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DEVELOPING INNOVATIVE VACCINES

UNIVERSITY OF OXFORD

Towards Human Challenge with NTS

Cal MacLennan
University of Oxford

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Overall Aims

Establish a controlled human infection model (CHIM) of nontyphoidal *Salmonellae* (NTS) to:

- understand the pathogenesis and immunobiology of NTS infection in man

- accelerate the development of NTS vaccines (and diagnostics)

Do we need a NTS controlled human infection model?

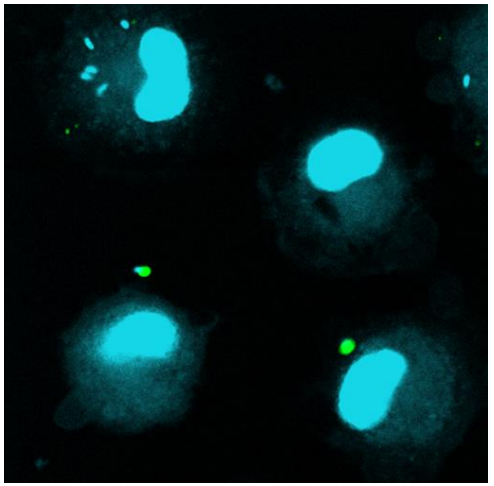
Disease burden data supports development of a NTS vaccine for Africa

Limited knowledge of human NTS infections

NTS vaccinology lags 100 years behind typhoid vaccinology

Modalities of protective immunity

- Facultative intracellular bacteria
- Evolved to survive within macrophages
- Capable of cell-free survival
- Consistent with role for:
  - T cells to clear disease
  - Antibody to prevent fatal bacteraemia



Current knowledge of NTS infections

1. Mouse studies

2. Studies of patients with primary immunodeficiencies

3. Limited studies of cases and at-risk populations from LMICs

Resistance and susceptibility to *Salmonella* infections: lessons from mice and patients with immunodeficiencies

Pietro Mastroeni, Sanja Ugrinovic, Anita Chandra[a], Calman Mac Lennan[b], Rainer Doffinger[a] and Dinakantha Kumararatne[a]

Reviews in Medical Microbiology 2003, **14**:1–10

Absent Bactericidal Activity of Mouse Serum against Invasive African Nontyphoidal *Salmonella* Results from Impaired Complement Function but Not a Lack of Antibody

Matthew K. Siggins,* Adam F. Cunningham,* Jennifer L. Marshall,* Jayne L. Chamberlain,* Ian R. Henderson,* and Calman A. MacLennan*,†

***The Journal of Immunology*, 2011, 186: 2365–2371.**

REVIEWS

Genetic susceptibility to invasive *Salmonella* disease

James J. Gilchrist[1], Calman A. MacLennan[2,3] and Adrian V. S. Hill[1,2]

(Nat Rev Immunol 2015)

Antibodies in immunity to invasive nontyphoidal *Salmonella* disease

Research article

The neglected role of antibody in protection against bacteremia caused by nontyphoidal strains of *Salmonella* in African children

(MacLennan CA, et al J Clin Invest 2008)

Dysregulated Humoral Immunity to Nontyphoidal *Salmonella* in HIV-Infected African Adults

Calman A. MacLennan,[1-4]* James J. Gilchrist,[1,2,5] Melita A. Gordon,[2,6,7] Adam F. Cunningham,[1] Mark Cobbold,[1] Margaret Goodall,[1] Robert A. Kingsley,[8] Joep J. G. van Oosterhout,[2,7] Chisomo L. Msefula,[2,4,9] Wilson L. Mandala,[2,9,10] Denisse L. Leyton,[11] Jennifer L. Marshall,[1] Esther N. Gondwe,[1,2,9] Saeeda Bobat,[1] Constantino López-Macías,[12] Rainer Doffinger,[13] Ian R. Henderson,[11] Eduard E. Zijlstra,[7] Gordon Dougan,[8] Mark T. Drayson,[1] Ian C. M. MacLennan,[1] Malcolm E. Molyneux[2,7,9]

(Science 2010)

Antibodies:
Can you have too much of a good thing?

Vaccines in development

Two candidate vaccines in development against iNTS disease

- GVGH bivalent *S*. Typhimurium and *S*. Enteritidis GMMA vaccine
- University of Maryland bivalent O:4-flagellinH_i and O:9-flagellin$H_{m,}$

Need for improved understanding of basis of protective immunity against iNTS disease and how to protect individuals with key comorbidities. Is antibody enough?

Issues:

1. Animal models indicate that T cell immunity is required for full elimination of infection

2. Inhibition of killing of *S*. Typhimurium by high levels of antibodies against O-antigen in HIV-infected Africans

Opportunity

Oxford experience of *S*. Typhi and *S*. Paratyphi A CHIM

Increasing understanding of how to maximise information derived from CHIM

S. Typhimurium ST313

Relative contributions of

1. the pathovar ST313
2. host immunity/immunocompromise
3. transmission

to frequency of iNTS disease is uncertain

CHIM will allow examination of ST313 infection without interference of differences in host immunity and transmission

Challenges

iNTS disease is by definition – invasive

Oral administration of *Salmonella*

Original portal of entry almost certainly through the GI tract

ST313 isolates found in invasive and diarrheal infections
(Robert Onsare and Sam Kariuki; Satheesh Nair)

Safety

iNTS bacteraemia almost never observed in immunocompetent adults

no established latent disease state – persistence?

12-hourly monitoring of volunteers

use of ciprofloxacin/ceftriaxone sensitive bacterial strains

availability of antibiotics

End-points

- Fever ≥ 38.0°C for 12 hours, or
- Positive blood culture for *S*. Typhimurium
- 3 or more lose stools in 24 hours, or

High-level outline

GMP manufacture of ST313 *S*. Typhimurium (ideally compare with ST19 *S*. Typhimurium)

Establish infecting dose for 65-70% of volunteers to develop clinical infection

Characterise clinical presentation, pathogenesis, and immune response

Identify potential correlates of protection/susceptibility

Identify new markers for exploitation as diagnostics

Next steps

1. For testing efficacy of candidate NTS vaccines

2. Potential transfer to developing world setting

Back up slides

JEM

Article

Increased severity of respiratory infections associated with elevated anti-LPS IgG2 which inhibits serum bactericidal killing

Timothy J. Wells,[1,2] Deborah Whitters,[3,4] Yanina R. Sevastsyanovich,[1,2] Jennifer N. Heath,[1,2] John Pravin,[1,2] Margaret Goodall,[2] Douglas F. Browning,[1,2] Matthew K. O'Shea,[5] Amy Cranston,[6] Anthony De Soyza,[7] Adam F. Cunningham,[1,2] Calman A. MacLennan,[1,2] Ian R. Henderson,[1,2] and Robert A. Stockley[4]

J. Exp. Med. 2014

Am J Respir Crit Care Med. 2017 Apr 1;195(7):955-958. doi: 10.1164/rccm.201603-0599LE.

The Use of Plasmapheresis in Patients with Bronchiectasis with Pseudomonas aeruginosa Infection and Inhibitory Antibodies.

Wells TJ[1], Davison J[2], Sheehan E[1], Kanagasundaram S[2], Spickett G[2], MacLennan CA[3], Stockley RA[4], Cunningham AF[1], Henderson IR[1], De Soyza A[2,5].

Resistance and susceptibility to *Salmonella* infections: lessons from mice and patients with immunodeficiencies

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