Development of affordable glycoconjugate vaccines for livestock to reduce food cost and improve food security

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Better affordable livestock vaccines means

Improved
food security,
productivity,
nutrition,
sustainability,
And contributes to
one health,
addressing zoonosis,
Etc.

UK Research and Innovation GCRF
UKRI GCRF Global Interdisciplinary Research Hubs
UK Research and Innovation
One Health Poultry Hub

bbsrc

MRC Medical Research Council

BILL & MELINDA GATES foundation

EPSRC Engineering and Physical Sciences Research Council

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Glycoconjugate-based vaccines

Polysaccharide-based vaccines produce a T-cell independent immune response with IgM that opsonises bacteria.

To convert to a more favourable T-cell dependent response polysaccharides are often conjugated to proteins

Examples of successful human glycoconjugate vaccines

1. ***Haemophilus influenzae***
2. ***Neisseria meningitidis*** **(except type B)**
3. ***Streptococcus pneumoniae*** **(some serotypes)**

Long lasting immunity & suitable for infants and elderly
Billion doses given per year!
Not used for animals?

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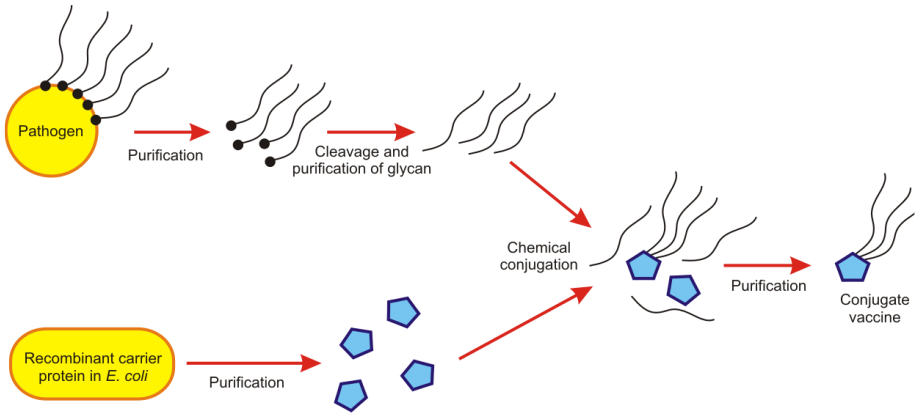
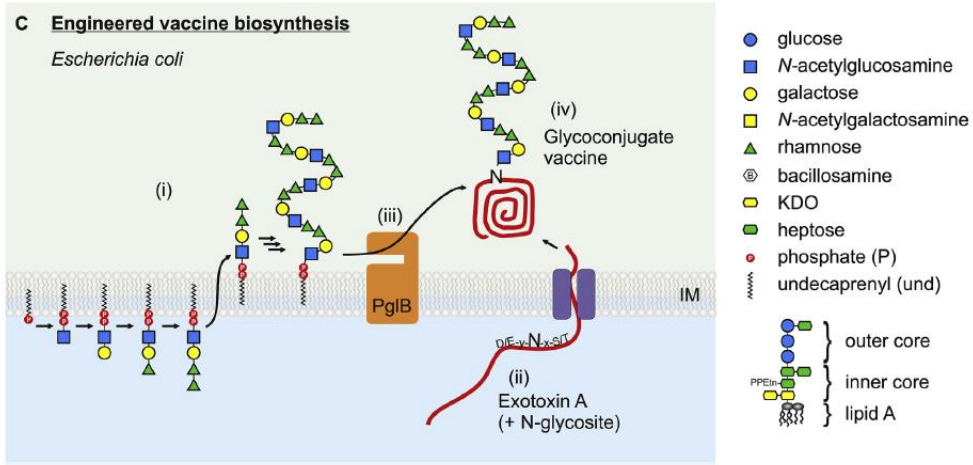
Traditional chemical conjugation v bioconjugation

Chemical



- **Multistep procedure > 300 quality control steps.**
- **Expensive**
- **Product often heterologous**

Bioconjugation (PGCT)



- **↓ complexity**
- **↓ cost**
- **↑ flexibility**

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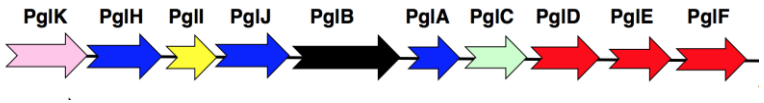
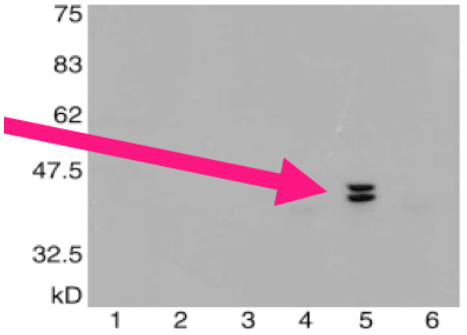
The genesis of bacterial glycoengineering

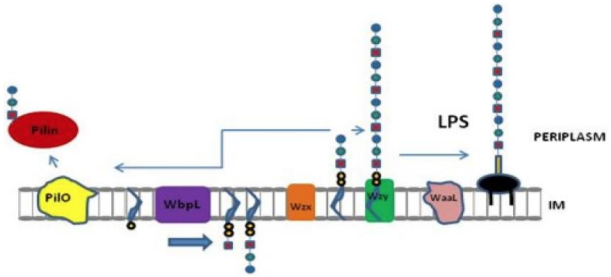
1. **Discovery of *Campylobacter N*-linked glycosylation system**
   (Parkhill *et al.* Nature 2001)



2. **Functional transfer of glycosylation system into *E. coli***
   (Wacker *et al.* Science 2002)



3. **Coupling of capsules and O-antigen to proteins in *E. coli***
   (Feldman *et al*. PNAS 2005)



New glyoengineering processes

- **Glycan Expression Technology (GET)**
- **Protein Glycan Coupling Technology (PGCT)**
- **Glycan Seeking Technology (GST)**

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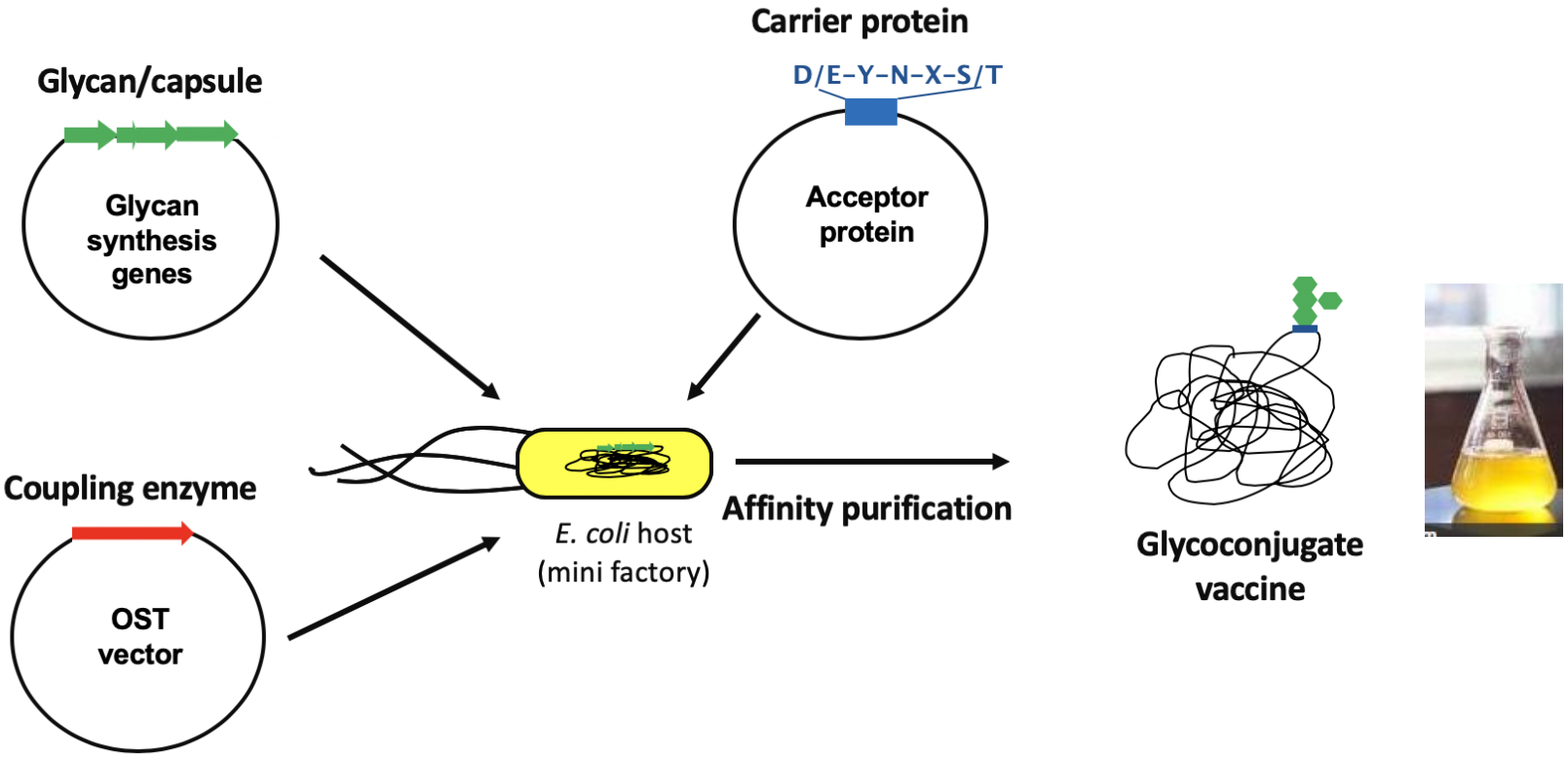
Stage 2. Protein Glycan Coupling Technology (bioconjugation)

PGCT allows the bioconjugation of selected glycans to chosen acceptor proteins



Recombinant approach in *E. coli* - one step purification procedure

Flexibility of mixing & matching of protein/glycan combinations

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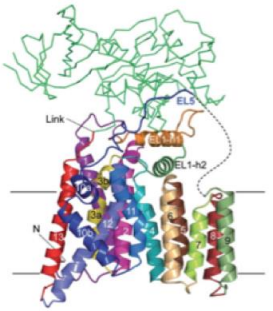
Current status - producing an inexpensive recombinant glycoconjugate vaccine in 3 easy steps

1. DNA synthesise target protein with glycotags and target glycan

2. Add DNA encoding protein and glycan to *E. coli* cells expressing coupling enzyme on chromosome



3. Grow *E. coli* and purify vaccine from column

Simple process – *E. coli* is a mini factory

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Current recombinant glycoconjugate vaccines

1. Improving existing glycoconjugate vaccines
Eg Streptococcus pneumoniae

2. New vaccines
***Eg Francisella tularensis, Burkholderia pseudomallei, Coxiella burnetii, Clostridium difficile, Brucella* species, Group A *Strep, Shigella* species, para typhi and Traveller's diarrhea**

3. New markets
***Eg* Poultry and pig glycoconjugate vaccines**

Glycoconjugate vaccine have not been used in animals?

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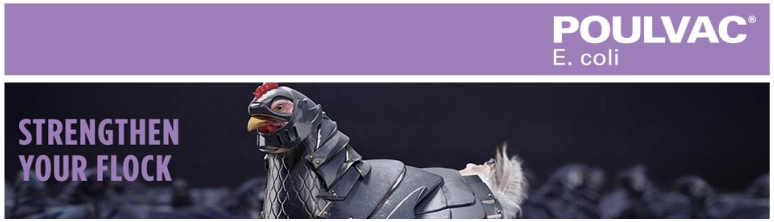
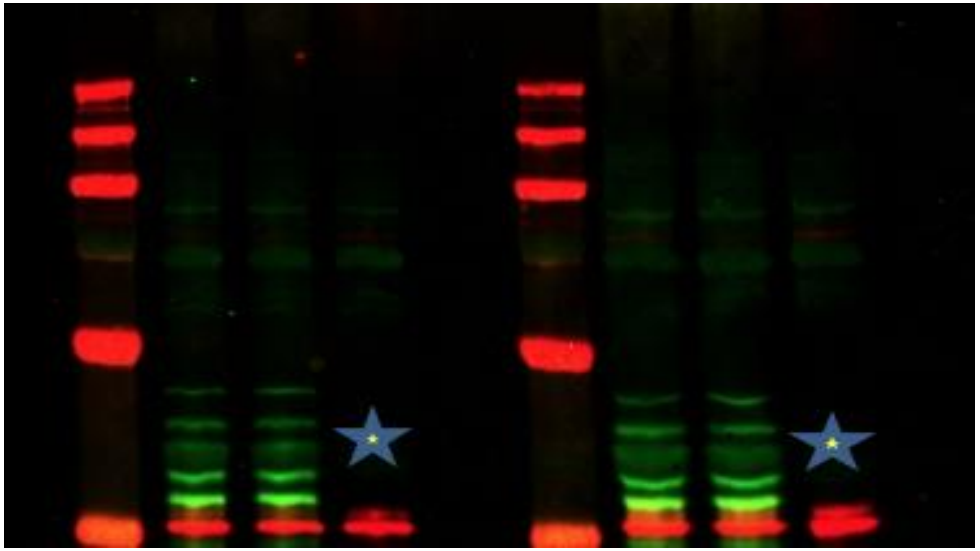
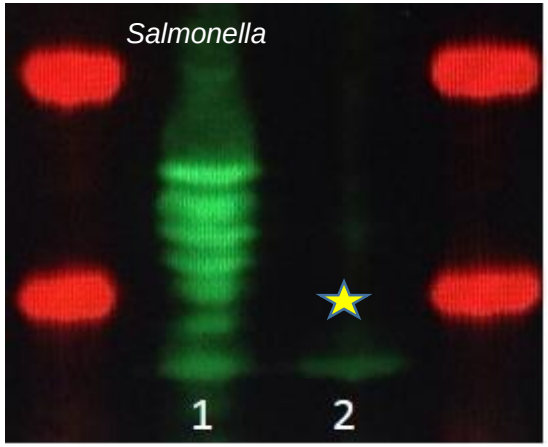
Glycoengineering for veterinary vaccines

1. Triple poultry vaccine – *Campy* glycan coupled to *perfringens* protein in attenuated *E. coli* or *Salmonella* strain







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Glycoengineering for veterinary vaccines

2. Dual pig vaccine – *Strep suis* capsule coupled to *Actinobacillus pleuropnemoniae* toxin

3. **Dual bovine vaccine** – *Coxiella* O-antigen coupled to epsilon *perfringens* toxin?

Or Brucella O-antigen coupled to Coxiella carrier protein candidate

BBSRC £5 million multicentre Lola grant

LSHTM spin out – ArcVax (animal vaccines)

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Conclusions and future perspectives

Basic curiosity driven research can lead to practical applications

1. **In-exhaustible and homogeneous supply of vaccine – low cost**
2. **Versatile technology - coupling glycans with carrier proteins**
3. **“Double-hit” vaccines (*eg S. suis* protein with *S. suis* capsule)**
4. **Piggy back onto existing attenuated vaccines for multiple protection**
5. **Animal vaccines, not just for animal health & economic prosperity, but blocking zoonotic infections reduces human disease (One Health)**
6. **Better vaccines (humans and animals), less antibiotic use**

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Glycobod team

What makes a good carrier protein?

How to upscale and manufacture glycoconjugates?

Develop the E. coli glycocell to express diverse glycan?

What makes a good glycoconjugate vaccine?

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