

Research Line: VASCULAR PHARMACOLOGY: VASOACTIVE FACTORS



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Our aim: **Analyze the mechanism of action of drugs and identify new therapeutic targets for cardiovascular disease**



The group in 2006 (from left to right): Federica Lodi, Valeria Queirolo, Angel Cogolludo, Francisco Perez Vizcaíno, Laura Moreno, Laura Cobeño, Giovanna Frazziano

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Research Lines

Line 1. Vasoactive factors involved in the control of pulmonary vascular tone.

Adult pulmonary hypertension is a syndrome characterized by an increase in the pulmonary vascular resistance. Its pathophysiology is unclear but it is assumed that the process is initiated by an imbalance of vasoactive factors. Without treatment the disease progresses to right heart failure and the life expectancy is below 5 years. Current available treatments can delay but not stop the disease.

The aim of this research line is to characterize the effects and mechanisms of vasoactive factors modulating pulmonary vascular tone and how they are altered under pathological conditions. Our aim is focused on the vasoconstrictor factors thromboxane A₂, isoprostanes, endothelin-1, angiotensin II and 5-HT and in hypoxia and in the vasodilators nitric oxide. We are interested in the intracellular signalling mechanisms intracellular: cytosolic Ca²⁺, ionic currents (Ca²⁺ and K⁺), protein kinases, reactive oxygen species, ceramide and sphingomyelinases, cyclic nucleotides and adapter proteins. We analyze the effects of drugs interfering with these pathways which could be potentially used in the treatment of pulmonary hypertension. We are also interested in the physiological changes that occur during the first hours and days of life in the pulmonary circulation and that might be involved in persistent pulmonary hypertension of the newborn and in the physiology and pathophysiology of the fetal vessel the ductus arteriosus.

Line 2. Mechanisms of vascular protection by dietary flavonoids.

Flavonoids are polyphenolic compounds that occur ubiquitously in plants and are consumed in the form of fruits, vegetables, nuts and derived products such as red wine and chocolate. There has been considerable interest in the flavonols, particularly quercetin, due to its potency in a number of in vitro assays of biological activity and its prevalence in the diet. The average daily intake in the occidental diet of flavonols plus flavones is estimated to be ≈ 23 mg, with quercetin contributing 60 to 75% of the total. Prospective studies have shown an inverse correlation between dietary flavonoid intake and mortality from coronary heart disease. Several studies using various animal models provide support for the observed protective effects of dietary flavonoids with respect to cardiovascular diseases. Our group together with Dr Juan Duarte from Universidad de Granada, characterized in 1993 the vasodilator effects of quercetin and related flavonoids and later the antihypertensive, antioxidant and end-organ protective effects in rat models of hypertension. We are specially interested in the protective effects of dietary flavonoids on endothelial dysfunction and the mechanisms involved such as protein kinases, NADPH oxidase, K⁺ currents. One of our current objectives is to analyze the effects of quercetin on blood pressure and endothelial function in essential hypertensives.

TECHNIQUES

Vascular contractility: isometric contraction in organ bath and resistance arteries in myograph. Perfusion pressure.

Cytosolic Ca^{2+} (fura-2 fluorescence).

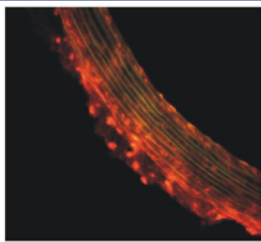
Ionic current recording (patch clamp).

Nitric oxide measurement (daf-2 fluorescence and amperometric electrode)

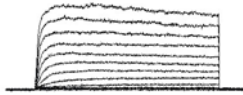
Reactive oxygen species (dihydroethidium, dichlorofluorescein)

Gene expression (Western blot, quantitative RT-PCR).

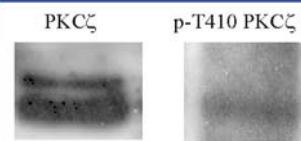
Immunohistochemistry and immunocytochemistry.



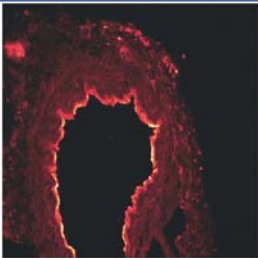
Producción de superóxido en aorta de rata. Fluorescencia de dihidroetidido.



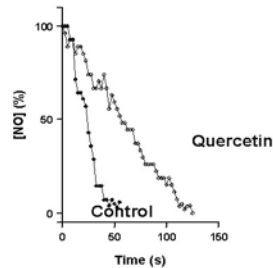
Corrientes de K^+ voltaje-dependientes (IK_v) en un miocito vascular pulmonar de rata. Patch clamp.



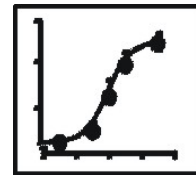
Expresión de PKC ζ y fosforilación de la T410 en arteria pulmonar de rata. Western blot.



Localización de ciclo-oxigenasa-1 en arteria pulmonar de lechón. Immunohistoquímica.



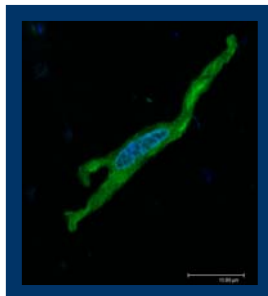
Inhibición del consumo de NO inducido por el generador de superóxido pirogaloI. Registro amperométrico.



NB 2 week
569 bp



Expresión de guanilato ciclasa soluble $\beta 1$ en arterias pulmonares de lechón recién nacido y de dos semanas de edad. Producto de RT-PCR.



SELECTED PUBLICATIONS (1997-2007)

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[Gonzalez-Luis G, Cogolludo A, Moreno L, Lodi F, Tamargo J, Perez-Vizcaino F, Villamor E.](#) Relaxant effects of the soluble guanylate cyclase activator and NO sensitizer YC-1 in piglet pulmonary arteries. *Biol Neonate.* 2006;90:66-72.

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[Villamor E, Ruiz T, Perez-Vizcaino F, Tamargo J, Moro M.](#) Endothelium-derived nitric oxide-dependent response to hypoxia in piglet intrapulmonary arteries. *Biol Neonate.* 1997;72:62-70.

Funded Research Projects

08.4/0019/1998 (CAM). Modulación farmacológica del sistema renina-angiotensina en arterias pulmonares de lechón. IP: J. Tamargo.

PR48/01-9893 (UCM) Expresión de las ciclooxigenasas 1 y 2 y su modulación de la respuesta vasodilatadora pulmonar a óxido nítrico en el periodo neonatal. IP: F. Pérez-Vizcaíno

08.4/0036.1/2001 (CAM). Maduración de la expresión de SOD, COX, PDE, NADPH oxidasa y canales Kv y su modulación de la respuesta vasodilatadora pulmonar neonatal a NO. IP: F. Pérez-Vizcaíno

PR248/02-11710 (Danone/UCM). Efectos del flavonoide quercetina sobre óxido nítrico y su significación biológica. IP: F. Pérez-Vizcaíno

PR32/04-127119 (Danone/UCM). Papel de los canales de K en el efecto vasodilatador de quercetina. IP: A. Cogolludo.

AGL2004-06685-C04-1ALi (MEC/CICYT). Flavonoides: hipertensión arterial y disfunción endotelial. Coordinated project. IP and coordinator: F. Pérez-Vizcaíno.

GR/SAL/0594/2004 (CAM). Implicación de la interacción proteína cinasa C zeta con la p62 y los canales Kv en la vasoconstricción pulmonar inducida por el tromboxano A2. IP: F. Pérez-Vizcaíno

SAF2005-03770 (MEC/CICYT). Vasoconstricción pulmonar inducida por la hipoxia y factores vasoactivos. Papel de los canales KV y la PKCzeta. Investigador principal: F. Pérez-Vizcaíno.

Fundación Médica Mutua Madrileña (2007-2010). Investigador Principal: Angel Luis Cogolludo Torralba. Vasoconstricción del ductus arteriosus inducida por oxígeno: papel de los canales Kv y vías de señalización implicadas.

AGL2007-66108-C04-01ALI (MEC/CICYT). Biodisponibilidad y efecto antihipertensivo de quercetina. Coordinated project. IP and coordinator: F. Pérez-Vizcaíno.

Doctoral Theses

- Estudio de la vasodilatación inducida por la activación de la vía del NO/GMP , de los canales KATP y de la ATPasa Na⁺/K⁺ en arterias pulmonares y mesentéricas de lechón (1998). Angel Cogolludo Torralba Sobresaliente *cum laude* y premio extraordinario.
- Efectos vasodilatadores del NO y de los dadores de NO en arterias pulmonares y mesentéricas de lechón: modulación por el estrés oxidativo (2001). JOSÉ GUSTAVO LÓPEZ LÓPEZ. Sobresaliente *cum laude* y premio extraordinario.
- Persistent pulmonary hypertension of the newborn. A point of view from vascular pharmacology (2001). Eduardo Villamor Zambrano. Universidad de Maastricht.
- Flavonoides y tono vascular: mecanismos de acción, selectividad vascular e interacción con el NO de la quercetina y sus metabolitos metilados (2003). Manuel Ibarra Lorente. Universidad de Alcalá de Henares. Sobresaliente *cum laude* y premio extraordinario.
- Maduración de la respuesta vasodilatadora pulmonar a óxido nítrico en lechones durante el periodo neonatal. (2003). Rocío Santiago Gómez. Sobresaliente *cum laude*.
- Mecanismos dependientes e independientes de la [Ca²⁺]_i estimulados a través de la vía NO/GMPc implicados en la vasodilatación de las arterias pulmonares de lechón” (2006). Francisco Zaragoza Arnáez. Sobresaliente *cum laude* y premio extraordinario.
- Regulación del tono vascular pulmonar y su maduración postnatal. Papel de lavía NO/GMPc y canales de K⁺ voltaje-dependientes (2006). Laura Moreno Gutiérrez. Mención doctor Europeo. Sobresaliente *cum laude* y premio extraordinario.
- Quercetina y sus metabolitos conjugados: estrés oxidativo y disfunción endotelial. (2007). Federica Lodi. Mención doctor Europeo. Sobresaliente *cum laude*.

Diploma de estudios avanzados

Laura Moreno Gutierrez 2003
Federica Lodi 2005
Giovanna Frazziano 2007
Laura cobeño 2007

Tesina de Licenciatura

Efectos de disopiramida en preparaciones vasculares aisladas. Cristina Fernández Montero. Universidad Alcalá de Henares (1996). Sobresaliente.

Tesi de Laurea

Effetti e conseguenze dello status ossidativo sull'azione vasrilassante indota dal flavonoide quercetina in anelli aortici di ratto Wistar (2004). Francesco Vargas-Macchiuca. Universidad de Milan.

Permanent and recent collaborations



Juan Duarte.
Univ. Granada



Eduardo Villamor
Universidad de Maastricht

- ✓ Constancio González. Universidad de Valladolid
- ✓ Jane A. Mitchell. Imperial College. London
- ✓ Timothy D. Warner & David Bishop-Bailey. William Harvey Res. Inst. London
- ✓ José Gustavo López-Lopez. Universidad de Puebla. Méjico
- ✓ Mercedes Salaíces y Ana Briones. Universidad Autónoma Madrid
- ✓ Celestino Santos Buelga. Universidad de Salamanca
- ✓ Paul Kroon & David Hughes. Institute of Food Research. Norwich. UK.
- ✓ José Luis Álvarez-Sala. Hospital Clínico Madrid
- ✓ Lisardo Boscá. Instituto de Investigaciones Biomédicas. Madrid.
- ✓ Ramaroson Andriantsitohaina. Universidad de Angers, Francia.
- ✓ Pilar D'Ocon. Universidad de Valencia.
- ✓ Claire Lugnier. Inserm. Université Louis Pasteur. Strasbourg. France.

Prizes

- VI Premio Científico Hospital Clínico San Carlos (1996).
- FAES. Real Academia de Farmacia (1996).
- Novartis. Sociedad Española de Neonatología (1997).
- Asociación Española de Pediatría (1997).
- Investigador Joven. Sociedad Española de Farmacología (1999, F. Perez-Vizcaino).
- CEPA SCHWARZ PHARMA. Real Academia de Farmacia (2000).
- Proyectos de Investigación. Sociedad Española de Neonatología (2001).
- Young Investigator Award. British Pharmacological Society (2003, A. Cogolludo).
- Investigador Joven. Sociedad Española de Farmacología (2006, A. Cogolludo).
- Premio de Investigación Básica Janssen-Cilag de la Facultad de Medicina (2007)

Doctorate Courses

Modelos y Técnicas Experimentales en Investigación Farmacológica.

F. Pérez-Vizcaino, S. Barrigón.

Terapéutica Cardiovascular.

J. Tamargo, E. Delpón, F. Pérez-Vizcaino.

Diseño experimental y análisis estadístico en Farmacología y Farmacocinética.

P. Zuluaga, A. Turrero S, Barrigón, F. Pérez-Vizcaino.

Our masters

Pigmaei gigantum humeris impositi plusquam ipsi gigantes vident



Prof. Juan Tamargo



Prof. John R. Vane



Prof. Timothy D. Warner



Prof. Arthur Weston



Prof. Urs. T Rüegg



Prof. Jane A. Mitchell

Past members & Visiting

- ✓ Begoña Losada (PhD student 2000-2002)
- ✓ Buensuceso Fernández del Pozo (PhD student 1994-96)
- ✓ Cristina Fernández (1995-96)
- ✓ Eva Serna (2003)
- ✓ Federica Lodi (PhD student 2003-07)
- ✓ Francesco Vargas-Macchiuca (Erasmus student 2003)
- ✓ Francisco Zaragoza-Arnaéz (PhD student 1999-2003)
- ✓ José Gustavo López-López (PhD student 1999-2001)
- ✓ Manuel Ibarra (PhD student 2000-2003)
- ✓ Regina Gisbert (2001)
- ✓ Rocio Santiago (PhD student 2001-2003)
- ✓ Susana Fajardo (1999)
- ✓ Tiziana Russo (2004)
- ✓ Valeria Queirolo (Erasmus student 2006)
- ✓ Visitación López-Miranda (2000)



Hard work at the BPS

Science is a lot like sex.
In rare occasions
something useful comes of it,
meanwhile we enjoy doing it.



Francesco & Laura in the lab



With our friends from the Autónoma



Snowing in Maastricht



The Italians cooking pasta at Paco's



Gustavo, Paco and wives Marta and Marbella
enjoying some micheladas" in Puebla