IrsiCaixa

Institut de Recerca de la Sida

"la Caixa" Foundation

Generalitat de Catalunya
Departament de Salut

IrsiCaixa
Scientific Report
2020

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IrsiCaixa

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. Over 25 years, **IrsiCaixa** has accumulated vast experience and knowledge in relation to that backbone of human health, the immune system, enabling it to tackle crucial challenges such as emerging infectious diseases, cancer, ageing and understanding of the microbiome.

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. **IrsiCaixa** also participates in clinical trials to evaluate innovative therapeutic strategies and actively cooperates with low-income countries in the global fight against AIDS.

IrsiCaixa places special emphasis on the formal training of young scientists, on innovation and on the transfer of knowledge generated in its laboratories.

Letter from the director

IrsiCaixa was founded in 1995, funded by "la Caixa" Foundation and the Department of Health of the Autonomous Government of Catalonia, with the aim of conducting basic research into AIDS, then a major health emergency. Fully **25 years** later, and numbering among the **world's leading HIV/AIDS research centres**, we are proud to have helped transform this life-threatening disease into a non-lethal illness. A **2020** milestone in HIV research was the giant step forward in the potential for HIV cure through stem-cell transplantation, taken by the IciStem consortium coordinated by **IrsiCaixa**. Furthermore, in the context of a cure for the 'London Patient', we described the 'Düsseldorf Patient' as a third case of long-term viral remission. Its experience in HIV research and acquired knowledge of the immune system has led **IrsiCaixa** to launch the H2020 MISTRAL project, aimed at decoding the role of the microbiome in HIV pathogenesis and cure.

The SARS-CoV-2 pandemic has most marked **2020**, reminding us of the capacity of a virus to wreak havoc on global health – as with AIDS in the 1980s. With research to find solutions for the new pandemic urgently needed, we rapidly launched a number of projects aimed at **detecting SARS-CoV-2, treating COVID-19 and preventing new infections.**

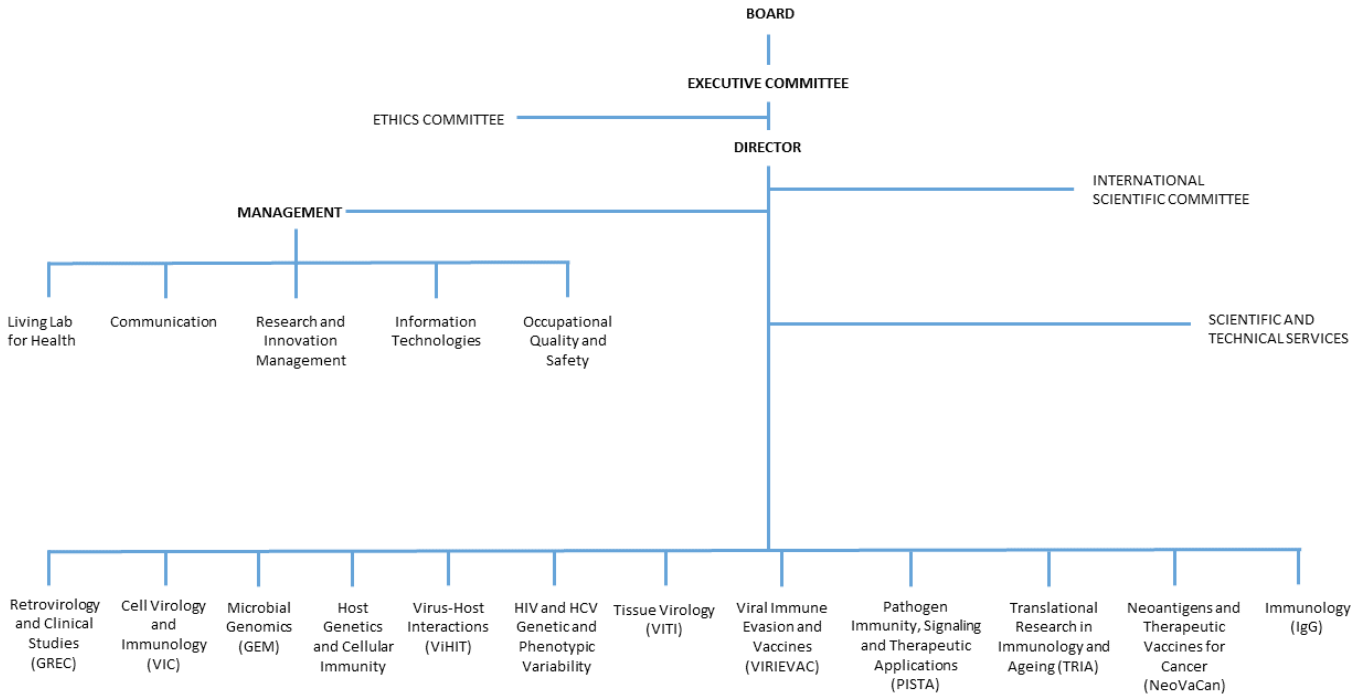
Along these lines, in **2020 IrsiCaixa** formed a consortium – funded by Grifols – with the Barcelona Supercomputing Center and IRTA-CReSA Animal Health Research Centre to develop antibodies, drugs and a vaccine against the new coronavirus. Achievements to date include the design of an ELISA antibody detection test, evaluation of the potential of currently available antiretroviral drugs to fight SARS-CoV-2 and an in-depth study of immune response to SARS-CoV-2. Strongly committed as we are to the principles of open and collaborative science, our findings were published in open access and real time during the health emergency. In **2020 IrsiCaixa** also researched new saliva tests to detect SARS-CoV-2 antigens and participated in different clinical trails to evaluate new coronavirus treatments, tests and vaccines.

We are increasingly vulnerable to emerging pathogens, given globalization and the interconnectedness of the human, animal and environmental worlds. It is precisely because IrsiCaixa is committed to the **One Health** concept – which recognizes that the health of people is closely connected to the health of animals and our shared environment – that it has initiated a collaboration with IRTA-CReSA to study emerging zoonotic diseases.

None of those milestones of **2020** would have been reached without key partners such as "la Caixa" Foundation and Grifols, whose support has enabled us to embark on new projects and to bolster existing research lines. We continue to be fully committed to meeting the needs of public health and firmly believe that research is crucial to planetary health.

Bonaventura Clotet
IrsiCaixa Director

Organizational Structure



Board

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Alba Vergés i Bosch
Health Minister of the Autonomous Government of Catalonia

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

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

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Esther Planas i Herrera
Antoni Vila Bertrán
Appointees of the Fundació Bancària Caixa d'Estalvis i Pensions de Barcelona "la Caixa" ("la Caixa" Foundation)

Montserrat Pinyol i Pina
Anna Veiga i Lluch
Appointees of the Board of the Fight 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
Jordi Casabona i Barbarà
Robert Fabregat i Fuentes

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. Charles Boucher
Professor at the Department of Virology of the Erasmus Medical Center at Erasmus University (Rotterdam, Netherlands).

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
Nikon

Key Figures 2020

Total **staff**

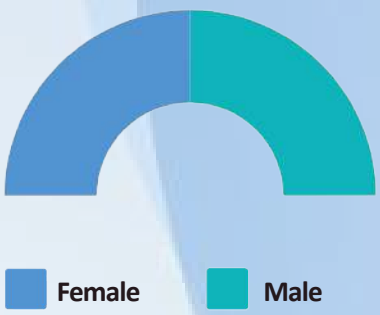
106

Sex

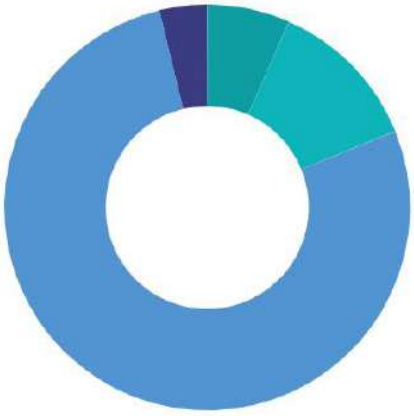
67% ♀

33% ♂

Principal investigators



Staff by **categories**



- **Scientific and technical Services** (6,6%)
- **Administration and research support** (12,26%)
- **Research** (77,36%)
- **Living Lab** (3,77%)

Theses read 2020

2

Daniel Pérez Zsolt
Retrovirology and Clinical Studies (GREC)

Maria Pujantell Graell
Virus-Host Interactions (ViHIT)

Projects awarded 2020

40

27 public

13 private

Projects active 2020

54

31 public

23 private

Publications 2020

101

Highlights 2020

January

IrsiCaixa celebrates its **25th anniversary** as an international center of reference in the field of HIV and infectious diseases.

Launch of MISTRAL, a 10-million-euro H2020 project coordinated by **IrsiCaixa** and with **Roger Paredes** as PI.

February

The CBIG Consortium, formed by **IrsiCaixa**, IRTA-CReSA and Barcelona Supercomputing Center, is constituted for the development of antibodies, drugs and a vaccine against the SARS-CoV-2.

March

The first results from the B-Argo-**ViHIT** multidisplinary team are published in *Cancers* journal.

The IciStem international consortium, coordinated by **IrsiCaixa** researcher **Javier Martínez-Picado**, describes the 2nd case of HIV-1 cure through allogeneic stem cell transplant.

The project *Development of a new SARS-CoV-2 vaccine* developed within the CBIG Consortium by the **IGG** team is granted.

April

"la Caixa" Foundation and **IrsiCaixa** promote the **Coronavirus Community Lab,** the first citizen science project to improve global health.

IrsiCaixa designs an open access protocol for the detection of SARS-CoV-2 antibodies without using commercial kits.

IrsiCaixa develops a study that confirms the safety of oncological immunotherapy treatments in people living with HIV.

May

New research group at **IrsiCaixa** led by **Jorge Carrillo**, IGG aims to characterize the immune response to infectious diseases, cancer and autoimmunity.

Julia G Prado is awarded with an ISCIII project to study long-term immunity in SARS-CoV-2 infection.

NeoVaCan team is awarded the prize *Ayuda Merck Investigación Clínica* in immuno-oncology.

Albajuna starts experiments in non-human primates.

The BCN02 results are published by **Mothe et al,** showing unprecedented levels of HIV control post vaccination.

June

VIRIEVAC team identifies a new mechanism of HIV resistance against protease inhibitors.

IrsiCaixa describes the 1st case of resistant HIV to all antiretroviral therapy combinations.

July

Maria Pujantell defends her thesis entitled *Molecular basis of innate immune activation pathways as regulators of susceptibility and clinical evolution of viral infections.*

The vaccine candidate of the CBIG Consortium is one of the world initiatives recognized by the WHO.

Julià Blanco joins the "Grup Col·laboratiu Multidisciplinari per el Seguiment Científic de la COVID-19".

Patent filed on SARS-Co-V2 consensus sequence serving for the development of vaccines against SARS-CoV-2.

August

First description of the epigenetic imprints of HIV infection was published at Plos Pathogens by **Bruna Oriol** et al.

September

PISTA team sign an agreement with Pharma Mar to perform an ***in vitro*** characterization of their antiviral compound Aplidin and file a patent application based on this work.

"la Caixa" Health Research award with a grant worth almost 700,000 € to the ETI-CURE project, which has **Julia G Prado** as one of its principal researchers.

Eudald Felip is awarded with a Rio Hortega contract from ISCIII.

October

PISTA and **IGG** teams publish a paper describing the outcome of hospitalized patients with COVID-19 pneumonia treated with high-dose immunoglobulin therapy in collaboration with Dr. Pedro-Botet and her team at the Infectious Unit of Germans Trias i Pujol.

November

IrsiCaixa start the first projects at the CMCiB with SARS-CoV-2 obtained from COVID-19 patients.

Participation of **Roger Paredes** in the development of WHO Antiretroviral Treatment Guidelines.

December

IrsiCaixa shows protective antibodies against COVID-19 are maintained for a minimum of six months.

PISTA team confirm that the CPC component of some mouthwashes reduces the infectivity of SARS-CoV-2.

RESEARCH GROUPS

Viral Immune Evasion and Vaccines (VIRIEVAC)

Projects awarded 2020

Identification and characterization of T cell protective responses against CoV2. ISCIII COV20/0660
Funding: ISCIII
Start/end dates: 05.21- 05.22
Research supervisor: **Julia García-Prado**
Participating entities: Irsicaixa, IGTP, HUGTIP, IDIAPJGol
IrsiCaixa groups linked in the project: VIRIEVAC, Host genetics and cellular immunity

SARS-CoV-2 infection among healthcare professionals: demographic characteristics and serological and immune responses related to progression's phenotype
Funding: DGRIS
Start/end dates: 05.21- 05.22
Research supervisor: Concha Violan Flors
Participating entities: Irsicaixa, IGTP, HUGTIP, IDIAPJGol

Enhancing Tissue-Specific Immune Microenvironments for the Cure of HIV.
Funding: ETI-CURE "La Caixa" Health Research HR20-00218
Start/end dates: 01.21- 01.24
Research supervisor: **Julia García-Prado**, María José Buzón
Participating entities: Irsicaixa, VHIR, Universidad Autónoma de Madrid

Grants Awarded 2020

Short-term fellowship mobility grant
Funding: RIS (Red nacional de SIDA)
Participating entities: Irsicaixa, Institut d'Investigació Sanitària Pere Virgili (IISPV)
Starting and finishing date: on hold due COVID19
Student granted: Oscar Blanch-Lombarte
Research supervisor: **Julia García-Prado**

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, selected member of the EATRIS-Spain Scientific Advisory Board

Filed patents

Title: *Polypeptides for eliciting humoral and cellular immune responses against coronavirus infections*
Inventors: **Christian Brander, Julia García Prado, Alex Olvera , Marc Noguera, Athina Kilpeläinen, Luis Romero**
Filling date: Jul 2020
Application number: US 62/828,195
Applicant: IrsiCaixa

Presentation

Our group's initial research interest was the identification of viral and host factors associated with HIV-1 extreme disease phenotypes. These studies brought to light the limitations of the antiviral CD8+ T-cell response in controlling the disease. In recent years, our research interest has switched to delineating the functional boundaries of viral pathogenesis and the role of the antiviral CD8+ T-cell response in controlling or eliminating viral infections. From a basic-translational research perspective, our group combines tools from molecular virology, biochemistry, T-cell immunology and systems immunology, focusing on the host-pathogen interaction interface, with the ultimate goal of designing advanced immunotherapies that restore antiviral immunity against HIV-1 and other chronic viral infections and so contribute to curing these diseases. In response to the COVID-19 pandemic this year, as a contribution to faster vaccine design, our group is actively working to understand protective T-cell immunity against SARS-CoV-2.

VIRIEVAC research lines during **2020** were as follows:
Pathogenesis. Identification of viral and host factors associated with disease outcomes. Our studies focus on various cohorts of HIV extreme disease phenotypes (both children and adults) associated with natural infection control (elite controllers and viraemic non-progressors) and also on rapid progressors.
Persistence, remission and cure. Delineation of the functional boundaries of the antiviral CD8+ T-cell response to HIV infection to control or eradicate the reservoir and translation of the 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 in both active and latent infection, as a major barrier to HIV remission and cure. Novel experimental models have been developed to monitor the reactivation and elimination of cells with latent HIV, identify new latency-reversing agents and design novel prototypes for immunotherapies to eliminate the HIV reservoir.
SARS-CoV2 cellular immunity. Characterization with high-resolution T-cell immunity to understand immunological memory against this novel virus to help drive forward pan-coronavirus vaccine development.

2020 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 HIV infection in non-progressor viraemics (NPVs). This collaborative project between **IrsiCaixa** and the University of Oxford has expanded to the study of a small, rare group of NPVs that lost virological control over time. This project, in collaboration with the Spanish AIDS Research Network (RIS) and the University of Oxford, has one manuscript under review (Colomer et al., 2020) and another in the process of preparation.
Prevention, eradication and functional cure. This research line, in successful and continuous expansion, is currently funded by several competitive projects led by Dr Prado (PI17/00164, GL19/00079) and includes a newly funded project through the "la Caixa" health research programme (HR20-00218). Our ongoing focus is the identification of long-term immune alterations despite long-term cART through the combination of single-cell cytofluorimetrics of 15 CD8+ T-cell markers including HIV-specific responses. We have identified subset-specific irreversible alterations of inhibitory receptors (IRs) in CD8+ T-cell memory and effector-like subset composition. These changes are defined by expression of TIGIT and TIGIT+TIM3 that postulate these markers for immunotherapies. Along these lines, we are working on the development of prototypes and their evaluation in functional assays. We have also continued our studies to evaluate the contribution of current immune checkpoint blockade (ICB) as a novel curative strategy and to understand the TRIM5 mechanism in controlling the viral reservoir. We have signed a material transfer agreement (MTA) with UCL to evaluate

candidate molecules with a potential for interfering with reservoir establishment. These studies, materialized in a single-cell analysis pipeline, have resulted in several publications (Blanch-Lombarte et al., 2019, JCM; Gonzalez-Cao, 2020, Jama Onco; Prado JG, 2020, editorial, Front Immunol) and two posters at CROI20. This line of research has led to successful national and international collaborations (Buzon´s laboratory at the Vall d´Hebron Research Institute (VHIR) and Sekaly's laboratory at Case Western).

SARS-CoV2 cellular immunity. Our group advanced the design of peptide libraries in silico against the complete SAR-CoV-2 proteome to assess the high-resolution cellular immune response through the development of cellular assays in non-seroconverters, asymptomatic patients, hospitalized individuals and other progression groups. We currently participate in two COVID-19 consortia (KING and PROHEPIC19) studies evaluating T-cell immunity. In the last eight months, our work in this line of research has materialized in two funded projects, a publication (Olvera et al., 2020, Vaccines), two additional papers under review and a filed patent.

Perspectives for the future

— 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 the potential of TRIM5 mimicking molecules to control the reservoir; 5) continue work on SARS-Cov2 infection during the next year.
— Increase and strength our internationalization through new alliances and collaborations with research groups of excellence across Europe, EEUU and Africa.

>1M € obtained from competitive funding for HIV and CoV2 research

7 Ongoing projects

7 Peer-review publications

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

Visiting Researcher
Eudald Vehí, Biology degree, University of Barcelona

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 2020

Microbiome-based stratification of individuals at risk of HIV-1 acquisition, chronic clinical complications, antimicrobial drug resistance, and unresponsiveness to therapeutic HIV-1 vaccination (MISTRAL)
Funding: European Commission
Participating entities: Méditerranée Infection, CHIP, Case Western Reserve, Karolinska Institutet, Hispanosida, IDIBAPS, ISGlobal, Asphalion, AELIX, Vedanta, Imperial College London and IrsiCaixa
Starting and finishing date: 2020-2025
Research supervisors: Roger Paredes (coordinator)
IrsiCaixa groups linked in the project: Microbial Genomics and Host Genetics and Cellular immunity

Optimization of SARS-CoV-2 full-genome sequencing
Funding: Phylantropy – YoMeCorono
Participating entities: IrsiCaixa
Starting and finishing date: 2020- 2020
Research supervisors: Marc Noguera and Roger Paredes
IrsiCaixa groups linked in the project: Microbial Genomics

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 the future

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.

10 Million € funding in projects where we have a leading role

4 Coordinated studies published at New England Journal of Medicine

1 Article published at The Lancet

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 2020

MISTRAL
Funding: EU H2020
Participating entities: IrsiCaixa coordinating the program, many international collaborators in the consortium
Starting and finishing date: 01.01.20 - 31.12.24
Research supervisors: **Christian Brander** and **Alex Olvera**
IrsiCaixa groups linked in the project: Microbial Genomics and Host Genetics and Cellular Immunity
Other participating bodies: AELIX Therapeutics, VedantaBio

Presentation

Our group is investigating cellular immunity against viral infections in hosts with compromised immunity, aiming to understand the underlying epigenetic mechanisms that regulate cellular immunity. The cohorts analysed in our studies include people with early HIV infection, people with controlled and uncontrolled HIV infection, and non-HIV-infected individuals who have received solid organ transplants or who have been diagnosed with viral-driven cancers, such as EBV lymphoma, or HPV-driven cancers. We are exploring different avenues to identify immunological correlates of HIV control in natural infection, and endeavouring to identify markers associated with HIV-related neurofunctional defects. These studies also include detailed analysis of the T-cell receptor repertoire of specific T-cell responses to HIV, in order to determine the molecular ontogeny of those responses and understand the transcriptional programme of these cells, with a view to guiding vaccination strategies that could induce robust, long-lasting and effective antiviral immunity. Finally, we also study possible factors governing HCV evolutionin liver transplant patients and immune determinants of organ rejection in HIV-infected patients who have received a kidney transplant from a donor who is also HIV-infected.

2020 Milestones and perspectives for the future

In **2020** we continued to advance the clinical development of the HTI T-cell immunogen, testing different vaccine regimens in pre-clinical animal models, including vaccinations with vaccine vectors such as RNA, DNA, ChAd, MVA and BCG- and lentiviral-based vectors. We unblinded the first clinical trial with humans – the AELIX-002 study – at the end of 2020. In this study individuals received several injections of the HTI vaccine vectored by DNA, MVA and ChAd. The data show an unprecedented level of vaccine effect on the length of time individuals can remain off ART and also identify a direct correlation between the magnitude of the vaccine-induced response and the time off ART. In the context of the EAVI consortium, we have also initiated an ongoing study in non-human primates combining our T-cell vaccine with some of the most advanced B cell SOSIP immunogen constructs; at the end of **2020**, our newest clinical trial, BCN-03, obtained provisional AEMPS approval. That trial, which will be run parallel to studies in NHP, will deliver HTI T-cell vaccines and SOSIP Env proteins in individuals with existing HIV infection as a novel approach for therapeutic vaccination and HIV cure strategies.

In **2020**, we finished immunological analyses for the CUTHIVAC-003 clinical trial conducted in Lima (Peru) that compared immunogenicity for intramuscular versus transcutaneous administration of an MVA-B-based vaccine. The published data has now been complemented with transcriptomics and microbiota data. The findings, supported by observations based on complete transcriptomic blood analyses, provide important indications on how to optimize vaccination outcomes. The data also highlight the impact of the microbiota on the vaccine-induced immune response. These data form the basis for the pre-clinical work we are now conducting in the MISTRAL project, where, in the last year, we have replaced natural murine microbiota with specific bacterial strains before vaccination with HTI vaccines. The immune analyses are currently ongoing and will now also include microbiota samples from the above mentioned AELIX-002 and BCN03 trials. These analyses will be used to validate the combined transcriptomics, methylome and protein-array analyses on samples from different time points and stages of the vaccination regimen in the BCN-02 clinical trial, in which specific methylome signatures were observed between individuals who controlled the virus after vaccination versus those that needed to quickly restart ART.

In the liver transplantation setting, we have further integrated data from the overall Spanishiver transplantation cohort and have identified risk factors for organ rejection between groups with HIV and/or HCV infection. Those risks include HIV infection, high CD4/8 T-cell ratios, high levels of HLA-class I mismatch between donor and organ recipients and elevated levels of alloreactivity.

Over the coming year, we will initiate the BCN03 clinical trial and conduct further functional analyses with the AELIX-002 samples, especially by integrating microbiota and methylome data into those analyses. In addition, the SARS-CoV-2 pandemic has led us to invest significant efforts in studying epigenetic imprints in patients with COVID-19, particularly in individuals with long-COVID featuring neurological manifestations. We have created partnerships with centers at Stanford University and UC Davis and in Barcelona to explore potential epigenetic mechanisms by which the effects of acute SARS-CoV-2 infection persist over time and how this can impact neurological functions. These analyses will go hand-in-hand with studies in HIV, where we have focused our attention on the neurological long-term consequences of this infection. Data generated over the last year have identified several key markers and potential new therapeutic targets related to the brain reservoir of HIV. This component of the viral reservoir may be especially hard to eliminate and its characterization is far from complete, so our analyses will potentially shed some light on the mechanisms that maintain this reservoir and will offer new strategies to more specifically target it.

5 Conferences in which group members gave invited talks

23 Publications grom the group

8 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 Peliguero

Pre-doc researchers
Miriam Rosàs
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(s): Marta Ruiz Riol

Around 50% of people living with HIV develop some form of HIV-associated neurodisorder (HAND), possibly as a consequence of viral reservoir persistence, treatment toxicity and inflammation in the brain. There is thus an unmet medical need to better understand the aetiology and treatment options for HIV-associated neurological diseases. Our objective is to identify factors in peripheral blood plasma that are associated with HIV control and that have a physiological link to neurofunction. Over the last year, we performed plasma proteome analyses in untreated HIV-infected individuals, which identified Sirtuin 2 (SIRT2) as the most relevant factor associated with HIV plasma viral loads and HIV-proviral levels in PBMC. SIRT2 also showed a strong correlation with different markers of neurodamage as well as with levels of brain-derived neurotrophic factor (BDNF), microtubule-associated protein Tau (MAPT) and neurofilament light polypeptide (NFL) in plasma, CSF and brain tissue from HIV-infected individuals. Further exploration of SIRT2 plasma levels in a cohort of longitudinally neuro-evaluated HIV-infected individuals showed elevated SIRT2 plasma levels in individuals who initiated cART treatment later. These elevated SIRT2 plasma levels were also associated with brain involution and reduced neurofunction, highlighting the importance of early HIV diagnosis and prompt treatment initiation.

Virus-Host Interactions (ViHIT)

Projects Awarded 2020

Role of host immune factors as potential biomarkers for predicting response and resistance acquisition to palbociclib-based treatment in metastatic hormono sensitive breast cancer
Funding: Pfizer
Start/end dates: 01.21- 12.21
Research supervisor: **Ester Ballana**, Mireia Margelí
Participating entities: ICO, IGTP, B-ARGO, ICO

Grants Awarded 2020

Rio Hortega contract
Funding: ISCIII
Participating entities: IrsiCaixa, IGTP, ICO
Starting and finishing date: 01.21- 12.22
Student granted: Eudald Felip Falgàs
Research supervisor: **Ester Ballana**

Awards and Achievements

Ester Ballana, member of Internal Scientific Advisory Board of IGTP.
Ester Ballana, associate Editor of the journal Viruses, section Antivirals and Vaccines.
Ester Ballana, member of Editorial Board of Scientific Reports.

Doctoral theses

Title: *Molecular basis of innate immune activation pathways as regulators of susceptibility and clinical evolution of viral infections*
Author: Maria Pujantell Graell
Director: **Ester Ballana**
Department of Cellular Biology, Physiology and Immunology, Autonomous University of Barcelona (UAB)
Date: 21.07.20
Grade: *Cum laude*

Presentation

Our research focus is the identification and study of host cofactors in viral infections with a view to developing new therapies targeting virus-host protein interactions. Our group is currently working on two main research lines:

1. Identification of new cellular factors in viral infections.
The aim is to characterize interactions between HIV-1 and the host cell 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.

2020 Milestones

During **2020**, our group has 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 some 5000 samples. In collaboration with Dr Marta Riera from the IMIM Nephrology Department, our group also developed a method to study virus-receptor interaction.

— 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 commenced immunophenotype characterization of breast cancer patients treated with CDK4/6 inhibitors.

Perspectives for 2021

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.

Research group consolidation and improved competitive funding will also represent core objectives for 2021.

1 Group of talented young researchers pursuing a common research goal

5 Funded competitive contracts for researchers ongoing

Principal investigator

Ester Ballana

Associate Researcher(s)
Roger Badia

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

Pre-doc researchers
Ifeanyi Jude Ezeonwumelu
Eudald Felip
Lucía Gutiérrez
Maria Pujantell

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 2020

Halt the entry of enveloped viruses into immune cells: novel monoclonal antibodies and blockage of intracellular cascade
Funding: Spanish Ministry of Science and Innovation, ref. PID2019-109870RB-I00
Start/end dates: 07.20 - 06.22
Research supervisor: **Javier Martínez-Picado**
Participating entities: IrsiCaixa

3D human organoids for biomarker identification and treatment assessment in COVID-19 (3D4COVID)
Funding: Merck SARS-CoV-2 competitive international call, ref. IISP # 60258
Start/end dates: 10.20 - 09.21
Research supervisor: **Javier Martínez-Picado**
Participating entities: IrsiCaixa, UPF

CRISPR Screen to Identify Drug- Repurposing Host Targets for SARS-CoV-2 Infection (CRISPR-CoV2)
Funding: CRUE Spanish Universities
Start/end dates: 10.20 - 09.21
Research supervisor: **Javier Martínez-Picado**
Participating entities: IrsiCaixa, UPF

Vaccine against Covid-19: pilot project of plasma-derived exosomes from patients (ExoCoVac)
Funding: ISGlobal and YoMeCorono (crowdfunding)
Start/end dates: 06.20 - 12.21
Research supervisor: **Javier Martínez-Picado**
Participating entities: IrsiCaixa, ISGlobal

COVID Human Genetic Effort
Funding: YoMeCorono (crowdfunding)
Start/end dates: 06.20 - 12.21
Research supervisor: **Javier Martínez-Picado**
Participating entities: IrsiCaixa

Nuevas estrategias terapéuticas basadas en inhibidores de tirosina kinasas para la eliminación del reservorio latente del VIH-1 (TKICure)
Funding: Spanish Ministry of Science and Innovation
Start/end dates: 07.20 - 06.23
Research supervisor: **Javier Martínez-Picado**
Participating entities: IrsiCaixa

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. During **2020,** our group included SARS-CoV-2 as an additional research line.

2020 Milestones

1. HIV-1 cure

— Participation in the study of two unique cases of HIV remission (the London and Düsseldorf patients) following allogeneic stem cell transplantation with a donor containing the CCR5Δ32/Δ32 mutation in the viral co-receptor. Both patients are part of an international cohort of 48 HIV-positive subjects who received this treatment for severe haematologic disease (IciStem), as the only therapeutic intervention available to date that is capable of reducing the viral reservoir to undetectable levels. The cohort subjects who received donor cells without the CCR5Δ32/Δ32 mutation are potential candidates for innovative immune therapies.
— Development of a new gene therapy for elimination of the CCR5 viral receptor through TALENs.
— Characterization of the main factors related with HIV latency reduction in patients in ART treatment with extremely low viral reservoirs (LoViReT).
— Comparison of differences in viral reservoirs in well characterized cell subtypes that have been proposed as the main reservoirs of viral quiescence.
— Development of a new nanoparticle technology targeting myeloid cells aimed at inducing viral reactivation and promoting a cytotoxic response.
— Study of the tumoral and viral effects of new immunotherapies with blocking monoclonal antibodies (α-PD-1 and α-PD-L1) in HIV-positive patients with cancer.
— Evaluation of new antiviral drugs and drug combinations for their ability to reduce the viral reservoir.
— Development of a novel technology to detect and measure the functional HIV reservoir at the single-cell level.
— Evaluation of the viral reservoir in vertically infected children with subtype C virus.

2. Role of myeloid cells in viral pathogenesis

— Translation of knowledge acquired regarding the Siglec-1 receptor to other infectious pathogens, including Ebola virus, arenaviruses and Mycobacterium tuberculosis.
— Generation of blocking monoclonal antibodies to inhibit Siglec-1 receptor interaction with viruses.
— Characterization of the molecular mechanisms involved in signalling by means of the Siglec-1 viral receptor in myeloid cells.
— Development of innovative biotechnology tools.

3. Extreme HIV infection phenotypes

— Study in adults and children of factors involved in the non-progressive viraemic phenotype, which emulates the natural host with SIV infection (sooty mangabey monkeys), presenting high viraemia but no pathogenesis.
— Study of methylation of the complete genome in association with HIV infection and disease progression.
— Study of cellular factors involved in resistance to HIV infection.

4. SARS-CoV-2

— 3D human organoids for biomarker identification and treatment assessment in COVID-19.
— CRISPR-Cas9 screening to identify drug-repurposing host targets for SARS-CoV-2 infection.
— Pilot project to study plasma-derived exosomes from patients as a potential COVID-19 vaccine.
— Participation in the COVID Human Genetic Effort consortium.

Perspectives for 2021

With a view to further development of new strategies for treatment and cure of HIV/AIDS and further work on COVID-19-related projects, our group aims to do as follows:

— Quantify viral reservoir size and analyse its role by developing virological monitoring tools for the blood and tissues of patients on ART therapy.

— Study clinical interventions aimed at reducing viral reservoirs and controlling viral persistence.

— Generate humanized versions of our recently developed anti-Siglec-1 mAbs with a potent capacity to block HIV-1, Ebola virus and arenavirus transmission via myeloid cells by inhibiting virus-Siglec-1 interaction.

27 PEER-REVIEW RESEARCH ARTICLES DURING 2020, WITH THE CONTRIBUTION OF THE GROUP

11 ACTIVE PROJECTS DURING 2020

— Build nanoliposomes that specifically target Siglec-1 as expressed in dendritic cells as a mechanism to deliver drugs, latency reactivation agents and viral immunogens.

— Explore the role of virus-host interactions in extreme HIV-1 infection phenotypes.

— Explore therapeutic applications of factors underlying the non-progressor viraemic phenotype, with a profile similar to that of the natural host in having an immune system that is not affected by high levels of viremia.

— Explore the functional and mechanistic bases of SARS-CoV-2 infection.

Principal investigator
Javier Martínez-Picado

Post-doc researchers
Jakub Chojnacki
Mª Carmen Puertas
Patricia Resa-Infante
María Salgado

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

Laboratory technicians
Itziar Erkizia
Mª Carmen García

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

Projects awarded 2020

Impact of synonymous HIV-1 genome recoding on virus immune response and latency
Funding: Spanish Ministry of Science and Innovation (PID2019-103955RB-100)
Start/end dates: 06.20- 05.23
Research supervisor: **Miguel Ángel Martínez**
Participating entities: Irsicaixa

Awards and Achievements

Miguel Ángel Martínez, guest editor to lead a special issue in the journal *Viruses* on "HIV-1 and HCV variation and evolution"

Doctoral theses

Title: *Determinación del papel de los microRNAs en el desarrollo de daño hepático en pacientes infectados con el virus de la inmunodeficiencia humana (VIH)*
Author: Daniela Buccione
Director: Cristina Tural
Co-director: **Miguel Angel Martínez**
Department of Medicine, Autonomous University of Barcelona (UAB)
Date: Dec 20

Published patents

Title: *Human Helicase DDX3 Inhibitors as Therapeutic Agents JP6749344*
Inventors: **Annalaura Brai, Roberta Fazi, Cristina Tintori, Maurizio Botta, José Esté Araque, Miguel Angel Martinez, Javier Martinez, Andreas Meyerhans**
Filling date: Sep 2020

Title: *Human Helicase DDX3 Inhibitors as Therapeutic Agents US16/734,788*
Inventors: **Annalaura Brai, Roberta Fazi, Cristina Tintori, Maurizio Botta, José Esté Araque, Miguel Angel Martinez, Javier Martinez, Andreas Meyerhans**
Filling date: Oct 2020

Presentation

Innate immune detection of HIV-1 has been reported to occur via a variety of mechanisms. In recent years we have demonstrated that HIV-1 replication capacity and evolvability can be modified by synonymously recoding the virus genome (Martinez et al., 2019, Nucleic Acids Research, 47:10506-10519). Codon or codon pair biases and the consequent effect on mRNA translation have been suggested as a possible mechanistic explanation for virus attenuation by synonymous substitutions. However, HIV-1 RNA dinucleotide frequencies, e.g., CpG/UpA, or codon usage can affect host innate response and, consequently, the viral mechanisms of latency and persistence. Understanding the mechanisms of induction of the immune response mediated by RNA dinucleotide frequencies and codon usage will increase our understanding of HIV-1 latency, inflammation and pathogenesis.

2020 milestones and perspectives for the future

We recently explored how synonymous codon mutations impacted HIV-1 Env protein expression and virus replication capacity. We changed a single codon, AGG to CGU, located in the gp41 coding region (env nucleotide residues 2125 to 2127) and included in the HIV-1 intronic splicing silencer, finding that this change completely abolished virus replication and Env expression. We also found that changing codon usage in the gp120 region by including an increased number of CpG dinucleotides did not significantly affect Env expression or virus viability. Our findings show that synonymous recoding is useful for altering viral phenotypes and exploring virus biology (Jordan-Paiz et al., 2020, Journal of Virology, 94:e01108-20).

Takata and colleagues showed that a previously described retroviral restriction factor, IFN-induced zinc finger antiviral protein (ZAP), recognizes self from non-self via detection of CpG dinucleotides in the HIV-1 RNA genome (Takata et al., 2017, Nature, 550:124-127). As HIV-1 and other RNA viruses have a low CpG dinucleotide composition, this potentially sets the stage for ZAP as an important driver in the evolution of RNA virus genomes (along with other related proteins). Takata and colleagues synonymously recoded the HIV-1 genome and found that CpG dinucleotide suppression is essential for HIV-1 replication. Interestingly, results from our group suggest that an increased frequency of CpG dinucleotides is not always deleterious for HIV-1 (Jordan-Paiz et al., 2021, in press). In order to know the implications of ZAP for the phenotype of our synonymously recoded mutants, we targeted ZAP with specific siRNAs. Two intriguing results were obtained with our synonymously recoded mutants. First, WT virus reduced its replication in the absence of ZAP, suggesting that ZAP is a virus co-factor rather than an antiviral protein or another factor involved in the ZAP-mediated activity. Second, mutants with a significantly increased number of CpGs did not increase their replication capacity in the absence of ZAP. Those results show that the role of ZAP and the frequency of CpG dinucleotides in HIV-1 replication are far from being completely elucidated. We hypothesize that when CpGs are located in a specific HIV-1 RNA region, ZAP inhibition allows viral replication of CpG-enriched viruses (restriction factor), whereas ZAP inhibition may decrease viral growth of WT viruses or CpG-enriched viruses in other genome regions (viral co-factor).

Interestingly, SARS-CoV-2 is restricted by ZAP (Nichoua et al., 2020, Mbio, 11:e01930-20). Moreover, extreme CpG deficiency has been also observed in SARS-CoV-2 in comparison with other coronaviruses (Xia, 2020, Mol Biol Evol, 37:2699-2705). We expect to analyse in silico the evolution of the frequency of CpGs and of synonymous

substitutions in the SARS-CoV-2 full-genome sequences deposited in the GISAID database throughout the COVID-19 pandemic.

In relation to our work with HCV, we continue to explore whether circulating microRNAs (miRs) can be biomarkers of liver disease progression in HIV-1-infected patients. The lack of available biomarkers to non-invasively diagnose and predict different stages of liver disease (e.g., NAFLD and NASH) is currently one of the main challenges facing clinicians. We conducted a large-scale deep sequencing analysis of small RNA expression on plasma samples from HIV-1/HCV co-infected patients that did not exhibit liver fibrosis at the time of sampling. Importantly, after a mean of ten years, half of the former patients developed liver fibrosis (F2-4), while some remained without signs of liver fibrosis (F0-1). At the time of sampling, there were no significant clinical differences between liver fibrosis progressing and non-progressing patients (age, AST, ALT, GGT, platelets, FIB-4, liver fibrosis). We identified a signature of seven miRs (100-5p, 192-5p, 99a-5p, 122-5p, 125b-2-3p, 1246 and 194-5p) that were highly correlated with progression to liver fibrosis, detecting this progression with an area under the curve (AUC) of 0.910-0.806. The two miRs that displayed the best AUC values, 100-5p and 192-5p, yielded sensitivity of 88% and specificity of 85% in detecting liver fibrosis progression (Franco et al., 2020, under review). Our results demonstrate the potential of circulating miRs as biomarkers in the progression of liver injury in HIV-infected patients.

Once SARS-CoV-2 infection is established, the clinical course of COVID-19 is variable, making both case identification and triage difficult. We hypothesize that circulating plasma miRs may be possible biomarkers of COVID-19 inflammation, coagulation, lung disease and other organ disease progression. To this end, we are performing large-scale deep sequencing analysis of small RNA expression on plasma samples from patients with COVID-19. We are currently analysing samples from patients hospitalized with severe symptoms for whom sample was obtained on entry to hospital.

PRINCIPAL INVESTIGATOR

Miguel Ángel Martínez

Post-doc researchers
Sandra Franco

1 FUNDED COMPETITIVE RESEARCH PROJECT AWARDED

5 PEER-REVIEW PUBLICATIONS

Cell Virology and Immunology (VIC)

Projects awarded 2020

Desenvolupament de proteïnes de fusió Fc contra SARS-COV-2
Funding: Generalitat de Catalunya
Participating entities: IrsiCaixa; CReSA; BSC, IGTP
Starting and finishing date: 06.20 - 12.20
Research supervisor(s): Julià Blanco
IrsiCaixa groups linked in the project: VIC and IgG

Impact of HIV envelope function and antigenicity on elite control of HIV replication
Funding: ISCIII
Participating entities: IrsiCaixa; ISCII; IGTP
Starting and finishing date: Jan 2021- Dec2023
Research supervisor(s): Julià Blanco

Awards and Achievements

Julià Blanco joins the "Grup Col.laboratiu Multidisciplinari per el Seguiment Científic de la COVID-19". This group has been promoted by ISGlobal, the College of Medical doctors of Barcelona, with the collaboration of the Catalan Association of Research Centres (ACER)
Julià Blanco is member of the Biosafety board of IrsiCaixa
Julià Blanco is member of the Biosafety board of IGTP
Julià Blanco is member of the Scientific Career working group of IGTP
Julià Blanco is member of the Gender Equity working group of IrsiCaixa
Ferran Tarrés is member of the Training working group of IsriCaixa

Presentation

The ultimate goal of our group is the development of protective vaccines against HIV infection and the definition of treatment strategies (based on antibodies or inflammageing modulators) for HIV-infected individuals that contribute to HIV functional cure or eradication. Our work with HIV has expanded in recent years to cancer and other infectious diseases. In **2020**, the new SARS-CoV-2 pandemic was a relevant additional focus of our research.
In this context our group has focused on three main research lines:

Humoral response to the HIV envelope glycoprotein (Env)

— We have completed a comprehensive screening of sera to identify neutralizing and non-neutralizing responses to HIV, which will provide valuable information on natural responses to HIV Env.
— We have demonstrated the role of Env in immunological damage, work expanded in collaboration with visiting scientist **Silvia Pérez.**
— Synthetic antibody development, with **AlbaJuna Therapeutics** switching to non-human primates and starting GMP production of anti-HIV therapeutic antibodies.

VLP vaccine platform for the development of preventive HIV and other vaccines

— Our work on preventive HIV vaccines (new project PI20/00093) involves developing new antigens based on specific Env sequences (in collaboration with the ISCIII and the BSC).
— Our collaboration with MSD on respiratory virus vaccines currently involves testing the immunogenicity of our VLPs in a non-retroviral context.
— In collaboration with Leticia de Mattos Arruda, our key cancer vaccines project to generate immune responses to cancer has new animal models and a vaccine design pipeline (in collaboration with the BSC) already in place.

COVID-19 research

Our research has focused on understanding the humoral immune response to SARS-CoV-2 and understanding its protective and pathogenic roles.

2020 Milestones and Perspectives for the future

The CBIG consortium

Expertise accumulated over the last 20 years on characterization of humoral responses, pathogenesis, translational and vaccine research allowed us to rapidly respond to the COVID-19 threat, an effort that crystalized in the CBIG consortium with BSC and CReSA, financially supported by Grifols.

New research platforms

We are proud to have developed, using HIV-based pseudoviruses, the first SARS-CoV/SARS CoV-2 neutralization assay in Barcelona and to have contributed to the new Can Ruti Campus biosafety laboratory and the development of murine models of SARS-CoV-2 infection. These unique platforms are indispensable tools for the CBIG vaccine and therapeutic antibody development programmes.

Immunomodulation in persons with HIV

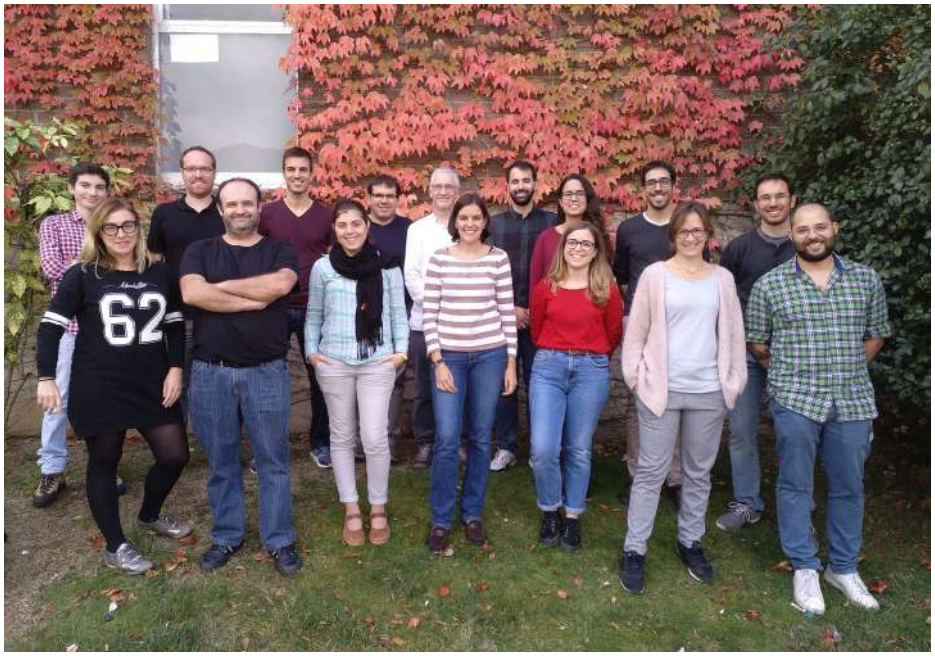
While much effort needs to be invested in COVID-19 research, HIV therapies continue to be a priority, with several collaborations with clinical and basic research teams at the Germans Trias i Pujol University Hospital HIV Clinical Unit, **IrsiCaixa**, ISGlobal and the Spanish AIDS Research Network maintaining this research line.

A redefinition of VIC research areas has led to identification of the following high-priority research lines:

— 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.

— 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.

— 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.



Principal Investigator

Julià Blanco

Associate researcher
Jorge Carrillo
Post-doc researchers
Carmen Aguilar
Benjamin Trinité
Pre-doc researchers
Montserrat Jiménez
Ferran Tarrés
Edwards Pradenas
Raquel Ortiz

Ana Barajas
Laboratory technicians
Silvia Marfil
Ismael Varela
Carla Rovirosa
Biostatistician
Víctor Urrea
Visiting researcher
Silvia Pérez

AlbaJuna Therapeutics, SL
Ester Aparicio, Victor Casanova, Francesc Cunyat, Wilmar Castillo, Cristina Val

15 Reseachers that changed their priorities to fight COVID-19

>2000 COVID-19 samples tested for neutralizing antibodies

2 New research groups at IrsiCaixa led by former VIC researchers

Grifols Projects

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

Senior researchers: Julià Blanco and Jorge Carrillo

The project aims, in collaboration with BSC, to develop a preventive HIV-1 vaccine based on the generation of HIV Gag VLPs with rationally designed HIV Env-antigens. A secondary aim is to exploit HIV-1 Gag VLPs as a vaccine platform to elicit humoral protective responses against other pathogens (treponema in collaboration with Oriol Mitjà), 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

This project aims to exploit engineered Gag as a vaccine platform (protein or DNA) to elicit cellular and humoral protective responses to tumours. The ultimate goal is to generate a platform of personalized DNA cancer vaccines. The necessary identification and selection of optimal tumoral antigens targeted by the immune system are tasks performed in collaboration with Dr Leticia de Mattos Arruda at IrsiCaixa and the BSC.

Tissue Virology

Projects awarded 2020

Macrophages autophagy as a MoA of IVIG

Funding: Grifols

Start/end dates: 09.20 - 07.21

Research supervisors: **Jordi Senserrich, Cecilia Cabrera, Bonaventura Clotet**

IrsiCaixa groups linked in the project: VITI, VIC, IgG

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.

2020 MILESTONES AND PERSPECTIVES FOR THE FUTURE

In 2020, our group achieved the following.

HIV pathogenesis and lymphoid tissue

— Studies of the effect of HIV infection on autophagy and of different modulators on HIV infection.
— Study of the effect of modulation of apoptosis on HIV replication.
— Characterization of the immune response of infiltrating immune cells in different tissues.

Bladder cancer

Therapeutic strategies for improving BCG treatment:
— RUTIVAC-1 clinical trial. Conclusion of recruitment and study intervention and commencement of clinical follow-up. Initiation of 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)

— Follow-up of a cohort of pregnant women infected by SARS-CoV-2.
— Study of the role of the ACE2 receptor in SARS-CoV-2 infection, in collaboration with the ViHIT group.
— 3D human lung tissue cultures: tissue explant cultures and organoids and in vitro infection with SARS-CoV-2.
— Characterization of innate immune response in children infected with SARS-CoV-2, in collaboration with Hospital Sant Joan de Déu.

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

7 ONGOING PROJECTS

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. All the group's research projects are carried out in collaboration with other researchers, both in and outside **IrsiCaixa**.

2020 milestones

— COVID-19. Characterization of SARS-CoV-2 immunopathogenesis and the immune response elicited after infection in human and animal models, and work on the development of novel tools for diagnosis and the evaluation of new treatments (such as IVIG) and on the design and development of COVID-19 vaccines. At the beginning of 2020 we responded to the need to urgently identify infected individuals and so limit new infections/control the COVID-19 pandemic by investigating the humoral response elicited by SARS-CoV-2 infection and designing an ELISA test to detect IgG, IgA and IgM antibodies against several SARS-CoV-2 antigens (spike, S1, S2 and receptor binding domain (RBD) subunits and the nucleocapsid protein). We also started producing key SARS-CoV-2 antigens to respond to the limited available resources. Using the ELISA test, we determined that the initial humoral response elicited against SARS-CoV-2 is characterized by an early rise in anti-S2 antibodies in the presence of IgM, IgG and IgA isotypes. We also fund that individuals with SARS-CoV-2 develop an early neutralizing humoral response, with neutralizing antibodies mostly targeting S1 and RBD.

— 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.

— 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.

— Basic immunology, immuno-oncology and autoimmune diseases. Characterization of the role of TACI in generating a T-cell-independent IgA response to commensal bacteria in the gut (with Dr Andrea Cerutti), establishment of the role of B-lymphocytes and antibodies in the development of Sjögren syndrome (with Dr Pablo Engel), development of personalized immunotherapies using neoantigens in the immuno-oncology area (with Dr Leticia De Mattos), evaluation of the immune response in patients treated with checkpoint inhibitors (with Dr Rafael Rosell and Dr María González-Cao) and exploration of the role of CD5L in the development of hepatic cancer (with Dr Rosa Maria Sarrias).

Projects awarded 2020

Development of a vaccine and therapeutics platform applied to the 2019 novel coronavirus (2019-nCoV): efficacy testing in different animal models
Funding: Grifols
Research supervisor: **Jorge Carrillo**
Participating entities: IrsiCaixa, IRTA-CReSA, BSC
IrsiCaixa groups linked in the project: IgG, VIC, PISTA
Other participating bodies: CMCiB

Development of a new SARS-CoV-2 vaccine
Funding: Departament de Salut de la Generalitat de Catalunya
Start/end dates: 01.20- 12.20
Research supervisor: **Jorge Carrillo**
Participating entities: IrsiCaixa, IRTA-CReSA, BSC
IrsiCaixa groups linked in the project: IgG, VIC, PISTA
Other participating bodies: CMCiB

Characterization of the humoral response to SARS-CoV-2. Implication for vaccine development
Funding: YoMeCorono crowdfunding campaign
Start/end dates: 05.20- 12.21
Research supervisor: **Jorge Carrillo**

Grants Awarded 2020

Ajuts per a la contractació de personal investigador novell
Funding: AGAUR
Starting and finishing date: 05.20- 04.23
Student granted: Carlos Ávila
Research supervisor: **Julià Blanco, Jorge Carrillo**

PERSPECTIVES FOR THE FUTURE

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

3 ONGOING PROJECTS

PRINCIPAL INVESTIGATOR

Jorge Carrillo

Post-doc researchers
Erola Ainsua
Maria Luisa Rodríguez

Pre-doc researcher
Carlos Ávila

Translational Research in Immunology and Ageing (TRIA)

Projects awarded 2020

Aging with HIV infection: causes and consequences of the premature immunoaging
Funding: Gala People in Red (philanthropy)
Start/end dates: 2020-2021
Research supervisor: **Marta Massanella**
Participating entities: IrsiCaixa, FLS

Persistent COVID-19 symptoms after viral clearance: manifestations and immunological alterations. Cohort KING
Funding:YoMeCorono crowdfunding campaign
Start/end dates: 2020-2021
Research supervisor: **Marta Massanella, Lourdes Mateu**
Participating entities: IrsiCaixa, FLS

Protective immune responses against SARS-CoV-2 developed by recovered elders living in nursing homes. Cohort CoronAVI@
Funding:YoMeCorono crowdfunding campaign
Start/end dates: 2020-2021
Research supervisor: **Marta Massanella, Nuria Prat**
Participating entities: IrsiCaixa, DAP-MN

IrsiCaixa SARS-CoV-2 Cohorts- The KING cohort and CoronAVI@S
Funding:YoMeCorono crowdfunding campaign
Start/end dates: 2020-2022
Research supervisor: **Marta Massanella, Nuria Prat**
Participating entities: IrsiCaixa, FLS

Awards and Achievements

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 and altered metabolism in ART-treated individuals to improve the quality of life of people living with HIV.

— Immunopathogenesis of COVID-19.
Our group is working on characterizing the immunopathogenic mechanisms and immune protection mechanisms associated with SARS-CoV-2 infection so as to develop new therapeutic strategies aimed at reducing mortality. It is also working on deciphering the immunology behind long-COVID in the substantial number of patients with COVID-19 who experience heterogeneous and persistent symptoms and is exploring the protective immune responses developed by recovered COVID-19 older adults living in senior facilities.

Working in close collaboration with the Infectious Diseases Unit of the Germans Trias i Pujol University Hospital and the Metropolitana Nord Primary Care Centre (DAP-MN), our ultimate goal is to better understand age-associated immune dysregulation and immunosenescence so as to identify novel strategies for immune rejuvenation, more effective vaccination responses and successful treatments for the older population.

2020 milestones

Inflammageing and immunosenescence during HIV infection
— 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
— Establishment, follow-up and coordination of the KING cohort of SARS-CoV-2 infected individuals with different levels of severity (asymptomatic to critical), a cohort that is of use to all **IrsiCaixa** groups.

— Exploration of the role of NK-cells in limiting overall hyperimmune activation in COVID-19.

— 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 Dr Mateu (FLS), exploration of immune dysfunction in individuals with long-COVID (individuals with persistent symptomatology despite viral clearance).

— In collaboration with DAP-MN, establishment of the CoronAVI@S cohort of older adults living in residences who have recovered from COVID-19 and characterization of their immune response and long-term immunity in order to identify protective responses in vulnerable populations.

— In collaboration with Progenika-Grifols, HUGTiP and DAP-MN, evaluation of a pooled-testing strategy for SARS-CoV-2 routine screening of senior residence staff to determine if it could prevent outbreaks, while concomitantly increasing high-throughput testing without losing sensitivity and reducing costs.

PERSPECTIVES FOR THE FUTURE

Ageing with HIV

Our group will continue to characterize accentuated immunoageing and immunosenescence in HIV-infected ART-treated individuals. 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.

COVID-19

We will continue our SARS-CoV-2 infection research, focusing especially on recovered individuals with long-COVID. The evidence indicates that good initial management of post-viral fatigue and syndromes reduces the likelihood of chronic impairment consisting of myalgic encephalomyelitis/chronic fatigue syndrome. Using extensive data collected on long-COVID-19, we will implement pilot interventions aimed at reducing persistent symptomology and improving the quality of life of recovered patients.

1 EMERGING GROUP FOCUSED ON AGEING STUDIES

3 MOTIVATED AND TALENTED YOUNG WOMEN RESEARCHERS

3 CLINICAL STUDIES OF HIV AND SARS-COV-2

PRINCIPAL INVESTIGATOR

Marta Massanella

Post-doc researcher
Maria Nevot

Pre-doc researcher
Macedonia Trigueros

Pathogen Immunity, Signaling and Therapeutic Applications (PISTA)

Projects awarded 2020

Fostering prophylactic and therapeutic strategies to fight the SARS-CoV-2 pandemic
Funding: Grifols
Start/end dates: 03.20- 03.22
Research supervisor(s): Bonaventura Clotet, Julià Blanco, Jorge Carrillo, **Nuria Izquierdo-Useros**, Joquim Segalés, Júlia Vergara-Alert, Alfonso Valencia, Victor Guallard
Participating entities: IrsiCaixa, IRTA-CReSA, BSC
IrsiCaixa groups linked in the project: PISTA, VIC, IgG

Antiviral activity of HCV protease inhibitors against SARS-CoV-2
Funding: IQS
Research supervisor: **Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa, IRTA-CReSA

Antiviral activity of Aplidin
Funding: Pharma Mar
Start/end dates: 2020-2021
Research supervisor: **Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa, IRTA-CReSA
IrsiCaixa groups linked in the project: PISTA, VIC, IgG

Immunomodulators for SARS-CoV-2
Funding: Mynoryx
Start/end dates: 2020-2021
Research supervisor: **Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa

Antivirals for SARS-CoV-2
Funding: ABIVAX
Start/end dates: 2020-2021
Research supervisor: **Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa

Novel antiviral approaches against SARS-CoV-2
Funding: Dentaid
Start/end dates: 2020-2021
Research supervisor: **Nuria Izquierdo-Useros**
Participating entities: IrsiCaixa

Novel inhibitors of the inflammasome for the mitigation of SARS-CoV-2 pathogenic effects in human type II pneumocytes and transgenic mouse models
Funding: ISCIII
Start/end dates: 2020-2021
Research supervisor: Timothy Thomson Okatsu
Participating entities: IrsiCaixa, CSIC
Other participating bodies: IIBB (Barcelona), Mount Sinai-Icahn School of Medicine (New York)

Awards and Achievements

Susana Benet, travel award to attend the Keystone Symposia on Tuberculosis: Immunity and Immune Evasion.
Nuria Izquierdo-Useros, member of the Reviewer Board of the Membranes MDPI Journal and collaborator at the "Asociación de Mujeres Investigadoras y Tecnólogas"
Nuria Izquierdo-Useros, member of the organizing committee of the Second Woman in Science Day at Can Ruti Campus.
Nuria Izquierdo-Useros, member of the grant review panel of Amfar for the first COVID-19 projects funded by this foundation.

Presentation

The world is becoming particularly vulnerable to emerging pathogens that thrive in new geographical areas due to globalization and climate change trends. Although infectious diseases can be contained by host defences, pathogens evolve to overcome immunity. The goal of this new group is to understand the underlying biology and features of human infection so as to develop novel therapeutic strategies against upcoming threats. As an emerging group studying emerging viruses, we aim to steer the rational design of broad antiviral treatments. Our research is framed within the **IrsiCaixa** strategic line of immunopathogenesis and other diseases. In our studies of emerging viruses and in our endeavour to develop innovative antiviral strategies and novel solutions to counteract microbial threats, our group collaborates with academic partners, different industries and clinical researchers based mainly at the Germans Trias i Pujol University Hospital.

2020 milestones

Our group was launched in February 2020 when the SARS-Cov-2 pandemic arrived in Europe, so we immediately focused our efforts on the new coronavirus. We actively participated in the response to SARS-CoV-2 by **IrsiCaixa** and are part of the Grifols-funded CBIG consortium established by Dr Clotet to identify new coronavirus therapies, antibodies and vaccines in collaboration with IRTA-CReSA and the Barcelona Supercomputing Center. Our group studied novel antivirals against SARS-CoV-2 while also searching for novel immunomodulatory agents that might prevent severe cases of COVID-19. We developed numerous tools in support of research by the CBIG teams, including different cellular assays to test the antivirals and immunomodulators currently being studied in different animal models to determine viral pathogenesis and the clinical potential of all compounds identified throughout the project.

During **2020**, our work focused on the following activities:

— Prioritization of agents approved for clinical use that could be repurposed for use against SARS-CoV-2 in collaboration with the CBIG consortium, working especially with Dr Júlia Vergara-Alert and Dr Joaquim Segalés (IRTA-CReSA) to study the efficacy of the most promising compounds in a humanized ACE2 murine model. This research line has identified potent clinically approved antivirals such as Aplidin, already assessed in phase II COVID-19 studies in which Dr Roger Paredes and the Fight AIDS and Infectious Diseases Foundation have actively participated.

— Development of novel cellular models to study different routes of SARS-CoV-2 entry and determination of the therapeutic efficacy of entry inhibitors in different cellular targets. These cellular models are now used in neutralization studies led by Dr Julià Blanco (VIC group).
— Study of primary cellular targets for COVID-19 immunopathogenesis (currently focused on kidney

cells), in collaboration with Drs Beatriu Bayes, Fritz Diekmann, Elisenda Banon and Maria José Ramirez at the Hospital Clínic de Barcelona experimental nephrology and transplantation laboratory.

— SARS-COV-2 testing of the antiviral efficacy of novel therapeutic strategies developed in four different collaborations, as follows: development of biotechnology strategies to generate genome-edited plants with high-value recombinant pharmaceuticals for testing against SARS-COV-2 (with Dr Paul Christou, ICREA research professor, University of Lleida); design of several aptamers to interfere with SARS-CoV-2 entry (with Dr Victor. M. González, Hospital Ramón y Cajal, Madrid); prioritization of several antivirals against other coronaviruses for testing against SARS-COV-2 (with Dr Cristina Risco, CNB-CISC, Madrid); and studies of novel inhibitors of the inflammasome intended to mitigate the pathogenic effects of SARS-CoV-2 (with Dr Timothy Thomson, CISC, Barcelona).

— Research into novel immunomodulatory agents that could decrease the cytokine storm induced by SARS-CoV-2 in critical COVID-19 cases. We set up an in vitro platform to detect the cytokine release induced by SARS-CoV-2, and have used this platform to identify novel immunomodulatory agents in collaboration with Mynorix pharmaceutical company.

— Participation in a prospective clinical case study, in collaboration with Dr Pedro-Botet, head of the Germans Trias i Pujol University Hospital Infectious Diseases Unit and **IrsiCaixa**'s IgG group. For hospitalized patients with COVID-19 pneumonia treated with high-dose intravenous immunoglobulin (IVIG) therapy we reported reduced inflammation, increased PaO2/FiO2 values, recovered lymphocyte count and improved pulmonary infiltrates. While randomized controlled trials will be needed to confirm this observation, identifying immunomodulatory treatments such as IVIG will be key to preventing COVID-19 pneumonia progression to severe respiratory failure.

PERSPECTIVES FOR THE FUTURE

We will consolidate our research line on antiviral strategies against SARS-CoV-2 and other coronaviruses in collaboration with new pharmaceutical companies and partner industries wishing to implement innovative solutions to control the current pandemic. To decipher the molecular pathways involved in SARS-CoV-2 infection and identify novel therapeutic targets, we are launching a collaboration with the Josep Carreras Leukemia Research Institute Proteomics Unit to analyse changes induced in key cellular targets.

PRINCIPAL INVESTIGATOR

Nuria Izquierdo-Useros

Post-doc researcher
Daniel Pérez-Zsolt

Pre-doc researcher
Susana Benet

Senior laboratory technician
Jordana Muñoz-Basagoiti

1 NEW TEAM WITH 4 EMERGENT RESEARCHERS TO COMBAT ONE NOVEL VIRUS

5 ACCEPTED PEER-REVIEWED PAPERS, AND 7 MANUSCRIPTS CURRENTLY UNDER REVIEW IN OUR FIRST YEAR OF TRAJECTORY

8 INVITED TALKS AND ORAL PRESENTATIONS WHERE ALL THE MEMBERS OF PISTA HAVE PRESENTED

Neoantigens and Therapeutic Vaccines for Cancer (NeoVaCan)

Presentation

Our group conducts research using multi-omics and immune characterization of solid tumours and liquid biopsies at several layers, with the goal of taking cancer patient therapy towards personalization and achieving a better understanding of tumour genomic and immune heterogeneity.

With **IrsiCaixa** VIC group and Barcelona Supercomputing Center teams, our group is working on co-developing a therapeutic neoantigen cancer vaccine for clinical application. As one of the two pillars of cancer vaccine development at **IrsiCaixa**, our group will coordinate the clinical side, translating next-generation sequencing-guided and experimental analyses of neoantigen prediction to therapeutic benefits for patients with cancer.

2020 Milestones and Perspectives for the future

—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.

Principal Investigator

Leticia de Mattos-Arruda

Post-doc researcher
Juan Blanco
Nuria de la Iglesia

Laboratory technician
Carla Dos Anjos

Projects awarded 2020

Genoma e inmunopeptidoma de biopsia líquida: una nueva perspectiva para el desarrollo de vacunas personalizadas contra el Cáncer de Mama Metastásico
Funding: Ayuda Merck Investigación Clínica en Inmuno-oncología
Start/end dates: 07.20- 07.22
Research supervisor: **Leticia de Mattos-Arruda**
Participating entities: IrsiCaixa, ICO-Badalona, Hospital Quiron Dexeus

Awards and Achievements

Leticia De Mattos-Arruda, Associate Editor of ESMO Open, a journal of the European Society for Medical Oncology
Leticia De Mattos-Arruda, ESMO faculty member for the Translational Research faculty group for the period 2021-2025

RESEARCH SUPPORT

Scientific and Technical Services

Sample Conservation and 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

25 Years of Sample Collection

Total of Samples Collected

38,133 cells
68,853 plasma
11,011 serum
30,890 other

Total: 148,887 samples

2020

Samples Collected

2,849 cells
3,008 plasma
250 serum
2,077 other

Total: 8,184 samples

435 Sequenced samples

294 public centres

141 private centres

360 Elisa Tests in COVID-19 diagnosis

Research and Innovation Management

Head
Lourdes Grau

Team
Noemí Carranza
Judith Dalmau
Chiara Mancuso
Laura Planells
Anna Sillero

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: Inhibitors of sialoadhesin for the treatment of diseases caused by enveloped viruses
Inventors: **Izquierdo Useros, Nuria; Kraüsslich, Hans-Georg; Lorizate, Maier; Martínez Picado, Javier**
Reference: WO/2013/092509; PCT/EP2012/075831
Priority Date: 22 Nov 2011
Publication date: 27 Jun 2013
Applicants: **IrsiCaixa**, Ruprecht-Karls-Universitaet Heidelberg, ICREA
Granted: US
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: Canada, Japan, US, Belgium, Switzerland, Germany, Spain, France, UK, Italy, The Netherlands, Sweden
Title: Method for identifying HIV neutralizing antibodies
Inventors: **Blanco Arbués, Julián Miguel; Carrillo Molina, Jorge**
Reference: WO/2014/037490; PCT/EP2013/068446
Priority Date: 6 Sep 2012
Publication date: 13 Mar 2014
Applicant: **IrsiCaixa**
Granted: US, Japan, Germany, Spain, France, UK, Italy, Hong Kong
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, Republic of Korea, Mexico, New Zealand, Russian Federation, South Africa
Pending: Brazil, Hong Kong
Published: Canada, India
Case inactive: EP
Licensed to: Aelix Therapeutics
Title: Immunogens for HIV vaccination
Inventor(s): **Meyerhans, Andreas; Martínez de la Sierra, Miguel Ángel; Brai, Annalaura; Itfazi, Roberta; Tintori, Cristina; Botta, Maurizio; Araque, José-Esté; Martínez, Javier**
Reference: WO/2016/128541; PCT/EP2016/052990
Priority Date: 13 Feb 2015
Publication date: 18 Aug 2016
Applicant(s): **IrsiCaixa**, Azienda Ospedaliera Universitaria Senese
Granted: Japan

Published

Title: Fc-fusion protein derivatives with high dual HIV antiviral and immunomodulatory activity.
Inventors: **Carrilo, Jorge; Blanco Arbués, Julián Miguel; Clotet Sala, Bonaventura**
Reference: WO/2018/207023; PCT/IB2018/00060
Priority Date: 10 May 2017
Publication date: 15 Nov 2018
Applicant: AlbaJuna Therapeutics, SL
Exploiting company(ies): Grifols, SA
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**
Licensed to: HIPRA
Title: Aurora kinase inhibitors for treating or preventing HIV infection or AIDS
Inventors: **Garcia-Vidal, Edurne; Badia, Roger; Riveira-Muñoz, Eva; Araque, José-Esté; Ballana Guix, Ester**
Reference: WO/2020/049208; PCT/ES2019/070596
Priority Date: 9 Sep 2018
Publication date: 12 Mar 2020
Applicants: **IrsiCaixa**, IGTP
Licensed to: Albajuna Therapeutics
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

Filed

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: not yet in national phases)
Applicant: **IrsiCaixa**
Title: Polypeptides for eliciting humoral and cellular immune responses against coronavirus infections
Inventors: **Garcia-Prado, Julia; Brander, Christian**
Jurisdiction: United States
Patent document: US63/051925
Filing date: 15 Jul 2020

Living Lab for Health

Head
Rosina Malagrida

Team
Aina Estany
Jessica Fernández
Marina Pino

Presentation

During 2020, IrsiCaixa's Living Lab for Health has facilitated changes in the governance of multistakeholder ecosystems through communities of practice (CoP) to find better open, collaborative and systemic solutions to persistent and complex health challenges. The Lab has contributed to improve the way we address our health challenges by promoting systemic research and innovation, with changes in both the research and innovation (R&I) system and the systems affected by the challenges to which the Lab intends to contribute. The proposed changes have as their ultimate goal to increase the impact of existing solutions and to stimulate the ideation and implementation of new solutions that better respond to the complexity of the systems as well as to the needs and expectations of different stakeholders. 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, one of which focused on SARS-CoV-2,. The Lab has also offered trainings to different universities, research centres and funding agencies, and has consolidated collaborations with local governments such as the Barcelona City Council.

The Lab follows 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 activities have been implemented within EC funded projects and with partnerships with the "la Caixa" Foundation.

Lines of action 2020

Projects to promote collaborative and systemic research and innovation

Two challenges: promotion of Healthy and Sustainable Diets and Promotion of Affective-Sexual Health

Challenge 1: promotion of Healthy and Sustainable Diets

Within the FIT4FOOD 2030 EC funded project and in collaboration with the Barcelona "la Caixa" Living Lab, the Lab has facilitated the advancement of the Fit4FoodBcn CoP and has organised a total of 14 workshops (with 90 attendees from 30 organizations) to facilitate mutual learning and to co-design a collective Strategic Plan and Action Plan. A systemic tool has been designed and piloted to help participants to better take into account the complexity. By 2021, new workshops will be implemented to ideate, prototype, validate and implement initiatives at collective and organizational level.

Challenge 2: promotion of afective-Sexual Health

The Co-ResponS(H)ibility Project, implemented within the InSPIRES EC funded project and in coordination with the Barcelona "la Caixa" Living Lab, has continued working towards a new model of promotion of Affective-Sexual Health. As a request of the Barcelona City Council, the project has started to focus specifically on youth and adolescents. Several preparatory meetings have been held to create a "steering committee" to start with the organization of workshops that will start in January 2021 to co-design a Collective Strategic Plan and Action Plan.

Coronavirus Community Lab

Initiative developed in collaboration with EduCaixa during spring of 2020 to mobilise and empower different communities to act as co-researchers to: 1) explore the complexity of the pandemic situation together and 2) design and generate evidence-based solutions aimed at improving community health in a broad sense.

Escoles Sentinella

The Departments of Health and Education of the government of Catalonia have launched the project "Escoles Sentinella" in order to monitor, evaluate and elaborate recommendations for the prevention of the Covid pandemic in educational centres. The Lab coordinates the participatory research processes in order to develop recommendations for the prevention with students, families and teachers. This part of the research will be conducted during the following 2 years in the framework of the EC funded project CONNECT.

Educational programmes and methodological guidelines

Training, consultancy and dissemination of RRI and Open Science for researchers, healthcare professionals, patients and other stakeholders

During 2020, 605 people have been trained through customized trainings. Some of the beneficiaries have been undergraduate and post-graduate scientists, healthcare professionals, policymakers, experts on public engagement and staff at funding organizations, among others.

The Lab has also offered support to 8 projects (from research groups at IrsiCaixa and from other organizations) during the design and writing of proposals to include co-creation, systemic and RRI approaches.

The Living Lab also participates in national and international conferences, seminars and workshops. For example in December 2020, the Living Lab offered a conference in the webinar "Societal Impact Learning

Series: Hands On Societal Impact" organised by the EIT Health with 152 attendees.

Educational programmes for youth aimed at facilitating science actions in collaboration with researchers and other stakeholders

STEAMxChange programme
In this programme, developed in collaboration with Educaixa and based on Xplore Health educational programme, students perform science-based activities to contribute to solve social challenges in their communities with innovative methodologies of transdisciplinary participatory research, in collaboration with families, community members, scientists and other stakeholders. During 2020 the Lab has improved the educational guide on Food and has helped in organising educational activities and in adapting the Xplore Health content to be published on the EduCaixa platform.

CONNECT
EC funded project to promote an inclusive, sustainable model for enabling secondary schools to adopt Open Schooling by embedding participatory science-action projects in the core curriculum. The Lab joined the Escoles Sentinella consortium to promote participatory research approaches in collaboration with students, teachers, families, researchers and other stakeholders (see Escoles Sentinella). The Lab has also developed a catalogue of best practices to promote STEAM and Open Schooling.

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.

Educational toolkits
Within the FIT4FOOD 2030 project, the Lab has collaborated in the development of the FIT4FOOD 2030 Knowledge Hub, a repository of tools for systemic transformation. With the collaboration of the Barcelona "La Caixa" Living Lab, three educational modules have been co-designed.

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. In 2020, the CAC has met once, introducing improvements to a research protocol and information document for participants in a clinical trial.

Projects in 2020

Projects to promote systemic research and innovation

InSPIRES. EC funded project to create co-creation spaces for different social actors and to evolve the concept of Science Shops under the new umbrella of RRI and Open Science.

Fit4Food2030. EC-funded project for the transformation of food and nutrition R&I by implementing a system-level RRI approach.

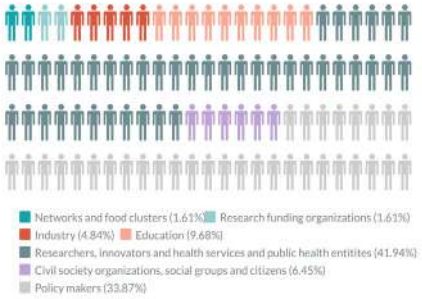
Barcelona "La Caixa" Living Lab. Project funded by "la Caixa" Foundation in collaboration with the Barcelona City Council to facilitate an intermediation structure to collaborate and optimize the processes of R&I, interventions and policy development in Barcelona.

Projects to promote innovation in science education
STEAMxChange and CONNECT

Projects to promote collaborative and systemic innovation
Fit4food BCN, Co-ResponS(H)ibility, Coronavirus Community Lab.

Educational programmes and methodological guidelines
RRI tools for professionals, Educational programmes for youth.

Participating stakeholders at Fit4food BCN



72 Participants in both challenges

656 Participants in the Coronavirus Community Lab

605 Participants trained in conferences and courses

20,102 Participants in Educational Modules for Youth

145,538 website visits

Communication

Team
Rita Casas
Elena Lapaz

Acknowledged as an essential step in the research process is dissemination, aimed at transmitting science to other researchers, patients and society in general. The Communications Department's role of bridging the gap between **IrsiCaixa**'s biomedical research and the public is not just a matter of transmitting knowledge from scientists to society, but also one of raising awareness of the importance of biomedical research. The Communications Department promotes **IrsiCaixa**'s values and fosters engagement by IrsiCaixa researchers and employees by providing internal support to them in making their work visible.

>6,000
followers on Twitter

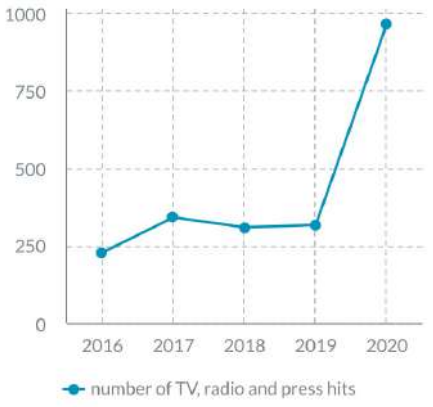
>500
subscribers in the monthly newsletter

966
press, radio and TV hits

303,724
visits to the www.irsicaixa.es website

Media

IrsiCaixa's commitment to the fight against SARS-CoV-2 and to sharing the results of its coronavirus research in open access and real time meant that, during **2020,** contact with the media was closer than ever. In view of the health emergency, the media strategy was of necessity different: no meetings were allowed so press conferences could not take place and press releases became the main means of media contact.



During **2020,** 17 press releases were issued, 39 news items were posted in the institutional website and 675 posts were made on social media. **IrsiCaixa** achieved a new record of 966 media hits in a single year, in TV, radio and press items referring to different **IrsiCaixa** research fields, including HIV eradication, disease resistance, SARS-CoV-2 research and immunity against infectious diseases. Some of the most successful media campaigns of 2020 are listed as follows:

— The IciStem international consortium, co-coordinated by **IrsiCaixa** researcher Javier Martínez-Picado, confirmed the second case of HIV eradication worldwide and presented a third case of drug-free long-term HIV remission.

— *The Lancet Microbe* published an IrsiCaixa-led study describing the first case of HIV resistance to all but one antiretroviral treatment combinations described to date.

— Early on during the COVID-19 pandemic, **IrsiCaixa** demonstrated that not all individuals testing positive for SARS-CoV-2 antibodies were immunized against the virus, highlighting the importance of maintaining hygiene and social distancing measures.

— **IrsiCaixa** researchers shared, with the entire scientific community, a list of molecules found in SARS-CoV-2 that enhance long-term cellular immunity against the virus.

Web and social media

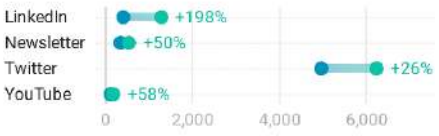
IrsiCaixa's presence in digital platforms increased greatly in 2020, especially in YouTube, for which the Communications Department produced and published 79 videos promoting **IrsiCaixa** – a huge increase over 2019 when 4 videos were published.

Regarding Twitter, LinkedIn and the monthly newsletter, **IrsiCaixa** consolidated its strategy to significantly increase visitors and readers. Social media campaigns designed in **2020** included #25anys25reptes, #PreguntaAUnaCientífica and #IANQuotes.

As for the institutional website, the statistics show a huge increase in visits in 2020; the 177,795 sessions and 152,627 users represented increases of ~194% and ~214%, respectively, over 2019.

Institutional communication

Increase of followers 2019-2020



During **2020**, the Communications Department worked on the launch of three new research groups to add to the nine existing groups, the design of corporate materials (including the annual report) and the coordination of commemorations for **IrsiCaixa**'s 25th anniversary.

Other projects

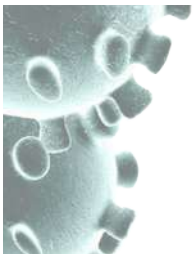
The Communications Department was active in developing **IrsiCaixa**'s Alumni Network and, with the support of the Spanish Foundation for Science and Technology (FECYT), in promoting the Let's talk about HIV project consisting of outreach sessions on HIV/AIDS implemented in prisons of Catalonia. Due to the COVID-19 pandemic, only two of the four planned sessions were organized during **2020** (in Brians2 and Quatre Camins prisons).

HIGHLIGHTED NEWS

PROJECT FOR THE DEVELOPMENT OF ANTIBODIES, DRUGS AND A VACCINE AGAINST CORONAVIRUS

A CONSORTIUM FORMED BY IRSICAIXA, THE BARCELONA SUPERCOMPUTING CENTER (BSC) AND THE ANIMAL HEALTH RESEARCH CENTER IRTA-CRESA DEVELOPS NEW STRATEGIES AGAINST THE SARS-COV-2, THE NEW CORONAVIRUS THAT HAS BECOME A WORLDWIDE PANDEMIC.

Scientists from the **IrsiCaixa** AIDS Research Institute, the Barcelona Supercomputing Center (BSC) and the IRTA-CReSA Animal Health Research Centre have launched a project to develop antibodies, drugs and a vaccine against SARS-CoV-2, the new coronavirus that emerged in late 2019 to become a worldwide pandemic. The project, funded by Grifols pharmaceutical company, combines virology, bioinformatics and animal model expertise from the three institutions. The coronaviruses are a family of viruses that cause different pathologies, ranging from the common cold to pneumonia, and possibly even causing death. The SARS-CoV-2 coronavirus was first reported in Wuhan (China) on 31 December 2019. Its rapid spread and the associated mortality meant that vaccines and antivirals are urgently required to control the disease. However, their design requires a profound understanding of the coronavirus and the capacity to test the efficacy and safety of any anti-viral drugs and vaccines developed. (March 2020).



"LA CAIXA" FOUNDATION AND IRSICAIXA PROMOTE THE CORONAVIRUS COMMUNITY LAB, THE FIRST CITIZEN SCIENCE PROJECT TO IMPROVE OVERALL HEALTH

In the context of the greatest health crisis of the century, "la Caixa" Foundation (through its EduCaixa programme) and **IrsiCaixa** Living Lab for Health have launched the Coronavirus Community Lab, the first participatory initiative inviting the public to present citizen science projects aimed at improving coronavirus management in urban communities. (April 2020).

IRSICAIXA OBTAINS A MERCK HEALTH FOUNDATION GRANT TO RESEARCH PERSONALIZED IMMUNOTHERAPIES AGAINST BREAST CANCER

IrsiCaixa Neoantigens and Therapeutic Vaccines for Cancer (NeoVaCan) research group has received a Merck Research Grant 2020 for their project – selected from 43 candidate projects – that aims to design personalized breast cancer therapies and to monitor disease progression without the need for complex and invasive clinical biopsies. (May 2020).

FIRST CASE OF HIV RESISTANT TO ALL ANTIRETROVIRAL TREATMENT COMBINATIONS DESCRIBED

The *Lancet Microbe* has published a study, led by **IrsiCaixa**, describing the case of a man living with HIV whose virus is resistant to all but one of the oral antiretroviral drugs in use. Antiretroviral treatments typically combine at least two or three drugs in order to block different viral replication cycle phases. The **IrsiCaixa** research highlights the need to develop new drugs to block alternative pathways. (June 2020).

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).

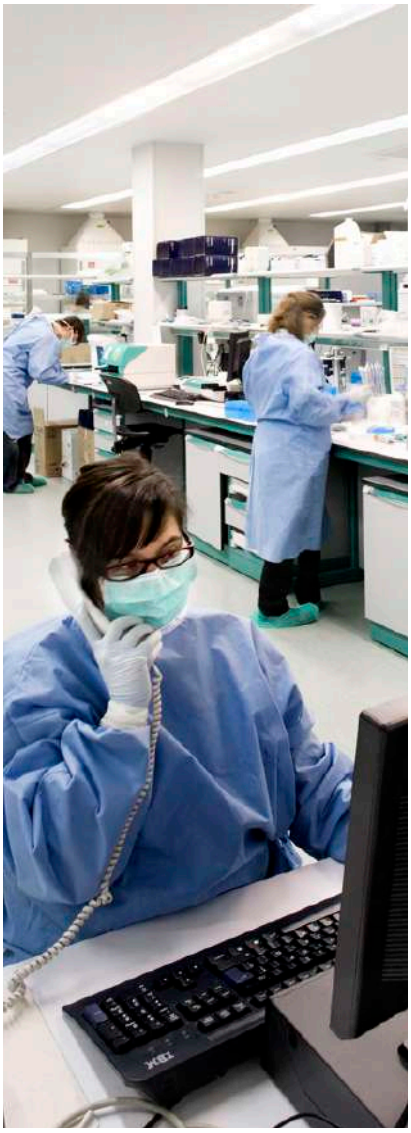
Staff in training

23 pre-doc researchers

33 post-doc researchers

Training activities

13 research results meetings



Internal and external training

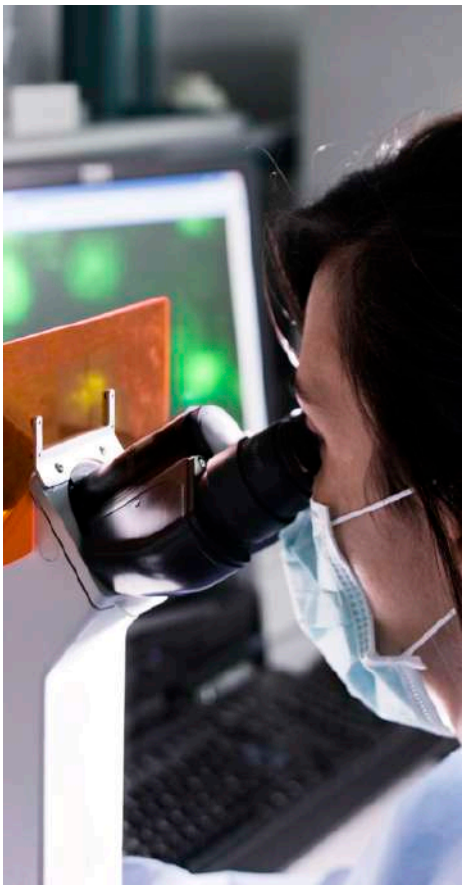
Weekly meetings at which group members present their results. These meetings develop capacity to structure and defend experimental data before a restricted audience of experts in the field.
— Fortnightly meetings at which group members present their results. These meetings develop capacity to structure 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, scientific activities, training and skills development initiatives organized jointly with the Germans Trias i Pujol Institute for Health Science Research (IGTP) and the Josep Carreras Institute. This integration and collaboration between different research groups and Can Ruti means greater **IrsiCaixa** visibility and attractiveness for researchers from abroad.
— 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.
— Stays at other research centres. **IrsiCaixa** actively fosters the mobility of its staff in training so that they are exposed to new techniques and methodologies and can establish collaborations with other centres.

Note that as a result of the COVID-19 pandemic, during **2020** 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 2020:



Date	Type of activity	Title	Place	Conducted by
January	Scientific dissemination lecture	Immunotherapy and personalized treatments	Museu dels Volcans, Olot	Julià Blanco
January	Lecture	Endocarditis	Faculty of Medicine, UVic-UCC	Lourdes Mateu
January-February	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 (online)	Mª Lluïsa Pedro-Botet
April	Seminar	Vaccines "induction of protective T cell immunity in HIV vaccines"	Faculty of Medicine, UVic-UCC	Christian Brander
May	Lecture	Gastroenteritis	Faculty of Medicine, UVic-UCC (online)	Mª Lluïsa Pedro-Botet
May	Lecture	Parasitosis	Faculty of Medicine, UVic-UCC (online)	Silvia Roure
May	Scientific debate	Covid-19: individual freedom vs. common good	Chair of Bioethics-Fundació Grifols-UVic UCC (online)	Bonaventura Clotet, Victòria Camps, Andreu Segura
June	Seminar	Telemedicine: teleictus	Faculty of Medicine, UVic-UCC (online)	Cora Loste
June	Seminar	Tuberculosis	Faculty of Medicine, UVic-UCC (online)	Roger Paredes
June	Seminar	Social determinants of health: the UN sustainable development goals	Faculty of Medicine, UVic-UCC (online)	Roger Paredes
September	Continuing education course	Update on HIV infection	Continuing Education, UVic-UCC	Bonaventura Clotet, Eugènia Negredo, Roger Paredes, et al.
November	Seminar	Monoclonal antibodies. Therapeutic technologies and applications	Faculty of Medicine, UVic-UCC (online)	Julià Blanco
November-December	Lectures	Lectures on virology and immunology	Specialization course on CAR-T cell therapy, UVic-UB-UAB (online)	Julià Blanco
December	Seminar	Monoclonal antibodies. Therapeutic technologies and applications	Faculty of Sciences, UVic-UCC (online)	Julià Blanco
December	Seminar	Induction of protective T cell immunity in Therapeutic HIV vaccines	Faculty of Sciences UVic-UCC (online)	Christian Brander
December	Seminar	Trends in Biomedical Biotechnology: IrsiCaixa Research.	Faculty of Sciences, UVic-UCC (online)	Julià Blanco

Clinical trials

1. AELIX-002

Safety and immunogenicity study in early treated HIV infected individuals to assess the safety and immunogenicity of HTI based vaccines

Study type: Interventional
Design: Double blind, randomized
Recruitment: Ongoing
Phase: I/IIa
Start–end: 2017- 2020
Sponsor: Aelix Therapeutics, SL
Principal investigator(s): **Dr. Beatriz Mothe**
Participating centre(s): Germans Trias i Pujol University Hospital(Fight AIDS Foundation); **IrsiCaixa**
NCT Code: NCT03204617

2. AELIX-003

Phase II study in early treated HIV infected individuals to assess the safety, immunogenicity and efficacy of a combination treatment including HTI based vaccines and TLR7 agonist Vesatolimod

Study type: Interventional
Design: Double blind, randomized
Recruitment: Ongoing
Phase: II
Start–end: 2017- 2020
Sponsor: Aelix Therapeutics, SL
Principal investigator(s): **Jose R.Arribas**
Participating centre(s): Germans Trias i Pujol University Hospital(Fight AIDS Foundation); **IrsiCaixa** and other 9 sites in Spain

3. BCN-03

Safety and immunogenicity of a combination of HTI based vaccines together with SOSIP-Envelope proteins as a combined T and B cell therapeutic vaccine strategy.

Study type: Interventional
Design: Double blind, randomized
Recruitment: approval, recruitment start 7-2021
Start – end: 2021-2022
Sponsor: **IrsiCaixa**
Principal investigator(s): **Dr. Beatriz Mothe**
Participating centre(s): Fight AIDS Foundation

4. Dual_TripleART

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 investigator(s): **Dr. José Moltó, Dr. Javier Martínez-Picado**
Participating centre(s): 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: 2019-002733-10

5. DURVAST

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

Summary and objectives: Phase II clinical trial to evaluate the effect of durvalumab (MEDI4736) in HIV-positive patients with advanced solid tumours.
Study type: Phase II
Recruitment: Finished with a total of 12 participants, 7 of those patients were included during 2020.
Start–end: 2017-
Principal investigator(s): Dr. Annemarie Wensing, Dr. Javier Martínez-Picado

6. ITATI

Immune Therapy and Analytical Treatment Interruption in HIV+ participants who received an allogeneic stem cell transplantation

Study type: Phase II
Recruitment: No patients recruited yet
Start–end: 2019 – 2022
Principal investigator(s): Dr. Annemarie Wensing, Dr. Javier Martínez-Picado
Participating centre(s): AIDS Research Institute **IrsiCaixa**, University Medical Center Utrecht, Hospital Gregorio Marañón, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, San Raffaele Scientific Institute, Fundació Lluita Contra la Sida, Hospital Universitario La Paz, Universitätsklinikum Hamburg-Eppendorf, Institut Pasteur, Rockefeller University (USA)
Eudra-CT number: 2019-001461-32
Observations: Study stopped before recruitment began as a result of loss of funding due to COVID. It is expected to be reactivated.

7. RESIST Project

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

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.
Phase: Pilot
Design: Prospective observational study in patients diagnosed with HR+/HER2- metastatic breast cancer, candidates for first- or second-line treatment with CDK4/6 inhibitors in combination with hormone therapy (aromatase inhibitors or faslodex)

Start–end: 1.1.18 -
Principal investigator(s): **Dr. Ester Ballana**, Dr. Mireia Margelí
Participating centre(s): **IrsiCaixa**, ICO
CEIC Code: PI-18-063

8. 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: Double blind, placebo-controlled, randomized
Phase: I
Start–end: 2017- 2021
Sponsor: Archivel Farma S.L
Principal investigator(s): **Dr. Cecilia Cabrera**
Participating centre(s): Germans Trias i Pujol University Hospital (Urology Department), Fight AIDS Foundation (CRO)
CEIC Code: AC-16-048-CEIM
EUDRA Code: 2016-004311-12

Publications and Conferences

Publications

Original publications

1. Abdel-Mohsen M, Richman D, Siliciano RF, Nussenzweig MC, Howell BJ, Chomont N et al. **Recommendations for measuring HIV reservoir size in cure-directed clinical trials.** *Nature medicine.* 2020;26(9):1339-1350. IF: 36,1300; doi: 10.1038/s41591-020-1022-1

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Visceral Abdominal Fat Accumulation and Severity of Liver Fibrosis in Nondiabetic Individuals Coinfected by Human Immunodeficiency Virus and Hepatitis C Virus. *AIDS research and human retroviruses*. 2020; IF: 1,7650; doi: 10.1089/AID.2019.0097

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Conference presentations and Talks

Presentations at conferences

1. Andrade VM, Mavian C, Babic D, Cordeiro Alvarado T, Sharkey M, Barrios L, Brander C, Dalmau J, Seaman MS, Salemi M, Martinez-Picado J, Stevenson M. **Presence of macrophage-tropic HIV-1 variantes following analytical treatment interruption**. 2020 *Conference on Retroviruses and Opportunistic Infections*. Boston (USA), March 8-11, 2020 Poster Presentation 323

2. Astorga Gamaza Antonio, Mireya L. Borrajo, Carla Serra Peinado, Laura Luque-Ballesteros, Oscar Blanch-Lombarte, Julia G Prado, Juan Lorente, Félix Pumarola, Marc Pellicer, Vicenç Falcó, Meritxell Genescà, Víctor Puntes, María J. Buzón. **BISPECIFIC AU NANOPARTICLES FOR THE ENHANCEMENT OF THE NK IMMUNE RESPONSE AGAINST HIV.** 2020 *Conference on Retroviruses and Opportunistic Infections.* Boston (USA), March 8-11, 2020. Poster ID 1497

3. Benet S, Gálvez C, Drobniewski F, Kontsevaya I, Arias L, Monguió-Tortajada M, Erkizia I, Urrea V, Ong RY, Luquin M, Dupont M, Chojnacki J, Dalmau J, Cardona P, Lugo G, Verollet C, Julián E, Furrer H, Günthard H, Crocker P, Tapia G, Borràs FE, Fellay J, McLaren PJ, Telenti, Cardona PJ, Clotet B, Vilaplana*, Izquierdo-Useros N*, Martinez-Picado J. **Impact of Siglec-1 variant on disseminated tuberculosis during HIV-1 co-infection.** *Keystone Symposia Conference – Tuberculosis: Immunity and Immune Evasion.* Santa Fe (NM, USA), January 16-20, 2020 Oral Presentation

4. Blanch-Lombarte Oscar, Esther Jimenez-Moyano, Dan Ouchi, Adam Pelletier, Aarthi Talla, Ashish Sharma, Ruth Penya, Judith Dalmau, José R. Santos, Rafick-Pierre Sekaly, Bonaventura Clotet, Julia G Prado P **CD8+ subset-dependent over-expression of TIGIT+ and TIGIT+TIM3+ by HIV-1 despite ART.** 2020 *Conference on Retroviruses and Opportunistic Infections.* Boston (USA), March 8-11, 2020 Poster Presentation 323. Grant: Oscar Blanch Lombarte, New investigator scholarship 2020

5. De Mattos L. *AACR ANNUAL MEETING 2020* – part I. April 27 - 28, 2020. San Diego Convention Center San Diego, California • Virtual Meeting

6. De Mattos L. *AACR Virtual Annual Meeting – part II:* June 22-24 • Virtual Meeting

7. De Mattos L. ESMO BREAST. May 23- 24, 2020 • Virtual Meeting

8. De Mattos L. ESMO Virtual Meeting. 19-22 September 2020 • Virtual Meeting

9. De Mattos L. *Molecular Analysis for Precision Oncology Virtual Congress,* 9 – 10 October 2020 • Virtual Meeting

10. De Mattos L. *ESMO Asia Congress*, Virtual. 20-22 November 2020• Virtual Meeting

11. Eberhard JM, Angin M, Passaes CP, Salgado M, Monceaux V, Hütter G, Balsalobre P, Kwon M, Diez JL, Nijhuis M, Wensing A, Martinez-Picado J, Schulze Zur Wiesch J, Saez-Cirion A, for the IciStem Study Group. **HIV-specific T-cell responses in an HIV-positive cohort post-allogeneic hemotological stem cell transplant.** *2020 Conference on Retroviruses and Opportunistic Infections.* Boston (USA), March 8-11, 2020 Poster Presentation 339

12. Ezeonwumelu Ifeanyi. **SAMHD1 Is a Modulator of Nucleos(t)ide Analogues' Efficacy.** *Viruses 2020 - Novel Concepts in Virology.* MDPI-Viruses. Barcelona. Spain. 5-7 february 2020

13. Gálvez C, Casado C, Pernas M, Tarancon-Diez L, Rodriguez C, Sánchez-Merino V, Vera M, De Pablo-Bernal RS, Merino-Mansilla A, Del Romero J, Lorenzo-Redondo R, Ruiz-Mateos E, Salgado M, Martinez-Picado J, Lopez-Galindez C. **Permanent control of HIV-1 pathogenesis in exceptional elite controllers.** *2020 Conference on Retroviruses and Opportunistic Infections*. Boston (USA), March 8-11, 2020 Poster Presentation 192

14. Gálvez C, Urrea V, Benet S, Bailon L, Martinez A, Mothe B, Dalmau J, Leal L, Garcia F, Martinez-Picado J, Salgado M. **ART-treated subjects with low viral reservoir show unusual HIV latency distribution.** 2020 Conference on Retroviruses and Opportunistic Infections. Boston (USA), March 8-11, 2020. Poster Presentation 374

15. Gupta RK, Peppa D, Pace M, Thornhill JP, Nastouli E, Grant P, McCoy L, Innes A, Edwards S, Wensing A, Nijhuis M, Martinez-Picado J, Frater J, Olavarria E, for the CHERUB and IciStem Study Groups. **Sustained HIV remission in the London patient: the case for HIV cure.** *2020 Conference on Retroviruses and Opportunistic Infections.* Boston (USA), March 8-11, 2020. Poster Presentation 346LB

16. Gutierrez Lucía. **ADAR1 Function Regulates Innate Immune Activation and Susceptibility to Viral Infections** *Viruses 2020 - Novel Concepts in Virology.* MDPI-Viruses. Barcelona. Spain. 5-7 february 2020

17. Imaz A, Tiraboschi JM, Niubo J, Martinez-Picado J, Cottrell ML, Domingo P, Chivite I, Negredo E, Morenilla S, Urrea V, Scevola S, Garcia B, Kashuba A, Podzamczer D. **Bictegravir distribution and bictegravir/FTC/TAF activity in genital tract and rectum.** *2020 Conference on Retroviruses and Opportunistic Infections.* Boston (USA), March 8-11, 2020 Poster Presentation 464LB

18. Jensen BO, Häussinger D, Knops E, Wensing A, Martinez-Picado J, Nijhuis M, Salgado M, Estes JD, Lübke N, Kaiser R, Harrer T, Fischer J, Schulze zur Wiesch J, Eberhard JM, Kobbe G. **CCR5Δ32SCT-induced HIV remission: trace of DNA but fading immune reactivity.** *2020 Conference on Retroviruses and Opportunistic Infections.* Boston (USA), March 8-11, 2020 Poster Presentation 348LB

19. Jiménez M, Pastor Palomo L, Urrea V, Izquierdo-Useros N, Martinez-Picado J, Mandomando I, Jairoce C, Clotet B, Carrillo J, Naniche D, Blanco J. **Uncoupled cellular and plasma markers of monocyte activation in early HIV infection.** *2020 Conference on Retroviruses and Opportunistic Infections.* Boston (USA), March 8-11, 2020 Poster Presentation 259

20. Jordan-Paiz A, Nevot M, Lamkiewicz K, Lataretu M, Franco S, Marz M and Martinez MA. **Disruption of an RNA secondary structure in HIV-1 gp41 induces viral lethality.** *Conference on Retrovirus and Opportunistic Infections (CROI).* International Antiviral Society–USA (IAS–USA). Boston. USA. Mars 8-11, 2020

21. Marin Miguel, Alba Ruiz, Esther Jimenez-Moyano, Dan Ouchi, Oscar Blanch-Lombarte, Dan Gorman, Ruth Peña, Richard Barnard, Christian Manzardo, Tomas Hanke, Christian Brander, Bonnie Howell, Bonaventura Clotet, Beatriz Mothe and Julia G Prado. **Impact of immune checkpoint inhibitors in vaccine-induced anti-HIV responses** *Conference on Retrovirus and Opportunistic Infections (CROI).* International Antiviral Society–USA (IAS–USA). Boston. USA. Mars 8-11, 2020. Poster ID 1741. Grant: Miguel Marin, New Investigator Scholarship - Foundation/IAS-USA

22. Martinez MA, Franco S, Buccione D, Mothe B, Cobarsi P, Ruiz L, Nevot M, Jordan-Paiz A, Pluvinet R, Sumoy L, Tural C. **Plasma miR-99a and miR-100 predict liver fibrosis progression in HIV/HCV subjects.** *Conference on Retrovirus and Opportunistic Infections (CROI*). SAF2016-75277-R

23. Martinez MA, Franco S, Buccione D, Mothe B, Cobarsi P, Ruiz L, Nevot M, Jordan-Paiz A, Pluvinet R, Sumoy L, Tural C. **Plasma miR-99a and miR-100 predict liver fibrosis progression in HIV/HCV subjects.** *Microbe 2020.*American Society for Microbiology. Chicago. USA. June 18-22, 2020.

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24. Moron-Lopez S, Bernal S, Steens J-M, Wong JK, Martinez-Picado J, Yukl SA. **ABX464 decreases the total HIV reservoir and HIV transcription initiation in vivo.** *2020 Conference on Retroviruses and Opportunistic Infections.* Boston (USA), March 8-11, 2020. Oral Presentation 335

25. Muñiz-Trabudua X, Borio C, Erkizia I, Perez-Zsolt D, Benet S, Martinez-Picado J, Izquierdo-Useros N. **Siglec-1 expressed on Dendritic cells is a new receptor implicated in arenavirus uptake.** *Viruses 2020*. Barcelona (Spain), February 5-7, 2020 Poster Presentation

26. Jordana Muñoz-Basagoiti, Jordi Rodon, Daniel Perez-Zsolt, Marc Noguera-Julian, Roger Paredes, Lourdes Mateu, Carles Quiñones, Itziar Erkizia, Ignacio Blanco, Alfonso Valencia, Víctor Guallar, Jorge Carrillo, Julià Blanco, Joaquim Segalés, Bonaventura Clotet, Júlia Vergara-Alert*, Nuria Izquierdo-Useros. **Cellular models for the study of SARS-CoV-2 pseudoviral entry**. *Second Research Symposium on Coronavirus of the Catalan Society of Biology.* 29-10-2020. Online. Oral presentation Oral presentation

27. Daniel Perez-Zsolt , Jordana Muñoz-Basagoiti, Jordi Rodon, Marc Noguera-Julian, Roger Paredes, Lourdes Mateu, Carles Quiñones, Itziar Erkizia, Ignacio Blanco, Alfonso Valencia, Víctor Guallar, Jorge Carrillo, Julià Blanco, Joaquim Segalés, Bonaventura Clotet, Júlia Vergara-Alert*, Nuria Izquierdo-Useros. **SARS-CoV-2 induces cytokine release by human macrophages in the absence of productive viral replication**. *Second Research Symposium on Coronavirus of the Catalan Society of Biology.* 29-10-2020. Online. Oral presentation

28. Resa-Infante P, Erkizia I, Nieto-Garai JA, Lorizate M, Izquierdo-Useros N, Martinez-Picado J. **Novel methodology for the detection of enveloped viruses.** *Viruses 2020.* Barcelona (Spain), February 5-7, 2020 Poster Presentation

29. Rodon Jordi, Marc Noguera-Julian, Itziar Erkizia, Alfonso Valencia, Víctor Guallar, Jorge Carrillo, Julià Blanco, Joaquim Segalés, Bonaventura Clotet, Júlia Vergara-Alert*, Nuria Izquierdo-Useros. **Search for SARS-COV-2 inhibitors in currently approved drugs to tackle COVID-19 pandemic.** *Research Symposium on Coronavirus of the Catalan Society of Biology* Poster presentation. 06-05-2020. Online

30. Jordi Rodon, Jordana Muñoz-Basagoiti, Daniel Perez-Zsolt, Marc Noguera-Julian, Roger Paredes, Lourdes Mateu, Carles Quiñones, Itziar Erkizia, Ignacio Blanco, Alfonso Valencia, Víctor Guallar, Jorge Carrillo, Julià Blanco, Joaquim Segalés, Bonaventura Clotet, Júlia Vergara-Alert*, Nuria Izquierdo-Useros. **Pre-clinical search of SARS-CoV-2 inhibitors and their combinations in approved drugs to tackle COVID-19 pandemic.** *Second Research Symposium on Coronavirus of the Catalan Society of Biology.* 29-10-2020. Online Oral presentation

31. Rodriguez de la Concepción Maria Luisa, Carlos Ávila-Nieto, Julia Vergara-Alert, Jordi Rodon, Victor Urrea, Carmen Aguilar-Gurrieri, Raquel Ortiz, Ana Barajas, Ferran Tarrés-Freixas, Benjamin Trinité, Lidia Ruiz, Eulalia Grau, Jordi Puig, Anna Chamorro, Nuria Izquierdo-Useros, Marc Noguera, Lourdes Mateu, Roger Paredes, Joaquim Segalés, Pep Amengual-Rigo, Rosalba Lepore, Alfonso Valencia, Victor Guallar, Bonaventura Clotet, Julià Blanco and Jorge Carrillo. **Early S2-targeting and rapid development of neutralizing antibodies after SARS-CoV-2 infection.** *Chasing COVID-19*. Biocat. Badalona. Spain. 22/10/2020

32. Jillian WP. Bracht, M. Gonzalez-Cao, T. Moran, J. Dalmau , J. Garcia-Corbacho, R. Bernabe, O. Juan, J. de Castro, A. Gimenez-Capitan, R. Blanco, E. Aldeguer, S. Rodriguez,A. Drozdowskyj, J. Argilaguet, J. Blanco, J. Prado, C. Brander, J. Carrillo, B. Clotet, B. Massuti, M. Provencio, CY. Huang, C. Mayo de las Casas, M. Garzon, AF. Cardona, O. Arrieta, A. Meyerhans, MA. Molina-Vila, J. Martinez-Picado, R. Rosell2,18 on behalf of the Spanish Lung CancerGroup. **Transcriptomic analysis of pre-treatment tissue samples to predict clinical benefit to durvalumab in HIV-infected cancer patients.** *AACR annual meeting*. American association of cancer research. online. USA . 22 June- 24 June 2020

Invited talks

1. Brander, Christian. **Virus-specific T cells with alternative effector function profiles and HIV control.** *NIH Cure Conference.* USA- United States of America, NIH. Washington DC, on line.

2. Cabrera, Cecilia. **Exploring immunologic features of SARS-CoV-2 infection.** *SEMINARIO SEI COVID 19 Y CITOMETRÍA ESPECTRAL.* 10 September 2020. Webinar

3. Carrillo, Jorge. **Desenvolupament d'una nova vacuna per la SARS-CoV-2**. Societat Catalana d'Immunologia. 30-4/20

4. Carrillo, Jorge. **Conceptos Básicos y su aplicación en la inmunoterapia avanzada.** FLS Science. *Inmunoterapia y Hemopatías*. 06/11/20

5. Carrillo, Jorge. **Desarrollando vacunas contra la COVID-19.** *Colegio oficial de Biólogos de Cataluña.* 30/11/20.

6. Carrillo, Jorge. **Biología de los linfocitos B y la respuesta humoral.** FLSScience. *Inmunodeficiencias primarias y secundarias en adultos.* 06/02/20.

7. Carrillo, Jorge. **Desarrollo de vacunas anti-COVID19: punto de las investigaciones y ensayos en desarrollo.** *Sociedad española de inmunología*. 06/04/20.

8. Carrillo, Jorge. **Immunopathogenesis of HIV.** *Universidad Politécnica de Valencia.* 08/05/20.

9. Carrillo, Jorge. **Humoral response in HIV infection**. *Banc de sang i Teixits*. Barcelona, 28/01/20

10. De Mattos-Arruda, Leticia. **Identificación de neoantígenos como dianas para nuevas terapias.** *III Jornadas de Investigación Traslacional en Tumores Urológicos* que se celebraran los días 30 y 31 de enero de 2020 en el Centro de Convenciones de Badalona (BCIN).

11. De Mattos-Arruda, Leticia. **Liquid Biopsy in Breast Cancer.** I*nnovation in Breast Cancer Symposium.* Pharma. Madrid. Spain. 14th&15th, 2020

12. De Mattos-Arruda, Leticia. **Liquid biopsies: in the clinics (trials most importantly).** *ESMO - Virtual - Advanced Course on Biomarkers for Precision medicine*. ESMO. Singapore. 4-5 September 2020

13. De Mattos-Arruda, Leticia. **Neoantigens Cancer Vaccines to Shape the Immune System - in the clinics.** *Worshop emergent immuno therapies. FLS/ IrsiCaixa.* Barcelona. Spain. 17 September 2020

14. De Mattos-Arruda, Leticia. **BIÓPSIA LÍQUIDA en cancer de mama.** *II SIMPÓSIO DE SAÚDE MAMÁRIA DE RIBEIRÃO PRETO. Sociedad e Brasileira de Mastologia.* Sao Paulo. Brazil. 11 November 2020

15. De Mattos-Arruda, Leticia. **Liquid Biopsy in Breast Cancer: where we stand now.** *15ª Jornadas de HITOS ONCOLÓGICOS*: lo mejor de

2020 - ponente de la charla Premium. Madrid. Spain. 18 November 2020

16. Garcia-Prado, Julia. **High resolution of CoV2 -specific T cell immunity to drive broad coronavirus vaccine development**. *Biocat*. 22 october 2020. Online

17. Garcia-Prado, Julia. **Bases moleculares de la inmunodeficiencia y el papel de la regulación de la respuesta antígeno específica: aprendiendo del VIH.** *VI Curso de Manejo Multidsiciplinar sobre el diagnostic y el manejo de Melanoma.* 3 December 2020. Online

18. Garcia-Prado, Julia. **Cellular immunity against SARS-COV2 infection.** *IGTP campus seminars.* 21 September 2020. Online

19. Izquierdo-Useros, Nuria. **Ebola and HIV-1: two wolves in sheep's clothing.** *Institut de Pharmacologie et de Biologie Structurale.* 18-02-2020. Tolouse, France.

20. Izquierdo-Useros, Nuria. **Ebola and HIV-1: two wolves in sheep's clothing.** *Seminarios del Departamento de Biología Molecular y Celular del CNB.* 26-02-2020. Centro Nacional de Biotecnología, Madrid

21. Izquierdo-Useros, Nuria. **Antivirals for SARS-CoV-2** FLS-Science. *Programa formativo onlline FLS-Science*. 01-05-2020. Online.

22. Martinez-Picado, Javier. **Does the size matter? Learning from cases with low-level viral reservoirs.** *BEAT-HIV Annual Meeting (adapted online due to Covid-19 restrictions)*. Philadelphia, June 9, 2020

23. Martinez-Picado, Javier. **αPD-1/αPD-L1 monoclonal antibodies on HIV-1 reservoirs**. *Workshop on cancer Treatment in Chronic infections and immunosuppression.* Barcelona, January 24, 2020

24. Martinez-Picado, Javier. **Cell & Gene therapies to eliminate HIV.** *Katholieke Universiteit Leuven. Leuven (Belgium)*, January 17, 2020

25. Martinez-Picado, Javier. **Cell & Gene therapies to eliminate HIV**. *Sant Pau Hospital.* Barcelona, January 08, 2020

26. Puertas, Mª Carmen. **Caracterización del reservorio viral en personas con VIH y evaluación de nuevas estrategias de curación.** *Curso de Aplicaciones Biométicas de la PCR Digital.* Hospital Sant Joan de Déu . Barcelona, October 21th, 2020

27. Salgado, Maria. **What determines a low level viral reservoir?** *Hot Topics in HIV*: Vaccines, immune recovery and eradication. Barcelona, 22nd October 2020

28. Salgado, Maria. **HIV and Stem cells.** *University of Barcelona, Master of Biomedicine,* Barcelona, 9th November 2020


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