Neue PD-Lösungen

Christoph Aufricht, Wien

Abteilung für
Pädiatrische Nephrologie und
Gastroenterologie

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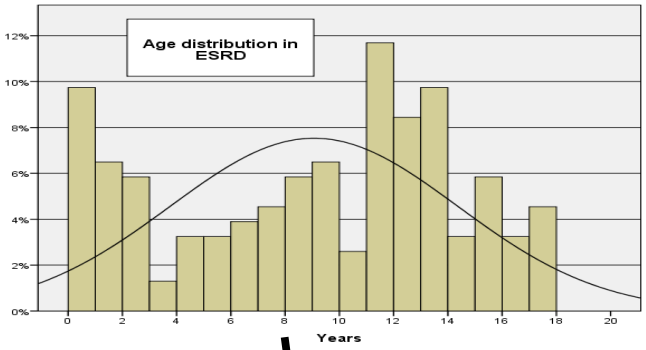
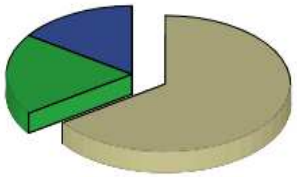
Neue PD-Lösungen

Christoph Aufricht, Wien

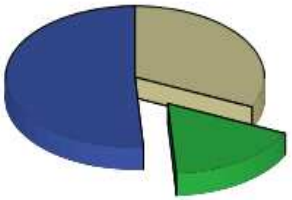
initial renal replacement therapy in Viennese children 1998-2007



abbreviations:
PD – peritoneal dialysis
HD - hemodialysis
RTX - renal transplantation
ESRD – end stage renal disease

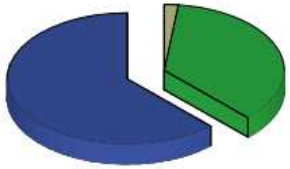


PD



HD

RTX



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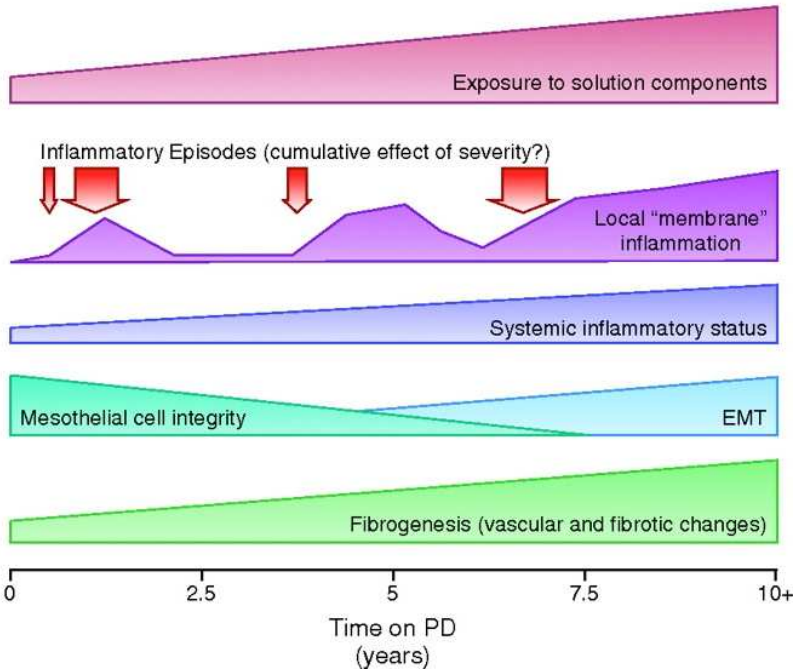
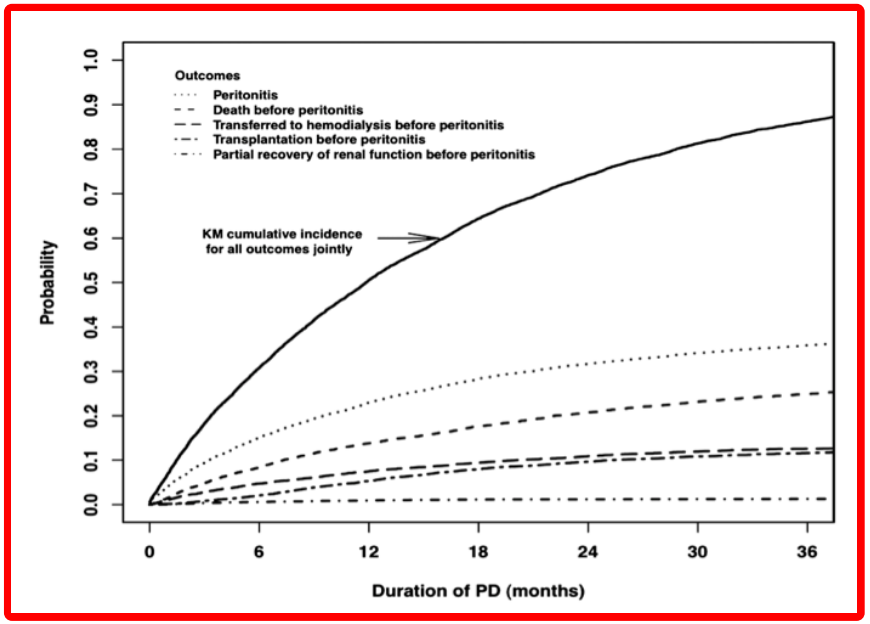
Medical Need to improve PD Outcome



Devuyst O et al., JASN 2010



Evans et al. Nephrol Dial Transplant 2010

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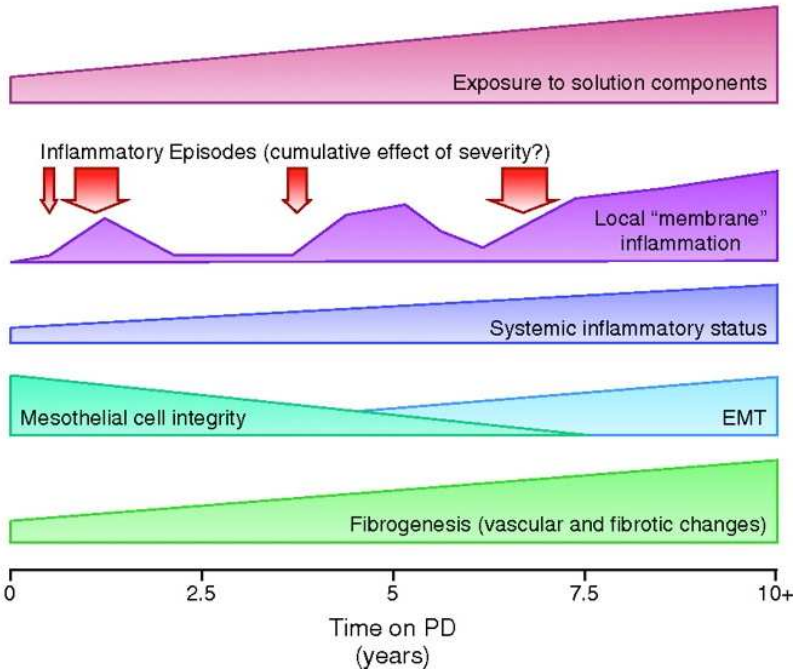
Medical Need to improve PD Outcome



Devuyst O et al., JASN 2010

<u>Outcome at 2 years of PD</u>:

- **44% Peritonitis (first)**
- **16% Switched to HD**
- **21% Died**

RDPFL 8711 Patients

Evans et al. Nephrol Dial Transplant 2010

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Choice of currently available PD Fluids (Cochrane 2014)

Biocompatible dialysis fluids for peritoneal dialysis (Review)

Cho Y, Johnson DW, Craig JC, Strippoli GFM, Badve SV, Wiggins KJ

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 3

http://www.thecochranelibrary.com

WILEY

Thirty-six eligible studies with 2719 patients (24 on low GDP PD Fluids and 12 on Icodextrin based PD Fluids)

Main results

Thirty-six eligible studies (2719 patients) were identified: Neutral pH, lactate-buffered/bicarbonate (± lactate)-buffered, low GDP PD solution (24); icodextrin (12). Allocation methods and concealment were generally incompletely reported, and adequate in only ten studies (27.8%). Patients lost to follow-up ranged from 0% to 83.4%.

Neutral pH, low GDP versus conventional glucose PD solution

Based on generally sub-optimal quality evidence, the use of neutral pH, low GDP PD solutions was associated with larger urine volumes at the end of the studies, up to three years of therapy duration (7 studies, 520 patients: MD 126.39 mL/d, 95% CI 26.73 to 226.05). Improved preservation of residual renal function was evident in studies with greater than 12 month follow-up (6 studies, 360 patients: SMD 0.31, 95% CI 0.10 to 0.52). There was no significant effect on peritonitis, technique failure or adverse events with the use of neutral pH, low GDP PD solutions.

Glucose polymer (icodextrin) versus conventional glucose PD solution

There was a significant reduction in episodes of uncontrolled fluid overload (2 studies, 100 patients: RR 0.30, 95% CI 0.15 to 0.59) and improvement in peritoneal ultrafiltration (4 studies, 102 patients, MD 448.54 mL/d, 95% CI 289.28 to 607.80) without compromising residual renal function (4 studies, 114 patients: SMD 0.12, 95% CI -0.26 to 0.49) or urine output (3 studies, 69 patients: MD -88.88 mL/d, 95% CI -356.88 to 179.12) with icodextrin use. A comparable incidence of adverse events with the icodextrin (four studies) was reported.

Authors' conclusions

Based on generally sub-optimal quality studies, use of neutral pH, low GDP PD solution led to greater urine output and higher residual renal function after use exceeded 12 months. Icodextrin prescription improved peritoneal ultrafiltration and mitigated uncontrolled fluid overload. There were no significant effects on peritonitis, technique survival, patient survival or harms identified with their use. Based on the best available evidence, the use of these 'biocompatible' PD solutions resulted in clinically relevant benefits without added risks of harm.

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Choice of currently available PD Fluids (Cochrane 2014)

Biocompatible dialysis fluids for peritoneal dialysis (Review)

Cho Y, Johnson DW, Craig JC, Strippoli GFM, Badve SV, Wiggins KJ

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Glucose polymer (icodextr

There was a significant reduc … 9) and improvement in peritoneal u … mising residual renal function (4 stu … -88.88 mL/d, 95% CI -356.88 to 1 … udies) was reported.

Major glucose-sparing Trial Data are not included

(PEN: unchanged UF, increased D/P crea, CA-125 & IL-6

→ PDI Editorial 2015: ... the jury is still out....

Authors' conclusions

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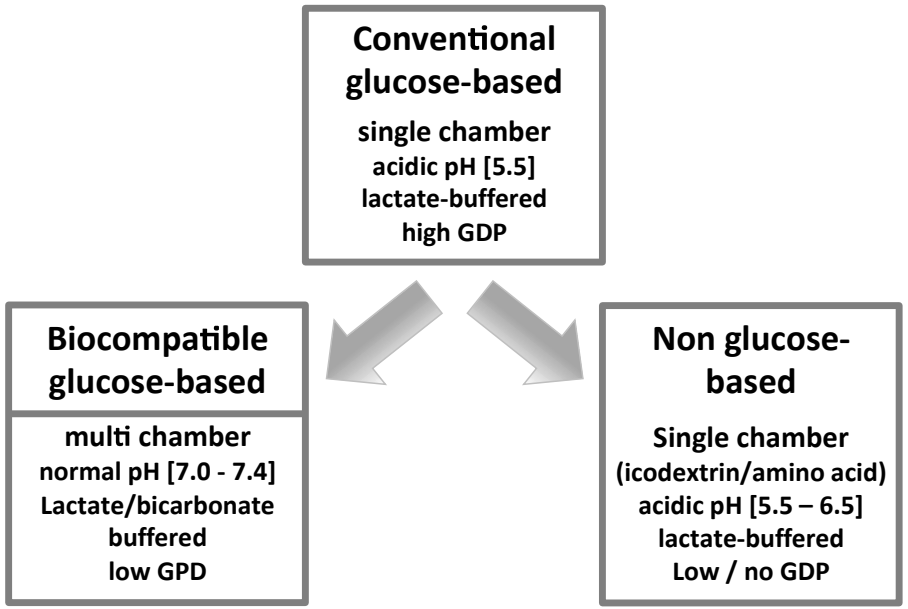
Choice of currently available PD Fluids



9

We all know: PD Fluids are Cytotoxic, mainly due to Glucose and Heat-Sterilization.

→ More research and better PD Fluids are needed.

Schmitt CP and Aufricht C, Pediatr Nephrol 2016

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“The Black Box Approach”

„extrinsic factors“
PD Fluid / Peritonitis

Healthy Peritoneum → **Biology of the Peritoneum under PD Stress Conditions** → **„PD“ Peritoneum**

Adapted from
Brownslee *et al.*

genetic Background
„intrinsic factors“

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Christian Doppler Forschungsgesellschaft

The "Story"

„extrinsic factors"
PD Fluid / Peritonitis

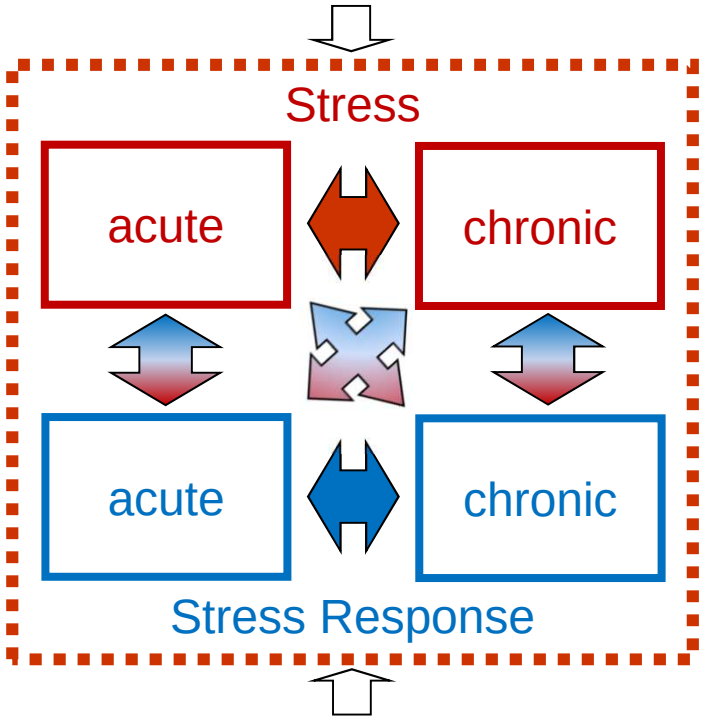
Acute PDF Toxicity

Infection

„diabetiform" PDF Toxicity

Oxidative Stress

Healthy Peritoneum



„PD" Peritoneum

Inflammation

Cytoprotection

Membrane Remodeling

Senescence

genetic Background
„intrinsic factors"

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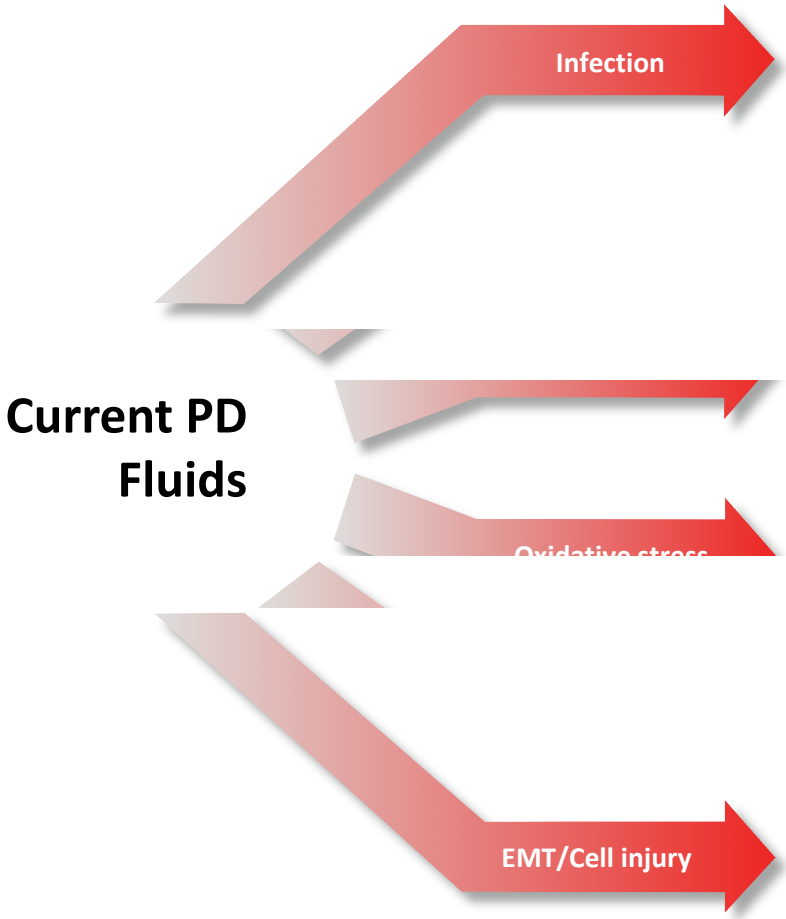
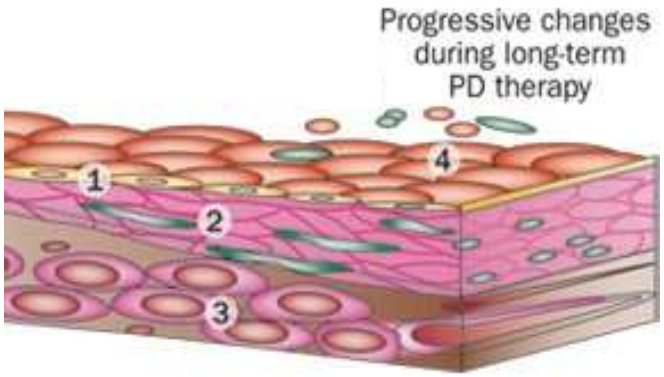
Summary of Peritoneal Damage by PD Fluids





adapted from García-López E et al., Nat. Rev. Nephrol 2012

Legend:

1 Mesothelial denudation
2 Interstitial fibrosis and peritoneal thickening
3 Neoangiogenesis and vasculopathy
4 Chronic sterile inflammation

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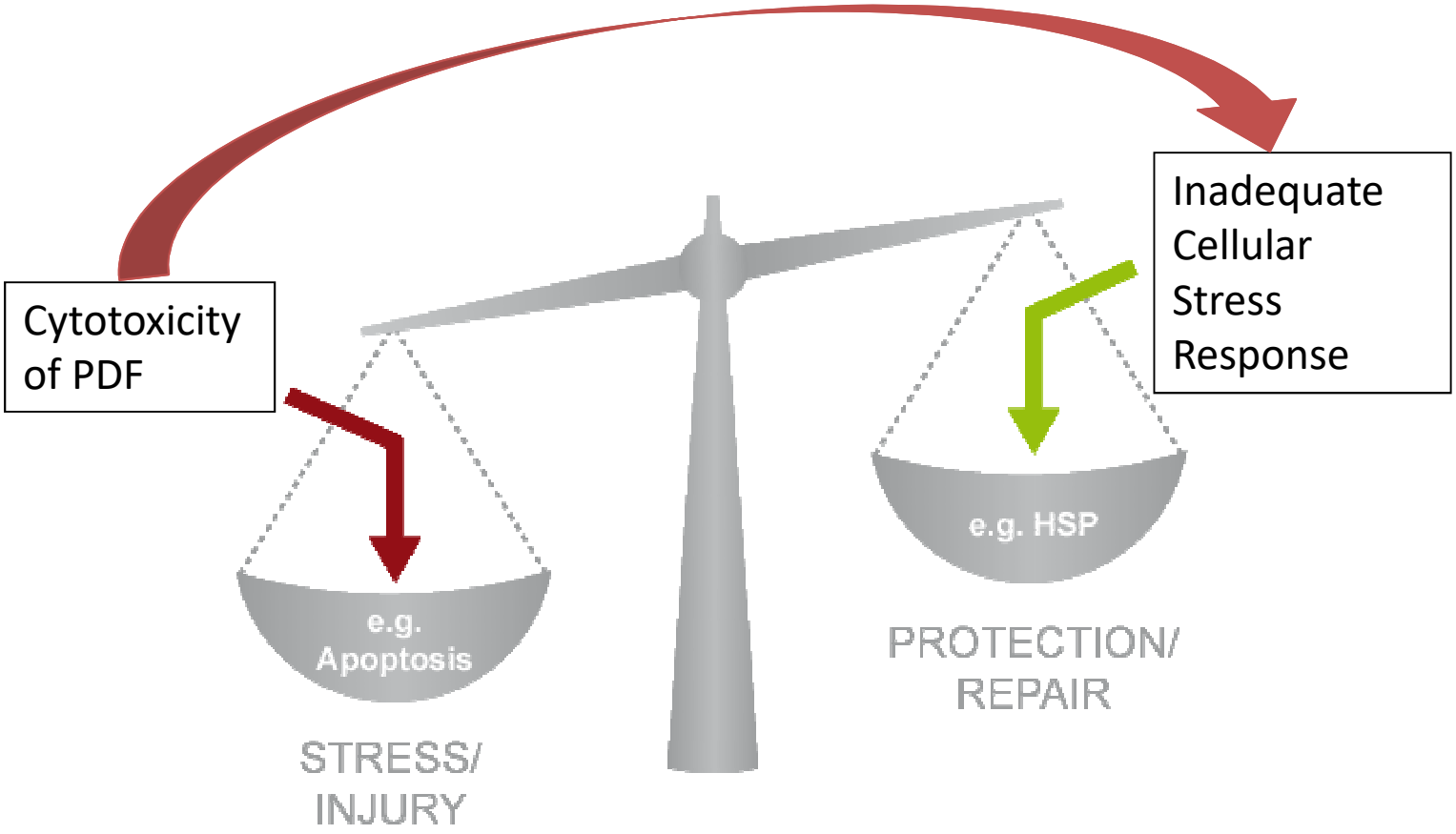
PDF induces inadequate HSR in PD



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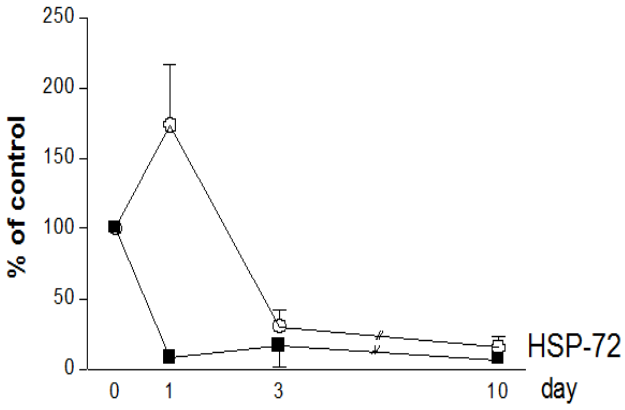
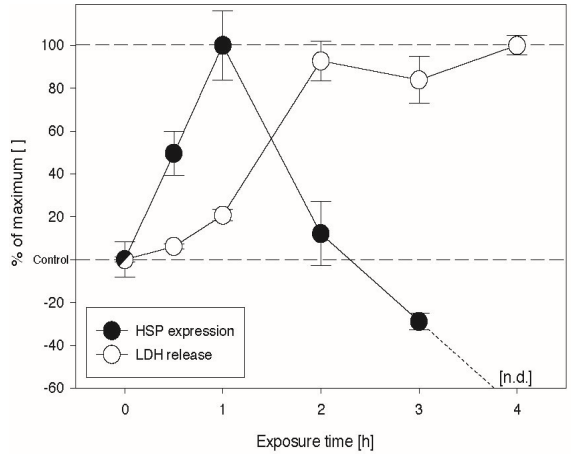
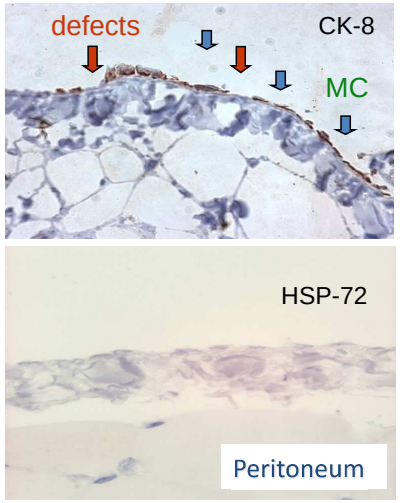


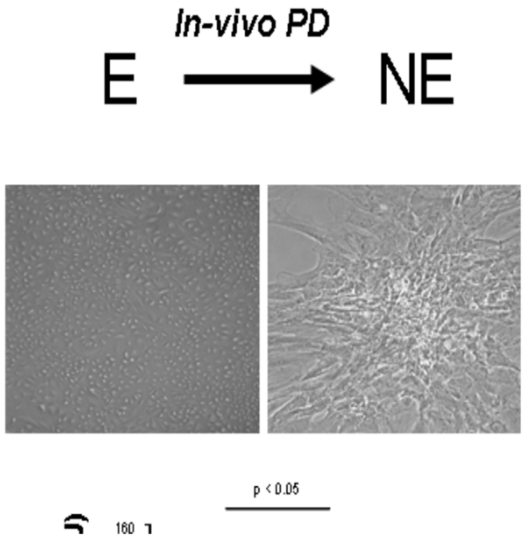
Bender *et al.*, Nephrol Dial Transplant 2011



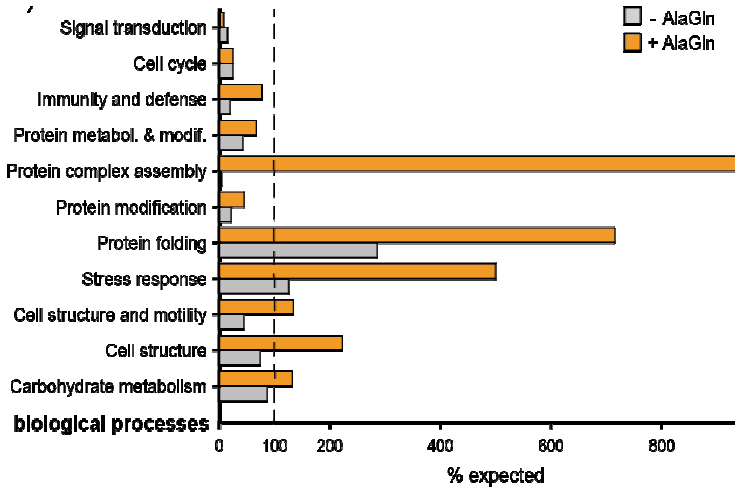
Kratochwill *et al.* Am J Pathol 2011



Endemann *et al.*, Am J Physiol 2007

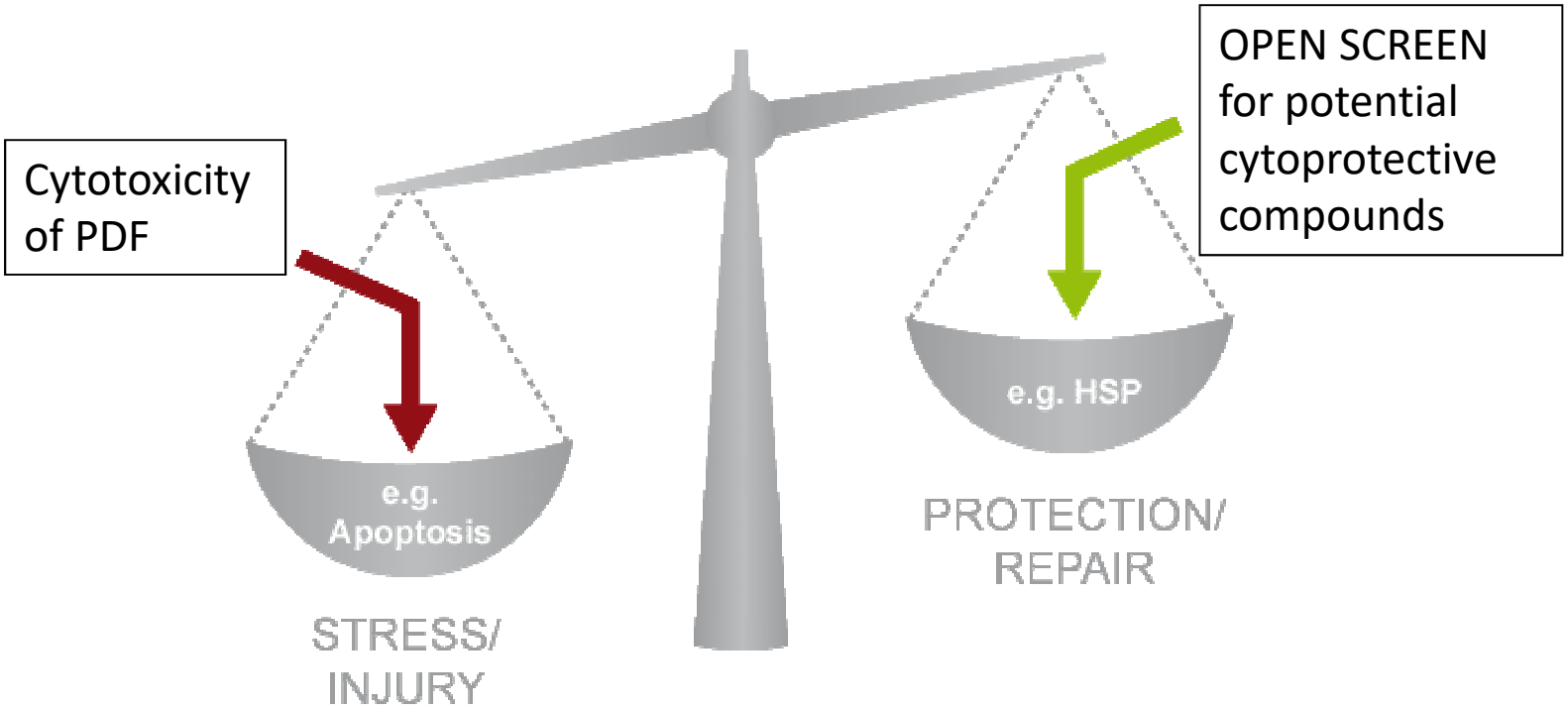


Vargha *et al.*, Nephrol Dial Transplant 2008

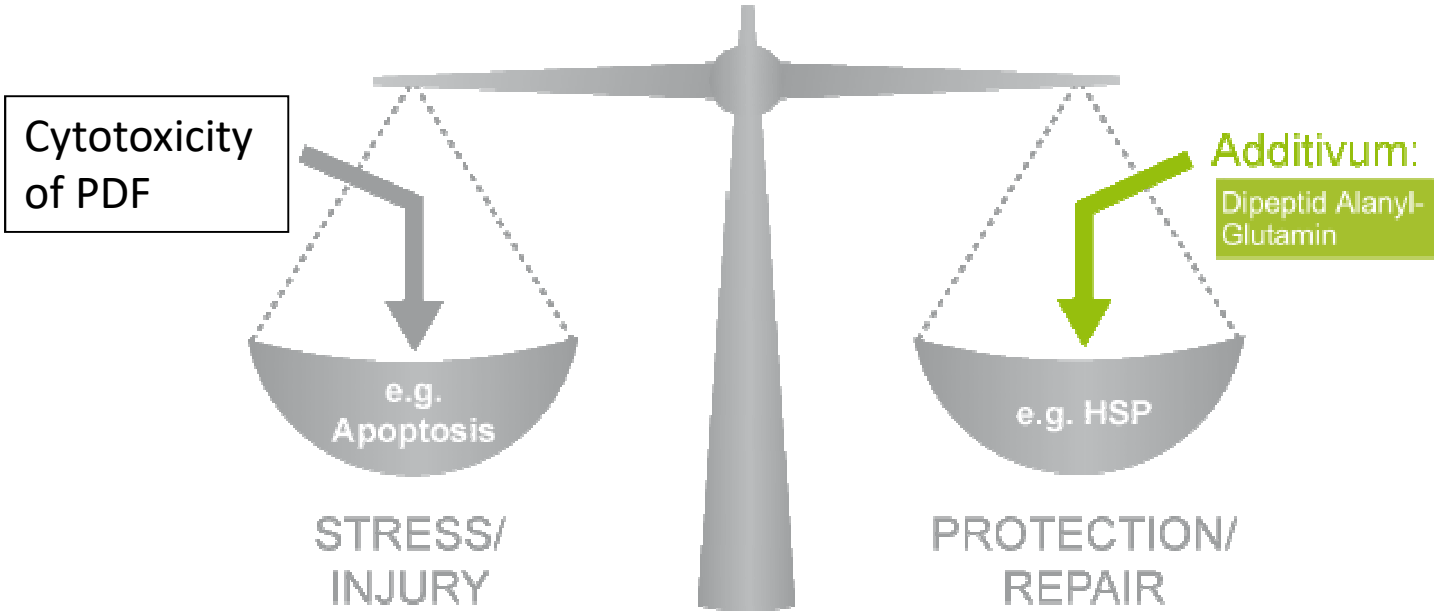


Kratochwill *et al.* Nephrol Dial Transplant 2012

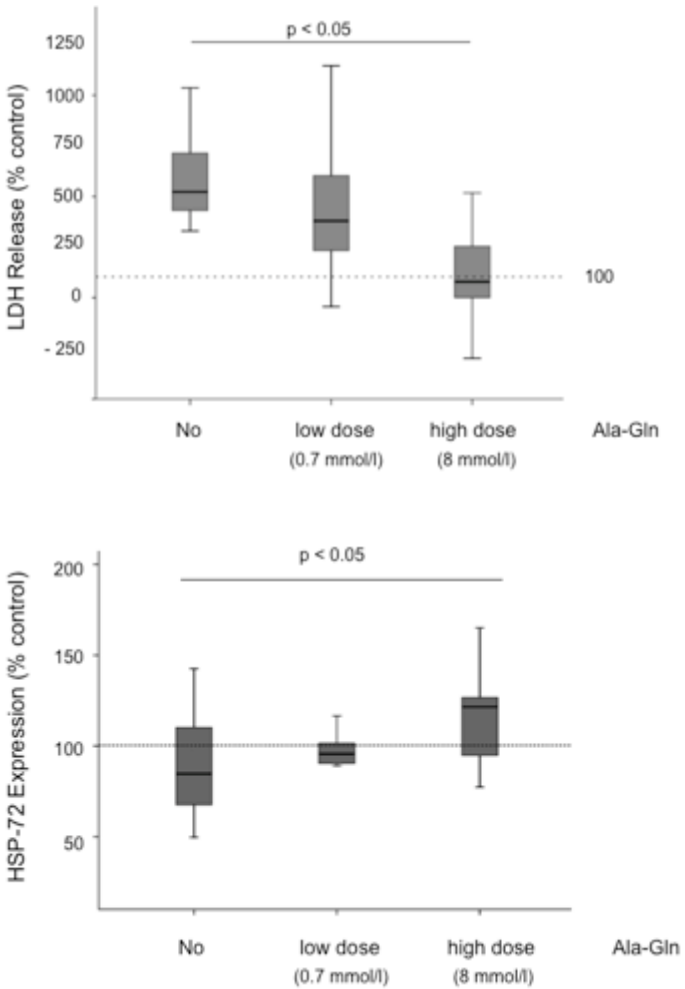
Simple Bio-Assay to Search for Cytoprotective Additives



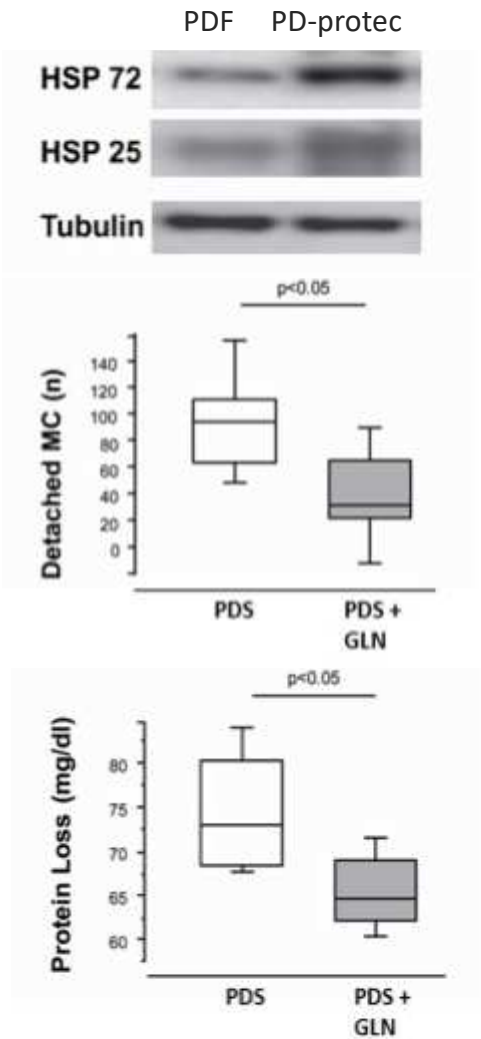
Simple Bio-Assay to Search for Cytoprotective Additives



AlaGln enhances HSR and Cytoprotection



Kratochwill *et al.*, NDT 2011



Bender *et al.*, PDI 2010

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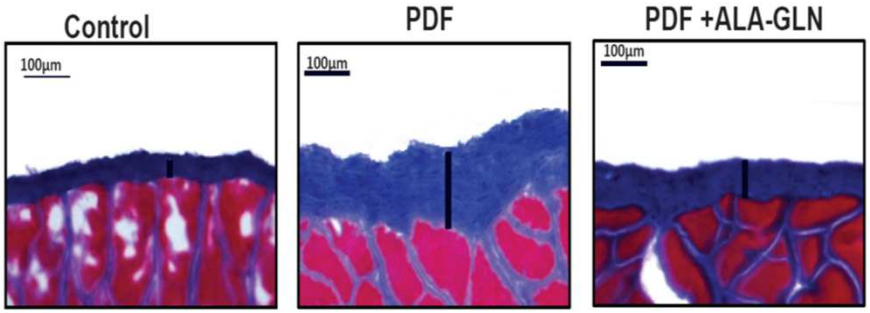
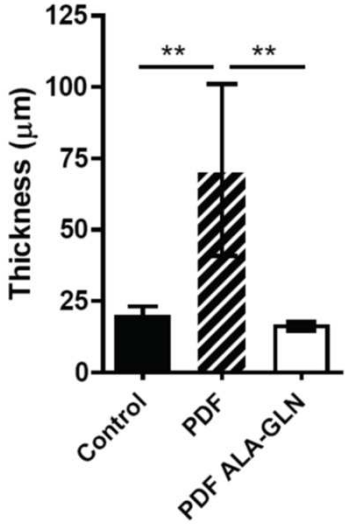
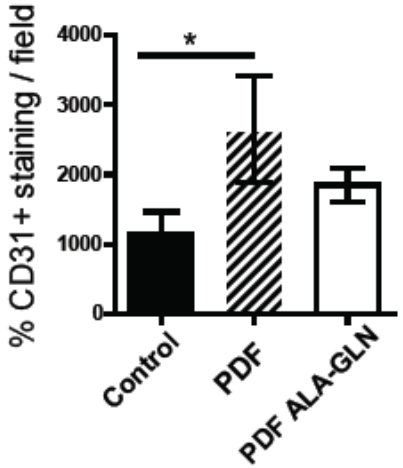
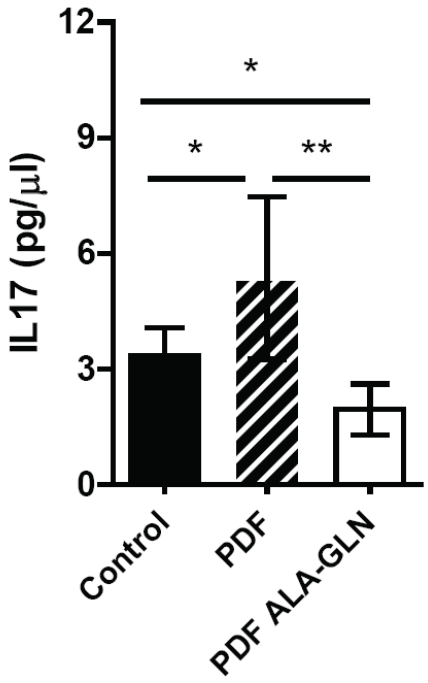
The “Amsterdam Uremic Rat Model of PD”

Peritoneal IL-17 and Membrane Damage are attenuated by AlaGln









Ferrantelli *et al.*, Kidney International 2016

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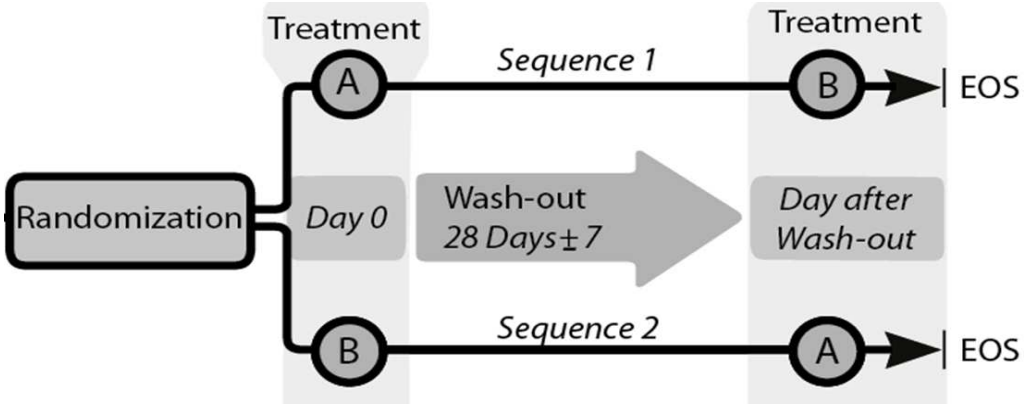
VU medisch centrum

Safety and Efficacy of the Addition of Alanyl-Glutamine-Dipeptide to Dianeal®

Monocenter open randomised cross-over Phase I/II



N=20

Sex: M : F = 65 : 35

Age: 55.8 ± 15.2 years

System APD : CAPD = 50 : 50

Residual renal function 4.6 ± 4.2 ml/min

History of peritonitis: 30%

Years on PD: 2.5 ± 1.9

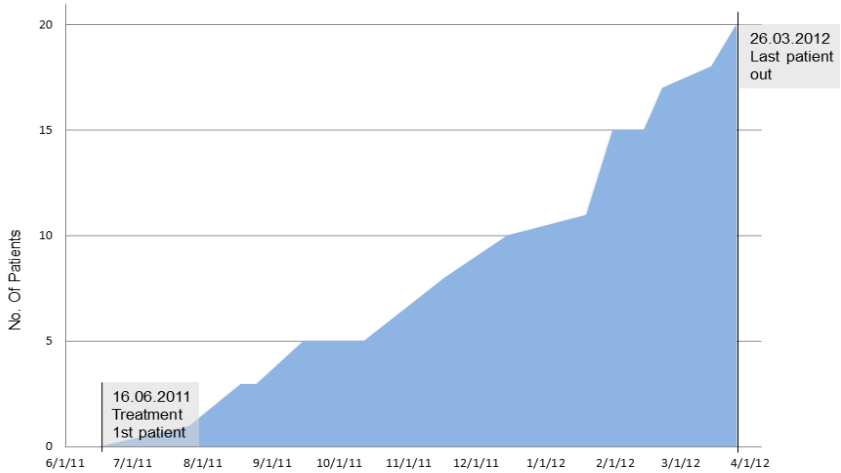


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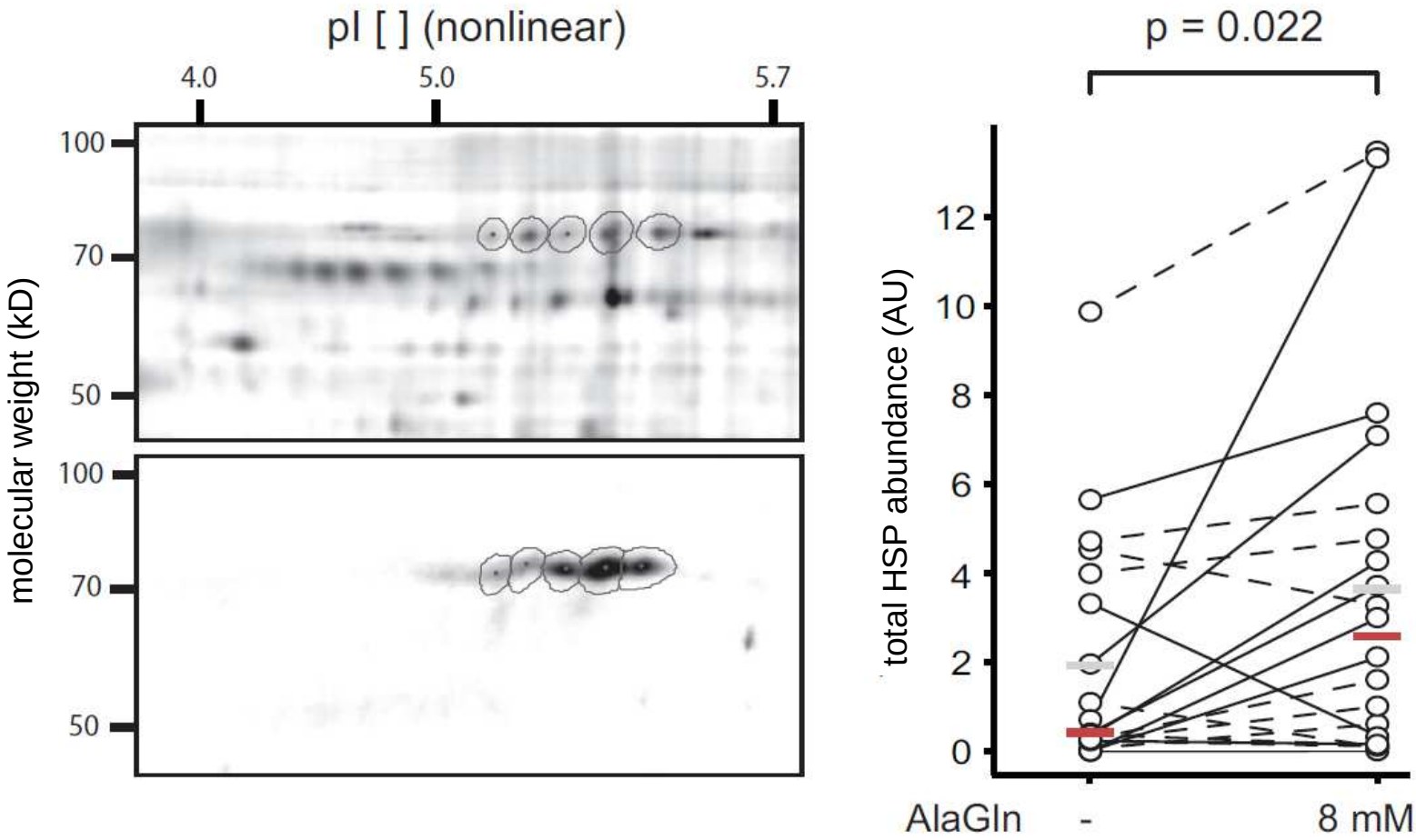
Fig 3. AlaGln treatment increased HSP expression in peritoneal effluent cells.



Kratochwill K, Boehm M, Herzog R, Gruber K, Lichtenauer AM, et al. (2016) Addition of Alanyl-Glutamine to Dialysis Fluid Restores Peritoneal Cellular Stress Responses – A First-In-Man Trial. PLoS ONE 11(10): e0165045. doi:10.1371/journal.pone.0165045
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0165045

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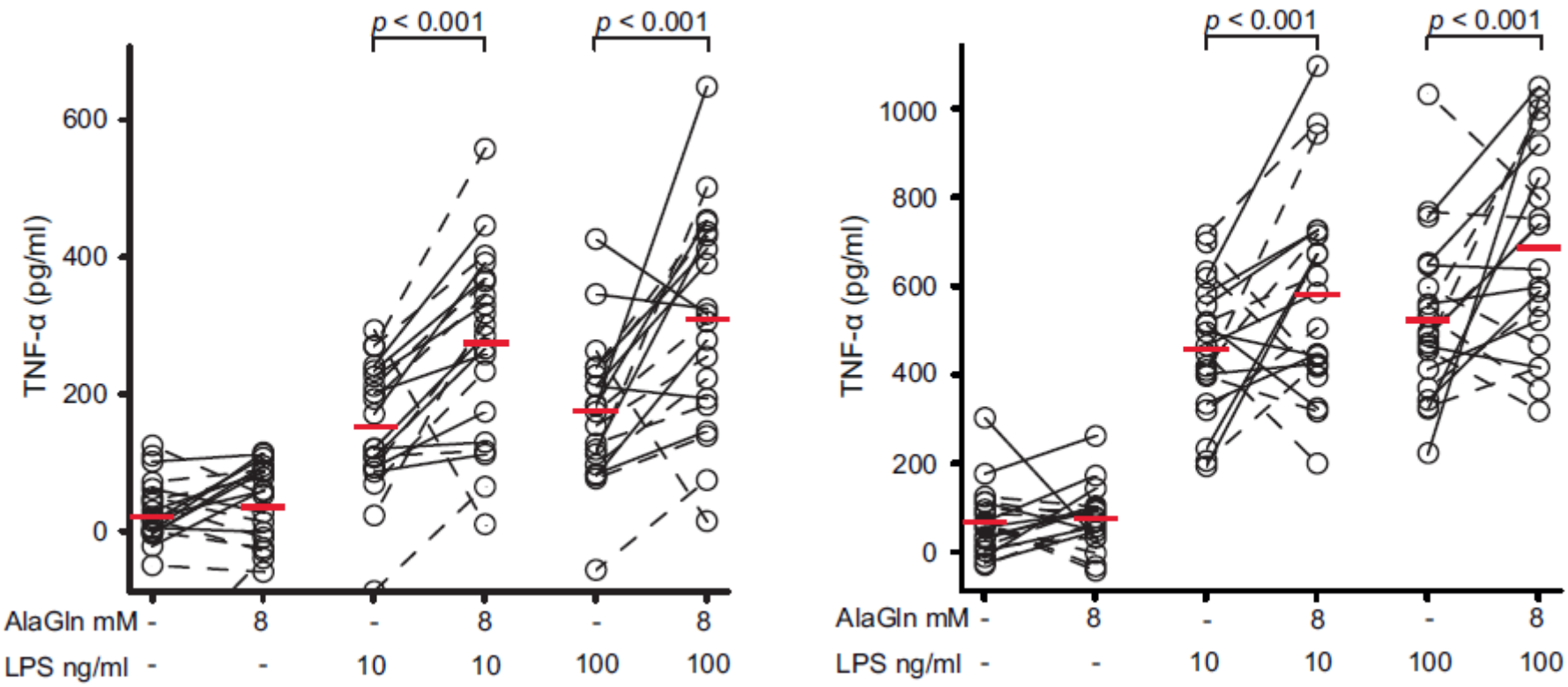
Fig 4. Lipopolysaccharide (LPS)-stimulated release of tumor necrosis factor alpha (TNF-α) by heterologous normal human peripheral blood mononuclear cells (PBMC) following a 4 h ex-vivo exposure to PD effluents obtained from the PET of patients treated with standard PDF or AlaGln-supplemented PDF.



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http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0165045

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Fig 6. Levels of interleukin 8 (IL-8) and interleukin 6 (IL-6) in PET effluents from patients treated with PDF in the absence or presence of 8mM AlaGln.

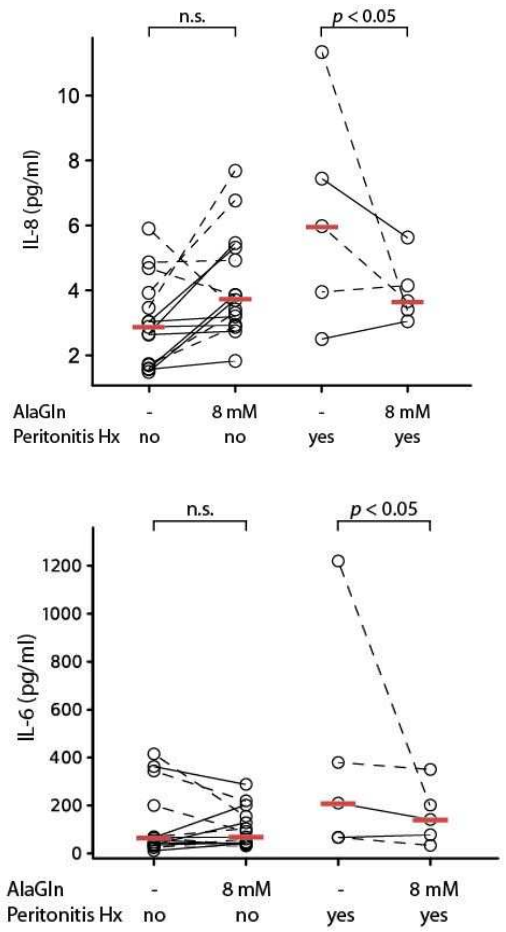
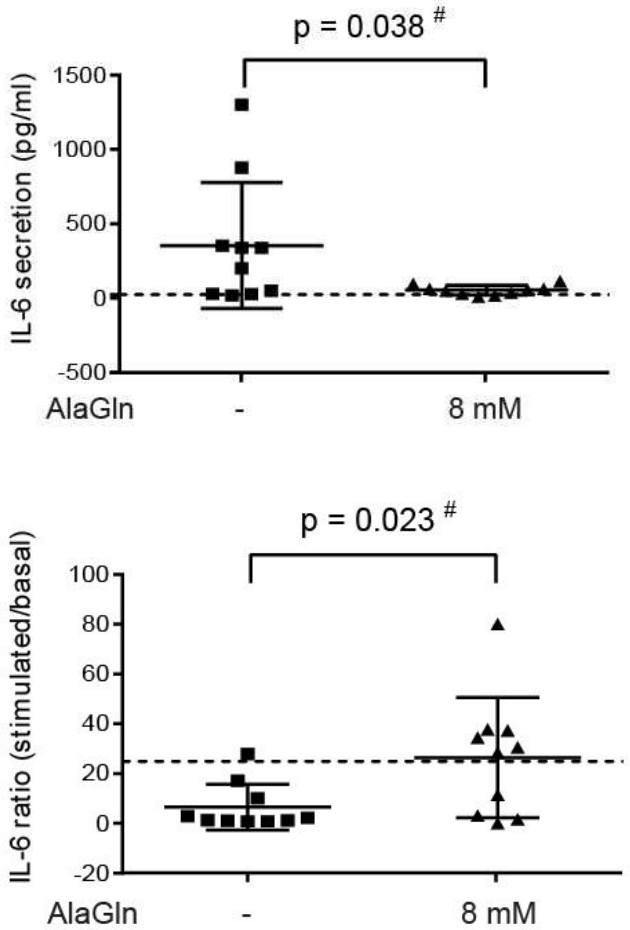


Fig 7. Inflammation and immuno-competence in the mouse model of PD- associated peritonitis.



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http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0165045

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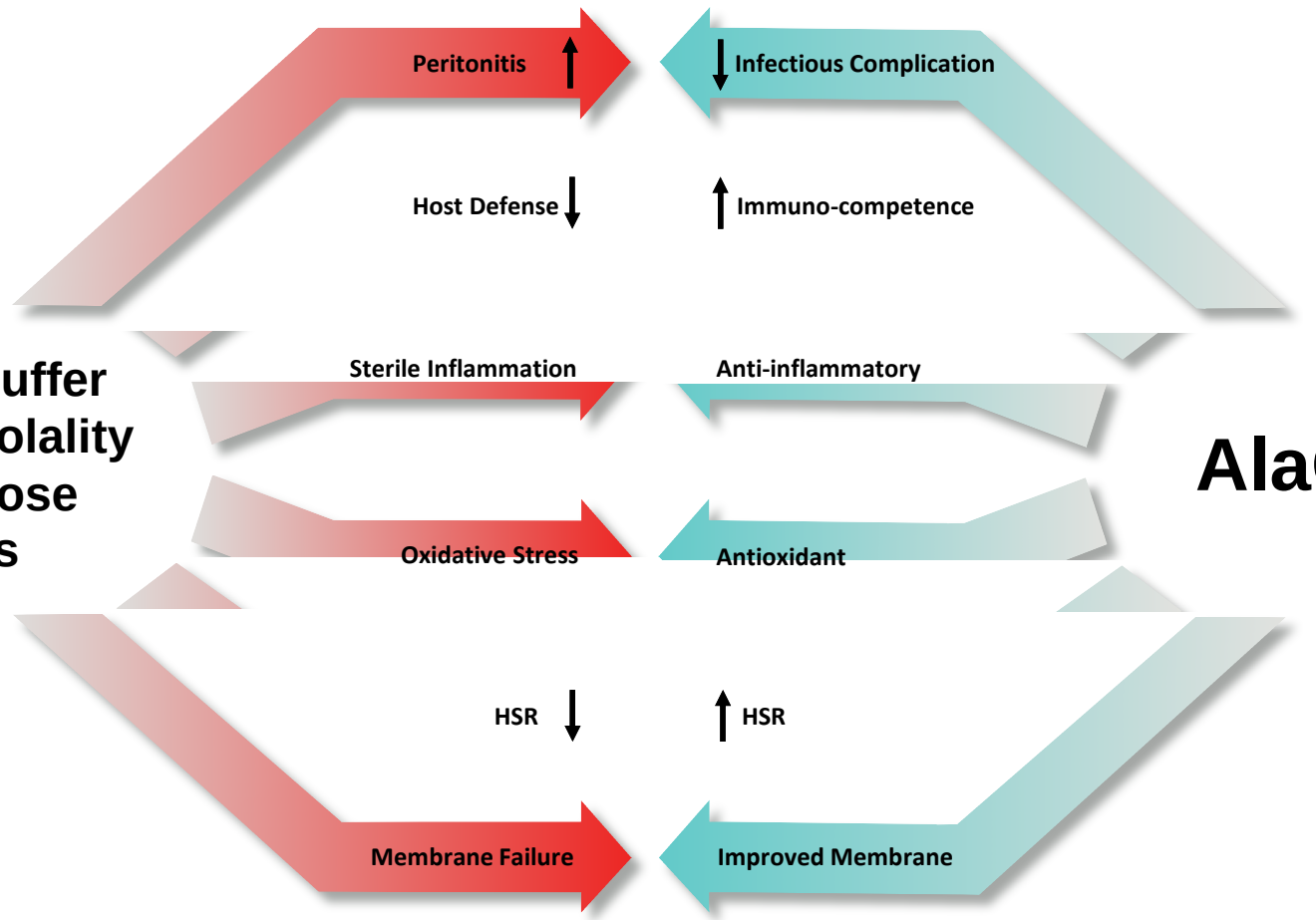
Potential Protective Effects of AlaGln in PD



- pH/Buffer
- Osmolality
- Glucose
- GDPs

AlaGln

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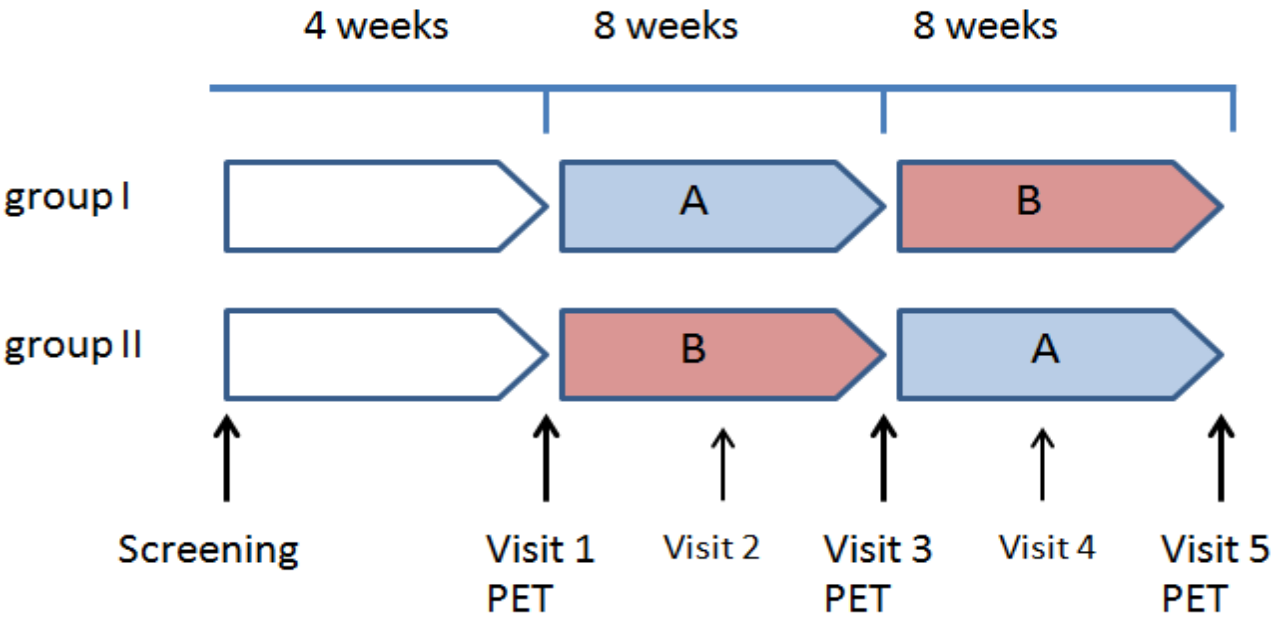
→ **AlaGln may Counteract Dysfunctional CSR in PD**

Randomized Controlled Double Blinded Phase II Trial



A: Standard Physioneal®

B: *PD-protec™* 8mM AlaGln

All Austrian Centers
with >10 Patients

EudraCT No. 2013-000400-42
PI: Prof. Andreas Vychytil, III Med

- **Two Primary Endpoints**
  - **Mesothelial cell mass/status**
  - **Peritoneal immunocompetence**

… and various secondary and exploratory Endpoints covering all Pathomechanisms relevant in PD

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Thank you!

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Dagmar Csaicsich
Thomas Müller
Michael Böhm
Silvia Tarantino
Andrea Ulbrich
Das Pflegeteam

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Rebecca Herzog
Katarzyna Bialas
Sophie Bromberger
Isabel Sobieszek
Kathrin Stampf
Anja Wagner
Markus Unterwurzacher
Ina Jaschinski

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