UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title
Pharmacokinetic and pharmacodynamic evaluation of new small molecules anti PCSK9
2) Abstract (max 500 words)
Pharmacological inhibition of Proprotein Convertase Subtilisin/Kexin 9 (PCSK9) have been firmly established to be an effective approach to reduce low-density lipoprotein (LDL) cholesterol levels and cardiovascular events. Subcutaneous administration of monoclonal antibodies (evolocumab and alirocumab) every 2 or 4 weeks determined a 60% reduction of LDL cholesterol levels, while the GalNac-siRNA anti PCSK9 (inclisiran) provided an effective lipid lowering activity (-50%) after an initial subcutaneous dose, repeated after 3 months and followed by a maintenance dose every 6 months. Although these two approaches have the potentiality to bring the majority of patients at high and very-high cardiovascular risk to the appropriate LDL cholesterol targets, their cost and subcutaneous administration represent a strong limitation for their large-scale use. These problems could be overcome by the development of small chemical molecules anti PCSK9 as oral therapy for controlling hypercholesterolemia. Four PCSK9 molecules are currently under clinical development (DC371739, CVI-LM001, and AZD0780), including the mimetic peptides enlicitide decanoate (MK-0616). In collaboration with Prof. Marco Radi we have previously selected additional small molecules with potent in vitro anti PCSK9 activity that deserve further investigation in vivo. Here, we propose to study the pharmacokinetic properties of two chemical entities named MR3 and MR767 in mice. In addition, we will study the effect of the most promising compound on PCSK9 levels and lipid profile of $PCSK9^{+/+}$ and $PCSK9^{-/-}$ mice fed normal chow diet and high fat diet. The effect of treatment on liver fat accumulation and insulin resistance will be also evaluated. These *in vivo* analyses will be also implemented with *in vitro* pharmacological studies on hepatic cell line, smooth muscle cells, and tubular kidney cell.

Previously published manuscript on this topic:

Optimization of 4-Amino-2-Pyridone Inhibitors of Proprotein Convertase Subtilisin/Kexin Type 9: Integrating Structure-Activity and Structure-Metabolism Relationships. Giannessi L, Lupo MG, Ugolotti M, Papotti B, Mattina B, Martina MG, Demurtas A, Padula C, Nicoli S, Crescenzio M, Ferri N, Zimetti F, Radi M. ChemMedChem. 2026 Jan; 21(1): e202500651. doi: 10.1002/cmdc.202500651.

Identification of 4-amino-2-Pyridones as new potent PCSK9 inhibitors: From phenotypic hit discovery to in vivo tolerability. Giannessi L, Lupo MG, Rossi I, Martina MG, Vilella A, Bodria M, Giuliani D, Zimetti F, Zanotti I, Potì F, Bernini F, Ferri N, Radi M. Eur J Med Chem. 2024 Feb 5; 265: 116063. doi: 10.1016/j.ejmech.2023.116063.