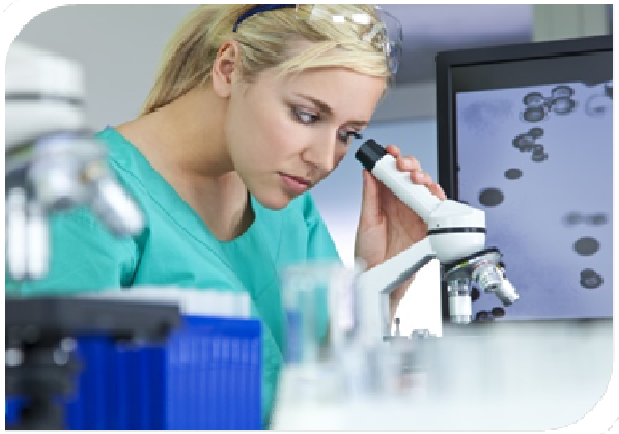
Prokarium

The Vaxonella® Platform for Oral Recombinant Vaccine Delivery

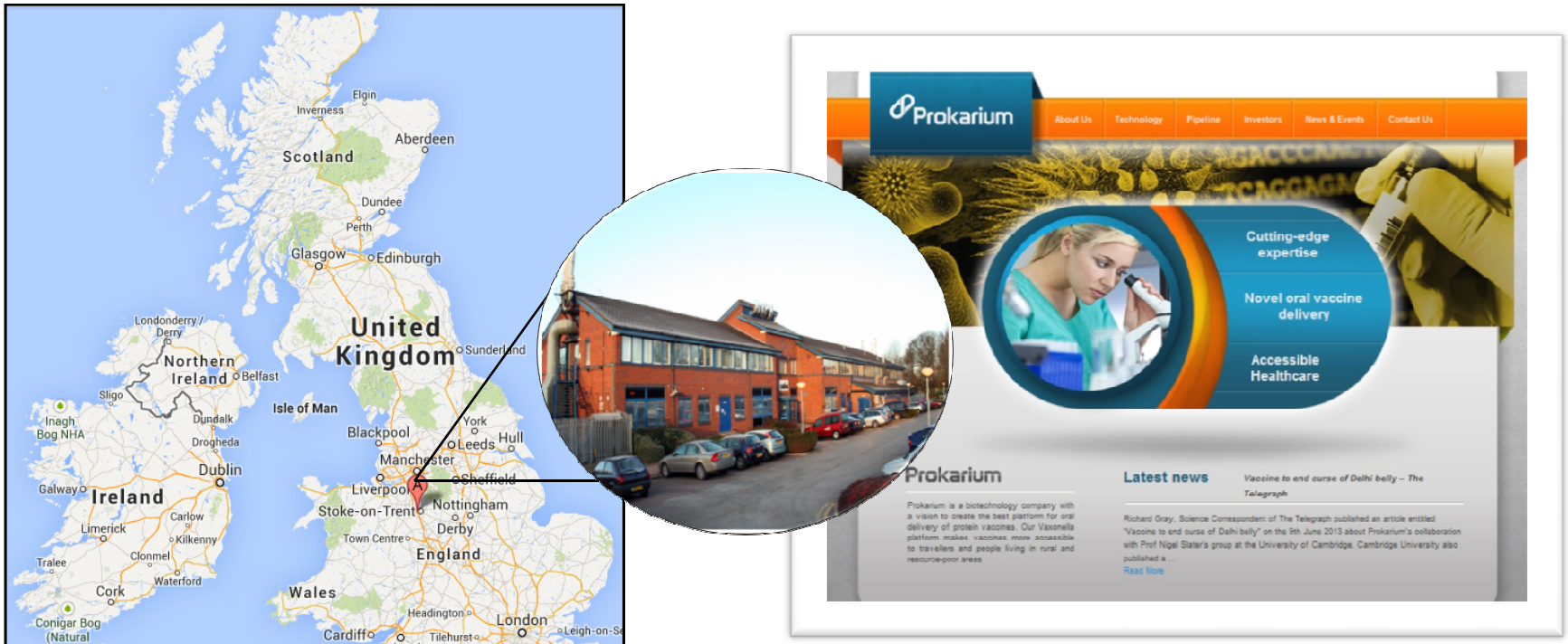
Dr Rocky Cranenburgh
Chief Scientific Officer

Friday 26th September 2014
4th International Conference on Vaccines & Vaccination, *Valencia*



Prokarium Ltd

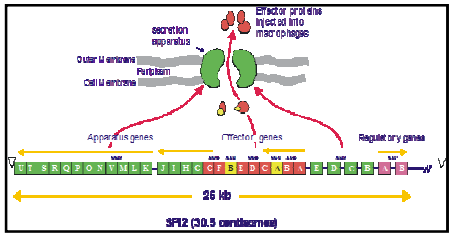
- Spun out from Cobra Biologics Ltd in June 2012
- Located in Keele (Staffordshire) and London, UK
- Oral recombinant antigen delivery using *Salmonella enterica*



www.prokarium.com

Re-engineering *Salmonella*

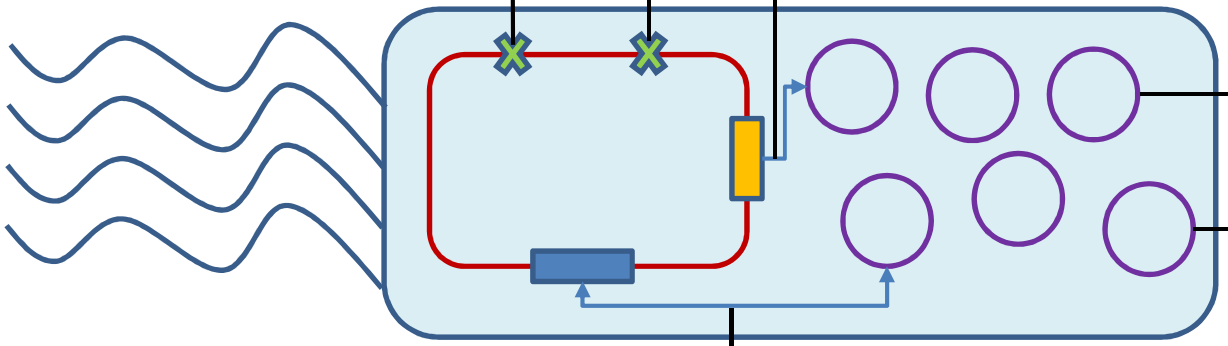
***Salmonella enterica* serovar Typhi** is a serious pathogen (ACDP 3)**:** we have used **synthetic biology** to modify it into a safe, precisely targeted oral vaccine delivery system



Δ*ssaV*: attenuation by preventing replication in macrophages

Δ*aroC*: prevents survival in the environment; attenuation

X-mark: automatic selectable marker gene deletion

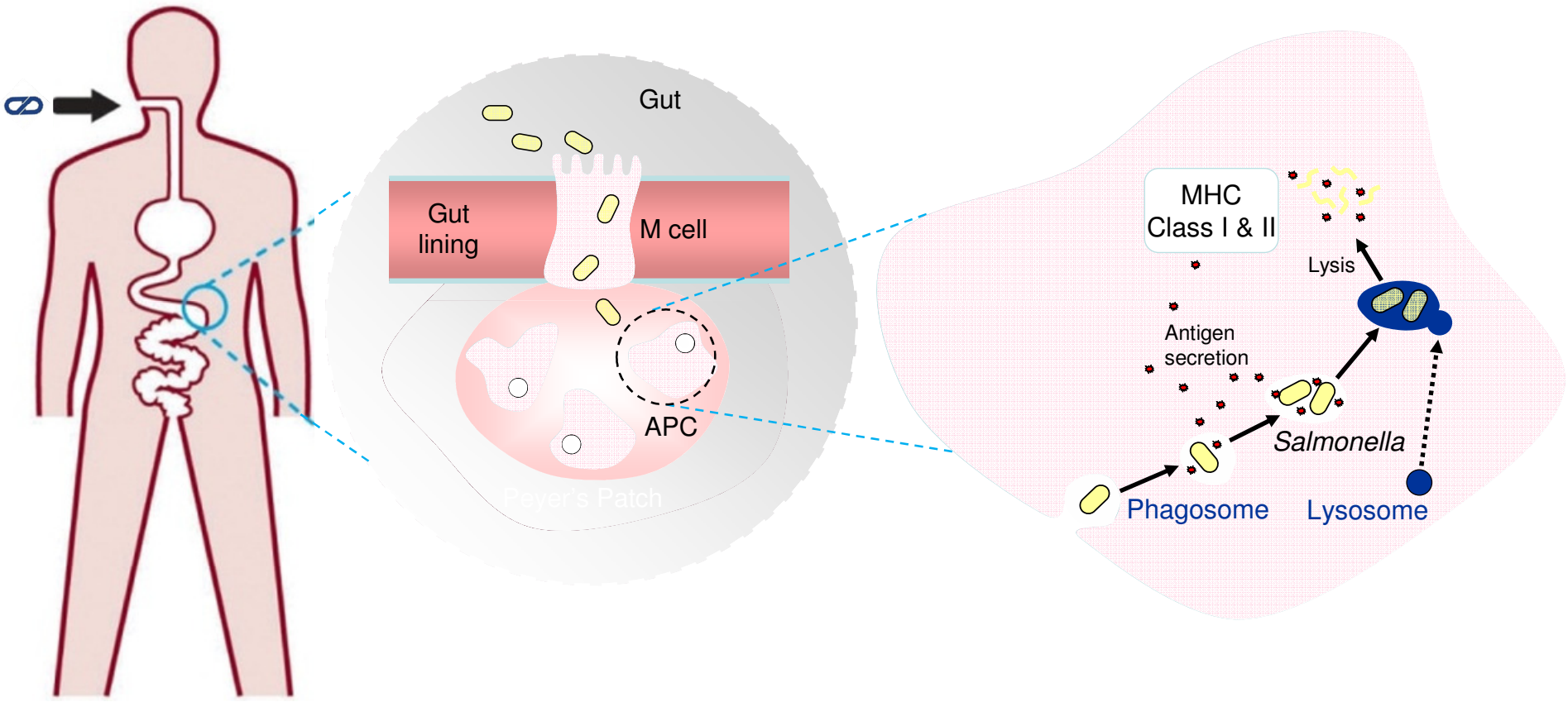


***ssaG* promoter**: induced in macrophages

Multi-copy plasmids: high-level antigen production

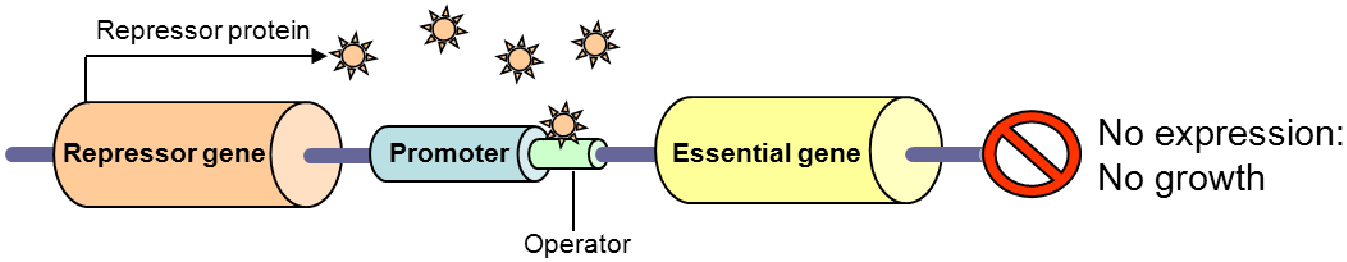
ORT-VAC: selectable marker gene-free plasmid stabilisation

Vaccine targeting using Vaxonella®

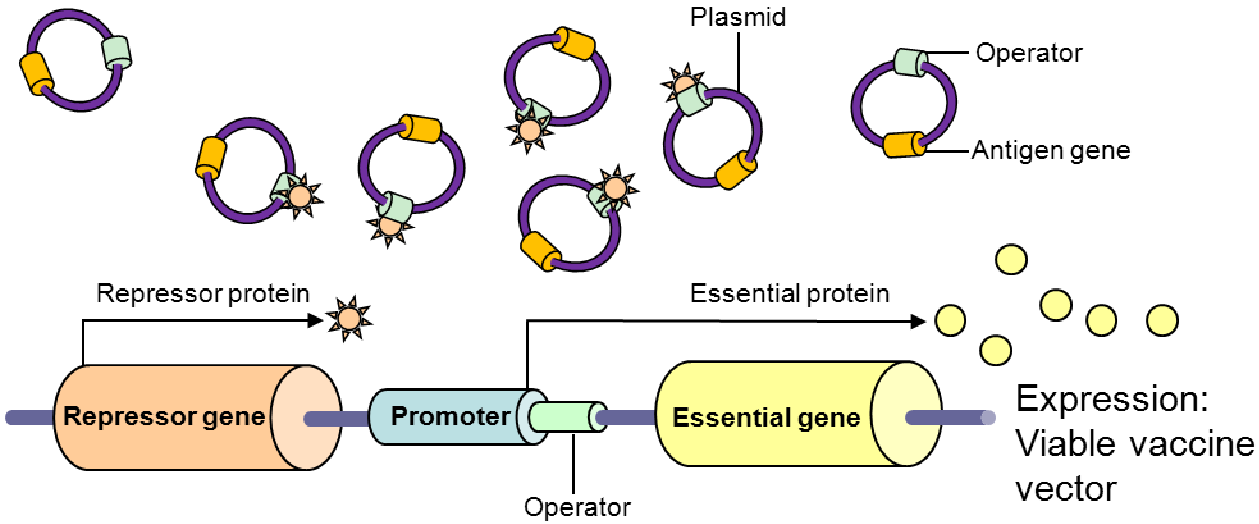


ORT-VAC™: Marker Gene-Free Plasmid Stabilisation

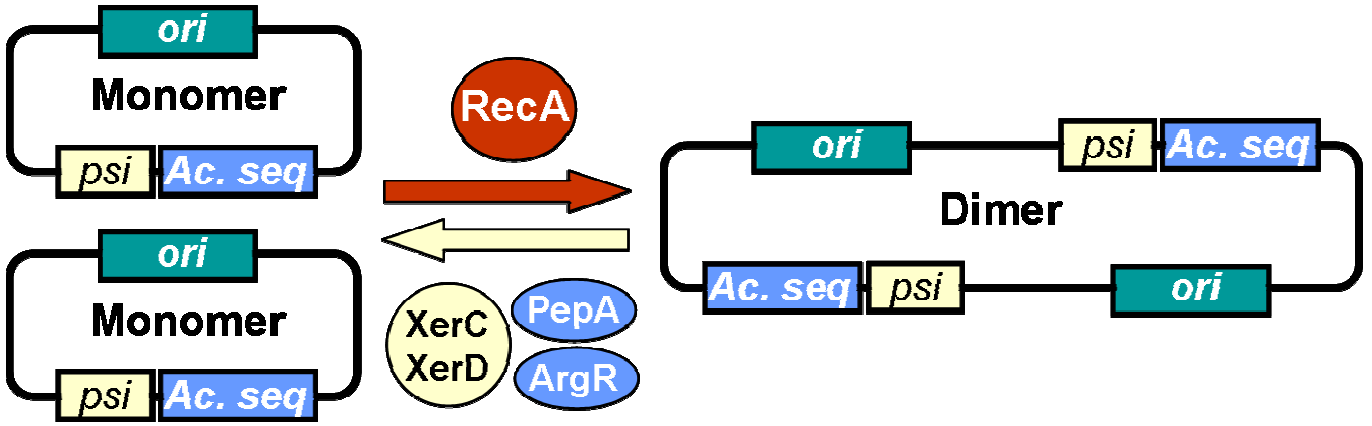
No plasmid



ORT-VAC plasmid



X-mark™ uses Natural Xer Recombination

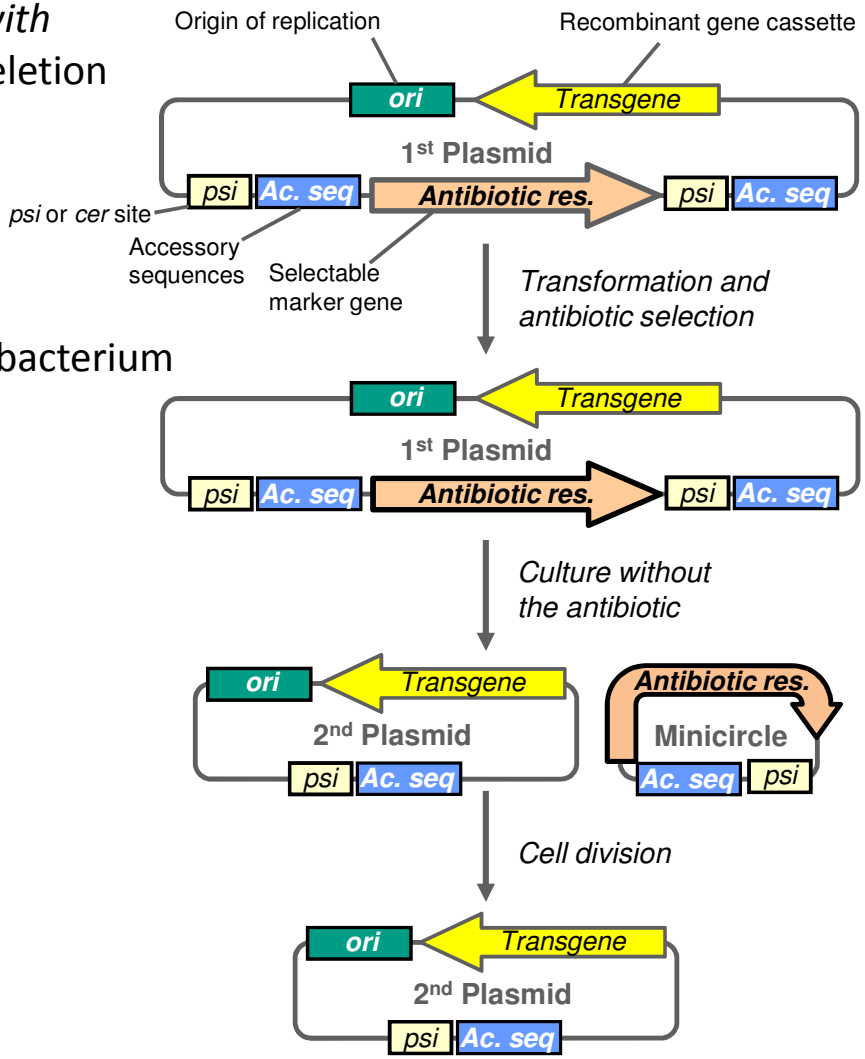


- Plasmid monomers in bacteria are recombined into dimers by RecA, which makes them unstable
- XerCD and accessory proteins PepA and ArgR convert dimers back to monomers by Xer site-specific intramolecular recombination at their recognition site *psi*, requiring accessory sequences (Ac. seq)
- Therefore DNA placed between Xer sites is effectively excised

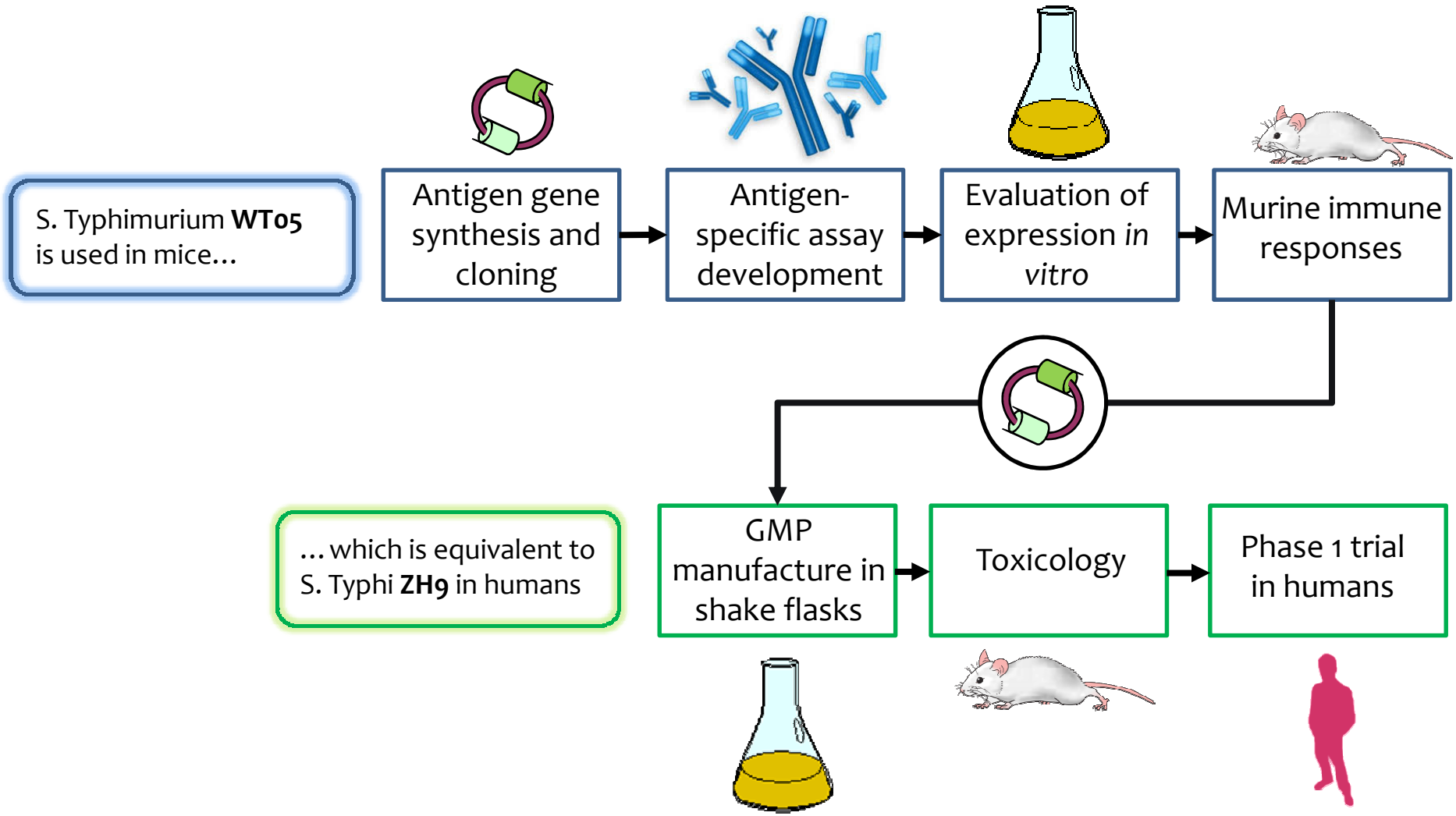
X-mark™: Auto-Deleting Plasmid Technology

The PepA accessory protein is needed for dimer resolution on plasmids *but not on chromosomes – pepA* mutants are viable

E. coli with pepA deletion



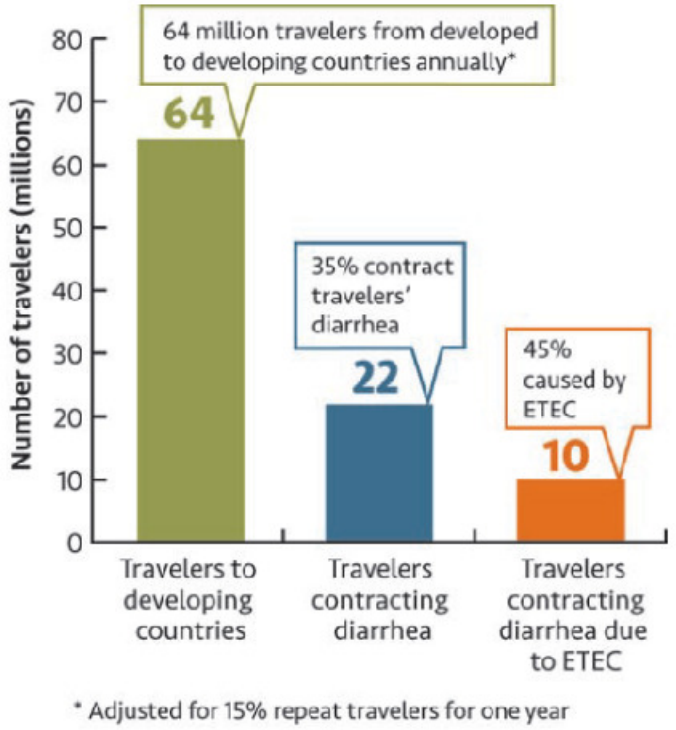
Vaxonella®: Simple Vaccine Development



Dual ETEC Diarrhoea-Typhoid Vaccine

- ETEC is a major cause of diarrhoea and of a most severe kind
  - Causes 45% of all travellers' diarrhoea (~10 million travellers infected annually)
  - Kills 300-500,000 <5 year olds each year and infects >10 million travellers
  - Unmet medical need – no dedicated vaccine
- Typhoid infects 17-22 million people and causes ~200,000 deaths p.a.
  - The combined ETEC and typhoid market is estimated at **$890 million** p.a.
- Prokarium is developing an oral typhoid-ETEC vaccine: Typhetec®

Estimated cases of travellers' diarrhoea due to ETEC

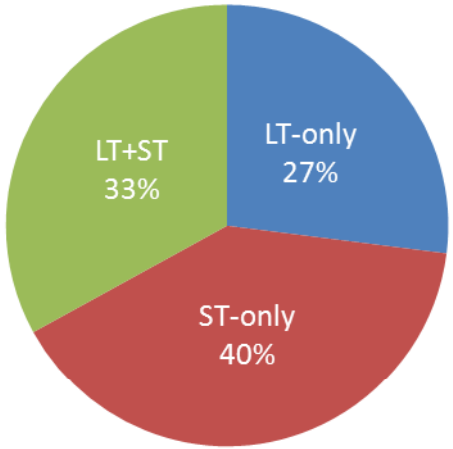


PATH/BVGH report 2011

Typhetec® Vaccine Design

- The typhoid component is the vector: S. Typhi ZH9, shown to be safe and immunogenic in eight clinical trials (Phase 1 & 2)
- The ETEC component is a fusion protein with epitopes from:
  - Labile toxin (LT)
  - Stable toxin (ST)
  - Colonisation factors (CFs)
- ETEC is defined by expression of ST and/or LT; our vaccine will be 100% protective against the many strains of ETEC (45% of all travellers' diarrhoea!)

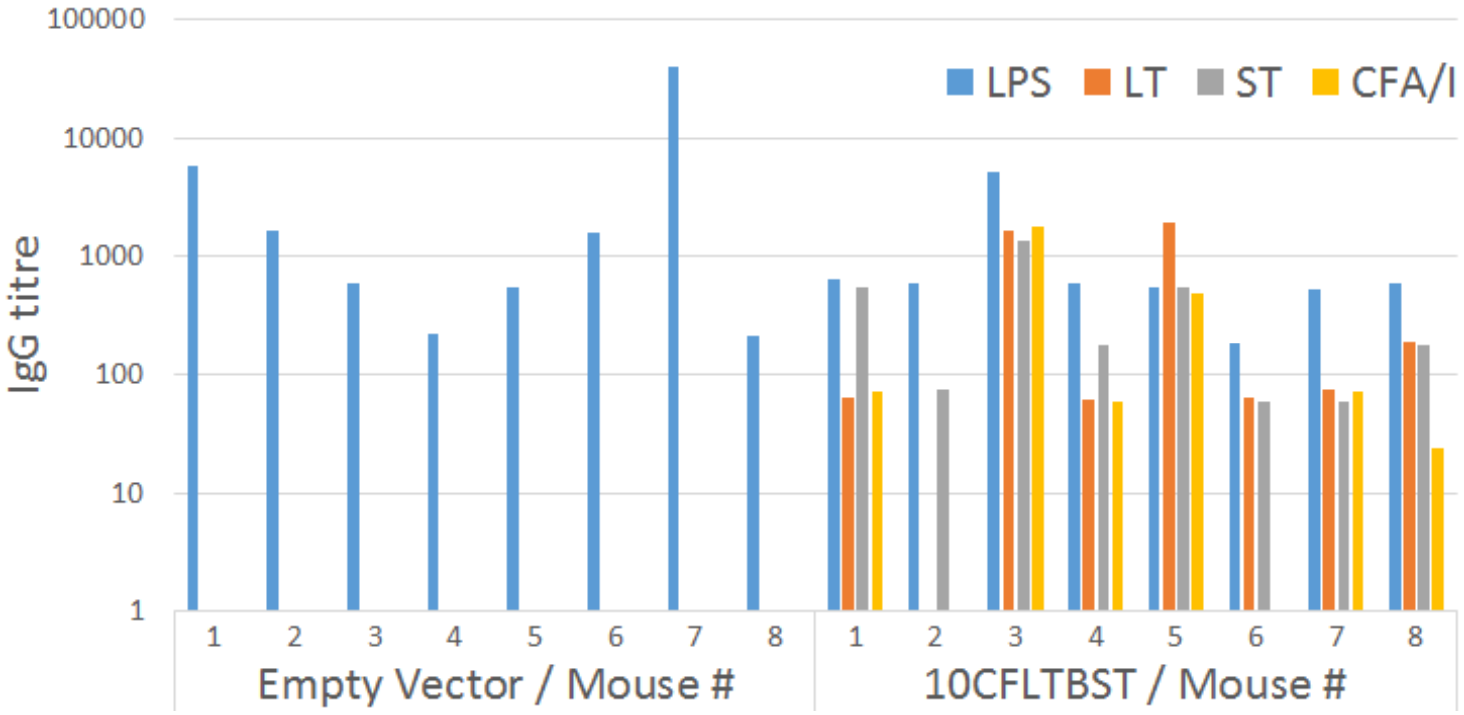
Global distribution of ETEC toxins



Data from Isidean *et al.* 2011

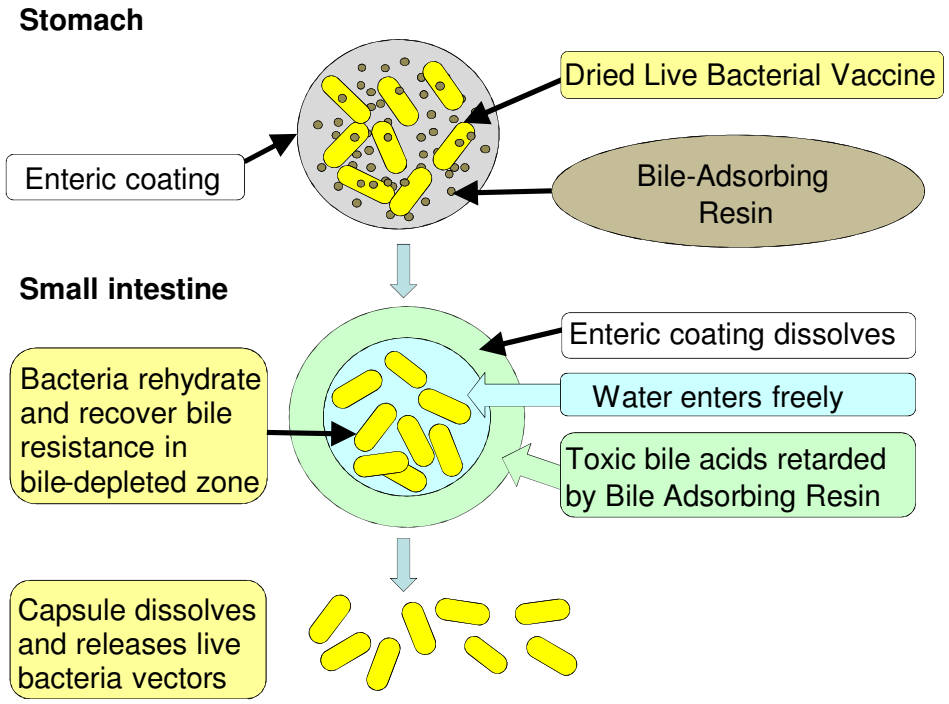
Antibody Responses to Vaccine

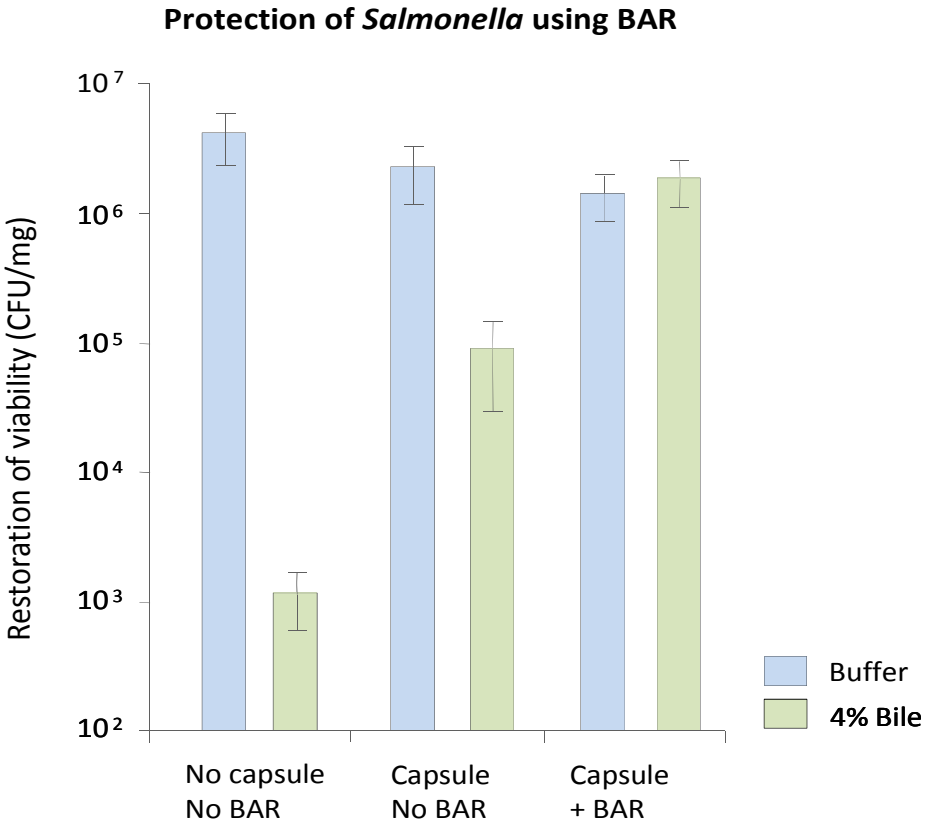
- Antibody (IgG) titres against vaccine components:



- LPS response: typhoid vaccine component on *Salmonella* surface
- LT, ST and CFA/I responses: ETEC toxin-colonisation factor recombinant protein

Bile-Adsorbing Resin (BAR)





- Final formulation will be capsular with BAR for adults

News

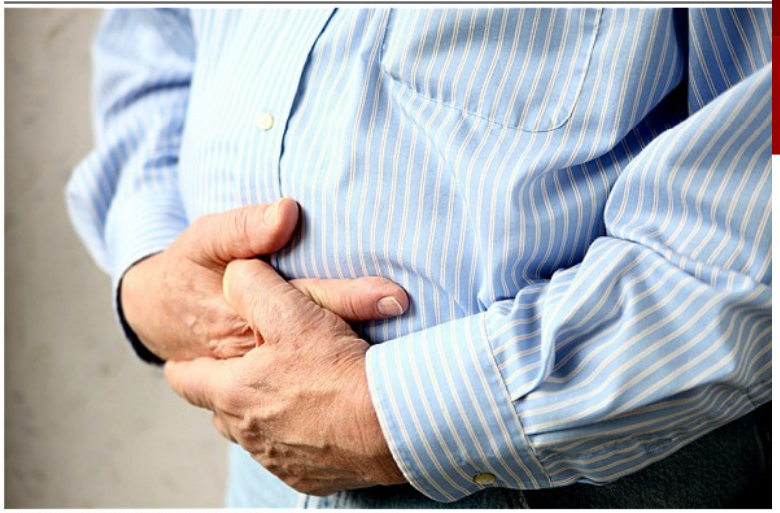
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Vaccine to end curse of Delhi belly

A vaccine against one of the main causes of Delhi belly could end the misery for millions of holiday makers who have their exotic holidays ruined.



Delhi belly could now become a thing of the past. Photo: ALAMY



By Richard Gray, Science Correspondent
8:20AM BST 09 Jun 2013

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HONDA
The Power of Dreams
So you wanted to see more?

New vaccine against 'Delhi belly' could end holiday misery for millions

- Vaccine in powder form could prevent stomach upsets
- Targets both E. Coli and salmonella bacteria
- 'Delhi belly' affects 10 million travellers per year

By SARA MALM
PUBLISHED: 06:54, 10 June 2013 | UPDATED: 13:08, 10 June 2013

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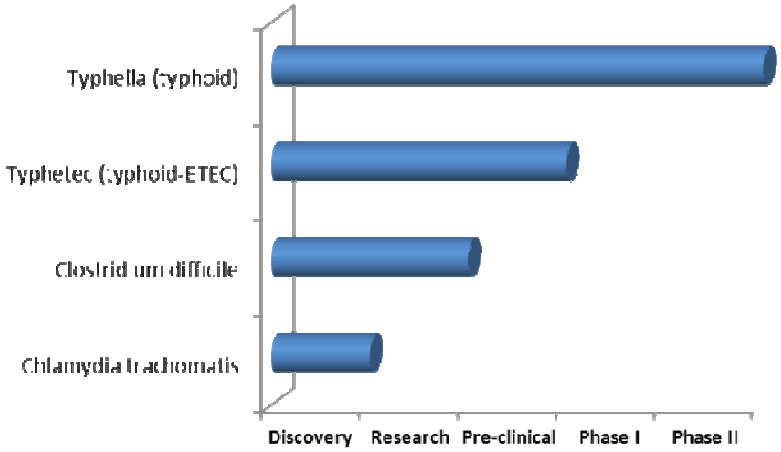
Big rise in volunteers for medical trials



24 May 2013 Last updated at 19:28

Prokarium's Vaccine Pipeline

- **Enterotoxigenic *E. coli* + Typhoid**
  - Dual ETEC-typhoid vaccine Typhetec®
  - Typhoid is responsible for 22 million cases and 200,000 deaths per year
  - Diarrhoea caused by ETEC affects 10 million travellers every year
- ***Clostridium difficile***
  - Major hospital-acquired infection
  - Causes ~3 million cases of diarrhoea and colitis annually in the USA alone
- ***Chlamydia trachomatis***
  - The most common STI, with >92 million new cases worldwide annually





Vaxonella® Advantages

- **Oral delivery –** a capsule containing a bile-adsorbing resin
- **No adjuvant required -** the vector is strongly immunostimulatory
- **Broad immune response –** systemic IgG, mucosal IgA, T-cell
- **Good mouse model –** *S.* Typhimurium in mice ≈ *S.* Typhi in humans
- **Safe vector –** ZH9 tested in 8 clinical trials, including in children
- **No downstream purification of proteins -** eliminates the most expensive element of biopharmaceutical production
- **A single, simple manufacturing process –** regardless of antigen
- **We are keen to collaborate on recombinant vaccine delivery!**

Acknowledgements

Prokarium
Paola Salerno
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