IrsiCaixa

Institut de Recerca de la Sida

"la Caixa" Foundation

Generalitat de Catalunya
Departament de Salut

IrsiCaixa
Scientific Report
2019

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IrsiCaixa

The **IrsiCaixa AIDS Research Institute** is an international landmark centre for research into the eradication of HIV/AIDS and related diseases. It also tackles other challenges facing biomedicine today, such as the microbiome, cancer and emerging infectious diseases.

IrsiCaixa was created as a private non-profit foundation in 1995 with the support of "la Caixa" and the Department of Health of the Autonomous Government of Catalonia. Its director is Dr Bonaventura Clotet.

The fact that both **IrsiCaixa** and the Fight AIDS Foundation 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 milestones towards the eradication of AIDS.

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

IrsiCaixa participates in clinical trials to evaluate innovative therapeutic strategies and actively cooperates with low-income countries in the global fight against HIV/AIDS. It 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, joining forces early on in the AIDS pandemic with "la Caixa" Foundation and the Autonomous Government of Catalonia to fight this disease. A quarter of a century on we are proud of our position as a leading international biomedical research centre. In **2019**, **IrsiCaixa**, which now employs some 100 committed people, passed the **CERCA evaluation** with excellent results.

Thanks to our vast experience in HIV research we have acquired a large body of expertise regarding the immune system that enables us to face new biomedical challenges related to ageing, the microbiome, cancer and emerging diseases. A highlight of **2019** was the publication in *Nature Microbiology* of an article on the development of antibodies that block one of the **Ebola virus** entry pathways in human cells. The year **2019** was also marked by the launch of a new research group, Neoantigens and Therapeutic Vaccines for Cancer (NeoVaCan), headed by Dr Leticia de Mattos. NeoVaCan focuses on **immune characterization of cancer specimens** using multi-omics strategies (such as next-generation sequencing), with the ultimate goal of generating new anti-cancer strategies with clinical applications.

In the HIV field, **IrsiCaixa** coordinates IciStem, an international consortium guiding research into a potential HIV cure by means of stem cell transplantation. In 2019, we published an article in *Nature* that described only the **second case in the world of long-term drug-free HIV remission**. This milestone study for the scientific community, providing key insights into a possible cure for HIV, attracted a great deal of mass media attention and also had a great impact on the general public.

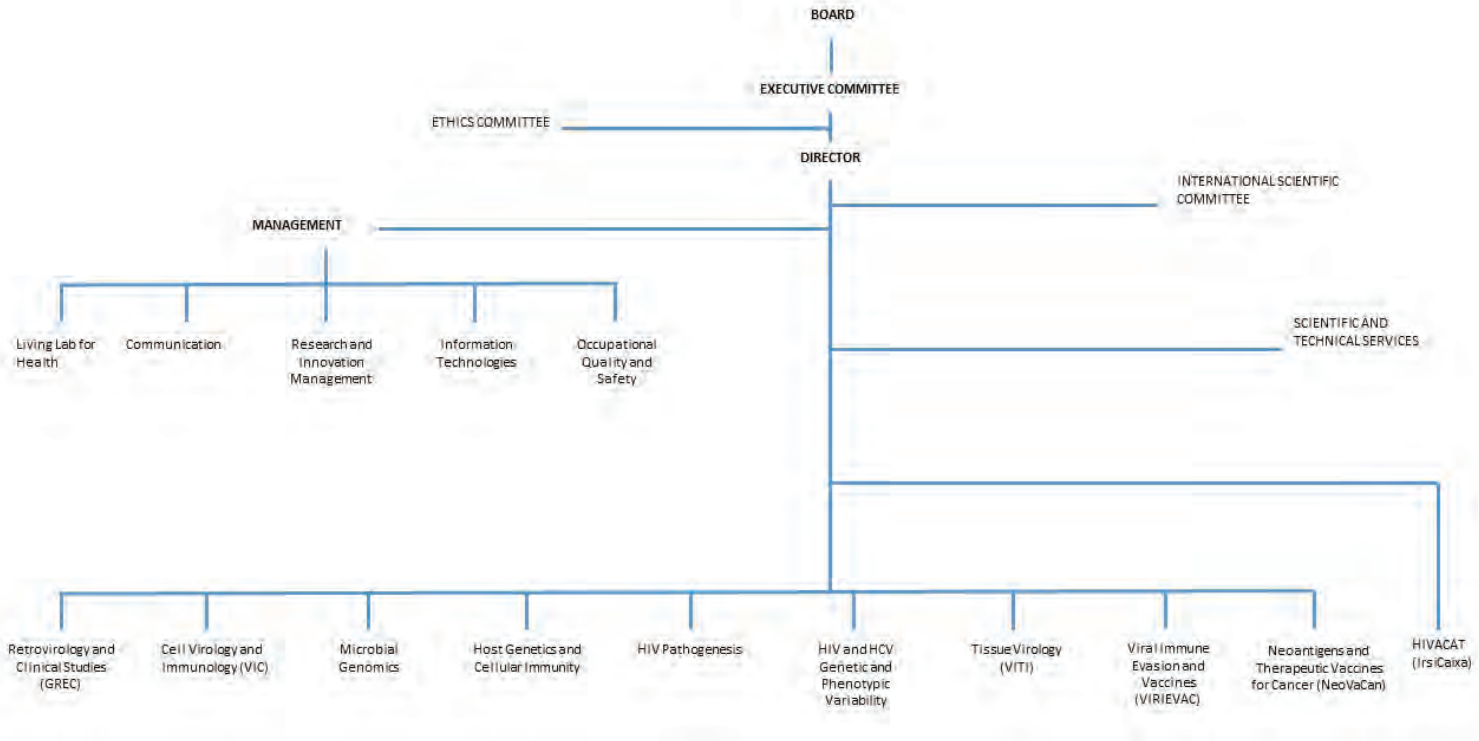
Over the years our primary goal has been to help patients with HIV by generating knowledge from basic research, developing better treatments, reducing the risk of associated diseases and inflammation, fighting stigma and, in general, improving their lives. Especially important in terms of **quality of life for people with HIV** and their partners globally was an article published in **2019** by **IrsiCaixa** in *The Lancet*, describing how people receiving HIV treatment who have an ongoing undetectable viral load cannot transmit HIV sexually to their partner.

The closing days of **2019** demonstrated our ability to respond to a **global health emergency**. Anticipating the possible public health impact of **COVID-19**, **IrsiCaixa** rapidly organized a working group to coordinate research into a vaccine against the as yet unnamed coronavirus and other potential coronavirus threats.

Achieving all these milestones would not have been possible without the support of key partners, most especially "la Caixa" Foundation and Grifols, as these have enabled us to launch new projects and to reinforce current research lines. We are committed to defending public health and strongly believe that research is key in this fight.

Bonaventura Clotet
IrsiCaixa Director

Organizational Structure



Board

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Health Minister of the Autonomous Government of Catalonia

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

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

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Esther Planas i Herrera
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:

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President
Marta Casals i Virosque
Secretary

Esther Planas i Herrera

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

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Sr. Jordi Casabona i Barbarà
Sr. Manel Puig i Domingo

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 2019

Total **staff**

106

Sex

67% ♀

33% ♂

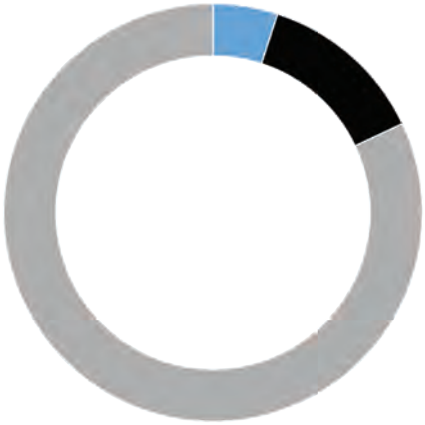
Researcher funding

16 public

24 private

9 other institutions (ICREA, IGTP)

Staff by **categories**



Scientific and technical **5%**

Administration and research support **13%**

Research **82%**

Theses read 2019

3

Edurne García Vidal
Virus-Host Interactions

Miriam Rosás Umbert
Host Genetics and Cellular Immunity

Ana Jordán de Paiz
HIV and HCV Genetic and Phenotypic Variability

Projects awarded 2019

20

8 public

12 private

Projects active 2019

70

35 public

35 private

Publications 2019

78

Highlights 2019

January

A new project funded by the "la Caixa" health programmme, ChronVirVac, is approved by ethics boards. The Host Genetics and Cellular Immunity group obtains the first human tissue samples to initiate the analysis.

A new VIC group project to characterize humoral responses to HIV-Env starts.

The VIRIEVAC group publishes an article in ***Frontiers in Immunology*** describing the main limitations of shock-and-kill therapies against the HIV reservoir.

February

Albajuna Therapeutics reaches its first milestone, demonstrating *in vivo* the activity of antibodies against HIV, which paves the way for preclinical development of these antibodies.

March

Second case in the world of long-term drug-free HIV remission reported in *Nature* by the international consortium IciStem led by **IrsiCaixa** and the Utrecht Medical Centre.

The Host Genetics and Cellular Immunity group gives great visibility to its ongoing work and to **IrsiCaixa** in three invited presentations at the Keystone HIV meeting in Whistler Mountain (Canada).

April

GREC publishes recommendations for analytical antiretroviral treatment interruptions in HIV research trials.

May

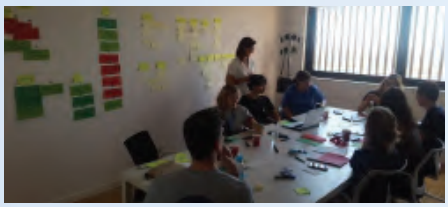
The Canadian Institutes of Health Research awards a grant worth $1,999,840 to *The microbiome in HIV prevention* project, which has **Roger Paredes** as one of its principal researchers.

June

New NeoVaCan research group led by **Leticia De Mattos-Arruda** launched, aiming to lead personalized cancer therapies and to better understand tumour genomic and immune heterogeneity.

July

Living Lab for Health and VIRIEVAC organize the *VIRIEVAC Strategy Lab* to pursue collective action in research.



Roger Paredes contributes to the development of the World Health Organization HIV treatment guidelines.

September

The Canadian Institutes of Health Research awards a grant worth $1,999,840 to ***The microbiome in cervical cancer project,*** which has **Roger Paredes** as one of its principal researchers.

A study of new antibodies that block an Ebola virus entry pathway into human cells is published in ***Nature Microbiology*** by GREC.

Roger Badia and **Ester Ballana** from the Vi-HIT group are awarded Miguel Servet I and II contracts, respectively.

A patent is filed on the use of Aurora kinase inhibitors for treating or preventing HIV infection or AIDS.

October

Cecilia Cabrera receives La Marató de TV3 funding to study response to chemotherapy in patients with bladder cancer.

Edurne Garcia Vidal presents her PhD thesis titled *Identification and characterization of novel latency-reversing agents to clear the HIV-1 viral reservoir*.

Julia G Prado is awarded a Gilead Fellowship for young investigators to develop novel HIV immunotherapies.

November

Míriam Rosás defends her PhD thesis entitled *Challenges and prospects for an immune-driven functional cure for HIV infection.*

Ana Jordan-Paiz defends her PhD thesis titled *Synonymous changes in the human immunodeficiency virus genome as a strategy to study virus biology.*

The VIC team signs a licence agreement with the Merck-Sharp and Dome Vaccine Department (USA) to develop new vaccines against human respiratory viruses based on **IrsiCaixa** VLPs.

The HIV and HCV Genetic and Phenotypic Variability group publishes an article in *Nucleic Acids Research* titled *Synonymous genome recoding: a tool to explore microbial biology and new therapeutic strategies.*

RESEARCH GROUPS

Viral Immune Evasion and Vaccines (VIRIEVAC)

Projects awarded 2019

Novel bispecific trimerbody targeting human 4-1BB and Env for immunotherapy-based HIV-1 curative therapeutics
Funding: Gilead
Start/end dates: 01.20 - 01.22
Research supervisor: **Julia García-Prado**
Other participating bodies: Hospital 12 de Octubre Research Institute

Achievements

Julia García Prado, member of ISCIII and MINECO scientific evaluation board
Julia García Prado, scientific director of the Germans Trias i Pujol Research Institute (IGTP)
Julia García Prado, member of the internal advisory board of the IGTP
Julia García Prado, member of the Spanish AIDS Research Network (RIS)
Julia García Prado, member of the American Society of Microbiology
Julia García Prado, member of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)
Julia García Prado, member of the Spanish GESIDA-SEIMC study group

Presentation

The VIRIEVAC group is currently working on two main lines of research with the final aim of developing new immune and cellular therapies for the control and cure of HIV-1.

The first line, within the HIV-1 immunopathogenesis area, focuses on rare phenotypes of HIV-1 infection control, in particular viraemic non-progressors (VNPs). Understanding why VNPs maintain CD4 T-cell counts in the presence of high viral loads is key to delineating the bases of non-pathogenic infections. This information is key to developing novel strategic therapies.

The second line, within the area of HIV-1 eradication and functional cure, has expanded in the last year to cover various projects aimed at identifying key factors limiting the functionality of HIV-1 specific CD8+ T-cell responses and including delineation of the complexity of immune regulatory pathways, identification of new targets for HIV-1 immunotherapies and development of gene therapies based on endogenous cellular proteins.

In its multidisciplinary and translational research to develop novel therapeutics to control or cure HIV-1 infection, VIRIEVAC combines tools from molecular virology, biochemistry and T-cell immunology.

2019 Milestones

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

Immunopathogenesis. This collaborative project between **IrsiCaixa** and the University of Oxford, covering studies of virological and host factors associated with natural infection control in VNPs, has expanded to include study of a small rare group of VNPs that have lost virological control over time. In collaboration with the Spanish AIDS Research Network (RIS) and the University of Oxford, this project was presented as a poster at the 44th Retrovirus Meeting (USA) and as an oral poster at the 11th National GESIDA Conference held in December (Toledo, Spain).

Prevention, eradication and functional cure. Work continued on two funded projects (PI17/00164 and MDS LKR 155762) aimed at understanding immune response limitations in controlling or eradicating the HIV-1 reservoir. This included delineation of CD8+ T-cell phenotypes altered despite long-term cART, focusing on alterations in inhibitory receptor (IR) expression. By combining single-cell cytofluorimetry of 15 lineage and functional CD8+ T-cell markers, we identified subset-specific irreversible alterations in IR in the composition of CD8+ T-cell memory and effector-like subsets. Those changes are defined by TIGIT or TIGIT+TIM3 expression or triple TIGIT-TIM3-LAG3 expression or CD39 expression. These findings postulate these markers as potential candidates for immunotherapies. We also evaluated the impact of currently approved cancer immunotherapies in boosting antiviral pre-existing or vaccine-induced HIV-1 responses. Our data support an expansion of vaccine-induced HIV-1 specific response by IR blockade as a novel strategy to boost antiviral responses.

We also continued exploring the role of the TRIM5 mechanism in controlling the viral reservoir with a view to designing new drugs and developing TRIM5-based gene therapy strategies. This research, materialized in a publication (Ruiz et al, Front Immunol, **2019**) and 3 posters and 1 oral presentation at international conferences (44th Retrovirus Meeting and 9th International Workshop on HIV Persistence, both in the USA). The communication of our research

has enhanced collaboration with national and international research teams (Buzon´s laboratory, Vall d´Hebron Research Institute (VHIR) in Spain and Sekaly's laboratory at Case Western USA) in the last year and has raised interest in our findings in the international scientific community.

Perspectives for the future

— Consolidation and continuation of existing lines of research with the following objectives: (1) to advance in the identification of natural infection control mechanisms, (2) to identify markers that predict the immune response to reactivation of the reservoir, (3) to underline the role of signature patterns of inhibitory receptors involved in dysfunctional antiviral responses, (4) to identify new target drugs and develop new drugs to improve the CD8 antiviral response, and (5) to develop a proof-of-concept for use of TRIM5 as a target in gene therapy.

— Strengthened alliances and collaborations with international laboratories with a view to seeking new funding opportunities for our research lines.

10 Active research projects

11 Presentations in conferences and as invited speakers

2 Active competitive contracts

Principal Investigator

Julia García Prado

Post-doc researchers
Marta Colomer Lluch
Julieta Carabelli

Pre-doc researchers
Óscar Blanch Lombarte
Miguel Ángel Marín López

Laboratory technicians
Esther Jiménez Moyano
Ruth Peña Poderós

Biostatistician
Dan Ouchi

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 2019

The microbiome in HIV prevention
Funding: Canadian Institutes of Health Research
Participating entities: University of Manitoba, Imperial College London, IrsiCaixa
Start/end dates: 01.20 - 12.24
Research supervisors: Adam Burgener (UManitoba), Carolina Herrera (ICL), Roger Paredes (IrsiCaixa)

The microbiome in cervical cancer
Funding: Canadian Institutes of Health Research
Participating entities: University Manitoba, IrsiCaixa
Start/end dates: 01.20 - 12.24
Research supervisors: Adam Burgener, Thomas T Murooka, Melanie C Murray, Vanessa Poliquin (UManitoba), Roger Paredes (IrsiCaixa)

Gut microbiota-on-a-chip for precision medicine
Funding: MINECO
Participating entities: National Microelectronics Centre (CNM), IrsiCaixa
Start/end dates: 01.19- 12.21
Research supervisor: Rosa Villa (CNM)

Prospective multicentric study to explore the relationship between Enterococcus faecalis bloodstream infections and colorectal cancer
Funding: ISCIII
Participating entities: IDIBAPS, HUGTiP, IrsiCaixa, other
Start/end dates: 01.20 - 12.22
Research supervisor: JM Pericàs (IDIBAPS)

Achievements

— **Roger Paredes** has been appointed Associate Editor of *HIV Medicine*

Master's theses

Title: *Evaluation and comparison of assembly and binning methods from real metagenomic data*
Author: **Andrea Vergara**
Tutor(s): **Marc Noguera-Julian**
University: Open University of Catalonia (UOC)
Date: 04.06.2019
Grade: Excellent

Title: *Investigating the human colorectal cancer microbiome from paired formalin-fixed paraffin-embedded and fresh-frozen specimens by 16S rRNA sequencing*
Author: **Alessandra Borgognone**
Tutor(s): **Marc Noguera-Julian**
University: University of Skövde (Sweden)
Date: 27.12.2019
Grade: Excellent

Presentation

Our work aims to achieve a better understanding of the microbiological determinants of immune regulation in health and disease. Such knowledge will allow the development of novel microbiome-based biomarkers for patient clinical stratification and also the discovery of novel microbiome-based therapies to prevent, improve or even cure HIV and other immune-mediated diseases. Currently, our main areas of interest are as follows:

1. Understanding the role of the gut microbiome in HIV infection prevention, pathogenesis and cure

We study:
— The influence of the gut microbiome on the ability of people living with HIV to achieve adequate immune reconstitution, control HIV-1 replication and limit HIV-associated chronic inflammation.
— The ability of the human microbiome to boost the efficacy of HIV immunotherapy and cure strategies.
— The ability of specific mucosal microbes to protect humans from HIV infection.
We identify:
— Human microbiome-derived biomarkers allowing stratification of HIV-infected individuals for research and clinical purposes.
— Novel microbiome-based concepts to improve the health of people living with HIV and prevent HIV-1 infection.
We are developing:
— Cloud-based software tools to enable massive sequencing data analysis and interpretation for HIV resistance (paseq.org) and microbiome analysis.
— A gut microbiota-on-a-chip device to evaluate the mechanistic effects of the microbiota on the immune system (in collaboration with the CNM).

2. Understanding the role of the gut microbiome in other immune-mediated diseases
— In collaboration with the ***Vall d'Hebron Institute of Oncology*** (VHIO), we investigate the role of the gut microbiome in the natural history of colorectal cancer.
— In collaboration with the ***ACE Foundation***, we investigate the influence of the human microbiome on the pathogenesis of Alzheimer disease.

3. Public health approaches to containing the global HIV drug resistance epidemic
— In collaboration with the WHO ResNet group and partners in Africa, we develop and evaluate strategies to contain the emergence of HIV drug resistance and maximize antiretroviral efficacy in resource-limited settings.
— In collaboration with WHO Europe, we contribute to the European Laboratory Initiative towards integrating HIV, TB and HCV diagnostics and linkage to care in Europe.
— As members of the IAS-USA group, we determine key drug resistance mutations to be used for clinical management worldwide.
— We contribute to the development of global WHO antiretroviral treatment guidelines.

2019 milestones and perspectives for the future

1. Microbiome
— We described early changes in the gut microbiome following HIV-1 infection. Specifically, 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 detected in chronically infected HIV-1 subjects. This work was published in the prestigious journal ***Microbiome.***

— The Canadian Institutes of Health Research awarded funding to the group, as co-principal investigators of an international team, for two projects aimed at understanding the role of the vaginal microbiome on women's health, vaccine responses, antiviral metabolism and cervical cancer.

— We launched the development of a microbiome-on-a-chip device to evaluate the mechanistic effects of the microbiota on the immune system.

25 ONGOING SCIENTIFIC PROJECTS

4 MILLION EURO SECURED IN FUNDING THROUGH GROUP-LED COLLABORATIVE INTERNATIONAL PROJECTS

— We are involved in the 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

— Since 2015, Dr Paredes has been a member of the WHO HIV Drug Resistance Steering Group, responsible for developing a global strategy against the emergence of resistant HIV-1.

— We are working as advisors to the WHO European Laboratory Initiative for the TB, HIV and the Viral Hepatitis core group, responsible for delineating a European strategy for integrated diagnosis of these diseases.

— We participated in the drafting of antiretroviral treatment guidelines for the WHO, which for the first time recommended dolutegravir as a first-line treatment for infected people, including pregnant women, thereby leading to a paradigm shift in the global strategy against HIV infection.

PRINCIPAL INVESTIGATOR

Roger Paredes

Associate researcher
Marc Noguera
Post-doc researchers
Alessandra Borgognone
Maria Casadellà
Aleix Elizalde

Programmer
Carmen Fuentes
Laboratory technician
Mariona Parera

Visiting researchers
Emma Elizabeth Ilett (Rigshospitalet, Copenhagen University Hospital, Denmark)
Andrea Vergara (Microbiology and Parasitology, Hospital Clínic, Barcelona)

GRIFOLS PROJECTS

MICROBIOME TRIGGERS OF ALZHEIMER DEMENTIA (MIND)

Senior researcher: Roger Paredes

— Characterization of the composition and functional potential of the faecal microbiome in subjects as follows: (1) with cognitive problems but not cognitively impaired, (2) with mild cognitive disability, and (3) with Alzheimer disease.

— Evaluation of longitudinal microbiome changes over one year in subjects with cognitive problems but without cognitive impairment.

— The provision of 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 meta-transcriptomic profile of the gut during a kick-and-kill strategy for treating HIV.

— The provision of mouse model biological evidence of the relationship between microbiota composition and T-cell vaccines.

Host Genetics and Cellular Immunity

Awarded projects 2019

MISTRAL
Funding: H2020
Participating entities: IrsiCaixa (coordinator), numerous international collaborators in the consortium
Start/end dates: 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

Awarded Grants 2019

EMBO Short Term Fellowship Grant
Participating entities: IrsiCaixa, INSERM Paris
Start/end dates: 07.17 – 10.19
Beneficiary: **Bruna Oriol**
Research supervisor: **Christian Brander,** Behazine Combadiere

Doctoral theses

Title: *Challenges and prospects for an immune-driven functional cure for HIV infection*
Author: **Miriam Rosás Umbert**
Tutors: **Christian Brander, Beatriz Mothe**
University: Autonomous University of Barcelona (UAB)
Date: 12.11.2019
Grade: Summa com laude

Presentation

Our research focus is the study of cellular immunity against viral infections in hosts with compromised immunity. This ranges from individuals with early and controlled HIV infection to studies in HIV-infected and non-HIV-infected individuals who have received an organ transplant. We explore different strategies for the identification of immunological correlates for HIV control in natural infection and are 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 to determine the molecular ontogeny of these responses and to 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 the evolution of HVC in 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.

2019 Milestones and perspectives for the future

We have continued to advance the clinical development of the HTI T-cell immunogen, which has entered the clinical trial phase with different vectors and combinations of vectors, including RNA, DNA and MVA. The first individuals in these trials have now stopped their antiretroviral treatment and are being followed up closely to monitor virus control. 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.

In **2019**, we continued the 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 data were complemented by transcriptomic analysis and studies of microbiota in faecal and skin samples. These analyses have identified a specific gene signature in individuals who mounted a neutralizing antibody response to the vaccine vector. While it was not the goal to induce nAb to MVA, the signature was also observed in a murine model in which vaccinated mice showed nAb to the HIV immunogen insert. These findings, supported by observations based on complete transcriptomic blood analyses, provide important indications on how to optimize vaccination outcomes.

Transcriptomics analyses, combined with methylome and protein-array analyses of samples from different time points and stages of the vaccination regimen in the BCN-02 clinical trial, were conducted during **2019**. They show different gene expression profiles before and after vaccination. These signatures, which are being compared to the level of virus control after treatment interruption, point towards an important role of methylation profiles in virus control, an observation that has also been made for the cohort of natural HIV controllers/non-controllers. In assessing these parameters in samples drawn before and after treatment with romidepsin, we have observed massive changes in transcriptional activities that are widely different between individuals and possibly not related to virus control in treatment interruption.

In the setting of liver transplantation, we have completed the analyses to identify predictors of acute rejection, a major clinical limitation for successful organ transplantation. HIV infection, CD4/8 T-cell ratio, HLA-class I mismatch between donor and organ recipient and level of alloreactivity were all associated with the risk of developing acute rejection. These insights are currently being applied to the study of acute organ rejection in liver and kidney transplantation, where organs from HIV infected individuals are being implanted in HIV-positive individuals.

The group has successfully competed in highly competitive funding calls for the 2019-2021 period by "la Caixa" Foundation Health Programme and the Retos-Colaboración programme (Spanish Ministry of the Economy, Industry and Competitiveness) and has also participated in the call that led to the newly awarded EU-based MISTRAL project.

2 Ongoing H2020 programme projects, with total funding of some 39M euros across the consortia

5 Clinical trial tests of different T-cell vaccine approaches to HIV cure

+20 Talk and presentation invitations to members of the group in the last year

Principal investigator

Christian Brander

Associate researcher
Beatriz Mothe

Post-doc researchers
Samandhy Cedeño
Anuska Llano
Alex Olvera

Marta Ruiz Riol
Sandra Silva Arrieta
Pre-doc researchers
Míriam Rosás
Bruna Oriol
Luis Romero Martín
Clara Duran
Clinical cohort coordinator/clinical researcher
Pep Coll
Laboratory technician
Tuixent Escribà

Grifols Project

Identification of epigenetically regulated plasma factors associated with neurodegeneration (Neuro-HIV)

Senior researcher: Christian Brander
Principal investigator(s): Marta Ruiz Riol

During 2019, omics analyses were expanded to several cohorts, including treatment-naïve patients with different levels of control of HIV infection (with available paired CSF-plasma samples), longitudinally neuro-evaluated patients (ARBRE study and BCN02 clinical trial) and elderly HIV-positive and HIV-negative subjects (>60 years, work ongoing).

Ongoing analyses include identification of plasma factors related with neurologic functions associated with HIV control. To this end, communicome analyses have been applied to samples from treatment-naïve HIV infected individuals with different levels of virus control. Different NAD+ deacetylases have been identified as prominent markers related to neurofunction and HIV control. Subsequent studies have revealed an association between their plasma and PBMC expression levels and viral parameters (plasma viral load and proviral levels) and this association has been confirmed by in vitro models. Additionally, CSF samples from HIV infected people show increased levels of these markers compared with sero-negatives and these levels are associated with markers of neurological damage. To evaluate the impact of cART treatment initiation and the association with neuro-outcomes, plasma levels of different NAD+ acetylases have been evaluated in samples from the local ARBRE study. In parallel, for the rest of cohorts, plasma proteomics analyses have been performed that allow measurement of soluble factors (about 300-plex) classified into inflammation, neurology and neuro-exploration panels. Data analysis is currently ongoing.

Virus-Host Interactions (ViHIT)

Awarded projects 2019

Immune strategies against HIV persistence (REF: PI19/00194)
Funding: ISCIII
Start/end dates: 01.01.20 – 31.12.22
Research supervisors: **Bonaventura Clotet, Roger Badia**

Scholarships and grants

Novell Research Personnel Programme (FI-2019), (REF: 2019 FI_B 00420)
Funding: Catalan Autonomous Government (AGAUR)
Start/end dates: 01.04.19 – 31.03.22
Beneficiary: **Lucia Gutiérrez**

Miguel Servet I Contract (REF: CP19/00011).
Funding: ISCIII
Start/end dates: 01.01.20 – 31.12.24
Beneficiary: **Roger Badia**

Miguel Servet II Contract (REF: CP19/00011)
Funding: ISCIII
Start/end dates: 01.01.20 – 31.12.22
Beneficiary: **Ester Ballana**

Achievements

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

Doctoral theses

Title: *Identification and characterization of novel latency-reversing agents to clear HIV-1 viral reservoir*
Author: **Edurne Garcia-Vidal**
Tutor(s): **Ester Ballana, José Esté**
Department of Cellular Biology, Physiology and Immunology, Autonomous University of Barcelona (UAB)
Date: 15.10.19
Grade: Cum laude

Filed patents

Title: *Aurora kinase inhibitors for treating or preventing HIV infection or AIDS*
Inventor(s): **Ester Ballana, Roger Badia, Edurne Garcia-Vidal, Eva Riveira-Muñoz, José Esté Araque**
Date: 09.09.19
Application number: PCT/ES2019/070596
Applicant(s): IrsiCaixa, IGTP

Presentation

Our research focus is the identification and study of host cofactors in HIV infection that allows the development of new therapies targeting virus-host protein interactions. The group is currently working on three main research lines:

1. Identification of new cellular cofactors in viral infections

We aim to characterize the interactions between HIV-1 and the host cell during the different steps of virus replication. Our work has especially focused on the description of cell proliferation mechanisms associated with HIV-1 replicative capacity and therefore allowing the identification of cell targets that affect cell cycle progression and the proliferation of HIV+ cells. Currently, we are working on a group 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 can potentially become targets for the development of new antiviral therapies.

2. Identification of new targets for HIV treatment: viral latency and persistence

We explore the mechanisms that govern HIV persistence in pursuit of new strategies to purge the viral reservoir. We are working on the identification of new latency reversing agents (LRAs) and on exploring their mechanisms of action so as to ultimately validate their use as new strategies for HIV cure, whether alone or in combination with current treatments.

3. Innate immune function as a biomarker of treatment response

The mechanisms that control the interface between the metabolism of nucleic acids and their detection by the immune system determine the onset of diseases such as viral infections and cancer and also their treatment. We are working on the development and validation of SAMHD1 as a biomarker of therapeutic response to nucleoside analogues currently used to treat viral infections and cancer. A second area of interest is the description and characterization of key cellular targets that determine the antiviral and antitumoral immune response, with particular emphasis on the identification of novel immunotherapeutic strategies.

2019 Milestones

During **2019**, our group achieved the following:
— Identification of novel cell factors involved in viral infections. We continued the study of cellular factors that affect viral infections, with a special focus on the role of ADAR1 as a modifier of disease progression in cohorts of HCV/HIV and HPV/HIV co-infected individuals.
— Identification of cell factors as new targets affecting viral latency reactivation. Aurora kinase inhibitors were identified as promising new LRAs and a patent has been filed based on the use of aurora kinase inhibitors for treating or preventing HIV infection. We continued the screening and validation of new cellular factors that affect HIV latency establishment and/or viral reactivation. We characterized the latency reactivation properties of midostaurin, a multi-kinase inhibitor approved for the treatment of AML in humans.
— Identification and validation of biomarkers of treatment response in cancer patients. We continued to work on the validation of SAMHD1 as a biomarker of treatment response to antimetabolites. In collaboration with Dr Mireia Margelí

from ICO-Badalona, we designed a retrospective study in patients with different cancer types to assess the predictive and prognostic value of SAMHD1. We also began the study of immune effectors in response to CDK4/6 inhibitors, in a prospective study of patients with breast cancer treated with this type of inhibitor.

Finally, during **2019**, our group was awarded four competitive research staff contracts that consolidate and reinforce the team and ensure the continuity of our research.

1 GROUP OF TALENTED YOUNG RESEARCHERS PURSUING A COMMON RESEARCH GOAL

4 AWARDED COMPETITIVE CONTRACTS FOR RESEARCH STAFF

9 PRESENTATIONS AT NATIONAL AND INTERNATIONAL CONFERENCES

PERSPECTIVES FOR 2020

Our goal is to develop new and more effective strategies to cure HIV and other diseases, based on the ability to inhibit key interactions between viral and cellular targets. We will continue the study of host-virus interactions to establish mechanisms of action and determine the role of cellular factors in the different steps of viral replication and evaluate their role in the establishment of the HIV viral reservoir. In cancer patients, the identification and validation of biomarkers of treatment response will enter a new phase focused on the in-depth study of cohorts of patients.

Consolidation of the research team and improved competitive funding will also represent key objectives for 2020.

PRINCIPAL INVESTIGATOR

Ester Ballana

Post-doc researchers
Roger Badia
Eva Riveira-Muñoz

Pre-doc researchers
Marc Castellví
Edurne García
Maria Pujantell
Lucía Gutiérrez
Ifeanyi Jude Ezeonwumelu
Eudald Felip

GRIFOLS PROJECT

NEW CELL TARGETS FOR HIV CURE (NECETAR)

Senior researcher: Ester Ballana

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

— To identify new cell targets associated with HIV-1 latency establishment and reactivation. Improved 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 LRAs will be characterized.

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

Retrovirology and Clinical Studies (grec)

Projects awarded 2019

Exploratory, open-label, randomized clinical trial to assess the efficacy of first-line dual vs. triple antiretroviral therapy in the HIV-1 reservoir and in peripheral compartments in HIV-infected patients
Date: 01.07.19 - 30.06.21
Funding: ViiV Healthcare
Research supervisor(s): José Moltó, **Javier Martinez-Picado**

Scholarships and Grants

Beatriu de Pinós Programme (Ref 2017 BP 00121)
Funding: Catalan Autonomous Government (AGAUR)
Start/end dates: 01.01.19 - 31.12.20
Beneficiary: **Patricia Resa Infante**

Achievements

Javier Martínez-Picado, member of the scientific/organizing committees of:
— 9th International Workshop on HIV Persistence during Therapy, Miami (USA), 10-13 December 2019
— 11th National GeSIDA Conference (GeSIDA–SEIMC), Toledo (Spain), 10-13 December 2019
— 10th Hot Topic in HIV (workshop): Vaccines, Immune Recovery and Eradication, Barcelona, 23 October 2019
Javier Martínez-Picado, scientific advisory board member of:
— Rebound P01 program, Northwestern University, Chicago (USA), October 2019

Filed patents

Title: *Siglec-1 monoclonal antibodies for treating and preventing HIV-1 and Ebola virus infections*
Inventors: **N Izquierdo-Useros, J Martinez-Picado, M Pino, D Perez- Zsolt, L Kremer**
Filing date: April 2019
Application number: US 62/828,195
Applicant: IrsiCaixa

Title: *Microbicide compositions comprising Siglec-1 monoclonal antibodies for HIV-1 prevention and treatment*
Inventor(s): **D Perez- Zsolt, N Izquierdo-Useros, J Martinez-Picado**
Filing date: April 2019
Application number: US 62/832,054
Applicant: IrsiCaixa

Presentation

Our group focuses on translational studies of HIV-1 infection and on investigations of potential new HIV/AIDS therapeutic strategies through both basic and applied research. We closely collaborate with other research groups within **IrsiCaixa**, as well as with national and international biomedical institutes. The translational character of our research keeps us in contact with some 3,000 individuals with HIV attending the outpatients unit in the Germans Trias i Pujol University Hospital. Our programme focuses on three priority areas: (1) HIV cure, (2) pathogenesis of HIV mediated by dendritic cells, and (3) extreme HIV infection phenotypes.

2019 Milestones

1. HIV-1 cure

— Follow-up of an international cohort of 48 HIV-positive subjects who received an allogeneic stem cell transplant as treatment for severe haematologic disease (IciStem). This is the only therapeutic intervention to date that has been shown to be capable of reducing the viral reservoir to undetectable levels. Two subjects who received donor cells containing the mutation CCR5Δ32/Δ32 in the viral coreceptor have stopped antiretroviral therapy with no signs of viral rebound after 2 years. Five more subjects who received donor cells without the mutation CCR5dΔ32/Δ32 have entered immunotherapy with broadly neutralizing antibodies.
— Development of a new gene therapy for elimination of the CCR5 viral receptor through TALENs
— Characterization of patients in antiretroviral treatment with extremely low viral reservoirs
— Characterization of viral reservoirs in different cell subtypes
— Development of a new nanoparticle technology targeting myeloid cells aimed at inducing viral reactivation and promoting a cytotoxic response
— Study of tumoral and viral level effects of new immunotherapies with blocking monoclonal antibodies (α-PD-1 and α-PD-L1) in HIV-positive patients with oncological disease
— Evaluation of new antiviral drugs and drug combinations for their ability to reduce the viral reservoir
— Evaluation of the viral reservoir in intra-uterinally infected children with subtype C virus.

2. Pathogenesis: role of myeloid cells

— Translation of knowledge acquired regarding the Siglec-1 receptor to other infectious pathogens, including Ebola virus, arenaviruses and *Mycobacterium tuberculosis*
— Characterization of primary cervical myeloid cells that interact with HIV-1 via the Siglec-1 receptor
— 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.

3. Extreme HIV infection phenotypes

— Study in adults and children of the 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.

Perspectives for 2020

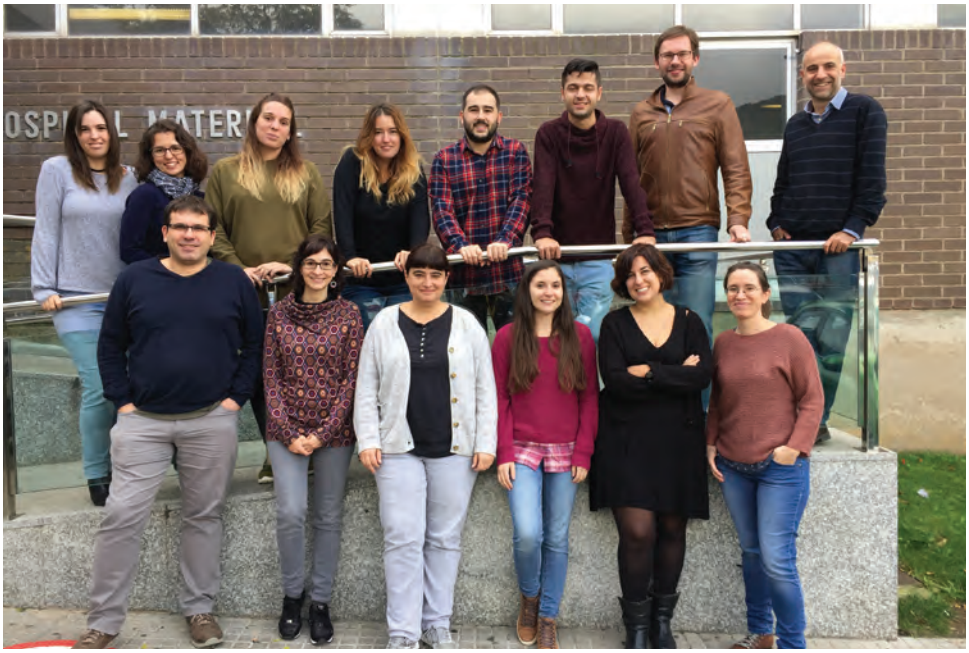
Our programmes will lead to the development of new strategies for treatment and cure of HIV/AIDS.

The group aims to the following:
1) Quantify the size and analyse the role of the viral reservoir by developing virological monitoring tools for the blood and tissues of patients on antiretroviral therapy
2) Study clinical interventions aimed at reducing viral reservoirs and controlling viral persistence
3) 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, specifically by inhibiting virus-Siglec-1 interaction
4) Build nanoliposomes that specifically target Siglec-1 as expressed in dendritic cells as a mechanism to deliver drugs, latency reactivation agents and viral immunogens
5) Explore the role of virus-host interactions in extreme HIV-1 infection phenotypes
6) Explore therapeutic applications of factors underlying the non-progressor viraemic phenotype, whose profile is similar to that of the natural host (with an immune system not affected by high levels of viraemia).

9 Ongoing projects

12 Peer-reviewed articles

14 Invited talks



Principal investigator

Javier Martínez-Picado

Associate researcher
Nuria Izquierdo-Useros
Post-doc researchers
Jakub Chojnacki
Mª Carmen Puertas
Patricia Resa-Infante
María Salgado
Pre-doc researchers
Ángel Bayón

Susana Benet
Silvia Bernal
Cristina Gálvez
Xabier Muñiz
Daniel Pérez-Zsolt
Laboratory technicians
Itziar Erkizia
MªCarmen García
Cohorts and project management
Judith Dalmau
Biostatistician
Víctor Urrea

Grifols Projects

Cutting edge strategies for HIV cure (VIROCURE)

Senior researcher: Javier Martínez-Picado
Principal investigator(s): María Salgado, Maria Carmen Puertas

— 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 antiretroviral-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 technologies mimicking virus-cell interaction to fight infectious diseases (SIGTECH)

Senior researcher: Javier Martínez-Picado
Principal investigator(s): 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 of primary myeloid cells)
— To develop nano-vehicles using clinically approved biomaterials that allow the construction of nanoparticles for therapeutic purposes and expand our studies to see if glycol-engineering of nanoparticles designed for clinical use can induce reactivation of HIV-1 latency and trigger immune antiviral control.
— To develop a detection platform based on Siglec-1 receptor capacity to detect 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 2019

Immune strategies against HIV persistence
Funding: Ministry of Science, Innovation and Universities, Carlos III Health Institute
Start/end dates: 1.01.20 - 31.12.22
Research supervisor: **Bonaventura Clotet**

Doctoral theses

Synonymous changes in the human immunodeficiency virus genome as a strategy to study virus biology
Author: **Ana Jordan Paiz**
Director(s): **Miguel Ángel Martínez**
University: Autonomous University of Barcelona (UAB)
Department: Advanced Immunology
Defence date: 29.11.19
Grade: Cum laude

Presentation

Innate immune detection of HIV-1 has been reported to occur via a variety of mechanisms. In the last few years, we have demonstrated that HIV-1 replication capacity and evolvability can be modified by synonymously recoding the virus genome (Martinez et al, Nucleic Acids Research, 2019). 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, as a consequence, the viral mechanisms of latency and persistence. Understanding the mechanisms of immune response induction mediated by RNA dinucleotide frequencies and codon usage will enhance our understanding of HIV-1 latency, inflammation and pathogenesis.

2019 milestones and perspectives for the future

In order to explore the impact of synonymous codon usage on HIV-1 Env expression and virus replication capacity, codons AGG, GAG, CCT, ACT, CTC and GGG of HIV-1 env were synonymously changed to CGT, GAA, CCG, ACG, TTA and GGA, respectively. A recoded env variant containing 39 mutations was lethal for the virus. Env expression analysis revealed that protein expression of this recoded variant was highly reduced. To further study the mutations responsible for this phenotype, new mutants were designed by reverting substitutions to WT or reducing the number of newly generated CpG dinucleotides. Most of the new virus variants were viable, although they showed different replication capacities. Interestingly, one variant that only reverted two nucleotides in the same codon showed indistinguishable replication capacity when compared to WT; moreover, other viable virus variants generated compensatory mutations next to this codon or reverted this codon to WT. Computational analyses revealed severe disruption in an RNA secondary structure of sequence variants containing this mutated codon. Importantly, the disrupted RNA structure was restored when this codon was reverted or new mutations were introduced nearby. Our findings indicate that codon usage of the HIV-1 env strongly impact the replication capacity of the virus. Furthermore, synonymous recoding of HIV-1 env has identified an evolutionary conserved local RNA secondary structure that may be essential to virus viability. Disruption of this RNA secondary structure leads to severe reduction in Env mRNA translation and virus replication capacity. We hypothesize that codon usage and modification of virus RNA secondary structures may impact on innate recognition and so we expect to explore this possibility in the near future.

It was recently shown 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, Nature, 2017). As HIV-1 and other RNA viruses have a low CpG dinucleotide composition, this potentially sets the stage for ZAP and related proteins as important drivers in the evolution of RNA virus genomes. 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. In order to understand the implications of ZAP for the phenotype of our synonymously recoded mutants, we targeted ZAP with specific siRNAs. As previously described by Takata and colleagues, a synonymously recoded HIV-1 variant with increased CpG numbers

in its Env coding region increases its replication when ZAP is targeted. However, two intriguing results were obtained with our synonymously recoded mutants. First, WT virus reduced its replication in the absence of ZAP, suggesting either that ZAP is a virus co-factor rather than an antiviral protein or another factor is involved in the ZAP-mediated activity. Second, mutants with significantly increased CpG numbers did not increase their replication capacity in the absence of ZAP. These results show that the role of ZAP, as well as the frequency of CpG dinucleotides, in the replication of HIV-1 is far from being completely elucidated. We hypothesize that that when CpGs are located in a specific HIV-1 RNA region, the inhibition of ZAP allows viral replication of CpG-enriched viruses (restriction factor), whereas ZAP inhibition may reduce viral growth of WT viruses or CpG-enriched viruses in other genome regions (viral co-factor).

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 a main challenge faced by clinicians. We performed 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 10 years, half of the former patients developed liver fibrosis (F2-4) and some remained without signs of liver fibrosis (F0-1). At the time of sampling, there were no significant clinical differences between liver-fibrosis progressors and non-progressors (i.e., in terms of age, AST, ALT, GGT, platelets, FIB-4, liver fibrosis). When compared with healthy donors, HIV-1/HCV patients showed significantly dysregulated expression of 44 miRs, 38 of them upregulated. Of the 38 upregulated miRs, 7 (miR-885-5p, miR-100-5p, miR-193-5p, miR-99a-5p, miR-203a-3p, miR-5588-5p and miR-99a-3p) were significantly upregulated in the progressors when compared to non-progressors. Our results demonstrate the potential of circulating miRs as biomarkers for liver injury progression in HIV-infected patients. We hypothesize that miRs may be suitable markers of liver fibrosis amelioration in HIV-1/HCV co-infected patients treated with HCV direct-acting antiviral agents and cured of HCV infection.

PRINCIPAL INVESTIGATOR

Miguel Ángel Martínez

Post-doc researchers
Sandra Franco
Maria Nevot

Pre-doc researcher
Ana Jordán

GRIFOLS PROJECT

CIRCULATING MICRORNAS AS POTENTIAL BIOMARKERS OF LIVER DISEASE IN HIV-INFECTED PATIENTS (MIRNA)

Senior researcher: Miguel Ángel Martínez

HIV-1-induced inflammation likely contributes to the evolution of liver disease in infected patients. The lack of exploitable non-invasive biomarkers to diagnose and predict different stages of liver disease is currently one of the biggest challenges faced by clinicians. Small noncoding RNAs (miRNAs) regulate diverse biological functions in the liver by shutting down protein translation and through excretion in exosomes as distress signals. Recent evidence indicates that the plasma levels of specific miRNAs may be significantly altered in subjects with liver injury. Indeed, we and others have demonstrated the presence of specific miRNAs signatures associated with liver injury progression in the circulating blood of individuals with HIV-1. Objectives: (1) to identify circulating plasma miRNAs as possible biomarkers of liver disease progression, (2) to elucidate the mechanism of action of the identified miRNAs in liver disease progression, and (3) to increase understanding of the mechanisms underlying liver disease and facilitate interventions that improve liver health and the longevity of patients infected with HIV-1.

Cell Virology and Immunology (VIC)

Projects awarded 2019

Identification, isolation and characterization of antibodies that interfere with neutralizing antibody action in persons infected with the human immunodeficiency virus (PI18/01332)
Funding: Ministry of Science, Innovation and Universities, Carlos III Health Institute
Start/end dates: 01.01.19 – 31.12.21
Research supervisor: **Jorge Carrillo**

Rational engineering of next-generation antibodies and vaccines against HIV. A synergic dry and wet lab effort
Funding: MAC AIDS FUND
Participating entities: IrsiCaixa
Start/end dates: 15.06.19 – 14.06.20
Research supervisor: **Julià Blanco**

Presentation

VIC has as its ultimate goal to develop protective vaccines against HIV infection and to define treatment strategies (based on antibodies or inflamm-ageing modulators) for HIV-infected individuals that contribute to functional cure or eradication of HIV.
Our work has continued to focus on three main research lines:

Humoral response against HIV envelope glycoprotein (Env)

— Antibody response to pathogens is polyclonal, encompassing neutralizing and non-neutralizing antibodies. **Jorge Carrillo** has explored the possibility that non-neutralizing antibodies interfere with the action of neutralizing antibodies, leading to an inefficient immune response.
— Exhaustive screening of neutralizing and anti-MPER response analysis. **Edwards Pradenas** has initiated comprehensive screening of sera to identify neutralizing and non-neutralizing responses to the gp41 MPER epitope. This work will provide valuable information on natural responses to HIV Env.
— Synthetic antibody development. AlbaJuna Therapeutics has achieved its first milestone in demonstrating activity in vivo. The discovery phase has generated a synthetic antibody optimal from the point of view of activity, biochemical characteristics and production.

VLP vaccine platform: development of preventive HIV and other vaccines

— Preventive HIV vaccines (project PI17/01518). New antigens have been developed based on MPER, the gp120 V1-V2 regions, the CD4bs (in collaboration with the BSC) and the full Env trimer.
— Feline leukaemia virus (FeLV) vaccines. A VLP based on FeLV is being developed in collaboration with HIPRA (animal health company) that will demonstrate the effectiveness of VLPs in vivo.
— Respiratory virus vaccines. A new collaboration with Merck will test the immunogenicity of our VLPs in a non-retroviral context.
— Syphilis and yaws. **Jorge Carrillo**, in collaboration with **Oriol Mitjà** and international groups, is working on a first vaccine candidate, already produced in vitro, that will demonstrate immunogenicity against bacterial antigens.
— Tumour vaccines. This key project, carried out in collaboration with Leticia de Mattos Arruda, aims to generate immune responses to fight cancer. Melanoma animal models and a new vaccine design pipeline (in collaboration with the BSC) are already in place.

Mechanisms of immunological damage and recovery in HIV+ individuals

Our studies focus on understanding the viral and immunological mechanisms that lead to CD4 cell destruction, chronic inflammation and ageing of the immune system (inflamm-ageing) in HIV+ patients and how the immune function is affected.
— The role of Env. We have demonstrated the role of Env in immunological damage, work that has further expanded with visiting scientist Silvia Pérez.
— Inflammation and ageing. In collaboration with different groups, we are exploring the consequences of HIV infection in acutely infected patients, patients receiving anti-inflammatory treatment and older patients with HIV (>60 years).

2019 Milestones and Perspectives for the future

Vaccine development

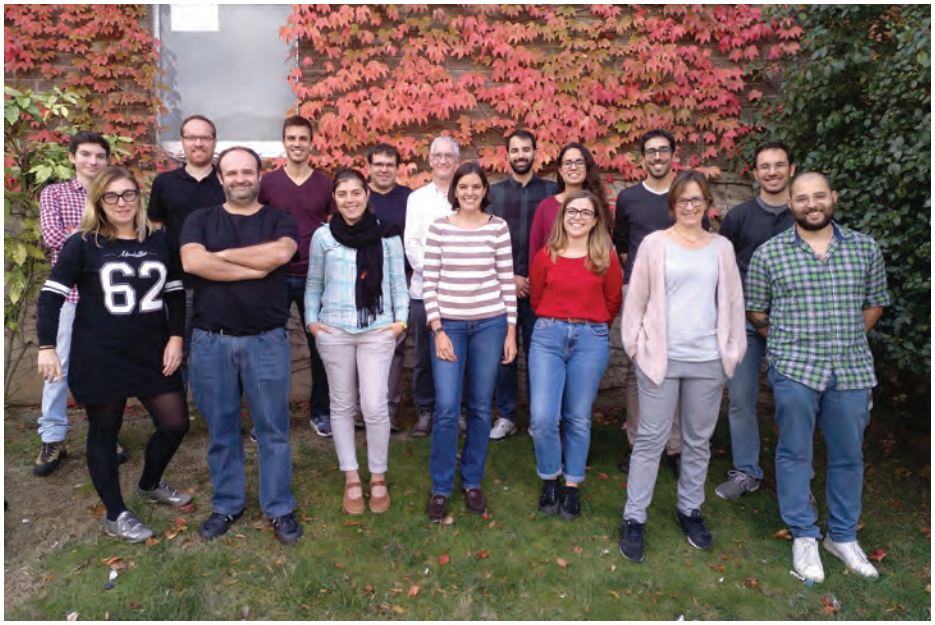
In **2019** we developed our VLP platform (patent EP1638234.4). The potential application of VLPs as preventive vaccines for HIV, yaws/syphilis, human respiratory viruses and animal viruses has been expanded to tumour vaccines (therapeutic or preventive). The latter is a field to be expanded in 2020 (an application in response to a Caixa Impulse call is pending).

Antibody characterization

The task of identifying new antibodies, coordinated by Dr. **Jorge Carrillo**, was redoubled in **2019**, with further funding fostering this research line.

Immune impairment in persons with HIV

Several collaborations with clinical and basic teams at the Germans Trias i Pujol University Hospital HIV unit and with **IrsiCaixa** maintain this research line. The added value of our proprietary software for multicolour flow cytometry analysis, called Ourflow, will be key for the future development of our work.



19 COMMITTED RESEARCHERS WITH COMPLEMENTARY KNOWLEDGE

3 TECHNOLOGIES FOR THE FUTURE (ANTIBODIES, VACCINES AND IMMUNOLOGICAL MARKERS)

1 SINGLE AIM: TO LEARN AND SHARE KNOWLEDGE TO IMPROVE HEALTH IN HIV AND OTHER FIELDS

PRINCIPAL INVESTIGATOR

Julià Blanco

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

Carlos Ávila
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

GRIFOLS PROJECTS

HIGH DENSITY VIRUS-LIKE PARTICLES: A NOVEL VACCINE PLATFORM AGAINST INFECTIOUS DISEASES (INDIVAC)

Senior researcher: Julià Blanco
Principal investigator(s): 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 second 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 TUMOUR NEOANTIGENS AS PERSONALIZED CANCER THERAPY VACCINES (NEOVAC)

Senior researcher: Julià Blanco
Principal investigator(s): Jorge Carrillo

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

Tissue Virology

Projects awarded 2019

Characterization and modulation of the cellular immune response in mucosa-associated lymphoid tissue and implications for the pathogenesis of HIV infection
Funding: ISCIII
Start/end dates: 2019- 2021
Research supervisor: **Cecilia Cabrera**

Genetic and immune signatures to predict response to neoadjuvant chemotherapy in bladder cancer
Funding: Marató de TV3
Participating entities: Fundació Institut Mar d'Investigacions Mèdiques (IMIM)
Start/end dates: 2019- 2021
Research supervisor: **Cecilia Cabrera**

Achievements

Cecilia Cabrera, lecturer in microbiology at the Autonomous University of Barcelona (UAB)
Cecilia Cabrera, member of the editorial board of *Scientific Reports*

Presentation

The group focuses on the following research lines:

HIV pathogenesis in lymphoid tissue

HIV infection is a mucosa-associated disease whose pathogenesis develops in two phases: (1) an acute phase, associated with a massive loss of CD4+ T-cells resident in the mucosa, especially in gut-associated lymphoid tissue (GALT), and (2) 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 pro-inflammatory cytokines. A current topic of debate is mechanisms of CD4+ T-cell destruction and the reasons for incomplete immune recovery in GALT despite effective antiretroviral treatment. The blood-tissue difference has highlighted the importance of assessing the effect of both the virus and antiretroviral therapy on lymphoid tissue. Cellular immune response in HIV infection is not able to control viral replication in most individuals, probably because the quality and pace of induction may not be adequate. The gastrointestinal mucosa is an important site of HIV acquisition, viral replication and pathogenesis. New therapeutic strategies or vaccines must be able to induce polyfunctional immune response in tissue-resident cells in order to prevent or eradicate infection. Microbiome alterations also have an impact on the immune response in other diseases, so we can hypothesize that the dysbiosis experienced by individuals with HIV will alter the specific response of tissue-resident cells against both HIV and commensal bacteria, which, in turn, will alter immune homeostasis and contribute to immune inflammation. Our group is interested in the evaluation of HIV pathogenesis, the impact of antiretroviral drugs and the immune response in tissue. Functional characterization and use of various immunomodulators in resident T-cells could help develop an effective strategy to activate the immune system and eradicate the infection.

Urinary bladder cancer

Bladder cancer is one of the most prevalent cancers in the world. Incidence rates are highest in southern Europe, while Spain figures as one of the countries with the highest estimated incidence and mortality, significantly contributing to the healthcare burden and affecting the quality of life of individuals.
Around 70%–80% of de novo bladder cancers are diagnosed in early stages with no muscular invasion (NMIBC). Patients are often managed with transurethral resection of the bladder tumour (TURBT) with or without adjuvant intravesical therapy. The standard treatment 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, 30% of patients have muscle-invasive bladder cancer (MIBC), highly fatal if untreated, with >85% of those patients dying within two 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. Treatment aims to eradicate micro-metastases early in the disease process when the burden of occult disease is minimal. However, a significant number of patients (up to 60%) do not respond to the treatment and are potentially harmed by side effects. There is therefore an overwhelming need to identify biomarkers of response to neoadjuvant cisplatin-based chemotherapy to prevent administration to patients unlikely to benefit. Our group is also working to improve current treatment by developing new therapeutic strategies and identifying biomarkers to predict response to treatments in both NMIBC and MIBC.

2019 MILESTONES AND PERSPECTIVES FOR THE FUTURE

In **2019**, the results obtained in different lines of work were as follows:

HIV pathogenesis and immune response in lymphoid tissue

— Effects of apoptosis/autophagy modulation on HIV infection. Our evaluation of the mechanisms of cell death using different drugs that modulate apoptosis and autophagy will enable us to determine possible new therapeutic targets.
— Characterization and modulation of cellular immune response in mucosa-associated lymphoid tissue. We have observed differences in tissue resident memory T-cell composition in male genital mucosa. A comprehensive characterization of the immune response could therefore help identify key pathways for regulation of resident immune cells involved in the transmission/maintenance of sexually transmitted diseases.

2 COMPETITIVE GRANTS

Bladder cancer

— Therapeutic strategies for improving BCG treatment. With a view to improving the clinical efficacy of BCG treatment, a phase I clinical trial is underway to study strategies for strengthening the immune system of individuals with superficial bladder cancer before intravesical BCG treatment.
— A new biomarker for response to BCG treatment. In describing alterations in the immune function (both local and systemic) implicated in the therapeutic response to BCG in a cohort of patients with superficial bladder cancer, our results point to the predictive value of a new biomarker based on combined assessment of peritumoral Th1/Th2 polarization and peripheral immunity. This new biomarker will enable us to identify individuals who would benefit from BCG treatment.

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

The mucosa-associated lymphoid tissue represents the major site of acquisition, viral replication and pathogenesis of HIV and other sexually transmitted infections, with genital and gastrointestinal mucosa as the most important targets.
Durable and robust specific immune responses in the genital and gastrointestinal sites are therefore key to the success of immune-based strategies to prevent and/or eradicate infections. The rapid and robust protective immune responses of immune-resident cells housed at mucosal sites have been characterized in murine models. However, their use as vaccines and immunotherapies designed to prevent and/or eradicate mucosal infections needs to be explored.

Neoantigens and Therapeutic Vaccines for Cancer (NeoVaCan)

Presentation

The NeoVaCan group was launched in **IrsiCaixa** in mid-**2019**. It leads research using multi-omics and immune characterization of solid tumours and liquid biopsies at several layers to guide cancer therapy towards personalization and to better understand tumour genomic and immune heterogeneity.

Working with **IrsiCaixa**'s VIC group and a Barcelona Supercomputing Centre team, the NeoVaCan group's goals are to co-develop a therapeutic neoantigen cancer vaccine for clinical application. As one of the two pillars of cancer vaccine development at **IrsiCaixa**, NeoVaCan will coordinate the clinical side and will translate next generation sequencing (NGS)-guided and experimental analyses of neoantigen prediction to therapeutic benefits for patients with cancer.

2019 milestones and perspectives for the future

— To co-develop a therapeutic neoantigen cancer vaccine for patients with solid tumours, working with immunologists and computational biologists and taking advantage of the expertise of **IrsiCaixa** scientists currently working on a vaccine against HIV and other infectious diseases.
— To apply cutting-edge molecular biology procedures to the generation of robust omics data for therapeutic neoantigen discovery and validation.
— To develop in-house cost-effective methods for profiling tumour samples by applying **IrsiCaixa** laboratory practices to the highest standards.
— To expand group bioinformatic proficiencies so as to provide the state-of-the-art tools and new solutions.
— To integrate omics and metadata in order to provide informative reports and data visualization for research groups and for clinician decision-making.

Projects awarded 2019

Profiling the genomics and tumour microenvironment to assess the modulation of therapeutic responses in triple-negative breast cancer patient over 5 years of disease
Funding: NanoString Technologies, Inc
Participating entities: Dexeus University Hospital, VHIO
Start/end dates: 2019- 2020
Research supervisor: **Leticia De Mattos-Arruda**

Grants awarded 2019

Deconvolving genomic and immune populations to battle heterogeneity in metastatic breast cancer: focus on radiological differential responses to therapy
Funding: Instituto Carlos III (FIS)
Participating entities: ICO-Badalona
Start/end dates: 2019- 2021
Research supervisor: **Leticia De Mattos-Arruda**

Achievements

Leticia De Mattos-Arruda, invited to co-edit a new European Society for Medical Oncology (ESMO) book: Genetics & Genomics of Cancer
Leticia De Mattos-Arruda, appointed member of the ESMO Translational Research and Precision Medicine Working Group
Leticia De Mattos-Arruda, part of the Editorial Board for Breast Cancer for ESMO Open-Cancer Horizons

Principal Investigator

Leticia De Mattos-Arruda

Post-doc researcher
Juan Blanco Heredia

Laboratory technician
Carla Dos Anjos de Souza

RESEARCH SUPPORT

Scientific and Technical Services

Sample Conservation and Processing Service

The **IrsiCaixa** Retrovirology Laboratory, which began operations in 1993, processes and preserves biological samples from HIV-infected patients for use in research projects.

Over the years, the laboratory has processed and conserved samples for numerous projects and clinical trials, promoted by both **IrsiCaixa** and external national and international sponsors. This activity has developed into a platform that aims to further research requiring human samples.

Currently, the service routinely processes and stores samples for 26 active studies and maintains a large sample collection (registered with the National Registry of Biobanks, No. C0000814) for research into HIV and other infections.

Sequencing Service

In 1999 the Sequencing Service was launched as a healthcare service to handle 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.

Since its launch **IrsiCaixa** has used HIV genotyping 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 all patients should have access to the technique.

In 2018 the Sequencing Service implemented next-generation sequencing technologies in collaboration with the Germans Trias i Pujol Institute for Health Science Research (IGTP). These highly sensitive technologies identify possible low-level resistance to drugs and may potentially play an important role in the success of antiretroviral treatments.

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

Coordinator
Lidia Ruiz

Sample Conservation and Processing Service
Eulàlia Grau
Rafi Ayen
Lucía Gómez

Sequencing Service
Teresa Puig
Cristina Ramírez

Assistant
Susana Esteban

Samples collected

34,366 cells

65,409 plasma

10,759 serum

28,955 other

Total: 139,489 samples

591 Sequenced samples

393 public centres

198 private centres

Research and Innovation Management

Head
Lourdes Grau

Team
Judith Dalmau
Diana Edo
Chiara Mancuso
Laura Planells

The Research and Innovation Management team works in close contact with all **IrsiCaixa** departments to promote the development of innovative and quality research.

Continuous communication with researchers ensures support at all levels: the detection of needs, the search for suitable funding opportunities, support in preparing proposals and managing projects, budget design and follow-up, and assistance in collaboration, transfer and innovation processes. The RIM team ensures alignment of **IrsiCaixa**'s practices with the rules and policies of funding entities and with national and international regulations.

The Research and Innovation Management team also undertakes transversal tasks at the institutional level in line with **IrsiCaixa**'s strategic research lines, participating in the development of support and management tools, optimizing mechanisms and maximizing synergies.

Updated patent portfolio 2019

Granted

Title: Inhibitors of sialoadhesin for the treatment of diseases caused by enveloped viruses
Inventors: **Izquierdo-Useros, N., Kraüsslich, H.G., Lorizate, M., Martínez Picado, J.**
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: Japan, USA

Title: Method for monitoring HIV-specific T-Cell responses
Reference: WO/2013/139972; PCT/EP2013/056110
Priority date: 23 Mar 2012
Publication date: 26 Sep 2013
Applicants: **IrsiCaixa**, ICREA
Granted: Canada, Japan, USA, Belgium, Switzerland, Germany, Spain, France, UK, Italy, Netherlands, Sweden
Title: Method for identifying HIV neutralizing antibodies
Inventors: **Blanco Arbués, J.M., Carrillo Molina, J.**
Reference: WO/2014/037490; PCT/EP2013/068446
Priority date: 6 Sep 2012
Publication date: 13 Mar 2014
Applicant: **IrsiCaixa**
Granted: USA, Japan, Germany, Spain, France, UK, Italy, Hong Kong
Title: Immunogens for HIV vaccination
Inventors: **Brander, C., Mothe-Pujadas, B., Llano, A.**
Reference: WO/2013/110818; PCT/EP2013/051596
Priority date: 27 Jan 2012
Publication date: 1 Aug 2013
Applicants: **IrsiCaixa**, ICREA
Granted: USA, Japan, Russia
Licensed to: Aelix Therapeutics

Published

Title: Virus-like particles with high-density coating for the production of neutralizing antibodies
Inventors: **Molinos, L., Carrillo, J., Blanco, J.**
Reference: WO/2018/020324; PCT/IB2017/001101
Priority date: 27 July 2016
Publication date: 01 Feb 2018
Applicant: **IrsiCaixa**
Licensed to: HIPRA
Title: Aurora kinase inhibitors for treating or preventing HIV infection or AIDS
Inventors: **Garcia-Vidal, E., Badia, R., Riveira-Muñoz, E., Este, J., Ballana Guix, E.**
Reference: WO/2020/049208; PCT/ES2019/070596
Priority date: 9 Sept 2018
Publication date: 12 Mar 2020
Applicants: **IrsiCaixa**, IGTP

Title: HIV antibody derivatives with dual antiviral and immunomodulatory activity
Inventors: **Carrillo Molina, J., Clotet Sala, B., Blanco Arbués, J.M.**
Reference: WO/2017/085563; PCT/IB2016/001868
Priority date: 21 Nov 2015
Publication date: 26 May 2017
Applicant: **IrsiCaixa**
Licensed to: Albajuna Therapeutics
Title: Human helicase DDX3 inhibitors as therapeutic agents
Inventors: **Meyerhans, A., Martinez-De La Sierra, M.A., Brai, A., Itfazi, R., Tintori, C., Botta, M., Esté, J., Martinez-Picado, J.**
Reference: WO/2016/128541; PCT/EP2016/052990
Priority date: 13 Feb 2015
Publication date: 18 Aug 2016
Applicants: AZIENDA OSPEDALIERA UNIVERSITARIA SENESE; **IrsiCaixa**

Filed

Title: Method for screening HIV-1 latency reversing agents
Inventor(s): Garcia-Prado, J., Ruiz de Andrés, A.
Reference: WO/2019/106427; PCT/IB2018/001456
Priority date: 22 Nov 2017
Publication date: 6 Jun 2019
Applicant: **IrsiCaixa**
Title: SIGLEC 1 monoclonal antibodies for treating and preventing HIV 1 and Ebola virus infections
Inventors: **Izquierdo-Useros, N., Martínez-Picado, J., Pérez-Zsolt, D., Pino-Claveria, M., Kremer, L., Resa-Infante, P.**
Reference: 62828195 (US)
Priority date: 2 Apr 2018
Publication date: NA
Applicant: **IrsiCaixa**
Title: Microbicide compositions comprising SIGLEC-1 monoclonal antibodies for HIV-1 prevention and treatment
Inventors: **Izquierdo-Useros, N., Martínez-Picado, J., Pérez-Zsolt, D.**
Reference: 62832054 (US)
Priority date: 10 Apr 2019
Publication date: NA
Applicant: **IrsiCaixa**

Living Lab for Health

Head
Rosina Malagrida

Team
Josep Carreras
Aina Estany
Marina Pino

Presentation

During **2019**, **IrsiCaixa**'s Living Lab for Health focused on facilitating change in the governance of multi-stakeholder ecosystems to find better solutions to persistent and complex health challenges. Among the different areas where change is being promoted, research and innovation (R&I) in health has been pinpointed as a key area for Living Lab for Health to improve its impact. It has consequently implemented activities to make R&I more open and inclusive following new trends defined by the European Commission (EC) under the umbrella of Responsible Research and Innovation (RRI), Open Innovation, Open Science and Mission-Oriented Research.

Methodologies for the collective reflection and co-creation processes needed for ecosystem transformation have also been applied to the development of educational modules targeted at professionals, stakeholders and secondary students. Living Lab for Health also offers training to universities and research centres and has established collaborations with authorities, e.g., Barcelona City Council. Some of those activities have been implemented within EC-funded projects and also by establishing new partnerships with the "la Caixa" Foundation.

Lines of action 2019

Projects to facilitate change in the governance of health promotion ecosystems

Living Lab has facilitated the development of ecosystems promoting change for two specific challenges: sexual health and healthy nutrition. The main aim is to bring about changes in the strategies, action plans, products, processes and services of the different individual and collective stakeholders in order to increase their impact.

Co-ResponsHIVility

12 Participating research centres, universities, public health entities and civil society organizations

Fit4Food2030

59 Representatives working on the project, including researchers, networks and food clusters, industry, education and others

Challenge 1. Promotion of sexual health in Catalonia and prevention of HIV and other STIs

The Co-ResponsHIVility project has continued with its aim of implementing changes in the model for promoting sexual health and prevention of HIV and other STIs in Catalonia. This project is being implemented within the EC-funded project InSPIRES, in coordination with Barcelona "la Caixa" Living Lab.

Challenge 2. Healthy and sustainable nutrition in Catalonia

Within the Fit4Food2030 EC-funded project, in collaboration with Barcelona "la Caixa" Living Lab, **IrsiCaixa** has continued with its efforts to advance the Fit4FoodCatalonia ecosystem, which also aims to transform the model for promoting healthy and sustainable diets. Within this ecosystem, two educational modules have been developed, one each for professionals and for stakeholders to learn about the complexity of the system and how to transform it.

For both challenges, during **2019** Living Lab for Health conducted a new cycle of workshops with key stakeholders, aimed at implementing a participatory and exhaustive analysis of the factors and interconnections between them. The result was the development of preliminary action plans with strategic solutions for each challenge. These action plans will be further defined for implementation during 2020, within the context of a third cycle of workshops that will make use of a systemic toolkit to improve the plans and better take complexity into account. The action plans will also implement changes at the collective and individual level. Preparatory meetings were held in **2019** with Barcelona City Council, the Catalan government and other stakeholders.

Barcelona – "La Caixa" Living Lab: growing through networking

During **2019**, Living Lab for Health signed an agreement with ISGlobal, "la Caixa" Foundation and Barcelona City Council to facilitate an intermediation structure at city level that would give continuity to the tasks of the Living Lab by promoting cooperation to optimize R&I processes, interventions and policy development in Barcelona. Within this project:

— Work carried out within the two challenges described above has been consolidated.

— In relation to the Immunotherapies Lab, internal reflection has taken place in relation to the complexity of immunotherapy research within **IrsiCaixa**'s research groups (a task to continue during 2020).

— Several research groups have received guidance on writing proposals to include co-creation and RRI so as to ultimately improve their impact.

Communicating IrsiCaixa's research through the Community Advisory Committee (CAC)

The CAC is an external body that facilitates communication and dialogue between **IrsiCaixa** researchers and healthcare professionals and patients, civil society representatives and policy makers. The mission of the CAC is to provide **IrsiCaixa** and its researchers with a broader and complementary perspective on the impact, consequences and feasibility of their research and on the changes implemented in action plans according to their input. In **2019**, the CAC met every 6 months and introduced improvements in a wide variety of research protocols and information documents for participants in clinical trials.

Training, advice and dissemination of RRI and Open Science for researchers, healthcare personnel, patients and other social actors

Living Lab for Health offers training mainly aimed at undergraduate and post-graduate scientists from universities and research centres, clinical researchers and healthcare personnel, experts in public engagement and science communication, staff in funding and performing organizations, public policymakers and patients. Training is customized and is also offered on doctoral, master and undergraduate courses. During **2019**, 282 people received training. Living Lab for Health also participates in national and international conferences, seminars and workshops. In October, it participated in the Association for Interdisciplinary Studies Conference **2019**.

Educational programmes aimed at reducing the gap between research and education

SteamxChange programme

Living Lab for Health has developed, with Educaixa, a new programme called SteamxChange that aims to promote health using innovative inquiry-based methodologies that focus on closing the gap between interdisciplinary research and secondary education. The programme, which is inspired by frameworks applied in other Lab activities, helps participants navigate the complexity of the system and possible changes and provides knowledge, skills and attitudes aimed at fostering responsible citizenship, informed decision-making and active contributions to the R&I system and else-where. This year, the programme has focused on promoting healthy and sustainable diets. SteamxChange is based on the Xplore Health educational programme, which is being adapted and is now part of Educaixa.

HIV/AIDS outreach programme

IrsiCaixa continues to offer dissemination sessions on current research in HIV/AIDS and the importance of prevention and diagnosis, while also inviting reflection and debate on disease-related issues such as stigma and discrimination. Sessions are conducted at CaixaForum and CosmoCaixa venues all over Spain and, in **2019**, were complemented by LaboCosmoCaixa, an activity organized by "la Caixa" Welfare Projects in collaboration with **IrsiCaixa** and aimed at encouraging young people to conduct research with a vaccine candidate developed by **IrsiCaixa**. This was the seventh year of the programme.

IRSICAIXA OUTREACH

4,032 TOTAL ATTENDEES AT THE OUTREACH ACTIVITES

4,620 WEBSITE VISITS

XPLORE HEALTH

60,912 WEBSITE VISITS

45,994 USERS

RRI TRAINING FOR PROFESSIONALS

2,207 PARTICIPANTS IN COURSES AND CONFERENCES

Other outreach activities

During **2019**, Living Lab for Health participated in several outreach activities at science festivals such as La Biennal Ciutat i Ciència and La Festa de la Ciència, both organized by Barcelona City Council. These activities were developed in collaboration with the InSPIRES and Fit4Food2030 European projects and Barcelona – "la Caixa" Living Lab.

PROJECTS IN 2019

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.

CRISH. EC-funded project by EIT Health aimed at facilitating training in RRI, Open Science and Patient Experience and in co-creation in different European cities.

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 Barcelona City Council and aimed at facilitating an intermediation structure to promote cooperation in optimizing R&I processes, interventions and policy development in Barcelona.

SteamxChange. Project funded by "la Caixa" Foundation to offer support in the development of inquiry-based education resources, paying special attention to learning in complexity and transdisciplinarity.

Communication

Team
Júlia Bestard
Rita Casas

A main goal of the Communication Department is to disseminate the results of **IrsiCaixa** research, aiming not only to give visibility to its progress in the fight against HIV/AIDS, but also to raise awareness of the importance of biomedical research. Another main goal is to be useful to **IrsiCaixa** researchers and employees, by making their work visible and supporting all those tasks that involve communication.

Media

In **2019**, 10 press releases were sent, 4 press conferences were organized and 10 news items and 5 posts were disseminated through the institutional website and social networks. These actions resulted in 317 TV, radio and press hits, slightly higher than in 2018 and in line with recent years.

TV, radio and press hits

The most successful media campaigns of **2019** referred to the following events:

— The international consortium IciStem, co-coordinated by **IrsiCaixa** researcher Javier Martínez-Picado, presented the second case of long-term drug-free HIV remission in the world, i.e., the *London patient*.

>5,000
followers on Twitter

>400
monthly newsletter subscribers

317
press, radio and TV hits

129,282
visits to the www.irsicaixa.es website

— *The Lancet* published an article, co-authored by **IrsiCaixa** researcher Pep Coll, confirming that an undetectable viral load renders an individual on HIV treatment sexually non-infectious.

— *Nature Microbiology* published an article, co-authored by Nuria Izquierdo-Useros and Javier Martínez-Picado, on the development of antibodies that block one of the entry pathways of the Ebola virus to human cells.

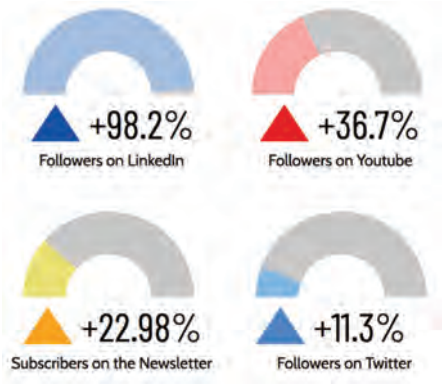
— The first results of a collaborative study with SEAT and Hospital Clínic de Barcelona and led by **IrsiCaixa** researcher Roger Paredes, showed that incorporating healthy habits improves the main health indicators within six months.

Web and social media

Noteworthy is the increase of followers on all the digital platforms, particularly on Linkedin, where the number of followers doubled in **2019** compared to 2018.

IrsiCaixa also consolidated its presence in YouTube, where it published 4 new videos in 2019. As for the institutional website, the statistics show a sustained increase since its launch in mid-2016. There were 60,498 sessions and 48,669 users in 2019, which means an increase of 8.8% and 18.9%, respectively, compared to the previous year.

Increase in followers 2018 to 2019



Institutional communication

In 2019 the Communication Department continued working on the planning and design of corporate materials, including the annual report, new lanyards, an institutional PPT template available to all employees and Christmas greetings. It also collaborated in the preparation of materials for the CERCA evaluation.

Other projects

The Communication Department contributed to the creation of the IrsiCaixa Alumni Network, an initiative of the researcher Patricia Resa. Financial support was obtained from the Spanish Foundation for Science and Technology for the project 'Let's talk about HIV'. This project consists of 4 outreach sessions on HIV/AIDS during 2019-2020 to be carried out in prisons in Catalonia and so reaching one of the groups at the highest risk of infection.


La ciència tanca una de les portes a l'Ebola

HIGHLIGHTED NEWS

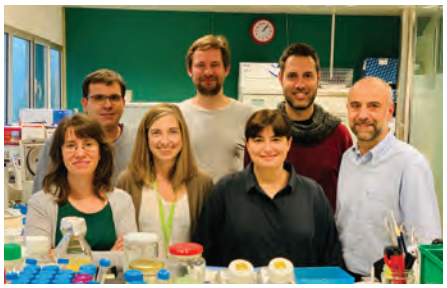
SECOND CASE OF LONG TERM DRUG-FREE HIV REMISSION IN THE WORLD

NATURE REPORTS THE CASE OF A PATIENT WHO UNDERWENT A STEM CELL TRANSPLANT FOR LYMPHOMA AND HAS BEEN IN HIV REMISSION FOR 18 MONTHS DESPITE ANTIRETROVIRAL THERAPY INTERRUPTION. IRSICAIXA PARTICIPATED IN THIS STUDY, WHICH WAS LED BY UNIVERSITY COLLEGE OF LONDON.

In **2019** *Nature* published the case of an HIV-infected adult who underwent a stem cell transplant to treat Hodgkin lymphoma and who has been in viral remission for 18 months in the absence of antiretroviral treatment (ART). The patient, HIV positive since 2003, was diagnosed with Hodgkin lymphoma in 2012 and underwent a stem cell transplant in 2016. However, the patient had a mutation called CCR5 Delta 32, which prevents viral entry in CD4 T-lymphocytes, the HIV target cells. Doctors interrupted ART 16 months after the stem cell transplant, and 18 months later, the virus was undetectable in the patient's blood. This ***London patient*** is only the second such case in the world (the first case was the 'Berlin patient' of 2009). Since then, all cases of ART interruption following a stem cell transplant have resulted in a HIV rebound within the first year. The study, led by University College London and carried out within the framework of the international IciStem consortium, was coordinated by **IrsiCaixa** and the University Medical Center of Utrecht, based in the Netherlands.

NEW PLAN TO PROMOTE SCIENCE AND INNOVATION IN BARCELONA

In 2019, Barcelona City Council and "la Caixa" signed an alliance to strengthen the Barcelona Science Plan and position Barcelona as the European capital of R&I. The results is the Barcelona – "la Caixa" Living Lab, based on the experiences of the **IrsiCaixa** and ISGlobal Living Labs, covering a wide range of initiatives in the research and health fields. The Barcelona – "la Caixa" Living Lab programme aims to be a space for collecting public opinion on current scientific issues.



IRSICAIXA DEVELOPS ANTIBODIES THAT BLOCK ONE OF THE EBOLA VIRUS' ENTRY PATHWAYS INTO HUMAN CELLS

Researchers from **IrsiCaixa** reported a study in *Nature Microbiology* on how the filoviruses (a virus family that includes Ebola) enter the myeloid cells through the same pathway as HIV, i.e., the SIGLEC-1 receptor. **IrsiCaixa** has developed antibodies against this receptor and has demonstrated their capacity to block Ebola entry in the myeloid cells, the main cells targeted before virus spread to other organs and tissues.

INCORPORATING HEALTHY HABITS IMPROVES KEY HEALTH INDICATORS WITHIN SIX MONTHS

In **2019**, SEAT, **IrsiCaixa**, Hospital Clínic de Barcelona, Harvard University and ITAE Enterprises presented the first results of the MedCARS study of a project to change the habits of some 500 employees working at SEAT. Following interventions in diet and activities over six months, scientists analysed different indicators and noted improvements in cardiovascular risk factors, sleep quality and mental and emotional health. To be further studied is microbiome data.

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:

— Work placements for undergraduate and master's students
— Placements for students completing their final undergraduate project or master's thesis
— 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

25 pre-doc researchers

24 post-doc researchers

Training activities

14 research results meetings

101 conference participations

Internal 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 area.
— 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 areas.
— Seminars. **IrsiCaixa** and other Can Ruti Campus groups regularly organize open seminars with invited internationally renowned researchers.
— The growing integration and collaboration between IrsiCaixa and the Can Ruti Campus means greater visibility and attractiveness of **IrsiCaixa** for researchers from abroad. In 2019, this interaction translated into participation in coffee talks, scientific activities, training courses and skills development, organized jointly with the Germans Trias i Pujol Institute for Health Science Research (IGTP) and the Josep Carreras Institute.
— 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 where researchers present an article of relevance to their own experimental work. These meetings develop critical vision regarding published data.
— 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.

Chair of Infectious Diseases and Immunity

In 2013, **IrsiCaixa** signed an agreement with the Fight AIDS Foundation and the University of Vic-Central University of Catalonia (UVic-UCC) to create the Chair in AIDS and Related Diseases. The Chair, headed by **Dr Bonaventura Clotet**, was founded to enhance collaboration between the three institutions in fostering HIV/AIDS and related diseases research at the UVic-UCC and promoting the teaching and training of new

researchers and healthcare professionals. In June 2019, the Chair was renamed the Chair in Infectious Diseases and Immunity to better describe the wide range of fields of expertise of the associated researchers.

The Chair in Infectious Diseases and Immunity undertook the following activities in 2019:

— Vaccines (seminar), 14 February 2019, UVic-UCC Faculty of Medicine, Christian Brander

— Clinical trials: design, types and development phases (seminar), 1 March 2019, UVic-UCC Faculty of Medicine, Beatriz Mothe

— Opening speech of the COHEHRE conference 2019: Integrated Care: Past, Present and Future, 3 April 2019, Les Clarisses Hotel, Vic, Bonaventura Clotet

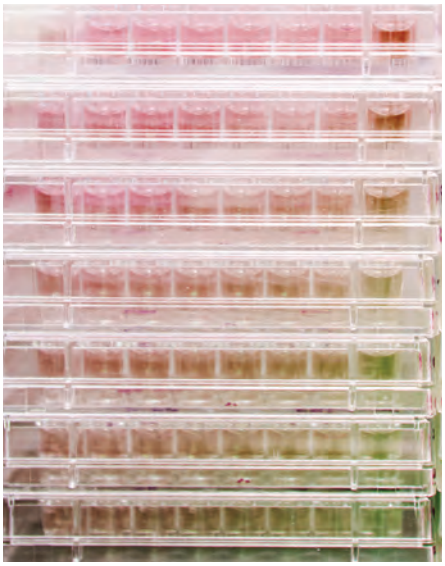
— Ageing (seminar), 12 April 2019, UVic-UCC Faculty of Medicine, Eugènia Negredo

— Tuberculosis/social determinants of health: the UN sustainable development goals (seminars), 11 June 2019, UVic-UCC Faculty of Medicine, Roger Paredes

— Art and medicine (seminar), 12 June 2019, UVic-UCC Faculty of Medicine, Javier Martínez-Picado

— Telemedicine: TeleIctus (seminar), 18 June 2019, UVic-UCC Faculty of Medicine, Cora Loste

— Update on HIV infection (continuous professional development), 14 May 2019, UVic-UCC Faculty of Medicine, Bonaventura Clotet, Cora Loste, Beatriz Mothe, Josep Coll



CLINICAL TRIALS

1. CONTROLLERS

Cohort study of HIV-positive elite controllers and non-progressors. Prospective follow-up.

Summary and objectives: This prospective study follows cohorts of HIV-positive people who maintain an undetectable or very low viral load in the absence of antiretroviral treatment, known as elite or viremic controllers. The objective of the study is to understand the virological and immunological mechanisms involved in the spontaneous control of HIV, which will help us to generate new therapeutic interventions against HIV. No clinical intervention is carried out beyond the extraction of biological samples.

Study type: Observational
Design: Prospective
Recruitment: Ongoing, >150
Start – end: 03/06/2009 - open-ended
Sponsor: HIVACAT, **IrsiCaixa**
Principal investigator(s): Dr. Beatriz Mothe
Participating centre(s):): Germans Trias i Pujol University Hospital (Fight AIDS Foundation); Hospital Vall d'Hebron; Prisons
CEIC Code: EO-09-042

2. Early_cART

Cohort study of individuals with documented acute/recent HIV-1 infection initiating antiretroviral therapy from diagnosis.

Summary and objectives: Prospective cohort and follow-up study of individuals with acute / recent HIV-1 infection who initiated treatment early after infection. One objective is to have a cohort of candidates to participate in clinical trials of therapeutic vaccines and eradication strategies. A second objective is to have uninfected biological samples collected early on with which to study the initial immune response, the establishment of the viral reservoir and changes in the intestinal microbiota. No clinical intervention is necessary beyond the extraction of additional biological samples and the collection of faeces.

Study type: Observational
Design: Cohort, prospective
Recruitment: Ongoing
Start – end: 24/07/2014- open-ended
Sponsor: **IrsiCaixa**
Principal investigator(s): Dr. Beatriz Mothe
Participating centre(s): Germans Trias i Pujol University Hospital (Fight AIDS Foundation)
CEIC Code: PI-14-072

3. Seronegative_genotyped

Biobank of biological samples from HIV-negative individuals with known HLA genotype for experimental use in immunological studies related to AIDS research.

Summary and objectives: Prospective cohort of healthy volunteers documented as HIV-negative for whom high-resolution HLA genotypes have been determined and whose biological samples (plasma and PBMC) are stored in the **IrsiCaixa** biobank.

Study type: Observational
Design: Cohort, prospective
Recruitment: Ongoing
Start–end: 30/10/2009- open-ended
Sponsor: HIVACAT, **IrsiCaixa**
Principal investigator(s): Dr. Beatriz Mothe
Participating centre(s): Germans Trias i Pujol University Hospital (Fight AIDS Foundation)
CEIC Code: EO-09-070

4. BCN02-ROMI

Safety and efficacy of HIVconsv vaccines administered in combination with romidepsin in achieving viral control after interruption of antiretroviral therapy in HIV-positive individuals treated from diagnosis.

Summary and objectives: The BCN02-Romi clinical trial is an eradication study that evaluates the effectiveness of a kick-and-kill strategy based on the use of therapeutic vaccines that have been shown to be most immunogenic (HIVconsv) in combination with the currently most potent viral latency reactive drug (RMD, romidepsin). HIV-positive people with early treated HIV infection represent an ideal group to demonstrate the effectiveness of this strategy based on combining viral reservoir reduction and induction of immunity aimed at viral rebound control. Studied is the relationship between romidepsin levels and in vivo effects on reservoir reactivation and the effects of romidepsin on the immune system are studied.

Study type: Interventional
Design: Open-label, multicentre
Recruitment: Closed (n=15)
Phase: I
Start – end: 02/2015- analysis ongoing
Sponsor: **IrsiCaixa**
Principal investigator(s): Dr. Beatriz Mothe, **Dr. José Moltó**
Participating centre(s): Germans Trias i Pujol University Hospital (Fight AIDS Foundation); Hospital Clínic de Barcelona; BCN Checkpoint
CT Code: NCT02616874
EUDRA Code 2015-002300-84

5. AELIX-002

Phase I randomized, double blind, placebo-controlled clinical trial to assess the safety, tolerance and immunogenicity of DNA.HTI vaccines administered in combination with MVA.HTI in 15 HIV-positive patients diagnosed and treated from an early stage.

Study type: Interventional
Design: Double blind, placebo-controlled, multicentre
Recruitment: Closed (n=45)
Phase: I
Start–end: 07/07/2017- ongoing
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

6. BCG-INMUNO-RESP

Prediction and improvement of clinical response to intravesical BCG treatment of superficial bladder cancer.

Summary and objectives: To evaluate correlation between recurrence and progression and synthetic and local immune response to BCG before and after intravesical therapy and to identify biological markers that predict clinical response to this treatment.

Study type: Observational
Design: Pilot study

Start–end: 2015- analysis ongoing
Sponsor: IrsiCaixa
Principal investigator(s): Dr. Cecilia Cabrera
Participating centre(s): Germans Trias i Pujol Hospital (Fight AIDS Foundation)

7. IciStem (amfAR)

Clinical observational study to evaluate the effect of allogenic transplants in HIV-positive patients with malignant haematological diseases.

Summary and objectives: A European consortium co-led by IrsiCaixa has been created to study the effect of allogenic transplants in HIV-infected patients with malignant haematological diseases. To date 17 patients have been recruited from different European countries, including Spain, Holland, Germany, Belgium and Italy. The main objective is to study the impact of this intervention on the viral reservoir and its potential for eradicating HIV infection.
Study type: Clinical observational
Design: Multicentre
Start–end: 01/07/2014-
Sponsor: University Medical Center Utrecht (Netherlands)
Principal investigator(s): Dr. Javier Martínez-Picado, Dr. Annemarie Wensing

8. LoViReT

Clinical observational study to evaluate predictors of extremely low viral reservoirs.

Summary and objectives: Clinical observational study involving the screening of some 400 patients for cellular proviral DNA to create a cohort of 20-30 patients with extremely low viral reservoirs. The factors involved in these reservoir levels and their possible application to treatment strategies will be exhaustively studied.
Study type: Clinical observational
Start–end: 01/01/2015-
Principal investigator(s): Dr. Javier Martínez-Picado

9. Durvast

Clinical trial to evaluate the effect of durvalumab (MEDI4736) in HIV-positive patients with advanced solid tumours.

Summary and objectives: Phase II clinical trial to evaluate the effect of durvalumab (MEDI4736) in HIV-positive patients with advanced solid tumours.
Phase: II
Start–end: 01/01/2015 -
Principal investigator(s): Dr. Javier Martínez-Picado

10. RUTIVAC-1

Phase I randomized, double-blind, placebo-controlled clinical trial to evaluate the immunomodulating effect of RUTI® in individuals with high-grade superficial bladder cancer treated with intravesical Bacillus Calmette-Guerin (BCG).

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 RUTI® administration to individuals with non-muscle invasive bladder cancer (NMIBC).
The study will enroll individuals treated with transurethral resection of bladder tumour (TURBT) diagnosed at high risk of NMIBC, considered suitable candidates for BCG therapy and meeting 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 (BCG) therapy based on an induction course (weekly BCG for six weeks) and a maintenance course (thrice 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 analysed. 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 individuals will be followed up for three years after TURBT.
Study type: Interventional
Design: Double blind, placebo-controlled, randomized
Phase: I
Start–end: 2017- 2021
Sponsor: Archivel Farma SL
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

11. AbiVax 005

An open-label study of the safety, pharmacokinetics and pharmacodynamics of ABX464 in HIV-1 seronegative and seropositive adults.

Summary and objectives: Clinical study to evaluate the distribution of ABX464 and its main metabolite (N-Glu) in various compartments in HIV-1 positive and negative adults.
Phase: Ib
Start–end: Q4 2016 -
Principal investigator(s): Dr. Ross Cranston

12. 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

13. Dual vs Triple

The objective is to compare the effect of first-line ART with BIC/TAF/FTC versus DTG + 3TC in HIV-1 persistence and immune activation in ART-naïve HIV-infected patients. The hypothesis is that first-line triple ART with BIC/TAF/FTC in HIV-infected patients without prior ART experience could result in greater decay of the HIV-1 reservoir, as well as in lower levels of residual viral replication and immune activation compared with dual ART with DTG + 3TC.
Study type: Exploratory, open-label, randomized clinical trial
Design: Exploratory, single-center, randomized, open-label clinical trial in ART-naïve HIV-infected patients.
Recruitment: The study will consist of a total of 44 adults infected by HIV-1 without prior ART experience.
Start–end: October 2019 – September 2021
Sponsor: Gilead Sciences SL
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)
NCT Code: AC-19-073-HGT-CEIM

14. ITATI

Immune Therapy and Analytical Treatment Interruption in HIV+ participants who received an allogeneic stem cell transplantation. The primary objective is to evaluate the effects of eight intravenous infusions of 3BNC117 and 10-1074, each dosed at 30 mg/kg, on maintaining viral suppression under cART discontinuation in HIV+ participants with undetectable replication competent HIV reservoir after allogeneic stem cell transplantation in presence of cART.
Study type: Phase II/exploratory proof-of-concept clinical trial
Design: Phase II/exploratory proof-of-concept clinical trial, multicenter and single arm, in which a (pre)defined number of subjects will be offered to discontinue their cART in combination with a transient HIV-specific immune therapy (the broadly neutralizing antibodies (bNAbs) 3BNC117 and 10-1074)
Recruitment: 5 HIV+ participants with undetectable replication competent HIV reservoir after allogeneic stem cell transplantation in presence of cART
Start–end: July 2019 – December 2021
Sponsor: The Foundation for AIDS Research, amfAR
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

Publications and Conferences

Publications

Original publications

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Collaborative publications

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Conference presentations and Talks

Presentations at national conferences

1. Benet S, C Gálvez, F Drobniewski, I Kontsevaya, L Arias, M Monguió-Tortajada, I Erkizia, V Urrea, Ruo-Yan Ong, M Luquin, M Dupont, J Dalmau, P Cardona, G Lugo, C Verollet, E Julián, H Furrer, H Günthard, P Crocker, G Tapia, F E. Borràs, J Fellay, PJ. McLaren, A Telenti, P J Cardona, B Clotet, C Vilaplana*, J Martinez-Picado. **Dissemination of Mycobacterium tuberculosis is associated to a SIGLEC-1 null variant that limits antigen exchange via trafficking extracellular vesicles.** XI Congreso Nacional de GeSIDA. Toledo (Spain). Dec 10-13, 2019. Oral Presentation.

2. Benet S, C Gálvez, F Drobniewski, I Kontsevaya, L Arias, M Monguió-Tortajada, I Erkizia, V Urrea, Ruo-Yan Ong, M Luquin, M Dupont, J Dalmau, P Cardona, G Lugo, C Verollet, E Julián, H Furrer, H Günthard, P Crocker, G Tapia, F E. Borràs, J Fellay, PJ. McLaren, A Telenti, P J Cardona, B Clotet, C Vilaplana, J Martinez-Picado, N Izquierdo-Useros. **Dissemination of Mycobacterium tuberculosis is associated to a SIGLEC-1 null variant that limits antigen exchange via trafficking extracellular vesicles.** 5th Geivex Symposium. Granada (Spain), Nov 06-08, 2019. Oral Presentation.

3. Bracht JWP., M. Gonzalez-Cao, T. Moran, J. Dalmau , J. Garcia-Corbacho, J, R. Bernabe, O. Juan, J. de Castro, A. Gimenez, 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, A. Meyerhans, MA. Molina, J. Martinez-Picado, R. Rosell on behalf of the Spanish Lung Cancer Group. **A 770 gene panel expression analysis to predict clinical benefit of durvalumab in HIV-infected cancer patients.** 13th Congress on Lung Cancer. Spanish Lung cancer group (GECP). Valencia (Spain). November 21-22, 2019.

4. Brander3,10-11, J. Carrillo3, B. Clotet2,3,11, B. Massuti12, M. Provencio13, MA. Molina1, J. Martinez-Picado3,10-11, R. Rosell1,14 on behalf of the Spanish Lung Cancer Group. **A 770 gene panel expression analysis to predict clinical benefit of durvalumab in HIV-infected cancer patients.** 13th Congress on Lung Cancer. GECP (Grupo Español en Cáncer Pulmón). Valencia (Spain). November 21-23, 2019. Oral Presentation

5. Colomer-Lluch M, Pernas M, Peña R, Jimenez-Moyano E, Dalmau J, Casado C, LópezGalíndez C, Martínez-Picado J, Prado JG. **Viral factors and T-cell sensitivity to activation dictate the loss of control in two cases of HIV-1 viremic non-progressors.** Congreso Nacional de GeSIDA 2019. GeSIDA. Toledo (Spain). December 10-13, 2019. Oral poster.

6. Ferran Tarrés. **An enveloped Virus-Like Particle (VLP) platform with high-density antigen display induces a strong humoral immune response.** XI Congrés Nacional GESIDA. GESIDA – SIDA-SEIMC. Toledo (Spain). December 10-13, 2019. Oral Presentation.

7. Franco Sandra, Laura Soldevila, Montse Tenesa, Daniela Buccione, Dan Ouchi, Ivan Galvan-Fermenia, Rafael de Cid, Lidia Ruiz, Ana Jordan de Paiz, Maria Nevot, Jordi Bechini, Ricardo Perez, Bonaventura Clotet, Miguel Angel Martinez and Cristina Tural. **Genetic and metabolic risk factors related with liver fibrosis in HIV/HCV co-infection.** XV Congreso Nacional de Virología. Sociedad Española de Virología. Barcelona (Spain). June, 2019. Poster

8. Garcia-Vidal Edurne, Maria Pujantell, Roger Badia, Marc Castellví, Bonaventura Clotet, Eva Riveira-Muñoz, Ester Ballana and José A. Esté. **Dual effect of the broad spectrum kinase inhibitor midostaurin in acute and latent HIV-1 infection.** Congreso Nacional de Virología. Sociedad Española de Virología. Barcelona (Spain). June 9-12, 2019. Poster.

9. Jiménez Montse. **Early and late alterations in B-cell subsets during acute HIV infection.** XI Congrés Nacional GESIDA. GESIDA – SIDA-SEIMC. Toledo (Spain). December 10-13, 2019. Oral Presentation.

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11. Jordan-Paiz Ana, Maria Nevot, Kevin Lamkiewicz, Marie Lataretu, Sandra Franco, Manja Marz, Miguel Angel Martinez. **Disruption of an RNA secondary structure in HIV-1 gp41 induces viral lethality.** XIV Jornada de Virologia. Societat Catalana de Biologia. Barcelona (Spain). November 2019. Oral.

12. Martí Anna, Esther Rodríguez-Gallego, Consuelo Viladés, Pere Domingo, Miguel López-Dupla, Yolanda María Pacheco, Sergi Veloso, Eugènia Negredo, Julià Blanco, Roger Paredes, Verónica Alba, Montserrat Vargas, Vicenç Falcó, Ezequiel Ruiz-Mateos, Alexy Inciarte, Josep Mallolas, Joaquim Peraire, Francesc Vidal, Anna Rull. **Microbial translocation as predictive marker of immune recovery and disease progression in successfully treated HIV-infected patients.** XI Congrés Nacional GESIDA . GESIDA – SIDA-SEIMC. Toledo (Spain). December 10-13, 2019. Oral Presentation.

13. Moyano A., N. Pedreño , L. Tarancón , O. Blanch-Lombarte, T. Alvaro , C. Casado, M. Vera, I. Olivares, C. Rodriguez, J. Del Romero, E. Ruiz-Mateos , C. López-Galíndez , J. G Prado, M. Pernas. **Env EL9 epitope driven by HLA B*1402 leads disease progression in LTNP patient after twenty seven years of HIV control.** Congreso Nacional de GeSIDA 2019. GeSIDA . Toledo. Spain. December 10-13, 2019. Oral Presentation.

14. Muñiz-Trabudua X, I Erkizia, P Resa-Infante, J Chojnacki, D Perez-Zsolt, L Kremer, J Martinez-Picado, N Izquierdo-Useros. **Exploring the therapeutic potential of Fabs derived from novel anti-Siglec-1 mAbs with the ability to block HIV-1 capture.** XI Congreso Nacional de GeSIDA. Toledo (Spain). December 10-13, 2019. Oral Presentation.

15. Noguera-Julian M. **Ya tengo mis secuencias, ¿ahora qué?** International Symposium on External Quality Assurance Strategies for NGS-based HIVDR testing. Formación SEIMC-Gesida. Barcelona(Spain). September 27th, 2019. Oral Presentation.

16. Noguera-Julian M. **The gut metabolome in HIV infection.** The Barcelona Debates on the Human Microbiome 2019. IrsiCaixa. Barcelona (Spain). June 20-21, 2019. Oral Presentation.

17. Pedreño-López Sònia, Elisabet García, Dolores Guerrero, Elisabet Gómez-Mora, Bonaventura Clotet and Cecilia Cabrera. **Autophagy inhibition prevents HIV replication, cell depletion and cell-to-cell HIV transmission in human lymphoid tissue cultured ex vivo.** XI Congreso Nacional de GeSIDA. Toledo (Spain). December 10-13, 2019. Oral Presentation.

18. Perez-Zsolt D., Cantero-Pérez J., Erkizia I., Benet S., Pino M., Serra-Peinado C., Hernández-Gallego A., Castellví J., Tapia G., Arnau-Saz V., Garrido J., Tarrats A., Buzón M. J., Martinez-Picado J., Izquierdo-Useros N. and Genescà M. **Dendritic cells from the cervical mucosa capture and transfer HIV-1 via Siglec-1.** XV Congress of the Spanish Society of Virology / 11th International Meeting GVN. Barcelona (Spain). Jun 10-12, 2019. Poster & FLASH Presentation.

19. Pujantell Maria, Eva Riveira-Muñoz, Alba Ruiz, Roger Badia, Bonaventura Clotet, Jose A.

Este, Ester Ballana. **Vpx induces an IFN-related innate immune response distinct from samhd1 abrogation.** Conference on Retroviruses and Opportunistic Infections. IAS-USA. Seattle (USA). March 4-7, 2019. Poster.

20. Resino, Salvador, Navarrete-Muñoz, María A, Blanco, Julià, Pacheco, Yolanda M, Castro, Iván, Berenguer, Juan, Santos, Jesús, Vera-Méndez, Francisco J, Górgolas, Miguel, Jiménez-Sousa, M A Ángeles, Benito, José M, Rallón, Norma, CoRIS and the HIV Biobank integrated in the Spanish AIDS Research Network Project RIS/EPICLIN 10_2015. **El polimorfismo rs6897932 en el genIL7RA está asociado con mejor recuperación de células T-CD4 en pacientes VIH iniciando TARc con bajos recuentos de CD4.** Oral Presentation. XI Congrés Nacional GESIDA . GESIDA – SIDA-SEIMC. Toledo (Spain). December 10-13, 2019.

21. Riveira-Muñoz Eva, Eudald Felip, Maria Pujantell, Edurne Garcia-Vidal, Bonaventura Clotet, Roger Badia, Mireia Margelí, José A. Esté, Ester Ballana. **Pharmacological inhibition of CDK4/6 enhances antiviral and cytotoxic activity of antimetabolites.** Congreso Nacional de Virología. Sociedad Española de Virología. Barcelona (Spain). June 9-12, 2019. Poster.

22. Rull Anna, Esther Rodríguez-Gallego, Consuelo Viladés, Pere Domingo, Miguel López-Dupla, Yolanda María Pacheco, Sergi Veloso, Verónica Alba, Eugènia Negredo, Julià Blanco, Roger Paredes, Anna Martí, Montserrat Vargas, Vicenç Falcó, Ezequiel Ruiz-Mateos, Alexy Inciarte, Josep Mallolas, Francesc Vidal, Joaquim Peraire. **A baseline pro-inflammatory profile is associated with discordant response to ART in HIV-1 infected patients.** XI Congrés Nacional GESIDA. GESIDA – SIDA-SEIMC. Toledo (Spain). December 10-13, 2019. Oral Presentation.

23. Tarrés Ferran, Marrero-Hernández Sara, Daniel Márquez-Arce, Romina Cabrera-Rodríguez, Judith Estévez-Herrera, Silvia Pérez-Yanes, Jonathan Barroso-González, Ricardo Madrid, José-David Machado, Julià Blanco and Agustín Valenzuela-Fernández. **HIV-1 Nef targets HDAC6 to degradation to assure viral production and virus infection.** XI Congrés Nacional GESIDA . GESIDA – SIDA-SEIMC. Toledo (Spain). December 10-13, 2019. Oral Presentation.

24. Verónica Alba, Esther Rodríguez-Gallego, Consuelo Viladés, Pere Domingo, Miguel López-Dupla, Yolanda María Pacheco, Sergi Veloso, Eugènia Negredo, Julià Blanco, Roger Paredes, Anna Martí, Montserrat Vargas, Vicenç Falcó, Ezequiel Ruiz-Mateos, Alexy Inciarte, Josep Mallolas, Joaquim Peraire, Francesc Vidal, Anna Rull. **EndoCAb and I-FABP as predictive markers of immune recovery in successfully treated HIV-infected subjects.** XI Congrés Nacional GESIDA. GESIDA – SIDA-SEIMC. Toledo (Spain). December 10-13, 2019. Oral Presentation.

Presentations at international conferences

1. Astorga Gamaza A, 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 (ID 1497)**. Conference on Retrovirus and Opportunistic Infections (CROI). International Antiviral Society-USA (IAS-USA). Boston (MA, USA). March 8-11.

2. Blanch-Lombarte Oscar, Cristina Gálvez, Boris Revollo, Esther Jiménez-Moyano, Josep M Llibre, Judith Dalmau, Daniel E. Speiser, Bonaventura Clotet, Julia G Prado#, Javier Martinez-Picado. **Enhancement of antiviral CD8+ T-cell responses and complete remission of metastatic melanoma in an HIV-1-infected subject treated with pembrolizumab.** 9th HIV persistence during therapy Overcome. Miami. USA. December 10–13, 2019. Poster. Granted.

3. Oscar Blanch-Lombarte, 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. **CD8+ Subset-Dependent overexpression of tigit and TIGIT+TIM3 by HIV despite art (ID 2706)**. Conference on Retrovirus and Opportunistic Infections (CROI). International Antiviral Society-USA (IAS-USA). Boston (MA,USA). March 8-11. Abstract number 0302, Session Number P-D08. Granted.

4. Colomer-Lluch M, Adland E, Dalmau J, Francés C, Peña R, Jiménez-Moyano E, Clotet B, Martínez-Picado J, Goulder P, Prado JG. **Characterization of viral factors in pediatric and adult HIV-1 viremic non-progressors.** Cold Spring Harbor 44th annual meeting on Retroviruses Cold Spring Harbor Laboratory. Cold Spring Harbor. New York (USA). May 20–25, 2019. Poster. Grant: Beatriu de Pinós fellowship.

5. Colomer-Lluch M, Adland E, Dalmau j, Francés C, Peña R, Jiménez-Moyano E, Clotet B, Martinez-Picado J, Goulder P, Prado JG. **Limited contribution of viral factors to the viremic nonprogressor phenotype in adult and pediatric HIV-1 infection.** Retroviruses. Cold Spring Harbor. New York, (USA). May 20-25, 2019. Poster Presentation.

6. Díaz-Varela M, Gualdrón-López M, Aparici-Herraiz I, Pedró-Cos L, Lauzurica-Valdemoros R, Izquierdo-Useros N, Martinez-Picado J, Fernández-Becerra C, del Portillo HA. **Reticulocyte-derived exosomes: a new vaccine approach against Plasmodium vivax malaria.** 7th International Conference on Plasmodium vivax Research. Paris (France). Jun 26-28, 2019. Poster Presentation.

7. Díaz-Varela M, Gualdrón-López M, Segui-Barber J, Lauzurica-Valdemoros R, Izquierdo-Useros N, Martinez-Picado J, Fernández-Becerra C, del Portillo HA. **Reticulocyte-derived exosomes: a new antigen discovery and vaccine delivery platform against Plasmodium vivax malaria.** Malaria Vaccines for the World 2019. Oxford (UK). May 8-10, 2019. Oral Presentation.

8. Duran-Castells C, Kawana-Tachikawa A, Llano A, Mothe B, Oriol-Tordera B, Galvez C, Ganoza C, Sanchez J, Clotet B, Martinez-Picado J, Muñoz-Moreno J.A, Wyss-Coray T, Brander C, Ruiz-Riol M. **Early and late cART treatment initiation have an impact on SIRT2 plasma levels associated with HIV viral load and proviral levels at PBMC.** 14th World Immune Regulation Meeting. Davos (Switzerland), March 4-7, 2019. Poster Presentation.

9. Felip Eudald, Marc Castellví, Ifeanyi Jude Ezeonwumelu, Roger Badia, Eva Riveira-Muñoz, José A. Esté, Mireia Margelí, Ester Ballana. **Cyclin-dependent kinases inhibitors as modulators of antimetabolite drugs cytotoxicity depending on SAMHD1 expression.** San Antonio Breast Cancer Symposium. American Association for Cancer Research (AACR). San Antonio, Texas. USA. December 10-14, 2019. Poster

10. Gonzalez-Cao M, Moran T, Dalmau J, Garcia-Corbacho J, Bernabe R, Juan O, de Castro J, Blanco R, Meyerhans A, Blanco J, Prado J, Karachaliou N, Brander C, Carrillo J, Clotet B, Massuti B, Provencio M, Molina MA, Martinez-Picado J, Rosell R. **Phase II study of durvalumab (MEDI4736) in HIV-1-infected cancer patients.** American Society of Clinical Oncology (ASCO). Chicago (USA), Jun 1-4, 2019. Oral Presentation 2501.

11. Jensen BEO, Knops E, Lübke N, Wensing A, Martinez-Picado J, Kaiser R, Nijhuis M, Salgado M, Harrer T, Heger E, Eberhard JM, Hauber I, Münk

C, Häussinger D, Kobbe G. **Analytical Treatment interruption (ATI) after allogeneic CCR5d32 HSCT for AML in 2013.** 2019 Conference on Retroviruses and Opportunistic Infections. Seattle (USA). March 4-7, 2019. Poster Presentation 394.

12. Jordan-Paiz Ana, Maria Nevot, Kevin Lamkiewicz, Marie Lataretu, Sandra Franco, Manja Marz, Miguel Angel Martinez. **Synonymous genome recoding identify a functional RNA element in the envelope coding region of HIV-1.** Positive-Strand RNA Viruses. Keystone Symposia. Dublin, Ireland. June 2019. Poster.

13. Margelí Mireia, Eudald Felip, M. Carmen Gómez, Vanesa Quiroga, Ricard Mesía, José A. Esté and Ester Ballana. **Predictive value of SAMHD1 expression in early relapse breast cancer.** San Antonio Breast Cancer Symposium. American Association for Cancer Research (AACR). San Antonio, Texas (USA). December 10-14, 2019. Poster.

14. Marin Lopez M., E. Jimenez-Moyano, D. Ouchi, O. Blanch-Lombarte, D. Gorman, T. Hanke, C. Brander ,B. Howell ,B. Mothe ,J.G Prado. **PD-1 blockade boost vaccine-induced anti-HIV responses in the absence of HIV reactivation.** 9th HIV persistence during therapy Overcome. Miami (USA). December 10-13, 2019. Oral. Grant: Pending.

15. Marin Miguel A, Ruiz Alba, Esther Jimenez-Moyano, Dan Ouchi, Oscar Blanch-Lombarte, Daniel Gorman, Ruth Penya, Richard Barnard, Christian Manzardo, Tomas Hanke, Christian Brander , Bonnie J. Howell, Bonaventura Clotet, Beatriz Mothe, Julia G Prado. **Impact of immune checkpoint inhibitors in vaccine-induced anti-HIV responses (ID 1741).** CROI 2020. Organizer: International Antiviral Society-USA. Boston USA . 8 March- 11 March. Granted.

16. Martinez Miguel Angel, Ana Jordan-Paiz, Sandra Franco and Maria Nevot. **Synonymous Recoded Envelope Gene Induce HIV-1 Lethality and Loss of Protein Expression.** Microbe 2019. American Society for Microbiology. San Francisco (USA). June 2019. Poster

17. Morón-López S, Puertas MC, Gálvez C, Navarro J, Carrasco A, Esteve M, Manyé J, Crespo M, Salgado M, Martinez-Picado J. **Sensitive quantification of the HIV-1 reservoir in gut-associated lymphoid tissue.** iChem2019. San Francisco (USA), Jul 1-3, 2019. Oral Presentation.

18. Noguera-Julian M. Ideal dry panels for NGS HIVDR: Reality and challenges. **International Symposium on External Quality Assurance Strategies for NGS-based HIVDR testing.** Public Health Agency of Canada (PHAC). Winnipeg (Canada). September 9-10, 2019. Oral Presentation.

19. Oriol-Tordera B, Llano A, Mothe B, Duran-Castells C, Olvera A, Galvez C, Ganoza C, Sanchez J. Gómez G, Negredo E, Clotet B, Martinez-Picado J, Blanco J, Wyss-Coray T, Brander C, Ruiz-Riol M. **TL1A/DR3 axis plays a key role in HIV control intensifying HIV specific CTL responses.** 14th World Immune Regulation Meeting. Davos (Switzerland). March 4-7, 2019. Poster Presentation.

20. Perez-Zsolt D., Cantero-Pérez J., Erkizia I., Benet S., Pino M., Serra-Peinado C., Hernández-Gallego A., Castellví J., Tapia G., Arnau-Saz V., Garrido J., Tarrats A., Buzón M. J., Martinez-Picado J., Izquierdo-Useros N. and Genescà M. **Dendritic cells from the cervical mucosa capture and transfer HIV-1 via Siglec-1.** 19th International Congress of Mucosal Immunology. Brisbane (Australia). Jun 16-20, 2019. Poster.

21. Pujantell M, Eva Riveira-Muñoz, Edurne García-Vidal, Lucía Gutierrez, Bonaventura Clotet, José A. Esté and Ester Ballana. **ADAR1 function regulates innate immune activation and susceptibility to viral infections.** Congreso Nacional de Virología. Sociedad Española de Virología. Barcelona (Spain). June 9-12, 2019. Oral presentation.

22. Riveira-Muñoz Eva, Ivan Galvan-Fermenia, Rafael de Cid, Antoni Tarrats, Marta Piñol, Francesc García-Cuyás, Jose A. Este, Roger Badia, Guillem Sirera, Ester Ballana. **Transcriptome analysis in HPV+/HIV+ tissue reveals markers of HPV-dependent dysplasia.** Conference on Retroviruses and Opportunistic Infections. IAS-USA. Seattle (USA). March 4-7, 2019. Poster.

23. Ruiz Alba, Miguel Marin, Esther Jimenez-Moyano, Dan Ouchi, Oscar Blanch-Lombarte, Ruth Peña, Christian Manzardo, Tomas Hanke, Christian Brander, Bonaventura Clotet Beatriz Mothe and Julia G Prado. **PD-1 Blockade boost vaccine-induced Antiviral CD8+ T-cell responses in Early treated HIV-1 infected individuals**. Cold Spring Harbor 44th annual meeting on Retroviruses. Cold Spring Harbor Laboratory. Cold Spring Harbor, New York (USA). May 20–25, 2019. Poster.

24. Salgado M, Martinez-Picado J, Gálvez C, Rodriguez-Mora S, Urrea V, Mateos E, Alcamí J, Coiras M. **In vivo antiviral effect of dasatinib in huminized mice infected with HIV-1.** Conference on Retroviruses and Opportunistic Infections 2019. Seattle (USA). March 4-7, 2019. Poster Presentation.

25. Salgado M, Gálvez C, Nijhuis M, Kwon M, Badiola J, Bandera A, Jensen B, Vandekerckhove L, Jurado M, Raj K, Schulze zur Wiesch J, Nabergoj M, Hutter G, Saldaña-Moreno R, Barrett L, Kuball J, Saez-Cirión A, Diez-Martin JL, Wensing A, Martinez-Picado J. **Allogeneic stem cell transplantation reduces HIV latent reservoir under cART independently of CCR5-mutated donor.** Keystone Symposium. Functional Cures and the Eradication of HIV. Whistler (Canada). March 24-28, 2019. Poster Presentation 3010.

26. Wensing AMJ, Salgado M, Kwon M, Eberhard JM, Saez-Cirion A, Schulze zur Wiesch J, Hütter G, Badiola-González J, Bandera A, Barrett L, Gupta RK, Jensen BE, Kuball JHE, Martín Carbonero L, Nabergoj M, Raj K, Saldaña-Moreno R, Scarlatti G, Vandekerckhove L, Díez Martín JL, Nijhuis M, Martinez-Picado J. **Allogeneic stem cell transplant in HIV-1 infected individuals; An update of the IciStem Consortium.** 10th IAS Conference on HIV Science. Mexico City (Mexico). Jul 21-24, 2019. Oral Presentation WEPEA065.

Invited talks

1. Leticia De Mattos Arruda- Invited Speaker. Taking diagnostics to the next level. **ROCHE Satellite Symposium "Cracking the code of Personalized Heath Care".** ESMO Congress. Barcelona (Spain). September 27th, 2019.

2. Leticia De Mattos Arruda - Invited Speaker. **Neoantigens identification as targets for cancer vaccines.** Breaking through the emergent immunotherapy and immune targets in cancer symposium. Barcelona (Spain). September 26th, 2019.

3. Leticia De Mattos Arruda - Invited Speaker. **Next gen sequencing-based neoantigen prediction in cancer: lessons learnt.** Immunotherapies and Hemopathies Workshop. Barcelona (Spain). Ocrober 11th, 2019.

4. Leticia De Mattos Arruda - Invited Speaker. **Young Oncologist mentorship session – Building a career in translational research.** ESMO Congress. Barcelona (Spain). September 27th, 2019.

5. Leticia De Mattos Arruda- Invited Speaker. L**iquid Biopsy: Circulating Tumour DNA & Bloodborne Biomarkers as Diagnostic Tools**. Cancer Precision Medicine Forum. Berlin (Germany). December 2nd, 2019.


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