grupo andaluz de infectología pediátrica

# Los artículos **más impactantes** del panorama actual

Antonio J. Conejo Fernández
Hospital Vithas Xanit Internacional

XI Jornadas de Vacunas CAV-AEP
9 de octubre de 2020

# Conflicto de intereses

He recibido honorarios por participar como ponente y asistente en actividades docentes de Pfizer, MSD, GSK, Astra-Zeneca y Sanofi Pasteur.

He participado en comités asesores remunerados de MSD y GSK.

Participo en la organización de actividades formativas financiadas por Pfizer, MSD, GSK, Sanofi Pasteur y Sequirus…

… y he dicho siempre **lo que me ha dado la gana**.

PLOS PATHOGENS

RESEARCH ARTICLE

# New live attenuated tuberculosis vaccine MTBVAC induces trained immunity and confers protection against experimental lethal pneumonia

**Raquel Tarancón[1,2☯], Jorge Domínguez-Andrés[3☯*], Santiago Uranga[1,2], Anaísa V. Ferreira[3,4], Laszlo A. Groh[3], Mirian Domenech[2,5], Fernando González-Camacho[2,5], Niels P. Riksen[3], Nacho Aguilo[1,2], José Yuste[2,5], Carlos Martín[1,2,6‡], Mihai G. Netea[3,7,8‡]**

**1** Department of Microbiology, Faculty of Medicine, University of Zaragoza, Zaragoza, Spain, **2** CIBERES and Research Network on Respiratory Diseases, Spanish Ministry of Health and Instituto de Salud Carlos III, Madrid, Spain, **3** Department of Internal Medicine and Radboud Center for Infectious diseases (RCI), Radboud University Nijmegen Medical Centre, Geert Grooteplein 8, Nijmegen, the Netherlands, **4** Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, Porto, Portugal, **5** Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain, **6** Servicio de Microbiología, Hospital Miguel Servet, ISS Aragón, Zaragoza, Spain, **7** Department for Genomics & Immunoregulation, Life and Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany, **8** Human Genomics Laboratory, Craiova University of Medicine and Pharmacy, Craiova, Romania

☯ These authors contributed equally to this work.
‡ These authors joint senior authors on this work
* jorge.dominguezandres@radboudumc.nl



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## Abstract

Among infectious diseases, tuberculosis is the leading cause of death worldwide, and represents a serious threat, especially in developing countries. The protective effects of *Bacillus Calmette-Guerin* (BCG), the current vaccine against tuberculosis, have been related not only to specific induction of T-cell immunity, but also with the long-term epigenetic and metabolic reprogramming of the cells from the innate immune system through a process termed trained immunity. Here we show that MTBVAC, a live attenuated strain of *Mycobacterium tuberculosis*, safe and immunogenic against tuberculosis antigens in adults and newborns, is also able to generate trained immunity through the induction of glycolysis and glutaminolysis and the accumulation of histone methylation marks at the promoters of proinflammatory genes, facilitating an enhanced response after secondary challenge with non-related bacterial stimuli. Importantly, these findings in human primary myeloid cells are complemented by a strong MTBVAC-induced heterologous protection against a lethal challenge with *Streptococcus pneumoniae* in an experimental murine model of pneumonia.

## Author summary

*Mycobacterium tuberculosis* has been causing infections in our species and our ancestors for at least thousands of years. Still today, the numbers of people affected by tuberculosis are alarming with more than 1,4 million deaths per year, representing the first cause of



frontiers in Immunology

ORIGINAL RESEARCH
published: 13 August 2020
doi: 10.3389/fimmu.2020.01996



# Treatment and Prevention of Lung Cancer Using a Virus-Infected Reprogrammed Somatic Cell-Derived Tumor Cell Vaccination (VIReST) Regime

***Zhe Zhang[1], Shuangshuang Lu[2], Louisa S. Chard Dunmall[3], Zhizhong Wang[2], Zhenguo Cheng[2], Zhongxian Zhang[2], Wenli Yan[2], Yongchao Chu[2], Dongling Gao[2], Na Wang[2], Yang Li[2], Jiwei Wang[2], Yuenan Li[2], Yupei Ji[2], Danyang Shan[2], Keke Li[2], Panpan Wang[2], Yunshu Dong[4], Jianzeng Dong[5], Nick R. Lemoine[2,3], Duanqing Pei[6], Lirong Zhang[7]* and Yaohe Wang[2,3]****

*[1] National Center for International Research in Cell and Gene Therapy, Sino-British Research Centre for Molecular Oncology, School of Basic Medical Sciences, Academy of Medical Sciences, Zhengzhou University, Zhengzhou, China, [2] National Center for International Research in Cell and Gene Therapy, Sino-British Research Centre for Molecular Oncology, Academy of Medical Sciences, Zhengzhou University, Zhengzhou, China, [3] Centre for Biomarkers and Biotherapeutics, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom, [4] CAS Key Laboratory of Infection and Immunity, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China, [5] Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China, [6] CAS Key Laboratory of Regenerative Biology, South China Institute for Stem Cell Biology and Regenerative Medicine, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China, [7] School of Basic Medical Sciences, Academy of Medical Sciences, Zhengzhou University, Zhengzhou, China*

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***Correspondence:**
*Lirong Zhang*
*lrzhang@zzu.edu.cn*
*Yaohe Wang*
*yaohe.wang@qmul.ac.uk*

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Lung cancer is one of the most commonly diagnosed cancer and despite therapeutic advances, mortality remains high. The long period of clinical latency associated with lung cancer provides an ideal window of opportunity to administer vaccines to at-risk individuals that can prevent tumor progression and initiate long-term anti-tumor immune surveillance. Here we describe a personalized vaccination regime that could be applied for both therapeutic and prophylactic prevention of lung cancer, based on the derivation of lung cancer cells from induced pluripotent stem cells. Stem cells from healthy mice were modified to express Cre-dependent $KRAS^{G12D}$ and $Trp53^{R172H}$ prior to differentiation to lung progenitor cells. Subsequent viral delivery of Cre caused activation of exogenous driver mutations, resulting in transformation and development of lung cancer cells. iPSC-derived lung cancer cells were highly antigenically related to lung cancer cells induced in LSL-$KRAS^{G12D/+}$; $Trp53^{R172H/+}$ transgenic mice and were antigenically unrelated to original pluripotent stem cells or pancreatic cancer cells derived using the same technological platform. For vaccination, induced lung cancer cells were infected with oncolytic Adenovirus or Vaccinia virus, to act as vaccine adjuvants, prior to delivery of vaccines sequentially to a murine inducible transgenic model of lung cancer. Application of this Virus-Infected, Reprogrammed Somatic cell-derived Tumor cell (VIReST) regime primed tumor-specific T cell responses that significantly prolonged

PLOS PATHOGENS

RESEARCH ARTICLE

# New live attenuated tuberculosis vaccine MTBVAC induces trained immunity and confers protection against experimental lethal pneumonia

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# Epidemiología TB

1ª causa de muerte global de causa infecciosa: **1,4 millones de muertes**

El **23 %** de la población mundial tiene ITBL

10 000 000 casos nuevos / año → **500 000 TB-XDR**



Tarancón R , *et al*. PLoS Pathog, 2020

# BCG

**Única** vacuna aprobada frente a TB

No buena protección frente a **formas leves e ITBL**

Casi **100 años** de antigüedad

Importancia de los **efectos heterólogos**



Tarancón R , *et al*. PLoS Pathog, 2020

# BCG y mortalidad por todas las causas

Lancet, 1995.

THE LANCET

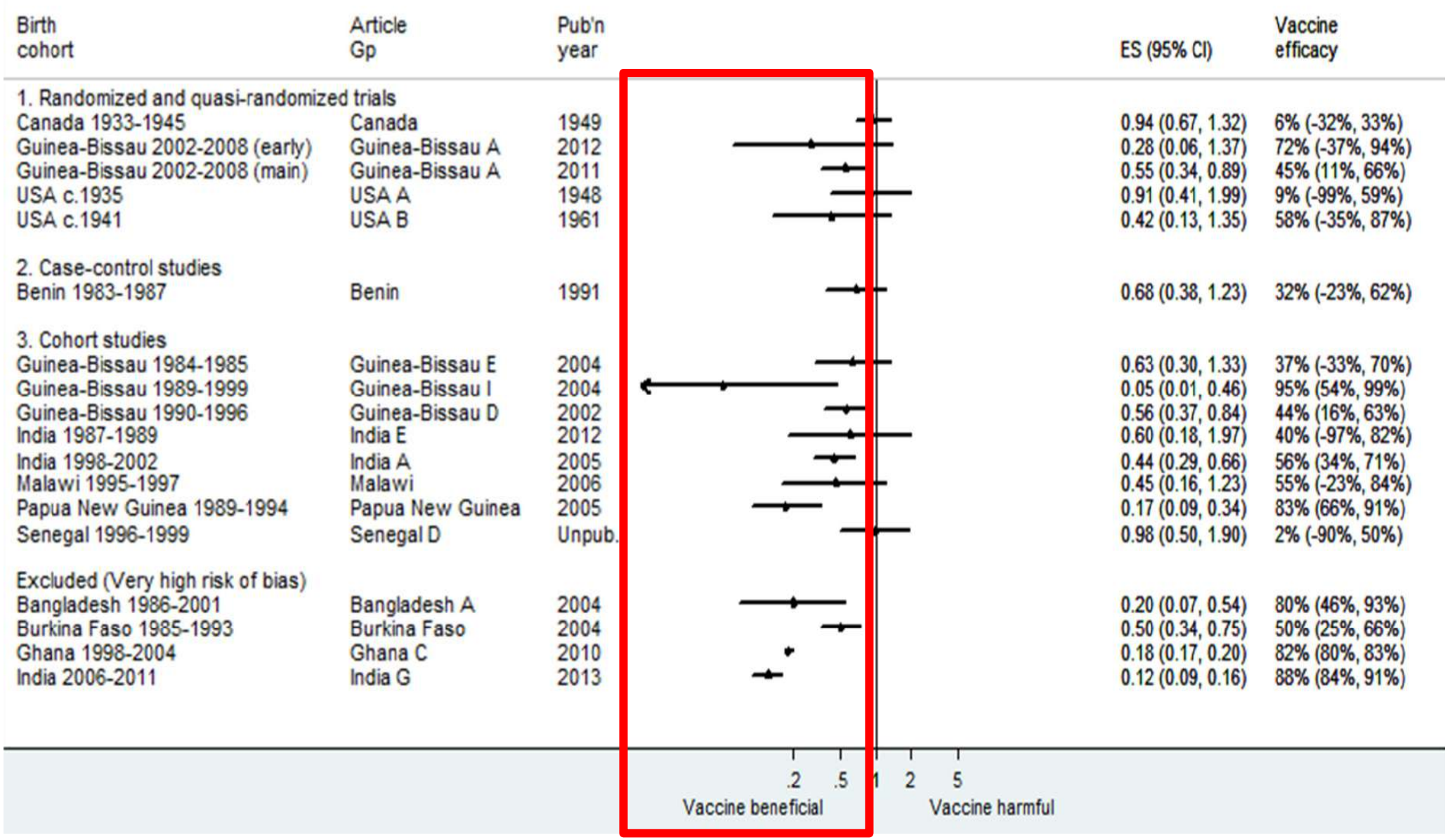
## Variation in protection by BCG: implications of and for heterologous immunity

*P E M Fine*

Besides being the world's most widely used vaccine, and being directed against the world's leading cause of infectious disease mortality, BCG is the most controversial vaccine in current use.[1,2] Estimates of protection imparted by BCG against pulmonary tuberculosis vary from nil to 80%. This variability has been attributed to strain variation in BCG preparations, to genetic or nutritional differences between populations, and to environmental influences such as sunlight exposure, poor cold-chain maintenance, or exposure to environmental mycobacterial infections. Evidence accumulated to date indicates that regional differences in

An alternative view, espoused early by Hart, argued that strain differences between BCG preparations were responsible for most of the observed variation in efficacy.[5] The fact that BCG vaccines produced by different manufacturers were known to differ microbiologically lent credence to this hypothesis. Though one cannot prove that strain differences are not responsible for some of the observed differences in efficacy,[6] the fact that similar vaccines perform very differently in different settings indicates that this cannot be the entire explanation. Prominent examples are provided by Glaxo freeze-dried BCG, which gave good protection against tuberculosis in

# BCG y mortalidad por todas las causas

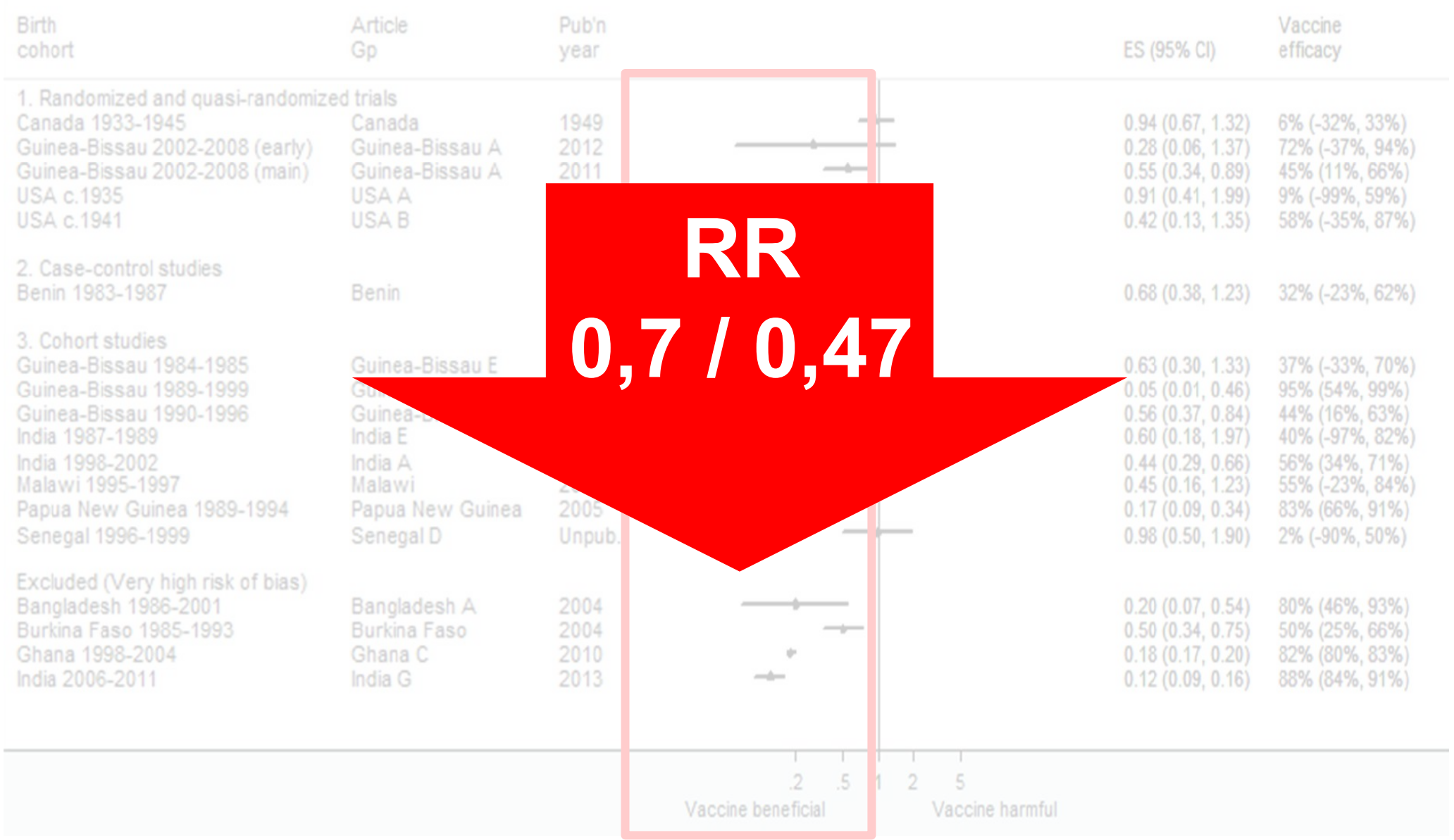


| Birth cohort | Article Gp | Pub'n year | ES (95% CI) | Vaccine efficacy |
|---|---|---|---|---|
| 1. Randomized and quasi-randomized trials | | | | |
| Canada 1933-1945 | Canada | 1949 | 0.94 (0.67, 1.32) | 6% (-32%, 33%) |
| Guinea-Bissau 2002-2008 (early) | Guinea-Bissau A | 2012 | 0.28 (0.06, 1.37) | 72% (-37%, 94%) |
| Guinea-Bissau 2002-2008 (main) | Guinea-Bissau A | 2011 | 0.55 (0.34, 0.89) | 45% (11%, 66%) |
| USA c.1935 | USA A | 1948 | 0.91 (0.41, 1.99) | 9% (-99%, 59%) |
| USA c.1941 | USA B | 1961 | 0.42 (0.13, 1.35) | 58% (-35%, 87%) |
| 2. Case-control studies | | | | |
| Benin 1983-1987 | Benin | 1991 | 0.68 (0.38, 1.23) | 32% (-23%, 62%) |
| 3. Cohort studies | | | | |
| Guinea-Bissau 1984-1985 | Guinea-Bissau E | 2004 | 0.63 (0.30, 1.33) | 37% (-33%, 70%) |
| Guinea-Bissau 1989-1999 | Guinea-Bissau I | 2004 | 0.05 (0.01, 0.46) | 95% (54%, 99%) |
| Guinea-Bissau 1990-1996 | Guinea-Bissau D | 2002 | 0.56 (0.37, 0.84) | 44% (16%, 63%) |
| India 1987-1989 | India E | 2012 | 0.60 (0.18, 1.97) | 40% (-97%, 82%) |
| India 1998-2002 | India A | 2005 | 0.44 (0.29, 0.66) | 56% (34%, 71%) |
| Malawi 1995-1997 | Malawi | 2006 | 0.45 (0.16, 1.23) | 55% (-23%, 84%) |
| Papua New Guinea 1989-1994 | Papua New Guinea | 2005 | 0.17 (0.09, 0.34) | 83% (66%, 91%) |
| Senegal 1996-1999 | Senegal D | Unpub. | 0.98 (0.50, 1.90) | 2% (-90%, 50%) |
| Excluded (Very high risk of bias) | | | | |
| Bangladesh 1986-2001 | Bangladesh A | 2004 | 0.20 (0.07, 0.54) | 80% (46%, 93%) |
| Burkina Faso 1985-1993 | Burkina Faso | 2004 | 0.50 (0.34, 0.75) | 50% (25%, 66%) |
| Ghana 1998-2004 | Ghana C | 2010 | 0.18 (0.17, 0.20) | 82% (80%, 83%) |
| India 2006-2011 | India G | 2013 | 0.12 (0.09, 0.16) | 88% (84%, 91%) |



https://www.who.int/immunization/sage/meetings/2014/april/3_NSE_Epidemiology_review_Report_to_SAGE_14_Mar_FINAL.pdf

# BCG y mortalidad por todas las causas




https://www.who.int/immunization/sage/meetings/2014/april/3_NSE_Epidemiology_review_Report_to_SAGE_14_Mar_FINAL.pdf

# BCG y mortalidad por todas las causas

MAJOR ARTICLE

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

**María José de Castro,[1] Jacobo Pardo-Seco,[2,3] and Federico Martinón-Torres[1,2]**

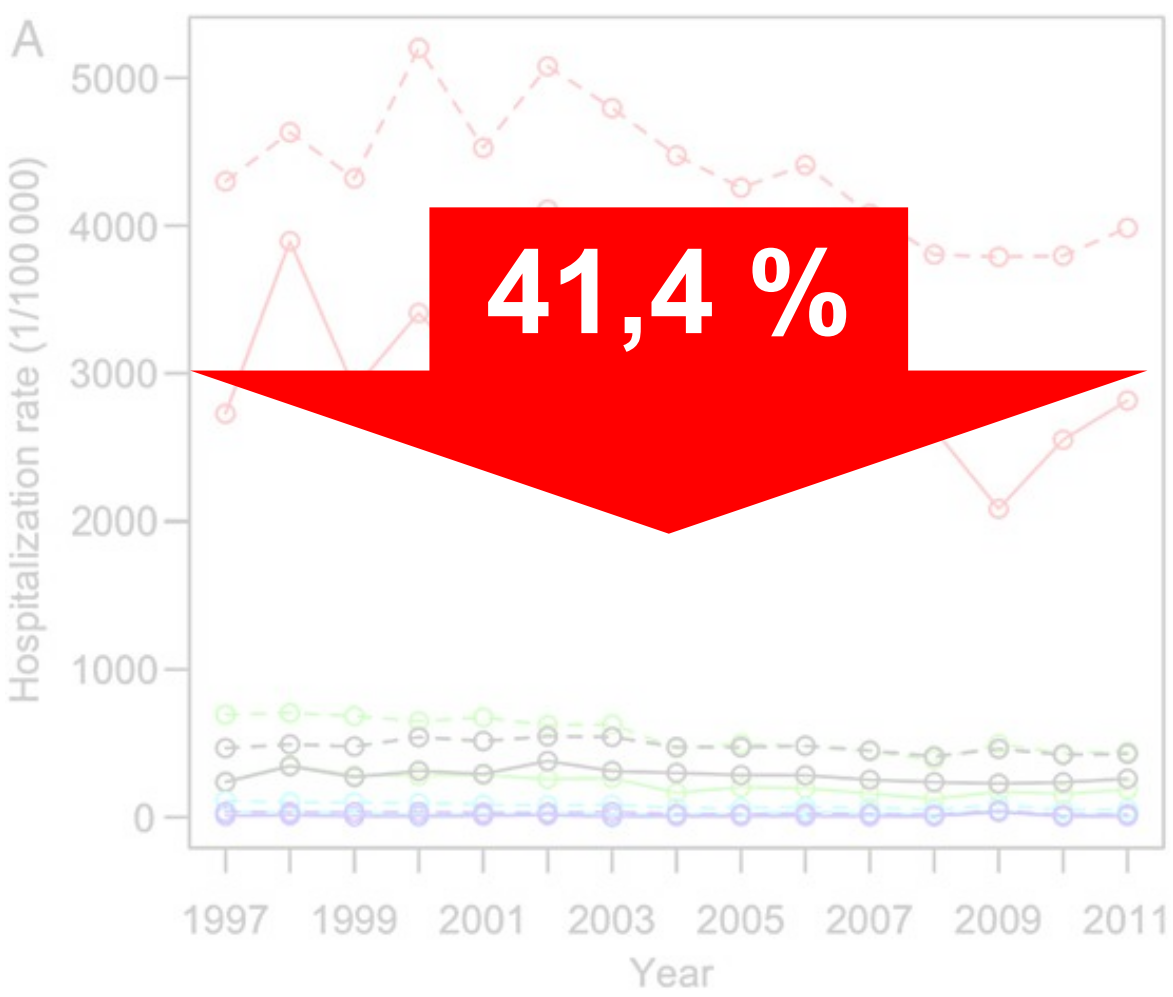
[1]Translational Pediatrics and Infectious Diseases Section, Pediatrics Department, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, [2]Grupo de Investigación en Genética, Vacunas, Infecciones y Pediatría (GENVIP), Instituto de Investigación Sanitaria de Santiago (IDIS), Santiago de Compostela, La Coruña, and [3]Unidad de Genética, Instituto de Ciencias Forenses y Departamento de Anatomía Patológica y Ciencias Forenses, Facultad de Medicina, Universidad de Santiago de Compostela, Galicia, Spain

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

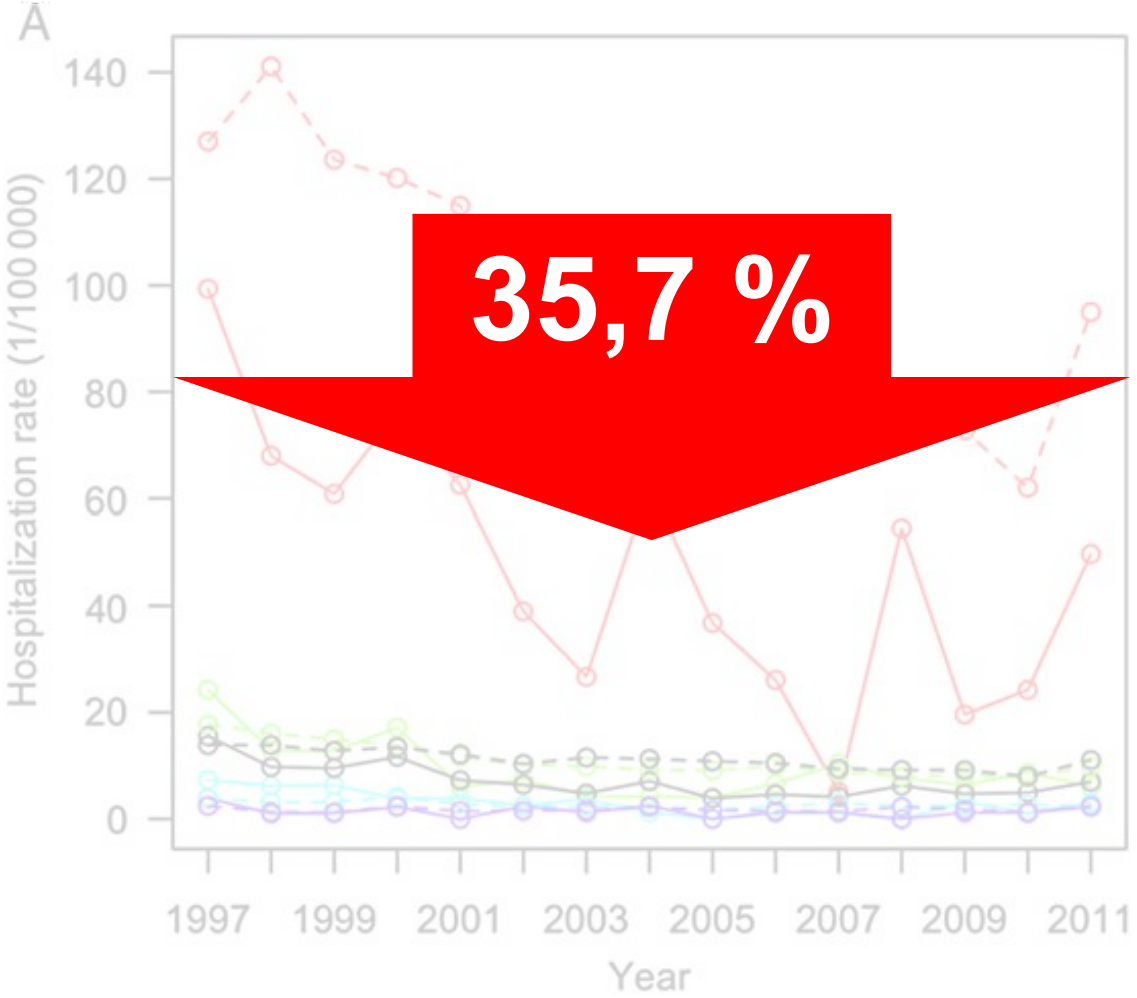
Clin Inf Dis, 2015

# BCG y mortalidad por todas las causas

Tasa de hospitalización
por infección respiratoria




Tasa de hospitalización
por sepsis

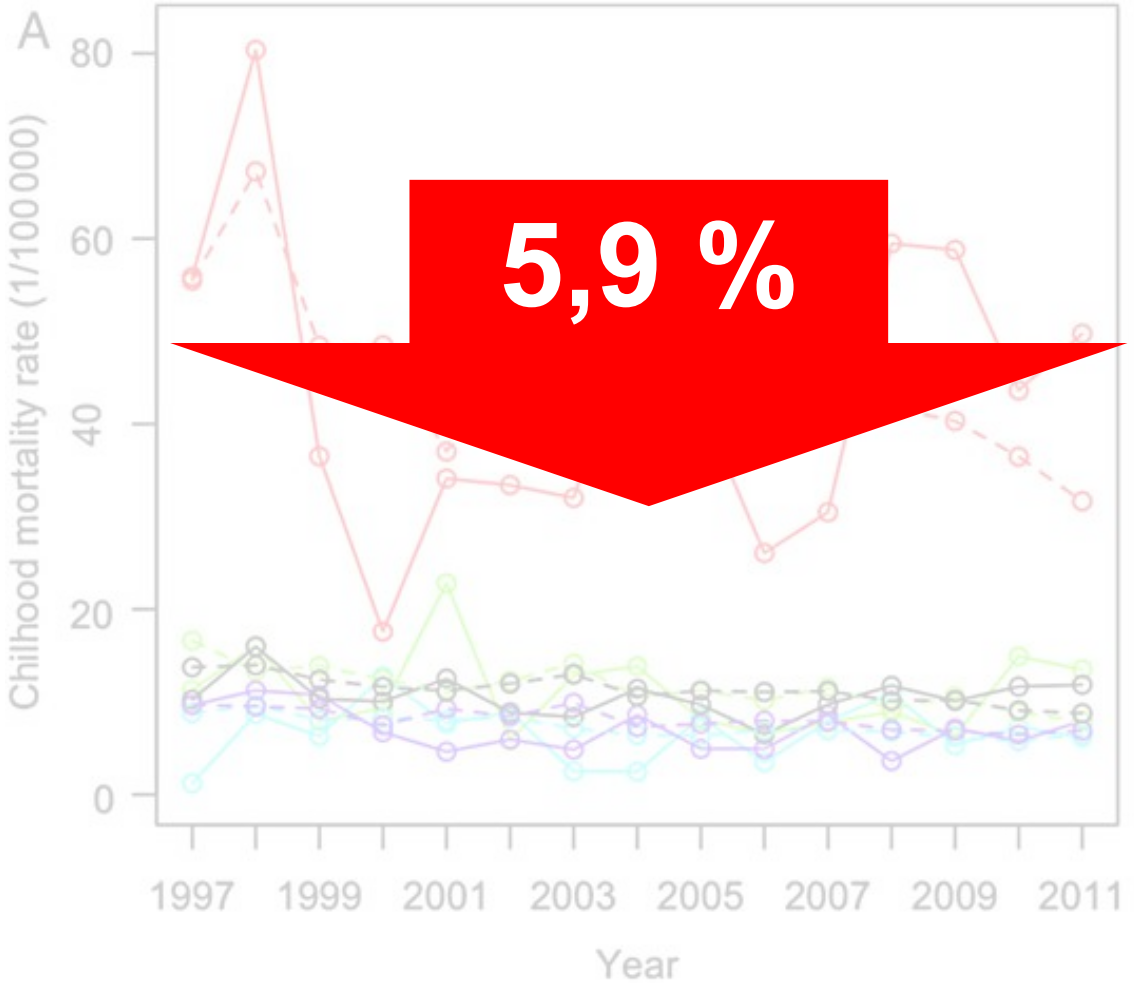



De Castro MJ, *et al*. Clin Inf Dis, 2015

# BCG y mortalidad por todas las causas

Tasa de hospitalización por tuberculosis


Mortalidad por todas las causas



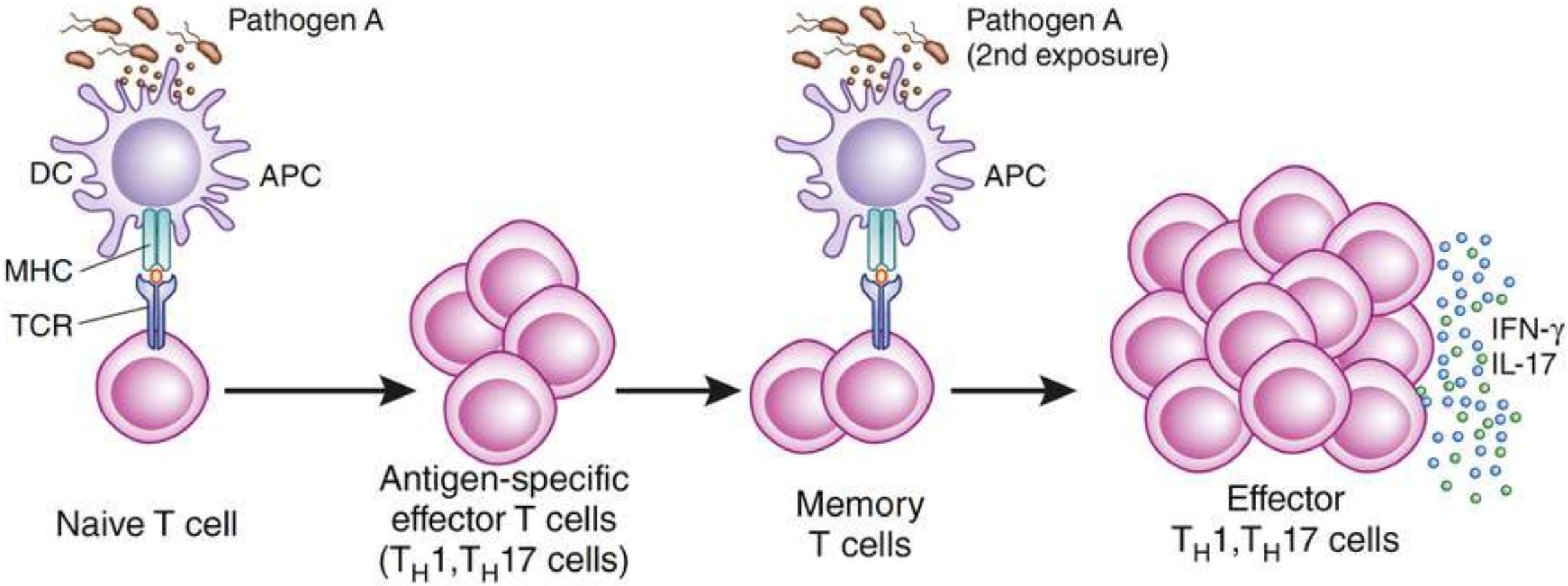

De Castro MJ, *et al*. Clin Inf Dis, 2015

# Efectos heterólogos y BGC: ¿Por qué?

**“Trained immunity”**

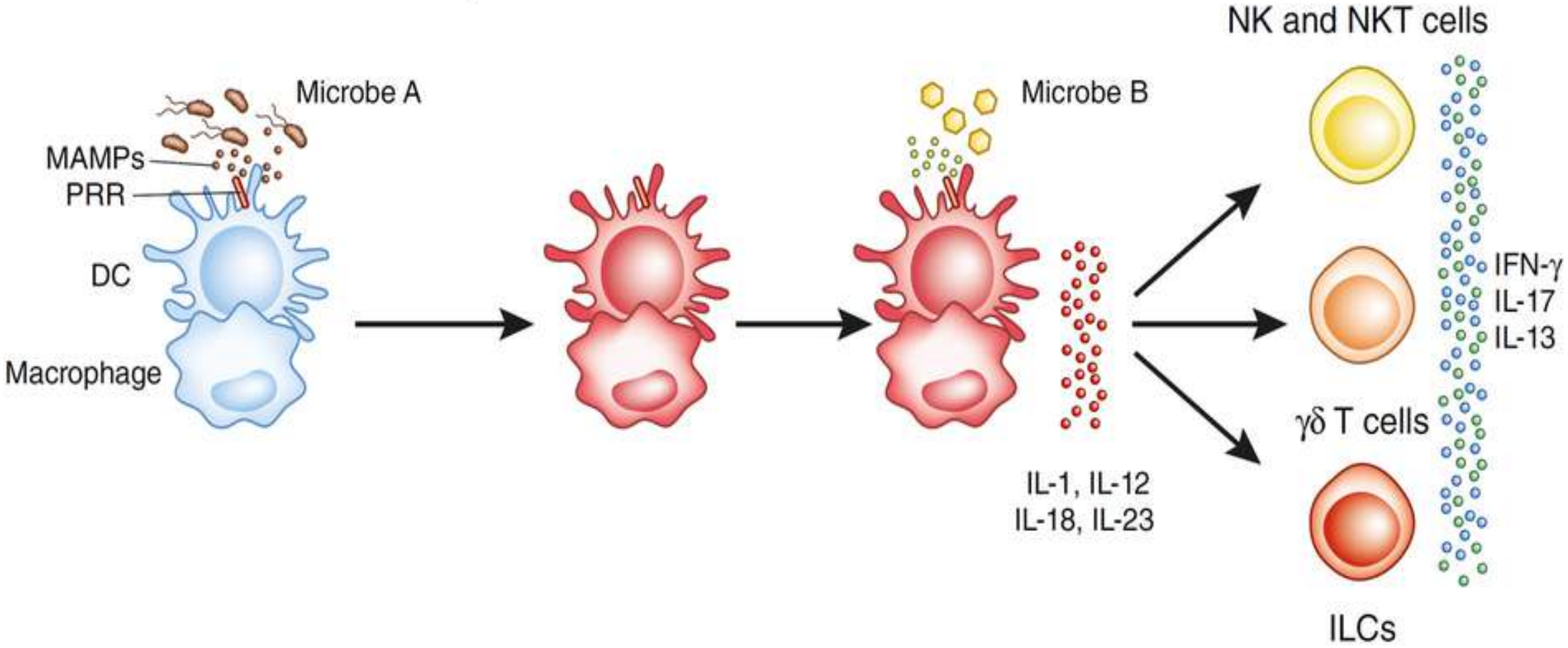
# Entrenamiento inmune

## Prevención **específica**

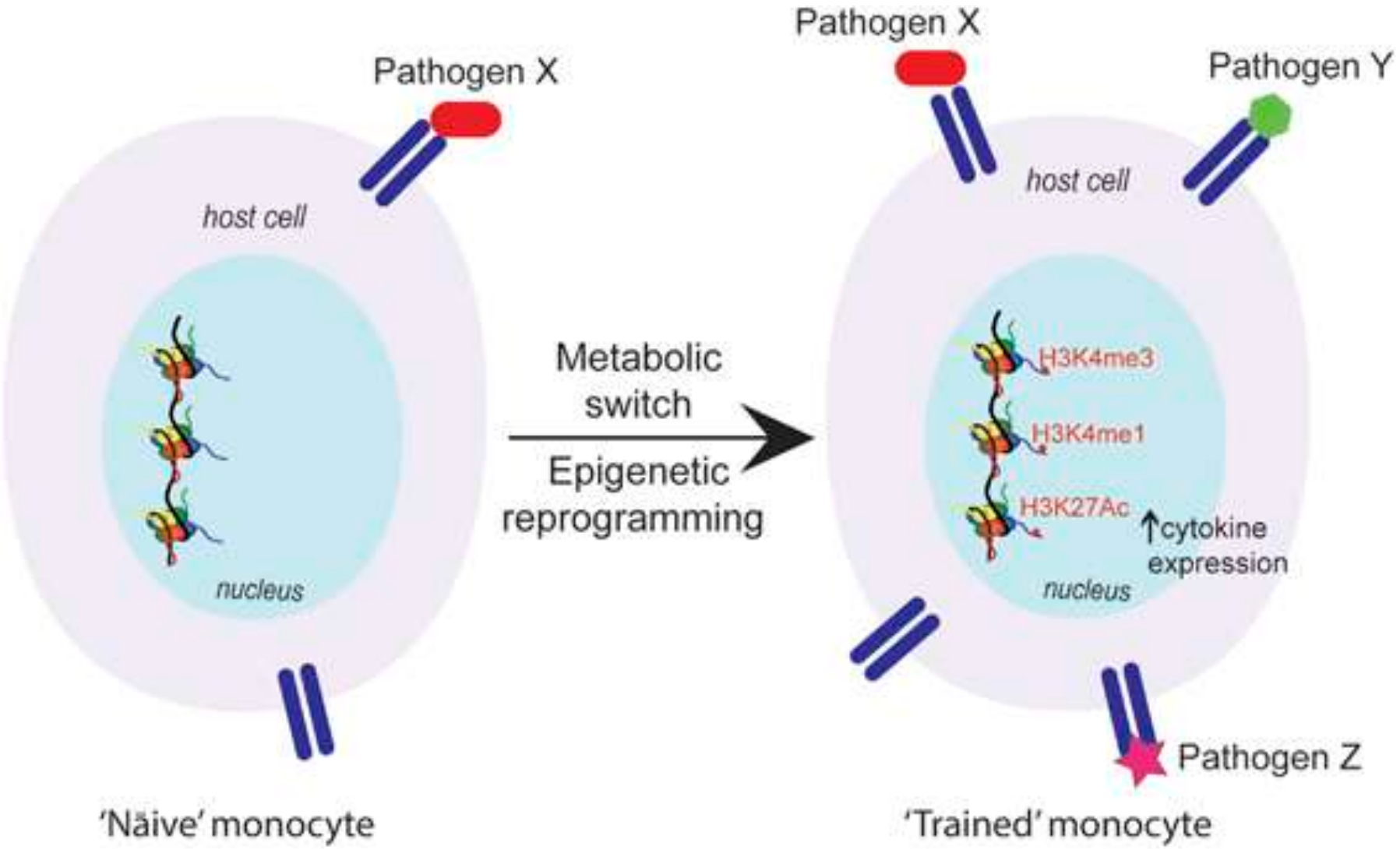


# Entrenamiento inmune

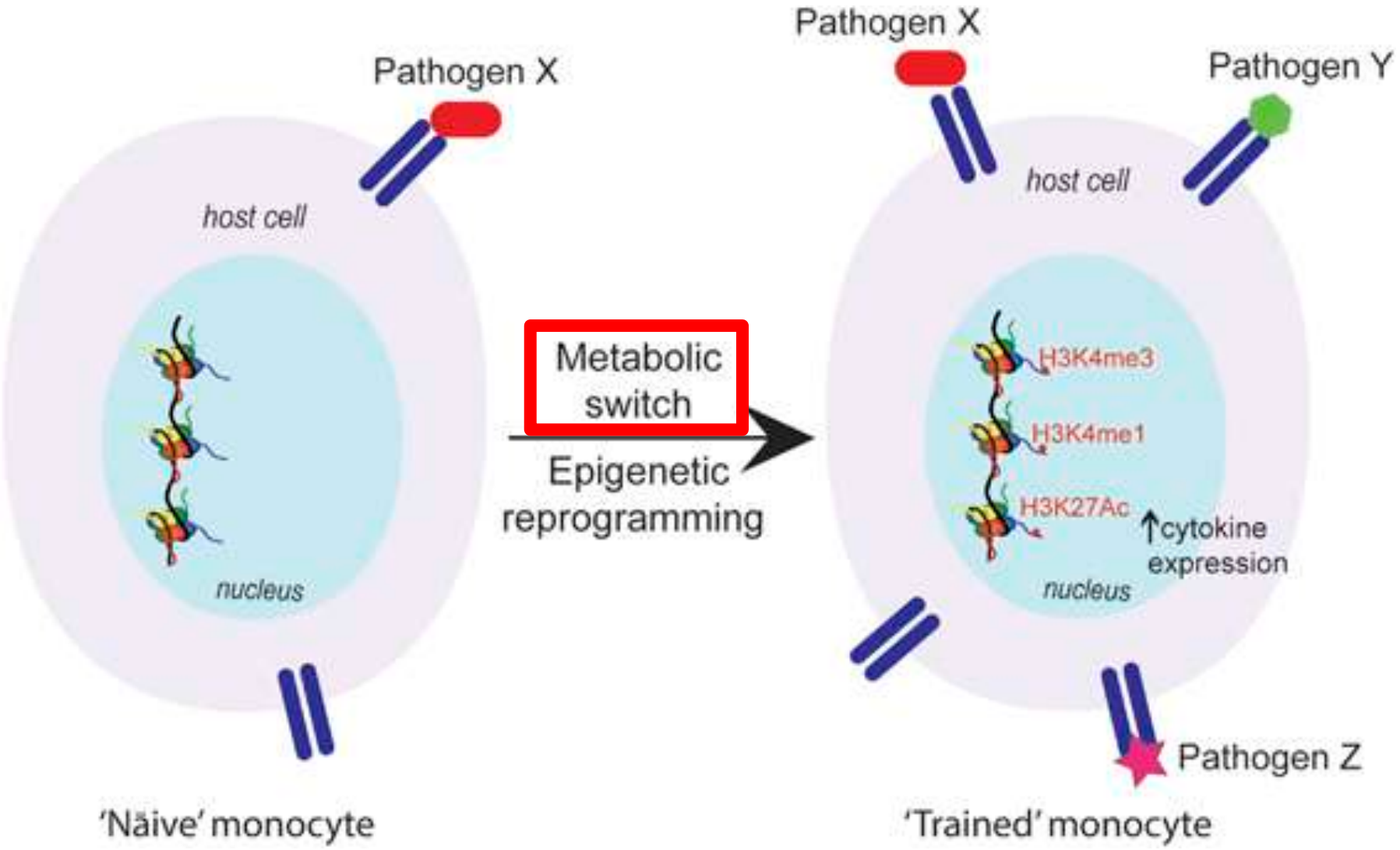
## Prevención **inespecífica**



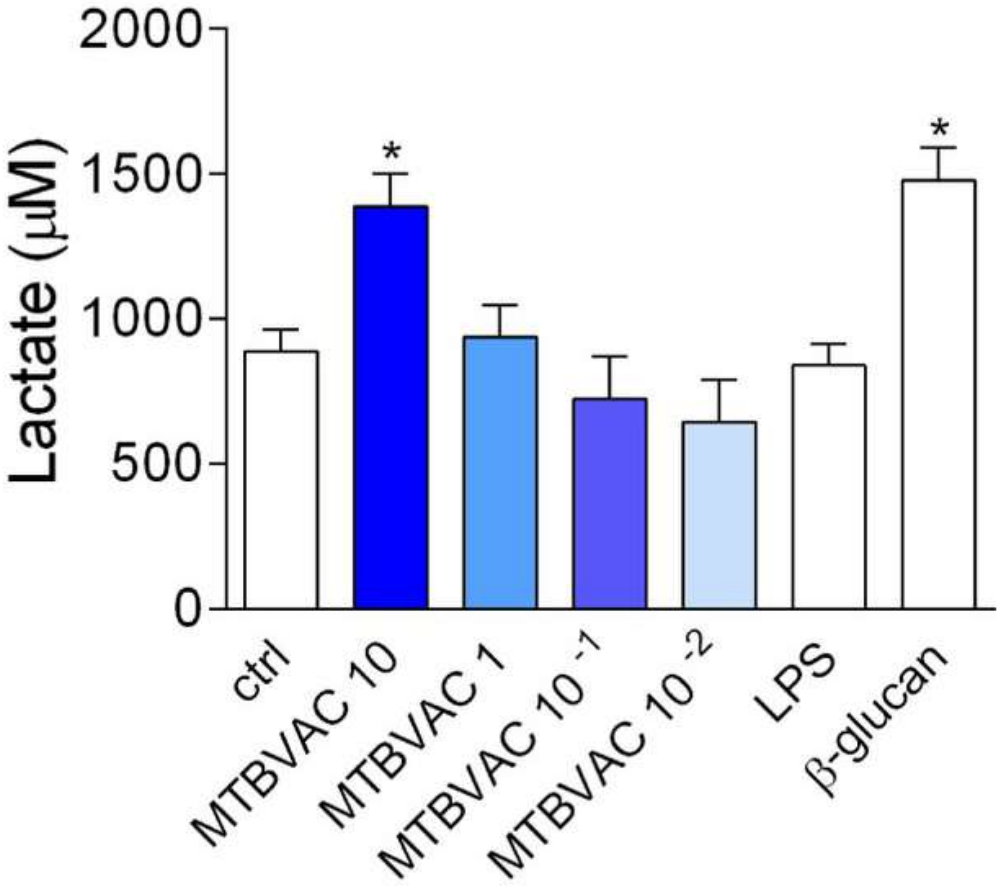
# Entrenamiento inmune

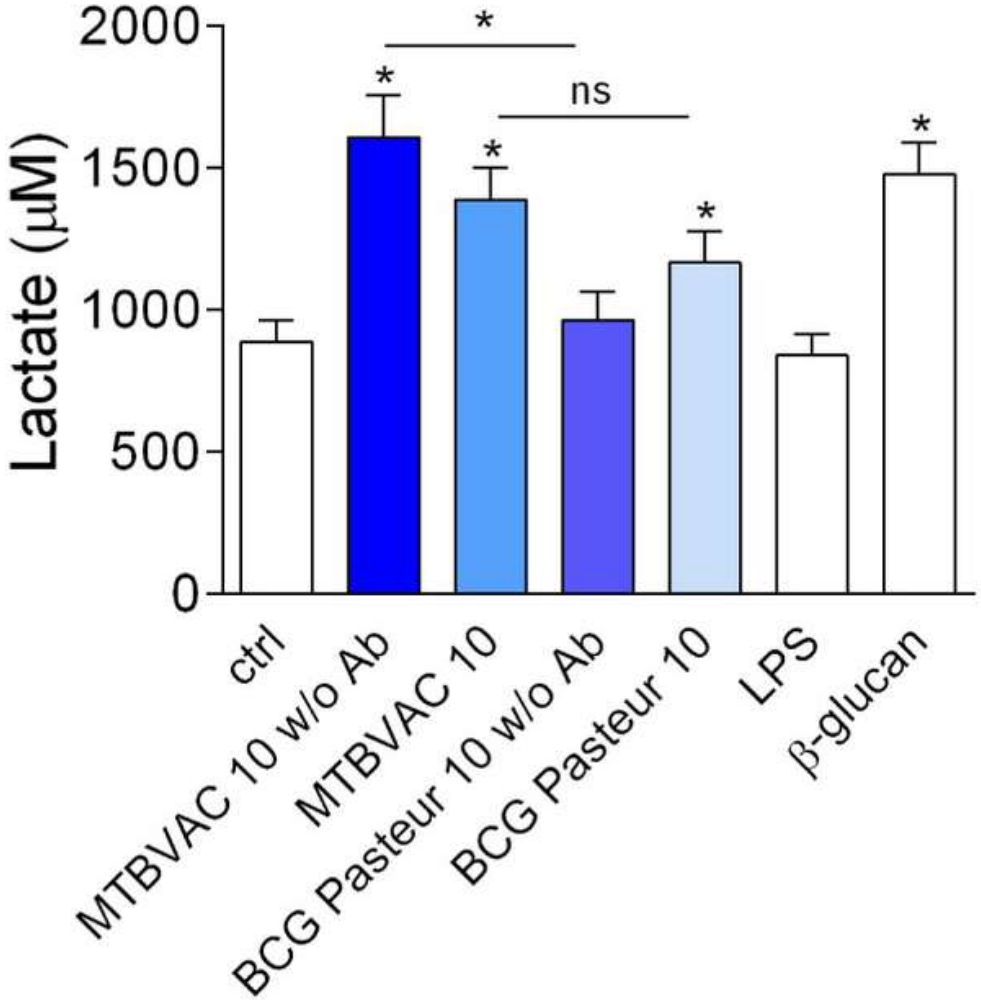


# Entrenamiento inmune



# Aumento de lactato dosis dependiente

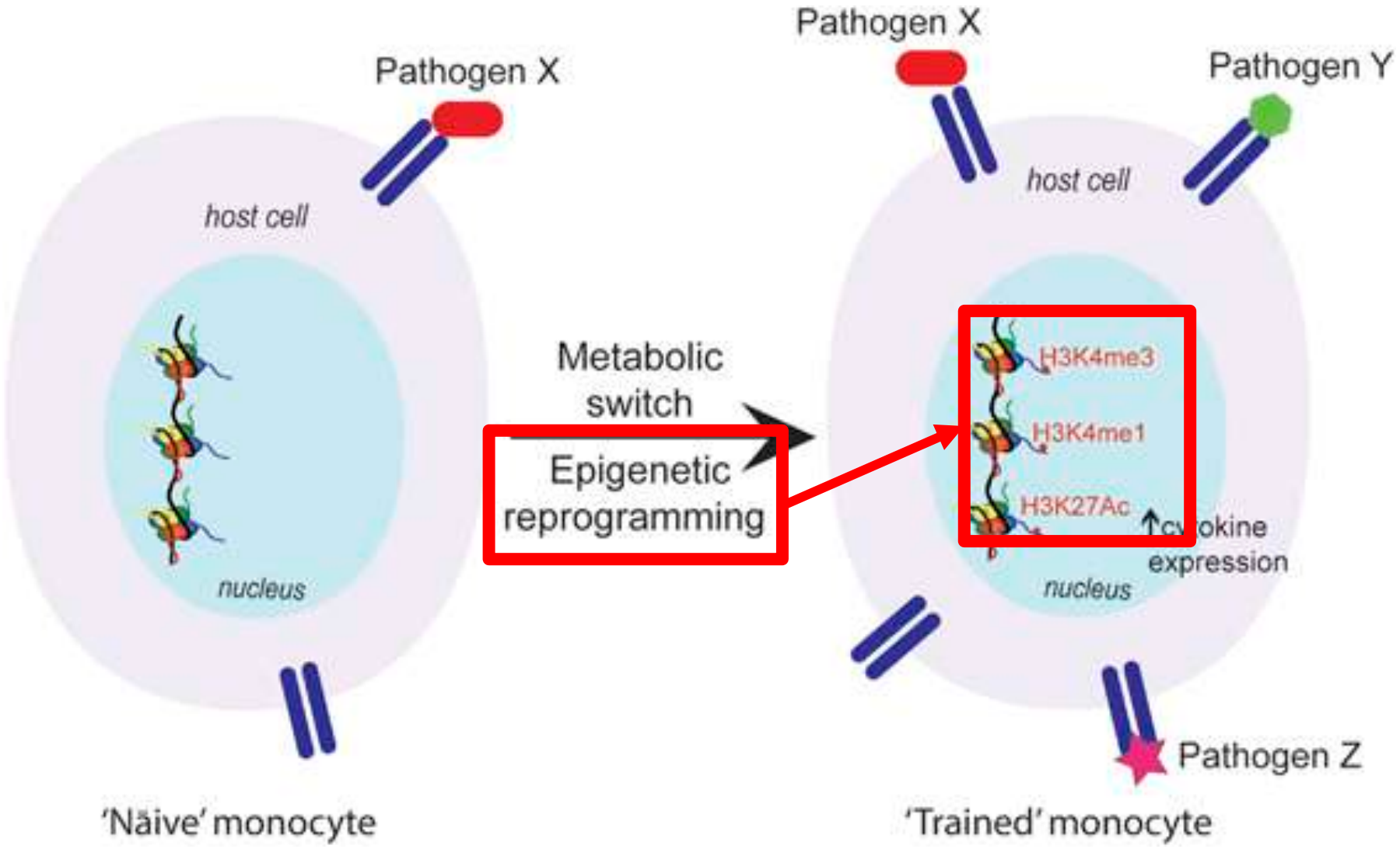


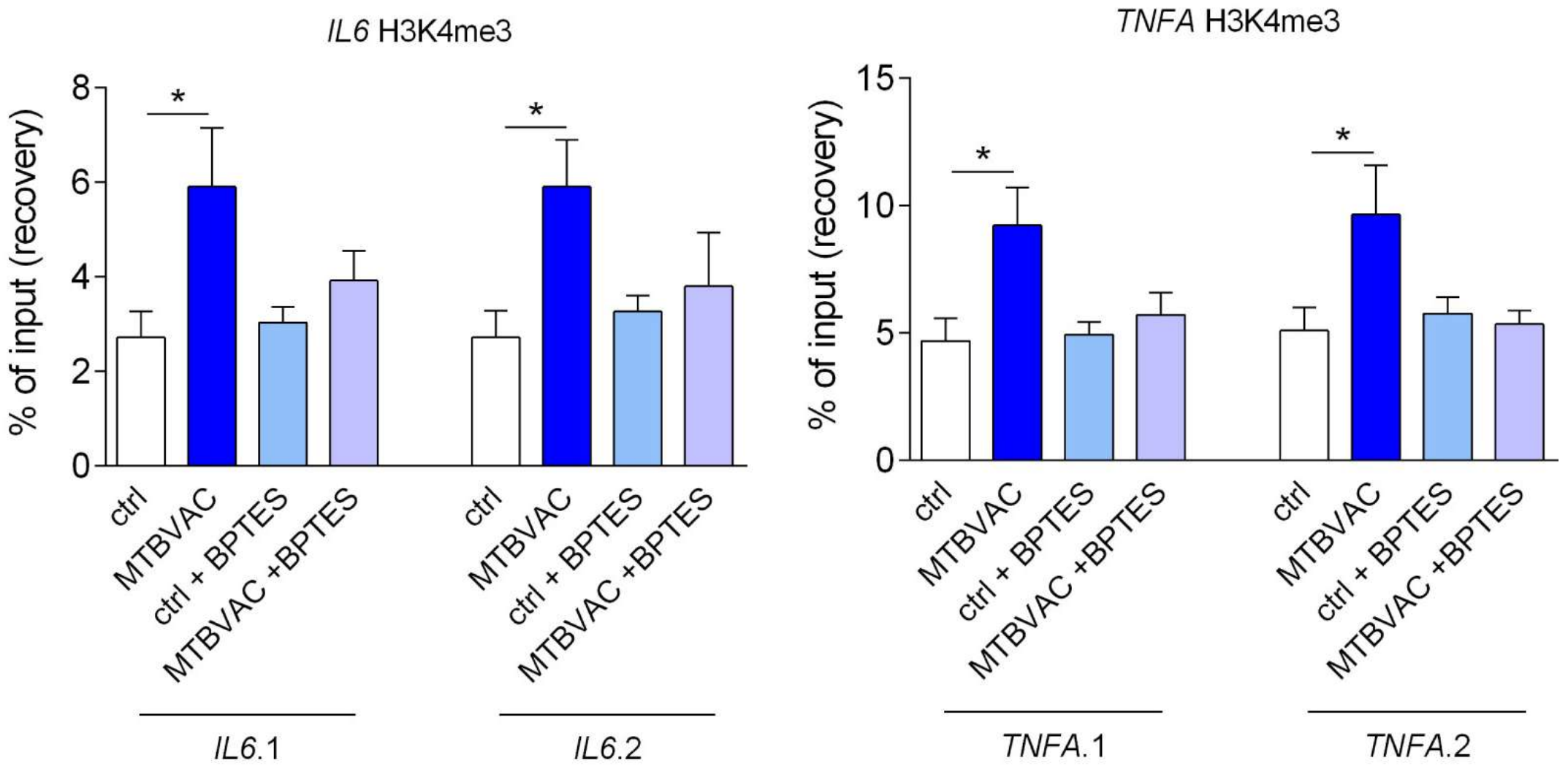



Tarancón R , *et al*. PLoS Pathog, 2020

# Entrenamiento inmune



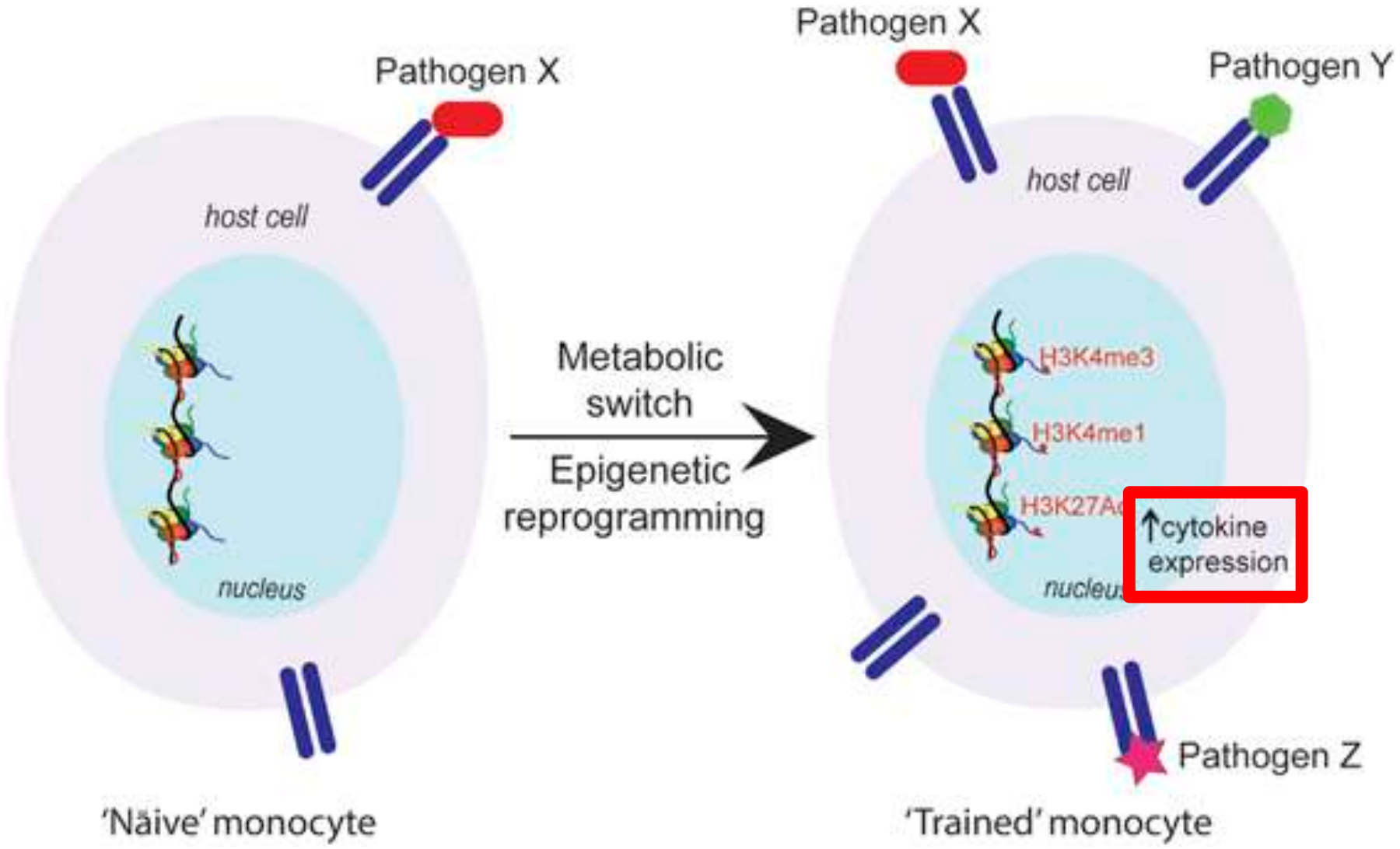
# Cambios epigenéticos en genes de citokinas



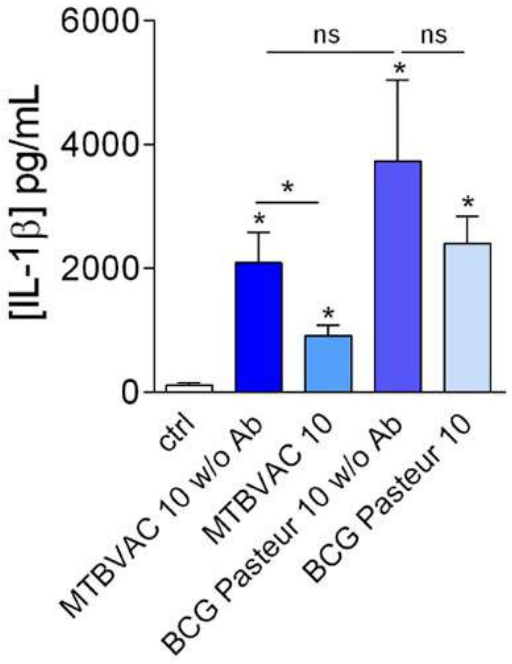


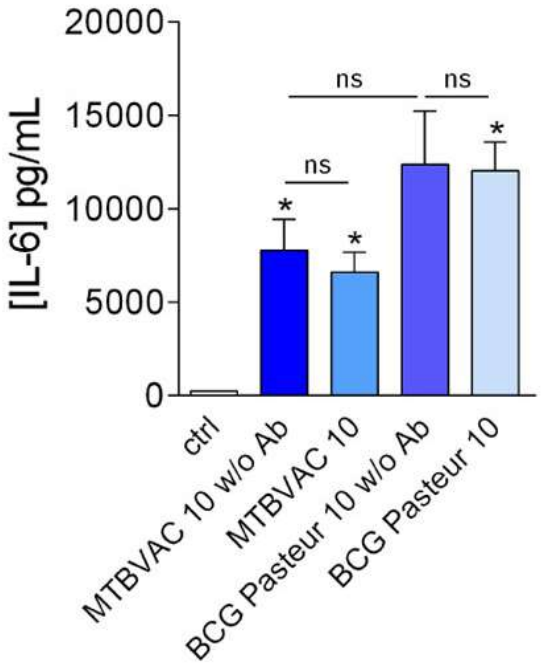

Tarancón R , *et al*. PLoS Pathog, 2020

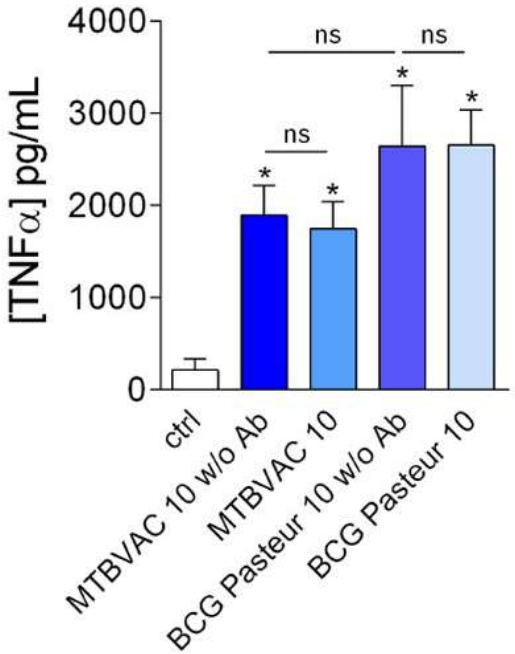
# Entrenamiento inmune

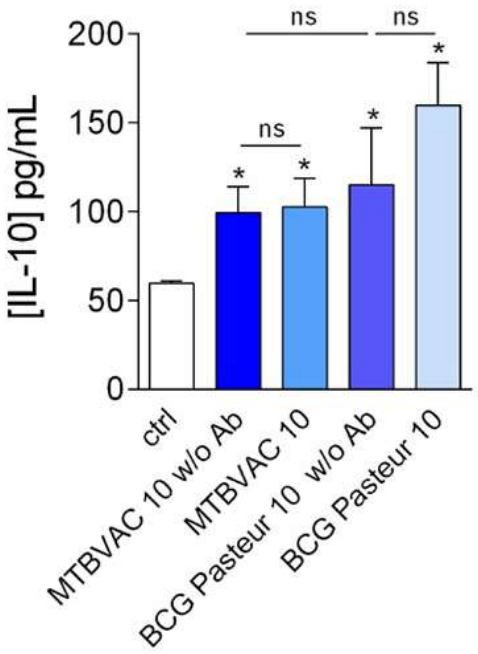


# Respuesta de citokinas *in vitro* similar a BCG






Tarancón R , *et al*. PLoS Pathog, 2020

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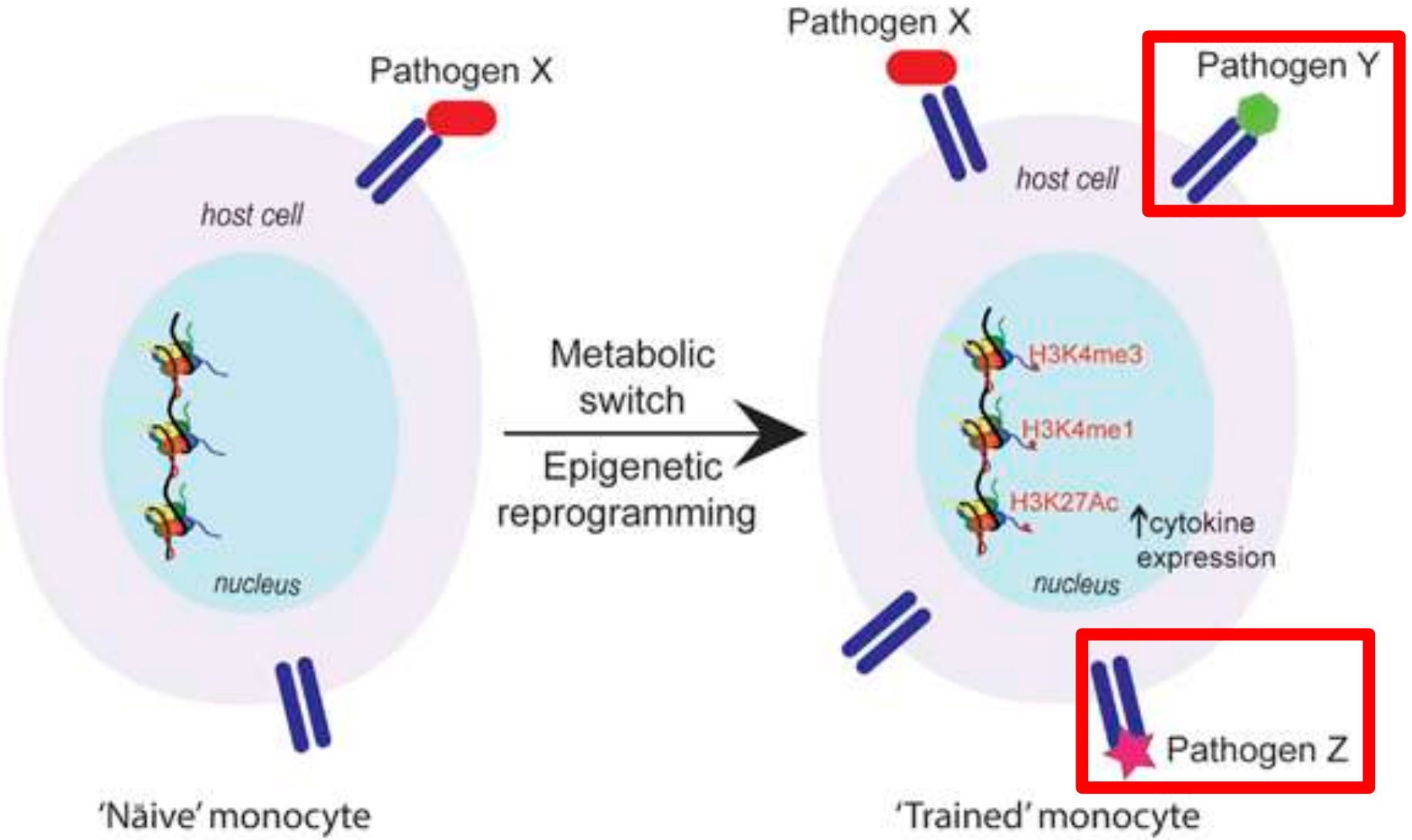
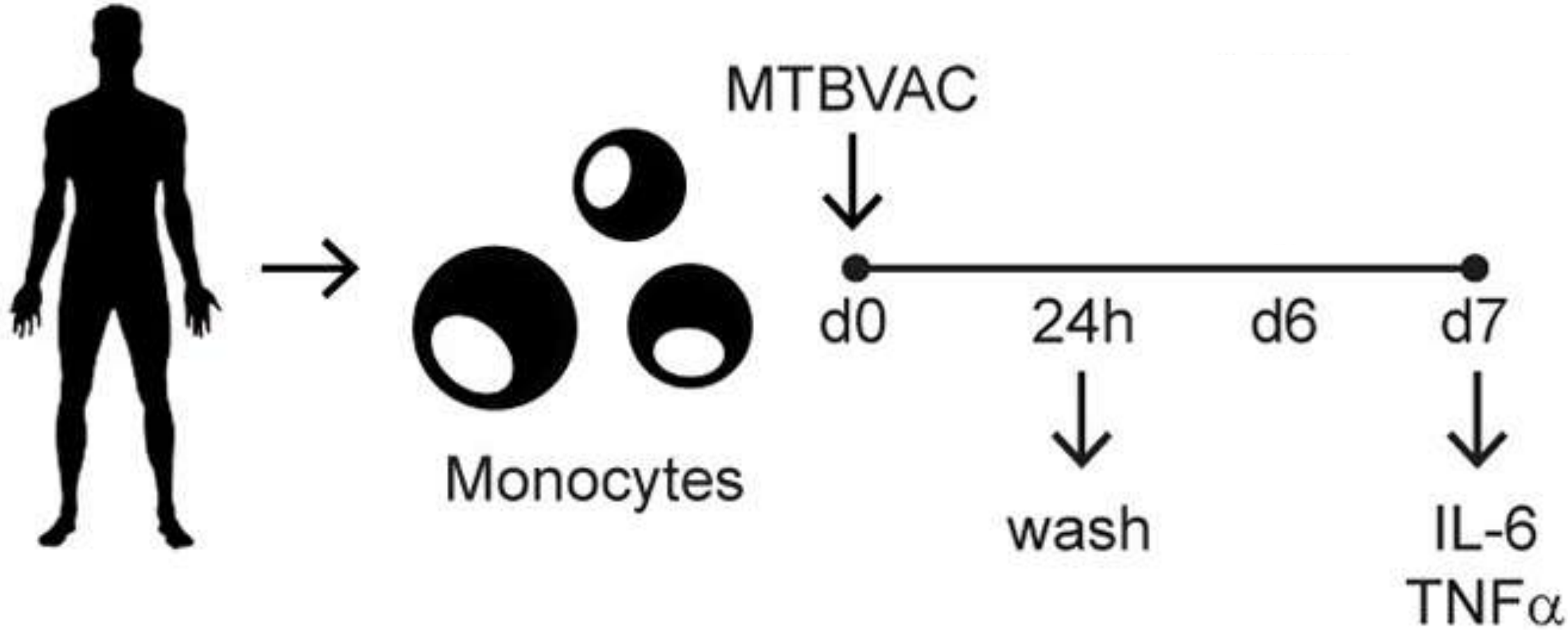


# Producción heteróloga de citokinas *in vitro*






Tarancón R , *et al*. PLoS Pathog, 2020

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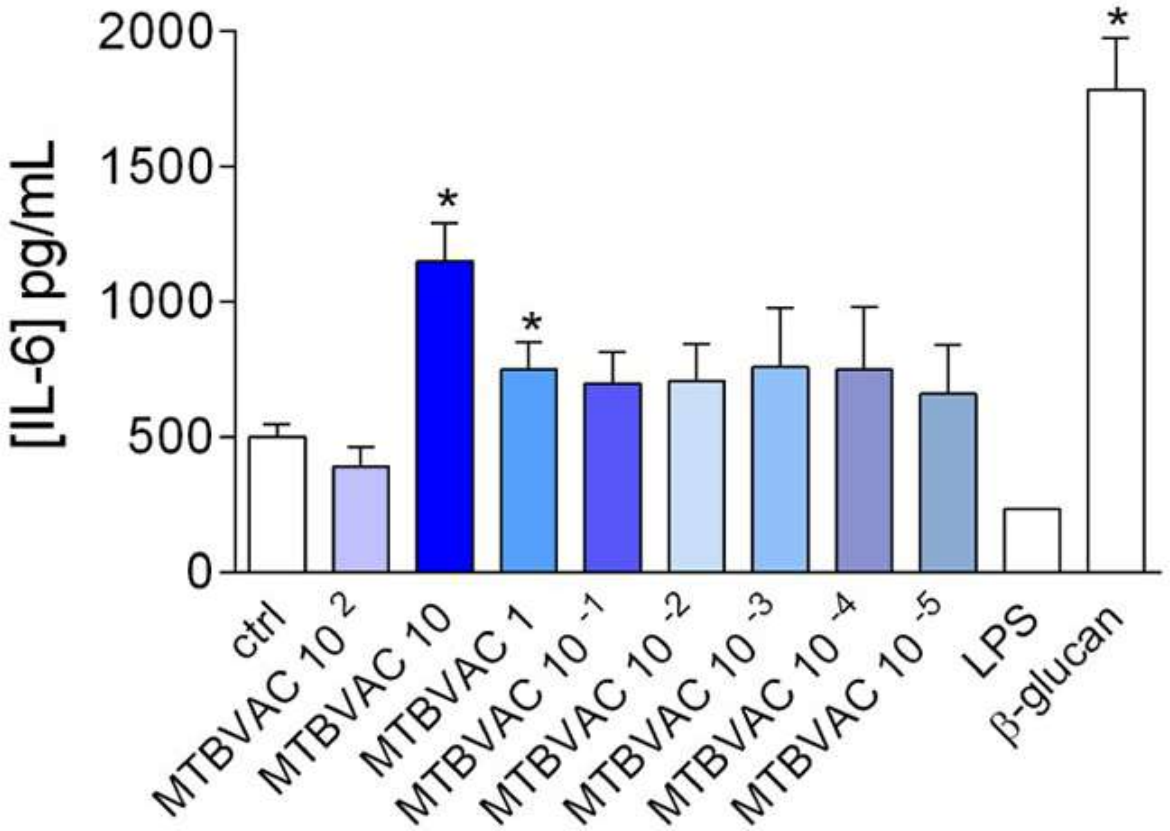
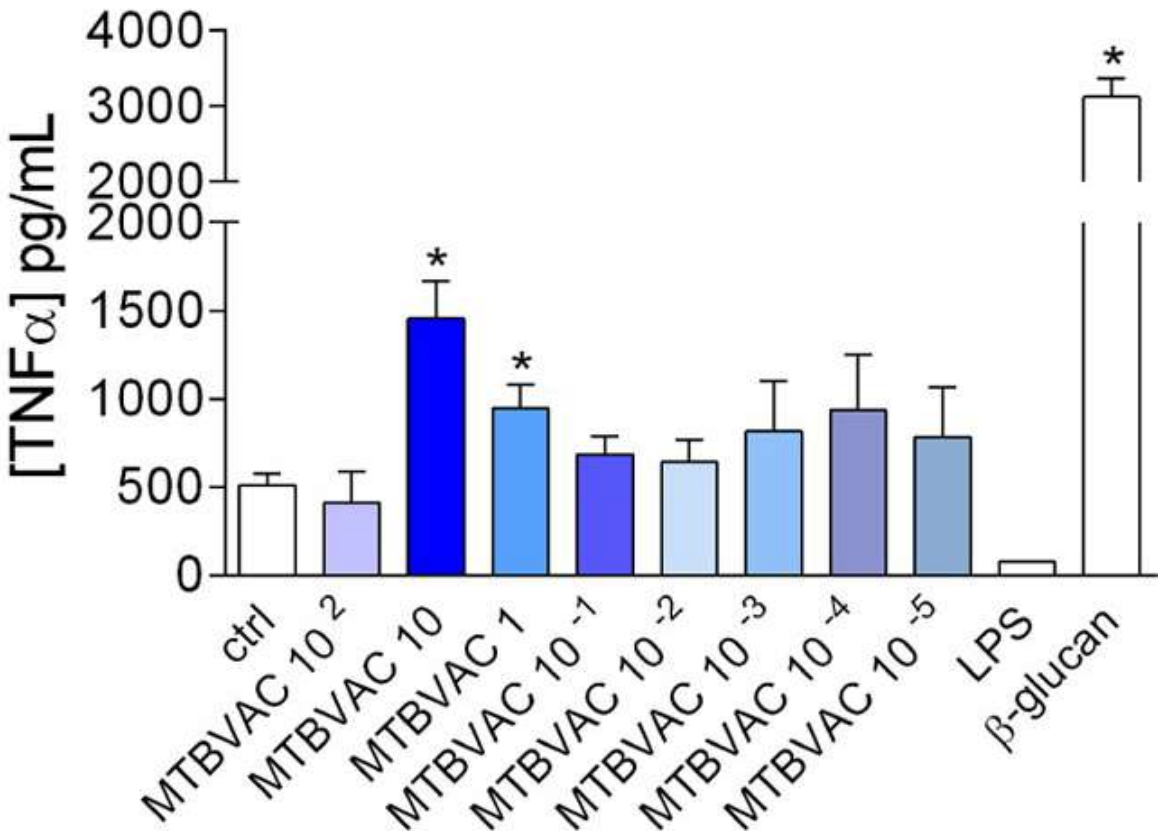
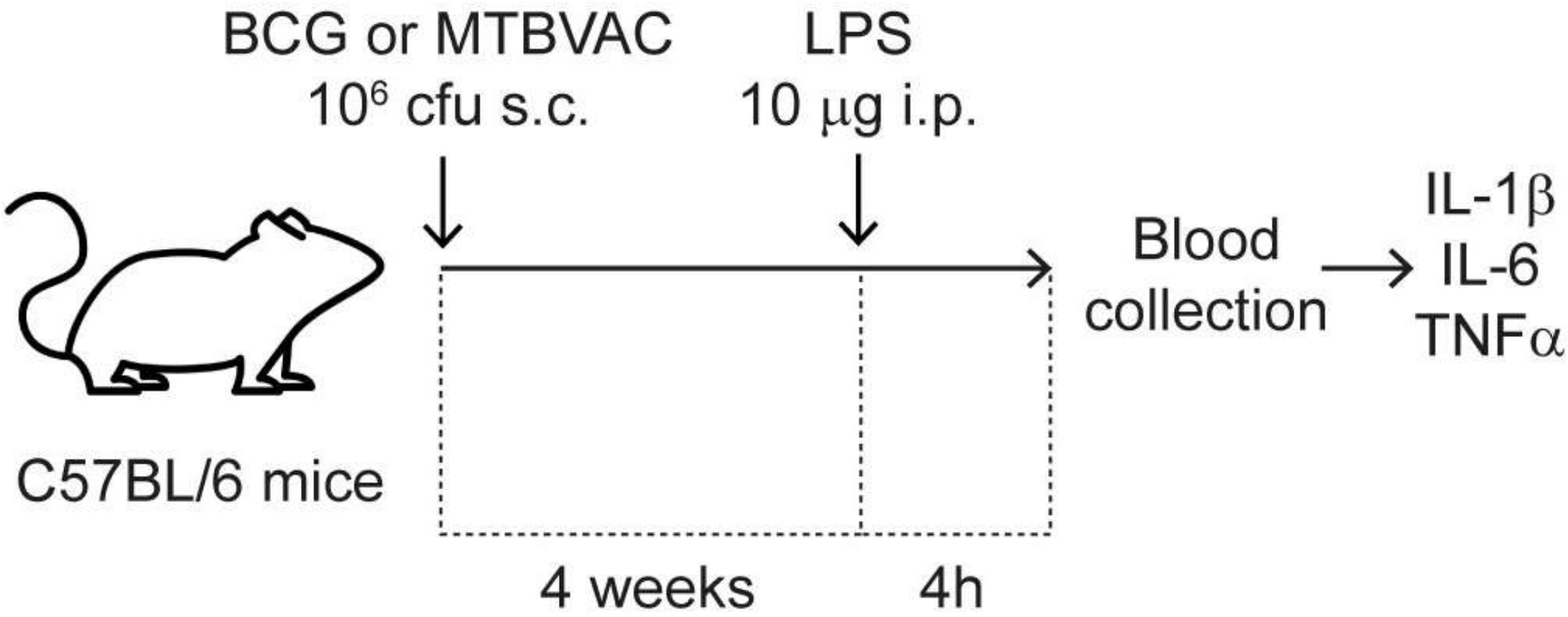





Tarancón R , *et al*. PLoS Pathog, 2020

# Producción heteróloga de citokinas *in vivo*






Tarancón R , *et al*. PLoS Pathog, 2020

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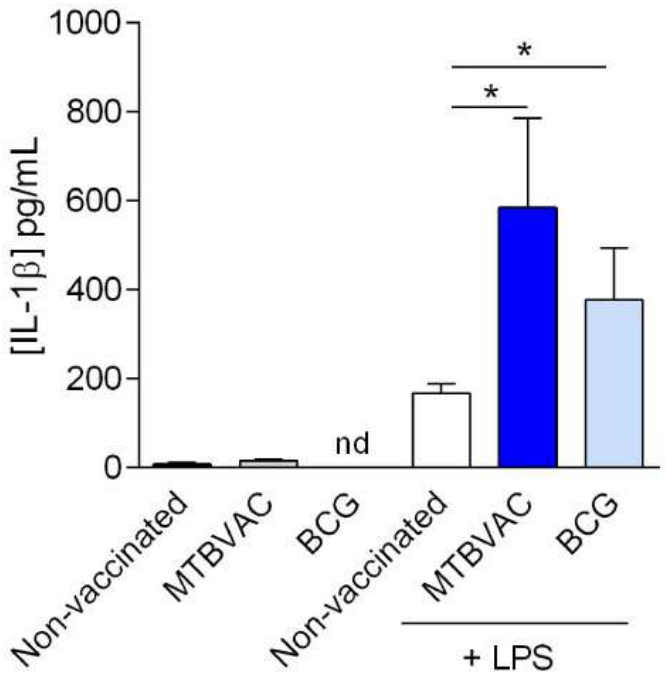
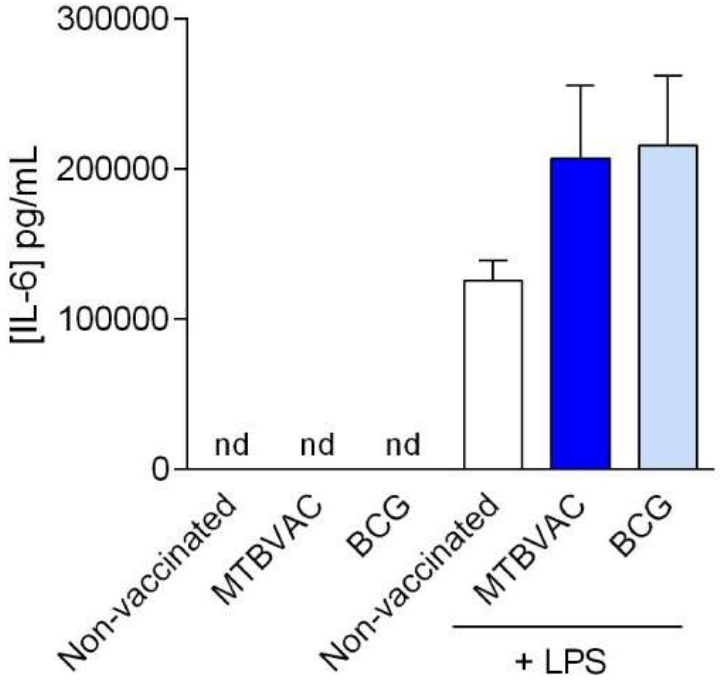
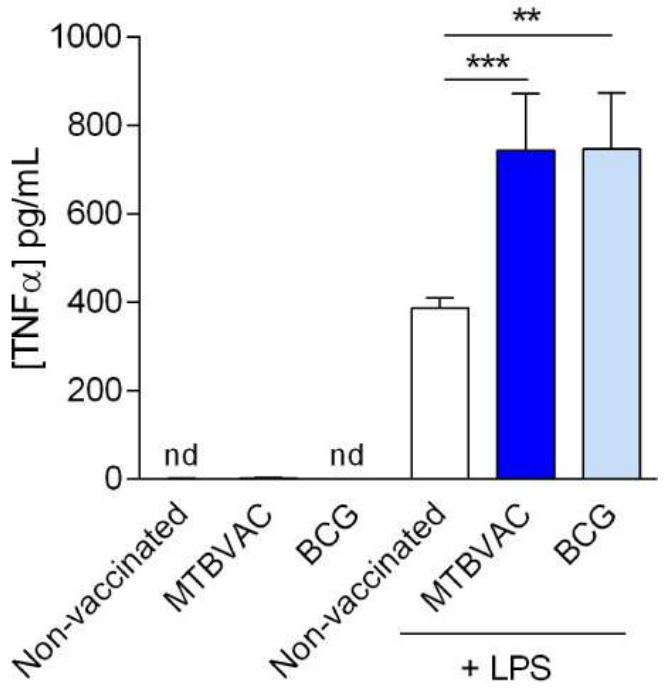


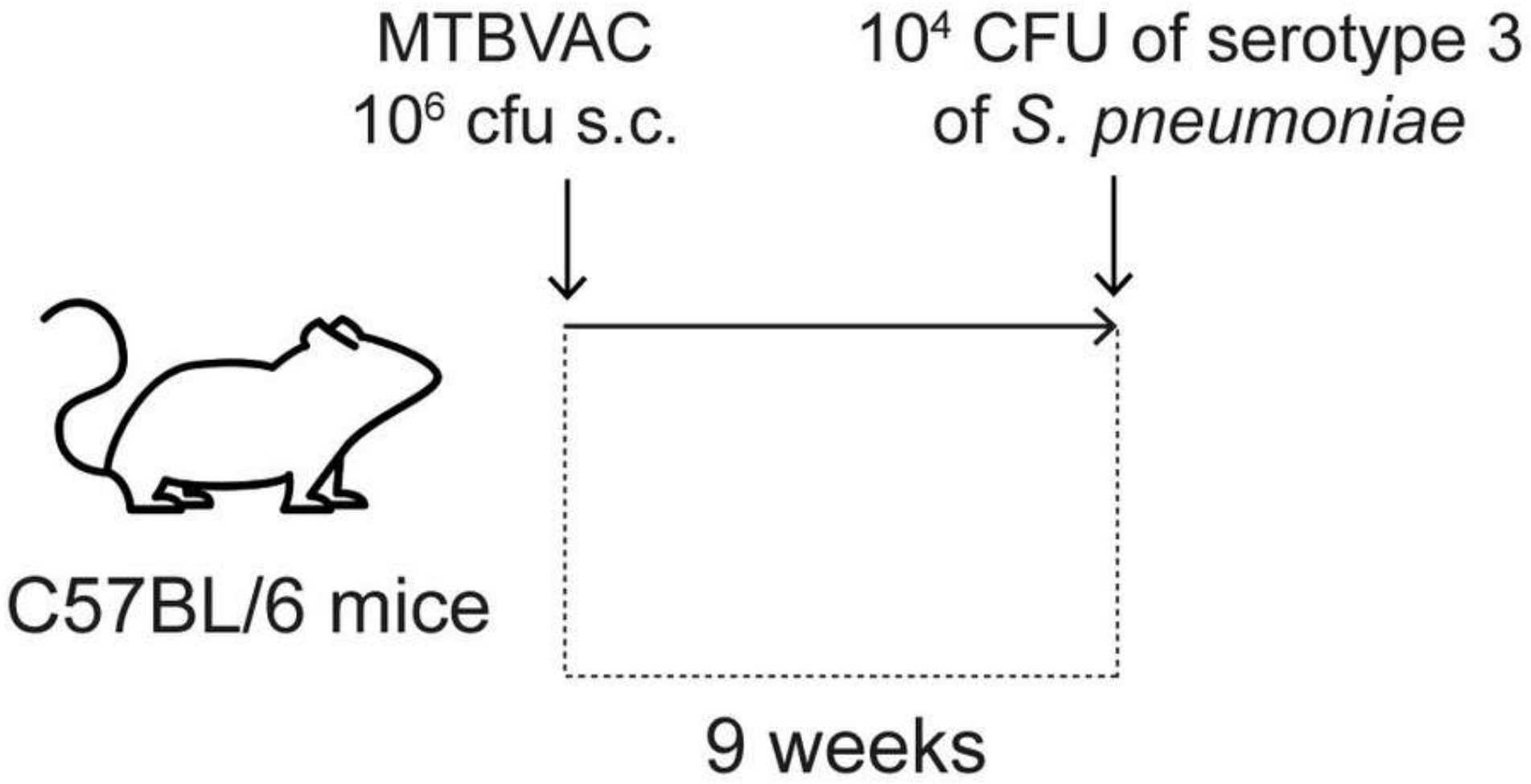






Tarancón R , *et al*. PLoS Pathog, 2020

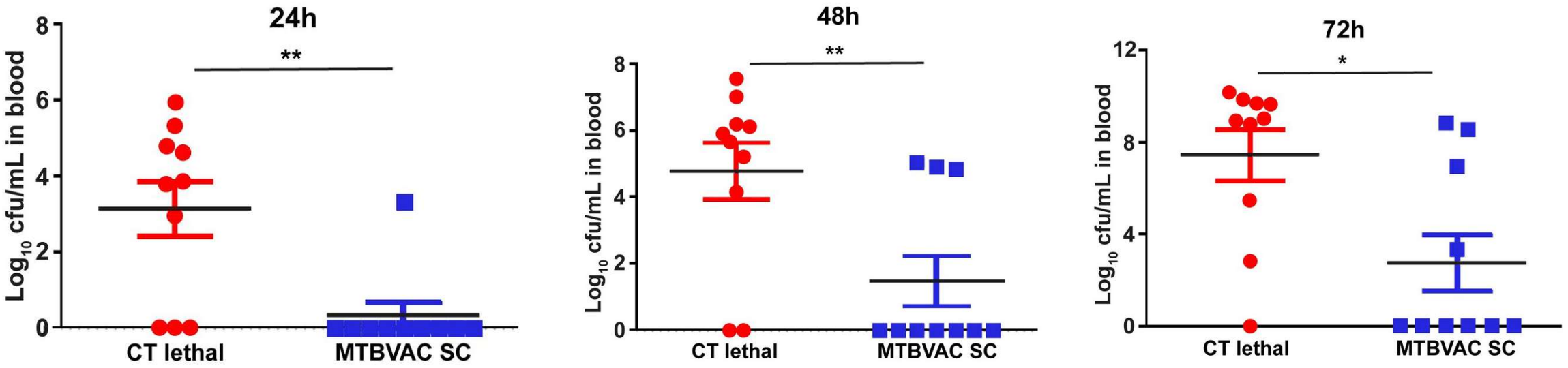
# Protección heteróloga *in vivo*






Tarancón R , *et al*. PLoS Pathog, 2020

# Protección heteróloga *in vivo*



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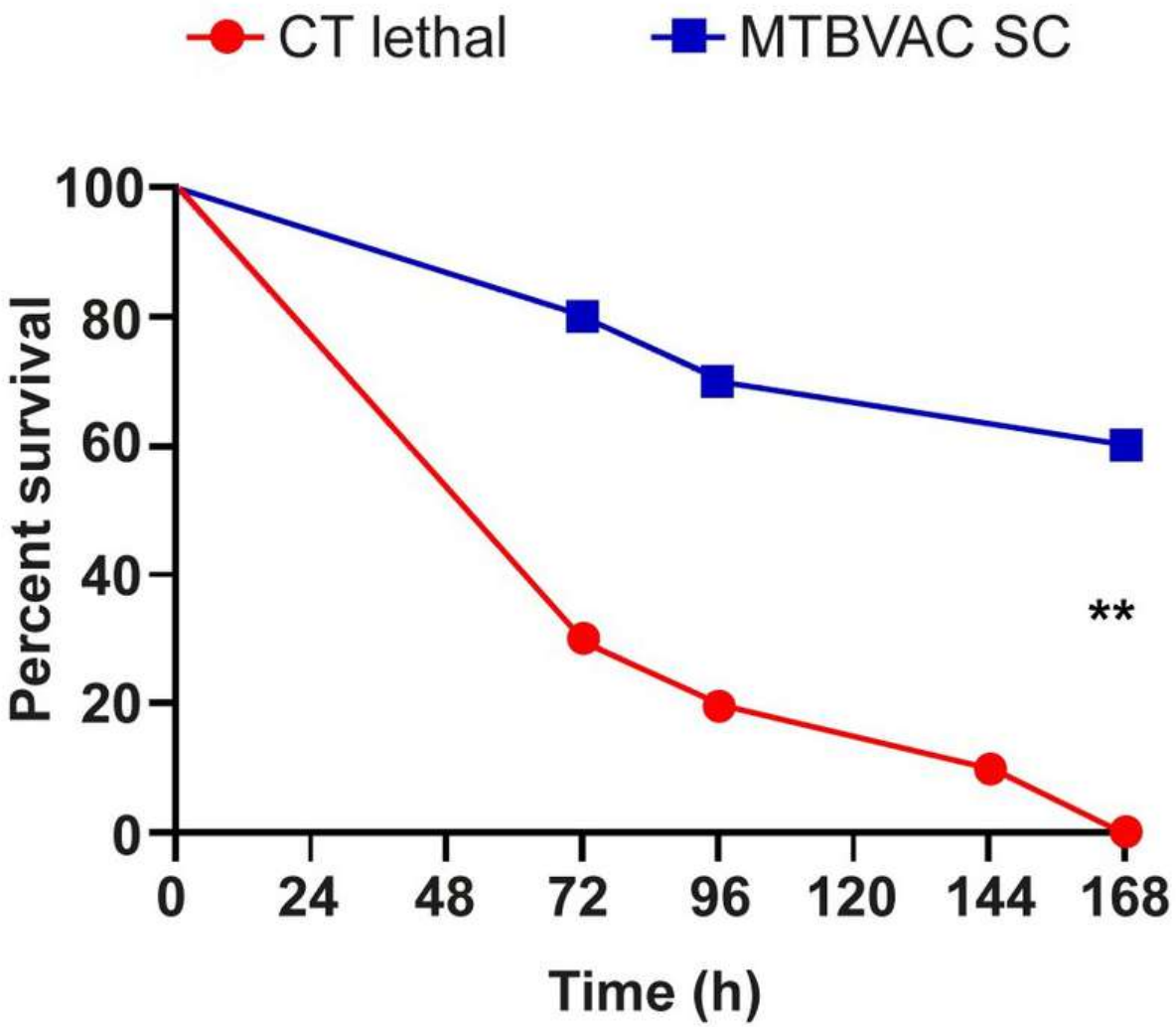




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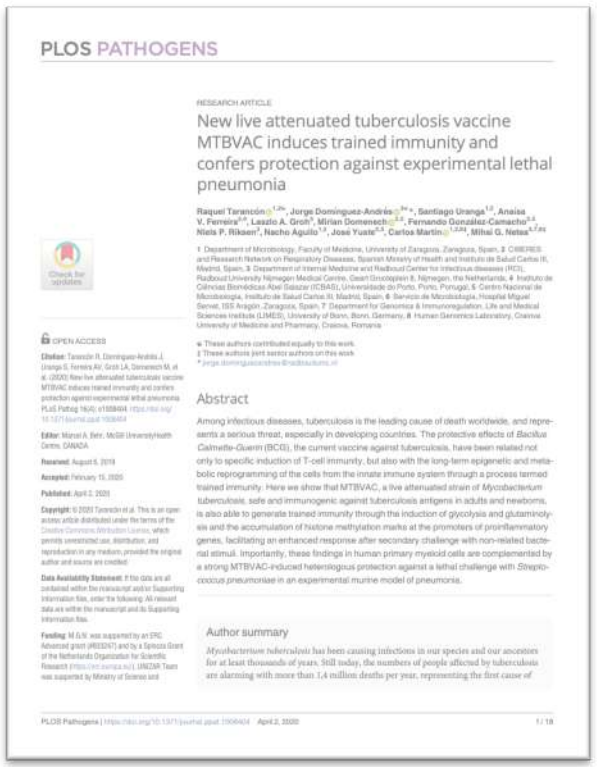

PLOS PATHOGENS

RESEARCH ARTICLE

New live attenuated tuberculosis vaccine MTBVAC induces trained immunity and confers protection against experimental lethal pneumonia

Raquel Tarancón[1,2☯], Jorge Domínguez-Andrés[3☯‡], Santiago Uranga[1,2], Anaisa V. Ferreira[3,4], Laszlo A. Groh[3], Mirian Domenech[1,2,5], Fernando González-Camacho[1,2], Niels P. Riksen[3], Nacho Aguiló[1,2], José Yuste[6,7], Carlos Martín[1,2,8‡], Mihai G. Netea[3,9‡]

1 Department of Microbiology, Faculty of Medicine, University of Zaragoza, Zaragoza, Spain, 2 CIBERES and Research Network on Respiratory Diseases, Spanish Ministry of Health and Instituto de Salud Carlos III, Madrid, Spain, 3 Department of Internal Medicine and Radboud Center for Infectious Diseases (RCI), Radboud University Nijmegen Medical Centre, Geert Grooteplein 8, Nijmegen, the Netherlands, 4 Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, Porto, Portugal, 5 Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain, 6 Servicio de Microbiología, Hospital Miguel Servet, IIS Aragón, Zaragoza, Spain, 7 Department for Genomics & Immunoregulation, Life and Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany, 8 Human Genomics Laboratory, Craiova University of Medicine and Pharmacy, Craiova, Romania

☯ These authors contributed equally to this work.
‡ These authors joint senior authors on this work.
* jorge.dominguezandres@radboudumc.nl

Abstract

Among infectious diseases, tuberculosis is the leading cause of death worldwide, and represents a serious threat, especially in developing countries. The protective effects of *Bacillus Calmette-Guerin* (BCG), the current vaccine against tuberculosis, have been related not only to specific induction of T-cell immunity, but also with the long-term epigenetic and metabolic reprogramming of the cells from the innate immune system through a process termed trained immunity. Here we show that MTBVAC, a live attenuated strain of *Mycobacterium tuberculosis*, safe and immunogenic against tuberculosis antigens in adults and newborns, is also able to generate trained immunity through the induction of glycolysis and glutaminolysis and the accumulation of histone methylation marks at the promoters of proinflammatory genes, facilitating an enhanced response after secondary challenge with non-related bacterial stimuli. Importantly, these findings in human primary myeloid cells are complemented by a strong MTBVAC-induced heterologous protection against a lethal challenge with *Streptococcus pneumoniae* in an experimental murine model of pneumonia.

Author summary

*Mycobacterium tuberculosis* has been causing infections in our species and our ancestors for at least thousands of years. Still today, the numbers of people affected by tuberculosis are alarming with more than 1.4 million deaths per year, representing the first cause of

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ASOCIACIÓN ESPAÑOLA DE PEDIATRÍA

# Actualización del documento de consenso sobre el diagnóstico y tratamiento de la faringoamigdalitis aguda

**Roi Piñeiro Pérez[a,e,*], Fernando Álvez González[a], Fernando Baquero-Artigao[a], Marta Cruz Cañete[a], Josep de la Flor i Bru[d], Ana Fernández Landaluce[b], César García Vera[c], Francisco Hijano Bandera[c], Carlos Pérez Cánovas[b], Juan Carlos Silva Rico[d] y Grupo Colaborador de Faringoamigdalitis Aguda en Pediatría[1]**

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[d] *Sociedad Española de Pediatría Extrahospitalaria y Atención Primaria (SEPEAP)*
[e] *Comité de Medicamentos de la Asociación Española de Pediatría (CM-AEP)*

Recibido el 27 de abril de 2020; aceptado el 12 de mayo de 2020

**PALABRAS CLAVE**
Adecuación;
Antibióticos;
Diagnóstico;
Documento de consenso;
Estreptococo;
Faringoamigdalitis;
Niños;
*Streptococcus pyogenes*;
Tratamiento;
Uso racional

**Resumen** Se presenta una actualización del documento de consenso sobre el diagnóstico y tratamiento de la faringoamigdalitis aguda, publicado en 2011. Las escalas de predicción clínica no deben ser utilizadas para iniciar antibioterapia, salvo que las pruebas microbiológicas no estén disponibles o exista riesgo de fiebre reumática. No existe ninguna escala que sea mejor que las expuestas en el consenso previo. Se proponen casos en los que se recomienda realizar pruebas microbiológicas, con independencia de los resultados de las escalas. El tratamiento de elección de la faringoamigdalitis estreptocócica es penicilina en dos dosis diarias y durante 10 días. Amoxicilina, en una o dos dosis diarias y durante el mismo tiempo, es la primera alternativa terapéutica. Las cefalosporinas de primera generación son el tratamiento de elección en niños con reacción retardada no grave a penicilina o amoxicilina. En reacciones alérgicas inmediatas deben utilizarse antibióticos no betalactámicos, siendo josamicina y diacetil-midecamicina las mejores opciones. En el fracaso terapéutico bacteriológico, y en el estado de portador, los tratamientos planteados en el consenso previo siguen siendo válidos.


* Autor para correspondencia.
*Correo electrónico:* roi.pineiro@hgvillalba.es (R. Piñeiro Pérez).
[1] Los miembros del Grupo Colaborador de Faringoamigdalitis Aguda en Pediatría se presentan en el Anexo 1.

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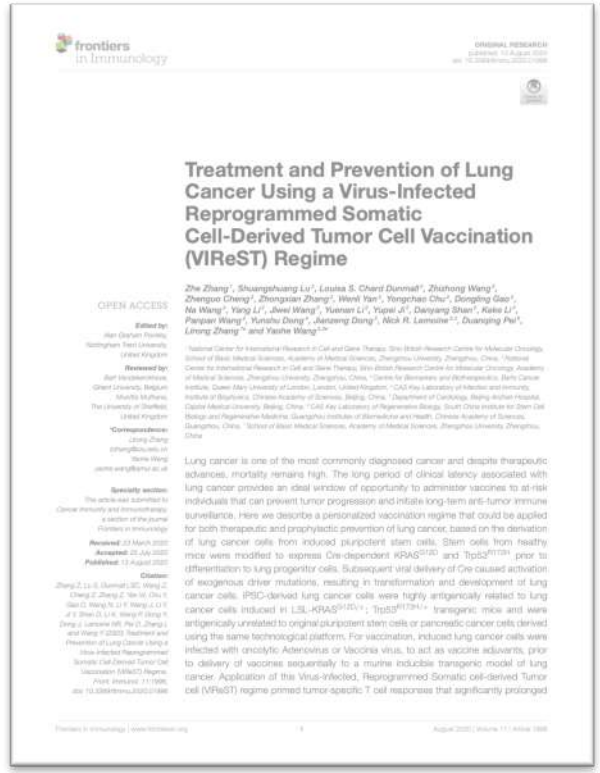

frontiers in Immunology

ORIGINAL RESEARCH

# Treatment and Prevention of Lung Cancer Using a Virus-Infected Reprogrammed Somatic Cell-Derived Tumor Cell Vaccination (VIReST) Regime

*Zhe Zhang[†], Shuangshuang Lu[†], Louisa S. Chard Dunmall[†], Zhizhong Wang[†], Zhengyu Cheng[†], Zhongxian Zhang[†], Wenli Yan[†], Yongchao Chu[†], Dongling Gao[†], Na Wang[†], Yang Li[†], Jiwei Wang[†], Yuenan Li[†], Yupei Ji[†], Danyang Shen[†], Keke Li[†], Panpan Wang[†], Yunshu Dong[†], Jiansong Dong[†], Nick R. Lemoine[†,‡], Duanqing Pei[§], Lirong Zhang[†]* and Yaohe Wang[†,¶]*

Lung cancer is one of the most commonly diagnosed cancer and despite therapeutic advances, mortality remains high. The long period of clinical latency associated with lung cancer provides an ideal window of opportunity to administer vaccines to at-risk individuals that can prevent tumor progression and initiate long-term anti-tumor immune surveillance. Here we describe a personalized vaccination regime that could be applied for both therapeutic and prophylactic prevention of lung cancer, based on the derivation of lung cancer cells from induced pluripotent stem cells. Stem cells from healthy mice were modified to express Cre-dependent $KRAS^{G12D}$ and $Trp53^{R172H}$ prior to differentiation to lung progenitor cells. Subsequent viral delivery of Cre caused activation of exogenous driver mutations, resulting in transformation and development of lung cancer cells. iPSC-derived lung cancer cells were highly antigenically related to lung cancer cells induced in LSL-$KRAS^{G12D/+}$; $Trp53^{R172H/+}$ transgenic mice and were antigenically unrelated to original pluripotent stem cells or pancreatic cancer cells derived using the same technological platform. For vaccination, induced lung cancer cells were infected with oncolytic Adenovirus or Vaccinia virus, to act as vaccine adjuvants, prior to delivery of vaccines sequentially to a murine inducible transgenic model of lung cancer. Application of this Virus-Infected, Reprogrammed Somatic cell-derived Tumor cell (VIReST) regime primed tumor-specific T cell responses that significantly prolonged

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Recibido el 27 de abril de 2020; aceptado el 12 de mayo de 2020

1. ¿Existen mejores escalas de predicción clínica?

2. ¿Las escalas clínicas son suficientes para iniciar tratamiento antibiótico?

3. ¿Son suficientes para indicar pruebas microbiológicas?

4. ¿Existen nuevas pruebas de diagnóstico microbiológico?

5. ¿Se mantienen amoxicilina y penicilina como antibióticos de primera elección?

6. ¿Se siguen recomendando en pautas de 1 o 2 dosis al día?

7. ¿Se mantiene la recomendación de 10 días de tratamiento antibiótico?

8. ¿Se mantienen las recomendaciones de tratamiento en alérgicos a penicilina?

9. ¿Se mantienen el tratamiento en fracaso bacteriológico y estado de colonización?

10. ¿Actitud en menores de 3 años?



Piñeiro Pérez R, *et al*. An Pediatr (Barc), 2020

# 2. ¿Las escalas clínicas son suficientes para iniciar tratamiento antibiótico?

**No**



Piñeiro Pérez R, *et al*. An Pediatr (Barc), 2020

# 2. ¿Las escalas clínicas son suficientes para iniciar tratamiento antibiótico?

**Tabla 2** Escalas clínicas de predicción en la faringoamigdalitis aguda por estreptococo beta-hemolítico del grupo A (EbhGA)

| Criterios clínicos | Centor | McIsaac | FeverPAIN |
|---|---|---|---|
| Fiebre > 38 °C | +1 | +1 | +1 |
| Ausencia de tos | +1 | +1 | |
| Ausencia de tos o coriza | | | +1 |
| Exudado amigdalar | +1 | | +1 |
| Inflamación o exudado amigdalar | | +1 | |
| Inflamación amigdalar importante | | | +1 |
| Adenopatías laterocervicales dolorosas | +1 | +1 | |
| Edad | | | |
| • 3- < 15 años | | +1 | |
| • 15- < 45 años | | 0 | |
| • ≥ 45 años | | −1 | |
| Visita rápida al médico (≤ 3 días) | | | +1 |
| | Puntuación | Puntuación | Puntuación |
| Probabilidad estimada de cultivo positivo para EbhGA | 0: 2,5%<br>1: 6-6,9%<br>2: 14,1-16,6%<br>3: 30,1-34,1%<br>4: 55,7% | 0: 1-2,5%<br>1: 5-10%<br>2: 11-17%<br>3: 28-35%<br>≥ 4: 51-53% | 0-1: 13-18%<br>2-3: 34-40%<br>4-5: 62-65% |



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**< 66 %**



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# 7. ¿Se mantiene la recomendación de 10 días de tratamiento antibiótico?

**Sí, pero…**



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# 7. ¿Se mantiene la recomendación de 10 días de tratamiento antibiótico?

**Ningún** tratamiento consigue erradicación del 100 %

Evidencia **no sólida**

**Resistencias** antibióticas

Posiblemente adecuado en **“determinados casos”**



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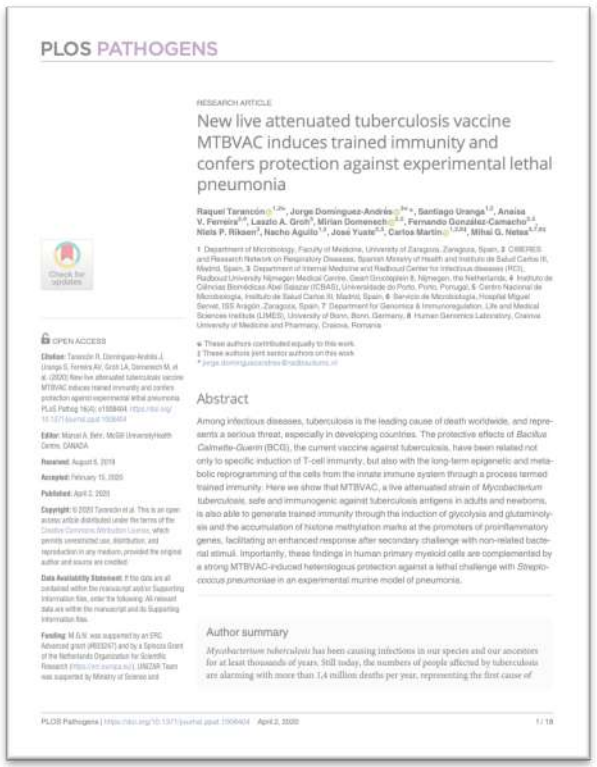

PLOS PATHOGENS

RESEARCH ARTICLE

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1 Department of Microbiology, Faculty of Medicine, University of Zaragoza, Zaragoza, Spain, 2 CIBERES and Research Network on Respiratory Diseases, Spanish Ministry of Health and Instituto de Salud Carlos III, Madrid, Spain, 3 Department of Internal Medicine and Radboud Center for Infectious Diseases (RCI), Radboud University Nijmegen Medical Centre, Geert Grooteplein 8, Nijmegen, the Netherlands, 4 Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, Porto, Portugal, 5 Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain, 6 Servicio de Microbiología, Hospital Miguel Servet, IIS Aragón, Zaragoza, Spain, 7 Department for Genomics & Immunoregulation, Life and Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany, 8 Human Genomics Laboratory, Craiova University of Medicine and Pharmacy, Craiova, Romania

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* jorge.dominguezandres@radboudumc.nl

Abstract

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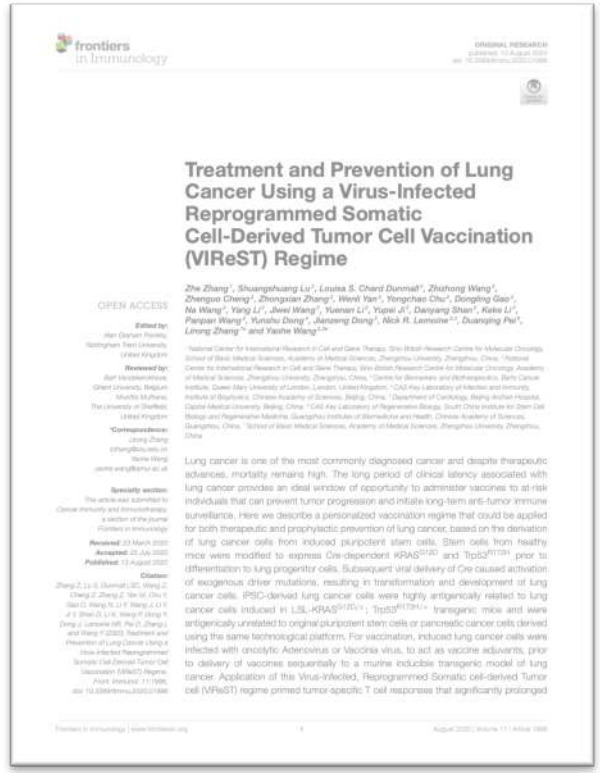

frontiers in Immunology

ORIGINAL RESEARCH

# Treatment and Prevention of Lung Cancer Using a Virus-Infected Reprogrammed Somatic Cell-Derived Tumor Cell Vaccination (VIReST) Regime

*Zhe Zhang[†], Shuangshuang Lu[†], Louisa S. Chard Dunmall[†], Zhizhong Wang[†], Zhengyu Cheng[†], Zhongxian Zhang[†], Wenli Yan[†], Yongchao Chu[†], Dongling Gao[†], Na Wang[†], Yang Li[†], Jiwei Wang[†], Yuenan Li[†], Yupei Ji[†], Danyang Shen[†], Keke Li[†], Panpan Wang[†], Yunshu Dong[†], Jiansong Dong[†], Nick R. Lemoine[†,‡], Duanqing Pei[§], Lirong Zhang[†]* and Yaohe Wang[†,¶]*

Lung cancer is one of the most commonly diagnosed cancer and despite therapeutic advances, mortality remains high. The long period of clinical latency associated with lung cancer provides an ideal window of opportunity to administer vaccines to at-risk individuals that can prevent tumor progression and initiate long-term anti-tumor immune surveillance. Here we describe a personalized vaccination regime that could be applied for both therapeutic and prophylactic prevention of lung cancer, based on the derivation of lung cancer cells from induced pluripotent stem cells. Stem cells from healthy mice were modified to express Cre-dependent $KRAS^{G12D}$ and $Trp53^{R172H}$ prior to differentiation to lung progenitor cells. Subsequent viral delivery of Cre caused activation of exogenous driver mutations, resulting in transformation and development of lung cancer cells. iPSC-derived lung cancer cells were highly antigenically related to lung cancer cells induced in LSL-$KRAS^{G12D/+}$; $Trp53^{R172H/+}$ transgenic mice and were antigenically unrelated to original pluripotent stem cells or pancreatic cancer cells derived using the same technological platform. For vaccination, induced lung cancer cells were infected with oncolytic Adenovirus or Vaccinia virus, to act as vaccine adjuvants, prior to delivery of vaccines sequentially to a murine inducible transgenic model of lung cancer. Application of this Virus-Infected, Reprogrammed Somatic cell-derived Tumor cell (VIReST) regime primed tumor-specific T cell responses that significantly prolonged

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ORIGINAL RESEARCH
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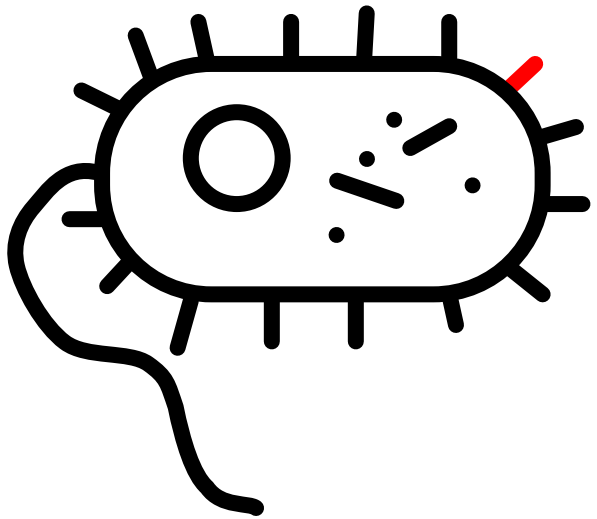
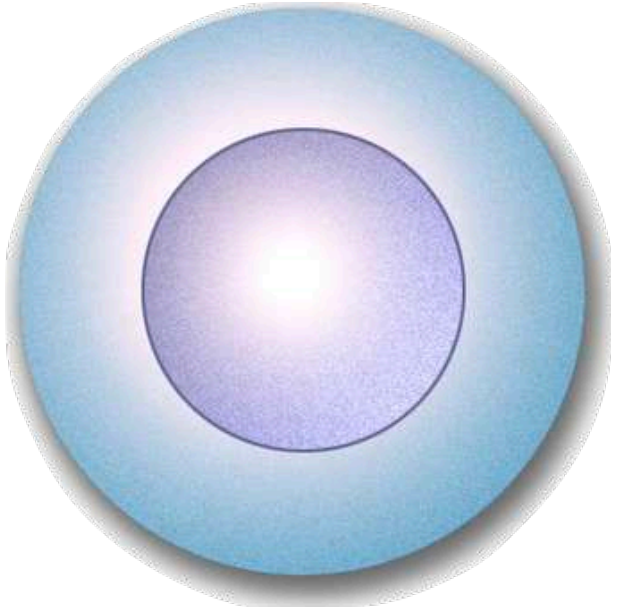
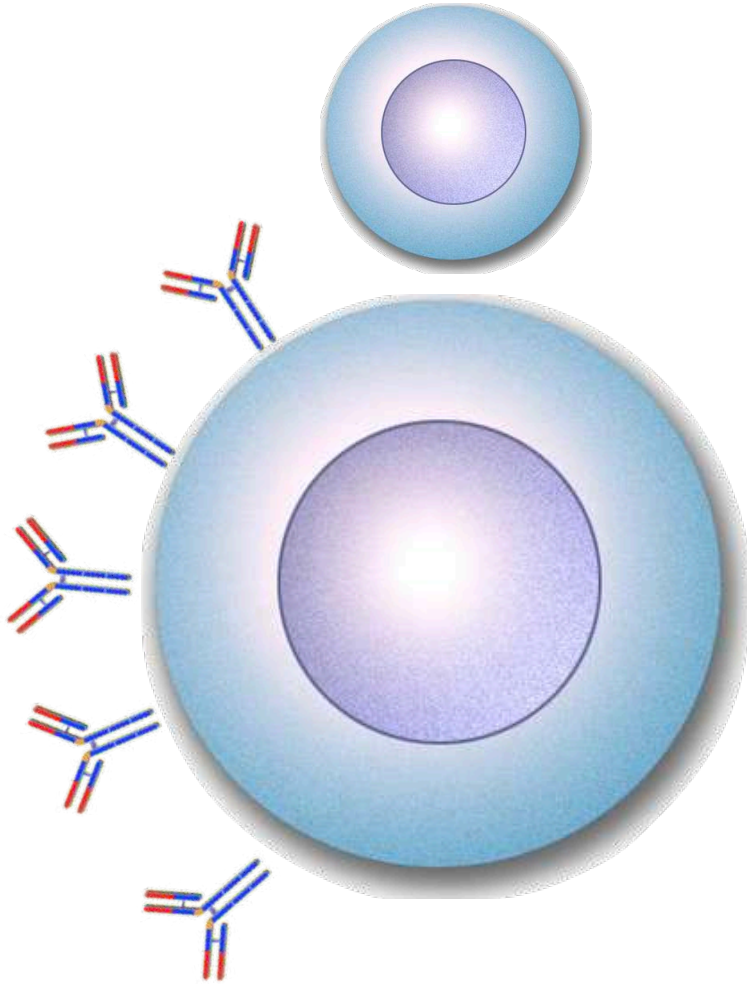
**Edited by:**
*Alan Graham Pockley,*
*Nottingham Trent University*

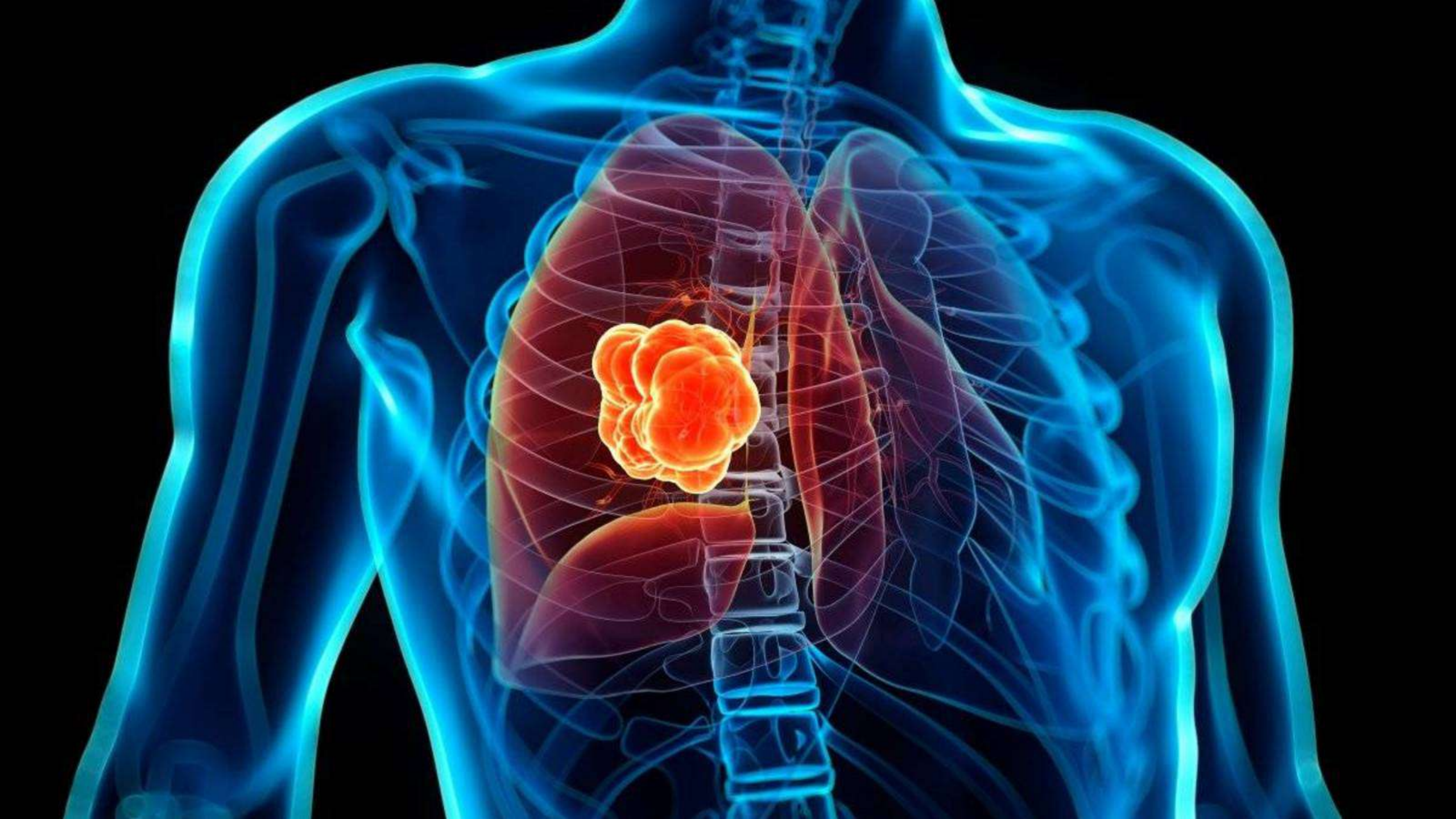
# ¿Cómo funciona una vacuna?



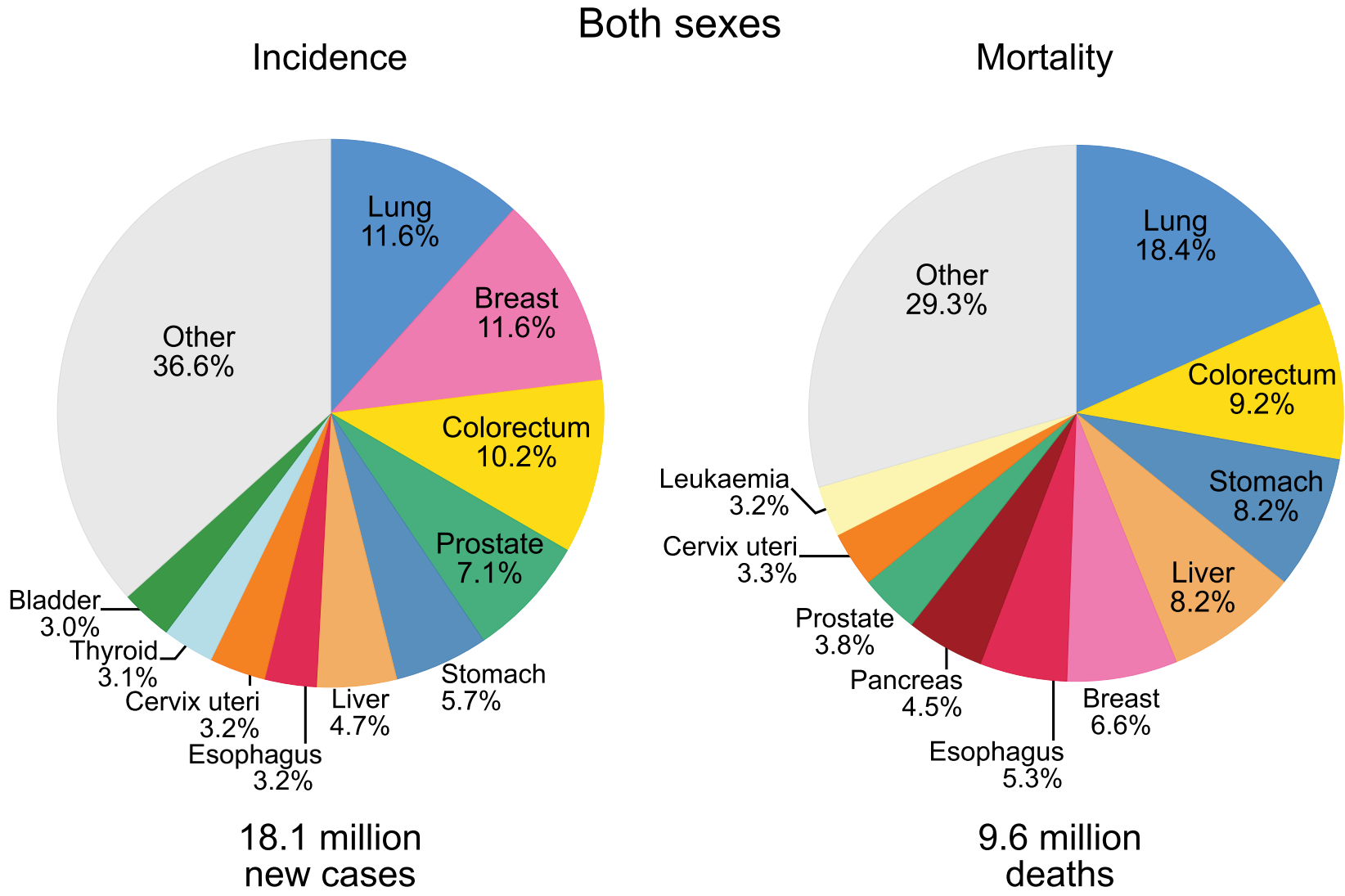


# ¿Cómo funciona una vacuna?





# Incidencia y mortalidad global por cáncer






Bray F, *et al*. Ca Cancer J Clin, 2018

# Estrategias vacunales antitumorales

Antígenos específicos
*(EGFR, MUC1…)*

Células enteras

# V I Re S T



Zhang Z, *et al*. An Pediatr (Barc), 2020

Pauta de vacunación con

**V**irus-**I**nfected **Re**programmed **S**omatic cell - derived **T**umor cell

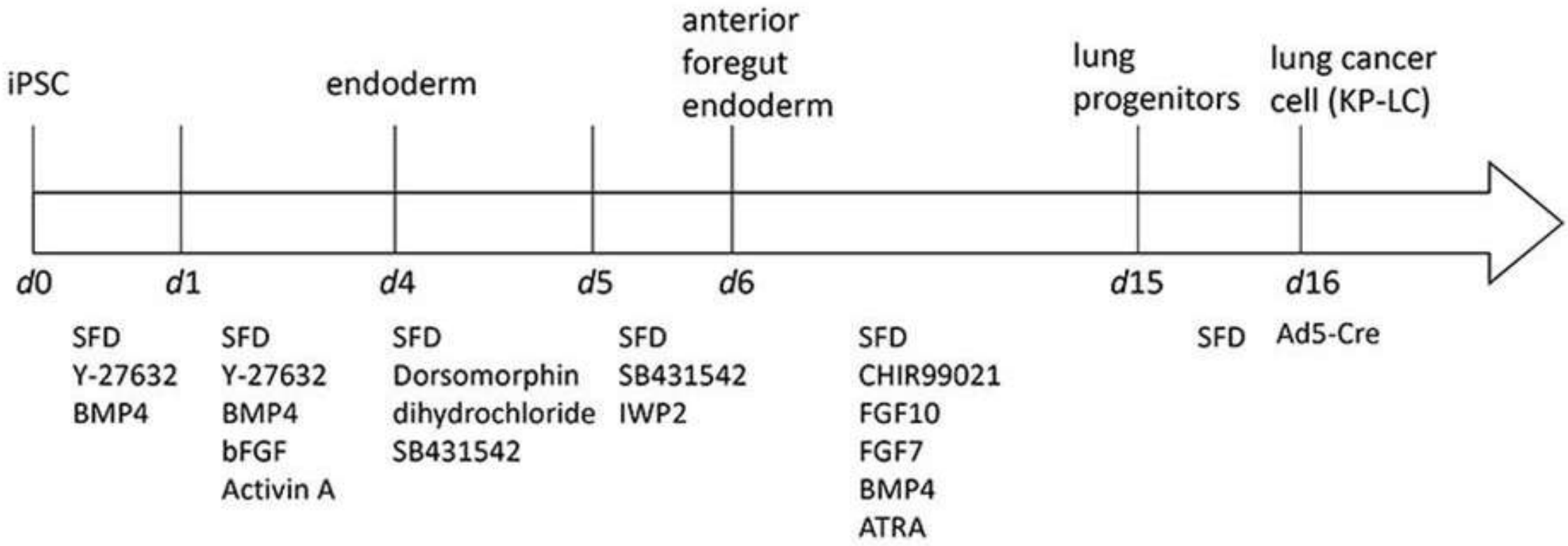


Zhang Z, *et al*. An Pediatr (Barc), 2020



Producir células tumorales in vitro a partir de iPSC

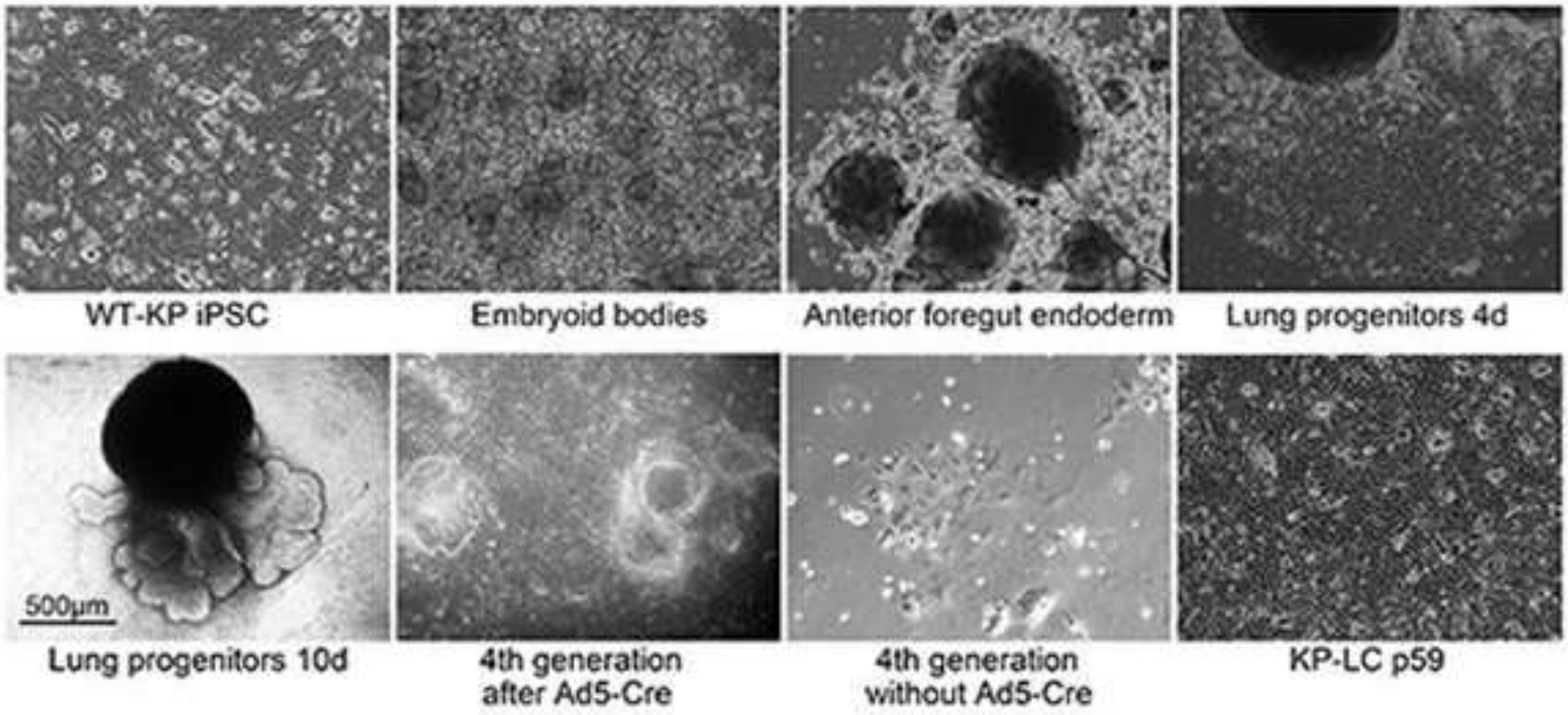
# Estimulación oncogénica






Zhang Z, *et al*. An Pediatr (Barc), 2020

# Estimulación oncogénica



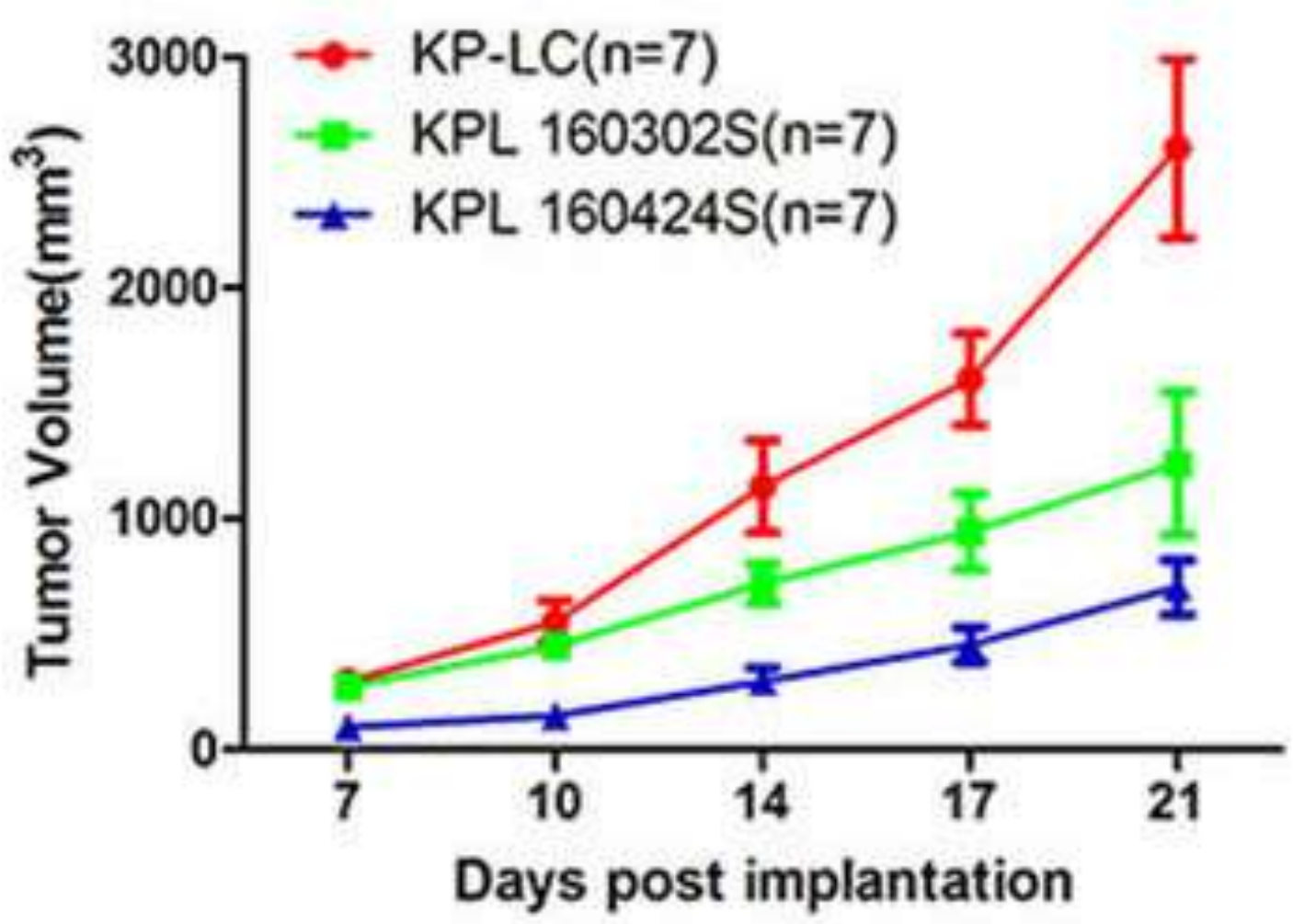



Zhang Z, *et al*. An Pediatr (Barc), 2020

Producir células tumorales in vitro a partir de iPSC

Comprobar que el crecimiento tumoral es similar al de líneas celulares tumorales conocidas

# Crecimiento tumoral




Zhang Z, *et al*. An Pediatr (Barc), 2020

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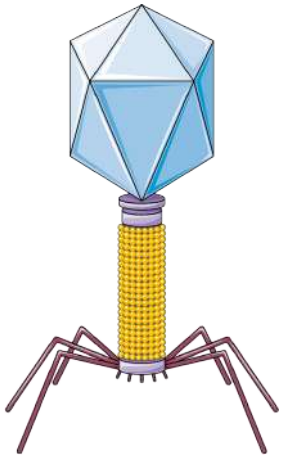
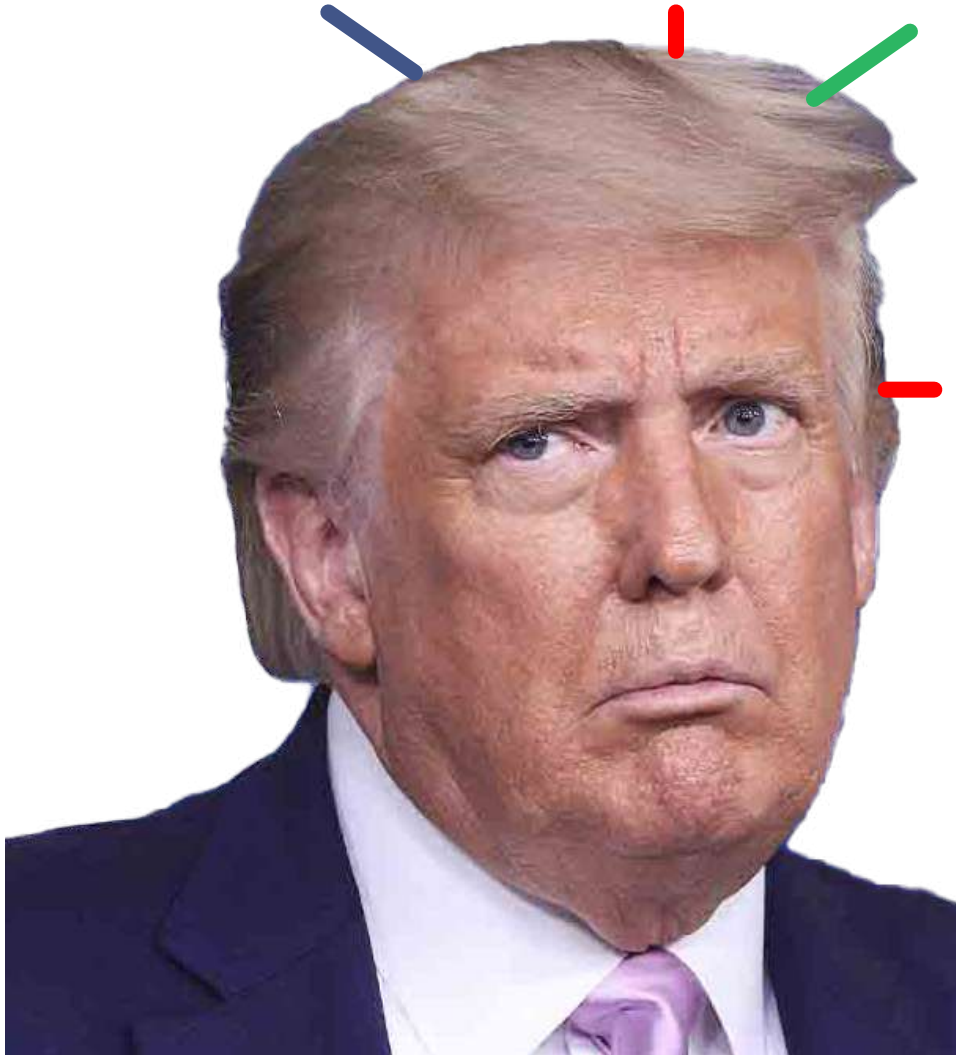
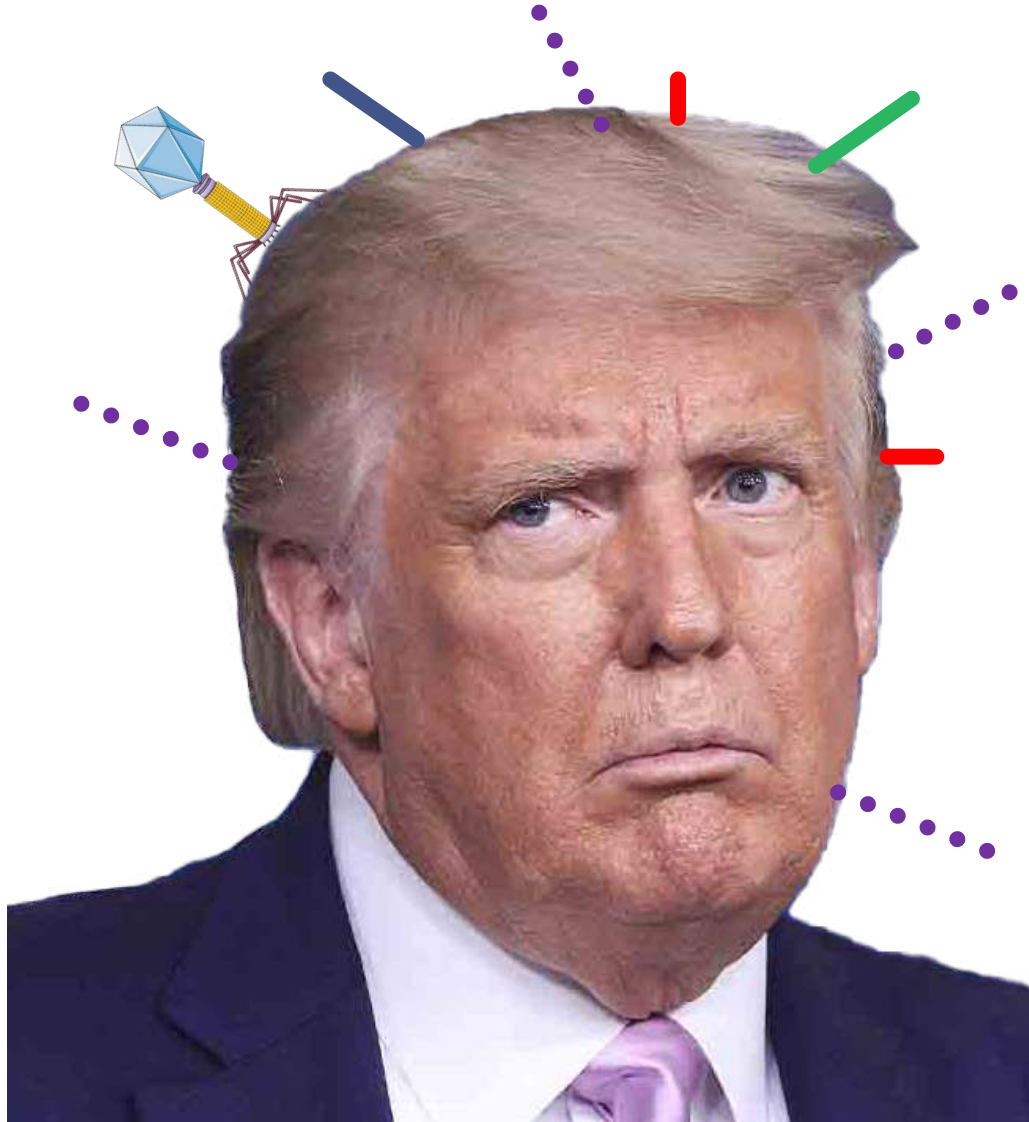
Infectar las células tumorales con Ad5 y VV

# Infección por Ad5 y VV





# Infección por Ad5 y VV



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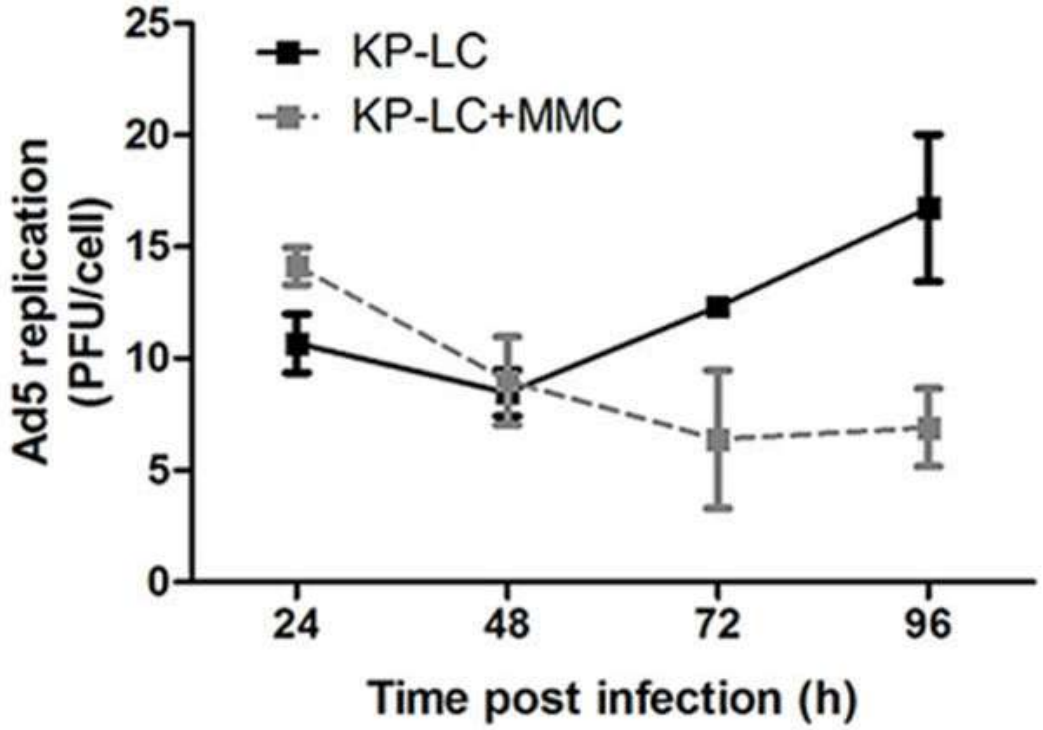
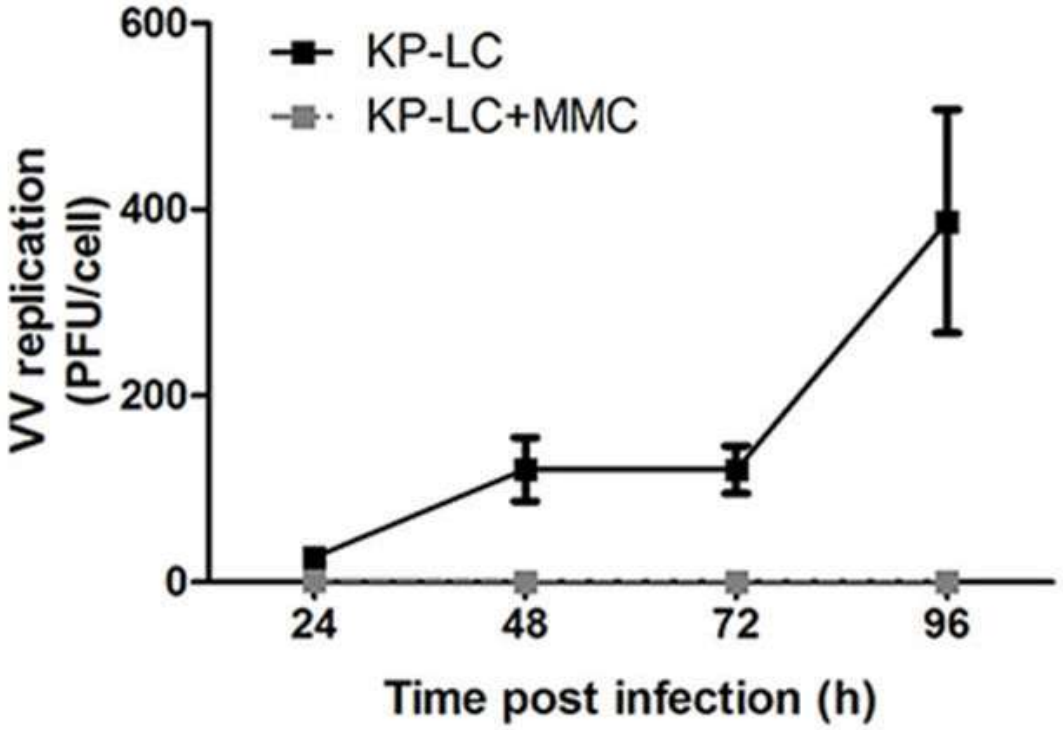
Inhibir la replicación viral y la proliferación celular, permitiendo la expresión de Ag

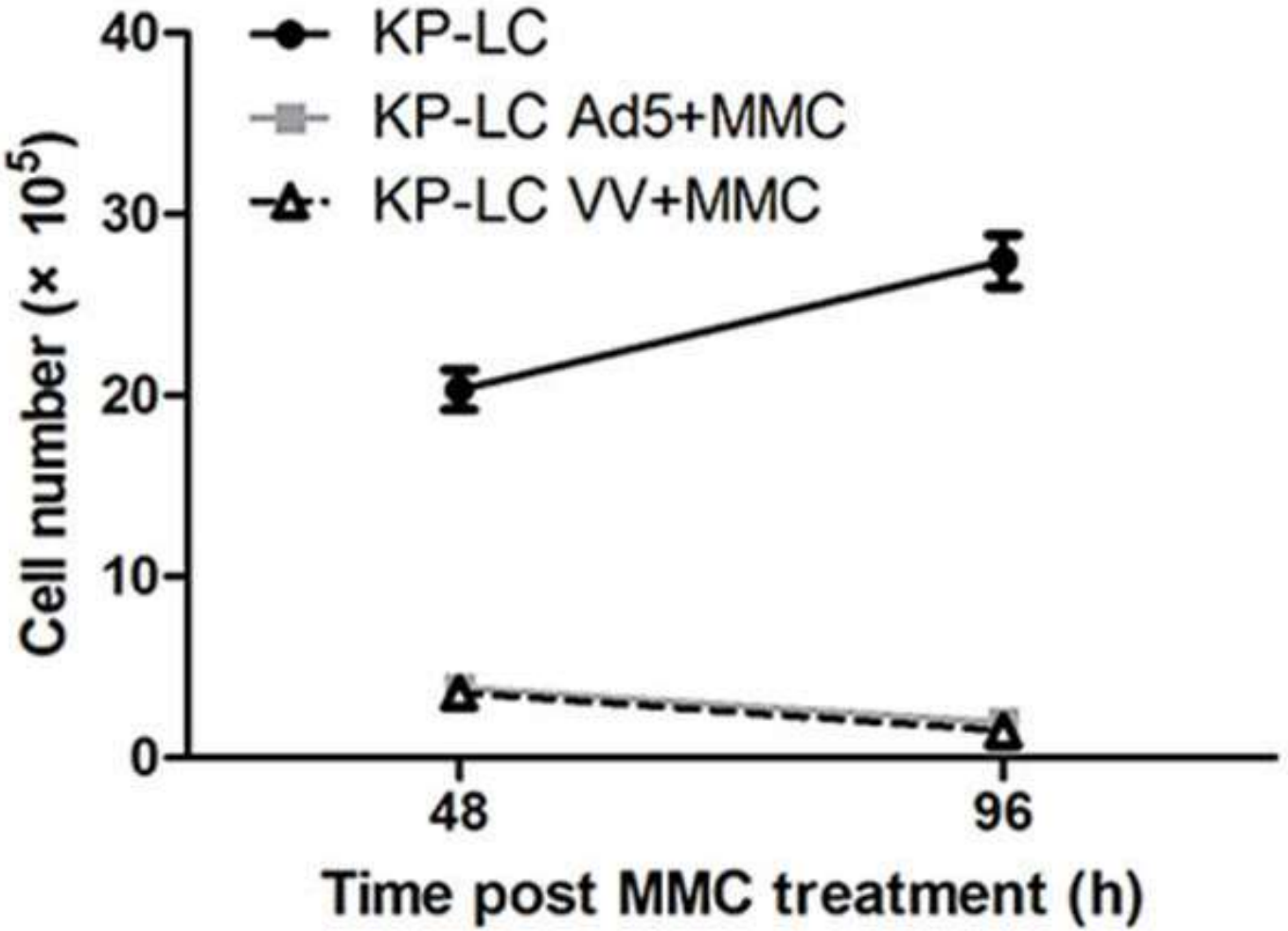
# Replicación viral




Zhang Z, *et al*. An Pediatr (Barc), 2020

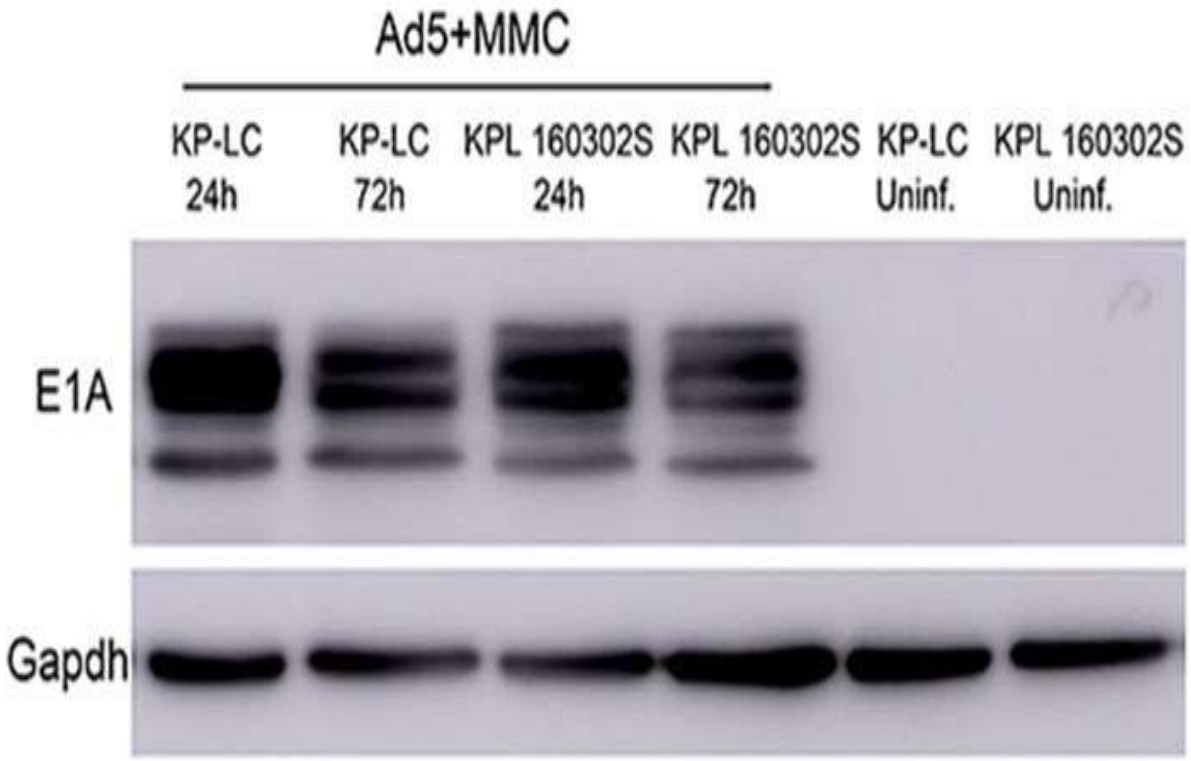
# Proliferación de células tumorales

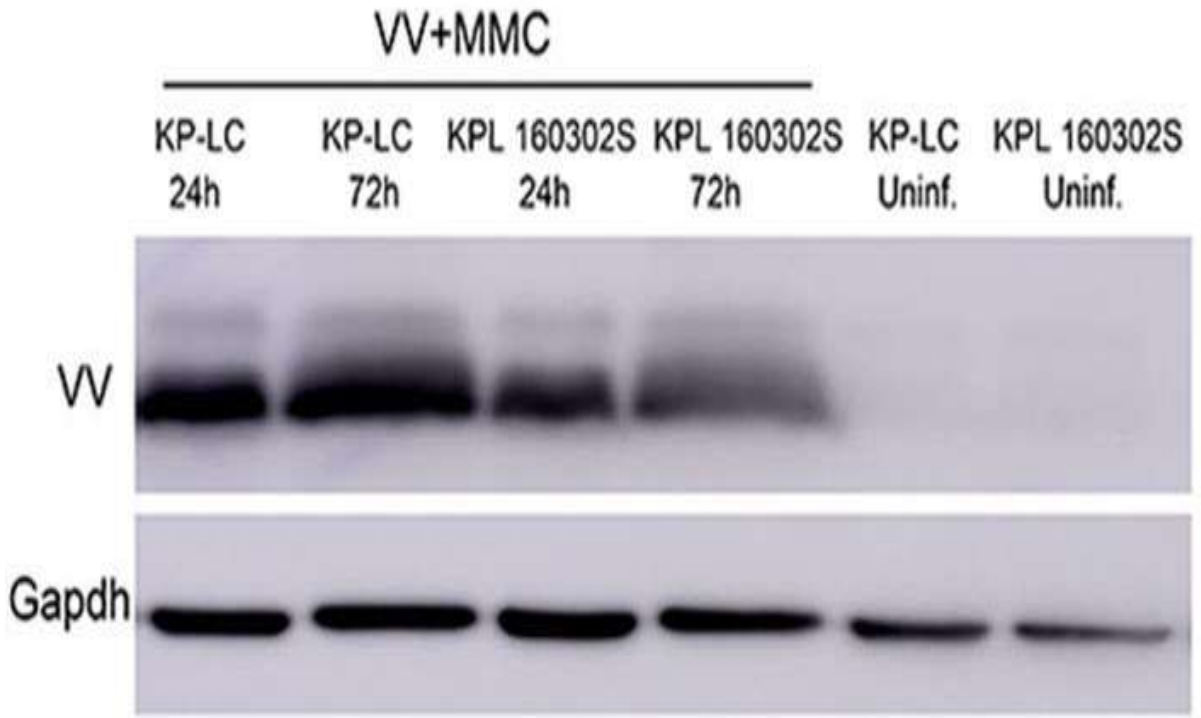





Zhang Z, *et al*. An Pediatr (Barc), 2020

# Expresión proteica de superficie






Zhang Z, *et al*. An Pediatr (Barc), 2020

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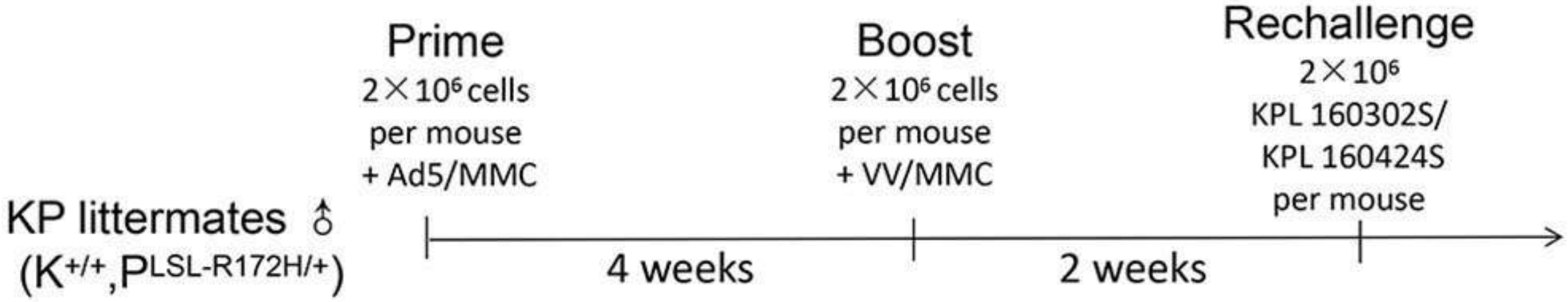
Probar eficacia de la vacuna en modelo murino

# Eficacia en modelo murino

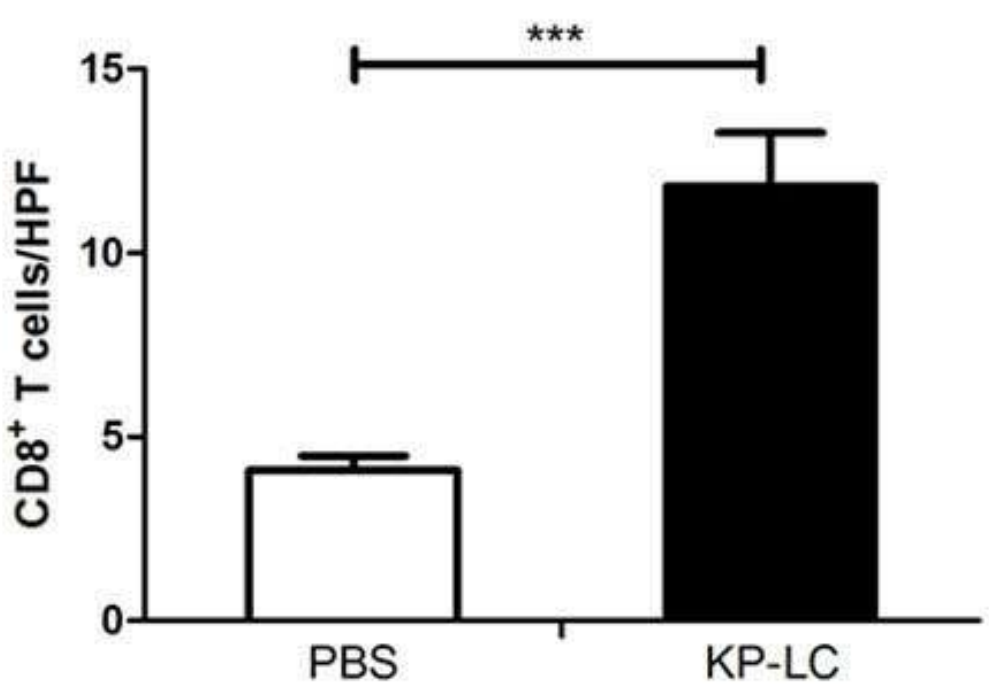


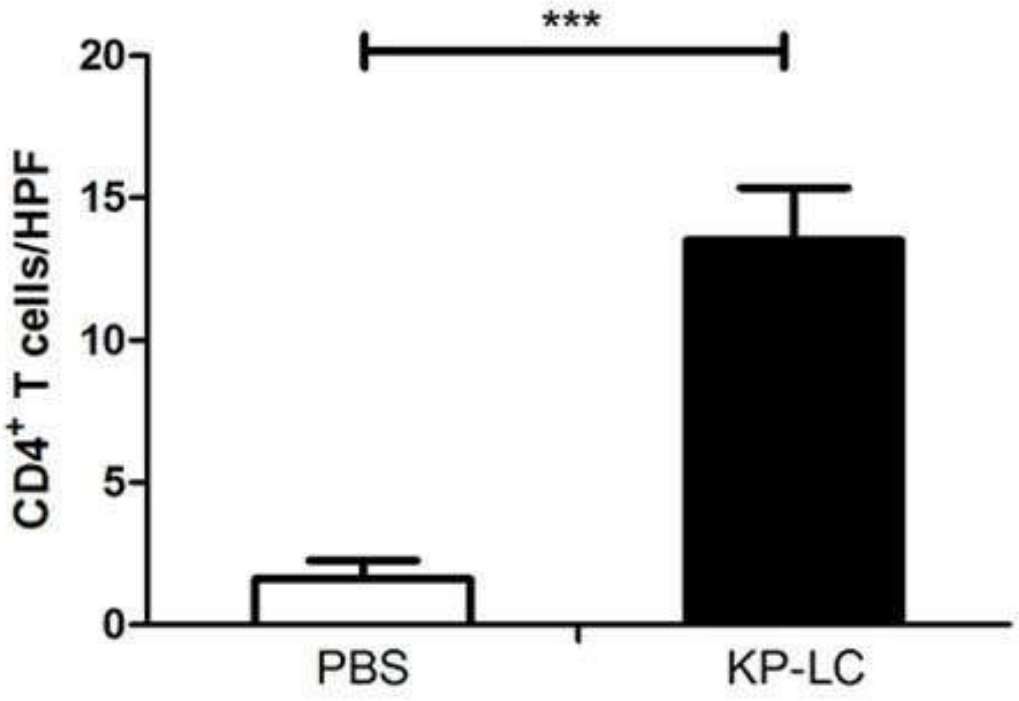



Zhang Z, *et al*. An Pediatr (Barc), 2020

# Concentración intratumoral de linfocitos

KPL 16302S

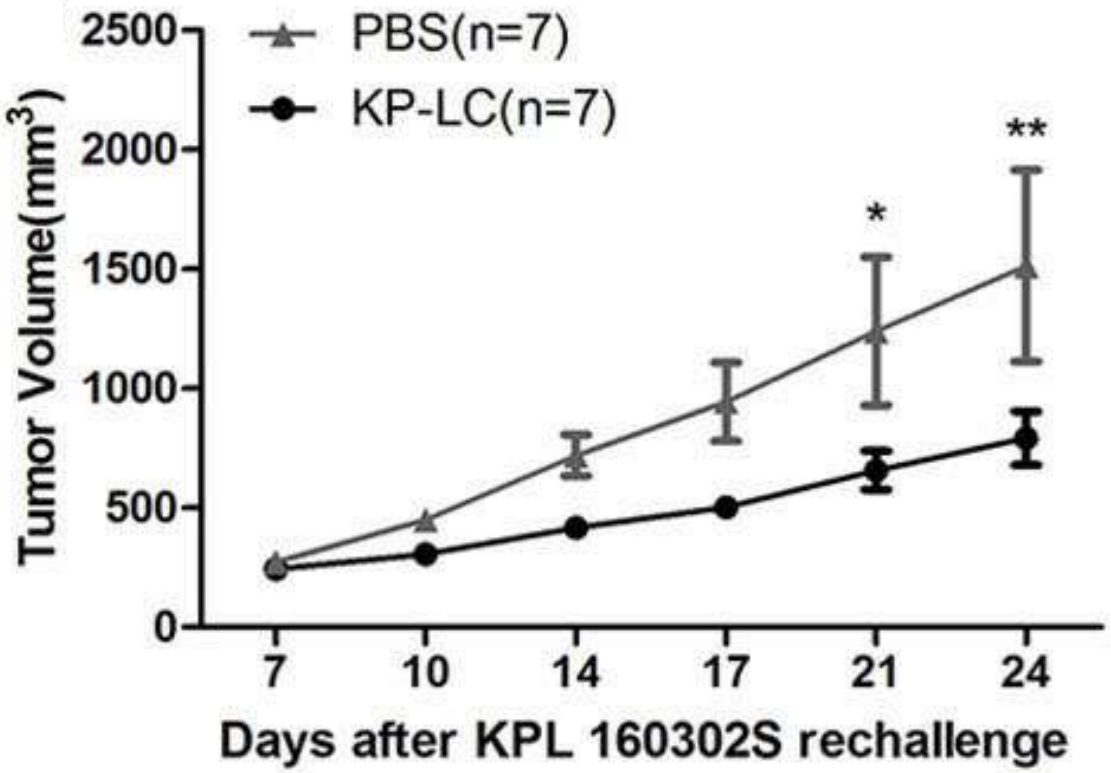


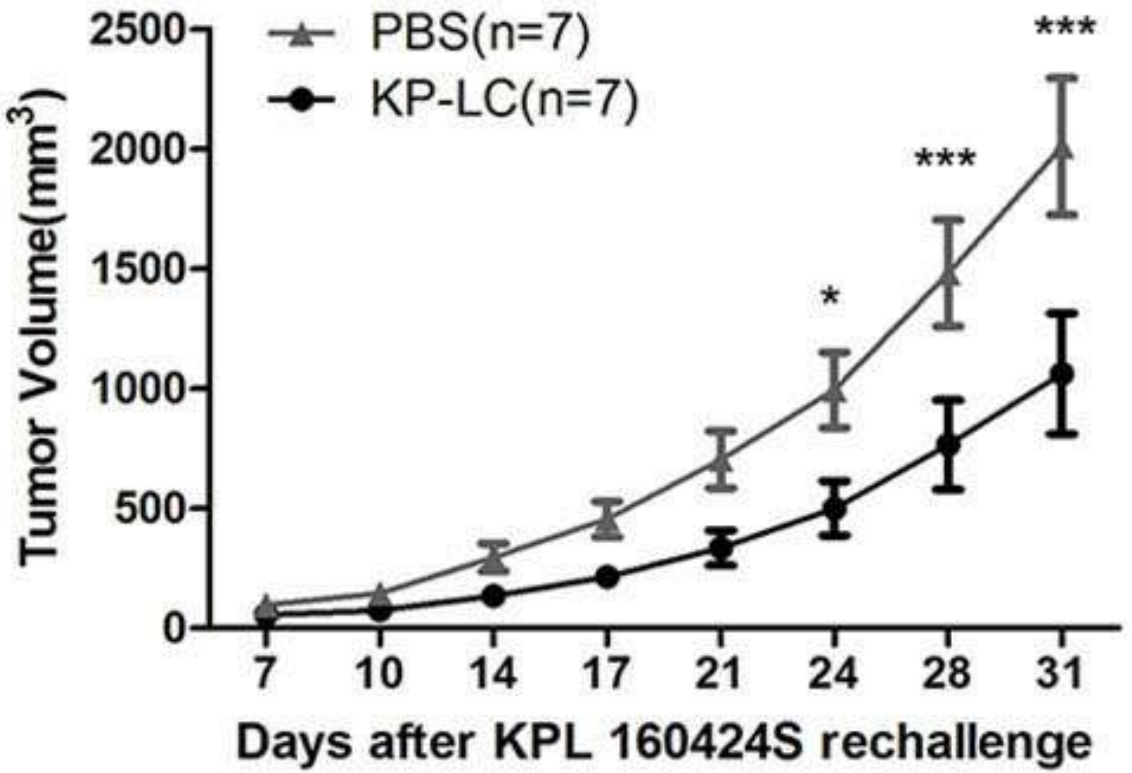






Zhang Z, *et al*. An Pediatr (Barc), 2020

# Tamaño tumoral en modelo murino subcutáneo

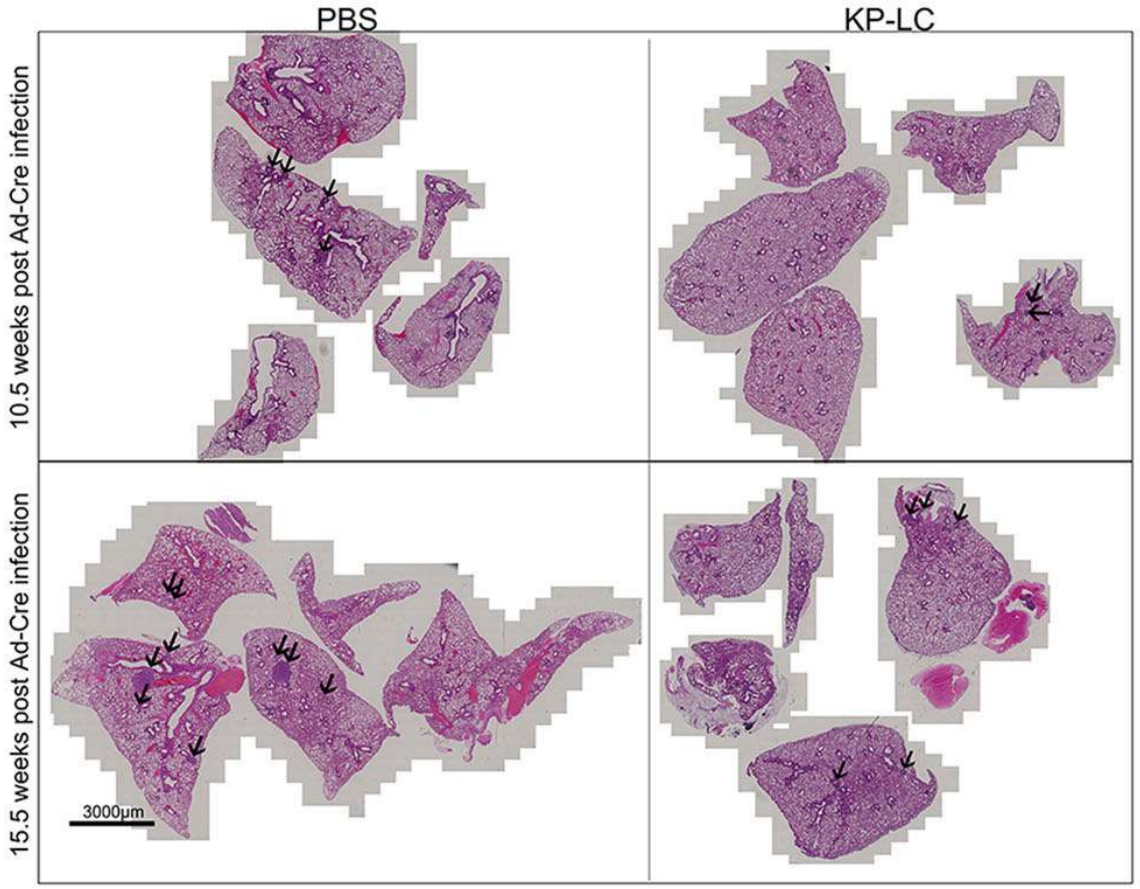


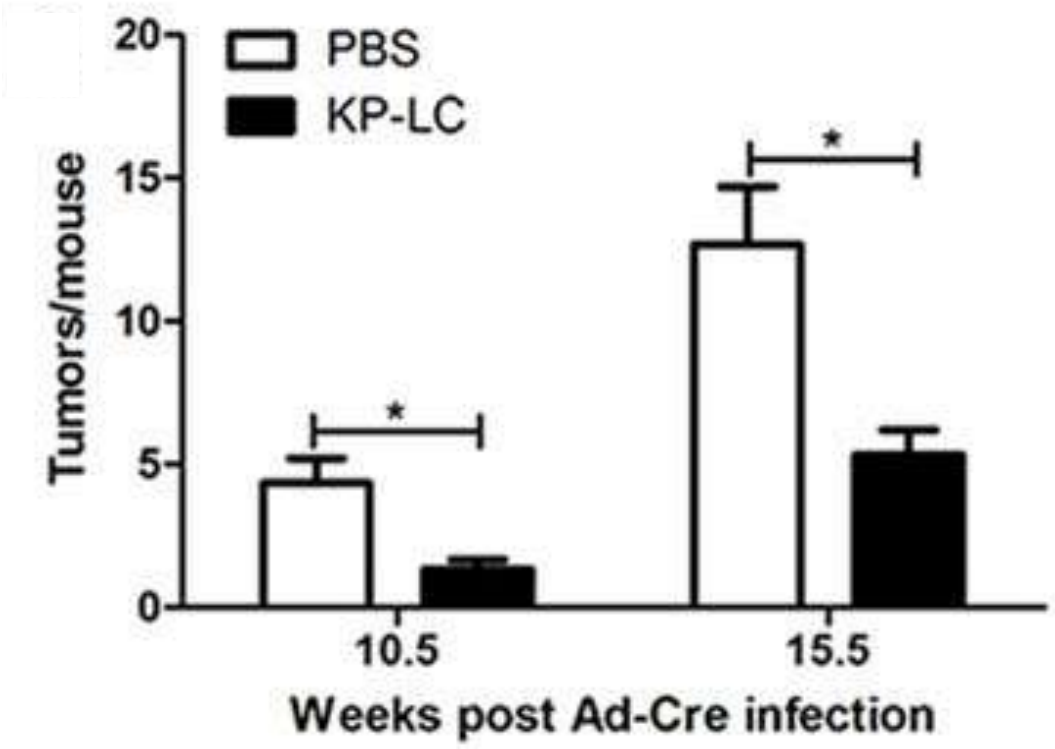






Zhang Z, *et al*. An Pediatr (Barc), 2020

# Número de tumores en modelo murino subcutáneo



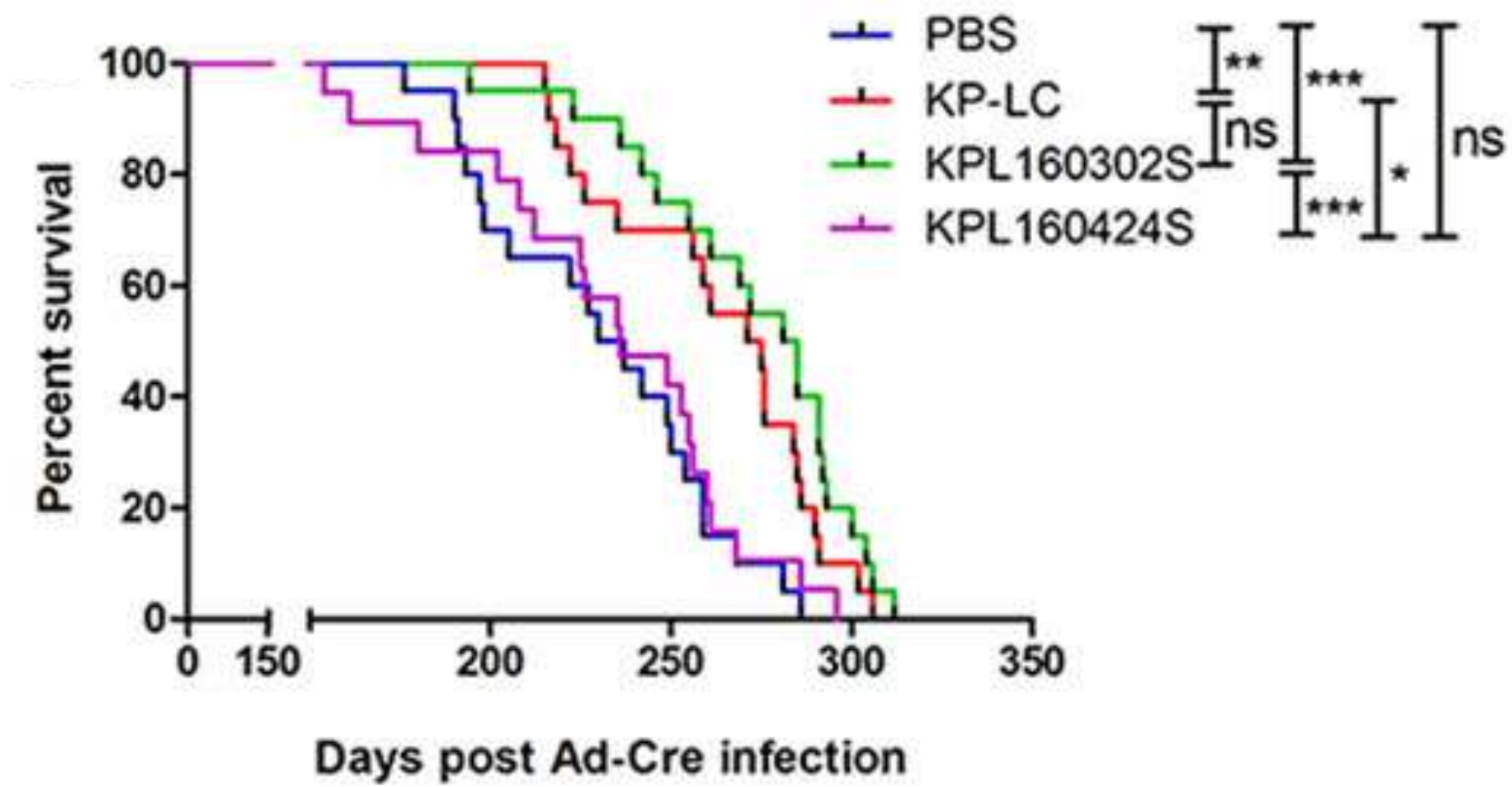






Zhang Z, *et al*. An Pediatr (Barc), 2020

# Mortalidad en modelo murino subcutáneo

17 %



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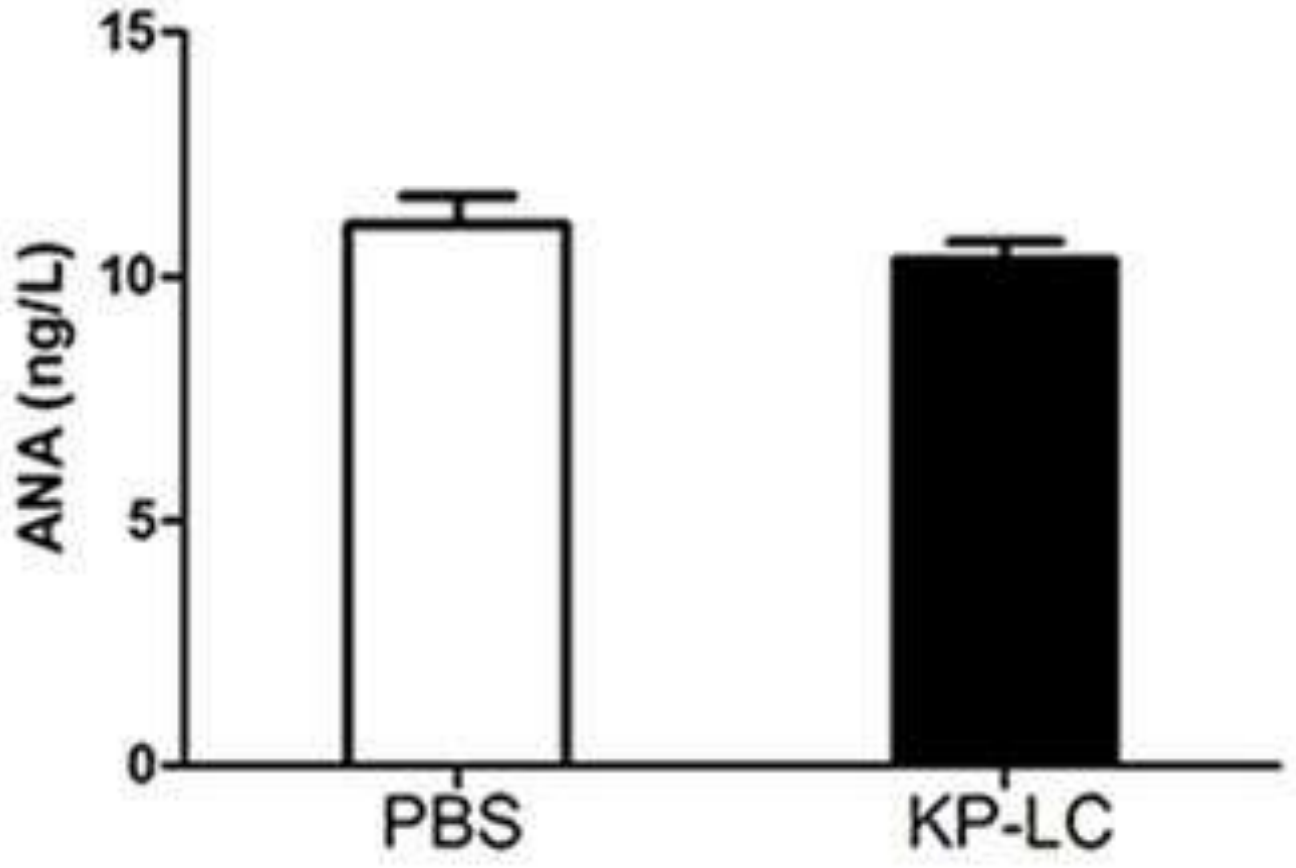
Probar eficacia de la vacuna en modelo murino

Demostrar ausencia de autoinmunidad

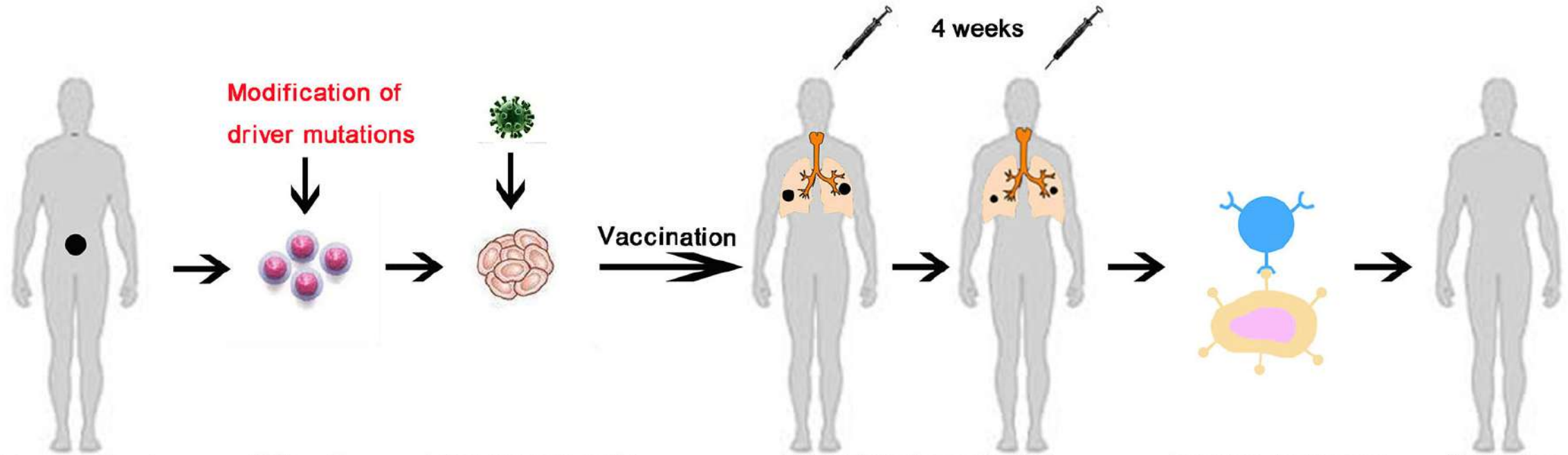
# ANA en modelo murino






Zhang Z, *et al*. An Pediatr (Barc), 2020

# Propuesta de pauta de administración






Zhang Z, *et al*. An Pediatr (Barc), 2020

PLOS PATHOGENS

RESEARCH ARTICLE

# New live attenuat MTBVAC induces confers protectio pneumonia

**Raquel Tarancón[1,2☯], Jorge Do V. Ferreira[3,4], Laszlo A. Groh[3], Mi Niels P. Riksen[3], Nacho Aguilo[1,2]**

**1** Department of Microbiology, Faculty o and Research Network on Respiratory D Madrid, Spain, **3** Department of Internal Radboud University Nijmegen Medical C Ciências Biomédicas Abel Salazar (ICB Microbiología, Instituto de Salud Carlos Servet, ISS Aragón, Zaragoza, Spain, **7** Sciences Institute (LIMES), University of University of Medicine and Pharmacy, C

☯ These authors contributed equally to t
‡ These authors joint senior authors on t
* jorge.dominguezandres@radboudum



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## Abstract

Among infectious diseases, tuber sents a serious threat, especially i *Calmette-Guerin* (BCG), the curre only to specific induction of T-cell bolic reprogramming of the cells fr trained immunity. Here we show t *tuberculosis*, safe and immunoger is also able to generate trained im sis and the accumulation of histon genes, facilitating an enhanced re rial stimuli. Importantly, these findi a strong MTBVAC-induced heterc *coccus pneumoniae* in an experim

## Author summary

*Mycobacterium tuberculosis* has for at least thousands of years. St are alarming with more than 1,4





An Pediatr (Barc). 2020;xxx(xx):xxx–xxx

anales de pediatría

www.analesdepediatria.org

ASOCIACIÓN ESPAÑOLA DE PEDIATRÍA

# Actualización del documento de consenso so diagnóstico y tratamiento de la faringoamigd aguda

**Roi Piñeiro Pérez[a,e,*], Fernando Álvez González[a], Fernando Marta Cruz Cañete[a], Josep de la Flor i Bru[d], Ana Fernández César García Vera[c], Francisco Hijano Bandera[c], Carlos Pére Juan Carlos Silva Rico[d] y Grupo Colaborador de Faringoamig**

[a] *Sociedad Española de Infectología Pediátrica (SEIP)*
[b] *Sociedad Española de Urgencias de Pediatría (SEUP)*
[c] *Asociación Española de Pediatría de Atención Primaria (AEPap)*
[d] *Sociedad Española de Pediatría Extrahospitalaria y Atención Primaria (SEPEAP)*
[e] *Comité de Medicamentos de la Asociación Española de Pediatría (CM-AEP)*

Recibido el 27 de abril de 2020; aceptado el 12 de mayo de 2020

**PALABRAS CLAVE**
Adecuación;
Antibióticos;
Diagnóstico;
Documento de consenso;
Estreptococo;
Faringoamigdalitis;
Niños;
*Streptococcus pyogenes*;
Tratamiento;
Uso racional

**Resumen** Se presenta una actualización del docu tratamiento de la faringoamigdalitis aguda, publicad no deben ser utilizadas para iniciar antibioterapia, estén disponibles o exista riesgo de fiebre reumátic que las expuestas en el consenso previo. Se propon pruebas microbiológicas, con independencia de los elección de la faringoamigdalitis estreptocócica es días. Amoxicilina, en una o dos dosis diarias y durante terapéutica. Las cefalosporinas de primera generac con reacción retardada no grave a penicilina o amox deben utilizarse antibióticos no betalactámicos, sie mejores opciones. En el fracaso terapéutico bacte tratamientos planteados en el consenso previo sigue


* Autor para correspondencia.
*Correo electrónico:* roi.pineiro@hgvillalba.es (R. Piñeiro Pérez).
[1] Los miembros del Grupo Colaborador de Faringoamigdalitis Aguda en Pediatría se presenta

https://doi.org/10.1016/j.anpedi.2020.05.004
1695-4033/

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frontiers in Immunology

ORIGINAL RESEARCH
published: 13 August 2020
doi: 10.3389/fimmu.2020.01996



# Treatment and Prevention of Lung Cancer Using a Virus-Infected Reprogrammed Somatic Cell-Derived Tumor Cell Vaccination (VIReST) Regime

*Zhe Zhang[1], Shuangshuang Lu[2], Louisa S. Chard Dunmall[3], Zhizhong Wang[2], Zhenguo Cheng[2], Zhongxian Zhang[2], Wenli Yan[2], Yongchao Chu[2], Dongling Gao[2], Na Wang[2], Yang Li[2], Jiwei Wang[2], Yuenan Li[2], Yupei Ji[2], Danyang Shan[2], Keke Li[2], Panpan Wang[2], Yunshu Dong[4], Jianzeng Dong[5], Nick R. Lemoine[2,3], Duanqing Pei[6], Lirong Zhang[7]* and Yaohe Wang[2,3]*

[1] National Center for International Research in Cell and Gene Therapy, Sino-British Research Centre for Molecular Oncology, School of Basic Medical Sciences, Academy of Medical Sciences, Zhengzhou University, Zhengzhou, China, [2] National Center for International Research in Cell and Gene Therapy, Sino-British Research Centre for Molecular Oncology, Academy of Medical Sciences, Zhengzhou University, Zhengzhou, China, [3] Centre for Biomarkers and Biotherapeutics, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom, [4] CAS Key Laboratory of Infection and Immunity, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China, [5] Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China, [6] CAS Key Laboratory of Regenerative Biology, South China Institute for Stem Cell Biology and Regenerative Medicine, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China, [7] School of Basic Medical Sciences, Academy of Medical Sciences, Zhengzhou University, Zhengzhou, China

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***Edited by:***
*Alan Graham Pockley, Nottingham Trent University, United Kingdom*

***Reviewed by:***
*Bart Vandekerckhove, Ghent University, Belgium*
*Munitta Muthana, The University of Sheffield, United Kingdom*

***Correspondence:**
*Lirong Zhang*
*lrzhang@zzu.edu.cn*
*Yaohe Wang*
*yaohe.wang@qmul.ac.uk*

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Lung cancer is one of the most commonly diagnosed cancer and despite therapeutic advances, mortality remains high. The long period of clinical latency associated with lung cancer provides an ideal window of opportunity to administer vaccines to at-risk individuals that can prevent tumor progression and initiate long-term anti-tumor immune surveillance. Here we describe a personalized vaccination regime that could be applied for both therapeutic and prophylactic prevention of lung cancer, based on the derivation of lung cancer cells from induced pluripotent stem cells. Stem cells from healthy mice were modified to express Cre-dependent $KRAS^{G12D}$ and $Trp53^{R172H}$ prior to differentiation to lung progenitor cells. Subsequent viral delivery of Cre caused activation of exogenous driver mutations, resulting in transformation and development of lung cancer cells. iPSC-derived lung cancer cells were highly antigenically related to lung cancer cells induced in LSL-$KRAS^{G12D/+}$; $Trp53^{R172H/+}$ transgenic mice and were antigenically unrelated to original pluripotent stem cells or pancreatic cancer cells derived using the same technological platform. For vaccination, induced lung cancer cells were infected with oncolytic Adenovirus or Vaccinia virus, to act as vaccine adjuvants, prior to delivery of vaccines sequentially to a murine inducible transgenic model of lung cancer. Application of this Virus-Infected, Reprogrammed Somatic cell-derived Tumor cell (VIReST) regime primed tumor-specific T cell responses that significantly prolonged

# Conclusiones facilonas

**MTBVAC** parece producir también efectos heterólogos, igual que BCG

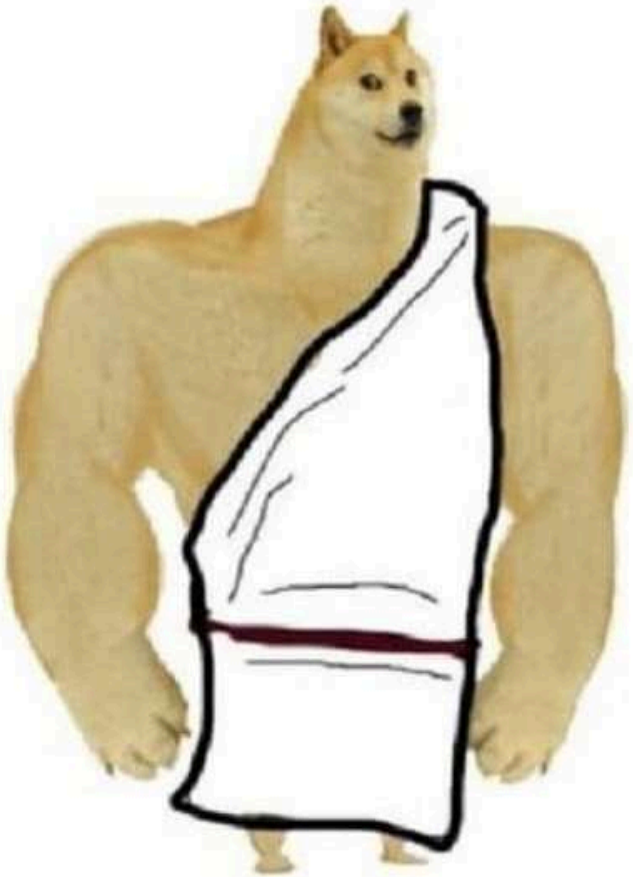
**No cambios** significativos en FAA, pero se siguen sin cumplir de forma óptima

Importantes pasos en el desarrollo de **vacunas individualizadas** frente a algunos tipos de cáncer

# Conclusión de verdad

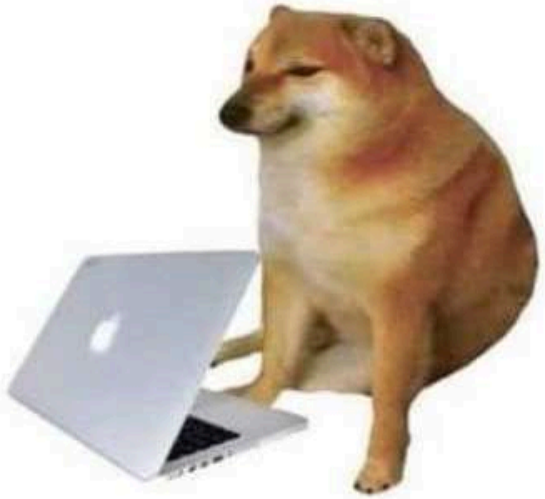
*(y un mensaje)*

Erastótenes de Cirene
(año 200 a. C.)

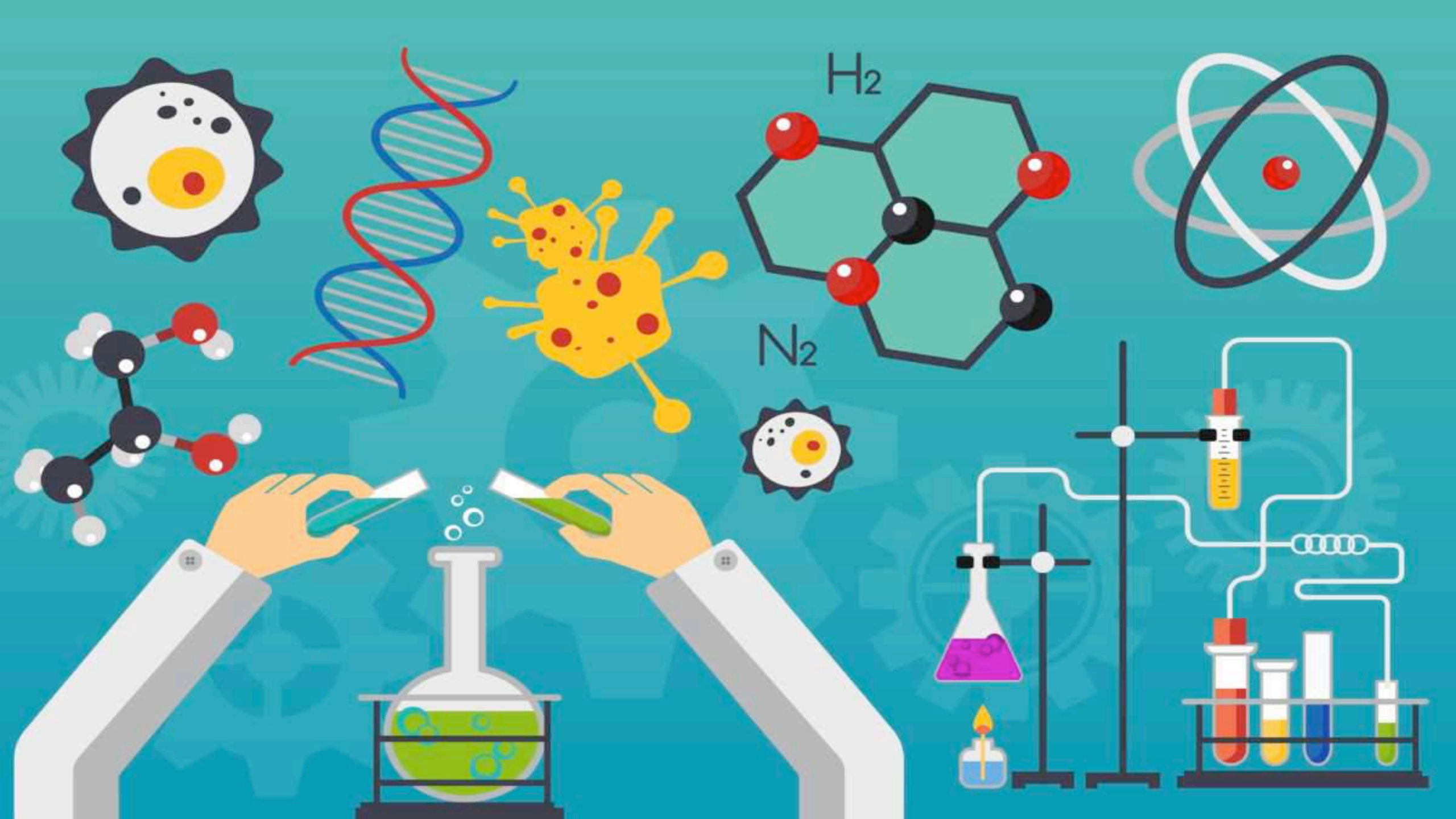


Midiendo la longitud de las sombras en diversas ciudades voy a calcular el tamaño de la circunferencia terrestre

Humanos hoy
(año 2020)



La Tierra es plana


H2
N2

# NATURALEZA 7

EDUCACIÓN GENERAL BÁSICA

santillana

# THE NOBEL PRIZE IN CHEMISTRY 2020

Emmanuelle Charpentier

Jennifer A. Doudna

"for the development of a method for genome editing"

THE ROYAL SWEDISH ACADEMY OF SCIENCES

# THE NOBEL PRIZE IN CHEMISTRY 2020


Emmanuelle Charpentier

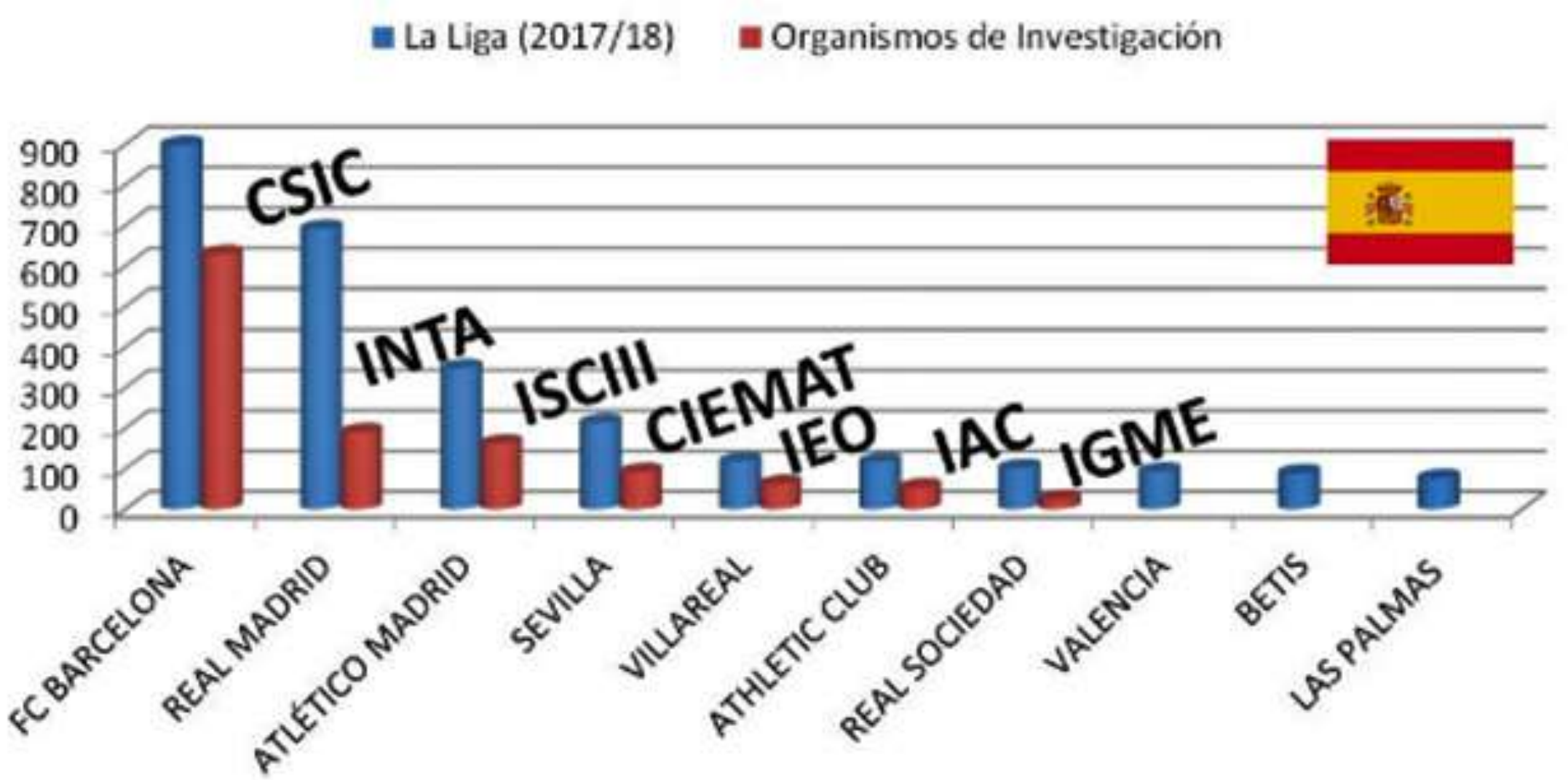
Jennifer A. Doudna

Francis M. Mojica

"for the development of a method for genome editing"

THE ROYAL SWEDISH ACADEMY OF SCIENCES

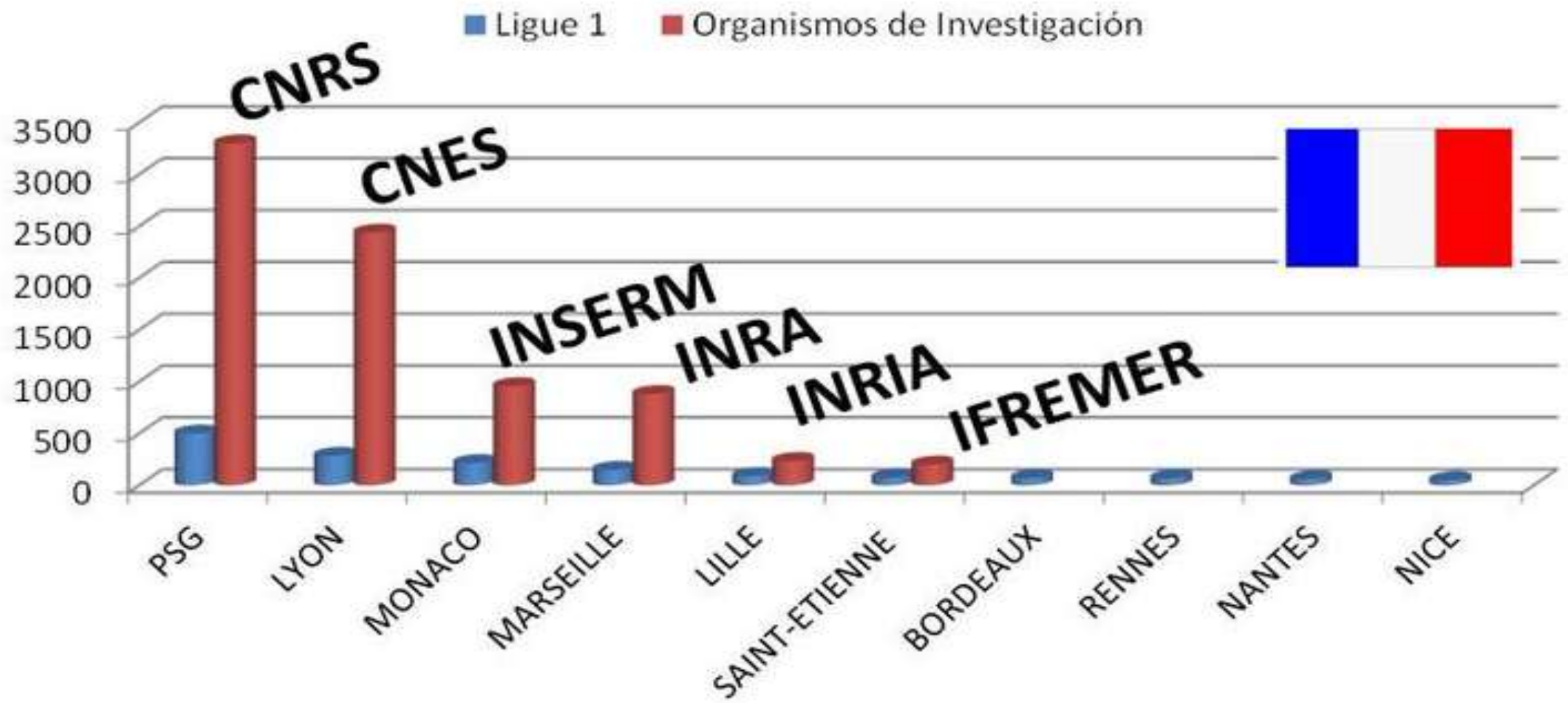
# Fútbol vs ciencia






https://www.elmundo.es/f5/descubre/2018/10/17/5bc70554ca474106148b45e0.html

# Fútbol vs ciencia






https://www.elmundo.es/f5/descubre/2018/10/17/5bc70554ca474106148b45e0.html

# Fútbol vs ciencia

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