport across membranes** and **prolong circulation** times to increase safety and efficacy

Nanomedicine could help overcome the limitations of conventional delivery — (**biodistribution barriers, intracellular trafficking barriers**)

Mitchel et al., Nat Rev Drug Discov . 2021

Example: Doxil, the first FDA-approved Nano Drug, 1995

Drug: **Doxorubicin**

- chemotherapy for multiple cancers
- Inhibits topoisomerase II, an enzyme that cancer cells need to divide and grow

Challenges:

-Cardiac toxicity

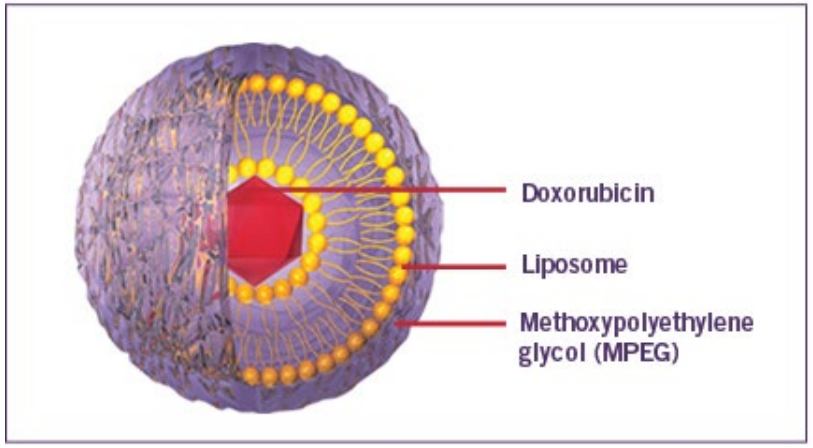
-Rapid clearance from the bloodstream

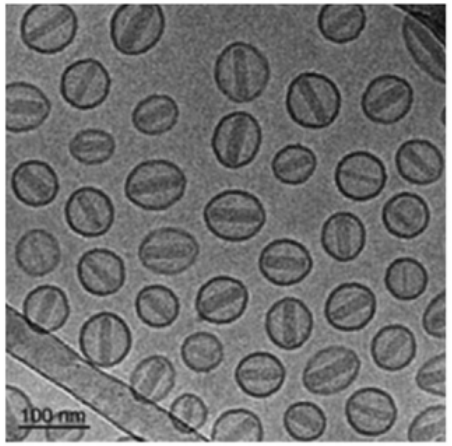
-Fast degradation

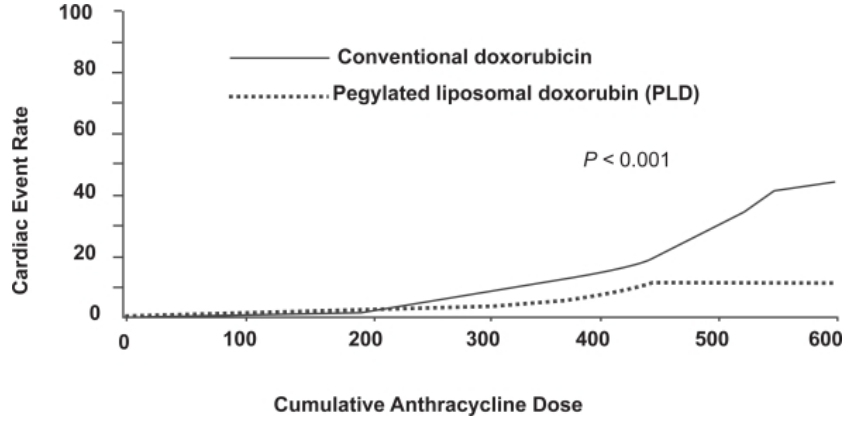
-Drug resistance

DDS Solution: **Doxil** (liposomal doxorubicin)

- Reduced Systemic Toxicity
- Improved Pharmacokinetics
- Enhanced Passive Targeting of Tumor Tissue (enhanced permeability and retention (EPR))
- Prevention of Drug Degradation
- Reduced Drug Resistance







Barenholz, Y., J. Control. Release 2012

Example: Taxol vs Abraxane, 1970

Drug: **Paclitaxel** (Taxol) – invented in 1970's

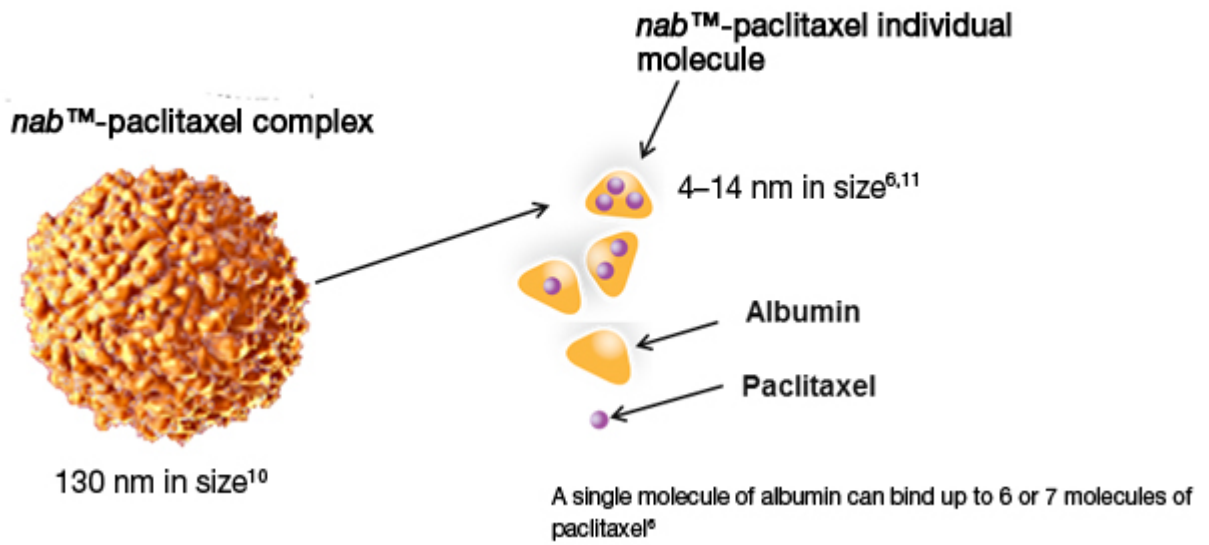
- chemotherapy for solid tumors (lung, ovarian, and breast cancer)
- a mitotic inhibitor

Challenges:

- Poor solubility requiring the use of solvents (castor oil and ethanol - Taxol), leading to toxic side effects.
- Limited bioavailability
- Rapid clearance from the bloodstream.

DDS Solution: **Abraxane** (Albumin-bound paclitaxel nanoparticles)

- Reduces the need for toxic solvents
- Same concentration in tumor, less in plasma
- Less breast cancer stem cells in mice tumors



Hebao et al., Mol Pharm. 2020

3. Macromolecule Delivery

Classes of Macromolecule Therapies

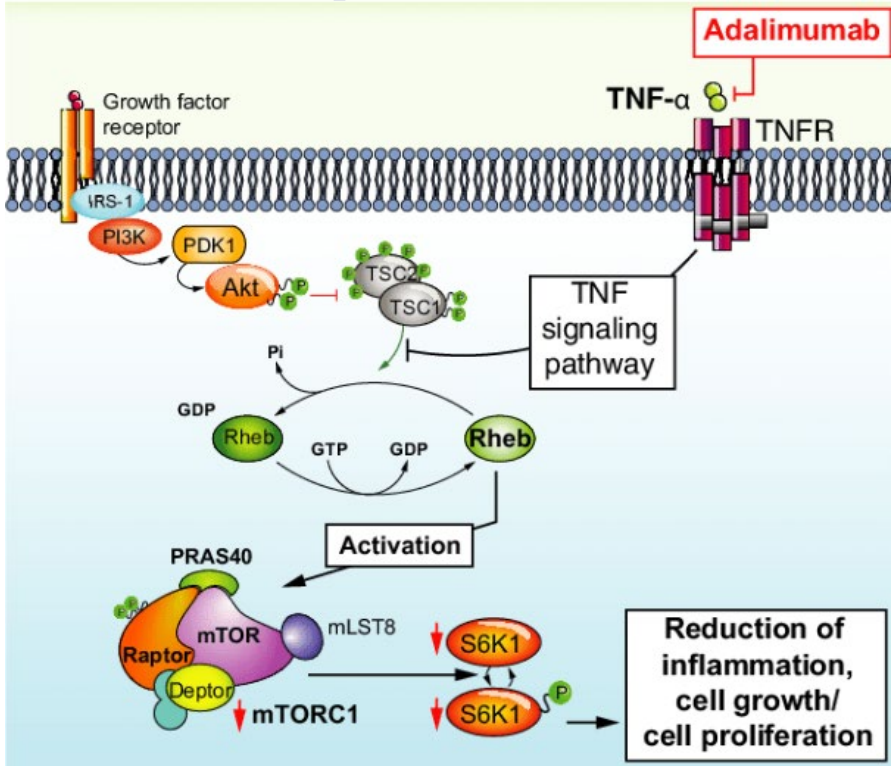
Peptide Therapies:
•Examples: GLP-1 analogs (e.g., Liraglutide)
•Size: ~3-4 kDa
•Small chains of amino acids, typically smaller than full proteins.

Therapeutic Proteins:
•Examples: Insulin (~5.8 kDa), Erythropoietin (~30.4 kDa)
•Size: Typically between 5-150 kDa
•Full-length proteins with more complex structures compared to peptides.

Classes of Macromolecule Therapies

Monoclonal Antibodies (mAbs):
•Examples: Rituximab (~145 kDa), Trastuzumab (~148 kDa)
•Size: ~145-150 kDa
•Large, Y-shaped proteins that specifically target antigens

Nucleic Acid-Based Therapies (Antisense Oligonucleotides, siRNA):
•Examples: Nusinersen (~7 kDa), Patisiran (~14 kDa)
•Size: Varies but generally ranges from 7-30 kDa
•Short synthetic sequences of nucleotides that interfere with gene expression.



Challenges of Macromolecule delivery

Poor Oral Bioavailability

1. Degradation in the GI tract
2. Poor absorption

Limited Cellular Uptake

Size and polarity
Endosomal entrapment (vs. passive diffusion)

Rapid Clearance and Short Circulatory Half-Life

Kidney filtration
Immune reactions/toxicity

Immunogenicity

Challenges of Macromolecule delivery

Poor Oral Bioavailability

1. Degradation in the GI tract
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Limited Cellular Uptake

Size and polarity
Endosomal entrapment (vs. passive diffusion)

Rapid Clearance and Short Circulatory Half-Life

Kidney filtration
Immune reactions/toxicity

Immunogenicity

Poor Stability

Degradation by enzymes (e.g. RNAses)
Structural sensitivity
Limited shelf-life

Crossing Biological Barriers

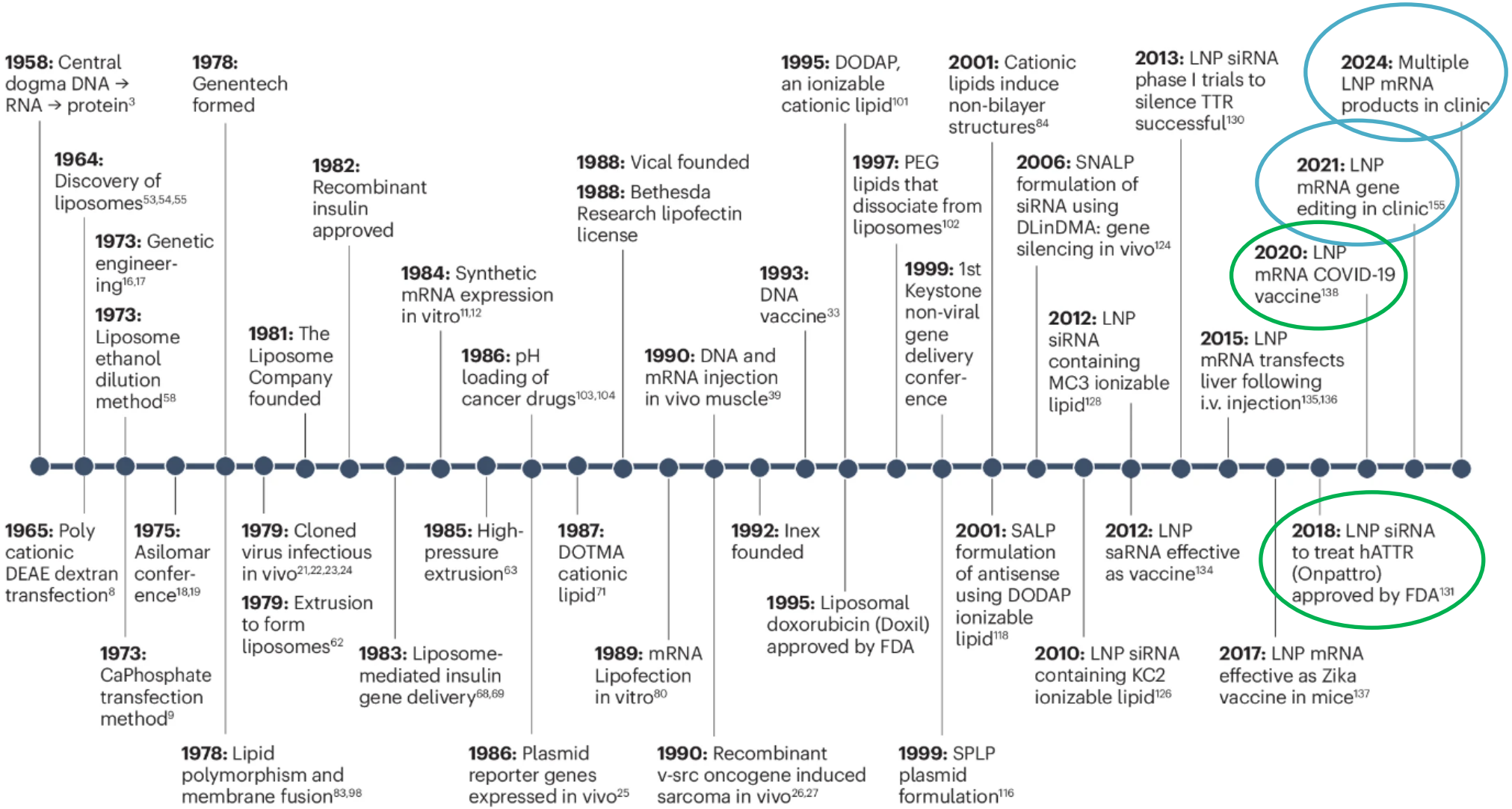
Blood-brain barrier (BBB)
Tumor penetration

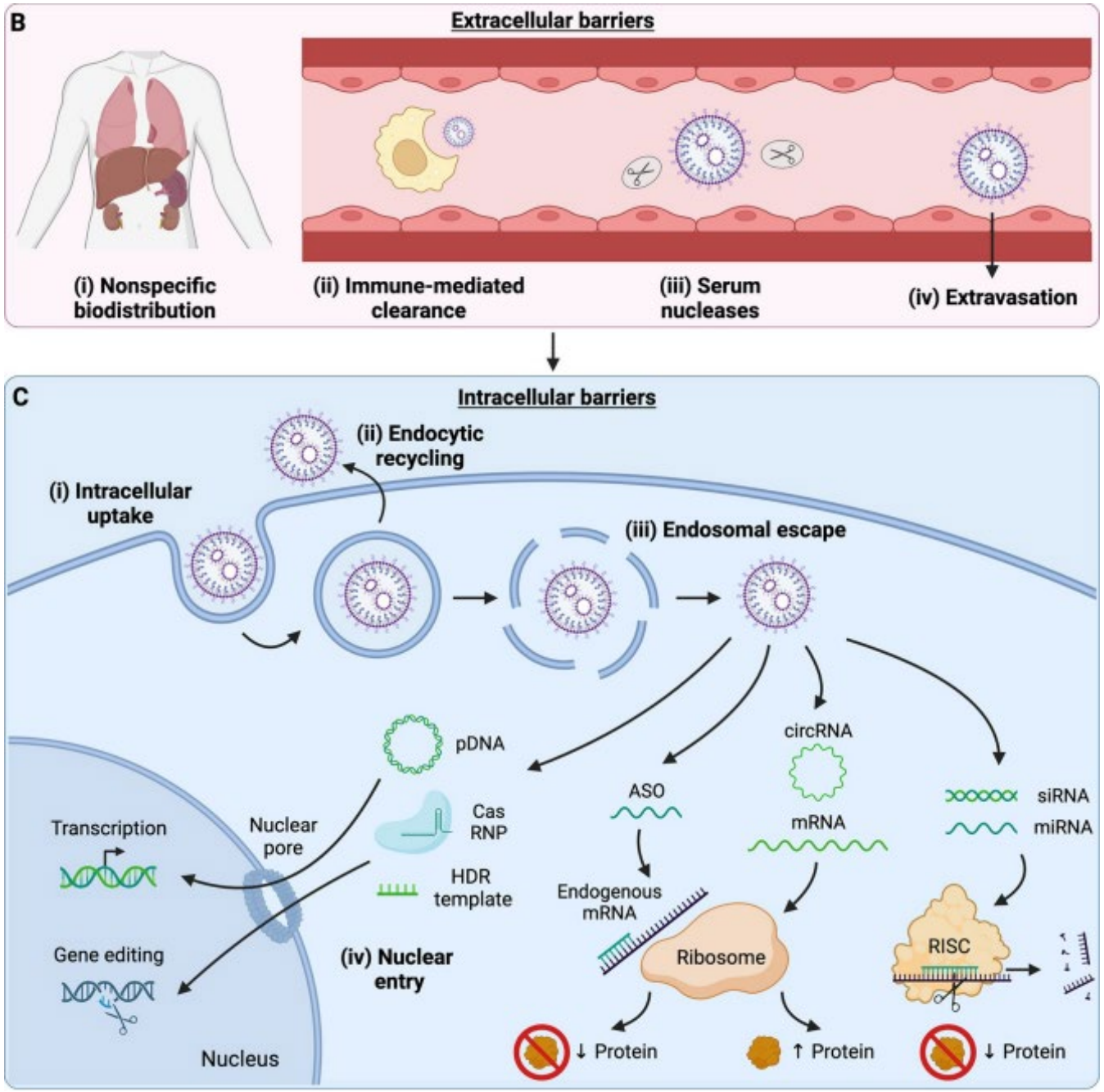
Patient Compliance

Invasive delivery methods
Frequent dosing

Delivery of siRNA, mRNA

Timeline of events leading to LNP-enabled RNA vaccines and therapeutics





Hamilton et al. PLoS Biol, 2023

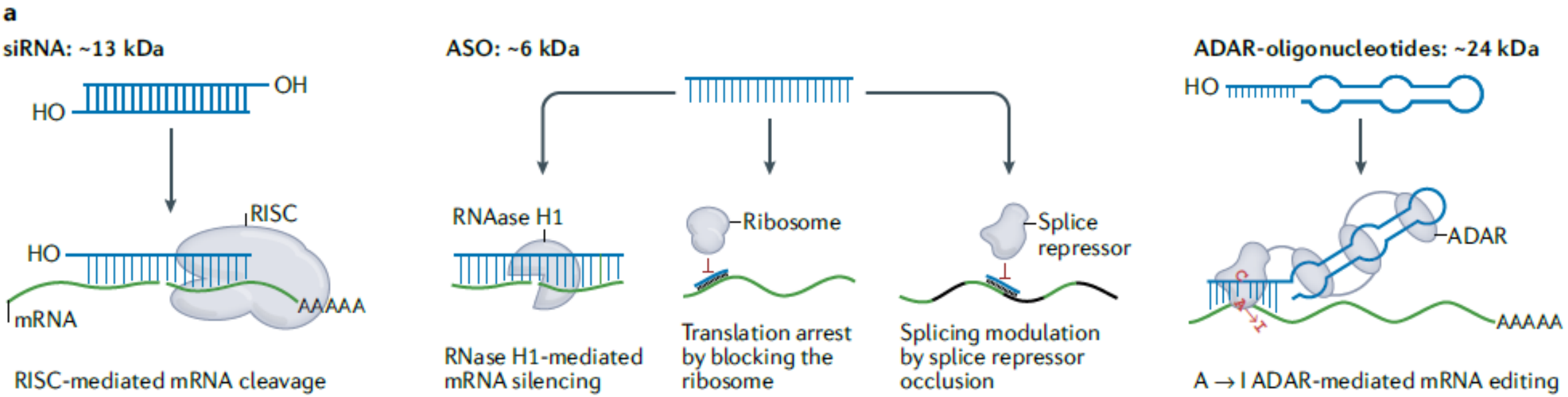
Challenges with nucleic acid delivery

- Stability
- Efficient Cellular Uptake & Release
- Immune Response
- Targeting Specific Cells
- Rapid Clearance
- Off-target effect

RNA
- Stability
- Rapid Clearance

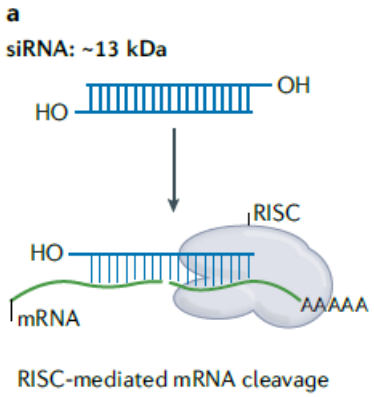
pDNA/ Gene therapy
- Nuclear Delivery
- Off-target Effects and Integration Risks (Insertion into unintended locations)
- Long-term Expression Control
- Immunogenicity

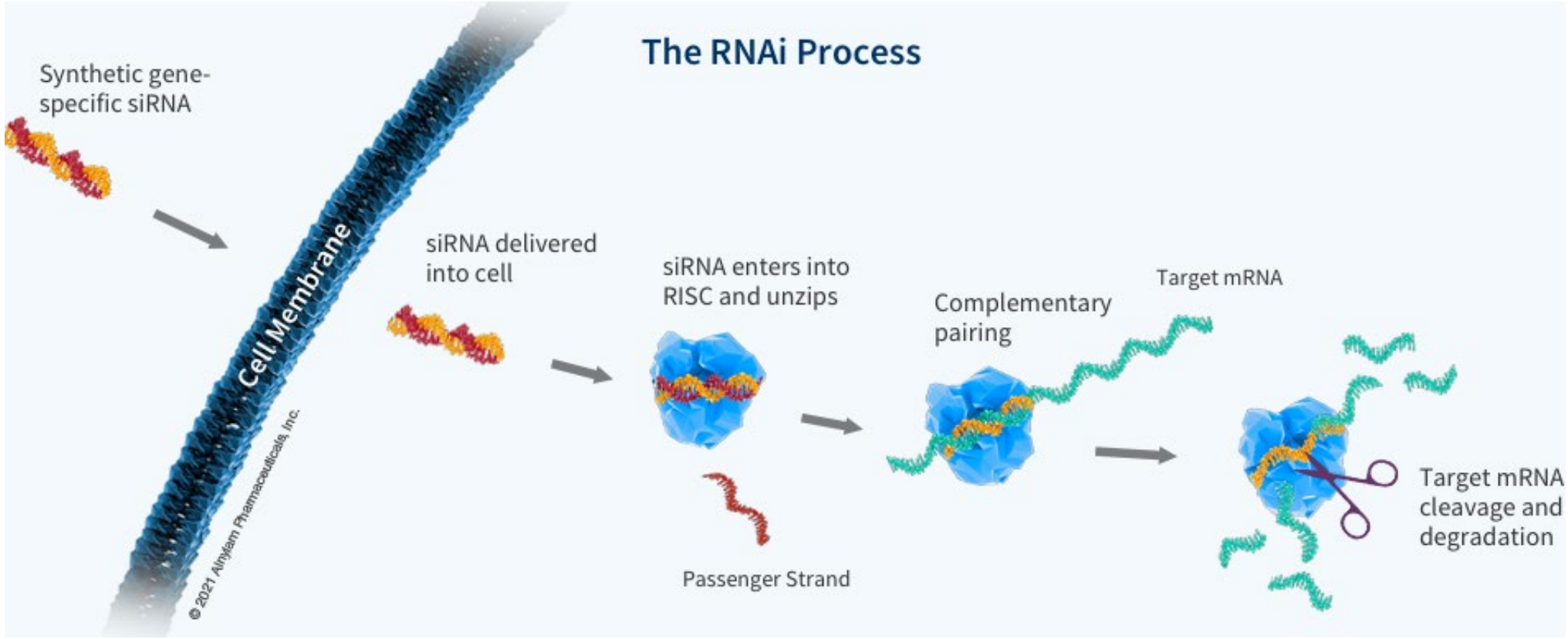
Small RNA therapeutics: siRNA, ASO, ADAR



Paunovska et al. Nat Rev Genet 2022

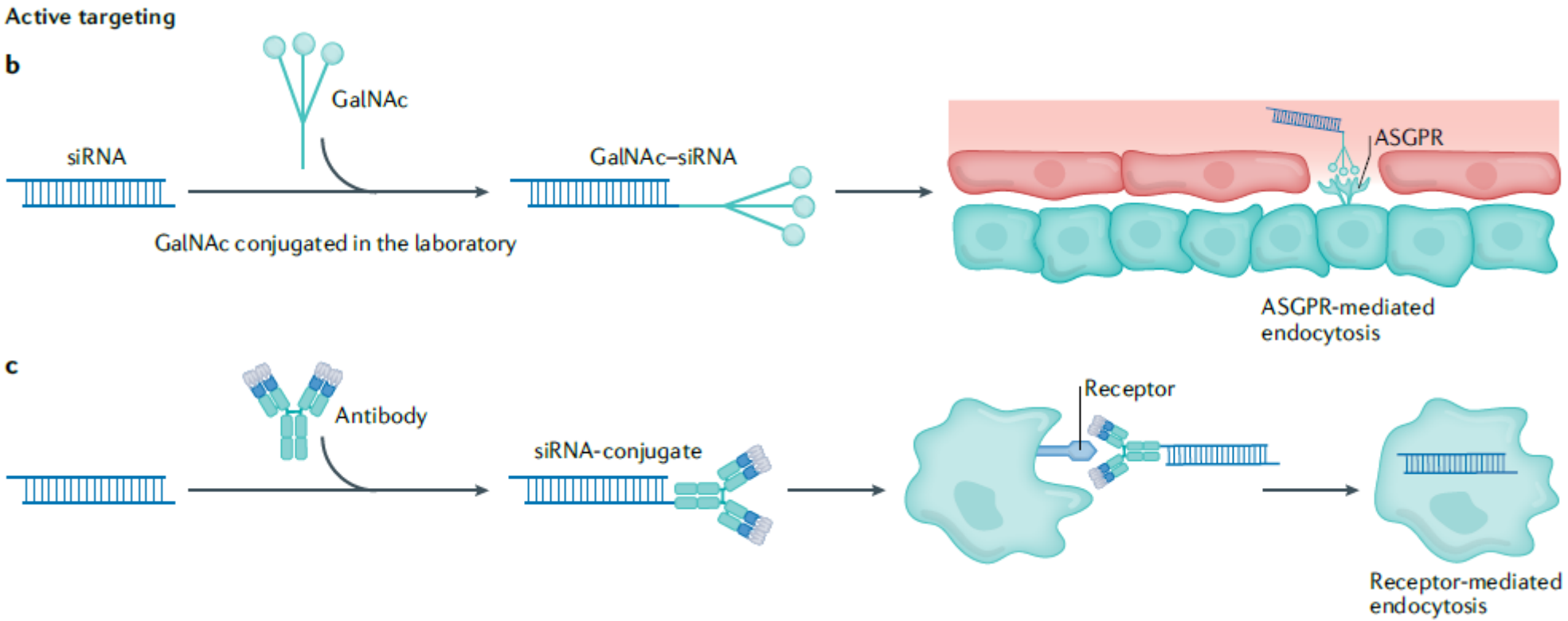
Small RNA therapeutics: siRNA





DDS for siRNA/ ASO delivery: ligand/antibody conjugation

Can be used for **siRNA/ ASO ONLY**, NOT mRNA or CRISPR



FDA-Approved siRNA with GalNAC conjugation

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

Acute hepatic porphyria (AHP)

2019

OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

Primary hyperoxaluria type 1 (PH1)

2020

LEQVIO® (inclisiran) injection 284 mg/1.5 mL

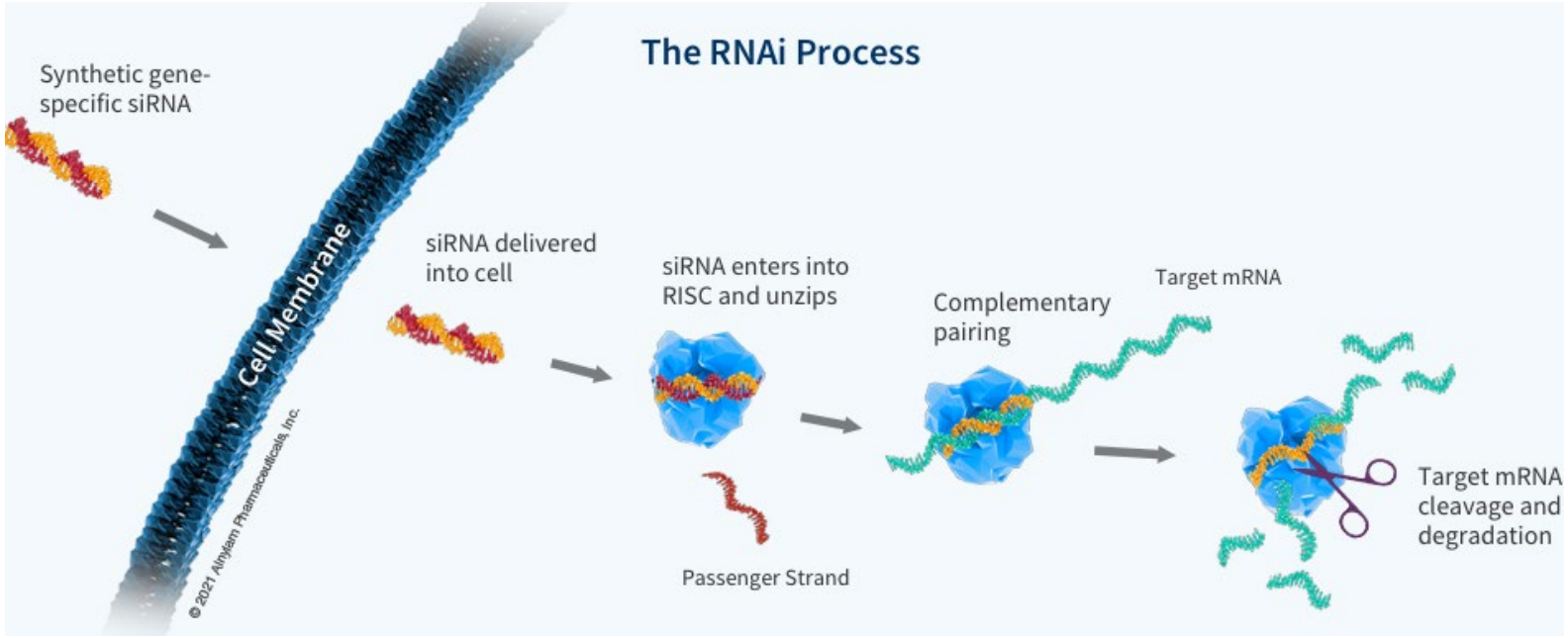
Hypercholesterolemia (high cholesterol)

2021

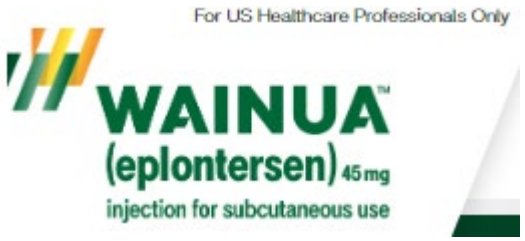
amvuttra® (vutrisiran) injection 25 mg/0.5 mL

Hereditary transthyretin-mediated amyloidosis (hATTR)

2022

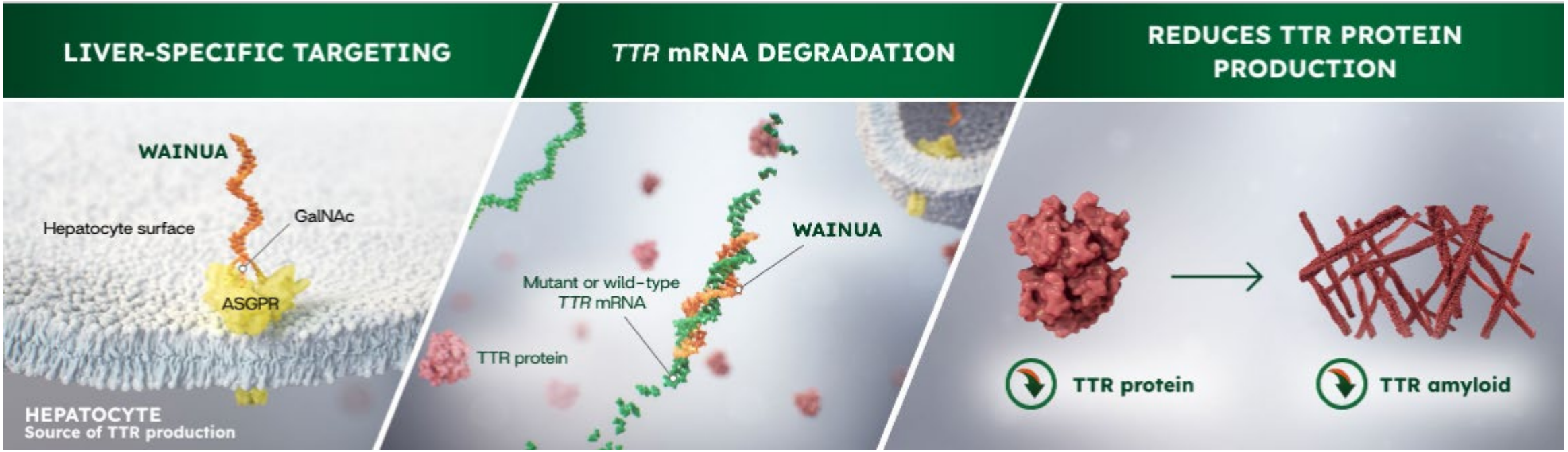


FDA-Approved ASO with GalNAC conjugation

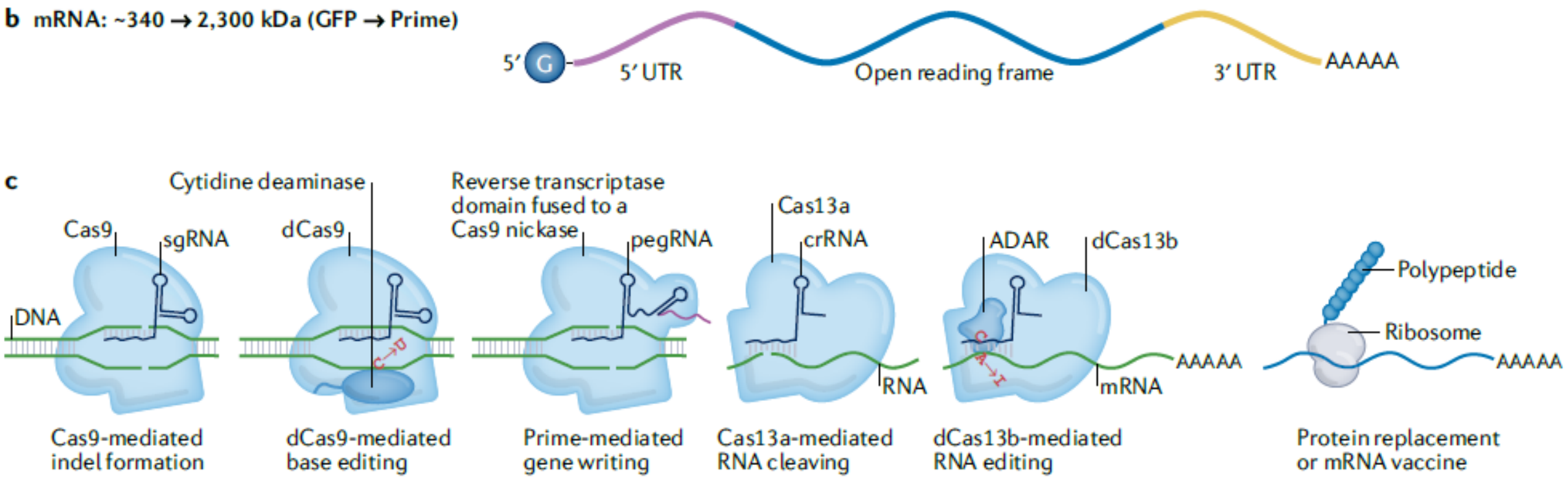


2023

polyneuropathy of hereditary transthyretin-mediated amyloidosis



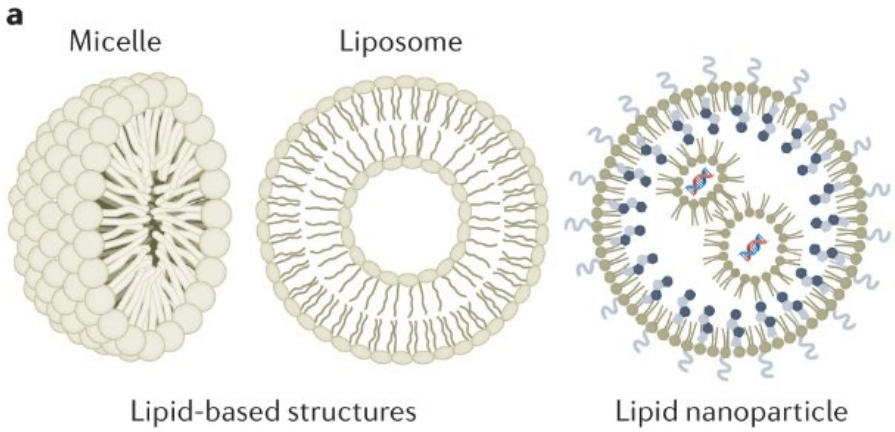
Large RNA therapeutic payloads: mRNA

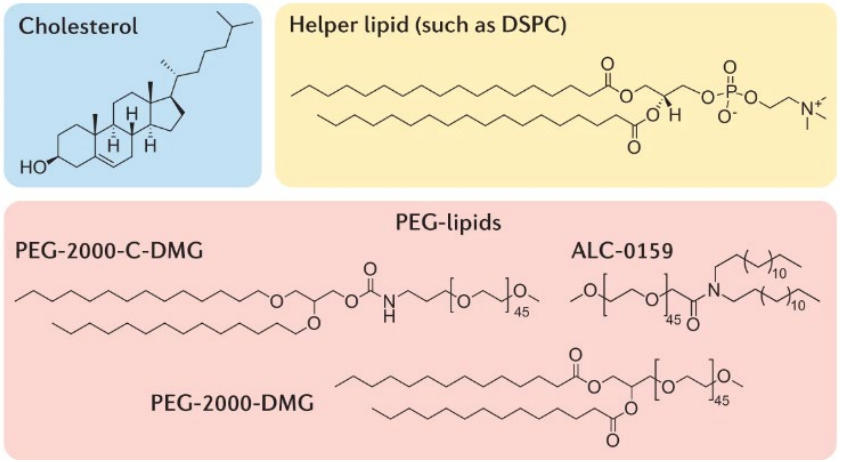


Paunovska et al. Nat Rev Genet 2022

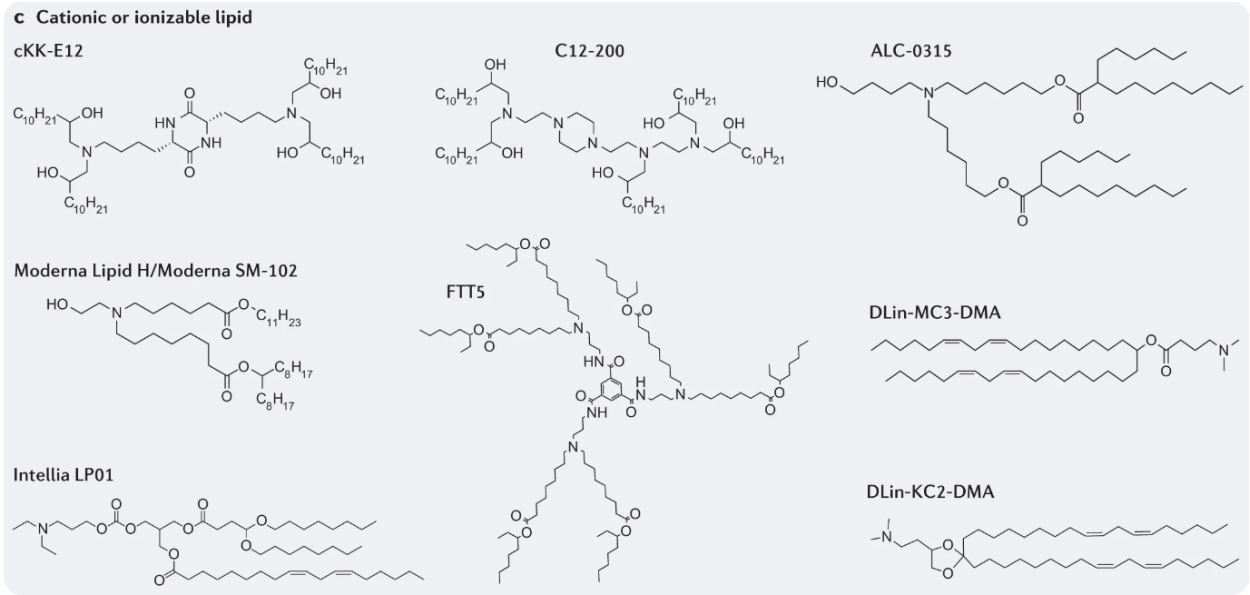
DDS for RNA delivery: Lipid nanoparticles

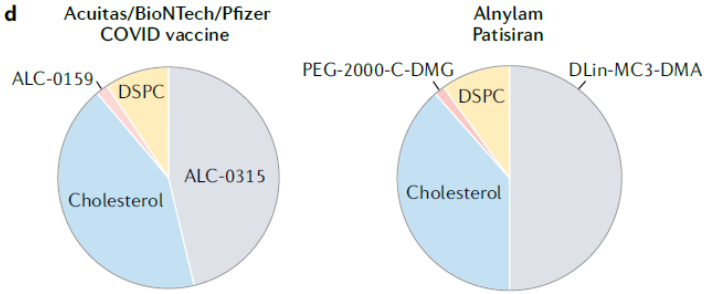
Can be used for **siRNA**, **mRNA** or **CRISPR**



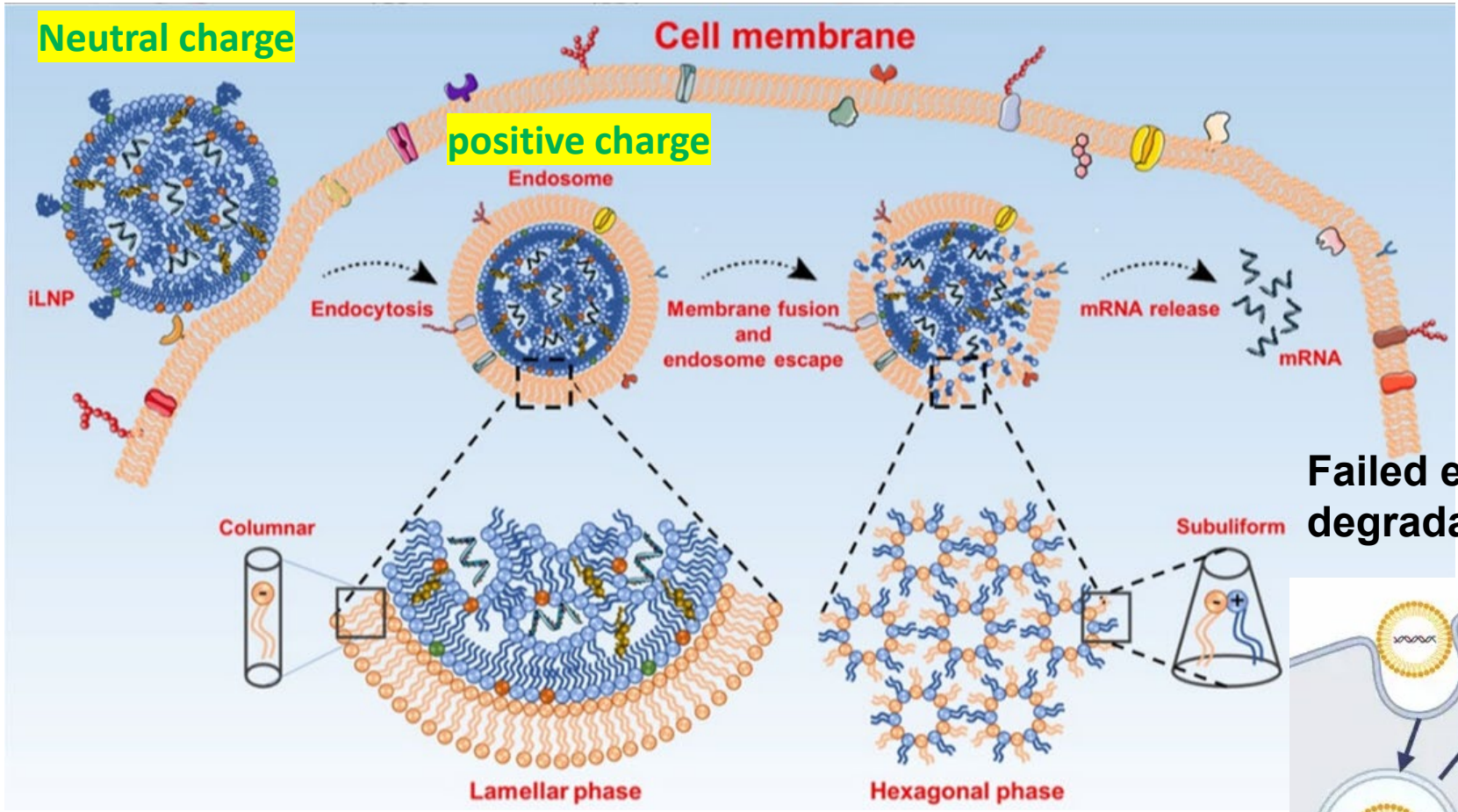


All the lipids in part **c** contain amine groups, which become positively charged at lower pH



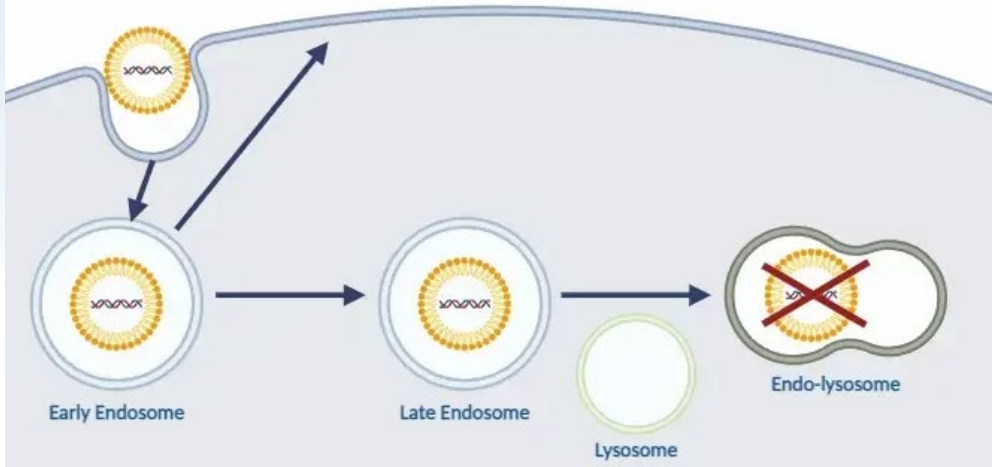


The role of ionizable lipids in endosomal escape



Successful endosomal escape-> cargo release

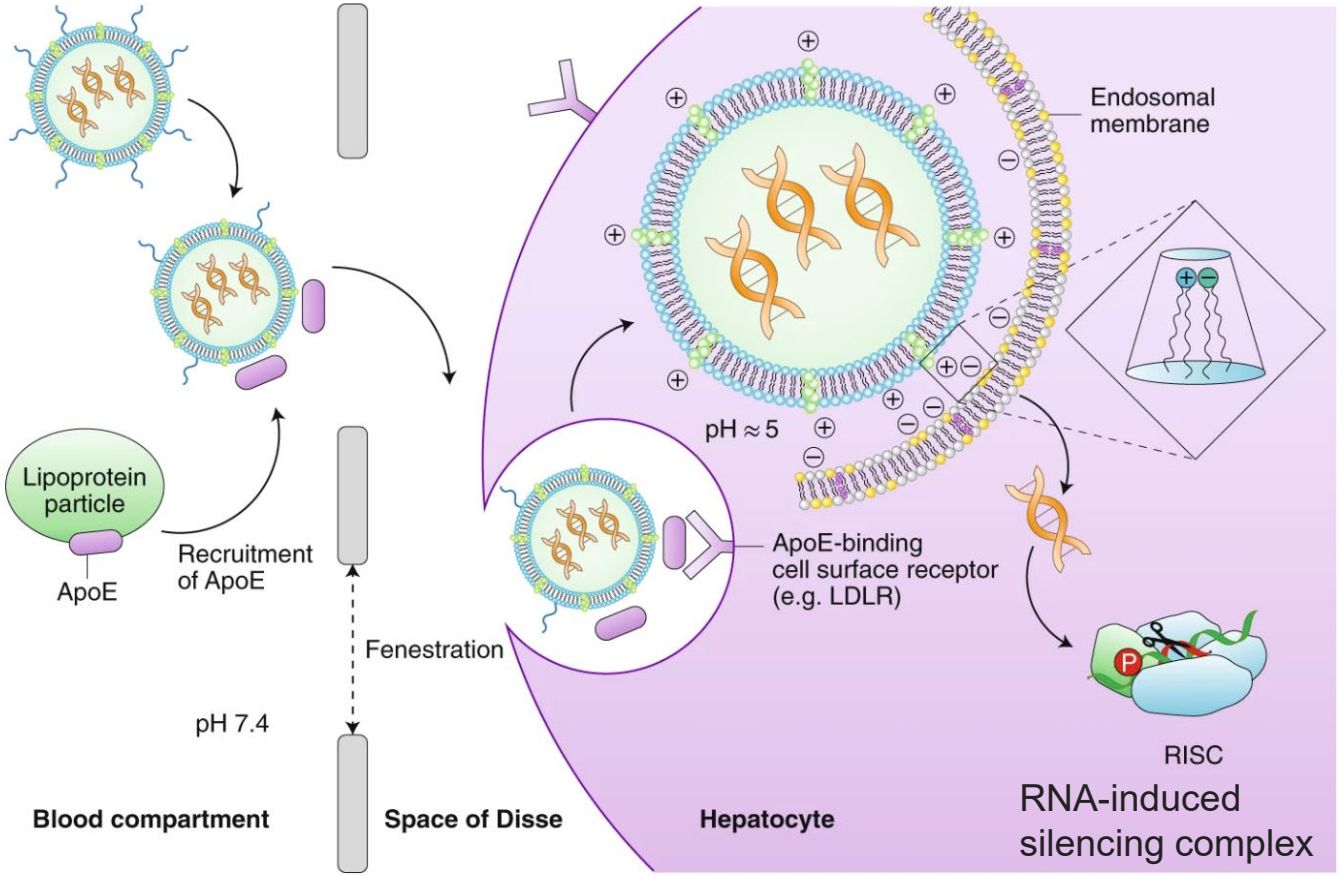
Failed endosomal escape-> cargo degradation



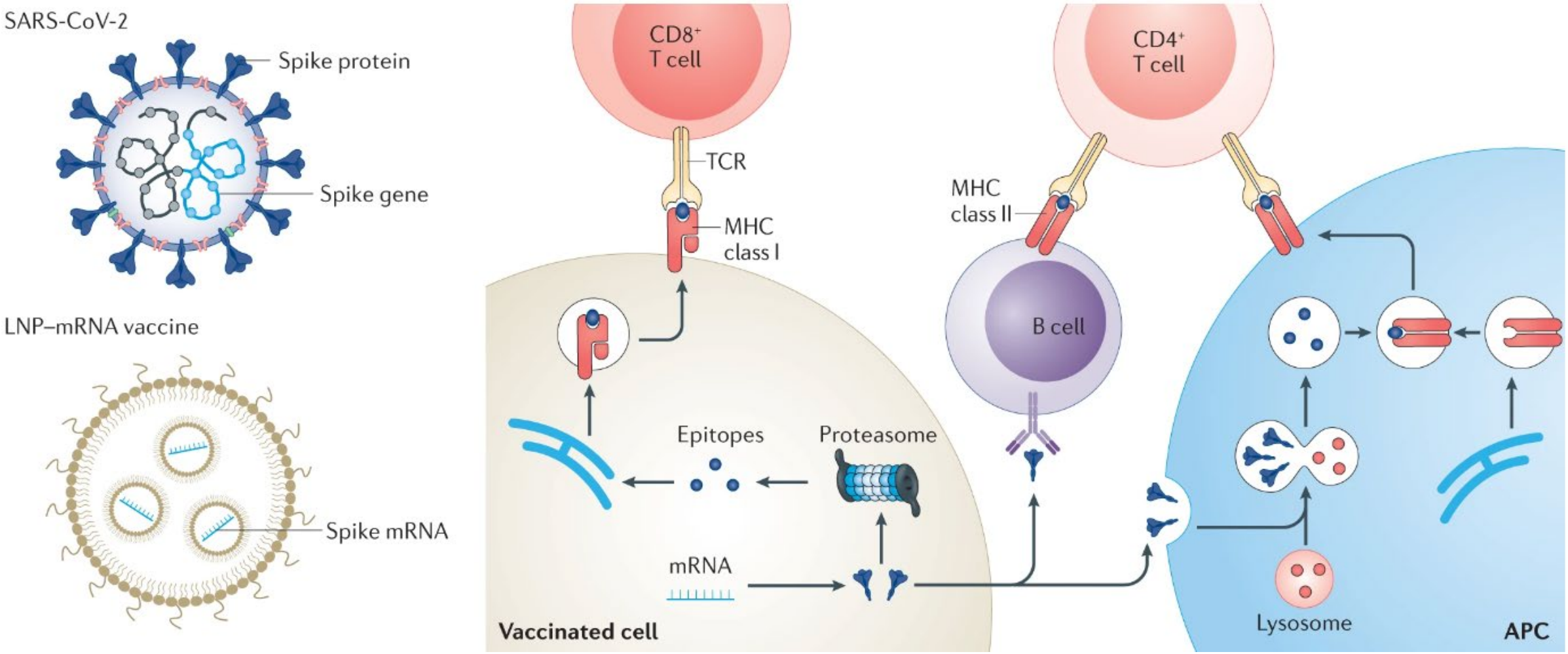
FDA-Approved siRNA-LNP: Patisiran (Onpattro) (2018)

- Treatment of polyneuropathies resulting from the hereditary disease t**ransthyretin-mediated** amyloidosis (hATTR).
- This drug acts by **inhibiting the synthesis of the transthyretin (TTR) protein** in the **liver**

onpattro (patisiran) lipid complex injection 10 mg/5 mL

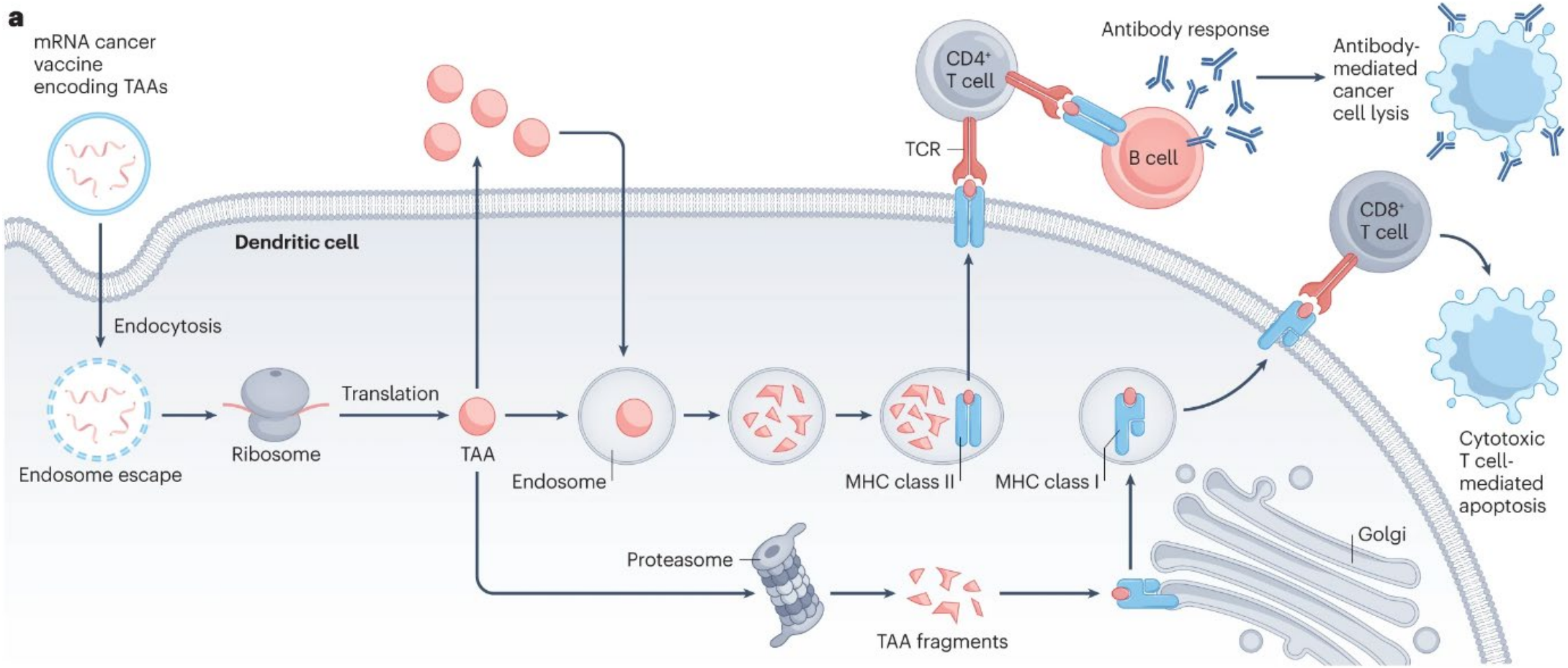


FDA-Approved mRNA-LNP: COVID19 Vaccines



Zaks et al. Nat Rev Mater 2021

mRNA for cancer therapy: cancer vaccines



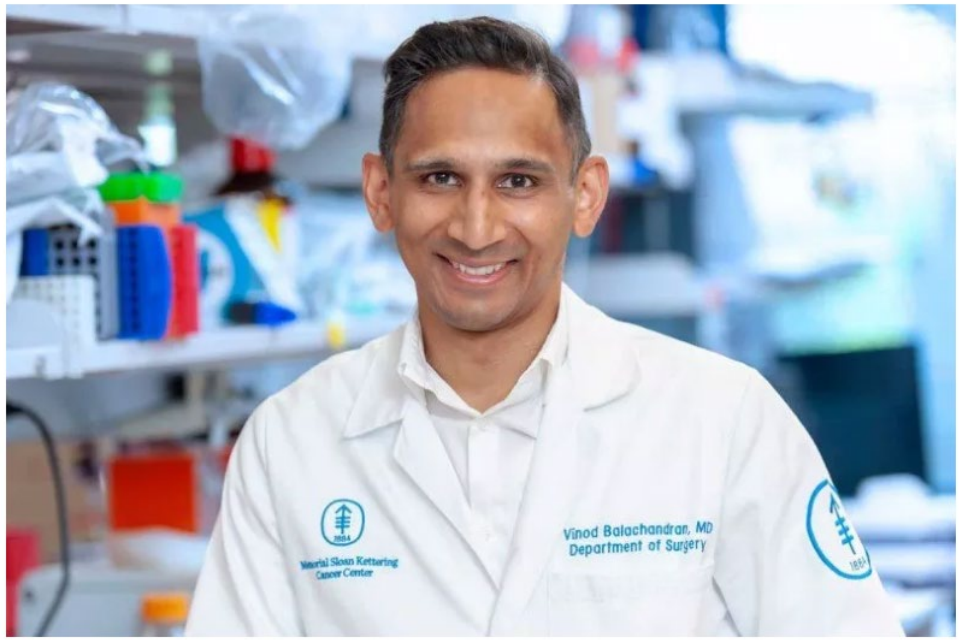
Liu et al, Nat Rev Cancer 2023

mRNA for cancer therapy: cancer vaccines

Investigational mRNA Vaccine Induced Persistent Immune Response in Phase 1 Trial of Patients With Pancreatic Cancer

Share

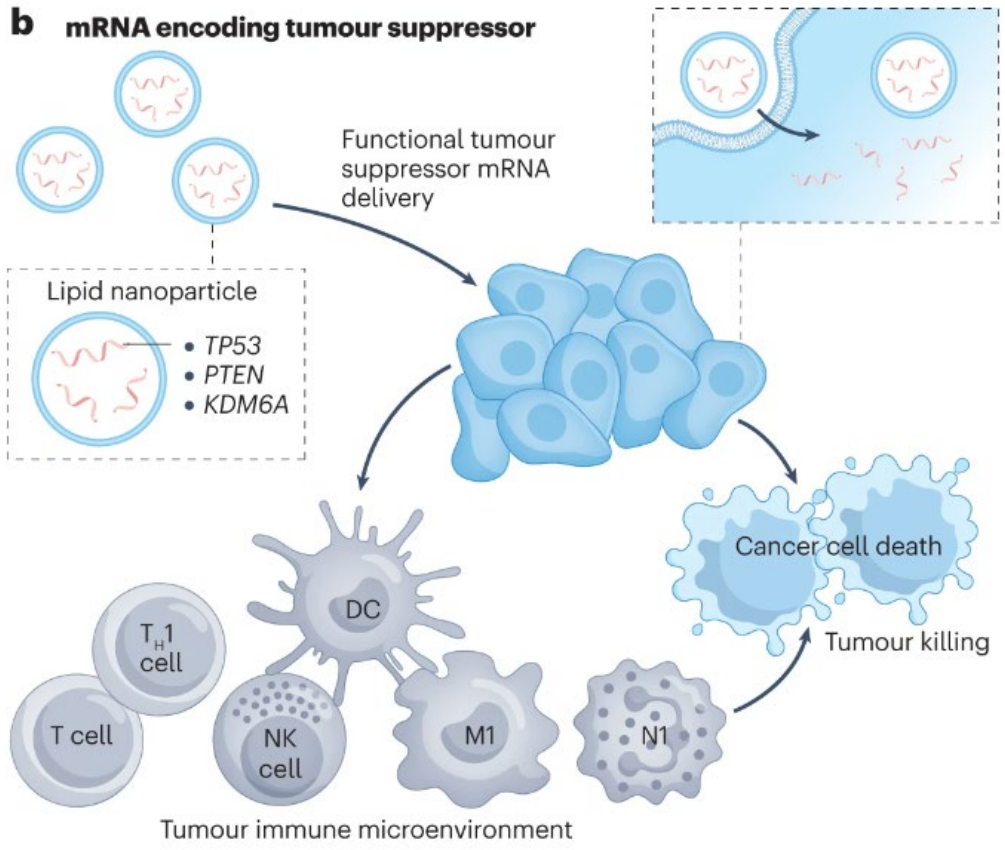
By Jim Stallard, **Sunday, April 7, 2024**



Dr. Vinod Balachandran says mRNA vaccines could stimulate the immune system to recognize and attack pancreatic cancer cells.

- In 8 patients, the vaccine activated a T cell response, and 6 of these patients had not seen their cancers return during the follow-up window. The other 2 patients relapsed.
- Cancer returned in 7 of the 8 patients whose immune systems did not respond to the vaccine during the study period.
- In the 8 patients who responded, 98% of the T cells specifically activated by the cancer vaccines were not present before vaccination.
- More than 80% of the vaccine-induced T cells persisted from two to up to three years after treatment.

mRNA for cancer therapy: tumor suppressors



Liu et al, Nat Rev Cancer 2023

Synthetic mRNA nanoparticle-mediated restoration of p53 tumor suppressor sensitizes *p53*-deficient cancers to mTOR inhibition

NA KONG, WEI TAO, XIANG LING, JUNQING WANG, YULING XIAO, SANJUN SHI, XIAOYUAN JI, ARAM SHAJII, SILVIA TIAN GAN, [...], AND JINJUN SHI
+4 authors Authors Info & Affiliations

SCIENCE TRANSLATIONAL MEDICINE · 18 Dec 2019 · Vol 11, Issue 523 · DOI: 10.1126/scitranslmed.aaw1565

Article | Published: 17 September 2018

Restoration of tumour-growth suppression in vivo via systemic nanoparticle-mediated delivery of *PTEN* mRNA

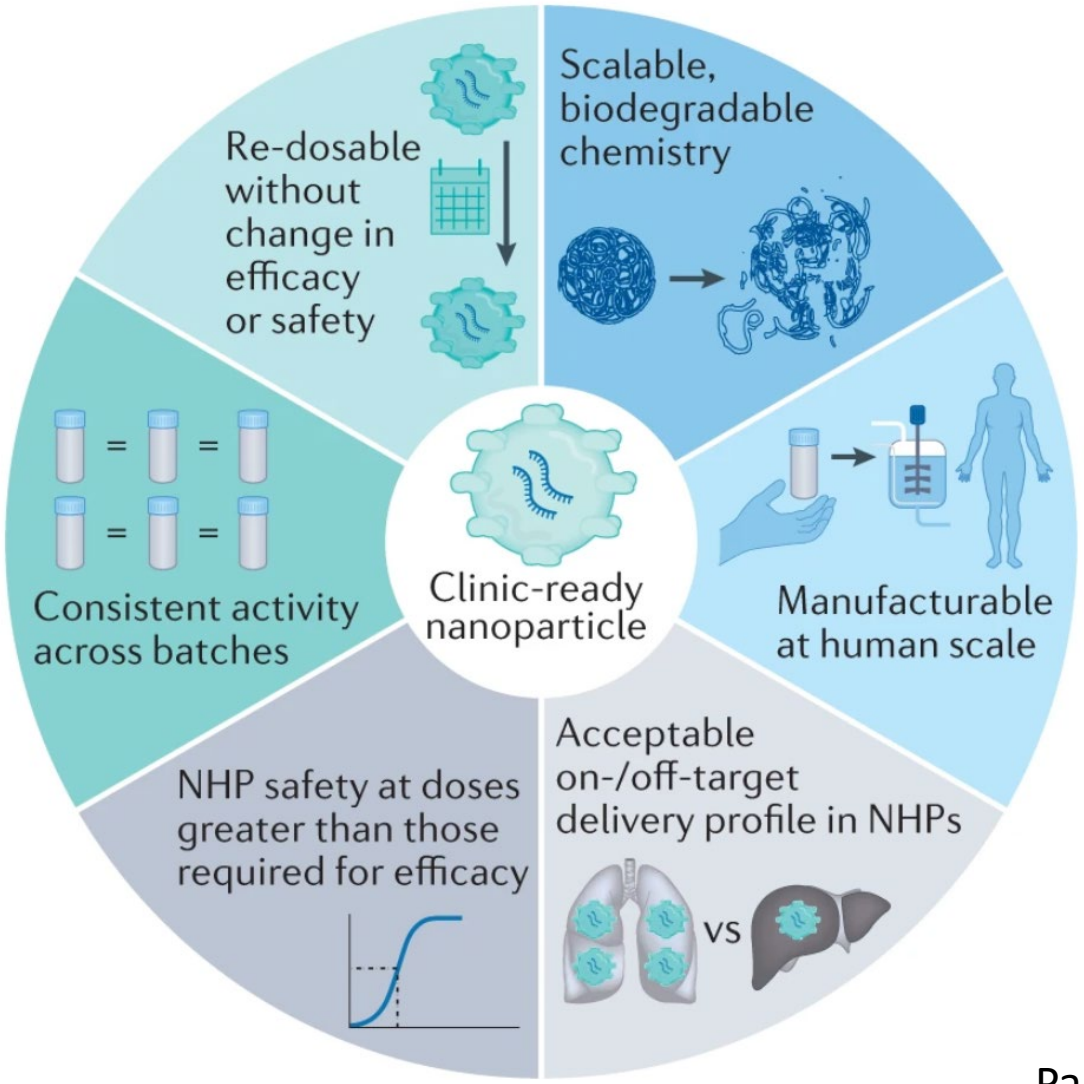
Mohammad Ariful Islam, Yingjie Xu, Wei Tao, Jessalyn M. Ubellacker, Michael Lim, Daniel Aum, Gha Young Lee, Kun Zhou, Harshal Zope, Mikyung Yu, Wuji Cao, James Trevor Oswald, Meshkat Dinarvand, Morteza Mahmoudi, Robert Langer, Philip W. Kantoff, Omid C. Farokhzad, Bruce R. Zetter & Jinjun Shi

Nature Biomedical Engineering **2**, 850–864 (2018) | Cite this article

4. Design Considerations for clinical translation

From Bench to Bedside: Nanoparticle Pipeline

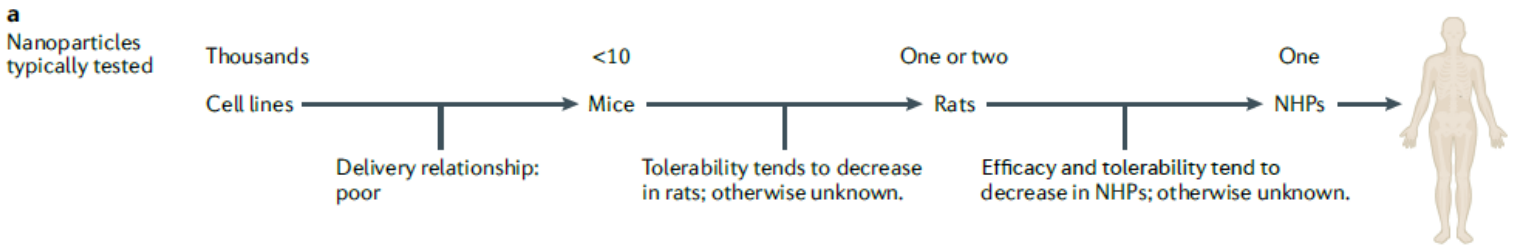
The hallmarks of a clinically relevant delivery system



Paunovska et al. Nat Rev Genet 2022

From Bench to Bedside: Nanoparticle Pipeline

a



b

	Mice	% of bw	Rats	% of bw	NHPs	% of bw	Humans	% of bw
Brain		2.1		0.9		1.4		1.9
Heart		0.6		0.4		0.4		0.4
Lung		0.7		0.5		0.6		1.0
Liver		4.5		3.0		2.2		2.0
Spleen		0.4		0.2		0.1		0.2
Kidney		1.4		0.8		0.4		0.3

Key Factors in DDS Design (Interactive!)

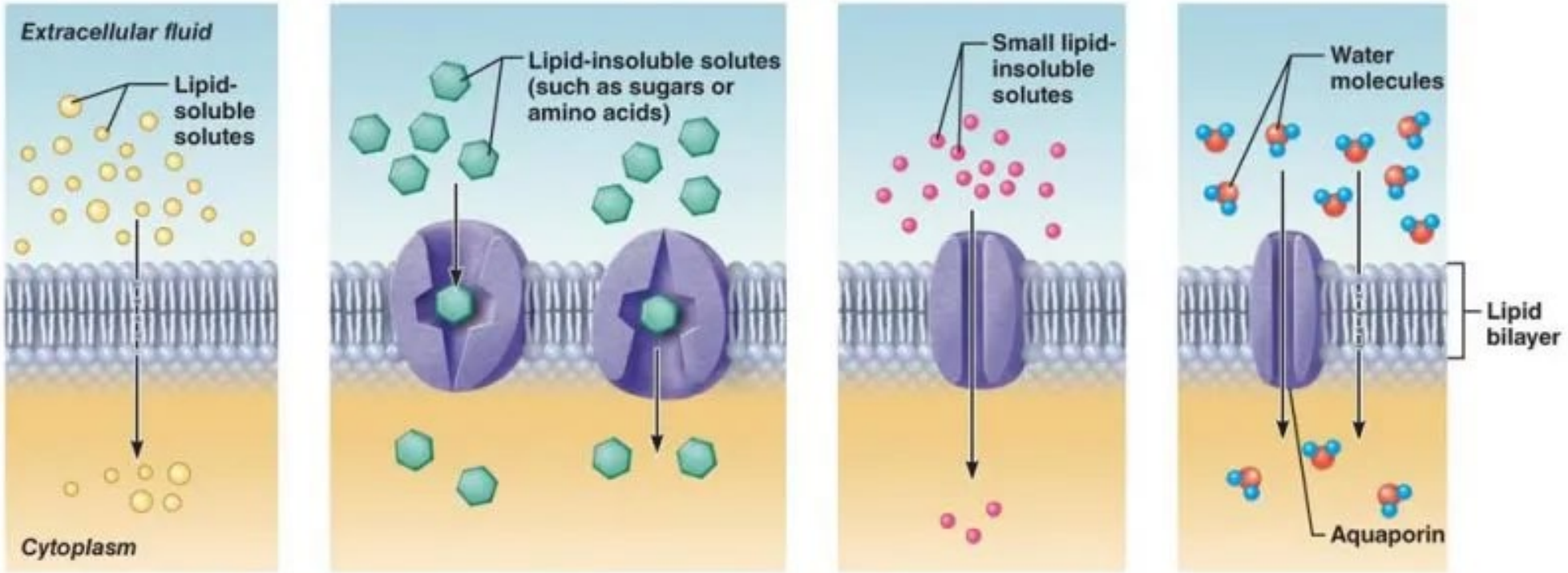
Which factors might influence your design in a new drug delivery system? (multiple)

Key Factors in DDS Design (Interactive!)

- Drug Properties: Solubility, stability, molecular size.
- Method of treatment: Local vs. systemic delivery.
- Therapeutic situation: Prevention or treatment?
- Route of Administration
- Desired Pharmacokinetics and Pharmacodynamics: Controlled release, half-life.
- Dosage Frequency
- Biocompatibility and Safety: Minimizing immune response.
- Cost and Scalability: Manufacturing feasibility and affordability.
- Patient age
- Patient condition (sedated vs awake)

Thank you for your attention! ☺

Back-up slides

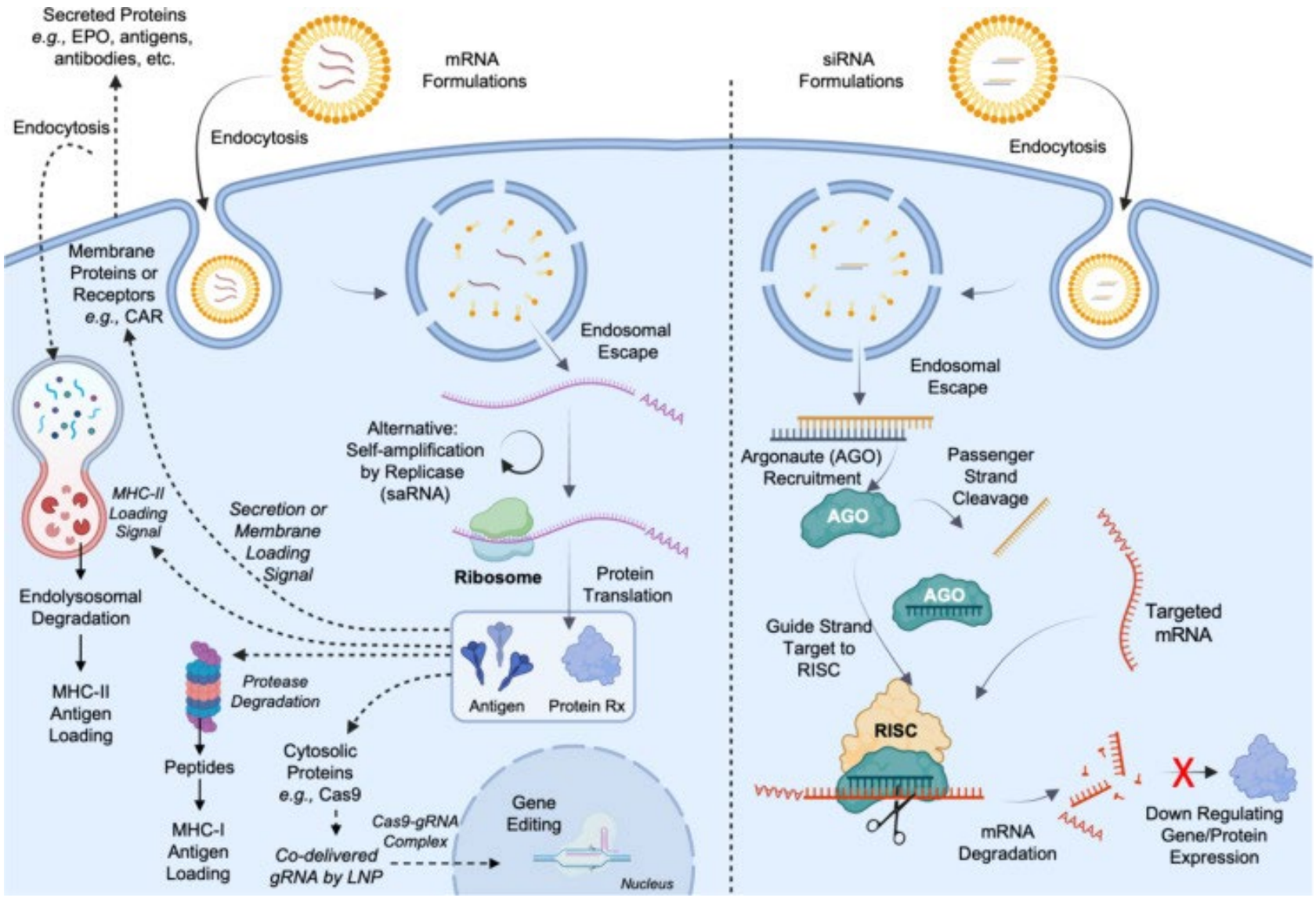


(a) Simple diffusion of fat-soluble molecules directly through the phospholipid bilayer

(b) Carrier-mediated facilitated diffusion via protein carrier specific for one chemical; binding of substrate causes transport protein to change shape

(c) Channel-mediated facilitated diffusion through a channel protein; mostly ions selected on basis of size and charge

(d) Osmosis, diffusion of a solvent such as water through a specific channel protein (aquaporin) or through the lipid bilayer


Secreted Proteins
e.g., EPO, antigens, antibodies, etc.
Endocytosis
mRNA Formulations
Endocytosis
Membrane Proteins or Receptors e.g., CAR
Endosomal Escape
Alternative: Self-amplification by Replicase (saRNA)
MHC-II Loading Signal
Secretion or Membrane Loading Signal
Ribosome
Protein Translation
Endolysosomal Degradation
MHC-II Antigen Loading
Protease Degradation
Antigen
Protein Rx
Peptides
MHC-I Antigen Loading
Cytosolic Proteins e.g., Cas9
Cas9-gRNA Complex
Co-delivered gRNA by LNP
Gene Editing
Nucleus
siRNA Formulations
Endocytosis
Endosomal Escape
Argonaute (AGO) Recruitment
Passenger Strand Cleavage
AGO
AGO
Guide Strand Target to RISC
Targeted mRNA
RISC
mRNA Degradation
Down Regulating Gene/Protein Expression