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PROPOSTA TOPIC – 38° CICLO - PNRR

Project title	Multi scale pharmacokinetic validation of RNA-based drugs in the CNS
Curriculum (standard or clinical)	standard
Principal Investigator	Matteo Fossati matteo.fossati@humanitasresearch.it Bianca Silva bianca.silva@humanitasresearch.it
Lab name	Laboratory of Pharmacology and Brain Pathology
Main field of interest	**Neuroscience**
Abstract	RNA therapeutics are an emerging class of drugs that can be assigned to three groups: 1) antisense oligonucleotides or RNA interference for modifying gene expression; 2) RNA aptamers that can modulate the function of proteins; and 3) mRNA drugs encoding proteins. A major advantage of RNA drugs is the possibility to chemically modify them to improve their bioavailability and pharmacokinetics. Moreover, RNA drugs can be included in several types of nanovectors to efficiently deliver them across lipidic barriers in particular the Blood Brain Barrier for reaching the CNS. Main objective of this project is to validate new RNA drugs for the treatment of genetic diseases impacting on the central nervous system by using innovative tools allowing an in-depth characterization of the pharmacodynamic profile and properties the new RNA drugs. Specifically, selected RNA drugs will be characterized in vivo through the use of mouse animal models. The following technologies and experimental systems will be used and implemented for in vivo study of pharmacodynamic properties of RNA drugs: - generation of tissue-specific or chimeric models of pathology and introduction of pathological mutations by in utero electroporation and in situ gene manipulation - Optogenetics) and Behavioral (cognitive and motor tests) analysis of specific animal models for the study of pharmacodynamic properties of drugs to be tested and for the evaluation of possible side effects - Analysis of cFos expression to study whole-brain connectivity and alteration of specific neuronal circuits - strategies based on lentiviral and adenoviral vectors (Adeno-associated Virus, AAV) to selectively mark specific neuronal populations and monitor neuronal network dynamics - Circulating biomarker analysis following drug administration - Delivery systems based on liposomes/lipoplex formulations for testing of RNA drugs delivery across the BBB.

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Brief description of the coherence of the Project in relation to the PNRR objectives	This project is placed within the WP2–RNA drug pharmacodymanics of the SPOKE9 "From target to therapy: pharmacology, safety and regulatory competence center" of the National Center for Gene Therapy and Drug Development with RNA Technology (CN3, Mission 4 Component 2 Investment 1.4 of the NRP). The project will exploit the state-of-the-art multidisciplinary expertise and tools characterizing the CNR located at Humanitas Neuro Center and collaborating with Hunimed groups to study and validate novel RNA drugs for the treatment of neurological diseases. The RNA drugs acting on the CNS are selected in collaboration with Spokes 1, 3, 6, 8 and Human Technopole.
PNRR project title	Multi scale functional validation of RNA-based drugs in the CNS (MULTIVAL) "*National Center for Gene Therapy and Drugs based on RNA Technology*". (CN3, Missione 4 Componente 2 Investimento 1.4 del PNRR).
CUP	B83C22002860006 CNR CN3
Required Skills to carry out the project	The ideal candidate must have basic skills in all or at least some of the following: cell culturing, microscopy, qPCR, western blot, tissue dissection, immunocytochemistry, animal handling.