UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT	
Tutor's Name	Prof. Nicola Ferri
Cotutor's Name	Dr.ssa Maria Giovanna Lupo

1) Project title

RNA-seq analysis in response to silencing of lipid-related genes PCSK9, ANGTL3, and ApoCIII in human hepatoma cell lines.

2) Abstract (max 500 words)

Introduction: Cardiovascular diseases (CVDs) are the leading cause of death globally, taking an estimated 17.9 million lives each year. Dyslipidemia is the main modifiable risk factor of CVD and many classes of drugs have been used and recently approved for controlling hypercholesterolemia and hypertriglyceridemia. Monoclonal antibodies, small interfering RNA, small molecules, and recombinant proteins have been approved and are currently under clinical development as PCSK9 inhibitors for the treatment of hypercholesterolemia. Similarly, antibodies and siRNA anti ANGPTL3 have approved for the treatment of homozygous familial hypercholesterolemia and are currently under investigation for reducing triglyceride levels. Finally, siRNA and oligonucleotide antisense anti ApoCIII have been approved for the treatment of familial chylomicronemia syndrome.

Aims: Considering this pharmacological scenario, patients affected by different forms of dyslipidemia associated to CVD may be treated with a personalized therapy for a better control of residual risk. Thus, a better understating of the biological response of hepatocytes to the pharmacological inhibition or gene silencing of PCSK9, ANGTL3, and ApoCIII, might help better understand possible pleiotropic effects related to the risk of CVDs.

Methods: To address this topic, we are planning to perform an RNA-seq analysis from human hepatoma cell line HuH7 after a selective gene silencing with siRNA anti PCSK9, ANGTL3, and ApoCIII. The results will be then analysed by bioinformatic tools in order to identify metabolic and/or signaling pathways affected in response to single gene silencing or clustered by silencing of two or three of the aforementioned genes. These pathways will be than validated by a more specific protein and gene expression analysis, such as western blot, ELISA, and real-time quantitative PCR. Finally, our results will be then validated in *in vivo* experimental model like PCSK9 and ANGPTL3 knock-out mice.

Results: The data obtained from this project will be submitted to peer-review international journals, *i.e.* atherosclerosis, ATVB, journal of cardiovascular pharmacology, pharmacological research *etc.* and being presented to national and international congresses (SIF, SISA, EAS, ELC, ESC *etc*).