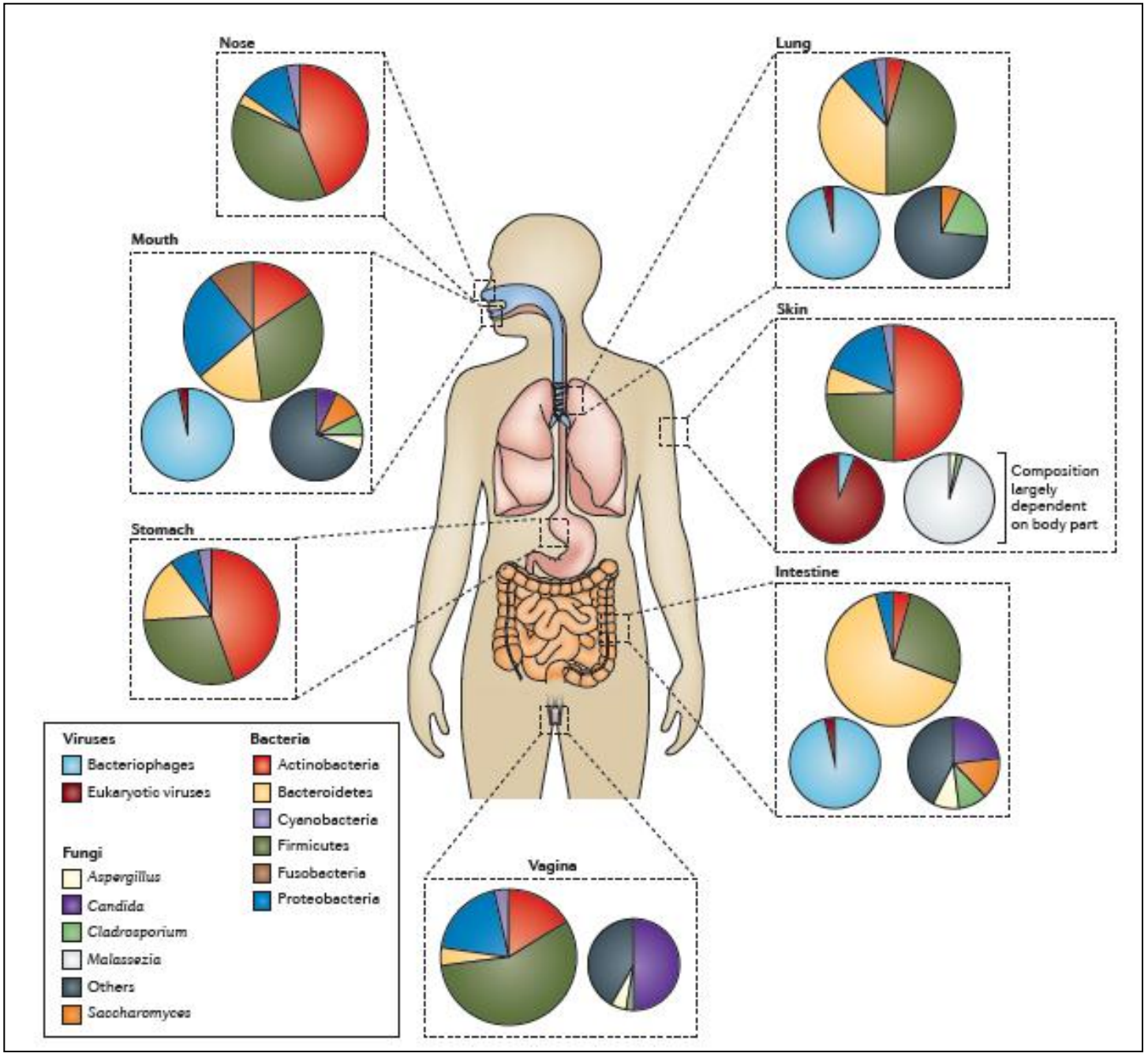
Fungi, fungal infections and immunity in the metagenomic era

Luigina Romani
University of Perugia

FunMeta

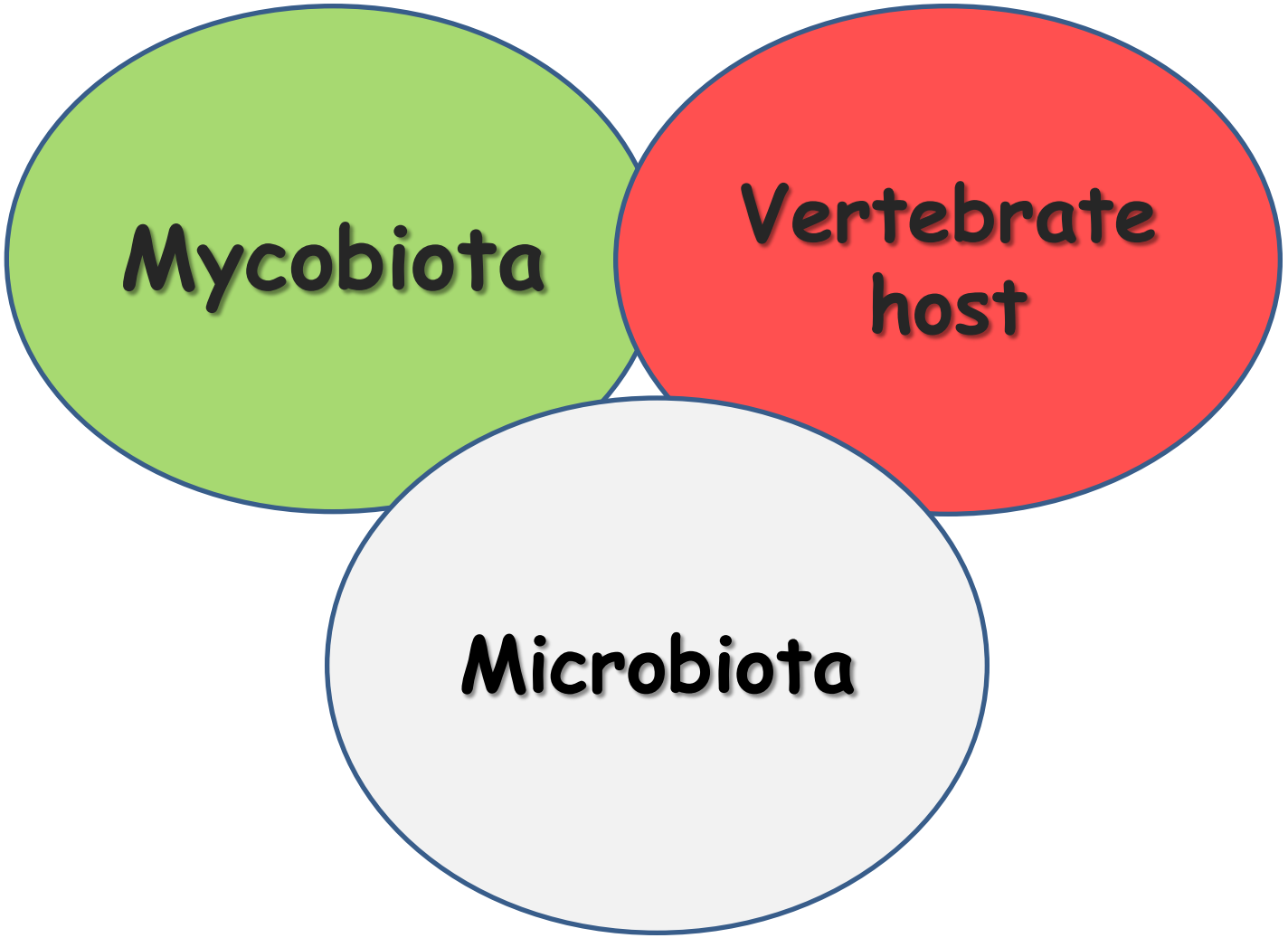
19° ISHAM, 4th-8th May 2015



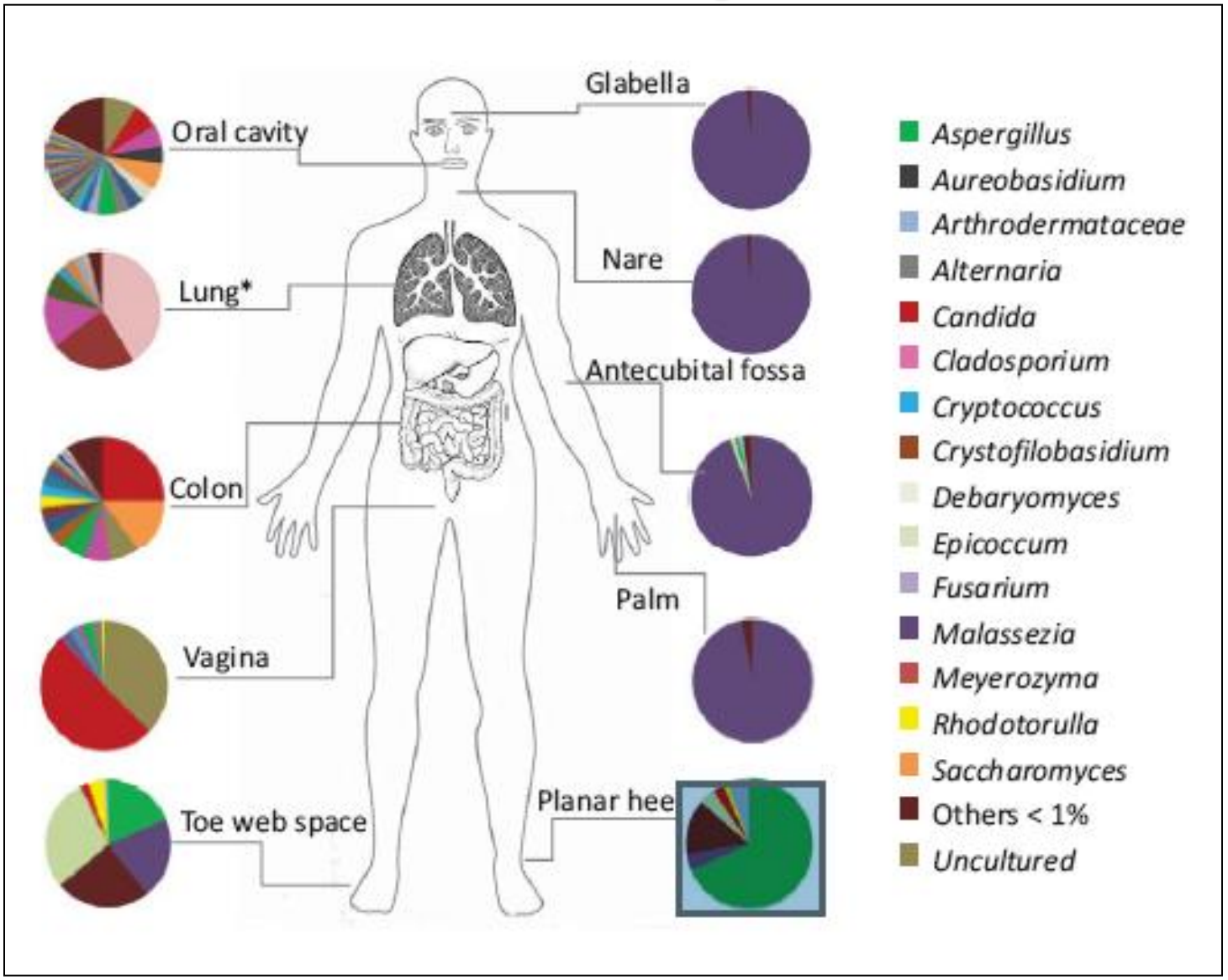
The composition of the bacterial, fungal and viral microbiota at distinct body sites

Nat Rev Immunol, 2014

Exploiting the triad for antifungal immunity



The human mycobiome



Nat Rev Immunol, 2014

A paradigm shift: From pathogen-centered to host-directed diagnostics/therapy

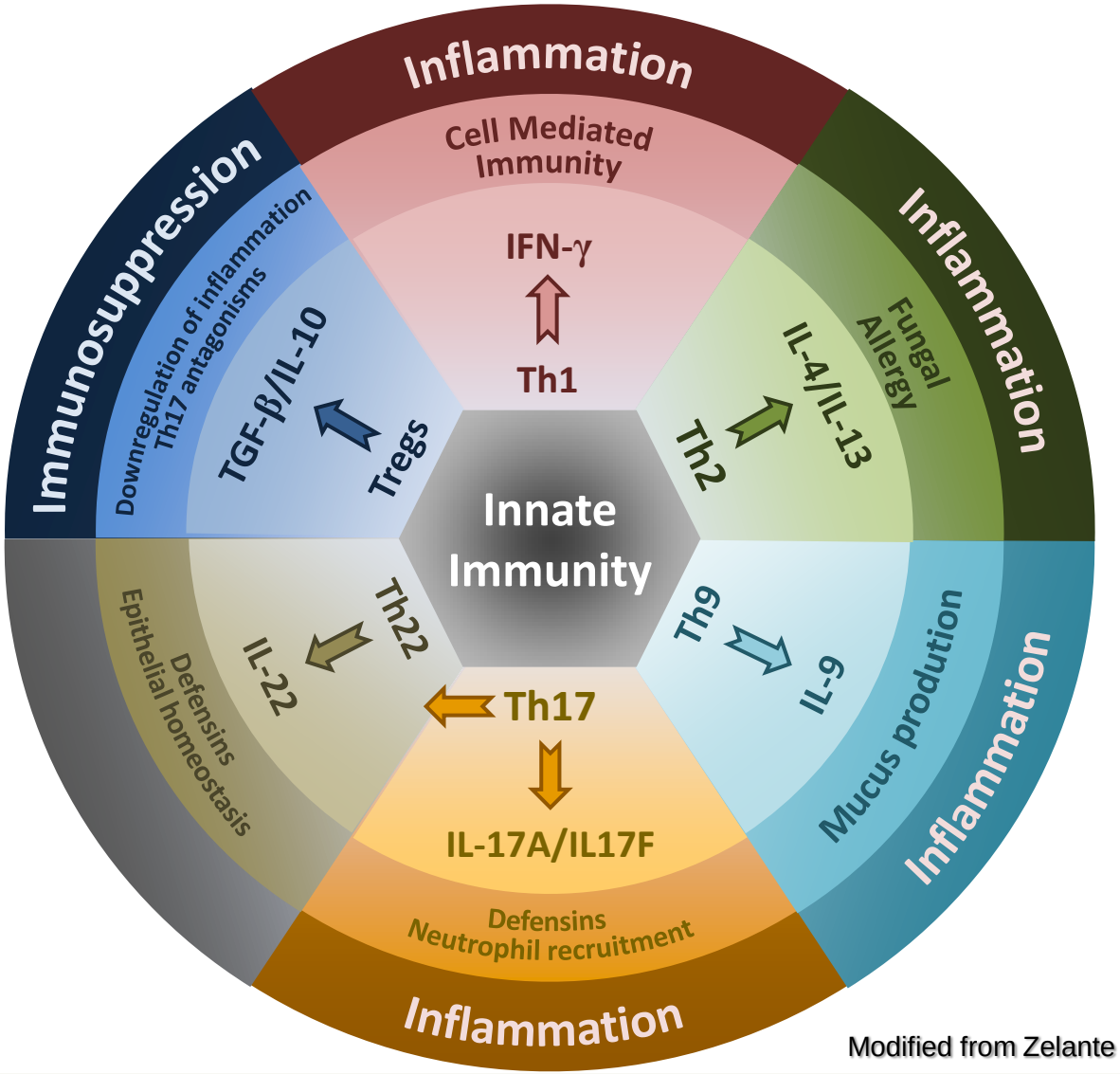
Resistance and tolerance

	COSTS	BENEFITS
Resistance	– Pain, swelling, and disruption of tissue function by inflammation. – Tissue damage by inflammatory mediators (immunopathology) – High energy cost – Risk of autoimmunity, hypersensitivity, allergy	– Reduces pathogen burden – Neutralizes toxins and eliminates dangerous organisms – Prevents parasitism
Tolerance	– Direct damage by pathogen (toxins, digestion, etc) – Energy and resources lost to pathogen	– Reduced tissue damage from immune response – Less selection pressure on pathogens for resistance – Promotes commensalism – Lower energy cost

Resistance typically protects the host at the expense of the parasite

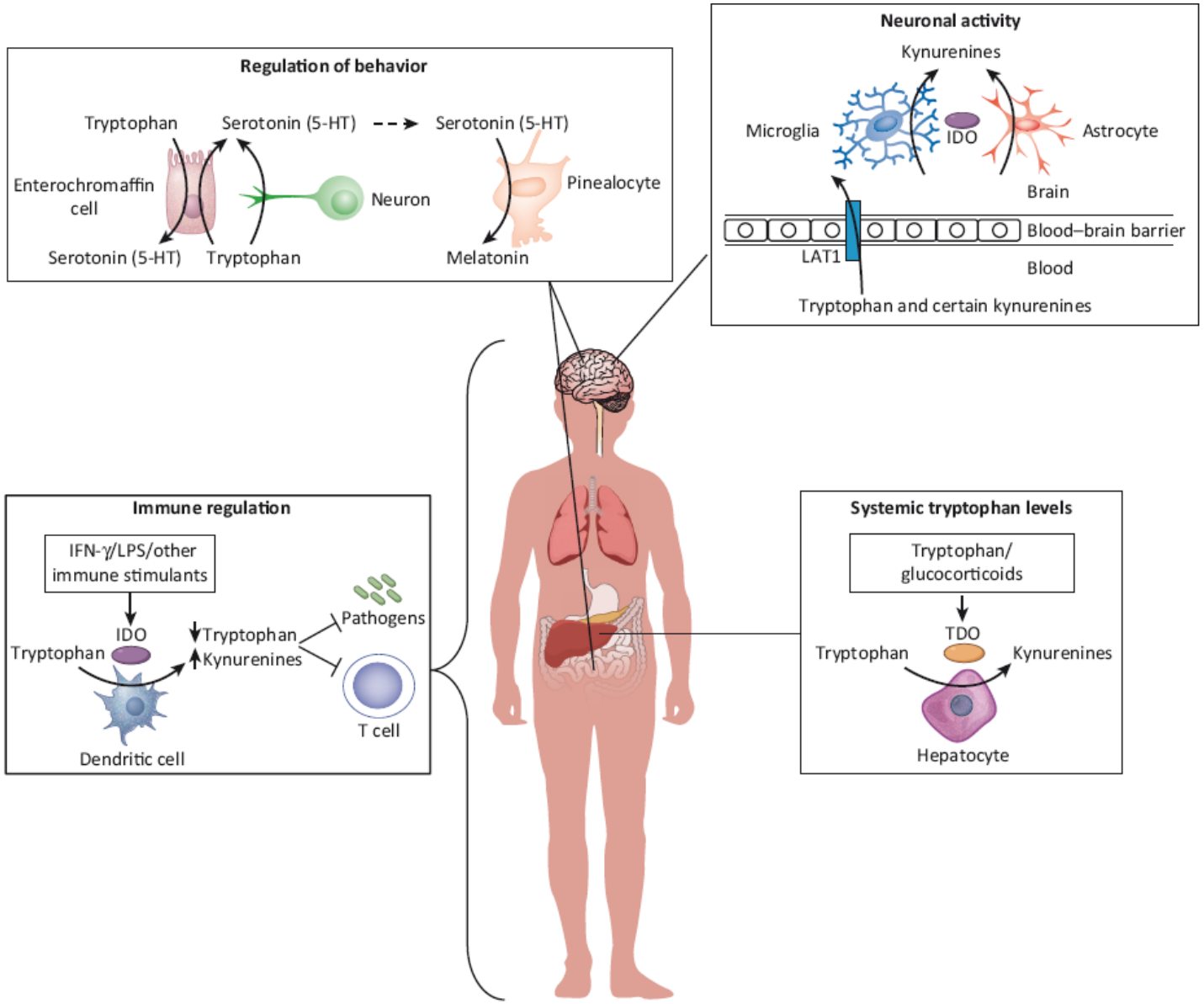
Tolerance reduces harm to the host without having any direct negative effects on the parasite.

Resistance and tolerance by the host



Modified from Zelante et al. 2011

Tryptophan metabolism in health and disease

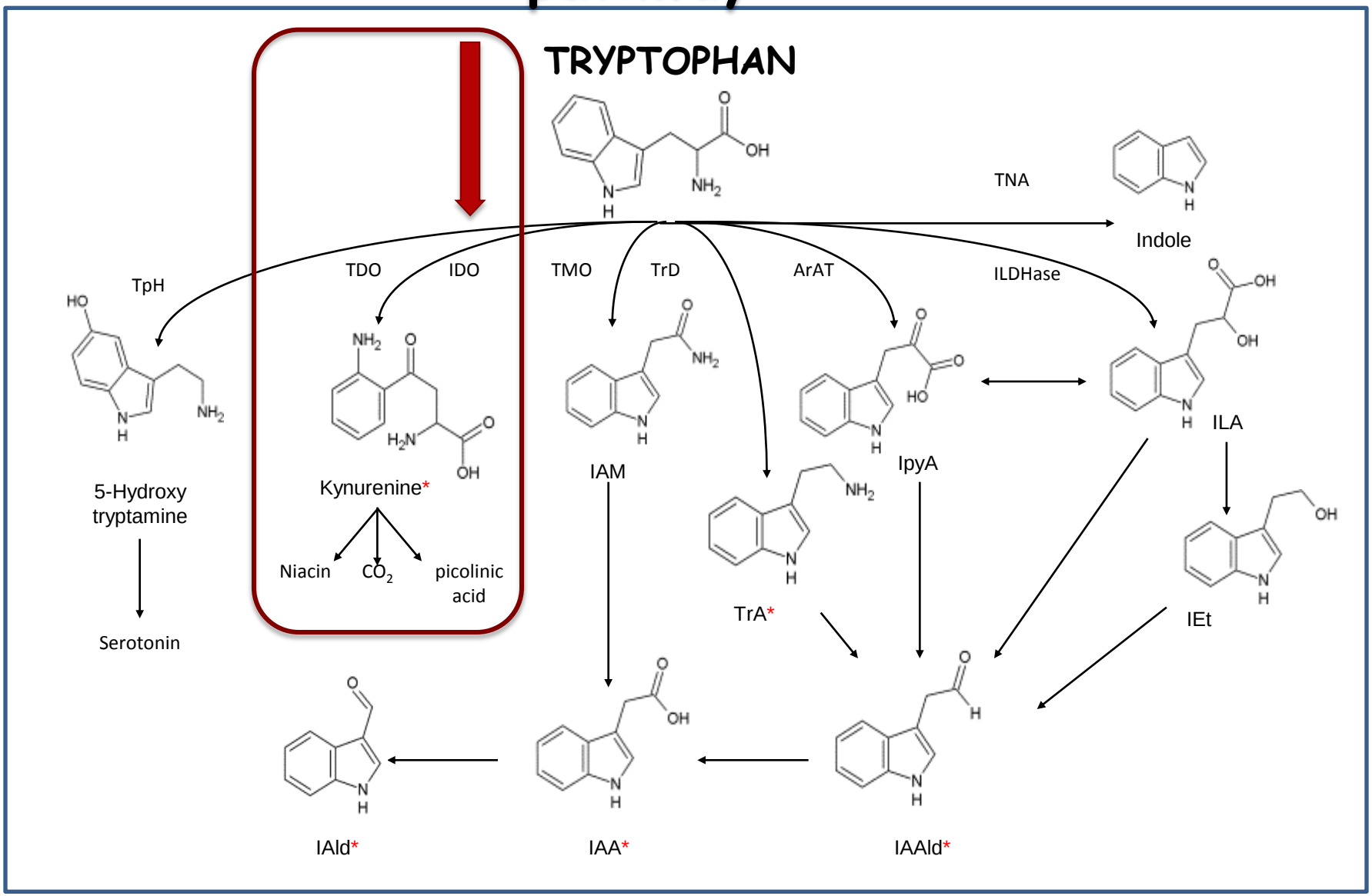


Trends Mol Med. 2013;19:336-44

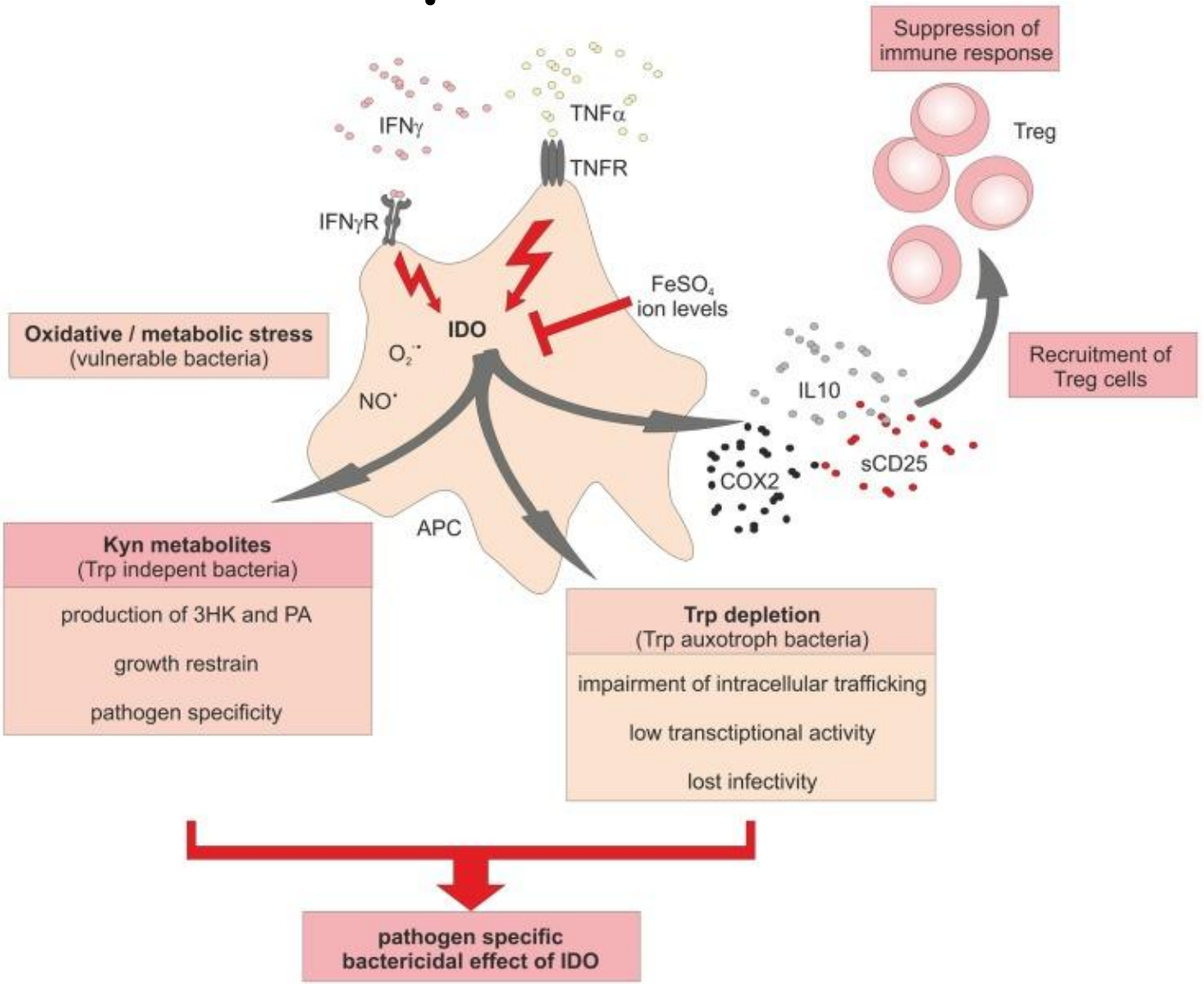
Tolerance by the Host

- Tryptophan
- IDO1
- Kynurenine
- Treg/IL-10

Tryptophan metabolism: IDO/TDO initiate tryptophan metabolism along the kynurenin pathway



Overview of the central role of IDOs in immune responses to infections



Host-directed therapy for a tolerant approach in fungal infections and diseases:

- Kynurenines

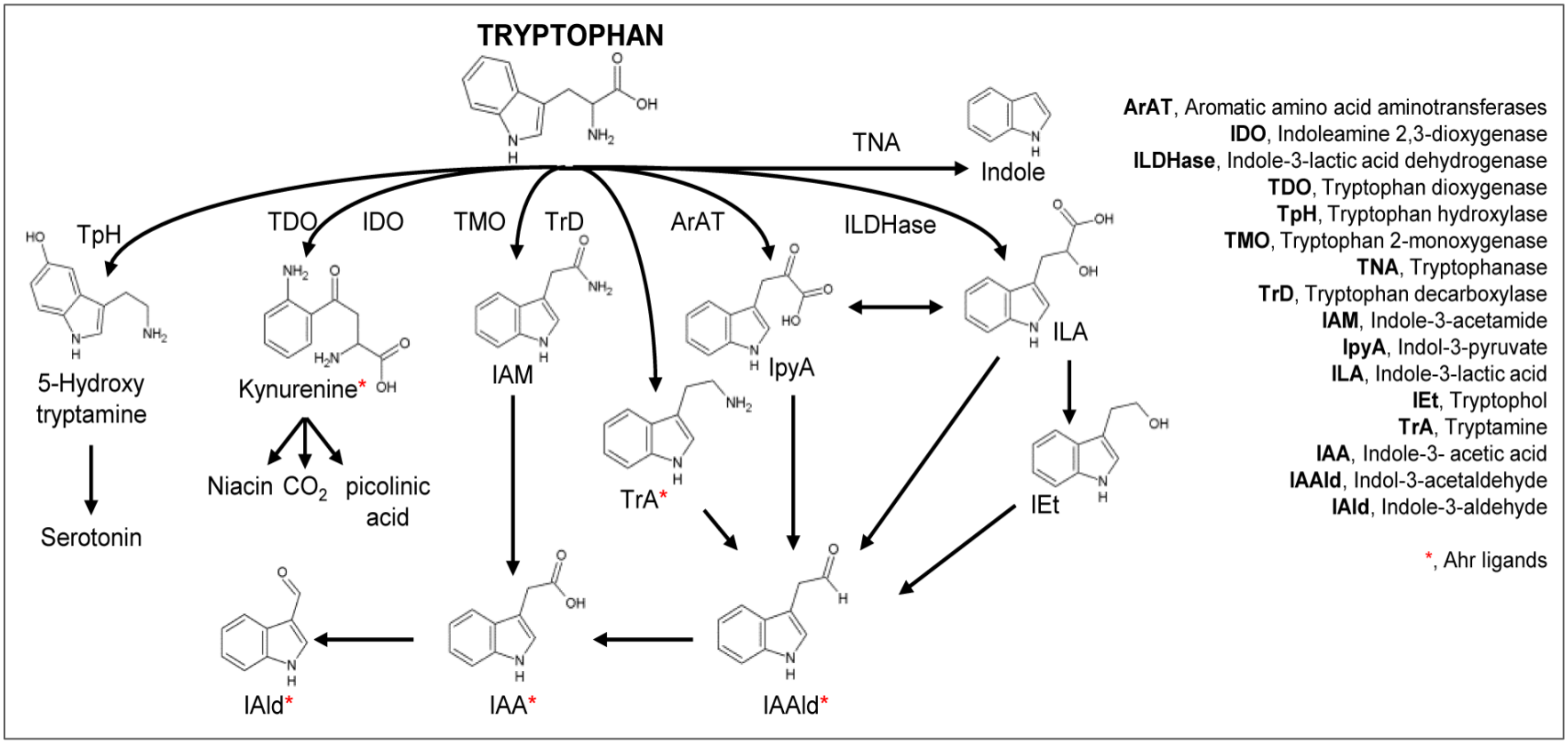
Host-directed diagnostics in fungal infections and diseases:

- Immunogenetics

Resistance and tolenace by the microbiota

- Tryptophan
- Indoles
- AhR
- IL-22

TRYPTOPHAN METABOLIC ENZYMES



Immunity 2013

IDO1-deficient mice

- More availability of tryptophan
- Defective adaptive immunity

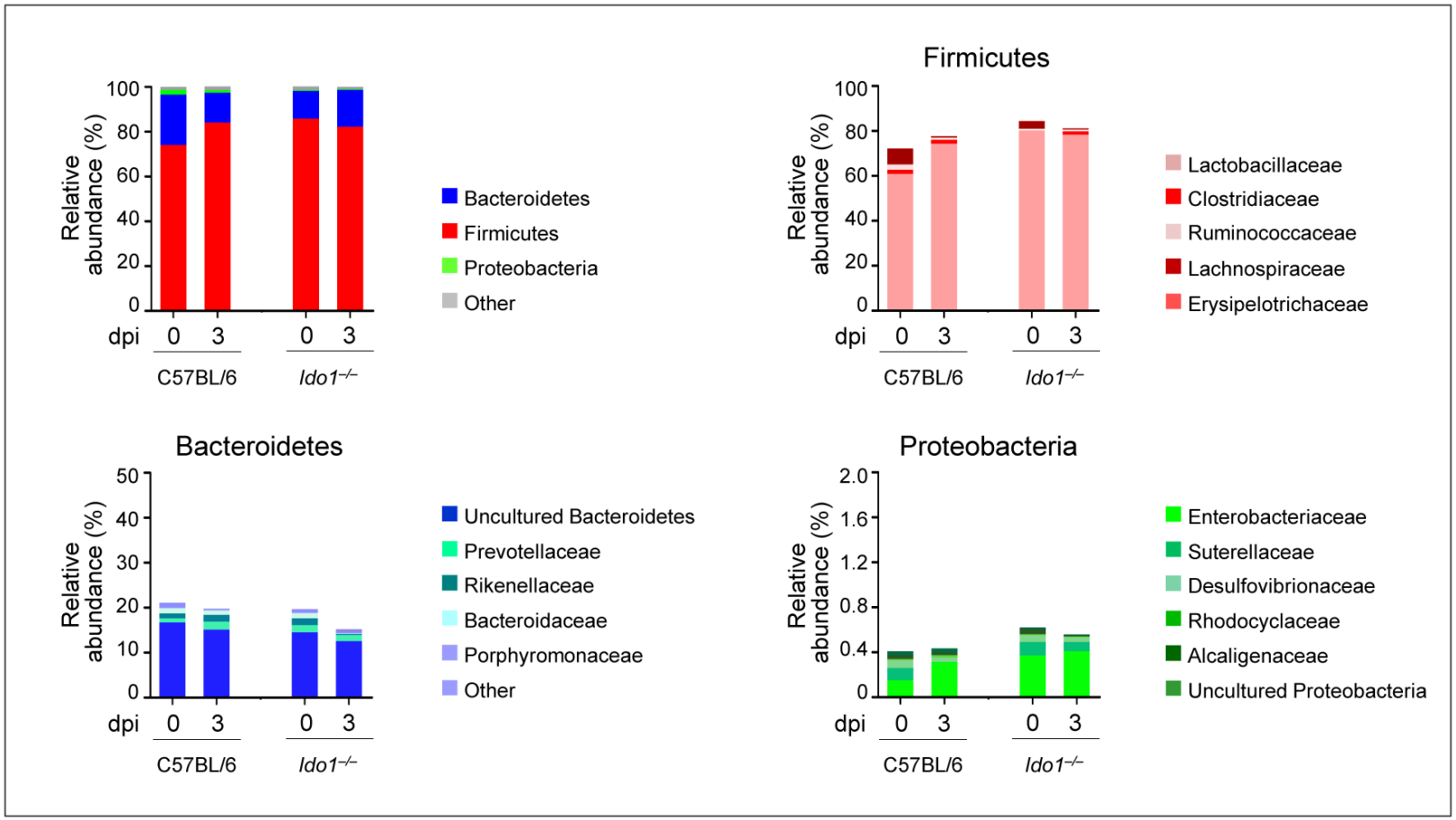
- **Metagenomics**

- **Targeted Metabolomics** through high performance liquid chromatography-high resolution mass spectrometry

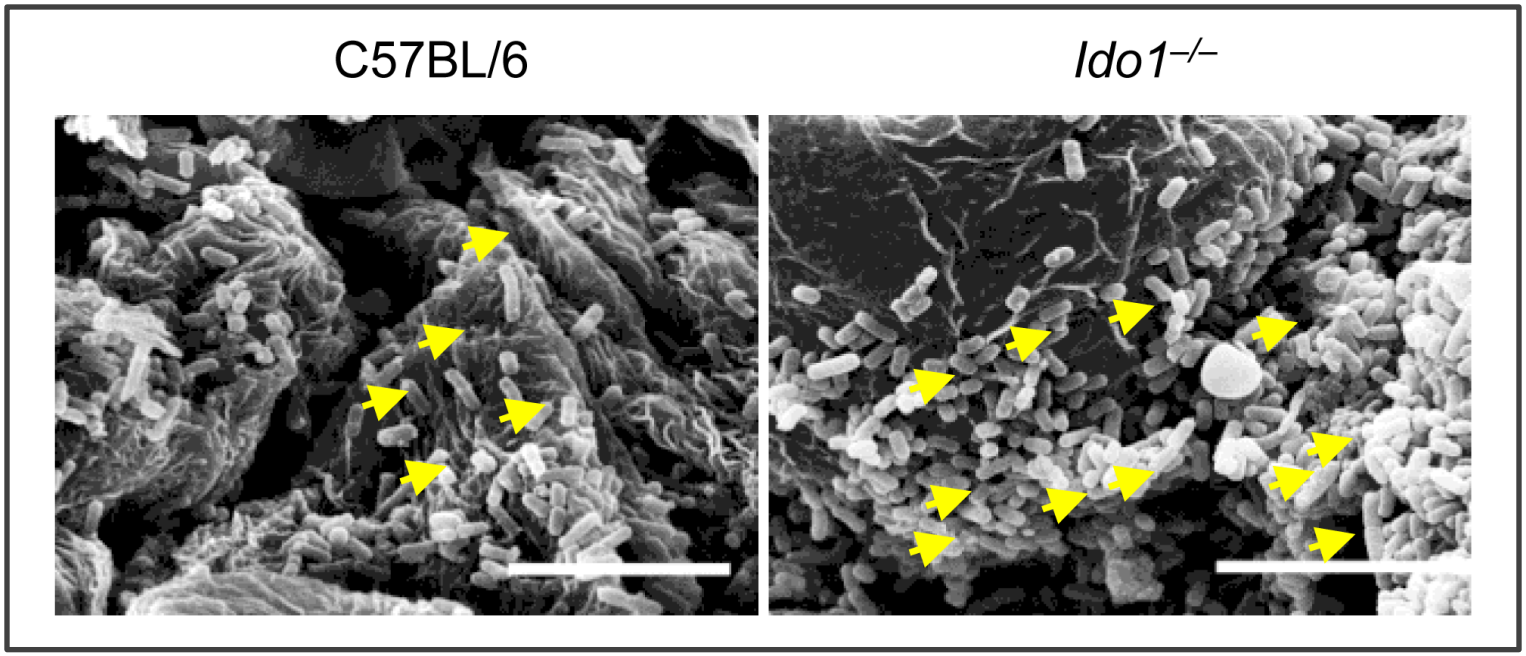
  - stomach/gastric fluids
  - feces
  - vagina/vaginal fluids

  of WT and IDO1-deficient mice with candidiasis

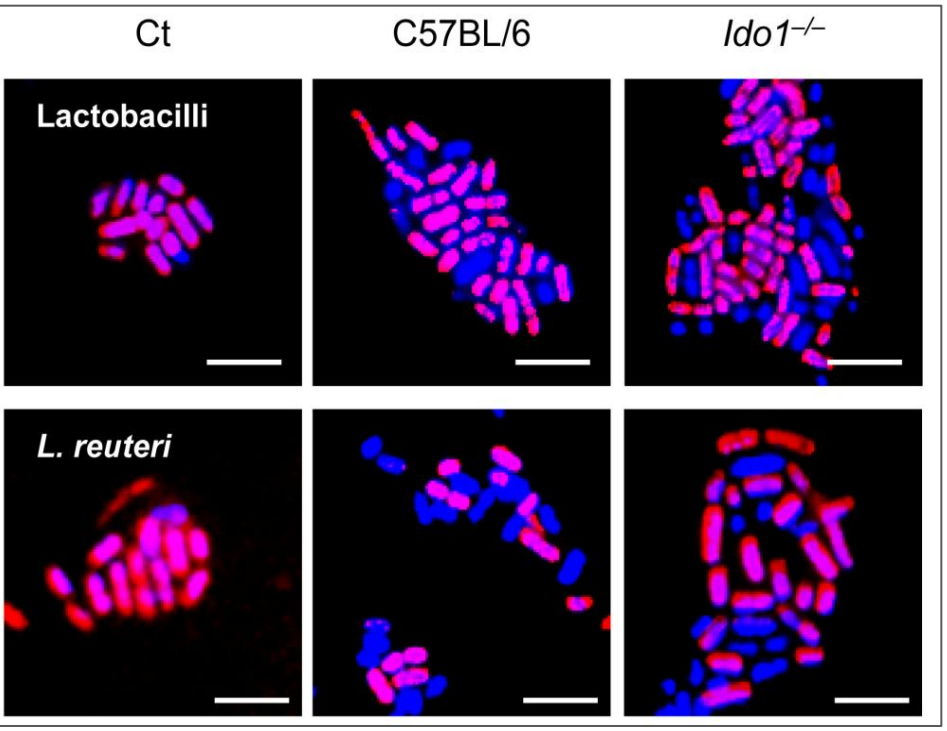
Bacterial 16S rRNA-based analysis of the stomach microbiota of WT and *Ido1*$^{-/-}$ mice

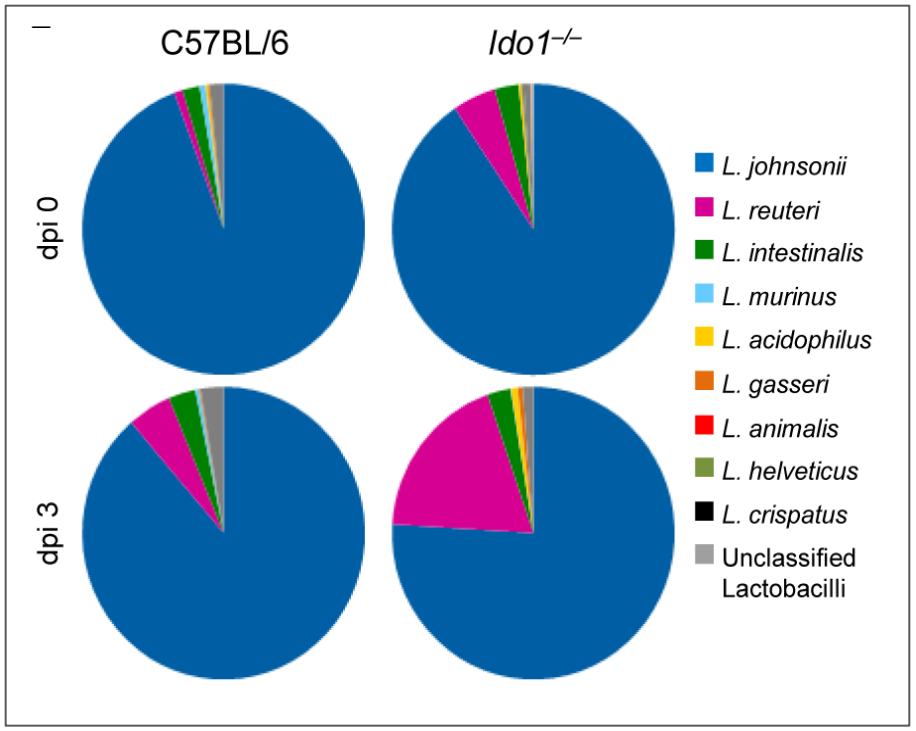


Lactobacilli expand in *Ido1*$^{-/-}$ mice



Bacterial 16S rRNA and FISH analyses of lactobacilli in WT and *Ido1*$^{-/-}$ mice





Proc Natl Acad Sci U S A. 2011 Mar 15;108 Suppl 1:4645-52. doi: 10.1073/pnas.1000099107. Epub 2010 Jun 25.

Host-microbial symbiosis in the vertebrate gastrointestinal tract and the Lactobacillus reuteri paradigm.

Walter J, Britton RA, Roos S.

Department of Food Science and Technology, University of Nebraska, Lincoln, NE 68583-0919, USA. jwalter2@unl.edu

Abstract

Vertebrates engage in symbiotic associations with vast and complex microbial communities that colonize their gastrointestinal tracts. Recent advances have provided mechanistic insight into the important contributions of the gut microbiome to vertebrate biology, but questions remain about the evolutionary processes that have shaped symbiotic interactions in the gut and the consequences that arise for both the microbes and the host. Here we discuss the biological principles that underlie microbial symbiosis in the vertebrate gut and the potential of the development of mutualism. We then review phylogenetic and experimental studies on the vertebrate symbiont Lactobacillus reuteri that have provided novel insight into the ecological and evolutionary strategy of a gut microbe and its relationship with the host. We argue that a mechanistic understanding of the microbial symbiosis in the vertebrate gut and its evolution will be important to determine how this relationship can go awry, and it may reveal possibilities by which the gut microbiome can be manipulated to support health.

PMID: 20615995 [PubMed - indexed for MEDLINE] PMCID: PMC3063604

In vivo expression technology has shown the lactobacilli may undergo gut-specific gene expression to adapt

ISME J. 2012 May;6(5):927-38. doi: 10.1038/ismej.2011.161. Epub 2011 Nov 17.

Resource partitioning in relation to cohabitation of Lactobacillus species in the mouse forestomach.

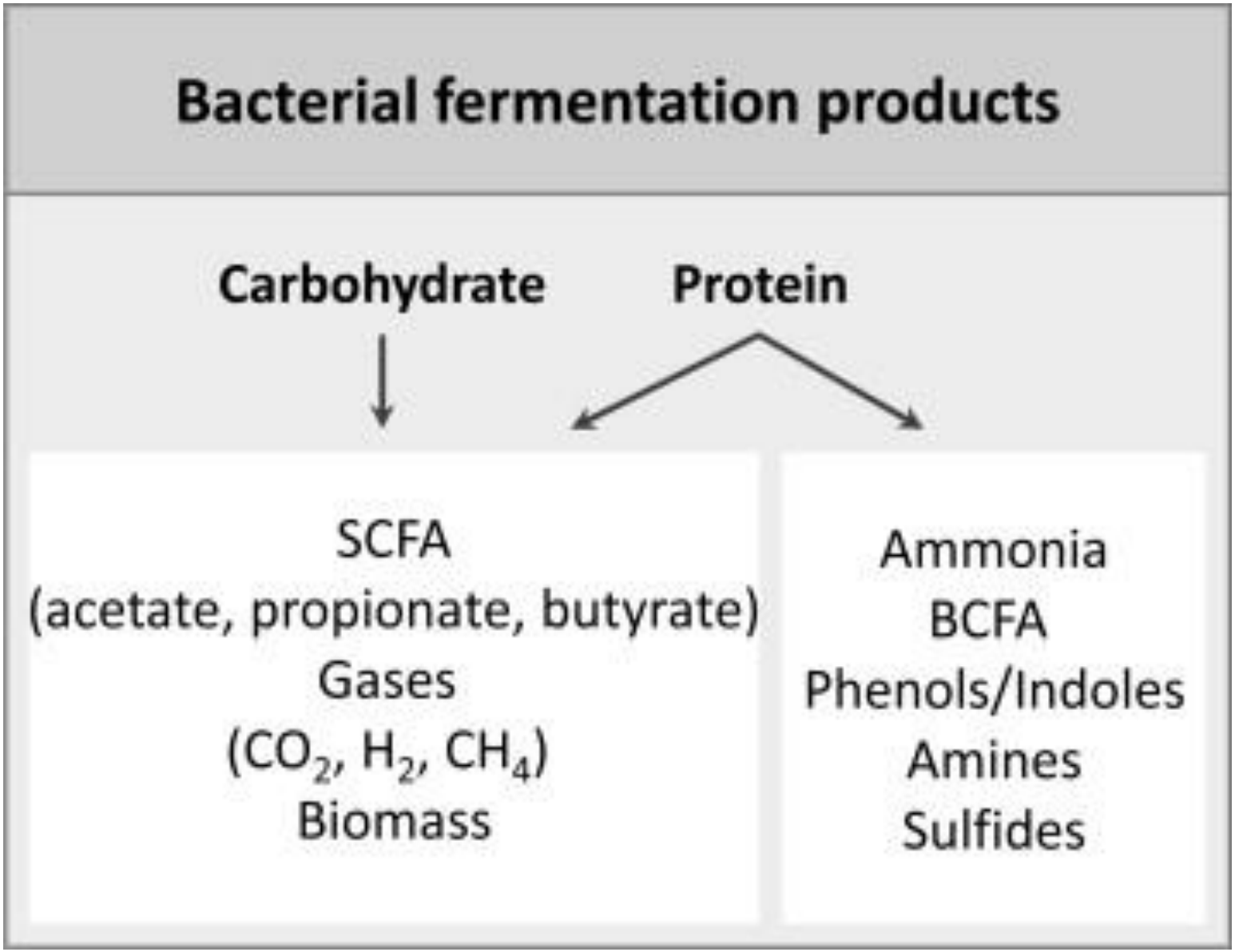
Tannock GW, Wilson CM, Loach D, Cook GM, Eason J, O'Toole PW, Holtrop G, Lawley B.

Department of Microbiology and Immunology, University of Otago, Dunedin, New Zealand. gerald.tannock@stonebow.otago.ac.nz

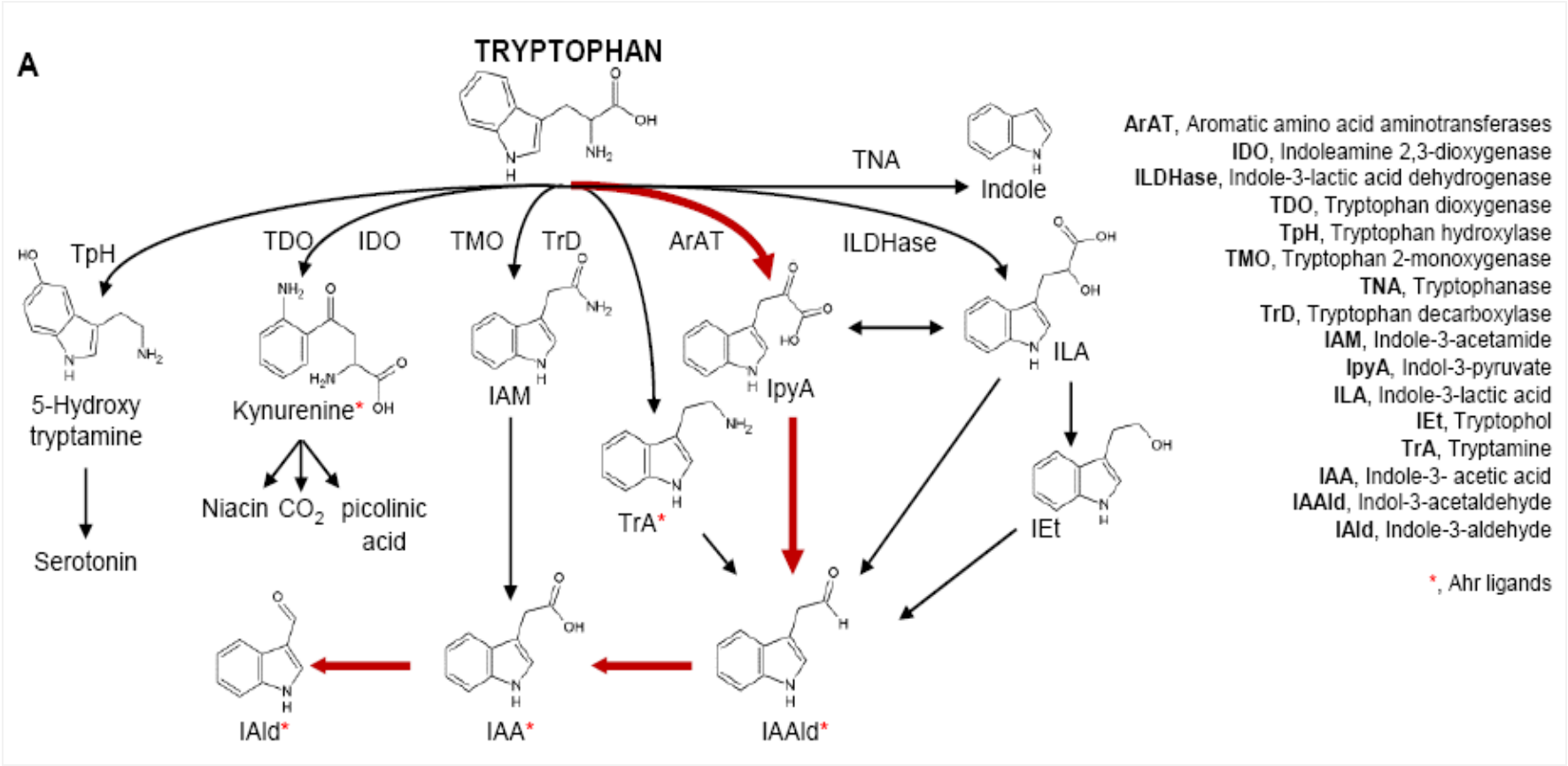
Abstract

Phylogenetic analysis of gut communities of vertebrates is advanced, but the relationships, especially at the trophic level, between commensals that share gut habitats of monogastric animals have not been investigated to any extent. Lactobacillus reuteri strain 100-23 and Lactobacillus johnsonii strain 100-33 cohabit in the forestomach of mice. According to the niche exclusion principle, this should not be possible because both strains can utilise the two main fermentable carbohydrates present in the stomach digesta: glucose and maltose. We show, based on gene transcription analysis, in vitro physiological assays, and in vivo experiments that the two strains can co-exist in the forestomach habitat because 100-23 grows more rapidly using maltose, whereas 100-33 preferentially utilises glucose. Mutation of the maltose phosphorylase gene (malA) of strain 100-23 prevented its growth on maltose-containing culture medium, and resulted in the numerical dominance of 100-33 in the forestomach. The fundamental niche of L. reuteri 100-23 in the mouse forestomach can be defined in terms of 'glucose and maltose trophism'. However, its realised niche when L. johnsonii 100-33 is present is 'maltose trophism'. Hence, nutritional adaptations provide niche differentiation that assists cohabitation by the two strains through resource partitioning in the mouse forestomach. This real life, trophic phenomenon conforms to a mathematical model based on in vitro bacterial doubling times, in vitro transport rates, and concentrations of maltose and glucose in mouse stomach digesta.

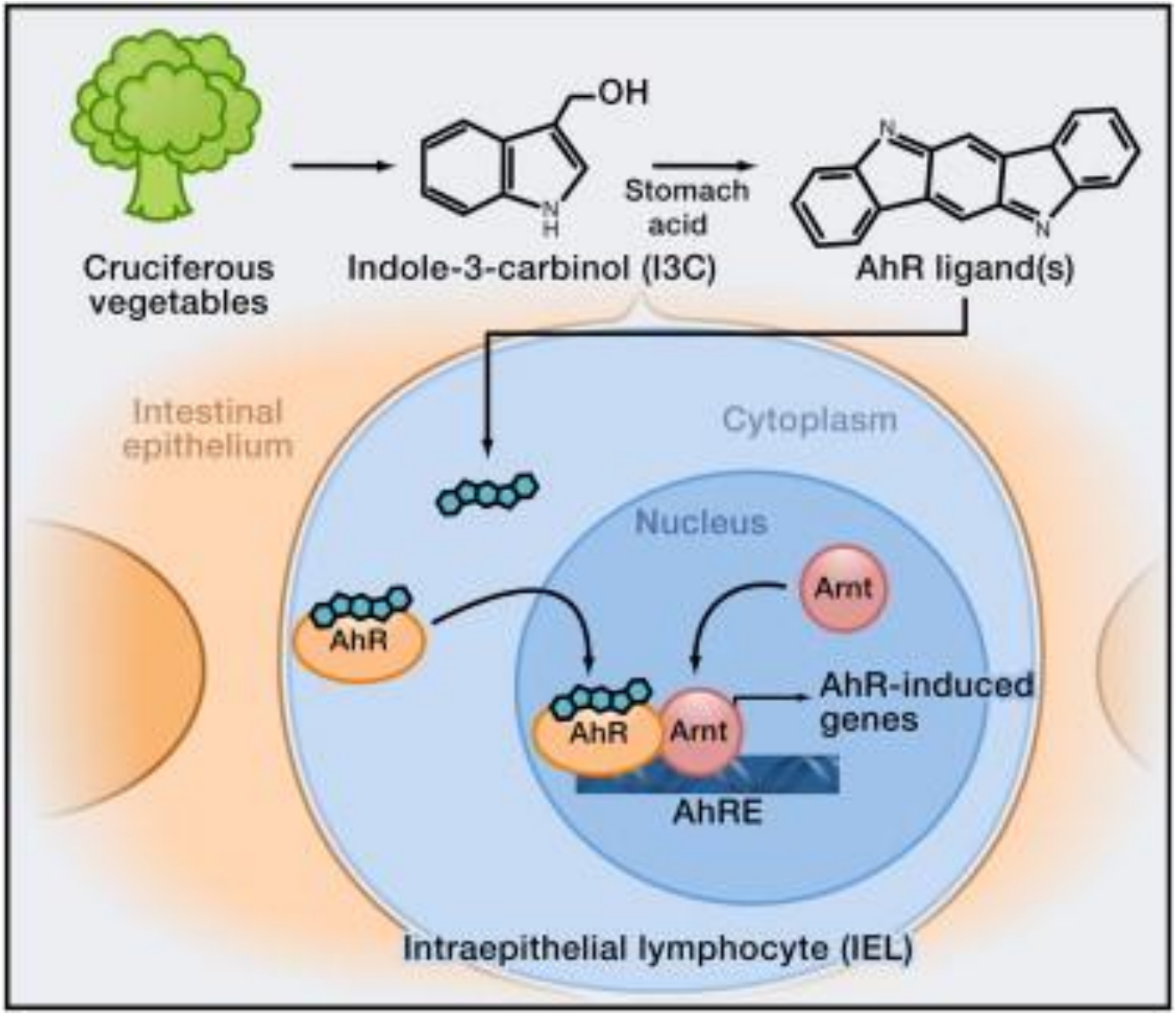
PMID: 22094343 [PubMed - indexed for MEDLINE] PMCID: PMC3329185 Free PMC Article


Bacterial fermentation products
Carbohydrate
Protein
SCFA
(acetate, propionate, butyrate)
Gases
(CO_2, H_2, CH_4)
Biomass
Ammonia
BCFA
Phenols/Indoles
Amines
Sulfides

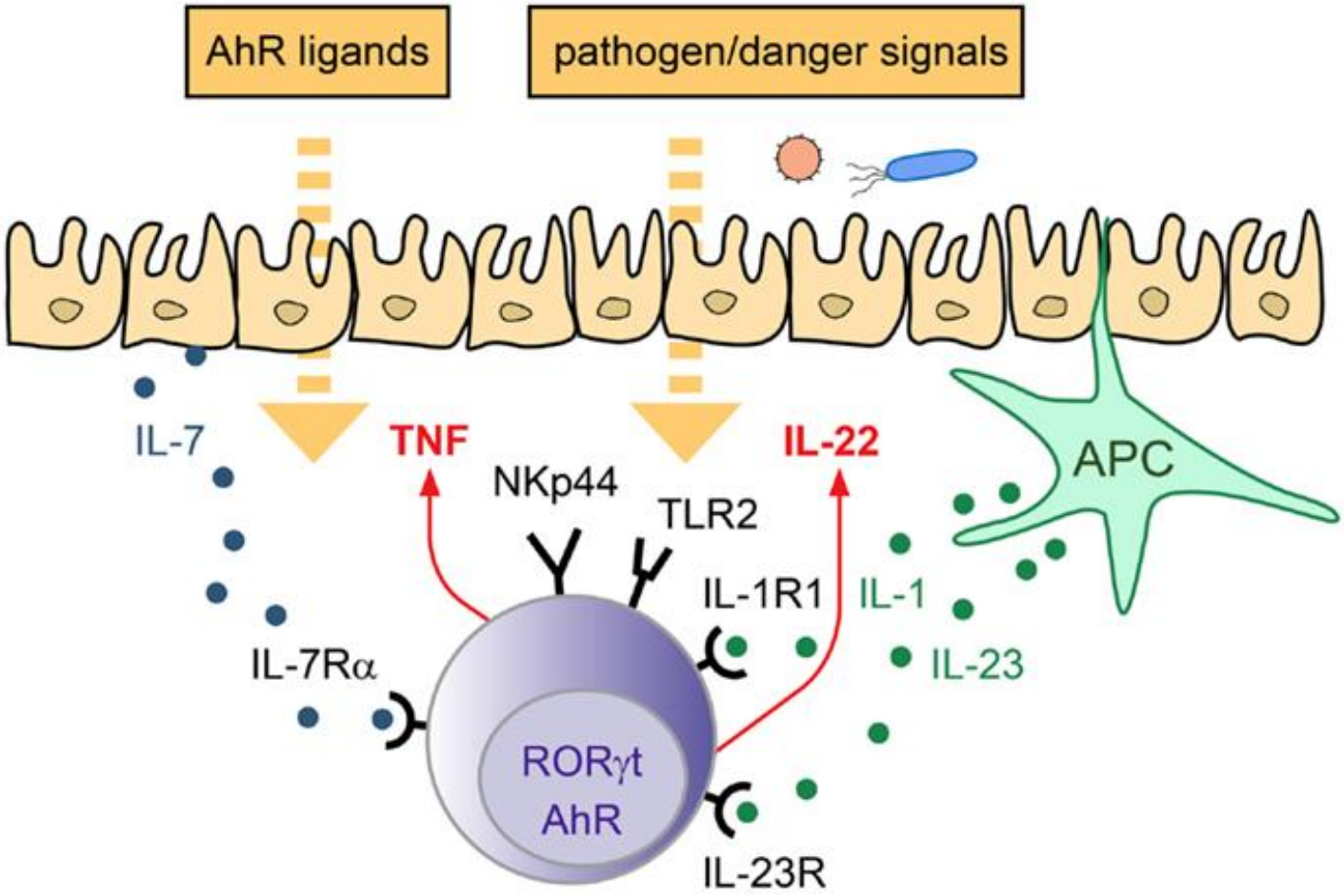
L. reuteri utilizes ArAT to degrade tryptophan



Linking diet to epithelium homeostasis via the aryl hydrocarbon receptor



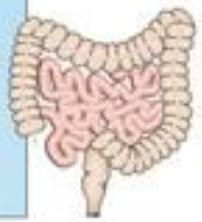
AhR induces IL-22 by ILC3



IL-22's activities

Epidermal keratinocytes
- Increased antibacterial defence
- Retarded differentiation and cornification
- Induced production of granulocyte-attracting chemokines
- Elevated migration and tissue remodelling
- Enhanced STAT3 and IL-20 expression

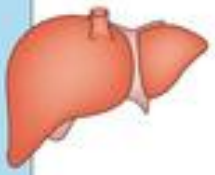
Intestinal epithelial cells
- Increased antibacterial defence
- Elevated mucus production
- Enhanced protection of mucus-producing cells and stem cells against damage



Respiratory epithelial cells
- Increased antibacterial defence
- Elevated mucus production
- Enhanced proliferation
- Raised production of granulocyte-attracting chemokines

IL-22

Hepatocytes
- Increased acute-phase protein production
- Increased protection against damage
- Elevated liver progenitor cell proliferation



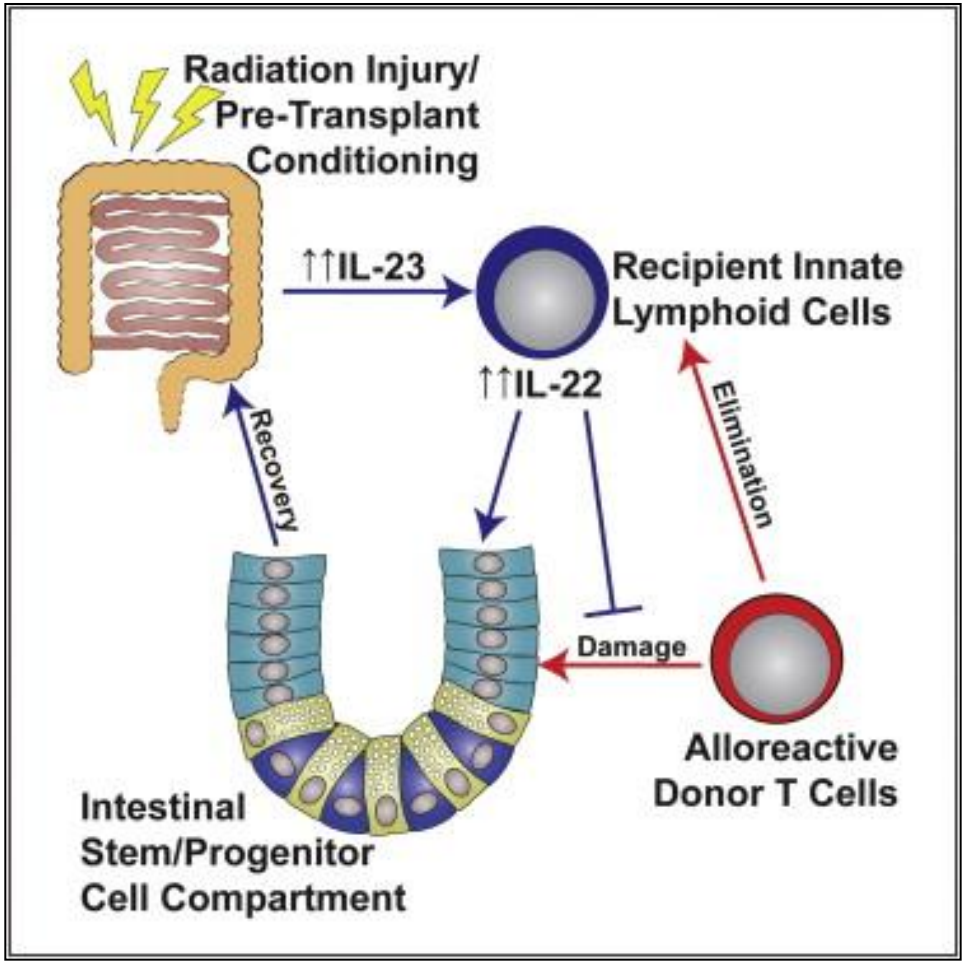
Synovial fibroblasts
- Elevated RANKL expression
- Increased production of monocyte-attracting chemokines

Pancreatic cells
- Increased protection against damage
- Inhibition of autophagy
- Enhanced islet cell proliferation

Nature Reviews | Drug Discovery

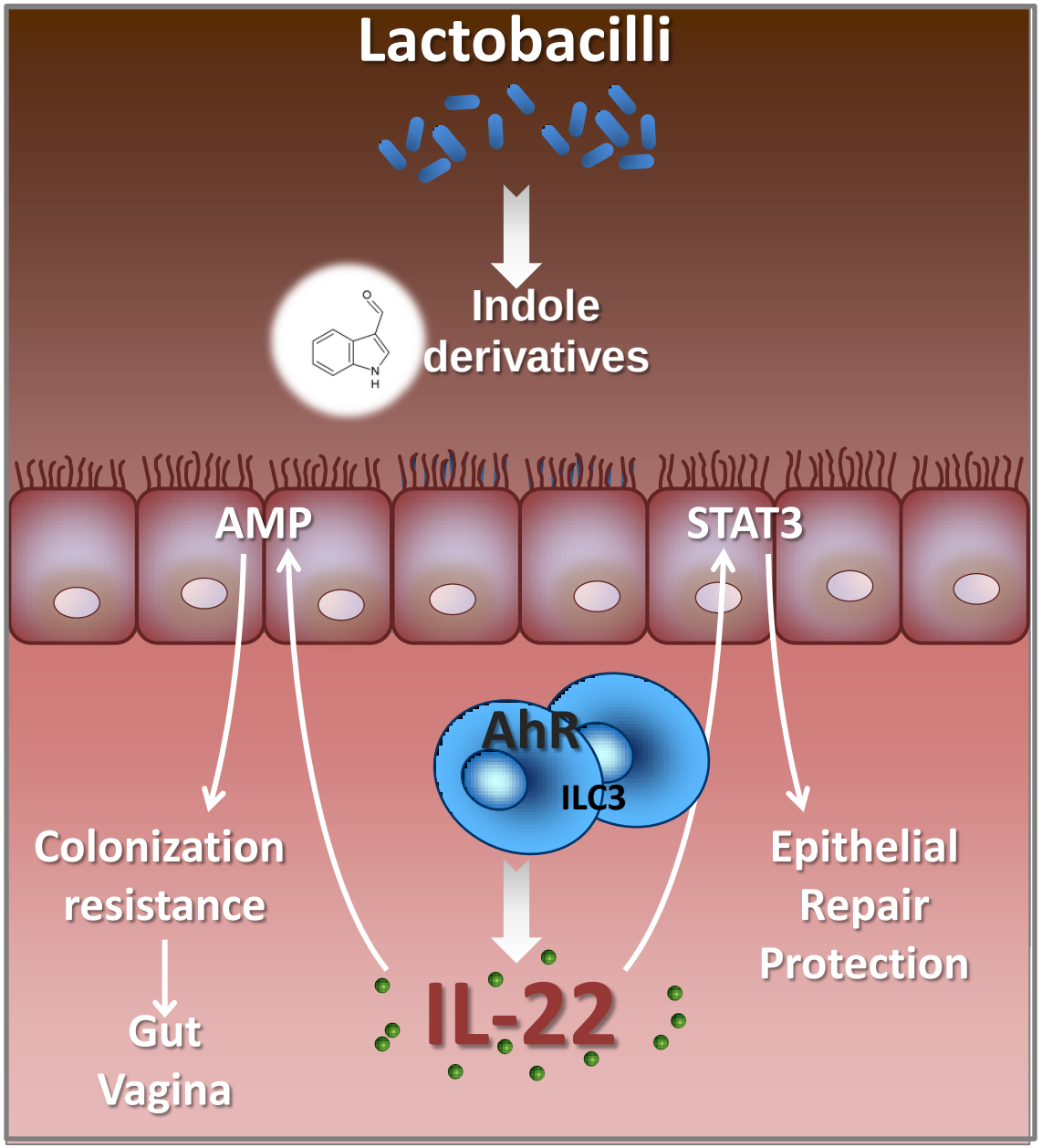
Interleukin-22 Protects Intestinal Stem Cells from Immune-Mediated Tissue Damage and Regulates Sensitivity to Graft versus Host Disease

Alan M. Hanash, Jarrod A. Dudakov, Guoqiang Hua,Margaret H. O'Connor, Lauren F. Young, Natalie V. Singer, Mallory L. West, Robert R. Jenq, Amanda M. Holland, Lucy W. Kappel, Arnab Ghosh, Jennifer J. Tsai, Uttam K. Rao, Nury L. Yim, Odette M. Smith, Enrico Velardi, Elena B. Hawryluk, George F. Murphy, Chen Liu, Lynette A. Fouser, Richard Kolesnick, Bruce R. Blazar, Marcel R.M. van den Brink

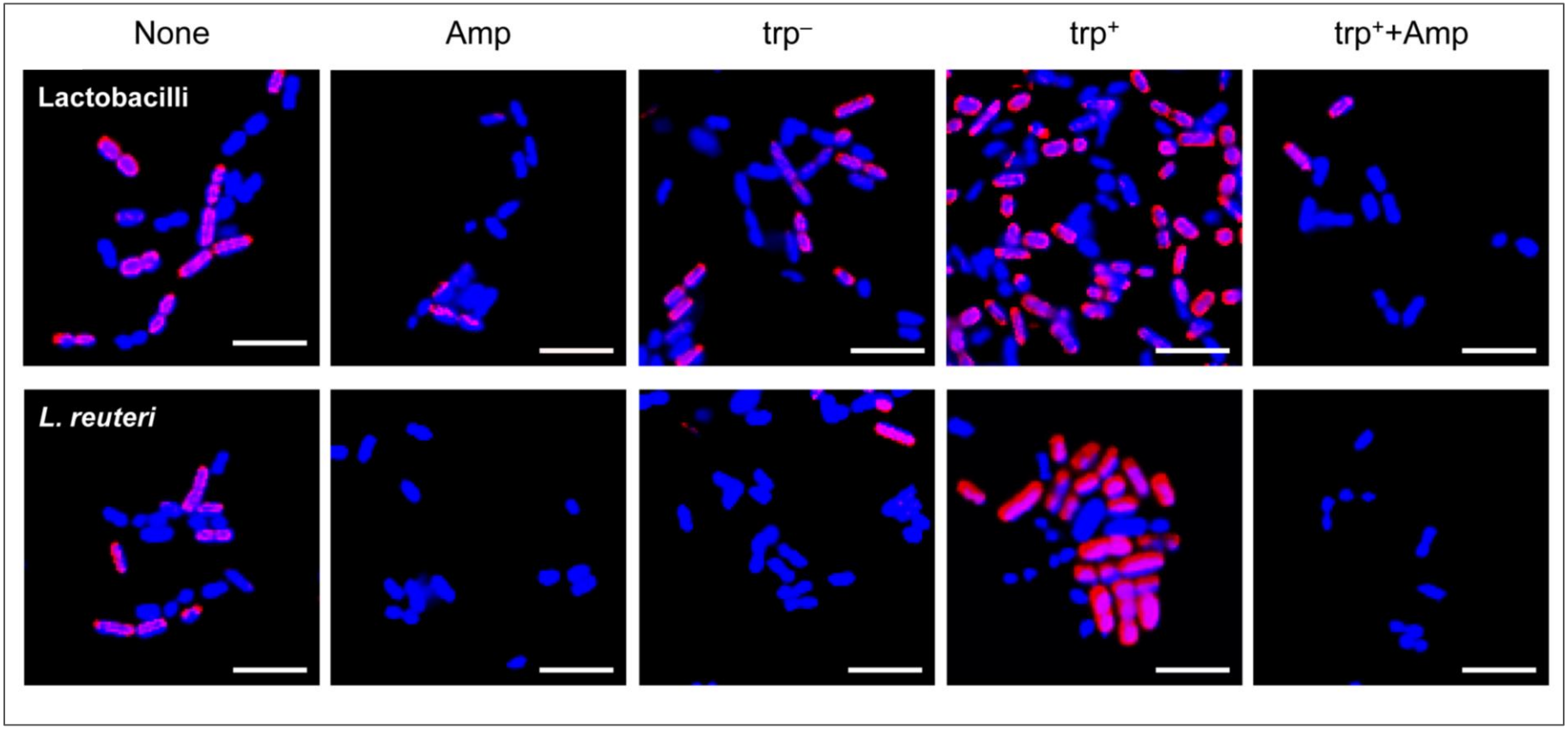


Immunity. 2012;37:339-50

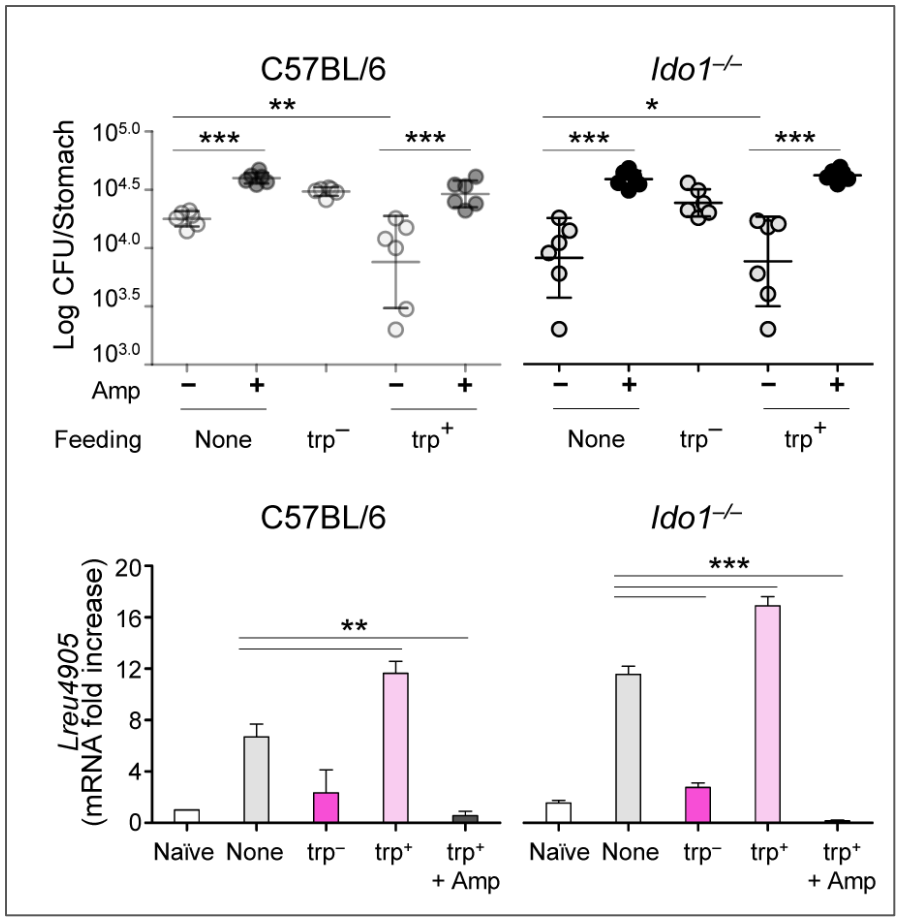
Lactobacilli provide resistance and tolerance

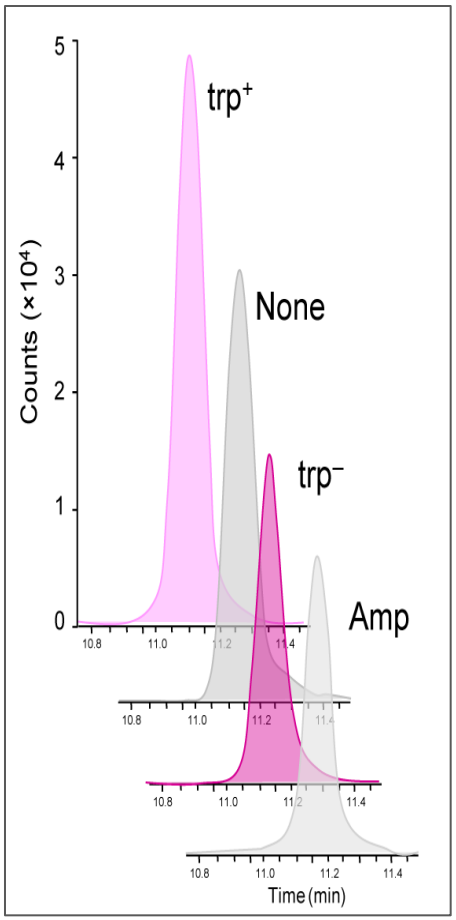


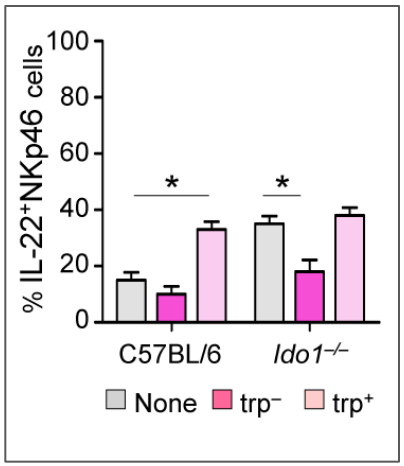
Dietary tryptophan affects *L. reuteri* expansion in the stomach

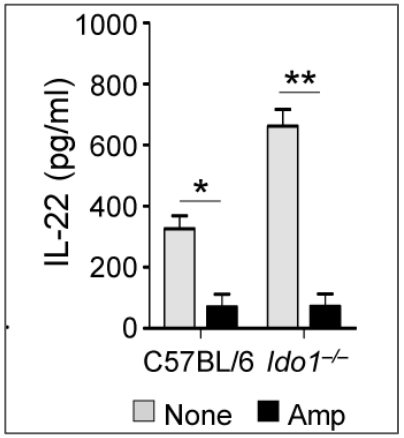


Dietary tryptophan affects levels of IL-22 in vivo

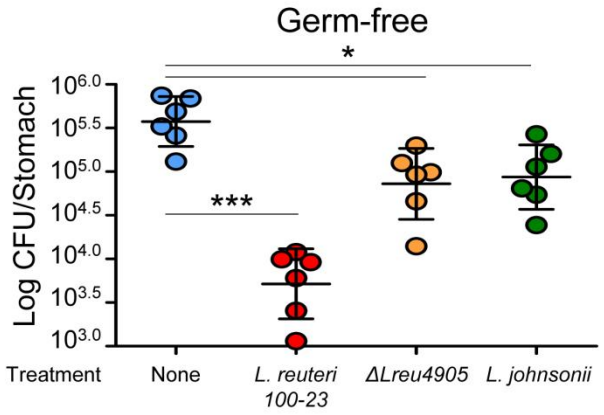


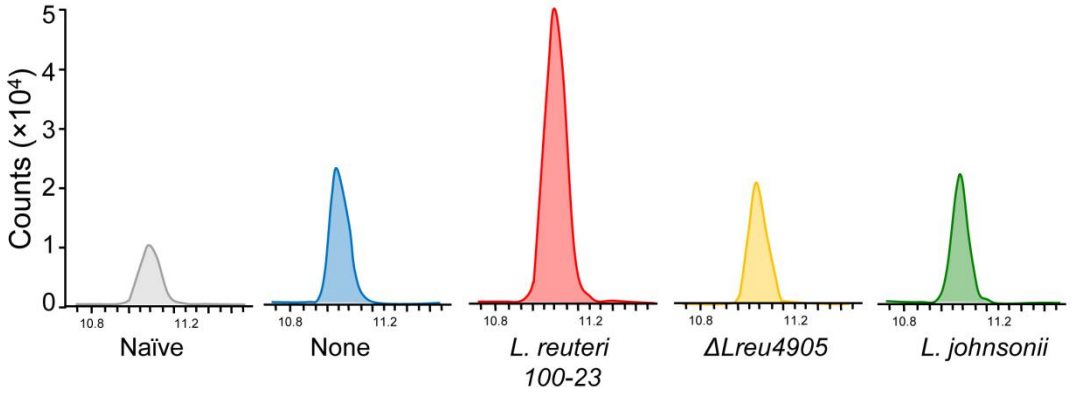


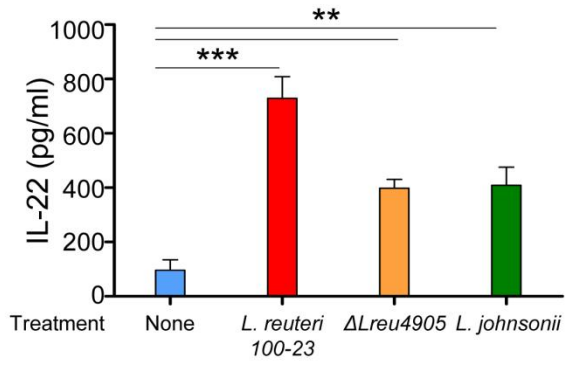


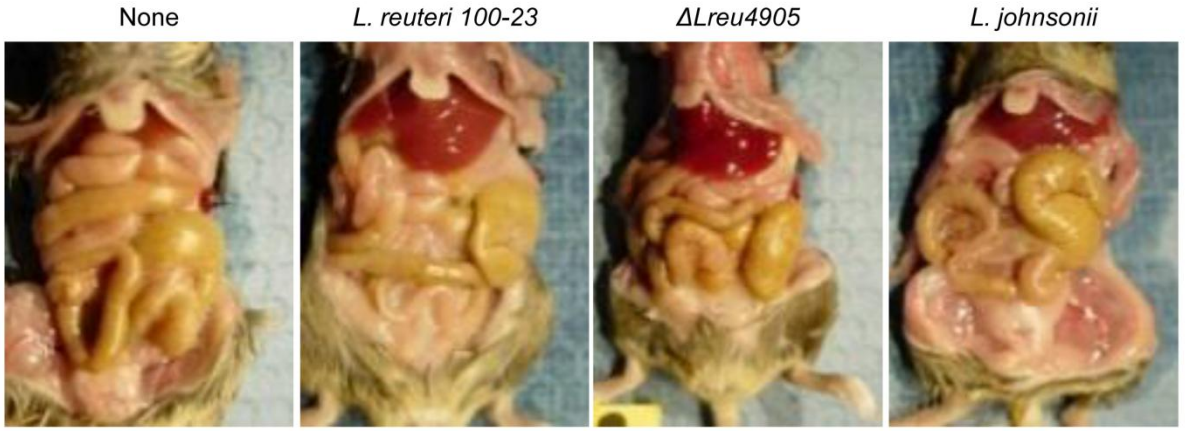


Probiotic lactobacilli exert species-specific effects in candidiasis



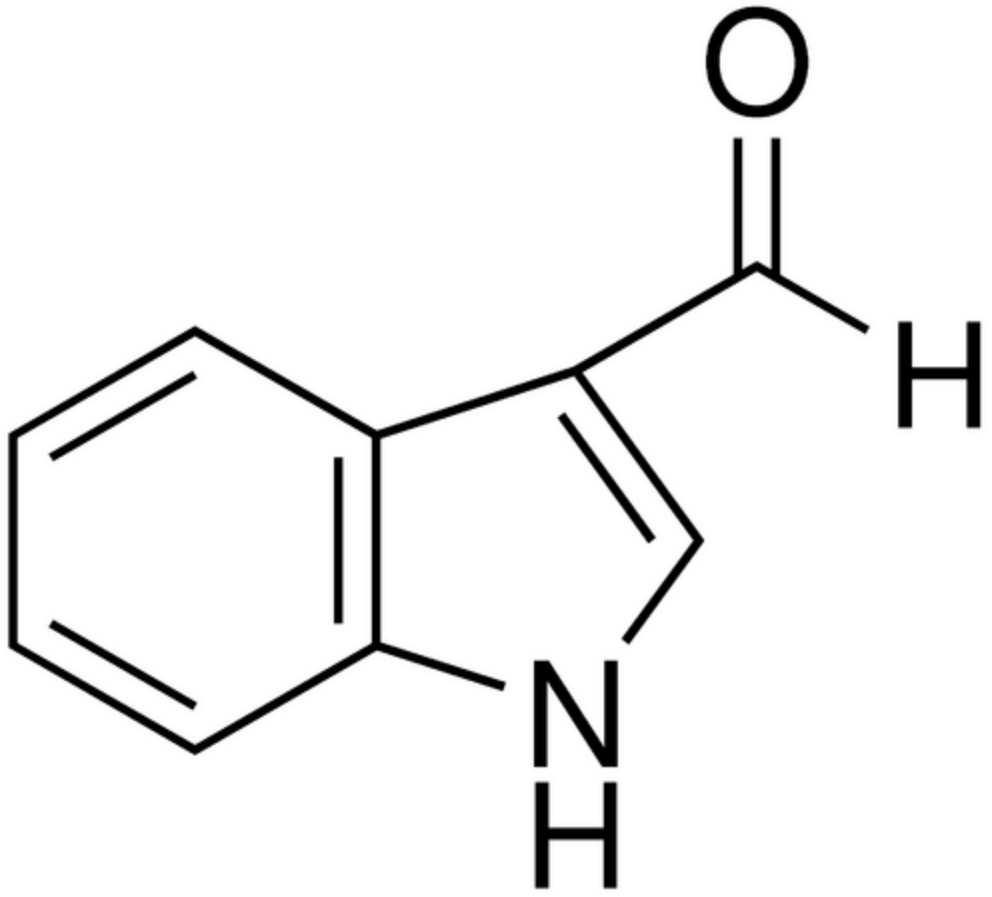




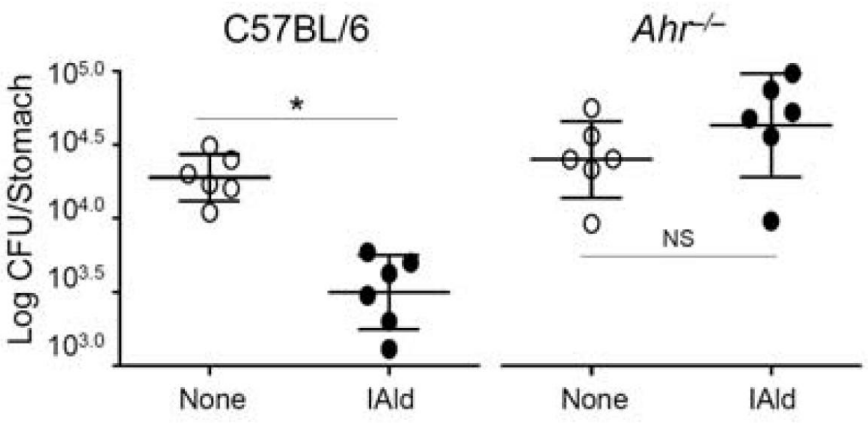


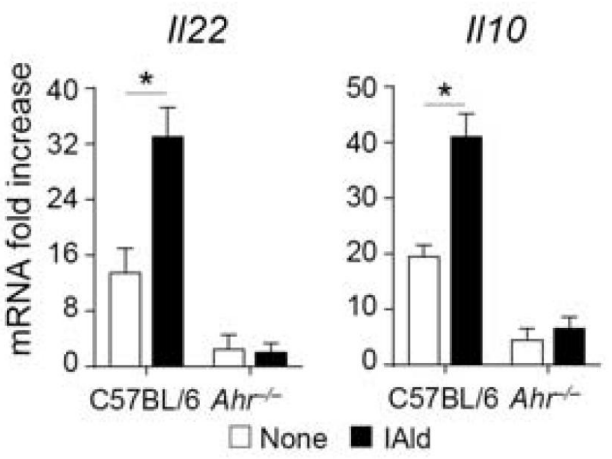
The Metabiotic era

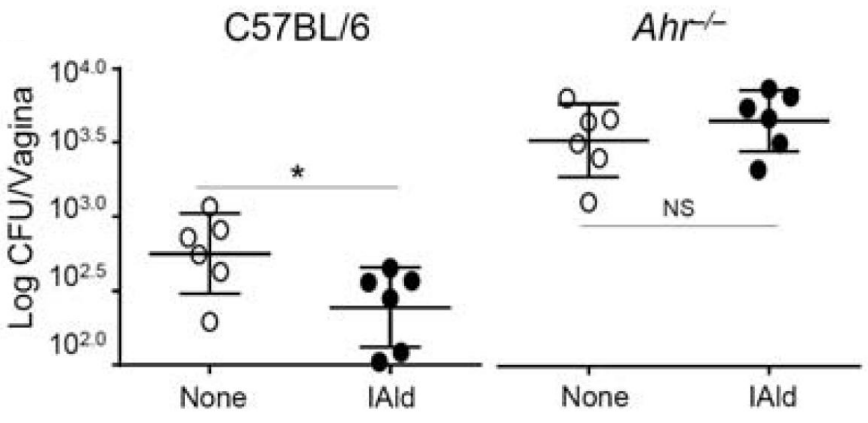
Indole-3-Aldehyde, IAld

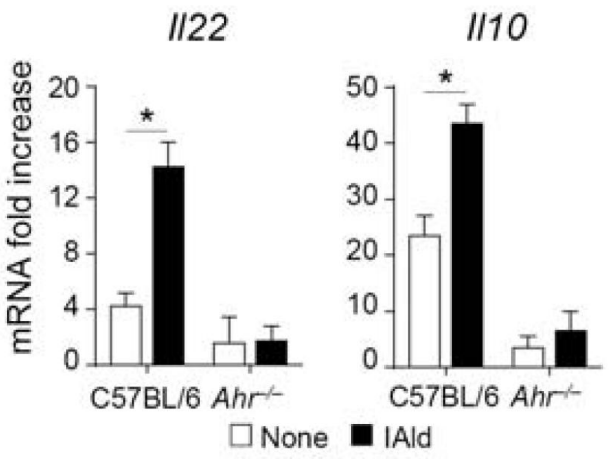


IAld protects from candidiasis

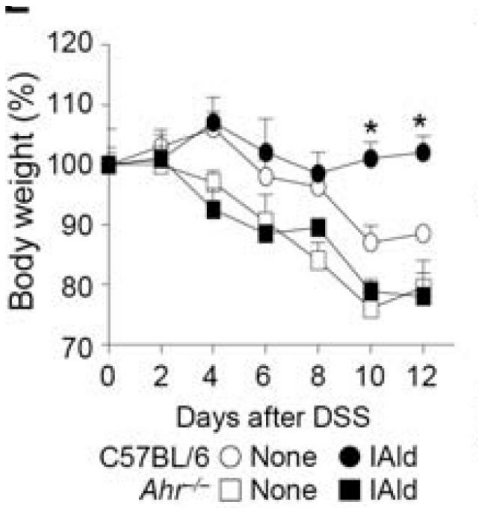


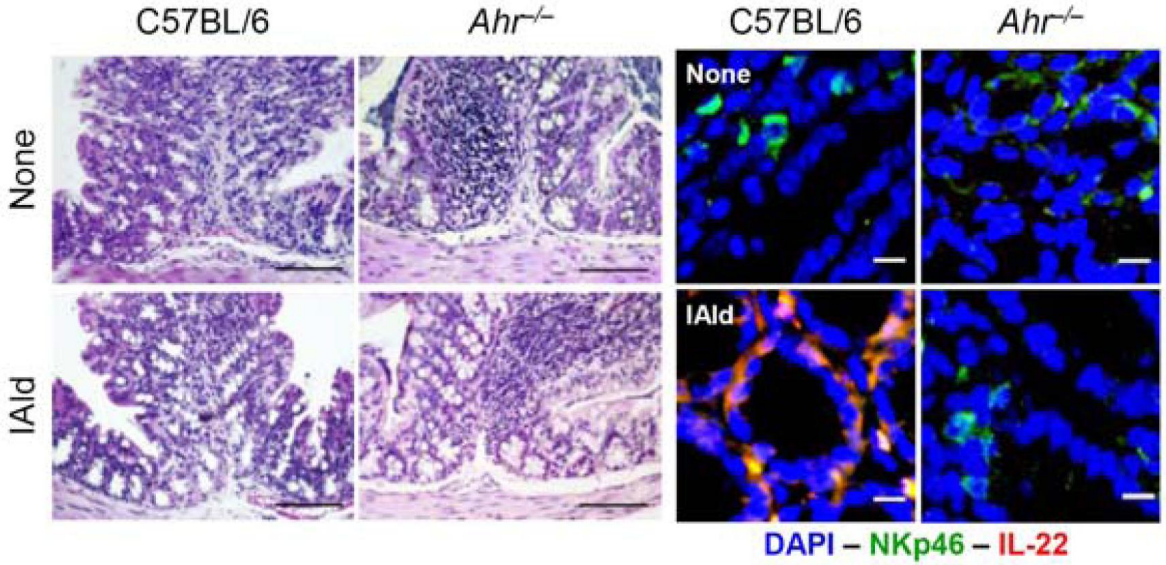






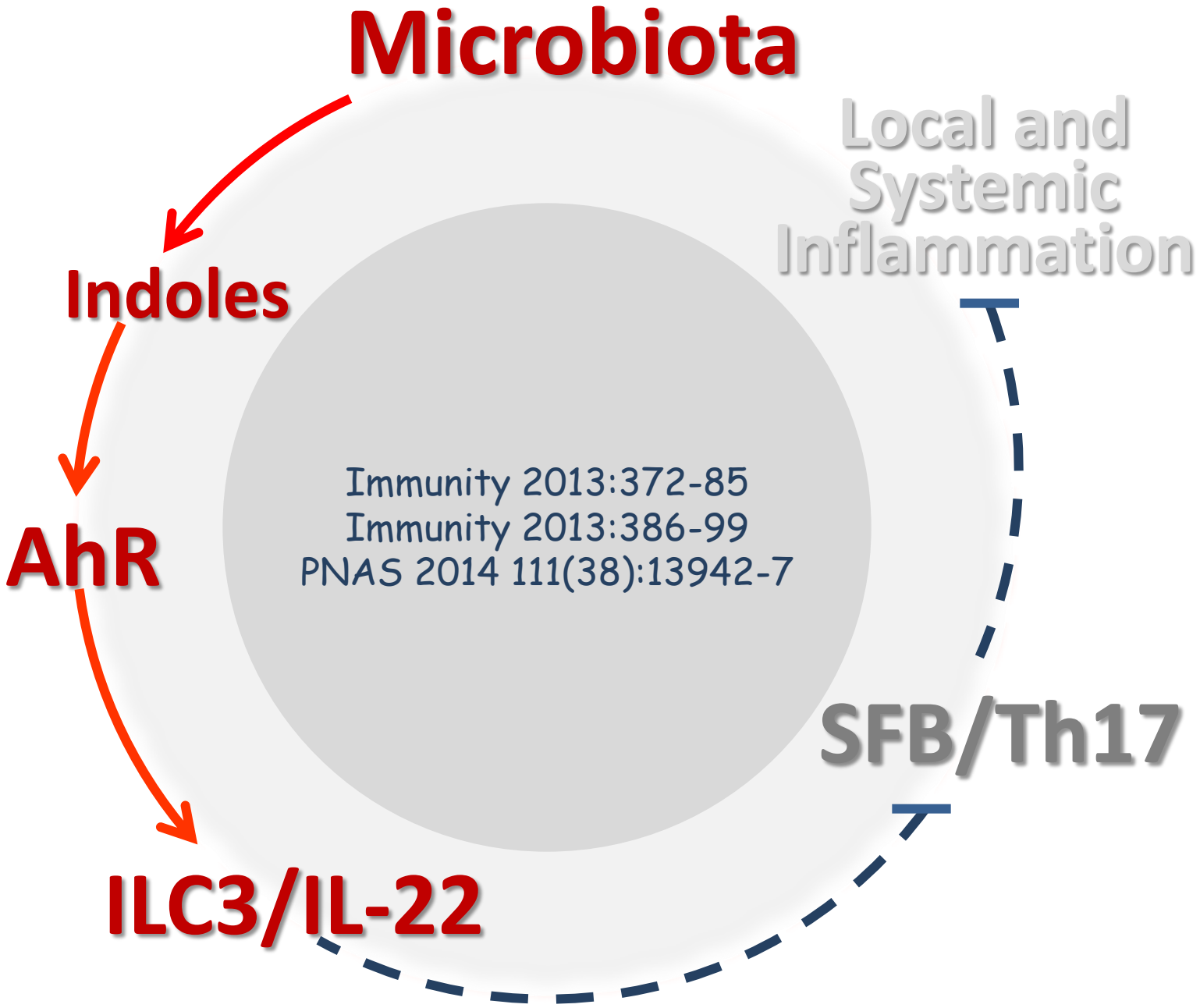
IAld protects from colitis



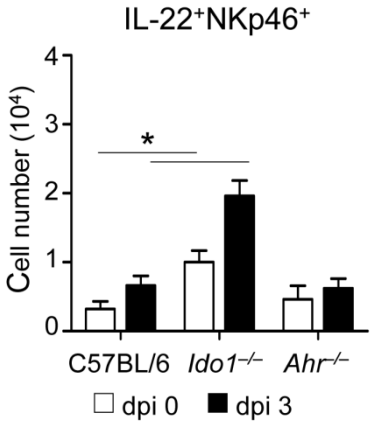


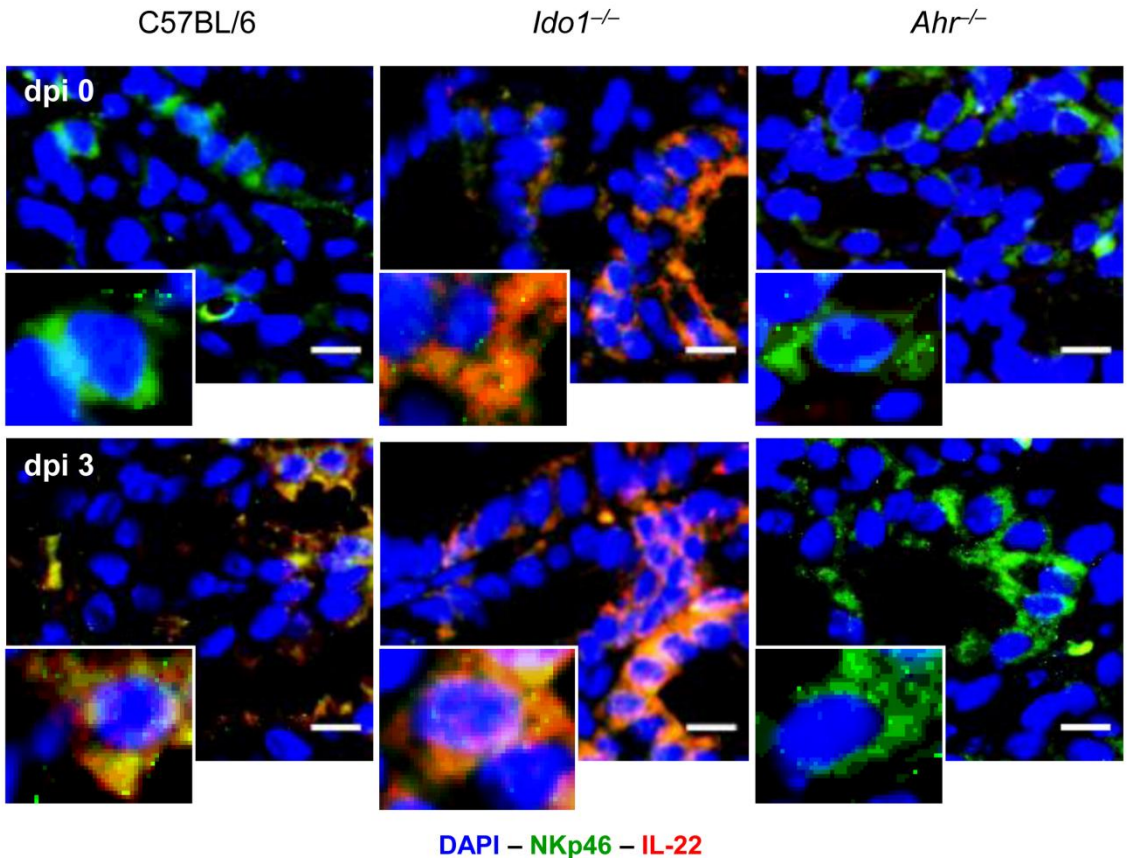
IAld has activity against:

- Gram+
- Gram-
- Yeasts
- Molds


Microbiota
Local and Systemic Inflammation
Indoles
AhR
Immunity 2013:372-85
Immunity 2013:386-99
PNAS 2014 111(38):13942-7
SFB/Th17
ILC3/IL-22

The AhR/IL-22 axis provides antifungal resistance in *Ido1*$^{-/-}$ mice





Prescribing antibiotics, the challenges!!!

- Can clinically useful **adjunctive therapies** be developed to prevent secondary infections?

- Can physicians be encouraged to use antibiotics with narrower activity spectra to minimize the collateral damage to bacterial mutualists?

- **Should diagnostics be designed to identify the etiologic agent of infection and then actively monitor the microbiota for signs of a secondary infection?**

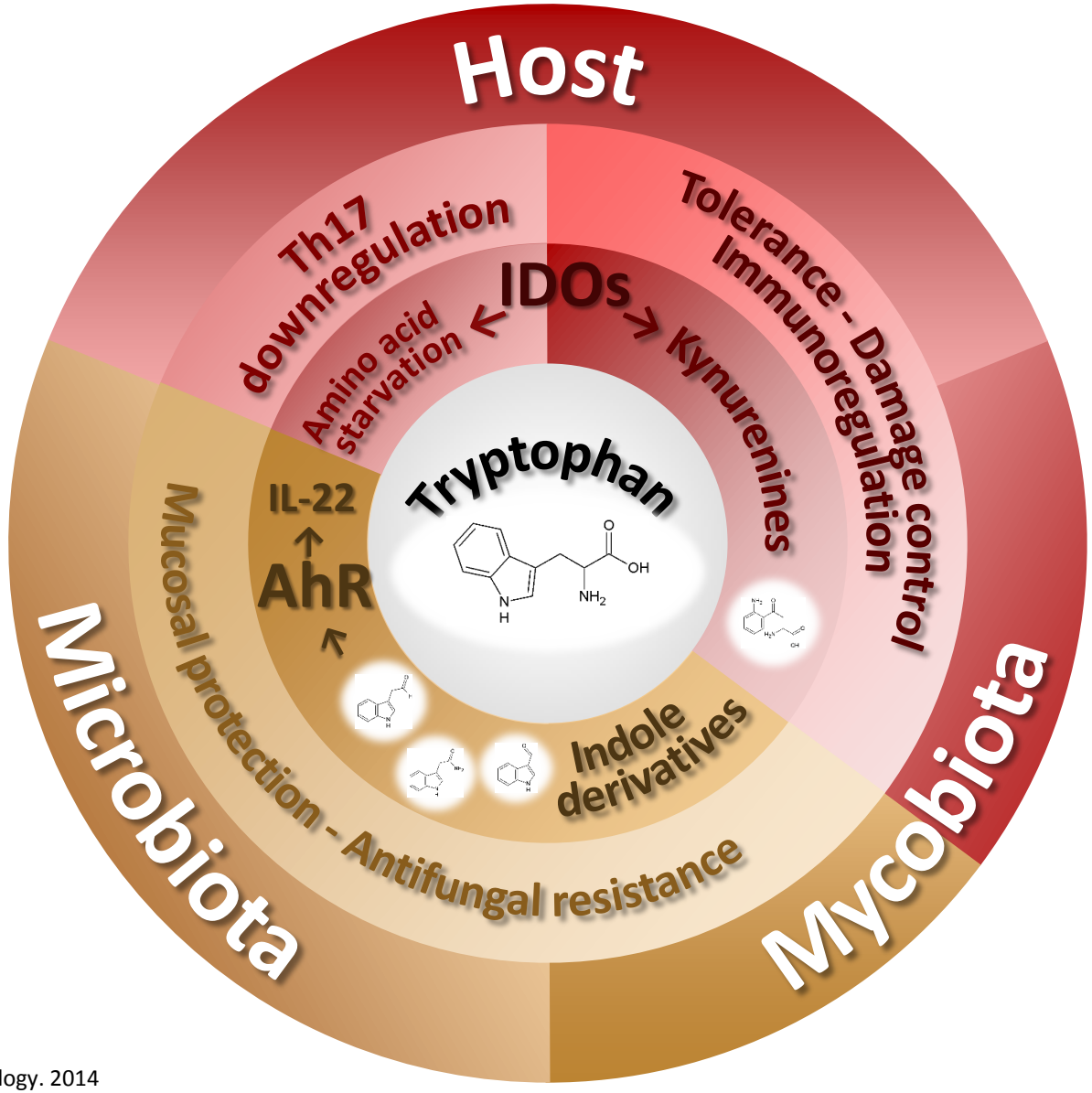
- Clinicians routinely monitor patients for adverse effects of antibiotics on the kidneys and liver, but apart from counseling patients to be alert for symptoms of *C. difficile*–associated diarrhea and candidiasis, they have no good way to monitor the state of the microbiota.

- **Can targeted antibiotics that cause minimal perturbation to the healthy microbiota be developed?**

Prescribing antifungals, the challenges!!!

	CASPOFUNGIN	L-AMB	VORICONAZOLE
Metronidazole			
Ciprofloxacin			
Vancomycin			
Ampicillin			

Full stomach, happy heart……



Seminars in Immunopathology. 2014

Caravaggio, The Cheaters 1594

Cristina Massi Benedetti

Monica Borghi

Silvia Bozza

Antonella De Luca

Francesca Fallarino

Claudia Galosi

Rossana Iannitti

Silvia Moretti

Vasiliou Oikonomou

Melissa Palmieri

Matteo Puccetti

Paolo Puccetti

Giorgia Renga

Rossana Riccini

Teresa Zelante

Thanks

Specific FP7 Targeted Research Projects

MANASP

SYBARIS

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FUNMETA