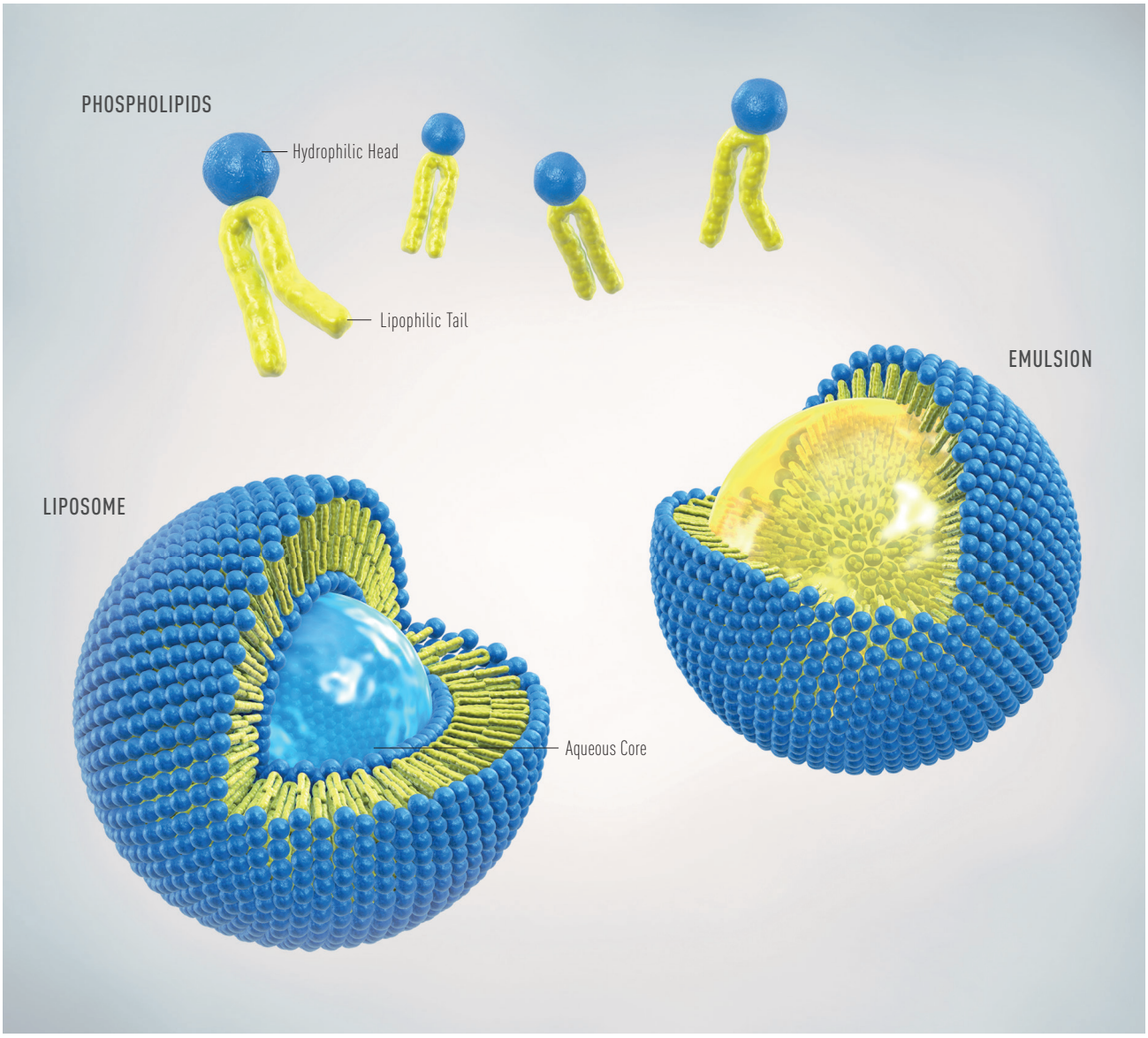
Lipoid

Phospholipid-Based
Delivery Systems

Advanced Vaccines in Modern Medicine

We Invest in Quality.



Schematic diagram of phospholipids, a liposome (phospholipid bilayer encapsulation of hydrophilic ingredients) and an emulsion.

WIDE RANGE | **HIGH EFFICIENCY** | **BIODEGRADABLE & SAFE**

Phospholipids are essential components of advanced vaccines

Phospholipids enable the delivery of immunostimulants, antigens and RNA to the target site and trigger the desired immune response

Cationic lipids are the most advanced complexing agents for RNA vaccines

Vaccine Adjuvants

The routine use of vaccines is one of the most outstanding accomplishments of modern medicine. The first major milestone was the eradication of smallpox. Nowadays, emerging pathogens like Sars-CoV-2 require innovative vaccination approaches [1]. Besides the prevention of infectious diseases, vaccination is also an emerging field to prevent and treat cancer.

The first generations of vaccines were made by use of live attenuated organisms or inactivated organisms, followed by specific antigens and most recently by antigen encoding mRNA. Antigens often induce only a low immune response. In such cases, adjuvants are needed to boost and/or modulate the immune response. Adjuvants can be classified into carrier systems and immunostimulants [2-4].

Carrier Systems

Carrier systems include e.g. oil-based emulsions, Immune Stimulating Complexes (ISCOMs), liposomes, lipoplexes and lipid nanoparticles [7-8].

Natural and synthetic phospholipids, mainly phosphatidylcholine, often called "lecithin" in American literature, and other phospholipids relevant for the adjuvant use are often explored and attract more and more attention (Fig. 1). Such systems are used as carriers for immunostimulants, antigens or mRNA along with cationic lipids like DOTAP for complexation (Fig. 2). In addition, certain phospholipids of the carrier systems like DOPC and DOPE play a major role in intracellular processing.

Immunostimulants

In 1925, Ramon demonstrated for the first time in horses that artificial enhancement of diphtheria and tetanus antitoxin levels by the addition of immunostimulants like agar, metallic salts and saponins is possible.

In the 1940s, first trials were performed with water-in-oil emulsions as adjuvants. These so-called Freund adjuvants comprised mineral oil emulsions. Freund adjuvants are no longer used in marketed vaccines as they are poorly tolerated due to the non-degradable mineral oils present. Although the use of aluminium salts is well established, immunostimulants like saponins, Monophosphoryl Lipid A (MPL) or catioinc lipids are used more frequently [3-6].

Phospholipid-based carrier systems exhibit advantages over other nanoparticles:

- **Wide range of particle sizes and compositions possible**
- **High efficiency of antigen entrapment-compatibility with hydrophilic, hydrophobic-, and amphiphilic antigens**
- **Biodegradable & safe after any route of administration**

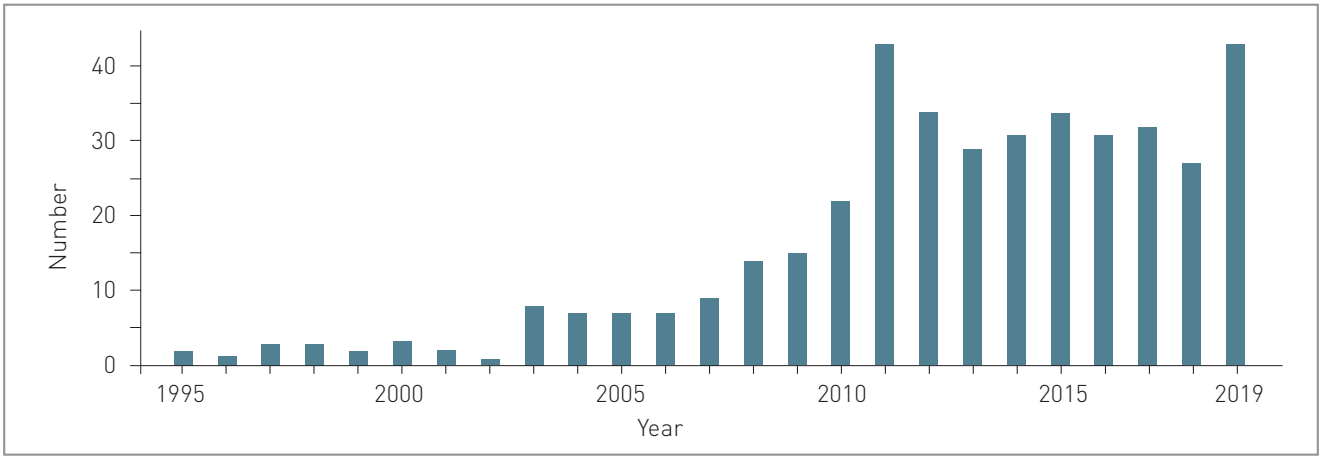


Fig. 1: Increasing interest in vaccines & phospholipids: Number of peer-reviewed publications from 1995 to 2019 (Source: Lipoid internal database)

Commercialized Vaccines with Phospholipids

The most prominent marketed vaccine with liposomal adjuvants technology is GSK's Shingrix® for vaccination against Varicella zoster virus infections (shingles). Beyond liposomes, ISCOMs, open cage-like lipid particles made of Quillaja saponins, cholesterol and phosphatidylcholine, are used. They can be found in commercial products, e.g. in animal vaccines against equine influenza (Tab. 1).

Table 1: Marketed vaccines with phospholipids

Trade Product	Indication	Formulation	Company
Equilis® Prequenza Te	Equine Influenza/Tetanus	ISCOM	MSD/Intervet International BV, Netherlands
Equilis West Nile suspension for injection	West Nile virus infection	ISCOM	MSD/Intervet International BV, Netherlands
Equip® FT	Influenza/Tetanus	ISCOM	Zoetis Inc., USA
Shingrix®	Shingles	liposomes	GSK plc, UK

Table 2: Vaccines in clinical research with phospholipids

Project/Product	Indication	Status 03/2020	Formulation	Company
ACI-24 and ACI-35 vaccine	Alzheimer	Phase I/II	liposomes	AC Immune SA, Switzerland
DepoVax™/VacciMax	Cancer, infectious diseases	Phase I/II	emulsion	Immuno Vaccine Technologies Inc., Canada
IvAC Mutanom	Cancer	Phase II	lipoplex liposome	BioNtech SE, Germany
Rabies Vaccine	Rabies, RSV	Phase I	lipid nanoparticles	CureVac AG, Germany
mRNA-1647	CMV mononucleosis	Phase I/II	lipid nanoparticles	Moderna Inc., USA
Versamune™	HPV associated cancers	Phase II	lipoplex	PDS Biotechnology Corp., USA
GSK3277511A GSK3844766A	COPD RSU	Phase II	liposomes	GSK plc, UK
Mosquirix™/M72/AS01E	Malaria/Tuberculosis	Phase I/II	liposomes	GSK plc, UK

Abbreviations:

AS01: Adjuvant system 01, **DOPC:** 1,2-Dioleoyl-sn-glycero-3-phosphocholine, **DOPE:** 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine, **DOTAP:** N-[1-(2,3-Dioleoyloxy)propyl]-N,N,N-trimethylammoniummethyl-sulfate, **DOTMA:** 1,2-di-O-octadecenyl-3-trimethylammonium propane (chloride salt), **GSK:** GlaxoSmithKline plc., **HIV:** Human Immunodeficiency Virus, **ISCOMS:** Immunestimulating complexes, **MPL:** Monophosphoryl Lipid A, **MSD:** Merck Sharp and Dohme, **PC:** Phosphatidylcholine, **PEG:** Polyethylene glycol, **QS21:** Highly purified saponin; derivative from the Quillaja saponaria Molina tree, **mRNA:** Messenger Ribonucleic acid, **RSV:** Respiratorisches Syncytial-Virus

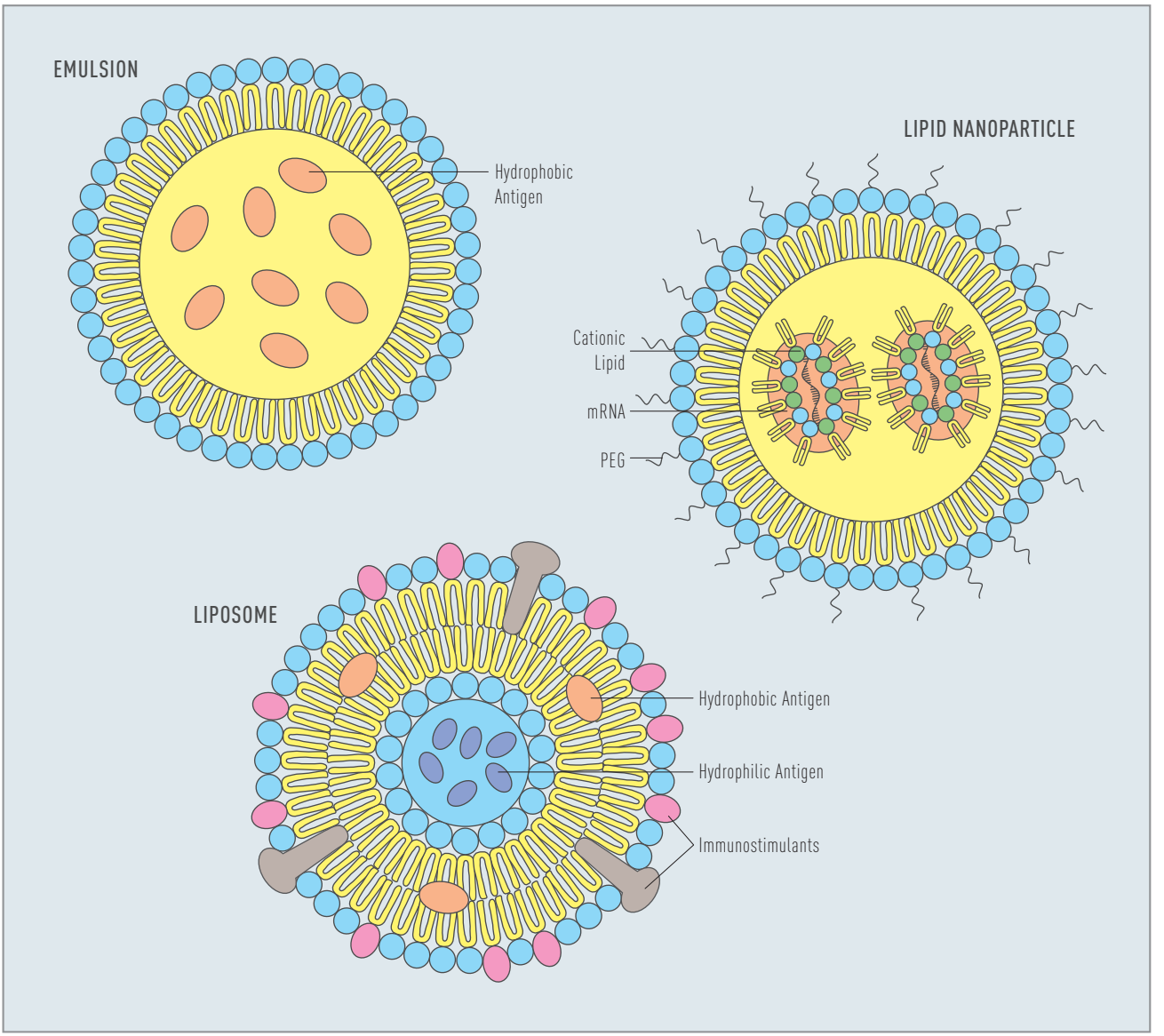


Fig. 2: Schematic illustration of carrier systems for immunostimulants, antigens and mRNA.

Vaccines in Clinical Research with Phospholipids

Promising clinical research with vaccines is underway, for instance the studies being performed by GSK with the AS01 adjuvant in various diseases (Tab. 2). The adjuvant is comprised of liposomes with DOPC, cholesterol, MPL and QS21 (Quillaja saponaria Molina). In addition, more and more mRNA-based vaccines are studied clinically, e.g. by BioNTech, CureVac and Moderna. mRNA is i.e. encapsulated in lipid nanoparticles (Fig. 2), which use e.g. phospholipids like DOPE and DOPC and cationic lipids like DOTAP and DOTMA as complexing agents.

Concluding Remarks

The extremely successful introduction of the Shingrix® vaccine product from GSK for prophylaxis of herpes zoster (2019: £ 1.8 billion) [9] and the market presence of veterinary vaccines show the enormous potential of phospholipids as components of adjuvants. The use of phospholipids like DOPC and DOPE in adjuvants may therefore become more relevant.

Cationic materials are needed as complexing agents for mRNA vaccines, and cationic lipids, especially DOTAP, are most advanced.

References

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