Annex 1 - Project proposal
(Article 10, paragraph 3 and Article 12 of the Call)

NAME OF THE NC:	National Center for Gene Therapy and Drugs based on RNA Technology
DURATION OF THE PROGRAM (MONTHS):	36
NAME OF THE PROPOSER:	Università degli Studi di Padova
IMPLEMENTING BODY HUB:	CNR, HUNIMED, IIT, OPBG, RI.MED, UMG, UNIBA, UNIBO, UNIBS, UNICA, UNICAMPANIA, UNICH, UNICT, UNIFI, UNIMI, UNIMIB, UNIMORE, UNINA, UNIPA, UNIPI, UNIPD. UNIPV, UNIROMA1, UNIROMA2, UNISA, UNISI, UNISR, UNITO, UNITS, UNIVR, TETTAMANTI, TELETHON (TIGEM/TIGET), Orgenesis, Chiesi, Novartis, Sanofi, Bracco, Astrazeneca, Antares, IRBM, Takis, PBL, Innovavector, Stevanato, Intesa San Paolo, Dompè, Eurofins
SPOKE AND AFFILIATE WITH THE SPOKE PERFORMING PARTIES:	CNR, HUNIMED, IIT, OPBG, RI.MED, UMG, UNIBA, UNIBO, UNIBS, UNICA, UNICAMPANIA, UNICH, UNICT, UNIFI, UNIMI, UNIMIB, UNIMORE, UNINA, UNIPA, UNIPI, UNIPD. UNIPV, UNIROMA1, UNIROMA2, UNISA, UNISI, UNISR, UNITO, UNITS, UNIVR, TETTAMANTI, TELETHON (TIGEM/TIGET), Orgenesis, Chiesi, Novartis. Biontech, Sanofi, Bracco, Astrazeneca, Antares, IRBM, Pfizer, Takis, PBL, Innovavector, Stevanato, Dompè, Eurofins
COST OF THE PROGRAM:	€320,2 Million MUR contribution + €8,77 Million of private co-funding. Total cost of the program €328,97 Million
NRRP THEMATIC AREA:	Gene Therapy and therapy based on RNA Technology

A SCIENTIFIC QUALITY

A.1 Objectives, relevance and motivation of the research program

The research program has two main goals: increasing the technological know-how necessary to design and deliver RNA-based and gene therapy medicinal products and identifying promising candidate drugs/genes in five major areas of human diseases (genetic diseases, cancer, metabolic/cardiovascular diseases, neurodegenerative disorders and inflammatory/infectious diseases).

The past few decades have seen a dramatic shift in the view of how human disorders can be treated. Molecularly personalized treatments, developed through a global rethinking of pharmacology, have become an ambitious goal for greatly increasing the efficacy of cures. The need for highly specific new drugs stems from the astounding advancements in the understanding of the molecular and cellular events responsible for human diseases. Indeed, large molecular diversity is not the exclusive hallmark of rare, inherited disorders but underlies the pathogenesis of the most common human diseases. The case of cancer is exemplary: it has become clear that neoplastic diseases with a similar clinical and phenotypical appearance, may differ from each other for the set of oncogenes and tumor suppressor genes involved through different pathogenic mutations, and innovative approaches targeting specifically the altered protein, or even the genetic mutations, show high efficacy. Thus, the development of drugs specific fora wide range of targets has become not only the principle of treatment of rare disorders, often neglected in thepriorities of pharmaceutical companies, but also the basis of a global new approach to cure, appropriately defined “precision medicine”. For this task, it is necessary to explore therapeutic strategies that go beyond the laborious identification of small chemical molecules fitting critical regulatory domains of enzymes, transporters and channels. Rather, a change in paradigm is needed, with the development of a class of drugs that share common synthetic and delivery platforms and can act, in principle, on any class of proteins with unprecedented accuracy. Clearly, the extraordinary power and flexibility of nucleic acids have made these molecules the ideal tools for this task, with a virtually limitless breadth of applications. The impact of RNA- based vaccines in the containment of the COVID-19 pandemic has provided direct, impressive evidence of how RNA-based drugs for specific targets can be rapidly and effectively developed.

While the success of mRNA vaccines, as well as the impact of targeted genome modifications using the CRISPR/Cas9 technology, has recently ignited a huge interest in DNA/RNA therapeutic applications, it should be remembered that DNA-based therapies have been pioneered and developed over three decades ago in the field of gene therapy of monogenic disorders. In this bright example of translational medicine, molecular understanding, development of the technology for directing transgenes into affected cells and construction of safe platforms of delivery have allowed to obtain clinical success in the correction of various inborn errors of metabolism. In this challenging process, Italian science has had a prominent role, and our country can count on established know-how and facilities in this field. Now, gene therapy has expanded its potential well beyond the replacement of a defective gene product. Targeted gene corrections (“gene editing”) have proved to be effective in the treatment of hemoglobinopathies, the most common genetic disorders of blood, and expression of chimeric antigen receptors in patient’s T cells (CAR-T) has been demonstrated to be a novel, successful approach for curing patients affected by relapsed/refractory B-cell malignancies. Counting on the presence of a group of centers of excellence in these new technologies, a key objective of the program is to expand these therapeutic options rapidly. Indeed, while the basic and pre-clinical research in the field of advanced gene-therapy-based medicinalproducts (AGTMP) in Italy is very productive and internationally recognized, the translation of results to the clinic remains often limited. To this aim, an ambitious national program for the creation/strengthening of infrastructures for drug product manufacturing, project management of innovative AGTMP and training and consultancy centers is desirable. As to the latter, one of the main bottlenecks currently faced by academia in moving AGTMP projects to the clinic is the lack of capacity for undertaking process development, scale-up and manufacturing under GMP conditions of these products; this frequently results in project drop out after the first *proof-of- principle*, high costs and long delays for the few survivors. A key part of the program is thusadvanced training and qualification of researchers and clinical operators in this emerging area of science and health. In particular, the National Center will implement the process of AGTMPs development, from early pre-clinical research to the clinical application, leveraging on already existing experience and infrastructures, to enable access to their services also to the other members. In accordance with the national strategies and the existing initiatives, this will be obtained by 3 layers of implementation: i) facilities for cell process and assay development, vector manufacturing and pre-clinical studies; ii) existing and revamped cell factories authorizedfor manufacturing of gene therapies using somatic cells; iii) service and teaching center. Once fully operational, an estimate of production capacity up to 250-300 gene therapy drug products per year will be reached, becoming available for all the members of the National Center, global academic institutions and private companies distributed over the entire country.

At the same time, thanks to the more detailed knowledge of the molecular mechanisms that concur to the control of gene expression, it is becoming clear that correction of disease-causing defects may be accomplished by the manipulation of gene expression at the post-transcriptional level, controlling the expression and function of specific RNA molecules. The ability of RNAs to both translate genetic information and exert catalytic/structural activities places these molecules at the center of a vast number of possible applications; moreover, high-throughput technologies have revealed a vast world of non-coding RNAs (ncRNAs), many ofwhich with high relevance in the control of RNA homeostasis. Finally, RNA has the unique feature to recognize other RNA molecules through very short base pairing (20 nucleotides), ensuring target selectivity and specificity. Therefore, RNA molecules can be appropriately engineered to design potent tools to control gene expression in a sequence-specific manner. Among such strategies, those based on RNAi, CRISPR/Cas9 gene editing and antisense RNAs have provided proof that they can be utilized for the treatment of several human disorders.

"Therapeutic RNAs" can be directly provided to the cells as nude RNAs; this is the case of the antisense strategy where *in vitro* synthesized AntiSense Oligos (ASO) recognize specific target RNAs and modify their splicing or even their stability and translation. One of the major recent successes of this strategy is the clinical treatment of Spinal Muscular Atrophy (SMA). In SMA patients, the intrathecal injection of modified ASO, resulted in the efficient correction of the splicing mode of SMN transcripts in the nuclei of peripheral motor neurons. More specific and efficient delivery of synthetic therapeutic RNA can be obtained by their incorporation into biocompatible nanocarriers. Such an approach is the one that has been successfully developed in mRNA vaccination strategies against Covid-19 infections. Based on these premises, it appears clear why RNA therapeutics is exponentially growing, and **it is strategic to bring together and develop the technological know-how and the biomedical and clinical science identifying crucial steps in pathogenesis to be targeted by new RNA-based drugs**.

Two aims will thus be pursued. **The first** is to identify the most promising candidate targets for RNA-based drugs in five major areas of human diseases (genetic diseases, cancer, metabolic and cardiovascular, neurodegenerative, and inflammatory/infectious disorders) by supporting the progress in TRL of projects presented by highly qualified biomedical and clinical scientists ("Vertical Spokes"). **The second** is to build and disseminate the technological know-how necessary for designing, delivering and producing RNA drugs ("Horizontal Spokes"). For this purpose, a network of experts is created with skills covering biophysical, computational and experimental aspects of RNA biology, in order to support the activity and the competitiveness of the scientists focused on the development of RNA drugs for specific targets and simultaneously train a new generation of scientists that would ensure the implementation of the most updated RNA-based technologies. In detail, the following **main tasks** will be addressed:

- design and production of therapeutic RNAs able to induce the knockdown of specific cellular RNAs (RNAi or gRNAs for CRISPR/Cas9) or to interfere with specific steps of their maturation (antisense RNAs), such as splicing, transport, stability and translation;
- (ii) evaluate the therapeuticrelevance of miRNAs, aptamers and other non-coding RNAs; improve current methods of RNA vaccination testing the effect of different RNA modifications or using circular RNAs (circRNAs) for directing efficient protein translation;
- (iii) develop computational tools for predicting RNA structure and interacting partners.
- (iv)develop novel materials and delivery solutions for directing therapeutic RNAs to the tissue of interest;
- (v) evaluate the efficiency of delivery, also by developing cutting edge new methodologies for visualizing RNAs and RNA activity inside the cell;
- (vi) evaluate immunogenicity and toxicity of the new compounds;
- (vii) set up effective protocols for large scale production of therapeutic RNAs.

Although RNA therapy is a coming-of-age technology and a growing number of RNA-based drugs are entering the clinic, important unresolved questions still remain as, for example, unproductive uptake due to poor release of ASO from late endosomal vesicles and lysosome degradation, undesirable or even toxic effects reflecting the interaction with proteins involved in RNA metabolism and their sequestration in pathologic complexes, limited stability of therapeutic molecules. It is also evident that the post-transcriptional modifications (epitranscriptome) and the 3D folding of RNA molecules influence the interaction with therapeutic oligonucleotides. To address these issues, a deep understanding of RNA metabolism, molecular and cellular biology skills together with advanced bio-computational approaches are required.

Spokes in collaboration with pharmaceutical and biotech companies will work together to develop innovative therapeutic approaches and technologies to tackle these hurdles. In particular, studies will focus on the non-

coding genome (introns, long and short non-coding RNA) which represent a novel and still poorly understood layer of gene expression regulation highly relevant in ageing processes and in disease of the elderly. In addition to being target of therapeutic approaches, ncRNAs can be therapeutic molecules. Indeed, a growing number of short ncRNA is being proved to regulated distinct tiers of gene expression from chromatin organisation to translation.

A.2 Specific research activities of the program

The research activities recognized as strategic to advance knowledge in **Gene Therapy and Drugs based on RNA Technology** are covered by 5 "**Vertical Spokes**" centered on the identification of the most promising candidate targets for RNA-based drugs in five major areas of human diseases and 5 "**Horizontal Spokes**" providing tools and know-how of general use to all the areas of pre-clinical and clinical applications. The expected outcomes are based on three pillars:

- Identification and validation of targets for both RNA-based drugs and gene-therapy/genome editing approaches;
- Technological advancement in the KET: from RNA drug design to delivery and pharmacology of the new drugs;
- Manufacturing and clinical application: implementation of core facilities for the production of high-quality RNA ("clinical grade") and gene therapy manufacturing centers that can provide support to the needs of Italian patients, as well as foster the dissemination of the clinical application of the new technologies.

For these purposes, the research activities inside each Spoke are intimately connected, aligned in linking the technological developments of horizontal Spokes in providing tools and know-how for application in diseases (**vertical Spokes**) and take benefits of the strategic collaboration with multinational (Pfizer, BioNtech, Novartis, AstraZeneca, Sanofi, Orgenisis) and Italian biomedical and Pharma companies (Stevanato, Chiesi, Dompè, Bracco, IRBM, Antares, Eurofins, PBL), of the largest Italian bank (Banca Intesa), and of a number of biotech companies active in the rapidly expanding field of RNA therapeutics and gene to identify opportunities for the transfer of knowledge from the Academia to industries and develop applicable and scalable solutions. Moreover, it is expected that the private-public research collaboration will synergize the respective capabilities creating a reference center known and recognized at national and international level thus providing its long-term sustainability.

A brief description of each Spoke is reported below:

Spoke #1: Genetic diseases. The Spoke aims at developing safe and efficacious therapy for incurable and severe monogenic diseases through novel RNA-based drugs, RNA/protein complex-based gene editing technology and delivery systems either in vitro, to transplantable somatic stem cells, or in vivo, to defined body districts. The ultimate, key goal is to expand the gene therapy approaches by providing early proof of concept with pre-clinical and clinical activities. The activities will encompass the definition of lead candidate molecules, development of enabling technologies for viral and non-viral delivery and genomic data analysis, achievement of pre-clinical proof of efficacy and safety in relevant in vitro and in vivo disease models, completion of Investigational New Drug (IND)-enabling non-clinical studies including biodistribution, pharmacology, toxicology, and genotoxicity and initiation of pilot clinical trials. A tight collaboration will be in place with **Spoke #3**, to jointly target mitochondria and neuro-neuromuscular disorders, 7, to optimize biocomputing and delivery strategies, 6 and 10, to share protocols and medicinal products. **Chiesi**, affiliated to **Spoke #1** is interested in partnering in regard to specific projects related to eye, blood, kidney and storage genetic disorders.

Spoke #2: Cancer. The activity of Spoke #2 will be dedicated to the development of RNA-based therapeutics for tumors and metastases. Main activities are focused on i) the identification of targets in human cancers and that can be effectively tuned by inhibitory RNAs, such as ASO or siRNAs ii) strategies to increase tumor immunogenicity by using RNA therapeutics and iii) develop pipelines for anti-cancer vaccines for solid tumors. Tumor-associated antigens and mutational neoantigens will be identified by implementing sequencing (genomics and transcriptomics) and novel bioinformatics tools for antigen prediction and polyvalent vaccination approaches. In this framework, **Spoke #2** will develop key interaction with the biocomputing infrastructures established in **Spoke #7** to facilitate neo-antigen discovery and -omics data analysis. A second key interaction will be with **Spoke #6** within research activities that have developed mew methods for nucleic acid encapsulations into ferritin nanoparticles, currently under GMP production. Regulatory studies will be performed in close cooperation with **Spoke #9** in order to pave the way to pharma development along innovative and agile procedures. In this framework lean operational schedules to access

the necessary financial networking has been implemented in a dedicated workpackage (WP4) in order to maximize the impact of the novel research results and foster the use of novel digital technologies for both data analysis and pharma strategies repositioning in the framework of an established cooperation with the **Intesa San Paolo group**. The well established cooperation's with **IRBM** will provide access to joint facilities aimed to help with clinical implementation under GMP methods. Clinical implementation will also be carried out in the framework of cooperation with existing facilities of the **SANOFI** group. Design and development of a lab-scale prototype integrated modular system for continuous monitoring of formulations of nanosized EVs loaded with RNA under continuous or pulsed flow with steady-state fill volumes will also be carried out with **ANTARES** and **Spoke #8** with the aim to characterize the formulations for EV size.

Spoke #3: Neurodegeneration. The activity of **Spoke#3** will be dedicated to the development of new RNA therapeutics for diseases of the nervous system including AD, PD, ALS, neurodevelopmental disorders and stroke. This will be accomplished by i. providing preclinical data to file for RNA-based Investigational New Drugs (INDs) for known RNA molecules with therapeutic potentials; ii. providing long-term sustainability of the pipeline with new programmable RNA drug platforms or with new single RNA drug candidates; iii. identifying new drug targets. A repertoire of RNA tools will be applied in animal pre-clinical models as well as patient-derived cells and brain organoids. To reach these goals, we plan to collaborate with Spoke#1 to share knowledge and tools to confront genetic diseases that involve the central nervous systems. Several collaborations are currently ongoing with project leaders in the two spokes, especially for the optimization of SINEUP RNAs to treat haploinsufficiencies. We will resort to **Spoke #6** for the development of new technological platforms of programmable RNAs to be applied to the nervous system, for the identification of post-transcriptional modifications of therapeutic value with nanopore sequencing technology and for imaging techniques in vivo to study RNA drugs dynamics in cells and tissues. **Spoke 7#** will provide knowledge and computational infrastructure to carry out predictions and simulations of RNA secondary structure and interactions with other nucleic acids and proteins. We will tightly collaborate with **Spoke #8** for the optimization of delivery technologies to the central nervous system: in particular, we will take advantage of expertise in the fields of nanoparticles optimization, microvesicles/exosome loading and delivery, technologies to pass the blood-brain barrier, molecules and peptides for homing nanoparticles to specific neuronal cell types. On the way to IND filing, a crucial step is represented by pharmacokinetics and pharmacodynamics analysis as carried out in **Spoke #9**. **Spoke #10** will be instrumental to streamline GMP production of RNA drug candidates. Clinical implementation will take advantage of the collaboration with existing facilities of the **SANOFI** group.

Spoke #4: Metabolic and cardiovascular diseases. The Spoke focuses on metabolic, cardiovascular, and skeletal muscle diseases both in adulthood and aging. These diseases have a major impact on global health and account worldwide for a high proportion of the pharmaceutical expenditure but show a very large variability in their response to therapy and outcome. Both low and high TLR projects are included, the former to test a wide array of putative targets, the latter to ensure stronger potential for advancement along the pipeline to an RNA-based drug. Specifically, the following topics will be covered: muscle atrophy and aging, developing sh/si/mRNAs drugs that target: muscle atrophy and aging (FoXOs, mIGF-1, MICU2 and FGF21), cardiovascular diseases related to aging and to genetic myopathies (LAV-BPIFB4 and mir206); obesity, metabolic syndrome, and type 2 diabetes (TCR, CD300e, MCU, miR-21/-214, p66shc); hypertension, meta-inflammation and diabetic nephropathy (aldosterone synthase, OSM and UBE2v1); cardiomyopathies, respectively, through Lnc-RNA targeting, iPS modelling and smRNA therapy with miR-199 and -1825, and tolerogenic vaccination to prevent cardio-toxic inflammation. Additionally, new collaborations will be established for the development of RNA-based therapies for specific targets (including, but not limited to, P2X7). To this aim, interactions with other spokes, both vertical (Spoke #5) and horizontal (spokes #6, #7, #8, #9, #10) will be established. The spoke will take advantage of active collaborations with pharmaceutical companies, including **AstraZeneca** and **Stevanato**. AstraZeneca is leader in R&D on cardio-renal-metabolic management, developing drugs for cardiovascular diseases and heart failure, chronic kidney disease, and metabolism. Stevanato is pioneering clinical-grade containment solutions for RNA-based drugs, and customized delivery of drugs for diabetes management.

Spoke #5: Inflammatory and infectious diseases. A multiple approaches strategy will be exploited to establishan integrated vaccine and pre-emptive therapy development platform against viral and bacterial pathogens and face novel emerging multidrug-resistant bacterial strains. In Spoke #5, novel strategies for the treatment of inflammation, immunological disorders and infectious diseases will be developed, including the use of viral vectors and non-viral RNA/DNA delivery vectors for cell-specific engineering or gene silencing. In addition, an innovative platform for circulating biomarker discovery and analysis will be established, focusing primarily on extracellular vesicle isolation, RNA profiling and immune factors. A combined

workflow will also allow to test mRNA/smRNAs-based nanovesicles (NVs) in inducing immune tolerance and treating autoimmune/inflammatory-based diseases. We will discover novel therapeutic targets and biomarkers based on high-throughput sequencing of NVs in autoimmune/inflammatory diseases and check NVs-therapy immune responses in pre-clinical and in clinical settings. The Spoke will adopt: (i) mRNA-vaccine technology and innovative viral-vectors designed to prime antigen-specific immune response; (ii) mRNA- encoding neutralizing monoclonal antibodies against viral and bacterial pathogens; (iii) phages libraries development to treat antibiotic multidrug resistance bacteria; (iv) CRISPR-CAS9-mediated viral genomes degradation. Spoke #5 will interact with the biocomputing infrastructures established in **Spoke #7** to facilitate neo-antigen discovery and analysis/access to -omics data across the **NC**. Of note, Spoke #5's research output will skyrocket through close interaction with **Spoke #8** to develop synthetic extracellular vesicles as therapeutic vectors for targeted release of newly discovered RNA molecules. In addition, the innovative RNA release technologies being developed in this Spoke will benefit the activities of **Spokes #1 and #2**. The established scientific collaboration with **BioNTech** providing fully automated and scalable cell manufacturing procedures, which will help with clinical implementation using GMP-certified methods, will increase the chances of success for Spoke #5 and TRLs advancement.

Spoke #6: RNA Drug Development. The Spoke aims at using state-of-the-art technologies and its own research to enhance stability, minimize off-target effects, cell toxicity and immunogeneity, maximize productive cellular uptake and sub-cellular distribution of ASO, siRNAs, *ad hoc* modified sg-RNAs, non-coding RNAs, aptamers and mRNAs, tailoring chemistry for specific *in vivo* applications. A particular focus will be on ncRNAs that are emerging as promising therapeutic targets because of their established role in gene expression regulation and epigenetic programs, and in several cellular functions, and because they are deregulated in many diseases. Spoke 6 will develop cutting-edge methods for visualizing low abundance RNAs and RNA-based therapeutics. It will characterize the epitranscriptome with third-generation sequencing technologies to re-engineer therapeutic RNAs and develop RNA-editing approaches. The Spoke is organized in three WPs, from in silico design to *in vivo* studies: a Technological Platform designed to provide a multimodal and multitarget approach to RNA therapeutics by sequencing, imaging and editing of RNAs, coupled with tailored computational and artificial intelligence approaches developed with **Spoke #7**; a Synthetic Platform, focused on chemical modifications of RNAs including Aptamers, ASOs and therapeutic mRNAs; an RNA Platform that implements know-how in RNA metabolism (non-coding RNA and RNA maturation) to identify new therapeutic RNAs and to test RNA targeting approaches. Strategic collaborations with Biotechnological companies affiliated to the Spoke have been established. **IRBM** will leverage its screening capabilities and collection of compounds to identify hit molecules capable to bind and modulate RNA target(s), which represent a valid alternative to target highly structured RNAs. **TAKIS**, in close collaboration with academic groups in this Spoke, will develop new vectors and RNA regulatory sequences to enhance mRNA expression and translation.

Spoke #7: Biocomputing. The Spoke, through the establishment of suitable dedicated infrastructures, will design, develop, implement, and validate state of the art and novel computational approaches for the analysis and integration of genomics, transcriptomics and other omics data to support the other Spokes in elucidating the molecular mechanisms underlying pathogenesis and elaborating the strategies to tackle diseases using gene therapies and RNA-based approaches. The activities will address several challenges, including: i) new algorithms for sequence and structure analysis also aimed at optimising effectiveness and biosafety of genome-editing approaches; ii) decipher the molecular basis of pathogenic splicing or epitranscriptomics abnormalities and identification of potential neo-antigens associated to different pathologies; iii) design and develop RNA drugs in different therapeutic areas through molecular dynamics simulations, molecular docking, RNA quantum enzymology and Cryo-EM maps analysis; iv) implementation of integrated data analysis models for the reconstruction of gene regulatory networks; v) prioritization of drug targets and actionable disease features through Knowledge Graphs and Artificial Intelligence approaches; vi) network-based multi omics data integration in cancer and other diseases for patient stratification and identification of disease vulnerabilities; vii) development of structural models to unveil gene expression regulation at single-cell level. Spoke #7 will establish a dedicated IT infrastructure for biocomputing with a state of the art ecosystem of data and tools supporting all the activities of the National Center. In particular, a major goal will be the prediction and characterization of new targets for RNA-based drugs and gene therapies (e.g. neo-antigen discovery) through large scale omics analyses, molecular dynamics simulations, molecular docking and integrative data analysis through Machine Learning and Artificial Intelligence approaches. A strong integration with other spokes activities has been planned (e.g. with **Spoke #6** for designing programmable RNA editing enzymes, with **Spokes #2 and #3** for their validation in cancer and neurodegeneration, and with **Spoke #10** for optimizing biosafety in cell-based immunotherapy approaches). Concerning the planned

interactions with private companies a collaborative action with **Intesa San Paolo** Innovation Center has been planned for integrating a smart IT platform for genomic surveillance during viral outbreaks.

Spoke #8: Platforms for RNA/DNA delivery. The Spoke will respond to the current and future needs of nucleic acid (NA) delivery, testing different concepts with a workflow covering crucial aspects for translating research findings from the bench to the bedside. The activities are clustered in three research areas: 1) development of smart delivery platforms engineered for precision RNA/DNA delivery up to a functional PoC; 2) Development and application of advanced 2D/3D cell models, organ-on-chip, organoids and in embryo models to evaluate the delivery efficiency and select the best performing platforms that can move-up TRL of therapeutic concepts; 3) innovation in production technologies focusing on mass production of nanoplatforms in a GMP-compliant environment, tools to speed up characterization of delivery platforms and key technologies in pharmaceutical manufacturing with the collaboration of companies. The high-throughput discovery pipeline will encompass non-viral and viral strategies for NA delivery, focusing on nanotechnologies and precision delivery to solid tumors, inflamed sites, and central nervous system. A significant effort will be made to develop novel precision nanoplatforms in close collaboration with **Spoke #6** (targeting aptamers) **and Spoke #7** (prioritization of targeting receptors). A functional PoC of delivery efficiency in a biological model will be provided for each platform to accurately select the lead candidates progressing to advanced preclinical studies in **Spoke #9**. We will also test the feasibility of skin delivery of nucleic acids via engineered microneedles and electroporation (in collaboration with **Takis**). We will develop novel human-relevant models to assess the delivery efficiency and integrate the most advanced human models (organoids) with omics sciences to get knowledge on toxicity and efficacy in an early discovery phase and speed up the animal pre-clinical phase in **Spoke #9**. We will look at innovation in production technologies focusing on the prototyping of the best candidates in GMP-compliant conditions by microfluidic and investigating novel fabrication techniques as supercritical fluids. Strategic cooperation **with companies affiliated to the Spoke** will drive the development of lead platforms toward industrial production, anticipating possible roadblocks. Companies will tackle the stability of the formulations and final products with research plans aimed at obtaining dry product by lyophilization (**Stevanato and Chiesi**), investigating the compatibility of products with primary container (**Dompé, Stevanato**), developing novel engineered packaging solutions (**Stevanato**) and strategies to monitor cold storage chain (**Antares**). Since we plan to get a massive amount of data deriving from the testing of large panels of nanoplatforms, Antares will apply AI to link input parameters (physico-chemical properties) to delivery efficiency of the developed platforms and handle the quality of research samples in their itinerary between laboratories. At the end of the project, we envisage the establishment of a fully operational technological platform ready to respond to the needs of CN and able of continuous renewal in line with the evolution of the international scenario on drug delivery technologies.

Spoke #9: From target to therapy: pharmacology, safety and regulatory competence center. The Spoke coordinates a broad spectrum of competencies and facilities provided by UNIMI and affiliated Institutions to develop science-based methodologies to study the distribution, metabolism, pharmacological activity and potential side effects of NA-based drugs and shorten the journey from target identification to phase 1 clinical trials. The short term objective of **Spoke #9** is to adapt and optimized technologies for the preclinical and clinical research necessary for the creation of the dossier to initiate a clinical trial in line with current legislation. The work done by **Spoke #9** in collaboration with **Spoke #8**, will provide the technological support required for the study of the pharmaco-toxicological profile of the compounds developed by the 5 **vertical Spokes** enabling the identification of those suitable for translation and the execution of the preclinical studies necessary for the initiation of clinical trials. The long term ambition is to create a unique competence center for RNA drug pharmacology able facilitate the translation of basic research and to create, test and optimize novel concepts aimed at speeding up preclinical studies by combining the steps currently required for ADMET in new protocols where novel biomarkers combined with reporter systems will suitable for in vivo imaging. The new protocols should enable to compress pharmacokinetics and pharmacodynamics studies in a single step with a significant improvement of sensitivity, reproducibility and accuracy of the results at the same time sensibly decreasing the number of animals to be euthanized in respect of the **3R principle**. The strict collaboration with Contract Research Organizations, Diagnostic and Pharma Industries is not only aimed at ensuring the creation of protocols that may move rapidly from lab-grade to large scale GMP-compatible processes ready for authorization and tech transfer (TT). In particular, the competence acquired by **Dompè** in the field of RNA vaccines immunotoxicology will be essential in task 9.3.3 to develop new methods and in vivo models for immuno-toxicological evaluations, and GLP toxicological studies; **Chiesi** will contribute, also though its collaboration with Moderna Inc., to the identification of the RNA drugs most suitable of development and in the definition of the technologies for the study of RNA drug distribution

(tasks 9.1.1 and 9.1.2); **Eurofins Biolabs** as a world leader in testing and research services will support the research on the optimization of current analytical procedures as well as the search for innovative methodologies (tasks 9.1.1 and 9.1.2); **Bracco** will prove essential for the development of in vivo imaging farmaco-toxicological studies (task 9.1.5) and in the application of appropriate biomarkers to the PK and PD studies (task 9.1.4); **Antares** will assist in the design of quality control methodologies and smart data and tools for the digitalization of the process (tasks 9.1.1 and 9.1.2); **IRBM** SpA with its experience in the translational research will facilitate the industrialization of the research tools developed by the Spoke. It is expected that in the course of the three years program the spoke will interact with most of the Companies currently present in the NC in particular for setting up TT operations at national and international level. The presence of expertise in regulatory sciences will provide regulatory advice related to the quality of innovative medicinal products for preclinical and clinical studies. In addition, **Spoke #9** will support in the preparation of Investigational Medicinal Products (IMP) and/or authorization dossier for the products developed in the vertical spokes. Facilities include academic and industrial (Antares and Eurofins) fully structured departments dedicated to pharmacological and immuno-toxicological (Dompè) studies including fully accredited GMP/GLP facilities and specific platforms for the generation of novel reporter systems suitable for the production of reporter cells, organoids and animals highlighting drug activity in vivo by combined 'omics', biophysical and imaging methods. The clinical pharmacology lab will carry out Phase I, randomized, double-blind studies in accordance with Good Clinical Practice requirements. As previously indicated, to pursue its aims, **Spoke #9** research will follow two separate lines of intervention: i.) development and optimization of analytical standard techniques for the quantitative analysis of RNA drug distribution and activity according to EMA and FDA Guidelines; ii.) test and optimize innovative concepts for RNA drug distribution, metabolism and activity based on state-of-the-art cellular and animal models and on the study of specific biomarkers. The Spoke will be organized in work packages covering pharmacokinetics, including pre-clinical and clinical studies (PK); pharmacodynamics, using cells, organoids and innovative animal models (PD); toxicology and immunotoxicology of RNA drugs. The final aim is to exploit the combination of interdisciplinary and transectoral expertise of the NC to develop a RNA-drug competence center able to create novel protocols tailored on RNA-drugs that will speed up the development of these product and ensure the qualitative parameters suitable to be proposed and accepted by the regulatory agencies and therefore, to be adopted by Companies/Research centers involved in RNA-drug development.

Spoke #10: Pre-clinical development, GMP manufacturing and clinical trials of GTMP. The Spoke aims at promoting the full valorization and deployment of Italian translational research on gene addition and genomeediting-based therapy. The Spoke will leverage on world-recognized scientific and technical expertise and pre-existing facilities available in some of the affiliated Institutions, which will be further upgraded and scaled-upfor serving the proposed national mission. Moreover, the capability and skills of the Spoke in translating state-of-the-art pre-clinical research into clinic trials of novel ATMPs will be advanced and brought to full effectiveness through the execution of several pilot projects, selected for their paradigmatic value in addressing some key outstanding hurdles and demonstrating potential solutions, proposed by its founding members. Among the pilot projects already selected, 8 target different types of cancer through innovative CAR approaches (i.e. tackling highly unmet medical needs, including brain tumors, T-cell acute lymphoblasticleukemia and acute myeloid leukemia, exploiting alternative cell platforms and allogeneic products and targeting novel promising tumor antigens), 5 target genetic diseases (including β-thalassemia, through different gene addition and genome editing approaches, several lysosomal storage diseases and inherited retinopathies), 1 will address B-cell mediated immune disorders targeting CD19+ cells with a CAR and 1 focuses on developing alternative and innovative approaches other than those based on viral vectors forgenetic modification of the target cells. Importantly, thanks to the advanced pre-clinical studies already conducted by the Institutions affiliated to the Spoke, the clinical translation to proof-of-concept studies for 11of the projects is expected. After this training and enabling phase, adopting an established international model, the Spoke services will become nationally available through open, competitive, peer-reviewed calls. The academic/research institutions will closely collaborate with biotech companies, including **Orgenesis**, **PBL** and **Stevanato**, to promote a decentralized model of GTMP manufacturing. In addition, when the proof-of-principle/phase I studies will obtain promising results, the industrial partners will have the opportunity to cooperate with the academic/research institutions to translate on a larger scale these innovative therapeutic approaches in a fruitful win-win model. A strong collaborative effort will be pursued between **Spoke #7** and 10 to develop a comprehensive bioinformatics environment for the analysis of -omic data to assess clonality of viral vector-transduced cell populations, with the aim to monitor the fate of individual gene-corrected cells in vivo, and to assess vector integration, and, thus, biosafety. Moreover, Computational Systems Biology and integrative data analysis infrastructure generated by Spoke #7 will provide computational tools to **Spoke #10**

activities with the goal of discovering novel targets for the immunotherapy approaches developed in **Spoke #10**.

A.2.1 Methodology for program implementation

The strategy of extensively scouting the Italian scientific community for recruiting competencies and research in perspective RNA drug and gene therapy targets in an ambitious National Center, with the aim of funneling the most promising candidates to the highest TRLs, requires not only a rigorous selection process but also the careful monitoring of the progress of individual activities, eventually refocusing effort and budget towards the most successful drug developments. For this purpose, in-depth evaluation of the qualification of the PIs, of the scientific quality and of the potential of generating a new RNA-based drug or gene therapy application was the basis of the selection of the participating groups and will inspire the implementation of the research program at the Spoke and Hub levels. Indeed, the 10 Spokes plan the activities of their affiliated members, proposinga budget for each project based on its scientific evaluation and TRL. Once funded, the Spoke coordinates all the activities and monitors their advancement, also through periodic meetings, in a concerted, iterative prioritization effort aimed at identifying suitable targets for RNA-drug development and their combination also with existing therapies. The Spoke launches both dedicated calls to extend the activity of funded projects or to initiate new projects by the affiliated members, and international open calls, to bring new expertise and/orresearch developments in a competitive manner. Each Spoke periodically submits Financial and Activity Reports to the Hub. The Spoke scientific activity is supervised by the National Center Scientific Committee,composed of a member designated by each Spoke and electing a Coordinator among its members. The Scientific Committee also assists the President in preparing the Strategic Planning Document.
The governing body of the Hub is the Board of Directors. It is nominated by the members of the Foundation as defined by the Foundation Bylaws, with most members representing Ministry of University (MUR)-supervised entities. The Board of Directors nominates a Scientific Advisory Board (SAB), composed of international high-profile scientists and managers. The Board defines the objectives and priorities of the National Center, by approving the Strategic Planning Document in light of its evaluation by the SAB and by the Industrial Board (the Assembly of the industrial affiliates). The Board of Directors also approves the Spokes Financial and Activity Reports and assigns the budget. The Board nominates a Director with administrative and coordination (Program Research Manager) functions.
The President chairs the Board of Directors, prepares and submits the Strategic Planning Document to the Board, and verifies its implementation, reporting to the Board on the advancements of the activities of the Center. He represents the Center in the relationships with public and private stakeholders.

A.2.2 Expertise and knowhow

As detailed in the following presentation of the Spokes and the affiliated members, the **Center** has recruited aroster of high-profile scientists and Institutions. In the recruitment phase, the criteria used for the selection of the submitted projects included qualification of the PI, as highlighted by publication history and specific expertise in the field, and a detailed plan aimed at developing an RNA-based new drug or a gene therapy clinical application, or at improving the technology. In all cases, the proposal had to include a detailed plan ofthe advancement in drug/gene therapy development, as defined by a TRL progression timescale. A selection committee evaluated the proposals. This committee was headed by Prof. Rosario Rizzuto, former rector of theUniversity of Padova and prominent biomedical scientist (member of EMBO and Academia Europaea, Scopush-index 104 and >42500 citations) and composed of a designated scientist from each university and research center with strong activities in the scientific areas relevant for the creation of the National Center: Giuseppe Biamonti (CNR), Alberto Boffi (University of Rome – Sapienza), Francesco Dotta (University of Siena), Stefano Gustincich (Italian Institute of Technology), Franco Locatelli (Bambino Gesù Children's Hospital), Adriana Maggi (University of Milano), Graziano Pesole (University of Bari), Antonello Pietrangelo (University of Modena and Reggio Emilia) and Angela Zampella (University of Napoli Federico II). Based on the evaluationof proposals, a list of Ministry-controlled universities (limited at 25, as requested by the call of the Ministry) and 7 other research entities were invited to act as founding members of the Hub. The extensive search of expertise and groundbreaking projects in the field of interest of the National Center allowed recruiting in the program top scientists from the biomedical and clinical sciences, chemistry and material sciences. They include6 top scientists with a Scopus h-index >100 (Lista, Priori, Locatelli, Pelicci, Rizzuto, Naldini), 6 with an h- index >90 (Zeviani, Biondi, Ballabio, Di Fiore, Sozzani, Zinzani), and overall >100 senior investigators with an h-index >50, >200 with h-index >40 and a large number of young, promising junior scientists. 17 participants are EMBO members (Bozzoni, Ciliberto, D'Adda Di Fagagna,

De Luca, De Matteis, Del Sal, Hirsch, Matteoli, Mavilio, Naldini, Pasini, Pelicci, Piccolo, Poli, Rizzuto, Scita, Scorrano). Talented young researchers from EU and non-EU countries will be attracted by opening approx. 200 non-tenured academic positions ("ricercatore T.D. di tipo A") and by offering a training in excellent science with an intensive (approx .200 positions) PhD student recruitment plan complemented by a new doctoral training program. The private-public ecosystem will be reinforced with the PharmaTech Academy, a new training programme based on the concept of Learning by Doing promising to educate the next generation of professionals in the pharmaceutical arena. This represents an unprecedented national multidisciplinary task force aiming at the common objective of consolidating and developing the national expertise in a Key Enabling Technology of major social and economic significance. Consolidating this task force and its capacity for coordinated action will be a primary goal of the National Center.

In the startup phase, the possible contribution of Pharma, biotech and financing firms was evaluated. The planned activity of the National Center was presented in meetings organized by Industry Associations (Farmindustria, Confindustria) and, following these presentations, several companies expressed their interest in the National Center. In addition, possible industrial partners were directly suggested by the scientists submitting the research proposals. After evaluating the global capacity and the specific contribution and commitment to the activities of the National Center, the selection committee decided to invite a shortlist of private entities for further in-depth discussion. At the end of this process, a number of private companies were invited to join the Hub as founding members, contributing to its activities and governance. The invited companies accepted, therefore the Hub sees the participation not only of a powerful network of scientists, but also of leading multinational (Pfizer, BioNtech, Novartis, AstraZeneca, Sanofi, Orgenisis) and Italian biomedical and Pharma companies (Stevanato, Chiesi, Dompè, Bracco, IRBM, Antares, Eurofins, PBL), of the largest Italian bank (Banca Intesa San Paolo), and of a number of biotech companies active in the rapidly expanding field of RNA therapeutics and GTMPs. The National Center envisages taking advantage of this strategic alliance in the creation of a Pharma-Tech Academy as a long-life learning initiative aimed at generating professional profiles ready to enter the highly competitive pharmaceutical arena.
The thorough selection of the participants, and the identification of leading scientific figures not only represents the best guarantee of success of the proposed activities, but also brings to the Center their international reputation and collaborations, their capacity of managing complex, groundbreaking projects (>20 participants have been grantees of the European Research Council and most senior participants have been coordinators of large EU-funded research networks and recipients through the years of major funding from national and international agencies). State-of-the-art scientific equipment is already present in their institutions, which include the most updated gen/prote/metabol-omics instrumentations, GMP facilities for GTMP production, biosafety level 2 and 3 laboratories, the European computing infrastructure Elixir, one/two-photon confocal microscopes, super-resolution imaging microscopes, cryo-EM, NMR, high-resolution mass spectrometry, and 7 Tesla magnetic resonance imaging. In addition, collaborations with other infrastructures, such as the Antipandemic Hub in Siena and Area Science Park in Trieste, have been formally agreed and will strengthen the activities of each initiative. Given the availability of the instrumentations needed for carrying out the scientific program, the Center mainly focuses its infrastructure requirements on the development and implementation of two major, high-cost facilities: a Gene Therapy Center that conducts the coordinated activity of four already existing centers in the Country, making it available to broader use and training the personnel of new facilities, and a platform for the production of high-quality RNA, as certified by regulatory agencies, that will serve the broad set of RNA users for the preparation of vaccines, monoclonal antibodies, gene editing, mi/siRNA silencing, etc. For the latter infrastructure, a collaborative partner from the private sector will be selected and additional funding will be searched in other granting schemes within NRRP and within other national and regional programmatic frameworks.
Investing in the coordinated action of the **Gene Therapy Center** has at least two major advantages. The first is that new gene therapy applications will move rapidly from lab-grade protocols through optimization and scale-up to GMP-compatible processes ready for tech transfer to an authorized GMP cell factory and adequate for early-stage clinical trials. Given the research already active in the country and the acceleration ensured bythe National Center, a highly efficient infrastructure operating in the final step guarantees the rapid transfer ofscientific advancements to the benefit of patients. Moreover, the accessibility to the other members of the **NC**,distributed over the entire Country, will greatly increase the accessibility of these innovative treatments, reducing the inter-regional differences and mitigating the sanitary migration. The second advantage is that the Gene Therapy Center will act as a service and training hub, reducing the heterogeneity of products such as gene-modified cells and vectors and establishing standardized procedures and common best practices.
As to the **RNA production platform**, the current RNA production and purification process and the development of standardized industrial protocols have not followed the explosive success of mRNA and

ncRNA applications. A facility for high-quality RNA production is missing in Italy and represents essential support for industrializing the R&D advancements of the "vertical", disease-oriented Spokes. At the same time, the Facility will be supported by the activity of "horizontal", technology-oriented Spokes: basic research on RNA synthesis, formulation and delivery (the 'RNA technology platform') as well as the necessary tools for the pre-clinical *in vitro* and *in vivo* testing of its biological activity. To produce material for clinical studies, the Facility will be equipped with a quality system that is approved by the regulatory agencies (AIFA, EMA) and will have a Qualified Person (QP) as required by cGMP guidelines to authorize the release materials for clinical use.

ABBREVATION	FULL NAME
CNR	Consiglio Nazionale delle Ricerche
HUNIMED	Humanitas University
IIT	Istituto Italiano di Tecnologia
OPBG	Ospedale Pediatrico Bambino Gesù
RI.MED	Fondazione Ri.MED
UMG	Università Magna Grecia
UNIBA	Università di Bari
UNIBO	Università di Bologna
UNIBS	Università di Brescia
UNICA	Università di Cagliari
UNICAMPANIA	Università della Campania - Vanvitelli
UNICH	Università G. D'Annunzio
UNICT	Università di Catania
UNIFI	Università di Firenze
UNIMI	Università di Milano
UNIMIB	Università Milano Bicocca
UNIMORE	Università di Modena e Reggio Emilia
UNINA	Università di Napoli Federico II
UNIPA	Università di Palermo
UNIPI	Università di Pisa
UNIPD	Università di Padova
UNIPV	Università di Pavia
UNIROMA1	Sapienza Università di Roma
UNIROMA2	Università di Roma Tor Vergata
UNISA	Università di Salerno
UNISI	Università di Siena
UNISR	Università Vita-Salute San Raffaele
UNITO	Università di Torino
UNITS	Università di Trieste
UNIVR	Università di Verona
TETTAMANTI	Fondazione Tettamanti
TELETHON (TIGEM/TIGET)	Fondazione Telethon

DOMPÈ	Dompè Farmaceutici SpA
TAKIS	Takis Biotech
CHIESI	Chiesi Farmaceutici SpA
EUROFINS	Eurofins Biolab
NOVARTIS	Novartis International AG
PFIZER	Pfizer INC
STEVANATO	Stevanato Group SpA
PBL	PBL Srl
INNOVAVECTOR	Innovavector Srl
SANOFI	Sanofi
ASTRAZENECA	Astrazeneca
BRACCO (CDI)	Bracco SpA
BIONTECH	BioNTech
ANTARES	Antares Vision Group
ORGENESIS	Orgenesis Italy Srl
IRBM	IRBM SpA
INTESA SAN PAOLO	Intesa Sanpaolo Group

B CHARACTERISTICS, FEASIBILITY AND CONTROL

B.1 Composition of the NC for Gene Therapy and Drugs based on RNA Technology

Spoke & Affiliates

The National Center for Gene Therapy and Drugs based on RNA Technology (hereafter **NC**) sees the involvement of 48 Organizations of which 32 Universities and Research Institutes and 16 Private Companies. Universities and Research Institutes are distributed over 10 spoke according to what shown in Figure B.1.

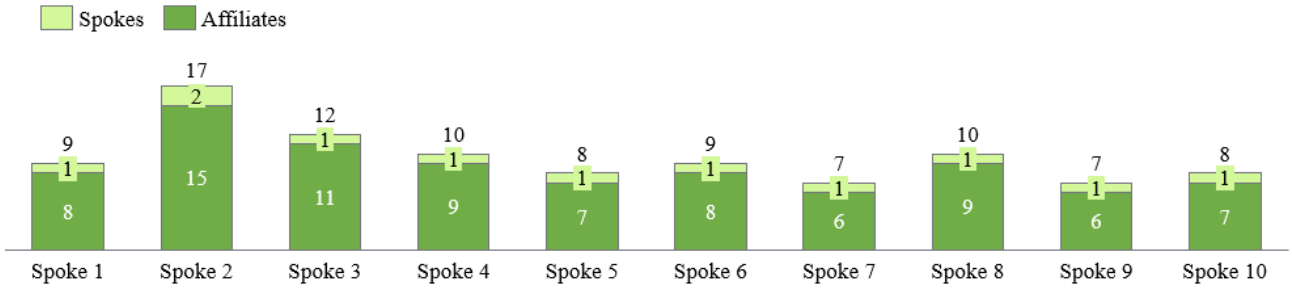

Figure B. 1 - Number of Participants: Spokes and Affiliates

The specific affiliations of private companies to spokes are reported in Figure B.2.

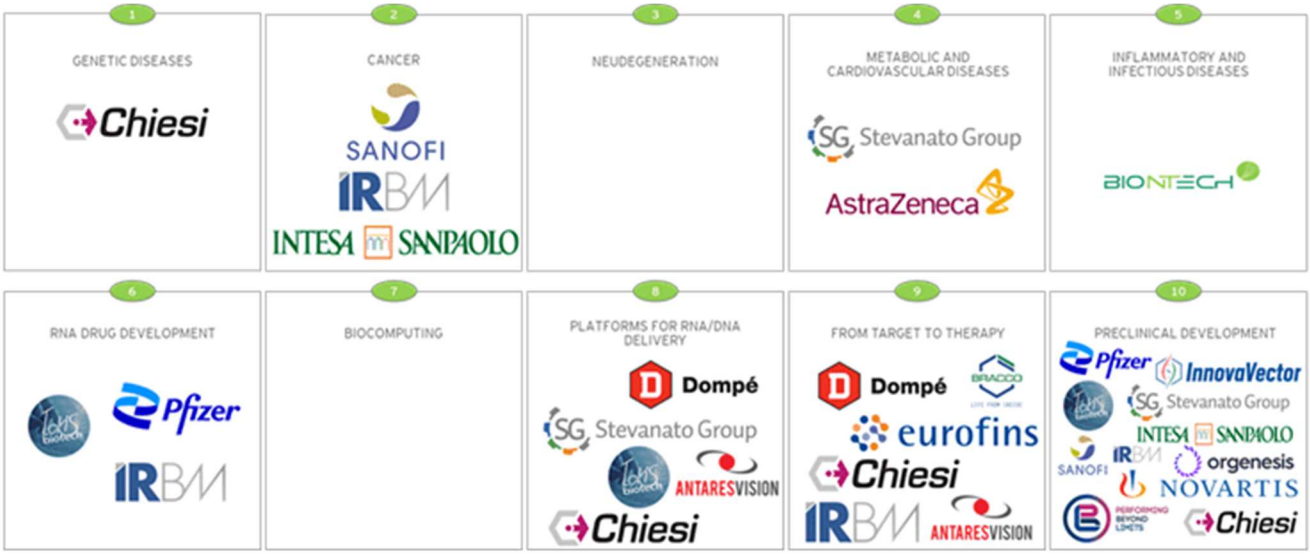

Figure B. 2 - Private companies for spoke of interest

Human Resources

The total number of Human Resources of Universities and Research Institutes dedicated to research activities is 940, both permanent and tenure track personnel as defined in the Call. They represent the critical mass, distributed among the Spokes as depicted in the Figure B.3. Overall, the critical mass of each Spoke and its affiliates is on average 95 resources, including more than 60 for at least 3 months/person/year. This meets the minimum requirements of Article 7, paragraph 3 of the Call: i) each Spoke devotes at least 7 researchers to the research programme, of which at least 5 for 3 months/person/year ii) each Affiliate dedicates at least 7 researchers to the Research Programme, including at least 4 for 3 months/person/year – further details are available in The Attachment 1 "**NC** for RNA technology drug development and gene therapy Critical Mass Details".

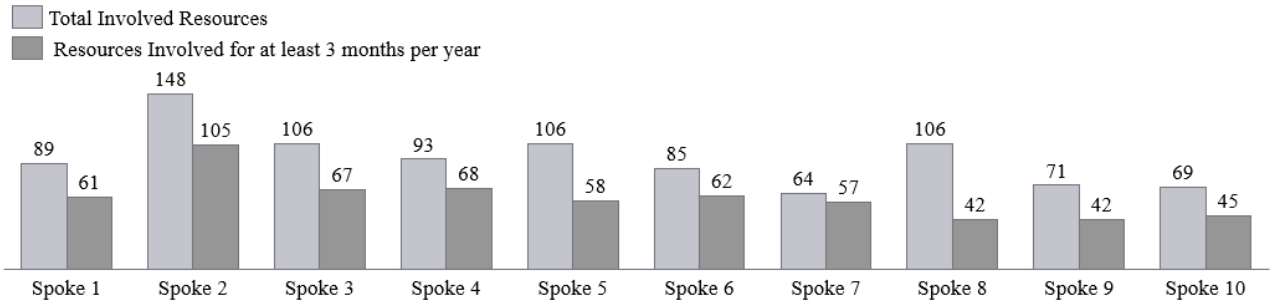

Figure B. 3 - Total Number of Resources and Number of Resources involved for at least 3 months per year

As to private companies, their personnel, who does not contribute to the total cost of the programme, will include at least 7 researchers including 4 for 3 months/person/year.

B.2 Management and Administrative Structure

Governance

The NC's Research Programme is managed by a Hub under the legal form of a Foundation in which the majority of the members (25 members) are Public Universities and Research Institutes supervised by MUR. Private Universities, IRCCS and Private Companies represent only the minorities, as requested by the Call (also in terms of voting rights in the appointment of the Supervisory Board/Management Board of directors' member). The table below (see Figure B.4) lists all the Founders of the Foundation and their legal form, clarifying the entities located in southern Italy.

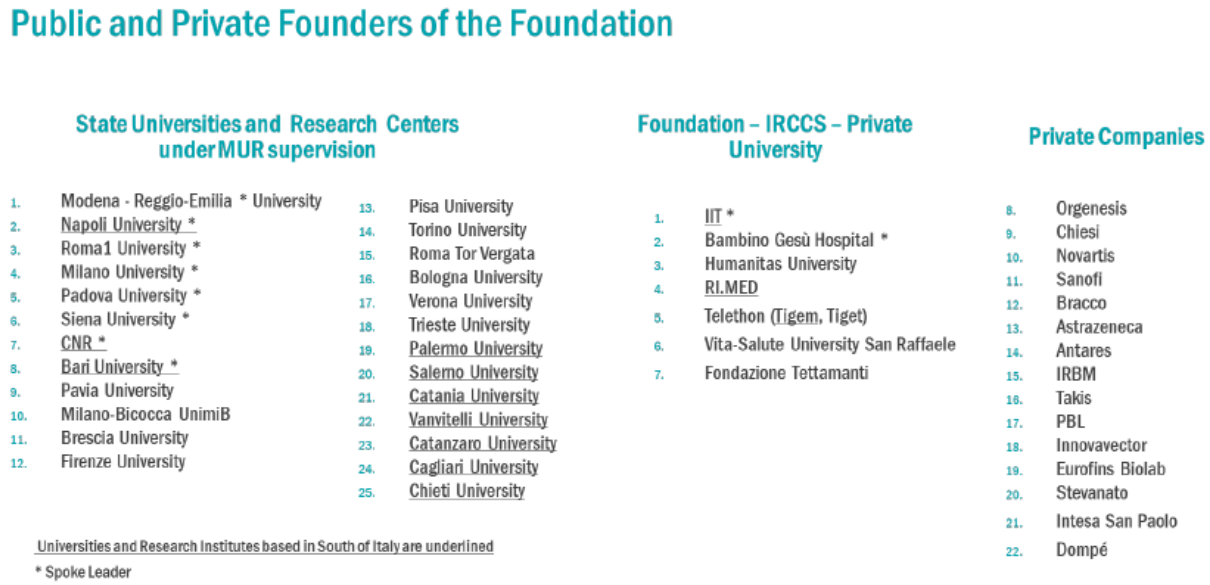

Figure B. 4 - List of the Founders of the Foundation

	MUR *State Universities and Research Centers under MUR supervision*	***PRIVATES*** *Foundation – IRCCS – Private University – Private Companies*	***Total***
Promoters	17	13	30
Participants	8	9	17
Total	***25***	***22***	47

Figure B. 5 – Number of Promoters and Participants at the current stage

The Foundation will have a two-tier governance system, with the Board of Directors (Management Board) having a strategic role and the Supervisory Board a monitoring one. The boards remain in office for four years and their members may be

reappointed. The Supervisory Board is made up by members appointed by each Promoter and minorities appointed by the Associated Partners. The Board of Directors is appointed by the Supervisory Board. The Foundation Bylaws will establish that the Board of Directors will be appointed by the Promoters under MUR supervision, while the Supervisory Board will be appointed by both Promoters and Participants. Finally, the Supervisory Board will appoint the Industrial Board, the International Scientific Advisory Board, Industrial Board and Ombudsman Team. The Industrial Board will ensure the appropriate level of synergies between research and the technology transfer activities. The Scientific Committee, made up by the Spoke leaders, coordinates the activities and the collaboration among the Spokes. Additionally, at the Spoke level, a Spoke Committee monitors the execution and implementation of the research programme. Finally, the International Scientific Advisory Board will provide independent assessment of the progress in the research programme (see Figure B.6).

The admission of a new member of the Foundation is decided by the Management Board upon the request of the interested party addressed to the same Management Board with an application that must prove the possession of the participation requirements. Membership is approved by a majority of these eligible to vote:

- Members of the Management Board
- At least 3 members of the Supervisory Board
- At least 7 members of the foundation.

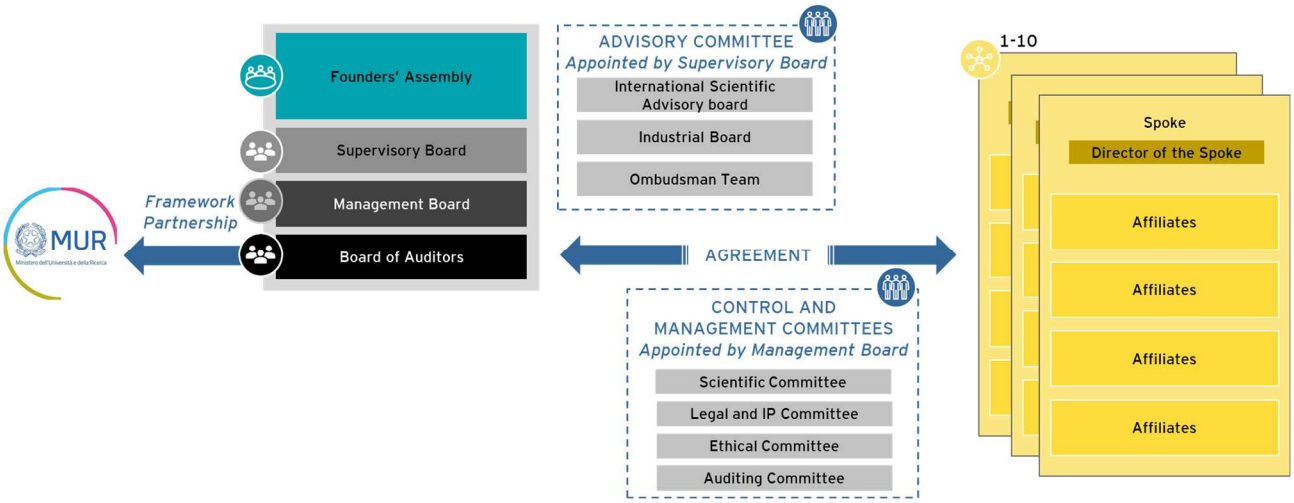

Figure B. 6 - The Governance structure of the Foundation

The Foundation Bylaw in order to establish an effective governance will clearly define the role and the responsibilities of the different decision-making bodies. To achieve Research Programme's milestones and targets, the Foundation Bylaw will be defined with the goal to guarantee a strong strategic decision-making power along with strong control mechanisms and processes. The choice of a two-tier governance system is linked with the need to ensure solid complexity management, decision and competence framework, empowerment, and process effectiveness as well as strong monitoring processes. The following Figure B.7 clarifies some of the main role of the decision-making bodies.

COMPOSITION	ROLE *(non-exhaustive)*
FOUNDERS' ASSEMBLY	
Founders - **Promoters:** Universities or Public Research Institutions overseen by MUR, public or private companies primarily active in the field of interest with full voting rights - **Participants:** public/private legal entities and institutions (Universities or companies) with limited voting rights	• Appoints the Supervisory Board (see note) and its President • Approves the code of ethics and deontology, on the proposal of the Supervisory Board • Determines the compensation of the Supervisory Board • Decides by a qualified majority of two thirds on the dissolution of the Foundation and the destination of its assets and on amendments to the Statute (with different voting rights between Promoters and participants: Ratio 4 to 1). It is convened at least once a year to report on the supervisory activities done by the Supervisory Board. Note: The appointment of the Supervisory board is carried out through list voting. The lists must contain the indication of all the members of the Supervisory board and must be signed by at least one third of the members. *The other roles, responsibilities and competences of the different Founders are defined in the Bylaw.*
SUPERVISORY BOARD	
Supervisory Board: composed of entities chosen among the Foundation's members. Of these. The Supervisory Board is chaired by the President of the National Center.	• Approves the budget and final accounts • Approves the strategic plan • Appoints the board of auditors and advisory committees. • Decides on the admission and exclusion of new members. • Prepares, after consulting the Ethics Committee and the Scientific Committee, the code of ethics and deontology regulating the expected behaviors and the conflict of interest and proposes it for approval to the Assembly. • Determines the compensation of the Management Board.
MANAGEMENT BOARD - PRESIDENT	
Management Board: composed of 10 people, designated by the Promoters, and the President, designated by the Proponent. Among the 10, 6 components are designated within the subjects supervised by the MUR and 4 among the subjects not supervised by the MUR. If there are not 4 subjects not supervised by the MUR, the missing components will be identified among the subjects supervised by the MUR. **President:** identified by the proposing subject, is the legal representative of the NC and exercises the powers vested in him/her by the Board.	• Has the power of ordinary and extraordinary administration within the limits of what is not expressly reserved to the other bodies. • Appoints the management and control committees. • Approves the recruitment plan and career development plan. • Determines the compensation of the President and any managing directors.
BOARD OF AUDITORS	
Audit committee: Appointed by the General Meeting, it is made up of 3 standing members and two alternates. Among the standing members, at least 2 must be enrolled in the register of auditors. Among the standing members, the Chairman is identified by the Supervisory Board.	
INTERNATIONAL SCIENTIFIC ADVISORY BOARD	
International Scientific Advisory board: Composed of a number between 3 and 7 independent experts with high technical or scientific qualifications. Appointed by the Supervisory Board The experts must be independent. The President is elected internally.	• Has a scientific advisory functions and expresses opinions on the level of achievement of the project's scientific results
INDUSTRIAL BOARD	
Industrial Board: composed of identified among the companies that are Promoters non-public promoter members with a representation of non-public Participants companies (which cannot exceed 1/3 of the total number of members of the Committee). The members must not be part of the MB and SB. Appointed by the Supervisory Board The experts must be independent. The President is elected internally.	• Evaluates the strategies, the economic vision of the life science & pharma sector and the industrial exploitation of the research products.
OMBUDSMAN TEAM	
Ombudsman Team: composed of 5 people appointed by the Supervisory Board, choosing them among external experts in organizational or legal matters and among internal people of the project (research and administrative staff) on the basis of an internal call. The external components consist of 3 people and the internal component consists of 2 people. The President is elected internally (Among the externals).	
SCIENTIFIC COMMITTEE	
Scientific Committee: appointed by the Management Board. composed of the spoke leaders and is chaired by the president of the Management Board or one of its delegate.	• Has functions of direction, coordination and monitoring of the scientific progress of the projects. • Proposes to the MB the internationalization plan of the research activities and supports the internal communication activities.
LEGAL AND IP COMMITTEE	
Legal and IP Committee (Industrial Property): Appointed by the MB, after consultation with the industrial board. The President is appointed by Management Board.	• Proposes to the MB the guidelines for the exploitation of intellectual property (IP) with particular reference to the patenting of research products and their exploitation (sale and licensing). • Expresses opinions on agreements relating to the exploitation of research, also at international level.
AUDITING COMMITTEE	
Auditing Committee: Appointed by the MB.	• Monitors economic, administrative and financial activities, the use of funds, the transparency of their use, and compliance with regulatory constraints of project reporting.
ETHICAL COMMITTEE	
Ethical Commitee: Appointed by the MB.	• Supervises compliance with European and national legislation on clinical trials in humans and animals. • Expresses the internal policies and monitors their implementation. • Expresses its opinion on conflict of interest.
SPOKE COMMITTEE	
• Representatives of the Spoke Leaders and Affiliates	• Monitors the Execution and implementation of the Research Programme at the spoke level • Issues call for proposals, defining the selection criteria • Receives funding from the Hub and carries out reporting and monitoring activities

Figure B. 7 – Composition and role of the governing bodies

Recruitment Plan

The recruitment plan is prepared by the Scientific committee and approved by the Board of Directors of the NC. Following the plan, young researchers will be recruited by the Universities involved in the projects, in compliance with the Italian legislation.

The recruitment of young researchers will take place through public selections and will be advertised using both mandatory channels (Official Journal of the Italian Republic - GURI - and Official Journal of the European Community - GUCE) and international online portals devoted to the recruitment in research, such as Research Gate. For the recruitment of the winners of international competitions, such as the MSCA, the Universities will make direct calls, subject to the authorization of the MUR under Italian legislation.

Organizational Model

In order to carry out the management and coordination activities required by the Research Program, the Hub nominates a General Director (the Program Research Manager), who is responsible for the implementation of the planned activities. The Director is supported by the Hub operational units, each assigned with specific functions relating to the obligations of the promoting entity. The following picture depicts the organizational model of the Hub and summarizes the main functions of each operational unit.

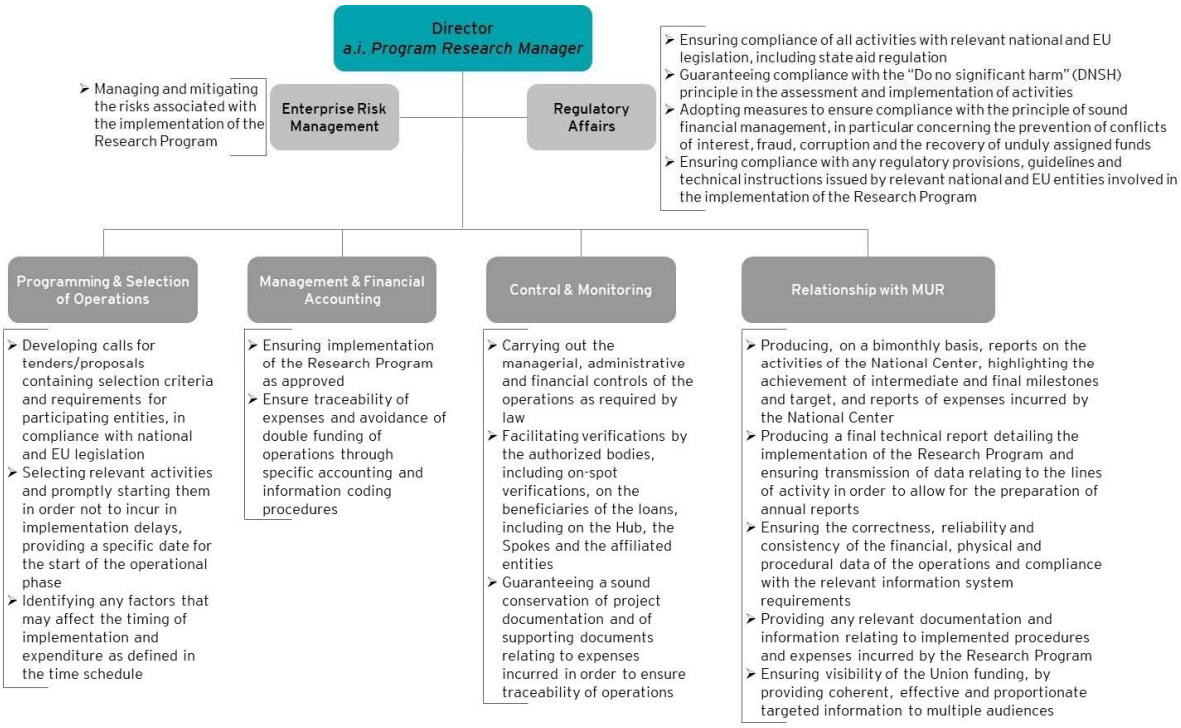

Figure B. 8 – Organizational structure of the Foundation

Financial Reporting

In order to account and report costs, the Hub shall ensure compliance of the Research Program with national and EU regulations, also considering the regulations relating to labor rights and public procurement. Moreover, financial reporting shall comply with rules related to the eligibility of expenditures under the European Structural and Investment Funds. For some costs a simplified cost options may be used: more specifically, staff costs shall be calculated with standard scales of unit costs, while a flat rate of up to 15% of direct staff costs shall be used to calculate indirect costs.

Generally, the costs incurred during the Research Program within the **NC** and carried out in the Spokes shall be reported to the Hub. The Hub, to report the costs of the Spokes and of the Hub itself, shall perform the management and administrative accounting controls required by the applicable regulations to ensure the regularity of the procedures and incurred expenses, as well as to demonstrate the traceability of all the costs related to the project. Moreover, the Hub shall prevent conflicts of interest, fraud, corruption and the recovery of unduly assigned funds: for example, the Hub shall ensure that the expenses of the Center are not covered by other financial aid from national and/or EU public funds.

A management accounting system capable of evaluating, monitoring and measuring the expenses incurred at Spoke level will be implemented by the Hub. Furthermore, the Hub will implement a shared process to standardize collection of financial data from each Spoke and transmit it regularly to the MUR through the dedicated information systems. The MUR, the MEF, the EC and other authorized bodies will indeed carry out surveillance, evaluation, financial management, verification and audit activities, including first level controls at the beneficiaries.

B.3 OPERATIONAL UNITS THAT ARE EXPECTED TO BE INVOLVED IN THE DEPLOYMENT OF THE RESEARCH ACTIVITIES FOR EACH PARTNERS

Partner	Operational Units
CNR	Institute of Systems Analysis and Informatics; Institute for Polymers, Composites and Biomaterials; Institute for Endocrinology and Oncology "Gaetano Salvatore"; Institute of Genetics and Biophysics "Adriano Buzzati Traverso"; Institute of Molecular Genetics; Institute of Clinical Physiology; Institute of biostructures and bioimaging; Institute of Biophysics; Nanoscience Institute; Institute of Chemical Sciences and Technologies Nanotec
UNIMIB	Department of Biotechnology and Bioscience; Department Medicines and Surgery; Department IT systems and communication; Department Physics "Giuseppe Occhialini"
HUMANITAS	Department Biomedical Sciences
IIT	Synaptic Plasticity of Inhibitory Networks; Brain Development and Disease; Non-coding RNAs and RNA-based therapeutics; Nanotechnologies for Neurosciences; RNA Systems Biology; Neurobiology of miRNA; Synthetic and Systems Biology for Biomedicine; Neuromodulation of Cortical and Subcortical Circuits; Nanoscopic & NIC@IIT; Molecular Microscopy and Spectroscopy; Genomic Science; Genetics and Epigenetics of Behavior; Analytical Chemistry Lab; Translational Pharmacology Facility; Computational & Chemical Biology; Molecular Modeling and Drug Discovery; D3 Pharma-chemistry; Bio-logic Materials; Polymers and Biomaterials; Nano-bio interactions & Nano-diagnostics; Molecular Medicine; Smart Materials
OPBG	Department of Hematology; Oncology and Gene & Cell Therapy; Direction of personalized medicine; Unit of Gene Therapy; GMP Facility
Ri.MED	Regenerative Medicine and Immunotherapy Area; Drug Discovery Area (Proteomic Group, Molecular Informatics, Medicinal Chemistry, HTS, Advanced Data Analysis Groups); Bio-engineering Group
TETTAMANTI	Department Experimental and Clinal Medicines; Functional Genomics and Molecular Pathology; Department Medicines and Surgery; Research center in Biochemistry and Advanced Molecular Biology; Neuroscience Research Center
TELETHON	Telethon Institute of Genetics and Medicine; San Raffaele Telethon Institute for Gene Therapy (SR-TIGET)
UMG	Department Experimental and Clinal Medicines; Functional Genomics and Molecular Pathology; Department Medicines and Surgery; Neuroscience Research Center; Research center in Biochemistry and Advanced Molecular Biology;
UNIBA	Department of Biosciences, Biotechnology & Biopharmaceutics; Department of Pharmacy and Pharmaceutical Sciences; Department of Biology; School of Medicine: Dept of Basic Medical Sciences, Neuroscience and Sense Organs, and Dept of Biomedical Sciences and Human Oncology; Interdisciplinary department of medicine; Department of Emergency and Organ Transplantation; Department of Physics; IT department
UNIBO	Departments: Medical and Surgical Sciences; Biomedical and Neuromotor Sciences; Pharmacy and Biotechnology; Experimental, Diagnostic and Specialty Medicine; Chemistry
UNIBS	Department of Molecular and Translational Medicine; Department of Experimental Clinical Sciences
UNICA	Department of Biomedical Sciences and Public Health; Department of Medical Sciences; Department of Environmental Sciences; Electrical and Electronic Engineering
UNICH	Department of Medical science, dental science and Biotechnology; Department of Pharmacy
UNICT	Department of Biomedical and Biotechnological; Department of Clinical and Experimental Medicine; Department of Medical, Surgical Sciences and Advanced Technologies; Department of Biological, Geological and Environmental Sciences; Department of General Surgery and Medical-Surgical Specialties; Department of Drug and Health Sciences

UNIFI	Biomedical, Experimental and Clinical Sciences “Mario Serio”; Department of Experimental and Clinical Medicine
UNIMORE	Department of Life Sciences; Department Medicines and Surgery, Maternal-Infantile and Adult; Regenerative Medicine Center "S. Ferrari"
UNINA	Department of Molecular Medicine and Medical Biotechnology; Department of Translational Medical Sciences; Department of Public Health; Neurosciences; Chemical, Materials and Production Engineering; Department of Pharmacy; Departments of Advanced Biomedical Sciences; Departments of Veterinary Medicine and Animal Production; Chemical Sciences; Physics; Electrical Engineering and Information Technologies; Biology
UNIPA	Department of Biological, Chemical and Pharmaceutical Sciences and Technologies; Department of Biomedicine, Neuroscience and Advanced Diagnostics
UNIPI	Department of Clinical and Experimental Medicine; Department of Translational Research and of New Surgical and Medical Technologies; Department of Biology; Department of Pharmacy; Department of Physics; Department of Chemistry and Industrial Chemistry; Department of surgical pathology, medical, molecular and of critical area
UNIMI	Bioscience; Pathophysiology and Transplantation; DIPO; Health Sciences; Medical Biotechnology and Translational Medicine; Oncology and Hematology-Oncology; Pharmacological and Biomolecular Sciences; Biomedical, Surgical and Dental Sciences; Biomedical and Clinical Sciences "L. Sacco"; Pharmaceutical Sciences; Health Science; Computer Science; Biosciences; Chemistry; BIOMETRA; Clinical Sciences and Community Health
UNIPD	Department of: Biology; Neuroscience; Women's and Child's Health; Biomedical Science; Information Engineering; Surgical, Oncological, Gastroenterological Science; Medicine; Molecular Medicine; Industrial Engineering; Biomedical Science; Study Center for Neurodegeneration; Pharmaceutical Sciences; Chemical Science; Biomedical Sciences, Medicine, Physics and Astronomy; General Psychology; Cardo-Thoracic-Vascular Science and Public Health;
UNIPV	Departments: Molecular medicines; Internal Medicine and Medical Therapy; Civil Engineering and Architecture; Dept Drug Sciences; Dept Chemistry; Dept Biology and Biotechnology
UNIROMA1	Department of Molecular Medicines; Department of Experimental Medicines; Department of chemistry and Pharmaceutical Technologies; Department of Physiology and Pharmacology; Department of Anatomical and Histological Sciences; Department of Biochemical Sciences; Department of Biology and Biotechnology; Department of Neurological science; Department of Translational Medicine
UNIROMA2	Department of Biomedicine and Prevention; Department of Systems Medicine; Department of Chemical Sciences and Technologies; Department of Biology; Department of Experimental Medicine
UNISA	Department of Medicine; Department of Pharmacy; National industrial engineering department
UNISI	Dept of Medical Biotechnologies; Dept. of Molecular and Developmental Medicine; Dept. of Medicine, Surgery and Neurosciences
UNISR	Faculty of Medicine and Surgery
UNITO	Department of Molecular Biotechnology and Health Sciences; Department of Drug Science and Technology; Department of Oncology; Department of Life Sciences and Biological Systems; Department of Medical Sciences; Department of Chemistry; Department of Veterinary Sciences
UNITS	Department of Life Science; Dep of Medical Science, Surgery and Health; Department of Chemical and Pharmaceutical Sciences
UNIVR	Departments of Medicine, of Diagnostics and Public Health, of Neuroscience, Biomedicine and Movement, of Computer Sciences, and of Biotechnologies
UNICAMPANIA	Department of Medical-Surgical and Dental Specialties; Department of Precision Medicine; Dep of Environmental, Biological and Pharmaceutical Sciences and Technologies; Department of Mental Health, Physics and of Preventive Medicine

B.4 WORKING PLAN & FEASIBILITY

The NC has the ambition of placing Italy at the leading edge of discovery in RNA therapeutics and gene therapy. In this fiercely competitive field, we plan to support the project proposals that effectively address the challenges and obstacles all along the way from discovery to clinical development. We will support projects proposing effective technological solutions and/or new breakthrough concepts that go far beyond the current state-of-the-art. We will take the opportunity of **TRL development grants** to further strengthen the areas necessary to the success of the Center and to further progress. We deliberately selected projects starting at a different TRL to create a pipeline of products ensuring sustainability in time. Furthermore, open calls (***bandi a cascata***) will allow each Spoke to extend beyond its competences by acquiring novel skills and technologies through a competitive selection process. To ensure the feasibility of the technical objectives, we decided to support the research activities with talented young researchers recruited to meet the deliverables of each project. We plan to open **194 positions for young researchers as Tenure Track Researchers Type A** (RTD-A) (65 by the end of 2022 and 129 by the end of 2023) and start the recruitment path in the first six months of the program. To encourage attraction of young talent **from other EU and non-EU countries** and extend the competences useful to advance research activities planned in NC, a starting research grant (**Start-up Package**) will be attributed.

The program is also devoted to training in excellent science covering all disciplines necessary to create innovation in the field of RNA therapeutics and gene therapy. To this purpose, we plan to support research activities with an intense **PhD student recruitment plan**. As a first step, we will co-fund selected PhD training programs relevant for the Center topics and already available near the Spokes/Spoke affiliates, supporting 170 supplementary PhD positions (56 for 1 cycle and 57 for 2/3 cycle).

As a second step, we propose a **new specific industrial national doctoral training programme** that goes beyond the 'classical division of sciences', enabling the doctoral candidates (DCs) to become ready to respond to the present and future challenges in the discovery area of RNA therapeutics and gene therapy. Through training, secondments, courses, and workshops, and intersectoral collaborations between National Center participants (University and Private Companies), participants, the DCs will experience a multidisciplinary research environment and be exposed to the academic, clinical and industrial sectors. In the short term, DCs will be ready to address the unmet needs in the different research area covered, and in the long-term, they will acquire the right set of skills to transfer this knowledge to other disease areas. A key aspect of the PhD program is to train DCs to comprehend the necessity to have a clinically relevant solution and how to find the economic and technological tools indispensable to carry out research. The students will be involved in the processes of dissemination and exploitation of the project results. The PhD program will train the DCs in IP-related issues, health-economic impact issues, market analysis and business-oriented processes. Training activities will be provided through the organization of workshops, schools and regular courses at Universities of NC consortium that also provide important networking opportunities for all ESRs. Local training will be organized in "Training through research" and "Training through university PhD courses". Besides, we envisage a Network-wide training that will cover 6 courses (3 introductory in the first 2 years of the programme, and 3 advanced in the middle period) and 2 workshops that are designed specifically to address education in the key topics of vertical and horizontal spokes. The programme will offer further an introductory and advanced course in Business and Entrepreneurship with a focus on pharmaceuticals. This training is complemented by obligatory courses in soft and transferable skills useful for personal career development.

As a long-life learning initiative, we envisage to adopt the successful model of Academies set up at University of Napoli Federico II creating the PharmaTech Academy. The objective is to propose a new training paradigm based on the concept of Learning by Doing, in which where University and Private Companies closely collaborate in the definition of the professional profile and in the training activities to meet the requirements of the next generation of young talents in the pharmaceutical arena.

PharmaTech Academy aims to broaden the skills provided in the degree courses with an experiential approach and direct contact with the world of the pharmaceutical companies, thus providing both specialized (hard) skills in high-tech sectors and personal (soft) skills. **PharmaTech Academy** is designed by combining traditional classroom training with practical activity sessions that can bring students closer to fill the gap on skills necessary to enter the job market, with increasingly updated and specific skills for the Pharma sector. The co-designing approach will be based on the close collaboration among **NC** participants, including Private Companies, providing the operational skills that the labour market requires with the teaching methodology centered on group work. The trans-disciplinary approach, i.e. combining technological and professionalizing subjects, with themes linked to the participants' design and conceptual skills, and their ability to manage processes, work in teams, and communicate effectively, will also be used in the **PharmaTech Academy**. Finally, spaces will be created to encourage this approach, abandoning the classic polarized classrooms favoring laboratories and co-working areas. The training programme, defined in a strict collaboration with Private Companies, will be based on a challenge-based approach, where the students will face real challenges offered by the companies involved, and on workshop sessions focused on very specific issues relating to the labor market, starting from the preparation of the Curriculum Vitae,

the job search, the preparation of the interview and its phases as well as the processing of the feedback. In this phase the training will take advantage of cutting-edge technology laboratories specifically equipped to train the candidates to modern technologies in RNA-based medicine and gene therapy. The laboratories will be designed and built to be empowered by the immersive reality laboratory, based on hologram technology, allowing a direct experience and visualization of complex structures, enabling to successfully adapt and apply what has been learned in a variety of real-life scenarios. This approach dramatically increases student engagement and allows students to assimilate complex information more efficiently and retain it longer. Industrial traineeship phase will be a key part of **PharmaTech Academy**, providing the participants a direct experience with the Pharma world and allowing a unique opportunity to test their soft and hard skills. The design of specific professional profiles meeting the needs of the pharmaceutical companies will provide options of training on a particular professional profile within the companies (e.g. discovery pipelines, analytics, cGxP, Quality-by-design, Regulatory Affairs -development, registration, market approval, manufacturing, distribution, and post-marketing surveillance- of Advanced Therapy Medicine and RNA-based medicine).

PharmaTech Academy will be set up in an area of around 1,000 sqm in the new Federico II building in the *Scampia district*. Other spaces (about 300 sqm) can be made available at the Department of Pharmacy. All the spaces will be designed according to the learning by doing paradigm, equipped in a way that is functional to the training objectives. Two open-space classrooms (overall around 500 sqm) for interactive teaching equipped for training methodologies based on team-work, and three laboratory spaces with cutting-edge technology for adequate technical training of highly specialized professional figures in the field of RNA-based therapeutics production and gene therapies will be established. Spaces will be prepared for a potential acceptance of up to 200 students/year.

Regarding the necessary **infrastructural requirements**, as detailed in the tables in Section B5, each participant has the equipment required to carry out the proposed work. The complementarity which exists among them in this regard is leveraged to the full in each of the WPs. We also plan to align infrastructures to the international standards (**Spoke flagship**) when needed.

In order to most efficiently transfer the research program to tangible results in terms of cure and economic developments, a significant effort is planned toward the critical bottlenecks of advanced therapies: the clinical centers of gene therapy and the construction of a National GMP Platform for RNA production.

The **Gene therapy Center** will base on the already existing GMP facilities at Ospedale Pediatrico Bambino Gesù (OPBG)/Fondazione Tettamanti, both authorized for the gene modification of somatic cells for manufacturing drug products. The facilities will be refurbished to increase their capability, the implementing scale-up to GMP-compatible processes of the innovative drug products to be tested subsequently in early-stage clinical trials.

The **RNA production platform** will serve the research groups of the Center and will be devoted to RNA synthesis and formulation. The Facility will be equipped with state-of-the-art instrumentation, capable of making the manufacturing processes “agile” but at the same time robust and reproducible. The Facility will be equipped with a quality system approved by the regulatory agencies (AIFA) and will have a Qualified Person (QP) according to European and US cGMP guidelines and will be able to release materials for clinical use.

We envision a future where every technology developed in Center is given the opportunity to make an economic impact. To this purpose, we plan to establish a **Technology Transfer Office (TTO)** at the Hub level serving the NC as a one-stop window for all the IP-related matters and in a position to bridge the gap between invention and commercialization. TTO is expected to create awareness and encourage researchers to establish an organizational culture that fosters technology transfer. The underpinning functions are: 1) serve as liaison officers between academic scientists and industry and manage the university’s IP; 2) support and foster spin-offs; 3) build a strong IP portfolio; 4) mediate between parties involved in the commercialization process like the inventors and industries; 5) negotiate with the prospective licensees.

MLS	Description
MLS1	Planning of the recruitment of RTDa identifying areas of expertise and all the detail needed to issue the public selection for RTDa (20% of the total number)
MLS2	Planning of the recruitment of RTDa identifying areas of expertise and all the detail needed to issue the public selection for RTDa (30% of the total number)
MLS3	Planning of the recruitment of RTDa identifying areas of expertise and all the detail needed to issue the public selection for RTDa (50% of the total number)
MLS4	Planning of the public selection for PhD by Spoke leader and affiliates identifying areas of expertise and all the other detail to issue the call (1/3 of the total number)
MLS5	Planning of the public selection for PhD by Spoke leader and affiliates identifying areas of expertise and all the other detail to issue the call (1/3 of the total number)
MLS6	Planning of the public selection for PhD by Spoke leader and affiliates identifying areas of expertise and all the other detail to issue the call (1/3 of the total number)
MLS7	Financing of staff and indirect related costs (at least of 10%of total person months)
MLS8	Financing of staff and indirect related costs (at least of 35%of total person months)
MLS9	Financing of staff and indirect related costs (at least of 85%of total person months)
MLS10	Financing of staff and indirect related costs (at least of 100%of total person months)
MLS11	Spoke flagship: identification and detailed plan of infrastructures and materials needed for Spoke activities
MLS12	Spoke flagship: Mid-term Identification and detailed plan of infrastructures and materials needed for Spoke activities
MLS13	Gene Therapy Center: Starting the infrastructure implementation
MLS14	Gene Therapy Center: Completing the infrastructure implementation
MLS15	RNA production platform: starting the infrastructure implementation at 50%
MLS16	RNA production platform: starting the infrastructure implementation refining
MLS17	Approval of the national PhD program
MLS18	Definition of the program and timetable of the training for the technicians
MLS19	Issue the call for the TRL development grants year 1
MLS20	Issue the call for the TRL development grants year 2
MLS21	Issue the call for the TRL development grants year 3
MLS22	Issue the open call year 1
MLS23	Issue the open call year 2
MLS24	Issue the open call year 3
MLS25	Spin off and start-up accelerators program year 2
MLS26	Spin off and start-up accelerators program year 3
MLS27	Technology transfer activities program year 1
MLS28	Technology transfer activities program year 2
MLS29	Technology transfer activities program year 3
MLS30	Approval and reporting administrative expensens year 1
MLS31	Approval and reporting administrative expensens years 2 and 3
MLS32	Recruitment of the Program manager and set-up of the management processes related to the control of research activities

Figure B. 5 - The Major Milestones (MS) of the overall program

Project Management Office (PMO)

The Project Management Office (PMO) function is introduced in order to ensure constant dialogue and collaboration Between the Hub and the Spokes about the progress of the Research Program. The Objective is to monitor, check and modify each process/activity managed by the Hub & Spokes to take faster decisions (Approval plan) and improve resources' allocation for the Spokes. Exploiting management and test instruments based on Agile methodology, productivity and service delivery of each process can be more efficient and effective.

The Functionalities of PMO are:

- Project Portfolio allows to manage a big range of processes, each composed by different and complex activities linked together between the Spokes and suggesting how to improve them
- Resources' Management allows to manage, forecast, and allocate all the available resources, depending on their skills and their loads to the most effective Spokes
- Demand Management centralizes all business strategic requests to the Hub in order to address the decisional process through the development of new initiatives and activities able to enhance business in order to accelerate the Spokes' activities
- Agile Development allows to overcome disconnections and changes between Hub & Spokes and exploit them as opportunities
- Test Management is a framework that helps project team and employees in achieving better processes' outputs to better satisfy the progress of the Research Program

Using PMO can bring many advantages to the Hub & Spokes such as:

- Project and process visibility is increased selecting and optimizing each phase of the Research program
- More effectiveness thanks to selection, standardization and planning of processes
- Alignment between strategic priorities and available capital pursuing a long-term planning
- More flexibility both in activities implementation and in budget allocation, depending on needs
- Enhanced Productivity and more efficiency through planning, forecasting, analysis and reports

All these advantages consequently will bring other ones such as agility to respond.

For the Hub and the Spoke approach it will be used a three level PMO structure. The Hub will define the policy, procedures, systems and plan whiles the local satellite PMO will support the projects day to day and then interacts with the Hub &

Spokes.

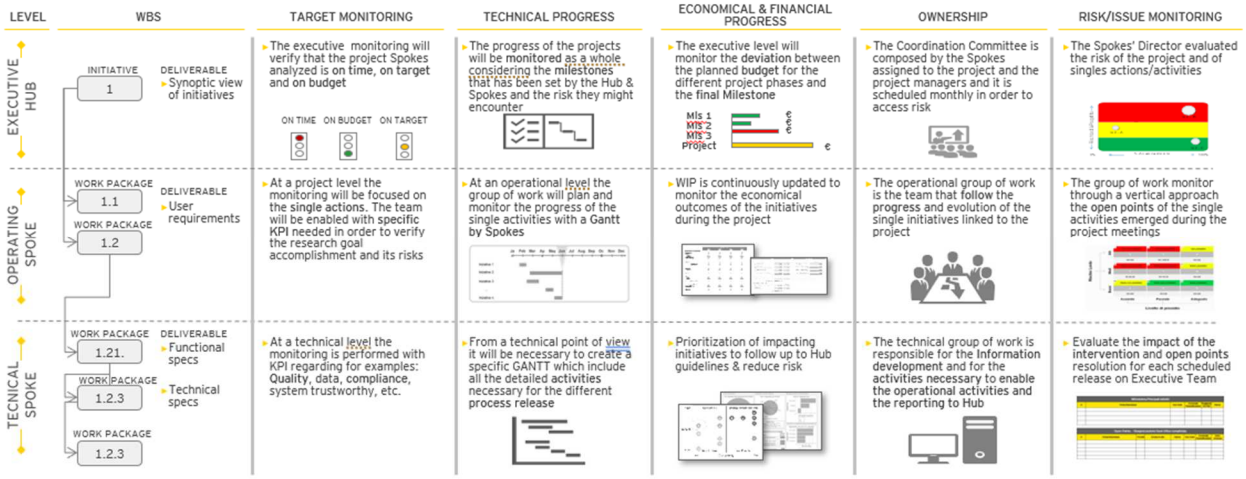

Figure B. 9 – Day to day support and interacts with the Hub & Spokes provided by PMO

WIP is to control project execution effectiveness, in order to ensure WIP Governance & control there are 3 main things to do: Recurrent Weekly status updates by the Spokes, Monthly reforecast thanks to the Coordination Committee outputs and Continuous WIP Monitoring to ensure cost & time effectiveness.

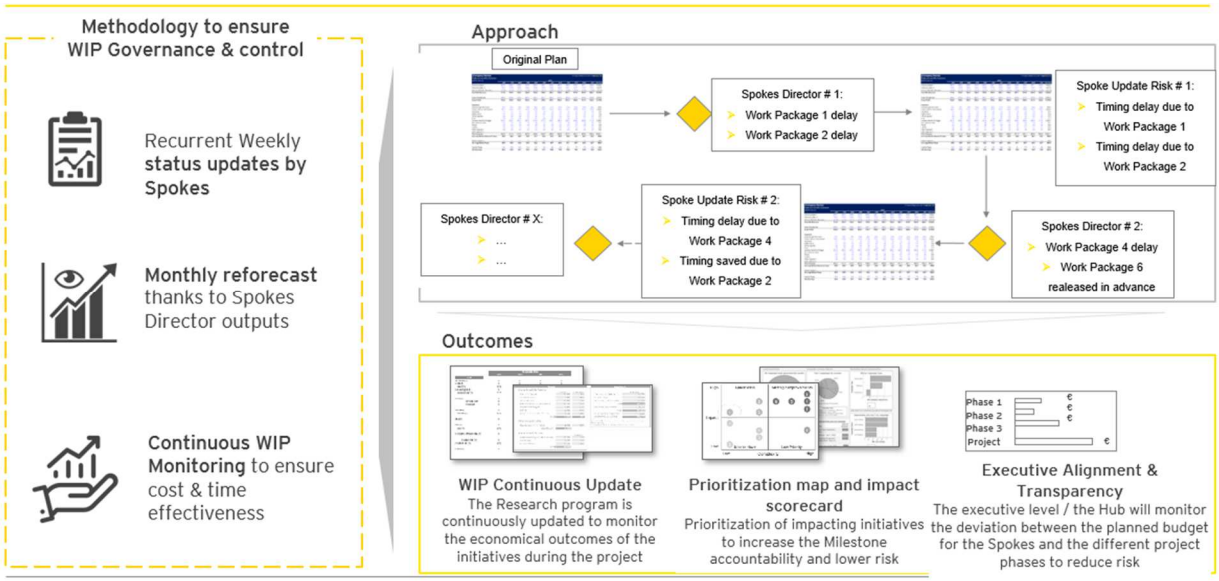

Figure B. 10 – Methodology to ensure WIP governance and control

Budget

The **NC** aims at starting the process of transformation of scientific knowledge in the development of RNA and gene therapies or procedures of pharmacological interest, testing them in preclinical and clinical trials aimed at demonstrating their safety and their potential effectiveness. The **NC** has been specifically designed to promote innovation and technology transfer and in this context the collaboration and the exploitation of the network created with private companies will be essential at several levels: from the selection of the project with higher possibility to become drugs to the development of secure and rapid testing programs and finally to start economic exploitation routes.

To pursue these goals, we confirm that the Total Cost of the Program (Total Grant) financed by the Minister is 320,20 M€. In addition, the **NC** will be supported by private companies with other contributions amounting to 8,77 M€. Therefore, the Total Budget of the program financed both by the Minister and private companies is 328,97 M€ (Total Grant including private co-funding).

Finally, to ensure the possibility to continue its activities at the end of the program the NC receives additional resources from the Founders of the Foundation for 4.9 M€ per year with a total of 14.9 M€ for the entire duration of the PNRR for National Research Centers.

Overall the NC will manage resources amounting to 343.87 M€.

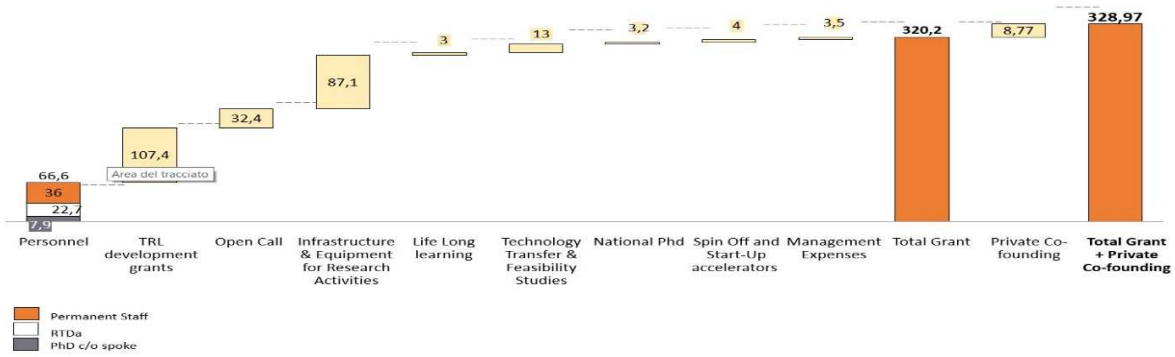

Figure B. 11 – Total Grant

Among the main objectives, the intense focus on innovation and promotion of young scientists are feasible by enhancing the peculiarities of each Spoke and - at the same time - ensuring the strategic guidance and coordination through the central structure of the Hub. Hence, in the definition of the budget, a series of initiatives and activities were considered to be managed centrally – at the Hub level- to ensure the long-term continuation and sustainability of the **NC**.

Nature of costs and allocation criteria
The cost items selected were as follows:

1) Personnel costs: i) Permanent Staff ii) RTDA iii) PhD
2) Infrastructure & Equipment for Research Activities
3) Open Calls & TRL Development Grants
4) Hub Services and Cross-Spokes Activities

Cost	Allocation Criteria
Personnel costs	Allocation on Participants
Infrastructure & Equipment for Research Activities	Allocation on Hub and Spokes according to Preliminary Proposal and Planned Activities
Open Calls & TRL Development Grants	Allocation on Spokes according to Preliminary Proposal and Planned Activities
PharmaTech Academy (Lifelong Learning)	Allocation on Spoke 8 as it will be enrolled by Università Federico II di Napoli
Hub Services and Cross-Spokes Activities	Allocation on Hub

Personnel

- **Permanent Staff:** in each Spoke and Affiliate, the number of permanent Staff will be on an average 9 per participant (including Full Professor, Associate Professor, RTDA/RTDB) with an average cost of 6,5 k€ per month (according to the proposals received by participants)
- **RTDA:** *about* 194 RTDA at a yearly cost of 50 k€
- **PhD:** *about* 170 PhD at a yearly cost of 23 k€

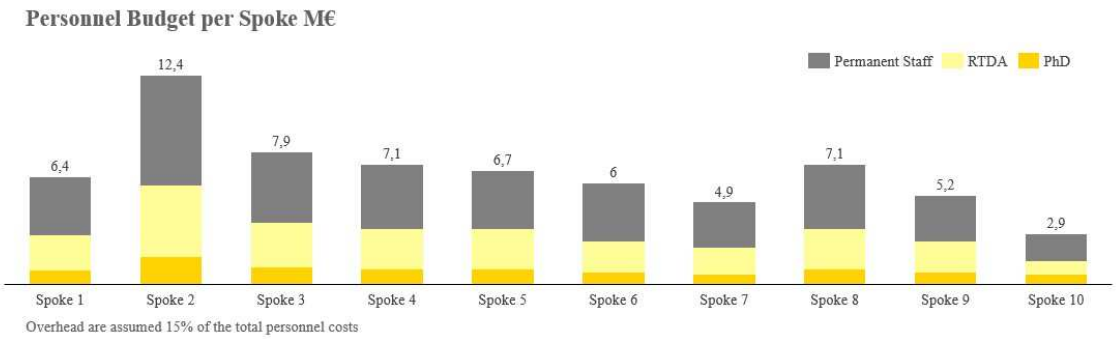

Figure B. 12 – Personnel Budget per Spoke