

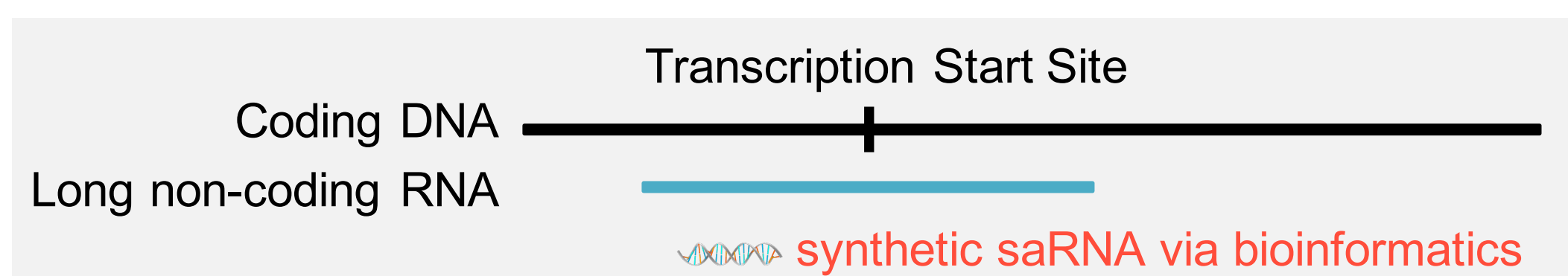
Activation of CEBPA by oligonucleotide saRNA therapy in progressive liver failure, reverses liver fibrosis and promotes liver regeneration

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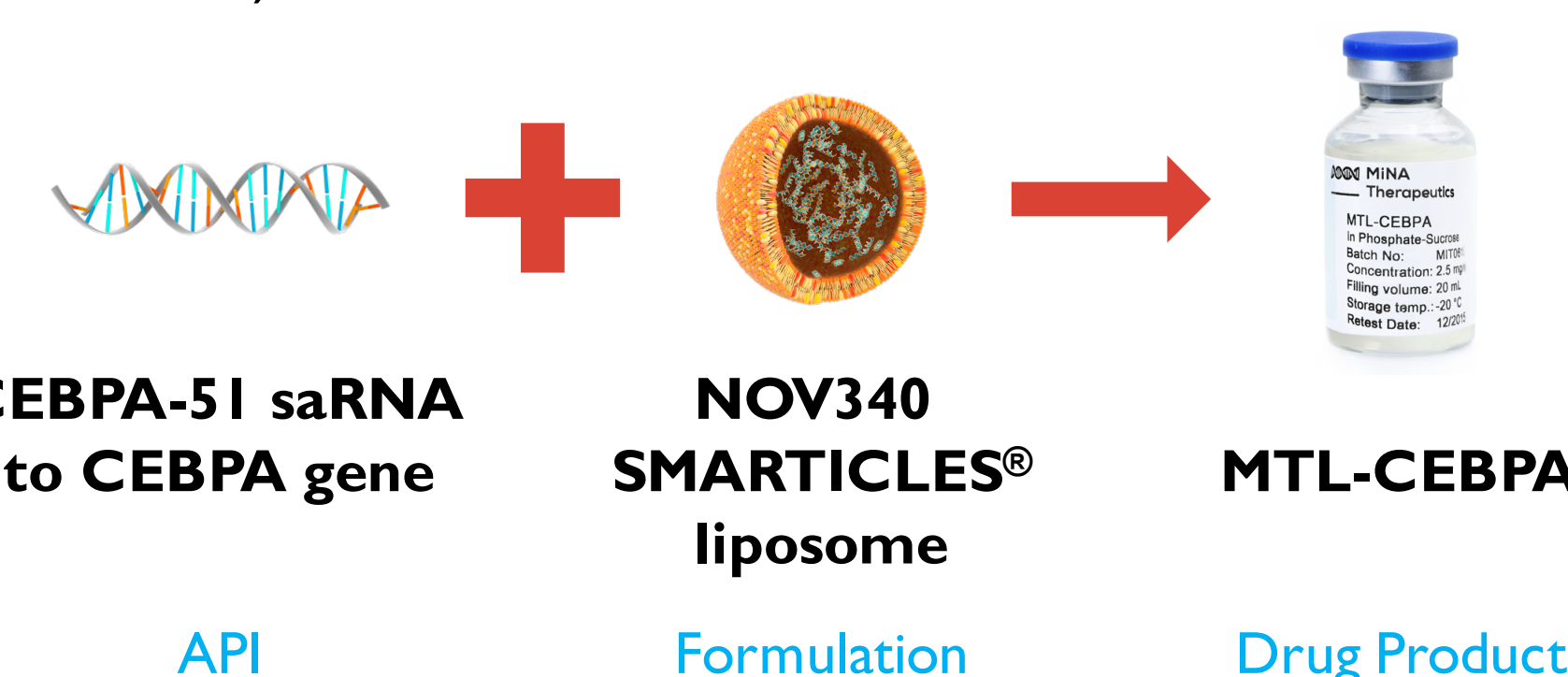
BACKGROUND

Small activating RNAs (saRNAs) are short double stranded oligonucleotides designed to up-regulate their target gene by transcriptional activation. MiNA Therapeutics has developed a proprietary algorithm that identifies saRNAs recognising long non-coding RNAs upstream and downstream of the transcription start site. Following transfection into cells the saRNA is loaded into Ago2 and translocates into the nucleus where it interacts specifically at the target gene leading to recruitment and activation of RNA Polymerase II (Portnoy et al, 2016; Kalantari et al, 2016). This leads to new messenger RNA production resulting in up-regulation of the target protein.



1. Loading of saRNA into Ago protein
2. saRNA-Ago targets gene promoter
3. saRNA-Ago activates gene transcription
4. Long lasting protein up-regulation

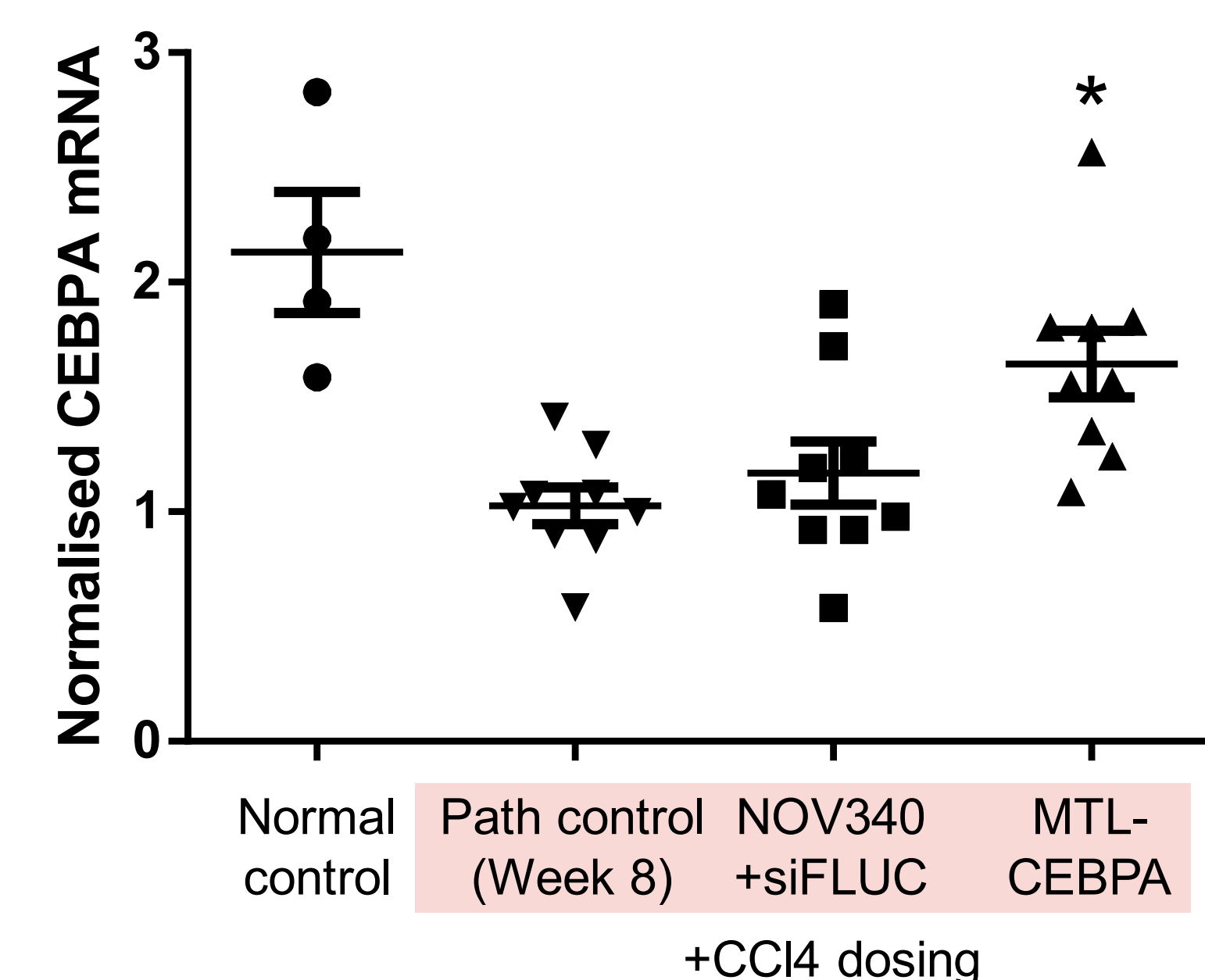
A saRNA has been identified to the transcription factor C/EBP- α (CCAAT/enhancer-binding protein alpha), a master regulator in the liver. The saRNA up-regulates CEBPA mRNA and protein resulting in improved liver function and anti-tumour activity in a model of hepatocellular cancer (Reebye et al, 2014). The original saRNA has been further optimised through gene walking and chemical modification to improve stability/ablate immunogenicity resulting in CEBPA-51. This saRNA has been formulated in the clinically validated SMARTICLESTM lipid nanoparticle resulting in the development candidate MTL-CEBPA which is now in clinical development in patients with liver cancer (ClinicalTrials.gov – NCT02716012).



In the studies reported here we demonstrate that MTL-CEBPA reverses liver fibrosis and steatosis and improves liver function in preclinical models of fibrosis and NASH, supporting the therapeutic potential of MTL-CEBPA in liver disease.

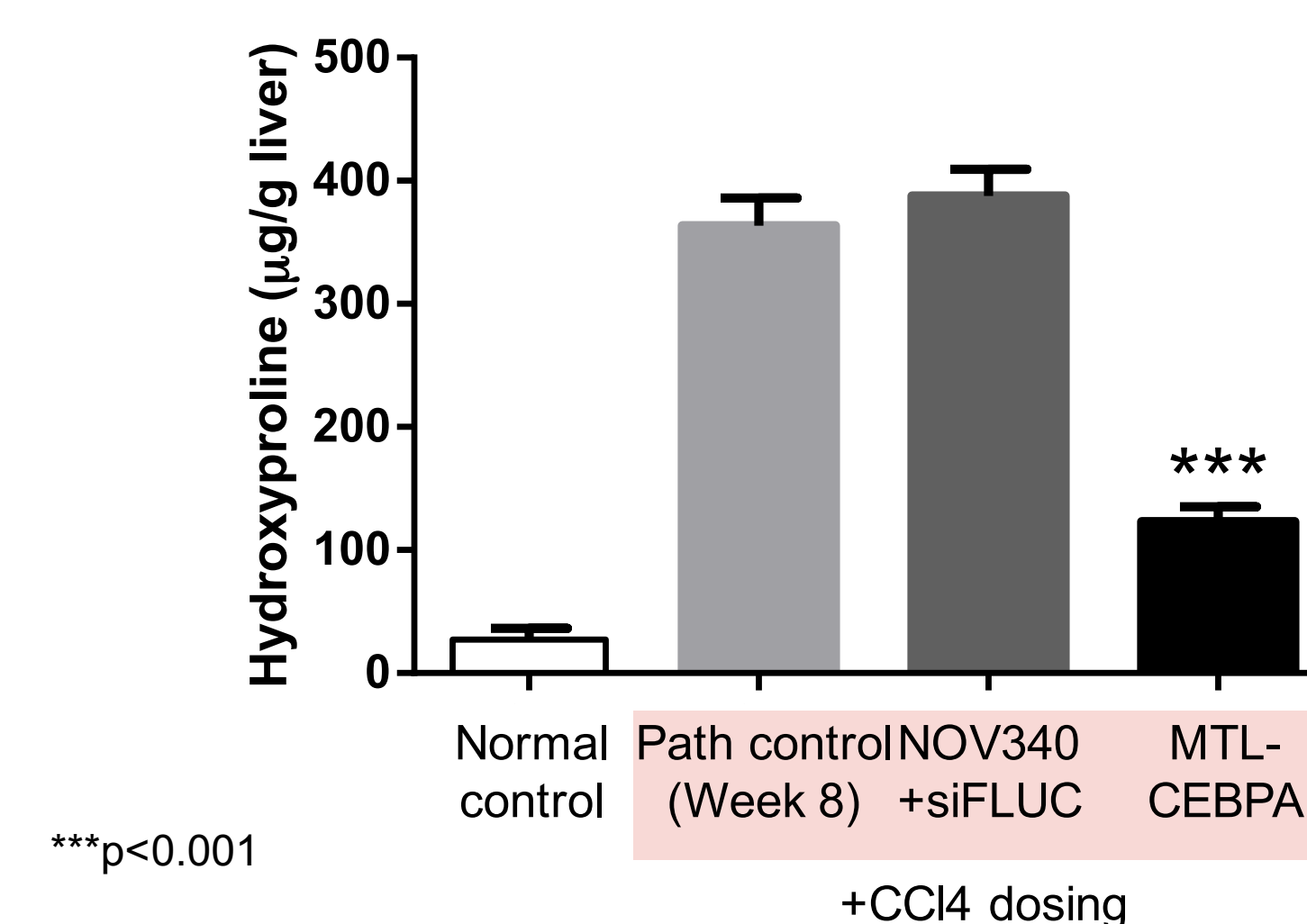
RESULTS

1. MTL-CEBPA restores CEBPA mRNA in CCl4 induced cirrhotic liver

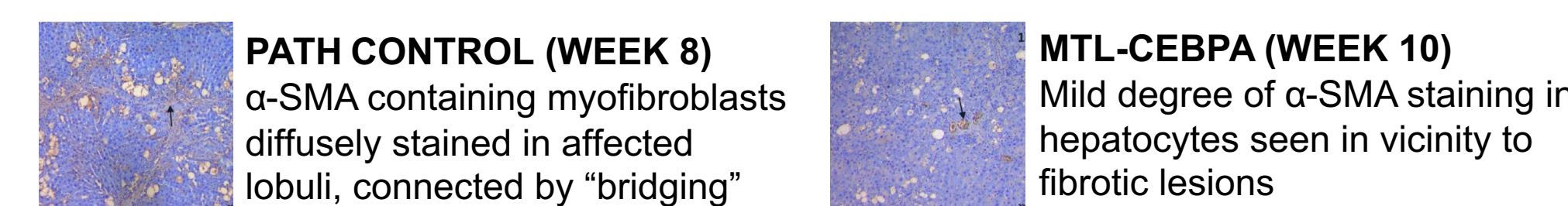


2. MTL-CEBPA reverses liver fibrosis in CCl4 model

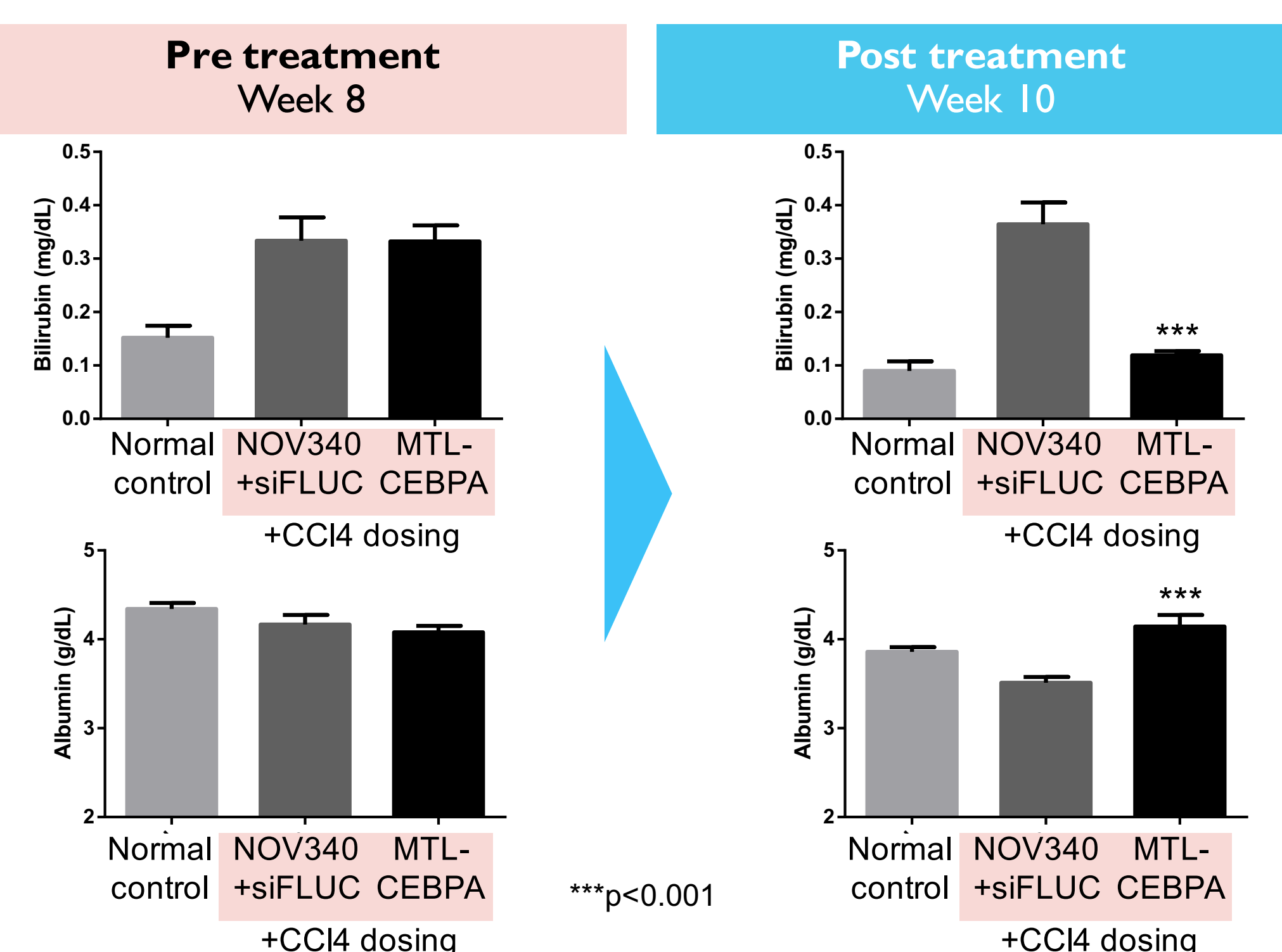
a) Reversal of liver collagen deposition at Week 10



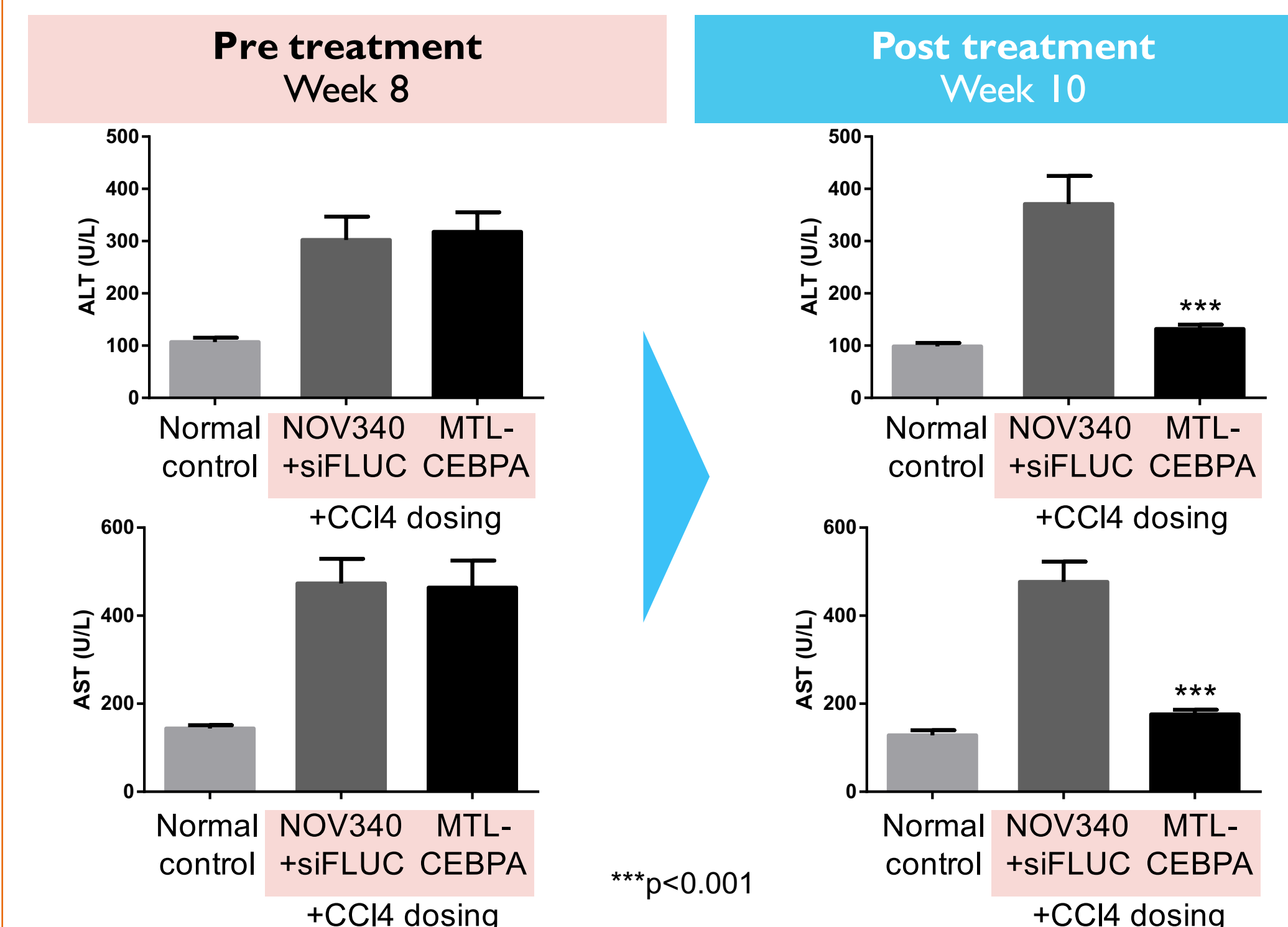
b) Reversal of liver stellate cell activation at Week 10



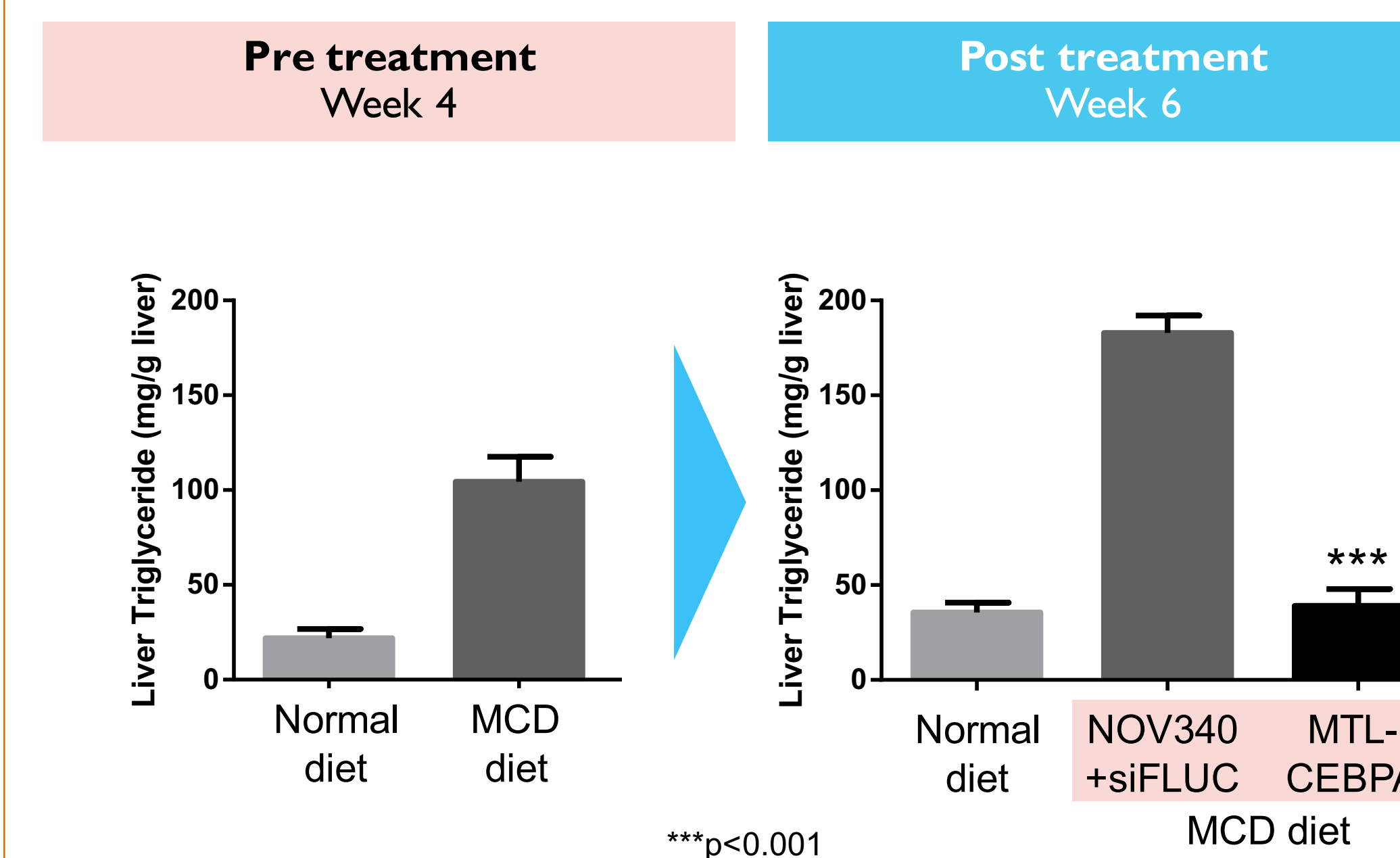
3. MTL-CEBPA restores normal liver function in CCl4 induced cirrhotic liver



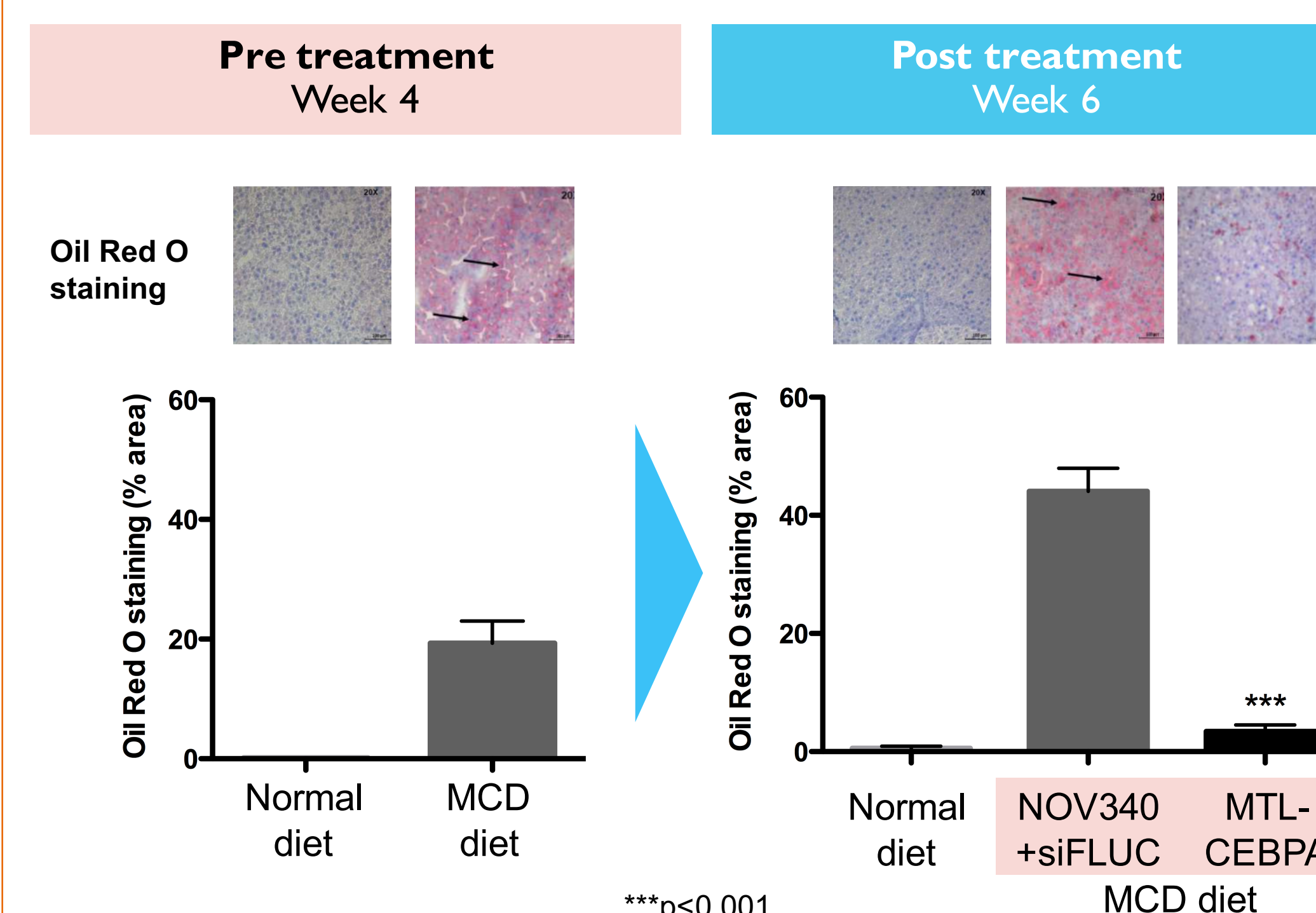
4. MTL-CEBPA reverses markers of liver injury in CCl4 induced cirrhotic liver



5. MTL-CEBPA reverses elevated liver triglycerides to normal levels in MCD diet model of NASH



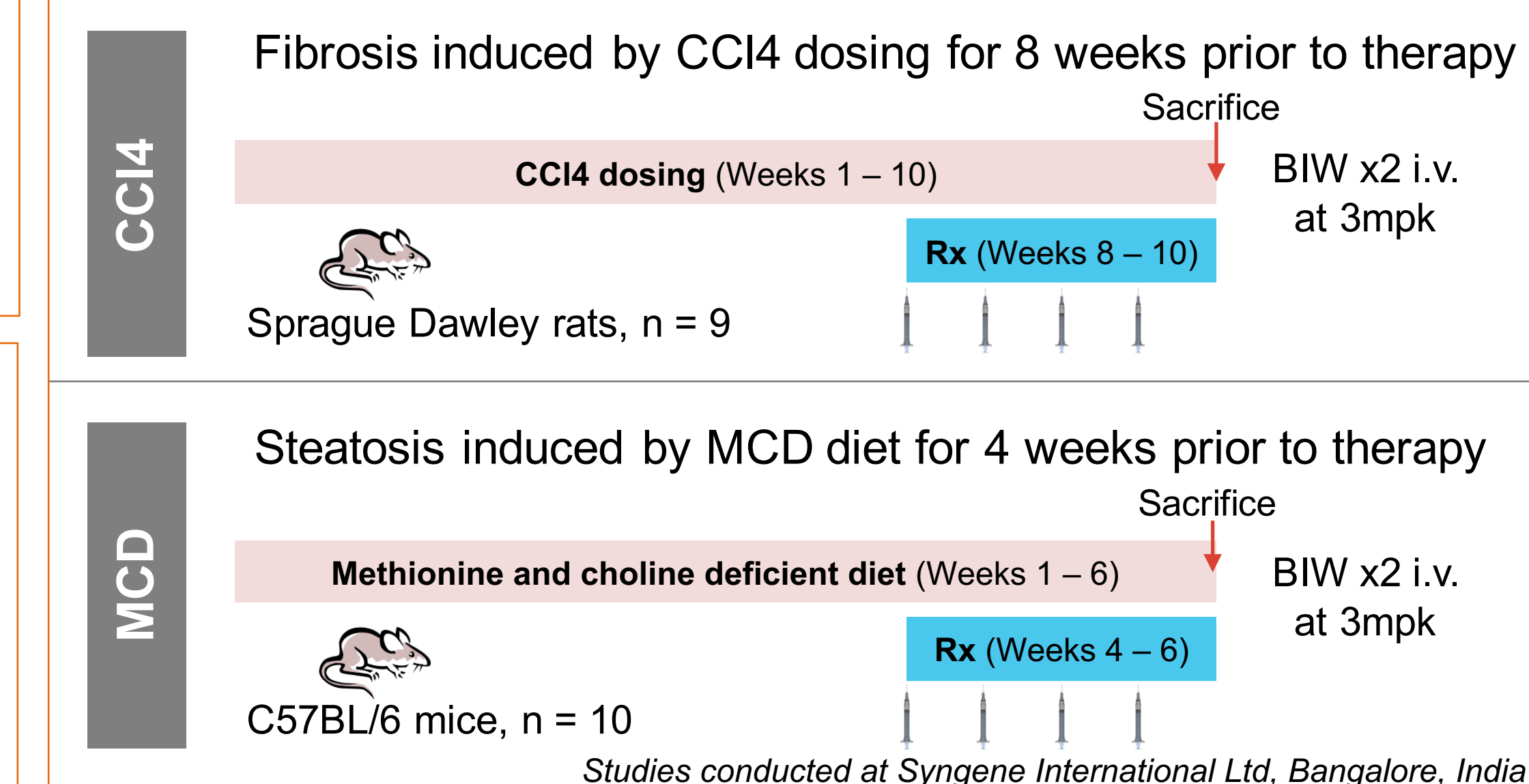
6. MTL-CEBPA reverses steatosis in MCD diet model of NASH



SUMMARY & CONCLUSIONS

- Administration of MTL-CEBPA to cirrhotic livers from CCl4 treated mice increased CEBPA mRNA levels confirming the ability of CEBPA-51 delivered with the SMARTICLESTM vehicle to restore CEBPA mRNA to near normal levels after just 4 doses of the drug (Fig 1).
- The increase in CEBPA mRNA was accompanied by a reduction in fibrosis (measured by levels of liver hydroxyproline) and stellate cell activation in the CCl4 fibrosis model (Fig 2). In the MCD diet model there was a dramatic reduction in liver triglyceride levels and reversal of liver steatosis (Fig 5 and 6).
- In the CCl4 model, treatment improved liver function as judged by a reduction in bilirubin to near normal levels and an increase in albumin (a target gene of C/EBP- α) (Fig 3) coupled with very significant reductions in ALT and AST (Fig 4). Similar improvements in liver function were also seen in the MCD diet model (results not shown).
- Overall the data demonstrate in these pre-clinical models that saRNA to CEBPA delivered to the liver using a SMARTICLESTM formulation can result in a very significant impact on both fibrosis and steatosis and improvement in liver function.
- Based on these results and also positive data in a liver cancer model (data not shown) MTL-CEBPA has advanced into a clinical trial in patients with liver cancer. The trial will look for evidence of improved liver function, impact on circulating triglyceride levels and liver fibrosis, aiming to validate clinically this exciting pre-clinical data in fibrosis and NASH models.

STUDY DESIGNS



REFERENCES

- Portnoy V et al, saRNA-guided Ago2 targets the RITA complex to promoters to stimulate transcription. Cell Research 26, 320-335, 2016
- Kalantari R et al, Regulation of mammalian transcription and splicing by nuclear RNAi. Nucleic Acids Research 44, 524-37, 2016
- Reebye V et al, A novel RNA oligonucleotide improves liver function and inhibits liver carcinogenesis in vivo. Hepatology 59, 216-27, 2014