The clinical candidate MTL-CEBPA leads to significant reduction in ascites and improvement in overall survival in a CCl4-induced liver failure model

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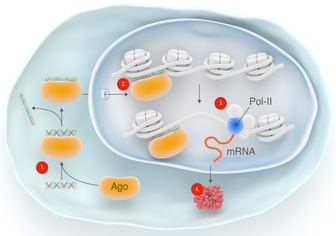
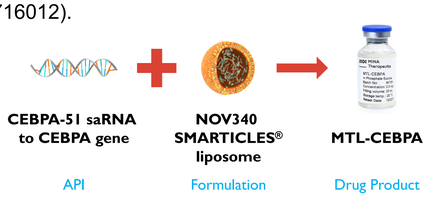
BACKGROUND

Small activating RNAs (saRNAs) are short double stranded oligonucleotides designed to up-regulate their target gene by transcriptional activation. 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.



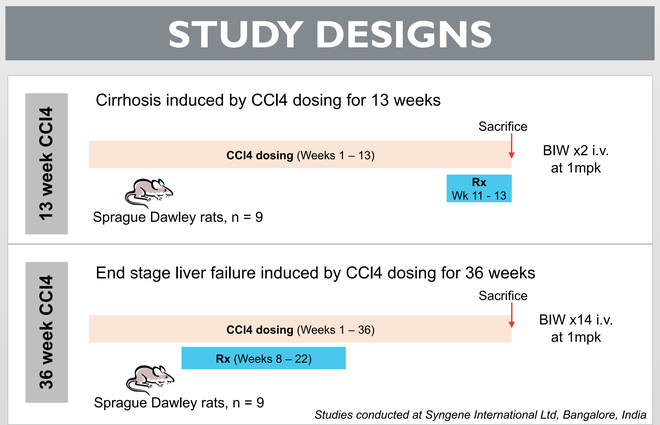
1. Loading of saRNA into Ago protein
2. saRNA-Ago targets gene promoter
3. saRNA-Ago activates gene transcription
4. Long lasting protein up-regulation

MTL-CEBPA is a liposomal formulation of a saRNA targeting for transcriptional up-regulation the transcription factor C/EBP-α (CCAAT/enhancer-binding protein alpha), a master regulator in the liver. In pre-clinical models MTL-CEBPA has previously been shown to restore expression of CEBPA liver mRNA to normal levels and to reverse liver fibrosis and liver steatosis. MTL-CEBPA is currently in clinical development in patients with liver cancer (ClinicalTrials.gov – NCT02716012).



In the studies reported here we demonstrate that MTL-CEBPA reverses features of liver cirrhosis and promotes increased survival in pre-clinical models of liver failure. The data supports clinical investigation of MTL-CEBPA in patients with liver failure.

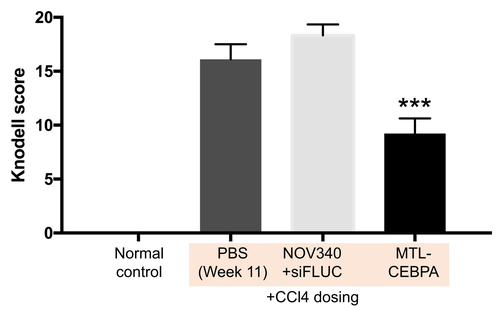
STUDY DESIGNS



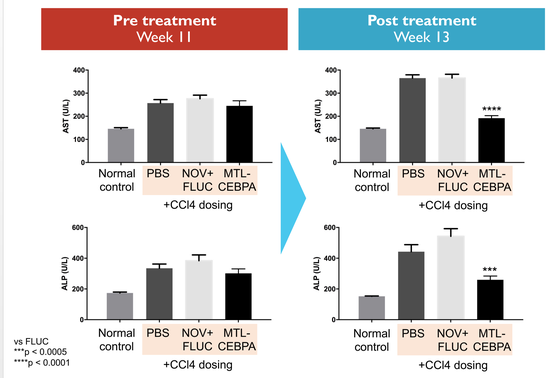
Studies conducted at Syngene International Ltd, Bangalore, India

RESULTS

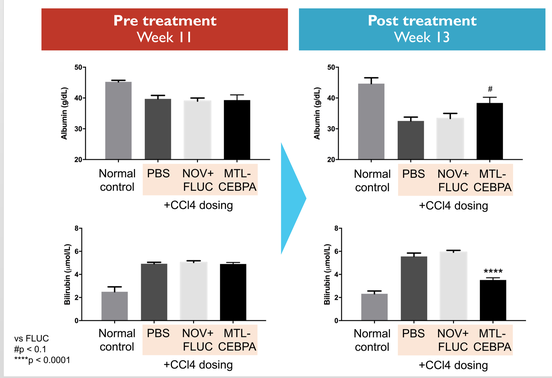
1. MTL-CEBPA reverses histological features of liver fibrosis at Week 13



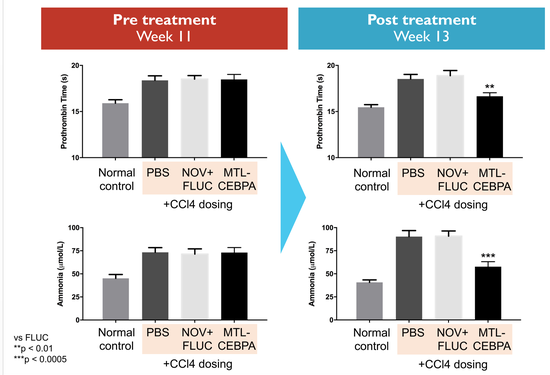
2. MTL-CEBPA reverses markers of liver injury at Week 13



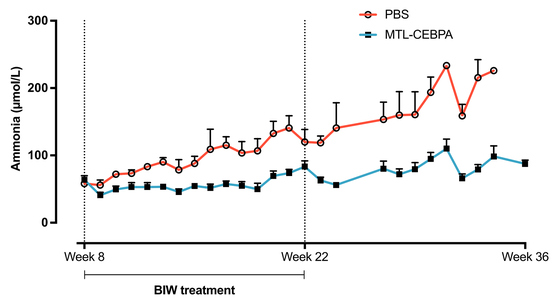
3. MTL-CEBPA restores normal liver function at Week 13



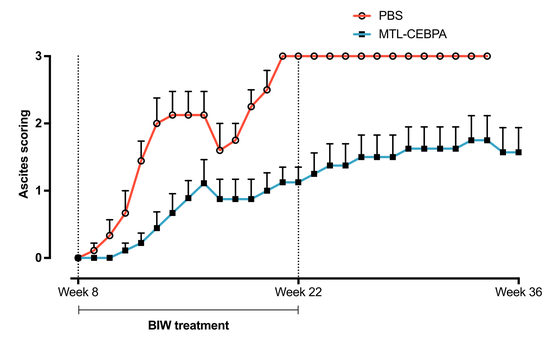
4. MTL-CEBPA restores normal liver function at Week 13



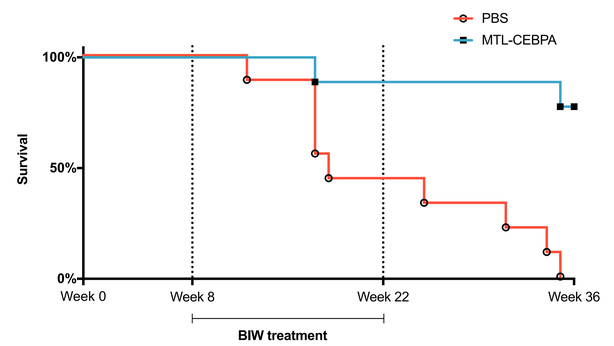
5. MTL-CEBPA attenuates hyper-ammonaemia up to Week 36



6. MTL-CEBPA attenuates ascites up to Week 36



7. MTL-CEBPA improves Week 36 survival



SUMMARY & CONCLUSIONS

- In the 13 week model, two week treatment of MTL-CEBPA reversed histological features of liver fibrosis (Fig 1) as well as markers of liver injury (Fig 2). 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).
- Similar liver function benefits were seen in the 36 week model both during and beyond 14 week treatment with MTL-CEBPA. In addition MTL-CEBPA attenuated hyperammonaemia (Fig 5) and ameliorated ascites (Fig 6). Liver function benefits culminated in a significant improvement in survival (Fig 7).
- Overall the data demonstrate in these pre-clinical models that saRNA to CEBPA delivered to the liver using a SMARTICLES® formulation can result in a very significant impact on both liver failure and survival.
- 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, aiming to validate clinically this exciting pre-clinical data in models of liver failure.

REFERENCES

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