PBI-4050, a novel first-in-class anti-diabetic and anti-inflammatory compound, protects against diabetic nephropathy in type II diabetes

Ming-Zhi Zhang and Raymond C. Harris
Vanderbilt University School of Medicine, Nashville, TN

Introduction

Extensive kidney fibrosis occurs in several types of chronic kidney diseases (CKDs), including severe diabetic nephropathy (DN). PBI-4050, a novel first-in-class orally active low molecular weight compound, has been shown to exhibit anti-fibrotic and anti-inflammatory properties in different *in vivo* models, including CKD models. Phase II clinical trials are underway to test its efficacy in patients with CKD and DN. In the present studies, we examined whether PBI-4050 affected the progression of DN in a mouse model of accelerated type II diabetes.

Methods

BKS *db/db* with eNOS knockout (eNOS$^{-/-}$ *db/db*) mice received vehicle (water) or PBI-4050 (200 mg/kg/day) by daily gastric gavage either from 8 to 20 weeks of age (early treatment) or from 16-24 weeks of age (late treatment). A subset of mice with late treatment was kept until death to achieve a survival curve. PBI-4050 was provided by ProMetic BioSciences Inc., Laval, QUEBEC.

Results

Fig 1. Early PBI-4050 treatment ameliorated the fasting hyperglycemia and abnormal glucose tolerance tests seen in vehicle-treated *db/db* eNOS-/- mice

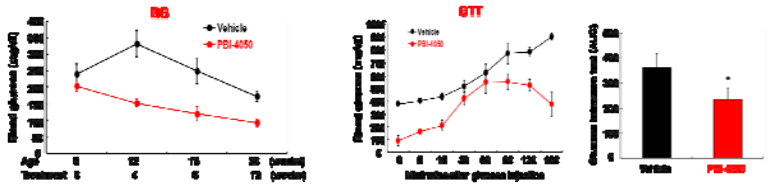


Fig 2. Early PBI-4050 treatment preserved glomerular filtration rate (GFR) and decreased ACR in *db/db* eNOS-/- mice.

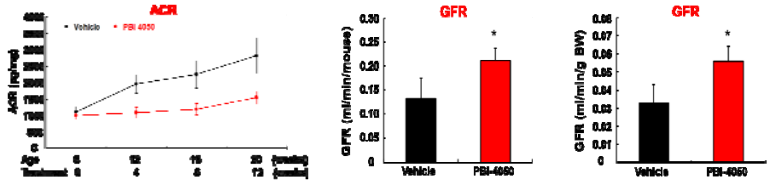


Fig 3. Late PBI-4050 treatment also decreased fasting hyperglycemia and prevented further ACR increase and increased lifespan in *db/db* eNOS-/- mice.

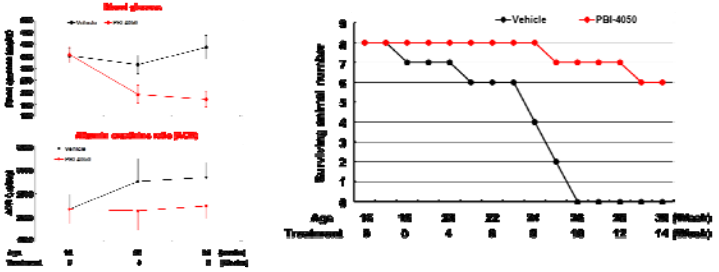


Fig 4. Early PBI-4050 treatment preserved and late treatment restored plasma and pancreatic islet insulin levels in *db/db* eNOS-/- mice

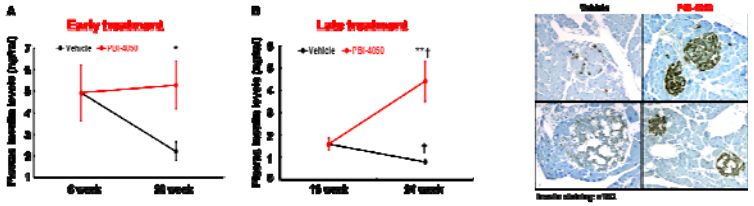
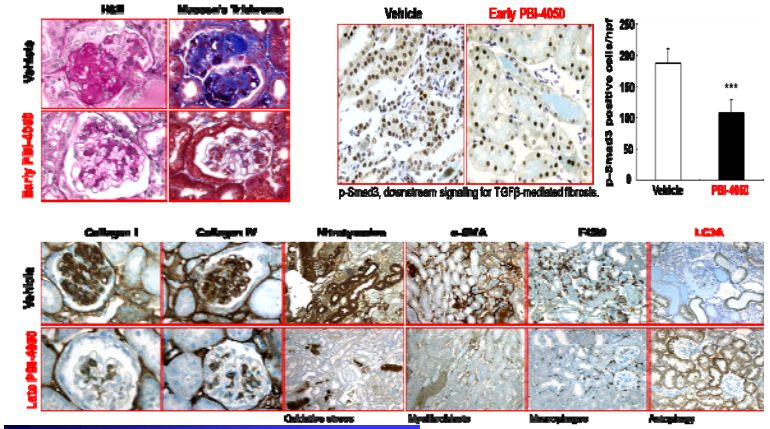


Fig 5. Both early and Late PBI-4050 treatment protected against progression of DN in *db/db* eNOS-/- mice



Conclusions

These studies suggest that PBI-4050 attenuates the development of DN in type II diabetes through multiple mechanisms, including improvement of glycemic control and inhibition of renal TGF-β-mediated fibrotic pathway in association with decreases in macrophage infiltration and oxidative stress and increase in autophagy.

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