CONTROL ID: 2548102

PRESENTATION TYPE: Oral or Poster

CURRENT CATEGORY: Portal Hypertension and Other Complications of Cirrhosis

CURRENT DESCRIPTORS: PO1. Experimental

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

AUTHORS (FIRST NAME, LAST NAME): Vikash Reebye[1], Jon Voutila[2], David Blakey[2], Robert Habib[2], Onkaramurthy Mallappa[3], Anjaneyulu Muragundla[3], Aravindakshan Jayaprakash[3], Hans Huber[4], Pal Saetrom[5], John Rossi[6], Nagy Habib[1]

INSTITUTIONS (ALL):

1. SURGERY, IMPERIAL COLLEGE LONDON, London, United Kingdom.
2. MiNA Therapeutics, London, United Kingdom.
3. Syngene International Ltd,, Bangalore, India.
4. BioTD Strategies, Lansdale, PA, United States.
5. Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.
6. Department of Molecular and Cellular Biology, Beckman Research Institute of City of Hope, City of Hope, Duarte, CA, United States.

ABSTRACT BODY:

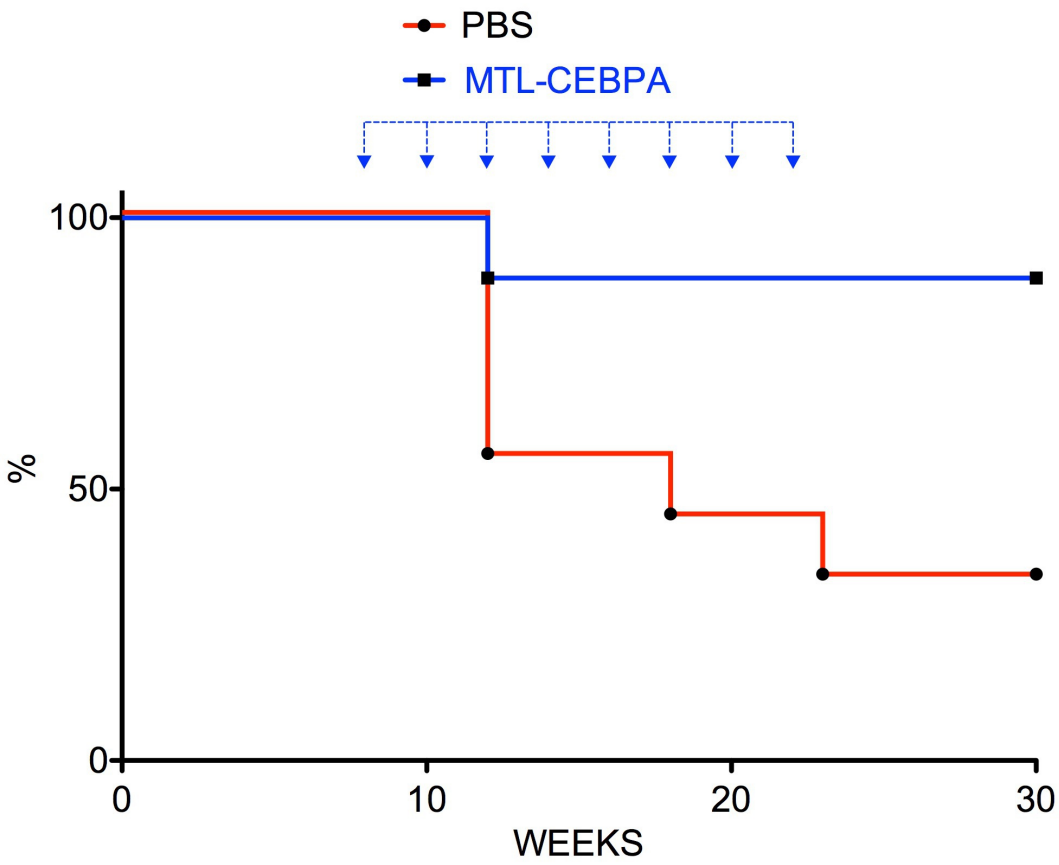
Abstract Body: Background: We have developed a small activating RNA, CEBPA-51, that upregulates the transcription factor CCATT/enhancer binding protein alpha (C/EBP-α) and formulated it in SMARTICLES® (MTL-CEBPA) for liver delivery. MTL-CEBPA is currently in clinical trials in patients with liver cancer. Here we show long term treatment of MTL-CEBPA improves survival in a CCl4 model of acute liver failure.

Methods: Liver fibrosis/acute failure was induced in Sprague Dawley rats by i.p. injection of CCl4 for 28 weeks. At week 8, rats (n=9) were treated with twice weekly i.v. of PBS or 1mg/kg MTL-CEBPA for 14 weeks. Liver function parameters and the degree of ascites and overall survival was monitored.

Results: After 4 weeks of MTL-CEBPA treatment, serum albumin (a direct target of C/EBP-α) significantly increased ($p<0.05$) and bilirubin levels significantly decreased ($p<0.001$) when compared to PBS. Liver toxicity and function: AST (50%), ALT (57%), prothrombin time (17%) and ammonia (42%) all showed significant improvement (% values) by week 14 when compared to PBS. All effects were maintained for 28 weeks. After 14 weeks of CCl4 treatment 8/9 of the PBS group animals had very significant ascites compared to only 2/9 in the MTL-CEBPA treatment animals. In terms of overall survival, by week 28, 6/9 animals in the PBS group were deceased vs just 1/9 animals in the MTL-CEBPA treated animals ($p<0.01$).

Conclusion: MTL-CEBPA increases serum albumin and decreases serum bilirubin. This was accompanied by a significant reduction in serum liver enzymes and improvement in liver function. The levels of ascites were dramatically reduced and a significant improvement in overall survival was seen post treatment with MTL-CEBPA. These data strongly support exploring the clinical development of MTL-CEBPA in liver failure.

(no table selected)



MTL-CEBPA survival

Co-Author Disclosure Status

The following authors have completed their AASLD 2016 disclosure:: Vikash Reebye: Disclosure completed | Jon Voutila: No Answer. | David Blakey: No Answer. | Robert Habib: No Answer. | Onkaramurthy Mallappa: No Answer. | Anjaneyulu Muragundla: No Answer. | Aravindakshan Jayaprakash: No Answer. | Hans Huber: No Answer. | Pal Saetrom: No Answer. | John Rossi: No Answer. | Nagy Habib: No Answer.