Public Health England

PHE Porton Down

Microbiology & Translational Research

Mission – Public Health England

"To protect and improve the nation's health and to address inequalities, working with national and local government, the NHS, industry, academia, the public and the voluntary and community sector."

PHE - Porton

- emergency response capability
- high containment of pathogenic agents [CL2-CL4]
- diagnostic capabilities [RIPL]
- culture collection (CC of PHE)
- developmental production
- biopharmaceutical manufacture
- translational research

Translational Research Model

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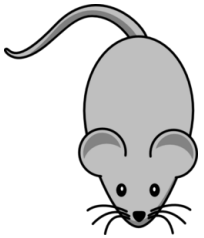
In vitro, *in vivo*, product development and clinical studies

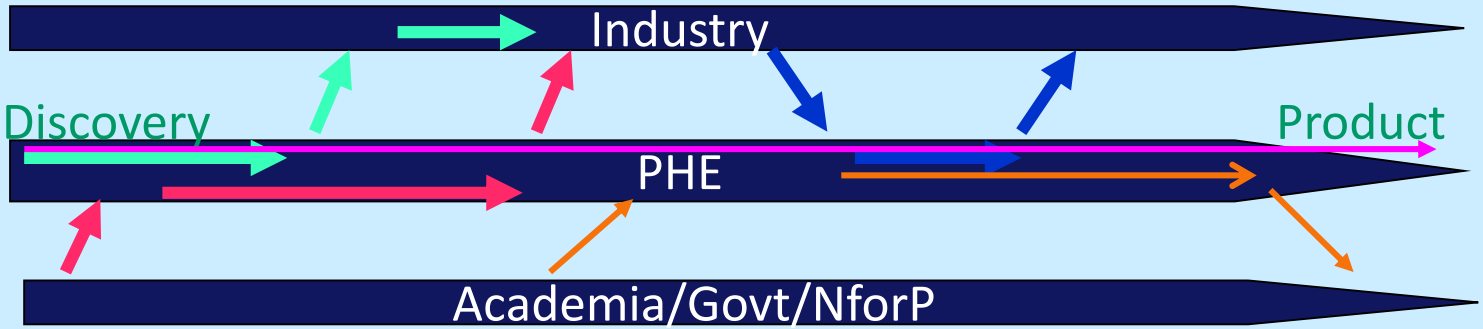


NVEC

Discovery → **Development** → **Licensure**

Applied research — Translational research

Flexible interactions with partners along the development pathway



Past successes: Whooping cough, Meningitis, **Anthrax**, Plague, **Dysport (cerebral Palsy)**, **Erwinase (childhood leukaemia),** Decontamination products.

Capabilities maintained for microbiological emergency response

Key role in UK Life Sciences Strategy

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Infectious Disease Programmes

TB
Vaccines
Antibiotics
Diagnostics

Toxins
Botulinum
Clostridium
Immunotherapy
Diagnostics

Mening & Pertussis
Correlates
Vaccines

Biosafety
Detection
Decontam
HCAI/vCJD
Training

Animal Models
Efficacy studies
Aerosol
Pathol/ Imaging
Immunology

Research

Diagnostics Technology
Diagnostics
Bio/Molecular

GxP
Immune Assay
Clinical Trials
Assay Validation
Product release assays

Immune Modulation
Inflammation
Adjuvants

Emerging Diseases
Virology/Influenza
Bacteriology

Medical Counter Measures
NIAID
Anthrax

Developing Interventions with academia, Govt and industry

US projects at PHE Porton

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Antibiotics, small molecules & therapies (A1, B1) ✓

Anthrax (C1) ✓
Plague (C18) ✓
Q fever (C19) ✓
Melioidosis (C19) ✓
Filoviruses (C20) ✓

BARDA BIO-0001 (Melioidosis) ✓
BARDA BIO-0004 (Anthrax)

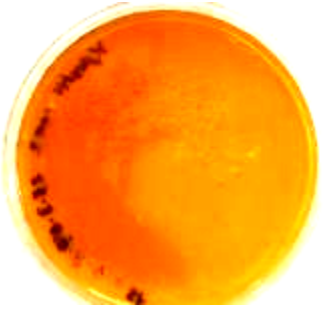
Discovery
Pure research

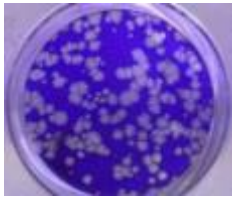
Development
Translational research

Licensure

GLP

Anthrax (D1) ✓
Melioidosis (D19)
Glanders (D19)
Multiple agents (D8, Dstl) ✓
Orthopox (D4/D7, D18, E07) ✓ C03
Flu (E10) ✓



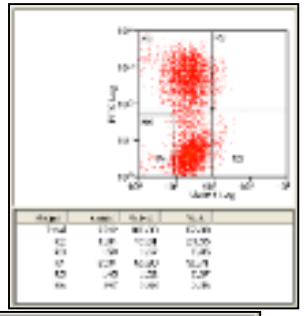


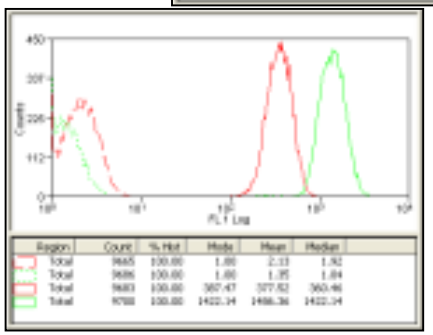
Capabilities - Chemostat

Applications

- Multiple pathogens including *M tuberculosis*
- Multiple parameters including growth rate and nutrient limitation

Rapid assay for drug evaluation
Live / dead fluorescence stains and flow cytometry





Defined populations:

- Live
- Dead
- Persistent

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Extensive In Vivo Modelling Capability: Vaccines & Therapeutics

Step-wise evaluation of interventions

Provide rational information to support decisions in clinical trials

Relevant in-vivo models for screening

- Appropriate dose and route of challenge
- Robust and reproducible measures of efficacy

Advanced in-vivo models

- Predictive for humans
- Parallel studies with early clinical trials

Clinical Trials

Systems for pre-screen to minimise animal use (3Rs)

***In vivo* Models must be**

- Well characterised
- Predictive
- Use clear readouts

Experimentally generated aerosols

Controlled aerosol delivery:
- **Collison nebuliser**
- **range of animal species**
- **nose-only exposure** <5 µm

Henderson apparatus controlled by AeroMP

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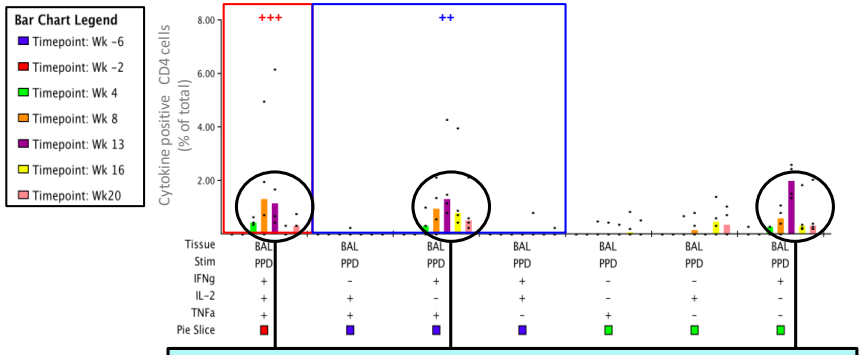
Preclinical testing for TB

- Range of species.
- Immunogenicity and challenge studies.
- ACDP3 containment facilities: *in vitro*, *in vivo*, *ex vivo* studies.
- Large capability

  (largest TB vaccine evaluator in Europe – small animal models).
- Advanced NHP capability.

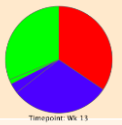
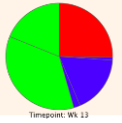
Clinically relevant mucosal delivery

Aerosol Route - TB Vaccine Delivery



- **Three distinct functional profiles**
- **Antigen-specific cells increase at the mucosal surface following BCG vaccination**

- **Responses peak 1 week following Booster vaccination**

	Mucosal CD4 T- cell profile (BAL)	Peripheral CD4 T- cell profile (PBMC)
Mucosal Booster vaccination group		
Intradermal Booster vaccination group		

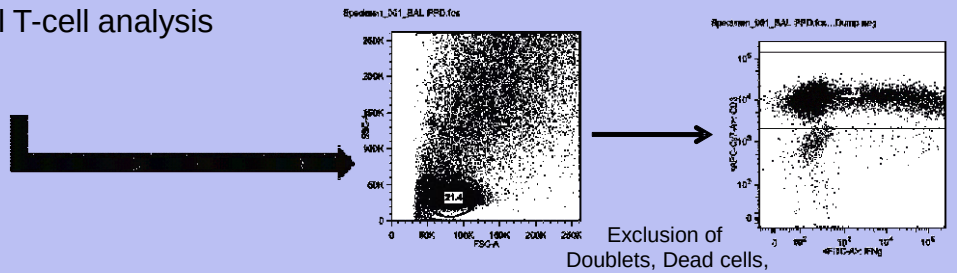
Functional profile of cell

- +++ Expressing 3 cytokines
- ++ Expressing 2 cytokines
- \+ Expressing 1 cytokine

Analysis of immune response using BAL

Cells isolated for flow cytometry &

Polyfunctional T-cell analysis



Relevant and natural routes of challenge

Animal modelling capability to study Tick Vector competency:

Tick transmission studies with Hazara, CCHF, TBE viruses.

- PHE PhD studentship [Liverpool – PHE HPRU]

Assessment of vector competence.
➔ Ability to test interventions using a natural route of infection

<u>Natural Transmission by airborne route</u>

- Influenza
- Tuberculosis

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In vivo CL4 facilities

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National & International Reference Centre

- Haemorrhagic Fever viruses
  - *Filoviridae*
  - *Arenaviridae*
- Arboviruses
  - *Flaviviridae*
  - *Bunyaviridae*
  - *Togaviridae*
  - *Reoviridae*
- Orthopoxviruses
- Hantaviruses
- Henipaviruses

World Health Organization

WHO Collaborative Centre for Viruses (Arboviruses & VHFs) Porton Down 1976

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Ebola studies

- **In –vivo studies to test interventions:**
  - Pharmacokinetic studies.
  - Pathogenesis studies
  - Vaccine assessment.
  - Repeat drug dosing.
  - Safe system of administration.

- **Collaborations:**
  - West Africa deployment of staff trained in high containment
  - On-going R&D projects [immune responses in humans, vaccine trial]

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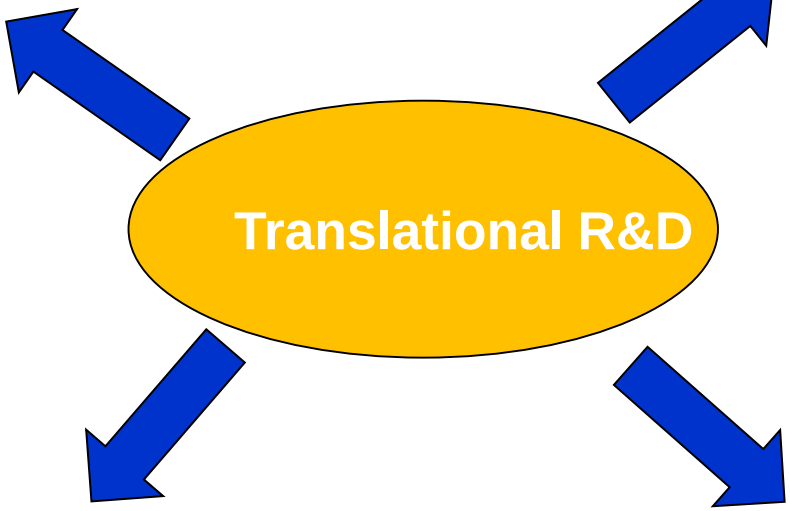
PHE Porton:
Unique Translational Research Capability

New antigens:
- meningitis
- TB
- anthrax
- *C. difficile*

Correlates of protection:
- meningitis
- pertussis
- TB



Evaluation [clinical trials]:
- NVEC
- grants
- commercial

Evaluation in preclinical models: [drugs, vaccines, etc]
- medical counter-measures
- TB
- 'flu
- .....& many others....

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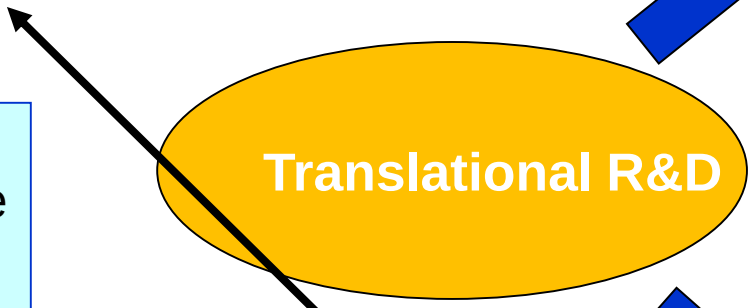
PHE Porton:
Unique Translational Research Capability

Animal model:
- range of species

Model design:
- aerosol challenge
- vaccine delivery
- high containment

Readouts:
- survival
- organ CFU
- immune response
- pathology
- clinical chemistry [PK]
- imaging



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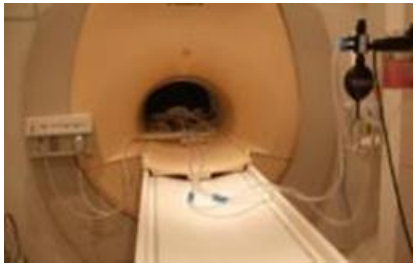
In life' imaging – use of mobile scanner units



'In life' imaging: CT

Approaches can be applied to any pathogen / intervention