Genetic Mutations that Severely Increase LDL-Cholesterol Levels and ASCVD (heart attacks and stroke) in Familial Hypercholesterolemic (FH) Patients: Key Therapeutic Targets

The worldwide prevalence of atherosclerotic cardiovascular diseases (ASCVD) such as heart attacks and stroke is a major public health and economic burden that is still expected to increase in the next decades.[1,2] Elevated circulating low-density lipoprotein cholesterol (LDL-Cholesterol) is positively correlated with premature development of ASCVD and death.[3-5] Subendothelial accumulation of LDL-Cholesterol in blood vessels is an important initiating event in atherosclerosis, leading to pathological accumulation of lipids, cell debris, chronic inflammation leading to severe ASCVD.[1,6] Through binding of apolipoprotein B100 (ApoB100), atherogenic plasma LDL particles are mainly cleared by LDL receptor (LDLR)-mediated endocytosis in the liver.[7] Heterozygous familial hypercholesterolemia (HeFH) is a common, underdiagnosed and undertreated genetic disease that affects 1 in 250 people.[8] FH patients inherit genetic mutations mostly in *LDLR* but also in *APOB*, *ARH* and *APOE* loci and have lifelong very high levels of circulating LDL-Cholesterol and premature development of ASCVD generally in their first decades of life.[9,10] In 2003, a third FH locus was identified in patients having a gain-of-function mutation in the gene encoding for proprotein convertase subtilisin/kexin type 9 *(PCSK9)*[11-13], a natural inducer of LDLR degradation.[14-16] A renewed clinical enthusiasm for new therapies originated from the discovery of loss-of-function genetic mutations at the *PCSK9* locus that robustly lower circulating LDL-Cholesterol (>80%) and reduce cardiovascular events up to ~88% in humans without any adverse effects.[17-21] Accordingly, PCSK9 was highlighted as a highly safe, genetically validated and unprecedented powerful target to lower LDL-Cholesterol and protect against ASCVD events such as heart attacks and stroke.

In hepatocytes[11], PCSK9 limits the capacity of the liver to clear excess of circulating LDL-Cholesterol by directly binding and inducing the degradation of the LDL receptor.[14,22] Clinical trials using anti-PCSK9 monoclonal antibodies that block PCSK9-LDLR interaction have shown to significantly reduce LDL-Cholesterol levels up to 70% on top of statins as compared to ~30% when statin is used as monotherapy.[23-25] In patients with stable cardiovascular disease, GLAGOV, FOURIER, OSLER and EBBINGHAUS Phase 3 clinical trials demonstrated that monthly-injected monoclonal PCSK9 antibodies significantly reduced LDL-Cholesterol, atherosclerotic plaque progression and prevented major cardiovascular events without any other adverse effects over a 2-year period.[26-29] With Pfizer that recently discontinued its PCSK9 Bococizumab program due to appearance of antidrug antibodies and lack of efficacy[30,31], only two PCSK9 monoclonal antibodies that got approval in 2015 (Repatha®, Amgen and Praluent®, Sanofi-Regeneron) and are used in the clinic. Unfortunately, due to high annual costs (~14,000$/year/patient) and chronic need of lipid-lowering therapies for the indicated group of patients, anti-PCSK9 antibodies do not reach incremental cost-effectiveness threshold and prescriptions are highly rejected from payers for high-risk patients with FH or history of ASCVD even with proven cardiovascular event reduction rates.[32,33] Alnylam Pharmaceuticals is developing PCSK9 RNA interfering injectable drugs that could potentially be used in the clinic at lower cost but safety still remains to be demonstrated in

much larger clinical trials.[34] Currently, there are no validated, cost-effective and orally available small molecule inhibitors targeting PCSK9 under development to fill the urgent needs of new lipid-lowering therapies for high-risk patients.

A recent international meta-analysis of over 200 clinical studies including more than 2 million participants with over 20 million person-years of follow-up and over 150 000 cardiovascular events unequivocally establishes a direct causal link between LDL-Cholesterol and incidence of major adverse cardiac events (MACE) such as heart attacks and stroke.[35] There is a consensus between clinicians and scientists that any mechanism of lowering plasma LDL-Cholesterol particle concentration significantly reduce the risk of ASCVD without no competing deleterious off-target effects.[36] A separate meta-analysis of data from 170 000 participants in 26 randomized trials concluded that annual rate of MACE decrease by 20% for each mmol/L reduction of circulating LDL-Cholesterol (~25% in normolipidemic patients).[37,38] Indeed, it is expected that PCSK9 inhibitors that increase LDL receptor and lower LDL-Cholesterol by 60% will prevent MACE by 50% over a 5-year period. Indeed, the FOURIER outcome trial already showed that anti-PCSK9 inhibitors (Repatha) reduced the risk for fatal or nonfatal MI or stroke by 19% at 1 year and by 33% at the end of 3 years.[27]

Statins, currently the most prescribed class of lipid-lowering drugs, decrease LDL-Cholesterol in the bloodstream only by ~30% mainly by increasing slightly LDL receptor levels in the liver.[39] In addition, combination of statins with ezetimibe, bile-acid sequestrants, or niacin produces an additional 10 to 20% decrease in LDL-Cholesterol.[40] However, even if these therapies can help achieve significant reductions in LDL-Cholesterol, more efficient lipid–lowering therapies are still needed, especially for patients with FH or history of ASCVD with very high, uncontrolled, LDL-Cholesterol levels. About 42 Million high-risk individuals in North America and Europe alone are either statin-intolerant and/or fail to achieve recommended LDL-Cholesterol targets.[41] In order to fill these important clinical needs, PCSK9 inhibitors or any therapies that strongly increase LDL receptor could be suitable to significantly reduce LDL-Cholesterol and prevent MACE in those high-risk patients. Indeed, a meta-regression analysis from 312 175 participants highlighted that upregulation of LDL receptor expression by statin and nonstatin therapies is the key target to reduce LDL-Cholesterol and to drastically reduce major cardiovascular events.[36]

MONOGENIC Pharmaceuticals have developed unprecedented and highly innovative cholesterol-lowering pipelines that robustly increase LDL receptor by targeting PCSK9 or other highly relevant and undisclosed mechanisms likely to be additive and distinct from statins. MONOGENIC Pharmaceuticals has prioritized orally available, nontoxic and highly potent small molecule inhibitors that robustly reduce LDL-Cholesterol in animal models fed a high cholesterol diet.

Our preclinical data demonstrated remarkable lipid-lowering proprieties of our orally available drug candidates similar to costly and injectable PCSK9 inhibitors. We are confident that our efforts will fulfill the urgent needs of affordable medications for high risk ASCVD and familial hypercholesterolemic patients.

Unmet Clinical Needs

US and European Population
~1 Billion

People with high cholesterol (35 to 74 years)
Eligible for Lipid-lowering therapy (LLTs)
(≥ 200mg/dL or ≥ 5.0 mmol/L)
~278 Million

Untreated or Underdiagnosed
~143 Million

~ 50% on LLTs
(~97% statins therapy)
~135 Million

~33% Uncontrolled Cholesterol
≥ 100 mg/dL (high risk)
≥ 130 mg/dL (intermediate risk)
≥ 160 mg/dL (low risk group)
~45 Million
MONO4

High risk patients (35 to 74 years)
Familial Hypercholesterolemia (FH)
and/or
History of Heart Disease (ASCVD)
(LDL-C ≥ 70mg/dL)
~41.2 Million
MONO4

On statins, statin-intolerant
Eligible for Additional LLTs
(LDL-C ≥ 70mg/dL)
~30.4 Million
MONO4

(LDL-C ≥ 240mg/dL)
~7.2 Million
Anti-PCSK9

MONO4

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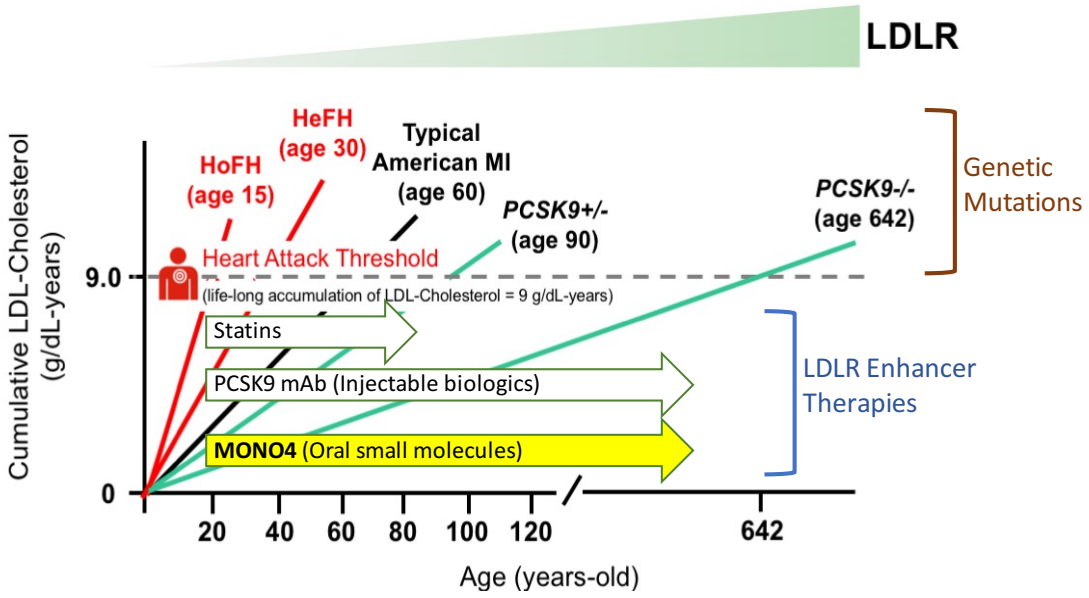
LDL Receptor (LDLR) Prevents Heart Attacks

Genetic Mutations vs Cumulative LDL-Cholesterol & Rel. Age of Heart Attacks and LDLR Enhancer Therapies vs Rel. Risk Reduction (proven and predicted; arrows)



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