Finanziato dall'Unione europea
NextGenerationEU

MISSIONE 4
ISTRUZIONE
RICERCA

Codice Progetto:

CN00000041

Beneficiario di progetto
Stefano FIORUCCI

Development of anti-super-enhancer of chemokines siRNAs engineered Nanocarriers for treatment of human Fibrotic disorders "NANOFIB"

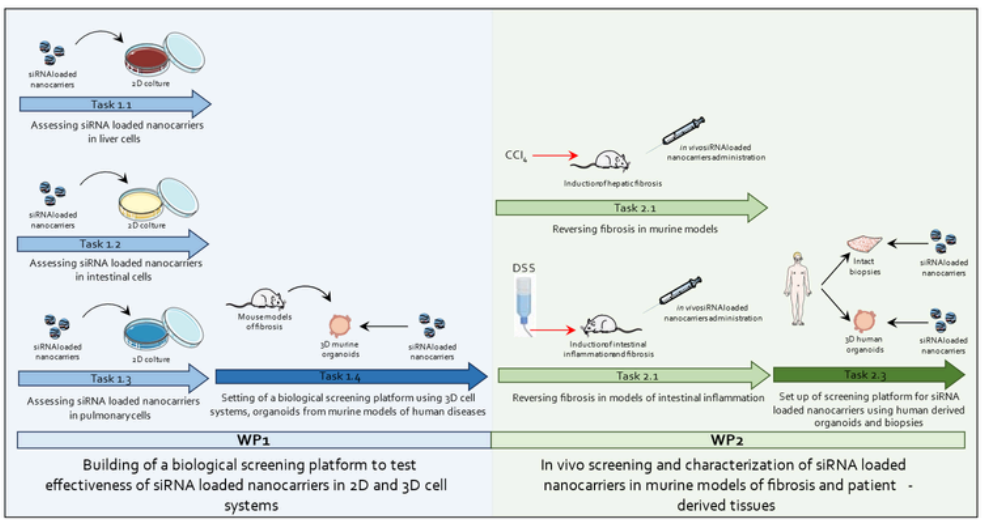
Obiettivo principale dell'operazione

The project is to design specific nanocarriers able to carry on siRNA directed against multiple chemokines simultaneously and more specifically to target super enhancers that regulate the expression of multiple chemokines in target tissues. This approach takes into consideration the broad and redundant nature of the chemokine pathway, where eliminating a single chemokine may prove ineffective and potentially enhance other signaling pathways. Specifically we aim to design and test nanocarriers loaded anti siRNA directed against the Bromodomain and Extraterminal (BET) proteins that regulate the expression of multiple chemokines. This approach is expected to result in the simultaneous down-regulation of multiple chemokines and therefore, to avoid or reverse macrophages-directed fibroblasts activation in tissues.

The goal of this project is to develop a biological screening platform to tackle fibrotic diseases with engineered nanocarriers. Specifically we aim to design and test engineering nanoparticle loaded siRNA able to reprogram the macrophages-dependent activation of fibroblasts in fibrotic disorders of liver, intestine and lung.

One of the key aspects in implementing siRNA therapy is the identification of target genes, the modulation of which will results in an effective reduction of fibrosis. For target identification we have carried out a series of preliminary investigations on RNAseq repositories of A) healthy and cirrhotic liver samples (Graupera I. et al -Molecular characterization of chronic liver disease dynamics: from liver fibrosis to acute-on-chronic liver failure deposited under the code GSE139602); B) intestinal fibrosis; C) lung fibrosis from IPF patients (Barrett T, et al. Ncbi geo: Archive for functional genomics data sets–update. Nucleic Acids Res (2013) 41(Database issue):D991–5. doi: 10.1093/nar/gks1193) and D) our own murine models of liver fibrosis induced through the administration of carbon tetrachloride (CCl4) to wild type mice (the data has already been published and deposited with the DOI: 10.17632/3xvs65zmhm.1).

From these studies, it appears that the most up-regulated genes in fibrosis across various human settings and murine models, are chemokines and their receptors. The mechanistic potential of chemokines and their receptors in the development of tissues fibrosis across various organ has been extensively validated by in vitro studies as well as genes knockout.



Workflow strategy representing the two Work Packages (WP).