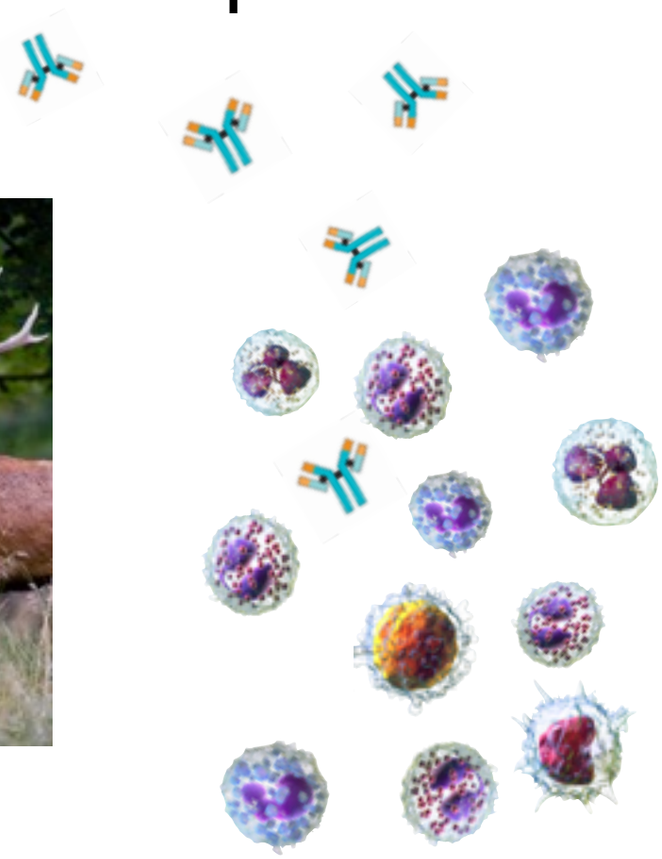
The immunology of bTB:
a multi-host multi-parasite perspective



Simon Babayan
Institute of Biodiversity, Animal Health & Comparative Medicine
✉ simon.babayan@glasgow.ac.uk @SimonAB

Immuno-epidemiology of infectious diseases

- Primary interest: host-parasite interactions at the level of the organism, and the effects of natural variation on the host's immune defences
- Foremost interface of this interaction is the immune response
- Biotic environmental factors: exposure via air, water, soil, vectors, & animal reservoirs; population density; nutritional resource availability...
- At the individual level:
    - Physiological factors: age, sex, nutritional status, past and current infections
    - Immunity: resistance/susceptibility, tolerance/virulence, health...
- At the Population: disease transmission, demographic structure & density

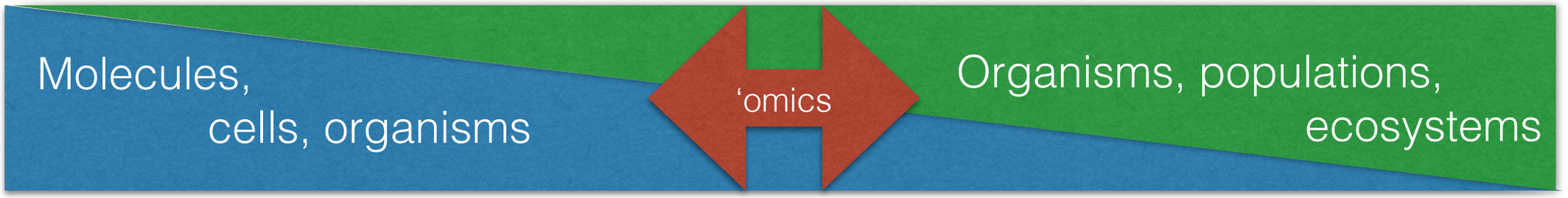
Wild Immunology

- Wild Immunology: how the immune system functions given natural variation in coinfection history, variable nutritional resources, etc. — emphasis on immune mechanisms, with a view to inform intervention strategies (see Pedersen & Babayan 2011)

- No lab experiment can satisfactorily simulate the interplay of an individual with its natural environment

- However, knowledge derived from past and concurrent lab immunology is crucial to disentangling causes & effects of such variation

Crosstalk between lab & wild



In the lab: controlled environmental and genetic variation allows the study of mechanisms that drive immunity.

In the wild: how natural variation affects the expression of immunity from individual organism to population levels.

Old methods and new opportunities

- Swelling in response to immunogenic inoculations: how to interpret these, e.g. sheep red blood cells or KLH?

- Serology: antibodies available for many species, but is it always a good enough predictor of protection? Detection limits? Active *or* past infection? Exposure *or* protection?

- PCR & co: requires knowledge of genome — very small fraction of target species have been sequenced

- More recently, ’omics, and specifically *de novo* transcriptomes + digital transcriptomics is often a necessary first step. Challenging in its own way (e.g. Curse of dimensionality), but it also opens up unprecedented insights into the study system

Basic requirements to study the relevant species

- Demographics: age, sex, reproductive status, weight, fat scores, etc.

- Diagnostics: pathogen presence and burdens

- Immunology: for non-model organisms, a combination of classical immune measures (differential leukocyte counts, bacterial killing essays, etc) and, increasingly, 'omics

- Computational biology: bioinformatics + scalable data analysis

Resources for studying *M. bovis* from a multi-host-pathogen angle

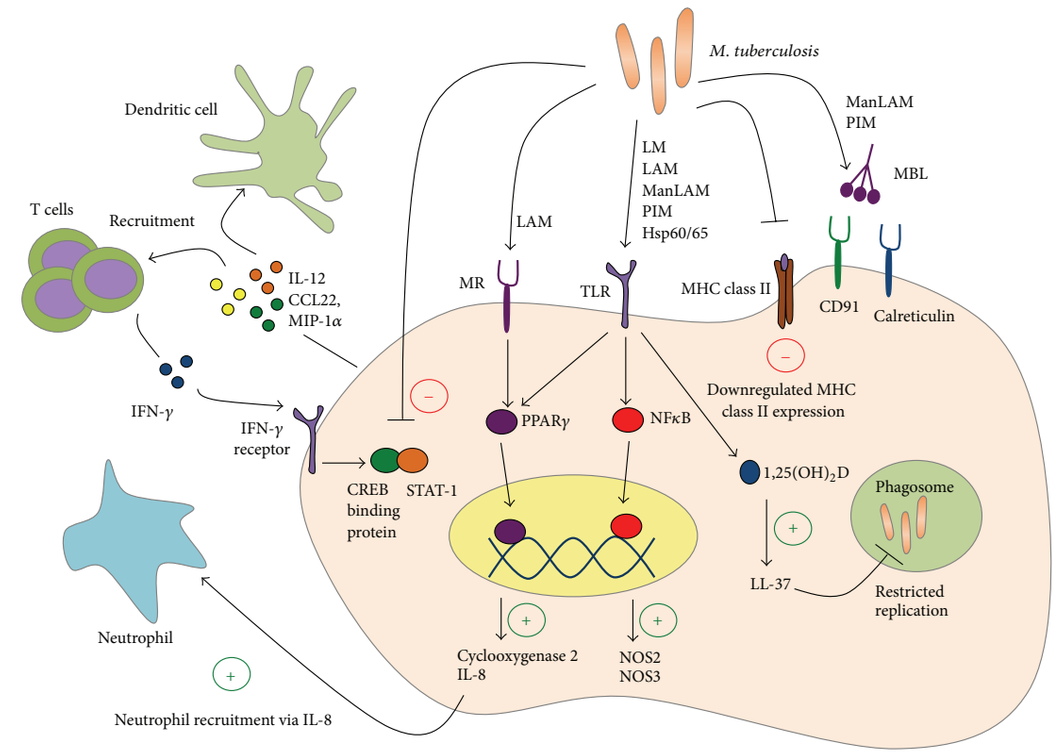
- *Mycobacterium spp.* genome: see Stephen Gordon's talk next!

- Bovine genome (*Bos taurus*): available, relatively mature, e.g. bovinegenome.org; bovine gene arrays from Affymetrix, etc.

- Bovine immune system relatively well studied, many reagents available

- Multiple host ('reservoir') species: badgers, fallow deer,… but unlikely to have published genomes nor specific immunological reagents. => *de novo* assembly, reagent development

Protective immunity to *Mycobacterium*



- Th1: IFN-γ producing CD4+ T cells (necessary but not sufficient for protection)
- γδ T cells: up to 70% PBMC in ruminants (5-10% in mice & humans; badgers?). Functionally diverse, innate/adaptive, anti-bacterial, anti-lipid responses.
- IL-17: early production by γδ T cells improves protective memory cells; late IL-17 (Th17) correlates with reduced lesions (though not necessary for protection)

Published August 8, 2011

JEM

Preexisting helminth infection induces inhibition of innate pulmonary anti-tuberculosis defense by engaging the IL-4 receptor pathway

Julius A. Potian,[1,2] Wasiulla Rafi,[1,2] Kamlesh Bhatt,[1,2] Amanda McBride,[1,2] William, C. Gause,[1,3] and Padmini Salgame[1,2]

[1]Department of Medicine, [2]Center for Emerging Pathogens, and [3]Center for Immunity and Inflammation, University of Medicine and Dentistry of New Jersey, Newark, NJ 07101

nature COMMUNICATIONS

OPEN

ARTICLE

Received 18 Jan 2012 | Accepted 11 Apr 2012 | Published 22 May 2012

DOI: 10.1038/ncomms1840

Fasciola hepatica is associated with the failure to detect bovine tuberculosis in dairy cattle

Jen Claridge[1], Peter Diggle[1,2], Catherine M. McCann[1,†], Grace Mulcahy[3], Rob Flynn[3,†], Jim McNair[4], Sam Strain[4], Michael Welsh[4], Matthew Baylis[1,*] & Diana J.L. Williams[1,*]

Infect Immun, 2015, 83:2118 –2126.

Protein Energy Malnutrition during Vaccination Has Limited Influence on Vaccine Efficacy but Abolishes Immunity if Administered during *Mycobacterium tuberculosis* Infection

Truc Hoang,[a] Else Marie Agger,[a] Joseph P. Cassidy,[b] Jan P. Christensen,[c] Peter Andersen[a]

Department of Infectious Disease Immunology, Statens Serum Institut, Copenhagen, Denmark[a]; Veterinary Sciences Centre, School of Veterinary Medicine, University College Dublin, Belfield, Dublin, Ireland[b]; International Health, Immunology and Microbiology, The Panum Institute, Copenhagen, Denmark[c]

Fine PE (1995) Variation in protection by BCG: implications of and for heterologous immunity. Lancet 346: 1339–1345.

STUDY	Lat	U/R	Type	OR and 99% CI VE
NORWAY, gen popn[42]	65	U+R	COH	81%
SWEDEN, gert popn[43]	62	U+R	COH	80%
SWEDEN, military[44]	62	U+R	COH	55%
DENMARK, school[45]	56	U	O/B	94%
IRELAND, school[46]	55	R	O/B	82%
CANADA Indians[47][*]	55	R	T	81%
CANADA ALBERTA Indians[48][*]	55	R	C.C	57%
CANADA MANITOBA Indians[49][*]	55	R	C.C	70%
UK, schoolchildren[50][*]	53	U+R	T	77%
UK, gen popn 1973[51]	53	U+R	COH	79%
UK, gert popn 1978[52]	53	U+R	COH	74%
UK, gen popn 1983[7]	53	U+R	COH	75%
UK, Asians[53][*]	53	U	C.C	49%
UK, BIRMINGHAM Asians[54][*]	52	U	C.C	64%
UK, BIRMINGHAM[55]	52	U	COH	88%
USA, indians[25][*]	52	R	T	79%
USA, CHICAGO infants[56][*]	42	U	T	72%
USA, NEW YORK infants[57]	41	U	T	7%a
KOREA, SEOUL[58]	38	U	H/H	74%
ARGENTINA, BUENOS AIRES[59][*]	35	U	C.C	73%
USA, GEORGIA school[26][*]	33	U+R	T	−56%a
USA, GEORGIA ALABAMA gen popn[60][*]	33	U+R	T	16%
ISRAEL, children[61]	31	U+R	COH	38%
SOUTH AFRICA, miners[62][*]	27	U+R	T	62%
AUSTRALIA, QUEENSLAND[63][*]	20	U+R	C.C	41%
PUERTO RICO[15][*]	18	R+U	T	29%
HAITI[64][*]	18	R+U	T	80%
BURMA, RANGOON[65][*]	17	U	C.C	38%
THAILAND, BANGKOK[66]	14	U	C.C	74%
THAILAND, BANGKOK[67]	14	U	C.C	83%
THAILAND, BANGKOK[68]	14	U	H/H	47%
INDIA, MADANAPALLE[27][*]	13	R	T	20%
INDIA, CHINGLEPUT[101][*]	13	R	T	−19%
PAPUA NEW GUINEA[69]	10	U+R	C.C	41%
MALAWI, KARONGA[8]	10	R	COH	−11%
INDONESIA, JAKARTA[70][*]	6	U	C.C	37%
TOGO LOME[71]	6	U	H/H	66%
COLUMBIA, CALl[72][*]	4	U	C.C	16%
CAMEROUN, YAOUNDE[73]	4	U	C.C	66%
KENYA, KISUMU[17]	0	R	C.C	22%

'Short' list of predictors of anti-TB protective immunity?

- Pre-existing infections that might degrade or prevent anti-M.b. immunity

- Nutritional status: trade-offs between competing physiological demands e.g. growth, pregnancy

- T cell phenotypes (Th1, Th2, Th17), inflammatory markers, chemokines

- Age: parental effects in the young, immunosenescence in the old

Beyond observational data: experimental manipulation

- Selective parasite removal: insecticides, anthelminthics, antibiotics, vaccines

- Nutrition: food availability, distribution, and quality

- Inter-individual contacts: barriers, feeders, water spots

- Sampling: longitudinal + cross-sectional; non-invasive + destructive

Exciting prospects

- Immune system as a black box is largely behind us
- We are getting better at studying non-model organisms
- Omics: cheaper and getting more powerful (come to Graham Hamilton's talk tomorrow!)
- Data analysis: biology is starting to benefit from the staggering progress in computer science