Investigational therapies for hepatic encephalopathy and soft tissue calcifications

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Ammonia is a potentially neurotoxic compound that is predominantly generated by the catabolism of amino acids and the hydrolysis of urea in the intestine. Defects in ammonia detoxification pathways due to an impaired liver function can lead to hyperammonemia and hepatic encephalopathy, a disease with a wide-spectrum of neurological symptoms (1). Unfortunately, treatment options for this disease are limited, and severe hyperammonemic cases necessitate the patients to be hemodialyzed in order to quickly clear ammonia from the bloodstream. We previously shown that transmembrane pH-gradient micrometer-sized liposomes with an acidic core could efficiently capture and retain ammonia in its protonated form after administration in the peritoneal cavity. The ammonia accumulates in the lumen of the liposomes, and the latter are then removed after the peritoneal dialysis session (2). These liposomes were shown to be effective and safe in rats and minipigs, prompting their advancement in clinical trials (2-4). Since ammonia is partly produced in the gut via the bacterial metabolism of urea, we also sought to develop a novel oral treatment of hepatic encephalopathy by reducing colonic production of ammonia via the use of urease inhibitors. Inspired by earlier work (8), we investigated the in vitro activity of a series of novel hydroxamic acids (HA) on rat caecum content. We identified a lead candidate with a potency largely exceeding that of HA derivatives tested in former clinical trials. Finally, another line of research involving the development of new calcification inhibitors has prospered in our laboratory. This work was in part inspired by our former research on polymeric chelating agents. We discovered that oligoethylene glycol (OEG) derivatives of the natural compound myo-inositol hexakisphosphate (IP6) were highly potent to inhibit vascular (5) and kidney calcifications (6), both originating from various chronic diseases.

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References

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