

Curriculum vitae

Nombre : **Mariano Esteban Rodríguez**
<https://poxvirusandvaccines.wordpress.com>

Fecha: enero 2025

Apellidos: **ESTEBAN RODRÍGUEZ** Nombre: **MARIANO**

Apellidos: **ESTEBAN RODRÍGUEZ** Nombre: **MARIANO**
Fecha de nacimiento : **26/7/1944** Sexo: **V**

SITUACIÓN PROFESIONAL ACTUAL

Organismo: **CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS**
Facultad, Escuela o Instituto: **CENTRO NACIONAL DE BIOTECNOLOGIA**
Depto./Secc./Unidad estr.: **Departamento de Biología Molecular y Celular**
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Especialización (Códigos UNESCO): **242007**
Categoría profesional: **Profesor de Investigación** Fecha de inicio: **1987**

Situación administrativa

Plantilla Contratado Interino Becario
 Otras situaciones especificar:

Dedicación A tiempo completo
A tiempo parcial

LÍNEAS DE INVESTIGACIÓN

Biología molecular y celular de poxvirus, interacción virus-célula, expresión génica, biología de sistemas, respuesta inmune, inmunomoduladores, citoquinas, interferones, vacunas, VIH/sida, malaria, leishmania, hepatitis C, chikungunya, ebola, zika, SARS-CoV-2, mpox, cáncer, virus oncolíticos.

FORMACIÓN ACADÉMICA

Fecha	Titulación Superior	Centro
	Licenciatura en Farmacia	Universidad de Santiago de Compostela
	Licenciatura en C. Biológicas	Universidad de Santiago de Compostela

Doctorado	Centro	Fecha
Dr. en Farmacia (Microbiología)	Universidad de Santiago de Compostela	1970

ACTIVIDADES ANTERIORES DE CARÁCTER CIENTÍFICO PROFESIONAL

Puesto	Institución	Fechas
Investigador Asociado	National Inst. for Medical Research, Londres (UK)	1970-74
Instructor	Rutgers Medical School (NJ) USA	1974-77
Profesor visitante	Mol. Biol. Institut, University of Gent (Bélgica)	1978
Assistant Professor	State University of New York, Medical School, NY	1979-1982
Associate Professor	State University of New York, Medical School, NY	1982-1985
Professor	State University of New York, Medical School, NY	1985-1992
Año Sábatico	National Inst. for Medical Research, Londres (UK)	1987-1988
Director	Centro Nacional de Biotecnología, CSIC, Madrid	1992-2003
Presidente	Real Academia Nacional de Farmacia (RANF), Spain	2012-2018

Idiomas (R = regular, B = bien, C = correctamente)

Idioma	Habla	Lee	Escribe
Inglés	C	C	C
Francés	R	B	R

PARTICIPACIÓN EN PROYECTOS DE I+D FINANCIADOS EN CONVOCATORIAS PÚBLICAS

Título del proyecto: Mechanism of action of interferon
Entidad financiadora: National Institutes of Health (NIH), USA
Duración, desde: 1983 hasta: 1986
Investigador responsable: Mariano Esteban

Título del proyecto: Thymidine kinase and interferon action.
Entidad financiadora: NIH (USA)
Duración, desde: 1983 hasta: 1986
Investigador responsable: Co-Principal Mariano Esteban

Título del proyecto: Mechanism of Antiviral Activity of Human Interferon
Entidad financiadora: Science and Technological Cooperation, Spain-USA
Duración, desde: 1986 hasta: 1988
Investigador responsable: Mariano Esteban

Título del proyecto: Mechanism of action of interferon
Entidad financiadora: NIH (USA)
Duración, desde: 1986 hasta: 1992
Investigador responsable: Mariano Esteban

Título del proyecto: Genetic variability and virulence of poxviruses
Entidad financiadora: National Science Foundation (NSF), USA
Duración, desde: 1987 hasta: 1991
Investigador responsable: Mariano Esteban

Título del proyecto: Genetic markers and attenuation of vaccinia virus
Entidad financiadora: Health Research Council of New York (USA)
Duración, desde: 1986 hasta: 1987
Investigador responsable: Mariano Esteban

Título del proyecto: Role of Poly A on virus induced inhibition of protein synthesis
Entidad financiadora: NIH (USA)
Duración, desde: 1987 hasta: 1990
Investigador responsable: Mariano Esteban

Título del proyecto: Pathogenesis of vaccinia virus
Entidad financiadora: HSC (USA)
Duración, desde: 1991 hasta: 1992
Investigador responsable: Mariano Esteban

Título del proyecto: Fusion proteins as immunogens against HIV infection
Entidad financiadora: NIH (USA)
Duración, desde: 1992 hasta: 1995
Investigador responsable: Mariano Esteban

Título del proyecto: Proteínas de fusión como vacunas recombinantes contra el SIDA
Entidad financiadora: CICYT
Duración, desde: 1992 hasta: 1995
Investigador responsable: Mariano Esteban

Título del proyecto: Uso de recombinantes atenuados de vaccinia como posible vacuna
contra Leishmaniasis
Entidad financiadora: CAM
Duración, desde: 1992 hasta: 1993
Investigador responsable: Mariano Esteban

Título del proyecto: Obtención de vacunas recombinantes del virus vaccinia que
expresan proteínas (gp46 y gp63) protectoras a la infección por Leishmania infantum.
Entidad financiadora: FIS
Duración, desde: 1994 hasta: 1996
Investigador responsable: Mariano Esteban

Título del proyecto: The role of intracellular membrane compartments in the assembly of viruses

Entidad financiadora: CE Human Capital and Mobility

Duración, desde: 1994 hasta: 1997

Investigador responsable: Mariano Esteban

Título del proyecto: Desarrollo de estrategias para controlar la infección por el virus de inmunodeficiencia humana (VIH-1)

Entidad financiadora: CICYT

Duración, desde: 1995 hasta: 1998

Investigador responsable: Mariano Esteban

Título del proyecto: Mecanismos reguladores de crecimiento y muerte celular por interferones

Entidad financiadora: CICYT

Duración, desde: 1996 hasta: 1999

Investigador responsable: Mariano Esteban

Título del proyecto: European Action Programme Against AIDS

Entidad financiadora: CE Biomed

Duración, desde: 1996 hasta: 1997

Investigador responsable: Mariano Esteban

Título del proyecto: European vaccine against AIDS

Entidad financiadora: CE biomed 2. Programme PL 96-2515

Duración, desde: 1996 hasta: 1998

Investigador responsable: Mariano Esteban

Título del proyecto: Molecular and cellular principles of membrane virus biosynthesis and infection

Entidad financiadora: European Union, FMRX-CT98-0225

Duración, desde: 1998 hasta: 2001

Investigador responsable: Mariano Esteban

Título del proyecto: Malaria vaccine: attenuated influenza and vaccinia vectors

Entidad financiadora: NIH (USA). AI36526.05

Duración, desde: 1998 hasta: 2003

Investigador responsable: Mariano Esteban

Título del proyecto: Estrategias de terapia génica en las infecciones por VIH

Entidad financiadora: Comunidad de Madrid. 08.6/0020/1997

Duración, desde: 1998 hasta: 2001

Investigador responsable: Mariano Esteban

Título del proyecto: Mecanismo de inducción de apoptosis por los interferones: papel de las enzimas proteína quinasa (PKR) y sistema 2-5A sintetasa/RnasaL.

Entidad financiadora: Ministerio de Educación y Cultura, PM-98-0112

Duración, desde: 1999 hasta: 2002

Investigador responsable: Mariano Esteban

Título del proyecto: Modulación de la respuesta inmune frente a antígenos del virus de la inmunodeficiencia humana (VIH)

Entidad financiadora: Comisión Interministerial de Ciencia y Tecnología (CICYT), SAF98-0056,

Duración, desde: 1998 hasta: 2001

Investigador responsable: Mariano Esteban

Título del proyecto: Development of immunogenic and safe vaccinia virus vaccines.

Entidad financiadora: European Union. BIOTECH Program. PL970456
Duración, desde: 1998 hasta: 2001
Investigador responsable: Mariano Esteban

Título del proyecto: Effector and memory anti-malaria CD8+ cell responses.
Entidad financiadora: National Institutes of Health (NIH), 1 RO1 AI44375-01
Duración, desde: 1999 hasta: 2003
Investigador responsable: Mariano Esteban

Título del proyecto: Project Leader of the EuroVac Cluster, European Vaccine Effort Against HIV/AIDS
Entidad financiadora: Fifth Framework Programme, QLRT-PL1999-01321
Duración, desde: 2000 hasta: 2003
Investigador responsable: Mariano Esteban

Título del proyecto: European Vaccine against AIDS
Entidad financiadora: Programme EVA CFAR, QLRT-PL1999-00609
Duración, desde: 2000 hasta: 2003
Investigador responsable: Mariano Esteban

Título del proyecto: Visceral Leishmaniasis Vaccine-Murine Model Studies
Entidad financiadora: National Institutes of Health (NIH), 5R01AI45044-02
Duración, desde: 1999 hasta: 2003
Investigador responsable: Mariano Esteban

Título del proyecto: Desarrollo de una vacuna contra Leishmaniasis
Entidad financiadora: Comunidad Autonoma de Madrid (CAM), 08.2/0057/2000
Duración, desde: 2001 hasta: 2003
Investigador responsable: Mariano Esteban

Título del proyecto: Desarrollo de una vacuna contra Leishmaniasis
Entidad financiadora: Comunidad Autonoma de Madrid (CAM), 08.2/0057/2000
Duración, desde: 2001 hasta: 2003
Investigador responsable: Mariano Esteban

Principal investigator. Desarrollo de una vacuna contra leishmaniasis. Comunidad Autónoma de Madrid (CAM) 08.2/0057/2000-2001.

Project Leader of the EuroVac Cluster, European Vaccine Effort Against HIV/AIDS, Fifth Framework Programme, QLRT-PL1999-01321, Euros 500.000, 2000-2005

Concerted Action, Fifth Framework Programme, European Vaccine against Aids (EVA) CFAR, QLRT-PL1999-00609, 2000-2003.

Principal investigator. Contract with MOLOGEN, Germany, 2000-2001

Principal investigator. Contract with ITALFARMACO, Spain, 2001

Principal investigator. Premio IBERDROLA Ciencia y Tecnología, Profesores Visitantes, 2000-2003

Principal Investigator. Desarrollo de nuevas herramientas moleculares para el estudio del virus de la hepatitis C y su aplicación a morfogénesis, estructura, resistencia del virus a interferon y caracterización de la respuesta inmune al virus. BIO2000-0340-P4, 2001-2003. 171.649 euros.

Principal investigator. Diseño y utilización del virus vaccinia como vacuna contra distintas enfermedades: análisis de la interacción virus-célula y modulación de la respuesta inmune. BIO2001-2269, 2001-2003, 170.000 Euros

Principal investigator. Analysis of the molecular mechanism of hepatitis C virus (HCV) resistance to antiviral therapy. EU QLK2-CT-2002-00954. 2002-2005, 124.313 Euros

Coordinator. Increasing the potency of vaccinia MVA vaccines. EU QLK2-CT-2002-01867. 2002-2006. 220.000 euros

Principal investigator. European vaccine effort against HIV/AIDS (EuroVac III). QLK2-CT-2002-01431. 2002-2007. 50.000 euros

Principal investigator. Potenciación de la respuesta inmune (sistémica y de mucosas) frente al virus de la inmunodeficiencia humana (VIH-1). FIPSE, 2002-2006, 209.365 Euros

Principal Investigator. Vaccine strategies for combined targeting of innate and adaptive immune pathways (VaccTIP). EU-2004-012161. 2005-2007. 177.000 euros

Principal Investigator. Host immune activation optimised vaccinia virus vectors for vaccine development (MVECTOR). LSHP-CT-2006-037536. 2006-2009. 175.000 euros

Principal investigator. Diseño de nuevas vacunas tanto preventivas como terapéuticas para las enfermedades de mayor prevalencia: sida, hepatitis C y cáncer de próstata. BIO2004-03954. 2004-2007. 180.000 euros.

Principal Investigator. Desarrollo de vacunas contra enfermedades prevalentes. Fundación Botín 2005-2010. 1.100.000 euros.

Principal Investigator. Caracterización funcional y utilización de la proteína quinasa (PKR) inducida por los interferones como mediador de apoptosis e inhibidor tumoral. 2005-2008. 150.000 euros.

Principal Investigator. Pox T cell vaccine Discovery Consortium (PTVDC). Foundation Bill y Melinda Gates. \$1.500.000. 2006-2013.

Principal Investigator. Red de SIDA, ISCIII-RETIC-RD06/006. 2007-2010. 248.000 euros.

Principal Investigator. Modificación genética y optimización inmunológica de una vacuna (MVA-B) contra el VIH-1 subtipo B. Fundación para la Investigación y la Prevención del Sida (FIPSE). 2007-2009. 172.374 euros

Principal Investigator. Biología del virus vaccinia y su aplicación como vacuna contra enfermedades prevalentes. SAF2008-02036. 2008-2013. 654.000 euros

Principal Investigator. Optimización de la vacuna española (MVA-B) contra el VIH/SIDA. Fundación para la Investigación y la Prevención del Sida (FIPSE). 36-0731-09. 2010-2013. 259.391 euros

Co-Principal Investigator. Estudio en fase I abierto para evaluar la seguridad e inmunogenicidad de la vacuna frente al VIH-1 MVA-B en pacientes infectados por VIH crónicos en tratamiento antirretroviral (RISVAC03). EudraCT 2099-016578-34. 2010-2011. 411.000 euros

Co-Principal Investigator. Desarrollo de una vacuna frente al VIH: Estudio de los cambios en la biología de células dendríticas humanas tras interacción con distintos inmunógenos. Fondo de Investigaciones Sanitarias (FIS). 2010-2013. 227.000 euros

Principal Investigator. Desarrollo y optimización de vectores virales vacunales contra subtipos B/F de VIH-1 circulantes en Argentina y países limítrofes. Cooperación Interuniversitaria en Investigación Científica con Argentina. A/025293/09. 2010-2011. 23.000 euros

Coinvestigador. Red Temática en SIDA. ISCIII-RETIC, RD12/0017/0038. 2013—2017. 178.250 euros

Principal Investigator. A Novel Replication Competent Flavivirus-based HIV Vaccine Platform, ie RepliVax®, as a Priming Component for Improving Antibody Response. Foundation Bill and Melinda Gates. 2012-2017. 510.000 euros.

Principal Investigator. ICRES: Integration of Chikungunya Research. EU 7th Framework Program. Grant agreement 261202. 2011-2014. 50.000 euros.

Principal Investigator. Mecanismo de acción de vacunas. CSIC-201420E064. 2014-2017. 135.000 euros

Principal Investigator. Vacunas frente a enfermedades humanas prevalentes y optimización de la respuesta immune humoral y celular. 2014-2017. SAF2013-45232-R. 592.900 euros

Principal Investigator. European HIV Vaccine Alliance (EHVA): an EU platform for the discovery and evaluation of novel prophylactic and therapeutic vaccine candidates. EU H2020, number 681032. 2016-2023. 415.000 euros

Principal Investigator. Red Temática de Investigación Cooperativa en Salud: Red Española de Investigación en Sida (RIS). RD16/0025/0014. 2017-2021. 132.000 euros.

Principal investigator. Evaluating a combination of Immune-based Therapies to Achieve a Functional Cure of HIV Infection (HIVACAR). H2020-731626. 2017-2022. 408.000 euros

Co-Principal investigator. Vacunas frente a enfermedades humanas prevalentes: papel de ISG15. SAF2017-88089-R. 2017-2020. 332.000 euros.

Principal investigator: Desarrollo de una vacuna MVA-COVID-19 expresando antígenos del SARS-CoV-2. PIE-CSIC 2020-2021. 105.000 euros; 2022-2025. 400.000

Principal investigator: CoV2-BMEP and CoV2-TMEP: two novel polyvalent multiepitopic vaccines against SARS-CoV2. La CaixaImpulse. 2020-2023- 298.000 euros.

Co-investigador. Development of a vaccine, MVA-COVID-19, expressing SARS-CoV-2 antigens. Instituto de Salud Carlos III. 2020-2021. 750.000 euros

Principal investigator. Preclinical development of innovative mRNA/MVA vaccines against SARS-CoV2. Instituto de Salud Carlos III. Fondo COVID-19 (COV20_00214). 2020-2021. 300.000 euros

Principal investigator. Desarrollo de una vacuna frente a COVID-19. Ferrovial. 125.000. 2020-2025

Co-PI.: Impact of the vector MVA-ISG15 in the infection by SARS-COV-2/COVID-19. Susana Guerra/ Mariano Esteban. PDC2021-121307-I00. 01/12/2021-31/8/2025. 130.000 euros

Co-Principal Investigator: Desarrollo, función inmune y eficacia de candidatos vacunales frente al SARS-CoV-2/COVID-19 basados en el vector poxvirus MVA. MICINN, Spanish Research Agency grant PID2020-114481RB-I00 (Juan García Arriaza/ Mariano Esteban). 1/09/2021-31/08/2025. 484.000 euros.

Principal investigator (Mariano Esteban/Juan García Arriaza). Título del proyecto: Grupo Pandemias – W8 Vacunas. Grupo Temático 4 de Terapias y Vacunas, Subtemática 4d de Vacunas. Subproyecto “Development of MVA Vaccine”. (SGL2103047). Entidad financiadora: PTI Salud Global, CSIC, Ministerio de Ciencia e Innovación, España. Mecanismo de Recuperación y Resiliencia de la Unión Europea. Duración, desde: 01/01/2021 hasta: 31/12/2022 (2 años). Cuantía de la subvención: 5.653.161 € (incluye presupuesto para CRO y viales lote GMP vacuna).

Principal Investigator. Donaciones ayuda investigación COVID-19. 2020-. 41.675€.

Co-Principal Investigator. Impact of the vector MVA-ISG15 in the infection by SARS-CoV-2/COVID-19. MICINN, Spanish Research Agency grant PDC2021-121307-100 (Susana Guerra/Mariano Esteban). 2021-2023. 149.000 euros.

Principal Investigator. CZ Veterinaria. 2022-2025. 139.000€

Principal Investigator: Sustainable COVID-19 Vaccination for Long-term Immunity and Effectiveness. Acronym: EU-Horizon SOLVE. EU263610_1 -101137185. Ref HE/CL1-HLTH/0423. 01/01/2024-31/12/2028. 1,03 million euros.

Principal Investigator. Proyecto europeo de Defensa: European Strategic alliance for research, development and innovation on medical countermeasures against CBRN threats (RESILIENCE). Activity 5: "New generation vaccines for orthopox viruses (VACC)". RESILIENCE-R-2023 (101168024), 01/11/2024-31/10/2027. CNB-CSIC (999.738,75 euros).

Co-Investigator. Development and characterization of pan-flavivirus vaccine candidate (FLAVIVACCINE). 101137006. EU-Horizon-HLTH-2023-DISEASE 03-18. 01/01/2024-31/12/2027 (IP Juan Garcia-Arriaza). 1.228.696 euros.

-Development of novel viral vectored vaccines against Marburgviruses inducing robust and cross-reactive protection (MARVAX). 101137183. HORIZON-HLTH-2023-DISEASE-03-18. PI: Juan García Arriaza. 01/12/2023-30/11/2027. 1.242.042,50 euros.

PUBLICACIONES / PUBLICATIONS

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1. Kerr, I.M., Dobos, P., Martin, E.M., Metz, D.H. and **Esteban**, M. (1972). Protein synthesis in interferon-treated and virus infected cells. Federation of European Biochemical Societies Academic Press. Vol. 22:45-64.
 2. Metz, D.H. and **Esteban**, M. (1972). Interferon inhibits viral protein synthesis in L-cells infected with vaccinia virus. Nature 238:385-388
 3. Friedman, R.M.; **Esteban**, M., Metz, D.H., Tovell, D.R. and Kerr, I.M. (1972). Translation of RNA by L-cell extracts: Effect of interferon. FEBS Letters 24:273-77.
 4. Friedman, R.M., Metz, D.H. **Esteban**, R.M., Tovell, D.R., Ball, L.A., and Kerr, I.M. (1973). Mechanism of interferon action. Inhibition of viral messenger ribonucleic acid (RNA) translation in L-cell extracts. J. Virol. 10: 1184-1198.
 5. **Esteban**, M. and Metz, D.H. (1973). Early viral protein synthesis in vaccinia infected L-cells. J. Gen. Virol. 19:201-216.
 6. **Esteban**, M. and Metz, D.H. (1973). Inhibition of early vaccinia virus protein synthesis in interferon-treated chicken embryo fibroblasts. J. Gen. Virol. 20:111-115.
 7. Fournier, F., Tovell, D.R., **Esteban**, M., Metz, D.H., Ball, L.A., and Kerr, I.M. (1973). The translation of vaccinia mRNA in animal cell-free systems. FEBS Letters 30:268-272.

8. Kerr, I.M. Friedman, R.M., **Esteban**, M., Brown, R.E., Ball, L.A., Metz, D.H., Risby, D., Tovell, D.R., and Sonnabend, J.A. (1973) The control of protein synthesis in interferon-treated infected cells. In "Advances in the Biosciences" II Pergamon Press. Vieweg, 109-126.
9. **Esteban**, M. and Kerr, I.M. (1974) The synthesis of Encephalomyocarditis virus polypeptides in infected L-cell and cell-free systems. Eur.J. Biochem. 45:567-576.
10. Metz, D.H., **Esteban**, M., and Danielescu, G. (1975) The effect of interferon on the formation of virus polyribosome in L-cell infected with vaccinia virus. J. Gen. Virol. 27:197-209.
11. Metz, D.H., **Esteban**, M., and Danielescu, G. (1975). The formation of polyribosomes in L-cells infected with vaccinia virus. J. Gen. Virol.27:181-195
12. **Esteban**, M. (1975). Interferon inhibits the translation of viral mRNA in animal cell-free systems. In "Effects of interferon on cells, viruses and the Immune System", ed. Gerald (Academic Press, London) 549-562.
13. **Esteban**, M. (1977). Rifampicin and Vaccinia DNA. J. Virol. 21:796-801.
14. **Esteban**, M. and Holowczak, J.A. (1977). Replication of vaccinia DNA in mouse L cells. I. In vivo DNA synthesis. Virology 78:57-75.
15. **Esteban**, M. and Holowczak, J.A. (1977). Replication of vaccinia DNA in mouse L-cells. I. In vitro DNA synthesis in cytoplasmic extracts. Virology 78:76-86.
16. **Esteban**, M. and Holowczak, J.A. (1977). Replication of vaccinia DNA in mouse L-cells. III. Intracellular forms of vaccinia DNA. Virology 82: 308-322.
17. **Esteban**, M., Flores, L. and Holowczak, J.A. (1977). Model for vaccinia virus DNA replication. Virology 83: 467-473.
18. **Esteban**, M., Flores, L. and Holowczak, J.A. (1977). Topography of vaccinia virus DNA. Virology 82; 163-181.
19. **Esteban**, M. and Holowczak, J.A. (1978). Replication of vaccinia DNA in mouse L-cells. IV. Protein synthesis and viral DNA replication. Virology 86:376-390.
20. Cabrera, C.V. and **Esteban**, M. (1978). A simple procedure to purify intact -DNA from vaccinia virus. J. Virol. 25: 442-445.
21. Soloski, M.J., **Esteban**, M. and Holowczak, J. (1978). DNA-binding proteins in the cytoplasm of vaccinia infected mouse L-cells. J. Virol. 25: 263-273.
22. Mc Carron, R.J., Cabrera, C.V., **Esteban**, M., Mc Allister, W.T. and Holowczak, J.A. (1978). Structure of vaccinia DNA: Analysis of the viral genome by restriction endonucleases. Virology 86: 88-101.
23. Cabrera, C.V., **Esteban**, M., Mc Carron, R.J., Mc Allister, W.T. and

- Holowczak, J.A. (1978). Vaccinia virus transcription: Hybridization of mRNA to restriction fragments of vaccinia DNA. *Virology* 86: 102-114.
24. Bablanian, R., **Esteban**, M., Baxt, B. and Sonnabend, J.A. (1978). Studies on the mechanism of vaccinia virus cytopathic effects: I. Inhibition of protein synthesis in infected cell is associated with virus-induced RNA synthesis. *J. Gen. Virol.* 39: 391-402.
 25. Bablanian, R., Baxt, B., Sonnabend, J.A., and **Esteban**, M. (1978). Studies on the mechanism of vaccinia virus cytopathic effects: II. Early cell rounding is associated with virus polypeptide synthesis. *J. Gen. Virol.* 39: 403-413.
 26. **Esteban**, M., Soloski, M., Cabrera, C.V. and Holowczak, J.A. (1979). Replication of vaccinia DNA and studies on the structure of the virus chromosome. *Cold Spring Harbor Symposia Quantitative Biology*. Vol. XLIII. DNA: Replication and recombination. 789-799.
 27. Soloski, M.J., Cabrera, C.V., **Esteban**, M. and Holowczak, J.A. (1979). Studies concerning the structure and organization of the vaccinia virus nucleoid. *Virology* 99, 209-217.
 28. **Esteban**, M. and Holowczak, J.A. Vaccinia virus DNA replication. (1980). In "Microbiology" (ed. D. Schlesinger) ASM publication 275-280.
 29. Bablanian, R., Coppola, G., Scribani, S. and **Esteban**, M. (1981). Inhibition of protein synthesis by vaccinia virus. The effect of UV-irradiated virus in the inhibition of protein synthesis. *Virology* 112, 1-12.
 30. Bablanian, R., Coppola, G., Scribani S. and **Esteban**, M. (1981). Inhibition of protein synthesis by vaccinia virus. The role of low molecular weight viral, RNA in the inhibition of protein synthesis. *Virology* 112, 13-24.
 31. Carrasco, L. and **Esteban**, M. (1982). Modification of membrane permeability in vaccinia virus-infected cells. *Virology* 117, 62-69.
 32. Pellicer, A. and **Esteban**, M. (1982). Gene-transfer, stability and biochemical properties of animal cells transformed with vaccinia DNA. *Virology* 122, 363-380.
 33. Santoro, M.G., Jaffe, B.M., Garaci, E. and **Esteban**, M. (1982). Antiviral effect of prostaglandins of the A series: Inhibition of vaccinia virus replication in cultured cells. *J. Gen. Virol.* 63, 435-440.
 34. Lewis, J.A., Mengheri, E. and **Esteban**, M. (1983). Induction of an antiviral state by interferon requires thymidine kinase. *Proc. Natl. Acad. Sci. USA* 80, 26-30.
 35. Mengheri, E., **Esteban**, M. and Lewis, J.A. (1983). Thymidine kinase genes and the induction of an antiviral response. *FEBS Letters* 157, 301-305.
 36. **Esteban**, M., Cabrera, C. and Holowczak, J.A. (1983). Electron microscopic studies of transcriptional complexes released from vaccinia cores during RNA-synthesis in vitro: methods for fractionation of

transcriptional complexes. *J. Virol. Methods* 7, 73-92.

37. Santoro, G., Jaffe, B.M. and **Esteban**, M. (1983). Prostaglandin A inhibits the replication of vesicular stomatitis virus: effect on virus glycoprotein. *J. Gen. Virol.* 64, 2797-2801.
38. Santoro, G.M., Jaffe, B., Paez, E. and **Esteban**, M. (1983). The relationship between the antiviral action of interferon and prostaglandins in virus-infected murine cells. *Biochem. Biophys. Res. Commun.* 116, 442-448.
39. Benavente, J., **Esteban**, M., Jaffe, B. and Santoro, G.M. (1984). Selective inhibition of viral gene expression as the mechanism for the antiviral action of PGA₁ in vaccinia virus-infected cells, *J. Gen. Virol.* 65, 599-608.
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PATENTES / PATENTS

-VECTORES RECOMBINANTES BASADOS EN EL VIRUS MODIFICADO DE ANKARA (MVA) COMO VACUNAS CONTRA LEISHMANIASIS. Solicitud de invención N° 200501886, 30 Julio 2005; PCT/ES2006/070122. US Application Serial No. 11/989.614, filing date January 29, 2008. Concedido Título de Patente de Invención, Oficina Española de Patentes y Marcas, 16 Febrero, 2009. N° publicación 2281252. Eva Pérez-Jiménez, Vicente Larraga y Mariano Esteban (licenciada).

- RECOMBINANT VECTORS BASED ON ANKARA MODIFIED VIRUS (MVA) AS PREVENTIVE AND THERAPEUTIC VACCINES AGAINST HIV. Carmen E. Gómez, José L. Nájera, Victoria Jiménez y Mariano Esteban- Application Number and priority date: P200501841, 27/07/2005 and P200600762 (24.03.2006)- International PCT Application: PCT/ES06/070114- Countries selected in National Phase: EU, US- Present situation: Exclusive license agreement to Laboratorios del Dr. Esteve S.A. y la Fundación Privada Institut de Recerca de la SIDA-CAIXA (Fundación Irsi-CAIXA). (30/06/2012). EU Patent has been granted (EP1921146 B1) and has been validated in the following countries: España, Francia, Austria, Bélgica, Dinamarca, Finlandia, Alemania, Grecia, Islandia, Irlanda, Italia, Letonia, Luxemburgo, Mónaco, Países Bajos, Portugal, Suecia, Suiza, Gran Bretaña, Polonia, Rumania y Chipre. US Patent has been granted (US 8,871,219 B2, 28/10/2014).

-MEJORAS INTRODUCIDAS EN EL OBJETO DE LA PATENTE PRINCIPAL N° ES200501841 PARA VECTORES RECOMBINANTES BASADOS EN EL VIRUS MODIFICADO DE ANKARA (MVA) COMO VACUNAS PREVENTIVAS Y TERAPÉUTICAS CONTRA EL SIDA. Solicitud P200600762. 24 Marzo, 2006; PCT/ES2006/070114. Carmen E. Gómez, José L. Nájera, Victoria Jiménez y Mariano Esteban (licenciada)

-VECTORES EN LOS QUE SE INSERTA EL GEN C7L Y USO DE LOS MISMOS EN LA FABRICACION DE VACUNAS Y DE COMPOSICIONES PARA TERAPIA GÉNICA. Solicitud de Invención N°200601240, 18 Mayo, 2006; PCT/ES2007/070091. José Luis Nájera, Carmen E. Gómez y Mariano Esteban.

-MODIFIED POXVIRUSES. US Provisional Patent Application No. 61/102,401. November 11, 2008. Michael Way, Antonio Postigo, Yoshiki Arakawa, Mariano Esteban, Susana Guerra.

--MODIFIED IMMUNIZATION VECTORS. US Patent 2,760,315, date 29/04/2018. Mariano Esteban, Bertram Jacobs, Giuseppe Pantaleo, Co-titularity with Arizona State University (AZ, USA), Centre Hospitalier Universitaire Vaudois (Switzerland) - International PCT Application: PCT/US10/032966- Countries selected in National Phase: EU, US, CA

-MÉTODO DE OBTENCIÓN DE DATOS ÚTILES PARA EVALUAR LA RESPUESTA AL TRATAMIENTO

CON 5-FLUOROURACILO (5-FU). Solicitud de invención N° P201130247, 24 Febrero 2011. García Cháves M.A., Aguilera Gómez M., Calleja Hernández M.A., Marchal Corrales J.A., Esteban Rodríguez M., Carrasco Pardo E., Jiménez Gonzalez G., Aránega Jiménez A.

-VECTORES RECOMBINANTES BASADOS EN EL VIRUS MODIFICADO DE ANKARA (MVA) CON DELECIÓN EN EL GEN C6L COMO VACUNA CONTRA EL VIH/SIDA Y OTRAS ENFERMEDADES. Presentada ante la Oficina Española de Patentes y Marcas el 19 de Julio de 2011. Número de solicitud 201131230. PCT/ES2012/070521 Juan F. García-Arriaza, Carmen E. Gómez y Mariano Esteban.

-ADJUVANT EFFECT OF PROTEIN A27 (14K) FROM VACCINIA VIRUS AND APPLICATIONS AS VACCINES. Presentada en la Oficina Española de Patentes y Marcas, 17 Noviembre de 2011. N° solicitud P201131854. Aneesh Vijayan, Carmen E. Gómez and Mariano Esteban.

-MVA-HCV AS VACCINE AGAINST HEPATITIS C. Mariano Esteban., Beatriz Perdiguero y Carmen E. Gómez. Application Number and priority date: P201330467, 02/04/2013.- International PCT Application: PCT/ES2014/070246, 31/03/2014. On 09/10/2014 the mentioned International Patent Application has been published as WO 2014/162031. - Present situation: Exclusive license agreement to Plant Bioscience Limited (PBL) (6/05/2014) but sublicensing rights are available from PBL.

-MVA-CHIKV AS VACCINE AGAINST CHIKUNGUNYA VIRUS. Mariano Esteban, Juan García-Arriaza and Peter Liljeström. PCT/EP2014/076310, 2 Dic 2014- Present situation: Exclusive license agreement to Plant Bioscience Limited (PBL) (14/07/2014) but sublicensing rights are available from PBL (licenciada). WO2016/086980-A1, June 9, 2016.

-MVA-BASED VACCINE AGAINST COVID-19 EXPRESSING SARS-COV-2 ANTIGENS. Juan García Arriaza; Mariano Esteban Rodríguez. Número de publicación: WO 2021/260065 A1 (30/12/2021), Número de solicitud: PCT/EP2021/067245 (23/06/2021); EP20383017.9 (20/11/2020); EP20382558.3. (24/06/2020), PCT/EP2021/067245 (26/06/2021). Fecha de prioridad: 24/06/2020. Entidad titular: Consejo Superior de Investigaciones Científicas (CSIC) (100%)

-MVA-BASED VACCINE AGAINST COVID-19 EXPRESSING A PREFUSION-STABILIZED SARS-COV-2 S PROTEIN. Juan García Arriaza; Patricia Pérez Ramírez, Adrián Lázaro Frías, Mariano Esteban Rodríguez. Número de solicitud: EP21382557.3 (23/06/2021), EP21383245.4 (31/12/2021), PCT/EP2022/067271 (23/06/2022). Fecha de prioridad: 23/06/2021. EP 4108257. Entered on January 23, 2024 into National Phase in Europe. Entidad titular: Consejo Superior de Investigaciones Científicas (CSIC) (100%).

- COMPOUNDS FOR USE IN THE TREATMENT OF NON-INTEGRATED DNA VIRAL INFECTIONS” Juan García Arriaza, Guillen Albericio, Mariano Esteban. Esta solicitud de Patente internacional No. PCT/EP2024/053510 de fecha 12/02/2024 se publicó el pasado 15/08/2024 bajo el número WO 2024/165764 A1.

COLLABORATION WITH INDUSTRY AND DONATIONS

- NAME company: BIOFABRI S.L.U, SPAIN

Transferred products from CNB to Biofabri:

- 1) Vaccine SARS-CoV-2, based on the poxvirus MVA expressing the entire S protein from SARS-CoV-2, Wuhan strain MVA (named MVA-CoV2-S)
- 2) Vaccine SARS-CoV-2, based on the poxvirus vector MVA expressing the fusion stabilized S protein (MVA-S(3P)).

Agreements:

- Confidentiality, May 7, 2020.
- Material Transfer Agreement (MTA), May 20, 2020, stock of MVA-CoV2-S (native full-length S from Wuhan strain).
- Material Transfer Agreement, February 23, 2021, MVA-CoV2-S(3P) (stabilized S protein from Wuhan strain).
- R&D contract, CNB-CSIC and CZ Veterinaria, July 25, 2020: CDTI project on vaccines against COVID-19.
- Contract for a phase I clinical trial with a CRO to evaluate the security, reactogenicity and immunogenicity of the vaccine candidate MVA-CoV2-S(3P), Acronym: COVIMVA.
- CSIC agreement with WHO through Medicines Patent Pool for the donation of the vaccine MVA-CoV2-S(3P) for most needed third world countries.

Donations: numerous donations from private sector and society were provided to the laboratory for vaccine development during the SARS-CoV-2 pandemic.

ESTANCIAS EN CENTROS EXTRANJEROS/ FOREIGN CENTERS

Centro: National Institute for Medical Research, Mill Hill

Localidad: Londres País Reino Unido Fecha: 1970-74

Duración: 4 años

Tema: Vaccinia virus, action of interferon, translation

Centro: Department of Microbiology. Rutgers Medical School

Localidad: New Jersey País USA Fecha: 1974-77

Duración: 4 años

Tema: Transcription and DNA replication of vaccinia virus

Centro: Molecular Biology Center. Ghent

Localidad: Ghent País Belgium

Fecha: 1978

Duración: 6 meses

Tema: Cloning and sequencing of viruses

Centro: Departments of Biochemistry and Microbiology and Immunology, State University of New York (SUNY), Downstate Medical Center

Localidad: New York País USA Fecha: 1979-1993

Duración: 14 años

Tema: Viral pathogenesis, gene expression, mechanism of action of interferons, vaccines against pathogens

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365. Pérez, P., Lázaro-Frías, A., Zamora, C., Sánchez-Cordón, P.J., Astorgano, D., Luczkowiak, J., Delgado, R., Casasnovas, J.M., **Esteban, M.**, & García-Arriaza, J., (2022). A single dose of an MVA vaccine expressing a prefusion-stabilized SARS-CoV-2 spike protein neutralizes variants of concern and protects mice from a lethal SARS-CoV-2 infection. XVI Congreso Nacional de Virología. Málaga, España, 6-9 Septiembre (Póster).
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373. Beatriz Perdiguero, Carmen Elena Gómez, Alexandra Hauser, David Peterhoff, Elefthería Sideris, Carlos Oscar S. Sorzano, Sarah Wilmschen, Marion Schaber, Dorothee von Laer, Christina Schmalzl, Song Ding, Janine Kimpel, Yves Levy, Giuseppe Pantaleo, **Mariano Esteban** and Ralf Wagner. (2022). Potency and durability of T and B cell immune responses with high broadly neutralizing antibody recognition after prime/boost combinations with recombinant VSV-GP, DNA or NYVAC vectors

expressing the novel HIV-1 Env clade C membrane-bound trimeric gp140:GΔ6 ConCv5 KIKO protein. XVI Congreso Nacional de Virología. Málaga, España, 6-9 Septiembre.

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375. Juan García-Arriaza, Patricia Pérez, Petra Mooij, Robbert Boudewijns, David Astorgano, Guillermo Albericio, Rana Abdelnabi, Kai Dallmeier, Gerrit Koopman, **Mariano Esteban** (2023). Poxvirus MVA-based vaccine candidates expressing the SARS-CoV-2 S protein induce potent humoral and T cellular immune responses and full efficacy against SARS-CoV-2 infection in several animal models. XVIth International Nidovirus Symposium, Montreux, Switzerland, May14th - 18th.
376. Garcia-Arriaza J, Perez P, Mooij P, Boudwijns R, Astorgano D, Albericio, G, Abdelnabi mR, Dallmeier, Koopman G and **Esteban M** (2023). MVA-based vaccine candidates against COVID-19 expressing SARS-CoV-2 S protein trigger robust immunogenicity and complete efficacy against SARS-CoV-2 infection in various animal models. XXIV International Poxvirus, Asfarvirus and Iridovirus Conference. Dusseldorf (Germany), September 2-6, 2023.
377. Jacobs, B, Kibler K, Szczerba M, Williams, J and **Esteban M** (2023). Replication-competent NYVAC-KC vector expressing modified spike protein and administered by intranasal route or by scarification protects against mouse-adapted SARS-CoV-2 in mice. XXIV International Poxvirus, Asfarvirus and Iridovirus Conference. Dusseldorf (Germany), September 2-6, 2023.
378. Gomez C.E, Marcos-Villar L, Perdiguero B, Lopez-Bravo M, Zamora C, Sin L, Alvarez E, Oscar S. Sorzano C, Sanchez-Cordon P, Garcia F, Plana M, Alonso M.J, **Esteban M** (2023). Immunogenicity and protective efficacy of trimeric SARS-CoV-2 receptor binding domain after heterologous mRNA/MVA regimen. XXIV International Poxvirus, Asfarvirus and Iridovirus Conference. Dusseldorf (Germany), September 2-6, 2023.
379. Perdiguero B, Marcos-Villar L, Lopez-Bravo M, Sanchez-Cordon P, Zamora C, Valverde J.R, Oscar S. Sorzano C, Sin L, Alvarez E, **Esteban M**, and Gomez C.E (2023). Immunogenicity and efficacy of a novel multi-patch SARS-CoV-2/COVID-19 vaccine candidate. XXIV International Poxvirus, Asfarvirus and Iridovirus Conference. Dusseldorf (Germany), September 2-6, 2023.
380. Guerra S, Falqui M, Perdiguero B, Coloma R, Albert M, Marcos L, McGrail J.P, Oscar S. Sorzano C, **Esteban M** and Gomez C.E (2023). An MVA vector expressing cell-free ISG15 increases IFN-I production and improves HIV-1-specific CD8 T cell immune responses. XXIV International Poxvirus, Asfarvirus and Iridovirus Conference. Dusseldorf (Germany), September 2-6, 2023.
381. Perez P, Astorgano D, Albericio G, Flores S, Sanchez-Cordon P, Luczkowiak J, Delgado R, Casasnovas J.M, **Esteban M** and Garcia-Arriaza J (2023). MVA-based vaccine candidates expressing prefusion-stabilized spike proteins from SARS-CoV-2 Wuhan and beta variant of concern are highly immunogenic and protects mice from a lethal challenge with SARS-CoV-2 beta variant. XXIV International Poxvirus, Asfarvirus and Iridovirus Conference. Dusseldorf (Germany), September 2-6, 2023.
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386. Guillermo Albericio, Alberto Gómez-Carballa, Julián Montoto-Louzao, Patricia Pérez, David Astorgano, Irene Rivero-Calle, Federico Martín-Torres, **Mariano Esteban**, Antonio Salas and Juan García-Arriaza (2024). Lung transcriptomics of K18-hACE2 mice highlights mechanisms and genes involved in the MVA-S vaccine-mediated immune response and protection against SARS-CoV-2 infection. XVII Congreso Nacional de Virología, Santiago de Compostela, 2-5 Septiembre, 2024
387. Guillermo Albericio, Patricia Pérez, Daniel Rodríguez-Martín, David Astorgano, Sara Flores, Cristina Sánchez-Corzo, María A. Noriega, **Mariano Esteban** and Juan García-Arriaza. (2024). Development of next-generation modified vaccinia virus Ankara-based vaccine candidates against Monkeypoxvirus by directed deletion of multiple immunomodulatory genes. XVII Congreso Nacional de Virología, Santiago de Compostela, 2-5 Septiembre, 2024
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389. Rocío Coloma, Michela Falqui, Beatriz Perdiguero, Laura Marcos-Villar, **Mariano Esteban**, Carmen Elena Gómez and Susana Guerra. (2024). New MVA-based vector expressing ISG15. XVII Congreso Nacional de Virología, Santiago de Compostela, 2-5 Septiembre, 2024
390. Juan García-Arriaza, Javier Villadiego, Reposo Ramírez-Lorca, Roberto García-Swinburn, Daniel Cabello-Rivera, Alicia E. Rosales-Nieves, María I. Álvarez-Vergara, Fernando Cala-Fernández, Ernesto García-Roldán, Juan L. López-Ogáyar, Carmen Zamora, David Astorgano, Guillermo Albericio, Patricia Pérez, Ana M. Muñoz-Cabello, Alberto Pascual, **Mariano Esteban**, José López-Barneo and Juan José Toledo-Aral. (2024). MVA-S vaccine candidate confers complete protection from SARS-CoV-2 brain infection and damage in susceptible transgenic K18-hACE2 mice. XVII Congreso Nacional de Virología, Santiago de Compostela, 2-5 Septiembre, 2024
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Diverse Nanocarriers Delivering mRNA for Spike Protein's Trimeric RBD Expression: COVARNA Consortium. XVII Congreso Nacional de Virología, Santiago de Compostela, 2-5 Septiembre, 2024

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393. Enrique Álvarez, Beatriz Perdiguero de la Torre, Laura Marcos-Villar, Laura Sin, Ralf Wagner, **Mariano Esteban**, Carmen Elena Gómez. (2024). MVA-ConCv5 KIKO and MVA-TMEP: A Combined Approach to Enhance HIV-1 Immunity. XVII Congreso Nacional de Virología, Santiago de Compostela, 2-5 Septiembre, 2024

394.

TESIS DOCTORALES DIRIGIDAS / PhD THESIS

1. Cabrera, Carlos V. (1978). Studies on the structure and genetic expression of poxvirus. Departments of Microbiology, Rutgers Medical School, CMDNJ, Piscataway, New Jersey and School of Pharmacy, Universidad de Santiago de Compostela, España.
2. Dallo, Shatha (1986). Isolation and characterization of spontaneous deletion mutants of vaccinia virus. Department of Microbiology and Immunology, SUNY Health Science Center at Brooklyn, NY. Premio extraordinario.
3. Maa, Juehn-Shin (1988). Biochemical and genetic characterization of immunodominant proteins of vaccinia virus. Department of Biochemistry, SUNY Health Science Center at Brooklyn, NY.
4. Kahn, Jeffrey S. (1990). Structural and functional studies of the vaccinia virus nucleic acid-dependent ATPase. Department of Microbiology and Immunology, SUNY Health Science Center at Brooklyn, NY.
5. Gong, Shiaoqing (1990). Genetic variability of the 14 KDa envelope protein of vaccinia virus and involvement of this protein in virus-induced cell fusion. Department of Biochemistry, SUNY Health Science Center at Brooklyn, NY.
6. Chingfeng Lai (1990). Structural and functional characterization of the vaccinia virus 14 KDa envelope protein synthesized in *Escherichia coli*. Department of Biochemistry, SUNY Health Science Center at Brooklyn, NY.
7. Walter E. Demkowicz (1991). Identification and immunologic characterization of two antigenic core proteins of vaccinia virus. Department of Microbiology and Immunology, SUNY Health Science Center at Brooklyn, NY.
8. Rodriguez, J-R (1992). Characterization of attenuated variants of vaccinia virus as safe recombinant vaccines: application as a vaccine against AIDS. Department of Biochemistry, SUNY Health Science Center at Brooklyn, NY. Universidad Autónoma de Madrid. Premio extraordinario.
9. Irvine, Martin (1993). Identification and characterization of mutants of vaccinia virus with increased sensitivity to interferon. Department of Microbiology and Immunology. SUNY, Health Science Center

at Brooklyn, N.Y.

10. Lee, S.B (1994). Structure and function of the interferon-induced double-stranded RNA-dependent protein kinase. Department of Microbiology, SUNY Health Science Center at Brooklyn, N.Y. Premio extraordinario.
 11. Melková, Zora (1995). Macrophage antiviral activity: Role of Interferon-gamma and nitric oxide in the inhibition of vaccinia virus growth in macrophages. State University of New York, Health Science Center at Brooklyn, N.Y. USA.
 12. Pavón, Miguel (1997). La proteína kinasa humana inducida por interferón y sensible a dsRNA (PKR): caracterización preliminar, proteínas de unión y algunas propiedades nuevas. Centro Nacional de Biotecnología. Universidad Autónoma de Madrid.
 13. Collado, Manuel (1997). Modulación de la respuesta inmunitaria frente a la proteína env del VIH-1, mediante su fusión a antígenos del virus vaccinia. Centro Nacional de Biotecnología. Universidad Autónoma de Madrid.
 14. Vazquez, Isabel (1998). Caracterización de los dominios funcionales de la proteína de 14 kDa del virus vaccinia que juega un papel importante en la interacción virus-célula. Centro Nacional de Biotecnología y Facultad de Farmacia de la Universidad de Santiago de Compostela.
 15. Gonzalo, Rosa (1999). Desarrollo de estrategias de inmunización frente a Leishmania basadas en virus vaccinia recombinantes en el modelo murino. Centro Nacional de Biotecnología, Universidad Autónoma de Madrid.
 16. Moratilla, Marta (1999). Análisis estructurales y funcionales del genoma del virus Molluscum contagiosum. Centro Nacional de Biotecnología. Universidad Autónoma de Madrid.
 17. Gil, Jesús (2000). Mecanismo de inducción de apoptosis y activación de NF- κ B por la proteína quinasa dependiente de dsRNA, PKR. Centro Nacional de Biotecnología, Universidad Autónoma de Madrid. Premio extraordinario
 18. Abaitúa, Fernando (2001). Potenciación de la respuesta inmune frente al antígeno de la envuelta del virus de la inmunodeficiencia humana (VIH-1) por recombinantes atenuados del virus vaccinia que expresan citoquinas I tipo Th1 (FN-gamma e IL-12). Universidad Autónoma de Madrid. Sobresaliente cum laude.
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19. Juan Carlos Gallego Gómez (2003). Biología celular de la infección y morfogénesis de mutantes atenuados del virus vaccinia. Universidad Autónoma de Madrid. 11 marzo. Sobresaliente cum laude.
 20. Carmen E. Gómez (2003). Respuesta inmune generada por sistemas combinados de vacunación frente a péptidos de la envuelta del VIH-1 incluidos en la proteína multiepitópica TAB-13. Universidad Autónoma de Madrid. 17 diciembre. Sobresaliente cum laude
 21. Maria Angel García Chaves (2004). Mecanismo de acción y regulación de la proteína quinasa inducida por interferon, PKR. Universidad Autónoma de Madrid. 30 abril de 2004. Sobresaliente cum laude. Premio Extraordinario de la UAM.
 22. Soledad Blanco Chapinal (2005). Estrategias de modulación de la respuesta inmune frente a malaria en el modelo murino de Plasmodium yoelii. Universidad Autónoma de Madrid. 16 diciembre de 2005. Sobresaliente Cum Laude.

23. Andrea Vandermeeren (2006). Study of the HCV polyprotein expresión from an inducible vaccinia virus recombinant and its implication in the host-cell responses. Universidad Autónoma de Madrid. 30 de marzo de 2006. Sobresaliente cum laude.
24. Eva Pérez Jiménez (2006). Desarrollo de una vacuna frente a leishmaniasis. Universidad Autónoma de Madrid. 29 mayo. Sobresaliente cum laude.
25. José Luis Nájera (2007). Caracterización “in vitro” e “in vivo” de los vectores atenuados de poxvirus MVA y NYVAC como candidatos vacunales frente al VIH/SIDA. Universidad Autónoma de Madrid. 23 de noviembre. Sobresaliente “cum laude”.
26. Elena Domingo Gil (2008). Caracterización de la apoptosis inducida por el sistema 2-5A/RNasa L. Universidad Autónoma de Madrid. 15 febrero. Sobresaliente “cum laude”.
27. Lucas Sanchez Sampedro (2012). Mutantes replicativos y atenuados del virus vaccinia como candidatos vacunales frente a leishmaniasis. Universidad Autónoma de Madrid. 19 octubre. Apto “cum laude”.
28. Ana Cáceres Núñez (2013). Papel de la fosfatasa celular DUSP-1 en la infección por el virus vaccinia. Universidad Autónoma de Madrid. 19 abril. Apto “cum laude”.
29. Aneesh Vijayan (2013). Adjuvant-like effect of vaccinia virus 14K protein: a case study with malaria vaccine based on circumsporozoite protein. Universidad Autónoma de Madrid. 13 junio. Apto
30. Mauro di Pilato (2015). Poxvirus vaccine strategies to improve T cell responses: neutrophil immunomodulation and promoter modification. Universidad Autónoma de Madrid. 3 mayo. Sobresaliente “cum laude”.
31. Ernesto Mejías (2017). Vectores virales basados en poxvirus como agentes oncolíticos. Universidad Autónoma de Madrid. 27 enero. Sobresaliente “cum laude”
32. Suresh Chithathur Raman (2018). Enhancing B and T cell immune responses against the HIV-1 envelope using protein and poxvirus-based vaccines. Universidad Autónoma de Madrid. 19 October. Sobresaliente “cum laude”
33. María Quirós Marín (2019). Aumento de la inmunogenicidad de una vacuna contra la hepatitis C (MVA-HCV) basada en el virus vaccinia modificado de Ankara (MVA). Universidad Autónoma de Madrid. 17 mayo. Sobresaliente “cum laude”.
34. Patricia Pérez Ramírez (2019). Novel vaccines based on poxvirus vector MVA against human viral diseases HIV/AIDS and Zika. Universidad Autónoma Madrid. June 14. Sobresaliente “cum laude”.
35. Adrián Lázaro Frias (2020). Generación de candidatos vacunales basados en el MVA frente a los ebolavirus Zaire y Sudan. Universidad Autónoma de Madrid. 2 octubre. Sobresaliente “cum laude”

EXPERIENCIA DE GESTIÓN DE I+D/ R&D

Título: Centro Nacional de Biotecnología del CSIC.

Tipo de actividad: Director

Fecha: 1992- 2003

Título: Presidente de la Real Academia Nacional de Farmacia (RANF)

Fecha: 2012-2018

Título: Presidente del Instituto de España

Fecha 2017-2018

Título: Presidente de Honor de la Real Academia Nacional de Farmacia (RANF)

Fecha 2020-indefinido

EXPERIENCIA EN ORGANIZACIÓN DE ACTIVIDADES DE I+D/R&D

Título: Fith European Conference on Experimental Aids Research (ECEAR), Presidente.

Tipo de actividad: Congreso, Madrid.

Fecha: 16-19 de Junio, 2000.

Título: XI International Poxvirus and Iridovirus Meeting, Presidente.

Tipo de actividad: Congreso, Toledo.

Fecha: 4-9 de mayo, 1996.

Título: II European Congress in Virology (EUROVIROLOGY-2004), Co-Presidente.

Tipo de actividad: Congreso, Madrid.

Fecha: Septiembre, 2004.

Título: 7th Vaccine Congress and ISV, Co-Chair

Tipo de actividad: Congreso, Sitges, Spain

Fecha: 27-29 October, 2013

EXPERIENCIA ACADÉMICA/ACADEMIC

En España, Facultad de Farmacia, Universidad de Santiago de Compostela. Profesor Ayudante de Prácticas en Microbiología, 1968-1970.

En EE.UU, Rutgers Medical School, Piscataway, New Jersey. Instructor, Department of Microbiology, 1974-1977

En EE.UU (Health Science Center, Brooklyn, New York). Professor, Departments of Biochemistry and of Microbiology and Immunology. 1979-1992

I. Medical School Courses:

(a) General Biochemistry

(b) Nine-week selective course in General Biochemistry

(c) Microbiology and Immunology

2. School of Graduate Studies

(a) Molecular Genetics, GI I02, 4 credits

(b) Animal Virology, G I03, 6 credits

(c) Biochemistry, G I03, 8 credits

(d) Microbial Genetics, G I02, 6 credits

(e) Techniques in Molecular Cloning, G-507, 4 credits

Member of President's Advisory Committee on Research Allocation,

1984-1987.

Member of Search Committee for Chairman of Microbiology and Immunology, 1981
Member of Search Committee for Chairman of Anatomy and Cell Biology, 1982-1984
Committee of the Graduate School Faculty, 1980
Co-Director of Molecular Genetics Course 1980-1986
Chairman, Recombinant Biohazards Committee, 1990-1992
Group Leader, AIDS Research, 1990-1993

En España, Universidad Autónoma de Madrid. Profesor Honorario, Departamento de Biología Molecular. Curso Sistema Inmune y Agentes infecciosos. 4 créditos. 1998-2008.
Participación en Masteres de Virología, Universidades Autónoma y Complutense de Madrid (2009-presente)

MIEMBRO DE SOCIEDADES CIENTIFICAS / MEMBERSHIP

- Miembro Honorario de las siguientes Sociedades:
 - American Society of Microbiology
 - American Society of Virology
 - British Society of Microbiology
 - Spanish Society of Microbiology
 - Harvey Society
 - The Society of Sigma Xi
 - New York Academy of Sciences
 - American Association for the Advancement of Science
-

PARTICIPACIÓN EN COMITÉS EUROPEOS / EU COMMITTEES

- Member of the European Action Programme Against AIDS. 1994-present
- Member of the COST /STD Initiative for a European Vaccine Program. 1994-97.
- Member of the European Concerted Action Against Malaria, 1996-98
- Member of External Advisory Group (EAG) of the European Commission, key action 2, Control of Infectious Diseases, Fifth Framework Programme. 1998-2002
- Member of WHO Advisory Committee on Variola Virus Research, 1998-present
- Member of Strategic Advisory Group of Experts (SAGE) for Immunization, Vaccines and Biologicals, WHO, 2002-2007
- Member of Advisory Group for the Science Foundation of Ireland, 2000-2004
- Member of European Science Foundation (ESF) Group for Research Infrastructures on Biomedical Sciences, 2003-2008
- Member of Scientific Advisory Group, Novartis, Spain. 2002-2008
- Founder and Board Member of the European Foundation Against AIDS (EuroVacc) 2002-present

EVALUACION DE TRABAJOS CIENTIFICOS / SCIENTIFIC EVALUATION

1) Revistas científicas: Science; EMBO J.; J. Virol; Virology; J. Gen. Virol.; Arch. Virology; Virus Research; J. Biol. Chem.; J. Interferon and Cytokine Research; ONCOGENE; Molecular Therapy; Vaccine. FEBS Lett. Apoptosis, Front. Immunol, Vaccines, Nature Commun.

2) Proyectos: National Science Foundation (NSF), USA; American Cancer Society, USA; Natural Sciences and Engineering Research Council of Canada (NSERC); Human Frontiers, EU; Austrian Science Fund; National Science Foundation of Ireland; Research Grants Council, Hong Kong; Medical Research Council of South Africa; Israel Science Foundation; Agencia Nacional de Evaluación y Prospectiva (ANEP); Fondo de Investigaciones Sanitarias (FIS); Comunidad Autónoma de Madrid (UAM); Fundación para la Investigación sobre el Sida (FIPSE). Fundación Marcelino Botín; Foundation Bill and Melinda Gates

3) Centros de investigación: Miembro del Comité Externo de Evaluación de los centros: Centro Nacional de Ingeniería y de Industria Tecnológica (INETI) del Ministerio de Ciencia y Tecnología de Portugal; Instituto de Investigaciones Bioquímicas, Fundación Campomar, Buenos Aires, Argentina (Abril, 2001), Molecular Virology Institut, Munich (2002).

LOGROS CIENTIFICOS / SCIENTIFIC ACHIEVEMENTS:

El objetivo de mi investigación es entender la biología molecular de agentes infecciosos para desarrollar estrategias que permitan su control. Los resultados mas significativos obtenidos en las líneas de investigación del laboratorio con su número de referencia (ref) de publicación en el CV han sido los siguientes:

LINEA: BIOLOGÍA DE LA INFECCIÓN VIRAL. *Estos estudios nos han permitido identificar procesos de entrada del virus en la célula, su transcripción en RNA mensajeros, control de la síntesis de proteínas, procesos de replicación del DNA, y ensamblaje viral.*

-Establecimiento de la entrada del virus vaccinia en células por fusión de membranas (ref. 31, 61, 80)

-Descubrimiento de que la cara basolateral de la célula está implicada en la entrada del virus vaccinia (ref. 85)

-Descubrimiento de la proteína p14 (A27L) del virus vaccinia como mediador de la entrada del virus en la célula por fusión e identificación de los dominios de unión y de neutralización (ref. 54, 62, 66, 74, 78, 80, 95, 136, 140)

-Descubrimiento de la proteína p32 (D8L) como mediador de la unión del virus vaccinia a la membrana celular (ref. 79, 84, 91)

-Establecimiento de un sistema libre de células para la traducción de los RNA mensajeros virales (ref. 3,4,7)

-Demostración *in vitro* de la traducción completa del genoma del virus de la encefalomiocarditis (ref. 9)

-Demostración de la regulación diferencial de la síntesis de proteínas por el virus vaccinia y de la existencia de una rápida inhibición traduccional (ref. 2,5, 6)

- Descubrimiento de los mecanismos de replicación (iniciación, elongación y terminación) del DNA del virus vaccinia (ref. 13 a 21, 26, 27, 28)
- Establecimiento de un sistema de purificación del DNA intacto del virus vaccinia (ref. 20)
- Identificación de proteínas de unión al DNA del virus vaccinia (ref. 21, 27)
- Primer mapa transcripcional del virus vaccinia (ref. 22, 23)
- Descubrimiento de RNAs virales de bajo peso molecular que actúan como reguladores de la traducción de los RNA mensajeros celulares (ref. 30, 71, 87, 99)
- Identificación de las proteínas del virus vaccinia que inducen protección frente a la infección y son inmunodominantes en individuos vacunados contra viruela (67, 79, 81, 84)
- Primera generación de una vacuna contra viruela basada en proteínas purificadas (88, 90, 172)
- Caracterización de las proteínas que son necesarias para el correcto ensamblaje del virus vaccinia y del reclutamiento de membranas en distintos compartimentos celulares (ref. 107, 113, 120, 124, 129, 130, 143, 161, 166)
- Primera definición por microscopía electrónica y por tomografía de la estructura del virus vaccinia a una resolución de 4-6 nm (199), del proceso de ensamblaje de membranas (240) y del proceso de morfogénesis por crió-Rayos X (244).
- Secuenciación parcial del genoma del poxvirus *Molluscum contagiosum*, su mapeo e identificación de genes con organización única (115, 118, 123, 174)
- Demostración de que las proteínas A27-A17 de vaccinia participan en el proceso de fusión del virus con la membrana celular y mapeo del dominio de fusión (ref. 229).

LINEA: MECANISMO DE ACCION DE LOS INTERFERONES (IFN). *Estos estudios pioneros nos han permitido demostrar el papel de los interferones como inhibidores de la replicación viral y como reguladores del crecimiento celular.*

- .-Descubrimiento de que los interferones (IFN) inhiben la replicación viral a nivel traduccional. Este trabajo (ref. 2) publicado en *Nature* mereció la distinción en la sección *News and Views* y fue pionero en el desciframiento de los mecanismos de acción de IFN por inhibición de la síntesis de proteínas (ref. 1-12; 43,47) e interés por el uso del IFN como droga en tratamiento de enfermedades infecciosas y cáncer.
- Descubrimiento de que los virus animales contienen genes que interfieren con la acción de los interferones (ref.44,45,56, 98)
- Descubrimiento de que los interferones inhiben la transformación genética y oncogénica por genes virales y celulares, así como procesos de recombinación viral (ref.48-52)
- Descubrimiento del modo de acción antiviral de la prostaglandina PGA1 y su relación con los interferones (ref.33,37,39,40,60,73)
- Descubrimiento de la proteína quinasa PKR dependiente de RNA bicatenario e inducida por los interferones como activador del proceso de muerte celular por apoptosis (ref.101), lo que explica la acción antitumoral de IFN. En una serie extensa de trabajos se caracterizó el modo de acción antiviral y anticelular de la PKR y su señalización molecular (ref. 92,93,102,117,122, 125,138,139,144,148-151,160,178,192).

-Identificación de genes virales (en poxvirus, herpesvirus, reovirus) y celulares cuyos productos víricos controlan la acción de la proteína quinasa PKR (ref. 116,156, 169,185,187)

-Descubrimiento de la proteína RNasaL inducida por IFN como inductor de apoptosis (ref.128)

-Identificación de la proteína E3L del virus vaccinia como inhibidor de la apoptosis inducida por el sistema de defensa celular 2-5A sintetasa/RNasa L (ref. 132, 176)

-Demostración del efecto antiviral y apoptótico de la proteína óxido nítrico sintetasa inducida por IFN (ref. 109, 126,154)

-Demostración de un nuevo mecanismo de acción de evasión viral (familia de flavivirus) que eluden a la acción de la proteína quinasa PKR por mediación de una estructura (*hairpin-loop*) en el extremo 5' de la forma subgenómica viral que codifica para las proteínas estructurales (ref. 207)

-Demostración de que la expresión del genoma del virus de la hepatitis C induce apoptosis por activación de las rutas de muerte, proteína quinasa PKR y sistema 2-5 A sintetasa/RNasa L (ref. 202).

-Demostración del papel de la mitocondria en la apoptosis mediada por el sistema 2-5A sintetasa/RNasa L inducido por los interferones (ref. 211)

-Primera generación de un ratón transgénico que al expresar la proteína E3 del virus vaccinia confiere mayor sensibilidad de los animales a la infección con virus y parásitos, ejerciendo estos efectos por interferencia con el sistema de los interferones y respuesta inmune (ref. 230)

-Demostración de que hay genes supresores de tumores que también actúan como inhibidores de la replicación de los virus (ref. 217, 220, 227,243,262)

-Hemos escrito revisiones extensas sobre el modo de acción de la proteína PKR inducida por los interferones ampliamente citadas (ref. 216, 221)

LINEA: INTERACCION VIRUS-CELULA. *Estos estudios tienen como objetivo definir el impacto que la infección tiene sobre el hospedador, así como identificar los genes celulares y sus productos que se inducen o reprimen durante el proceso de infección viral y que juegan un papel importante en la patogénesis vírica.*

-Demostración del reclutamiento de ribosomas por los RNA mensajeros virales producidos por el virus vaccinia y formación del complejo de iniciación en la traducción (ref. 11)

-Identificación y demostración de la enzima ATPasa-dependiente de DNA en la regulación de la expresión génica viral (ref. 57, 83)

-Establecimiento de un sistema de expresión regulada de genes celulares por la polimerasa del bacteriófago T3 (ref. 82).

-Identificación por microarrays de los genes celulares que se inducen y reprimen durante la infección de células HeLa con el virus vaccinia, estirpes salvajes WR y atenuadas MVA y NYVAC (ref. 183, 192, 208), así como en células dendríticas humanas (ref. 223).

-Identificación de los genes celulares inducidos por la activación del sistema de interferon, 2-5A sintetasa/RNasaL (253)

-Identificación de los genes celulares inducidos en células dendríticas humanas por los candidatos vacunales frente al VIH, los vectores MVA-B (255) y MVA-C (281).

-Descubrimiento del gen humano ATF-3 como necesario para la inducción de apoptosis por activación de la proteína quinasa PKR (ref. 215).

-Demostración de que genes supresores de tumores tienen capacidad antiviral y que este efecto es ejercido, en el caso de ARF, por supresión de la acción de la proteína quinasa PKR (216, 217,220,221,227)

-Identificación del gen celular ISG15 como inhibidor de la replicación del virus vaccinia y demostración del gen viral E3L que al interactuar con ISG15 modula su capacidad antiviral (237, 298)

-Revisión de las múltiples funciones inmunomoduladoras de ISG-15 (407).

LINEA: PATOGENESIS DE LA INFECCION VIRAL. *Estos estudios tienen como objetivo definir los mecanismos que utilizan los virus animales para provocar la muerte del hospedador*

-Demostración de que el efecto citopático inducido por el virus vaccinia es dependiente de la expresión génica viral (ref. 24,25, 29)

-Demostración de que las drogas antiinflamatorias aumentan la patogenicidad vírica (ref. 60)

-Establecimiento del primer sistema de seguimiento de la infección viral en tejidos animales con el marcador fluorescente luciferasa (ref. 69)

-Establecimiento de una infección vírica persistente, demostración de generación de mutaciones y de su papel en patogénesis (51,63-65,70,77,78)

-Descubrimiento del gen humano Wiskott-Aldrich (WASP) como necesario para la patogénesis del virus vaccinia (ref. 198)

-Identificación del gen de vaccinia C7L como regulador traduccional y de apoptosis (ref. 212)

-Establecimiento de un sistema de imagen *in vivo* para el seguimiento de la infección en tejidos de ratones inoculados con poxvirus virulentos y atenuados (ref. 222)

--Demostración de un gen viral E3L capaz de revertir las defensas del hospedador y producir mayor sensibilidad a infecciones virales y parasitarias en modelo de ratón transgénico (230)

-Demostración de una nueva estrategia por el virus vaccinia para aumentar la migración de neutrófilos por la activación del factor NFκB (317)

LINEA: DESARROLLO DE VACUNAS CONTRA ENFERMEDADES PREVALENTES. *Estos estudios, pioneros en el campo de las vacunas, han permitido desarrollar candidatos vacunales frente a distintos patógenos y a establecer protocolos de inmunización combinada de vectores que inducen una fuerte respuesta inmune celular y protección frente a distintas enfermedades. Estos protocolos se están aplicando en ensayos clínicos. El objetivo es modular el sistema inmune para provocar un mayor control de patógenos y tumores.*

-Descubrimiento de que la **inmunización combinada** con dos vectores distintos (**prime/boost**) aumenta considerablemente la respuesta inmune celular de **linfocitos T CD8+** frente a un antígeno, dando lugar a una **alta protección** contra **malaria** que expresa dicho antígeno (ref. 103)

-Establecimiento del **ensayo ELISPOT** para cuantificar a los linfocitos CD8+ que son específicamente activados en procesos de vacunación (ref. 105).

-Establecimiento de **protocolos de inmunización combinada** que inducen protección **frente a malaria** y caracterización de la respuesta inmune humoral y celular (ref. 103, 112,131,147,158,189)

-Establecimiento de protocolos de inmunización combinada que inducen protección frente a leishmaniasis y caracterización de la respuesta inmune (ref. 94, 159, 176, 180, 183, 286)

-Desarrollo de una **vacuna contra leishmania infantum** (ref. 203, 209, 234; **Patente** solicitud de invención **Nº 200501886**)

-Demostración del incremento de células memoria y protección frente a leishmaniasis por activación intradermal de células NFKT α en inmunización conjunta de vectores virales y adyuvantes (234)

-Establecimiento de protocolos de inmunización combinada que inducen una fuerte respuesta celular sistémica y de mucosas específica frente a antígenos del VIH-1 con valor pronóstico en protección contra el Sida (ref. 133,142,182,194)

-Demostración del papel de las citoquinas IL-12, IL-18, GM-CSF e IFN- γ en la respuesta inmune frente a distintos antígenos y su efecto en protección contra patógenos (ref. 135,141,154,180, 186,191)

-Generación de **candidatos vacunales** con potencial clínico frente al **sida, malaria y leishmania** (ref 51,75,86,146,151,171,183,189)

-Desarrollo de dos **vacunas contra el VIH/SIDA** basadas en MVA frente a los **subtipos B y C** (MVA-B y MVA-C), que representan el 80% de los casos de SIDA en el mundo (**Patent US 8,871,219 B2**, 28/10/2014; ref. 218, 219)

-Demostración en ensayos preclínicos en monos, que los vectores MVA y NYVAC inducen distinto tipo de respuestas celulares frente a antígenos del VIH/SIV y confieren una alta protección frente al virus patógeno SHIV89.6p (ref. 232).

-Demostración en monos de que se pueden administrar los vectores MVA y NYVAC por vía respiratoria y conseguir niveles semejantes de activación de la respuesta inmune que por inyección intramuscular de los mismos vectores. Esta aplicación respiratoria facilita vacunar frente al VIH a una gran población en países pobres (ref. 231).

-Demostración en **ensayo clínico profiláctico de fase I** que el protocolo con los candidatos vacunales DNA/NYVAC induce una alta inmunogenicidad (más del 90% de los vacunados) frente a los antígenos del VIH, manteniéndose esta respuesta inmune durante más de un año con activación polifuncional de la población de células T CD4 y CD8+ (ref. 233, 236).

-Demostración que el candidato vacunal MVA-B frente al VIH en células dendríticas humanas activa la expresión de genes inmunomoduladores con actividad polifuncional (255, 268).

-Demostración en ensayo clínico en fase I con el candidato vacunal MVA-B administrado en tres dosis a individuos sanos, que esta vacuna induce una potente respuesta inmune frente al VIH en la mayor parte de los voluntarios, siendo polifuncional y duradera (269, 270).

-Optimización de **candidatos vacunales frente al VIH basados en NYVAC** (266, 276, 283) y **MVA** (256, 259, 271, 280, 281) con mayor capacidad para activar respuestas inmunes de amplio rango y duraderas contra el VIH.

-Desarrollo de protocolos de inmunización con mayor capacidad para activar células dendríticas (241, 260, 264).

-Desarrollo de un **candidato vacunal** frente a **cáncer de próstata** (263) y uso de **vectores** de delección del virus vaccinia (WR-delta4) como agentes **oncolíticos** (345).

-Desarrollo de un **candidato vacunal (MVA-Flu)** frente al virus de la **gripe** (275).

- Desarrollo de un **candidato vacunal (MVA-CS) frente a malaria** con inducción de esterilidad (284; **patente** solicitud **P201131854**).
- Identificación del gen C6L del virus vaccinia como inhibidor del interferon beta y su aplicación en vacunas (271; solicitud de **patente P201131230**).
- Desarrollo de un **candidato vacunal (MVA-HCV) frente al virus de la hepatitis C** (295, 357, 370): patente solicitud **P201330467**
- Desarrollo de un **candidato vacunal (MVA-CHIKV) efectivo frente al virus Chikungunya: patente** solicitud **PCT/EP2014/076310**, 2 Dic 2014 (303, 309, 310, 320, 333, 337).
- Demostración de que la combinación en **prime/boost de vectores basados en replicones de alfavirus** y en el vector de **poxvirus MVA** induce una mayor respuesta inmune y protección frente a patógenos que cuando dichos vectores se administran de forma homóloga (333, 337, 350, 357).
- Demostración de que la **combinación heteróloga de vacunas basadas en mRNA y MVA** inducen una mayor respuesta inmune que la combinación homóloga (382)
- Identificado un nuevo mecanismo de activación celular de la respuesta inmune por poxvirus (317, 321).
- Modificación de promotores del virus vaccinia con mayor capacidad para expresar antígenos heterólogos e incrementar su respuesta inmune (299, 322)
- Generado un **prototipo vacunal frente al VIH basado en el vector NYVAC** que expresa la protein Gp140 en forma trimérica y Gag como VLPs junto con Pol-Nef del subtipo C del VIH y demostración de su capacidad inmunogénica en modelos de ratón y de monos (314, 324, 368).
- Demostración en **ensayo clínico terapéutico en fase I** con el candidato vacunal MVA-B administrado en tres dosis a individuos infectados por **VIH** y en terapia antirretroviral (cART), de que la vacunación induce activación de células T CD4+ específicas y reduce de forma transitoria la viremia después de la retirada de cART (315, 326).
- Demostración de **marcadores inmunes**, celulares y humorales, que se **correlacionan con protección frente al VIH en modelo de macacos** tratados con la vacuna basada en vector NYVAC-KC replicativo (336, 353, 354).
- Demostración en un **ensayo clínico fase 1b** multivalente de que la administración de **candidatos vacunales basados en proteína, DNA y NYVAC** inducen respuestas inmunes amplias **frente al VIH** (363).
- Desarrollo de **candidatos vacunales frente al virus de ebola (MVA-EBOV)** que inducen con una sola dosis 80% de protección (348).
- Desarrollo de un **candidato vacunal (MVA-Zika)** con alta protección (100%) frente al **virus Zika** (355).
- Desarrollo de un **candidato vacunal (MVA-CoV2-S)** frente a **SARS-CoV-2/COVID-19** que en modelo de ratón protege completamente (100%) frente a la morbilidad y mortalidad provocada por la infección del coronavirus SARS-CoV-2 y que esta protección se correlaciona con inducción de altos niveles de anticuerpos neutralizantes y de activación de linfocitos T CD4+ y CD8+. **Patente** solicitud **EP20382558.3**. 23-06-2020 (375, 384, 385).
- Demostración de que la **vacuna MVA-CoV2-S** produce una alta producción de anticuerpos neutralizantes y protección frente al SARS-CoV-2 en modelos animales de **hamsteres y macacos** (387, 388).
- Demostración de la eficacia de la **vacuna optimizada MVA-S(3P)** frente a las distintas **variantes del SARS-CoV-2. Patente** solicitud (23/06/2022). **EP 4108257** (385, 400, 405).

-Demostración de que una sólo dosis de la vacuna MVA-CoV2-S administrada por ruta intranasal previene completamente frente a la infección por SARS-CoV2 (391).

-Demostración de que la **vacuna MVA-CoV2-S protege completamente frente al daño cerebral** del coronavirus (349).

-Demostración de la capacidad de **anticuerpos biespecíficos** para el control de la infección por SARS-CoV-2 (401).

-Demostración de la **durabilidad de las respuestas inmunes B y T** mediante la inmunización de la proteína Env estabilizada del VIH dirigida a la membrana celular (403).

Demostración de la **modulación de las respuestas inmunes B y T** por distintas nanopartículas de mRNA frente al SARS-CoV-2 y **combinación eficaz de mRNA/MVA como proceso vacunal contra el coronavirus** (408, 410).

-Publicado extensos artículos de revisión sobre la evolución de las vacunas de poxvirus y de vectores atenuados frente a distintos patógenos (318, 399)

Resumen de Investigación del grupo POXVIRUS Y VACUNAS

Los objetivos fundamentales de nuestro laboratorio van dirigidos a comprender las bases moleculares en la patogenia de agentes infecciosos y su relación con el huésped, así como utilizar estos conocimientos para desarrollar vacunas que puedan ser efectivas en el control de enfermedades prevalentes con gran impacto en la población y con potencial epidémico/pandémico. Como sistema modelo de agente infeccioso y como vector de expresión, utilizamos el virus vaccinia que pertenece a la familia de los poxvirus. Las líneas de investigación son:

1. Mecanismo de ensamblaje del virus vaccinia.

El ensamblaje del virus vaccinia, y en general de los poxvirus, es un proceso complejo en el que intervienen más de 100 proteínas y cuyo estudio puede aportar conocimientos relevantes en biología. Nuestros trabajos van dirigidos a conocer a nivel molecular y celular cómo se forman las membranas y los cores virales para dar lugar a partículas infectivas. Utilizando mutantes condicionales para determinados genes virales y su estudio ultraestructural por microscopía electrónica de células infectadas, llevado a cabo en colaboración con los Drs C. Risco y J.L Carrascosa (CNB), hemos demostrado el papel que distintas proteínas del core (A4L, A10L) y de la membrana (A14L, A17L, A27L) viral ejercen en los procesos morfogenéticos. El objetivo a largo plazo es identificar todos los estadios de morfogénesis, el papel de las proteínas de membrana en ensamblaje, su modo de interacción y definir por técnicas de alta resolución por Crió-tomografía de rayos X la organización estructural del virión y proteínas asociadas.

2. Mecanismos de acción antiviral y antitumoral de los interferones

Durante años, nuestro grupo viene trabajando sobre el mecanismo de acción de los interferones (IFN), debido al papel tan importante que este tipo de moléculas biológicas juegan como primera línea de defensa del organismo frente a infecciones, como inhibidores del crecimiento celular con efecto antitumoral y como reguladores del sistema inmune. Hemos estudiado, en sistemas inducibles, el papel que enzimas inducidas por IFN pueden tener como antivirales y antitumorales: proteínas 2-5A sintetasa/RNasa L, óxido nítrico sintetasa (iNOS) y proteína quinasa p68 (PKR). Nuestros estudios futuros van dirigidos a conocer en profundidad la señalización de PKR, las proteínas con las que interacciona formando un complejo, su papel en la regulación de la síntesis de proteínas, así como los genes celulares que son activados, aplicando las tecnologías de genómica, proteómica y modelos celulares y animales. También estamos estudiando el papel de varios genes virales (E3L de VV, MC159L de molluscum contagiosum, sigma 2 de reovirus aviar, LANA3 de herpesvirus 8 y E2-NS5A de HCV), así como celulares (PACT, p67, NF90, ISG15) como reguladores del proceso antiviral y de apoptosis inducido por IFN. Esta investigación puede beneficiar la aplicación clínica del IFN en terapia antiviral y antitumoral

3. Interacción virus-célula

Por microarrays de DNA hemos identificando genes celulares inducidos en respuesta a la infección por el virus vaccinia (estirpe salvaje y mutantes) y por acción de estímulos apoptóticos. Nuestro objetivo es identificar por tecnología RNA-seq, exoma completo, genes celulares importantes en el proceso infeccioso y apoptótico y desarrollar modelos celulares y animales para su estudio funcional. Estos estudios ayudarán a entender los mecanismos de patogénesis viral y cómo el huésped responde a la infección. Hemos descubierto la proteína celular WASP como responsable de la transmisión del virus en animales y la proteína ISG15 como inhibidor de la replicación viral e inmunoregulator.

4. Desarrollo de vacunas contra enfermedades prevalentes.

Nuestro laboratorio está desarrollando estrategias de inmunización contra VIH, hepatitis C, chikungunya, malaria, leishmania, ebola, zika, SARS-CoV-2 y cáncer de próstata basadas en la utilización de recombinantes del virus vaccinia, estirpes MVA y NYVAC, solos o en combinación con otros inmunógenos como proteínas+adyuvante, mRNA, replicones, DNA y vectores virales heterólogos. Nuestro grupo ha sido pionero en el establecimiento de protocolos de inmunización combinada de vectores que inducen una fuerte respuesta inmune y protección frente a patógenos en modelo murino de malaria (*Plasmodium yoelii*) y leishmania (*L. major* y *L. infantum*). Estos estudios han permitido definir parámetros básicos para conseguir la inducción primaria de linfocitos T CD8+ y las condiciones para generar una fuerte respuesta secundaria, lo que puede tener interés para el desarrollo de estrategias profilácticas y terapéuticas para prevenir enfermedades infecciosas y tumorales. Con el fin de modular la respuesta inmune frente a antígenos de interés, estamos evaluando el efecto sobre dicha respuesta (sistémica y de mucosas) de la coexpresión de diversas citoquinas (IL-12, IFN- γ , GM-CSF, IL-18, IL-15), de adyuvantes como mega CD40L y ligandos de muerte celular como PD-L1. Hemos llevado a cabo ensayos de inmunogenicidad y protección en distintos modelos animales, que han demostrado su eficacia. El objetivo final es conseguir candidatos vacunales eficaces frente a patógenos emergentes y re-emergentes con potencial epidémico/pandémico y antitumoral.

a) Desarrollo de una vacuna frente al VIH/SIDA

Llevamos muchos años trabajando en el desarrollo de una vacuna frente al VIH utilizando distintas aproximaciones, que incluyen vectores de poxvirus MVA y NYVAC, ácido nucleico DNA, proteína Env recombinante y más recientemente nanopartículas con mRNA. Hemos demostrado que la combinación de vectores de DNA y de poxvirus (NYVAC) inducen una alta respuesta inmune frente al VIH con activación de células T CD4+ y CD8+ en ratones, macacos y humanos. En 2009 iniciamos en España el primer ensayo clínico en fase I con la vacuna MVA-B expresando cuatro antígenos Env-Gag-Pol-Nef generada por el grupo en el CNB con resultados muy positivos de inmunogenicidad y en 2012 iniciamos otro ensayo clínico fase I con individuos VIH positivos, con resultados prometedores. Se ha completado también en el Reino Unido otro ensayo clínico profiláctico fase I con la combinación de DNA/MVA-C y proteína Env con resultados de incremento de la inmunogenicidad. El vector MVA-C para el subtipo C del VIH también expresando cuatro antígenos del VIH fue desarrollado en el CNB. Como parte de proyectos de colaboración con la Fundación Bill y Melinda Gates, así como junto con consorcios europeos financiados en el programa H2020, llevaremos a cabo varios ensayos en ratones, macacos para determinar el protocolo óptimo de inmunización con capacidad para producir anticuerpos neutralizantes de amplio espectro de acción y su eficacia frente al VIH, así como un análisis profundo de los mecanismos moleculares, celulares e inmunes importantes en el control de la infección. En un ensayo clínico fase Ib hemos demostrado la importancia de la administración simultánea de inmunógenos de NYVAC, DNA y proteína Env en el grado de inmunogenicidad y durabilidad. Estamos mejorando la capacidad inmune de los vectores de poxvirus por modificación genética mediante deleciones específicas en genes que bloquean la respuesta inmune del hospedador para futuros ensayos clínicos, así como la combinación de inmunógenos con el objetivo de poder controlar la infección y eliminar los reservorios del VIH en el organismo.

b). Desarrollo de vacunas contra hepatitis C, chikungunya, Ebola, SARS-CoV-2, mpox y cáncer de próstata.

En el caso de **hepatitis C** (HCV), nuestro objetivo es desarrollar una vacuna basada en un procedimiento de inmunización combinada de vectores (“prime/boost”), que expresan la poliproteína del virus de la hepatitis C (VHC). Hemos conseguido un virus recombinante de vaccinia, estirpe MVA, que expresa todas las proteínas del VHC-1a de forma estable y que induce respuestas inmunes amplias frente a HCV en modelos animales. Estamos optimizando el vector MVA por delección de genes inmunomoduladores y en combinación con otros vectores de DNA y mRNA para conseguir una mayor potenciación de la respuesta inmune humoral y celular. El objetivo es trasladar esta investigación a la clínica.

En relación a **chikungunya**, hemos generado un vector de MVA-CHIKV que expresa todas las proteínas estructurales del virus chikungunya y demostrado su capacidad protectora esterilizante en modelo murino. Estos estudios se han extendido al modelo de macaco con resultados semejantes al modelo murino y queremos entender los mecanismos moleculares e inmunes de protección, y llevar esta vacuna a fases clínicas. Colaboramos con el grupo de Peter Liljeström en el Instituto Karolinska de Suecia en la combinación de replicones y MVA.

En relación al virus **Ebola**, hemos generado un vector de MVA-EBOV que expresa los antígenos GP y VP40 del virus Ebola, que en modelo de ratón protege con una sola dosis en un 80% frente a la infección por la estirpe Zaire. Estamos caracterizando la naturaleza de las respuestas inmunes que se activan y son esenciales para el control de la infección por el virus ébola. Colaboramos con el grupo de Cesar Muñoz-Fontela en Hamburgo que dispone de un animalario BSL-4. El objetivo es establecer un proceso óptimo de vacunación que confiera inmunidad duradera.

En relación al virus de la **viruela símica (mpox)** causante de la epidemia vírica por el clado IIb que afectó a España en el año 2022 y se extendió a muchos países, así como mpox del clado Ib en 2024 surgido en África, lo que produjo la consideración de la Organización Mundial de la Salud (OMS) a declarar la Emergencia de Salud Pública de Importancia Internacional (ESPII) en agosto de 2024, estamos trabajando como parte del proyecto europeo H2020-RESILIENCE en la optimización de vacunas con vectores de MVA y NYVAC, mRNA y proteínas con mayor capacidad inmunogénica y durabilidad que las vacunas actuales frente a viruela humana y símica.

En relación al **SARS-CoV-2**, con la reciente pandemia del coronavirus, hemos desarrollado un candidato vacunal MVA-CoV2-S que expresa la proteína S completa y demostrando en modelo de ratón transgénico permisible a la infección, que la vacunación protege al 100% de la infección por el coronavirus y que esta protección se correlaciona con la producción de altos niveles de anticuerpos neutralizantes y de activación de linfocitos T CD4+ y CD8+. Estos ensayos se han extendido a hamsteres y macacos para establecer los criterios de inmunogenicidad y eficacia de la vacuna. También hemos demostrado que la vacuna MVA-CoV2-S es eficaz frente a las distintas variantes del SARS-CoV-2 y que una sola dosis administrada por ruta intranasal protege completamente frente a la infección por el coronavirus y al daño cerebral. La vacuna ha sido optimizada con expresión de la forma estabilizada de la proteína S (MVA-CoV2-S(3P) producida en condiciones GMP por la empresa española Biofabri y transferida por el CSIC a la OMS a través de Medicines Patent Pool para su uso por los países más necesitados. Como parte del proyecto europeo H2020-SOLVE iniciado en 2024 llevaremos a cabo un ensayo clínico fase I, cuyo objetivo es entender los mecanismos celulares, moleculares e inmunológicos del comportamiento de nuestra vacuna optimizada MVA-S(3P) en comparación con otras vacunas usadas en la pandemia basadas en nanopartículas de mRNA y proteína S contra el SARS-CoV-2.

En cuanto al proyecto de **vacunas contra cancer**, hemos clonado en MVA varios genes tumorales que se expresan selectivamente en tumores prostáticos. Disponemos de modelos de ratón que producen tumores de próstata y que son de utilidad para establecer procedimientos de inmunización que generen protección frente a la aparición de tumores en dichos animales. Se han obtenido resultados de reducción de tumores prostáticos así como de melanoma mediante vacunación con nuestros vectores. Para mejorar la eficacia antitumoral estamos desarrollando nuevos vectores de poxvirus con capacidad oncolítica mediante delección selectiva de genes virales y por inserción en su genoma de genes inmunomoduladores, así como genes de ligandos de muerte programada. Mediante la combinación de la capacidad oncolítica e inmunogénica de vectores de poxvirus, el objetivo es conseguir una amplia activación de linfocitos T CD8+ específicos con alta eficacia para el control tumoral.

Research objectives:

The main objectives of our laboratory are geared to understand the molecular basis in the pathogenesis of infectious agents and their interaction with the host, as well as to use this knowledge in the development of vaccines that might be effective against prevalent diseases like HIV/AIDS, hepatitis C, Ebola, zika, chikungunya, SARS-CoV-2, mpox, malaria, leishmania and cancer. As a model system of infectious agent and as a delivery vector for expression of genes of interest, we used vaccinia virus (VACV) and the attenuated strains MVA and NYVAC as members of the Orthopoxvirus genus. The research areas of our lab are.

1. Vaccinia virus (VACV) assembly.

VACV assembly is a complex process in which more than 100 proteins participate, and by studying this process we might also provide important insights in cell biology. Our objectives are to understand, at the molecular and cellular levels, how viral membranes and cores are formed, and what are the viral proteins involved in these events that lead to virion assembly.

2. Mechanism of antiviral and anticellular action of interferons.

For years, our laboratory has been investigating the mechanism of action of interferons (IFN), since these molecules play major roles as a first-line of host defense against viral infections, tumor cell growth and regulation of the immune system. We have provided important insights into the mechanism of antiviral and apoptosis action by the IFN-induced ds-RNA dependent protein kinase (PKR), and we have identified the inhibitory effects exerted over PKR by a number of viral genes. The role of these proteins in defense, particularly on innate immune responses is being investigated.

3. Virus-host cell interactions

How poxviruses alter host cell responses following virus infection is a poorly characterized process. Our objective is to know the impact of vaccinia virus in host cell gene expression profiling in order to identify cellular genes relevant for VACV replication as well as for host cell defense, and to develop cell culture and animal models for functional gene studies. To this aim, we used microarrays and RNA-seq to identify cellular genes specifically induced in the course of virus infection using virulent and attenuated VACV strains with potential as human vaccines. A number of host genes have been identified and their role in virus pathogenesis is being investigated using animal model systems. The impact of virus infection over organoids is also being sought.

5. Development of vaccines against prevalent diseases.

Our laboratory has been developing immunization strategies against human pathogens based on the use of attenuated strains of VACV. We have pioneered the development of protocols based on heterologous immunization approaches (prime/boost) with vectors that induced enhanced cellular immune responses, leading to protection in murine models against malaria (*Plasmodium yoelii*), leishmania (*L. major* and *L. infantum*) and of virus infections (chikungunya, zika, Ebola, SARS-CoV-2). These studies have defined immunological parameters to expand B and CD8+ T cells during primary and secondary immunizations, with significance in the development of prophylactic and therapeutic strategies against infectious agents and tumor diseases. We have engineered potential vaccines against HIV/AIDS based on VACV attenuated strains NYVAC and MVA and phase I clinical studies, prophylactic and therapeutic have been completed. Novel vaccines with enhanced and durable immunogenicity against HIV are being developed in our lab for testing in animal models, as well as we are producing new vaccines against hepatitis C, chikungunya, ebola, zika, SARS-CoV-2, mpox, and cancer.

Scientific, technological and socioeconomic impact

In spite of the spectacular scientific advances provided by the new technologies, genomics, proteomics and bioinformatics, and the elucidation of the human genome, the genomes of other species and of many microorganisms, we find ourselves in the the XXI century with major diseases for which there is no cure, like HIV/AIDS (0.7 million (M) deaths in 2022 and 38M infections), malaria (229 M infections and 0.5M deaths/year mostly children), tuberculosis (1.4 M deaths/year), hepatitis C (71 M infections), coronavirus SARS-CoV-2 (704 M infections and 7 M deaths), leishmaniasis (12 M infections), and cancer (9.6 M, the second leading cause of

human deaths). WHO considers a priority to develop prophylactic and therapeutic vaccines against these different deadly diseases and of those emerging and reemerging pathogens with epidemic/pandemic potential.

Our group at the CNB has developed two prototype vaccines against HIV/AIDS based on subtypes B (MVA-B) and C (MVA-C) that account for nearly 80% of all HIV infections worldwide (patent PCT/ES2006/070114). In preclinical studies in mice and in macaques the prototype vaccines expressing four HIV antigens (Env/Gag-Pol-Nef) have fulfilled the expected characteristics of a potential good vaccine, ie, high immunogenicity, elicit in monkeys protection after challenge with pathogenic simian immunodeficiency virus, the vaccines can be safely delivered by aerosol which facilitates their easy administration specially in poor countries, and when given to human healthy volunteers triggered HIV-specific T-cell immune responses in over 90% of volunteers, being the immune response polyfunctional and durable. With the vaccine prototype MVA-B, we have performed in Spain two phase I clinical trials in healthy and in HIV-infected individuals, that has received wide attention by the media. Both trials showed good immunogenicity for HIV antigen-specific CD4+ and CD8+ T cells. We are improving the poxvirus vectors and combination of immunogens to obtain stronger immune responses, broader humoral and celular, with wider specificities.

We have also generated potential vaccines based on the poxvirus strain MVA against, leishmaniasis (patent PCT/ES2006/070122), malaria, hepatitis C (patent PCT/ES2014/070246), chikungunya (patent PCT/EP2014/076310), ebola, zika, coronavirus SARS-CoV-2 (EP20382558.3) and prostate cancer. The efficacy of these vaccines in animal models was 80-100% against ebola, chikungunya, zika and SARS-CoV-2.

A phase I clinical trial for our optimized MVA-CoV2-S(3P) vaccine in comparison to other approved COVID-19 vaccines is being planned for 2025 as part of the EU-Horizon2020 SOLVE funded project.

Our current studies are focused in the development of optimized vaccines against emerging and reemerging human pathogens, to establish best-in class protocols of immunization leading to long-term immune responses with high efficacy, understanding the role of immune cells, define correlates of protection and of potential assays of these vaccines in clinical trials.

GRUPO DE INVESTIGACIÓN / RESEARCH GROUP 2025

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Mariano Esteban, es Profesor de Investigación vinculado Ad Honorem del Centro Nacional de Biotecnología (CNB) del CSIC y Jefe del grupo de Poxvirus y Vacunas del CNB. Es natural e hijo predilecto de Villalón de Campos (Valladolid), se licenció en Farmacia (1967) y en Ciencias Biológicas (1972), obteniendo el título de Doctor en 1970 en la especialidad de Microbiología por la Facultad de Farmacia, Universidad de Santiago de Compostela.

Entre 1970-74 trabajó como postdoctoral en el Centro Nacional de Investigaciones Médicas de Londres (MRC) sobre mecanismo de acción de los interferones y control de la síntesis de proteínas, siendo contratado posteriormente, 1974-77, como Instructor en el Departamento de Microbiología de la Facultad de Medicina de la Universidad de Rutgers en Nueva Jersey, Estados Unidos de América, sobre replicación del DNA del virus vaccinia. Tras una breve estancia en 1978 en el Centro de Biología Molecular de Gante en Bélgica sobre secuenciación de genomas virales, le fue concedida en 1979 una plaza de Profesor Titular (Assistant Professor) en el Departamento de Bioquímica de la Facultad de Medicina en la Universidad del Estado de Nueva York (SUNY), pasando luego a ser nombrado en 1982 Profesor Asociado (Associate Professor) con nivel funcionario y en 1985 Catedrático (full Professor) del Departamento de Bioquímica de la mencionada Facultad de Medicina de SUNY, donde trabajó sobre el modo de acción de los interferones y vacunas.

En 1987 fue nombrado Profesor de Investigación del Consejo Superior de Investigaciones Científicas. En 1992, tras una estancia de 22 años en el extranjero, regresa a España para dirigir el nuevo Centro Nacional de Biotecnología (CNB) del CSIC, cargo que ocupó durante más unos 12 años (1992-2003). En un período corto reclutó excelentes líderes científicos y el Centro adquirió credibilidad internacional como lugar de excelencia en investigación biotecnológica en las áreas de salud humana y animal, agricultura y medio ambiente. Además, el CNB fue un polo de atracción de empresas estableciendo modelos de colaboración con compañías nacionales e internacionales. El CNB ha sido evaluado varias veces por Comités Científicos Internacionales que lo consideran como "centro de excelencia en biotecnología", siendo acreditado como Centro de Excelencia Severo Ochoa.

El interés de las investigaciones de Mariano Esteban se ha centrado en el conocimiento de la biología molecular de agentes patógenos como los virus, para de esta forma desarrollar procedimientos que permitan el control de enfermedades infecciosas. Sus descubrimientos sobre la biología del virus vacunal, que fue utilizado como vacuna para erradicar la viruela, le ha servido para generar nuevas vacunas basadas en vectores poxvirales (MVA y NYVAC) contra enfermedades prevalentes como el sida, hepatitis C, chikungunya, ébola, zika, malaria y leishmania, habiendo sido pionero en el campo de las vacunas al desarrollar procedimientos de inmunización combinada heteróloga de vectores (*prime/boost*) que incrementan la respuesta inmune celular y confieren protección frente a distintos patógenos. Estos protocolos de vacunación están siendo experimentados en ensayos clínicos de fases I/II contra patógenos y cáncer. Su grupo está participando en el programa EuroVacc y de la Fundación Bill y Melinda Gates para el desarrollo de una vacuna contra el SIDA habiendo generado dos vacunas contra el VIH, subtipos B y C, que han sido analizadas en ensayos clínicos en fase I/II en España y Reino Unido con buenos resultados inmunológicos y otros prototipos vacunales con la estirpe NYVAC que se han ensayado en fase 1b en Europa y EE.UU. Con algunas vacunas frente a virus emergentes (ébola, chikungunya y zika) su grupo ha demostrado en modelos animales una alta eficacia (80-100%) de protección frente a la infección por dichos agentes virales, y de un 70% frente a leishmania y malaria.

Mariano Esteban ha sido pionero en España al desarrollar en 2020 durante la pandemia de SARS-CoV-2/COVID-19 una vacuna MVA-S con 100% de protección en tres modelos animales (ratón, hámster y macaco), con amplio espectro de acción contra SARS-CoV-2 y sus variantes, con protección completa frente al daño cerebral, y que esta protección se correlaciona con la producción de altos niveles de anticuerpos neutralizantes y de activación de linfocitos T CD4+ y CD8+. La vacuna ha sido optimizada y producida en condiciones GMP

por la empresa española Biofabri para ensayos clínicos. Mediante un convenio del CSIC con la OMS y su agencia Medicines Patent Pool, la vacuna ha sido donada a la OMS para su uso por los países más necesitados. El modo de acción de dicha vacuna en comparación con otras tres vacunas forma parte de un ensayo clínico europeo H2020-SOLVE.

Otra área de las investigaciones de Mariano Esteban ha sido el entendimiento del modo de acción de los interferones. Sus contribuciones científicas en este campo han sido pioneras, al demostrar que los interferones actúan frente a los virus inhibiendo la iniciación de la síntesis de proteínas. Además, ha demostrado el papel que varios de los genes inducidos por los interferones, como la proteína quinasa PKR y el sistema 2-5A sintetasa/RNasa L, tienen como reguladores de la muerte celular programada (apoptosis). Estas contribuciones han potenciando el interés clínico de estos fármacos como agentes antivirales y antitumorales.

Las contribuciones científicas representan 406 trabajos publicados en revistas internacionales de impacto, 13 patentes, 35 tesis doctorales y más de 390 comunicaciones en congresos nacionales e internacionales. Según Google Scholar sus publicaciones se han citado 26.956 veces con un índice h (Hirsch Factor) de 91 y de 346 (índice i10).

Sus investigaciones en Estados Unidos de América fueron financiadas por los Institutos Nacionales de Salud (NIH) y la Fundación Nacional de las Ciencias (NSF). Desde su regreso a España, sus investigaciones están siendo financiadas por la Unión Europea, NIH, el Plan Nacional de Investigación y Desarrollo, Fondo de Investigación Sanitaria, Comunidad Autónoma de Madrid, Fundación para la Investigación sobre el Sida (FIPSE), Red de Sida, Instituto de Salud Carlos III, Fundación Botín, Fundación Bill y Melinda Gates, Fundación La Caixa y empresas.

En su laboratorio se han formado estudiantes de varias nacionalidades, pre y postdoctorales, y cuenta actualmente con 19 investigadores. Participa en actividades académicas de Master con la Universidad Autónoma de Madrid (UAM) y con la Universidad Complutense.

Mariano Esteban ha sido y es miembro de prestigiosas sociedades internacionales (American Society of Microbiology; American Society of Virology; British Society of Microbiology; Spanish Society of Microbiology; Harvey Society; The Society of Sigma Xi; New York Academy of Sciences; American Association for the Advancement of Science). Miembro Editorial, y evaluador de artículos de revistas prestigiosas y de proyectos nacionales e internacionales. Ha participado en varios Comites Europeos (Member of the European Action Programme Against AIDS. 1994-1997; Member of the COST /STD Initiative for a European Vaccine Program, 1994-97; Member of the European Concerted Action Against Malaria, 1996-98; Member of External Advisory Group (EAG) of the European Commission, key action 2, Control of Infectious Diseases, Fifth Framework Programme (1998-2002). Member of WHO Advisory Committee on Variola Virus Research, 1998-actual. Member of Strategic Advisory Group of Experts (SAGE) for Vaccines and Biologicals, WHO, 2003-2007. Member of Advisory Group for the Science Foundation of Ireland, 2000. Member of European Science Foundation (ESF) Group for Research Infrastructures on Biomedical Sciences, 2003, y nacionales (ANEP; Grandes Instalaciones Científicas, 2003-2013). Entre 2013-2017 ha sido miembro del Comité Científico Asesor del CSIC y entre 2020-2021 fue miembro del Grupo de Trabajo Multidisciplinar (GTM) que asesoró al Ministerio de Ciencia e Innovación en los temas de SARS-CoV-2/COVID-19 preparando más de 30 informes sobre distintos aspectos de la pandemia.

Ha impartido un gran número de conferencias en varios países, organizado cursos, workshops. Ha organizado congresos internacionales: presidente del XI International Poxvirus and Iridovirus Meeting, Toledo, 1996; presidente, Fifth European Conference on Experimental AIDS Research (ECEAR-2000), Madrid, Co-Presidente II European Virology Congress (EuroVirology-2004) en Madrid y Co-Chair del 7th Vaccine & ISV Congress-2013 in Sitges, Spain.

Ha sido socio fundador y presidente (1991-1992) de la primera asociación de profesionales españoles en el extranjero, Asociación de Licenciados y Doctores Españoles en Estados Unidos (ALDEEU), habiendo recibido en 2012 el máximo galardón, medallón de oro ALDEEU. Es fundador y miembro de la Fundación Europea contra el Sida (EuroVacc). En 2006 fue nombrado Académico de Número de la Real Academia

Nacional de Farmacia (RANF) de España, posteriormente presidente (2013-2019) y desde 2022 es Presidente de Honor de dicha academia. En octubre de 2017 fue nombrado presidente del Instituto de España, institución que integra a las diez Reales Academias. Es también miembro correspondiente de la Real Academia de Farmacia de Galicia y de la Académie Nationale de Pharmacie de Francia.

Ha obtenido varias distinciones científicas, entre ellas, el premio del Consejo de Salud de Nueva York, premio de la Universidad del Estado de Nueva York, premio Farmacéutico del Año. Premio IBERDROLA de Ciencia para Profesores visitantes. Premio de la Sociedad Española de Virología, Premio Medalla de Oro Carracedo de la Real Academia Nacional de Farmacia. En 2016 fue elegido miembro de la Selección Española de Ciencia en reconocimiento a los mejores científicos del año por la revista QUO. En 2020 recibió la Medalla al Mérito en la Investigación y en la Educación Universitaria otorgada por el Ministerio de Ciencia e Innovación. También recibió el Premio Castilla y León de Investigación Científica y Técnica e Innovación 2020. Entre 2021-2023 recibió los siguientes premios: Premio "Admirables" del Diario Médico; XXI Premio Fundación Neumomadrid en investigación médica; Distinción Honorífica del Colegio Oficial de Farmacéuticos de Madrid (COFM); Medalla de Honor de la Real Academia de Medicina y Cirugía de Valladolid; Premio TELVA a las ciencias; Premio de investigación "Mayores en acción" CEOMA; Premio Foro de Empresas Innovadoras (FEI); Premio Fundación Ana de la Paz en investigación; Premio H-de oro Colegio Oficial de Farmacéuticos de Málaga en investigación; Premio de TV La Sexta "Contantes y Vitales" a la trayectoria científica en investigación biomédica; premio IPfest 2023 "Allende La Transferencia de Conocimiento".

Actualmente, Mariano Esteban y su laboratorio están generando candidatos vacunales con amplio espectro de acción y durabilidad para proteger frente a las distintas variantes del SARS-CoV-2 que vayan surgiendo por mutaciones y se hagan resistentes a las vacunas actuales, así como el desarrollo de vacunas y combinación de inmunógenos (DNA, LNP-mRNA, replicon de alphavirus, vectores virales, proteína), frente a otros virus emergentes y reemergentes con potencial para producir futuras epidemias y pandemias. El grupo sigue trabajando en la optimización de vacunas frente al VIH/SIDA con capacidad para producir anticuerpos neutralizantes de amplio espectro de acción y eficacia para el control de la infección. El plan del grupo es hacer contribuciones científicas relevantes sobre los mecanismos moleculares, celulares e inmunes de activación de las células B y T que confieren la inmunidad de las vacunas, correlatos de protección, duración de las respuestas inmunes y establecer la eficacia de las vacunas en modelos animales, con traslación hacia los ensayos clínicos. Para el período 2024-2028, sus investigaciones sobre vacunas frente a virus emergentes y reemergentes están siendo financiadas por 4 proyectos europeos concedidos a su laboratorio en 2024, así como proyectos nacionales. El objetivo final es desarrollar inmunógenos óptimos y procesos de vacunación que confieran seguridad, eficacia y protección duradera contra agentes infecciosos con potencial epidémico y pandémico.

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Mariano Esteban is currently Professor Ad-Honorem of the Spanish Research Council (CSIC) at the National Center of Biotechnology (CNB) in Madrid, Spain and Head of the Poxvirus and Vaccines Group. He obtained his PhD in Microbiology at the School of Pharmacy, University of Santiago de Compostela and spent 22 years abroad in various research centers: postdoctoral (1970-74) at the National Institute for Medical Research, Mill Hill (London); Instructor (1974-77) at the Department of Microbiology, Rutgers Medical School, Piscataway, New Jersey, USA; research scientist (1978) at the Molecular Biology Institute, Ghent, Belgium; Assistant (1979-82), Associate with tenure (1982-85) and full Professor (1985-92) of SUNY at the Department of Biochemistry, Downstate Medical Center, Brooklyn, New York. In 1987 he was appointed Professor of Science by the Spanish Research Council of Spain (CSIC), and Director (1992-2003) of the newly created National Center for Biotechnology (CNB) in Madrid. Within a short time, he recruited excellent Group Leaders and the CNB won international credibility, as a place of excellence for basic and applied science in biotechnology in the areas of health, agriculture and environment.

Prof. Esteban is a well-recognized scientist with a long experience in molecular and immunological basis of pathogenesis by infectious agents and in translational research. In particular, his group has made major contributions on the biology of vaccinia virus (from virion structure, entry into cells, transcription, translation, DNA replication and virus assembly), the mechanism of action of interferon (particularly on its role in the inhibition of virus mRNA translation and apoptosis action of the IFN-induced enzymes, PKR, 2-5A synthetase/RNase L and nitric oxide synthase), and development of vaccines against major diseases like HIV/Aids, hepatitis C, chikungunya, ebola, zika, malaria, leishmaniasis, and recently SARS-CoV-2. His group pioneered a heterologous prime/boost approach that has gained acceptance as an immunization protocol against different diseases, and has made significant contributions in the biology and application of the attenuated poxvirus vectors MVA and NYVAC as vaccine candidates. With some of the Esteban vaccines, an efficacy of 80-100% was observed in preclinical trials against Ebola, chikungunya, zika and SARS-CoV-2, as well as about 70% inhibition against malaria and leishmania. Two of Esteban's developed vaccines for the most prevalent HIV clades B and C (MVA-B and MVA-C) were used in prophylactic phase I clinical trials in Spain, UK and Peru, and in a therapeutic trial in Spain, while a NYVAC-C vaccine was used in a phase Ib clinical trial, showing in all cases good immunological B and T cell behavior and neutralization against tier 1 HIV. Further improvements of HIV vaccines for induction of broadly neutralizing antibodies against tier 2 viruses are currently ongoing in the laboratory.

With the advent of the SARS-CoV-2 pandemic, Esteban and his group got in January 2020 deeply involved in the development of a vaccine based on MVA expressing SARS-CoV-2 S protein. The vaccine showed excellent immune profiles with activation of B and T cell immune responses that elicited broad and durable immune responses, leading to 100% efficacy in animal models (mice, hamsters and macaques) against SARS-CoV-2 infection and completely prevented brain damage. An optimized vaccine MVA-S(3P) was produced by the Spanish company Biofabri and donated by CSIC to WHO through the Medicines Patent Pool as a worldwide license, mainly for the low-income countries. The work developed on the SARS-CoV-2 vaccine by Esteban group received wide coverage from the press, radio and TV, and grants from national and international institutions as well as from public donations. The SARS-S(3P) vaccine will be tested during 2025-2026 for detailed molecular, cellular and immunological action in a phase I clinical trial in comparison with two other approved vaccines as part of EU-funded H2020-SOLVE project.

Prof. Esteban has published 406 articles in prestigious journals, with an h-index of 91 and 26.956 cites with an h-index (Hirsch Factor) of 91 and of 346 (index i10) (Google Scholar), 13 patents, directed 35 PhD Thesis, and presented over 390 communications to national and international meetings. His research has been supported by grants from national (MICINN; FIS; FIPSE, Foundation Botín, Foundation La Caixa), international agencies (NIH, USA; Bill y Melinda Gates, European Union) and industries. Prof. Esteban collaborates actively with international teams in both Europe and USA.

He is Member of a number of prestigious scientific international societies, in 2012 was elected President of the Royal Academy of Pharmacy of Spain, currently is his Honorary President, and in 2017 he became President of the Royal Society of Spain that integrates the ten Royal Academies. In 2020 Esteban received the Medal for Research and University Education from the Ministry of Science and Innovation of Spain, and in 2021 was awarded the Prize for Science by the Autonomous region of Castilla and León. He has also received numerous awards from different institutions.

Prof Esteban has organized international scientific meetings: President of XI International Poxvirus and Iridovirus Meeting, Toledo, 1996; President of the Fifth European Conference on Experimental AIDS Research (ECEAR-2000), Madrid; Vice-president of the European Virology meeting in Madrid, in 2004; Co-Chair of the 7th Vaccine and ISV Congress-2013, Sitges, Spain. He participates in academic activities at the Autonomous and of Complutense Universities of Madrid, is founder of EuroVacc and of Spanish Professionals in the USA (ALDEEU).

The current research interest of the laboratory on Poxvirus and Vaccines is in the control of emerging and reemerging human pathogens, by developing safe and effective vaccines. By studying the molecular, cellular and immunological behavior of the poxvirus vectors MVA and NYVAC expressing selected antigens from pathogens, alone and in combination with other immunogens (DNA, LNP-mRNA, alphavirus replicon, viral

vectors, protein), Prof. Esteban group plan to make important contributions in the immune biology of vaccines, the mechanism of T cell and B cell immune responses, correlates of protection, durability of the immune responses, efficacy in animal models, and to eventually perform clinical trials. The goal is to develop the best-in-class immunogens and vaccination protocols that can confer safe, effective and long-term protection against prevalent human diseases with epidemic and pandemic potential.