CONFLICT OF INTEREST
Manuel Romero-Gómez was inventor of THDP-17, a glutaminase inhibitor, which was licensed by Janus Development, S.L. He has ongoing research collaboration with Umecrine, S.A., Sweden. He has also received speaker fees from Bama-Geve, Merz and Norgine, S.A.

Hepatic encephalopathy (HE) is a major complication of liver cirrhosis, and is classified into three types: Type A (acute) HE is due to with acute liver failure (ALF); Type B (by-pass) HE is due to portal-systemic shunting without intrinsic liver disease; and Type C (cirrhosis) HE occurs in patients with underlying cirrhosis. However, the appearance of hepatic encephalopathy in patients with acute-on-chronic liver failure was not included in this classification. HE manifests as a spectrum ranging from minimal disturbance in mental function that impacts on attention, cognition and quality of life to coma. Hepatic encephalopathy is a complex neuropsychiatric syndrome in patients with liver dysfunction or porto-systemic shunts. Stages of HE have been defined by West-Haven criteria: Stage 0 means no abnormality detected. Stage 1 trivial lack of awareness with shortened attention span, euphoria and anxiety and inability to do easy calculations. Stage 2 is characterized by lethargy, disorientation for time, changes in personality, inappropriate behaviour. Stage 3 was defined by somnolence and semi stupor, keeping response to stimuli with confusion, gross disorientation for time and space and bizarre behaviour. Stage 4 was defined by coma.

HE in patients with cirrhosis decompensation without criteria for ACLF has been strongly related to previous episodes of hepatic encephalopathy and the abuse of diuretics, but not with hyponatremia, infections or alcohol binge. Interestingly, GI bleeding seems to protect against HE instead to promote it. Improvement in the management of variceal bleeding avoiding infections and controlling bleeding could explain, at least in part, this result. On the other hand, in patients with ACLF, HE was also associated with previous bouts of overt HE but not with diuretics abuse, GI bleeding, alcohol binge or infections. These precipitant factors were equally distributed in patients with and without HE. The strong association between previous bouts of overt HE and HE support the hypothesis of the impact of gene alteration on the risk of developing HE. A microsatellite in the promoter region of glutaminase type K gene has been associated with increased risk of HE (form long-long of the microsatellite). However, other genes could be implicated on HE and a GWAS analysis is warranted to define the
genetic profile associated with risk of overt HE in cirrhotics. Diuretics-induced renal insufficiency seems to be a major cause of HE in cirrhotics with acute decompensation, highlighting the role of kidneys on HE. Brain impairment appeared as consequence of hyperammonemia in the brain, oxidative stress, activation of microglia, hyponatremia and benzodiazepine-like substances able to promote an astrocyte-neuron dysfunction, neurological basis for HE.

In the management of patients with HE and liver dysfunction is mandatory to exclude other causes of neurological or psychiatric disorders and keep in mind other types of encephalopathy like sepsis or hyponatremia. Mental status should be explored using Glasgow scale. Nutritional assessment should also be included. Biochemical analysis include: full blood count, liver and kidney function, electrolytes, ammonia, thyroid function, inflammatory reactant, glycaemia, vitamin B12 and urine analysis. Patients with HE and ACLF should be admitted in the intensive care unit. The first step is removing any precipitant factor or treating it (infections by antibiotics; diuretics abuse: volume expansion; alcohol binge: thiamine and in cases of malnutrition nutritional support). If no precipitant factor was detected with have to focus on modulation of inflammation plus ammonia lowering drugs. In patients without response and preserved liver function, large porto-systemic shunts should be ruled out and embolised if present. Lastly, liver transplantation remained as the therapeutic option in patients with HE without response to all mentioned measures.

Several ammonia-lowering drugs are also able to avoid glutamine accumulation (that could serve as substrate for glutaminase transforming it into glutamate and ammonia –Trojan Horse hypothesis-) excreting by urine it in form of phenylacetyl-glutamine. Ornithine-phenylacetate and glycerol or sodium phenylacetate belonged to this type of drugs. CB-839 a glutaminase inhibitor demonstrated in portacaval shunted rats its ability as ammonia lowering drug. The role of these drugs in management of overt HE requires future studies.