CONTROLLO GLICEMICO, INFIAMMAZIONE e DANNO RENALE

Diapositiva preparata da GIUSEPPE PENNO e ceduta alla Società Italiana di Diabetologia.
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Giuseppe Penno

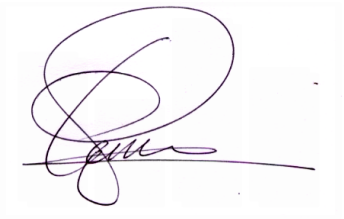
UNIVERSITÀ DI PISA

Bologna, 20-21 gennaio 2023

Disclosure

Il Dr. **Giuseppe Penno**
dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

AstraZeneca, Boerhinger Ingelheim, Eli-Lilly, Merck Sharp & Dohme, Mundipharma Pharmaceuticals, Novo Nordisk, Takeda



Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

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The contribution of inflammation to the pathogenesis of DKD

The discontinuation of undergoing clinical testing of promising anti-inflammatory agents for DKD

The current landscape of inflammation in DKD pathogenesis and treatment

An uphill road: any novel (anti-inflammatory) drug should show improvement over RAAS-blockade and SGLT2-inhibition (and finerenone)

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The contribution of inflammation to the pathogenesis of DKD

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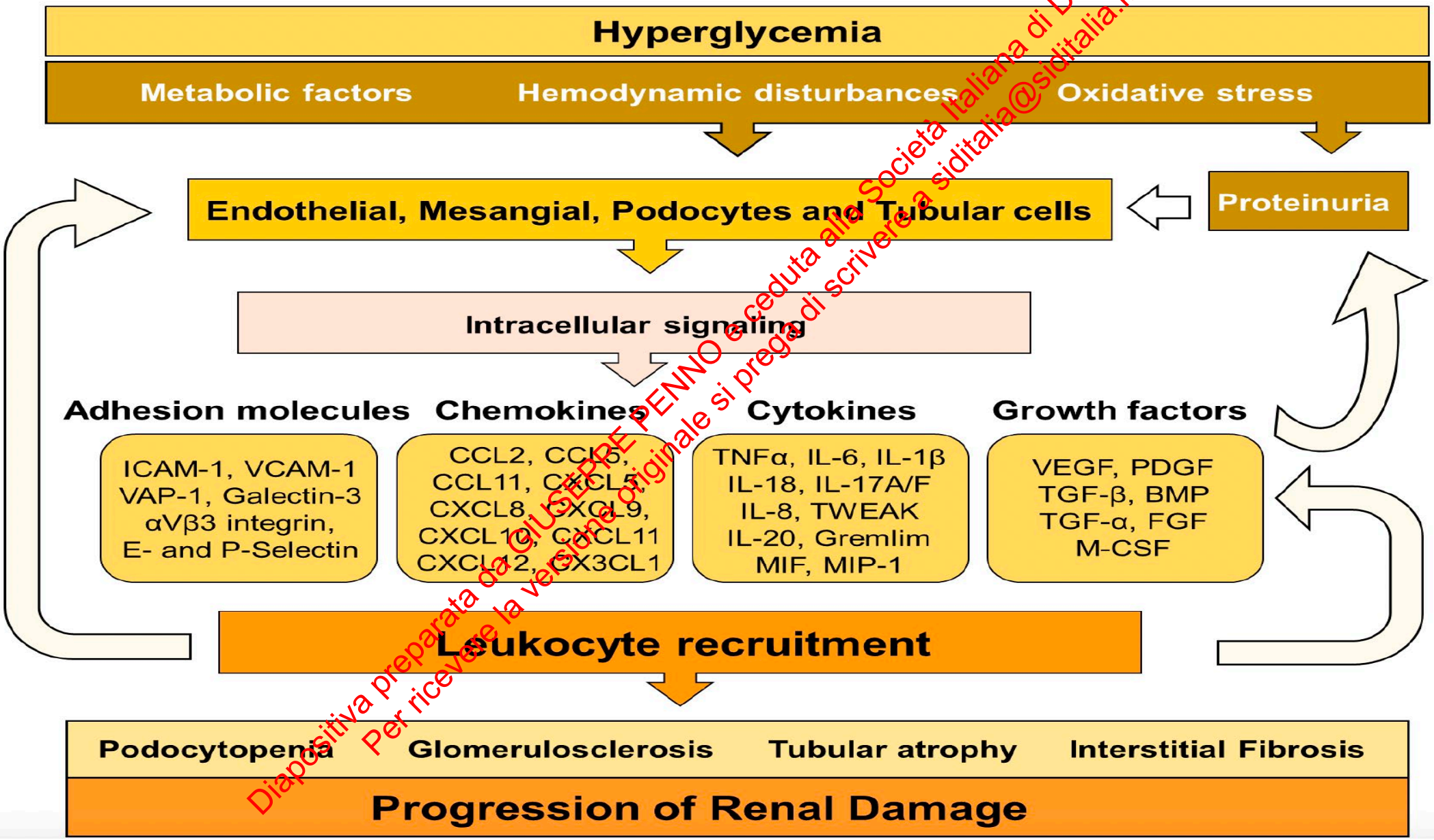
Mechanisms involved in inflammation, tissue injury and progression of renal damage in DKD



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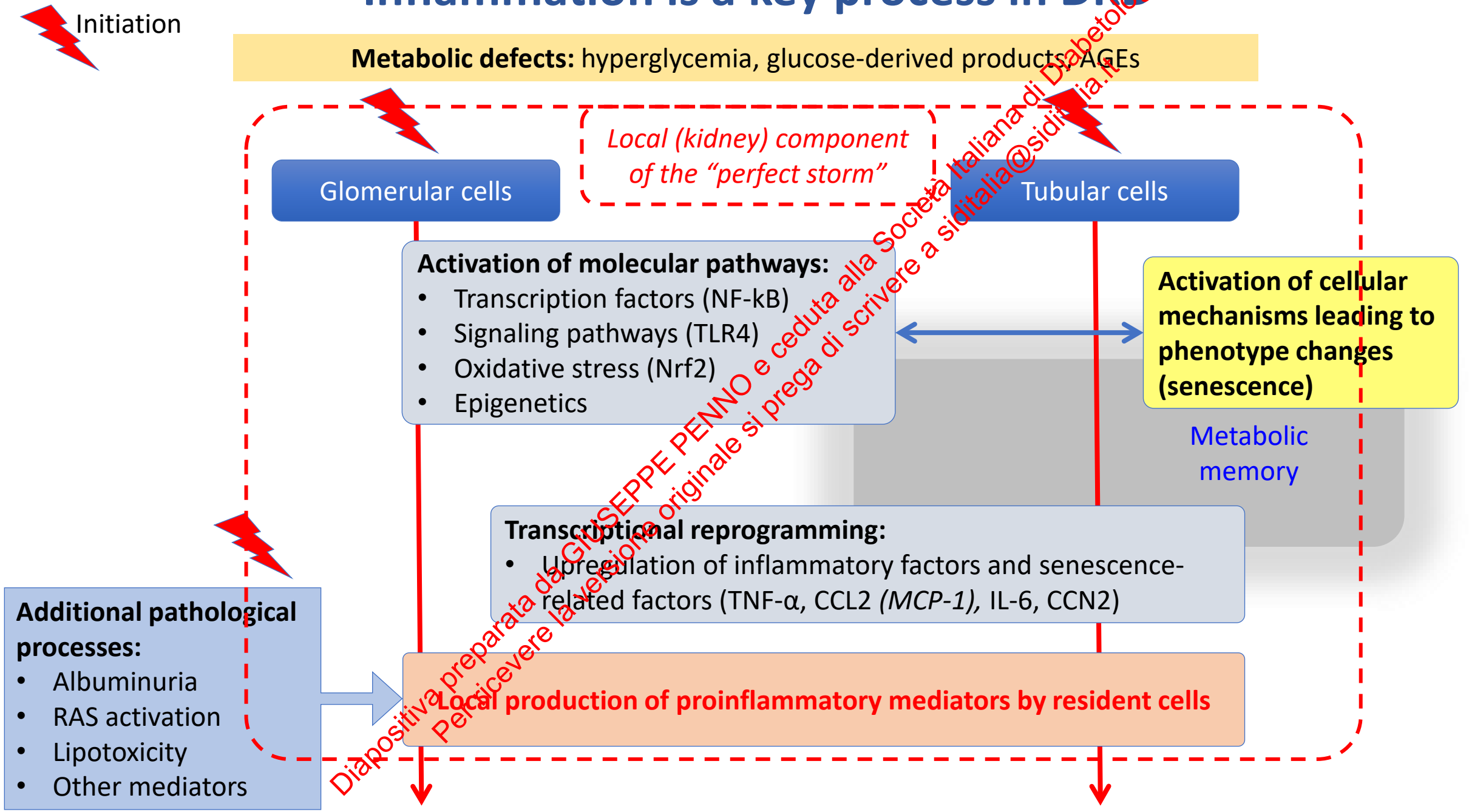
Rayego-Mateos S. et al., Int J Mol Sci. 2020; 21: 3798.

Inflammation is a key process in DKD



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Rayego-Mateos S. et al., Kidney International 2022.

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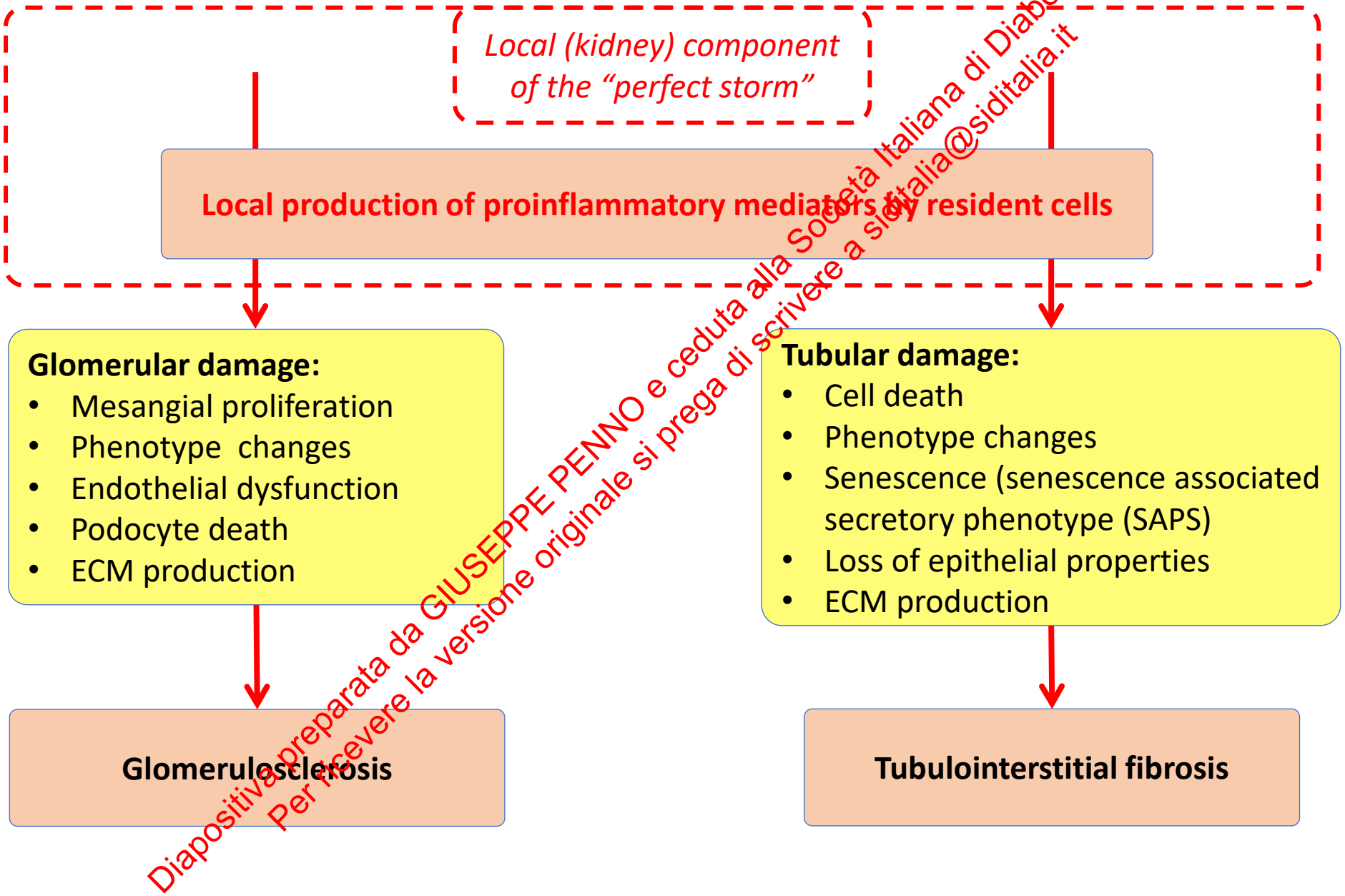

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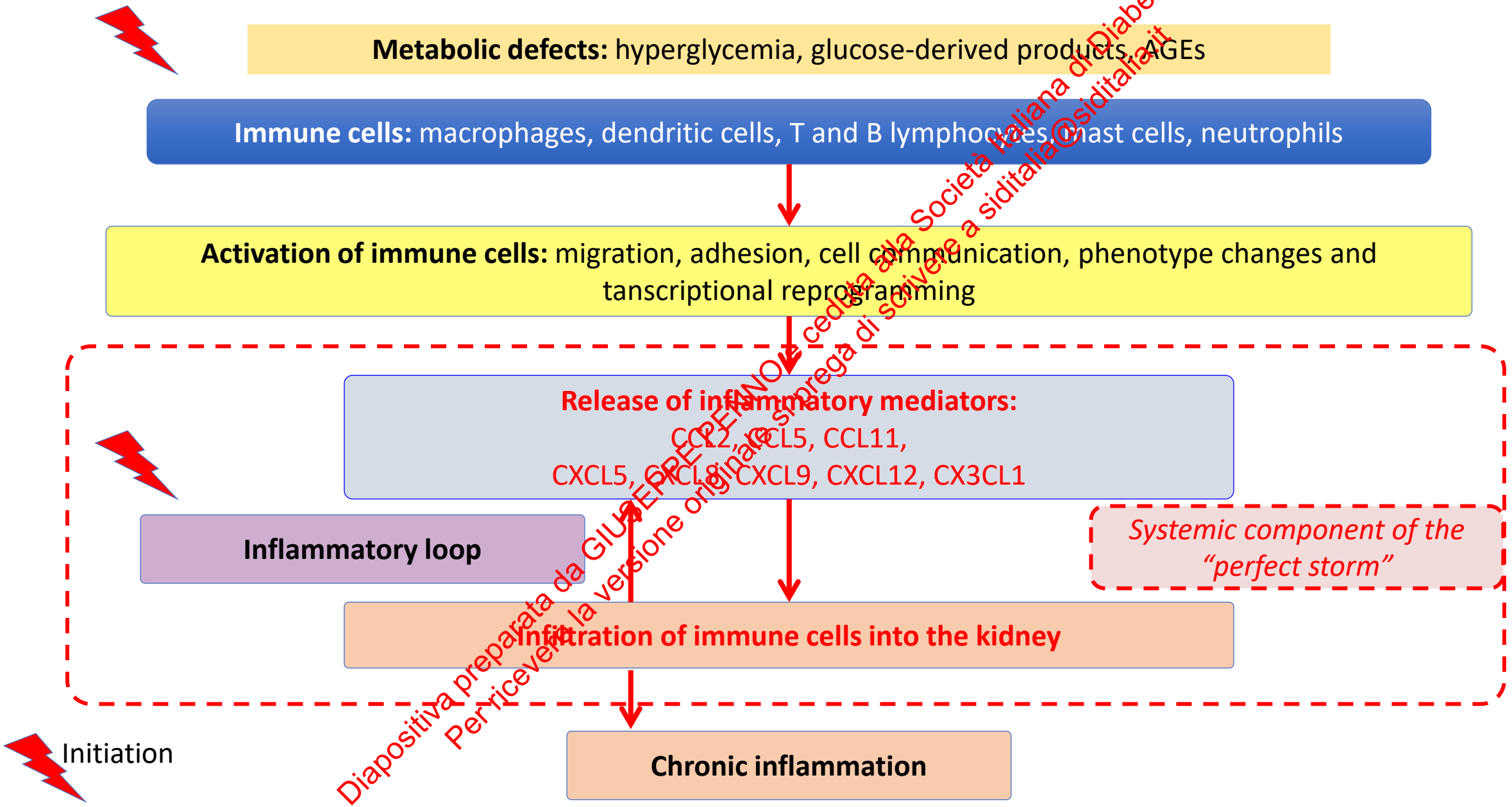
Rayego-Mateos S. et al., Kidney International 2022.

Inflammation is a key process in DKD



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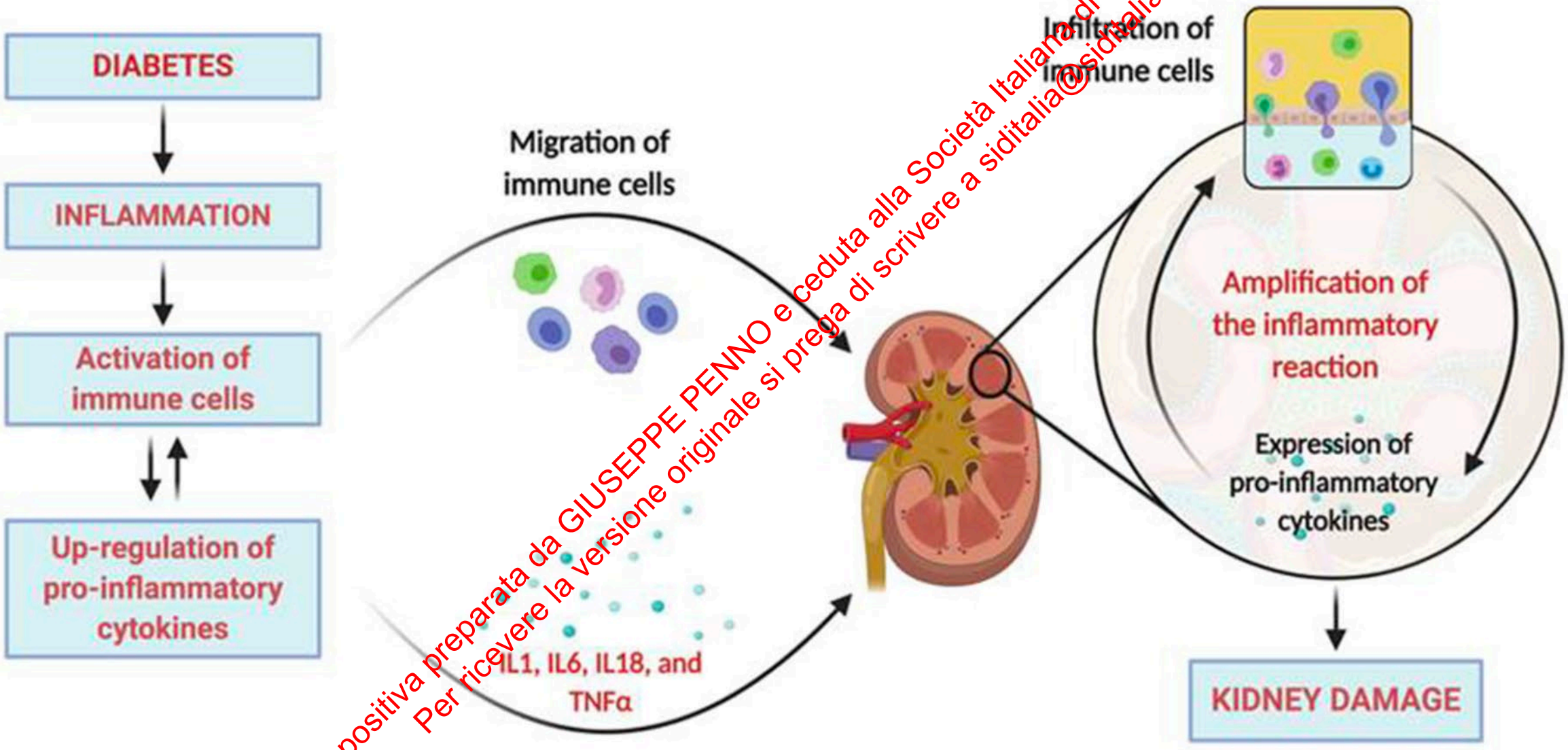
Rayego-Mateos S. et al., Kidney International 2022.

Mechanisms involved in inflammation, tissue injury and progression of renal damage in DKD



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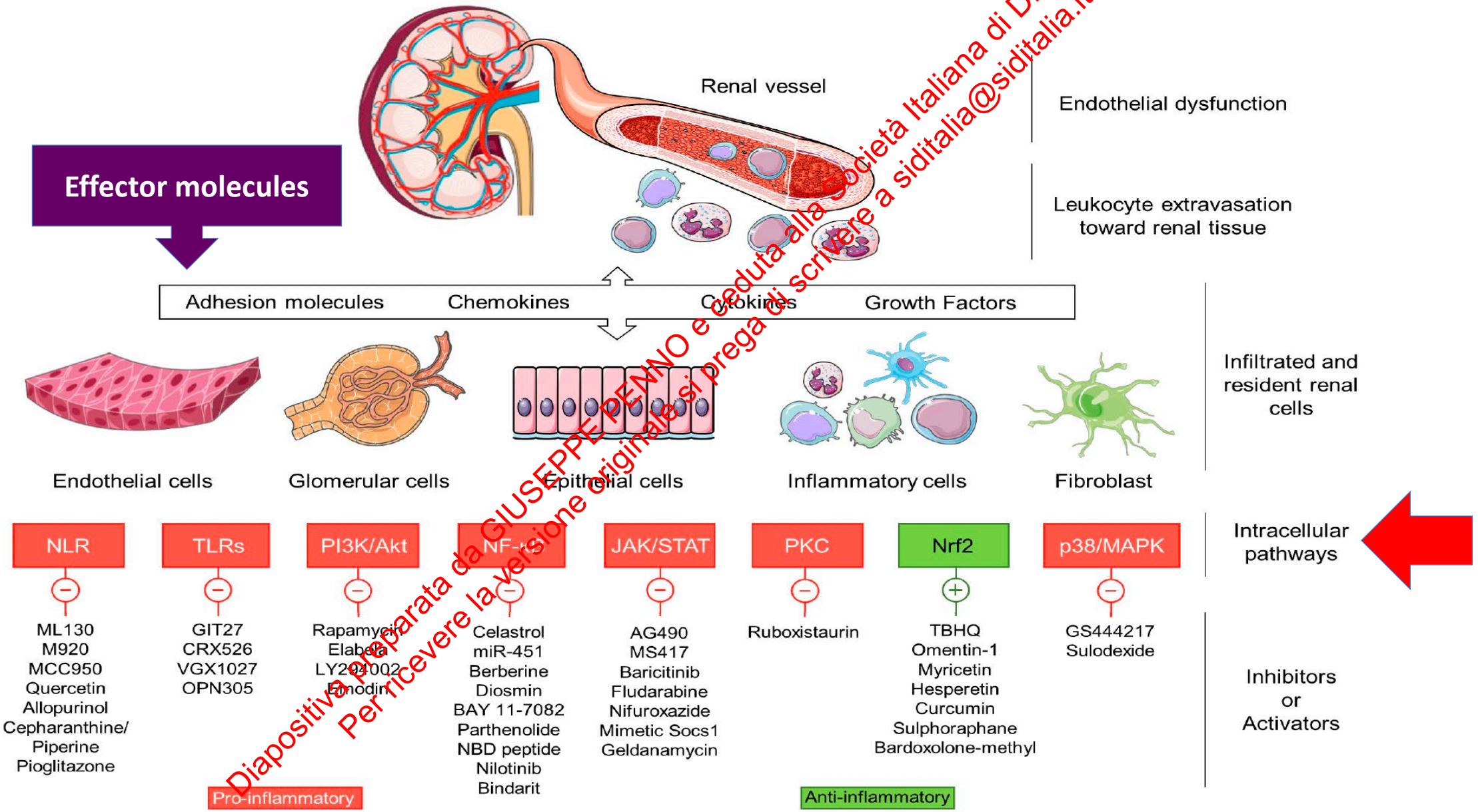
Donate-Correa J. et al., Front Med. 2021; 7: 628829.

Therapeutic compounds targeting proinflammatory intracellular signaling pathways in DKD



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Rayego-Mateos S. et al., Int J Mol Sci. 2020; 21: 3798.

Selected preclinical studies targeting inflammatory mediators in DKD

Target	Diabetic Model	Strategy	Category	Conclusion	Ref.
Adhesion molecules	SD rats (65 mg/kg)	Anti-ICAM-1 antibody	ICAM-1 antagonist	Prevents glomerular mononuclear cell infiltration.	
	Yorkshire pigs + STZ (50 mg/kg)	Anti-αVβ3 antibody	αVβ3 antagonist	Attenuates proteinuria and renal histological changes.	
	ZSF1 rats	MK-0429	αVβ3 inhibitor	Reduces proteinuria and renal fibrosis	
Chemokines	SD rats + STZ (60 mg/kg)	AMD3100	CXCR4 inhibitor	Increases albuminuria and accelerated tubular cell death.	
	db/db mice	NOX-A12	CXCL12 inhibitor	Decreases glomerulosclerosis and albuminuria.	
	db/db mice	Recombinant CXCL10	Mimetic CXCL10	Reduces mesangial matrix expansion, albuminuria, and glomerular hypertrophy.	
	iNOS-Tg mice	Propagermanium	CCR2 antagonist	Decreases mesangial matrix expansion and macrophage infiltration.	
	db/db mice	RS504393	CCR2 antagonist	Ameliorates inflammation, oxidative stress, and fibrosis.	
	db/db mice	CCX140-B	CCR2 antagonist	Reduces albuminuria, glomerular hypertrophy and increases podocyte number.	
Cytokines	Wistar rats + STZ (40 mg/kg)	Infliximab	TNF-α inhibitor	Decreases albuminuria.	
	KK-A(y) mice	Etanercept	TNF-α inhibitor	Improves albuminuria, macrophage infiltrate and CAM expression.	
	SD rats + STZ (65 mg/kg)	Tocilizumab	IL-6 inhibitor	Decreases albuminuria, oxidative stress, inflammation.	
	BKS db/db mice	Anti-IL-1β antibody	IL-1β inhibitor	Improves kidney injury markers and attenuates decline of eGFR.	
	db/db, and Akita mice; STZ (150 mg/kg)	Recombinant IL-17A	Mimetic IL-17A	Prevents fibrosis, podocytes loss, tubular atrophy, and albuminuria.	
	BTBR ob/ob mice	Anti-IL-17A antibody	IL-17A inhibitor	Ameliorates renal function, macrophage infiltration and podocyte loss.	
	Wistar rats + STZ (70 mg kg)	Anti-IL-20 antibody	IL-20 inhibitor	Reduces glomerular area and improves renal functions.	
	db/db mice	ISO-1	MIF inhibitor	Decreases albuminuria, fibrosis and inflammation.	
	Wistar rats + STZ (50 mg kg)	p425	MIF antagonist	Decreases UACR, serum BUN and creatinine.	

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Rayego-Mateos S. et al., Int J Mol Sci. 2020; 21: 3798.

Selected preclinical studies targeting **inflammatory intracellular signaling pathways** in DKD

Target	Diabetic Model	Strategy	Category	Conclusion	Ref.
Nucleotide-binding oligomerization domain **(NOD)-like receptors** (NLR)	SD rats + STZ (55 mg/kg)	Quercetin or allopurinol	Flavonoid or XO inhibitor	Ameliorates hyperuricemia and reduces IL-1β and IL-18 levels.	
	SD rats + STZ (50 mg/kg)	Cepharanthine and Piperine	Nutraceuticals	Decreases cytokines NLRP3-dependent.	
	ApoE-/- mice + STZ (80 mg/kg)	Pioglitazone	PPARγ agonist	Restores renal function. Downregulates AGEs, RAGEs and cytokines NLRP3-dependent.	
	db/db mice	MCC950	Selective NLRP3 inhibitor	Ameliorates GBM thickness, podocyte injury and renal fibrosis.	
	db/db mice	M920	Pan-caspase inhibitor	Reduces NLRP3-inflammasome (IL-1β, IL-18, NLRP3, caspase-1) and profibrotic markers.	
Toll-like receptors (TLRs)	eNOS$^{-/-}$ + STZ mice	CRX-526	TLR4 antagonist	Ameliorates histological changes, inflammatory and profibrotic markers.	
	db/db mice	GIT27	TLR4 inhibitor	Reduces proinflammatory, oxidative stress and lipid metabolism markers.	
PI3K/Akt/mTOR (Phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin)	SD + STZ (60 mg/kg)	Rapamycin	mTOR inhibitor	Ameliorates histological changes, inflammation and fibrotic markers.	
	C57BL/6 + STZ (60 mg/kg)	Mangiferin	Natural phenolic xanthonoid	Reduces inflammation, oxidative stress and profibrotic markers.	
	C57BL/6J + STZ (50 mg/kg)	Elabela	Peptide agonist Apelin/APJ receptor	Reduces GBM thickening, podocyte damage, inflammation, apoptosis and fibrosis markers.	
	Wistar rats + STZ (60 mg/kg)	Emodin	Derived from root rhubarb	Attenuates inflammation, oxidative stress and apoptosis markers.	
	db/db mice	Celastrol	Celastrus regelii root extracts	Improves lipid accumulation, oxidative stress and proinflammatory markers.	
	db/db mice	miR-451	LMP7 modulator	Decreases histological lesions, inflammation and fibrosis markers.	
NF-kB (Nuclear Factor kappa B)	Wistar rats + STZ (65 mg/kg)	Berberine	Flavonoid	Improves systemic and renal cortex inflammatory response.	
	SD rats + STZ (50 mg/kg).	BAY 11-7082	Phospho-IκB inhibitor	Reduces proinflammatory cytokines and oxidative stress markers.	
	ApoE$^{-/-}$ mice + STZ (125 mg/kg -2 days)	NBD peptide	Mimetic IKKβ-NEMO complex	Decreases histological lesions, inflammation and fibrosis.	
	SD rats + STZ (50 mg/kg)	Nilotinib hydrochloride	BCR-ABL tyrosine kinase inhibitor	Reduces oxidative stress, inflammation and profibrotic marker expression.	

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Rayego-Mateos S. et al., Int J Mol Sci. 2020; 21: 3798.

Selected preclinical studies targeting inflammatory intracellular signalir pathways in DKD

JAK/STAT (Janus kinases/signal trasducer and activators of transcription

PKC (Protein Kinase C)

Nrf2 (Nuclear factor (erythroid-derived 2)-like 2)

P38/MAPK (P38 mitogen-activated protein kinases)

Target	Diabetic Model	Strategy	Category	Conclusion	Ref.
	SD rats + STZ (60 mg/kg)	AG-490 (Tyrphostin)	JAK 2 inhibitor	Prevents JAK2 and STATs phosphorylation.	
	Akita mice + JAK2 Pod-overexpression	Tyrphostin or Baricitinib	JAK 2 inhibitors	Ameliorates histological changes, serum amyloid A3 plasma and kidney tissue.	
	SD rats + STZ (50 mg/kg)	Nifuroxazide	STAT3 inhibitor	Diminishes inflammatory and profibrotic factors and infiltrating cells.	
	Double db/db-SIRT-1$^{-/-}$ mice	MS417	BET-specific BRD4 inhibitor	Attenuates histological changes and STAT3 activity.	
	CD-1 mice + STZ (150 mg/kg)	Gene delivery SOCS1	SOCS1 Overexpression	Attenuates renal hypertrophy, inflammation and profibrotic markers.	
	ApoE$^{-/-}$ + STZ (125 mg/kg)	SOCS1 delivery system	Mimetic SOCS1-bIR region	Reduces atherosclerosis, structural changes and inflammatory markers.	
	Wistar rats + STZ (55 mg/kg)	Ruboxustaurin	Selective PKCβ inhibitor	Improves histological changes and attenuates TGFβ/Smad2/3 pathway.	
	Swiprosin-1$^{-/-}$ C57BL/6 mice + STZ (150 mg/kg)	Ruboxistaurin	Selective PKCβ inhibitor	Ameliorates histological changes, apoptosis and Swiprosin-1 expression.	
	SD rats + IR injury + STZ (65 mg/kg)	TBHQ	Synthetic antioxidant	Ameliorates oxidative stress, inflammation and apoptosis.	
	db/db and C57BL/6 mice + HFD	γ-glutamyl transpeptidase	Bardoxolone methyl analog	Reduces body weight, histological changes and GBM thickening.	
	Wistar rats + STZ (58 mg/kg)	Sulforaphane	Cruciferous vegetables extracts	Diminishes inflammation, oxidative stress markers, DNA damage and cell death.	
	SD rats + STZ (60 mg/kg)	Hesperetin	Flavonoid	Ameliorates histological changes, inhibition AGEs/RAGE axis and inflammation.	
	C57BL/6 + STZ (50 mg/kg) and Nrf2 knockdown mice	Myricetin	Flavonoid	Mitigates inflammation, oxidative stress and fibrosis markers.	
	db/db mice	Omentin-1	Adipokine	Reduces proinflammatory cytokines and oxidative stress markers.	
	SD rats + STZ (55 mg/kg)	Curcumin	Flavonoid	Lipid accumulation, angiogenesis, profibrotic and podocyte damage markers.	
	eNOS$^{-/-}$ mice + STZ (55 mg/kg)	GS-444217	ASK1 inhibitor (Selonsertib)	Ameliorates histological changes, inflammatory and profibrotic markers.	
	eNOS$^{-/-}$ db/db mice	GS-444217 + ACEi			
	OLETF rats	Sulodexide	Sulfated GAGs	Reduces histological changes, urinary VEGF and profibrotic markers.	

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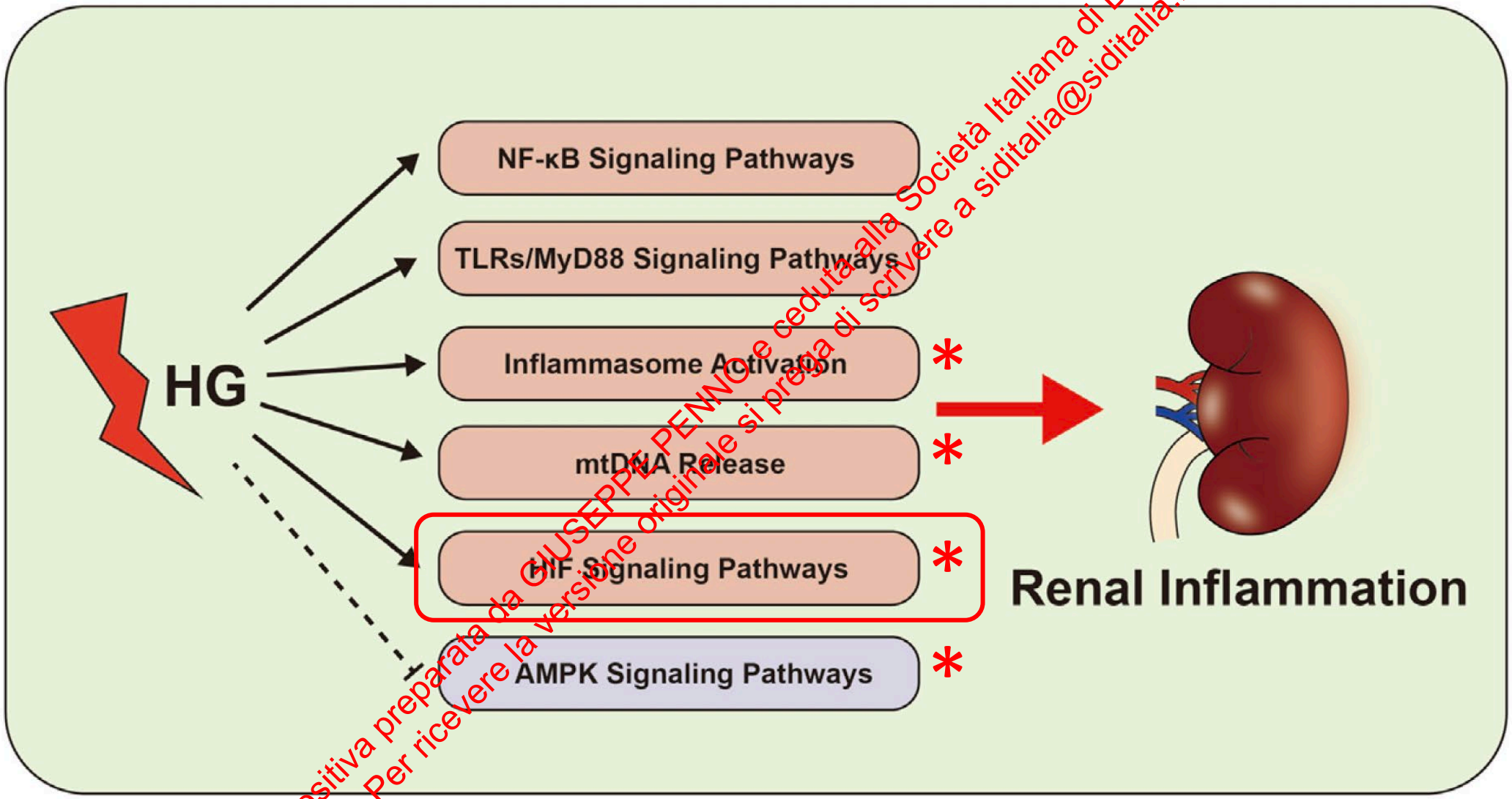
Rayego-Mateos S. et al., Int J Mol Sci. 2020; 21: 3798.

Inflammation-related signaling pathways in the development of DKD



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Liu C, et al., Front. Physiol. 2022; 13: 909569.

The contribution of inflammation to the pathogenesis of DKD

The discontinuation of undergoing clinical testing of promising anti-inflammatory agents for DKD

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Selected clinical trials targeting inflammation in DKD

Target	Compound	Enrollment	Phase	Status	1stor 2nd Outcome	Identification
Chymase inhibitor	BAY1142524 Fulacimstat	152	2	C	UACR	NCT03412006
VAP-1 inhibitor	ASP8232	55	2	C	AE—UACR	NCT02218099
Galectin-3 antagonist	GCS-100	375	2	U	eGFR	NCT02312050
Anti-Human αVβ3	VPI-2690B Monoclonal antibody	165	2	C	Albuminuria—eGFR	NCT02251067
CCL2 inhibitor	AF2838 Bindarit	100	2	C	UACR	NCT01109212
CCL2 inhibitor	Spiegelmer® NOX-E36	76	2	C	UACR	NCT01547897
CCR2 inhibitor	Propagermanium	45	2	A	UACR—eGFR	NCT03627715
CCR2 inhibitor	CCX140-B	332	2	C	UACR	NCT01447147
CCR2/5 antagonist	PF-04634817	226	2	C	UACR	NCT01712061
CCR2/5 antagonist	BMS-813160	319	2	T	UACR	NCT01752985
PDE inhibitor	Pentoxifylline	196	4	R	eGFR	NCT03664414
PDE inhibitor	Pentoxifylline	2510	4	A	Death—ESRD—UACR	NCT03625648
Anti-Human IL-1β	Canakinumab	10066	3	C	MACE—UACR—eGFR	NCT01327846
Anti-Human IL-18	GSK1070806 Monoclonal antibody	37	2	C	UACR, HbA1c and metabolic changes	NCT01648153
Anti-Human IL-33	MEDI3506 Monoclonal Antibody	168	2	R	UACR	NCT04170543

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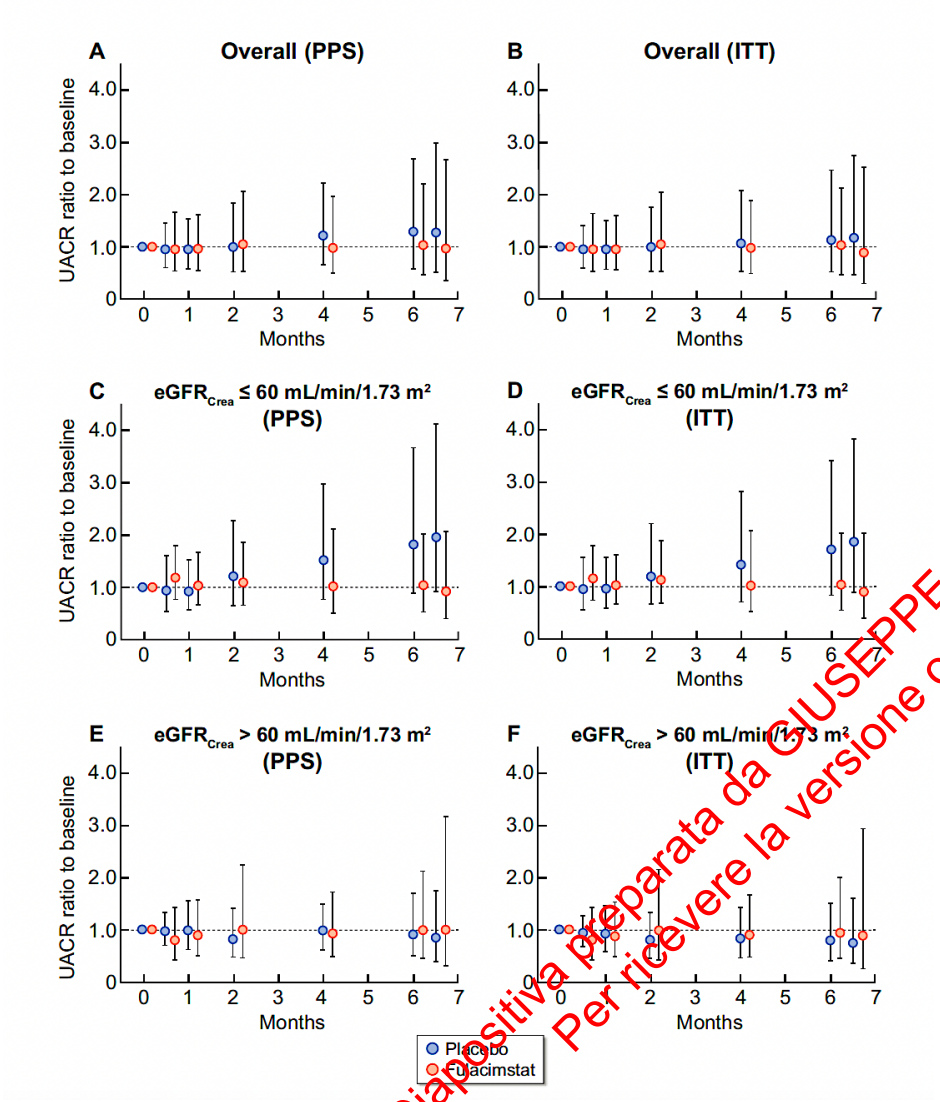
Rayego-Mateos S. et al., Int J Mol Sci. 2020; 21: 3798.

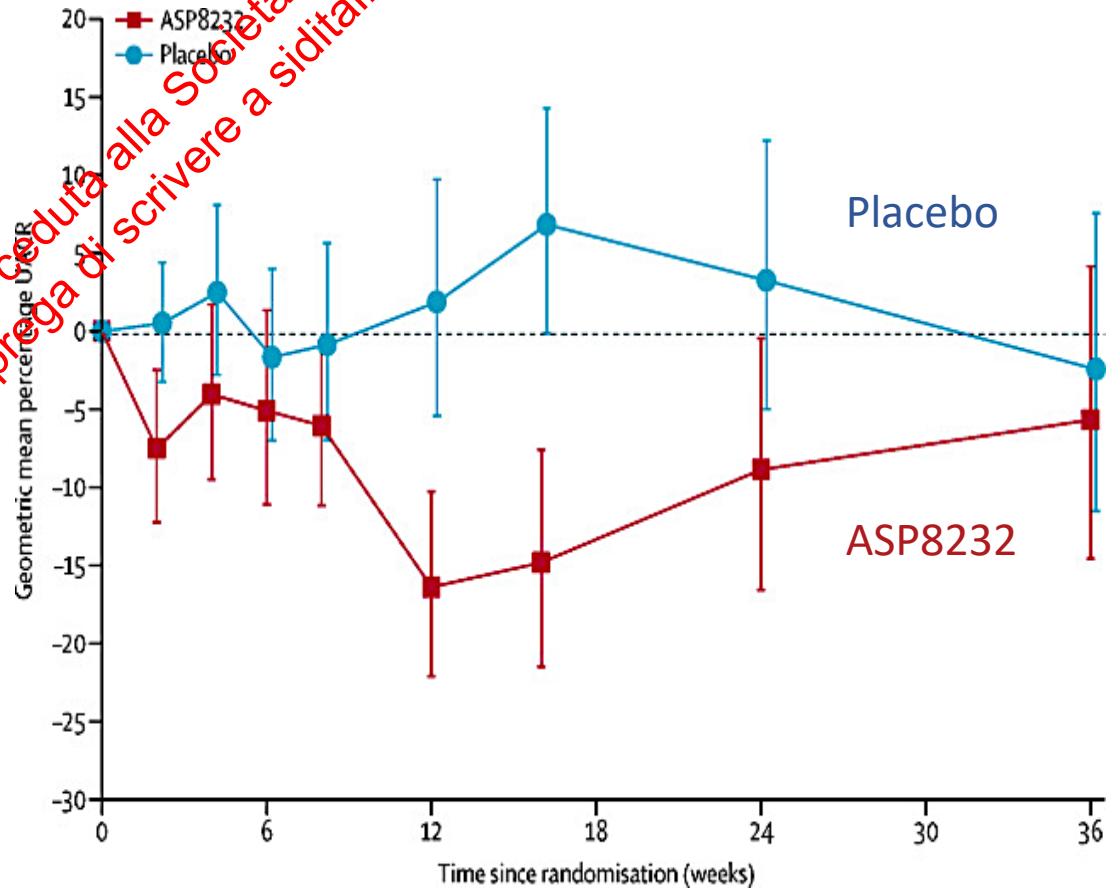
Selected clinical trials targeting inflammation in DKD

Effect of the chymase inhibitor fulacimstat in DKD – results from the CADA DIA trial



Rossing P, et al., Nephrol Dial Transplant. 2021; 36: 2263-2273.

Efficacy of a novel inhibitor of vascular adhesion protein-1 in reducing albuminuria in patients with diabetic kidney disease (ALBUM): a randomised, placebo-controlled, phase 2 trial



de Zeeuw D et al., Lancet Diabetes Endocrinol. 2018; 6: 925-933.

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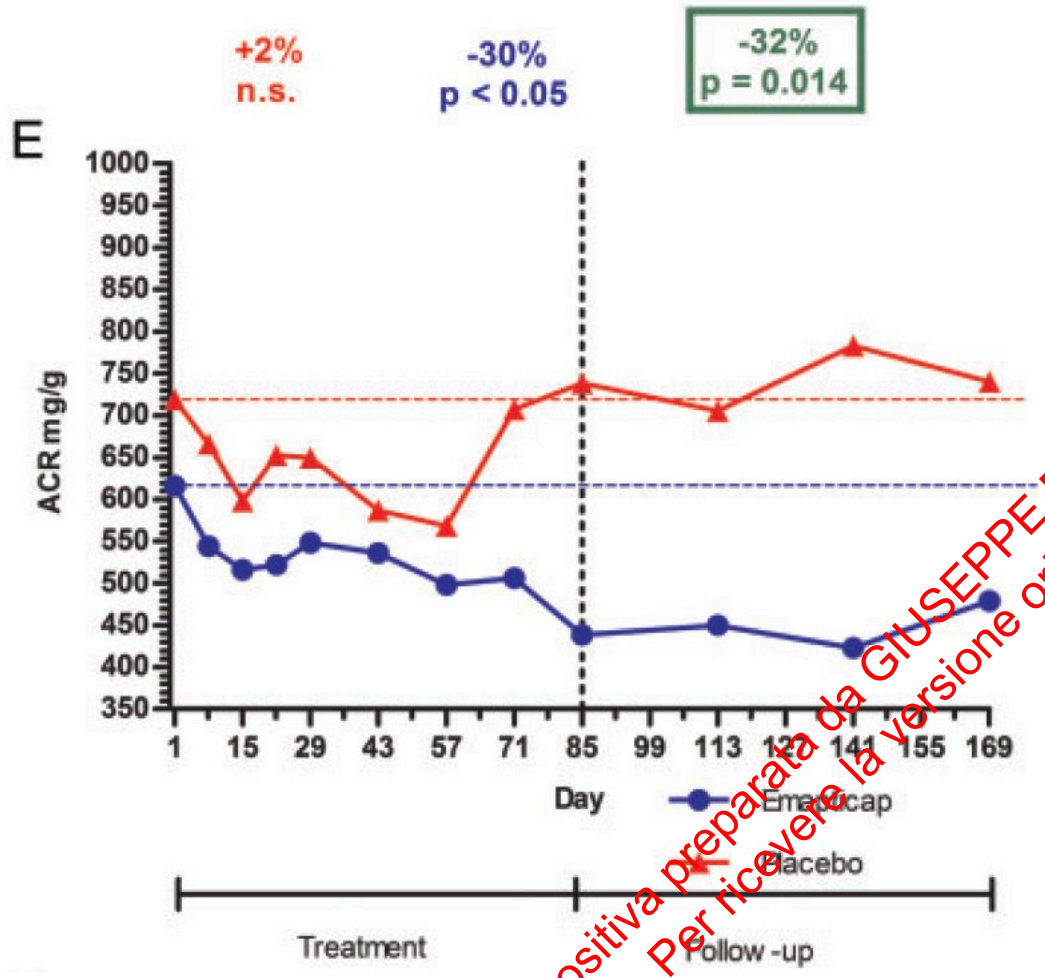
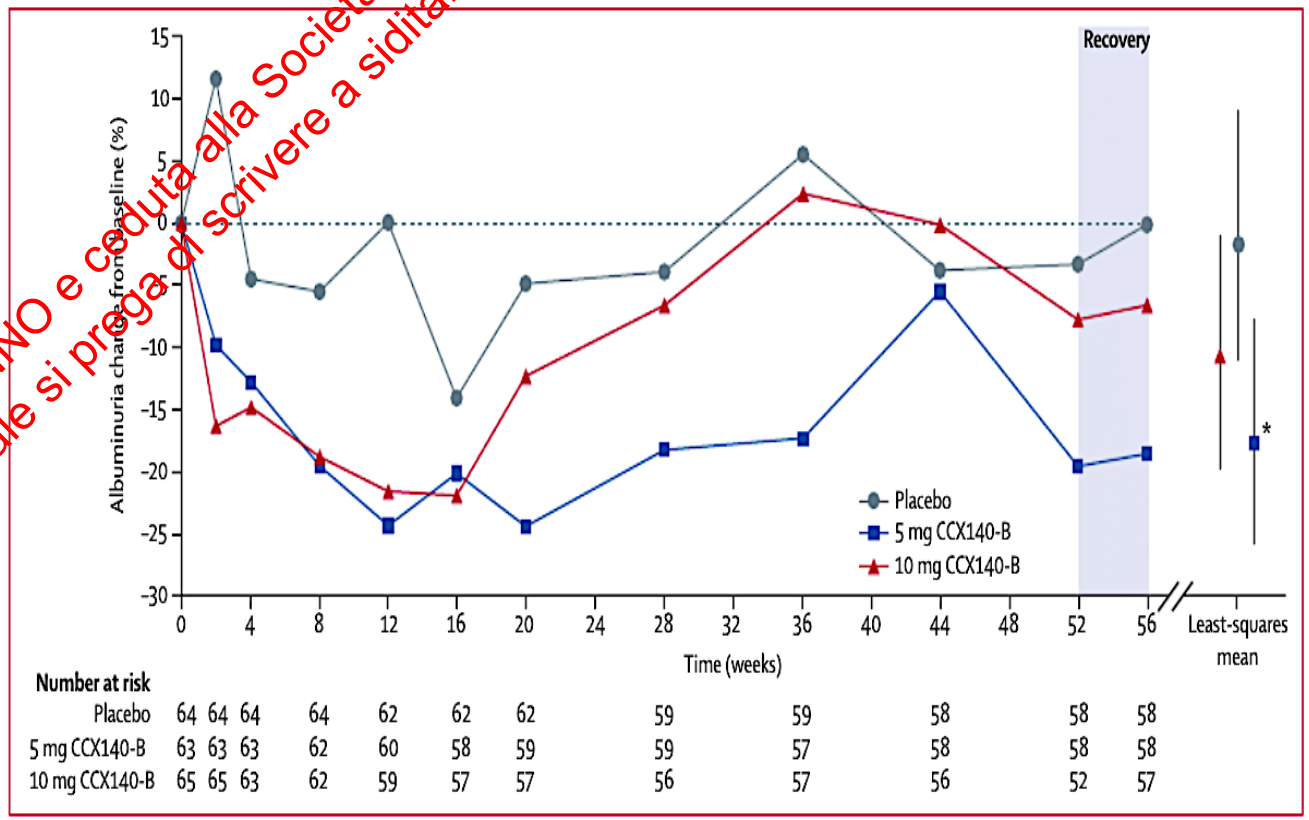
Selected clinical trials targeting inflammation in DKD

C-C motif-ligand 2 (CCL2; MCP-1) inhibition with emapticap pegol (NOX-E36) in type 2 diabetic patients with albuminuria *(post hoc analysis)*



Menne J, et al., Nephrol Dial Transplant. 2017; 32: 307-315.

The effect of CCR2 inhibitor CCX140-B on residual albuminuria in patients with type 2 diabetes and nephropathy: a randomised trial



de Zeeuw D, et al., Lancet Diabetes Endocrinol. 2015; 3: 687-96.

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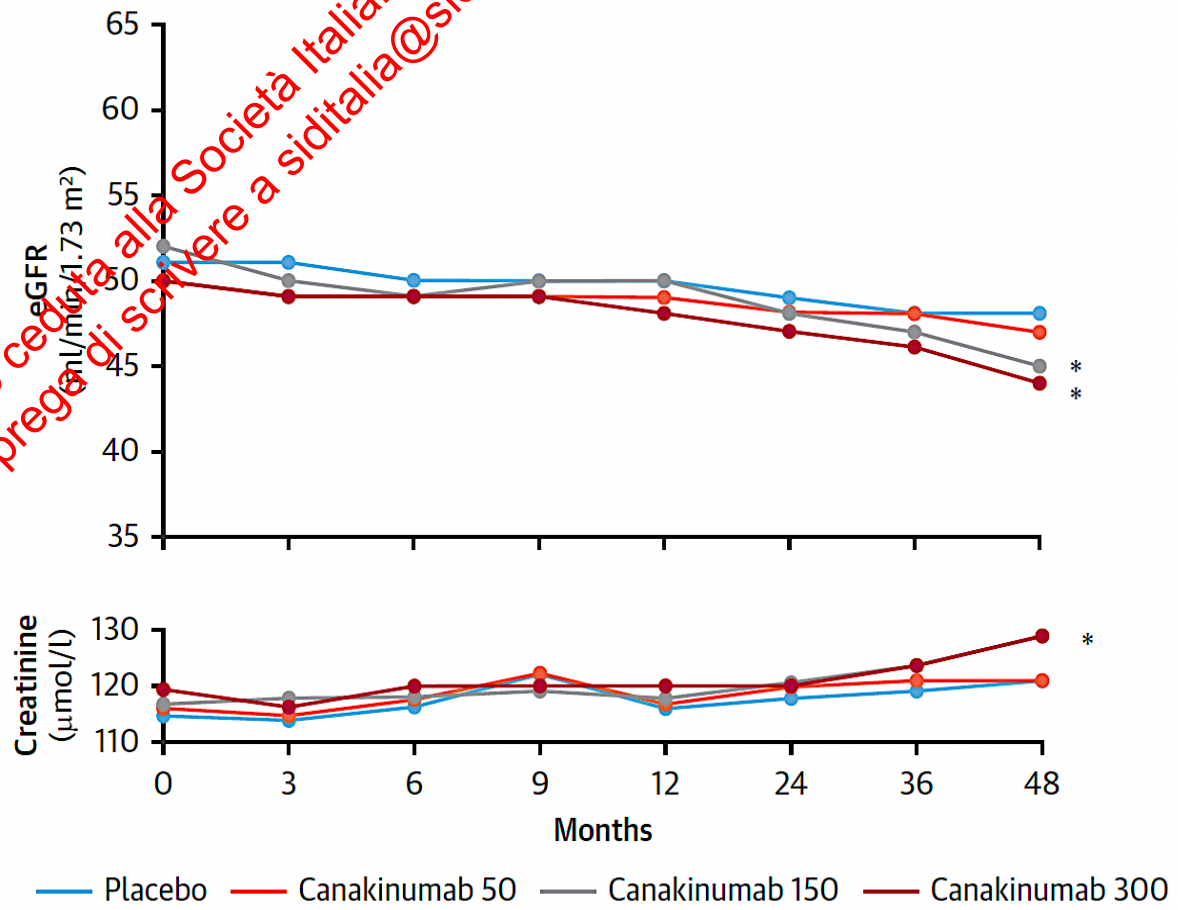
Selected clinical trials targeting inflammation in DKD

Pentoxifylline in diabetic kidney disease (VA PTXRx): protocol for a pragmatic randomised controlled trial

- Large randomised, controlled, pragmatic, multicentre clinical trial to determine if pentoxifylline (PTX), a phosphodiesterase inhibitor, can prevent ESRD and/or death in patients with DKD.
- PTX is a readily available, safe and inexpensive medication which might be effectively **repurposed** to treat this condition.
- Study medication is added to standard of care therapy in both the active intervention and placebo control groups. Standard of care is determined by the treating physicians.
- The primary outcome is time to ESRD or death (all-cause mortality).
- **An example of drug repositioning**

Leehey DJ, et al., BMJ Open. 2021; 11: e053019.

Inhibition of Interleukin-1β by Canakinumab and Cardiovascular Outcomes in Patients With Chronic Kidney Disease



*p < 0.05 for canakinumab 150 mg and 300 mg at 48 months for eGFR and for canakinumab 300 mg at 48 months for creatinine

Ridker PM, et al., J Am Coll Cardiol. 2018; 71: 2405-2414.

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Selected clinical trials targeting inflammation in DKD

Target	Compound	Enrollment	Phase	Status	1stor 2nd Outcome	Identification
Anti-Human TGFβ1	Galunisertib Monoclonal Antibody	417	2	T	UACR	NCT01113801
Anti-Human TGFα/Epiregulin	LY3016859 Monoclonal antibody	60	2	C	UACR	NCT01774981
JAK2 inhibitor	Baricitinib	130	2	C	UACR—eGFR	NCT01703234
PKCβ Inhibitor	Ruboxistaurin	20	3	C	UACR	NCT00297401
NRF2 inducer	Bardoxolone Methyl	1323	3	A	eGFR or ESRD	NCT03550443
NRF2 inducer	Bardoxolone Methyl	2185	3	C	ESRD or death	NCT01351675
NRF2 inducer	Bardoxolone Methyl	216	2	C	AE—eGFR	NCT02316821
Anti-inflammatory inhibitor	Colchicine	160	NA	A	UACR	NCT02035891
Sulfated GAGs	KRX-101 Sulodexide	1248	4	T	ESRD—UACR	NCT00130312
ASK-1 inhibitor	GS-4997 Selonsertib	3300	3	A	eGFR—ESRD	NCT04026165

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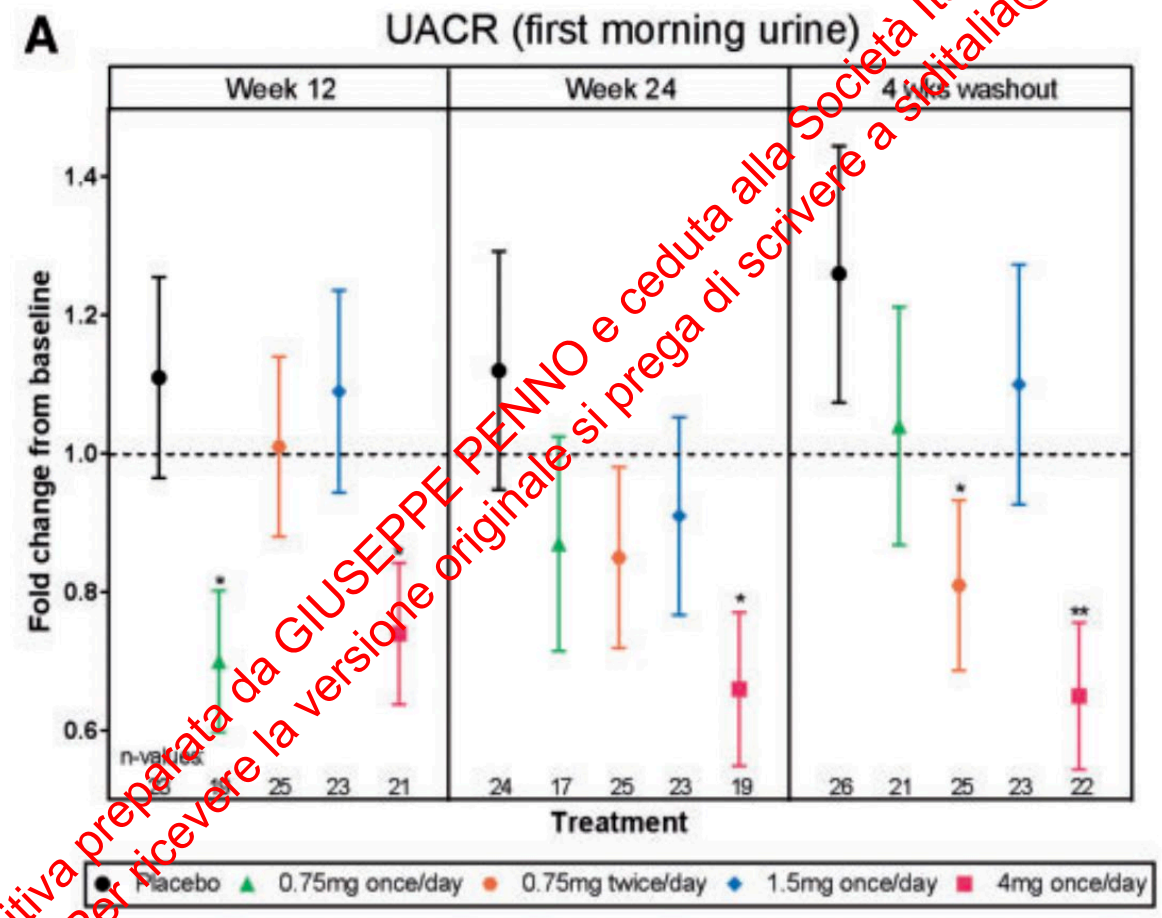
Rayego-Mateos S. et al., Int J Mol Sci. 2020; 21: 3798.

Selected clinical trials targeting inflammation in DKD

JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a Phase 2 randomized controlled clinical trial



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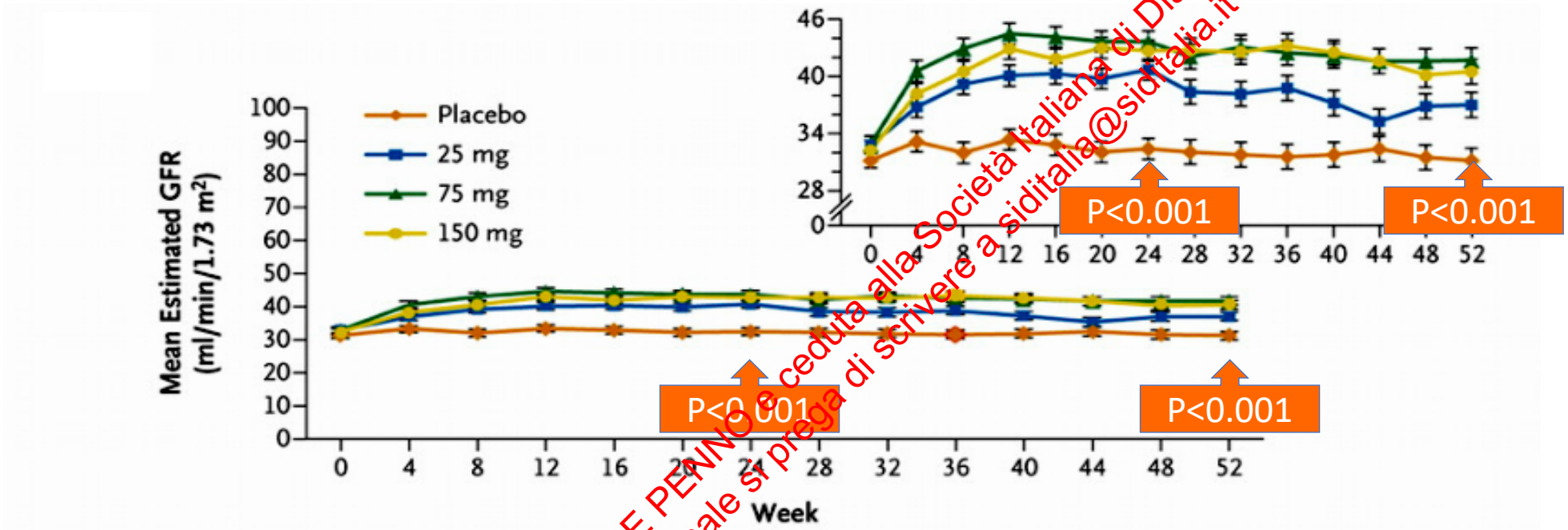
Tuttle KR, et al., Nephrol Dial Transplant. 2018; 33: 1950-1959.

Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes
The BEAM Study



No. at Risk														
Placebo	57	56	55	53	54	54	54	53	53	52	53	51	53	52
Bardoxolone methyl, 25 mg	57	53	52	52	52	51	51	49	49	47	48	48	48	48
Bardoxolone methyl, 75 mg	57	55	54	54	53	52	52	51	48	50	50	48	48	48
Bardoxolone methyl, 150 mg	56	55	55	54	53	52	52	48	48	47	47	46	46	44

227 subjects with type 2 diabetes and eGFR = 20-45 ml/min/1.73m^2

Baseline eGFR Bardoxolone methyl an oral antioxidant inflammation modulator, was associated with improvement in the estimated GFR in patients with advanced CKD and type 2 diabetes at 24 weeks. The improvement persisted at 52 weeks.

Pergola PE et al., N Engl J Med 365: 327-336, 2011

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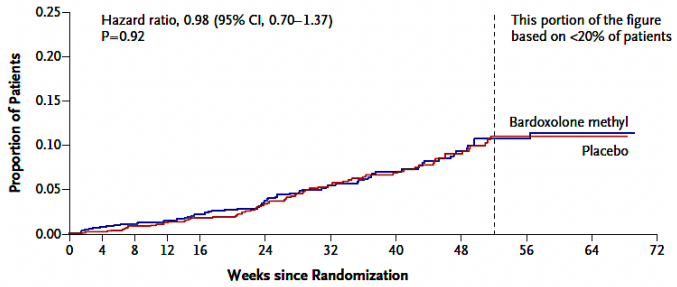
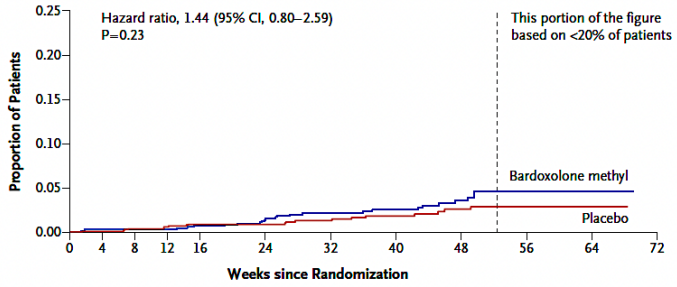
Bardoxolone Methyl in Type 2 Diabetes and Stage 4 CKD
BEACON Trial Investigators

A Primary Composite Outcome



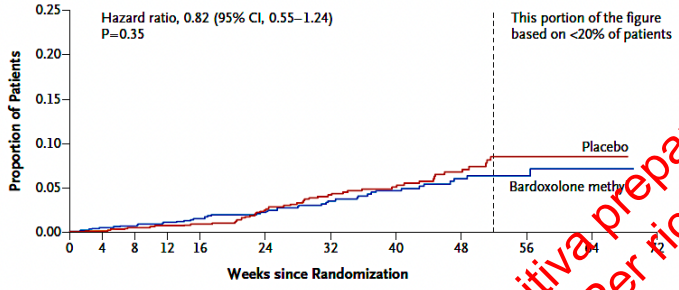
No. at Risk												
Bardoxolone methyl	1088	1077	1050	982	904	756	571	429	297	137	16	0
Placebo	1097	1095	1076	1004	922	768	596	439	318	142	19	0

B Death from Cardiovascular Causes



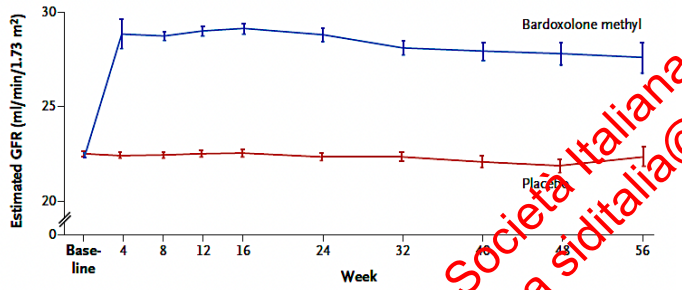
No. at Risk												
Bardoxolone methyl	1088	1082	1055	991	916	770	590	450	315	144	18	0
Placebo	1097	1096	1081	1010	930	786	622	464	340	156	23	0

C ESRD



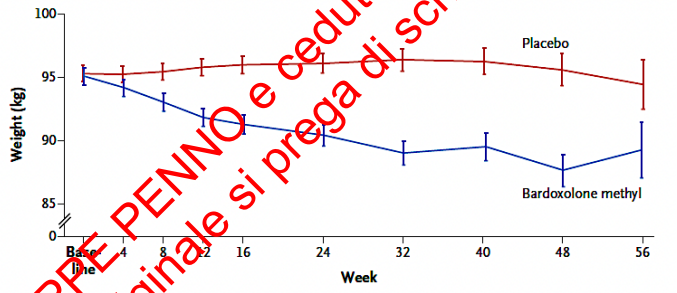
No. at Risk												
Bardoxolone methyl	1088	1077	1050	982	904	756	571	429	297	137	16	0
Placebo	1097	1095	1076	1004	922	768	596	439	318	142	19	0

A



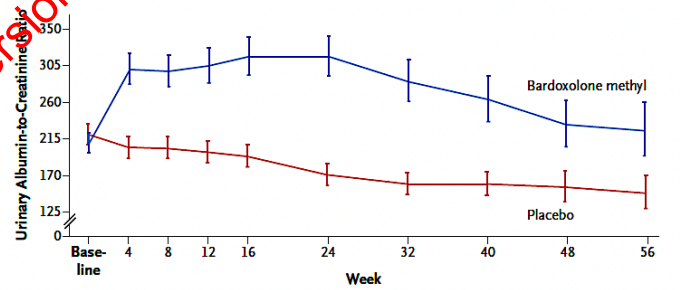
No. at Risk												
Placebo	1097	1074	1041	971	898	743	565	414	290	134		
Bardoxolone methyl	1088	1041	1007	921	860	693	524	384	268	116		

B



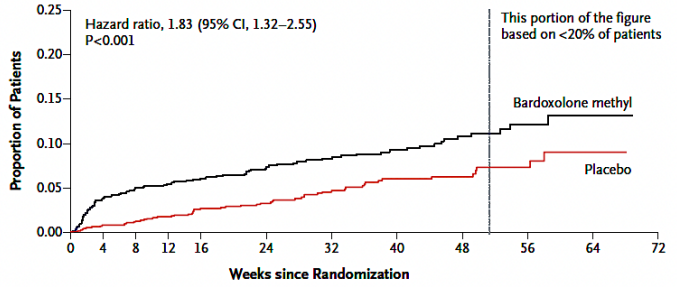
No. at Risk												
Placebo	1097	1066	1031	969	890	730	553	407	282	126		
Bardoxolone methyl	1088	1001	957	859	791	633	416	342	241	106		

C



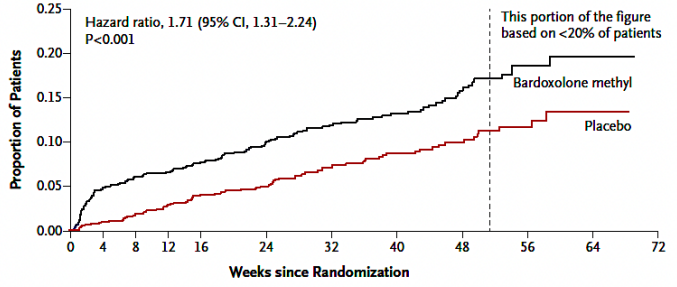
No. at Risk												
Placebo	1097	1075	1038	994	947	812	640	497	346	225		
Bardoxolone methyl	1088	1038	982	908	849	709	552	401	298	185		

A Heart Failure



No. at Risk												
Bardoxolone methyl	1088	1045	1006	942	864	723	548	417	288	133	15	0
Placebo	1097	1089	1070	994	907	762	591	436	315	135	20	0

B Secondary Composite Outcome



No. at Risk												
Bardoxolone methyl	1088	1038	999	935	855	712	537	409	278	126	15	0
Placebo	1097	1088	1068	990	902	754	582	430	310	132	20	0

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De Zeeuw D et al., N Engl J Med 369: 2492-503, 2013

Sulodexide therapy for the treatment of diabetic nephropathy, a meta-analysis and literature review

Study or subgroup	Sulodexide Events	Total	Placebo Events	Total	Weight	Odds ratio M–H, random, 95% CI
Bu et al[51]	30	38	24	37	18.6%	2.03 (0.72, 5.70)
Dedov et al[18]	37	37	1	19	5.8%	925.00 (35.91, 23,824.79)
Gambaro et al[22]	27	53	1	50	10.8%	50.88 (6.54, 395.98)
Heerspink et al[21]	12	42	5	39	17.5%	2.72 (0.86, 8.62)
Lewis et al[11]	76	492	87	494	23.8%	0.85 (0.61, 1.20)
Packham et al[12]	70	619	49	629	23.5%	1.51 (1.03, 2.21)
Total (95% CI)		**1,281**		**1,268**	**100%**	**3.28 (1.34, 8.06)**
Total events	252		167			

Heterogeneity: τ^2=0.85; χ^2=39.57, df=5 (P<0.00001); I^2=87%
Test for overall effect: z=2.59 (P=0.010)

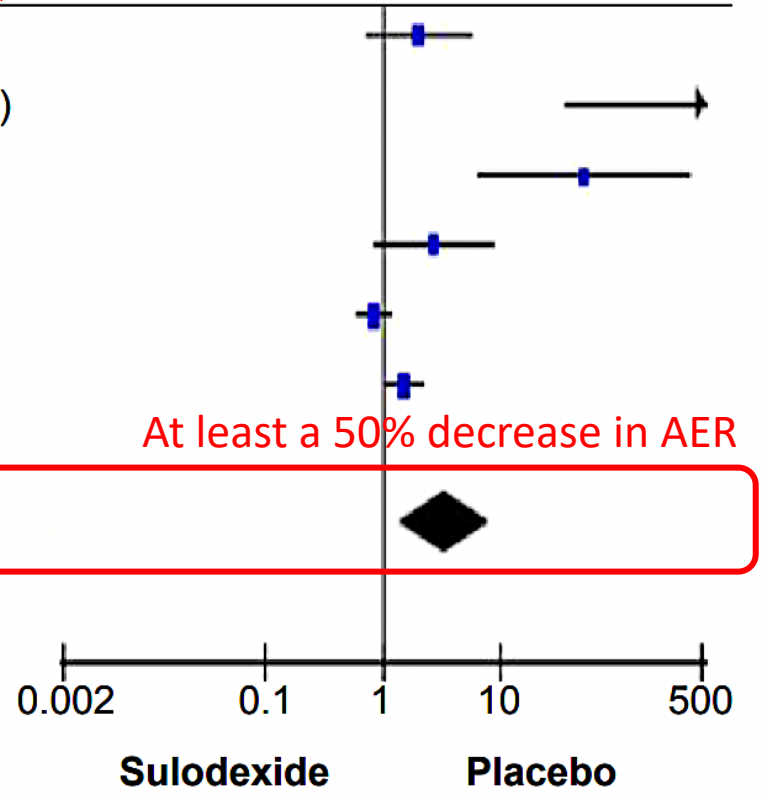

Figure 3 Antiproteinuric effects of sulodexide, as assessed by the proportion of patients to achieve the therapeutic effect from six studies.
Notes: OR=3.28, 95% CI, 1.34–8.06, P=0.01.
Abbreviations: CI, confidence interval; OR, odds ratio; M–H, Mantel–Haenszel test.

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Li R, et al., Drug Des Devel Ther. 2015; 9: 6275-83.

Effects of Selonsertib (ASK-1 inhibitor) in Patients with Diabetic Kidney Disease

Cohort

333 Patients with T2DM

DM

Mean Age 62

With Diabetic Nephropathy

DKD

68% Male

31 ml/min/1.73m²

eGFR

Methods

Randomize

Placebo n=85

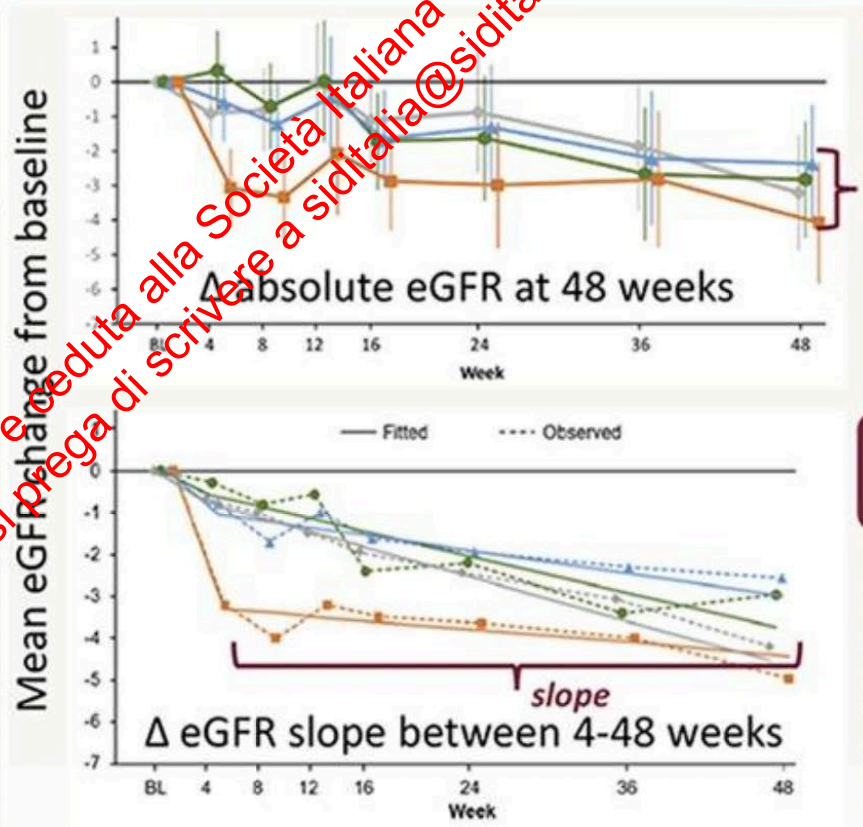
Selonsertib

2 mg n=81

6 mg n=84

18 mg n=8[illegible]

eGFR Decrease



Primary analysis

Difference in eGFR similar across groups

Exploratory analysis

eGFR slope reduced 71% in 18 mg group vs placebo

CONCLUSION Although the trial did not meet its primary endpoint, exploratory post-hoc analyses suggest that selonsertib may slow DKD progression.

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Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Chertow GM, et al., J Am Soc Nephrol. 2019; 30: 1980-1990.

The contribution of inflammation to the pathogenesis of DKD

The discontinuation of undergoing clinical testing of promising anti-inflammatory agents for DKD

The current landscape of inflammation in DKD pathogenesis and treatment

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Therapeutic strategies in DKD with potential anti-inflammatory properties

Drug	Primary target	Main outcomes in DKD	Anti-inflammatory effects	References
RAS blockers	Inhibition of ACE or blockade of angiotensin II receptor.	Reduce proteinuria and the progression of nephropathy.	Inhibition of NF-κB, MCP1 gene expression, and macrophage infiltration.	(68, 69)
SGLT2 inhibitors	Blockade of glucose reabsorption by SGLT2 at the proximal tubule.	Improved glycemic control. Slower progression of kidney disease and lower rates of clinically relevant renal events.	Reduction of inflammation by targeting the IL1ß and reduction of hsCRP, TNFα, IL6, and IFNγ.	(70–90)
DPP4 inhibitors and GLP-1 receptor agonists	Stimulation of glucose-dependent insulin release.	Improved glycemic control and body weight reductions. Renoprotective actions	Reduction in levels of inflammatory markers including CRP, TNFα, IL6, and IL18.	(91–97)
Pentoxifylline	Inhibition of phosphodiesterases.	Reduced progression of renal disease and proteinuria.	Downregulation of NF-κB signaling and reduction of inflammatory biomarkers.	(98–114)

RAAS, Renin-Angiotensin Aldosterone System; ACEI, angiotensin converting enzyme; NF-κB, nuclear factor-κB; MCP1, monocyte chemoattractant protein 1; SGLT2, type 2 sodium-glucose cotransporter; IL, interleukin; hsCRP, high sensitivity C reactive protein; TNFα, tumor necrosis factor α; IFN-γ, interferon γ; DPP4, dipeptidyl-peptidase-4; GLP-1, glucagon-like peptide-1.

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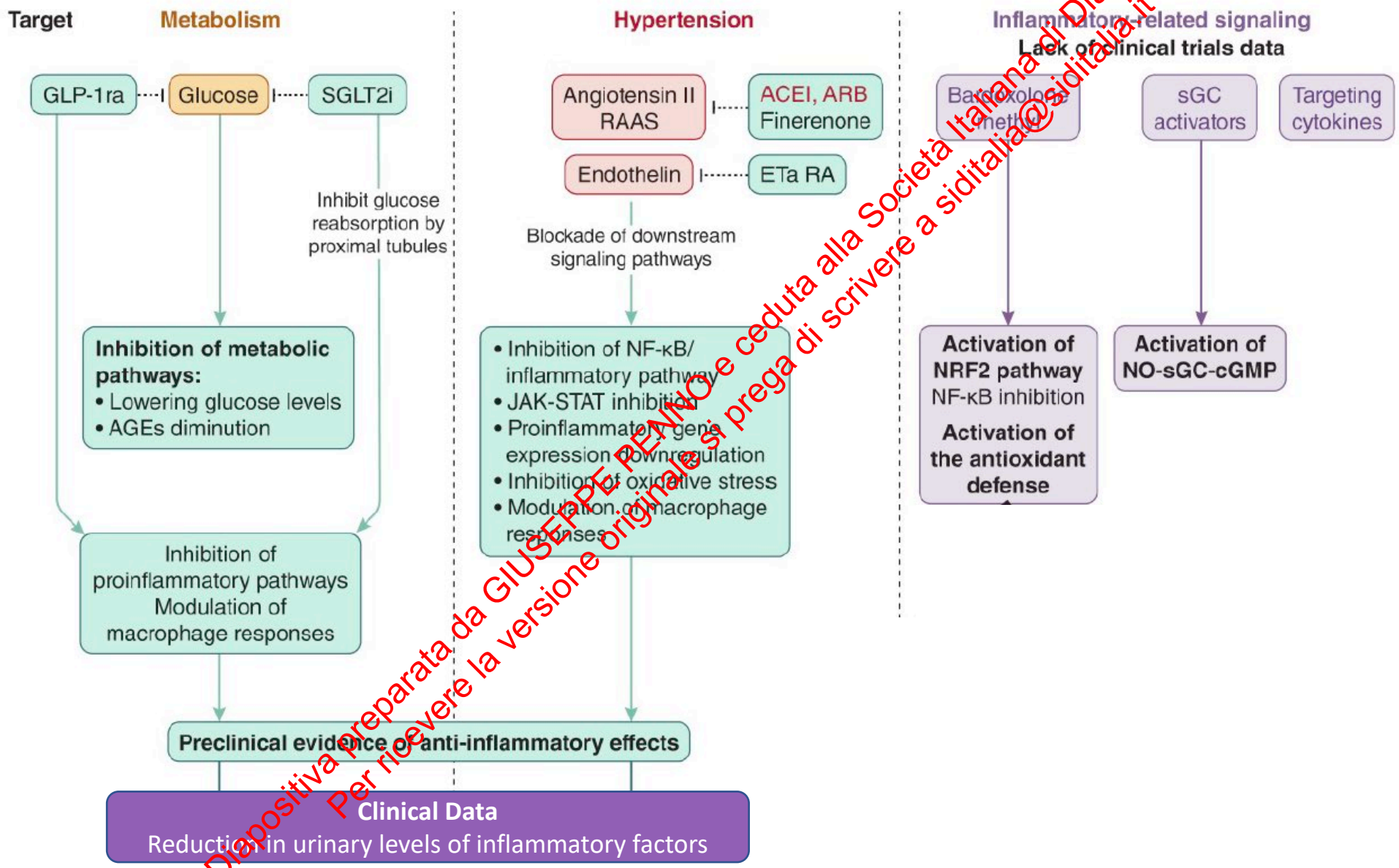
Donate-Correa J. et al., Front Med. 2021; 7: 628829.

Therapeutic strategies in DKD with potential anti-inflammatory properties



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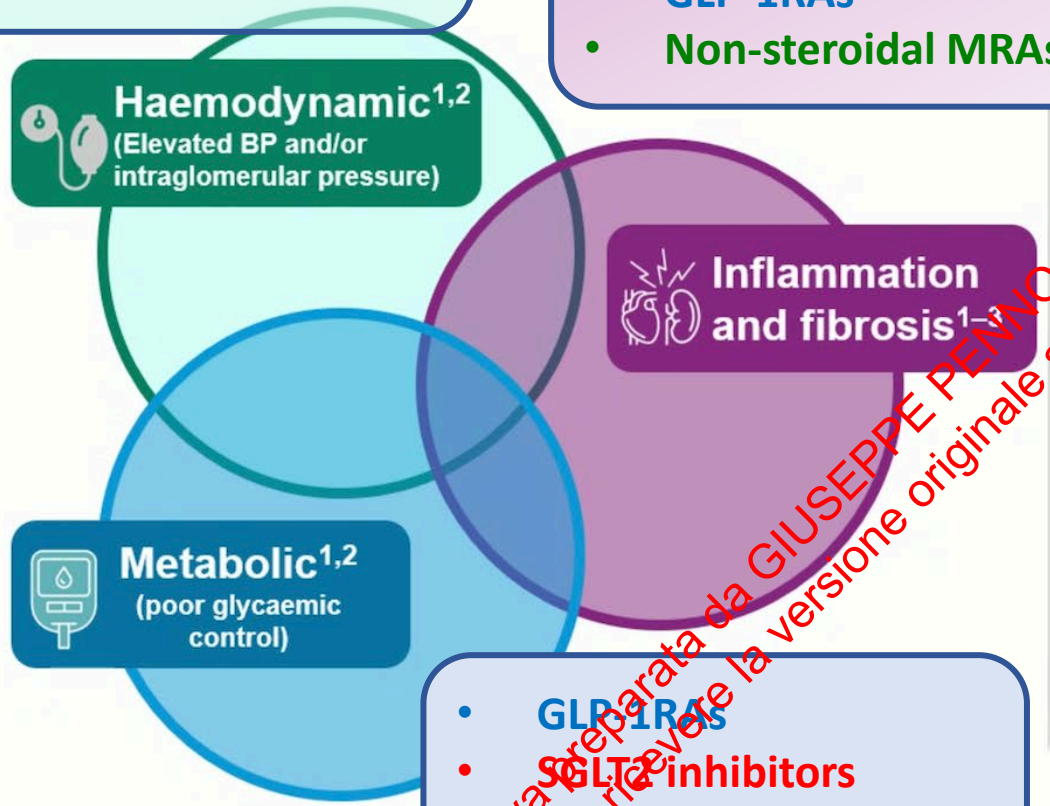
Rayego-Mateos S. et al., Kidney International 2022.

Drivers of DKD Progression

- RAAS inhibitors
- **SGLT2 inhibitors**
- **Non-steroidal MRAs**
- Endothelin RA

- RAAS inhibitors
- **SGLT2 inhibitors**
- **GLP-1RAs**
- **Non-steroidal MRAs**



- **GLP-1RAs**
- **SGLT2 inhibitors**
- Other BG-lowering agents

Tubulointerstitial damage and inflammation[1–3]

Glomerulosclerosis[1–3]

Mesangial expansion[1,2]

Glomerular hypertrophy[1,3]

Kidney fibrosis

CKD PROGRESSION

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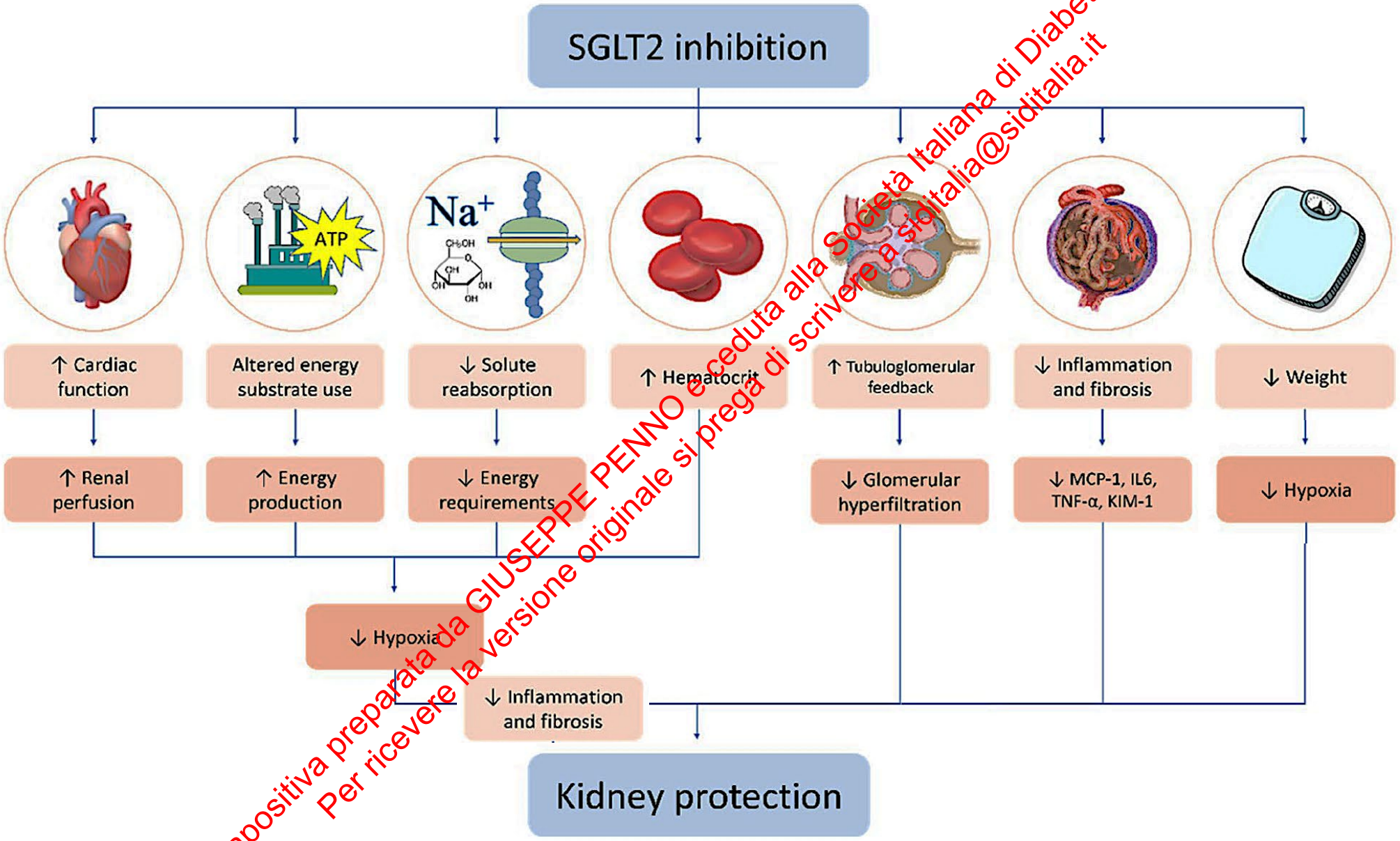
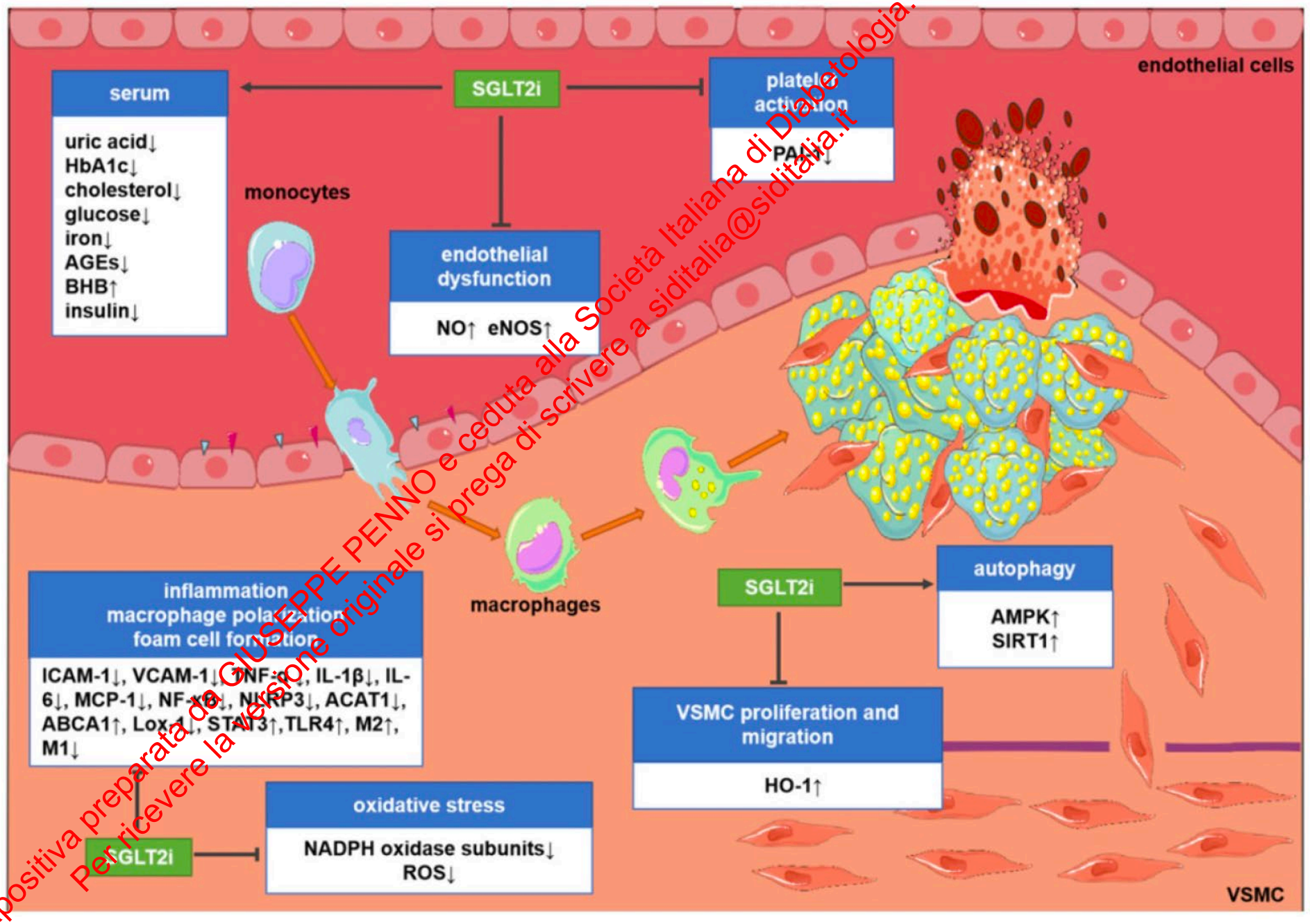
Potential mechanisms for kidney protection with SGLT2 inhibitors



Diapositiva preparata da GIUSEPPE PENNO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Liu H et al., Current Diabetes Reports 22: 317–332, 2022

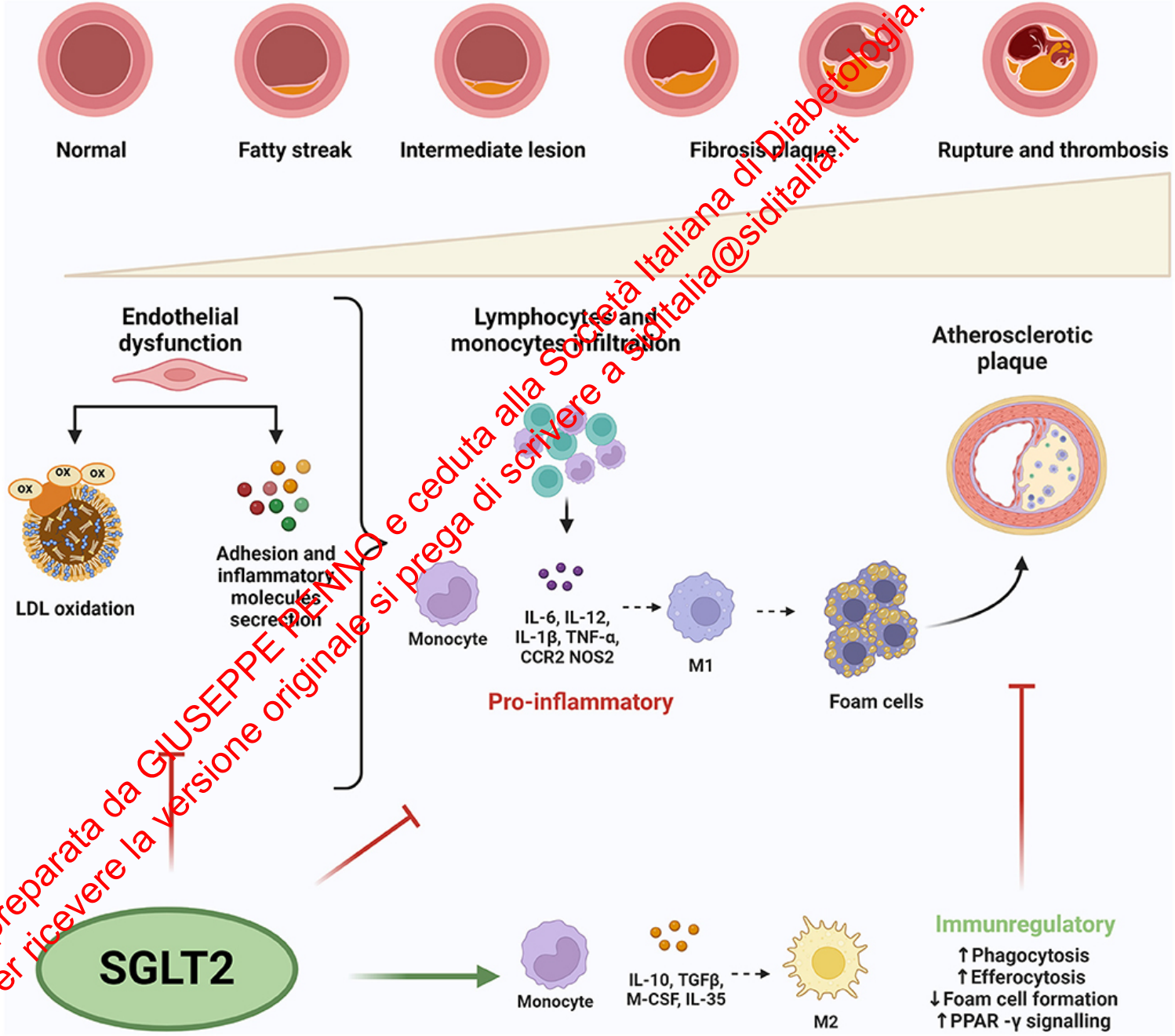
Among others, potential anti-inflammatory mechanisms for vascular (and kidney) protection with SGLT2 inhibitors



Diapositiva preparata da GIUSEPPE PENNO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Liu H et al., Theranostics 11: 4502-4515, 2021

Sodium-glucose co-transport 2 inhibitors' effects on inflammation in atherosclerosis.



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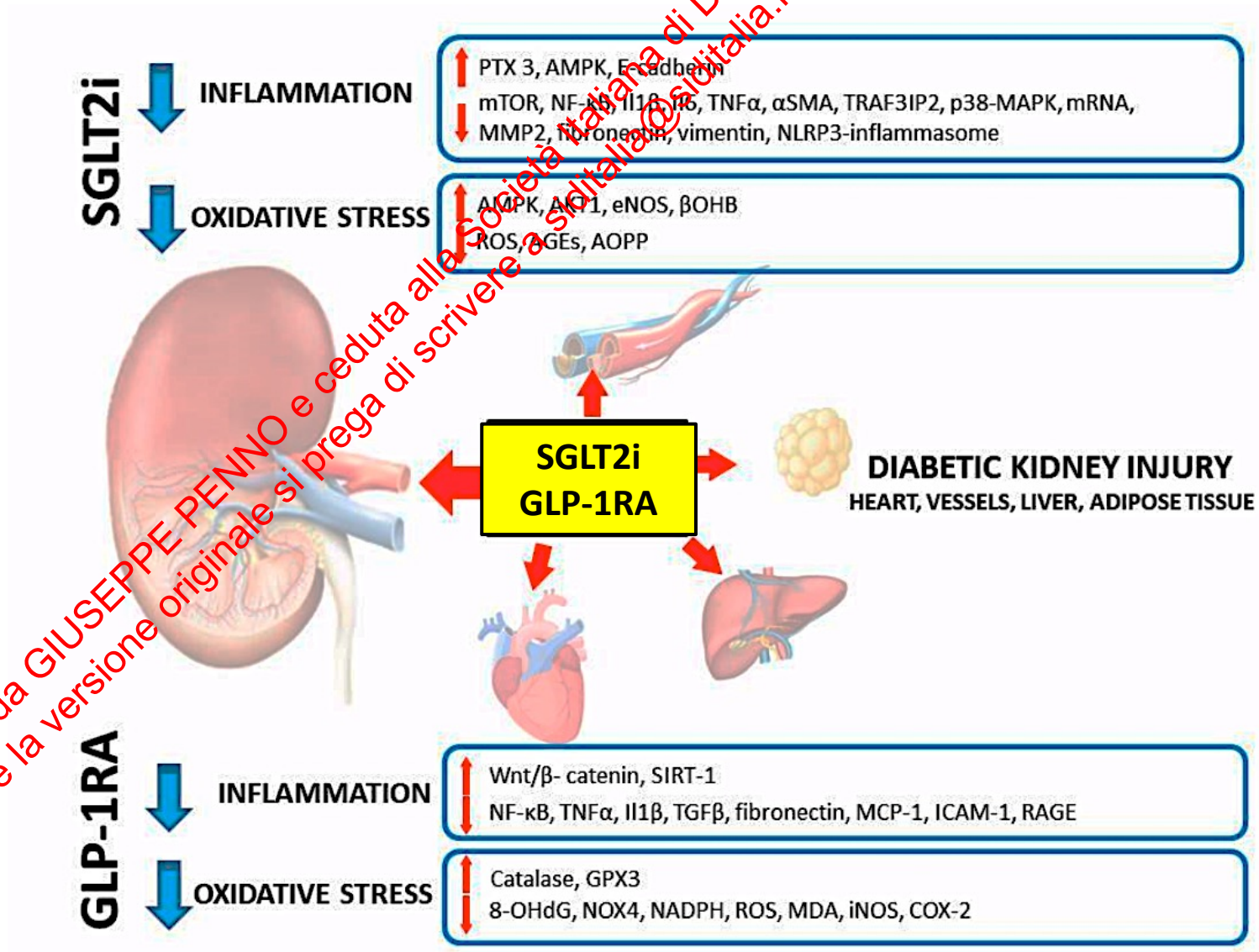
Scisciola L et al., Front Cardiovasc Med, 2022

Inflammation and Oxidative Stress in Diabetic Kidney Disease: The Targets for SGLT2 Inhibitors and GLP-1 Receptor Agonists

Selected mechanisms of interaction between SGLT2i, GLP1RA and inflammation/oxidative stress in the kidney and other target organs/tissues.

Inflammation and oxidative stress are among the key pathways contributing to organ damage in the course of diabetes.



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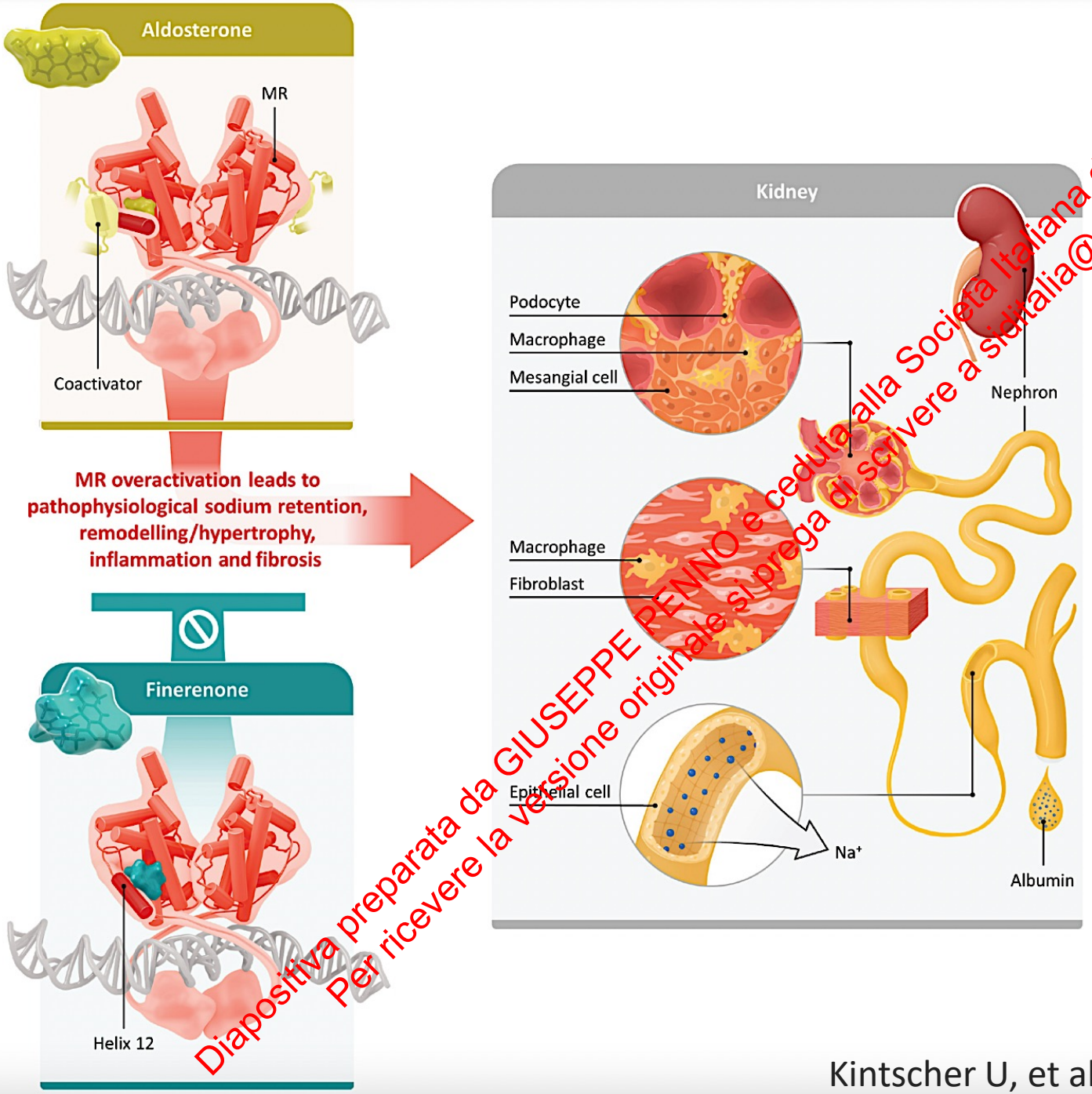
Winiarska A et al. Int J Mol Sci 2021; 22, 10822

Mechanism of action of the non-steroidal mineralocorticoid receptor (MR) antagonist finerenone



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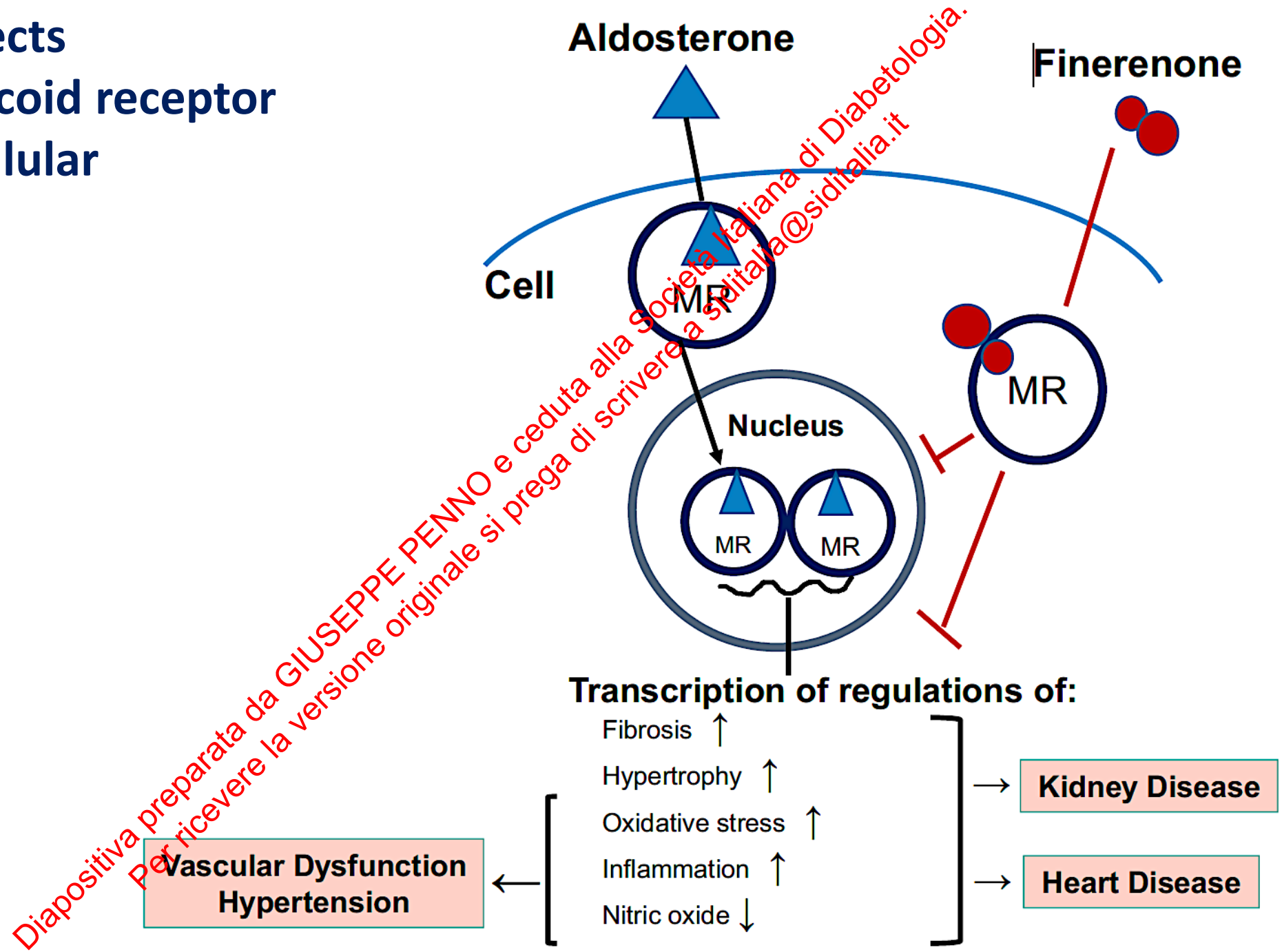
Kintscher U, et al., Br J Pharmacol. 2022; 179: 3220-3234.

Finerenone's effects on mineralocorticoid receptor (MR)-induced cellular pathways.



Ravid JD et al. Current Cardiology Reports (Published online: 4 August 2022)

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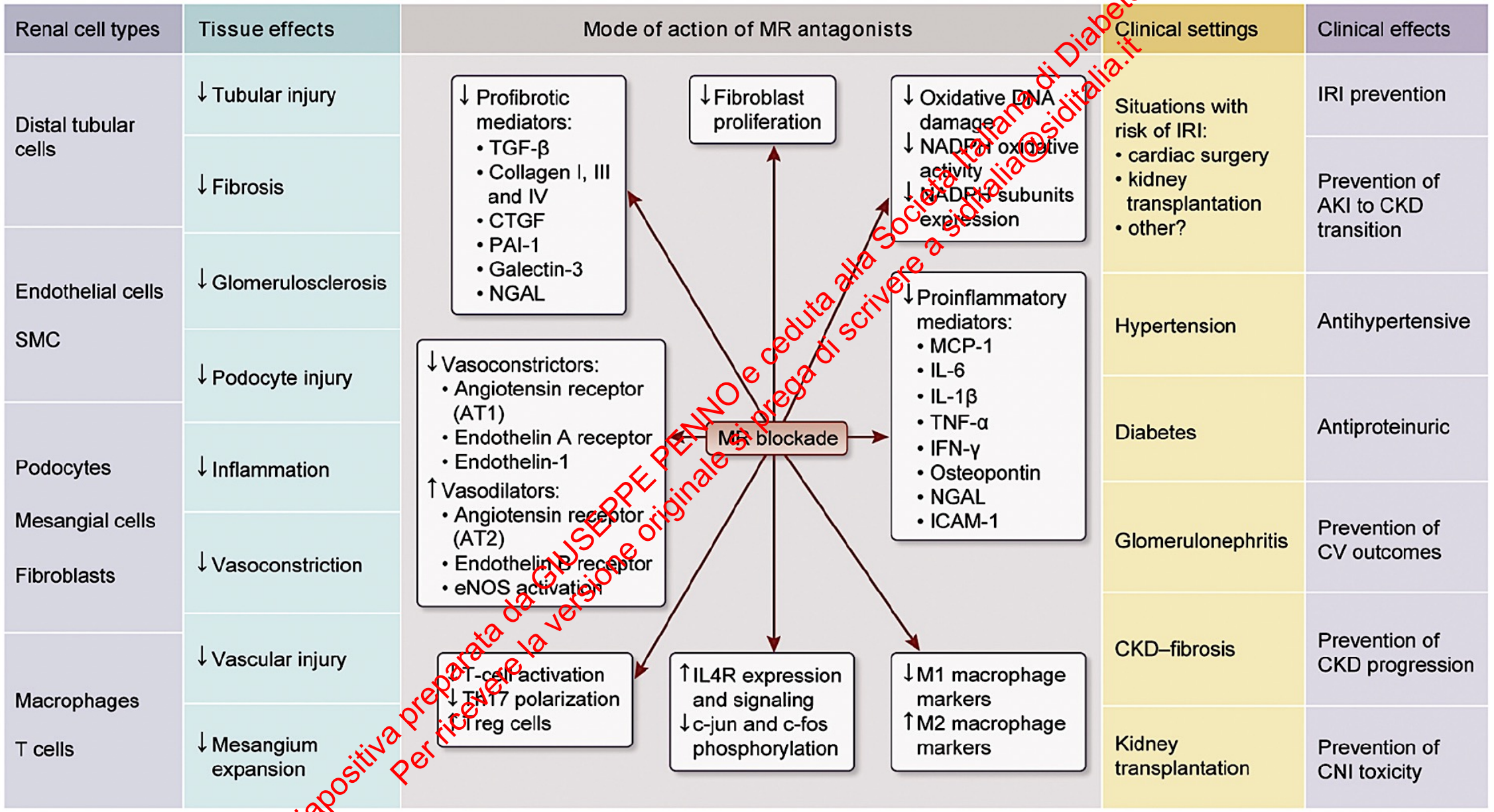
Finerenone: a MRA for the treatment of CKD associated with T2DM



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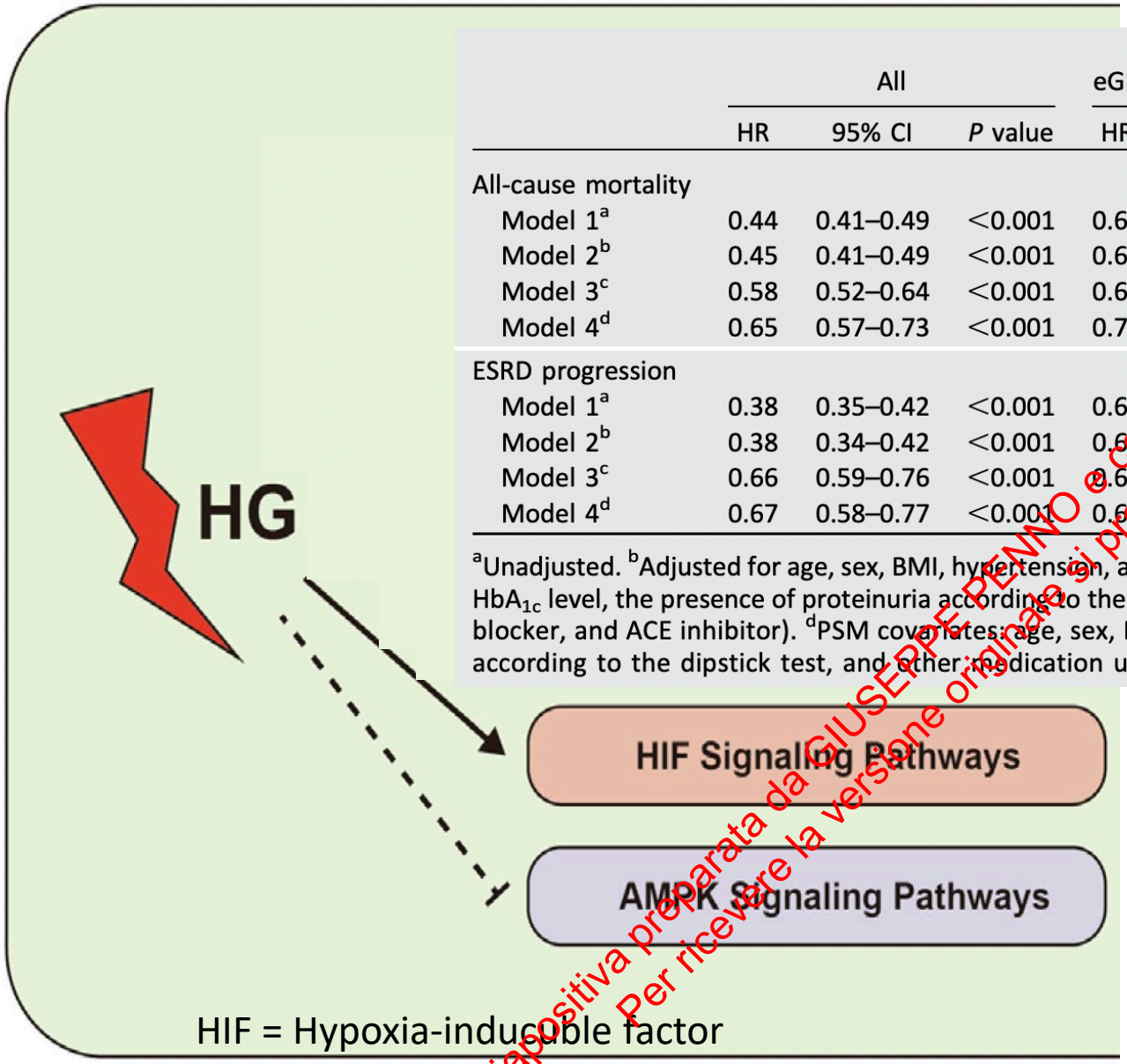
Lerma EV, et al. Expert Review of Clinical Pharmacology 15: 501-513, 2022.

The Long-term Effects of Metformin on Patients With Type 2 DKD

	All			eGFR ≥45 mL/min/1.73 m^2			30 mL/min/1.73 m^2 ≤ eGFR <45 mL/min/1.73 m^2			eGFR <30 mL/min/1.73 m^2		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
All-cause mortality												
Model 1[a]	0.44	0.41–0.49	<0.001	0.67	0.60–0.75	<0.001	0.56	0.45–0.71	<0.001	0.35	0.25–0.49	<0.001
Model 2[b]	0.45	0.41–0.49	<0.001	0.66	0.59–0.74	<0.001	0.59	0.47–0.75	<0.001	0.42	0.30–0.59	<0.001
Model 3[c]	0.58	0.52–0.64	<0.001	0.61	0.54–0.70	<0.001	0.58	0.45–0.75	<0.001	0.49	0.35–0.69	<0.001
Model 4[d]	0.65	0.57–0.73	<0.001	0.70	0.60–0.82	<0.001	0.64	0.47–0.86	0.003	0.55	0.37–0.81	0.003
ESRD progression												
Model 1[a]	0.38	0.35–0.42	<0.001	0.69	0.60–0.80	<0.001	0.69	0.54–0.88	0.003	0.90	0.73–1.10	0.300
Model 2[b]	0.38	0.34–0.42	<0.001	0.68	0.59–0.79	<0.001	0.71	0.55–0.91	0.007	0.85	0.69–1.50	0.135
Model 3[c]	0.66	0.59–0.76	<0.001	0.62	0.53–0.73	<0.001	0.77	0.58–1.00	0.052	0.88	0.71–1.10	0.257
Model 4[d]	0.67	0.58–0.77	<0.001	0.62	0.51–0.76	<0.001	0.73	0.54–0.99	0.049	0.87	0.67–1.12	0.278

[a]Unadjusted. [b]Adjusted for age, sex, BMI, hypertension, and liver disease. [c]Adjusted for age, sex, BMI, hypertension, liver disease, initial eGFR, initial HbA_{1c} level, the presence of proteinuria according to the urine dipstick test, and other medication use (sulfonylurea, insulin, angiotensin II receptor blocker, and ACE inhibitor). [d]PSM covariates: age, sex, BMI, hypertension, liver disease, initial eGFR, initial HbA_{1c} level, presence of proteinuria according to the dipstick test, and other medication use (sulfonylurea, insulin, angiotensin II receptor blocker, and ACE inhibitor).



HIF = Hypoxia-inducible factor

AMPK = AMP-activated protein kinase

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Kwon S. et al., Diabetes Care. 2020; 43: 948-955.

Ongoing clinical trials: potential anti-inflammatory actions

Target	Intervention	Conditions	Key outcomes	Note	Phases
Thromboxane synthase/receptor blocker	SER150	Macroalb.	ACR (and eGFR)	NCT04881123	2/3
Nrf2 activators (negative regulation of the NF-kB pathway)	Bardoxolone methyl (AYAME)	DKD	eGFR or ESRD	NCT03550443	3
	Curcumin	Early DKD	eGFR and ACR	NCT03262363	2/3
	Resveratrol & losartan	Early DKD	eGFR and ACR	NCT02704494	1
Endothelin-1 (ET-1)	Zibotentan & dapagliflozin (ZENITH-CKD)	(CKD, incl. DKD)	eGFR and ACR	NCT04724837	2
Guanyl cyclase activators (sGC)	Runcaciguat (CONCORD)	DKD	ACR	NCT04507061	2
	BI 68509	DKD	ACR	NCT04750577	2
Apoptosis signal regulating kinase 1 (ASK1)	Selonsertib	DKD	eGFR	Drug no longer in sponsor pipeline	2
Phosphodiesterase-4 inhibitor	Roflumilast	DKD	ACR, eGFR and MCP-1	NCT04755946	3
Fatty acid oxidation inhibitor	Trimetazidine	DKD	ACR	NCT05147194	2
TRPC5 Channel Inhibitor	GFB-887	CKD, incl. DKD)	PCR and UCR	NCT04387448	2
Mab: Anti IL-33	Tozorakimab*	DKD	ACR	NCT04170543	2
Mab: Anti FEGF-B	MEDI3506	DKD	ACR	NCT04419467	2
Cell therapy (several trials)	Mesenchimal stem/stromal cells or renal autologous cells	DKD	Mainly safety (eGFR)	---	1/2

* On top of RAS blockers and dapagliflozin

Rayego-Mateos S. et al., Kidney International 2022.

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Renal Autologous Cell Therapy (REACT®) to Stabilize Function in Diabetes-Related Chronic Kidney Disease: Corroboration of Mechanistic Action With Cell Marker Analysis

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

22 adults with Type 2 D-CKD

Kidney biopsy

2 subcortical injections of SRCs:
- 7±3 months apart
- Phenotypic markers identify 3 kidney cell lineages

Baseline Characteristics

DM duration:
18.4 ± 8.8 years

Hemoglobin A1C:
7.0 ± 1.05

Estimated GFR:
40.3 ± 9.35
ml/min/1.73m^2
combined cystatin C and creatinine calculation

Annualized eGFR slope

Pre-injection:
-4.63 ml/min/1.73m^2/yr

p=0.015

Post-injection:
-1.69 ml/min/1.73m^2/yr

7 patients had a positive eGFR slope of +5.88 ml/min/1.73m^2/yr

D-CKD, diabetic chronic kidney disease; SRC, selected renal cells; REACT®, renal autologous cell therapy

KI REPORTS
Kidney International Reports

Stavas J, 2023

Visual abstract by:
Brian Rifkin MD
@brian_rifkin

Conclusion Our cell marker analysis suggests selected renal cells may enable REACT® to stabilize and improve kidney function, possibly halting Type 2 diabetic kidney disease progression.

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The contribution of inflammation to the pathogenesis of DKD

The discontinuation of undergoing clinical testing of promising anti-inflammatory agents for DKD

The current landscape of inflammation in DKD pathogenesis and treatment

An uphill road: any novel (anti-inflammatory) drug should show improvement over RAAS-blockade and SGLT2-inhibition (and finerenone)

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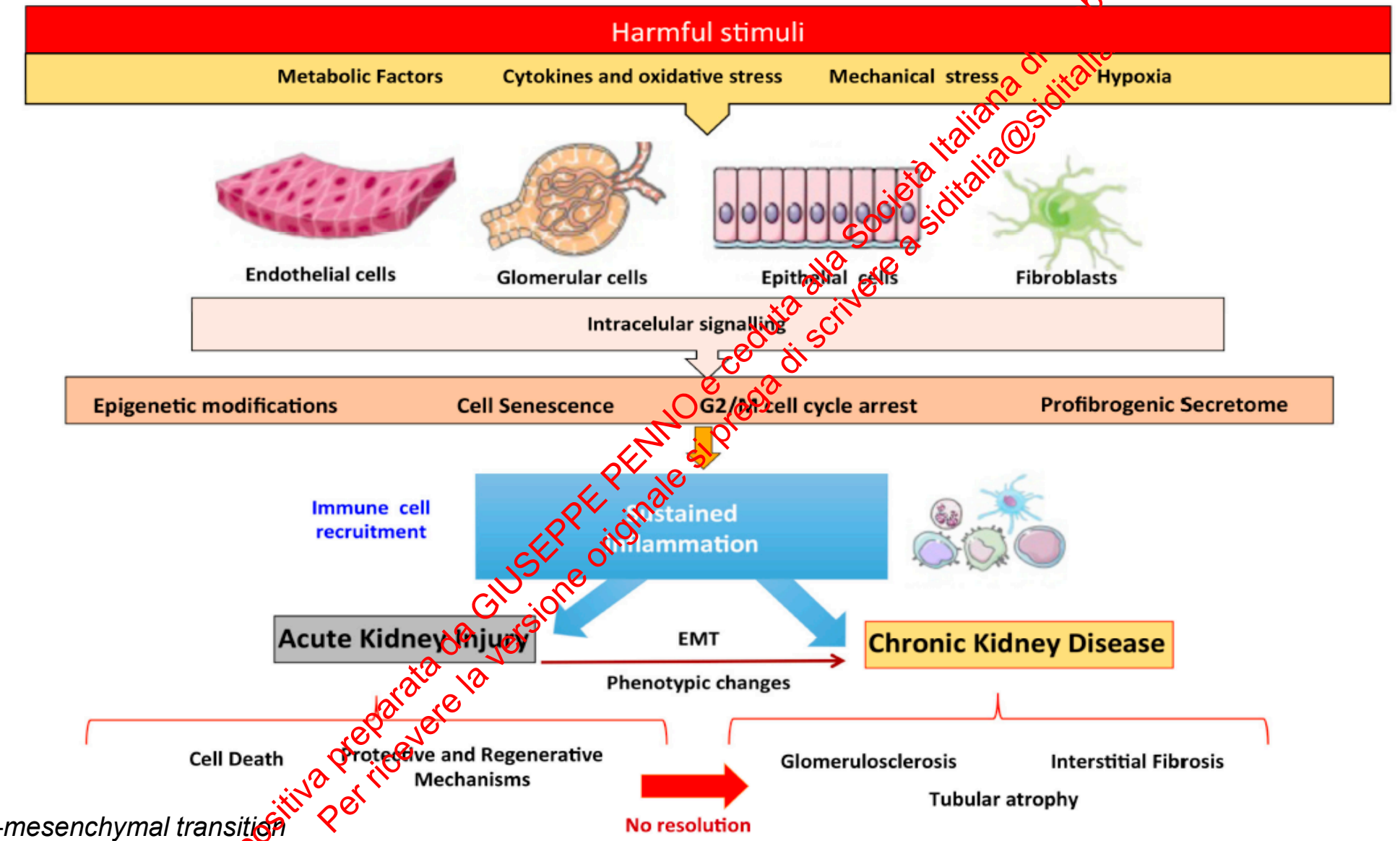
Mechanisms of kidney injury and repair



EMT: epithelial–mesenchymal transition

Rayego-Meteos S, et al. In J Mol Sci 23: 1542, 2022.

Diapositiva preparata da GIUSEPPE PENNO e ceduta alla Società Italiana di nefrologia.
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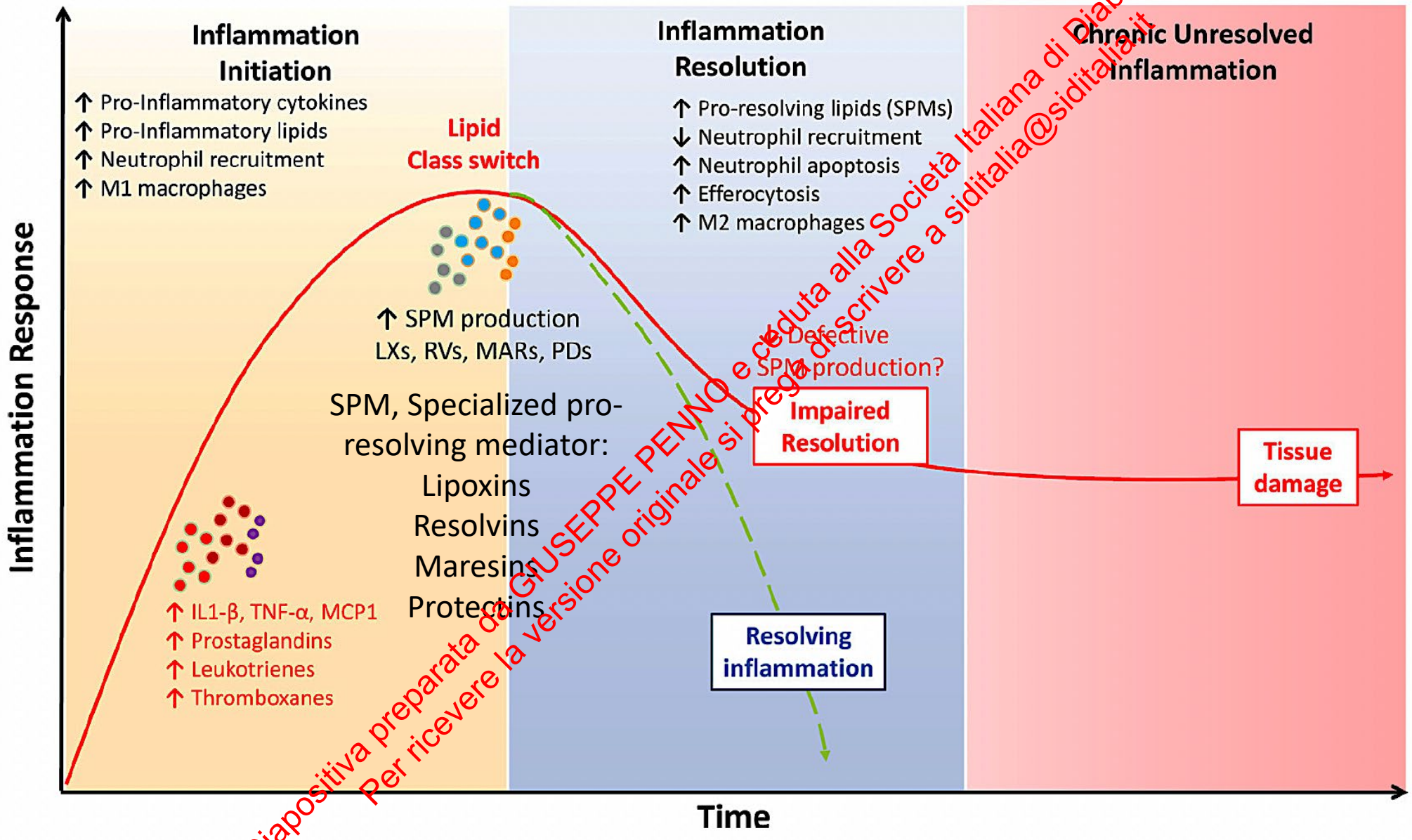
Regulation of inflammation



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Vartak T, et al. Advanced Drug Delivery Reviews 178: 113965, 2021.

Finerenone in Predominantly Advanced CKD in Type 2 Diabetes With or Without SGLT-2i Therapy

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods

Subgroup Analysis of FIDELIO-DKD

Placebo (with or without SGLT-2i)

vs

Finerenone (with or without SGLT-2i)

FIDELIO-DKD design

Global, multicenter, RCT, double blind, phase III trial (n = 5674)

eGFR 25-75 ml/min/1.73m^2

UACR 30-5000 mg/g

Type 2 diabetes

Finerenone vs Placebo

Findings

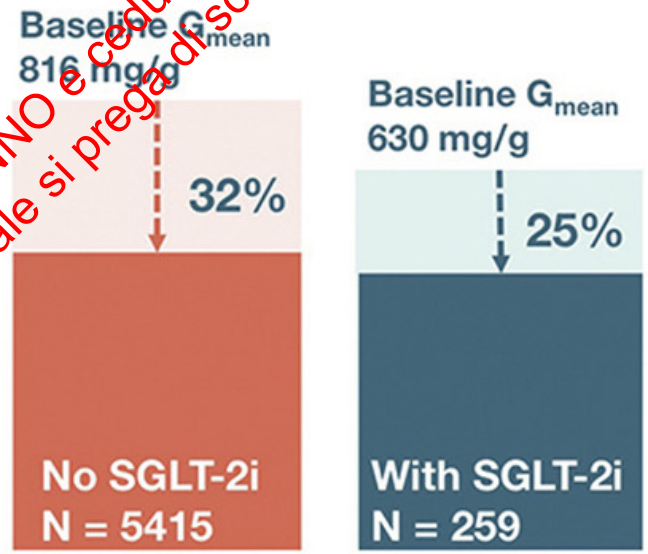
*Compared to those not treated with SGLT-2i

Finerenone with SGLT-2i use characteristics at baseline*

Higher eGFR

Lower UACR

UACR reduction (compared to placebo)



Compared to placebo, the kidney and CV benefits of Finerenone were consistent irrespective of SGLT2i use

Patients on SGLT-2i had fewer hyperkalemia events

SGLT-2i, sodium glucose cotransporter-2 inhibitor; RCT, randomized controlled trial; UACR, urine albumin creatinine ratio; CV, cardiovascular; G_{mean}, geometric mean

KI REPORTS
Kidney International Reports

Rossing et al. 2022

Visual abstract by:
Sophia Ambruso, DO
@Sophia_kidney

Conclusion UACR improvement was observed with finerenone in patients with CKD and T2D already receiving SGLT-2i at baseline and benefits on kidney and cardiovascular outcomes appear consistent irrespective of SGLT-2i use.

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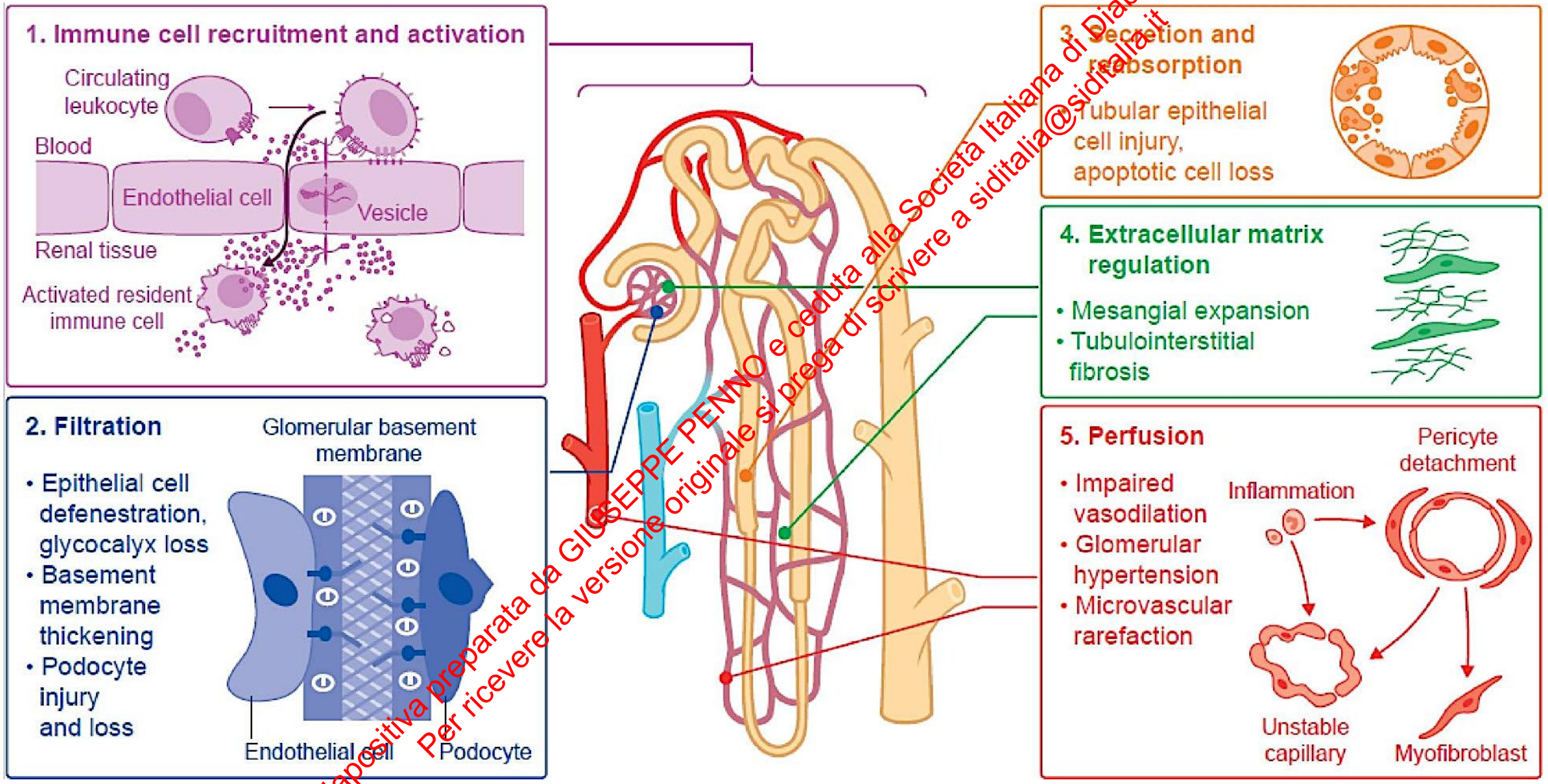
Targeting inflammation for the treatment of Diabetic Kidney Disease: a five-compartment mechanistic model



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Hofherr A, et al., *BMC Nephrol*. 2022; 23: 208.

Designing future RCT of therapy targeting inflammation in Diabetic Kidney Disease

1st

Anti-inflammatory therapy in routine clinical use for non-kidney indications

Prospective follow-up of impact on eGFR/ACR:

- In diseases whose epidemiology overlaps with DKD;
- Registries (worldwide) tracking the impact on eGFR/ACR of novel approaches targeting inflammation on behalf of Scientific Societies.

2nd

Baseline biology assessment from subjects with recently diagnosed DKD:

- Genomics
- Others

3rd

Biology assessment from subjects receiving SOC:

- Others

DKD

Standard of care (SOC):

- BG control; BP control
- Weight control
- CVD and risk factors control
- RAS blockade
- SGLT2i
- MRA (finerenone)

Design novel interventions

Identify candidate drugs for DKD RCTs

Identify markers of suboptimal response (inflammation focused)

Candidate subjects for anti-inflammatory therapy

Suboptimal kidney response

Optimal kidney response

SOC scape

Persistent optimal kidney response

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Rayego-Mateos S. et al., Kidney International 2022 (adapted).

Grazie dell'attenzione

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