PRESS RELEASE

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InFlaMe project: addressing virus-host interactions and defense strategies to design new therapeutics against flaviviruses

From the 1st of January 2025, Institut *Imagine* (Inserm, AP-HP, Université Paris Cité) is participating in the transnational InFlaMe project, funded through Horizon Europe's '*Pandemic preparedness and response: Host-pathogen interactions of infectious diseases with epidemic potential*' call.

Flaviviruses, such as **Dengue virus (DENV)** and **West Nile virus (WNW)**, are viruses spread by mosquitoes that cause serious illnesses in humans and animals. They are becoming increasingly common in Europe, with both imported and local cases on the rise due to urban growth, climate change, and global travel. Consequently, almost half the world's population is at risk, and the economic impact is huge ($12 billion per year). Currently, only a few vaccines with limited effectiveness on DENV and WNW exist, and no specific treatment for humans is available. Therefore, better understanding of the immune response and improving diagnosis is crucial to controlling these viruses. **InFlaMe project aims to help the EU better prepare for, and respond to the outbreaks of DENV and WNV.** This four-year project focuses on three main areas: **understanding why some people get more seriously ill** compared to others when infected, **developing new treatments**, particularly ones that can block how the viruses interact with the human body, and **tracking the spread of the viruses** in both people and animals using a "One Health" approach, which looks at human, animal, and environmental health together. Based on these outcomes, the project ultimately **aims to strengthen the EU's ability to fight DENV and WNV epidemic and pandemic threats and develop effective emergency plans**.

InFlaMe consortium, led by the Professor Fausto Baldanti from the Fondazione IRCCS Policlinico San Matteo in Pavia, Italy, unites partners from Italy (Fondazione Istituto Nazionale di Genetica Molecolare INGM, Universita Degli Studi di Firenze, Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia Romagna Bruno Ubertini, Consiglio Nazionale delle Ricerche), France (**Institut *Imagine***, Institut Pasteur), Austria (Medizinische Universitaet Wien), Czechia (Masarykova Univerzita), and Spain (Asociacion Centro De Investigacion Cooperativa En Biociencias) that bring unparallel expertise in diagnosis of flavivirus infections in humans and animals, host-pathogen interactions and drug discovery.

The consortium will enable the EU to work out an integrated contingency plan (pandemic preparedness) that will go beyond individual national emergencies.

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The official start of the project, set for the 1st of January 2025, was marked with a first in-person meeting of the consortium members, with the participation of the Project Officer from European Health and Digital Executive Agency (HaDEA) and members of the Advisory Board, **at the Palazzo Bellisomi-Vistarino in Pavia, Italy, on the 4th and 5th of February 2025.**The meeting provided an excellent opportunity for each partner of the consortium to introduce their teams, expertise, and roles within the project, as well as to engage in detailed discussion on the objectives and tasks for each work package and assess potential risks, along with strategies for mitigation. In his welcoming speech, **the coordinator emphasized the consortium's responsibility to deliver results, highlighting their significance for the future, especially in light of recent outbreaks**, as well as the importance of InFlaMe for policymakers in relation to the "One Health" approach.

The project website, which has recently been launched, will serve as a platform to inform and educate the citizens on the goals and milestones of the consortium in their effort to understand, fight, and prevent future DNV and WNV pandemics and epidemics.

In parallel, study and consortium news will also be continuously shared through the project's LinkedIn page.

Partners:

► About **Fondazione IRCCS Policlinico San Matteo (IRCCS-OSM)**

The Foundation is one of the most important scientific hospitals and care institutions in Europe, and it has served as a clinical experimentation laboratory for healthcare activities since 1400. The Fondazione IRCCS Policlinico San Matteo, established in 2006, is a public institution of national and international significance, with a strong presence in the university sector. It is located in both Pavia and Belgioioso and is known for its highly specialised hospitalisation and care services. The integration of scientific research and education in diagnostic, treatment, and laboratory facilities is a key strength.

The IRCCS has more than 1,000 accredited beds and over 3,500 employees, which include doctors, nurses, technicians, and administrators. Thanks to technological investments made over the years, high-complexity performances have increased. The Microbiology and Virology Department headed by Prof. F. Baldanti is a regional reference laboratory for the Lombardia Region (Italy) for arboviral infections, and it is involved in National surveillance programs. In the project, as coordinator, IRCCS OSM will oversee the management and will be involved in patient recruitment and sample collection. The Institute has a longstanding competence in diagnostic and research activity on viral diseases and expertise in the development of assays for immune response against viruses as well as molecular approaches of metagenomics and next-generation sequencing, therefore leading the work package focused on the dissection of T-cell mediated response against flaviviruses.

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► About **Fondazione Istituto Nazionale di Genetica Molecolare (INGM)**

The Fondazione Istituto Nazionale di Genetica Molecolare-INGM is a 25,000-square-meter building located inside the Policlinic of Milan grounds. INGM biomedical research is based on "state of the art" technological platforms with strong connections to clinical needs; its location facilitates the establishment of clinically oriented research programs and offers a dynamic and collaborative environment. Its focus is mainly related to molecular genetics and methods of detection and diagnosis. The Foundation hosts more than 100 researchers working in the laboratories with about 40 projects funded by national and international agencies.

INGM has in place the technological platforms and consolidated know-how for molecular and cellular profiling of immune responses. Research activities at INGM are supported by facilities equipped with the most advanced tools, instruments and technologies such as a Microscopy Facility, a Flow Cytometry Facility, a Bioinformatics Unit and a Center for Engineered Organoids. Moreover, INGM holds a BL3 laboratory equipped with a FACS aria cell sorter for handling infectious material.

Researchers involved in InFlaMe will work on immunological and transcriptomics analyses at the single cell level, antigen-specificity assessment, selection and generation of neutralizing human mAbs. Bioinformatic tools will be applied to each "-omic" platform, and- imaging platforms for in vitro. Moreover, functional studies will be used to investigate the mode and etiological factors of flavivirus infection. INGM leads the WP, which is focused on the dissection of the B cell response and selection of human mAbs.

► About **Universita Degli Studi di Firenze (UNIFI)**

UNIFI has its origins in the Studium Générale that the Florentine Republic established in 1321, with disciplines taught at the time being civil and canon law, literature and medicine. In 1924, a special decree officially instituted the University. Today, UNIFI is one of the largest research and higher education organisations in Italy, with 1,800 lecturers and researchers, around 1,600 technical and administrative staff, and over 1,600 doctoral and post-doctoral students.

Researchers at UNIFI belong to 21 departments and have access to around 40 research facilities, including inter-departmental and inter-university centres, as well as research, transfer and higher education centres.

The Chemistry Department of UNIFI plays a key role in InFlaMe activities, thanks to the access to all materials and labs for organic synthesis, purification and characterization of synthesis, and for functionalization of glycans, as well as access to NMR instrumentations and the EU infrastructure INSTRUCT for high field spectroscopic studies. The PI of this Unit has a long-lasting experience in glycans' bioconjugation, glycosylation of proteins and peptides and glycosylation of multivalent nanomaterials.

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► About **Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia Romagna Bruno Ubertini (IZSLER)**

IZSLER is a governmental Organization providing services to the Veterinary Authorities and Farmers. It took its current name in 1999, however, it was in 1907 when the first "Experimental Station for Infectious Livestock Diseases" was established in Italy. The IZSLER currently employs over 700 people, 100 of whom are veterinarians, biologists and chemists. It has an extensive state-of-the-art analytical infrastructure and conducts research, surveillance and diagnosis of various etiological agents, especially zoonotic viruses and arboviruses circulating in domestic and wild animals and vectors, using a one-health approach.

IZSLER has participated in many European and international research projects in the field of Arboviruses and has well-equipped laboratories for work in virology, NGS sequencing, electron and confocal microscopy, and immunoassay technologies. It is also equipped with BSL3 plus facilities and equipment for experimental vector infection in a BSL3 plus environment. IZSLER leads the WP focused on flaviviviridae epidemiology in humans, animals, and the environment for a 'One Health' approach.

► About **Consiglio Nazionale delle Ricerche (CNR)**

The National Research Council (CNR) participates in InFlaMe with two different institutions.

The Institute of Molecular Genetics "Luigi Luca Cavalli-Sforza" of the National Research Council (IGM-CNR) is a multidisciplinary center for the study of both normal and pathological cells with a systemic approach. IGM-CNR is directly involved in scientific training in genetics and molecular biology at the undergraduate, graduate and post-doctoral levels, with about 80 PhD students, fellows and students of master being involved annually in research activities. IGM-CNR is located in Pavia and has access to the facilities of the University of Pavia and the Institute of the Italian Foundation for Cancer Research (IFOM) key for activities in InFlaMe.

The Institute on Atmospheric Pollution of the CNR (CNR-IIA) was established in the late 60s. Its mission is part of a highly topical framework for the ecosystemic balance of the planet. CNR-IIA is focused on the development of methods and new innovative technologies for the determination of the concentrations of many organic and inorganic pollutants present in the atmosphere.

Moreover, CNR-IIA has great expertise in the sharing and processing of Big Earth Data from Earth Observation (EO) for multi- and interdisciplinary applications and developed tools for model-driven applications for interdisciplinary applications. In InFlaMe, CNR-IIA coordinates the tasks that will deal with the development of data-driven methodologies for estimating the impact of climate change on the epidemic/pandemic risk from Flavivirus (Dengue, West Nile).

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► About **Institut *Imagine* (IMAGINE)**

Located on the campus of the Necker-Enfants malades hospital, Institut *Imagine* is an european leader in research, care and teaching on genetic diseases. Its unique architecture, designed by Jean Nouvel and Bernard Valéro, brings together 1,000 researchers, physicians, teacher-researchers, engineers and health care personnel in a single location to work with patients, with the ambition of accelerating research and diagnosis and therapeutic innovation to change the lives of families affected by genetic diseases. Institut *Imagine* has been certified "Institut hospitalo universitaire" (IHU), in 2011 and 2019 and a "Institut Carnot", in 2020. It is supported by six founding members, including AP-HP, Inserm and Université Paris Cité, as well as by private partners and patrons. Every day in France, 64 babies are born with a genetic disease. Nearly 8,000 genetic diseases affect more than 3 million people, of which nearly one in two is undiagnosed and more than 8 in 10 have no dedicated treatment. Faced with this public health emergency, the challenge is twofold: to diagnose and to cure. **www.institutimagine.org**

The Laboratory of Human Genetics of Infectious Diseases (co-funded by Prof. Jean-Laurent Casanova and Dr Laurent Abel), is an international leader in the research of human genetic and immunological determinants of life-threatening infectious diseases. The lab discovered inborn errors impairing type I IFN immunity causing life-threatening viral diseases such as critical COVID-19 and viral encephalitis. Since 2020, the team has developed a methodology for detecting autoantibodies that neutralize type I IFNs, an immunological phenocopy of these inborn errors that contributes to severe viral infections.

The team, led by Dr. Shen Ying Zhang, has identified the critical role of autoantibodies to type I IFNs in severe viral infections, including COVID-19, influenza, and various flaviviruses (West Nile virus, Tick-borne encephalitis virus, Powassan virus, Usutu virus). Its research focuses on the molecular and cellular mechanisms of antiviral immunity in the central nervous system. The team will have an important role in InFlaMe in investigating the role of human genetic deficiency and autoantibodies against type I interferons underlying severe flaviviral infections.

► About **Institut Pasteur (IP)**

Established in 1887, IP is a private, non-profit foundation with the mission to help prevent and treat diseases, mainly those of infectious origin, through research, teaching, and public health initiatives. With around 3000 employees, including 300 PhD students on the IP campus, it is composed of 142 research units, 32 technological platforms and core facilities and 12 research departments and is committed to undertaking cutting-edge research to improve health around the word.

The team of Nolwenn Jouvenet is based within the Virology Department of the Institute. For more than 12 years, she has been investigating molecular interactions between host cells and flaviviruses. IP will coordinate a WP focused on virus-host interactions and drug development.

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► About **Medizinische Universitaet Wien (MUW)**

Founded in 1365 as a Medical Faculty of the University of Vienna, MUW is now one of the world's largest and most renowned medical universities. With more than 6,500 employees, 30 departments, two clinical institutes, 12 medical theory centres and numerous highly specialised laboratories, it is one of Europe's leading research establishments in the biomedical sector.

At MUW, the Center for Virology has a long tradition in basic flavivirus research and serves as the designated Austrian National Reference Laboratory for Human Arbovirus Infections (including flaviviruses). Major research interests are in the area of flavivirus molecular biology and immunology, including virus-antibody interactions, structural determinants of flavivirus T cell immunity, as well as the serological and molecular diagnosis of flavivirus infections. Research at MUW will focus on the immunological and virological determinants of severe disease.

► About **Masarykova Univerzita (MU)**

Masaryk University, located in Brno, Czech Republic, is one of the country's largest and most prestigious institutions of higher education. Founded in 1919, it is named after Tomáš Garrigue Masaryk, the first President of Czechoslovakia, who envisioned a university that would foster intellectual and cultural growth. The university offers a wide range of academic programs across various fields, including humanities, science, engineering, social sciences, and law. MU currently now consists of ten faculties, offers 400 study programmes and has 35,115 students.

The Laboratory of Virology at MU directed by D. Ruzek stores one of the largest arbovirus collections in Europe that include about 800 individual virus strains. The Laboratory is involved in the development and testing of new antibodies for preventive or therapeutic use, a new generation of antiviral vaccines and antiviral drugs. The lab houses an animal BSL3 laboratory for small rodents key for MU's activities in InFlaMe.

► About **Asociacion Centro De Investigacion Cooperativa En Biociencias (CIC BIOGUNE)**

CIC bioGUNE, located in the Science and Technology Park of Bizkaia in Derio, Bilbao, operates in a space of 8,200 sq meters and it is the largest non-profit biomedical research organisation in the Basque region, dedicated to cutting-edge life sciences research, technology transfer, industrial and basic research, training, international collaboration, and dissemination. It focuses its scientific leadership on two strategic research areas: 'molecular recognition and host-pathogen interactions' and 'metabolism and cell signalling in disease'.

The more than 200 scientists and technicians are organized into 19 research groups and 6 technology platforms focused on investigating scientific topics within these two core programs by developing more than 120 research projects annually.

In InFlaMe CIC bioGUNE has a major role considering access to state-of-the-art research infrastructure, including genomics, proteomics, metabolomics, NMR, cryoEM, X-ray facilities, AAALAC-approved

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animal facilities. The NMR facility is Singular Scientific & Technological Infrastructure in Spain, with 400, 600 (x3), 800, and 1000 MHz instruments.

The cryoEM facility is part of the Basque Research Technological Alliance-EM (BRTA-EM) network, which, together with the Basque Resource for Electron Microscopy (BREM) facility, houses the most powerful cryoEM instrumentation in Spain.

► About **Université Paris Cité (UPCité)**

Université Paris Cité is a world-class, research-intensive, omnidisciplinary university with an IdEx label and a strong professionalization dimension. It is positioned at the top international level for the influence and originality of its research, the diversity and attractiveness of its training courses, its capacity for innovation and its active participation in the construction of the European research and training area. Université Paris Cité comprises three faculties (Health, Sciences, Societies & Humanities), a component institution, the Institut de Physique du Globe de Paris, and a partner research organization, Institut Pasteur. It has 63,000 students, 7,500 teaching and research staff, 21 doctoral schools and 117 research units. A university with a positive societal impact, it is committed to "planetary health: healthy humans, in a healthy society, on a healthy planet".

www.u-paris.fr

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