



X ISNIM CONGRESS & III SIPNEI CONGRESS
TRANSLATIONAL NEUROIMMUNOMODULATION
PSYCHONEUROENDOCRINEIMMUNOLOGY:
FROM RESEARCH TO CLINICAL PRACTICE

Infertility: the role of microbiota

Marina Risi



PNEI CURE INTEGRATE
PSICONEUROENDOCRINOIMMUNOLOGIA

Magazine

Some of My Best Friends Are Germs

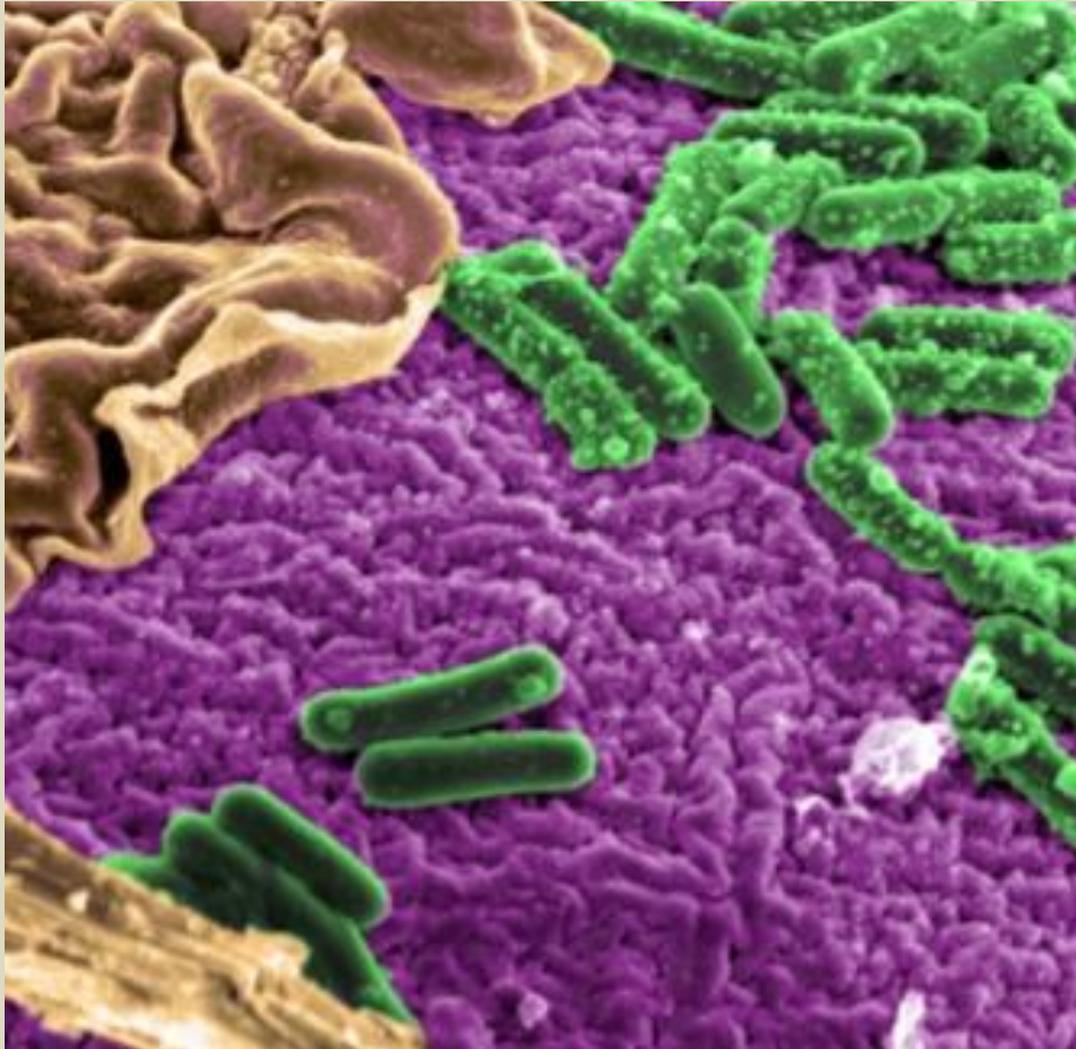
By MICHAEL POLLAN MAY 15, 2013



Hannah Whitaker for The New York Times. Prop stylist: Emily Mullin.

I can tell you the exact date that I began to think of myself in the first-person plural — as a superorganism, that is, rather than a plain old individual human being. It happened on March 7. That's when I opened my e-mail to find a huge, processor-choking file of charts and raw data from a laboratory located at the [BioFrontiers Institute](#) at the University of Colorado, Boulder. As part of a new citizen-science initiative called the [American Gut project](#), the lab sequenced my microbiome — that is, the genes not of “me,” exactly, but of the several hundred microbial species with whom I share this body. These bacteria, which number around 100 trillion, are living

My microbial fingerprints





Since 2007

- Characterize the communities of microorganisms that are found in the major ecological niches in humans
- Assess the ecology of microbial metabolic and functional pathways
- Understand the mechanisms that are responsible for the differences and similarities in the microbes people share
- Determine their functional roles in health maintenance and disease development

www.metahit.eu

2008-2012



Metagenomics of the Human Intestinal Tract

Home	Paris 2012	Live News	Project	WPs	Our Team	Publications	Conf 2010	Media	Links	Intranet
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Project

Metagenomics of the Human Intestinal Tract

The number of microbes that are present on surfaces and in cavities of our body largely exceeds that of our own cells and the number of genes they encode largely exceeds that of our own genes. This complex and dynamic microbiota has a profound influence on human physiology and nutrition. Defining this dynamic

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News

www.mynewgut.eu

2013-2018



My
New
GUT

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MyNewGut will shed light on the role of the human gut microbiome and its relevance to neuro-immune development during pregnancy.

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NEWS

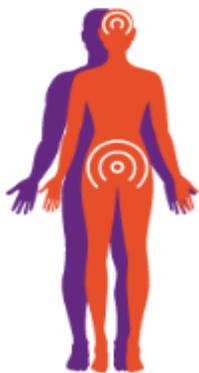
Dietary Fibre Conference 2015 meets the MyNewGut project

13 May 2015

The MyNewGut project will organise a pre-conference

Welcome

The human gut microbiome is the bacterial ecosystem of our intestines. It is known to affect our body's ability to extract energy from a diet and to influence brain functions. Currently there is a lack of understanding generally about the importance of the gut microbiome's role in health and well-being. Finding out more about the gut microbiome could lead to the development of dietary interventions, allowing more control of its functions, therefore preventing diet-related and behavioural disorders.



My New GUT



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MyNewGut will study the role of the human microbiome in behaviour including anxiety, depression and eating behaviour.

About MyNewGut

Expected Outcomes

Research

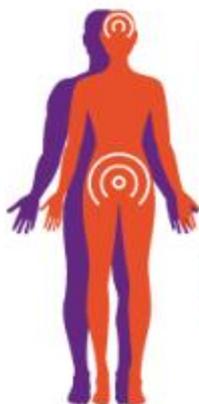
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My New GUT



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MyNewGut will provide information about how specific diets and food ingredients can help prevent obesity and behavioural disorders.

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NEWS

Dietary Fibre Conference 2015 meets the MyNewGut project

13 May 2015

Welcome

The human gut microbiome is the bacterial ecosystem of our intestines. It is known to affect our body's ability to extract energy from a diet and to influence brain functions. Currently there is a lack of understanding generally about the importance of the gut microbiome's role in health and well-being. Finding out more about the gut microbiome could lead to the development of dietary interventions, allowing more



\$17
American Gut T-Shirt

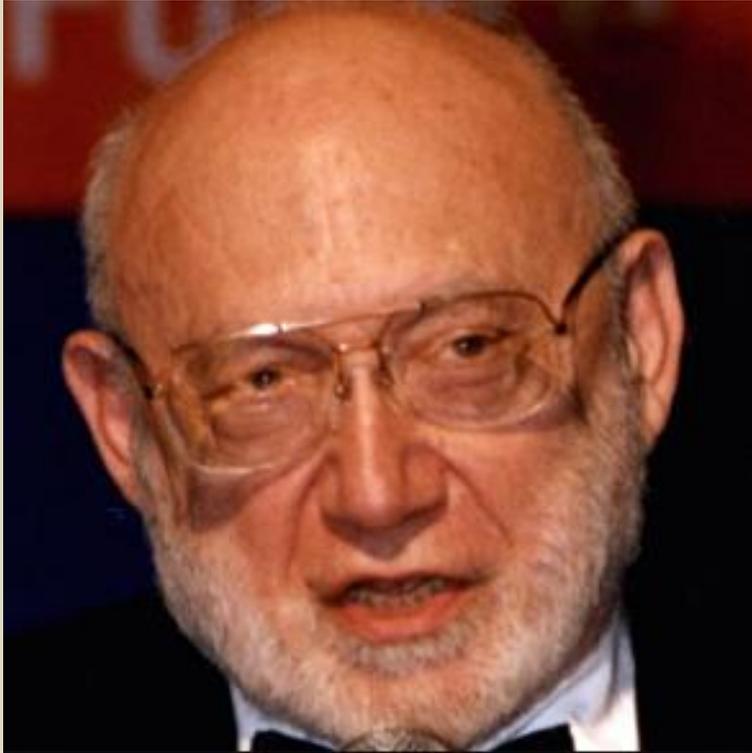


\$500
A Week Of Feces



\$25,000
Hundreds Of Genomes From Your Gut

Joshua Lederberg 1925-2008



**1958
Nobel Prize in
Medicine**

**He coined the term:
Microbiota**

Term	Definition
Microbiota	The microbial taxa that are associated with an environment and are revealed using molecular techniques such as 16S rRNA sequencing (Cho and Blaser, 2012; Ursell et al., 2012).
Microbiome	Refers to the habitat as a whole, thus incorporating the biotic and abiotic factors, encompassing host and microorganism genomes and environmental conditions (Cho and Blaser, 2012).
Metagenome	The collection of genomes and genes from the inhabitants of a microbiome (Marchesi and Ravel, 2015).
Metatranscriptome	The total content of gene transcripts in a community at a specific sampling time (Parro and Paz, 2015).
Metaproteomics	Interrogation of the entire protein complement of a community at a given time point (Wilmes and Bond, 2004).
Culturomics	Method allowing the determination of microbial community composition by high-throughput culture (Greub, 2012).
Biofilm	A structured consortium attached to a living or inert surface formed by microbial cells adherent to each other and surrounded by the self-produced extracellular polymeric matrix (de la Fuente-Nunez et al., 2013; Hall-Stoodley et al., 2004).
Dysbiosis	Qualitative and quantitative changes, their metabolic activity and their local distribution (Holzapfel et al., 1998).
Probiotic	Live microorganisms which when administered in adequate amounts confer a health benefit on the host (Sanders, 2008).
Prebiotic	A non-digestible food ingredient that benefits the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health (Gibson and Roberfroid, 1995).

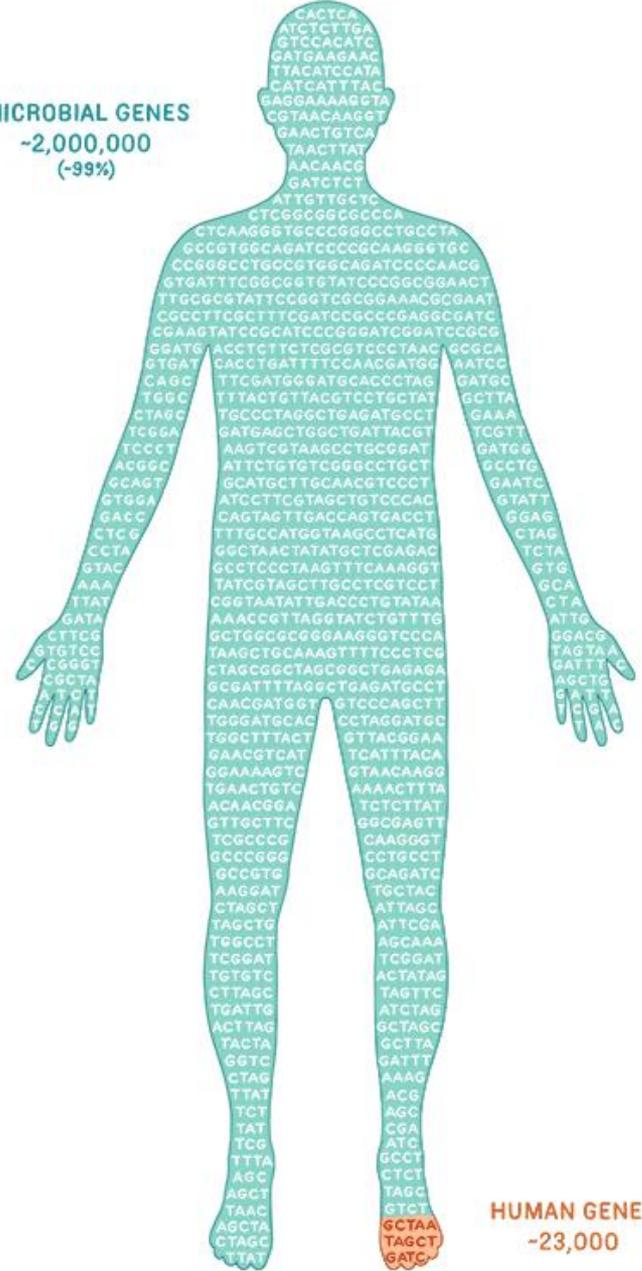
rRNA = ribosomal RNA.

MICROBIAL CELLS
-100 TRILLION
(-70-90%)



HUMAN CELLS
-30 TRILLION

MICROBIAL GENES
-2,000,000
(-99%)

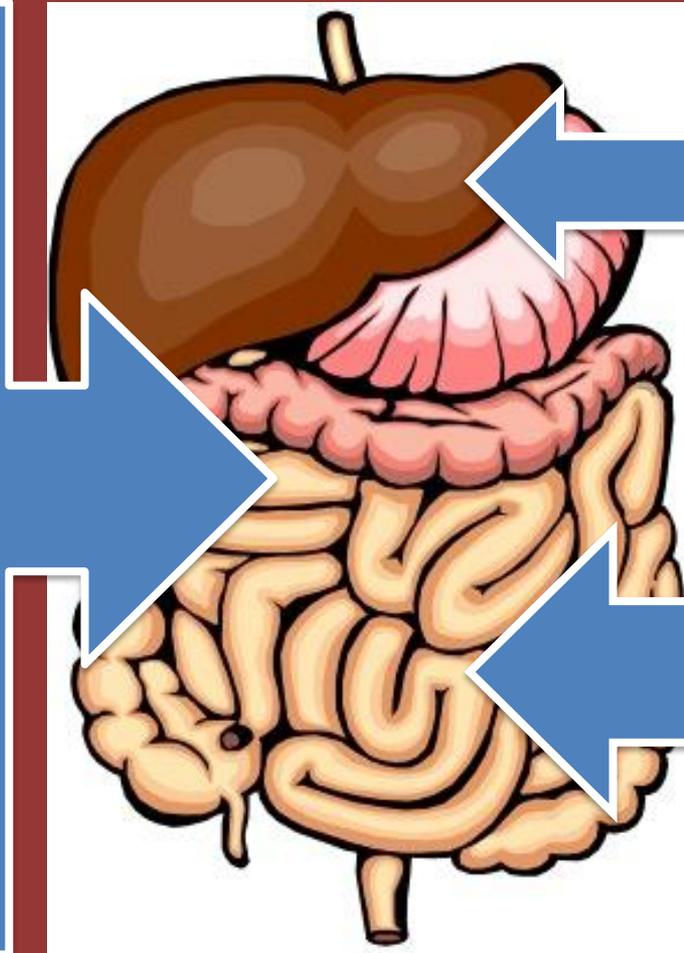


HUMAN GENES
-23,000

COLON

10^{10} - 10^{12} CFU/ml

Bacteroidi
Clostridi
Pseudomonas
Bifidobatteri
Streptococchi
Lactobacilli
Veillonelle
Protozoi, Funghi
Fusobatteri
Proteus
Enterobacter
Stafilococchi



STOMACO, DUODENO

10^1 - 10^3 CFU/ml

Lattobacilli
Streptococchi
Funghi

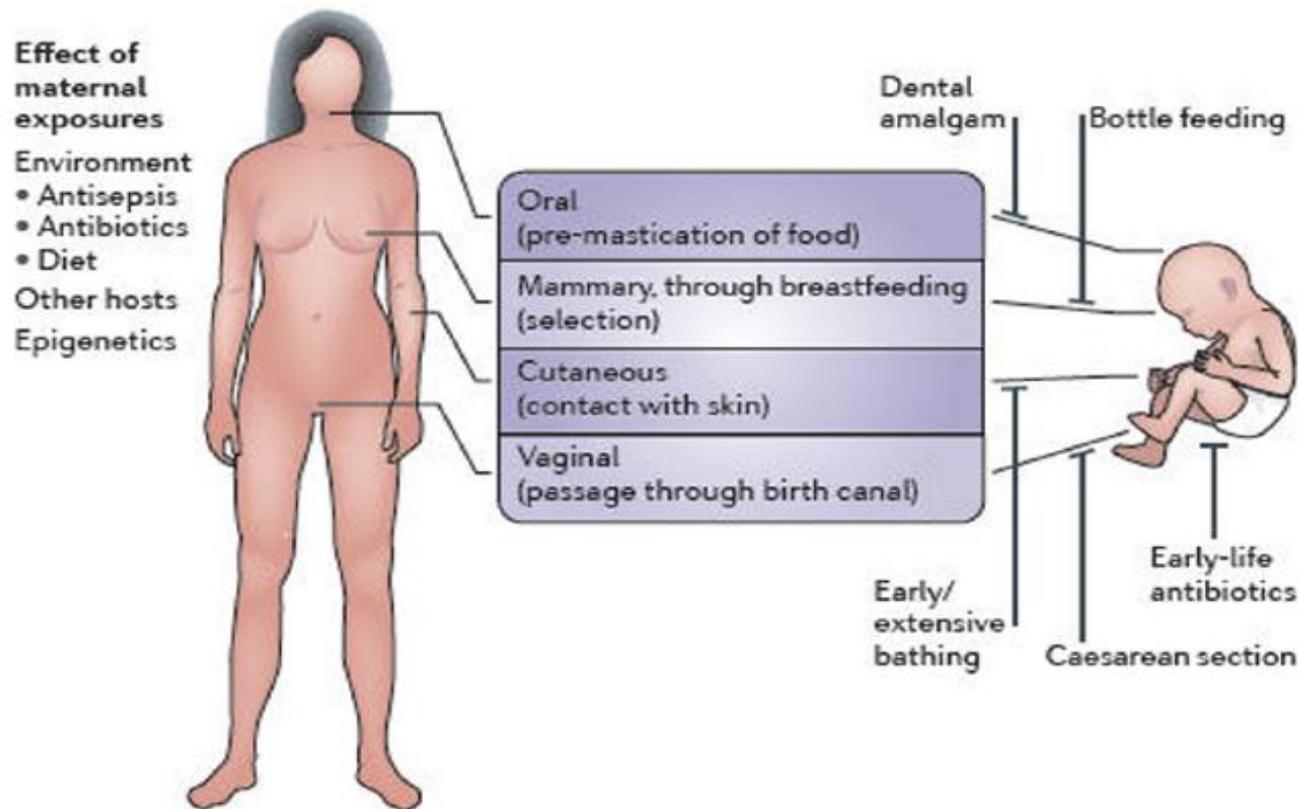
INTESTINO TENUE

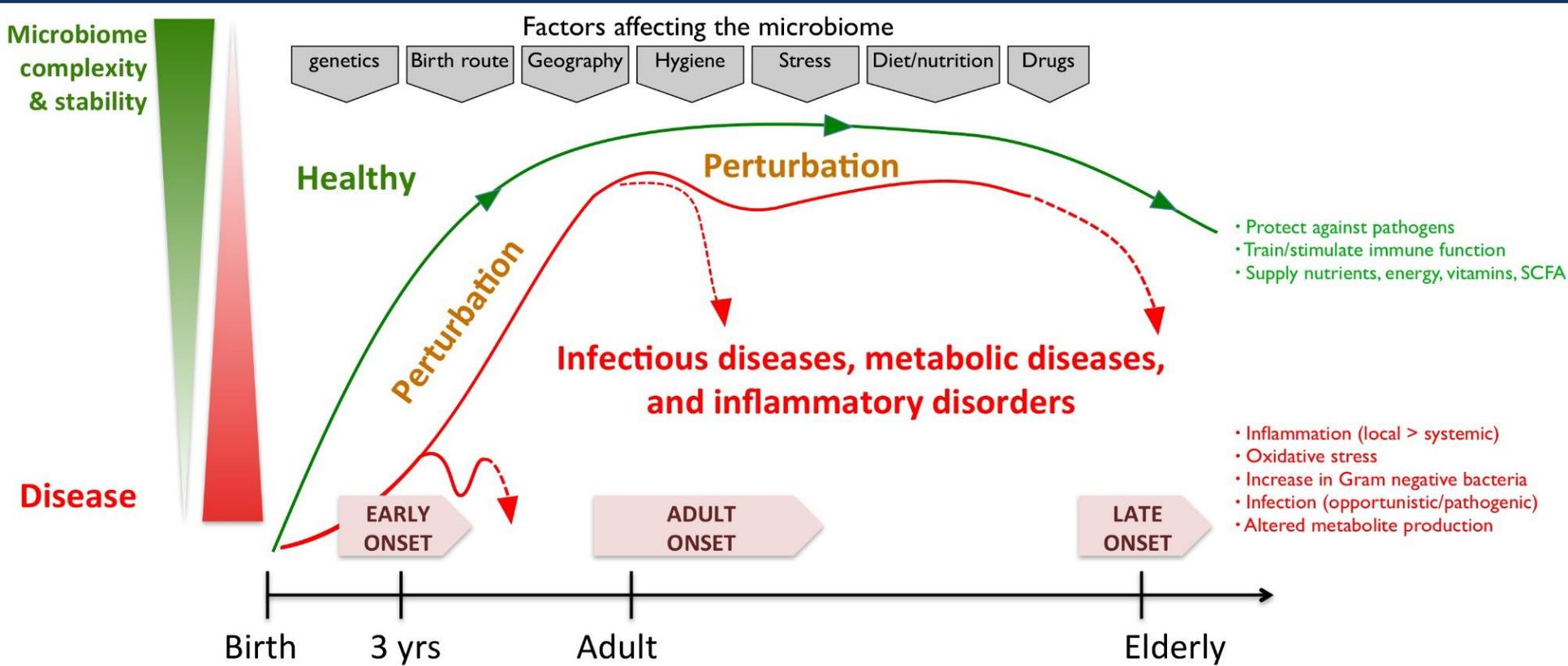
10^4 - 10^8 CFU/ml

Lattobacilli
Streptococchi
Enterobatteri
Bacterioidi
Fusobatteri
Bifidobatteri

Gut Microbiota: Where do they come from?

- Initial exposure occurs during passage through birth canal
- During first year of life, heavily influenced by mother and environment







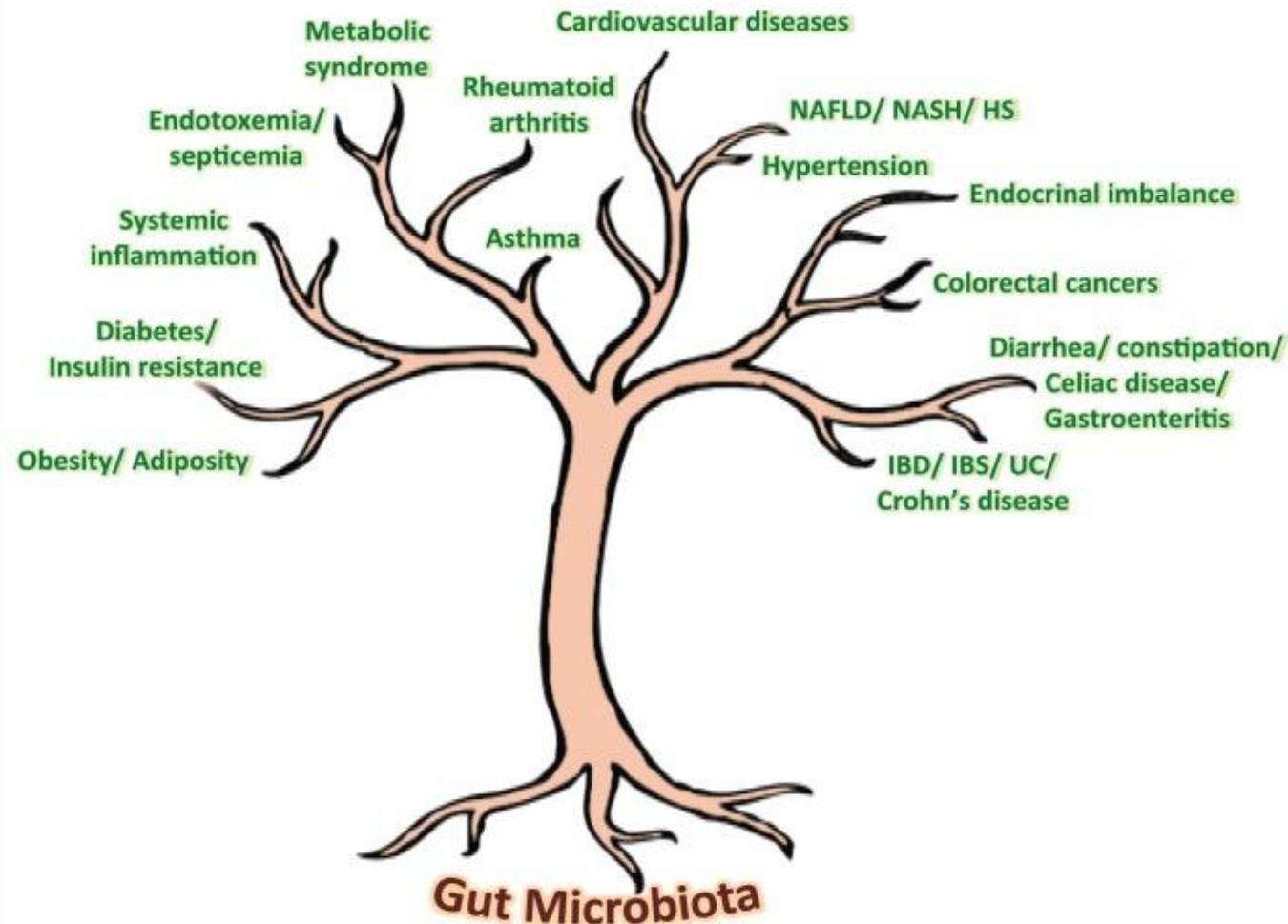
Gut microbiota: the next-gen frontier in preventive and therapeutic medicine?

Ravinder Nagpal^{1†}, Hariom Yadav^{2†} and Francesco Marotta^{3*}

¹ Division of Laboratories for Probiotic Research, Juntendo University Graduate School of Medicine, Tokyo, Japan

² National Institute of Diabetes, Digestive and Kidney Diseases, National Institute of Health, Bethesda, MD, USA

³ ReGenera Research Group for Aging Intervention, Milan, Italy





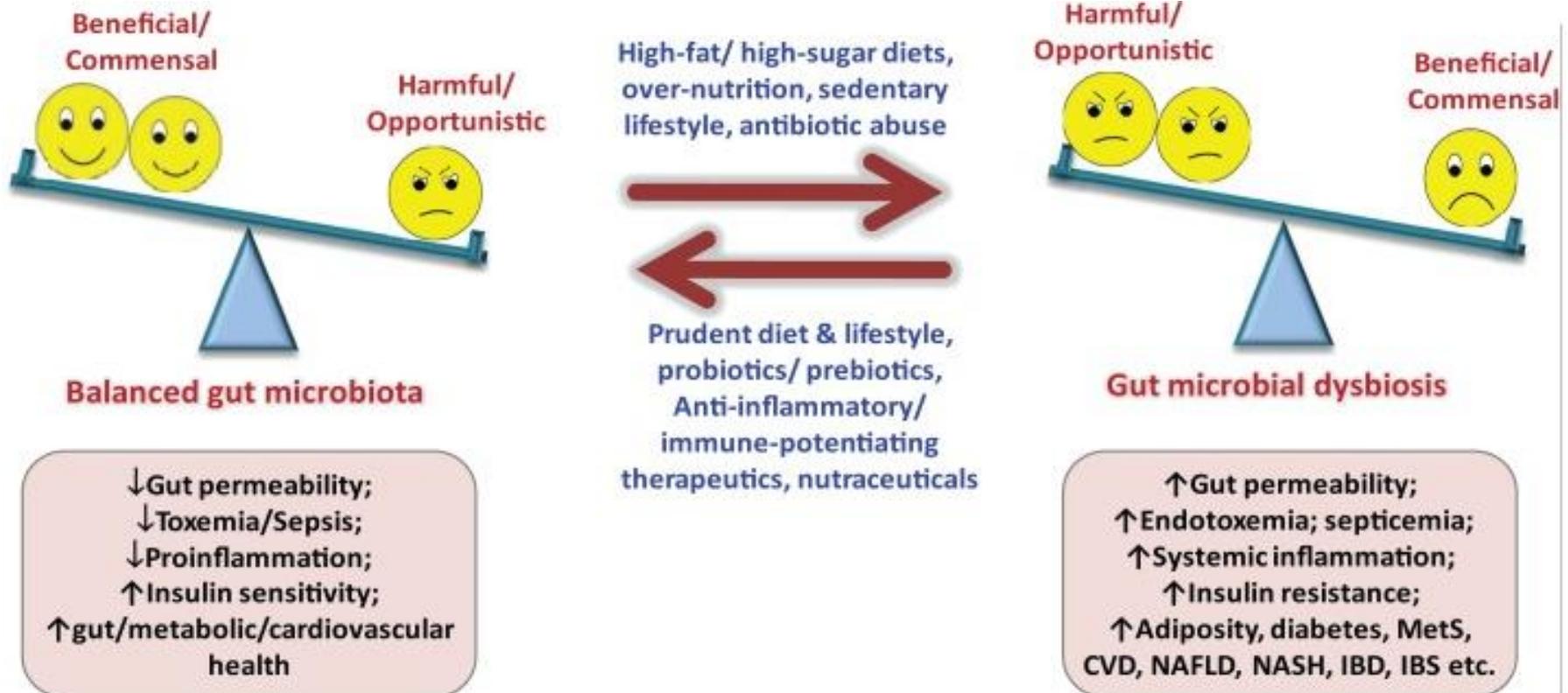
Gut microbiota: the next-gen frontier in preventive and therapeutic medicine?

Ravinder Nagpal^{1†}, Hariom Yadav^{2†} and Francesco Marotta^{3*}

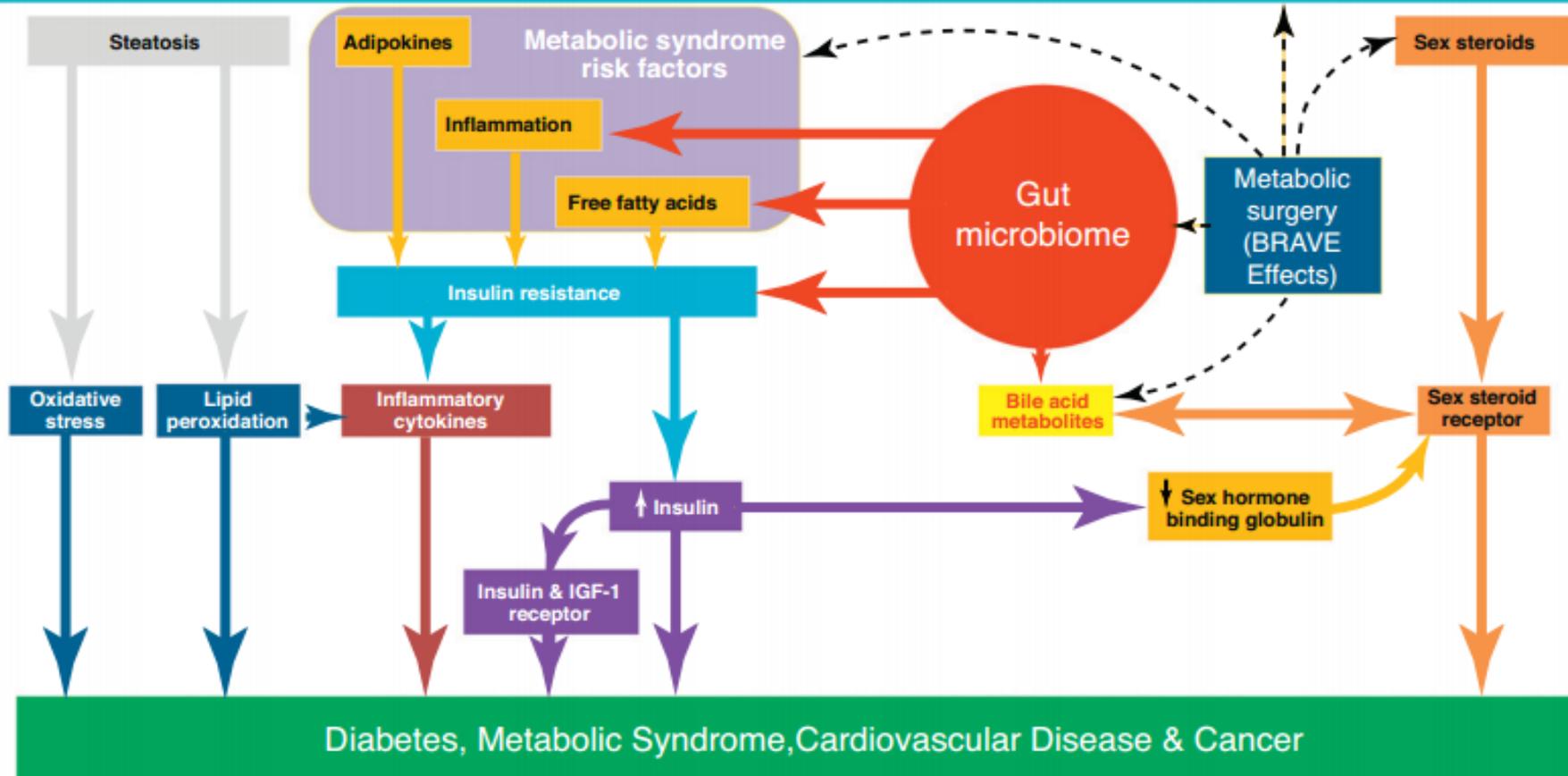
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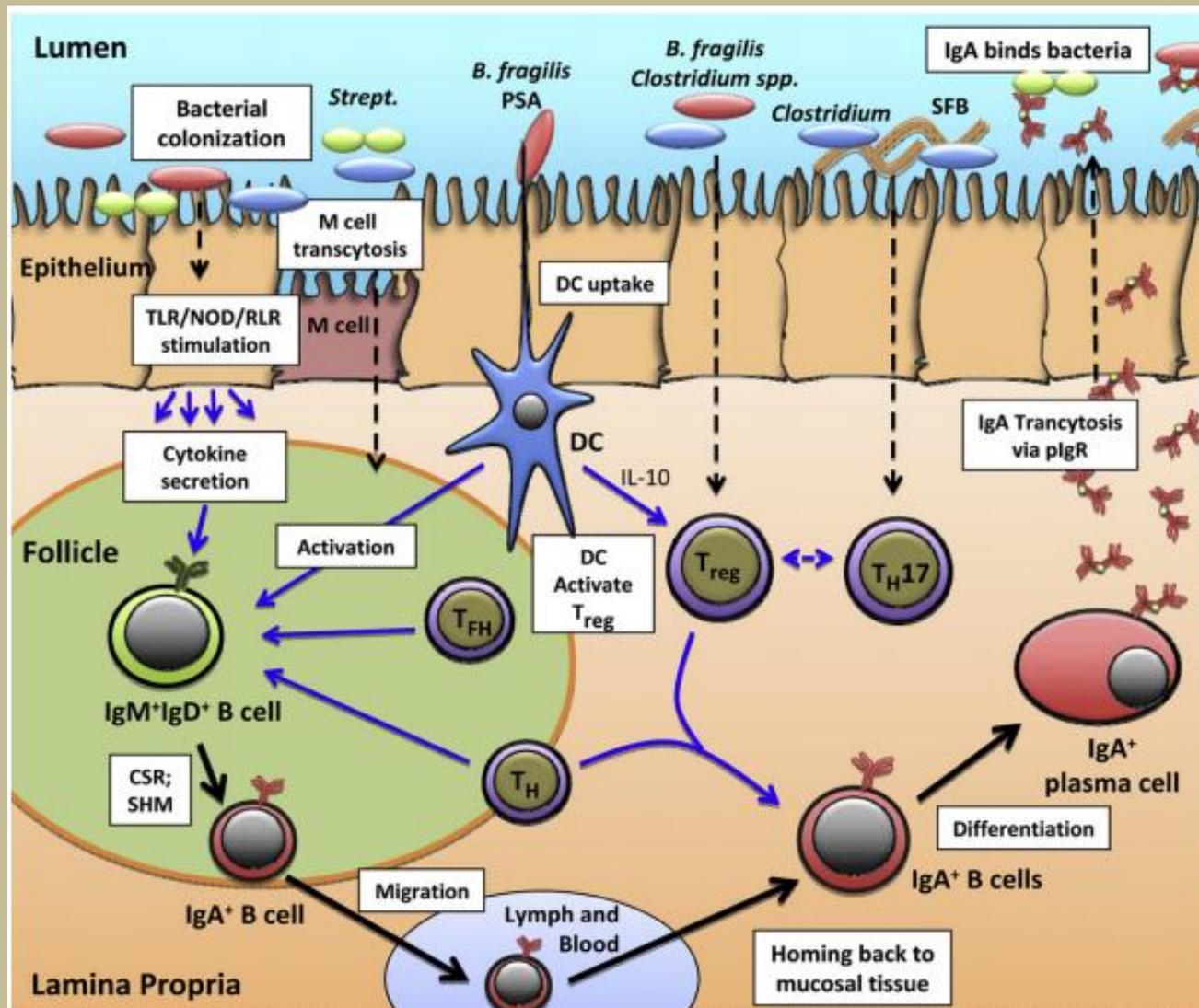
OBESITY



The world within:
living with our microbial guests and guides

Janoff E et al

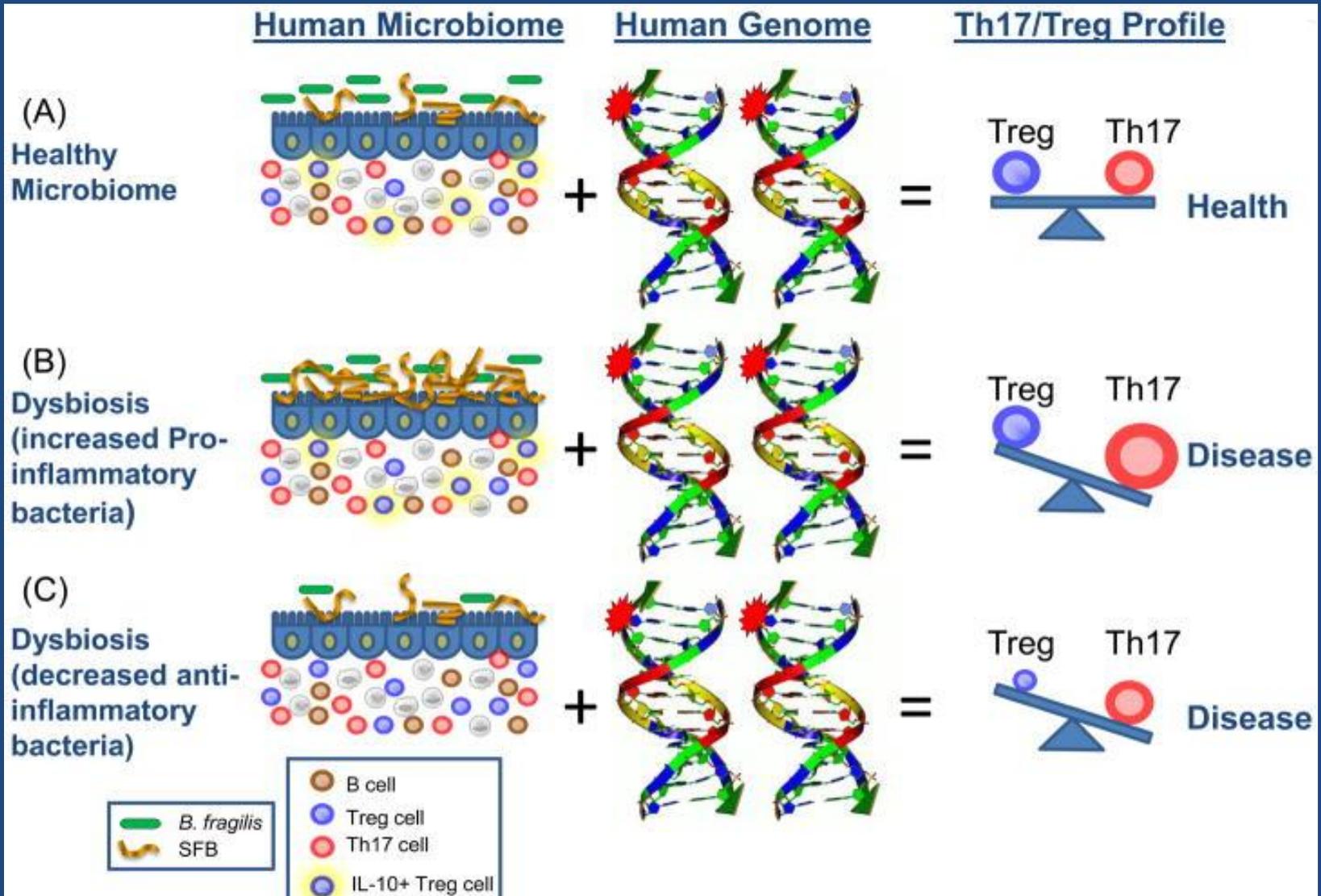
Traslational Research, 2012



Has the microbiota played a critical role in the evolution of the adaptive immune system?

Yun Kyung Lee and Sarkis K. Mazmanian*

Science. 2010



The interaction of microbiome with the immune system

Intestinal microbiota drives immune development and maturation from birth and contributes to the maintenance of intestinal homeostasis between immune competence and tolerance

Highly colonised

Low level colonisation

Oral cavity

Brain

Skin

Breast tissue

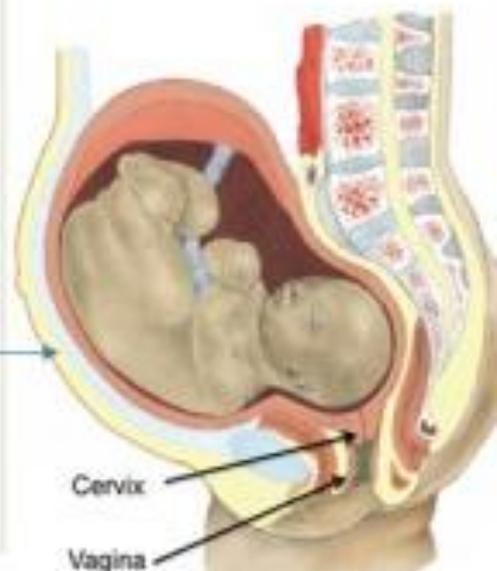
Breast milk

Fetus

Alimentary tract

Placenta

Urogenital tract



Cervix

Vagina

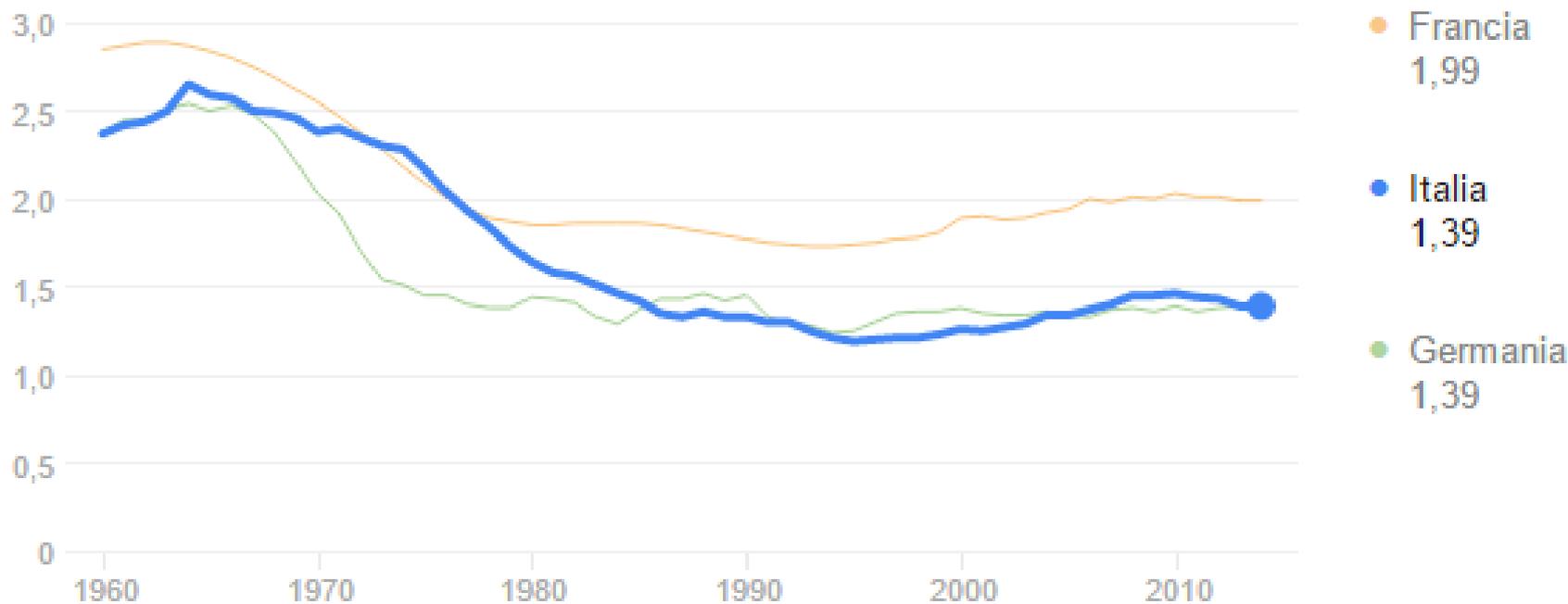
Pos. 	Stato 	Tasso di natalità (nati/1000 abitanti) 
174	 Polonia	9.5
175	Channel Islands ( Regno Unito)	9.4
176	 Bielorussia	9.4
177	 Grecia	9.3
178	 Ungheria	9.3
179	 Corea del Sud	9.3
180	 Lettonia	9.3
181	 Austria	9.2
182	 Rep. Ceca	9.2
183	 Italia	9.2
184	 Svizzera	9.2
185	 Ucraina	9.2
186	 Lituania	9.1
187	 Croazia	9.0
188	 Slovenia	9.0
189	 Bulgaria	8.9
190	 Bosnia ed Erzegovina	8.8
191	 Giappone	8.3
192	 Germania	8.2
193	 Singapore	8.2
194	 Hong Kong	7.6
195	 Macao	7.6

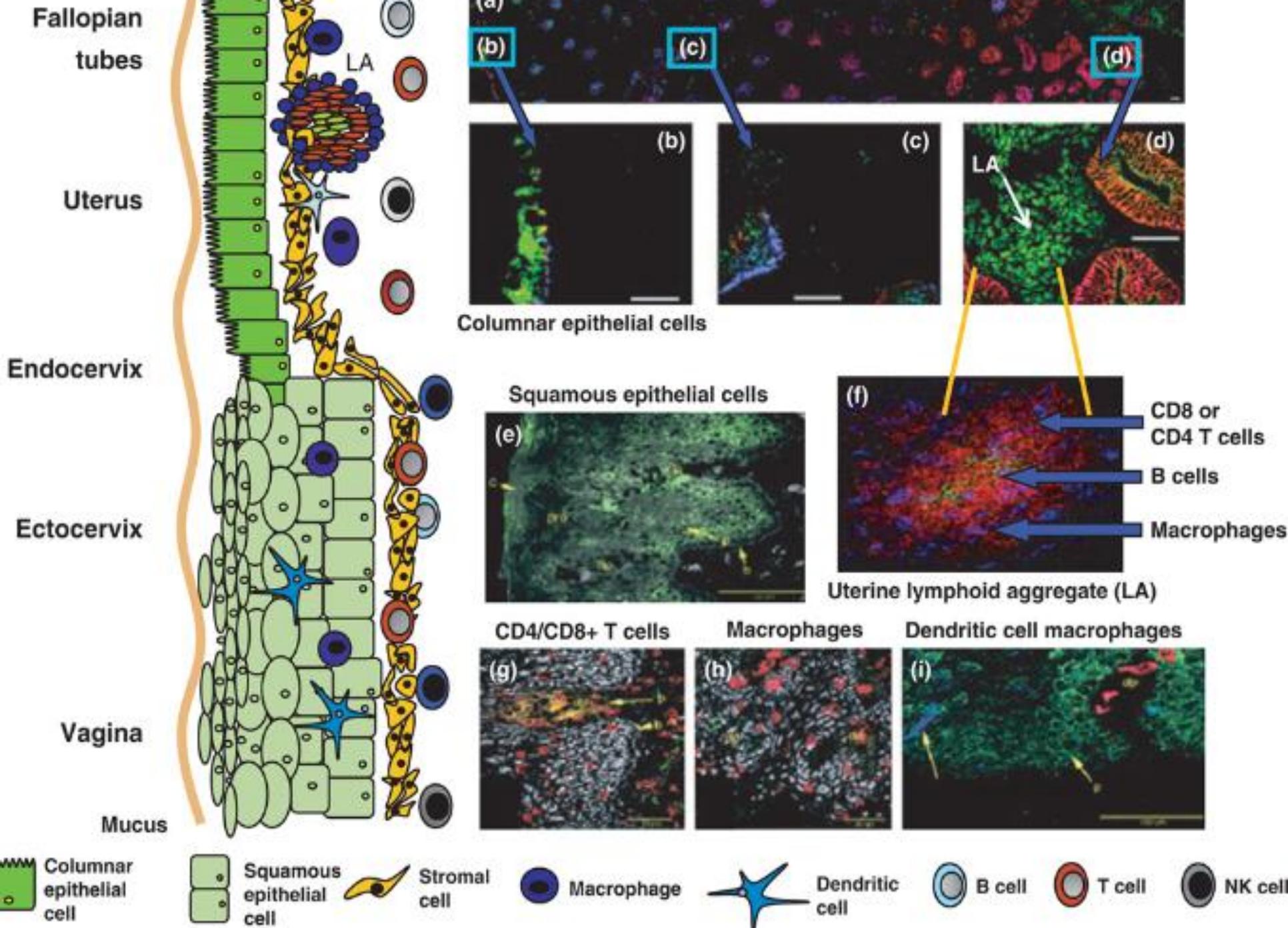
Birth rate is the ratio between the number of births in a community in a given period time and the average population during the same period



Italia / Tasso di fertilità

1,39 nascite per donna (2014)





Microscopy and culture-dependent methods demonstrated that the composition of normal vaginal flora may also fluctuate within an individual woman; for example, throughout the menstrual cycle or as a result of sexual activity

The species of Lactobacilli that dominate the vaginal environment may have implications for gynecologic health: it seems that various species may differentially predispose to dysbiosis

Batterio

Malattia

Quadro clinico

		Uomo	Donna
<i>Neisseria gonorrhoeae</i>	Gonorrea	Uretrite (secrezione purulenta) epididimite, orchite	Cervicite, endometrite, salpingite, malattia infiammatoria pelvica (PID)
<i>Chlamydia trachomatis</i>	Infezione da Clamidia	Uretrite (secrezione chiara), epididimite, orchite	Cervicite, endometrite, salpingite, malattia infiammatoria pelvica (PID)
<i>Chlamydia trachomatis</i> , stipiti L1-L3	Linfogranuloma venereo	Ulcere genitali con adenopatia, proctite	Ulcere genitali con adenopatia, proctite
<i>Treponema pallidum</i>	Sifilide	Ulcere genitale indolente con adenopatia	Ulcere genitale indolente con adenopatia Aborto, parto prematuro
<i>Haemophilus Ducreyi</i>	Ulcera molle o cancroide	Ulcere genitali dolenti eventuale linfadenite	Ulcere genitali dolenti eventuale linfadenite
<i>Klebsiella granulomatis</i>	Granuloma inguinale o Donovanosi	Tumefazione nodulare e lesioni ulcerative inguinali e della regione anale	Tumefazione nodulare e lesioni ulcerative inguinali e della regione anale
<i>Mycoplasma genitalium</i>		Uretrite (secrezione chiara)	Vaginite batterica, malattia infiammatoria pelvica (PID)
<i>Ureaplasma urealyticum</i>		Uretrite (secrezione chiara)	Vaginite batterica, malattia infiammatoria pelvica (PID)

Infezioni Sessualmente Trasmesse da agenti virali

Agente patogeno	Malattia	Quadro clinico	
		Uomo	Donna
HIV	AIDS	Immunodeficienza acquisita e patologie correlate	Immunodeficienza acquisita e patologie correlate
Herpes simplex HSV1 e HSV2	Herpes genitale	Lesioni vescicolari e ulcerative regione genitale e anale	Lesioni vescicolari e ulcerative regione genitale e anale
Papillomavirus umano HPV	Condilomi	Condilomi del pene , area genitale e regione anale	Condilomi area genitale e regione anale
Epatite HAV, HBV, HCV	Epatite	Epatite acuta e cronica, cirrosi epatica, neoplasia del fegato	Epatite acuta e cronica, cirrosi epatica, neoplasia del fegato
Poxvirus	Mollusco contagioso	Noduli ombelicati genitali e/o extragenitali	Noduli ombelicati genitali e/o extragenitali

IST da Protozoi, Miceti e Parassiti

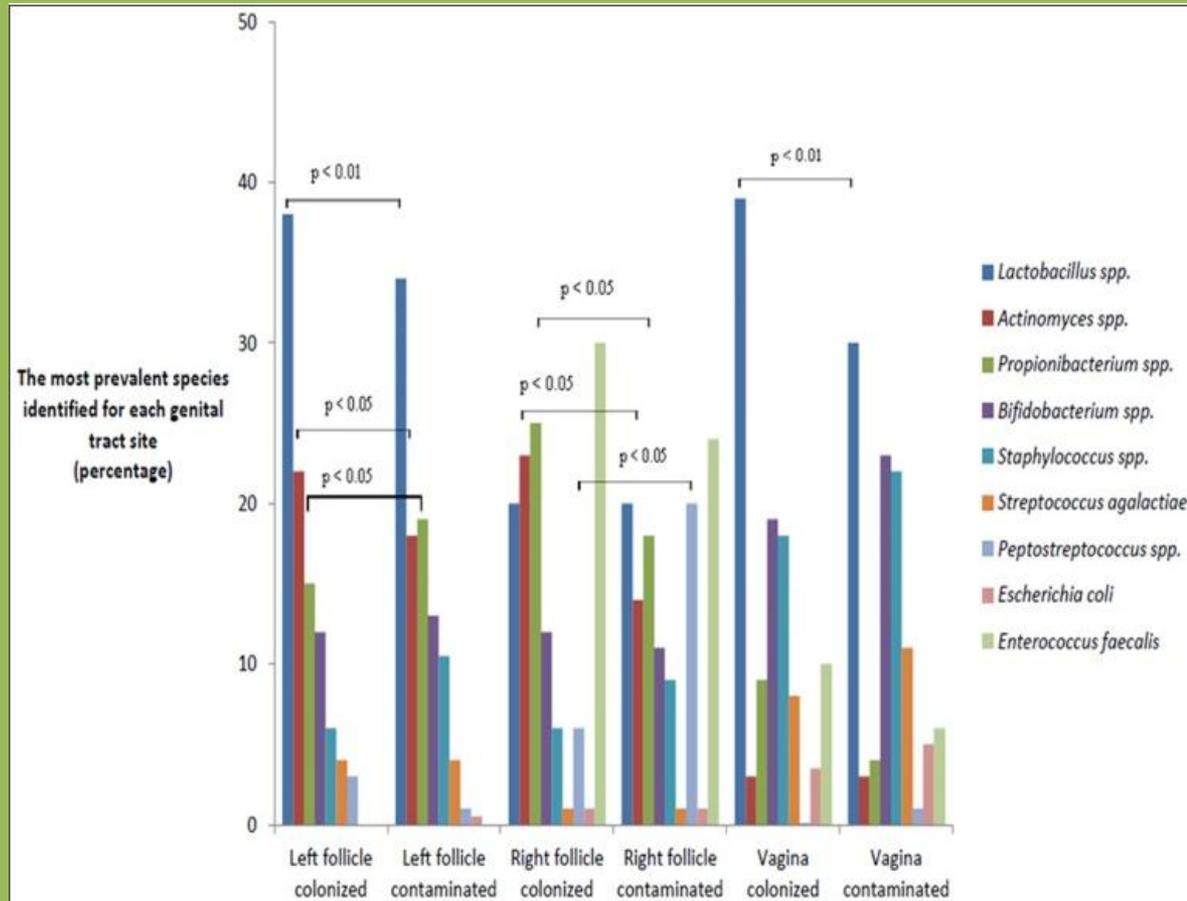
Agente patogeno	Malattia	Quadro clinico	
		Uomo	Donna
Protozoi			
<i>Trichomonas vaginalis</i>	Tricomoniiasi	Uretrite secretiva, spesso asintomatica	Vaginite secretiva, parto prematuro
Miceti			
<i>Candida albicans</i>	Candidosi	Lesioni superficiali del glande, uretrite	Vulvovaginiti, prurito vulvare, uretrite, cistite
Parassiti			
<i>Phthirus pubis</i>	Pediculosi	Infestazione dei peli pubici, prurito	Infestazione dei peli pubici, prurito
<i>Sarcoptes scabiei</i>	Scabbia	Prurito, cunicoli scabbiosi, lesioni da grattamento, rush cutaneo	Prurito, cunicoli scabbiosi, lesioni da grattamento, rush cutaneo

The failure of the sperm–egg conception process is not infrequent.

The study of infertility has provided useful insights into the details of the fertilization process

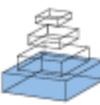
Microorganisms within Human Follicular Fluid: Effects on IVF

Elise S. Pelzer^{1,2*}, John A. Allan³, Mary A. Waterhouse², Tara Ross³, Kenneth W. Beagley¹, Christine L. Knox¹



There is a small but active microbiome in the uterine cavity and in the fallopian tubes of women without obvious pathology.

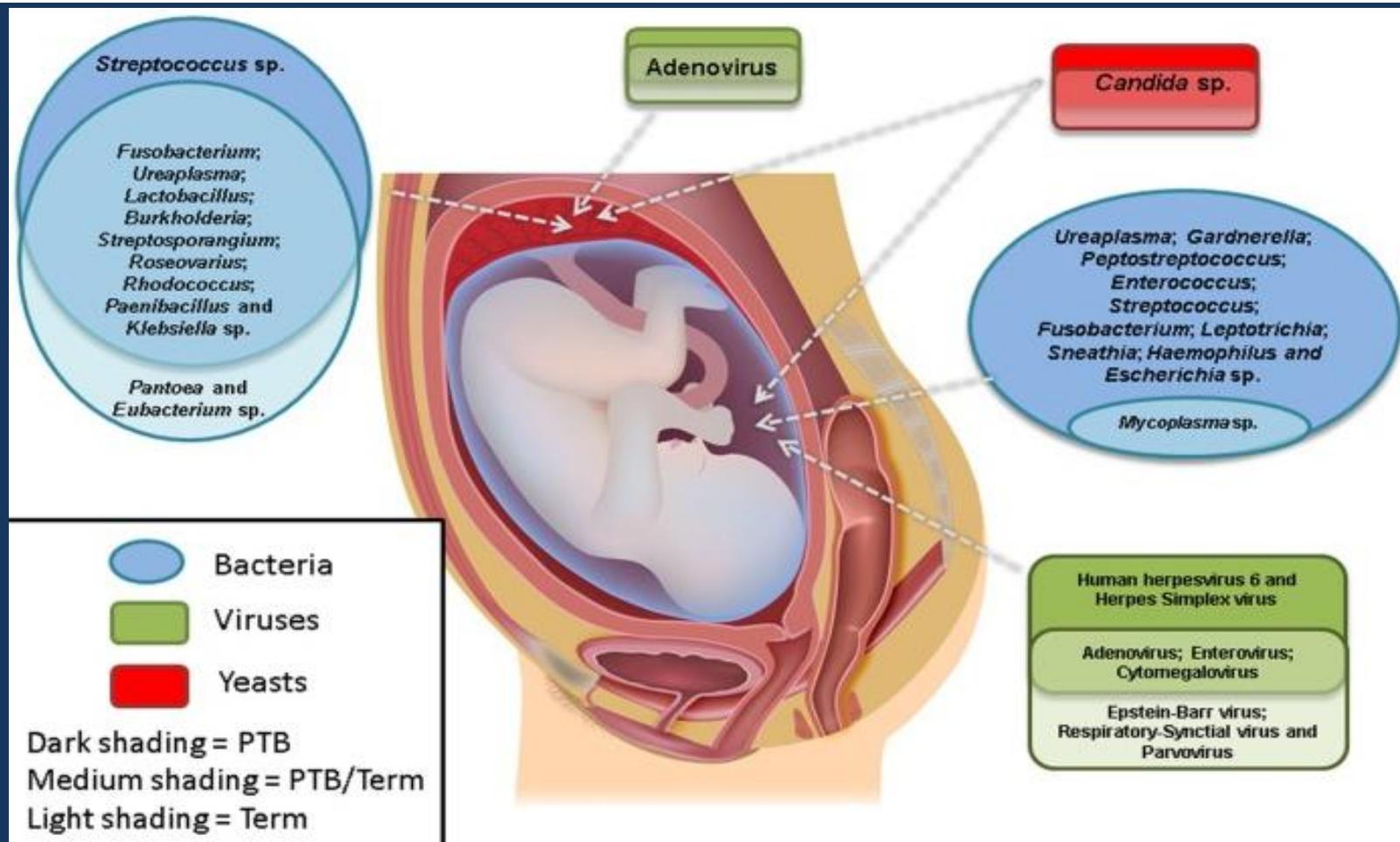
The addition of metagenomic tools allowed descriptions of much broader and more complex microbiome, even in men without evidence of acute or chronic inflammation of their reproductive tract.



Exploring preterm birth as a polymicrobial disease: an overview of the uterine microbiome

Matthew S. Payne* and Sara Bayatibojakhi

School of Women's and Infants' Health, The University of Western Australia, Perth, WA, Australia





Infection is a leading cause of preterm birth.

A focus of many studies has been to characterize microorganisms present in the uterine cavity and document any association with negative pregnancy outcome.

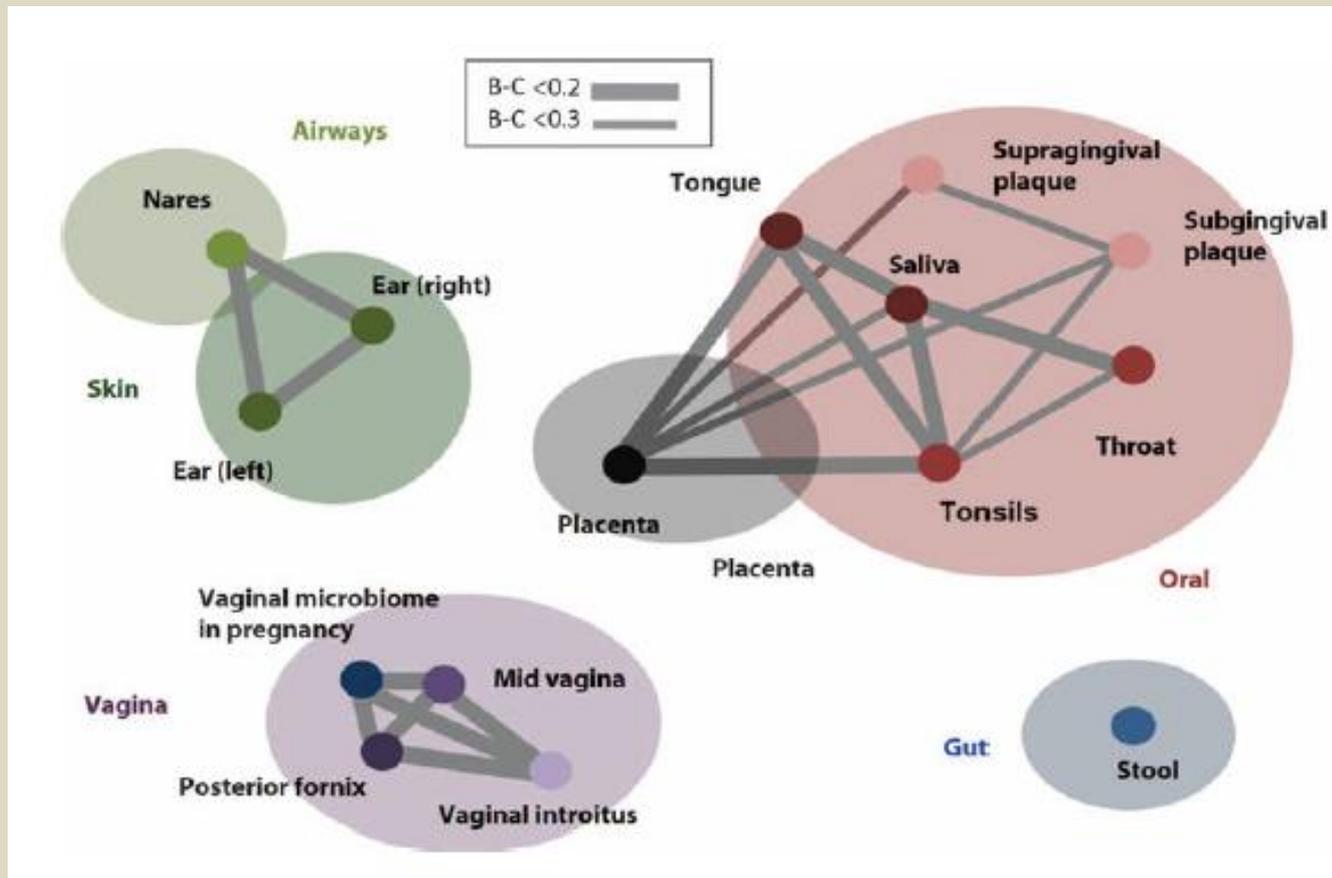


Many studies have contributed vast amounts of data toward characterization of the uterine microbiome, specifically that present in the amniotic fluid, fetal membranes, and placenta.

The emphasis has been placed on the bacterial microbiome, with less data produced on the viral and fungal/yeast microbiomes

The Placenta Harbors a Unique Microbiome

Kjersti Aagaard^{1,2,3,*}, Jun Ma^{1,2}, Kathleen M. Antony¹, Radhika Ganu¹, Joseph Petrosino⁴, and James Versalovic⁵



The placental microbiome has a taxonomic profile that is similar to the oral microbiome

Effect of vaginal probiotic lactobacilli on in vitro–induced sperm lipid peroxidation and its impact on sperm motility and viability

[Arcangelo Barbonetti, M.D.](#), [Benedetta Cinque, Ph.D.](#), [Maria Rosaria Caterina Vassallo, Ph.D.](#), [Salvatore Mineo, Ph.D.](#), [Sandro Francavilla, M.D.](#), [Maria Grazia Cifone, Ph.D.](#), [Felice Francavilla, M.D.](#)  

This study provides evidence that probiotic lactobacilli, whose effectiveness in treating BV in the form of vaginal tablets has been reported recently, may also protect human spermatozoa from lipid peroxidation induced in vitro by Fe^{2+} and from its negative effects on sperm motility and viability

Antibiotics prior to embryo transfer in ART. (Review)

Kroon, B., Hart, R.J., Wong, B.M., Ford, E., Yazdani, A. 

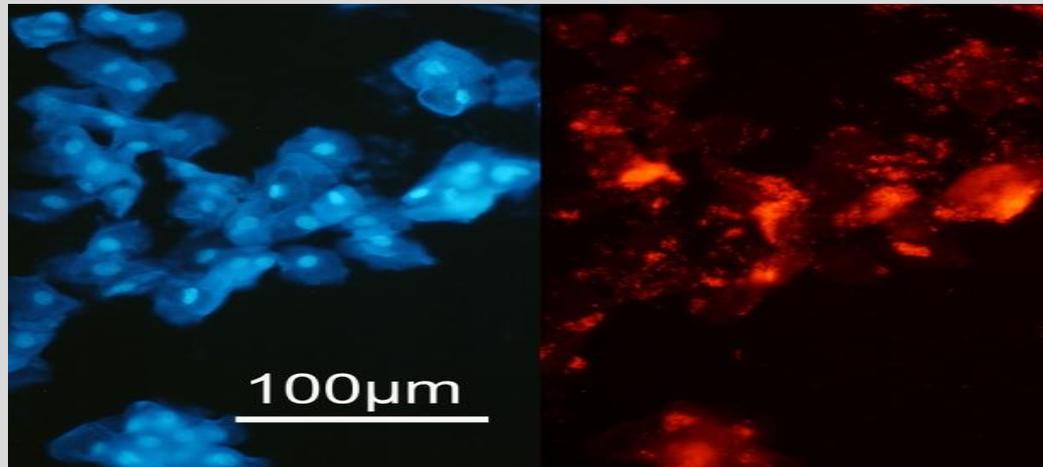
University of Queensland, Queensland Fertility Group Research Foundation, Brisbane,

To evaluate the effectiveness and safety of antibiotic administration prior to ET during ART cycles.

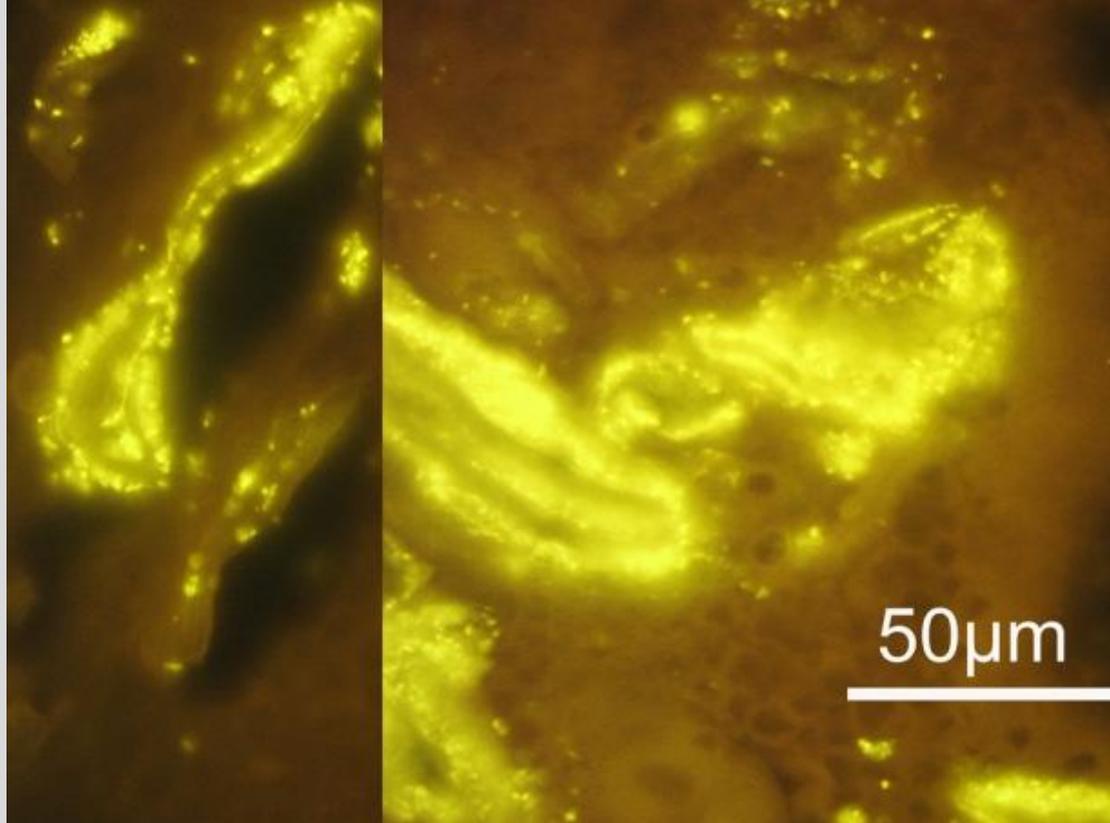
There was no evidence of a difference in clinical pregnancy rate between those receiving an amoxicillin and clavulanic acid antibiotic combination (64/178: 36%) and those not (61/172: 35.5%) (OR1.02, 95% CI 0.66 to 1.58)

This review suggests that the administration of amoxicillin and clavulanic acid prior to embryo transfer reduced upper genital tract microbial contamination but did not alter clinical pregnancy rates.

It is becoming increasingly evident that the aggregate microbiome is not a simple accumulation of free-floating bacteria on the surface of a human tissue.

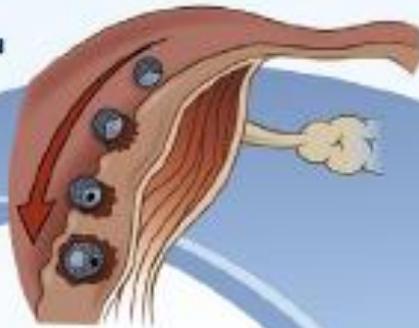


A protective outer coating composed of polysaccharide, nucleic acid, and protein may develop



These biofilms may inhibit immune detection and reduce the effectiveness of antimicrobial treatment

- ALTERED IMMUNE MILIEU
- DECREASED IMPLANTATION
- INCREASED EARLY PREGNANCY LOSS



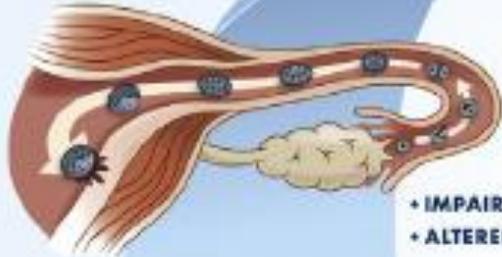
- INCREASED LATE PREGNANCY LOSS



- INTRAAMNIOTIC INFECTION
- PRETERM BIRTH
- INTRAUTERINE GROWTH RESTRICTION



- IMPAIRED FERTILIZATION
- ALTERED EMBRYO MIGRATION



- IMPAIRED FOLLICULOGENESIS
- ALTERED GONADOTROPIN RESPONSE



- ASTHENOSPERMIA
- OLIGOSPERMIA
- LEUKOSPERMIA

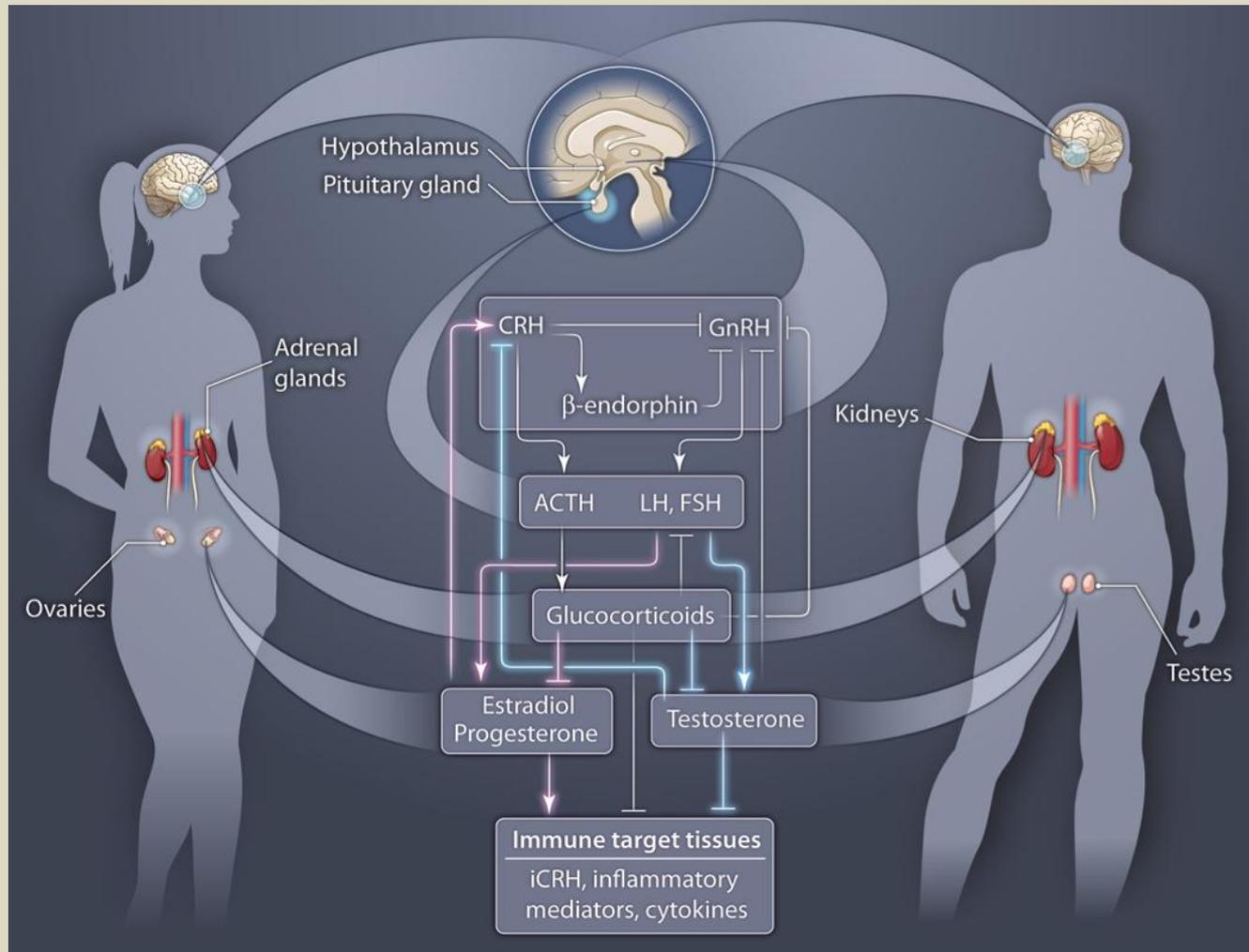


- PUERPERAL INFECTION
- NEONATAL COLONIZATION

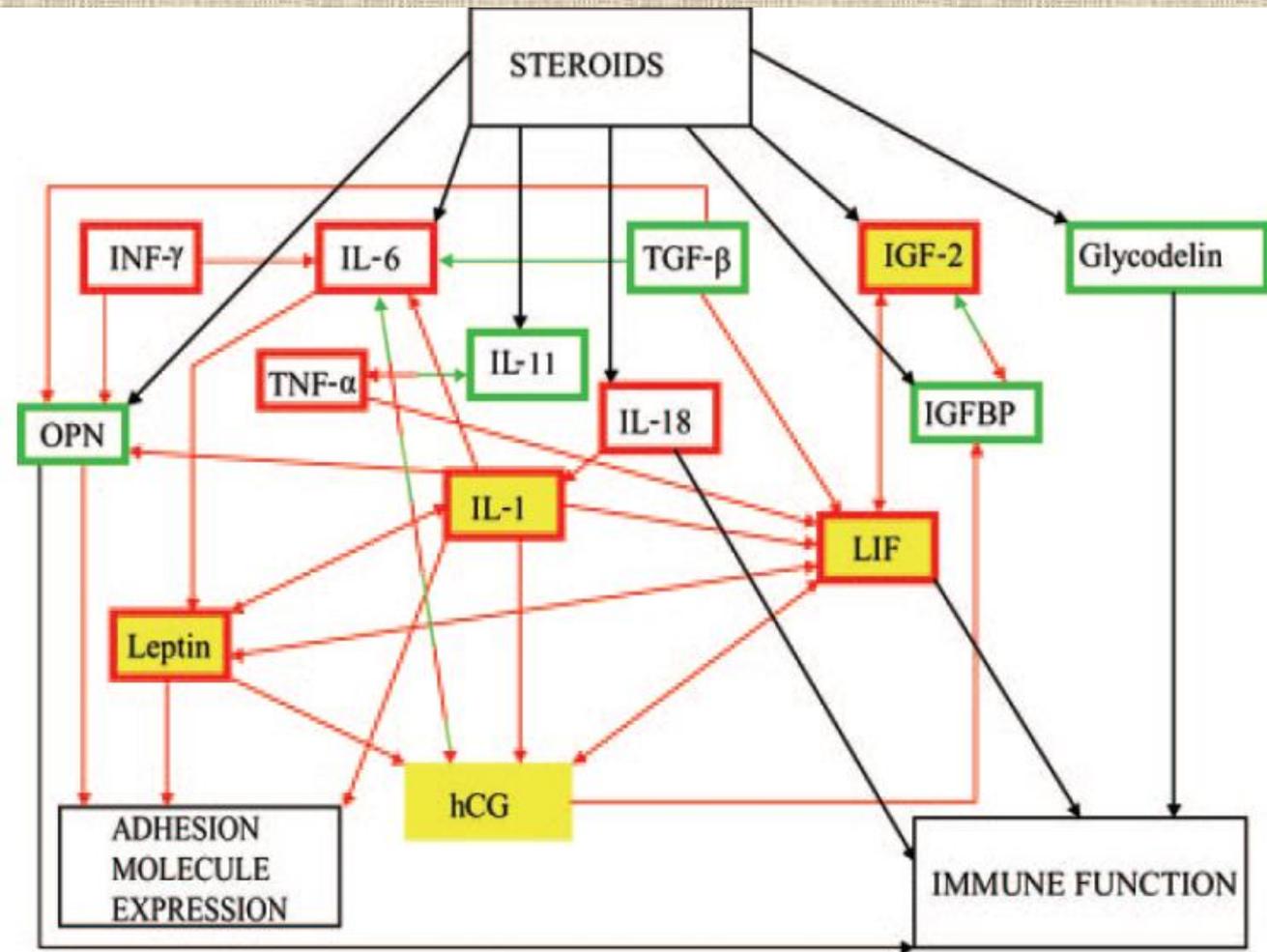


The Microbiome in Human Reproduction

Fig. 1 Interactions between the HPA axis and the female and male reproductive systems and their actions on the immune and inflammatory reaction



Implantation



BOX

Red: pro-inflammatory

Green: anti-inflammatory

Yellow: blastocyst products

ARROWS

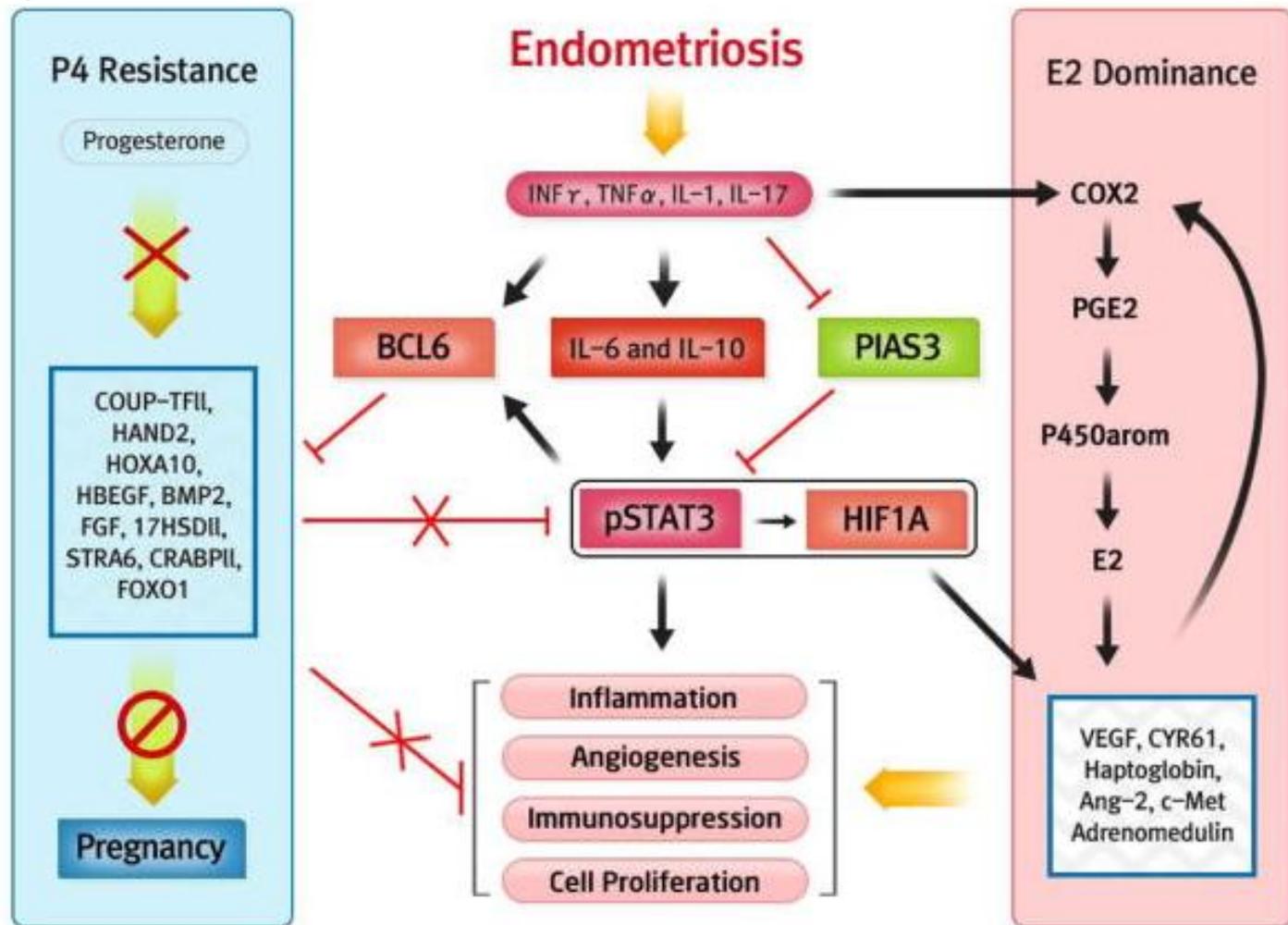
Red: activation

Green: inhibition

Black: regulation

Local and Systemic Factors and Implantation: what is the Evidence?

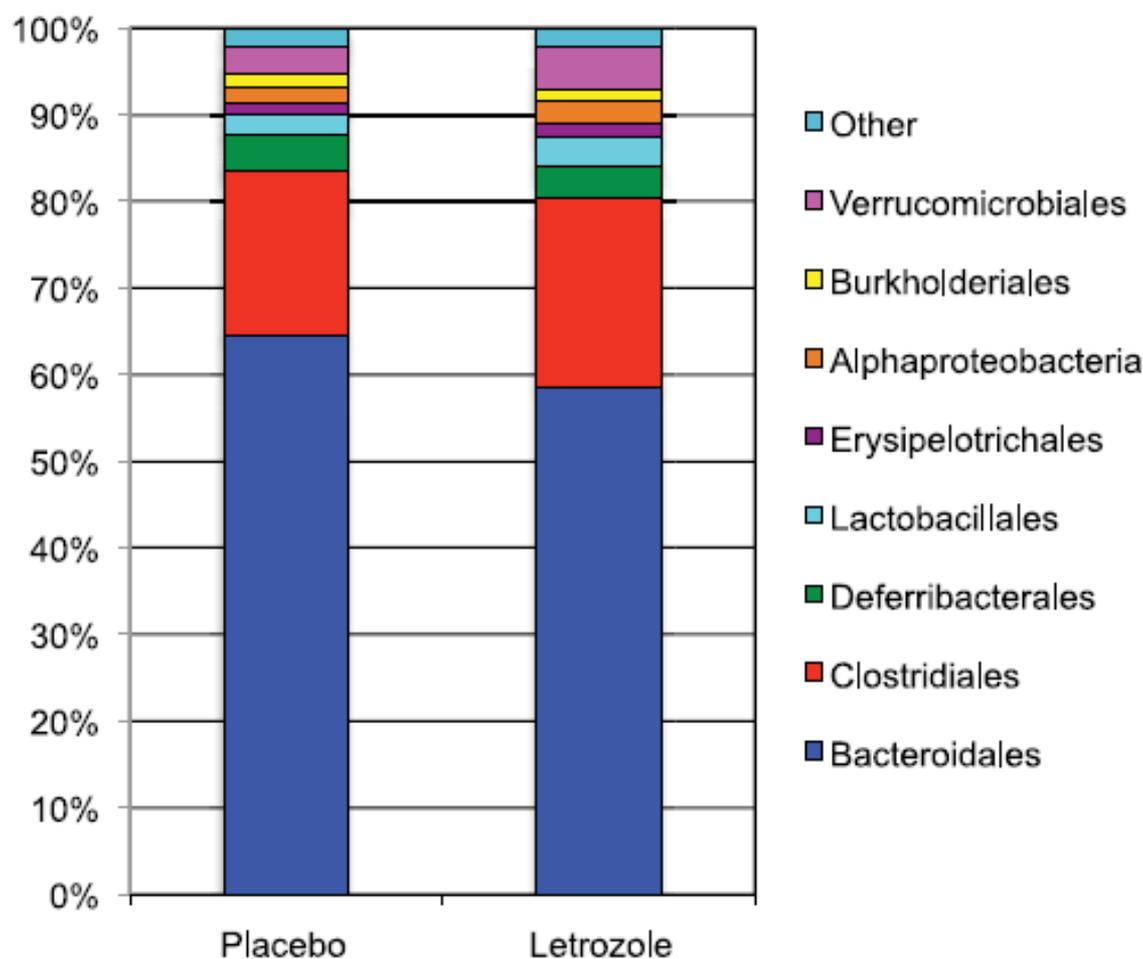
Chelsea Fox, MD^a, Scott Morin, MD^{b,c}, Jae-Wook Jeong, PhD^d, Richard T. Scott Jr., MD^{b,c}, and Bruce A Lessey, MD, PhD^a



RESEARCH ARTICLE

The Gut Microbiome Is Altered in a Letrozole-Induced Mouse Model of Polycystic Ovary Syndrome

Scott T. Kelley¹, Danalea V. Skarra², Alissa J. Rivera², Varykina G. Thackray^{2,3*}



RESEARCH ARTICLE

Association between Polycystic Ovary Syndrome and Gut Microbiota

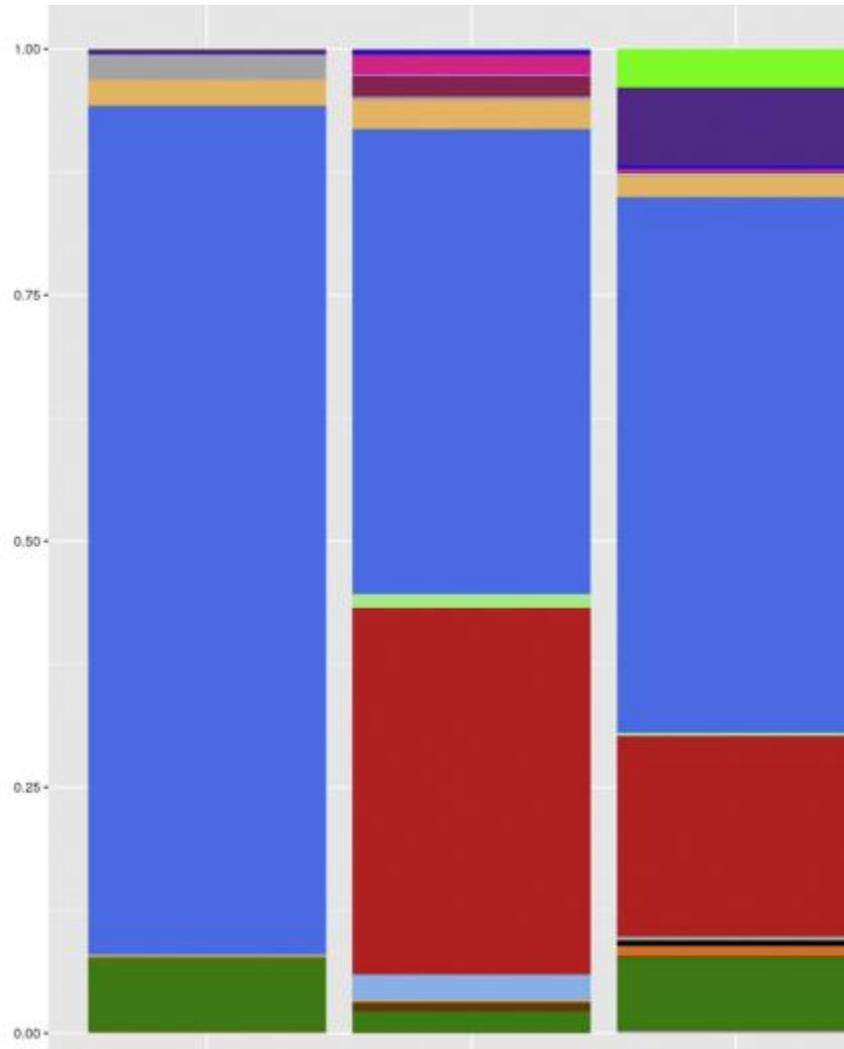
Yanjie Guo, Yane Qi, Xuefei Yang, Lihui Zhao, Shu Wen, Yinhui Liu, Li Tang*

After treating PCOS rats with *Lactobacillus* and fecal microbiota transplantation (FMT) from healthy rats, it was found that the estrous cycles were improved in all 8 rats in FMT group, and in 6 of the 8 rats in *Lactobacillus* transplantation group with decreasing androgen biosynthesis. Their ovarian morphologies normalized.

LB

MISC

NP



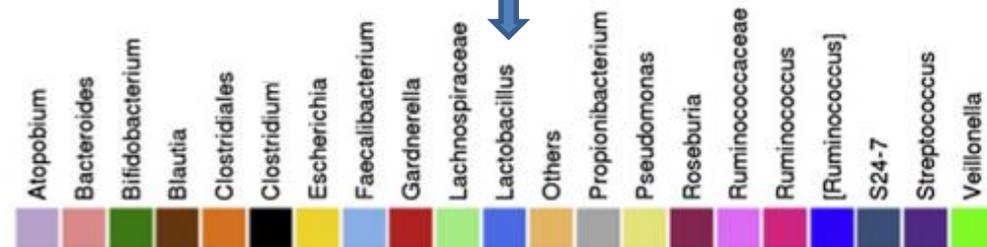
Report of Major Impact

ajog.org

Evidence that the endometrial microbiota has an effect on implantation success or failure



Inmaculada Moreno, PhD¹; Francisco M. Codoñer, PhD¹; Felipe Vilella, PhD¹; Diana Valbuena, MD, PhD; Juan F. Martinez-Blanch, PhD; Jorge Jimenez-Almazán, PhD; Roberto Alonso; Pilar Alamá, MD, PhD; Jose Remohí, MD, PhD; Antonio Pellicer, MD, PhD; Daniel Ramon, PhD²; Carlos Simon, MD, PhD²



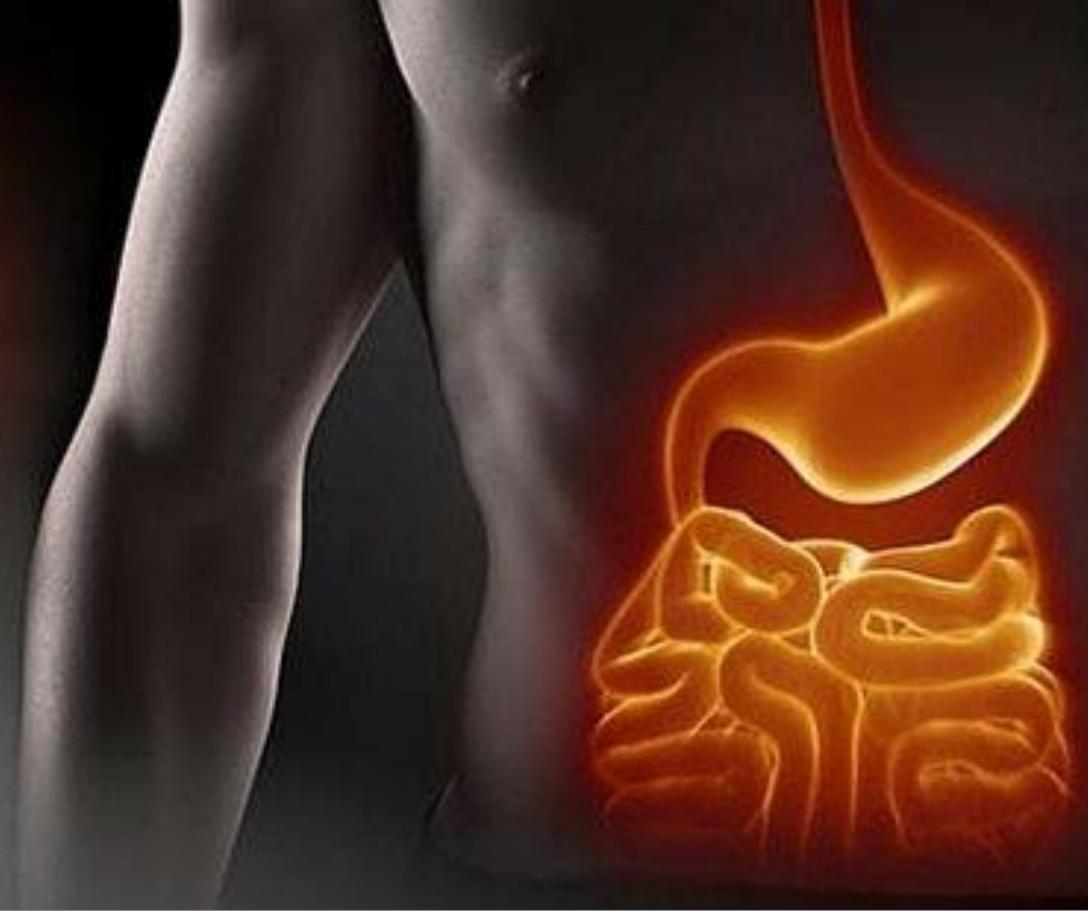
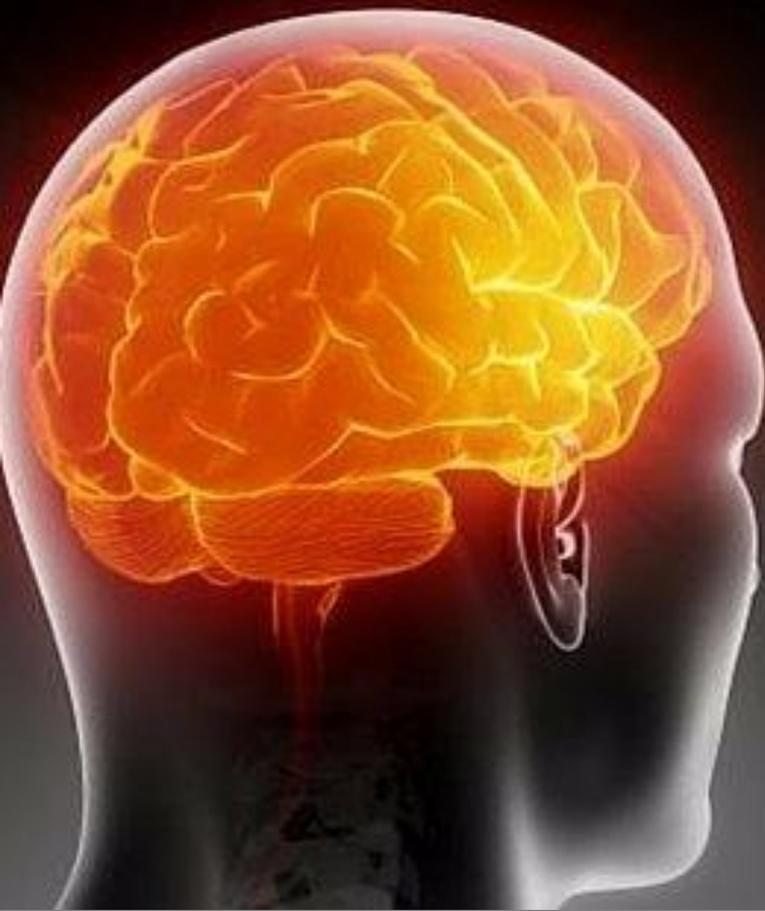
Reproductive tract microbiome in assisted reproductive technologies

Fertil Steril, 2015

Jason M. Franasiak, M.D.,^{a,b} and Richard T. Scott, Jr., M.D., H.C.L.D.^{a,b}

The study of the microbiome and its relationship to the efficiency of conception and early pregnancy maintenance is just beginning

Given the influence which the microbiome has in virtually every organ system, it is not surprising that subtle changes in the microbiome are associated with meaningful changes in gamete quality and ultimate clinical outcomes.

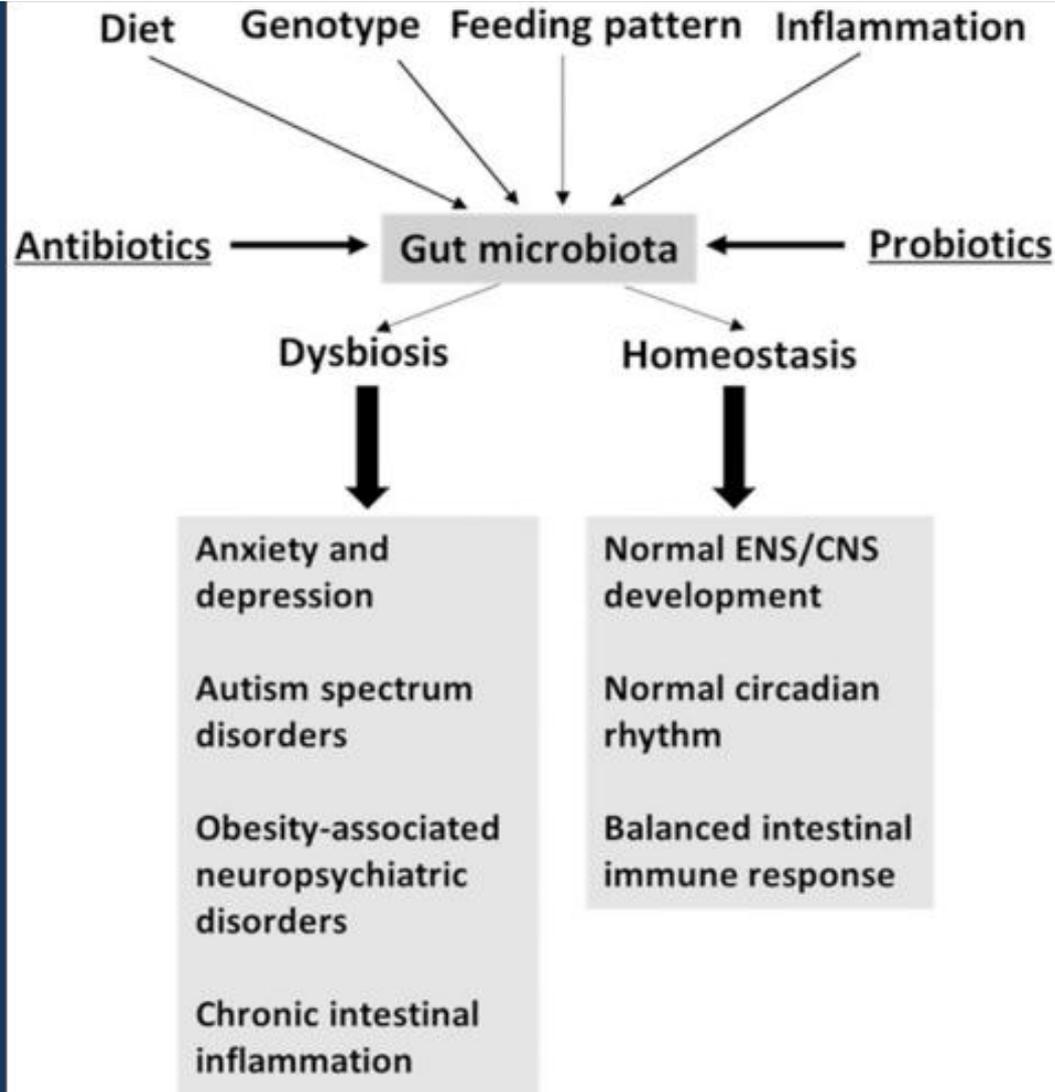


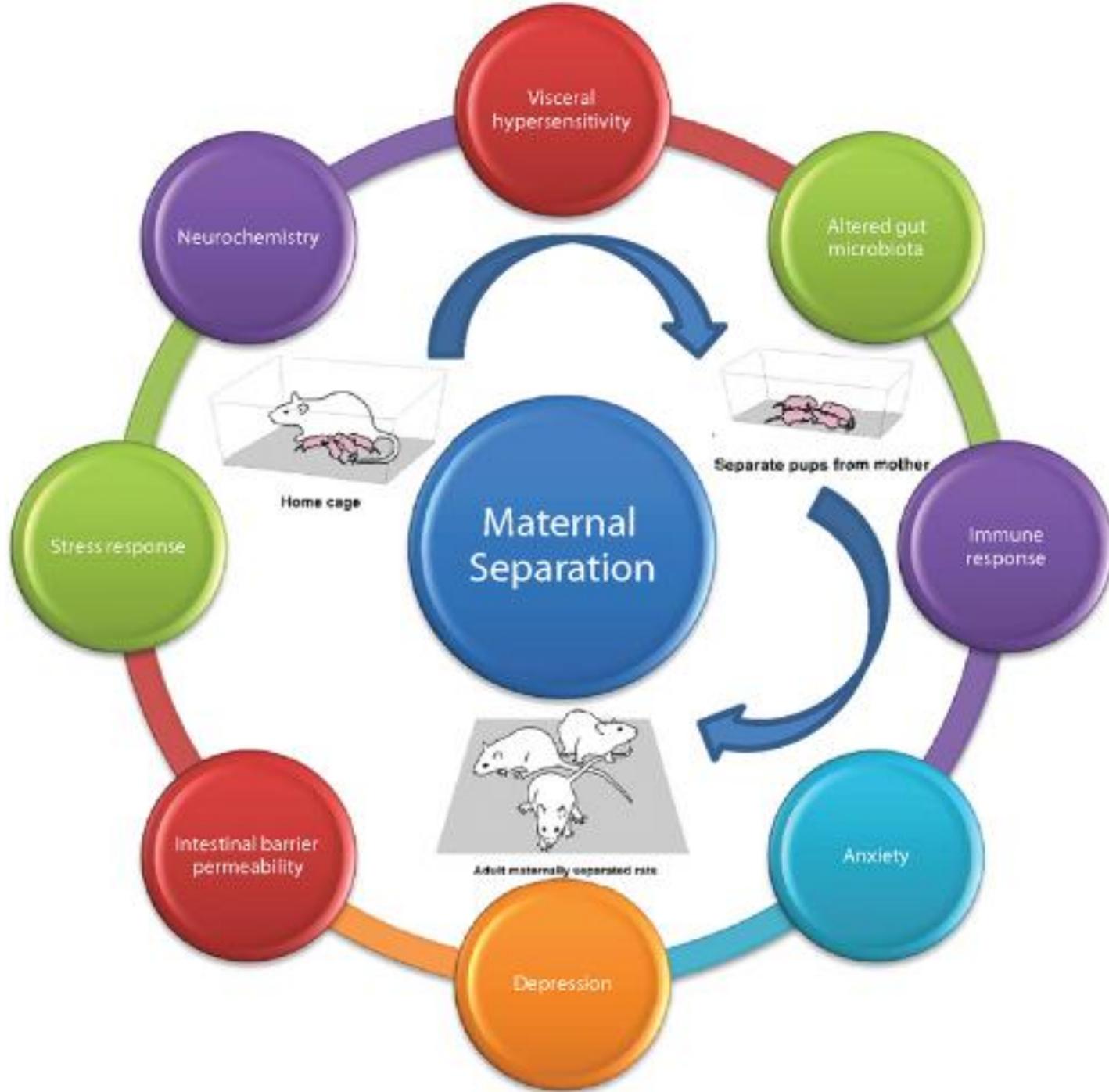
Gut Microbiota: The Brain Peacekeeper.

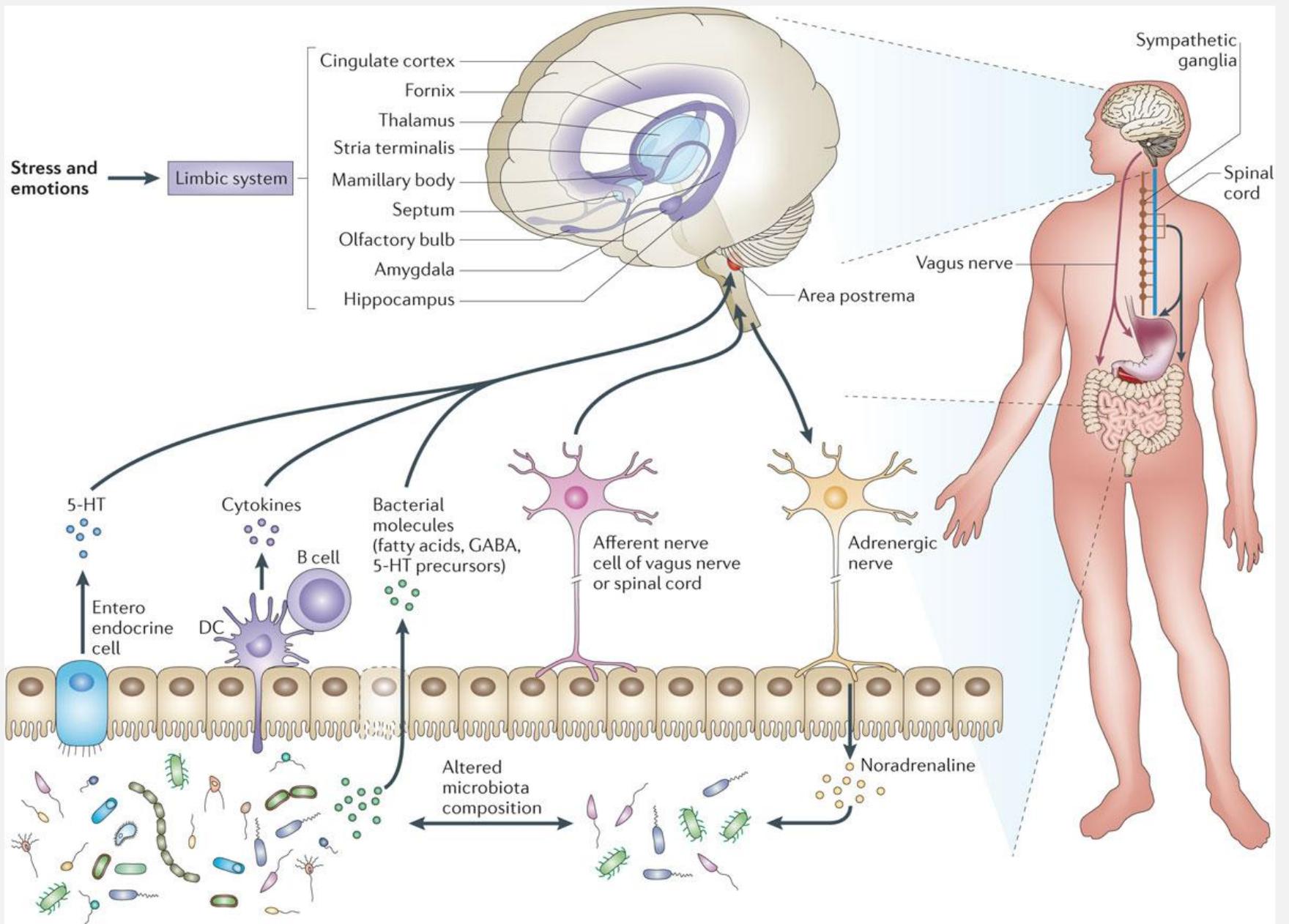
Mu C¹, Yang Y¹, Zhu W¹.

Author information

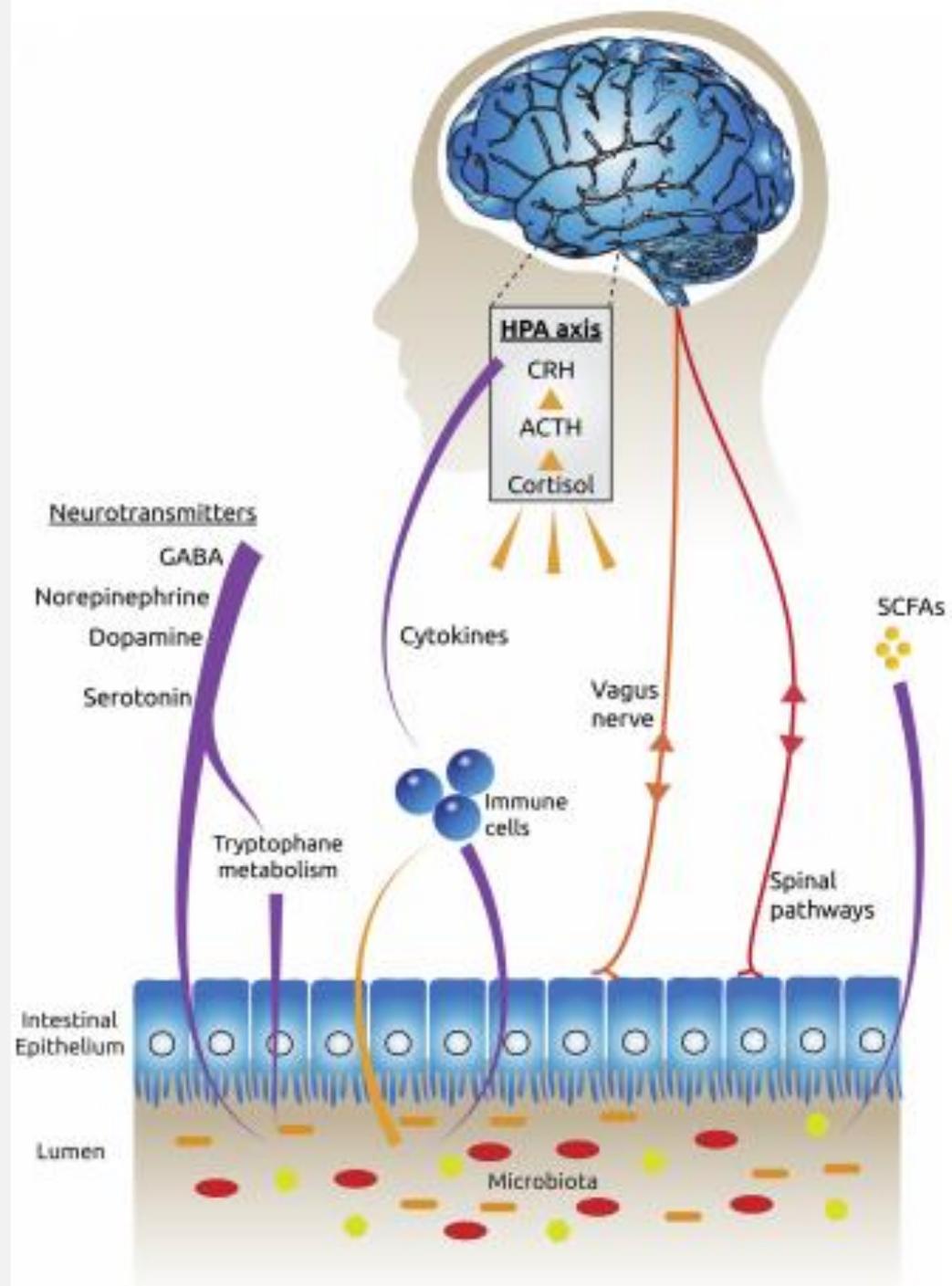
¹Jiangsu Key Laboratory of Gastrointestinal Nutrition and Animal Health, Laboratory of Gastrointestinal Microbiology, College of Animal Science and Technology, Nanjing Agricultural University Nanjing, China.

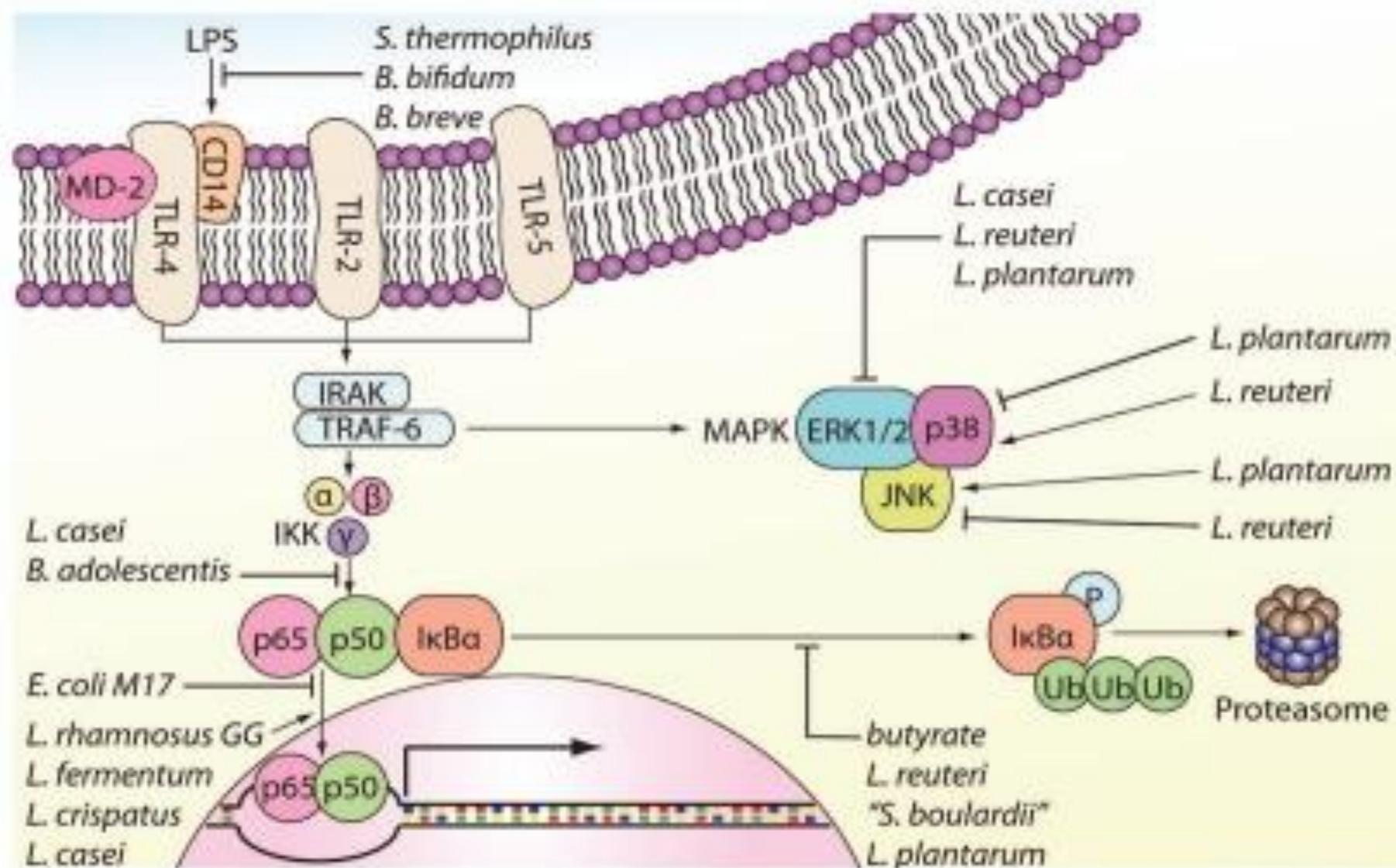






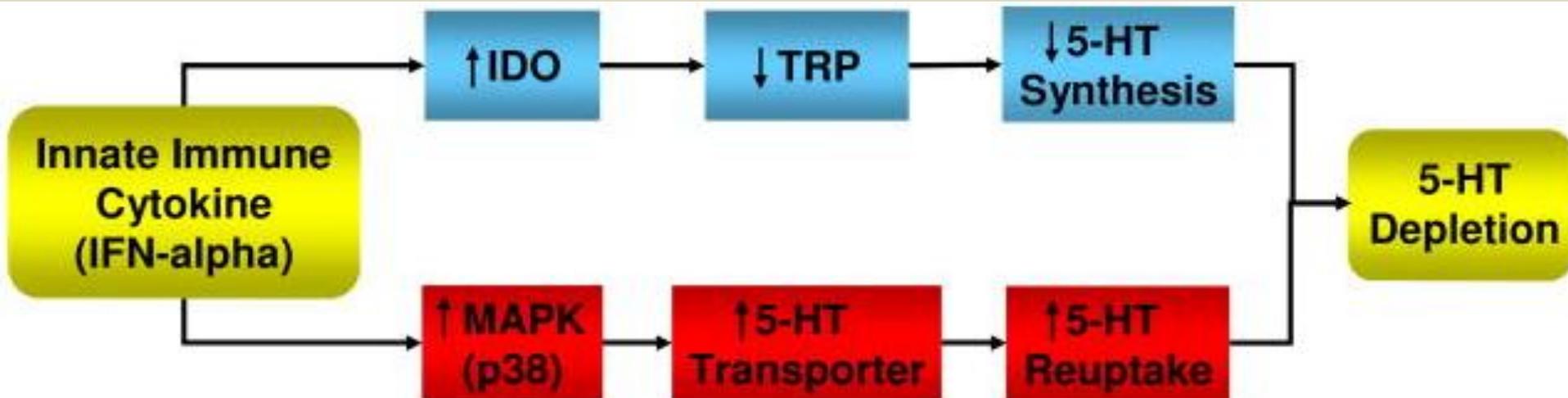
The multiple bidirectional routes of communication between the brain and the gut microbiota





Mechanisms of Cytokine-Induced Behavioral Changes: Psychoneuroimmunology at the Translational Interface Norman Cousins Lecture

[Andrew H. Miller](#), M.D.  and [William P. Timmie](#), Professor of Psychiatry and Behavioral Sciences



Anatomy of an Illness

As perceived by the Patient

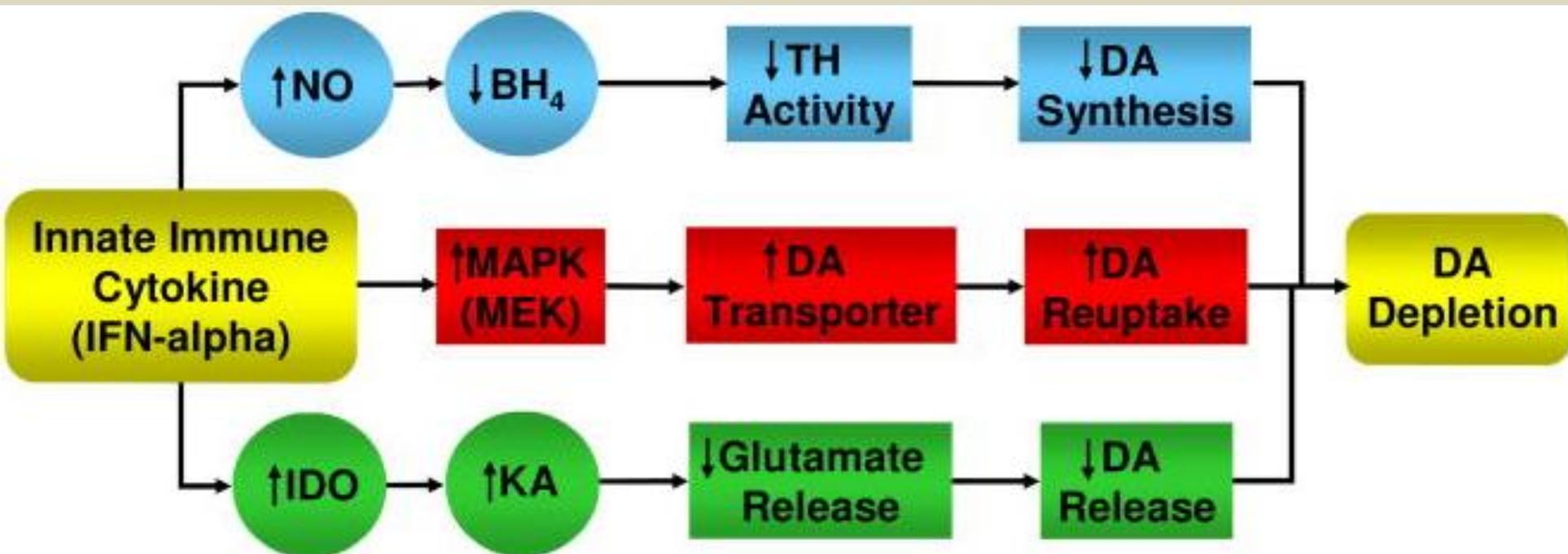
Reflections on Healing and Regeneration

by

Norman Cousins

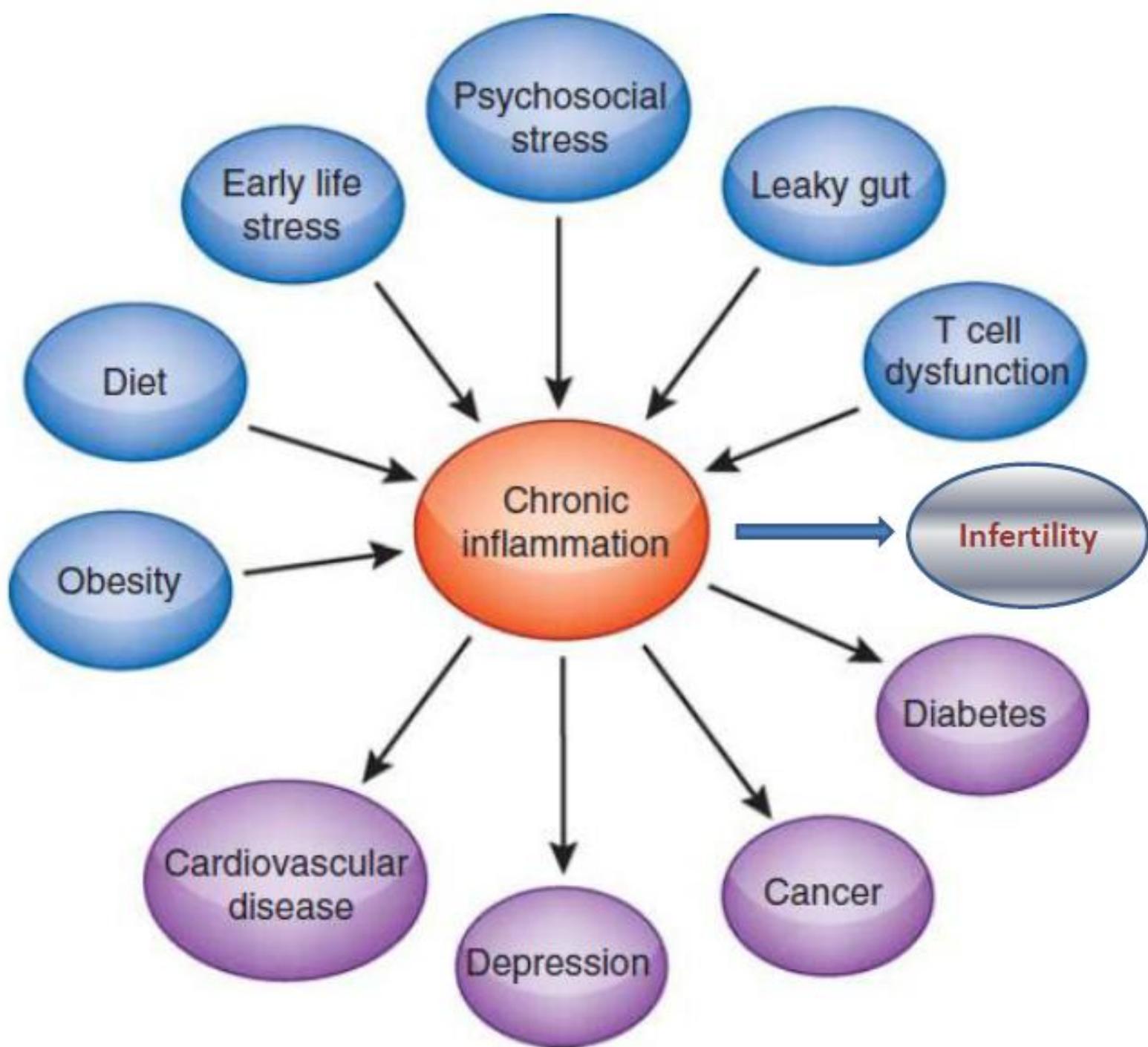
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Gutsy move
...for a brain!





Our "Gut Bug" Cultivation

- Respect them
- Love them
- Care for them:
 - Feed them healthfully
 - Makes sure they get enough sleep
 - Exercise them
- You and they will be much more healthy



The Invisible Universe Of The Human Microbiome



감사하십시오

Merci

ありがとう

obrigada

you

谢谢

choukran

Asante

bighmimi

gracias

당신을 spasiba

grazie

arigato

thank

Danke