“Peritonitis esclerosante encapsulante (EPS): una visión desde los macrófagos peritoneales”

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Madrid

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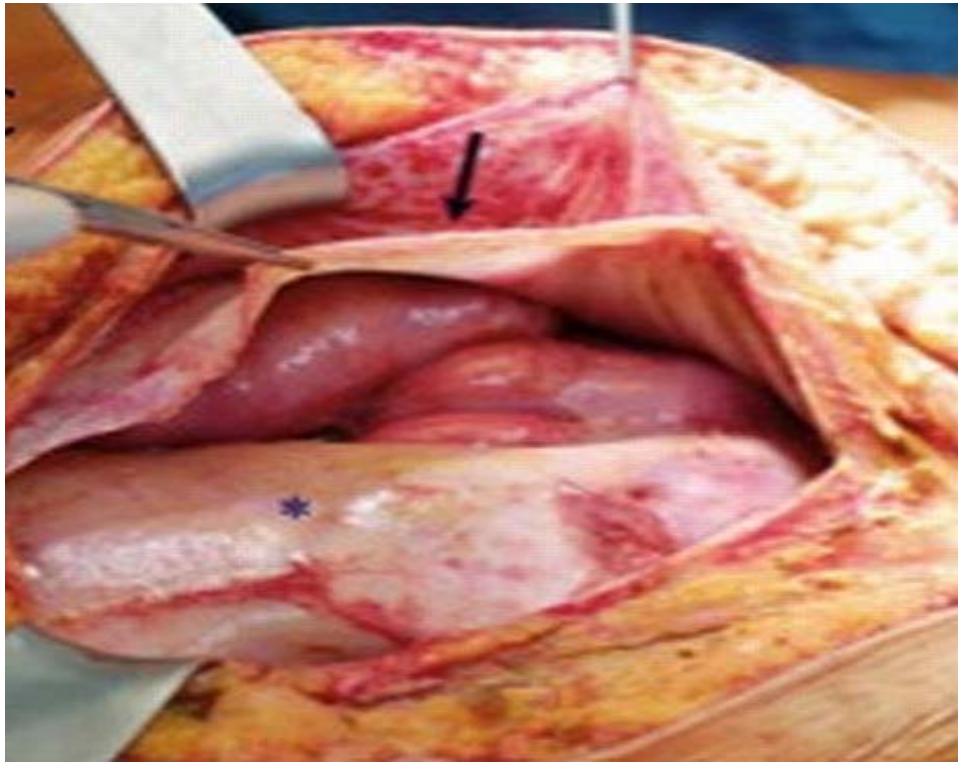
Instituto de Investigación
Hospital Universitario La Paz

La membrana peritoneal, una estructura que bien cuidada tiene potencial de larga vida útil

- Algunos pacientes lo demostraron en la era anterior (18-25 años)
- Para los actuales, deberemos tratar la membrana lo mejor que sepamos

claves del éxito:
conocerla, no agredirla y curarla

En oposición a este idea está la EPS (Peritonitis Esclerosante Encapsulante)



Latus PDI 2013

Peritoneal Dialysis International, Vol. 37, pp. 362–374
www.PDIConnect.com

0896-8608/17 $3.00 + .00

ISPD GUIDELINES/RECOMMENDATIONS

LENGTH OF TIME ON PERITONEAL DIALYSIS AND ENCAPSULATING PERITONEAL SCLEROSIS — POSITION PAPER FOR ISPD: 2017 UPDATE

Edwina A. Brown,[1] Joanne Bargman,[2] Wim van Biesen,[3] Ming-Yang Chang,[4] Frederic O. Finkelstein,[5] Helen Hurst,[6] David W. Johnson,[7] Hideki Kawanishi,[8] Mark Lambie,[9] Thyago Proença de Moraes,[10] Johann Morelle,[11] and Graham Woodrow[12]

TABLE 1
Studies Examining the Epidemiology of EPS*

Country	Time period	Study design	N	Prevalence	EPS epidemiology Incidence rate (/1,000 patient-yrs)	Risk with time	Reference
Italy	1						
Japan	1						
Spain	1980–2012	Single-center, retrospective, observational cohort	679	2.9% (overall) 5.6% (1980–1990) 3.9% (1991–2000) 0.3% (2000–2012)	NA	NA	De Sousa-Amorim *et al.* 2014 (17)

Some studies from Germany (16), Spain (17), Japan (18), Australia (13,19), and the Netherlands (20) have further suggested that the incidence of EPS may be decreasing over time, although the reported incidence/prevalence estimates have been too imprecise to be certain of this. If EPS is indeed becoming less common, the reasons remain uncertain.

Situación actual (2010-2017) de incidencia de la EPS

- **Factor intervenido**
  - Reducción del tiempo en DP
  - Uso de soluciones biocompatibles
  - Uso de Tamoxifeno en situaciones propensas
  - Otros….¿VDR?

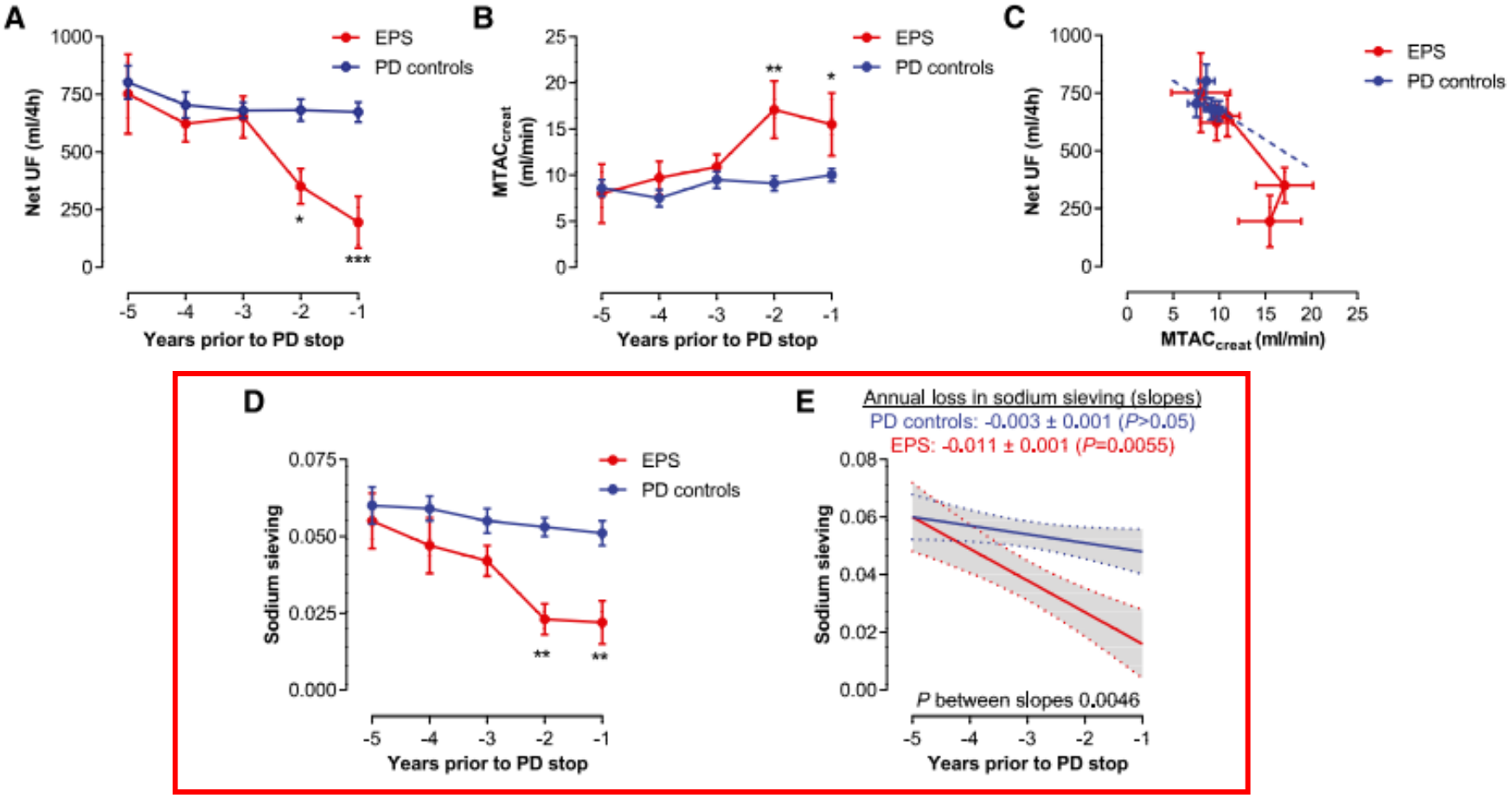
Diagnóstico adelantado de EPS 2017

- **Disminución de transporte de agua libre por engrosamiento del colágeno submesotelial** (*Morelle JASN 2015*)

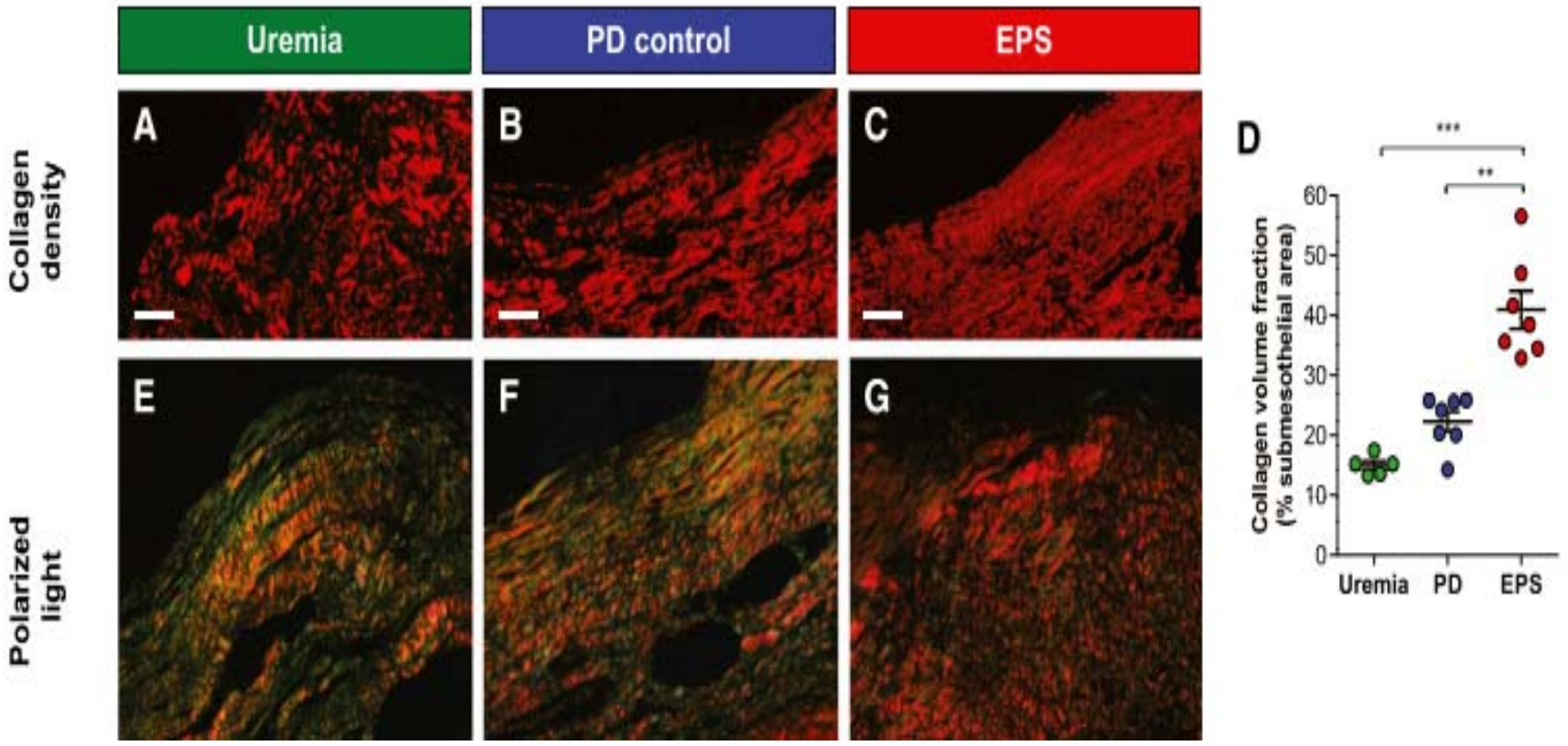
- **Incremento** de producción **de PAI-1** en efluente *(Lopez Barreto 2014)*

Interstitial Fibrosis Restricts Osmotic Water Transport in Encapsulating Peritoneal Sclerosis

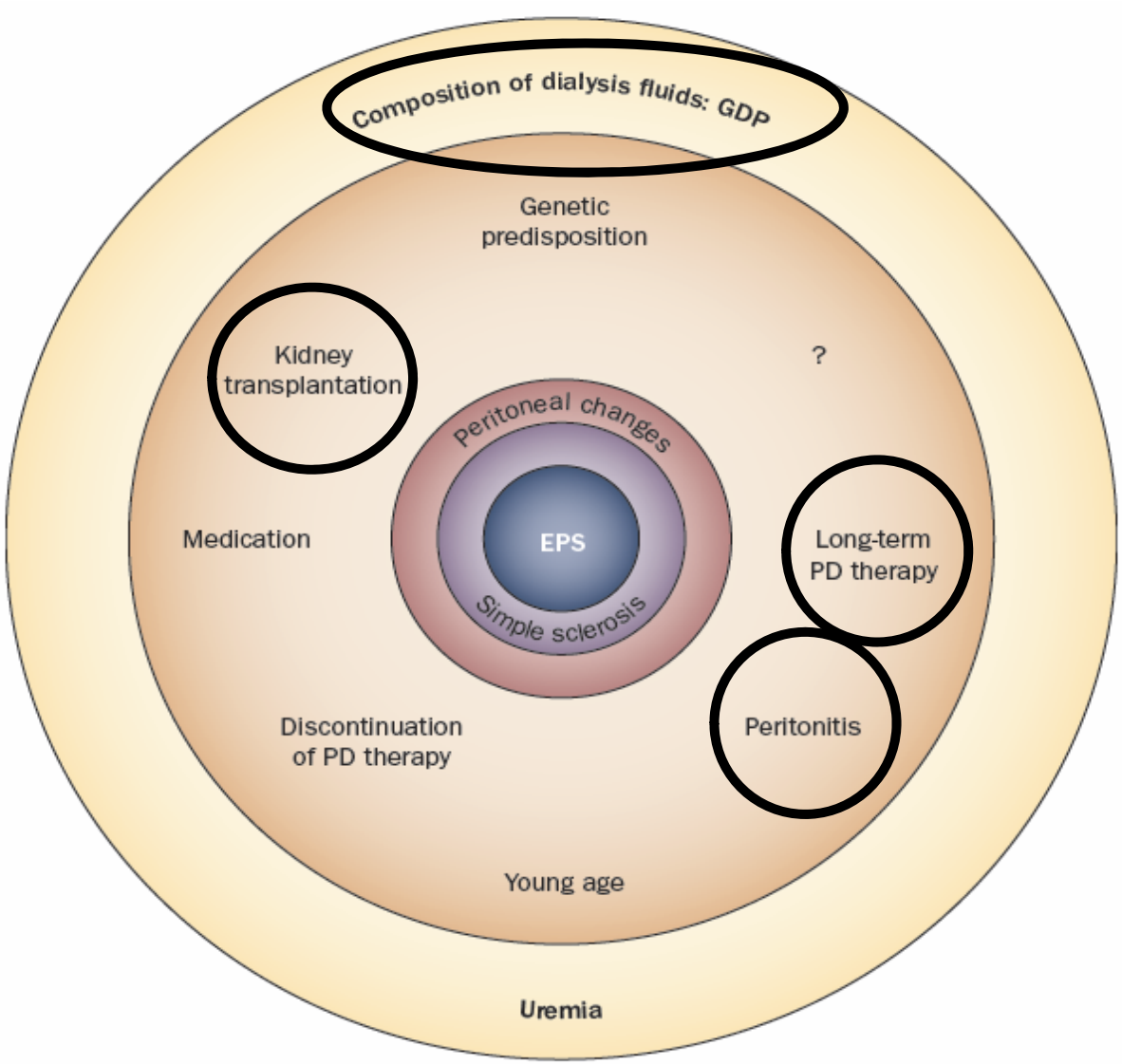
Johann Morelle,* Amadou Sow,* Nicolas Hautem,* Caroline Bouzin,† Ralph Crott,‡ Olivier Devuyst,*§ and Eric Goffin*



Dense peritoneal Interstitium,
but not less water channels (AQP1), is responsible for UF deficiency and lower free water transport



Factores de Riesgo



Análisis proteómico del efluente previo a EPS

Biomarker research to improve clinical outcomes of peritoneal dialysis: consensus of the European Training and Research in Peritoneal Dialysis (EuTRiPD) network

Kidney International (2017) **92,** 824–835; http://dx.doi.org/10.1016/j.kint.2017.02.037

Christoph Aufricht[1], Robert Beelen[2], Matthias Eberl[3], Michel Fischbach[4], Donald Fraser[3], Achim Jörres[5,6], Klaus Kratochwill[7,8], Manuel LópezCabrera[9], Peter Rutherford[10], Claus-Peter Schmitt[11], Nicholas Topley[3] and Janusz Witowski[12]

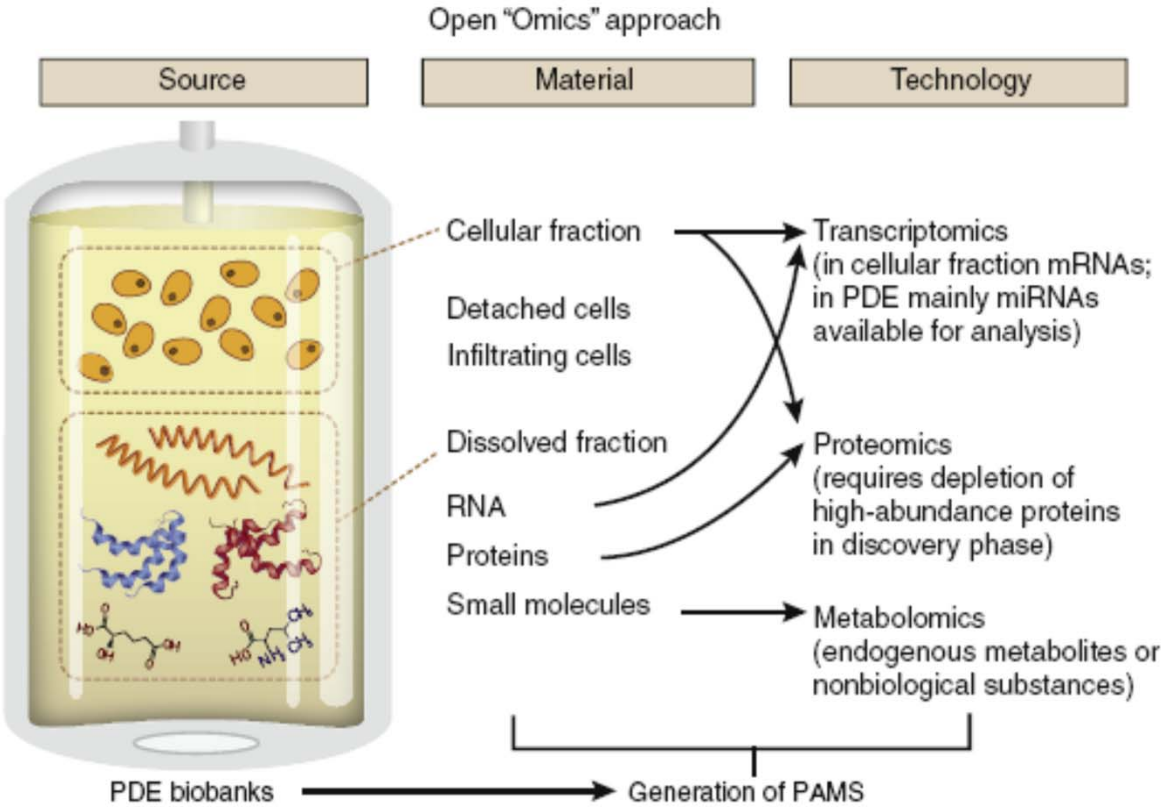


Figure 3 | Nonhypothesis-driven biomarker research following an open omics approach is particularly attractive using peritoneal dialysis effluent (PDE) as a source of sample material. The cellular fraction suspended in PDE can be analyzed using transcriptomics

A prospective, proteomics study identified potential biomarkers of encapsulating peritoneal sclerosis in peritoneal effluent

Vasileios Zavvos[1,2], Anthony T. Buxton[2], Caroline Evans[3], Mark Lambie[4], Simon J. Davies[4], Nicholas Topley[5], Martin Wilkie[2], Angela Summers[6], Paul Brenchley[6], Dimitrios S. Goumenos[1] and Timothy S. Johnson[2]

[1]Department of Nephrology, University Hospital of Patras, Patras, Greece; [2]Academic Nephrology Unit and Sheffield Kidney Institute, University of Sheffield, Sheffield, UK; [3]Proteomics Unit, Chemical Engineering, University of Sheffield, Sheffield, UK; [4]Institute of Applied Clinical Sciences, Keele University, Keele, UK; [5]Wales Kidney Research Unit, Division of Infection and Immunity, Cardiff University School of Medicine, Cardiff, UK; and [6]Kidney Research Laboratories, Manchester Royal Infirmary, Manchester, UK

Encapsulating peritoneal sclerosis (EPS) is a potentially devastating complication of peritoneal dialysis (PD).

Kidney International (2017) **92,** 988–1002; http://dx.doi.org/10.1016/j.kint.2017.03.030

Collagen I and Gamma-Actin elevated five years prior EPS

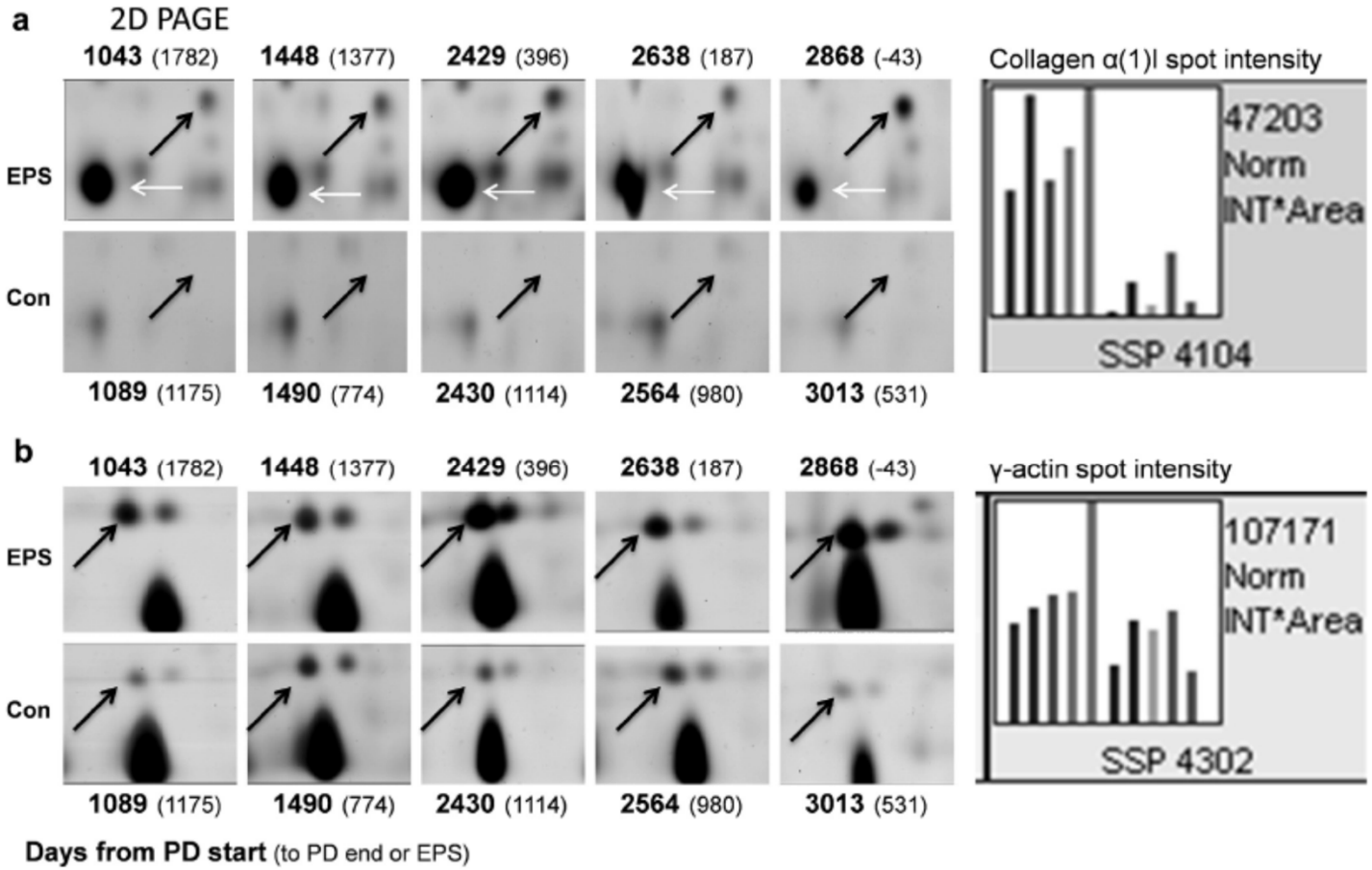


Figure 3 | Collagen a(1)I (a) and γ-actin (b) are elevated in a patient with encapsulating peritoneal sclerosis (EPS) 5 years before EPS diagnosis (exemplar images). Exemplar images are from GFS patients G05-072 (confirmed EPS) and G05-068 (stable membrane function). Five

Complement elevated five years prior EPS

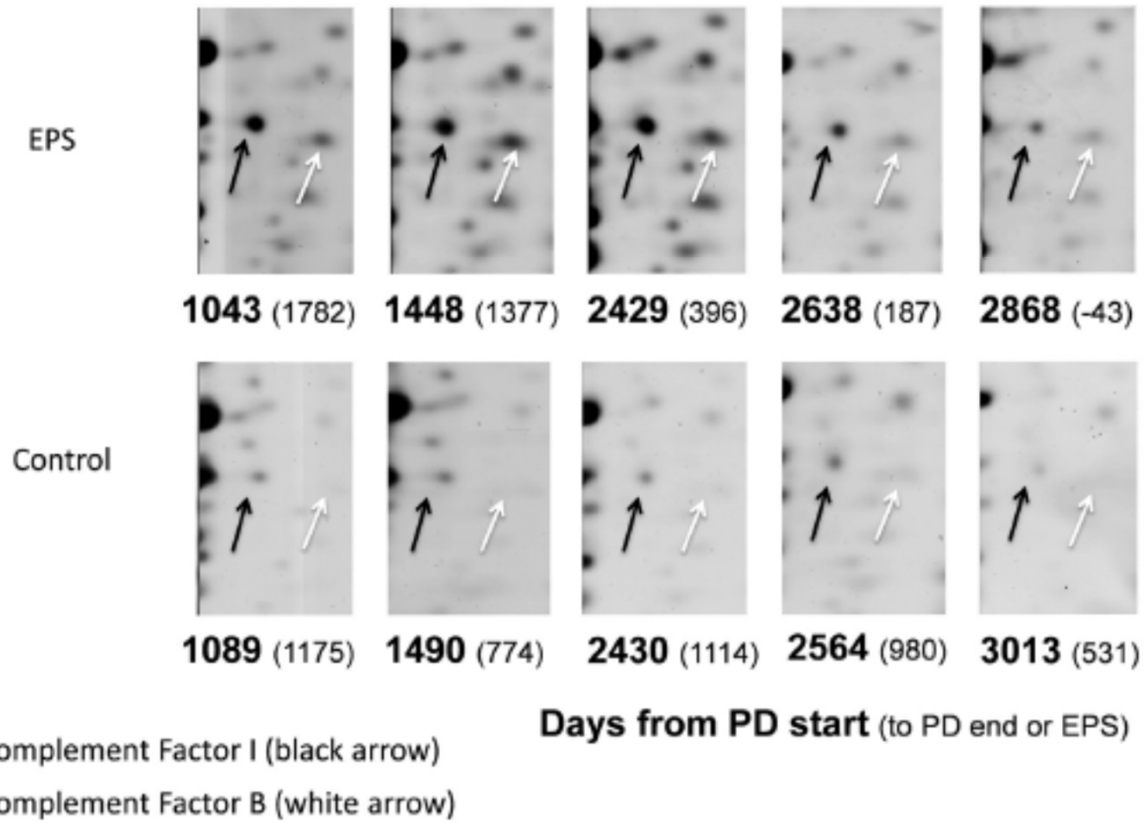


Figure 4| Complement factors I and B increase in encapsulating peritoneal sclerosis (EPS) 5 years before diagnosis (exemplar images)..

Actin, Collagen α1 and Complement

Table 2 | Top potential hits for EPS biomarkers from 2D SDS PAGE and iTRAQ proteomics

Protein	Change in EPS PDE: 2D gel FP	2D gel MP	iTRAQ FP	iTRAQ MP	Frequency of occurrence in 2D gels (times of change)
γ–Actin	↑				6 of 6 patients (early or elevated >3 yr before EPS)
Collagen-α1(I)	↑				6 of 6 patients (early or >3 yr before EPS)
α1 Antitrypsin	↓		↓		3 of 6 patients plus iTRAQ (slow reduction with time very low at EPS)
α-2-HS-glycoprotein-B			↑	↑	NA (mid or 6–12 mo before EPS)
Serotransferrin			↑		NA (early or >12 months before EPS)
Complement C4B			↑		NA (early or >12 months before EPS)
Complement B	↑			↑	5 of 6 patients (early or elevated ≤6 years before EPS)
Complement I	↑			↑	5 of 6 patients (early or elevated ≤6 years before EPS)
Apolipoprotein A-IV	↓		↓	↓	3 of 6 plus iTRAQ (late or from 12 months; −80% at EPS)
Orosomucoid-1			↑	↑	NA (Early or >1 yr before EPS)
Intelectin-1		↑		↑	3 of 3 patients and pooled (late or within 6 mo of EPS)
Dermatopontin		↑			3 of 3 patients (unknown)
RBP-4		↑			3 of 3 patients (unknown)
Gelsolin				↑	Pooled (mid or elevated ≤1 yr before EPS)
Hemaglobin b				↑	Pooled (late or elevated ≤12 mo before EPS)
Apolipoprotein A-II				↓	Pooled (late or low for ≤12 mo before EPS)

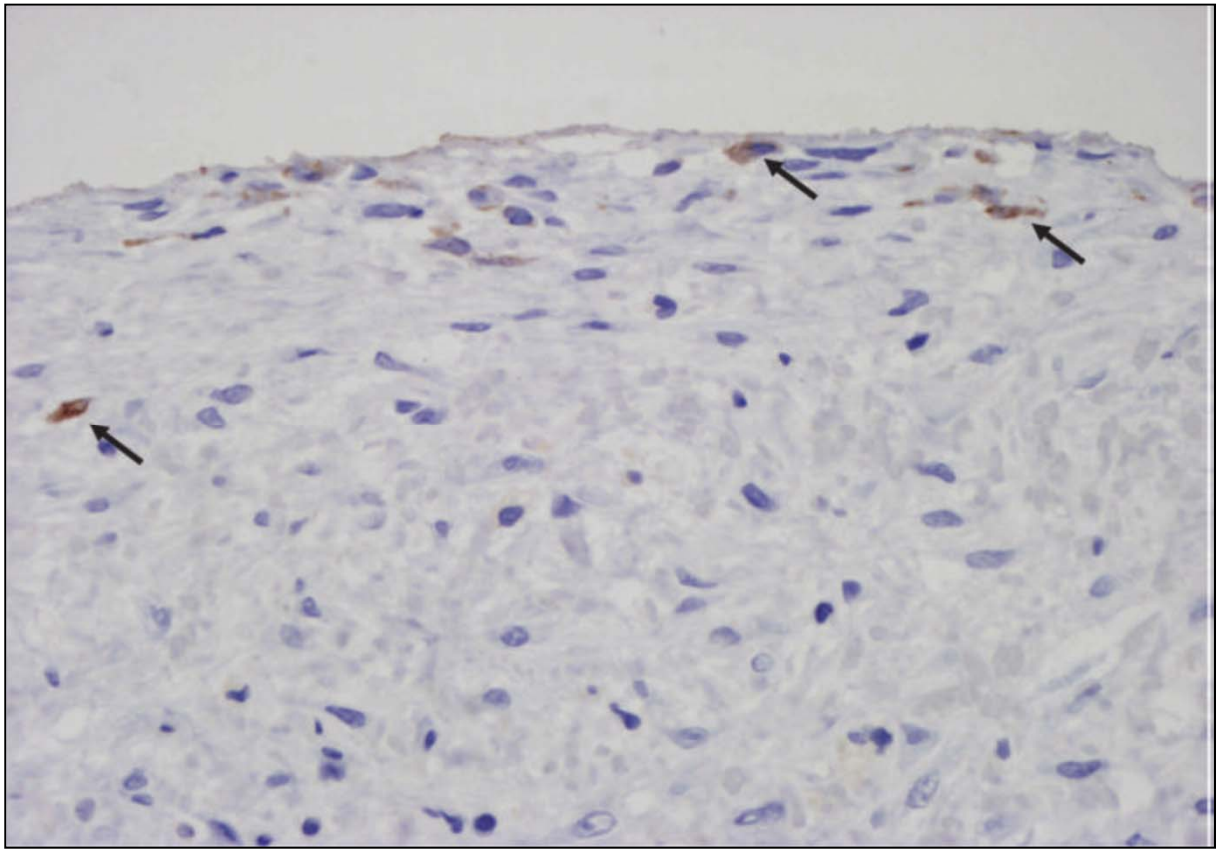
El paso de la esclerosis/fibrosis peritoneal a la EPS

Loureiro J, et al

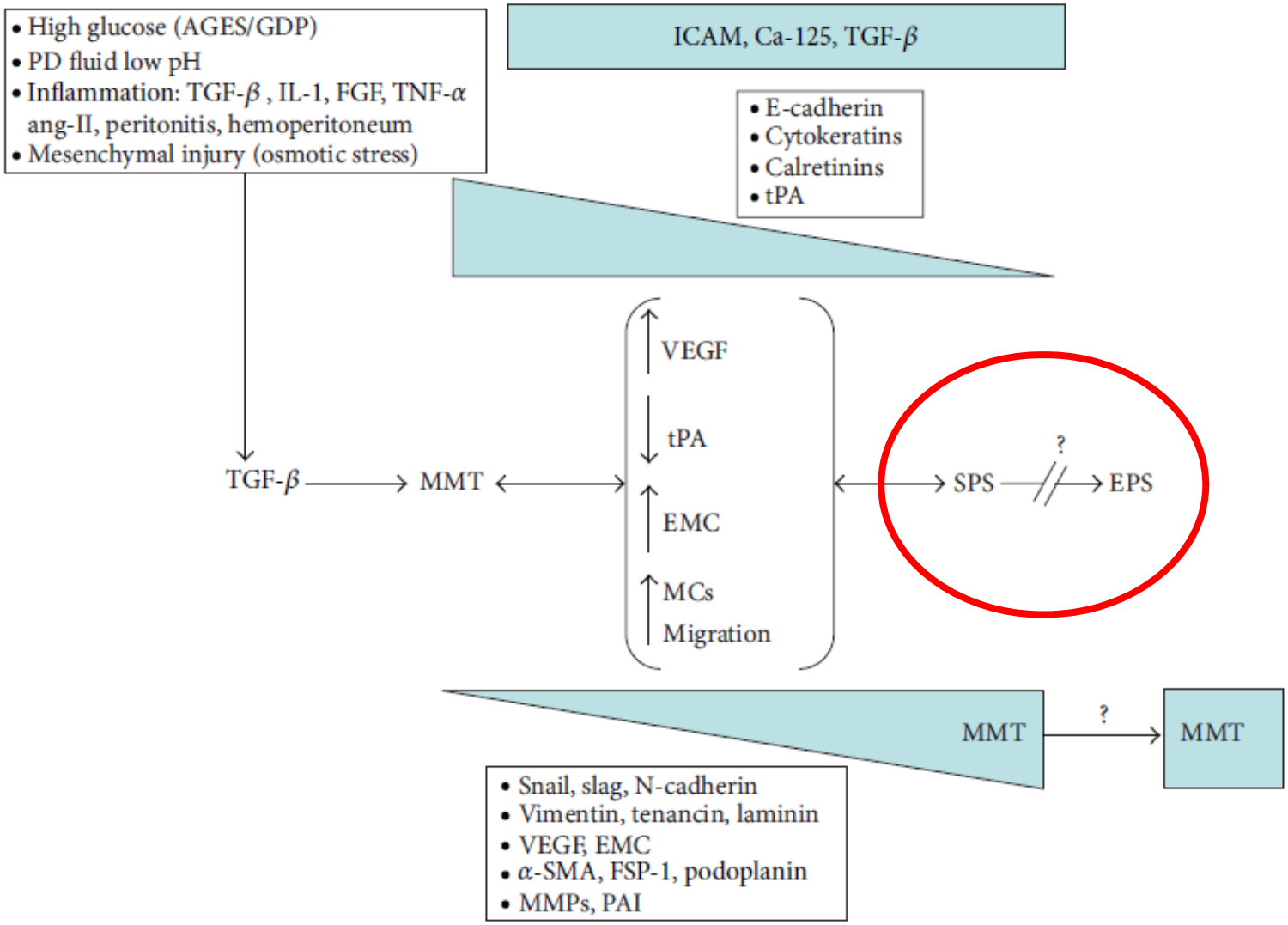
Are the Mesothelial-to-Mesenchymal Transition, Sclerotic Peritonitis Syndromes, and Encapsulating Peritoneal Sclerosis Part of the Same Process?

Int J Nephrol. 2013; 2013: 263285

Evidencia de MMT en EPS

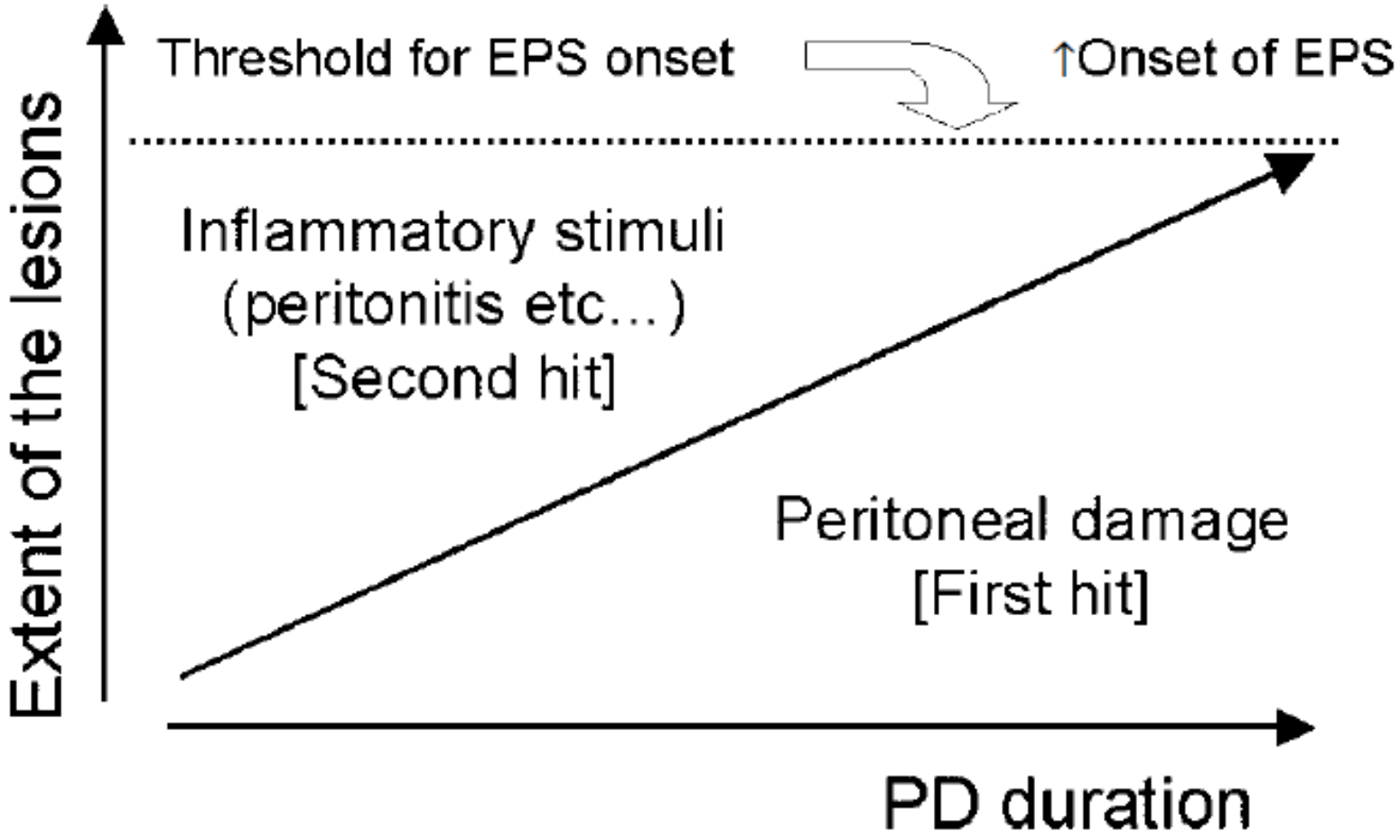


Fisiopatología de la respuesta de la membrana a los líquidos bioincompatibles



Loureiro et al. Int J Nephrol 2013

Teoría del doble golpe
"Two-hit" Theory

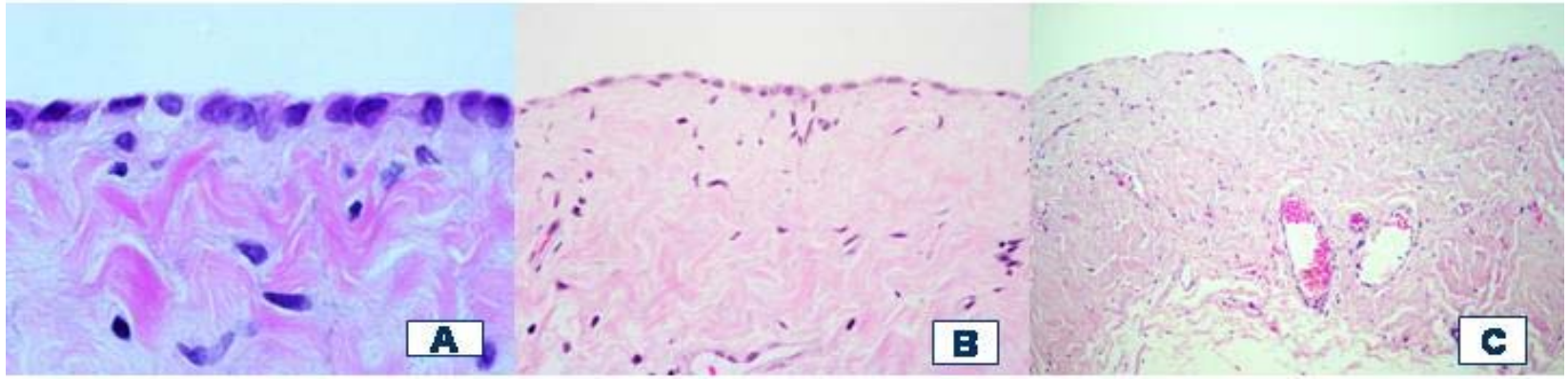


Honda et al. PDI 2005

Procesos clave en
el primer golpe
sobre la membrana

- la fibrosis primaria
- la inflamación

La Fibrosis primaria dependiente de la Transición Mesotelio-Mesenquimal



No fibrosis

Diferentes grados de fibrosis

Peritoneal Dialysis International, Vol. 36, pp. 129–134
www.PDIConnect.com

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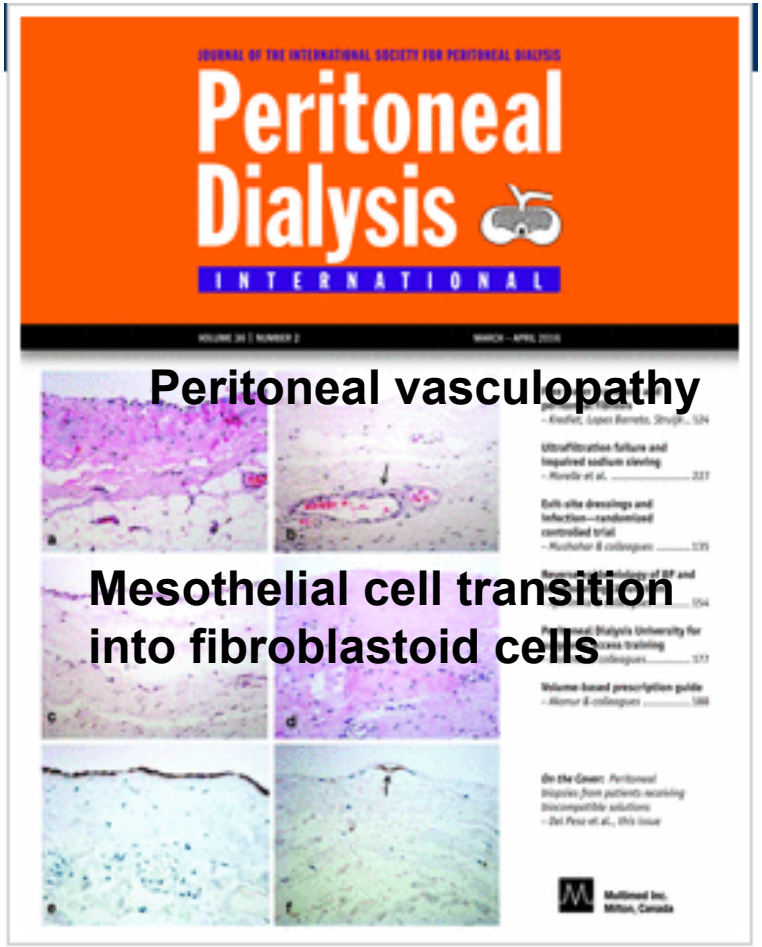
ORIGINAL ARTICLES

BIOCOMPATIBLE DIALYSIS SOLUTIONS PRESERVE PERITONEAL MESOTHELIAL CELL AND VESSEL WALL INTEGRITY. A CASE-CONTROL STUDY ON HUMAN BIOPSIES

Gloria del Peso,[1] José Antonio Jiménez-Heffernan,[2] Rafael Selgas,[1] César Remón,[3] Marta Ossorio,[1] Antonio Fernández-Perpén,[4] José Antonio Sánchez-Tomero,[4] Antonio Cirugeda,[5] Erika de Sousa,[1] Pilar Sandoval,[6] Raquel Díaz,[1] Manuel López-Cabrera,[6] and María Auxiliadora Bajo[1]

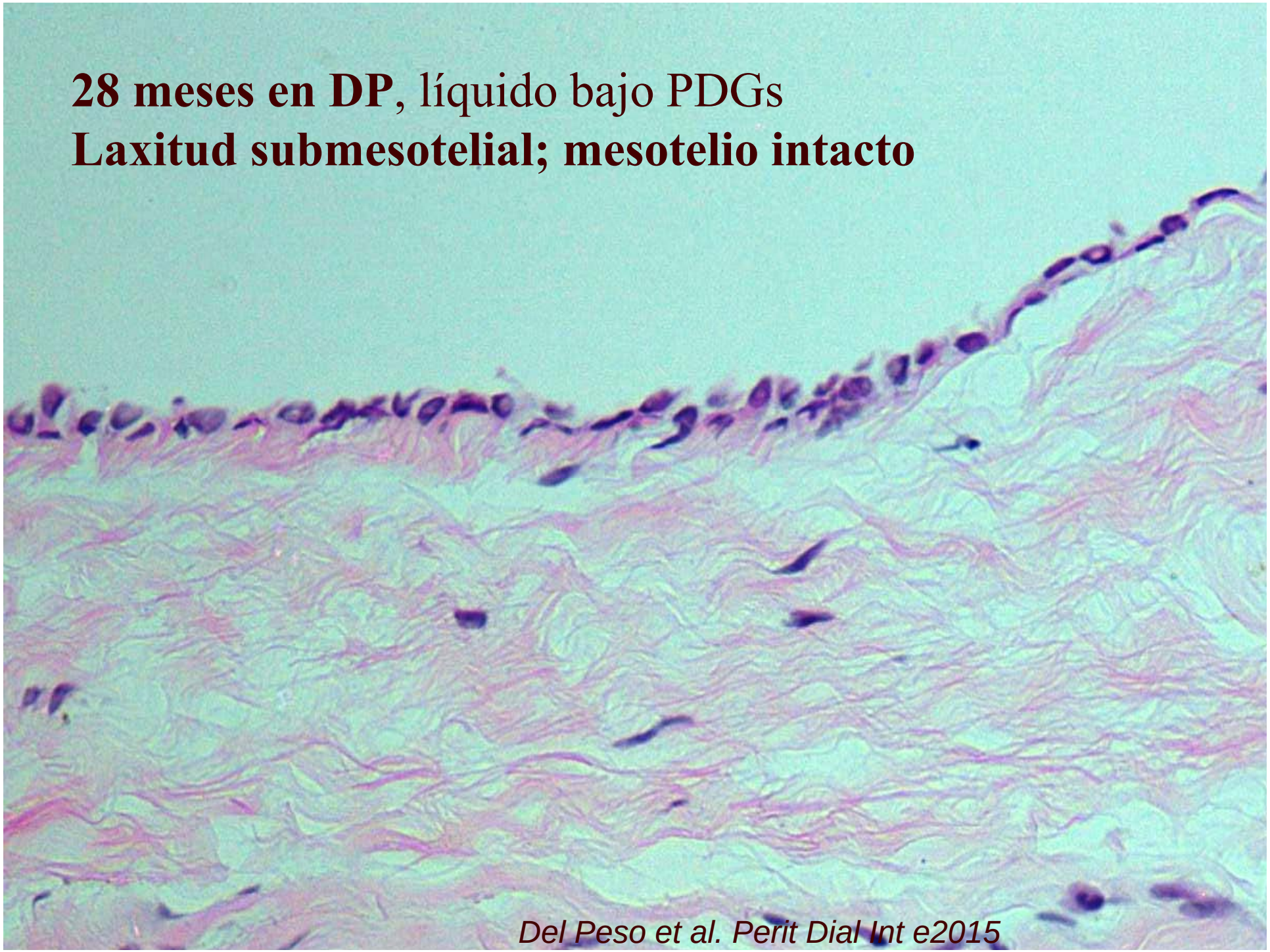


Biopsias peritoneales con líquidos biocompatibles durante trasplante renal y en condiciones normales

Del Peso et al. Perit Dial Int (2016)

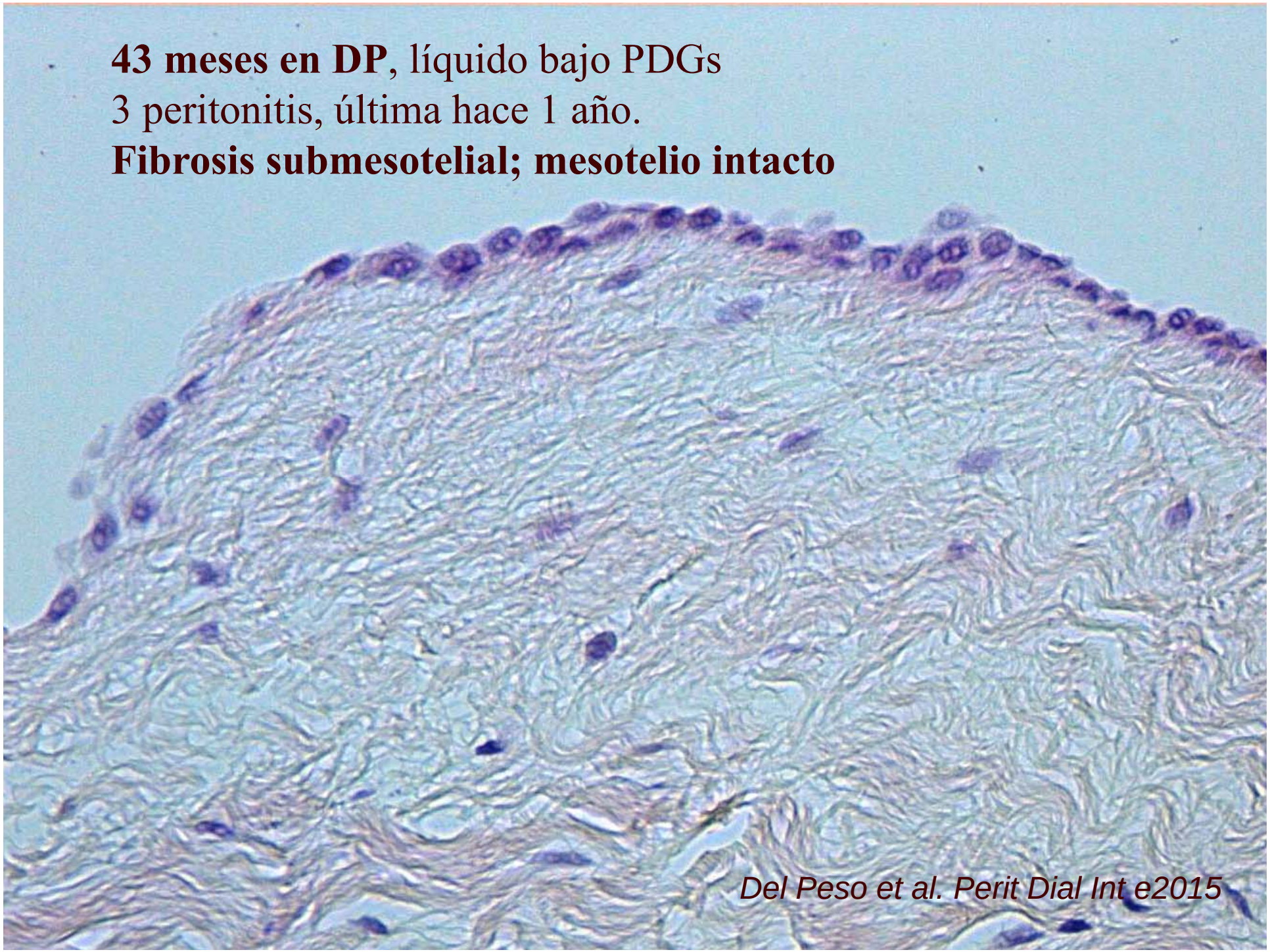
- **23 pacientes**
- Destaca
  - **preservación de la capa mesotelial**
  - **ausencia de vasculopatia**
    tras periodos medios de tiempo en DP

28 meses en DP, líquido bajo PDGs
Laxitud submesotelial; mesotelio intacto



Del Peso et al. Perit Dial Int e2015

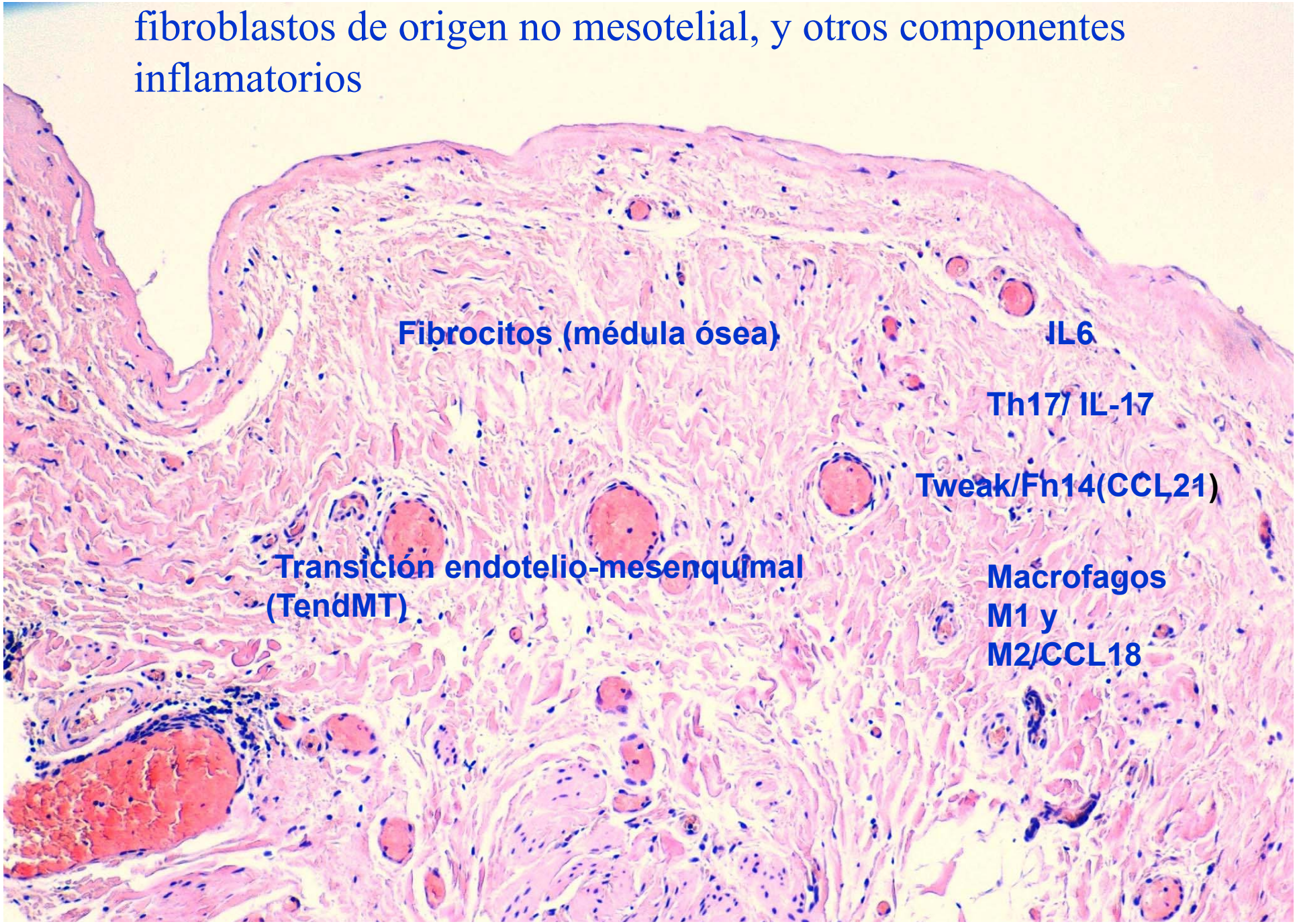
43 meses en DP, líquido bajo PDGs
3 peritonitis, última hace 1 año.
Fibrosis submesotelial; mesotelio intacto



Del Peso et al. Perit Dial Int e2015

Preservación mesotelial, fibrosis, angiogenesis=

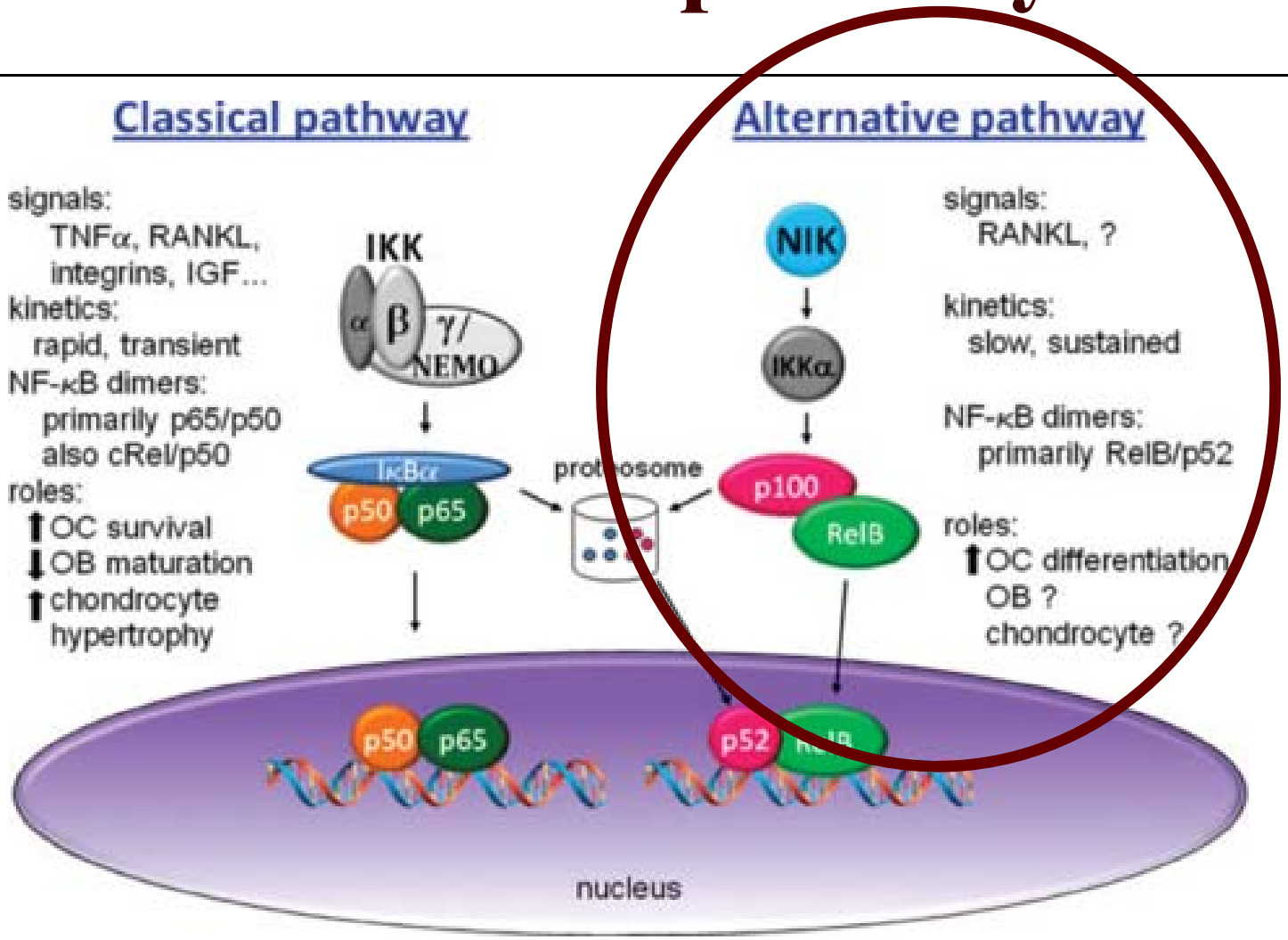
fibroblastos de origen no mesotelial, y otros componentes inflamatorios



Sistemas en la inflamación peritoneal

- IL-6
- Macrófagos M2/CCL18
- Tweak/Fn14 (Macrófagos M1/CCL21)
- Th17 / IL17A

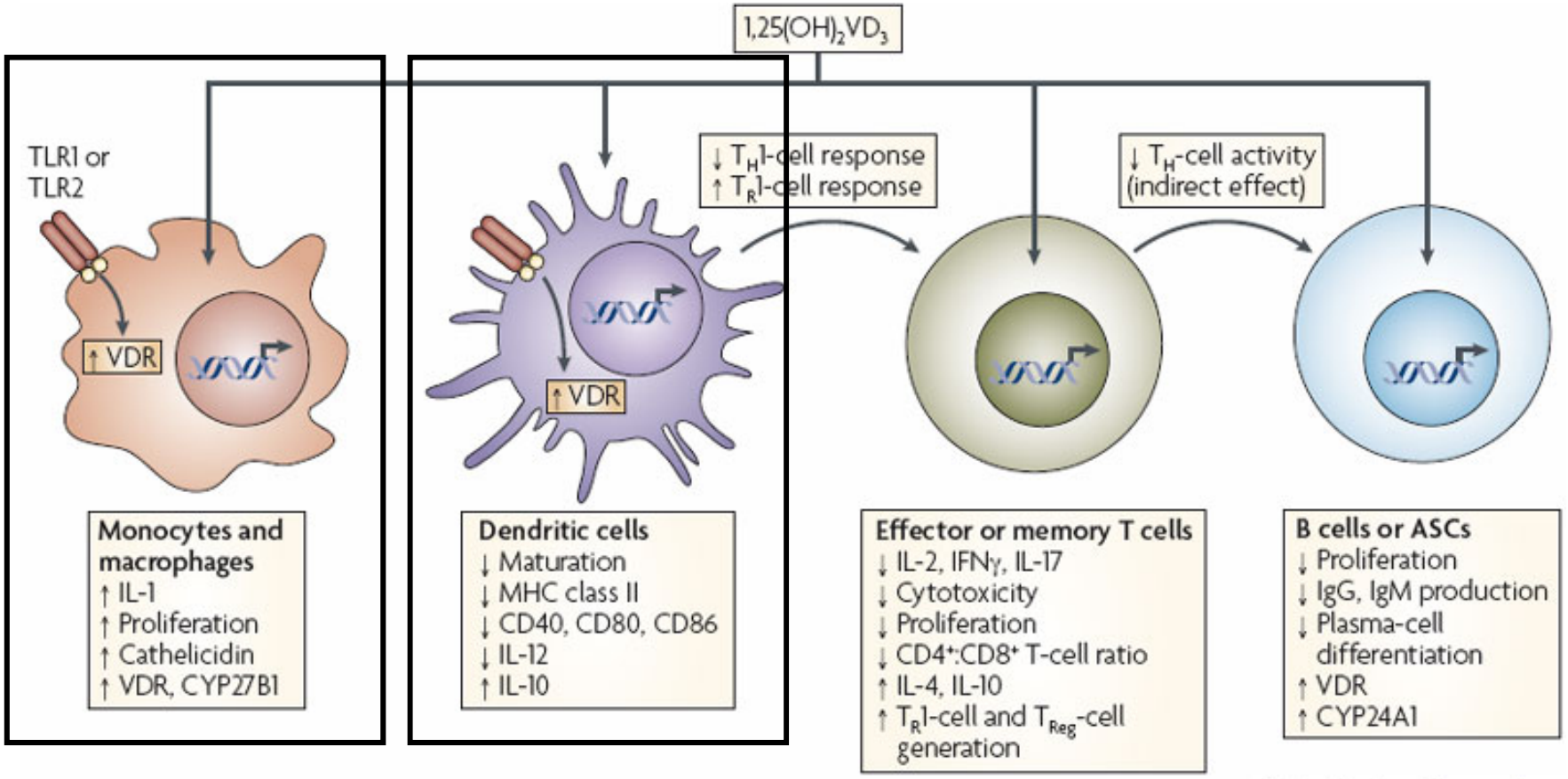
NFκB activation pathways



Vitamin D Receptor in macrophages

nature REVIEWS IMMUNOLOGY

J. Rodrigo Mora, Makoto Iwata & Ulrich H. von Andrian
***Nature Reviews Immunology* 8, 685-698 (2008)**



1,25 VitD and inhibition of sclerosis

- *Li Y, et al.*

  1,25-dihydroxyvitamin D inhibits renal interstitial myofibroblast activation by inducing hepatocyte growth factor expression.

  Kidney Int 68 (2005): 1500–1510.

- *Artaza JN, et al*

  Vitamin D reduces the expression of collagen and key profibrotic factors by inducing an antifibrotic phenotype in mesenchymal multipotent cells.

  J Endocrinol 2009: 207–221.

ARTICLE IN PRESS

www.kidney-international.org

basic research

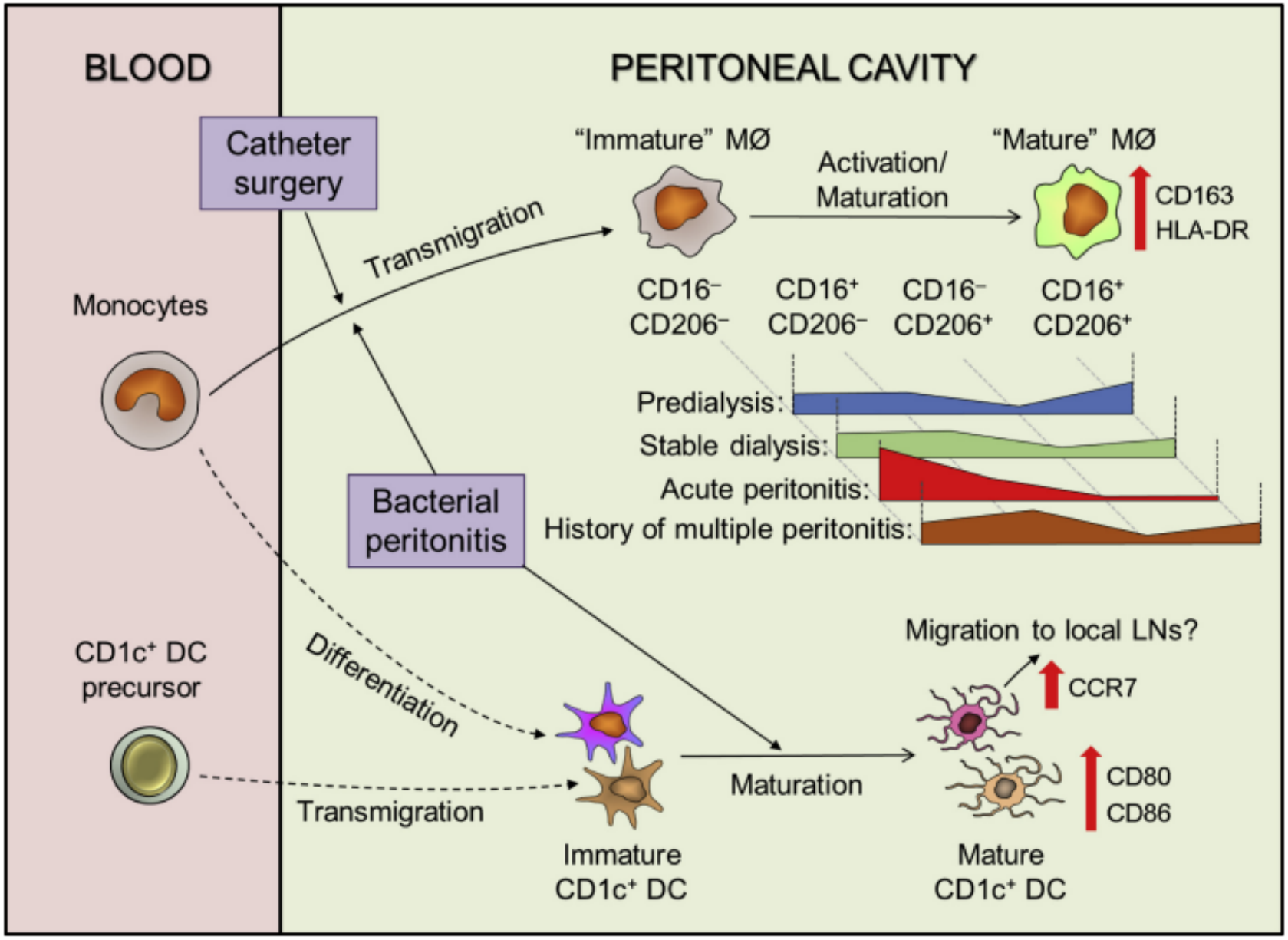
Peritoneal macrophage heterogeneity is associated with different peritoneal dialysis outcomes

OPEN

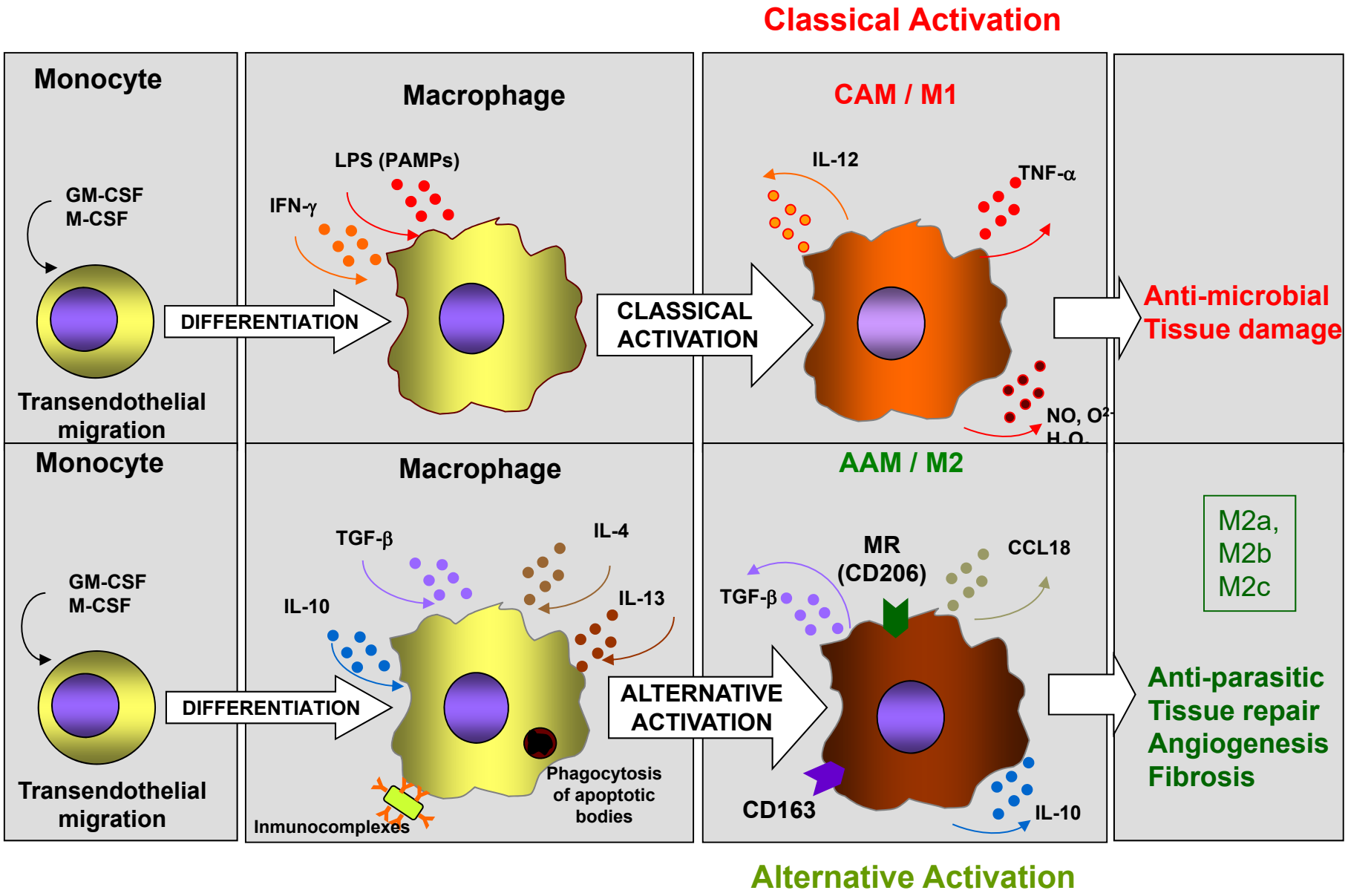
Chia-Te Liao[1], Robert Andrews[1], Leah E. Wallace[1], Mohd Wajid A. Khan[1], Ann Kift-Morgan[1], Nicholas Topley[2], Donald J. Fraser[1,2] and Philip R. Taylor[1]

[1]Systems Immunity University Research Institute and Division of Infection and Immunity, Cardiff University School of Medicine, Heath Park, Cardiff, UK; and [2]Wales Kidney Research Unit, Cardiff University School of Medicine, Heath Park, Cardiff, UK

Kidney International (2016) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2016.10.030



Kidney International (2016) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2016.10.030



Activation of Macrophages according to stimulus

The interaction between type 2 macrophages (M2) and myofibroblasts develops fibrosis

Review

Trends in Immunology Vol.31 No.3

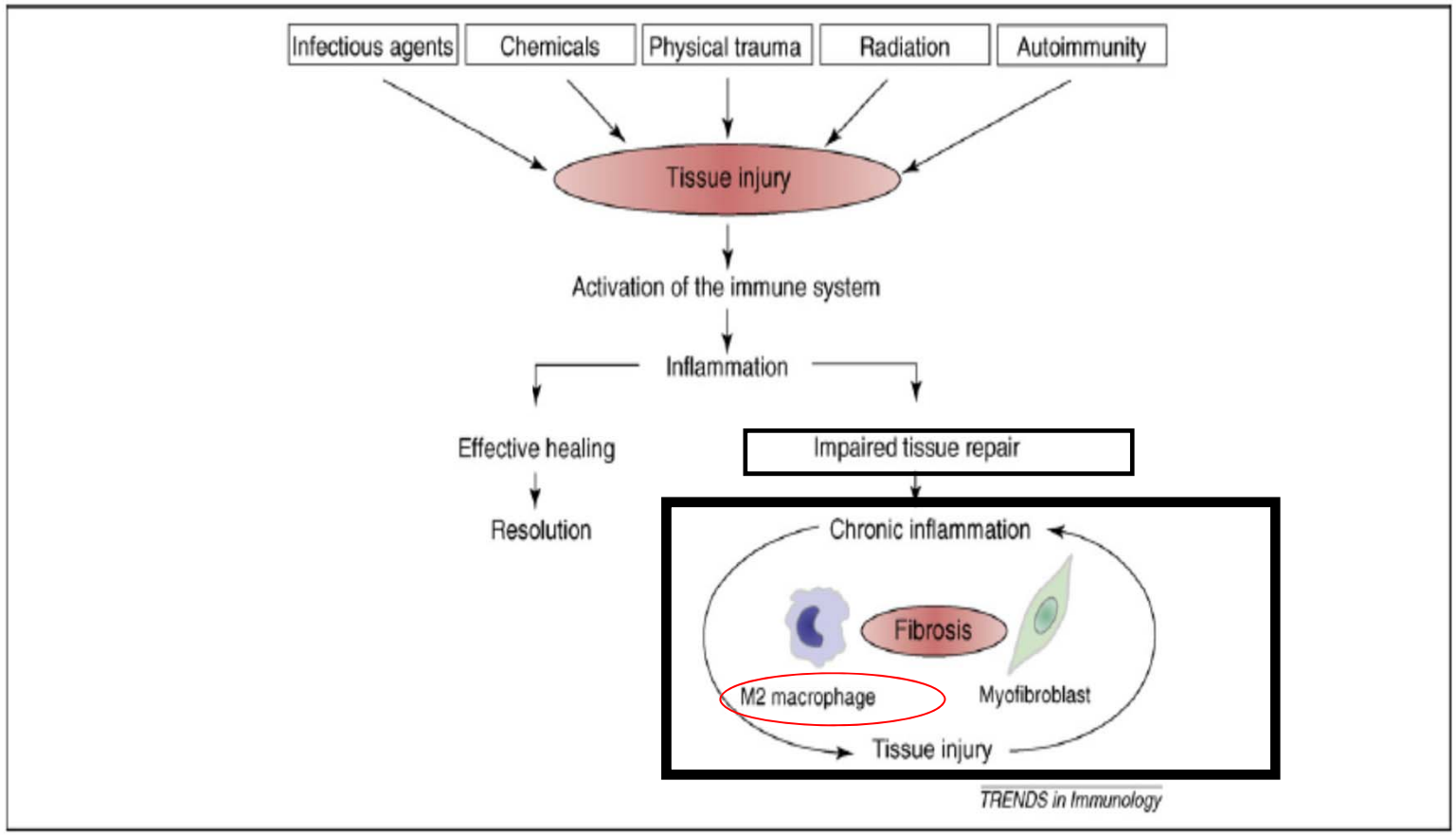


Figure 1. Pathogenesis of fibrosis. Tissue injuries, caused by infection, chemicals, mechanical stress or autoimmune reactions, activate the immune system and repair mechanisms. Effective healing is usually characterized by a dominant Th1 response, whereas a shift of the balance towards Th2 cells, alternatively-activated (M2) macrophages, and myofibroblasts leads to chronic inflammation that can ultimately result in fibrosis.

Wick G. et al. Trends Immunol 2010

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 157834, 14 pages
http://dx.doi.org/10.1155/2015/157834

Research Article

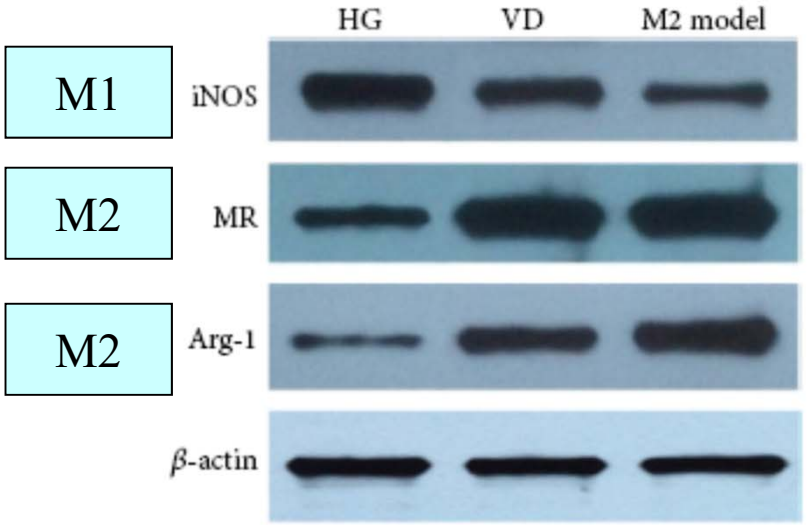
1,25-Dihydroxyvitamin D_3 Promotes High Glucose-Induced M1 Macrophage Switching to M2 via the VDR-PPARγ Signaling Pathway

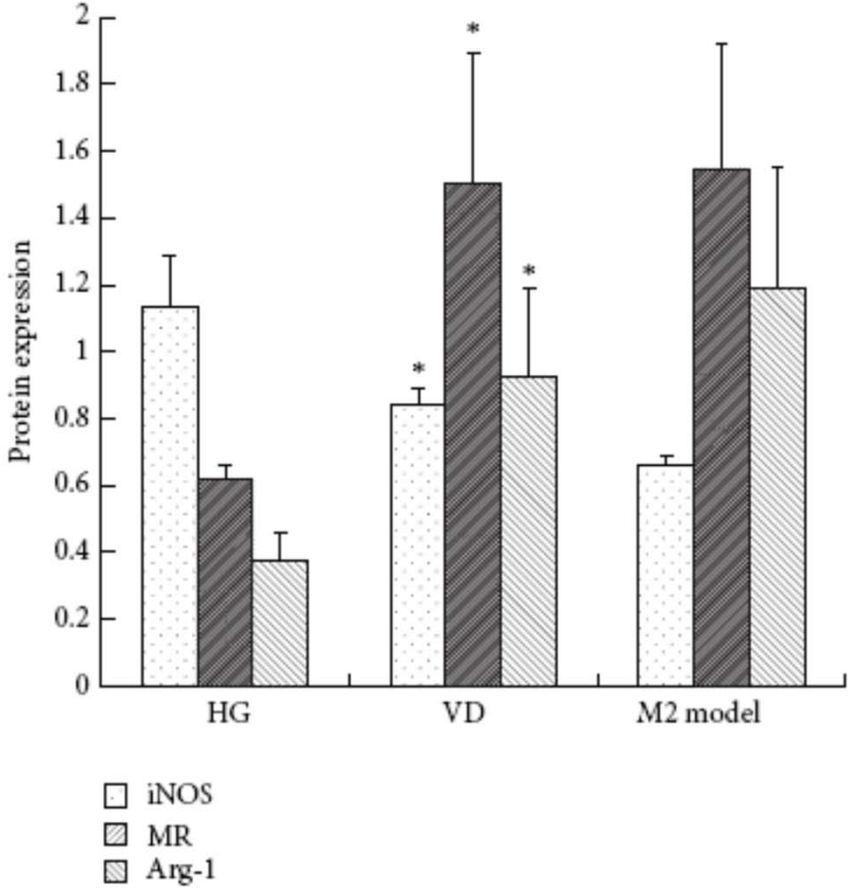
Xiaoliang Zhang, Min Zhou, Yinfeng Guo, Zhixia Song, and Bicheng Liu

RAW264.7 macrophages model:

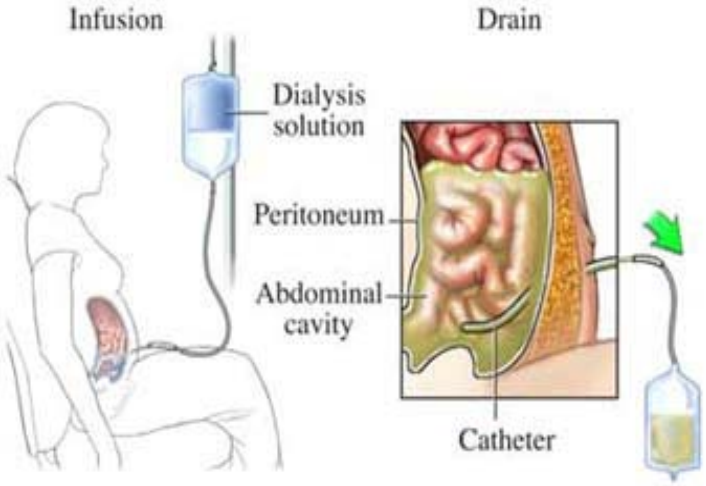
-High glucose switches to M1
-1,25D3 inhibits M1 and enhances M2
- This requires co-activation of PPARγ

The effect of 1,25(OH)2D3 on M1/M2 macrophage-specific markers





Peritoneal dialysis as a fibrosis model



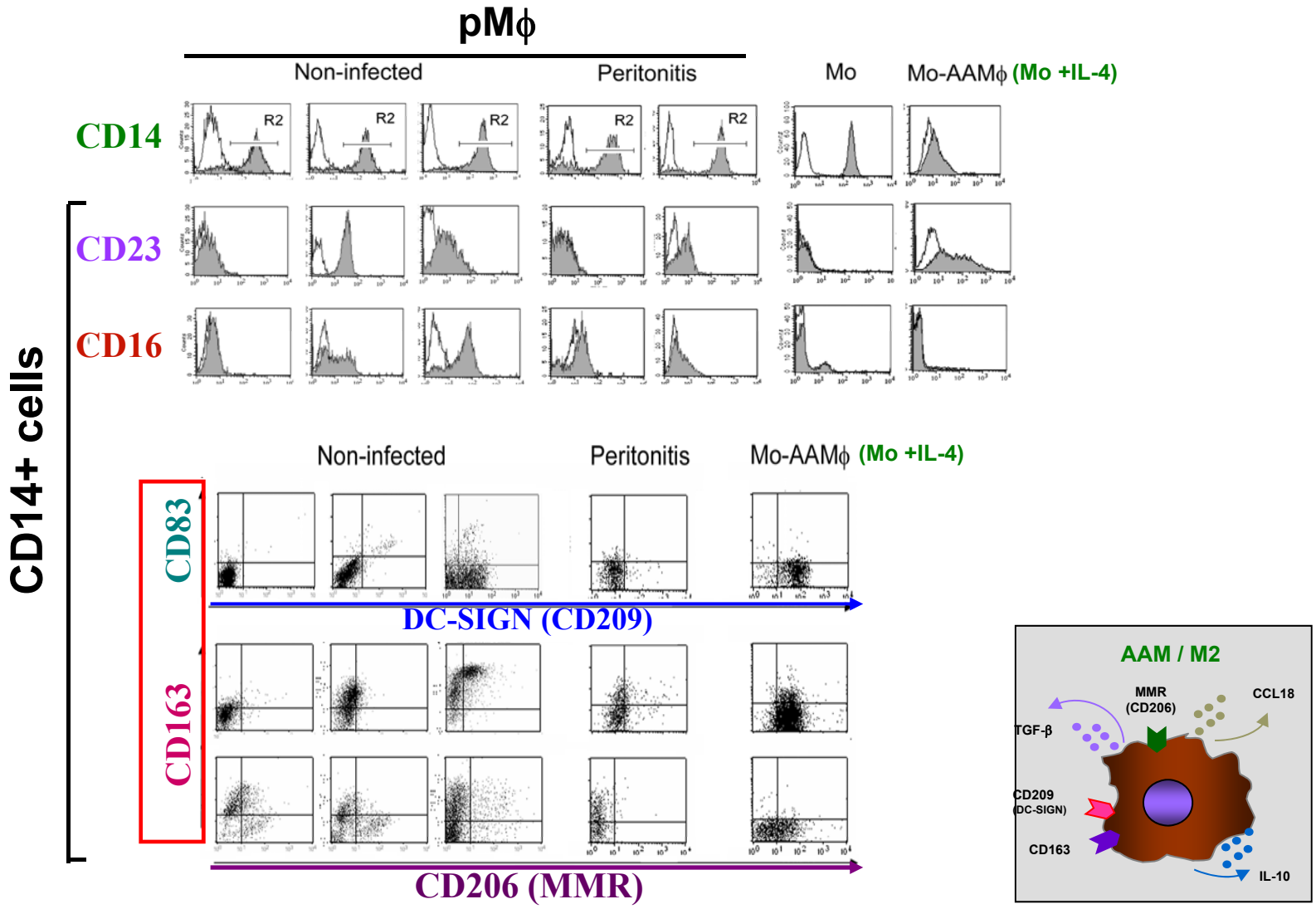
Nephrol Dial Transplant (2011) 26: 2995–3005
doi: 10.1093/ndt/gfq771
Advance Access publication 15 February 2011

Alternative activation of macrophages in human peritoneum: implications for peritoneal fibrosis

Teresa Bellón[1], Virginia Martínez[1], Baltasar Lucendo[1], Gloria del Peso[2], María José Castro[2], Luiz S. Aroeira[1], Aranzazu Rodríguez-Sanz[1], Marta Ossorio[2], Rafael Sánchez-Villanueva[2], Rafael Selgas[2] and María Auxiliadora Bajo[2]

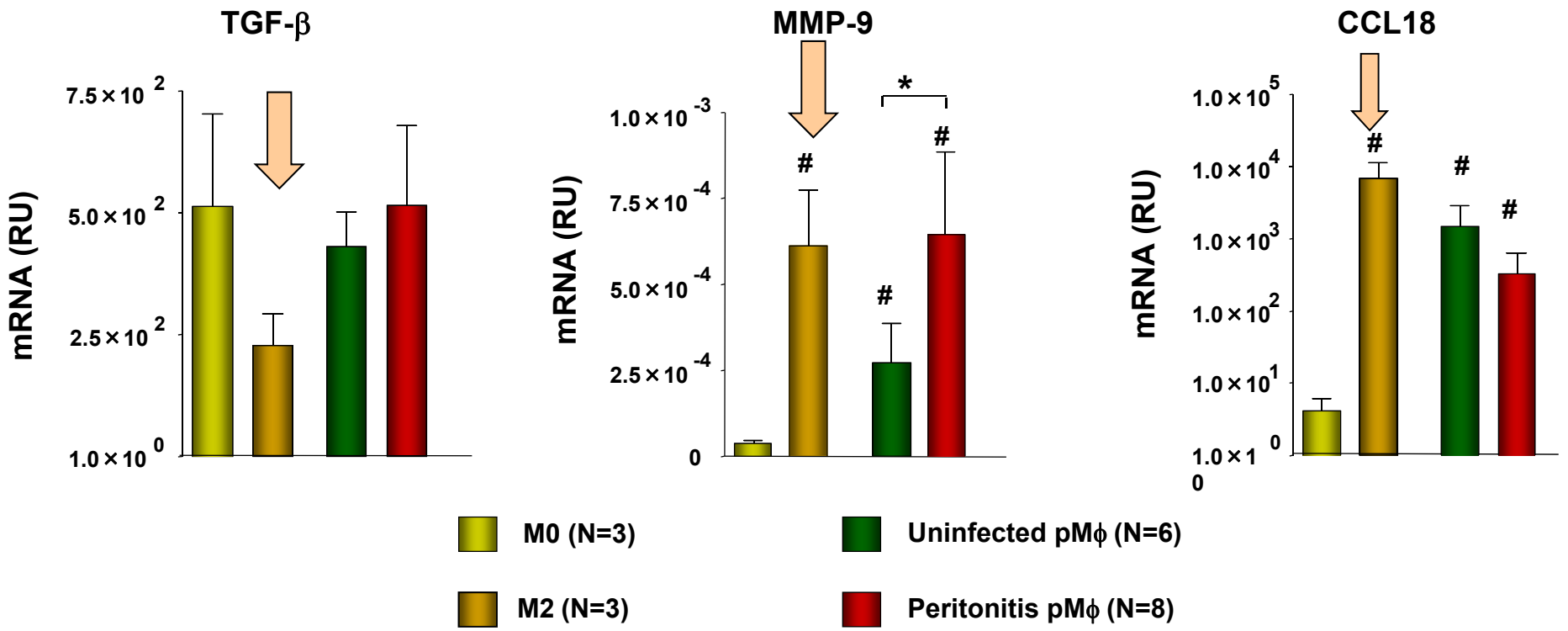
[1]Research Unit, Hospital Universitario 'La Paz'-FIBHULP, Madrid, Spain and [2]Nephrology Department, Hospital Universitario 'La Paz', Madrid, Spain

Peritoneal effluent macrophages (CD14+) show a heterogeneous phenotype, including M2 (AAM) phenotype (CD209, CD206)



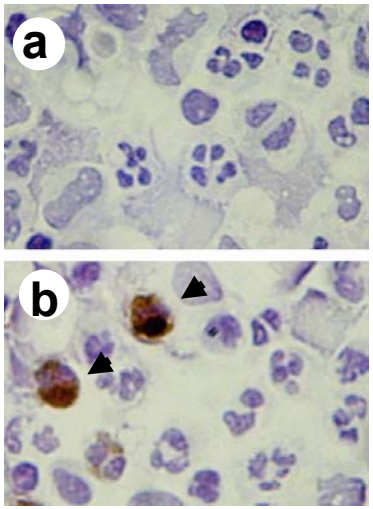
Flow cytometry analysis of cell surface expression of several macrophage-specific receptors, some of which have been reported to be induced in M2/AAMf

Peritoneal M2 macrophages express soluble mediators: TGF-β, MMP9 and CCL18

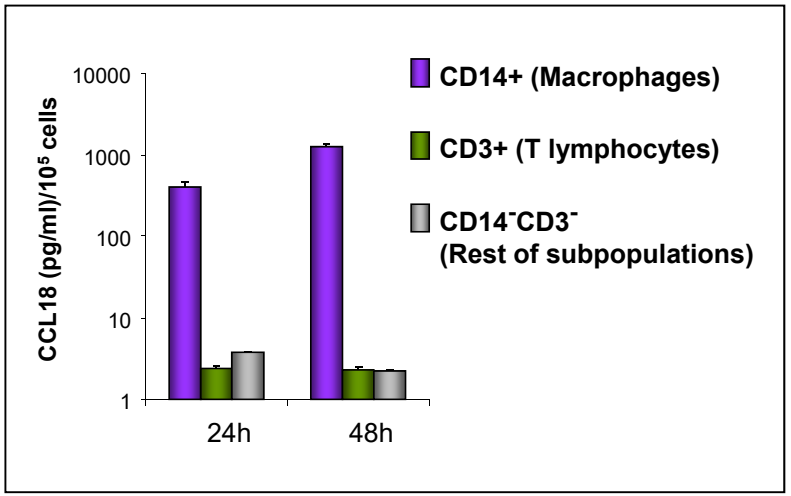


M2 are the principal source of CCL18 at the peritoneum

Control serum



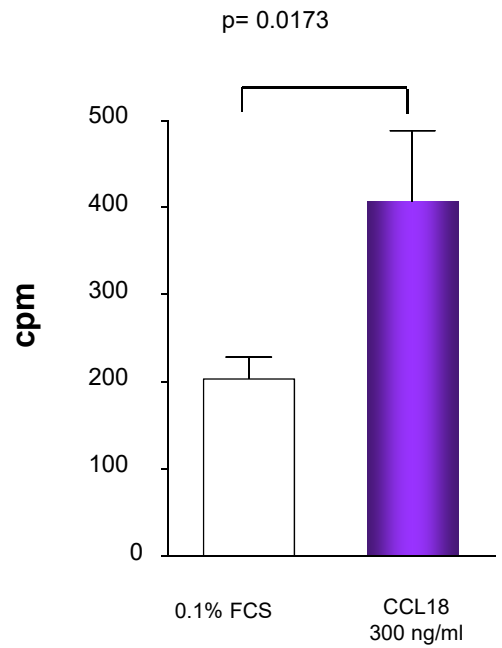
Anti-CCL18



There is a direct correlation between M2 CCL18 expression and fibroblast proliferation

D

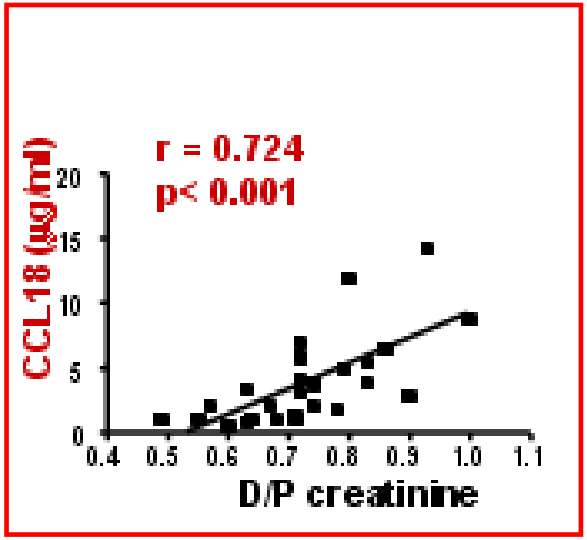
Peritoneal Fibroblast Proliferation

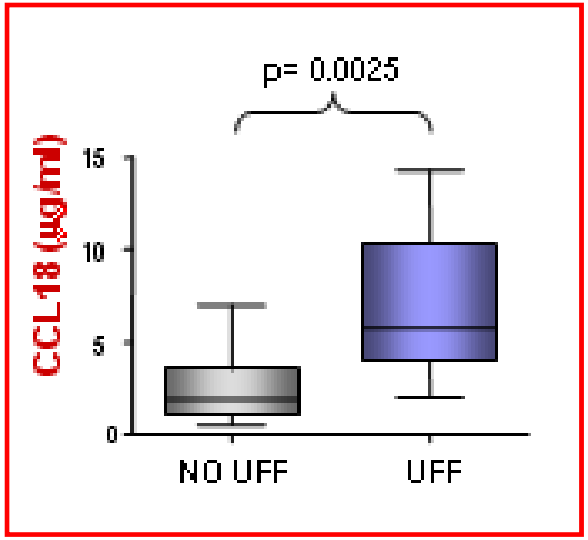


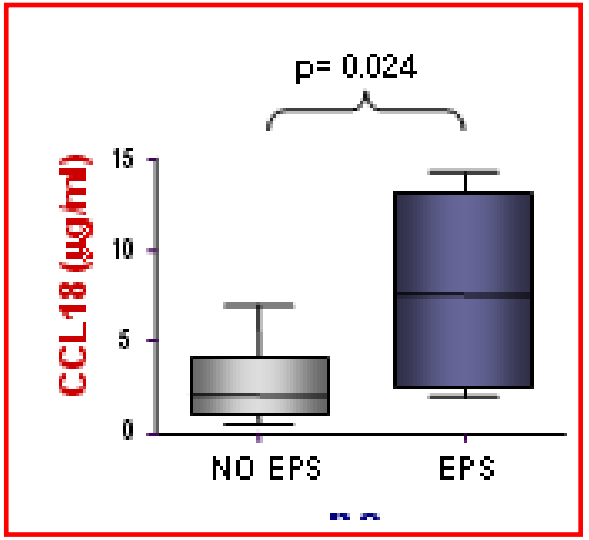
Elevated peritoneal effluent CCL18 levels relate to creatinine D/P and associate with ulterior

Ultrafiltration Failure and

Encapsulating Peritoneal Sclerosis (EPS)







PLOS ONE

RESEARCH ARTICLE

Sustained low peritoneal effluent CCL18 levels are associated with preservation of peritoneal membrane function in peritoneal dialysis

Marta Ossorio[1], María Auxiliadora Bajo[1‡], Gloria del Peso[1], Virginia Martínez[2], María Fernández[1], María José Castro[1], Aranzazu Rodríguez-Sanz[2], Rosario Madero[3], Teresa Bellón[2‡*], Rafael Selgas[1,2‡]

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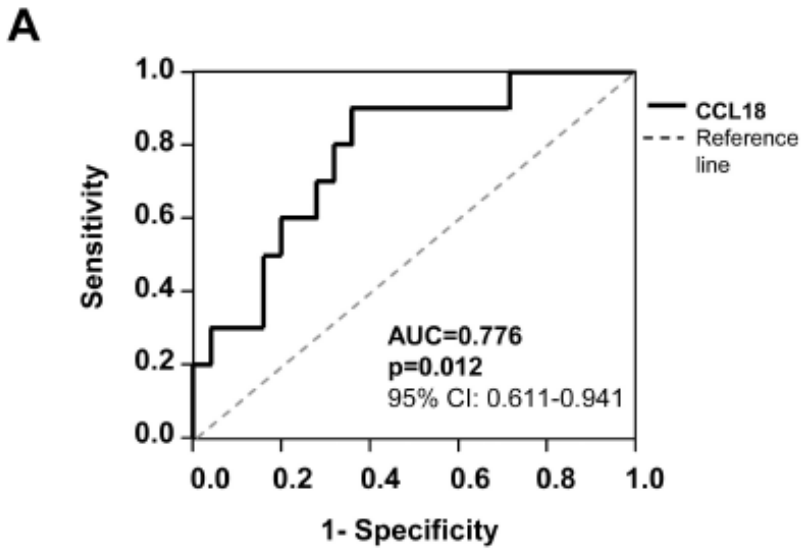
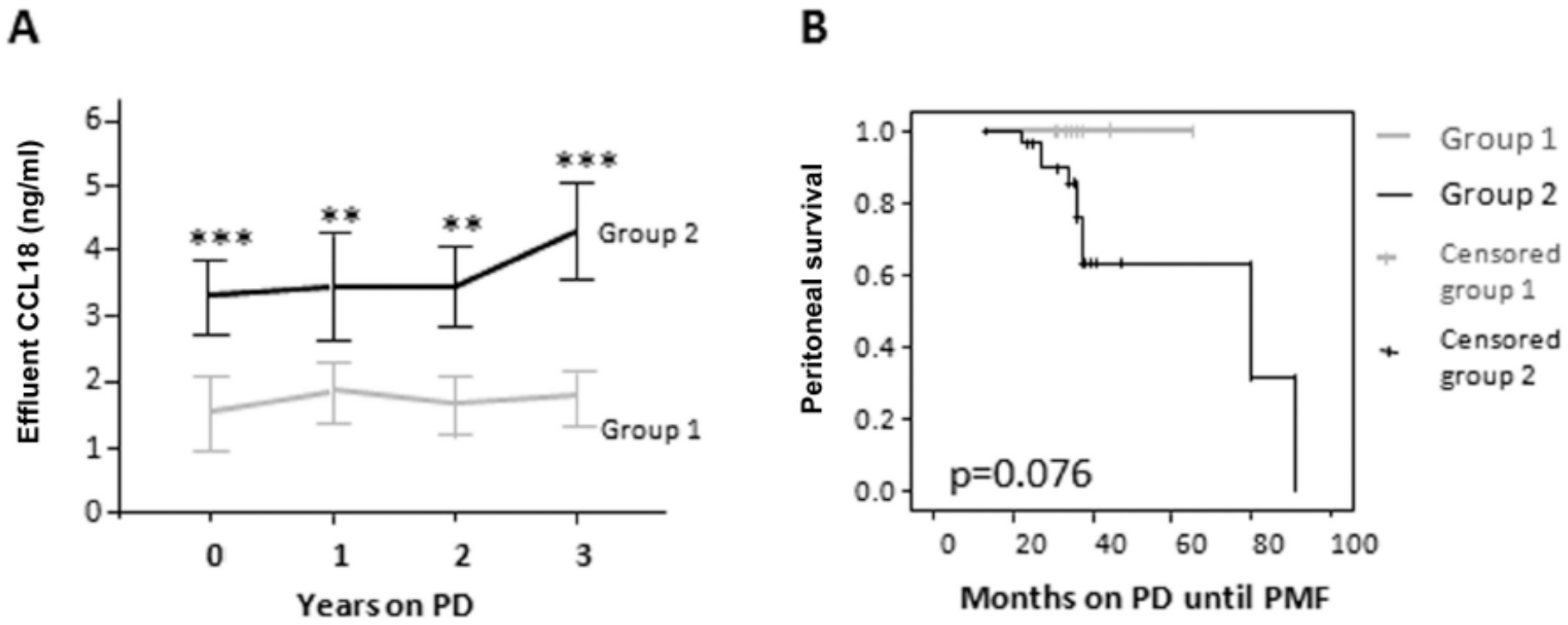


Niveles altos de CCL18 en efluente se asocian a una disfunción de membrana



PLOS ONE | https://doi.org/10.1371/journal.pone.0175835 April 17, 2017

Un aumento de CCL18 en efluente anuncia una disfunción de membrana

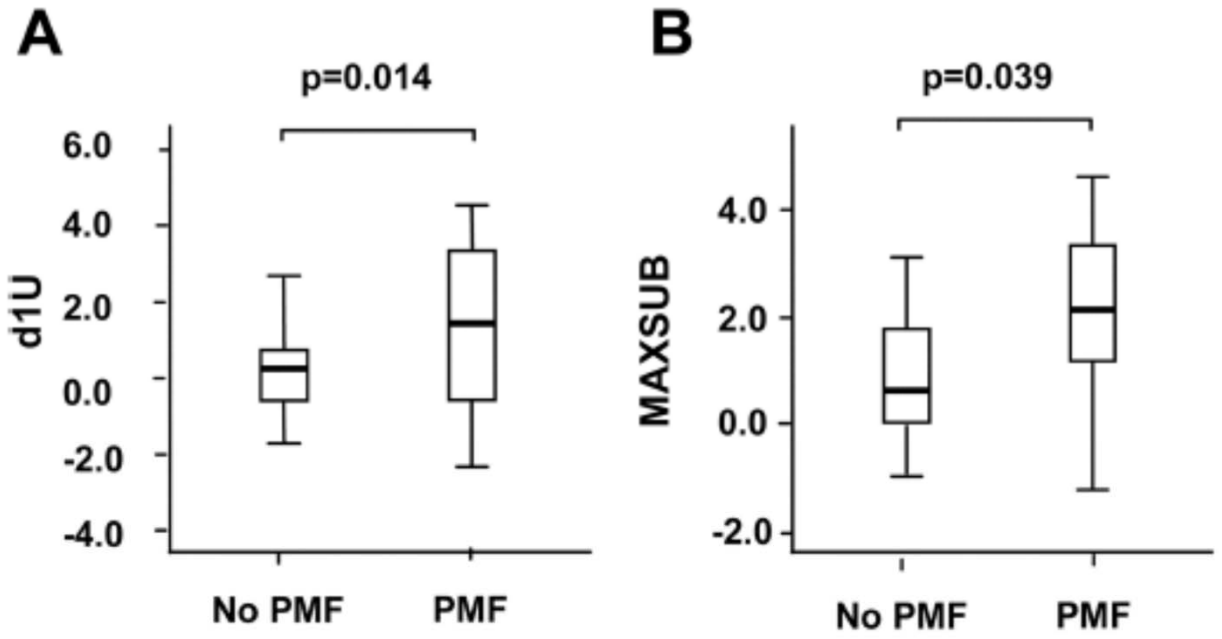
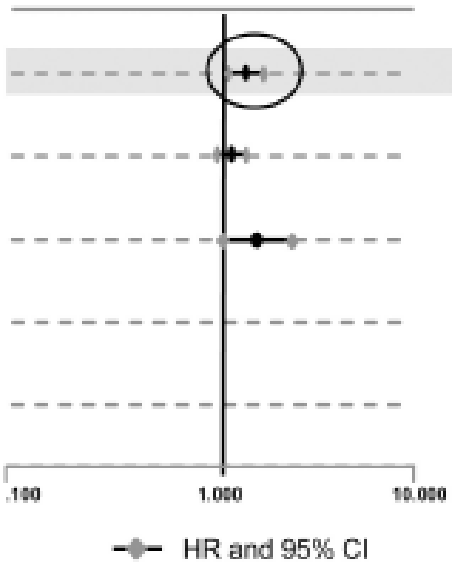


Fig 2. An increase in effluent CCL18 concentration heralds peritoneal membrane dysfunction. **(A)** The variable d1U was defined as the last CCL18 effluent value minus the baseline level in each patient included in the longitudinal analysis. **(B)** The variable Maxub was defined as the maximum minus the minimum CCL18 effluent concentration measured in each patient. A Cox hazard analysis of differences was performed on the patients who developed PMF (N = 10) and the patients who did not (N = 33).

https://doi.org/10.1371/journal.pone.0175835.g002

CCL18 predice supervivencia de la membrana independientemente de los parámetros de transporte (Creat y UF)

C



	p value	HR	LCI	UCI
CCL18	0.014	1.280	1.051	1.558
Urea MTAC	0.207	1.077	0.960	1.209
Cr MTAC	0.093	1.418	0.944	2.129
UF<400 ml	0.061	3.372	0.974	12.014
D/P Cr	0.295	0.000	0.000	6.546

Fig 4. Effluent CCL18 concentrations predict the survival of the peritoneal membrane independent of classical transport parameters. (A) Receiver operating characteristic (ROC) curve analysis of CCL18 effluent concentrations in samples from patients at 3 years of PD treatment who did or did not develop PMF. (AUC: area under the curve; CI: confidence interval). **(B)** Forest plot showing the hazard ratio (HR) and 95%

Niveles mas altos de PAI-1 en efluente diferenciaron pronóstico de la membrana sólo para FUF pero no para EPS

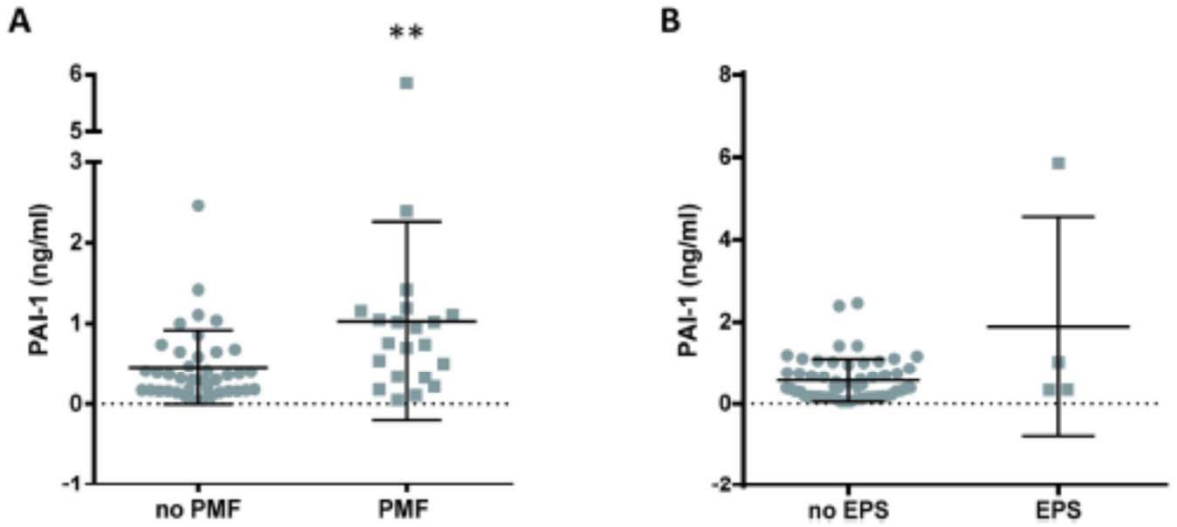


Fig 6. Cross-sectional study of PAI-1 values in 61 patients treated with PD with late (>3 years) peritoneal samples. Scatter plots showing mean, and SD values (A) Significantly higher levels were found in effluent samples from the patients who developed PMF (p = .0038; Mann-Witney U test). (B) PAI-1 effluent concentrations in patients who developed EPS. No significant differences were detected (Mann-Witney U test).

https://doi.org/10.1371/journal.pone.0175835.g006

M2 macrophages equilibrium:

repairing tissue *ad integrum* *vs.* tissue uncontrolled sclerosis

The Journal of Clinical Investigation RESEARCH ARTICLE

Alternatively activated macrophages determine repair of the infarcted adult murine heart

Manabu Shiraishi,[1,2] Yasunori Shintani,[1] Yusuke Shintani,[1] Hidekazu Ishida,[1] Rie Saba,[1] Atsushi Yamaguchi,[2] Hideo Adachi,[2] Kenta Yashiro,[1] and Ken Suzuki[1]

[1]William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom. [2]Department of Cardiovascular Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan.

Depletion of M2-like macrophages led to impaired fibroblast-mediated repair of the infarcted myocardium

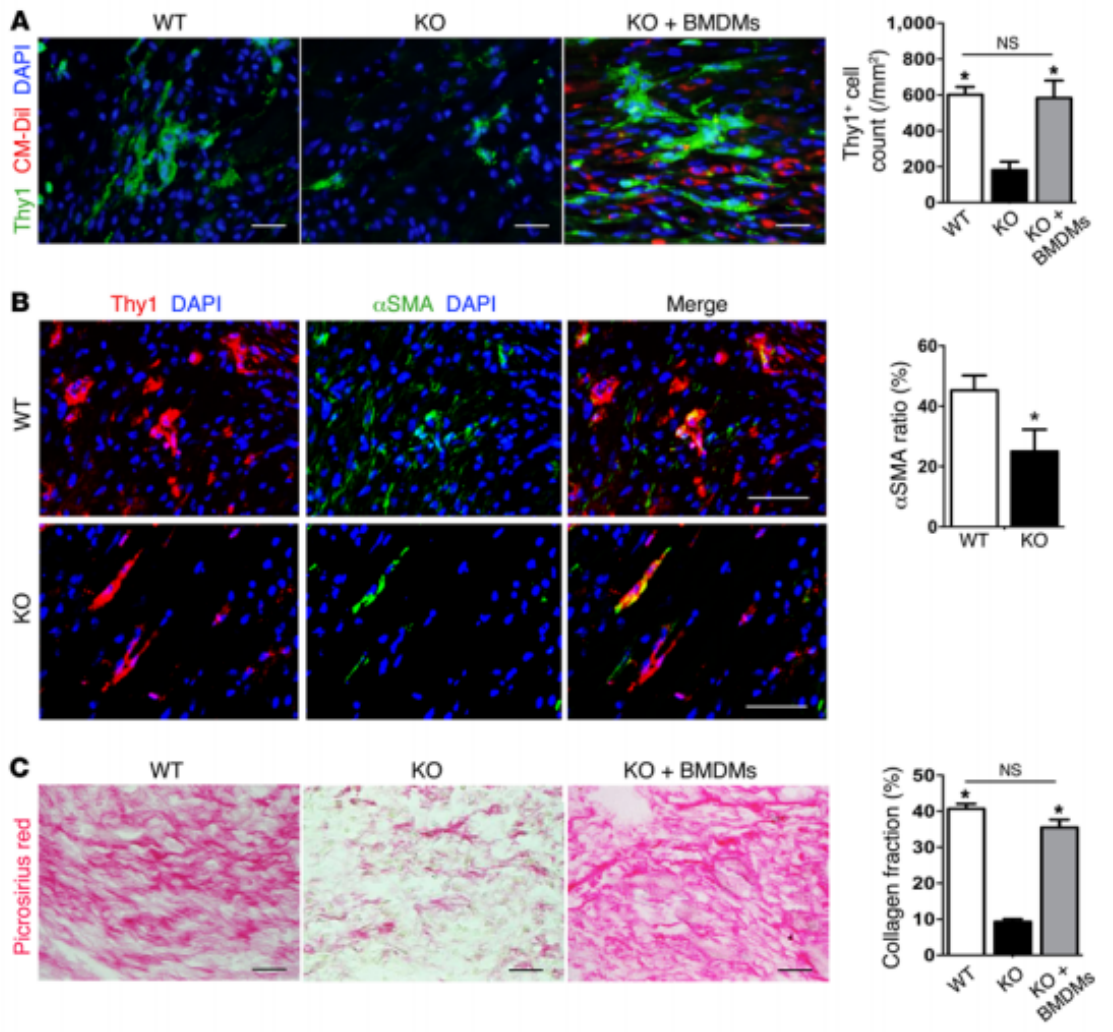
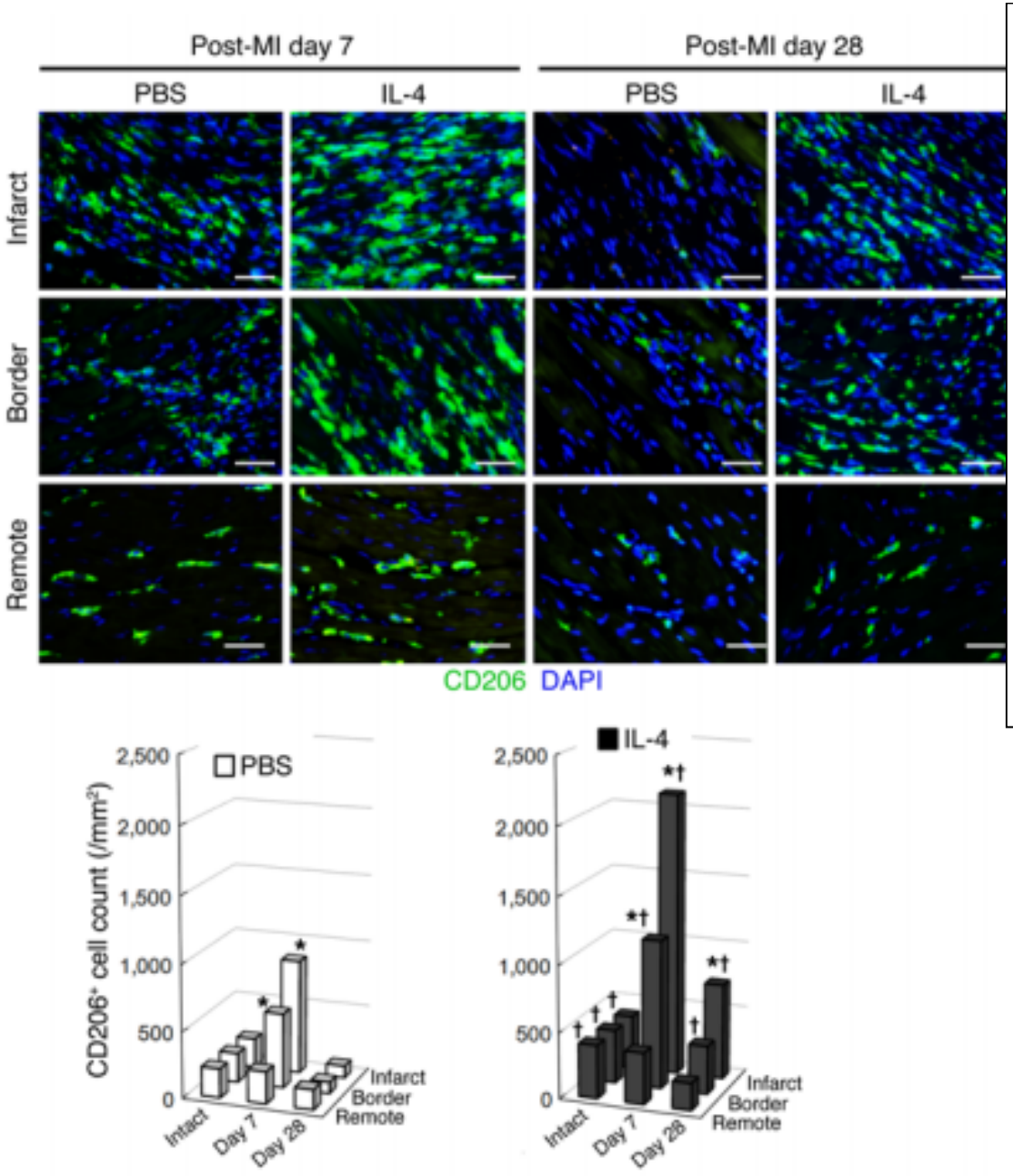
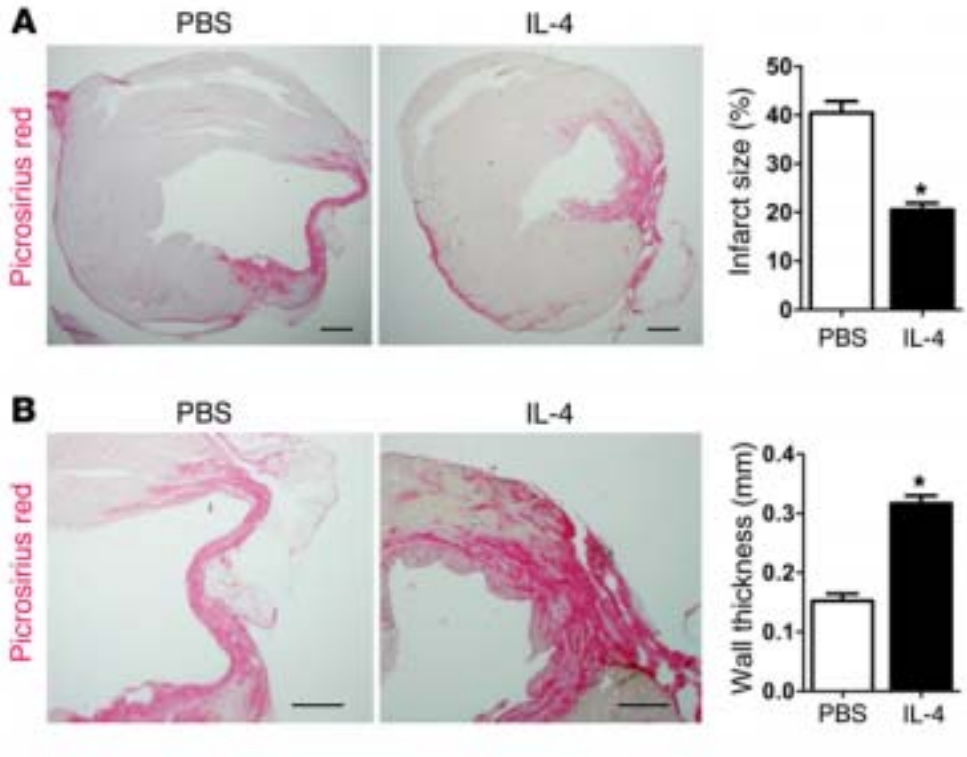


Figure 6. Depletion of M2-like macrophages in *Trib1*$^{-/-}$ mice led to impaired fibroblast-mediated repair of the infarcted myocardium. (A) I



IL-4 administration amplified the post-MI augmentation of cardiac M2-like macrophages in damaged myocardium

IL-4 administration reduced infarct size and increased infarct wall thickness



Conclusion

M2 macrophages govern the activity of fibroblasts and myofibroblasts in the infarcted adult murine heart, controlling the degree of rigidity and determining the heart functional recovery

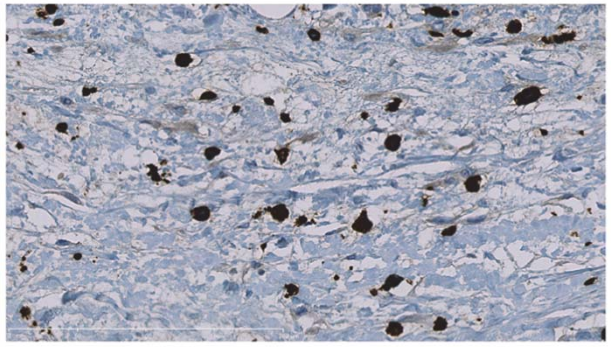
M2, peritoneal fibrosis and Encapsulating Peritoneal Sclerosis

CD4-Positive T Cells and M2 Macrophages Dominate the Peritoneal Infiltrate of Patients with Encapsulating Peritoneal Sclerosis

Sayed M. Habib[1]*, Alferso C. Abrahams[2], Mario R. Korte[3], Robert Zietse[1], Lisette L. de Vogel[4], Walther H. Boer[2], Amélie Dendooven[5], Marian C. Clahsen-van Groningen[4], Michiel G. H. Betjes[1]

PLOS ONE | DOI:10.1371/journal.pone.0120174 April 24, 2015

M2 (CD163) macrophage markers in the peritoneal membrane of EPS patients and PD controls



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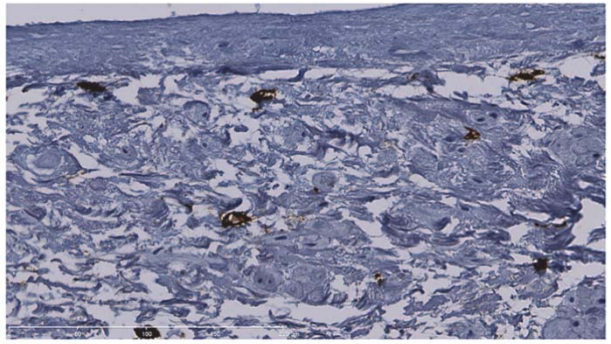

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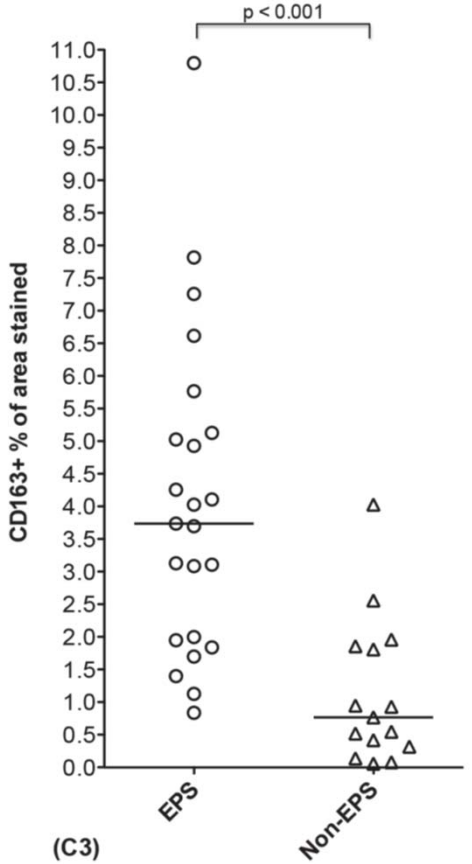

(C3)

PLOS ONE | DOI:10.1371/journal.pone.0120174 April 24, 2015

CD4-Positive T Cells and M2 Macrophages Dominate the Peritoneal Infiltrate of Patients with Encapsulating Peritoneal Sclerosis

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A characteristic mononuclear cell infiltrate (CD4+ and CD163+ cells) dominates the peritoneum of EPS patients

A role for both CD4+ T cells and M2 macrophages in the pathogenesis of EPS is suggested

PLOS ONE | DOI:10.1371/journal.pone.0120174 April 24, 2015

Peritoneal Dialysis International, Vol. 31, pp. 291-300
doi: 10.3747/pdi.2010.00118

0896-8608/11 $3.00 + .00

DIFFERENCE IN THE EXPRESSION OF HORMONE RECEPTORS AND FIBROTIC MARKERS IN THE HUMAN PERITONEUM—IMPLICATIONS FOR THERAPEUTIC TARGETS TO PREVENT ENCAPSULATING PERITONEAL SCLEROSIS

Niko Braun,[1] Peter Fritz,[2] Dagmar Biegger,[3] Martin Kimmel,[1] Fabian Reimold,[1] Christoph Ulmer,[4] and M. Dominik Alscher[1]

- **72 peritoneal biopsy specimens (22 from EPS patients, 11 from PD patients and 15 from uremic patients)**
- **For immunophenotyping, antibodies against VDR and TGFβ1, were used.**

Peritoneal Dialysis International, Vol. 31, pp. 291-300
doi: 10.3747/pdi.2010.00118

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VDR positivity

- blood vessels

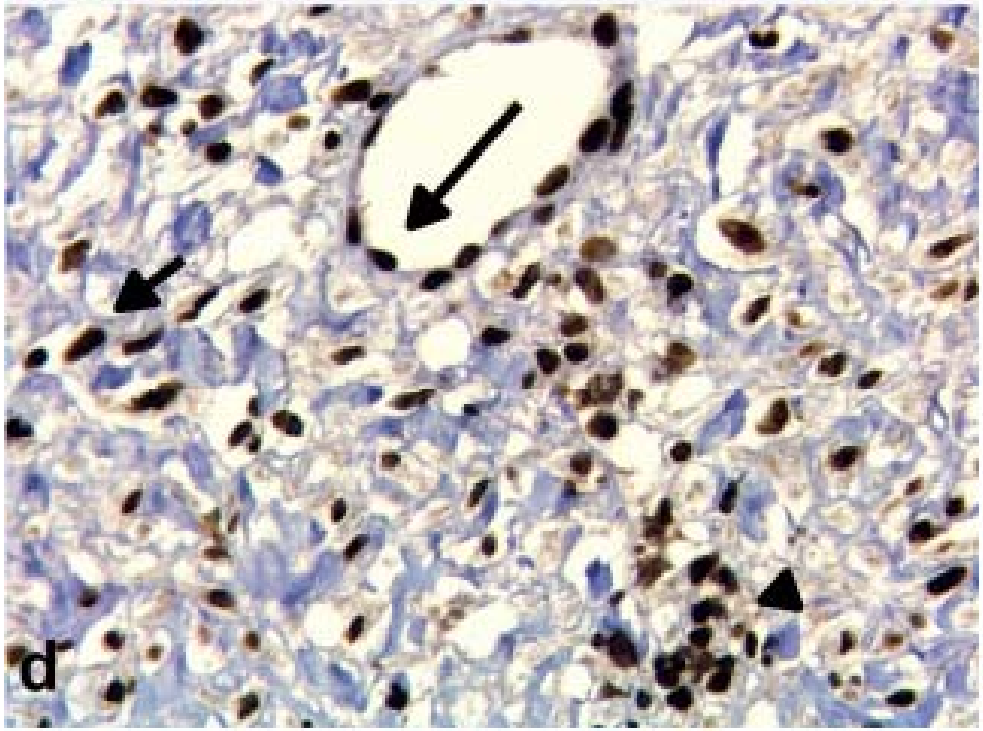
(long arrow)

-fibroblasts

(short arrow)

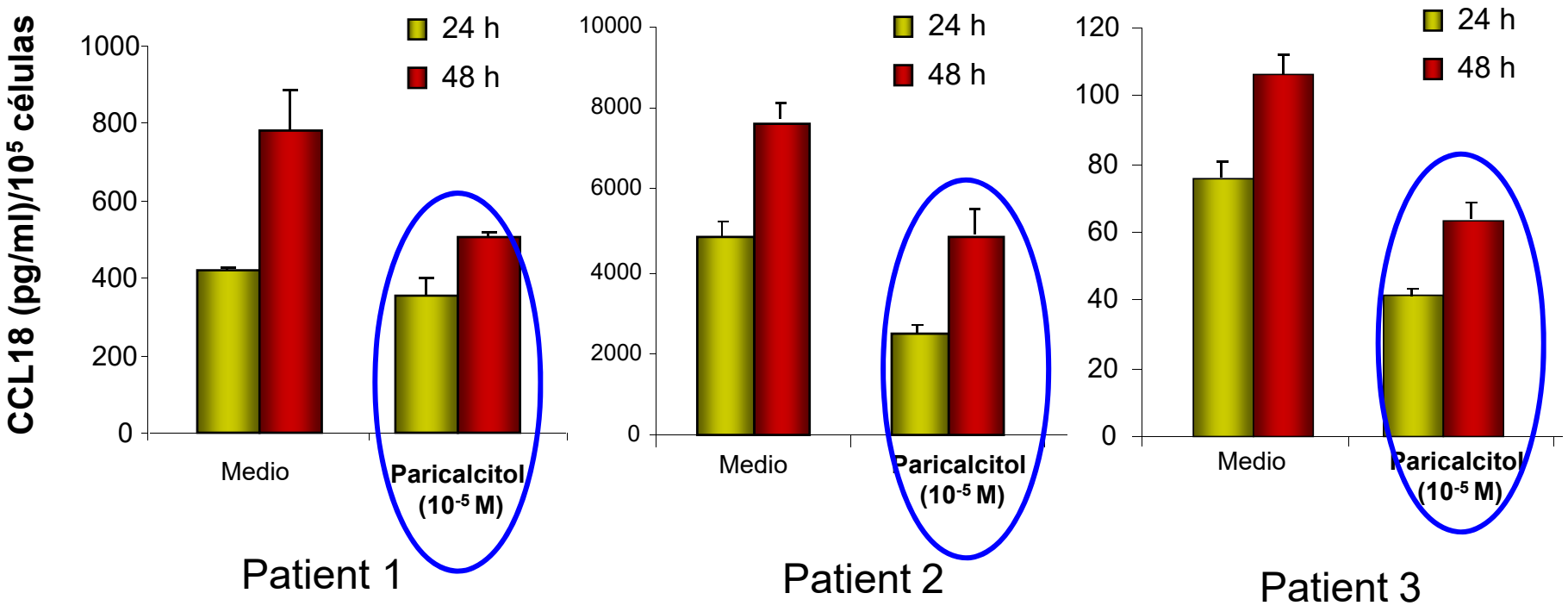
-inflammatory cells

(arrowhead)

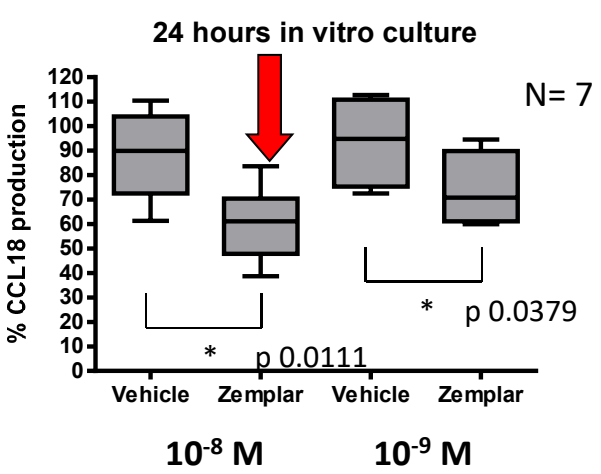


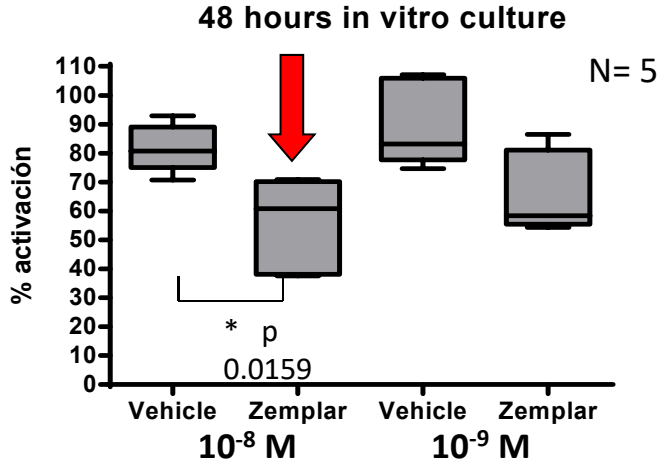
Paricalcitol effects on CCL18 production by M2

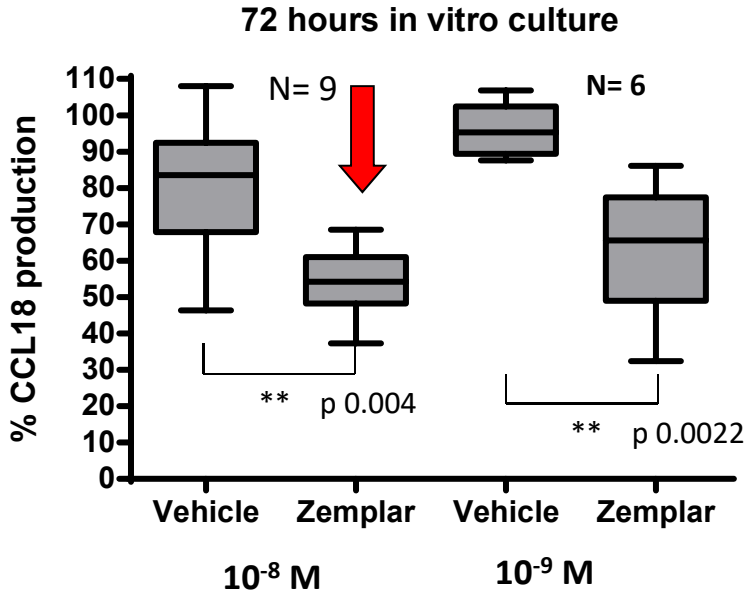
CCL18 production by peritoneal M2 isolated from effluent is inhibited by paricalcitol (10^{-5}M)



CCL18 production by human peritoneal effluent macrophages is attenuated by paricalcitol (10^{-5}M)

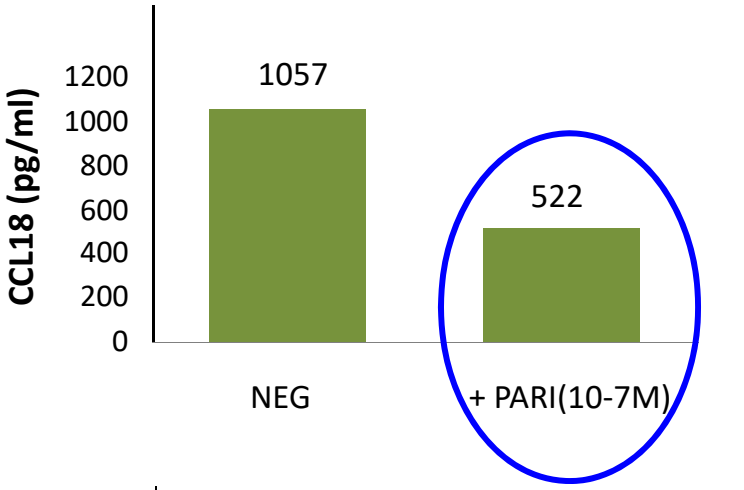


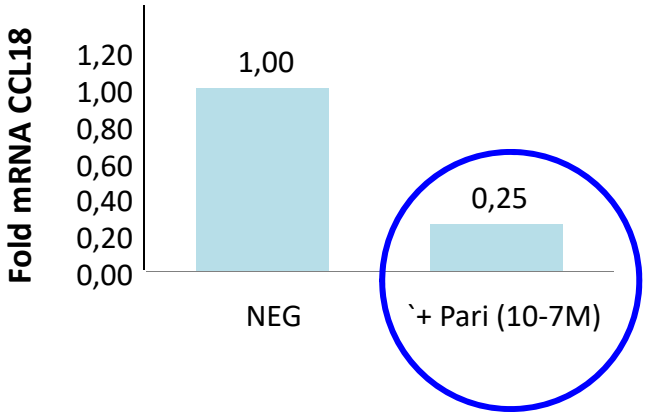


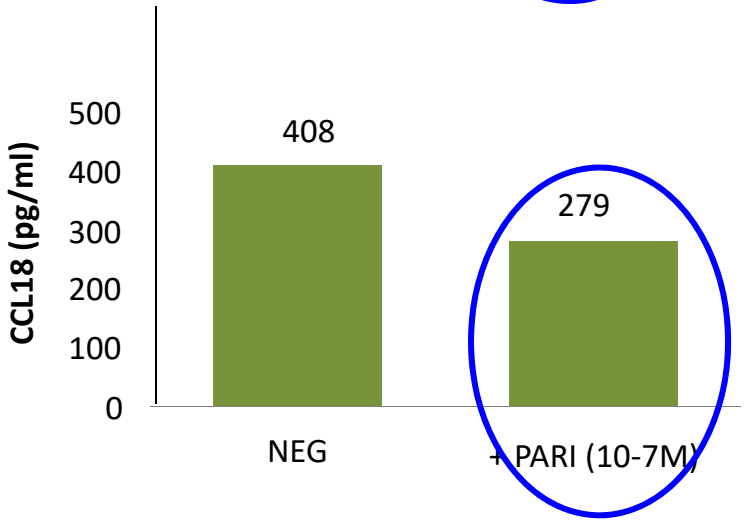


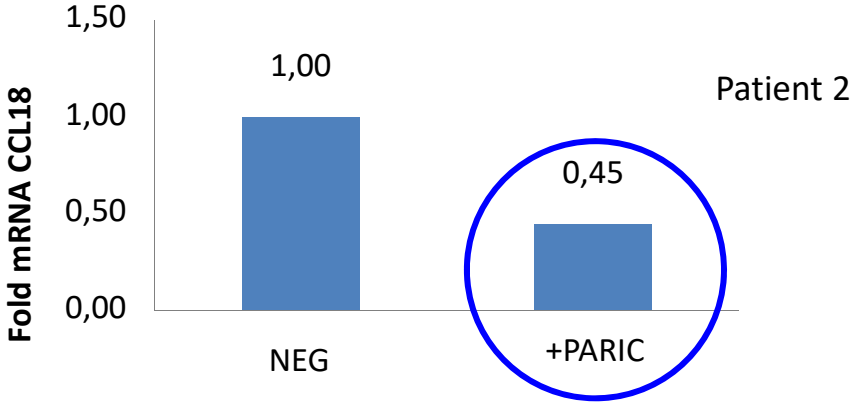
Mann Whitney test

mRNA and protein (CCL18) by human peritoneal effluent macrophages are attenuated by paricalcitol (10^{-5}M)









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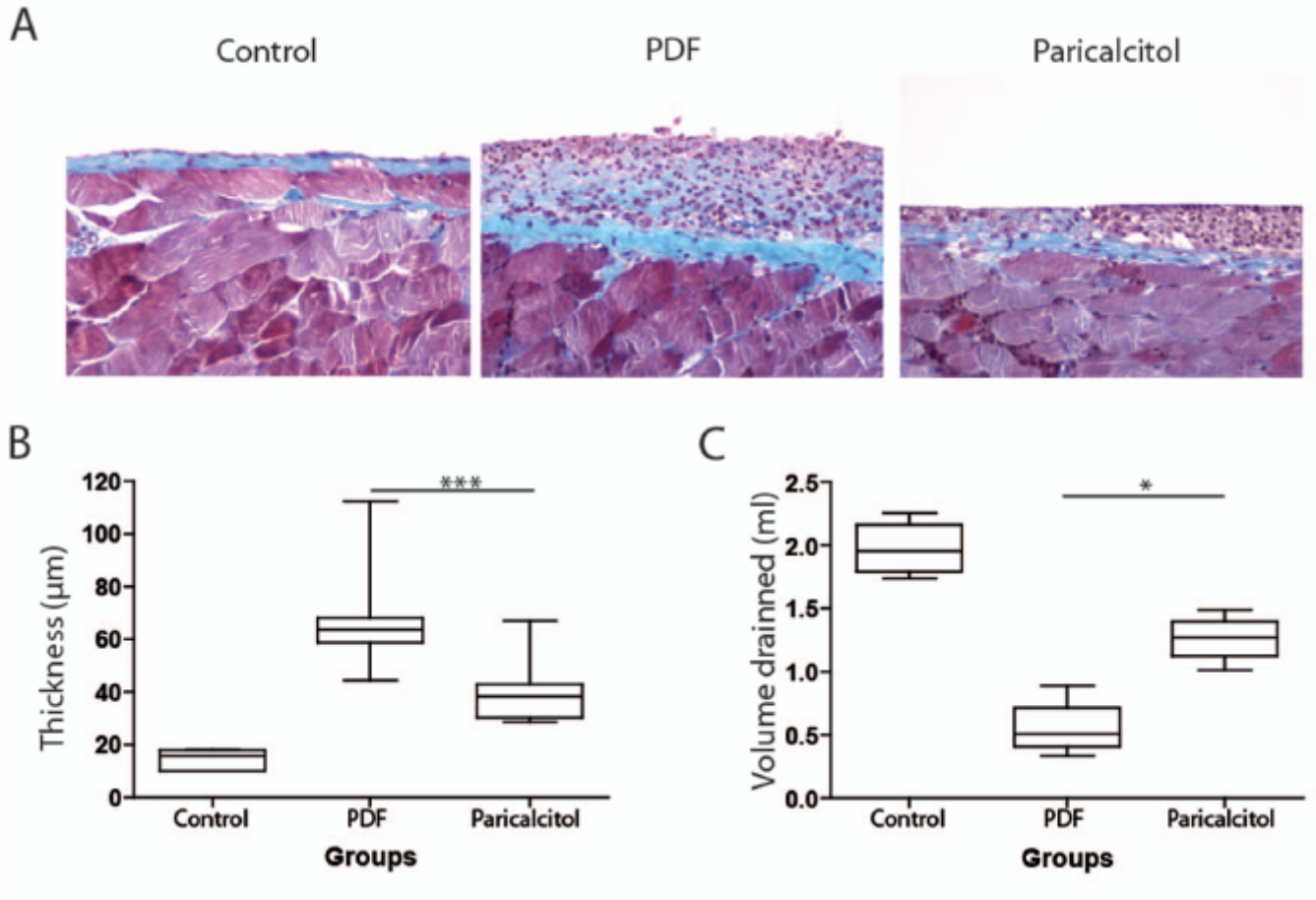
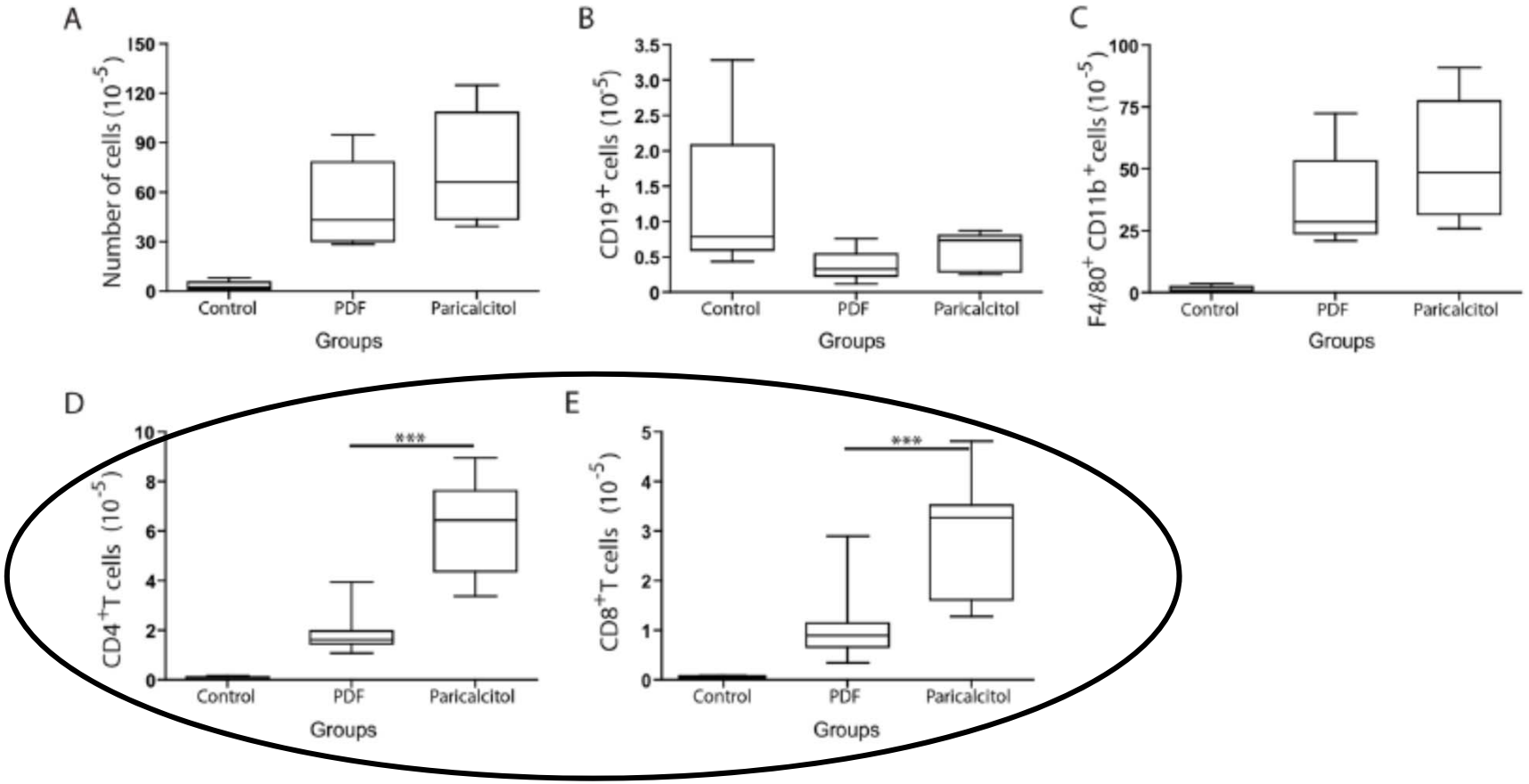
Paricalcitol Reduces Peritoneal Fibrosis in Mice through the Activation of Regulatory T Cells and Reduction in IL-17 Production

Guadalupe T. González-Mateo[1,2], Vanessa Fernández-Míllara[1], Teresa Bellón[1], Georgios Liappas[2], Marta Ruiz-Ortega[3], Manuel López-Cabrera[2], Rafael Selgas[1,4], Luiz S. Aroeira[5]*

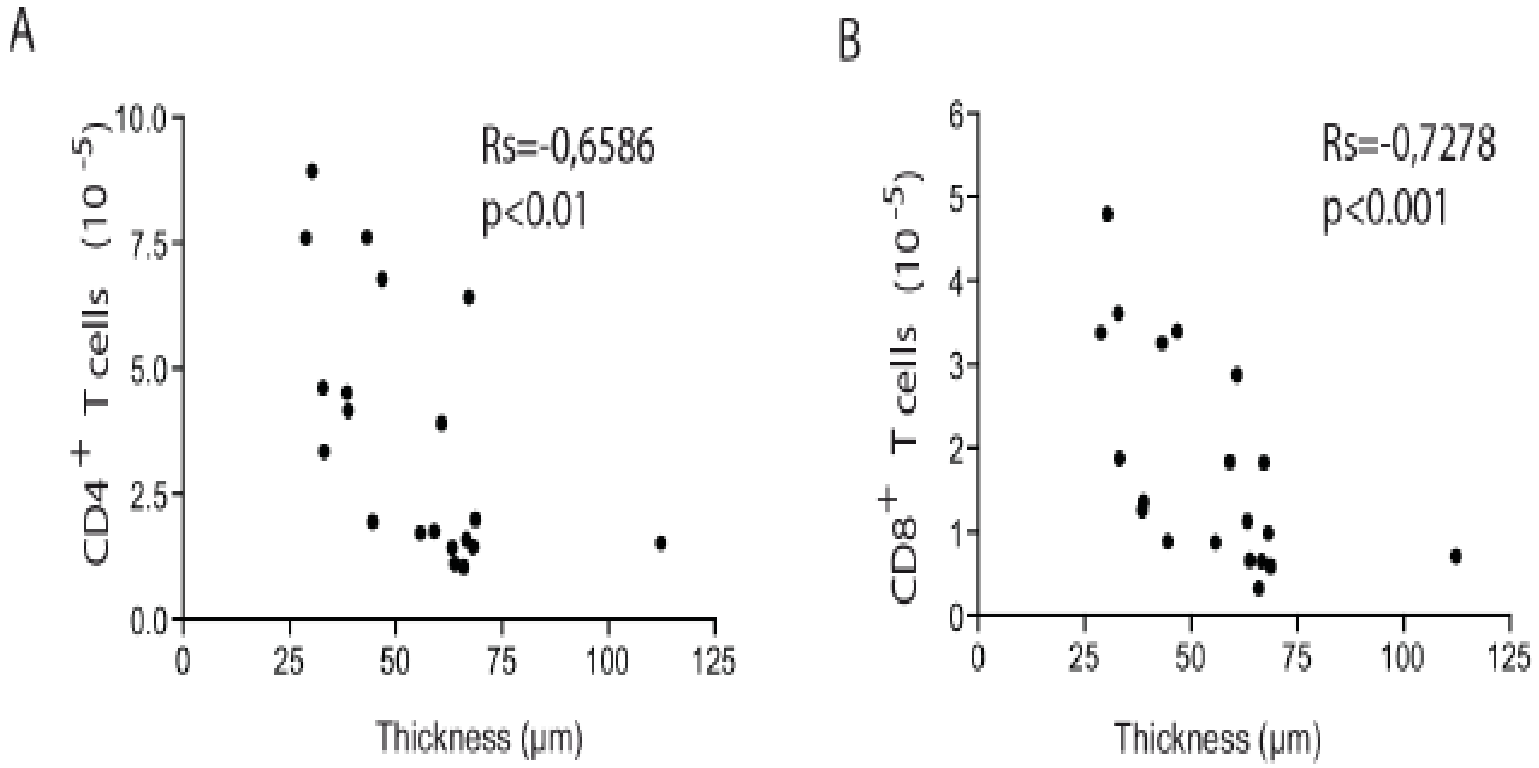
Paricalcitol reduced peritoneal membrane fibrosis, inflammation and ultrafiltration failure in mice exposed to PDF (*peritoneal dialysis fluid*).



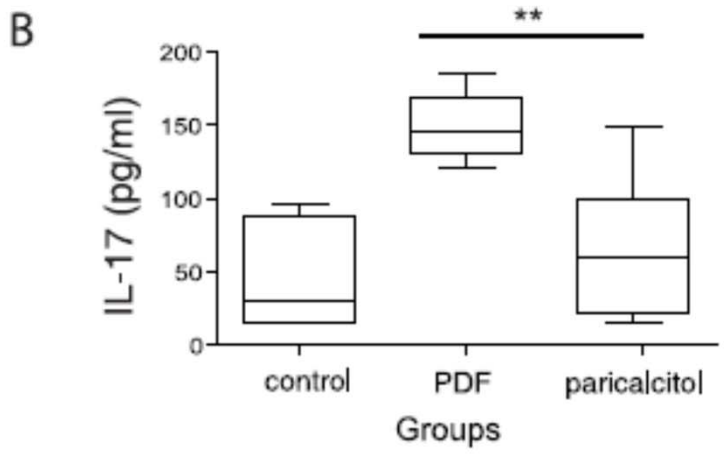
Paricalcitol changed the peritoneal T cell population in mice instilled with PDF

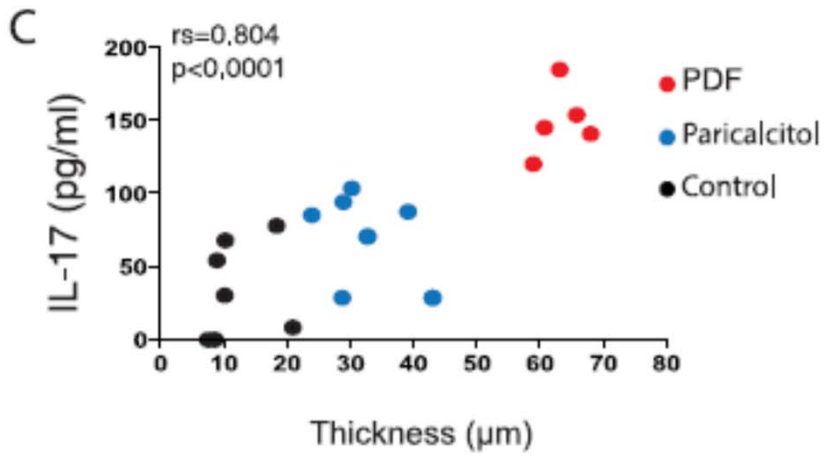


Paricalcitol's enhancement of T cell number is inversely correlated with peritoneal thickness

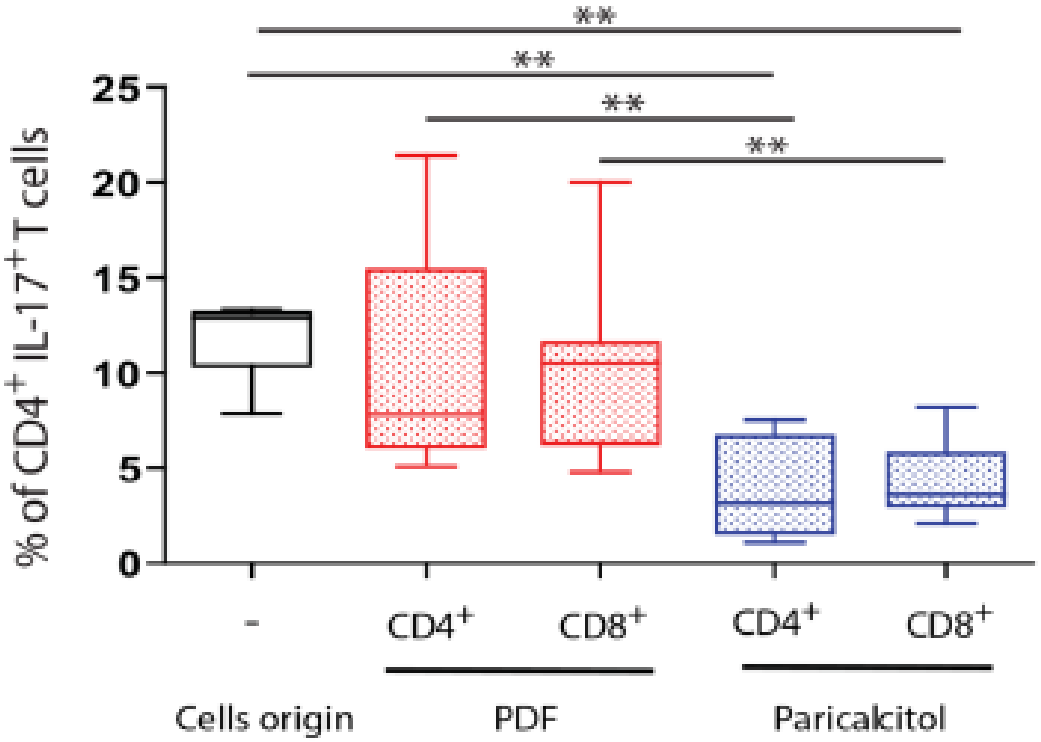


Paricalcitol induced the regulation of IL-17 production and affected peritoneal fibrosis outcomes





CD4+ and CD8+ T cells from paricalcitol-treated mice regulate IL-17 production



Conclusions of the PD Fluid Animal Model

VDR signaling by Paricalcitol

- **Recruits CD4+ and CD8+ T cells with regulatory activity into peritoneal cavity**
- **Reduces IL-17 production**
- **Diminishes PDF induced peritoneal inflammation and fibrosis.**

http://www.kidney-international.org

IL-17A is a novel player in dialysis-induced peritoneal damage

Raquel Rodrigues-Díez[1], Luiz S. Aroeira[2], Macarena Orejudo[2], M-Auxiliadora Bajo[2], José Jiménez Heffernan[3], Raúl R. Rodrigues-Díez[1], Sandra Rayego-Mateos[1], Alberto Ortiz[4], Guadalupe Gonzalez-Mateo[2], Manuel López-Cabrera[5], Rafael Selgas[2], Jesús Egido[4] and Marta Ruiz-Ortega[1]

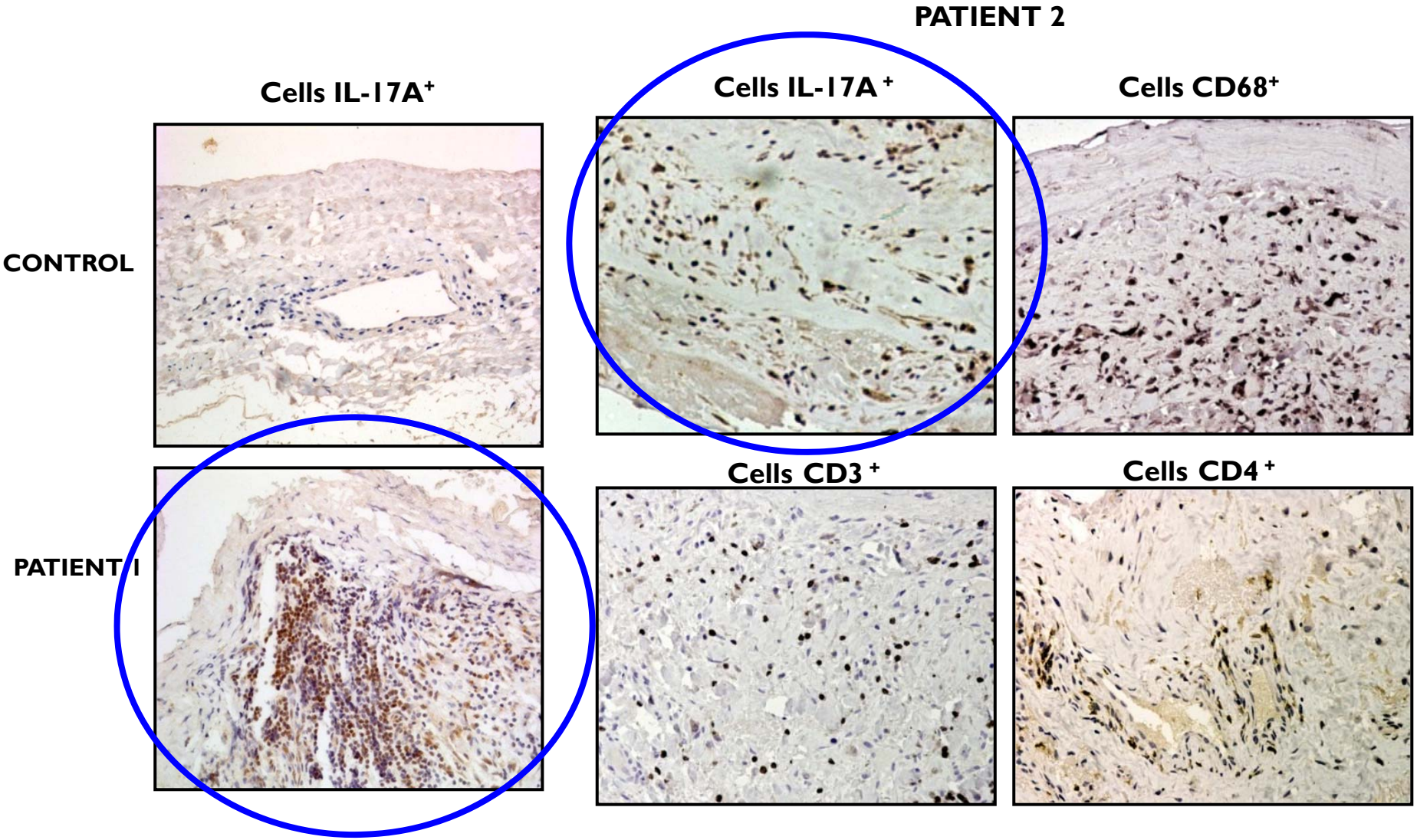
[1]Cellular Biology in Renal Diseases Laboratory, IIS-Fundación Jiménez Díaz/Universidad Autónoma Madrid, Madrid, Spain; [2]Division of Nephrology, Hospital Universitario La Paz- IdiPAZ, Madrid, Spain; [3]Servicio de Anatomia Patológica, Hospital de la Princesa, Madrid, Spain; [4]Division of Nephrology and Hypertension, IIS-Fundación Jiménez Díaz/Universidad Autónoma Madrid, Madrid, Spain and [5]Centro de Biología Molecular-Severo Ochoa, CSIC-UAM, Madrid, Spain

Th *NAÏVE* lymphocyte differentiation

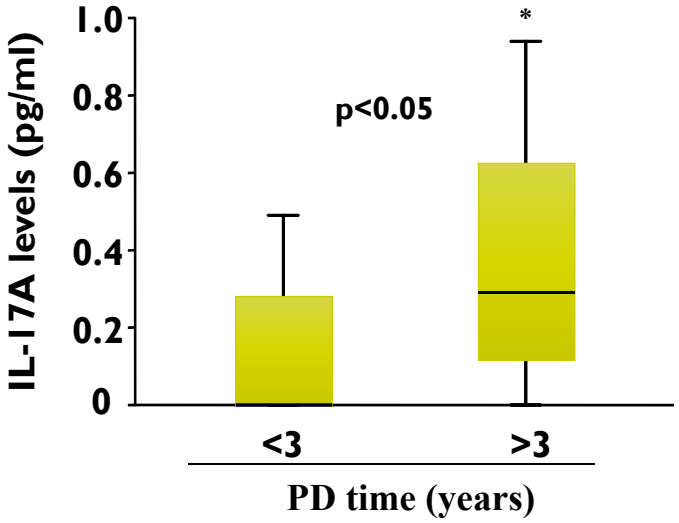
Inducing cytokine	Transcription Factor	Response	Effecting cytokine	Pathogenesis
IL-6	 RORγt STAT-3	 Th-17	IL-17A	Autoimmune diseases Chronic inflammation and FIBROSIS Lung. Skin. Vessel. Liver

Modified from Jetten AM. Nucl Recept Signal. 2009.

IL-17A expression *(brown)* at the peritoneum in PD patients

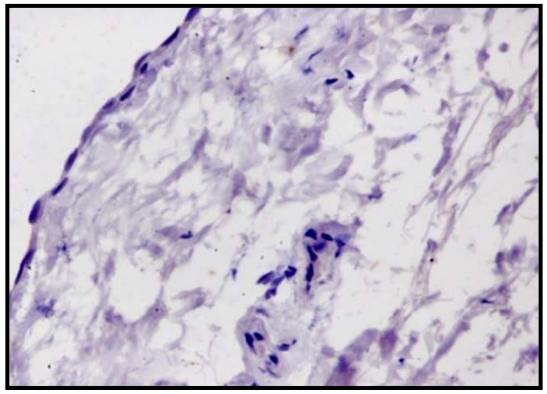


IL-17A levels in peritoneal effluent increase over time on PD

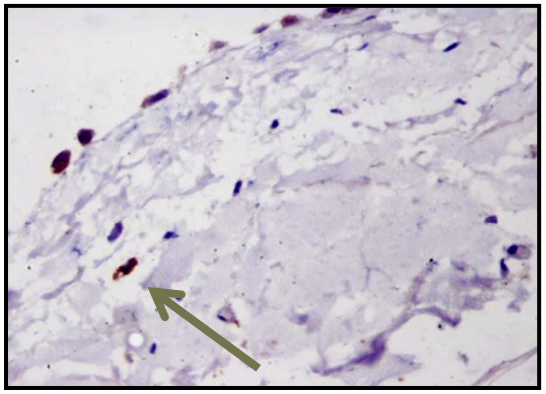


Cells IL-17A $^{+}$

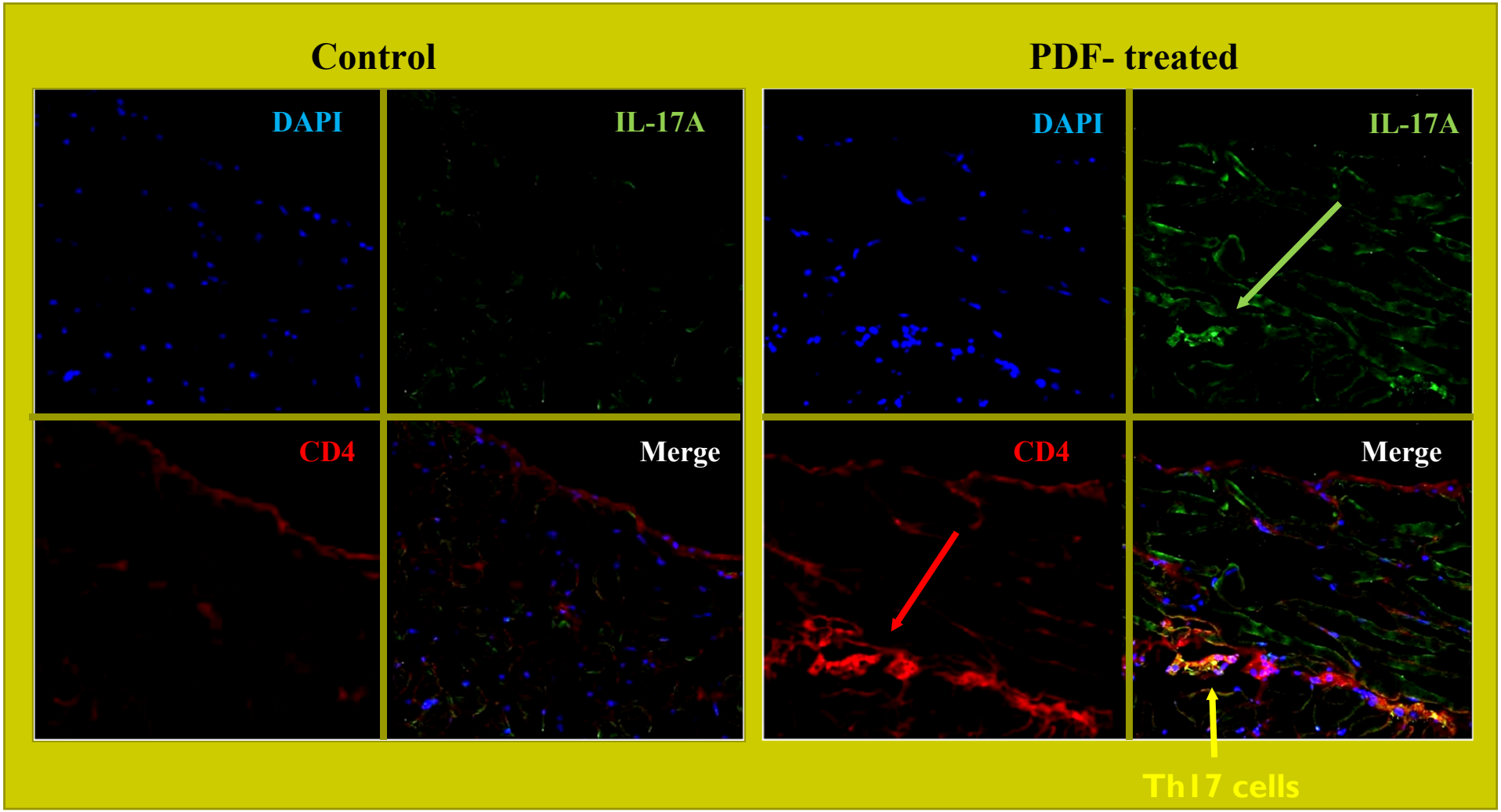
Pre-dialysis



3 years on PD



Mice peritoneum treated with bio-incompatible high glucose-PD fluids showed Th 17 lymphocyte (CD4) infiltrate expressing IL-17



1,25(OH)2D3 inhibits high glucose-induced apoptosis and ROS production in human peritoneal mesothelial cells via the MAPK/P38 pathway

Mol Med Rep. 2016 Jul;14(1):839-44

- Human **mesothelial cell exposure to high glucose increased**:
  - apoptosis
  - ROS
- **Pretreatment with 1,25(OH)2D3** via the MAPK/P38 pathway significantly **inhibited**:
  - apoptosis
  - ROS production

Mensajes para casa-1

- **EPS es un proceso que empieza por transformación peritoneal tipo MMT (actina y colágeno)**
- **El segundo golpe depende de la inflamación (M1 y M2)**
- **Los macrófagos alternativamente activados** (M2) están presentes en el peritoneo inflamado bajo DP
- M2 **promueven actividad fibroblastica**
- M2 están anatomica y funcionalmente (VDR) implicados en la **EPS. IL-17 es un mediador**
- M2 producen importantes cantidades de **CCL18 que precede al FUF y la EPS**

Mensajes para casa-2

- **La señalización de VDR por Paricalcitol**
  - **. Inhibe producción de CCL18 por los M2**
  - **. Reduce la producción peritoneal de IL-17**
  - **. Protege a las cels. mesoteliales** de la glucosa

- Disminuye la **inflamación y fibrosis peritoneal inducida por PDGs**
- ¿Limita el desarrollo de la EPS?

Co-autores

- MA Bajo, G del Peso, M Ossorio, R Sánchez-Villanueva, E Gonzalez, Mª J Castro
- J Jiménez-Heffernan, M Ruiz-Ortega, Raquel Rodrigues-Díez
- T Bellón, L S Aroeira, G Gonzalez,V Martinez
- M. López Cabrera, A Aguilera, P Sandoval, P Albar, J Loureiro, Mª Luisa Pérez-Lozano, G.Liappas, V Ruiz-Carpio
- A Fernandez-Perpén, JA Sánchez Tomero
- M Ruiz Ortega, R Rodriguez-Diez

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