

Murine Double Minute-2 (MDM-2) inhibition ameliorates cisplatin nephropathy

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Introduction

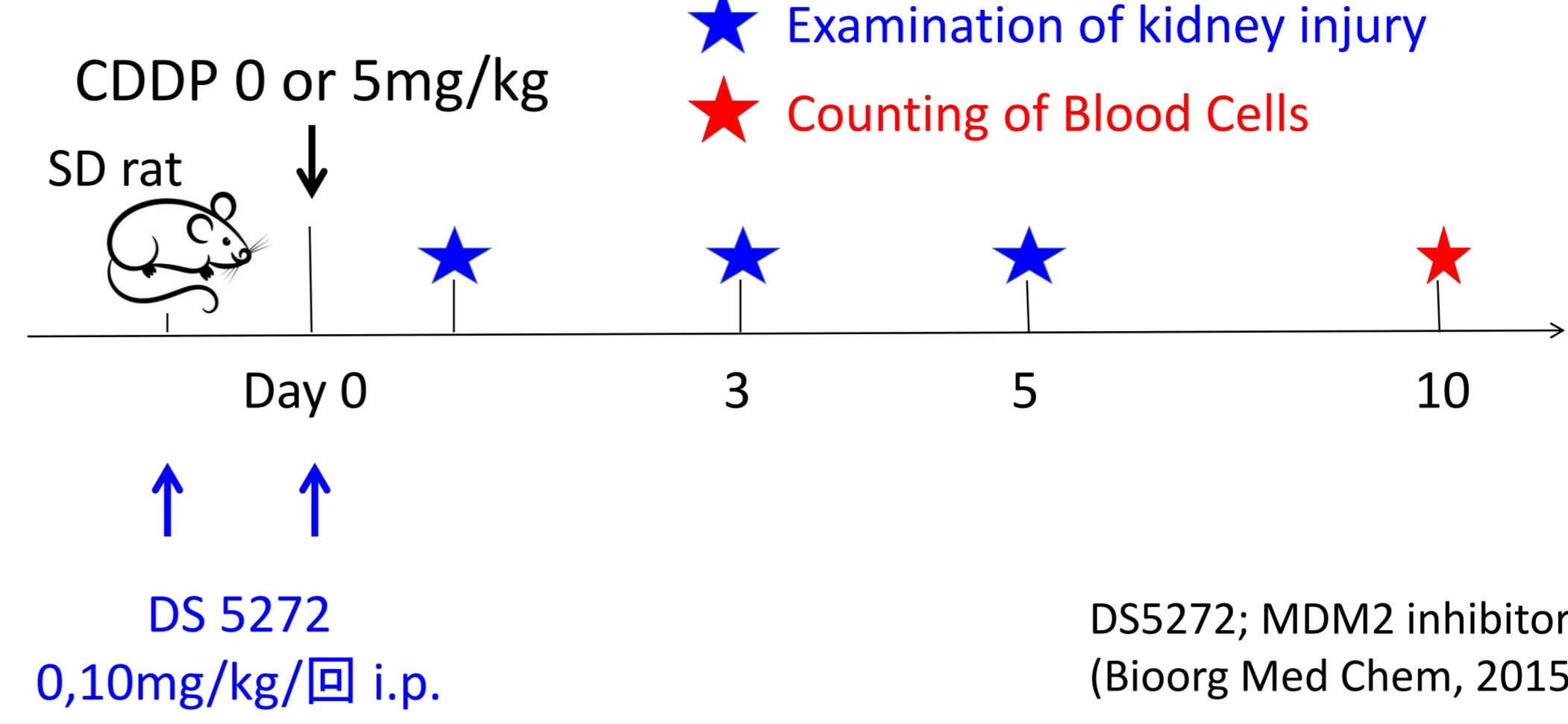
Cisplatin (CDDP) is a cancer therapy drug, which is widely used and highly effective drugs for solid tumors. The prevalence of nephrotoxicity is about one third, and some of those have progressive or irreversible renal failure (Semin Nephrol, 2003).

Murine double minute-2 (MDM-2) is the E3 ubiquitin ligase of p53, which can work as cancer therapy (Science, 2004). Combined therapy with MDM-2 inhibitor and cisplatin can result in the synergic effects (Oncotarget, 2015).

We have already reported that it has protective effects in acute ischemic kidney injury or crescentic glomerulonephritis via NF- κ B signal inhibition. Here, we examined that MDM2 inhibitor has a protective effect against cisplatin nephropathy in vivo.

Methods

in vivo:



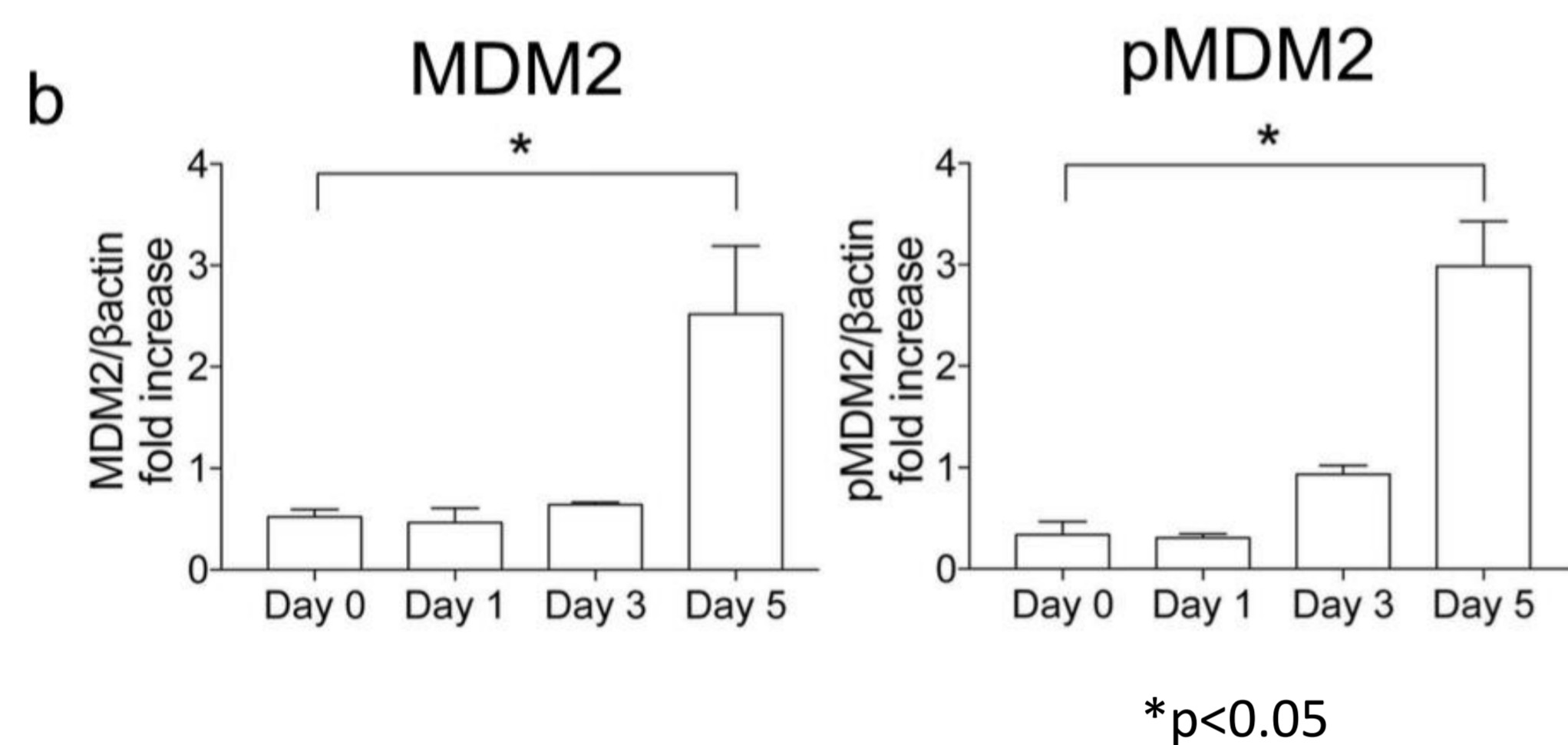
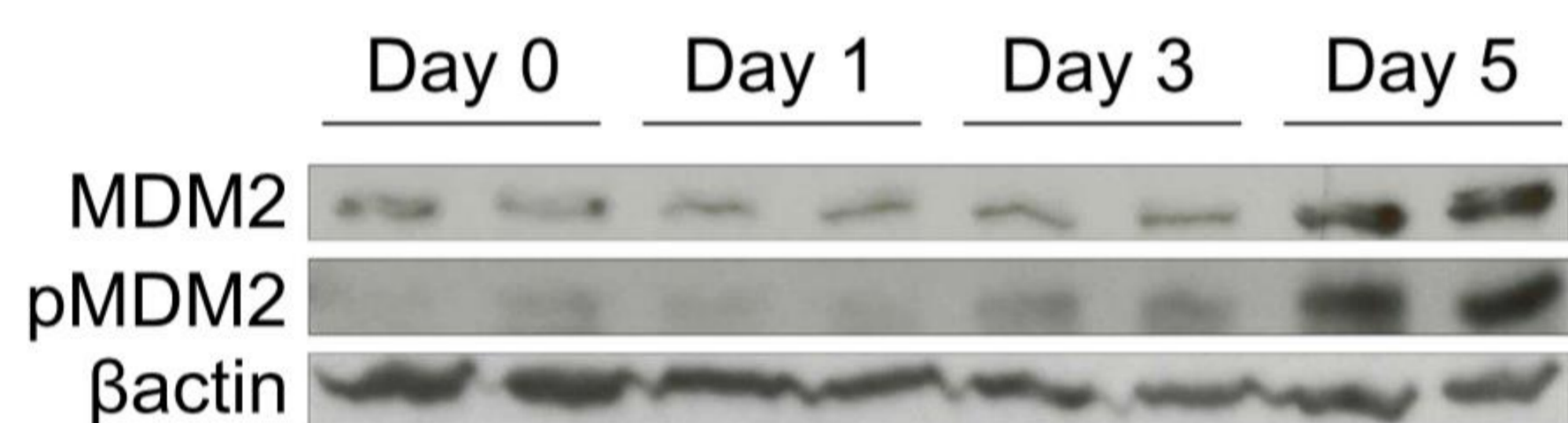
in vitro:

- ✓ HEK293 was utilized.
- ✓ DS5272 was co-incubated with CDDP.
- ✓ Cytotoxicity was analyzed after 24 hours using LDH assay.

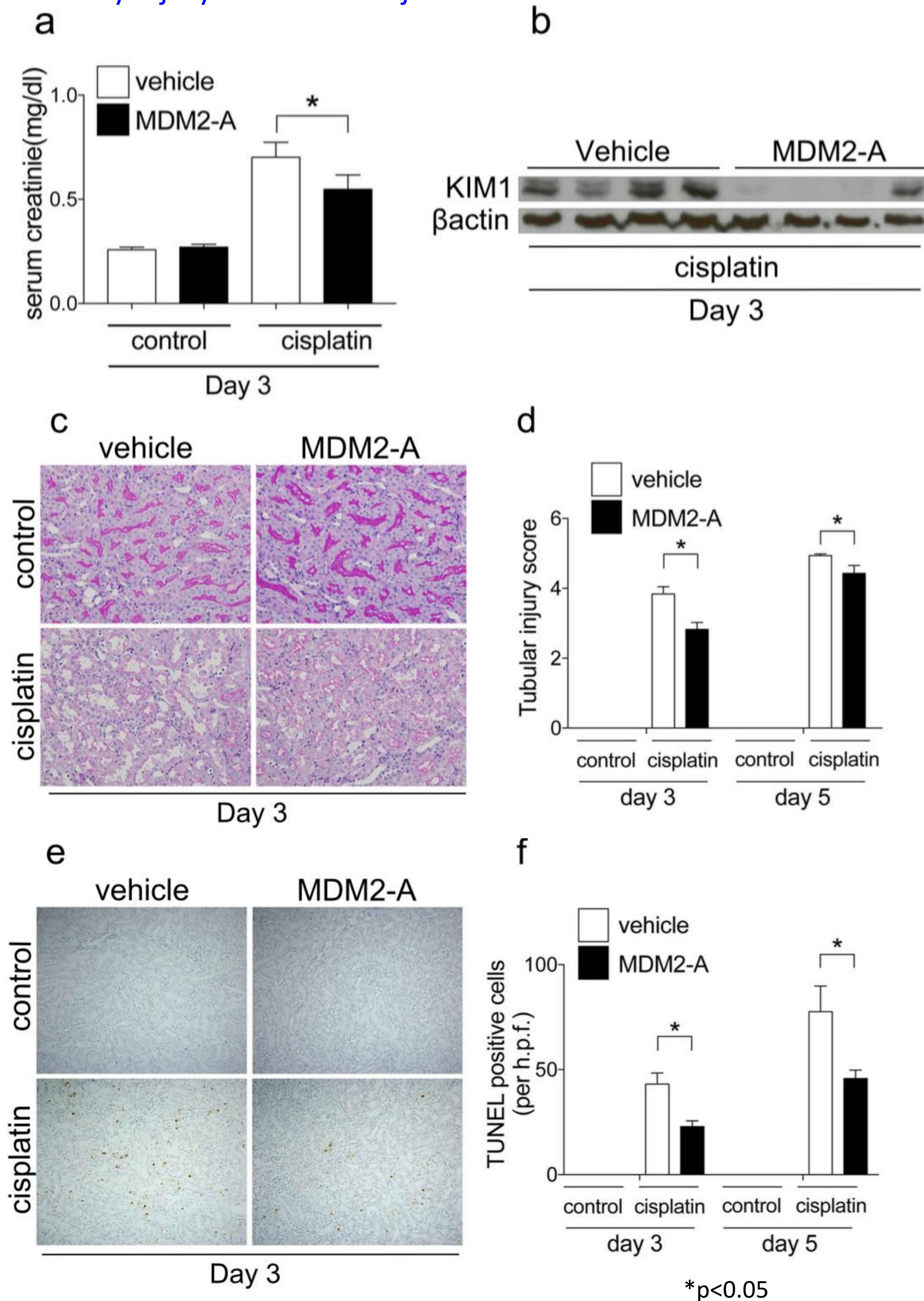
DS5272; MDM2 inhibitor (Bioorg Med Chem, 2015)

Results

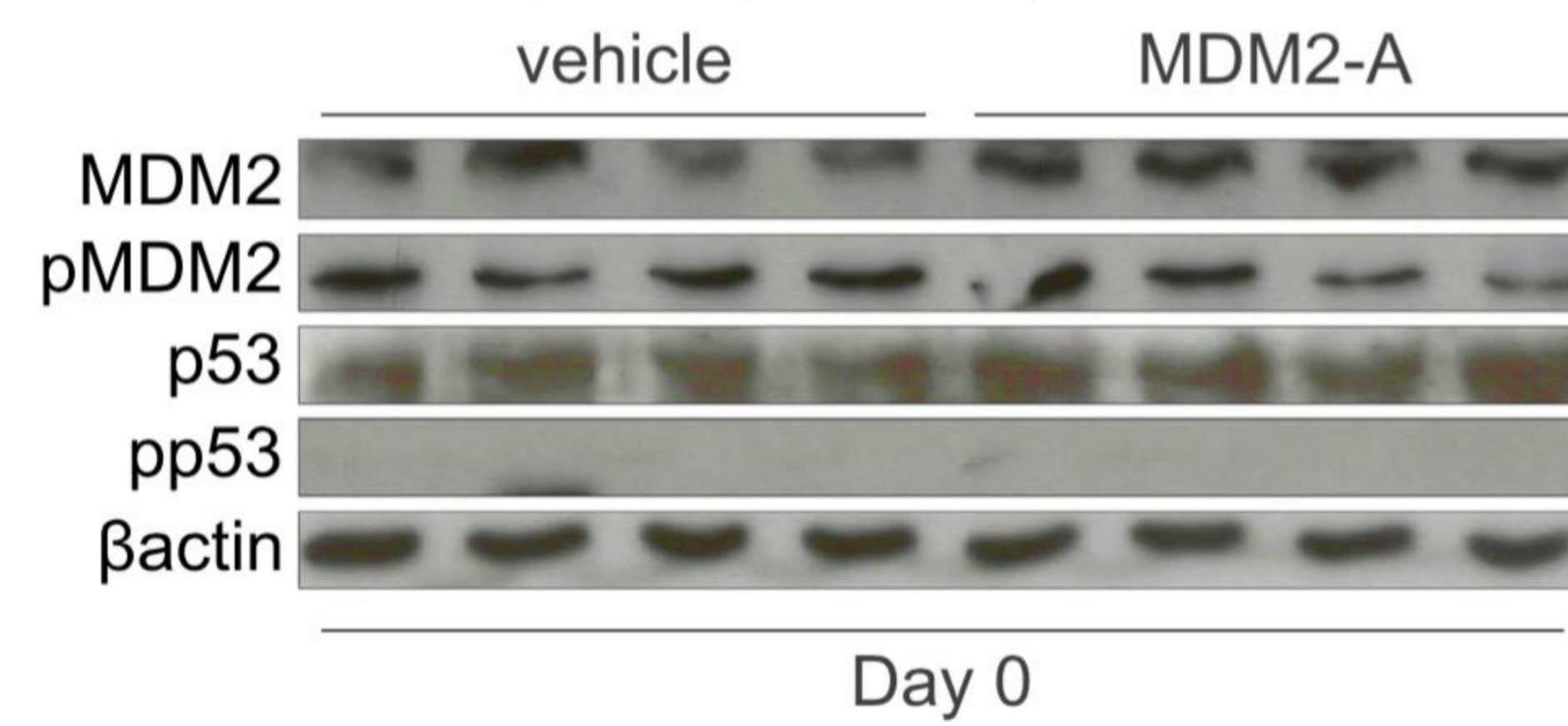
1. Renal MDM-2 expression after CDDP injection



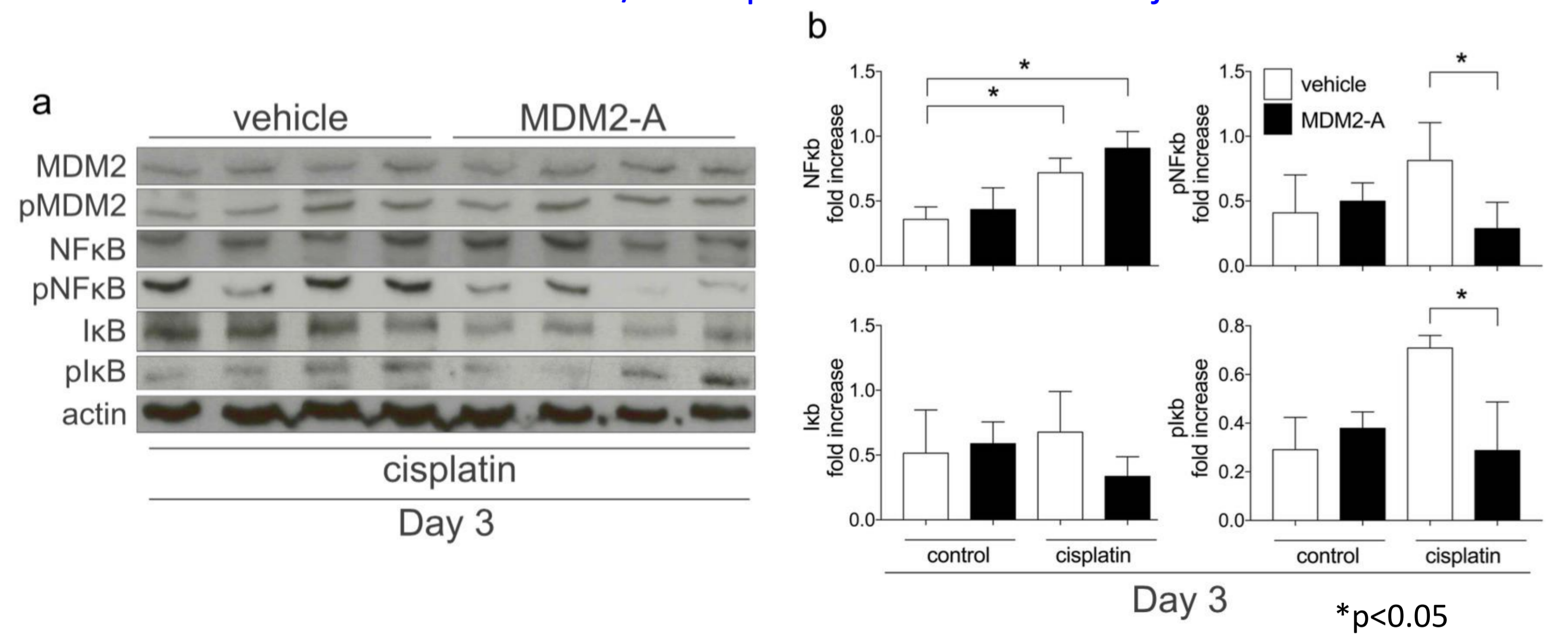
2. Kidney injury after CDDP injection with MDM-2 inhibition



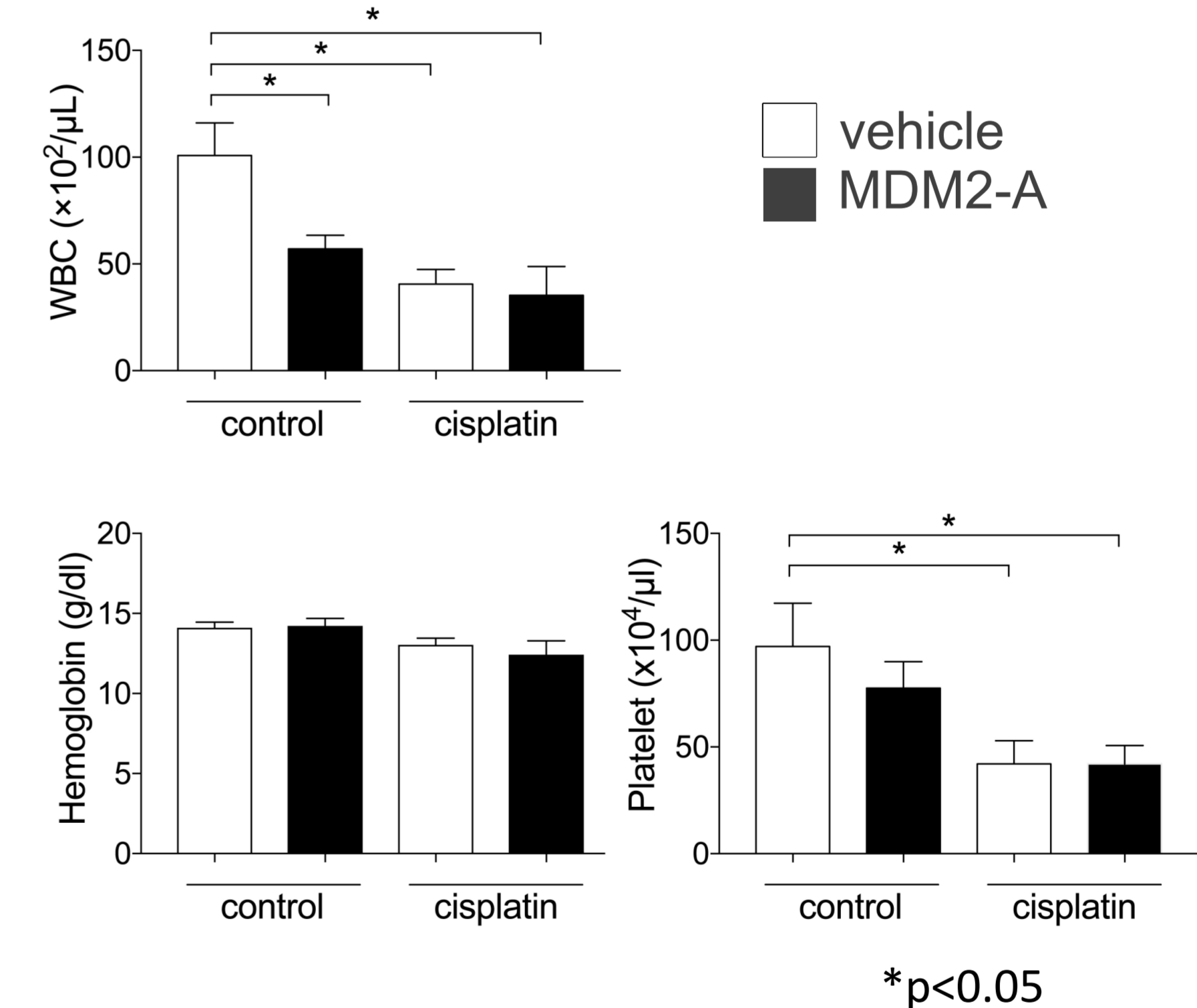
3. MDM-2/p53 expression just before CDDP injection



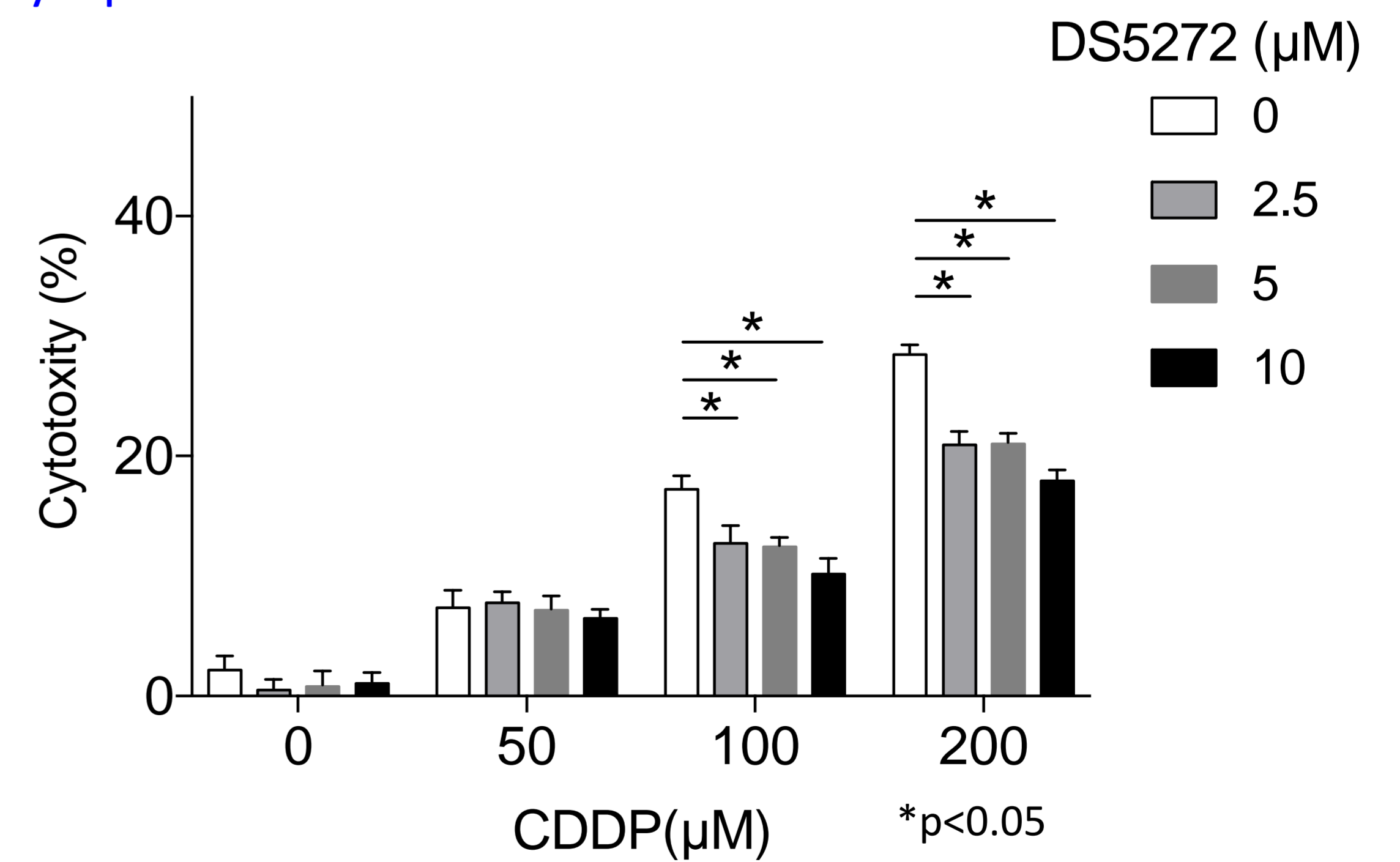
4. MDM-2 or NFκB/IκB expression after CDDP injection



5. Bone Marrow Suppression with MDM-2 inhibition



6. Cytoprotective effect of MDM-2 inhibition in vitro



Conclusion

✓ These findings suggest that MDM-2 inhibition ameliorates CDDP induced nephropathy through NF- κ B signal inhibition.