A11/00

Design and optimization of nanomedicines

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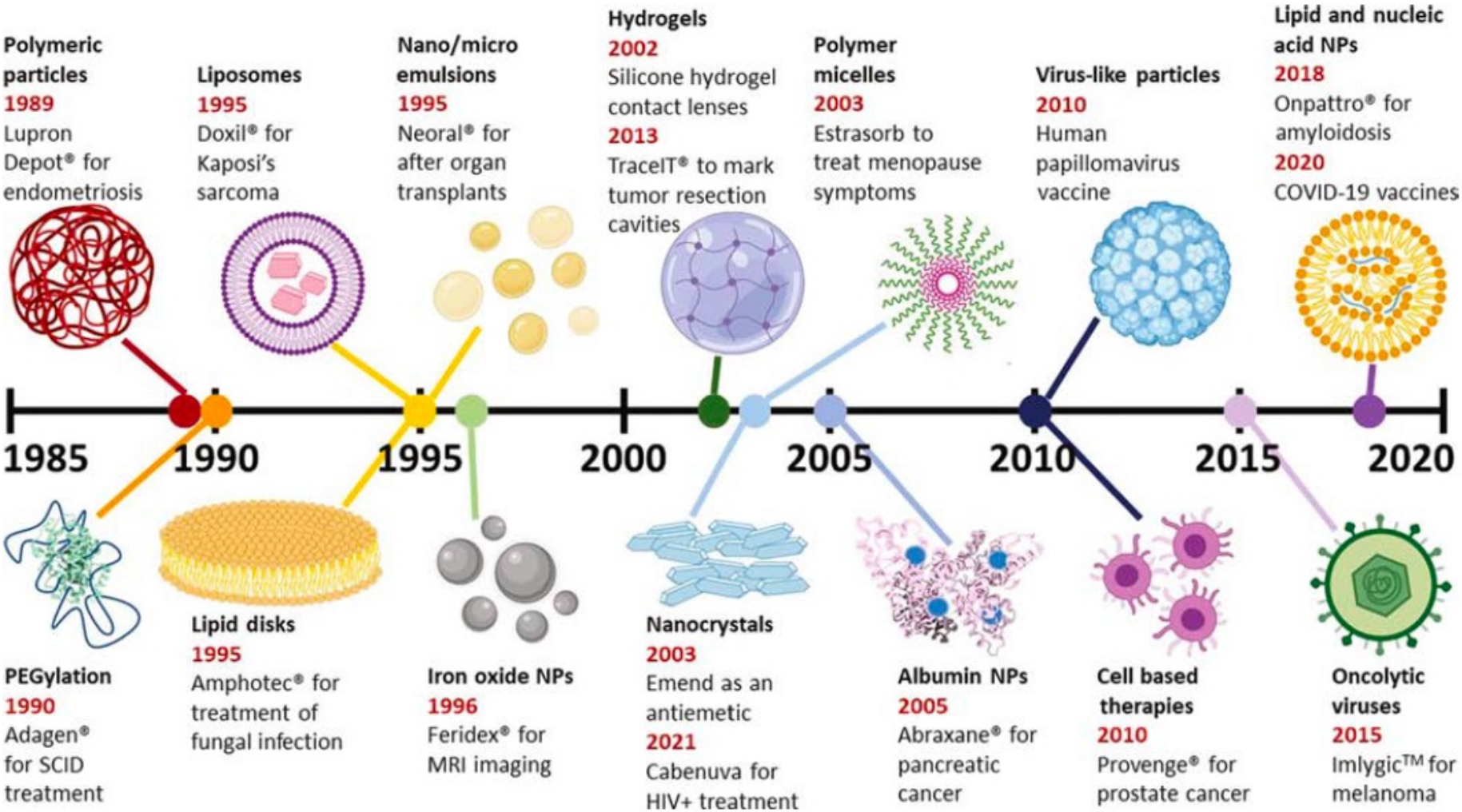
Nanotechnology for Drug Delivery Applications

Where is a nanoparticle?



Batty et al, Trends in Molecular Medicine, 27, 6, 2021

Nanotechnology for Drug Delivery Applications

Where is a nanoparticle?

Material	Example formulations made from material	Advantages	Drawbacks
Lipids Fatty acids or their derivatives that are soluble in organic solvents but not water	**Liposomes** Doxil® AmBiosome® **Lipid Disks** Amphotec® **Lipid Nanoparticles** Onpattro® COVID-19 vaccines	• Tendency to assemble into nanostructures • Low molecular weight and biodegradability can mean low toxicity • Good encapsulation of hydrophobic drugs	• Expensive synthesis with limited scalability • Can be difficult to encapsulate some hydrophilic drugs • Cationic lipids can cause inflammatory response and toxicity
Polymers Macromolecules with repeated subunits (monomers)	**Polymeric particles** Lupron Depot® Risperdal Consta® **Hydrogels** Cervidil® TraceIT® **PEGylated therapeutics** Adagen® Cimzia® **PEGylated particles** Doxil® COVID-19 vaccines	• Inexpensive synthesis • Sustained and often tunable release of drug cargo • Excellent encapsulation of hydrophobic drugs with hydrophobic polymers and hydrophilic drugs with hydrophilic polymers • PEGylation can reduce opsonization to prolong circulation time	• Molecular-weight dependent toxicity • Hydrophobic polymer-based formulations have the tendency to aggregate in aqueous solutions • Potential immune response may occur against polymer and results in increased clearance of formulation
Surfactants Amphiphilic molecules that reduce surface tension.	**Micelles** Estrasorb® **Emulsions** Neoral® SMOFlipid®	• Solubilizes hydrophobic drugs • Reduce aggregation/stabilize most formulations • Can increase bioavailability	• Some can demonstrate toxicity through membrane disruption

Batty et al, Trends in Molecular Medicine, 27, 6, 2021

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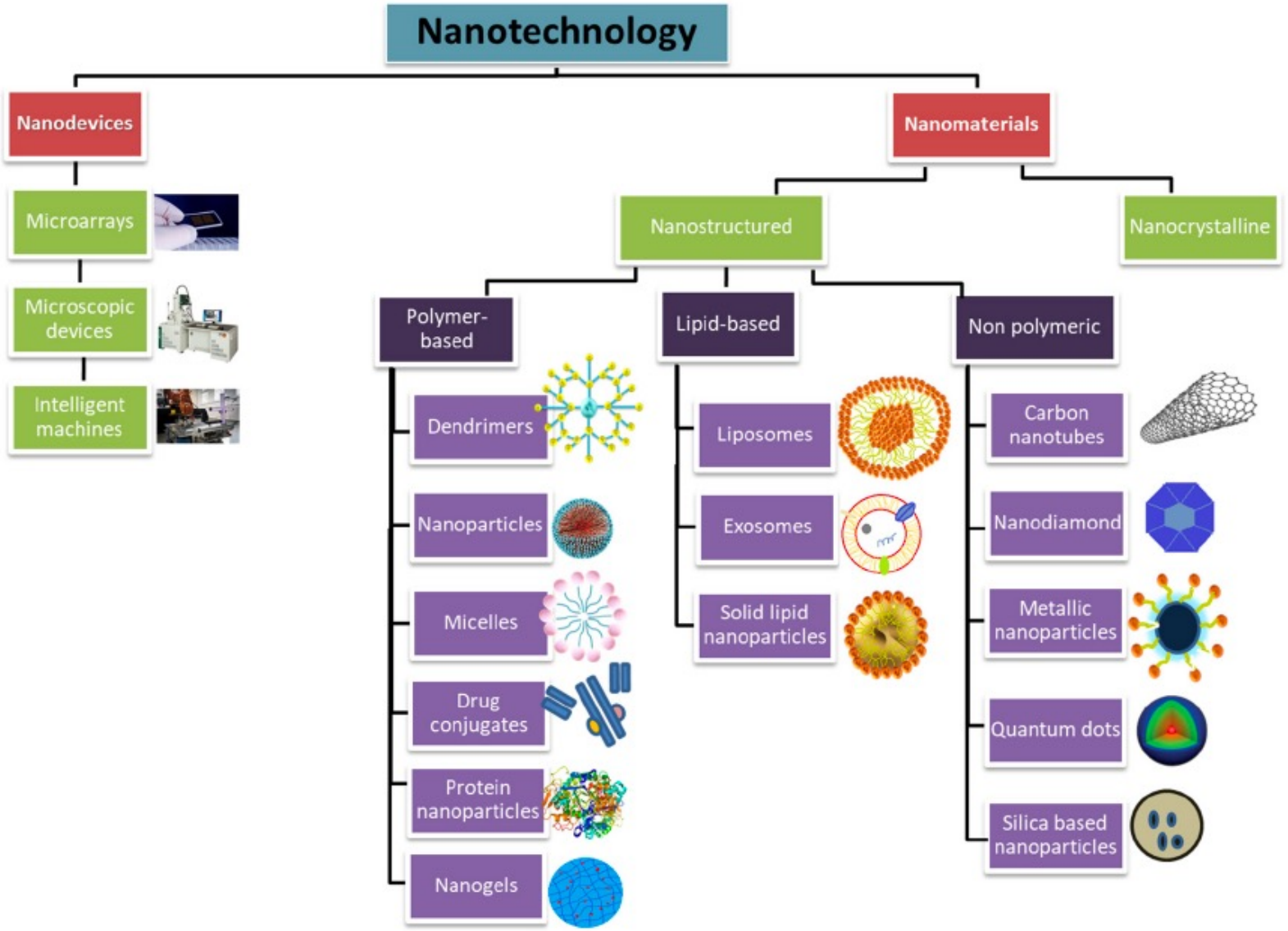

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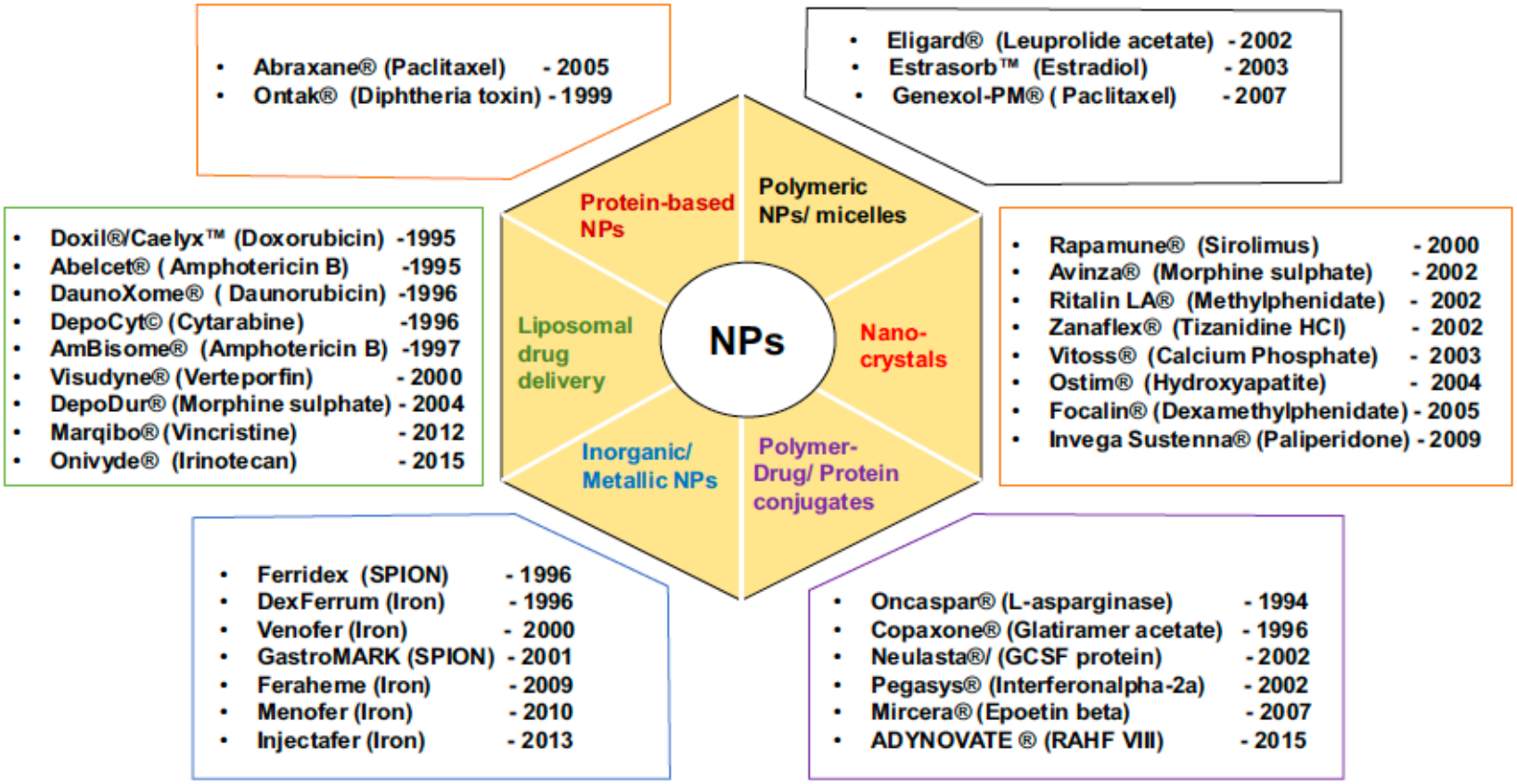

Gadekar et al, J Control Rel 330, 372–393, 2021

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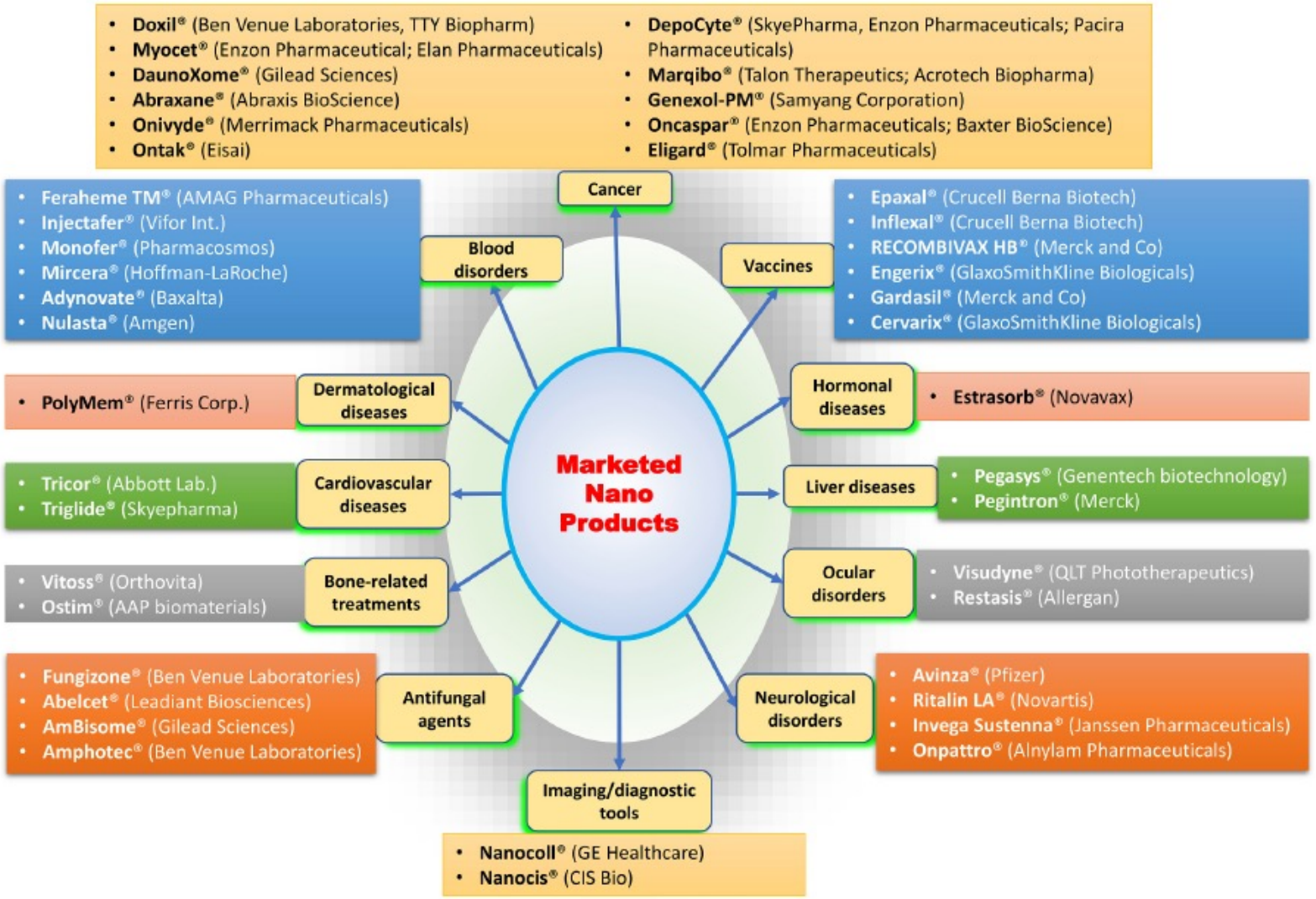

Gadekar et al, J Control Rel 330, 372–393, 2021

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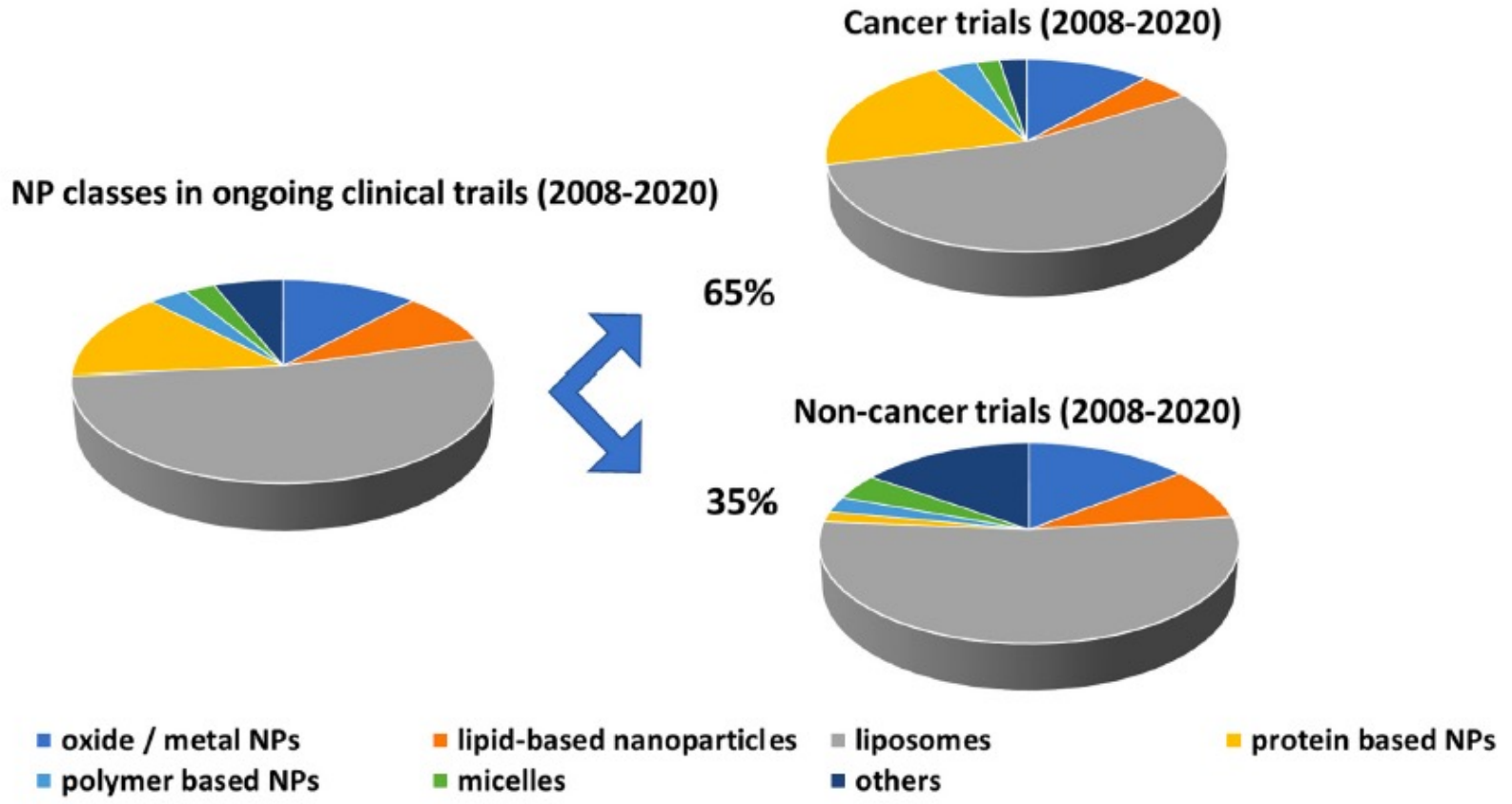
Nanotechnology for Drug Delivery Applications

Nanoparticle classes investigated in ongoing clinical trials



Germain et al, J Control Rel 326, 164–171, 2020

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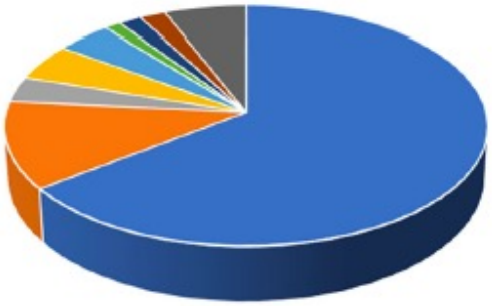
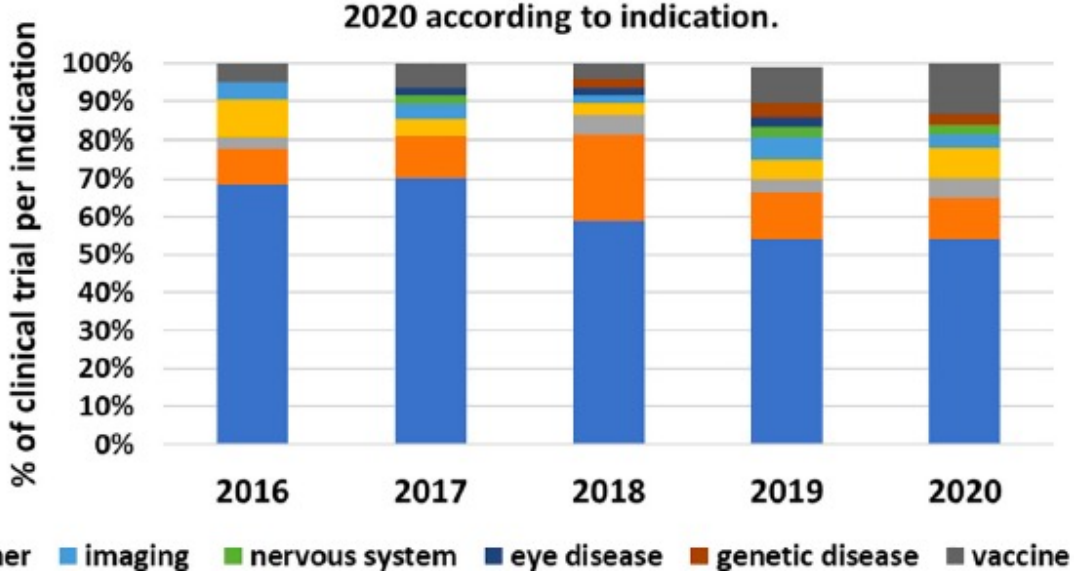
Nanotechnology for Drug Delivery Applications

Clinical trials based on nanomedicine formulation per indication

A) Clinical indications in ongoing clinical trials



B) Categorization of clinical trials on nanomedicines from 2016 to 2020 according to indication.



Germain et al, J Control Rel 326, 164–171, 2020

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Drug delivery – Nanoparticle strategy

The added value of "NANO" **– Does size really matters?**

Improved drug properties

- Solubility
- Dissolution Rate
- Bioavailability
- Drug delivery
- Targeting ability and/or mode of action

Improved dosage properties

- Low dose administration
- Improvement of adverse event profile
- Better usage of dosage forms

Improved patient outcomes

- Efficacy
- Safety and tolerability
- Patient preference
- Patient acceptability
- Administration errors
- Adherence

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Drug delivery – Nanoparticle strategy

The success of the design and optimization of nanoparticles depends on:

- Stability of the delivery system
- Stability of the drug during preparation, delivery, and long-term storage

Stability has been identified as one of the major advantages for the nanoencapsulation of therapeutics.

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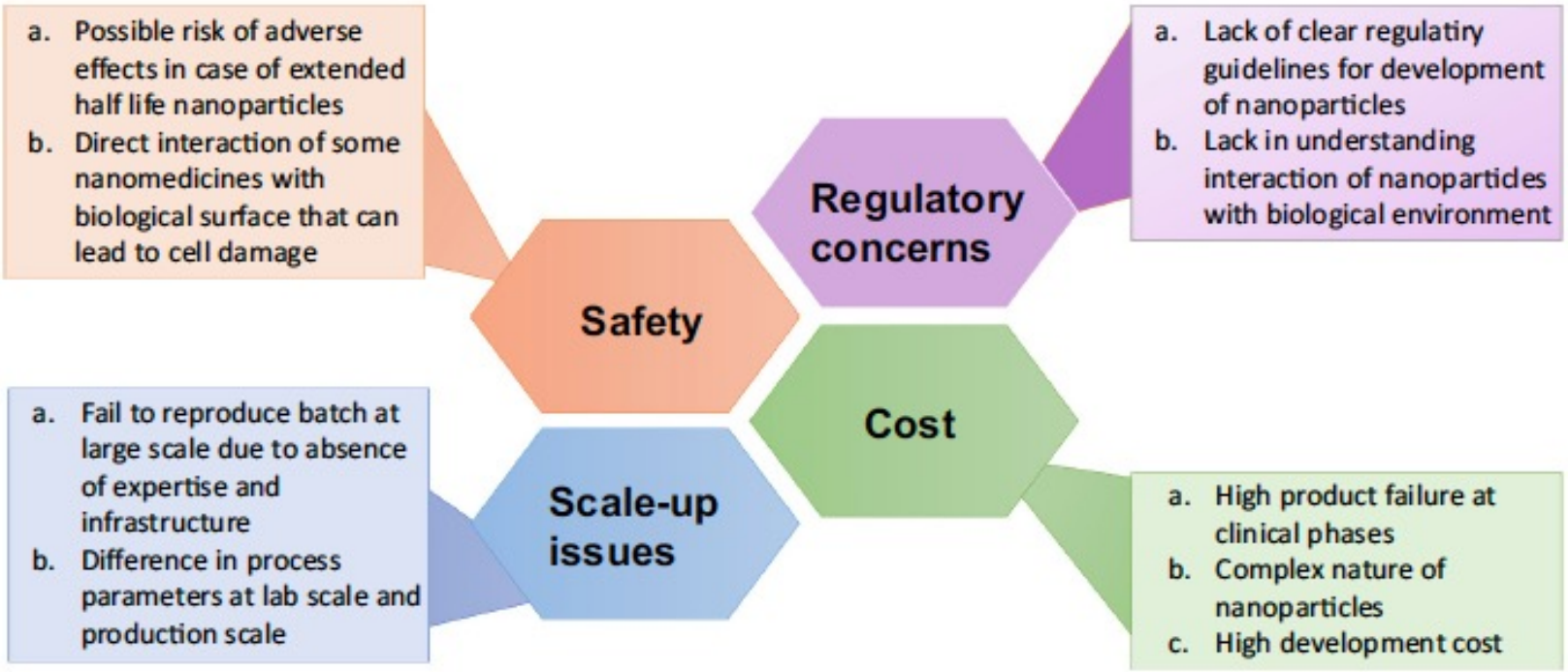
Drug delivery – Nanoparticle strategy

Issues associated with the commercialization of nanomedicines



The lack of proper and rational characterization of nanomedicines is one of the main stumbling blocks for their translation from bench to bedside.

Gadekar et al, J Control Rel 330, 372–393, 2021

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Considerations during the development of nanomedicines

- High drug capacity and low possibility of immediate release of the API
- API should be released from nanoparticles at an optimal rate based on the formulation design
- Ability to be combined with ligands for targeted drug delivery
- Stable enough to pass through the biological barriers with respect to their physicochemical properties
- Must be biocompatible, biodegradable, and nonimmunogenic
- Organic solvents and toxic ingredients should be excluded from the manufacturing process.

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Considerations during the development of nanomedicines

- Components of formulation must be safe, affordable and commercially available
- Simplicity, affordability, and ease of scaling up of manufacturing process
- Nanoparticle formulation should have the ability to be involved in different processes during the manufacturing process, such as lyophilization, sterilization, drying, blending, granulation, compression, capsule filling, and packaging
- Nanoparticles should be stable in storage

CMC considerations in the development of nanomedicines

Unique chemistry, manufacturing and controls (CMC) challenges:

- Feasibility – can a formulation be sufficiently characterized, manufactured, and controlled with adequate quality and economics?
- Adequate physical, chemical, and function-based characterization of early nanomedicine candidates is critical.
- Ability to manufacture nanomedicine products at clinical and commercial scales reproducibly and within a reasonable cost structure is also crucial.

CMC considerations in the development of nanomedicines

Unique chemistry, manufacturing and controls (CMC) challenges:

- Understanding how processing conditions and/or starting material qualities impact the character of the product allows to assess the ability to successfully manufacture and control nanomedicines.
- The concepts of quality by design (QbD) and risk management introduced by ICH [ICH Q8 and Q9] provide a foundation for managing the CMC complexities of nanomedicine development.
- Economic considerations need to be taken into account, as well as the level of investment required to support the CMC development.

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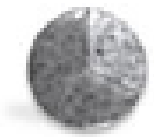
Manufacturing of Polymeric Nanoparticlesc

POLYMERIZATION METHODS

Emulsion/miniemulsion/microemulsion polymerization



Nanosphere

Core-corona nanosphere

Interfacial polymerization

Oil-containing nanocapsule

Water-containing nanocapsule

POLYMERS

EMULSIONS

Precipitation

Solvent evaporation

Nanosphere

Core-corona nanosphere

Oil-containing nanocapsule

Solvent extraction

Nanosphere

Core-corona nanosphere

Oil-containing nanocapsule

Gelation

Nanogel

SOLUTIONS

Precipitation

Solvent diffusion

Nanosphere

Core-corona nanosphere

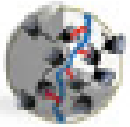
Oil-containing nanocapsule

Gelation

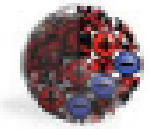
Nanogel

Self - assembling

Complex formation



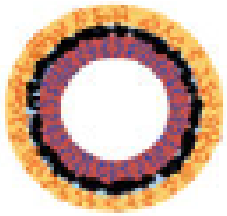
Nanogel



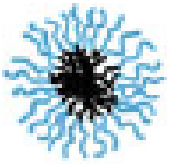
Polyelectrolyte complex

Micelle-polyelectrolyte complex core

Amphiphilic copolymers



Polymersome



Micelle-hydrophobic core

Manufacturing of Nanoparticles

Crystalline Nanoparticle formulations

- Nanoprecipitation
- Wet milling
- High-pressure homogenization
- Supercritical fluid

Polymeric Nanoparticle formulations

- Nanoprecipitation
- Supercritical fluid
- Solvent evaporation
- Solvent diffusion
- Salting out

Lipid Nanoparticle formulations

- High-pressure homogenization
- Solvent evaporation
- Solvent diffusion
- Ultrasonication

Metallic Nanoparticle formulations

- Coprecipitation
- Thermal decomposition
- Microemulsion

Nazende et al. In Nanotechnology for oral drug delivery, Elsevier, 2021

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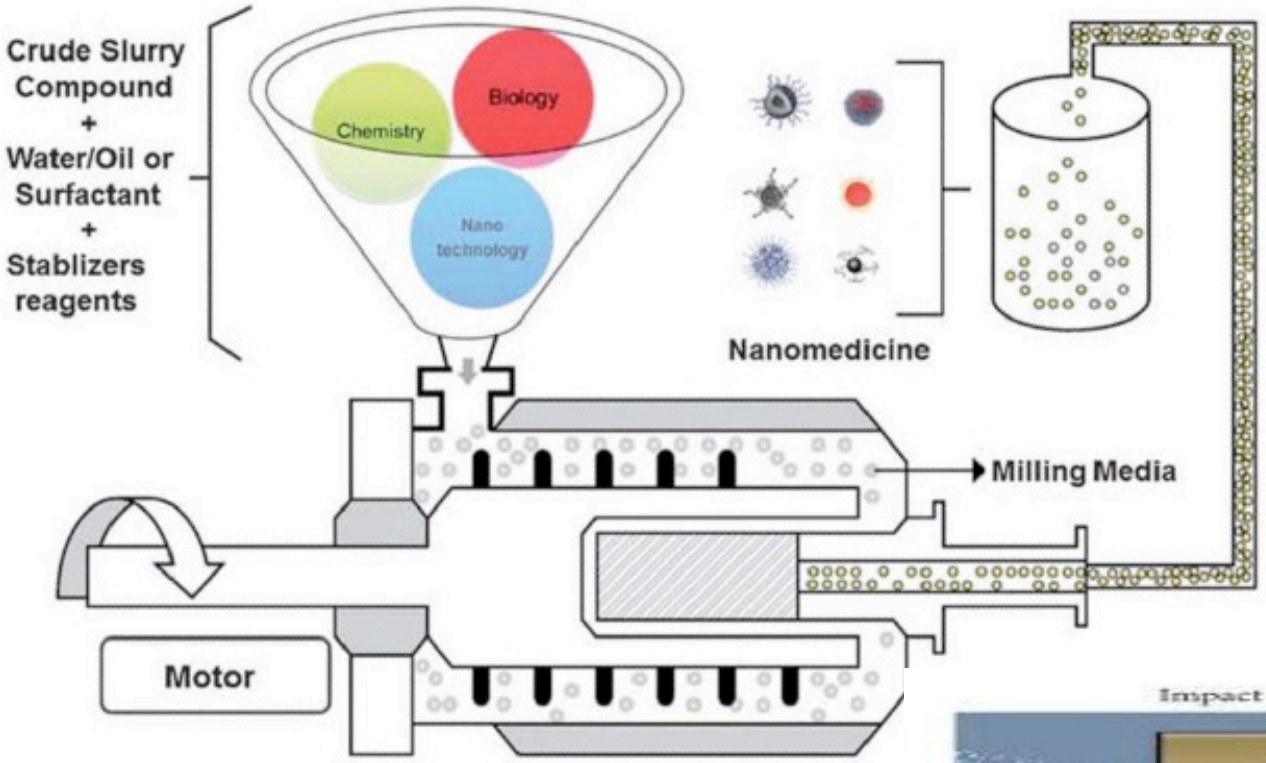
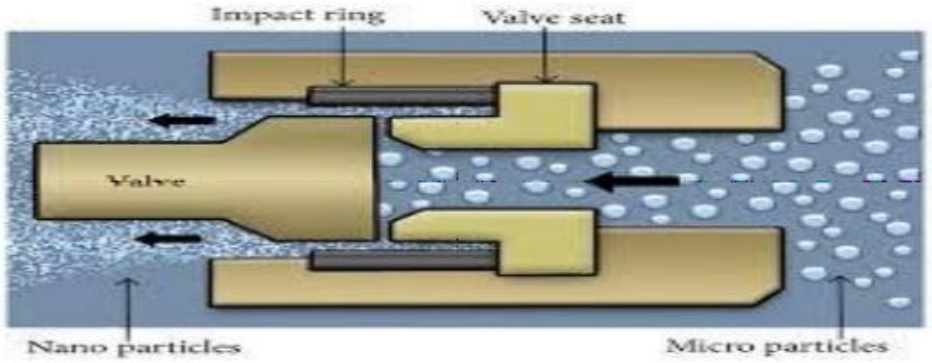
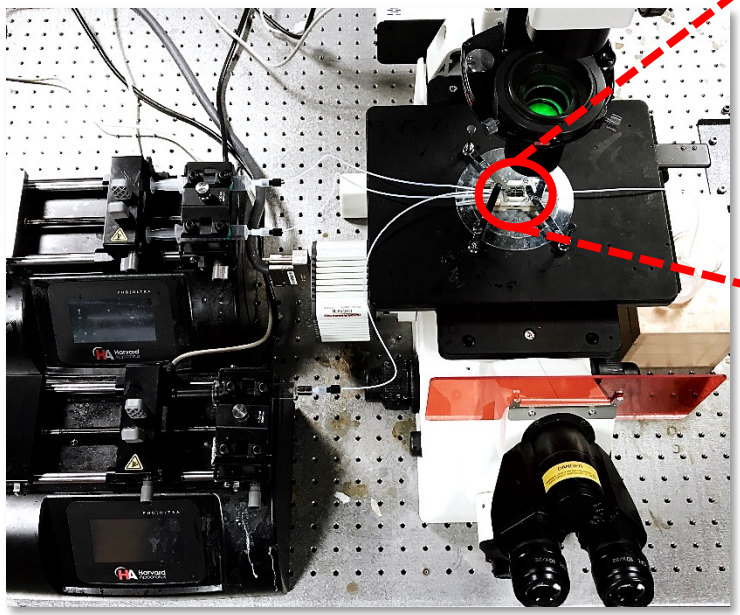
Manufacturing of Nanoparticles - Scalability

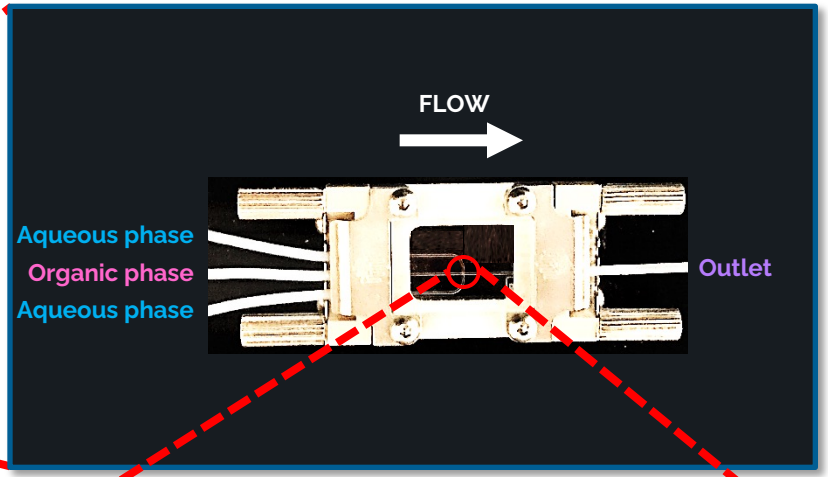


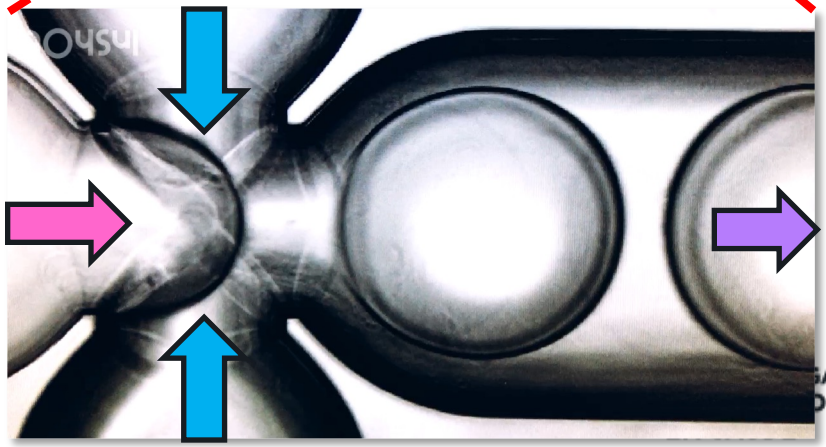


Manufacturing of Nanoparticles - Scalability

Microfluidics setup







Nanomedicines - Optimization towards quality control

Objectives

- Predict the behavior of nanoparticles in biological systems
- Fast and hightroughput experiments
- Increasing complexity of biological systems
  (biomolecules ➔ cells ➔ tissues/organs ➔ animals)
- Essential in order to proceed to clinical testing and regulatory approval

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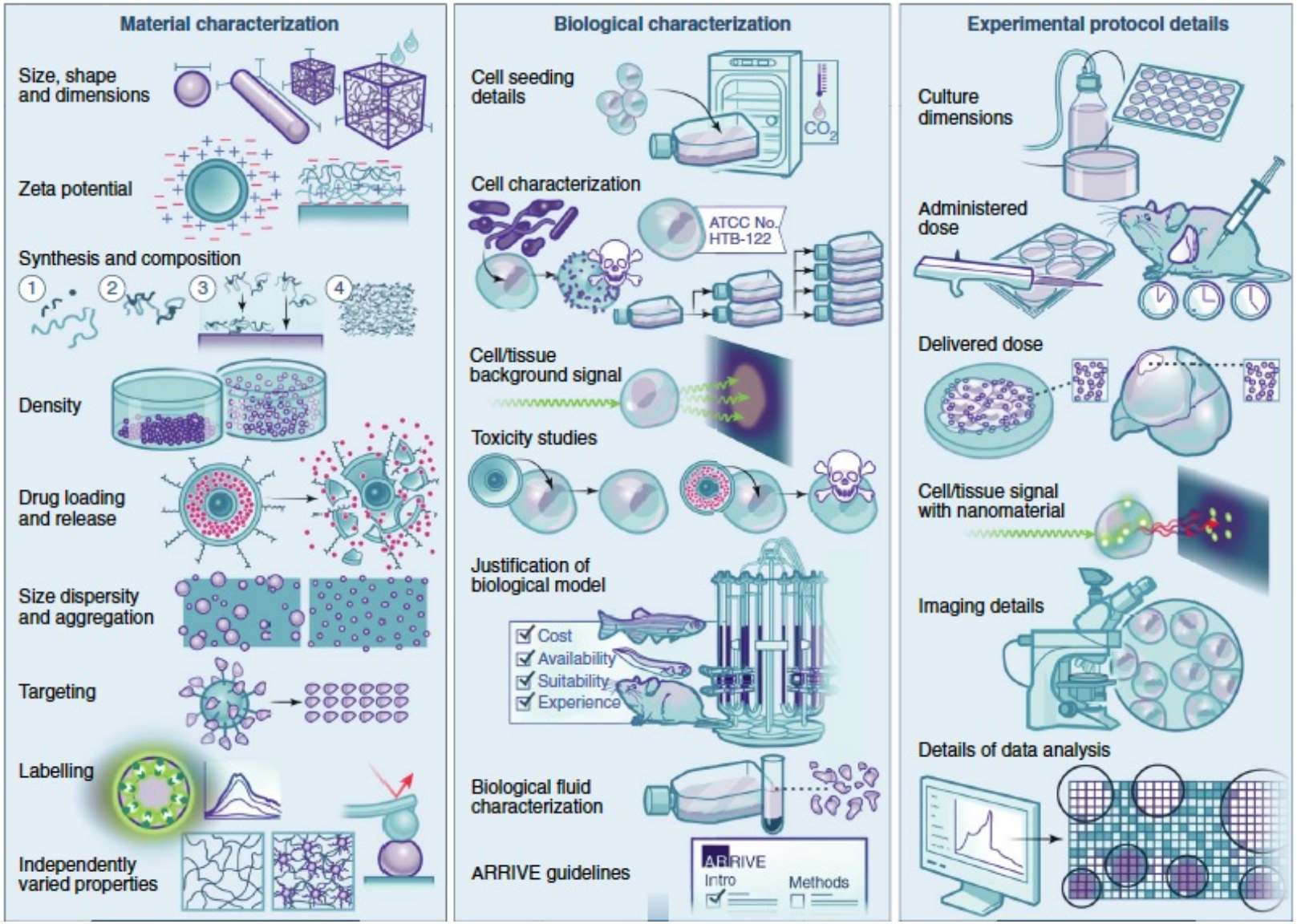
Nanomedicines - Optimization towards quality control



Faria et al. Nat Nanotechnol 13, 777.785, 2018

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Nanomedicines - Optimization towards quality control

Establishment of comprehensive measures to allow faster and effective translation of nanomaterials into the clinics:

- Characterization of the starting materials and their quality, ideally GMP grade
- Detailed quality characterization sheet
- Selection of raw materials and APIs clearly regulated and documented
- Production methodologies of nanomedicines during early stage of drug product development should be chosen with the straightforward industrial framework in mind, instead of the more complex lab-scale setting.
- Description of the **most relevant critical quality attributes** for scaling-up methodologies and for clinical translation.

Nature Nanotechnology , 14, 626–635, 2019

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Nanomedicines - Optimization towards quality control

- To allow industrial production, processes for the purification of nanoformulations that do not compromise their quality specifications must be established.
- These, and potential methods for nanomedicine's sterilization, should also be ready for industrial implementation.
- Batch-to-batch variability of nanomedicines must be minimized particularly for critical quality attributes that impact the strength, purity, safety, and efficacy

Nature Nanotechnology , 14, 626–635, 2019

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Nanomedicines - Optimization towards quality control

Major differences between conventional drug medicines and nanomedicines when bridging the translation gap

	Conventional medicine	Nanomedicine
Composition	Active Pharmaceutical ingredient (API) + excipients	Complex assembly: Self-active NM or API within the nanocarrier (NC)
Transport of the API	Single molecule solubilized	Within the NC (biodistribution and release profile modified)
Biological activity	API dependent	NM dependent or Nanocarrier + API dependent
Characterization	API identity (chemical signature by NMR, UV, IR) Solubility – Dissolution rate Purity, contaminants free	API identity (if associated) NM properties: Size, charge, morphology, drug loading and release Purity, contaminants free
	Biological activity and safety warranted	**Not enough to ensure full biological activity and safety**

Journal of Controlled Release 275, 254–268, 2018

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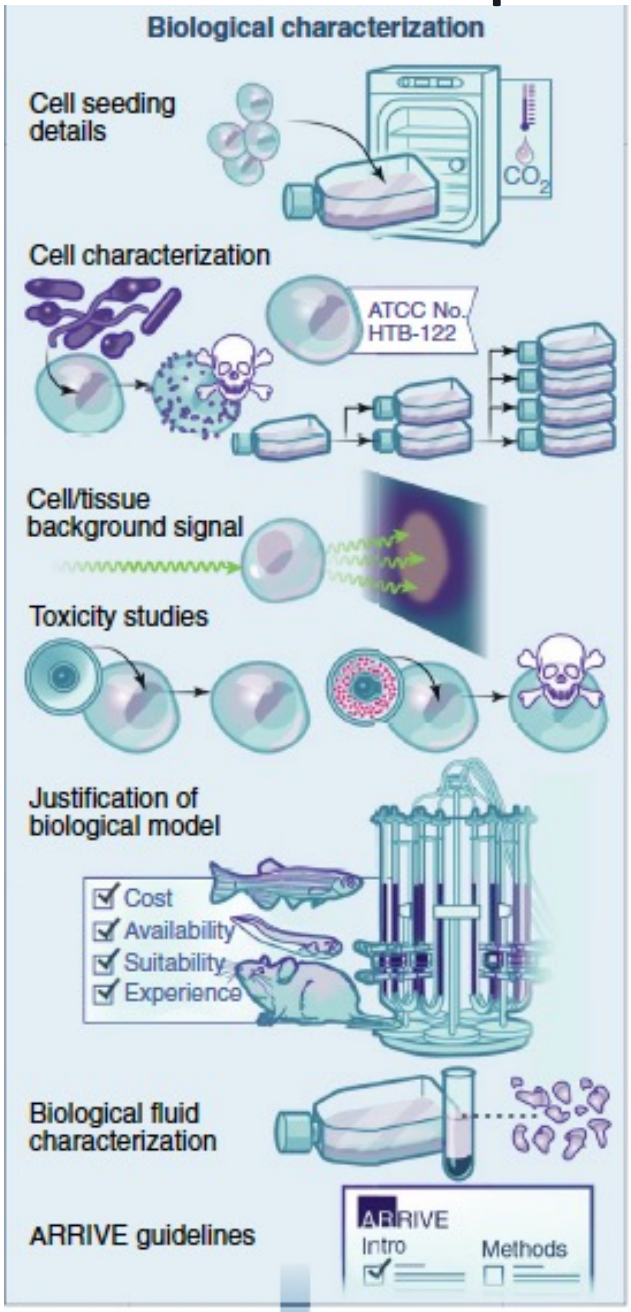
Nanomedicines - Optimization towards quality control

Minimum information report



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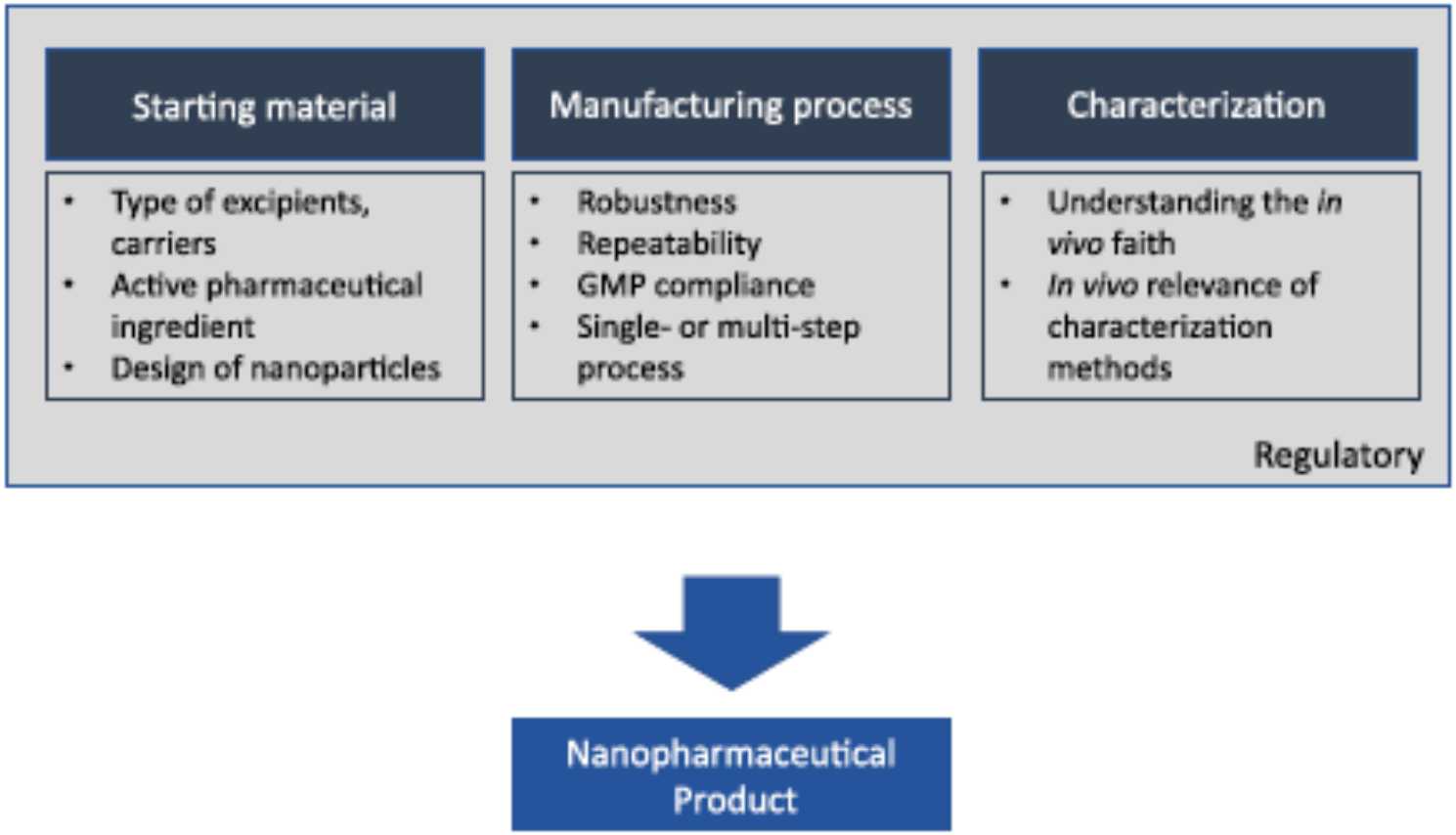
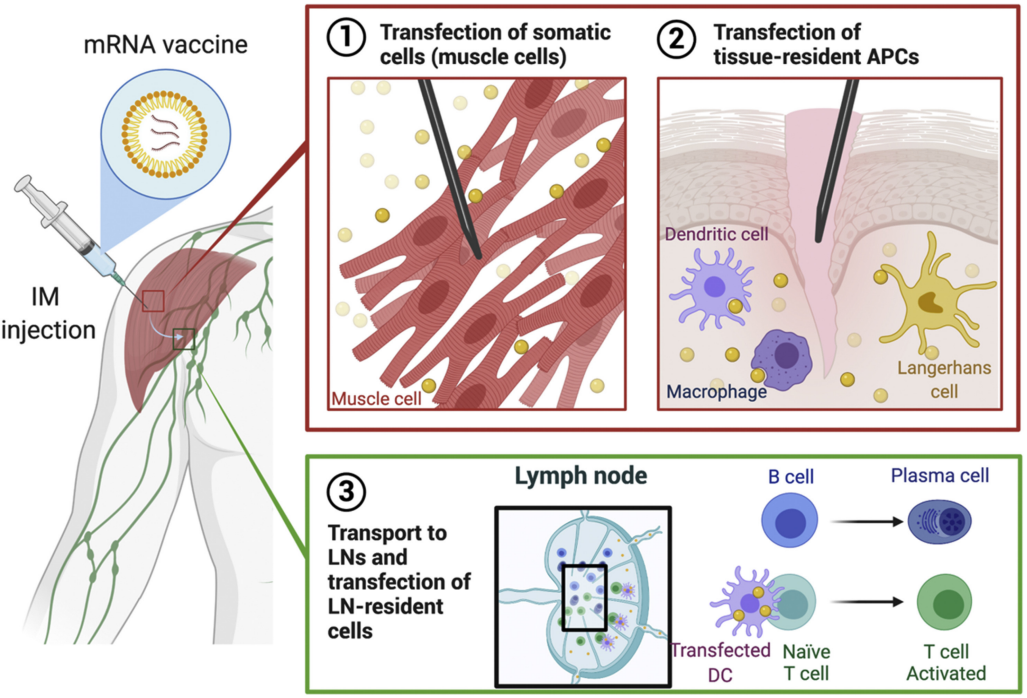


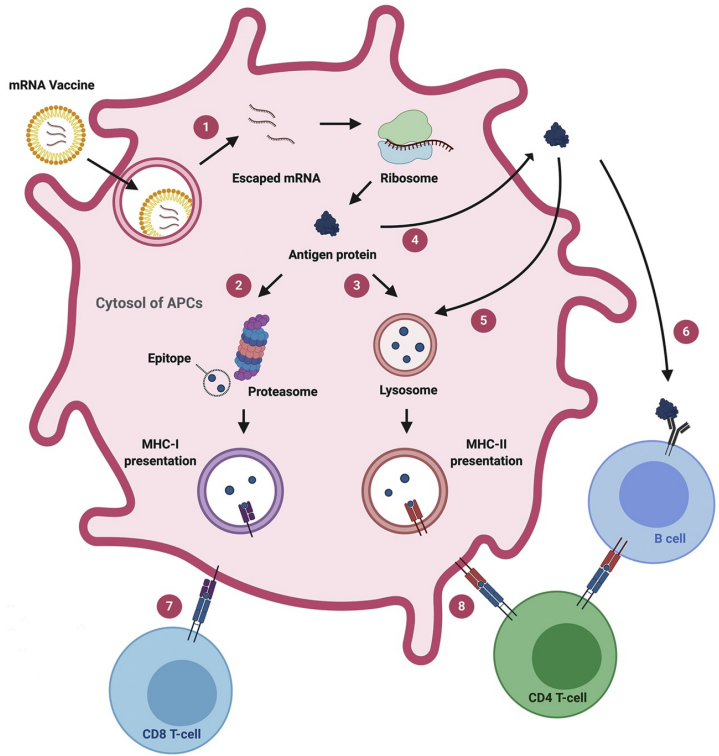
Nazende et al. In Nanotechnology for oral drug delivery, Elsevier, 2021

Without lipid nanoparticles, there would be no mRNA vaccines for COVID-19

mRNA can transfect (1) muscle cells or (2) tissue-resident APCs near the injection site. mRNA vaccines can flow into proximal lymph nodes (LNs) and transfect LN-resident cells, resulting in activation of T and B cell development (3).



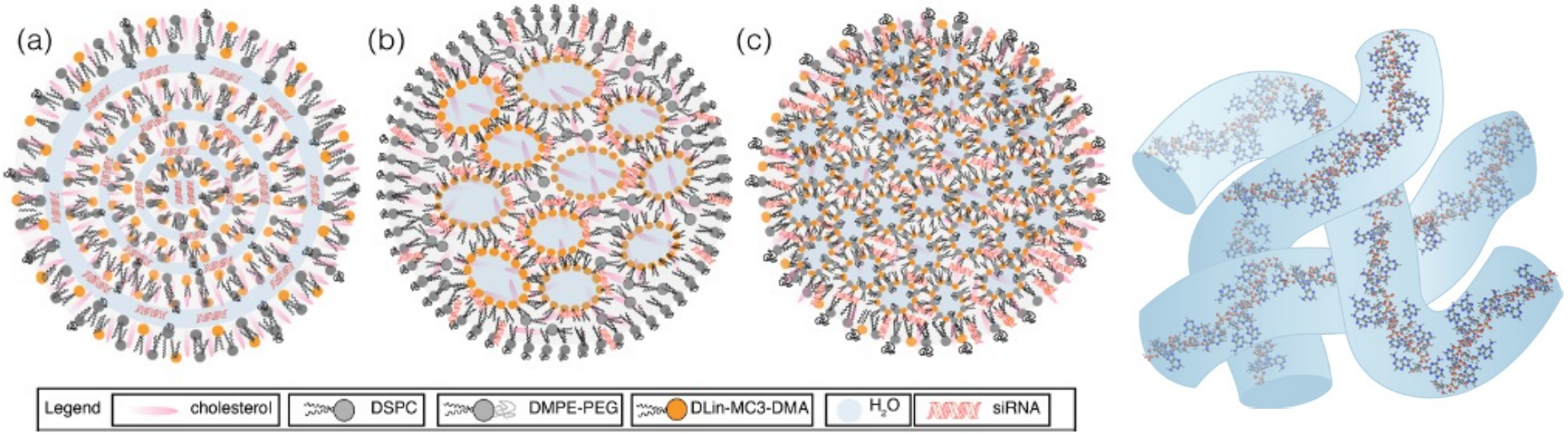
Endosomal escape of mRNA to the cytosol



Kim et al. Advanced Drug Delivery Reviews 170, 83–11, 2021

Without lipid nanoparticles, there would be no mRNA vaccines for COVID-19

Schematic representation of proposed models for mRNA-LNP structure and mRNA-water cylinders structure in the core of mRNA- LNPs



Schoenmaker et al. Int J Pharm 601, 120586, 2021

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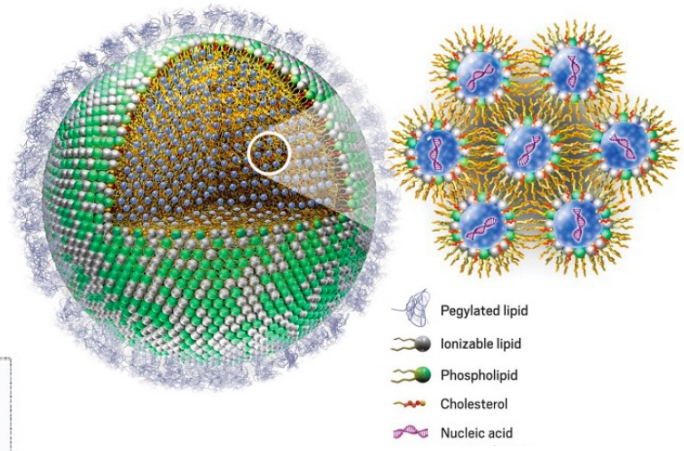
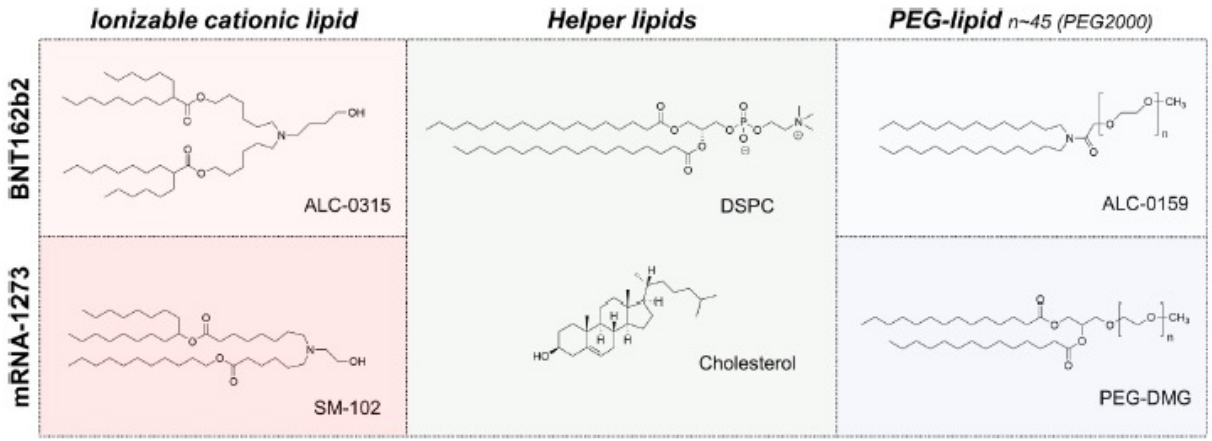
mRNA vaccines for COVID-19

The LNPs in mRNA COVID-19 vaccines consist of four main componentes:

- **ionizable cationic lipid** - interact with the anionic mRNA during particle formation and also facilitate membrane fusion during internalization
- **polyethylene-glycol (PEG)-lipid** - control the particle size and act as a steric barrier to prevent aggregation during storage
- **neutral phospholipid**
- **cholesterol**





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In summary…

- The effectiveness of nanomedicines is intrinsically related to their physicochemical properties
- Their biological responses are highly susceptible to factors such as the type and quantity of each material that is employed, and method used to production
- Quality-oriented manufacturing of nanomedicines is an important strategy to understand and to optimize the factors involved in their production

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