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SUPPLEMENTARY INFORMATION

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De novo NAD$^+$ biosynthetic impairment in acute kidney injury in humans

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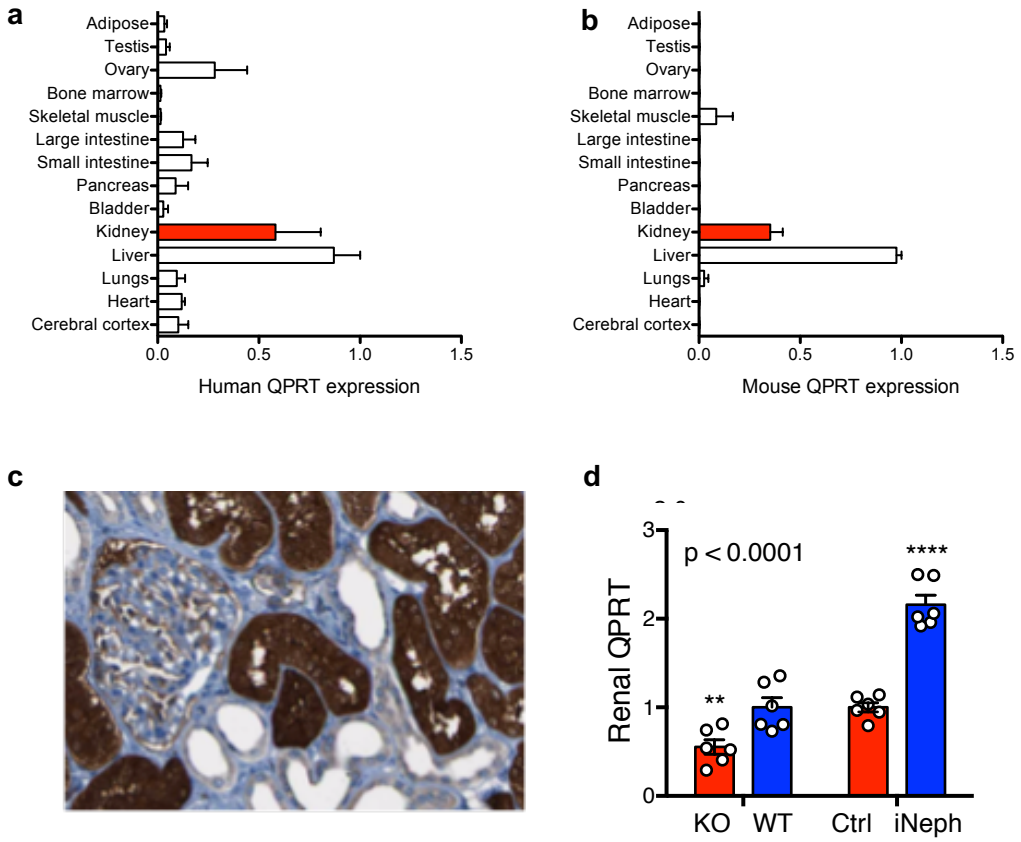
Supplemental Figure 1: QPRT expression among organs, within kidney, and in response to PGC1α. (**a,b**) Relative mRNA expression of QPRT by organ was abstracted from public repositories ncbi.nlm.nih.gov/unigene, biogps.org and gtexportal.org for mouse (**a**) and human (**b**). (**c**) Representative image from Human Protein Atlas showing renal QPRT expression localization to the proximal tubular epithelium (image credit: Human Protein Atlas Version 17, available at https://www.proteinatlas.org/ENSG00000103485-QPRT/tissue/kidney). (**d**) Renal QPRT expression in global PGC1α knockout mice and in inducible nephron-specific PGC1α transgenic mice (iNeph, Pax8rtTA x tetO-PGC1α published in [1]). N = 6 animals per group. Two-sided p-value in (d) by ANOVA, **** for Bonferroni-corrected pairwise comparison.



1. Tran, M.T., *et al.* PGC1alpha drives NAD biosynthesis linking oxidative metabolism to renal protection. *Nature* **531**, 528-532 (2016).

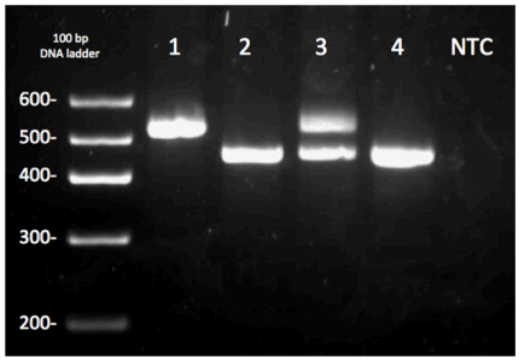
Supplemental Figure 2: Development of QPRT-deficient mouse. (**a**) QPRT deficient mice were generated using the CRISPR/Cas9 system with the below single guide RNA (sgRNA) sequences. (**b**) DNA agarose gel showing amplification of an approximately 500 bp region surrounding the sgRNA target site in several founder mice. Shown are a wild-type C57BL/6 control mouse (lane 1), mice homozygous for the QPRT gene deletion (lanes 2 and 4), mouse heterozygous for QPRT (lane 3), and a no-template control PCR reaction (NTC). Representative results of n = 20 animals per genotype.

a

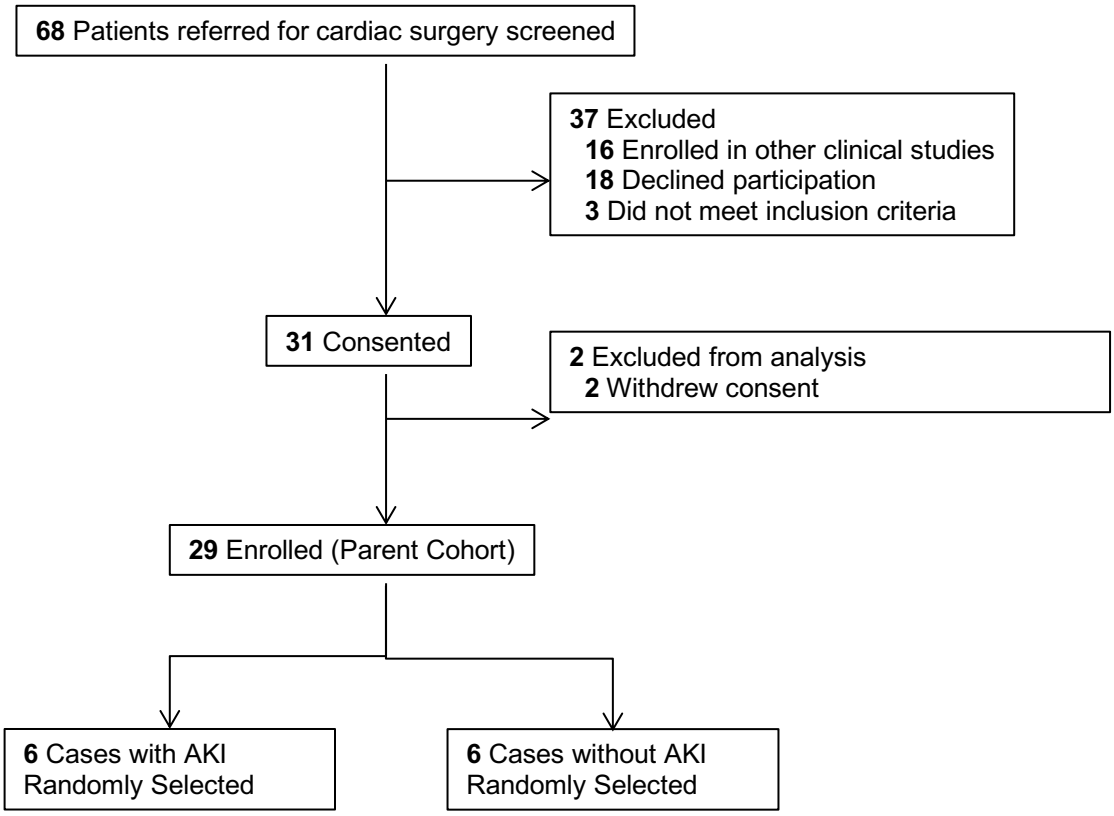
sgRNA pair for nickase

sgQPRT_1F 5'-GGGTGCCGACCCGGTAACCA-3'
sgQPRT_1R 5'-GGCCAAATCTCCTGGGGTTC-3'
sgQPRT_2F 5'-GGGTGCCGACCCGGTAACCA-3'
sgQPRT_2R 5'-GCTGTGGGCCAAATCTCCTG-3'

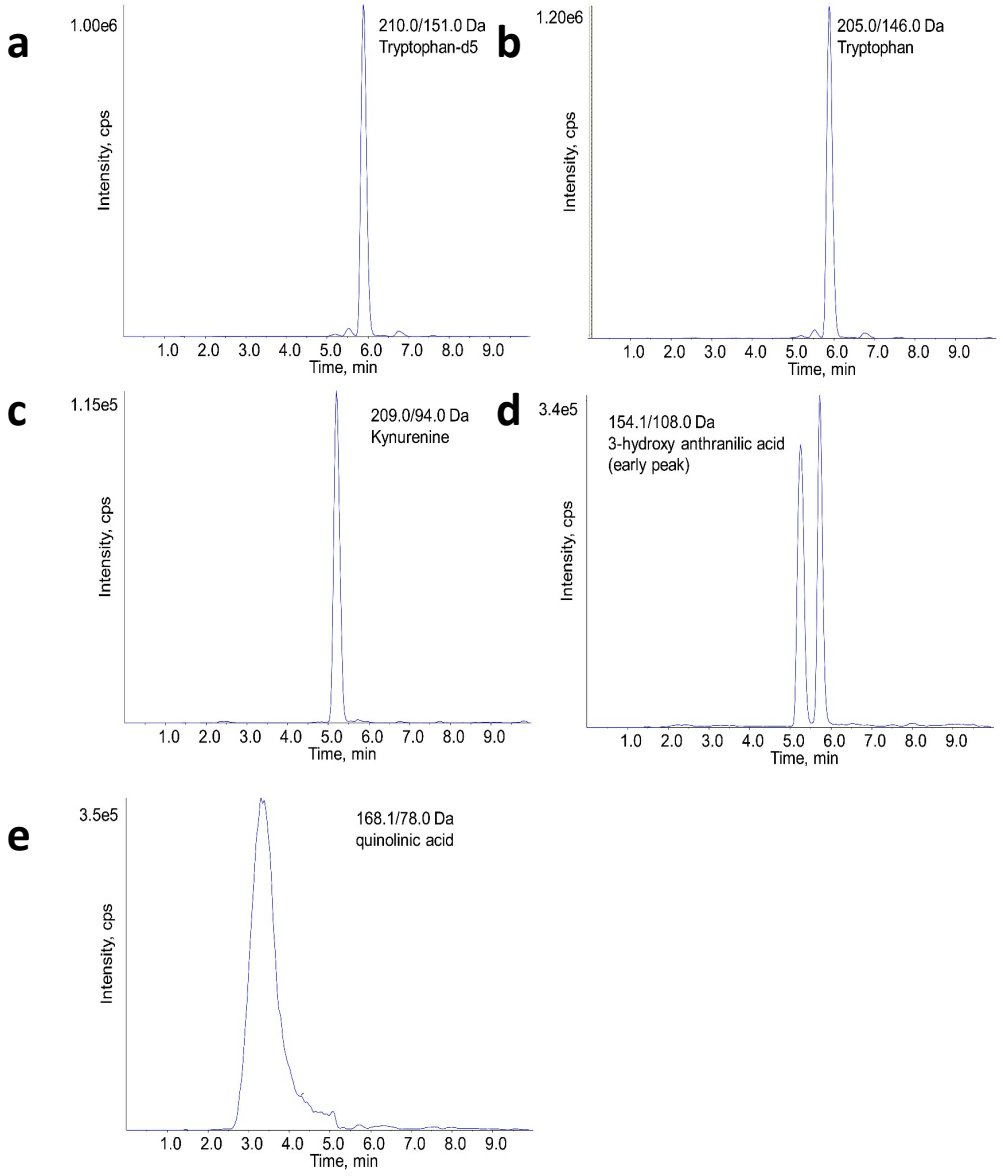
b



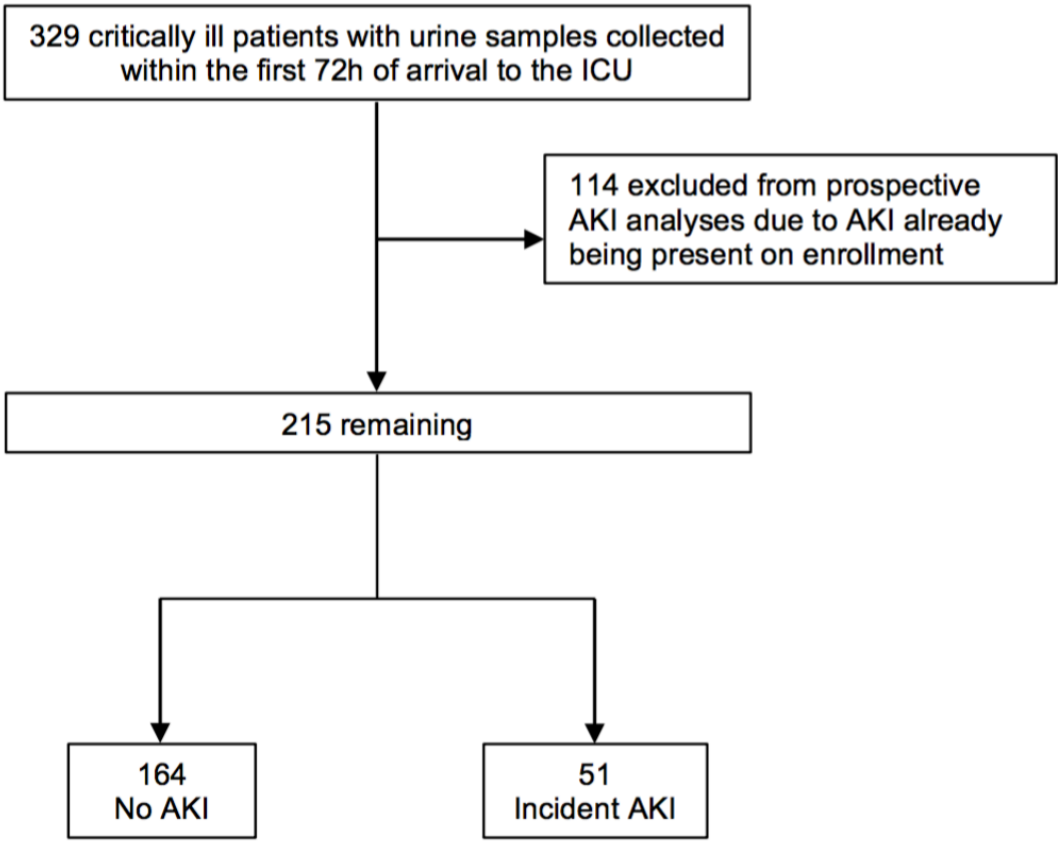
Supplemental Figure 3: Flow of participants through uQ:T discovery study



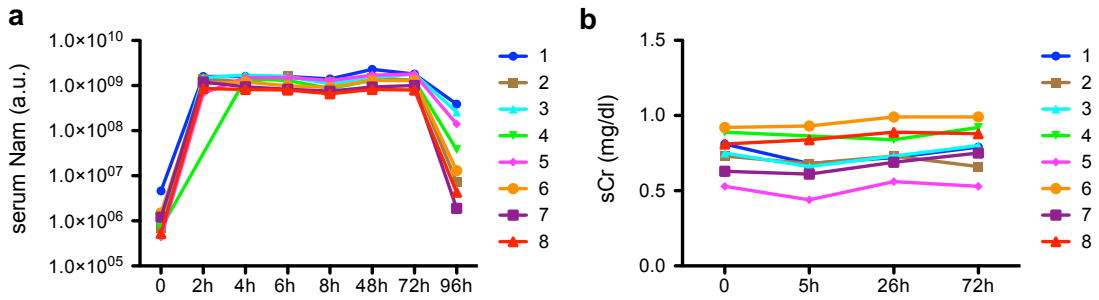
Supplemental Figure 4: Development of targeted metabolite assays. A protocol was developed to measure several of de novo NAD+ biosynthesis metabolites using liquid chromatography-tandem mass spectroscopy. Shown are chromatograms for the measurement of (a) deuterated tryptophan, (b) tryptophan, (c) kynurenine, (d) 3-hydroxyanthranilic acid and (e) quinolinic acid. Results representative of 5 independent replicates per analyte.



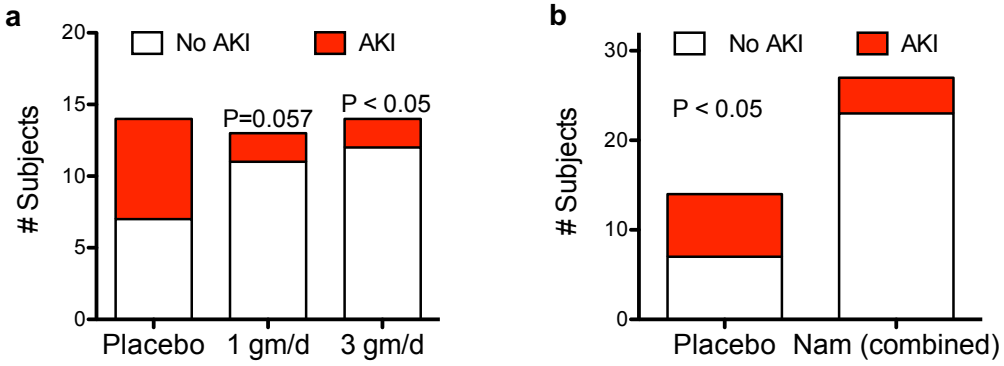
Supplemental Figure 5: Flow of participants through uQ:T ICU validation study



Supplemental Figure 6: Serum Nam and creatinine in healthy subject oral Nam PK study. (**a**) Nam was given to healthy volunteers (n = 8) at a dose of 3 grams by mouth per day for three consecutive days at times 0, 24, and 48 hrs. Blood samples were obtained at hours 0, 1, 2, 3, 5 hours on the first day and 2 hours after the oral Nam dose on days two and three. Additionally, a blood sample was collected 24 hours after the last Nam dose (96h time point). (**b**) Serum creatinine concentration over time per subject. Each subject represented as one line.



Supplemental Figure 7: AKI events in Phase 1 pilot study of oral Nam in cardiac surgery patients. Proportions of subjects developing AKI stage 1 or greater by (**a**) study arm (n = 14, 13, and 14 subjects respectively) and (**b**) with Nam treatment groups combined (n = 27 in combined Nam treatment group). AKI definition was adopted from KDIGO and applied in a recent Phase 3 trial for AKI among cardiac surgery patients.[1,2] Results were analyzed by chi-square test, in (**a**) comparing each treatment group to the placebo group. A total of 9 subjects developed AKI stage 1 (n = 1 in 1gm/d, n = 2 in 2 gm/d, and n = 6 in placebo), and 2 subjects developed AKI stage 2 (n = 1 in 1gm/dl and n = 1 in placebo). No AKI stage 3 event was observed in this study.



1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney international* **Suppl**, 1-138 (2012).
2. Hausenloy, D.J.*, et al.* Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. *The New England journal of medicine* **373**, 1408-1417 (2015).

Supplemental Table 1: List of metabolites measured in mouse urine

quin/trp
niacinamide
kynurenic acid
tryptophan
quinolinate
1-methylnicotinamide
1-methyladenosine
1-methylhistamine
2-deoxycytidine
3-OHanthranilic acid
acetylglycine
adenosine
ADMA
alanine
allantoin
α-glycerophosphocholine
aminoisobutyric acid
anserine
arginine
asparagine
aspartate
β-alanine
betaine
C10 carnitine
C10:2 carnitine
C12 carnitine
C12:1 carnitine
C16 carnitine
C18 carnitine
C18:1 carnitine
C2 carnitine
C3 carnitine
C3-DC carnitine
C3-DC-CH3 carnitine
C4 carnitine
C4-OH carnitine
C5 carnitine
C5:1 carnitine
C5-DC carnitine
C6 carnitine
C8 carnitine
C9 carnitine
cAMP
carnitine
carnosine
choline
cinnamoylglycine
citrulline
creatine
dimethylglycine
DMGV
GABA
glutamate
glutamine
glycine
Guanosine
histamine
histidine
hydroxyproline
isoleucine
leucine
lysine
methionine
methionine sulfoxide
methylthioadenosine
N1-Acetylspermidine
N-carbamoyl-β-alanine
NMMA
ornithine
phenylalanine
phosphocholine
proline
putrescine
pyroglutamic acid
s-adenosylmethionine
sarcosine
SDMA
serine
serotonin
taurine
thiamine
threonine
thymidine
trimethylamine-N-oxide
tyrosine
valine
xanthosine
1-methylurate
2-aminoadipate
2-aminobutyrate
2-aminoheptanoate
2-aminooctanoate
2-OH-3-methylbutyrate
2-OH-3-Me-pentanoate
2-hydroxyglutarate
3-3-OH-phenylpropionate
3-hydroxymethylglutarate
3-methyladipate/pimelate
3-phosphoglycerate
4-hydroxybenzaldehyde
4-hydroxyphenylpyruvate
4-pyridoxate
aconitate
adipate
adonitol
α-glycerophosphate
α-keto-β-Me-valerate
α-ketoglutarate
α-ketoisocaproate
α-ketoisovalerate
arabitol
azelate
β-hydroxybutyrate
cAMP
caprylate
cinnamoylglycine
cystathionine
cystine
erythronate
erythrose-4-phosphate
fructose/glucose/galactose
fumarate/maleate
gentisate
gluconolactone
glucuronate
glycerate
guanidinosuccinate
guanine
guanosine
hexose diphosphate
hexose monophosphate
hippurate
homogentisate
homovanillate
hydroxyisobutyrate
hydroxyisocaproate
hydroxyisovalerate
hypoxanthine
imidazolelactate
indolelactate
indoxylsulfate
inosine
inositol
lactate
lactose
malate
malonate
methylglutarate
methylmalonate
methylsuccinate
Me-2-Pyr-5-carboxamide
N2-dimethylguanosine
N4-acetylcytidine
N6-acetyllysine
N-acetylcarnosine
N-acetylglutamate
N-acetylglutamine
N-acetylserine
orotate
oxalate
oxypurinol
pantothenate
PEP
phenylacetylglutamine
phenylalanine
phenyllactate
p-hydroxybenzoate
pseudouridine
riboflavin
ribonate lactone
salicylate
sebacate
S-Me-L-Cys-S-oxide
sorbitol
suberate
succinate
sucrose
tartarate
taurine
threitol
threonate
thymine
trehalose
trigonelline
uracil
urate
uridine
valerate
xanthine
xanthurenate
eicosapentaenoate
gamma-linolenate
myristate
docosahexaenoate
palmitoleate
arachidonate
docosapentaenoate
linoleate
eicosatrienoate
palmitate
oleate
eicosadienoate
stearate
eicosenoate

Supplemental Table 2: List of differentially regulated urinary metabolites in AKI vs. control urines. FC = fold-change relative to control and negative value indicates greater abundance in controls. Two-sided P-value cutoff < 0.05, i.e. $-\log_{10}P > 1.301$. N = 4 control animals compared to N = 4 AKI animals by unpaired t-test without adjustment for multiple comparisons.

Metabolite (AKI/ctrl)	**$\log_2$FC**	**$-\log_{10}$P**
homogentisate	0.481	1.366
alanine	0.597	1.369
N6-acetyllysine	1.704	1.378
arachidonate	2.710	1.386
ribonate lactone	-0.493	1.438
serine	1.301	1.506
C3-DC carnitine	-2.060	1.508
niacinamide	-1.835	1.525
asparagine	0.560	1.533
1-methylhistamine	-0.740	1.577
methionine	2.066	1.581
C10 carnitine	-1.535	1.597
threitol	-0.258	1.600
cystathionine	1.526	1.604
C5:1 carnitine	2.657	1.646
2-aminobutyrate	-0.396	1.659
3-hydroxymethylglutarate	0.928	1.663
docosapentaenoate	4.017	1.665
N-acetylserine	0.604	1.666
alpha-glycerophosphocholine	-1.632	1.675
gentisate	0.891	1.749
riboflavin	1.193	1.773
stearate	-0.415	1.781
Guanosine	-0.602	1.802
isoleucine	-0.447	1.838
1-methylurate	1.290	1.846
aspartate	0.739	1.867
ornithine	0.664	1.896
2-aminoadipate	2.807	1.930
guanine	-1.826	2.050
1-methylnicotinamide	-1.648	2.099
proline	0.675	2.126
DMGV	-0.488	2.175
2-deoxycytidine	-0.589	2.181
eicosapentaenoate	5.040	2.357

homovanillate	1.637	2.466
eicosenoate	3.857	2.583
3-3-hydroxyphenylpropionate	-2.061	2.610
quinolinate	1.510	2.613
N-acetylglutamate	1.110	2.615
suberate	0.512	2.633
s-adenosylmethionine	-0.943	2.639
gamma-linolenate	4.216	2.726
carnitine	1.456	2.734
lactose	1.738	2.805
palmitoleate	1.577	2.828
N1-methyl-2-pyridone-5-carboxamide	-1.206	2.851
putrescine	-1.736	2.860
creatine	2.337	2.894
trehalose	1.774	2.923
sucrose	1.835	2.924
linoleate	3.696	3.099
eicosadienoate	3.625	3.105
tartarate	1.876	3.218
glycine	0.896	3.322
thymine	0.435	3.530
oleate	2.293	4.077
glycerate	2.191	4.084
trigonelline	0.621	4.332

Supplemental Table 3: List of differentially regulated urinary metabolites in QPRT+/- vs. WT. FC = fold-change relative to control and negative value indicates greater abundance in WT controls. Two-sided P-value cutoff < 0.05, i.e. $-\log_{10}P > 1.301$. N = 4 control animals compared to N = 5 QPRT+/- animals by unpaired t-test without adjustment for multiple comparisons.

Metabolite (QPRT/ctrl)	$\log_2$FC	$-\log_{10}$P
trigonelline	0.41123635	1.31687632
carnitine	0.97622063	1.33489657
C18 carnitine	-3.8092946	1.35984285
citrulline	0.24003088	1.3607666
taurine	0.37083223	1.36541883
C9 carnitine	2.41173281	1.36948602
imidazolelactate	-0.9415726	1.38737074
1-methylurate	1.77693613	1.42439117
2-deoxycytidine	-0.5082396	1.43238908
inosine	-1.402734	1.44309113
creatine	1.40305619	1.44663098
myristate	-0.4268277	1.47332749
gentisate	1.69377129	1.56335119
phenyllactate	-1.69795	1.57131185
hypoxanthine	-1.7425742	1.58501385
palmitoleate	-0.4572154	1.59000813
thymine	0.42635847	1.64935929
niacinamide	-1.0563262	1.66392143
cAMP	0.47032275	1.67436438
adenosine	1.68992298	1.70988979
3-3-hydroxyphenylpropionate	-1.4710888	1.74728363
C12:1 carnitine	2.03649048	1.74983721
s-adenosylmethionine	-0.5817972	1.75147165
quinolinate	4.53220429	1.75891584
riboflavin	1.3155065	1.77326482
thiamine	-1.622155	1.79083155
cAMP	0.85042716	1.80576944
pseudouridine	0.43491855	1.83655745
orotate	-1.7652152	1.86654129
N6-acetyllysine	0.66133053	1.90470343
C3-DC-CH3 carnitine	1.32025616	1.91009849
NMMA	-1.8765729	1.9145403
N1-methyl-2-pyridone-5-carboxamide	-0.747363	1.96524495

carnosine	-2.1684814	1.9667745
histidine	-0.4928095	1.97976988
suberate	0.71868708	2.02579495
arginine	-1.0570692	2.18640931
guanidinosuccinate	2.47386118	2.25453907
2-hydroxy-3-methylpentanoate	-3.0439995	2.30901286
hydroxyisocaproate	-3.0439995	2.30901286
erythrose-4-phosphate	1.35081715	2.33303538
sebacate	-1.7518986	2.33649168
dimethylglycine	-1.5889973	2.37790926
caprylate	-5.2671272	2.46088056
homogentisate	0.70900188	2.58503724
guanosine	0.8056601	2.68739318
N4-acetylcytidine	0.8747538	2.83156606
hydroxyproline	-1.3780804	2.87198486
azelate	-1.8969679	3.072548
indoxylsulfate	1.4581736	3.11750619
proline	-1.2727727	3.13043424
cinnamoylglycine	-1.1291536	3.17194263
stearate	-0.7117214	3.39703642
isoleucine	-1.5677102	3.51535867
guanine	-2.1618422	3.70926005
putrescine	-1.9057815	3.9694562
2-aminobutyrate	-0.8117531	4.01537497
sarcosine	-2.3747759	4.29064072

Supplemental Table 4: Baseline characteristics for uQ:T discovery parent cohort. *Definition of abbreviations*: Baseline creatinine was defined as the most recent creatinine value prior to cardiac surgery.

Baseline Characteristics	**Parent Cohort (n=29)**
Age, y, mean (SD)	66.7±12
BMI, kg/m^2, mean (SD)	29.2±4.7
Female sex, n (%)	10 (34)
African-American, n (%)	1 (3)
Baseline creatinine, mg/dL mean (SD)	1.1±0.4
Tobacco use, n (%)	5 (17)
Heart failure, n (%)	8 28)
EF <35%, n (%)	4 (14)
Hypertension, n (%)	25 (86)
Diabetes, n (%)	14 (48)
Cardiopulmonary bypass time, min., mean (SD)	86.9±22.3
Aortic cross-clamp time, min., mean (SD)	68.3±18.5
Valve replacement, n (%)	7 (24)
Intra-aortic balloon pump, n (%)	3 (10)

Supplemental Table 5: Characteristics of cases vs. controls for uQ:T discovery study.

Baseline Characteristics		
	No AKI (n=6)	**AKI (n=6)**
Age, y, mean (SD)	69±9	70±6
BMI, kg/m^2, mean (SD)	29.3±4.7	28.3±4.4
Female sex, n (%)	1 (17)	4 (67)
African-American, n (%)	0	1 (17)
Baseline creatinine, mg/dL mean (SD)	1.1±0.2	1.3±0.4
Tobacco use, n (%)	1 (17)	1 (17)
Heart failure, n (%)	2 (33)	3 (50)
EF <35%, n (%)	1 (17)	1 (17)
Hypertension, n (%)	6 (100)	6 (100)
Diabetes, n (%)	3 (50)	4 (67)
Cardiopulmonary bypass time, min., mean (SD)	94±22	77±15
Aortic cross-clamp time, min., mean (SD)	69±14	57±16
Valve replacement, n (%)	1 (17)	1 (17)
Intra-aortic balloon pump, n (%)	0	0

Characteristic	All (n=329)	AKI on Enrollment (n=114)	No AKI on Enrollment (n=215)				
			uQ:T quartiles				
			Q1 (n=53)	Q2 (n=54)	Q3 (n=54)	Q4 (n=54)	*P*-value
Urinary Quin/Trp ratio							
Range (min, max)	0.03, 54.9	0.05, 23.79	0.03, 0.19	0.19, 0.49	0.51, 1.16	1.18, 54.91	
Median (IQR)	0.67 (0.26–1.72)	1.11 (0.47–2.57)	0.11 (0.07–0.14)	0.29 (0.24–0.40)	0.73 (0.60–0.88)	2.17 (1.56 – 5.13)	<0.001
Demographic							
Age, yr, median (IQR)	62 (54–70)	64 (55–73)	59 (50–65)	61 (52–69)	63 (54–73)	62 (55–67)	0.32
Male gender, n (%)	185 (56)	66 (58)	37 (70)	30 (56)	32 (59)	20 (37)	0.007
White race, n (%)	288 (88)	99 (87)	46 (87)	53 (98)	45 (83)	45 (83)	0.06
Baseline renal function							
SCr (mg/dl), median (IQR)*	0.8 (0.6–1.0)	0.9 (0.7–1.1)	0.7 (0.5–0.9)	0.7 (0.5–0.9)	0.8 (0.6–0.9)	0.8 (0.7–0.9)	0.09
eGFR (ml/min per 1.73m^2), median (IQR)†	93 (75–105)	83 (66–95)	102 (93–114)	100 (80–112)	95 (84–105)	87 (75–103)	0.01
Comorbidities, n (%)							
Hypertension	178 (54)	72 (63)	25 (47)	26 (48)	30 (56)	25 (46)	0.76
Diabetes mellitus	79 (24)	35 (31)	12 (23)	12 (23)	12 (23)	8 (15)	0.70
Congestive heart failure	39 (12)	21 (18)	4 (8)	4 (7)	3 (6)	7 (13)	0.54
Active malignancy	126 (38)	50 (44)	22 (42)	19 (35)	13 (24)	22 (41)	0.21
Surgical ICU, n (%)	118 (36)	24 (21)	26 (49)	32 (59)	19 (35)	17 (31)	0.01
Severity of illness							
APACHE II score, median (IQR)§	20 (14–26)	25 (20–31)	17 (13–22)	16 (11–22)	17 (14–21)	20 (14–24)	0.13
Urgent surgery, n (%)	68 (21)	21 (18)	16 (30)	13 (24)	7 (13)	11 (20)	0.18
Mechanical ventilation, n (%)	255 (78)	82 (72)	40 (75)	42 (78)	44 (81)	47 (87)	0.46

Supplemental Table 6: Baseline characteristics for uQ:T ICU validation cohort. *Definition of abbreviations*: AKI = acute kidney injury; APACHE II = Acute Physiology and Chronic Health Evaluation II; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; IQR = interquartile range; SCr = serum creatinine; uQ:T = urinary quinolinate/tryptophan ratio. *Baseline SCr was defined as the lowest value within 365 days prior to hospitalization. If no SCr values were available prior to hospitalization, the lowest SCr during hospitalization (excluding values obtained during renal replacement therapy) was used as the baseline. †eGFR was determined using the CKD-EPI equation. §APACHE II = ICU severity of illness scoring system ranging from 0 to 71, with higher scores indicating more severe disease. Two-sided P-values were calculated using Kruskal-Wallis and chi-squared tests for continuous and categorical variables, respectively.

End Points	#Events*	Model 1		Model 2		Model 3	
		Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value
Primary End Point							
Incident AKI	51	2.47 (1.71–3.58)	<0.001	2.52 (1.66–3.82)	<0.001	2.43 (1.57–3.74)	<0.001
Secondary End Points							
AKI/Death	78	2.49 (1.76–3.51)	<0.001	2.59 (1.76–3.81)	<0.001	2.41 (1.62–3.59)	<0.001
Severe AKI[†]	27	2.01 (1.33–3.02)	<0.001	1.95 (1.25–3.03)	0.003	2.02 (1.24–3.29)	0.005
RRT/Death	52	1.83 (1.32–2.55)	<0.001	1.94 (1.35–2.79)	<0.001	1.77 (1.20–2.61)	0.004
Hospital Mortality	86	1.74 (1.34–2.26)	<0.001	1.84 (1.39–2.45)	<0.001	1.63 (1.20–2.21)	0.002
1-year Mortality	153	1.30 (1.04–1.62)	0.02	1.35 (1.06–1.73)	0.014	1.20 (0.92–1.55)	0.17

Supplemental Table 7: uQ:T (urinary quinolinate/tryptophan) ratio and incident AKI and other adverse outcomes in critically ill patients. Odds ratios are shown per 1 unit standard deviation of log-transformed values of uQ:T. Model 1 is unadjusted. Model 2 is adjusted for demographics and comorbidities (age, gender, race, baseline eGFR, hypertension, and diabetes mellitus). Model 3 is further adjusted for severity of illness (ICU type, mechanical ventilation, and APACHE II score). *Analyses that include AKI or RRT as an end point are restricted to patients who did not have AKI at the time of sample collection (n = 215). All other analyses include the entire cohort (n = 329). [†]Severe AKI was defined as doubling of serum creatinine or need for RRT. Two-sided p-values were calculated by multivariable logistic regression.

Definition of abbreviations: AKI = acute kidney injury, defined as an increase in serum creatinine ≥ 0.3 mg/dl within 48 hours, ≥ 50% within 7 days, or need for renal replacement therapy, consistent with the criteria established by the Kidney Disease Improving Global Outcomes Work Group (KDIGO).[1] AKI/death = composite endpoint of AKI occurring within 7 days or in-hospital mortality; APACHE II = Acute Physiology and Chronic Health Evaluation II; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; IQR = interquartile range.

Reference

1. Kidney Disease;: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl 2***:** 1-138, 2012.

Supplemental Table 8: Baseline characteristics of healthy subject oral Nam PK study

Baseline Characteristics	n=8
Female gender, n (%)	6 (75)
Age, mean ± SD, y	34±12
Race/Ethnicity	
Caucasian, n (%)	5 (63)
Asian, n (%)	2 (25)
Hispanic, n (%)	2 (25)
BMI, mean ± SD, y	28.1±6.5
Smoking status	
Active, n (%)	0
Never, n (%)	7 (88)
Previous, n (%)	1 (13)
Chronic Illness	
Diabetes, n (%)	0
Hypertension, n (%)	0
Liver Disease, n (%)	0
Chronic Kidney Disease, n (%)	0
Chronic Migraines, n (%)	0
Cancer, n (%)	0
Side effects from Nam Ingestion	
Mild Headache, n (%)	2 (25)
Mild Nausea, n (%)	1 (13)

Supplemental Table 9: Cleveland Clinic Foundation Cardiac Surgery Risk Score. Data source for each criterion as indicated in middle column. Point basis for tabulating summary score shown in right column.[1]

Risk factor	Data source	Points
Female gender	Electronic medical record: Self-identified	1
Congestive heart failure	Electronic medical record: Anesthesia peri-operative assessment, cardiac surgery clinic notes, inpatient charts.	1
Left ventricular ejection fraction <35%	Electronic medical record: Echocardiogram	1
Preoperative use of Intra-aortic balloon pump	OR records, anesthesia records, critical care records	2
Chronic obstructive pulmonary disease	Electronic medical records, provider notes	1
Insulin requiring diabetes	Electronic medical records, provider notes, medication list	1
Previous cardiac surgery	Electronic medical records: office notes, admission notes	1
Emergency surgery	Provider notes, anesthesia records and operative report	2
Valve surgery	operative report	1
CABG + valve surgery	operative report	2
Other cardiac surgeries	operative report	2
Preoperative creatinine 1.2 to <2.1 mg/dl	Electronic medical records	2
Preoperative creatinine >2.1 mg/dl	Electronic medical records	5

1. Thakar, C.V., Arrigain, S., Worley, S., Yared, J.P. & Paganini, E.P. A clinical score to predict acute renal failure after cardiac surgery. *Journal of the American Society of Nephrology : JASN* **16**, 162-168 (2005).

Supplemental Table 10: Schedule of assessment for Phase 1 pilot study of oral Nam in cardiac surgery patients.

Study Period:	Screening Period	Treatment Period			Follow-up Period		
	Up to 8 weeks	Day -1	Day 0	Day1	Day 2	Day 3	Day 30 +/-7 days
Signed informed consent	X						
Inclusion and exclusion criteria verification	X						
Demographic characteristics (date of birth, height, weight, sex)	X						
Medical history	X						X
Concurrent medication and vitamin supplementation	X	X	X	X	X	X	
Vital signs and hemodynamics (MAP, HR, CVP)		X	X	X	X	X	
Respiratory parameter (pH, PaO2, PaCO2, SaO2, FiO2; ventilation mode, respiratory rate, respiratory minute volume, PEEP)			X	X	X	X	
Intraoperative and postoperative vasopressor use			X	X	X	X	
24-hour fluid balance			X	X	X	X	
Safety laboratory test	x		X	X	X	X	
Blood and urine sampling for determination of biomarkers	X		X	X	X	X	
Current medications and vitamins	X	X	X	X	X	X	
SOFA-Score			X	X	X	X	
APACHE II			X	X	X	X	
Dispense study drug		X	X	X			
Mortality							X
Length of stay (ICU, Hospital)							X
Adverse event recording	X	X	X	X	X	X	X

Supplemental Table 11: Phase 1 pilot study of oral Nam in cardiac surgery patients peri-operative AKI definition. AKI was staged over the first three post-operative days according to the below definitions, which are adopted from KDIGO and were applied in a recent Phase 3 trial for AKI among cardiac surgery patients.[1,2] Baseline creatinine was defined as the closest serum creatinine obtained prior to surgery. All subjects had stable renal function in the 7 days prior to surgery.

AKI Stage	Creatinine criteria
1	A rise of ≥ 0.3 mg/dl or 150-200% of baseline
2	A rise of 200-300% of baseline
3	An increase of >300%; or increase in serum creatinine to ≥4.0 mg/dl or Initiation of renal replacement therapy

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney international* **Suppl**, 1-138 (2012).
2. Hausenloy, D.J.*, et al.* Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. *The New England journal of medicine* **373**, 1408-1417 (2015).

Supplemental Table 12: Primer and single guide RNA (sgRNA) sequences

sgRNAs	**5' → 3'**
sgQPRT_1F	GGGTGCCGACCCGGTAACCA
sgQPRT_1R	GGCCAAATCTCCTGGGGTTC
sgQPRT_2F	GGGTGCCGACCCGGTAACCA
sgQPRT_2R	GCTGTGGGCCAAATCTCCTG
CRISPR genotyping primers	
CRISPR-Qprt_IN	ACAGCACAGCCTGCGA
CRISPR-Qprt_OUT	GAGCCCATACTTCTCCACCA
Real-time PCR primers	
Actin_fwd	TGACAGGATGCAGAAGGAGA
Actin_rev	GCTGGAAGGTGGACAGTGAG
Qprt-fwd	CCGGGCCTCAATTTTGCATC
Qprt-rev	GGTGTTAAGAGCCACCCGTT