Building better medicines, together.
Company Overview
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Bencard Adjuvant Systems is a division of Allergy Therapeutics UK, a fully integrated, specialty pharmaceutical company. Allergy Therapeutics plc is listed on the London Stock Exchange: AIM ticker AGY.

Located in Worthing, on England’s south coast, Bencard Adjuvant Systems specialise in developing and optimising adjuvants for infectious diseases, cancer immunotherapy and allergen immunotherapy.

We at Bencard Adjuvant Systems are committed to engaging in long-term partnerships with those who require our patented platform of adjuvant technologies to enable successful vaccine or immunotherapy development.

In addition to providing novel and efficacious adjuvant platforms, Bencard Adjuvant Systems have over 70 years of experience in manufacture, QC testing, regulatory filing and compliance. Whatever your project, we can build better medicines together.

Bencard Adjuvant Systems has an adjuvant portfolio that considers optimal immunogenicity and clinical relevance of antibody response.

Our adjuvant technologies are readily adaptable and offer optimal flexibility. Our people have a wealth of intellect to help you develop the best vaccines for efficacy and safety.

Contact us:
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+44 (0)1903 844 733

History of Vaccine Development

Adapted from Ennio De Gregorio & Rino Rappuoli. From empiricism to rational design: a personal perspective of the evolution of vaccine development. Nature Reviews Immunology 14, 505–514 (2014)
Unmet Needs

- Vaccine market tripled in value from $5bn in 2000 to almost $24bn in 2013\(^1\)
- Vaccine market projected to rise to $100bn by 2025\(^1\)
- Modern synthetic or recombinant antigens are less immunogenic than older-style live or killed organism vaccines\(^2\)
- There is an urgent need for depots and adjuvants for these new vaccines
- Alum is an approved adjuvant that is able to stimulate good Th2 responses, however has little capacity to stimulate a Th1 response which is vital for protection against many pathogens\(^2\)
- Consequently there is a major unmet need for safer and more effective adjuvants suitable for human use.

Choosing the ideal adjuvant

The aim of vaccination is to induce a protective adaptive immune response against a specific pathogen. When designing a new vaccine, it is important to take into account several factors, one of them is the adjuvant.

Adjuvants are an essential component of modern vaccine development.\(^2\)

Why is it important to use an adjuvant?\(^3\)
- Adjuvants enhance the immunogenicity of the antigen, especially important when using antigens that are poorly immunogenic.
- A depot effect of some adjuvants permits a slow release of the antigen and therefore extends immune presentation.

Microcrystalline Tyrosine (MCT\(^\circledR\))

- Naturally metabolised
- Established antigen binding capacity\(^4\)
- Extensive experience in humans
- Potent immune system potentiator\(^5, 6\)

AdSys-VCT

- Dual power of MCT\(^\circledR\) and Virus-like Particles (VLP)
- VLP induces strong humoral and cellular immune responses
- Potential to enhance weakly reactive vaccine candidates\(^7\)
- MCT/VLP induces higher protective cellular immunity compared with other adjuvants\(^7\)

AdSys-PS

- Phosphatidylserine derivatives effect different antibody subclasses and their levels\(^8\):
  - DOPS – stimulator of IgG
  - LOPS – stimulator of IgA
  - SAPS – inhibitor of IgE
- AdSys-PS exhibit no mutagenic properties or cytotoxic effects\(^9\)

4. Bell A.J. et al., Protein and MPL adsorption capacities for MCT\(^\circledR\) compared against existing adjuvants. Poster at EAACI 2015.
7. Cunha-Mendes G. et al. Virus-like particle (VLP) plus microcrystalline tyrosine (MCT) adjuvants enhance vaccine efficacy improving T and B cell immunogenicity and protection against Plasmodium berghei. Vaccines 2017, 5, 10
9. Data on file
Microcrystalline Tyrosine
Microcrystalline Tyrosine (MCT®)

Microcrystalline tyrosine is a patented depot adjuvant formulation of the biodegradable amino acid L-tyrosine that combines optimal drug stability profile and short-course vaccine delivery with extensive safety data consistent with its natural origin.

Why MCT®?

MCT® has been designed to provide defined particle size and morphology along with strong antigen binding capacity to enhance its use as a powerful immune system potentiator.

MCT® is formulated and manufactured using automated ‘steam-in-place’ and ‘clean-in-place’ systems enabling it to be administered as a sterile product.

MCT® has been designed to provide defined particle size and morphology along with strong antigen binding capacity to enhance its use as a powerful immune system potentiator.

Right: Two images illustrating defined particle sizes.

- Natural amino acid
- Patented biodegradable depot adjuvant
- Formulated in state of the art GMP processes
- Used in over 6.2 million injections in allergen immunotherapy
- Naturally metabolised
- Quickly removed
- Defined particle morphology and size
- Extensive experience in humans

Limitations of existing adjuvants

- Most commonly used adjuvant is Aluminium which mediates Th2 immunological pathway
- Regulatory authorities set aluminium limits per dose (125 mg/dose)
- Aluminium has a propensity to accumulate in tissues
- The repeated administration of aluminium containing adjuvants will likely contribute directly and significantly to an individual's total body burden of aluminium

Physicochemical and biological attributes of adjuvants

<table>
<thead>
<tr>
<th>Traditional Adjuvant / Depot</th>
<th>Second generation adjuvant</th>
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</thead>
<tbody>
<tr>
<td>Ideal properties of adjuvants</td>
<td>Microcrystalline Tyrosine (MCT®)</td>
</tr>
<tr>
<td>Physicochemical</td>
<td></td>
</tr>
<tr>
<td>Degree of characterisation:</td>
<td></td>
</tr>
<tr>
<td>Antigen adsorption</td>
<td></td>
</tr>
<tr>
<td>Particle size</td>
<td></td>
</tr>
<tr>
<td>Effective in variety of administration routes:</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous immunotherapy</td>
<td></td>
</tr>
<tr>
<td>Sublingual immunotherapy</td>
<td>N/A</td>
</tr>
<tr>
<td>Stable</td>
<td></td>
</tr>
</tbody>
</table>

Biological

- Depot function to:
  - Extend immune system exposure
  - Boost specific antibody/effector titre
  - Th1
  - Th2
  - Biodegradable/Metabolised by the host
  - Dose sparing effects

- =least characterised
- =most characterised from literature in allergen immunotherapy

All components in a vaccine need to be metabolised

MCT® is naturally metabolised and is quickly removed unlike Aluminium adjuvants that can persist at dose site.

MCT® metabolism

MCT® is metabolised with a half-life of 48 hours.

MCT® metabolism

- [McDougall, S. et al., Analysis of aluminium in rat following administration of allergen immunotherapy using either aluminium or microcrystalline-tyrosine-based adjuvants. Bioreline (2016) 8(6), 547–556.
- Table adapted from: Klimek, L et al., Clinical use of adjuvants in allergen immunotherapy. EXPERT REVIEW OF CLINICAL IMMUNOLOGY, 2017 VOL. 13, NO. 6, 599–610.
- Data on file.}
Vaccines need a strong adsorption capacity

**MCT® properties**

- The adsorption of adjuvant and antigen in vaccines has been shown to affect efficacy.  
- MCT® is shown to be consistently adsorbed with Antigens and other adjuvants (TLR-4 agonist).  
- MCT® exceeds WAO recommendations for depot adsorption capacity which underpin product stability and potency.

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>BSA Adsorption Capacity</th>
<th>Lysozyme Adsorption Capacity</th>
<th>TLR4 receptor agonist Adsorption Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% Alhydrogel®</td>
<td>420 µg/mg</td>
<td>1446 µg/mg</td>
<td>17 µg/mg</td>
</tr>
<tr>
<td>Calcium Phosphate</td>
<td>70 µg/mg</td>
<td>≤10 µg/mg</td>
<td>≤2 µg/mg</td>
</tr>
<tr>
<td>2% MCT®</td>
<td>≤10 µg/mg</td>
<td>1689 µg/mg</td>
<td>2.5 µg/mg</td>
</tr>
</tbody>
</table>

**MCT® has the greatest adsorption capacity for Lysozyme and TLR4® compared to Alhydrogel® and calcium phosphate**

**Vaccines need to be stable**

**MCT® Stability**

ICH stability profile exists with data in support of use at 2-8°C, ambient and elevated temperatures.

The Adsorption of Allergoids and 3-O-desacyl-4'-monophosphoryl lipid A (MPL®) to Microcrystalline Tyrosine (MCT®) in Formulations for use in Allergy Immunotherapy:

- Binding forces between MPL® and MCT® were investigated by competition binding experiments using Naphthalene as a competitor. It was shown that MPL® adsorption to L-tyrosine in MCT® formulations is based on interactions between the 2-deoxy-2-aminoglucose backbone on MPL® and aromatic ring of L-tyrosine in MCT®, such as C–H...π interact.

Vaccines need to stimulate the immune system

MCT® immunogenic responses in OVA allergy mouse model

MCT® is a Th1 specific immunomodulator¹

MCT® triggers higher amount of CD 11c+ cells³

MCT® triggers less IgE but similar IgG responses compared to alum²

Immunisation with MCT® triggered stronger IFN-γ and IL-10 than alum²

MCT® works in synergy with antigens to get a higher immune response⁴

Adjuvant efficacy evaluation

Vaccines need to be effective

3. Data on file
4. Wheeler, et al., A Th1-Inducing Adjuvant, MPL, Enhances Antibody Profiles in Experimental Animals Suggesting It Has the Potential to Improve the Efficacy of Allergy Vaccines. Int Arch Allergy Immunol 2001;126:135-139
Case study: MCT® in an influenza model vaccine

Unmet needs:
- Vaccination against seasonal influenza strains is recommended for high-risk patient groups.
- Seasonal vaccines against influenza viruses have to be updated on an annual basis due to the mutagenic characteristics of the virus.
- The effectiveness of influenza vaccines range from 56-58%.
- The addition of an adjuvant to influenza vaccines has been approached to promote both immunogenicity and dose sparing in pandemic situations.

MCT® as an adjuvant in a ferret influenza model:

H1N1 content (µg/ml)

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.09</td>
<td>1.19</td>
<td>0.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

MCT® possesses high protein-binding capacity

Analysis confirmed ≥95% antigen - MCT® adsorption

Adjuvant efficacy evaluation:

HAI titres showed higher levels for MCT compared to Aluminium or non-adjuvanted H1N1 vaccine

A single dose of MCT® adjuvanted vaccine generates a sero-positive titre (≥20 HAI titre)

MCT® showed a higher immune response compared to non-adjuvanted vaccine

Case study: MCT® in a malaria (P. vivax) model vaccine

Unmet needs:
- Malaria is a massive global health problem
- No licensed malaria tertiana (P. vivax) vaccine for human use

MCT® as an adjuvant in a mouse malaria model:

MCT® induced a more balanced response compared to Alum triggering markedly higher IgG2 isotypes and propensity to develop central memory T cells.

Vaccine efficacy evaluation:

- MCT® exhibits better protection for malaria than Aluminium.


2. WHO. Malaria vaccine development: http://www.who.int/malaria/areas/vaccine/en/
AdSys-VCT

AdSys-VCT is a vaccine platform where virus like particles (VLP) and Microcrystalline Tyrosine (MCT®) are combined to potentially increase vaccine efficacy.

Why AdSys-VCT®?

- MCT® has been shown to be a potent adjuvant in a malaria and influenza mouse model.
- VLP are highly organised 3-dimensional particular structures with repetitive surfaces which incorporate the key immunological features of viruses, although they do not contain viral RNA or DNA.
- AdSys-VCT uses a VLP model that contains integral Pan T cell epitopes to enhance Th1 capacity.
- VLP have a high capacity to induce strong humoral and cellular immune responses.
- MCT® is bound effectively to VLP.
- Their combined effect may result in a potent adjuvant system.

AdSys-VCT in a malaria model

Vaccines need to stimulate the immune system

**MCTVLP immunogenic response in a P. vivax model²**

Vaccines need to be effective

**Vaccine efficacy evaluation²**

2. Cabr al-Miranda G. et al., Virus like particle (VLP) plus microcrystalline tyrosine (MCT) adjuvants enhance vaccine efficacy improving T and B cell immunogenicity and protection against Plasmodium berghei. Vaccines 2017, 5, 10.
**Phosphatidylserine**

Apoptosis or programmed cell death is the process whereby dead cells are removed by phagocytosis, this leads to no inflammation.

This process is initiated by the expression of phosphatidyl serine (PS) on the outer cell membrane.

This ensures the removal of dead cells while preventing leakage of the cell contents that would lead to inflammation.

Phagocytosis of apoptotic cells results in the inhibition of inflammatory mediators e.g. IL-1β by macrophage while stimulating anti-inflammatory mediators e.g. TGF-β.

Stimulation of macrophages to express anti-inflammatory or suppressive phenotypes is likely to be crucial in the resolution of inflammation.

Delivery of PS containing vaccines would alter the antigen response resulting in a shift away from inflammatory antibody production to anti-inflammatory antibody production.

Three different PS derivatives effect different antibody subclasses and their levels:
- **DOPS** – stimulator of IgG
- **LOPS** – stimulator of IgA
- **SAPS** – inhibitor of IgE

DOPS stimulates a significant increase in IgG2a (human IgG1) in a Brown Norway rat model.

DOPS stimulates a significant increase in IgG1 (human IgG4) in a Brown Norway rat model.

DOPS stimulates a significant increase in IgA in a Brown Norway rat model.

DOPS stimulates a significant increase in IgE in a Brown Norway rat model.

Three different PS derivatives effect different antibody subclasses and their levels:

Lyso oleoyl Phosphatidylserine (LOPS)

- 250µg LOPS stimulates a significant increase in IgA in a Brown Norway rat model.

SAPS significantly reduces levels of IgE below control values in a Brown Norway rat model.

SAPS1
- Significantly inhibits levels of IgE
- Has no effect on levels of anti-inflammatory antibodies IgA and IgG2a

DOPS1
- Stimulates anti-inflammatory IgG1 (human IgG4) and IgA production
- Has no significant effect on levels of IgE
- Stimulates IgG2a (human IgG1)

LOPS1
- 250µg LOPS increases levels of IgA
- No significant effect on IgG1 (human IgG4)
- Has no significant effect on levels of IgE or IgG2a (human IgG1)

1. Data on file
Safety

Cytotoxicity
MTS assay results suggested that the three PS formulations, LPS and MPL up to 100µg had no cytotoxic effects on U937 cells.

1. Data on file

Mutagenicity
DOPS, LOPS, SAPS and MPL were all found to have no mutagenic properties up to a concentration of 250µg.
Services
How can we collaborate?

Bencard Adjuvant Systems tailor-made solutions

- Supply and license of patent protected depot adjuvants
- Technical transfer to enable materials to be formulated independently
- Co-administration of our adjuvant technologies
- On-site manufacture, pre-clinical and clinical development facilities
- Collaborative and joint research and development programmes
- Royalty and up-front cost models

“Whatever stage of the journey you’re on, we’re here to help build better medicines together”

Our facilities

“We have a 70 year heritage in pharmaceutical and adjuvant development. We have spent over $100 million in clinical development over the last 10 years investigating the use of novel adjuvant systems in study centres in Europe and USA.

“Our people have a wealth of intellect; our academic base is strong in immunology, biology, microbiology, chemistry and biochemistry”
Building quality into your vaccine solutions

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Biochemistry/Microbiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td>SDS profile</td>
</tr>
<tr>
<td>HPLC</td>
<td>Western Blotting</td>
</tr>
<tr>
<td>EP/USP Testing</td>
<td>Iso-Electric Focussing</td>
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<tr>
<td>Karl Fischer</td>
<td>Competitive ELISAs</td>
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<tr>
<td>Proteomics</td>
<td>Monoclonal Sandwich ELISAs</td>
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<tr>
<td>Particle Size Analysis</td>
<td>Identification Methods</td>
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<tr>
<td>Mass Spectrometry</td>
<td>In-house Sterility</td>
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<tr>
<td>Excipient Analysis</td>
<td>Endotoxin, bioburden</td>
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<tr>
<td>FTIR (Fourier Transform Infrared Spectroscopy)</td>
<td>Environmental monitoring</td>
</tr>
</tbody>
</table>

These services are available independently of any manufacturing requirements.

Our people have a wealth of intellect and are positively impacting lives through applying science and service to our products and patients.

Guiding you through registration

We have a proven track record in getting products to market with a motivated quality-driven regulatory affairs team to guide you through to product registration.

- Regulatory submissions (EU, USA and ROW)
- Worldwide pharmacovigilance, monitoring and reporting capabilities
- Distribution, supply and coordination of clinical trial materials

**We have experienced teams in clinical development (phase I, II and III) using adjuvants**