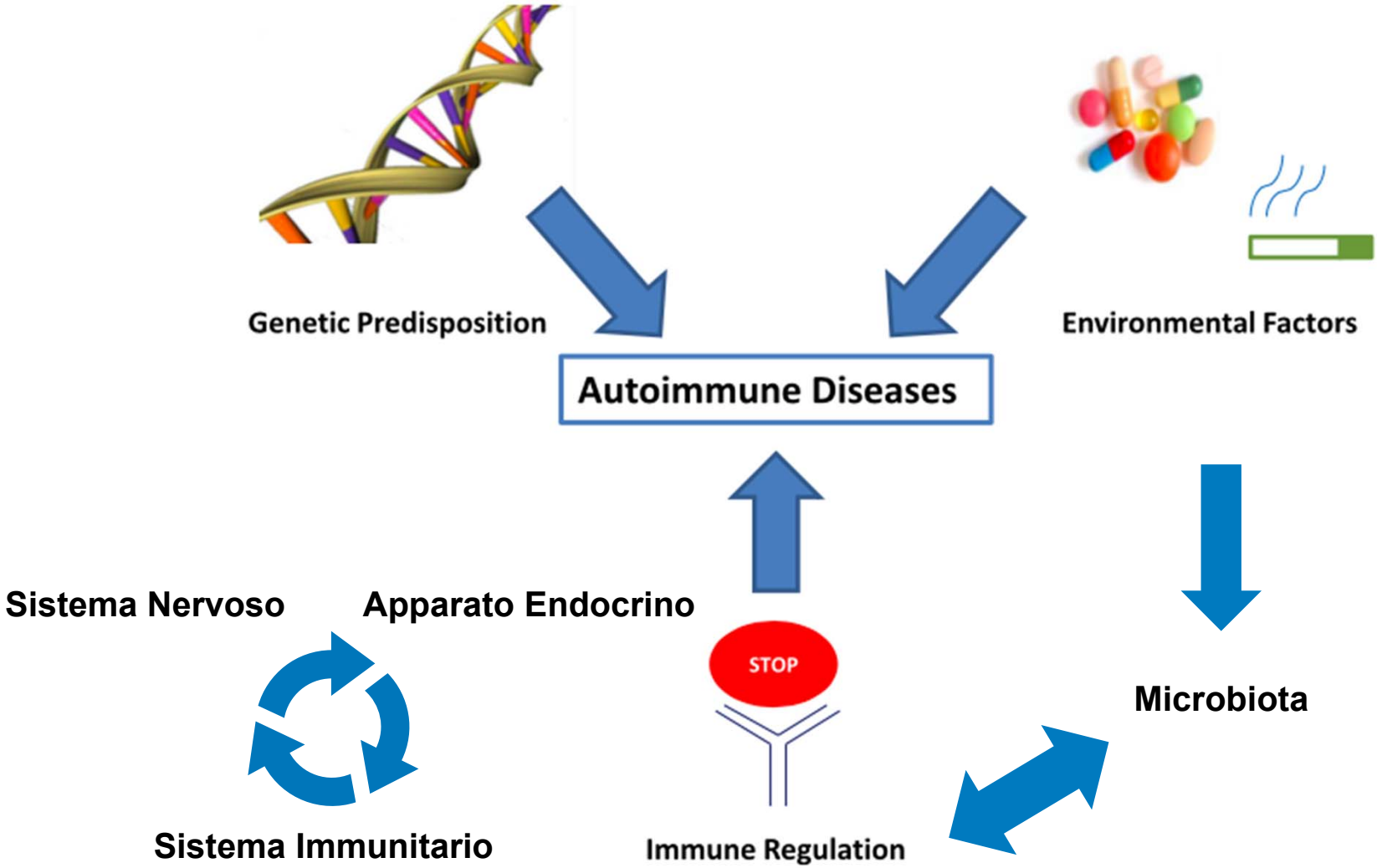
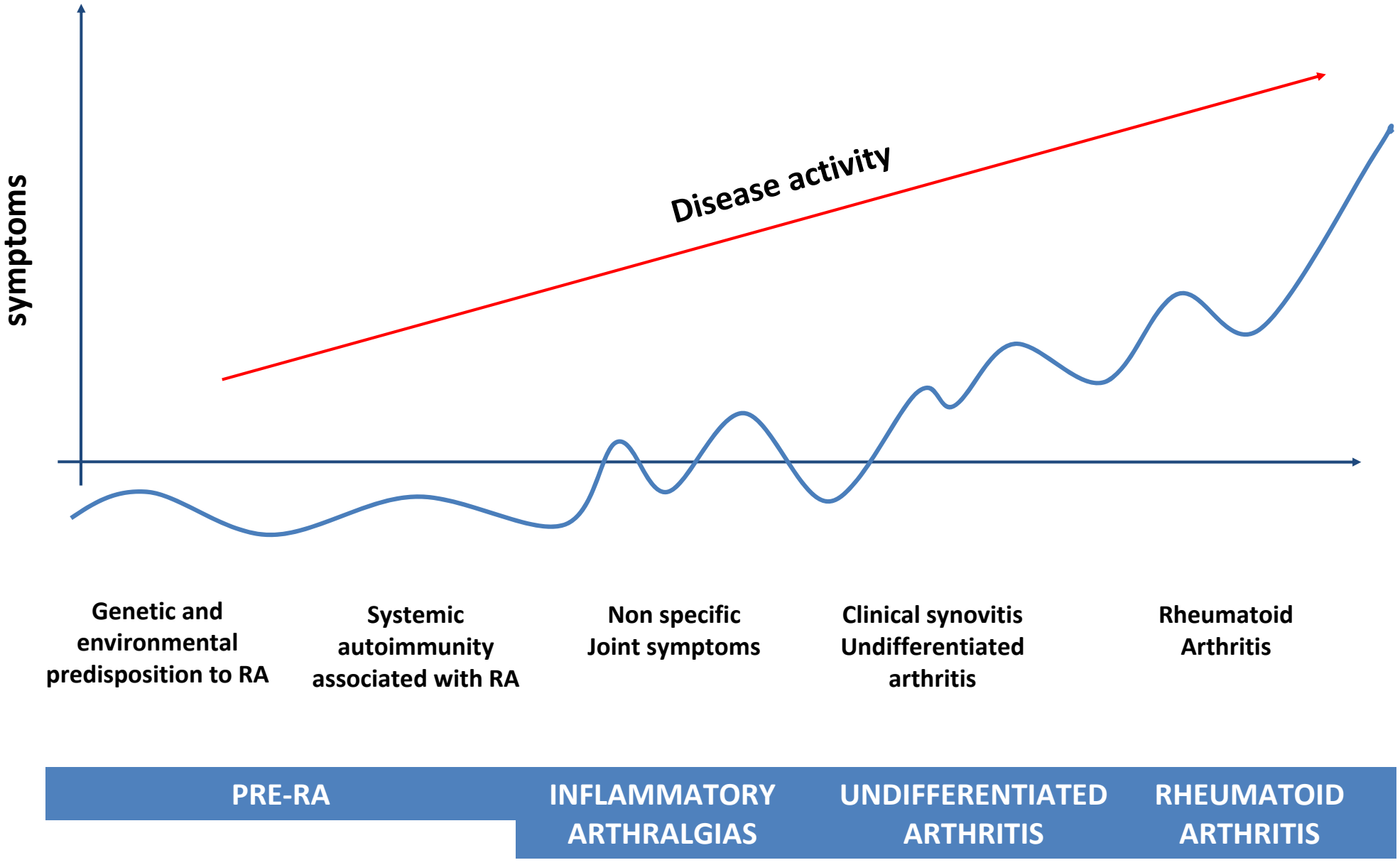
Permeabilità intestinale nelle malattie infiammatorie ed autoimmuni

Dr Gianluca Santoboni
Specialista in Reumatologia

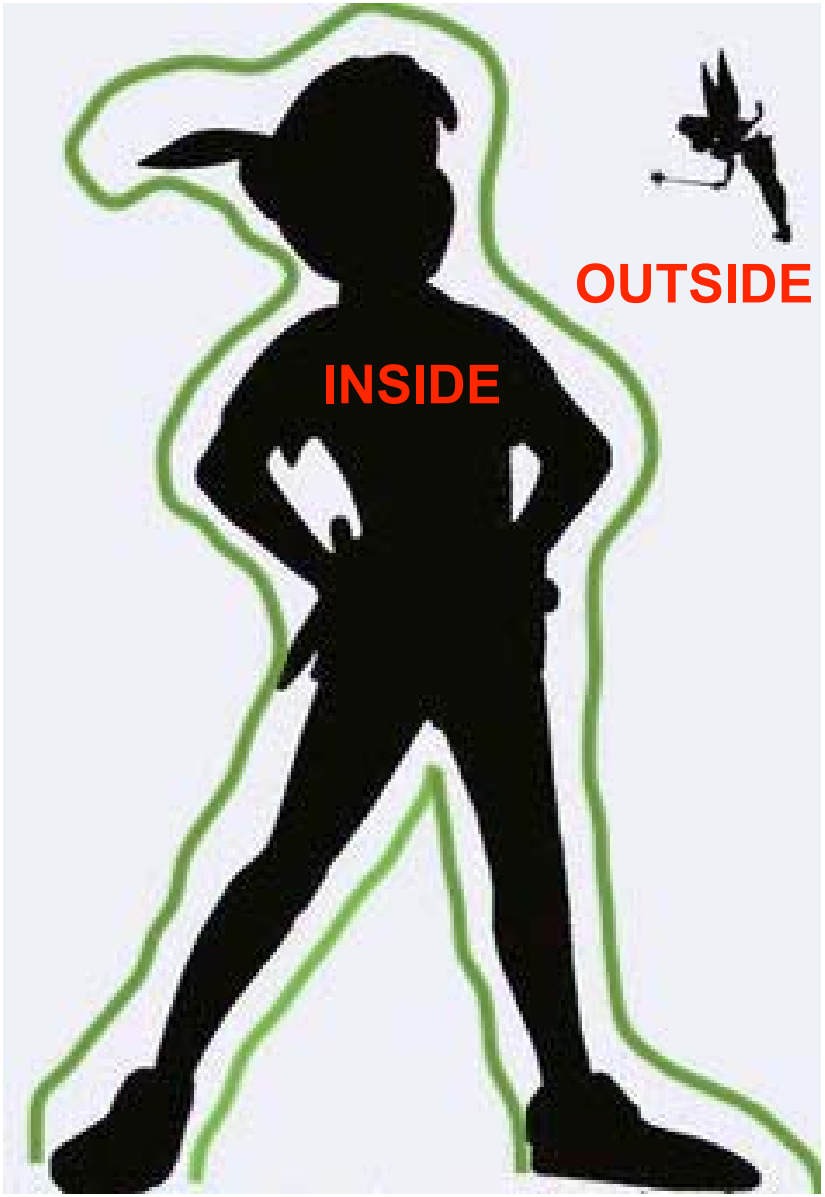
Dxwrlp p xqlw





Gerlag D et al, Ann Rheum Dis 2012; 71: 638-641

Scambio di informazioni



Sviluppo ed Evoluzione

Barriera PSICO-FISICA

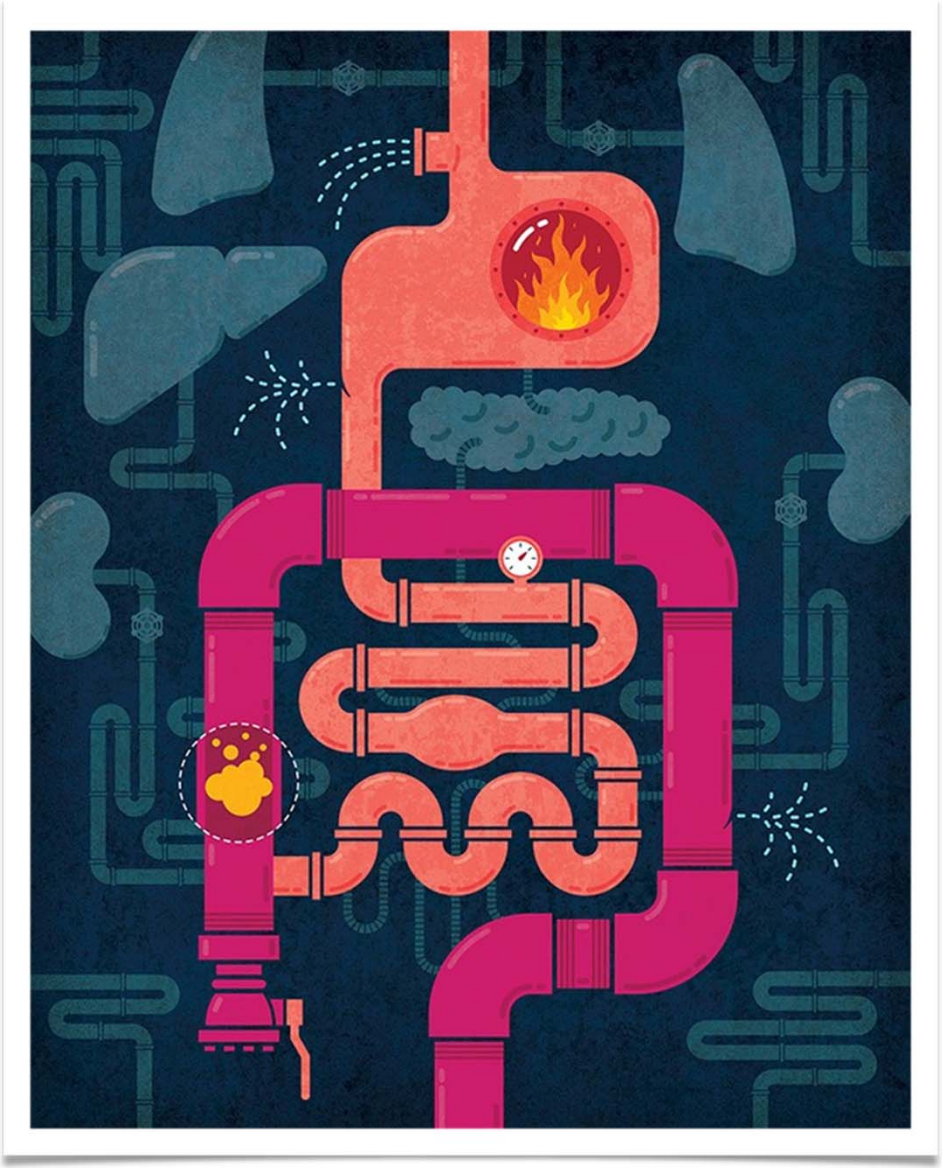
GALT 70% del sistema immunitario umano

Il più **grande** e **complesso** compartimento del **sistema immunitario**

Pericoloso

Harmful

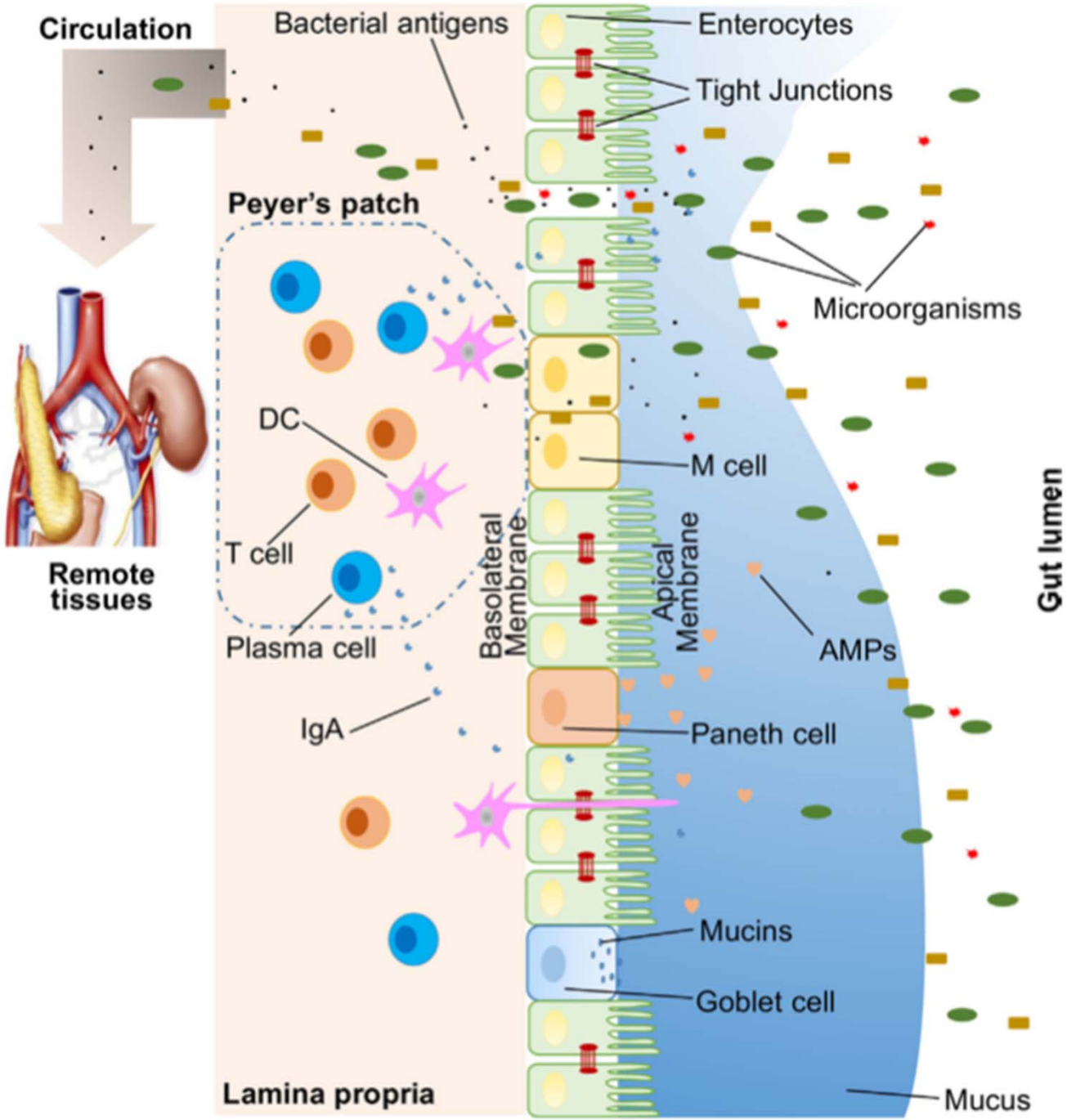
(immunity)



Innocuo

Harmless

(tolerance)



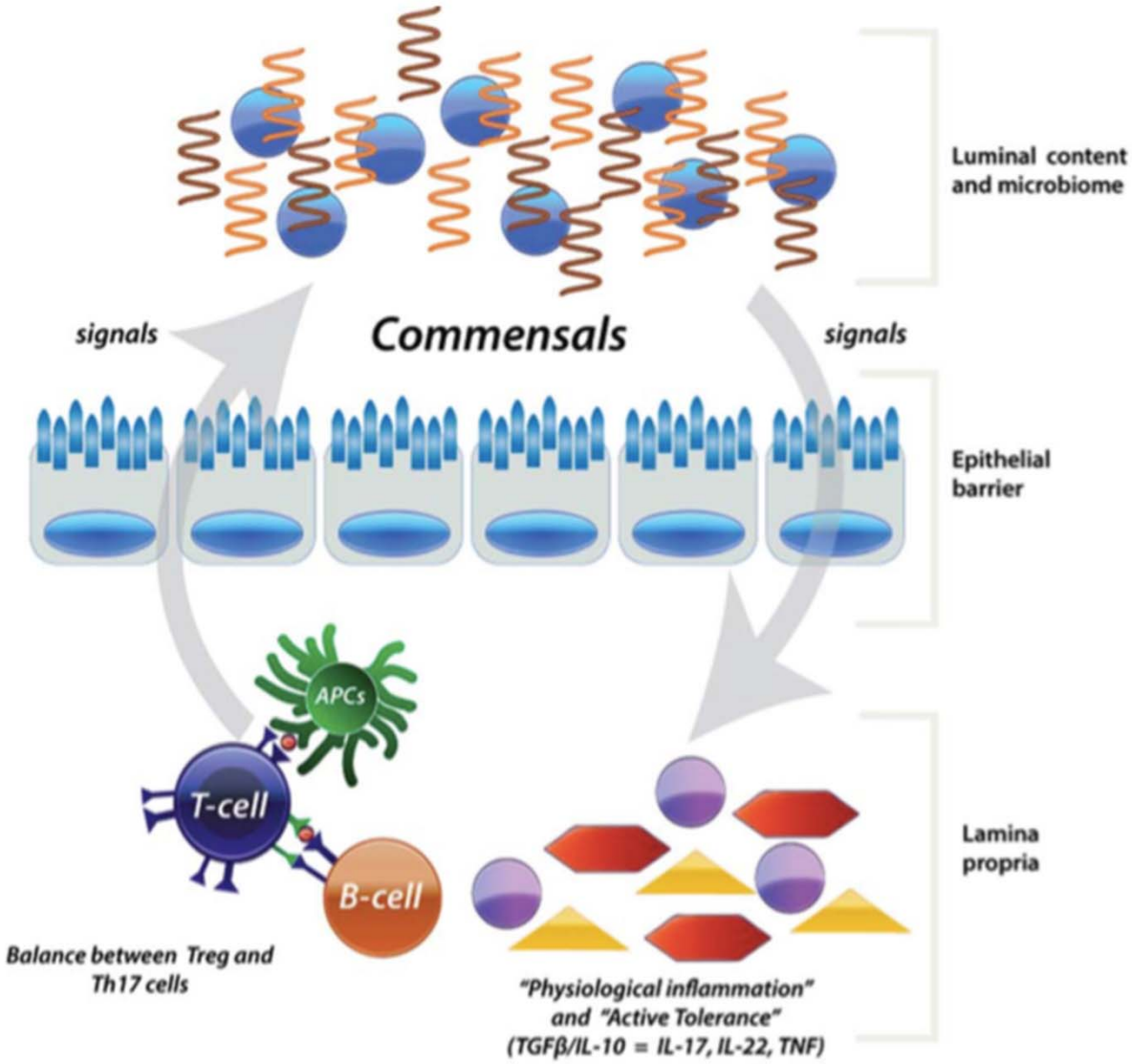
Barriera Fisica
Epitelio intestinale
Muco
Microbiota commensale

Barriera BioChimica
AMPs

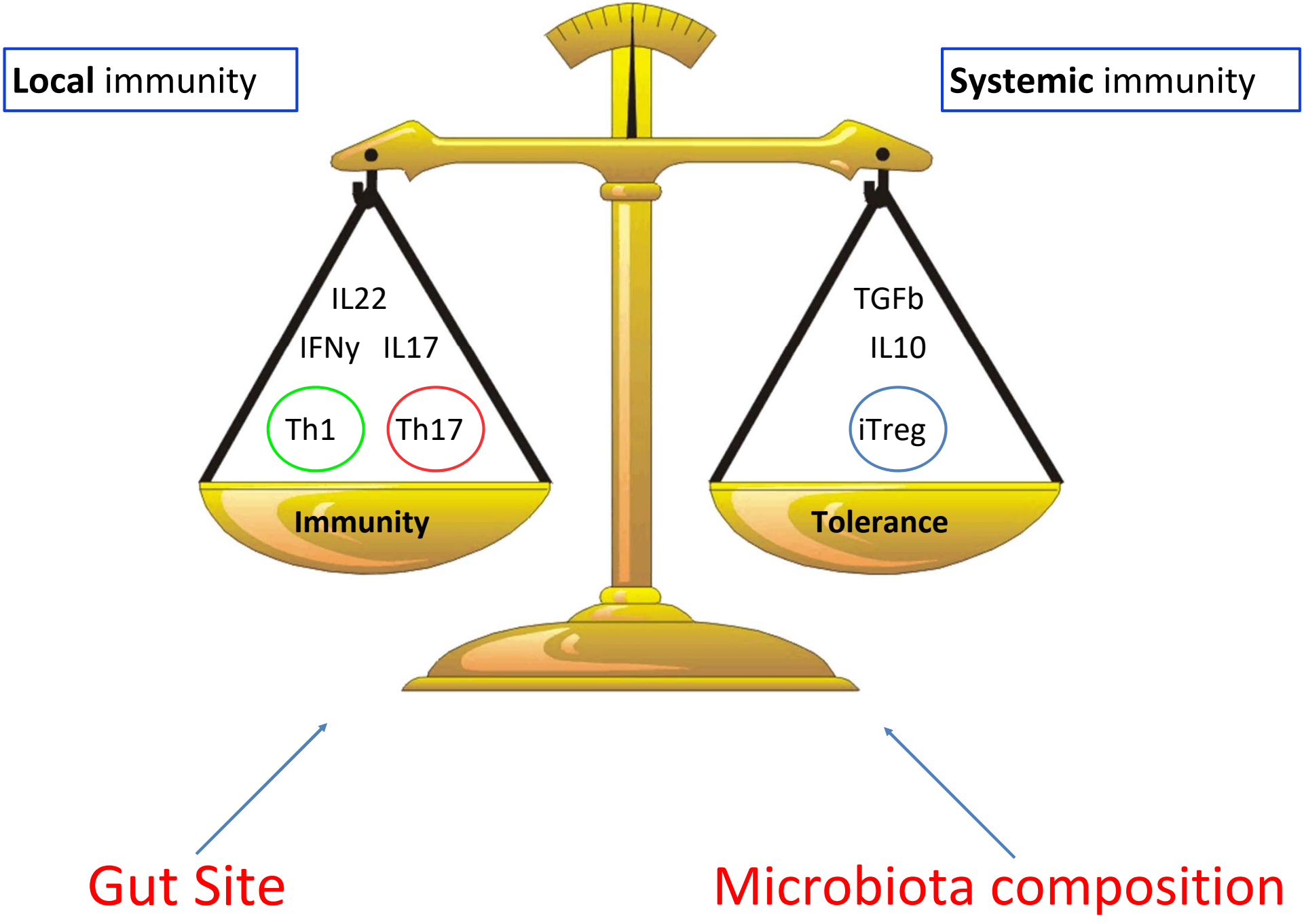
Barriera Immunologica

Quinhui Mu et al, Front Imm 2017

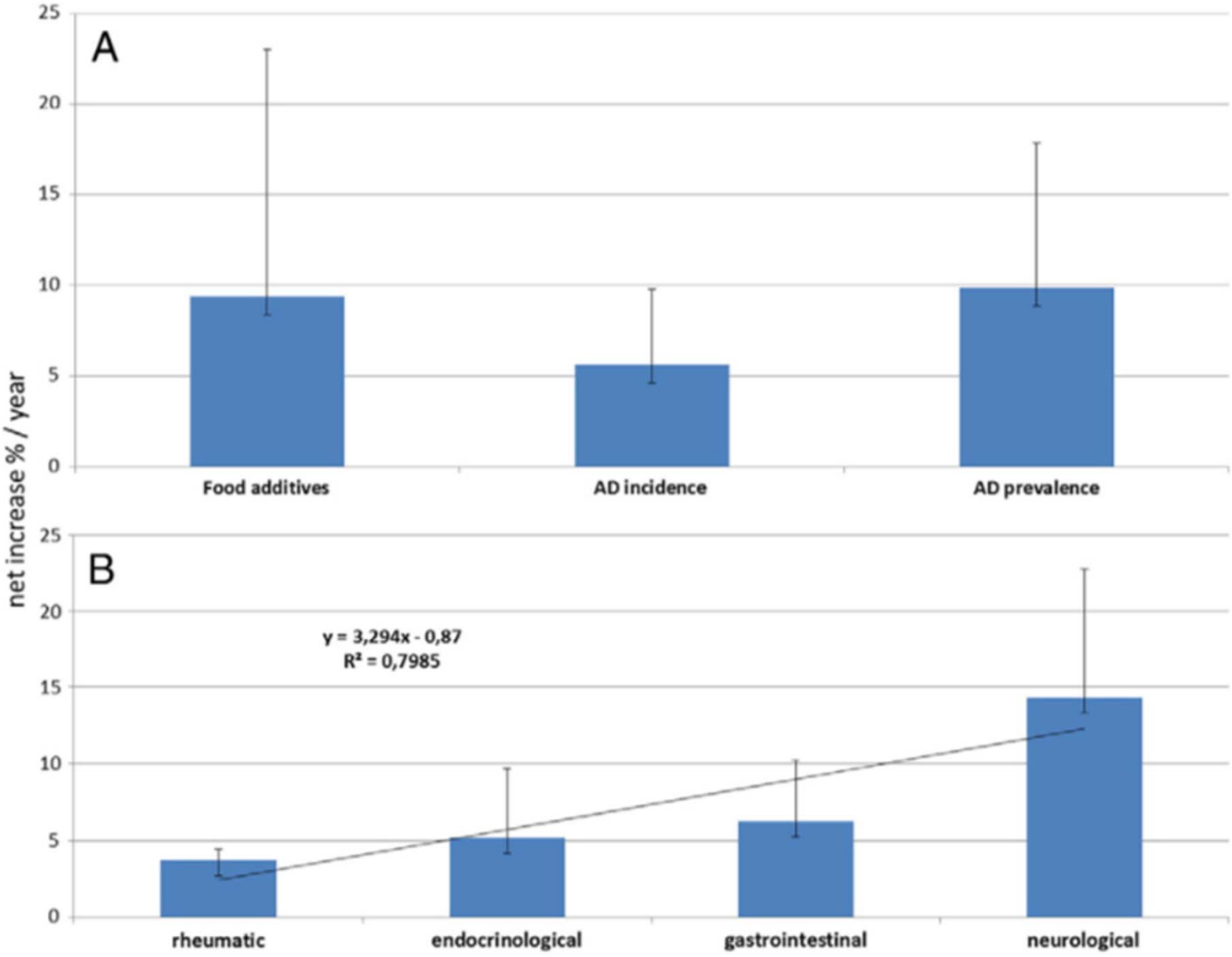
Regulatory role of Gut Microbiota



Scher JU, *A&R 2016*

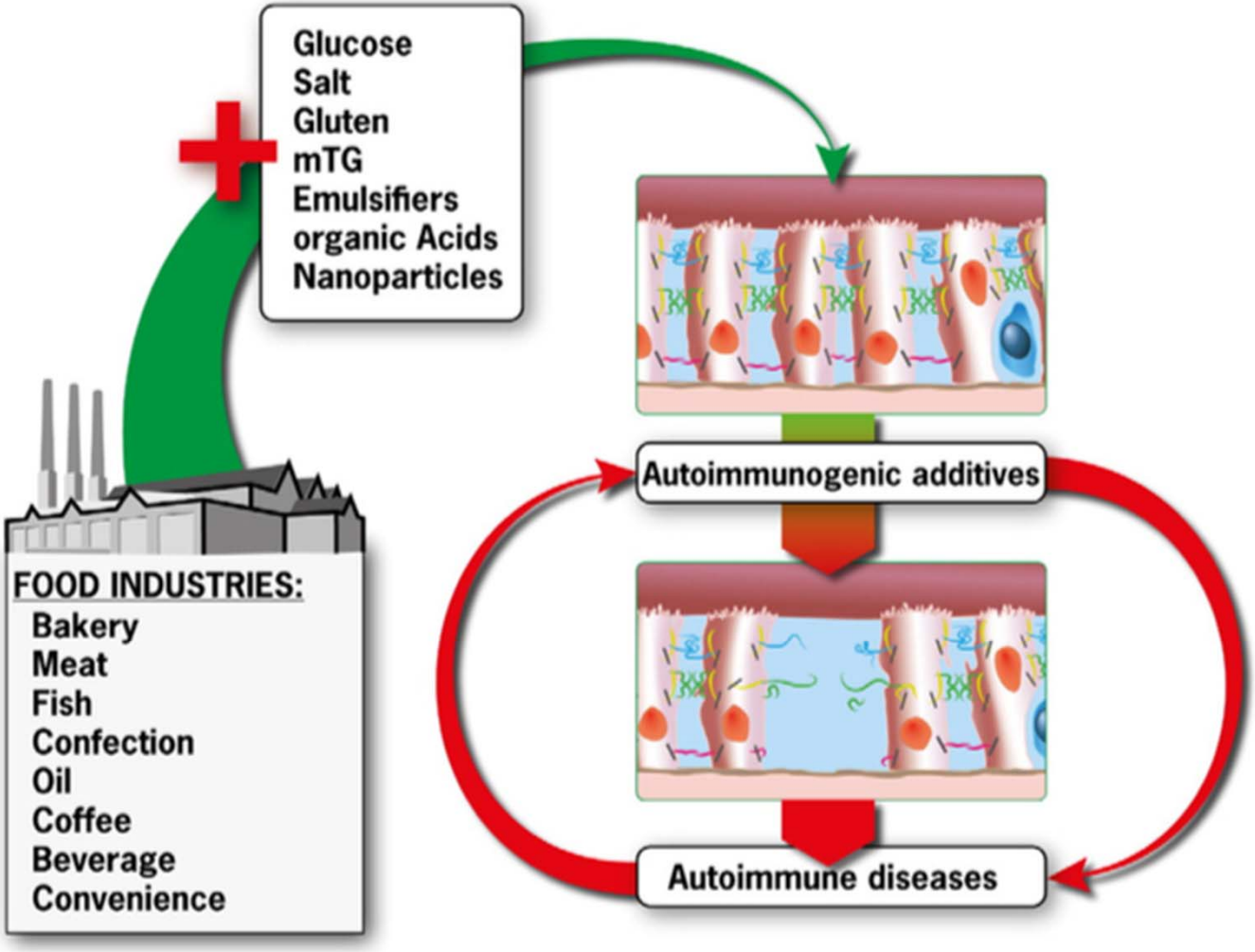

Local immunity
Systemic immunity
IL22
IFNy
IL17
Th1
Th17
Immunity
TGFb
IL10
iTreg
Tolerance
Gut Site
Microbiota composition

L’incidenza e la prevalenza delle malattie autoimmuni è in crescente aumento



Lerner A, Aut Rev 2015

Alterazione della permeabilità intestinale



Mimetismo molecolare

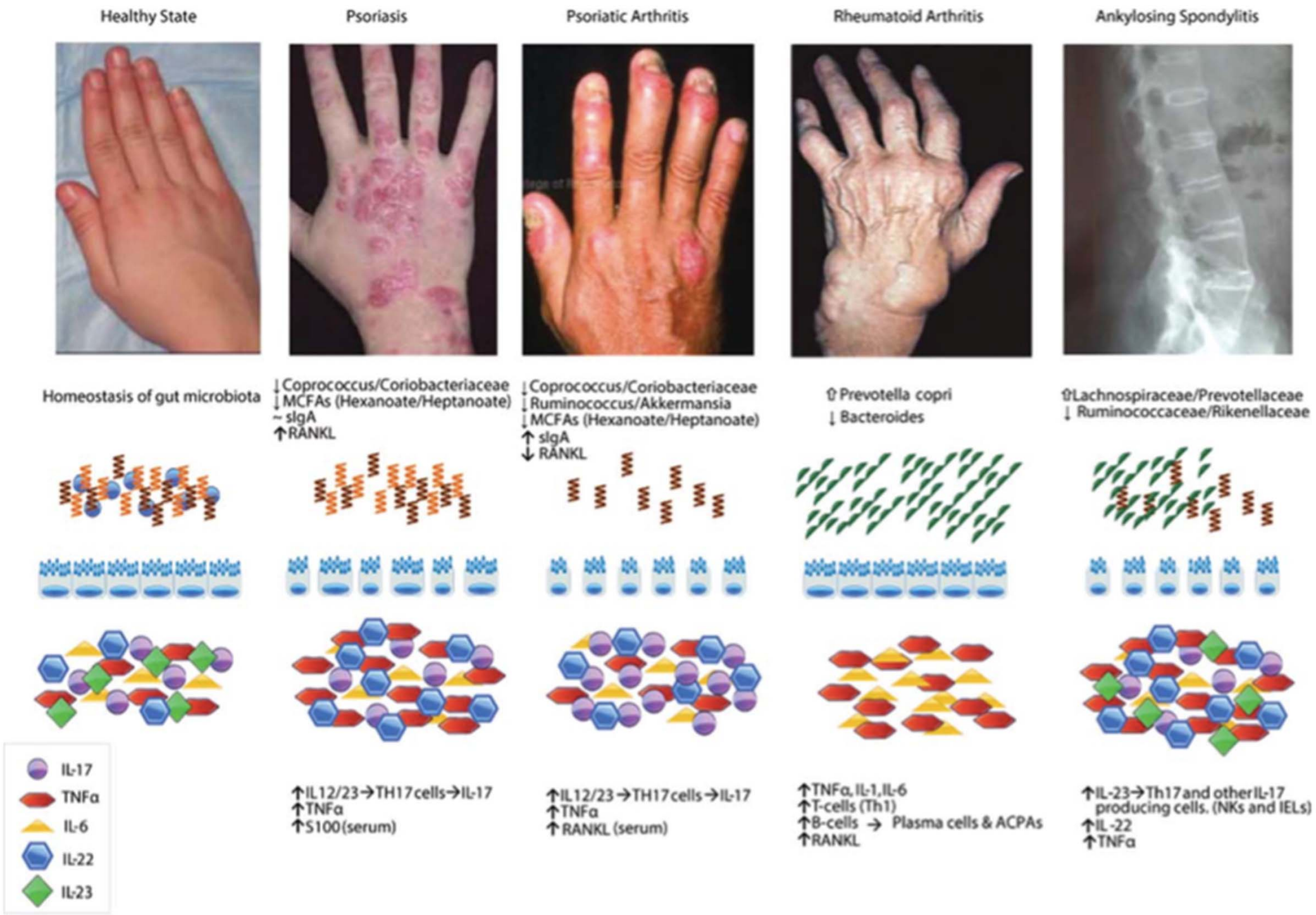
Immunogenicità dei nutrienti

Alterazioni del microbiota

Modificazione della metilazione del DNA e degli istoni (epigenetica)

Apteni

Lerner A, Aut Rev 2015



Scher JU, *A&R 2016*

AD e permeabilità intestinale

- Celiachia
- Malattie infiammatorie intestinali
- Diabete Mellito tipo 1
- Sclerosi multipla
- Artrite Reumatoide
- Spondilite Anchilosante

Permeabilità intestinale nelle malattie reumatiche autoimmuni

Table 2 Demographic characteristics of the patients and the percentages of ^{51}Cr- EDTA excreted

*Groups**	*Sex and age (years (SD))*	*Excretion (% (SD))*
BS (n=34)	20M, 14F (37 (10))	4.6 (2.6)
AS (n=10)	8M, 2F (33 (13))	6 (2.4)
IBD (n=6)	2M, 4F (40 (18))	5.2 (1.9)
SLE (n=17)	9F (29 (11))	5.56 (1.78)
HC (n=15)	9M, 6F (35 (10))	2.3 (1)

Analysis of variance: f=6.4, p=0.0002. The significance disappears once the healthy group is removed.

Fresko I et al, Ann Rheum Dis 2011

AS

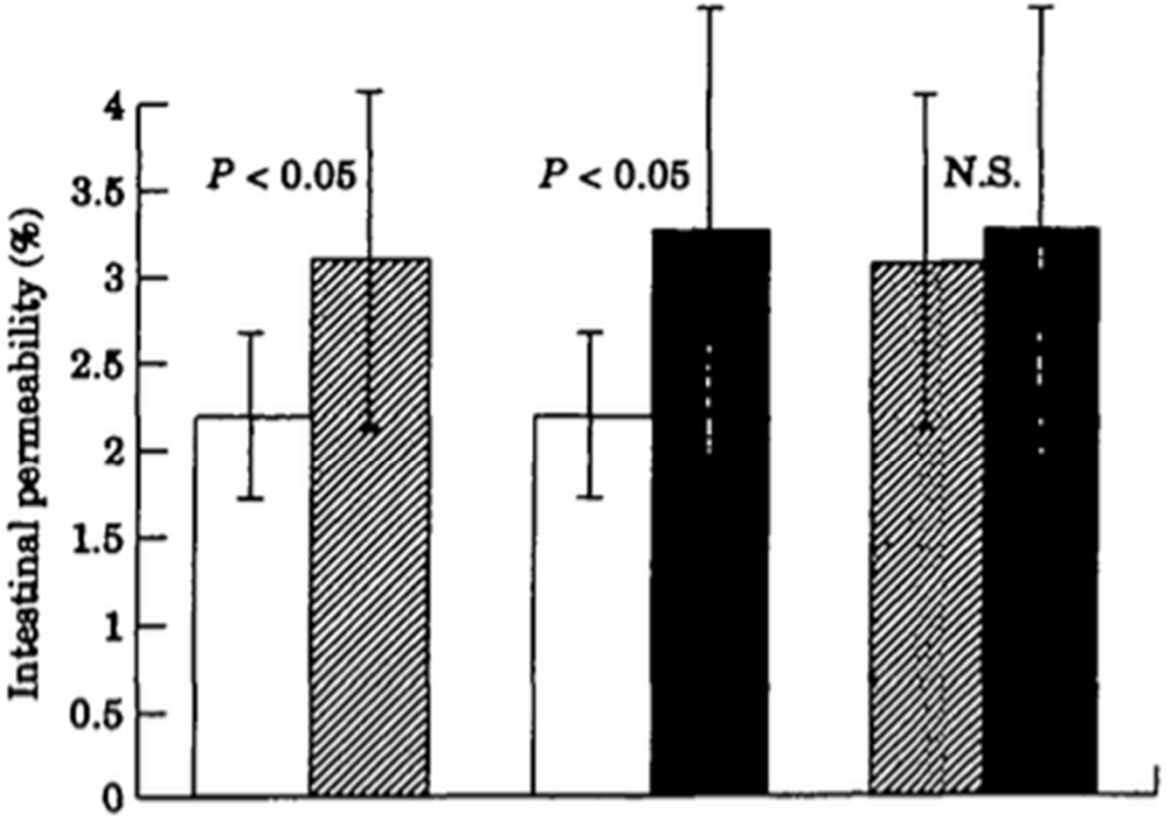
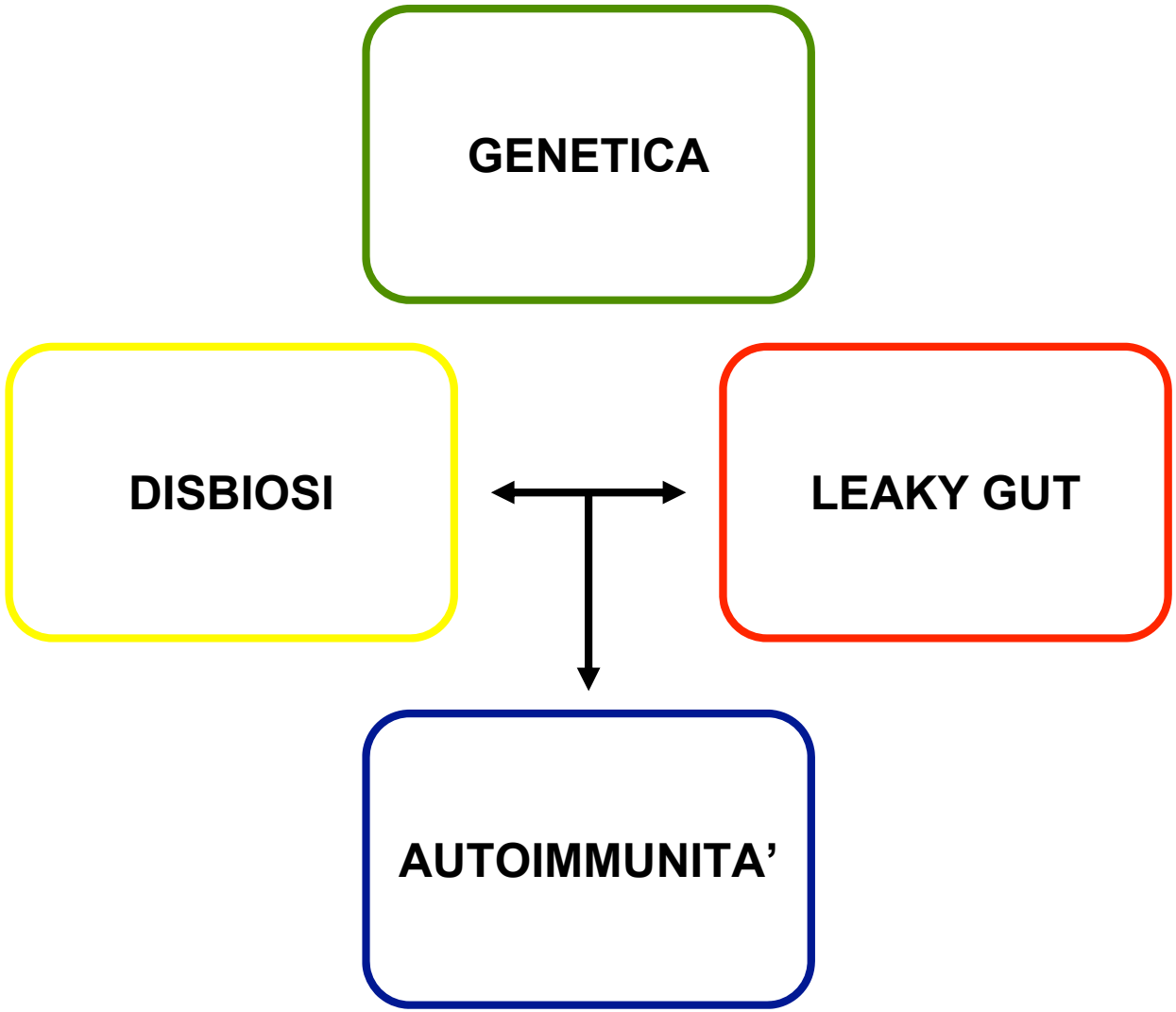


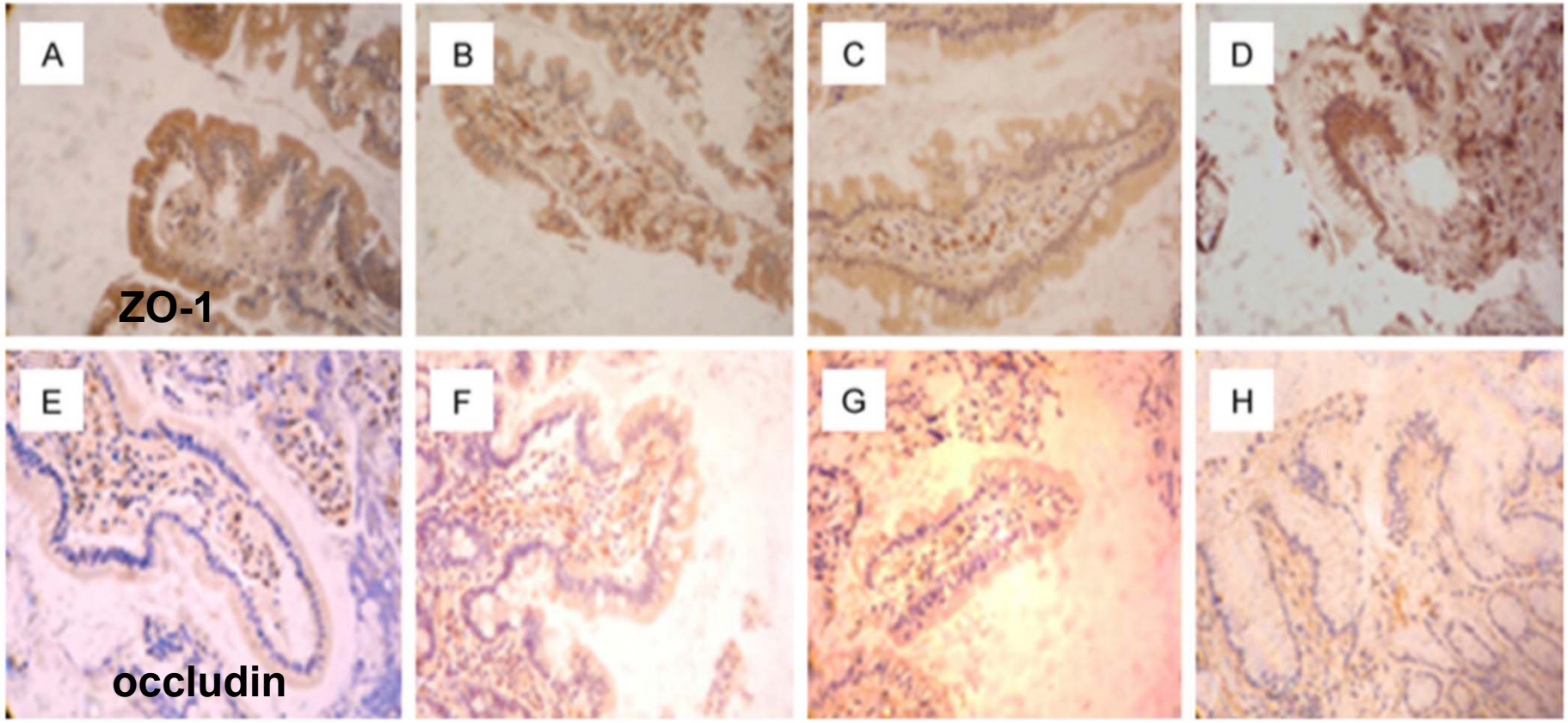
FIG. 1.—Comparison of intestinal permeability values (%) in patients with AS (▨), their relatives (■) and controls (□).

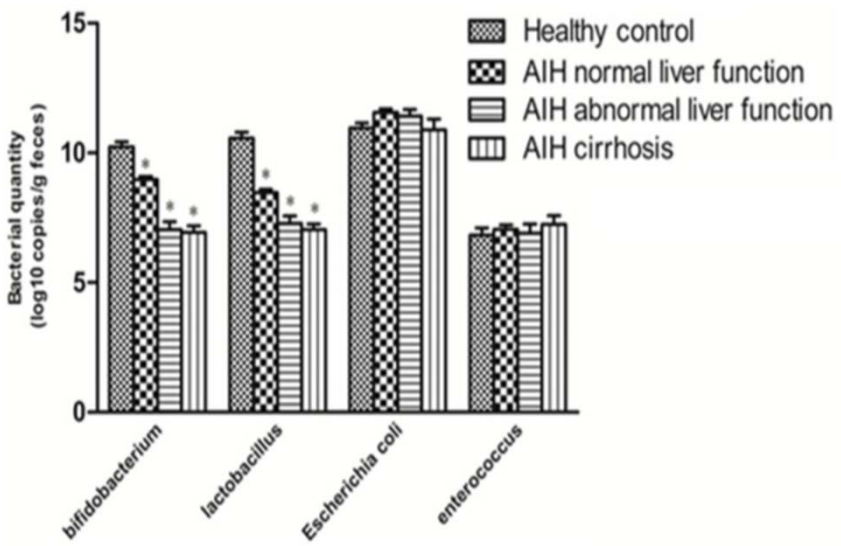
No difference in gut permeability was found between patients and relatives **regardless of** whether they had the **HLA B27 antigen or not.** The increased intestinal permeability in the patients had **no relation to the disease activity, to the presence of peripheral arthritis or to the intake of NS AIDs.** Gut permeability was shown to bear **no relation to IgA levels, ESR or CRP**

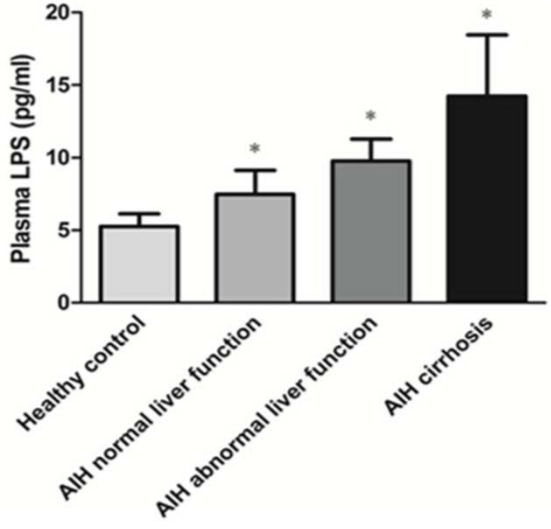
Martinez-Gonzalez O et al, *Rheum* 1994


GENETICA
DISBIOSI
LEAKY GUT
AUTOIMMUNITA’

AIH





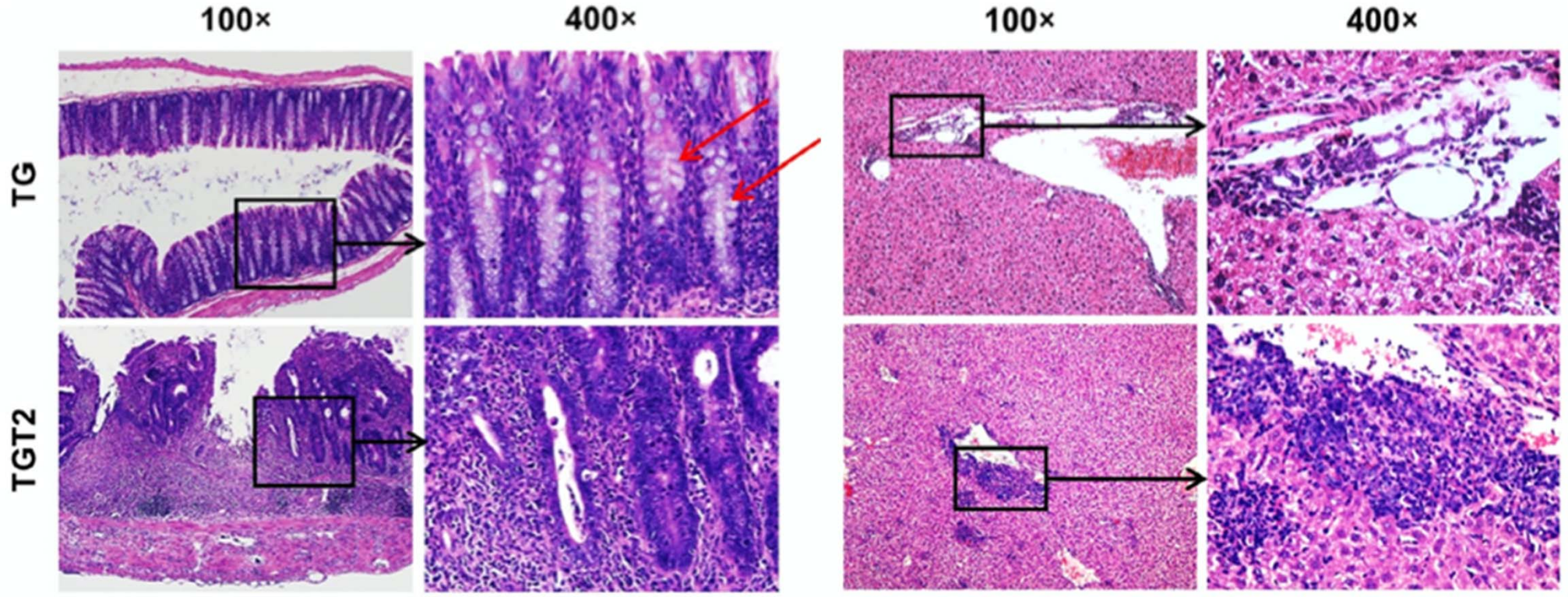


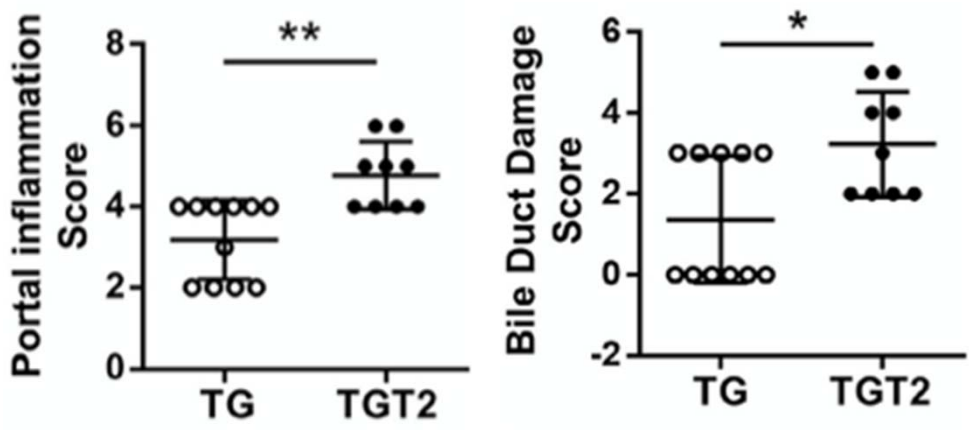
Rui Lin et al, Int Jour Clin Exp Pathol 2015

dnTGFbetaRII
(TG)

TLR2 deficient-dnTGFbetaRII
(TGT2)

PBC





Hong-Di Ma et al, J Autoimmun 2018

dnTGFbetaRII
(TG)

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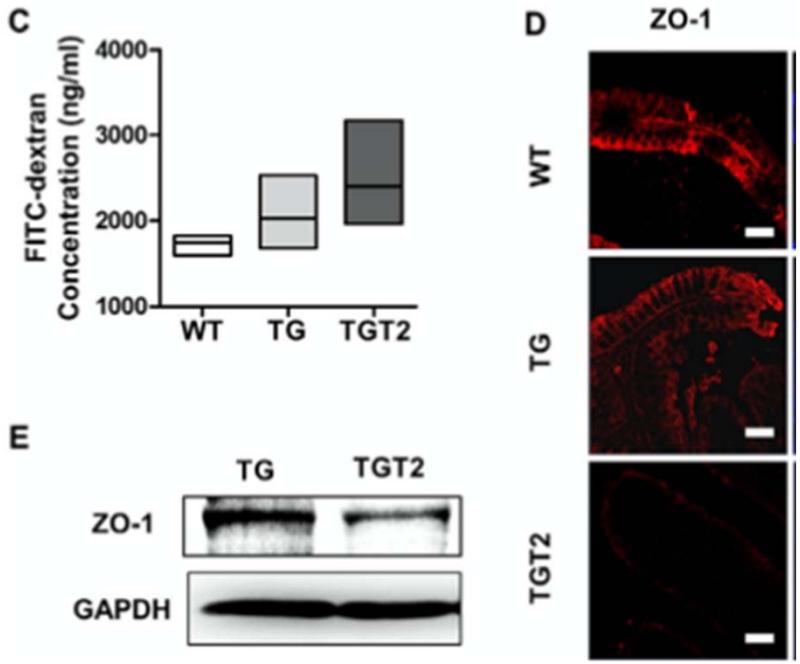
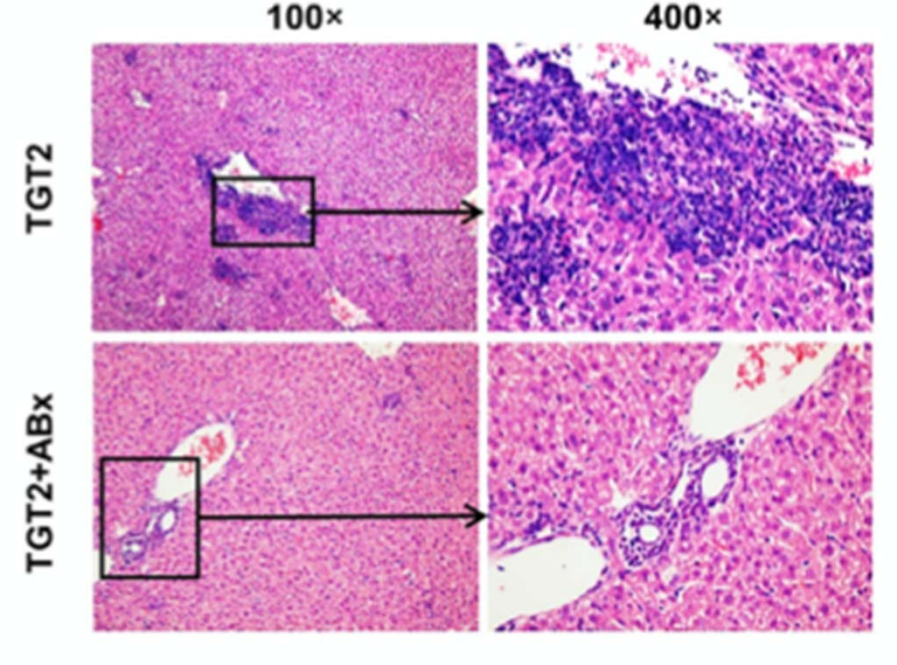
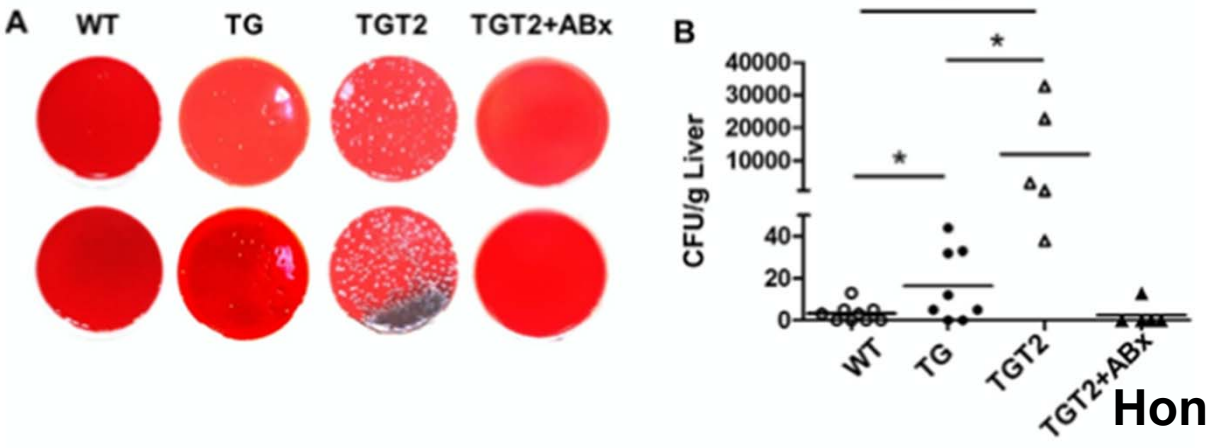
PBC





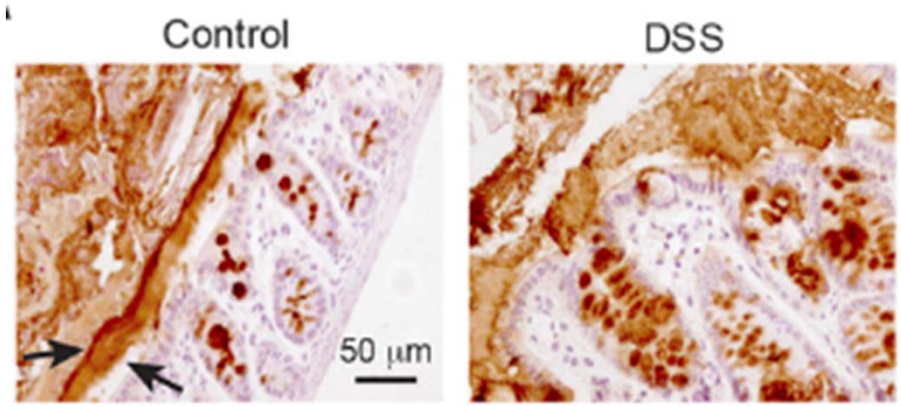


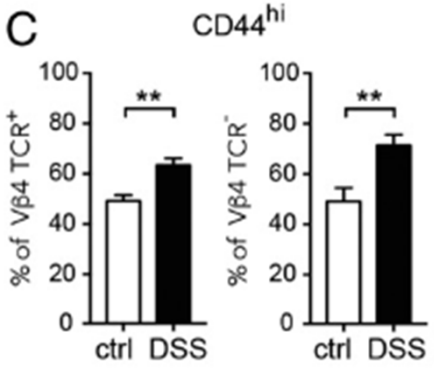
Hong-Di Ma et al, J Autoimmun 2018

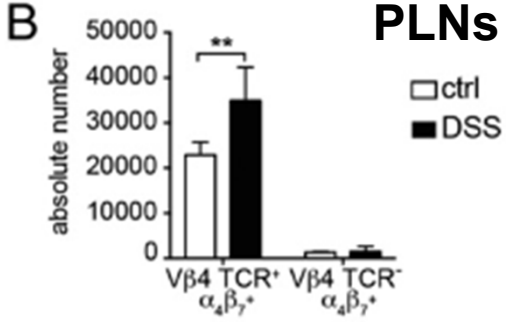
BDC2.5XNOD mice

dextrane sulfate sodium (DSS)

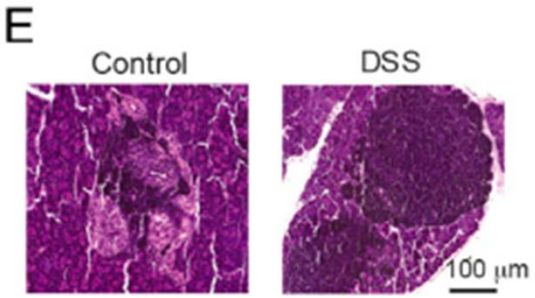
DM1

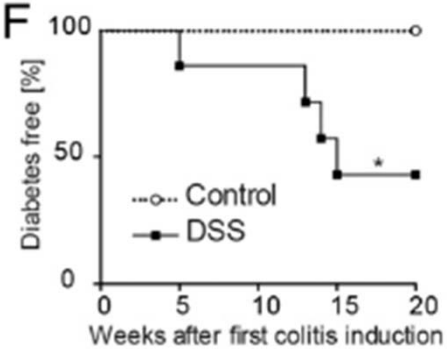




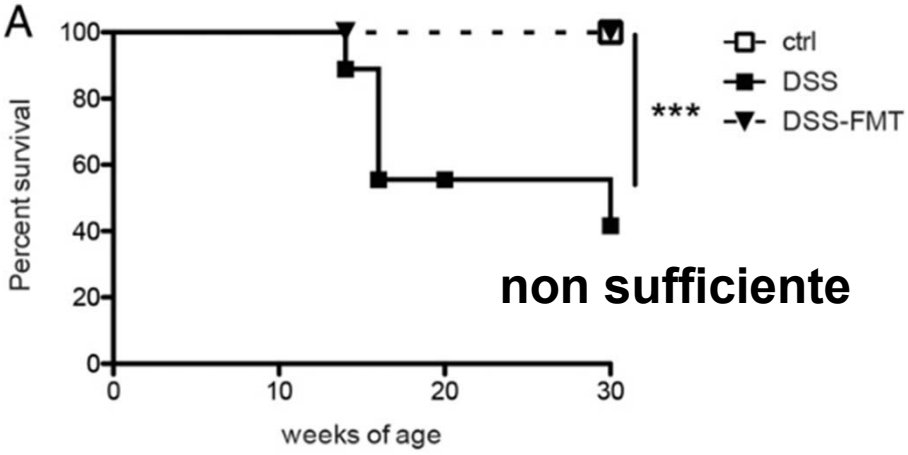


PLNs

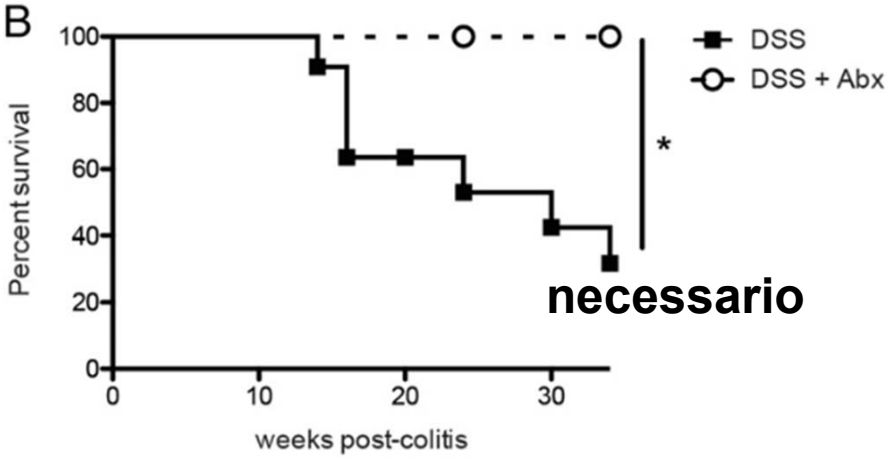




microbiota..



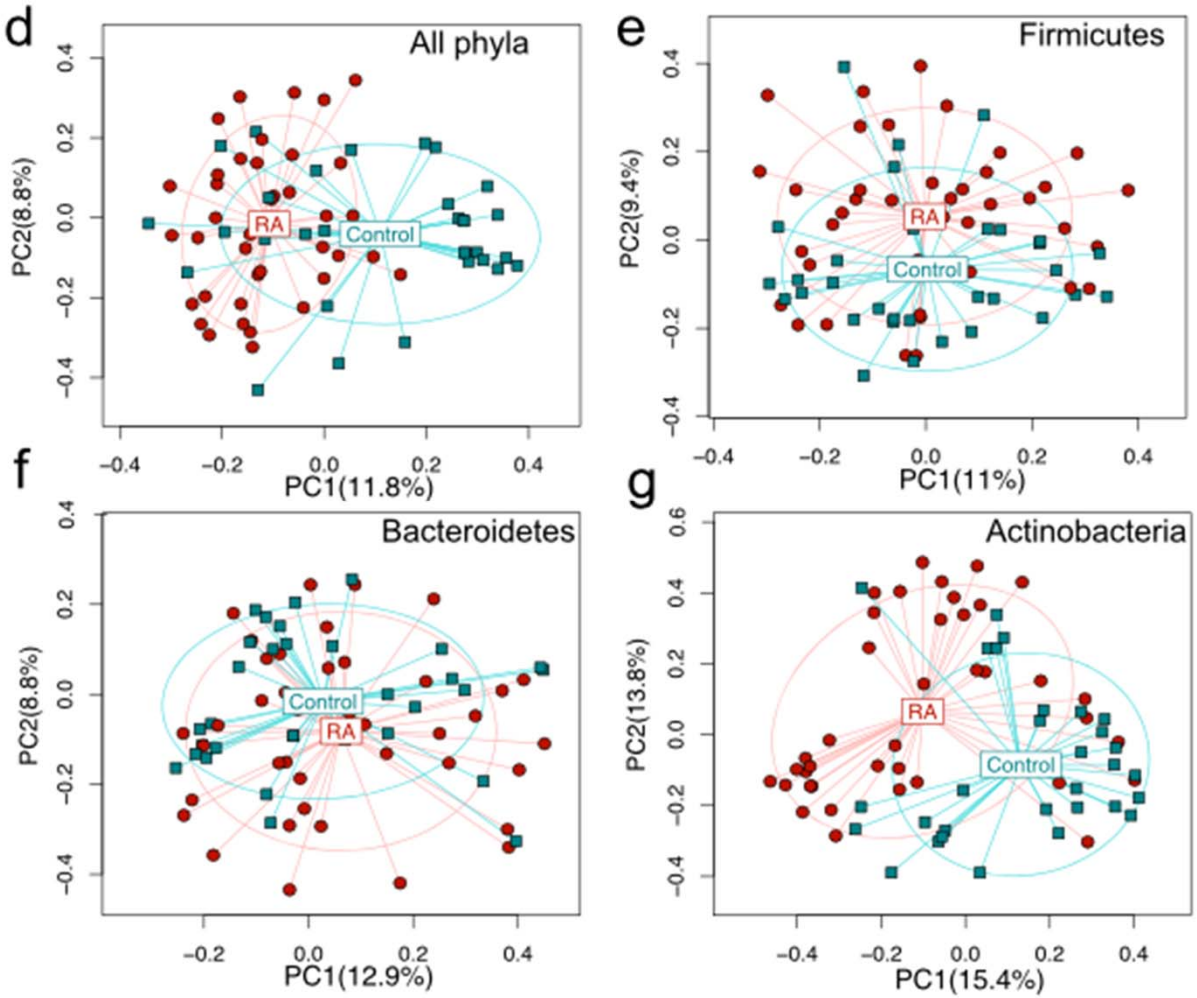
non sufficiente

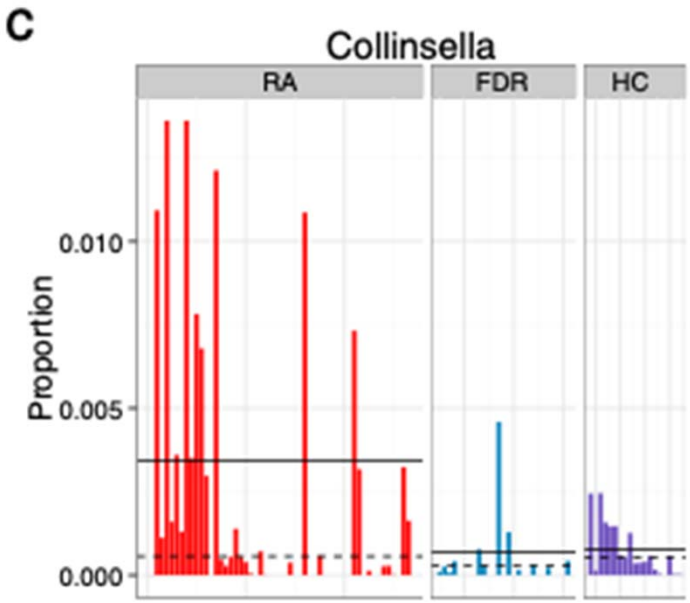


necessario

Sorini C et al, PNAS 2019

RA

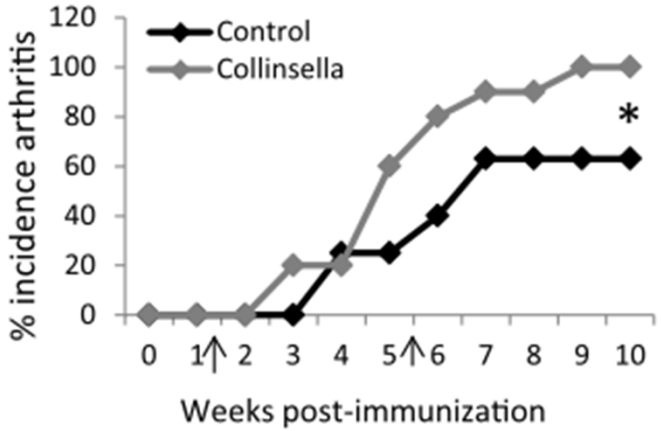


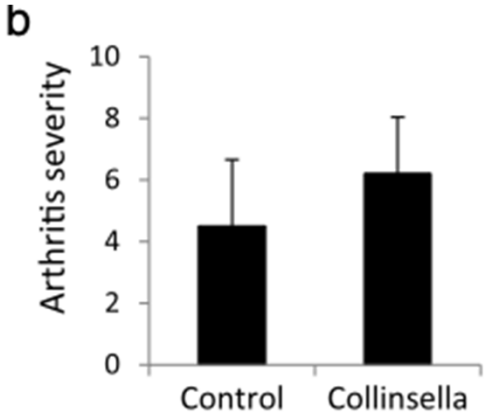


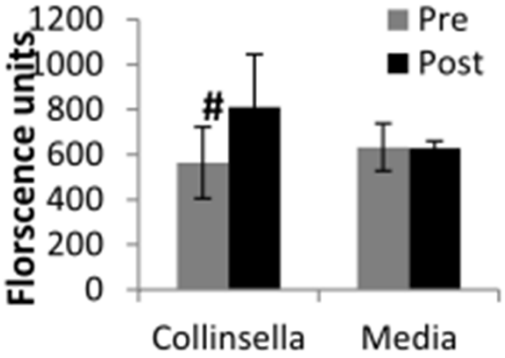
Chen J et al, Genome Med 2016

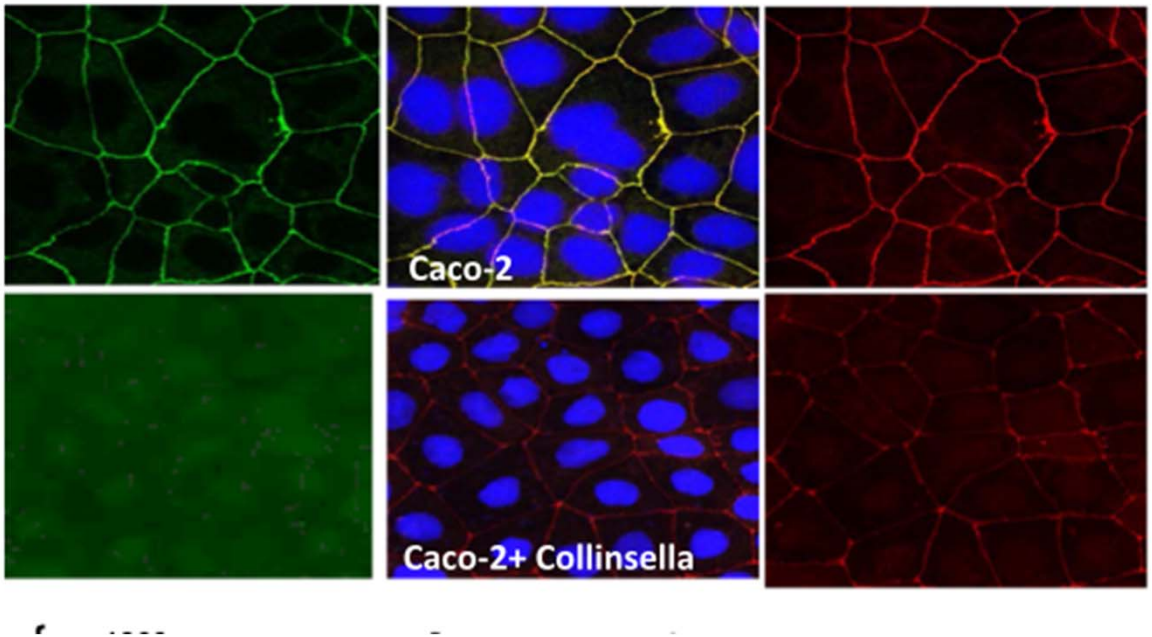
collagen induced arthritis susceptible DQ8 mice

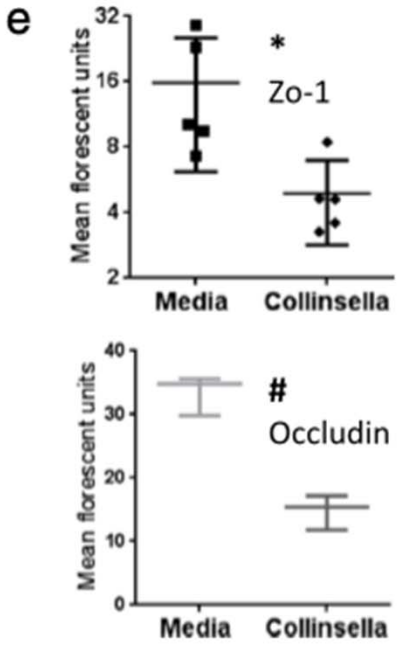
RA





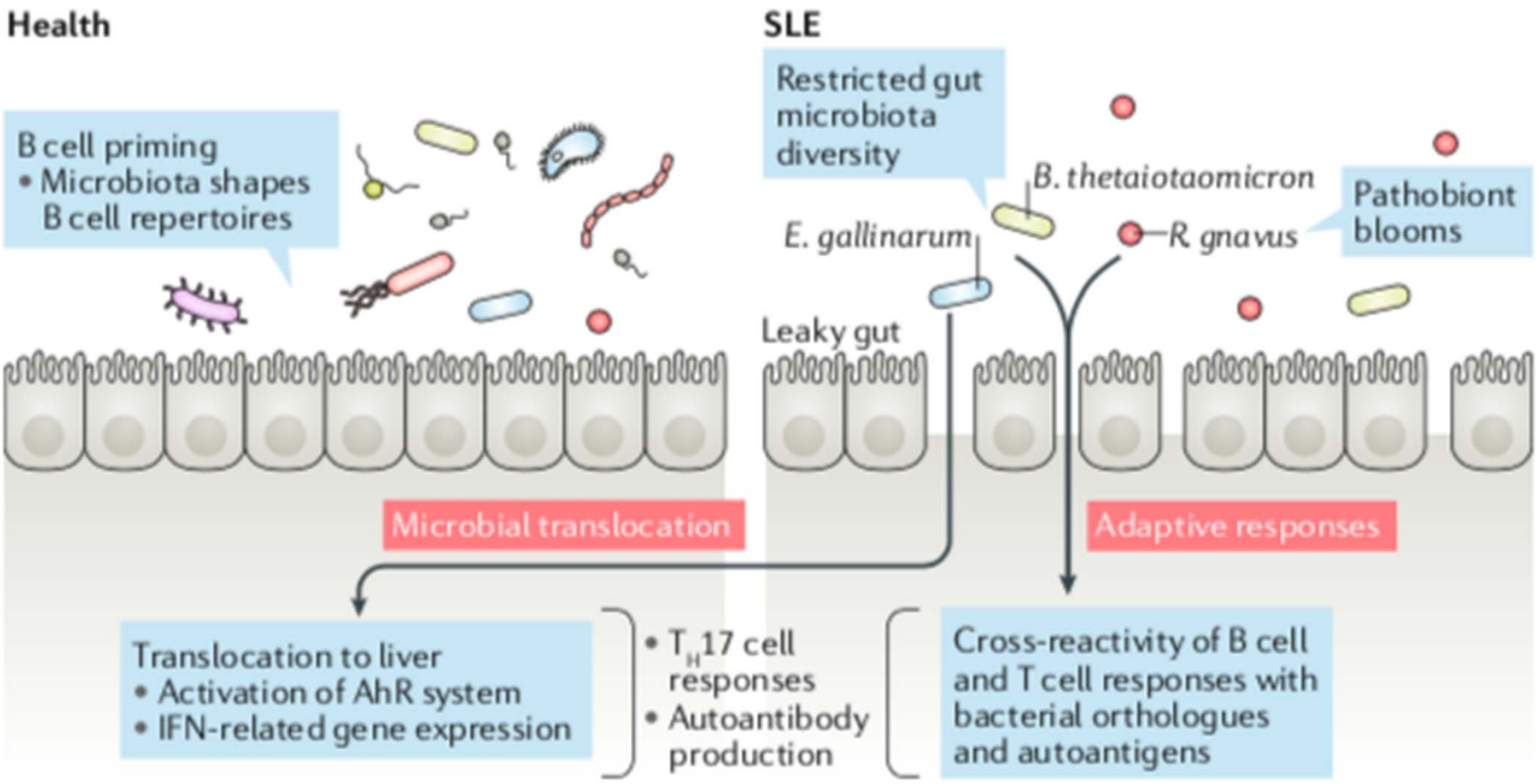






Chen J et al, Genome Med 2016

LES



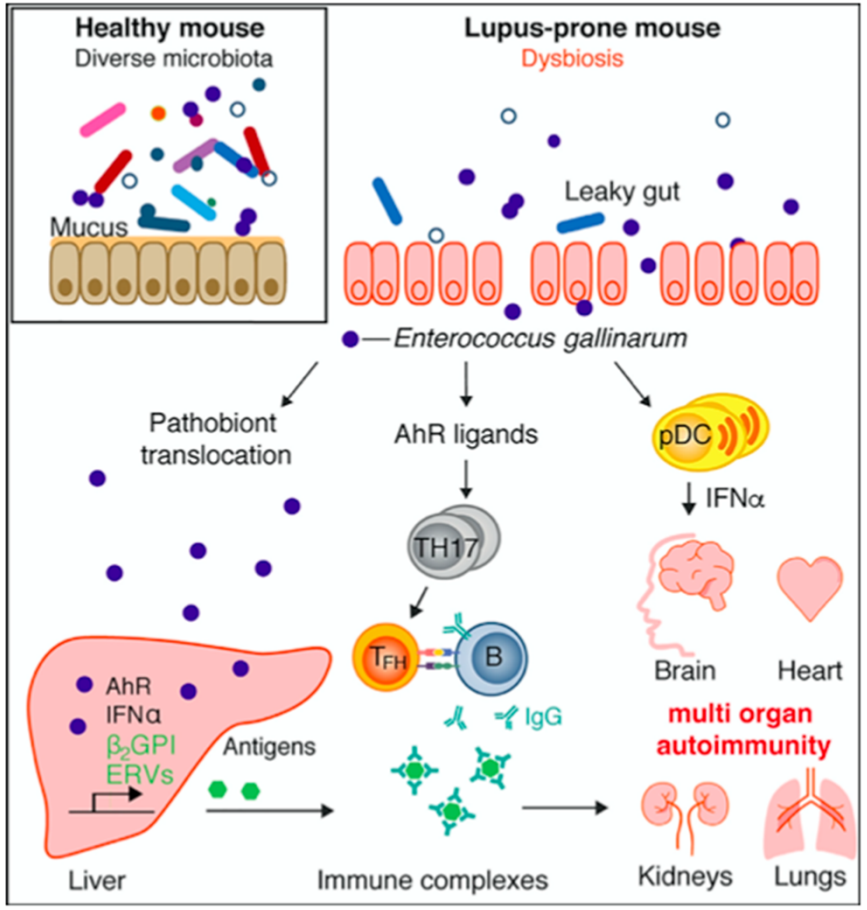
Silverman GJ et al, Nat Rev Rheum 2019

LES

- **Enterococcus Gallinarum** down-regola le molecole ileali correlate alla funzione di barriera (es. occludina, claudina), produzione di muco ed up-regola le molecole correlate ad uno stato pro-infiammatorio

- In un modello murino di autoimmunità - (NZW × BXSB)F_1 hybrid mice -
l' **Enterococcus Gallinarum**, patobionte intestinale, è in grado di traslocare nell'intestino e di indurre una risposta infiammatoria (IFN signature) ed auto-anticorpale (Ab anti ds DNA, Ab anti B2GP1) attraverso l'attivazione del sistema AhR con induzione di una risposta Th17

- Il trattamento con un antibiotico specifico (**vancomicina**) e con la **vaccinazione** sono in grado di ridurre la produzione auto-anticorpale e la mortalità nel modello murino



Manfredo Vieira S et al, Science 2018
Guerrini M, Cell Host 2018

Ro60

LES

1. Batteri commensali contenenti **Ro60-ortologhi** sono comuni nel **microbiota cutaneo, orale ed intestinale umano** (***Corynebacterium, Propionibacterium, Bacteroides***)

2. Pazienti affetti da LES con Ab anti Ro60 presentano una risposta in vitro dei linfociti B e T contro Ro60-ortologhi dei batteri commensali

3. Monocolonizzazione di topo germ-free con commensali contenenti hRo60-ortologhi induce una risposta T e B cellulare anti-Ro60 in vivo

> antibodies directed against Ro60 are known to precede the onset of disease

Greiling TM et al, Sci Transl Med 2018

LES

ABSTRACT NUMBER: 1786

Lupus Nephritis Is Linked to Immunity to an Intestinal Commensal Lachnospiracaea Species

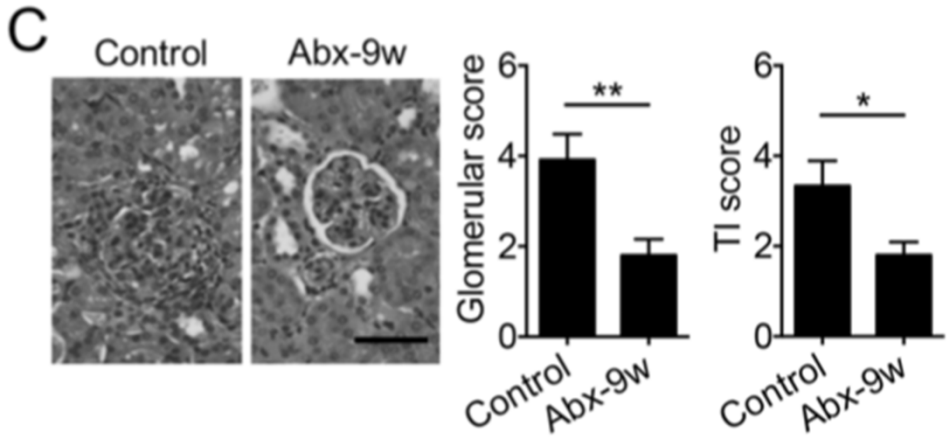
Gregg J. Silverman[1], Doua F. Azzouz[2], Hanane El Bannoudi[2], Aidana Omarbekova[3], Brad H. Rovin[4], Roberto Caricchio[5], Alexander Alekseyenko[6] and Jill P. Buyon[2], [1]Department of Medicine, New York University School of Medicine, New York, NY, [2]Medicine, New York University School of Medicine, New York, NY, [3]New York University School of Medicine, New York, NY, [4]Ohio State University Medical Center, Columbus, OH, [5]Medicine/Rheumatology, Temple University, Philadelphia, PA, [6]Medical University of South Carolina, Charleston, SC

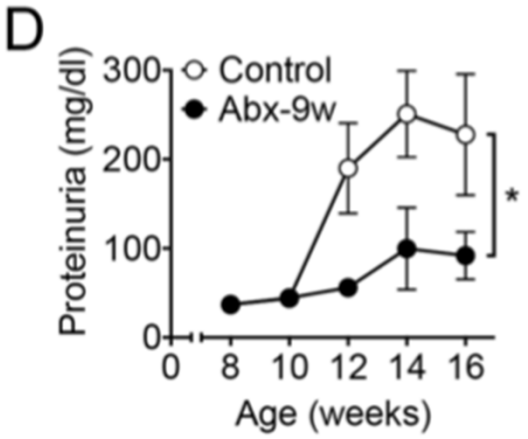
ABSTRACT NUMBER: 104

Identification of a Gut Pathobiont Immunostimulatory Lipoglycan Antigen Linked to Lupus Nephritis

Gregg Silverman[1], Nicolas Gisch[2], Aidana Omarbekova[3] and Doua F. Azzouz[4], [1]Department of Medicine, New York University School of Medicine, New York, NY, [2]Research Center Borstel, Schleswig-Holstein, Germany, [3]New York University School of Medicine, New York, NY, [4]Medicine, New York University School of Medicine, New York, NY

I pazienti con **LES attivo** presentano una **ridotta biodiversità del microbiota.**
Maggiore rappresentazione di una specie appartenente alla **famiglia Lachnospiracaea (RUMINOCOCCUS GNAVUS)**
Correlazione con IgG anti ceppo, Ab anti dsDNA, SLEDAI, attività renale.
Ruminococcus Gnavus cell-wall lipoglycan immunodominant antigen

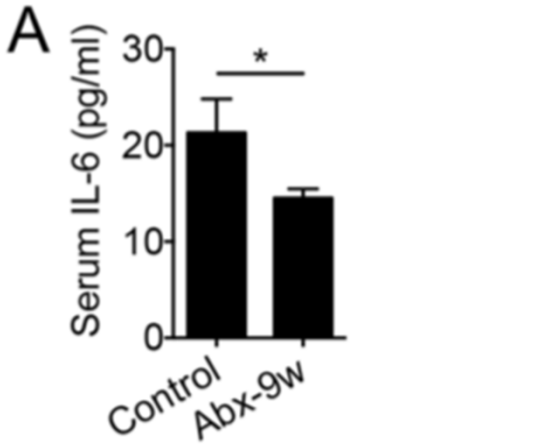


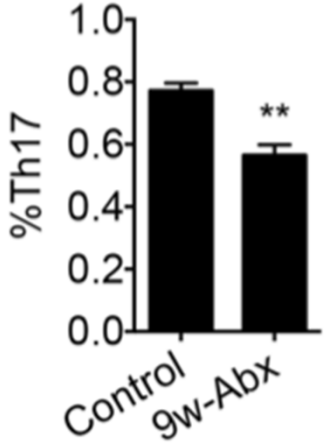


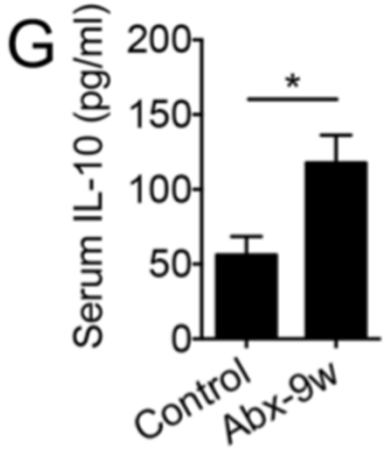
LES

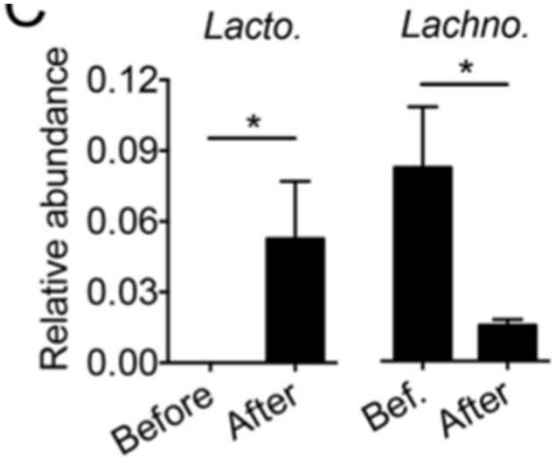
MRL/lpr mice

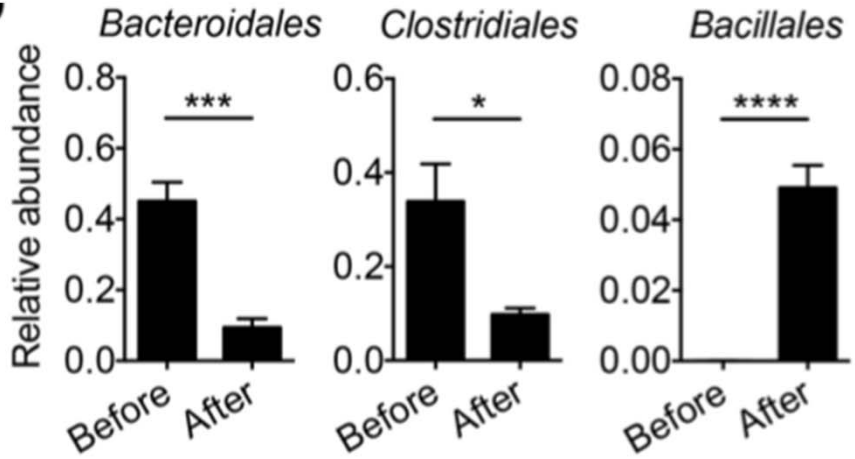
Amp+Neo+Met+Vanc



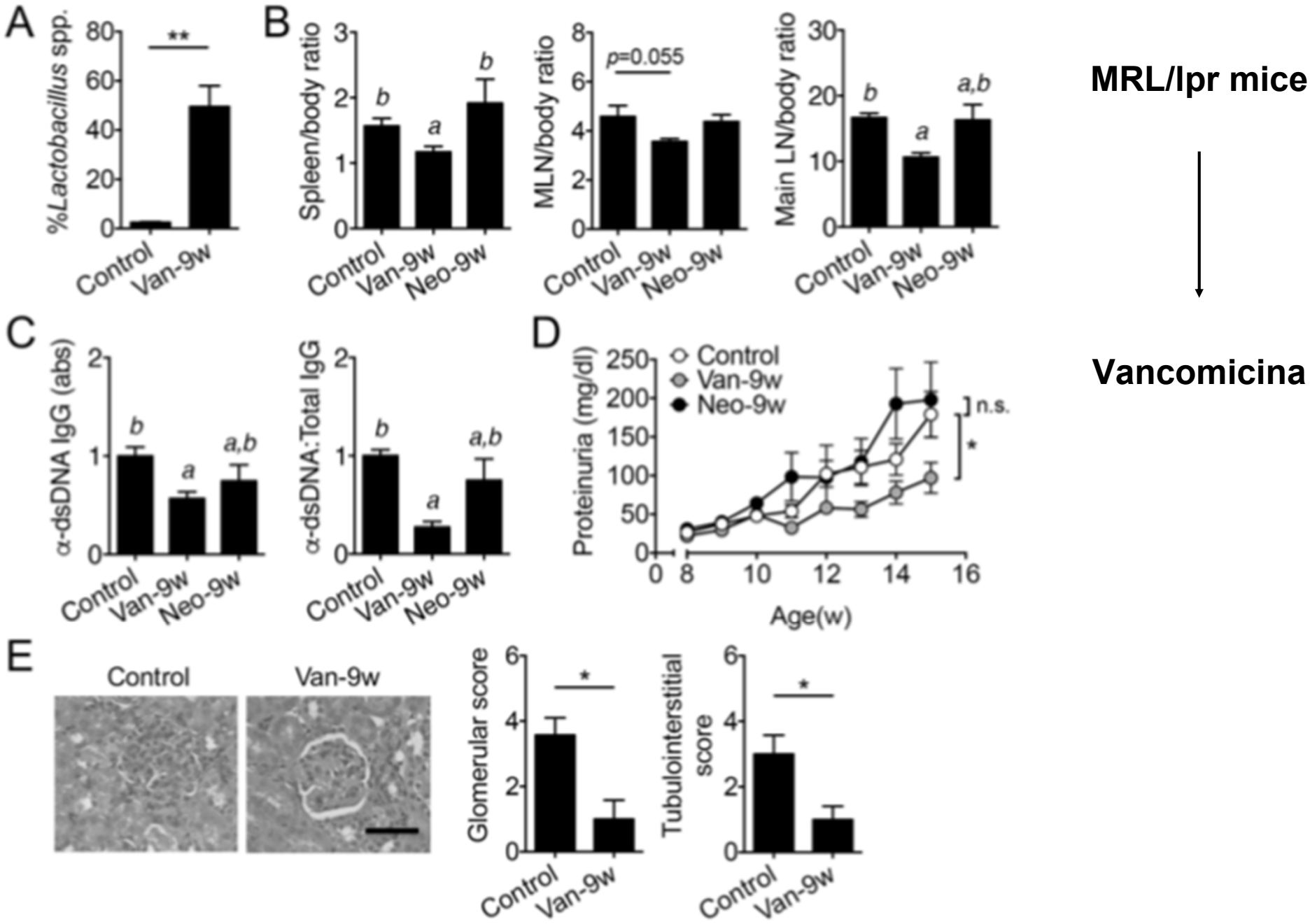








Quinghui M et al, Scie Rep 2017

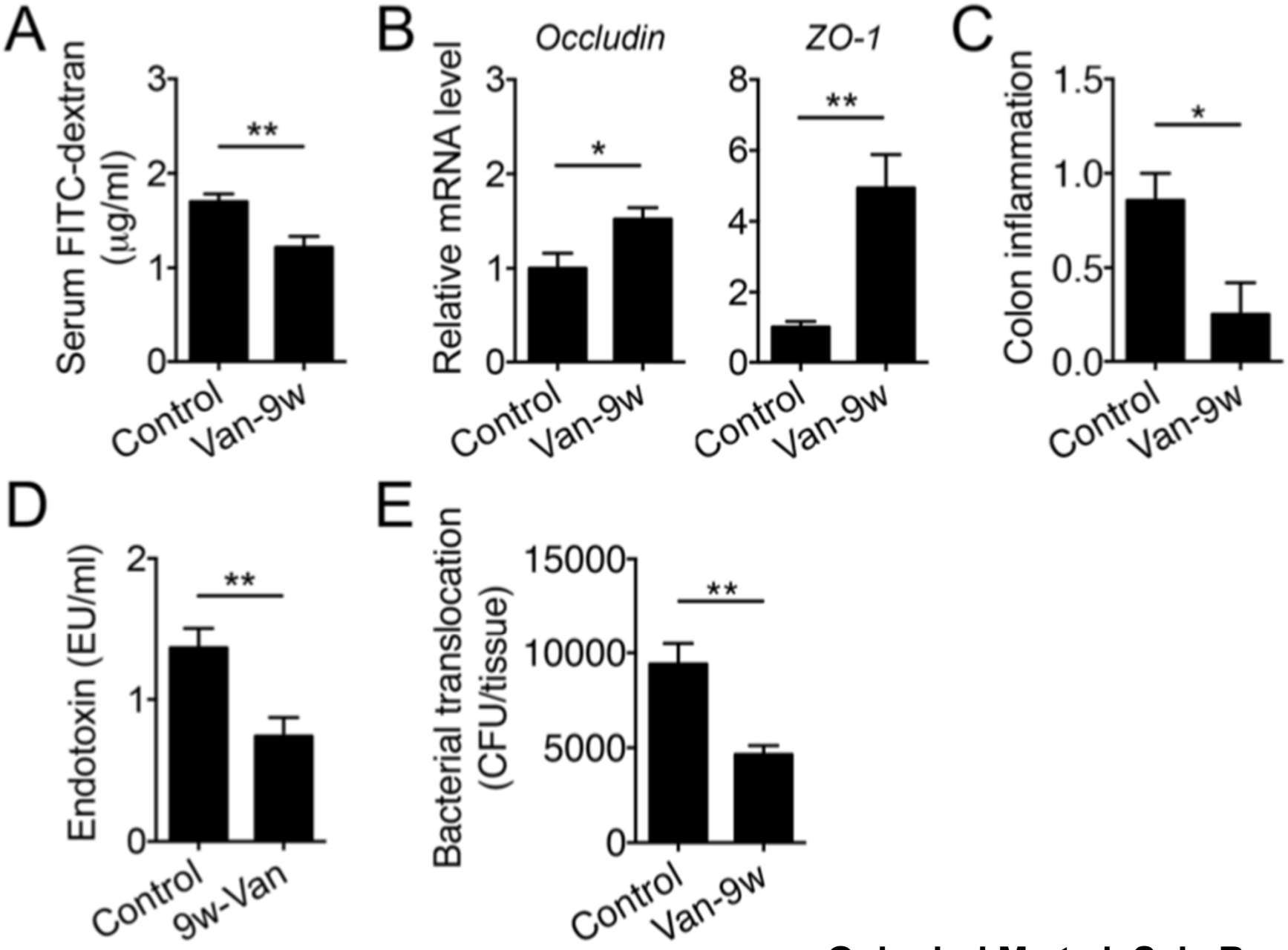


MRL/lpr mice

Vancomicina

Quinghui M et al, Scie Rep 2017

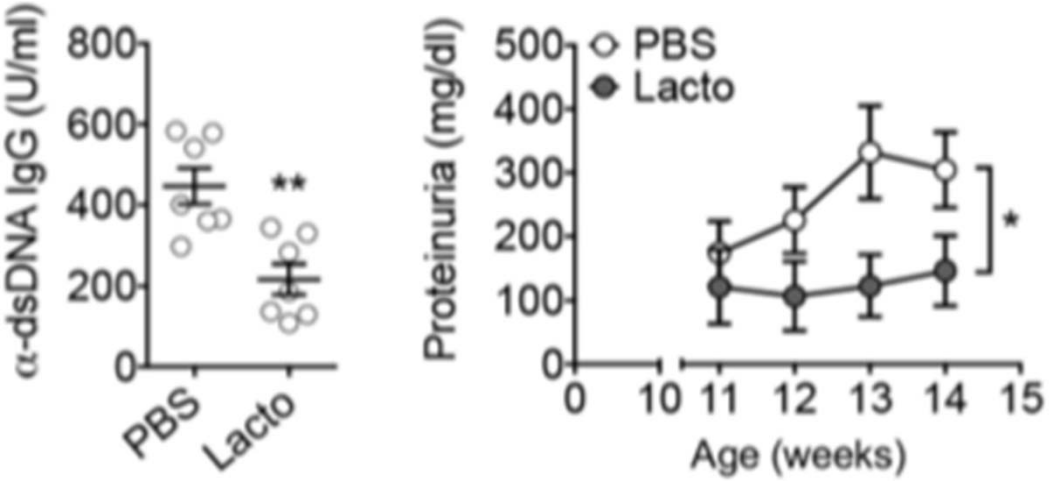
La Vancomicina riduce la permeabilità intestinale



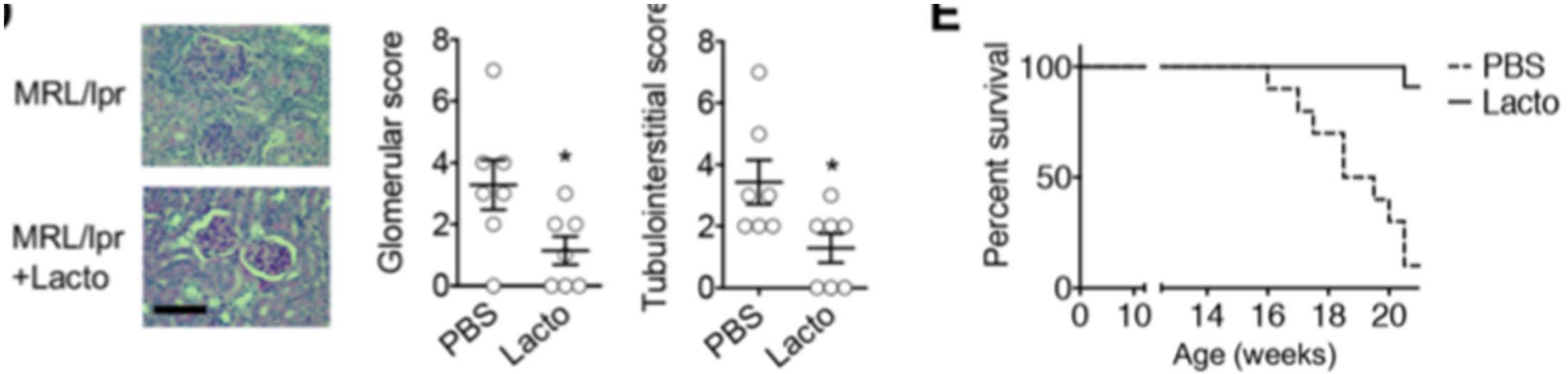
Quinghui M et al, Scie Rep 2017

LES

MRL/lpr mice

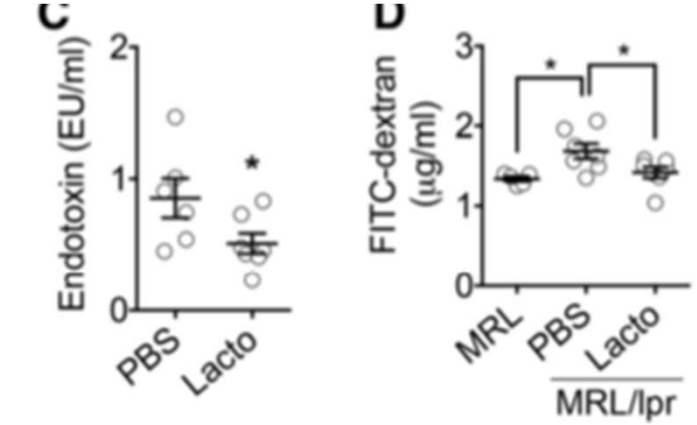


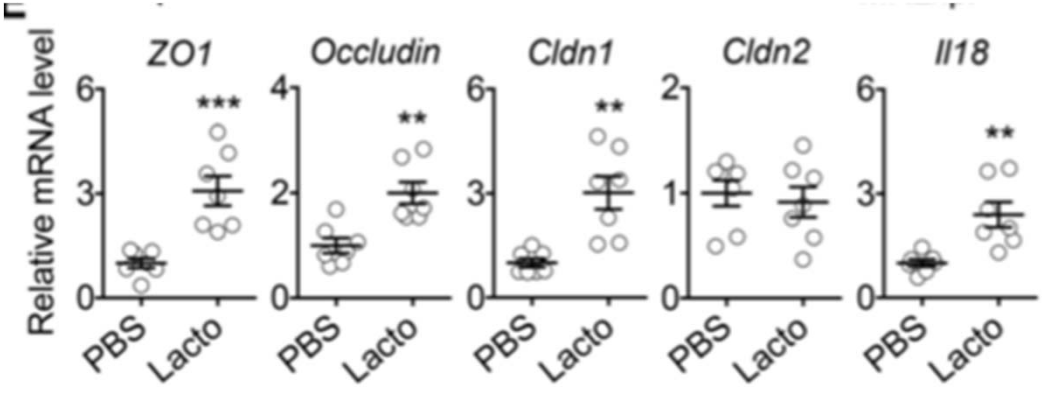
L. oris-reuteri-rhamnosus, johnsonii, gasseri (prima dell'esordio della malattia)

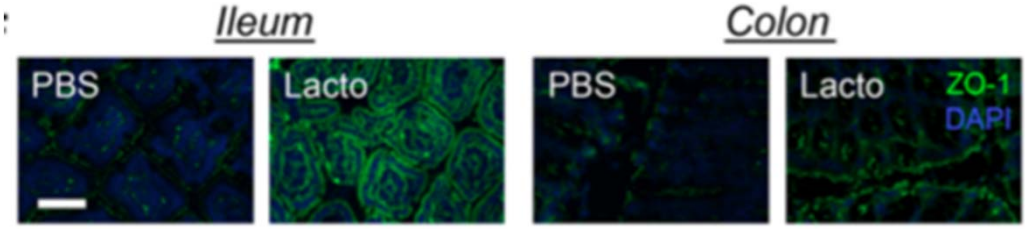


Quinghui Mu et al, Microbiome 2017

LES





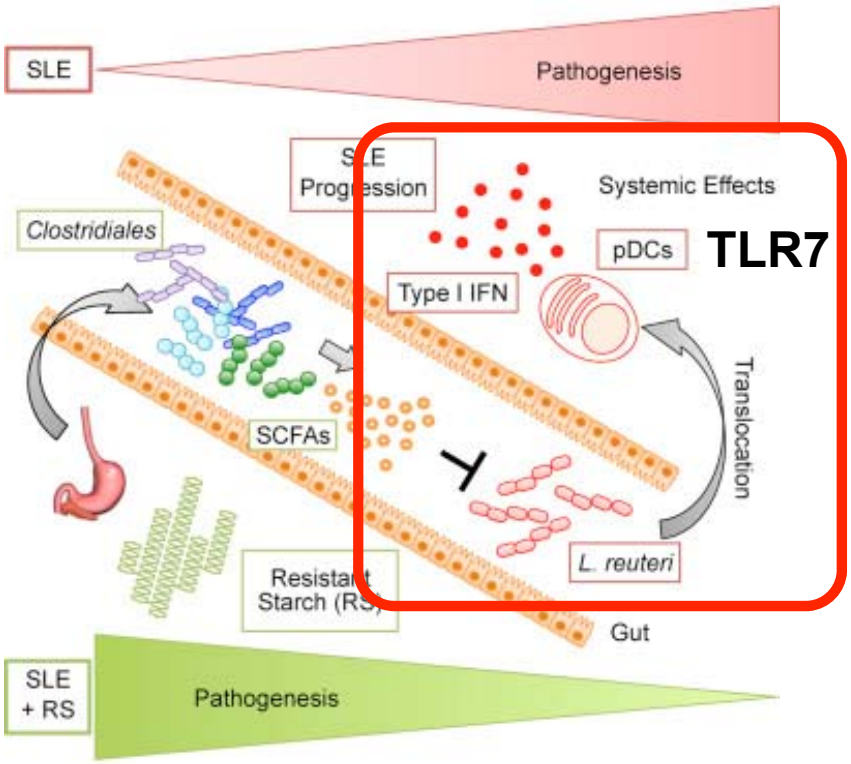


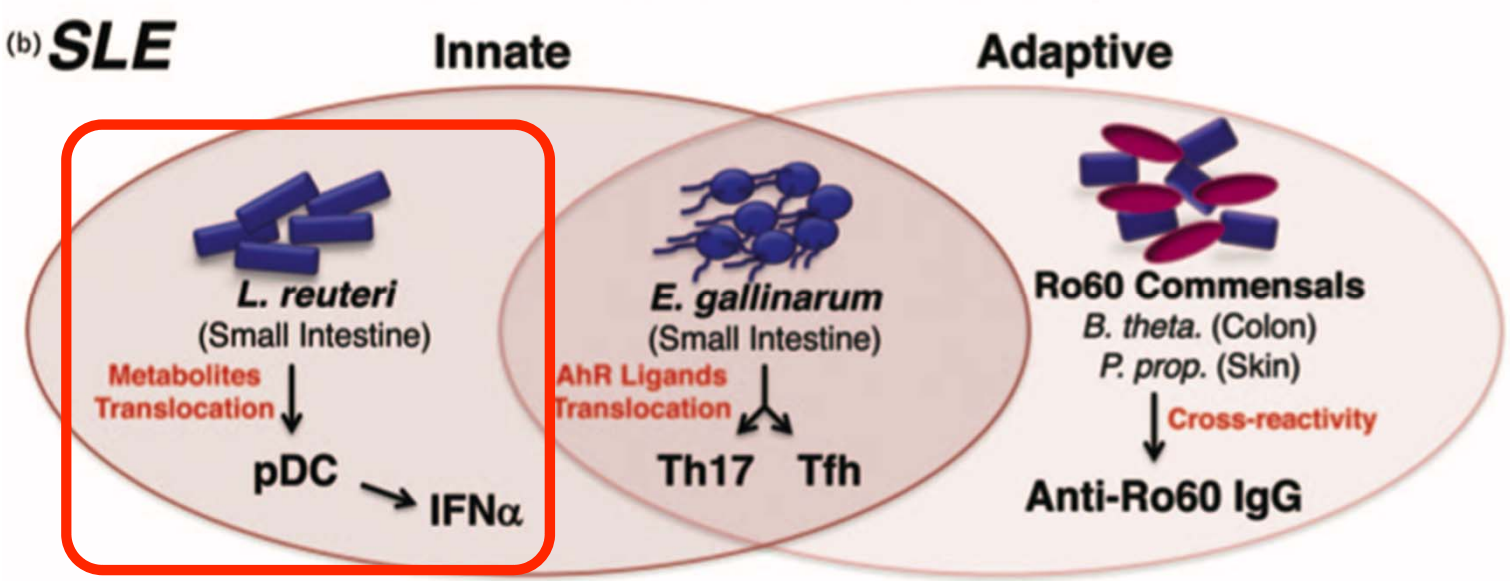
L'inoculazione di Lattobacilli riduce la permeabilità intestinale ed i livelli di endotossina sistemica

Quinghui Mu et al, Microbiome 2017

LES

lupus prone TLR 7.1 trangenic mice

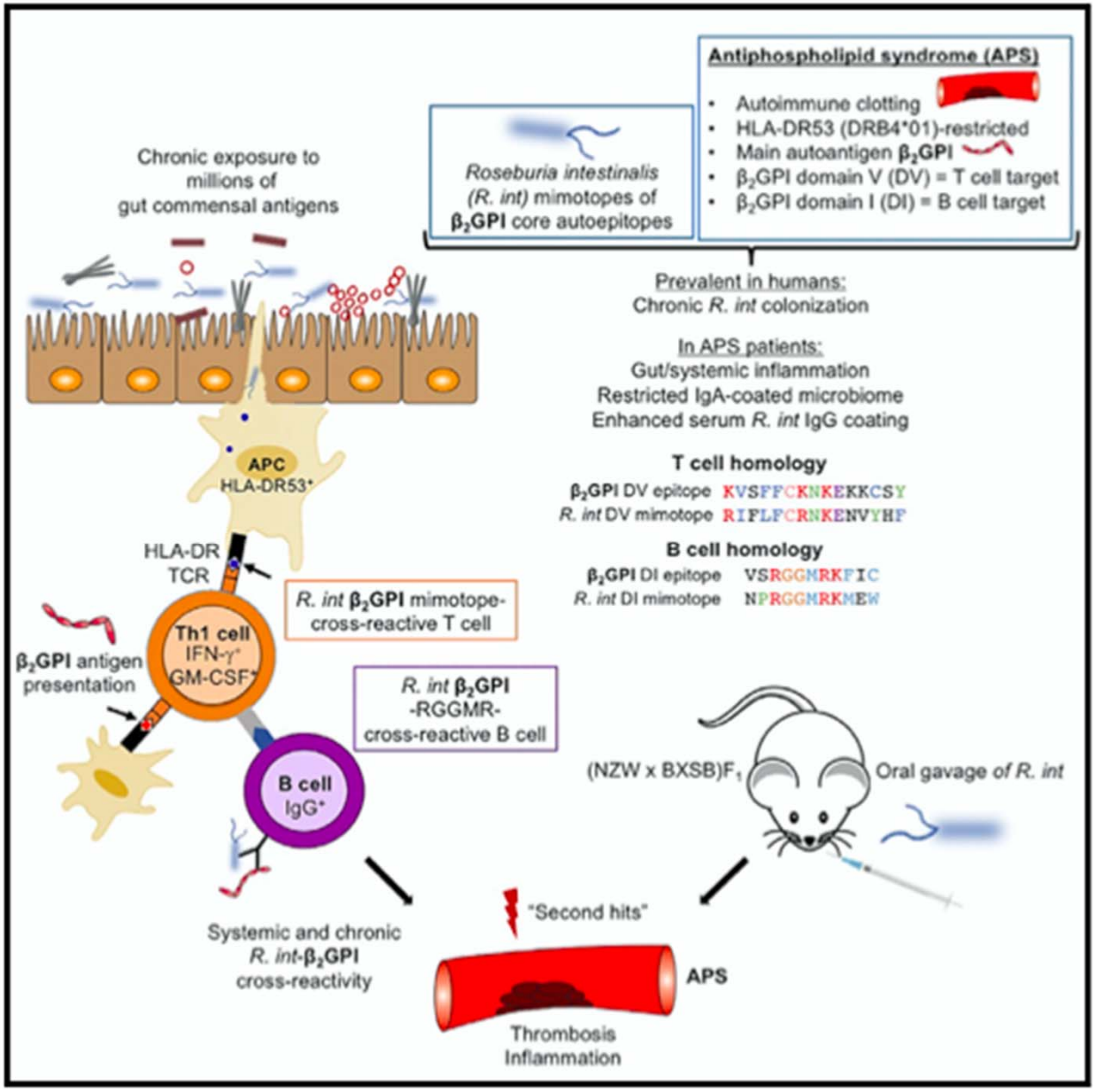




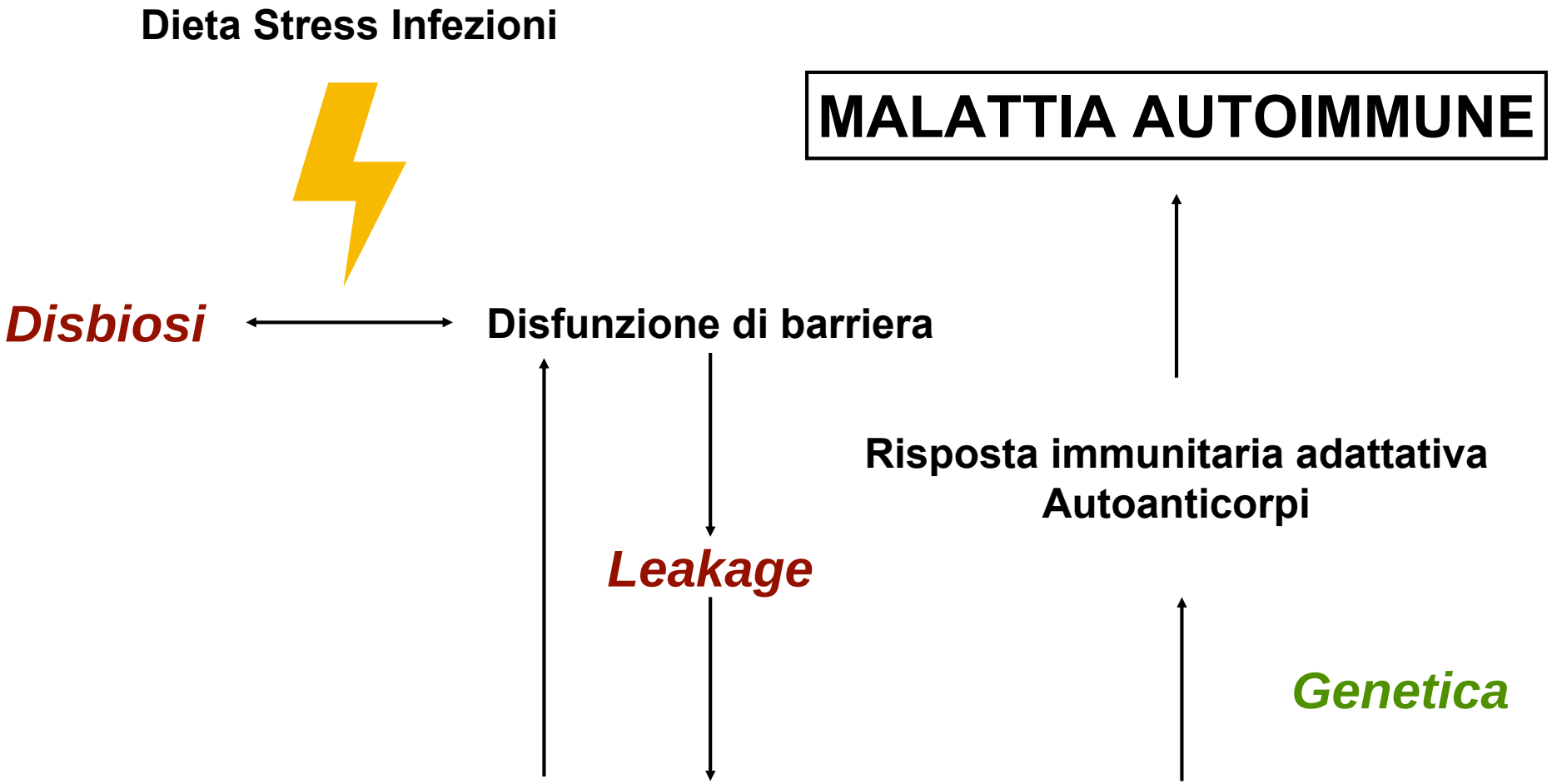
Dehner C et al, Curr Op Rheum 2019
Zegarra Ruiz DF et al, Cell Host 2019

APS

In APS pts:
- **calprotectin and plasma lipocalin-2 elevated**
- **contracted gut mucosal IgA targets**
- **gut microbiota no different**

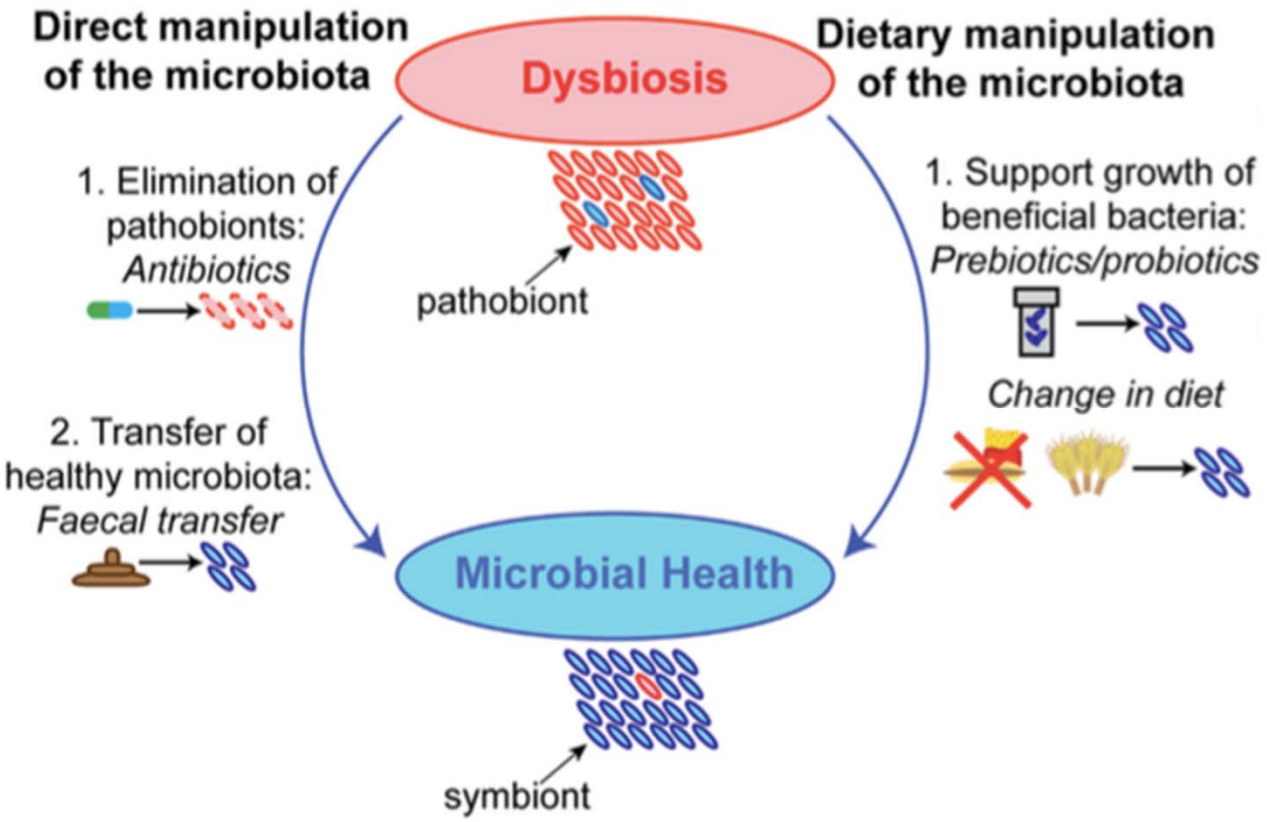


Ruff W et al, Cell Host Microbe 2019



Attivazione del sistema immunitario sottomucoso
Produzione di citochine proinfiammatorie (TNF, IFN gamma)
Contatto antigene-APC (modifiche post-traslazionali di autoantigeni, componenti ortologhi del commensale ad autoantigeni)
Traslocazione di commensali intestinali in siti distanti

Il microbiota e l'intestino possono essere un bersaglio terapeutico nelle malattie reumatiche?



Rosser EC et al, J Autoimm 2016

Conclusioni

- L’ incidenza e la prevalenza delle malattie autoimmuni sono in progressiva crescita
- Ruolo dei fattori ambientali (**nutrizione**)
- Crescenti evidenze dimostrano un **ruolo patogenetico della disbiosi e dell’alterazione della permeabilità intestinale** nello sviluppo delle **malattie autoimmuni**
- **Nutrizione e probiotici** possono rappresentare una strategia per **prevenzione e terapia integrata** delle malattie autoimmuni (necessari investimenti in ulteriori studi clinici)
- Nel futuro **genetica** e **studio del microbiota** per un impiego personalizzato e mirato della nutrizione e dei probiotici nel trattamento di pazienti affetti da malattie autoimmuni (**terapia biologica personalizzata**)

Grazie!