Adjuvant technology transfer hub

An example of transferring «enabling technologies»

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WHO Collaborating Centre
Outline

The challenges of adjuvant access

The Lausanne platform: context and main objectives

Case study: transfer of oil-in-water emulsion technology

Perspectives of the “hub-model”
Vaccine adjuvants

Adjuvant: any substance that enhances, re-directs, and/or sustains the immune response to a co-administered antigen

Essential ingredient of modern vaccines (subunit, recombinant vaccines)

Adjuvants playing an increasingly important role in vaccine development

- Malaria: AS02 critical to the efficacy of RTS,S.
- Pandemic influenza: MF59, AS03, AF03 permit dose reduction
- HPV: AS04 permits longer duration of antibody
- HBV: AS04 overcomes non-response
- Allergy: MPL drives Th1, fewer injections needed
A new era for vaccine adjuvants

Adjuvants in approved human vaccines
- Aluminium salts: aluminium hydroxide, aluminium phosphate
- Oil-in-water emulsions: MF59, AS03, AF03
- TLR 4 agonists: MPL

Adjuvant in clinical trials
- Saponins: QS21, Iscoms, AS01, AS02
- TLR 3 agonists: poly I:C
- TLR 4 agonists: GLA, Eisai
- TLR 5 agonists: Flagellin
- TLR 7-8 agonists: R848, imiquimod
- TLR 9 agonists: CpG, IC31
- Cationic liposomes
- Water-in-oil emulsions: Montanide ISA720, ISA51
- Polysaccharides: Inulin
The problem

Need of adjuvants for pandemic influenza vaccines (dose-reduction), malaria vaccines, TB vaccines (cellular immunity), and for new vaccines / new concepts

Limited access to adjuvants + Lack of know-how and expertise

Use of inappropriate adjuvants & inappropriate use of adjuvants

How to increase appropriate adjuvant use by vaccine manufacturers in low and middle income countries?

Public Sector
Know-how, freedom to operate, no commercial interest: A role to play in technology transfer?
Missions of the WHO Global Adjuvant Development Initiative:

1. Supply portfolio of proven adjuvants accessible to public sector
2. Provide vaccine formulation services and training courses
3. Facilitate technology transfer of adjuvants to developing countries

Jan 2010: creation of a center in Vaccine Formulation and Adjuvants at University of Lausanne, Switzerland
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Perspectives of the “hub-model”
Vaccine Formulation Laboratory

History

2010

Inauguration of the laboratory

Jan

0.5M€ grant from EC

Oct

1.8M$ grant from US-HHS

Dec

Technology transfer start

Technology transfer start

1.8M$ grant from US-HHS

Creation of the technology transfer hub

2010

Hiring staff
Building partnerships
Buying equipment
Standard Operating Procedures
Network
Communication

Workshop on Technology Transfer for Local Manufacturing Capacity of Vaccines, WHO – 1 December 2010
Expertise gathered in the hub

Knowledge management

Intellectual Property Management

Supply of adjuvants (generic, under MTA…) – focus on “mature technologies”

Saponins, oil-in-water, water-in-oil emulsions, mineral salts, liposomes…

Establishment of industrial process for adjuvant production: non-GMP

Partner with GMP, training and technology transfer experience

Letter of intent UNIL-NVI May 2010

Set-up of harmonization platform for adjuvant read-outs / standard reagents
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Perspectives of the “hub model”
July 2010: HHS / BARDA Funding Opportunity Announcement

«Development and Sustainable Manufacturing of Adjuvanted Pandemic Influenza Vaccines in Developing Countries»

. Global vaccine capacity insufficient to cover needs in case of pandemic

. Pandemic H1N1 (2009) experience:
  . Advance purchase agreements by industrialized countries
  . 8 months after pandemic: maximum of 500 M vaccine doses

*Partridge et al., 2010*
Which adjuvant for pandemic influenza vaccines?

**Pandemic influenza vaccines**

H5 inactivated virion: 90 µg HA (2 doses) needed for meeting registration criteria

.Split H5N1 virion + AlOH  →  30 – 45 µg

- Moderate antigen-sparing effect of aluminium salts

*Nolan et al., 2008*
Oil-in-water emulsions in pandemic influenza vaccines

**Pandemic influenza vaccines**

H5 inactivated virion: 90 µg HA (2 doses) needed for meeting registration criteria

- Subunit H5 virion + MF59 → 7.5 µg
- Split H5 virion + AS03 → 3.8 µg
- Split H5 virion + AF03 → 3.8 µg

MF59™-adjuvanted H5N3 vaccine
Non-adjuvanted H5N3 vaccine

![Graph showing GMTs SRH titers](image)

Nicholson et al. 2001
Oil-in-water emulsions

Different from water-in-oil emulsions
Appearance: milky
Composition:
- Squalene: shark oil
- Surfactants
- Water
- + / - DL-α tocopherol
- + / - block copolymer
- + / - immunostimulants

MF59 (Novartis), AS03 (GSK), AF03 (Sanofi-Pasteur), SE (IDRI)...

Oil-in-water emulsions vary in their composition

Can be added extemporaneously: production / logistic advantage
# Pros and cons of oil-in-water emulsions

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<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
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<td>Cheap, feasible, stable</td>
<td>Higher incidence of mild adverse reactions</td>
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<td>Extensive safety record (&gt;140 M people including children)</td>
<td>Public perception of the safety of adjuvants (especially for squalene)</td>
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<td>Possibility for extemporaneous combination</td>
<td>Role of pre-existing immunity not fully understood</td>
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Remarkable antigen-sparing for pandemic influenza vaccines

Quick conversion of unadjuvanted seasonal vaccine capacity into adjuvanted pandemic vaccine capacity: (expected multiplication factor: 5 to 25)
Project strategy

Knowledge management

Oil-in-water emulsions suitable for pandemic influenza vaccine

Intellectual Property Management

Freedom to operate in Europe and in developing countries

Supply of generic adjuvants or under MTA

Standard Operating Procedures for generic oil-in-water emulsion...

Establishment of industrial process for adjuvant production (non-GMP)

Hardware acquisition, staff with industrial expertise

Partner with cGMP, training and technology transfer experience

Application with Netherlands Vaccine Institute as consultant

First recipient of the technology

Bio Farma, Indonesia

Other DCVM provided letters of commitment / informal consent
Overview of process / QC

Release assays:
- Visual appearance
- pH
- Average particle size
- Squalene concentration
- Endotoxin content
- Bioburden
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<td><strong>Kick-off meeting</strong></td>
<td>Bandung</td>
<td><strong>Homogenizer UNIL</strong></td>
<td><strong>HPLC UNIL</strong></td>
<td><strong>Zetasizer UNIL</strong></td>
<td><strong>Microfluidizer UNIL</strong></td>
<td><strong>cGMP SOP at UNIL (English)</strong></td>
<td><strong>Training at UNIL 2 weeks</strong></td>
<td><strong>SAG meeting Lausanne</strong></td>
<td><strong>Training at Bio Farma 2 weeks</strong></td>
<td><strong>SAG meeting Bandung</strong></td>
<td><strong>Mil1</strong> 3 lots + QC</td>
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**Preclinical study**

*Workshop on Technology Transfer for Local Manufacturing Capacity of Vaccines, WHO – 1 December 2010*
Budget for future recipients

**Year 1**
Technology acquisition: process and QC

- Hardware
- Raw material - lab supplies
- Human resources
- Logistics

$1.2 M

**Year 2**
Preclinical study

- Hardware
- Raw material - lab supplies
- Human resources
- Logistics

$0.8 M
Outline

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Perspectives of the “hub-model”
Hub-model under construction
Resource optimization

Harmonization
Head-to-head evaluation

Distribution
Generic adjuvants or MTA

Training courses
Jul 2012
Jul 2013

Technology transfer
Standard Operating Procedures
Vaccine formulation
Service

Recipient 1
Recipient 2
Recipient 3
Recipient 4
Recipient 5
Technology transfer to more recipients

Training of National Regulatory Authorities

Provide know-how on second generation adjuvants (Saponins, TLR4…)

Malaria, TB, Cancer vaccines…

Technology transfer of **enabling technology**: leads to capacity of developing several new products
Potential of the “hub-model”

Harmonized evaluation

Help in evaluating own technology / technology provided by 3rd party

Potential applications of hub-model to other “enabling technologies”

Baculovirus production, reverse genetics, plant-based production...

Promotion of vaccine development self-sufficiency

Innovative Research & Development Capacity in LMIC
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Bio Farma

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