



## **CURRICULUM VITAE OF ESTEBAN DOMINGO**

**Birth date:** Sept. 27, 1943, in Barcelona, Spain.

**Present address:** Centro de Biología Molecular "Severo Ochoa" (CBMSO). Universidad Autónoma de Madrid. 28049-Cantoblanco, Madrid (edomingo@cbm.uam.es) (Spain). Tel. 34-91-1964540, Fax: 34-91-1964420.

**Position:** Professor of Research at the Spanish Research Council (CSIC).

**Education:** B.Sc. in Chemistry at the University of Barcelona (1965). Ph.D. in Biochemistry, University of Barcelona (1969). Maximum grades: "Premio Extraordinario" for B.Sc. (1965) and for Ph.D. (1969).

### **Postdoctoral experience:**

- Oct. 1969-Dec. 1973: With Prof. Robert C. Warner, Department of Molecular Biology and Biochemistry, University of California at Irvine, California (USA). *In vitro* transcription.
- Jan. 1974-July 1976: With Prof. Charles Weissmann, Institut für Molekularbiologie I, Universität Zürich, 8093 Zürich (Switzerland). Genetics of phage Q $\beta$ .

### **Visits to other laboratories and sabbaticals:**

- 1980-81: BIOGEN S.A. (Switzerland). Molecular cloning and gene expression.
- August 1983: National Institute for Medical Research, Mil Hill, London (UK), with Dr. J. Skehel. Dideoxy sequencing of influenza virus genes.
- August 1988 - August 1989: Sabbatical year at the Univ. of California, San Diego (USA), with Dr. J. Holland. RNA virus heterogeneity.
- Jan. 1991 - April 1991: Additional visit at UCSD, with Dr. J. Holland. RNA virus heterogeneity.
- Oct. 1999 - Nov. 1999: Scripps Research Institute, with Drs. M.B.A. Oldstone and J.C. de la Torre. Genetics of lymphocytic choriomeningitis virus.

### **Membership:**

- Editorial board of: *Microbiologia S.E.M.* (since 1985) / *Virus Research* (since 1987) / *J. Gen. Virology* (1988-1993; and since 2003) / *J. Virol.* (since 1995) / *Viral Immunology* (1994-1999) / *Archives in Virology* (since 1997) / *Virologie* (France) (since 1997) / *AIDS Reviews* (1999-2003) / *Virology* (since 2002) / Associate editor, *PLoS Pathogens* (since 2008).
- Editor of *J.Gen.Virol.* (1998-2002).
- Spanish representative in the Standing Technical Committee of FAO on FMD research (1986-1992).
- Member of the Advisory Committee of the Division of Virology of the International Union of Microbiological Societies (IUMS) (1999-2005).

- Founder member and scientific board member of Institute Para Limes, The Netherlands (since 2006).
- President of the Spanish Society for Virology (since 2007).
- Editor of Virus Research (since 2012).

**Teaching:** At the Univ. Calif. Irvine (1971-73) and Univ. Autónoma de Madrid (Spain) 1978-1992 / Director of "Master in Biotechnology" given at the CBMSO (1992-1993), and coordinator (1994-1995). Professor at the "Cours de Virologie Fondamentale", Institut Pasteur, Paris, France (since 1993). Professor at the course "Genetics and Evolution of Viruses"(since 2003), Univ. of Helsinki, Finland. Organizer: Dr. A. Plyusnin.

Director or co-director of 26 Doctoral Theses.

**Publications:** 390 papers in international journals and books; H index = 73 (October 2015).  
Author or editor of 6 books.

**Main scientific achievements:** Demonstration of high mutation rates and quasispecies dynamics of RNA viruses. Establishment of cell lines persistently infected with foot-and-mouth disease virus. Lethal mutagenesis as a new antiviral strategy.

**Main scientific interests:** Biological implications of quasispecies dynamics. Molecular basis of virus extinction by enhanced mutagenesis. Antiviral activity of nucleoside analogues.

**Main scientific distinctions:**

- Member of the EMBO (since 1991).
- Honorary Member of the European Society for Veterinary Virology (since 1997).
- Member of the European Academy (since 1998).
- Doctor *Honoris causa* from the Université de Liège, Belgium (1999).
- Doctor *Honoris causa* from the University of Bern, Switzerland (2004).
- Premio Cultura Viva (2010).
- Member of Real Academia de Ciencias Exactas, Físicas y Naturales, from the Natural Sciences Section (since 2012).

**Selected publications until 2014:**

Domingo, E., Flavell, R.A. and Weissmann, C. (1976). *In vitro* site-directed mutagenesis: Generation and properties of an infectious extracistronic mutant of bacteriophage Q $\beta$ . *Gene* 1, 3-25.

**[First construction of a viable virus mutant by site-directed mutagenesis]**

Batschelet, E., Domingo, E. and Weissmann, C. (1976). The proportion of revertant and mutant phage in a growing population, as a function of mutation and growth rate. *Gene* 1, 27-32.

**[First calculation of a mutation rate for an RNA virus]**

Domingo, E., Sabo, D.L., Taniguchi, T. and Weissmann, C. (1978). Nucleotide sequence heterogeneity of an RNA phage population. *Cell* 13, 735-744.

**[First evidence of quasispecies dynamics in an RNA virus]**

Domingo, E., Dávila, M. and Ortín J. (1980). Nucleotide sequence heterogeneity of the RNA from a natural population of foot-and-mouth disease virus. *Gene* 11, 333-346.

**[First calculation of population heterogeneity of an animal RNA virus *in vivo*]**

Sobrino, F., Dávila, M., Ortín, J. and Domingo, E. (1983). Multiple genetic variants arise in the course of replication of foot-and-mouth disease virus in cell culture. *Virology* 128, 310-318.

**[Demonstration of quasispecies dynamics in an animal virus]**

Mateu, M.G., Martínez, M.A., Rocha, E., Andreu, D., Parejo, J., Giralt, E., Sobrino, F. and Domingo, E. (1989). Implications of a quasispecies genome structure: effect of frequent, naturally occurring amino acid substitutions on the antigenicity of foot-and-mouth disease virus. *Proc. Natl. Acad. Sci. USA* 86, 5883-5887.

**[Demonstration of the implication of quasispecies dynamics in antigenic variation]**

Holland, J.J., Domingo, E., de la Torre, J.C. and Steinhauer, D.A. (1990). Mutation frequencies at defined single codon sites in vesicular stomatitis virus and poliovirus can be increased only slightly by chemical mutagenesis. *J. Virol.* 64, 3960-3962.

**[Initial study that documented the feasibility of an error catastrophe-lethal mutagenesis approach for an RNA virus]**

Verdaguer, N., Mateu, M.G., Andreu, D., Giralt, E., Domingo, E. and Fita, I. (1995). Structure of the major antigenic loop of foot-and-mouth disease virus complexed with a neutralizing antibody: direct involvement of the Arg-Gly-Asp motif in the interaction. *EMBO J.* 14, 1690-1696.

**[First evidence that a receptor-recognition domain can overlap with an antigenic site of a virus]**

Escarmís, C., Dávila, M., Charpentier, N., Bracho, A., Moya, A. and Domingo, E. (1996). Genetic lesions associated with Muller's ratchet in an RNA virus. *J. Mol. Biol.* 264, 255-267.

**[First molecular characterization of the genetic changes in a virus as a result of Muller's ratchet]**

Ruiz-Jarabo, C.M., Arias, A., Baranowski, E., Escarmís, C. and Domingo, E. (2000). Memory in viral quasispecies. *J. Virol.* 74, 3543-3547.

**[First evidence of the presence of a molecular memory in a viral quasispecies]**

Domingo, E., Biebricher, C., Eigen, M. and Holland, J.J. (2001). Quasispecies and RNA Virus Evolution: Principles and Consequences. Landes Bioscience, Austin.

**[Book on quasispecies and its implications]**

Baranowski, E., Ruiz-Jarabo, C. M. and Domingo, E. (2001). Evolution of cell recognition by viruses. *Science* 292, 1102-1105.

**[Review of the consequences of quasispecies dynamics for host cell tropism variations]**

Grande-Perez, A., Sierra, S., Castro, M.G., Domingo, E. and Lowenstein, P. (2002). Molecular intertermination in the transition to error catastrophe. Systematic elimination of lymphocytic choriomeningitis virus through mutagenesis does not correlate linearly with large increases in mutant spectrum complexity. *Proc. Natl. Acad. Sci. USA*, 99 (20), 12938-43.

**[Evidence that viral extinction may be achieved through modest mutagenesis]**

Woolhouse, M.E.J., Webster, J.P., Domingo, E., Charlesworth, B. and Levin, B.R. (2002). Biological and biomedical implications of the coevolution of pathogens and their hosts. *Nature Genetics* 32, 569-577.

**[A general perspective on virus-host coevolution]**

Ruiz-Jarabo, C.M., Ly, C., Domingo, E. and de la Torre, J.C. (2003). Lethal mutagenesis of the prototypic arenavirus lymphocytic choriomeningitis virus (LCMV). *Virology* 308, 37-47.

**[Proof of principle of the feasibility of lethal mutagenesis *in vivo*]**

Manrubia, S.C., Lázaro, E., Pérez-Mercader, J., Escarmís, C. and Domingo, E. (2003). Fitness distributions in exponentially growing asexual populations. *Phys. Rev. Lett.*, 90, 188101-188104.

**[Model of evolution of error-prone replicators, inspired in experimental findings]**

Lázaro, E., Escarmís, C., Pérez-Mercader, J., Manrubia, S.C. and Domingo, E. (2003). Resistance of virus to extinction on bottleneck passages: Study of a decaying and fluctuating pattern of fitness loss. *Proc. Natl. Acad. Sci. USA*, 100, 10830-10835.

**[Survival capacity of virus to serial population bottlenecks]**

Gonzalez-Lopez, C., Arias, A., Pariente, N., Gomez-Mariano, G. and Domingo, E. (2004). Preextinction viral RNA can interfere with infectivity. *J. Virol.*, 78, 3319-3324.

**[Evidence of intra-population interactions in viral quasispecies, and the detrimental effect of mutagenized mutant clouds]**

García-Arriaza, J., Manrubia, S.C., Toja, M., Domingo, E. and Escarmís, C. (2004). An evolutionary transition towards defective RNAs that are infectious by complementation. *J. Virol.*, 78, 11678-11685.

**[An evolutionary transition towards viral genome segmentation, observed in the laboratory]**

Ferrer-Orta, C., Arias, A., Perez-Luque, R., Escarmís, C., Domingo, E. and Verdaguier, N. (2004). Crystal structure of foot-and-mouth disease virus RNA-dependent RNA polymerase and its complex with a template-primer RNA. *J. Biol. Chem.*, 279, 47212-47221.

**[First complete three-dimensional structure of a picornaviral polymerase]**

Herrera, M., García-Arriaza, J., Pariente, N., Escarmís, C. and Domingo, E. (2007). Molecular basis for a lack of correlation between viral fitness and cell killing capacity. *PLoS Pathog.* 3(4):e53. doi: 10.1371/journal.ppat.0030053.

**[The connection between viral fitness and virulence]**

Ferrer-Orta, C., Arias, A., Pérez-Luque, R., Escarmís, C., Domingo, E., and Verdaguier N. (2007). Sequential structures provide insights into the fidelity of RNA replication. *Proc. Natl. Acad. Sci. USA*, 104(22), 9463-8.

**[Structural information on polymerase copying fidelity]**

Perales, C., Agudo, R., Tejero, H., Manrubia, S.C. and Domingo, E. (2009). Potential benefits of sequential inhibitor-mutagen treatments of RNA virus infections. *PLoS Pathogens*, 5(11): e1000658.

**[Proposal of sequential antiviral treatments based on lethal mutagenesis]**

Ojosnegros, S., Beerenwinkel, N., Antal, T., Nowak, M.A., Escarmís, C. and Domingo, E. (2010). Competition-colonization dynamics in an RNA virus. *Proc. Natl. Acad. Sci. USA*. 107(5), 2108-12.

**[Application of an ecology model to the understanding of intra-population viral dynamics]**

Ojosnegros, S., García-Arriaza, J., Escarmís, C. Manrubia, S.C., Perales, C., Arias, A., García-Mateu, M. and Domingo, E. (2011). Viral genome segmentation can result from a trade-off between genetic content and particle stability. *PLoS Genetics*, 7(3): e1001344.

**[Virion stability as a factor of viral genome segmentation]**

Iranzo, J., Perales, C., Domingo, E., Manrubia, S.C. (2011). Tempo and mode of inhibitor-mutagen antiviral therapies: A multidisciplinary approach. *Proc Natl Acad Sci USA*. 108(38), 16008-13.

**[Theoretical and experimental aspects of antiviral designs based on lethal mutagenesis]**

Domingo, E., Sheldon, J. and Perales, C. (2012). Viral quasispecies evolution. *Microbiology and Molecular Biology Reviews* 76(2), 159-216.

**[Review of quasispecies and its implications for antiviral interventions]**

Moreno, E., Ojosnegros, S., García-Arriaza, J., Escarmís, C., Domingo, E. and Perales C. (2014). Exploration of sequence space as the basis of viral RNA genome segmentation. *Proc Natl Acad Sci USA*, 111(18):6678-6683.

**[Role of point mutations in viral genome segmentation]**

Sheldon, J., Beach, N.M., Moreno, E., Gallego, I., Piñeiro, D., Martínez-Salas, E., Gregori, J., Quer, J., Esteban, J.I., Rice, C.M., Domingo, E., Perales, C. (2014). Increased replicative fitness can lead to decreased drug sensitivity of hepatitis C virus. *J Virol.*, 88(20):12098-12111.

**[First evidence of viral fitness as a drug resistance determinant]**