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TITLE: Systemic administration of a novel development candidate, MTL-CEBPA, up-regulates the liver-enriched transcription factor C/EBP-α and reverses CCl_4-induced liver failure *in vivo*.
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ABSTRACT BODY:
Abstract Body: The transcription factor CCATT/enhancer binding protein alpha (C/EBP-α) is known to have an important regulatory role in the maintenance of normal hepatocyte function and response to injury. We developed a small activating RNA (saRNA) that was demonstrated to significantly up-regulate C/EBP-α expression in primary hepatocytes. This saRNA was subsequently encapsulated in an anionic liposome as a development candidate for clinical use (MTL-CEBPA). Liver failure was induced in Sprague Dawley rats by twice weekly i.p. injection of CCl_4 for a duration of 8 weeks. For a further 2 weeks of the CCl_4 regiment, animals were treated by twice weekly i.v. injection of MTL-CEBPA via tail vein at 0.3mg/kg, 1mg/kg and 3mg/kg.

We demonstrate reversal and near normalisation of clinically relevant parameters following all treatment doses of MTL-CEBPA including, at 3mg/kg, bilirubin (64% decrease), circulating alanine and aspartate aminotransferase (59% and 62% decrease respectively) and prothrombin time (19% decrease). We also observed a significant increase in serum albumin and total protein as well as a significant decrease in alkaline phosphatase and gamma-glutamyl-transpeptidase. Liver hydroxyproline significantly decreased in a dose-dependent manner in addition to a significant increase in body weight with no associated toxicity.

Here we present a novel development candidate, MTL-CEBPA, that safely up-regulates C/EBP-α, as a potential treatment for liver failure *in vivo*. Clinical studies with MTL-CEBPA are expected to begin in early 2016.
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Co-Author Disclosure Status

The following authors have completed their AASLD 2015 disclosure:: Vikash Reebye: Disclosure completed | Jon Voutila: Disclosure completed | Kai-Wen Huang: Disclosure completed | Anjaneyulu Muragundla: Disclosure completed | Aravindakshan Jayaprakash: Disclosure completed | Prashant Vadnal: Disclosure completed | Hans Huber: Disclosure completed | Robert Habib: Disclosure completed | Pål Sætrom: Disclosure completed | John Rossi: No Answer. | Nagy Habib: Disclosure completed