

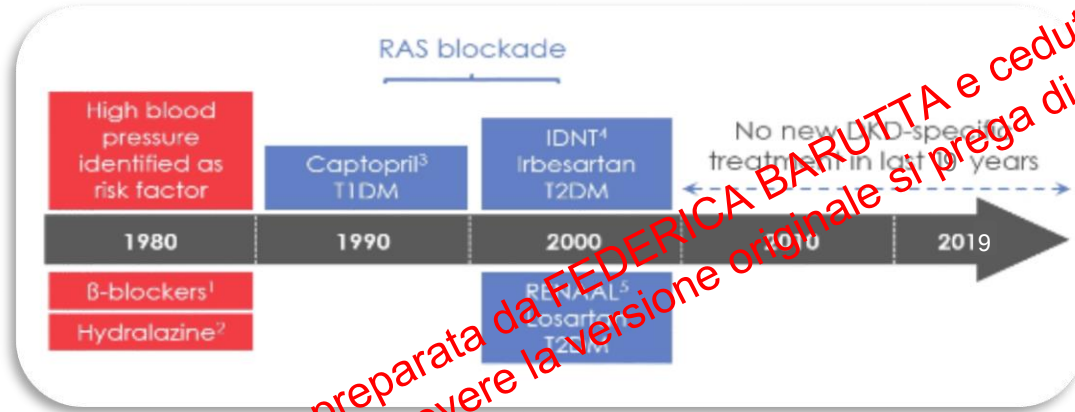
IL FUTURO DELLA TERAPIA DKD: STUDI SPERIMENTALI

Barutta Federica

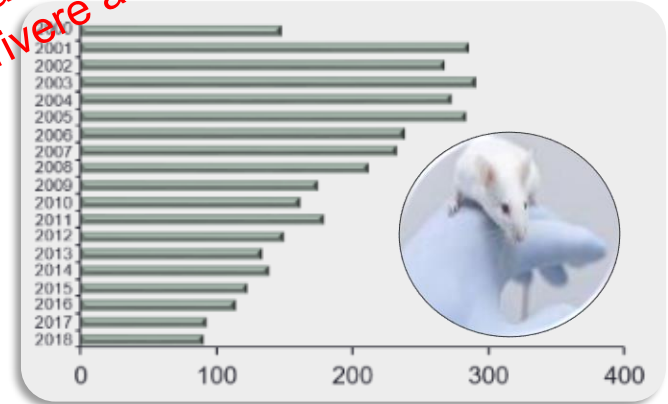
Dipartimento di Scienze Mediche
Università di Torino

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DIABETIC NEPHROPATHY



PubMed: keyword experimental diabetic nephropathy

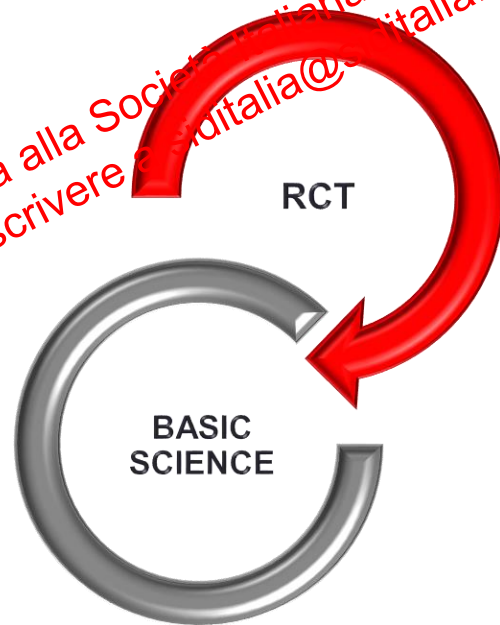


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SGLT2i: NEPHROPROTECTION



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RESIDUAL RISK FOR RENAL ENDPOINTS



The comparator for RENAAL and IDNT was placebo/absence of RAS blockade, while the comparator for CREDENCE was placebo + RAS blockade

OVERVIEW: Future experimental therapy in DN

Primary metabolic defect

Hyperglycemia

Secondary mediators and receptor

AGEs

Chemokines

IL-1 β

Vasoactive peptides with pleiotropic actions

Angiotensin II

Endothelin

MS

Xantine Oxidase

RAGE

CB1/CB2

Aldosterone

MR

ET_A

Uric Acid

Signalling

NF κ B

NOX5

JAK/STAT

ASK-1

Phosphodiesterase

Phenyl Sulfate

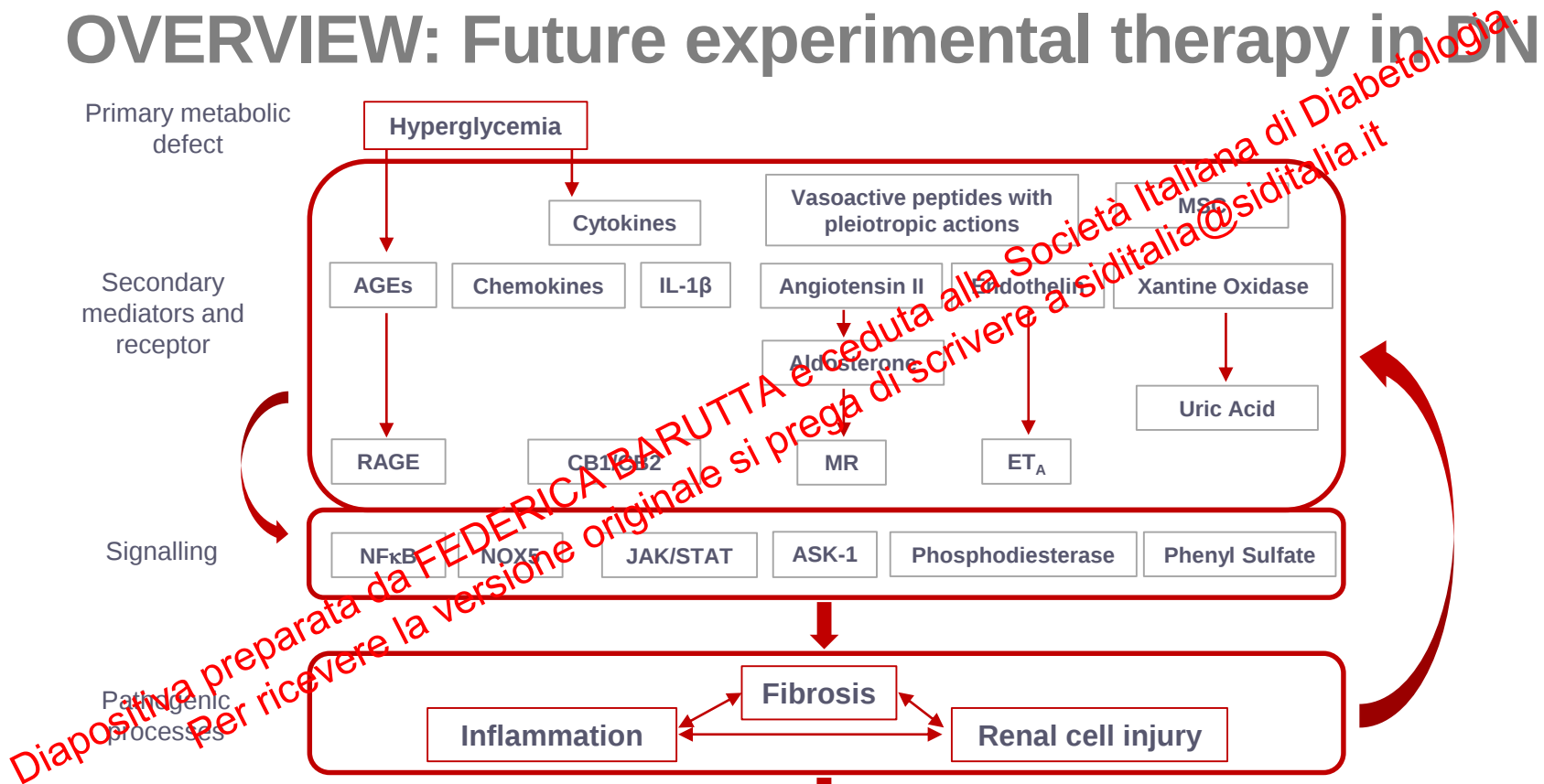
Pathogenic processes

Inflammation

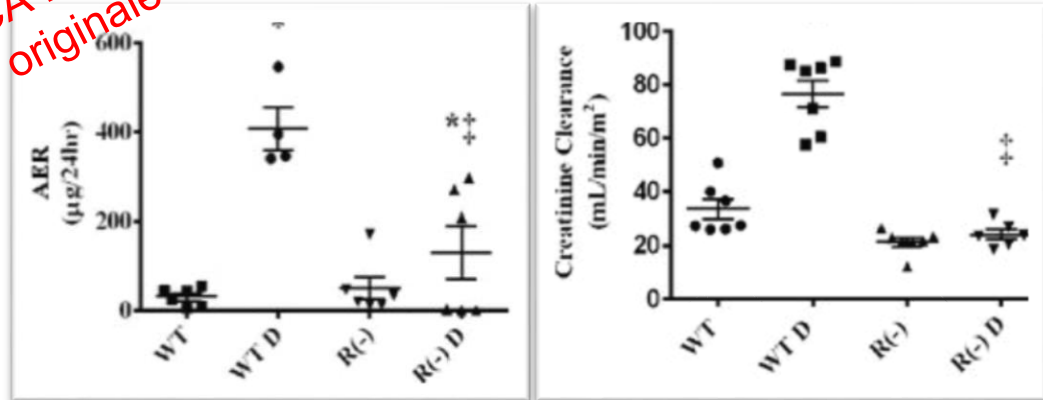
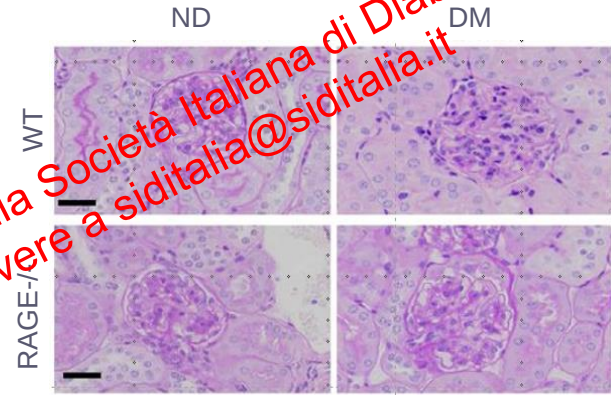
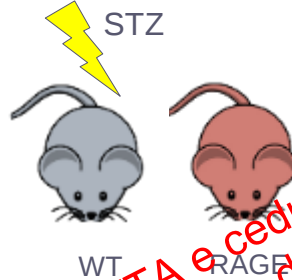
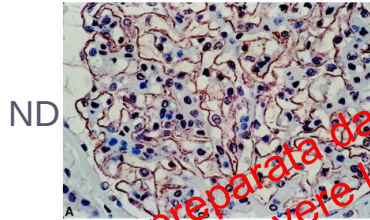
Fibrosis

Renal cell injury

Progression of diabetic kidney diseases



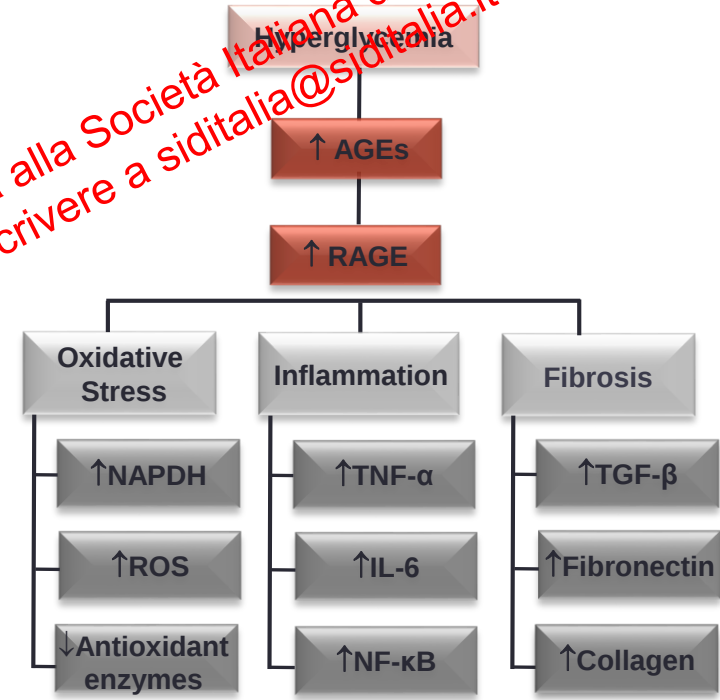
RAGE and DN



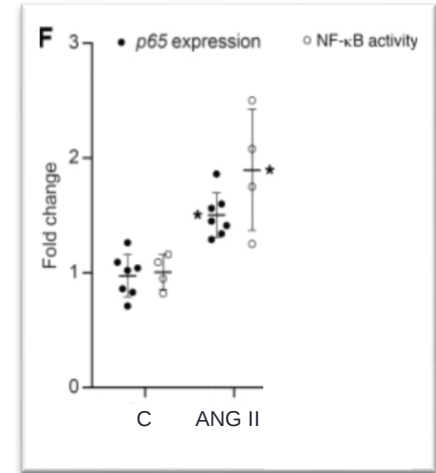
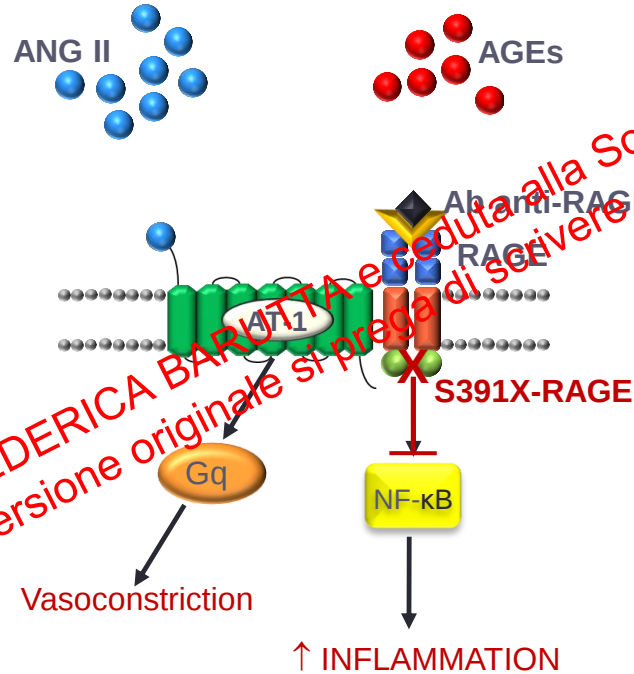
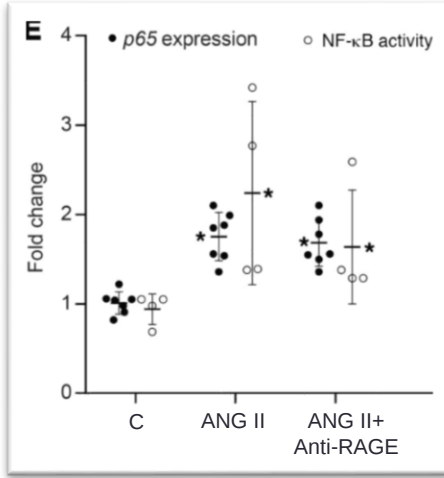
Direct RAGE Blockade in DN



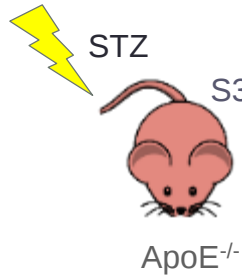
Type 1 DM (STZ mice)	Neutralizing RAGE antibody	8 weeks	↓ Albuminuria Normalized CrCl = CTGF and COLIV
Type 2 DM (db/db mice)	Neutralizing RAGE antibody	8 weeks	↓ Albuminuria ↓ Mesangial expansion Normalized CrCl
Type 1 DM (STZ mice)	RAGE-aptamer	4 weeks	↓ Albuminuria ↓ ECM accumulation ↓ Oxidative stress ↓ Inflammation
CD1 mice AGE overload	FPS-Zn RAGE antagonist		↓ A/C ratio ↓ Tubulo-interstitial inflammation ↓ ROS



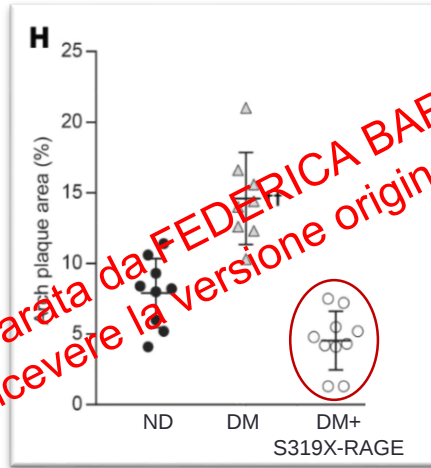
The «NEW» RAGE-AT1 Axis



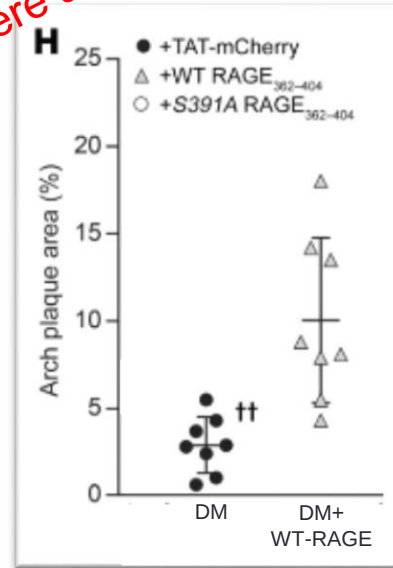
IN VIVO: Inhibition of RAGE Transactivation



Mice Treated with
S319X-RAGE for 10w



Mice Treated with
WT RAGE for 10w



RAGE as potential therapeutic target?



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- Receptor for Advanced Glycation Endproducts (RAGE)
- NADPH-Oxidase (NOX)
- Endocannabinoid System (ECS)
- Gut microbiome-derived Phenil Sulphate
- Mesenchimal Stem Cells

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NOX Isoforms and DKD



NOX-4^{-/-}
NOX4/1 inhibitor: GKT137831

↓ ROS
↓ Pro-inflammatory factors
↓ Pro-sclerotic factors
↓ Mesangial expansion
↓ Glomerulosclerosis
↓ Albuminuria

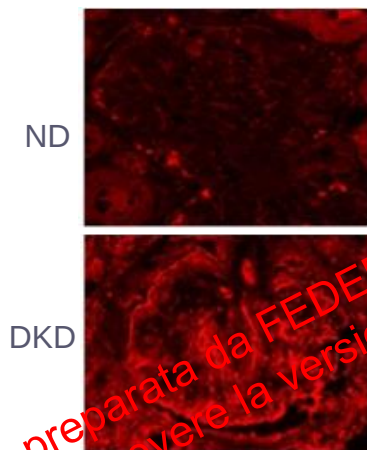


GKT137831 in combination with
ACE inhibitor in patients with DKD

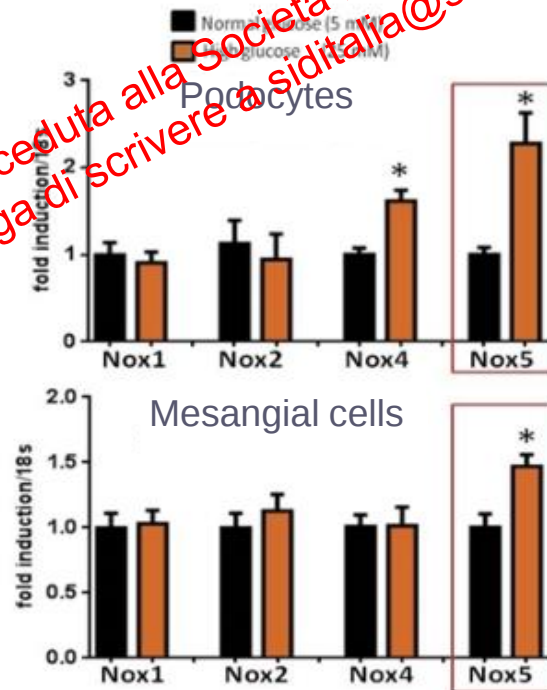
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NOX-5 in human DKD

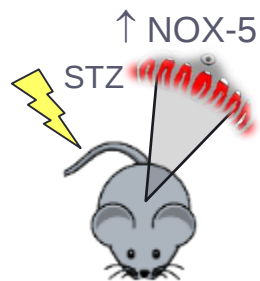
Upregulation of Nox5 in human diabetic kidney biopsies



Upregulation of Nox5 in human renal cells in response to high glucose



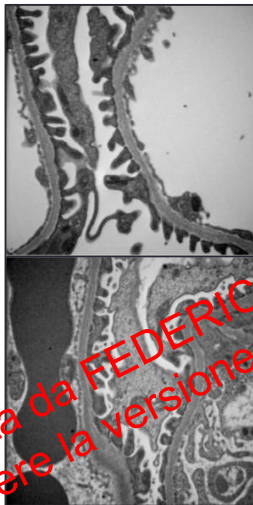
NOX-5 Expression in Podocytes



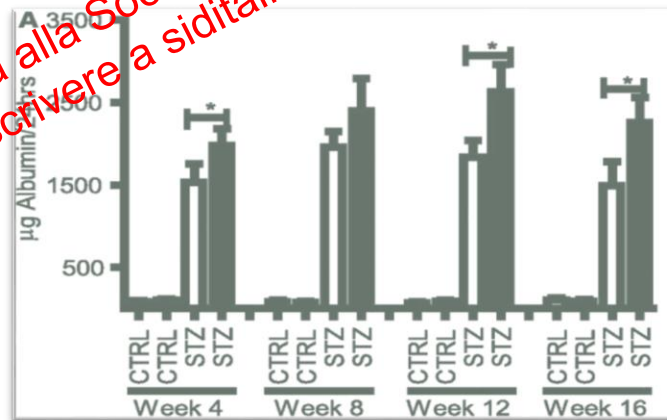
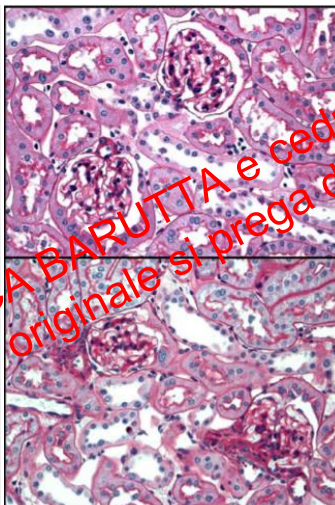
Diabetic
WT

Diabetic
NOX5^{+/+}

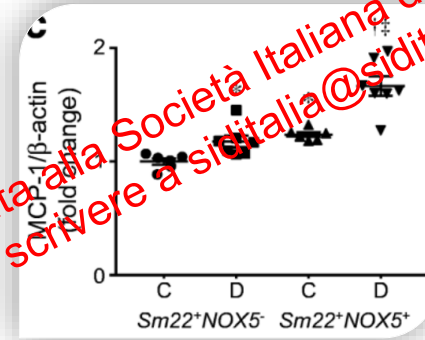
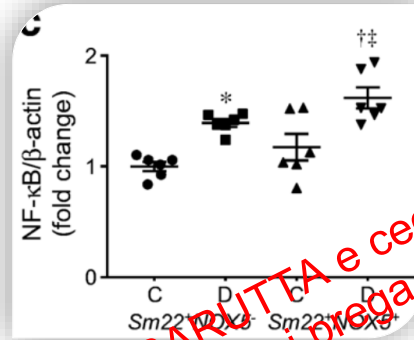
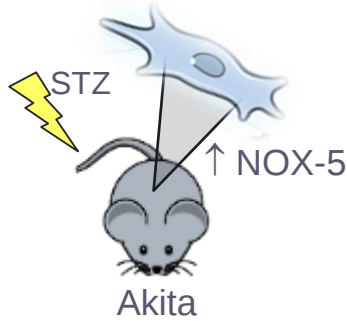
Foot process
effacement



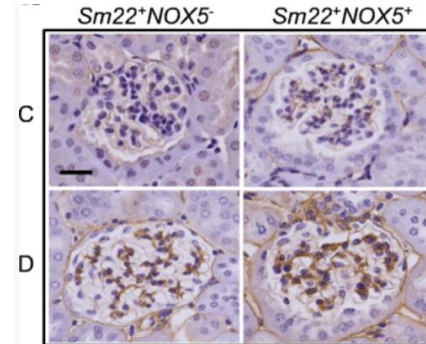
Glomerulosclerosis



NOX-5 Expression in Mesangial cells

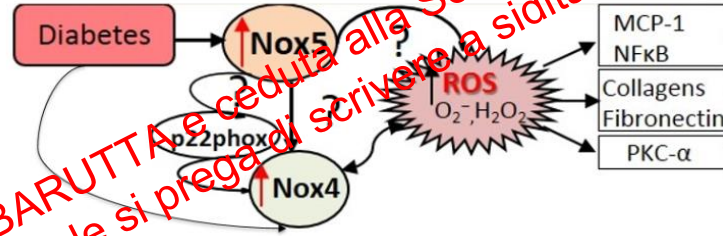
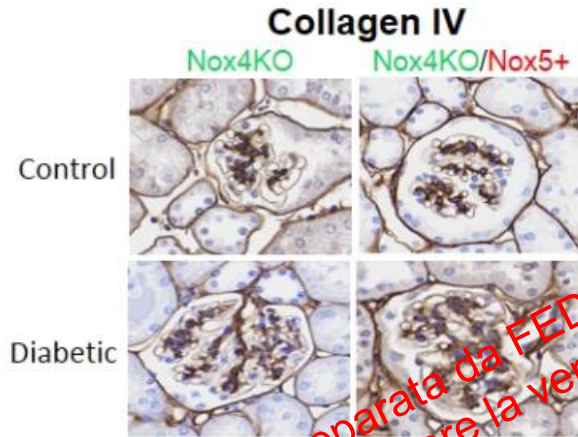


	Albuminuria (μg/24h)
WT	27 ± 2
WT-DM	438 ± 152*
NOX5Tg-C	38 ± 4
NOX5Tg-DM	596 ± 135



Fibronectin

NOX-5 as potential therapeutic target?



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- Receptor for Advanced Glycation Endproducts (RAGE)
- NADPH-Oxidase (NOx)
- Endocannabinoid System (ECS)
- Gut microbiome-derived Phenyl Sulfate
- Mesenchymal Stem Cells

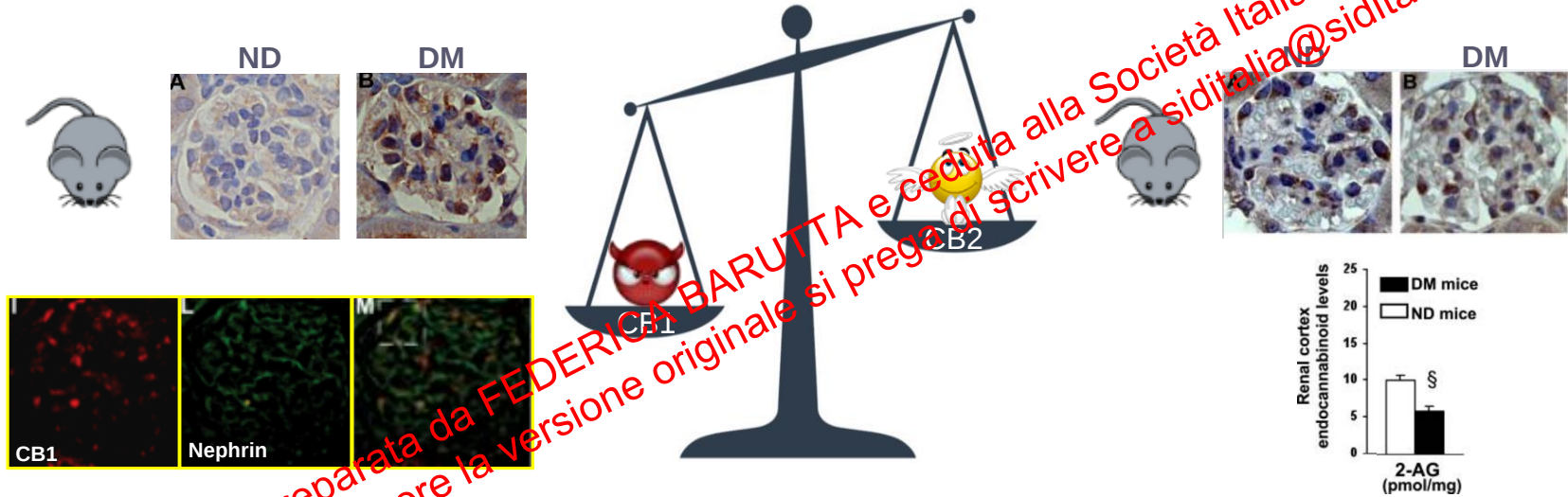
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CB1 e CB2: *Yin e Yang*



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CB1 and CB2 Expression in DN



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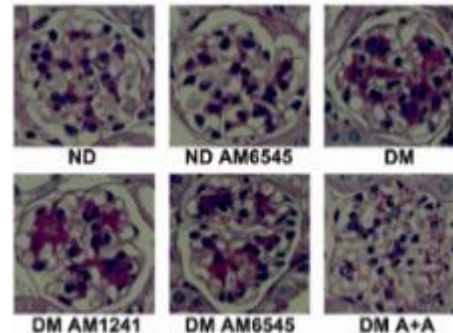
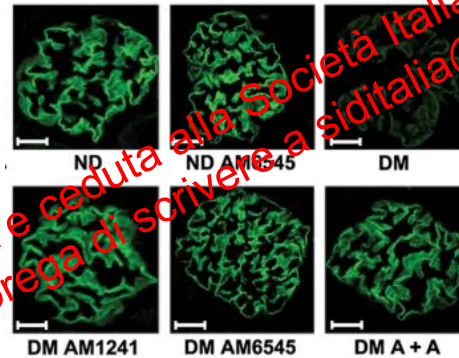
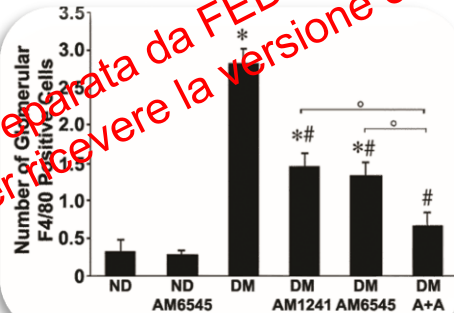
CB1 Blockade
AM6545

CB2 Activation
AM1241

Treatment with AM6545 and AM1241



	AER	NAG
ND	79.5 (70.7-109.3)	159 ± 3.2
DM	310.23 (243.8-342)*	467 ± 65.7*
DM AM1241	169.17 (155.5-177.5)*#	461 ± 30.7*
DM AM6545	163.7 (135.1-197.6)*#	452 ± 30.7*
DM A+A	92.1 (69.8-111.2)*	295 ± 30.8*

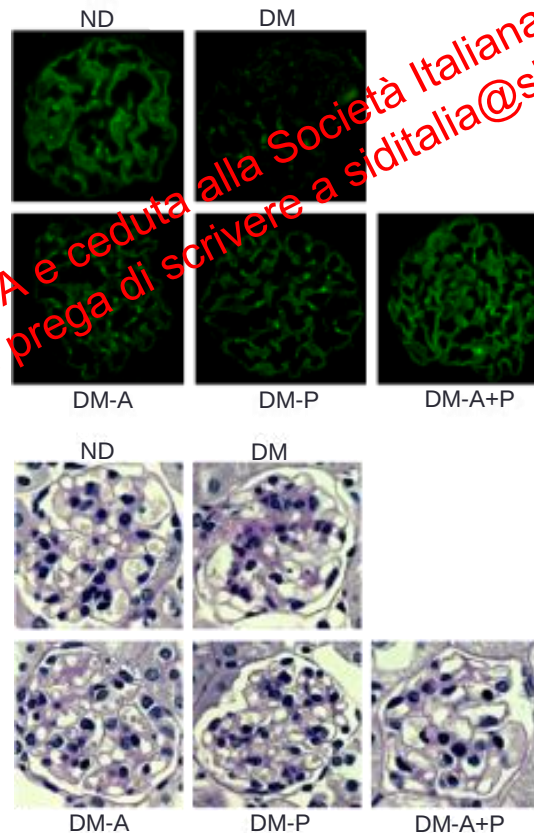


CB1 Blockade and Secondary Prevention



Mice treated with **AM6545**
and/or perindopril

	AER ($\mu\text{g}/18\text{h}$)
ND	118.38 (110.7-124.6)
DM	429.89 (382.8-513.7)*
DM-A	242.60 (213.2-298.0)**
DM-P	225.15 (177.4-268.6)**
DM-A+P	144.82 (112.2-204.5)



ECS as potential therapeutic target?



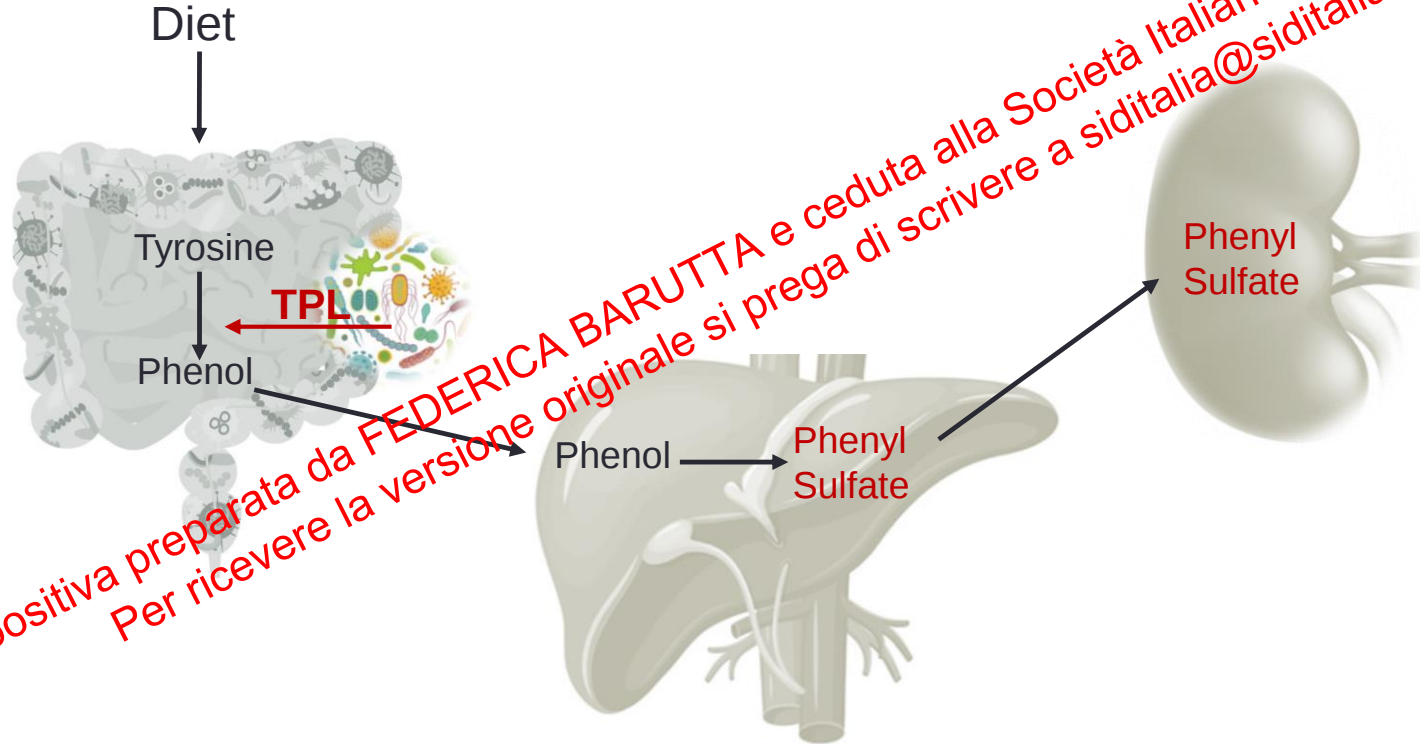
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- Receptor for Advanced Glycation Endproducts (RAGE)
- NADPH-Oxidase (NOx)
- Endocannabinoid System (ECS)
- Gut Microbiome-derived phenyl sulfate
- Mesenchymal Stem Cells

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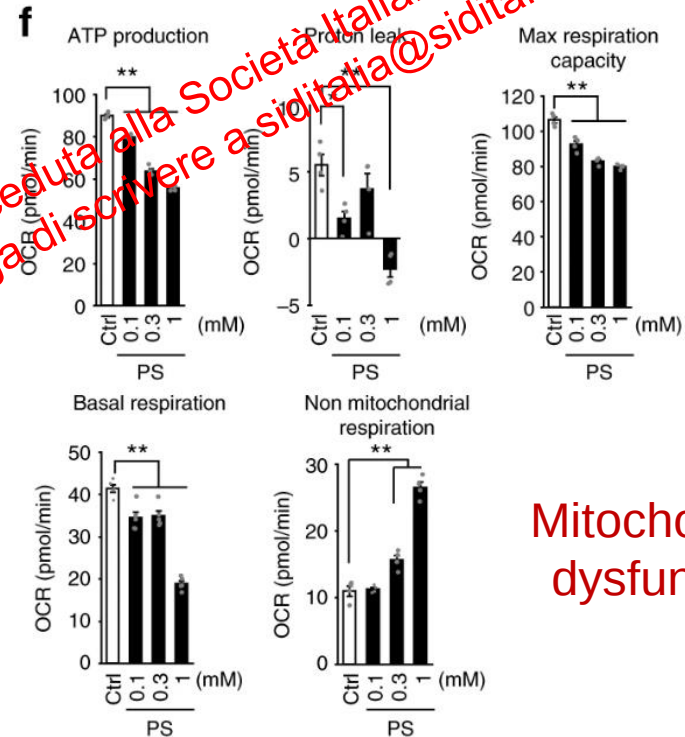
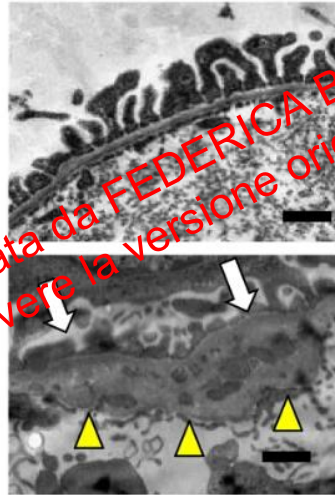
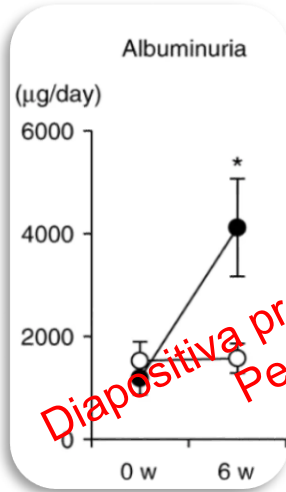
Gut microbiome-derived phenyl sulfate (PS)



PS induced-podocyte damage in DKD

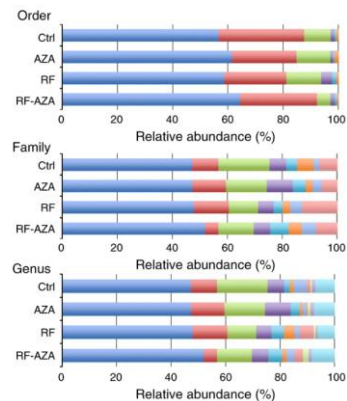
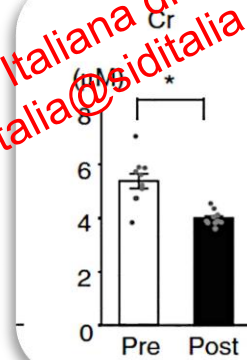
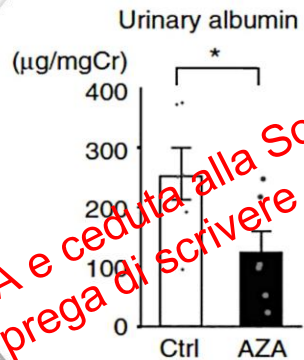
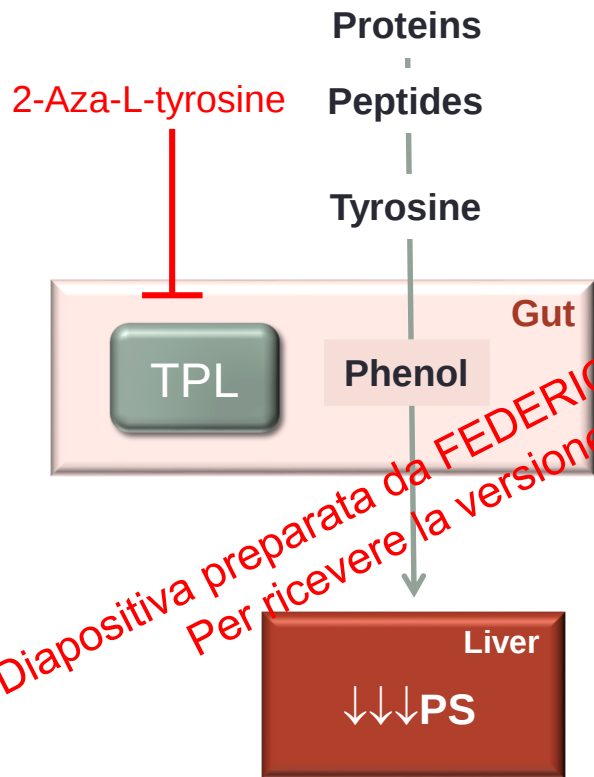


PS orally-treated
mice



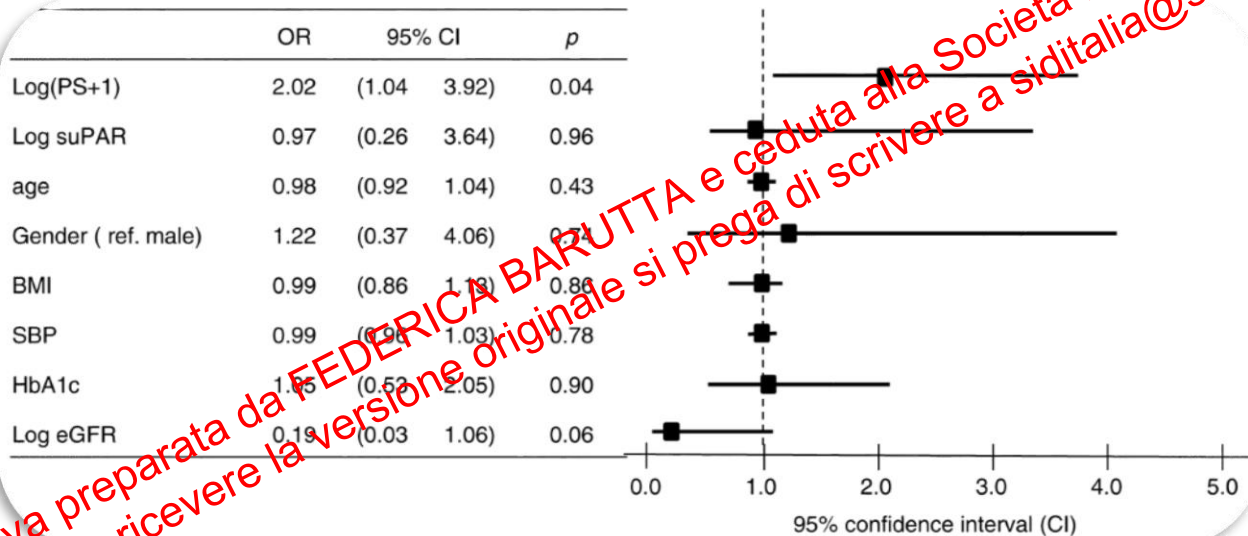
Mitochondrial
dysfunction

PS inhibition as potential therapeutic target?



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PS is a predictor of ACR progression in humans



• Micro → Macro or Micro: 2 x ACR

• N° 87 patients

• FU 2 yrs

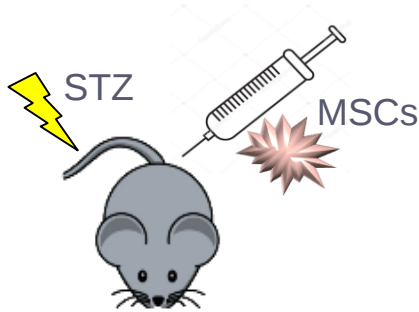
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MSC-based Therapy and DN



NEPHSTROM for DKD

- Phase 1b/2a

- T2D patients with progressive DKD and mild to moderate renal insufficiency

- ↓Albuminuria
- ↓Mesangial expansion
- ↑Podocyte Number
- ↑Nephrin, podocin expression
- ↓Foot process effacement
- ↓Oxidative stress
- ↓Inflammation

Limits:

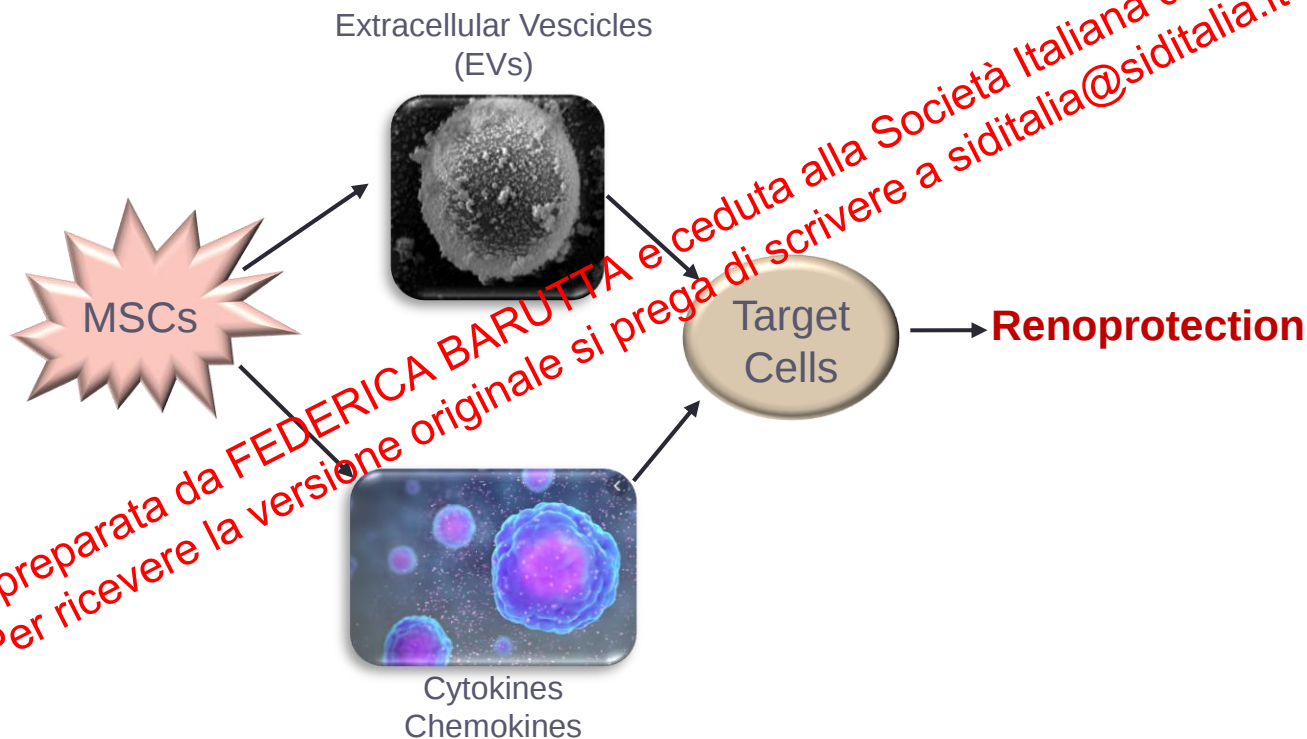
- Heterogeneity
- Dedifferentiation
- Delivery

Nagaishi K, et al. *Sci Rep*. 2016;10;6:34842.

Khalilpourfarshbafi M, et al. *Tissue Eng Regen Med*. 2017;14:201-210.

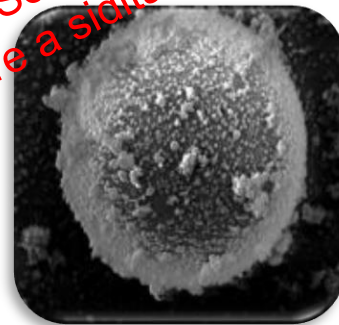
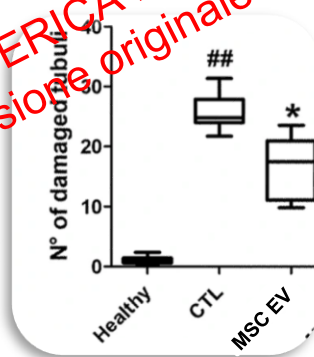
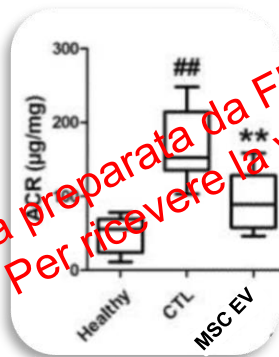
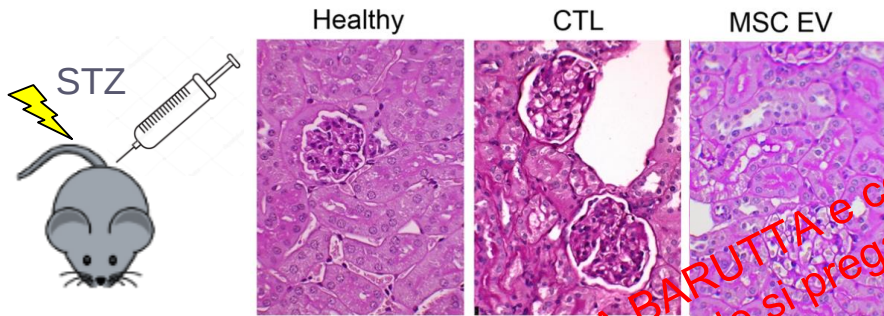
Xian Y et al. *Diabetes Res Clin Pract*. 2019;156:107755.

MSC: Paracrine Effects



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MSC-Derived Extracellular Vesicles (EVs)



OVERVIEW: Future experimental therapy in DN

Primary metabolic defect

Hyperglycemia

RAS blockade

High blood pressure identified as risk factor

Captopril³
T1DM

IDNT⁴
Irbesartan
T2DM

No new DKD-specific treatment in last 19 years

1980

1990

2000

2010

2019

β -blockers¹

Hydralazine²

RENAAL⁵

Losartan

T2DM

Pathogenic processes

Inflammation

Fibrosis

Renal cell injury

Progression of diabetic kidney diseases

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Conclusions

Phenotype

Old, obese, G2-4
(db/db/5/6 nephrectomy)

Animal Model

DM2
Transcriptional profile

Outcomes

Pre-specified
outcomes ACR and
eGFR

Secondary prevention

Established DN



Inclusion Criteria

Baseline BG, AER,
eGFR

On top of standard TXT

Anti-DM, RASi,
SGLT2i

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VI RINGRAZIO PER
L'ATTENZIONE