IrsiCaixa Scientific Report 2023

IrsiCaixa

"la Caixa" Foundation

Generalitat de Catalunya
Departament de Salut

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IrsiCaixa

Established in 1995 with the backing of the "la Caixa" Foundation and the Department of Health of the Autonomous Government of Catalonia, the creation of **IrsiCaixa** was a response to the HIV/AIDS crisis.

With Dr. Bonaventura Clotet at the helm, **IrsiCaixa** has evolved into a renowned international institution, uniquely positioned due to its extensive experience in studying the immune system through HIV research. Dr. Clotet also holds the positions of president and founder of the Fight Infections Foundation and serves as the Clinical Director for Infectious Diseases at the Catalan Health Institute (ICS) for the Barcelona Northern Metropolitan Area.

The collaborative hub formed by **IrsiCaixa**, the Fight Infections Foundation and the eight other research centers situated at the Can Ruti Campus cultivates a unique model of cooperation. This environment actively encourages the exchange of knowledge among researchers, healthcare professionals, patients, and community representatives, promoting collaboration and joint advancement in scientific research.

With nearly 30 years of experience in the immune system research, **IrsiCaixa**'s 12 research groups and more than 130 staff members address key challenges in human health across six strategic lines: global infectious diseases (including HIV/AIDS and SARS-CoV-2), emerging infectious diseases, immunopathology, microbiome, cancer, and the development of new therapies and vaccines.

Letter from the director

Science embodies perseverance, dedication, and steadfastness. Despite the challenges and demanding efforts required by the onset of COVID-19, and with no respite from the pandemic in sight, **IrsiCaixa** has successfully solidified its research pursuits this 2023. This year has seen significant progress in tackling HIV, combating both COVID-19 and long COVID, exploring new infectious diseases, and expanding studies in cancer, microbiome, neurodegenerative diseases and multidrug-resistant bacteria, among other domains. The team's dedication to maintaining the quality and quantity of our annual work has been outstanding. In 2023, we published 83 articles and actively worked on 116 projects, collaborating with centers around the world. Training and dissemination accompanied our scientific output. We're proud that 7 individuals defended their doctoral theses alongside us this year, and that our findings accumulated an audience of over 30 million people through the media.

In the field of COVID-19, a pivotal moment in 2023 was the approval of the HIPRA COVID-19 vaccine by the European Medicines Agency. The development of this vaccine, with knowledge transfer and guidance from **IrsiCaixa**, marked a significant milestone as the first vaccine to receive standard marketing authorization in the European Union. Throughout the year, **IrsiCaixa** not only continued various projects addressing the pandemic but also played a key role in long COVID research. Notably, **IrsiCaixa** contributed to studies identifying potential factors associated with persistent COVID-19 symptoms and underscored the rarity of recovery from this condition after two years (7.6%). The team also made strides in HIV, with the confirmation of the third documented case of HIV cure after a stem cell transplant globally—the patient from Düsseldorf remaining virus-free after four years without treatment. Beyond current diseases, we also addressed potential infectious threats. In 2023, the European Union allocated over 5 million euros to a study coordinated by **IrsiCaixa** against West Nile Virus, a widespread emerging pathogen. This study adds to our ongoing initiatives in seeking solutions for Syphilis, Respiratory Syncytial Virus, multidrug-resistant bacteria, and numerous other global pathogens.

Our research extended to diseases closely linked to the immune system, a pivotal component of human health and our research. Substantial efforts were dedicated to ongoing research into potential cancer immunotherapies, including those based on vaccines, and understanding the role of the microbiome in various diseases. Recognizing that research should yield tangible societal benefits, **IrsiCaixa** invested significantly in establishing an innovation and transfer department in 2023. This department will collaborate with the clinical management team, IrsiCaixa's Living Lab for Health, communication, and training units, aiming to disseminate, involve, educate, and provide solutions to society.

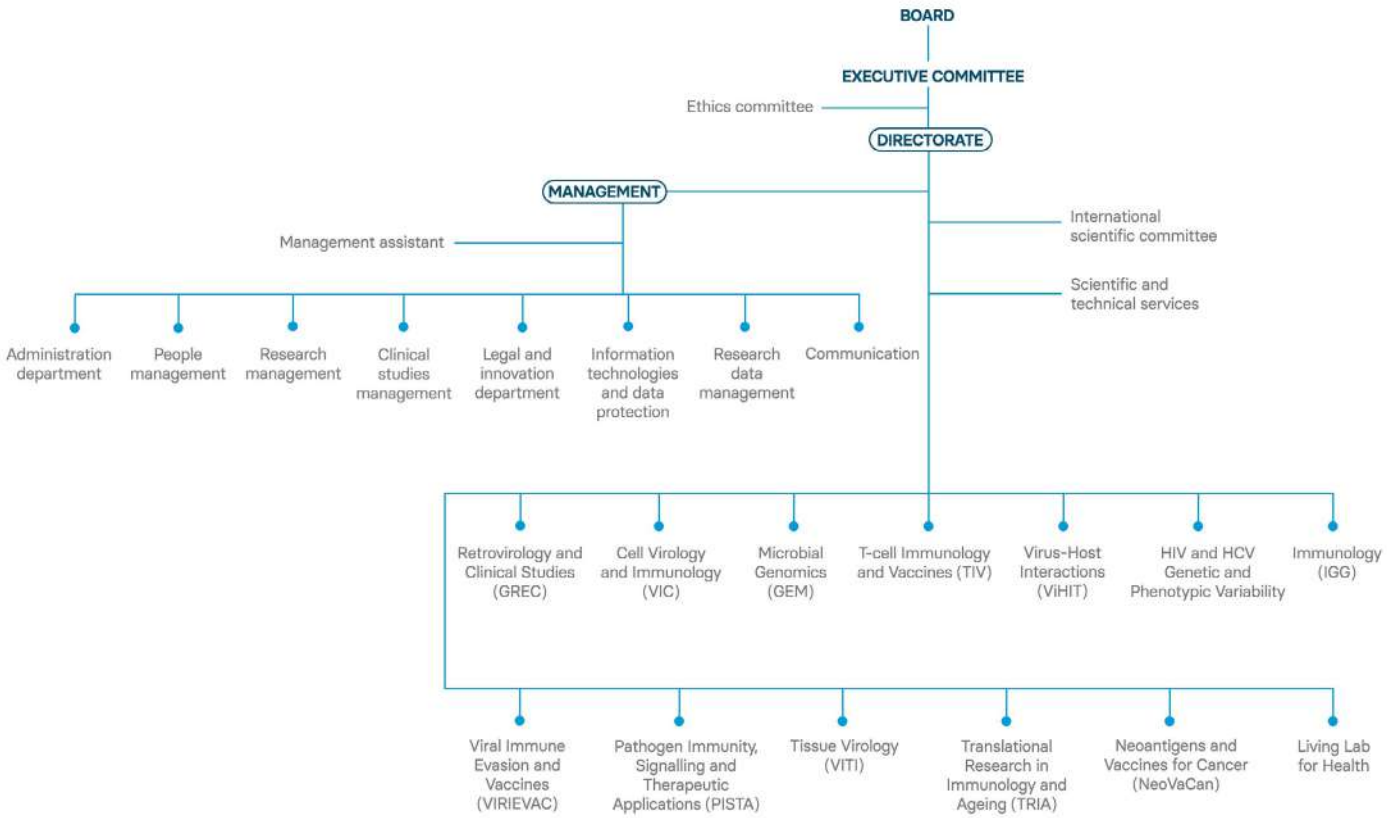
We extend our heartfelt gratitude to the entities and individuals who make **IrsiCaixa** a reality. To "la Caixa" Foundation and the Government of Catalonia for your sustained commitment and support. To the dedicated individuals who are an integral part of our team for your passion, expertise, and tireless efforts. Additionally, we express our appreciation to those who stand by our cause and believe in the importance of our work. Thank you for being the pillars of support that enable us to work in science and make our world healthier and safer.

In memory of Carlos Blázquez, who left us too soon and whose legacy lives on.

Bonaventura Clotet Sala

IrsiCaixa director

Organizational structure



Board

President
Manel Balcells i Díaz
Health Minister of the Autonomous Government of Catalonia

Vice-President
Josep Vilarasau i Salat
Appointee of the Fundació Bancària Caixa d'Estalvis i Pensions de Barcelona "la Caixa" ("la Caixa" Foundation)

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Marta Casals i Virosque
Appointee of the Fundació Bancària Caixa d'Estalvis i Pensions de Barcelona "la Caixa" ("la Caixa" Foundation)

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Research Deputy Director General of the Department of Research and Universities of the Government of Catalonia

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Carmen Cabezas Peña
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Montserrat Llavayol i Giralt
Aina Plaza Tesías
Appointees of the Department of Health of the Autonomous Government of Catalonia

Jaume Lanaspa i Gatnau
Ignasi López Verdaguer
Esther Planas i Herrera
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Appointees of the Fundació Bancària Caixa d'Estalvis i Pensions de Barcelona "la Caixa" ("la Caixa" Foundation)

Montserrat Pinyol i Pina
Anna Veiga i Lluch
Appointees of the Board of the Fight Infections Foundation

Vice-Secretary (non board member)
Sara Freire i Garcia
Appointee of the Corporate Governance of the Fundació Bancària Caixa d'Estalvis i Pensions de Barcelona "la Caixa" ("la Caixa" Foundation)

Organizational structure

Executive Committee

For "la Caixa" Foundation:

Esther Planas i Herrera
President

Marta Casals i Virosque
Secretary

Ignasi López Verdaguer

For the Department of Health of the Autonomous Government of Catalonia:

Jordi Barretina i Ginesta
Jordi Casabona i Barbarà
Montserrat Llavayol i Giralt

Director

Dr. Bonaventura Clotet Sala

Manager

Lourdes Grau Paré

Administration
Arnau Creus Orodea
Cristina Mesa Real
Penélope Riquelme Nevado

Information Technologies
Julián Eslava Campo

International Scientific Committee

Dr. Daria Hazuda
Merck's Vice President of Infectious Diseases Discovery, Chief Scientific Officer of MRL Cambridge Exploratory Science Center (Massachusetts, USA).

Dr. Daniel Kuritzkes
Professor of Medicine at Harvard Medical School, Director of AIDS Research at Brigham and Women's Hospital and Co-Director of the NIH-funded AIDS Clinical Trials Group (USA).

Dr. Douglas Richman
Professor of Pathology and Medicine at the University of California San Diego (UCSD) (USA). Director of the Research Center for AIDS and HIV Infection at the VA San Diego Healthcare System and Director of the Center for AIDS Research at the University of California San Diego (UCSD) (USA).

Dr. Gabriella Scarlatti
Head of the Viral Evolution and Transmission Group at the IRCCS Ospedale San Raffaele (Milano, Italy).

Dr. Jonathan Schapiro
Director of the HIV/AIDS Clinic at the National Hemophilia Center (Tel Aviv, Israel).

Dr. Lucy Dorrell
Senior Director of the Infectious Diseases and Clinical Development at Immunocore and professor at the Oxford University (UK).

Dr. Mario Stevenson
Head of the Infectious Diseases Division (Department of Medicine) of the University of Miami (Florida, USA).

Dr. Monique Nijhuis
Associate Researcher of Translational Virology of the Department of Medical Microbiology, University Medical Center (Utrecht, the Netherlands).


ACCESORIOS
Nikon

Key figures 2023

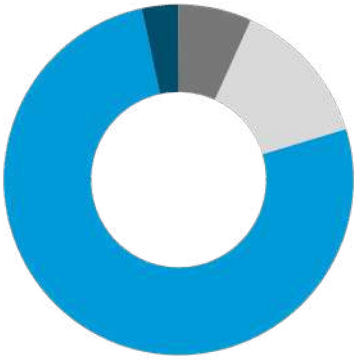
Total staff

129

Sex

67% ♀ **33%** ♂

Staff by categories



- Scientific and technical Services (6%)
- Administration and research support (15%)
- Research (77%)
- Living Lab for Health (2%)

7 Theses defended in 2023

Carlos Ávila Nieto
Immunology (IGG)

Ana Barajas Molina
Cell Virology and Immunology (VIC)

Silvia Bernal Santateresa
Retrovirology and Clinical Studies (GREC)

Clara Duran Castells
Host Genetics and Cellular Immunity (TIV)

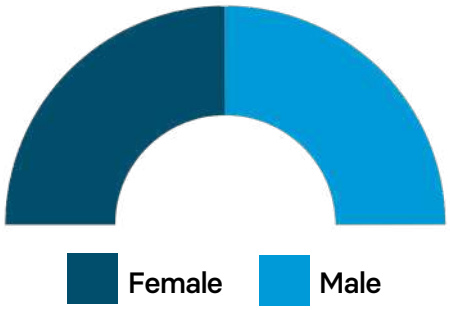
Eudald Felip Falgàs
Virus-Host Interactions (ViHIT)

Lucía Gutiérrez Chamorro
Virus-Host Interactions (ViHIT)

Xabier Muñiz Trabudua
Retrovirology and Clinical Studies (GREC)

Edwards Pradenas Saavedra
Cell Virology and Immunology (VIC)

Principal investigators



Projects awarded in 2023

23

14 public

9 private

Active projects in 2023

116

60 coordinated by IrsiCaixa

Publications in 2023

81

777 Impact Factor

Highlights 2023

January

IrsiCaixa participates in the preparation of a document written by health professionals from all over Catalonia comprehensively analysing the current situation of Long Covid in Catalonia.

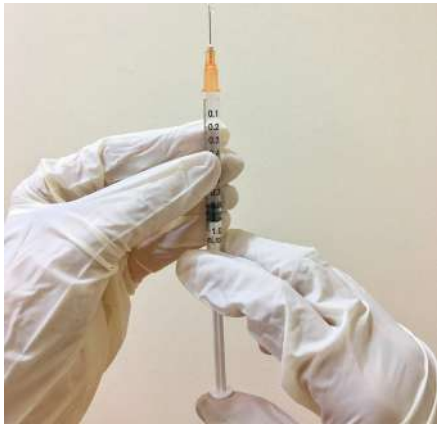
February

The IciStem consortium, coordinated by **IrsiCaixa**, presents the third case of HIV cure in the world after receiving a stem cell transplant to treat leukaemia.

March

IrsiCaixa contributes to the approval of SARS-CoV-2 vaccine Bimervax by regulatory agents such as the EMA and WHO.

Creation of the first biobank of farm animal organoids in Spain based on a project with the participation of **IrsiCaixa**.



April

IrsiCaixa, together with ICFO, provides new insights on the early stages of HIV infection in the human body.

May

IrsiCaixa designs HIV-like particles that induce an effective immune response in preclinical studies.

June

IrsiCaixa organizes the ninth edition of The Barcelona Debates on the Human Microbiome 2023, one of the most important scientific conferences worldwide in the field of the microbiome.

July

Presenting a first-of-its-kind proof-of-concept study, **IrsiCaixa** demonstrates the prophylactic antiviral potential of beta-cyclodextrins against SARS-CoV-2.

IrsiCaixa designs a new health promotion model for schools.

August

Identification of a new genetic variant that could help control HIV, thanks to an **IrsiCaixa** study.

September

Organization of the 5th Oxford-**IrsiCaixa** meeting.

IrsiCaixa participates in the publication of the 2-year follow-up of the KING cohort studying the clinical features associated with risk of suffering and recovering of Long Covid.

October

The international recognition of the "European Hector Research Award in HIV 2023" was conferred to **IrsiCaixa** researchers for the research carried out on the therapeutic vaccine against HIV.

November

IrsiCaixa researchers emerge as leading figures in the global scientific community, earning recognition in the worldwide list of scientific personnel making the greatest impact through their publications and citations.

December

IrsiCaixa receives 5.7 million euros from the European research programme Horizon-Europe to design therapies to tackle the effects of the West Nile Virus (WNV), an emerging pathogen which lacks treatments and for which there is no human vaccine.

Research groups

Viral Immune Evasion and Vaccines (VIRIEVAC)

PROJECTS AWARDED

Immunemonitoring of T cell responses in SARS-CoV2 vaccine trials
Funding: HIPRA
Participating entities: IrsiCaixa
Starting and finishing date: 08/23-08/24
Principal investigator(s): Julia García Prado

HIV-Open Science
Funding: FECYT
Participating entities: IrsiCaixa, VHIR, UAM, IISGaliciaSur, IBIS
Starting and finishing date: 01/24-01/25
Principal investigator(s): Eva Poveda

Limiting West Nile Virus impact by novel vaccines and therapeutics approaches (LWNVIVAT)
Funding: Horizon Europe
Participating entities: IrsiCaixa, Université Montpellier, Technische Universitaet Braunschweig, Kobenhavns Universitet, Centre de Regulació Genòmica, HIPRA, BSC-CNS
Starting and finishing date: 12/23-11/27
Principal investigator(s): Jorge Carrillo Molina

AWARDS AND ACHIEVEMENTS

Julia García Prado, member of the scientific committee of GESIDA 2023
Julia García Prado, member of the Joint Access Advisory Mechanism (JAAM) for European ATPs
Julia García Prado, granted with the R3 certificate
Raúl Pérez Caballero, member of the training committee at IrsiCaixa
Raúl Pérez Caballero, member of the HRS4R committee at IrsiCaixa
Raúl Pérez Caballero, member of the German Society of Parasitology
Raúl Pérez Caballero, member of the European Federation of Animal Science (EAAP)
Raúl Pérez Caballero, member of the American Society of Tropical Medicine & Higiene
Raúl Pérez Caballero, member of the American Committee of Molecular, Cellular and Immunoparasitology (ACMCIP) Subgroup

Presentation

The VIRIEVAC group focus in the identification of functional boundaries of viral pathogenesis and the role of antiviral T-cell responses to control or eliminate viral infections. From a basic-translational perspective, VIRIEVAC combines virology, cellular immunology, and bioinformatics in the study of virus-immune interactions so as to understand the role played by T-cells in controlling HIV-1 and SARS-CoV-2 infections. Its ultimate goal is, by defining the functional features behind long-term effective cellular immunity against viral infections, to develop innovative immune monitoring tools and immune interventions.

VIRIEVAC research lines during 2023:

— **Immunopathology:** HIV-1 natural extreme phenotypes. Identify viral and host factors associated with natural disease outcomes in HIV-1 infection. The studies focus on cohort studies of HIV disease extreme phenotypes in children and adults associated particularly to viremic non-progressors in the last years.

— **Global infections:** persistence, remission, and HIV cure. Delineate the functional boundaries of antiviral CD8+ T-cell responses in HIV infection to control or eradicate the reservoir. This line of research aims to characterize the mechanisms of CD8+ T-cell immune dysfunction/exhaustion both in active and latent infection as a significant barrier to HIV remission and cure. This research line aims to characterize the mechanisms underlying immune dysfunction/exhaustion in PLWH on ART and identify targets to design innovative immune therapeutics and advance towards preclinical studies.

— **SARS-CoV2 cellular immunity:** characterize T-cell responses against SARS-CoV-2 elicited by infection and vaccination from immune monitoring studies to the functional characterization of peptide-specific CD4+ and CD8+ T-cell responses. Also, we are working to characterize the potential impact of cellular immunity in Neurocognitive disorders in individuals with Long-Covid disease.

2023 milestones

Milestones in 2023 within IrsiCaixa's strategic lines were as follows:

— **Immunopathology:** HIV-1 natural extreme phenotypes. Studies of virological and host factors associated with natural control of the infection in viremic non-progressors (VNPs). This collaborative project between IrsiCaixa and the University of Oxford has expanded to the study of a rare small group of pediatric VNPs. This line of research extend the collaboration with our partners in South Africa has led to a publication this year (Vieira et al, JCI insight 2023) and future collaborative projects.

— **Global infections:** persistence, remission, and HIV cure. This research line has been successful and in continuous expansion during this year. This line of research is currently funded by several projects lead by Dr Prado (PI22/01120, RECOVIR) and ongoing funded project through la Caixa Health Research program (HR20-00218). This line of research has provided the identification of immune alterations in T cells in PWH on ART published this year (Blanch-Lombarte et al, Elife 2023). These findings have provided the rational developed several prototypes tested this year in preclinical models based on LCMV infection in mouse. These studies are ongoing. These studies materialized in a publication (Blanch-Lombarte et al, Elife 2023), a poster at CROI23 and an oral presentation at SCI and 2 posters in GESIDA and invited talks. This line of research has led to successful national and international

6 Peer review publications in international scientific journals

Principal Investigator
Julia García Prado

Postdoc researchers
María Lázaro Díez
Raúl Pérez Caballero

Predoc researchers
Laia Bernad Rosa
Miguel Marín López
Eudald Vehí Piqué

Research technicians
Ruth Peña Poderós

Bioinformatician
Gabriel Felipe Rodríguez Lozano

collaborations that are ongoing (Buzon´s Lab, VHIR, Barcelona; Martin-Gyo Lab, UAM, Madrid; Sekalys Lab, Case Western USA, African Health Research Institute, Kloverpris Lab, South Africa).

— SARS-CoV2 cellular immunity. VIRIEVAC have continued working in the assessment of the cellular immune response to SARS-CoV-2 infection through the development of immune assays (ELISpot and flow-cytometry). Virievac is characterizing CoV-2 T cell responses in multiple study groups in the context of natural and vaccine induce immunity in the context of vaccine clinical trials and cohort studies (the King and the Prohepic19 cohorts). During this year we have ongoing several funded calls (SLT021/21/000038, SLT021/21/000055, CORONA-01/101046118_RBDCOV) and we have been leading the WP5 for immunemonitoring of immune responses in vulnerable populations, mainly people with immunodeficiencies and adolescents in the context of HH4 and HH3 clinical trials. These studies materialized in 3 publications (Porru S et al, JEpiGH, Corominas et al, Lancet Reg Health, Barreiro et al, iScience), poster (CROI23), an oral presentation at SCI and invited talks. This line of research has led to successful national and international collaborations and strength our R&D contracts.

Perspectives for the future

— Consolidate ongoing research lines with the following objectives:

1) to identify immunological signatures associated with dysfunctional antiviral responses, 2) to advance preclinical studies for candidate prototypes for novel HIV Cure immunoterapeutics, and

2) to characterize SARS-CoV-2 protective and long-term T-cell immunity for immune monitoring and vaccine development and novel vaccine design.

3) to increase and strength our internationalization through new alliances and collaborations with research groups of excellence across Europe, EEUU and Africa in the search of new projects and European funding opportunities.

Microbial Genomics (GEM)

Presentation

Our group aims to achieve a better understanding of the microbiological determinants of immune regulation in health and disease. This knowledge will enable the development of novel microbiome-based biomarkers to clinically stratify patients and of microbiome-based therapies that prevent, improve or even cure HIV and other immune-mediated diseases. Our work relies on next-generation sequencing techniques and big data analysis. Thanks to our expertise and knowledge of infectious diseases, we were able to respond to the COVID-19 health emergency and contribute to SARS-CoV-2 research.

1. Role of the gut microbiome in HIV infection prevention, pathogenesis and cure. We study: **a.** Gut microbiome influence on adequate immune reconstitution, HIV-1 replication control and HIV-associated chronic inflammation reduction in people living with HIV (PLWH). **b.** Human microbiome ability to boost the efficacy of HIV immunotherapy and cure strategies. **c.** The ability of specific mucosal microbes to protect humans from HIV infection. We identify: **a.** Human microbiome-derived biomarkers that enable stratification of HIV-infected individuals for research and clinical purposes. **b.** Novel microbiome-based concepts to improve the health of PLWH and prevent HIV-1 infection. We are developing: **a.** Cloud-based software tools to enable massively sequenced data analysis and interpretation for HIV resistance (paseq.org) and microbiome analyses. **b.** A gut-on-a-chip device to evaluate the mechanistic effects of the microbiota on the immune system, in collaboration with the National Microelectronics Centre (CNB).

2. Role of the gut microbiome in other immune-mediated diseases. a. In collaboration with the Vall d'Hebron Institute of Oncology (VHIO), research into the role of the gut microbiome in the natural history of colorectal and small gut neuroendocrine cancer. **b.** In collaboration with the ACE foundation, research into human microbiome influence on the pathogenesis of Alzheimer disease. **c.** In collaboration with the Esther Koplowitz Research Center (CEK), research into the role of the gut microbiome in the progression of skin melanoma.

3. Public health approaches to the global HIV drug resistance epidemic. a. In collaboration with the WHO ResNet group and partners in Africa, development and evaluation of strategies to contain emerging HIV drug resistance and maximize ART efficacy in resource-limited settings. **b.** In collaboration with WHO Europe, integration of HIV, TB and HCV diagnostics and care in Europe as our contribution to the European Laboratory Initiative. **c.** As members of the IAS-USA group, determination of key drug resistance mutations to be used for clinical management worldwide. **d.** Contribution to the development of global WHO ART treatment guidelines.

4. Translational research in COVID-19 therapeutics and virus sequencing. a. Roger Paredes: Spanish National Coordinator of seminal NIH/NIAID-funded randomized clinical trials to define current hospital care standards for COVID-19 and leader of clinical research into COVID-19 treatments and treatment strategies for hospitalized patients and outpatients. **b.** Marc Noguera: Coordinator for the development of SARS-CoV-2 sequencing capacities and for strategic collaboration with Germans Trias i Pujol University Hospital for epidemiological tracking of SARS-CoV-2 variants of concern.

2023 milestones and perspectives for the future

1. Microbiome. a. Description of gut microbiome signatures of HIV vaccine response from a small pilot clinicall (published as Borgognone et al, 2022, Microbiome). Relative abundance of specific bacterial classes are associated to improved immunological response to HTI-based HIV vaccines and viremia control in a small-sized clinical trial. **b.** Description of the effects of probiotic/prebiotic intake for immune recovery in immune discordant HIV patients (published as Blazquez-Bondia et al, 2022, Frontiers in Immunology). The intake of probiotics/prebiotics slightly improved inflammatory markers and immune parameters in a double-blind, randomized clinical trial, showin

Principal Investigator
Roger Paredes Deiros

Senior research scientists
Maria Casadellà Fontdevila
Marc Noguera Julian

Postdoc researchers
Alessandra Borgognone
Aleix Elizalde Torrent

Predoc researcher
Carlos Blázquez Bondia

Data steward
Francesc Català Moll

Research technician
Mariona Parera Sallent

subtle effects on the composition of the gut microbiome. **c.** Appointment by the Canadian Institutes of Health Research as co-PIs of an international team undertaking two projects to understand the vaginal microbiome's role in women's health, vaccine responses, antiviral metabolism and cervical cancer. **d.** Early-stage development of a gut-on-a-chip device to evaluate the mechanistic effects of the microbiota on the immune system. **e.** Organization of the Barcelona Debates on the Human microbiome, Barcelona,, 2022.

2. Global HIV. a. Roger Paredes (since 2015): member of the WHO HIV Drug Resistance Steering Group, responsible for developing a global strategy to tackle the emergence of resistant HIV-1. **b.** Advisors to the WHO European Laboratory Initiative TB, HIV and HCV Core Group, responsible for delineating the European strategy for integrated HIV, TB and HCV diagnostics and care in Europe. **c.** Participation in the drafting of the WHO ART treatment guidelines 2020, recommending dolutegravir for the first time as a first-line treatment for all infected people, including pregnant women (representing a major paradigm shift in the global fight against HIV infection). **d.** Participation in updating the WHO ART treatment guidelines.

3. COVID-19. Four manuscripts published in the New England Journal of Medicine, with Roger Paredes as co-author or corporate (ACTT-2 Study Group) co-author: **a.** Early clinical evidence that remdesivir is effective in treating COVID-19 in humans (Beigel et al., 2020: Remdesivir for the Treatment of Covid-19 – Preliminary Report). **b.** Confirmation and extension of the preliminary report on remdesivir and COVID-19 (Beigel et al., 2020: Remdesivir for the Treatment of Covid-19 – Final Report). **c.** Evidence that baricitinib plus remdesivir is more effective and safer than remdesivir alone in reducing recovery time and accelerating clinical improvement, especially among patients requiring high-flow oxygen or non-invasive mechanical ventilation (Kalil et al., 2021: Baricitinib plus remdesivir for the treatment of hospitalized adults with COVID-19). **d.** Efficacy is not demonstrated for the neutralizing monoclonal antibody LY-CoV555 administered with remdesivir in hospitalized COVID-19 patients without end-organ failure (Lundgren et al., 2021: A neutralizing monoclonal antibody for hospitalized patients with COVID-19. Preliminary report of a randomized trial by the ACTIV-3/TICO LY-CoV555 study group).

T-cell Immunology & Vaccines (TIV)

PROJECTS AWARDED

Security and Impact of DASATINIB on Viral Persistence and Inflammation in Chronic HIV-Infected Patients on Antiretroviral Treatment (BCN04-DASA)
Funding: MICINN
Participating entities: IrsiCaixa, Lluita, IGTP, Centro Nacional de Microbiología
Starting and finishing date: 01/23-12/26
Principal investigator(s): Beatriz Mothe Pujadas

Multi-omic understanding of the transformed host T-cell response to HIV following therapeutic vaccination
Funding: NIH
Participating entities: IrsiCaixa, University of California
Starting and finishing date: 05/23-05/28
Principal investigator(s): Christian Brander

AWARDS AND ACHIEVEMENTS

Beatriz Mothe Pujadas, awarded with the European Hector Research Award in HIV 2023 for the research carried out on the therapeutic vaccine against HIV.

Presentation

A critical component of the immunity against the acquisition of viral infections is a strong, pathogen-specific cellular immune response. Over the last years, we have determined the characteristics of this arm of the host immune responses to different viral pathogens, including HIV and SARS-CoV-2. We have also translated these insights into a therapeutic vaccine candidate that has reached successfully phase 2 clinical testing. While this remains a strong focus of our work and includes COVID-19 and monkeypox vaccine trials in individuals with acquired or inborn immune deficiencies, we have become increasingly interested in the molecular pathways that regulate this cellular immunity in different patient populations and which can be mediated by mechanisms governing cell differentiation, immune checkpoints and epigenetic processes. Our study populations include people with early HIV infection, controlled and uncontrolled HIV disease, as well as people with or without HIV infection that received solid organ transplants. In particular, we have set out to understand the epigenetic mechanisms involved in neurological manifestations of Long-Covid-19. In our investigation, we also include individuals that have been diagnosed with virus driven cancers, such as EBV lymphoma (Epstein-Barr Virus) or HPV-derived cancers (Human Papillomavirus), as well as individuals of advanced age who often show a gradual decline of immune competence. To track virus-specific T cell responses in different compartments, including the CNS, our work also includes the analysis of the T cell receptor repertoires in the cellular immune responses against the different viruses. Our emerging data have helped to start characterize the molecular ontogeny of T-cell immune responses and understand the transcriptional programs of these cells that are under tight epigenetic control. These insights offer novel approaches for therapeutic interventions and identify druggable targets that we aim to develop in order to potentiate immune-based therapeutic strategies for the prevention or treatment of viral infections and virus-driven cancers.

2023 milestones and perspectives for the future

During 2023, we have showcased the emerging results from the AELIX-003 clinical trial which combined a therapeutic vaccine (HTI) and the TLR9 ligand Vesatolimod. The data presented at CROI 2023 confirmed the observations in the earlier AELIX-002 study and demonstrate that HTI-specific,

8 Conferences in which group members gave invited talks

12 Publications from the group

13 Ongoing projects

Principal Investigator
Christian Brander

Senior research scientists
Beatriz Mothe Pujadas
Àlex Olvera van der Stoep
Cristina Peligero Cruz
Marta Ruiz Riol
Sandra Silva Arrieta

Bioinformatician
Lluís Revilla Sancho

Cohort coordinator
Josep Coll Verd

Postdoc researcher
Sonia Villanueva Hernández

Predoc researchers
Clara Duran Castells
Igor Moraes Cardoso

Senior research technician
Samandhy Cedeño Briceño

Research technician
Tuixent Escribà Bel

vaccine-induced T cell responses are critical for the sustained reduction in viral replication. We have also continued the immune monitoring of the participants in the **IrsiCaixa** sponsored trial BCN-03. The BCN-03 trial is the first trial to combine potent T- and B-cell vaccines in the therapeutic setting and was completed at the end of 2023, with first immune results expected for mid 2024. In all these clinical trials, we are also exploring the role of the microbiota on the vaccine-induced immune responses and have been able to show, in the mouse model, how modulation of the microbiota prior to vaccination impacts the vaccine T cell immunity and, in humans, how the microbiota composition may predict virus control after vaccination. In fact, a recently published study (Elizalde-Torrent, 2023) shows that the depletion of the gut microbiota did not result in significant differences in the magnitude or breadth of the immunogen-specific IFNγ T-cell response after vaccination. However, we observed marked changes in the serum levels of four cytokines after vaccinating microbiota-depleted animals, particularly a significant reduction in IL-22 levels. Interestingly, the level of IL-22 in serum correlated with the abundance of Roseburia in the large intestine, providing a link between microbiome and adaptive immunity.

Within the European Horizon 2020 EPIVINF project, we published interesting data on the involvement of the vagus nerve in the COVID-19 pathology. These findings are of high relevance as long lasting COVID-19 condition (PCC) is a disabling syndrome affecting at least 5%-10% of subjects who survive COVID-19, among them individuals with a large range of PCC symptoms, such as dysphonia, dysphagia, dyspnea, dizziness, tachycardia, orthostatic hypotension, gastrointestinal disturbances, or neurocognitive complaints. In these settings, the vagus nerve dysfunction may play a pivotal role and treatment strategies that target vagus nerve function may provide urgently needed relieve. Within the same project, we have made further progress in establishing small animal models that can recapitulate some of the COVID-19 symptomology, especially neuro-dysfunction.

We have also been able to further identify potential markers of disease control in the HIV setting, particularly also in individuals with HIV associated neurological disease. For this, we looked in samples from the BCN02 clinical trial and characterized longitudinal plasma proteomes in trial participants who did or did not control viral replication after stopping anti-HIV treatment. Inflammatory plasma proteomes in these participants identified CD33/Siglec-3 as a plasma marker with the ability to discriminate between controllers and non-controllers at all study timepoints, even before initiating vaccination. Interestingly, adding an anti-CD33 antibody to in vitro virus cultures significantly reduced HIV-1 replication and proviral levels in T cells and macrophages, suggesting that CD33 could serve as a novel target to interfere with viral replication, while also having beneficial effects on neurofunction, as evidenced by data from pre-clinical models of Alzheimer's disease that employ CD33 targeting.

Finally, also in 2023, we initiated a study to compare immune responses to Monkeypox infection up to 6 months after infection in people without HIV (PWoH) and with HIV (PWH) co-infection, to better understand the role of host immunity on disease severity and viral clearance dynamics. Interestingly, both groups had similar clinical severity and time to MPXV clearance in skin lesions, however antibody titters declined more rapidly in PWH possibly reducing their immunity and protection from reinfection.

Virus-Host Interactions (ViHIT)

PROJECTS AWARDED

Juan Rodés Fellowship
Funding: ISCIII
Participating entities: IrsiCaixa, ICO-IGTP
Starting and finishing date: 07/23-12/28
Principal investigator(s): Eudald Felip Falgàs

New Immunotherapeutic Opportunities in Metastatic Breast Cancer: CDK4/6 Inhibitors and Their Impact on the Immune System
Funding: Complementary Plans of Biotechnology Applied to Health (MICINN, NextGenerationEU)
Participating entities: IrsiCaixa, IGTP, IIS Biocruces Bizkaia
Starting and finishing date: 01/23-12/24
Principal investigator(s): Ester Ballana Guix

Development of an artificial intelligence model based on radiomics to predict tumor immune microenvironment (TME) and inmune response in triple-negative breast cancer
Funding: Gilead
Participating entities: IrsiCaixa, ICO-IGTP
Starting and finishing date: 11/23-12/25
Principal investigator(s): Ester Ballana Guix, Mireia Margelí Vila

AWARDS AND ACHIEVEMENTS

Lucía Gutiérrez-Chamorro, awarded with excellence for her PhD thesis entitled *Evaluation of SAMHD1 role as a predictive and prognostic biomarker in solid tumours: deciphering its function in innate immune signalling* (UAB)
Eudald Felip, awarded Summa cum laude for his PhD thesis entitled *Identification of biomarkers in metastatic RH+/HER2- breast cancer under treatment with cyclin-dependent kinase 4/6 inhibitors* (UAB)
Eudald Felip, granted with a Juan Rodés contract
Edurne Garcia-Vidal, awarded with a fellowship to attend EACS 2023 in Warsaw
Sara Cabrero de las Heras, member of the Can Ruti Women in Science group

Presentation

Our research focus is the study and characterization of innate immune system activation mediated by nucleic acid metabolism and its role in different human diseases characterized by an imbalance in intracellular nucleic acid metabolism, such as viral and non-viral infections, inflammatory diseases or cancer, with a view to developing new therapeutic strategies. Our group is currently working on two main research lines:

1. Identification and characterization of cellular factors in persistent viral infections. We have been working in the characterization of virus-host interactions at different stages of virus replication, focusing especially on describing innate immune pathways and modulators that impact HIV-1 replication and respiratory infections as SARS-CoV2 and more recently, influenza. In the field of HIV, we are specially interested in targeting latent HIV reservoirs, one of the main roadblocks for advancing towards an HIV-1 cure. Indeed, emerging evidence suggests that modulation of innate immune stimulation could impact viral latency and contribute to the clearing of HIV reservoir. Thus, we have been focusing on the latency reactivation capacity of a distinct innate immune modulators, including JAK and TBK inhibitors. Specifically, we have characterized a subclass of selective JAK2 inhibitors was characterized as a potential novel therapeutic strategy for HIV-1 cure, demonstrating significant HIV reactivation capacity through the modulation of IRF7. Overall, our data represent a promising step towards HIV eradication by demonstrating the potential of innate immune modulation for reducing the viral reservoir through a novel pathway driven by IRF7. Morevoer, based on robust and versatile in vitro models capable of high-throughput testing of antiviral compounds, we have been able to identify a group of compounds that through the modulation of innate immune response exert potent antiviral activity against respiratory viruses. In this scenario, we have also expanded the tools and types of viruses available for in vitro studies, including herpesviruses, papillomaviruses and influenza viruses. Since April 2020, our group has also focused on understanding SARS-CoV-2 infection and its associated pathogenesis, by developing sensitive and reproducible methods for the quantification of SARS-CoV-2 viral load in COVID-19 patients and tissues from distinct animal models has been developed. Ongoing work also includes elucidating the role of the innate immune response in COVID-19 pathogenesis and deciphering and characterizing early events that might determine infection outcomes, with particular interest in cellular proteins that might be important for the development of broad spectrum agents that can be used as new therapeutic strategies against viral infections.

2. Immune cell function in cancer: mechanisms, biomarkers and immunotherapeutic opportunities. Cancer immunotherapy —the science of mobilizing the immune system to kill cancer— has taken a center stage in oncology in the past few years, with unprecedented progress in clinical responses, rapid drug development, and first-in-kind approvals. However, despite the successful application of cancer immunotherapy across a broad range of human cancers, only a minority

2 PhD thesis presented

6 Funded competitive contracts for researchers ongoing

9 Published papers

of patients from specific subgroups of tumors experience life-long durable benefits and most of the patients do not respond or eventually relapse. In close collaboration with ICO-Badalona and B-ARGO research team, we work to contribute to a better understanding of breast cancer complexity in general, but specifically to the interactions between tumor and host immune cells, by using high-resolution transcriptomics and further investigation and validation of the underlying molecular mechanisms in in vitro immune-organoid models. Our multidisciplinary research team brings together a group of healthcare professionals from different fields, including immunology, molecular biology, medical oncology, pathology, genomics and computer science, all focused on the generation of novel and disruptive knowledge on tumor-immune cell crosstalk and explore their translation into the clinical practice by looking for their applicability into novel treatments.

2023 milestones

Our group achieved the following milestones:

— Development of novel and versatile in vitro tools for in depth characterization of immune function. We have developed and validated novel in vitro models for the in depth characterization of immune cell function across distinct disciplines, from non-clonal models of HIV persistence to 3D immuno-oncology culture models for breast cancer research, among others.

— Advances in research into viral infections. We have expanded the number of tools and types of viruses readily available for the characterization of virus-host interplay. Indeed, in collaboratiion with Dentaid we evaluated the use of mouthwashes containing cetylpyridinium chloride (CPC) as a toold to reduce, in cell cultures, up to 100 times the infection capacity of herpes simplex type 1 (HSV-1).

— Identification and validation of prognostic and predictive biomarkers in cancer patients. In collaboration with Breast Cancer Unit of B-ARGO research team, we have characterized immune cell function in a cohort of breast cancer patients treated with CDK4/6 inhibitors. Since 2018, our group in collaboration with Dr. Miregia Margelí team has been recruiting patients with metastatic breast cancer diagnosis that were scheduled for starting treatment with CDK4/6 inhibitors, currently involving a cohort of 113 patients with available tumor biopsies and longitudinal blood samples. Initial characterization of the cohort, (funded by ISCIII-FIS, PI21/00642) resulted in the identification of important differences in expression of immune checkpoint molecules both in circulating CD4+ and CD8+ T lymphocytes, associated to disease progression. Similarly, the evaluation of plasma cytokine and inflammation markers also identified the existence of immune-mediated processes that determine CDK4/6 inhibitors efficacy, overall suggesting that immune cell dysfunction before treatment initiation is the main factor determining treatment failure. More importantly, evaluation of gene expression in tumor biopsies also identified enhanced expression of similar immune cell signatures in patients that do not response to therapy . These results allowed us to propose a group of intrinsic immunologic characteristics that influence immune system capacity to respond to anticancer immunomodulatory agents.

Principal Investigator
Ester Ballana Guix

Senior research scientists
Roger Badia Córcoles
Eva Riveira Muñoz

Postdoc researchers
Sara Cabrero de las Heras
Edurne García Vidal

Predoc researchers
Ignasi Calba Iñiguez
Ifeanyi Jude Ezeonwumelu
Eudald Felip Falgàs
Lucía Gutiérrez Chamorro

Perspectives for the future

Our goal is to develop new and more effective therapeutic strategies to fight viral infections and cancer. Studies of host-virus interactions will continue, based on the inhibition of key interactions between viral and cellular targets, so as to establish mechanisms of action, determine the role played by cellular factors in different viral replication stages and evaluate new therapeutic targets.

Thanks to fruitful collaboration with B-ARGO, the identification and validation of prognostic and predictive biomarkers in patients with cancer will enter a new phase focused on in-depth study of breast cancer cohorts by single cell transcriptomics and TCR sequencing. Morevoer, we have started the development of immuno-organoids containing autologous tumor and immune cells from patients, with the aim to provide novel tools and expertise for the study of immune function in breast cancer.

Retrovirology & Clinical Studies (GREC)

PROJECTS AWARDED

Security and Impact of DASATINIB on Viral Persistence and Inflammation in Chronic HIV-Infected Patients on Antiretroviral Treatment (BCN04-DASA)
Funding: MICINN
Participating entities: IrsiCaixa, Lluita, IGTP, Centro Nacional de Microbiología
Starting and finishing date: 01/23-12/26
Principal investigator(s): Beatriz Mothe Pujadas

Analysis of Endocytic Mechanisms Triggered by CD169 in Myeloid Cells and Its Contribution to Viral Dissemination
Funding: MICINN-AES
Participating entities: IrsiCaixa
Starting and finishing date: 09/23-08/26
Principal investigator(s): Javier Martínez-Picado, Patricia Resa-Infante

Multi-OMICS identification and validation of mechanisms triggered by Immune interventions aimed at reducing the size of the replication competent Reservoir
Funding: NIH
Participating entities: IrsiCaixa, Emory University, Ghent University
Starting and finishing date: 07/23-04/28
Principal investigator(s): Javier Martínez-Picado

Characterization and Rehabilitation of Post-COVID-19 Condition in Pediatric Population
Funding: philanthropy
Participating entities: IrsiCaixa, IGTP
Starting and finishing date: 09/23-08/28
Principal investigator(s): Sara Morón López

Impact and viability of a novel mass PCR testing method as a pandemic-fighting strategy
Funding: Horizon Europe
Participating entities: IrsiCaixa
Starting and finishing date: 04/23-11/26
Principal investigator(s): Javier Martínez-Picado

AWARDS AND ACHIEVEMENTS

Silvia Bernal Santateresa, awarded Summa cum laude for her PhD thesis entitled *A new therapeutical approach to reduce viral persistence, immune activation, and inflammation in people with HIV-1 on antiretroviral therapy* (UVic-UCC)
Xabier Muñiz Trabudua, awarded Summa cum laude for his PhD thesis entitled *The potential role of Siglec-1 receptor as a therapeutic target against dendritic cell mediated dissemination of enveloped viruses* (UAB)
Cristina Gálvez Celada, former predoc researcher of the GREC group, awarded best doctoral thesis by the UAB

Presentation

The current scientific interests of our group focus on characterising the immuno-virological mechanisms of viral pathogenesis in human diseases, including HIV-1, Ebola virus, SARS-CoV-2, arenaviruses and syncytial respiratory virus. Our programme has a translational character with the aim of investigating potential new viral therapeutic strategies through basic and applied research. We work closely with other IrsiCaixa research groups and with national and international biomedical institutes, focusing on three priority areas in HIV research: HIV cure, viral pathogenesis mediated by dendritic cells and extreme HIV infection phenotypes.

2023 milestones

1. Understanding viral persistence to tackle HIV cure strategies. We evaluate the persistence of replication in the presence of effective antiretroviral treatment, study the location of viral reservoirs and their consequences, and work on clinical studies focused on the development of therapeutic interventions aimed at reducing these reservoirs and achieving drug-free immune control of HIV. Our group co-leads the first consortium of allogeneic stem cell transplantation in HIV patients (IciStem), a project that has resulted in the second and third case in the history of HIV remission in the absence of antiretroviral treatment, and participates in an NIH-sponsored study to reverse immune dysfunction for HIV-1 eradication.

2. Extreme phenotypes of HIV infection (rapid progressors, exceptional natural controllers, viremic non-progressors, exposed uninfected, and pediatric populations). We evaluate the immune- viological features involved in these profiles that may contribute to the understanding of the pathogenesis of the infection and their application in new therapeutic, diagnostic and personalised patient follow-up strategies.

3. Dendritic cell-mediated HIV pathogenesis. We base our work on our discovery of the recognition axis between viral gangliosides and their receptor CD169/Siglec-1, as well as its role in viral spread and the design of therapeutic strategies that can take advantage of this mechanism. This research has been explored in the context of HIV-1, Ebola/Marburg virus, Lassa virus and SARS-CoV-2.

4. SARS-CoV-2 and COVID-19. We collaborate in projects that include the interaction between the virus and the host through immuno-genomic studies of cases of severe disease, the capacity of exosomes to transport viral antigens, the use of CRISPR to identify potential cellular factors relevant to virus replication, the development of lung/brain organoid models and endothelial organ-on-a- chips to study potential antiviral and anti-inflammatory therapies, and the long-term effects of the disease in paediatric patients.

14 Ongoing research projects

18 Peer-reviewed scientific publications

+20 Presentations in scientific conferences

Principal Investigator
Javier Martínez-Picado

Senior research scientists
Jakub Chojnacki
Sara Morón López
Mª Carmen Puertas Castro
Patricia Resa Infante
Maria Salgado Bernal

Postdoc researcher
Silvia Ribó Gené

Predoc researchers
Ángel Bayón Gil
Silvia Bernal Santateresa
Gerard Campos Gonzalez
Irene González Navarro
Jon Izquierdo Pujol
Fernando Laguía Nueda
Xabier Muñiz Trabudua

Research statician
Víctor Urrea Gales

Bioinformatician
Lidia Garrido Sanz

Senior research technician
Patricia Piñol Jurado

Research technicians
Mª Carmen García Guerrero
Gisela Zamorano García

Perspectives for the future

— Finding mechanisms to revert the immune dysfunction induced by HIV infection in people on stable antiretroviral therapy: a path for HIV eradication.
— Multiomics identification and validation of mechanisms triggered by immune interventions aimed at reducing the size of the replication competent reservoir.
— Deepening the characterization of the persistent HIV- 1 antigen production in people with HIV on stable antiretroviral therapy and its central role in inflammation and chronic immune activation.
— Discovery and preclinical approach to eliminate the HIV-1 latent reservoir by using novel anti-CD4 chimeric antigen receptor T cells.
— Discovery and preclinical approach of novel HIV-1 RNA biogenesis inhibitors based on disrupting the RRE-Rev ribonucleoprotein.
— Modulating viral splicing as a strategy to cure HIV.
— Exploring the role of virus-host interactions in extreme HIV-1 infection phenotypes, including viremic non-progressors, whose immune system is not damaged by high levels of viremia, and HIV- exposed non-infected people.
— Dissecting CD169-mediated endocytic mechanisms in myeloid cells and their contribution to virus dissemination.
— Preclinical studies of the efficacy of humanized CD169 monoclonal antibodies with capacity to block HIV-1, Ebola virus, and SARS-CoV-2 transmission via myeloid cells.
— Designing nanocarriers that specifically target CD169 in myeloid cells as a mechanism to deliver drugs and immunogens.
— Designing nanotechnological devices based on the binding capacities of CD169 to capture enveloped viruses as well as extracellular vesicles.
— Development of a new cutting-edge mass PCR testing as a pandemic-fighting strategy: technological development, population-based implementation, epidemiological relevance and socio-economic impact.
— Investigation of the human genetic and immunological determinants of the clinical manifestations of SARS-CoV-2 infection: towards personalised medicine.
— Analytical and predictive value of brain organoids to investigate the neurodegeneration triggered by SARS-CoV-2.
— Unravelling the biological mechanisms causing long COVID in the pediatric population.

HIV and HCV Genetic and Phenotypic Variability

Presentation

The research interests of our group are focused in understand the molecular mechanisms implicated in human virus pathogenesis. In the last two decades, we have being studying how the genetic variability of HIV-1 and HCV has influenced virus pathogenesis, immunogenicity and response to antiviral therapy (reviewed in Martinez and Franco, Viruses 2021a; Martinez, Viruses 2021b). Recently, we have explored how synonymous codon mutations impact HIV-1 protein expression and virus replication capacity. Codon or codon pair biases and HIV-1 RNA dinucleotide frequencies (e.g. CpG/UpA) affect host innate response, virus latency and pathogenesis (reviewed in Jordan-Paiz, Franco and Martinez, Frontiers in Microbiology 2021). In relation to our work with HCV, we are quantifying the levels of plasma circulating microRNAs (miRNAs) as biomarkers of liver disease progression in HIV-1 and/or HCV infected patients (reviewed in Martinez, Tural and Franco Viruses 2022). ıiRNAs are predicted to regulate over half of the human transcriptome. The lack of available biomarkers for diagnosing and predicting different stages of liver disease (e.g., NAFLD and NASH) is currently one of the main challenges that clinicians are facing. Lastly, we have explored the specific circulating miRNA signature in hospitalized patients infected with SARS-CoV-2 (reviewed in Martinez Drug Discovery Today 2022; Martinez Frontiers in Microbiology 2022).

2023 milestones

1. Synonymous genome recoding of HIV-1. Synonymous replacement of CpG dinucleotides in the HIV-1 envelope (env) coding region has been correlated with evasion of the antiviral activity of the zinc-finger antiviral protein (ZAP). To explore the effect of depleting HIV-1 env CpG dinucleotides by synonymous substitution on ex vivo viral replication capacity, we eliminated 11 env CpG dinucleotides through synonymous substitutions in the CXCR4-tropic HXB2 strain (Jordan-Paiz, Franco and Martinez Virus Research 2022). We have studied the genetic stability and evolution of the former variant and other env synonymous variants in MT-4 cells and ZAP depleted 239T cells. We aimed to explore whether the synonymous sequence space influences HIV-1 evolution. Our results demonstrate that the frequency of CpGs in the HIV-1 env region delineates the evolution of its mutant spectrum (Franco, Jordan and Martinez, manuscript in preparation). Intriguingly, we have also found that ZAP cell depletion significantly impacts the cytoplasmatic miRNA repertoire (Franco and Martinez, manuscript in preparation).

2. miRNAs as disease biomarkers and antiviral targets. We previously recognized three plasma circulating microRNAs (miRNAs)—miR-100-5p_iso3p:-2, miR-122-5p, and miR-192-5p—that correlate largely with liver fibrosis evolution in human immunodeficiency virus type 1 (HIV-1)/hepatitis C virus (HCV) co-infected patients (Franco et al AIDS 2021a). Similarly, we previously demonstrate that single nucleotide polymorphisms (SNPs) in PNPLA3, ADAR-1 and IFIH1 are associated with advanced liver fibrosis in patients co-infected with HIV-1/HCV (Franco et al AIDS 2021b). To evaluate the impact of functional SNPs on the plasma levels of miRNAs, we have evaluated the association between miRNA plasma levels and three SNPs in PNPLA3/rs738409, ADAR-1/rs1127313 and IFIH1/rs1990760 in our cohort of HIV-1/HCV co-infected individuals. Notably, our results demonstrate that SNPs affect circulating plasma levels of miRNAs. These results indicate that a genetic background can modify the biomarker value of a particular miRNAs independently of the individual disease stage (Franco and Martinez submitted 2023).

3. To determine whether circulating plasma miRNAs can be possible biomarkers of COVID-19 inflammation, coagulation, lung disease and other organ disease progression (reviewed in Martinez Frontiers in Immunology 2021; Martinez and Franco Hepatology Communications 2021), we performed large-scale deep sequencing analysis of small RNA expression on plasma samples from SARS-CoV-2 infected patients with COVID-19. Our results indicate that there are circulating miRNA directly involved with SARS-CoV-2 infection and may be used as an effective biomarker of COVID-19 severity (Franco et al submitted 2023).

Principal Investigator
Miguel Ángel Martínez de la Sierra

Senior research scientist
Sandra Franco Cirera

Cell Virology & Immunology (VIC)

PROJECTS AWARDED

Development of an ACE2/FC fusion protein with prophylactic and therapeutic activity against all variants of SARS-CoV-2
Funding: ISCIII
Participating entities: IrsiCaixa
Starting and finishing date: 12/22-12/25
Principal investigator(s): Benjamin Trinité

Limiting West Nile Virus impact by novel vaccines and therapeutics approaches (LWNVIVAT)
Funding: Horizon Europe
Participating entities: IrsiCaixa, Université Montpellier, Technische Universitaet Braunschweig, Kobenhavns Universitet, Centre de Regulació Genòmica, HIPRA, BSC-CNS
Starting and finishing date: 12/23-11/27
Principal investigator(s): Jorge Carrillo Molina

AWARDS AND ACHIEVEMENTS

Edwards Pradenas Saavedra, awarded Summa cum laude for his PhD thesis entitled *Naturally Acquired and Vaccine-Induced Neutralizing Humoral Responses to SARS-CoV-2* (University of Barcelona)

Ana Barajas Molina, awarded Summa cum laude for her PhD thesis entitled *Optimisation of HIV-1 enveloped Virus-Like Particles as a personalised vaccine platform for the delivery of cancer neoantigens* (University of Vic – Central of Catalonia)

Benjamin Trinité, granted with a first competitive project to develop neutralizing anti-SARS-CoV-2 antibodies

Presentation

The four years of COVID-19 pandemic have leaved a considerable imprint in our group. Our original focus on the HIV envelope glycoprotein (Env) as the main target of preventative HIV vaccines has been broadened to the Spike protein of SARS-CoV-2 and its associated neutralizing response.

The pseudovirus neutralization technology developed by our team to quantify neutralizing antibodies has been determinant to understand the immune responses to both viruses and has allowed for the development of a large number of collaborations. In addition, the continuous emergence of SARS-CoV-2 variants requiring virological and immunological characterization has resulted in a large volume of work, making the study of SARS-COV-2 neutralization the current main activity of our group.

However, we have maintained our work on HIV vaccines and treatments, which are based on a novel highly immunogenic VLP platform and synthetic antibodies with improved antiviral activity, respectively. A new grant from the "Instituto de Salud Carlos III" will maintain this activity. Both vaccine and antibody approaches have been extended to other relevant infectious diseases for human health and to cancer immunotherapies.

A second grant from the "Instituto Carlos III" will fund the development of new anti SARS-CoV-2 antibodies with pan neutralizing activity

Regarding cancer vaccine research (in collaboration with the NeoVaCan group) and the Barcelona Supercomputing Center, the work of the last years has seen its first outcomes with two manuscripts accepted, one doctoral thesis and several project applications.

2023 milestones

1. First predoctoral theses on COVID-19 and on cancer vaccines.
2. Approval by the EMA of Bimervax anti SARS-CoV-2 vaccine, manufactured by HIPRA with a relevant contribution of our group and the whole IrsiCaixa team.
3. First competitive project to develop pan neutralizing anti-SARS-CoV-2 antibodies

Perspectives for the future

— The recently awarded projects maintain our work on HIV vaccines and open new perspectives on other infectious diseases and cancer vaccines.

— The vaccine platform based on VLPs has been tested against FeLV, RSV (manuscript submitted) and will envisage new applications on West Nile Virus.In addition, cancer vaccines have taken advantage of technical progresses and envisage new projects based on the mRNA platform.

— The antibody technology keeps growing with new collaborations on cryoelectronic microscopy and structure-based improvements.

4 **New projects awarded**

16 **Scientific articles published, mostly on SARS-CoV-2**

14 **Committed researchers to explore the One Health concept**

Principal Investigator
Julià Blanco Arbués

Senior research scientists
Carmen Aguilar Gurrieri
Francesc Cunyat Viaplana
Benjamin Trinité

Predoc researchers
Ferran Abancó i Espuga
Júlia Albó Delgado
Ana Barajas Molina
Tetyana Pidkova
Anna Pons Grifols
Edwards Pradenas Saavedra

Research statician
Victor Urrea Gales

Researcher
Amaya Blanco Perera

Research technicians
Ester Aparicio Prats
Silvia Marfil Verchili
Carla Rovirosa Martí

Tissue Virology (VITI)

PROJECTS AWARDED

Digital Twins Enabled Indoor Air Quality Management for Healthy Living
Funding: European Commission (Horizon Europe)
Participating entities: IrsiCaixa
Starting and finishing date: 04/23-09/26
Principal investigator(s): Cecilia Cabrera Navarro

Comprehensive analysis of urine biomarkers to predict pathologic complete response in muscle invasive bladder cancer patients treated with neoadjuvant therapy
Funding: GILEAD
Participating entities: IrsiCaixa, IGTP, ICO
Starting and finishing date: 01/23-12/24
Principal investigator(s): Albert Font

Presentation

The study of the impact of HIV on immune cells present in tissues, particularly in mucosa-associated lymphoid tissue became the hallmark of the research group. However, in recent years, the evaluation of the immune response present in tissues has emerged as a critical field in the study of several pathologies including infectious diseases and cancer. In this scenario, the research group has broadened its objectives by applying the knowledge acquired, the tools and biomodels developed, and has established a line of research focused on the characterization of tissue-specific immunopathogenesis. The group has been working in three different settings (infectious diseases, bladder cancer and lung pathologies).

— **Evaluation of viral associated immunopathogenesis:** HIV infection is a mucosa-associated disease, with pathogenesis in two phases: an acute phase, associated with a massive loss of CD4+ T-cells resident in the mucosa, especially in the gut-associated lymphoid tissue (GALT), and a chronic phase, responsible for the gradual destruction of CD4+ T-cells in peripheral blood and characterized by elevated immunological activation and elevated production of proinflammatory cytokines. Cellular immune response in HIV infection is not capable of controlling viral replication in most individuals, probably because the quality and place of induction may not be suitable. During this year the group has been working in the evaluation of the mechanisms of HIV associated cell death and in the characterization of new strategies to improve the antiviral response of the cells present in the tissues. In ex vivo tissue cultures we have characterized the tissue resident immune cells functionality and described a new immunomodulator capable of increase their functionality by the modulation of the innate immune response.

3 Ongoing projects

1 European research project ongoing

1 Group of committed people fighting human diseases

— **Immunopathogenesis in bladder cancer:** bladder cancer is one of the most prevalent cancers in the world. Around 70%–80% of de novo bladder cancers are diagnosed in early stages with no muscular invasion (NMIBC). These patients are often managed with transurethral resection of bladder tumor (TURBT) with or without adjuvant intravesical therapy. The standard treatment in these patients is intravesical administration of BCG (Mycobacterium bovis). Although the mechanism of action is not fully understood, it is thought that the immune system is activated and immune cells are attracted to the bladder wall. While BCG is effective in preventing the development of new tumours, many patients fail to respond and no alternative is as yet available. Therefore, new strategies that improve the clinical management of patients are urgently needed. Using an animal model, we have been working in the evaluation of bladder tumor immune microenvironment profile after BCG intravesical treatment. In addition, we are currently working in the evaluation of the role of the immune system in invasive muscle bladder cancer (MIBC) and its impact on the efficacy of neoadjuvant chemotherapy (NAC).

— **Development of new pre-clinical models:** our group is interested in the development of three-dimensional (3D) models for understanding mechanisms underlying human pathologies. In this regard, we are working on the establishment of different cell culture models to study the role of the tumor microenvironment and the effect of indoor air composition on the respiratory system.

2023 milestones

— **Comprehensive molecular characterization of pan-caspase inhibitor effects.** In collaboration with Dr. Nuria de Iglesia and Dr. Gustavo Rodriguez from NeoVanCan group we have been able to identify the mechanism of action of a pan-caspase inhibitor using transcriptomic analysis.

— **A wide collaborative network has been established to evaluate bladder cancer at molecular level.** In collaboration with Dr. Joaquin Bellmunt and the Dana Faber Institute we evaluated the host immune response (systemic and in the tumor) in patients with invasive muscle bladder cancer (MIBC). In collaboration with the Urologic Tumors Unit of the ICO we have carried out the molecular characterization of urine from patients with bladder cancer for the identification of predictive biomarkers of pathologic complete response in muscle invasive bladder cancer patients treated with neoadjuvant therapy.

— **Establishment of a 3D lung model.** We have established an air-liquid interface (ALI) lung model able to promote cell differentiation to evaluate the impact of indoor air quality in human health.

Perspectives for the future

Our goal is to increase the knowledge that the immune system is playing in the pathogenesis of bladder cancer and to design new and more effective therapeutic strategies to fight cancer or even other diseases in which the immune system needs to be modulated. To establish new clinically relevant models that recapitulate the complexity of the human diseases and may be used in personalized medicine approaches. Consolidation of the research group and improve competitive funding in the cancer field will be one of our main objectives for 2024.

Principal Investigator
Cecilia Cabrera Navarro

Senior research scientist
Jordi Senserrich Velasco

Predoc researcher
Joan Pagés Oliveras

Research technician
Elisabet García Rodríguez

Immunology (IGG)

PROJECTS AWARDED

Juan de la Cierva Fellowship
Funding: MICINN
Participating entities: IrsiCaixa
Starting and finishing date: 01/23-12/24
Principal investigator(s): Núria Pedreño López

Development of a vaccine against HIV-1 based on highly conserved envelope vulnerability regions with improved administration routes.
Funding: MICINN
Participating entities: IrsiCaixa
Starting and finishing date: 09/23-08/26
Principal investigator(s): Jorge Carrillo Molina

Limiting West Nile Virus impact by novel vaccines and therapeutics approaches (LWNVIVAT)
Funding: Horizon Europe
Participating entities: IrsiCaixa, Université Montpellier, Technische Universitaet Braunschweig, Kobenhavns Universitet, Centre de Regulació Genòmica, HIPRA, BSC-CNS
Starting and finishing date: 12/23-11/27
Principal investigator(s): Jorge Carrillo Molina

AWARDS AND ACHIEVEMENTS

Jorge Carrillo Molina, head of the IGTP's Ethics Committee on Animal Experiments
Jorge Carrillo Molina, member of the Spanish Society of Immunology
Carlos Ávila Nieto, awarded Summa cum laude for his PhD thesis entitled *Development of Protein Subunit-Based Vaccines for COVID-19 and Syphilis* (Autonomous University of Barcelona)
Jorge Carrillo Molina, granted with two new projects to develop vaccines against HIV and WNV
Jorge Carrillo Molina, granted with the R3 certificate

Presentation

Our main interest focuses on the study of the immune system in the context of infectious diseases for developing novel prophylactic approaches based on vaccines and antibodies. Particularly, we are working on HIV-1 (AIDS), SARS-CoV-2 (COVID-19), T. pallidum (Syphilis) and West Nile Virus (West Nile Fever). Moreover, we are also conducting research activities related to immuno-oncology, basic immunology, and autoimmunity. We collaborate with many national and international researchers, and with several industrial companies, to speed up the expected impact of our research into the society.

HIV/AIDS
Beyond broadly neutralizing antibodies (bNAbs), HIV infection induce the development of a vast array of non-neutralizing antibodies with unknown roles. While a subset of them can mediate antiviral functions through the recruitment and activation of innate immune cells (e.g. NK cells and macrophages), other might be pathogenic promoting viral infection and spread. We are characterizing a subset of the later ones that may hamper the action of bNAbs by competing for binding to the HIV envelope glycoprotein. We call these antibodies as "Neutralization interfering antibodies (NiAbs) and their characterization, particularly their epitopes, might improve the design of novel immunogens that promote the generation of strong and broadly neutralizing responses. This project was supported by the Instituto de Salut Carlos III (PI18/01332) Accordingly, our second research line in the HIV field aimed to develop a novel HIV vaccine that reduce the generation of non-neutralizing antibodies and promote the development of protective anti-HIV immune responses. This project is funded by the Ministerio de Ciencia e Innovacion (PID2022-139831OB-I00).

SARS-CoV-2/COVID-19
In collaboration with many other researchers from IrsiCaixa and other research centers (i.e. Barcelona Supercomputing center and IRTA-CRESA), we have been working on the generation and characterization of a novel COVID-19 vaccine based on Spike prefusion-stabilized trimers with enhanced production. These immunogens have demonstrated to induce protective immune responses against different SARS-CoV-2 variants, such as the D614G, Beta and Omicron BQ1.1. This project was funded by Grifols and the Health department of the Generalitat de Catalunya". In addition, we are characterizing the pathologic role of the strong humoral response elicited in those people that develop a severe form of COVID-19 upon SARS-CoV-2 infection. This project was funded by "la marató de TV3". We are also collaborating in the characterization of the immune response elicited by the BIMERVAX vaccine (Hipra) in immunodeficient individuals, a project funded by the European Commission with code 101046118.

***T pallidum*/Syphilis**
Treponema pallidum subspecie pallidum (TPA) is the etiologic agent of syphilis, a global health concern that affects millions of individuals worldwide, particularly in low-income countries, and whose incidence is notably increasing in the last years. Syphilis is responsible of more than 200,000 stillbirths and newborn deaths per year. Despite syphilis is treatable with antibiotics, previous control initiatives that were based on screening and subsequent treatment have failed. These mass campaigns

12 Publications

7 Active projects

5 Invited talks

pinpointed the necessity of additional prophylactic measures to reduce new cases and re-infections. However, a syphilis vaccine is not available yet. TPA has several immune evasion mechanisms that could explain the lack of success of previous approaches. Here, we focus on the development of a TPA prophylactic vaccine that overcome these limitations.

West Nile Virus/West Nile Fever
West Nile virus (WNV) is one of the most widespread mosquito-borne pathogens in the world. While most WNV infected individuals (80%) are asymptomatic, 1% of the cases develop a severe illness with central nervous system affectation that, eventually, cause the death. The case-fatality rate increases in immunosuppressed individuals and in population over 60 years old (up to 30%) and, to date, there is no prophylaxis or treatment for this disease. Here, we aim to develop a novel WNV vaccine that protect from infection and/or WNV induced disease, and particularly, from neuroinvasion. We are coordinating thios ambisious project that have been funded by the European Commission (Project: 101137248 — LWNVIVAT) in the last HORIZON-HLTH-2023-DISEASE-03 call.

2023 milestones

HIV/AIDS
We have identified, isolated and characterize several NiAbs that reduce the neutralizing activity of CD4bs bNAbs. This achievement has been pivotal for the consecution of the objectives defined in this research line.

SARS-CoV-2/COVID-19
A patent protecting the novel immunogens developed in this research line was presented. In addition, we demonstrated that our immunogens protect from the highly pathogenic SARS-CoV-2 Beta variant and the Omicron BQ1.1, a variant that escape from the immune response elicited against previous SARS-CoV-2 variants.

***T pallidum*/Syphilis**
We have successfully produced several TPA immunogens and evaluated their immunogenicity in animal models. The results are very promising and showed that the elicited antibodies blocked the binding of the TPA proteins to extracellular matrix elements, suggesting that they might prevent bacterial invasion and dissemination.

West Nile Virus/West Nile Fever
The project for the development of the WNV vaccine was granted by the European Commission.

Principal Investigator
Jorge Carrillo Molina

Senior research scientist
Erola Ainsua Enrich

Postdoc researchers
Núria Pedreño López
Julieta Carabelli

Predoc researcher
Carlos Ávila Nieto

Senior research technician
Marisa Rodríguez de la Concepción

Perspectives for the future

We will continue working on the characterization of the immune response against challenging pathogens such as HIV, T. pallidum, SARS-CoV-2 and WNV with the aim to develop safe and effective vaccines in a near future. With this aim, we will work to strengthen our national and international collaborations, and to contribute to the formation of highly motivated and enthusiastic researchers, that want to see how their job translate in a positive impact to our society: reducing disease burden, improving the quality and life expectancy of the population, and strengthen the biotechnological sector.

Our priority will be:

— to develop prophylactic vaccine for HIV, T. pallidum and WNV.
— to characterize the role of humoral responses in severe
COVID-19.
— to characterize the role of non-neutralizing antibodies in HIV infection.

Translational Research in Immunology and Ageing (TRIA)

PROJECTS AWARDED

Security and Impact of DASATINIB on Viral Persistence and Inflammation in Chronic HIV-Infected Patients on Antiretroviral Treatment (BCN04-DASA)
Funding: MICINN
Participating entities: IrsiCaixa, Lluita, IGTP, Centro Nacional de Microbiología
Starting and finishing date: 01/23-12/26
Principal investigator(s): Beatriz Mothe Pujadas

Advanced Technologies for Precise and Efficient Gene Insertion
Funding: MICINN
Participating entities: IrsiCaixa
Starting and finishing date: 01/23-12/26
Principal investigator(s): Marissa Flores Santamaría

Presentation

The Translational Research in Immunology and Ageing (TRIA) research group focuses on translational studies to investigate the remodeling of the immune system after viral infections and during the process of ageing, focusing on three main lines of research: inflammageing and immunosenescence during HIV infection, COVID-19 vaccine response in older adults and studies on Long-Covid.

— **Inflammageing and immunosenescence during HIV infection.** Despite the great improvement brought by ART, the prevalence of age-related comorbidities is higher in people with HIV (PWH). We study this accentuated ageing and characterize immune dysfunction, HIV reservoir and altered metabolism in PWH on ART. PWH have a higher prevalence of cardiovascular events than the general population, associated with persistent systemic inflammation, which has also been associated with epigenetic and metabolic changes in monocytes. In addition and in collaboration with Mutua de Terrassa, we put special interest in the role of monocytes in the development of cardiovascular diseases in PWH.

— **COVID-19 vaccine response in older adults.** We are working in close collaboration with the Metropolitana Nord Primary Care Centre (DAP-MN) to evaluate the immune response generated by COVID-19 vaccines in previously infected and uninfected older adults living in long-term care facilities as well as noninstitutionalized older individuals, to adapt the SARS-CoV-2 booster vaccination calendar to their specific immune needs.

— **Studies on Post-COVID-19 condition.** In addition, our group has contributed to the establishment of the referral national clinical unit of post-COVID-19 condition at Germans Trias i Pujol Hospital, where patients who experience heterogeneous and debilitating persistent symptoms for months after SARS-CoV-2 infection are followed. In this unit, clinical care management is completely linked to longitudinal research studies to assure the well-being of the patient as well to determine the origin(s) of the persistent symptomatology. In our group, we are characterizing the immune dysfunctions behind Long-Covid, to find diagnostic markers and identify treatment interventions that could lead to the recovery of these patients. We are currently participating in a clinical intervention to treat this condition.

2023 milestones

— Inflammageing and immunosenescence during HIV infection.
— Characterization of the metabolic status of T cells across ages in HIV infection and its impact in immunosenescence and in the persistence and inducibility of the HIV reservoir (MetabolHIV project funded by MICINN; PID2020-114929RA-I00).

>1800 Participants in our clinical studies

10 Coordinated clinical studies of HIV and SARS-CoV-2

2 Publications on Long Covid with high impact

— In collaboration with Dr Negredo from Fundació Lluita contra les Infeccions (FLI), characterization of the immune system and immunosenescence (including telomere length) in subjects older than 70 years (OVER50 cohort). This study was presented at CROI 2023 and Gesida 2023.

— In collaboration with Dr Negredo (FLI) and Dr Martin of the Autonomous University of Barcelona (UAB), characterization of alterations in DNA repair mechanisms in HIV-infected older adults so as to associate them with accentuated immunosenescence (funded by ISCIII, PI19/00947)

— In collaboration with Dr David Dalmau (Mútua de Terrassa), characterization of the metabolic profile of monocytes in the development of cardiovascular diseases in PWH (funded by SCMIMC)

— In collaboration with Dr David Dalmau (Mútua de Terrassa), characterization of miRNA signatures as predictive hallmark of cardiovascular disease in PWH.

— In collaboration with Dr MC Puertas (GREC), characterization of the HIV reservoir in late presenters (X4SEED project funded by Becas Gilead)

COVID-19

— Coordination of the KING cohort extension of SARS-CoV-2 infected individuals (N>1000) with different levels of severity (asymptomatic to critical), a cohort that is of use to all **IrsiCaixa** groups. This cohort includes also more than 650 individuals suffering from post-COVID-19 condition.

— In collaboration with Dr Lourdes Mateu (FLI), exploration of pro-inflammatory status, immune dysfunctions, SARS-CoV-2 persistence and reactivation of other viruses (i.e. EBV, CMV, HHV6, among other) in individuals with Long-Covid, and its association with specific persistent symptomatology (Funded by Becas Gilead, GLD21-00070).

— Exploration of the specific role of NK-cells in the post-COVID-19 condition. (LoNK-COVID project funded by MICINN, PID2021-124226OB-I00)

— In collaboration with Dr. Pere Toran (IDIAP-Jordi Gol) and Dr Julia Garcia-Prado (VIRIEVAC), deep neurological and immune characterization of individuals with Long-Covid with persistent neurologic complaints (funded by PERIS-AP, SLT021/21/000055).

— In collaboration with Dr. Christian Brander (TIV), epigenetic studies of individuals with Long-Covid with persistent neurologic complaints (EPIVINF and EPIVIRCO projects, funded by HORIZON-HLTH-2021-DISEASE-04

— In collaboration with Drs Nuria Prat (DAP-MN) and Concepció Violán (IDIAP-Jordi Gol), coordination of the CoronAVI@S and IMMERSION studies of residents of long-term care facilities or non-institutionalized older adults to evaluate the quality and duration of immune responses elicited by SARS-CoV-2 vaccine (Funded by Gloria Soler).

— In collaboration with Drs Concepció Violán (IDIAP-Jordi Gol) and Julia Garcia-Prado (**IrsiCaixa**, VIRIEVAC group), evaluation of the SARS-CoV-2-specific immune responses in individuals susceptible to develop severe COVID-19 after breaktrough infections (BREAKCOVID project funded by PERIS-AP).

— In collaboration with Dr Elisa Martró (HUGTiP, Microbiology lab), Dr José Ramon Santos (FLI) and Dr. Marc Noguera (**IrsiCaixa** Microbial Genomics group), evaluation of clinical characteristics and outcomes of patients with SARS-CoV-2 reinfection (RECOVID).

Principal Investigator
Marta Massanella Luna

Senior research scientist
Maria Nevot Banús

Research technician
Gooya Banaei

Predoc researchers
Marissa Flores Santamaria
Marina Martínez Velasco
Franciso Manuel Muñoz López
Macedonia Trigueros Peña

Perspectives for the future

Ageing with HIV

Our group will continue to characterize accentuated immunoageing and immunosenescence in PWH on ART compared to their uninfected counterparts. The aim is to determine the origin of immune dysfunction and develop new senolytic and metabolic interventions. We will also explore how the process of natural ageing in PWH induces changes in the nature of the viral reservoir. We will evaluate also the role of cellular metabolism in the persistence of the HIV reservoir.

COVID-19

We will continue our SARS-CoV-2 infection research, focusing especially on recovered individuals with post-COVID-19 condition. Using extensive data collected on these patients, we will implement pilot interventions aimed at reducing persistent symptomology and improving the quality of life of recovered patients.
In addition, we will further characterize the immune responses in older adults living in long-term care facilities to adjust their vaccination calendar and ensure their protection against SARS-CoV-2 infection.

Pathogen Immunity, Signalling & Therapeutic Applications (PISTA)

PROJECTS AWARDED

Assess the immunomodulatory effect of leriglitazone on macrophages exposed to SARS-CoV-2 or to LPS
Funding: Minoryx Therapeutics SL
Participating entities: IrsiCaixa
Starting and finishing date: 07/23-12/25
Principal investigator(s): Nuria Izquierdo Useros

Replicative virus neutralization assay
Funding: HIPRA
Participating entities: IrsiCaixa
Starting and finishing date: ongoing
Principal investigator(s): Nuria Izquierdo Useros

Limiting West Nile Virus impact by novel vaccines and therapeutics approaches (LWNVIVAT)
Funding: Horizon Europe
Participating entities: IrsiCaixa, Université Montpellier, Technische Universitaet Braunschweig, Kobenhavns Universitet, Centre de Regulació Genòmica, HIPRA, BSC-CNS
Starting and finishing date: 12/23-11/27
Principal investigator(s): Jorge Carrillo Molina

Thermal disinfection by magnetic induction: A study with SARS-CoV-2 Pseudoviruses
Funding: Fundació Institut Català de Nanociència i Nanotecnologia
Participating entities: IrsiCaixa
Starting and finishing date: 07/23-12/25
Principal investigator(s): Nuria Izquierdo Useros

AWARDS AND ACHIEVEMENTS

Elisa Molina Molina, selected to present her first results at the European Congress of Virology in Poland
Dàlia Raich Regué, Elisa Molina Molina and **Nuria Izquierdo Useros**, members of the organizing committee of the Women in Science day at Can Ruti
Nuria Izquierdo Useros, granted with the R3 certificate
Nuria Izquierdo Useros, expert member of the committee of Immunité et cancer for Hceres evaluation at Curie Institut.
Nuria Izquierdo Useros, part of the scientific organizing committee of the Jornadas de Virología de la Sociedad Catalana de Virología and the Immunology meeting of the Societat Catalana de Immunologia.

Presentation

We are an emergent pathogens research group interested in finding novel therapeutic solutions while understanding the molecular basis of infectious diseases. Our team PISTA studies Pathogen Immunity, Signaling & Therapeutic Applications.

In a constantly evolving world where climate warming and globalization trends are changing the geographical distribution of infectious diseases, our goal is to combat emerging viruses designing novel therapeutic tools. PISTA was launched in February 2020 and immediately devoted all efforts to tackle SARS-CoV-2 pandemic. Many of the techniques implemented have helped us fighting other viral threats, including including mpox (MPXV) or the respiratory syncytial virus (RSV). The main 3 axis of our team are:

1. Identify and develop effective antivirals
2. Find and potentiate efficacy of immunomodulators
3. Provide reliable tools to test and validate novel vaccines

Our group collaborates with academic partners, clinical researchers and different industries to bring up together innovative antiviral strategies and novel solutions to counteract microbial threats.

2023 milestones

We have expanded our initial work to identify novel antivirals, immunomodulators and vaccines against SARS-CoV-2 and now are working with other viruses, including the MPXV and RSV. We aim to implement new strategies that could avoid emergent virus transmission. Currently, we are working to translate all the gained knowledge to tackle new viral threats and develop novel therapeutic approaches. During this year, our work has been devoted to the following activities:

1. Search for novel antivirals against SARS-CoV-2 has led to the identification of broad-spectrum therapies.
— Along with Drs. Risco (CNB-CSIC, Madrid) and Cerón (Univ. Cartagena, Murcia), we have identified beta-cyclodextrins as promising broad-spectrum antivirals against different SARS-CoV-2 variants and distant alphacoronaviruses (Raïch-Regué et al. Biomedicine & Pharmacotherapy, 2023). Beta-cyclodextrins had a prophylactic effect in the nasal epithelium of hamsters *in vivo*, as demonstrated in collaboration with Drs. Segalés and Vergara from IRTA-CReSA. Given the wide use of beta-cyclodextrins for drug

1 Goal to work together as a team: fight against new viruses

10 Accepted peer-reviewed papers

9 Presentations in international congresses

encapsulation and their high safety profile, our results support their clinical testing as prophylactic antivirals and we have filed a patent application to pursue this development.

— In collaboration with the team led by Dr. O'Keefe of the NCI (Frederick, USA) and researchers from Brazil, Girona and Barcelona, our team has contributed to the identification of Cyanovirin as a possible broad anti-coronavirus agent that prevents infection by a different range of SARS-CoV-2 strains (Muñoz-Basagoiti et al. PNAS, 2023).

— We are pursuing deep quantitative proteomic and transcriptomic analyses coupled to functional infectious assays to define the antiviral molecular landscape induced by host directed antivirals in collaboration with Dr. De La Torre at Institute Josep Carreras. This research is a collaborative effort involving several groups at **IrsiCaixa**. By unraveling the cellular antiviral landscape elicited by host targeted therapies we aim to identify novel broad-spectrum antivirals with potential to counteract future pandemic viruses.

2. The study of immunomodulators for SARS-CoV-2 points to therapies with broad-spectrum potential.
— We have used an *in vitro* platform to detect the cytokines induced by SARS-CoV-2 exposure, with the aim of identifying new immunomodulators and decrease immune hyperactivation. We have optimized a primary myeloid cellular model to evaluate immunomodulators in collaboration with diverse groups, including Drs. T. Thompson from CSIC and O. Mitjà from HUGTiP and different companies, such as Minoryx and PharmaMar.

3. Regulatory approval of vaccines.
— We have set up a validated SARS-CoV-2 neutralization assay critical for the regulatory approval of Bimervax, the first Spanish COVID-19 vaccine of HIPRA. We have participated in the phase I and phase II clinical trials (Leal et al. NPJ Vaccines, 2023; Corominas et al. Lancet Regional Health, 2023) that led to the approval of Bimervax by the European Medicine Agency (EMA), the UK Medicines & Healthcare Products Regulatory Agency (MHRA) and the pre-approval by the World health organization (WHO).

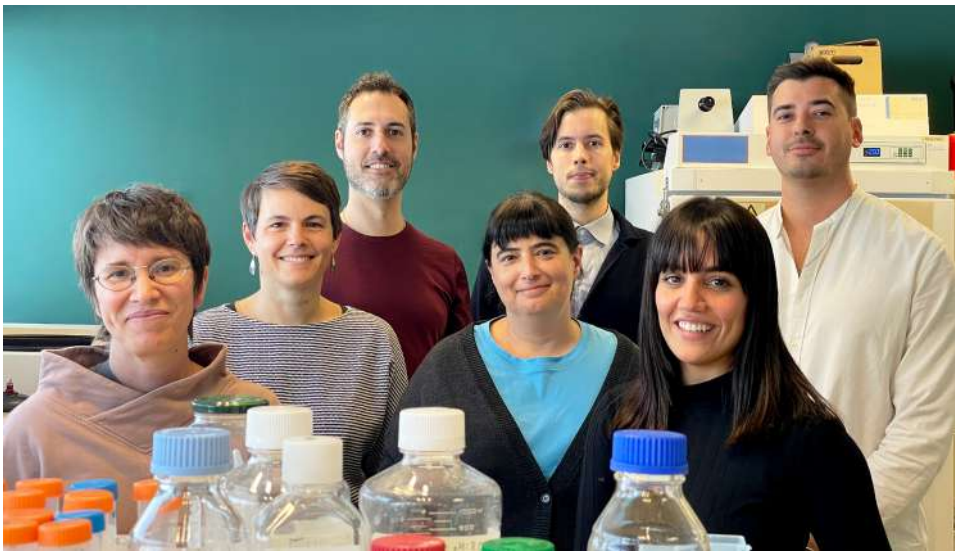
— Our group also participates in two European vaccine projects to prove the effectiveness of Bimervax vaccine in immunocompromised patients and to generate new immunogens against emerging viruses like West Nile Virus in a project led by Dr. Carrillo.

— We have also joined a preclinical project funded by CDTI Misiones led by HIPRA, IQS and Curapath for the development of a novel vaccine for RSV in collaboration with Hospital Clínic.

4. Study of re-emergent viruses.
— Several protocols and circuits implemented for viral isolation at the BSL3 facilities for respiratory viruses allowed us to respond to the m pox outbreak in summer 2022 caused by MPXV. In collaboration with the Center for Epidemiological Studies on Sexually Transmitted Infections and AIDS of Catalonia (CEEISCAT), we showed that unrecognized m pox cases of participants from high-risk populations had replication competent MPXV in samples collected during the outbreak, and could therefore shed infectious viruses (Agustí et al. Nat. Comm, 2023).

— We have also set up a viral neutralization assay to characterize neutralizing immune responses associated with MPXV clearance in a prospective observational cohort of people living with and without HIV in Spain set up by Drs. Mothe and Mitjà from our hospital.

— We have also started the isolation of RSV from clinical samples to generate a prospective collection of circulating viruses in collaboration with Dr. Martrò from our Hospital and HIPRA.



Principal Investigator
Nuria Izquierdo Useros

Senior research scientist
Dàlia Raïch Regué

Postdoc researcher
Eloi Franco Trepat
Daniel Pérez Zsolt

Predoc researcher
Elisa Molina Molina

Senior research technician
Rytis Boreika
Itziar Erkizia Jauregi
Marçal Gallemí Rovira
Jordana Muñoz Basagoiti

Perspectives for the future

We pursue translational impacts of our research, focusing on:

— The discovery of mechanisms of action of antivirals and immunomodulators to foresee their clinical potential and anticipate side effects.
— The validation of methodologies that can facilitate vaccine approvals;
— Contributing to the design of clinical trials aimed at combating viral infections;
— The application of all the gained knowledge by the team to limit respiratory viruses and emergent threats.

Neoantigens and Vaccines against Cancer (NeoVaCan)

PROJECTS AWARDED

Tumor-specific neoantigens as targets for personalized vaccines
Funding: ISCIII
Participating entities: IrsiCaixa, ICO, Hospital Universitari Germans Trias i Pujol, CNAG-CRG
Starting and finishing date: 01/22-12/24
Principal investigator(s): Núria de la Iglesia Zaragoza

Presentation

The NeoVaCan group performs immunogenomic analyses of solid tumours and liquid biopsies to study the interplay between tumor cells and the immune microenvironment. We are using multi-omics coupled to functional immune cell-based assays to get a deeper understanding of the host immune response against cancer and identify mechanisms of immune escape, ultimately taking cancer patient therapy towards personalization.

Our research has two main pillars:

1. Study of the immunobiology of specific tumor types, such as pancreatic cancer, to understand the roots of immune failure to control tumor development.

2. Identification and characterization of neoantigens to be used as targets for immunotherapies, with a special focus on neoantigen vaccines.

Together with the Cell Virology and Immunology (VIC) group at **IrsiCaixa**, we are co-developing preventive and therapeutic neoantigen vaccines using an in-house VLP-based vaccine platform.

2023 milestones

1. Our collaboration with the EAPM group at Barcelona Supercomputing Center (IP: Dr. Guallar) has allowed us to improve a novel neoantigen prediction pipeline that has been tested to predict neoantigens in human patient samples in a personalized manner. Experimental validation of the in silico predictions is ongoing.

2. Dr. de la Iglesia has co-authored a paper, led by the VIC group at **IrsiCaixa**, testing the effect of different spacers on neoantigen processing and presentation in neoantigen polytope vaccines (Aguilar-Gurrieri C, Barajas A, Rovirosa C, Ortiz R, Urrea V, de la Iglesia N, Clotet B, Blanco J, Carrillo J. Cancer Immunol Immunother. 2023 Jul;72(7):2113-2125. doi: 10.1007/s00262-023-03409-3. Epub 2023 Feb 23).

3. The manuscript "Converging and evolving immuno-genomic routes leading to immune escape in breast cancer" has been provisionally accepted for publication at Nature Communications.

4. The NeoVaCan group is incorporated as a collaborating member in the european project Transcan 3 (ERA-NET, JTC 2021) entitled "Innovative mRNA vaccine against NSCLC: Designing a platform of targeted polymeric nanoparticles for efficient personalized therapy", and coordinated by Dr. Cristina Fornaguera at IQS.

2 Published peer-reviewed paper

1 Invited talk

2 Posters presented at the Alicante Winter Immunology Symposium in Health 2023

Principal Investigator
Núria de la Iglesia Zaragoza

Bioinformatician
Gustavo Rodríguez Esteban

Senior research technician
Anna López Plana

Perspectives for the future

To apply next-generation sequencing strategies, coupled with improved and novel bioinformatic pipelines and cutting-edge molecular biology procedures, to the identification and validation of immunogenic tumor-associated antigens.

— Working with immunologists and computational biologists, to lay solid foundations for the development of a therapeutic cancer vaccine for patients with solid tumours, taking advantage of the expertise of **IrsiCaixa** researchers currently working on vaccines against HIV, COVID-19 and other infectious diseases.

— To expand the team, secure collaborations with external partners and incorporate state-of-the-art molecular tools and new cost-effective in-house solutions for cancer immunotherapy.

Research support

Scientific and technical services

Sample conservation and processing service

Since its inception in 1993, **IrsiCaixa** has dedicated a special effort to the processing and conservation of biological samples to drive diverse research projects. Initially centered on supporting internal studies within the field of HIV infection, this activity has undergone significant expansion. Over the years, collaborations have increased, and samples have been processed and preserved for a multitude of projects and clinical trials in the field of Infectious Diseases and Cancer. Theses projects were promoted by both **IrsiCaixa** and external sponsors, on a national and international scale. The center's commitment to this activity has allowed it to become a solid platform that actively supports and facilitates research efforts based on human samples.

Currently, the service routinely processes and stores samples for 35 active studies and maintains two large collections of samples (registered in the National Biobank Registry, No. C0000814 and No. C0006008) for research on HIV and other infectious diseases.

Sequencing service

Since its launch **IrsiCaixa** has used HIV genotyping technique to determine resistance to antiretrovirals, initially on an experimental basis for patients included in clinical trials. The technique was soon found to be very useful for optimizing antiretroviral treatments and it eventually became evident that there was a need for all HIV-infected patients to have access to this technique.

In 1999 the Sequencing Service was launched as a healthcare service to manage samples from the Germans Trias i Pujol University Hospital and other public and private centres. In addition to its healthcare role, the Sequencing Service also participates in research projects and clinical trials in collaboration with research groups and pharmaceutical companies.

In 2018, the Sequencing Service implemented next-generation sequencing (NGS) technologies. In 2019, **IrsiCaixa** incorporated the Sentosa® SQ HIV genotyping assay to detect HIV drug resistance. This assay is validated in the highly automated Sentosa® NGS workflow, which enables automated RNA extraction, library construction, template preparation, sequencing, data analysis and automated reporting. The Sentosa® NGS workflow also ensures clear sample traceability, with seamless laboratory information system (LIS) integration and connectivity.

To ensure the quality of its results, the Sequencing Service undergoes regular external quality controls (QCMD ENVA HIV-1 Drug Resistance Genotyping Proficiency Programme).

Other services

Identifying SARS-CoV-2 infected individuals by means of sensitive diagnostic tools is crucial to reducing new infections and to developing strategies to control the ongoing COVID-19 pandemic at the individual and societal levels. Quantification of the humoral response elicited in SARS-CoV-2 infected individuals is a very promising line of research, as it may provide information on the immune response in those individuals. **IrsiCaixa** has recently introduced a specific ELISA test to detect SARS-CoV-2 antibodies.

Coordinator
Lidia Ruiz Tabuenca

Sample conservation and processing service
Eulàlia Grau Segú
Rafaela Ayen Aparicio
Lucía Gómez Espada
Mireia Martínez Gamero

Sequencing service
Teresa Puig Oliva
Cristina Ramírez Soto

Assistant
Susana Esteban Raya

28 years of sample collection

Total of samples collected

47,414 cells
79,285 plasma
11,045 serum
36,362 other

Total: **174,106 samples**

2023

Samples collected

2,926 cells
2,969 plasma
1,233 other

Total: **7,128 samples**

456 Sequenced samples

400 public centres

56 private centres

1815 Elisa tests in COVID-19 diagnosis

Grants office

Head
Judith Dalmau Moreno

Team
Sonia Bange Singh
Elisabet Fernández Rosas
Manel Garcia de la Fuente
Maria Belén Gómez Hornillos
Natàlia Marrugat Vila
Antonio Navarro Alcaraz
Miriam Planell Molina
Laura Planells Ferrer
Anaí Villanueva Delgado

The Grants office works closely with all **IrsiCaixa** departments and groups to promote the development of innovative and quality research. Continuous communication with researchers ensures support at all levels, whether in detecting needs, seeking suitable funding opportunities, performing projects follow-up and justification, assisting with proposal preparation and project management, designing and following up budgets and assisting in collaboration, transfer and innovation processes. The office ensures alignment of **IrsiCaixa**'s practices with the rules, regulations, and policies of funding entities, as well as with current national and international regulations.

In 2023, **IrsiCaixa** dedicated important efforts to expand and strengthen the office to ensure its capacity to manage the large increase in the number and dimension of the current active projects, including much higher number of projects coordinated by our center and increased internationalization.

Clinical Management Unit

Head
Judith Dalmau Moreno

Team
Daniela Benítez Cano
Cristina Gálvez Celada
Antonio Navarro Alcaraz
Miriam Planell Molina

In 2023, given the escalating volume and intricacy of Clinical Studies at **IrsiCaixa**, many of which are coordinated internally, coupled with the heightened legal, administrative, and ethical requirements associated with such projects, **IrsiCaixa** has strategically established the Clinical Management Unit (CMU). This unit provides comprehensive support to ensure the seamless implementation and progression of clinical research projects at **IrsiCaixa**, offering guidance on all facets related to their execution and development.

The pivotal support areas of the CMU encompass:

1. Regulatory aspects, such as CEIC approvals and legal compliance in collaboration with IrsiCaixa's legal department.

2. Guidance on the design and methodology of clinical studies, encompassing the development of protocols and documentation to ensure regulatory compliance and adherence to GCPs.

3. Direction on data collection, storage, and dissemination in collaboration with Data Management.

4. Counsel and/or design of databases, flowcharts, and CRDs, emphasizing the utilization of REDCap; and, in specific cases, support for patient/sample selection, coordination of multicenter projects, and internal and external communication with diverse partners and stakeholders.

Living Lab for Health

Head
Rosina Malagrida Escala

Team
Marina Pino Cebrián
Laia Vives Adrián

Presentation

During 2023, the Living Lab for Health at **IrsiCaixa** has continued working on its mission to improve the **social impact of research and innovation (R&I) of (complex) health challenges** by facilitating support services on **strategic planning** to research groups, (international) consortiums, innovation networks and governments in collaboration with a wide diversity of stakeholders (researchers in different disciplines, healthcare providers, policy makers, professionals working with affected communities, patients and citizens). Through participatory and transdisciplinary processes, they explore the complexity of the challenges and co-design and implement collective strategies with systems innovation approaches.

The results lead to collective impact with decentralized and collaborative solutions that result in a more integrated and least fragmented health approach, that address different parts of the challenges and include different types of innovation (e.g. organizational and social, product, service, process, technological, educational, communication, governance).

The Living Lab works on two typologies of (complex) health challenges: (1) Development of therapeutic and diagnostic tools (e.g. Long Covid, immunotherapies, WNV vaccine) and (2) Pilot interventions for prevention and health promotion (e.g. healthy and sustainable diets, mental health, infectious diseases).

The methods to facilitate the Lab's services are based on frameworks and approaches defined by the European Commission (EC) under the umbrella of Responsible Research and Innovation (RRI), Open Science, Mission Oriented Research, "partnerships" of the Horizon Europe programme, and other ones such as "Community Based Participatory Research", "systems innovation" and "transdisciplinary research".

The Lab has also offered training to more than 450 professionals and university students and, as part of its research to constantly improve its contribution to increase social impact of research, one paper has been published in the International Journal of Public Health where the team disseminate their methodology for collective strategic planning called "System-Oriented Dialogue Model".

The Lab has carried out its initiatives with EU funded projects and also with the support of the department of health of Generalitat de Catalunya, through "the Sentinel Schools Network" and the "la Caixa" Foundation through the Barcelona CaixaResearch Living Lab.

Milestones 2023

1. Strategic planning for research on the development of therapeutic and diagnostic tools

The Lab has designed an impact strategy for **IrsiCaixa** and the following actions have been implemented:

— **Initial diagnosis.** Two impact narratives are being developed with IrsiCaixa's research groups.

— **Consultancy services.** To design and implement impact strategies for research groups, projects, consortiums & innovation networks:

a. ***Impact Strategies for research groups:*** The Lab has designed a methodology for their design which has been piloted with the VIRIEVAC research group during a one-day workshop and an internal meeting.

b. ***Long Covid Unit***. The Lab has contributed to the implementation of the Impact Strategy developed in 2021-22 for the Hospital Germans Trias i Pujol, Fight Infections Foundation, Institut Català de la Salut -North Metropolitan area & **IrsiCaixa**. The Plan was the basis to develop a roadmap with international leaders in the field and an application for a COST action coordinated by **IrsiCaixa**. During 2023 one of the action lines of the plan was also implemented (see section 3 on Patient Experience).

c. ***LWNVIVAT EU funded project.*** The Lab has started in this project which aims to develop a vaccine against the West Nile Virus. Its role is to design & implement an impact strategy to improve policies for control and prevention of emerging infectious diseases in European countries.

2. Patient experience to improve healthcare services (in primary care & hospitals)

Main projects:

— **Hospitals' nutritional education pilot.** Implementation of in-person nutritional education pilots during the hospitalization of patients who have suffered a myocardial infarction. In collaboration with the Germans Trias i Pujol University Hospital, the Fight Infections Foundation, and the Clinic-IDIBAPS Hospital, among others.

— **Neurocognitive rehabilitation intervention for Long Covid patients.** Recommendations report to improve a clinical study protocol on a new neurocognitive rehabilitation application developed by the Fight Infections Foundation (Carles Capdevila scholarship). Workshops with patients and healthcare providers.

— **Care model for Long Covid.** As part of the Impact Plan of the Long Covid Unit, recommendations were designed to improve the transversal healthcare protocol for Long Covid patients. Workshops with healthcare providers, researchers and patients from primary care and hospitals

— **Improving the patient experience of the PragmaTIL oncologic clinical trial,** led by Vall Hebron Hospital. Development and implementation of a methodology to design, validate and implement recommendations. Creation of a "Patient Advisory Committee" involving healthcare providers and patients.

3. Strategic planning for pilot interventions on prevention and health promotion

— **Alison network for more healthy and sustainable food environments.** The Living Lab aims to enhance healthy and sustainable food environments in neighborhoods with vulnerable populations. In 2023, actions included consolidating the multistakeholder network called "Alison network" in the Metropolitan Area of Barcelona (AMB). The network, that started with the support of the CaixaResearch Living Lab and one EU funded project, now also counts with extra funding from 3 EU projects, contributing to its growth. During 2023, we designed a new strategic plan for the city-region promoting participatory

research and designing interventions to be piloted in two neighborhoods (Fondo and Sant Cosme). During 2023, the Lab also fostered the co-design and implementation of pilot programs addressed to health education and consultancy for retailing offerings (in bars, restaurants and shops). A digital platform for network collaboration within a neighbourhood and across different neighbourhoods was conceptualized, and it is expected to be released in 2024. Preparatory tasks have been initiated to pilot interventions also in a third neighorhood in 2024, when the Lab will also start its participation in a EU funded partnership.

— Sentinel Schools Network: participatory research with direct impact on health promotion in schools (the case of mental health and infectious diseases). The Lab has designed health promotion pilot interventions, in collaboration with educational centers, that aim to empower students to actively contribute to their community's health promotion by designing and implementing personalized and integrated action plans through participatory research. These pilots, funded by the EU project CONNECT, the Sentinel Schools Network of the Generalitat de Catalunya and EduCaixa, have been designed with the results of previous research with more than 2500 students, their families and healthcare professionals. In 2023 educational guidelines were developed for primary and secondary education and they were disseminated and piloted with mentoring services for teachers that reached nearly 3.000 students and their families. To disseminate this work, the Lab has contributed to the organization of an international conference on "Open Schooling" in collaboration with the CONNECT project and of the 3rd Sentinel Schools Conference.

— Research, education and outreach.

a. ***Research topics and main results.*** (1) impact of the Living Lab (Journal Health Expectations, submitted), (2) impact of research groups (protocol), (3) methodologies for participatory strategic planning (paper published on the "System-Oriented Dialogue Model", International Journal of Public Health), (4) facilitation of system innovation networks, (5) training on RRI (paper published in 2022) and (5) impact of health promotion interventions (implementation of pilots).

b. ***Training on research impact, Responsible Research and Innovation (RRI), System Innovation and Open Science.*** A total of 469 professionals and university students have been trained through customized training sessions, webinars, conferences, and workshops.

c. ***Outreach programs for youth.*** More than 2.966 students participated in the HIV/AIDS outreach programme to disseminate basic knowledge, current research and the importance of prevention and diagnosis, through reflexive debates and an open lab to conduct research with a vaccine candidate developed by **IrsiCaixa**. During 2023, the Lab has also updated several multimedia resources for EduCaixa.

Main projects

CLEVERFOOD, Labs for Food system transformation
Funding: European Commission
Participants: 22 partners
Start and end date: 01/23-12/25

FoodCLIC, integrated urban FOOD policies
Funding: European Commission
Participants: 26 partners
Start and end date: 09/22-02/28

FOSTER, fostering food system transformation
Funding: European Commission
Participants: 18 partners
Start and end date: 09/22-08/27

Escoles Sentinella / CONNECT
Funding: European Commission & Departament de Salut, Generalitat de Catalunya
Participants: 12 partners
Start and end date: 01/21-12/24

CaixaResearch Living Lab
Funding: "la Caixa" Foundation
Participants: Living Lab for Health at **IrsiCaixa** & ISGlobal
Start and end date: 01-12/2023

PragmaTIL, Pragmatic approach to Adoptive Cell Therapy
Funding: "la Caixa" Foundation, European Commission
Participants: 12 partners and the Living Lab for Health as subcontractor
Start and end date: 4/23-3/28

LWNVIVAT, Limiting West Nile Virus impact by novel vaccines and therapeutics approaches
Funding: European Commission
Participants: 8 partners, including the Living Lab for Health
Start and end date: 12/23-11/27

Accepted projects

FutureFoodS Partnership
Funding: European Commission
Participants: 87 partners
Start and end date: 2024-2034

5
Innovation networks

7
Strategic plans and policy briefs

213
Academic and non-academic participants

6
Protocols for piloting health promotion interventions designed

4
Pilots of health promotion

8329
Participants in the health promotion interventions

469
Professionals and university-students

1
Scientific publication

Communication

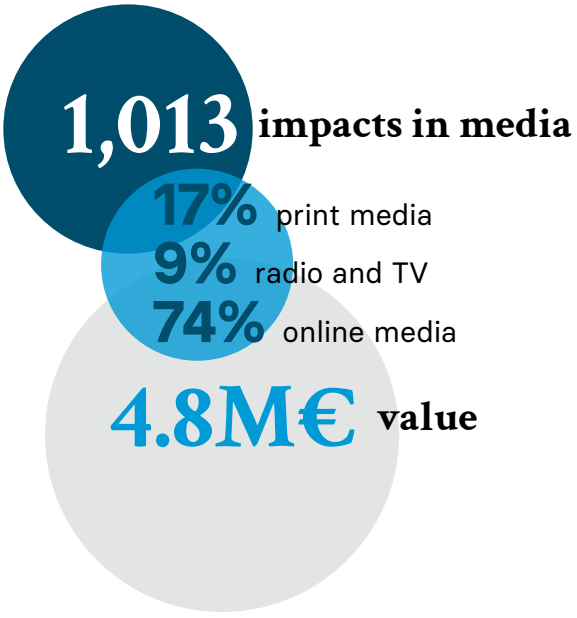
Team

Rita Casas Costa
Elena Lapaz Lorenzo

In recent years, the imperative for laboratory-generated knowledge to reach society has gained unprecedented significance, emerging as a dynamic trend on the international stage. The **IrsiCaixa** department is committed to this idea and acts as a bridge between the scientific community and the general public, aiming to bring science closer to society. This includes translating complex research findings into accessible and understandable information, promoting public knowledge, engagement, and support for scientific projects. To effectively realize these objectives, the communication department plays a pivotal role in collaborating with the media, online platforms, social networks, internal communication, and cultivating relationships with key stakeholders. Below, we provide a concise overview of the evolution and solidification of the diverse communication channels employed by **IrsiCaixa**, along with a look into the varied projects undertaken within the department.

Media

The communication department's ability to bring scientific results to the press is crucial, not only to promote the center's reputation but also to extend the impact of its work beyond the scientific community. **IrsiCaixa** can have a high impact in the media due to the quality of its research and society's interest in its field of work, but also because of the connection with key stakeholders in the information circuit. In 2023, **IrsiCaixa** has issued 7 press releases, achieving 1,013 impacts in digital and print media, radio, and TV. These impacts have a total value of 4.8 million euros and have reached an audience of more than 268 million people.

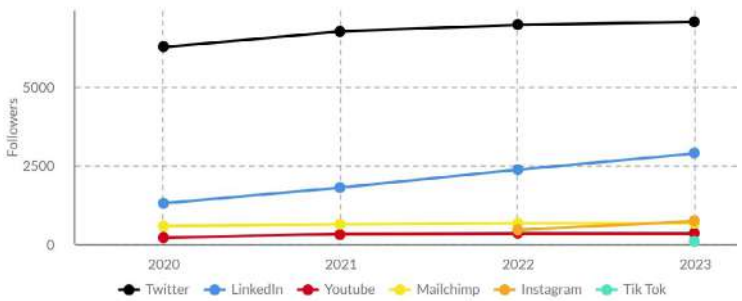


Website and social media

Considering the growth of the TikTok digital platform, the communication department has made the strategic decision to embrace this social network in July 2023 by creating a user account for **IrsiCaixa**. The launch of this new platform enables **IrsiCaixa** to connect with today's digital age and communicate science in a more creative format. As a result, the recent additions of **IrsiCaixa** to both TikTok and Instagram have a positive response from followers. In the case of TikTok, the videos have garnered 54,980 views in just six months, with one video being viewed more than 12,600 times. Meanwhile, Instagram continues its growth, reaching 40,769 accounts. Notably, the rest of **IrsiCaixa**'s social media channels and its website have sustained and, in some cases, increased their impact, reinforcing their presence in the digital landscape.

Impact / production		Followers
141,241	visits to irsicaixa.es	
160,372	impressions in "X"	7053
40,769	accounts reached in Instagram	726
1,123	reactions to posts on LinkedIn	2,877
54,980	video views in TikTok	75
12	external newsletters	662

Progress of followers



Internal communication

The tasks of the communication department include both external and internal communication. The latter is a cornerstone for the institution as it fosters a cohesive and motivating work environment, encouraging employees to share ideas and concerns. With the goal of promoting teamwork and a positive atmosphere among the team, the communication department organizes sports events, contests, meals, or talks annually. In 2023, a volleyball, paddle tennis, and soccer tournament, a Christmas decoration contest, the Christmas dinner, a book exchange for Sant Jordi, and alumni talks from **IrsiCaixa** (IAN Talks) were held.

7 internal communication projects completed

- **3** sport tournaments
- **1** book exchange
- **1** contest
- **1** alumni talks
- **1** annual dinner

24 internal newsletters sent

1 IrsiCaixa Alumni Network (IAN)

Coordination of European project communication

IrsiCaixa coordinates 3 European projects, and their communication is managed internally. In this regard, the communication team in 2023 has developed action plans and necessary content to maintain the Twitter, newsletters, and websites of the MISTRAL and EPIVINF projects. Simultaneously, they have handled the communication for the launch of the recently awarded European project LWNVIVAT.

3 European projects coordinated

- MISTRAL
- EPIVINF
- LWNVIVAT

Websites and social media

MISTRAL
- www.mistral-hiv.eu
- @mistralhiv
- internal newsletter

EPIVINF
- www.epivinf.eu
- @epivinf

Institutional news

Beatriz Mothe recieve the international recognition "European Hector Research Award in HIV 2023" for the research carried out on the therapeutic vaccine against HIV

Beatriz Mothe, IrsiCaixa resarcher and doctor at Hospital Germans Trias, together with doctor Lucía Bailón collected the award for the great scientific challenges achieved in 2023 in the field of HIV. In concrete, the award recognizes the results of the clinical trial AELIX-002 carried out with the therapeutic vaccine against HIV from AELIX Therapeutics, designed at IrsiCaixa.

IrsiCaixa coordinates €5 Million EU-funded research project to tackle globally prevalent West Nile Virus

The team involved will design therapies to tackle the effects of the West Nile Virus (WNV), an emerging pathogen which lacks treatments and for which there is no human vaccine. The scientific team of LWNVIVAT, comprising researchers from eight research centres across four different countries, will test the efficacy of both the vaccine and antibodies.

Training

IrsiCaixa has been committed, from its inception, to training young researchers and developing successful careers in biomedical research. Its training objectives are realized as follows:

— Training of pre-doctoral researchers
— Training of post-doctoral researchers
— 2 training master and undergraduates' students
— Continuing professional development for staff
— 2 visiting researcher placements (we particularly welcome trainee researchers interested in learning from IrsiCaixa research groups).

32 Predoc researchers

32 Postdoc and senior researchers

488 Training attendees

12 Research results meetings

10 Journal clubs

68 Courses

Internal and external training

— **Weekly meetings at which group members present their results.** These meetings develop capacity to structure and defend experimental data before a restricted audience of experts in the field.

— **Fortnightly meetings at which group members present their results.** These meetings develop capacity to structure and defend experimental data before a restricted audience of experts in different fields.

— **Seminars.** IrsiCaixa and other Can Ruti Campus groups regularly organize open seminars with invited internationally renowned researchers.

— **Greater integration and collaboration between IrsiCaixa and the Can Ruti Campus.** This collaboration is translated into participation in coffee talks and scientific activities.

— **Training in skills to support you in your professional career.** To increase the ability of an individual in one or more areas of the professional career. Increase an individual's motivation to do their job well.

— **National and international conferences.** All staff are encouraged to participate in scientific encounters and to present their results at conferences.

— **Specialization/perfection courses in experimental techniques.**

— **Journal clubs.** Fortnightly meetings aimed at developing critical vision regarding published data in which researchers present an article of relevance to their own experimental work.

— **Newsletter.** Dissemination of a monthly IrsiCaixa Newsletter highlighting the most relevant scientific articles published by IrsiCaixa groups, courses and events organized by other entities and articles of general interest in matters of equality, compliance, biosafety, etc.

Chair in infectious diseases and immunity

In 2013, **IrsiCaixa** signed an agreement with the Fight Infections Foundation (FLI) and the University of Vic-Central University of Catalonia (UVic-UCC) to create what was then called the Chair in AIDS and Related Diseases, renamed in June 2019 as the Chair in Infectious Diseases and Immunity so as to better reflect the wide range of fields of expertise of the researchers involved in the Chair.

Headed by Dr. Bonaventura Clotet, the Chair aims to enhance collaboration between **IrsiCaixa**, the FLI and the UVic-UCC in fostering research into infections and related diseases and to promote the teaching and training of new researchers and healthcare professionals.

The Chair in Infectious Diseases and Immunity undertook the following training activities in 2023:

Date	Type of activity	Title	Place	Conducted by
January	Workshop	Infections in Oncological-Haematological patients	Faculty of Medicine, UVic-UCC	Rosa Benítez
February	Workshop	Diabetic Foot	Faculty of Medicine, UVic-UCC	Esteban Reynaga
February	Workshop	Acute febrile syndrome in primary care	Faculty of Medicine, UVic-UCC (online)	Alba Romero
February	Seminar	Vaccines	Faculty of Medicine, UVic-UCC (online)	Christian Brander
March	Lecture	Infections in patients with transplants (solid organs) or in treatment with immunomodulators	Faculty of Medicine, UVic-UCC (online)	Rosa Benítez
March	Workshop	Most prevalent infections in the elderly	Faculty of Medicine, UVic-UCC	José Ramón Santos
April	Lecture	Gastroenteritis	Faculty of Medicine, UVic-UCC (online)	José Ramón Santos
April	Lecture	Parasitosis	Faculty of Medicine, UVic-UCC (online)	Silvia Roure
April	Continuing education course	Update on HIV infection and the pandemic of COVID-19	Faculty of Medicine, UVic-UCC	B Clotet, E Negredo, J Blanco, J Martínez-Picado, B Mothe, D Ruiz, R Paredes
May	Workshop	Aging	Faculty of Medicine, UVic-UCC	Eugènia Negredo
June	Lecture	Social determinants of health: the UN sustainable development goals	Faculty of Medicine, UVic-UCC	Sergio España
June	Lecture	Tuberculosis	Faculty of Medicine, UVic-UCC	Sergio España
June	Seminar	Telemedicine: telelctus	Faculty of Medicine, UVic-UCC	Cora Loste
June	Seminar	Research methodologies and research with clinical trials	Faculty of Medicine, UVic-UCC (online)	Javier Martínez-Picado
November	Seminar	Monoclonal Antibodies	Faculty of Medicine, UVic-UCC	Julià Blanco Arbués
November	Seminar	Monoclonal Antibodies. From biotechnology to clinical use	Faculty of Science, Technology and Engineering, UVic-UCC	Julià Blanco Arbués
November	Lecture	Social determinants of health: the UN sustainable development goals	Faculty of Science, Technology and Engineering, UVic-UCC	Roger Paredes
November	Workshop	Tuberculosis	Faculty of Science, Technology and Engineering, UVic-UCC	Sergio España
December	Lecture	Coronavirus	Faculty of Medicine, UVic-UCC	Lourdes Mateu
December	Workshop	Endocarditis	Faculty of Medicine, UVic-UCC	Lourdes Mateu
December	Workshop	Tuberculosis and extrapulmonar	Faculty of Medicine, UVic-UCC	Laura Soldevila
December	Symposium	Research in Infectious Diseases	Faculty of Science, Technology and Engineering, UVic-UCC	Beatriz Mothe, Javier Martínez-Picado

Innovation

Team
Cristina Val Cid
José Luis Pérez Guillamón

During 2023, **IrsiCaixa** has established a new Innovation Department with the addition of two individuals with complementary knowledge and experience in innovation and technology transfer. The creation of this new department has led to the implementation of innovation management and governance routines, including ongoing support for research groups and the monitoring of research outcomes through regular meetings.

With a strategic focus, **IrsiCaixa** has invested in the creation of the Innovation Department to drive the transfer of research results and ensure they align with the values, needs, and expectations of society. Collaboration with industry, intellectual property protection, and active promotion are key elements in achieving successful transfer, and the Innovation Department will provide support throughout the project to ensure its transferability and valorization.

Rowing in the same direction, **IrsiCaixa** has joined forces with other entities to create a collaborative ecosystem aimed at maximizing its impact through cooperation with other institutes. We highlight the collaboration with the CaixaResearch Institute (CRI), under whose initiative innovation hub has been created with the commitment of raising awareness and training personnel from associated centers to develop competencies in the field. Furthermore, **IrsiCaixa** has joined Innomed, an innovation node supported by the ITEMAS platform of the Carlos III Health Institute, under the direction of the Germans Trias i Pujol Research Institute (IGTP).

Innovation

Patent portfolio

Granted

Title: HIV antibody derivates with dual antiviral and immunomodulatory activity
Inventors: Carrillo, Jorge; Clotet Sala, Bonaventura; Blanco Arbués, Julián Miguel
Reference: WO/2017/085563
Priority date: 21 Nov 2015
Publication date: 26 May 2017
Applicant: IrsiCaixa
Assigned to: AlbaJuna Therapeutics, SL

Title: Virus-like particles with high-density coating for the production of neutralizing antibodies
Inventors: Molinos, Luis; Carrillo, Jorge; Blanco Arbués, Julián Miguel
Reference: WO/2018/020324
Priority date: 27 Jul 2016
Publication date: 01 Feb 2018
Applicant: IrsiCaixa
Licensed to: HIPRA

Title: Immunogens for HIV vaccination
Inventors: Brander, Christian; Mothe Pujadas, Beatriz; Llano, Anuska
Reference: WO/2013/110818
Priority date: 27 Jan 2012
Publication date: 1 Aug 2013
Applicants: IrsiCaixa, ICREA, Laboratorios del Dr. Esteve, S.A.
Licensed to: Aelix Therapeutics, S.L.

Title: Human Helicase DDX3 Inhibitors as Therapeutic Agents
Inventor(s): Meyerhans, Andreas; Martínez de la Sierra, Miguel Ángel; Brai, Annalaura; Itfazi, Roberta; Tintori, Cristina; Botta, Maurizio; Araque, José-Esté; Martínez-Picado, Javier
Reference: WO/2016/128541
Priority date: 13 Feb 2015
Publication date: 18 Aug 2016
Applicants: IrsiCaixa, Azienda Ospedaliera Universitaria Senese

Filed

Title: PLD for use in combination in the treatment of coronavirus
Inventors: Izquierdo-Useros, Nuria; Vergara-Alert, Júlia; Avilés-Marín, Pablo
Priority date: 02 Mar 2020
Reference: WO/2021/175823
Applicants: IrsiCaixa, PharmaMar

Title: Soluble TIGIT recombinant proteins
Inventors: García Prado, Julia; Marín López, Miguel Ángel; Carabelli, Julieta
Priority date: 11 Dec 2021
Reference: WO/2023/105281
Applicant: IrsiCaixa

Title: Boosted immune monitoring methods for assaying antigen-specific T cell responses
Inventors: Ruiz Riol, Marta; Olvera van der Stoep, Alexandre; Romero Martín, Luis; Brander, Christian
Priority date: 09 Mar 2022
PCT Application: WO/2023/170189
Applicant: IrsiCaixa

Title: Leriglitazone for treating lung inflammation and interstitial lung disease
Inventors: Martinell, Marc; Pizcueta, Maria Pilar; Vilalta Saura, Anna; Traver López, Estefanía; Poli, Sonia Maria; Izquierdo-Useros, Nuria
Priority date: 30 Apr 2021
Reference: WO/2021/220250
Applicant: Minoryx Therapeutics

Title: Cyclodextrins for use in Coronavirus infection therapy
Inventors: Risco Ortiz, Cristina; Fernández de Castro Martín, Isabel; Tenorio Vela, Raquel; Sachse, Martin; Ortega González, Paula; Fernández Oliva, Alberto; Fernández Sánchez, Sara Yolanda; Izquierdo-Useros, Nuria; Pérez Zsolt, Daniel; Muñoz Basagoiti, Jordana; Raïch-Regué, Dàlia; Cerón Carrasco, José Pedro; Gabaldón Hernández, José Antonio; Núñez Delicado, Estrella
Priority date: 25 Mar 2022
Reference: WO/2023/180567
Applicants: IrsiCaixa, CSIC; CUD; UCAM

Title: Anti-SARS-COV-2 Antibodies
Inventors: Blanco Arbués, Julián Miguel; Pradenas Saavedra, Edwards; Trinité, Benjamin; Magri, Giuliana; Tejedor, Sonia; de Campos-Mata, Leire; Carolis, Carlo
Priority date: 06 Oct 2022
Priority application: EP22382940
Applicants: IrsiCaixa, CRG, IMIM

Title: Nucleoside reverse transcriptase inhibitors for use in Down syndrome and Alzheimer's disease therapy
Inventors: Clotet Sala, Bonaventura; Paredes, Roger; Elizalde Torrent, Aleix; Dierssen, María del Mar; Martínez de Lagrán, María
Priority date: 08 Dec 2021
PCT application: PCT/ES2022/070780
Applicants: IrsiCaixa, FLI, CRG

Title: SARS-CoV-2 Immunogenic Polypeptides And Uses Thereof
Inventors: Carrillo Molina, Jorge; Clotet Sala, Bonaventura; Blanco Arbués, Julián Miguel; Ávila Nieto, Carlos; Guallard, Victor; Amengual, Pep; Segalés, Joaquim; Vergara-Alert, Júlia
Priority date: 23 Mar 2023
Reference: EP23382270
Applicants: IrsiCaixa, BSC, IRTA

Title: Antibodies and Uses Thereof for The Treatment of Infections Caused by Enveloped Viruses
Inventors: Martínez-Picado, Javier; Resa-Infante, Patricia; Izquierdo-Useros, Nuria; Erkizia Jauregi, Itziar; Clotet Sala, Bonaventura
Priority date: 27 Jan 2023
Reference: PCT/ES2022/070780
Applicant: IrsiCaixa

Title: CD33 as a marker of HIV control
Inventors: Brander, Christian; Ruiz Riol, Marta; Duran Castells, Clara
Priority date: 12 Feb 2023
Reference: EP23382150
Applicant: IrsiCaixa

Title: Elvitegravir as a bacterial agent
Inventors: Brander, Christian; Ruiz Riol, Marta; Duran Castells, Clara
Priority date: 12 Feb 2023
Reference: EP23383054
Applicants: IrsiCaixa

Clinical and observational studies

1. BCN003

A Phase I, Randomized, Double-Blind, Placebo-Controlled Safety, Tolerability and Immunogenicity Study of Candidate HIV-1 Vaccines ChAdOx1. HTI and MVA. HTI with Recombinant HIV-1 Envelope Protein ConM SOSIP.v7 gp140 Vaccine, Adjuvanted with MPLA Liposomes in ARTSuppressed HIV-1 Positive Individuals

Study type: interventional
Design: phase I, randomized, double-blind, placebo-controlled
Summary and objectives: BCN03 tests a novel combined regimen with T- and B-cell immunogens, and the primary endpoints of BCN03 will be safety and tolerability. BCN03 is designed as a pilot study, and the sample size has been chosen that will only allow the detection of large response differences. The BCN03 Phase I study will evaluate the safety, tolerability, immunogenicity, and efficacy of a vaccine regimen that includes a sequence of the T- and B-cell immunogens ChAdOx1. HTI and MVA.HTI and ConM SOSIP.v7 gp140 adjuvanted with MPLA liposomes in virologically-suppressed ART-treated HIV-1 positive individuals. The primary objective of this study is to assess the safety and tolerability of the vaccine components, and secondary objectives include immunogenicity and efficacy of the vaccine components.
Start–end: 2021-2023
Sponsor: European Comission–EAVI2021
Principal investigators: Dr Beatriz Mothe Pujadas, Dr Christian Brander
Code/reference: 2020-000292-20

2. RUTIVAC-1

A Randomized, Double-Blind, Placebo Controlled Phase I Trial to Evaluate the Immunomodulatory Effect of RUTI® in Individuals with High-Risk Non-MuscleInvasive Bladder Cancer (NMIBC) Treated with Intravesical Bacillus Calmette-Guerin (BCG)

Study type: interventional
Design: phase I, double blind, placebocontrolled, randomized
Summary and objectives: the RUTIVAC-1 study is a Phase I Clinical Trial designed to evaluate the systemic and mucosal immunological response and provide safety information after the use of RUTI® administration to individuals with NMIBC. The study will enroll individuals treated with Transurethral resection of bladder tumor (TURBT), diagnosed to have highrisk Non-muscle invasive bladder cancer (NMIBC) and suitable candidates for BCG therapy and who meet all eligibility criteria. Forty individuals will be recruited and randomized 1:1 to receive two subcutaneous shots of 25g RUTI® or placebo. After vaccination, individuals will receive the standard intravesical Bacillus Calmette–Guerin (BCG) therapy with induction course (weekly BCG for six weeks) and maintenance course (three courses of weekly BCG for three weeks at 3, 6 and 12 months after induction). After the last intravesical BCG administration (BCG15, end of Interventional Phase) immunological assays will be performed and data will be analyzed. At the end of the Interventional Phase the blind will be opened, except for the study physicians who will remain blind during all the follow-up. All the individuals will be followed up for three years since TURBT.
Start–end: 2016-2023
Sponsor: Archivel Farma S.L
Principal investigator: Dr Cecilia Cabrera Navarro
Participating centres: Germans Trias i Pujol University Hospital (Urology Department), Fight Infections Foundation (CRO), IrsiCaixa
Code/reference: AC-16-048-CEIM (CEIC Code)

3. DUAL TRIPLE ART

Exploratory, open-label, randomized clinical trial to assess the efficacy of firstline dual vs. triple antiretroviral therapy (ART) in HIV-1 reservoir and in peripheral compartments in HIV-infected patients (Dual_TripleART)

Design: phase III
Recruitment: completed
Start–end: 2019 – 2023
Sponsor: ViiV Healthcare
Principal investigators: Dr José Moltó, Dr Javier Martínez-Picado
Participating centres: Germans Trias i Pujol University Hospital (Fight Infections Foundation); IrsiCaixa; University of North Carolina (Chapel Hill, USA), and the Oregon Health & Sciences University (Beaverton, USA)
Code/reference: 2019-002733-10

4. KING COHORT

Prospective Comparative Observational Cohort of individuals with documented SARS-CoV-2 infection (King cohort extension)

Study type: observational
Design: prospective cohort
Recruitment: ongoing
Summary and objectives: the KING cohort extension aims to be a prospective comparative observational cohort of infected SARS-CoV-2 individuals to have a unique clinical platform of biological specimens to study the virology and immunopathogenesis of SARS-CoV-2, during acute infection and after recovery of COVID-19. An uninfected group of individuals and a vaccinated group will be included. Patients suffering from PostCOVID-19 condition are also included in this cohort.
Start–end: 2020-ongoing
Sponsor: YoMeCorono crowdfunding campaign
Principal investigators: Dr Bonaventura Clotet Sala, Dr Marta Massanella Luna, Dr Lourdes Mateu
Participating centres: Germans Trias i Pujol University Hospital, Fight Infections Foundation, IrsiCaixa
Code/reference: HUGTiP/20-P-217

5. Aliança ProHEpiC-19 Neurocognitiu

Neurocognitive profile of Long Covid in adults living in Catalonia

Study type: observational
Design: retrosprospective/prospective observational study
Summary and objectives: clinical study dedicated to describe the neurological sequelae of people presenting with persistent neurocognitive-type COVID-19 syndrome, analyzing their relationship with the functional alterations and/or structural cerebral, with the inflammatory and immunological state, the vascular and vestibular involvement, and its impact on the activities of daily life through the experiences they have experienced in coexistence with the persistent symptomatology.
Start–end: 2022-2024
Sponsor: Department of Health, Government of Catalonia
Principal investigators: Dr Julia Garcia Prado
Code/reference: SLT021/21/000038

Clinical and observational studies

6. BreakCOVID
SARS-CoV-2 post-vaccination infection: cohort study for the characterization of the immune response and development of a predictive model to establish revaccination criteria in Catalonia
Study type: observational
Design: retrosprospective/prospective observational study
Summary and objectives: clinical study dedicated to describing the neurological sequelae of people presenting with persistent neurocognitive-type COVID-19 syndrome, analyzing their relationship with the functional alterations and/ or structural cerebral, with the inflammatory and immunological state, the vascular and vestibular involvement, and its impact on the activities of daily life through the experiences they have experienced in coexistence with the persistent symptomatology.
Start–end: 2022-2024
Sponsor: Department of Health, Government of Catalonia
Principal investigators: Dr Marta Massanella Luna
Code/reference: SLT021/21/000055

7. EPIVIRCO
Epigenetic regulation of host immunity and neurological long-term consequences of SARS-CoV-2 infection
Study type: observational
Design: retrospective/prospective observational study
Summary and objectives: the project examines if long-lasting epigenetic changes occurring after SARS-CoV-2 (COVID) infection determine the immunological and neurological longlasting effects observed in post-COVID conditions. After epigenetic profiling of different cell types from patients with long-COVID symptoms, the proposal will validate the hypotheses in a transgenic mouse model, which will be also used to evaluate therapeutic interventions and open new treatment options.
Start–end: 2022-2025
Sponsor: Fundació Bancària "la Caixa"
Principal investigators: Dr Christian Brander, Dr Marta Ruiz-Riol
Code/reference: HR22-00681

8. VRSVAC
Investigación de nueva vacuna para enfermedad respiratoria humana
Study type: observational
Design: preclinical study
Summary and objectives: the scope of the project is the development of a vaccine for a human respiratory disease (RSV or Respiratory Syncytial Virus).
Start–end: 2022-
Sponsor: HIPRA
Principal investigators: Dr Julià Blanco Arbués, Dr Nuria Izquierdo Useros
Code/reference: MIG-20211034

9. MetabolHIV
Ageing with HIV: The role of metabolism in viral persistence and accentuated immunoageing
Study type: observational
Design: prospective observational study
Summary and objectives: this project aims to understand the metabolic mechanisms that contribute to the immunosenescent phenotype, and giving new insights on the ongoing debate of premature or accentuated ageing of the HIV population. In addition, we will determine the role of metabolism in HIV persistence, which offer novel perspectives for the development of clinical strategies for HIV eradication.
Start–end: 2021-2025
Sponsor: MICINN, Proyectos de I+D+i 2020
Principal investigator: Dr Marta Massanella Luna
Code/reference: PID2020-114929RA-I00

10. Long-CovidCIBERINFEC
Biomarkers and underlying immunopathological mechanisms of post COVID-19 condition
Study type: observational
Design: restrospective observational study
Summary and objectives: this project aims at identifying biomarkers of PCC to improve the diagnostic of PCC and provide understanding on the mechanisms underlying this condition, with the ultimate goal of determining treatment targets and interventions to improve the management and quality of life of PCC patients. Specific objectives are: 1) To assess SARS-CoV-2 persistence in blood and feces and reactivation of other viral latent infections, which may lead to chronic immune inflammation and dysfunction; 2) To determine immune dysregulation; 3) To quantify autoantibodies and markers of autoimmunity; 4) To assess metabolic dysregulation.
Sponsor: CIBERINFEC
Principal investigator: Dr Marta Massanella Luna
Code/reference: IM22/INF/5

11. PediaCOVID
Pediatric long-COVID: clinical, immunological, genetic and virological evaluation of a cohort of children and adolescences
Study type: observational and interventional
Design: restrospective observational study
Summary and objectives: the primary objective of the project is to evaluate the causes and consequences of long-COVID in a unique pediatric cohort. Specific aims include: 1) to describe the main clinical, epidemiological and radiological characteristics, and the physical, psychological, academic and social consequences, 2) to unveil the genetic causes that may predispose to longCOVID, 3) to evaluate the immunological and inflammatory profile, 4) to investigate viral persistence, and 5) to analyze the neuronal damage to evaluate the longterm effect of COVID-19 on cognitive impairment. The project should allow to define specific clinical guidelines and personalized treatment strategies that should directly impact in the quality of life of the affected kids and their families.
Principal investigators: Dr Sara Morón López, Dr Javier Martínez Picado
Code/reference: PediaCOVID

12. RIDHIV
Reversing Immune Dysfunction for HIV eradication (RIDHIV)
Study type: observational
Design: restrospective observational study
Summary and objectives: the general aim of the project is to analyze the characteristics related to the reduction of the viral reservoirs in HIV+ participants and the main factors that

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can drive to absence of viral rebound after treatment interruption strategies. Moreover, one of the specific aims of the study will be to test the impact of the microbiome and metabolome on cognate CD4 T cell help and effector CD8 and B cell function and their capacity to control HIV reservoir size and HIV viral rebound. The hypothesis that host and microbial derived metabolomes will drive the development and persistence of cognate help which in turn will trigger an effector CD8 T cell response capable of maintaining low levels of replication competent virus will be tested. This will be tested in human cohorts, specifically in the LoViReT cohort, characterized for having a low HIV reservoir in absence of any intervention. The mechanisms downstream of the host and microbial metabolomes that control the adaptive immune response which is associated to the magnitude of the replication competent reservoir will be also assessed.

Sponsor: National Institutes of Health, USA (NIH)

Principal investigators: Dr Javier Martínez Picado, Dr. Maria Salgado Bernal

Code/reference award (subaward): 1UM1AI164561-01 (70457-13543-IRSI)

13. Long-CovidCIBERINFEC

Evaluation of epigenetic regulated factors in peripheral blood and CSF in individuals with documented SARS-CoV-2 infection

Study type: observational

Design: comparative ambispective observational study

Summary and objectives: the main objective of the study is the identification of epigenetic imprints associated with CoV-2 infection in cells in the peripheral blood and the CSF and how these epigenetic marks arº e related to the long-term sequels and persistent symptomatology of CoV-2 infection, with especial focus on neurological disorders, for its targeting in vitro models for the identification of novels therapeutic strategies.

Principal investigator: Dr Christian Brander

Code/reference: PI-21-281

14. RBDCOV

Phase I/II study to evaluate the safety and immunogenicity of RBDCOV SARS-CoV-2 Vaccine in children and adolescents

Study type: observational/ interventional

Design: prospective Phase I/II clinical trial

Summary and objectives: the general project aims is a Phase I/II clinical trial in children and adolescents participants of the first RBDCOV COVID vaccine, which is based on a recombinant protein codifying for the SARS-CoV-2 RBD protein based on the sequence of the Wuhan variant. The aim is to test that COVID-19 Vaccine can be administered to the paediatric population and to find the best dose according to the age of children and adolescents. In addition, a variant vaccine, which contains the RBD for both the South African and UK variants, is also tested in adult participants with and without mild-to-moderate comorbidities and immunocompromised individuals. In IrsiCaixa, specific tasks include combining high-throughput and deep immune analyses to provide the required information for vaccine immune monitoring following the most updated regulatory recommendations and at the same time to generate novel mechanistic insights of response to vaccines with a particular focus on recognition of SARS-CoV-2 and related coronavirus variants, which will be crucial in the success of second-generation COVID-19 vaccine candidates.

Sponsor: European Comission (Horizon Europe)

Principal investigator: Dr Julia García Prado (WP leader in IrsiCaixa)

Code/reference: 101046118

15. BCN04-DASA

Safety and Impact of Dasatinib on Viral Persistence and Inflammation in People with HIV under Antiretroviral Treatment

Study type: interventional

Design: Phase II, single-center, randomized, double-blind, placebo-controlled clinical trial in PWH

Summary and objectives: the primary objectives of the study are to evaluate the safety and tolerability of dasatinib administered at 70 mg once daily during 24 weeks in PWH on suppressive ART; and to evaluate the on-target/biological effect of dasatinib administered at 70 mg once daily during 24 weeks in PWH on suppressive ART on the reduction of SAMHD1 phosphorylation upon in-vitro T-cell activation, and its durability after completion of dasatinib treatment. Experimental exploratory aims are focused on: 1) to characterize the impact of dasatinib and its durability on the reservoir repertoire and maturation phenotypes; 2) to evaluate if the immunomodulatory effect of dasatinib on NK cells is driven by simultaneous CMV infection; 3) to further characterize immunological, viral, and microbiological responses to dasatinib therapy; and 4) to assess the impact of dasatinib and its durability on physical and cognitive functions in PWH with functional and/or cognitive decline.

Sponsor: ISCIII

Principal investigator: Dr Beatriz Mothe Pujadas

Code/reference: EudraCT 2023-000061-14

Publications & conference presentations

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63. Raïch-Regué D, Tenorio R, Fernández de Castro I, Tarrés-Freixas F, Sachse M, Perez-Zsolt D et al. **Beta-Cyclodextrins as affordable antivirals to treat coronavirus infection**. *Biomedicine & Pharmacotherapy*. 2023;164:114997. DOI: 10.1016/j.biopha.2023.114997

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Publications

66. Riveira-Muñoz E, Garcia-Vidal E, Bañó-Polo M, León R, Blanc V, Clotet B et al. **Cetylpyridinium Chloride - Containing Mouthwashes Show Virucidal Activity against Herpes Simplex Virus Type 1**. *Viruses*. 2023;15(7). DOI: 10.3390/v15071433

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Conference presentations

International conferences

1. Bayón-Gil A. **Low Tryptophan Catabolism Marks Immune Preservation in HIV+ Viremic Non-Progressors**. *30th Conference on Retroviruses and Opportunistic Infections (CROI) 2023*. Seattle, USA, February 16-22, 2023. Poster.

2. Borgognone A. **Interactions between gut microbiota signatures and CNS status in a HIV cure strategy**. *30th Conference on Retroviruses and Opportunistic Infections (CROI) 2023*. Seattle, USA, February 16-22, 2023. Poster.

3. Cabrera C, Senserrich J. **Pan-caspase inhibition prevents HIV replication by the induction of the IFN I pathway**. *30th Conference on Retroviruses and Opportunistic Infections (CROI) 2023*. Seattle, USA, February 16-22, 2023. Poster.

4. Izquierdo-Pujol J. **PBMC immuno-phenotyping and plasma inflammatory profile in children with Long Covid**. *30th Conference on Retroviruses and Opportunistic Infections (CROI) 2023*. Seattle, USA, February 16-22, 2023. Poster.

5. Muñoz-López FM. **Identification of clinical features associated with SARS-CoV-2 reinfections**. *30th Conference on Retroviruses and Opportunistic Infections (CROI) 2023*. Seattle, USA, February 16-22, 2023. Poster.

6. Nevot-Banús M. **Cytokine profile in different post COVID-19 condition phenotypes**. *30th Conference on Retroviruses and Opportunistic Infections (CROI) 2023*. Seattle, USA, February 16-22, 2023. Poster.

7. Pérez-Caballero R. **High-resolution mapping of T-cell hybrid immunity to the entire SARS-CoV-2 proteome**. *30th Conference on Retroviruses and Opportunistic Infections (CROI) 2023*. Seattle, USA, February 16-22, 2023. Poster.

8. Pérez-Zsolt D. **Plitidepsin is a Broad-Spectrum Antiviral Shaping the Cell Proteostatic Balance**. *30th Conference on Retroviruses and Opportunistic Infections (CROI) 2023*. Seattle, USA, February 16-22, 2023. Poster.

9. Trigueros-Peña M. **Multiparametric characterization of telomere length in T cells from PLWH by Flow-Fish**. *30th Conference on Retroviruses and Opportunistic Infections (CROI) 2023*. Seattle, USA, February 16-22, 2023. Poster.

10. Izquierdo-Useros N. **Plitidepsin is a Host-Directed Antiviral that Transiently Inhibits Protein Translation of Distant Viruses while Shaping a Protective Proteostatic Cellular Response**. *36 International Conference of Antiretroviral Research (ICAR)*. Lyon, France, March 13-17, 2023. Poster.

11. Raïch-Regué D. **Beta-Cyclodextrins as affordable antivirals to treat coronavirus infection**. *Cell Symposia Viruses in health and disease*. Sitges, March 19-21, 2023. Poster.

12. Izquierdo-Useros N. **Plitidepsin is a Host-Directed Antiviral that Transiently Inhibits Protein Translation of Distant Viruses while Shaping a Protective Proteostatic Cellular Response**. *Cell Symposia Viruses in health and disease*. Sitges, March 19-21, 2023. Poster.

13. Molina E. **Plitidepsin is a host-directed antiviral that transiently inhibits protein translation of distant viruses while shaping a protective proteostatic cellular response**. *8th European Congress for Virology 2023*. Gdansk, Poland, May 4-7, 2023. Poster.

14. Trigueros-Peña M. **Multiparametric Characterization of Telomere Length in T cells from PLWH by Full Spectrum Flow-FISH**. *Congress for the International Society for the Advancement of Cytometry (CYTO 2023)*. Montreal, Canada, May 20-24, 2023. Talk.

15. Pérez-Zsolt D. **SARS-CoV-2 is detected on antigen-presenting cells expressing Siglec-1 in pulmonary tissues**. *Symposium: Macrophage markers in cancer and inflammation*. Barcelona, May 24, 2023. Talk.

16. Vives-Adrián L. **Open Schooling for mental health promotiony**. *2023 Ecsite Annual Conference*. Malta,, June 15-17, 2023. Talk.

17. Izquierdo-Pujol J. **Immunophenotyping of Long COVID in children with a 37-color panel using full-spectrum cytometry**. Amsterdam, The Netherlands, June 21, 2023. Talk.

18. Morón-López S. **Immunophenotypic characterization of long COVID**. *Cytek Speaker Series*. Online, August 2, 2023. Talk.

19. Català Moll F. **Consensus-based robustness for differential abundance testing in microbiome data analysis**. *BioC2023 (Bioconductor Conference 2023)*. Boston, USA, August 2-4, 2023. Poster.

20. Nevot-Banús M. **Cytokine profile associated with post-COVID-19 condition**. *Keystone Symposia on Long COVID and Post Acute Sequalae of SARS CoV 2 (PASC)*. Santa Fe, NM, USA, August 27-30, 2023. Poster.

21. Izquierdo-Pujol J. **PBMC immunophenotyping, plasma inflammatory profile and antibody levels of children with Long COVID**. *Keystone Symposia on Long COVID and Post Acute Sequalae of SARS CoV 2 (PASC)*. Santa Fe, NM, USA, August 27-30, 2023. Talk.

22. Malagrida Escalas R. **Open Schooling to improve Health Promotion**. *Open Living Lab Days*. Barcelona, September 21-23, 2023. Talk.

23. González Navarro I. **Taming the Viral Reservoir Over Three Decades of Advancements in HIV Treatment**. *The HIV Reservoirs and Immune Control Conference*. Malahide, Ireland, September 1-4, 2023. Talk.

24. Garcia Vidal E. **Identification of therapeutic targets for HIV cure through high-throughput screening in novel in vitro non-clonal HIV-1 latency models**. *19th European AIDS Conference*. Varsovia, Poland, October 18-21, 2023. Poster.

25. Moraes Cardoso I. **Dynamics of immune responses to Mpox infection in people with and without HIV co-infection Immunity to Viruses**. *18th International Congress of Immunology (IUIS 2023)*. Cape Town, South Africa, November 27-December 2, 2023. Poster.

26. Massanella Luna M. **Cytokine profile associated with post-COVID-19 condition**. *Demystifying Long COVID-19 International Conference 2023*. Madrid, Spain, December 7-9, 2023. Talk.

27. Izquierdo Pujol J. **PBMC Immunophenotyping, Plamsa Inflammatory Profile and Antibody Levels of Children with Long COVID**. *Demystifying Long COVID-19 International Conference 2023*. Madrid, Spain, December 7-9, 2023. Talk.

Conference presentations

National conferences

1. Malagrida R, Pino M. **Xarxa Alison per a la promoció de l'alimentació saludable i sostenible**. El Prat de Llobregat, January 30, 2023. Talk.

2. Muñoz-López FM. **Characterization of post-COVID-19 condition subsyndromes through hierarchical clustering**. *2023 PhD in bioinformatics workshop*. Vic, February 3, 2023. Poster.

3. Malagrida R. **Research Impact Experiences in Catalonia**. Barcelona, March 6, 2023. Talk.

4. Morón-López S. **Immunophenotypic characterization of long COVID**. *XVIII Congress of the Iberian Society of Cytometry 2023.* Madrid, April 19-21, 2023. Talk.

5. Trigueros-Peña M. **Multiparametric Characterization of Telomere Length in T cells from PLWH by Full Spectrum Flow-FISH**. *XVIII Congress of the Iberian Society of Cytometry 2023.* Madrid, April 19-21, 2023. Talk.

6. Trigueros-Peña M. **Multiparametric characterization of telomere length in T cells from PLWH by FULL SPECTRUM Flow-FISH**. *XVIII Congress of the Iberian Society of Cytometry 2023.* Madrid, April 19-21, 2023. Talk.

7. Malagrida R. **Heading towards Responsible Research and Innovation. A new paradigm for how we solve our problems**. Vic, April 26, 2023. Talk.

8. Blanco J. **HIV Infection Induces the Development of Neutralization-Interfering Antibodies that Hamper the Function of Neutralizing Antibodies**. *44 Congreso de la Sociedad Española de Inmunología (SEI).* Bilbao, May 10-13, 2023. Poster.

9. Trinité B. **Impact of hybrid immunity, booster vaccination and Omicron breakthrough infection on cross-neutralization against Delta, BA.1, BA.2 and BA.4/5 SARS-CoV-2 variants**. *44 Congreso de la Sociedad Española de Inmunología (SEI).* Bilbao, May 10-13, 2023. Poster.

10. Blanco J. **Vacunas bivalentes, *update***. *XIII Jornadas de Enfermedades Emergentes.* Barcelona, May 16, 2023. Talk.

11. Massanella M. **Multiparametric characterization of telomere length in T cells from PLWH by Flow-Fish**. *I jornadas jovenes investigadores en formacion CIBERES-CIBERINFEC.* Madrid, June 15-16, 2023. Poster.

12. Villanueva S. **Comprehensive Management of Aging in HIV**. Barcelona, October 23, 2023. Talk.

13. Bayón-Gil A. **Young Investigator's Talk: VNPs**. *Hot Topics in HIV.* Barcelona, October 26, 2023. Talk.

14. Morón López S. **Effects of HIV infection on single cell epigenome and transcriptome**. *Hot Topics in HIV.* Barcelona, October 26, 2023. Talk.

15. Badia R. **Harnessing the innate immune response through NOD1 agonists prevents SARS-CoV-2 infection in human lung epithelial cells**. *XXII Jornada de Virologia - Virology meeting 2023* Barcelona, October 27, 2023. Talk.

16. Molina E. **Plitidepsin is a host-directed antiviral that transiently inhibits protein translation of distant viruses while shaping a protective proteostatic cel**
lular response. *XXII Jornada de Virologia - Virology meeting 2023* Barcelona, October 27, 2023. Talk.

17. Pérez Zsolt D. **In vitro platform to detect replication-competent monkeypox virus in swabs from asymptomatic and mildly symptomatic individuals**. *XXII Jornada de Virologia - Virology meeting 2023* Barcelona, October 27, 2023. Talk.

18. Bayón Gil Á. **Lack of HIV-associated pathogenicity in Viremic Non-Progressors is related with preserved TLR4 responsiveness**. *XVII Congrés de la Societat Catalana d'Immunologia.* Barcelona, November 2-3, 2023. Talk.

19. Bernad Rosa L. **Long-term immunodominant T-cell responses to S, Nsp3, NC, Env and M proteins of SARS-CoV-2 during hybrid immunity**. *XVII Congrés de la Societat Catalana d'Immunologia.* Barcelona, November 2-3, 2023. Talk.

20. Campos G. **Alfa-CD4 CAR T cellsproduce anin vitroeffective cytotoxic effect against CD4 T cells**. *XVII Congrés de la Societat Catalana d'Immunologia.* Barcelona, November 2-3, 2023. Poster.

21. Lázaro Díez M. **Dual blockade of PD-L1 and TIGIT pathways activated DCs and partially restores proinflammatory function in chronic viral infection**. *XVII Congrés de la Societat Catalana d'Immunologia.* Barcelona, November 2-3, 2023. Talk.

22. Pedreño López N. **Unvaccinated individuals with severe COVID-19 show a distinctive humoral response characterized by high levels of anti-S2 IgG and IgA antibodies and low avidity anti-RBD IgG responses**. *XVII Congrés de la Societat Catalana d'Immunologia.* Barcelona, November 2-3, 2023. Talk.

23. Rodríguez de la Concepción ML. **HIV Infection Induces Neutralization-Interfering Antibodies that Hamper the Function of Neutralizing Antibodies**. *XVII Congrés de la Societat Catalana d'Immunologia.* Barcelona, November 2-3, 2023. Talk.

24. Senserrich J. **CD4 T cell CD39 as a predictive biomarker of response to neoadjuvant chemotherapy in muscle invasive bladder cancer patients**. *ASEICA 40th Anniversary Congress.* A Coruña, November 14-16, 2023. Poster.

25. Malagrida R. **Xarxa de Long Covid per millorar l'impacte. Comunitat de pràctica d'impacte de CERCA**. Barcelona, November 17, 2023. Talk.

26. Brander C, Morón López S. **Impact of HIV infection on the metabolome and lipidome**. *XIV Congreso Nacional GESIDA.* A Coruña, November 26-29, 2023. Talk.

27. Campos González G. **Alfa-CD4 CAR-T cells produce an in vitro effective cytotoxic effect against CD4+ T cells**. *XIV Congreso Nacional GESIDA.* A Coruña, November 26-29, 2023. Poster.

28. Flores Santamaria M. **Functional characterization of the HIV Reservoir in Late Presenters on ART**. *XIV Congreso Nacional GESIDA.* A Coruña, November 26-29, 2023. Poster.

29. González Navarro I, Martínez-Picado J, Salgado Bernal M. **Taming the viral reservoir over three decades of advancements in HIV treatment**. *XIV Congreso Nacional GESIDA.* A Coruña, November 26-29, 2023. Talk.

Conference presentations

30. Martínez-Picado J, Salgado Bernal M. **Taller sobre erradicación vs cura funcional**. *XIV Congreso Nacional GESIDA.* A Coruña, November 26-29, 2023. Talk.

31. Pons Grífols A. **Ancestral envelope glycoproteins from elite controllers show decreased infectivity and higher exposure of BNAB epitope**. *XIV Congreso Nacional GESIDA.* A Coruña, November 26-29, 2023. Poster.

32. Trigueros-Peña M. **Deep phenotyping of immune cell populations in older people living with HIV identifies a persistent immune dysfunction that was not associated with increased comorbidities**. *XIV Congreso Nacional GESIDA.* A Coruña, November 26-29, 2023. Talk.

33. Malagrida R, Vives L. **Sana Ment: promovem la salut mental amb i per als joves**. *Jornades Anuals SOM360.* Barcelona, December 1, 2023. Talk.

34. Malagrida R. **El rol de la participació per millorar l'impacte en el marc de les Estratègies d'Open Science. Dimarts de Ciència Transformadora**. Barcelona, December 12, 2023. Talk.

35. Malagrida R, Pino M, Vives L. **Promoting collective impact with integrated, collavorative and decentralized approaches**. *6a Jornada Anual del CEEISCAT.* Barcelona, December 12, 2023. Talk.

36. Aguilar Gurrieri C. **A new and flexible vaccine platform for personalized cancer immunotherapy**. *Alicante Winter Immunology Symposium in Health.* Alicante, December 14, 2023. Poster.

37. Aguilar Gurrieri C. **Short alanine-based spacers included in poly-neoantigen vaccines improve peptide progressing and presentation to CD8+ T cells**. *Alicante Winter Immunology Symposium in Health.* Alicante, December 14, 2023. Poster.


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