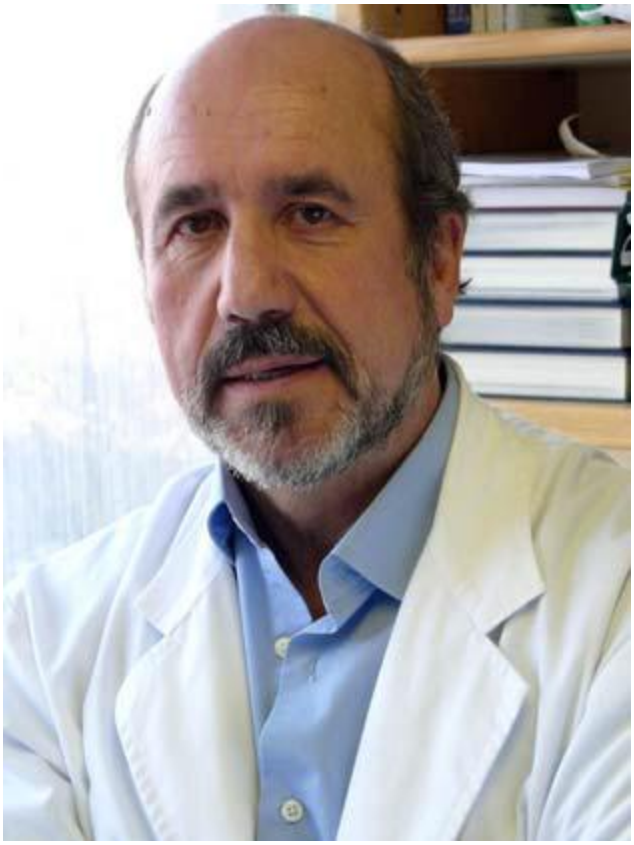
**Curriculum vitae**



Nombre: **Mariano Esteban Rodríguez**

Fecha: Junio de 2013

Apellidos: **ESTEBAN RODRÍGUEZ** Nombre: **MARIANO**
DNI: **12.666.094-V** Fecha de nacimiento : **26/7/1944** Sexo: **V**

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## SITUACIÓN PROFESIONAL ACTUAL

Organismo: **CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS**
Facultad, Escuela o Instituto: **CENTRO NACIONAL DE BIOTECNOLOGIA**
Depto./Secc./Unidad estr.: **Departamento de Biología Molecular y Celular**
Dirección postal: **Campus Universidad Autónoma. Cantoblanco. 28049-Madrid**
Teléfono (indicar prefijo, número y extensión): **(91) 585.45.53**
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Especialización (Códigos UNESCO): **242007**
Categoria profesional: **Profesor de Investigación** Fecha de inicio: **1987**
Situación administrativa
**X** Plantilla ☐ Contratado ☐ Interino ☐ Becario
☐ Otras situaciones especificar:

Dedicación A tiempo completo **X** ☐
A tiempo parcial

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## LÍNEAS DE INVESTIGACIÓN

**Biología molecular y celular de poxvirus, interacción virus-célula, expresión génica, microarrays, sistema inmune, inmunomoduladores, citoquinas, interferones, vacunas, sida, malaria, hepatitis C, Leishmania, cáncer próstata.**

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## FORMACIÓN ACADÉMICA

| Titulación Superior | Centro | Fecha |
|---|---|---|
| **Licenciatura en Farmacia** | **Universidad de Santiago de Compostela** | **1967** |
| **Licenciatura en C. Biológicas** | **Universidad de Santiago de Compostela** | **1972** |

| 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-** |

**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 human (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 Progamme 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: papél de las enzimas proteina 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 Tecnologia (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 responsible: 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 responsible: 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. 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. 2000-2003, 171.649 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 (MVACTOR). 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. Fundation Bill and Melinda Gates. $1.500.000. 2006-2013.

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

Principal Investigator. Modificación genetica 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. Fundacion 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 tratasmiento 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

Principal Investigator. Pox T cell vaccine Discovery Consortium. Fundation Bill and Melinda Gates. $2.000.000. 2006-2014.

Coinvestigator. Red Temática en SIDA. ISCIII-RETIC, RD12/0017/0038. 2013—2016

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. 2012-2015. 510.000 euros

Prinicipal Investigator. Integration of Chikungunya Research (ICRES). EU FP7-HEALTH-2010. Project

number 261202. Oct. 2010- Nov 2014.

## PUBLICACIONES


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 fo 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. Geraldes (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.A. (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 cytophatic effects: I. Inhibition of protein synthesis in infected cell is associated with virus-induced RNA synthesis. J. Gen. Virol. 39: 39l-402 .

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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.

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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.

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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.

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41. **Esteban**, M. (1984). Defective vaccinia virus particles in interferon-treated, infected cells. Virology 133, 220-227 .

42. Boni, C., **Esteban**, M. and Pellicer, A. (1984). Expression of cloned vaccinia DNA sequences introduced into animal cells. J. Gen. Virol 65, 1245-1251.

43. **Esteban**, M., Benavente, J. and Paez, E. (1984). Effect of interferon on integrity of vaccinia virus and ribosomal RNAs in infected cells. Virology 134, 40-51.

44. Paez, E. and **Esteban**, M. (1984). Resistance of vaccinia virus to interferon is related to an interference phenomenon between the virus and the interferon system. Virology 134, 12-28.

45. Paez, E. and **Esteban**, M. (1984). Nature and mode of action of vaccinia virus products that block activation of the interferon-mediated ppp(A2'p)nA-synthetase. Virology 134, 29-39.

46. Lewis, J.A. and **Esteban**, M. (1984). Induction of an antiviral response and 2',5'oligo A synthetase by interferon in several thymidine kinase deficient cell-lines. Virology 134, 464-469.

47. Benavente, J., Paez, E. and **Esteban**, M. (1984). Indiscriminate degradation of RNAs in interferon-treated, vaccinia virus infected mouse L cells. J. Virol 51, 866-871.

48. Paez, E and **Esteban**, M. (1985). Interferon inhibits marker rescue of vaccinia virus. J. Interferon Research 5, 247-256.

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57. Rodriquez, J.F., Kahn, J. and **Esteban**, M. (1986). Molecular cloning, encoding sequences and expression of the nucleic acid dependent phosphohydrolase gene of vaccinia virus. Proc. Natl. Acad. Sci. USA 83, 9566-9570.

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**-VECTORES RECOMBINANTES BASADOS EN EL VIRUS MODIFICADO DE ANKARA (MVA) CON DELECIÓN EN EL GEN C6L COMO VACUNA CONTRA EL VHI/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.**

**-EFECTO ADYUVANTE DE LA PROTEÍNA A27 DEL VIRUS VACCINIA (14K) Y SUS APLICACIONES EN VACUNAS. Presentada en la Oficina Española de Patentes y Marcas, 17 Noviembre de 2011. Nº solicitud P201131854. Aneesh Vijayan, Carmen E. Gómez and Mariano Esteban.**

**-MVA-HCV como vacuna contra hepatitis C. Mariano Esteban., Beatriz Perdiguero y Carmen E. Gómez. Nº solicitud P201330467, 2 abril, 2013.**

## ESTANCIAS EN CENTROS EXTRANJEROS

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Centro: National Institute for Medical Research, Mill Hill
Localidad: Londres País Reino Unido Fecha: 1970-74 Duración: 4 años
Tema: Virus vaccinia, acción del interferón, control traduccional

Centro: Departamento de Microbiología. Rutgers Medical School
Localidad: New Jersey País USA Fecha: 1974-77 Duración : 4 años
Tema: Transcripción y replicación del DNA del virus vaccinia

Centro: Laboratorio de Biología Molecular. Universidad de Gante
Localidad: Gante País Bélgica Fecha: 1978 Duración: 6 meses
Tema: Clonaje y secuenciación de DNA

Centro: Departamento de Microbiología e Inmunología. State University of New York, Downstate Medical Center

Localidad: New York País USA Fecha: 1979-92 Duración: 13 años
Tema: Patogénesis viral y expresión génica, accion del interferon.

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## TESIS DOCTORALES DIRIGIDAS

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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, Shiaoching (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.

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mediante su fusión a antígenos del virus vaccinia. Centro Nacional de Biotecnologia. Universidad Autónoma de Madrid.

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15. Gonzalo, Rosa (1999). Desarrollo de estrategias de inmunización frente a Leishmania basadas en virus vaccinia recombinantes en el modelo murino. Centro Nacional de Biotecnologia, Universidad Autónoma de Madrid.

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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".

## EXPERIENCIA DE GESTIÓN DE I+D

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Título: Centro Nacional de Biotecnología del CSIC.

Tipo de actividad: Director
Fecha: 1992- 2003

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Fecha: 2012-

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## EXPERIENCIA EN ORGANIZACIÓN DE ACTIVIDADES DE I+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.

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## EXPERIENCIA ACADÉMICA:

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. 1992-actual. Curso Sistema Inmune y Agentes infecciosos. 4 créditos. 1998-2008.
Participación en Masters de Virología, Universidades Autónoma y Complutense de Madrid (2009-present)

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**MIEMBRO DE SOCIEDADES CIENTIFICAS**

- 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

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**PARTICIPACION EN COMITES EUROPEOS**

**-** Member of the European Action Progamme 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 Reseach, 1998-present

- Member of Strategic Advisory Group of Experts (SAGE) for Immunization, Vaccines and Biologicals, WHO, 2002-2007

- Member of Advisory Group for the Sciende Foundation of Ireland, 2000-2004

- Member of European Science Foundation (ESF) Group for Research Infraestructures on Biomedical Sciences, 2003-2008

- Member of Scientific Advisory Group, Novartis, Spain. 2002-present

-Founder and Board Member of the European Foundation Against AIDS (EuroVacc) 2002-present

Member of Scientific Advisory Group, CSIC, 2012-

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**EVALUACION DE TRABAJOS CIENTIFICOS**

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

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 Evaluacion 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:**

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 los últimos 34 años en las líneas de investigación del laboratorio 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 fusion de membranes (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 union y de neutralización (ref. 54, 62, 66, 74, 78, 80, 95, 136, 140)

-Descubrimiento de la proteína p32 (D8L) como mediador de la union del virus vaccinia a la membrana cellular (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 union 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 membranes en distintos compartimentos celulares (ref. 107, 113, 120, 124, 129, 130, 143, 161, 166)

-Demostración de que la forma inmadura del virus vaccinia contiene una doble membrana (ref. 170)

-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 crio-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 celulary mapeo del dominio de fusión (ref. 229).

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

.-Descubrimiento de que los interferones (IFN) inhiben la replicación viral a nivél traduccional. Este trabajo (ref. 2) publicado en Nature mereció la distinción en la sección News and Views y fue pionero en el desciframiento de mecanismos de acción (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 transformaión 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 proteina 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 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 como inhibidor de la apoptosis inducida por el sistema de defensa 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 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 una revisión extensa sobre el modo de acción de la proteína PKR inducida por los interferones (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 papél importante en la patogénesis vírica.*

-Demostración del reclutamiento de ribosomas por los RNA mensajeros virales 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 salvaje 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, OAS/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 proteina 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 interaccionar con ISG15 modula su capacidad antiviral (238)

**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 un marcador fluorescente (ref. 69)

-Establecimiento de una infección vírica persistente, demostración 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)

**LINEA: DESARROLLO DE VACUNAS CONTRA SIDA, MALARIA Y LEISHMANIA.** *Estos estudios, pioneros en el campo de las vacunas, han permitido establecer protocolos de inmunización combinada de vectores que inducen una fuerte respuesta inmune celular y protección frente a distintos patógenos. Estos protocolos se estan 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/booster*) aumenta considerablemente la respuesta inmune celular frente a un antígeno, dando lugar a una alta protección contra un patógeno que expresa dicho antígeno(ref. 103)

-Establecimiento del ensayo ELISPOT para cuantificar a los linfocitos CD8+ que son específicamnte 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; Solicitud de invención Nº 200501886)

-Demostración del incremento de células memoria y protección frente a leishmaniasis por activación intradermal de células NFKTi 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 prognóstico en protección contra el Sida ( ref. 133,142,182,194)

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

-Generación de vectores recombinantes 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 frente a los subtipos B y C, que representan el 80% de los casos de SIDA en el mundo (Solicitud de invención Nº 200501841; 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 via respiratoria y conseguir niveles semejantes de activación de la respuesta inmune que por inyección de los mismos vectores. Esta aplicación facilida vacunar frente a SIDA a una gran población en paises pobres (ref. 231).

-Demostración en ensayo clínico en fase I que el protocolo DNA/NYVAC induce una alta inmunogenicidad (mas 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 vector MVA-B en células dendríticas humanas activa la expresión de genes inmunomoduladores con actividad polifuncional (255, 268).

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

-Generación de nuevos vectores de NYVAC ( 266, 276, 283) y MVA (256, 259, 271, 280, 281) con mayor capacidad para activar respuesta inmunes de amplio rango y duraderas frente al VIH.

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

-Desarrollo de una candidato vacunal frente a cáncer de próstata (263).

-Deasarrollo de un candidato vacunal frente a gripe (275).

-Desarrollo de un candidato vacunal frente a malaria con inducción de esterilidad (284; patente solicitud **P201131854**).

-Identificación del gen C6L de vaccinia como inhibidor del interferon beta y su aplicación en vacunas de poxvirus (271; solicitud de patente **P201131230).**

**-**Desarrollo de un candidato vacunal frente al virus de la hepatitis C: patente solicitud **P201330467**

**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 huesped, así como utilizar estos conocimientos para desarrollar vacunas que puedan ser efectivas en el control de enfermedades como Sida, Malaria y Leishmaniasis. 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 mas 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 microscopia electrónica de células infectadas, llevado a cabo en colaboración con C.Risco y J.L.Carrascosa (CNB), hemos demostrado el papél 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 estadíos de morfogénesis, el papél de las proteínas de membrana en ensamblaje, su modo de interacción y definir por técnicas de alta resolución la organización estructural del virion y la estructura tridimensional de algunas de estas proteínas.

**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: proteinas 2-5A sintetasa/RNasa L, óxido nítrico sintetasa (iNOS) y proteina quinasa p68 (PKR). Nuestros estudios futuros van dirigidos a conocer el receptor que activa la señalización de PKR, todas 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) 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 estamos identificando genes celulares inducidos en respuesta a la infección por VV (estirpe salvaje y mutantes) y por acción de estímulos apoptóticos. Nuestro objetivo es identificar genes celulares importantes en el proceso infectivo 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. Recientemente hemos descubierto la proteína celular WASP como responsable de la transmisión del virus en animales y la proteina ISG15 como inhibidor de la replicación viral.

**4. *Desarrollo de vacunas contra sida, malaria y leishmania*.**

Nuestro laboratorio está desarrollando estrategias de inmunización contra VIH, malaria y leishmania basadas en la utilización de VV recombinantes. 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-$\gamma$, GM-CSF, IL-18, IL-15) y de adyuvantes como mega CD40. En colaboración con otros grupos, hemos llevado a cabo con alguna de las vacunas generadas por nosotros, ensayos de protección en perro frente a leishmaniasis y frente al SIV en macacos, que han demostrao su eficacia. También formamos parte del grupo europeo de desarrollo de una vacuna contra VIH/SIDA (EuroVacc), habiendo 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 un ensayo clínico en fase I con la vacuna MVA-B generada por mi grupo en el CNB con resultados muy positivos de inmunogenicidad y en 2012 iniciamos otro ensayo clínico fase I con individuos VIH positivos. Estamos mejorando la capacidad de los vectores de poxvirus por modificación genética mediante deleciones específicas en genes que bloquean la respuesta inmune del hospedador para futuros ensayos clínicos.

**5. *Desarrollo de vacunas contra hepatitis C y cáncer de próstata.***

Nuestro objetivo es desarrollar una vacuna basada en un procedimiento de inmunización combinada de vectores ("prime/boost"), que expresan la poliproteina 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 constitutiva y que induce respuestas inmunes amplias frente a HCV en modelos animales. Recientemente hemos iniciado un proyecto de diseño de vacunas contra cáncer de próstata y hemos clonado varios genes 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 la aparición de tumores en dichos animales. Se han obtenido resultados de reducción de tumores prostáticos mediante vacunación con nuestros vectores. Para mejorar la eficacia antitumoral estamos desarrollando nuevos vectores con capacidad oncolítica. Es predecible que la combinación de la capacidad oncolítica e inmunogénica de vectores de poxvirus sea la mas eficaz para el control tumoral.

**Research:**

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 diseases like AIDS, malaria and leishmaniasis. As a model system of infectious agent and as a delivery vector for expression of genes of interest, we used vaccinia virus (VV) a member of the poxvirus family. The research areas of our lab are.

**1. *Vaccinia virus (VV) assembly*.**

VV 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 host defense against viral infections, tumor cell growth and regulation of the immune system. We have provided important insights into the mechanism of apoptosis action by the IFN-induced ds-RNA dependent protein kinase (PKR), and we have identified the inhibitory effects exerted over PKR by some 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 was to know the impact of vaccinia virus on host cell gene expression profiling in order to identify cellular genes relevant for VV 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 to identify cellular genes specifically induced in the course of virus infection using virulent and attenuated VV 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.

**5. *Developmen of vaccines against Aids, malaria and leishmaniasis.***

Our laboratory has been developing immunization strategies against HIV, malaria and leishmania based on the use of VV recombinants. We have pioneered the development of protocols based on heterologous immunization approaches (prime/booster) with vectors that induced enhanced cellular immune responses, leading to protection in murine models against malaria (*Plasmodium yoelii*) and leishmania (*L. major and L. infantum)*. These studies have defined immunological parameters to expand 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 and clinical studies are underway. Novel vaccines with enhanced immunogenicity against HIV are being developed in our lab for testing in non-human primate models, as well as we are producing new vaccines against hepatitis C, leishmania 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 XXI century with major diseases for which there is no cure, like AIDS (22 million (M) deaths and 40M infections), malaria (300 M infections and 3M deaths/year mostly childrem), tuberculosis (2-3 M deaths/year), hepatitis C (300 M infections), leishmaniasis (12 M infections), and cancer (the second leading cause of human deaths). WHO considers a priority to develop prophylactic and therapeutic vaccines against these different deathly diseases. 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 wordlwide (patent PCT/ES2006/070114). In preclinical studies in mice and in macaques the prototype vaccines expressing four HIV antigens (Env/Gag-Pol-Nef) have fullfiled 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 in DNA/poxvirus combination 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 initiated in 2009 a phase I clinical study in Spain, with the participation of hospitals Clinic from Barcelona and Gregorio Marañón in Madrid, that has received wide attention by the media. This prophylactic clinical trial has shown excellent immunological profiles with greater than 90% responders within the vaccinees. Another phase I clinical trial but with HIV positive individuals with HAART therapy was inititated in 2012 with MVA-B, to asses safety and immunogenicity of the vaccine protocols. The results will be known in 2013.

Our group has also generated potential vaccines agains leishmaniasis (patent PCT/ES2006/070122), malaria, hepatitis C and prostate cancer, all of which are now under preclinical and patent evaluation.

**GRUPO DE INVESTIGACIÓN**

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**Breve C.V: MARIANO ESTEBAN RODRIGUEZ**

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Mariano Esteban, natural 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 posdoctoral en el Centro Nacional de Investigaciones Médicas de Londres (MRC) con David Metz e Ian Kerr, 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, con John Holowzack. Tras una breve estancia en 1978 en el Centro de Biología Molecular de Gante en Bélgica con Walter Fiers, le fue concedida en 1979 una plaza de Profesor Titular 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 con nivel funcionario y en 1985 Profesor (Catedrático) de los Departamentos de Bioquímica y de Microbiología e Inmunología de la mencionada Facultad de Medicina.

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 11 años. 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 Centro fue un polo de atracción de empresas estableciendo modelos de colaboración con compañias nacionales e internacionales. El Centro ha sido evaluado varias veces por Comités Científicos Internacionales que lo consideran como "centro de excelencia en biotecnología".

El interés de las investigaciones de Mariano Esteban se han 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 contra Sida, Malaria y Leishmania, habiendo sido pionero en el campo de la vacunas al desarrollar procedimientos de inmunización combinada de vectores (*prime/booster*) que aumentan la respuesta inmune celular y confieren protección frente a distintos patógenos. Estos protocolos de vacunación están siendo experimentados en ensayos clínicos de fase 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 están siendo analizadas en ensayos clinicos en fase I en Europa y otros prototipos vacunales que se ensayarán en África en 2014.. Actualmente ha iniciado el desarrollo de nuevas vacunas contra hepatitis C y cáncer de próstata, así como una nueva generación de vectores con mayor capacidad inmunogénica y oncolítica.

Las contribuciones científicas sobre el modo de acción de los interferones han sido pioneras, potenciando el interés clínico de estos fármacos como agentes antivirales y antitumorales. Estudios recientes en su laboratorio han demostrado el papel que varios de los genes inducidos por los interferones tienen como reguladores de la muerte celular programada (apoptosis), lo que servirá para establecer pautas terapéuticas más eficaces en el uso de los interferones en pacientes con tumores y en terapia génica.

Estas contribuciones científicas representan más de 290 trabajos publicados en revistas internacionales y mas de 280 comunicaciones en congresos nacionales e internacionales.

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 estan 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) y varias empresas. En el año 2005 obtuvo un acuerdo de colaboración con la Fundación Botín por cinco años para realizar investigaciones en vacunas contra enfermedades prevalentes y tambien su grupo ha sido galardonado en 2006 con un proyecto por la Fundación Bill y Melinda Gates para la generación de una vacuna contra el VIH/SIDA, que ha sido prorrogado en 2012 por otros tres años.

En su laboratorio se han formado estudiantes de varias nacionalidades y recibe periódicamente Profesores visitantes. Ha dirigido 28 Tesis Doctorales y actualmente trabajan en su laboratorio 14 personas, pre y posddoctorales de distintas nacionalidades. Participa en actividades académicas de Master con la Universidad Autónoma de Madrid, (UAM), de la que es Profesor Honorífico, habiendo organizando el curso de Enfermedades Infecciosas y Sistema inmune.

Mariano Esteban 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 y participa en varios Comites Europeos (Member of the European Action Progamme 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 Reseach, 1998-actual. Member of Strategic Advisory Group of Experts (SAGE) for Vaccines and Biologicals, WHO, 2003-2007. Member of Advisory Group for the Sciende Foundation of Ireland, 2000l. Member of European Science

Foundation (ESF) Group for Research Infraestructures on Biomedical Sciences, 2003, y nacionales (ANEP; Grandes Instalaciones Científicas, 2003-actual). En 2013 fue nombrado miembro del Comité Científico Asesor del CSIC.

Ha impartido un gran número de conferencias en varios países, organizado cursos, workshops. Ha organizado congresos internacionales: Presidente, XI International Poxvirus and Iridovirus Meeting, Toledo, 1996; Presidente, Fifth European Conference on Experimental AIDS Research (ECEAR-2000), Madrid, y Co-Presidente "II European Virology Congress (EuroVirology-2004) en Madrid.

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, Farmacéutico del Año. Premio IBERDROLA de Ciencia para Profesores visitantes. Ha sido fundador y Presidente 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 medallón de 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 y en Diciembre de 2012 fue elegido Presidente de la RANF.

**GRUPO DE INVESTIGACIÓN**

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**SHORT CV: MARIANO ESTEBAN**

Mariano Esteban return to Spain in 1992 after 22 years of stay in Medical Research Centers in both UK and USA where he was full Professor, to direct the newly created National Center for Biotechnology (CNB) of CSIC in Madrid. Within a short time, he recruited excellent Group Leaders and the Center won international credibility, as a place of excellence for basic science in biotechnology in the areas of health, agriculture and environment.

Prof. Esteban is a well-recognised scientist with a long experience in molecular basis of pathogenesis by infectious agents and in translational research. In particular, his group in Spain has made major contributions on the biology of vaccinia virus, the mechanism of action of interferons and development of vaccines against major diseases like Aids, malaria and leishmaniasis, some of which have advanced phase I clinical trials (HIV). In the period 2005-2009 his work was supported by grants from national (MICINN; FIS; FIPSE, Foundation Botín), international agencies (NIH, USA; Bill y Melinda Gates, European Union) and industries.

Prof. Esteban has published over 290 papers in prestigious journals presented over 280 communications to international meetings and has given many seminars worldwide. He is a Member of a number of

prestigious scientific international societies, Member of Editorial Boards and peer-review in major journals. He is also a Member of European and Spanish organizations He 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, and Vice-president of the European Virology meeting in Madrid, in 2004. He participates in academic activities at the Autonomous University of Madrid, is member of the Royal Society of Pharmacy of Spain (RANF), in 2012 was elected President of RANF and is also founder of EuroVacc.

Achivements

Development of a vaccine against HIV/AIDS remains a major challenge in the control of this pandemic that has produced more than 25 million deaths since it was first diagnosed in 1981 and continues unabated worldwide. The group of Prof. Esteban at the CNB-CSIC has developed candidate vaccines against HIV/AIDS based on poxvirus vectors (MVA and NYVAC) that have shown excellent immunological profiles in animal models (mouse and macaques) and efficacy against simian immunodeficiency virus in macaques. Moreover, some of these vectors have entered phase I clinical trials giving responses in about 90% of the volunteers. Further improvement of the immunization protocols has been achieved in monkeys providing higher transmission of HIV specific cellular immune responses from mothers to lactating infants and selective targetting of HIV antigens to dendritic cells. The aim is to enter phase II/III clinical trials with some of the Esteban´s developed candidate vaccines in the next five years. Prof. Esteban HIV research is supported by national and international grants (i.e, Bill and Melinda Gates) and collaborates actively with international teams in both Europe and USA.