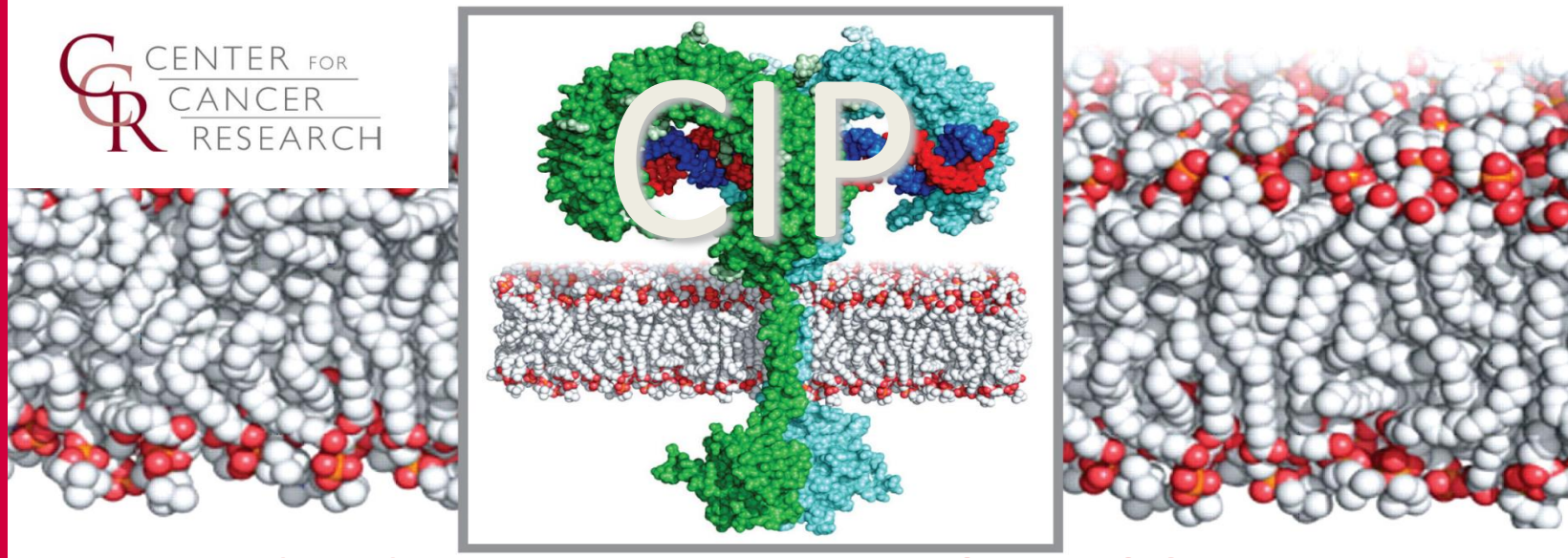
National Cancer Institute

CENTER FOR CANCER RESEARCH



CANCER AND INFLAMMATION PROGRAM

Giorgio Trinchieri

Cancer

as a Disease of the Metaorganism

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

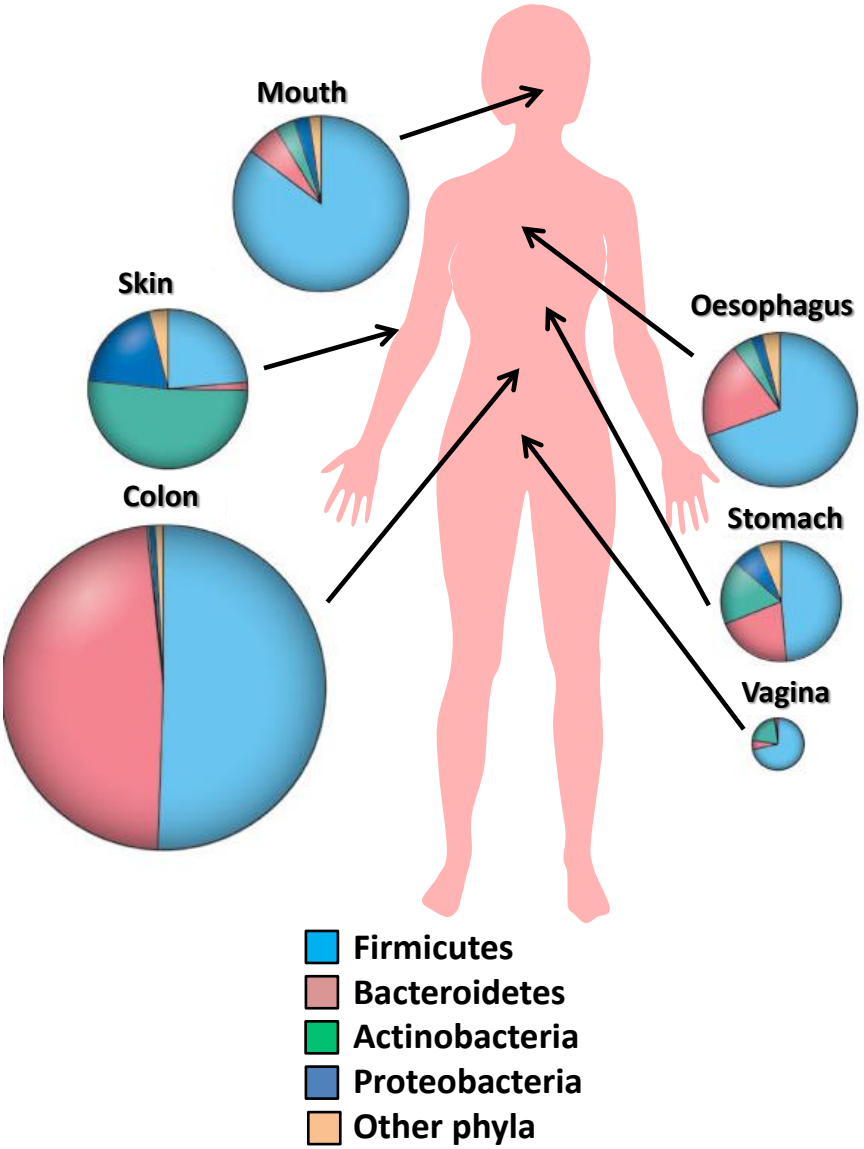
sitc

Richard V. Smalley, MD Memorial Lectureship 2014

Society for Immunotherapy of Cancer

Advancing the science and application of cancer immunotherapy

Humans have co-evolved with microbial partners



- We are a composite of species: bacteria, fungi, viruses, bacteriophages
- Commensal microorganisms
  - inhabit all barrier surfaces of our organism
  - outnumber the human cells by about 3-10 fold
  - their DNA (the microbiome) contains 100 times more genes than our 'own' human genome
- The microbiome is an integral part of our genetic landscape and plays a central role in the maintenance and control of host homeostasis

Humans are **metaorganisms (symbionts)** composed of host and microbial cells with their own genes (metagenome) and shared metabolic processes and products (metabolome).

The human metaorganism

Both microbial and human cells act as sensors for environmental changes communicating reciprocally via signaling pathways that, in part, utilize innate immunity mechanisms.

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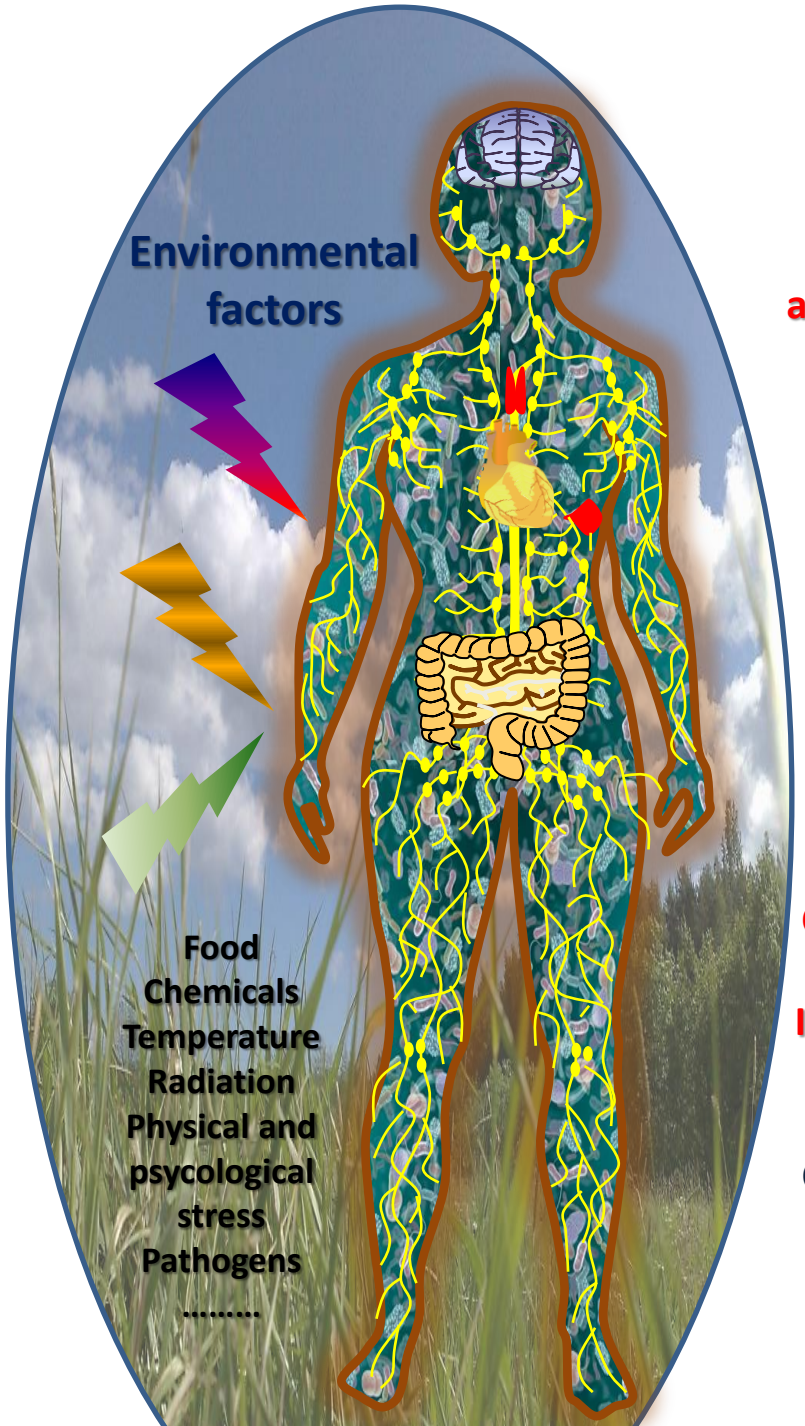


Metabolism

Cardiovascular, Excretory, Musculoskeletal, and Adipose tissue functions

Neurological. behavioral and cognitive functions

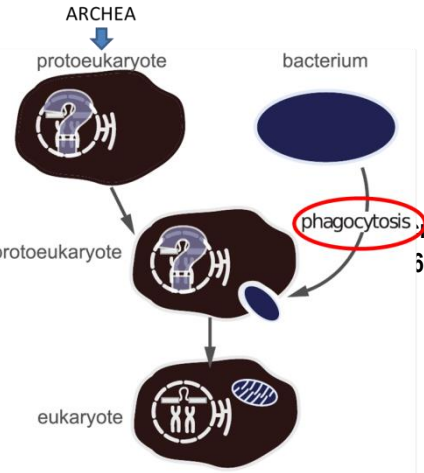
Aging

Hematopoiesis

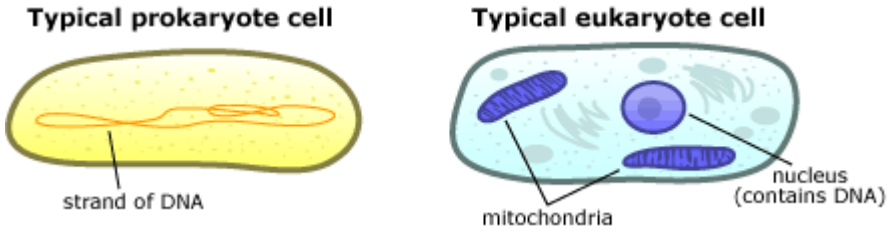
Circadian rhythm

Inflammation and Immunity

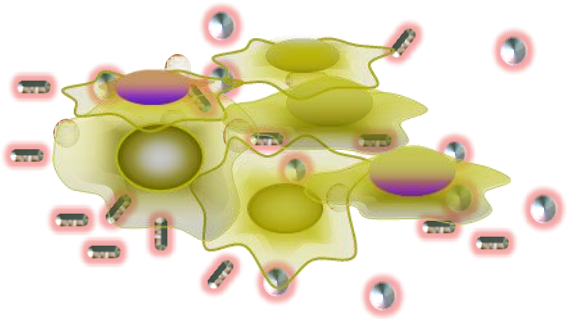
Cancer initiation, progression and response to therapy



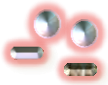
Chu H, Mazmanian
promotes host-mic
robiota
58-75.



Endosymbiosis of α-proteobacteria (SAR11 clade)



Multicellular symbionts

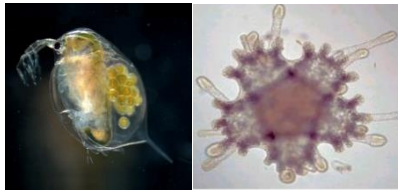


Commensal microbes

Pattern recognition (innate) receptors may have evolved to mediate the bidirectional cross-talk between microbial symbionts and their host

Chu H, Mazmanian SK. Innate immune recognition of the microbiota promotes host-microbial symbiosis. Nat Immunol. 2013; 14:668-75.

Mobile phagocytes
Metchnikoff 1882



Daphnia Starfish larva

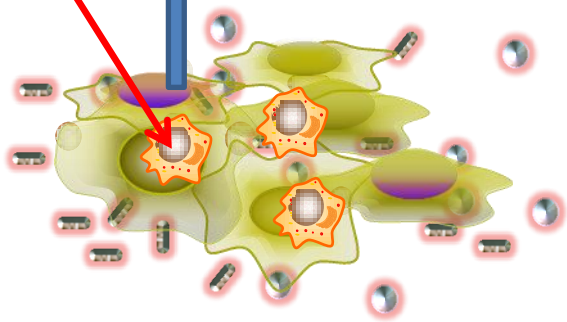
Pattern recognition receptors

Innate Resistance & Adaptive Immunity to infections

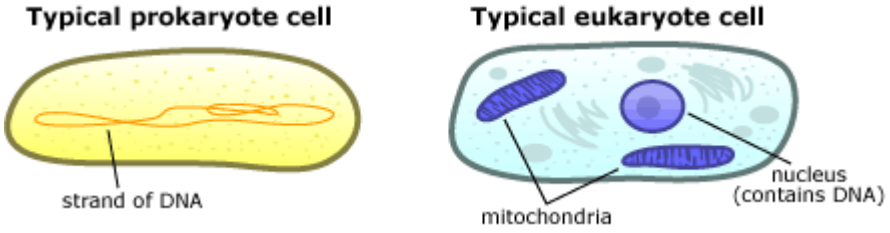
Metabolism
Homeostasis
(Morphogenesis)

Pattern recognition receptors

Metabolism
Morphogenesis
Homeostasis
Innate resistance



Multicellular symbionts



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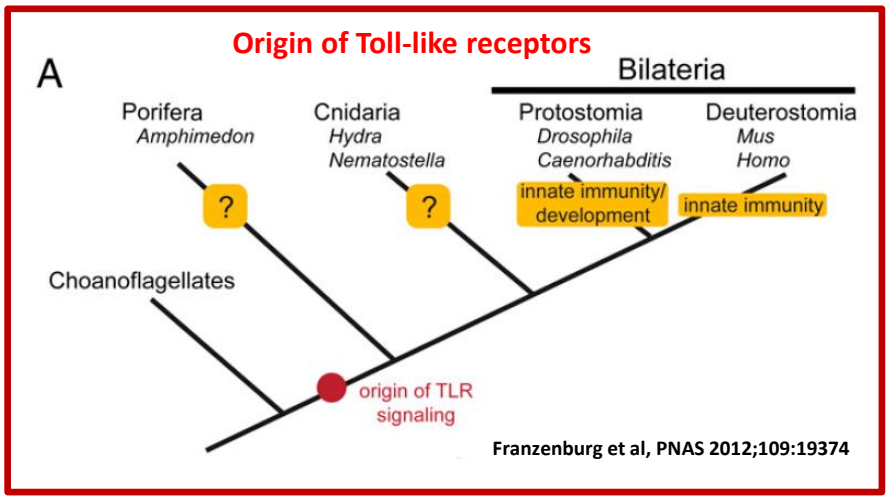
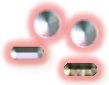


Franzenburg et al, PNAS 2012;109:19374

Innate resistance (phagocytic, myeloid) cells



Commensal microbes

Mammalian metaorganisms

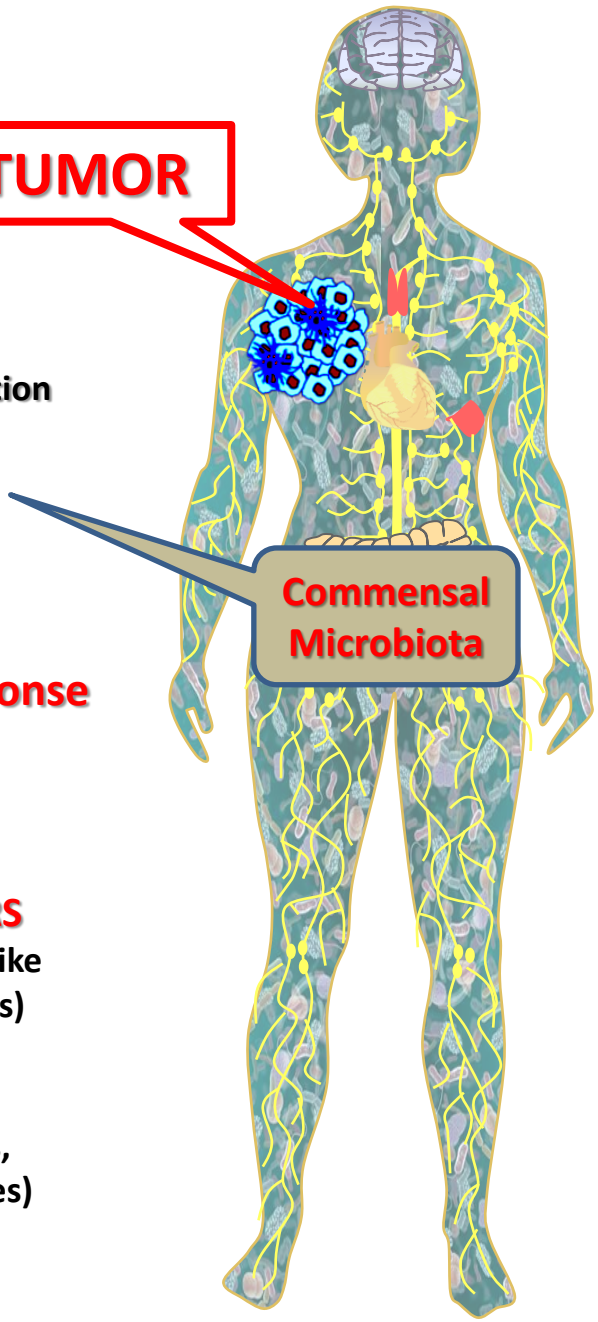
Cancer as a disease of the human metaorganism

TUMOR (cancer genetics)
Intrinsic (oncogene mediated) inflammation

Extrinsic inflammation
Microenvironment
Innate and adaptive immune response

PATTERN RECOGNITION RECEPTORS
(Toll-like receptors, IL-1 receptors, NOD-like receptors, chemotactic receptors, others)

INNATE/IMMUNE CELLS
(myeloid cells, antigen-presenting cells, innate lymphocytes, T and B lymphocytes)



Metabolism

Cardiovascular, Excretory, Musculoskeletal, and Adipose tissue functions

Neurological. behavioral and cognitive functions

Hematopoiesis

Circadian rhythm

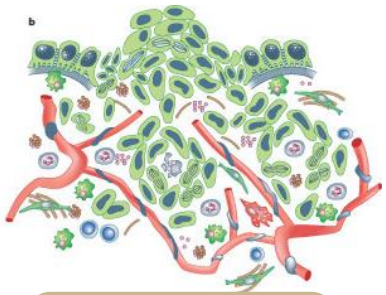
Inflammation and Immunity

Cancer initiation, progression and response to therapy

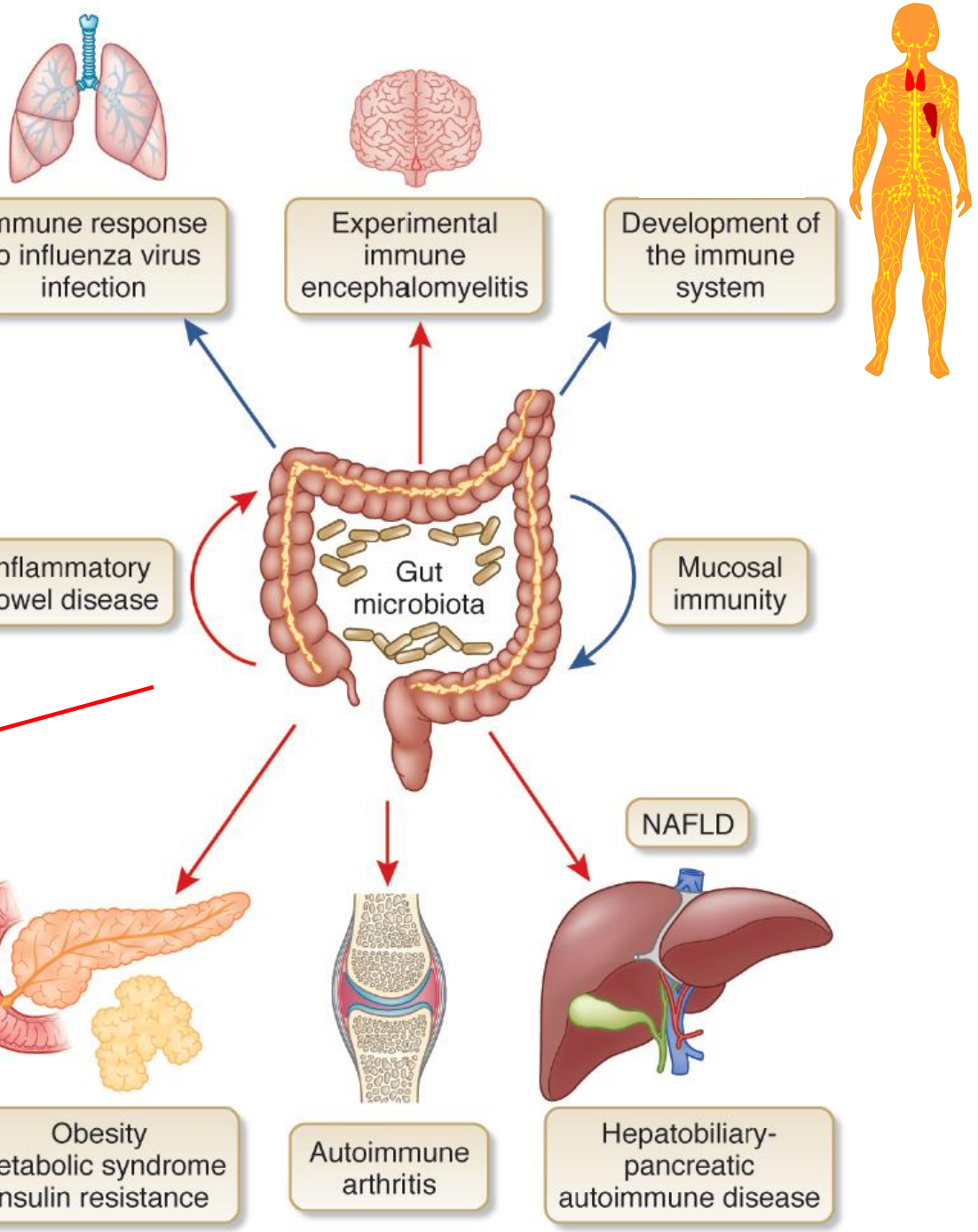
Colon rectal carcinoma
Stomach cancer

Malt lymphoma
Hepatocellular carcinoma
Mammary carcinoma
Thymic lymphoma

Cancer progression and response to immunotherapy and chemotherapy



Tumors

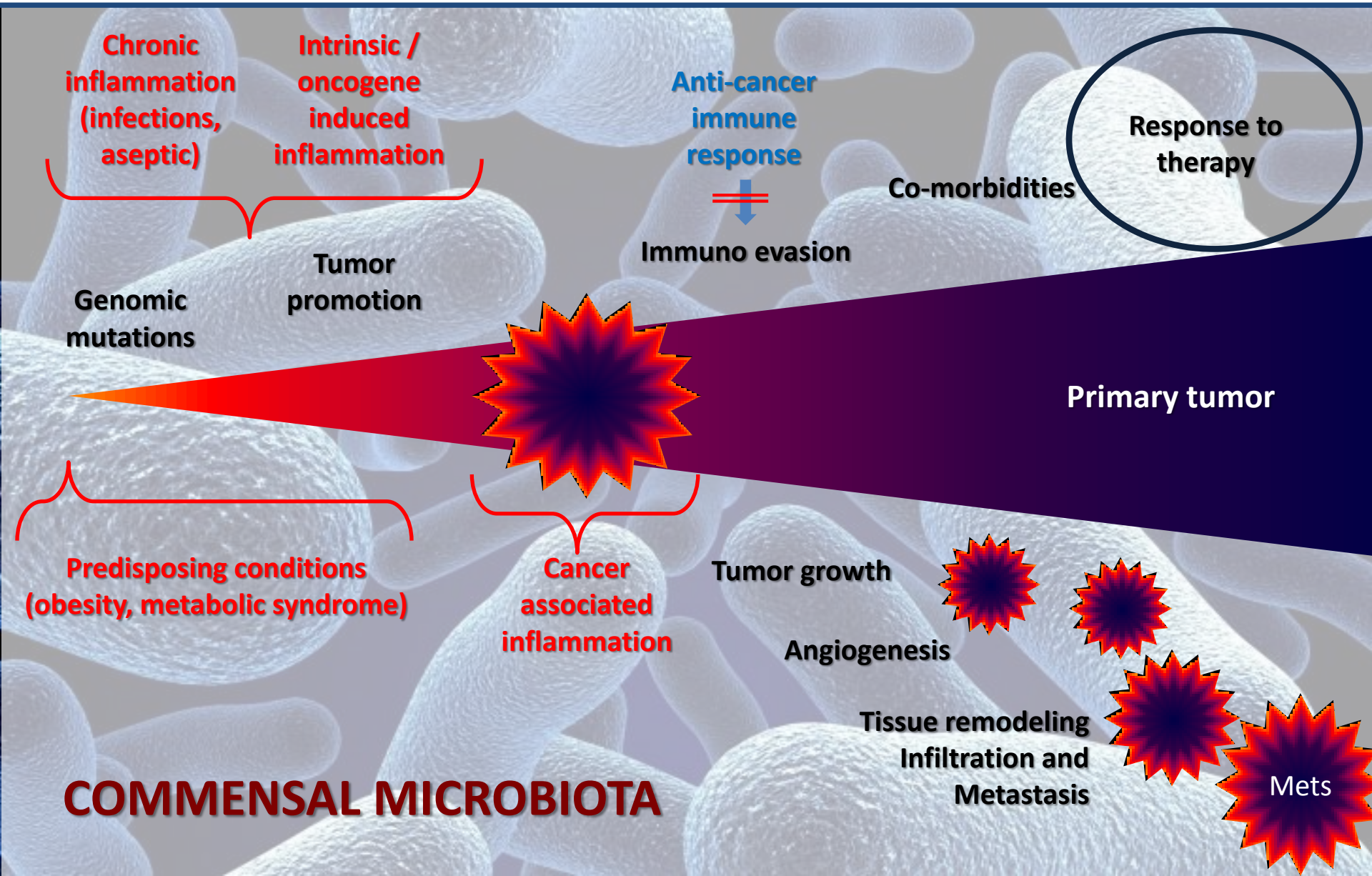


The price of immunity

Romina S Goldszmid & Giorgio Trinchieri

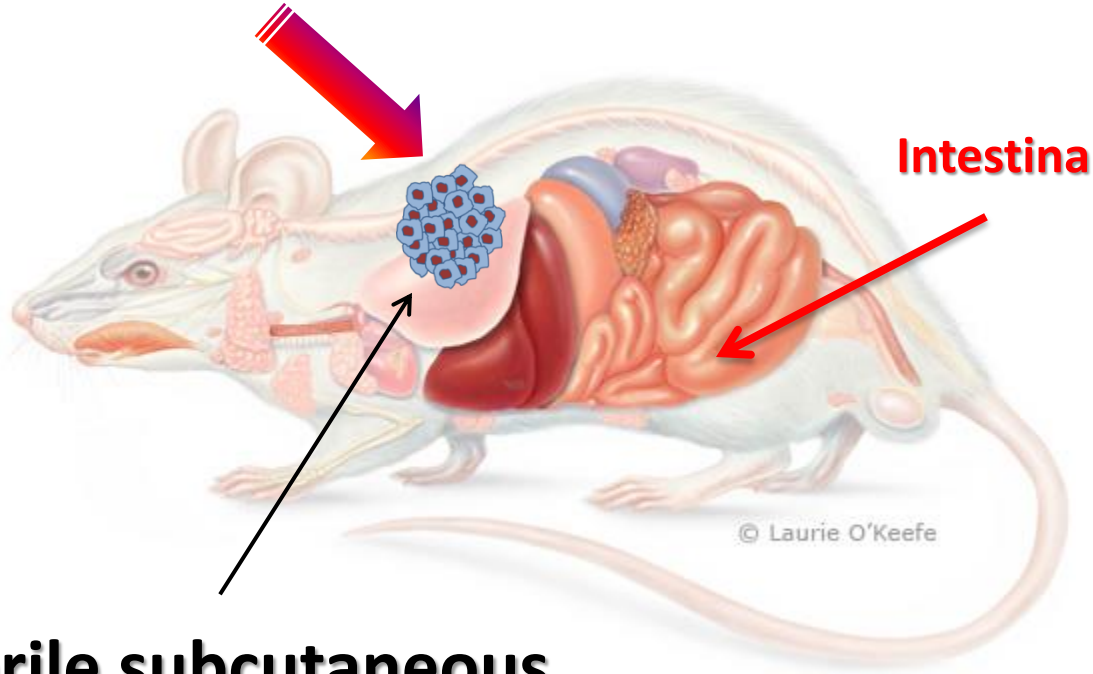
nature immunology

Inflammation, immunity and cancer



Is the response to cancer therapy regulated by the commensal bacteria?

Systemic anti-IL-10R + Intratumor CpG-OGN immunotherapy
Platinum compound (oxaliplatin, cisplatin) chemotherapy



Sterile subcutaneous transplanted tumor

Noriho Iida, Amiran Dzutsev, C. Andrew Stewart, …… Giorgio Trinchieri, Romina S. Goldszmid
Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment
Science, 2013; 342:967-70

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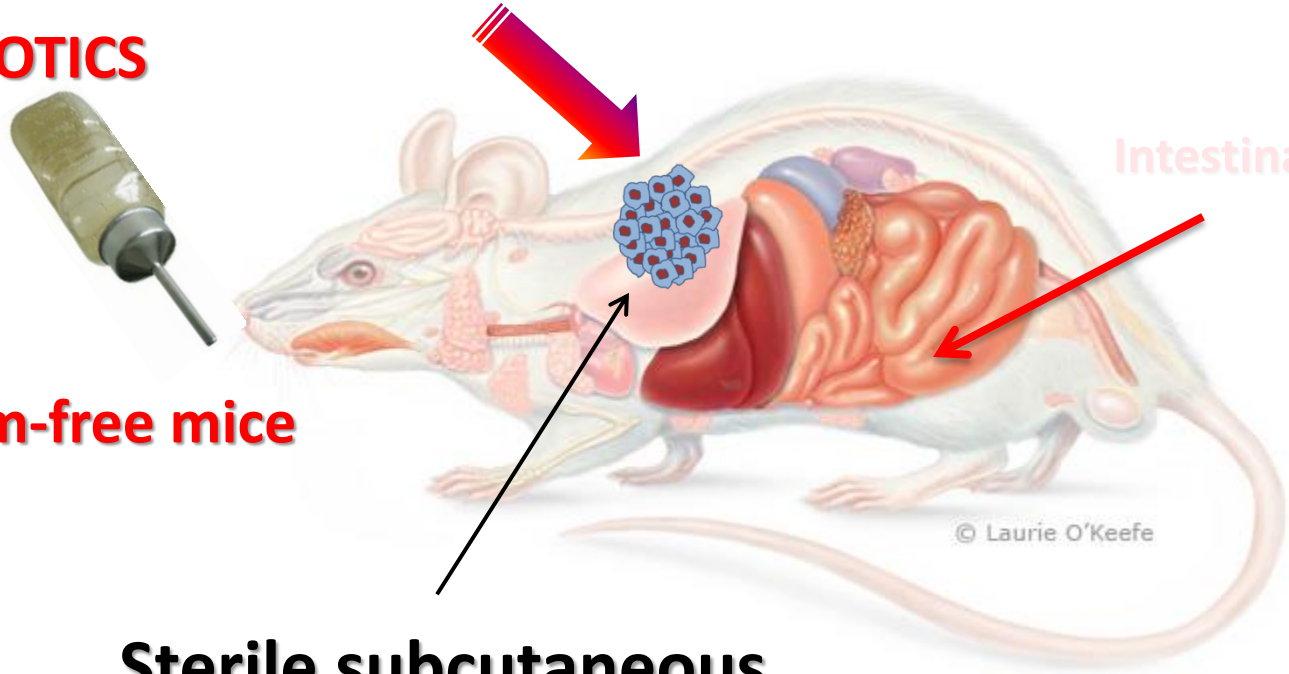
Systemic anti-IL-10R + Intratumor CpG-OGN immunotherapy
Platinum compound (oxaliplatin, cisplatin) chemotherapy

ANTIBIOTICS

Neomycin
Vancomycin
Imipenem



or Germ-free mice

Sterile subcutaneous transplanted tumor

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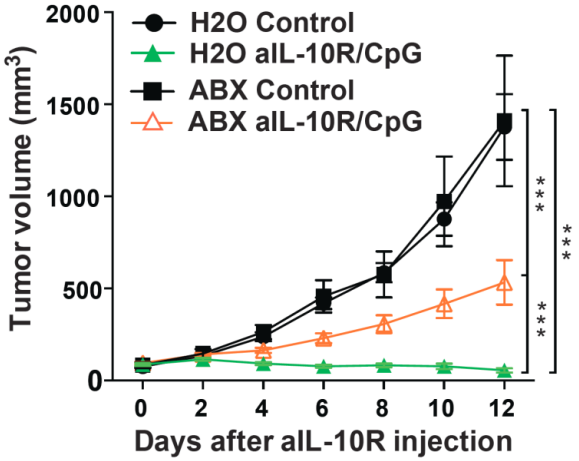
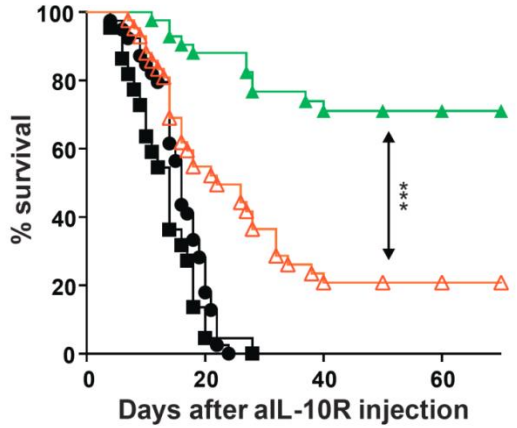
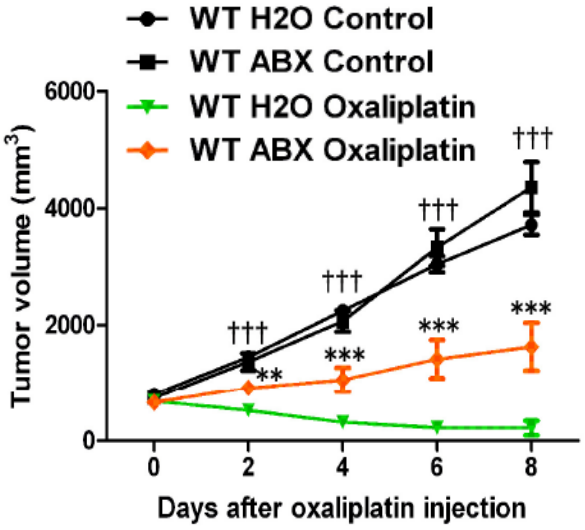
Antibiotics (ABX) suppress the anti-tumor effect of immune and chemo therapy

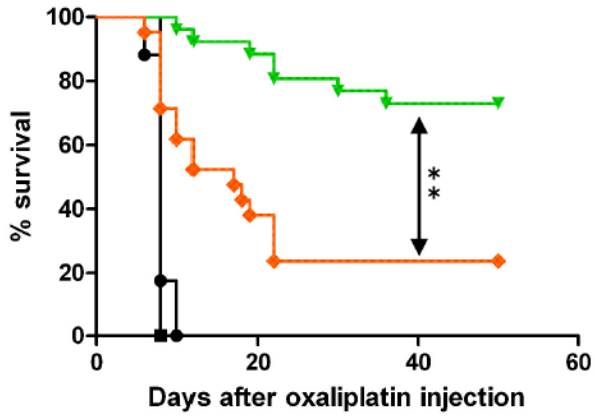
Anti-IL-10R/CpG



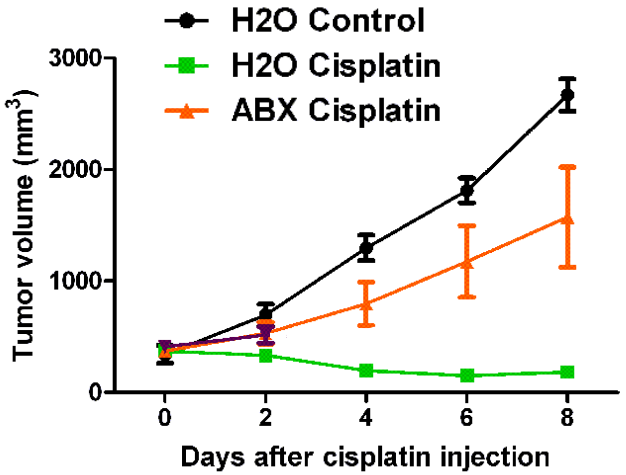


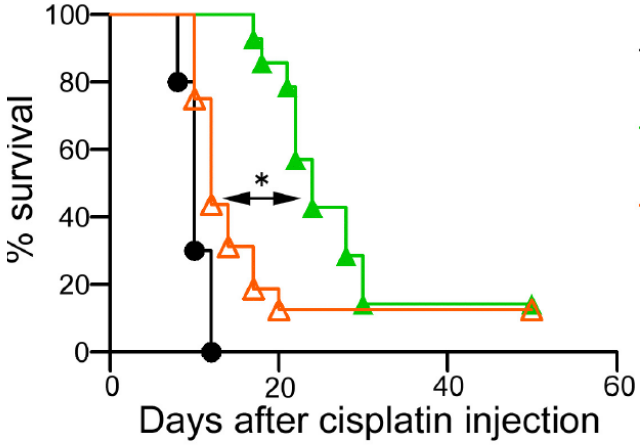
Oxaliplatin





Cisplatin

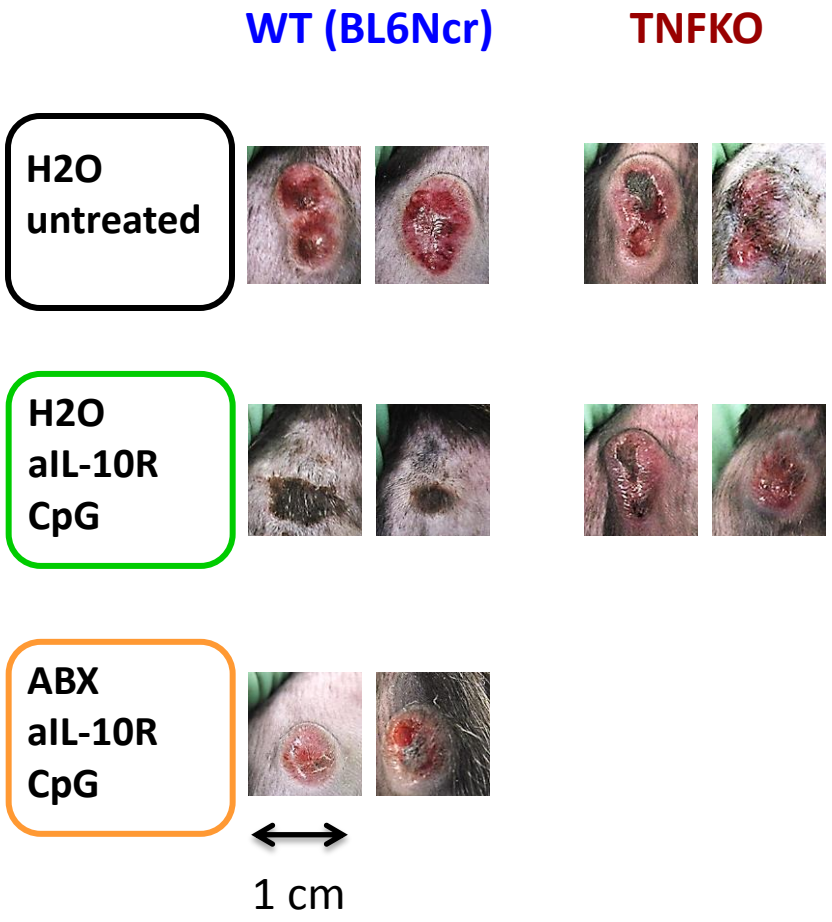




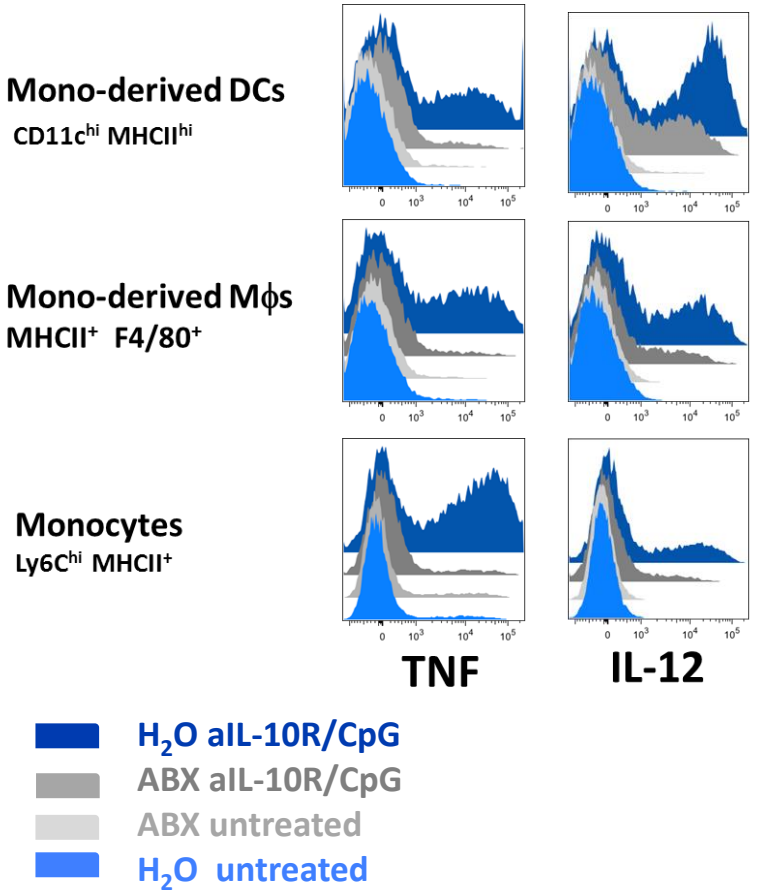
MC38 subcutaneous tumor

EL4 subcutaneous tumor

Antibiotics (ABX) suppress TNF-mediated early necrosis of the tumor and decrease inflammatory cytokine production following anti-IL-10R/CpG



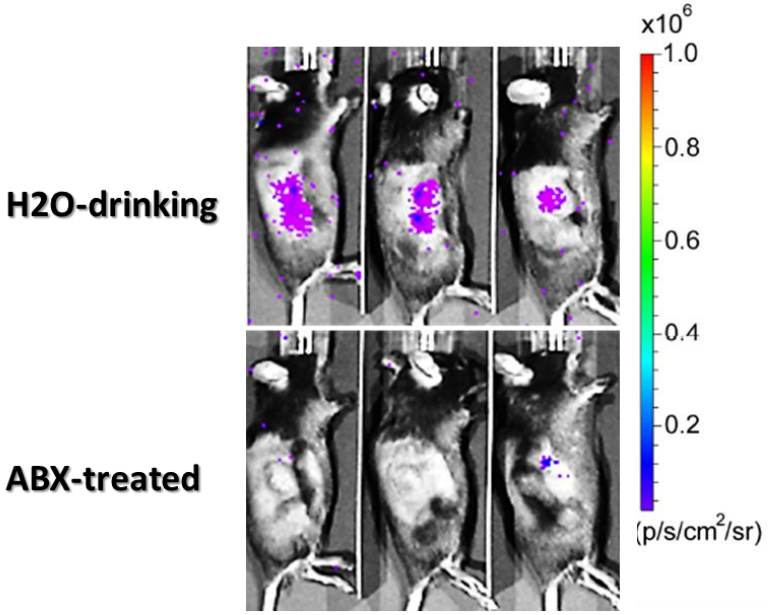
ABX decrease TNF and IL-12 production by tumor-infiltrating myeloid cells following aIL-10R/CpG



MC38 tumor, 72 h after CpG treatment

Antibiotics (ABX) impair oxaliplatin chemotherapy by preventing ROS production from NOX2 (*Cybb*) expressing myeloid cells

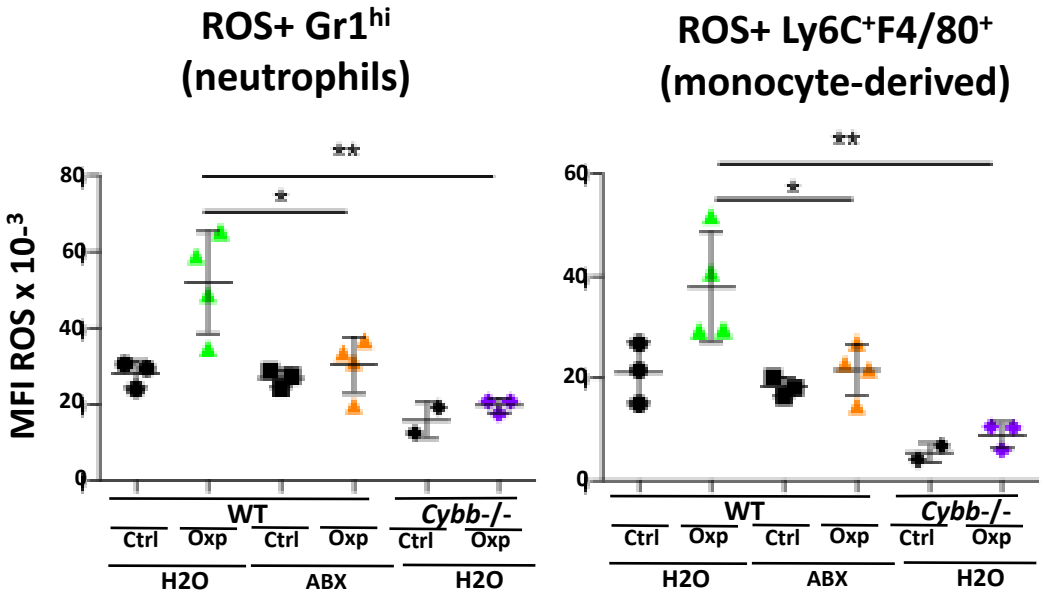
Oxaliplatin induces ROS production in tumors of control but not ABX-treated mice



Oxaliplatin-induced L-012 Bioluminescence (ROS)

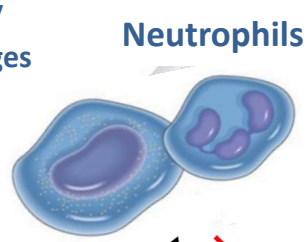
- EL4 tumors-bearing B6 mice were treated with 10mg/kg oxaliplatin
- ROS-induced bioluminescence using the L-012 probe was analyzed 24 hours after oxaliplatin injection

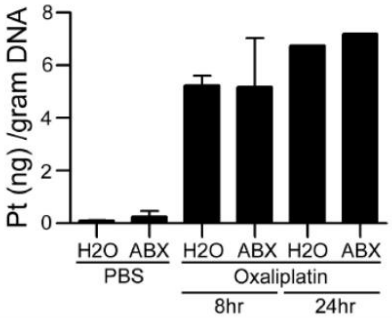
Oxaliplatin induces NOX2 (Cybb)-mediated ROS production in tumor-associated myeloid cells



ROS- production analyzed by flow cytofluorimetry in EL-4 tumor-infiltrating myeloid cells *ex-vivo* 24 hours after oxaliplatin injection

ROS production in oxaliplatin treated tumors is blocked by ABX and it is required for DNA damage after formation of platinum DNA adducts



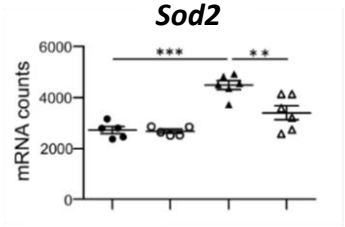


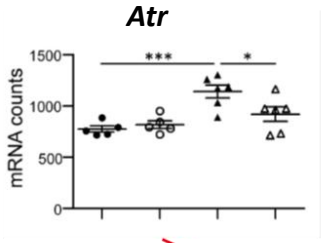
Platinum DNA Adducts

Platinum compounds

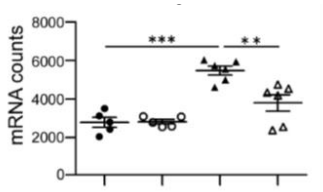
ROS

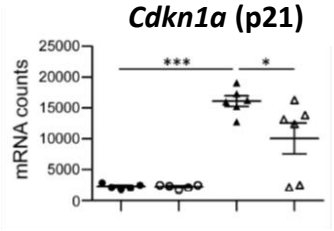
DNA DAMAGE



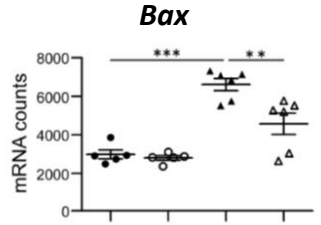


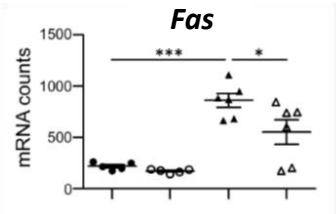
P53



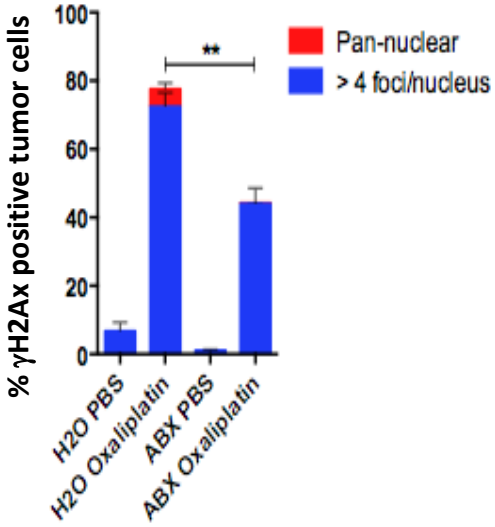


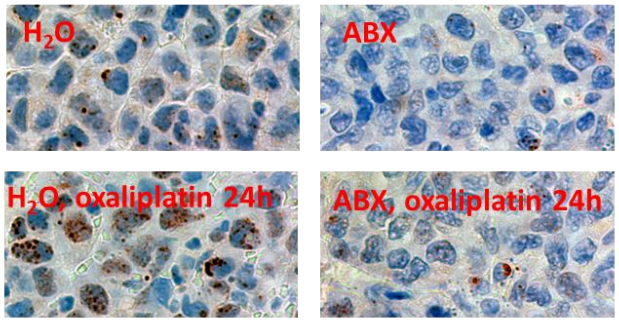
Cell cycle inhibition



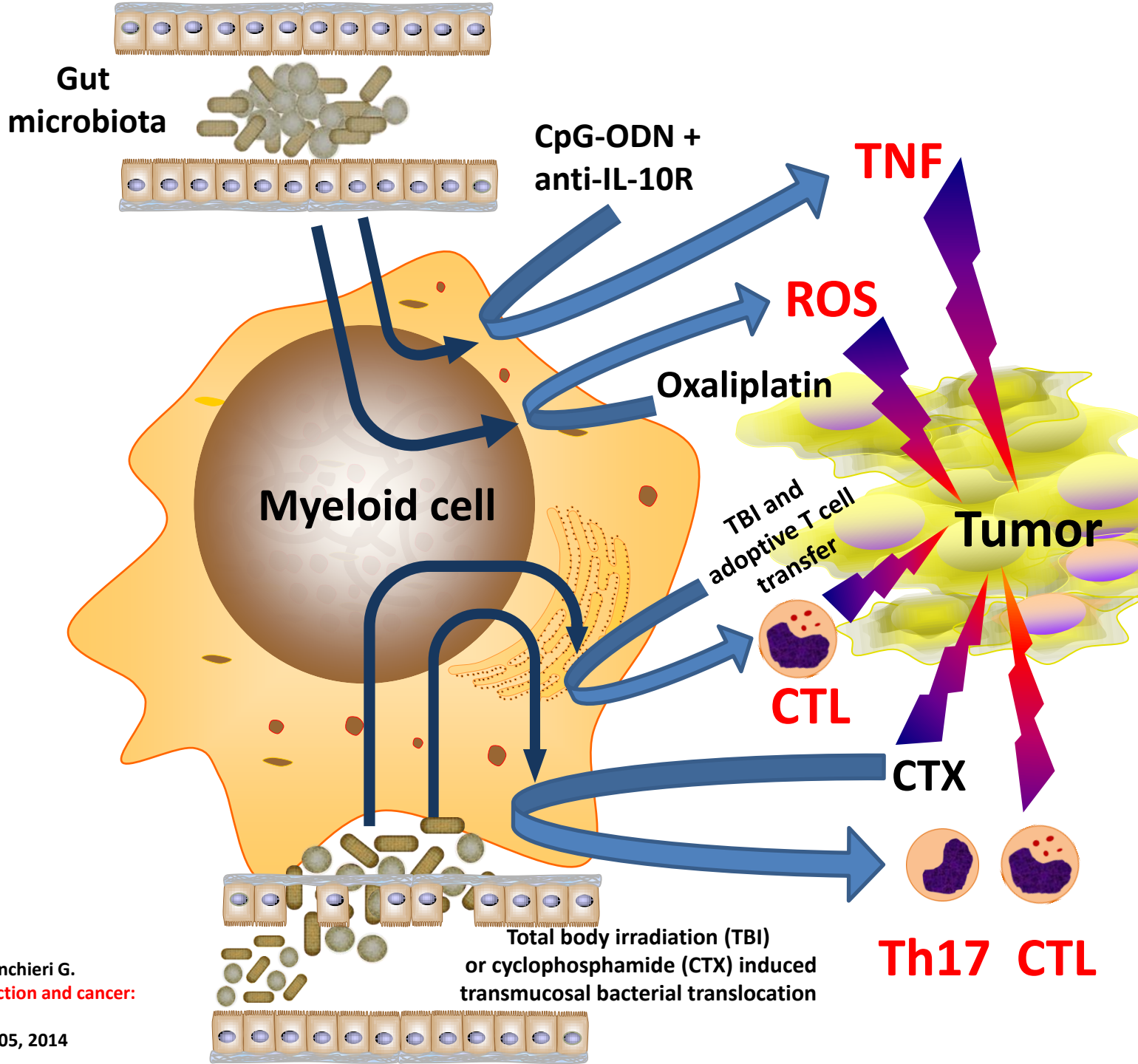


Apoptosis





γH2Ax staining



Goldszmid R.S., Dzutsev A., Trinchieri G.
Host immune response to infection and cancer: unexpected commonalities
Cell Host & Microbe, 15, 295-305, 2014

1. Identification of bacterial species

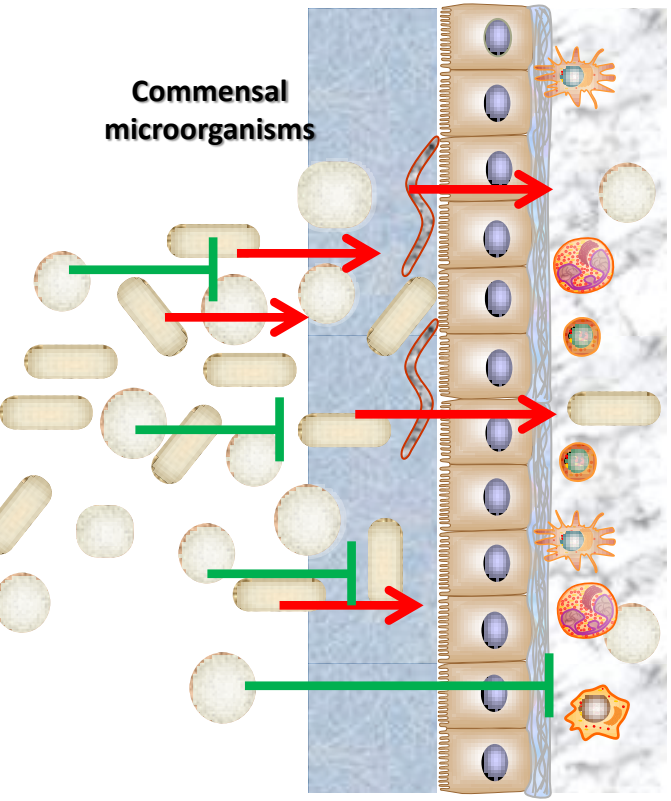
2. Identification of receptors, factors, cell types

3. Cellular and molecular characterization of myeloid cells

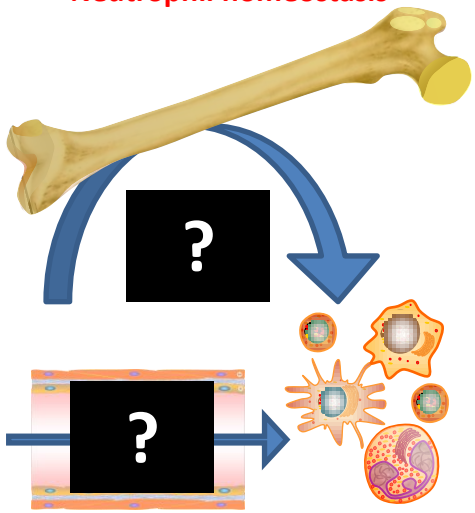
Local barrier homeostasis and immunity

Systemic "inflammatory tone" and immune response

Cancer therapy



Myelopoiesis
DCpoiesis
Neutrophil homeostasis



Myeloid cells

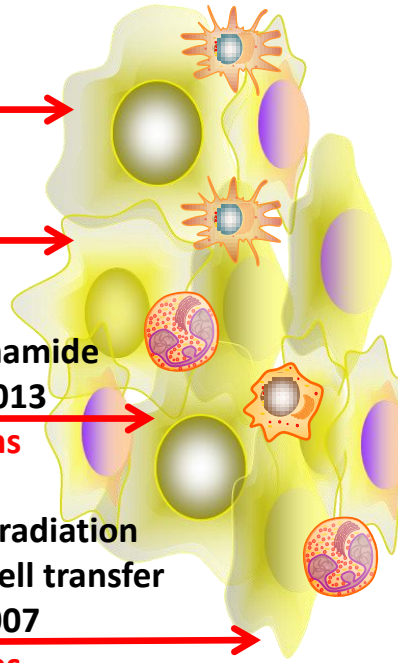
Migration
Differentiation
Activation
Epigenetic regulation

CpG-OGN
TNF, IL-12, …

Oxaliplatin
ROS

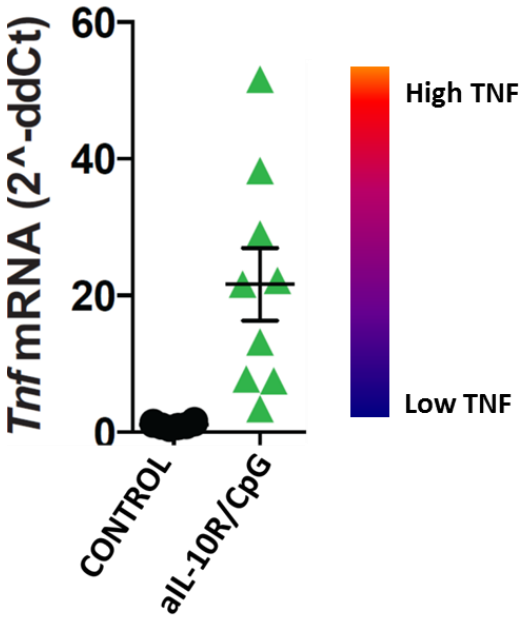
Cyclophosphamide
L. Zitvogel 2013
APC functions

Total body irradiation
Adoptive T cell transfer
N. Restifo 2007
APC functions

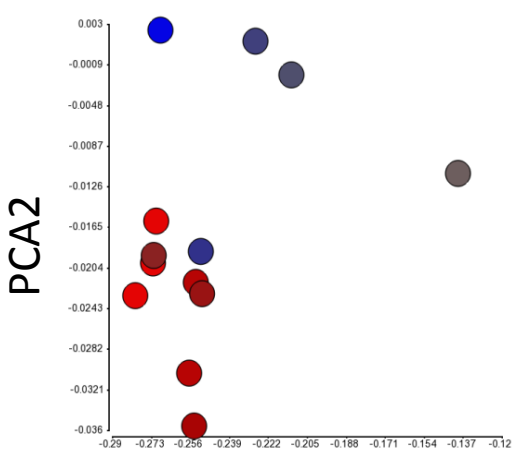


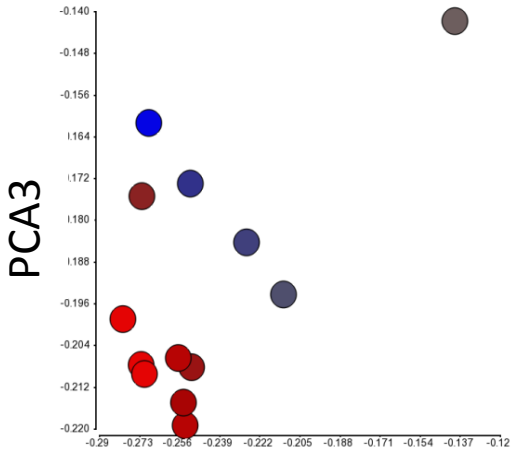
Tumor

Composition of fecal microbiota can be used to segregate mice with high and low intratumoral TNF in response to CpG



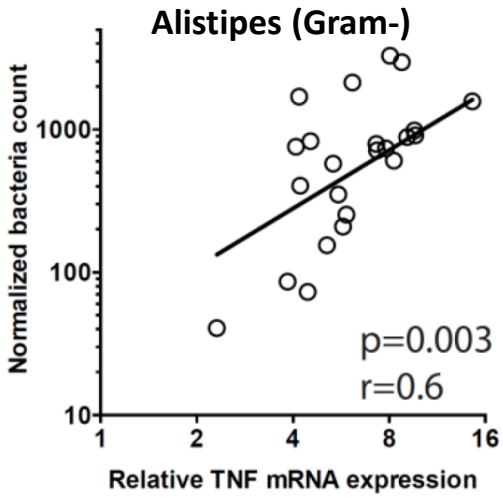
Unweighted Unifrac
H_2O- drinking mice

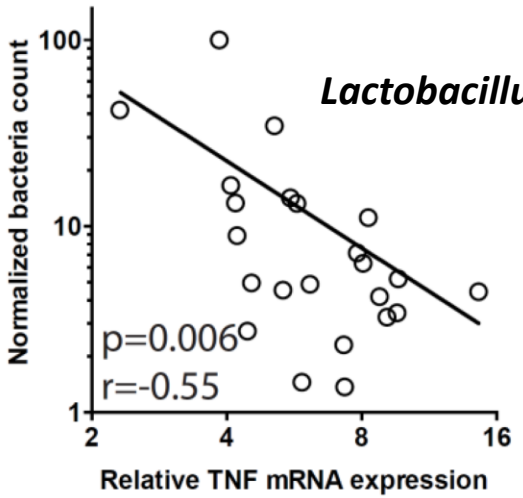




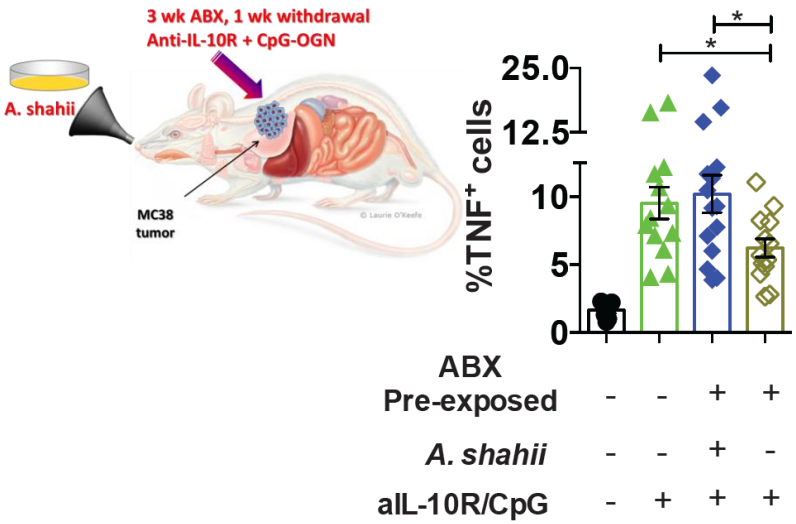
16S rDNA analysis using 454 pyrosequencing

Identification of bacterial genera positively and negatively correlating with intratumoral TNF levels after CpG in microbiota perturbation experiments

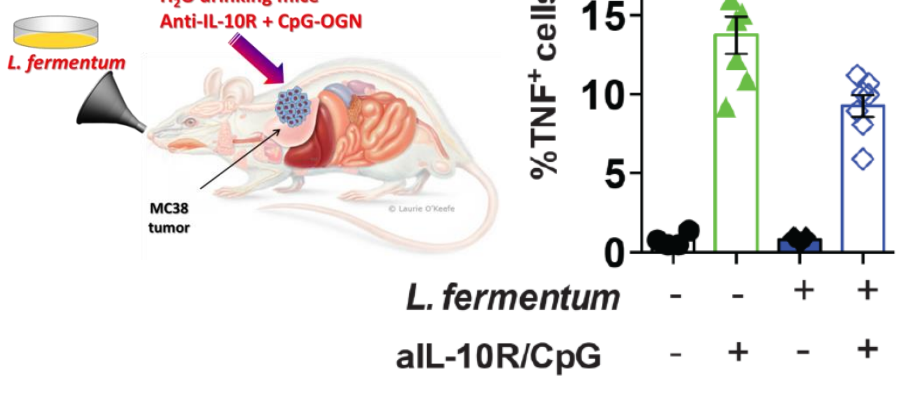




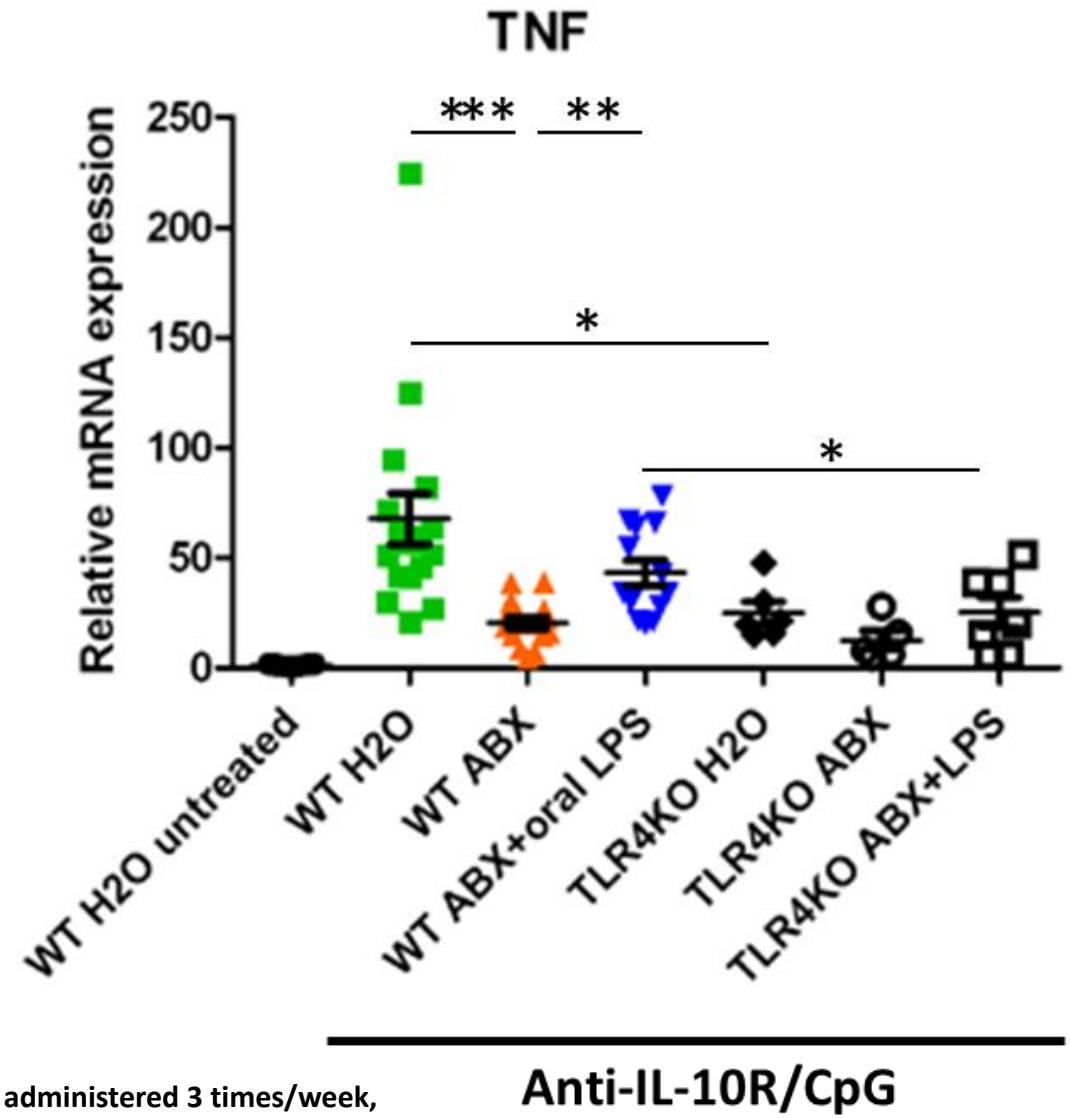
A. shahii



L. murinum
L. intestinalis
L. fermentum

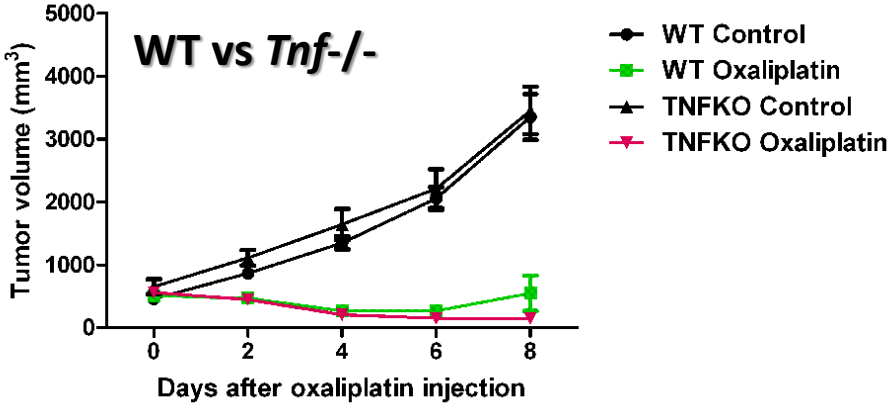


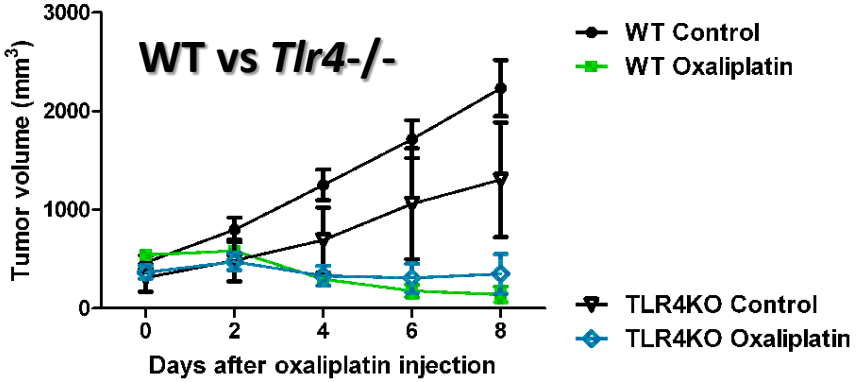
Oral LPS restores the TNF production impaired by ABX and TLR4 is required for optimal response to i.t. CpG

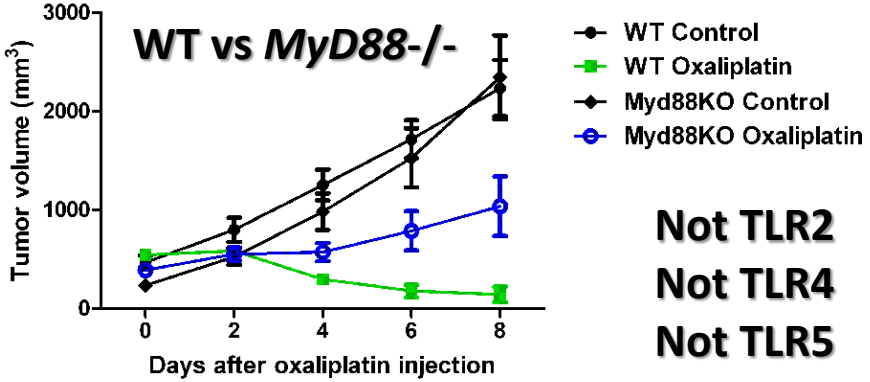


25 mg/kg BW of LPS was orally administered 3 times/week,
2 weeks prior and 1week after MCA38 injection

Oxaliplatin tumor treatment requires MyD88 but, unlike CpG, neither TLR4 nor TNF



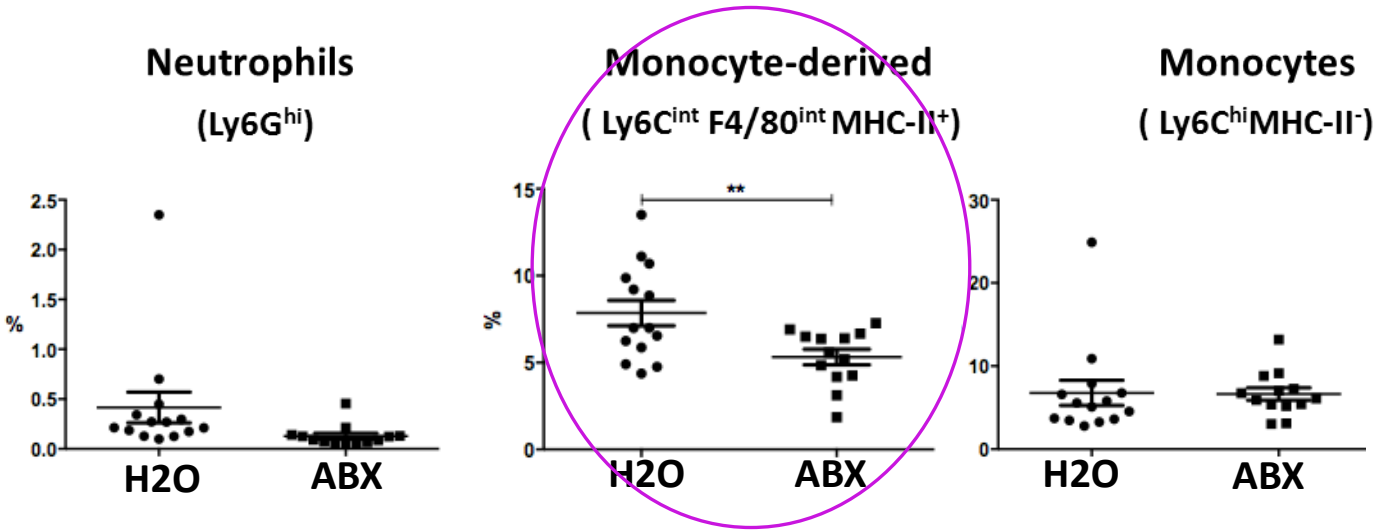




Not TLR2
Not TLR4
Not TLR5
Not TLR9
Not IL-1R
Not IL-18R

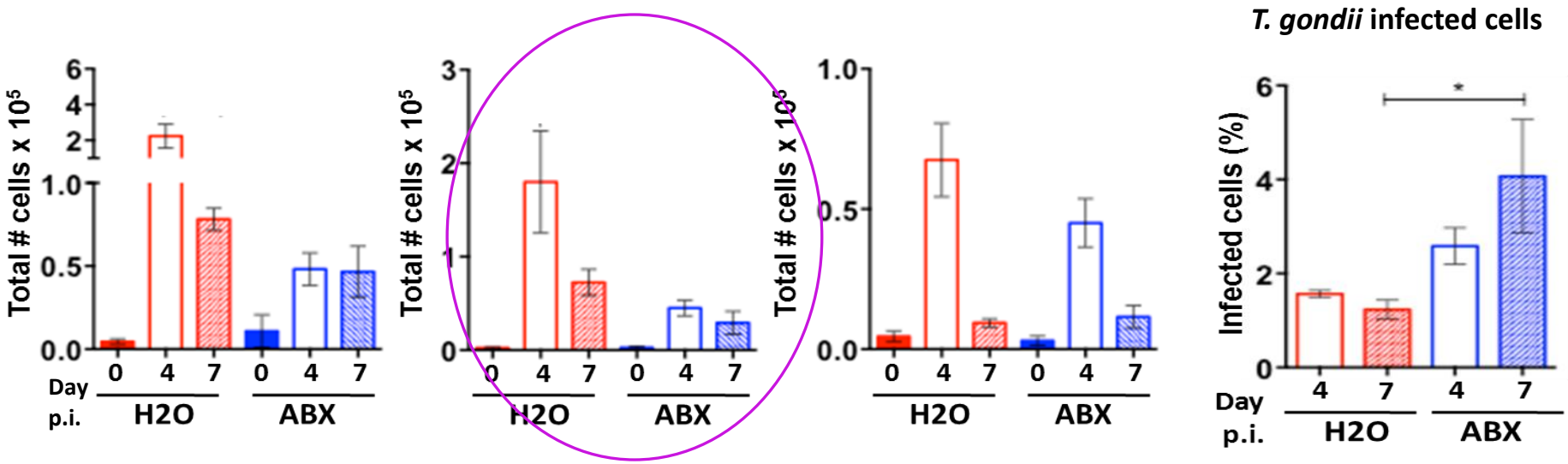
Oxaliplatin (10mg/kg) was i.p. injected on day 7 after EL4 s.c. tumor inoculation

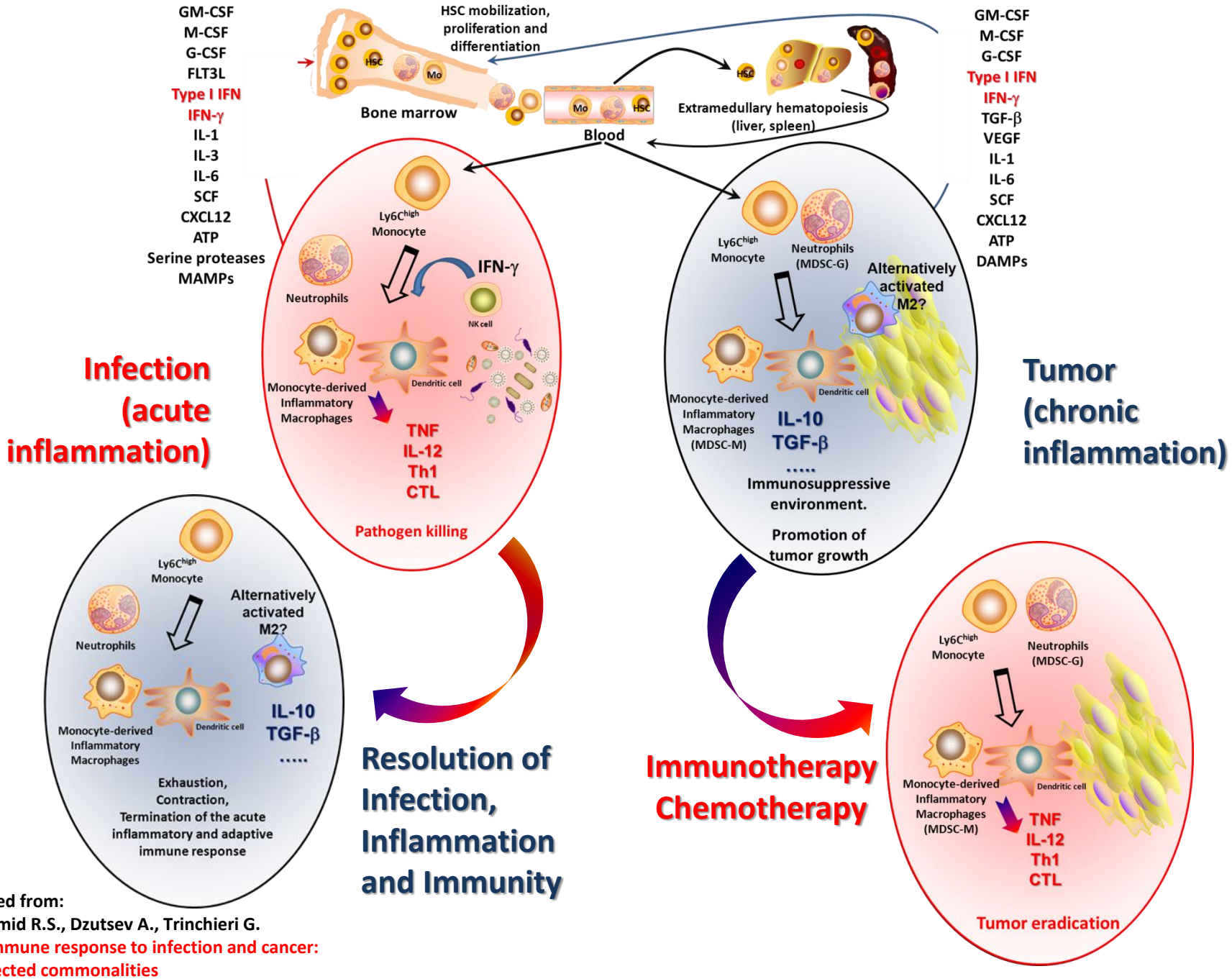
Changes in tumor-infiltrating myeloid cells in ABX treated mice



MCA38 tumor

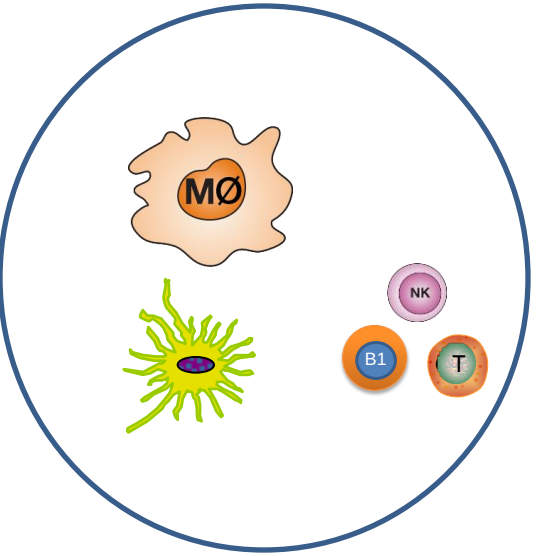
Toxoplasma gondii I.P. infection in ABX treated mice: changes in inflammatory myeloid cells in the infected tissue and decreased resistance to infection



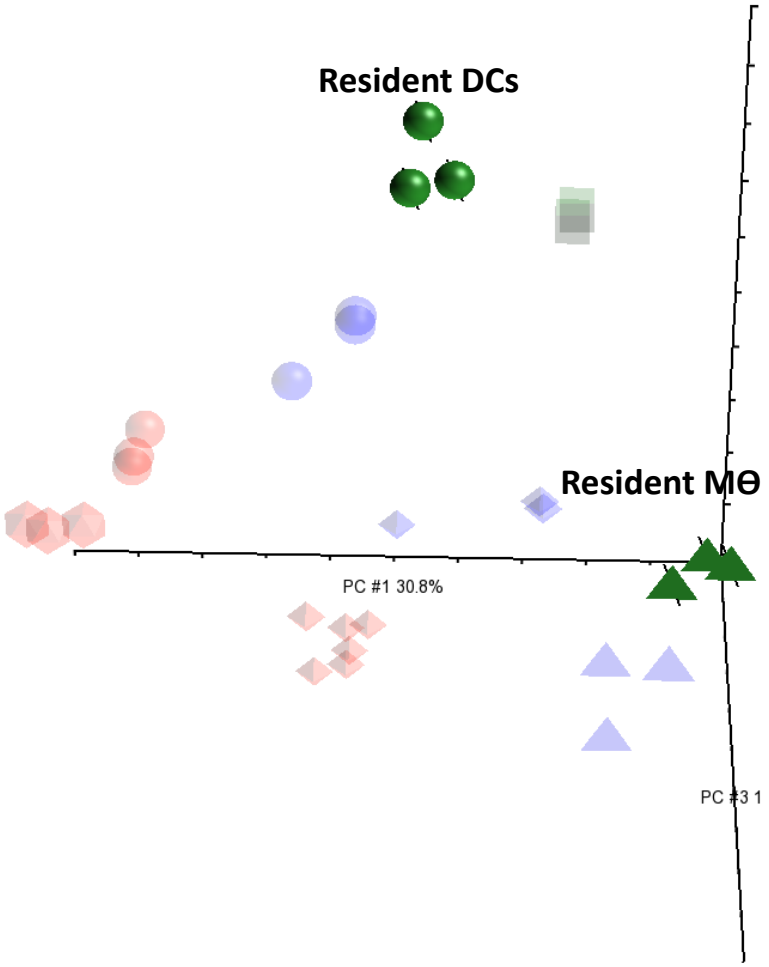


Modified from:
Goldszmid R.S., Dzutsev A., Trinchieri G.
Host immune response to infection and cancer: unexpected commonalities
Cell Host & Microbe, 15, 295-305, 2014

Toxoplasma gondii peritoneal infection allowed a molecular characterization of inflammatory monocyte differentiation in infected tissues



Before T. gondii infection



Goldszmid RS, Caspar P, Rivollier A, White S, Dzutsev A, Hieny S, Kelsall B, Trinchieri G, Sher A.
NK cell-derived interferon-γ orchestrates cellular and the differentiation of monocytes into dendritic cells at the site of infection.
Immunity. 2012;36:1047-59

Principal component analysis of expression of 125 genes relevant for myeloid cell differentiation and function as determined by Nanostring in sorted cell subsets.

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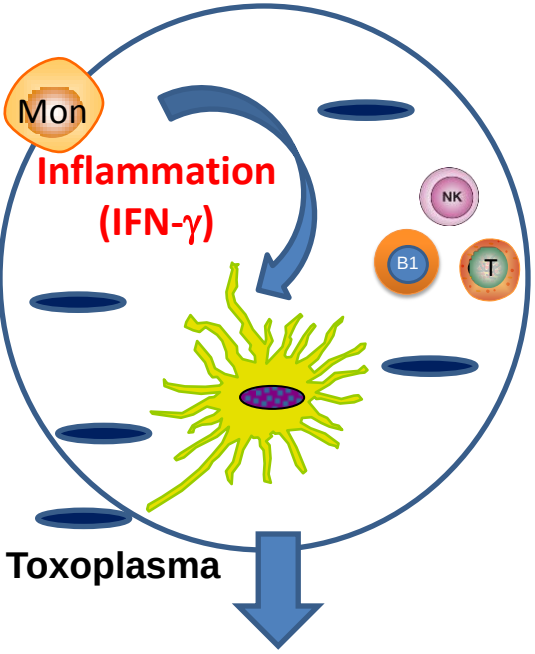
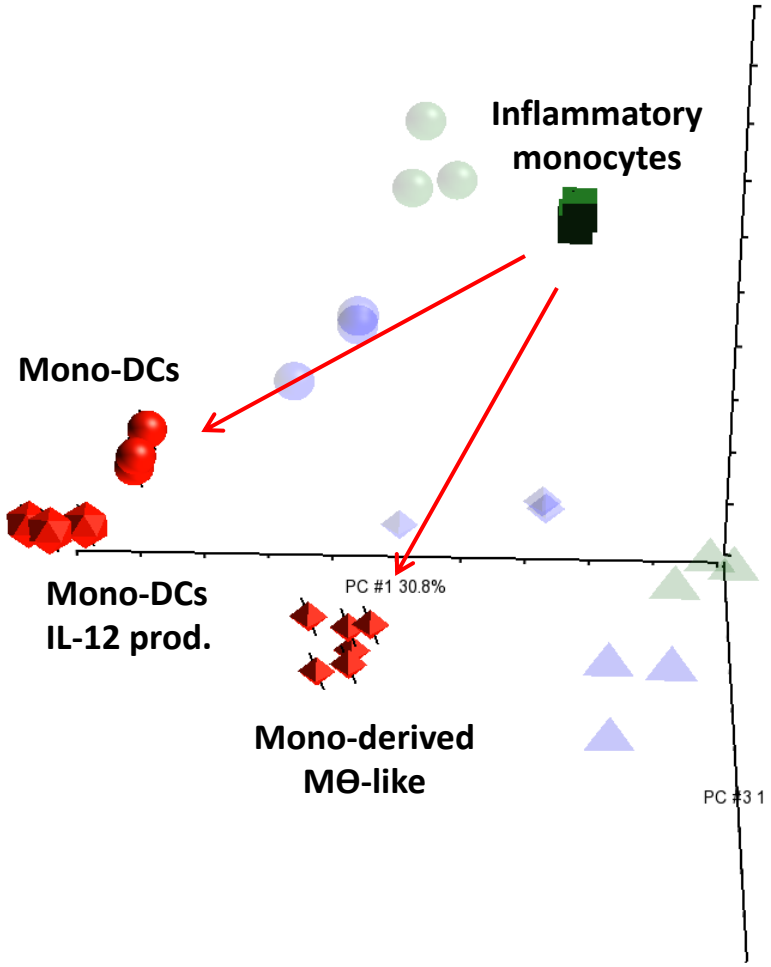


Protection **IL-12**
Th1

After T. gondii infection



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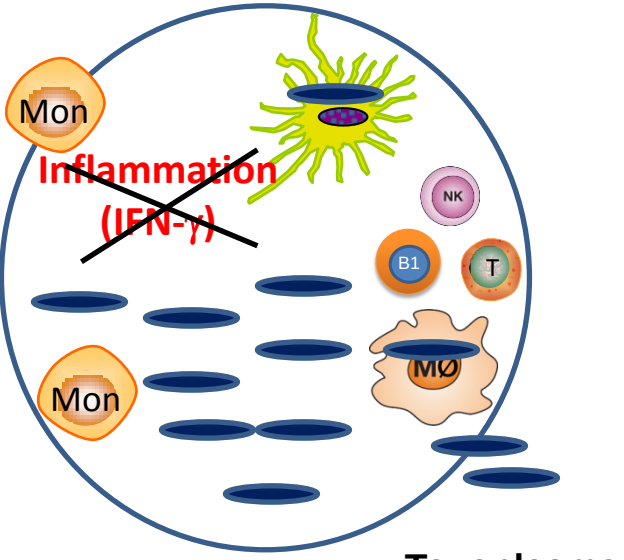
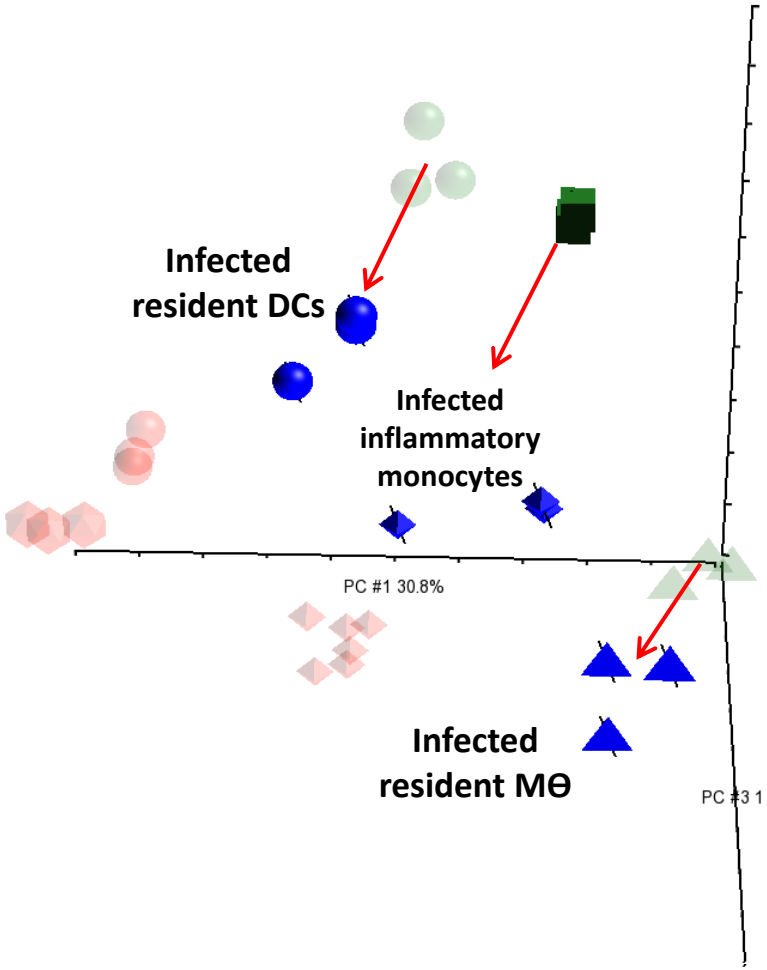


Toxoplasma

Uncontrolled infection **No IL-12 Impaired Th1**

After T. gondii infection in the absence of IFN-γ



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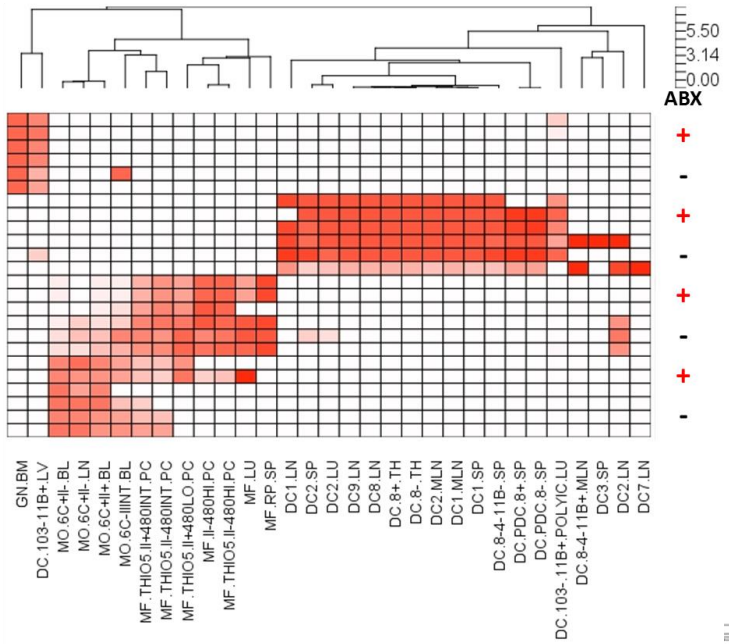
NK cell-derived interferon-γ orchestrates cellular and the differentiation of monocytes into dendritic cells at the site of infection.
Immunity. 2012;36:1047-59

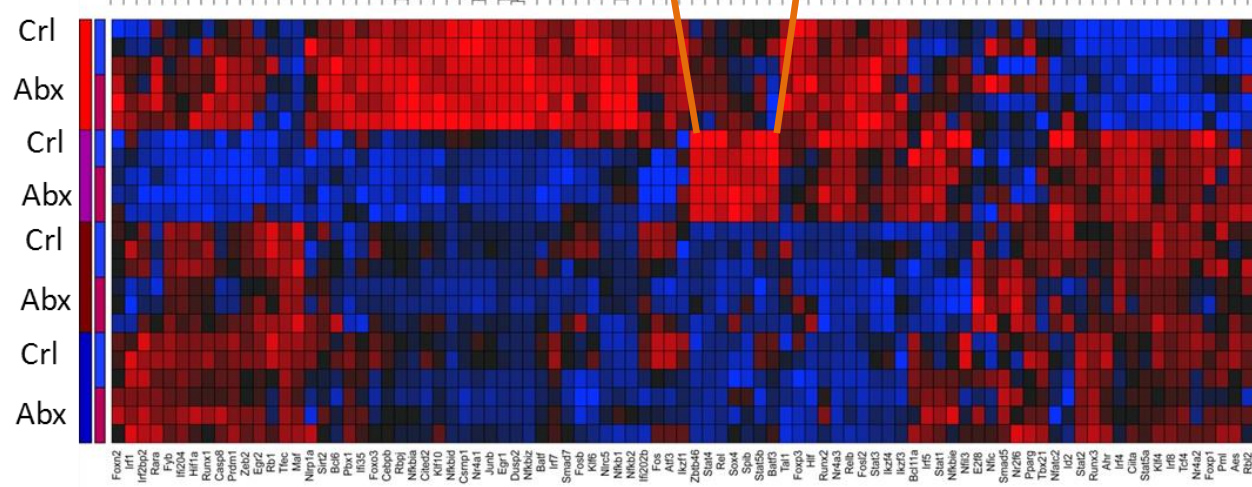
Cellular and molecular characterization of tumor-associated myeloid cells:

Immgen cell populations identified by the complete NanoString geneset using Gene Set Enrichment Analysis (GSEA) analysis



The CD11c++, MHCII++DC population consists of a mixture of DC types, majority of whom have CD103-CD11b+ phenotype, however there is a visible signature of CD8α+ DCs and pDCs.

ZBTB46
STAT4
REL
SOX4
SPIB
STAT5B
BATF3



Neutrophils (Ly6G +++)

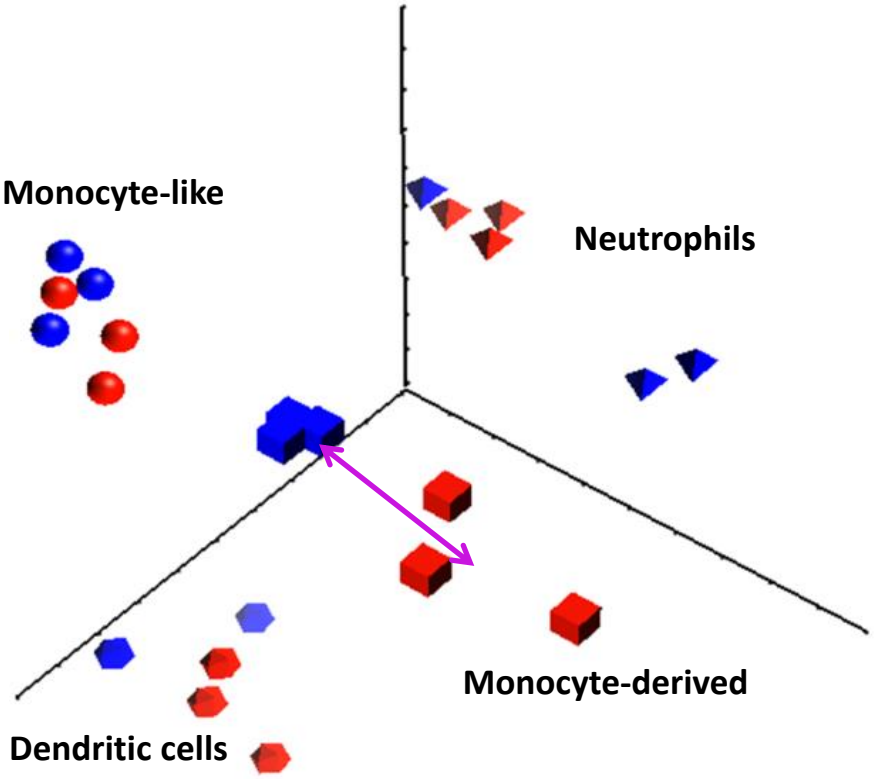
Dendritic cells (CD11c ++; MHCII ++)

Monocyte-derived (Ly6C +; F4/80 +)

Monocyte-like (Ly6C +++)

EL4 tumor (Nanostring, 500 genes)

Gene expression changes in tumor-infiltrating myeloid cells in ABX treated mice



- Monocyte-derived (Ly6C int; F4/80 int)
- Monocyte-like (Ly6C high)
- Neutrophil-like (Ly6G high)
- Dendritic cells (CD11c high; MHCII high)

Untreated

Antibiotics

EL-4 tumor, Nanostring , 500 gene expression (PCA analysis)

Commensal Microbiota

Pathogens & Pathobionts

Patter Recognition (Innate) Receptors

TLRs
IL-1Rs
SCFA-Rs
NODs
NRLPs
AHR
FXR
.....

Microbial & Host Factors

LPS
Formyl-Met-Leu-Phe
SCFA
DNA, RNA
.....
IL-18
IL-1
IL-10
IL-23
IL-22
IL-33
TGF-β
Vitamin A
Serum Amyloid A
IFNs
.....

Innate & Adaptive Immunity Effector Cells

Macrophages
Neutrophils
Monocytes
Dendritic Cells
.....
Th17
Th1
Treg
NK cells
ILC3
.....

Tumor initiation, growth progression and dissemination, response to therapy

Tissue homeostasis, metabolism, innate and adaptive immunity

Medicine's battlefield strategy: Human body as a battleground

Freely adapted from ideas expressed by Costello et al. Science 336:1255 (2012)

Medicine as park management: Humans as habitat (targeted removal of invasive, restoration, promotion of native species)

THANKS to:

Our friendly gut bacteria

Franco Marincola
Ena Wang

Sidra Research Center, Doha, Qatar

Amiran Dzutsev
Noriho Iida
Andy Charles Stewart
Romina Goldszmid
Rosalba Salcedo

Cancer and Inflammation Program,
CCR, NCI, Frederick, MD

Shruti Naik
Nicolas Bouladoux
Yasmine Belkaid

Rebecca Weingarten
Karen Frank

NIH, Bethesda, MD