















CÓRDOBA, 1 Y 2 DE MARZO DE 2019

Vacunómica. Vacunación de precisión.

Prof. Dr. F. Martinón-Torres (@fedemartinon)

Jefe Servicio de Pediatria, Director de Pediatría Clínica, Infectológica y Traslacional, Hospital Clínico Universitario de Santiago, Spain Genetics, Vaccines, Infections and Pediatrics Research Group (GENVIP) Healthcare Research Institute of Santiago (IDIS)

Declaration of Potential Conflict of Interests

Vacunómica. Vacunación de precisión

Prof. Dr. F. Martinón-Torres

Related to this presentation, the following relationships might be perceived as potential conflict of interest:







Creo que no hay un conflicto de intereses obvio para esta charla

(excepto mi amistad con los organizadores)



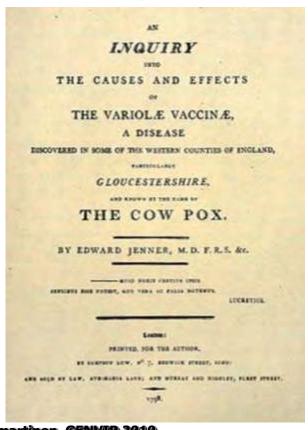


Los dos han ¿Québtienen en dosis de 0.5 ml comium lasodos 1350 PFU de supetomede la varicella virus fotografía?

VACUNOLOGÍA CLÁSICA



- (Casi) totalmente empírica
- Principio "Aislar-Inactivar-Inyectar"

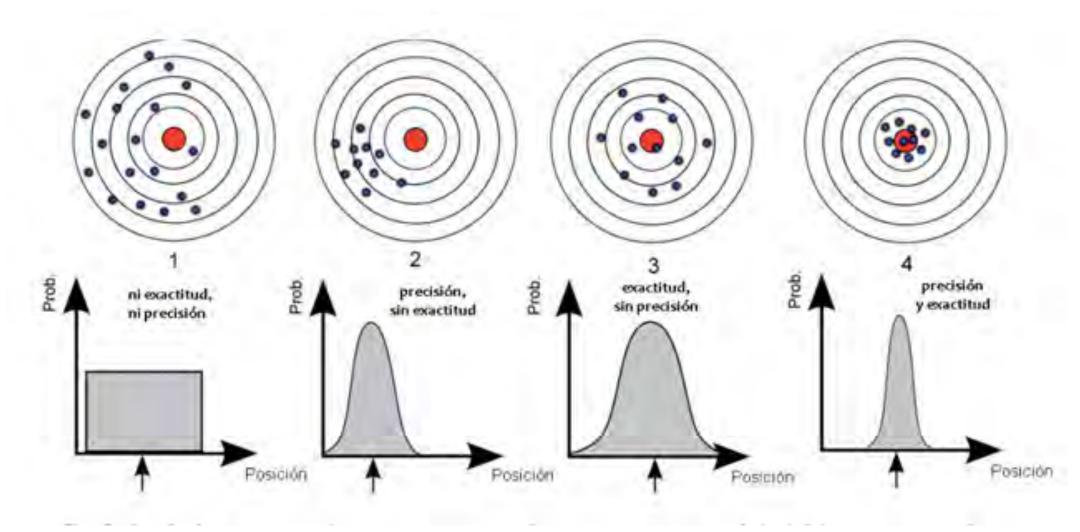




Vacunación clásica vs precisión



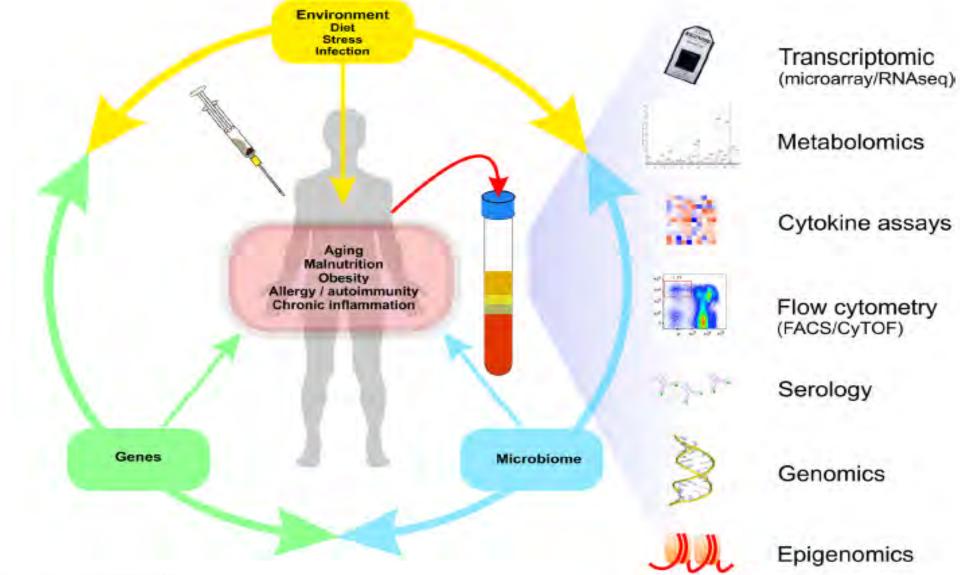




Todómica







Evolución de la vacunología





Aislamiento Inactivación Inyección Era MOLECULAR

Recombinación Conjugación VLPs Era VACUNÓMICA

Inmunogenética Bioinformática Transcriptómica

Vacunología predictiva y personalizada

Todómica y vacunas ¿para qué? 🥀

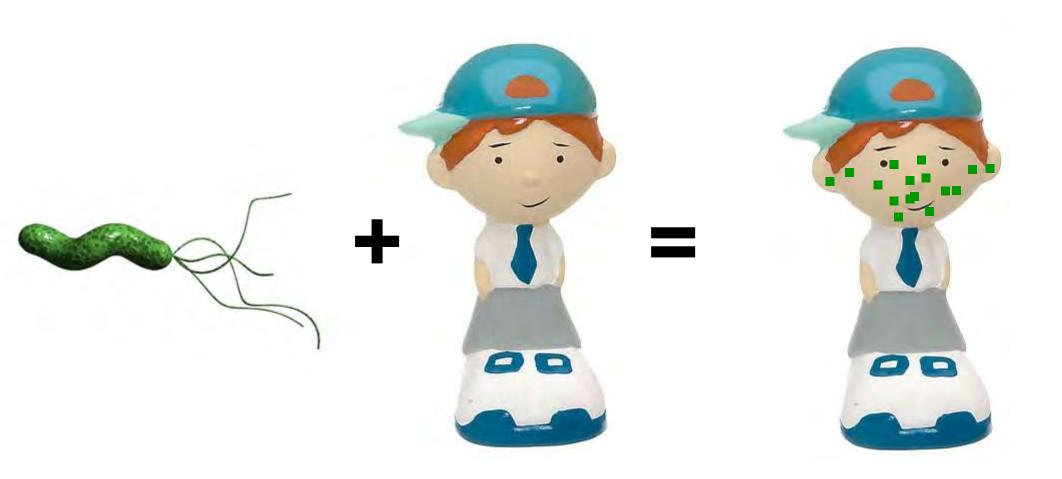




- Identificar quien tiene riesgo de infección (infectómica)
- Identificar el riesgo de baja respuesta inmune a la vacuna (vacunómica)
- Identificar el riesgo de efectos adversos graves (adversómica)
- Identificar el tipo y dosis de vacuna necesaria para proteger a un individuo en particular (vacunación de precisión)

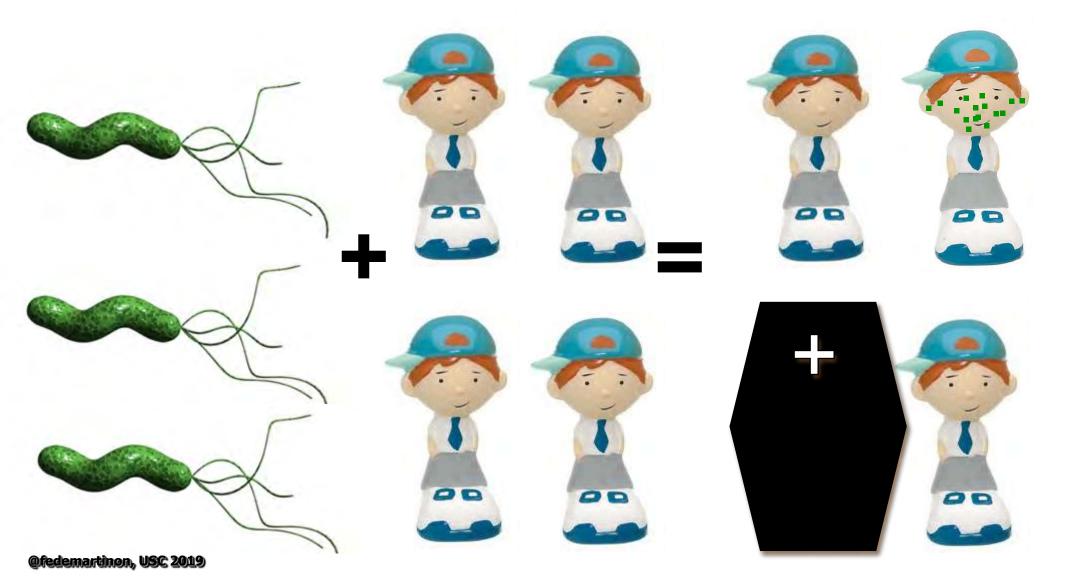
Concepto de infección





Concept of infection

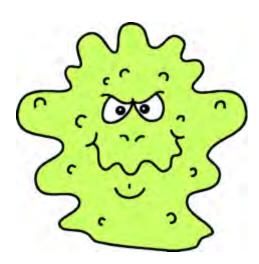




¿Cómo elige el microorganismo 🛍 🚓 a sus víctimas?









¿Cuales són los criterios?

El meningococo infecta a quien puede, no a quien quiere





OPEN

Natural resistance to Meningococcal Disease related to CFH loci: Meta-analysis of genome-wide association studies

Received: 07 June 2016 Accepted: 06 October 2016 Published: 02 November 2016

Federico Martinón-Torres¹*, Eileen Png²*, Chiea Chuen Khor³, Sonia Davila³,

Victoria

PERSONAS

Enitan C

Elvira M

NATURALMENTE

Pilar Azı

Padilla¹¹

RESISTENTES

Antonio Salas¹²², ESIGEM network, ESPID meningococcal consortium & EUCLIDS consortium

Genome-wide association study identifies variants in the CFH region associated with host susceptibility to meningococcal disease

Sonia Davila^{1,15}, Victoria J Wright^{2,15}, Chiea Chuen Khor¹, Kar Seng Sim³, Alexander Binder⁴,

Willemijn B Breunis⁵, David Inwald², Simon Nadel², Helen Betts², Enitan D Carrol⁶, Ronald de Groot⁷,

Peter W M Hermans⁷, Jan Haze

PERSONAS

Pederico Martinon-Torres^{10,11},

SUSCEPTIBLES

the International Meningococcal Genetics Consortium¹⁷

Davila S et al. Nature Genetics 2010

Martinon-Torres F. Nature Scientific Reports 2016

Susceptibilidad genética frente a neumococo







Article

Whole Exome Sequencing Identifies New Host Genomic Susceptibility Factors in Empyema Caused by Streptococcus pneumoniae in Children: A Pilot Study

Antonio Salas 1,2,3,4,5,*, Jacobo Pardo-Seco 1,2,3,4,5, Ruth Barral-Arca 1,2,3,4,5, Miriam Cebey-López 4,5, Alberto Gómez-Carballa 1,2,3,4,5, Irene Rivero-Calle 4,5, Sara Pischedda 1,2,3,4,5, María-José Currás-Tuala 1,2,3,4,5, Jorge Amigo 1,2,3,4,5, José Gómez-Rial 4,5, Federico Martinón-Torres 4,5 and on behalf of GENDRES Network †

Genes 2018, 9, 240; doi:10.3390/genes9050240







www.nature.com/scientificreports

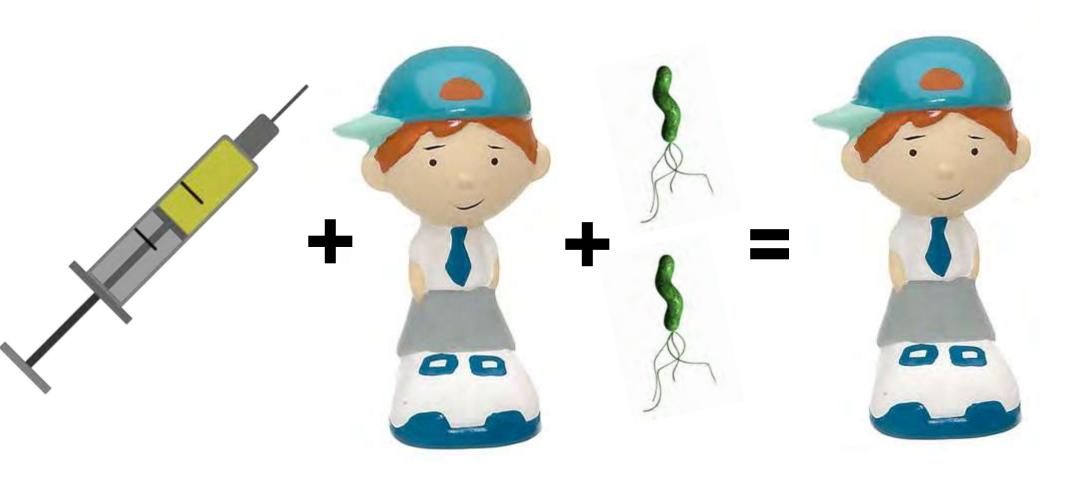
SCIENTIFIC REPORTS

Whole Exome Sequencing reveals new candidate genes in host genomic susceptibility to Respiratory Syncytial Virus Disease

Antonio Salas^{1,2,7}, Jacobo Pardo-Seco^{1,2}, Miriam Cebey-López², Alberto Gómez-Carballa^{1,2}, Pablo Obando-Pacheco², Irene Rivero-Calle², María-José Currás-Tuala^{1,2}, Jorge Amigo^{1,2}, José Gómez-Rial², Federico Martinón-Torres², on behalf of GENDRES network (www.gendres.org)³

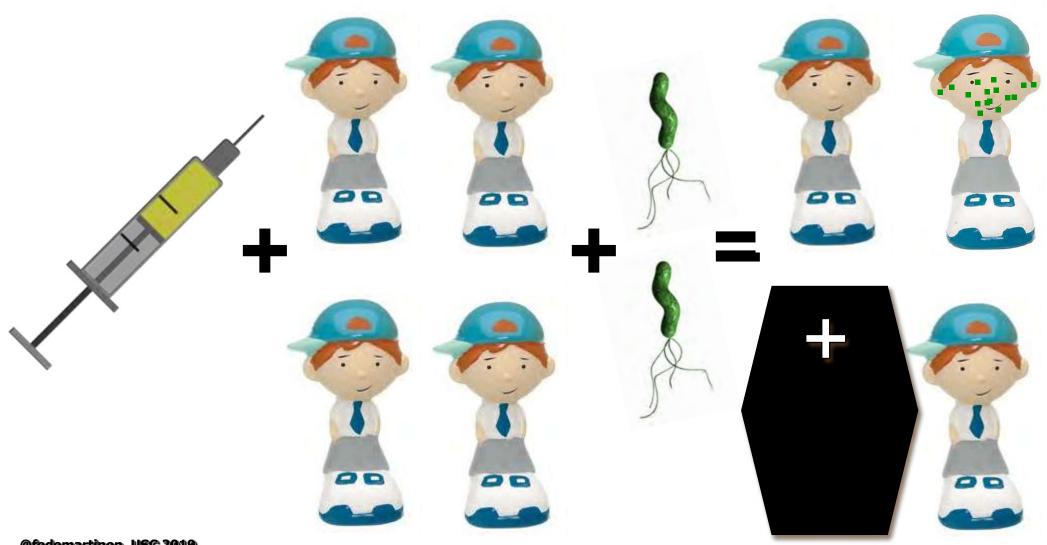
Concepto de vacunación @= 4





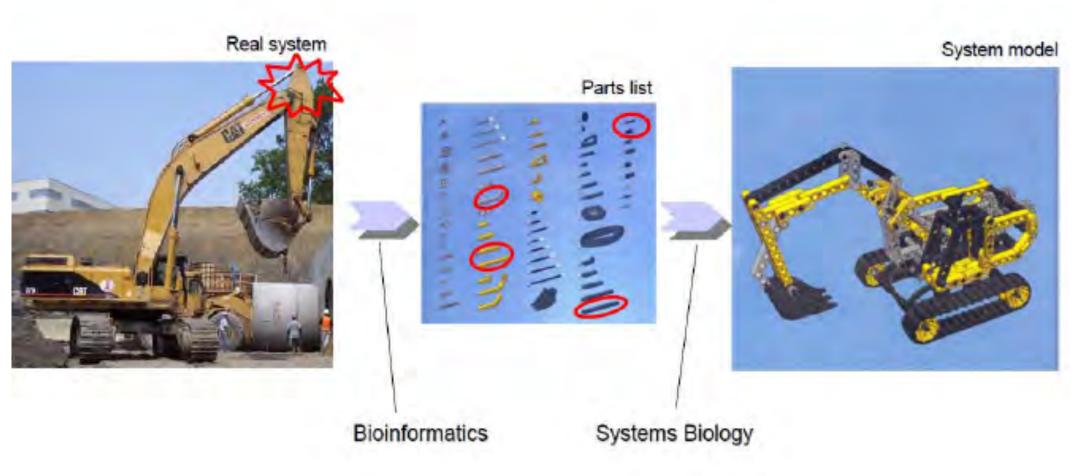
Concepto de vacunación @s





Biología de sistemas

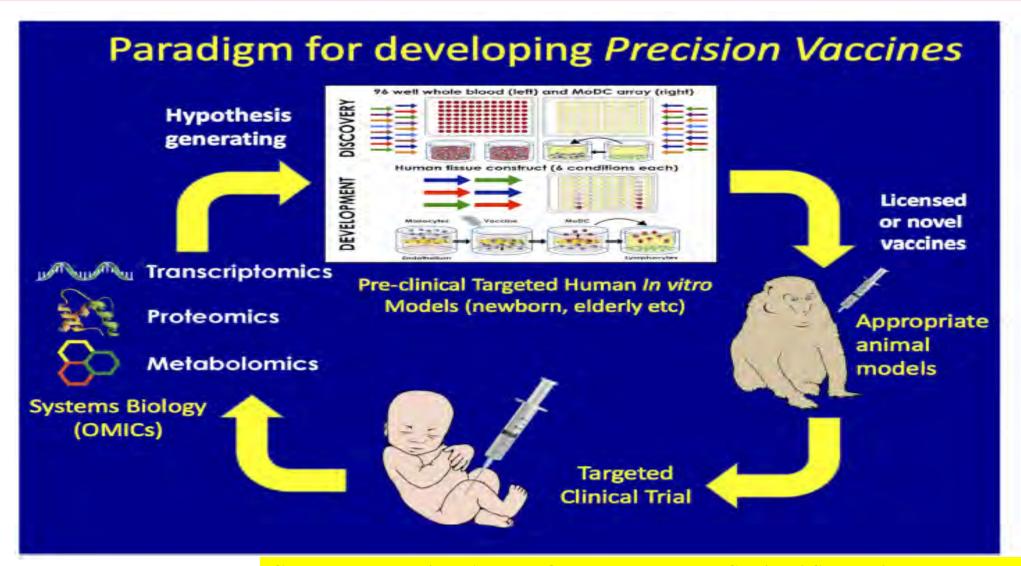




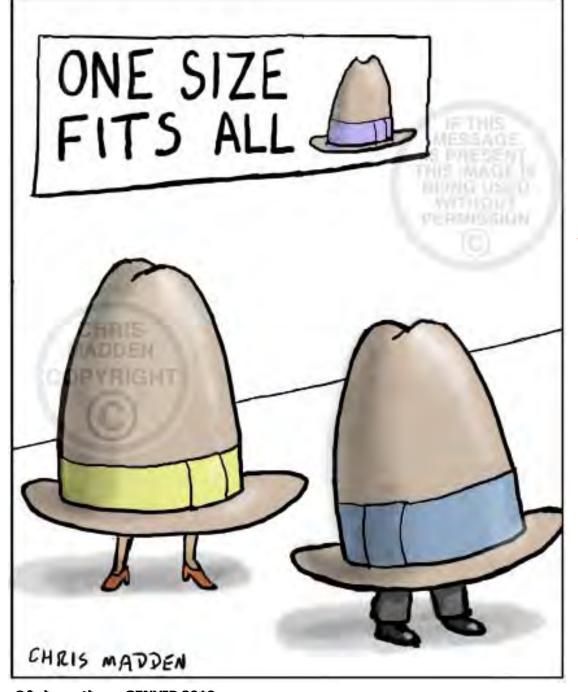
Vacunación de precisión







Cotugno N, Ruggiero A, Levy O, Manno E, Rocca S, Zicari S, Martinon-Torres F, Santilli V, Pollard AJ, Palma P. Journal of Inmunological Research 2019 in press





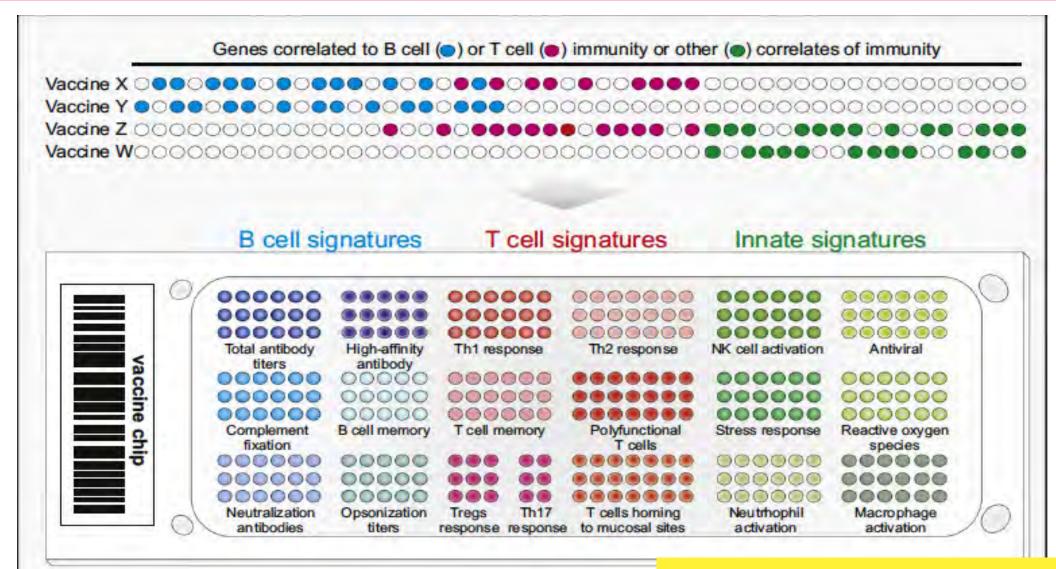
VACUNOLOGÍA BASADA EN "TALLA ÚNICA"

- Eliminar antígenos innecesarios
- Dirigir individual, grupal o
 poblacionalmente la adyuvación
- Dirigir la respuestasTh1/Th2
- Biomarcadores poblacionales para decisiones go-no go
- Predicción individual rápida
- Considerar las diferencias x edad

Vacunología de sistemas



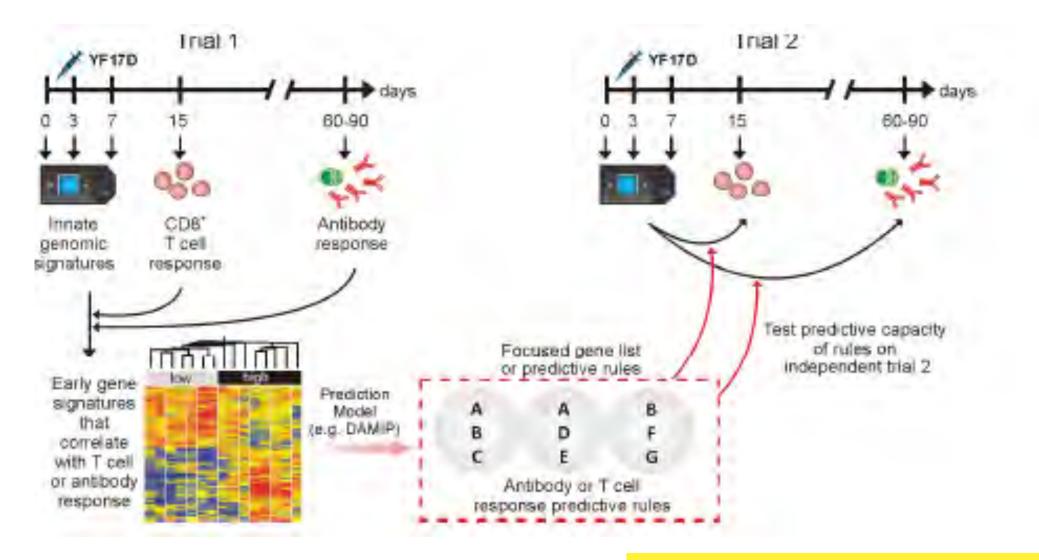




Vacunología de sistemas







Vacunología de sistemas







Systems biology of immunity to MF59-adjuvanted versus nonadjuvanted trivalent seasonal influenza vaccines in early childhood

Helder I. Nakaya^{a,b,1}, Elizabeth Clutterbuck^{c,1}, Dmitri Kazmin^{d,1}, Lili Wang^{e,1}, Mario Cortese^d, Steven E. Bosinger^{d,f}, Nirav B. Patel^f, Daniel E. Zak^g, Alan Aderem^g, Tao Dong^e, Giuseppe Del Giudice^h, Rino Rappuoli^{h,2}, Vincenzo Cerundolo^e, Andrew J. Pollard^c, Bali Pulendran^{b,d,2}, and Claire-Anne Siegrist^{i,2}

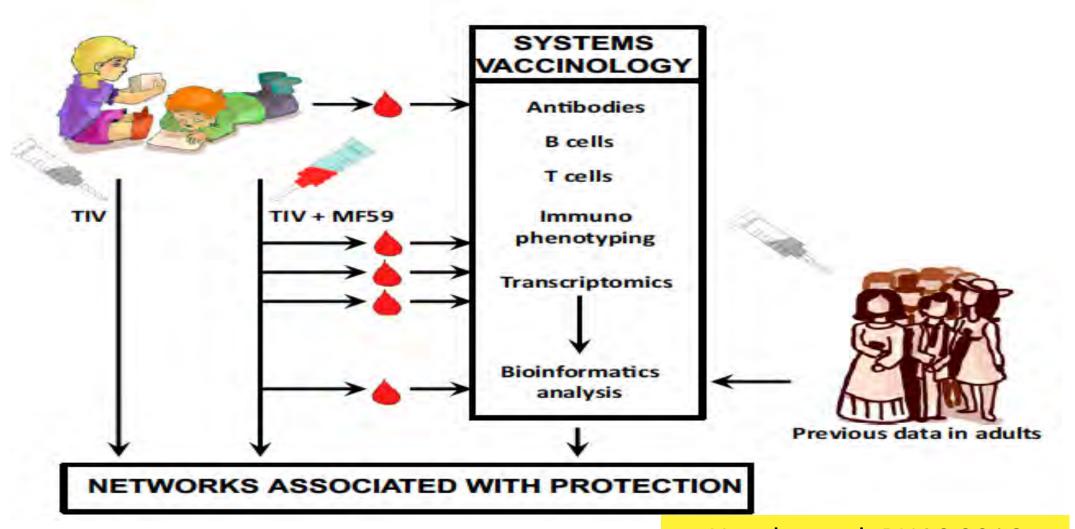
^aDepartment of Pathophysiology and Toxicology, School of Pharmaceutical Sciences, University of São Paulo, 05508, São Paulo, Brazil; ^bDepartment of Pathology, Emory University School of Medicine, Atlanta, GA 30322; ^cOxford Vaccine Group, Department of Pediatrics, University of Oxford and the National Institute for Health Research Oxford Biomedical Research Centre, Oxford OX3 9DU, United Kingdom; ^dEmory Vaccine Center, Yerkes National Primate Research Center, Atlanta, GA 30329; ^eMedical Research Council Human Immunology Unit, Radcliffe Department of Medicine, University of Oxford, Oxford OX3 9DU, United Kingdom; ^fDivision of Microbiology and Immunology, Emory Vaccine Center, Yerkes National Primate Research Center, Atlanta, GA 30322; ^gCenter for Infectious Disease Research, Seattle, WA 98109; ^hResearch Center, Novartis Vaccines, 53100 Siena, Italy; and ^hWHO Collaborative Center for Vaccine Immunology, Departments of Pathology-Immunology and Pediatrics, University of Geneva, 1211 Geneva, Switzerland

Contributed by Rino Rappuoli, November 24, 2015 (sent for review April 29, 2015; reviewed by Adolfo Garcia-Sastre, Stefan H. E. Kaufmann, and Federica Sallusto)

Nayaka et al. PNAS 2016

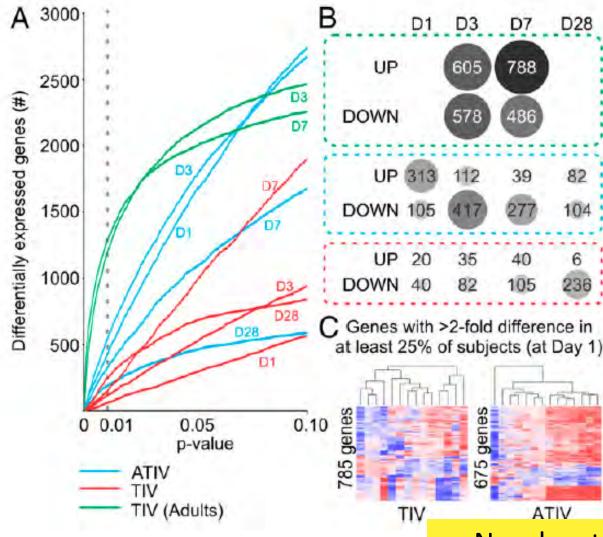
Vacunología de sistemas aplicada a la gripe





Vacunología de sistemas aplicada a la gripe









TLR5-Mediated Sensing of Gut Microbiota Is Necessary for Antibody Responses to Seasonal Influenza Vaccination

Jason Z. Oh,^{1,2} Rajesh Ravindran,^{1,2} Benoit Chassaing,⁴ Frederic A. Carvalho,^{4,5} Mohan S. Maddur,^{1,2} Maureen Bower,⁶ Paul Hakimpour,² Kiran P. Gill,^{1,2} Helder I. Nakaya,^{3,7} Felix Yarovinsky,⁸ R. Balfour Sartor,⁶ Andrew T. Gewirtz,⁴ and Bali Pulendran^{1,2,3,*}

¹Emory Vaccine Center

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Emory University, Atlanta, GA 30329, USA

⁴Center for Inflammation, Immunity, and Infection, Georgia State University, Atlanta, GA 30302, USA

5INSERM U1107, Universite d'Auvergne, 63001 Clermont-Ferrand Cedex 1, France

⁶National Gnotobiotic Rodent Resource Center, University of North Carolina, Chapel Hill, NC 27514, USA

⁷Department of Clinical and Toxicological Analyses, Institute of Pharmaceutical Sciences, University of Sao Paulo, Sao Paulo 05508-000, Brazil

⁸Department of Immunology, University of Texas Southwestern Medical Center, Dallas, TX 75235, USA

*Correspondence: bpulend@emory.edu

http://dx.doi.org/10.1016/j.immuni.2014.08.009

Systems biology of vaccination for seasonal influenza in humans

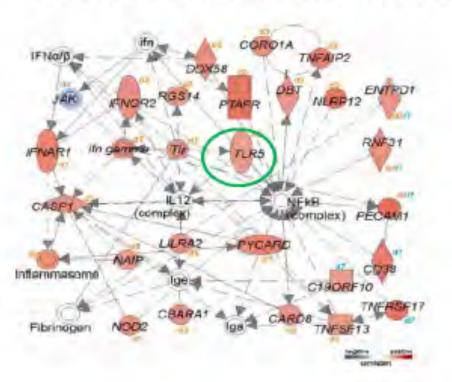
Management



Helder I Nakaya^{1,2}, Jens Wrammert^{1,3}, Eva K Lee⁴, Luigi Racioppi^{5,6}, Stephanie Marie-Kunze^{1,2}, W Nicholas Haining⁷, Anthony R Means⁶, Sudhir P Kasturi^{1,2}, Nooruddin Khan^{1,2}, Gui-Mei Li^{1,3}, Megan McCausland^{1,3}, Vibhu Kanchan^{1,3}, Kenneth E Kokko⁸, Shuzhao Li^{1,2}, Rivka Elbein⁹, Aneesh K Mehta⁹, Alan Aderem¹⁰, Kanta Subbarao¹¹, Rafi Ahmed^{1,3} & Bali Pulendran^{1,2,12}

VOLUME 12 NUMBER 8 AUGUST 2011 NATURE IMMUNOLOGY

Early expression of TLR5 is positively correlated with productive antibody responses against influenza HA following vaccination with the seasonal inactivated flu vaccine



Natural Ligand for TLR5 is Flagellin



Vacunología de sistemas y ACWY





Table 2 Correlations between frequency of total and plasma cell subsets and day 28 MenA and MenC-specific serum bactericidal assay titres

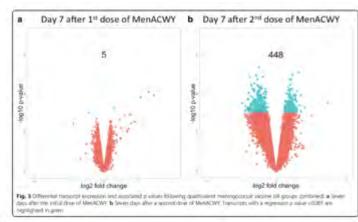
Plasma cell subset	MenA SBA correlation (r)	MenA SBA correlation (p value)	MenC SBA correlation (r)	MenC SBA correlation (p value)		
otal plasma cells 0.147		0.560	0.615	0.007		
HLADR + CXCR3+	0.364	0.137	0.631	0.005		
HLADR-CXCR3+	0.174	0.489	0.576	0.012		
HLADR + CXCR3-	0.204	0.417	0,549	0.018		
HLADR-CXCR3-	-0.015	0.954	0,504	0.033		

MenA capsular group A meningococcus, MenC capsular group C meningococcus, r correlation coefficient

Table 1 Overview of study time points, interventions and analyses

	Study day 0	Study day 7	Study day 21	Study day 28	Study day 35	Study day 49	Study day 56
Group							
Group 1 (n = 5)	MenACWY-CRM (i/m)			MenACWY-CRM (I/m)			
Group 2 (n = 5)	MenACWY-PS (i/m)			MenACWY-CRM (i/m)			
Group 3 (n = 5)	MenACWY-PS (s/d)			MenACWY-CRM (I/m)			
Group 4 (n = 5)	MenACWY-P5 (1/s l/m)			MenACWY-CRM (i/m)			
Immunological phenotypes							
SBA (MenA and MenC)	1			1			1
B mem ELISpots (MenA, MenC, DT)	1			1			1
Systems tools							
Flow cytometry	1	1	1	1	1	1	1
Transcriptomics	1	1			1		

i/m intramuscular, s/c subcutaneous, ²/₅ a fifth of the standard dose was administered, SBA serum bactericidal assay, B mem ELISpots B-cell memory enzyme-linked immunospot, DT diphtheria toxoid



A plasma cell gene signature is evident in whole blood 7 days after the initial dose of MenACWY vaccine with similarities and differences between plain polysaccharide and conjugate vaccines

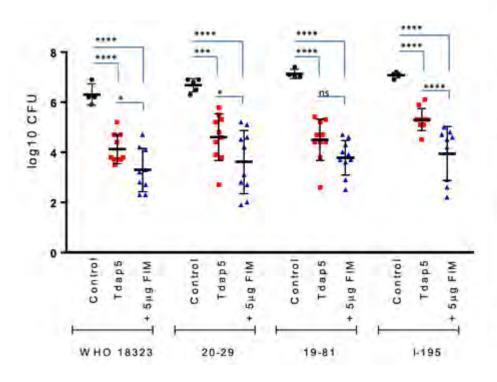
O, Connor D et al. Genome Research 2017

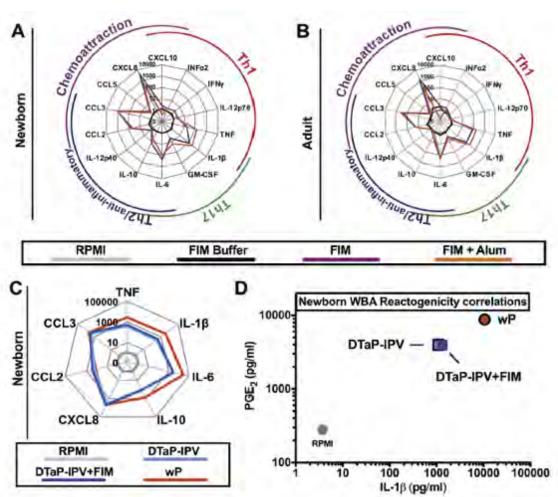
Vacunología de sistemas y Pertussis





¿Añadir más dosis antigénica de FIM2/3 podría mejorar la eficacia de las vacunas disponibles frente a cepas PRN negativas sin que por ello aumente su reactividad





Efectos heterólogos de las vacunas





Martinon-Torres F. (2017) Expected and Unexpected Effects of Vaccination. In: Vesikari T., Van Damme P. (eds) Pediatric Vaccines and Vaccinations. Springer, Cham

elCorreoGallego.eS Portada Santiago Área de Composieia Galida Panorama Deportes Tendencias Opinión El fempo Falos Poemicafidad de Santiago de Composiein

De Castro: "Las vacunas son mejores de lo que podíamos llegar a imaginar"

santiago@elcorreogallego.es

El IDIS concluye que hay un 40 % de menos ingresos por infección respiratoria al inocularse contra la tuberculosis // Pediatría investigará nuevas vías con Harvard



ÅNGELA ARES. SANTIAGO | 19.11.2015



El Instituto de Investigación Sanitaria de Santiago acaba de ser distinguido con una de las Mejores Ideas de 2015 por un trabajo del grupo de Genvip, de Pediatría del CHUS, que concluye que

Nonspecific (Heterologous) Protection of Neonatal BCG Vaccination Against Hospitalization Due to Respiratory Infection and Sepsis

Maria José de Castro. Jacoba Parda-Seco. 21 and Federico Martinón-Torres 1.1

Translational Pediatrics and Intercous Diseases Section, Pediatrics Department, Housitin Conco. Universities of Santiago de Compostete, Santiago de Compostete, Santiago de Compostete, Santiago de Compostete, Parado de Santiago de Compostete, Department de America Santiago de Disease, Vaccione de Concisio de Concisio

(See the Editorial Commentary by Iglesias and Martin on pages 1620-1.)

Buckground. Bacille Calmette-Goerin (BCG) vaccination has been suggested to have nonspecific beneficial of fects in children from developing countries, reducing morbidity and mortality caused by unrelated pathogens.

Objective. We aimed to assess the heterologous protective effects of BCG succination against respiratory infection (RI) and sepsis not attributable to tuberculosis in children born in Spain.

Meliads. We conducted a retrospective epidemiological study using data from the Official Spanish Registry of Hospitalizations (CMBD-HA) to identify differences in hospitalization rates (HR) in BCG-vaccinated children (Hasque Country, where neonatal BCG is part of the immunization schedule and has a 100% coverage) as compared to non-BCG-vaccinated children (from the rest of Spans, where BCG is not used).

BCG Heterologous Protection in Children • CID 2015:60 (1 June) • 1611

14ª edición

Las Mejores Ideas 2015







ARTICLE OPEN

Long-term reduction in hyperglycemia in advanced type 1 diabetes: the value of induced aerobic glycolysis with BCG vaccinations

Willem M. Kühtreiber¹, Lisa Tran¹, Taesoo Kim¹, Michael Dybala¹, Brian Nguyen¹, Sara Plager¹, Daniel Huang ¹, Sophie Janes¹, Audrey Defusco¹, Danielle Baum¹, Hui Zheng² and Denise L. Faustman¹

Mycobacterium are among the oldest co-evolutionary partners of humans. The attenuated Mycobacterium bovis Bacillus Calmette Guérin (BCG) strain has been administered globally for 100 years as a vaccine against tuberculosis. BCG also shows promise as treatment for numerous inflammatory and autoimmune diseases. Here, we report on a randomized 8-year long prospective examination of type 1 diabetic subjects with long-term disease who received two doses of the BCG vaccine. After year 3, BCG lowered hemoglobin A1c to near normal levels for the next 5 years. The BCG impact on blood sugars appeared to be driven by a novel systemic and blood sugar lowering mechanism in diabetes. We observe a systemic shift in glucose metabolism from oxidative phosphorylation to aerobic glycolysis, a state of high glucose utilization. Confirmation is gained by metabolomics, mRNAseq, and functional assays of cellular glucose uptake after BCG vaccinations. To prove BCG could induce a systemic change to promote accelerated glucose utilization and impact blood sugars, murine data demonstrated reduced blood sugars and aerobic induction in non-autoimmune mice made chemically diabetic. BCG via epigenetics also resets six central T-regulatory genes for genetic reprogramming of tolerance. These findings set the stage for further testing of a known safe vaccine therapy for improved blood sugar control through changes in metabolism and durability with epigenetic changes even in advanced Type 1 diabetes.

npj Vaccines (2018)3:23; doi:10.1038/s41541-018-0062-8

TIPICO X

¡Bloquea tu agenda!

21 y 22

Noviembre 2019 Santiago de Compostela

Ab OSTERHAUS

Umesh PARASHAR

Brad GESSNER

Ron DAGAN

Robb BUTLER

Xavi BOSCH

Louis BONT

Andrew POLLARD

Myrsini KAFOROU

Denisse FAUSTMAN

...and more surprises

@fedemartinon / @TIPICO SANTIAGO /

#TIPICO10



Trained immunity: consequences for the heterologous effects of BCG vaccination

Johanneke Kleinnijenhuis, Reinout van Crevel and Mihai G. Netea*

Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Geert Grooteplein Zuid 8, 6525 GA, Nijmegen, The Netherlands

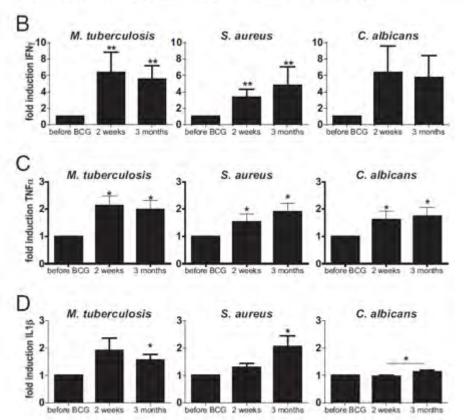
*Corresponding author: Tel: +31 24 3618819; Fax: +31 24 3541734; E-mail: mihai.netea@radboudumc.nl

Received 14 June 2014; revised 21 September 2014; accepted 29 September 2014

A growing body of evidence from epidemiologic and immunologic studies have shown that in addition to target disease-specific effects, vaccines have heterologous effects towards unrelated pathogens. Like some other vaccines, bacille Calmette-Guerin (BCG) has shown in observational studies and randomized clinical trials to increase survival beyond the disease burden of the target disease. The immunologic substrate for these non-specific protective effects have been ascertained to heterologous T cell effects on the one hand, and to priming of innate immunity on the other hand. The term 'trained immunity' has been proposed to describe these potentiating effects of vaccines on innate immune responses. This process can explain the rapid effects of BCG vaccination and has been suggested to be mediated by epigenetic programming of monocytes or macrophages. This novel concept has important implications for the possible use of vaccines, for vaccination policy and even for the design of novel immunotherapeutic approaches.

Bacille Calmette-Guérin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes

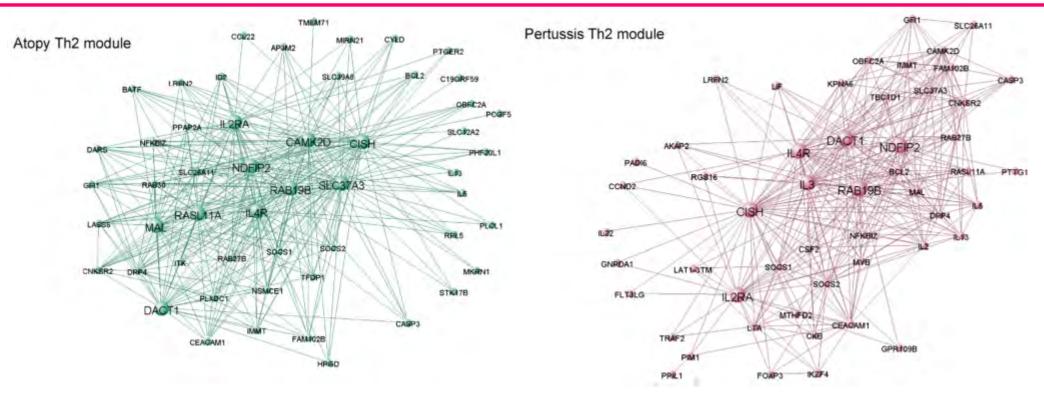
Johanneke Kleinnijenhuis^{a,b,1}, Jessica Quintin^{a,b,1}, Frank Preijers^c, Leo A. B. Joosten^{a,b}, Daniela C. Ifrim^{a,b}, Sadia Saeed^d, Cor Jacobs^{a,b}, Joke van Loenhout^e, Dirk de Jong^f, Hendrik G. Stunnenberg^d, Ramnik J. Xavier^{g,h}, Jos W. M. van der Meer^{a,b}, Reinout van Crevel^{a,b}, and Mihai G. Netea^{a,b,2}



BCG innate immunity
training by NOD2dpendent reporgramming
of monocytes



INMUNOGENÓMICA Y ADVERSÓMICA



- La respuesta Th2 es parecida en atópico expuesto a polvo y en sujeto vacunado con DTaP
 - Tanto arquitecturalmente (conectividad)
 - Como en hub genes

La vacunación es una estimulación controlada de nuestro sistema inmune







Vaccination



Vaccination



@fedemartinon, USC 2019

Natural infection



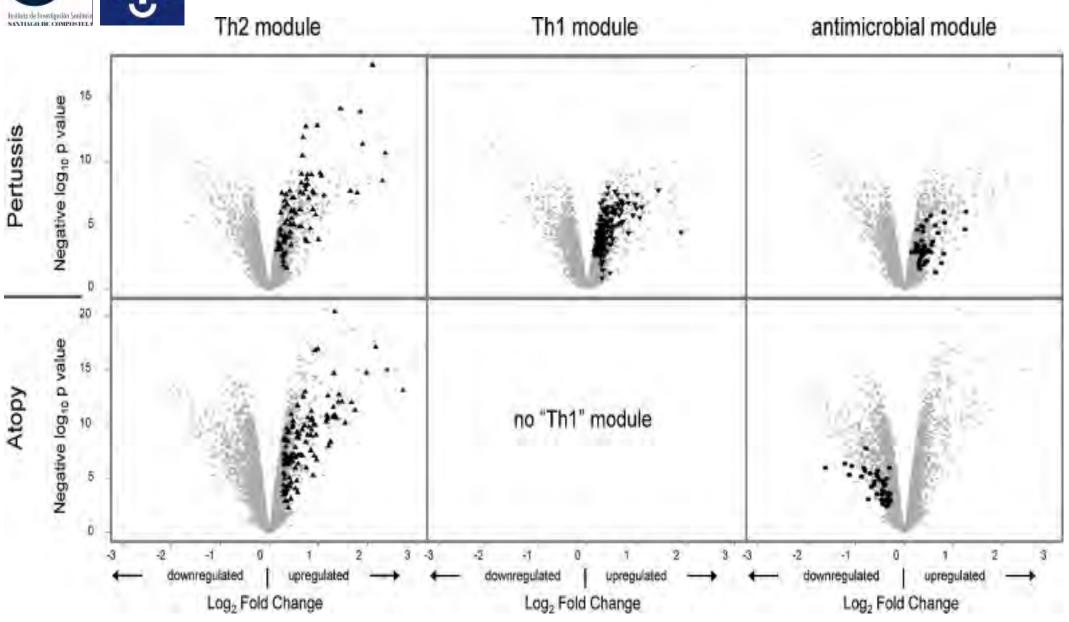
Natural infection





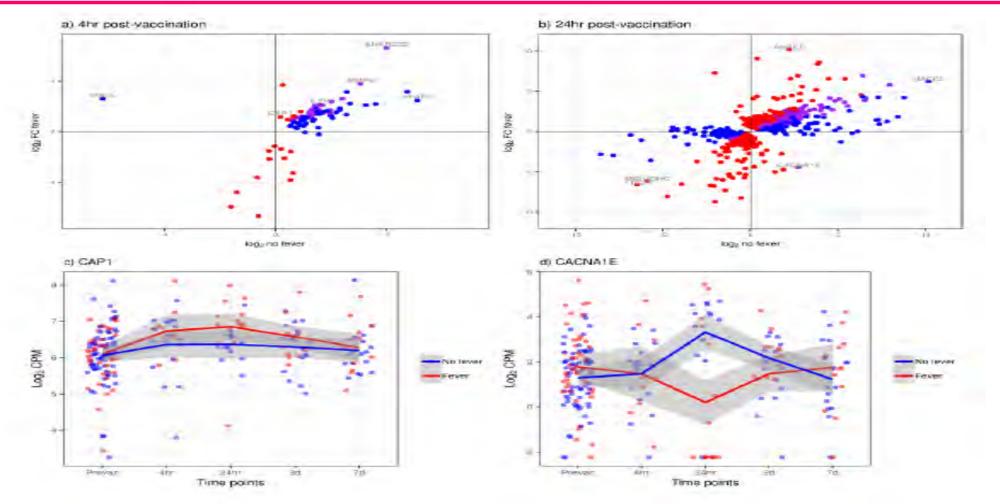


INMUNOGENÓMICA Y ADVERSÓMICA





LA FIEBRE DE LA VACUNA DE MENINGO-B: 4CMENB Y ADVERSÓMICA



El patrón de expresión genética diferencia perfectamente a los niños que desarrollan fiebre con la vacuna de los que no la desarrollan

Mientras tanto...

GUIA ENFERMEDADES

¿Vienes a mi fiesta del sarampión? Habrá piruletas infectadas



¿Pagaría usted 50 euros por una piruleta? Por supuesto que esta golosina, que se anuncia en internet, no es un caramelo de azúcar sin más. Se trata de una invitación a una exclusiva 'pox' o 'measles party', que es como se conocen las fiestas de la varicela y el sarampión, "una tendencia de moda en los países anglosajones, que ya ha llegado a España", según el pediatra del Hospital de Basurto, Javier Arístegui.

YOU'RE INVITED! CHICKENPOX PARTY

Las 'Pox party' (fiesta de la varicela) o 'Measles party' (fiesta del sarampión) son eventos infantiles, organizadas por los padres del niño enfermo, cuyo fin es contagiar a los invitados con la ayuda de caramelos o ropa infectados, para que se inmunicen de la enfermedad de forma natural. También se pueden comprar a domicilio, a través de internet, chucherías con el virus.

Lo que para algunos es un juego de niños, para otros como el **dr. Federico Martinón-Torres**, pediatra del **Hospital Clínico Universitario de Santiago**, es una aberración. "No debemos olvidar que el sarampión mata y los afectados pueden sufrir complicaciones respiratorias, neumonías y encefalitis".

Mientras tanto...





As measles outbreak spreads, one antivaxxer asks how to keep her child safe

Published: Jan 31, 2019 2:33 p.m. ET















LANGLOIS SOCIAL-MEDIA EDITOR

After a measles outbreak, sparked by a rise in the number of unvaccinated children, led to a state of emergency in the Pacific Northwest, health officials across the country in Georgia confirmed this week that three people in the Atlanta area have been diagnosed with the highly contagious virus.

Facebook Fit. -0.59% group, "Natural Health Anti-Vaxx Community." My 3 year old is not vaccinated and there is currently a measles outbreak in my state. Any suggestions for precautions I can take to protect her would be very much appreciated. The responses were swift and merciless. Josee Leveille Bring her to the edge of the flat earth. The air is cleaner there.

Amanda Webb Have you tried thoughts and prayers?



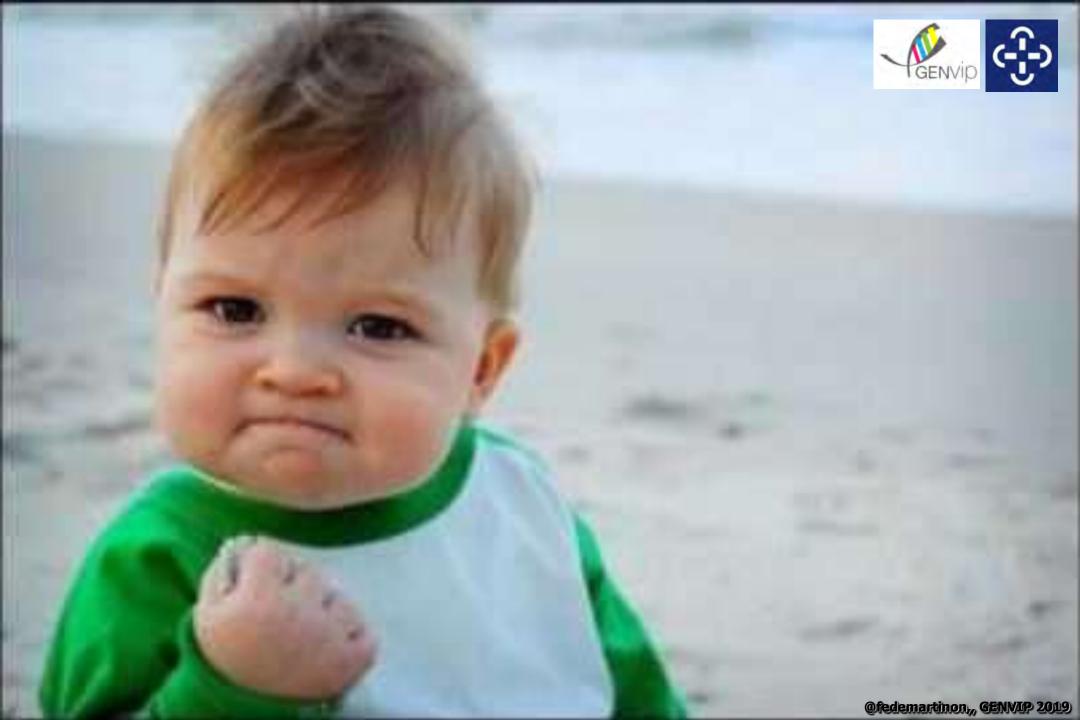
Jeremy Leonard Build a wall around her and make the vaccinated people pay for it! Sending my thoughts and prayers.





Andrew Burnside Did you try sharing her picture on facebook with the caption " 1 like equal one prayer 1





MENSAJES PARA CASA



- Las vacunas son aun mejores de lo que nos podemos imaginar..... pero sólo ahora empezamos a entender sus mecanismos íntimos de funcionamiento gracias a la vacunómica.
- La vacunación de precisión es una realidad inminente tanto en el desarrollo de vacunas como en la vacunación a la carta













@fedemartinon



¡Unete a nosotros!

(+info en <u>bmosper@gmail.com</u>)

Genetics, Vaccines and Infections in Pediatrics Research Group (GENVIP)

Healthcare Research Institute of Santiago (IDIS)

www.genvip.org