Oxidative stress and hypoxia as novel therapeutic targets in kidney disease

Masaomi Nangaku
President of the Asian Pacific Society of Nephrology
APSN 40th anniversary
I have the following relationships to disclose.

Potential Financial Conflicts of Interest

(1) Employment: No
(2) Stock ownership or options: No
(3) Patent royalties/licensing fees: No
(4) Honoraria and advisory fees: Kyowa-Hakko-Kirin, Astellas, Astra Zeneca, GSK, Daiichi-Sankyo, Tanabe-Mitsubishi, Chugai, Torii, JT
(5) Research funding: Kyowa-Hakko-Kirin, Daiichi-Sankyo, Astellas, Ono, Tanabe-Mitsubishi, JT, Chugai, Bayer, Torii, Takeda
Inflammation and oxidative stress are important in the pathogenesis of acute kidney injury.

**STAT3 in T cells contributes to ischemia-reperfusion injury through Th17 activation**

![Histological damage score comparison](image)

Lee JW et al. NDT e-Pub
sphingosine kinase 2 is essential for cell-survival pathways after ischemia-reperfusion injury

Effect of SphK on infiltrating leukocytes

Jo SK, Okusa MD et al. Kidney Int 2009
Neuro-immune interactions in inflammation and AKI: Vagus nerve stimulation protects the kidney against IRI

Inoue, Okusa et al. JCI 2016
Abe, Inoue et al. Nat Neurosci 2017

Inoue, Tanaka & Okusa et al. Front Immunol 2017
Inoue, Nangaku, Okusa et al. KI 2019
Whole kidney 3D-imaging reveals the progression of renal sympathetic denervation after IRI

Transparent kidney by tissue clearing with CUBIC

Hasegawa, Nangaku et al. Kidney Int 2019
Whole kidney 3D-imaging reveals the progression of renal sympathetic denervation after IRI

Hasegawa, Nangaku et al. Kidney Int 2019
Whole kidney 3D-imaging reveals renal sympathetic denervation after IRI

Day 4

Day 10

Day 28

Hasegawa, Nangaku et al. Kidney Int 2019
VAP-1 in pericytes enhances neutrophil infiltration into the IR-injured kidney by generating H$_2$O$_2$
The Nexus of Acute Kidney Injury, Chronic Kidney Disease, and World Kidney Day 2009

Mark D. Okusa,* Glenn M. Chertow,† and Didier Portilla,‡ for the Acute Kidney Injury Advisory Group of the American Society of Nephrology

[Graph showing the progression of GFR over time, with AKI: No CKD Progression and AKI: CKD Progression indicated.]
AKI-to-CKD transition mediated by hypoxic memory

AKI

Capillary rarefaction

Hypoxia

Epigenetic changes
DNA methylation, histone modification (e.g., H3K9me2 ↓ by KDM3A ↑, H3K27me3 ↓ by KDM6B ↑), chromosome conformational change, IncRNA (e.g., DARS-ASI ↑), miRNA

Fibrosis

Nangaku et al. Nephron 2017
Amelioration of AKI-to-CKD transition after IRI by Dznep

Dznep: inhibitor of EZH2

EZH2 (Enhancer of zeste homolog 2): histone methyltransferase of H3K27me

Mimura, Nangaku et al. Sci Rep 2018
Inhibition of kidney fibrosis by pan-HDAC inhibitor, SB939

Kang SW et al. Int Immunopharmacol 2017
Changes in CKD Disability Adjusted Life Years from 1990 to 2016: Global Burden of Disease Study

Diabetes

DALY
Disability Adjusted Life Year is a measure of overall disease burden, expressed as the cumulative number of years lost due to ill health, disability or early death

= YLD
Years Lived with Disability

+ YLL
Years of Life Lost

Xie et al. Kidney Int 2018
ALBUM study

VAP-1 inhibitor reduced albuminuria in DKD

de Zeeuw, Nangaku et al. Lancet D & E 2018
Metformin ameliorates oxidative stress of peritoneal mesothelial cells

Shin HS, Kang DH et al. Sci Rep 2017
DPP4 inhibitor attenuates kidney injury

rat remnant kidney model

Joo KW et al.
BMC Nephrol 2013
Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and CKD

Pollock et al. Lancet D & E 2019
Vlado Perkovic
Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death

Hazard Ratio 0.70 (95% CI, 0.59-0.82)

Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death

Hazard Ratio 0.70 (95% CI, 0.59-0.82)  
\( p = 0.00001 \)

ISN should publicize the relevant KI issue through all possible channels because this is a post-ISN congress issue and the importance of the clinical trials presented in Melbourne is huge for the renal community.

Pierre
Light of dawn in Melbourne: SONAR and CREDENCE


KEYWORDS: diabetic kidney disease; endothelin; sodium-glucose cotransporter 2 (SGLT2) inhibitor

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The International Society of Nephrology's (ISN) World Congress of Nephrology 2019 was held in Melbourne, Australia, from April 12 to 15. The congress was planned and organized by David Harris (ISN president), Peter Kerr (local organizing committee chair), Masaomi Nangaku (scientific program committee chair), and Vivek Jha and Marcello Tonelli (scientific program committee deputy chairs). This was the last biennial meeting; beginning in 2020, World Congress of...
SGLT2 inhibitor and kidney outcomes in Asian patients with type 2 diabetes: results from the EMPA-REG OUTCOME

Kadowaki, Nangaku et al. J Diabetes Invest *in press*
Multifactorial mechanisms of renoprotection by SGLT2 inhibition

Heerspink et al. Kidney Int 2018
Accumulation of the TCA cycle metabolites in diabetic kidney

citrate imaging mass spectrometry data and metabolomics data of the TCA cycle

Tanaka S, Tanaka T, Nangaku et al. Kidney Int 2018
Hirakawa, Tanaka, Nangaku. J Diabetes Investig 2017
Repression of the NRF2 pathway in premature aging of Hutchinson-Gilford progeria syndrome

Progerin sequesters NRF2 and thereby causes its subnuclear mislocalization, resulting in impaired NRF2 transcriptional activity and increased chronic oxidative stress.

Identification of a novel Nrf2 activator

cell-based, high-throughput screen using a Nrf2-dependent luciferase reporter

Bollong et al. Nature 2018
BEAM trial: Increase in eGFR by bardoxolone methyl

Pergola et al.  
BEACON trial

HR=1.8; 95% CI = (1.3, 2.6); p<0.001


kidney protection

eGFR (mL/min/1.73 m²)

heart failure

No. at risk (ITT Population)
BARD 1068 1045 1006 942 884 723 548 417 288 133 15
PBO 1097 1098 1070 994 907 762 591 436 315 135 20

Weeks Since Randomization

Estimated Proportion of Patients, free of HF Hospitalization/HF Death through SDT

mean observed

weeks

Placebo

Bardoxolone Methyl
post-hoc analyses of BEACON: improvement of obesity

the rate and magnitude of body weight loss were proportional to baseline BMI

Chertow et al.
J Diabetes Complications 2018
24-Hour urinary creatinine excretion over time and change from baseline

There was no reduction in 24-hour urinary creatinine excretion, suggesting that the loss in body weight was not due to muscle wasting.

<table>
<thead>
<tr>
<th>Urinary creatinine (mg/24 h)</th>
<th>Placebo</th>
<th>Bardoxolone methyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 65</td>
<td></td>
<td>N = 61</td>
</tr>
<tr>
<td>Baseline</td>
<td>1159 ± 471</td>
<td>1191 ± 339</td>
</tr>
<tr>
<td>Week 4</td>
<td>1155 ± 457</td>
<td>1134 ± 394</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>−4 ± 327</td>
<td>−57 ± 280</td>
</tr>
</tbody>
</table>

Data are mean values ± SD and only include patients with baseline and Week 4 urinary creatinine values.

Chertow et al. J Diabetes Complications 2018
The increase in eGFR was highly consistent among patients. Over 75% of patients had some increase from baseline levels in eGFR at week 48.
The phase II Study of BArdoxolone methyl in patients with chronic Kidney disease and type 2 diabetes; TSUBAKI study

Nangaku et al. manuscript in submission
Primary Endpoint: GFR (interim result)

- Change in GFR assessed by inulin clearance from baseline at week 16

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=23</th>
<th>BARD N=17</th>
<th>Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>48.13 ± 9.86</td>
<td>48.95 ± 9.62</td>
<td>—</td>
</tr>
<tr>
<td>Week 16</td>
<td>47.71 ±11.63</td>
<td>54.54 ±12.21</td>
<td>—</td>
</tr>
<tr>
<td>Difference</td>
<td>-0.69</td>
<td>5.95</td>
<td>6.64</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or LS mean (mL/min/1.73 m²). LS mean was adjusted by baseline eGFR and baseline ACR.

Nangaku et al. *manuscript in submission*
Multifactorial mechanisms of renoprotection by SGLT2 inhibition

Heerspink et al. Kidney Int 2018
Hypoxia as the final common pathway to End Stage Kidney Disease

Measurement of intracellular oxygenation by a novel phosphofluorescence probe

pseudocolored PLIM image

(Phosphorescence lifetime imaging microscopy)

U: upstream tubules
D: downstream tubules

Hirakawa, Nangaku et al. Kidney Int 2018
Reduced cortical oxygenation predicts a progressive decline in kidney function

112 patients with CKD (25% DM)
47 with hypertension without CKD
24 healthy control individuals

CKD with $R^*_2 < 90^{th}$ percentile
CKD with $R^*_2 \geq 90^{th}$ percentile

Pruijm et al. Kidney Int 2018
Reduced oxygenation but not fibrosis defined by functional MRI predicts the long-term progression of CKD

\[ n = 91 \text{ (DM 42\%)} \]

<table>
<thead>
<tr>
<th>B. Multivariate</th>
<th>Estimate</th>
<th>Lower</th>
<th>Upper</th>
<th>( t )-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>-0.018</td>
<td>-0.060</td>
<td>0.025</td>
<td>-0.840</td>
<td>0.405</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.080</td>
<td>-0.474</td>
<td>0.634</td>
<td>0.290</td>
<td>0.775</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-0.464</td>
<td>-1.028</td>
<td>0.100</td>
<td>-1.640</td>
<td>0.105</td>
</tr>
<tr>
<td>Mean blood pressure (per 10 mmHg)</td>
<td>-0.031</td>
<td>-0.087</td>
<td>0.025</td>
<td>-1.100</td>
<td>0.273</td>
</tr>
<tr>
<td>Treatment with ACE-I/ARB</td>
<td>-0.259</td>
<td>-0.832</td>
<td>0.315</td>
<td>-0.900</td>
<td>0.372</td>
</tr>
<tr>
<td>eGFR (per mL/min)</td>
<td>-0.027</td>
<td>-0.052</td>
<td>0.003</td>
<td>-2.200</td>
<td>0.031*</td>
</tr>
<tr>
<td>Urine protein:creatinine ratio</td>
<td>-1.084</td>
<td>-1.447</td>
<td>-0.720</td>
<td>-5.940</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Uric acid (per 10 μmol/L)</td>
<td>-0.493</td>
<td>-0.987</td>
<td>0.001</td>
<td>-1.990</td>
<td>0.051</td>
</tr>
<tr>
<td>T2* (per ms)</td>
<td>0.104</td>
<td>0.035</td>
<td>0.174</td>
<td>2.980</td>
<td>0.004*</td>
</tr>
<tr>
<td>ADC (per ( \times 10^{-5} \text{ mm}^2/s ))</td>
<td>-1.714</td>
<td>-6.111</td>
<td>2.683</td>
<td>-0.780</td>
<td>0.440</td>
</tr>
</tbody>
</table>

Sugiyama et al. NDT 2018
SGLT inhibition improved oxygen tension in the kidney cortex

SGLT2 inhibitor improved oxygen tension in the kidney cortex

Kamezaki et al. Sci Rep 2018
Mesenchymal stem cell-derived microparticles ameliorate peritubular capillary rarefaction

KMSC: kidney-derived mesenchymal stem cells
MP: microparticles

UOO model

Choi HY, Park HC et al. Stem Cell Res Ther 2015
Hirakawa, Tanaka, Nangaku. J Diabetes Investig 2017

**HIF**

- Normoxia: HIF-α degradation
- Hypoxia or PHD inhibition: HIF-α stabilization

**HIF-α**

- Proteasomal degradation
- Activation of HIF-downstream genes

**Nrf2**

- Unstressed condition: Nrf2 degradation
- Stressed condition or KEAP1 inhibition: Nrf2 stabilization

**Nrf2**

- Proteasomal degradation
- Activation of Nrf2-downstream genes

**Defense against hypoxia**

**Defense against oxidative stress**
Dapagliflozin activates HIF-1 in HK2 cells

Chang YK et al. PLoS ONE 2016
HIF activation improves AKI

Positive correlation between creatinine and tubular injury

HIF activation improves DKD

HIF activation improves anemia in CKD

daprodustat in Japanese HD patients

Akizawa, Nangaku et al.
Am J Nephrol 2017

enarodustat in Japanese non-HD patients

Akizawa, Nangaku et al.
Am J Nephrol 2019
Enarodustat, Conversion and Maintenance Therapy for Anemia in Hemodialysis Patients: A Randomized, Placebo-Controlled Phase 2b Trial Followed by Long-Term Trial

Tadao Akizawaa, Masaomi Nangaku, Takuhiro Yamaguchic, Masanobu Arai, Ryosuke Koretomo, Kazuo Maeda, Yuya Miyazawa, Hideki Hirakata
HIF activation improves anemia: HD patients

Akizawa, Nangaku et al. Nephron 2019
### Clinical trials of HIF activator (PH inhibitor)

<table>
<thead>
<tr>
<th></th>
<th>Non-dialysis CKD patients</th>
<th>Dialysis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roxadustat</td>
<td>Alps, Olympus, Dolomites</td>
<td>Pyrenees, Himalayas, Sierras, Andes, Rockies</td>
</tr>
<tr>
<td>Vadadustat</td>
<td>PRO2TECT-CORRECTION/CONVERSION</td>
<td>INNO2VATE-CORRECTION/CONVERSION</td>
</tr>
<tr>
<td>Daprodustat</td>
<td>ASCEND-ND, ASCEND-NHQ</td>
<td>ASCEND-ID, ASCEND-D, ASCEND-TD</td>
</tr>
<tr>
<td>Molidustat</td>
<td>DIALOGUE 1 and 2, MIYABI-ND</td>
<td>DIALOGUE 4, MIYABI-HD</td>
</tr>
<tr>
<td>Enarodustat</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hypoxia-Inducible Factor Stabilization as an Emerging Therapy for CKD Related Anemia

A Scientific Workshop Sponsored by the National Kidney Foundation

March 22-23, 2019
Philadelphia, PA USA

Chaired by Kai-Uwe Eckardt & Jeff Berns
TAKE HOME MESSAGE

OK I THINK I GOT IT

BUT JUST IN CASE EXPLAIN IT ALL AGAIN I WASN'T LISTENING
TAKE HOME MESSAGE

• Hypoxia and oxidative stress are important therapeutic targets in kidney disease.

• SGLT2 inhibitor improves hypoxia and oxidative stress along with amelioration of glomerular hyperfiltration.

• Nrf2 activation can be an optimal anti-oxidative therapy.

• HIF activator (PH inhibitor) will be available as a new therapy of anemia in CKD soon.
Hyojin Nam, Haneul Kim from Hanyang University
Christian Hugo
William Couser
Duk-Hee Kang
Program Committee of the 50th Anniversary of ASN

Ray Harris
David Harris