# Table of Contents

Abstract ................................. i  
Acknowledgments ........................ ii  
Table of Contents ................................ iii  
List of Figures ............................. viii  
List of Tables .............................. xi  
List of Abbreviations ......................... xiii  
Dedication .................................. xvi  

Chapter 1 Introduction ......................... 1  

1.1 Non-Alcoholic Fatty Liver Disease (NAFLD) 2  
1.1.1 Non-Alcoholic Fatty Liver (NAFL) ........ 2  
1.1.2 Non-Alcoholic SteatoHepatitis (NASH) ... 2  
1.1.3 NASH associated with fibrosis and cirrhosis 3  
1.1.4 Epidemiology .......................... 4  
1.1.5 Unmet Medical Need ..................... 4  

1.2 Pathophysiology of NASH ................. 4  
1.2.1 Hepatic Steatosis ....................... 4  
1.2.2 Insulin Resistance ..................... 5  
1.2.3 Inflammation and Oxidative Stress .... 5  
1.2.4 Multiple Parallel Hit Theory .......... 6  
1.2.5 Fibrosis ................................ 8  
1.2.6 Diagnosis of NASH ................. 8  

1.3 References ............................ 9  

Chapter 2 Current Pharmacotherapies for NASH 12  

2.1 Incretin Based Therapies .................. 14
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.1 GLP-1 Receptor Agonists</td>
<td>15</td>
</tr>
<tr>
<td>2.1.2 DPPIV Inhibitors</td>
<td>15</td>
</tr>
<tr>
<td>2.2 Anti-dyslipidemic Agents</td>
<td>16</td>
</tr>
<tr>
<td>2.2.1 Fibrates</td>
<td>16</td>
</tr>
<tr>
<td>2.3 GPR119: A Novel Therapeutic Target for NASH</td>
<td>17</td>
</tr>
<tr>
<td>2.3.1 GPR119: Discovery and Receptor Expression</td>
<td>17</td>
</tr>
<tr>
<td>2.3.2 GPR119: Signaling and Physiological Functions</td>
<td>18</td>
</tr>
<tr>
<td>2.3.3 GPR119 Agonists: Preclinical Pharmacology</td>
<td>19</td>
</tr>
<tr>
<td>2.3.4 GPR119 Agonist: Anti-diabetes Therapy</td>
<td>20</td>
</tr>
<tr>
<td>2.3.5 GPR119 Agonist: Anti-obesity Therapy</td>
<td>21</td>
</tr>
<tr>
<td>2.3.6 GPR119 Agonist: Anti-NASH Therapy</td>
<td>22</td>
</tr>
<tr>
<td>2.3.7 GPR119 Agonists: Clinical Pharmacology</td>
<td>24</td>
</tr>
<tr>
<td>2.4 Hypothesis</td>
<td>25</td>
</tr>
<tr>
<td>2.5 Aim</td>
<td>27</td>
</tr>
<tr>
<td>2.6 References</td>
<td>27</td>
</tr>
</tbody>
</table>

**Chapter 3** APD668, a G protein-coupled receptor 119 agonist improves fat tolerance and attenuates fatty liver in high trans-fat diet induced steatohepatitis model in C57BL/6 mice

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Abstract</td>
<td>41</td>
</tr>
<tr>
<td>3.2 Introduction</td>
<td>42</td>
</tr>
<tr>
<td>3.3 Material and Methods</td>
<td>43</td>
</tr>
<tr>
<td>3.3.1 Chemicals</td>
<td>43</td>
</tr>
<tr>
<td>3.3.2 Animals and experimental protocol</td>
<td>44</td>
</tr>
<tr>
<td>3.3.3 Oral Fat Tolerance Test (OFTT)</td>
<td>44</td>
</tr>
<tr>
<td>3.3.4 Effect of APD668 on gastric emptying in mice</td>
<td>46</td>
</tr>
</tbody>
</table>
3.3.5 Tyloxapol induced acute hyperlipidemia in mice

3.3.6 Repeat administration of APD668 in HTF diet induced steatohepatitis model in mice

3.3.7 Measurement of hepatic triglyceride and cholesterol

3.3.8 Statistical Analysis

3.4 Results

3.5 Discussion

3.6 References

Chapter 4 Co-administration of APD668, a G protein-coupled receptor 119 agonist and Linagliptin, a DPPIV inhibitor, prevents progression of steatohepatitis in mice fed on a high trans-fat diet

4.1 Abstract

4.2 Introduction

4.3 Material and Methods

4.3.1 Chemicals

4.3.2 Animals and experimental protocol

4.3.3 Measurement of plasma biochemical and metabolic markers

4.3.4 Measurement of hepatic triglyceride and cholesterol

4.3.5 Histological analysis

4.3.6 Statistical Analysis

4.4 Results

4.5 Discussion

4.6 References

Chapter 5 Combination of APD668, a G protein-coupled receptor 119 agonist with Linagliptin, a DPPIV inhibitor, prevents progression of
6.3.2 Animals and experimental protocol…………………………………… 115
6.3.3 Effect of APD668 (6.25, 12.5 and 25 mg/kg) on the development of steatohepatitis in MCD diet fed mice…………………………………… 116
6.3.4 Time-dependent activity of different regimens of APD668 (25 mg/kg) on the development of steatohepatitis in MCD diet fed mice…………………………………………………………………... 116
6.3.5 Effect of combination of APD668 with linagliptin or fenofibrate on the development of steatohepatitis in MCD diet fed mice………………… 117
6.3.6 Determination of plasma ALT, AST and lipid levels………………….. 117
6.3.7 Determination of hepatic triglyceride and cholesterol………………… 117
6.3.8 APD668 levels in Plasma……………………………………………… 118
6.3.9 Statistical Analysis……………………………………………………… 119
6.4 Results…………………………………………………………………… 120
6.5 Discussion………………………………………………………………… 128
6.6 References………………………………………………………………… 131

Chapter 7 Conclusions and Future directions…………………………….. 135

List of Approved IAEC Protocols…………………………………………… 138

List of Publications…………………………………………………………… 139

List of Conferences attended……………………………………………… 143