

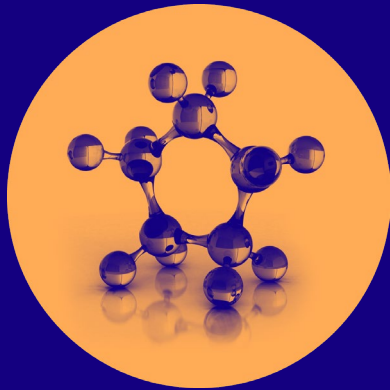
Innovative solutions for Nucleic Acid Delivery

Content

- About Croda Pharma
- Nucleic Acid Delivery:
 - Our offering
 - Innovation pipeline
 - A history of our lipids development and Avanti
- Services and capabilities



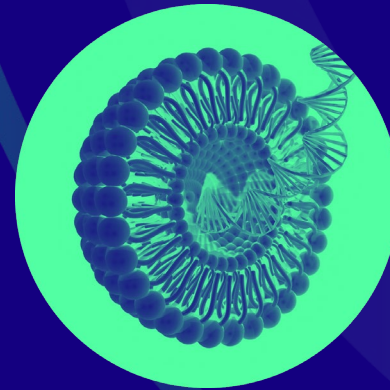
Croda Pharma platforms



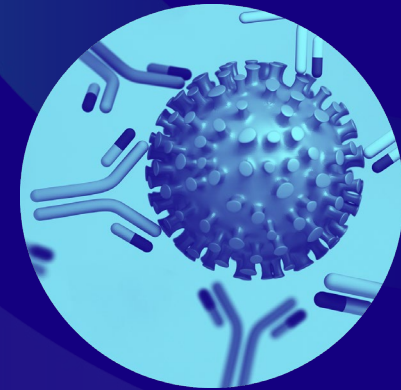
**Small Molecule
Delivery**



**Protein
Delivery**



**Nucleic Acid
Delivery**



**Adjuvant
Systems**

Human and Veterinary Health

How we empower biologics delivery



Innovation

Enabling breakthrough innovation

Dedicated to enabling development of **next generation of excipients** and **delivery systems** to empower biopharma.



Formulation

Access to specialist formulation support

Enabling over 250 on-going clinical projects targeting a range of therapeutic areas across **biologics** and **small molecules**.



Application

Focused scientific expertise

Leading the way with **specialist knowledge** and **synthesis expertise** in excipients, adjuvants and lipids.

Expansion through R&D and partnerships

1925

Croda was founded



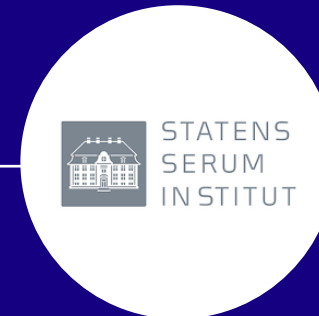
2018

Biosector acquisition, industry leading vaccine adjuvants



2022

Partnership with Statens Serum Institut



Our Health Care business becomes



2000 onwards

Ongoing investments in high purity excipients



2020

Acquisition of world leading lipid portfolio



Your pharma solutions partner



High purity excipients

Optimising the performance of formulations to solve your stability and solubility challenges.



Vaccine adjuvants

Committed to the highest standards, with +80 years of expertise in adjuvant research and development.

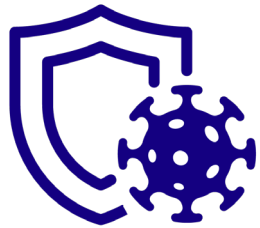


Innovative lipids

Enabling the delivery and stability of nucleic acid-based vaccines, therapeutics and gene editing technology.



Decades of driving biopharma forward



1st supplier of lipids for
COVID-19 mRNA
vaccine



Winner of **Best Supplier**
for **COVID-19** vaccine
development 2022



More than 30 years of
development for **gene**
therapy trials



Investing in Nucleic Acid Delivery



Innovation

Future extensions to pipeline from Croda R&D and licensing
New Avanti products to improve lipid nanoparticle delivery systems
New transfection agents for cell & gene therapy

Knowledge

Formulation services for lipid delivery systems
CDMO services for proprietary lipids
Dedicated sales and marketing to accelerate growth strategy

Global expansion of capacity

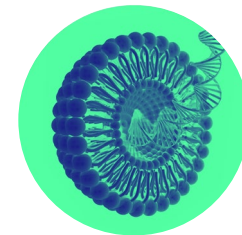
Continued investment across 3 major manufacturing sites
Backed by UK and US government co-investment to expand lipid systems capabilities

Nucleic Acid Delivery

- Our offering
- Innovation pipeline
- History of Avanti and lipids development



Key applications for our technologies



Viral applications

Adeno-associated virus
(AAV)

Lentivirus

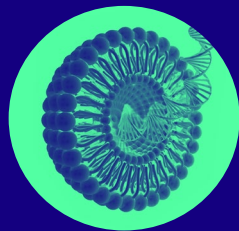
Adenovirus

Non-viral applications

Lipid Nanoparticles
(LNP)

Lipoplexes

Cationic nanoemulsions



GMP materials for Nucleic Acid Delivery

Clinical and
commercial

Phospholipids

DSPC
DOPC
DOPE

PEG lipids

DMG-PEG2000
DSPE-PEG2000
ALC-0159*

Cationic lipids

ALC-0315*

Sterols

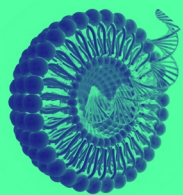
Parenteral
Grade Plant
Cholesterol

Functionalised lipids

DSPE-PEG2000 Carboxy

Polysorbates

Super Refined™ Polysorbate 20 and 80
Tween™ 20 HP and Tween™ 80 HP



Research grade for Nucleic Acid Delivery

Custom
synthesis and
catalogue

2000+ Unique Research
Catalog Items

>15 synthetic chemists
(12 PhDs)

~600 new research products
launched in the past 4 years.

250+ years of combined
experience

Cationic/Ionizable lipids

Phospholipids

Functionalised lipids

Neutral lipids

Sterols

Polymers & polymerizable lipids

Leading lipids innovation – pipeline preview

Sitosterol

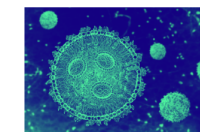
- Investigated as a cholesterol substitute in **lipid-based mRNA delivery systems**
- Reported that β -sitosterol-substituted LNPs maintained comparable size /encapsulation but were **considerably more effective at mRNA transfection than cholesterol**
- Product currently available in **research grade material**

Polysarcosine Lipids

- Improved **mRNA transfection efficiency & safety profile**
- 5 products available in **research grade** – from Oct 2022

Innovative Lipids for Your Nucleic Acid Delivery Research

Posted on November 22, 2022



The History and Evolution of Nucleic Acid Delivery Systems

mRNA and liposomes were both first discovered in the 1960s, and liposomes were used to deliver mRNA into eukaryotic cells in 1978.^{1,2} Even with the ability to inject mRNA into cells, there were several technical challenges to overcome before mRNA could be used as a therapeutic, primarily the rapid degradation of mRNA once injected into the body. In 1990, naked mRNA was injected into the muscles of rats to prove that in vivo direct gene transfer was possible.³ As early as 1995 the first mRNA vaccine carrying cancer antigens was reported.⁴ And more recently, lipid nanoparticles (LNPs) have been used to deliver mRNA

capable of fighting SARS-CoV-2, as well as CRISPR/Cas-9 gene editing technologies.

Our understanding of mRNA and its delivery has evolved substantially in the past few decades - from naked mRNA delivery to liposomal delivery and then LNPs. We are far from where we started and probably equally as far away, if not farther, from where we are headed.

Not only do delivery systems change, but their individual components are constantly evolving to meet current challenges and demands. To date, LNPs have primarily been formulated using the following components:

- Cationic Lipids (DOTAP, ALC-0315, DLin-MC3-DMA, and SM-102)
- PEG-lipid Conjugates (DSPE-PEG2000, DMG-PEG2000, DSG-PEG2000, and ALC-0159)
- Phospholipids (DSPC and DOPE)
- Cholesterol



Visit our **blog section** at
<https://avantilipids.com/>
to read the **full article**.

A history of lipids development

1967

Avanti founded
to supply research
market



1985

Good Manufacturing
Practice initiated

1990

First market
approval containing
Avanti lipids



1990-2017

Clinical support of
gene therapy trials

2020

Croda acquires Avanti
expanding reach into Nucleic
acid delivery



First to supply clinical and
commercial lipids for **mRNA**
COVID-19 vaccine

2022

Government investment
(US/UK) to **expand lipid**
systems capacity



+£90 million investment
Lamar (US), Leek (UK)

Services and capabilities



Lipids supporting services

CDMO cGMP Manufacturing

CDMO project management from R&D through commercialization.

Contract manufacturing of proprietary lipid products.

Custom Synthesis

Synthesis of research use materials for a variety of applications.

Custom synthesis of reference standards or impurities.

Formulation

Development of a suitable formulation for lipid-based delivery system.

Custom lipid blends for use in delivery or diagnostic application.



Lipid formulation services

Custom formulation Development

Formulation screening
Feasibility
Process development
Optimisation

Capabilities

HPAPI handling
Lyophilisation
Homogenisation
Extrusion
Solvent injection

Smart science to improve lives™

*HPAPI (High Potency Active
Pharmaceutical Ingredients)



CRODA



Lipids - From concept to commercial

Partner with Croda to develop, scale and manufacture your lipid



Technology development

Leading global R&D expert



Project Planning and Initiation

Project plan



R&D

Collaboration based on technical expertise



Feasibility

Manufacturing initial research grade material



Pilot Production

Engineering the final process and developing analytical methods



Clinical cGMP Production

Manufacturing GMP material for clinical use



Scale-up and Commercial Production

Late clinical and commercial support to bring a product to market

Quality Control

50+ scientists with **over 500 years** of Analytical Laboratory Experience

Instrumentation

GC-FID, GC-MS
NMR: Proton, Phosphorus, Carbon
UV/VIS
Ion Chromatography
LC-MS, QQQ, Q-TOF Mass Spec
TLC Analysis
Peroxide Value
Solubility Analysis
Color Testing
Karl Fischer Water Content
Particle Size / Zeta Potential
ICP-MS
FTIR
HPLC-ELSD, HPLC-CAD, HPLC-UV

Smart science to improve lives™



CRODA





Quality and Compliance

Lipids regulatory history

>35 years
supporting
APIs and novel
excipients

Dossiers
with **7+**
health
authorities

FDA
Inspected
since **1990**

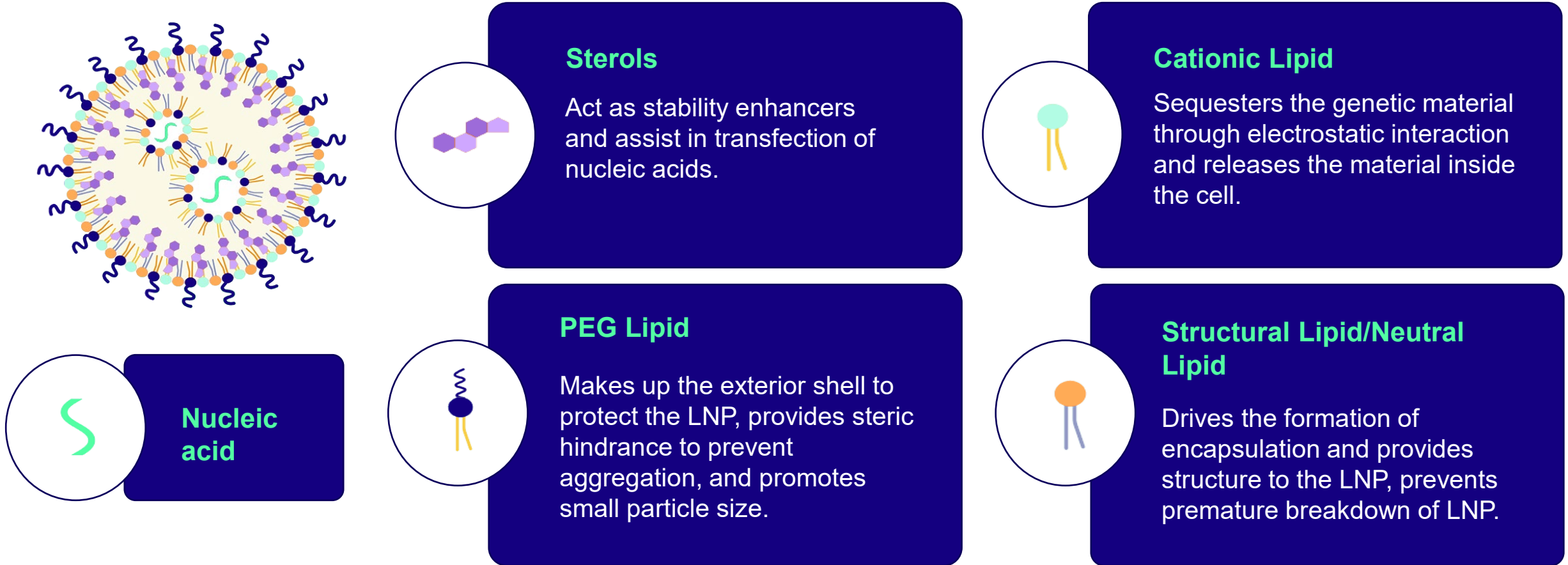
Support

LOA Issuance
Open DMFs
Responses to health authorities
Product Assurance Statements
Audits (Virtual and On-site)
Quality Agreements
Supplier Qualification Questionnaires

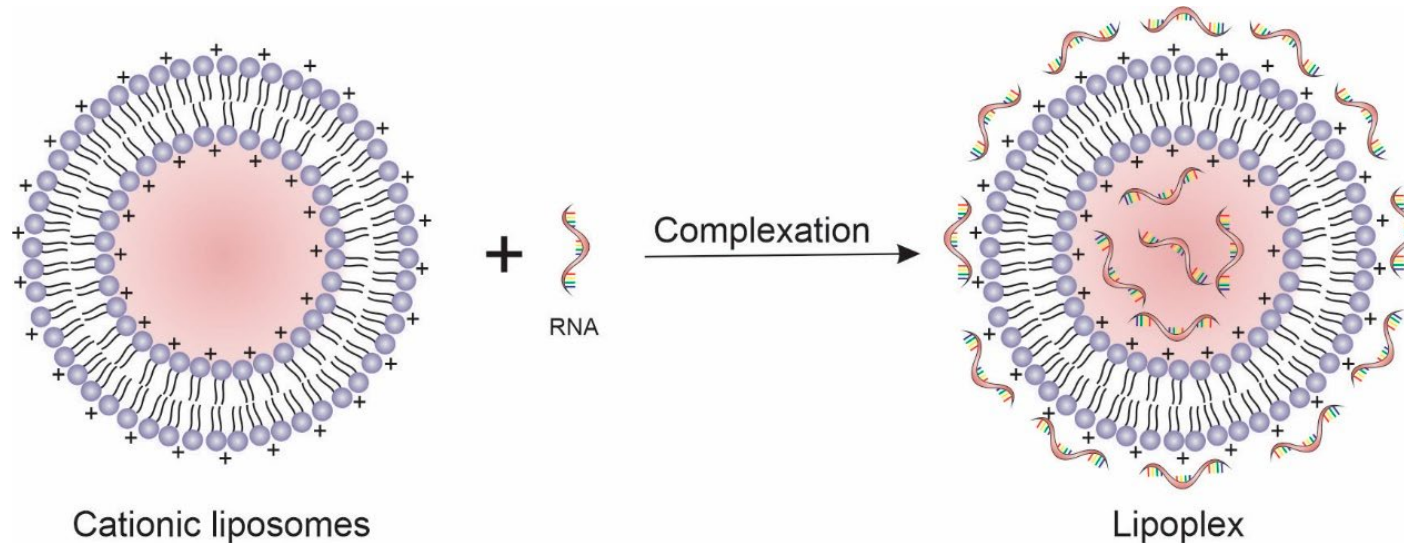
Smart science to improve lives™



Technology Focus: Lipid Nanoparticle (LNP) System



Technology Focus: Lipoplexes



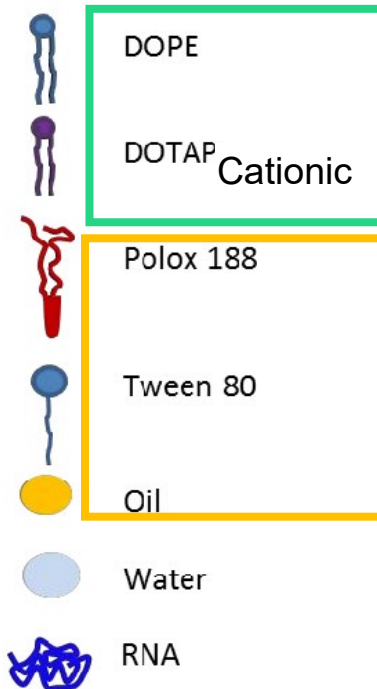
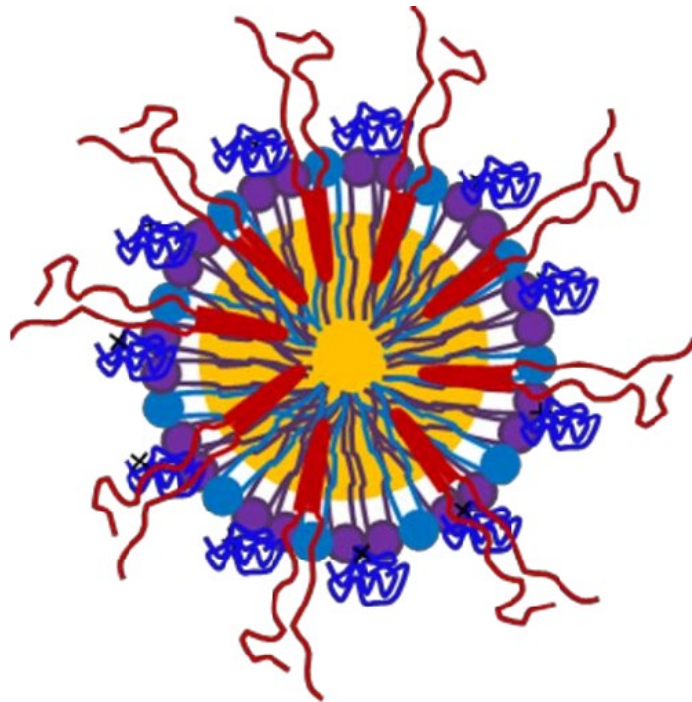
The Avanti lipid portfolio includes **cationic lipids** for lipoplex formation.

Lipoplexes are ordered phase structures that result from a complexation of cationic lipids and nucleic acids.

Aldosari, Basmah N et al. "Lipid Nanoparticles as Delivery Systems for RNA-Based Vaccines." *Pharmaceutics* vol. 13,2 206. 2 Feb. 2021.

Luiz, Marcela Tavares et al. "Targeted Liposomes: A Nonviral Gene Delivery System for Cancer Therapy." *Pharmaceutics* vol. 14,4 821.

Technology Focus: Cationic nanoemulsions



Lipids: offered by Croda Pharma as part of the Avanti lipid portfolio

Surfactants: offered by Croda Pharma. May also include: Polysorbate 80 and Span 85

Cationic nanoemulsions can be used in the formulation of self-amplifying RNA vaccines.

Luiz, Marcela Tavares et al. "Targeted Liposomes: A Nonviral Gene Delivery System for Cancer Therapy." Pharmaceuticals vol. 14,4 821.

Thank you!

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