IrsiCaixa

Institut de Recerca de la Sida

"la Caixa" Foundation

Generalitat de Catalunya
Departament de Salut

IRSICAIXA
SCIENTIFIC REPORT
2021

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IrsiCaixa

Letter from the director

The **IrsiCaixa AIDS Research Institute** was created as a private non-profit foundation in 1995 with the support of "la Caixa" Foundation and the Department of Health of the Autonomous Government of Catalonia. With Dr. Bonaventura Clotet as its director, it has become an international landmark and leading centre for research into the eradication of HIV/AIDS and related diseases.

The fact that both **IrsiCaixa** and the Fight AIDS and Infectious Diseases Foundation (FLS) are located in the Germans Trias i Pujol University Hospital makes for a unique model of collaboration between researchers, healthcare professionals, patients and community representatives. The transfer of knowledge among these social agents facilitates the search for new solutions and the translation of biomedical research to new clinical treatments.

In relation to its core work of eradicating AIDS, **IrsiCaixa** applies a combined approach based on five strategic lines: prevention, eradication and functional cure; the microbiome; innovative treatments and resistance to antiretrovirals; immunopathogenesis and other diseases.

The wide experience on HIV/AIDS provided a large expertise on the backbone of the human health, the immune system. This knowledge gathered during more than 25 years enables **IrsiCaixa** to face crucial challenges of human health, such as emerging infectious diseases, cancer, microbiome or ageing. Currently, and due to the COVID-19 pandemic, **IrsiCaixa** is putting so much effort into working in cooperation with other institutions to develop a coronavirus vaccine and drugs, and is participating in different clinical trials to reduce transmission and treat the progression of the disease.

A year after the beginning of the COVID-19 pandemic, in **2021** **IrsiCaixa** has been able to resume all its scientific activity and work at full speed on all its main lines of research; HIV/AIDS, emerging diseases, cancer and microbiome. Year after year we are proud to count among the world's leading HIV/AIDS research centres and to be able to expand our expertise, as well as face new biomedical challenges related to the immune system.

Notable progress in the HIV care and eradication line is the presentation of the HTI therapeutic vaccine phase I/IIa clinical trial results at the Conference on Retroviruses and Opportunistic Infections **2021** (CROI), one of the world's leading conferences in the field of HIV/AIDS. This therapeutic vaccine, promoted by AELIX Therapeutics and designed at **IrsiCaixa**, showed on march 2021 to be able to educate the immune system in order to improve the response against HIV; 40% of the vaccinated participants were able to remain off treatment during the 6 months of the study.

With the aim of finding solutions for the COVID-19 pandemic, during this past year significant efforts have been invested in studying the immune response against SARS-CoV-2. Thanks to our research we have been able to demonstrate that SARS-CoV-2 infection generates protective antibodies that are maintained beyond one year and, also, to confirm the importance of cell-mediated immunity to fight the severity of the disease. Another **2021** milestone in this field is the study of the immune response of people living in nursing homes. With this study **IrsiCaixa** observed that those aged more than 65 years who were vaccinated but have not undergone COVID-19 had low levels of protective antibodies at 3 months follow-up and suggested the possibility to readjust the vaccination schedule in this group of people in order to reinforce their protective response against the virus.

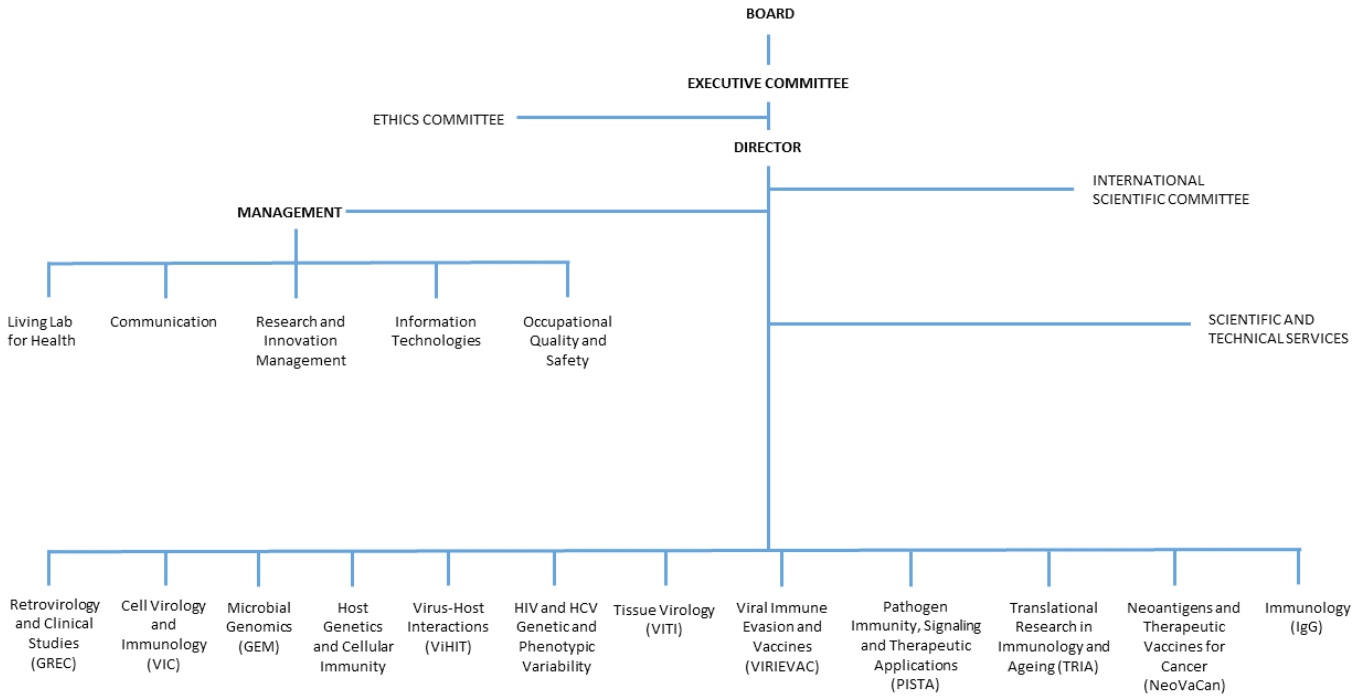
Along these lines, **IrsiCaixa** continued to develop a new vaccine against SARS-CoV-2 and contributed to the preclinical studies of HIPRA vaccine, which is currently in human clinical trials. Moreover, **IrsiCaixa** is strongly committed to the One Health concept and therefore is working on new pan-coronavirus strategies and the study of zoonotic diseases that will allow us to be prepared for future pandemics that may occur.

The significance of our research is reflected in the increase of projects awarded and the high impact of the scientific publications, which are the highest in Spain regarding infectious diseases. This productivity led to a considerable increase in the number of researchers working in **IrsiCaixa** and created the need to improve the facilities. To this end, **IrsiCaixa** carried out major works to extend its offices and facilitate a great working environment.

As I usually say, ideas are easy to get if there is talent, and I can assure that there is a lot of talent, but we need financial support to carry them out. This is precisely why I want to thank our key partners such as "la Caixa" Foundation, the Autonomous Government of Catalonia and Grifols for their sustained support to our research. All these milestones would not have been possible without their trust in our project and their continued enthusiasm on science.

Bonaventura Clotet
IrsiCaixa Director

Organizational Structure



Board

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Josep Maria Argimón Pallàs
Health Minister of the Autonomous Government of Catalonia

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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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Appointees of the Fundació Bancària Caixa d'Estalvis i Pensions de Barcelona "la Caixa" ("la Caixa" Foundation)

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Appointees of the Board of the Fight AIDS Foundation

Executive Committee

For "la Caixa" Foundation:

Àngel Font Vidal
President

Marta Casals i Virosque
Secretary

Esther Planas i Herrera

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

Jordi Barretina i Ginesta
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Director

Dr. Bonaventura Clotet

Manager

Lourdes Grau

Administration
Arnau Creus
Cristina Mesa
Penélope Riquelme

Information Technologies
Julián Eslava

International Scientific Committee

Dr. Brigitte Autran
Professor of Medicine (Immunology) at the Pierre and Marie Curie University (UPMC) (Paris, France) and Director of the Immunology Department and of the Biology and Medical Pathology Division of the Pitié-Salpêtrière University Hospital (Paris, France).

Dr. Daria Hazuda
Vice-President of Infectious Disease Identification at Merck and Scientific Director of the MRL Cambridge Exploratory Science Center (Massachusetts, USA).

Dr. Danniel 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. Jürgen Rockstroh
Professor of Medicine and Head of the Outpatient HIV Clinic at the University of Bonn (Germany).

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

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

Dr. Bruce Walker
Director of the Ragon Institute of MGH, MIT and Harvard University and researcher at the Harvard Howard Hughes Medical Institute (USA).


ACCESORIOS

Key Figures 2021

Total **staff**

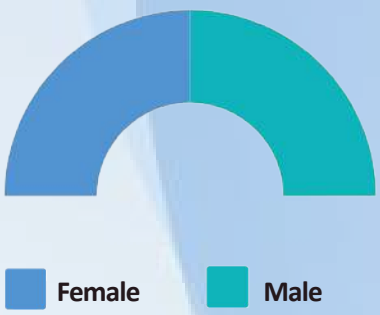
109

Sex

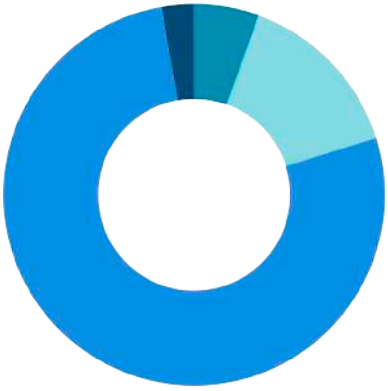
67% ♀

33% ♂

Principal investigators



Staff by **categories**



- **Scientific and technical Services** (5,5%)
- **Administration and research support** (14,7%)
- **Research** (77%)
- **Living Lab** (2,8%)

5 **Theses** read 2021

Susana Benet
Retrovirology and Clinical Studies (GREC) & Pathogen Immunity, Signalling and Therapeutic Applications (PISTA)

Sònia Pedreño
Tissue Virology (VITI)

Ferran Tarrés
Cell Virology and Immunology (VIC)

Cristina Gálvez
Retrovirology and Clinical Studies (GREC)

Bruna Oriol *(Dec 21)*
Host Genetics and Cellular Immunity

Projects awarded 2021

32

9 public

23 private

Projects active 2021

56

32 coordinated by IrsiCaixa

Publications 2021

80

912 Impact Factor

Highlights 2021

January

Marta Massanella, together with Lourdes Mateu, consolidate the Post COVID-19 Unit at the HUGTIP as coordinators.

Cristina Gálvez defends her thesis entitled *Identification of immunovirological factors that determine an extremely low viral load reservoir: approaching the cure of HIV-1 infection.*

February

Susana Benet defends her thesis entitled *Impact of a SIGLEC1 null variant on the pathogenesis of HIV-1 and Mtb infection*.

March

The **Host Genetics and Cellular Immunity** team presents at the CROI that the AELIX Therapeutics HIV vaccine achieves an immune response that improves viral control when antiretroviral treatment is interrupted.

April

Edurne Garcia-Vidal is awarded with a PERIS Personal de support contract from Generalitat de Catalunya.

May

GEM team develops the CovidTag website to monitor SARS-CoV-2 variants in Spain.

VIRIEVAC identify the presence of cellular immunity in SARS-CoV-2 infected individuals in the absence of antibodies.

Julia Garcia-Prado present at the COVID-19 vaccines–WHO consultation meeting on correlates of protection.

June

IrsiCaixa receives funding from La Marató to carry out 5 research projects on SARS-CoV-2.

GEM team presents at the IHMC Congress a pilot study to understand the difference between the intestinal microbiome of people who respond successfully to the HIV vaccine and those who do not.

A study with the participation of **NeoVaCan** team and which characterizes the changes produced in breast tumors during treatment with preoperative chemotherapy is published.

Sara Morón-López receives one of two global Gilead grants for HIV research.

July

PISTA team prove that CPC in mouthwashes is effective against different variants of SARS-CoV-2 thanks to its mechanism of action.

August

VIC team demonstrates the durability of the neutralizing humoral responses in COVID-19 patients.

The CoronAVI@S study, led by **TRIA** team, reveals that uninfected elders living in senior facilities require a boost of SARS-CoV-2 vaccine.

IGG team proves that high-dose intravenous immunoglobulins administration may be useful as a treatment for COVID-19 in people with severe symptomatology.

IrsiCaixa contributes to the success of the COVID-19 vaccine developed by HIPRA.

The **ViHIT** team work "SARS-CoV-2 Infection Modulates ACE2 Function and Subsequent Inflammatory Responses in Swabs and Plasma of COVID-19 Patients" is published in the journal Viruses.

September

Julià Blanco and **Roger Paredes** become members of the COVID-19 Scientific Advisory Committee of the Department of Health at the Generalitat de Catalunya.

A project to diagnose and monitor infectious diseases led by **Marta Ruiz-Riol** is among the selected projects by the CaixaResearch Validate 2021 call.

VIRIEVAC team takes part in the European Science Night.

October

Ferran Tarrés defends his thesis entitled *HIV-1 Virus-Like particles engineered to display a high antigen content. A step forward to a definitive candidate on HIV vaccine*.

November

Sònia Pedreño defends her thesis entitled *Modulaton of cellular pathways as a therapeutic strategy in HIV infection*.

RESEARCH GROUPS

Viral Immune Evasion and Vaccines (VIRIEVAC)

Projects awarded 2021

RBD Dimer recombinant protein vaccine against SARS-CoV-2
Funding: European Comission H2020
Start/end dates: 05.21 –
Research supervisors: **Christian Brander**, **Julia García-Prado**, **Julià Blanco**, **Jorge Carrillo, Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa, FLS, HIPRA

Incorporation of a new subject and new groups to the Consortium of the Centro de Investigación Biomédica en Red M.P. (CIBER)
Funding: ISCIII
Start/end dates: 01.22 –
Research supervisors: **Julia García-Prado**, **Javier Martínez-Picado**
Participating entities: IrsiCaixa, IGTP

Awards and achievements

Julia García-Prado, president of the internal Scientific Advisory board of the Germans Trias i Pujol Research Institute (IGTP)
Julia García-Prado, associate editor Frontiers immunology
Julia García-Prado, editor of HIV&Co
Julia García Prado, elected member of the EATRIS-Spain Scientific Advisory Board
Julia García-Prado, member of the Spanish AIDS Research Network (RIS)
Julia García-Prado, member of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)
Julia García-Prado, member of the Equality comisión at IrsiCaixa
Julia García-Prado, member of the Can Ruti Women in Science group

Presentation

The initial research interest of VIRIEVAC focused in the identification of viral and host factors associated with HIV-1 extreme disease phenotypes. These studies brought to the light limitations of antiviral CD8+ T-cell responses for the control of the disease. In the last years, these studies have shifted our research interest towards delineating the functional boundaries of viral pathogenesis and the role of antiviral CD8+ T-cell responses to control or eliminate viral infections. From a basic-translational perspective, VIRIEVAC combines tools from molecular virology, biochemistry and T-cell immunology and systems immunology focusing in the interface of host-pathogen interactions with the ultimate goal to design advance immunotherapies that restore antiviral immunity against HIV-1 and other chronic viral infections and contribute to the cure of these diseases. Moreover, during the COVID-19 pandemic VIRIEVAC move to the field of T cell immunity against CoV-2 infection. The group is currently working to understand cellular immunity in the context of natural infection and vaccination in healthy and immune compromised individuals. VIRIEVAC research lines during **2021**:

— Pathogenesis. To identify viral and host factors associated with disease outcome. The studies focus in various cohorts of HIV extreme disease phenotypes in both children and adults associated with natural control of infection (elite controllers and viremic non-progressors) but also with rapid progression of the disease (rapid progressors).

— Persistence, remission and cure. To delineate the functional boundaries of antiviral CD8+ T-cell responses in HIV infection to control or eradicate the reservoir and to translate these findings to other persistent viral infections. This line of research aims to characterize the mechanisms of CD8+ T-cell recognition of latently infected cells and understand "T cell immune dysfunction/exhaustion" both in active and latent infection as a major barrier to HIV remission and cure. This line has developed novel experimental models to monitor the reactivation and elimination of cells with latent HIV to identify new latency-reversing agents. Also, this line is research is working in the design of novel immunotherapeutics to reinvigorate or boost the immune system in the context of chronic infection.

— SARS-CoV2 cellular immunity. To characterize T cell immunity in SARS-CoV-2 infection in natural and vaccine-induced immunity in healthy and immune compromised individuals.

2021 Milestones

Milestones in the past year within **IrsiCaixa**'s strategic lines were as follows:

— Immunopathogenesis. 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 VNP that lost the virological control overtime. In collaboration with the Spanish AIDS Research Network (RIS) and the University of Oxford, this project has one manuscript published (Colomer et al, JVI 2021) and other in process of preparation.

— Prevention, eradication and functional cure. This research line has been successful and in continuous expansion during this year. This line of research is currently funded by several competitive project leaded by Dr Prado (PI17/00164, GL19/00079) and a newly funded project through la Caixa Health Research program (HR20-00218). Our ongoing work focus in the identification of long-term immune alterations despite long-term cART by the combination of single-cell cytofluorimetrics and single-cell bioinformatics. We have identified subset-specific irreversible alterations of Inhibitory receptors (IRs) in the composition of CD8+ T-cell memory and effector like subset. These changes are defined by the expression of TIGIT, TIGIT+TIM3 and postulate these markers for immunotherapeutics. In this line, we have the first prototypes tested in vitro and we are working to understand their mode of action. Besides, we continued our studies to evaluate the contribution of current ICB as novel curative strategies. We have also continued to understand the mechanism of TRIM5 in controlling the viral reservoir. This we have evaluated candidate molecules to evaluate the antiviral potential in the context of HIV-1 infected CD4+s. The experimental

model established will be extend to test novel and more potent molecules. These studies materialized in pipeline for single-cell analysis, several publications, 2 posters at CROI21 and 3 posters at the GESIDA conference. This line of research has led to successful national and international collaborations that are ongoing (Buzon's Lab, VHIR, Barcelona, Sekalys Lab, Case Western USA).

— SARS-CoV2 cellular immunity. VIRIEVAC has been 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. Also, VIRIEVAC continues participating in two COVID-19 consortia, the king and the prohepic19 cohort studies. During the last year, we have extended the collaboration to work on the immune monitoring of T cell responses in ongoing clinical trials for CoV-2 vaccine development. These studies materialized in several publications, 2 posters at CROI21 and several invited talks. This line of research has led to successful national and international collaborations.

Perspectives for 2022

— Consolidation and continuation of existing lines of research with the following objectives: 1) advance in the identification of mechanisms of non-pathogenic control of HIV, 2) to identify immunological signatures associated with dysfunctional antiviral responses, 3) to develop and validate candidate prototypes for novel immunoterapeutics, and 4) to evaluate small-molecules to control the HIV-1 reservoir; 5) Extend our research in SARS-CoV-2 T-cell immunity.

— 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 funding opportunities.

8 Ongoing projects

1 Invited talk to the WHO consultaion on COVID-19 vaccines

>10 Communications and presentations in conferences

Principal Investigator

Julia García Prado

Post-doc researchers
Julieta Carabelli
Athina Kilpeläinen

Pre-doc researchers
Óscar Blanch
Miguel Marín

Laboratory technicians
Esther Jiménez
Ruth Peña

Biostatistician
Dan Ouchi
Gabriel Felipe Rodríguez

Visiting Researcher
Eudald Vehí, MsC in Translational Medicine, University of Barcelona
Femke Walraven, Erasmus University Rotterdam, Netherlands

Grifols Projects

TRIM5 based gene-therapy approaches to inducible cellular resistance to HIV

Senior researcher: Julia García Prado

The CELLRE-HIV project aims to explore innate cellular sensors, particularly TRIM5 proteins, to generate novel gene therapy-based approaches to inducible cellular resistance to HIV-1. Proposed is the innovative concept by which a single protein has the autonomous potential to connect innate and adaptive immune functions and to induce cellular resistance to HIV-1.

Breaking the immune exhaustion barrier to recover antiviral immunity for a HIV-1 cure

Senior researcher: Julia García Prado

The RECOViR project aims to bring new insights to the immune regulation of chronic infections by IR, laying the basis for and proposing the proof-of-concept for novel immune therapeutics for a HIV-1 cure. RECOViR will also identify new tools for personalized treatments and potential biomarkers of responses to treatment. All these developments are expected to have far-reaching applications not only for chronic infectious diseases (HIV, HVB, TB or malaria) but also for cancer.

Microbial Genomics

Projects awarded 2021

Genomic epidemiology of SARS-CoV-2 in Catalonia: virologic surveillance and outbreak control
Funding: La Marató de TV3
Start/end dates: 09.21-09.23
Research supervisors: **Marc Noguera**
Participating entities: IrsiCaixa, IGTP

CovidSeq
Funding: YoMeCorono
Start/end dates: 01.21-12.21
Research supervisors: **Roger Paredes**, **Marc Noguera Julián**
Participating entities: IrsiCaixa

Awards and achievements 2021

Roger Paredes, member of the *Comitè Científic Assessor de la COVID-19* at the Health Department of the Generalitat de Catalunya

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.

Our main areas of interest are as follows:
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 cancer. b. In collaboration with the ACE foundation, research into human microbiome influence on the pathogenesis of Alzheimer disease.
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.

2020 milestones and perspectives for 2022

1. Microbiome
a. Description of early changes in the gut microbiome following HIV-1 infection (published as Rocafort et al, 2019, *Microbiome*). Recent HIV-1 infection is associated with increased faecal shedding of eukaryotic viruses, transient loss of bacterial taxonomic richness and long-term reductions in microbial gene richness. An important finding is that, despite early resilience to change, an HIV-1-specific signature in the gut bacteriome (featuring depletion of *Akkermansia, Anaerovibrio, Bifidobacterium* and *Clostridium*) previously associated with chronic inflammation, CD8+ T cell anergy and metabolic disorders is eventually identified in chronically HIV-1-infected subjects. b. 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. c. Early-stage development of a gut-on-a-chip device to evaluate the mechanistic effects of the microbiota on the immune system. d. Organization of several key microbiome meetings, including the International Human Microbiome Consortium Congress 2020 (Barcelona), the Barcelona Debates on the Human

Microbiome and the International Workshop on Microbiome in HIV Pathogenesis, Prevention and Treatment.

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.

1 Website developed by the group to monitor the SARS-CoV-2 variants in Spain

2 Article published at the New England Journal of Medicine

1 Article published at The Lancet HIV journal

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: 1. 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); 2. 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); 3. 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). 4. 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).

Principal investigator
Roger Paredes

Associate researcher
Marc Noguera

Post-doc researchers
Alessandra Borgognone
Maria Casadellà
Francesc Català
Aleix Elizalde

Pre-doc researcher
Carlos Blázquez

Programmer
Carmen Fuentes

Laboratory technician
Mariona Parera

Grifols Projects

Microbiome Triggers of Alheimer Dementia (MIND)

Senior researcher: Roger Paredes

— Characterization of the composition and functional potential of the faecal microbiome in subjects with cognitive problems but not cognitively impaired, subjects with mild cognitive disability, and subjects with Alzheimer disease.
— Evaluation of longitudinal microbiome changes over one year in subjects with cognitive problems but without cognitive impairment.
— Biological evidence that the gut microbiome contains activators and/or accelerators of Alzheimer disease.

The gut microbiome in HIV infection: from microbial function to immune therapeutics (GIFT)

Senior researcher: Roger Paredes

— Characterization of species changes in the microbiome in SIV-infected Rhesus monkeys as a model to understand HIV-1 infection effects on the gut microbiome.
— Characterization of the metatranscriptomic profile of the gut during a kick-and-kill strategy for treating HIV.
— Mouse model biological evidence of the relationship between microbiota composition and T-cell vaccines.

Host Genetics and Cellular Immunity

Awarded projects 2021

Eclipse Ts2R-FL Inverted Research Microscope
Funding: Dormeur Foundation, Vaduz
Start/end dates: 07.21-06.24
Research supervisor: **Christian Brander**
Participating entities: IrsiCaixa

The epigenetic cascade of neurotropic viral infections
Funding: Spanish Ministry of Science and Innovation
Start/end dates: 09.21-08.24
Research supervisor: **Christian Brander**
Participating entities: IrsiCaixa, FLS

Boosted Flow Cytometry as a Diagnostic and Monitoring Tool for Virus/Pathogen specific T-Cell immune Profiles in HIV, TB and COVID Diseases
Funding: CaixaImpulse Validate
Start/end dates: 01.22-12.24
Research supervisors: **Marta Ruiz-Riol**
Participating entities: IrsiCaixa

RBD Dimer recombinant protein vaccine against SARS-CoV-2
Funding: European Comission H2020
Start/end dates: 05.21 –
Research supervisors: **Christian Brander**, **Julia García-Prado**, **Julià Blanco**, **Jorge Carrillo, Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa, FLS, HIPRA

Doctoral theses

Title: Systems biology for the identification of epigenetic biomarkers and host factors associated with HIV-1 control
Author: **Bruna Oriol**
To be presented on December 2021

Awards and achievements

Marta Ruiz-Riol, awarded as first IrsiCaxia researcher the prestigious CaixaImpulse Validate award for the further commercial development of the Boosted Flow Cytometry technology platform
Christian Brander, obtained funding for equipment purchase for IrsiCaixa from the Foundation Dormeur
Beatriz Mothe, invited to present the emerging data on the therapeutic HIV vaccine trial AELIX-002 at the Late Breaker session of the CROI 2021 Meeting
Luis Romero, awarded with the New Investigator Awards of the HIVR4P Conference for his outstanding research

Presentation

Cellular immunity is a critical component of the host defense against viral infections. Our group aims to understand the regulatory mechanisms (including T cell fate decisions that drive differentiation, immune checkpoints and epigenetics) that regulate this cellular immunity in different patient populations. This includes people with early HIV infection, controlled and uncontrolled HIV disease, as well as people with or without HIV infection that received solid organs transplants. In our investigation, we also include individuals that have been diagnosed with a virus driven cancer, 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. We are exploring different cellular pathways, host genetics and antigen-specificity of the antiviral immunity to identify immune correlates of virus control. Since several of these infections are associated with the development of neurological disease, we are also working to identify markers associated with neurofunctional defects related to these viruses.Our studies also include the analysis of the T cell receptor repertoires in the cellular immune responses against the different viruses. Through these studies, we aim to determine the molecular ontogeny of T-cell immune responses and understand the transcriptional programme of these cells in order to guide therapeutic vaccination strategies to induce robust, effective and long-lasting antiviral immunity. We also study possible factors that regulate HCV (Hepatitis C Virus) evolution in HIV-infected patients who have undergone liver transplantation and evaluate immune system determinants related to kidney organ rejection in patients with HIV infection who have received a transplant from a HIV-infected organ donor. Finally, we continue work in clinical trials that test different therapeutic HIV vaccine concepts. This includes several ongoing clinical trials that use autologous immunogen designs or a combination of T- and B-cell immunogens and clinical and pre-clinical studies that test the role of the microbiota on the outcome of therapeutic vaccination.

2021 Milestones and perspectives for 2022

During **2021**, we have seen the unblinding of the ALX-002 clinical trial that uses the HTI immunogen and vector combinations developed at **IrsiCaixa**. This clinical trial has achieved a durable viral suppression in 40% of the vaccinated individuals that did not possess a beneficial HLA genetics. These are the most significant results in the field of HIV therapeutic vaccination to date and we are continuing the development of these vaccines in collaboration with our spin-off AELIX Therapeutics as well as 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 use and has the potential to further strengthen the antiviral immunity in vaccinated individuals so that more individuals can control the virus for longer and to lower levels, without taking antiretroviral treatment. In parallel, and in the context of the EAVI 2020 consortium (European AIDS Vaccine Initiative), we have started a study in Non-Human Primates (NHP) that combine our vaccine against T cells with some B cells immunogenic constructs (SOSIP). This study has shown an interesting modulation of the virus-specific B cell responses in the presence or absence of a T cell immunogen and will continue with booster vaccinations into 2022. In addition, in **2021** we have published the results from CUTHIVAC-003 clinical trial, performed in Lima (Perú), which compared the immunogenicity created by the intramuscular administration with the transcutaneous administration of a vaccine based on MVA-B. In this trial we also asked how the in vivo immunogenicity of these vaccines depends on the microbiota in the vaccinated individual as well as how the epigenetic landscape and gene expression signatures in HIV infection impact response to vaccination. These results constitute the base for a preclinical study that we are undergoing within the MISTRAL project, in which we have removed the natural murine microbiota before vaccination with HTI vaccines. These data show that the natural microbiota is critical in vaccine take and the development of strong cellular immunity. Currently, we are conducting experiments where the natural microbiota is being replaced by specific bacteria consortia with the intention to drive functionally different immune responses to the vaccine. During **2021**, the analysis of host genetics,

especially polymorphisms in the HLA region, have yielded surprising results. In close collaboration with structural chemists and experts of innate immunity at UC Davis, we were able to explain how minor differences in HLA-E molecules may impact the function of the adaptive as well as innate cellular immune response to HIV infection and how this could translate into exhausted immune phenotypes. These analyses also let us identify direct links between the presence of follicular CD8 T cells and improved humoral immunity to HIV infection; both insights that could guide preventive as well as therapeutic interventions for this infection. In **2021**, we have also completed the analysis of the risk factors associated with transplanted liver organ failure among groups with HIV and/or HCV infection. These analyses are based on the large Spanish cohort of liver transplantation, that includes more than 1000 liver transplanted patients, of which more than 270 individuals are HIV infected. The identified risk factors for organ rejection included HIV infection, a high proportion of CD4/8 T-cells, high HLA class I incompatibility between donor and recipient organs, as well as high levels of alloreactivity. The pandemic caused by SARS-CoV-2 has led us to invest significant efforts to study the epigenetic implications in patients with COVID-19, particularly in individuals with persistent COVID who have neurological manifestations. We have collaborated with Stanford University, UC Davis and other entities in Barcelona to explore possible epigenetic mechanisms by which the effects of acute SARS-CoV-2 infection persist over time, and how these events may affect neurological functions. These analyses will go hand in hand with studies in HIV infection, focusing on the long-term neurological consequences of HIV infection. Data generated over the past year have identified several markers related to the brain reservoir of HIV and HIV disease-related neuro-impairment. We have developed now in vitro models that will be used over the next year to identify possible new therapeutic targets for these disorders.

4 Conferences in which group members gave invited talks

20 Publications from the group

15 Ongoing projects

Principal investigator
Christian Brander

Associate researcher
Beatriz Mothe

Post-doc researchers
Samandhy Cedeño
Anuska Llano
Alex Olvera
Marta Ruiz-Riol
Sandra Silva
Cristina Peligero

Pre-doc researchers
Bruna Oriol
Luis Romero
Clara Duran

Clinical cohort coordinator/clinical researcher
Josep Coll

Laboratory technician
Tuixent Escribà

Grifols Project

Identification of Epigenetically regulated plasma factors associated with neuro-degeneration (Neuro-HIV)

Senior researcher: Christian Brander | Principal investigator: Marta Ruiz Riol

About half of the HIV population will suffer some form of neurological deficiencies due to the viral infection. This is even more pronounced now as the HIV infected population grows older, thanks to the wide availability of antiretroviral medication. Our group is interested in identifying peripheral blood plasma factors associated with HIV control and which have a physiological links to neurofunction. During the last year, we have identified the Sirtuin 2 (SIRT2), as the most relevant and strongly associated factor to HIV viral loads in plasma and the HIV pro-viral levels in peripheral blood mononuclear cells. The SIRT2 levels also showed a strong correlation with different markers of neuronal damage, as well as the levels of brain-derived neurotrophic factor, the Microtubule Associated Protein Tau and the Neurofilament-linked polypeptide (NFL) in plasma as well as in the cerebrospinal fluid and in brain tissue of HIV-infected individuals. We have now been able to use described inhibitors of SIRT2 to block HIV replication in vitro models, including glial cells, and have shown that SIRT2 blockade is also reducing the reactivation of virus from the latent viral reservoir. The observation that SIRT2 levels correlate with the degree of the brain involution and reduced neuronal function, are in line with the use of SIRT2 as a therapeutic target in other brain diseases, including Alzheimer's Disease and may offer novel ways to clinically manage HIV related neurodegeneration in the future.

Virus-Host Interactions (ViHIT)

Projects Awarded 2021

In vitro antiviral screening of compounds provided by Pharma Mar on Ebola virus entry and on the replication of HIV-1, Zika and SARS-CoV-2
Funding: PharmaMar
Start/end dates: 01.21- 12.22
Research supervisors: **Ester Ballana**, **Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa

Validation of a lateral flow system for the detection of structural proteins of SARS-CoV-2
Funding: LincBiotech S.L.
Start/end dates: 02.21- 02.22
Research supervisors: **Ester Ballana**, **Marta Massanella**
Participating entities: IrsiCaixa

Grants Awarded 2021

PERIS support personnel
Funding: Department of Health of Generalitat de Catalunya
Participating entities: IrsiCaixa
Start/end dates: 07.21- 12.23
Student granted: Edurne García-Vidal
Research supervisor: **Ester Ballana**

Awards and Achievements

Best oral presentation in the 51st Spanish Congress of Nephrology for the work *ACE2 function and SARS-CoV2 virus,* in collaboration with IMIM Nephrology Research Group.
SAMHD1 confers resistance to platinum-based drugs through modification of DNA damage response by Gutierrez-Chamorro et al. was selected as one of the Best Scoring e-Posters during EACR 2021 Virtual Congress.
Ester Ballana, associate editor of the journal Frontiers in Virology, section Antivirals and Vaccines.
Ester Ballana, member of Internal Scientific Advisory Board of IGTP.
Ifeanyi Ezeonwumelu, best oral presentation award at the XX Jornada de Virologia – Virology meeting 2021 – 3rd Symposium on Coronavirus Research

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 levels, such as 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 viral infections

We have been working in the characterization of HIV-host interactions at different stages of virus replication, focusing especially on describing cell proliferation mechanisms associated with HIV-1 replication capacity in order to identify cell targets that affect cell cycle progression and HIV+ cell proliferation. Our group is currently working on a set of cellular factors at different stages of development, ranging from identification and validation of new targets to the monitoring of drugs approved for treatment. Once validated, these cellular factors potentially become targets for the development of new antiviral therapies.

Since April 2020, our group has also focused on understanding SARS-CoV-2 infection and its associated pathogenesis. A method for the quantification of SARS-CoV-2 viral load in COVID-19 patients has been developed. Work has also been ongoing on 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 new therapeutic strategies against viral infections.

2. Innate immune function in viral infections and cancer

The mechanisms that control the interface between the metabolism of nucleic acids and their detection by the immune system determine the onset and treatment of diseases like viral infections and cancer. Our group is currently working on the development and validation of SAMHD1 as a biomarker of therapeutic response to the nucleoside analogues currently used to treat viral infections and cancer. It is also working on describing and characterizing key cellular targets that determine the antiviral and antitumoral immune response, with a particular emphasis on identifying novel immunotherapeutic strategies.

2021 Milestones

Our group achieved the following milestones:

— Identification of novel cell factors involved in viral infections. Our research continued into cellular factors that affect viral infections, with special focus on the role of innate immune factors as putative therapeutic targets for acute and chronic viral infections.

— Advances in research into the SARS-CoV-2 infection. Our group developed a method for determining viral load in COVID-19 patients that allowed the quantification of more than 5000 samples, including patients from different study cohorts, distinct tissues from animal models and evaluation of in vitro infection on cell lines and 3D cultures. In collaboration

with Dr Marta Riera from the IMIM Nephrology Department, our group also developed a method to study virus-receptor interaction, that led to our first joint publication (Gutierrez-Chamorro et al., Viruses 2021).

— Identification and validation of prognostic and predictive biomarkers in cancer patients. In collaboration with the ICO-Badalona B-ARGO research group, our group finalized a retrospective study in patients with different types of cancer that evaluated the predictive and prognostic value of SAMHD1. In collaboration with Dr Mireia Margelí, head of the ICO-Badalona Breast Cancer Functional Unit, our group also has started the immunophenotypic characterization of breast cancer patients treated with CDK4/6 inhibitors.

Perspectives for 2022

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.

Consolidation of the research groups and improved competitive funding will also represent core objectives for 2022.

1 Group of talented young researchers pursuing a common research goal

6 Funded competitive contracts for researchers ongoing

4 Invited talks in scientific meetings

Principal investigator
Ester Ballana

Associate Researcher
Roger Badia

Post-doc researchers
Edurne García-Vidal
Eva Riveira-Muñoz

Pre-doc researchers
Ifeanyi Jude Ezeonwumelu
Eudald Felip
Lucía Gutiérrez

Grifols Project

New Cell Targets for HIV cure (NeCeTar)

Senior researcher: Ester Ballana

Antiretroviral therapy is effective in reducing circulating viral load at undetectable levels but does not cure HIV infection. Although promising, current "shock and kill" strategies aimed at reactivation latent HIV and subsequent clearance of infected cells, have not succeed in providing a functional cure for HIV infection. Based on the need of novel agents and strategies to achieve an efficient clearance of the latent reservoir, the objectives of the project are:

— To identify new cell targets associated to HIV-1 latency establishment and reactivation. An increased understanding of the mechanisms of HIV latency, persistence and reactivation will provide novel targets for drug development.

— To identify chemical compounds that reactivate latent HIV-1 and/or limit persistence. Once identified, the mechanism of action of novel latency reversing agents will be characterized.

— To propose and validate novel therapeutic strategies for HIV cure, alone or in combination with current treatments.

Retrovirology and Clinical Studies (grec)

Projects awarded 2021

EU Research Scholars Program in HIV
Funding: GILEAD
Start/end dates: 07.21 - 06.23
Research supervisor: **Sara Morón-López**
Participating entities: IrsiCaixa

Discovery of novel inhibitors of HIV-1 RNA biogenesis based on the inhibition of the ribonucleoprotein RRE-Rev
Funding: Generalitat Valenciana
Start/end dates: 01.21- 11.24
Research supervisors: **Javier Martínez-Picado**, José Alcamí, Vicente Marchán
Participating entities: IrsiCaixa, ISCIII, University of Barcelona, Catholic University of Valencia

Reversing Immune Dysfunction for HIV-1 eradication
Funding: National Institutes of Health (NIH)
Start/end dates: 08.21- 04.26
Research supervisors: **Javier Martínez-Picado**, **María Salgado**
Participating entities: IrsiCaixa, Emory University, University of Southern California, Scripps Research College

Elimination of the HIV latent reservoir by using novel anti-CD4 chimeric antigen receptor T cells
Funding: Spanish Ministry of Science and Innovation
Start/end dates: 09.21- 08.24
Research supervisor: **María Salgado**
Participating entities: IrsiCaixa, Josep Carreras Leukaemia Research Institute

High-throughput synthetic biology platform for surveillance and therapeutics development against current and future SARS-Coronaviruses
Funding: La Marató de TV3 Foundation
Start/end dates: 07.21- 07.24
Research supervisors: **María Salgado,** Rafael Sanjuan
Participating entities: IrsiCaixa, IBE (CSIC:UPF), UPF

Doctoral theses

Title: Identification of immunovirological factors that determine an extremely low viral reservoir: approaching the cure of HIV-1 infection
Author: **Cristina Gálvez**

Title: Impact of a SIGLEC1 null variant on the pathogenesis of HIV-1 and Mycobacterium tuberculosis infection
Author: **Susana Benet**

Awards and Achievements

Sara Morón-López, granted with an EU Research Scholars Program in HIV

Presentation

Our group focuses on characterizing the immune-virological mechanisms of viral pathogenesis in human diseases, including HIV-1, Ebola virus, arenaviruses and, most recently, SARS-CoV-2. Our translational programme has the ultimate goal of investigating potential new viral therapeutic strategies, especially in the HIV/AIDS field, through both 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. As a result of the COVID-19 pandemic, we have extended our research to the pathogenesis of SARS-CoV-2, implementing organoid models to assess viral infection and inflammatory response.

2021 Milestones

1. HIV-1 cure

— Award of the Martin Delaney Collaboratory "Reversing Immune Dysfunction for HIV Eradication" by the National Institute of Health (2021-26), with 10 other international partners.
— Award of the project "Elimination of the HIV latent reservoir by using novel anti-CD4 chimeric antigen receptor T cells" by the Spanish Ministry of Science and Innovation (2021-23).
— Award of the project "Discovery of novel HIV-1 RNA biogenesis inhibitors based on disrupting the RRE-Rev ribonucleoprotein", by the Generalitat Valenciana (2021-23), with 3 other partners.
— Article "VIP-SPOT: an innovative assay to quantify the productive HIV-1 reservoir in the monitoring of cure strategies" in mBio. A patent application of the assay was also filed.
— Article "Atlas of the HIV-1 reservoir in peripheral CD4 T cells of individuals on successful antiretroviral therapy" in mBio.
— Article: "ABX464 decreases the total HIV reservoir and HIV transcription initiation in CD4+ T cells from HIV-infected ART-suppressed individuals" in Clinical Infectious Diseases.
— Two articles exploring the role of the HIV-1 reservoir in pediatrics, in Journal of Infectious Diseases and AIDS.
— Article "Provirus reactivation is impaired in HIV-1 infected individuals on treatment with dasatinib and antiretroviral therapy" in Biochemical Pharmacology.

2. Role of myeloid cells in viral pathogenesis

— Article "Dissemination of Mycobacterium tuberculosis is associated to a SIGLEC1 null variant that limits antigen exchange via trafficking extracellular vesicles" in Journal of Extracellular Vesicles.
— Article "Lectins enhance SARS-CoV-2 infection and influence neutralizing antibodies" in Nature.

3. Extreme HIV infection phenotypes

— Article "Viral and cellular factors leading to the loss of CD4 homeostasis in HIV-1 viremic nonprogressors" in Journal of Virology.

4. SARS-CoV-2

— Award of the project "Neurodegeneration triggered by SARS-CoV-2: brain organoids as an analytical and predictive model" by the Marató of TV3 (2021-23), with 2 other partners.
— Award of the project "High-throughput synthetic biology platform for surveillance and therapeutics development against current and future SARS-coronaviruses" by the Marató of TV3 (2021-23), with 2 other partners.

— Award of the project extension "Examining vascular dysfunction related to SARS-CoV-2 infection using human in vitro vessels" by Merck (2021-22), with another partner, as part of the program "3D human organoids for biomarker identification and treatment assessment in COVID-19 (3D4COVID)".
— Article "Lectins enhance SARS-CoV-2 infection and influence neutralizing

antibodies" in Nature.
— Article "Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths" in Science Immunology, as part of the COVID Human Genetic Effort consortium.

Perspectives for 2022

— Understanding how to measure the reservoir in blood and tissues.
— Exploring the host and viral factors that determine viral persistence and reservoir dynamics.
— Developing strategies to achieve substantial reductions in the size of the viral reservoir, specially of the rebound-competent reservoir.
— Developing immune restorative strategies for durable control of viral rebound by defining host and viral determinants for viral control in absence of antiretroviral therapy.
— Identifying and characterizing small molecules with new mechanisms of action that specifically block the biogenesis of the viral RNA.
— Optimizing humanized αCD169 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.

6 Research projects have been awarded to the group

16 Peer-review scientific publications

2 Doctoral Theses have been defended

— Designing nanotechnological devices based on the binding capacities of CD169 to capture enveloped viruses as well as extracellular vesicles.
— 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.
— Digging into the functional and mechanistic basis of SARS-CoV-2 infection by using organoid models.

Principal investigator
Javier Martínez-Picado

Associate researcher
María Salgado

Post-doc researchers
Jakub Chojnacki
Sara Morón-López
Patricia Resa-Infante

Pre-doc researchers
Ángel Bayón
Silvia Bernal
Cristina Gálvez
Fernando Laguía
Xabier Muñiz

Laboratory technicians
Itziar Erkizia
Mª Carmen García
Mª Carmen Puertas

Cohorts and project management
Judith Dalmau

Biostatistician
Víctor Urrea

Grifols Projects

Cutting edge strategies on HIV cure (VIROCURE)

Senior researcher: J. Martínez-Picado
Principal investigator(s): María Salgado and Maria Carmen Puertas
This project has the following aims:
— To develop and evaluate new improved-sensitivity technologies (VIP-SPOT, mVOA, etc) to detect and quantify viral persistence in blood and tissue samples.
— To design and evaluate medical strategies aimed at achieving an ART-free HIV remission (i.e. therapies combining new antiviral compounds and immune-modulators to be tested in our unique cohorts with extremely low viral reservoirs).

New techonologies mimicking virus-cell interaction to fight infectious diseases (SIGTECH)

Senior researcher: J. Martínez-Picado
Principal investigator(s): Patricia Resa-Infante
In collaboration with: Nuria Izquierdo-Useros
— To generate a humanized version of the best murine blocking monoclonal antibody (mAb) against the Siglec-1 protein, which is able to block HIV capture and trans-infection as well as Ebola viral-like-particle capture and fusion, essential processes for infection on primary myeloid cells.
— To develop nano-vehicles using clinically approved biomaterials that allow construction of nanoparticles for therapeutic purposes. We will expand our studies to see if glycol-engineering of nanoparticles designed for clinical use can induce the reactivation of HIV-1 latency and trigger immune antiviral control.
— To develop a detection platform based on Siglec-1 receptor capacity to diagnose the presence of different enveloped viruses, and to isolate exosomes in liquid biopsies from cancer patients.

HIV and HCV Genetic and Phenotypic Variability

Awards and Achievements

Miguel Ángel Martínez, associated editor of Frontiers in Microbiology.
Miguel Ángel Martínez, editor of Microbiology Spectrum
Miguel Ángel Martínez, editorial board member of Viruses
Miguel Ángel Martínez, invited editor for the Viruses Special Issue 'HIV-HCV Co-infection"

Presentation

The research interests of our group are focused in understand the molecular mechanisms implicated in human viruses 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. miRNAs 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 hypothesized that an alternative antiviral agent is to target specific miRNAs associated with SARS-CoV-2 infection and subsequent manifestation of COVID-19.

2021 milestones

1. Synonymous genome recoding of HIV-1

To unravel the underlying mechanism implicated in virus attenuation by synonymous codon pair deoptimization, we optimized and deoptimized the codon pair bias of the HIV-1 envelope gene (Jordan-Paiz, Franco and Martinez Cells 2021). We found that envelope CPB deoptimization did not always generate attenuation, whereas codon pair bias optimization attenuated virus replication in MT-4 cells. Furthermore, virus attenuation correlated with reduced envelope protein production but not with decreased viral RNA synthesis. Remarkably, in our model, increasing the number of CpG dinucleotides in the 5' end of envelope did not reduce the replication capacity of HIV-1. These results indicate that factors other than codon pair bias or CpG content may have affected the viral fitness of the synonymously recoded study variants. Our findings provide evidence that codon pair bias recoding-associated attenuation can affect translation efficiency. Moreover, we demonstrated that an increased number of CpGs in the 5' end of HIV-1 envelope is not always associated with reduced virus replication capacity. Although codon pair deoptimization has been mainly used for virus attenuation, our results expand the utility of this approach for other biotechnological applications—for example, to attenuate a vector sequence. This method has the potential to add synergistic mechanisms to other approaches to sequence optimization or deoptimization.

2. miRNAs as disease biomarkers and antiviral targets

To explore the capacity of plasma circulating miRNAs for predicting liver fibrosis progression before signs of fibrosis (i.e. stage F0–1) or other clinical parameters were evident, we performed a large-scale deep sequencing analysis of small RNA expression on plasma samples from HIV-1/HCV coinfected patients that showed no liver fibrosis (fibrosis stage F0–1) (Franco, Buccione et al AIDS 2021a). After a mean of 10.3 years, 57% of these patients developed liver fibrosis (stage F2–4) and 43% remained without signs of liver fibrosis. Importantly, we identified a signature of seven miRNAs: 100–5p, 192–5p, 99a-5p, 122–5p, 125b-2–3p, 1246 and 194–5p, which were highly correlated with progression to liver fibrosis. Our results demonstrated that circulating miRNA levels had potential in predicting liver fibrosis progression before the clinical

detection of liver fibrosis or significant clinical signs, such as elevated liver transaminases or platelets. In addition, in this cohort of HIV-1/HCV coinfected patients we also identified that host single nucleotide polymorphisms in PNPLA3, ADAR-1 and IFIH1 are associated with advanced liver fibrosis (Franco, Horneros et al AIDS 2021b). Overall, our results might facilitate predictions of liver injury progression in patients with HIV-1-infections.

To determine whether circulating plasma miRNAs can be possible biomarkers of COVID-19 inflammation, coagulation, lung disease and other organ disease progression (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 (Franco et al manuscript in preparation 2021). 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.

Perspectives for 2022

In the next future, we will continue to study the molecular basis of how HIV-1 genome synonymous variability affects virus pathogenesis. We also expect to further explore the interactions between host miRNAs and SARS-CoV-2, which are multifaceted. Specifically, we aim: 1) to study the impact of innate response, e.g. ZAP, Schlafen 11, on shaping HIV-1 nucleotide content and virus replication capacity and evolvability, 2) to characterize the mechanisms of induction of the immune response associated with the HIV-1 RNA genome nucleotide content, 3) to correlate blood levels of miRNAs and SARS-CoV-2 viral load and 4)to identify miRNAs that may directly regulate and drive a COVID-19 response. Specific miRNAs may represent an effective antiviral therapeutic.

10 Published peer-reviewed and indexed papers

2 Ongoing projects on HIV-1, HCV and SARS-CoV-2

Principal investigator

Miguel Ángel Martínez

Post-doc researcher
Sandra Franco

Cell Virology and Immunology (VIC)

Projects awarded 2021

Identification and validation of early biomarkers of acute COVID-19 to predict evolution
Funding: La Marató de TV3 Foundation
Participating entities: IrsiCaixa, IRB Barcelona, Parc Taulí Foundation
Start/end dates: 07.21 - 07.24
Research supervisor: **Julià Blanco**

Development of therapeutic antibodies against SARS-CoV-2
Funding: Glòria Soler Foundation
Participating entities: IrsiCaixa
Start/end dates: 07.21- 06.22
Research supervisor: **Julià Blanco**

Impact of HIV envelope function and antigenicity on elite control of HIV replication
Funding: ISCIII
Participating entities: IrsiCaixa, ISCIII, IBIS, University of La Laguna
Start/end dates: 01.21- 12.23
Research supervisors: **Julià Blanco**, Concepción Casado

Immunity against SARS-CoV-2
Funding: YoMeCorono crowdfunding campaign
Participating entities: IrsiCaixa
Start/end dates: 01.21- 12.23
Research supervisor: **Julià Blanco**

Engineered enveloped VLP's with high-density antigen coating. A proof of concept for their application in animal health. FeLV vaccines
Funding: HIPRA
Participating entities: IrsiCaixa
Start/end dates: 12.21- 05.22
Research supervisor: **Julià Blanco**

RBD Dimer recombinant protein vaccine against SARS-CoV-2
Funding: European Comission H2020
Start/end dates: 05.21 –
Research supervisors: **Christian Brander**, **Julia García-Prado**, **Julià Blanco**, **Jorge Carrillo, Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa, FLS, HIPRA

Doctoral theses

Title: HIV-1 Virus-Like Particles engineered to display a high antigen density
Author: **Ferran Tarrés**

Awards and Achievements

Julià Blanco, member of the *Comitè Científic Assessor de la COVID-19* at the Health Department of the Generalitat de Catalunya

Presentation

Our group maintain the focus on the HIV envelope glycoprotein (Env) as the main target of preventative vaccines and a major target for treatments against HIV, seeking for optimal strategies to functionally cure or eradicate AIDS. Our work on HIV vaccines is based on a novel highly immunogenic VLP platform, while therapeutic approaches are based on the design of synthetic antibodies with improved antiviral activity. Both approaches have been extended to other relevant infectious diseases for human health and to cancer immunotherapies. In addition, the new SARS-CoV-2 pandemic has been a relevant additional focus of our research. In this highly dynamic research context, our group has maintained three main research lines, balancing the different objectives:

1. Translating knowledge on the HIV envelope glycoprotein (Env) and its humoral response to the development of preventative HIV vaccines
a) Analysis of the functions of HIV Ennv and the natural responses elicited by infection. b) This work has allowed for the developement of new antigens based on specific Env sequences (in collaboration with the ISCIII and the BSC) that will be tested as candidate vaccines. c) Synthetic antibody development (**AlbaJuna Therapeutics**) has completed a study in non-human primates and startin GMP production for a Phase I clinical trial in humans is in progress.

2. Extending the VLP vaccine platform to other diseases
a) FeLV vaccines, in collaboration with HIPRA. We have translated our VLP technology to a different retrovirus. b) Our collaboration with MSD on respiratory virus vaccines has completed the first immunogenicity assay of our VLPs in a mice model. c) In collaboration with Leticia de Mattos Arruda, our cancer vaccines project aims to generate immune responses to cancer has new animal models and a vaccine design pipeline (in collaboration with the BSC) already in place.

3. COVID-19 research
a) Our research, in the hallmark of the CBIG consortium, has focused on understanding the humoral immune response to SARS-CoV-2 and understanding its protective role. A pseudovirus neutralization assay covering different variants of the virus is already in place. b) New synthetic antibodies against SARS-CoV-2 have been developed and tested in vitro and in vivo. Antibodies cover all variants of the virus. c) In collaboration with the company Nesapor, we have developed a new rapid antigen test with high sensitivity and specificity.

2021 Milestones

1. A wide collaborative network to neutralize SARS-CoV-2
The development and optimization of an assay to quantify the levels of neutralizing antibodies against SARS-CoV-2 in biological samples has been one of our priorities in **2021**. The method has been extended to the different viral varints (alpha, beta, gamma, delta mu and lambda, and also the latest delta+ or AY.4 variant). This unique platform has allowed us to create a wide collaborative network and we have tested samples from Clinic Hospital, Bellvitge Hospital, Univertitat de Lleida, Progenika, ISGlobal, Leitat, Grífols, HIPRA, among other.

2. COVID vaccine research
Of particular interest, the neutralizing capacity of plasma samples is the main parameter measured in vaccine responses. Therefore, our expertise has been useful for the development of vaccines in the CBIG consortium (led by Jorge Carrillo). Our neutralization assay has been also Key in the Phase I clinical trial developed by HIPRA with its candidate vaccine. All samples from this trial have been analyzed in our laboratory. Our technology will be transferred to HIPRA to be used in further clinical trials (Phases II and III).

3. HIV and other pathogens
While much effort needs to be invested in COVID-19 research, HIV therapies continue to be a priority. In this regard, AlbaJuna has demonstrated antiviral activity of its lead candidate in non-human primates. The COVID-19 pandemic has strongly impacted VIC research areas has led to identification of the following high-priority research lines:

a) Vaccine approaches, with the VLP vaccine platform operating as the basis for our work on generating new basic HIV knowledge (FIS PI20/00093 project), RSV vaccines (a priority to demonstrate the potential of our platform) and cancer vaccines, all part of a large project in collaboration with different teams. b) Towards a phase I clinical trial of monoclonal antibodies, a main project of AlbaJuna Therapeutics, given that an institutional priority is bringing these molecules to clinical trials in humans. c) COVID-19 research, with coordination of our current consortium to be combined with the following research priorities: understanding immune responses to SARS-CoV-2 (durability of antibodies), developing synthetic antibodies as therapeutic/preventative drugs and applying our VLP technology to vaccine research.

Perspectives for 2022

— CBIG consortium COVID research. The expertise accumulated over the last 20 years on characterization of humoral responses, pathogenesis, translational and vaccine research in HIV allowed us to rapidly respond to the COVID-19 threat, an effort that crystalized in the CBIG consortium with BSC and CReSA, supported by Grifols. The extensive work performed on the new virus the development of new experimental tools and the new biosafety facilities at the CMCiB are excellent basis for future work.

— New research platforms. The pseudovirus-based neutralization platform and the VLP platform for vaccine research are being expanded to other viruses. New vaccine programs in collaboration with different companies (including HIPRA) are being developed and will be a priority in the future.

— Immunomodulation in people with HIV. HIV therapies continue to be a priority, in this regard the new VLP technology and the development of new animal models (HIV-1 Virus-Like particles engineered to display a high antigen content, Doctoral Theses 2021, Ferran Tarrés) paves the way for the preclinical development of our vaccine platform. Moving the assays to non-human primates will be a priority.

1 Multidisciplinary team committed with research on human health

10 Variants of SARS-CoV-2 have been analyzed in our lab to assess their impact on vaccine efficacy

>50 Interviews in press, radio or TV

Principal Investigator
Julià Blanco

Post-doc researchers
Carmen Aguilar
Benjamin Trinité

Pre-doc researchers
Ana Barajas
Raquel Ortiz
Anna Pons
Edwards Pradenas
Ferran Tarrés

Laboratory technicians
Silvia Marfil
Carla Rovirosa
Ismael Varela

Biostatistician
Víctor Urrea

AlbaJuna Therapeutics, SL
Ester Aparicio, Amaya Blanco, Victor Casanova, Francesc Cunyat, Cristina Val

Grifols Projects

High Density Virus-Like Particles: a Novel Vaccine Platform Against Infectious Diseases (INDIVAC)

Senior researchers: Julià Blanco and Jorge Carrillo

Developing a preventative HIV-1 vaccine based on the generation of HIV Gag VLPs with rationally designed HIV Env-antigens. Candidate antigens have been already selected and new animal model to assess functionality of immune responses have been developed. A secondary aim is to expand the VLP technology to other pathogens (treponema in collaboration with Jorge Carrillo), FeLV (in collaboration with HIPRA) and human respiratory viruses (in collaboration with MSD).

VLPs Expressing Tumor Neoantigens as Personalized Cancer Therapeutic Vaccines (NEOVAC)

Senior researchers: Julià Blanco and Jorge Carrillo

Exploiting VLP technology as a vaccine platform (protein or DNA) to elicit cellular and humoral protective responses to tumors. The aim is to generate a platform of personalized DNA cancer vaccines. It requires the identification and selection of optimal tumoral antigens that will be included in the VLP vaccine and will activate the immune system. Animal models for melanoma and pancreatic cancer are already in place. The project is a collaboration with Dr de Mattos-Arruda at IrsiCaixa and BSC.

Tissue Virology

Doctoral theses

Title: Modulation of cellular pathways as a therapeutic strategy in HIV infection
Author: **Sònia Pedreño**

Title: Predicción de la respuesta al tratamiento con BCG endovesical en pacientes con carcinoma vesical no músculo invasivo de alto riesgo.
Author: Roberto Hugo Martínez

Presentation

Our group focuses on the following research lines:

HIV pathogenesis in lymphoid tissue

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. Because the gut mucosa is an important site of HIV acquisition, viral replication and pathogenesis, to prevent or eradicate infection, new therapeutic strategies and vaccines must be able to induce polyfunctional immune response in tissue-resident cells. Our group evaluates HIV pathogenesis, the impact of ART drugs and the immune response in tissue, as functional characterization and the use of various immunomodulators in resident-T cells could lead to an effective strategy for activating the immune system and eradicating the infection.

Urinary 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 mycobacterium*). 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. In addition, the remaining 30 percent of patients have muscle-invasive bladder cancer (MIBC). MIBC is highly fatal, and if untreated, >85% of patients die within 2 years of diagnosis. In patients with localized MIBC, neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy and pelvic lymph node dissection is the standard of care. However, there are a significant number of patients (up to 60%) who do not respond to the treatment and are potentially harmed by the treatment side effects. Therefore, there is, an overwhelming need to identify biomarkers of response to neoadjuvant cisplatin-based chemotherapy to prevent its administration to patients unlikely to benefit. Our group is working to improve current treatment by developing new therapeutic strategies and identifying biomarkers to predict response to treatments in both NMIBC and MIBC.

COVID-19

SARS-CoV-2 has already infected some 79 million people and COVID-19 has caused some 1.7 million deaths worldwide as of December 2020. In the early phase of the pandemic, the virus was believed to behave like other respiratory viruses leading to severe adult respiratory syndrome (ARDS). However, it is now clear that this very unusual pathogen causes manifestations outside the respiratory apparatus leading to fatal outcomes in vulnerable people. Pathological mechanisms in the respiratory tract are still not well understood, especially the cellular and molecular processes that need to be targeted. One important as yet unanswered question is whether SARS-CoV-2 can be transmitted from a pregnant woman to her foetus and, if so, to determine the mechanism(s). Objectives of our group is to obtain reliable data on the risk of vertical transmission through the placenta, birth canal and/or breastfeeding, to describe the impact of peripartum infection in maternal and neonatal outcomes and to evaluate the innate immune response in children infected with the virus.

2021 MILESTONES AND PERSPECTIVES FOR 2022

HIV pathogenesis and lymphoid tissue

— Studies of the effect of HIV infection on autophagy and of different modulators on HIV infection.

— Role of caspase inhibitors in HIV infection.

— Characterization of the immune response of infiltrating immune cells in different tissues.

Bladder cancer

Therapeutic strategies for improving BCG treatment:

— RUTIVAC-1 clinical trial. Immunological characterization of samples of patients in the study. Characterization of changes in acquired immunity. Evaluation of trained innate immunity induced by BCG and RUTI vaccines.

— Evaluation of immunological changes in bladders of mice with cancer treated with different strains of mycobacteria (In collaboration with the UAB).

— Characterization of immune infiltration in the bladder of patients with invasive bladder cancer due to receive chemotherapy treatment.

— Evaluation of immunological changes in the peripheral blood of patients with NMIBC after intravesical treatment with BCG.

SARS-CoV-2 (COVID-19)

— Evaluation of the presence of SARS_Cov2 in several samples in a cohort of pregnant women infected by SARS-Cov2 (in collaboration with Ester Ballana Group). Evaluation of humoral response (in collaboration with Julià Blanco and Jorge Carrillo groups)

— Evaluation of the role of the ACE2 receptor in SARS-CoV2 infection (in collaboration with the HIVIT group of irsiCaixa).

— 3D human tissue cultures establishment: tissue-explant cultures and organoids of differen tissues and in vitro infection with SARS-Cov-2.

— Characterization of innate immune response in children infected with SARS-Cov2 (In collaboration with the Hospital Sant Joan de Deu).

1 GROUP OF PEOPLE COMMITTED FIGHTING HIV AND SARS-COV-2

7 ONGOING PROJECTS

3 HORIZON 2020 PROJECTS IN WHICH THE GROUP HAS COLLABORATED

PRINCIPAL INVESTIGATOR

Cecilia Cabrera

Post-doc researcher
Jordi Senserrich

Pre-doc researcher
Sònia Pedreño

Laboratory technician
Elisabet García

GRIFOLS PROJECT

TISSUE-RESIDENT MEMORY CELLS AS A POTENTIAL IMMUNOTHERAPEUTIC TARGET FOR COMBATING MUCOSAL INFECTIONS. TISRESP

Senior researcher: Cecilia Cabrera

Objectives:

— Characterize the phenotypic and functional properties of resident-immune cells present in mucosal-associated lymphoid tissues: identification of a tissue-resident memory T cells (TRM) surface marker signature in different human tissues; evaluation of the cytotoxic profile of TRM; functional characterization after polyclonal stimulation.

— Identify strategies of “residency induction” that can be applied in the development of therapeutic and preventive strategies against mucosal pathogens.

— Evaluate the efficacy of immune modulators in HIV and SARS-CoV-2 infection in 3D tissue cultures: ex vivo, efficacy of immune modulators in the SARS-CoV-2 infection in human lung explants and organoids; in vivo, efficacy of immune modulators in HIV and SARS-CoV-2 infection in a mouse model.

Immunology Group (IgG)

Presentation

The main interest of this recently created research group, headed by Dr Jorge Carrillo, is the study of the immune system in infectious diseases (particularly, HIV-1, SARS-CoV-2 and syphilis) and research related to immuno-oncology, basic immunology and autoimmunity. The Immunology group at IrsiCaixa collaborates with many other groups, both in and outside **IrsiCaixa**.

2021 milestones

1. COVID-19

— Characterization of SARS-CoV-2 immunopathogenesis and the immune response elicited after infection or vaccination in human and animal models.
— Development of novel tools for diagnosis (flow virometry) and the evaluation of new treatments (such as IVIG).
— Isolation and characterization of anti-SARS-CoV-2 antibodies.
— Deciphering the role of non-neutralizing anti-SARS-CoV-2 antibodies and they association with the development of severe COVID-19.
— Collaboration in a study aimed to compare the immunopathogenesis of COVID-19-related paediatric inflammatory multisystem syndrome and Kawasaki disease.

2. HIV-1 infection

— Characterization of the humoral response in HIV-1 infected individuals, with progress achieved especially with project PI18/01332 (Identification, isolation and characterization of neutralizing interfering antibodies (NIAbs) in HIV infected individuals), whose results we expect may uncover whether NIAbs act as a HIV mechanism to avoid the humoral response; knowledge that might be a key point for future design of vaccine immunogens that improve the neutralizing response against HIV. Moreover, since high titres of NIAbs may hamper the therapeutic capacity of neutralizing antibodies, the results may help identify HIV patients that can benefit from immunotherapy based on neutralizing antibodies.
— Characterization of how primary HIV infection affect the B cell compartment and the humoral response

3. Vaccine development

— Work on the development of a SARS-CoV-2 vaccine, based on a modified spike protein, capable of inducing neutralizing antibodies and evaluation of protective capacities in two different animal models for SARS-CoV-2 challenge: K18-ACE2 mice and golden Syrian hamsters.
— Work on the development of a syphilis vaccine based on outer membrane proteins.

4. Basic immunology, immuno-oncology and autoimmune diseases

— Establishment of the role of B- lymphocytes and antibodies in the development of Sjögren syndrome (in collaboration with Dr Pablo Engel).
— Evaluation of the immune response in patients treated with checkpoint inhibitors (in collaboration with Dr Rafael Rosell and Dr María González-Cao) and exploration of the role of CD5L in the development of hepatic cancer (In collaboration with Dr Rosa Maria Sarrias).

Perspectives for 2022

We expect to further consolidate our research lines and strengthen our national and international collaborations. Our priority will be to contribute with the development of a COVID-19 and syphilis vaccine. In addition, we will conduct

Projects awarded 2021

Unravelling the role of humoral response in the development of severe SARS-CoV-2 infection during natural infection and after immunisation
Funding: La Marató de TV3 Foundation
Start/end dates: 09.21- 09.23
Research supervisors: **Jorge Carrillo**, Júlia Vergara
Participating entities: IrsiCaixa, IRTA-CReSA, FLS

Characterization of the humoral response against SARS-CoV-2 and development of a COVID-19 vaccine
Funding: YoMeCorono crowdfunding campaign
Start/end dates: 01.21- 12.22
Research supervisor: **Jorge Carrillo**
Participating entities: IrsiCaixa

RBD Dimer recombinant protein vaccine against SARS-CoV-2
Funding: European Comission H2020
Start/end dates: 05.21 –
Research supervisors: **Christian Brander**, **Julia García-Prado**, **Julià Blanco**, **Jorge Carrillo, Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa, FLS, HIPRA

experiments to evaluate the effect of checkpoint inhibitors on immune response development. Finally, we expect to conclude our study on the role of NIAbs in HIV-1 infection.

7 ACTIVE PROJECTS

12 PUBLICATIONS

5 INVITED TALKS

PRINCIPAL INVESTIGATOR

Jorge Carrillo

Post-doc researchers
Erola Ainsua
Núria Pedreño
Maria Luisa Rodríguez

Pre-doc researcher
Carlos Ávila

Translational Research in Immunology and Ageing (TRIA)

Projects awarded 2021

HIV-infection, immunosenescence and genomic instability: Identification of biomarkers in chronic HIVinfected patients and its relationship with premature aging
Funding: ISCIII
Start/end dates: 2021-2022
Research supervisor: **Marta Massanella**
Participating entities: IrsiCaixa, IGTP

Protective immune responses against SARS-CoV-2 developed by recovered elders
Funding: YoMeCorono crowdfunding campaign
Start/end dates: 2021-2023
Research supervisor: **Marta Massanella**
Participating entities: IrsiCaixa, DAP-MN

Ageing with HIV: the role of metabolism in HIV persistence and pronounced immune ageing
Funding: ISCIII
Start/end dates: 2021-2024
Research supervisor: **Marta Massanella**
Participating entities: IrsiCaixa, FLS

Validation of a lateral flow system for the detection of structural proteins of SARS-CoV-2
Funding: LincBiotech S.L.
Start/end dates: 2021-2022
Research supervisors: **Marta Massanella**, **Ester Ballana**
Participating entities: IrsiCaixa

Grants Awarded 2020

Grants for the recruitment of junior researchers
Funding: AGAUR
Starting and finishing date: 04.21- 03.24
Student granted: Macedonia Trigueros
Research supervisor: **Marta Massanella**

Awards and Achievements

Marta Massanella, topic editor from Viruses
Marta Massanella, rapporteur of track A (basic science) of IAS Conference 2021
Marta Massanella, member of the Research Data Management group at IrsiCaixa
Marta Massanella, member of the Scientific Committee of the XII Congreso Nacional de GeSIDA

Presentation

TRIA focuses on translational studies to investigate remodelling of the immune system during the ageing process in an infectious disease context. Our group focuses on two main lines of research:

— Inflammageing and immunosenescence during HIV infection. Despite the great improvement brought about by ART therapy, the prevalence of age-related comorbidities is higher in HIV-infected population. We study this accentuated ageing and characterize immune dysfunction, HIV reservoir and altered metabolism in ART-treated individuals.

— COVID-19 vaccine response in elders living in senior facilities. 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 to adapt the SARS-CoV-2 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 immunedysfunctions behind post-COVID-19 condition, to find diagnostic markers and identify treatment interventions that could lead to the recovery of these patients.

2021 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.

— In collaboration with Dr Negredo from the Fight AIDS and Infectious Diseases Foundation (FLS), characterization of the immune system and immunosenescence (including telomere length) in subjects older than 50 years (OVER50 cohort).

— In collaboration with Dr Negredo (FLS) 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.

COVID-19

— Coordination of the KING cohort extension of SARS-CoV-2 infected individuals (N=750) with different levels of severity (asymptomatic to critical), a cohort that is of use to all IrsiCaixa groups. This cohort includes also more than 350 individuals suffering from post-COVID-19 condition.

— In collaboration with Dr Lourdes Mateu (FLS), exploration of immune dysfunctions and viral persistence in individuals with post-COVID-19 condition, and its association with specific persistent symptomatology.

— Exploration of the specific role of NK-cells in the post-COVID-19 condition.

— In collaboration with DAP-MN, coordination of the CoronAVI@S cohort of older adults living in long-term care facilities to evaluate the quality and duration of immune responses elicited by SARS-CoV-2 vaccine.

— In collaboration with Dr Julia Garcia-Prado (IrsiCaixa VIRIEVAC group), evaluation of the immune response of SARS-CoV-2 non-seroconverters (individuals who were infected but did not develop a humoral response).

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

PERSPECTIVES FOR 2022

Ageing with HIV

Our group will continue to characterize accentuated immunoageing and immunosenescence in HIV-infected ART-treated individuals compared to the uninfected counterpart. The aim is to determine the origins of immune dysfunction and develop new senolytic strategies. We will also explore how the process of natural ageing in people living with HIV 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 elders living in long-term care facilities to adjust their vaccination calendar and ensure their protection against SARS-CoV-2 infection.

PRINCIPAL INVESTIGATOR

Marta Massanella

Post-doc researcher
Maria Nevot

Pre-doc researchers
Francisco Manuel Muñoz
Macedonia Trigueros

>800 PARTICIPANTS IN OUR CLINICAL STUDIES

9 ACTIVE CLINICAL STUDIES OF HIV AND SARS-COV-2

4 MOTIVATED AND TALENTED YOUNG RESEARCHERS

Pathogen Immunity, Signaling and Therapeutic Applications (PISTA)

Projects awarded 2021

New antiviral and immunomodulatory therapies against SARS-CoV-2
Funding: Spanish Ministry of Science and Innovation
Start/end dates: 09.21- 08.24
Research supervisor: **Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa

In vitro antiviral screening of compounds provided by Pharma Mar on Ebola virus entry and on the replication of HIV-1, Zika and SARS-CoV-2
Funding: PharmaMar
Start/end dates: 01.21- 12.22
Research supervisors: **Nuria Izquierdo-Useros**, **Ester Ballana**
Participating entities: IrsiCaixa

Assessment of the immunomodulatory effect of AAT on cytokine production in macrophages in the presence of SARS-COV-2
Funding: Grifols
Start/end dates: 07.21- 01.22
Research supervisor: **Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa

Assessment of the antiviral activity against SARS-COV2 of certain mouthwashes (3 subprojects)
Funding: DENTAID S.L.
Start/end dates: 04.21- 05.22
Participating entities: IrsiCaixa
Research supervisor: **Nuria Izquierdo-Useros**

Antiviral efficacy studies in in vitro and ex vivo models to determine the antiviral activity of different compounds
Funding: Palobiofarma SL
Start/end dates: 04.21- 10.21
Research supervisor: **Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa

Study of pan-coronavirus entry inhibition mediated by LightAir IonFlow technology
Funding: LightAir International AB
Start/end dates: 02.21- 04.21
Research supervisor: **Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa

RBD Dimer recombinant protein vaccine against SARS-CoV-2
Funding: European Comission H2020
Start/end dates: 05.21 –
Research supervisors: **Christian Brander**, **Julia García-Prado**, **Julià Blanco**, **Jorge Carrillo, Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa, FLS, HIPRA

Doctoral Theses

Title: Impact of a SIGLEC1 null variant on the pathogenesis of HIV-1 and Mycobacterium tuberculosis infection
Author: **Susana Benet**

Awards and Achievements

Nuria Izquierdo-Useros, member of the Reviewer Board of the Frontiers in Virology Journal and collaborates with the "Asociación de Mujeres Investigadoras y Tecnólogas"
Nuria Izquierdo-Useros, member of the scientific committee of the "Virology Meeting 2021" of the Catalan Society of Biology and "3rd Research Symposium on coronavirus"
Nuria Izquierdo-Useros, member of the organizing committee of the Third Woman in Science Day at Can Ruti Campus

Presentation

The world is becoming particularly vulnerable to emerging pathogens that thrive in new geographical areas due to globalization trends and climate warming. Although infectious diseases can be contained by host defenses, pathogens evolve to counteract human immunity. The goal of the group PISTA (Pathogen Immunity, Signaling and Therapeutic Applications) is to understand the underlying biology and basic aspects of human infection to develop novel therapeutic strategies against forthcoming threats. We are a novel research group studying emergent viruses to steer the rational design of broad antiviral treatments.

Our research is framed within two strategic lines promoted by **IrsiCaixa**: immunopathogenesis and the study of other diseases.

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

2021 milestones

Our team started working when the COVID-19 pandemic arrived to Europe in February 2020, so we immediately devoted our efforts to study the new coronavirus. We continue our work to identify novel antivirals against SARS-CoV-2 while searching for innovative immunomodulatory agents that could help to avoid COVID-19 severe progression. This line of research is performed within the CBIG Consortium established by Dr. Clotet to identify new therapies, antibodies and vaccines in collaborations with IRTA-CReSA and the Barcelona Supercomputing Center, thanks to the support of Grifols. We also collaborate with different companies including PharmaMar, Dentaid, VIR Biotech, and other business partners to study the clinical potential of specific products against SARS-CoV-2. As part of our commitment, we are also actively working to implement new strategies that could avoid SARS-CoV-2 transmission.

During this year, our work has been devoted to the following activities:

1. Study promising antivirals against SARS-CoV-2. In collaboration with Drs. Vergara-Alert and Segalés from IRTA-CReSA, we have continued efficacy studies in murine model testing Aplidin. In collaboration with Dr. Cristina Risco from CNB we are using ultrastructural electron microscopy and immunogold staining to dissect the mechanism of action of Aplidin and other new promising antivirals. A phase III clinical

study coordinated by Dr. Roger Paredes is also ongoing. We have consolidated our collaboration with PharmaMar and have started a search for pan antiviral solutions in collaboration with Dr. Ballana and other teams of IRTA-CReSA.

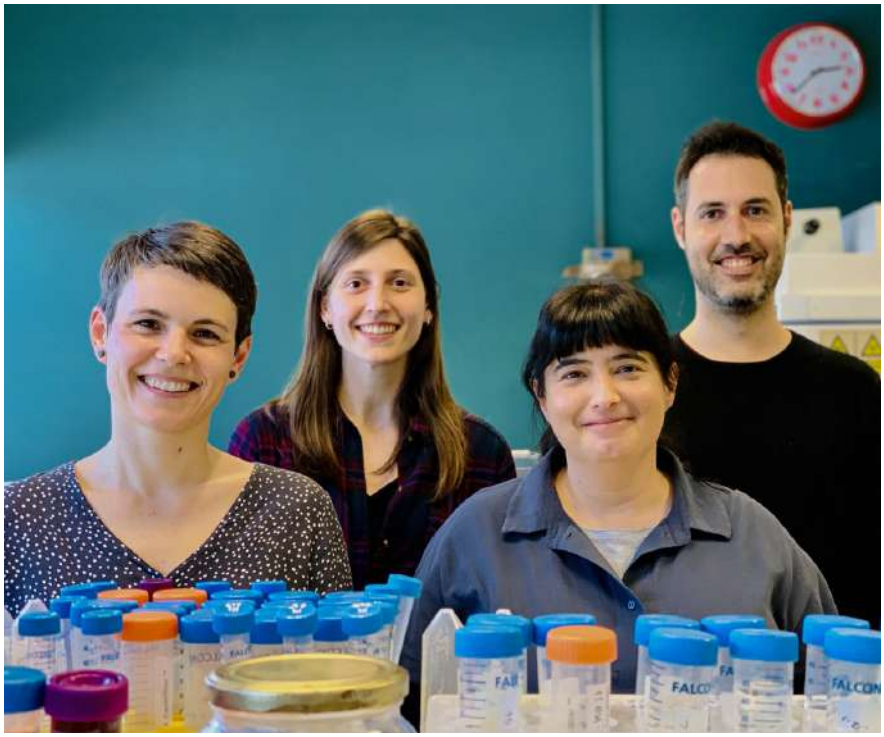
2. Identify novel strategies that could decrease SARS-CoV-2 transmission. We have taken part in studies led by Drs. Llibre and Revollo from the infectious diseases section of the Hospital Germans Trias i Pujol to test the utility of antigen-detecting rapid diagnostic tests (Ag-RDT) in mass gathering events to avoid novel infections. We have also evaluated different commercial Ag-RDT against novel variants of concern including the Delta variant along with Dr. Blanco. In addition, we have identified that CPC, a virucidal compound present in many oral mouth washes, is able to disrupt SARS-CoV-2 lipidic membranes and also to reduce viral infectivity. In collaboration with Dr. Mitjà from the infectious diseases section of the Hospital Germans Trias i Pujol we have confirmed that in a randomized clinical trial, CPC containing mouthwashes also disrupts viral particles in the saliva of SARS-CoV-2 infected individuals.

3. Understand the role of antigen-presenting cells during COVID-19 immunopathogenesis. We have identified that Siglec-1 is a key receptor that binds to SARS-CoV-2 in collaboration with Dr. Martínez-Picado and VIR biotechnology.

Our findings highlight the utility of novel mAbs developed by this company that target Siglec-1-mediated mechanisms of SARS-CoV-2 transmission.

4. Search for novel immunomodulatory agents that could decrease the cytokine storm induced by SARS-CoV-2 in critically ill COVID-19 patients. We are using an in vitro platform to detect the cytokines released induced by SARS-CoV-2 exposure, with the aim to identify novel immunomodulatory agents in collaboration with Grifols and Amassence.

5. Participate in the clinical trials launched by HIPRA to test the safety and efficacy of the first SARS-CoV-2 vaccine produced in Catalonia. We are assessing the levels of neutralizing antibodies in collaboration with the team of Dr. Blanco. We are about to finish the first Phase 2 clinical trial and will shortly begin an international Phase 2b/3 trial in Malaysia, Vietnam and Spain. These studies will be key for the European Project coordinated by HIPRA to develop a dimer recombinant protein vaccine that is led by Drs. Prado and Mothe in which we also participate.



6. Monitor the levels of neutralizing antibodies in HIV-1 infected patients followed at Hospital Germans Trias i Pujol, to identify vulnerable individuals that could benefit from additional vaccinations in collaboration with Drs. Mothe and Benet.

7. Integrate multiple OMIC studies to identify novel therapeutic targets, in collaboration with the Proteomics unit of the IJC to analyze relevant changes induced in key cellular targets and decipher the molecular pathways involved in SARS-CoV-2 infection.

8. Continue ongoing collaborations with the experimental nephrology and transplantation unit of the Hospital Clinic with Drs. Bayes, Diekmann, Banon and Ramirez; Dr Christou from the University of Lleida, and Dr. Timothy Thomson from CISC (Barcelona) which have ongoing projects related to the development of novel antivirals and immunomodulators.

PERSPECTIVES FOR 2022

Upcoming projects with the group of Dr. Carrillo to understand ADE during COVID-19 are about to commence. We will continue to develop novel strategies against SARS-CoV-2 that could dimmish viral transmission, offer new antiviral approaches and identify potent immunomodulators to prevent critical disease. In turn we aim to apply all these gained knowledge to combat other respiratory viruses and emergent threats.

PRINCIPAL INVESTIGATOR

Nuria Izquierdo-Useros

Post-doc researcher
Daniel Pérez-Zsolt
Dàlia Raïch-Regué

Senior laboratory technician
Jordana Muñoz-Basagoiti

4 RESEARCHERS COMMITTED TO FIGHT EMERGENT VIRUSES

>15 ACCEPTED PEER-REVIEWED PAPERS

8 NEW AGREEMENTS SIGNED

Neoantigens and Therapeutic Vaccines for Cancer (NeoVaCan)

Presentation

The group conducts research using multi-omics and immune characterization of solid tumors and liquid biopsies at several layers, to get a better understanding of the interplay between tumor genomics and the host immune response and ultimately taking cancer patient therapy towards personalization. Together with the VIC group at **IrsiCaixa** and the EAPM group at Barcelona Supercomputing Center, our group is co-developing a therapeutic neoantigen cancer vaccine for clinical application. As one of the two pillars of cancer vaccine development at **IrsiCaixa**, our group coordinates the clinical side, translating next-generation sequencing-guided and experimental analyses of neoantigen prediction to therapeutic benefits for patients with cancer.

2021 Milestones and Perspectives for 2022

— To apply next-generation sequencing strategies, coupled with improved and novel bioinformatics pipelines and cutting-edge molecular biology procedures, to the identification and validation of immunogenic neoantigens.
— Working with immunologists and computational biologists, to lay solid foundations for the development of a therapeutic neoantigen 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 and incorporate state-of-the-art molecular tools and new cost-effective in-house solutions.

Associate researcher
Núria de la Iglesia

Former Principal Investigator
Leticia de Mattos-Arruda

Post-doc researcher
Juan Blanco

Laboratory technician
Carla Dos Anjos

RESEARCH SUPPORT

Scientific and Technical Services

Sample Conservation & Processing Service

The **IrsiCaixa** Retrovirology Laboratory, which began its activity in 1993, processes and preserves biological samples from HIV-infected patients for use in research projects. Over the years, it has processed and conserved samples for numerous projects and clinical trials, promoted by both **IrsiCaixa** and external national and international sponsors. This activity has evolved into a platform that aims to further research requiring human samples.

Currently, the service routinely processes and stores samples for 38 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

Sample Conservation and Processing Service
Eulàlia Grau
Rafi Ayen
Lucía Gómez
Mireia Martínez

Sequencing Service
Teresa Puig
Cristina Ramírez

Assistant
Susana Esteban

26 Years of Sample Collection

Total of Samples Collected

41,867 cells
73,606 plasma
11,036 serum
33,255 other

Total: 159,764 samples

2021

Samples Collected

3,402 cells
4,399 plasma
2,016 other

Total: 9,817 samples

403 Sequenced samples

336 public centres

67 private centres

3987 Elisa Tests in COVID-19 diagnosis

Research and Innovation Management

Head
Lourdes Grau

Team
Judith Dalmau
Elisabet Fernández
Valentín Lafuente
Chiara Mancuso
Natàlia Marrugat
Laura Planells

The Research and Innovation Management team (RIM) 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, assisting with proposal preparation and project management, designing and following up budgets and assisting in collaboration, transfer and innovation processes. RIM ensures alignment of **IrsiCaixa**s practices with the rules, regulations and policies of funding entities, as well as with current national and international regulations.

PATENT PORTFOLIO

Granted

Title: Method for monitoring HIV specific T Cell responses
Inventors: **Ruiz-Riol, Marta; Brander, Christian; Ibarrondo, Javier**
Reference: WO/2013/139972; PCT/EP2013/056110
Priority Date: 23 Mar 2012
Publication date: 26 Sep 2013
Applicants: **IrsiCaixa**, ICREA
Granted: EP, Belgium, China, Germany, Spain, France, GB, Italy, The Netherlands, Sweden, Canada, Japan, US

Title: Methods for identifying HIV neutralizing antibodies
Inventors: **Blanco Arbués, Julián Miguel**
Reference: WO/2014/037490; PCT/EP2013/068446
Priority Date: 6 Sep 2012
Publication date: 12 Mar 2014
Applicant: **IrsiCaixa**
Granted: US, Australia, China, Iceland, Japan, South Korea, Mexico, New Zeland, Russia, South Africa

Title: HIV antibody derivates with dual antiviral and immunomodulatory activity
Inventors: **Carrillo, Jorge; Clotet Sala, Bonaventura**; **Blanco Arbués, Julián Miguel**
Reference: WO/2017/085563; PCT/IB2016/001868
Priority Date: 21 Nov 2015
Publication date: 26 May 2017
Applicant: **IrsiCaixa**
Licensed 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; PCT/IB2017/001101
Priority Date: 27 Jul 2016
Publication date: 01 Feb 2018
Applicants: **IrsiCaixa**
Granted: US
Licensed to: HIPRA

Title: Immunogens for HIV vaccination
Inventors: **Brander, Christian; Mothe Pujadas, Beatriz; Llano, Anuska**
Reference: WO/2013/110818; PCT/EP2013/051596
Priority Date: 27 Jan 2012
Publication date: 1 Aug 2013
Applicants: **IrsiCaixa**, ICREA
Granted: US, AU, China, Israel, Japan, Rep. of Korea, Mexico, New Zealand, Russian Federation, South Africa
Pending: Brazil, Hong Kong
Published: Canada, India
Case inactive: EP
Licensed to: Aelix Therapeutics

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; PCT/EP2016/052990
Priority Date: 13 Feb 2015
Publication date: 18 Aug 2016
Applicants: **IrsiCaixa**, Azienda Ospedaliera Universitaria Senese
Granted: Japan

Filed/Published

Title: SIGLEC 1 monoclonal antibodies for treating and preventing HIV 1 and ebola virus infections
Inventors: **Izquierdo-Useros, Nuria; Martínez-Picado, Javier; Pérez-Zsolt, Dani; Pino Claveria, Maria; Kremer, Leonor; Resa-Infante, Patricia**
Reference: 62828195 (US)
Priority Date: 2 Apr 2018
International (PCT) Application No.: PCT/US20/26256
International (PCT) Filing Date: 01/04/2020
PCT Application: no national phase yet
Applicant: **IrsiCaixa**

Title: Polypeptides for eliciting humoral and cellular immune responses against coronavirus infections
Inventors: **Garcia-Prado, Julia; Brander, Christian; Olvera, Alex; Noguera, Marc; Kilpelainen, Athina; Romero Martín, Luis**
Jurisdiction: United States
Patent document: US63/051925
Filing date: 15 Jul 2020
Applicant: **IrsiCaixa**

Title: Siglec-1 inhibitors for preventing, inhibiting the progression or treating Coronavirus infections
Inventors: **Izquierdo-Useros, Nuria; Martínez-Picado, Javier; Clotet Sala, Bonaventura**
Priority number: US 63/152,346
Priority date: 23 Feb 2021
Applicant: **IrsiCaixa**

Title: Method for detecting and quantifying inducible HIV reservoirs
Inventors: **Puertas Castro, Mari Carmen; Martínez-Picado, Javier**
Priority number: US 63/193,261
Priority date: 26 May 2021
Applicant: **IrsiCaixa**

Title: PLD for use in combination in the treatment of coronavirus
Inventors: **Izquierdo-Useros, Nuria; Vergara-Alert, Júlia; Avilés-Marín, Pablo**
Reference: WO 2021/175823; PCT/EP2021/055131
Priority date: 2 Mar 2020
Publication date: 10 Sep 2021
Applicants: **IrsiCaixa**, PharmaMar

Living Lab for Health

Head
Rosina Malagrida

Team
Aina Estany
Jessica Fernández
Marina Pino
Laia Vives

Presentation

During **2021**, the Living Lab for Health at **IrsiCaixa** has contributed to improve the way we address persistent and complex health challenges within multistakeholder innovation ecosystems by facilitating transformative networks to find better collaborative, decentralised and systemic solutions. Through participatory processes, a wide variety of organizations collectively explore the complexity of the challenges and co-design solutions for both the research and innovation (R&I) system and the systems affected by the challenges to which the Lab intends to contribute.

The methodologies needed for the systems transformations have also been applied to develop educational modules targeted both at professionals and different stakeholders, and at secondary school students. The Lab has also offered trainings to different universities, research centres and funding agencies.

The methodologies implemented in the Lab are based on new trends 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 global initiatives such as "Community Based Participatory Research", "system thinking" and "transdisciplinary research".

The Lab implements its initiatives within EC funded projects, "la Caixa Foundation" programmes and within the Barcelona CaixaResearch Living Lab, also funded by "la Caixa" Foundation in collaboration with the Barcelona City Council to facilitate an intermediation structure to optimize the processes of R&I, interventions and policy development in Barcelona.

Lines of action 2021

Promotion of innovation ecosystems to address complex health challenges

Challenge 1: Promotion of Healthy and Sustainable Diets (Fi4FoodBcn)

Within the Barcelona CaixaResearch Living Lab and the Fit4Food2030 (EC funded project finished in January **2021**), the Lab has facilitated the advancement of the Fit4FoodBcn network and its pilot implementation in a neighbourhood in Barcelona named La Verneda i La Pau. The network aims to improve the promotion of Healthy and Sustainable Diets in this neighbourhood with a more effective, systemic, collaborative and decentralised approach. The Lab has co-designed a collective Strategic and Action Plan for this pilot, in collaboration with 22 organisations such as universities and research centres, healthcare, social and formal and non-formal educational services, food businesses and other organisations and citizens at large. During the last semester of **2021**, the prototyping phase will be implemented before the implementation of the actions during 2022.

Challenge 2: Promotion of affective-Sexual Health (Co – ResponS(H)ibility)

Within the Barcelona CaixaResearch Living Lab and the InSPIRES (EC funded project finished in June **2021**), the Lab has continued working towards a more effective, systemic, collaborative and decentralised model of promotion of Affective-Sexual Health for youth and adolescents. After the creation of a "steering committee" with key stakeholders, the Lab has organised several workshops to co-design a Collective Strategic and Action Plan in which more than 15 organizations have participated (healthcare professionals, researchers, communication and education experts, civil society organisations, youth entities, different departments of the administration, etc.). This Plan includes the ideation of initiatives to implement during 2022.

Challenge 3: Prevention of SARS-CoV-2

The Departments of Health and Education of the government of Catalonia launched in 2020 the project "Escoles Sentinella" in order to monitor, evaluate and elaborate recommendations for the prevention of the Covid pandemic in educational centres. The project is coordinated by CEEISCAT and, during 2020-**2021** the Lab coordinated the participatory research processes in order to develop recommendations to improve prevention with 866 students and their families and teachers. This part of the research is being conducted in the framework of the EC funded project CONNECT.

Challenge 4: Promotion of mental health

The results obtained from the participatory research on prevention of SARS-CoV-2 showed the urgency to improve the way we promote mental health in schools. To respond to this need, during **2021**-22 the Lab is coordinating another participatory research process to develop recommendations with and for the education community. This challenge is being addressed within the projects "Escoles Sentinella" and CONNECT.

Challenge 5: Healthcare and research on Long Covid

The Lab is supporting the Long Covid Unit of the Hospital Germans Trias i Pujol, Fundació Lluita contra la Sida i les Malalties Infeccioses and **IrsiCaixa** to collectively develop a strategic and action plan with a systemic and collaborative approach.

Educational programmes

Training and consultancy on RRI, System Innovation and Open Science for students and professionals

During **2021**, 905 professionals have been trained through customized trainings, webinars, conferences and workshops for undergraduate and

post-graduate scientists, healthcare professionals, policymakers, experts on public engagement, educators and staff at funding organizations, among others.

Within the InSPIRES project, the Lab has collaborated in the development of training materials for setting up and managing Science Shops and for conducting participatory research.

Educational programmes for youth aimed at facilitating participatory research and outreach

STEAMxChange programme: programme developed in collaboration with EduCaixa and based on Xplore Health educational programme. Students perform participatory research to contribute to solve local social challenges in collaboration with families, community members, scientists and other stakeholders. During **2021** the Lab has improved an educational guide on Food, has developed a new one on vaccination, has contributed in a series of webinars to train teachers and has adapted Xplore Health content for EduCaixa (the Xplore Health website has been closed as most of its contents have already been published in EduCaixa). A total of 498 schools registered in the programme and 17 participated in the STEAM award in June **2021**.

CONNECT and Escoles Sentinella: EC funded project to promote secondary schools to adopt a movement called Open Schooling, which promotes participatory research projects. The Lab joined the "Escoles Sentinella" consortium to develop guidelines and implement participatory research processes (see challenges 3 and 4 above). During **2021**, the Lab has also developed an Engagement Toolkit to guide organizations and schools to implement OpenSchooling.

HIV/AIDS outreach programme: IrsiCaixa has offered dissemination sessions on HIV/AIDS, focusing on basic knowledge, current research and the importance of prevention and diagnosis, with reflection and debates around social issues (e.g. stigma). These sessions were complemented by the LaboCosmoCaixa, an activity initiated 8 years ago and organized by "la Caixa" Foundation in collaboration with **IrsiCaixa** that encourages young people to conduct research with a vaccine candidate developed by IrsiCaixa. These activities stopped in March 2020 due to the Covid pandemic and will start again in February 2022.

Opening IrsiCaixa's Research through the Community Advisory Committee (CAC)

This external body facilitates communication and dialogue between the researchers and healthcare professionals at IrsiCaixa and patients, civil society representatives and policy makers. The specific CAC for the follow-up of the HIV preventive vaccine study (MOSAICO) has met on 2 occasions during **2021**.

70 ORGANIZATIONS INVOLVED

2 COLLECTIVE STRATEGIC ACTION PLANS

13 INNOVATION PROGRAMMES CO-DESIGNED

905 PROFESSIONALS TRAINED

3 TRAINING RESOURCES DEVELOPED

4 EDUCATIONAL GUIDELINES DEVELOPED

1 ENGAGEMENT TOOLKIT DEVELOPED

498 SCHOOLS REGISTERED IN THE STEAMXCHANGE PROGRAMME

866 STUDENTS FROM 6 SCHOOLS INVOLVED

58 SARS-COV-2 RECOMMENDATIONS WERE COMMUNICATED

908 SOCIAL ACTORS ATTENDED A CONGRESS ON SARS-COV-2

Communication

Team
Rita Casas
Elena Lapaz

A main goal of **IrsiCaixa** Communications Department is to share science with the public, aiming not only to give visibility to the researchers working at the institution, but also to raise awareness of the importance of biomedical research. With this commitment, the Communications Department works to bring the gap between research and the society promoting the dissemination of the scientific achievements through different channels, such as media and social media. Another main goal is to establish a strong brand identity to act as a comfort factor and set differentiation and personality to the institution. Finally, the Communication Department pursues to be useful for IrsiCaixa employees and to foster engagement by **IrsiCaixa** researchers by providing internal support to them in making their work visible.

>6,600
followers on Twitter

>600
subscribers in the monthly newsletter

622
press, radio and TV hits

203,205
visits to the www.irsicaixa.es website

Media

IrsiCaixa's commitment to sharing the results of its coronavirus research in open access and real time meant that, the **IrsiCaixa** media presence tripled in 2020. This high communication requirement was maintained throughout **2021**, a year in which **IrsiCaixa** researchers have become leading figures for science journalists.

During **2021**, 13 press releases were issued, 34 news items were posted in the institutional website and 354 posts were made on social media. These media campaigns led to the achievement of 620 media hits in TV, radio and press items referring to different **IrsiCaixa** research fields. Some of the most successful impacts in the media of 2020 are listed as follows:

— Both antibodies generated by vaccination and by natural infection block the SARS-CoV-2 variant described in England.
— SARS-CoV-2 infection generates protective antibodies that are maintained beyond one year.
— COVID-19 recovered people living in nursing homes have high levels of protective antibodies three months after receiving the vaccine, in contrast to those who have not undergone the disease.
— **IrsiCaixa** develops a website to monitor SARS-CoV-2 variants in Spain.

Web and social media

IrsiCaixa has further consolidated its presence in Twitter and LinkedIn. On the one hand, 423 people started following the @IrsiCaixa user on Twitter in **2021** and the posts on this channel got more than 1,500 reactions throughout the year, confirming the engagement of users. On the other hand, the sustained growth of LinkedIn followers since it was created in 2017 has been maintained and the platform now counts with 1,761 followers. Social media campaigns designed in **2021** included #HerStepForward, #IrsiCaixaAlumniNetwork, #IrsiCaixaContesta and #CoronoFACTS. As for the institutional website, traffic data endorse the high impact of the website: 110,000 users, 125,121 sessions and 185,485 visits in the website pages.

Institutional communication

The Communications Department continued working on the planning and design of corporate materials, as well as on the monitoring of the correct inclusion of the institutional image in congress materials, web pages, press releases, among others. Moreover, in **2021** the department redesigned the Living Lab for Health page and created a new landing page in the institutional website to include all the information related to equality, diversity and inclusion.

Other projects

In **2021**, thanks to the support of the Spanish Foundation for Science and Technology (FECYT), the Communications Department organized outreach sessions on HIV/AIDS in Brians1, Lledoners, Quatre Camins and Dones, four prisons of Catalonia. It also elaborated a guideline in order to endure the gender-inclusive and non-stigmatizing communication language at **IrsiCaixa**.

HIGHLIGHTED INSTITUTIONAL NEWS

THE DIRECTOR OF IRSICAIXA BONAVENTURA CLOTET IS AWARDED WITH THE 2020 'PREMI NACIONAL DE RECERCA'

THE 'PREMI NACIONAL DE RECERCA' RECOGNIZES THE SCIENTIFIC PROGRESS CARRIED OUT BY RESEARCHERS THROUGHOUT THEIR CAREER. THE AWARD GRANTED TO THE DIRECTOR OF IRSICAIXA HIGHLIGHTS HIS RESEARCH OF INTERNATIONAL SCOPE FOR MORE THAN 40 YEARS IN THE FIELD OF INFECTIOUS DISEASES, SPECIALLY HIV

In its 31st edition, the Government of Catalonia and the Catalan Foundation for Research and Innovation (FCRI) have awarded ex aequo with the 'Premi Nacional de Recerca' 2020 to the physician and infectiologist Bonaventura Clotet, director of **IrsiCaixa**, and the mathematician specialist in robotics and artificial intelligence Carme Torras. The 'Premi Nacional de Recerca' honors the researcher who has contributed significantly and internationally during their career to the advancement of a scientific discipline in any of its fields: human and social sciences, life and health sciences, engineering and technology, and experimental sciences. Bonaventura Clotet received the award for his international research over more than 40 years in the field of HIV and related diseases, which positions him as one of the most important international researchers in the development and application of therapeutic strategies for the eradication and prevention of AIDS. (June 2021)

IRSICAIXA RECEIVES FUNDING FROM LA MARATÓ TO CARRY OUT 5 RESEARCH PROJECTS ON SARS-COV-2

Of the >10M€ raised by La Marató 2020, **IrsiCaixa** will receive almost 830,000€ to keep making progress in research on SARS-CoV-2. A year after the outbreak of the COVID-19 pandemic, further study of this virus is essential. **IrsiCaixa** is launching 5 projects focused on the SARS-CoV-2 surveillance and outbreak control, the study of the immunological response against the COVID-19 disease and the development of new therapies, among others. (June 2021).

IRSICAIXA RESEARCHER SARA MORÓN-LÓPEZ RECEIVES ONE OF TWO GLOBAL GILEAD GRANTS FOR HIV RESEARCH

The grant ($130,000) will be used to continue the project that the researcher began during her postdoc at the University of California, focused on how to eliminate HIV from the body, or keep it silenced. This 2-year project is one of the 2 projects in the HIV field worldwide funded by GILEAD. With this grant, the researcher will face one of the greatest challenges in the fight against HIV, which is the study of the reservoir. (June 2021).

AN IRSICAIXA PROJECT TO DIAGNOSE AND MONITOR INFECTIOUS DISEASES, AMONG THE SELECTED PROJECTS BY CAIXARESEARCH VALIDATE 2021 CALL

From a total of 97 projects submitted, the "la Caixa" Foundation, within the framework of the CaixaResearch Validate call, will offer financial and training support to 17 Spanish projects, including one from **IrsiCaixa**, led by postdoctoral researcher Marta Ruiz-Riol. The aim of the project is to provide society with a tool to improve the diagnosis and monitoring of infections caused by HIV, SARS-CoV-2 and *M tuberculosis*. (September 2021).

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 students
— Training of post-doctoral researchers
— Continuing professional development for staff
— Visiting researcher placements (we particularly welcome trainee researchers interested in learning from **IrsiCaixa** research groups).

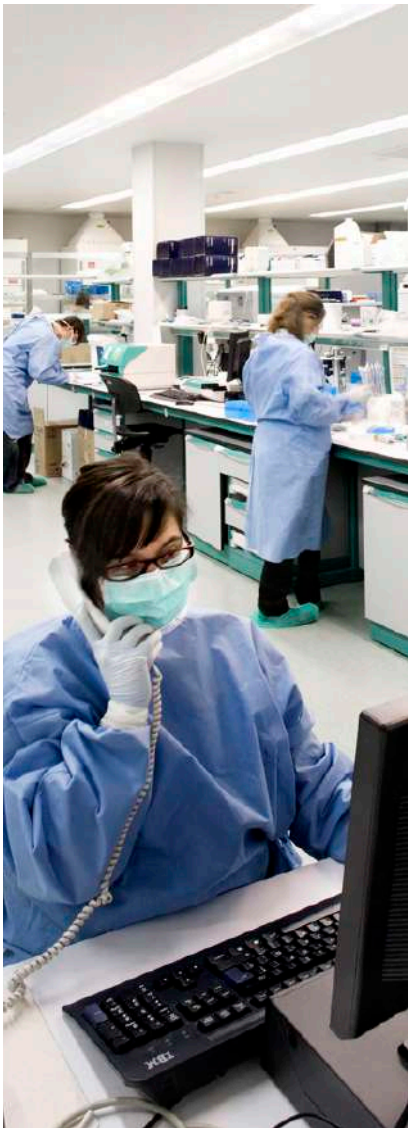
Staff in training

22 pre-doc researchers

34 post-doc researchers

Training activities

13 research results meetings



Internal and external training

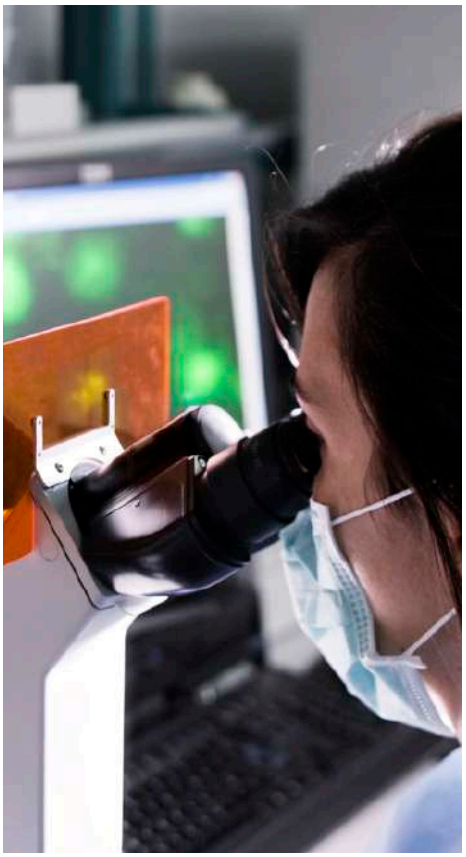
— Weekly meetings at which group members present their results. These meetings develop capacity to structure and defend experimental data before a restricted audience of experts in the field.
— Fortnightly meetings at which group members present their results. These meetings develop capacity to structure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

Note that as a result of the COVID-19 pandemic, during **2021** in-person attendance at all internal and external meetings, at seminars and conferences and in face-to-face training was cancelled. There has, however, been a substantial increase in national and international training and other encounters online.

Chair in Infectious Diseases and Immunity

In 2013, **IrsiCaixa** signed an agreement with the Fight AIDS and Infectious Diseases Foundation (FLS) 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 FLS and the UVic-UCC in fostering research into HIV/AIDS 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 activities in **2021**:



Date	Type of activity	Title	Place	Conducted by
January	Lecture	Endocarditis	Faculty of Medicine, UVic-UCC	Lourdes Mateu
January-Februray	Lecture	Infections in Oncological-Hematological patients	Faculty of Medicine, UVic-UCC	Esteban Reynaga
March	Seminar	Aging	Faculty of Medicine, UVic-UCC	Eugènia Negredo
March	Lecture	Infections in patients with transplants (solid organs) or in treatment with immunomodulators	Faculty of Medicine, UVic-UCC (on line)	Rosa Benítez
April	Seminar	Induction of protective T cell immunity in HIV vaccines	Faculty of Medicine, UVic-UCC	Christian Brander
May	Lecture	Gastroenteritis	Faculty of Medicine, UVic-UCC (on line)	José Ramón Santos
May	Lecture	Parasitosis	Faculty of Medicine, UVic-UCC (on line)	Silvia Roure
June	Seminar	Telemedicine: teleictus	Faculty of Medicine, UVic-UCC (on line)	Cora Loste
June	Seminar	Tuberculosis	Faculty of Medicine, UVic-UCC (on line)	Roger Paredes
June	Seminar	Social determinants of health: the UN sustainable development goals	Faculty of Medicine, UVic-UCC (online)	Roger Paredes
June	Continuing education course	Update on HIV infection	Continuing Education, UVic-UCC	B Clotet, E Negredo, P Coll, C Loste, J Puig, J Blanco, J Martínez-Picado, B Mothe
October	Seminar	Next Generation Sequencing i Big Data en malalties infeccioses	Faculty of Medicine, UVic-UCC (on line)	Marc Noguera
Scheduled on November	Seminar	Monoclonal antibodies, therapeutic technologies and applications	Faculty of Medicine, UVic-UCC (on line)	Julià Blanco
Scheduled on November	Seminar	Induction of protective T cell immunity in therapeutic HIV vaccines	Faculty of Medicine, UVic-UCC (on line)	Christian Brander

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 ART-Suppressed 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. *Approval is expected in Dec 2021.*

Sponsor: European Comission– EAVI2021

Principal investigators: **Dr. Beatriz Mothe, Dr Christian Brander**

Code/reference: 2020-000292-20

2. **AELIX-002**

A Phase I, Randomized, Double-Blind, Placebo-Controlled Safety, Tolerability and Immunogenicity Study of Candidate HIV-1 Vaccines DNA.HTI and MVA.HTI in Early Treated HIV-1 Positive Individuals

Study type: interventional

Design: phase I, randomized, double-Blind, placebo-controlled

Recruitment: completed

Start–end: 2017- 2021

Sponsor: Aelix Therapeutics, SL

Principal investigator: **Dr. Beatriz Mothe**

Participating centres: Germans Trias i Pujol University Hospital; AELIX Therapeutics; **IrsiCaixa**

Code/reference: NCT03204617

3. **RV 306**

Randomized, Double Blind Evaluation of Late Boost Strategies With IHV01 (FLSC in Aluminum Phosphate) and A244 With or Without ALFQ for HIV-uninfected Participants in the HIV Vaccine Trial RV306 / WRAIR 1920

Study type: interventional

Design: phase I, randomized, double-blind

Summary and objectives: the purpose of this study is to define the safety and immunogenicity of IHV01 and A244/AHFG with and without ALFQ at a full dose and at a fractional dose (one-fifth of a full dose) in a late boost setting for participants who had previously received a late boost of AIDSVAX®B/E with or without ALVAC in RV306. Safety will be assessed through the frequency of the overall and specific post-vaccination reactions. Blood, lymph nodes, sigmoid tissue, and mucosal specimens/secretions will be collected to assess humoral, cell-mediated, innate, and mucosal immune responses. Healthy, HIV-uninfected participants, at a low risk for HIV infection, available for 12 months, who were randomized to receive active vaccine in RV306 and completed all vaccinations will be enrolled. A total of 120 participants will be enrolled across four vaccination groups. In each group, 25 participants will receive IHV01 and A244/AHFG at a full or fractional dose with or without ALFQ and 5 participants will receive placebo. All injections, whether vaccine or placebo, will be a one-time intramuscular (IM) administration into the quadriceps muscle at study Day 0. Participants will be followed-up for up to 48 weeks after enrollment on days 1, 7, 14, 168 and 336. Mucosal secretion collections and endocervical cytobrush/swab procedures will be performed at Weeks 0, 2, 24, and 48 on consenting participants. Leukapheresis, sigmoid biopsy, and lymph node biopsy procedures will be performed only at Week 2 on consenting participants.

Recruitment: not yet recruiting

Start–end: 2021-2026

Sponsor: US Army Medical Research and Development Command & Canadian Institutes for Health Research (microbiome studies)

Principal investigator: **Dr Roger Paredes**

Code/reference: NCT04658667

4. **RESIST PROJECT**

Detection of markers of immune reconstruction and resistance to cyclin-dependent kinase (CDK) inhibitors in metastatic HR+/HER2- breast cancer

Study type: observational

Design: prospective observational study

Summary and objectives: in recent decades, there has been an increase in survival and an improvement in quality of life for patients with metastatic breast cancer, thanks to new drugs and a better classification by immunophenotype. Despite these advances, however, metastatic breast cancer remains incurable. Of these patients, 70% present with a hormone-sensitive tumour, with hormone receptor expression and no HER2 overexpression. Until recently, these patients received sequential hormonal treatment that benefited survival but led to treatment resistance and disease progression. A new scenario has been opened up, however, with the incorporation of CDK4/6 inhibitors such as palociclib, ribociclib and abemaciclib as first- and second-line treatments. Our study aims to detect predictive response and resistance factors for CDK4/6 inhibitors on the basis of prior knowledge of the functioning of SAMDH1 and also to establish how the CDK4/6 mechanism intervenes in viral and oncogene pathological processes.We will analyse 50 patients with metastatic breast cancer who will initiate first- or second-line therapy with hormonal treatment plus CDK4/6 inhibitors. Blood will be extracted at baseline, at 15 days and every three months until progression, thereby combining healthcare with a study of predictive response factors, susceptibility to viral infections (HIV) and resistance to treatment

Start–end: 2018-2021

Principal investigators: **Dr Ester Ballana,** Dr Mireia Margelí

Participating centres: Catalan Oncology Institute; **IrsiCaixa**

Code/reference: PI-18-063 (CEIC Code)

5. **RUTIVAC-1**

A Randomized, Double-Blind, Placebo-Controlled Phase I Trial to Evaluate the Immunomodulatory Effect of RUTI® in Individuals with High-Risk Non-Muscle-Invasive Bladder Cancer (NMIBC) Treated

with Intravesical Bacillus Calmette-Guerin (BCG) (RUTIVAC-1)

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 high-risk 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 25 µg 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

Study type: interventional

Design: phase I, double blind, placebo-controlled, randomized

Start–end: 2016-2023

Sponsor: Archivel Farma S.L

Principal investigator: **Dr Cecilia Cabrera**

Participating centres: Germans Trias i Pujol University Hospital (Urology Department), Fight AIDS Foundation (CRO), **IrsiCaixa**

Code/reference: AC-16-048-CEIM (CEIC Code)

6. DUAL TRIPLE ART

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

Design: phase III

Recruitment: the study included 28 patients this year, reaching a total of 40 people recriuted.

Start–end: 2019 – 2022

Sponsor: ViiV Healthcare

Principal investigators: Dr José Moltó, **Dr Javier Martínez-Picado**

Participating centres: Germans Trias i Pujol University Hospital (Fight AIDS Foundation); **IrsiCaixa**; University of North Carolina (Chapel Hill, USA), and the Oregon Health & Sciences University (Beaverton, USA)

Code/reference: 2019-002733-10

7. DURVAST

A phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors

Summary and objectives: evaluating the effect of durvalumab (MEDI4736) in HIV-positive patients with advanced solid tumours

Phase: II

Recruitment: finished with a total of 12 participants, 7 of those patients were included during 2020

Start–end: 2017-

Principal investigators: Dr Annemarie Wensing, **Dr Javier Martínez-Picado**

8. 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 og 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 Post-COVID-19 condition are also included in this cohort.

Start–end: 2020-ongoing

Sponsor: YoMeCorono

Principal investigators: **Dr Bonaventura Clotet, Dr Marta Massanella**, Dr Lourdes Mateu

Participating centres: Germans Trias i Pujol University Hospital, Fight AIDS and Infectious Diseases Foundation, **IrsiCaixa**

Code/reference: HUGTiP/20-P-217

9. CoronAVI@S

Immune response to SARS-CoV-2 vaccine in institutionalized elders: the challenge for a long-term immunity

Study type: observational

Design: prospective comparative study

Recruitment: finished with a total of 98 participants

Summary and objectives: older adults have been disproportionately affected by the COVID-19 pandemic. Among them, residents from long-term care facilities (LTCF), who live in a congregate setting (with increased risk of transmission and infection) showed higher mortality rates than the general population of the same age. Therefore, vaccination of residents from LTCF against SARS-CoV-2 has been a priority in most countries. Ageing is associated with an immunosenescent phenotype characterized by a progressive increase of a proinflammatory state and, a diminished immune response to pathogens and vaccines. Therefore, there is an urgent need to determine the quality and the duration of immune responses of the elderly population, which could be very useful for designing specific SARS-CoV-2 vaccination calendars adapted to their immune needs. The aim of the study is to evaluate the quality and the duration of immune response generated by SARS-CoV-2 Vaccine in institutionalized elders living on LTCF, comparing individuals recovered from SARS-CoV-2 infection with elders who never got infected by SARS-CoV-2 living in the same senior facilities. In addition, we will compare the immune responses generated by elders with a younger population.

Start–end: 2020-2022

Sponsor: YoMeCorono, Fundació Glòria Soler

Principal investigators: **Dr Marta Massanella**, Dr Núria Prat

Participating centres: ICASS long-term care facilities, **IrsiCaixa**

Code/reference: IDIAP/ 20/116-P

10. ReCOVID

Clinical Characteristics and Outcomes of Patients with SARS-CoV-2 Reinfection

Study type: observational

Design: retrosprospective study
Summary and objectives: cases with suspected or possible reinfection with SARS-CoV-2 have been reported worldwide since September 2020. It remains unknown the durability of immune responses to this virus, and it is a current public health problem. Whereas infections by the closely related betacoronaviruses SARS-CoV and MERS-CoV elicit long-lasting protective immunity, immune responses to common-cold coronaviruses are short-lived. Reinfections may occur after a few months from first episode, but usually with mild symptoms. The possibility of reinfection implies that individuals that have been infected once cannot be definitively considered to be immune. Although so far confirmed reinfections appear to rare events, more evidence and longer follow-up time is required to better understand duration of immunity (natural or after vaccination), transmissibility and the likelihood and implications of reinfection. Identification of predictor clinical risk factors for reinfection would be useful for implementing interventions focusing on the reduction of disease burden in populations at risk, including special vaccination efforts. The aim of this study is to evaluate the clinical characteristics and outcomes of patients with SARS-CoV-2 reinfection.
Start–end: 2021-2022
Sponsor: YoMeCorono
Principal investigators: **Dr Marta Massanella**, Dr José Ramón Santos
Participating centres: Germans Trias i Pujol University Hospital, Fight AIDS and Infectious Diseases Foundation, **IrsiCaixa**
Code/reference: HUGTIP/ PI-21-235

11. CRICOV

Pool testing screening study for faster and more efficient screening of the prevalence of SARS-CoV-2 infection in the northern metropolitan area

Study type: observational
Design: prospective observational study
Summary and objectives: pooling testing combes the same type of specimen from several people and conducting one NAAT laboratory test on the combined pool of specimens to detect SARS-CoV-2. Pooled tests that return positive results will require each specimen in the pool to be retested individually to determine which individual(s) are positive. The advantages of pooling include preserving testing reagents and resources, reducing the amount of time required to test large numbers of specimens (increasing throughput), and lowering the overall cost of testing. The aim of the study is to determine if pool testing is an efficient technique that could be used to identify SARS-CoV-2 infected individuals rapidly and at lower cost.
Start–end: 2021
Sponsor: YoMeCorono, Progenika-GRIFOLS
Principal investigators: **Dr Marta Massanella**
Participating centres: Germans Trias i Pujol University Hospital, Fight AIDS and Infectious Diseases Foundation, **IrsiCaixa**
Code/reference: HUGTiP/ PI-20-282

Publications and Conferences

Publications

Original publications

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International congresses

1. Aguilar-Gurrieri C, Barajas A, Pons-Grifols A, Varela I, Amengual-Rigo P, et al. **High immunogenic VLP-based vaccines elicit new T cell specificities against melanoma neoantigens in mice.** *8th ImmunoTherapy of Cancer Conference (ITOC8).* On-line, 8-9 October 2021. Poster #P03.01

2. Aguilar-Gurrieri C, Barajas-Molina A, Varela-Tang I, Rigo-Aemngual P, Vazquez M, Lapore A, de Mattos-Arruda L, Guallar V, Carrillo J, Blanco J. **A new and flexible VLP vaccine platform for personalized cancer immunotherapy.** *EACR 2021 Virtual Congress: Innovative Cancer Science.* On-line, 9-12 June 2021. Oral Poster #EACR21v-0327

3. Blanco-Heredia J, Anjos-Souza C, Gonçalves-Ribeiro S, Gonzalez-Cao M, Callari M, Tresserra F, Rossell R, Caldas C, de Mattos-Arruda L. **The genomic and anti-tumor immune evolution of breast cancer.** On-line, 10-15 April 2021. Poster #2174.

4. Blanch-Lombarte, Ouchi D, Carabelli J, Marin MA, Jiménez-Moyano E, Peña R, Pelletier A, Talla A, Sharma A, Dalmau J, Ramón-Santos J, Clotet B, Sékaly RP, García-Prado J. **Selective depletion of TIGIT expressing memory HIV-specific CD8+s in HIV-1 and cART.** *Conference on Retroviruses and Opportunistic Infections 2021.* 6-10 March 2021. Oral Presentation.

5. Borgognone A, Guillén Y, Noguera-Julian M, Parera M, Ruiz-Riol M, Casadellà M, Duran C, Noël-Romas L, De Leon M, Birse K, Tamilselvan, Manzardo C, Sékaly R, Burgener A, Moltó J, Mothe B, Clotet B, Brander C, Paredes R. **Baseline gut-associated microbial signatures may help predict HIV-1 viral control after treatment interruption.** *6th International Workshop on Microbiome in HIV.* On-line, 7-8 April 2021. Oral Presentation.

6. Margelí M, Felip E, Romeo M, Gutiérrez-Chamorro L, Riviera-Muñoz E, Cirauqui B, Quiroga V, Teruel L, Ferrando A, Martínez-Cardús A, Ballana E. **Prognostic significance of SAMHD1 expression in breast cancer.** *ESMO Breast Cancer Virtual Congress.* On-line, 5-8 May 2021. Poster.

7. Margelí M, Felip E, Gutiérrez-Chamorro L, Riviera-Muñoz E, Layos L, Moran T, Romeo M, Martínez-Cardús A, Ballana E. SAMHD1: **A new Prognostic Marker in Breast Cancer (BC).** *American Association for Cancer Research (AACR) Annual Meeting 2021.* On-line, 10-15 April 2021. Poster.

8. Gálvez C, Grau-Expósito J, Urrea V, Buzón MJ, Martinez-Picado J. **The peripheral CD4+ T-cell reservoir atlas in cART treated HIV-infected individuals.** *28th Conference on Retroviruses and Opportunistic Infections.* On-line, 6-10 March 2021. Poster #300.

9. Gutiérrez-Chamorro L, Felip E, Romero M, Moran-Bueno T, Layos L, Riviera-Muñoz E, Margelí M, Ballana E. **SAMHD1 confers resistance to platinum-based drugs through modification of DNA damage response.** *EACR 2021 Virtual Congress - Innovative Cancer Science: Better Outcomes Through Research.* On-line, 9-12 June 2021. Poster.

10. Gutiérrez-Chamorro L, Riviera-Muñoz E, Palau V, Massanella M, García Vidal E, Badia R, Pedreño-López S, Senserrich J, Clotet B, Cabrera C, Crespo M, Pascual J, Riera M, Ballana E. **Supression of ACE2 function and antiviral immune response by SRAS-CoV-2 infection.** *Conference on Retroviruses and Opportunistic Infections.* On-line, 6-10 March 2021. Poster #1443.

11. Revollo B, Blanco I, Soler P, Toro J, Izquierdo-Useros N, Puig J, Puig X, Navarro V, Casañ C, Ruiz-Tabueca L, Pérez-Zsolt D, Videla S, Clotet B, Llibre JM. **SARS-CoV-2 transmission in an indoor large-scale live music event: a randomised clinical trial.** *31st ECCMID, the European Congress of Clinical Microbiology and Infectious Diseases.* On-line, 9-12 July 2021. Poster.

12. Kilpelainen A, Jiménez-Moyano E, Peña-Poderós R, Blanch-Lombarte O, Chamorro A, Martínez-Caceres E, Blanco I, Carrillo-Molina J, Blanco-Arbués J, Brander C, Mateu L, Paredes-Deirós R, Clotet B, García-Prado J. **SARS-CoV-2 non-seroconvertors present T-cell responses with decreased activation.** *CROI 2021.* 6-10 March 2021. Poster.

13. Kilpelaeinen A, Romero-Martín L, Blanch-Lombarte O, Quirant B, Jiménez-Moyano E, Ouchi-Vernet D, Pujol-Gimeno A, Lamonja-Vicente N, Martínez-Caceres E, Violán-Flors C, Torán-Monserrat P, Clotet B, Olvera-VanDerStoep A, García-Prado J. **High-Resolution mapping of T-cell immunity to the entire SARS-CoV-2 proteome.** *Conference on Retroviruses and Opportunistic Infections 2021.* On-line, 6-10 March 2021. Poster.

14. Marin M, Carabelli J, Quirant B, Ouchi D, Pujol-Gimeno A, Blanch-Lombarte O, Peña R, Lamonja-Vicente N, Manresa-Dominguez-JM, Ramos-Roure F, Clotet B, Martínez-Cáceres E, Violán-Fors C, Torán Monserrat P, García-Prado J. **Early core signature of soluble factors in mild to moderate SARS-CoV-2 infection.** *Conference on Retroviruses and Opportunistic Infections 2021.* On-line, 6-10 March 2021. Oral Presentation.

15. Martinez-Picado J. **Basic research: HIV cure and neutralizing antibodies.** *Update on the 28th Conference on Retroviruses and Opportunistic Infections (CROI 2021).* On-line, 16 March 2021. Invited Session Talk.

16. Martinez-Picado J. **Update on HIV Cure Progress.** *European Meeting on HIV & Hepatitis: Treatment Strategies & Antiviral Drug Resistance.* 26-28 May 2021. Plenum.

17. Martin-Alonso S, Álvarez M, Nevot M, Martinez MA, Menendez-Arias L. **HIV reverse transcriptases defective in strand displacement activity.** *2nd PhD Research Symposium in Health Sciences and Biomedicine.* Madrid, 21 May 2021. Oral Presentation.

18. Oriol-Tordera B, Esteve-Codina A, Berdasco M, Gonçalves E, Esteller M, Hanke T, Moltó J, Clotet B, Calle ML, Combadiere B, Sanchez-Pla A, Mothe B, Ruiz-Riol M, Brander C. **Impact of HIV kick-and-kill therapy on host epigenetic and transcriptional programs in PBMC, and viral rebound after cART interruption.** *4th HIV Research for prevention Conference.* On-line, 27 January – 4 February 2021. Oral Presentation #OA14.

19. Pérez-Yanes S, Casado C, Pernas M, Cabrera-Rodríguez R, Estévez-Herrera J, Márquez-Arce D, Olivares I, Urrea V, Marfil S, Ortiz R, Rovirosa C, López-Galíndez C, Valenzuela-Fernández A, Blanco J. **Defective functions of HIV envelope glycoprotein associate with long-term HIV control.** *Virtual Conference on Retroviruses and Opportunistic Infections 2021 (CROI).* On-line, 6-10 March 2021. Poster #226.

20. Pradenas E, Rodríguez-de la Concepción ML, Rovirosa C, Marfil S, Clotet B, Blanco J, Carrillo J. **Analysis of IgG1 and IgG3 humoral response against the membrane proximal external region of HIV-1 envelope glycoprotein**. *4th HIV Research for Prevention Conference (HIVR4P/Virtual).* On-line, 27 January – 4 February 2021. Poster #1008.

21. Pradenas E, Trinité B, Urrea V, Marfil S, Ávila-Nieto C, Rodriguez-de la Concepción ML, Tarrés-Freixas F, Izquierdo-Useros N, Paredes R, Mateu L, Chamorro A, Massanella M, Carrillo J, Clotet B, Blanco J. **Stable neutralizing antibody levels six months after mild and severe COVID-19 episode.** *Virtual Conference on Retroviruses and Opportunistic Infections 2021 (CROI).* On-line, 6-10 March 2021. Poster #2358.

22. Romero-Martin L, Duran-Castells C, Olivella M, Rosàs-Umbert M, Ruiz-Riol M, Olvera-Van Der Stoep A, Brader C. **Role of HLA-E antigen presentation on NK control of HIV infection.** *HIV Research for Prevention 2021.* On-line, 27 January – 4 February 2021. Oral Presentation.

23. Romero-Martín L, Tarrés Freixas F, Rodríguez-De la Concepción MC, Cunyat-Viaplana F, Carrillo JC, Blanco JB, Ruiz-Riol M, Brander C, Olvera A. **Alternative T cell effector functions are linked to humoral resposnes to HIV.** *HIV Research for Prevention 2021.* On-line, 27 January – 4 February 2021. Oral Presentation.

National congresses

24. Ainsua-Enrich E, Rodríguez-De la Concepción ML, Reynaga E, Ávila-Nieto C, Santos JR, Roure S, Mateu L, Paredes R, Puig J, Jimenez JM, Izquierdo-Useros N, Clotet B, Pedro-Botet ML, Carrillo J. **High-dose intravenous immunoglobulins might modulate inflammation in COVID-19 patients.** *XV Congrés de la Societat Catalana d'Immunologia.* On-line, 25-26 November 2021. Oral Presentation.

25. Bayon-Gil A, Hernandez I, Dalmau-Moreno J, Nieto J, Urrea Gales V, García-Guerrero MC, Gálvez-Celada C, Salgado-Bernal M, Heyn H, Martínez-Picado J, Puertas-Castro MC. **Immune preservation in HIV+ Viremic Non-Progressors is associated with downregulation of IFN-type I pathway and reduced activation of cytotoxic compartments.** *XII Congreso Nacional GeSIDA.* Málaga, 29 November – 2 December 2021. Oral Presentation #CO-14.

26. Blanco-Arbués, J. **Gestionant la incertesa - Immunitat enfront de la COVID-19.** *XIX Jornada*

vacunes i profilaxi CAMFiC. Les vacunes més enllà de la Pandèmia. Barcelona, 25 October 2021. Plenum.

27. Blanco-Arbués, J. **Vaccines and immunity against SARS-CoV-2, lessons learned.** *XV Jornadas Anuales CIBER-BBN.* On-line, 15 November 2021. Plenum.

28. Blanco-Parera A, Amrario-Najera V, Muñoz-Basagoiti J, Pérez-Zsolt D, Raïch-Regué D, Marfil S, Pradenas Saavedra E, Izquierdo-Useros N, Blanco J, Capell T, O'Keefe BR, Christou P. **Cyanovirin-N expressed in rice endosperm neutralizes SARS-CoV-2 via a mechanism involving interactions between the spike S1 protein and rice globulins.** *4th Biennial Conference of the International Society for Plant Molecular Farming.* On-line, 28-29 September 2021. Poster.

29. Gálvez C. **HIV-1 infected individuals with a Low Viral Reservoir: the LoViReT cohort.** RIS Fridays. On-line, 17 September 2021. Invited Session Talk.

30. Gutiérrez-Chamorro L, Riviera-Muñoz E, Ballana-Guix E. **La función de ECA2 y la respuesta antiviral a SARS-CoV-2.** *51 Congreso de la Sociedad Española de Nefrología.* On-line, 15-18 October 2021. Oral Presentation.

31. Izquierdo-Useros N. **El potencial de los colutorios para reducir la transmisión del SARS-CoV-2.** *Congreso Interdisciplinar SEPA JOVEN.* On-line, 4-6 March 2021. Invited Session Talk.

32. Izquierdo-Useros N. **¿Pueden los colutorios con CPC reducir la transmisión del SARS-CoV-2?** *2º Congreso Interdisciplinar COVID-19.* On-line, 12-16 April 2021. Invited Session Talk.

33. Vargheese A, Blanco-Parera A, Shenoy S, Sun Y, Marfil S, Pradenas E, Muñoz-Basagoiti J, Pérez-Zsolt D, et al. **Scytovirin domain 1 produced in rice endosperm shows potent microbicidal activity against HIV-1.** *4th Biennial Conference of the International Society for Plant Molecular Farming.* On-line, 28 September 2021. Poster.

34. Martínez-Picado J. **Nuevas estrategias de curación.** *XII Congreso Nacional de GESIDA.* Málaga, 29 November – 2 December 2021. Plenum.

35. Martínez-Picado J. **HIV cure strategies.** *Conference on Pathogenesis of HIV Infection.* On-line, 24 February 2021. Invited Session Talk.

36. Martínez-Picado J. **VIHsión de futuro: la erradicación del VIH.** *Punto de encuentro VIH 2021.* On-line, 21 April 2021. Invited Session Talk.

37. Martínez-Picado J. **Genetic factors and severity of COVID-19.** *Update on HIV infection and the COVID-19 pandemic.* On-line, 1 June 2021. Invited Session Talk.

38. Martínez-Picado J, Erkizia-Jauregi I, Muñiz-Trabadua X. **SARS-CoV-2 interaction with Siglec-1 mediates trans-infection by dendritic cells.** *Virology meeting 2021 – 3rd Symposium on Coronavirus Research.* 5 November 2021. Oral Presentation.

39. Muñoz-Basagoiti J, Alemany A, Pérez-Zsolt D, Ouchi D, Raïch-Regué D, Trinité B, Pradenas E, Blanco J, León R, Blanc V, Gispert J, Clotet B, Mitjà O, Izquierdo-Useros N. **Cetylpyridinium Chloride mouthwashes to reduce the shedding of viable SARS-CoV-2.** *3rd research Symposyum on Coronavirus / Virology Meeting 2021.* Barcelona, 5 November 2021. Oral Presentation.

40. Raïch-Regué D, Muñoz-Basagoiti J, Pérez-Zsolt D, Noguera-Julián M, Riveira-Muñoz E, Giménez N, Carabaza A, Giménez F, Blanco I, Paredes R, Ballana E, Clotet B, Blanco J, Izquierdo-Useros N. **Reduced detection of Delta and other VOCs by antigen-detecting diagnostic tests.** *XX Jornada de Virologia-Virology meeting 2021/ 3rd Research Symposium on Coronavirus.* Barcelona, 5 November 2021. Oral Presentation.

41. Pérez-Zsolt D, Muñoz-Basagoiti J, Rodon J, Elosua-Bayes M, Raïch-Regué D, Risco C, Sachse M, Pino M, Gumber S, Paiardini M, Chojnacki J, Erkizia I, Muñiz-Trabadua X, Ballana E, Riveira-Muñoz E, Noguera M, Paredes R, Trinité B, Tarrés-Freixas F, Blanco I, Guallar V, Carrillo J, Blanco J, Talenti A, Heyn H, Segalés J, Clotet B, Martínez-Picado J, Vergara-Alert J, Izquierdo-Useros N. **SARS-CoV-2 interaction with Siglec-1 mediates trans-infection by dendritic cells.** *XX Jornada de Virologia-Virology meeting 2021/ 3rd Research Symposium on Coronavirus.* On-line, 5 November 2021. Oral Presentation.

42. Salgado Bernal M. VIH **¿Podemos llegar a curarlo?** *Seminarios Online Col·legi de Biòlegs de Catalunya.* On-line, 3 March 2021. Invited Session Talk.

43. Tarrés-Freixas F, Aguilar-Gurrieri C, Molinos-Albert LM, Varela I, Ortiz R, Rodríguez-De la Concepción ML, Pradenas E, Trinité B, Marfil S, Ávila-Nieto C, Cervera L, Gutiérrez-Granados S, Segura MM, Gòdia F, Clotet B, Carrillo J, Blanco J. **A high-valency antigen displaying Gag-based VLP induces an antibody-dependent functional immune response.** *Keystone eSymposia on HIV Vaccines (EK42).* On-line, 1-5 June 2021. Scientific Committee.

44. Blanch-Lombarte O, Ouchi D, Jiménez-Moyano E, Carabelli J, Marin M, Peña R, Pelletier A, Talla A, Sharma A, Dalmau J, Ramón Santos J, Sékaly R-P, Clotet B, Garcia-Prado J. **Selective depletion of CD107ahi TIGIThi memory HIV-1 specific CD8+ T cells during long-term suppressive cART**. *PhD Day 2021, Can Ruti Campus.* 16 June 2021.

45. Carabelli J, Blanch-Lombarte O, Ouchi D, Jiménez-Moyano E, Marin M, Peña R, Dalmau J, Santos J, Clotet B and Garcia-Prado J. **TIGIT blockade restored CD107a degranulation of HIV-1 specific CD8+ T- cell subsets in individuals with long-term cART.** *Congreso Nacional GeSIDA XII 2021.* 29 November-2 December 2021.

46. Marin M, Ruiz A, Jimenez-Moyano E, Ouchi D, Blanch-Lombarte O, Gorman D, Peña R, Carabelli J, Barnard R, Manzardo C, Hanke T, Brander C, Howell, B Clotet B, Mothe, and Julia G Prado. **PD-1 blockade enhances vaccine-induced anti-HIV responses in early treated HIV-1 infected individual receiving therapeutic vaccination**. *Congreso Nacional GeSIDA XII 2021.* 29 November-2 December 2021.

47. Quirant B, Rodríguez C, Boigues M, Barallat J, Garcia-Prado J, Toran P, Violan C, Martinez E. **Evaluation of IgG, IgM and IgA anti-SARS-CoV-2 ELISA assays**. I *Congreso Nacional COVID-19.* 13-19 September 2021.


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