Finanziato dall'Unione europea NextGenerationEU
Ministero dell'Università e della Ricerca
Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
SAPIENZA UNIVERSITÀ DI ROMA

SPOKE N. 4: S4D PRECISION DIAGNOSTICS

An integrative diagnostic model to automatically detect clinical and molecular profile of PCSK9 inhibitors effects in patients with severe dyslipidemia and coronary heart disease:

iMPACT

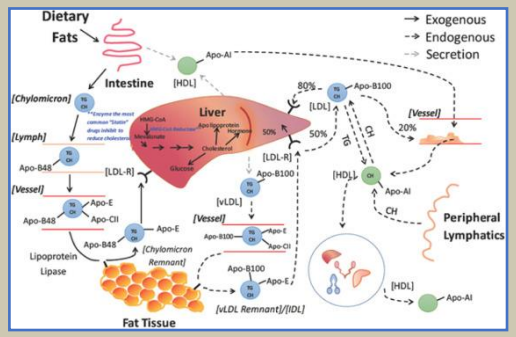
UNIVERSITÀ DEGLI STUDI DI ENNA "KORE"

The Kore University of Enna supports and encourages collaboration with universities and research bodies worldwide. The focus on quality research at the University of Enna "Kore" is embodied in the pursuit of the following main strategic objectives: support fundamental and applied research and technology transfer activities; developing new interdisciplinary lines of research in order to tackle increasingly demanding social challenges; developing strategic partnerships to increase the impact of research on society with a focus on sustainable development; Incorporating the research results into university education so that it can be continuously updated.

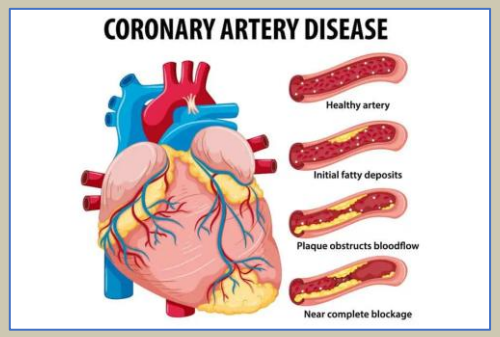
SYNLAB IRCCS SDN

IRCSS SYNLAB SDN and its advanced technology laboratories carries out scientific and clinical research in the biomedical field in a wide range of specialized disciplines (from high-level nuclear image diagnostics to advanced molecular biology and pharmacology) and promotes the transfer of research results to clinical practice and industry. The heavy commitment on research takes advantage of a strict integration of diagnostics and laboratory which has been strengthened over the years also thanks to institutional funding from the Ministry of Health, collaborations and synergies with individual research institutions both Italian and at the international level.

Finanziato dall'Unione europea NextGenerationEU
Ministero dell'Università e della Ricerca
Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
SAPIENZA UNIVERSITÀ DI ROMA

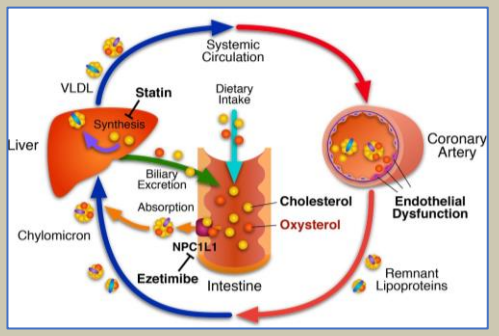


Hepatocytes play a pivotal role in systemic cholesterol homeostasis through the assembly and secretion of plasma lipoproteins, and eventually by their clearance through the low-density lipoprotein (LDL) receptor.



Imbalances in hepatic cholesterol synthesis and uptake can result in elevated levels of LDL cholesterol, a strong, independent risk factor for atherosclerotic cardiovascular disease

ACUTE CORONARY SYNDROME



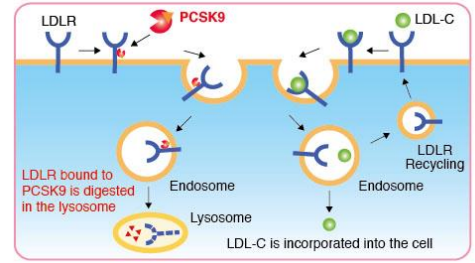
Statins constitute the milestone in dyslipidemia management and remain the most commonly prescribed lipid-lowering agents. They act by shutting off cholesterol biosynthesis by inhibiting 3-hydroxy-3-methylglutaryl-coenzyma A reductase (3-HMG-CoA reductase-HMGCR).

- **up to 40% of patients on statin therapy continue to suffer from cardiovascular events**
- **Compliance issues**
- **Side effects?**

Significant improvements in CV outcomes

UNIVERSITÀ DEGLI STUDI DI ENNA "KORE"
SYNLAB IRCCS SDN

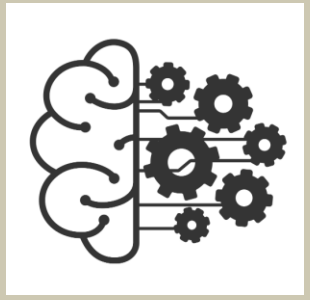
PCSK9 inhibitors (Alirocumab and Evolocumab) in patients with recent acute coronary syndrome (ACS) are associated with a lower risk of further cardiovascular (CV) events



Despite human monoclonal antibodies that bind PCSK9 are able to reduce LDL-C up to 60% in clinical trials, there is still much to be learned about PCSK9's regulation and function, which may inform not only additional facets of PCSK9 biology but also alternative mechanisms of PCSK9 antagonism.

Possibility to further tailor patients' treatment and the success rate in lowering cardiovascular morbidity and mortality

AIM



Prioritize informative variables in clinical, molecular, and diagnostic data to build patient clusters and machine learning prediction models to predict **responders vs non responders**. Construction of diagnostic and/or prognostic signatures able to integrate different clinical variables, molecular markers, miRNome profiling and diagnostic parameters from imaging.

Finanziato dall'Unione europea NextGenerationEU
Ministero dell'Università e della Ricerca
Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
SAPIENZA UNIVERSITÀ DI ROMA

Contributo al Programma di Ricerca dello Spoke - Contributo al Programma HEAL ITALIA ed alla Medicina di Precisione

Starting TRL - Data available in literature strongly support the use of PCSK9 inhibitors in clinical practice in subjects with ACS. In particular, their use in subjects with inadequate LDL-C has proven to be safe and effective in reducing CV consequences. Nonetheless, the cost-effectiveness of these drugs is still discussed as up to 40% of subjects still show an insufficient response and are prone to secondary CV events. Despite preliminary data, neither a molecular marker nor a validated predictive tool exists to estimate “a priori" the chance of therapeutic success in terms of clinical response. Furthermore, effects of PCSK9i at the molecular level are still insufficiently detailed in literature, missing the opportunity to adequately tailor the patient treatment in terms of both effectiveness and costs.

Expected final TRL - iMPACT final aim is to benefit from its multidisciplinary and multilevel approach (both clinical and molecular) to better understand and characterize the molecular profile of PCSK9 inhibitors in ACS subjects. This integrative approach is expected to provide an improved understanding of molecular markers in subjects responders/non responders to PCSK9i treatment (cytokines, miRNAs, exosomes, etc.) and to use this knowledge to create a combined database. This will, in turn, provide the data to create an integrated diagnostic tool which will be further validated in our caseload. This is finally expected to provide multiple benefits: apart from its possibly invaluable role to assist patient care in terms of treatment tailoring and follow up of subjects expected to have an insufficient response, the successful application of our theoretical model could also be applied as support for pharmaco-economic policies as it could allow a more thorough

UNIVERSITÀ DEGLI STUDI DI ENNA “KORE”
SYNLAB IRCCS SDN