Chapter 7

Conclusions and Future directions
7. Conclusions and future directions

In summary (Chapter 3), the present studies for the first time report that APD668, a GPR119 agonist inhibits intestinal lipid absorption in oral fat tolerance test in mice. APD668 improved fat tolerance could be due to increased GLP-1 levels and inhibition of gastric emptying through via GPR119 receptor activation in mice. In addition, our results demonstrate strong in-vivo evidence of protection of fatty liver by APD668 in three different murine models of NASH. In High Trans-Fat (HTF) diet model, APD668 showed reduction in circulating cholesterol, glucose, triglyceride, ALT, AST levels and improved insulin sensitivity which might be beneficial effect for NASH patients. In Chapter 4, combination of APD668 with linagliptin additively prevented development of non-alcoholic steatohepatitis in HTF diet fed mice. We thought that APD668 showed beneficial effects could be due to combination of direct activation of GPR119 receptors in intestine and hepatic tissues and elevated GLP-1 (indirect effect) may simultaneously contribute to the reduction in triglyceride uptake and hepatic lipogenesis in HTF diet fed mice. In Chapter 5, we found that combination of APD668 with linagliptin has the potential to improve NASH associated with fibrosis through its anti-steatotic, anti-oxidant and anti-inflammatory activity in low dose streptozotocin plus high fat diet induced steatohepatitis with diabetes in neonatal C57BL/6 mice. In Chapter 6, APD668 at an optimum doses demonstrated attenuation of fatty liver in MCD diet induced steatohepatitis mice model. Once daily (25 mg/kg) regimen of APD668 showed greater and sustained reduction in ALT levels compared with b.i.d. and alternate day b.i.d. regimen in mice. In this study, APD668 alone or in combination with linagliptin improved hepatic injury markers and raised HDL-cholesterol levels in MCD diet fed mice. Taken together, all these findings suggest that GPR119 receptor agonist alone or in
combination with DPPIV inhibitors may represent a promising therapeutic strategy for the treatment of non-alcoholic steatohepatitis.

The present thesis work had some limitations. At present, we have not investigated the molecular mechanisms responsible for protective effects of APD668 in aforementioned NASH models such as lipogenesis gene expressions/proteins in hepatic tissues. However, previously the mechanism of action for anti-steatotic effect of GPR119 agonist (MBX2982) has been reported. In addition, the expression of GPR119 receptors in liver or adipose tissues during NASH/NAFLD progression has not yet been investigated. Therefore, it is important to assess potential effect of APD668 on relevant gene expressions/proteins in liver or adipose tissues preferentially in high fat diet induced NASH models. Moreover, we observed paradoxical effects at a high dose of APD668 (25 mg/kg; b.i.d.) which could be due to desensitization of GPR119 receptors in both HTF and MCD diet induced NASH models. Thus, extensive investigative studies are warranted to verify whether desensitization is compound specific or a target related phenomenon with respect to end parameter(s) and dosage regimen. To date, there are limited publications that have explored the role of GPR119 in the development of fibrosis. Certainly, recent scientific findings warrant further investigations to elucidate the role of GPR119 in the progression of NASH/NAFLD.