Finanziato dall'Unione europea
NextGenerationEU

Ministero dell'Università e della Ricerca

Segretariato Generale

Direzione Generale della Ricerca

PRIN: PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE – Bando 2022
Prot. 2022X2KWRK

PART A

1. Research project title

Deciphering the key virological determinants underlying the replicative and pathogenetic activity of Hepatitis D Virus (HDV) in treated and untreated Hepatitis B Virus and HDV coinfected patients.

2. Duration (months)

24 months

3. Main ERC field

LS - Life Sciences

4. Possible other ERC field

5. ERC subfields

1.	LS6_6 Infectious diseases
2.	LS7_9 Public health and epidemiology
3.	LS7_2 Medical technologies and tools (including genetic tools and biomarkers) for prevention, diagnosis, monitoring and treatment of diseases

6. Keywords

nº	**Testo inglese**

1.	Virology
2.	HBV and HDV coinfection
3.	HDV genetic variability
4.	Biomarkers of HDV and HBV coinfection
5.	Pathogenesis of HDV infection
6.	Evolution of HDV and HBV infection under antiviral treatment

7. Principal Investigator

POLLICINO (Surname)	**TERESA** (Name)
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Age limits derogation

The PI and/or the substitute PI are over 40 and they don’t intend to benefit from derogations to the age limits for the amount allocated to under 40 PI;

8. List of the Research Units

nº	Associated Investigator	Qualification	University/ Research Institution	Registered office (address)	Operating office (address)	e-mail address
1.	POLLICINO Teresa	Professore Ordinario (L. 240/10)	Università degli Studi di MESSINA	P.zza S. Pugliatti, 1 - MESSINA (ME)	City: Messina (ME) Address AOU G. Martino di Messina, Via	tpollicino@unime.it

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2.	DI MARCO Vito	Professore Ordinario (L. 240/10)	Università degli Studi di PALERMO	P.zza della Marina, 61 Pal. Steri - PALERMO (PA)	City: Palermo (PA) Address Piazza Marina, 61	vito.dimarco@unipa.it
3.	SVICHER Valentina	Professore Associato (L. 240/10)	Università degli Studi di ROMA "Tor Vergata"	Via Cracovia n. 50 - ROMA (RM)	City: Roma (RM) Address Via Cracovia n. 50	valentina.svicher@uniroma2.it

9 - Substitute Principal Investigator (To be identified among one of the associated investigators participating in the project).

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10. Brief description of the proposal

HBV and HDV coinfection causes the most severe form of viral hepatitis, leading to the development of cirrhosis in 15% of cases within 1–2 years and in 70–80% of cases within 5–10 years. The rates of hepatocellular carcinoma and hepatic decompensation are also 2–3-fold higher than for HBV monoinfection. Although not FDA or EMA approved, IFNα treatments have been widely used as anti-HDV strategy in the last 20–30 years with only limited sustained responses. More recently, novel treatment options with regard to their mode of action and their clinical effectiveness have been identified. Of those, the entry-inhibitor Bulevirtide has received conditional marketing authorisation by EMA in 2020, and it will be introduced in Italy within the first half of 2022, indicating the beginning of a new era for these difficult to treat/cure patients. Nevertheless, many questions related to HDV virology that affect sustained treatment responses to novel drugs remain to be solved. A deeper understanding of virological mechanisms contributing to viral replication and pathogenesis will help in identifying key factors implicated in the control of HDV infection liver disease progression.

The project will generate new knowledge and fill a number of gaps in our understanding of:

• The virological determinants that can modulate the outcome of chronic HBV-HDV coinfection and the response to new anti-HDV treatment

• The interplay between HBV and HDV replicative activity in peripheral and intrahepatic compartments and their correlation with the onset of advanced liver diseases
• The role of HDV and HBV genomic variability in liver damage
• The physio-pathological impact of HBV integration on the natural history of the HDV infection
• The impact of HDV infection on hepatocytes' transcriptome and integrated HBV-DNA.
• The kinetics of serum HDV-RNA as well as of old and novel serum HBV and HDV markers during treatment with entry inhibitors and their correlation with treatment response
• The role of HBV genomic variability and modified surface glycoproteins in modulating treatment response
The project brings together 3 research units and the VIRONET C subunit with a broad conceptual, technological and clinical expertise on HBV infection and on HBV-HDV coinfection.

The achievement of the above-mentioned aims will be possible thanks to:

- The collection of one of the largest cohort of patients with chronic HBV-HDV coinfection in Italy.
- The availability of advanced methodologies for the full-length sequencing of HBV and HDV genomes and for the quantification of serum and intrahepatic viral biomarkers
- The availability of advanced phylogenetic and bioinformatic models to unravel the HBV and HDV genetic evolution and quasispecies composition
- The availability of next-generation-sequencing approaches to define the contribution of integrated HBV-DNA to HDV infection, liver disease progression, and HCC development.

11. Total cost of the research project identified by items

Associated Investigator	item A.1	item A.2.1	item B	item C	item D	item E	sub-total	Total
POLLICINO Teresa	30.218	24.000	32.531	0	35.000	33.600	155.349	**155.349**
DI MARCO Vito	28.451	0	17.071	0	0	36.550	82.072	**82.072**
SVICHER Valentina	21.232	24.028	27.156	0	0	20.000	92.416	**92.416**
Total	**79.901**	**48.028**	**76.758**	**0**	**35.000**	**90.150**	**329.837**	**329.837**

N.B. The Item B and TOTAL columns will be filled in automatically

- item A.1: enhancement of months/person of permanent employees
- item A.2.1: cost of contracts of non-employees, specifically to recruit
- item B: overhead (flat rate equal to 60% of the total personnel cost, A.1+A.2.1, for each research unit)
- item C: cost of equipment, tools and software products
- item D: cost of consulting and similar services
- item E: other operating costs

PART B

B.1

1. State of the art

Hepatitis D virus (HDV) is the smallest known human virus with a ~1.7 kb single stranded circular RNA molecule of negative polarity [defined in relation to the (+) stranded mRNA encoding the hepatitis D antigen (HDAg)]. HDV exploits the HBV surface proteins (Small-, Middle- and Large-HBsAg) for the release of its progeny and de novo entry into hepatocytes. In particular, through incorporation of the Large-HBsAg, the particles gain infectivity and support transmission into sodium taurocholate co-transporting polypeptide (NTCP)-receptor expressing cells to disseminate within the liver and between hosts (1,2). Alternatively, HDV RNA can propagate through proliferation of hepatocytes in the absence of HBV (3). Although HDV seroprevalence is still controversial, a recent metanalysis has shown that up to 60-70 million of subjects are infected with HDV worldwide (4). Italy has historically represented a large basin of HDV infection in Europe, characterized by high HDV endemicity (seroprevalence >20% among HBV chronically infected patients in the 1980s). Although the introduction of universal anti-HBV vaccination in 1991 has resulted in an initial decline in HDV circulation, in the last decade the prevalence of HDV infection has shown a stable trend mainly fueled by immigration from highly endemic areas (5). So far, it has been estimated that in Italy, around 10% of HBV chronically infected patients are also infected by HDV (5). Chronic HDV infection leads the most severe form of chronic viral hepatitis, usually

characterized by a rapid progression towards cirrhosis and hepatocellular carcinoma often requiring liver transplantation or resulting in patients' death. There is also evidence of a fraction of patients (around 25%) with a stable and not-evolving liver disease (6). So far, interferon-alfa treatment was used as the only therapeutic strategy against HDV but unfortunately it is associated with a less than 20% virological response and a high risk of post-treatment virological relapse (7). More recently, novel compounds for HDV therapy have been identified. Among them, the entry inhibitor Bulevirtide has received conditional approval from the EMA in July 2020 for the therapy of adult patients with compensated chronic hepatitis delta (8), and will be introduced in clinical practice in Italy within the first half of 2022. Bulevirtide interacts with the NTCP receptor and prevents viral entry into the hepatocytes. This novel strategy appears promising even if different rates of viral decay and a still high rate of virological rebound after therapeutic suspension emerged from clinical trials (8). So far, the mechanisms promoting HDV persistence and factors underlying the clinical outcome of HDV infection and response to antiviral treatment are largely unknown. At this regard, HDV is endowed by a high degree of genetic variability. Eight different genotypes exist, with genotype 1 being the most widespread worldwide (9,10). Nevertheless, very limited information is available on the extent of HDV genetic evolution over time, and the relationship between HDV genetic asset and the clinical presentations of HDV infection. In a similar direction, paucity of data are available on the interplay between HDV and HBV replicative activity and the impact of HDV on intrahepatic markers of HBV replication (11). Even more, it is known that HBV DNA can integrate into the hepatocyte genome, and this integrated HBV-DNA can represent an additional source of HBsAg, even when the circular covalently closed HBV-DNA is completely silenced (12-14). So far, there is the need to unravel the contribution of integrated HBV-DNA in the production of the different forms of HBsAg and in turn in fueling HDV replication and jeopardize the full efficacy of treatment. Furthermore, the extent of genetic variability of the Large-HBsAg can play a role in modulating HDV replicative activity by enhancing the binding for NCTP receptor. It is also conceivable that specific mutational profiles in viral surface glycoproteins can allow the binding to the receptor even despite the drug, thus posing the basis for the drug resistance emergence. Again, this point has not been elucidated yet. Finally, there is evidence for an HBsAg-independent spread that may be important for HDV persistence and that would bypass the effect of drugs blocking de novo virus entry (3,15). At this regard, a mechanism recently explored as "Trojan horse" strategy for the spreading of viruses is represented by the release of viral genomes within circulating extracellular microvescicles (exosomes). To date, preliminary information is available on HDV release in exosomes in the setting of HBV-HDV chronic infection (15) and on mechanism of exosome trafficking. It is conceivable that a small RNA virus as HDV could be packaged within exosomes, providing a hidden source of reinfection cycles of hepatocytes, fueling HDV persistence even despite treatment and, in turn, its related pathogenesis.

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2. Detailed description of the project: methodologies, objectives and results that the project aims to achieve and its interest for the advancement of knowledge, as well as methods of dissemination of the results achieved

Objectives:

This proposal aims at unravelling virological determinants that can modulate the outcome of chronic HBV-HDV coinfection and the response to new anti-HDV treatment. This will be pursued by the following specific aims:

In drug-naïve patients:
a. To characterize HDV and HBV genetic asset throughout the full-length HDV and HBV genome and its correlation with end-stage liver disease (cirrhosis and HCC).
b. To unravel the interplay between HBV and HDV replicative activity in peripheral and intrahepatic compartments and their correlation with the onset of end-stage liver diseases.
c. To evaluate HBV DNA integration into the host genome and their clonal espansion
d. Analysis of hepatocytes' transcriptome to
- define the contribution of integrated HBV-DNA in the production of HBsAg isoforms and its contribution in modulating HDV replicative activity and liver disease
- define the impact of HDV infection on hepatocytes' transcriptome and integrated HBV-DNA.

In patients receiving treatment with entry inhibitors:
e. To characterize the kinetics of serum HDV-RNA as well as of old and innovative serum HBV and HDV markers (quantification of the 3 HBsAg isoforms, HBV-RNA, HBcrAg, and HDV-RNA obtained from exosomes) during treatment with entry inhibitors and their correlation with treatment response
f. To define the role of HBV genomic variability and modified surface glycoproteins in modulating treatment response
The achievement of the above-mentioned aims is feasible thanks to:
1. The collection of one of the largest cohort of patients in Italy with chronic HBV-HDV coinfection, thanks to the involvement of VIRONET C Onlus Foundation and the Sicilian Network for the Selection of Therapy in Patients with Chronic HBV Disease (RESIST-HBV)that are two well-consolidated networks involving the main clinical and virological Centers throughout Italy. These networks have enabled the establishment of cohort of 1100 patients with chronic HBV and HDV coinfection from 35 Clinical Centers throughout Italy. For all patients, a detailed clinical, therapeutic and virological history is available along with longitudinal samples already collected, and including serum and liver tissue samples. From both cohorts, subsets of patients will be "ad hoc" selected to achieve the above-mentioned aims.
2. The availability of advanced and accurate methodologies for the full-length sequencing of viral genome and for the quantification

of parameters indicative of viral replicative activity.
3. The availability of advanced phylogenetic and bioinformatic models to unravel the HBV and HDV genetic evolution and the composition of HBV and HDV quasispecies.
4. Third generation sequencing approach based on long-read sequencing to characterize the contribution of integrated HBV-DNA in the production of the different HBsAg forms

Experimental design

Specific aim a. To characterize HDV genetic asset in the full-length HDV genome and its correlation with the occurrence of the end-stage liver disease.

To achieve this aim, a set of 300 patients with chronic HBV-HDV coinfection matched for demographics and naïve to anti-HDV drugs will be analysed. For each patient, the sequencing of the full length HDV genome will be carried out following an in-house Sequencing method. In particular, HDV-RNA will be extracted from 1 ml of serum by using an automatic extraction system, based on magnetic beads technology. HDV full-length genome will be then amplified by two different protocols of 2-step RT-PCR, targeting the genetic regions encoding the Delta antigen and the ribozyme region of HDV genome, respectively. The obtained DNA libraries will be then sequenced by using Illumina MiSeq platform and the 2x250bp paired-end reads sequencing kit, with a depth ensuring a minimum coverage at each base (>100X) to confidently identify HDV variants. The obtained reads will be then analysed by a refined bioinformatics pipeline, including a preliminary quality control by Trimmomatic software in order to remove PCR primers and poor quality reads; a paired-end reads merge by PEAR software and lastly the analysis of HDV variants by VirVarSeq software, restricted only to variants with frequency >1%. This bioinformatic approach will permit to identify HDV mutations along the whole HDV genome and their relative intra-patient prevalence.
HDV genotypes will be assessed by phylogenetic analysis using as references HDV sequences representing all known HDV genotypes retrieved from the Genbank. In details, the phylogenetic trees will be generated by applying the Tamura–Nei model, available in Mega software. The statistical robustness within each phylogenetic tree will be confirmed with a bootstrap-analysis using 1000 replicates.
Patients will be stratified according to the occurrence of end-stage liver diseases (cirrhosis and HCC). The genetic characteristics of HDV genome in these groups of patients will be compared, with the aim to identify genetic markers correlated with a fast progression to advanced liver disease by applying the genetic analysis, described below.
The degree of quasi-specie heterogeneity in HDV genome from the 2 groups of patients will be specifically evaluated by different parameters such as mean genetic divergence, Shannon Entropy and dN/dS. In particular, in each group of patients, the overall degree of genetic variability in the different HDV domains will be assessed by calculating the genetic divergence respect to a reference HDV genome, based on Tajima Nei model (Mega 8). Furthermore, the entire amino acid strain of Delta Antigen will be analysed for determining the Shannon Entropy value by using HIV Los Alamos National Laboratory (LANL) Entropy tool (https://www.hiv.lanl.gov/content/sequence/ENTROPY/entropy.html). Only Delta antigen positions with a value >0.1 and a $P \leq 0.05$ after Benjamini-Hochberg correction will be considered as under statistically significant pressure. The ratio of non-synonymous and synonymous substitutions (dN/dS) will be analysed across HDV sequence encoding HDV antigen by applying McDonald-Kreitman Test. These analyses will allow to identify viral aa positions within the different domains of HDV antigen undergoing positive selective pressure, thus more prone to accumulate amino acid mutations, in patients with faster liver disease progression.
HDV genome sequences will be lastly analyzed by using an advanced mathematical model developed in collaboration with Yale University. In particular, we will apply a Bayesian variable partition model, and a recursive model selection procedure to define HDV specific genetic mutations either independently or interactively associated with end-stage liver disease. A multivariable logistic regression analysis will be lastly carried out in order to support the correlation of HDV mutations and other clinical and virological parameters with a faster progression towards end-stage liver diseases.
After the identification of HDV genetic determinants correlated with end-stage liver disease, their prevalence over a 15-year time window will be also assessed in order to understand the potential evolutionary trend of hepatitis delta virus towards the selection of viral species with an increased or weakened pathogenic potential.

Specific aim b. To unravel the interplay between HBV and HDV replicative activity over time and their correlation with the onset of end-stage liver diseases.

In a set of 50 patients naïve to anti-HDV and anti-HBV drugs, each with at least 3 serial serum sample available collected every 6 months, the interplay between HDV and HBV replicative activity will be evaluated and correlated with the occurrence of end-stage liver diseases. In each patient the following methodology will be applied:

Quantification of serum HDV-RNA and serum HBV-DNA
Serum HDV-RNA will be quantified by the commercial assay Robogene (lower limit of quantification: 6IU/ml) while serum HBV-DNA will be quantified by the cobas® HBV (Roche)commercially assay (lower limit of quantification:6,6 lU/ml).

Quantification of HBsAg isoforms: The levels of the three different forms of HBsAg (Large, Middle and Small HBsAg) will be quantified by using three different ad-hoc designed ELISA assays, characterized by high sensitivity (detection limit for each protein is 0.1 ng/mL) and a high specificity, taking advantage of a sandwich system using two types of antibodies, anti-PreS1, anti-PreS2 and anti-S, respectively (16). For each patient, total HBs, L-HBs, M-HBs and S-HBs levels will quantified in duplicate.
Quantitative detection of HBsAg in human serum or plasma withe the use of Lumipulse® G HBsAg-Quant Fujirebio; LLOQ: 0.005

IU/mL)
Hepatitis B core-related antigen (HBcrAg) will be quantified by a chemiluminescent assay, Lumipulse GHBcrAg assay (Fujirebio; LLOQ: 3 logU/mL).
Serum HBV-RNA levels will be determined by an in-house digital droplet PCR assay, based on the use of ad-hoc designed primers and a probe targeting a conserved region of HBV Core region, tthus specific for pregenomic HBV-RNA recognition.

Quantification of HDV-containing exosomes: Exosomes will be isolated from 1 ml of serum sample by size exclusion chromatography by using qEV/35 nm original columns (Izon Science) according to the manufacturer's protocol. These agarose columns are optimized for ensuring the purification of microvescicles with a size >35 nm (such as exosomes), while discarding all smaller particles as HDV free virions (22 nm), excluding their contamination of exosome fraction. Quality of EV preparations will be verified by Western Blot according to the recommendations of the International Society for Extracellular Vesicles (MISEV2018). Exosomes RNA cargo will be then extracted by using Total Exosome RNA and Protein Isolation Kit (Invitrogen) according to the manufacturer's protocol. Exosome-extracted HDV-RNA will be quantified by the above-mentioned ddPCR assay.

Quantification of intrahepatic HBV cccDNA and pre-genomic RNA. In the subset of 50 patients with a liver biopsy available at one of the time-points analyzed, the quantification of cccDNA also in open or closed conformation and pre-genomic RNA will be carried out by using a ddPCR approach (REF).

Patients will be classified as HDV- or HBV-dominant if the viral load of one virus will exceed that of the other virus by more than 1log10 at each time-point analyzed. Otherwise, fluctuating dominance will be stated. In order to provide a finer characterization of the HDV and HBV interplay, the serum levels of HBsAg isoforms, HBcrAg and serum HBV-RNA and HDV-RNA containing exosomes will be compared across the 3 different viral dominance profiles. Similarly, the intrahepatic levels of cccDNA and pre-genomic RNA will be assessed across the 3 groups of patients. This will enable to characterize the role of HDV infection on the burden and transcriptional activity of cccDNA. In particular, this will enable to verify if the lowest levels of serum HBV-DNA observed in HDV-dominant profile can be explained by down-regulation of pre-genomic RNA production.
Mann Whitney and Kruskal Wallis tests will be used to assess statistically significant differences among groups. The 3 patterns of HDV and HBV interplay will be also correlated with the occurrence and the time to develop end-stage liver disease by Cox proportional hazard model and Kaplan-Meier analysis.

Specific aim c. To evaluate HBV DNA integration into the host genome and their clonal espansion

Identification of HBV DNA integration into the host genome will be performed by applying newly developed high-throughput HBV Sequencing (HBIS) and bioinformatic pipelines. By these approaches, HBV integration sites will be recovered by semi-nested ligation-mediated PCR from host DNA and the use of either forward or reverse primers specific to different HBV genomic regions and different HBV genotypes. PHBV integration libraries are generated by a modification of the integration sequencing method developed profile HIV-1 integration in CD4+ T cells (17). HBV integration sites are recovered by a semi-nested ligation-mediated PCR on cellular DNA fragmented by sonication, A-tailed and ligated to asymmetric DNA linkers using either forward or reverse primers specific to multiple HBV genomic regions. Targeted sequences are then further enriched by performing a nested PCR with forward/reverse HBV primers and forward/reverse Illumina Linkers that contain an Illumina adapter for flow cell surface annealing. Amplicons are paired-end sequenced on an Illumina MiSeq and reads will be aligned to a hybrid genome obtained by linking an end of human genome (GRCh38.p10) to an end of HBV genome (NC_003977). Identical reads are clustered as single events. Preliminary results obtained by RU1 (Abstract CO16, Dig Liv Dis, March 2021) indicate that the HBIS approach allow an efficient mapping and quantification of each unique integration site together with the identification of expanded clones of cells with identical integrations.

Specific aim d. To define the impact of HDV infection on hepatocytes' transcriptome and on the production of HBsAg isoforms from integrated HBV-DNA.

To achieve this aim, whole human and HBV transcriptome sequencing will be performed on the above-mentioned set of 50 patients with an available liver biopsy, in order to evaluate the different levels of human and HBV mRNAs expression in liver biopsies. RNA libraries will be sequenced with Illumina technology by using the kit Infinity for long reads (10 kb). In particular, total intrahepatic RNA will be isolated from patients' liver biopsies by using AllPrep DNA/RNA Mini Kit (QIAGEN, Hilden, Germany). RNA library preparation will be carried out by using NEB Next Ultra RNA Library Prep kit (New England BioLabs Inc), and ribosomal RNAs will be removed from total RNA using Ribo-Zero Gold rRNA Removal kit, Illumina). RNA libraries will be then sequenced with an Illumina NextSeq (Illumina Inc.,CA) and by applying the novel third generation technology of long reads (Infinity sequencing assay, Illumina). After a quality control step, performed by Trimmomatic, the expression of transcripts will be quantified by Salmon software estimating the relative abundance of each annotated transcript for each sample in units of transcripts-per-million (TPM), an accurate and widely-used parameter to express transcript. Statistically significant differences (adjusted P value) in the expression levels of all transcripts were evaluated by DESeq.
The hepatocytes' transcriptome will be analyzed and compared across patients with different patterns of viral dominance and also according to the rate of progression towards end-stage liver diseases. This will enable to unravel the impact of HDV in modulating intracellular pathways of human gene expression according to its replicative and pathogenetic potential.
Furthermore, the third generation sequencing approach based on long reads will also offer the unique opportunity to measure the intrahepatic amount of ORF S mRNAs derived from cccDNA and from integrated HBV-DNA. Indeed, ORF S mRNAs derived from

cccDNA are characterized by the conventional poly-A signals, while those derived from integrated HBV-DNA are characterized by the cryptic poly-A signals. The intrahepatic amount of ORF S mRNAs derived from cccDNA and from integrated HBV-DNA will be estimated by a bioinformatics approach capturing all reads, mapping to HBs region and including the classical or cryptic poly-A signal. The relative amount of cccDNA derived- of HBV integrated- derived mRNAs will be correlated with the levels of serum HBsAg isoforms, serum HDV-RNA and biochemical parameters in order to weigh the contribution of cccDNA and integrated HBV-DNA in the production of surface glycoproteins, HDV replicative activity, markers of liver inflammation as well as the occurrence of end-stage liver disease.

Specific aim e: To characterize the kinetics of serum and intrahepatic viral biomarkers
during treatment with entry inhibitors and their correlation with treatment response.

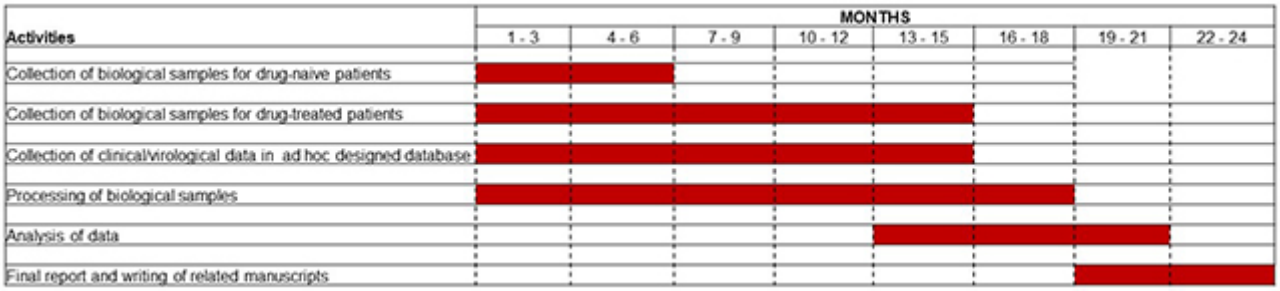
This proposal will analyze a set of 50 patients receiving treatment with entry inhibitor. For these patients, serum and tissue samples will be collected at baseline and during treatment (months 3, 6 and 12). Twenty-three of them have already been treated with entry inhibitors and biological samples have already been collected.
The following serum markers will be quantified: serum HDV-RNA, HBsAg isoforms, HBcrAg, serum HBV-RNA and of HDV-RNA containing exosomes according to the above-mentioned methodologies.
The following intrahepatic markers will be quantified: total HBV-DNA, cccDNA (total, open and closed conformation), pre-genomic RNA, HDV-RNA according to published (11,18) and the above-mentioned methodologies.

The serum parameters will be quantified at baseline and at each time-point analyzed while intrahepatic parameters at baseline. Their levels at baseline and/or their on-treatment variations will be correlated with virological response to treatment with entry inhibitors observed at month 12. Furthermore, AUROC will be carried out to assess the diagnostic performance of these parameters in predicting the achievement of virological success under treatment with entry inhibitors.

Specific aim f. To define the role of genetic variability in viral surface glycoproteins in modulating treatment response

In the subset of patients with a liver biopsy available, HBV-DNA will be extracted and used to sequence the pre-S1 region known to encode the domain of the Large-HBsAg responsible for the interaction with the NCTP receptor. The extent of genetic variability in this domain will be determined by calculating the Shannon Entropy at each amino acid position and will be compared in patients achieving or not achieving virological success at month 12 of treatment with entry inhibitor. This will allow to define genetic signature in pre-S1 region that can modulate virological response to treatment with entry inhibitors.

The Gantt chart to report the timeline of the proposed activities is reported below



Results that the project aims to achieve and its interest for the advancement of knowledge

Our proposal offers the unique and unprecedented opportunity to unveil, in one of the largest cohort of HBV-HDV coinfected patients analyzed in Italy, the virological factors that can modulate HDV replicative and pathogenetic activity as well as response to new anti-HDV drugs. This is crucial considering that HDV coinfection can cause the most severe forms of hepatitis also in young adults. HDV is endowed by a high degree of genetic variability, comparable to that observed for HIV and HCV. Nevertheless, paucity of information is available on the process underlying HDV genetic evolution and its impact on HDV replication and on clinical presentation. In this light, this proposal will enable to finely trace the evolutionary dynamics of HDV infection over an extended period of time in order to characterize the regions of HDV genome under positive selection pressure and their impact on the occurrence of end-stage liver disease. This will also enable to define viral genetic markers correlated with a higher HDV replicative and pathogenetic potential, an information that can be crucial to prioritize treatment with new anti-HDV drug and to optimize patients' monitoring.
Furthermore, it is known that HDV usually exerts a viral dominance pattern that can lead to the suppression of HBV replication. Nevertheless, preliminary findings (led on small sample size) have proposed that the interplay between the 2 viruses can be more complex than currently known and can be characterized by fluctuating patterns of HDV and even HBV dominance over time (6,19). On this basis, thanks to the availability of longitudinal samples coupled with liver tissues, this proposal will also offer the opportunity to finely characterize the so far poorly understood interplay between HDV and HBV at serum and intrahepatic and to correlate the different virological patterns with clinical presentations. The availability of novel biomarkers such as the quantification of the different HBsAg isoforms and of HDV-RNA containing exosomes will also provide an added value for a fine characterization of HBV and HDV interplay.
Another issue that is currently being discussed by the Scientific Community is the contribution of integrated HBV-DNA in the

production of HBV surface glycoproteins. Understanding this issue is critical since integrated HBV-DNA can provide a source for HBsAg isoforms even in presence of a completely silenced cccDNA. Thanks to the availability of a well-characterized set of liver biopsies coupled with third generation transcriptome profiling and HBsAg isoforms quantification, this proposal will shed light on the role of integrated HBV-DNA in contributing to HBsAg isoforms production and in turn in fueling HDV persistence. So far, no studies have addressed this issue. Transcriptome profiling will also enable to unravel the impact of HDV on modulating hepatocytes' gene expression, thus shedding light on HDV capability in perturbing intracellular pathways.

Finally, this proposal will also enable to define virological factors that can predict virological response to the new class of entry inhibitors. Although promising, the new class of entry inhibitors is associated with variable decays of serum HDV-RNA and thus with different kinetics of treatment response. In this light, this proposal will offer the opportunity to characterize the role of classical and novel biomarkers in modulating response to treatment. Notably, the role of HDV-RNA containing exosomes in modulating response to entry inhibitors will be evaluated, thus providing new insights on a novel mechanism contributing to fuel HDV persistence and replication even during treatment.
Overall this proposal will shed light on determinants underlying HDV replicative and pathogenetic activity with the ultimate goal to optimize the management of patients with chronic HBV-HDV coinfection in term of monitoring and antiviral treatment.

Methods of dissemination of the results achieved

Effective communication and dissemination of results within the consortium will be ensured by regular teleconferences and by meetings in person. Dissemination outside the consortium will be actively pursued but taking into careful consideration Intellectual Property (IP) protection. Dissemination actions will include: a) presentations at workshops and congresses in and outside Europe; b) publications in peer-reviewed journals and abstracts submission to national and international conferences; c) the diffusion of press releases through the institutional university channels in case of scientific breakthroughs particularly in the perspective of achieving a cure for patients with HDV infection.

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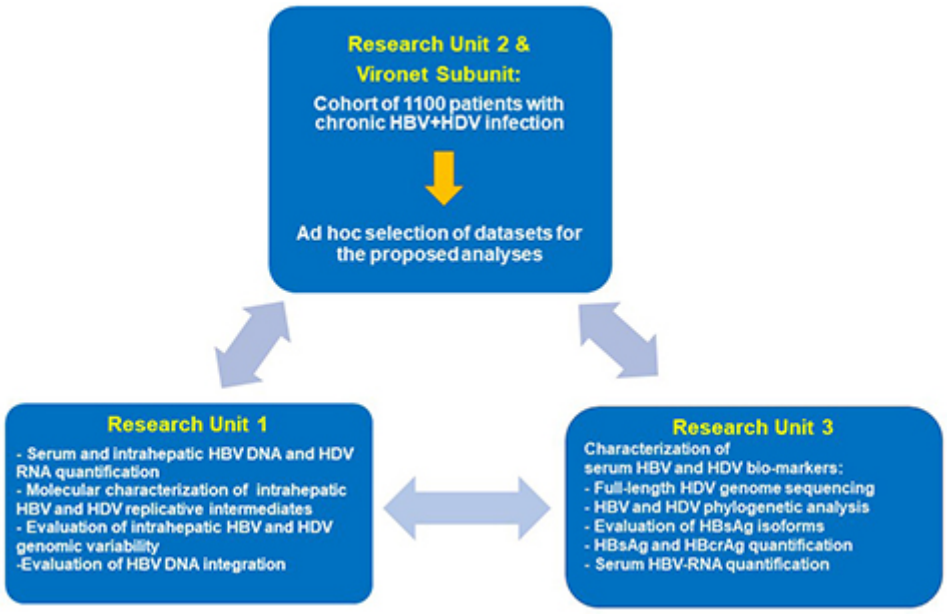
3. Project development, with identification of the role of each research unit, with regards to related modalities of integration and collaboration

This proposal will involve 3 Research Units that will cooperatively work to achieve the above-mentioned aims. A description of the role of each Unit is reported below and represented in the following Figure



Unit 1 (University of Messina)
Research Unit 1 (RU1, PI) includes the Laboratory of Molecular Hepatology of the University of Messina and the "VIRONET C Onlus Foundation" Network. The Molecular Hepatology Laboratory has an internationally recognized expertise in the research field of molecular virology of HBV and HDV coinfection. Of particular note is the fact that the Molecular Hepatology Laboratory was one of the 20 European Laboratories that tested the first international quality control for quantification of HDV viral load. The Laboratory disposes of a large area with spaces and instrumentations dedicated exclusively to the study of hepatitis viruses. In addition, the Laboratory performs qualitative (Agilent Bioanalyzer and PerkinElmer LabChip GX Touch bioanalyzer, Qubit Fluorimeter, and Nanodrop spectrophotometer), and quantitative DNA and RNA Analysis (Applied Biosystem and Biorad Real Time PCR amplification instruments and Thermo Fisher Scientific digital PCR, Nanostring nCounter Analysis System), including both Sanger-Analysis (Applied Biosystem 3500 DX Genetic Analyzer) and Next-Generation Sequencing (Illumina MiSeq platform). In addition, the Laboratory is provided with the Lumipulse G600II for the detection and quantification by highly sensitive approaches of HBsAg, HBcrAg, and

anti-HBc antibodies.
Vironet C Foundation ONLUS (https://www.vironetc.org/) is a non-profit organization of social utility established in Italy in July 2017, with the aim of pursuing purposes of social solidarity in promoting (nationally and internationally) medical-scientific research concerning the pathogenesis, prevention, diagnosis and treatment of viral hepatitis -in particular of viral hepatitis C - and viral liver diseases.
Sixty-six clinical and research Centers located throughout the Italian territory have joined the network set up by Vironet C ONLUS and participated to several studies (> 10 publications in international "peer reviewed" journals), approved by the local ethical committees. To date, within the Italian VIRONET-C database, there are clinical and virological data of 4527 patients infected with HCV. Vironet C ONLUS has also recently launched a new project for the study and sequencing of HDV. To date, 30 clinical and research Centers located throughout the Country have joined this new project with the possibility to include >1000 patients with chronic HBV and HDV infection
The Laboratory of Molecular Hepatology will coordinate the activities of the Research Units involved in the project and will relate with the VIRONET C foundation subunit for the collection of available retrospective serum and liver biopsy samples, as well as of the demographic, virological, clinical, and therapeutic data from the HBV-HDV coinfected patients that will be included in the study. Experimental activities of the Laboratory will specifically be focused on the above-mentioned molecular analysis of needle liver biopsy and serum samples from the “RESIST HBV-HDV” Network (Research Unit 2) and to the evaluation of the obtained results also in relation to the patients’ clinical information.

Unit 2 (University of Palermo)
Research Unit 2 (RU2) coordinates a Sicilian Network for the diagnostic, clinical, and therapeutic management of chronic hepatitis B infected patients [the Network for the Selection of Therapy in Patients with Chronic HBV Disease (RESIST-HBV)]. The Network includes 32 Sicilian academic and community centers for liver disease or infectious disease, which record clinical and virologic data of patients with HBV liver disease as well as of patients with chronic HDV infection on a web-based regional database. Liver and blood samples from the patients are collected at the time of liver biopsy or within six months from liver biopsy; part of the tissue in excess for pathological evaluation is stored for the study. With this method RESIST HBV is able to obtain specimens from the different phases of HBV infection. Physicians at each RESIST-HBV center record data about the progression to cirrhosis, development of HCC, complications of liver disease, causes of liver related death directly on the web-platform. Patients who not attend clinical control of disease are called by telephone in order to verify the occurrence of liver events, and a questionnaire about complications of the liver disease is proposed. For patients who will not be reachable by telephone, clinical data and/or cause of death are obtained from the Regional Office of Health that is responsible for the epidemiologic survey in Sicily. RU2 foresees the inclusion in the platform of about 4000 patients with HBV infection in the next 2 years. All patients included in the platform will undergo non-invasive assessment of liver damage by fibroscan and when indicated by a liver biopsy. HDV infection will be evaluated by testing for anti-HDV antibodies. Moreover, all patients with positive anti-HDV antibodies will be tested for serum HDV-RNA. Therefore, RU2 will collaborate with RU1 and RU3 by providing needle liver biopsy specimens, serum samples as well as clinical data from treated and untreated HBV-HDV coinfected patients.

Unit 3 (University of Rome Tor Vergata):
Research Unit 3 (RU3)has a consolidated and widely recognized experience in sequencing of viral genomes by both population-based and next generation sequencing (NGS). Indeed, RU3 has different platforms for sequencing (Sanger and Illumina) and can take advantage of refined and innovative bioinformatic approaches to characterize viral genetic variability. Furthermore, RU3 has an in-depth expertise and the full equipment for the quantification of innovative serological and molecular markers of viral replication allowing to accurately define viral replicative activity. Based on this expertise, RU3 will be specifically dedicated to the processing of serum samples and to the analysis of related results. In particular, serum samples provided by VIRONET C network, will be used for the following activities:
- Sequencing of full-length HDV genome by an already available protocol based on next generation sequencing approach (Illumina Platform). Sequences will be then analyzed by applying an ad hoc designed bioinformatic pipeline that will allow to defined HDV genotype and to characterize the extent of genetic variability across the different regions of viral genome.
- Quantification of HBsAg isoforms by applying specifically designed ELISA assays. These assays will be used to evaluate the on-treatment kinetics of HBsAg isoforms and their role in stratifying patients according to the patterns of viral dominance and treatment response.
- Quantification of HDV-RNA containing exosomes. After purification of exosomes, HDV-RNA will be quantified by highly sensitive droplet digital PCR. This will allow to unravel the role of HDV-RNA containing exosomes as a mechanism fueling HDV persistence thus contributing to viral rebound during anti-HDV treatment.

4. Possible application potentialities and scientific and/or technological and/or social and/or economic impact

This proposal has the potential to provide significant scientific, economic and social impact as it will create a collaborative network between clinicians and scientists working to improve the life quality of patients with chronic HBV and HDV co-infection, known to be associated with the most severe forms of hepatitis. In particular, this proposal will contribute to generate novel, state-of-the art scientific knowledge on the interplay between HBV and HDV with the ultimate goal to identify critical signatures that can help predicting the clinical outcome of chronic HBV and HDV co-infection and response to treatment with new anti-HDV drugs.

A deeper comprehension on the interplay between these two viruses may help in:

i) unravelling the molecular epidemiology of HBV-HDV coinfection the Country and potential correlations with clinical outcome;
ii) optimizing diagnostic protocols/tests to optimize the management of patients with chronic HBV-HDV coinfection
iii) promoting screening and prevention programs, based on innovative methods. This in turn can have an impact on health expenses and therefore have a positive economic effect for the National Health System.

Specific potential applications of the results obtained will be:

1. Reinforcement of the Italian network for HDV surveillance. The Network will strengthen the knowledge about the prevalence of HDV infection and about the HDV genotypes and variants circulating in Italy and will establish a national platform of technical expertise to support a surveillance system for early diagnosis and monitoring of HDV infection.
2. Definition of biomarkers for stratifying the risk of disease progression and response to new anti-HDV drugs. This is critical to prioritize the access to antiviral treatment and to set up an optimal clinical monitoring.
3. Developing standard protocols and procedures for the successful implementation of HDV detection, sequencing and quantification at national level.
4. Capacity building: the involvement in this project of young investigators, PhD and post-doc fellows, will contribute to the training of the next generation scientists interested in molecular and translational medicine.
8. Research infrastructure and collaborations: this grant will be instrumental in improving the skills and expertise in virological translational research, and will significantly help to strengthen the already in place.

5. Financial aspects: costs and funding for each research unit

nº		Total cost (euro)	Co-funding (item A.1) (euro)	MUR funding (other items) (euro)
1.	POLLICINO Teresa	155.349	30.218	125.131
2.	DI MARCO Vito	82.072	28.451	53.621
3.	SVICHER Valentina	92.416	21.232	71.184
	Total	**329.837**	**79.901**	**249.936**

6. Bibliography

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2. Lucifora J, Delphin M. Current knowledge on hepatitis delta virus replication. Antiviral Res 2020;179:104812
3. Giersch K, Bhadra OD, Volz T, Allweiss L, Riecken K, Fehse B, et al.Hepatitis delta virus persists during liver regeneration and is amplified through cell division both in vitro and in vivo. Gut 2019;68:150–157.
4. Chen HY, Shen DT, Ji DZ, Han PC, Zhang WM, Ma JF, Chen WS, Goyal H, Pan S, Xu HG. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. Gut. 2019 Mar;68(3):512-521.
5. Caviglia GP, Martini S, Ciancio A, Niro GA, Olivero A, Fontana R, Tandoi F, Rosso C, Romagnoli R, Saracco GM, Smedile A, Rizzetto M. The hepatitis D virus in Italy. A vanishing infection, not yet a vanished disease. J Adv Res. 2021 Mar2;33:183-187.
6. Schaper M, Rodriguez-Frias F, Jardi R, Tabernero D, Homs M, Ruiz G, Quer J, Esteban R, Buti M. Quantitative longitudinal evaluations of hepatitis delta virus RNA and hepatitis B virus DNA shows a dynamic, complex replicative profile in chronic hepatitis B and D. J Hepatol. 2010 May;52(5):658-64.
7. Urban S, Neumann-Haefelin C, Lampertico P. Hepatitis D virus in 2021: virology, immunology and new treatment approaches for a difficult-to-treat disease. Gut. 2021 Sep;70(9):1782-1794.
8. Yardeni D, Koh C. Bulevirtide for HBV and HDV infections. Drugs Today (Barc). 2021 Jul;57(7):433-448.
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10. Radjef N, Gordien E, Ivaniushina V, Gault E, Anais P, Drugan T, et al. Molecular phylogenetic analyses indicate a wide and ancient radiation of African hepatitis delta virus, suggesting a deltavirus genus of at least seven major clades. J Virol 2004;78:2537–2544.
11. Pollicino T, Raffa G, Santantonio T, Gaeta GB, Iannello G, Alibrandi A, et al Replicative and transcriptional activities of hepatitis B virus in patients coinfected with hepatitis B and hepatitis delta viruses. J Virol. 2011; 85:432-439

12. Liaw YF. Clinical utility of HBV surface antigen quantification in HBV e antigen-negative chronic HBV infection. Nat Rev Gastroenterol Hepatol. 2019 Oct;16(10):631-641.
13. Dusheiko G, Wang B. Hepatitis B Surface Antigen Loss: Too Little, Too Late and the Challenge for the Future. Gastroenterology. 2019 Feb;156(3):548-551.
14. Pollicino T, Caminiti G. HBV-Integration Studies in the Clinic: Role in the Natural History of Infection. Viruses. 2021;13:368.
15. Jung S, Altstetter SM, Wilsch F, Shein M, Schütz AK, Ulrike Protzer et al., Extracellular vesicles derived from Hepatitis-D Virus infected cells induce a proinflammatory cytokine response in human peripheral blood mononuclear cells and macrophages. Matters. 2020; 1-10
16. Brancaccio G, Salpini R, Piermatteo L, Surdo M, Fini V, Colagrossi L, Cantone M, Battisti A, Oda Y, Di Carlo D, Ceccherini-Silberstein F, Perno CF, Gaeta GB, Svicher V. An Increase in the Levels of Middle Surface Antigen Characterizes Patients Developing HBV-Driven Liver Cancer Despite Prolonged Virological Suppression. Microorganisms. 2021 Apr 2;9(4):752
17. Cohn, L. B., I. T. Silva, T. Y. Oliveira, R. A. Rosales, E. H. Parrish, G. H. Learn, B. H. et al (2015). "HIV-1 integration landscape during latent and active infection." Cell 160(3): 420-432.
18. Pollicino T, Belloni L, Raffa G, Pediconi N, Squadrito G, Raimondo G, Levrero M. Hepatitis B Virus (HBV) replication is regulated by the acetylation status of HBV cccDNA-bound H3 and H4 histones.Gastroenterology, 2006; 130:823-3719.
19. Raimondo G, Brunetto MR, Pontisso P, Smedile A, Maina AM, Saitta C, Squadrito G, Tono N; Associazione Italiana Studio Fegato Cooperative Group Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis B virus/hepatitis C virus-coinfected patients. Hepatology. 2006;43:100-7.

B.2

1. Scientific Curriculum of the Principal Investigator

Name: Teresa Pollicino
• Date of birth: July 20, 1964
• Place of birth: Monforte S. Giorgio (ME), Italy
• Citizenship: Italian
• Business Address: Laboratory of Molecular Hepatology, Department of Human Pathology, University of Messina, University Hospital “G. Martino”of Messina, Via Consolare Valeria, 98124 Messina
• Tel: +39(090)2213703
• e-mail: tpollicino@unime.it; teresa.pollicino@unime.it

CURRENT POSITIONS:
• Full Professor of General Pathology, Department of Human Pathology, University of Messina, Italy
• Chief, Laboratory of Molecular Hepatology, Department of Human Pathology, University of Messina
• Chief, Division of Advanced Diagnostic Laboratories, University Hospital “G. Martino” of Messina, Italy
EDUCATION and TRAINING
• 1990: Doctor of Medicine (MD) Degree - Medical School Graduation, University of Messina, Italy
• 1990: Medical Licensure, University of Messina, Italy
• 1994: Board Certified in Hematology, University of Messina, Italy
• 2001: Board Certified in Internal Medicine, University of Messina, Italy
ACADEMIC APPOINTMENTS
• 1991 and 1992: Visiting fellow, Unit of Molecular Immunoregulation, Istituto di Ricerche Farmacologiche “Mario Negri”, Milan, Italy.
• 1993: Visiting scientist, Department of Virology, “Heinrich-Pette-Institut”, Hamburg University, Hamburg, Germany.
• 1994 - 1996: Senior fellow, Laboratory of Molecular Biology, Department of Internal Medicine, University of Messina, Italy.
• 1996 - 1998: Visiting fellow, at the “Unité de Recombinaison et Expression Génétique – Department de Retrovirus” Institut Pasteur, Paris, France.
• 1998 - 2015: Assistant Professor of Laboratory Medicine, University of Messina, Italy.
• 2002 and 2003: Visiting Scientist, Laboratory of Gene Expression, Experimental Research Center, Regina Elena Institute, Rome, Italy.
• 2011 to date: Chief, Laboratory of Molecular Hepatology, Department of Human Pathology, University of Messina
• 2015 and 2016: “Senior Research Scientist”, Hepatic Pathogenesis Section, Laboratory of Infectious Diseases, NIAID, NIH, Bethesda, MD, USA
• 2015 – 2020: Associate Professor of General Pathology, Department of Human Pathology, University of Messina, Italy

• Sept. 2020 to date: Chief, Division of Advanced Diagnostics Laboratories, University Hospital “G. Martino” of Messina, Italy
• Jan. 2021 to date: Full Professor of General Pathology, Department of Human Pathology, University of Messina, Italy
HONORS
• 2018: Fellowship research program prize (Gilead Science), Milan, Italy
• 2015: Prize "en honor a su notable trayectoria y aportes académicos en tan importante ambito de las ciencias de la salud" from University of Guadalajara and Civil Hospital of Guadalajara, Mexico, during the "XVII Congreso Internacional Avances en Medicina, Hospital Civil de Guadalajara, Mexico, February 26, 2015"
• 2012: Fellowship research program prize (Gilead Science), Milan, Italy
• 2006: A.I.S.F.-FADE Prize for the best 2004 Italian publication in Hepatology [Pollicino T. et al., Gastroenterology 2004; 126:102–110].
• 2005: Fellowship research program prize (Gilead Science), Milan, Italy
• 2003: “Prize for best oral presentation”, 38th Annual Meeting of the European Association for the Study of the Liver. Geneva, Switzerland, July 3 – 6, 2003 for the study “Class I Deacetylases Inhibitors Affect HBV Replication by Modulating the Acetylation Status of cccDNA-Bound H3 and H4 Histones”.
MEMBERSHIP, BOARD, and ACADEMIES
• 2006 – 2009: Member of the Governing Board of the Italian Association for the Study of the Liver (AISF)
• 2009 – 2012: Member of the Executive Board of the Italian Foundation for Liver Research (FIRE)
• 2016 - 2019: Member of the Scientific Advisory Council for the HBV Meeting
• Febr. 2020 to date: Member of The Accademia Peloritana dei Pericolanti of Messina

• Member of the European Association for the Study of the Liver (EASL)
• Member of the Italian Association for the Study of the Liver (AISF)
• Member of the Italian Society of Pathology and Translational Medicine (SIPMeT)
ORGANIZER OF INTERNATIONAL SCIENTIFIC MEETINGS
• “2018 International Meeting on the Molecular Biology of the Hepatitis B viruses” October 3-7, 2018, Taormina, Italy
• “Occult hepatitis B virus infection: biology and clinical impact”. The Taormina International Expert Meeting. March 7 - 8, 2008, Taormina, Italy
• “Workshop: Occult Hepadnavirus Infection”. The 2007 International Meeting: “The Molecular Biology of Hepatitis B viruses”. September 16-20, 2007, Rome, Italy
RESEARCH INTERESTS
• Molecular and translational aspects of the hepatitis viruses, which are the main causative agents of acute and chronic liver diseases.
• Hepatitis B Virus (HBV) research:
- Molecular characterization and clinical impact of occult hepatitis B virus (HBV) infection
- Role of HBV in hepatocellular carcinoma (HCC) development: (a) HBV DNA integration into the host genome, (b) pro-oncogenic activities of HBV genomic variants and HBV mutated proteins (HBx, preS/S envelope proteins)
- the impact of HBV genomic variability in the outcome of the infection and in the progression of liver disease
- Clinical virological aspects (new serological HBV biomarkers: cccDNA quantification, HBV RNA, HBV 3.5 kb RNAs, HBcrAg, and HBsAg quantification)
• Hepatitis D Virus (HDV) research:
- molecular and virologic characterization of HBV and HDV co-infection
• Hepatitis C Virus (HCV) research:
Impact of HCV genomic variability on antiviral therapy and viral resistance to Direct Antiviral Agents (DAAs)

SCIENTIFIC PRODUCTION
• Author of 98 publication in peer reviewed journals:
- Impact Factor (IF) > 10.00: 36 journal articles
• 4 book chapters
• > 70 seminars, talks and plenary presentation at International Meeting and Conferences, 34 as invited speaker (2007-2021)
• List of Journals with IF > 5.0: New England Journal of Medicine, Lancet, Gastroenterology, Journal of Hepatology, GUT, Blood, Hepatology, Journal of Clinical Investigation, American Journal of Gastroenterology, Proc Natl Acad Sci USA (PNAS), Plos Pathogens, Haematologica, Oncogene, Cancer, Liver Int.

METRICS

• Sum of the Times Cited (Scopus): 6988; (Scholar): 10,721
• Hirsch (H) index (Scopus): 40; (Scholar): 46
• IF (total): 1172,40

VALORIZATION
• Networks and research contracts (Principal Investigator).
- Member of the first international quality control network for the quantification of HDV viral load.
- Member of the GRT Validation Board of the HCV Virology Italian Resistance Network Study group: Vironet C
- Co-Principal Investigator ricerca finalizzata project RF-2016-02362422
- Fellowship Program 2018, Gilead Science, (ID: 04127)
- Fellowship Program 2015, Gilead Science (ID: FP-2015-365)
- Fellowship Program 2012, Gilead Science (ID: FP-2012-611)
- PRIN 2008 (ID: 20088HNWSP_003)
- PRIN 2005 (ID: 2005064913_002)

TEACHING ACTIVITIES
As a Full Professor of General Pathology Teresa Pollicino has teaching commitments with undergraduate and graduate students in the Medicine and Surgery School (International Medical School), Medical School, Biotechnology School, and Dental School of the University of Messina, Italy. These include formal teaching and tutorials. Dr. Pollicino also supervises trainees in Immunology and Allergology, Microbiology, Internal Medicine, Geriatric Medicine, and Nephrology and she is a key member of the student assessment board. During her academic career Prof. Pollicino has supervised both students and scientists to obtain Biotechnology, MD and PhD degrees in their research projects leading to thesis development. This is a fundamental part of her academic commitments which can be verified through the offices of the University of Messina, Italy.
Prof. Teresa Pollicino is a component of the Board of Teachers of the “International PhD Translational Molecular Medicine and Surgery Course” of Messina University.

MEDICAL ACTIVITIES
As a Chief of the Laboratory of Molecular Hepatology, Teresa Pollicino coordinates the activity of 3 MScs, 1 technician, 2 PhD students, and 2 MScs with non-tenured contracts paid by research grants. The Laboratory is a leader in Southern Italy in offering new and innovative diagnostic tests for viral hepatitis. It offers a comprehensive portfolio of assays based on antigen/antibody and nucleic acid detection of hepatitis viruses that can identify and classify infection, determine viral genotype/subtype, quantitate viral replication, and evaluate the effectiveness of antiviral treatment, including the presence of pre-existing and acquired drug resistant variants. A deep knowledge base, excellent technical skills, and a uniform dedication to continuing improvement are the hallmarks of the Laboratory whose activity is also particularly concerned with devising new diagnostic approaches, including that for the quantification of Hepatitis Delta virus (HDV). Of particular note is the fact that Teresa Pollicino’s Laboratory is one of the 20 European Laboratories that are testing the first international quality control for quantification of HDV viral load. Dr. Pollicino is also member of the GRT Validation Board of the HCV Virology Italian Resistance Network Study group: Vironet C.

2. Scientific Curriculum of the associated investigators

1. DI MARCO Vito
Investigator Curriculum Vitae

I. Name
First name: VITO
Last name: DI MARCO
Academic Title: Full Professor of Gastroenterology – University of Palermo

II. Current position and work address
Position: Chief of the program in Diagnosis and Therapy of Chronic Viral Hepatitis and Cirrhosis Start date: _01_/12__/2010____
Institution Name: Department of Internal Medicine-Section of Gastroenterology and Hepatology

Institution Address: Azienda Ospedaliera Universitaria Policlinico Giaccone – Via del Vespro, 129 – 90127 Palermo (Italy)
Phone: 0039-0916552106 Email address: vito.dimarco@unipa.it

III. Education
Degree Awarded From (year) To
(year) Institution City Country
Medicine and Surgery 1976 1982 University of Palermo Palermo Italy
Medical License/Diploma Number: n. 0000002148 – Provincial Board of Physicians of Agrigento

IV. Postgraduate education/Training courses/Professional Affiliations
Degree awarded/Name of training course From (year) To (year) Institution City Country
Member of EASL Ongoing EASL (European Association for the Study of the Liver) - -
Member of AISF ongoing AISF (Associazione Italiana per lo Studio del Fegato) - -
Specialization in Gastroenterology 1983 1987 University of Palermo Palermo Italy

V. Previous appointments
Position From (year) To
(year) Institution City Country
Full Professor of Gastroenterology 01-12-2016 To day University of Palermo Palermo Italy
Associate Professor of Gastroenterology 2010 2016 University of Palermo Palermo Italy
Senior Lecturer in Gastroenterology 2000 2010 University of Palermo Palermo Italy
Research Fellow 1996 2000 University of Palermo Palermo Italy

VI. Clinical research experience
Clinical Trial Phase Therapeutic Area
Principal Investigator or Sub-Investigator at more than 50 phase II-III-IV studies on liver diseases Chronic hepatitis B, Chronic
hepatitis C, Cirrhosis, Hepatocellular carcinoma

VII. Research interests
• Epidemiology of acute and chronic liver disease
• Non-invasive methods for the diagnosis of chronic liver disease;
• Diagnosis, natural history and therapy of chronic hepatitis C
• Diagnosis, natural history and therapy of chronic hepatitis B
• Therapy of HBV and HCV cirrhosis
• Autoimmune hepatitis and PBC,
• NAFLD,
• diagnosis and therapy of hepatocellular carcinoma
• Virus infection, siderosis and liver damage in Thalassemia patients

VIII. ICH-GCP training completed:
Yes X(Palermo October 2000)
No

VIII. Publications (list of publications may be appended)
More than 230 full papers in international journals and many presentations at national and international conferences.

HI Scopus 56; citations 8.780
Orcid ID 0000-0001-6397-4206
Scopus ID 7006039520

2. SVICHER Valentina

Personal data:
Born in Rome on March 2, 1977

Current academic and research positions:
Associate Professor, University of Rome "Tor Vergata"
Contract Professor of Clinical Microbiology, University of L'Aquila
Qualification for the role of Full Professor
Member of the teaching staff of the Research Doctorate in "Microbiology, Immunology, Infectious Diseases, Organ Transplants (MIMIT)".
Member of the teaching staff of the School of Specialization in Microbiology, University of Rome "Tor Vergata".
Member of the teaching staff of the School of Specialization in Infectious Disease, University of Rome "Tor Vergata"
Member of the teaching staff of the School of Specialization in Hematology, University of Rome "Tor Vergata"

Education
2001: Degree "cum laude" in Biological Sciences at the University of Rome "La Sapienza".
2004: Visiting Researcher Max Planck Institute for Informatics, Saarbrucken, Germany
2006: PhD in Microbiology and Medical Immunology, at the University of Rome "Tor Vergata".

Scientific Activity
She is the author of 450 publications (of which 129 in extenso and over 300 conference presentations in the form of abstracts published in proceedings or in peer reviewed journals cited on PubMed). She has an h-index of 32 and a total number of citations of 2982 (source: google scholar).
She has many years of experience in the study of viral replication kinetics (with particular reference to HBV, HDV and HIV) in response to antiviral drugs and the mechanisms that modulate viral pathogenicity and oncogenicity

Awards received for scientific publications:

1. "GB Rossi" Scientific Award as an Italian researcher distinguished in the field of AIDS research for the best work published in the period from 1 July 2008 to 30 June 2009 (V. Svicher et al., Antimicrob Agents Chemother. 2009).
2. "Readfiles" Scientific Award as an Italian researcher distinguished in the field of AIDS research for the best work published in the period from 1 July 2007 to 30 June 2008 (V. Svicher et al., J Infect Dis. 2008).
3. "GB Rossi" Scientific Award for the best publication in the field of HIV research in the period between 1 July 2007 - 30 June 2008 (second author, F. Ceccherini-Silberstein et al., J. Virol., 2007).
4. Scientific Prize "Infection Lab 2016 - YOUNG INFECTIVOLOGISTS IN COMPARISON" for the best scientific project presented in the competition (presenter of the research project and latest author of the related publication (Salpini et al., Oncotarget 2017).

Awards received for presentations of scientific works at national and international conferences:

5. Award ICAR CROI Award 2021 for young Italian investigators for the oral presentation in the setting of "Conference on Retroviruses and Opportunistic Infections" (CROI) 2021 (senior author of the award-winning presentation)
6. Award for the best oral presentation at the "European Meeting on HIV & Hepatitis 2020" Conference, held in digital version from 28 to 30 October 2020 (last author of the award-winning presentation)
7. Award for the best oral presentation in the context of "Basic Science" at the "International Liver Meeting 2019" promoted by the "European Association for the Study of the Liver" (EASL) (first author of the presentation). The International Liver Congress is one of the main international conferences in the hepatology field
8. SIM 2019 "Francesco Galdiero" Award for the best poster in the Virology area, awarded by the Italian Society of Microbiology as part of the 47th National Congress, held in Rome from 18 to 21 September 2019 (last author of the award-winning presentation).
9. Award for the best oral presentation at the "11th Italian Conference on AIDS and Antiviral Research" (2019) (last author of the award-winning presentation)
10. Award for the best oral communication at the congress "4th Italian experience in biomedical research: young minds at work" Desenzano 18-19 November 2016 (last author of the award-winning communication, A Battisti et al., 2016)
11. Best poster award at the 13th EU HIV & Hepatitis Workshop 3–5 June 2015, Barcelona, Spain (latest author of the award-winning poster, A Battisti et al., 2015).
12. Award for the best oral presentation at the 2rd Italian Conference on AIDS and Retroviruses, Brescia, Italy, 20-22 June, 2010 (second author, C. Alteri et al, 2010).
13. Best poster award at the XXXVI AMCLI National Congress, Rimini, Italy, 2-5 October 2007 (co-author, G. Cappiello et al, 2007).

14. Award for the best oral presentation at the 3rd European HIV Drug Resistance Workshop, Athens, Greece, March 30 - April 1, 2005 (first author and presenter of oral communication, V. Svicher et al, 2005).
15. Best poster award at the XIV International HIV Drug Resistance Workshop, Basic Principles & Clinical Implications, Quebec City, Quebec, Canada, June 7-11, 2005 (second author, F. Ceccherini-Silberstein et al., 2005).

Coordination and management of projects
She has collaborated and continues to collaborate with numerous National and International Research Institutes for the realization of the following projects:

2022-: Principal Investigator of the project "Establishment of biomarker assays to support hepatitis B virus (HBV) cure strategies" promoted by Roche Pharma Research & Early Development

2021-: Principal Investigator of the scientific project aimed at investigating anti-HIV activity of DDX3 inhibitors in vitro promoted by First Health Pharmaceutical.

2019-ongoing: Principal Investigator of Working Unit in the Project “IMmuno-VIrological DYnamics triggered by anti-HIV therapy Suspension (IMVIDYS)” granted by the Italian Ministry of Education and Research.
2018-2019: Principal Investigator of the project "DIRECT - Definition of regulatory non-coding RNA Expression Profiling in Hepatitis B and C Virus-Induced Hepatocellular Tumors" Unique Project Code (CUP): E81I18000380005, funded under the "Mission: Sustainability Program".
2013-2015: Principal Investigator of the project "From Functional Cure to Reactivation of HBV Infection: Identification and Functional Characterization of Genetic Elements in HBV Genome Correlated with reactivation in the setting of Immunosuppression" as part of the research program "Partnering for Cure research project "Sponsored by Bristol Meyer Squibb for 2 years.
2012-2018: WP1 Coordinator "Application of full length sequencing methods for the definition of viral genetic markers predictive of persistence and oncogenesis" within the project "Omics Applications in Virology" of the InterOmics Flag Research Project PB05 1 ° "Development of an integrated platform for the application of the" omics "sciences to the definition of biomarkers and diagnostic, predictive and teranostic profiles", financed by the Ministry of University and Research.
2009-2014: Workpackage Deputy 7 under the CHAIN European Research Project, the "Collaborative HIV and Anti-HIV Drug Resistance Network", Integrated Project no. 223131 funded for 5 years by the European Commission Framework 7 Program.
2018-2019: Principal Investigator of the study "Characterization of HBeAg levels in the natural history of HBV infection and its role in predicting patients' therapeutic outcome and liver disease progression" funded thanks to the educational grant promoted by Diasorin.
2014-2016: Co-Principal Investigator of the study "Combined Analysis of the Prevalence of HBsAg Immune Escape Mutations and Stop Codons in Antiviral Therapy Experienced HBV-infected patients" conducted within the Scientific Society "the European Society for Translational Antiviral Research" (ESAR).
2011-2013: Co-principal Investigator of the study "Combined Analysis of the Prevalence of drug Resistant HBV in antiviral therapy Experienced patients" conducted within the Scientific Society "the European Society for Translational Antiviral Research" (ESAR).
2009-2010: Management of activities related to the project OSCAR (Optimizing the Susceptibility to CCR5 Antagonists Response)
2011-2013: Management of the activities related to the project "Characterization of innovative genetic markers in the HBV genome and related HCV with the development of hepatocellular carcinoma (HCC) to viral etiology
2011-2012: Management of the activities related to the DIVA (DNA Tropism Italian Validation Concerted Action) project.
The methods developed within these 2 projects are currently used at national level in the diagnostic practice as reference methods for the determination of HIV tropism on RNA and proviral DNA.
2011: Management of the activities related to the CHIMERA (Chronic Hepatitis Italian Management & Education in Regional Areas) project aimed at the optimization and diffusion in the clinical field of the genotypic test for HBV's drug resistance.

Other Activities

• Member of the Council of the Scientific Society "European Society for Antiviral Research (ESAR)"

• Member of the Scientific Committee of ICoNA (Italian Cohort of Naive Antiretrovirals)
• Member of the study group on the treatment and prophylaxis of HBV in haematological patients. The group involves the following Scientific Societies: SIMIT, SIVIM, SIE, GITMO
• Member of the Working Group aimed at updating the Italian recommendations on the treatment of chronic hepatitis B which involved the SIMIT and AISF Scientific Societies
• Member of the European Consensus Group "for the drafting of the European Guidelines for the determination of HIV tropism in clinical practice.
• Invited as Guest Editor for the scientific journals Frontiers in Microbiology, Viruses, Vaccines
• Reviewer of scientific articles for several "peer reviewed" journals.
• Moderator in several sessions of national and international conferences. In particular, he moderated the session "HIV: Innovative Therapeutic Approaches, ART and Drug Resistance" at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, MA, USA (February 28, 2011).

3. Main Principal Investigator's scientific publications (Max. 20)

1. Pollicino T., Caminiti G. (2021). HBV-integration studies in the clinic: Role in the natural history of infection. VIRUSES, vol. 13, p. 4-21, ISSN: 1999-4915, doi: 10.3390/v13030368 - **Articolo in rivista**
2. Raimondo G., Saitta C., Lombardo D., Giraudi P. J., Rosso N., Ieni A., Lazzara S., Palmisano S., Bonazza D., Alibrandi A., Navarra G., Tiribelli C., Pollicino T. (2020). Occult hepatitis B virus infection predicts non-alcoholic steatohepatitis in severely obese individuals from Italy. LIVER INTERNATIONAL, p. 1-9, ISSN: 1478-3223, doi: 10.1111/liv.14473 - **Articolo in rivista**
3. Allweiss, Lena, Volz, Tassilo, Giersch, Katja, Kah, Janine, RAFFA, GIUSEPPINA, Petersen, Joerg, Lohse, Ansgar W, BENINATI, Concetta, POLLICINO, Teresa, Urban, Stephan...(2018). Proliferation of primary human hepatocytes and prevention of hepatitis B virus reinfection efficiently deplete nuclear cccDNA in vivo. GUT, vol. 67, p. 542-552, ISSN: 0017-5749, doi: 10.1136/gutjnl-2016-312162 - **Articolo in rivista**
4. Chen, Zhaochun, Diaz, Giacomo, Pollicino, Teresa, Zhao, Huaying, Engle, Ronald E, Schuck, Peter, Shen, Chen-Hsiang, Zamboni, Fausto, Long, Zhifeng, Kabat, Juraj...(2018). Role of humoral immunity against hepatitis B virus core antigen in the pathogenesis of acute liver failure. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 115, p. E11369-E11378, ISSN: 0027-8424, doi: 10.1073/pnas.1809028115 - **Articolo in rivista**
5. Larsson SB, Tripodi G, Raimondo G, Saitta C, Norkrans G, Pollicino T, Lindh M. (2018). Integration of hepatitis B virus DNA in chronically infected patients assessed by Alu-PCR.. JOURNAL OF MEDICAL VIROLOGY, vol. 90, p. 1568-1575, ISSN: 0146-6615, doi: 10.1002/jmv.25227 - **Articolo in rivista**
6. Pollicino T, Musolino C, Irrera N, Bitto A, Lombardo D, Timmoneri M, Minutoli L, Raimondo G, Squadrito G, Squadrito F, Altavilla D. (2018). Flavocoxid exerts a potent antiviral effect against hepatitis B virus.. INFLAMMATION RESEARCH, vol. 67, p. 89-103, ISSN: 1023-3830, doi: 10.1007/s00011-017-1099-2 - **Articolo in rivista**
7. Sekhar, Vandana, Pollicino, Teresa, Diaz, Giacomo, Engle, Ronald E, Alayli, Farah, Melis, Marta, Kabat, Juraj, Tice, Ashley, Pomerenke, Anna, Altan-Bonnet, Nihal...(2018). Infection with hepatitis C virus depends on TACSTD2, a regulator of claudin-1 and occludin highly downregulated in hepatocellular carcinoma. PLOS PATHOGENS, vol. 14, p. 1-30, ISSN: 1553-7374, doi: 10.1371/journal.ppat.1006916 - **Articolo in rivista**
8. Giersch, Katja, Homs, Maria, Volz, Tassilo, Helbig, Martina, Allweiss, Lena, Lohse, Ansgar W., Petersen, Jörg, Buti, Maria, POLLICINO, Teresa, Sureau, Camille...(2017). Both interferon alpha and lambda can reduce all intrahepatic HDV infection markers in HBV/HDV infected humanized mice. SCIENTIFIC REPORTS, vol. 7, p. 1-11, ISSN: 2045-2322, doi: 10.1038/s41598-017-03946-9 - **Articolo in rivista**
9. Villa, E, Critelli, R, Lei, B, Marzocchi, G, Cammà, C, Giannelli, G, Pontisso, P, Cabibbo, G, Enea, M, Colopi, S... (2016). Neoangiogenesis-related genes are hallmarks of fast-growing hepatocellular carcinomas and worst survival. Results from a prospective study. GUT, vol. 65, p. 861-869, ISSN: 0017-5749, doi: 10.1136/gutjnl-2014-308483 - **Articolo in rivista**

10. SAITTA, CARLO, LANZA, MARIKA, BERTUCCIO, ANTONIO, LAZZARA, Salvatore, NAVARRA, Giuseppe, RAIMONDO, Giovanni, POLLICINO, Teresa (2015). Evaluation of CTNNB1 and TP53 variability in patients with hepatocellular carcinoma and occult hepatitis B virus infection. CANCER GENETICS, vol. 208, p. 513-516, ISSN: 2210-7762, doi: 10.1016/j.cancergen.2015.07.002 - **Articolo in rivista**

11. SAITTA, CARLO, TRIPODI, GIANLUCA, BARBERA, Adalberto, BERTUCCIO, Antonino, Smedile A, Ciancio A, RAFFA, GIUSEPPINA, Sangiovanni A, NAVARRA, Giuseppe, RAIMONDO, Giovanni, POLLICINO, Teresa (2015). Hepatitis B virus (HBV) DNA integration in patients with occult HBV infection and hepatocellular carcinoma.. LIVER INTERNATIONAL, vol. 35, p. 2311-2317, ISSN: 1478-3223, doi: 10.1111/liv.12807 - **Articolo in rivista**

12. POLLICINO, Teresa, CACCIOLA, Irene, SAFFIOTI, FRANCESCA, RAIMONDO, Giovanni (2014). Hepatitis B virus PreS/S gene variants: Pathobiology and clinical implications.. JOURNAL OF HEPATOLOGY, vol. 61, p. 408-417, ISSN: 0168-8278, doi: 10.1016/j.jhep.2014.04.041 - **Articolo in rivista**

13. POLLICINO, Teresa, Bellinghieri, L., Restuccia, A., RAFFA, GIUSEPPINA, MUSOLINO, CRISTINA, ALIBRANDI, Angela, TETI, Diana, RAIMONDO, Giovanni (2013). Hepatitis B virus (HBV) induces the expression of interleukin-8 that in turn reduces HBV sensitivity to interferon-alpha.. VIROLOGY, vol. 444, p. 317-328, ISSN: 0042-6822, doi: 10.1016/j.virol.2013.06.028 - **Articolo in rivista**

14. POLLICINO, Teresa, Vegetti, A., SAITTA, CARLO, Ferrara, F., Corradini, E., RAFFA, GIUSEPPINA, Pietrangelo, A., RAIMONDO, Giovanni (2013). Hepatitis B virus DNA integration in tumour tissue of a non-cirrhotic HFE-haemochromatosis patient with hepatocellular carcinoma.. JOURNAL OF HEPATOLOGY, vol. 58, p. 190-193, ISSN: 0168-8278, doi: 10.1016/j.jhep.2012.09.005 - **Articolo in rivista**

15. Laura Belloni, Lena Allweiss, Francesca Guerrieri, Natalia Pediconi, Tassilo Volz, POLLICINO, Teresa, Joerg Petersen, RAIMONDO, Giovanni, Maura Dandri, Massimo Levrero (2012). IFN-α inhibits HBV transcription and replication in cell culture and in humanized mice by targeting the epigenetic regulation of the nuclear cccDNA minichromosome. THE JOURNAL OF CLINICAL INVESTIGATION, vol. 122, p. 529-537, ISSN: 0021-9738, doi: 10.1172/JCI58847 - **Articolo in rivista**

16. POLLICINO, Teresa, AMADDEO, GIULIANA, Restuccia, A., RAFFA, GIUSEPPINA, ALIBRANDI, Angela, CUTRONEO, Giuseppina, FAVALORO, Angelo, MAIMONE, SERGIO, SQUADRITO, Giovanni, RAIMONDO, Giovanni (2012). Impact of hepatitis B virus (HBV) preS/S genomic variability on HBV surface antigen and HBV DNA serum levels.. HEPATOLOGY, vol. 56, p. 434-443, ISSN: 0270-9139, doi: 10.1002/hep.25592 - **Articolo in rivista**

17. POLLICINO, Teresa, RAFFA, GIUSEPPINA, T. Santantonio, G. B. Gaeta, G. Iannello, ALIBRANDI, Angela, SQUADRITO, Giovanni, CACCIOLA, Irene, C. Calvi, G. Colucci, M. Levrero, RAIMONDO, Giovanni (2011). Replicative and transcriptional activities of hepatitis B virus in patients coinfected with hepatitis B and hepatitis delta viruses.. JOURNAL OF VIROLOGY, vol. 85, p. 432-439, ISSN: 0022-538X, doi: 10.1128/JVI.01609-10 - **Articolo in rivista**

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20. POLLICINO T, BELLONI L, RAFFA G, PEDICONI N, SQUADRITO G., RAIMODO G, LEVRERO M (2006). Hepatitis B Virus Replication Is Regulated by the Acetylation Status of Hepatitis B Virus cccDNA-Bound H3 and H4 Histones. GASTROENTEROLOGY, vol. 130, p. 823-837, ISSN: 0016-5085, doi: 10.1053/j.gastro.2006.01.001 - **Articolo in rivista**

4. Main scientific publications of the associated investigators (Max. 20, for each research unit)

1. **DI MARCO Vito**

1. Caraceni P., Tufoni M., Zaccherini G., Riggio O., Angeli P., Alessandria C., Neri S., Foschi F. G., Levantesi F., Airoldi A., Simone L., Svegliati-Baroni G., Fagiuoli S., Laffi G., Cozzolongo R., Di Marco V., Sangiovanni V., Morisco F., Toniutto P., Gasbarrini A.[...](2020). On-treatment serum albumin level can guide long-term treatment in patients with cirrhosis and uncomplicated ascites. JOURNAL OF HEPATOLOGY, vol. 74, p. 340-349, ISSN: 0168-8278, doi: 10.1016/j.jhep.2020.08.021 - **Articolo in rivista**
2. Lampertico P., Berg T., Buti M., Pathil A., Petersen J., Ryder S. D., Zoulim F., Botros I., Flaherty J. F., Jump B., Op den Brouw M. L., van Troostenburg A., Ramroth H., Bourliere M., De Ledinghen V., Riachi G., Zoulim F., Loustaud-Ratti V., Tran A., Larrey D.[...](2020). Treatment with tenofovir disoproxil fumarate or entecavir in chronic hepatitis B virus-infected patients with renal impairment: results from a 7-year, multicentre retrospective cohort study. ALIMENTARY PHARMACOLOGY & THERAPEUTICS, vol. 52, p. 500-512, ISSN: 0269-2813, doi: 10.1111/apt.15901 - **Articolo in rivista**
3. Raimondo G., Locarnini S., Pollicino T., Levrero M., Zoulim F., Lok A. S., Allain J. -P., Berg T., Bertoletti A., Brunetto M. R., Bruno R., Chen D. -S., Coppola N., Cornberg M., Craxi A., Dandri M., Di Marco V., Ferrari C., Gaeta G. B., Glebe D. [...](2019). Update of the statements on biology and clinical impact of occult hepatitis B virus infection. JOURNAL OF HEPATOLOGY, vol. 71, p. 397-408, ISSN: 0168-8278, doi: 10.1016/j.jhep.2019.03.034 - **Articolo in rivista**
4. Calvaruso, Vincenza, Cabibbo, Giuseppe, Cacciola, Irene, Petta, Salvatore, Madonia, Salvatore, Bellia, Alessandro, Tinè, Fabio, Distefano, Marco, Licata, Anna, Giannitrapani, Lydia[...](2018). Incidence of Hepatocellular Carcinoma in Patients With HCV-Associated Cirrhosis Treated With Direct-Acting Antiviral Agents. GASTROENTEROLOGY, vol. 155, p. 411-421, ISSN: 0016-5085, doi: 10.1053/j.gastro.2018.04.008 - **Articolo in rivista**
5. Caraceni P1, Riggio O2, Angeli P3, Alessandria C4, Neri S5, Foschi FG6, Levantesi F7, Airoldi A8, Boccia S9, Svegliati-Baroni G10, Fagiuoli S11, Romanelli RG12, Cozzolongo R13, Di Marco Vito, Sangiovanni V15, Morisco F16, Toniutto P17, Tortora A18, De Marco R19, Angelico M20[...](2018). Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial.. THE LANCET, vol. 391, p. 2417-2429, ISSN: 0099-5355, doi: 10.1016/S0140-6736(18)30840-7 - **Articolo in rivista**
6. Lampertico, P, Viganò, M, Di Costanzo, GG, Sagnelli, E, Fasano, M, DI MARCO, Vito, Boninsegna, S, Farci, P, Fargion, S, Giuberti, T[...](2013). Randomised study comparing 48 and 96 weeks peginterferon α-2a therapy in genotype D HBeAg-negative chronic hepatitis B. GUT, vol. 62, p. 290-298, ISSN: 0017-5749, doi: 10.1136/gutjnl-2011-301430 - **Articolo in rivista**
7. FERRARO, Donatella, Urone N, Pizzillo P, Gussio M, Magliocco S, Cacopardo B, CRAXI, Antonio, DI MARCO, Vito, DI STEFANO, Rosa (2012). Phylogenetic Analysis of isolates from new cases of HBV infection in Southern Italy.. INFECTION GENETICS AND EVOLUTION, vol. 12, p. 1591-1596, ISSN: 1567-1348, doi: 10.1016/j.meegid.2012.07.006 - **Articolo in rivista**
8. Fasano, M, Lampertico, P, Marzano, A, DI MARCO, Vito, Niro, GA, Brancaccio, G, Marengo, A, Scotto, G, Brunetto, MR, Gaeta, GB[...](2012). HBV DNA suppression and HBsAg clearance in HBeAg negative chronic hepatitis B patients on lamivudine therapy for over 5 years. JOURNAL OF HEPATOLOGY, vol. 56, p. 1254-1258, ISSN: 0168-8278 - **Articolo in rivista**
9. Stroffolini, T, Spadaro, A, DI MARCO, Vito, Scifo, G, Russello, M, MONTALTO, Giuseppe, Bertino, G, Surace, L, Caroleo, B, Foti, G[...](2012). Current practice of chronic hepatitis B treatment in Southern Italy.. EUROPEAN JOURNAL OF INTERNAL MEDICINE, vol. 23, ISSN: 0953-6205 - **Articolo in rivista**
10. Carosi, G, Rizzetto, M, Alberti, A, Cariti, G, Colombo, M, CRAXI, Antonio, Filice, G, Levrero, M, Mazzotta, F, Pastore, G [...](2011). Treatment of chronic
hepatitis B: update of the recommendations from the 2007 Italian Workshop. DIGESTIVE AND LIVER DISEASE, vol. 43, ISSN: 1590-8658 - **Articolo in rivista**
11. DI MARCO, Vito, CRAXI, Antonio (2009). Chronic hepatitis B: who to treat and which choice of treatment?. EXPERT REVIEW OF ANTI-INFECTIVE THERAPY, vol. 2009-04-01, p. 281-291, ISSN: 1478-7210, doi: 10.1586/ERI.09.4 - **Articolo in rivista**
12. FERRARO, Donatella, PIZZILLO, Paola, DI MARCO, Vito, VULTAGGIO, A, IANNITTO, E, VENEZIA, G, CRAXI, Antonio, DI STEFANO, Rosa (2009). EVALUATING THE RISK OF HEPATITIS B REACTIVATION IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES: IS THE SERUM HEPATITIS B PROFILE RELIABLE?. LIVER INTERNATIONAL, vol. 2009, p. 1171-1177, ISSN: 1478-3223, doi: 10.1111/j.1478-3231.2009.02071x - **Articolo in rivista**
13. Pollicino, T, Isgrò, G, DI STEFANO, Rosa, FERRARO, Donatella, Maimone, S, Brancatelli, S, Squadrito, G, DI MARCO, Vito, CRAXI, Antonio, Raimondo, G. (2009). Variability of reverse transcriptase and overlapping S gene in hepatitis B virus isolates from untreated and lamivudine-resistant chronic hepatitis B patients.. ANTIVIRAL THERAPY, vol. 14, p. 649-654, ISSN: 1359-6535 - **Articolo in rivista**
14. DI MARCO V, CRAXÌ A (2007). Adefovir for lamivudine resistant HBV: more than meets the eye. JOURNAL OF HEPATOLOGY, vol. 47, p. 618-619, ISSN: 0168-8278 - **Articolo in rivista**
15. MARZANO A, ANGELUCCI E, ANDREONE P, BRUNETTO M, BRUNO R, BURRA P, CARACENI P, DANIELE B, DI MARCO V, FABRIZI F, FAGIUOLI S, GROSSI P, LAMPERTICO P, MELICONI R, MANGIA A, PUOTI M, RAIMONDO G, SMEDILE A,

ITALIAN ASSOCIATION FOR THE STUDY OF, THE LIVER (2007). Prophylaxis and treatment of hepatitis B in immunocompromised patients. DIGESTIVE AND LIVER DISEASE, vol. 39, p. 397-411, ISSN: 1590-8658 - **Articolo in rivista**

16. DI MARCO V, DE LISI S, LI VECCHI M, MARINGHINI S, BARBARIA F (2006). Therapy with lamivudine and steroids in a patient with acute hepatitis B and rapidly progressive glomerulonephritis. KIDNEY INTERNATIONAL, vol. 70, p. 1187-1188, ISSN: 0085-2538 - **Articolo in rivista**
17. DI MARCO, Vito, DI STEFANO, Rosa, FERRARO, Donatella, ALMASIO, Pier Luigi, BONURA, Celestino, GIGLIO, Maria, PARISI, P, CAPPELLO M, ALAIMO G, CRAXI, Antonio (2005). HBV-DNA suppression and disease course in HBV cirrhosis patients on long-term lamivudine therapy. ANTIVIRAL THERAPY, vol. 10, p. 431-439, ISSN: 1359-6535 - **Articolo in rivista**
18. DI MARCO, Vito, MARZANO, A, LAMPERTICO, P, ANDREONE, P, SANTANTONIO, T, ALMASIO, Pier Luigi, RIZZETTO, M, CRAXI, Antonio (2004). Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine. HEPATOLOGY, vol. 40, p. 883-891, ISSN: 0270-9139, doi: 10.1002/hep.20381 - **Articolo in rivista**
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20. DI MARCO V, LO IACONO O, CAMMA C, VACCARO A, GIUNTA M, MARTORANA G, FUSCHI P, ALMASIO PL, CRAXI A. (1999). The long-term course of chronic hepatitis B. HEPATOLOGY, vol. 30, p. 257-264, ISSN: 0270-9139 - **Articolo in rivista**

2. SVICHER Valentina

1. Cerva C, Salpini R, Alkhatib M, Malagnino V, Piermatteo L, Battisti A, Bertoli A, Gersch J, Holzmayer V, Kuhns M, Cloherty G, Ferrari L, Laura C, Teti E, Cantonetti M, Arcese W, Ceccherini-Silberstein F, Perno CF, Andreoni M, Svicher V...(2022). Highly Sensitive HBsAg, Anti-HBc and Anti HBsAg Titres in Early Diagnosis of HBV Reactivation in Anti-HBc-Positive Onco-Haematological Patients . BIOMEDICINES, ISSN: 2227-9059 - **Articolo in rivista**
2. Brancaccio G, Salpini R, Piermatteo L, Surdo M, Fini V, Colagrossi L, Cantone M, Battisti A, Oda Y, Di Carlo D, Ceccherini-Silberstein F, Perno CF, Gaeta GB, Svicher V (2021). An Increase in the Levels of Middle Surface Antigen Characterizes Patients Developing HBV-Driven Liver Cancer Despite Prolonged Virological Suppression . MICROORGANISMS, ISSN: 2076-2607, doi: 10.3390/microorganisms9040752 - **Articolo in rivista**
3. Piermatteo L, Alkhatib M, D'Anna S, Malagnino V, Bertoli A, Andreassi E, Basile E, Iuvara A, De Cristofaro M, Cappiello G, Cerva C, Minichini C, Pisaturo M, Starace M, Coppola N, Fontana C, Grelli S, Ceccherini-Silberstein F, Andreoni M, Gill US...(2021). HBeAg Levels Vary across the Different Stages of HBV Infection According to the Extent of Immunological Pressure and Are Associated with Therapeutic Outcome in the Setting of Immunosuppression-Driven HBV Reactivation . BIOMEDICINES, ISSN: 2227-9059, doi: 10.3390/biomedicines9101352 - **Articolo in rivista**
4. Piermatteo L, Scutari R, Chirichiello R, Alkhatib M, Malagnino V, Bertoli A, Iapadre N, Ciotti M, Sarmati L, Andreoni M, Ceccherini-Silberstein F, Salpini R, Svicher V (2021). Droplet digital PCR assay as an innovative and promising highly sensitive assay to unveil residual and cryptic HBV replication in peripheral compartment . METHODS, ISSN: 1046-2023, doi: 10.1016/j.ymeth.2021.05.011 - **Articolo in rivista**
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6. Salpini R, Malagnino V, Piermatteo L, Mulas T, Alkhatib M, Scutari R, Teti E, Cerva C, Yu La Rosa K, Brugneti M, Bertoli A, Rossi B, Holzmayer V, Gersch J, Kuhns M, Cloherty G, Ceccherini-Silberstein F, Perno CF, Iannetta M, Andreoni M...(2020). Cryptic HBV Replicative Activity Is Frequently Revealed in

Anti-HBc-Positive/HBsAg-Negative Patients with HIV Infection by Highly Sensitive Molecular Assays, and Can Be Predicted by Integrating Classical and Novel Serological HBV Markers
. MICROORGANISMS, ISSN: 2076-2607, doi: 10.3390/microorganisms8111819 - **Articolo in rivista**

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8. Svicher V, Salpini R, Piermatteo L, Carioti L, Battisti A, Colagrossi L, Scutari R, Surdo M, Cacciafesta V, Nuccitelli A, Hansi N, Ceccherini Silberstein F, Perno CF, Gill US, Kennedy PTF. (2020). Whole exome HBV DNA integration is independent of the intrahepatic HBV reservoir in HBeAg-negative chronic hepatitis B.. GUT, ISSN: 0017-5749 - **Articolo in rivista**
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13. Colagrossi L., Salpini R., Scutari R., Carioti L., Battisti A., Piermatteo L., Bertoli A., Fabeni L., Minichini C., Trimoulet P., Fleury H., Nebuloso E., De Cristofaro M., Cappiello G., Spano A., Malagnino V., Mari T., Barlattani A., Iapadre N., Lichtner M....(2018). HDV can constrain HBV genetic evolution in hbsag: Implications for the identification of innovative pharmacological targets. VIRUSES, vol. 10, ISSN: 1999-4915, doi: 10.3390/v10070363 - **Articolo in rivista**
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5. Main staff involved (max 10 professors/researchers for each research unit, in addition to the PI or associated investigator), highlighting the time commitment expected

List of the Research Units

Unit 1 - POLLICINO Teresa

Personnel of the research unit

nº	Surname Name	Qualification	University/ Research Institution	e-mail address	Months/person expected
1.	POLLICINO Teresa	Professore Ordinario (L. 240/10)	Università degli Studi di MESSINA	tpollicino@unime.it	2,0
2.	CACCIOLA Irene	Professore Associato (L. 240/10)	Università degli Studi di MESSINA	icacciola@unime.it	2,0

Possible sub-unit

Surname	Name	Qualification	e-mail address	Months/person expected
CRAXÌ	ANTONIO	Presidente e rappresentante legale	presidente@vironetc.org	
CECCHERINI SILBERSTEIN	FRANCESCA	Vicepresidente e Direttore Scientifico	direttorescientifico@vironetc.org	
BRUNO	ANDREA	Segretario	segreteria@vironetc.org	
Institution: FONDAZIONE VIRONET C ONLUS				

Unit 2 - DI MARCO Vito

Personnel of the research unit

nº	Surname Name	Qualification	University/ Research Institution	e-mail address	Months/person expected

1.	DI MARCO Vito	Professore Ordinario (L. 240/10)	Università degli Studi di PALERMO	vito.dimarco@unipa.it	2,0
2.	CALVARUSO Vincenza	Professore Associato (L. 240/10)	Università degli Studi di PALERMO	vincenza.calvaruso@unipa.it	3,0

Unit 3 - SVICHER Valentina

Personnel of the research unit

nº	Surname Name	Qualification	University/ Research Institution	e-mail address	Months/person expected
1.	SVICHER Valentina	Professore Associato (L. 240/10)	Università degli Studi di ROMA "Tor Vergata"	valentina.svicher@uniroma2.it	2,0
2.	LA FRAZIA Simone	Ricercatore confermato	Università degli Studi di ROMA "Tor Vergata"	Simone.La.Frazia@uniroma2.it	2,0
3.	D'ANNA Stefano	Dottorando	Università degli Studi di ROMA "Tor Vergata"	stefanodanna26@gmail.com	6,0

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6. Information on the new contracts for personnel to be specifically recruited

nº	Associated or principal investigator	Number of expected RTD contracts	Number of research grants expected	Number of PhD scholarships expected	Overall expected time commitment (months)
1.	POLLICINO Teresa	0	1	0	12
2.	DI MARCO Vito	0	0	0	0
3.	SVICHER Valentina	0	1	0	12
	Total	**0**	**2**	**0**	**24**

7. PI "Do No Significant Harm (DNSH)" declaration, in compliance with article n. 17, EU Regulation 852/2020. (upload PDF)

Upload:

The CINECA, Department of Services for MUR, is data controller. The consultation is also reserved to universities, research institutes and institutions (each for its respective competence), MUR - Directorate-General Research- Office III, CNVR, CdV, and the reviewers in charge of the evaluation peer review.
MUR also has the right to the dissemination of the main economic and scientific data related to the funded projects.”.

Date 30/03/2022 ore 23:08

Suddivisione fondi

Codice progetto: **2022X2KWRK**

Titolo:
Deciphering the key virological determinants underlying the replicative and pathogenetic activity of Hepatitis D Virus (HDV) in treated and untreated Hepatitis B Virus and HDV coinfected patients.

Coordinatore: **POLLICINO Teresa**

Contributo MIUR per Ricerca: **202,449**

Cofinanziamento Ateneo/Ente: **64,720**

Costo totale: **267,169**

Suddivisione dei costi delle Unità

La suddivisione fondi è stata trasmessa il 5/29/2023

N°	Sede dell'Unità	Responsabile Scientifico	Contributo MUR per ricerca	Cofinanziamento Ateneo/Ente	Costo Totale	Gestione responsabile	Autorizzato
1	Università degli Studi di MESSINA	POLLICINO Teresa	108,557	24,477	133,034		
2	Università degli Studi di PALERMO	DI MARCO Vito	36,233	23,045	59,278		
3	Università degli Studi di ROMA "Tor Vergata"	SVICHER Valentina	57,659	17,198	74,857		
Totale			202,449	64,720	267,169		