



Part A. PERSONAL INFORMATION

CV date 07/07/2020

First and Family name	Vicente Felipo		
Social Security, Passport, ID number		Age	
Researcher numbers	Researcher ID	A-9265-2014	
	Author ID	7005676305	
	ORCID code	0000-0003-3145-9538	

A.1. Current position

Name of University/Institution	Centro de Investigacion Principe Felipe, Valencia, Spain		
Department	Laboratory of Neurobiology		
Address and Country	Calle Eduardo primo Yúfera, 3, 46012 Valencia		
Phone number	963289680	E-mail	vfelipo@cipf.es
Current position	Head of Laboratory	From	01/01/1990
UNESCO code	2490 / 320711		
Key words	Hepatic Encephalopathy, hyperammonemia, cognitive impairment,		

A.2. Education

Degree/PhD	University	Year
Licenciado C. Químicas (Chemistry)	Universidad de Valencia	1979
Doctor en C. Químicas (PhD Chemistry)	Universidad de Valencia	1983

A.3. General indicators of the scientific production quality

Ph.D. thesis directed: 27; in the last 10 years: 15 defended, 7 in course.

H index: 54. July 7, 2020: **Total citations: 10.009.** Citations/year: 2015:630; 2016:622; 2017:569; 2018: 523; 2019: 661; 2020: 300 at July 7th.

Publication in the first decile: 48; first quartile: 160; total: 320.

The group is world leader in hepatic encephalopathy (HE) and hyperammonemia. This is reflected by:

- The Swedish company Umecrine contracted us to assess the therapeutic utility of a molecule of their property to treat cognitive and motor impairment in HE. Umecrine has included us in the patent;
- Nature Reviews Neuroscience, the best journal in the Neuroscience field (I.F. 31.67) requested me a review entitled: "Hepatic encephalopathy: effects of liver failure on brain function", published on December 2013.

Principal Investigator (PI) of 89 scientific grants (58 in the last 10 years) from: European Union 10; International cooperation (AECID, Ministerio Asuntos Exteriores) 9; CONSOLIDER 1; PETRI Program; National Plan I+D+I 20; Redes de Investigación Cooperativa del FIS-ISCIII, National Coordinator 1; Generalitat Valenciana 29; Prometeo of Generalitat Valenciana for Groups of Excellence 3; Fundació La Marató de TV3 2; Fundación Abertis 1; Instituto Tecnológico Textil (AITEK) 3; Umecrine Cognition, Sweden, 7. 3 patents, 2 international in the last 8 years (see section C.4)

Member of Editorial Board of: J Hepatol; Neurochem Res; Metab Brain Dis; Int J Mol Med; World J Gastroenterol; Open Gastroenterol J; Front Neuroenergetics; J Alz Dis; World J Exp Med; Open J Medicine; Neuroimmunol Neuroinflam.

Editor of 7 books in Advances in Experimental Medicine and Biology Springer, New York. USA.

Guest Editor of 5 Special issues in Metab Brain Dis; Neurochem Int and Cells.

Reviewer of more than 330 articles in 66 international journals.

Organizer of: 20 international symposium in Valencia y 11 Master Courses of the Chair Santiago Grisolia, taught by 7 Nobel Prize

Invited speaker in 72 international and 6 national congresses or symposia.

Member of the committee of experts of the Science Museum "Príncipe Felipe", Valencia. 2002-

Member of the Jury of Prizes: "Premio Rey Jaime I", for 4 years, and of "Premios Idea", 5 years.

Reviewer of scientific projects for all Spanish agencies and for 14 foreign agencies.

Member of the following International Committees:

- First Secretary and member of the Executive Committee of International Society for Hepatic Encephalopathy (ISHEN)
- Review Working Group (ERWG) de la European Food Safety Authority (EFSA)
- Action Group A3 "Prevention and early diagnosis of cognitive and functional decline" European Innovation Partnership on Active and Healthy Ageing (EIP on AHA), European commission.

Prizes: "Alberto Sols" Health Sciences, 2012; "Severo Ochoa" biomedical research, Fundación Ferrer 2002; and other 6 prizes.



Director of the: Laboratory of Neurobiology of CIPF(1990-); Cognitive impairment program of CIPF (2012-); Santiago Grisolia Chair, 2000- ; Centro Investigación Príncipe Felipe (CIPF), 2011- 2012; Valencian Fundación Valenciana Investigaciones Biomédicas 2000-2002; Co-director of Neurologic Impairment Program of Instituto de Investigación Sanitaria INCLIVA (2015-), National Coordinator of the Spanish Network on Hepatic Encephalopathy, Instituto Carlos III, 2002-2007.

Part B. CV SUMMARY (max. 3500 characters, including spaces)

Our investigation focuses on the identification of the mechanisms by which chronic liver diseases (cirrhosis) lead to cognitive and motor impairment in patients with minimal hepatic encephalopathy (MHE) and on the identification of new treatments and biomarkers for early diagnosis for MHE. We have made very relevant contributions to the knowledge of these mechanisms. We have identified therapeutic targets and successfully designed and tested pharmacological treatments that have allowed reversing cognitive and motor alterations in HE models. We are pioneers and international leaders in these type of studies. We have demonstrated that hyperammonemia reduces the function of the Glutamate-Nitric oxide-cGMP (Glu-NO-cGMP) pathway in brain in vivo, thus reducing learning ability in rats with HE. We have identified the mechanisms responsible for the alteration of this pathway and restored extracellular cGMP levels and learning ability in HE rats using 6 different treatments. We have demonstrated that extracellular cGMP modulates learning ability through the glycine receptor and Glu-NO-cGMP pathway. This has been the first demonstration of a physiological role for extracellular cGMP in brain.

We have also identified in rats with HE the cause of hypokinesia, which is due to the increase of extracellular glutamate in SNr and the excessive activation of its metabotropic receptors. We have resolved hypokinesia and normalized motor activity by blocking these receptors. We have shown that hyperammonemia induces microglia activation and neuroinflammation, which contribute to cognitive and motor impairment. We have restored learning and motor activity with anti-inflammatory agents. We have shown that peripheral inflammation induced by hepatic failure leads to neuroinflammation, with activation of microglia and astrocytes and increased inflammatory factors in cerebellum and hippocampus. These factors alter glutamatergic and GABAergic neurotransmission altering membrane expression of glutamate and GABA receptors and transporters, and the extracellular concentration of these neurotransmitters. These alterations in neurotransmission lead to cognitive and motor alterations. We have been able to reverse neuroinflammation, alterations in neurotransmission and cognitive and motor impairment by reducing peripheral inflammation with anti-TNF α or ibuprofen and acting on 5 different brain therapeutic targets identified in the above mechanistic studies. We have identified the first peripheral biomarker for early diagnosis of MHE in cirrhotic patients with high sensibility and specificity. We have obtained the patent of this (the first) diagnostic procedure in blood. We are also co-authors in the first patent of a molecule (of the Swedish company Umercrine) for HE treatment acting on a brain therapeutic target, identified of the bases of our mechanisms studies.

Our investigation has allowed:

- 1) to prevent death due to acute ammonium poisoning
- 2) to prolong and increase survival in models of acute liver failure
- 3) restoring the learning ability in rats with chronic mHE by different procedures
- 4) to reverse hypokinesia and motor incoordination in these rats
- 5) to identify a blood marker for the diagnosis of mHE in patients with liver cirrhosis

Part C. RELEVANT MERITS

C.1. Publications (including books) 320 publications; in the first decile: 48; in the first quartile: 160.

Although I have many articles with a higher number of citations (e.g. 442), the following articles are those that have contributed most relevant advances to the knowledge in the field in the last years.

1. Felipo, V. (2013) Hepatic encephalopathy: effects of liver failure on brain function. *Nature Reviews Neuroscience*. 14(12):851-858. IF = 33.16; times cited = 167
2. Balzano T, (13 more) and Felipo V. (2020) Chronic hyperammonemia induces peripheral inflammation that leads to neuroinflammation and cognitive impairment in rats. Reversal by anti-TNF α treatment. *Journal of Hepatology*; 73 (3). 82-93 IF = 18.95, times cited = 6
3. Cabrera-Pastor A, (10 more), Felipo V. (2019) Peripheral inflammation induces neuroinflammation that alters neurotransmission and cognitive and motor function in hepatic encephalopathy: Underlying mechanisms and therapeutic implications. *Acta Physiologica (Oxf)* :e13270 IF = 5.87, times cited = 6
4. De Chiara F, (10 more), Felipo V, ... Thomsen KL. (2018) Urea cycle dysregulation in non-alcoholic fatty liver disease. *Journal of Hepatology* 69(4):905-915. IF = 18.95, times cited = 21
5. Cabrera-Pastor A, (4 more) Felipo V (2016) In vivo administration of extracellular cGMP normalizes TNF- α and membrane expression of AMPA receptors in hippocampus and spatial reference memory but not IL-

1b, NMDA receptors in membrane and working memory in hyperammonemic rats. Brain Behavior and Immunity 57:360-70 IF = 6.17, times cited = 17

6. Hernandez-Rabaza V, Agusti A, Cabrera-Pastor A, Fustero S, Delgado O, Taoro-Gonzalez L, Montoliu C, Llansola M and Felipo V. (2015) Sildenafil reduces neuroinflammation and restores spatial learning in rats with hepatic encephalopathy. Underlying mechanisms. Journal of Neuroinflammation 12:195, IF = 5.70, times cited = 41
7. Montoliu C, ... (11 more) .. Felipo V (2014) Reduced white matter microstructural integrity correlates with cognitive deficits in minimal hepatic encephalopathy. Gut. 63:1028-30; IF=17.94; citations = 9
8. Felipo, V, ... (7 more authors) .., J, and Montoliu, C. (2012) Patients with minimal hepatic encephalopathy show impaired mismatch negativity correlating with reduced performance in attention tests. Hepatology; 55(2):530-9. IF = 14.68; citations = 57
9. Cauli O. (6 more) .., Felipo V. 2011 Brain region selective mechanisms contribute to the progression of cerebral alterations in acute liver failure in rats. Gastroenterology 140:638-45, IF=19.23, citations = 42
10. Agusti A, Cauli O, ... (3 more) .., and Felipo, V. (2011) p38 MAP kinase is a therapeutic target for hepatic encephalopathy in rats with portacaval shunts. Gut 60 (11):1572-9. IF=17.94; citations = 41
11. Rodrigo R, (5 co-authors more), Felipo V. 2010 Hyperammonemia induces neuroinflammation that contributes to cognitive impairment in rats with hepatic encephalopathy. Gastroenterology 139(2):675-684 IF = 19.23; citations = 178
12. Cauli O, .. (2 co-authors more) .., Felipo V. 2009 Hyperammonemia increases GABAergic tone in cerebellum but decreases it in rat cortex. Gastroenterology 136:1359-1367, IF = 19.23, citations = 76
13. Cauli O, .. (3 more) .., Felipo V. 2007 Inflammation and hepatic encephalopathy: ibuprofen restores learning ability in rats with porto-caval shunts. Hepatology 46, 514-519. FI = 14.68; citations = 138
14. Romero-Gómez M, .. (8 more) .. and Felipo, V. (2007) Value of the Critical Flicker Frequency in patients with Minimal Hepatic Encephalopathy. Hepatology 45:879-885, FI= 14.68; citations = 192

Complete list at: <https://www.ncbi.nlm.nih.gov/myncbi/1lwyQta66QN/bibliography/public/>

C.2. Research projects and grants Principal investigator (PI) of 89 projects grants (58 in the last 10 years) with the distribution indicated in the section A.3. I have also been PI of 10 Complementary grants from National R&D Plan for the organization of International Symposia. 4 recent projects are:

European Union. 1. Project reference: FP7-ENV-2011 Grant agreement no: 282957 Title: Developmental neurotoxicity assessment of mixtures in children, DENAMIC Principal Investigator: Vicente Felipo; Financial entity: European Commission. Duration: 01/01/2012-31/12/2015; Funding: 649.000 euros

National Plan 2.

2. Project reference: SAF2014-51851-R. Title: Molecular bases of the neurological alterations (cognitive and motor) in hyperammonemia and hepatic encephalopathy. Therapeutic implications. Financing organization: Ministry of Economy and Competitiveness. Principal investigator: Vicente Felipo, Amount: 363,000 euros, Duration: 2015-2017

Project reference: SAF2017-82917-R. Title: Molecular bases of the neurological alterations (cognitive and motor) in hyperammonemia and hepatic encephalopathy. Therapeutic implications. Financing organization: Ministry of Economy and Competitiveness. Principal investigator: Vicente Felipo, Amount: 326,700 euros, Duration: 2018-2020

Valencian Community. 4. Project reference: PROMETEU/2018/051. Title: Molecular bases of neurological alterations (cognitive, motor and in circadian rhythms) in hyperammonemia and hepatic encephalopathy. Therapeutic implications. Principal investigator: Vicente Felipo. Financing entity: Ministry of Education. Valencian Community. Grant for Research Groups of Excellence - Prometeo Program Duration 2018-2021. Amount: 289,196.

C.3. Contracts The latest two:

1. Title: GAMS A for the treatment of hepatic encephalopathy in rats. PI: Vicente Felipo; Financing Company: Umecrine Cognition AB, Sweden. Duration 01/04/2013 - 31/12/2014; Amount: 200,876 euro

2. Title: BIOCELL -II- Application of biotechnology techniques in the process of functionalizations of textile cellulosic materials for their application in the health and cosmetic sector "- AITEX, Instituto Tecnológico Textil, Alcoy, Valencia, Spain; PI: Vicente Felipo; Amount: 53,500 euros; 2013-2015.

C.4. Patents

In the last 10 years: 1. Authors: Vicente Felipo, Omar Cauli, Carmen Montoliu Felix; Title: *Ex-vivo method for the early diagnostic of minimal hepatic encephalopathy through the determination of 3-nitrotyrosine in serum*; application no: P201000899, 12 July 2010; International patent application no: PCT/ES2011/070509 published on 19 January 2012, with number WO2012007624; National patent granted on 1 August 2013. Publication no: 2372842. Int CI: G01N 33/48;



2. Authors: Magnus Doverskog; Hanns Möhler, Vicente Felipo and Torbjörn Bäckström. Title: *Compound 3b*, ethynyl, 3 β -hydroxy, androstan-17-one oxime or a pharmaceutically acceptable salt thereof, for use in treatment of hepatic encephalopathy. Swedish Patent Office application number: SE1450089-6. 2014. International Patent Application No.: PCT/GB2015/050060 filed on 14 January 2015. Applicant company: Umecrine Cognition AB, SE-171 65 Solna, Sweden.

C.5. Editorial work. Editorial member of: 1) Neurochemical Research, 1993-2007; 2) Metabolic Brain Disease, 1994 - ; 3) International Journal Molecular Medicine 1997 - ; 4) World Journal Gastroenterology, 2005 - ; 5) Open Gastroenterology Journal, 2008 - ; 6) Journal of Hepatology, 2009 - ; 7) Frontiers in Neuroenergetics 2008 - ; 8) Journal of Alzheimer's Disease, 2011; 9) World Journal of Experimental Medicine, 2011-; 10) The Open Journal of Medicine 2014-; 11) New Horizons in Translational Medicine 2014- ; 12) Neuroimmunology and Neuroinflammation, 2014- 13) 16. World Academy of Sciences Journal, 2018-

Editor of 7 books in Advances in Experimental Medicine and Biology Springer, New York. USA.

Reviewer of more than 350 articles in 66 international journal

C.6. International Congress: Organization and Invited Presentations

Host of: 20 International Symposium in Valencia and 11 Master Courses of the Santiago Grisolia Chair, taught by 22 international recognized researcher, including 7 Nobel Prize.

Guest of : 72 international congress or symposium and 6 Nationals.

C.7. Evaluator or Advisor. Member of:

Committee of Expert Advisors of the Prince Felipe Science Museum, Valencia, Spain. 2002-; Jury of the Rey Jaime I Prize, 4 years; Jury of the Idea Awards, 5 years; Commission for the Selection of Research Projects 2009, National Plan R&D Biomedicine Area (SAF); Monitoring and Evaluation Commission of the National R&D Plan (Life Sciences) of the FECYT of the Ministry of Science and Innovation, 2009. Evaluator of Contracts of Researchers of the Ministry of Science and Innovation Programs Ramón y Cajal, Juan de la Cierva and Torres Quevedo.

Evaluator of Scientific Projects for 1) The European Commission; Quality of Life and Management of Living Resources Programme Neurosciences (Area 9), 2) ERA-NET-Neuron; 3) The Wellcome Foundation, United Kingdom; 4) The Biotechnology Biological Sciences Research Council. United Kingdom; 5) Neurological Foundation New Zealand; 6) Health Research Board, Irlanda; 7) Medical Research Council, United Kingdom; 8) all Spanish agencies: ANEP, FIS, 9) Comunidades Autónomas: Madrid, Valencia, Andalucía y Extremadura.

C.8. International Committees. Member of:

- Executive Committee and first Secretary of International Society for Hepatic Encephalopathy (ISHEN)
- Committee on experimental models of hepatic encephalopathy of ISHEN
- External Review Working Group (ERWG) of the European Food Safety Authority (EFSA)
- Action Group A3 "Prevention and early diagnosis of cognitive and functional decline" European Innovation Partnership on Active and Healthy Aging (EIP on AHA), European Commission
- Global Translational Medicine Consortium of the European Society for Translational Medicine.

C.9. Research Awards: "Alberto Sols" in Health Sciences, 2012; and 6 other awards.

C.10. Gestión de Investigación.

Director of Laboratory of Neurobiology (1990-) of the Centro de Investigación "Príncipe Felipe" (CIPF) Director of the Cognitive Impairment Program (2012-) CIPF; Co-coordinador of the program Neurologic Impairment (2015-), Instituto de Investigación Sanitaria INCLIVA; Director of Santiago Grisolia Chair, 2000- ; Director of Centro de Investigación "Príncipe Felipe", Nov 2011 - Abril 2012; Director of Fundación Valenciana de Investigaciones Biomédicas Sept 2000- Dic 2002; National Coordinator of Red Española de Encefalopatía Hepática. Instituto Carlos III, 2002-2007.

C.11. Training Activities and Formation Capacity

Directed thesis: 27; in the last 10 years: 15, in course 7. The group supervises an average of 6 master degree thesis and 5 degree thesis every year. 26 of 27 Ph.D. trained in our group have obtained competitive contracts. The other one defended her thesis recently. The laboratory lead the research line "Cognitive and Motor Function. Mechanism. Neurologic Impairment. Mechanisms and therapeutic" in the Doctoral Program of Neuroscience of Valencia University. V Felipo is member of Comisión Académica de Doctorado on Neurosciences of Valencia University. This allows our students to acquire a solid formation and facilitates their integration in the Doctoral Program. The activities for the formation of young researchers include: publications in journal with a good level, promotion of the acquisition of skills to effectively present and critically discuss scientific research through weekly group meetings; participation in Congresses; visits and stays of invited researchers; stays in other laboratories; collaborations with other groups; participation in European Union projects and the use of multidisciplinary technology (see details in the formative capacity section of the project's report). This set of activities place the young people of the group in a very favourable environment to get a solid scientific formation.