

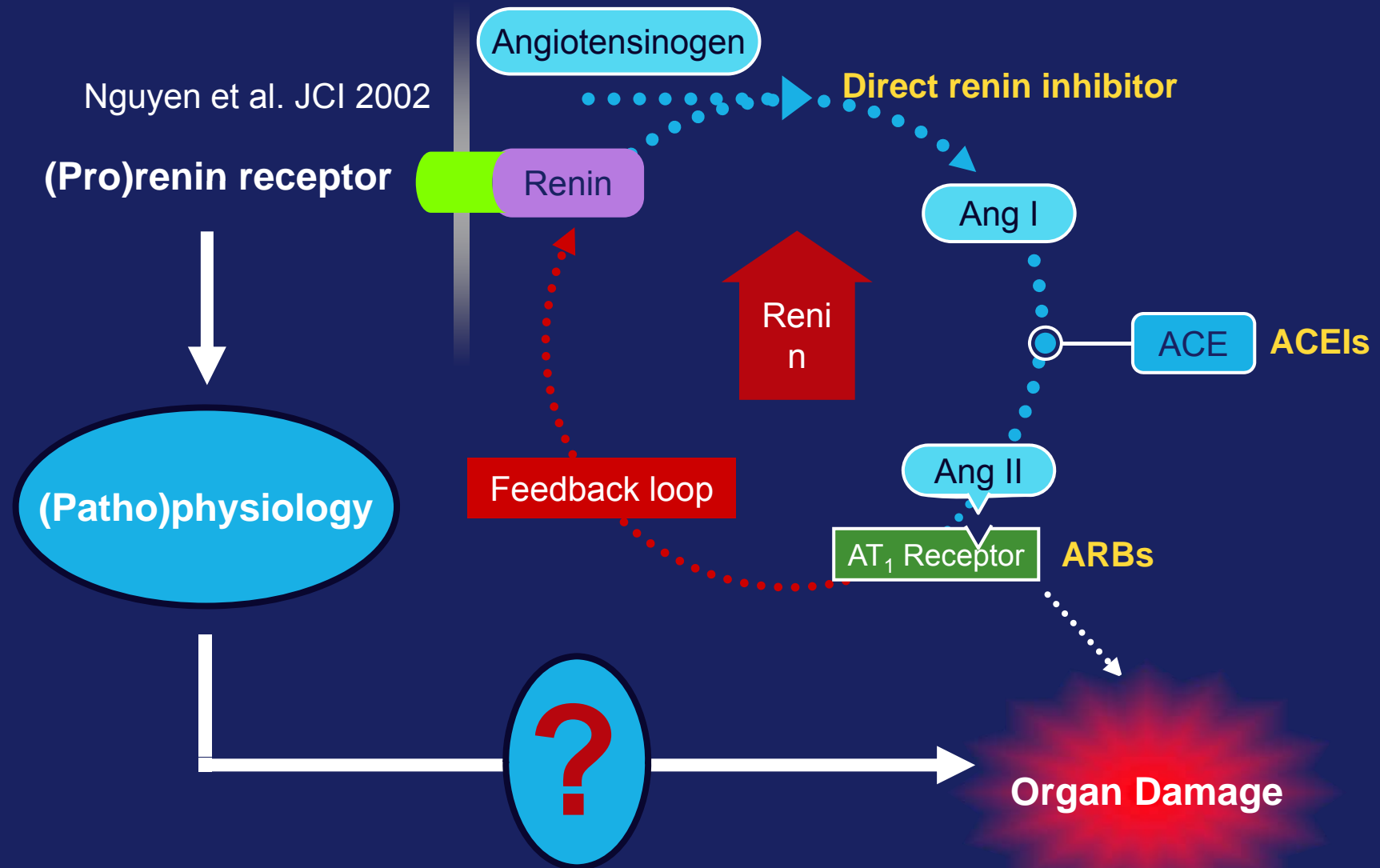
(Pro)Renin and the (Pro)Renin Receptor: An Update

Dominik N. Müller

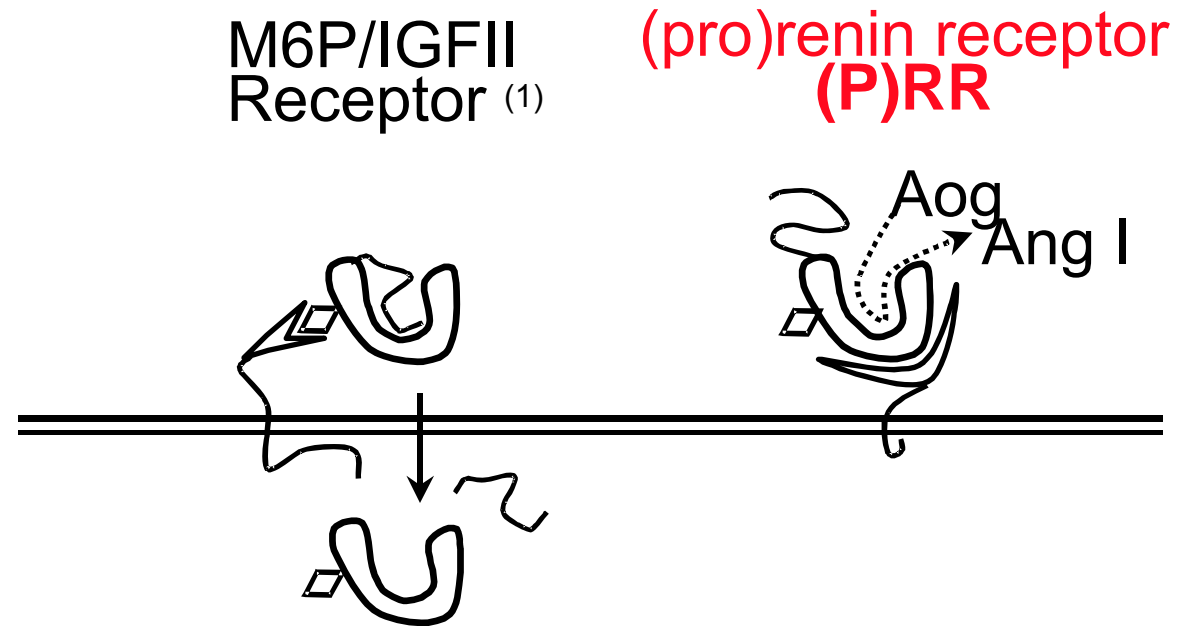
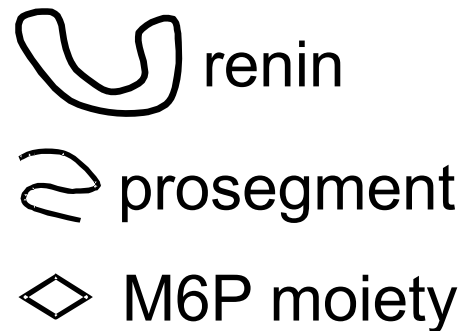


Seoul, Korea, October 2007

The new renin angiotensin system?



(Pro)Renin Receptors



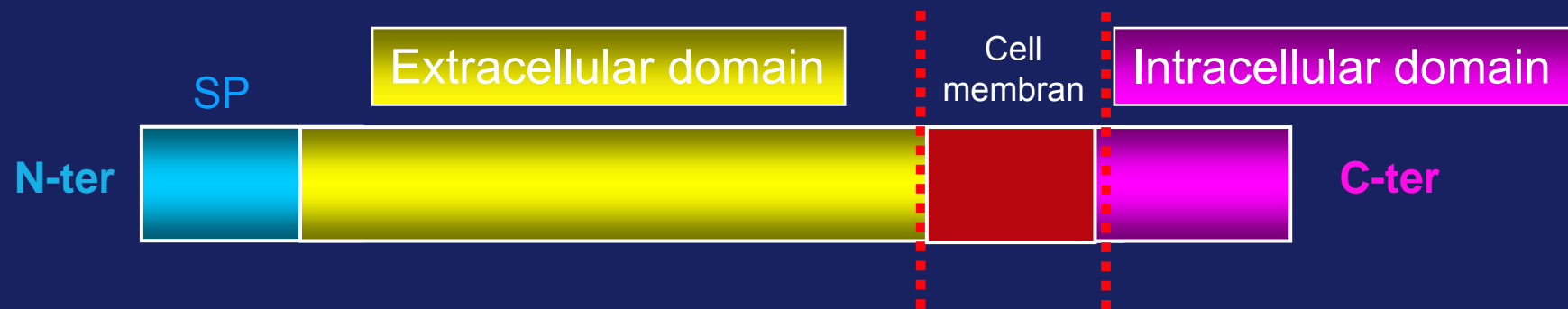
Angiotensin I generation:	Intracellular	Cell surface
Activation of prorenin:	Proteolytic	Non-proteolytic
Signalling:	No, Clearance receptor	ERK1/2 P38, HSP70 ⁽²⁾

From Danser & Deinum, *Hypertension* 2005

1. Saris *Am J Physiol*, 2001 and 2 Saris *Hypertension* 2006

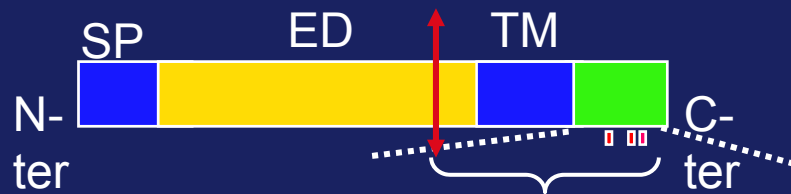
Structure of the (Pro)renin Receptor (P)RR

350 amino acid-protein, no homology



Potential Relation of the (P)RR with v-ATPase

Nishi & Forgac, Nature Reviews 2002, vol3, 94-103

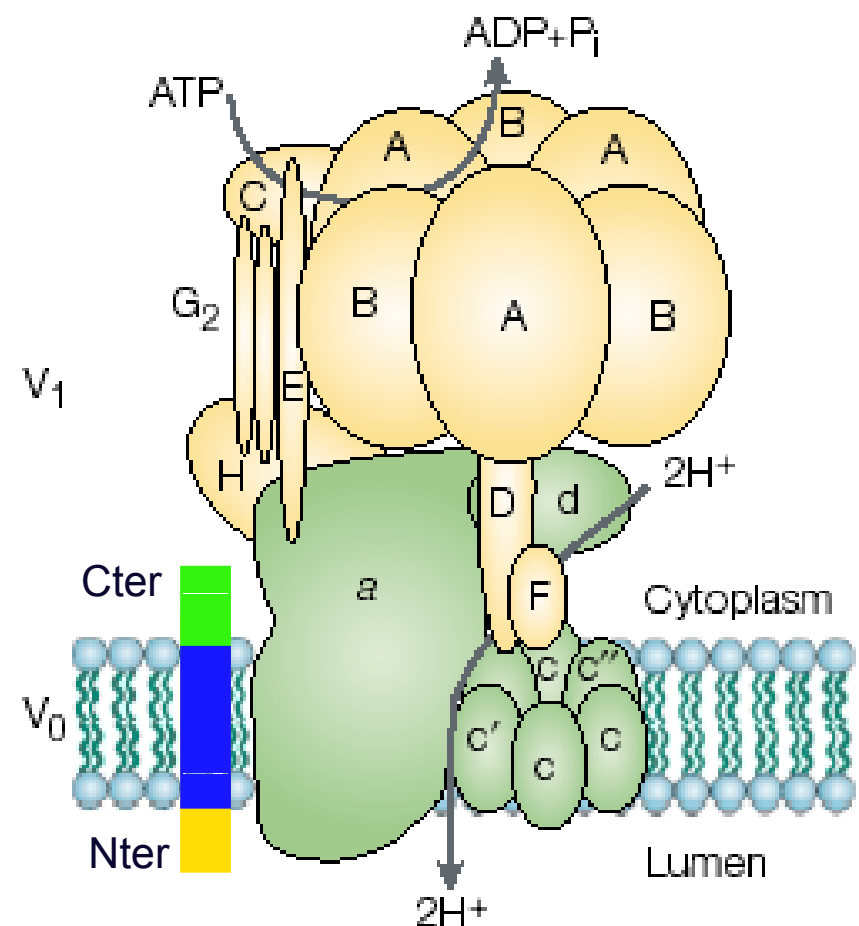


8.9 kD fragment = M 8.9
(Ludwig et al., JBC, 1998, 273:10939)

Vacuolar proton-ATPase pumps proton across membranes of different compartment

- acidification of endosome, lysosome
- essential for neurotransmitter concentration into synaptic vesicles

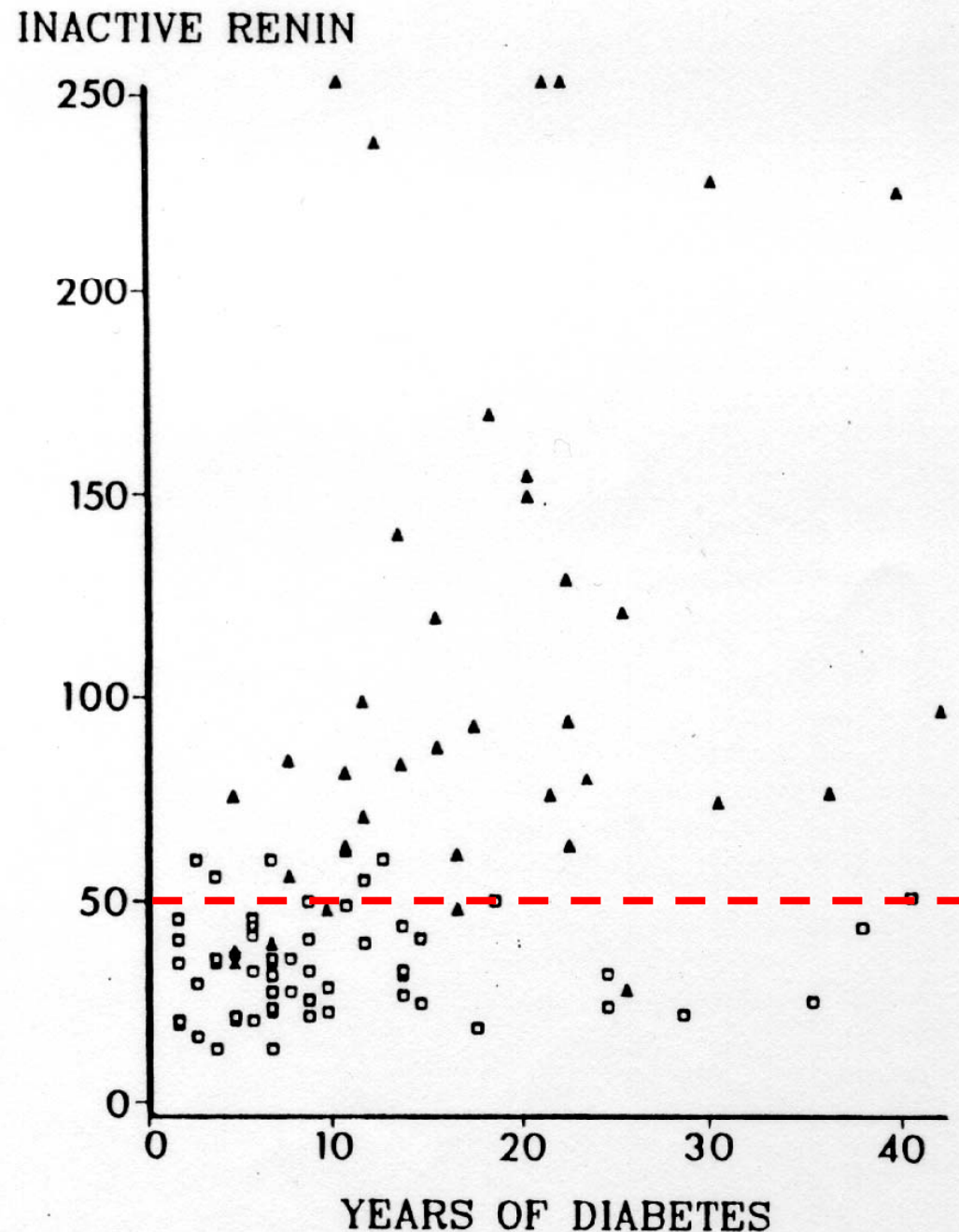
V-ATPase



Prorenin as a marker of microvascular complications in diabetes

Luetscher et al.,
NEJM 1985

▲ patient with microvascular complications

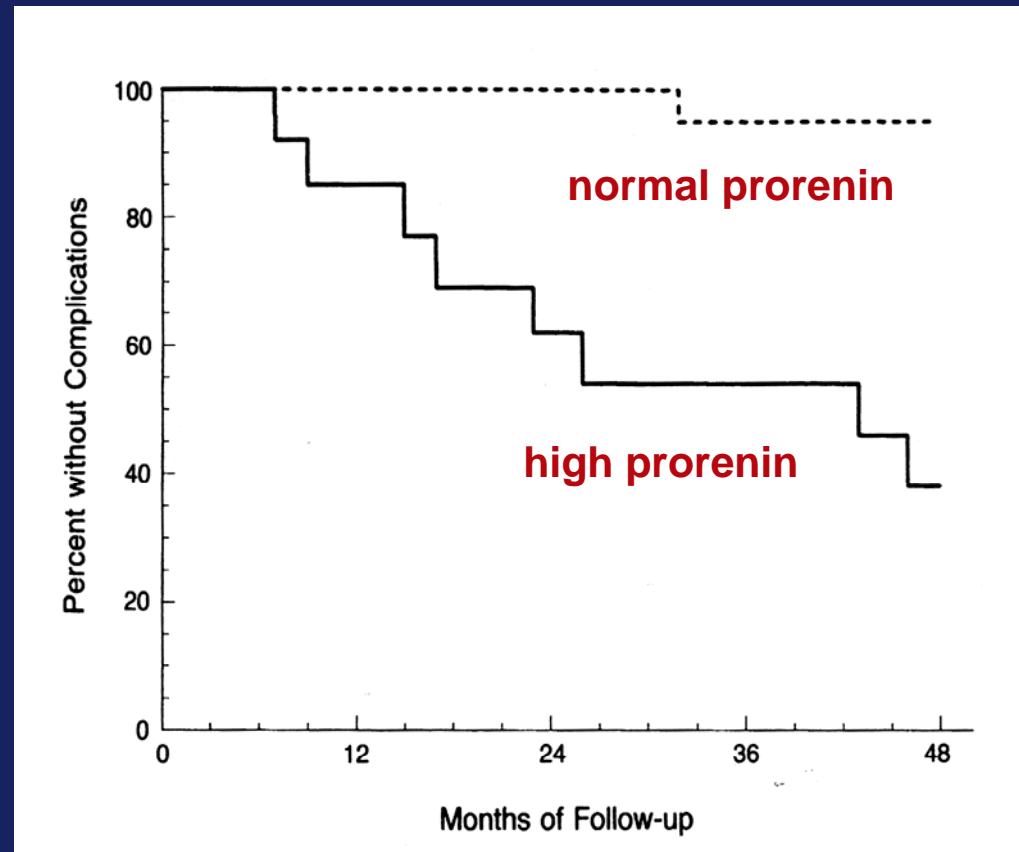


Prorenin is a marker of microvascular complications in diabetes

Incidence of retinopathy or albuminuria in children with insulin-dependent diabetes with:

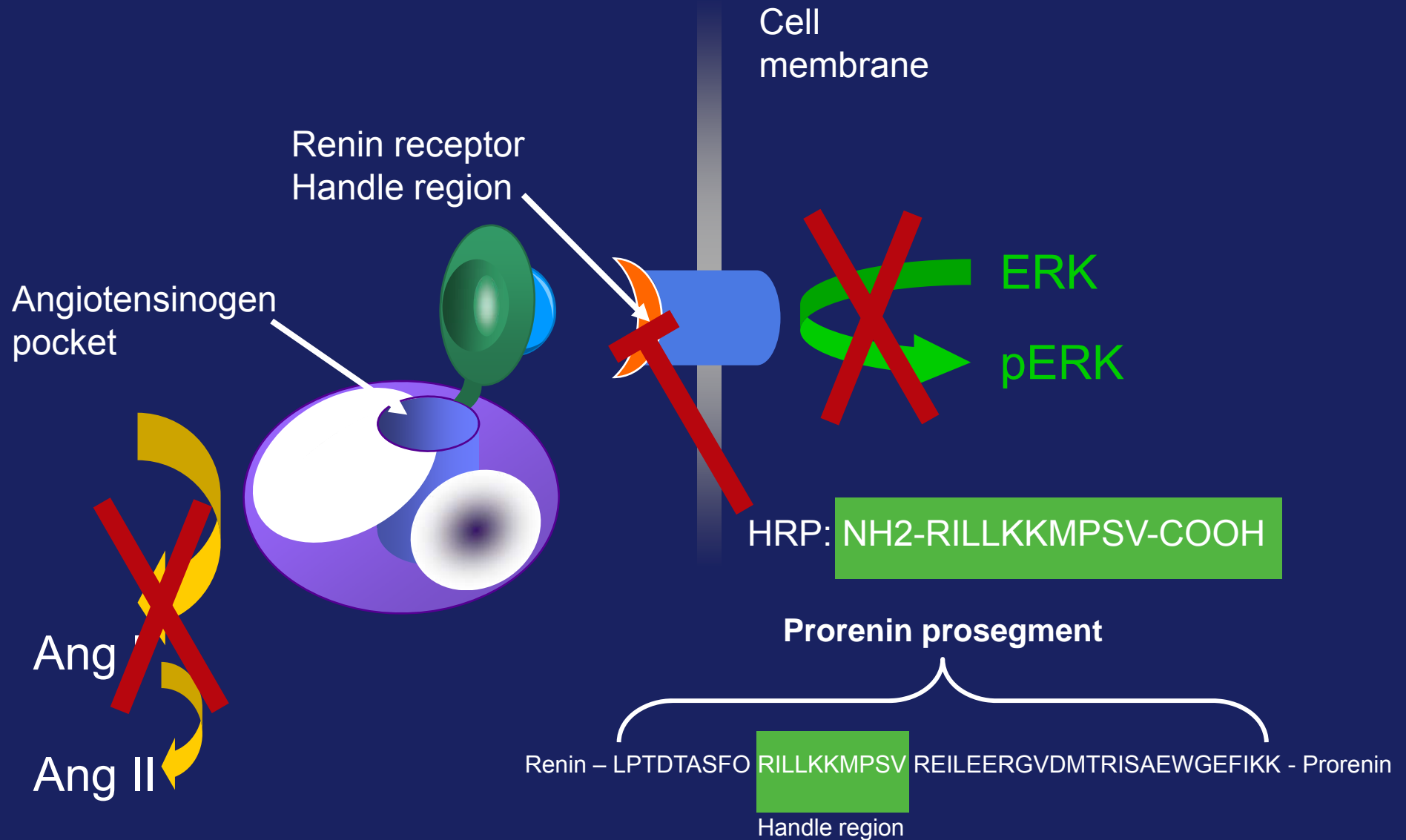
Prorenin in the normal range -----

Prorenin above upper limit ———



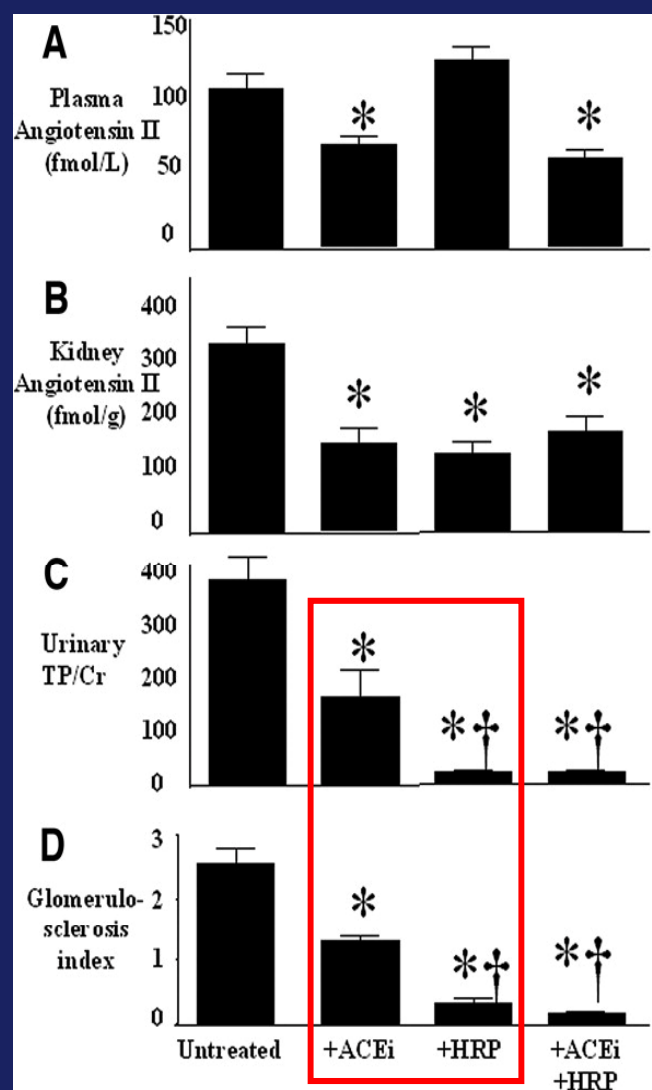
Wilson and Luetscher, NEJM 1990

Handle region peptide (HRP) blocks the (pro)renin receptor (Ichihara and Suzuki et al.)



Role of the renin receptor blockade on diabetic nephropathy

WT mice

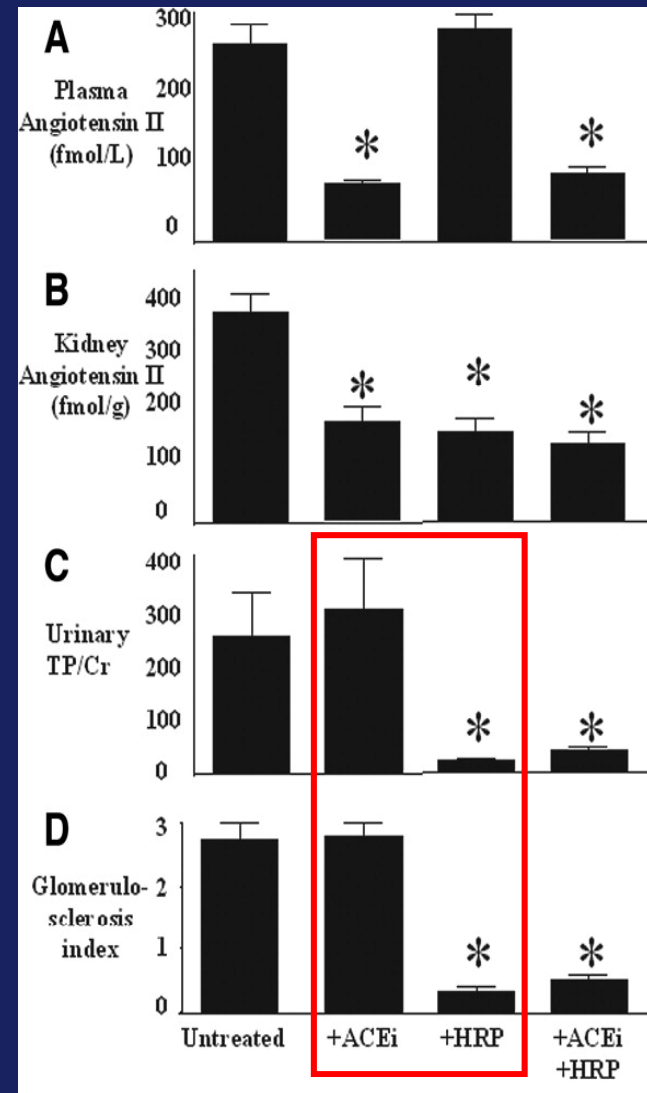


Both treatments and combined treatment are highly effective in WT (normal) mice

Role of the Renin Receptor Blockade on Diabetic Nephropathy (Ichihara et al.)

AT1 receptor KO mice

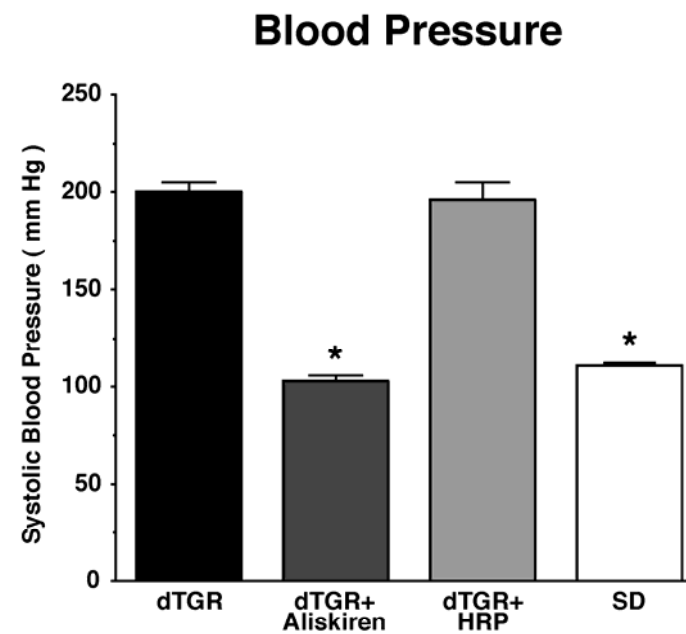
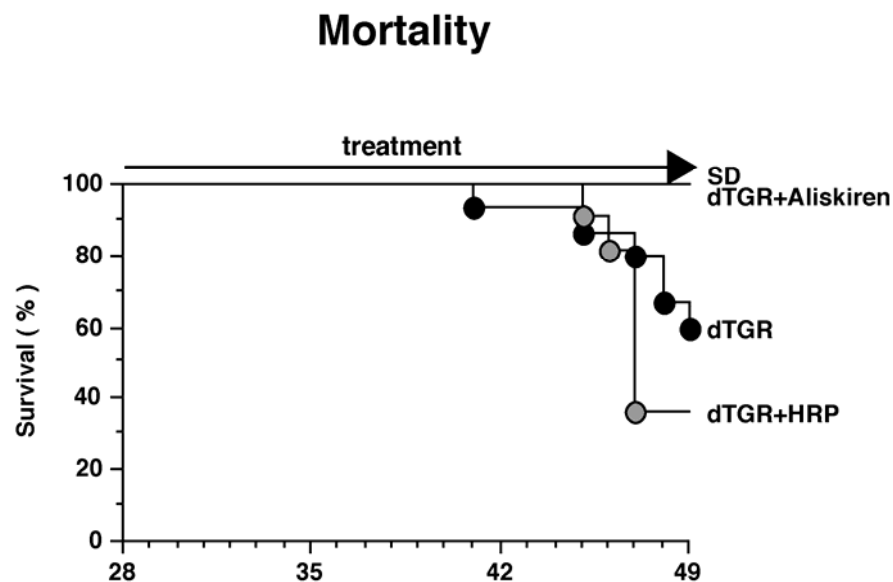
HRP works while ACEi does not in AT1a KO (abnormal) mice



Role of the renin receptor blockade vs. renin inhibition in dTGR



dTGR(hREN*hAOGEN)

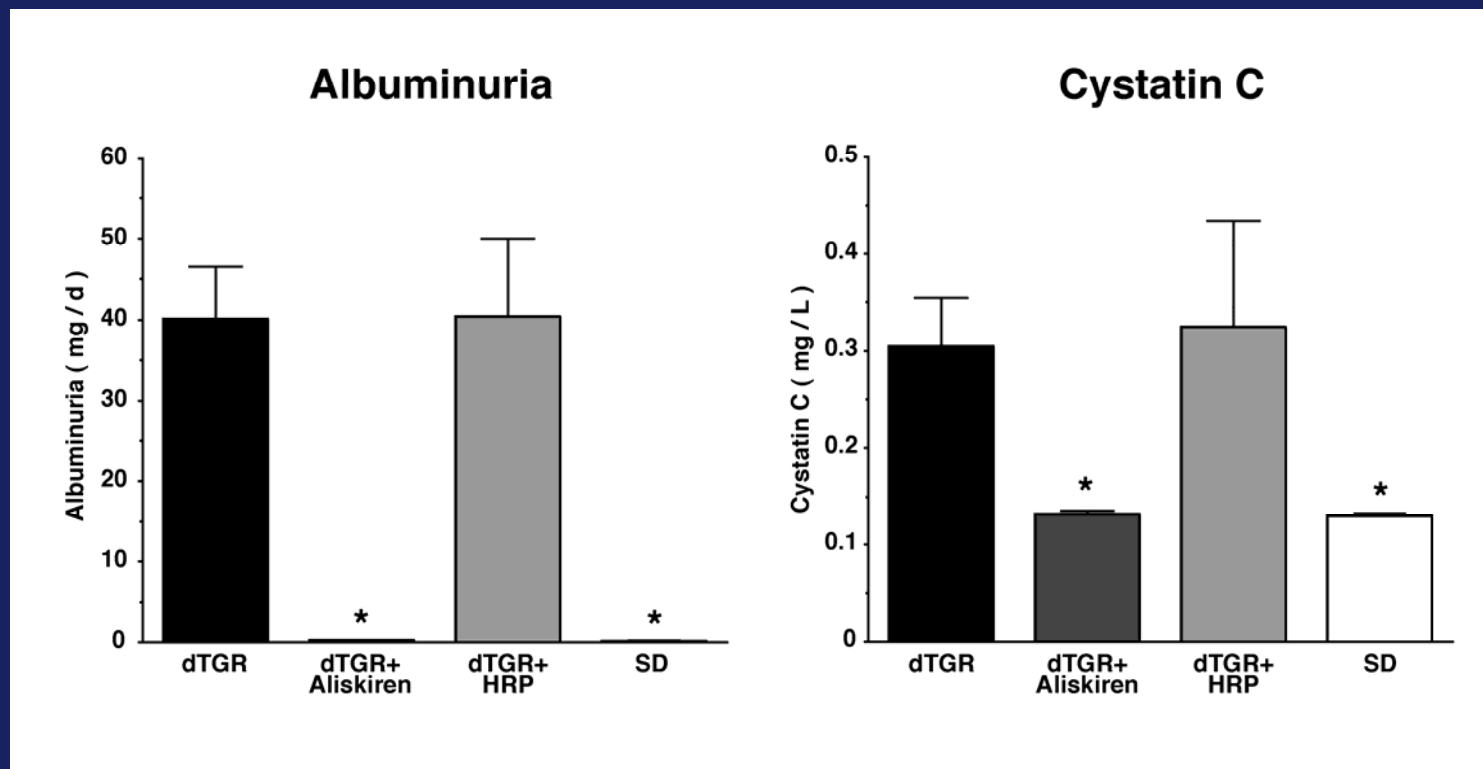


Role of the renin receptor blockade vs. renin inhibition in dTGR

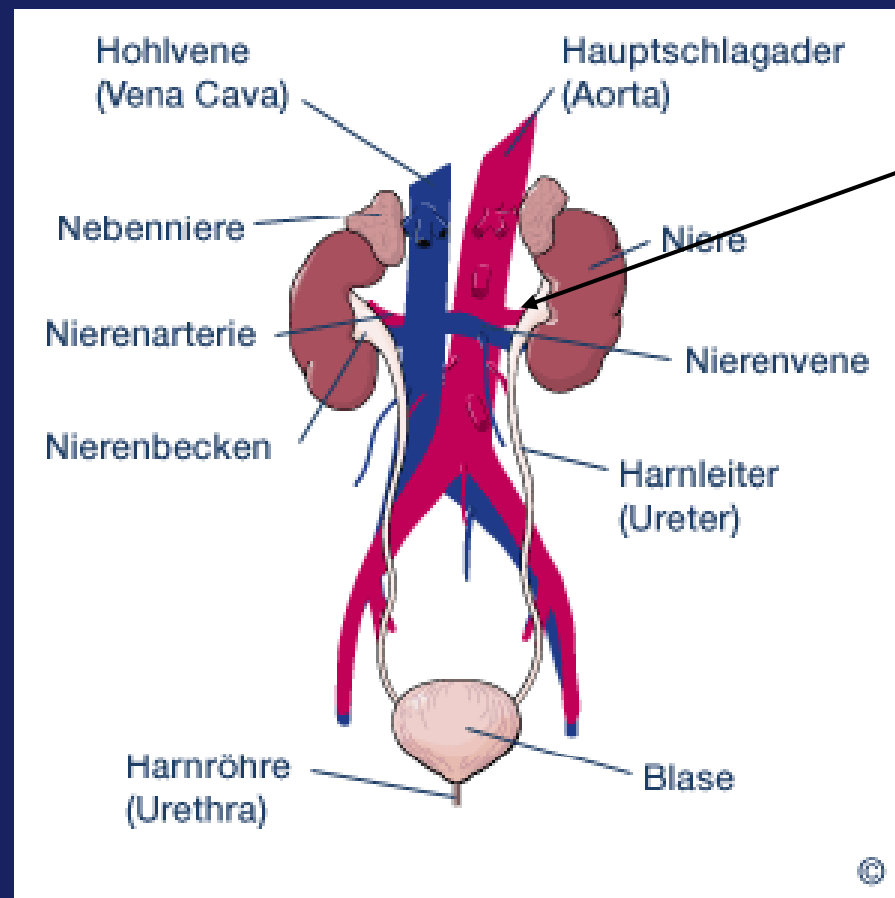


Aliskiren works
while HRP does
not

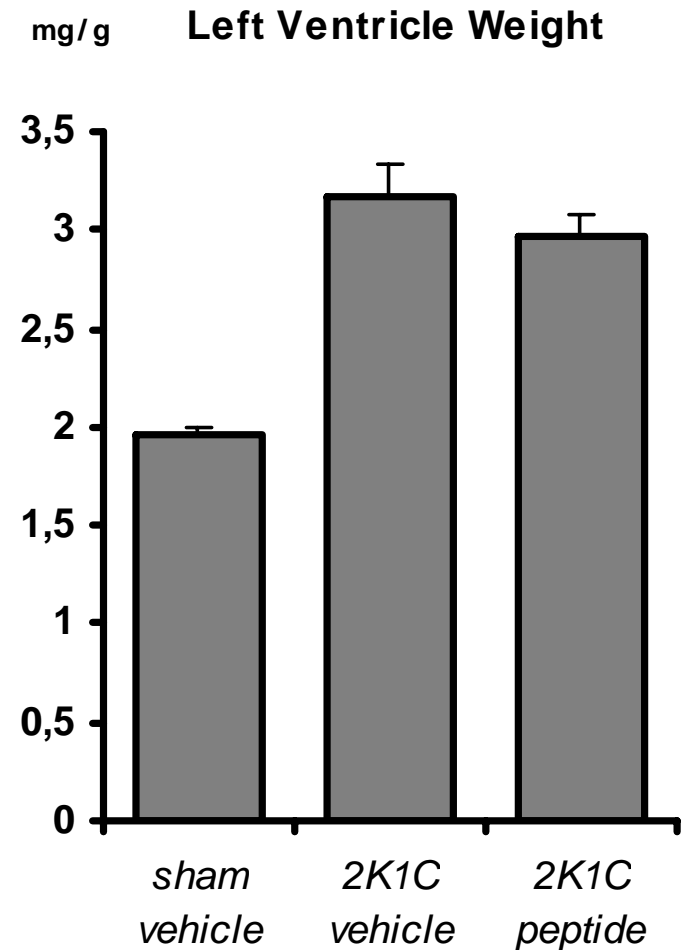
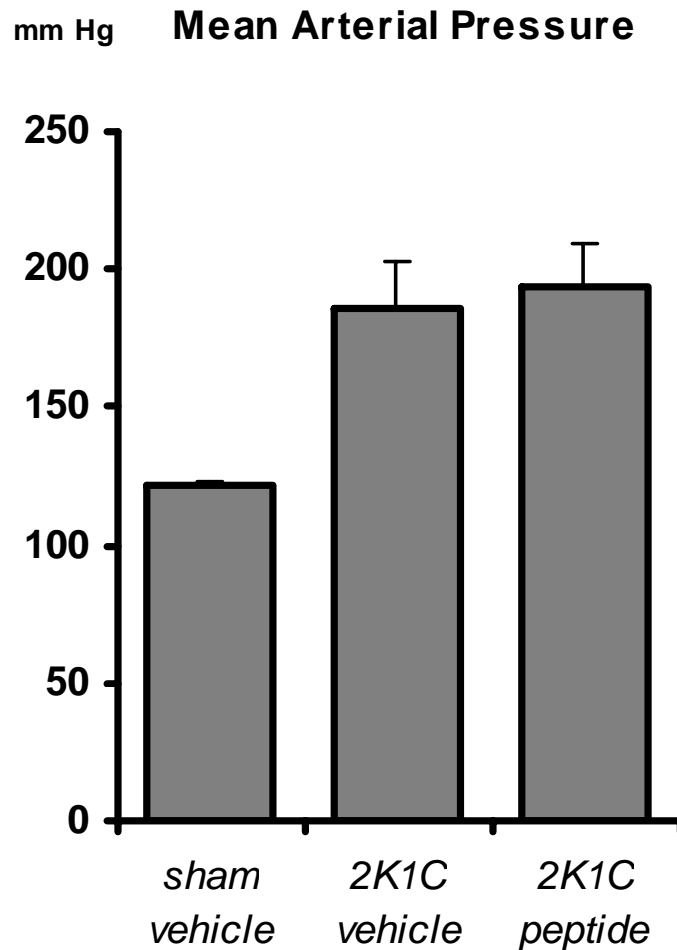
dTGR(hREN*hAOGEN)



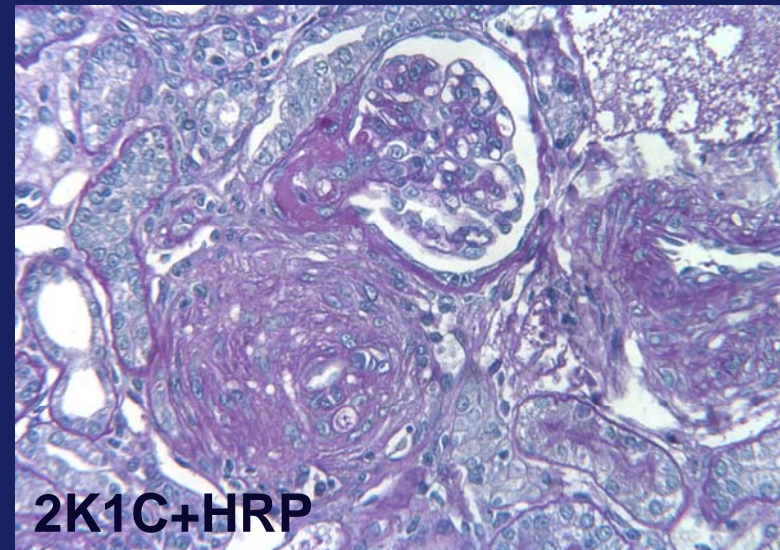
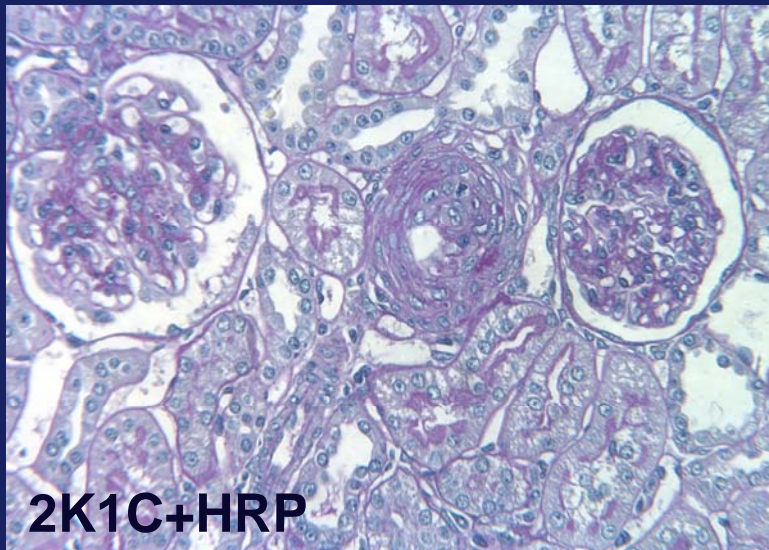
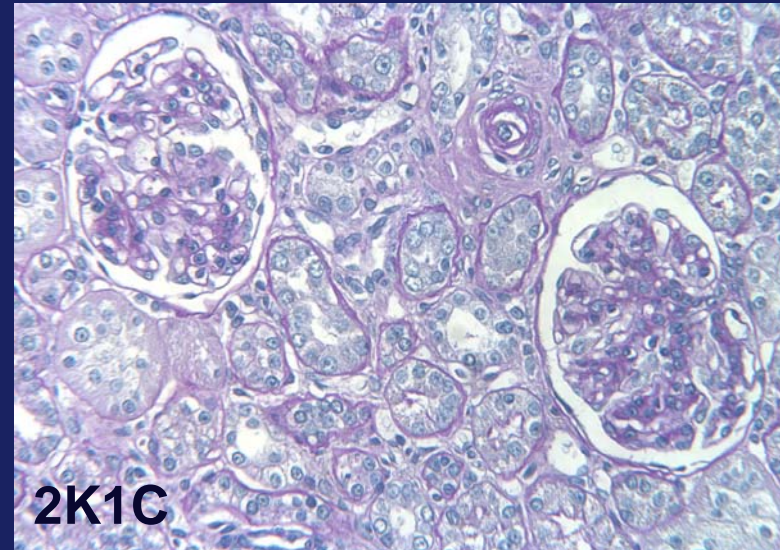
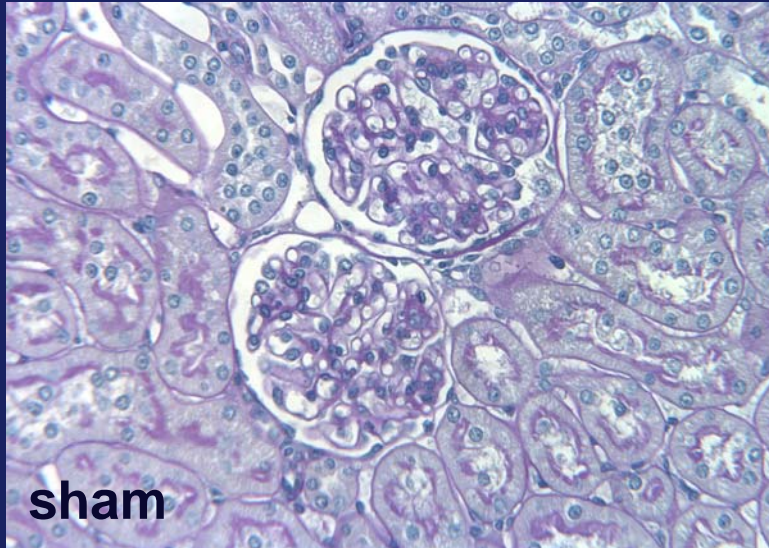
Role of (Pro)renin Receptor Blockade with HRP in 2K1C Renovascular Hypertension



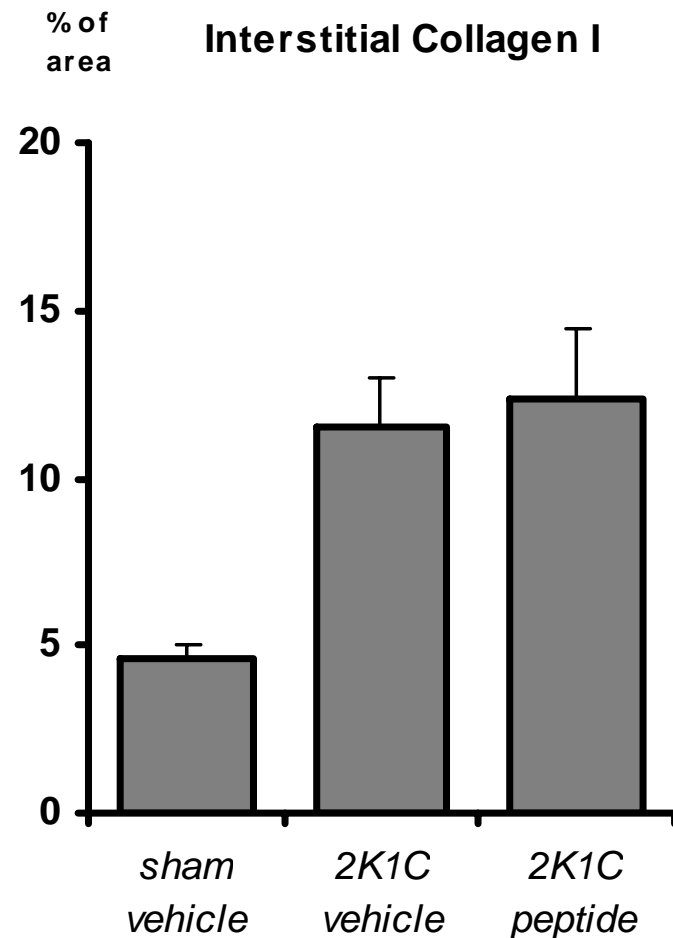
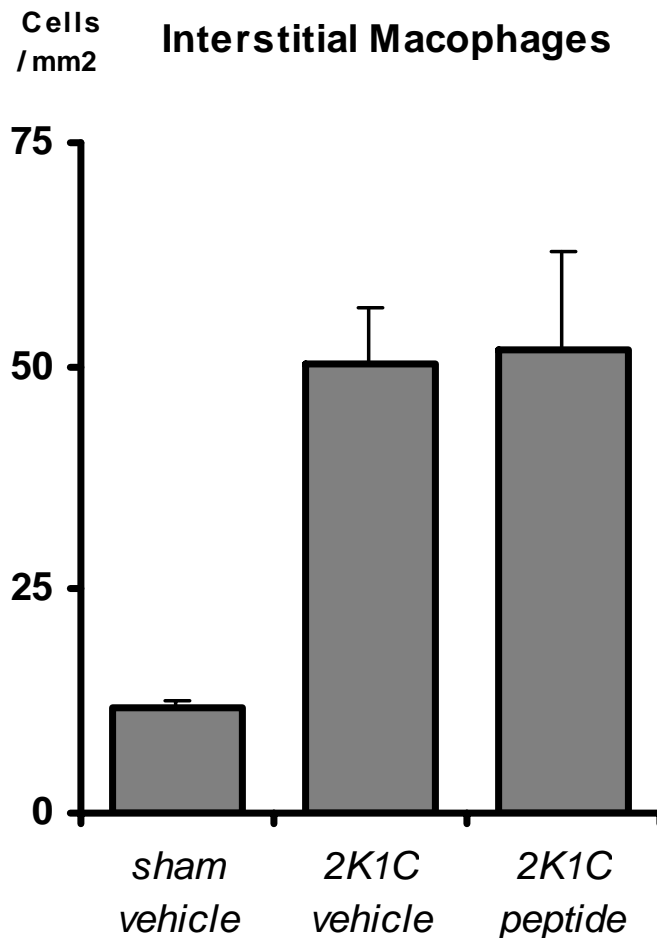
MAP and Cardiac Hypertrophy in 2K1C Rats



Histology in 2K1C Rats



Renal Macrophages and Collagen I in 2K1C Rats



Renin - (Pro)Renin Receptor Signaling

<http://www.kidney-international.org>

original article

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see commentary on page 13

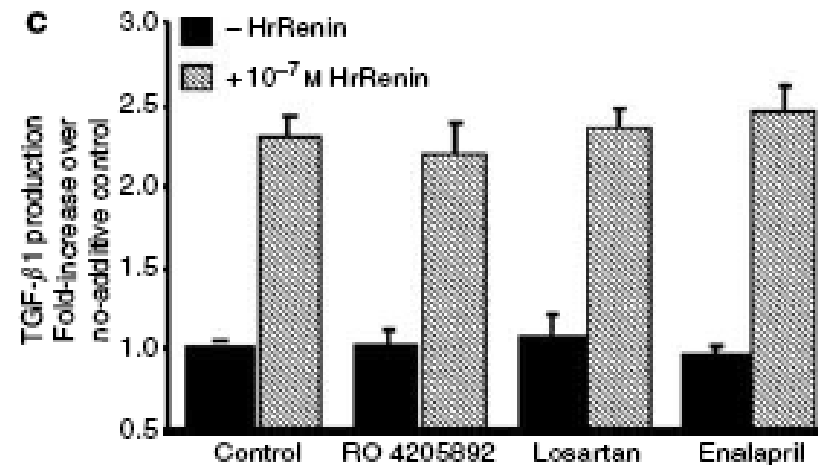
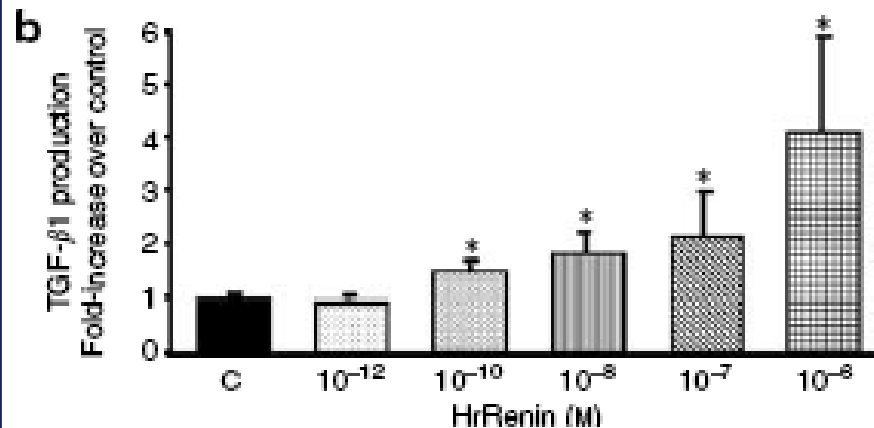
Renin increases mesangial cell transforming growth factor- β 1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms

Y Huang¹, S Wongamorntham¹, J Kasting¹, D McQuillan², RT Owens², L Yu¹, NA Noble¹ and W Border¹

¹Fibrosis Research Laboratory, Division of Nephrology, Department of Medicine, University of Utah, Salt Lake City, Utah, USA and

²Life Cell Corporation, Branchburg, New Jersey, USA

Human Renin-induced TGF- β mRNA Expression



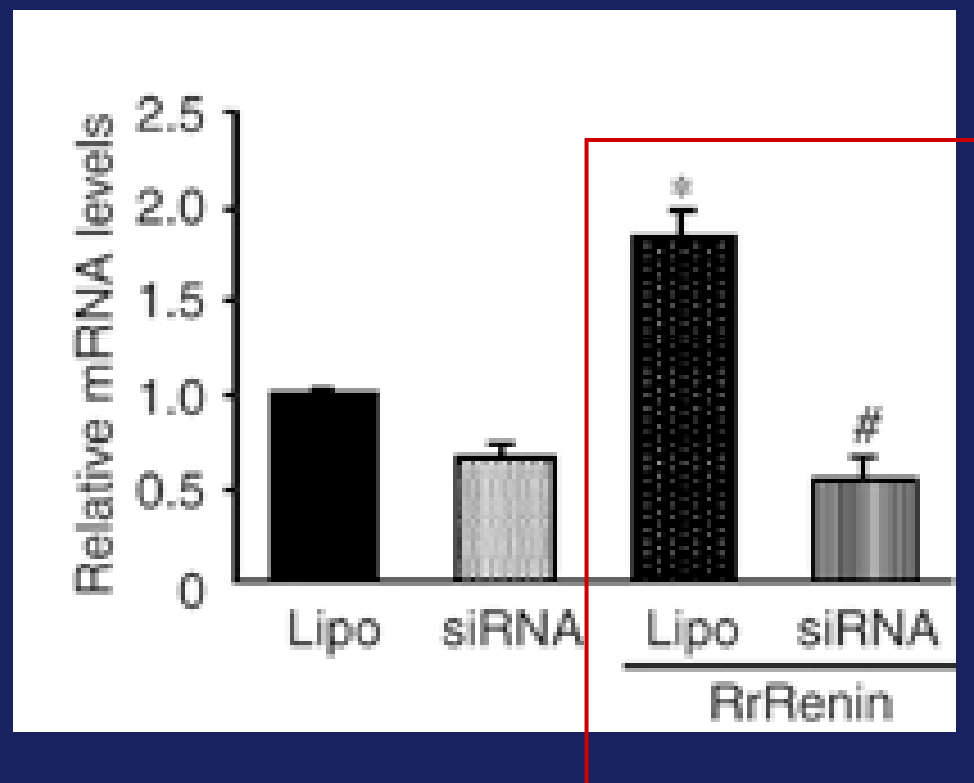
→ dose-dependent

→ Ang II-independent

→ Fibronectin and Collagen I

Renin-induced TGF- β mRNA Expression is mediated via the (Pro)Renin Receptor

TGF- β mRNA

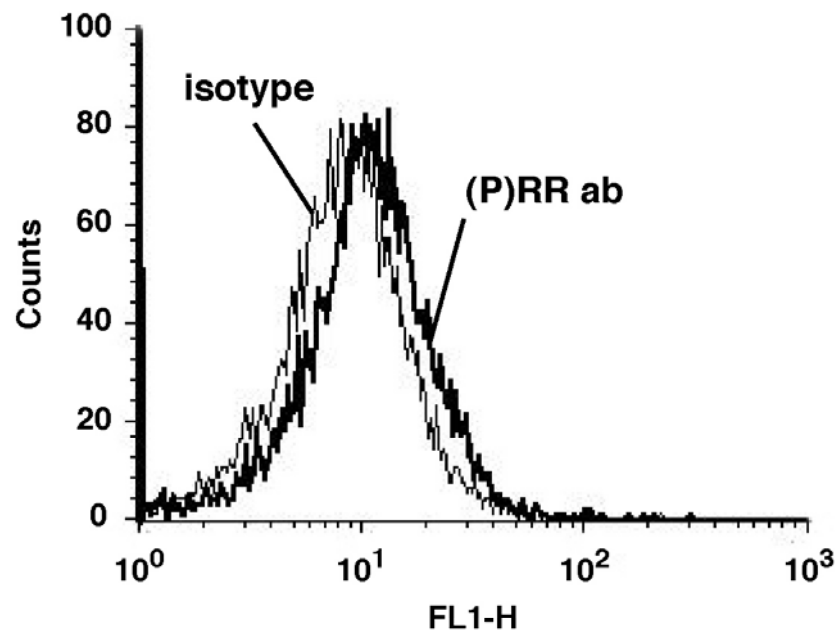


Effect of (pro)renin signaling in U937 cells and VSMC

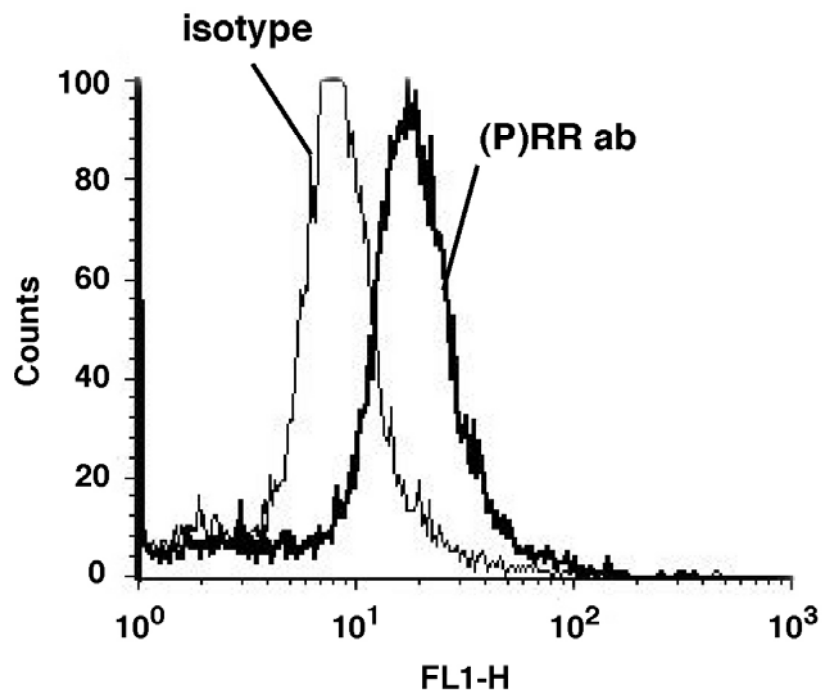
DN Muller unpublished data

FACS for (P)RR in U937

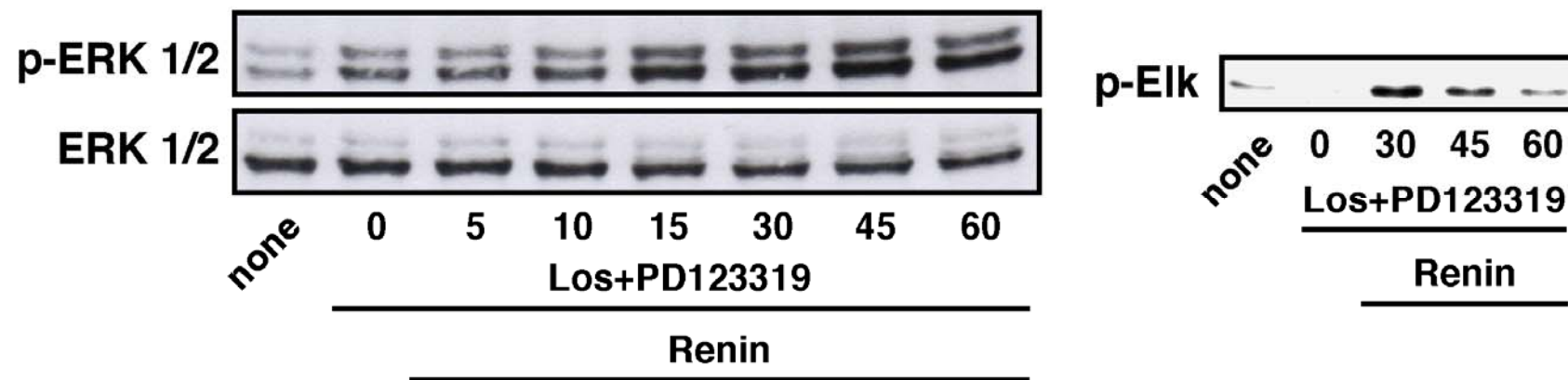
U937 Cells



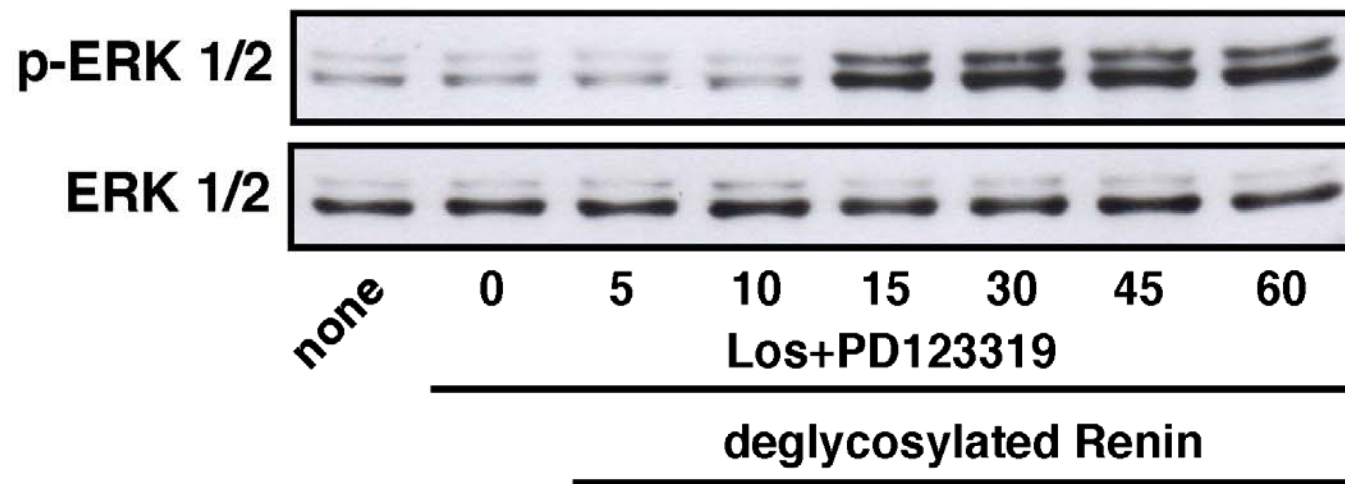
Permeabilized U937 Cells



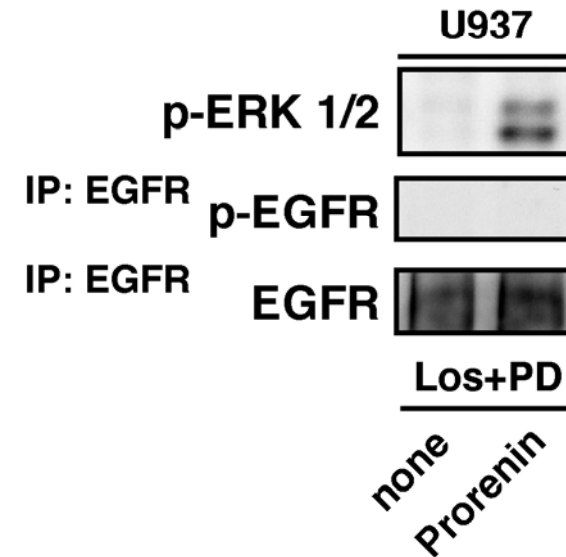
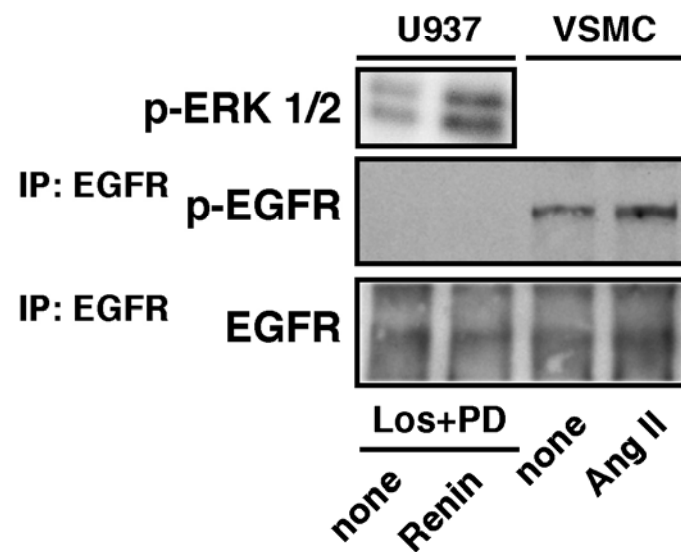
Renin induces p-ERK 1/2 in U937



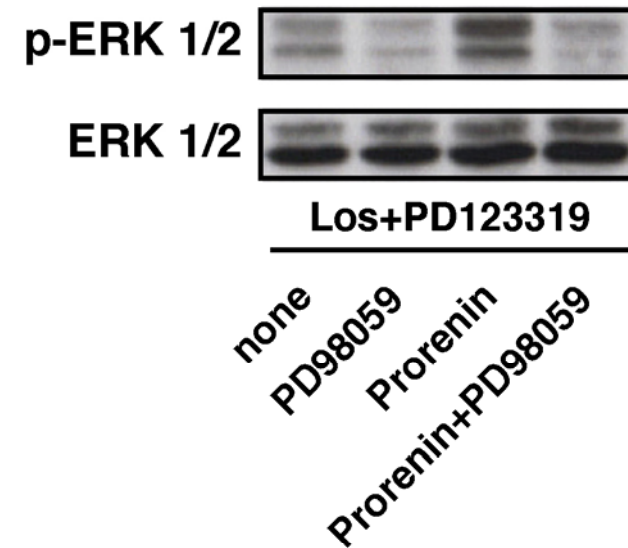
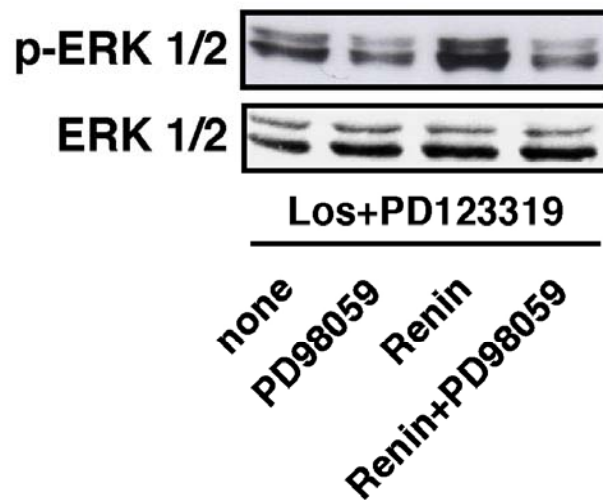
Deglycosylated Renin induces ERK 1/2 phosphorylation in U937



(Pro)renin activates ERK 1/2 independent of the EGF receptor

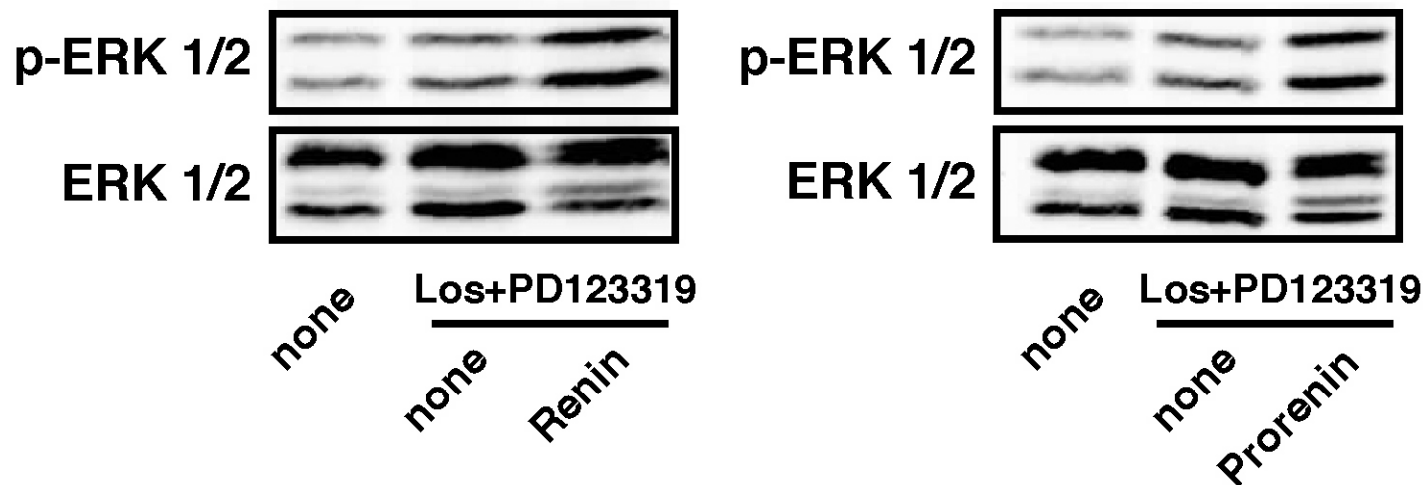


(Pro)renin activates ERK 1/2 through MEK 1/2 Kinase

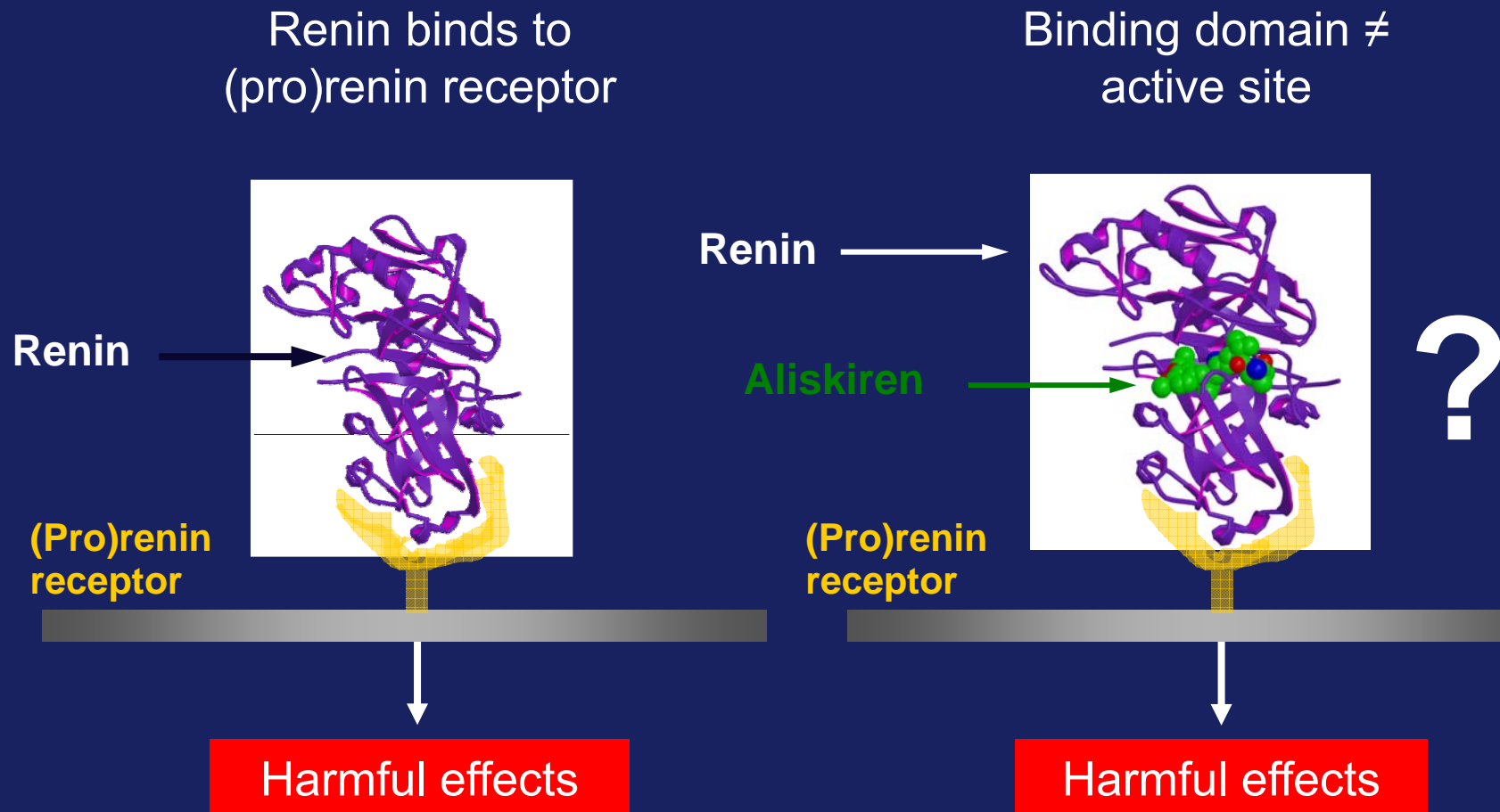


(Pro)renin induces p-ERK 1/2 in AT1_A Receptor-deficient VSMC

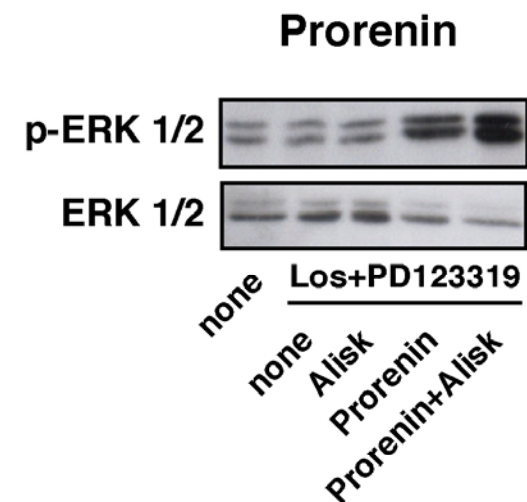
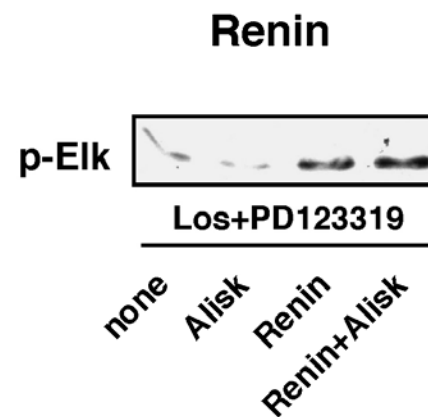
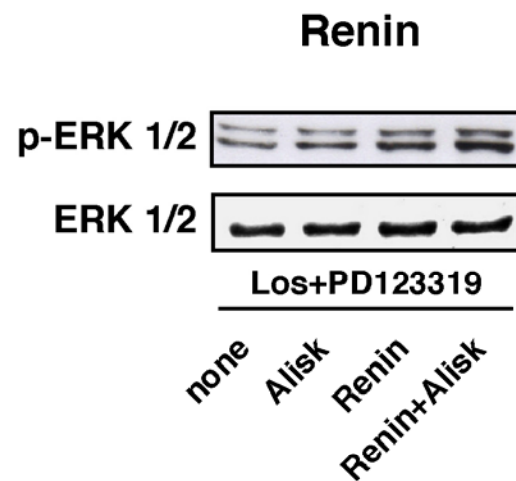
AT1_A receptor deficient VSMC



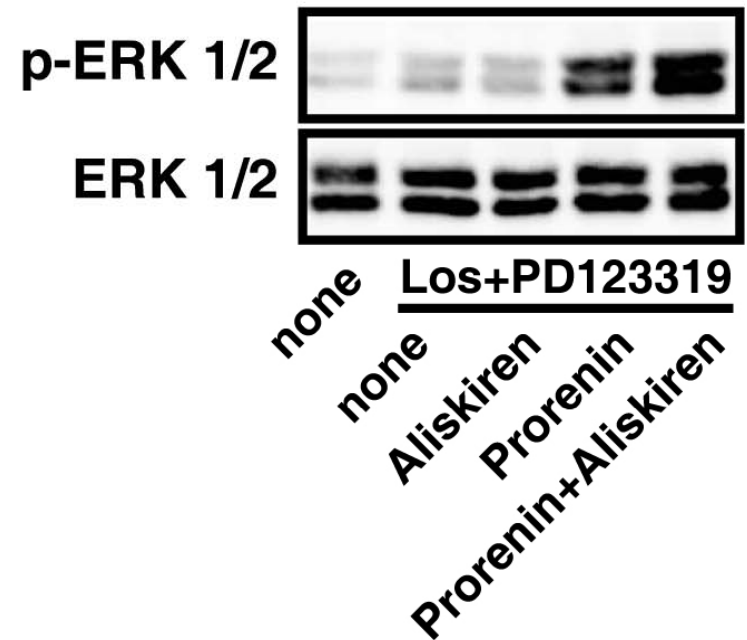
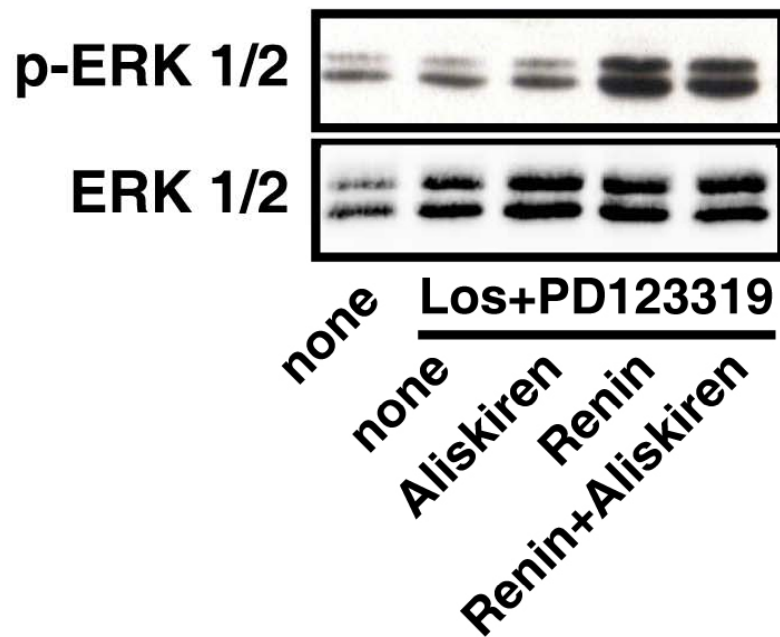
Could a direct renin inhibitor block renin from binding to the (pro)renin receptor?



Aliskiren does not block (Pro)Renin-induced Signal Transduction in U937 Monocytes

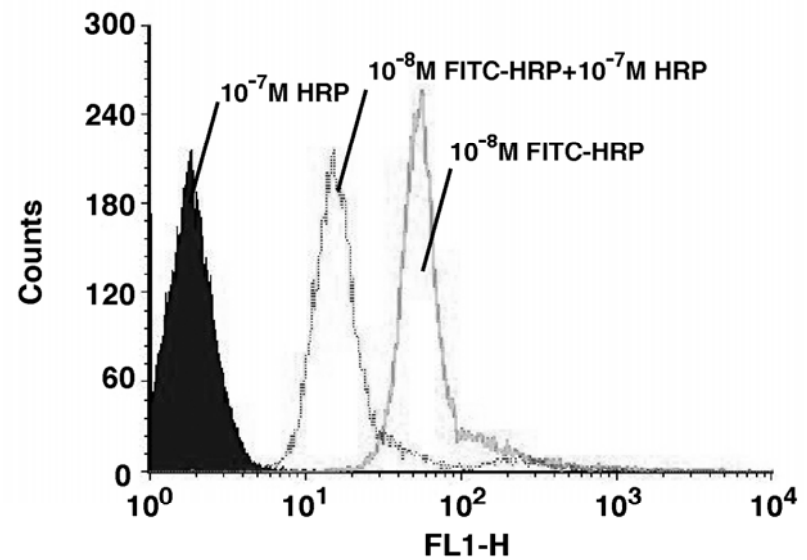
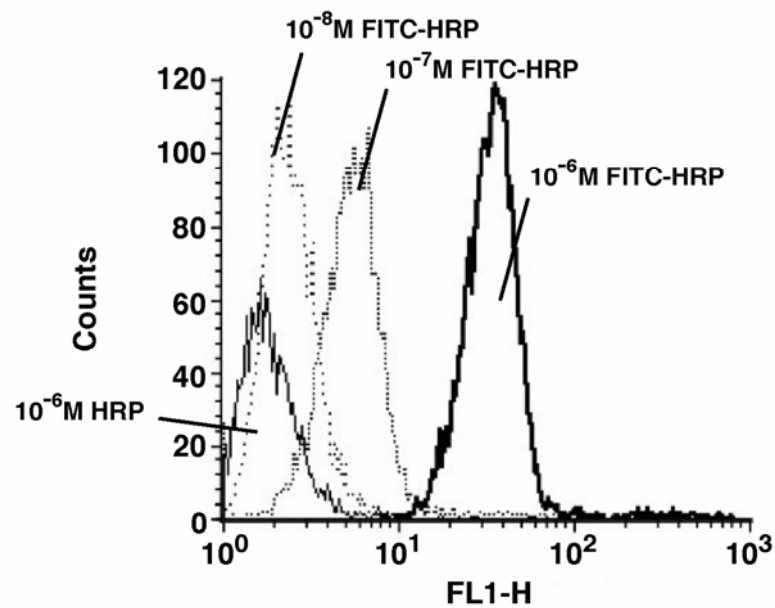


Aliskiren does not block (Pro)Renin-induced Signal Transduction in VSMC

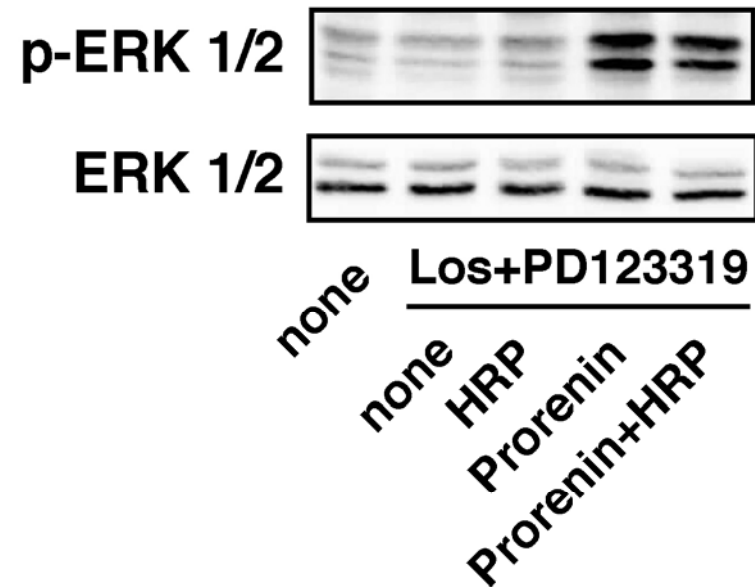
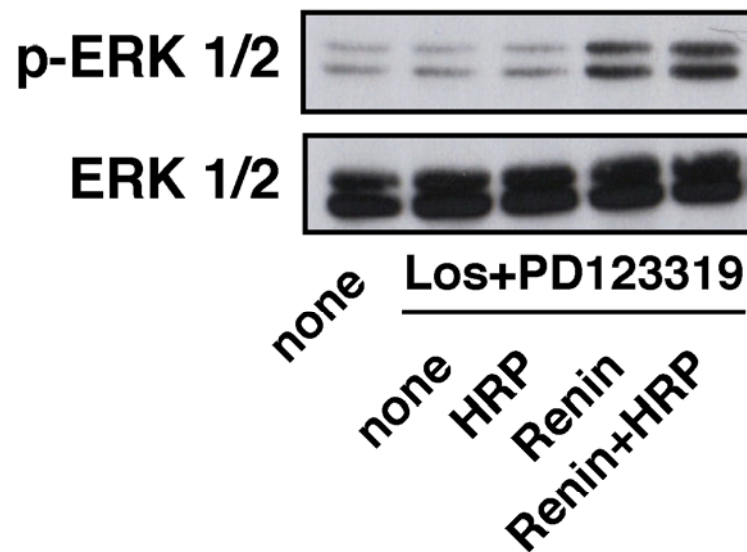


Effect of HRP on (pro)renin signaling in U937 cells and VSMC

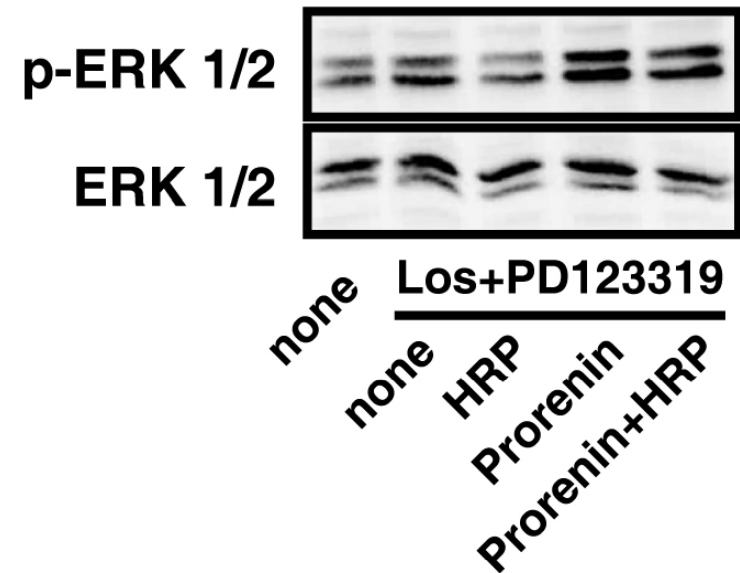
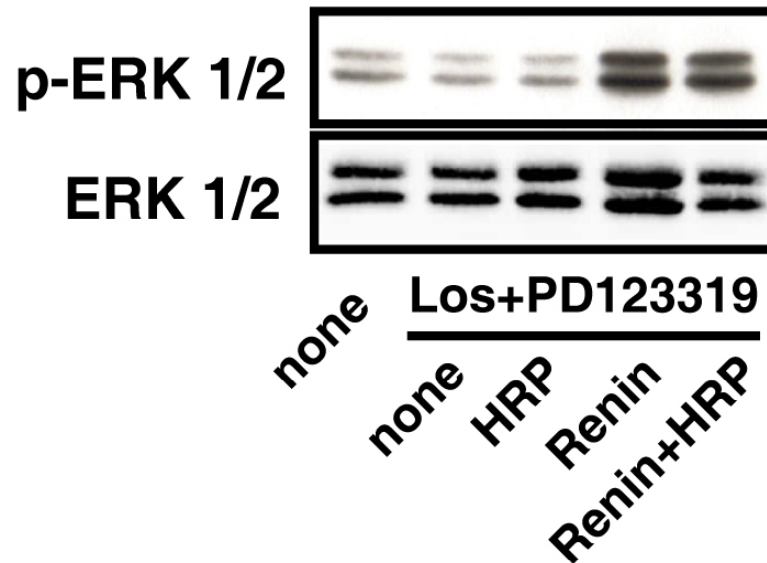
HRP Binding



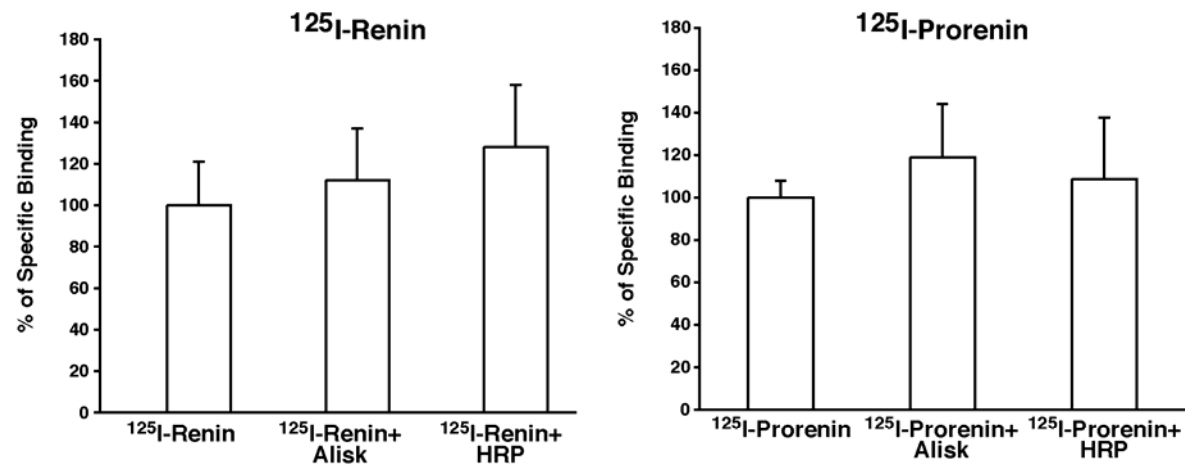
HRP does not block (Pro)Renin-induced Signal Transduction in U937



HRP does not block (Pro)Renin-induced Signal Transduction in VSMC

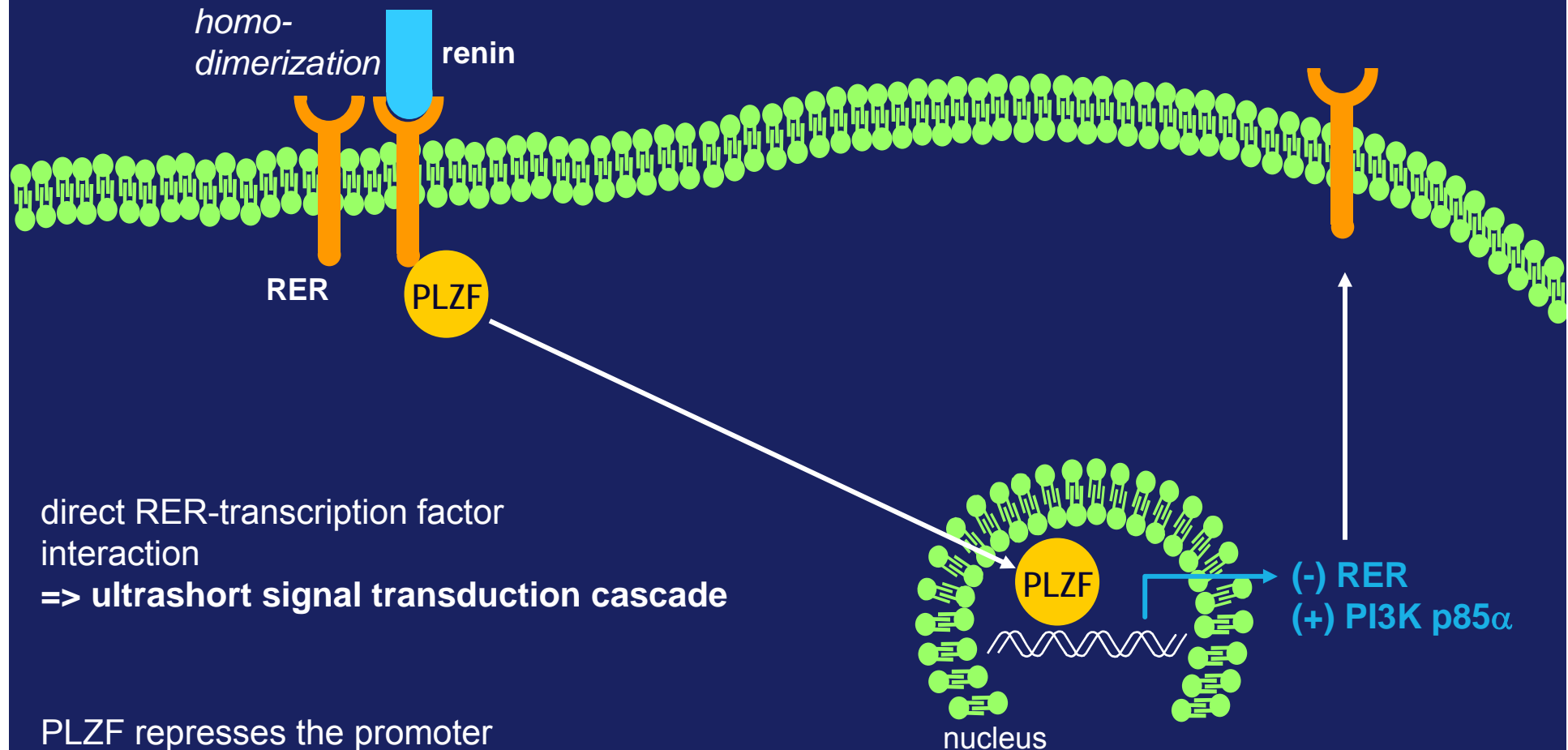


HRP and Aliskiren do NOT block Renin and Prorenin Binding in U937 Monocytes



G Nguyen & DN Muller unpublished data

Novel signal transduction pathway (Unger *et al.*)



direct RER-transcription factor
interaction

=> **ultrashort signal transduction cascade**

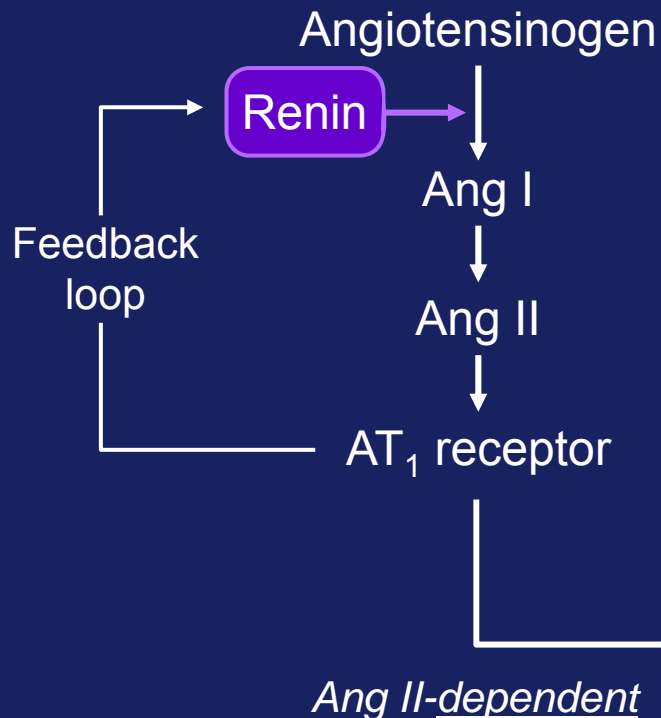
PLZF represses the promoter
of its direct binding partner RER

=> **ultrashort negative feedback loop**

Emerging concept: (Pro)renin receptor

Renin may cause organ damage independent of Ang II

Traditional thinking



Emerging concept

(Pro)renin binds to cell receptor

- Bound prorenin becomes activated
- ↑catalytic activity of bound renin
- Activation of ERK 1/2
- Production of TGF- β
 - Growth responses
 - Fibrotic responses



Organ damage

Ang II-independent

Perspectives

- Renin inhibition protects against target organ damage.
- Aldosterone escape after renin inhibition is an open question.
- In humans, we have to wait for end point studies to evaluate the concept of renin inhibition for cardiovascular disease.
- Aliskiren does not block the (pro)renin receptor.
- We still have to elucidate whether the major function of the renin receptor is related to cardiovascular disease.
- Further studies are needed to confirm that blockade of the (pro)renin receptor ameliorates diabetic nephropathy.

„Clinical“ Perspectives

The (P)RR is a novel intriguing receptor.

Specific (P)RR blockers as well as the generation of (P)RR-deficient mice will elucidate the function in cardiovascular disease and cell biology.

The Berlin Team

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- Robert Fischer
- Anette Fiebeler
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- Jutta Meisel
- Gabriele N'diaye
- Friedrich C. Luft

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- Genevieve Nguyen
- Aureli Contrepas
- Michael Bader
- Joon-Keun Park
- Hermann Haller

PKC α/β is not involved in(Pro)renin-induced ERK 1/2 activation

