



Novel vaccine design and biosecurity

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Experience of working with defence science



**Positive experience for over 15 years
(plague vaccine)**

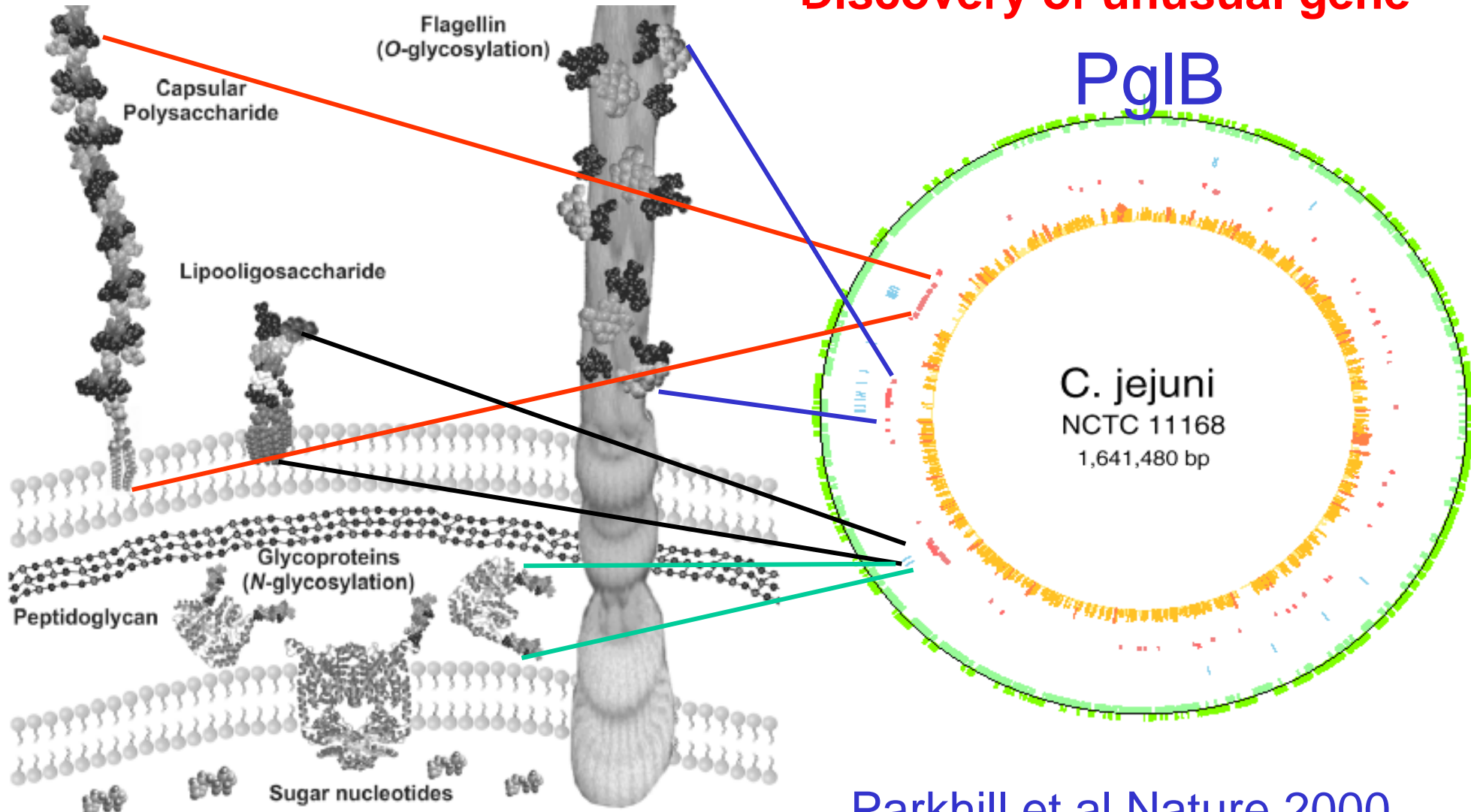
**Mutually beneficial in terms of intellectual input and
technology**

**Significant added value in career development for
both defence scientists and academics**

Example 1 Vaccine development



Glycostructures - from genome project to structure & function
Discovery of unusual gene



Parkhill et al Nature 2000



PglB a magic enzyme that can couple any protein any glycan

For the first time produce recombinant glycoproteins in *E. coli*

Spawned new era in glyco-engineering and vaccine design

Termed Protein Glycan Coupling Technology (PGCT)

Glycoconjugate-based human vaccines



Polysaccharide-based vaccines produce a T-independent immune response. To convert to a more favourable T-dependent response polysaccharides are often conjugated to proteins (eg inactivated cholera toxins)

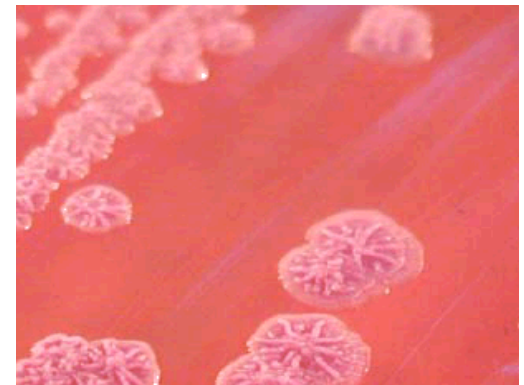
Examples of successful human vaccines

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

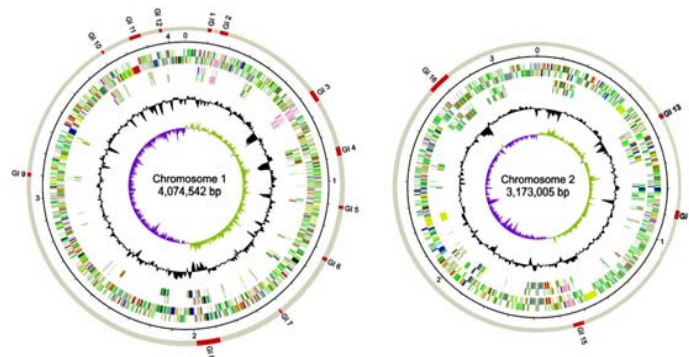
Burkholderia pseudomallei



Causative agent of melioidosis (paddy field black foot)



Acute septicemia, up to 40% lethal disease - no vaccine

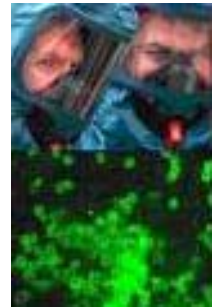




Francisella tularensis



- Incubation period 3-5 days. Pneumonic tularemia symptoms include chest pain often resulting in death
- Associated with rabbits (reported cases of human death after lawn mower accidents!!)
- No current vaccine



Traveller's diarrhoea vaccine



Multi combination vaccine to protect against *E. coli*, *Campylobacter*, *shigella*, cholerae



1. Use *E. coli* LT triple attenuated strain that has been evaluated in human clinical trials
2. Couple appropriate *Campylobacter* glyco-acceptor to appropriate glyco-structure of *Shigella* LPS
3. Couple *Campy* glycan to cholera B subunit

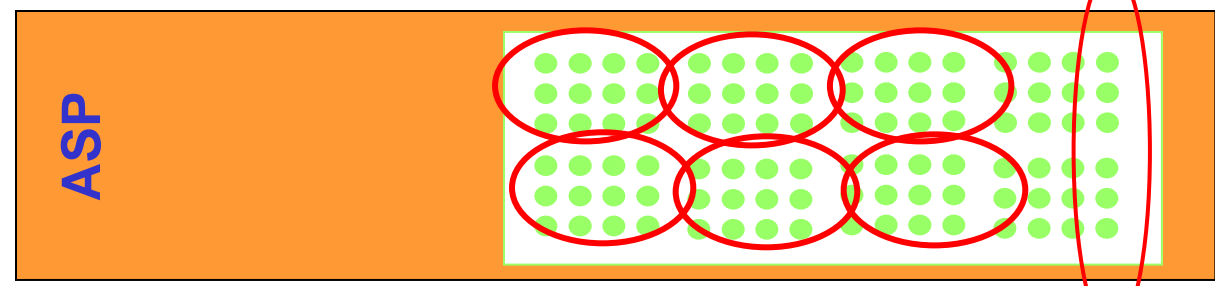


Example 2 Diagnostics

The active surveillance of pathogens (ASP) array

Concept - simultaneously identify bacterial pathogen and monitor gene flux

98% of reporters for genes acquired by lateral transfer



2% of reporters for bacterial identification

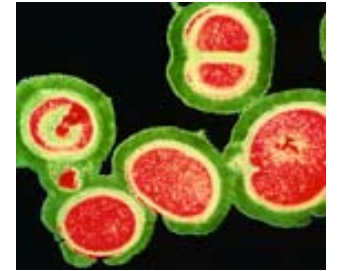
- Pathogenicity islands
- Mobile genetic elements
- Toxins
- Virulence determinants
- Antibiotic resistance

Current ASP v7.3 has 36,678 reporters



Known knowns?

MRSA



ASP contains data from sequenced MRSA strain

Test with community acquired *S. aureus* strain

- Identify all expected virulence markers
- Additionally identified

Panton Valentine toxin

Bleomycin resistance



Known unknown's

Enterobacter sakazakii

Occasional pathogen found in dried baby milk. Can cause meningitis, septicaemia & necrotizing enterocolitis



No Enterobacter reporters on ASPv5.3

Reporter	Gene	Function	Category
Cv50850163	<i>fofB</i>	fosfomycin resistance protein fofB	Virulence
Ec26951446		putative virulence factor	Virulence
Vc25050327	<i>rplL</i>	ribosomal protein L7/L12	Identification
Vc25052592	<i>rpsS</i>	ribosomal protein S19	Identification
Yp58100215	<i>rpmC</i>	50S ribosomal protein L29	Identification

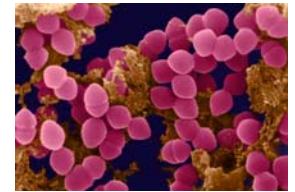
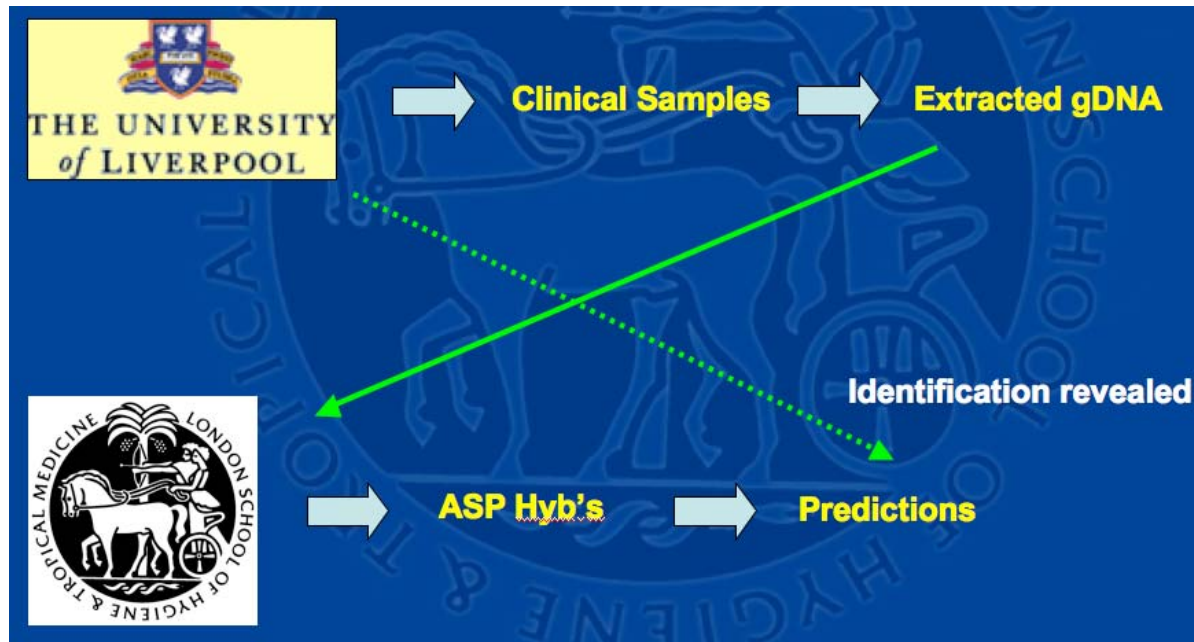
Use information in next iteration of ASP - ie self learning



Unknown unknowns



Blind samples - Tony Hart's mysterious pathogens



- From Liverpool Vancomycin resistant *Enterococcus faecium* (with additional virulence determinants and antibiotic resistance genes)
- From Vietnam antibiotic resistant *Shigella sonnei* (12/12) - evolving
- From Thailand *Burkholderia pseudomallei* (15/15) - typing



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Suppliers of DNA & strains (world-wide)

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