PCSK9 Inhibition: 
From Genetics to Patients

John Chapman BSc, Ph.D., D.Sc., FESC
Research Professor, University of Pierre and Marie Curie
Director Emeritus, INSERM Dyslipidemia and Atherosclerosis Research Unit,
Past-President, European Atherosclerosis Society
Pitié-Salpetriere University Hospital, Paris, France
Unmet clinical needs in CVD: Focus on lipids

- LDL-C not at goal
- Familial hypercholesterolaemia
- Elevated Lp(a)
- Elevated TG-rich LPs, remnants
  - Low HDL-C

35% Statins / LDL-C
65% CV EVENTS (%)
What are the principal factors which regulate circulating LDL-C levels?

Can such mechanistic understanding identify new therapeutic targets?
Regulation of plasma LDL-C levels

- Rates of hepatic production of precursor VLDL
- Rates of intravascular remodelling of VLDL and LDL
- Rates of direct hepatic production of LDL
- Rates of hepatic LDL-R-mediated catabolism
- Rates of non-LDL-R-mediated LDL catabolism

VLDL very low-density lipoprotein; LDL low-density lipoprotein; LDL-R, LDL-receptor
Regulation of plasma LDL-C levels

- Rates of hepatic production of precursor VLDL
- Rates of intravascular remodelling of VLDL and LDL
- Rates of direct hepatic production of LDL
- Rates of hepatic LDL-R-mediated catabolism
- Rates of non-LDL-R-mediated LDL catabolism

VLDL very low-density lipoprotein; LDL low-density lipoprotein; LDL-R, LDL-receptor
Catabolism of LDL by the hepatic LDL-R

(Accessed January 2014)
PCSK9: Key regulator of LDL-R expression and LDL degradation

What is PCSK9?

Pro-protein convertase subtilisin-like kexin type 9

- A secreted protease which is a 692 amino acid mature protein, consisting of 3 domains: prodomain, catalytic and C-terminal
- Primarily expressed in liver, intestine and kidney
- Rapid turnover in plasma (<10 mins); plasma removal principally via the LDL-R
PCSK9 binding to the LDL-R

Impact of PCSK9 on the hepatic LDL-R

- LDL receptor numbers on the cell surface decrease as a result of enhanced intracellular degradation of the LDL-R
- Plasma LDL levels rise
Does variation in the PCSK9 gene alter its function, with impact on circulating LDL levels?

- **Gain of function (GoF) missense mutations** = genetic hypercholesterolaemia (FH phenotype)

- **Loss of function (LoF) nonsense mutations** = hypocholesterolaemia with low LDL levels and major reduction in CHD incidence
PCSK9 GoF mutations =

Severe hypercholesterolaemia

Clinical characteristics and fasting lipid values (mmol/l) in patients heterozygous for mutations N157K and D374Y in the PCSK9 gene and close relatives

<table>
<thead>
<tr>
<th>Family</th>
<th>ID</th>
<th>Sex</th>
<th>Age</th>
<th>Mutation</th>
<th>Total serum cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglycerides</th>
<th>LDL cholesterol</th>
<th>Xanthomas</th>
<th>CHDa</th>
</tr>
</thead>
<tbody>
<tr>
<td>0034</td>
<td>FH122</td>
<td>Female</td>
<td>42</td>
<td>D374Y</td>
<td>13.6</td>
<td>1.0</td>
<td>1.01</td>
<td>12.1</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>0034</td>
<td>FH123</td>
<td>Male</td>
<td>45</td>
<td>-</td>
<td>6.5</td>
<td>Not determined</td>
<td>Not determined</td>
<td>Not determined</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0034</td>
<td>FH121</td>
<td>Female</td>
<td>19</td>
<td>D374Y</td>
<td>13.6</td>
<td>0.8</td>
<td>2.05</td>
<td>11.9</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>0034</td>
<td>FH120</td>
<td>Female</td>
<td>21</td>
<td>D274Y</td>
<td>8.9</td>
<td>1.0</td>
<td>0.56</td>
<td>7.4</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>0075</td>
<td>FH75a</td>
<td>Male</td>
<td>40</td>
<td>D374Y</td>
<td>11.6</td>
<td>1.4</td>
<td>1.4</td>
<td>9.6</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>0075</td>
<td>FH85c</td>
<td>Female</td>
<td>35</td>
<td>-</td>
<td>6.3</td>
<td>Not determined</td>
<td>Not determined</td>
<td>Not determined</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0075</td>
<td>FH75d</td>
<td>Male</td>
<td>7</td>
<td>D374Y</td>
<td>8.8</td>
<td>1.5</td>
<td>0.9</td>
<td>6.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0075</td>
<td>FH75b</td>
<td>Female</td>
<td>16</td>
<td>D374Y</td>
<td>8.1</td>
<td>1.0</td>
<td>0.8</td>
<td>6.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0305</td>
<td>0481</td>
<td>Female</td>
<td>25</td>
<td>N157K</td>
<td>11.8</td>
<td>Not determined</td>
<td>0.7</td>
<td>Not determined</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*CHD, coronary heart disease manifested as angina pectoris and myocardial infarction.

Leren TP. Clin Genet 2004; 65: 419–22
### Population studies: PCSK9 LoF mutations

- **Subjects with LoF mutations in PCSK9 or total lack of PCSK9**

- **Have naturally low levels of LDL-C and reduced CHD (→ efficacy)**

- **These mutations are not associated with other detectable abnormalities (→ safety)**

<table>
<thead>
<tr>
<th></th>
<th>PCSK9 Mutation</th>
<th>LDL-C Reduction</th>
<th>CHD Reduction</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benn et al. JACC 2010</td>
<td>R46L</td>
<td>12%</td>
<td>46%</td>
<td>Copenhagen City Heart Study n=10,032</td>
</tr>
<tr>
<td>Benn et al. JACC 2010</td>
<td>R46L</td>
<td>14%</td>
<td>47%</td>
<td>Copenhagen General Population Study n=26,013</td>
</tr>
<tr>
<td>Benn et al. JACC 2010</td>
<td>Y142X or C679X</td>
<td>28%</td>
<td>88%</td>
<td>Copenhagen Ischemic Heart Disease Study n=9654</td>
</tr>
<tr>
<td>Cohen et al. NEJM 2006</td>
<td>R46L</td>
<td>12%</td>
<td>46%</td>
<td>Atherosclerosis Risk Community Study (US)</td>
</tr>
<tr>
<td>Cohen et al. NEJM 2006</td>
<td>Y142X or C679X</td>
<td>14%</td>
<td>47%</td>
<td>(Black patients, n=3363; white patients, n=9524)</td>
</tr>
</tbody>
</table>

LoF PCSK9 mutations are associated with low LDL-C and low prevalence of CHD events

ARIC=Atherosclerosis Risk in the Community
PCSK9

Emergence as a new therapeutic target in hypercholesterolaemia and related CHD
PCSK9

Potential targets in the PCSK9 pathway

1. Reduction of PCSK9 protein production
2. Reduction of PCSK9 mRNA expression
3. Inhibition of PCSK9 binding to the LDL-R
4. Inhibition of PCSK9-mediated degradation of the LDL-R

Therapeutic agents targeting PCSK9

- Inhibition of the binding of PCSK9 to the LDL-R
  e.g. MABs, small peptides

- Inhibition of PCSK9 synthesis e.g. ASOs, siRNAs

- Inhibition of the intracellular processing of PCSK9 to the mature protein (small molecules)
PCSK9

A new therapeutic target in hypercholesterolaemia