

About me

Basic Discovery Research Scientist - preclinical models, cohort studies
Telethon Kids Institute, Wal Yan Respiratory Research Centre

Immune System-

Respiratory homeostatic regulation

Disease pathogenesis - asthma, respiratory virus infection

Early life disease risk and prevention



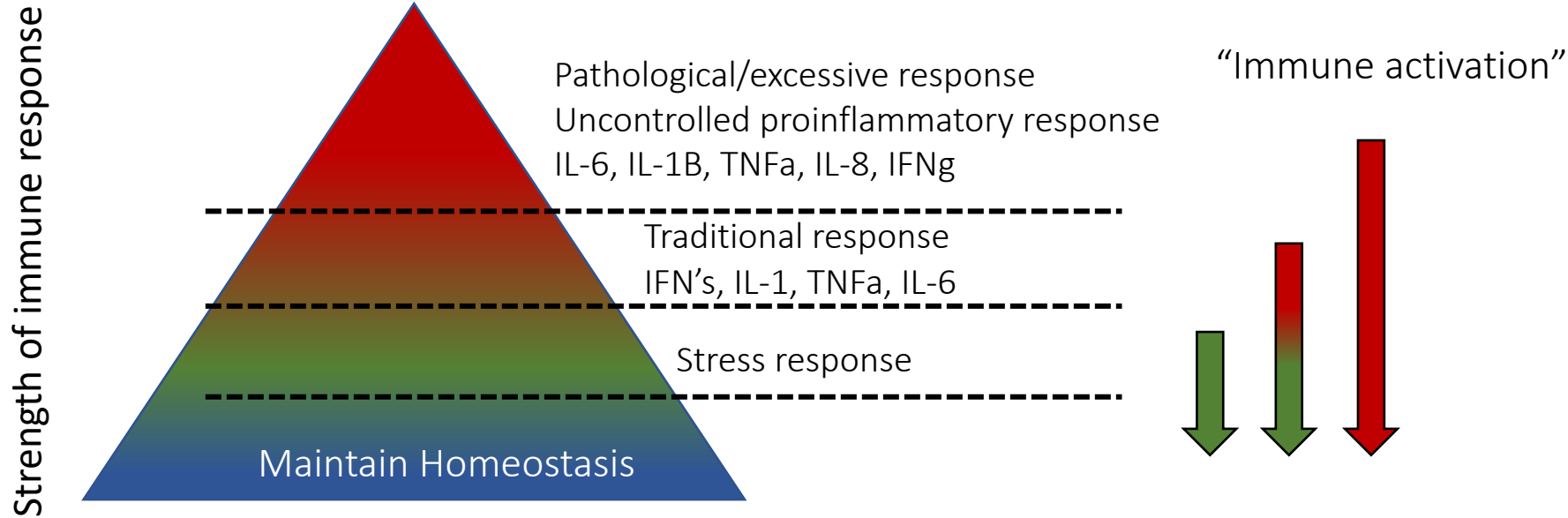
Pat Holt



Peter Sly

Let's explore an overview of emerging strategies for prevention of infection

Immune system- function



Micro-organisms are master inducers and regulators of immunity

- Balance of promoting pro-inflammatory effector mechanism and antimicrobial immunity with parallel anti-inflammatory/immunoregulatory mechanisms

Underlying chronic conditions
Early/late life
Pregnancy

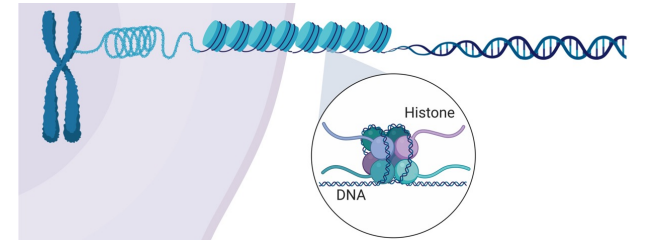
Immune system- modulation



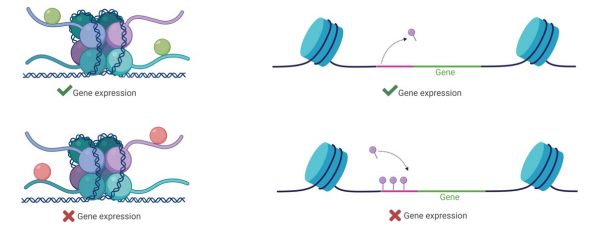
Gene
Environment

Immune system
function

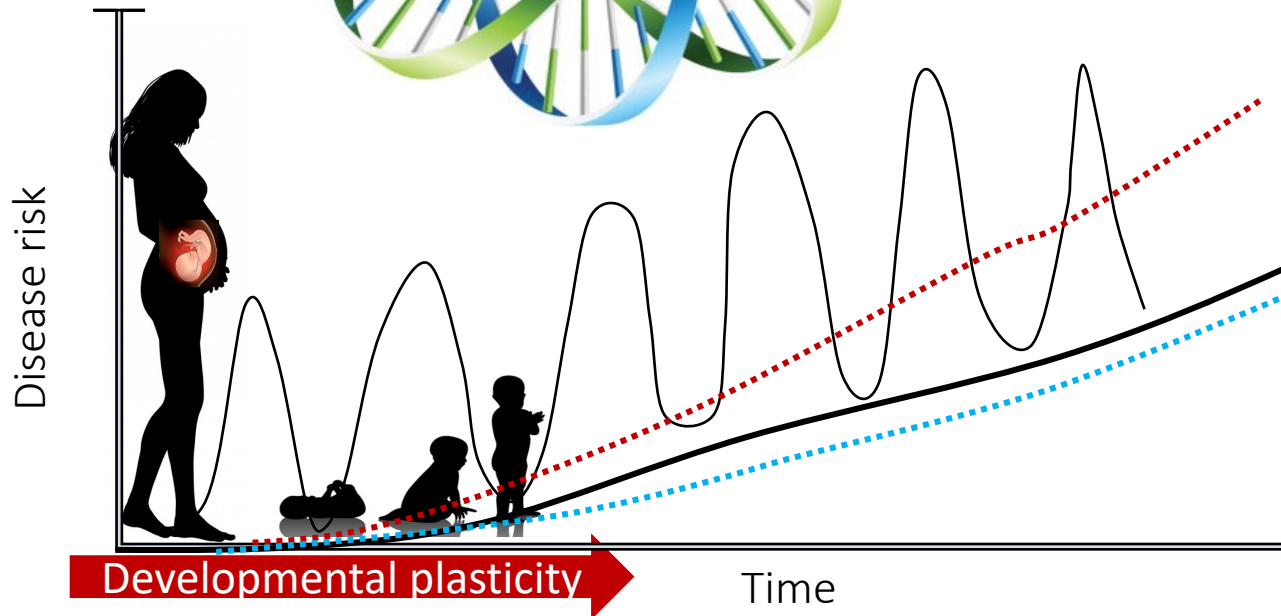
Epigenetic modification



Cells can turn genes on and off by adding chemical groups to histone proteins or to DNA.



Canadian Epigenetics, Environment and Health Research Consortium

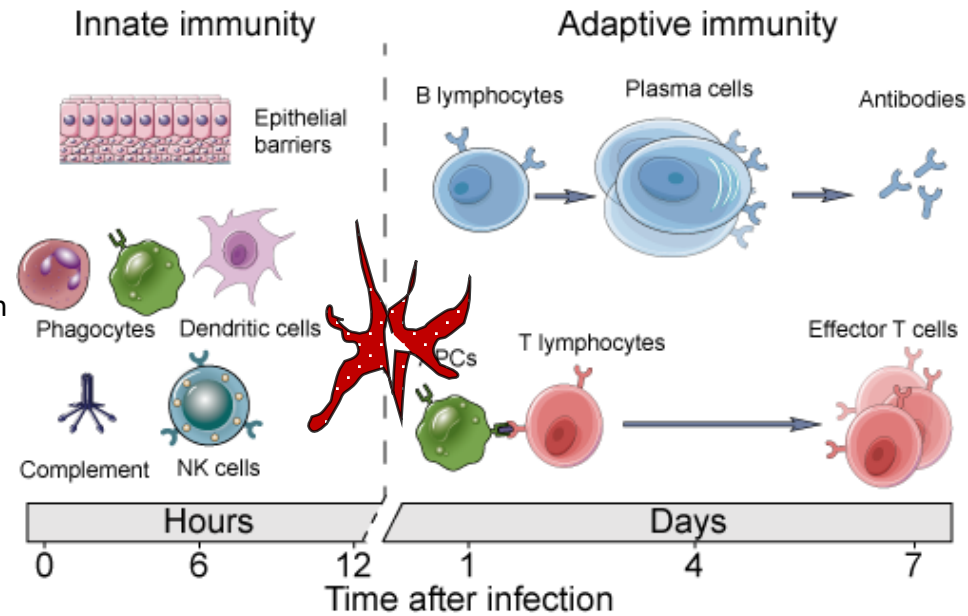


- *DOHaD*: Environmental factors skew developmental trajectory of immune system function and alter susceptibility for development of chronic disease
- *Hygiene Hypothesis*: imbalance in signals during early life programs dysregulated immune development and susceptibility to chronic diseases.

Immune system function

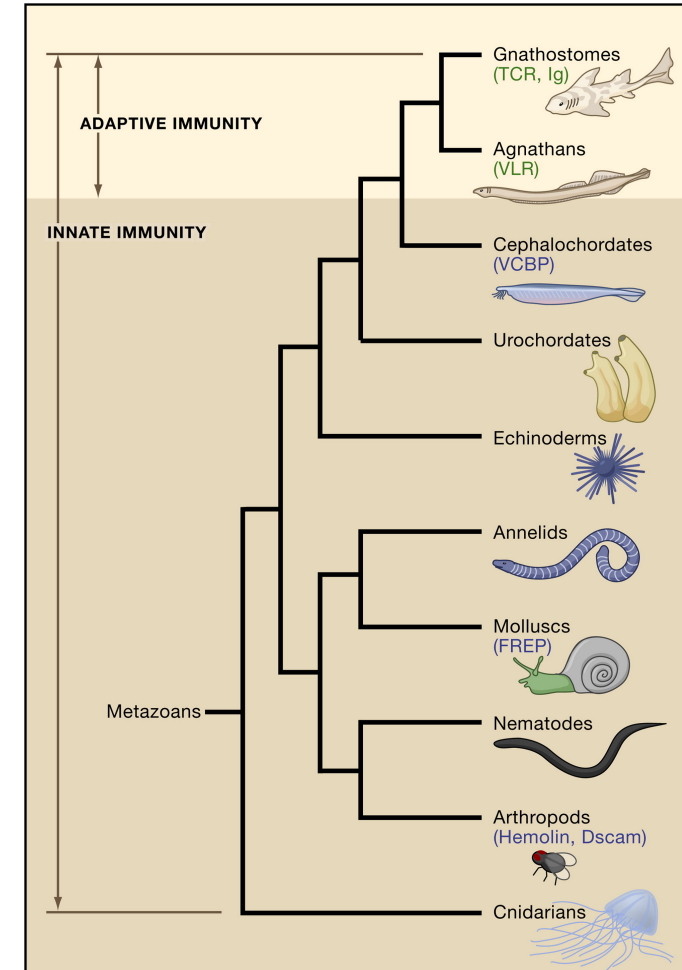
Innate and Adaptive

Microorganism recognition through germ line encoded expression of various **Pathogen Recognition Receptors PRR**



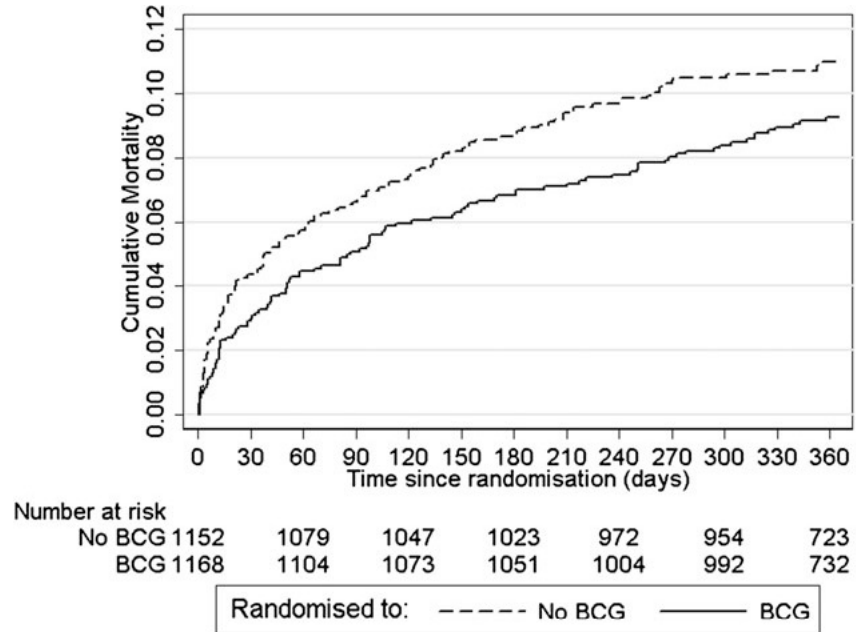
	Innate Non-specific	Adaptive specific
Major cell types	Epithelial, dendritic, NK, monocytes, macrophages, neutrophils, ILC	T and B cells
Pathogen detection	Germline encoded receptors (TLR, NLR, RLR etc)	Somatic gene rearrangements- diverse receptors
Response specificity	Target structures shared across pathogen groups (PAMPs)	Pathogen specific
Response kinetics	immediate	gradual
memory	no	Rapid enhanced protection against re-infection

vaccines

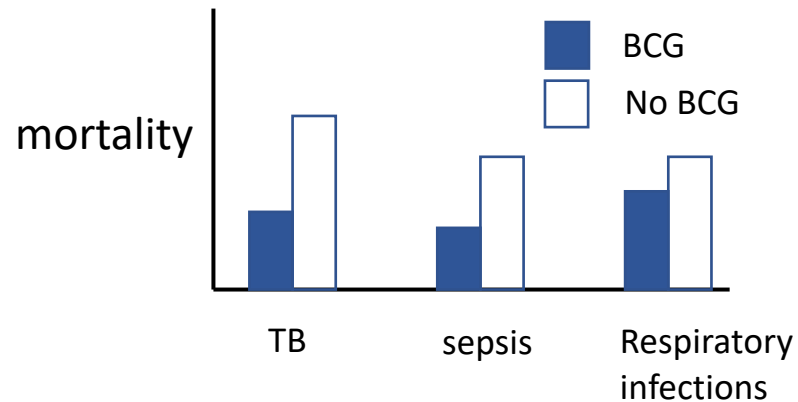


Recent studies have helped in understanding this

The non-specific effects of vaccines- Smallpox, measles, polio, inactivated Influenza, BCG



BCG protects non-specifically against heterologous infection reducing mortality



Prentice et al Lancet Infectious diseases 2021

Nemes et al NEJM 2018

Aaby et al J Infectious diseases

Roth et al BMJ 2010, Epidemiology 2006

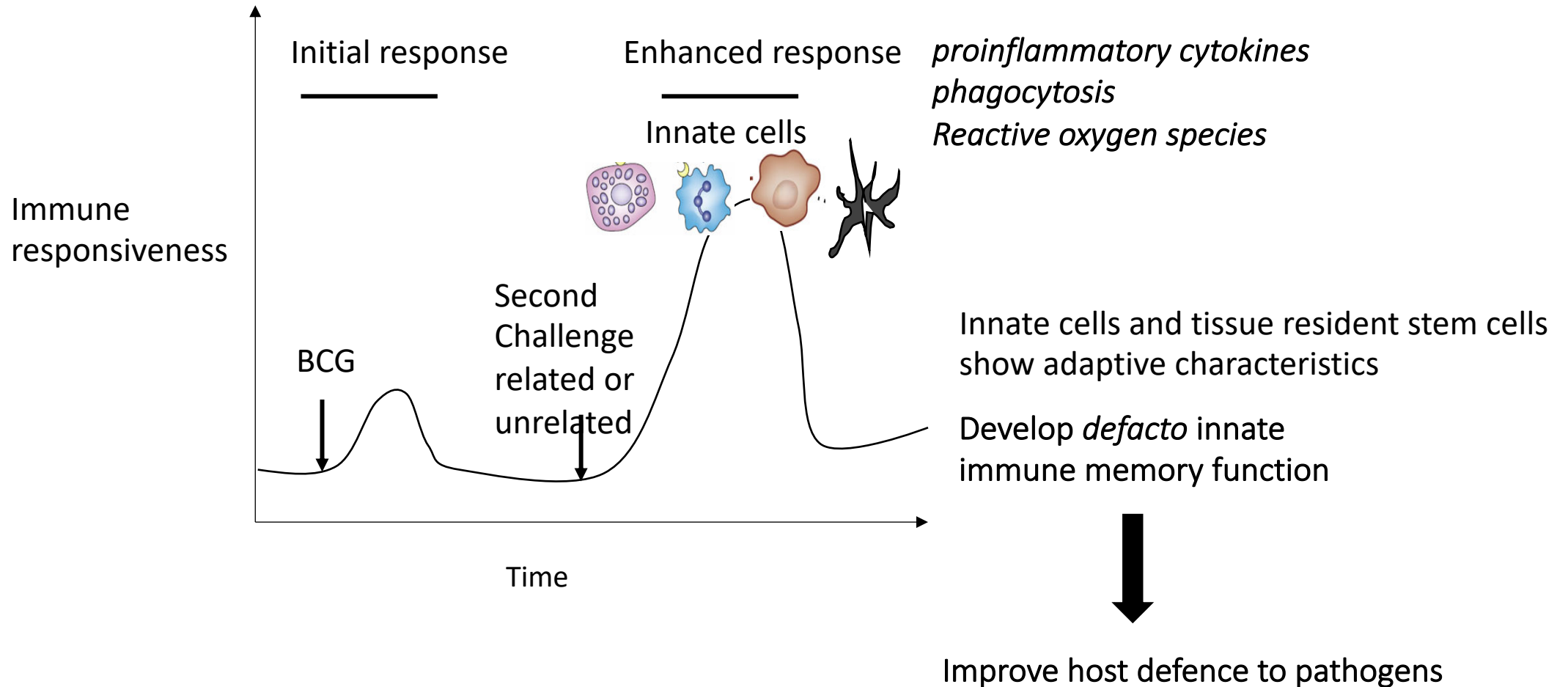
Stensballe et al Vaccine 2005

Kleinnijenhuis et al PNAS 2012

Arts et al Cell Host Microbe 2018

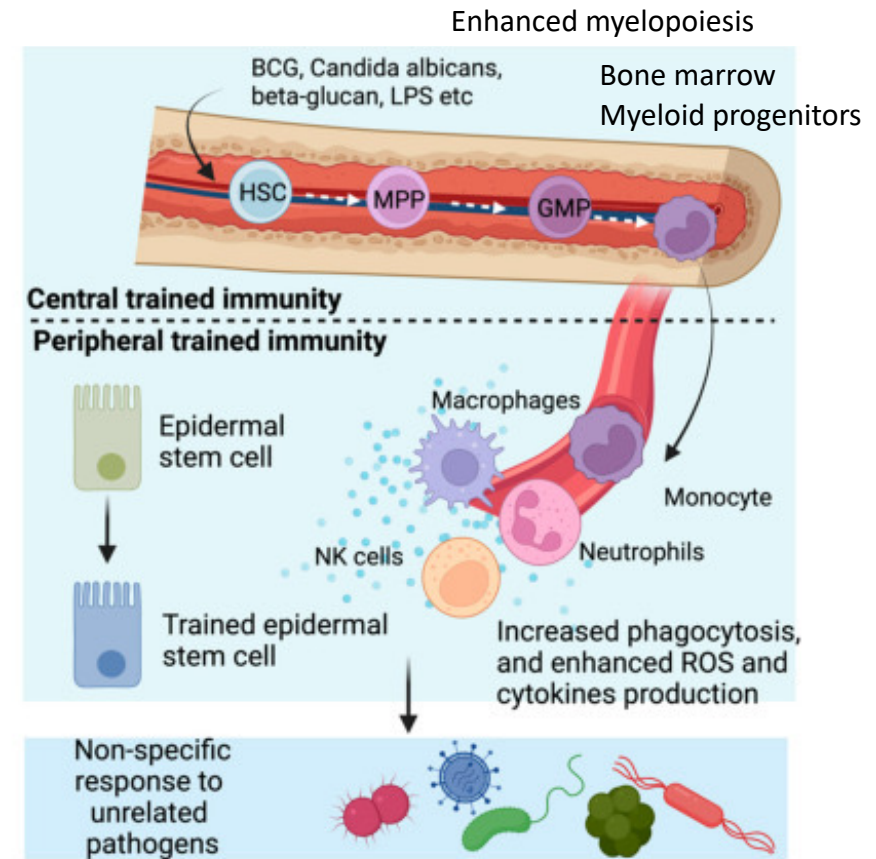
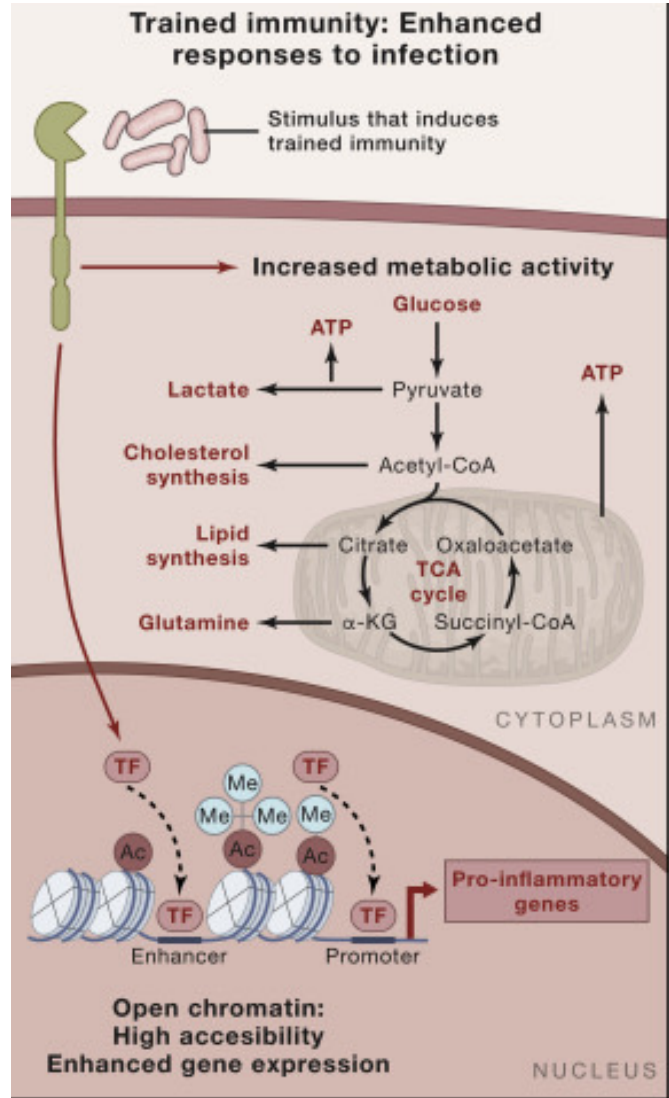
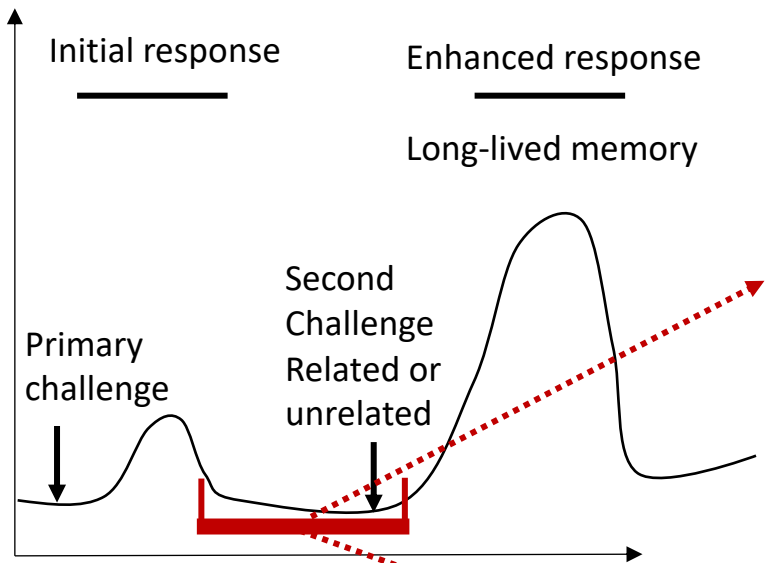
controlled infections in humans-yellow fever vaccine, malaria

BCG non-specific protection against diseases - How does it work?



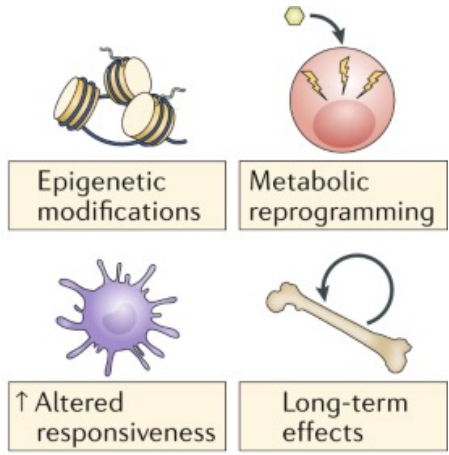
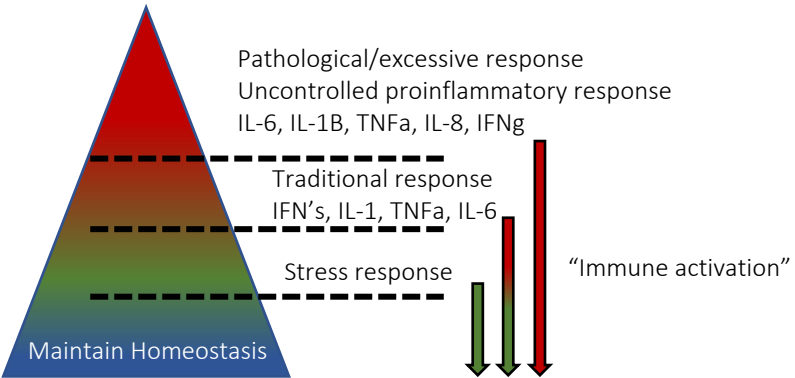
BCG non-specific protection against diseases – Innate Immune Training or Trained Immunity

What happens in the cell to mediate this?

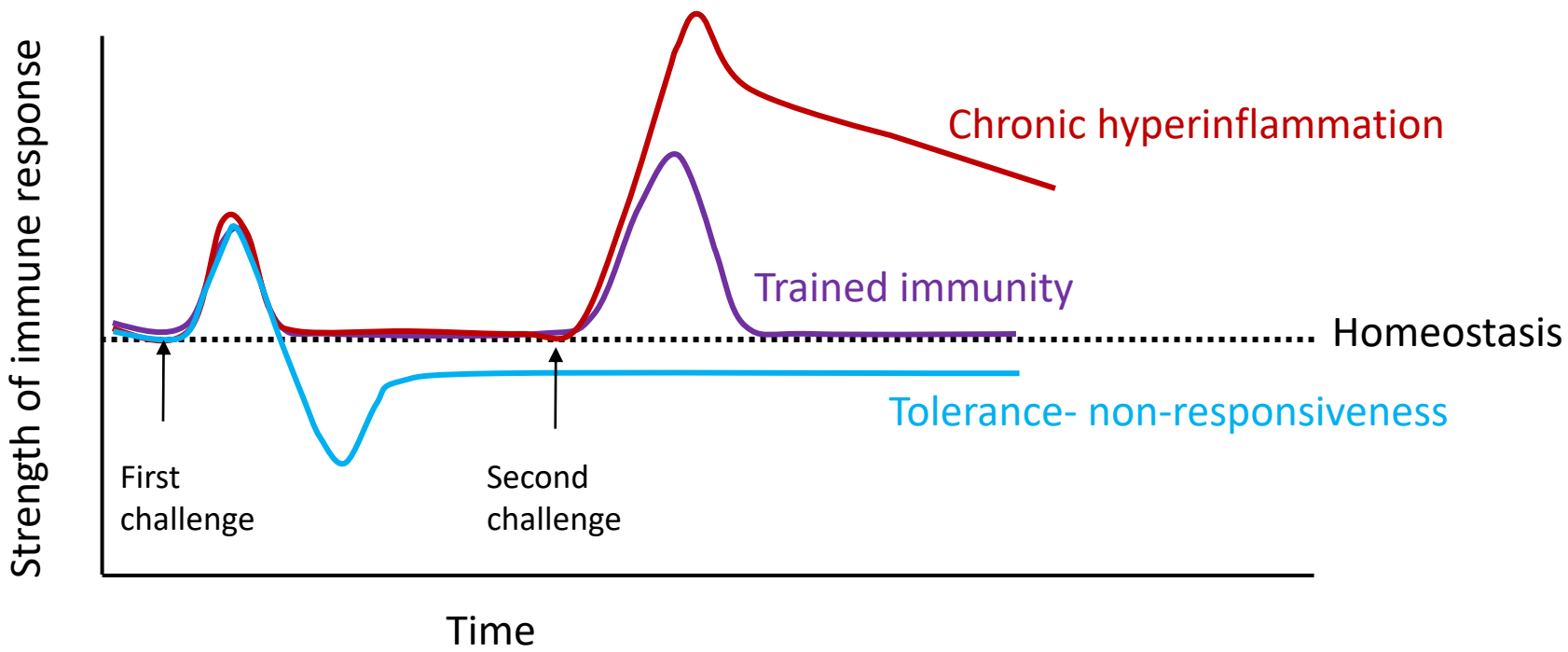


prototypical innate cells
 Monocytes, macrophages, dendritic cells,
 Neutrophils, ILC
 Epithelial cells, stem cells, progenitor cells
 reprogrammed for enhanced responses

Trained Immunity

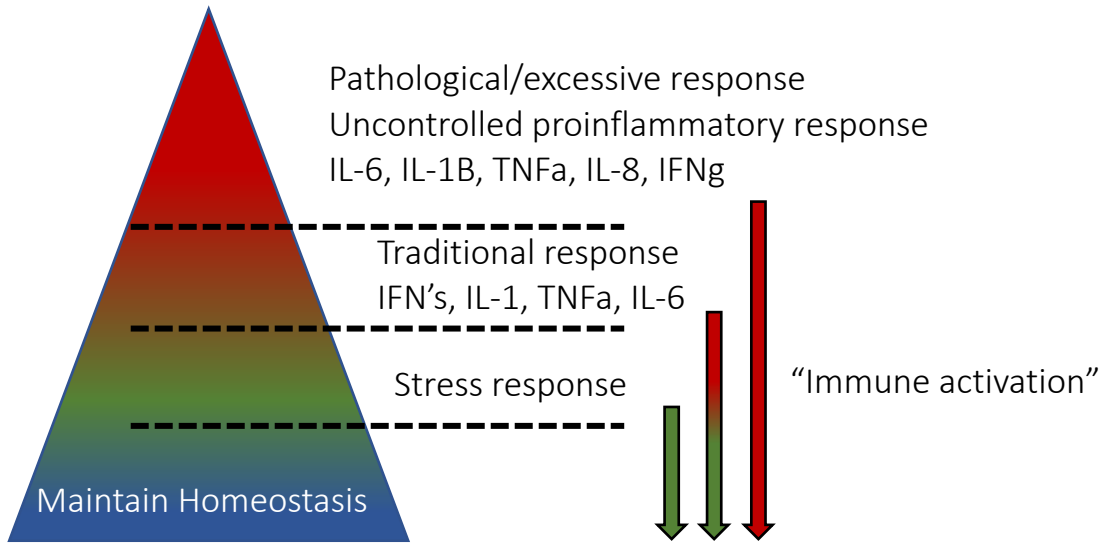


Netea et al
Nature Reviews 2020

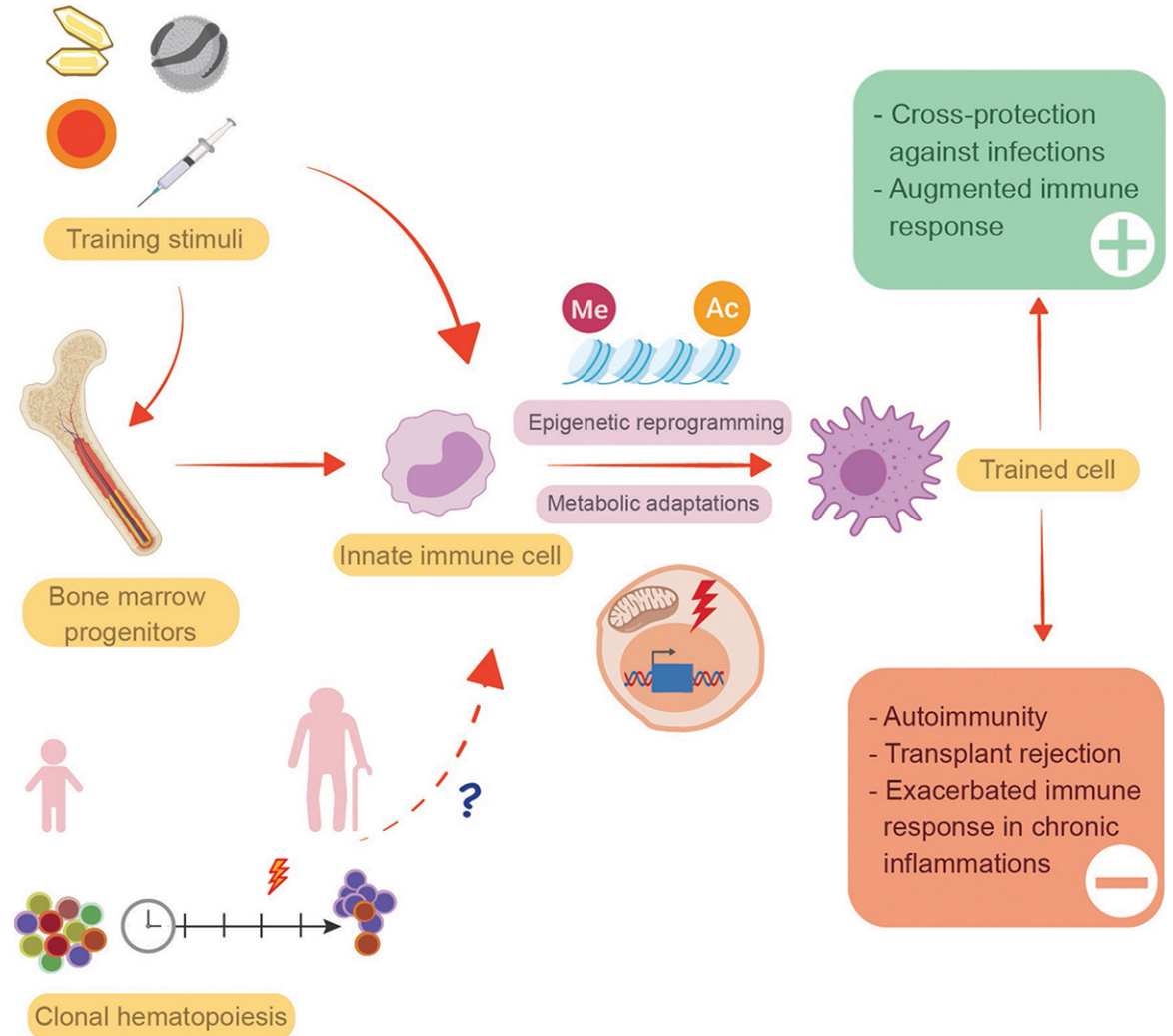


Trained Immunity: Long-term epigenetic and metabolic reprogramming of transcriptional pathways and function of innate immune cells, evoked by endogenous or exogenous stimuli which leads to an altered response to a secondary challenge.

Potential for detrimental impacts of Trained Immunity



Chronic inflammatory conditions
Immunocompromised
Early/late life
pregnancy



Tercan et al. Arteriosclerosis, Thrombosis, and Vascular Biology 2020.

An elegant example of protection against disease in nature

Traditional European farming environments

Traditional versus industrialised farming practices USA

von Mutius E, Vercelli D. Nat Rev Immunol. 2010;10(12):861-8.
Stein et al NEJM 2016.

Profound protection in children

- Allergic asthma
- Early infections
- Allergic rhinitis

- Protection mediated by exposure to microbial compounds
Respiratory (microbes in barn dust) & Gastrointestinal (unpasteurised milk)
- Exposure of pregnant mother (transplacental) and infant
- Replicated in multiple locations
- Innate and adaptive changes
- Exvivo, invitro, animal models provide mechanistic insight

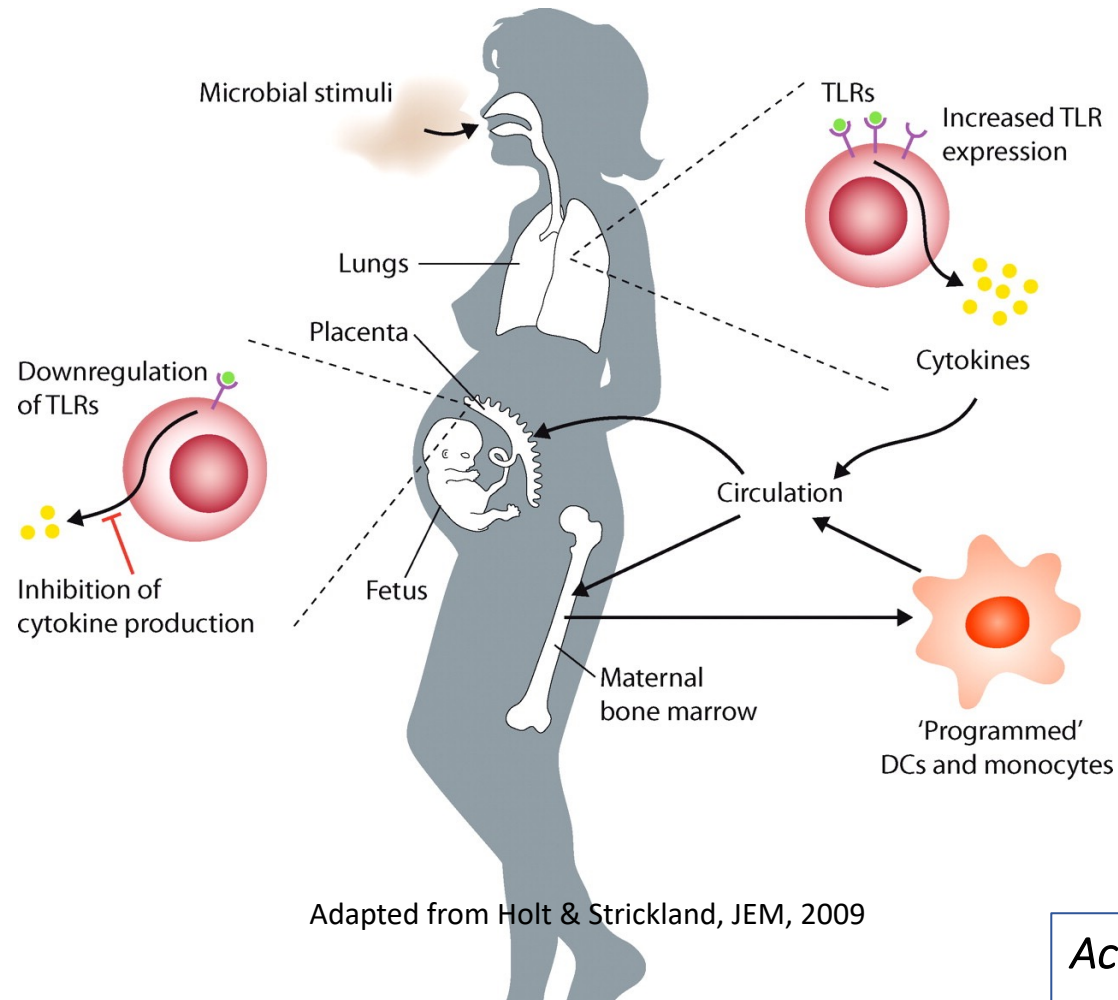
- [Childcare attendance](#). Ball TM et al. NEJM 2000.

- [Household pets](#). Ownby et al. JAMA 2002.



Traditional farm environments: hallmark characteristics of Trained Immunity

Pivotal to considering strategies for asthma prevention



Adapted from Holt & Strickland, JEM, 2009

TLR dependent-
Activation/maturation/Epigenetic changes in myeloid cells conferring functional immune competence
Direct sensing by maternal immune system
Regulated development of immune competence in children

Enhanced regulatory functions

Attenuated microbial sensing in placenta

¹Ege MJ et al. JACI 2006.
²Schaub B et al. JACI 2009
Stein et al, NEJM 2016

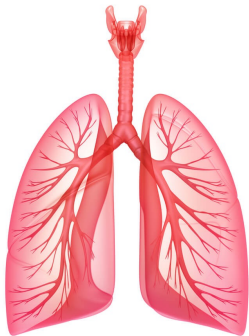


Activation of innate and regulatory pathways to equip the infant with capacity to appropriately shape and calibrate downstream immune responses

Microbial based therapeutics used to boost immune system function for the prevention of infections

- Lactobacillus
- Flagellin
- Endotoxin
- Streptococcus bacteriotherapy
- Probiotics
- Poly Bacterial lysates : MV130, OM85

↓ *respiratory viral infections-*



reduced number, severity, febrile time, duration, hospital days, wheeze, antibiotic use.

Influenza, RSV, RV (SARS-CoV-2)
Protects against secondary bacterial infections

infants, children, adults (COPD, HIV).

Schaad et al. Immunostimulation with OM-85 in children with recurrent infections of the upper respiratory tract: a double-blind, placebo-controlled multicentre study. *Chest* 2002.

Collet et al Effects of an immunostimulating agent on acute exacerbations and hospitalisations in patients with COPD. The PARI-IS steering committee and research group. *AJRCCM* 1997.

Alecsandru et al. Sublingual therapeutic immunization with a polyvalent bacterial preparation in patients with recurrent respiratory infections: immunomodulatory effect on antigen-specific memory CD4+ T cells and impact on clinical outcome. *Clin Exp Immunol* (2011)

Esposito et al. A randomized, placebo-controlled, double-blinded, single-centre, phase IV trial to assess the efficacy and safety of OM-85 in children suffering from recurrent respiratory tract infections. *J Transl Med.* 2019

Rozy et al Bacterial immunostimulants—mechanism of action and clinical application in respiratory diseases. *Pneumonol Alergo Pol.* 2008.

Razi et al. The immunostimulant OM-85 BV prevents wheezing attacks in preschool children. *JACI* 2010

Schaad. OM-85BV, an immunostimulant in pediatric recurrent respiratory tract infections: a systematic review. *World J Pediatr.* 2010

Steurer-Stey et al Oral purified bacterial extracts in chronic bronchitis and COPD: systematic review. *Chest* (2004)

Capetti et al [Four years of immunization with OM-85 BV to prevent respiratory infections in HIV+ patients.](#) *Hum Vaccin Immunother.* 2013

Koatz et al. [Clinical and Immunological Benefits of OM-85 Bacterial Lysate in Patients with Allergic Rhinitis, Asthma, and COPD and Recurrent Respiratory Infections](#) *Lung.* 2016

Parola, et al. Selective activation of human dendritic cells by OM-85 through a NF- κ B and MAPK dependent pathway. *PloS One* 2013

De Boer et al. Bacterial lysate therapy for the prevention of wheezing episodes and asthma exacerbations: a systematic review and meta-analysis. *Eur Resp Review* 2020.

Pivniouk et al The Om-85 Bacterial lysate inhibits SARS-CoV-2 infection of epithelial cells by downregulating SARS-CoV-2 receptor expression. *JACI* 2022.

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OM PHARMA'S STORY

Ricard family, 1937

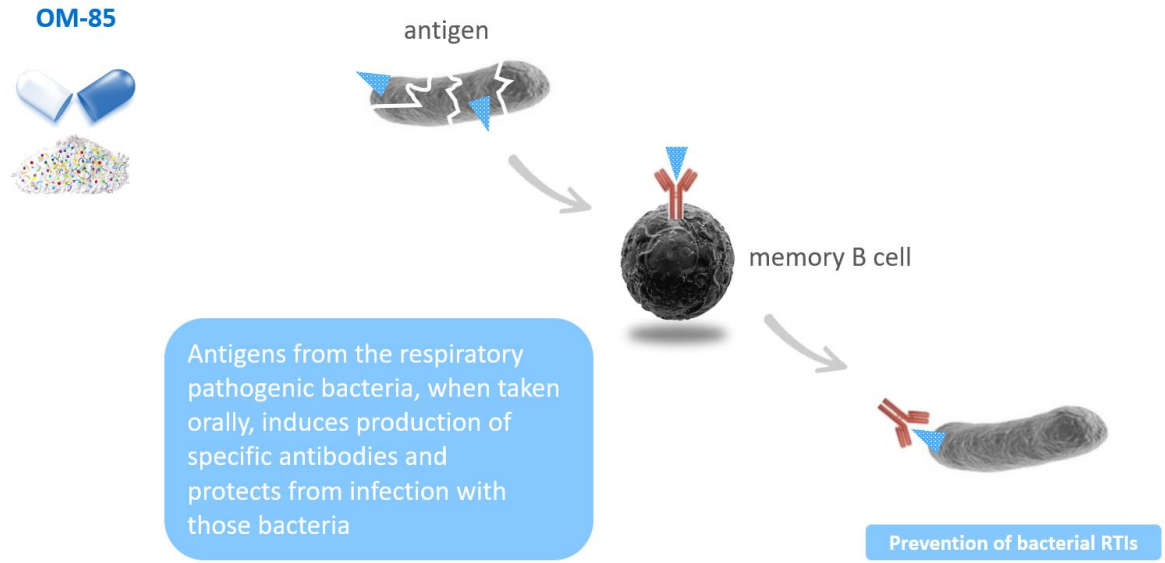
The invention and vision: Oriented science
An oral vaccine for bacterial infections



Ricard family, 1937

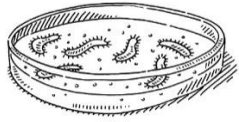
FROM WHAT WE THOUGHT: FAMILY RICARD, 1979

THE VACCINE HYPOTHESIS

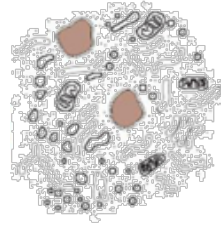


About OM-85

Haemophilus influenzae
Streptococcus pneumoniae
Klebsiella pneumoniae
Klebsiella ozaenae
Staphylococcus aureus
Streptococcus pyogenes
Streptococcus viridans
Moraxella catarrhalis
Total : 21 strains



Fermentation



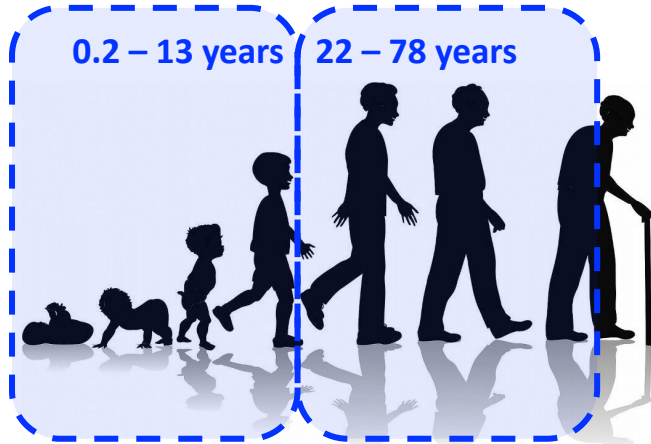
Chemical Lysis & Purification



Lyophilization /
Encapsulation



Gut-lung axis

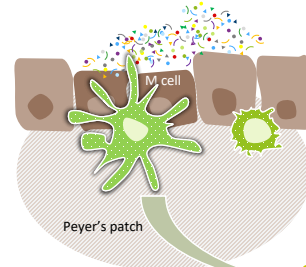


Extensive safety profile

Oral administration
(Mucosal activation in the gut)

Distant mucosal activation
(e.g. lung or skin)

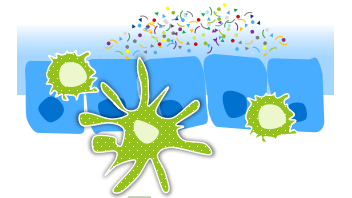
Local administration
(Mucosal activation e.g. in nose)



IgA, MIP1alpha
DC activation



Migration of immune
cells armed for
strong but controlled
reaction



mucosal activation by microbial content prime the immune system for tolerogenic, protective immune responses

Pasquali et al Front Med 2014
 Navarro et al. Mucosal Immunology 2011
 Strickland et al Mucosal Immunology 2011

The immune modulating agent OM-85: MoA

Prevents respiratory tract infections (and secondary bacterial infections)

- Activity is dependent on PRR engagement and activation of key signaling pathways (MyD88, Trif, NFkB)
- Acts on a variety of innate cell types in the periphery and bone marrow precursors
- Broad non-specific antimicrobial cellular and humoral immunity (IgA, IgG, AMP, improved barrier integrity)
- Activation/maturation of myeloid cells- facilitating strong antiviral responses (activation of IRF transcription factors and type I IFNs)
- Expression of cytokines/chemokines to control inflammation and cell recruitment
- Modulates myeloid cell surface molecule expression (antigen recognition) important for instruction of adaptive immune responses
- Modulates key pathways involved in inflammation, controlling levels of proinflammatory cytokine production (IL-1-Inflammasome axis)
- Induces a strong immunoregulatory signal (Treg cells, reduced Th2)

Describes a Trained Immunity that promotes antimicrobial responses. Selective activation and priming of innate cells with concomitant activation of immunoregulatory immune functions. Combat infection and Control inflammation.

Does OM-85 protect against development of allergic airways disease?

Can we replicate traditional farming environmental effects with OM-85?

Strickland et al. Boosting airway T-regulatory cells by gastrointestinal stimulation as a strategy for asthma control. Mucosal Immunology 2011.

Navarro et al. The oral administration of bacterial extracts prevents asthma via the recruitment of regulatory T cells to the Airways. Mucosal Immunology 2011.

De Jong et al. IRF-7-associated phenotypes have dichotomous responses to virus/allergen co-exposure and OM-85-induced programming. Frontiers Immunology 2021.

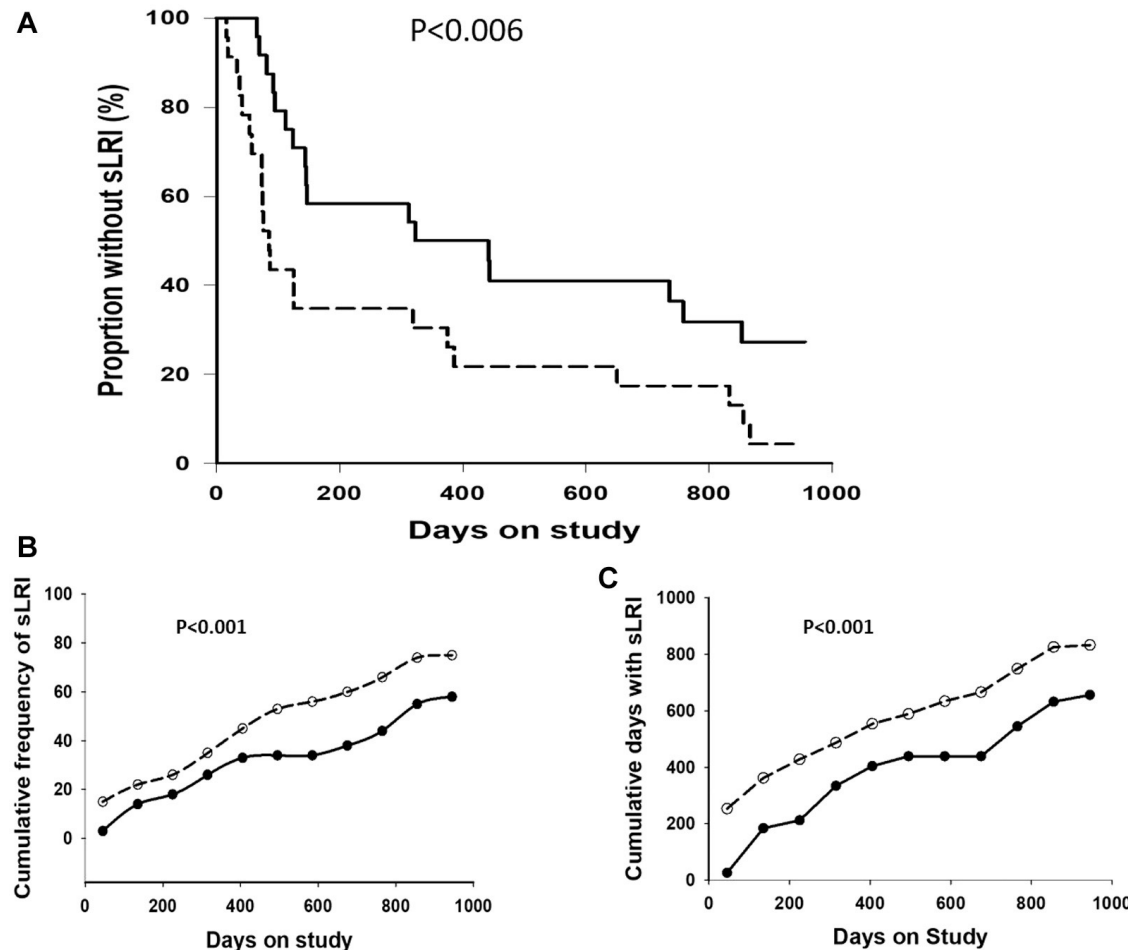
Pivniouk et al. [Airway administration of OM-85, a bacterial lysate, blocks experimental asthma by targeting dendritic cells and the epithelium/IL-33/ILC2 axis.](#) J Allergy Clin Immunol. 2022.

OM-85 in the primary prevention of respiratory viral infections in infants at high risk for asthma development – the OMPAC study.

Sly et al JACI 2019



Phase2 double blind, randomized, placebo-controlled trial in infants 3-9 months old at high risk for asthma development



A. The time to the first sLRI was significantly longer for children receiving OM85 than for those receiving placebo

median, 442.0 days [25% to 75%, >853.0-124.0 days] vs 85.0 days [25% to 75%, 386.0-54.0 days]

B. The cumulative frequency of sLRIs was greater in the placebo group

total, 58; median, 2.00 [25% to 75%, 0.00-3.00] vs total, 75; median, 1.00 [25% to 75%, 1.00-5.00]

C. Throughout the study period, children in the placebo group had more days of sLRIs than those randomized to OM85

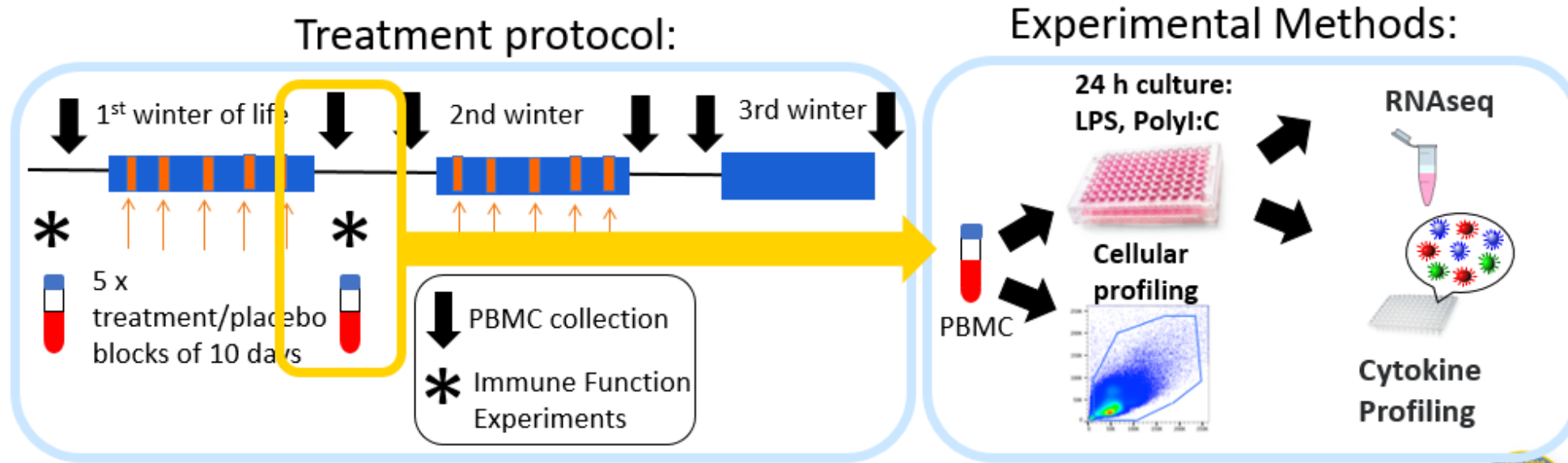
total, 838 days; median, 589 days [25% to 75%, 428-749 days] vs total, 656 days; median, 439 days [25% to 75%, 212-545 days]

Nieto et al. AJRCCM 2021.

MV130-protects against childhood recurrent wheeze

OMPAC study - mechanism

- Two groups: OM85 treatment (n=29) and placebo (n=30)

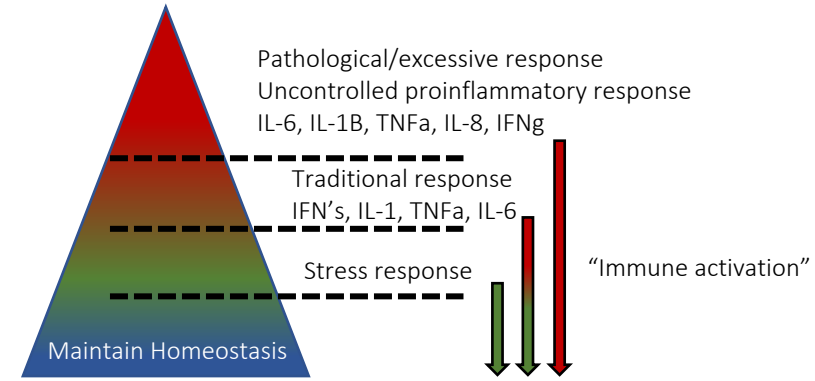


Boosts immunity associated with protection against severe respiratory infection and asthma (Type I IFN/IRF7)
Rewires innate inflammatory gene networks in response to LPS*
Decrease proinflammatory response
OM85 reprograms the antibacterial arm of the immune response to protect against sLRI's.
Increase in circulating T-reg cells

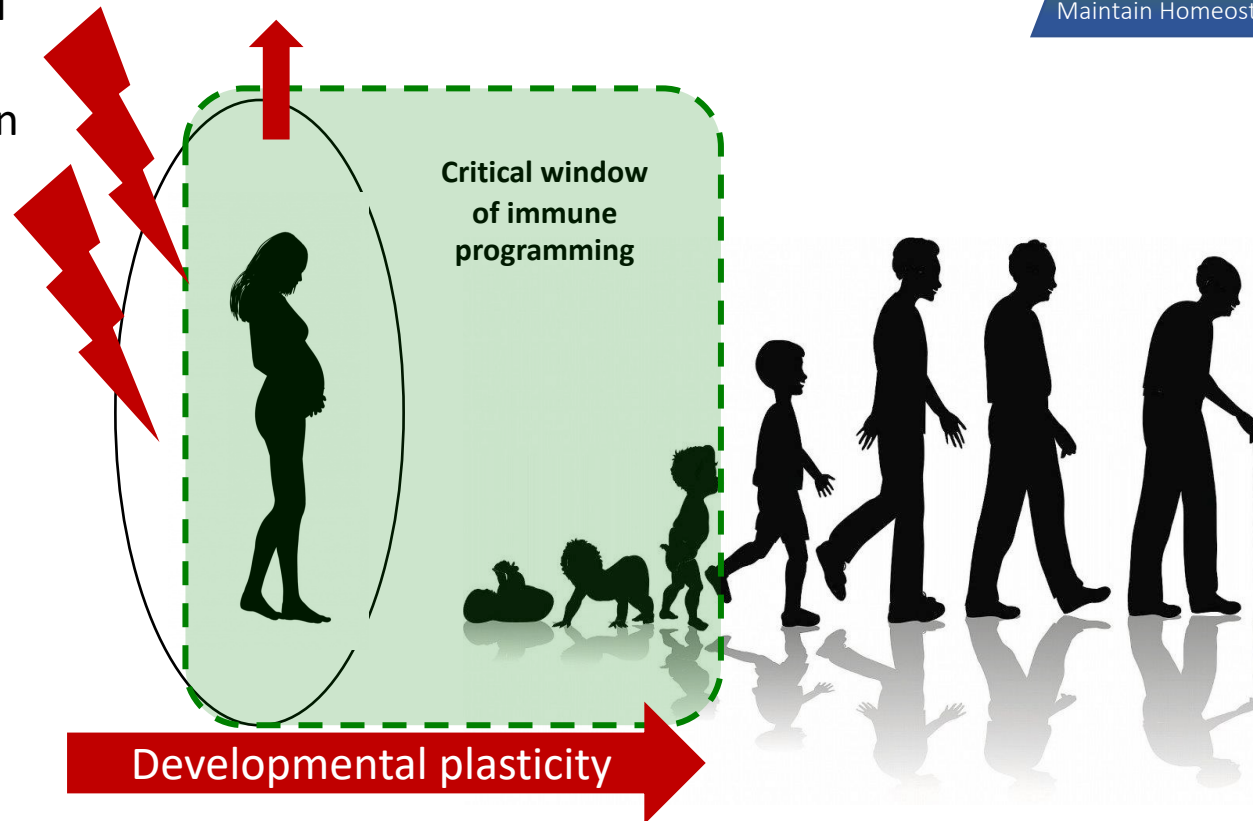
Number of trials underway evaluating OM85 in prevention of childhood wheezing
ORBEX trial- US
PRCISE (comparative study of treatment modalities)-US

Trained Immunity – opportunities during pregnancy/early life for prevention of exaggerated responses to respiratory infections & development of asthma

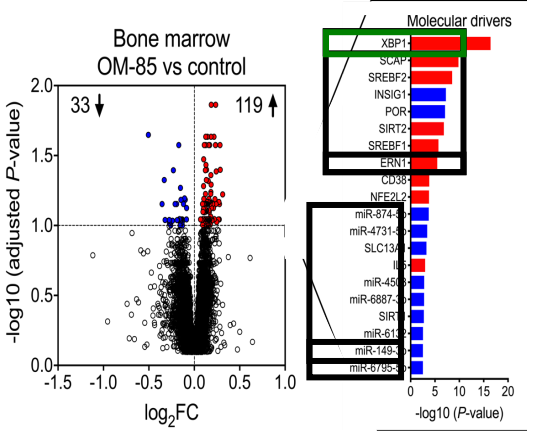
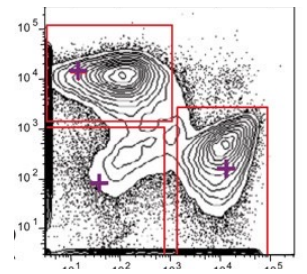
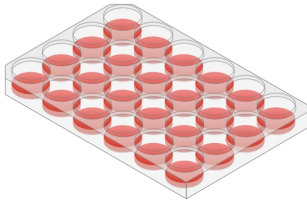
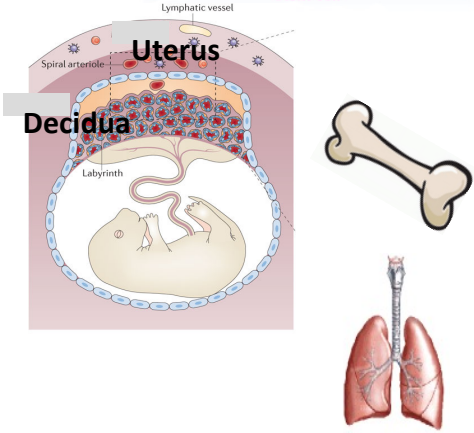
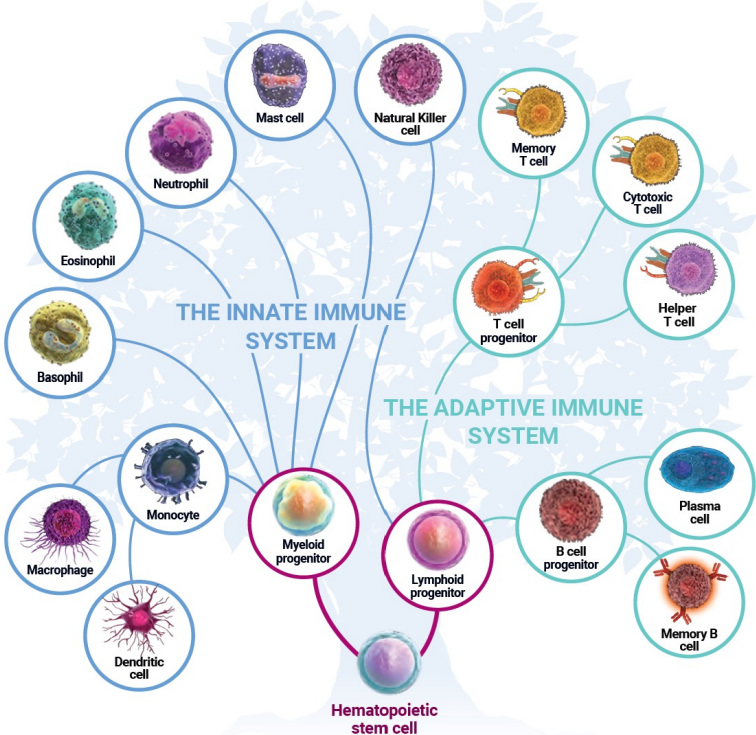
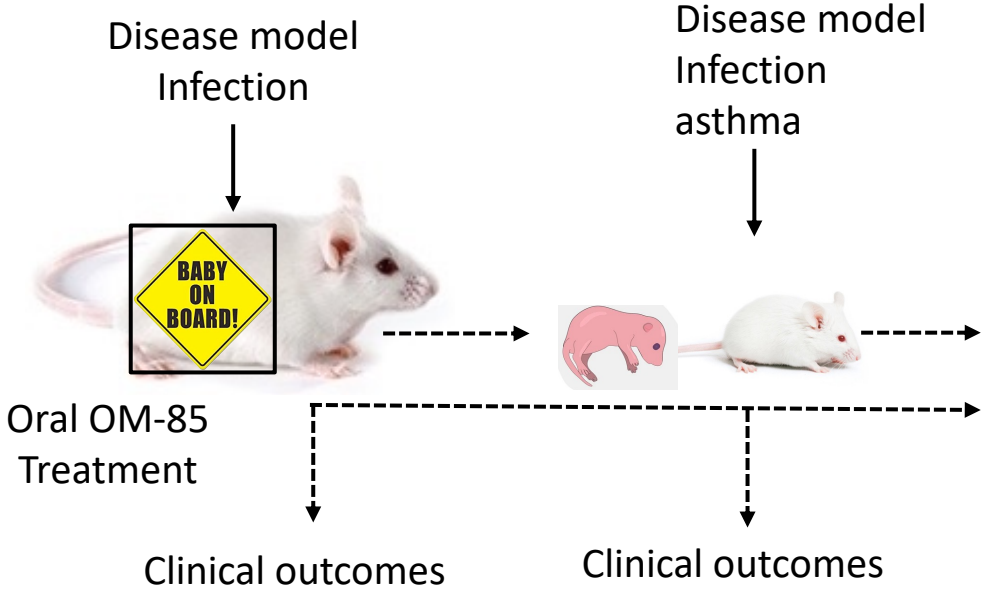
Pregnancy- heightened susceptibility to dysregulated inflammatory responses
Pre-term birth, fetal growth restriction, increased mortality, morbidity
Program immune dysregulation in developing fetus



Maternal immune activation



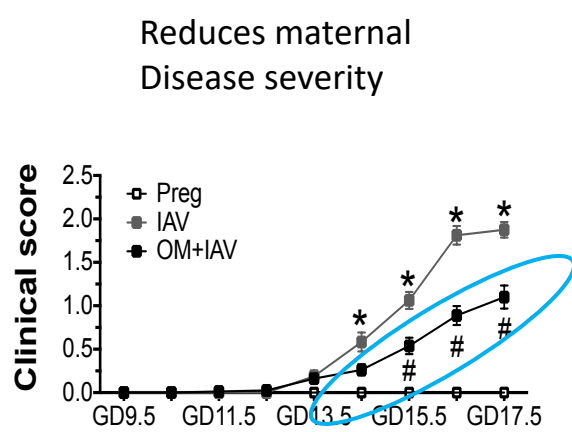
OM-85 studies- preclinical models and methodology



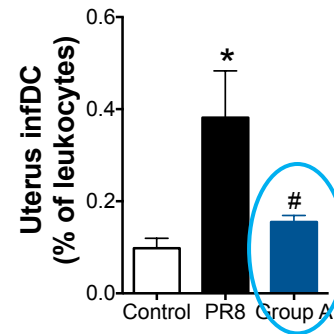
OM85 in pregnancy- summary of key findings

Beneficial maternal/ fetal effects to combat infection

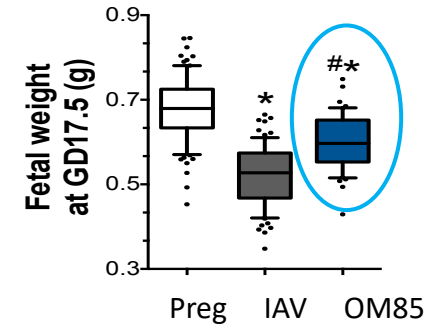
Maternal
Influenza
infection



Stabilises responses in
Gestational tissues

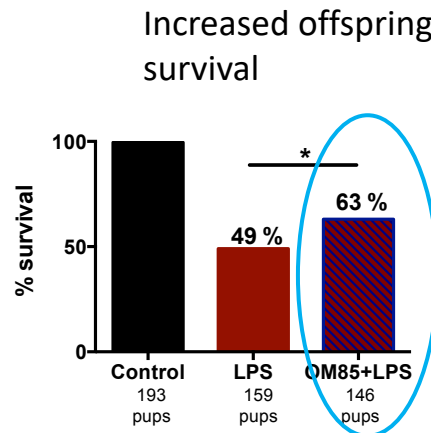


Protects fetal growth

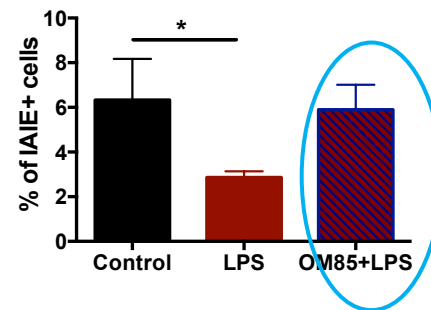


Scott et al
Mucosal Immunol 2017

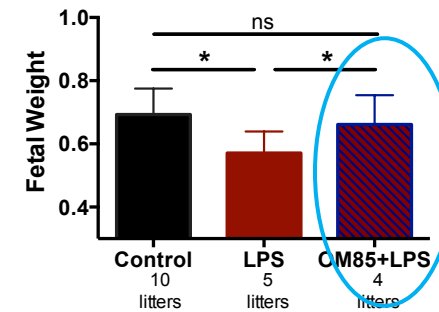
Maternal
LPS model



regulates cell responses
in gestational tissues



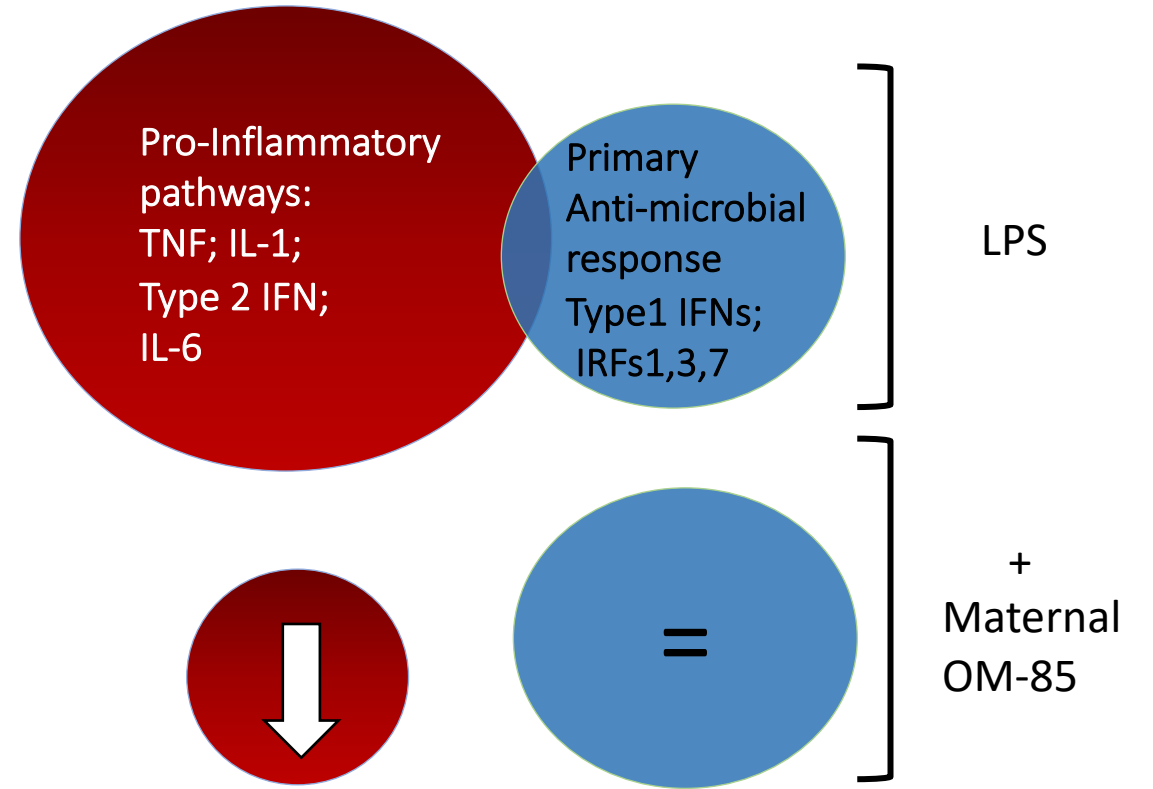
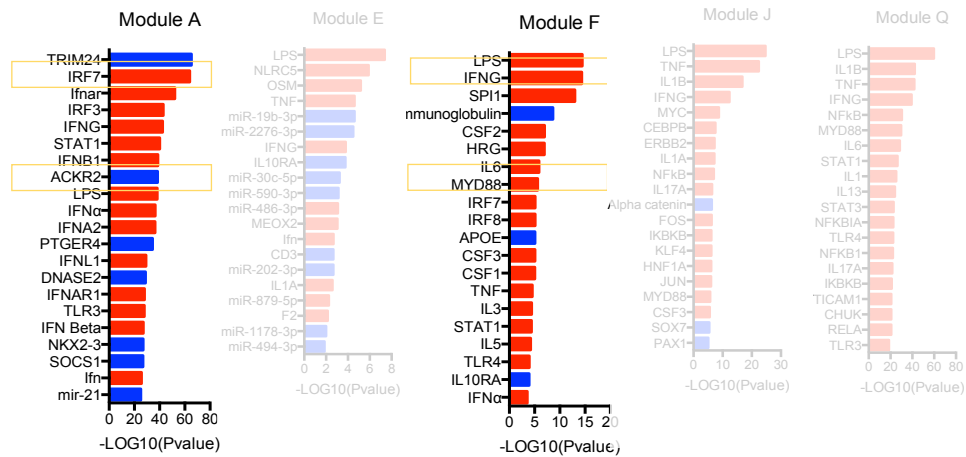
Protects fetal growth



*OM85 reduces maternal disease severity
maintains gestational tissue homeostasis supports fetal growth and development*

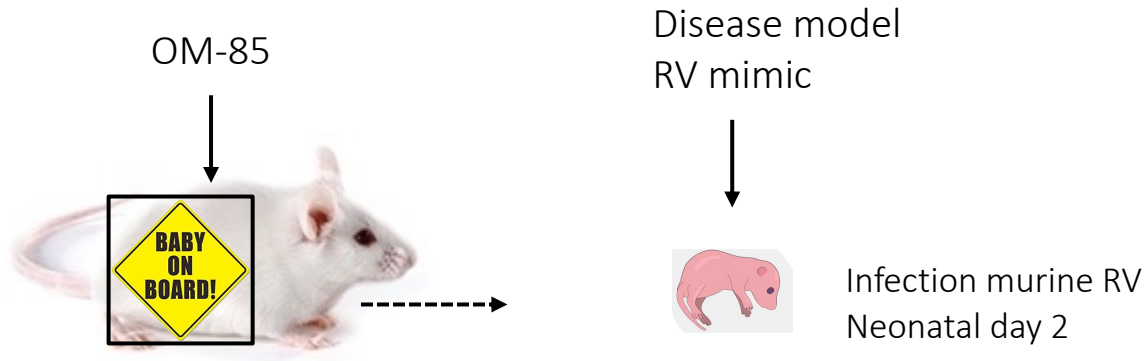
OM85 in pregnancy provides beneficial maternal/ fetal effects to combat infection

OM-85 reprograms transcriptional inflammatory networks

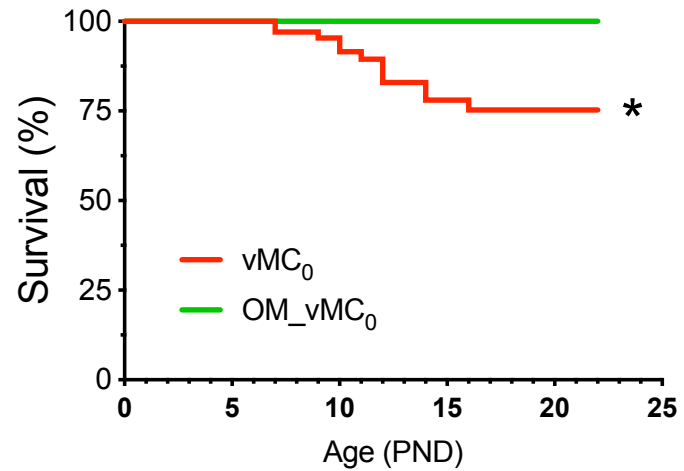
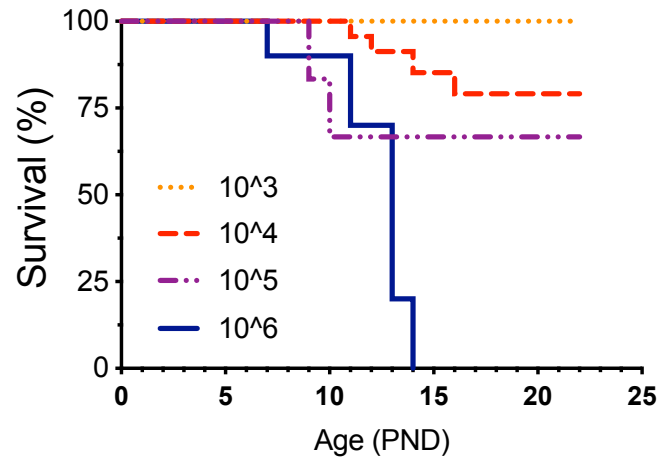


Protection is mediated by selectively constraining proinflammatory responses and preserving/promoting IRF7 responses.

OM85 treatment during pregnancy protects against early life viral infection severity



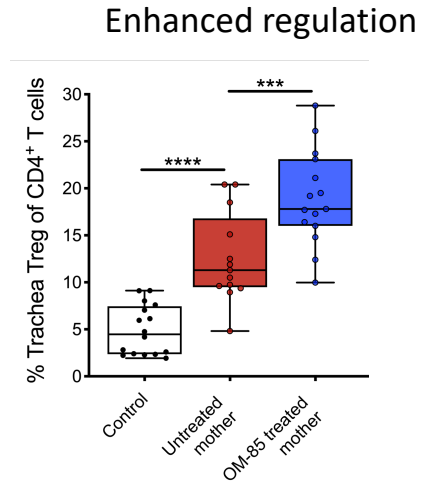
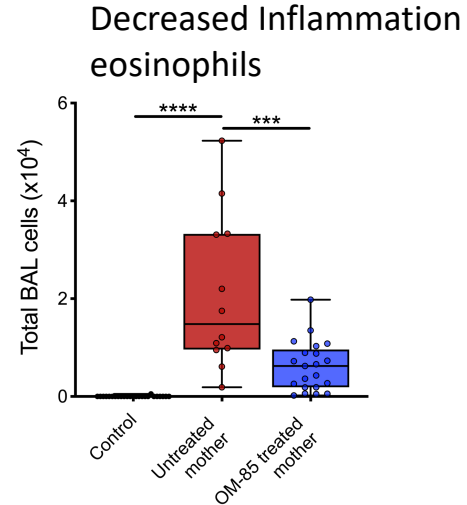
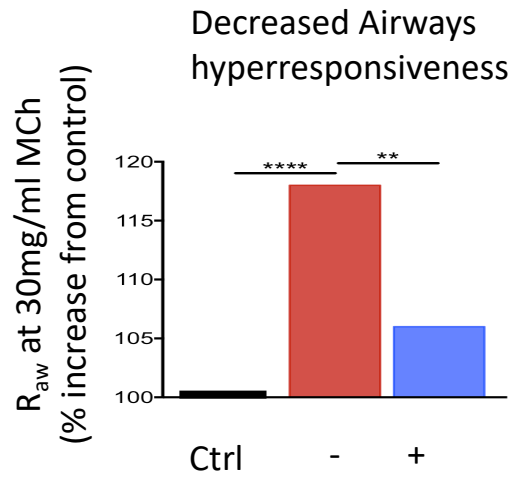
Lauzon-Joset et al
Clin Trans Immunol 2021



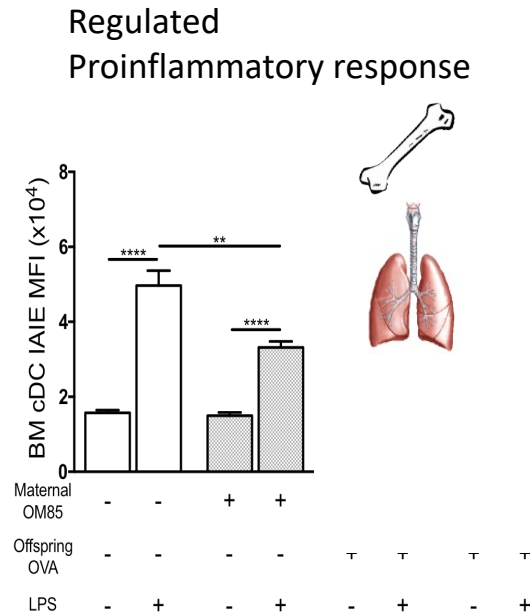
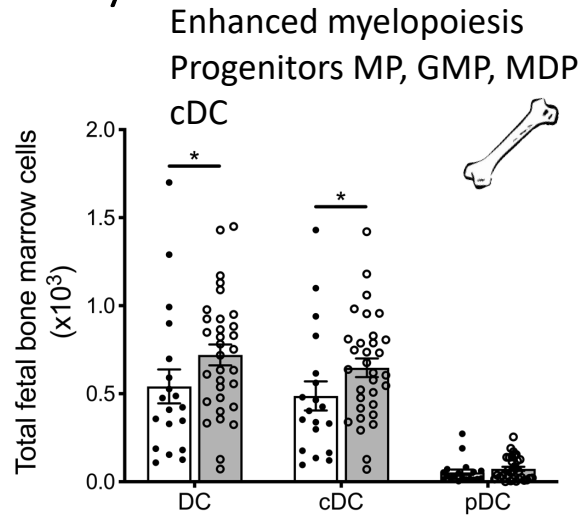
OM-85 studies- asthma

Prevention of Allergic Asthma transplacental

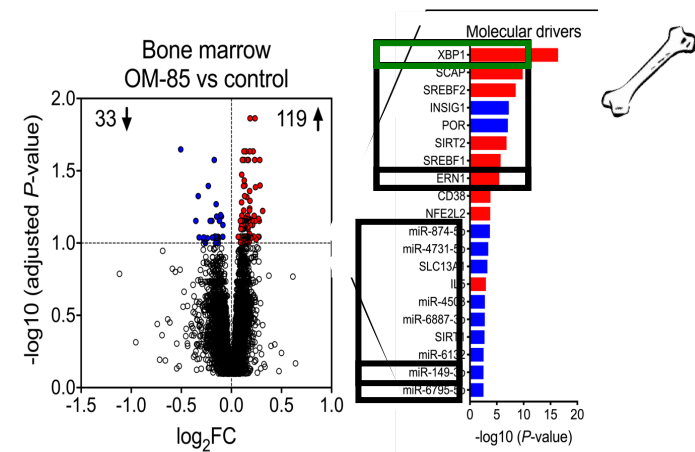
Hallmark signatures of regulated Trained Immunity



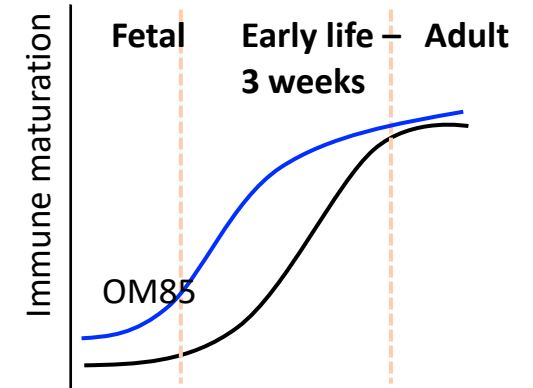
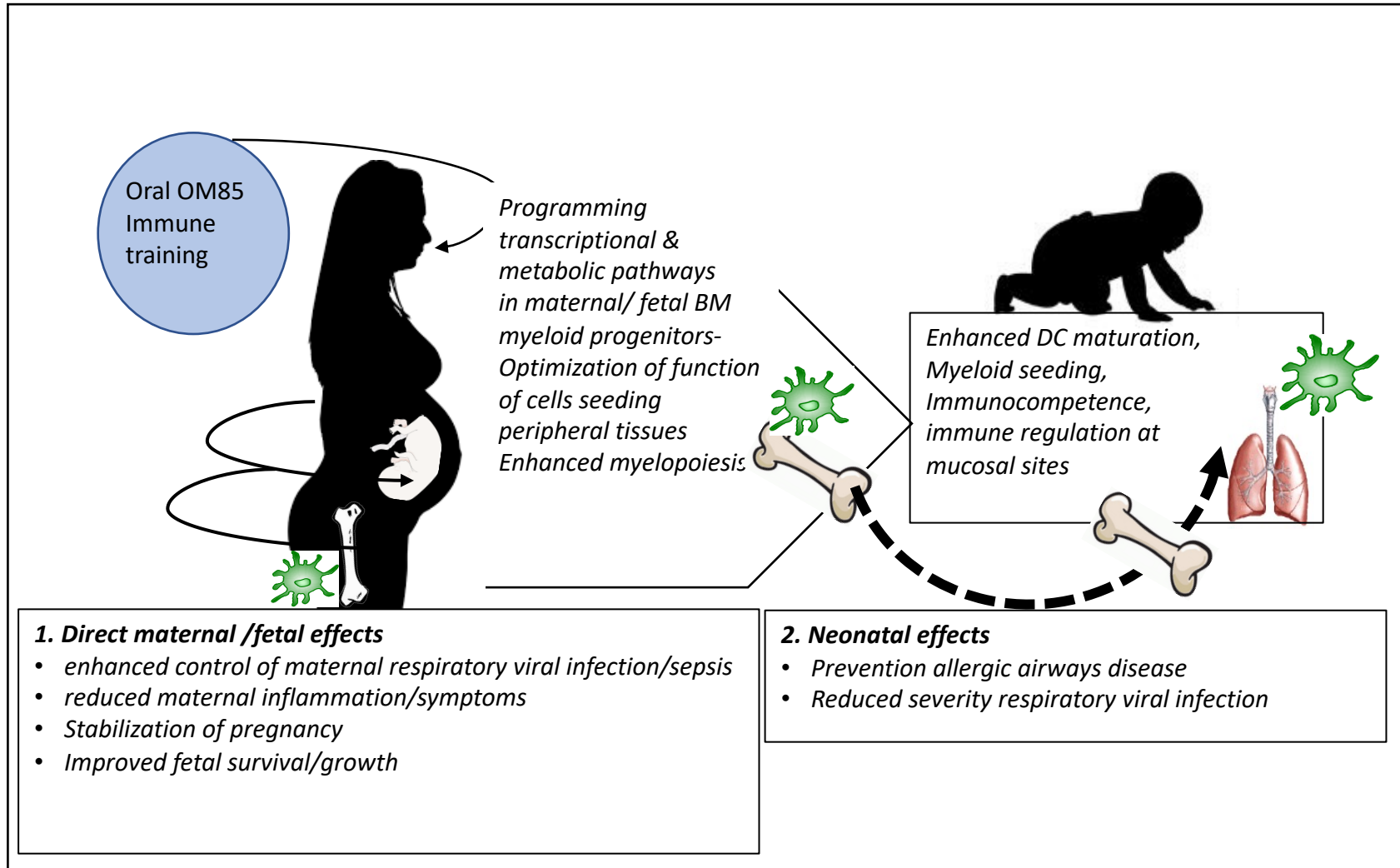
Mincham et al.
J Clin Invest. 2018
Front Immunol. 2020



Transcriptional reprogramming DC survival and function Upregulation of cholesterol biosynthesis



Maternal and transplacental benefits of OM85 trained immunity during pregnancy



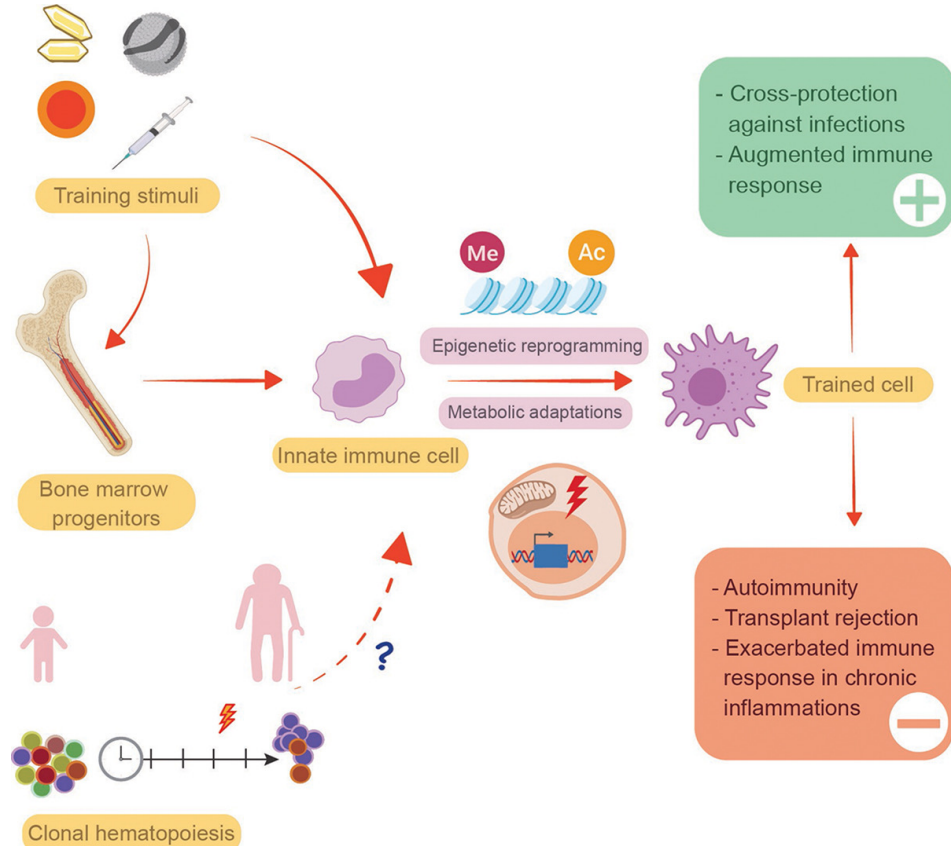
Accelerated Post-natal development of immunity

Pathogen clearance enhanced
Type1 IFNs; IRFs1,3,7

Controlled pro-inflammatory responses
TNF; IL-1; Type 2 IFN; IL-6

Immunoregulation- limit exaggerated
Response and Th2

Broader application of immune modulatory agents



Sánchez-Ramón et al. [Sublingual Bacterial Vaccination Reduces Recurrent Infections in Patients With Autoimmune Diseases Under Immunosuppressant Treatment](#). *Front Immunol.* 2021

Pérez-Sancristóbal et al. [Long-Term Benefit of Perlingual Polybacterial Vaccines in Patients with Systemic Autoimmune Diseases and Active Immunosuppression](#). *Biomedicines.* 2023

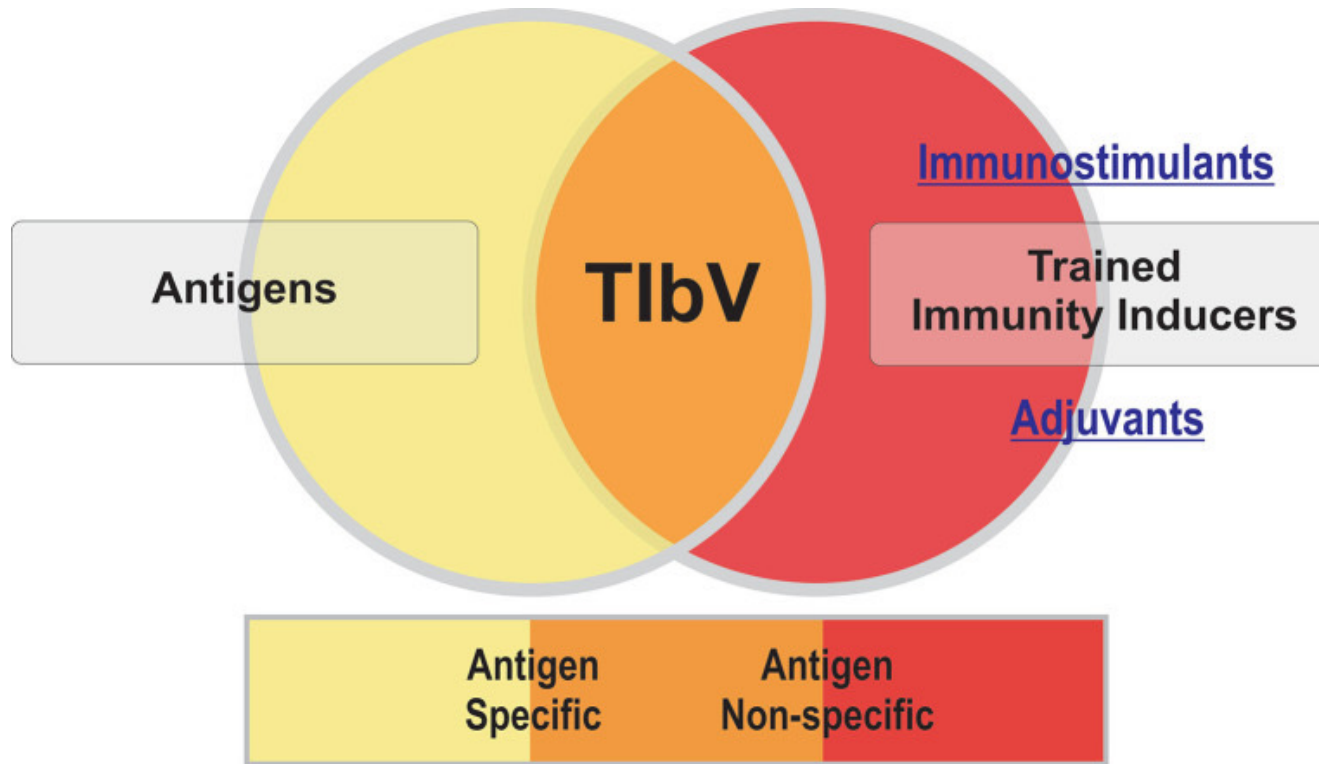
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Thank you