Tenapanor inhibits phosphorous absorption and protects against vascular calcification in nephrectomized rats

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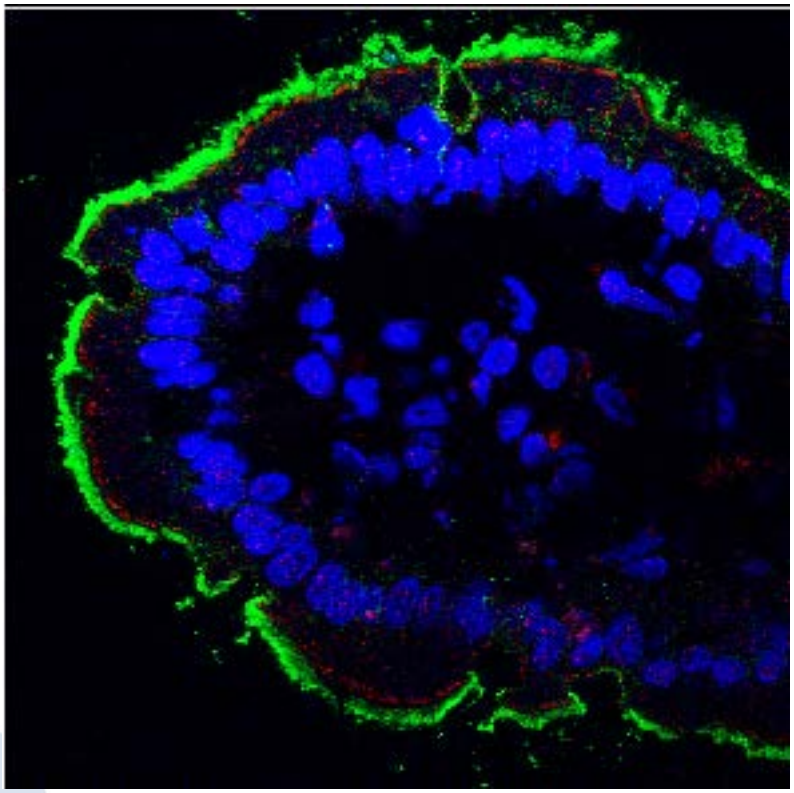
Na^+/H^+ exchanger, isoform 3: SLC9A3 or NHE3

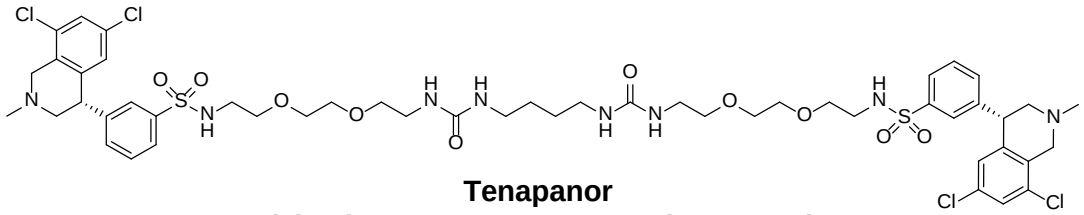


Confocal microscopy – rat jejunum
NHE3 DAPI

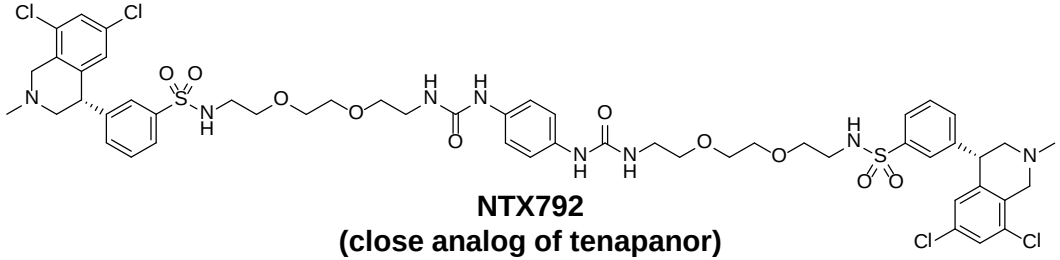
- Apically expressed on luminal surface of the gut
- NHE3 knockout phenotype: role in sodium-fluid homeostasis in gut and kidney
- Major absorptive Na^+/H^+ exchanger in the gut (there are other paths for sodium: NHE2, NHE8, ENaC)

Tenapanor

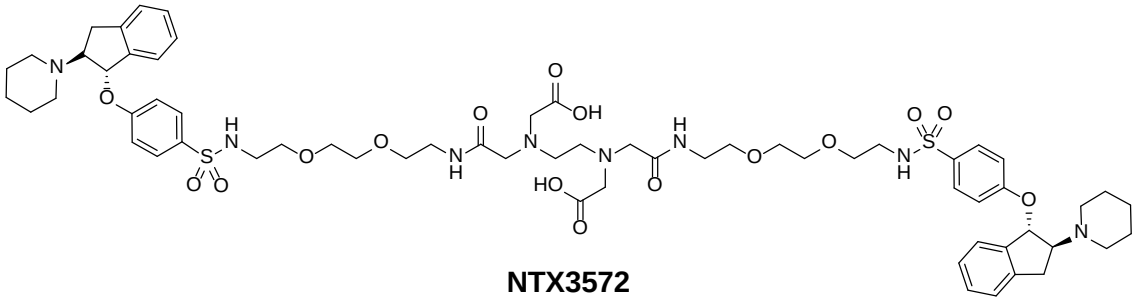
- Minimally systemic inhibitor of NHE3
- Oral agent that reduces sodium uptake in the intestine



Tenapanor
(also known as RDX5791 and AZD1722)



NTX792
(close analog of tenapanor)



NTX3572
(tool compound with reduced potency & persistence)

Potency and specificity of tenapanor

Cell-based assays of selected intestinal membrane proteins

Target	IC_{50}
Human NHE3	5 ± 4 nM (n>50)
Rat NHE3	10 ± 7 nM (n>50)
Human NHE1	> 10 μM
Human NHE2	> 10 μM
Human NaPi2b	> 10 μM
Human Pit1	> 10 μM

Summary: Observations with tenapanor

Minimally systemic

- Plasma drug levels normally absent, rarely detected
- Rodent radiolabeled ADME study confirmed minimal systemic exposure

Reduces sodium absorption

- Reduces urinary sodium excretion
- Increases stool sodium in humans

Active in rodent disease models

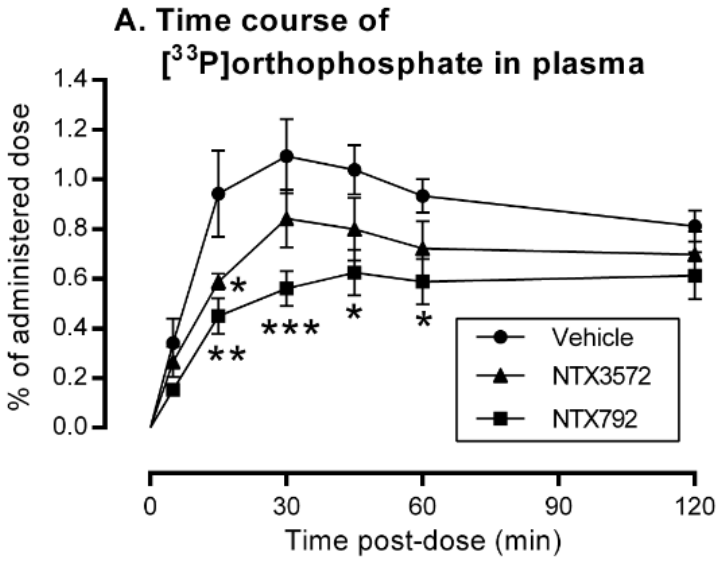
- Sodium-driven model of fluid overload, high BP, CV harm
- Worked well in combination with ACEi, improving PWV

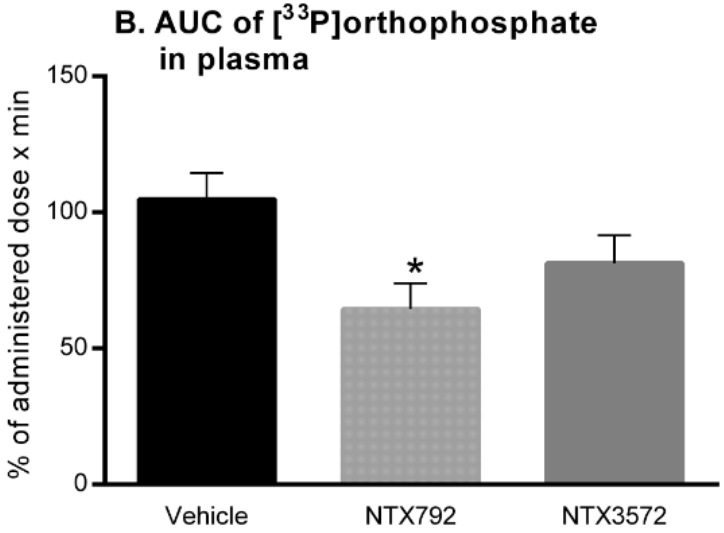
Inhibits sodium uptake in humans

- Increases stool Na^+ by 20-50 mEq/day (up to ~3 g of salt)
- Effects may be modulated via dose and dose regimens (qd, bid)

*Spencer et al. Sci Transl Med. 2014 Mar 12;**6**(227):227 (2014)*

A non-systemic NHE3 inhibitor decreases acute phosphorus (P) absorption in rats

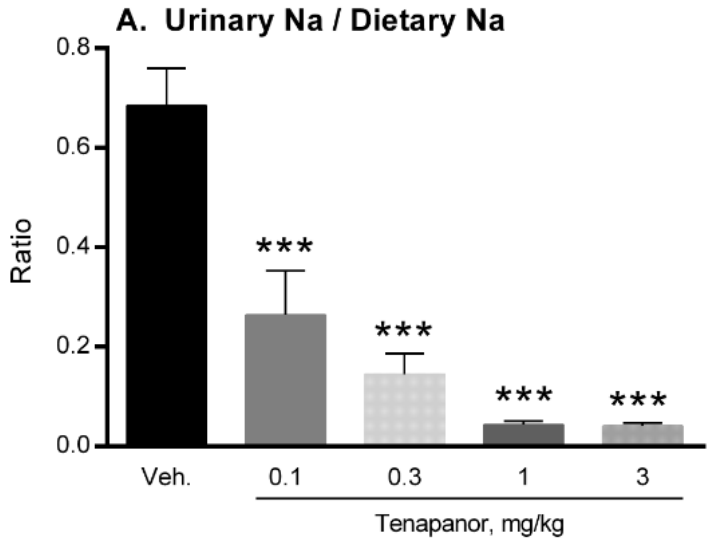


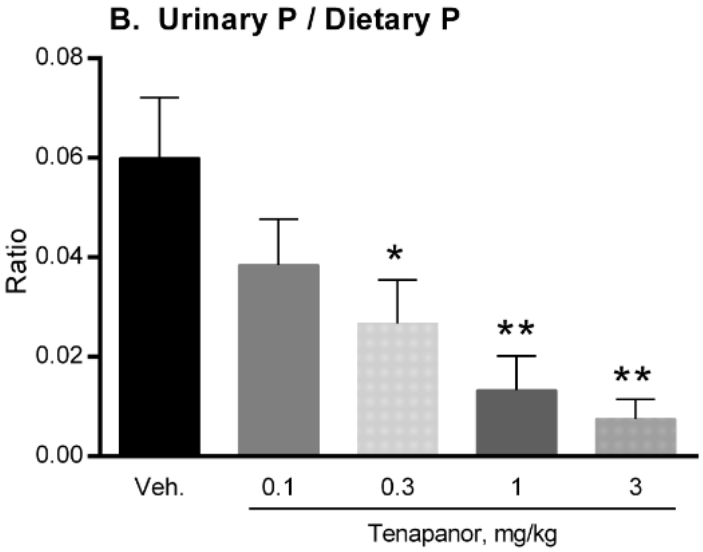


- Oral co-administration of NTX792, NTX3572, or vehicle at 10 mg/kg to rats (*n*=4-5) along with a phosphate meal containing [^{33}P]orthophosphate
- NTX3572 is a minimally-systemic tool compound with reduced potency & persistence
- Data are represented by mean ± SEM with statistical significance from mean comparison with vehicle group indicated by *, $p \leq 0.05$; **, $p \leq 0.01$; and ***, $p \leq 0.001$

Labonte et al. JASN ***26*** *(2015)*

A non-systemic NHE3 inhibitor decreases urinary Na and P in normal kidney function rats

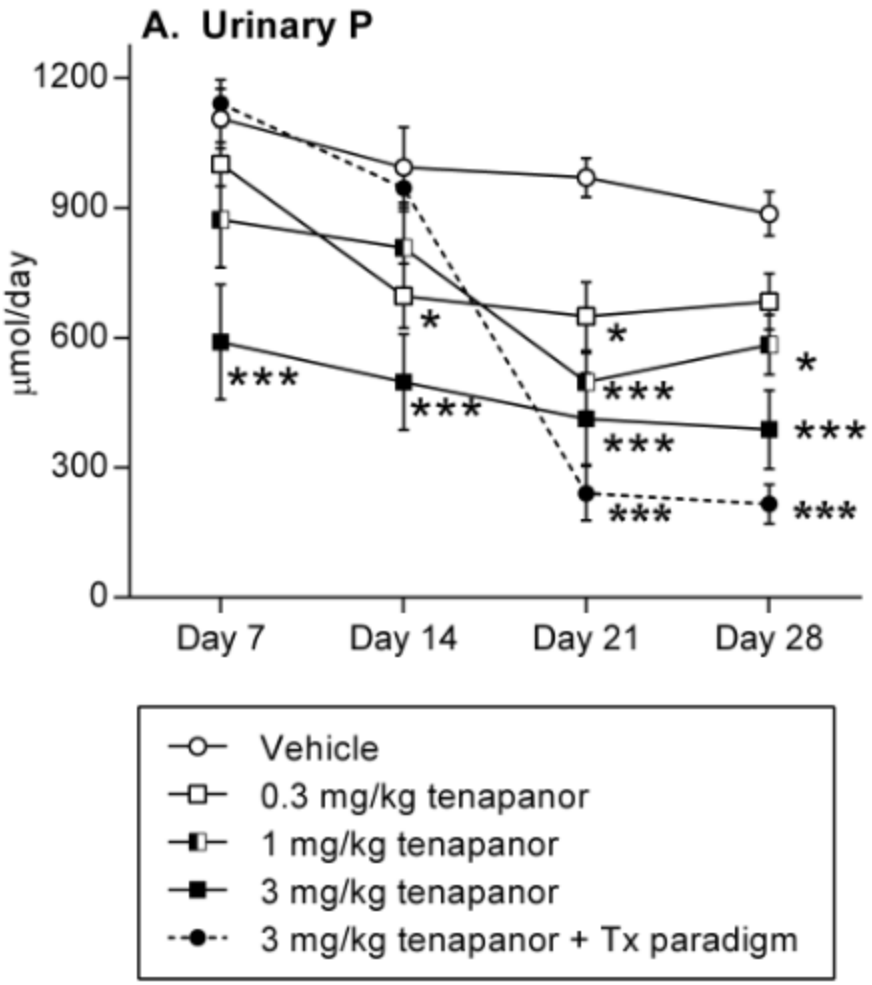




- Male Sprague-Dawley rats (*n*=6) were orally administered vehicle (water) or tenapanor at the indicated doses by oral gavage just before the dark phase and then placed in metabolic cages for urine collection over a 16 h period

*Labonte et al. JASN **26** (2015)*

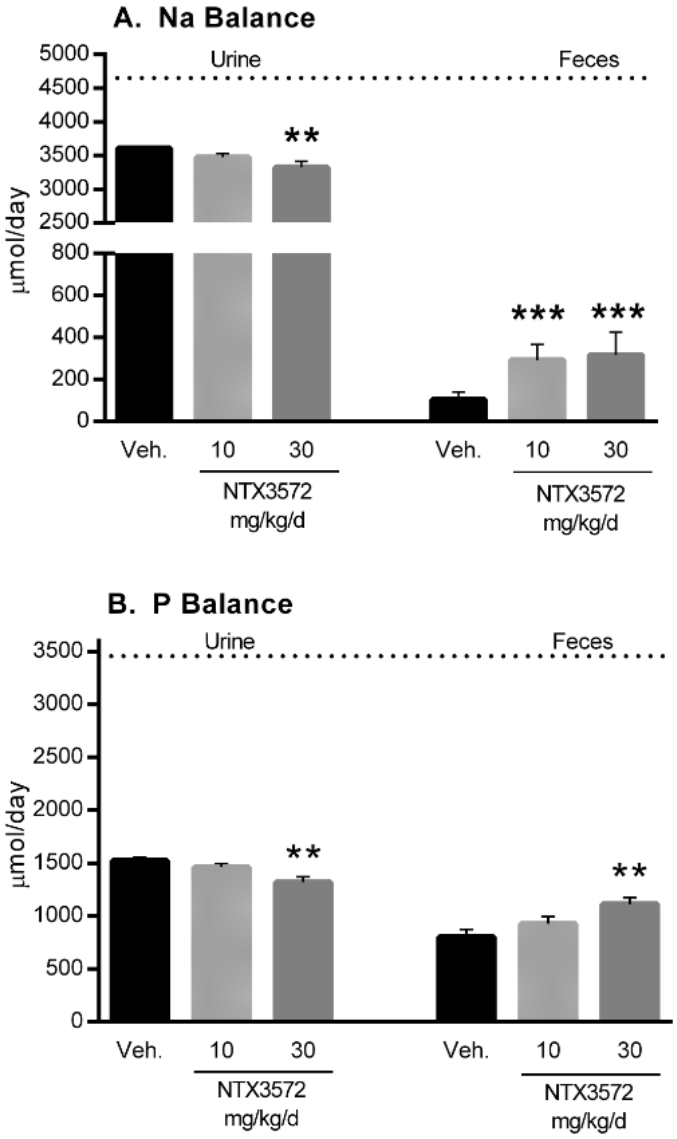
A non-systemic NHE3 inhibitor decreases urinary P in 5/6th CKD rats



- 5/6th nephrectomized rats fed a 4% NaCl diet (Spencer et al, STM 2014) were dosed vehicle or tenapanor daily for 4 weeks. Weekly 24 h urine collections were measured for P
- In one arm of the study (Tx paradigm) , tenapanor was given two weeks after the initiation of the high Na diet regimen (therapeutic intervention vs. prophylactic)

*Labonte et al. JASN **26 (**2015)*

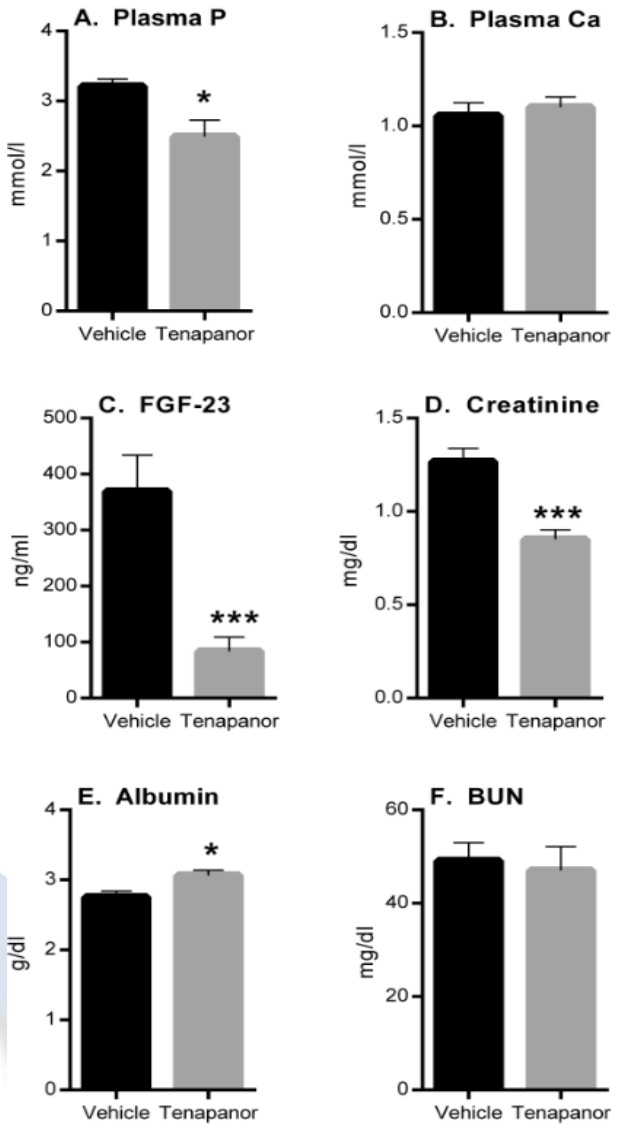
A non-systemic NHE3 inhibitor increases fecal excretion of Na and P in rats



- NTX3572, a minimally-systemic tool compound with reduced potency & persistence was used to facilitate stool collection
- Rats (*n*=9) were fed a 0.6% bioavailable P diet for 4 days with or without NTX3572 mixed in the chow at the indicated doses
- Daily urine and feces were collected and the masses of excreted of Na (A) and P (B) from each rat were determined and averaged from the last three 24 h periods (days 2 to 4)
- The dotted line indicates the daily average intake of Na or P of all rats; 4654 µmol/day and 3455 µmol/day, respectively

Labonte et al. JASN ***26 (****2015)*

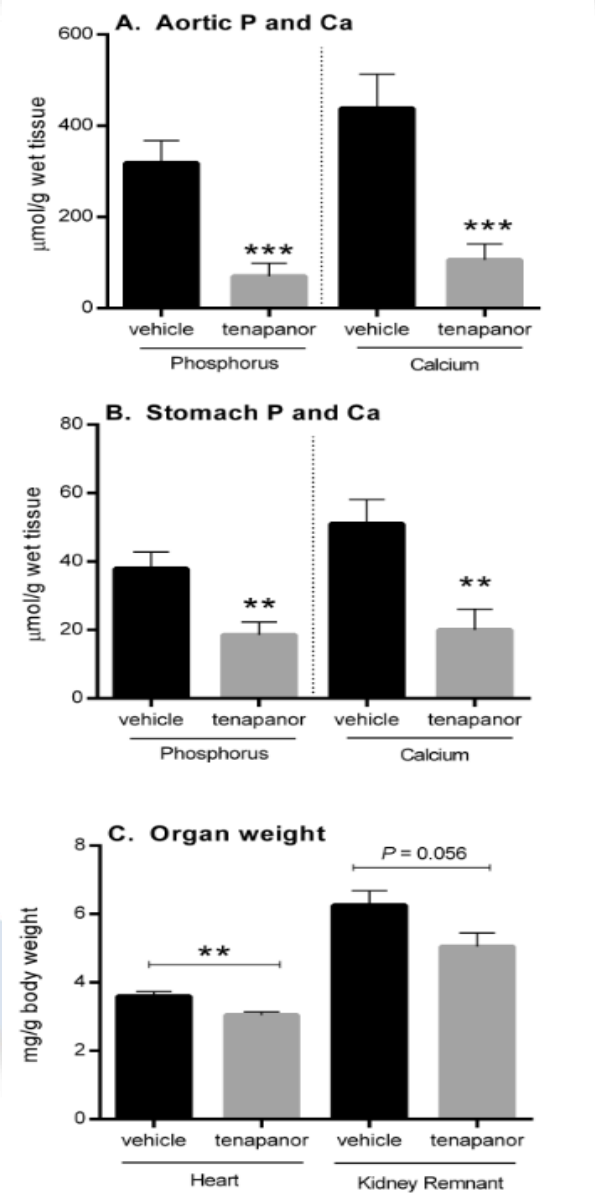
Tenapanor (5 mg/kg/d) improves uremic markers in rat CKD model



- Vascular calcification model (Lopez et al., JASN 17:795 (2006)) induced by
  - 5/6th nephectomy
  - 0.9% inorganic P – 0.6% Ca diet
  - Calcitriol injection thrice a week
- At day 27 (48 hours after the last calcitriol injection), blood was collected for plasma from the remaining rats on study and measured for P, Ca, FGF-23, creatinine, BUN, and albumin.

*Labonte et al. JASN **26** (2015)*

Tenapanor reduces vascular calcification, heart and kidney hypertrophy in CKD rats



- P and Ca content were assessed in the aortic arch (A) and the stomach (B) collected from NPX rats after 28 days of calcitriol treatment. Kidney remnant and heart weights as related to body weight were also measured for each rat (C)

Labonte et al. JASN ***26 (****2015)*

Non-systemic NHE3 inhibitors (illustrated by tenapanor)

- Reduce intestinal absorption of Na and P
- Improve uremic markers (serum P, creatinine, FGF-23) in a 5/6th Nx–vascular calcification rat model
- Reduce ectopic calcification
- Reduce heart and kidney hypertrophy
- Therapeutic dose (5 mg/kg) is far below that of phosphate binders (>1000-fold less)
- Mechanism of action is being investigated
- Human data on the dietary P reduction effect of tenapanor are reported during ASN 2014 in several posters / oral communication sponsored by Ardelyx and AstraZeneca