

A Positive Functional Modulator of ABCC6 Decreases Vascular Calcification and Improves Kidney Function in a Rat Adenine Diet Model of Chronic Kidney Disease

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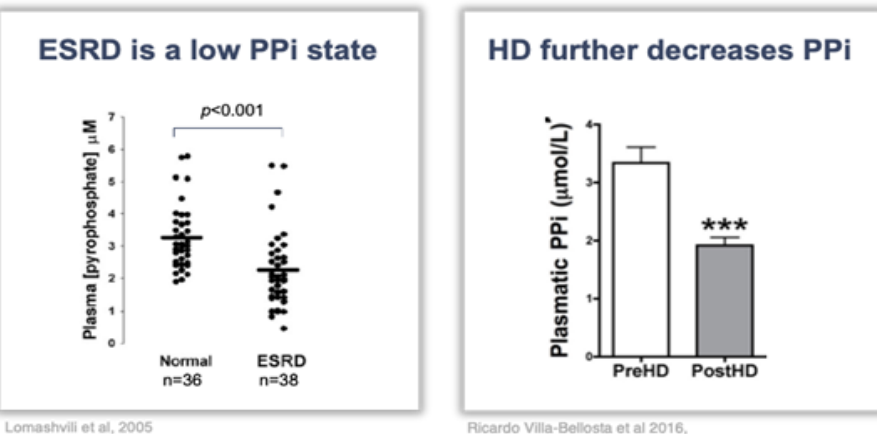
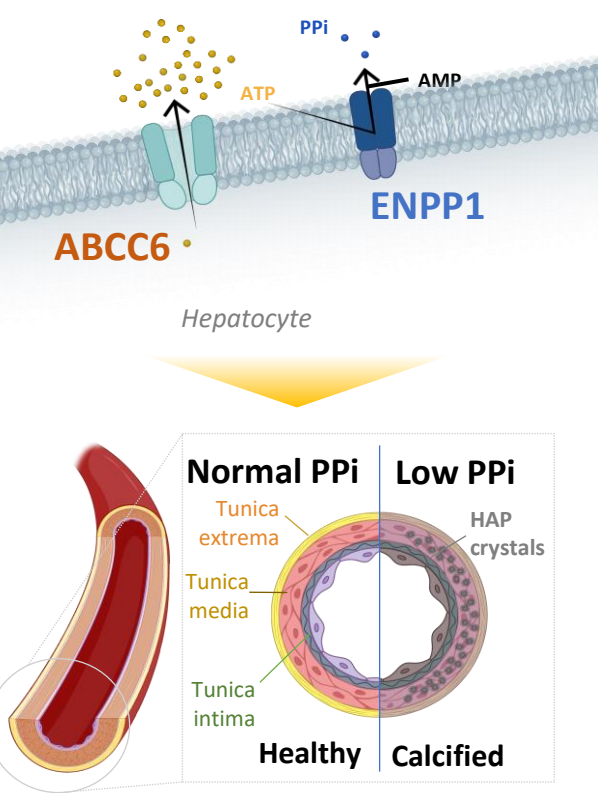
ABCC6 and PPI in Chronic Kidney Disease

ABCC6 is a key regulator of circulating PPI levels

- Inorganic pyrophosphate (PPI) is the most potent anti-calcific factor
- ABCC6 accounts for ~60% of plasma PPI

Low PPI promotes vascular calcification

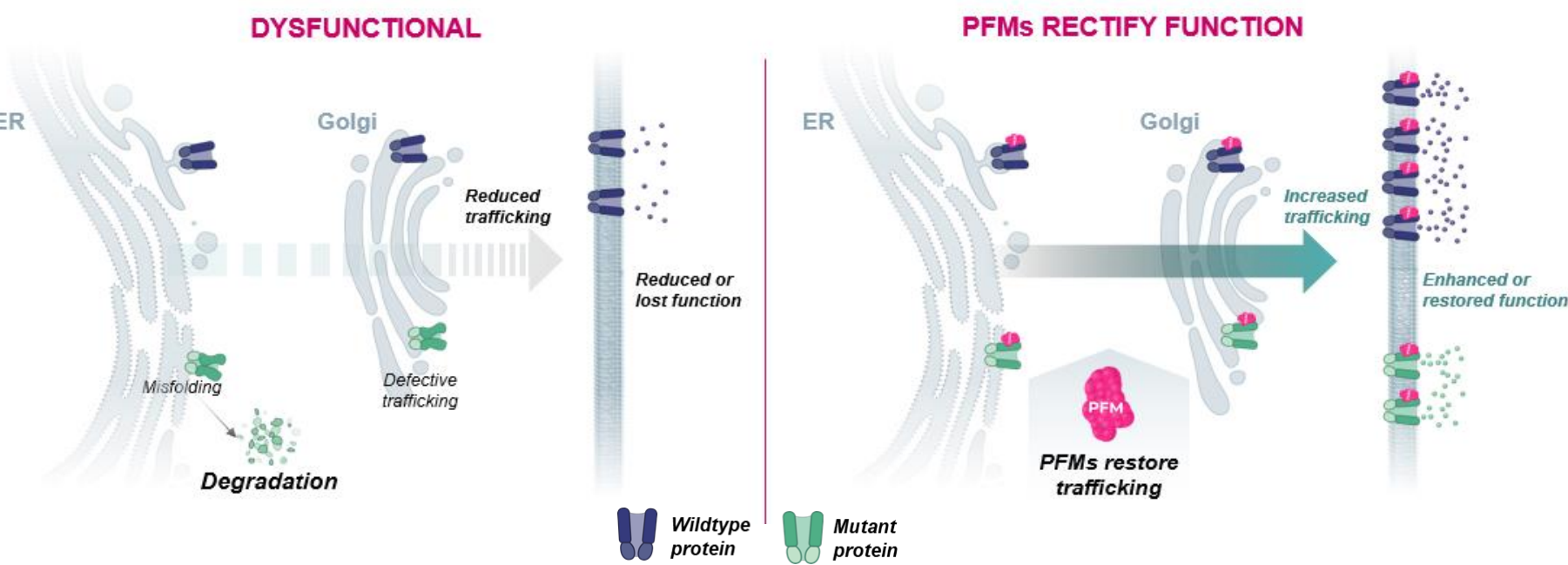
- Homozygous mutations to ABCC6 cause monogenic calcification diseases (GACI and PXE)
- Heterozygous mutations drive vascular calcification in CKD



Low PPI in CKD

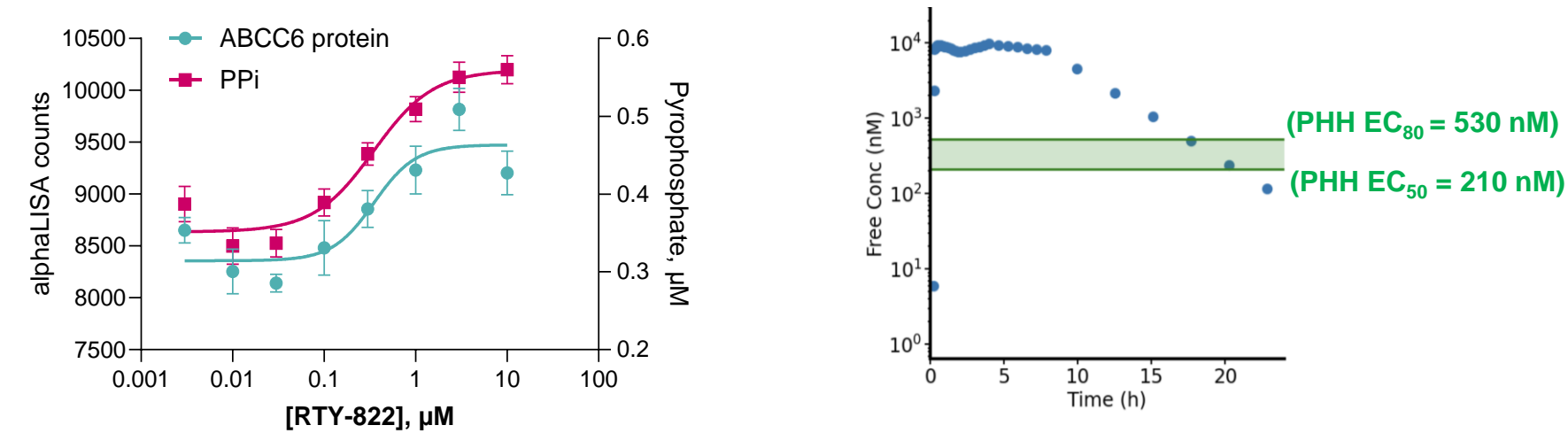
- End stage renal disease (ESRD) patients have reduced PPI
- Hemodialysis (HD) further reduces PPI

Positive Functional Modulators (PFMs)



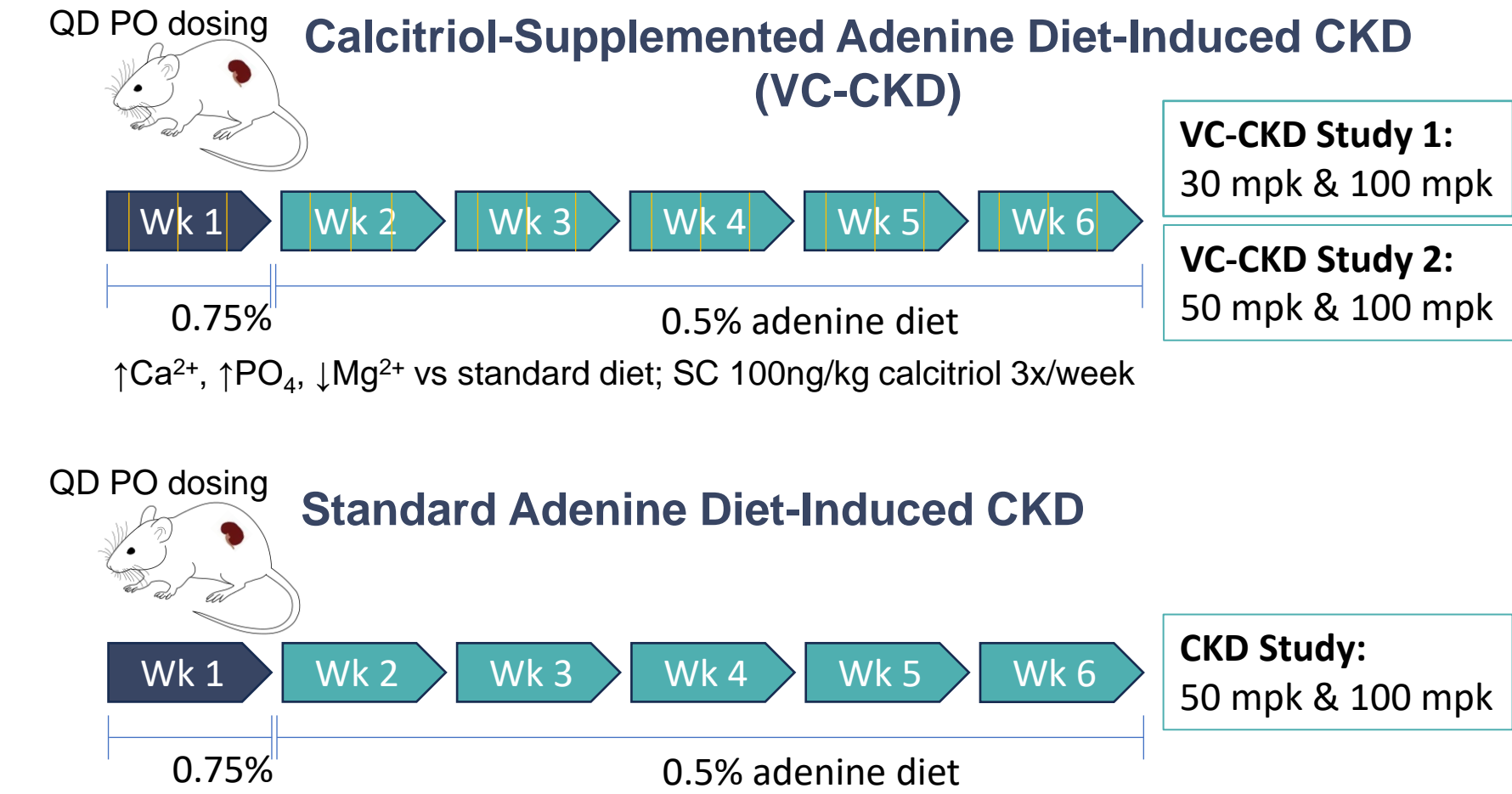
PFM RTY-822 Increases ABCC6 Protein and PPI

↑ABCC6 protein and function in PHHs Rat PK profile (100 mpk)

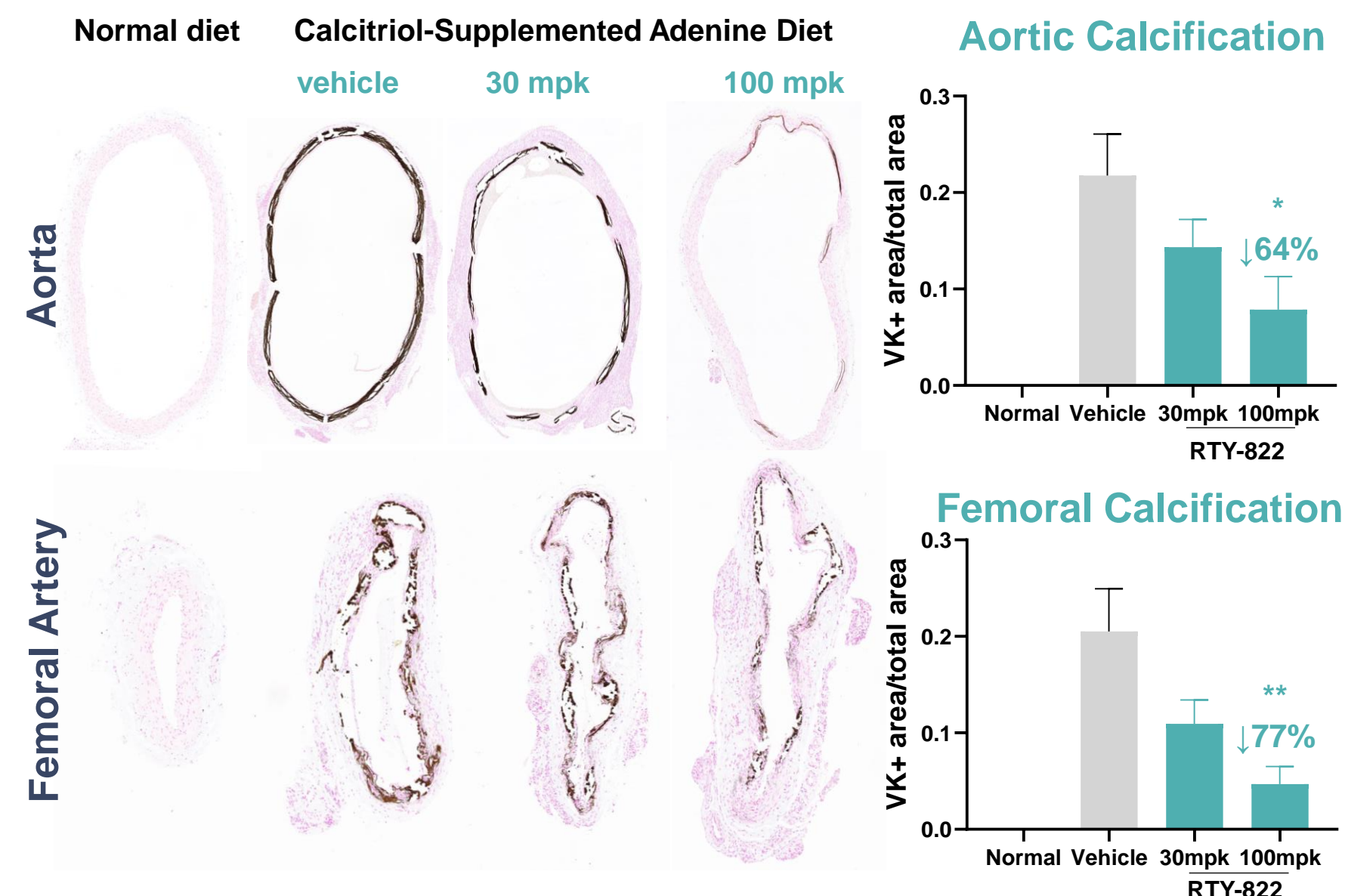


- RTY-822, a potent and selective PFM, increases ABCC6 in primary human hepatocytes (PHHs)
- PK profile and potency make RTY-822 an excellent PFM to establish in vivo POC

Rat Models of Vascular Calcification CKD and CKD

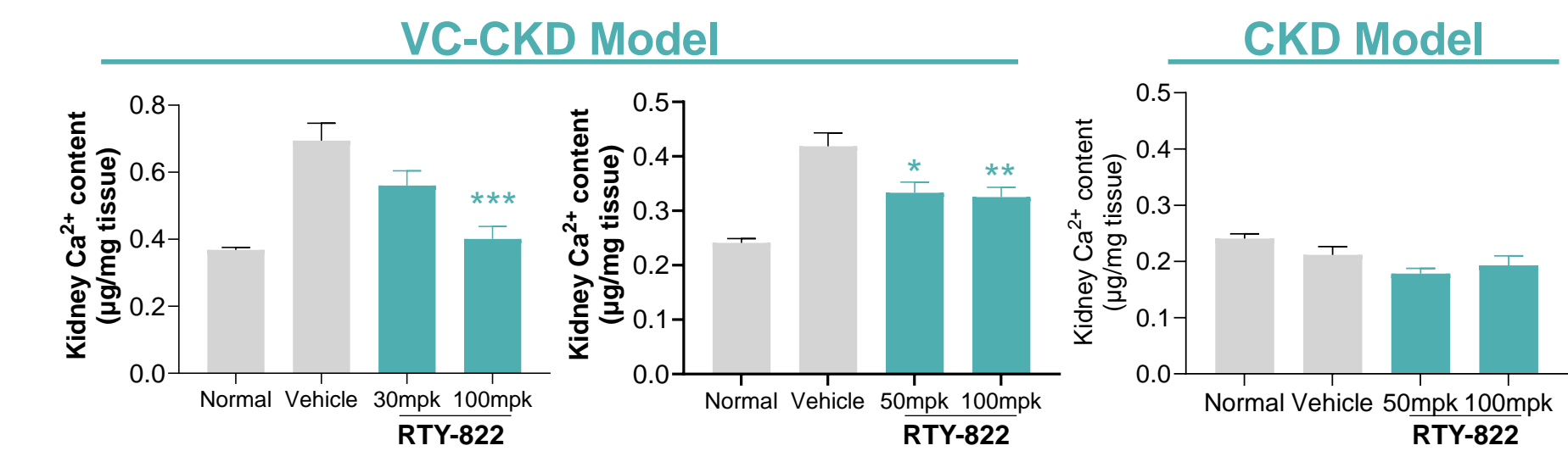


RTY-822 Reduces Vascular Calcification



- Von Kossa histological staining indicates that RTY-822 reduced vascular calcification in the aorta and femoral artery

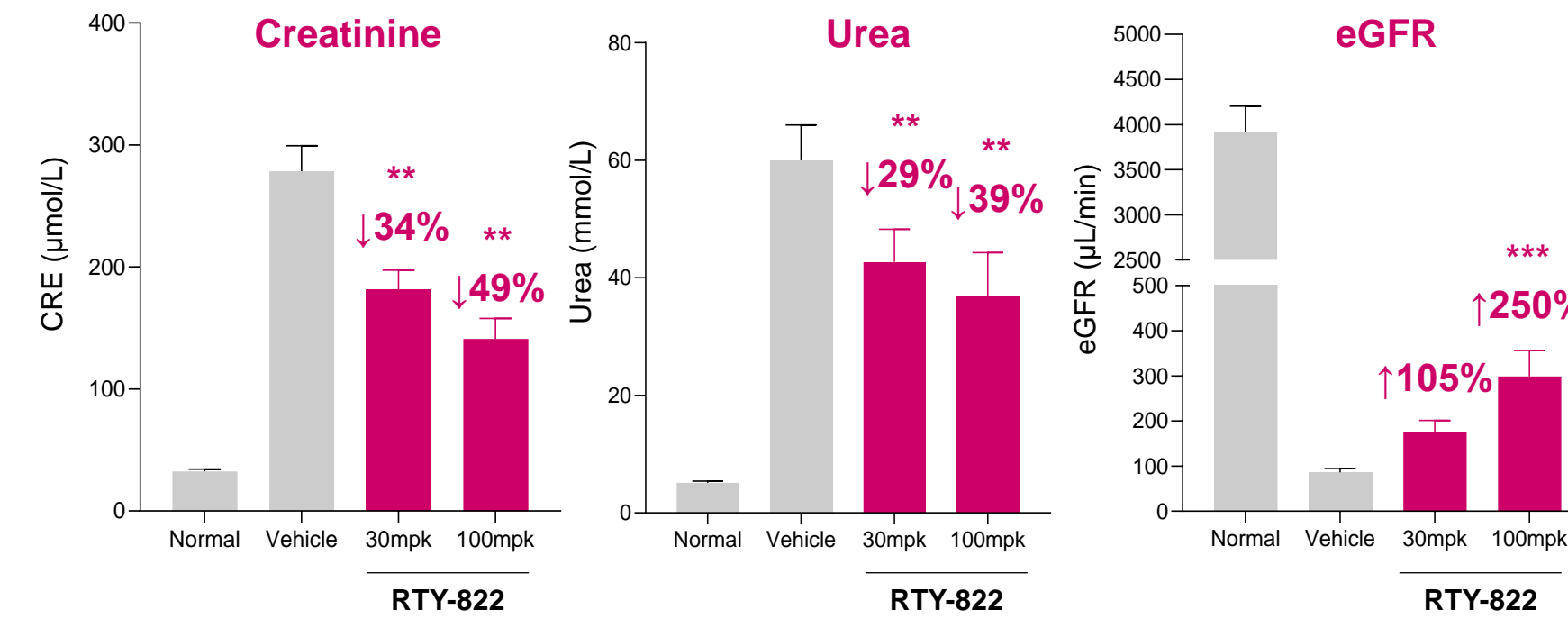
RTY-822 Reduces Kidney Calcium Content



- RTY-822 reduced calcium (Ca²⁺) in the kidney in the model with calcitriol, with a trend towards lowering in the animals on standard adenine diet

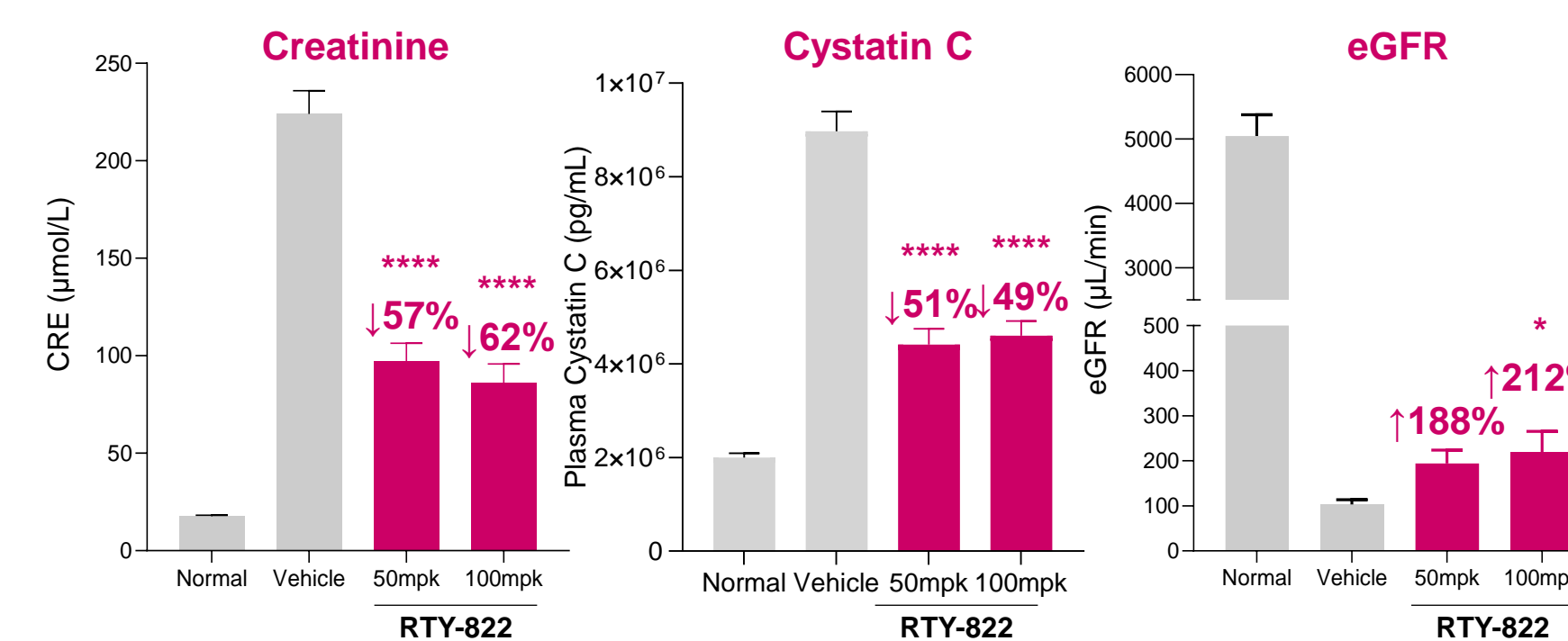
RTY-822 Increases Kidney Function

VC-CKD Model



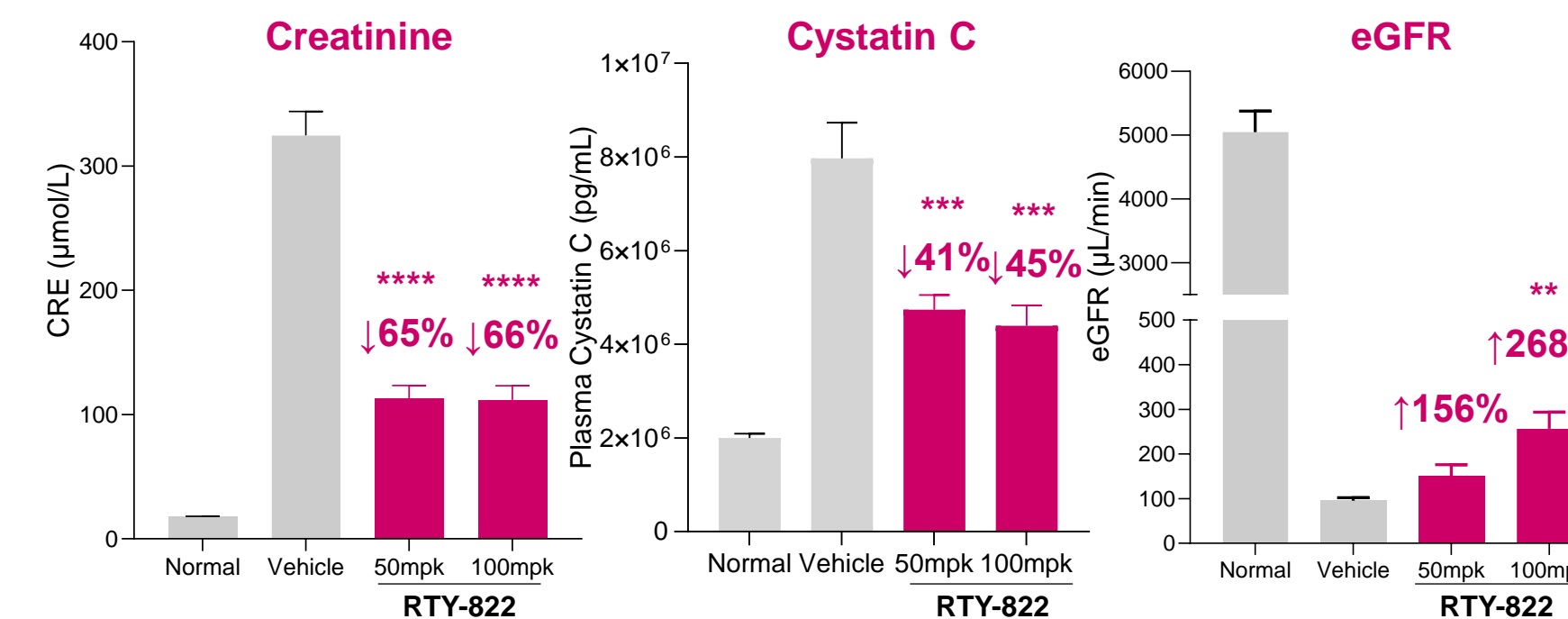
- Rat adenine diet model with calcitriol shows 98% reduction in eGFR after 6 weeks on diet
- 6 weeks oral QD dosing with 30mpk and 100mpk RTY-822 improves kidney function

VC-CKD Model



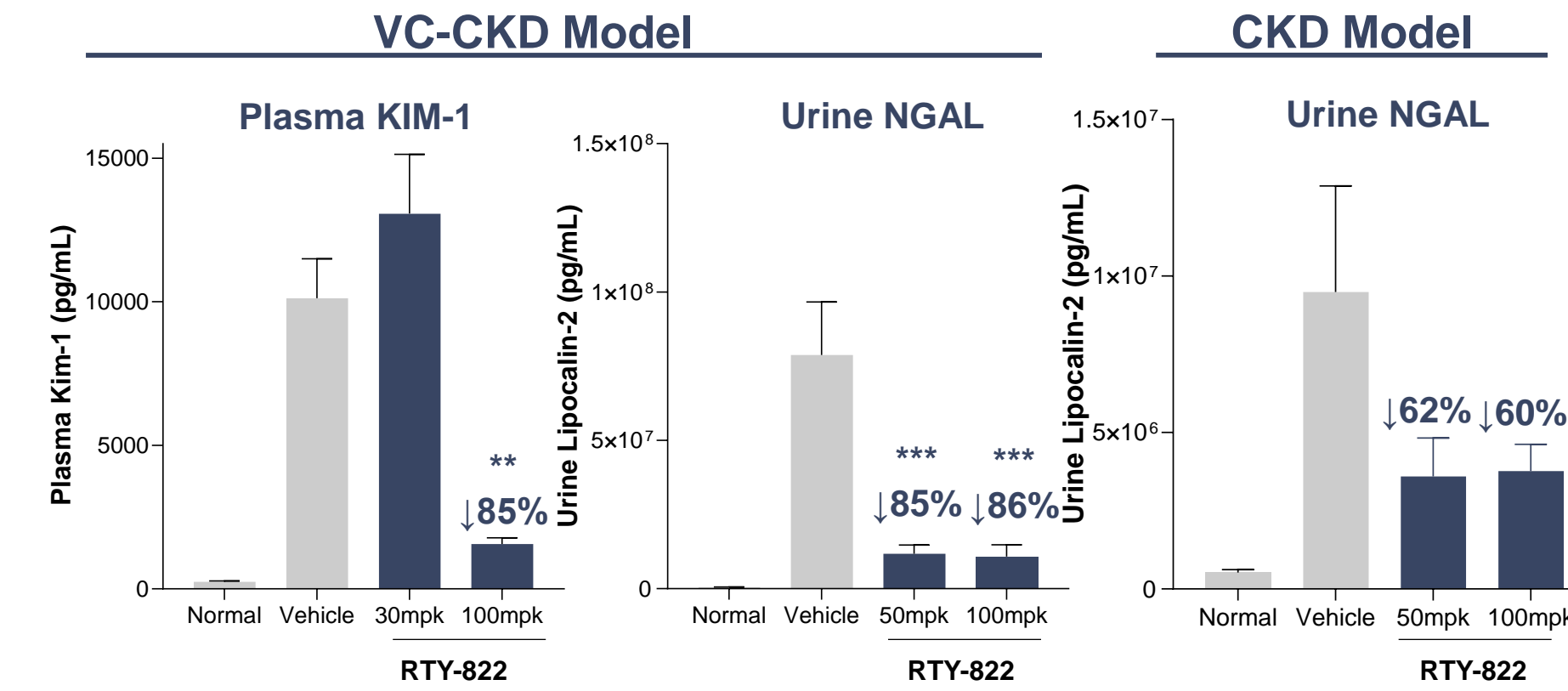
- 50mpk and 100mpk RTY-822 showing approximate doubling of eGFR
- Serum urea was also significantly reduced at both dose levels

CKD Model



- Rat adenine diet models severe CKD, resulting in 98% reduction in eGFR after 6 weeks
- 6 weeks oral QD dosing with RTY-822 improves kidney function
- RTY-822 positive impact on kidney function does not require calcitriol-enhanced vascular calcification

RTY-822 Reduces Kidney Injury



- Rat adenine diet models severe CKD, with drastic increases in kidney injury markers after 6 weeks on diet
- Similar reduction in plasma KIM-1 and urine NGAL with 100mpk RTY-822 in independent studies with calcitriol supplementation
- Calcitriol supplementation enhances injury relative to standard adenine diet CKD model

Conclusions

- The Rectify platform has delivered PFMs that target ABC transporters spanning a range of indications including hepatobiliary and cardio-renal-metabolic therapeutic areas
- RTY-822 shows positive pharmacologic activity in an in vivo model of vascular calcification and CKD:
 - ✓ Reducing vascular calcification
 - ✓ Increasing kidney function
 - ✓ Reducing kidney injury
- RTY-822 also shows positive pharmacologic activity in an in vivo model of CKD:
 - ✓ Increasing kidney function
 - ✓ Reducing kidney injury
- Rectify's ABCC6 PFMs offer a promising new class of therapeutics with potential for the treatment of CKD and vascular calcification

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