IrsiCaixa
Institut de Recerca de la Sida

"la Caixa"

Generalitat de Catalunya
Departament de Salut

IrsiCaixa
Scientific Report
2018

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IrsiCaixa

The **IrsiCaixa AIDS Research Institute** is an international landmark and leading 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 faciltates the search for new solutions and progress towards 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 also participates in clinical trials to evaluate innovative therapeutic strategies and actively cooperates with low-income countries in the global fight against the pandemic. **IrsiCaixa** places special emphasis on the formal training of young scientists, on innovation and on the transfer of knowledge generated in its laboratories.

Letter from the director

In **IrsiCaixa** we are proud, year after year, to count among the world's leading HIV/AIDS research centres. All the knowledge we have acquired in our 23 years of existence enables us to now expand our work and focus research in other biomedical areas affecting the entire population, such as cancer, neurodegenerative diseases, emerging infectious diseases and the role played by the gut microbiome in people's health.

A result of this diversification is the signing of a collaboration agreement with Grifols pharmaceutical company in **2018** that will help fund current and future lines of research. **That investment is crucial for the future of our institution** and will allow us to consolidate **IrsiCaixa** further as one of Spain's most forward-looking research centres.

Notable progress in the HIV care and eradication line is a recent article in *Annals of Internal Medicine* describing a study – co-led by **IrsiCaixa** and carried out in the framework of the international IciStem consortium – that identifies factors related to stem cell transplantation that could lead to elimination of the viral reservoir. The significance of this research is reflected not only in the high impact factor of the journal and the reactions of the scientific community, but also by the impact achieved in the mass media.

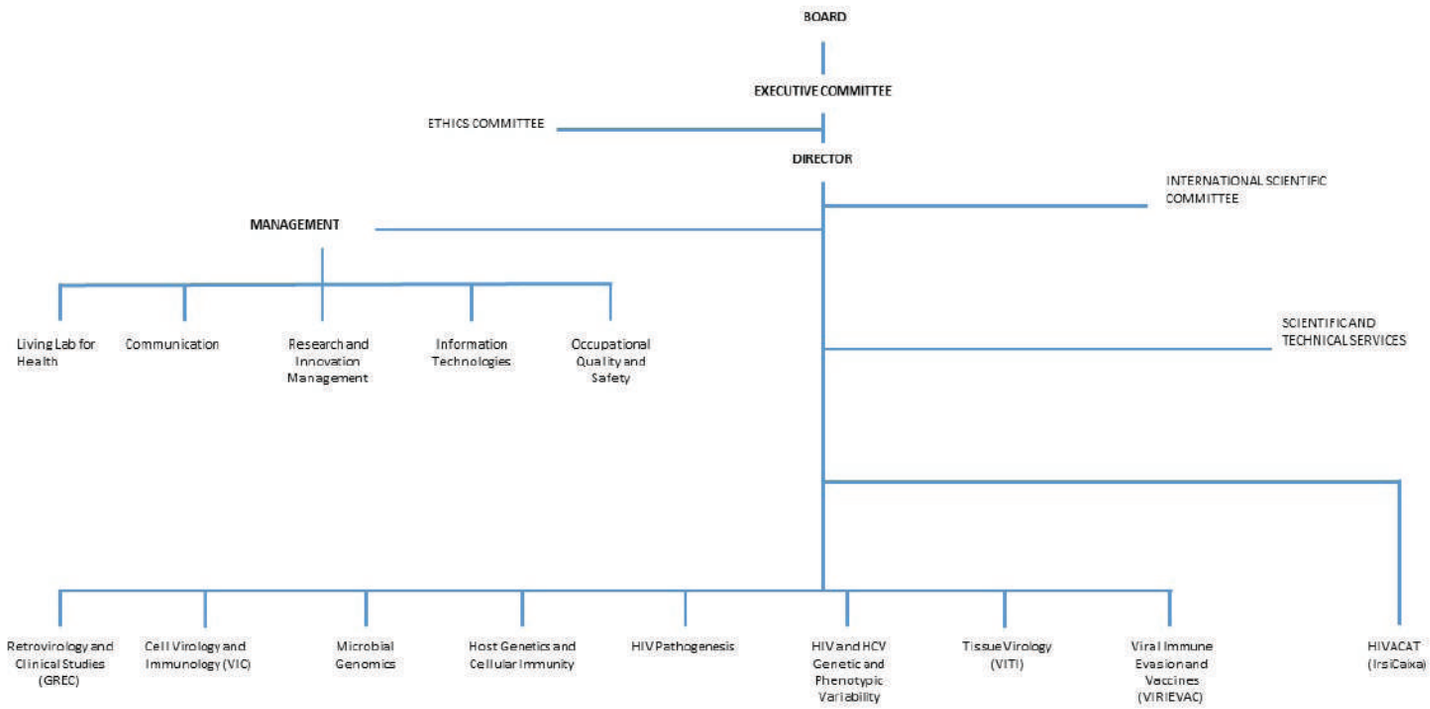
This past year was also marked by confirmation that **IrsiCaixa** will organize the eighth edition of the International Human Microbiome Congress – the world's most important such conference – to be held in Barcelona in 2020. This opportunity arose out of the success of four editions of The Barcelona Debates on the Human Microbiome organized by **IrsiCaixa**. We can also underline our commitment to implementing an increasingly open science, reflected in the growth of **IrsiCaixa**´s Living Lab for Health and its ongoing participation in new European and national initiatives to promote responsible, participatory and open innovation and research in society.

All these achievements have led to a considerable increase in the number of researchers working in **IrsiCaixa**. In **2018**, we were honoured with the European Commission's HR Excellence in Research award, which reflects **IrsiCaixa**'s commitment to ongoing improvement of its human resource policies.

All these developments are crucially important for us to be able to implement a research agenda as ambitious, complex and successful as ours. We are deeply grateful for the annual funding received from Fundació Bancària "la Caixa" and the Autonomous Government of Catalonia, as well as past contributions from bodies such as the Glòria Soler Foundation and the Esteve Foundation. In the near future **it will be necessary to expand our premises** to encompass the breadth of our research and the size of our workforce and so maintain our competitiveness worldwide.

Bonaventura Clotet
IrsiCaixa Director

Organizational Structure



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Dr. Bonaventura Clotet

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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 2018

Total **staff**

94

Sex

66% ♀

34% ♂

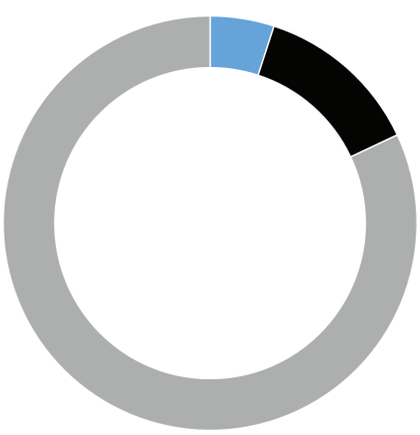
Researcher funding

16 public

16 private

7 other institutions (ICREA, IGTP)

Staff by **categories**



Scientific and technical **5%**

Administration and research support **13%**

Research **82%**

Theses read 2018

2

Muntsa Rocafort
Microbial Genomics

Javier Rivera
Microbial Genomics

Projects awarded 2018

26

10 public

16 private

Projects active 2018

56

27 public

29 private

Publications 2018

95

Highlights 2018

January

Living Lab for Health participates in the European Parliament ceremony to conclude the European ENRRICH project.

February

The Cell Virology and Immunology (VIC) group licenses patent EP1638234.4 (VLPs) to HIPRA (animal health company) for development. A proof of concept trial for the development of a feline retrovirus FeLV vaccine is launched.

Living Lab for Health launches four participatory and transdisciplinary research projects aimed at improving HIV prevention.

April

Grifols and **IrsiCaixa** sign a collaboration agreement to promote biomedical research into HIV and related diseases, whereby Grifols will fund **IrsiCaixa** research to the tune of 1.5 million euros annually over five years.

The collaboration agreement with Grifols and funding from the US NIH will enable the Host Genetics and Cellular Immunity group to expand its research into the neurological consequences of HIV infection.

June

Beatriz Mothe receives (*ex aequo*) the Young Investigator Award of the Catalan Institute of Health (ICS).

IrsiCaixa organizes the fourth edition, in CosmoCaixa, of The Barcelona Debates on the Human Microbiome. From Microbes to Medicines, in which international experts debate the crucial health role of the gut microbiome.

The first PhD Day at the Can Ruti Campus is held, with **IrsiCaixa** doctoral students **Bruna Oriol** and **Ana Jordán** participating in the organizing committee.

José A. Esté is Chair of the 31st International Conference on Antiviral Research, held in Porto (Portugal).

Ester Ballana receives an award from the International Society for Antiviral Research for her work in the antivirals field.

Living Lab for Health celebrates the 2nd Co-ResponsaVIHlitat Conference in CosmoCaixa with some 400 participants.

August

IrsiCaixa receives the European Commission's HR Excellence in Research award.

September

Receiving a score of 9.4 out of 10, **IrsiCaixa** is awarded funding to support its activities as a Consolidated Research Group (SGR 2017-2019) by the Catalan grants agency (AGAUR).

Living Lab for Health creates the Fit4FOOD 2030 Catalonia network and launches the first series of participatory workshops aimed at building an R&D agenda for healthy and sustainable nutrition in Catalonia.

The Lancet HIV publishes a study by the Microbial Genomics group that indicates that antiretroviral treatment needs only be changed if more than 5% of the viral variants infecting an individual are resistant to drugs.

Together with Aelix Therapeutics and the Fight AIDS Foundation, the Host Genetics and Cellular Immunity group receives a new Spanish government Retos Colaboración grant to fund in-depth analysis of potential HIV post-vaccination control biomarkers.

October

Living Lab for Health co-organizes, with local institutions and international experts, a B·Debate on Open Science that culminates in the publication of recommendations regarding more open and inclusive research.

The Retrovirology and Clinical Studies (GREC) group publishes an article in *Annals of Internal Medicine* on stem cell transplantation factors that could lead to HIV eradication from the body.

A patent is filed for new Siglec-1-blocking monoclonal antibodies providing cross-resistance against Ebola and HIV-1, also the subject of a presentation at the international Keystone Symposia Conference on Framing the Response to Emerging Virus Infections, held in Hong Kong.

AlbaJuna Therapeutics reaches its pre-phase I study milestone and marks 2020 as the next milestone for its ongoing synthetic antibody development project.

For a Spanish cohort of persons co-infected with HIV and HCV undergoing liver transplantation, the Host Genetics and Cellular Immunity group identifies new markers that predict the transplant outcome.

RESEARCH GROUPS

Viral Immune Evasion and Vaccines (VIRIEVAC)

Projects awarded 2018

Glycoengineering nanovehicles to eliminate viral reservoirs (SAF2017-91767-EXP)
January 2019- January 2021
Funding: Ministry of the Economy and Business
Research supervisor(s): **Nuria Izquierdo-Useros**
Other participating bodies: ICN2, UPV-CSIC
Other linked IrsiCaixa groups: GREC, VIRIEVAC

Grants

Connecting innate and adaptive immunity via TRIM5 proteins for cellular resistance to HIV
January 2018- January 2020
Funding: Beatriu de Pinós post-doctoral grant (AGAUR) to Marta Colomer Lluch
Research supervisor(s): **Julia García Prado**

Translational study of inhibitory receptors in HIV-1 infection: identification of new immunotherapeutic targets to reverse immune exhaustion
April 2018- March 2021
Funding: FI predoctoral grant (AGAUR) to Oscar Blanch Lombarte
Research supervisor(s): **Julia García Prado**

Awards and achievements

Julia García Prado, evaluation Panel for Ramón y Cajal Contracts 2018
Julia García Prado, reviewer of AES 2018 ISCIII projects
Julia García Prado, editor for *Frontiers in Immunology* of the topic Immune Surveillance of the HIV Reservoir: Mechanisms, Therapeutic Targeting and New Avenues for HIV Cure

Master's theses

Development of an ex vivo model for evaluation of the response to shock-and-kill treatment strategies in HIV-infected individuals
Author: **Carlos Ávila**
Tutor(s): **Alba Ruiz de Andrés, Julia García Prado**
Inter-University Master in Advanced Immunology (UB-UAB)
Date: September 2018
Grade: Excellent

Presentation

The VIRIEVAC group is currently working on three lines of research with the 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 understanding CD4 T-cell maintenance in individuals with high viral loads (viremic non-progressors). The dissociation between the presence of the virus and the absence of CD4 T-cell depletion emulates the non-pathogenic infection that occurs in some non-human primates.

The second line, in the area of new treatments and resistances, focuses on identifying new resistance mechanisms in antiretrovirals, such as the boosted protease inhibitors (PIs) Lopinavir and Darunavir, with a high genetic barrier to resistance.

Finally, within the area of HIV-1 eradication and functional cure, the group is working on new immune and cellular therapeutic strategies to control and cure HIV-1. The focus of the research is to identify the functional limitations of the HIV-1-specific CD8+ T-cell response in recognizing the viral reservoir and its immune surveillance mechanism against reactivated cells. We are also evaluating the role of TRIM5 in controlling the reservoir. Thus, .

All our studies address the interconnection between molecular virology, cell biology and immunology, seeking to improve the health of individuals infected with HIV-1 by developing new antiviral and immune therapies.

2018 Milestones

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

Immunopathogenesis. Studies of virological and host factors associated with natural control of the infection in non-progressor viremics (NPVs). In collaboration with the Spanish AIDS Research Network (RIS) and Oxford University, this project was presented as an oral poster at the national GESIDA conference in November 2018 in Madrid.

New treatments and resistance to antiretrovirals. Data identifying resistance to boosted PIs with a high genetic barrier in the absence of mutations in the protease gave rise to a poster presentation at the Conference on Retroviruses and Opportunistic Infections (CROI) in Boston (USA) in February 2018. Our data point to the Gag protein being directly involved in this new mechanism of resistance to PIs.

Prevention, eradication and functional cure. This year has seen work on two funded projects (PI17/00164 and MDS LKR 155762) and a patent has been filed based on the development of new shock-and-kill strategies mediated by CD8+ T-cells. We have worked on identifying the functional characteristics of specific CD8+ T-cells for HIV that define a good shock response to eliminating the reservoir. Our studies indicate that there is a correlation between the expression of inhibitory receptors and the magnitude of the kill response to reactivated cells. We are currently characterizing the immunophenotype of HIV-1-specific CD8+ T-cell responses and evaluating the potential of inhibitory receptor blockade (PD1, LAG3, TIM3, TIGIT and CD39) to reboost antiviral immunity. We have also evaluated the role of TRIM5 in controlling the viral reservoir in order to design new drugs and develop TRIM5-based gene therapy strategies.

These studies, materialized in four posters and four oral presentations by our research team at international conferences such as IAS 2018 (Amsterdam, Holland) and national conferences such as RIS (Madrid) and GESIDA (Madrid). The communication of our findings to the scientific community has enhanced collaboration with national and international research teams and 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 continue with existing lines of research and advance in the identification of natural infection control mechanisms, 2) to advance in the search for more powerful drugs with higher genetic barriers and so advance in developing personalized therapies, 3) to identify markers to predict the immune response to reactivation of the reservoir, 4) to characterize the role of receptor inhibitors in the functionality of the antiviral response, 5) to identify potential functional blocking pathways in order to improve the CD8 antiviral response function, and 6) to develop a proof of concept for use of TRIM5 as a target in gene therapy.
— Expansion of funding at the European level.

Principal Investigator
Julia García Prado

Post-doc researcher(s)
Marta Colomer Lluch
Alba Ruiz de Andrés

Pre-doc researcher(s)
Óscar Blanch Lombarte
Miguel Ángel Marín López

Laboratory technician(s)
Esther Jiménez Moyano
Ruth Peña Poderós

2 Competitive contracts for research staff in 2018

9 National and international conference communications led by the group in 2018

Grifols Projects

TRIM5 based gene-therapy approaches for inducible cellular resistance to HIV (CELLRE)

Senior researcher: Julia García Prado

The CELLRE-VI project aims to explore innate cell sensors, in particular TRIM5 proteins, with a view to developing new approaches based on gene therapy to inducible cellular HIV-1 resistance.
Our project is based on the innovative concept that a single protein has the autonomous potential to connect innate and adaptive immune functions and induce cellular resistance to HIV-1.

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

Senior researcher: Julia García Prado

The RECOViR project aims to generate new ideas regarding the immune regulation of chronic infections by inhibitory receptors, establishing the bases and proof of concept for new immune therapeutic strategies for HIV-1. It will also identify new tools for personalized treatment and possible treatment response biomarkers. Applications will not only be to treating chronic infectious diseases (HIV, HBV, TB and malaria) but also cancer.

Microbial Genomics

Projects awarded 2018

PERSIMUNE: Microbiome Research Collaboration
2018 - 2019
Funding: The PERSIMUNE Centre of Excellence, CHIP (supported by the Danish National Research Foundation)
Research supervisor(s): **Roger Paredes**
Other participating bodies: AELIX Therapeutics, Fight AIDS Foundation

Prizes and awards

Roger Paredes has been appointed:
— Associate Editor of *HIV Medicine*
— Coordinator of Working Group 3 (Research & Innovation) of the WHO ResNet Steering Committee

Doctoral theses

Title: *The gut microbiome in HIV Infection*
Author: **Muntsa Rocafort**
Tutor(s): **Roger Paredes**, **Marc Noguera**
Department of Microbiology, Autonomous University of Barcelona (UAB)
Date: 29 de Novembre del 2018
Grade: Cum laude

Title: *Statistical methods for the analysis of microbiome compositional data in HIV studies*
Author: **Javier Rivera**
Tutor(s): **Marc Noguera, Maria Luz Calle**
Chair of AIDS and Related Diseases, University of Vic-Central University of Catalonia (UVic-UCC)
Date: 30 November 2018
Grade: Cum laude

Presentation

Our goal is to advance in the development of more effective and personalized treatments for microbial-based human diseases through a better understanding of the biological determinants of health and disease. Our main areas of research are as follows:

1. Investigating the role of the gut microbiome in human health and disease.

Via sequencing we study the role played by the human gut microbiota in different states of health:
— We analyse the influence of the gut microbiome in the ability of HIV-1 infected individuals to achieve adequate immune reconstitution, control HIV-1 replication and limit the chronic inflammation associated with the infection.
— We characterize co-evolution of the gut microbiome and the immune system following acute HIV-1 infection.
— We study how the human microbiome may affect response to the AIDS vaccine and how vaccines and other strategies for eliminating HIV-1 affect the microbiome.

2. Developing and evaluating interventions as follows:
— Improving response to the HIV/AIDS vaccine.
— Mitigating chronic complications of HIV/AIDS infection.

3. Improving genotypic viral diagnostic tools to maximize antiretroviral efficacy.

As a pioneer in next-generation sequencing of HIV-1 in Europe, we lead a number of studies to evaluate the clinical value of ultrasensitive tests of HIV-1 resistance and tropism in response to antiretroviral treatment.

4. Defining HIV-1 global clinical epidemiology.

We work with leading European clinical cohorts (ESAR and EuroSIDA) toinvestigate virus effects in terms of response to treatment, clinical progression to AIDS and death.

2018 milestones and perspectives for the future

During 2018, our group continued to advance knowledge regarding causes and clinical and health implications of resistance to antiretroviral treatments. We also progressed in the study of the microbiome and HIV infection pathogenesis.

1. Resistance to antiretrovirals

— Translational research: In an article piblished in *The Lancet HIV* we reported the results of a multicentre study in several African countries that identifies sensitivity cutoff points for the most suitable ultrasensitive resistance tests to decide which patients need treatments other than those currently available in low-income countries.
— Bioinformatics: We have continued developing PASeq.org as an open web server for automatic high-quality analysis of HIV sequences obtained by new mass sequencing methods, suitable for users without knowledge of bioinformatics. This is a fundamental step in advancing the fight against resistant HIV worldwide. During 2018, PASeq had 160 users in some 25 different countries and has made some 10,000 resistance analyses worldwide.
During 2018 we met with the developers of another two analytical pipelines equivalent to PASeq and agreed guidelines that will govern the development of these and other new applications to analyse HIV resistance worldwide. This will allow data from the different pipelines to be shared, improving the epidemiology of resistant HIV on a global scale.
— Public health and policy:
a) As members of the WHO HIV Resilience Steering Group, we have been appointed, together with Dr. Jonathan Shapiro (Tel Aviv) and Dr. Anne-Geneviève Marcelin (Sorbonne, Paris), to coordinate

the Working Group on Research and Development. This group of international experts will monitor new research worldwide to mitigate the emergence of resistant HIV and will report to WHO.
b) We have developed widely used guidelines for the study and treatment of resistant HIV for the International AIDS Society (USA).

2. Microbiome

— Our group has become a world reference for the microbiome and HIV. Our findings suggesting a strong association between microbiome composition and risk factors for HIV acquisition have been confirmed by several international cohorts.
— In an article published in *Mucosal Immunology* we showed that intestinal dysbiosis occurs mainly in people with a very impaired immune system following HIV-1 infection.
— In an article published in *MSystems*, we described a new microbiome analysis algorithm based on compositional theory.

16 Projects underway with external funding

19 Publications during 2018

14 Invited talks during 2018

— With support from the Glòria Soler Foundation, we are working on developing new diagnostic markers of chronic inflammation and intestinal dysbiosis in HIV-infected persons as well as new probiotic candidates. We are investigating interactions between the microbiome and kick-and-kill strategies to eradicate HIV and the impact of antiretroviral therapy on the microbiome. We have also begun work on animal models of HIV infection in collaboration with US centres.
— Using mass sequencing tools, we have identified four new microbial agents associated with tropical ulcer in patients in Papua New Guinea.

Principal investigator

Roger Paredes

Associate researcher(s)
Marc Noguera
Post-doc researcher(s)
Alessandra Borgognone

Maria Casadellà
Aleix Elizalde
Yolanda Guillen (to oct 2018)
Pre-doc researcher(s)
Javier Rivera (to des 2018)
Muntsa Rocafort (to des 2018)
Programmer(s)
Carmen Fuentes
Laboratory technician(s)
Mariona Parera

Grifols Projects

Microbiome Triggers of Alheimer Dementia (MIND)

Senior researcher: Roger Paredes

— Characterization of the composition and functional potential of the faecal microbiome in subjects as follows: a) with cognitive problems but not cognitively impaired, b) wilth mild cognitive disability, and c) 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 metatranscriptomic 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 2018

Retos Colaboración: Nuvatera project
January 2018- December 2021
Funding: Ministry of the Economy, Industry and Competitiveness
Research supervisor(s): **Jordi Naval**
Other participating bodies: Aelix Therapeutics, Fight AIDS Foundation

Towards a universal therapeutic vaccine against chronic virus infections
January 2019- December 2021
Funding: Fundació "la Caixa"
Research supervisor(s): **Christian Brander, Sandra Silva**
Other participating bodies: Pompeu Fabra University (UPF)

Prizes and Achievements

Beatriz Mothe, Catalan Health Institute (ICS) Young Investigator Award (*ex aequo*)

Master's theses

Title:*Immunogenicity of the HIV T-Cell immunogen HTI vectored by RNA in mice*
Author: **Luis Romero Martín**
Tutor(s): **Christian Brander**
Inter-University Master in Advanced Immunology (UB-UAB)
Date: 16 July 2018
Grade: Excellent

Presentation

Our research focus is the study of cellular immunity against viral infections in hosts with compromised immunity. Studies cover HIV-infected individuals and HIV-infected and non-HIV-infected individuals who have received an organ transplant. As well as identifying immunological correlates for HIV control, we endeavour to identify markers associated with HIV-related neurofunctional defects. These studies are further complemented by analyses of individuals highly exposed to HIV and recently infected by HIV who have remained uninfected that attempt to decipher key information that could contribute to the development of preventive vaccines. Also included are detailed analysis of the T-cell receptor repertoire of specific T-cell responses to HIV to determine the molecular ontogeny of these responses and progress towards vaccine development. Finally, we also study possible factors governing the evolution of HVC in liver transplant patientes and immune determinants of organ rejection in HIV-infected patients who have received a kidney transplant from a donor who is also HIV-infected.

2018 Milestones and perspectives for the future

We have continued to advance in the HIVACAT study of the HTI T-cell immunogen, now entering the clinical trial phase with different vectors and combinations of vectors, including RNA, DNA and MVA. The fact that we have started producing HTI expressed in a chimpanzee adenovirus vector means that AELIX Theraeutics, a HIVACAT spin-off created in 2016, can commence clinical trials in 2019 aimed at comparing different administration regimens in terms of response stimulation and amplification. We have demonstrated the immunogenicity of the various vaccine vectors in different mouse strains and in regimens designed to maximize the longevity of vaccine-induced HTI-specific T-cells.

In 2018, we completed 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. Preliminary data show that the vaccination outcome is influenced by the condition of the microbiota before vaccine administration and that the vaccine subsequently influences the composition of the microbiota. These findings, supported by observations based on complete transcriptomic blood analyses, provide important indications on how to optimize vaccination outcomes.

Studies in collaboration with the National Genome Analysis Centre (CNAG) have focused on samples from the BCN-02 clinical trial and include methylome and transcriptome analyses at different stages of the vaccination regimen. The results show different gene expression profiles before and after vaccination and after treatment with romidepsin and are also related to the level of viral control once participants interrupt antiretroviral treatment. Immune correlation analysis in this clinical trial also suggests that the specificity of the T-cell response induced by the vaccine greatly contributes to viral evolution and viral control after vaccination. Data, to be fully compiled in 2019, will yield a detailed description of the viral and immunological factors controlling the virus after therapeutic vaccination and treatment interruption.

Progress has also been made in identifying plasma soluble factors associated with virus control, especially those factors whose expression is epigenetically regulated as a result of HIV infection. Among the most prominent factors, molecules involved in cell proliferation and survival provide a model that could explain the strong immune response to HIV in the early infection stages and the possible failure of this responses in subsequently controlling viral replication. It is important to note that these studies have also

identified new markers of the pathological consequences of the infection, including effects on the neuro-function. Currently, marker levels are determined in blood and cerebrospinal fluid and related to the neurocognitive function.

Research into liver transplant patients has enhanced understanding of the impact of host and donor genetic factors on survival and organ rejection. More specifically, we have identified genetic markers in the HLA class I and IL28 genes in patients and donor organs, as well as soluble cytokine levels in peripheral blood before transplantation that may determine organ rejection and fibrosis after liver transplantation.

The group has successfully competed in highly competitive funding calls for the 2019-2021 period from the Fundació "la Caixa" Health Programme and the Spanish Ministry of the Economy, Industry and Competitivieness Retos-Colaboración programme.

2 Projects underway within the H2020 program, with total funding within the consortium of some 30M€

5 Involvement in the design, execution and analysis of five clinical trials to test specific T-cell vaccines against HIV

+20 Invitations to talks and presentations to members of the group in the last year

Principal investigator

Christian Brander

Associate researcher(s)
Beatriz Mothe
Post-doc researcher(s)
Samandhy Cedeño
Anuska Llano

Alex Olvera
Marta Ruiz Riol
Sandra Silva Arrieta
Pre-doc researcher(s)
Miriam Rosàs
Bruna Oriol
Luis Romero Martín
Clara Duran
Clinical cohort coordinator/clinical researcher
Josep Coll

Grifols Project

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

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

The objectives of Neuro-HIV are to carry out complete analyses of blood and cerebrospinal fluid markers associated with HIV-associated neurocognitive disorder (HAND) and identify the characteristics and differences between HAND, normal healthy ageing and different forms of dementia, including familial Alzheimer disease (FAD) and late onset Alzheimer disease (LOAD).

Different integrated omics analyses (including methylome, communicom and transcriptome) applied to samples from these unique cohorts, together with detailed characterization of virological parameters and immunological markers and in vitro and in vivo studies, will be used to identify mechanisms of HIV-induced dementia. If successful, the resulting information may have a significant translational impact on the clinical management of ageing in people with or without HIV infection, opening a door to the development of new therapeutic interventions in this area.

HIV Pathogenesis

Awarded projects 2018

Identification of novel therapeutic strategies to block virus persistence (Ref: MSCA_Inphinit Programmme)
September 2018- August 2021
Funding: European Comission (H2020)
Research supervisor(s): **José A. Esté**, **Ifeanyi Ezeonwumelu**

Scholarships and grants

Lucia Gutiérrez. Novell Research Personnel Program (FI-2019), 2019 FI_B 00420
01.04.2019 – 31.03.2022
Catalan Autonomous Government (AGAUR)

Prizes and achievements

José A. Esté, Microbiology and Immunology Expert Panel, Belgium Research Foundation Flanders (FWO), 2018- 2021
José A. Esté, Chair and member of the Scientific Programme and Organizing Committee of the 31st International Congress on Antiviral Research (Porto, Portugal, 2018)
Ester Ballana, William Prusoff Young Investigator Award 2018

Filed patents

Title: *Aurora kinase inhibitors for treating or preventing HIV infection or AIDS*
Inventor(s): **Garcia-Vidal E**, **Badia R**, **Riveira-Muñoz E**, **Este JA**
Date: 9 September 2018
Application number: USPTO 62728824
Applicant(s): IrsiCaixa, IGTP

Presentation

The HIV Pathogenesis laboratory focuses on four main lines of research:

1. Identification of new cellular cofactors in viral infections

Our work over the past few years has focused on the study of cell targets as an antiviral intervention strategy and on validation of these targets in cohorts of HIV-positive patients. This work has allowed us to build a portfolio of cellular factors at different stages of development, ranging from identification and validation of new targets and the monitoring of drugs approved for treatment to technology transfers through reports to pharmaceutical companies or patent registration

2. Identification of new targets for HIV treatment

Antiretroviral therapy is effective in reducing circulating viral load at undetectable levels but does not cure HIV infection. A shock-and-kill strategy, which induces HIV reactivation in a controlled way and causes the death of infection reservoir cells, is one approach being studied with agents such as histone deacetylase (HDAC) inhibitors in clinical trials. However, current knowledge of the mechanisms that govern HIV persistence is insufficient and strategies to purge the viral reservoir have failed.
Our goal is to validate the development of new target cells as HIV-1 latency and reactivation factors and to identify new molecules as inducers of HIV reactivation, explore their mechanisms of action and validate their possible use as strategies to cure HIV, alone or in combination with current treatments.

3. New antiviral development

We continue to screen and characterize the antiviral activity of new compounds, placing special emphasis on the development of active compounds against viral strains resistant to other drugs and on the validation of new therapeutic targets based on cell viral infection cofactors.

4. Coinfection as a model for studying the virus-host relationship

The role of mucosal immunology and host genetic factors in susceptibility to the human papillomavirus (HPV) is poorly understood. Pre-existing HPV infection may act as a cofactor for HIV-1 transmission and infection through cellular and molecular mechanisms that generate an environment conducive to coinfection. Our group proposes to study the expression of HIV infection cofactors modulated by early infection events or HPV reactivation in infected cell models and in patients coinfected to varying degrees. Our project results will lay the foundations for new treatment strategies, prophylaxis and the prevention of sexually transmitted viral infections.

2018 Milestones

We plan to continue work underway and to improve both the quantity and quality of our publications. Significant efforts have been invested in applying for and obtaining competitive funding to improve the quantity and quality of our scientific output and to acquire more staff. A new Spanish Health Research Fund (FIS) project to continue with the development of SAMHD1 as a possible therapeutic marker was started in 2018. The group now receives external funding from five projects. All our researchers are funded or are principal investigators of projects.

Dr. Esté continues to be an expert advisor to the Research Executive Agency of the European Commission and has been appointed as a member of the Microbiology and Immunology Panel of the Research Foundation Flanders (Belgium).

Perspectives for 2019

Basic research will continue to be a cornerstone in generating the necessary knowledge to discover new and effective strategies to cure HIV, AIDS and other infectious diseases. Our goal is to continue our research into HIV cellular cofactors and restriction factors so as to establish mechanisms of action and determine their possible role in the formation of viral reservoirs in patients. Preliminary results will enable possible therapeutic targets to be identified that will limit or reduce the viral reservoir and induce immunity to HIV and maybe even assist in eradication of HIV. Based on these preliminary results, the group is confident that it will be able to contribute important findings in terms of both understanding HIV/AIDS immunopathogenesis and identifying new treatment and immune reconstitution options.

Principal investigator

José A. Esté

Associate researcher(s)
Ester Ballana

Post-doc researcher(s)
Roger Badia
Eva Riveira-Muñoz

Pre-doc researcher(s)
Marc Castellví
Edurne García
Maria Pujantell
Lucía Gutiérrez
Ifeanyi Ezeonwumelu

Grifols Project

New Cell Targets for HIV cure (NeCeTar)

Senior researcher: José A. Esté

Antiretroviral therapy is effective in reducing circulating viral load at undetectable levels but does not cure HIV infection. A shock-and-kill strategy, which induces HIV reactivation in a controlled way and causes the death of infection reservoir cells, is one approach being studied in clinical trials of agents such as histone deacetylase (HDAC) inhibitors. However, current knowledge of the mechanisms that govern HIV persistence is insufficient and strategies to purge the viral reservoir have failed.

Our goal is to validate the development of new target cells as HIV-1 latency and reactivation factors and to identify new molecules that induce HIV reactivation, explore their mechanisms of action and validate their possible use in strategies to cure HIV, whether alone or in combination with current treatments.

Retrovirology and Clinical Studies (GREC)

Projects awarded 2018

Allogeneic stem-cell transplantation in HIV-1 infected individuals and first immunotherapy + analytical treatment interruption (IATI) strategy
01.07.18 - 30.06.20. Funding: Foundation for AIDS research amfAR (ARCHE program) Ref 109858-64-RSRL
Research supervisor(s): **J. Martínez-Picado**

Immunological checkpoint inhibitor treatment of HIV-infected subjects with cancer
01.07.18 - 30.06.23. Funding: Merck, Sharp & Dohme Spain, S.A Ref IISP 57699
Research supervisor(s): **J. Martínez-Picado**

Characterization of single molecule dynamics within HIV-1 reservoirs as a target for interference with virus persistence and immune evasion. Ref MSCA_793830-HIV VCC Interference
01.01.19 - 31.12.20. Funding: European Commission (H2020)
Research supervisor(s): **J. Martínez-Picado, Jakub Chojnacki**

Glycoengineering nanovehicles to eliminate viral reservoirs. Ref SAF2017-91767-EXP
01.11.18 - 31.10.20. Funding: Spanish Ministry of Science, Innovation and Universities
Research supervisor(s): **Nuria Izquierdo-Useros**

Scholarships and Grants

Jakub Chojnacki. PERIS - Instrumental action for the incorporation of scientists and technologists. Ref SLT006/17/214. 01.03.18 - 31.12.18. Catalan Autonomous Government

Ángel Bayón. Predoctoral contracts for the training of university teaching staff (FPU17/04766). 29.10.18 - 28.10.22. Spanish Ministry of Science, Innovation and Universities

Patricia Resa Infante. Beatriu de Pinós Programme (BP) Ref 2017 BP 00121. 01.01.2019 – 31.12.2020. Catalan Autonomous Government-AGAUR

Awards and achievements

Javier Martínez-Picado:

— Member of the MHRP RV254/RV217 Virology/Reservoir Working Group for studies in acute HIV infection in Thailand and Africa
— Ad hoc member of the Evaluation Panel for Professional Promotion of the University of Sydney (Australia)
— Member of the Scientific Committee of the 22nd International AIDS Conference in Amsterdam (Netherlands)
— Member of the Scientific Programme and Organizing Committee of the 10th Workshop of the conference Hot Topics in HIV: Vaccines, Immune Recovery and Eradication (Barcelona)
— Member of the Scientific Programme and Organizing Committee of the 10th National GESIDA Congress (Madrid)

Master's Theses

Title: *Dynamics of the viral reservoir in patients receiving early treatment after HIV infection*
Author: **Ángel Bayón**
Tutor(s): **Mª Carmen Puertas, Javier Martínez-Picado**
Master's Degree in Advanced Microbiology (UB)
Date: 20 July 2018
Grade: Excellent

Presentation

Our group focuses on translational studies of HIV-1 infection and on investigating potential new HIV/AIDS therapeutic strategies through both basic and applied research. The group works closely with HIV outpatients unit at the Germans Trias i Pujol University Hospital, attending some 3,000 individuals with the infection. Its research programme focuses on three priority areas:
1) HIV cure
2) Pathogenesis of HIV mediated by dendritic cells
3) Extreme HIV infection phenotypes.

2018 Milestones

1. HIV-1 cure

— Follow-up of an international cohort of HIV-positive patients who have received allogeneic stem-cell transplants as treatment for severe haematologic disease (IciStem). Around 30 people with this type of transplant have been recruited in Europe and Canada (this is the only therapeutic intervention available to date that is capable of significantly reducing the viral reservoir)
— Study of the effects at the tumoral and viral levels of new immunotherapies with blocking monoclonal antibodies (α-PD-1 and α-PD-L1) in HIV-positive patients with oncological disease
— Evaluation of the viral reservoir in intrauterinally infected children with subtype C virus
— Evaluation of drugs with new antiviral action mechanisms for their ability to reduce the viral reservoir
— Evaluation of the impact of therapeutic vaccines, with and without viral latency reactivators, on the size of the viral reservoir
— Development of a new gene therapy for elimination of the CCR5 viral receptor through TALENs
— Development of a new nanoparticle technology targeting myeloid cells aimed at inducing viral reactivation and promoting a cytotoxic response
— Characterization of patients in antiretroviral treatment with extremely low viral reservoirs
— Characterization of viral reservoirs in different cell subtypes

2. Role of myeloid cells in viral pathogenesis

— Translation of knowledge acquired regarding the Siglec-1 receptor to other infectious pathologies, including Ebola and tuberculosis
— Characterization of primary cervical myeloid cells that interact with HIV-1 via Siglec-1
— Generation of blocking monoclonal antibodies to inhibit the Siglec-1 receptor
— 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 of patients who have spontaneously controlled viral replication for more than ten years without antiretroviral treatment
— Study in adults and children of the factors involved in the non-progressive viremic phenotype, which emulates the natural host with SIV infection (sooty mangabey monkeys), presenting high viremia but no pathogenesis .
— Study of inversions in three IFITIM genes and the potential association with disease progression and infection resistance
— Study of methylation of the complete genome in association with HIV infection and disease progression

Perspectives for the future

Our programmes will lead to the development of new strategies for treatment and cure of HIV/AIDS.
Regarding all its projects, the group aims to do the following:
1) to 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) to study clinical interventions aimed at reducing viral reservoirs and controlling viral persistence,
3) to generate new therapeutic agents to block HIV-1 and Ebola cell-cell transmission via myeloids, specifically by interrupting virus-Siglec-1 interaction,
4) to 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) to continue exploring the role of virus-host interactions in extreme HIV-1 infection phenotypes.

12 PROJECTS UNDERWAY WITH EXTERNAL FUNDING

7 FUNDED STAFF CONTRACTS

2 TRAVEL GRANTS FOR RESEARCH STAYS

11 ORIGINAL ARTICLES IN INTERNATIONAL JOURNALS

15 PRESENTATIONS AT CONFERENCES AND INVITED TALKS

6) to explore therapeutic applications of factors underlying the non-progressor viremic phenotype, whose profile is similar to that of the natural host in having an immune system that is not affected by high levels of viremia, and
7) to understand cellular mechanisms of protection against HIV-1 infection in individuals who remain uninfected despite exposure to the virus.

Principal investigator

Javier Martínez-Picado

Associate researcher(s)
Nuria Izquierdo-Useros
Post-doc researcher(s)
Jakub Chojnacki
Mª Carmen Puertas
Patricia Resa-Infante
María Salgado

Pre-doc researcher(s)
Ángel Bayón
Susana Benet
Silvia Bernal
Cristina Gálvez
Xavier Muñiz
Daniel Pérez-Zsolt
Laboratory technician(s)
Itziar Erkizia
Cohorts and project management
Judith Dalmau
Biostatistician(s)
Víctor Urrea

Grifols Projects

Cutting edge strategies on HIV cure (VIROCURE)

Senior researcher: J. Martínez-Picado
Principal investigator(s): María Salgado and Maria Carmen Puertas

This project has the following aims:
— To develop and evaluate new improved-sensitivity technologies (VIP-SPOT, mVOA, etc) to detect and quantify viral persistence in blood and tissue samples.
— To design and evaluate medical strategies aimed at achieving HIV remission without ART, testing treatments that combine new immunomodulating antiviral compounds in unique cohorts of individuals with extremely low viral reservoirs.

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

Senior researcher: J. Martínez-Picado
Principal investigator(s): Nuria Izquierdo-Useros

— To generate a human version of the best murine monoclonal antibody (mAb) against Siglec-1, capable of blocking HIV and Ebola capture and infection.
— To develop nanovehicles that allow the construction of nanoparticles for therapeutic purposes.
— To develop a detection platform based on the Siglec-1 receptor to diagnose the presence of different enveloped viruses and to isolate exosomes in liquid biopsies from patients with cancer.

HIV and HCV Genetic and Phenotypic Variability

Awards and achievements

Miguel Ángel Martínez, Review Editor in Virology for *Frontiers in Plant Science*

Master's theses

Altering EGFP expression by modifying the number of CpG dinucleotides and the repercussions for HIV-1 replication
Author: **Dominique Pope**
Tutor(s): **Miguel Ángel Martínez**
Master in Immunology, Autonomous University of Barcelona (UAB)
Date: July 2018
Grade: Excellent

Graduate projects

Construction of a transgenic plasmid with the HIV-1 genome replacing nef for EGFP
Author: **María Lara**
Tutor(s): **Miguel Ángel Martínez**
Degree in Biomedical Sciences, University of Barcelona (UB)
Grade: Excellent

Presentation

Our group is developing a strategy based on a new technology called synthetic attenuated virus engineering (SAVE), which recodes and synthesizes parts of the viral genome while maintaining the amino-acid sequence present in the wild virus and altering virulence and phenotype (Martinez et al., *Trends in Microbiology* 2016).

2018 milestones and perspectives for the future

Our group is currently studying the stability of synonymously recoded viruses and the possibility of obtaining a new recoded virus by deoptimizing other viral genes. Recoding has been done by introducing different codon pairs in the gag (1502 nucleotides), pol (3011 nucleotides) and env (2069 nucleotides) regions of HIV-1 (pNL4-3). Only synonymous substitutions have been introduced. The recoded segments have the same amino-acid sequence as the wild-type virus, but have different arrangements of pairs of synonymous codons. That these viruses have an attenuated phenotype depends, on the one hand, on the presence of mutations in certain gag, pol or env regions that do not allow synonymous nucleotide changes — whether because they affect the secondary RNA structure or because of their effect on the transcription or translation of the corresponding messenger — and, on the other hand, on base pair content (e.g., the presence of CpG and/or TPA).

An unexplored aspect of HIV-1 genetic architecture is how choice of synonymous codons influences the diversity and evolutionary capacity of the virus. To be clarified is whether HIV genome sequences are optimized not only in the amino-acid sequences but also in the viral RNA and proviral DNA sequences. We have explored whether viruses recoded in the pol region — with 13% of synonymous mutations that alter codon pair usage but not viral replicative capacity — are capable of developing genotypic and phenotypic resistance to viral protease inhibitors in a similar way to wild-type viruses. Our results show that viruses recoded in the pol region show a pattern of resistance to protease inhibitors that is different from that of the wild-type virus (Nevot et al., 2018, *Journal of Virology*).

We have also explored the impact of synonymous codons on the ability to express the Env viral protein and to replicate the virus. The six env-HIV-1 gene codons AGG, GAG, CCT, ACT, CTC and GGG were synonymously changed to CGT, GAA, CCG, ACG, TTA and GGA, respectively, generating a new Env protein. Our results show that the ability to replicate HIV-1 is affected by codon use and also indicate that mutations in the Env 3' region can induce lethality. Ex vivo expression experiments have shown that Env protein translation is affected. Our results underline the importance of synonymous substitutions in the configuration of the viral phenotype. (Jordan-Paiz et al., CROI 2018, in press). In the future we plan to further deepen our knowledge of the SAVE technology. We also plan to study the possible effect of bias in the codon use in HIV transcription, translation and evolutionary capacity, as well as the stability of recoded viral variants. These variants will also be used to identify functionally redundant RNA elements in the coded sequences for HIV-1. Because synonymous recoding is directed to a basic function like transcription or translation,our hypothesis is that bias in the use of codons, codon pairs or dinucleotide composition potentially has a general application in terms of altering the phenotypes of other viruses or organisms.

In relation to our work with HCV, we have started a new line of research whose objective is the identification of circulating microRNAs (miRNAs) as biomarkers of liver disease in HIV-1-infected patients. Inflammation resulting from HIV infection can contribute to the development of liver disease. Liver damage is also exacerbated by chronic HCV, alcohol abuse, non-alcoholic hepatic steatosis and

hepatotoxicity induced by antiretroviral therapy. Liver cirrhosis and hepatocellular carcinoma are important complications in patients infected with HIV. Results obtained by our group have allowed us to identify, in the plasma of patients infected with HIV-1, a repertoire of 1425 miRNAs, of whom 193 had altered expression levels depending on the presence of HCV coinfection, high transaminases, focal nodular hyperplasia and/or liver fibrosis (Franco et al., *Antiviral Research* 2018; Martinez et al., Abstract CROI 2018). In the future, it is intended to correlate the levels of those 193 circulating miRNAs with liver disease progression, maintenance or regression (F2/3/4) in patients with HIV-1 coinfected with HCV and in whom HCV has been eradicated by treatment with the new direct-acting antivirals (DAAs). Still to be determined is whether the absence of HCV will result in reversal of liver damage in patients at different stages of liver injury. We also intend to determine the association between the levels of these 193 circulating miRNAs and liver steatosis, accumulated abdominal fat and liver damage in patients with HIV.

PRINCIPAL INVESTIGATOR

Miguel Ángel Martínez

Post-doc researcher(s)
Sandra Franco
Maria Nevot

Pre-doc researcher(s)
Ana Jordán

Visiting researcher(s)
Dominique Pope (University of California San Diego)

GRIFOLS PROJECT

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

Senior researcher: Miguel Ángel Martínez

Inflammation resulting from HIV infection can contribute to the development of liver disease. Liver damage is also exacerbated by chronic HCV, alcohol abuse, non-alcoholic hepatic steatosis and hepatotoxicity induced by antiretroviral therapy. Liver cirrhosis and hepatocellular carcinoma are important complications in patients infected with HIV.

Currently, thanks to the new DAAs, HCV infection is being eliminated in almost all patients, including patients with severe damage. Still to be determined is whether the absence of HCV will result in reversal of liver damage in patients at different stages of liver injury (liver fibrosis F2/3/4).

We also propose to identify circulating miRNAs in plasma as progression biomarkers of liver disease in patients infected with HIV.

Cell Virology and Immunology (VIC)

Projects awarded 2018

Engineered enveloped VLPs with high-density antigen coating. A proof of concept for their application to animal health
February 2018- January 2019
Funding: Hipra, SA
Research supervisor(s): **Julià Blanco**

Scholarships and grants

Edwards Pradenas. Advanced human capital training programme. February 2019- January 2021
CONICYT (Chile)

Awards and Achievements

Julià Blanco:
— Member of the French High Council for Evaluation of Research and Higher Education (HCÉRES)
— Rapporteur for Vaccines and Antibodies for the HIV Research for Prevention Conference (HIVR4P)
— Member of the CMCiBC Biosafety Committee for the Can Ruti Campus
— Organizer of the Biomedical Research Seminars at the Can Ruti Campus
— Member of the Scientific Committee of the GESIDA 2018 Congress
— Editor of the Viruses and Hosts section of *Frontiers in Cellular and Infection MIcrobiology*
Jorge Carrillo:
— Member of the Spanish Immunology Society (SEI)
— President of the Animal Experimentation Ethics Committee at the Can Ruti Campus
— Member of the Scientific Committee of Spanish Immunology Society SEI 2019 Congress

Published patents

Title: Fc-fusion protein derivatives with high dual HIV antiviral and immunomodulatory activity
Inventor(s): **Jorge Carrillo, Julià Blanco, Bonaventura Clotet**
Patent number: P1607ES-US/ EP3377524A1 / WO2017/085563Al / PCT/IB2016/001868
Date: 26 September 2018
Organization: AlbaJuna Therapeutics, S.L
Exploiting company(ies): Grifols, S.A

Title: Virus-like particles with high density coating for the production of neutralizing antibodies
Inventor(s): **Luis Molinos, Jorge Carrillo, Julià Blanco**
Patent number: P13141EP00 / EP1638234.4
Date: 31 January 2018
Organization: **IrsiCaixa**

Presentation

The group has continued to focus on three main research lines:

Humoral response to the viral envelope

— Interfering antibody identification. Antibody response to pathogens is polyclonal, consisting of neutralizing and non-neutralizing antibodies. **Jorge Carrillo** has explored the possibility that non-neutralizing antibodies block the action of neutralizing antibodies, leading to a switch from a neutral to a deleterious immune response. These results, highly relevant to the design of vaccines, were presented at the HIVR4P conference in October 2018.
— Exhaustive anti-MPER response analysis. **Edwards Pradenas** has initiated comprehensive screening of serums to identify neutralizing and non-neutralizing responses to the gp41 MPER epitope. A particular focus will be the IgG3 antibody, an IgG subtype of particular importance due to its structural characteristics.
— Synthetic antibody development. AlbaJuna Therapeutics has now terminated the discovery phase and has generated a synthetic antibody optimal from the point of view of activity, biochemical characteristics and production. Preclinical development has begun and Phase I in humans is expected to get underway by the end of 2020.
— Antibody effector functions To complement the above activities, new functional tests and technologies are being developed and optimized for the isolation and production of antibodies to be used in therapies.

Development of preventive HIV vaccines

— Preventive HIV vaccines (project PI17/01518), development of antigens based onMPER, the gp120 V1-V2 regions and (in collaboration with the BSC) CD4bs.
— Therapeutic HIV vaccines, exploring the therapeutic capacity of the VLP platform for generating anti-Gag responses.
— Feline leukemia 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 Dr. Oriol Mitjà and international groups, is working on a first vaccine candidate, already produced in vitro, that will demonstrate immunogenicity against bacterial antigens.
— Melanoma and vaccines based on neoantigens (tumour cells). This key project, carried out in collaboration with VHIO, aims to generate immune responses as the main mechanism to fight cancer.

Immunological mechanisms in HIV+ individuals

Our studies focus on understanding the viral and immunological mechanisms that lead to CD4 cell destruction, chronic inflammation and immune system ageing (inflamm-ageing) in HIV+ patients, and how this ageing affects the immune function.
— Viral envelope role. We have been able to demonstrate how viruses with an inefficient envelope result in a non-progressor phenotype.
— Viral reservoir. In the LoViReT study and in collaboration with **Javier Martínez-Picado** we have analysed the immune systems of patients with low viral reservoirs.
— Inflammation and ageing. In collaboration with Eugènia Negredo, we have analysed the immune systems of patients receiving anti-inflammatory treatment and older patients with HIV (>60 years).
— OurFlow. Development of OurFlow automatic analysis software was completed in 2018.

Our ultimate goal is to develop vaccines to protect against HIV infection and to develop treatment strategies (based on antibodies or inflamm-ageing modulators) for HIV-infected individuals that contribute to functional cure or eradication of HIV.

2018 Milestones and Perspectives for the future

Vaccine development

In 2018 we patented the invention of new VLPs (patent EP1638234.4). These VLPs offer a platform for the development of vaccines against HIV and other pathogens and also have applications in oncology. These applications are a priority and our VLP research has been reinforced by the recruitment of a pre-doctoral student (**Raquel Ortiz**), a technician (**Ismael Varela**) and a post-doc researcher (**Benjamin Trinité**).

Antibody characterization

The task of identifying new antibodies, directed by Dr. **Jorge Carrillo,** was redoubled in 2018. Their characterization is already underway and collaborations with other institutions (including the BSC) have been established in order to develop the project in optimal technical conditions. This research has been reinforced by the recruitment of **Edwards Pradenas**.

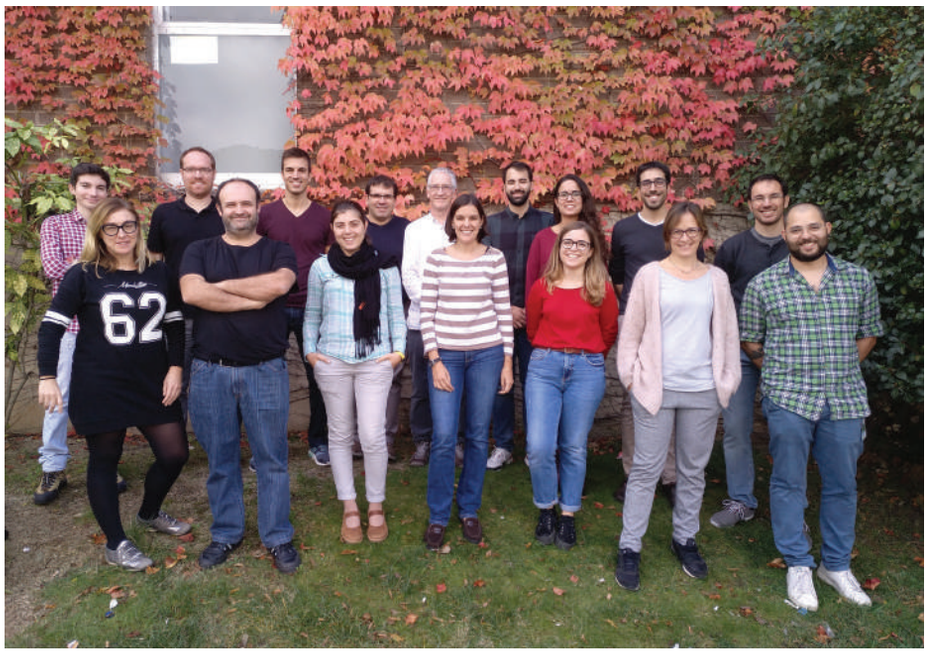
17 COMMITTED, PROFESSIONAL AND DEDICATED GROUP MEMBERS

6 PROJECTS ON VACCINES FOR DIFFERENT INFECTIOUS DISEASES AND CANCER

1 COMMON PROJECT: TO LEARN AND TO SHARE KNOWLEDGE

Immune impairment in persons with HIV

The OurFlow web platform opened in 2018 and will soon be made available to external users. This external use will help improve the platform and position the group internationally. The OurFlow software project (DTS15/00185), which is aided by **Víctor Urrea** as a visiting researcher, is key to rapidly analysing complex immunological data (multicolour flow cytometry).



Principal Investigator

Julià Blanco

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

Laboratory technician(s)
Silvia Marfil
Ismael Varela
Biostatistician(s)
Víctor Urrea
Visiting researcher(s)
Manuel Sáez (UB)

AlbaJuna Therapeutics, SL
Ester Aparicio, Carlos Ávila, Victor Casanova, Francesc Cunyat, Cristina Lorca (fins febrer 2018)

Grifols Projects

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

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

This project has the following aims:

— To develop a preventive HIV-1 vaccine based on the generation of HIV Gag VLPs with a high density of HIV-derived antigens on their surface.
— To exploit the HIV-1 Gag VLP as a vaccine platform for humoral protection responses against other pathogens.

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

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

— To design Gag to accommodate short heterologic immunogenic sequences that maintain the ability to generate VLPs.
— To exploit Gag as a vaccine platform to obtain cellular and humoral protection against tumours.
— To generate a platform of customized DNA cancer vaccines and to test them in combinations with immune checkpoint inhibitors.

Tissue Virology

Projects awarded 2018

PI18/01226. Cellular immune response characterization and modulation in lymphoid tissue associated with mucous membranes:implications for HIV infection pathogenesis
2019 - 2021
Funding: Carlos III Health Institute (ISCIII)
Research supervisor(s): **Cecilia Cabrera**

Awards and 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 can be viewed as 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 mass production of pro-inflammatory cytokines.
A current topic of debate is CD4+ T-cell destruction mechanisms and the reasons for GALT incomplete immune recovery despite antiretroviral treatment (unlike what happens with peripheral blood. This blood-tissue difference has highlighted the importance of assessing the effect of both the virus and antiretroviral therapy on lymphoid tissue, as this is where latent viral infection (the viral reservoir) is established. Further studies are needed in this area to achieve total eradication of the virus. Our group evaluates viral pathogenic effects of both HIV and SIV, the impact of antiretroviral drugs on the tissue of HIV-positive individuals with different levels of viral and/or immune control and on healthy donor tissue from ex vivo models.

Urinary bladder cancer

Bladder cancer is one of the most prevalent cancers in the world and around 80% of patients present with superficial bladder cancer confined to the mucosa. 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. Our group is working to improve current treatment by developing new therapeutic strategies and identifying biomarkers to predict response to treatments.

2018 milestones and perspectives for the future

In 2018, the results obtained in different lines of work were as follows:

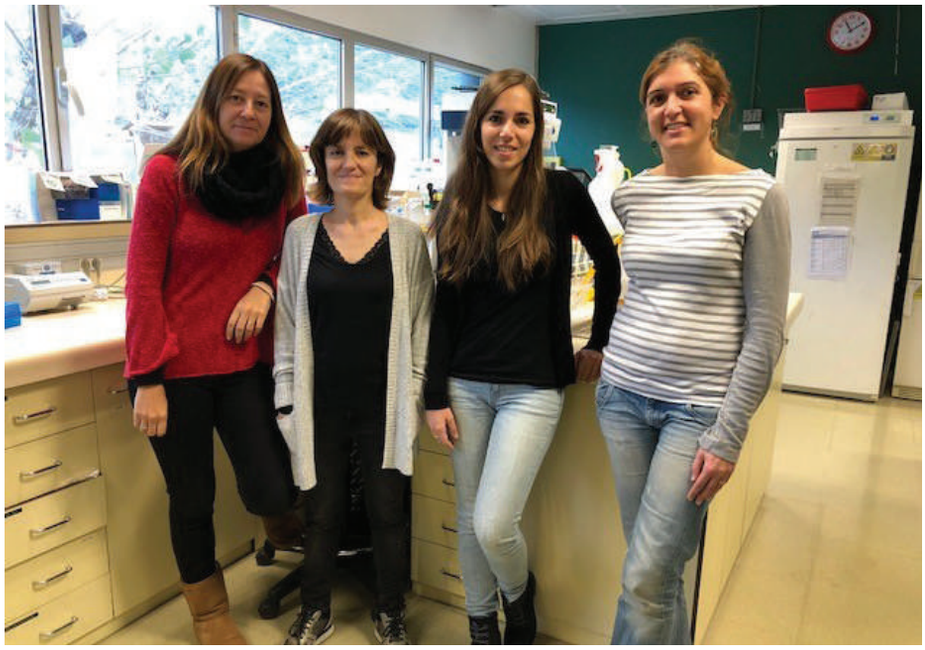
HIV pathogenesis in lymphoid tissue

— Effects of autophagy modulation on HIV infection. Our evaluation of the effects of different drugs that modulate autophagy, apoptosis and pyroptosis in infection will enable us to determine possible new therapeutic targets.

Bladder cancer

— Therapeutic strategies for improving BCG treatment. With a view to improving the clinical efficacy of BCG treatment, recruitment has commenced for a phase I clinical trial to study strategies for strengthening the immune system of individuals with superficial bladder cancer before intravesical BCG treatment.
— Local and systemic immune responses and bladder tumour elimination. Using an orthotopic mouse model we have shown that intravenous mycobacterial treatment triggers local and systemic immune responses implicated in bladder tumour elimination. Detailed characterization of these immune responses will lead to improved BCG treatment and the design of new treatments that promote beneficial while avoiding non-beneficial immune responses.

— A new biomarker for response to BCG treatment. We have described 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(s)
Silvia de Muga

Pre-doc researcher(s)
Sònia Pedreño

Laboratory technician(s)
Elisabet García

GRIFOLS PROJECT

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

Senior researcher: Cecilia Cabrera

The project focuses on:
— Characterizing the phenotypic and functional properties of immune cells resident in various lymphoid tissues associated with the mucosa.
— Identifying key pathways regulating the generation and activation of immune cells resident in various lymphoid tissues associated with the mucosa thatparticipate in the transmission and maintenance of various sexually transmitted diseases,including herpes simplex, *Neisseria gonorrhoeae*, HPV, *Chlamydia trachomatis* and HIV-1.

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 39 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

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

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.

In 2018, the Sequencing Service implemented next-generation sequencing techniques in collaboration with the Germans Trias i Pujol Institute for Health Science Research (IGTP). These highly sensitive techniques identify possible low-level resistance to drugs and 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

32,261
cells

63,452
plasma

10,742
serum

26,548
other

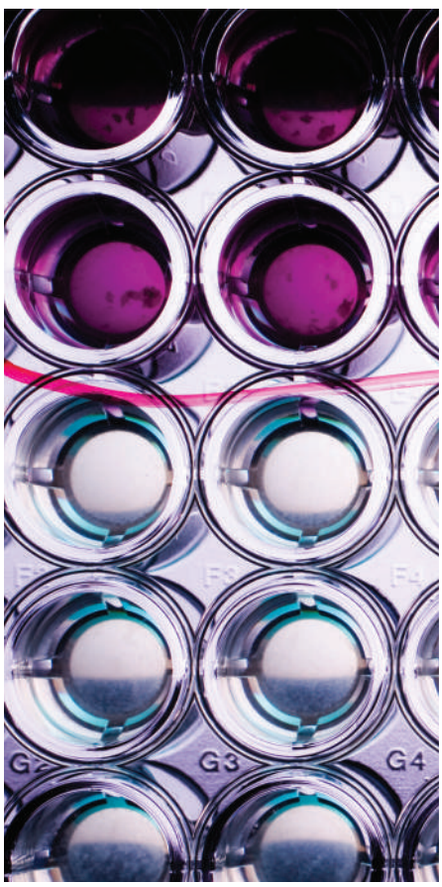
Total: 133.003 samples

598 Sequenced samples

408
public centres

190
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 in ensuring funding for the development of innovative and quality research.

Continuous communication with researchers ensures support at all levels: the detection of needs, the search for suitable finance, support in preparing proposals and managing projects and assistance in collaboration, transfer and innovation processes. The Research and Innovation Management team ensures alignment of **IrsiCaixa** practices with financing entity policies and current legislation.

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.

The additional staff recruited in 2018 has enabled the unit to be internally restructured so as to improve the quality of its services, provide a more personalized service, and open new lines of work, including intellectual property management.

Patents

Published

Title: Fc-fusion protein derivatives with high dual HIV antiviral and immunomodulatory activity
Inventor(s): **Jorge Carrillo, Julià Blanco, Bonaventura Clotet**
Patent number: P1607ES-US/ EP3377524A1 / WO2017/085563Al / PCT/IB2016/001868
Date: 26.09.2018
Organization(s): AlbaJuna Therapeutics, S.L
Exploiting company(ies): Grifols, S.A

Title: Virus-like particles with high density coating for the production of neutralizing antibodies
Inventor(s): **Luis Molinos, Jorge Carrillo, Julià Blanco**
Patent number: P13141EP00 / EP1638234.4
Date: 31.01.2018
Organization(s): IrsiCaixa

Filed

Title: Aurora kinase inhibitors for treating or preventing HIV infection or AIDS
Inventor(s): **Garcia-Vidal E**, **Badia R**, **Riveira-Muñoz E**, **Este JA**.
Date: 09.01.2018
Application number: USPTO 62728824
Applicant(s): IrsiCaixa, IGTP

Living Lab for Health

Head
Rosina Malagrida

Team
Josep Carreras
Marina Pino
Aina Estany

PRESENTATION

During **2018,** **IrsiCaixa**'s Living Lab for Health continued with its tasks focused on improving the social impact of health research and promoting more open and inclusive R&D, following new trends defined by the EU under the umbrella of Responsible Research and Innovation (RRI), Open Innovation and Open Science.

LINES OF ACTION 2018

Living Lab projects fall into one of four categories:

Projects to improve R&D governance through a systematic and collaborative approach to developing better solutions to persistent and complex challenges.

Challenge 1: HIV prevention in Catalonia

Through the Co-ResponsaVIHlitat project, which involves some 680 social agents from 16 academic disciplines and civil society organizations, Living Lab coordinates participatory and interdisciplinary research and innovation projects. These projects respond to unmet needs identified in a collaborative way in the R&D agenda for the prevention of HIV and other STDs developed in 2017. The **2018** projects focused on the effects of stigma in HIV prevention, teenager access to diagnostic tests, analyses of how secondary schools integrate affective-sexual education and, finally, the co-creation of a social media communication campaign to promote prevention.

Challenge 2: Healthy and sustainable nutrition in Catalonia

The goal is to create a Fit4Food 2030 Catalonia network, involving different agents and seeking to improve food R&D governance in Catalonia through systematic and transdisciplinary analyses. During **2018**, Living Lab organized a first series of participatory workshops that culminated with a consensus on an agenda of R&D priorities that should inspire future food policies. These workshops involved discussions and the distribution of materials that encouraged learning on different aspects of the food system (trends, visions, areas where change is needed, etc).

Initiatives to open IrsiCaixa's research to collaboration with other social agents such as patients, civil society representatives, policy makers, healthcare personnel and industry.

Community Advisory Committee (CAC)

This external body facilitates communication and dialogue between the scientific community and HIV-affected and at-risk individuals and groups. 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. In **2018**, the CAC met every two months, introducing improvements in a wide variety of research protocols and information documents for participants in clinical trials.

CO-RESPONSAVIHLITAT

10 Participating research centres, universities and public health entities

8 Entities and civil society organizations

680 Total participants

400 Attendees at the co-responsavihlitat conference

4 Participatory and transdisciplinary research projects

RRI TRAINING FOR PROFESSIONALS

2,207 Participants in courses and conferences

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

Living Lab offers training mainly aimed at researchers, healthcare personnel, public policymakers and patients in various universities and research centres. Training is customized and is also offered on doctoral, master and undergraduate courses.

Living Lab also participates in national and international conferences, seminars and workshops. In October, Living Lab co-organized, with local institutions and international experts, a B·Debate on *Open Science: from Values to Practice*, which culminated in the publication of recommendations regarding more open and inclusive research.

Educational programmes aimed at reducing the gap between research and education.

Xplore Health educational programme

Living Lab has developed new educational resources on vaccination and related ethical, legal and social issues and has given face-to-face courses to secondary school teachers. It has also coordinated participation of secondary school teachers and students in Co-ResponsaVIHlitat participative research projects. Finally, Living Lab contributed to designing the CosmoCaixa Challenge aimed at promoting research projects in secondary schools and involving different actors in projects aimed at resolving the nutrition crisis affecting society.

IRSICAIXA OUTREACH

1,235 Participants in courses and conferences

5,437 Website visits

XPLORE HEALTH

107,370 Website visits

14,904 Facebook Followers

3,002 Twitter Followers

HIVAIDS outreach programme

IrsiCaixa continues to offer reflection and dissemination sessions regarding HIV prevention at CaixaForum and CosmoCaixa events in Barcelona. These sessions in 2018 were complemented by the LaboCosmoCaixa, an activity organized by "la Caixa" Welfare Projects in collaboration with IrsiCaixa, aimed at encouraging young people to conduct research with a vaccine candidate developed by **IrsiCaixa** This was the seventh year of the programme.

Projects in 2018

InSPIRES. Project financed by the EU to create co-creation spaces for different social agents and to evolve the concept of Science Shops under the new umbrella of RRI and Open Science.

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

Fit4Food2030. An EU-funded project for the transformation of food and nutrition RD&I by implementing a system-level RRI programme.

Xplore Health. An EU-funded project for the transformation of food and nutrition RD&I by implementing a system-level RRI programme.

Living Lab also participated in an ENRRICH open day in the European Parliament (Enhancing RRI through Curricula in Higher Education), financed by the EU.

Communication

Head
Júlia Bestard

IrsiCaixa's Department of Communication disseminates the results of research. In this way it not only gives visibility to research and raises awareness of advances in the fight against AIDS among the general public, but also highlights the importance of research and promotes a better understanding of research findings in areas of major importance for society.

In **2018**, 311 impacts were achieved in TV, radio and written press (excluding the online media), a notable achievement considering that research often has difficulties finding a space in the mass media. Efforts were also invested in giving a local focus to the news, as was done with the news on the international award to **Ester Ballana** from Torrelló in central Catalonia, the CosmoCaixa Co-ResponsaVIHlitat Conference held in central-western Catalonia, the Catalan Health Institute (ICS) award to **Beatriz Mothe**, the appointment of **Beatriz Mothe** to preside over the medical graduation ceremony at the University of LLeida (UdL), and the participation of **Maria Salgado** in a study on HIV treatment by means of stem cell transplantation (Salamanca, Castilla-Leon).

The following were among the most successful media events of the year:
— The signing of a collaboration agreement between **IrsiCaixa** and Grifols, according to which this pharmaceutical company will fund research in **IrsiCaixa** for the next five years.
— The publication of an article in *mBIO* on defects in the HIV-1 envelope protein that explain why five patients with different immunological profiles managed to control the virus for 25 years without treatment.
— The press conference to present the findings of a retrospective study with the SEAT company in which the data of 30,000 employees were analysed and announce the launch of a joint study on nutrition and healthy living.
— The publication of an article in *PNAS,* in collaboration with the University of Lleida- Agrotecnio Centre, describing how a cocktail of three proteins produced in rice seeds neutralized HIV in vitro.
— The publication of an article in *The Lancet* HIV that defines the threshold from which resistant HIV requires specific treatment.
— The publication of an article in *Annals of Internal Medicine*, co-authored by **IrsiCaixa** and Hospital Gregorio Marañón, on stem cell transplantation factors that could lead to HIV eradication from the body.

890
new followers on Twitter

55.1%
increase in the number of monthly newsletter subscribers

311
written press, radio and TV impacts

65.5%
increase in www.irsicaixa.es sessions

In total, **14 press releases** were sent out in **2018, double the number of 2017**, to which can be added nine other news stories and six Blog365 posts that were shared on the institutional website and in social networks.

IrsiCaixa has further consolidated its presence in Linkedin and also in YouTube, where five videos were uploaded in **2018. We are grateful to all the researchers in IrsiCaixa, without whom our work would be impossible.**

Work has also advanced in the **planning and design of corporate materials,** such as the annual report, information dossiers and presentations.

Regarding the **IrsiCaixa** website, the statistics point to a sustained increase in visitors since its launch in mid-2016. During **2018,** there were 55,585 sessions and 40,923 users, increases of 65.5% and 85.9%, respectively, over 2017.

Our department has also contributed to **communicating biomedical research, STD prevention and eradication of the stigma associated with HIV and AIDS**. In June, two informative workshops on STD transmission within groups were organized at the Science Festival organized by Barcelona City Council in Parc de la Ciutadella. In November, for the first time, a talk on HIV/AIDS prevention and elimination of the associated stigma was given to Brians2 prison staff and inmates.

Institutional news

Grifols and IrsiCaixa join forces to promote biomedical research

Especially important news in 2018 was the signature of a collaboration agreement between **IrsiCaixa** and **Grifols** in April, under which **Grifols** will provide funding amounting to 1.5 million euros annually for the next five years. This financial injection will be crucial to advancing **IrsiCaixa**'s HIV/AIDS and other research lines, including cancer, microbiome and neurodegenerative diseases.

The agreement makes **Grifols**, with the **Fundació Bancària "la Caixa"**, a major funder of new lines of research launched by **IrsiCaixa**, a leading centre in research to eradicate AIDS and related diseases.

This development will be fundamental for IrsiCaixa to tackle the biomedical challenges affecting the general population, including emerging infectious diseases and neurodegenerative diseases.

Grifols will have the right to exploit the results and patents that result from **IrsiCaixa** projects, although ownership will be retained by IrsiCaixa, which will also retain the right to use the results for internal research purposes.

A monitoring committee composed of representatives of **Grifols** and **IrsiCaixa** will be set up to evaluate progress in the different research projects.

IrsiCaixa recieves the European Commission's HR Excellence in Research Award

In **2018**, **IrsiCaixa** was granted the European Commission's HR Excellence in Research award. The award recognizes **IrsiCaixa**'s commitment to continuously improving its human resource policies, in line with the European Charter for Researchers and Code of Conduct for the Recruitment of Researchers. In particular, it emphasizes commitments to establish fair and transparent procedures for recruitment and evaluation.

In May 2017, **IrsiCaixa** signed a declaration to respect the principles of the Charter and Code, with the aim of improving the working conditions of its researchers and making the institution a more attractive place to do quality research. **IrsiCaixa** thus underlined its interest in the HR Strategy for Researchers as a tool for the self-evaluation of departments and services in human resource terms. The implementation of the Charter and Code enhances **IrsiCaixa**'s attractiveness for researchers seeking a new job or centre in which to undertake their research project.

HR EXCELLENCE IN RESEARCH

IrsiCaixa has adopted an Action Plan that will enable it to comply with the vision, strategic objectives and principles of the Charter and Code.

The Barcelona Debates on the Human Microbiome. From Microbes to Medicines

The fourth edition of The Barcelona Debates on the Human Microbiome. From Microbes to Medicines took place on 21-22 June at CosmoCaixa. The meeting once again brought together internationally renowned experts in microbes, a field which offers great potential in many areas of biomedical research.

The debate was organized by **IrsiCaixa**'s Microbial Genomics group in collaboration with the Vall d'Hebron Research Institute, the Dr. Josep Trueta Biomedical Research Institute of Girona, the University of Vic-Central University of Catalonia, the National Centre for Oncology Research (CNIO) and the Germans Trias i Pujol University Hospital. It was sponsored by "la Caixa", MSD and the Mandarin Oriental Hotel and received logistical support from FLS-Science.

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

5 undergraduate and master's students

25 pre-doc researchers

24 post-doc researchers

Training activities

12 research results meetings

64 conference participations

Course	Place and data	Attendees
Introduction to splines with penalties	Bilbao, January 2018	2
HIBIC	Madrid, February 2018	6
How to communicate your science project in a 60-minute video	Barcelona, March 2018	1
Extracellular vesicles: from biology to biomedical applications	Heidelberg, March 2018	1
Hands on workshop on git and github for software development	Vic, May 2018	
Financial aspects of H2020	Barcelona, May 2018	2
Personnel training and laboratory accreditation	Barcelona, May 2018	2
20th Course on Flow Cytometry Principles and Applications	Badalona, June 2018	4
Practical course on the construction of multicoloured panels for flow cytometry	Barcelona, June 2018	1
Statistical inference with R	Bellaterra, June 2018	2

Course	Place and data	Attendees
20th Course on Flow Cytometry Principles and Applications	Bellaterra, July 2018	1
Multivariate dimension reduction for biological data integration	Barcelona, July 2018	1
ENLIGHT-TENed by big data: advancing T-cell immunology	Amsterdam, September 2018	1
3rd Annual European Congress on Immunotherapies in Cancer	Barcelona, September 2018	4
Innovative approaches for identification of antiviral agents (summer school)	Cagliari, September 2018	2
Comprehensive management of aging in HIV	Barcelona, September 2018	1
University expert in research in HIV/AIDS and associated diseases	Online, October 2018 - June 2020	1
Strategies for oncology and immuno-oncology therapeutic development	Paris, October 2018	1
Hazards in the storage of chemicals	Barcelona, October 2018	1
EMBO laboratory leadership for post-docs	Frankfurt, October 2018	1

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 expert 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 expert in different areas.

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

— 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.

Researchers in training	Group	Centre	City, country	Date
Daniel Pérez	Retrovirology and Clinical Studies (GREC)	Institut Imagine	Paris, France	1 Sept-21 Dec
Ana Jordán	HIV and HCV Genetic and Phenotypic Variability	Friedrich-Schiller University	Jena, Germany	29 Sept-1 Dec
Cristina Gálvez	Retrovirology and Clinical Studies (GREC)	The Ragon Institute	Boston, USA	1-31 May

Chair of AIDS and Related Diseases

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 of AIDS and Related Diseases. The Chair, headed by **Dr. Bonaventura Clotet**, was founded to enhance collaboration between the three institutions in fostering biomedical research at the UVic-UCC and promoting the teaching and training of new researchers and healthcare professionals.

Although HIV and AIDS are the core elements in this initiative, the Chair also covers research into related conditions such as ageing, hepatitis and cancer.

Chair activities in **2018** were as follows:

— Ageing (seminar), 9 January 2018, UVic-UCC Faculty of Medicine, Eugènia Negredo
— Microbiome (seminar), 1 March 2018, UVic-UCC Faculty of Medicine, **Roger Paredes**
— Update on HIV infection (continuous professional development), 8 May 2018, UVic-UCC Faculty of Medicine, **Bonaventura Clotet**, Cora Loste, **Beatriz Mothe**, Eugènia Negredo, **Roger Paredes**, Rafel Pérez, Guillem Sirera, Josep Vilaró
— Telemedicine: TeleIctus (seminar), 14 June 2018, UVic-UCC Faculty of Medicine, Cora Loste
— Art and medicine (seminar), 19 June 2018, UVic-UCC Faculty of Medicine, **Javier Martínez-Picado**
— Inaugural speech (welcome ceremony for first-year medical students), 21 September 2018, UVic-UCC Faculty of Medicine, **Bonaventura Clotet**
— Monoclonal antibody design (seminar), 4 December 2018, UVic-UCC Faculty of Medicine, **Julià Blanco**
— Immunology (seminar), 5 December 2018, UVic-UCC Faculty of Science and Technology, **Christian Brander**
— Immunology (seminar), 19 December 2018, UVic-UCC Faculty of Science and Technology, **Julià Blanco**

CLINICAL TRIALS

1. CONTROLLERS

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

Summary and objectives: Cohort study with prospective follow-up of HIV-positive individuals with an undetectable or very low viral load in the absence of antiretroviral treatment (known as elite or viremic controllers). The aim is to study the virological and immunological mechanisms involved in spontaneously controlling the HIV virus in order to advance towards the development of new therapeutic vaccines. There is no clinical intervention other than the extraction of additional biological samples.
Design: Cohort, prospective
Recruitment: Open
Start – end: 03/06/2009 -
Sponsor: 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 study to monitor individuals with documented acute/recent HIV-1 infection initiating early-stage antiretroviral therapy. The objective is to have a clinical platform of candidates for clinical trials of therapeutic vaccination and eradication strategies and also to prospectively obtain biological samples from the outset of antiretroviral therapy to study initial transmission of HIV, immune response, the establishment of viral reservoirs and changes in the gut microbiome. There is no clinical intervention other than the extraction of additional biological samples and the collection of faecal samples.
Study type: Observational
Design: Cohort, prospective
Recruitment: Open
Start – end: 24/07/2014-
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 whose HIV seronegative status and high-resolution HLA genotype is documented, for whom biological samples (plasma and PBMCs) — stored in the IrsiCaixa Retrovirology Laboratory biobank — are available for use in the study of immunological aspects of HIV infection and related diseases.
Study type: Observational
Design: Cohort, prospective
Recruitment: Open
Start–end: 30/10/2009-
Sponsor: 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 to evaluate the effectiveness of a kick-and-kill strategy based on the use of the most immunogenic therapeutic vaccines known to date (HIVconsv) and the most powerful viral latency reactivation drug currently available (RMD, romidepsin). HIV-positive individuals treated from diagnosis and previously vaccinated in the BCN01 trial represent an ideal group for demonstrating the effectiveness of this strategy that combines viral reservoir reduction with control of viral rebound once treatment ends. By means of a populational PK/PD analysis, the relationship between romidepsin levels, in-vivo effects on induced expression of reservoir HIV and the impact on the immune system is investigated. Results will enable the romidepsin dose to be optimized and will identify markers to help assess the efficacy of currently studied eradication strategies.
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. iHIVARNA-02

Phase IIa multicentre, double-blind, placebo-controlled clinical trial to evaluate the safety and immunogenicity of the new iHIVARNA-01 therapeutic vaccine in HIV-infected patients.

Summary and objectives: Phase IIa multicentre, double-blind, placebo-controlled clinical trial of the iHIVARNA therapeutic vaccine candidate. Included are 70 individuals with chronic fully suppressed HIV-1 infection, randomized to receive either three intranodal consecutive doses of the iHIVARNA vaccine containing 900 g of the HTI immunogen and 300 g of the the adjuvant TriMix (n=40) or three doses of placebo (n=15). Two weeks after the last vaccination, the antiretroviral treatment is interrupted, viral rebound is monitored for 12 weeks, and if viral rebound occurs, the treatment is resumed. Objectives include studying vaccine administration safety, immune response and viral control once treatment stops.

Study type: Interventional
Design: Double blind, placebo-controlled, multicentre
Recruitment: Closed
Phase: IIa
Start–end: 04/04/2017 - analysis ongoing
Sponsor: Erasmus MC, Rotterdam (Netherlands)
Principal investigator(s): Dr. Rob Gruters
Participating centre(s): Erasmus MC, Rotterdam (Netherlands);Hospital Clínic de Barcelona and Germans Trias i Pujol University Hospital (Fight AIDS Foundation); **IrsiCaixa** (Badalona, Spain); Instituut voor Tropische Geneeskunde (Antwerp, Belgium); Vrije Universiteit Brussel/UZ Brussel (Belgium)
NCT Code: NCT02888756

6. 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- 31/05/2018
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

7. 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-
Sponsor: IrsiCaixa
Principal investigator(s): Dr. Cecilia Cabrera
Participating centre(s): Germans Trias i Pujol University Hospital(Fight AIDS Foundation)

8. 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

9. 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

10. 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

11. 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 and collect safety information on systemic and mucosal immune response to RUTI® administered to individuals with high-grade superficial bladder cancer.
Design: Double blind, placebo-controlled, randomized
Phase: I
Start–end: 2017- 2019
Sponsor: Archivel Farma S.L
Principal investigator(s): Dr. Cecilia Cabrera
Participating centre(s): Germans Trias i Pujol University Hospital (Urology Department), Fight AIDS Foundation (CRO)
CEIC Code: AC-16-048-CEIM
EUDRA Code: 2016-004311-12

12. 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

13. LT-EC

Analysis of the presence of infectious viruses in the blood of elite non-progressor controllers.

Summary and objectives: A clinical trial to study the characteristics of both host and virus in elite controllers of more than ten years in order to explore and better understand pathogenic mechanisms and spontaneous control of infection.
Study type: Clinical observational
Start–end: 01/01/2017-
Principal investigator(s): Dr. Cecilio López-Galíndez (CNM-ISCIII)

14. VNP

Adult and paediatric HIV viremic non-progression: clues from immune preservation for the CURE.

Summary and objectives: Clinical trial to study the factors associated with the phenotype of viremic non-progressors, who, despite having a high viral load, maintain their health and immunity.
Study type: Clinical observational
Start–end: Q4 2014 -
Principal investigator(s): Dr. Philip Goulder, **Dr. Javier Martínez-Picado** i **Dr. Julia Garcia-Prado**

15. 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

Publications and Conferences

Publications

Original publications

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Collaborative publications

1. Conway A, Anna Esteve, Manuel Fernández-Quevedo, Jordi Casabona, PISCIS Study. **Determinants and Outcomes of Late Presentation of HIV Infection in Migrants in Catalonia, Spain: PISCIS Cohort 2004–2016**. *Journal of Immigrant and Minority Health*. 2018. First Online 30 October 2018. https://doi.org/10.1007/s10903-018-0834-2. IF: 0,428

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7. Ruiz-de-León MJ, Jiménez-Sousa MA, Moreno S, García M, Gutiérrez-Rivas M, León A, Montero-Alonso M, González-García J, Resino S, Rallón N, Benito JM, Vallejo A; ECRIS Network integrated in the Spanish AIDS Research Network. **Lower expression of plasma-derived exosome miR-21 levels in HIV-1 elite controllers with decreasing CD4 T cell count**. *J Microbiol Immunol Infect*. 2018 Aug 24. pii: S1684-1182(18)30308-6. doi: 10.1016/j.jmii.2018.07.007. IF: 0,698

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9. Shepherd L, Borges ÁH, Harvey R, Bower M, Grulich A, Silverberg M, Weber J, Ristola M, Viard JP, Bogner JR, Gargalianos-Kakolyris P, Mussini C, Mansinho K, Yust I, Paduta D, Jilich D, Smiatacz T, Radoi R, Tomazic J, Plomgaard P, Frikke-Schmidt R, Lundgren J, Mocroft A; EuroSIDA in EuroCOORD. **The extent of B-cell activation and dysfunction preceding lymphoma development in HIV-positive people**. *HIV Med*. 2018 Feb;19(2):90-101. doi: 10.1111/hiv.12546. Epub 2017 Aug 31. IF: 0,977

Conference presentations and Talks

Presentations at national conferences

1. Bayón-Gil A, V. Urrea, B. Mothe, C. Brander, M.C. Puertas and J. Martínez-Picado. **Dynamics of HIV-1 reservoir decay in early-treated individuals.** IX Congreso Nacional de Gesida. Madrid, 6-9 Nov 2018 . Oral Poster #PO-41

2. Bayón-Gil A, V. Urrea, B. Mothe, C. Brander, M.C. Puertas and J. Martínez-Picado. **Dynamics of HIV-1 reservoir decay in early-treated individuals.** XVII Jornada de Virologia. Barcelona, 30 Oct 2018: Poster #P-8

3. Blanch-Lombarte O, Esther Jiménez-Moyano, José Ramón Santos, Ruth Peña, Judith Dalmau, Alba Ruiz, Bonaventura Clotet and Julia G Prado. **TIGIT levels remain high in Transitional and Central Memory CD8+ T cells after long-term suppressive ART in HIV-1 infection**. X Congreso nacional GeSIDA y XII Reunión docente de la red de Investigación en SIDA. GeSIDA, SEIMC. Madrid. Spain. 06/11/2018 - 09/11/2018. Scholaship RIS-GeSIDA for Young Researchers. Poster and Oral presentation.

4. Colomer-Lluch M, Adland E, Dalmau J, Francés C, Peña R, Jiménez-Moyano E, Clotet B, Martínez-Picado J, Goulder P and Prado JG. **Characterization of viral factors in pediatric and adult HIV-1 viremic non-progressors**. X Congreso nacional GeSIDA y XII Reunión docente de la red de Investigación en SIDA. GeSIDA, SEIMC. Madrid. Spain. 06/11/2018 - 09/11/2018. Scholaship RIS-GeSIDA for Young Researchers. (Dra. Colomer Lluch). Oral Poster.

5. Coll P. **Fortalezas de la PrEP.** 63 Congreso Nacional de la SEFH. Sociedad Española de Farmacia Hospitalaria. Palma de Mallorca. Spain. November 10th 2018. Invited session talk.

6. Coll J. **Modelos de implementación de PrEP en España**. X Congreso Nacional GeSIDA. SEIMC. Madrid. Spain. 06/11/2018 - 09/11/2018. Invited session talk.

7. Coll J. **Más allá del preservativo: nuevas herramientas de prevención. XIV Congreso Español de Sexología**. Federación Española de Sociedades de Sexología. Barcelona. Spain. 1st 2018. Invited session talk.

8. Coll J. **Sexo y drogas: el fenómeno del ChemSex.** V Congreso Nacional de Patología Bio-Psicosocial. Departamento de Psicología Clínica. Universidad de La Laguna. Tenerife. Spain. November 16th 2018. Invited session talk.

9. Chojnacki J, C. Favard, D. Muriaux and C. Eggeling. **Probing lipid and protein dynamics at individual HIV-1 assembly sites**. IX Congreso Nacional de Gesida. Madrid, 6-9 Nov 2018 Poster Oral #PO-17

10. Chojnacki J, C. Favard, D. Muriaux and C. Eggeling. **Probing lipid and protein dynamics at individual HIV-1 assembly sites**. XVII Jornada de Virologia. Barcelona, 30 Oct 2018. Poster.

11. Manzardo C, Silva Arrieta S, Rafecas A, Resino S, Franco S, Del Campo S, Cordero E, Castells L, Muñoz-Fernández MA, Subirana M, Martínez MA, Rimola A, Brander C, Miró JM. **Factores de riesgo de desarrollo de fibrosis grave del injerto en receptores de transplante hepático en coinfectados VIH/VHC.** XXII Congreso Nacional de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC2018). XVII Jornada de Virologia. Societat Catalana de Biologia. Barcelona. Spain. October 30. Oral Presentation.

12. Nevot M, Sandra Franco, Daniela Buccione, Beatriz Mothe, Lidia Ruiz, Ana Jordan-Paiz, Raquel Pluvinet, Susanna Aussó, Rosa M. Morillas, Lauro Sumoy, Miguel Angel Martinez, Cristina Tural. **MicroRNAs circulantes en pacientes VIH revelan signaturas específicas para daños hepáticos**. X Congreso Nacional GeSIDA. GeSIDA. Madrid. Spain. 6-9 Novembre 2018. Poster.

13. Nevot M, Ana Jordan-Paiz, Glori Martrus, Cristina Andrés, Damir García-Cehic, Josep Gregori, Sandra Franco, Josep Quer and Miguel Angel Martinez. **HIV-1 rotease evolvability is affected by synonymous nucleotide recoding.** Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. Bilbao. Spain. May, 24-26. Oral Presentation.

14. Oriol B, M.Ruiz-Riol, C.Brander. **DNA methylation profiles identify epigenetically regulated host factors associated with immune control of HIV infection**. III Jornadas Científicas de Estudiantes de la SEB. Jóvenes de la sociedad española de Biometría. Bilbao. Spain. January 18nd-19th, 2018. Oral Communication.

15. Puertas MC, Morón-López S, Miranda C, López M, Hanke T, Manzardo C, Miró JM, Brander C, Mothe B, Moltó J and Martínez-Picado J. **In vivo dynamics of HIV-1 in a combined HIVCONSV vaccine & Romidepsin strategy**. IX Congreso Nacional de Gesida. Madrid, 6-9 Nov 2018 Comunicación Oral #OR-11.

16. Rodríguez de la Concepción Maria Luisa, Silvia Marfil, Luis Manuel Molinos-Albert, Ferran Tarres, Carmen Aguilar, Bonaventura Clotet, Julià Blanco, Jorge Carrillo. **HIV Infection Leads to the Development of Neutralization-Interfering Antibodies that Hamper the Function of Neutralizing Antibodies**. GESIDA 2018. Gesida-Seimc. Madrid. España. 6-9 noviembre. Scholarship. Poster presentation.

17. Ruiz A, Jimenez-Moyano E, Blanch-Lombarte O, Mothe B, Clotet B and G. Prado J. **Evaluation of HIV-1 specific-CD8+ T cell reinvigoration by ex vivo PD-1 and TIM3 blockade in Early Treated HIV-1 infected individuals**. X Congreso nacional GeSIDA y XII Reunión docente de la Red de Investigación en SIDA. GeSIDA, SEIMC. Madrid. Spain. 06/11/2018 - 09/11/2018. Scholaship RIS-GeSIDA for Young Researchers. Oral Poster.

Presentations at international conferences

1. Blanch-Lombarte O, José Ramón Santos, Ruth Peña, Alba Ruiz, Esther Jimenez-Moyano, Roger Paredes, Bonaventura Clotet, Julia G Prado. **HIV-1 Gag mutations reduce PI-susceptibility in the absence of Protease resistance mutations.** Conference on Retroviruses and Opportunistic. Boston. EEUU. 03/03/2018 - 09/03/2018. New Investigator Scholarship. Poster.

2. Coll J. **Long Acting HIV drugs for the prevention: what are the data?** 16th European Meeting on HIV and Hepatitis. Virology Education. Rome. Italy. May 30th 2018. Invited session talk

3. Herms J, Cristina Rodriguez, Maria Casadella, Teresa Puig, Bonaventura Clotet, Roger Paredes, Marc Noguera-Julian. **PASEQ: One-click, cloud-based web service for NGS-based HIV genotyping data analysis.** 23rd Conference on Retrovirus and Opportunistic Infections (CROI). International Antiviral Society–USA (IAS–USA). Boston. USA. March 4-7, 2018. (ABSTRACT 555).

4. Inzaule SC, Raph L. Hamers, Marc Noguera-Julian, Maria Casadella, Mariona Parera, Bonaventura Clotet, Tobias F. Rinke de Wit, Roger Paredes. **Defining clinically relevant threshold for ultrasensitive HIV resistance testing**. 23rd Conference on Retrovirus and Opportunistic Infections (CROI). International Antiviral Society–USA (IAS–USA). Boston. USA. March 4-7, 2018. (ABSTRACT 260).

5. Jordan-Paiz A, Maria Nevot, Sandra Franco and Miguel Angel Martinez. **Synonymous recoded env gene induce lethality and loss of protein**

expression in HIV-1. 23rd Conference on Retrovirus and Opportunistic Infections (CROI). International Antiviral Society–USA (IAS–USA). Boston. USA. March 4-7, 2018. Poster.

6. Leal L, Guardo AC, Moron-Lopez S, Salgado M, Mothe B, Heirman C, Thielemans K, Pannus P, Brander C, Gruters R, Andeweg A, Martinez-Picado J, Plana M, Garcia F. **Phase I clinical trial of an mRNA-based therapeutic vaccine against HIV-1 infection**. 23rd Conference on Retroviruses and Opportunistic Infections. International Antiviral Society–USA (IAS–USA). Poster presentation #311 Boston (MA, USA), Mar 4-7, 2018.

7. Martinez MA, Franco S, Buccione D, Mothe B, Ruiz L, Nevot M, Jordan-Paiz A, Pluvinet R, Aussó S, Morillas RM, Sumoy L, Tural C. **Circulating micro-RNAs in HIV patients reveal specific signatures for liver damage**. Conference on Retrovirus and Opportunistic Infections (CROI). International Antiviral Society–USA (IAS–USA). Boston. USA. 4-7 de març 2018. Oral Presentation.

8. Pujantell M, Sandra Franco, Eva Riveira-Muñoz, Cristina Tural, Bonaventura Clotet, Miguel Angel Martinez, José A. Esté, Ester Ballana. **ADAR1 is a regulator of innate and antiviral immune function in HCV infection**. 23rd Conference on Retrovirus and Opportunistic Infections (CROI). International Antiviral Society–USA (IAS–USA). Boston. USA. 4-7 de març 2018. Poster. Scholarship (Maria Pujantell).

9. Moron-Lopez S, Urrea V, Navarro J, Puertas MC, Torrella A, Salgado M, Gálvez C, Planas B, Vandekerckhove L, Blanco J, Crespo M, Martinez-Picado J. **Effect of switching to integrase inhibitor on the HIV reservoir in ileum biopsies**. 23rd Conference on Retroviruses and Opportunistic Infections. Boston (MA, USA), Mar 4-7, 2018. Poster presentation #501.

10. Oriol B, M.Ruiz-Riol, C.Brander. **DNA methylation profiles identify epigenetically regulated host factors associated with immune control of HIV infection**. European Congress of Immunology. European Federation of Immunological Societies. Amsterdam. Netherlands. September 2nd-5th, 2018. Poster presentation.

11. Revollo B, Sebastia Videla, Arelly Ornelas, Roger Paredes, Josep Coll, Marta Piñol, Francesc García-Cuyás, Antoni Tarrats, David Parés, Ross Cranston, Bonaventura Clotet, Guillem Sirera. **Effectiveness os screening for anal cancer prevention in HIV-infected patients**. CROI 2018. March 4–7, 2018 | Boston, Massachusetts. (ABSTRACT 666).

12. Romero, L, Oriol, B, Vogel, A, Brander, C, Olvera, A. **Immunogenicity of the HIV T-cell immunogen HTI vectored by RNA in mice**. EAVI2020 GAM. EU Consortium. Madrid. October 18-19th 2018. EAVI2020. Poster Presentation.

13. Rocafort Muntsa, Noguera M, Rivera J, Pastor L, Guillén Y, Langhorst J, Parera M, Mandomando I, Carrillo J, Clotet B, Blanco J, Naniche D, Paredes R. **Evolution of The Gut Microbiome Following Primary HIV-1 infection**. 23rd Conference on Retroviruses and Opportunistic Infections, CROI. The International Antiviral Society–USA. Boston. Estats Units. 4-7 març de 2018. (ABSTRACT 260).

14. Rodríguez de la Concepción ML, Marfil S, Molinos-Albert LM, Tarres F, Aguilar C, Clotet B, Blanco J, Carrillo J. **HIV Infection Leads to the Development of Neutralization-Interfering Antibodies that Hamper the Function of Neutralizing Antibodies**. HIVR4P 2018. Global HIV Vaccine Enterprise. Madrid. Spain. 21-25 octubre. Scholarship. Poster presentation.

15. Rosas-Umbert M. **Effect of the histone deacetylase inhibitor romidepsin on clinical trial BCN02-Romi**. EAVI2020 GAM. EU Consortium. Madrid. Spain. October 18th 2018. Scholarship EAVI2020. Invited speaker.

16. Ruiz A, Oscar Blanch-Lombarte, Esther Jimenez-Moyano, Beatriz Mothe, Ruth Peña, Meritxell Genescà, Philip Goulder, Richard Barnard, Bonnie Howell, Bonaventura Clotet and Julia G. Prado. **Potency of latency-reversing agents and CTL exhaustion balance the killing of HIV inducible provirus**. 22nd International Conference AIDS: Breaking Barriers – Building Bridges. International AIDS Society. Amsterdam. Holanda. 23-27 Juliol 2018. AIDS2018 Scholarship. Poster presentation.

17. Ruiz-Riol M, Oriol-Tordera B, Llano A, Mothe B, Pérez-Álvarez S, Galvez C, Berdnik D3, Martínez-Picado J, Ganoza C, Sánchez J, Gómez G, Clotet B, Wyss-Coray T, Brander C. **Communicome analyses identify the TNF/TRAIL receptor family as a potential determinant of virus control and CD4 T cells counts in natural chronic HIV infection**. European Congress of Immunology. European Federation of Immunological Societies. Amsterdam. Netherlands. September 2nd-5th, 2018. Poster presentation.

18. Salgado M, González V, Rivaya B, Gálvez C, Kwon M, Badiola J, Bandera A, Jensen B, Vandekerckhove L, Raj K, Nijhuis M, Diez JL, Wensing A, Martinez-Picado J. **HIV-seroreversion dynamics after allogeneic stem cell transplantation**. 23rd Conference on Retroviruses and Opportunistic Infections. Boston (MA, USA), Mar 4-7, 2018. Poster presentation #386.

19. Santos JR, Casadellà M, Noguera-Julian M, González J, Antela A, Portilla J, Sanz J, Gutiérrez M, Montero-Alonso M, Navarro J, Gutiérrez F, Mariño A, Ocampo A, Blanco JR, Pasquau J, Moreno S, Podzamczer D, Iribarren JA, Hernández Quero J, Knobel H, Force L, and Paredes R, on behalf of the INSTINCT study group. **Sustained Virological Suppression under INSTI first line ART in HIV-1 infected subjects with transmitted INSTI resistance**. XXVII International Workshop on HIV Drug resistance and treatment Strategies, October 22 to 23. 2018, Johannesburg, South Africa. (Abstract 27).

20. Serra-Moreno R, Colomer-Lluch M, Castro-González S. **BCA2 hinders HIV transcription and enforces proviral latency by blocking NF-Kb.** American Society for Virology's (ASV) 37th Annual meeting. American Society for Virology. University of Maryland, Maryland. USA. July 14-18. Oral Presentation (Dra. Serra-Moreno).

21. Serra Peinado C, Grau-Expósito J, Genescà M, Luque-Ballesteros L, Gálvez C, Castellví J, Willekens R, Montaner L, Falcó V, Martinez-Picado J, Buzón MJ. **Productive HIV-1 infection upregulates CD32 in vitro and in vivo**. 23rd Conference on Retroviruses and Opportunistic Infections Boston (MA, USA), Mar 4-7, 2018. Poster presentation #390.

22. Wensing A, Bosman K, Bruns A, Ellerbroek P, de Jong T, Tesselaar K, Stam A, Salgado M, Hutter G, Brosens L, Kwon M, Diez Martin J, Boelens J, Martinez-Picado J, Kuball J, Nijhuis M, IciStem Consortium. **Dominant HIV DNA populations present in different T-cell subsets before stem cell transplantation persist in tissues early after transplantation with CCR5Δ32 stem cells**. Oral presentation (TUAA0203). 22nd International AIDS Conference Amsterdam (the Netherlands), 23-27 July 2018.

Invited talks

1. Brander C. **What defines a protective T cell response to HIV?** HIVR4P International AIDS Society. EAVI2020. 21-25 October 2018. Invited session talk.

2. Brander C. **A human focused approach to T cell immunogen design**. HIVR4P International AIDS Society. EAVI2020. October 22nd 2018. Madrid, Spain. Invited satellite symposium talk.

3. Brander C. **Vaccines Against HIV: Current Development and Future Perspective**. 28th Annual Meeting of the ECCMID. ECCMID. Madrid. Spain. April 21st 2018. Invited session speaker.

4. Brander C. **Autologous T cell Immunogen design**. Autors: HIVACAR GAM EU Consortium October 26th 2018. Madrid. Beca: HIVACAR. Invited speaker.

5. Brander C. **Current challenges in HIV vaccine development**. Seminar Series Catalan Society for Immunology. SIC. Barcelona. Spain. October 24th 2018. Invited seminar series talk. Invited speaker.

6. C. Brander. **Claus per Bioemprendre 2018**. Biocat Claus per Bioemprendre 2018. Biocat. Barcelona. Spain. May 24th 2018.

7. Coll J. **HIV PrEP**. 4th Central and Eastern European Meeting on Viral Hepatitis and HIV Virology Education. Prague. Czech Republic. October 12th 2018. Invited session talk.

8. Coll J. **HIV prevention and the rol of integrase inhibitors**. HIV Clinical Forum Sociedade Brasileira de Infectologia and Virology Education. Rio de Janeiro. Brazil, August 22th 2018. Invited session talk.

9. Izquierdo-Useros N. **The role of dendritic cells during HIV-1 infection: viruses as DC riders.** University of Copenhagen. Faculty of Health and Medical Sciences, Department of Immunology and Microbiology. Annual Meeting 2018 Immunology and Infectious Diseases. Helsingør, Denmark, Aug 22-24, 2018. Invited lecture.

10. Izquierdo-Useros N. **¿Qué sabes del VIH/sida?** Cosmocaixa Sevilla Sevilla (Spain), 20 Feb, 2018.

11. Izquierdo-Useros N. **¿Qué sabes del VIH/sida?** Centro Penitenciario Brians 2. Tarragona, 27 Noviembre, 2018.

12. Martínez-Picado J. **Allogeneic stem cell transplantation. L'approccio multidisciplinare nella cura dei linfomi HIV-associati**. Milan (Italy), November 9, 2018. Invited Keynote Speaker.

13. Martínez-Picado J. **Making HIV cure a reality: what separates us from a cure?** HIV Standalone 2018. Amsterdam (Netherlands), June 7, 2018. Invited Keynote Speaker.

14. Martínez-Picado J. **HIV persistance and approaches to cure**. Mauro Moroni Memorial Lecture. 10th Italian Conference on AIDS and Antiviral Research. Rome (Italy), May 22, 2018. Invited Speaker.

15. Martínez-Picado J. **Functional cure vs. eradication: will it be feasible?** 28th European Congress of Clinical Microbiology and Infectious Diseases. Madrid (Spain), April 21, 2018. Invited speaker.

16. Paredes R. **Effect of an HIV therapeutic vaccine on The skin & gut Microbiome**. The Barcelona Debates on the Human Microbiome 2018, Barcelona, Catalonia, Spain. 21 June 2018.

17. Roger Paredes. **Mechanisms of Resistance to 2nd geneneration instis**. XXVII International Workshop on HIV Drug Resistance / Treatment Strategies, 22-23 October, Johannesburg 2018. 22 October 2018. Invited speaker.

18. Paredes R. **Resistance Characteristics of HIV Integrase Inhibitors.** HIV Clinical Fora Series Brazil: Integrase Inhibitors 2018, Sao Paulo, Salvador de Bahia, Rio de Janeiro, Belo Horizonte, PortoAlegre, Brazil. 19-23 May 2018.

19. Paredes R. **New technologies for testing of DR HIV**. World health Organization European Laboratory Initiative (ELI) on TB, HIV and viral Hepatitis Core Group meeting, Copenhaguen, Denmark. 1st November 2018.

20. Paredes R. **Resistències del VIH als antiretrovirals: Iimplicacions clíniques i de salut pública**. Jornada de Salut Internacional a la Metropolitana Nord, Barcelona, Catalonia, Spain. 15 june 2018.

21. Paredes R. **The gut microbiome in HIV infection**. Gilead Headquarters, Foster City California USA. 15 October 2018.

22. Paredes R. **Resistance to Integrase Inhibitors -What Clinicians Need to Know**. European HIV Clinical Forum 2018, Glasgow, UK. 27 October 2018.

23. Paredes R. **The microbiome in HIV Immunopathogenesis**. Hot topics in HIV: Vaccines, Immune recovery and Eradication, Barcelona, Spain. 18 October 2018.

22. Paredes R. **The gut microbiome in infectious diseases: opportunities and challenges**. The challenge of MDR and XDR infections European HIV Clinical Forum 2018, Barcelona, Spain. 14 September 2018.

23. Rivera-Pinto J. **Introducción a los splines con penalizaciones**. Sociedad Española de Biometría. Bilbao, Spain. 18/1/2018.

24. Rivera-Pinto J. **Hands on workshop on git and github for software development**. Universitat de Vic - Universitat Central de Catalunya. Vic. 3/5/2018.


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