

CRODA | Pharma
SMART SCIENCE TO IMPROVE LIVES™

 **Avanti Research**
A CRODA BRAND

100
1925-2025
YEARS OF SMART SCIENCE

Architects of immunity: Improving access to adjuvants for clinical vaccine development and beyond

Dennis Christensen

Head of Global R&D, Vaccine Adjuvant Systems, Croda Pharma
Research Professor, Vaccinology, Statens Serum Institut, DK

Vaccination is all about.....



Presenting
sufficient
amounts of
the right
antigen



In the right
conformation



To the right
cavity in the
right cell
populations



While
supporting
with the right
co-stimuli

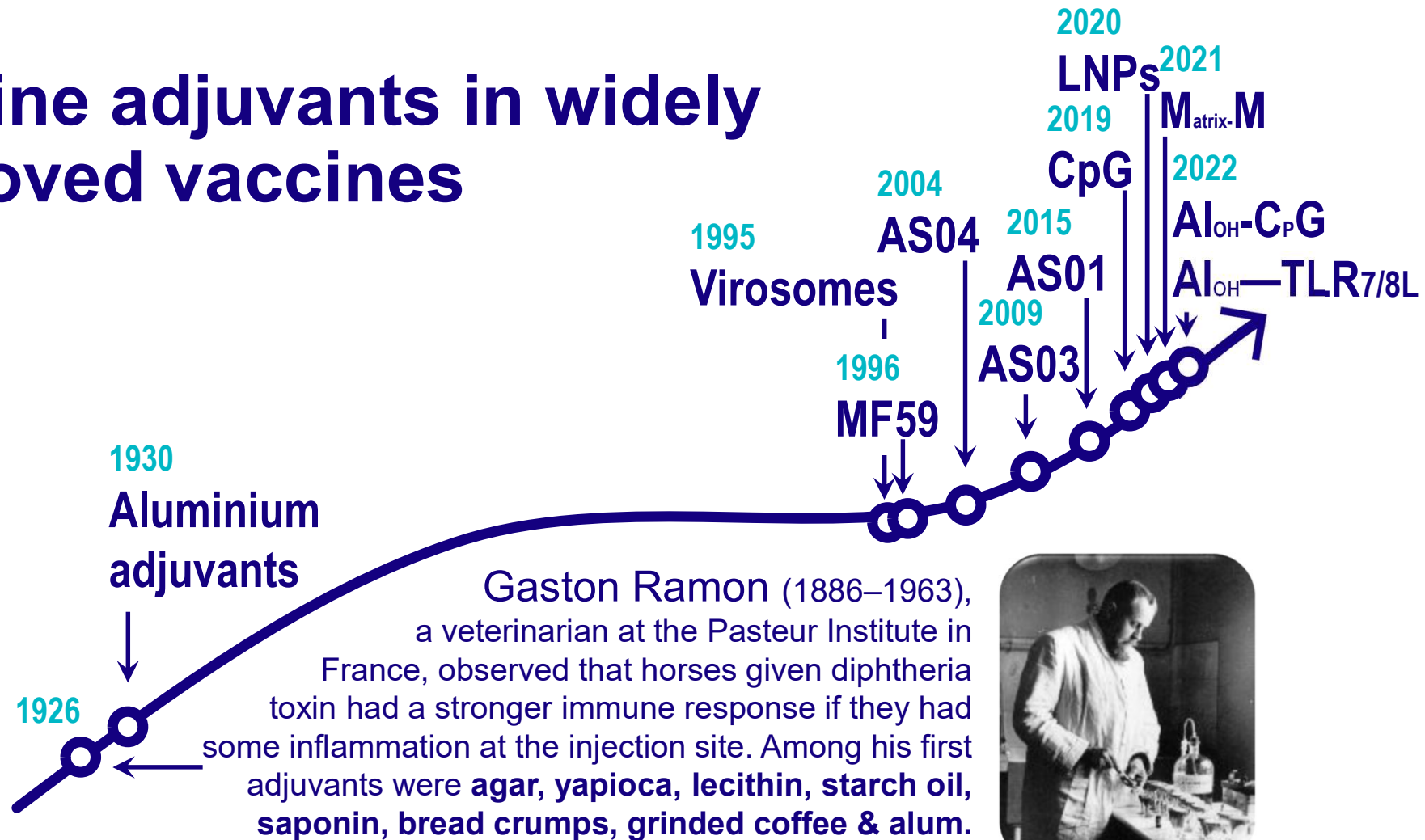


For a
sufficient
amount of
time

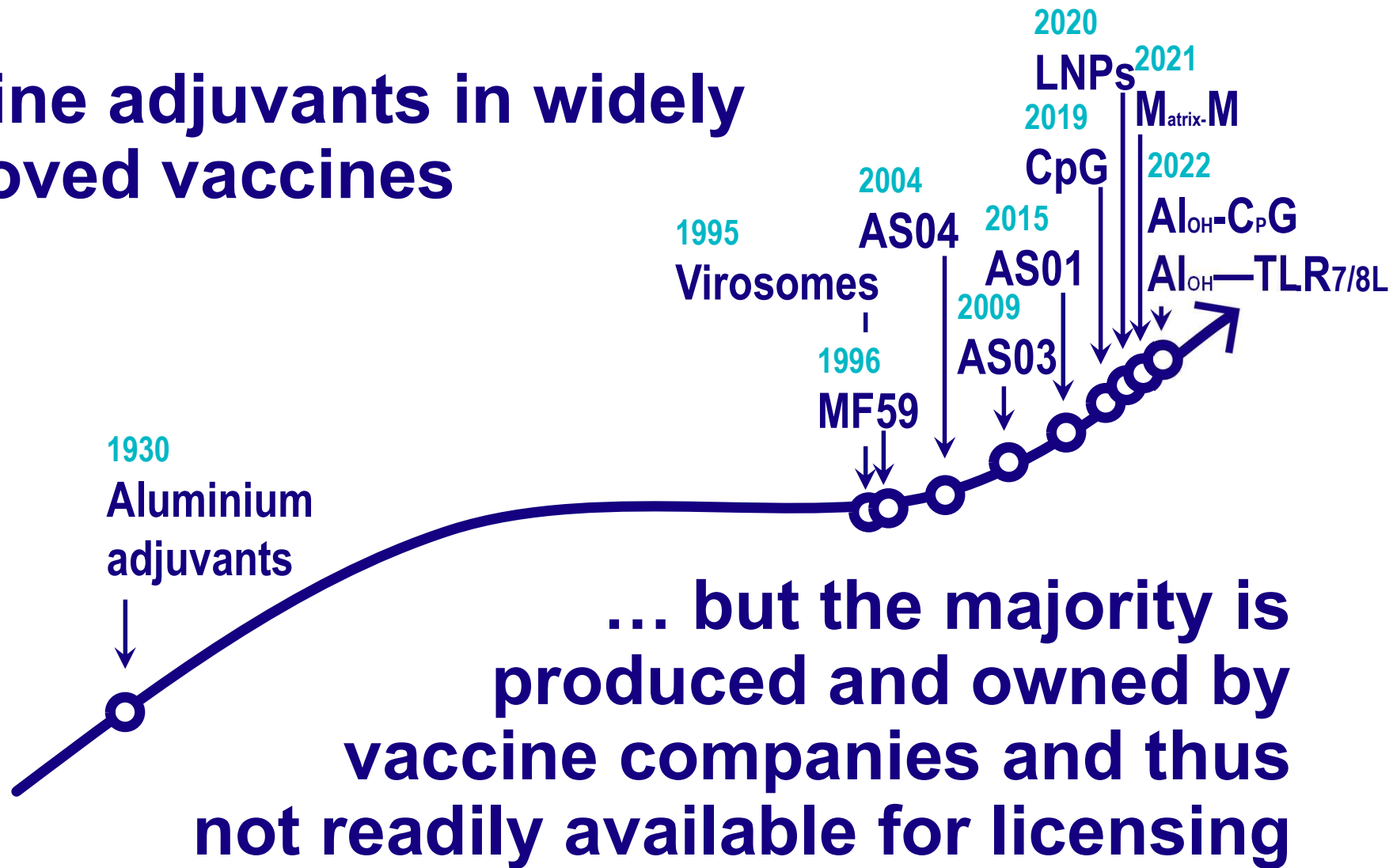
ANTIGEN

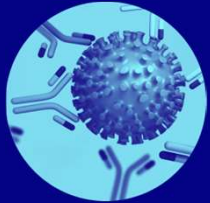
ADJUVANT

Vaccine adjuvants in widely approved vaccines



Vaccine adjuvants in widely approved vaccines





Adjuvant Systems

85+ years of
expertise in
adjuvants

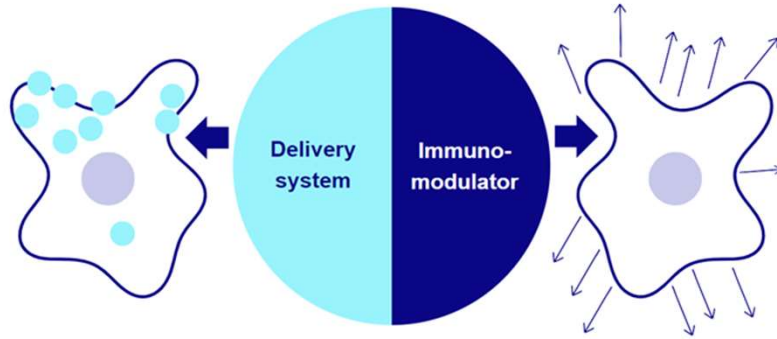


Our purpose

- To design and develop vaccine adjuvants for any purpose needed
- To mature vaccine adjuvant technologies by developing manufacturability and scalability.
- To make novel vaccine adjuvants reliably available to vaccine innovators
- To supply developmental and commercial volumes in line with our customers readiness.
- To bring forth safe and effective vaccine adjuvants to the world

CRODA | Pharma

From research to GMP grade supply



Our portfolio

Delivery System building blocks

Cationic lipids
Ionisable lipids
PEG lipids
Structural lipids
Neutral lipids
Super Refined™
• Polysorbate 20
• Polysorbate 80
Span™ 85 Pharma
Sterols



Immuno-stimulators

PHAD™ range
TDB
QS 21
Sustainably Sourced Squalene



Adjuvant systems

Alhydrogel™
Adju-Phos™

CAF®01
CAF®09b
sMPLA/QS21 liposomes
Squalene emulsions

Quil-A (vet)
NanoQuil™ (vet)

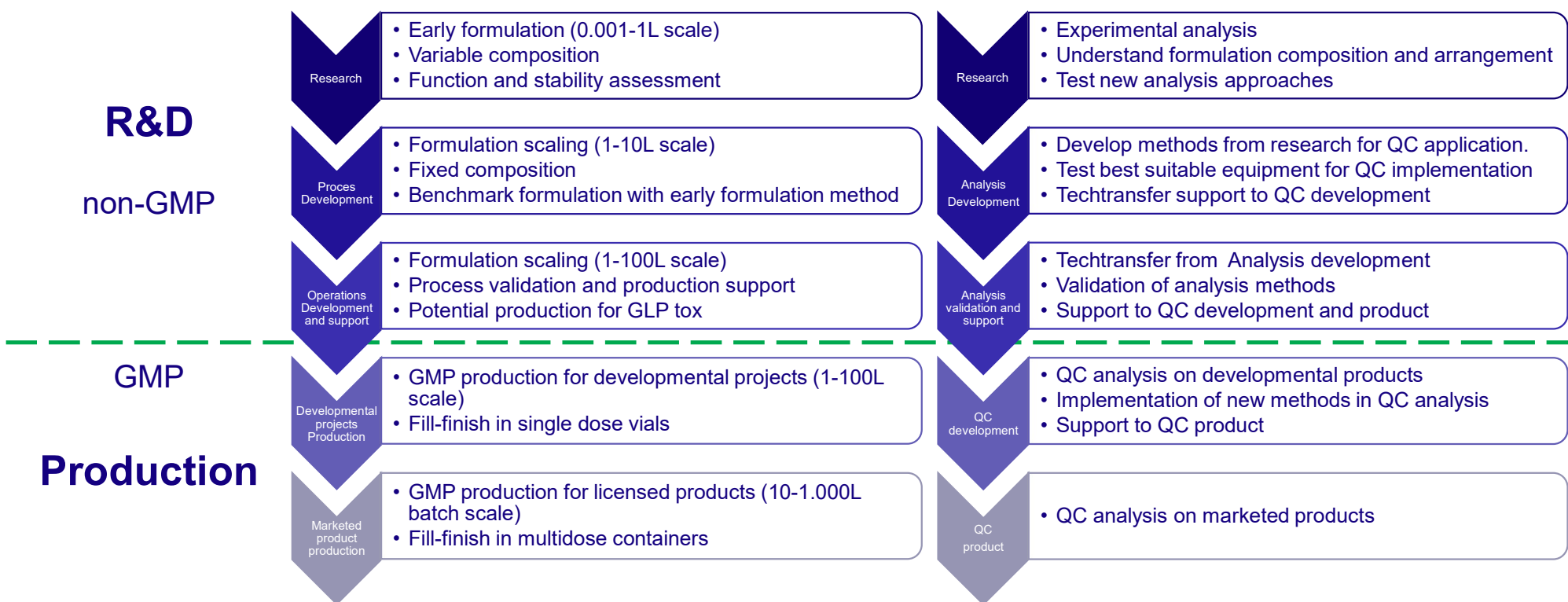
2000+ Unique Research Catalog Items

CRODA Pharma

Strategy plan - Bench to bed infrastructure

Production

Quality control

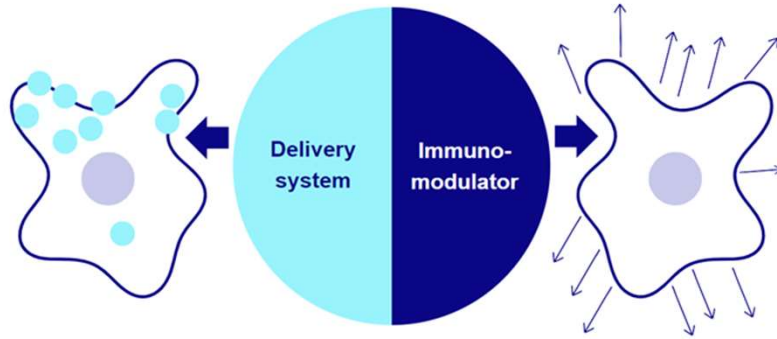


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Croda Pharma

Securing Vaccine Adjuvant Ingredients and Systems supply chain

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CRODA Pharma

Research & cGMP excipients

2000+ Unique Research Catalog Items

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

>15 synthetic chemists (12 PhDs)

250+ years of combined experience

Semi-Synthetic: Phosphatidylcholine, Phosphatidylethanolamine, Phosphatidylserine, and Phosphatidylglycerol

Lipid	Product number	CAS	DMF
DMPC	730345	18194-24-6	✓
DPPC	730355	63-89-8	✓
DSPC	730365	816-94-4	✓
DOPC	730375	4235-95-4	✓
POPC	770557	26853-31-6	✓
DEPC	730398	51779-95-4	✓
DPPC (Ultra high purity)	738555	63-89-8	
DMPC (Ultra high purity)	738345	18194-24-6	
DOPE	770725	4004-05-1	✓
DOPS	770035	90693-88-2	
DMPG	730445	200880-40-6	✓
DPPG	730455	200880-41-7	✓
DSPG	730465	200880-42-8	✓

PEG Lipids

Lipid	Product number	CAS	DMF
DMG-PEG2000	770151	160743-62-4	✓
DSPE-PEG2000	770120	474922-77-5	✓
DSPE-PEG2000-Carboxylic acid	770135	1403744-37-5	
DMPE-PEG2000	730150	474922-82-2	✓
ALC-0159*	770159	1849616-42-7	✓

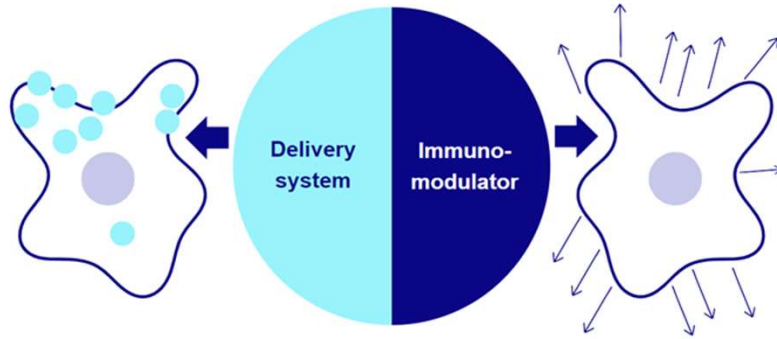
Miscellaneous

Lipid	Product number	CAS	DMF
Tricaprylin	730412	538-23-8	✓
Cholesterol (Plant, Parenteral)	730100	57-88-5	Not applicable (compendial material)
ALC-0315*	CM04017	2036272-55-4	✓
DDM	770520	69227-93-6	
DPC	770336	29557-51-5	✓

Synthetic Monophosphoryl Lipid A (MPLA) Adjuvants

Lipid	Product number	CAS	DMF
PHAD™	770030	1246298-63-4	✓
3D-PHAD™	770040	1699735-79-9	✓
3D(6-acyl)-PHAD™	770050	252042-59-4	✓

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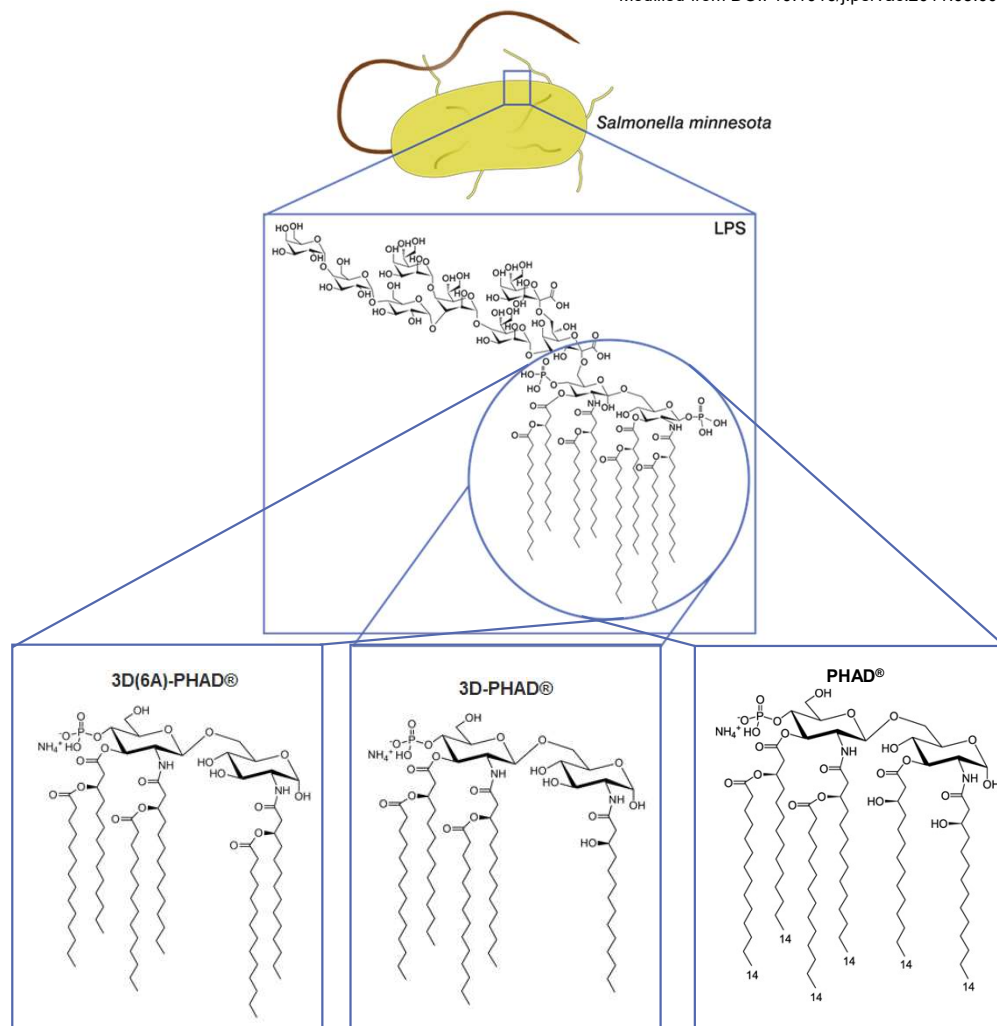
CRODA Pharma

PHAD®

Phosphorylated HexaAcyl Disaccharide (PHAD)

- Fully synthetic equivalent to bacterial-derived MPL-A
- TLR4 agonist inducing Th1 responses
- 3 types available in GMP quality
 - PHAD (also referred as GLA)*
 - 3D-PHAD
 - 3D(6-acyl)-PHAD

*proven safety and tolerability in >30 clinical trials



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Squalene

- **Is a vaccine adjuvant component** used for parenteral vaccine emulsions.
- **Is included** in the MF59 and AS03 adjuvants, which is widely used in flu vaccines, and other similar systems in development.
- **Is named after** the Latin word for shark – *squalus* - because it **is sourced from** deep-sea shark livers.
- This sourcing has the potential to further **devastate shark populations** and have long-lasting ecological consequences.



Finucci et al. Science 383, 1135-1141(2024)
DOI:10.1126/science.ade9121

NEW Sustainable Squalene

Engineered by synthetic biology, non-shark-derived

Sourcing squalene from **deep-sea sharks is unsustainable**.
Its use in life-saving vaccine formulations creates a strong
demand for viable alternatives to secure supply.

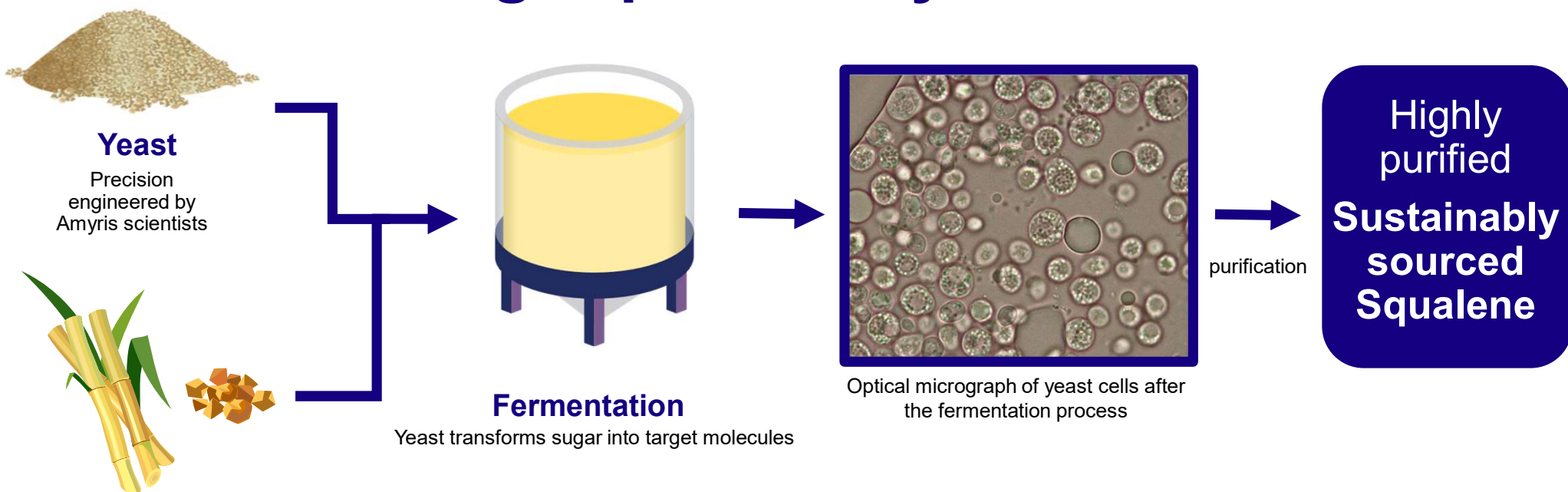
Sustainable Squalene offers:

- Superior purity of at least 99% in line with stringent requirements of vaccine manufacturers
- Molecularly identical with shark squalene
- Equivalent stability in emulsion adjuvants
- Sustainable production via cutting-edge, proprietary technology
- Non-animal derived, protecting shark populations and dependent marine ecosystems
- Consistent and secure supply
- Life Cycle Analysis including carbon emission and land utilisation impacts

Smart science to improve lives™

CRODA Pharma
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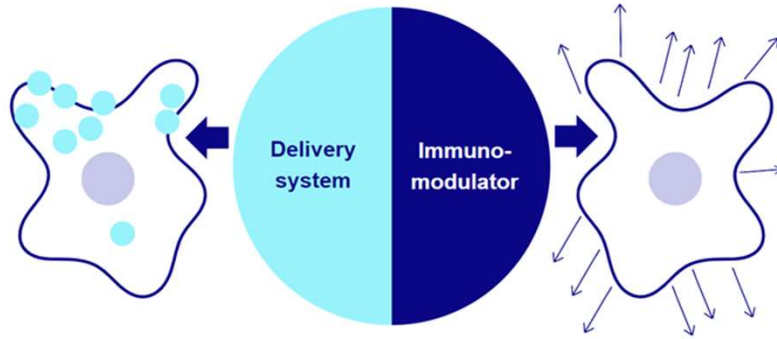
Manufacturing Squalene by fermentation



Sustainably sourced squalene is:

- Similar to shark based squalene $\geq 99\%$ pure (area%)
- Compliant with EP monograph 2805 specifications - the minimum specification required by vaccine producers
- No ChP, JP or USP monograph for squalene as a vaccine adjuvant exists at present

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Smart science to improve lives™

Alum is still the gold standard

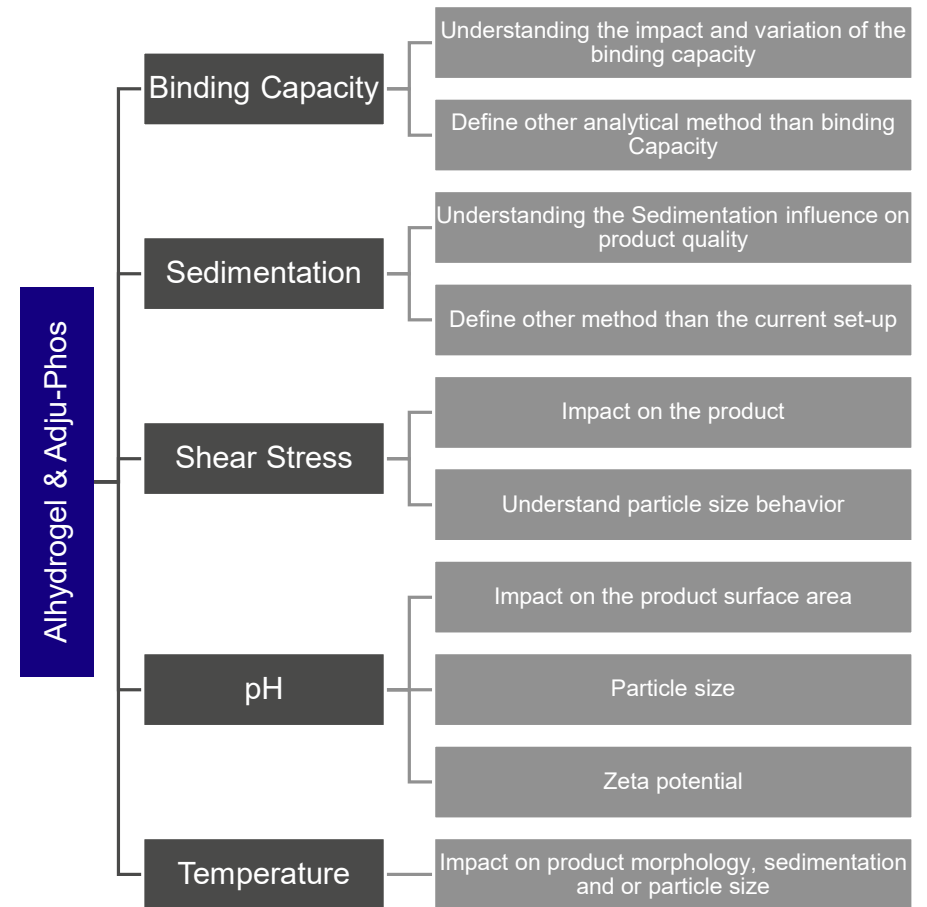
- Acts as an "amplifier" for the innate immune response and enables a boost in antibody production
- Can be combined with other adjuvants (such as Monophosphoryl Lipid) to achieve a balanced Th1/Th2 immune response
- More than **80 years of safe and effective use** in commercial vaccines
- The widely recognised and market-leading adjuvants **Alhydrogel™** and **Adju-Phos™** are produced in the only aseptic manufacturing site for aluminium-based adjuvants globally

GRAS Generally Recognized As Safe

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Alum R&D support

- Support with drug-product formulation optimization and characterization
 - Consulting on formulation issues
 - Hands on optimization, characterization, analysis development, CPP definition etc.
- Aluminum based adjuvants with gradually shifting zero-point of charge



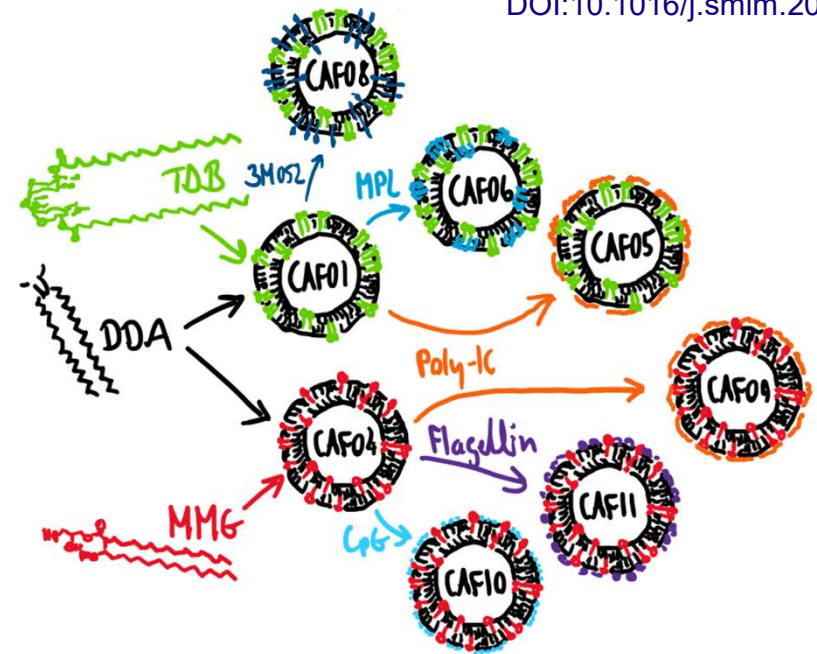
The CAF[®] adjuvants

Croda has entered a strategic collaboration with the renowned **Statens Serum Institut**



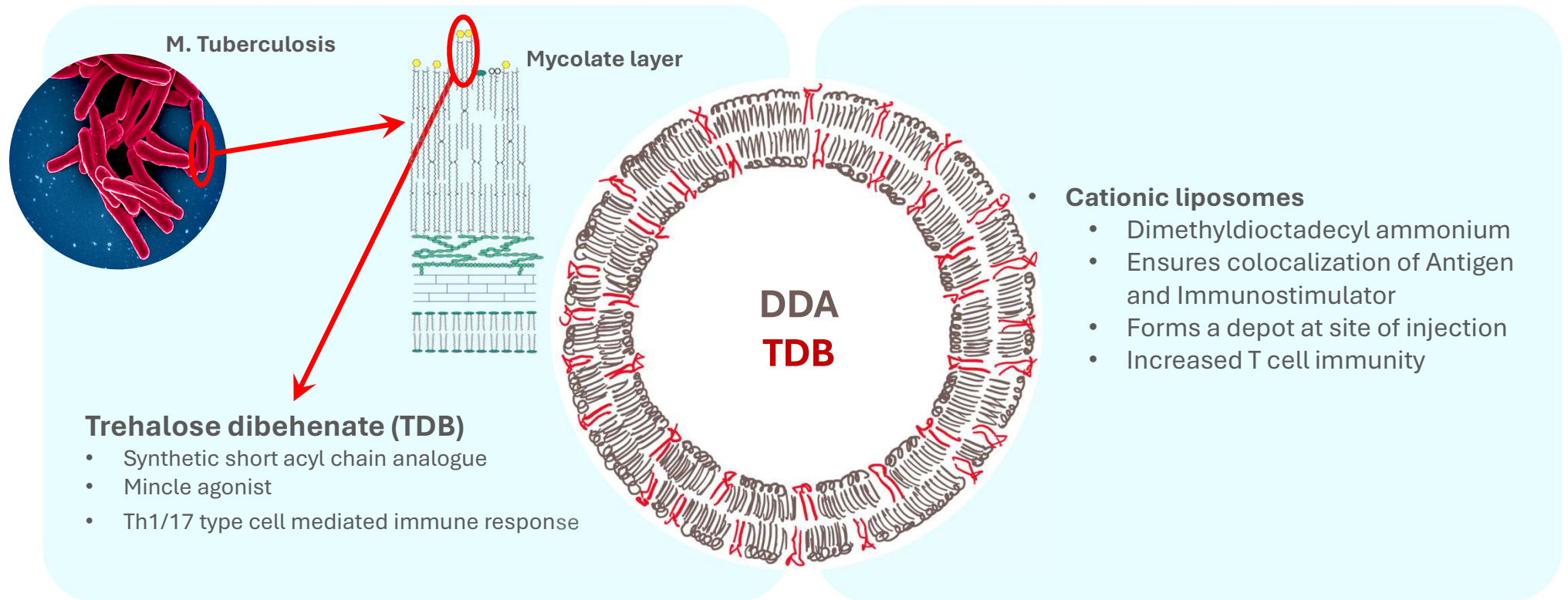
Croda will exclusively manufacture and commercialise **CAF01, CAF09b** and potentially **new CAF adjuvants** in clinical development.

The CAF range offers opportunities for new prophylactic and therapeutic vaccines.



Adjuvant	Ab resp.	Th1 eff	Th2 eff	Th17 eff	Tcm	CTL	Neonate
CAF01	★★★★	★★	★	★★	★★★★	-	★★
CAF04	★★★★	★	-	★	★★★	-	★
CAF05	★★	★★★	-	-	★★	★★★	-
CAF06	★★★★	★★★★	★	★	★	★	-
CAF08	★★★★	-	-	-	★★★	-	★★★
CAF09b	★★	★★	-	-	★★	★★★	-
CAF10	★★★★	★★★★	★	★★★★	★★★	-	★★
CAF11	★★★★	★★★	★	★	★★★	-	★★

CAF01: Th1/17 type CMI response and strong Ab responses



CAF09b: Mucosal adjuvant for strong CTL/Th1 and IgA/IgG responses

M. Tuberculosis

Mycolate layer

DDA
MMG
PolyIC

- **Polyinosinic:polycytidylic acid**
 - structurally similar to dsRNA, present in some viruses
 - Stimulant of TLR3.

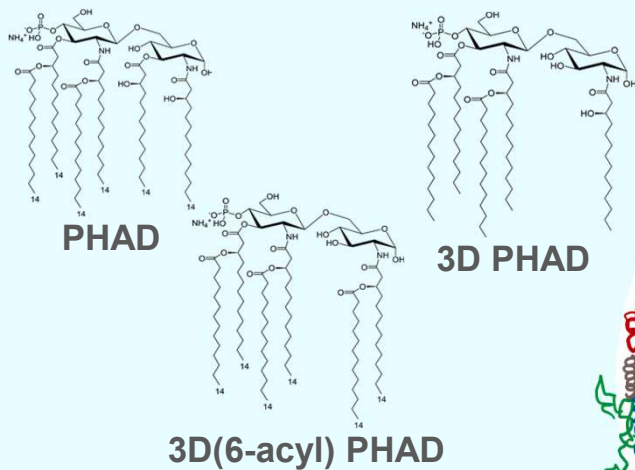
Monomycoloylglycerol (MMG)

- Synthetic short acyl chain analogue
- Mincle agonist
- Th1/17 type cell mediated immune response

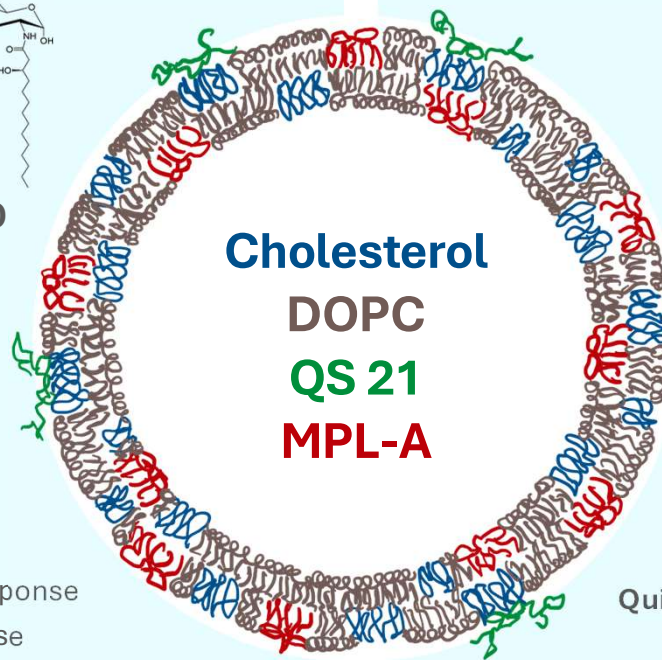
PolyIC

CC1=NC2=C(N1)N=CN=C2N3C=NC(=O)N3C4=NC=CC(=O)N4C5C=CC(=O)N5C6C=CC(=O)N6C7C=CC(=O)N7C8C=CC(=O)N8C9C=CC(=O)N9C10C=CC(=O)N10C11C=CC(=O)N11C12C=CC(=O)N12C13C=CC(=O)N13C14C=CC(=O)N14C15C=CC(=O)N15C16C=CC(=O)N16C17C=CC(=O)N17C18C=CC(=O)N18C19C=CC(=O)N19C20C=CC(=O)N20C21C=CC(=O)N21C22C=CC(=O)N22C23C=CC(=O)N23C24C=CC(=O)N24C25C=CC(=O)N25C26C=CC(=O)N26C27C=CC(=O)N27C28C=CC(=O)N28C29C=CC(=O)N29C30C=CC(=O)N30C31C=CC(=O)N31C32C=CC(=O)N32C33C=CC(=O)N33C34C=CC(=O)N34C35C=CC(=O)N35C36C=CC(=O)N36C37C=CC(=O)N37C38C=CC(=O)N38C39C=CC(=O)N39C40C=CC(=O)N40C41C=CC(=O)N41C42C=CC(=O)N42C43C=CC(=O)N43C44C=CC(=O)N44C45C=CC(=O)N45C46C=CC(=O)N46C47C=CC(=O)N47C48C=CC(=O)N48C49C=CC(=O)N49C50C=CC(=O)N50C51C=CC(=O)N51C52C=CC(=O)N52C53C=CC(=O)N53C54C=CC(=O)N54C55C=CC(=O)N55C56C=CC(=O)N56C57C=CC(=O)N57C58C=CC(=O)N58C59C=CC(=O)N59C60C=CC(=O)N60C61C=CC(=O)N61C62C=CC(=O)N62C63C=CC(=O)N63C64C=CC(=O)N64C65C=CC(=O)N65C66C=CC(=O)N66C67C=CC(=O)N67C68C=CC(=O)N68C69C=CC(=O)N69C70C=CC(=O)N70C71C=CC(=O)N71C72C=CC(=O)N72C73C=CC(=O)N73C74C=CC(=O)N74C75C=CC(=O)N75C76C=CC(=O)N76C77C=CC(=O)N77C78C=CC(=O)N78C79C=CC(=O)N79C80C=CC(=O)N80C81C=CC(=O)N81C82C=CC(=O)N82C83C=CC(=O)N83C84C=CC(=O)N84C85C=CC(=O)N85C86C=CC(=O)N86C87C=CC(=O)N87C88C=CC(=O)N88C89C=CC(=O)N89C90C=CC(=O)N90C91C=CC(=O)N91C92C=CC(=O)N92C93C=CC(=O)N93C94C=CC(=O)N94C95C=CC(=O)N95C96C=CC(=O)N96C97C=CC(=O)N97C98C=CC(=O)N98C99C=CC(=O)N99C100C=CC(=O)N100

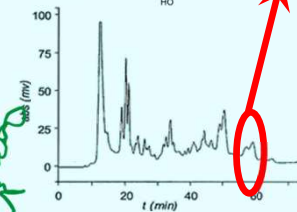
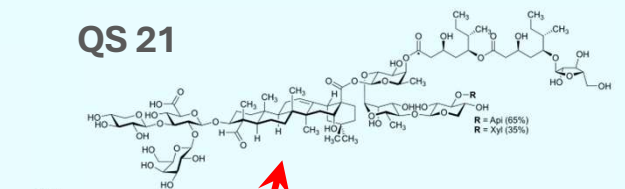
AS01 alternative: Strong Th1 and Ab responses



- PHADs are synthetic analogs of MPL
- TLR4 agonist
- MyD88 dependent proinflammatory response
- Th1 type cell mediated immune response

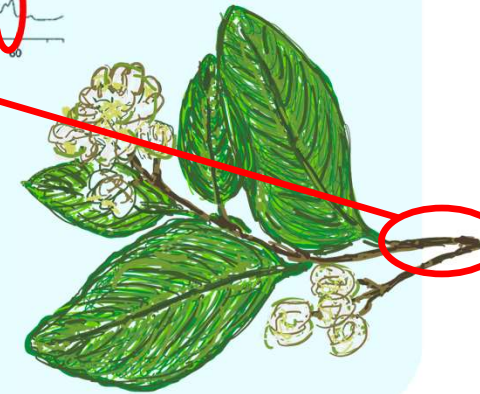


QS 21



Quil-A

Quillaja Saponaria

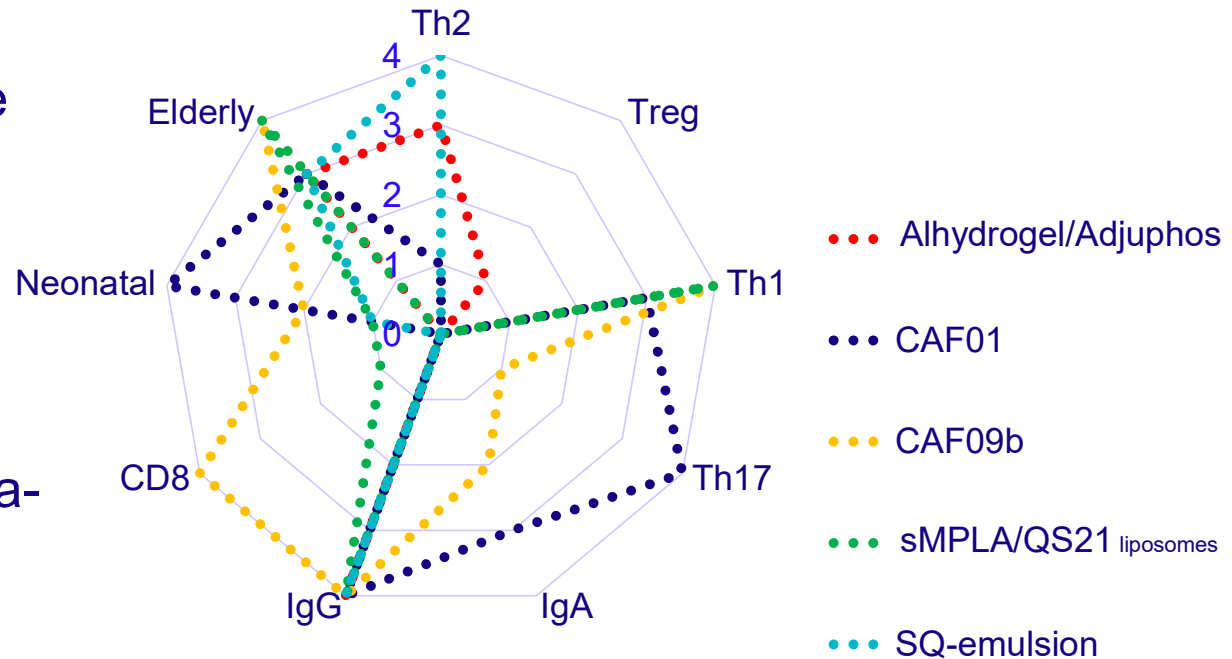


CRODA | Pharma

Which adjuvant to chose and how to use it?

We can help you, which vaccine adjuvant to choose

- There is **no** "one solution fits all"
- Selection should depend on the immune fingerprint requested
 - **correlates of protection**
 - most often based on availability
 - "Lemming effect" vs novel technology
- Selection often based on comparative studies in small animals
 - Can we utilize these models better?
 - Optimal vaccination regime is differing with platforms



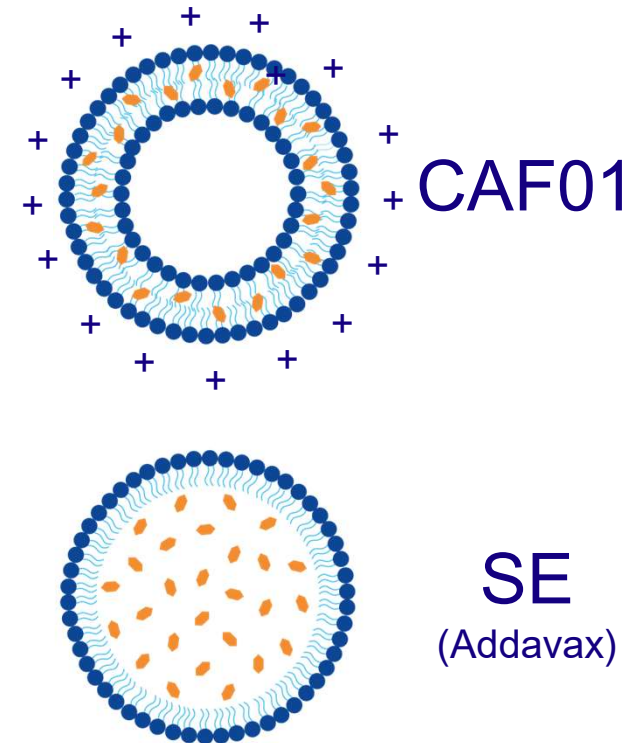
An example: Squalene Emulsion vs CAF[®]01

- Immune responses after *ONE* immunization

- Addavax[™] from Invivogen (analogue to MF59)
- CAF[®]01 from SSI
- Chlamydia vaccine candidate CTH522 as model antigen

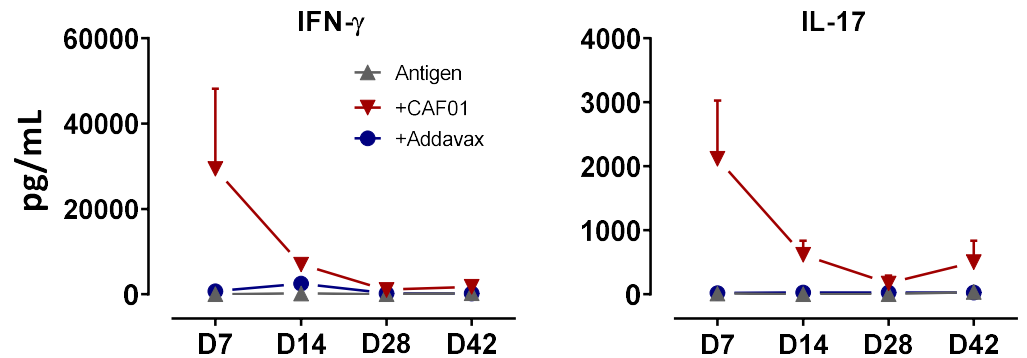
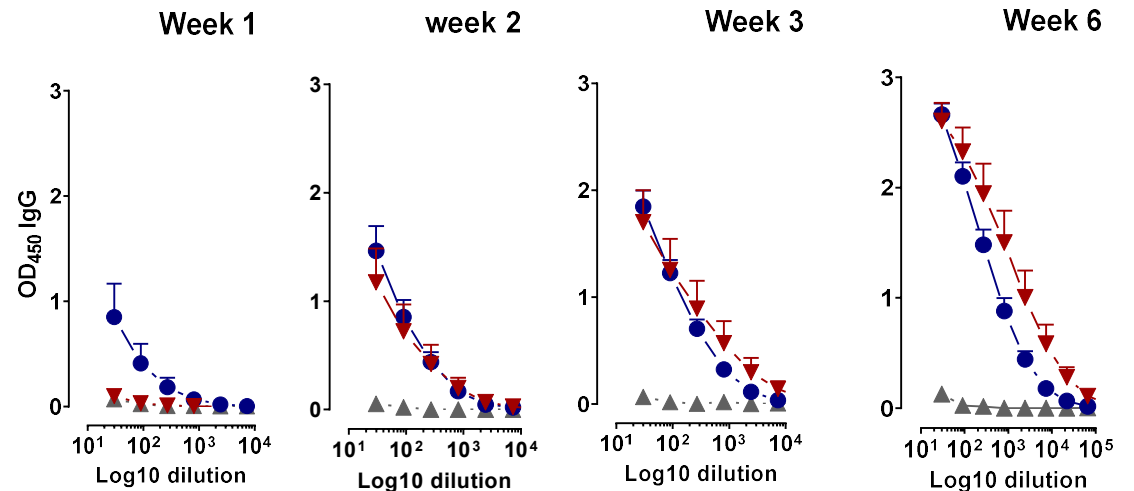
- Kinetic study focusing on

- Antibody responses
- Antigen kinetics and uptake
- Development of Germinal centers
- Depot removal



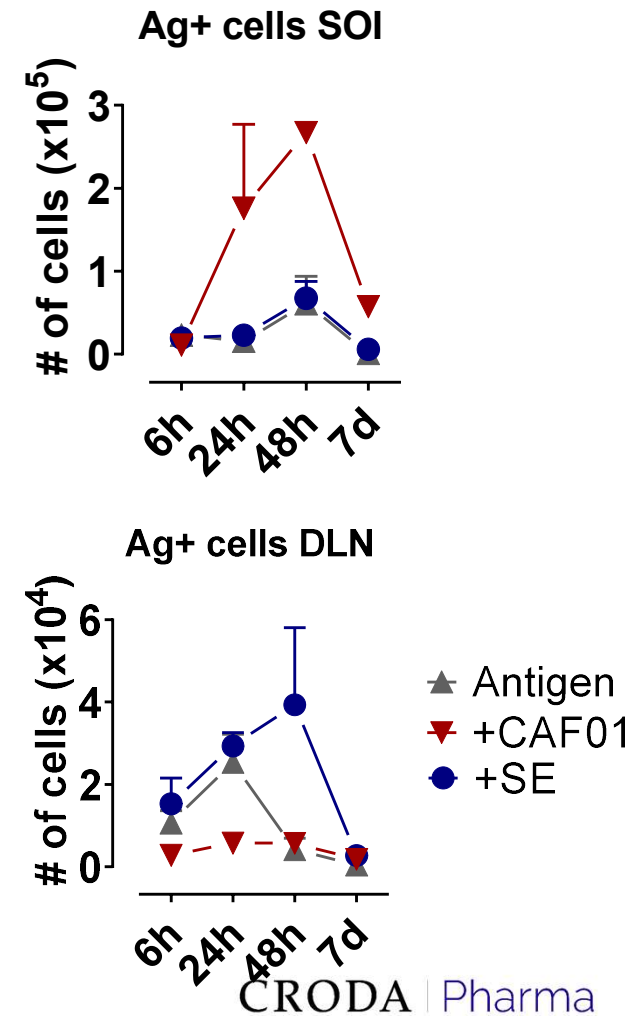
Antibody and T cell responses

- Fast Ab response by SE
- Slow but eventually higher Ab response by CAF[®]01
- No T cell responses with SE
- Detectable Th1/17 responses early after immunization w. CAF[®]01

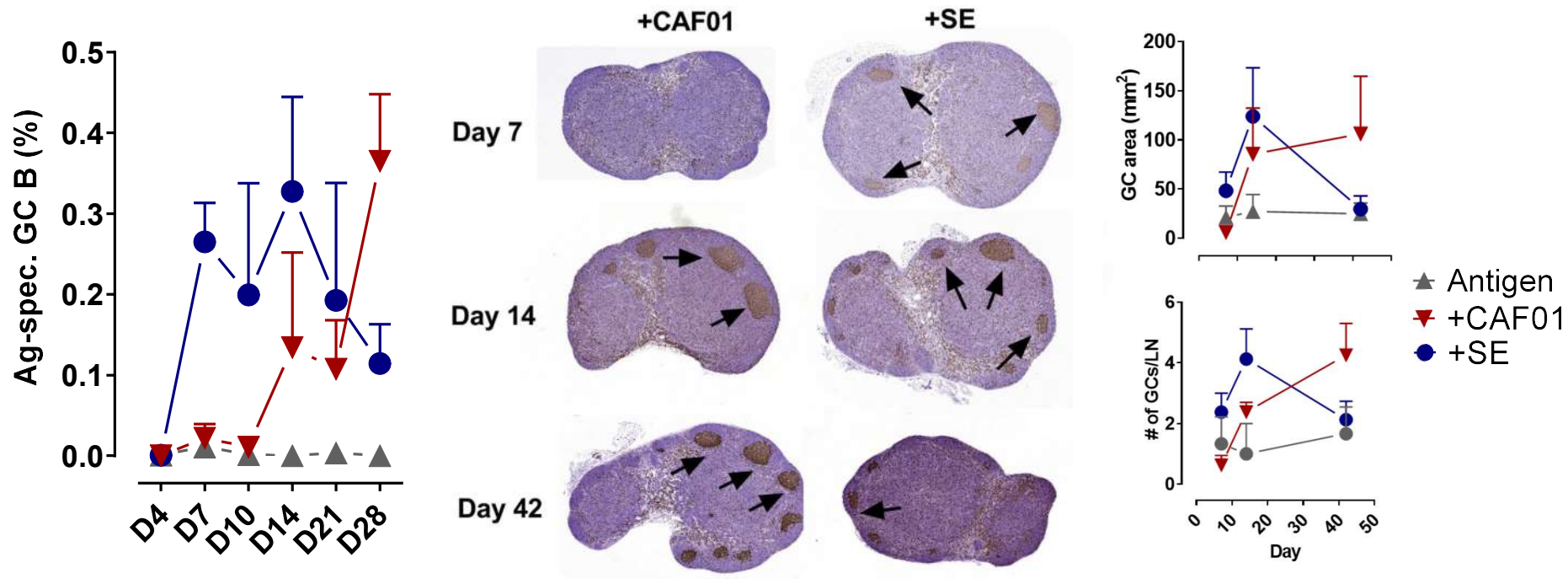


Antigen pharmacokinetics

- SE facilitate Ag drainage to the draining LN
- CAF[®]01 forms an Ag depot at the Site-of-injection



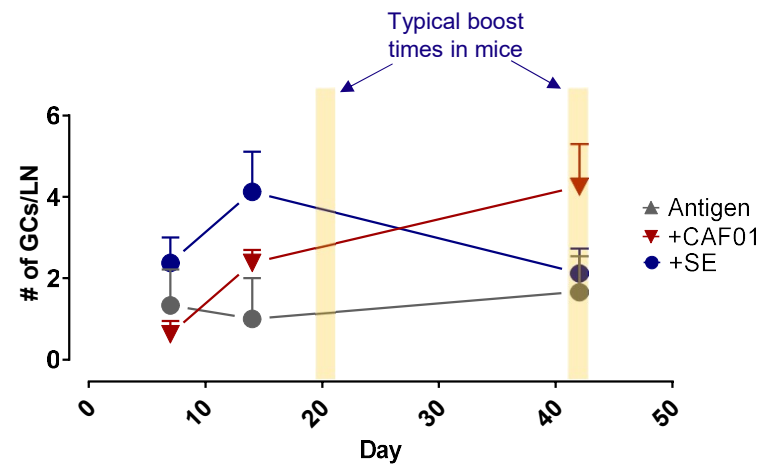
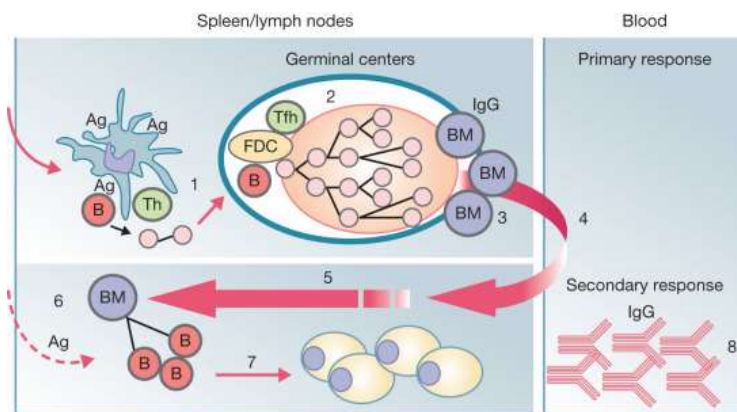
Germinal center formation



- SE fast GC formation, that is almost disappeared 42 days after immunization.
- GC formation with CAF01™ is delayed and I still big after 42 days.

Implication for vaccination protocol

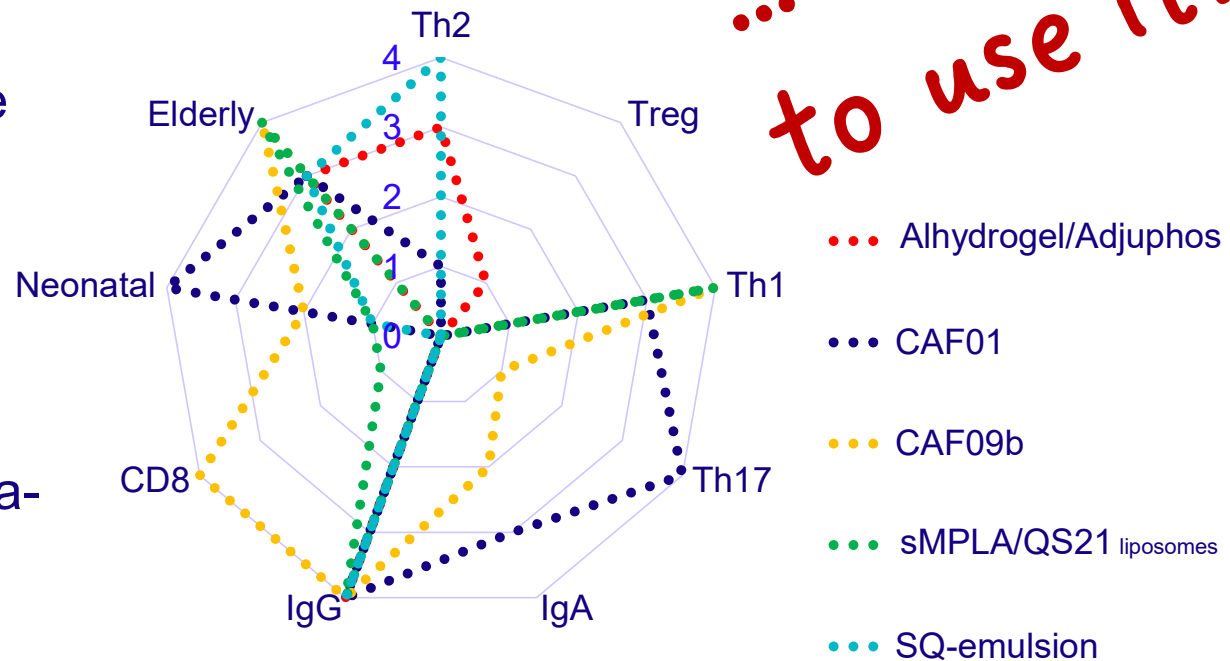
- Vaccine adjuvant selection often based on comparative studies in small animals e.g. mice
 - Classical protocol: 2-3 vaccines with 2-3 weeks interval



- Optimal booster time is differing with adjuvants
- Should be taken into consideration when designing comparative studies

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Thank you

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Empowering biologics delivery

A world leader in pharmaceutical excipients, vaccine adjuvants, lipids and bioprocessing ingredients for human and veterinary applications.

Non-warranty

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