Oral vaccines to protect patients against *Clostridium difficile* infection

Jonathan Kearsey: Leads To Development

*Antibiotics and their alternatives-fixing and feeding the pipeline*
**Clostridium difficile infection (CDI)**

- A major threat to public health
- Affects elderly patients causing severe diarrhoea & acute colitis
- Mortality rates are four times greater than MRSA
- Hypervirulent and multiple drug resistant
- There are no marketed vaccines for CDI
Why an oral vaccine?

Three lines of defence:

1. Prevent entry
2. Stop attack once the first wall is breached
3. Repel invasion once inner wall is breached

Therapeutic options:

- Mucosal immunity (oral vaccines)
- Systemic immunity (injectable vaccines)
- Antibiotics
Current treatment options

• Extensive use of antibiotics

• Antibiotic treatments are becoming problematic

• As CD is multidrug resistant then antibiotic approaches alone are unsustainable

• Future management of CDI will therefore hinge upon oral prophylactic vaccines
The need for a mucosal vaccine

- Current pharmaceutical research is focused on injectable CD vaccines
  - They produce very poor IgA mucosal immunity
  - They are unable to fully protect against relapse
- Mucosal vaccines
  - Induction of mucosal IgA required to prevent CDI
  - Optimal mucosal immunity is induced by oral or sublingual administration routes
**Bacillus spore vaccines**

- *Bacillus subtilis* spores are safe for human consumption (GRAS status)

- Spores possess natural adjuvant properties

- Spores can be engineered to express immunogenic sequences on their surface

- Inactivated (killed) spores can be used as an oral vaccine delivery platform
CDVAX objectives

• Develop a novel, safe & efficacious oral vaccine delivery platform

• Optimise spore vaccine expressing CD immunogen

• Undertake preclinical development (production, pharmacology & toxicology)

• Complete a phase I clinical POC study in healthy volunteers
Immunogenicity

Hamster vaccination

Oral vaccination with *bacillus* spores expressing toxin A (PP108: days 0, 14, 35 & 57)

- Toxin A specific mucosal (IgA) & systemic (IgG1 & IgG2) antibodies detected
- Antibodies (IgA & IgG) show toxin A neutralising activity in cellular assays

Permpoonpattana *et al.* Infection and Immunity, 2011: 2295–2302
In vivo Proof Of Concept

Oral vaccination with *bacillus* spores expressing toxin A (PP108: days 0, 14, 35 & 57)

Challenge with *C. difficile* (Day 71)

Hamster vaccination & challenge

- CDVAX vaccination protected all animals from relapse (second challenge)

PY79 Non-recombinant spores
PP108 Toxin A expressing spores
rA16-39 = recomb. Toxin A protein

Permpoonpattana *et al.* Infection and Immunity, 2011: 2295–2302

CDVAX.org
Development challenges

Pharmacology

- Dosage form
- Oral or sublingual administration
- Optimal/maximal dosage
- Single administration/Optimal administration schedule
Development challenges

- Scale-up (petri dishes to 100 L fermenters)
- Optimal Biomass generation
- Optimal sporulation
- Development of a potency test for product release
Development challenges

- Method development: cellular & humoral responses
- Characterise toxicity & any dose-relationship
- Characterise the immune response induced
- Determine starting dose for clinical trials
Development challenges

- Regulatory product classification (GMO, ATMP or infectious disease vaccine)
- Scientific advice
- Establishment of a regulatory compliant preclinical development plan
Development challenges

- Pharmacology
- Production (CMC)
- Safety pharmacology & Toxicology
- Regulatory & project management
- First-in-man study

- Starting dose
- Administration schedule
- Number of healthy volunteers
- Study design
Expert consortium

France

Belgium

United Kingdom

France

Germany
Seventh Framework Programme

• The FP7-Health-2013-Innovation 2 programme is for three years
• The total value of the grant is nearly six million Euros
• Project launched on the 1\textsuperscript{st} June 2013
A novel vaccine for Clostridium difficile

Overview

CDVAX is a project funded under the European Union 7th Framework Programme. The aim of CDVAX is to take forward a novel and highly innovative oral vaccine that will provide protection against Clostridium difficile infection. This novel approach will use the spores of a genetically engineered harmless bacteria to generate a vaccine to protect vulnerable patients against this serious and life threatening hospital acquired infection. This project will develop the vaccine and evaluate it in a human clinical trial.

To learn more about Clostridium difficile and the illness it causes click here.

Project title
Oral Vaccination against Clostridium difficile Infection.

Work Programme

HEALTH.2013.2.3.1-1
"Drugs and vaccines for infections that have developed or are at risk of developing significant anti-microbial resistance".