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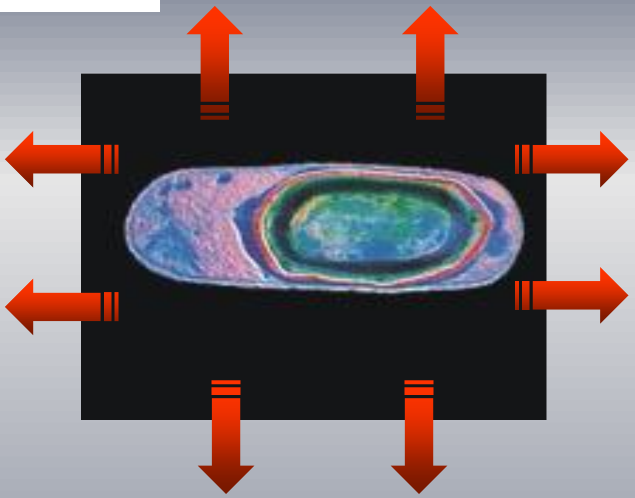

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VI CONGRESO DE ESTERILIZACIÓN Y DESINFECCIÓN 2018 Rosario

DESINFECTANTES, SU EFICACIA, Y LIMPIEZA DE SUPERFICIES HOSPITALARIAS:

Características estructurales de las esporas y biofilms microbianos que confieren resistencia y persistencia a la desinfección

NUEVAS ESTRATEGIAS

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Universidad Nacional de Rosario – Facultad de Ciencias Bioquímicas y Farmacéuticas

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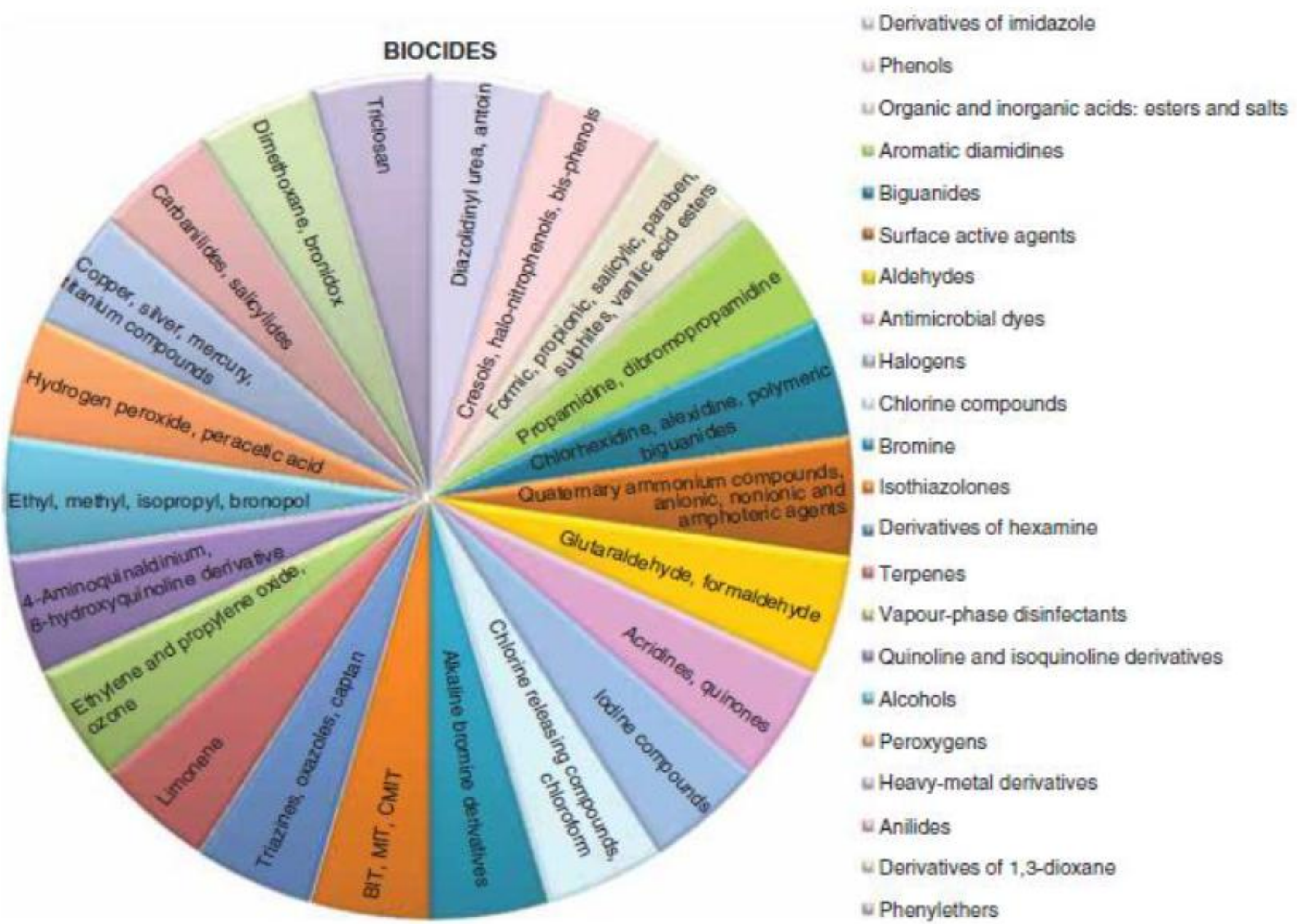


Figure 1. Classes of biocides based on the functional groups.

Review

Biocides – resistance, cross-resistance mechanisms and assessment

Divya Prakash Gnanadhas, Sandhya Amol Marathe & Dipshikha Chakravortty[†]
Department of Microbiology and Cell Biology, Centre for Infectious Disease Research and Biosafety Laboratories, Indian Institute of Science, Bangalore, India

Review

Biocide tolerance in bacteria

Elena Ortega Morente, Miguel Angel Fernández-Fuentes, Maria José Grande Burgos, Hikmate Abriouel, Rubén Pérez Pulido, Antonio Gálvez*

Área de Microbiología, Departamento de Ciencias de la Salud, Facultad de Ciencias Experimentales, Universidad de Jaén, 23071-Jaén, Spain

The role of the surface environment in healthcare-associated infections

David J. Weber[a,b], Deverick Anderson[c], and William A. Rutala[a,b]

BMC Infectious Diseases

BioMed Central

Research article

Open Access

How long do nosocomial pathogens persist on inanimate surfaces? A systematic review

Axel Kramer*[1], Ingeborg Schwebke[2] and Günter Kampf[1,3]

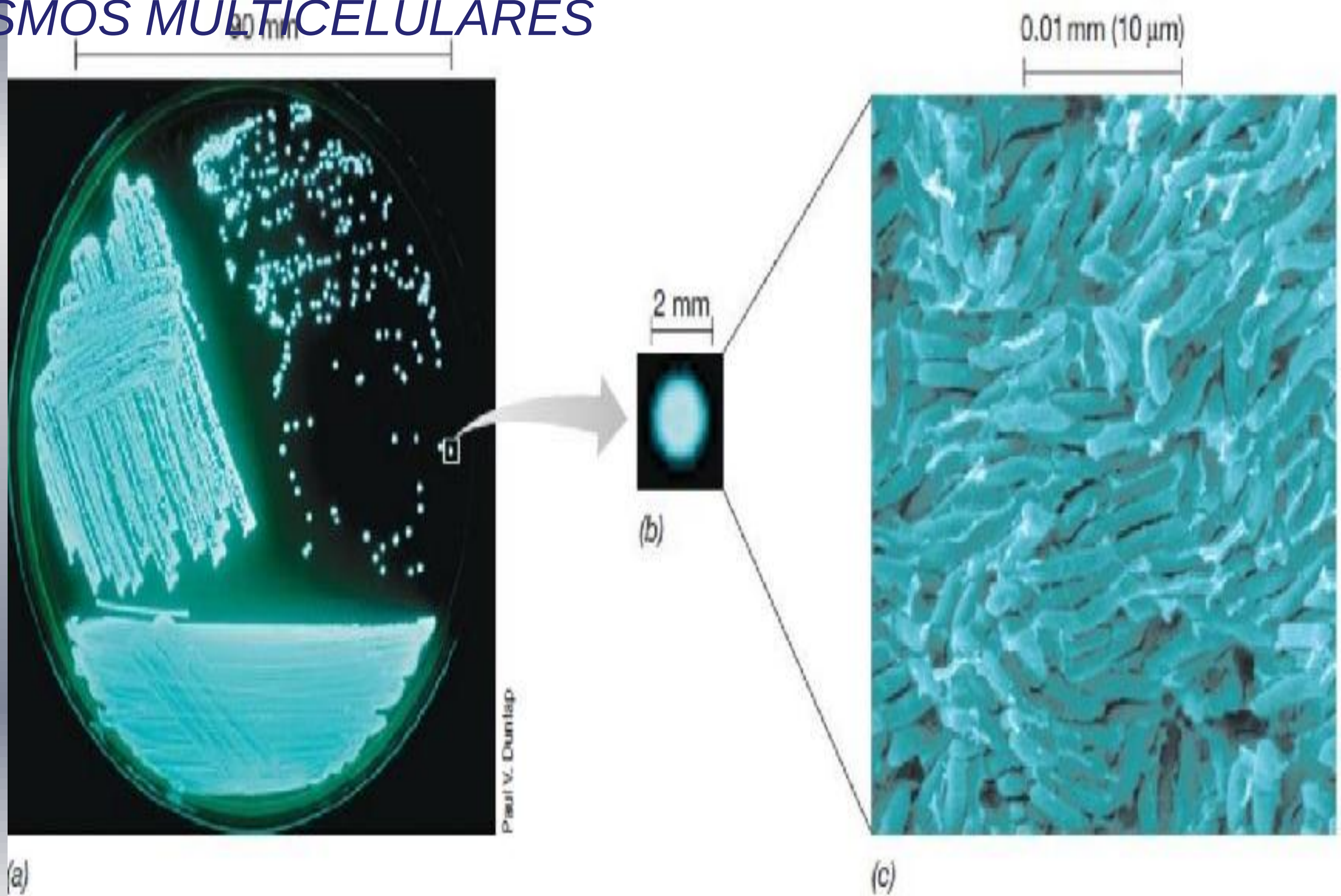
Table 1: Persistence of clinically relevant bacteria on dry inanimate surfaces.

Type of bacterium	Duration of persistence (range)	Reference(s)
Acinetobacter spp.	3 days to 5 months	[18, 25, 28, 29, 87, 88]
Bordetella pertussis	3 – 5 days	[89, 90]
Campylobacter jejuni	up to 6 days	[91]
Clostridium difficile (spores)	5 months	[92–94]
Chlamydia pneumoniae, C. trachomatis	≤ 30 hours	[14, 95]
Chlamydia psittaci	15 days	[90]
Corynebacterium diphtheriae	7 days – 6 months	[90, 96]
Corynebacterium pseudotuberculosis	1–8 days	[21]
Escherichia coli	1.5 hours – 16 months	[12, 16, 17, 22, 28, 52, 90, 97–99]
Enterococcus spp. including VRE and VSE	5 days – 4 months	[9, 26, 28, 100, 101]
Haemophilus influenzae	12 days	[90]
Helicobacter pylori	≤ 90 minutes	[23]
Klebsiella spp.	2 hours to > 30 months	[12, 16, 28, 52, 90]
Listeria spp.	1 day – months	[15, 90, 102]
Mycobacterium bovis	> 2 months	[13, 90]
Mycobacterium tuberculosis	1 day – 4 months	[30, 90]
Neisseria gonorrhoeae	1 – 3 days	[24, 27, 90]
Proteus vulgaris	1 – 2 days	[90]
Pseudomonas aeruginosa	6 hours – 16 months; on dry floor: 5 weeks	[12, 16, 28, 52, 99, 103, 104]
Salmonella typhi	6 hours – 4 weeks	[90]
Salmonella typhimurium	10 days – 4.2 years	[15, 90, 105]
Salmonella spp.	1 day	[52]
Serratia marcescens	3 days – 2 months; on dry floor: 5 weeks	[12, 90]
Shigella spp.	2 days – 5 months	[90, 106, 107]
Staphylococcus aureus, including MRSA	7 days – 7 months	[9, 10, 16, 52, 99, 108]
Streptococcus pneumoniae	1 – 20 days	[90]
Streptococcus pyogenes	3 days – 6.5 months	[90]
Vibrio cholerae	1 – 7 days	[90, 109]

Ciertas estructuras microbianas como los biofilms y las esporas se ubican (junto a los priones) en el podio de los agentes infecciosos resistentes a la desinfección y esterilización.

VI CONGRESO DE ESTERILIZACIÓN Y DESINFECCIÓN 2018 Rosario

LAS BACTERIAS SON MUCHO MÁS QUE “BOLSITAS LLENAS DE ENZIMAS” SINO QUE SE COMPORTAN COMO “VERDADEROS” ORGANISMOS MULTICELULARES



THE BIOFILM LIFESTYLE

J.W. COSTERTON
ZBIGNIEW LEWANDOWSKI

Center for Biofilm Engineering
Montana State University
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Bozeman, Montana 59717

Adv Dent Res 11(2):192-195, April, 1997

in certain medical, industrial, or environmental systems. Our objective was to take the same approach as the organisms themselves, which show no obvious regard for anthrocentric points of view and simply make themselves as safe and as comfortable as possible by adhering to available surfaces and forming biofilms in virtually all aquatic systems. Similarly, we have sought to understand the basic advantages of the "biofilm lifestyle" for bacteria growing in any and all aquatic ecosystems.

THE STRUCTURE OF BIOFILMS

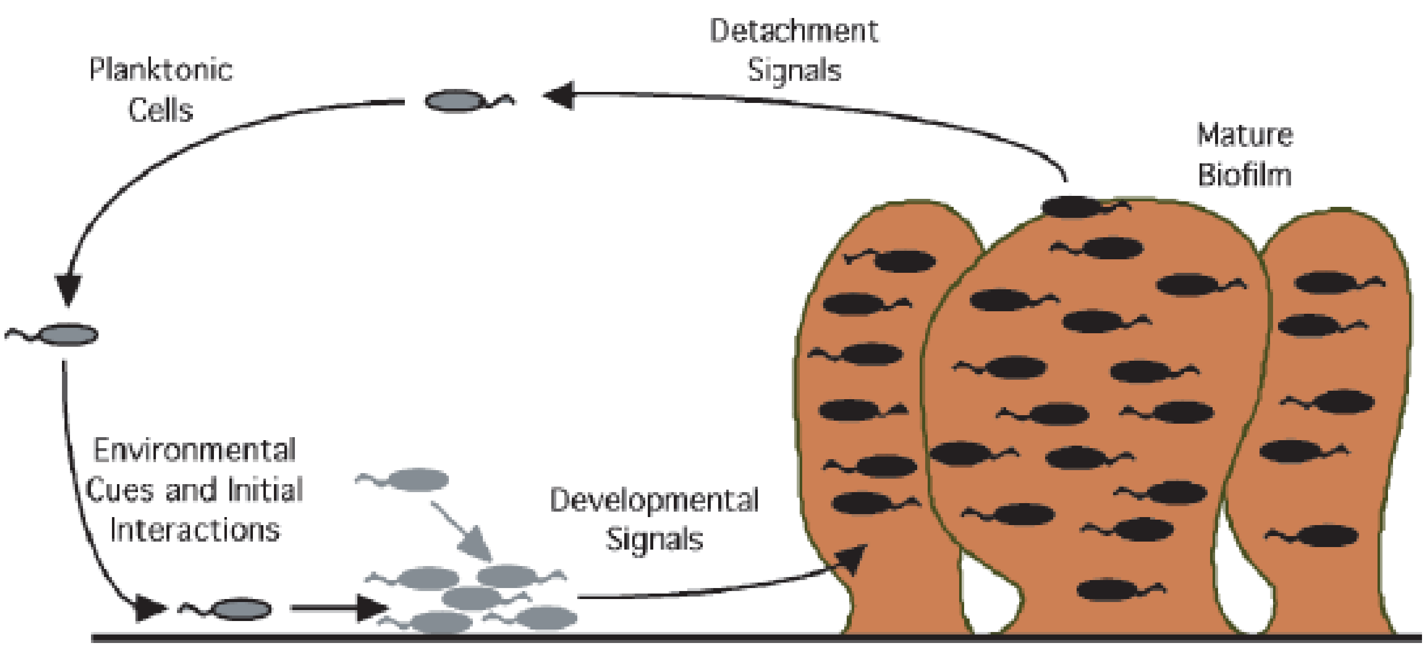
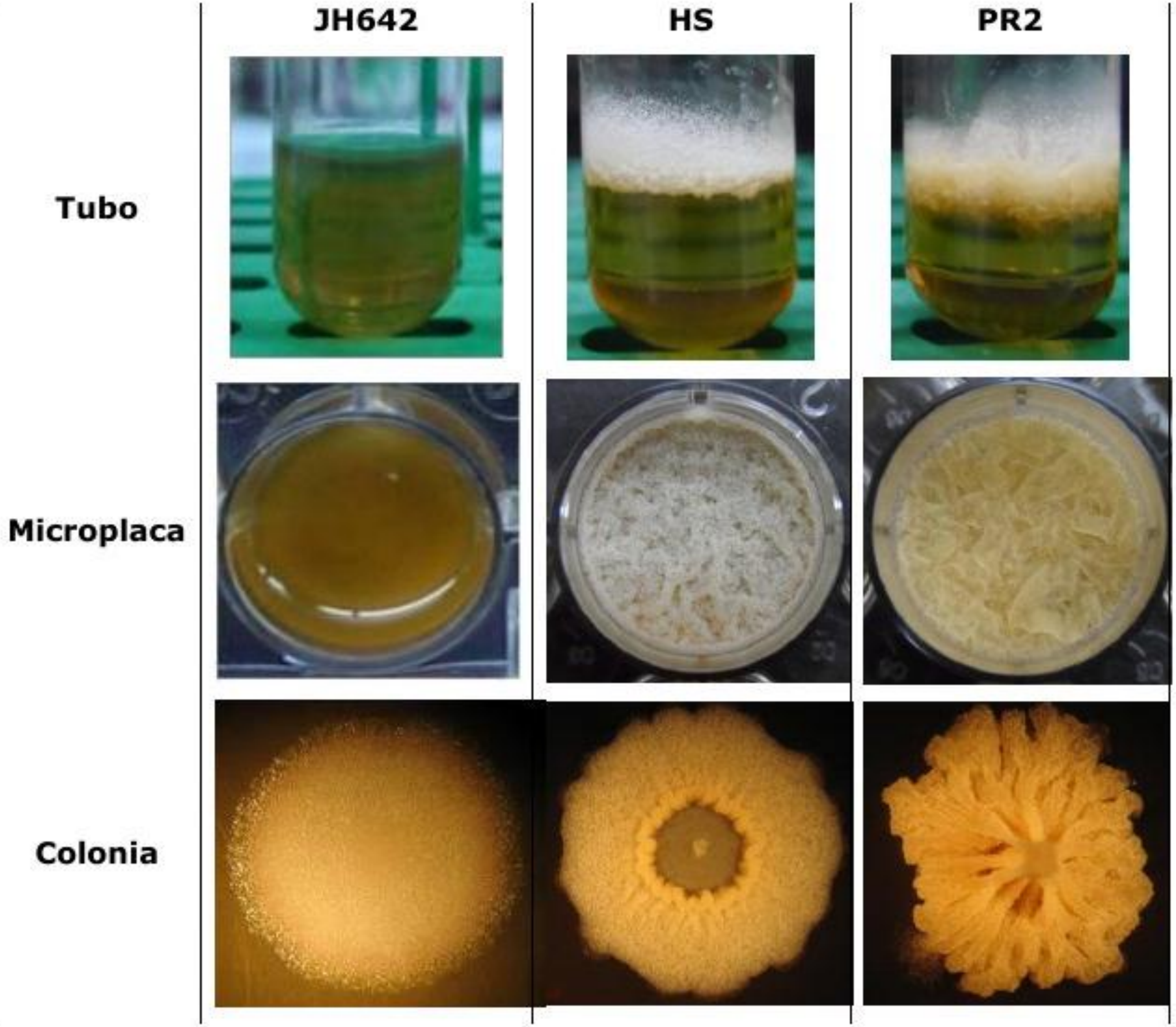
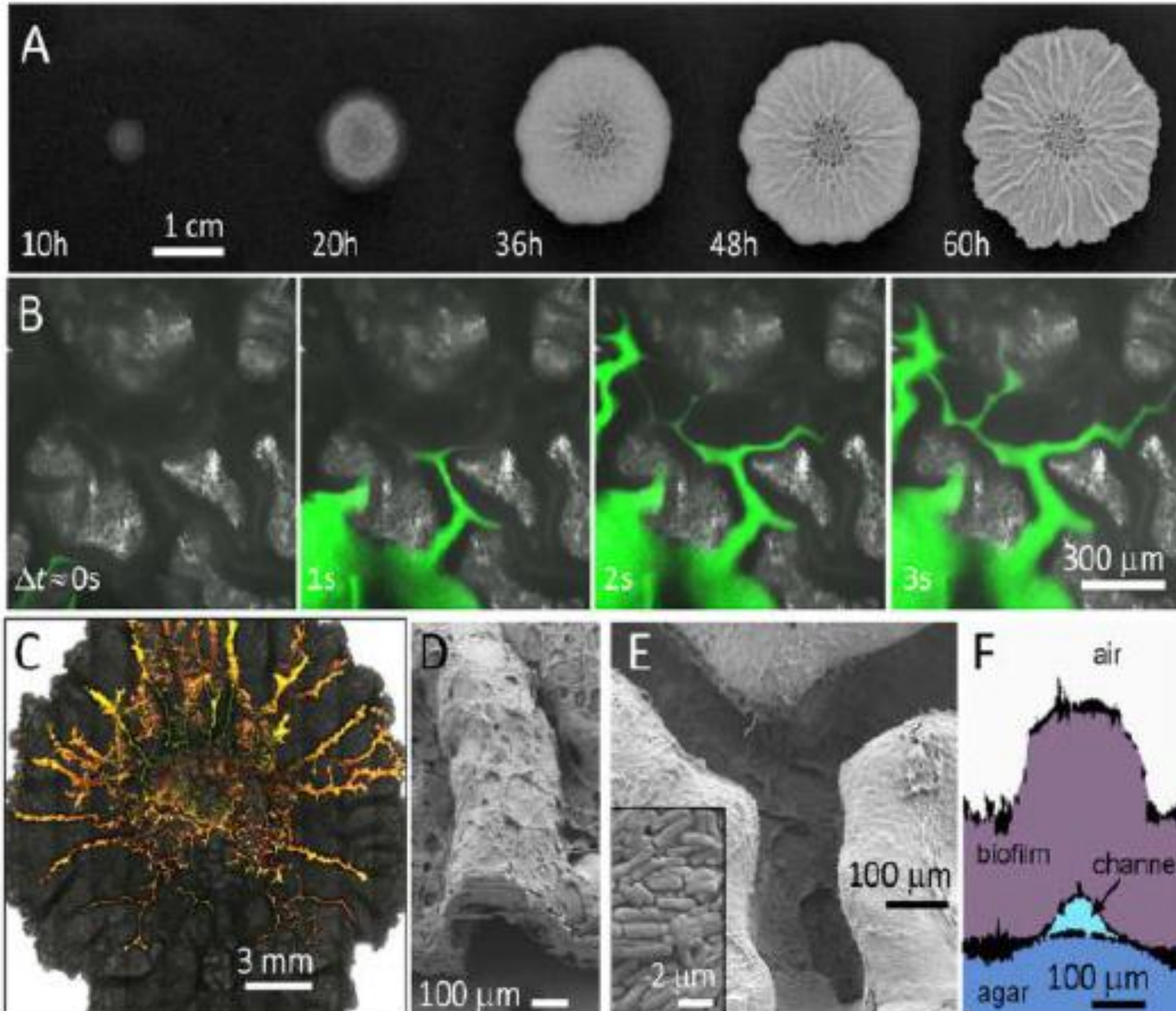


Figure 1 Model of biofilm development. Individual planktonic cells can form cell-to-surface and cel-to-cell contacts resulting in the formation of microcolonies. The hallmark architecture of the biofilms form in an acylhomoserine lactone-dependent process. Cells in the biofilm can return to a planktonic lifestyle to complete the cycle of biofilm development.

BIOFILMS DESARROLLADOS




A
10h
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36h
48h
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B
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1s
2s
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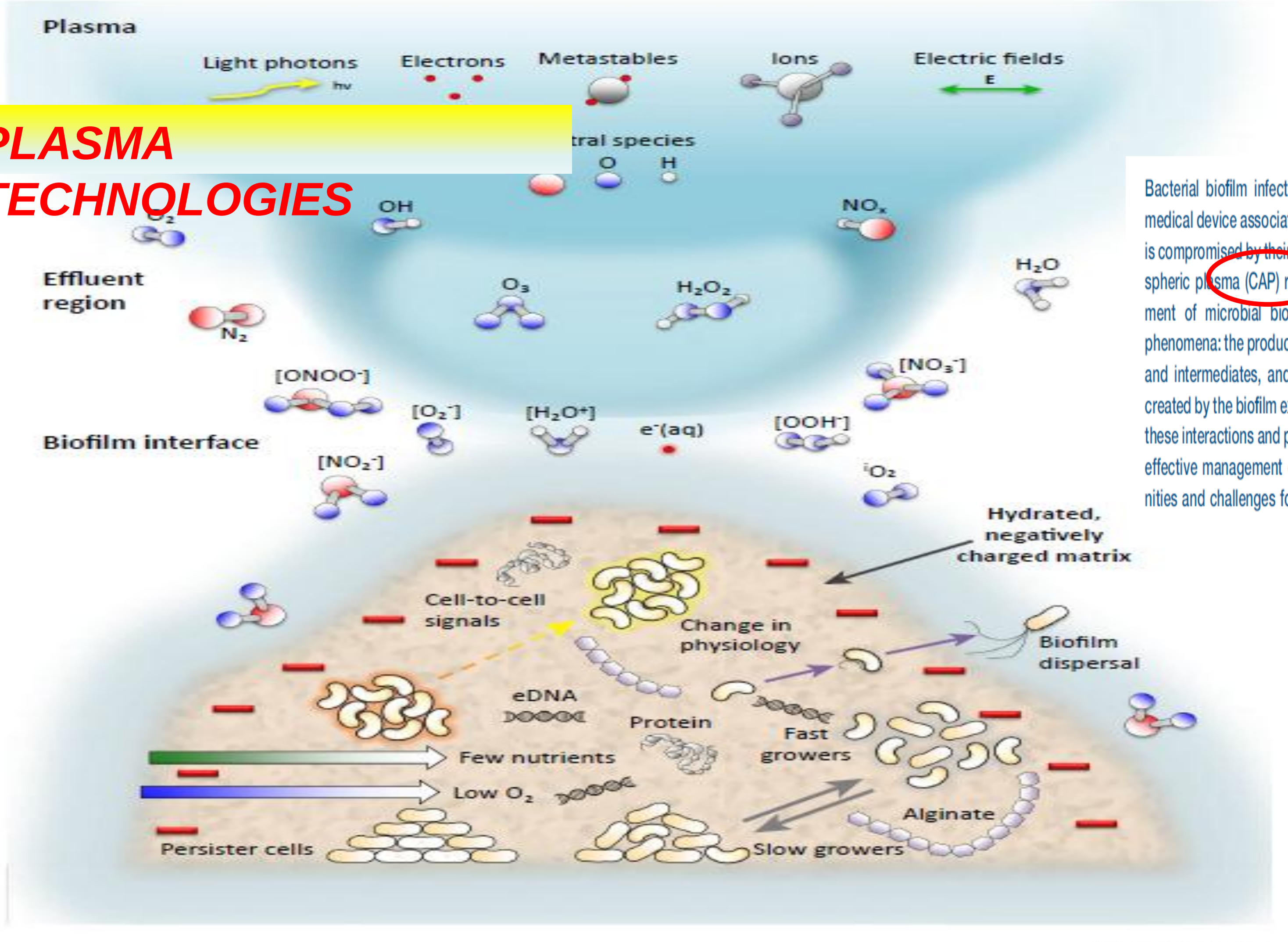
PLASMA TECHNOLOGIES



Bacterial biofilm infections account for a major proportion of chronic and medical device associated infections in humans, yet our ability to control them is compromised by their inherent tolerance to antimicrobial agents. Cold atmospheric plasma (CAP) represents a promising therapeutic option. CAP treatment of microbial biofilms represents the convergence of two complex phenomena: the production of a chemically diverse mixture of reactive species and intermediates, and their interaction with a heterogeneous 3D interface created by the biofilm extracellular polymeric matrix. Therefore, understanding these interactions and physiological responses to CAP exposure are central to effective management of infectious biofilms. We review the unique opportunities and challenges for translating CAP to the management of biofilms.

Figure 1. The Plasma–Biofilm Interface. The plasma-derived reactive species that diffuse into the biofilm encounter a hydrated, cationic extracellular polymeric matrix which may sequester RONS and attenuate plasma cidal efficacy and maintains a 3D architecture supporting heterogeneous microenvironments that in turn support multispecies microcolonies. Growth rate may be reduced due to nutrient and O_2 limitations within the biofilm, leading to elevated tolerance and persister formation. Quorum sensing, leading to alterations in microbial physiology may also affect microbial tolerance to plasma-derived RONS. Finally, RONS-mediated dispersal of microbes from the biofilm may reverse plasma tolerance. Adapted from [7,87]. Abbreviations: eDNA, extracellular DNA; RONS, reactive oxygen and nitrogen species.

PLASMA TECHNOLOGIES

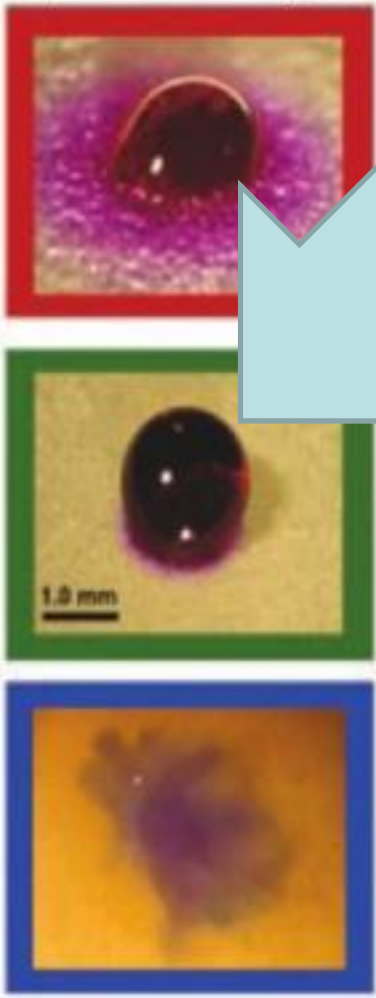
Bacterial biofilm infections account for a major proportion of chronic and medical device associated infections in humans, yet our ability to control them is compromised by their inherent tolerance to antimicrobial agents. Cold atmospheric plasma (CAP) represents a promising therapeutic option. CAP treatment of microbial biofilms represents the convergence of two complex phenomena: the production of a chemically diverse mixture of reactive species and intermediates, and their interaction with a heterogeneous 3D interface created by the biofilm extracellular polymeric matrix. Therefore, understanding these interactions and physiological responses to CAP exposure are central to ... unique opportu- ... t of biofilms.

SIN EMBARGO, HAY QUE CONSIDERAR LA ALTA IMPERMEABILIDAD DEL BIOFILM A LOS LÍQUIDOS Y GASES

Figure 1. The Plasma–Biofilm Interface. The plasma-derived reactive species that diffuse into the biofilm encounter a hydrated, cationic extracellular polymeric matrix which may sequester RONS and attenuate plasma cidal efficacy and maintains a 3D architecture supporting heterogeneous microenvironments that in turn support multispecies microcolonies. Growth rate may be reduced due to nutrient and O_2 limitations within the biofilm, leading to elevated tolerance and persister formation. Quorum sensing, leading to alterations in microbial physiology may also affect microbial tolerance to plasma-derived RONS. Finally, RONS-mediated dispersal of microbes from the biofilm may reverse plasma tolerance. Adapted from [7,87]. Abbreviations: eDNA, extracellular DNA; RONS, reactive oxygen and nitrogen species.

Hidrofobicidad
repelencia al agua

ALTA IMPERMEABILIDAD DEL BIOFILM A LOS LÍQUIDOS Y GASES

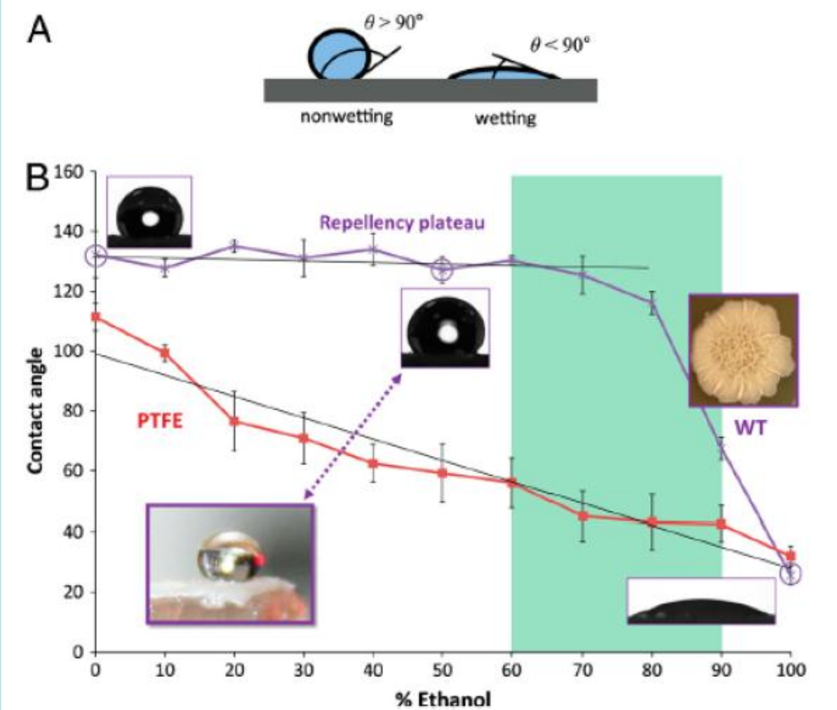


RG4365 (wt)

bslA

Hidrofabicidad celular
Reparto

	NCIB36110	RG4365	*bslA*
$\text{Reparto}_{heptane}$	1.2 ± 0.02	2.2 ± 0.02	< 0.02
Reparto_{octane}	1.45 ± 0.02	3.87 ± 0.02	< 0.02



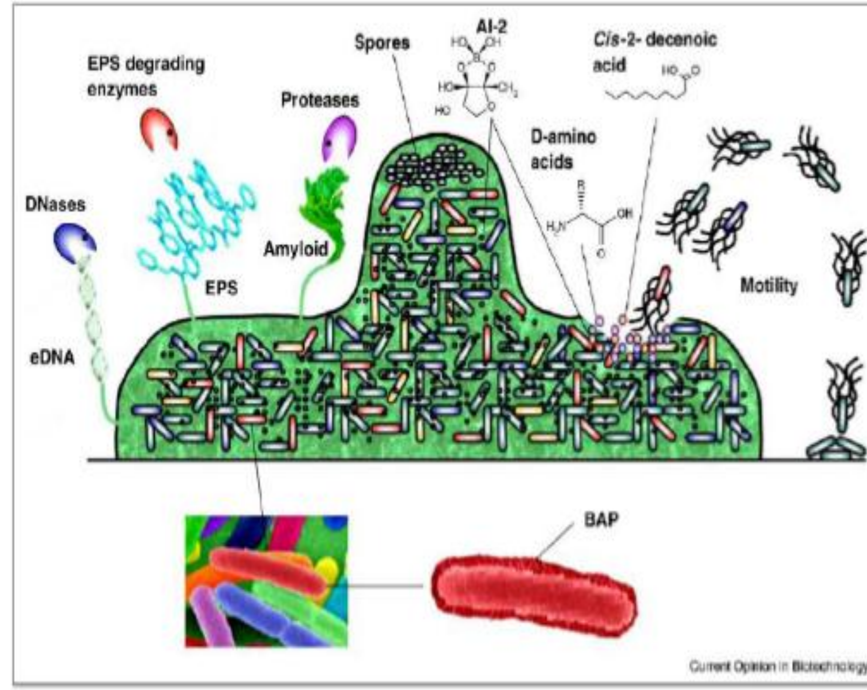


Table 2. Commercial biocides on *B. subtilis* WT biofilms

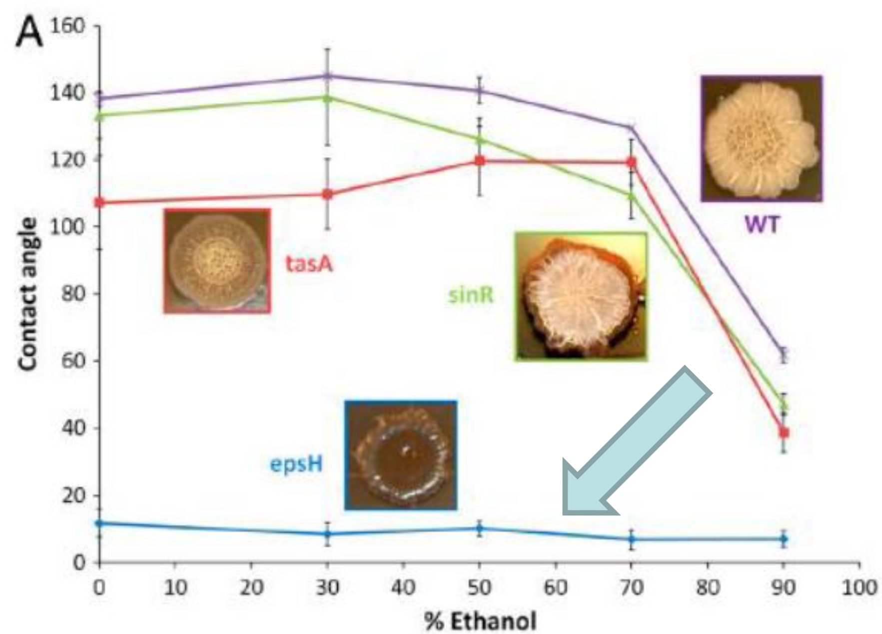
Test liquid	Contact angle (°)
Clorox bleach	45.9 ± 9.4
Lysol Professional	121.9 ± 6.3
Hibiclens	130.8 ± 10.2
Drain opener (10 s)	123.0 ± 13.7
Drain opener (5 min)	47.0 ± 0.52

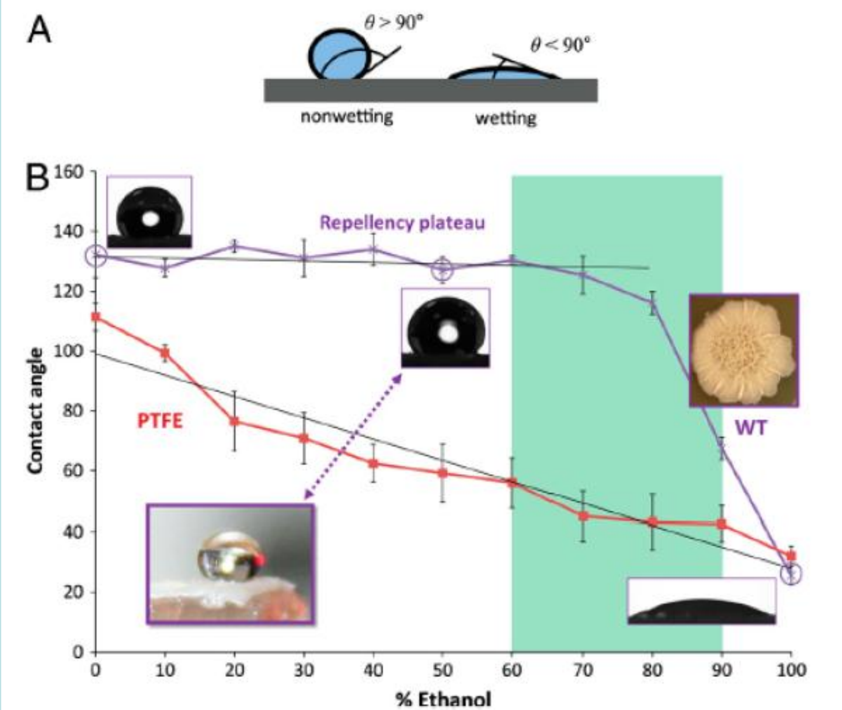
Error = standard deviation; $n = 9$

Table 1. Contact angles of aqueous solutions of organic solvents on *B. subtilis* biofilms

	WT	epsH	tasA	sinR
50% Ethanol	139.0 ± 3.9	10.2 ± 2.2	119.7 ± 10.3	128.9 ± 6.3
50% Isopropanol	125.3 ± 2.6	11 ± 1.5	110.9 ± 6.6	112.6 ± 2.1
50% Methanol	137.9 ± 4.0	8.4 ± 1.1	119.3 ± 8.3	115 ± 7.2
50% Acetone	139.7 ± 3.5	7.7 ± 3.0	117.2 ± 9.8	119.8 ± 3.6

Error = standard deviation; $n = 7$ for WT, 8+ for tasA, 8+ for epsH, 12+ for sinR.





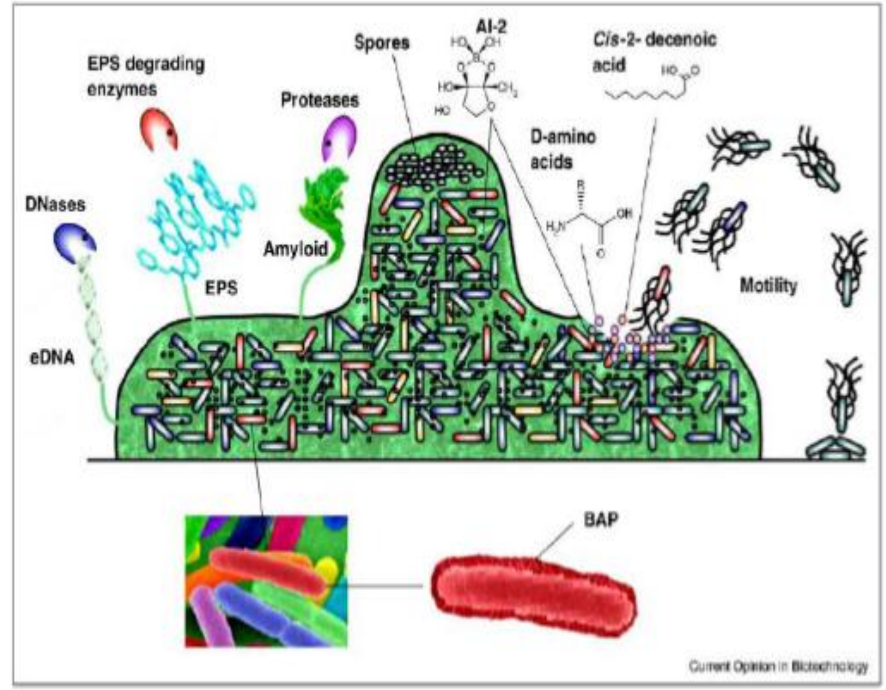


Table 2. Commercial biocides on *B. subtilis* WT biofilms

Test liquid	Contact angle (°)
Clorox bleach	45.9 ± 9.4
Lysol Professional	121.9 ± 6.3
Hibiclens	[illegible]
Drain opener ([illegible] s)	[illegible]
Drain opener ([illegible] min)	[illegible]

Error = sta[illegible]ard deviatio[illegible]

Table 1. Contact [illegible]gles of aqueous [illegible] on *B. subtilis* biofilms

	WT	epsH	tasA	sinR
50% Ethanol	139.0 ± 3.9	10.2 ± 2.2	119.7 ± 10.3	128.9 ± 6.3
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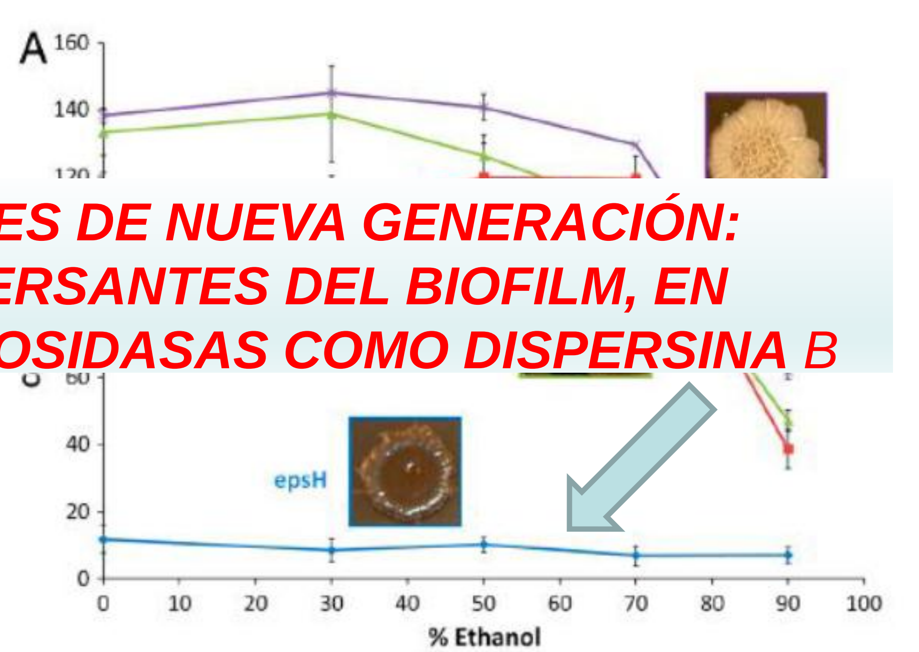
50% Acetone	139.7 ± 3.5	7.7 ± 3.0	117.2 ± 9.8	119.8 ± 3.6

Error = standard d[illegible]viation; $n = 7$ for [illegible]T, 8+ for tasA, 8+ for epsH, 12+ for sinR.

DESINFECTANTES DE NUEVA GENERACIÓN: AGENTES DISPERSANTES DEL BIOFILM, EN ESPECIAL GLICOSIDASAS COMO DISPERSINA B



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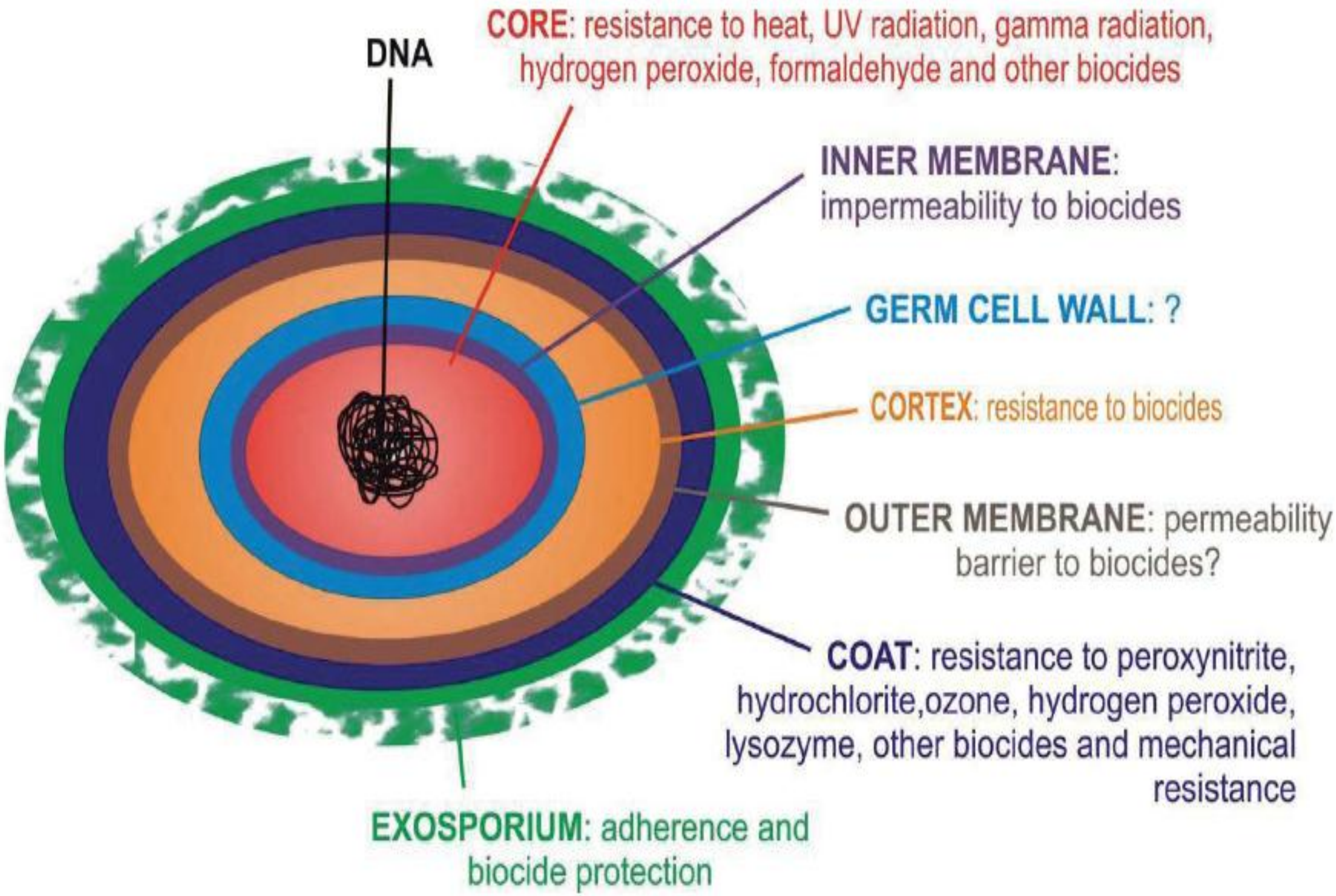


Figure 1: Cartoon of a typical bacterial spore. The different structural components of the spores of *Bacilli* and *Clostridia* and their roles in resistance to biocides and chemical/physical treatments are indicated here and explained in the text.

Adhesion and removal kinetics of *Bacillus cereus* biofilms on Ni-PTFE modified stainless steel

Kang Huang, Lynne A. McLandsborough and Julie M. Goddard

Department of Food Science, University of Massachusetts, Amherst, MA, USA

ABSTRACT

Biofilm control remains a challenge to food safety. A well-studied non-fouling coating involves codeposition of polytetrafluoroethylene (PTFE) during electroless plating. This coating has been reported to reduce foulant build-up during pasteurization, but opportunities remain in demonstrating its efficacy in inhibiting biofilm formation. Herein, the initial adhesion, biofilm formation, and removal kinetics of *Bacillus cereus* on Ni-PTFE-modified stainless steel (SS) are characterized. Coatings lowered the surface energy of SS and reduced biofilm formation by > 2 log CFU cm^{-2}. Characterization of the kinetics of biofilm removal during cleaning demonstrated improved cleanability on the Ni-PTFE coated steel. There was no evidence of biofilm after cleaning by either solution on the Ni-PTFE coated steel, whereas more than 3 log and 1 log CFU cm^{-2} of bacteria remained on the native steel after cleaning with water and an alkaline cleaner, respectively. This work demonstrates the potential application of Ni-PTFE non-fouling coatings on SS to improve food safety by reducing biofilm formation and improving the cleaning efficiency of food processing equipment.

ARTICLE HISTORY
Received 13 October 2015
Accepted 25 February 2016

KEYWORDS
Nickel polytetrafluoroethylene (Ni-PTFE); non-fouling stainless steel; biofilm; *Bacillus cereus*; fouling release coatings; biofouling

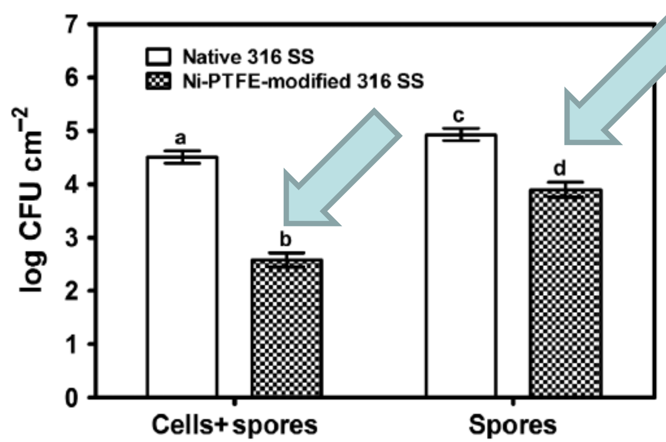


Figure 3. Initial adhesion behavior of vegetative cells and spores after 2 h exposure to native and Ni-PTFE-modified SS surfaces (n = 12). Treatments with different letters are significantly different ($p < 0.05$).

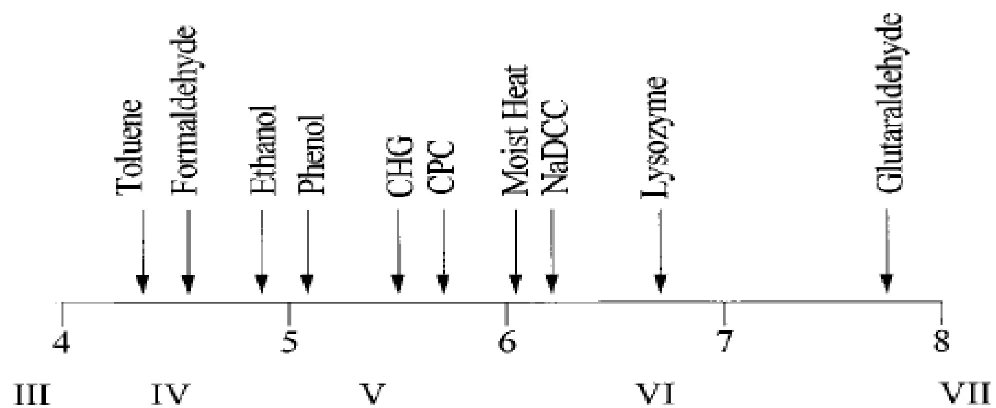


FIG. 2. Development of resistance of *Bacillus subtilis* during sporulation. Roman numerals indicate the sporulation stage from III (engulfment of the forespore) to VII (release of the mature spore). Arabic numbers indicate the time (hours) following the onset of sporulation and the approximate times at which resistance develops against biocides (262). CHG, chlorhexidine; CPC, cetylpyridinium chloride; NaDCC, sodium dichloroisocyanurate.

Las superficies contaminadas de un hospital son reservorios de patógenos que contribuye al aumento de las infecciones intrahospitalarias.

En un hospital "limpio" deberían dismunuir las IAH (Infecciones Asociadas a la Hospitalización).

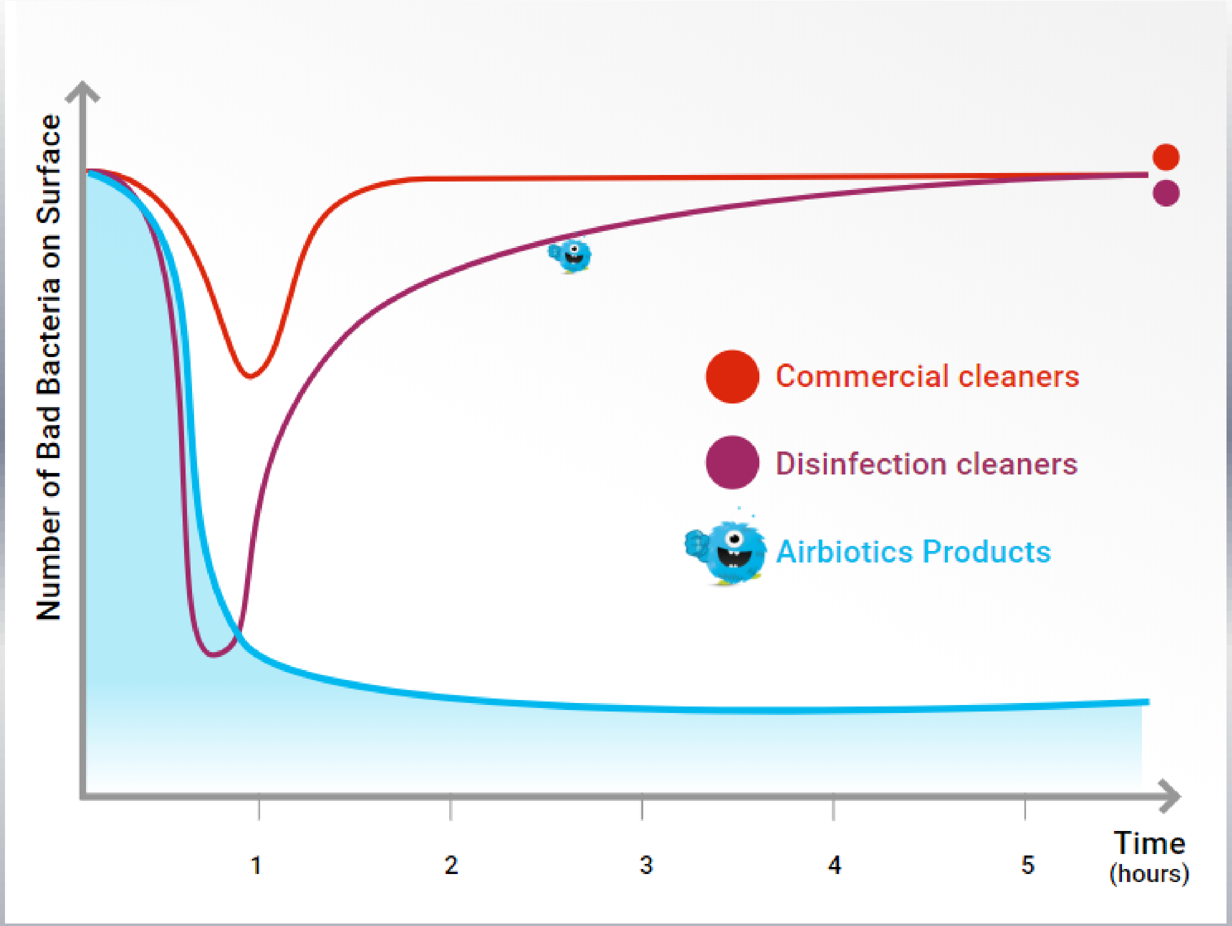
La desinfección convencional (química) de una superficie NO PREVIENE la re-contaminación de la misma (30 minutos).

Como los biocidas, al igual que los antibióticos, afectan todo tipo de microbio sin discriminar entre "microbios buenos" y "microbios malos", y tomando la idea del PROYECTO MICROBIOMA HUMANO:

Una novedosa estrategia consiste en más que erradicar los patógenos ya presentes, reemplazarlos por microbios benéficos, por ejemplo bacterias probióticas.

Principio de exclusión competitiva por bacterias probióticas

Dentro de los probióticos, y a diferencia de los lácticos (todos ellos lábiles), ciertas especies no patógenas del género formador de esporas ***Bacillus*** *(B. subtilis, B. coagulans) funcionan como excelentes probióticos para humanos.*



Principio de exclusión competitiva por bacterias probióticas

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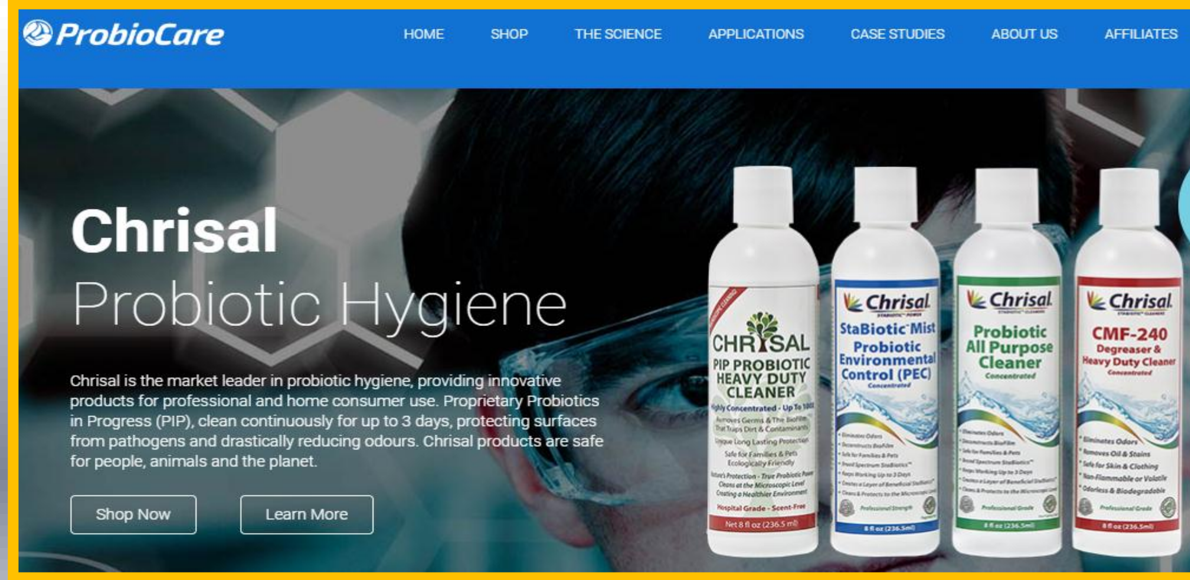
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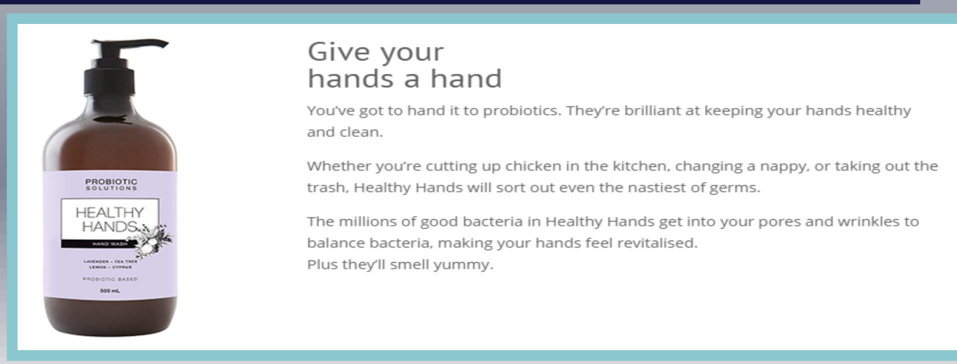
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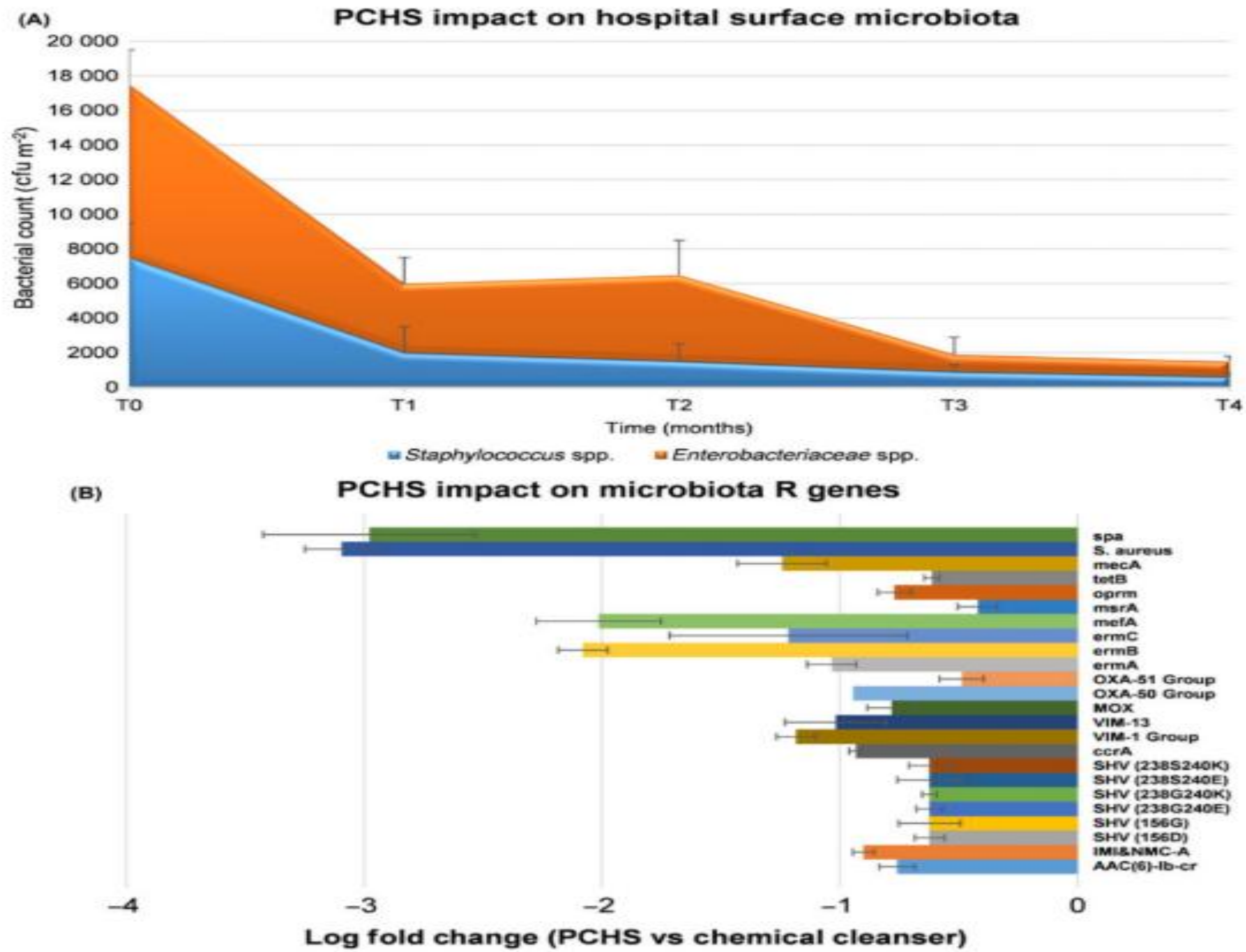

Fig. 1. Impact of the probiotic-based microbial cleaning on microbiota contaminating hospital surfaces.
A. PCHS effect on Gram-positive (*Staphylococcus* spp.) and Gram-negative (*Enterobacteriaceae* spp.) pathogens amounts on treated surfaces after 1, 2, 3, 4 months of PCHS continuous sanitation (T0 values are those obtained with chemical sanitation); results are expressed as median CFU counts per m^2.
B. PCHS effect on the R genes of the whole residual microbiota (resistome) after 1–4 months of PCHS sanitation; results were obtained by PCR microarray and are expressed as of log fold change in R genes compared to the values detected at T0; mean values of the 4 months ± SD are reported.

VI CONGRESO DE ESTERILIZACIÓN Y DESINFECCIÓN 2018 Rosario

Muchas gracias!

Roberto Ricardo Grau

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Metal nanoparticles as a novel and safe strategy to fight pathogenic spores and antibiotic-resistant microbial biofilms

*Sebastián Cogliati, Francisco Marcos, Victoria Clementi, Celina Lobais, Victoria Boselli, Estanislao Porta, Virginia Roldán, Nora Pellegri, and **Roberto Grau***

Facultades de Ciencias Bioquímicas y de Ciencias Exactas y Naturales.
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Infectious diseases were always a cause for human concern

THE FOUR HORSEMEN OF THE APOCALYPSE:

1- DEATH

2- THE WAR

3- HUNGER

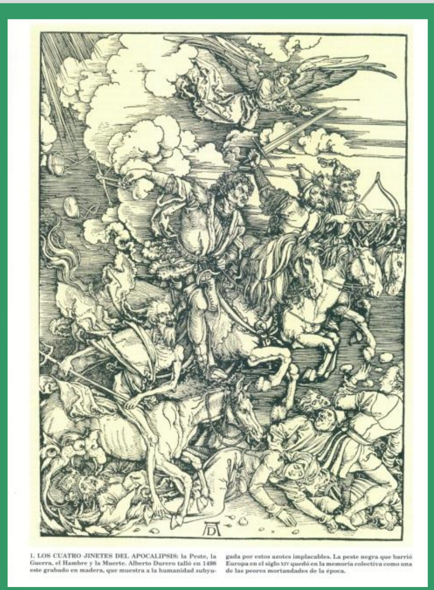
4- THE PLAGUE

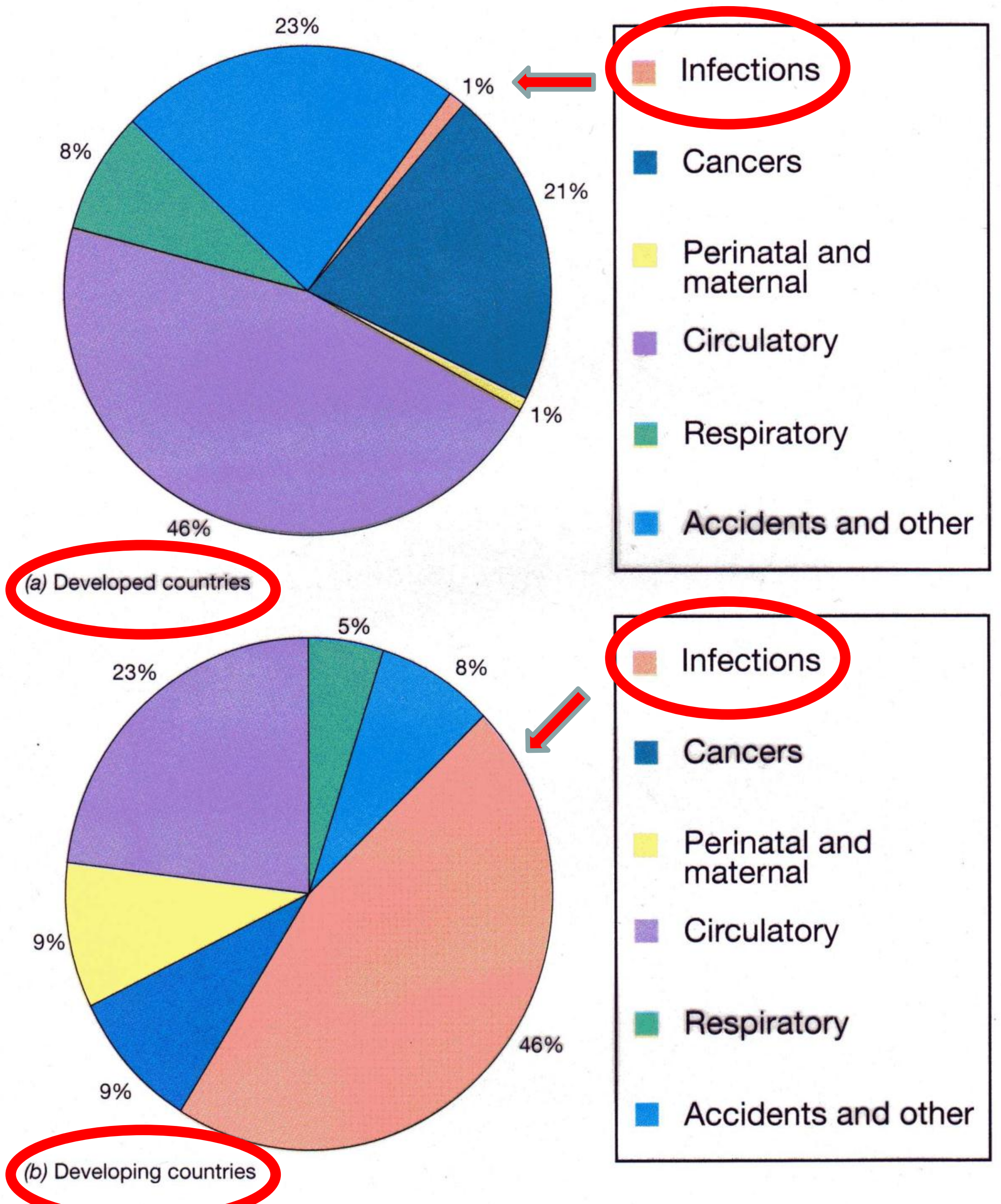
Alberto Durero 1498

Coming to modern times….

1. LOS CUATRO JINETES DEL APOCALIPSIS: la Peste, la Guerra, el Hambre y la Muerte. Alberto Durero talló en 1498 este grabado en madera, que muestra a la humanidad subyugada por estos azotes implacables. La peste negra que barrió Europa en el siglo XIV quedó en la memoria colectiva como una de las peores mortandades de la época.

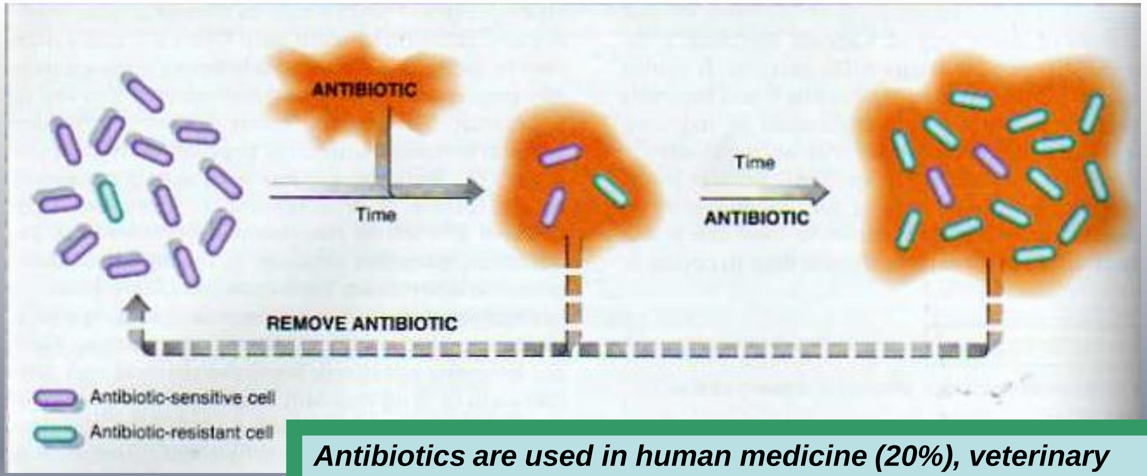
During the 90'…..



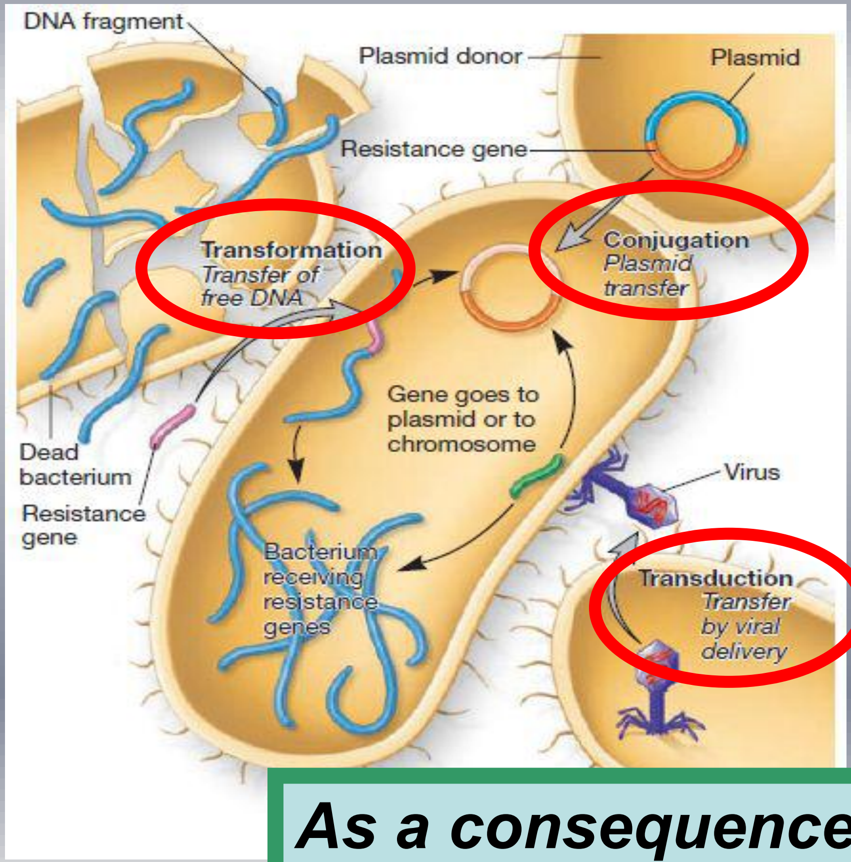


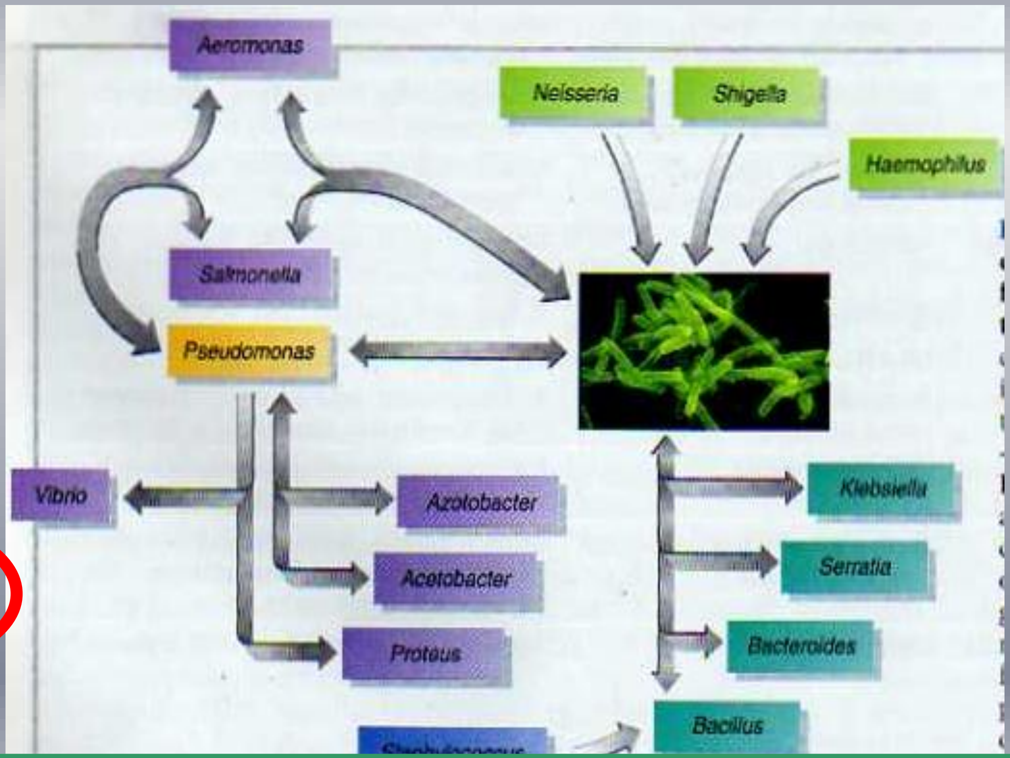
What is the current situation during XXI century about infectious diseases worldwide?

The global problem of the emergence of antibiotic resistance and its spread



Antibiotics are used in human medicine (20%), veterinary (10%) and as supplements of animal feed (70%).





As a consequence, also in developed countries….

DRUG-RESISTANT NON-TYPHOIDAL SALMONELLA

THREAT LEVEL SERIOUS

This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

100,000 DRUG-RESISTANT *SALMONELLA* INFECTIONS PER YEAR

1,200,000 *SALMONELLA* INFECTIONS PER YEAR

$365,000,000 IN MEDICAL COSTS PER YEAR

Non-typhoidal *Salmonella* (serotypes other than Typhi, Paratyphi A, Paratyphi B, and Paratyphi C) usually causes diarrhea (sometimes bloody), fever, and abdominal cramps. Some infections spread to the blood and can have life-threatening complications.

RESISTANCE OF CONCERN

Physicians rely on drugs, such as ceftriaxone and ciprofloxacin, for treating patients with complicated *Salmonella* infections. Resistant infections are more severe and have higher hospitalization rates. Non-typhoidal *Salmonella* is showing resistance to:

- ceftriaxone
- ciprofloxacin
- multiple classes of drugs

	Percentage of all non-typhoidal *Salmonella**	Estimated number of illnesses per year	Estimated illnesses per 100,000 U.S. population	Estimated number of deaths per year
Ceftriaxone resistance	3%	36,000	12.0	13
Ciprofloxacin resistance or partial resistance	3%	33,000	10.9	12
Resistance to 5 or more antibiotic classes	5%	66,000	21.9	24
Any resistance pattern above	8%	100,000	34.1	38

PUBLIC HEALTH THREAT

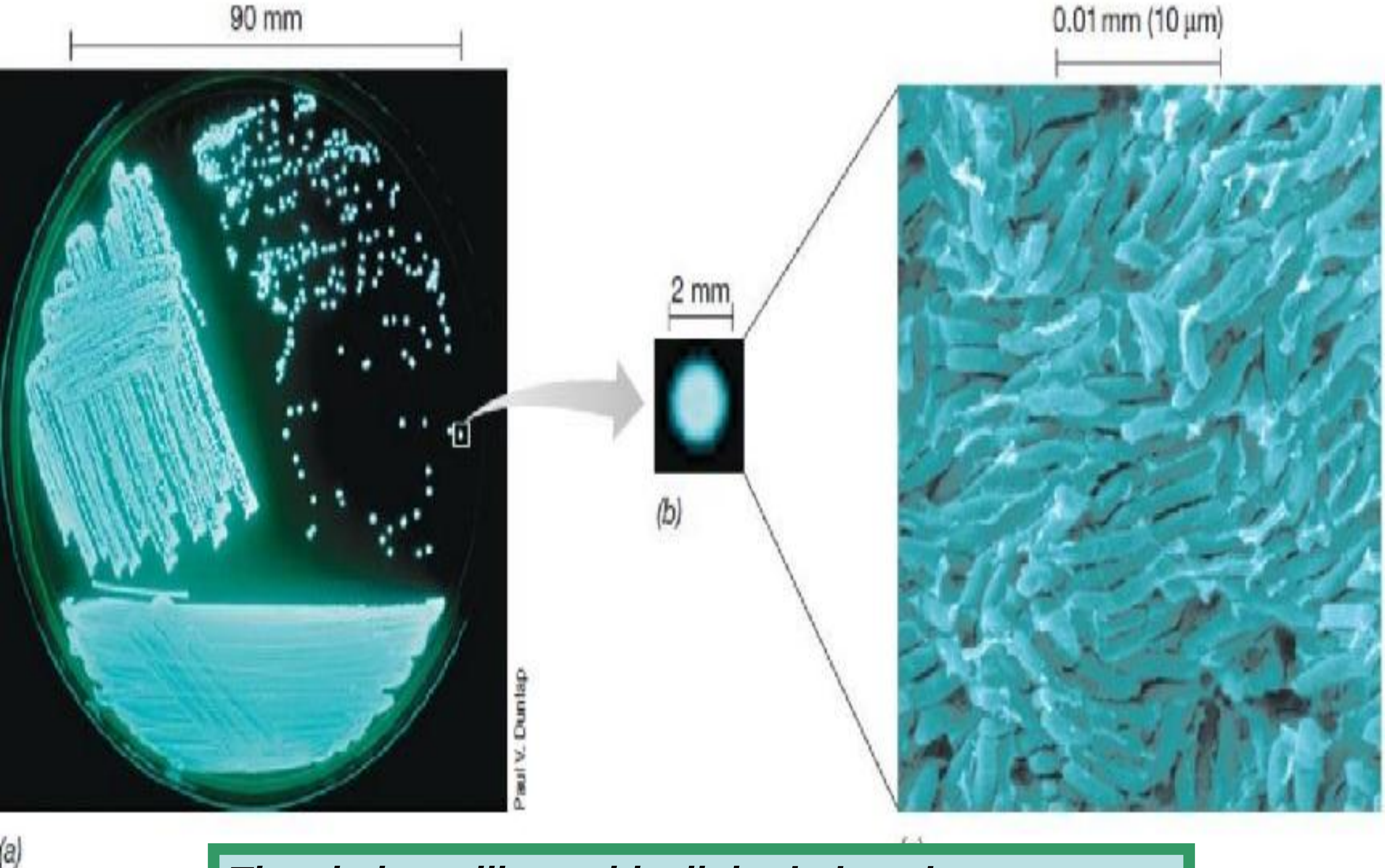
Non-typhoidal *Salmonella* causes approximately 1.2 million illnesses, 23,000

Another problem in our battle against pathogenic bacteria is that …….

more types of drugs. Costs are expected to be higher for resistant than for susceptible infections because resistant infections are more severe, those patients are more likely to be hospitalized, and treatment is less effective.

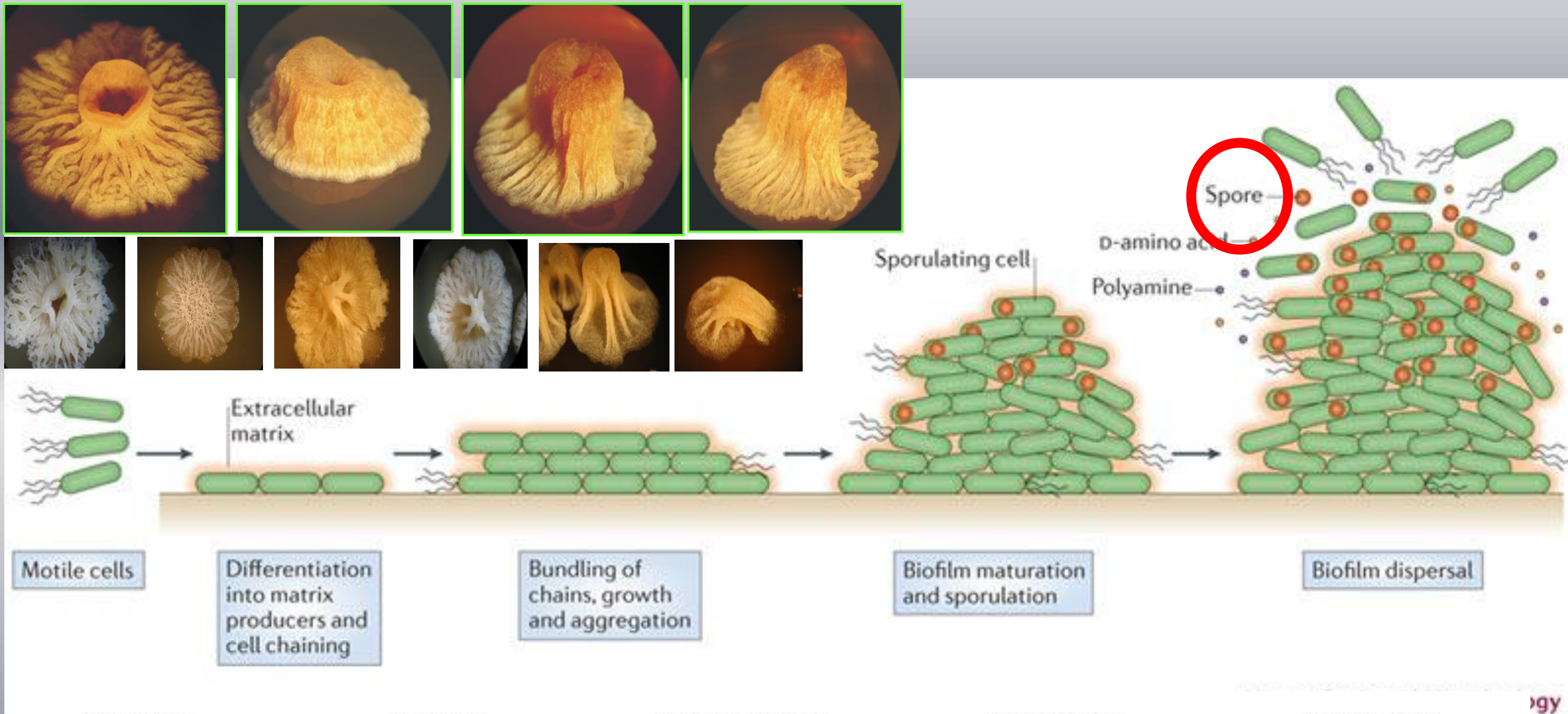
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

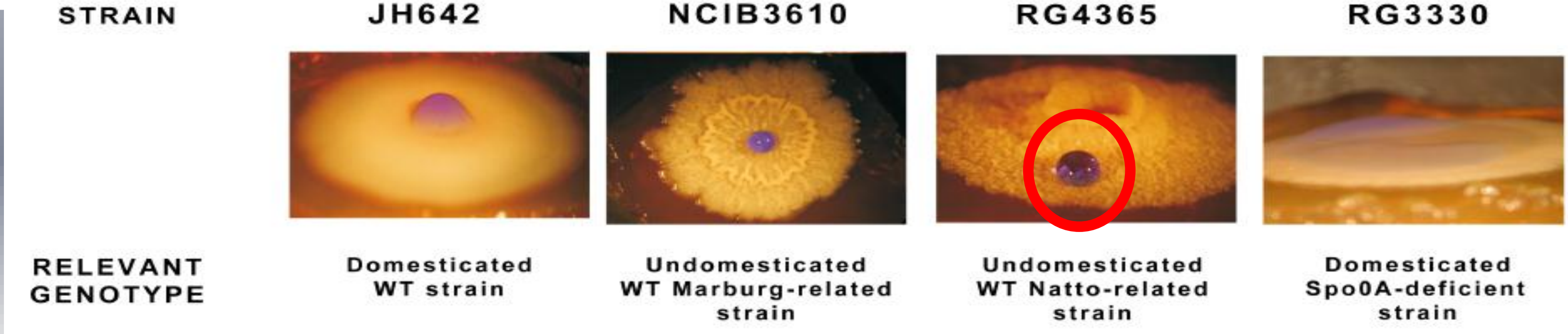
Bacteria, although they are unicellular beings (prokaryotes)….



They behave like multicellular beings because….

Bacteria construct multicellular three-dimensional structures in which there is a spatio-temporal regulation of gene expression (division of labor). These socially organized communities are named BIOFILMS or cities of microbes





Resistance of *Bacillus* Endospores to Extreme Terrestrial and Extraterrestrial Environments

WAYNE L. NICHOLSON,[1*] NOBUO MUNAKATA,[2] GERDA HORNECK,[3] HENRY J. MELOSH,[4] AND PETER SETLOW[5]

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Review article Open Access

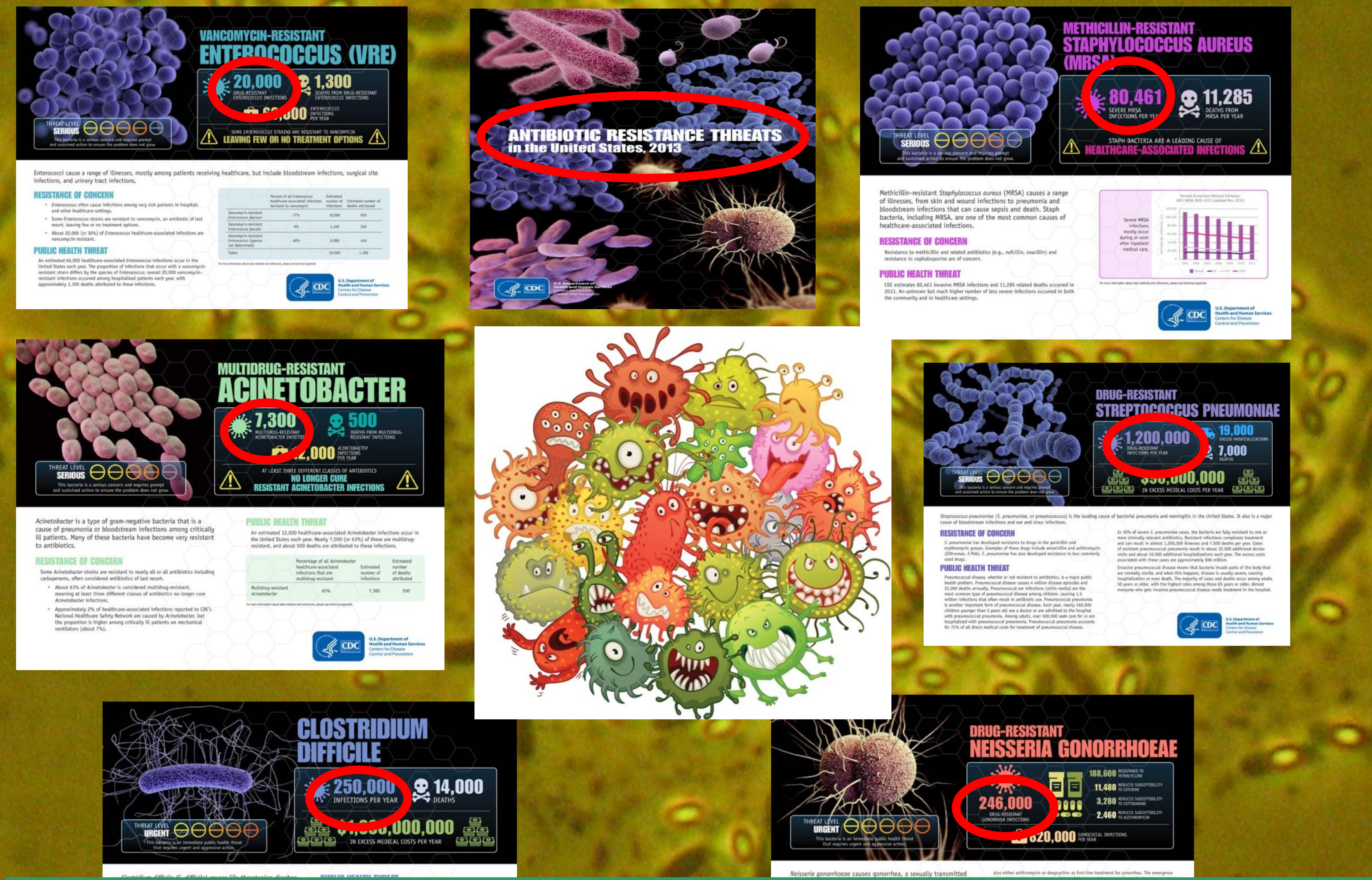
Bacterial Spores and its Relatives as Agents of Mass Destruction

Sebastián Cogliati, Juan Gabriel Costa, Facundo Rodriguez Ayala, Verónica Donato and Roberto Grau*

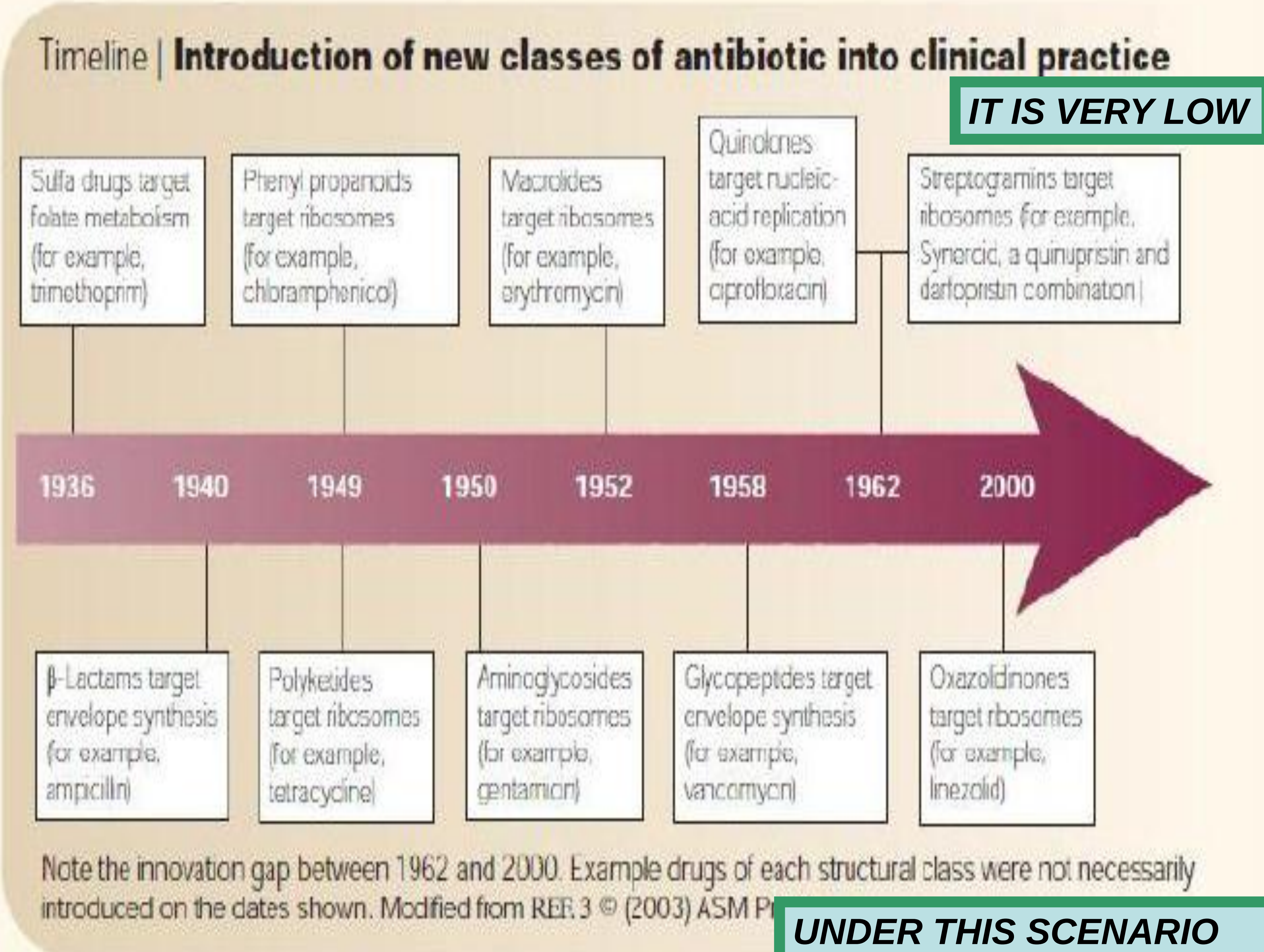
Departamento de Microbiología, Universidad Nacional de Rosario, Argentina and CONICET

Abstract

The term bioterrorism has acquired full force for the planetary consciousness from the very beginning of the new century. Indeed, from the events that occurred during October and November of 2001 with the intentional contamination with spores of pathogenic *Bacillus anthracis*, of letters distributed by the US public postal service and the terrorist attacks in the last months of 2015 in Egypt, France, Mali, Afghanistan, Turkey, USA and other countries have warned again about the reality of the bioterrorist threat and its immeasurable cultural and undesirable economic and political consequences. In this review, we summarize the main structural characteristics that make the spores of Bacilli and Clostridia as the ideal agents for use in bioterrorism. In addition, we discuss the properties of non-sporulating *Coxiella burnetii*, the causative agent of Q fever, because of its peculiar resistance, high infectivity and environmental persistence that resembles true spores.



All these arguments make vital the development of new types of antibiotics with sporocice and anti-biofilm activities.



IT IS VERY LOW

UNDER THIS SCENARIO

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Photocatalytic and biocidal activities of novel coating systems of mesoporous and dense TiO_2-anatase containing silver nanoparticles

María V. Roldán[a], Paula de Oña[b], Yolanda Castro[c], Alicia Durán[c], Pablo Faccendini[d], Claudia Lagier[d], Roberto Grau[b,*], Nora S. Pellegri[a,**]

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Stable colloidal copper nanoparticles in ethylene glycol functionalized with siloxanes and its microbicidal behavior.

Estanislao PORTA RAMBALDI (1), Sebastián COGLIATI (2), Marcos FRANCISCO (2), María Virginia ROLDÁN (1), Nadia MAMANA (1), Roberto GRAU (2)*, Nora PELLEGRI (1) *

1 Universidad Nacional de Rosario CONICET, Laboratorio Materiales Cerámicos, Instituto de Física Rosario, Rosario, Argentina.

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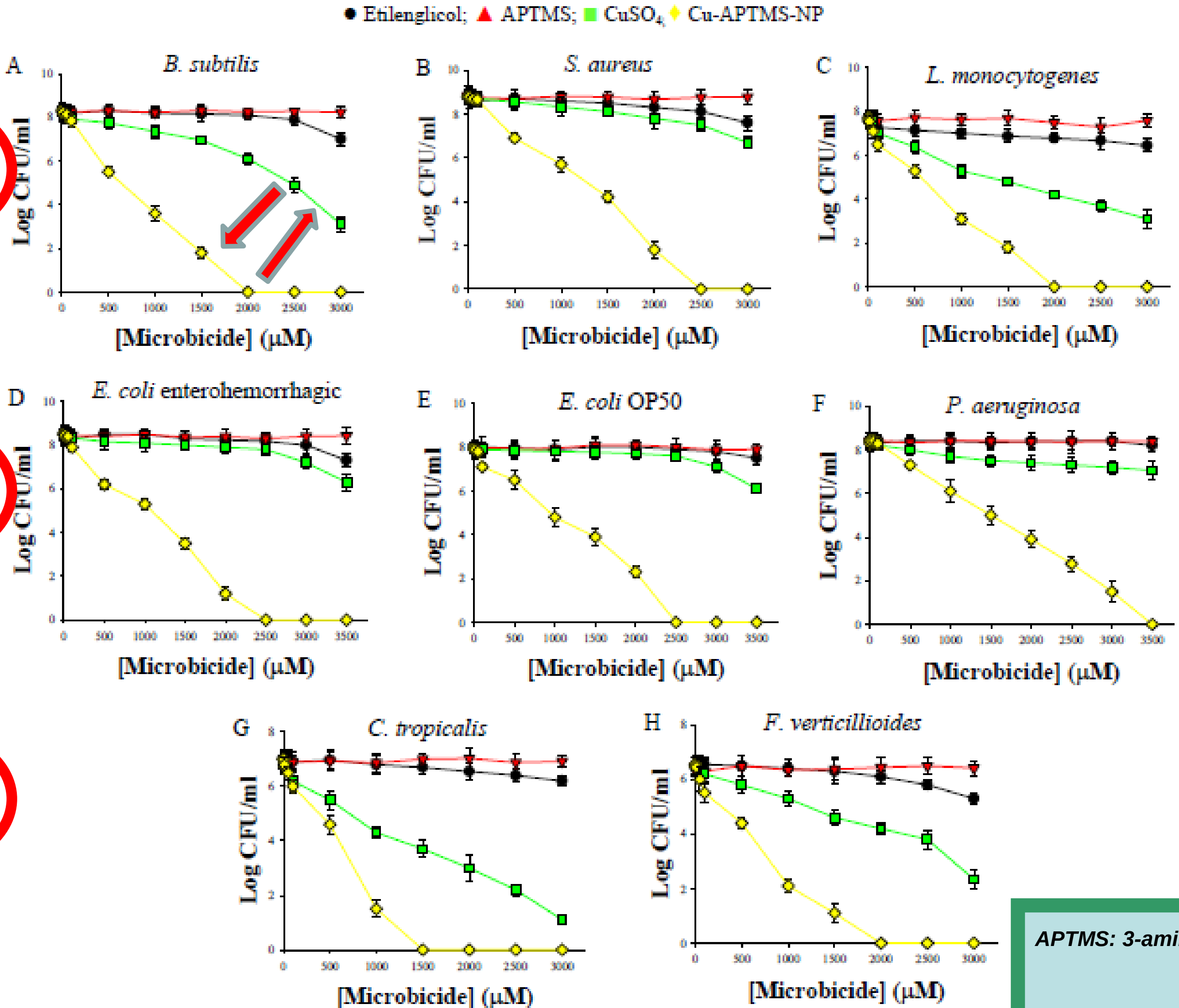
MICROBICIDE ACTIVITY OF Cu-NPs AGAINST PLANKTONIC (FREE-LIVING) MICROORGANISMS

Microbicide activity of Cu-APTMS NPs against Gram-positive and Gram-negative bacteria and fungi



Gram-positive bacteria

Gram-negative bacteria

Fungi

APTMS: 3-aminopropyltrimethoxysilane

MICROBICIDE ACTIVITY OF Cu-NPs AGAINST PLANKTONIC (FREE-LIVING) MICROORGANISMS

MIC and MMC of $CuSO_4$ and Cu-APTMS-NP

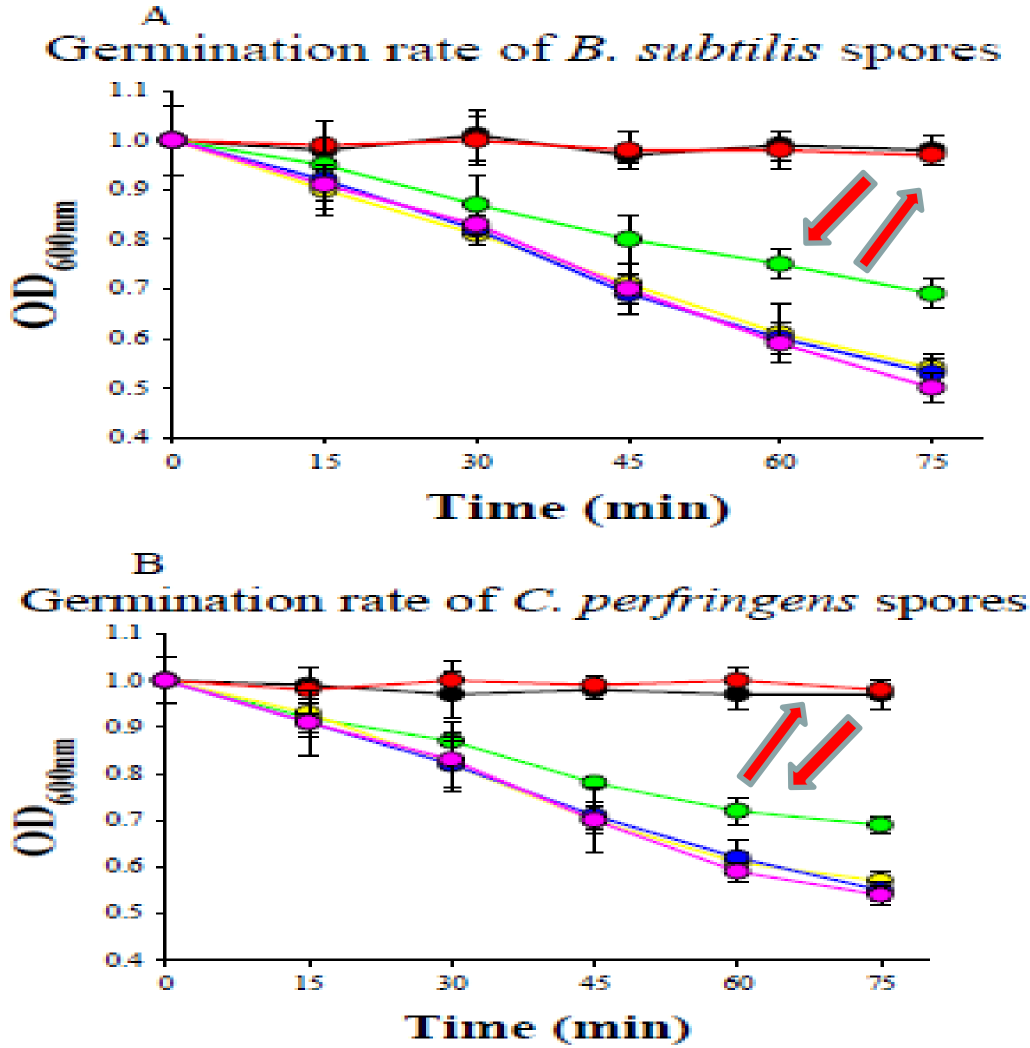
I

Microorganisms	MIC (mM)		MMC (mM)	
	Cu-APTES-NP	**$CuS0_4$**	**Cu-APTES-NP**	**$CuS0_4$**
B. subtilis	2.0±0.020	4.5±0.045	2.0±0.020	4.5±0.045
S. aureus	2.5±0.035	> 10	3.0±0.030	> 10
L. Monocytogenes	2.0±0.020	5.0±0.070	2.0±0.020	5.0±0.070
EHEC	2.5±0.035	> 10	2.5±0.035	> 10
E. coli OP50	2.5±0.035	> 10	2.5±0.035	> 10
P. aeruginosa	3.5±0.050	> 10	4.0±0.020	> 10
C. Tropicales	1.5±0.010	3.5±0.050	1.5±0.010	4.5±0.045
F. verticillioides	2.0±0.020	4.0±0.030	2.0±0.020	4.0±0.030

APTMS: 3-aminopropyltrimethoxysilane

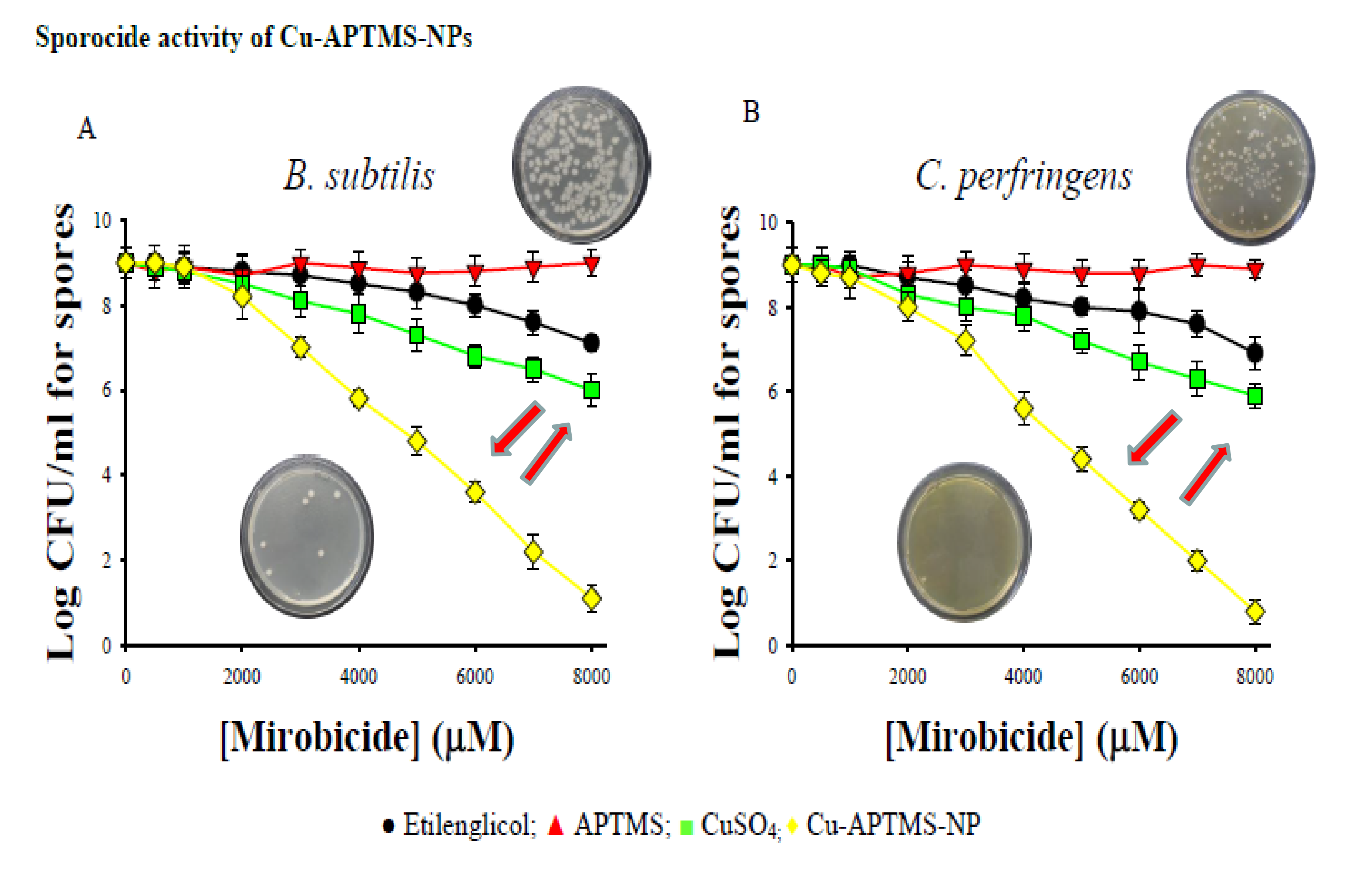
INHIBITION OF SPORE GERMINATION BY Cu-NPs

Anti-germinative activity of Cu-APTMS-NPs

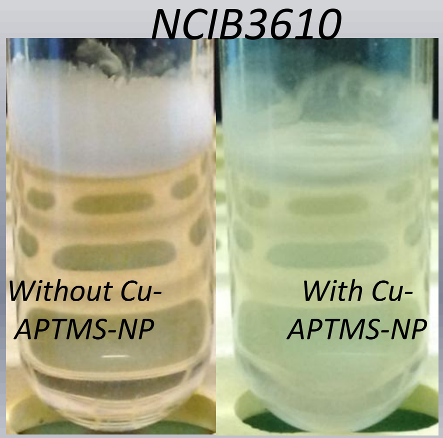


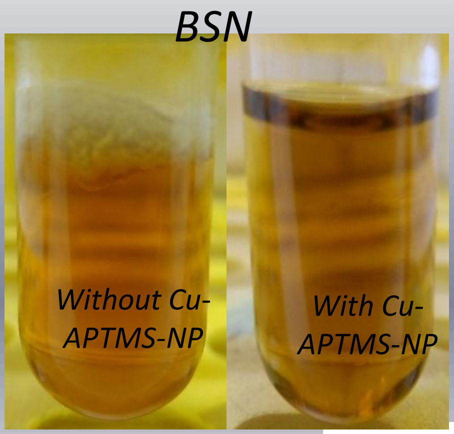
• PBS; • PBS plus germinant plus Cu-APTMS-NP; • PBS plus germinant plus $CuSO_4$; • PBS plus germinant plus ethyleneglycol; • PBS plus germinant plus APTMS; • PBS plus germinant

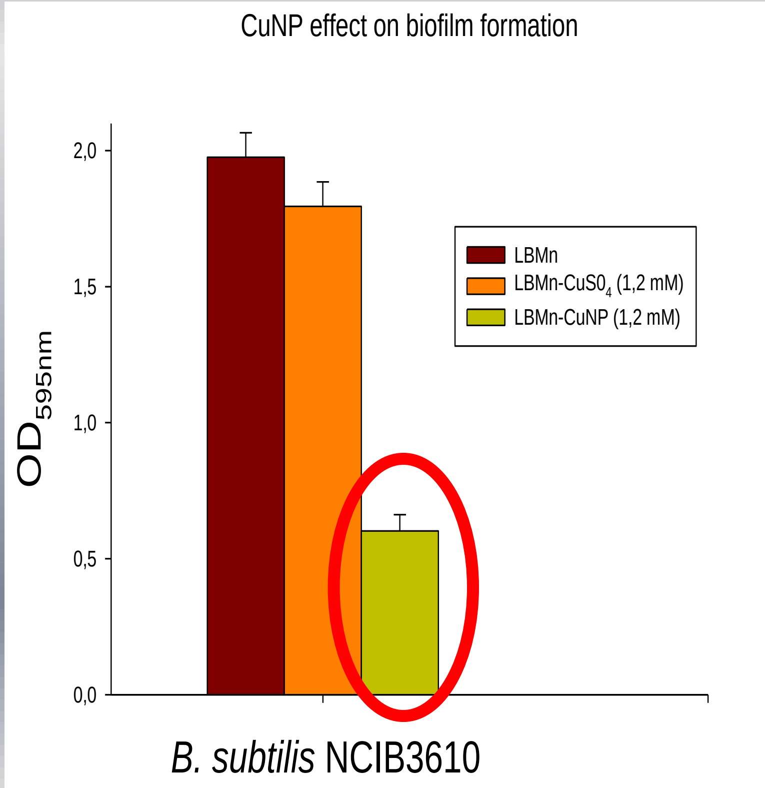
SPOROCIDE ACTIVITY OF Cu-NPs

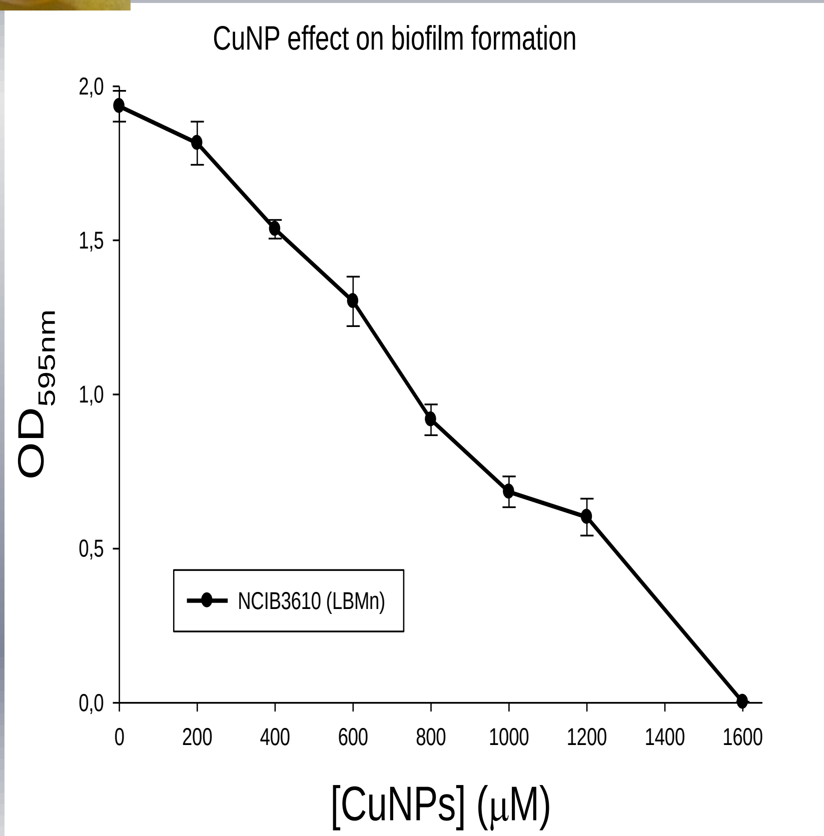


INHIBITION OF LIQUID BIOFILM (PELLICLE) SYNTHESIS BY Cu-NPs



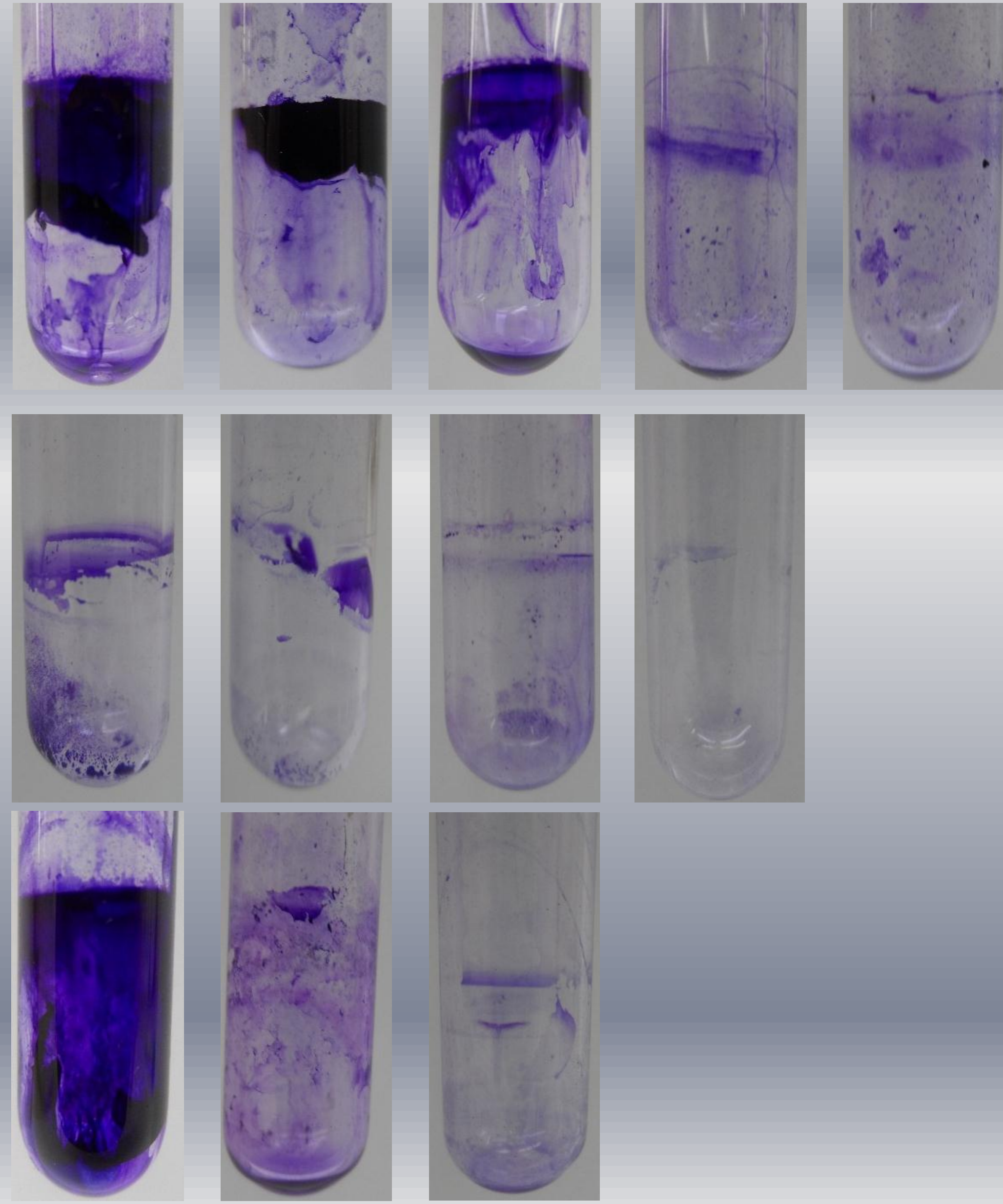






INHIBITION OF LIQUID BIOFILM (PELLICLES) SYNTHESIS BY Cu-NPs

Cu-APTMS-NP (mM): 0 1 2 4 6



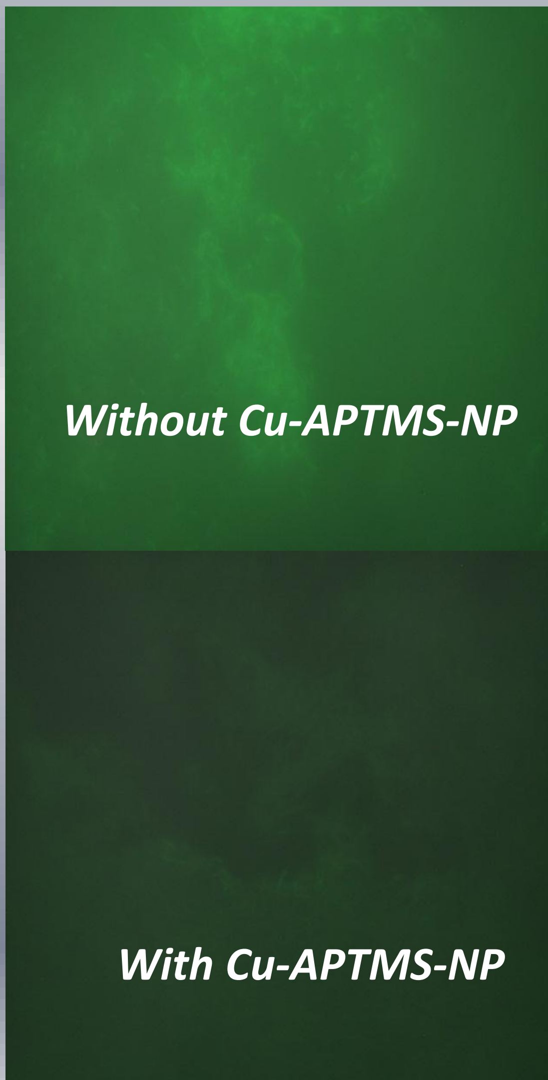
Pseudomonas aeruginosa

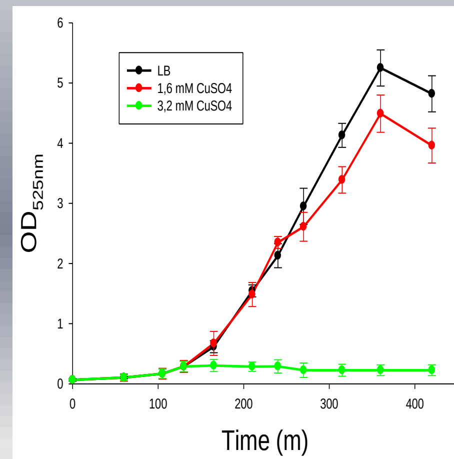
Staphylococcus aureus

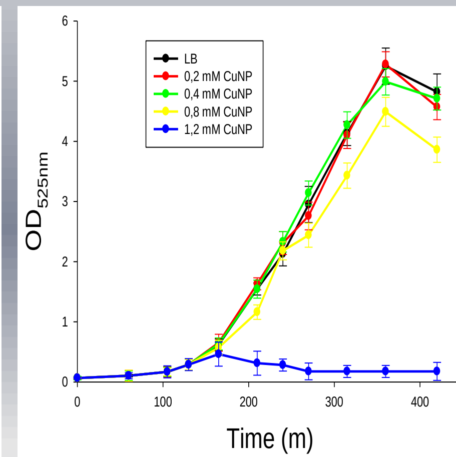
Bacillus anthracis

Cu-NPs inhibits the expression of genes involved in the synthesis of extracellular matrix components of the biofilm

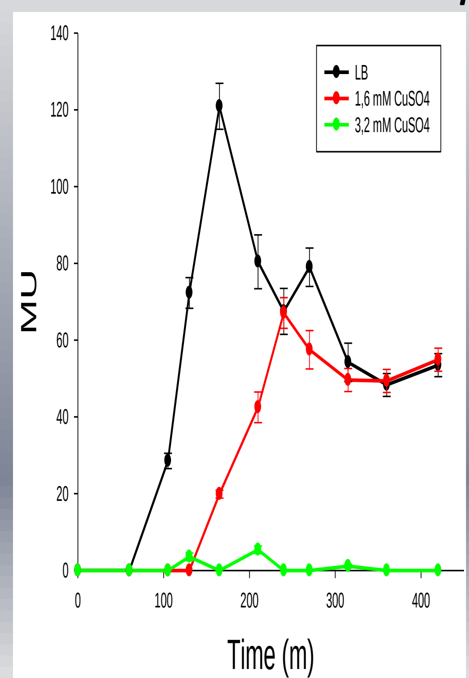
Pbsla-gfp

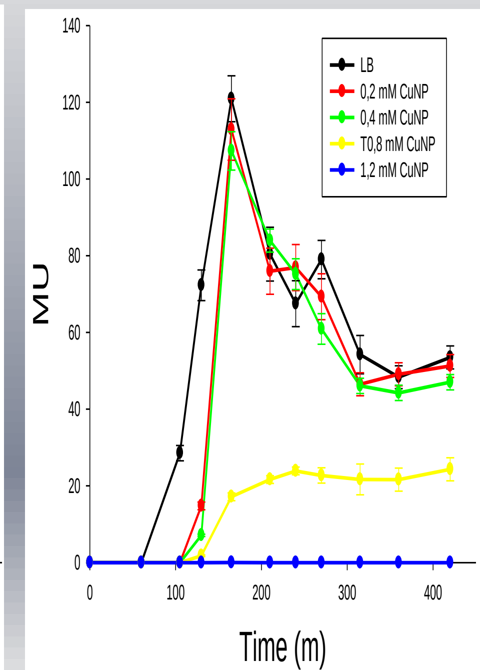






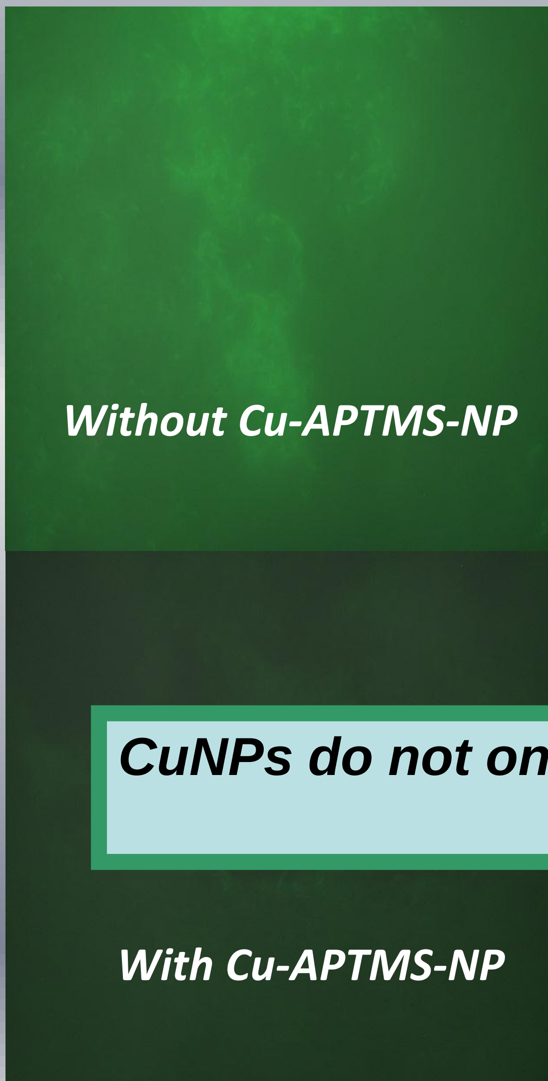
Peps-lacZ

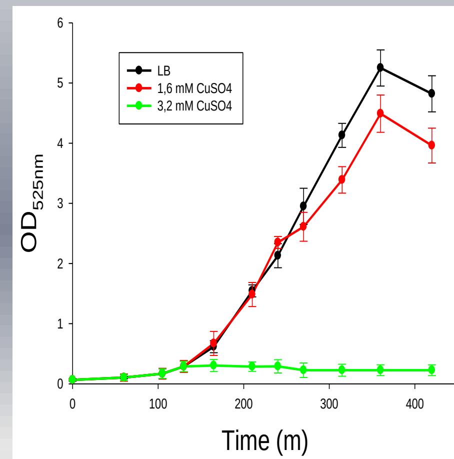


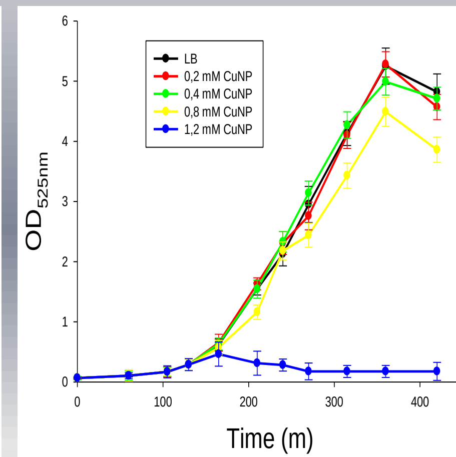


Cu-NPs inhibits the expression of genes involved in the synthesis of extracellular matrix components of the biofilm

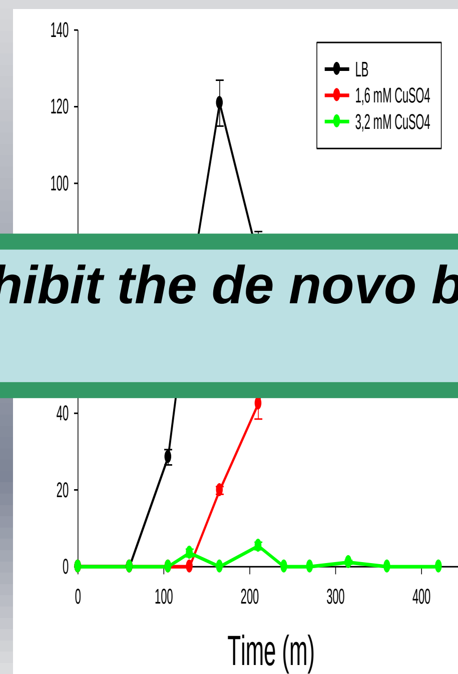
Pbsla-gfp

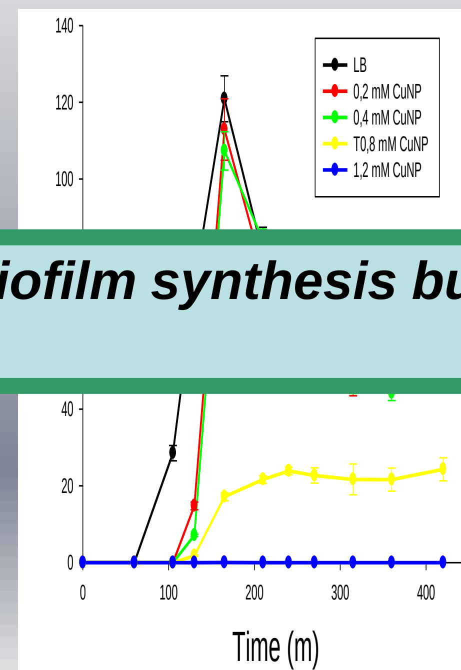






Peps-lacZ





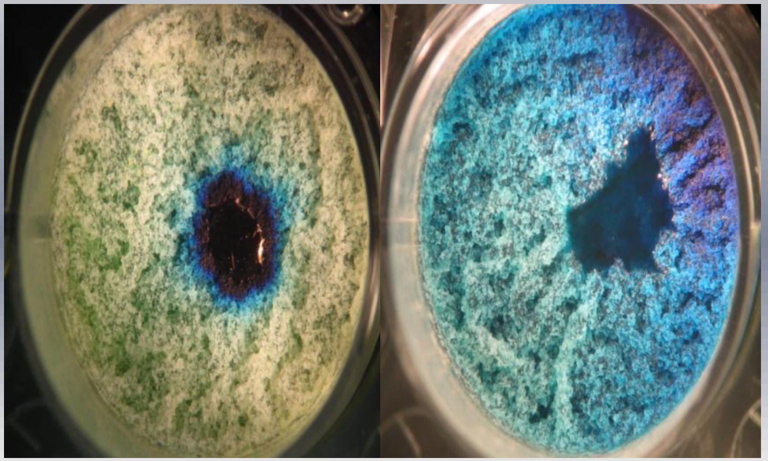
CuNPs do not only inhibit the de novo biofilm synthesis but also…

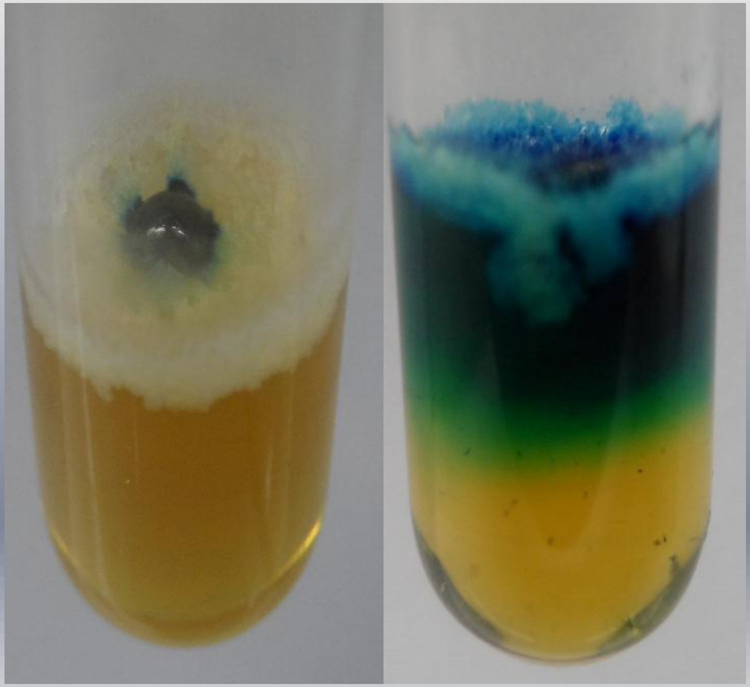
CuNPs triggers the disassembling of preformed biofilms

- ***Biofilms (pellicles) are developed during 24 h at 37 °C***

- ***Addition of 5 µl of 1 mM Cu-NP carefully added by one side of one of the biofilms so as not to disturb its architecture***

- ***After another 24 h of incubation, addition of 20 µl Methylene Blue on top of both types of biofilms***





CONCLUSIONS

Metal-NPs constitute an efficient new class of microbicides to fight not only the vegetative (planktonic) forms of microbial pathogens, but also their spores and biofilms.

THANKS FOR THE ATTENTION

FLORA INTESTINAL Y PROBIÓTICOS COMO ALIMENTOS DEL NUEVO MILENIO

Ministerio de Ciencia, Tecnología e Innovación Productiva
Presidencia de la Nación

CONICET

AGENCIA

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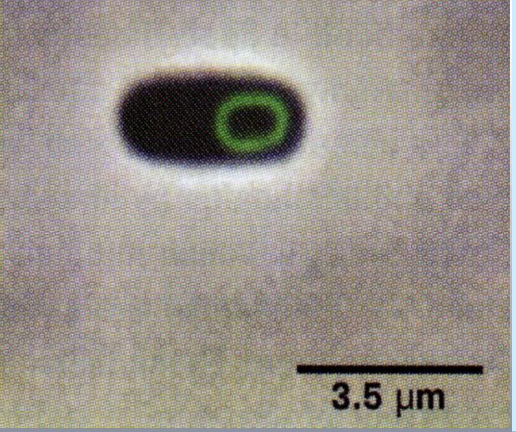
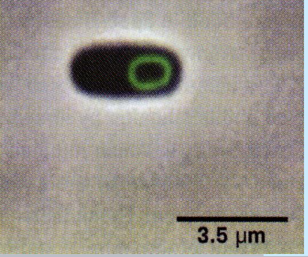
22 de Octubre de 2018



INTERACCIÓN ENTRE LA FLORA INTESTINAL PROBIÓTICA Y EL SISTEMA INMUNOLÓGICO

¿ QUÉ ENTENDEMOS POR PROBIÓTICO ?

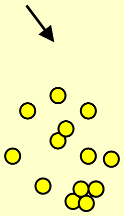


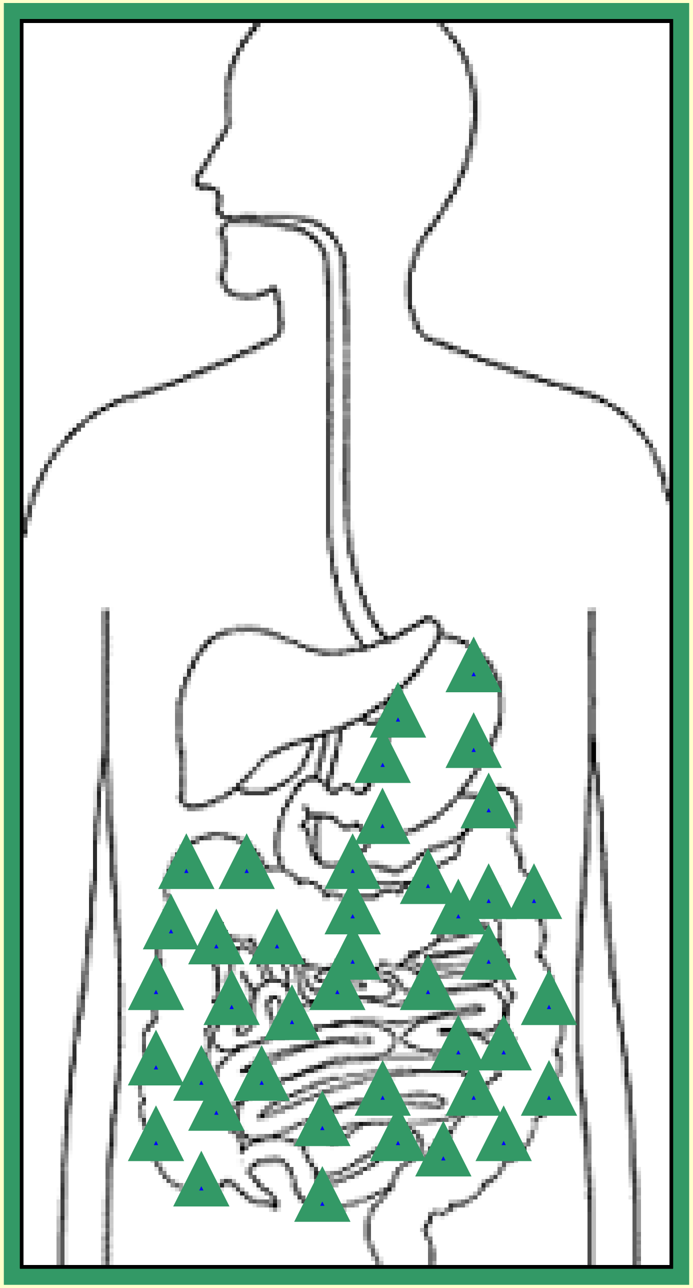
DEFINICIÓN DE PROBIÓTICO

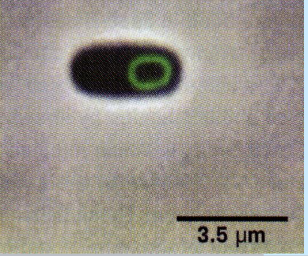
Una definición reciente, aceptada internacionalmente, indica que:

"Los probióticos son microorganismos vivos que, ingeridos en una cantidad adecuada, deben llegar vivos a su sitio de acción (mucosas) y producir efectos beneficiosos sobre la salud del que los consume más allá del aporte nutricional intrínseco de esos microorganismos (por ejemplo ser fuente de aminoácidos y vitaminas"

Patógenos



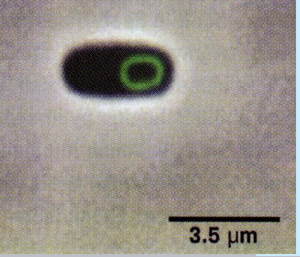




¿CUÁLES SON LOS MICROORGANISMOS PROBIÓTICOS MÁS TRADICIONALES?

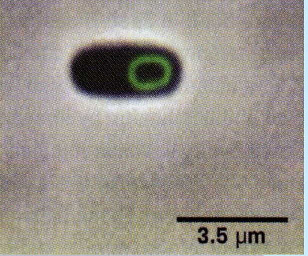
- ***Lactobacillus*: *L. acidophilus, L. bulgaricus, L. casei, L. salivarius, L. plantarum, L. kefir.***
- ***Lactococcus*: *L. lactis, L. cremoris, L. diacetylactis.***
- ***Streptococcus*: *S. thermophilus, S. lactis.***
- ***Bifidobacterium*: *B. bifidum, B. longum, B. infantis, B. lactis, B. adolescentis.***
- **Otros**:***Enterococcus* spp., *Sacharomyces cereviseae*, *Leuconostoc* spp.**

EXISTE UNA GRAN PREDOMINANCIA DE LAS BACTERIAS LÁCTICAS



¿CUÁLES SON LOS EFECTOS BENEFICIOSOS DE LOS MICROORGANISMOS PROBIÓTICOS?

- Producción de compuestos antimicrobianos
- Estimulación de la inmunidad celular y humoral
- Actividad antimutagénica y anticancerígena
- Mejoramiento del metabolismo de la lactosa
- Reducción del colesterol sérico
- Control de diferentes tipos de diarreas y alergias
- Aumento de la proporción de BAL y disminución de clostridios
- Sensación de bienestar general y aumento de la esperanza de vida (life-span).
- Etc. etc. etc…..



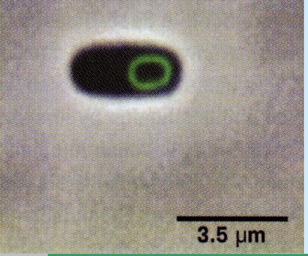
ALGUNOS MICROBIOS SON MUY BUENOS COMPAÑEROS

Probiotics-host communication

Modulation of signaling pathways in the intestine

Carissa M. Thomas[1,2] and James Versalovic[1-3,*]

[1]Interdepartmental Program of Cell and Molecular Biology; and [2]Department of Pathology and Immunology; Baylor College of Medicine; Houston, TX USA; [3]Department of Pathology; Texas Children's Hospital; Houston, TX USA



ALGUNOS MICROBIOS SON MUY BUENOS COMPAÑEROS

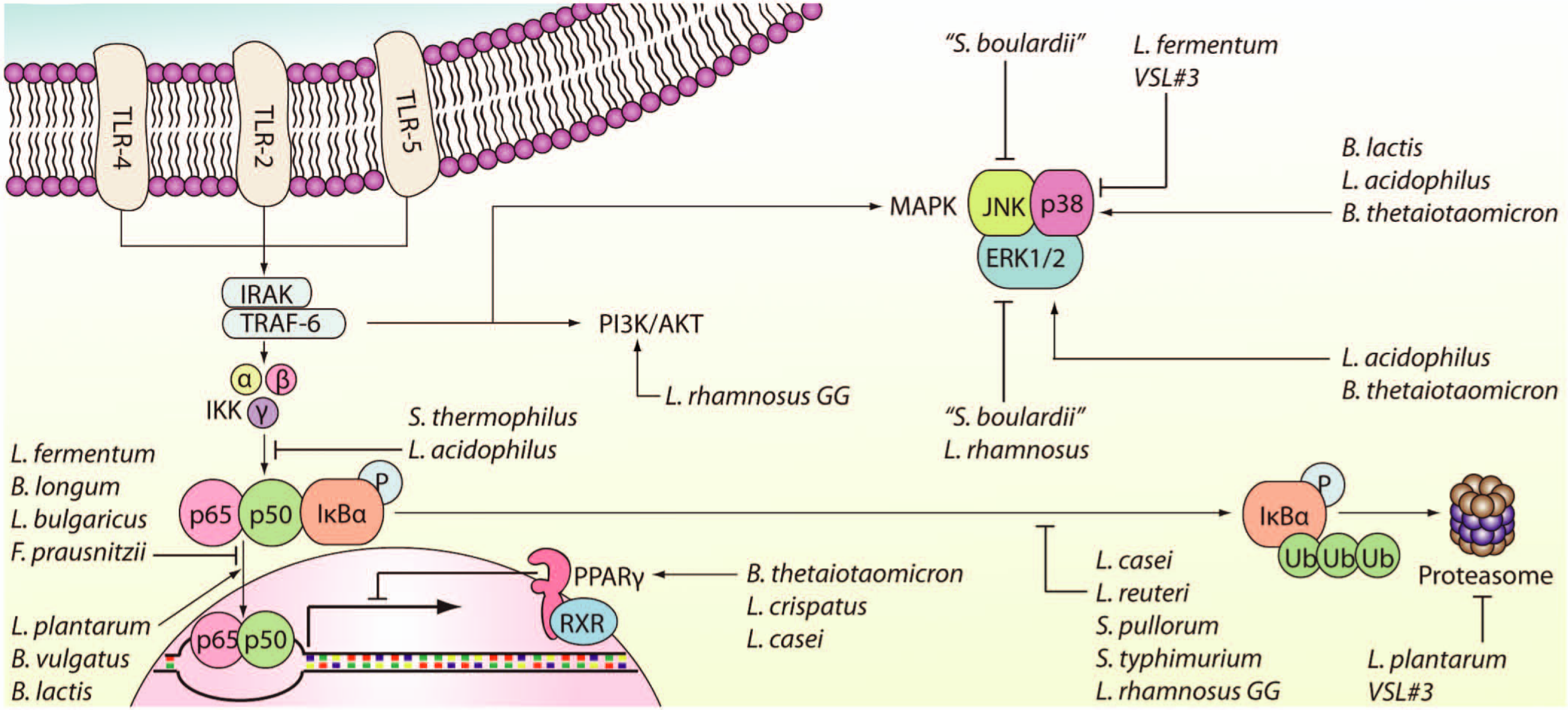


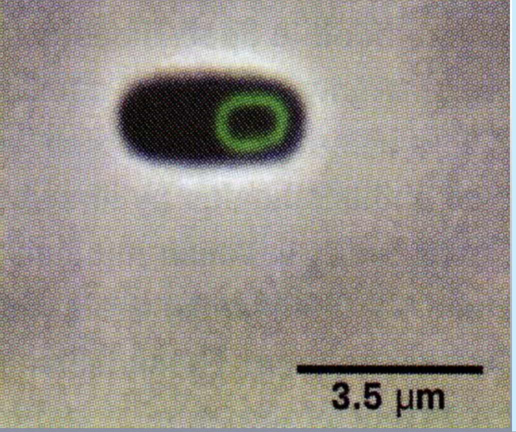
Figure 2. Probiotics modulate key signaling pathways in intestinal epithelial cells. Various probiotics prevent NFκB activation by inhibiting IκBα phosphorylation, ubiquitination, proteasomal degradation, or translocation of NFκB into the nucleus (suppression is indicated by a block sign "⊣"). Probiotics can also enhance RelA export from the nucleus via PPARγ. Other probiotics increase NFκB activation through enhanced translocation into the nucleus (activation is indicated by an arrow sign "→"). Apoptosis of intestinal epithelial cells can be prevented by probiotic modulation of the PI3K/Akt pathway. Probiotic-induced changes in phosphorylation levels of p38, JNK, and ERK1/2 MAPKs can affect cytokine secretion and apoptosis. ERK, extracellular signal-regulated kinases; IκBα, inhibitor of NFκB α; IKK, IκB kinase; IRAK, interleukin-1 receptor-associated kinase; JNK, c-Jun N-terminal kinase; P, phosphorylation; PPARγ, peroxisome proliferator activated receptor-γ; RXR, retinoid X receptor; TLR, Toll-like receptor; Ub, ubiquitin.

Table 1. Probiotic modulation of signaling pathways in intestinal epithelial cells and macrophages

Probiotic species	Model system	Signaling pathway	Probiotic effect(s)	Reference(s)
Bacillus subtilis JH642	IECs	hsp	Induces hsp27, hsp25 and hsp70	Fujiya, et al. 2007,[30]
Bacillus subtilis JH642	IECs	MAPKs	Increases p38 phosphorylation	Fujiya, et al. 2007,[30]
Bacteroides fragilis ATCC 23745	IECs	hsp	Induces hsp25 and hsp72	Kojima, et al. 2003,[29]
Bacteroides thetaiotaomicron ATCC 29184	IECs	MAPKs	Activation of ERK1/2 and p38	Resta-Lenert, et al. 2006,[46]
Bacteroides thetaiotaomicron	IECs	NFκB	Enhances RelA nuclear export via PPARγ	Kelly, et al. 2004,[49]
Bacteroides vulgatus	IECs	NFκB	Increases IκBα phosphorylation	Haller, et al. 2002,[44]
Bifidobacterium adolescentis ATCC 15703	Macrophages	NFκB	Decreases IκBα phosphorylation, increases SOCS	Okada, et al. 2009,[67]
Bifidobacterium bifidum B536	Macrophages	NFκB	Decreases LPS binding to CD14	Menard, et al. 2004,[62]
Bifidobacterium breve BbC50	Macrophages	NFκB	Decreases LPS binding to CD14	Menard, et al. 2004,[62]
Bifidobacterium lactis BB12	IECs	NFκB	Activates RelA	Ruiz, et al. 2005,[43]
Bifidobacterium lactis BB12	IECs	MAPKs	Increases p38 phosphorylation	Ruiz, et al. 2005,[43]
Bifidobacterium longum	IECs	NFκB	Decreases p65 translocation	Bai, et al. 2004;[39] Bai, et al. 2006,[40]
Enterococcus faecalis EC1/EC3/EC15/ EC16	IECs	PPARγ	Induced phosphorylation of PPARγ1	Are, et al. 2008,[50]
Escherichia coli M17	Macrophages	NFκB	Inhibits p65 nuclear binding	Fitzpatrick, et al. 2008,[58]
Faecalibacterium prausnitzii DSM 17677	IECs	NFκB	Inhibits NFκB activation	Sokol, et al. 2008,[41]
Lactobacillus acidophilus ATCC 4356	IECs	MAPKs	Activation of ERK1/2 and p38	Resta-Lenert, et al. 2006,[46]
Lactobacillus acidophilus ATCC 4356	IECs	NFκB	Decreases IκBα phosphorylation	Resta-Lenert, et al. 2006,[46]

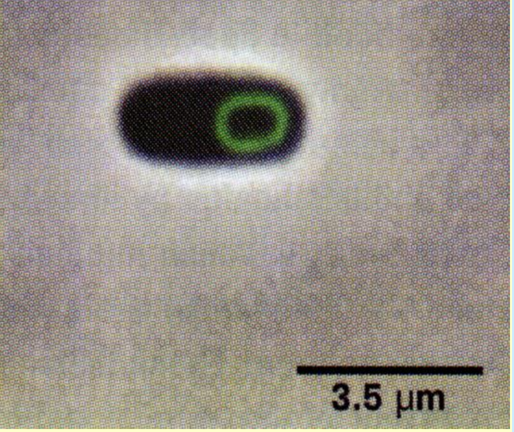
POR LO TANTO ES MUY DIFÍCIL NO ESTAR A FAVOR DE LOS PROBIÓTICOS

LAS BACTERIAS LÁCTICAS O LACTOBACILOS SON LOS PROBIÓTICOS MÁS COMUNES



INTERACCIÓN ENTRE LA FLORA INTESTINAL PROBIÓTICA Y EL SISTEMA INMUNOLÓGICO

¿ DE DÓNDE PROVIENEN LOS PROBIÓTICOS ?



INTERACCIÓN ENTRE LA FLORA INTESTINAL PROBIÓTICA Y EL SISTEMA INMUNOLÓGICO

¿ QUÉ ENTENDEMOS POR FLORA INTESTINAL O COMENSAL?

ESTÁ INTEGRADA PRINCIPALMENTE POR BACTERIAS DE LAS “BUENAS”

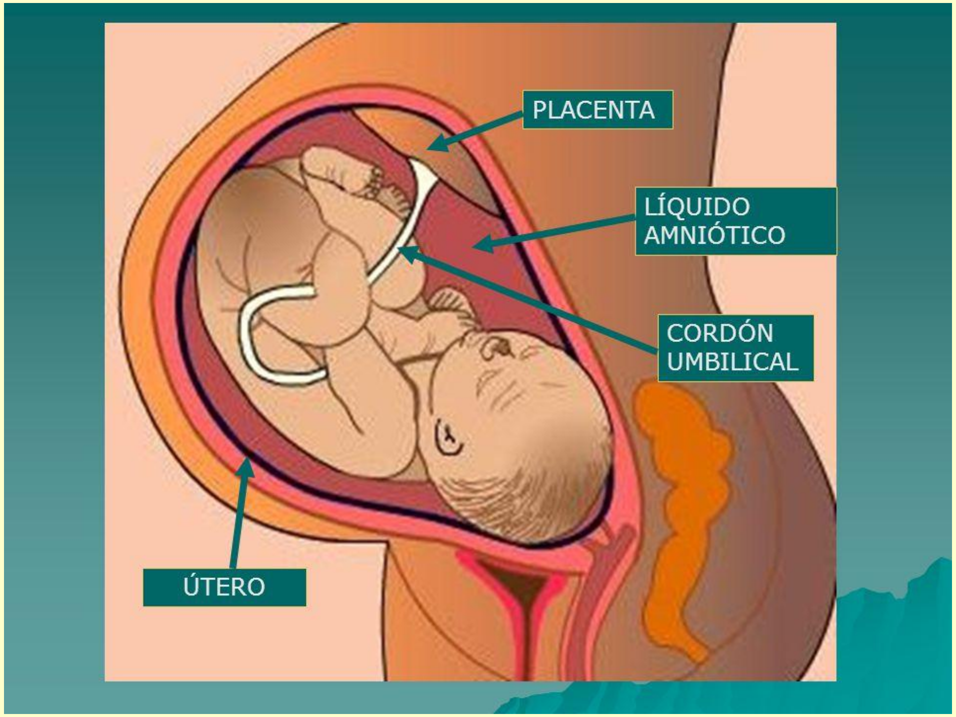
¿ CUÁNDO Y DESDE DÓNDE LA ADQUIRIMOS ?

NEUROMICROBIOLOGÍA
Microbiota intestinal y sus efectos sobre el sistema nervioso y longevidad

1

DURANTE EL EMBARAZO NINGUNA BACTERIA

"Desde la placenta y el líquido amniótico"



2

EN EL MOMENTO DEL PARTO POR LA FLORA VAGINAL DE LA MADRE

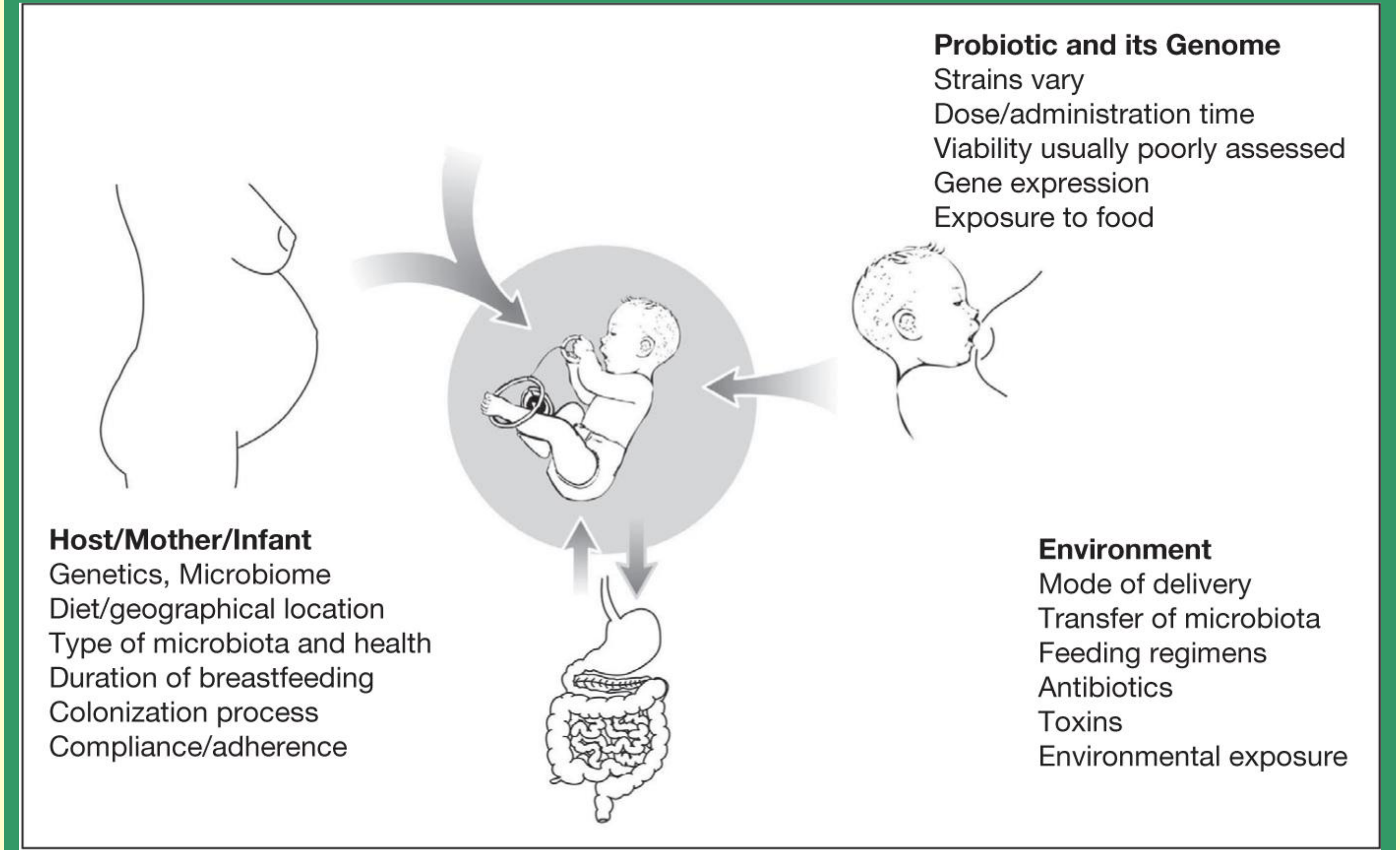
El parto por cesárea se asocia con problemas de salud a futuro: asma, alergias, enfermedad celíaca y eczemas

NEUROMICROBIOLOGÍA
Microbiota intestinal y sus efectos sobre el sistema nervioso y longevidad

3

LUEGO DEL NACIMIENTO

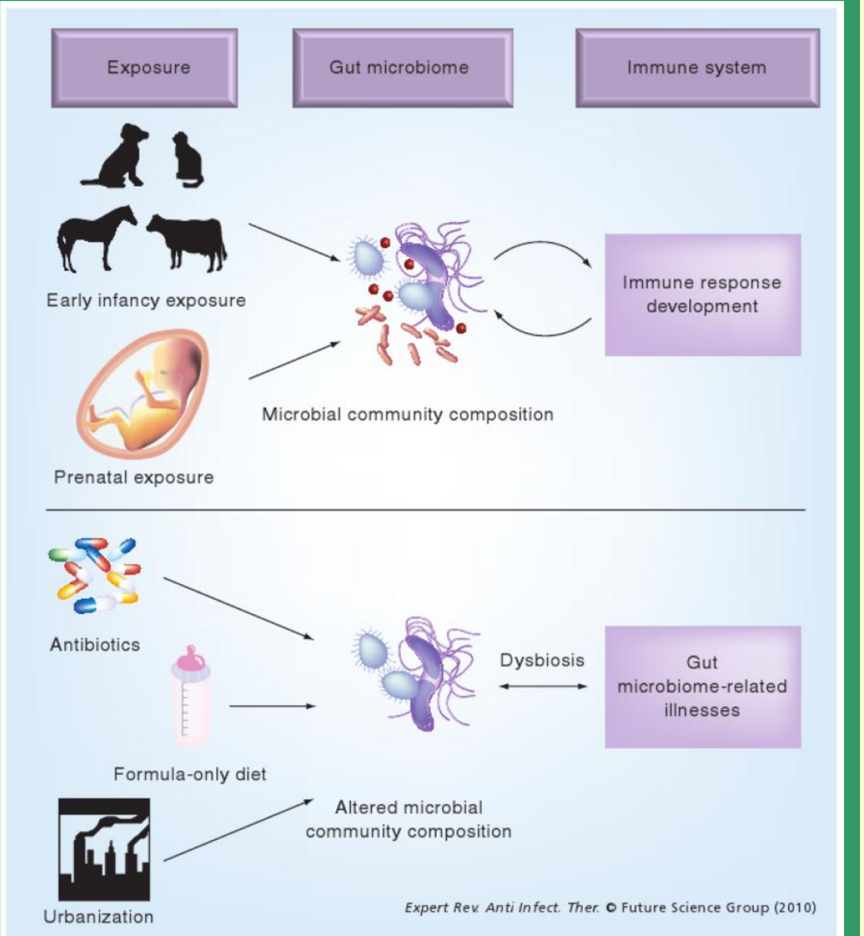
ADQUIRIMOS PARTE DE LA FLORA A TRAVÉS DEL AMAMANTA-MIIENTO



NEUROMICROBIOLOGÍA
Microbiota intestinal y sus efectos sobre el sistema nervioso y longevidad

4

POR ÚLTIMO DEL MEDIO AMBIENTE Y LOS ALIMENTOS



SON 4 FACTORES QUE AFECTAN LA FLORA INTESTINAL DEL INFANTE Y EL DESARROLLO TEMPRANO DEL SISTEMA INMUNOLÓGICO Y NERVIOSO

"5"

Desde la placenta???

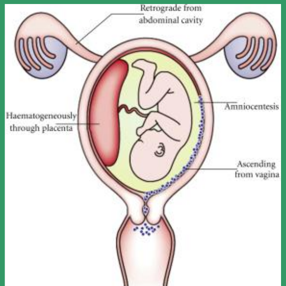


Figure 3: Potential routes of intrauterine infection (Source: Goldenberg et al. [16])

The placenta harbors a unique microbiome (Mayo de 2014)

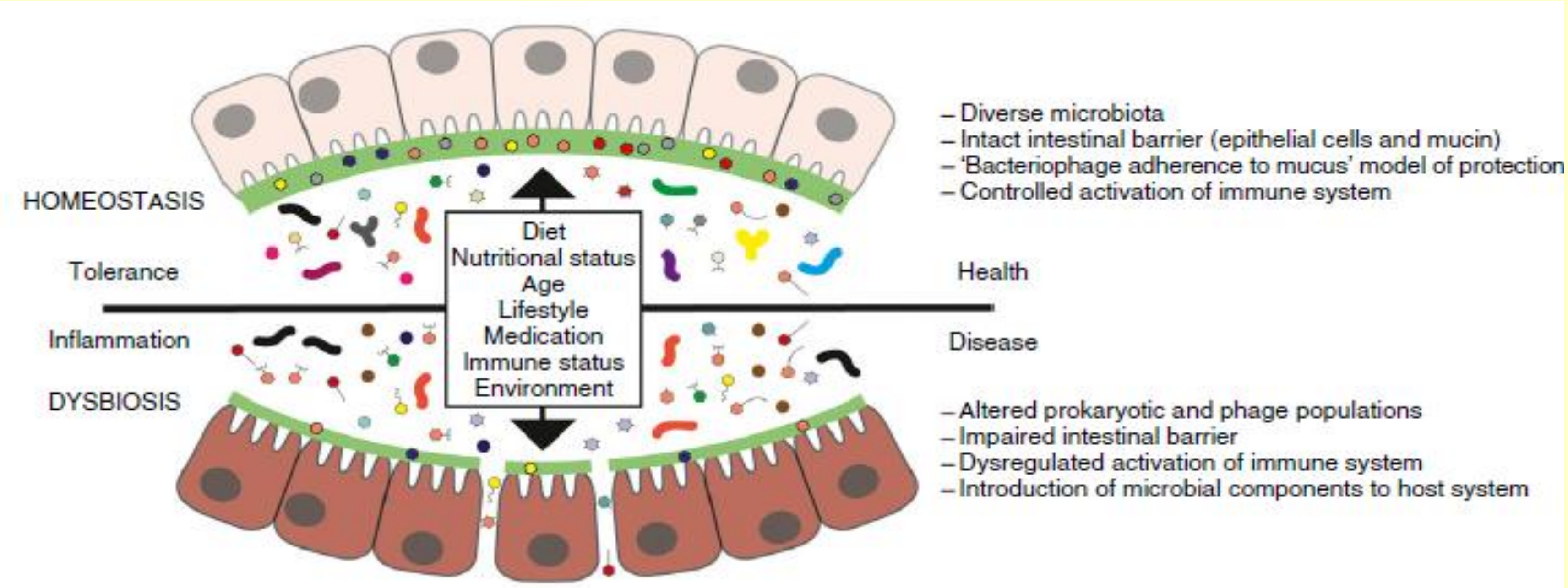
Humans and their microbiomes have coevolved as a physiologic community composed of distinct body site niches with metabolic and antigenic diversity. **The placental microbiome has not been robustly interrogated, despite recent demonstrations of intracellular bacteria with diverse metabolic and immune regulatory functions.** A population-based cohort of placental specimens collected under sterile conditions from 320 subjects with extensive clinical data was established for comparative 16S ribosomal DNA-based and whole-genome shotgun (WGS) metagenomic studies. Identified taxa and their gene carriage patterns were compared to other human body site niches, including the oral, skin, airway (nasal), vaginal, and gut microbiomes from nonpregnant controls**. We characterized a unique placental microbiome niche, composed of nonpathogenic commensal microbiota from the Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria phyla.** In aggregate, the placental microbiome profiles were most akin (Bray-Curtis dissimilarity <0.3) to the human oral microbiome. 16S-based operational taxonomic unit analyses **revealed associations of the placental microbiome with a remote history of antenatal infection** (permutational multivariate analysis of variance, P = 0.006), **such as urinary tract infection in the first trimester, as well as with preterm birth <37 weeks** (P = 0.001).

Comment on "the placenta harbors a unique microbiome".

Y CONTINUA………

NEUROMICROBIOLOGÍA
Microbiota intestinal y sus efectos sobre el sistema nervioso y longevidad

- LA DIETA DE LA PERSONA TAMBIÉN CUMPLE UN ROL CLAVE EN LA COMPOSICIÓN DE LA FLORA INESTINAL.
- UNA DIETA RICA EN GRASAS Y POBRE EN FIBRAS PRODUCE UNA DISMINUCIÓN EN LA DIVERSIDAD MICROBIANA DE LA FLORA DE LA PERSONA.
- ESTO SE ASOCIA FUERTEMENTE A UNA MENOR SALUD DEL INDIVIDUO
- AFORTUNADAMENTE ESTO ES REVERSIBLE CAMBIANDO LA DIETA
- SI LA DIETA NO SE CAMBIA, ESTA POBRE DIVERSIDAD MICROBIANA ES TRANSMITIBLE A LA DESCENDENCIA



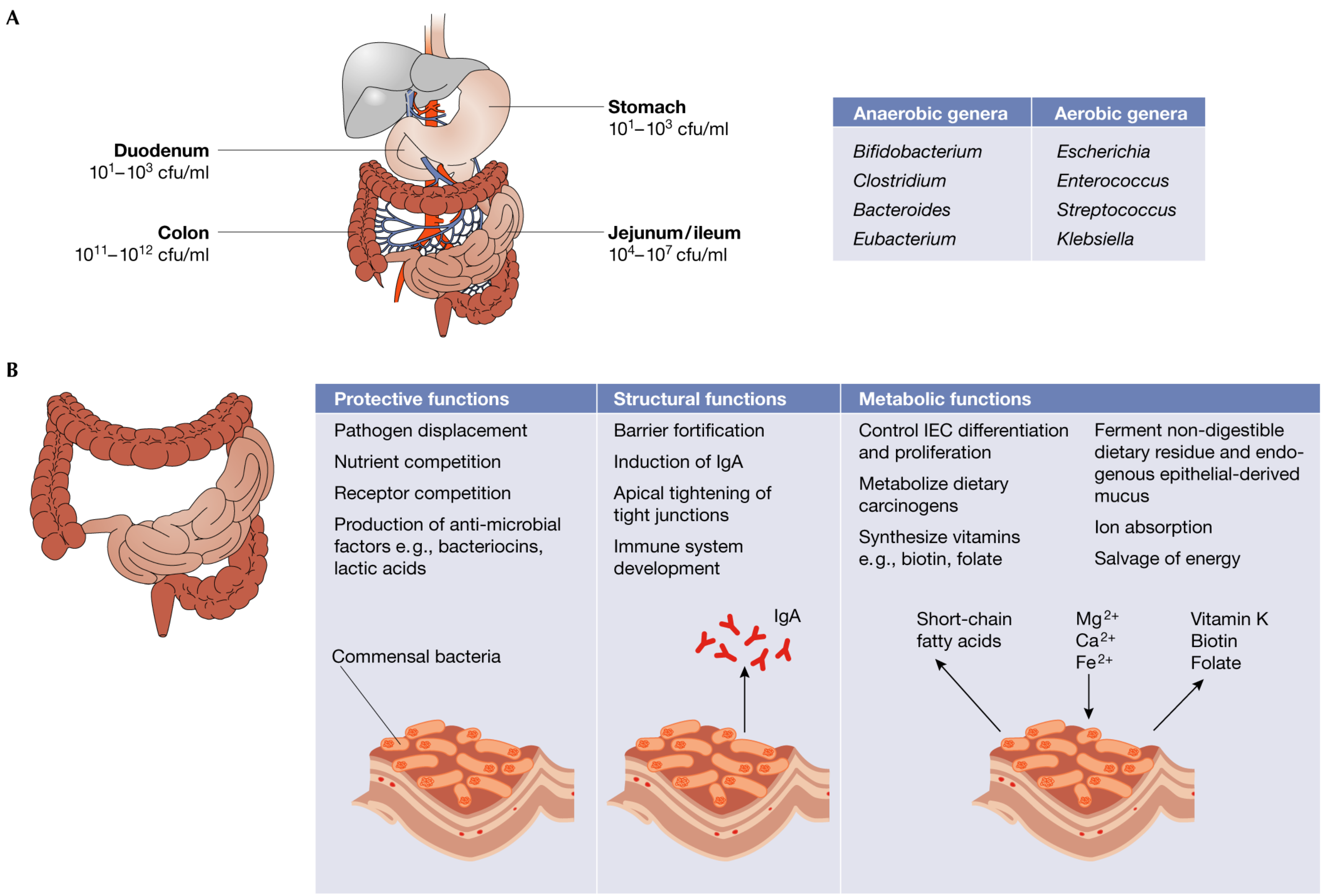
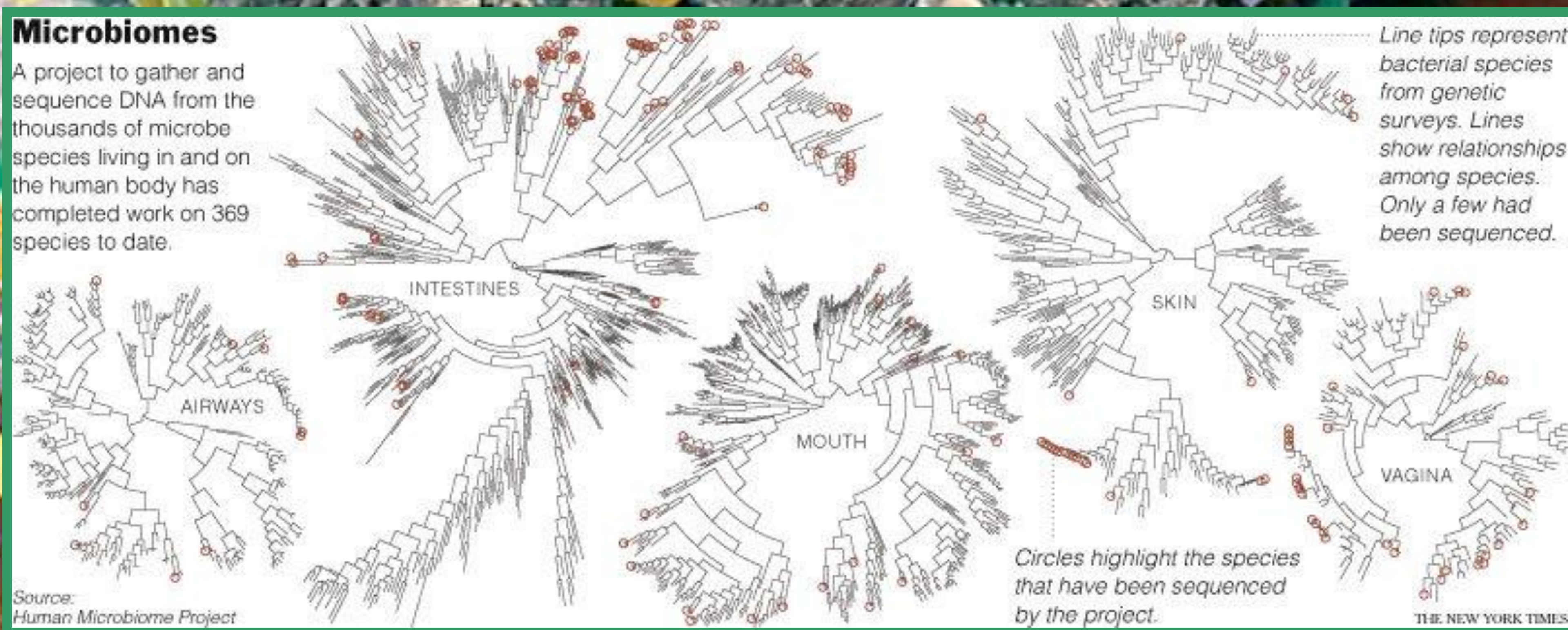


Fig 1 | Functions of the intestinal flora. (A) Bacteria density increases in the jejunum/ileum from the stomach and duodenum, and in the large intestine, colon-residing bacteria achieve the highest cell densities recorded for any ecosystem. The most common anaerobic and aerobic genera are listed. (B) Commensal bacteria exert a miscellany of protective, structural and metabolic effects on the intestinal mucosa.

EL SER HUMANO NO ESTÁ CONFORMADO ÚNICAMENTE POR CÉLULAS HUMANAS SINO TAMBIÉN POR CÉLULAS BACTERIANAS: SOMOS UN HOLOBIONTE



The gut flora as a forgotten organ

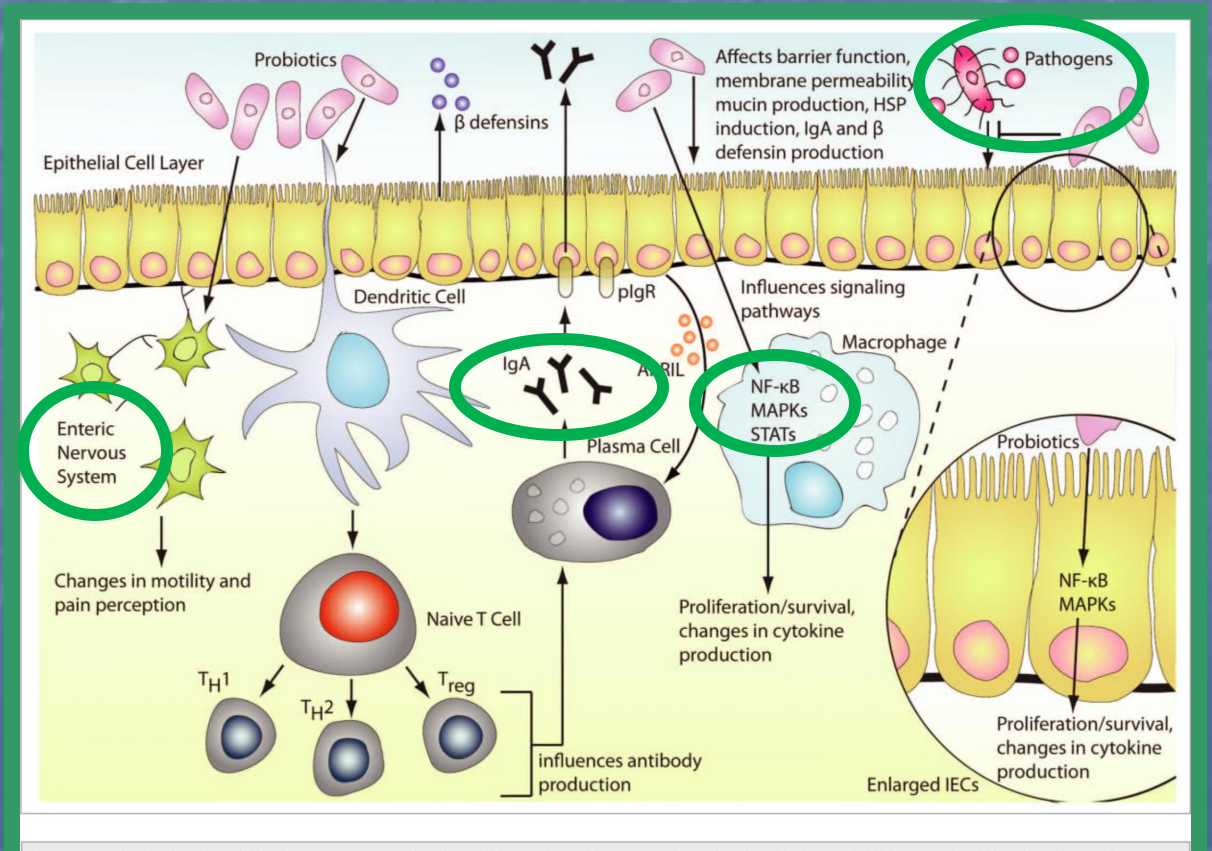
Ann M. O'Hara[1] & Fergus Shanahan[1,2+]

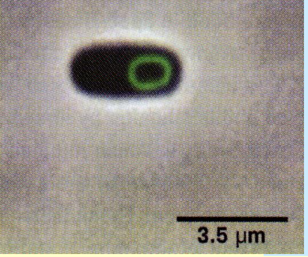
Alimentary Pharmabiotic Centre, University College Cork, National University of Ireland, Cork, Ireland

The intestinal microflora is a positive health asset that crucially influences the normal structural and functional development of the mucosal immune system. Mucosal immune responses to resident intestinal microflora require precise control and an immunosensory capacity for distinguishing commensal from pathogenic bacteria. In genetically susceptible individuals, some components of the flora can become a liability and contribute to the pathogenesis of various intestinal disorders, including inflammatory bowel diseases. It follows that manipulation of the flora to enhance the beneficial components represents a promising therapeutic strategy. The flora has a collective metabolic activity equal to a virtual organ within an organ, and the mechanisms underlying the conditioning influence of the bacteria on mucosal homeostasis and immune responses are beginning to be unravelled. An improved understanding of this hidden organ will reveal secrets that are relevant to human health and to several infectious, inflammatory and neoplastic disease processes.

EXISTE UNA RELACIÓN ESTRECHA ENTRE LA FLORA COMENSAL Y EL SISTEMA INMUNOLÓGICO

NEUROMICROBIOLOGÍA
Microbiota intestinal y sus efectos sobre el sistema nervioso y la longevidad





ALGUNOS MICROBIOS SON MUY BUENOS COMPAÑEROS

- EXISTE UNA RELACIÓN ENTRE LA FLORA NORMAL Y EL SISTEMA INMUNOLÓGICO

⇓

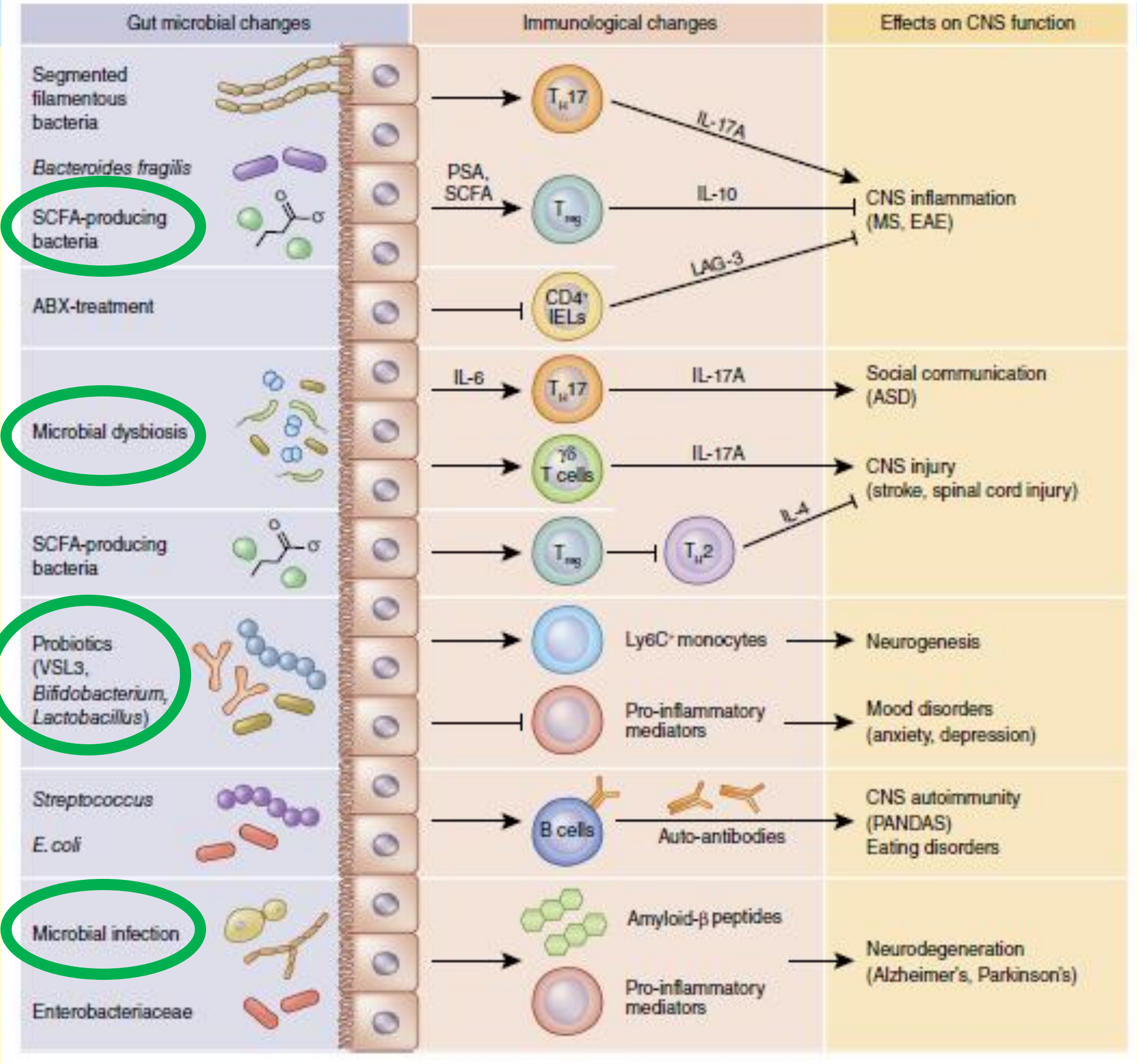
- EXISTE UNA RELACIÓN ENTRE EL SISTEMA INMUNOLÓGICO Y EL SISTEMA NERVIOSO

⇓

- ENTONCES DEBE EXISTIR UNA RELACIÓN (DIRECTA O INDIRECTA) ENTRE LA FLORA NORMAL Y EL SISTEMA NERVIOSO

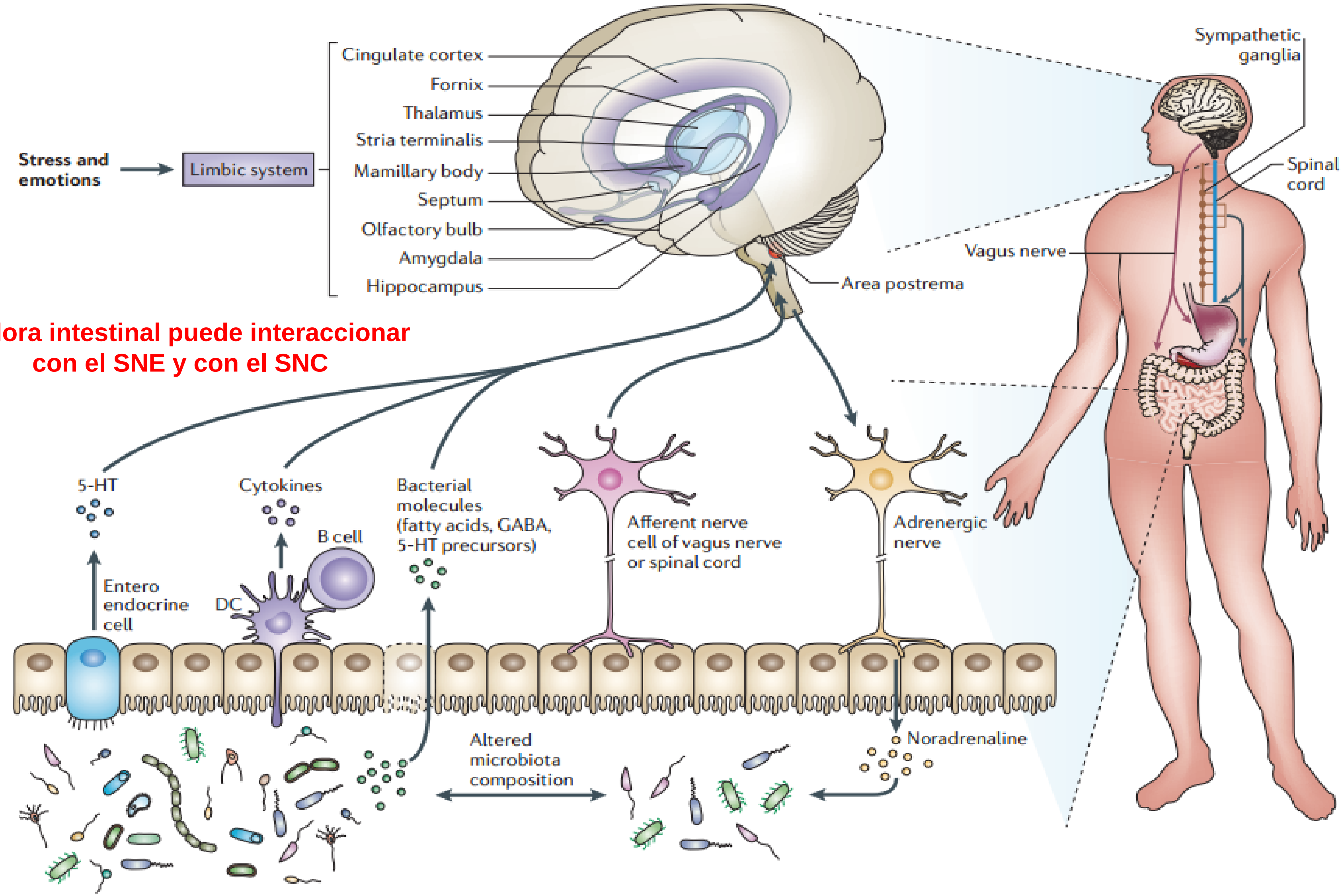
Interactions between the microbiota, immune and nervous systems in health and disease

NATURE NEUROSCIENCE VOLUME 20 | NUMBER 2 | FEBRUARY 2017



DENTRO DE LA FLORA INTESTINAL ESTÁN LOS PROBIÓTICOS

NEUROMICROBIOLOGÍA
Microbiota intestinal y sus efectos sobre el sistema nervioso y la longevidad



La flora intestinal puede interaccionar con el SNE y con el SNC

Diet-induced extinctions in the gut microbiota compound over generations

NATURE | VOL 529 | 14 JANUARY 2016

- La OBESIDAD DURANTE EL EMBARAZO aumenta el riesgo de AUTISMO en ratones. Esto se correlacionaba con la flora intestinal de la madre y las crías.
- Mezclando crías normales con aquellas con un comportamiento alterado, se normalizó la flora y el comportamiento de los animales.
- Una sola especie bacteriana, *Lactobacillus reuteri*, fue suficiente para revertir el comportamiento anormal de los ratones.
- *L. reuteri* producía y liberaba Oxitocina (rol importante en el comportamiento social y de vínculos interpersonales).
- Transtornos del espectro autista (en EE.UU. 1 de cada 40 niños): autismo, syndrome de Asperger y transtornos generalizados del desarrollo.

Microbial regulation of microRNA expression in the amygdala and prefrontal cortex

Hoban *et al. Microbiome* (2017) 5:102
DOI 10.1186/s40168-017-0321-3

EL ESTRÉS NEONATAL PRODUCE CAMBIOS EN LA FLORA INTESTINAL QUE REPERCUTE EN EL FUNCIONAMIENTO CEREBRAL INDUCIENDO PROBLEMAS DE ANSIEDAD, DEPRESIÓN, TRANSTORNOS COGNITIVOS Y DE SOCIABILIDAD.

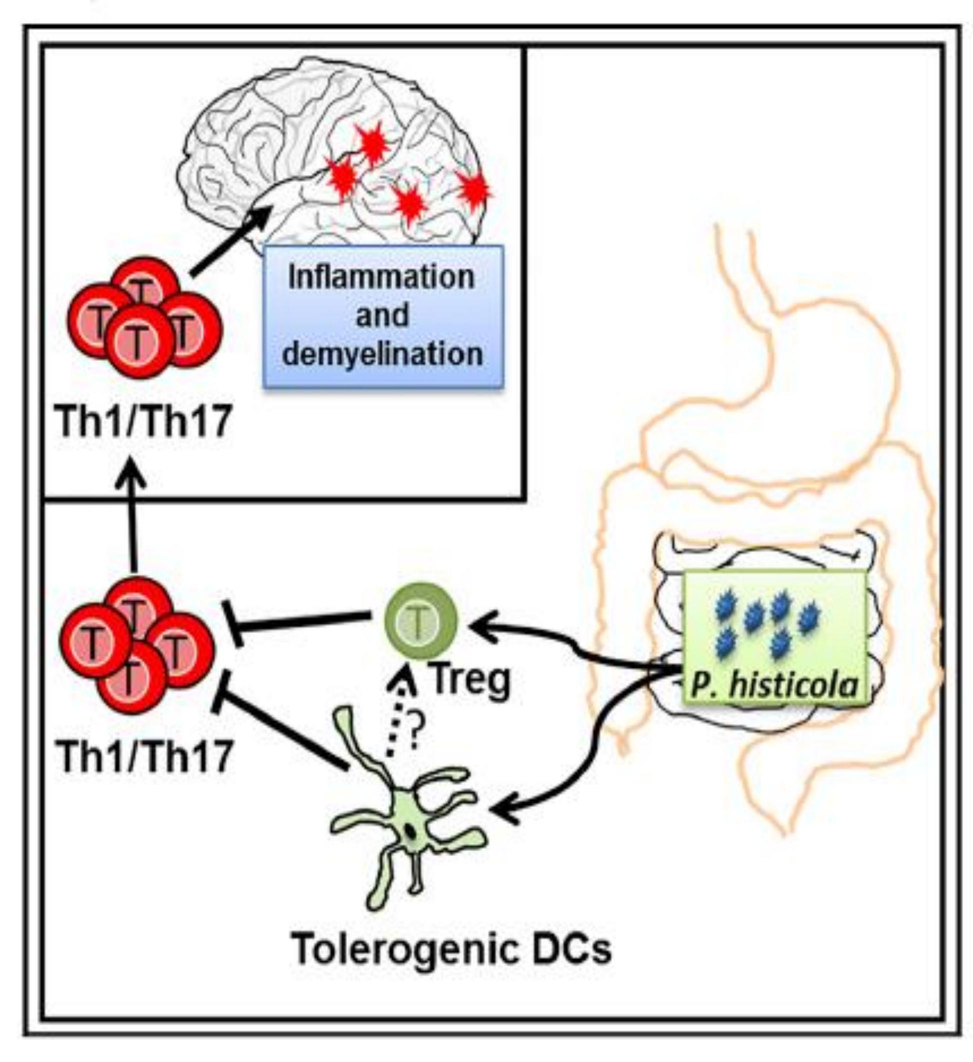
ESTOS FENÓMENOS SE CORRELACIONARON CON LA AUSENCIA O ALTERACIONES DE LOS MICRO-ARNs EN AMÍGDALA (procesamiento de las emociones) Y EN EL CORTEX PRE-FRONTAL (rol en el control de las emociones impulsivas, planeamiento y comportamiento) DEL CEREBRO.

CUANDO SE NORMALIZABA LA COMPOSICIÓN DE LA MICROBIOTA, SE NORMALIZARON LOS NIVELES DE LOS miRNAs Y LOS PROBLEMAS DE COMPORTAMIENTO DE LOS ANIMALES.

SOLAMENTE EN EE.UU. HAY 40 MILLONES DE PERSONAS CON ESTE TIPO DE PROBLEMAS.

Human Gut-Derived Commensal Bacteria Suppress CNS Inflammatory and Demyelinating Disease

Mangalam et al., 2017, Cell Reports *20*, 1269–1277
August 8, 2017



The human gut is colonized by a large number of microorganisms (~10^{13} bacteria) that support various physiologic functions. A perturbation in the healthy gut microbiome might lead to the development of inflammatory diseases, such as multiple sclerosis (MS). Therefore, gut commensals might provide promising therapeutic options for treating MS and other diseases. We report the identification of human gut-derived commensal bacteria, *Prevotella histicola*, which can suppress experimental autoimmune encephalomyelitis (EAE) in a human leukocyte antigen (HLA) class II transgenic mouse model. *P. histicola* suppresses disease through the modulation of systemic immune responses. *P. histicola* challenge led to a decrease in pro-inflammatory Th1 and Th17 cells and an increase in the frequencies of $CD4^+FoxP3^+$ regulatory T cells, tolerogenic dendritic cells, and suppressive macrophages. Our study provides evidence that the administration of gut commensals may regulate a systemic immune response and may, therefore, have a possible role in treatment strategies for MS.

RESEARCH ARTICLE

The Nasal and Gut Microbiome in Parkinson's Disease and Idiopathic Rapid Eye Movement Sleep Behavior Disorder

Movement Disorders, Vol. 00, No. 00, 2017

LAS PERSONAS CON PARKINSON POSEEN UNA FLORA INTESTINAL ALTERADA.

AÑOS ANTES DE QUE EL PARKINSON SE MANIFIESTE LÍNICAMENTE, LA PERSONAS MANIFIESTAN PROBLEMAS INTESTINALES.

PERSONAS CON PARKINSON POSEEN UN MENOR CONTENIDO DE BACTERIAS DEL GÉNERO *PREVOTELLA* ¿ES ESTO CAUSA O CONSECUENCIA?

EXISTE LA POSIBILIDAD DE QUE LA ENFERMEDAD DE PARKINSON COMIENCE FUERA DEL CEREBRO. Infección nasal y/o gastrointestinal, plegamiento incorrecto de la alfa-sinucleína, propagación por las neuronas, su agregación y muerte (cuerpos de Lewy). En EE.UU. SE SUMAN AL AÑO 100.000 PERSONAS CON PARKINSON.

¿ESTÁN EL ALZHEIMER Y EL PARKINSON RELACIONADOS A LAS ENFERMEDADES PRIÓNICAS?

INVESTIGACIÓN CIENTÍFICA

EL OTRO CEREBRO

Se descubrió que el intestino influye en trastornos como el autismo o la infertilidad. La nueva revolución de las bacterias y las dietas que ayudan a pensar mejor.

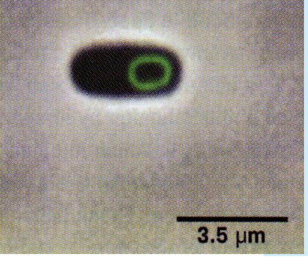
Normal gut microbiota modulates brain development and behavior

Rochellys Diaz Heijtz[a,b,1], Shugui Wang[c], Farhana Anuar[d], Yu Qian[a,b], Britta Björkholm[d], Annika Samuelsson[d], Martin L. Hibberd[c], Hans Forssberg[b,e], and Sven Pettersson[c,d,1]

Departments of [a]Neuroscience, and [d]Microbiology, Cell and Tumor Biology, Karolinska Institutet, 171 77 Stockholm, Sweden; [b]Stockholm Brain Institute, 171 77 Stockholm, Sweden; [c]Genome Institute of Singapore, 02-01 Genome 138672, Singapore; and [e]Department of Women's and Children's Health, Karolinska Institutet, 171 76 Stockholm, Sweden

Edited by Arturo Zychlinsky, Max Planck Institute for Infection Biology, Berlin, Germany, and accepted by the Editorial Board January 4, 2011 (received for review August 11, 2010)

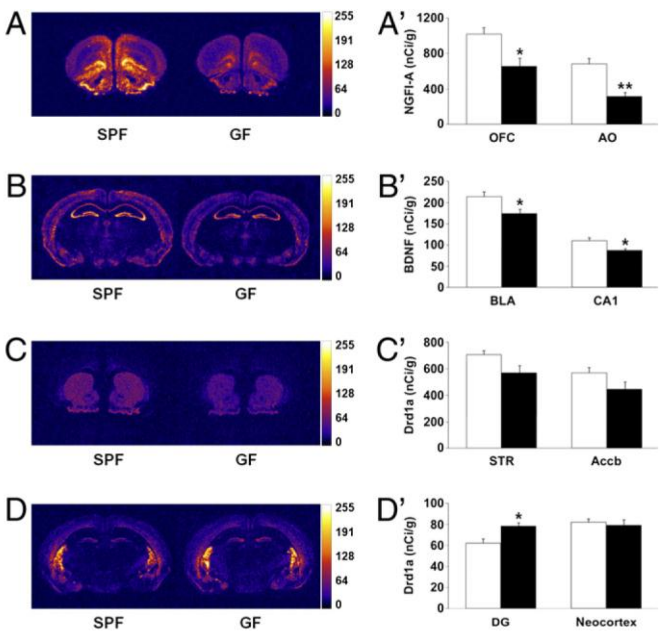
Microbial colonization of mammals is an evolution-driven process that modulate host physiology, many of which are associated with immunity and nutrient intake. **Here, we report that colonization by gut microbiota impacts mammalian brain development and subsequent adult behavior**. Using measures of motor activity and anxiety-like behavior, we demonstrate that germ free (GF) mice display increased motor activity and reduced anxiety, compared with specific pathogen free (SPF) mice with a normal gut microbiota. This behavioral phenotype is associated with altered expression of genes known to be involved in second messenger pathways and synaptic long-term potentiation in brain regions implicated in motor control and anxiety-like behavior. GF mice exposed to gut microbiota early in life display similar characteristics as SPF mice, including reduced expression of PSD-95 and synaptophysin in the striatum. Hence, our results suggest that the microbial colonization process initiates signaling mechanisms that affect



PROBIÓTICOS EN MEDICINA

Normal gut microbiota modulates brain development and behavior

Rochellys Diaz Heijtz[a,b,1], Shugui Wang[c], Farhana Anuar[d], Yu Qian[a,b], Britta Björkholm[d], Annika Samuelsson[d], Martin L. Hibberd[c], Hans Forssberg[b,e], and Sven Pettersson[c,d,1]



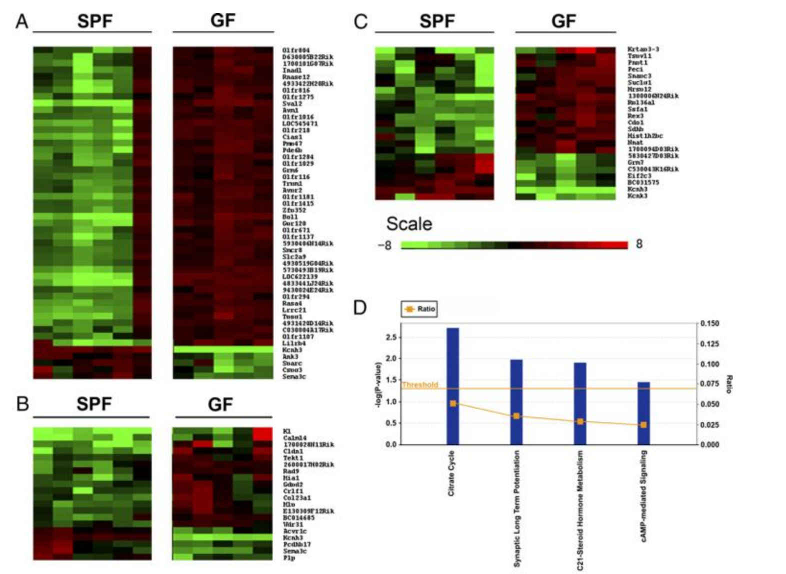
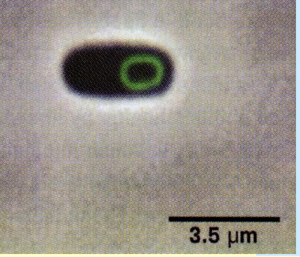


Fig. 5. Expression profiling of GF mice and SPF mice brains. A heatmap of genes showing statistically significant ($q < 5\%$) and fold change (>2) differences, between SPF ($n = 6$) and GF ($n = 5$) mice in the hippocampus (*A*), frontal cortex (*B*), and striatum (*C*). Each row represents the relative levels of expression of a single gene across all mice; each column represents the levels of expression for a single mouse. The colors red and green denote high and low expression, respectively. Differentially expressed genes were investigated for functional clustering by using Ingenuity Pathway Analysis software for canonical pathways (*D*), as described in *Experimental Procedures*.

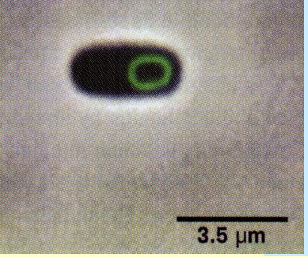
DENTRO DE LA FLORA COMENSAL ESTÁN LOS PROBIÓTICOS



¿CUÁLES SON LOS EFECTOS BENEFICIOSOS DE LOS MICROORGANISMOS PROBIÓTICOS?

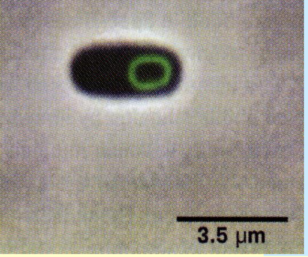
POR LO TANTO, ES MUY DIFÍCIL NO ESTAR A FAVOR DE LOS PROBIÓTICOS

LA FLORA INTESTINAL CONSTITUYE LA CUARTA HERIDA AL NARCICISMO DE LA HUMANIDAD

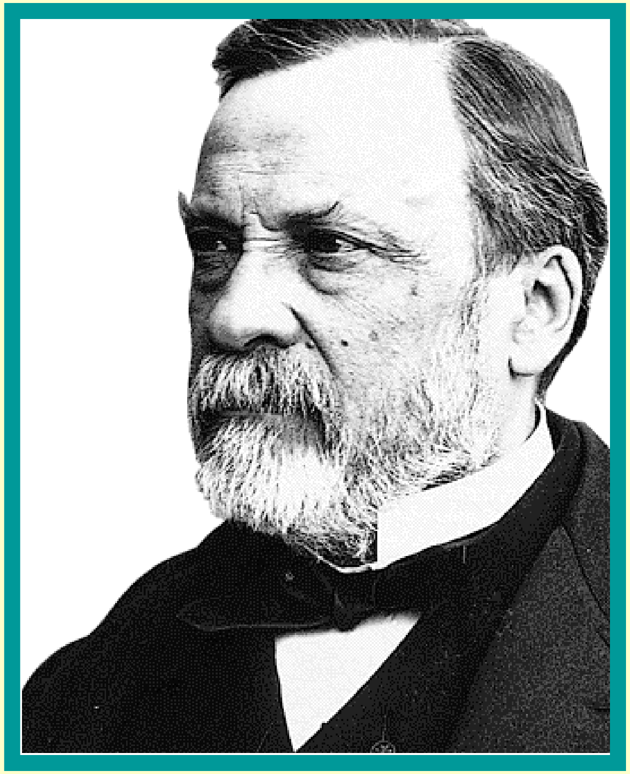


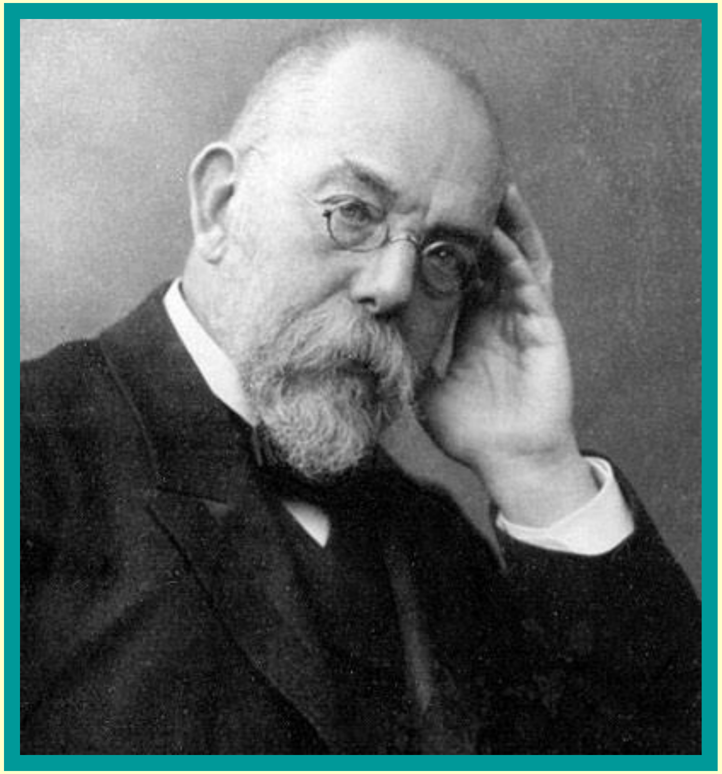
¿ CUÁLES SON ALGUNOS “INCONVENIENTES” DE LOS PROBIÓTICOS TRADICIONALES ?

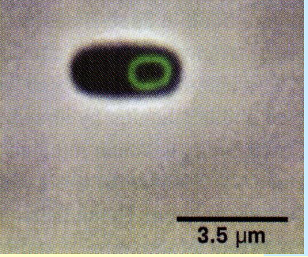
- VIDA MEDIA EN EL ESTANTE (SUPERVIVENCIA DEL PROBIÓTICO)
- INFRAESTRUCTURA DE CADENA DE FRÍO
- ACEPTABILIDAD DEL PRODUCTO
- COSTO (PRECIO)
- ¿CUÁNTO PROBIÓTICO DEBO CONSUMIR?



LA ERA DORADA DE LA MICROBIOLOGÍA (SIGLO XIX)





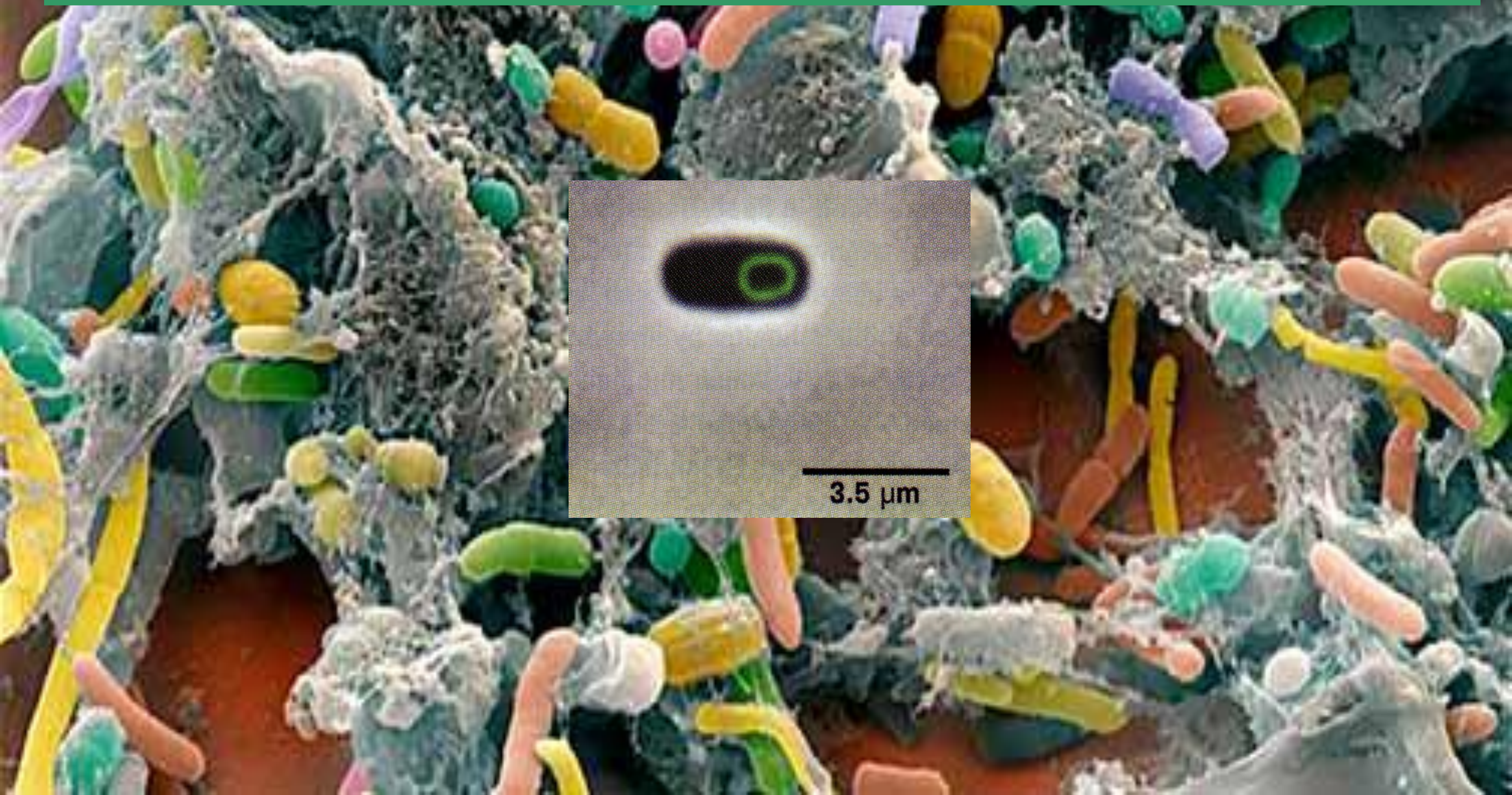


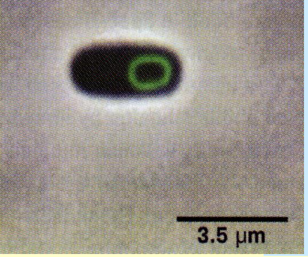
ESPORAS PROBIÓTICAS: SUS PRECURSORES (SIGLO XXI)

Linc Sonenshein
Tufts University
Boston - USA

Simon Cutting
Royal Holloway University of London
UK

UNA NUEVA ALTERNATIVA:
BACTERIAS FORMADORAS DE ESPORAS COMO PROBIÓTICOS DE NUEVA GENERACIÓN
BACILLUS SUBTILIS

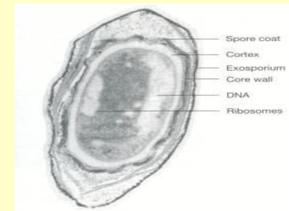




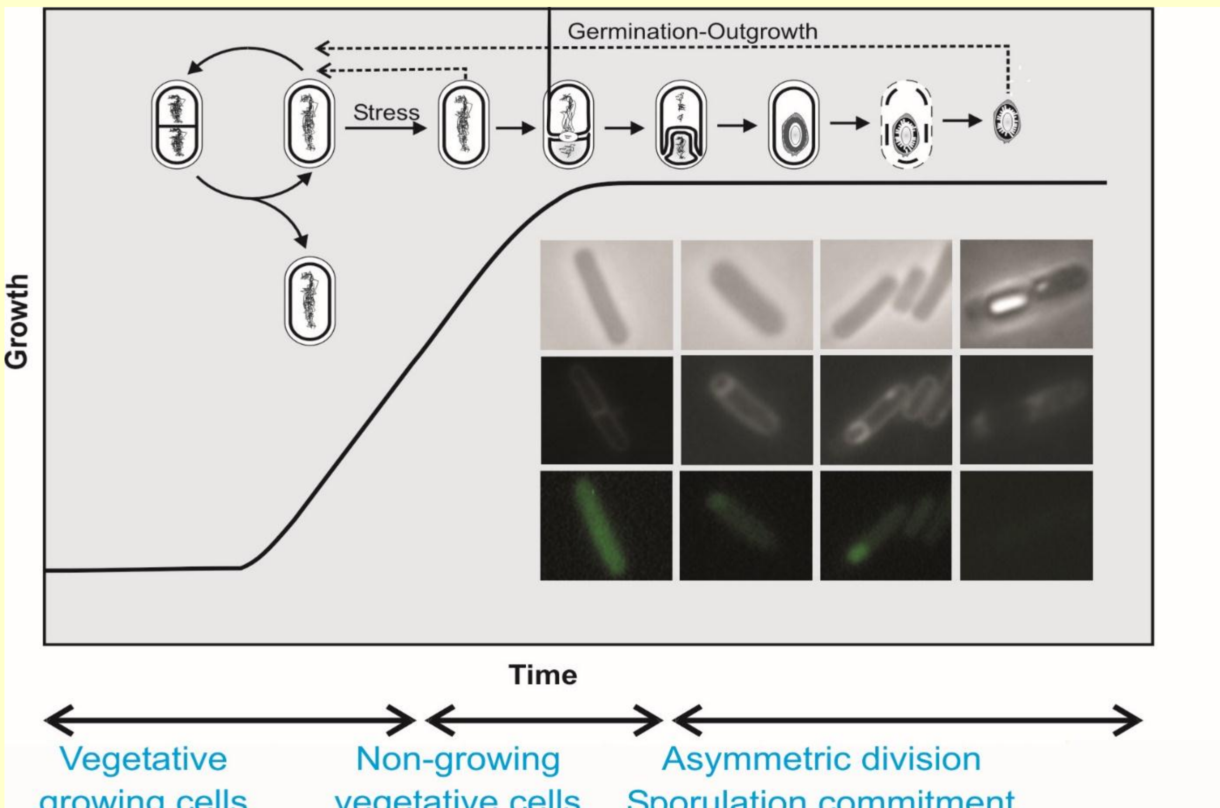
UNA NUEVA ALTERNATIVA: LAS BACTERIAS FORMADORAS DE ESPORAS COMO PROBIÓTICOS DE NUEVA GENERACIÓN

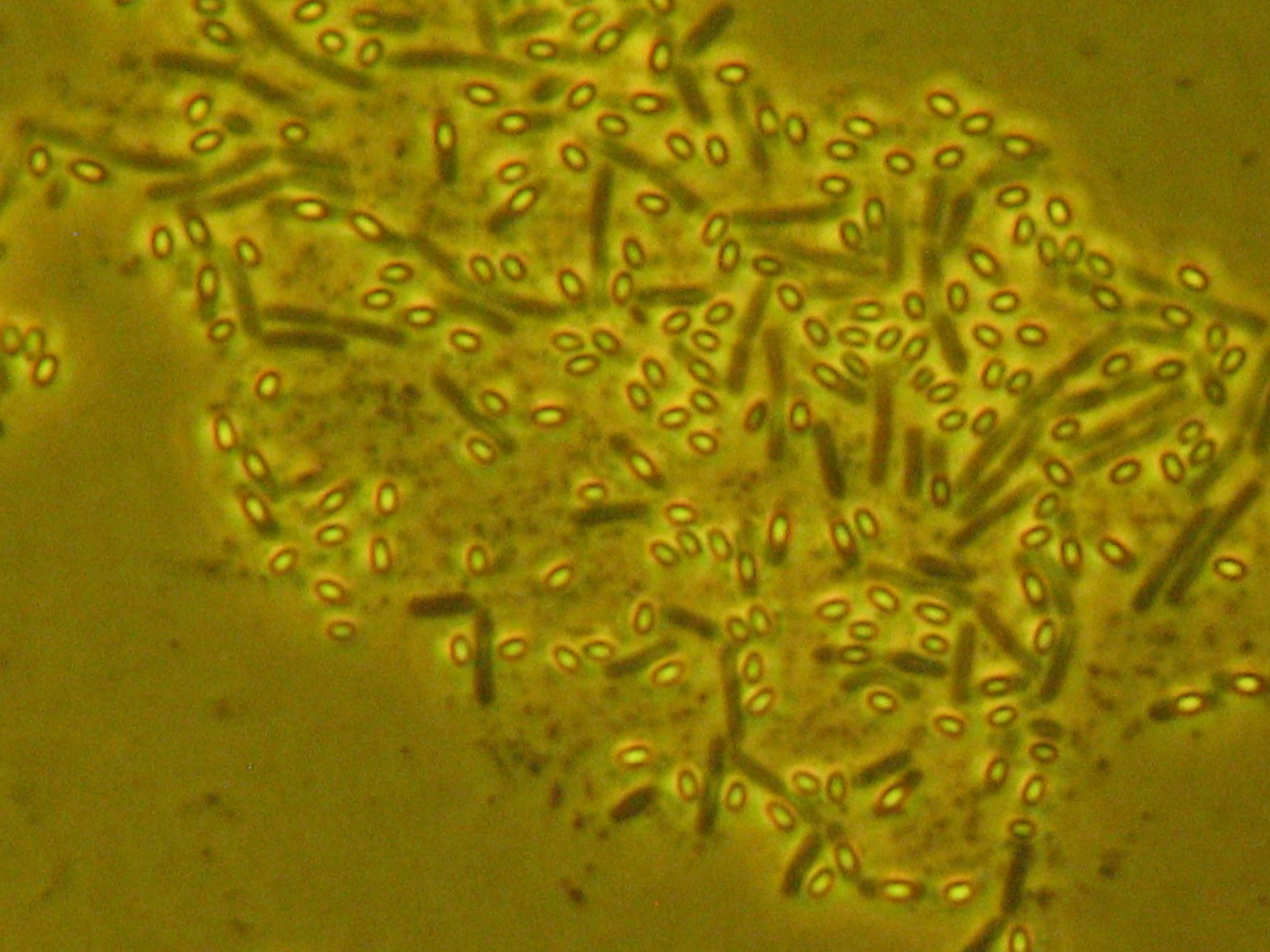
BACILLUS SUBTILIS

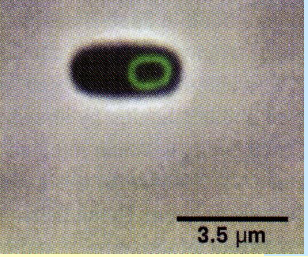
HAMBREADO



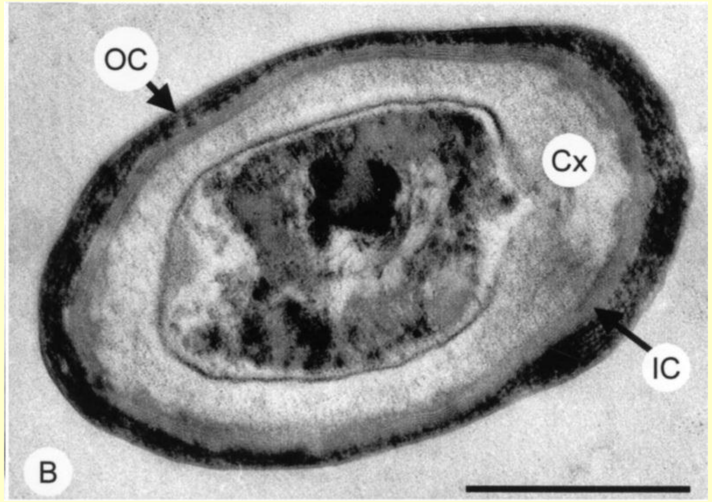
CÉLULA VEGETATIVA | **DESARROLLO** | **ESPORA**





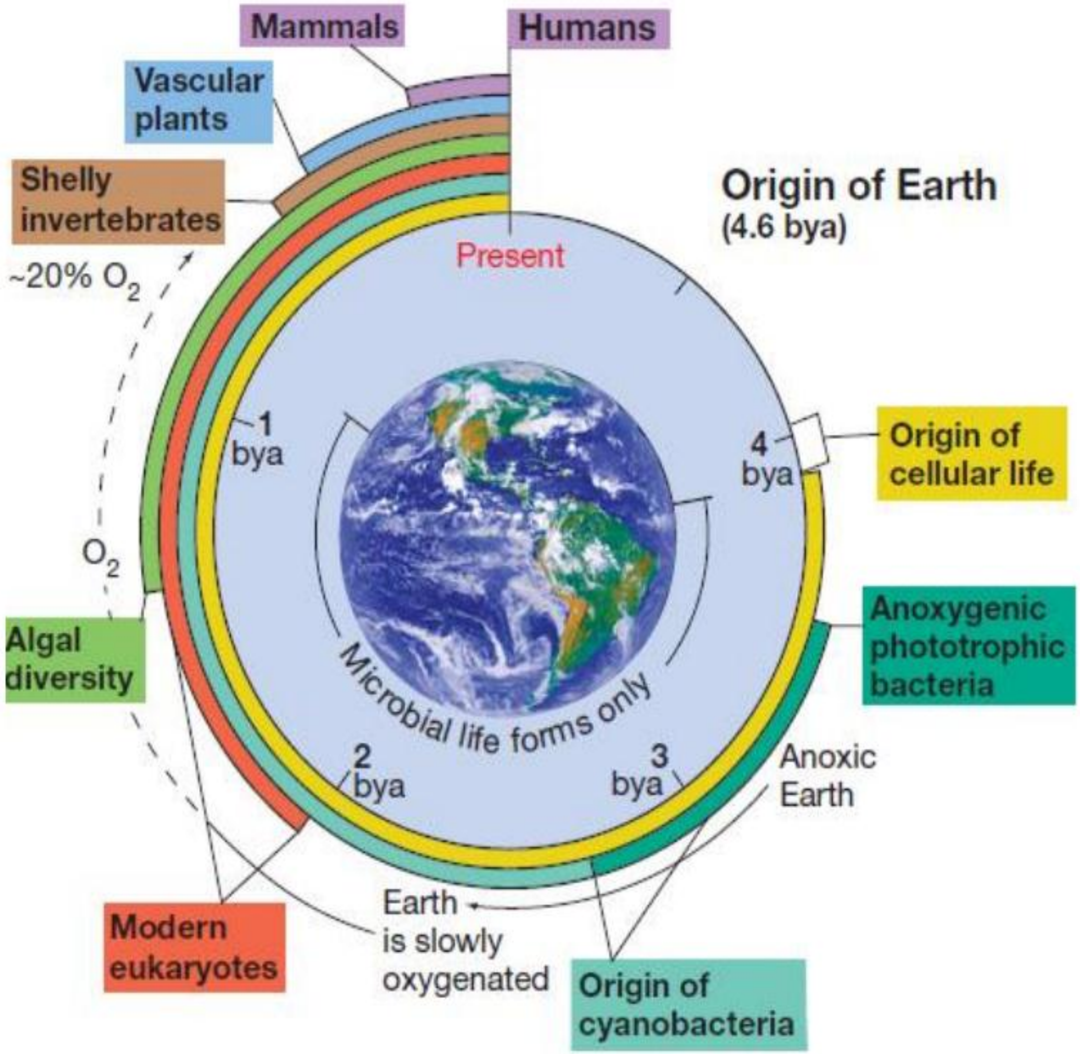


ALGUNAS PROPIEDADES DE LAS ESPORAS BACTERIANAS

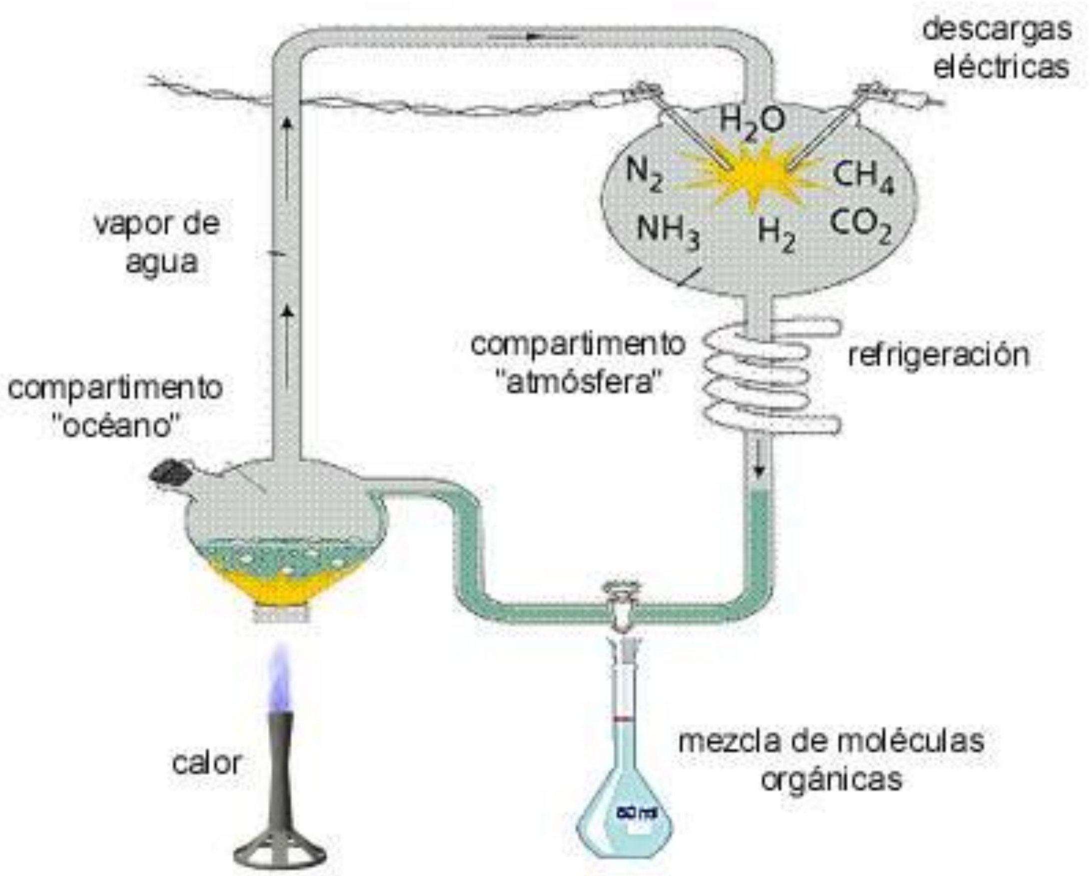


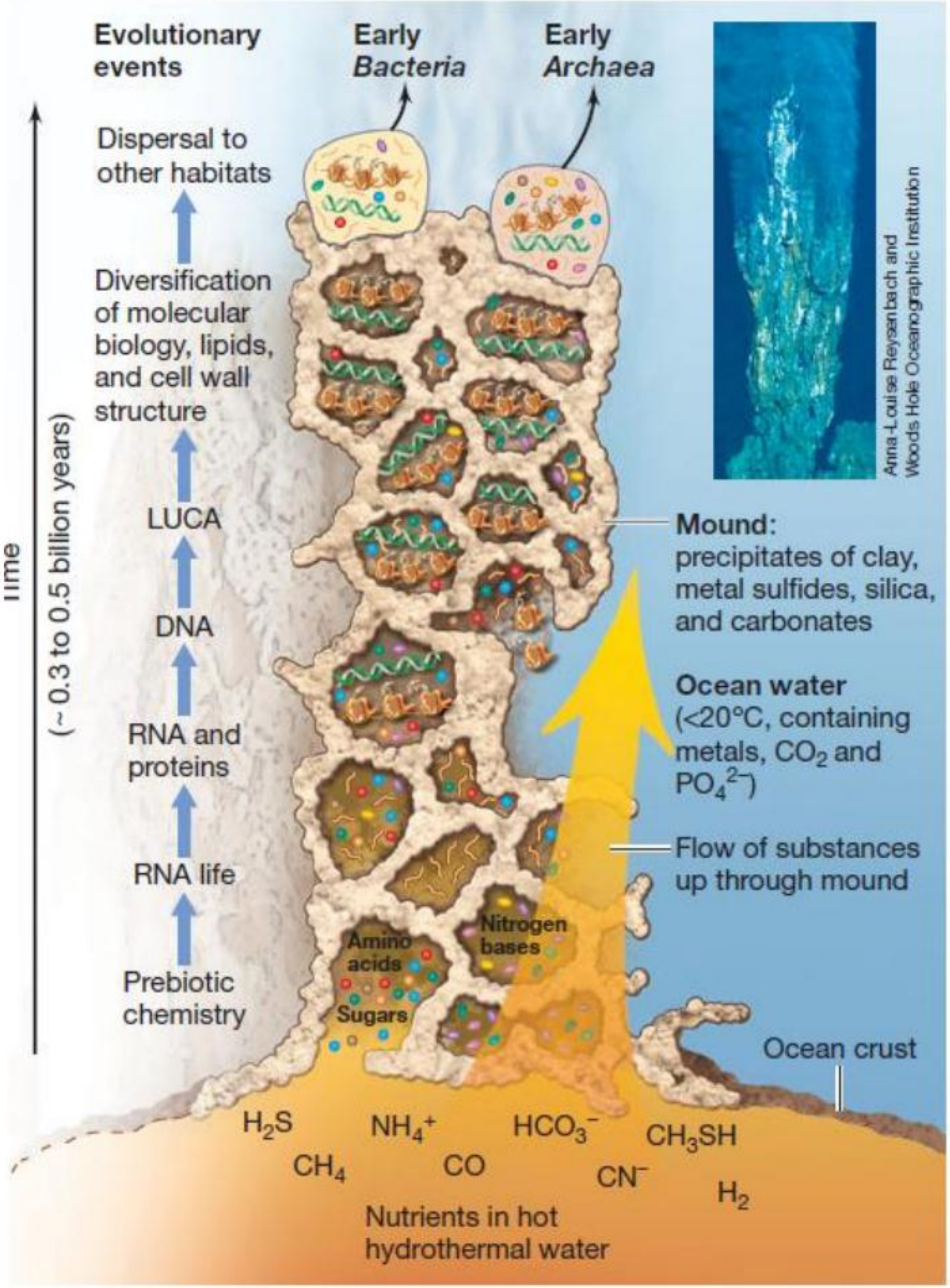
- **Resistencia a las temperaturas extremas,**
- **Resistencia a la desecación y la presión,**
- **Resistencia a los cambiosa de pH y salinidad,**
- **Resistencia a la radiación UV y solar,**
- **Resistencia a los procesos industriales de fabricación,**
- **Resistencia a los ataques por enzimas y detergentes,**
- **100% durmientes, metabolismo cero, agua cero, actividad enzimática cero,**
- **Alta longevidad (las esporas bacterianas son prácticamente inmortales e indestructibles)**

Vida en la Tierra a traves del tiempo



-*TEORÍA DE OPARÍN Y HALDANE*





Evolutionary events
Early *Bacteria*
Early *Archaea*
Time
(~ 0.3 to 0.5 billion years)
Dispersal to other habitats
Diversification of molecular biology, lipids, and cell wall structure
LUCA
DNA
RNA and proteins
RNA life
Prebiotic chemistry
Amino acids
Nitrogen bases
Sugars
Anna-Louise Reysenbach and Woods Hole Oceanographic Institution
Mound: precipitates of clay, metal sulfides, silica, and carbonates
Ocean water (<20°C, containing metals, CO_2 and PO_4^{2-})
Flow of substances up through mound
Ocean crust
H_2S
NH_4^+
HCO_3^-
CH_3SH
CH_4
CO
CN^-
H_2
Nutrients in hot hydrothermal water

OTRA HIPÓTESIS

LA LITOPANSPERMIA

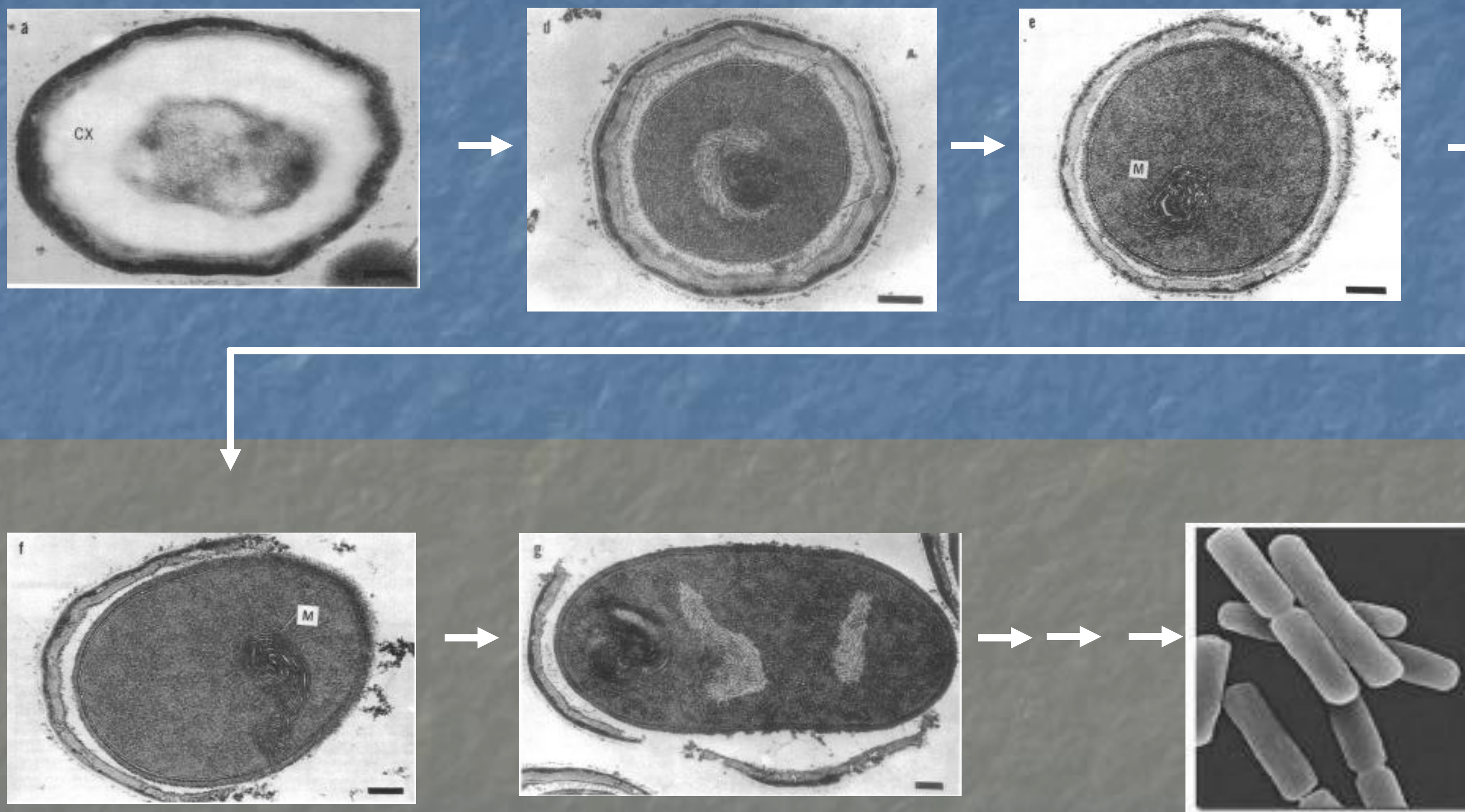
Resistance of *Bacillus* Endospores to Extreme Terrestrial and Extraterrestrial Environments

WAYNE L. NICHOLSON,[1*] NOBUO MUNAKATA,[2] GERDA HORNECK,[3] HENRY J. MELOSH,[4] AND PETER SETLOW[5]

Department of Veterinary Science and Microbiology[1] and Lunar and Planetary Laboratory,[4] University of Arizona, Tucson, Arizona 85721; Radiobiology Division, National Cancer Center Research Institute, Tokyo, Japan 104-0045[2]; Radiobiology Section, DLR, Institute of Aerospace Medicine, Cologne, Germany[3]; and Department of Biochemistry, University of Connecticut Health Center, Farmington, Connecticut 06032[5]

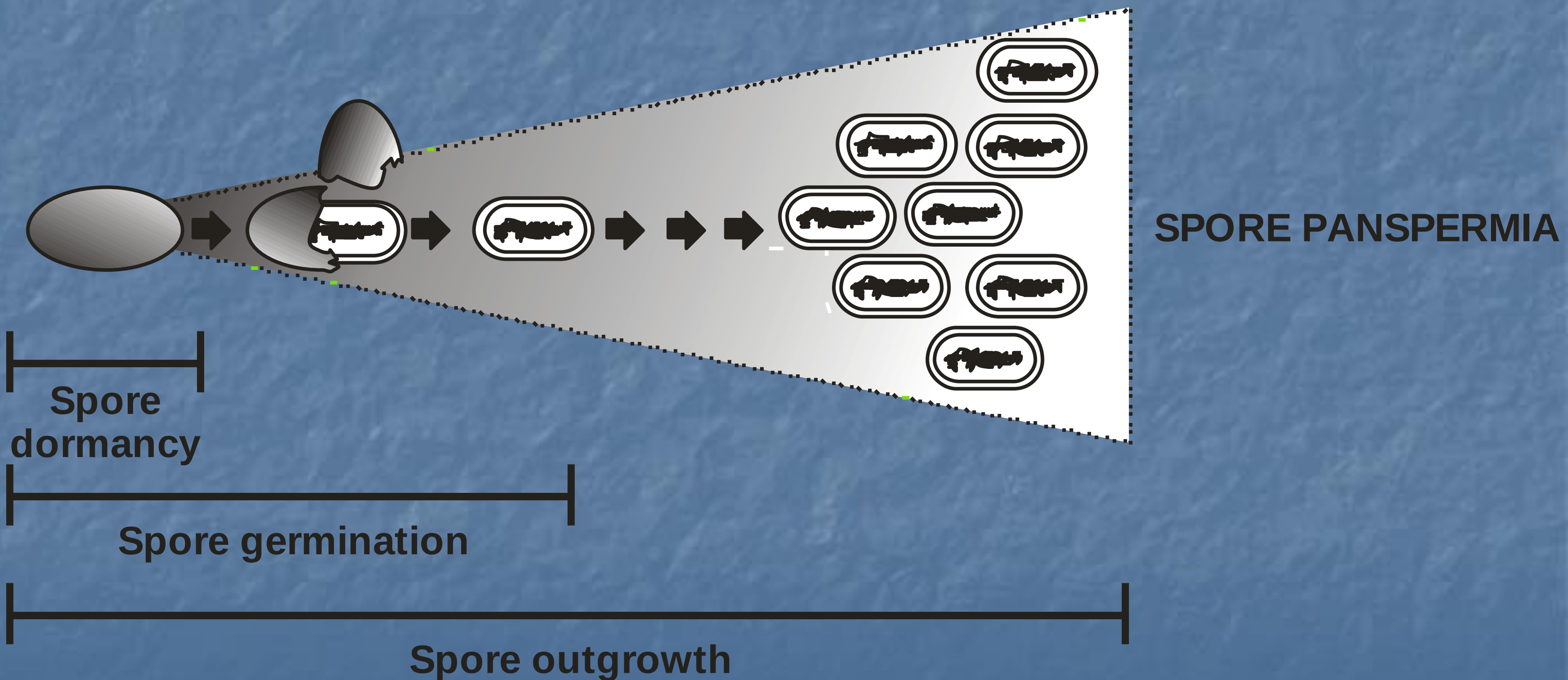
GERMINATION

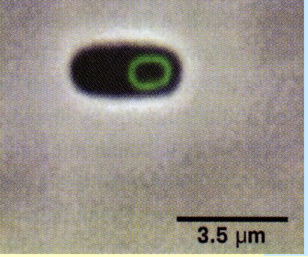
(MECHANICAL AND ENZIMATIC PROCESS)



OUTGROWTH

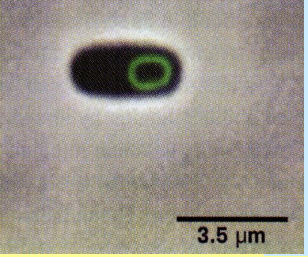
(METABOLIC REACTIVATION WITH *DE NOVO* SYNTHESIS)


SPORE PANSPERMIA
Spore
dormancy
Spore germination
Spore outgrowth



INCONVENIENTES SOLUCIONADOS

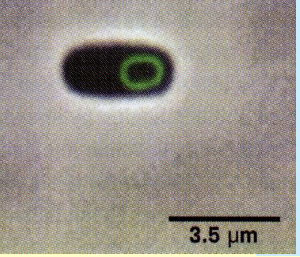
- VIDA MEDIA EN EL ESTANTE √
- CADENA DE FRÍO √
- ACEPTABILIDAD DEL PRODUCTO √
- COSTO O PRECIO √



OTRAS PROPIEDADES DE LAS ESPORAS BACTERIANAS

ADEMÁS

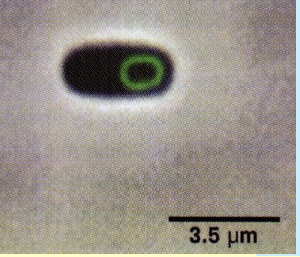
***B. SUBTILIS*…**



¿CUÁLES SON LOS EFECTOS BENEFICIOSOS DE LOS MICROORGANISMOS PROBIÓTICOS?

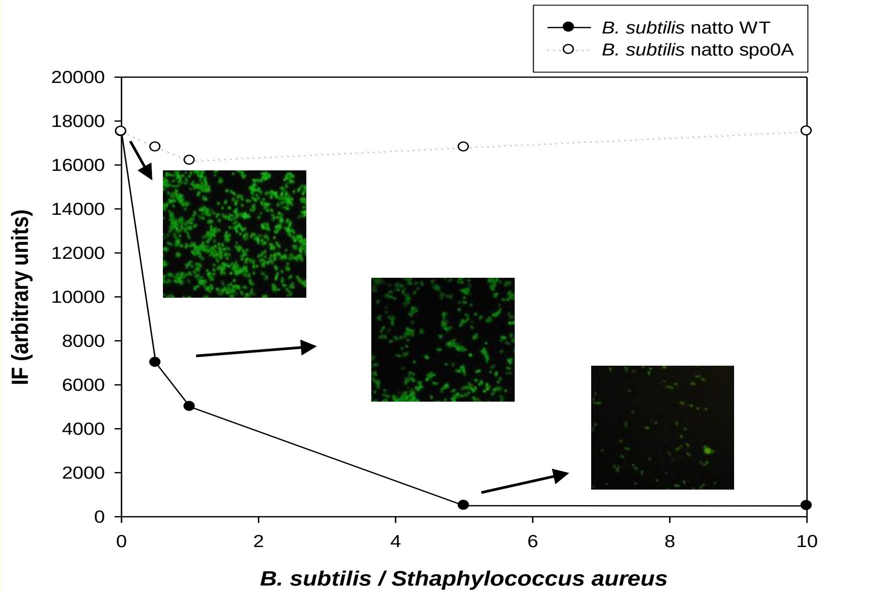
Cell PRESS

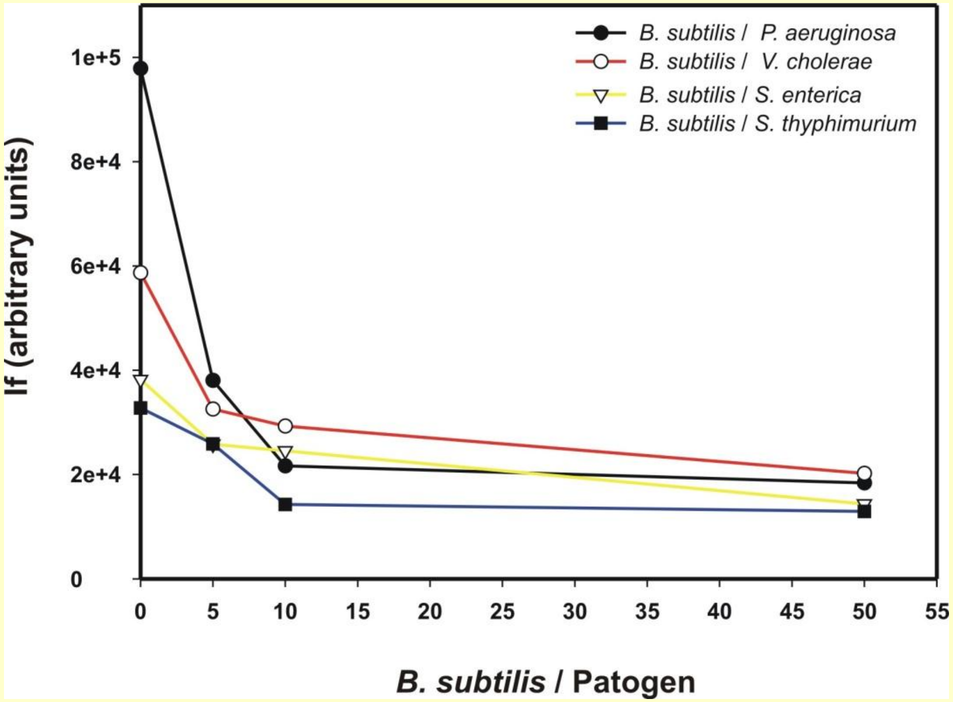
The *Bacillus subtilis* Quorum-Sensing Molecule CSF Contributes to Intestinal Homeostasis via OCTN2, a Host Cell Membrane Transporter

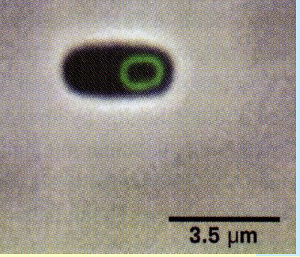


¿CUÁLES SON LOS EFECTOS BENEFICIOSOS DE LOS MICROORGANISMOS PROBIÓTICOS?

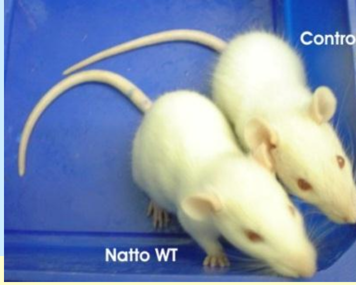
B. Subtilis inhibe competittivamente la adherencia de patógenos humanos a mucosas



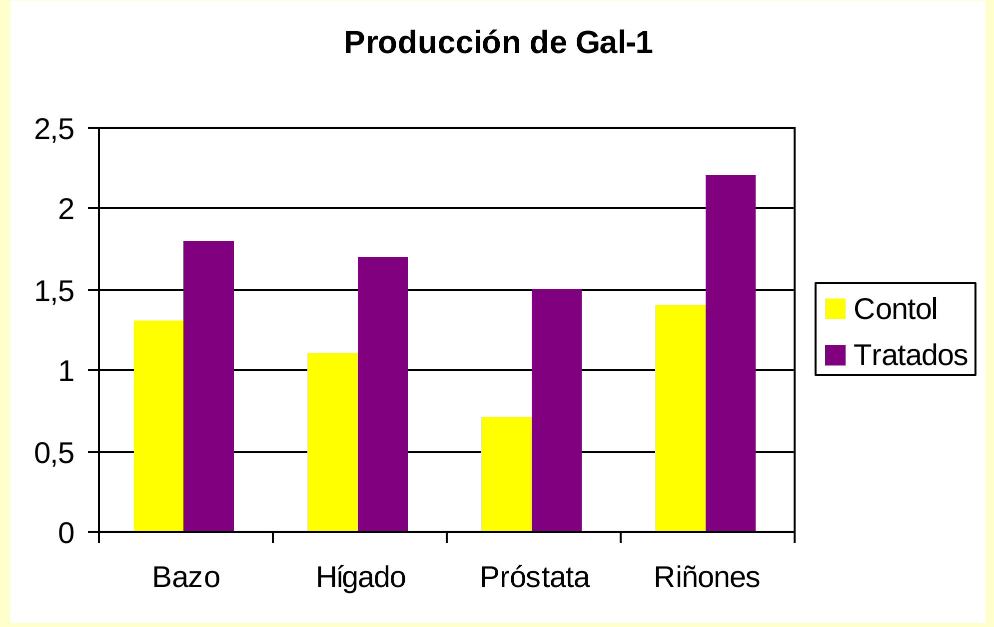


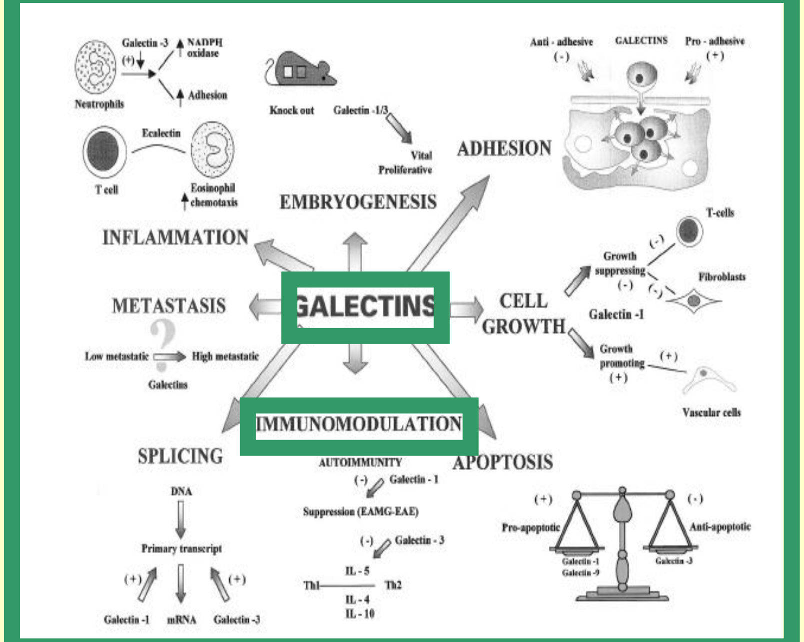


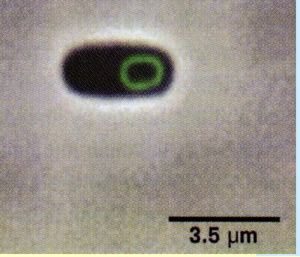
¿CUÁLES SON LOS EFECTOS BENEFICIOSOS DE LOS MICROORGANISMOS PROBIÓTICOS?



B. Subtilis induce la producción de Galectina-1 en órganos

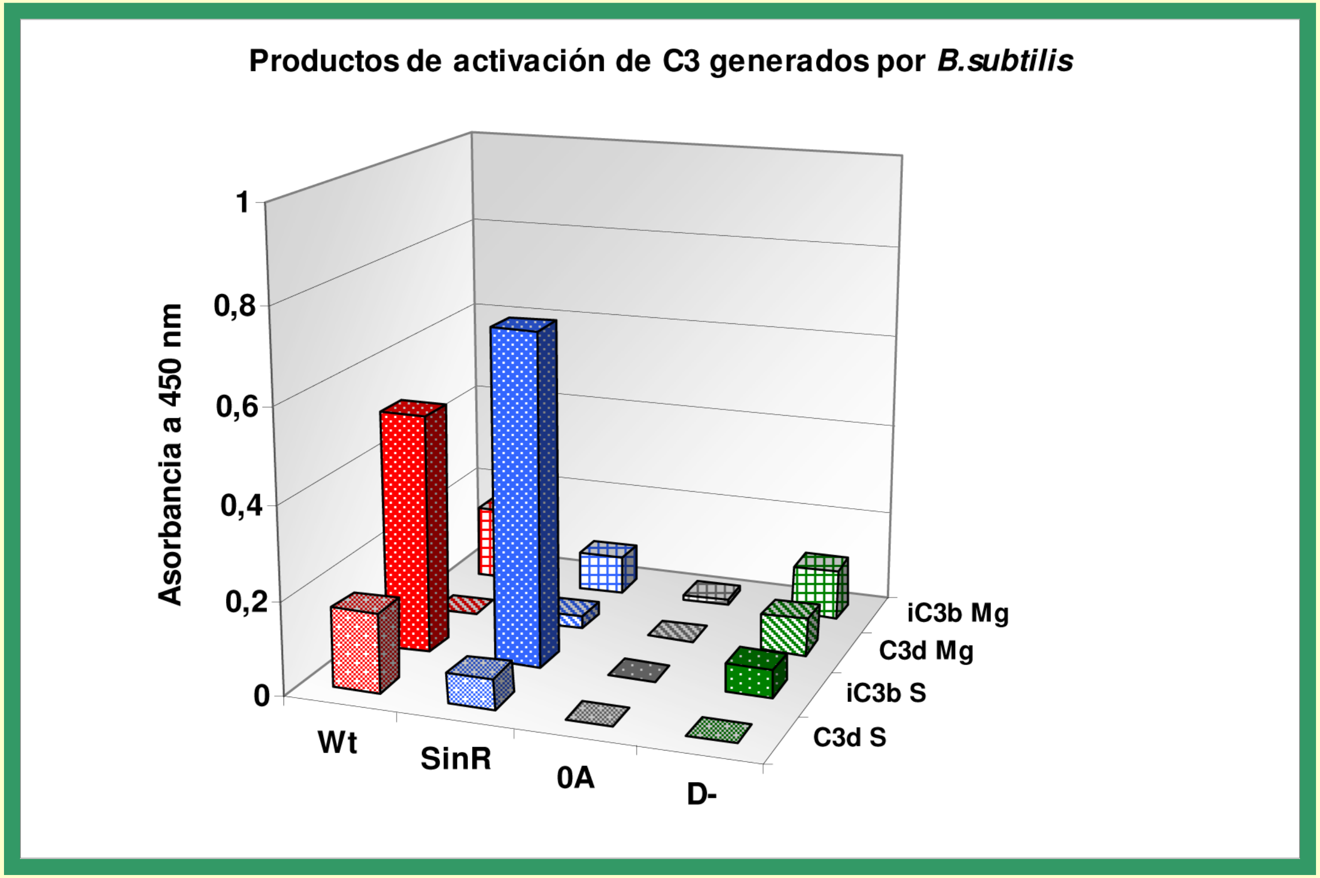


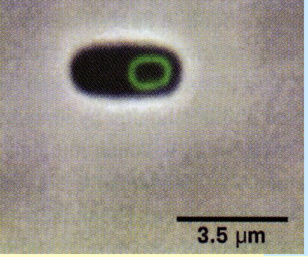




¿CUÁLES SON LOS EFECTOS BENEFICIOSOS DE LOS MICROORGANISMOS PROBIÓTICOS?

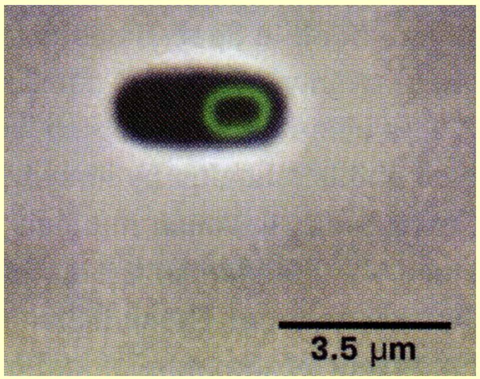
B. SUBTILIS ACTIVA LAS TRES VÍAS DEL SISTEMA DEL COMPLEMENTO A TRAVÉS DEL REGULADOR MAESTRO DE LA EXPRESIÓN DE GENES LA PROTEÍNA Spo0A

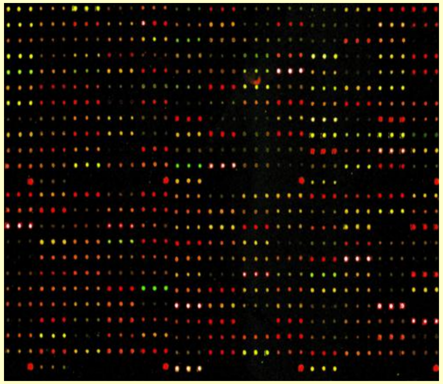


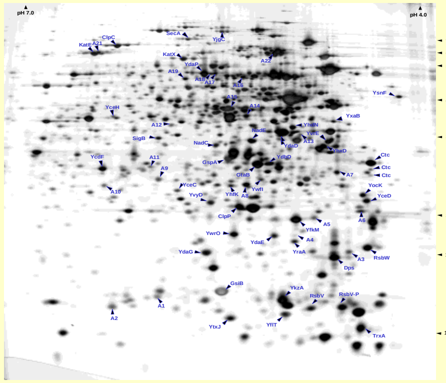


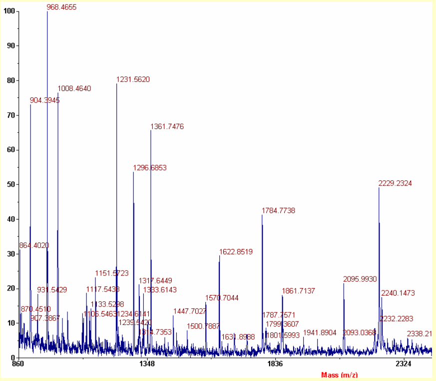
CONOCIMIENTO Y DOMINIO DE TODAS LAS OMICAS DE *B. SUBTILIS* DENTRO DE UNA PERSPECTIVA FISIOLÓGICA

ADN	ARN	Proteinas	Metabolitos





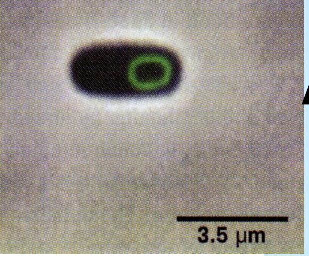




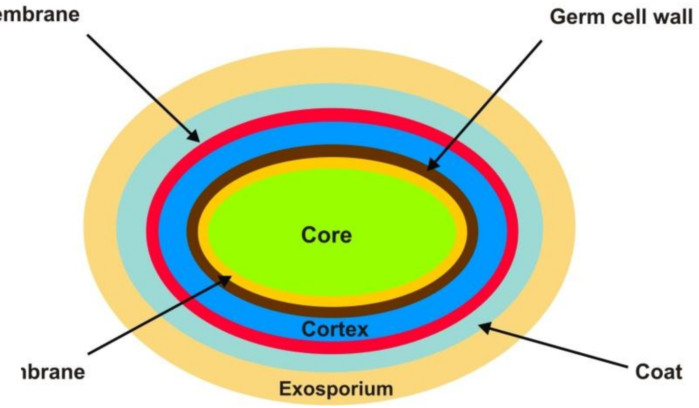
Gen**ómica**	Transcript**ómica**	Prote**ómica**	Metabol**ómica**

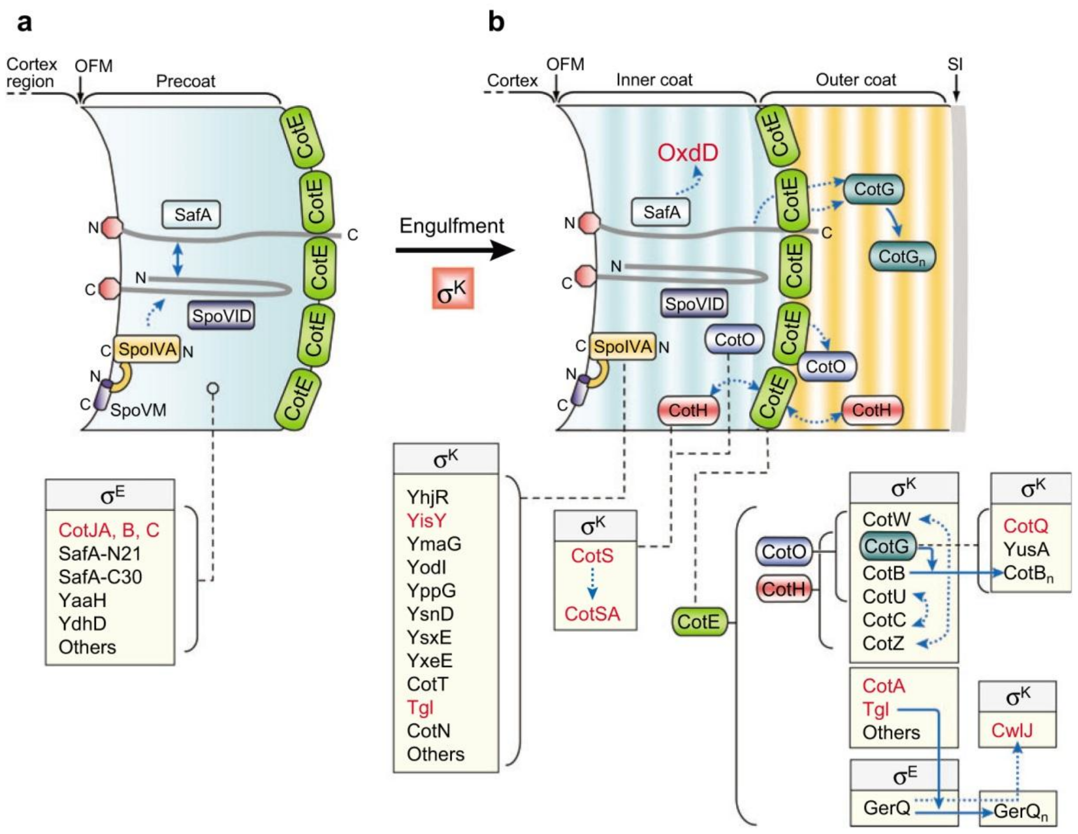
bioinformática

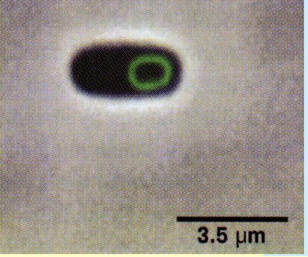
¿Qué podría posiblemente ocurrir ?	¿Qué ha ocurrido aparentemente?	¿Qué es lo que hace que esto ocurra?	¿ Qué ha ocurrido?



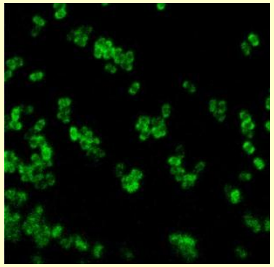
ALGUNAS OTRAS PROPIEDADES DE LAS ESPORAS
LAS PROTEÍNAS DE LA CUBIERTA

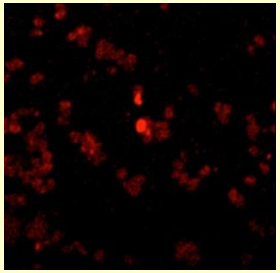


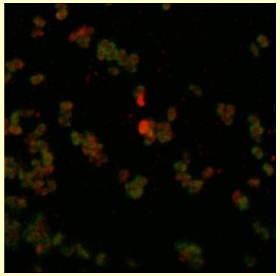




ADSORCIÓN DE VIRIONES INACTIVADOS DE H5N1 EN ESPORAS



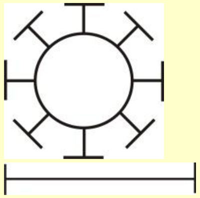




Esporas-FICT **NIBRG-14-TMR** **Superposición**

Song, Cutting et al., Vaccine: 2012

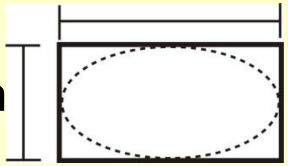
Virus H5N1

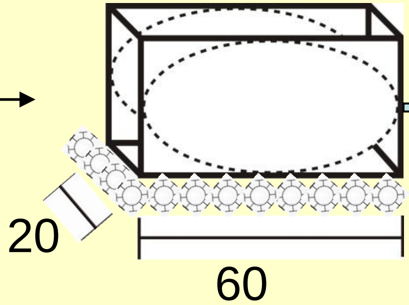


50 nm (0.05 μm)

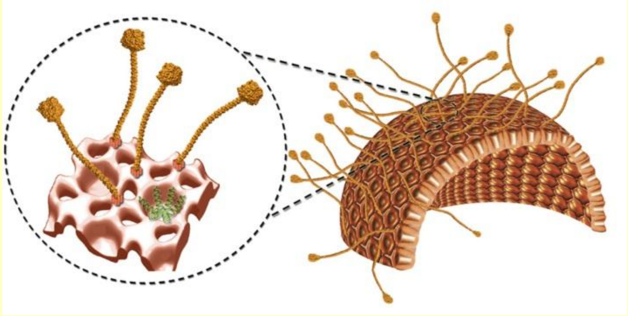
3.0 μm

1.0 μm

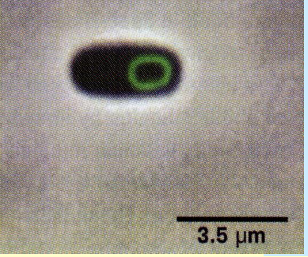




5600 virus / espora

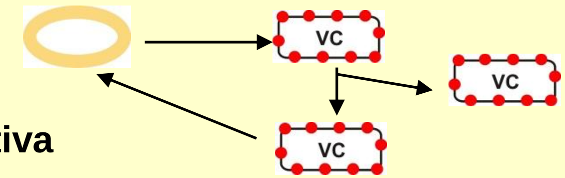


ESPORAS COMO VACUNAS MUCOSALES CON PROPIEDADES ADYUVANTES INTRÍNSECAS CONTRA INFLUENZA



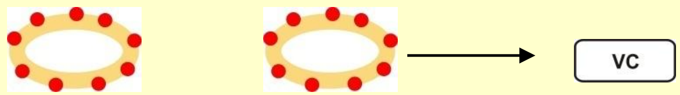
ESPORAS PROBIÓTICAS COMO ADYUVANTES, INMUNOPOTENCIADORES, INMUNOMODULADORES Y COMO VACUNAS NO-REFRIGERADAS MUCOSALES

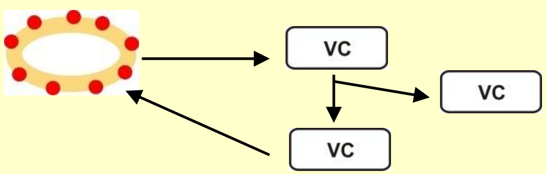
1- Espora viva



Antígeno expresado en la membrana de la Célula Vegetativa

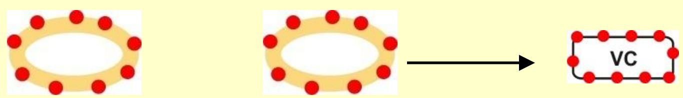
2- Espora viva

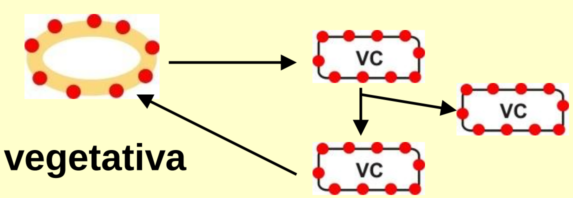




Antígeno expresado en la superficie de la espora

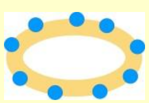
3- Espora viva





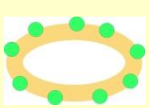
Antígeno expresado tanto en la espora como en la célula vegetativa

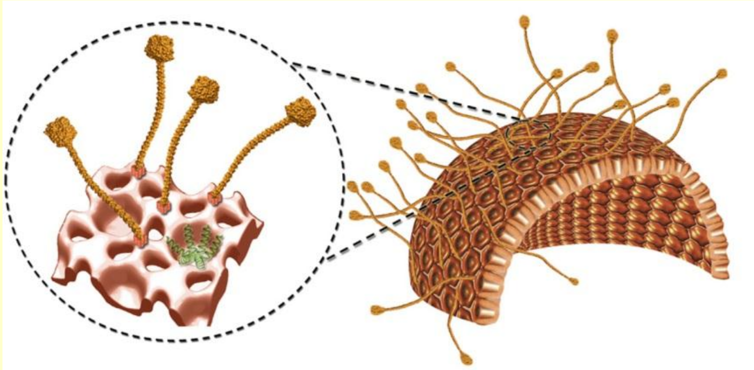
4- Espora muerta

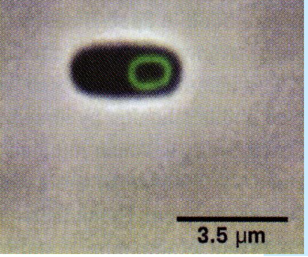


Antígeno expresado en la superficie de la espora

5- Espora muerta o viva con el antígeno adsorbido

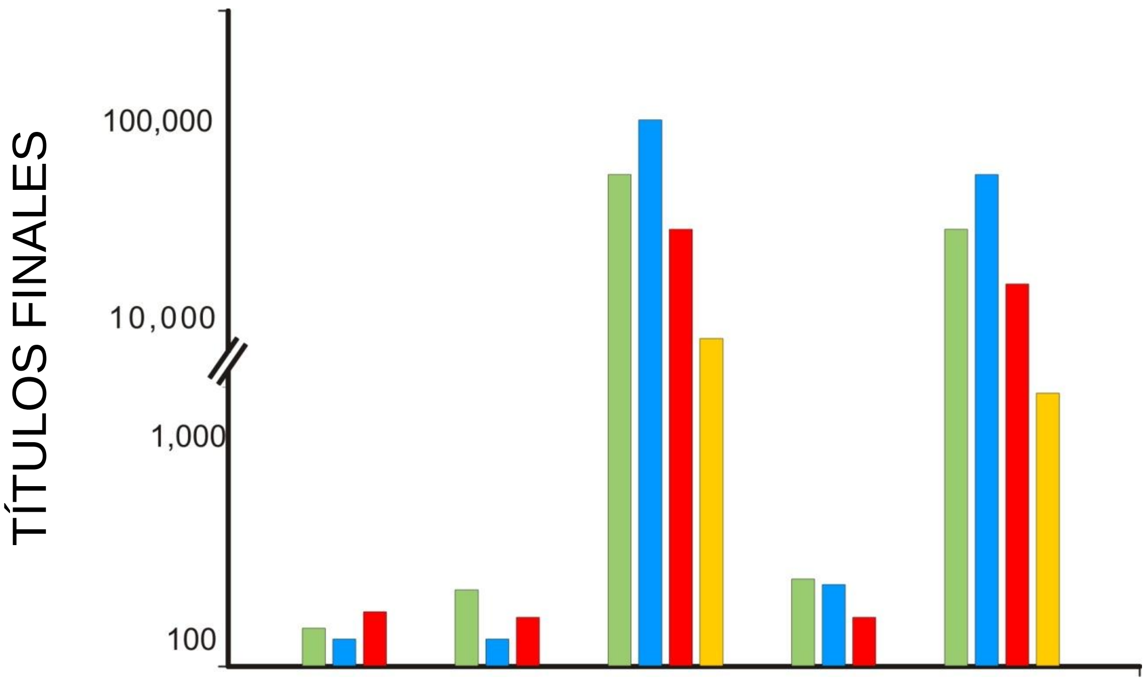




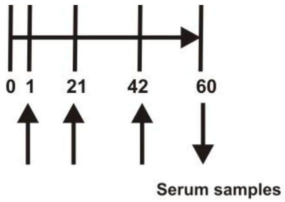


VACUNACIÓN POR VÍA NASAL CON ESPORAS RECOMBINANTES Ó CON ANTÍGENO ADSORBIDO

Vacunación contra Anthrax

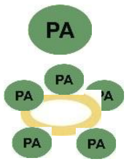


Producción de Ac específicos contra PA

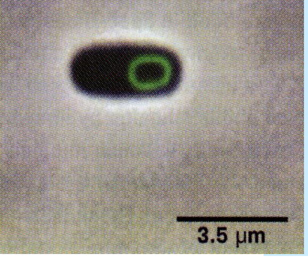


Ruta intranasal

Adaptado de Huang, Cutting et al., 2010

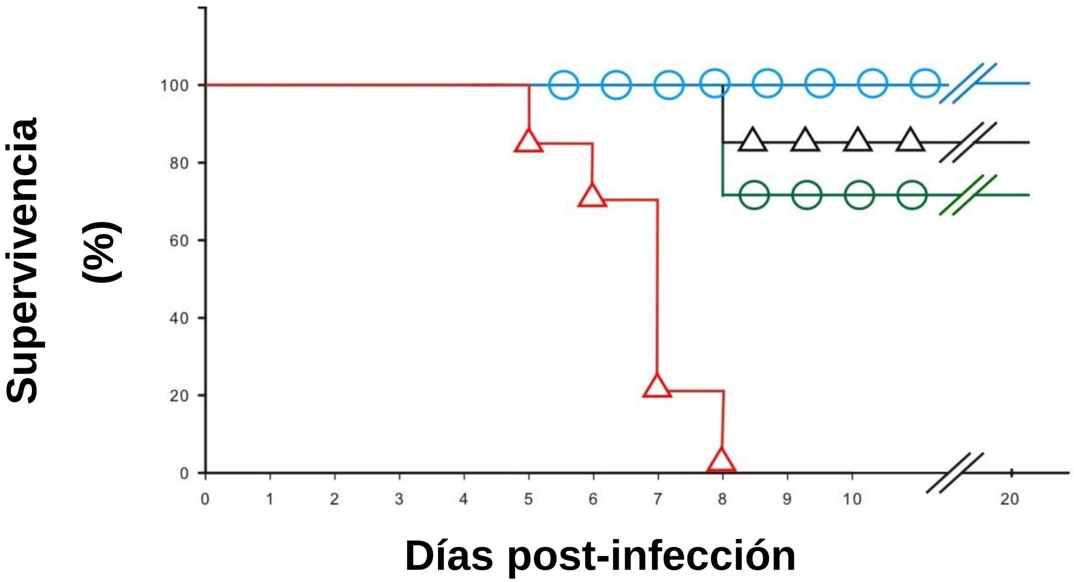


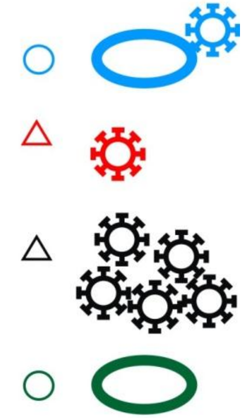
PA	-	-	-	+	-
PA adsorbido a espora	-	-	+	-	-
Espora recombinantee (amyE::cotB-GST-Cpa	-	-	-	-	+

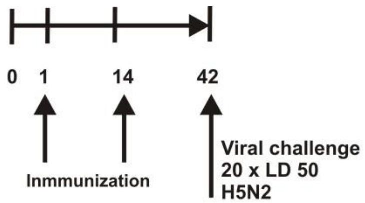


IMMUNIZACIÓN CONTRA INFLUENZA (H5N1) CON ESPORAS CON Ag ADSORBIDOS

Experimento de protección contra desafíos con dosis letales (20 x LD50) de influenza (H5N2)



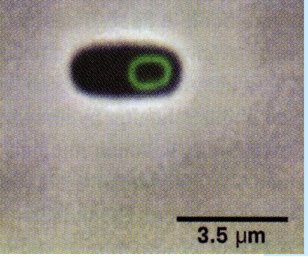




Adaptado de Song M., Cuttings S.M. et al

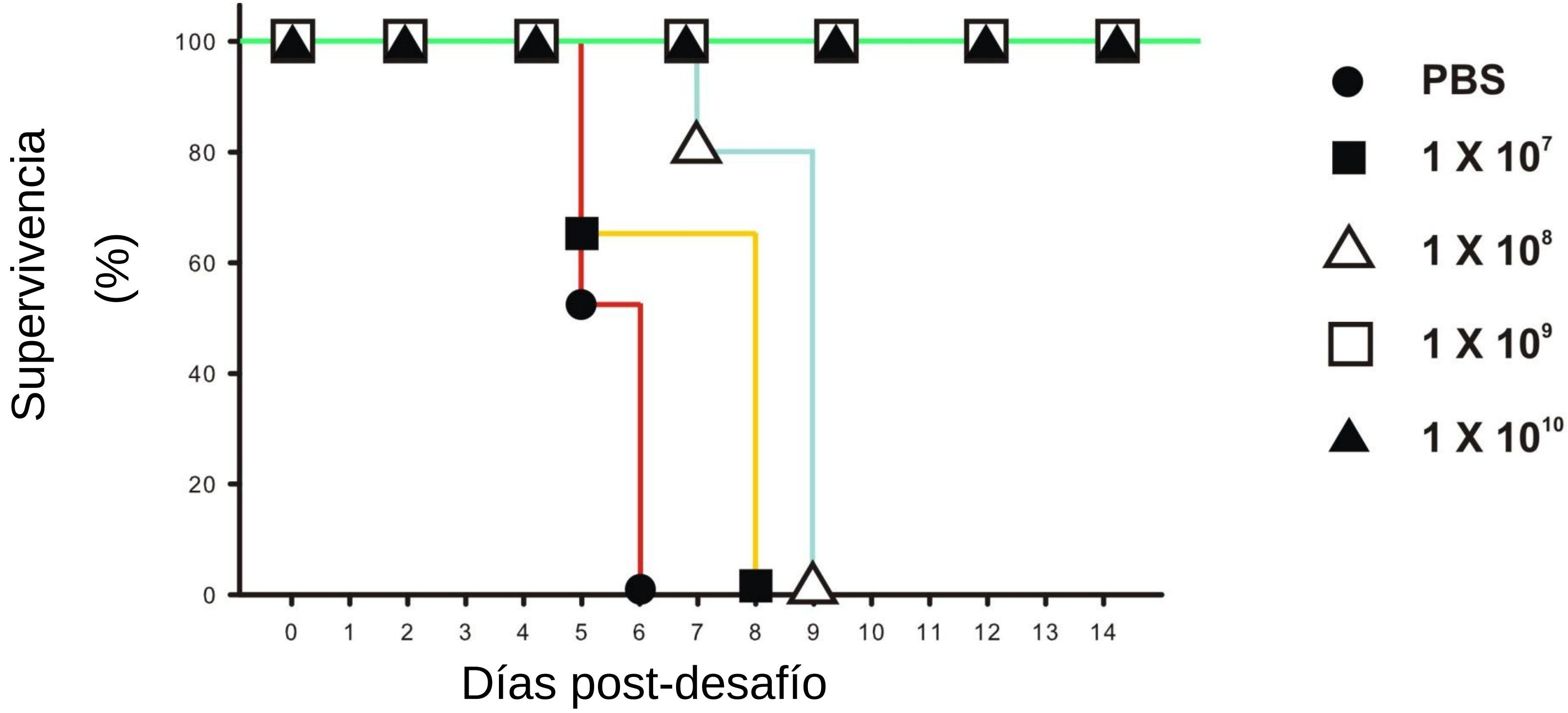
Vaccine: 2012

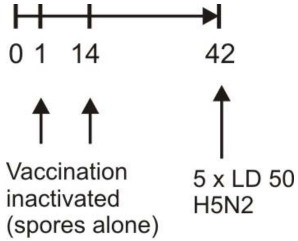
NIBRG-14 inactivado
Y / o esporas



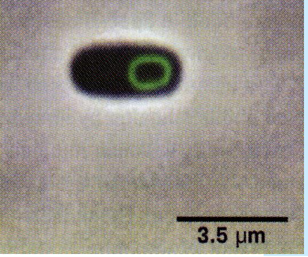
IMMUNIZACIÓN CONTRA INFLUENZA (H5N2) CON ESPORAS SOLAMENTE

Protección brindada por esporas desnudas contra (5 x LD50) de virus H5N2



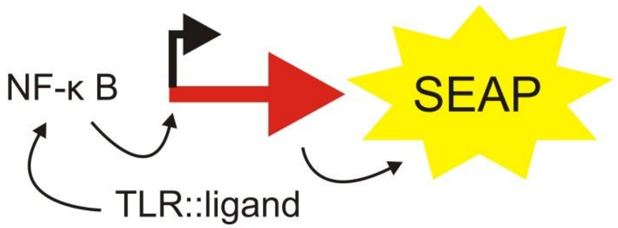


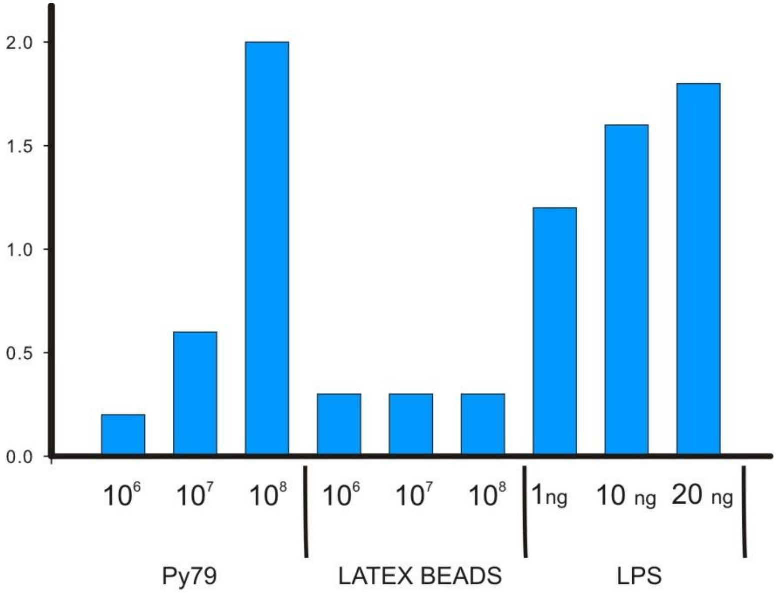
LA IMPORTANCIA DE LA ESTIMULACIÓN DE LA INMUNIDAD INNATA PARA PREVENIR INFECCIONES



INDUCCIÓN TLR ("Toll-Like Receptor") DEPENDIENTE DE NF-KB POR ESPORAS

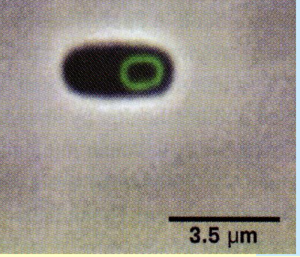
Línea celular de macrófagos murinos Raw blue de INVITROGEN





Las esporas también inducen

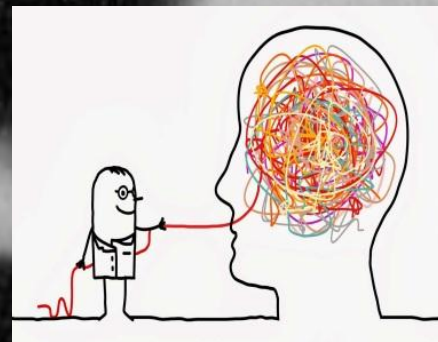
- **Maduración de las Dc**
- **Reclutamiento de células NK en las vías aéreas**
- **Expresión de TLRs (TLR2, TLR4)**
- **Proliferación celular en las Placas de Peyer**
- **Desarrollo del Tejido Linfoideo Asociado a Intestino (GALT)**
- **Diversificación somática de los genes IgM VDJ -Cμ de células B**

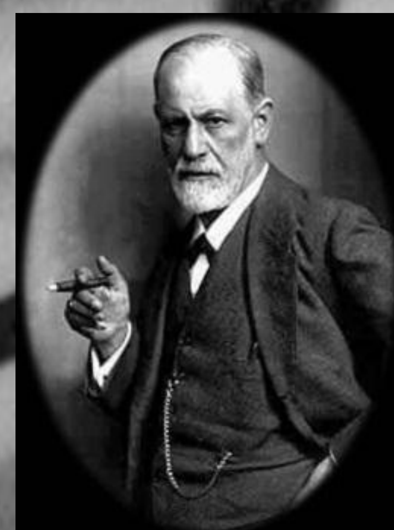


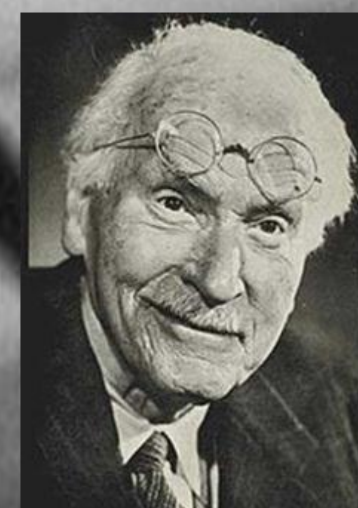
¿CUÁLES SON LOS EFECTOS BENEFICIOSOS DE LOS MICROORGANISMOS PROBIÓTICOS?

Y AÚN MÁS…

¿CUÁLES SON LOS PRINCIPALES MIEDOS DE LAS PERSONAS?

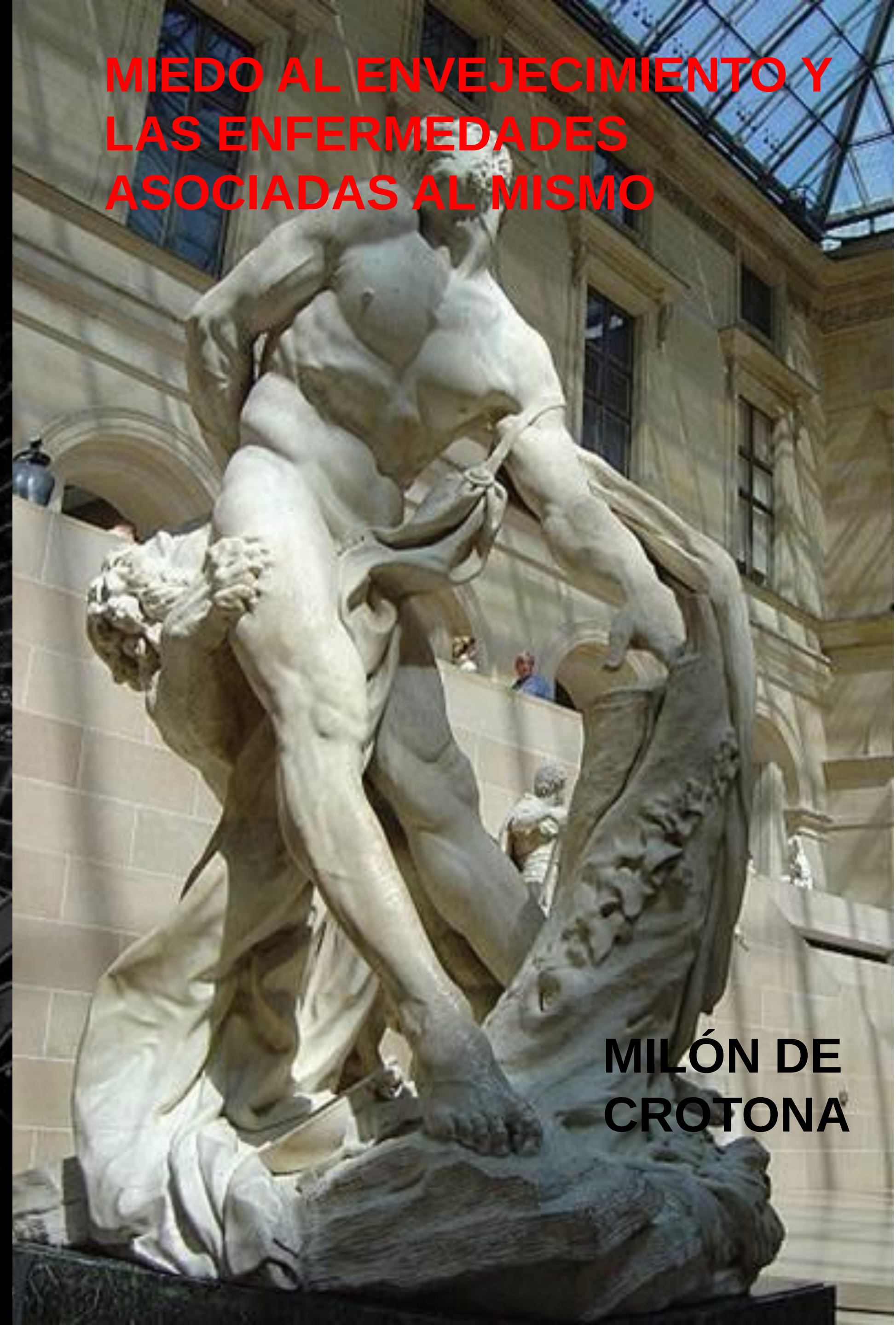






MIEDO A LA MUERTE

MIEDO AL ENVEJECIMIENTO Y LAS ENFERMEDADES ASOCIADAS AL MISMO



MILÓN DE CROTONA

¿POR QUÉ MUERE LA GENTE?

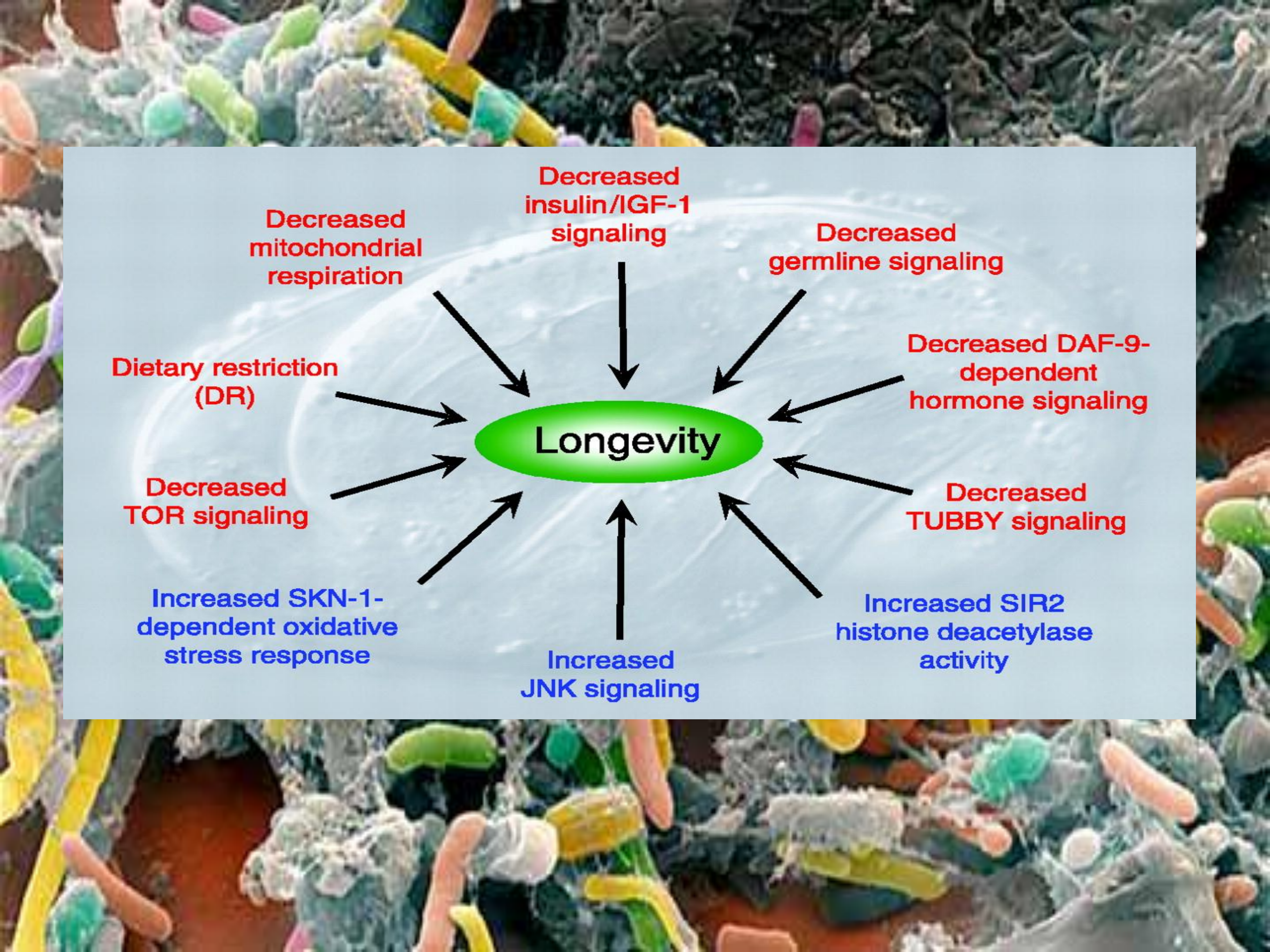
DEJANDO DE LADO LAS MUERTES VIOLENTAS POR ACCIDENTES, GUERRAS, ASESINATOS, ATENTADOS….

LA MUERTE NATURAL SE PRODUCE POR DOS CAUSAS:

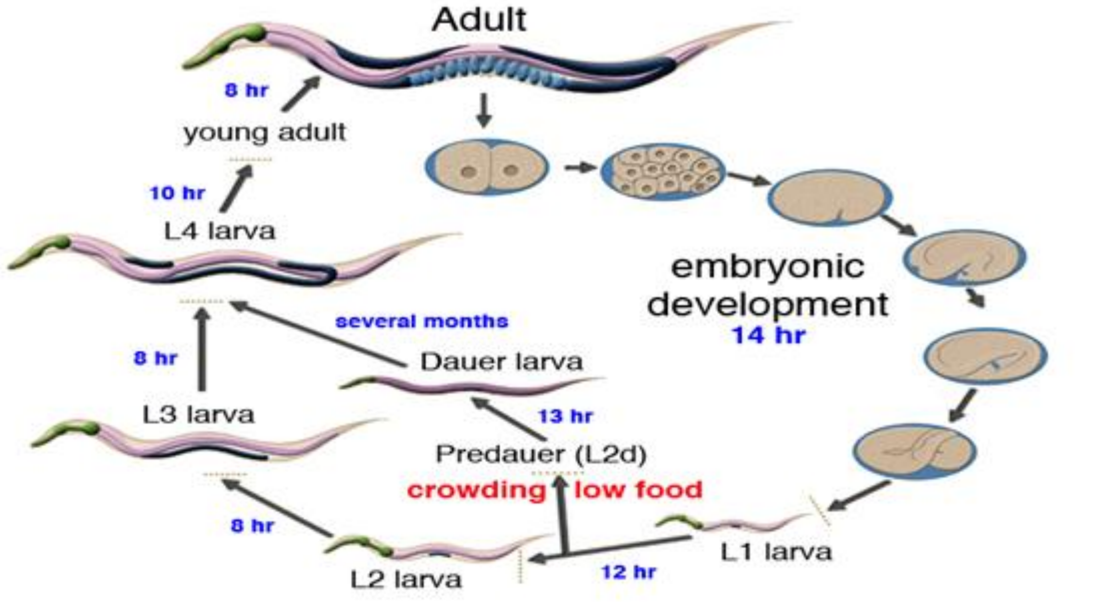
1- MORIMOS PORQUE NOS ENFERMAMOS

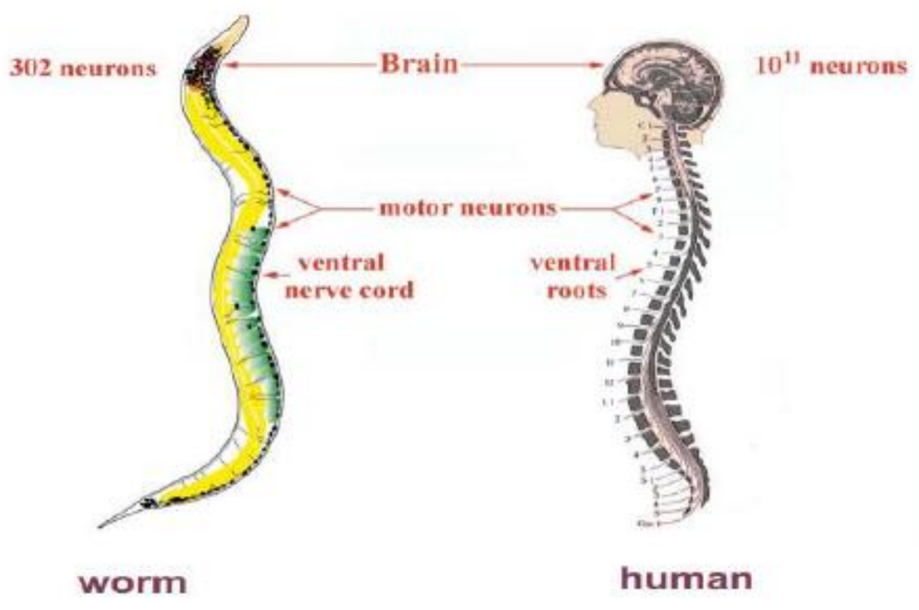
2- MORIMOS PORQUE ENVEJECEMOS

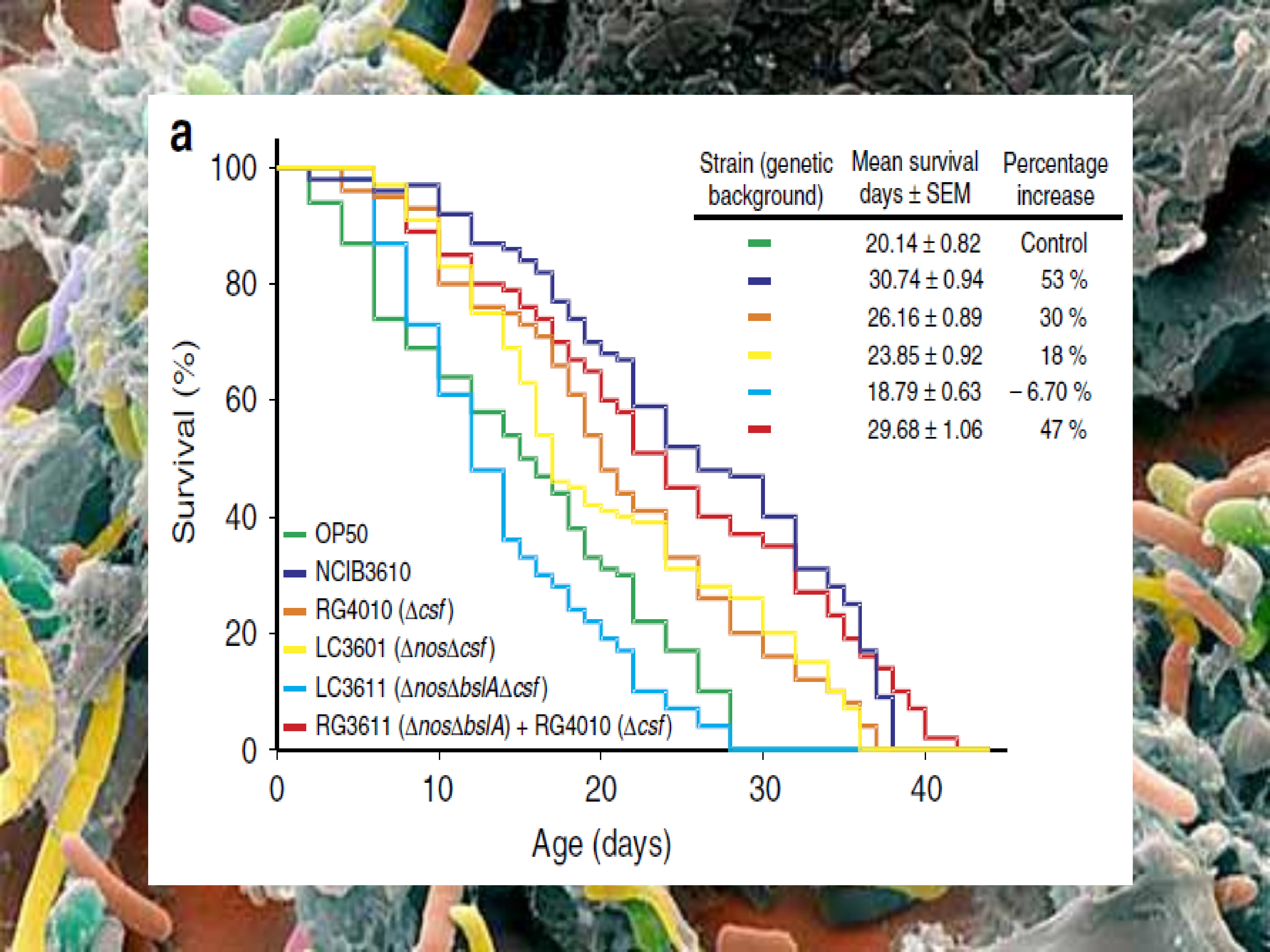
¿PUEDEN LOS PROBIÓTICOS CONTRIBUIR PARA ENVEJECER MÁS LENTAMENTE Y ASÍ ALCANZAR UNA MAYOR LONGEVIDAD?


Decreased insulin/IGF-1 signaling
Decreased mitochondrial respiration
Decreased germline signaling
Dietary restriction (DR)
Decreased DAF-9-dependent hormone signaling
Longevity
Decreased TOR signaling
Decreased TUBBY signaling
Increased SKN-1-dependent oxidative stress response
Increased SIR2 histone deacetylase activity
Increased JNK signaling

Ciclo de vida de *C. elegans*






a
Survival (%)
Age (days)
0
10
20
30
40
100
80
60
40
20
0
Strain (genetic background)
Mean survival days ± SEM
Percentage increase
20.14 ± 0.82
Control
30.74 ± 0.94
53 %
26.16 ± 0.89
30 %
23.85 ± 0.92
18 %
18.79 ± 0.63
− 6.70 %
29.68 ± 1.06
47 %
OP50
NCIB3610
RG4010 (Δcsf)
LC3601 (ΔnosΔcsf)
LC3611 (ΔnosΔbslAΔcsf)
RG3611 (ΔnosΔbslA) + RG4010 (Δcsf)

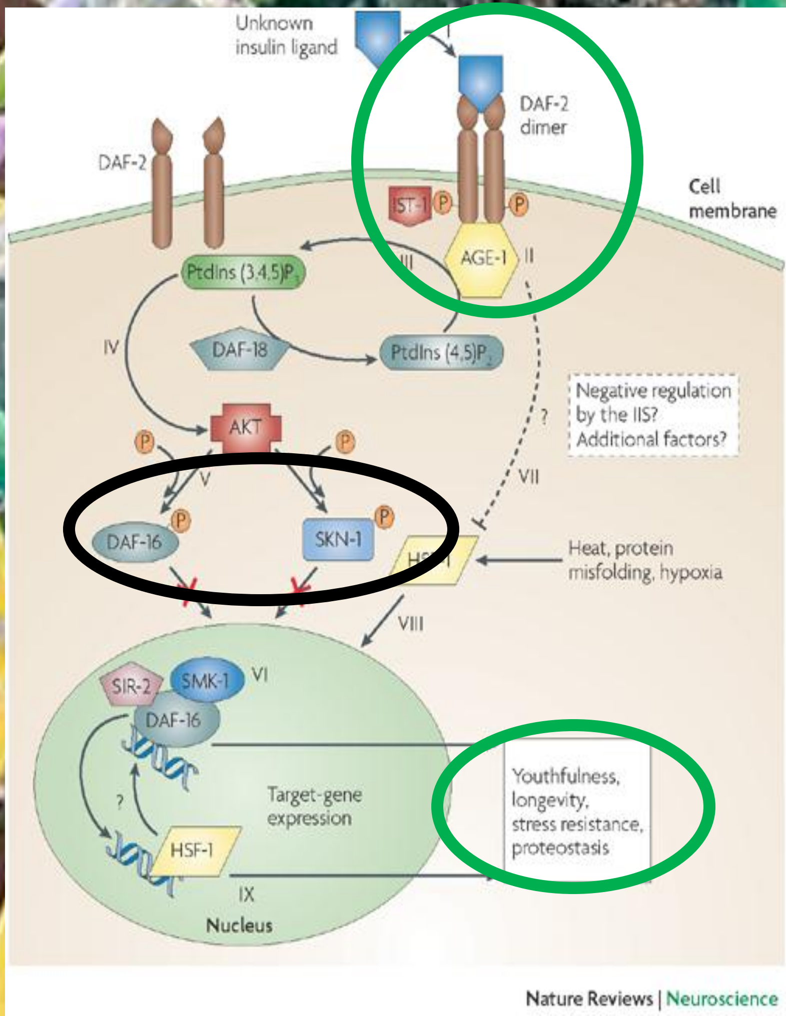
nature COMMUNICATIONS

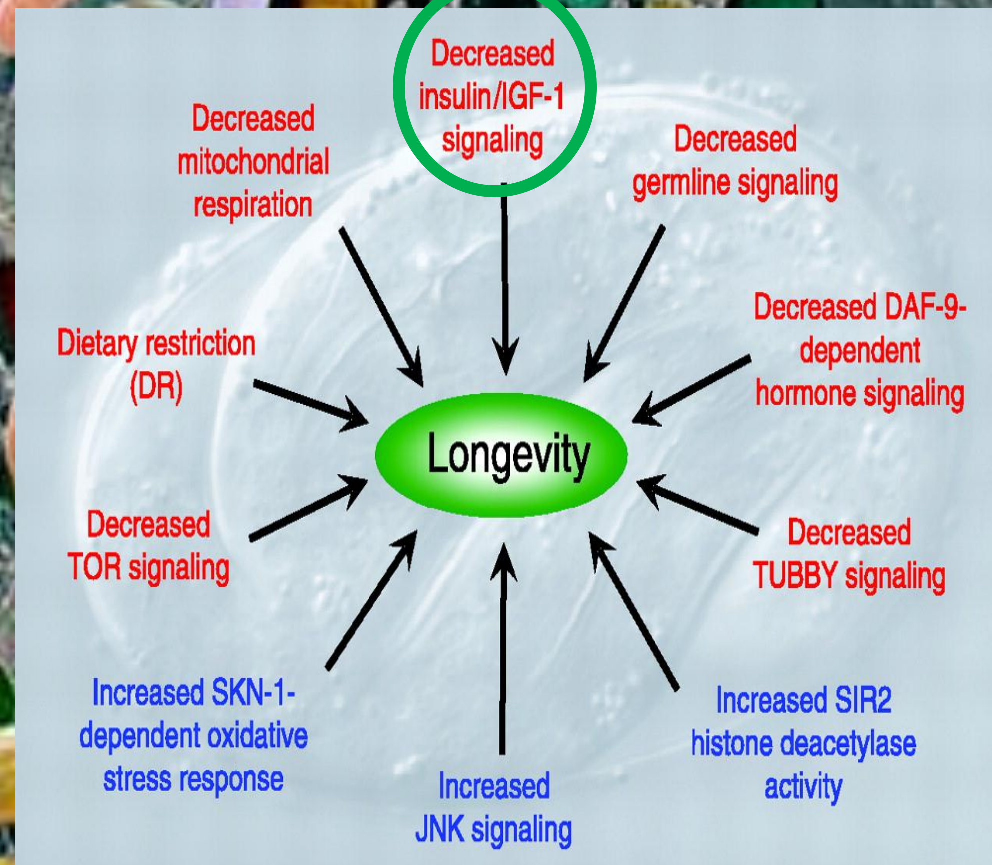
ARTICLE

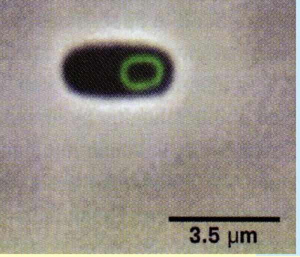
Received 17 Jul 2016 | Accepted 19 Dec 2016 | Published 30 Jan 2017 DOI: 10.1038/ncomms14332 OPEN

Bacillus subtilis biofilm extends *Caenorhabditis elegans* longevity through downregulation of the insulin-like signalling pathway

Verónica Donato[1,*], Facundo Rodríguez Ayala[1,*], Sebastián Cogliati[1,*], Carlos Bauman[1], Juan Gabriel Costa[1], Cecilia Leñini[1] & Roberto Grau[1]





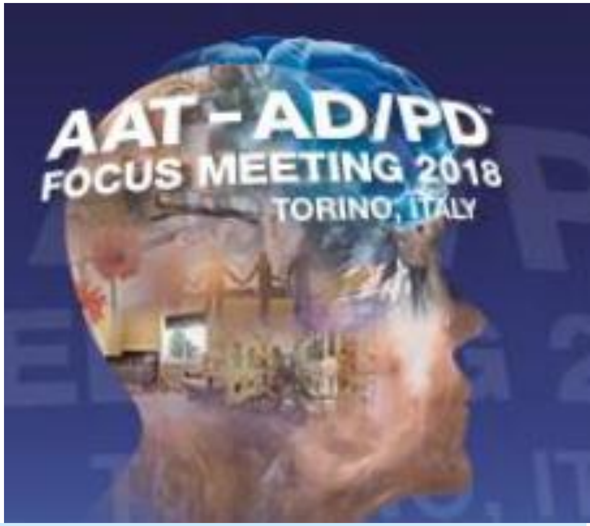


¿CUÁLES SON LOS EFECTOS BENEFICIOSOS DE LOS MICROORGANISMOS PROBIÓTICOS?

Y AÚN Y MÁS,MÁS Y MUCHO MÁS…

ADVANCES IN ALZHEIMER'S AND PARKINSON'S THERAPIES AN AAT-AD/PD FOCUS MEETING

15-18 MARCH 2018 I TORINO, ITALY



PROBIOTIC Bacillus subtilis PREVENTS ALFA-SYNUCLEIN AGGREGATION AND EXTENDS THE HEALTHY LIFESPAN IN PARKINSON DISEASE MODEL Caenorhabditis elegans

Dr. Roberto Ricardo Grau and Marcos Francisco

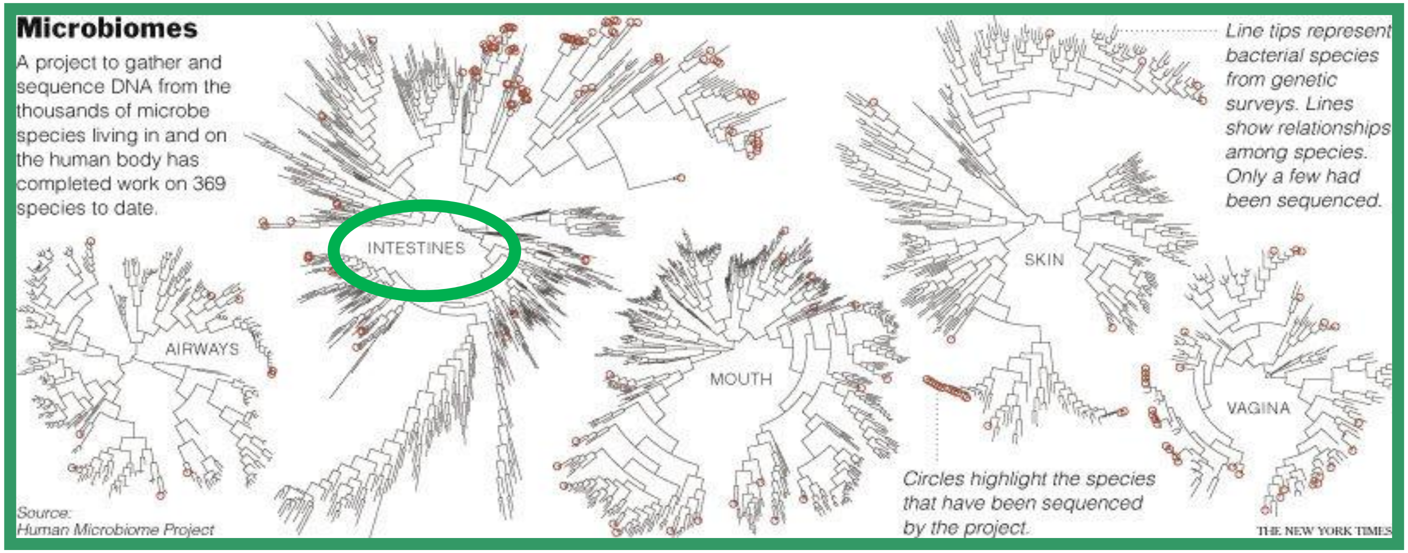
Departamento de Microbiología. Facultad de Bioquímica y Farmacia, Universidad Nacional de Rosario.
CONICET – Rosario
www.microbiologyrosario.org
ARGENTINA

Universidad Nacional de Rosario

Consejo Nacional de Investigaciones

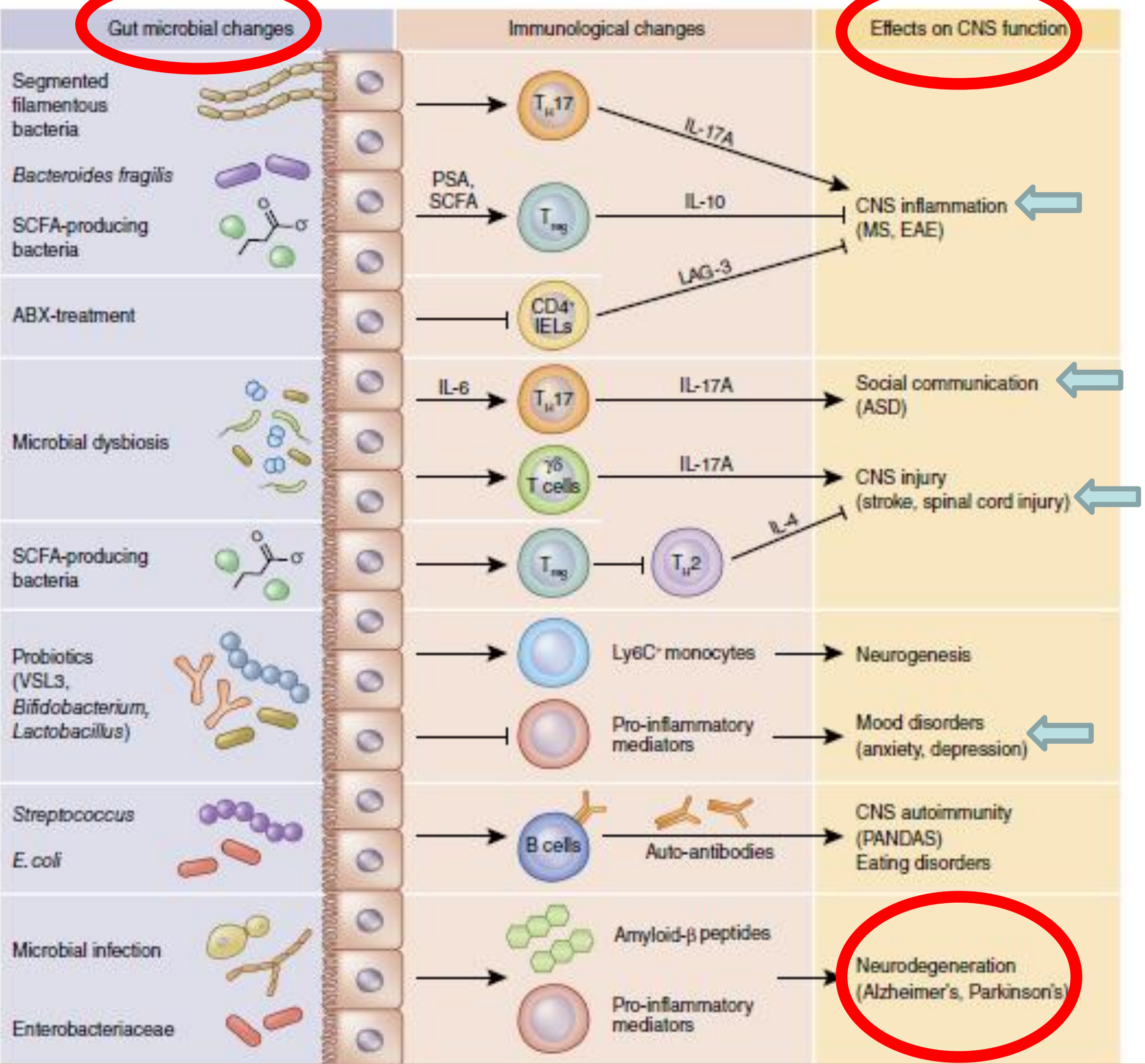
The number of microbes contained in 1 mL of intestinal juice represents 100,000 times the total human population.

HMP
HUMAN MICROBIOME PROJECT



Interactions between the microbiota, immune and nervous systems in health and disease

NATURE NEUROSCIENCE VOLUME 20 | NUMBER 2 | FEBRUARY 2017



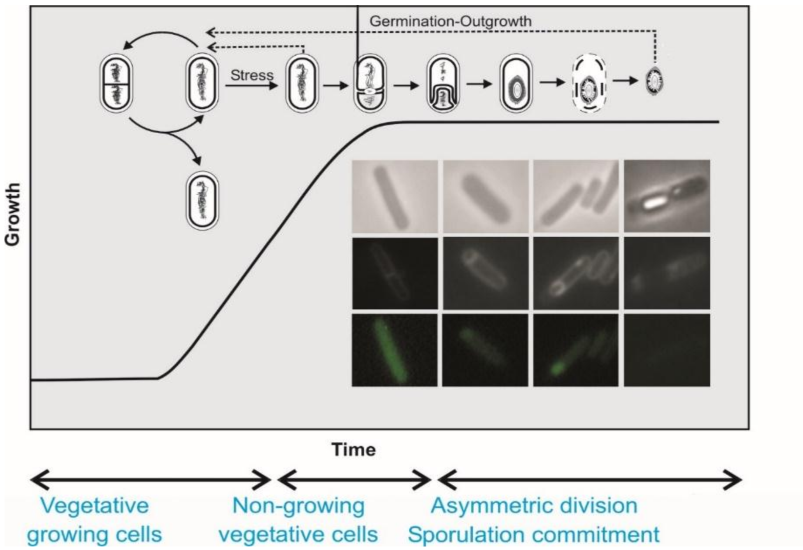
THE GUT FLORA IS VERY IMPORTANT FOR THE BRAIN FUNCTIONS, AND PROBIOTICS CONSTITUTE AN IMPORTANT COMPONENT OF THAT FLORA

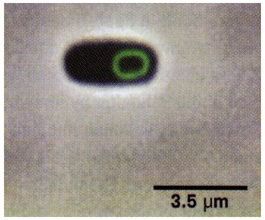
WHAT IS A PROBIOTIC?

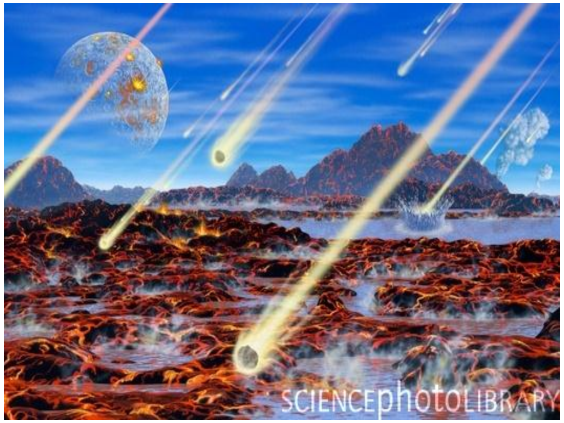
Probiotics are live microorganisms (mainly bacteria) that, when consumed in adequate amounts and arrive to the mucosa, produce beneficial health effects on host.

WHAT BACTERIA DO WE USE AS A PROBIOTIC?

Bacillus subtilis



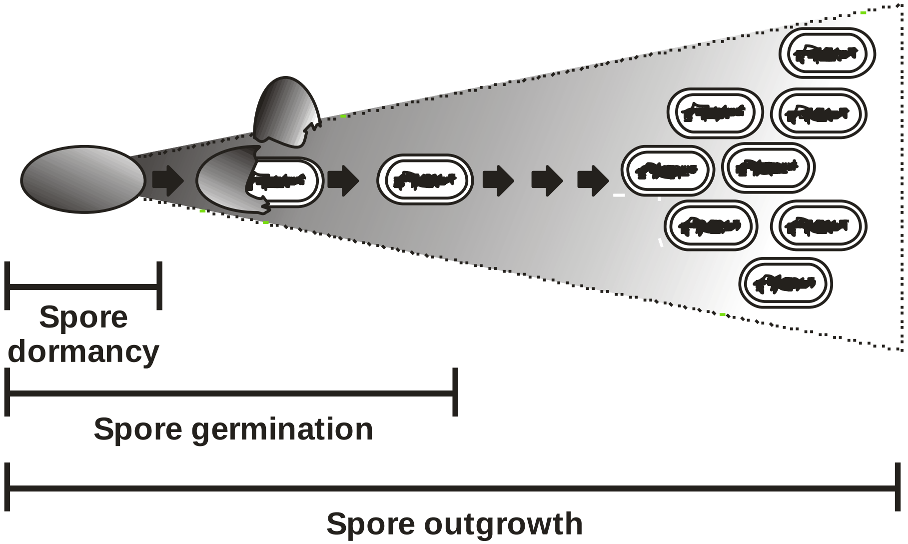




Resistance of *Bacillus* Endospores to Extreme Terrestrial and Extraterrestrial Environments

WAYNE L. NICHOLSON,[1*] NOBUO MUNAKATA,[2] GERDA HORNECK,[3] HENRY J. MELOSH,[4] AND PETER SETLOW[5]

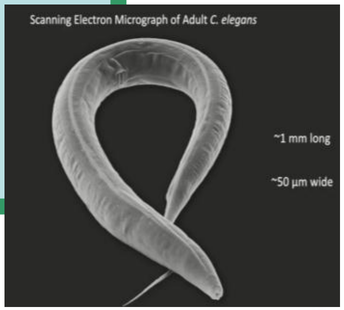
Department of Veterinary Science and Microbiology[1] and Lunar and Planetary Laboratory,[4] University of Arizona, Tucson, Arizona 85721; Radiobiology Division, National Cancer Center Research Institute, Tokyo, Japan 104-0045[2]; Radiobiology Section, DLR, Institute of Aerospace Medicine, Cologne, Germany[3]; and Department of Biochemistry, University of Connecticut Health Center, Farmington, Connecticut 06032[5]



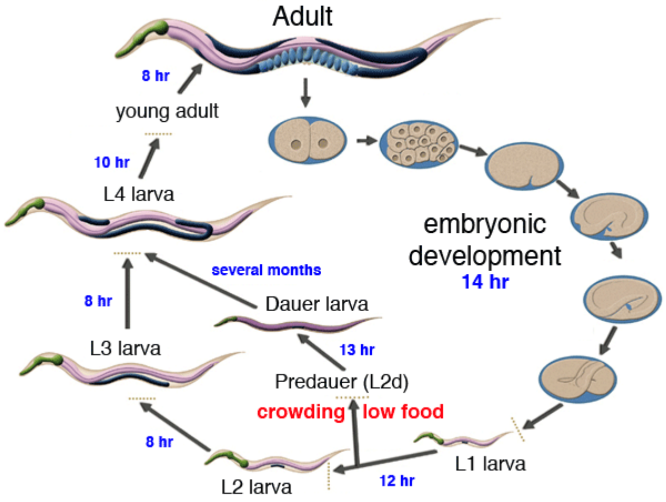
SPORE PANSPERMIA

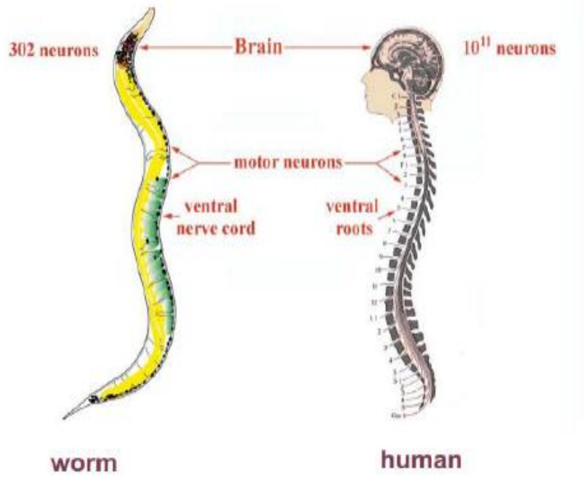
PROBIOTIC EFFECTS

WHAT MODEL ORGANISM DO WE USE TO STUDY THE PROBIOTIC EFFECT ON PARKINSON DISEASE?



The Genetics of Caenorhabditis elegans, 1973





ELSEVIER

Parkinsonism and Related Disorders 7 (2001) 185–191

Parkinsonism & Related Disorders

www.elsevier.com/locate/parkreldis

C. elegans: a novel pharmacogenetic model to study Parkinson's disease

R. Nass[a,c], D.M. Miller III[b,c], R.D. Blakely[a,c,*]

[a]*Department of Pharmacology, Vanderbilt University School of Medicine, MRBII, Room 419, Nashville, TN 37232-6600, USA*
[b]*Department of Cell Biology, Vanderbilt University School of Medicine, Nashville, TN 37232-2175, USA*
[c]*Center for Molecular Neuroscience, Vanderbilt University School of Medicine, Nashville, TN 37232-6420, USA*

Bacillus subtilis colonizes the gut of C. elegans and extends its longevity

nature COMMUNICATIONS

ARTICLE

Received 17 Jul 2016 | Accepted 19 Dec 2016 | Published 30 Jan 2017

DOI: 10.1038/ncomms14332

OPEN

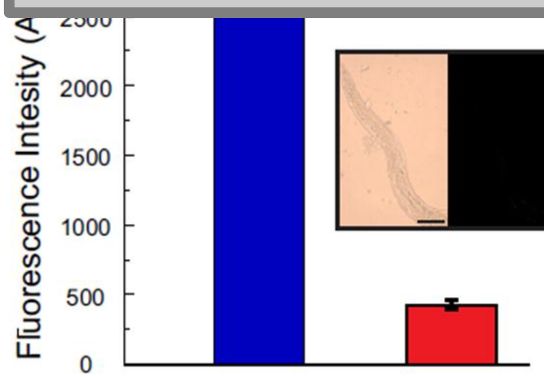
Bacillus subtilis biofilm extends *Caenorhabditis elegans* longevity through downregulation of the insulin-like signalling pathway

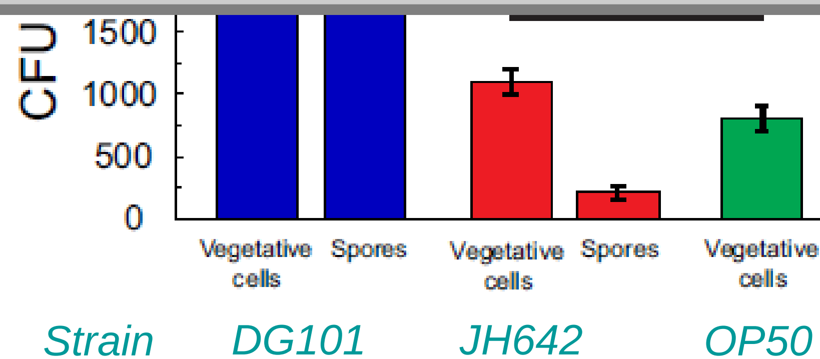
Verónica Donato[1,*], Facundo Rodríguez Ayala[1,*], Sebastián Cogliati[1,*], Carlos Bauman[1], Juan Gabriel Costa[1], Cecilia Leñini[1] & Roberto Grau[1]

***B. subtilis* delays aging and improves healthy lifespan,**

and delaying aging is neuroprotective in PD.

Then, does B. subtilis protect against PD?

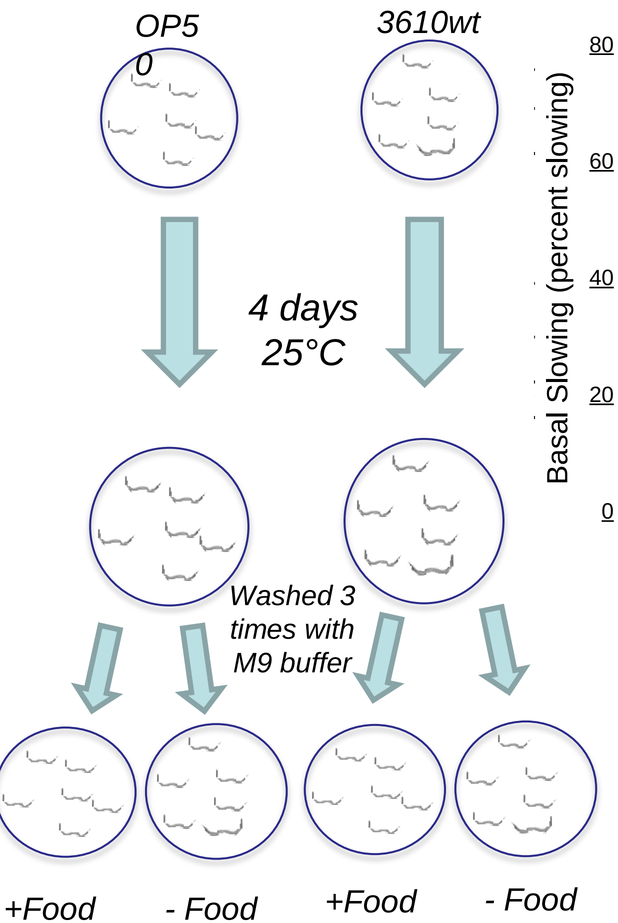


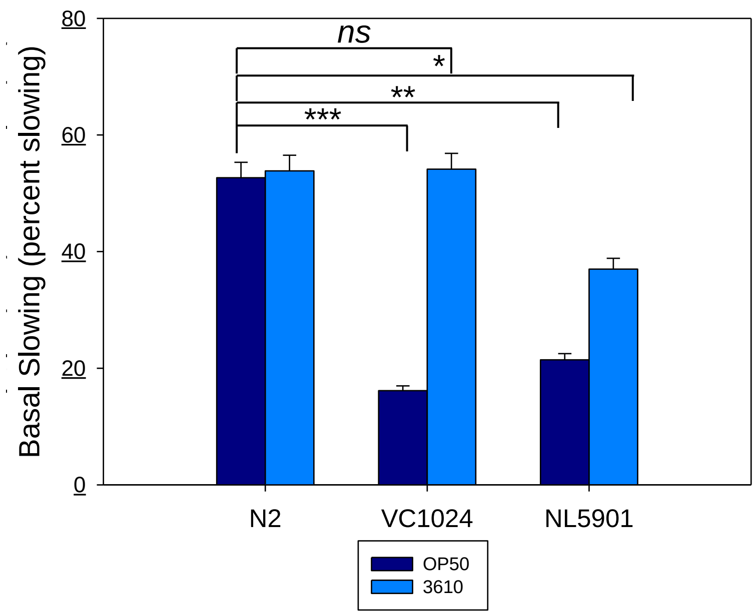


Bacillus subtilis restores dopamine-dependent behaviors

Basal Response to food

OP50: no probiotic E. coli strain
3610: Probiotic B. subtilis strain DG101





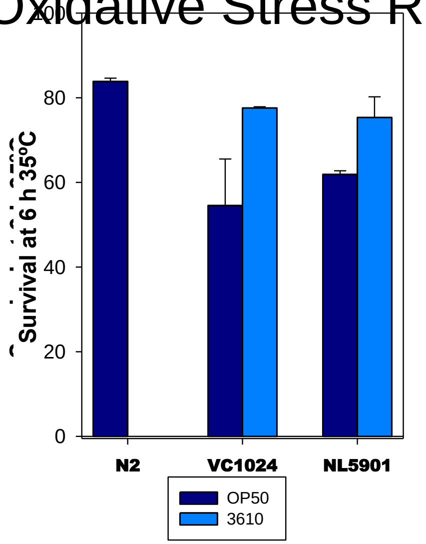
Strain	% Slowing + SEM
N2 OP50	52,674 ± 2,633
N2 NCBI3610 wt	53,846 ± 2,692
VC1024 OP50	16,161 ± 0,808
VC1024 NCBI3610 wt	54,144 ± 2,707
NL5901 OP50	21,428 ± 1,071
NL5901 NCBI3610 wt	37,007 ± 1,850

$$Basal\ Slowing = \frac{body\ bends(-Food) - body\ bends(+Food)}{body\ bends(-Food)}$$

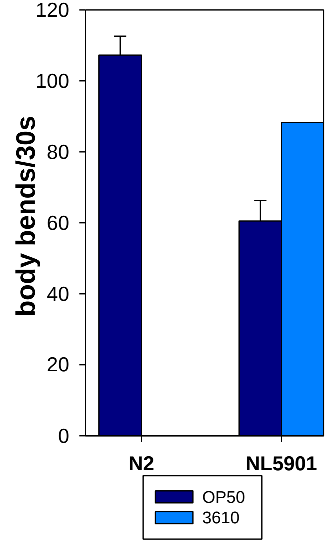
- **NL5901**: *over-expresses human PARK1 (alpha-synuclein)*
- **VC1024**: *Pdr1 (PARK2) mutant*

Bacillus subtilis restores most of dopamine-dependent behaviors

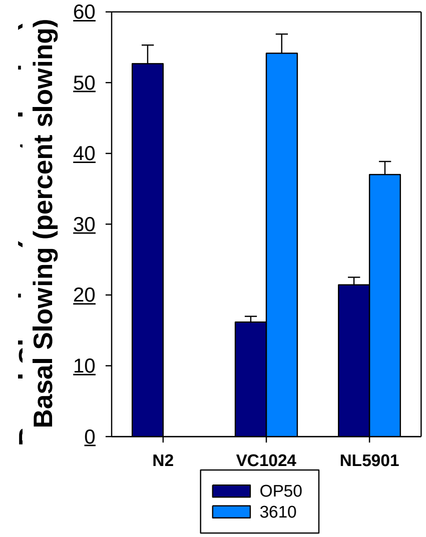
Oxidative Stress Response



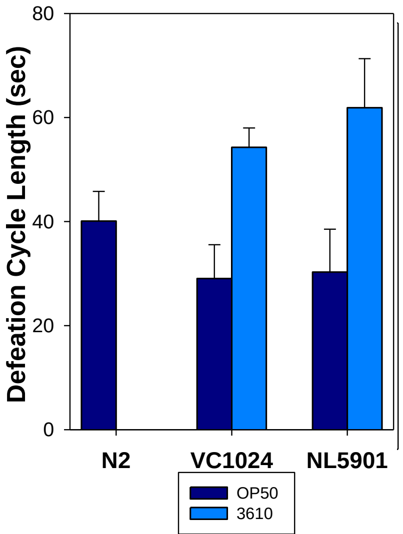
Movement Deficits



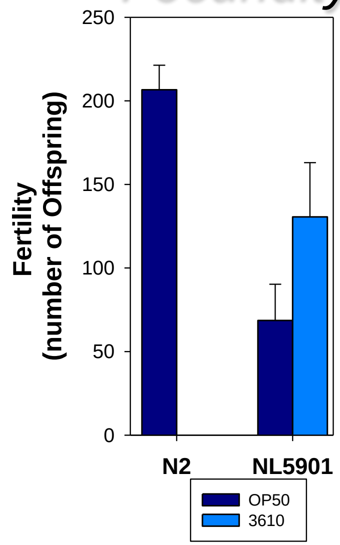
Food behavior



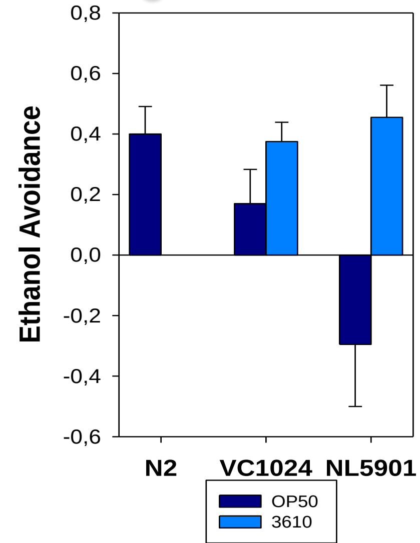
Constipation



Fecundity



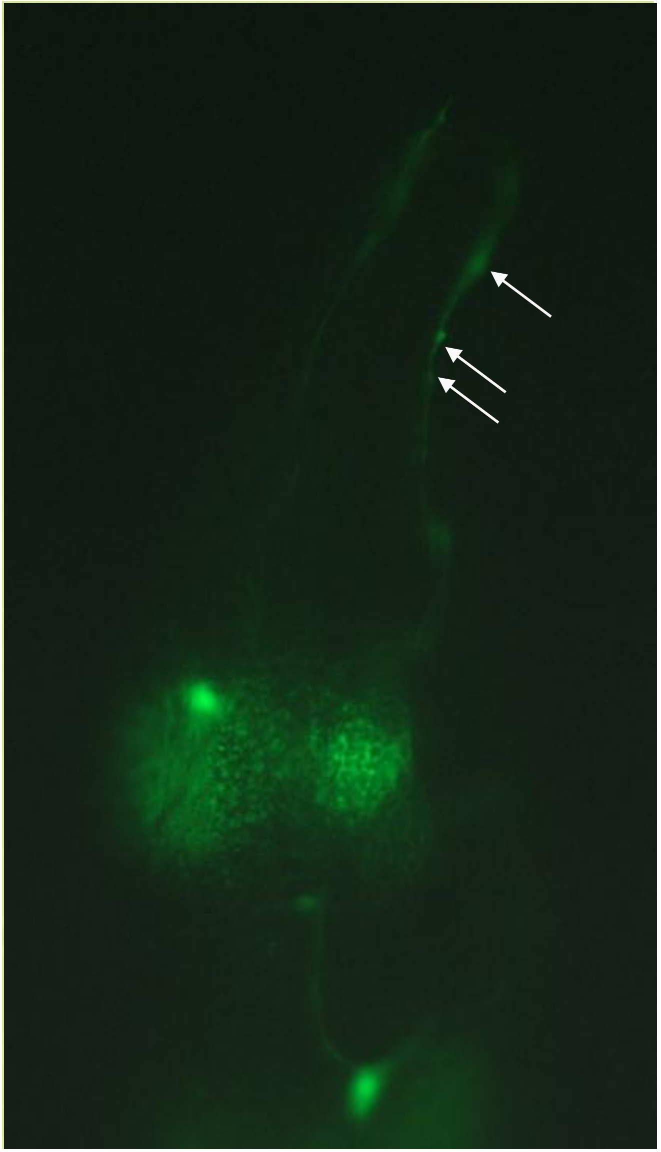
Danger Avoidance



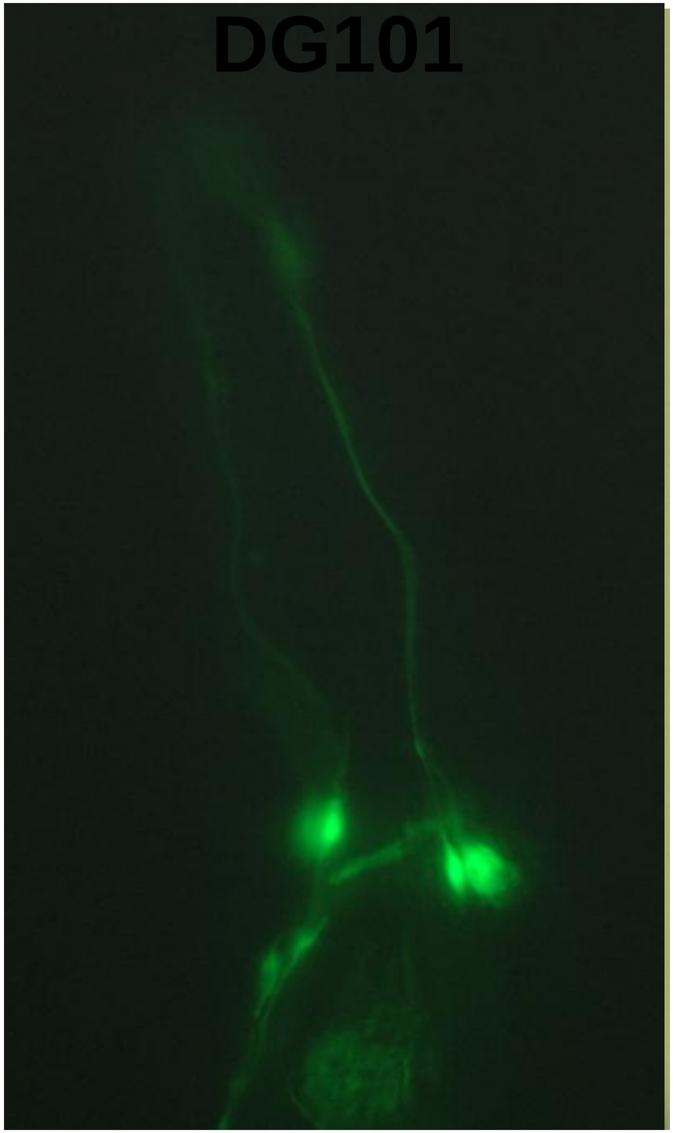
B. subtilis prevents degeneration of dopaminergic neurons

DOPA-neurons express GFP and also overporduce dopamine that accelerates their death. Arrows indictae dendritic gaps and ampoules.

UA57 fed on OP50



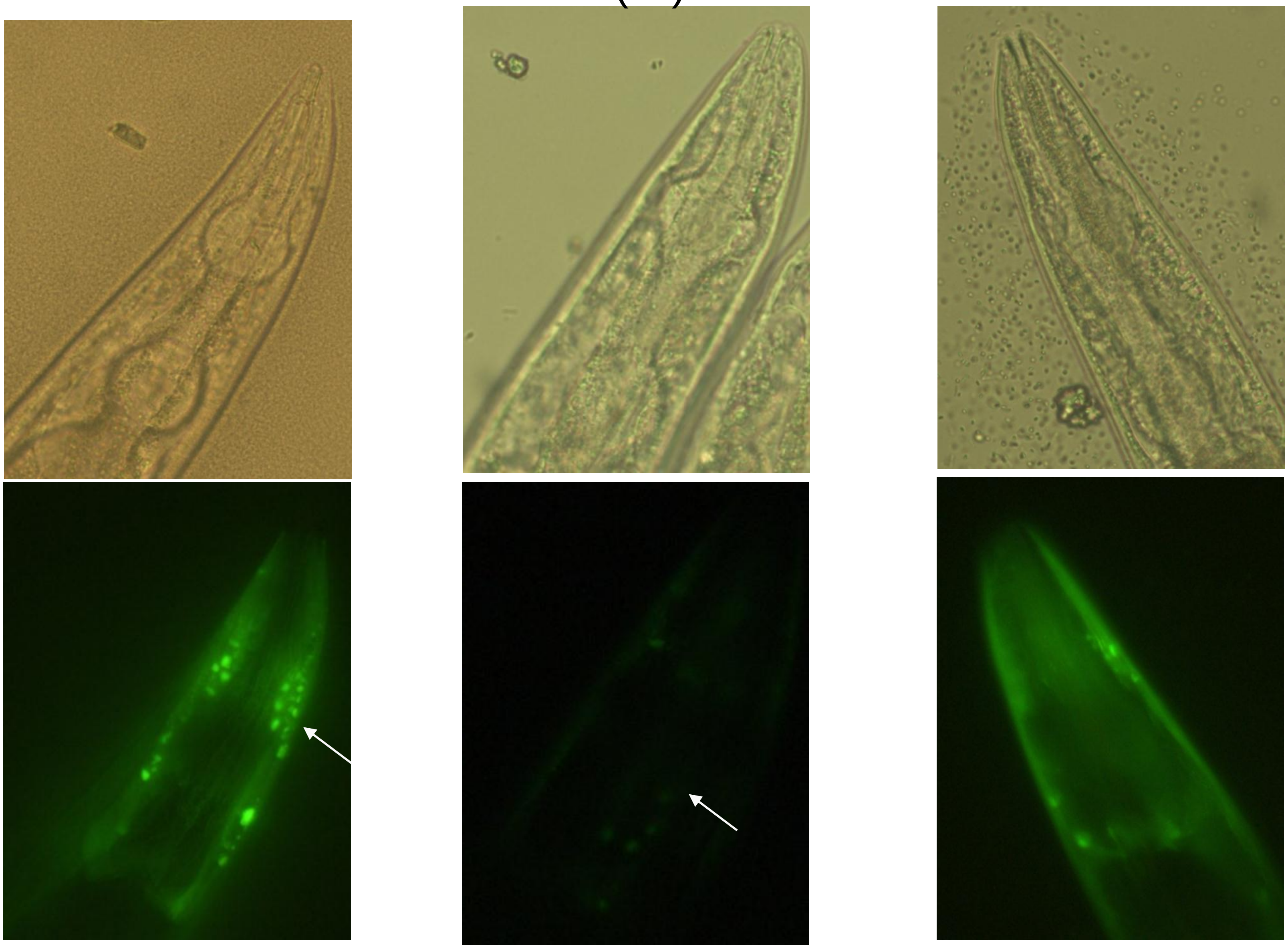
UA57 fed on DG101



Bacillus subtilis prevents α-synuclein aggregation

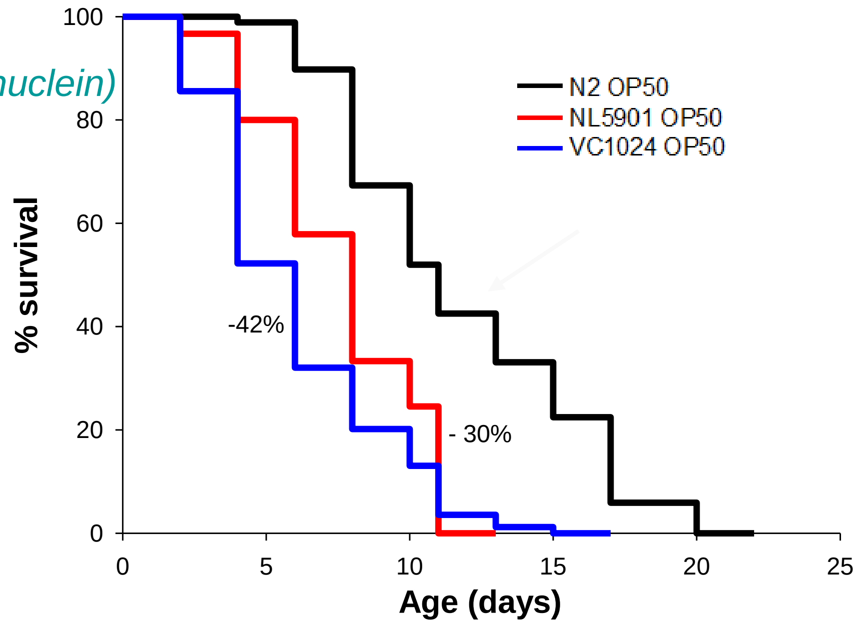
Alpha-synuclein is overexpressed and is fused to GFP. Arrows indicate LB formation.
The BslA B. subtilis mutant is deficient in biofilm formation and produces a partial probiotic effect compared with the wt DG101

NL5901 fed with OP50 | NL5901 fed with DG101 (wt) | *NL5901 fed with ΔbslA*

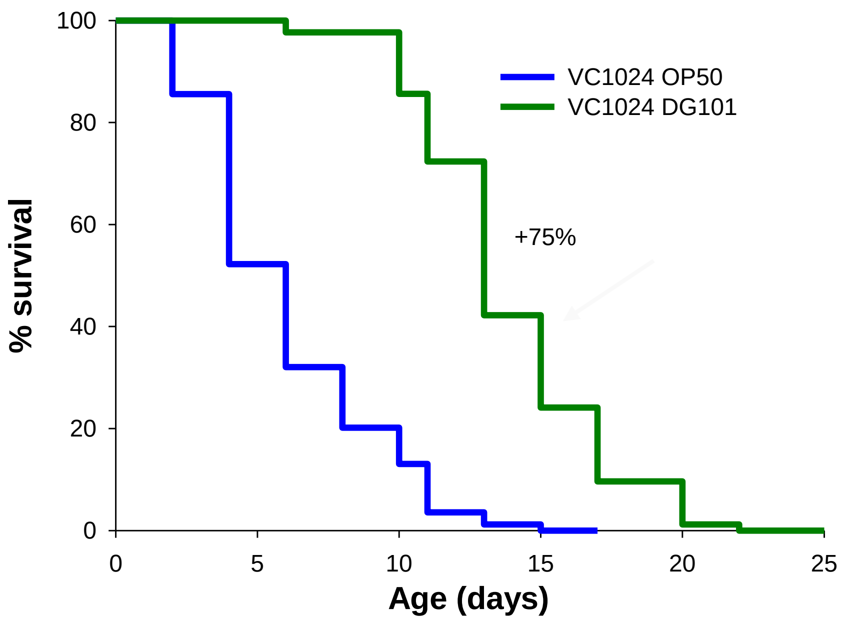


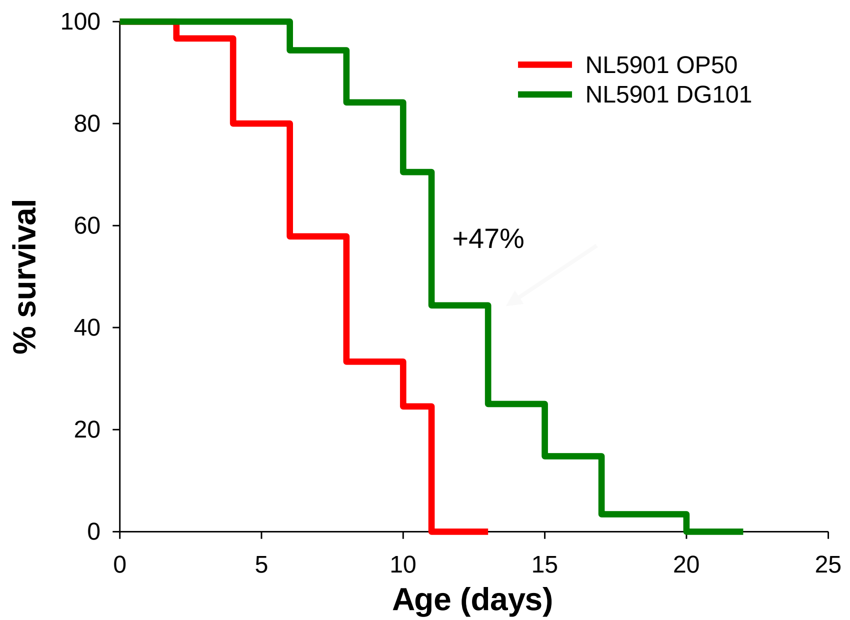
B. subtilis extends the healthy longevity of Parkinson disease model worm strains

- ***NL5901***: *over-expresses human PARK1 (alpha-synuclein)*
- ***VC1024***: *Pdr1 (PARK2) mutant*



Arrows indicate that Parkinsonian worms fed on B. subtilis live normally without signs of Parkinson disease.





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Microreview

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Microbial flora, probiotics, *Bacillus subtilis* and the search for a long and healthy human longevity

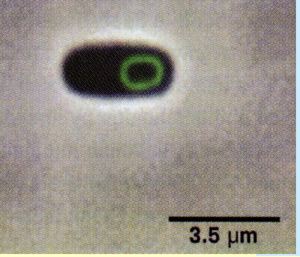
Facundo Rodriguez Ayala, Carlos Bauman, Sebastián Cogliati, Cecilia Leñini, Marco Bartolini and Roberto Grau*

Departamento de Microbiología, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario. CONICET – Rosario. Argentina.

* Corresponding Author:

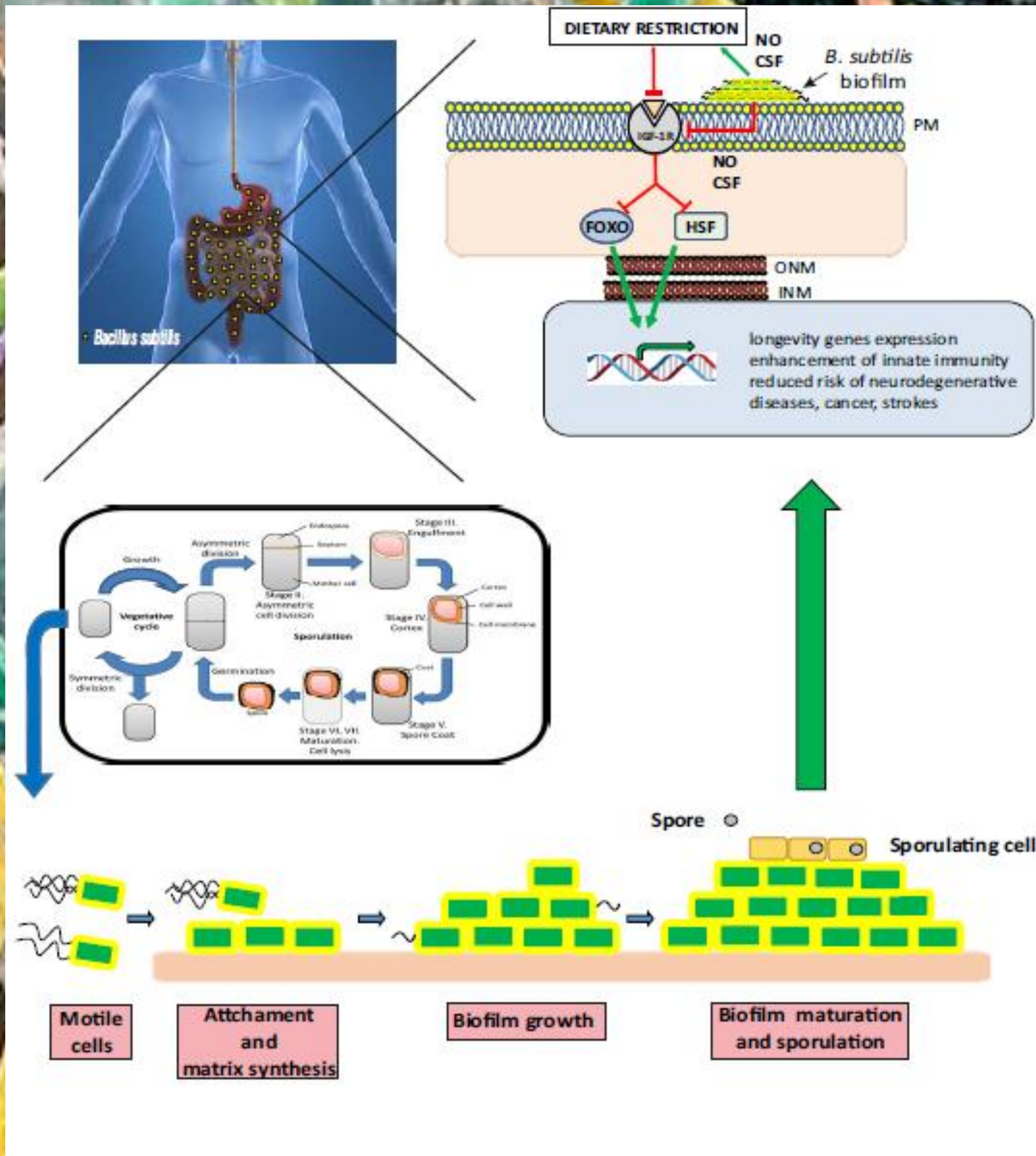
Roberto Grau, E-mail: robertograu@fulbrightmail.org

THANKS FOR THE ATTENTION



¿ QUÉ BUSCAMOS?

AUMENTO DE LA LONGEVIDAD EN HUMANOS



BACILLUS SUBTILIS **PRODUJO UN AUMENTO DEL 55 % SOBRE LA LONGEVIDAD DEL ANIMAL MODELO DE ESTUDIO AFECTANDO DE MANERA POSITIVA LOS MISMOS GENES RESPONSABLES DE LA LONGEVIDAD DE LOS HUMANOS CENTENARIOS QUE VIVEN EN LA ACTUALIDAD.**

EXTENDER LA EXPECTATIVA DE VIDA DE LOS HUMANOS DE 80 AÑOS A 120 AÑOS!

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Microbial flora, probiotics, *Bacillus subtilis* and the search for a long and healthy human longevity

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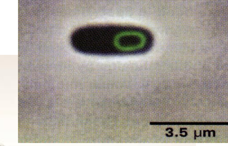
Roberto Grau, E-mail: robertograu@fulbrightmail.org

- Yogures deshidratados - Leche en polvo
- Yerba mate - Café - Té
- Sopas instantáneas Frutas
- Pastas - Helados
- Bebidas - Chocolates
- Galletitas Cereales
- Aguas
- Etc. Etc. Etc.


DE ESTA MANERA CONSUMIENDO ALIMENTOS Y BEBIDAS CON ESPORAS PROBIÓTICAS ESTAREMOS CONSIGUIENDO
AUMENTO DE LAS DEFENSAS INMUNOLÓGICAS
EFECTOS ANTITUMORALES
PREVENCIÓN DE ACVs
AUMENTO DE LA LONGEVIDAD
PREVENCIÓN DE ENFERMEDADES NEURODEGENERATIVAS PARKINSON Y ALZHEIMER

¿ QUÉ BUSCAMOS?



1 3 9 16 30 54 69 93 130

AÑOS DE VIDA