IrsiCaixa
Institut de Recerca de la Sida

Obra Social "la Caixa"

Generalitat de Catalunya
Departament de Salut

IRSICAIXA

SCIENTIFIC REPORT

2016

Contents

About 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 and emerging infectious diseases.

IrsiCaixa was created as a private non-profit foundation in 1995 with the support of Obra Social "la Caixa" and the Department of Health of the Generalitat 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. This transfer of knowledge between the various stakeholders with an interest in HIV leads to novel solutions that facilitate progress towards eradication of this disease.

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

IrsiCaixa also participates in clinical trials to evaluate novel therapeutic strategies and actively cooperates with low-income countries in the global fight against the pandemic. It places special emphasis on the formal training of young scientists, on innovation and on the transfer of knowledge generated in its laboratories.

Letter from the Director

During **2016**, **IrsiCaixa** retained its position as an international reference centre for research into HIV/AIDS. In carrying out quality, translational, multidisciplinary and collaborative research, **IrsiCaixa** is one of the few centres in the world with the capacity to develop all the lines considered fundamental to eradicating HIV/AIDS and set as priorities by the US National Institutes of Health.

In a coordinated, planned and strategic manner, the different **IrsiCaixa** research groups continue to make key contributions by advancing in various key HIV research areas (updated this year), namely: prevention, eradication and functional care; the microbiome; novel treatments and resistance to antiretrovirals; immunopathogenesis; and other diseases.

IrsiCaixa is unique in how it brings together a wide range of expertise in a single centre —ensuring synergies between advances in the different research areas and so creating a unique value-added chain— while simultaneously participating as a member of the most prestigious international scientific and healthcare agencies, including the WHO, the International AIDS Society, the Towards an HIV Cure programme and the International AIDS Vaccine Initiative.

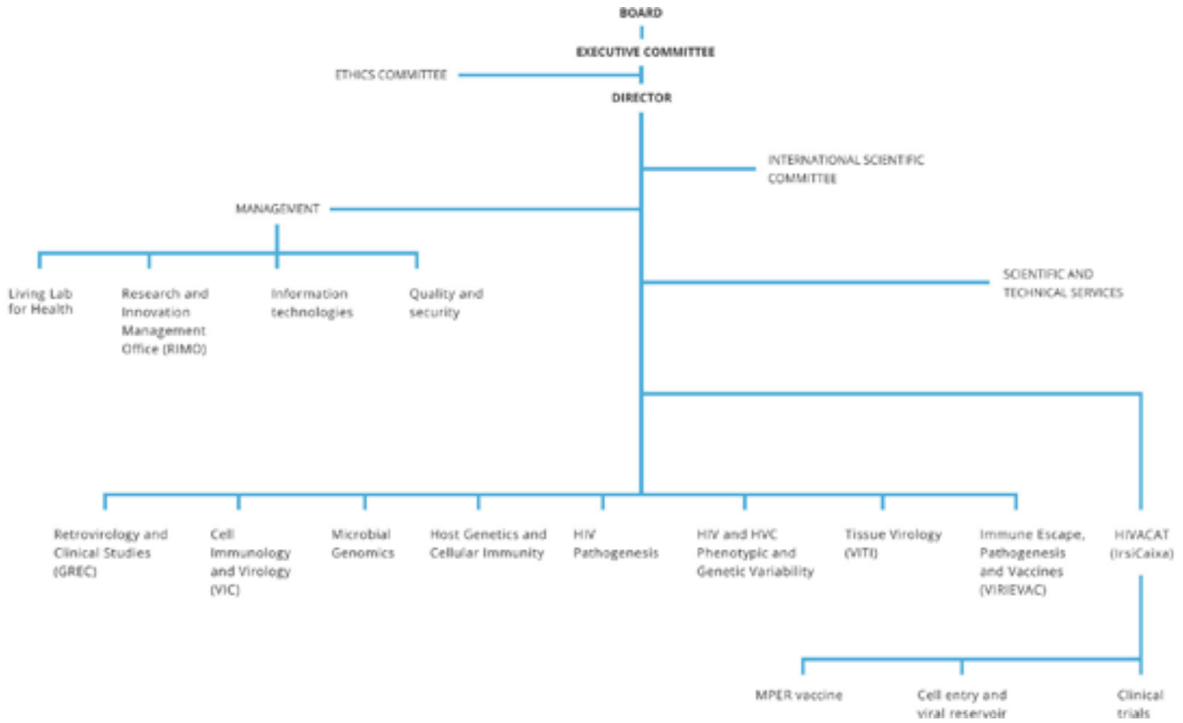
IrsiCaixa collaborates actively with the best HIV research centres worldwide, includes some of the top international scientists in our International Scientific Committee and works closely with the Infectious Diseases and the HIV/AIDS Units of the Germans Tries i Pujol University Hospital, as well as with other national and international clinics. Also noteworthy is the support received, since 2015, from the Glòria Soler Foundation for the development of innovative and strategic studies.

To ensure that our research results benefit patients, as part of our commitment to innovation and technology transfer, this year we created a second spin-off that has attracted investment from a leading international pharmaceutical company.

Finally, crucially important for our centre is its continued commitment to initiatives in the field of Responsible Research and Innovation (RRI) and health education, designed to enable us to progress towards a new quadruple-helix model of innovation. As pioneers in this field in Spain, over the course of this year we have given courses and lectures on RRI and have provided advice to some 1,400 professionals in Spain and Europe. We are also proud of our Living Lab for Health, created to ensure that we maintain an open dialogue with our various stakeholders so as to be able to better meet their needs and expectations. Living Lab was created under the auspices of a wide range of European projects, through collaboration with other research centres and with support from Obra Social "la Caixa" and the Amgen Foundation.

Bonaventura Clotet
IrsiCaixa Director

Organizational Structure



Board

President
Head of the Generalitat de Catalunya department responsible for health policy
Hon. Antoni Comín i Oliveres

Vice-president
Appointee of the Fundació Bancària "la Caixa"
Josep Vilarasau i Salat

Members
Appointee of the Director of the Catalan Health Service (CatSalut)
Joan Serra i Manetas

Appointee of the Generalitat de Catalunya department responsible for research
Iolanda Font de Rubinat Garcia

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Joan Guix i Oliver
Antoni Andreu Périz
Jordi Casabona i Barbarà
Manel Puig Domingo

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Jaume Giró i Ribas
Jaume Lanaspa Gatnau
Esther Planas i Herrera
Jordi Portabella i Calvete
Marta Casals i Virosque

Representatives of the Fight AIDS Foundation
Montserrat Pinyol i Pina
Anna Veiga i Lluch

Secretary
Marta Casals Virosque

Executive Committee

For Fundació Bancària "la Caixa"
Esther Planas i Herrera (President)
Marta Casals i Virosque (Secretary)
Jordi Portabella i Calvete

For the Generalitat de Catalunya department responsible for health policy
Jordi Casabona i Barbarà
Manel Puig Domingo
Antoni Andreu Périz

Director

Bonaventura Clotet

Financial Manager

Lourdes Grau

Administration
Arnau Creus
Cristina Mesa
Penélope Riquelme

Information Technologies
Julián Eslava

International Scientific Committee

Dr. Brigitte Autran
Professor of Medicine (Immunology) at the Pierre and Marie Curie University (UPMC) (Paris, France) and Director of the Department of Immunology 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. Danniel Kuritzkes
Professor of Medicine at Harvard Medical School (USA), Director of AIDS Research at Brigham and Women's Hospital (USA) and Co-Director of the NIH-funded AIDS Clinical Trials Group.

Dr. Jim Mullins
Professor at the University of Washington (Seattle, USA).

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

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


eppendorf
Centrifuge 5810 R

Key Figures

Total **staff**

75

By sex

72% ♀

28% ♂

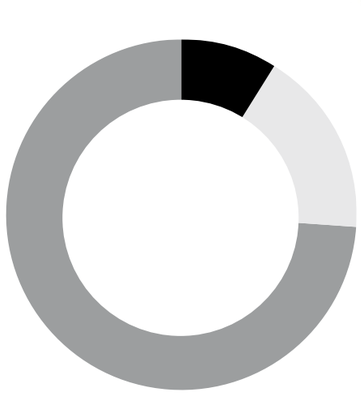
Funding

32 public

35 private

8 external

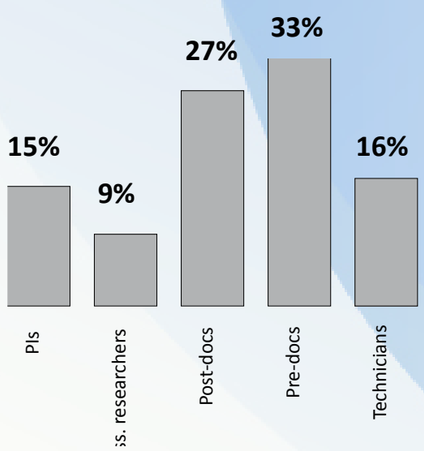
Staff by **categories**



Research Administration and Support **17%**

Scientific and Technical Services **9%**

Research staff **74%**



Theses read 2016

4

Retrovirology and Clinical Studies (GREC) **2**

Cell Virology and Immunology (VIC) **1**

Microbial Genomics **1**

Publications 2016

98

Awarded **projects** 2016

23

Highlights 2016

January

AlbaJuna Therapeutics SL, with funding from Grifols, is created to develop therapeutic antibodies against HIV.

February

Publication of the first study of the gut microbiome in HIV+ patients, showing that this infection is associated with reduced bacterial diversity.

March

The prestigious Mathilde Krim Fellowship is renewed for **IrsiCaixa** associate researcher **Nuria Izquierdo**.

A new website is launched for the Xplore Health educational project aimed at promoting health, which receives some 10,000 monthly visits.

April

IrsiCaixa Director, **Dr. Bonaventura Clotet**, is distinguished with the Creu de Sant Jordi of the Generalitat of Catalonia.

May

First meeting of the Crossroads Programme of Clinical Research Applied to AIDS, organized by the Retrovirology and Clinical Studies group as a forum for exchanging experiences in applied research in HIV and other biomedical specialties.

June

Some 350 students participate in the conference on the RRI Sana Ment (Healthy Mind) educational and participatory project.

IrsiCaixa, Obra Social "la Caixa" and Biocat jointly organize the second edition of the *Barcelona Debates on the Human Microbiome. From Microbes to Medicines*, led by **Bonaventura Clotet** and **Roger Paredes**.

Javier Martínez-Picado is invited to give a talk at the ASM Microbe Meeting in Boston, with 12,000 attendees.

July

The Glòria Soler Foundation signs two agreements with **IrsiCaixa** to develop a research project each on the microbiome and HIV eradication.

Julia García Prado makes an oral presentation at the Towards an HIV Cure symposium in Durban (South Africa).

Maria Pino, from the Retrovirology and Clinical Studies group (GREC), is awarded her PhD *cum laude*.

Luis Molinos, from the Virology and Cellular Immunology (VIC) group, is awarded his PhD *cum laude.*

August

Nature Communications publishes a study demonstrating the existence of a mutation that blocks one of the HIV mechanisms for spreading infection in the body.

September

Sara Morón-López, from the Retrovirology and Clinical Studies group (GREC), is awarded her PhD *cum laude.*

October

IrsiCaixa launches a new website.

Maria Casadellà, from the Microbial Genomics group, is awarded her PhD *cum laude.*

November

Scientists involved in the European AIDS Vaccine Initiative (EAVI2020) consortium meet in Barcelona to analyse their first year's results, at an event organized by **IrsiCaixa**.

Symposium — *What will it take to end HIV in Africa? Fighting the emerging HIV drug resistance epidemic* — organized by **Roger Paredes** and participated in by Silvia Bertagnolio, Head of the WHO HIV Drug Resistance Program.

Julià Blanco (VIC) summarizes progress over the previous year in basic research into HIV in the closing speech of the GESIDA conference in San Sebastián.

December

The RRI Tools project, via which **IrsiCaixa** trained 3,100 research and innovation professionals in responsible research and innovation, concludes.

Research Groups

Viral Immune Evasion and Vaccines (VIRIEVAC)

Networks
- Thematic AIDS Research Network (ISCIII RETIC RIS RD12/0017/0002)
- Recognized Group SGR2014/211
- Clinical and Basic AIDS Research Group
- Member of the American Society for Microbiology **(JGP)**
- Member of the International AIDS Society **(JGP)**

Projects
Combined use of vaccines and immune checkpoint blockers to boost CTL activity against the HIV-1 reservoir.
Funding body(ies): MDS
Jan 2017- Apr 2018
Research supervisor(s): **Julia García Prado**

Mechanisms of paediatric non-progression in HIV infection.
Funding body(ies): Gilead
Jan 2016- Jan 2018
Research supervisor(s): **Julia García Prado**

Scholarships and grants
Alba Ruiz de Andrés
Funding body(ies): International AIDS Society
Young researcher scholarship to attend the HIV Cure Symposium (Durban, South Africa)

Julia García Prado
Funding body(ies): International AIDS Society
Young researcher scholarship to attend the HIV Cure Symposium (Durban, South Africa)

Julia García Prado
Funding body(ies): Spanish National AIDS Network
Scholarship to attend GESIDA meeting 2016 (San Sebastián)

Oscar Blanch Lombarte
Funding body(ies): Spanish National AIDS Network
Scholarship to attend GESIDA meeting 2016 (San Sebastián)

Principal investigator

Julia García Prado
jgarciaprado@irsicaixa.es

Dr. Prado has a degree in Biochemistry and a PhD in Immunology (2005) with honours from the Autonomous University of Barcelona (UAB). In 2006 she received a prestigious Marie Curie (ERC) grant to carry out research at the University of Oxford (UK). In 2010 she was awarded a Miguel Servet contract (ISCIII), recently renewed, placing her among the top ten national researchers in Spain. Since 2010 she has been supervisor of undergraduate and postgraduate students at different universities and, since 2011, has taught on the University Master's in AIDS Pathogenesis and Treatment. She is a reviewer for a number of international scientific journals (*PlosPathogens, Retrovirology, Antiviral Therapy*) and for the South African Medical Research Council and the Carlos III Health Institute (ISCIII). She has contributed 34 articles to international scientific journals (H-index 17) and 54 presentations at national and international conferences.

Team
Post-doc researcher(s)
Alba Ruiz de Andrés

Pre-doc researcher(s)
Óscar Blanch

Laboratory technician(s)
Esther Jiménez
Ruth Peña

Presentation
Our group was established in early 2013 with the aim of identifying patterns of viral evasion from host immunity and determining the implications for infectious disease progression. The group's primary research focus is HIV-1, a virus characterized by its great adaptive ability exercised through multiple strategies of evasion against host immunity. This evasive ability is a major obstacle to the design and development of new drugs and vaccines. Our challenge is to discover mechanisms of viral evasion from immune response by identifying new viral factors and key immune mechanisms.

Our group has developed three main lines of research to date: (1) mechanisms of HIV-1 infection immune evasion in extreme progression phenotypes; (2) identification of cellular responses during antiretroviral treatment of HIV-1 infection so as to optimize the design of new vaccines against HIV-1; and (3) identification of immune mechanisms and application to the control of persistent viral infections.

The results of these studies are crucial for the development of new therapeutic strategies and drugs aimed at controlling and curing HIV-1 infection. All our projects — strongly multidisciplinary and with translational potential for clinical practice — tackle the interconnection between molecular virology and cellular immunology.

2016 milestones
Milestones in the past year within IrsiCaixa's strategic lines were as follows:

1. Immunopathogenesis: viraemic studies of elite controllers and non-progressors
— Elite HIV-1 controllers (in collaboration with the Pasteur Institute in Paris and with funding from the French ANRS). This line has resulted in a publication (Noel et al, JVI, 2016) and a co-authored publication (Koofhethile et al, JVI 2016).
— Viraemic non-progressors. This project, funded through a Gilead fellowship program (GLD15/00298), aims to understand non-pathogenic HIV-1 infection so as to be able to design new immunotherapies.

2. Prevention, eradication and functional cure
This year has seen the continuation of two funded projects (PI14/01058 and MDS LKR 136618) and the recruitment of a pre-doctoral researcher. In vitro models of HIV-1 reactivation have been implemented to analyse the functionality of CD8+ response regarding elimination of the viral reservoir in the presence of latency reactivating molecules. These studies, which have attracted the interest of the international scientific community, have resulted in two oral presentations at the Towards an HIV-1 Cure Symposium (Durban, South Africa) and GESIDA (San Sebastian, Spain). Our studies indicate that agents that reactivate HIV-1 latency induce specific immune recognition of the reactivated cells. We are currently preparing an article and evaluating the innovation component in our methodology. We are also evaluating the role of cellular restriction factors in controlling the viral reservoir and improving the immune response to HIV-1. This work has been published (Jimenez-Moyano et al, JVI, 2016) and has been presented at the 21st IAS Meeting.

Perspectives for 2017
— Establishment and consolidation of the research team and incorporation of new staff.
— Continuation of existing lines of research and advancing in the identification of natural infection control mechanisms, with a view to developing new immunotherapies and, through improving cellular response, investigating possible drugs to control or eliminate the viral reservoir.
— Expansion of funding for our emerging group of young researchers.

Alba Ruiz de Andrés
Funding body(ies): GESIDA Viif Scholarship to attend GESIDA meeting 2016 (San Sebastián)

Awards and recognition
- External PhD examiner for the University of KwaZulu-Natal (South Africa) **(JGP)**
- Evaluation of HR Grants Monitoring actions for the Carlos III Health Institute (ISCIII) **(JGP)**

Master's theses
Title: *Genotypic and phenotypic characterization of HIV-1 during virological failure to Protease inhibitors in monotherapy*.
Name: **Óscar Blanch**
Master's in AIDS Pathogenesis and Treatment.
Autonomous University of Barcelona (UAB)
Submitted: June 2016
Grade: Excellent

Microbial Genomics

Networks
- Thematic AIDS Research Network (ISCIII RETIC RIS RD12/0017/0002)
- EuroSIDA
- European Society of Antiviral Research (ESAR)
- WHO ResNet
- International Antiviral Society-USA (IAS-USA)
- Centre for Personalised Medicine Managing Infectious Complications in Immune Deficiency (PERSIMUNE)
- Recognized Group SGR2014/211
- Clinical and Basic AIDS Research Group

Projects
HIV and microbiome research programme.
Funding body(ies):
Glòria Soler Foundation.
Jul 2016 – Dec 2018
Research supervisor(s):
Roger Paredes

Precision-medicine platform based on development and clinical use of next-next generation sequencing (NNGS) applications and technology.
Funding body(ies):
Centre for Industrial Technological Development (CDTI)
Research supervisor(s): **Roger Paredes**

The DTGut Study: Restoring intestinal microbiome composition and function with dolutegravir vs. darunavir/ritonavir.
Funding body(ies):
ViiV HealthCare
Research supervisor(s):
Roger Paredes

Influence of the gut microbiome on HIV-1 eradication mediated by a kick-and-kill strategy (PI16/01421).
Funding body(ies):
Spanish Ministry of the Economy and Competitiveness

Principal investigator

Roger Paredes
rparedes@irsicaixa.es

Roger Paredes is a doctor in Medicine and Surgery from the Autonomous University of Barcelona (UAB). Funded by a post-doctoral scholarship from "la Caixa", he specialized in HIV resistance at Brigham & Women's Hospital and Harvard Medical School in Boston (USA). He has demonstrated the clinical utility of new methods of sequencing HIV in both high- and low-income countries. He is a member of the WHO HIV ResNet Steering Group (the principal advisory group to WHO in the field of resistance) and a member of the International Antiviral Society-USA, which annually publishes an international reference list of antiretroviral resistance mutations. He is co-creator of the Rega algorithm for interpreting resistance to antiretrovirals, has participated in updating the algorithm at Stanford University and is a virologist to the EuroSIDA European cohort. His Microbial Genomics group does pioneering research into the role played by the gut microbiome in HIV infection pathogenesis and chronic inflammation. He combines his research with a medical care role in the HIV Unit of the Germans Trias i Pujol University Hospital.

Team
Associate researcher(s)
Marc Noguera

Post-doc researcher(s)
Yolanda Guillén

Pre-doc researcher(s)
Maria Casadellà
Muntsa Rocafort
Javier Rivera

Laboratory technician(s)
Mariona Parera

Computer technician(s)
Cristina Rodríguez

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 chronic inflammation.
— 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.
— We investigate how the gut microbiota affects the development of the frailty syndrome in elderly individuals not infected with HIV.

2. 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.

3. Defining HIV-1 global clinical epidemiology
We work with leading European clinical cohorts (ESAR and EuroSIDA) and with African and American research groups to understand the effects of the virus on response to treatment, clinical progression to AIDS and death.

2016 milestones and perspectives for the future
During 2016, our group continued to advance knowledge regarding causes and clinical and health implications of resistance to antiretrovirals. We also progressed in the study of the microbiome and HIV pathogenesis.

1. Resistance to antiretrovirals
— Translational research. In collaboration with Harvard Medical School, Emory University School of Medicine and the University of KwaZulu-Natal, we have demonstrated by massive sequencing that over 70% of people who fail to respond to treatment with tenofovir in South Africa have high-level resistance to this drug and accompanying treatments. The effectiveness of second-line treatments is thus compromised and more toxic or more expensive drugs need to be administered. This epidemic of resistant viruses compromises the ability to eliminate HIV/AIDS in the medium-term in low- and middle-income countries.
— Bioinformatics. In partnership with the Barcelona Supercomputing Centre, we have developed a method for estimating resistance to protease inhibitors that is also applicable to new inhibitors.
— Public health and policy. Our group participates in the WHO HIV ResNet Steering Group and the Global Action Plan on HIV Drug Resistance 2017-2021, which, in 2017, will set overall guidelines for HIV prevention and development of HIV-resistant drugs . We also participate in the Consultation on Global Trends of HIV Drug Resistance initiative and have started work on addressing research gaps in resistance to HIV in low- and middle-income countries.

2. Microbiome
— We published the first global evidence that gut microbiota may be influenced by sexual practices. Demonstrated in 240 patients in two cohorts in Barcelona and Stockholm was the predominance of *Prevotella* mainly in MSM with a significantly richer and more diverse microbiome than non-MSM. The fact that HIV infection is associated with less richness and diversity has been confirmed for subsequent international cohorts. Via shotgun metagenomics, we have worked on characterizing the microbiome by species and on determining microbial function in people with and without HIV-1.
— Thanks to the Glòria Soler Foundation, we have worked on developing new diagnostic markers of chronic inflammation and intestinal dysbiosis in HIV-infected persons and on new probiotic candidates. Interaction between the microbiome and kick-and-kill strategies to eradicate HIV is being investigated, as well as the impact of antiretroviral therapy on the microbiome.

Carlos III Health Institute (ISCIII)
Jan 2017- Dec 2019
Research supervisor(s): **Roger Paredes**

Investigation and development of a new therapy for gut microbiome reconstruction in patients with HIV (RTC-2016-5223-1).
Funding body(ies):
Spanish Ministry of the Economy and Competitiveness
Jan 2017- Dec 2018
Research supervisor(s): **Roger Paredes**

Awards and recognition
Professional Excellence Award for Biomedical Research. Official College of Physicians Barcelona (**RP**)

Doctoral theses
Title: *Next-generation virus genotyping for HIV-1 surveillance and clinical management.*
Author: **Maria Casadellà**
Defended: 28 Oct 2016
Autonomous University of Barcelona (UAB)
Director(s): **Roger Paredes**
Grade: *Cum Laude*

Host Genetics and Cellular Immunity

Networks
- Thematic AIDS Research Network (ISCIII RETIC RIS RD12/0017/0002)
- Recognized Group SGR2014/211

Projects
HIVACAR.
Funding body(ies): European Commission
Jan 2017 - Dec 2021
Research supervisor(s): **Christian Brander**

BCN02-Romi clinical trial on eradication.
Funding body(ies): Glòria Soler Foundation
1 Jul 2018 - 31 Dec 2018
Research supervisor(s): **Beatriz Mothe**

Awards and recognition
- Member of the ACTG focus group on therapeutic HIV vaccines, funded by the US NIH **(CB)**
- External consultant for the PEEACHI project for developing HCV vaccines funded by the EU **(CB)**
- Grants to attend the Chicago R4P Meeting **(MR)**

Master's theses
Author: **Jesús Poch**
Changes in the degree of methylation at the DNA level with implications for protein expression due to HIV infection leading to possible infection control.
University Master's in AIDS Pathogenesis and Treatment (UAB)
Tutor(s): **C. Brander** and **M. Ruiz**

Author: **Bruna Oriol**
Exploring HLA-II associations with HIV disease progression markers.
University of Vic-Central University of Catalonia (UVic-UCC).
Tutor(s): **Alex Olvera** and **Malu Calle**

Principal investigator

Christian Brander
cbrander@irsicaixa.es

Christian Brander graduated from the University of Bern (Switzerland) in 1994 with a PhD in Immunology, having studied exogenous antigen re-presentation and HLA- and T-cell-mediated hyper-reactivity to penicillin. He spent the next 13 years at Harvard University, where he focused on cellular immunity to viral infections and the impact of host genetics on the immune response. A senior Institute for Research and Advanced Studies (ICREA) research professor since 2008, he has continued his research into host genetics and cellular immunity to viral infections, including HIV, HCV and herpesviruses such as EBV and KSHV. He is curator of the Los Alamos HIV Immunology database, scientific director of the Catalan HIVACAT programme for the development of effective preventive and therapeutic HIV vaccines and an associate lecturer at the University of Vic-Central University of Catalonia (UVic-UCC). Dr. Brander was rated among the most highly cited researchers of 2014 and 2015 by Thompson Reuters.

Equip

Associate researcher(s)
Beatriz Mothe

Post-doc researcher(s)
Samandhy Cedeño
Anuska Llano
Marta Marszalek
Alex Olvera
Marta Ruiz Riol
Sandra Silva Arrieta

Pre-doc researcher(s)
Miriam Rosás
Bruna Oriol

Clinical cohort coordinator(s)/clinical researcher(s)
Josep Coll

Presentation
Our focus is the study of cellular immunity against viral infections in hosts with compromised immunity. One of our main activities is to identify biological HIV control markers and determine how to translate these into rational preventive and therapeutic vaccine designs. Our group has implemented a number of ex-vivo immunological analyses in samples taken from individuals infected by HIV and individuals with different disease control profiles. As a result, we have developed an immunogen as a therapeutic vaccine and created a spin-off, Aelix Therapeutics, to lead the clinical development of this vaccine platform. These studies are further complemented by analyses of individuals exposed to HIV who have remained uninfected and of individuals who have been closely monitored from the pre-infection to the chronic infection stages. All this has helped to identify potential markers related to neurofunctional defects, leading to a new line of research aimed at identifying molecular signals associated with HIV control and neurofunction.

We also study factors that may govern the evolution of HCV in liver transplant patients. These include host genetic factors of donors and recipients and the immune response of the transplanted liver to the re-infecting virus. A kidney transplant model is used to determine the effects of ablative treatment on pre-transplant conditioning in the repertoire of post-transplant T-cells and to evaluate how this repertoire contributes to the control of opportunistic infections, including pathogens such as EBV and KSHV, associated with the development of post-transplant lymphoproliferative diseases and other malignant disorders.

2016 milestones and perspectives for the future
During 2016 significant progress was made in the clinical study of the HTI immunogen within the HIVACAT project. Clinical batches of the DNA.HTI and MVA.HTI vectors were produced in GMP conditions and toxicity studies were conducted of these vectors in a combined vaccination regimen. A request for authorization of the corresponding clinical trial has been submitted to the AEMPS. The fact that we have started producing HTI expressed in a chimpanzee adenovirus vector means that, in the near future, we can commence clinical trials to compare different administration regimens in terms of response stimulation and amplification.

In 2016, we ran a clinical trial in Lima (Peru) to compare the immunogenicity of the MVA-B vaccine candidate for intramuscular versus transcutaneous administration. The intervention, which was safe and well tolerated, resulted in activation of innate immunity mechanisms. Results regarding adaptive immunity vaccination, due in mid-2017, are expected to also include useful data on microbiota in faeces and skin samples that will enable evaluation of the link with vaccine immunogenicity. The Peru cohort has also been studied in terms of obtaining a better understanding of viral evolution for this particular genetic background and ethnicity. These studies have identified new HLA class I and class II alleles associated with relative viral control and slowed or accelerated disease progression and have also identified new response targets for T-cells restricted by HLA class II.

In 2016, thanks to the Glòria Soler Foundation, we launched the BCN02 clinical trial — a follow-up to BCN01 — in which HIV-positive individuals in early treatment received an additional vaccination as well as treatment designed to reactivate the dormant virus. The intervention proved safe and the initial results, obtained at the end of 2016, revealed partial control of viral replication in subjects who discontinued treatment. These encouraging results are expected to be confirmed for the remaining subjects during 2017.

Progress has also been made in identifying plasma soluble factors associated with infection control, whose expression is epigenetically regulated as a result of HIV infection. These results have originated several lines of research, including studies of molecular mechanisms with direct anti-viral action, immunomodulator actions and the impact of host restrictive factors on viral replication and infectivity. Cytokine IL27 and its specific receptor have been found to be positively associated with viral load and, more importantly, with the size of the viral reservoir. Levels of IL27 have also been related to the potency of the antiviral T-cell response. This first study that relates a plasma soluble biomarker with host immunity and the size of the viral reservoir offers great promise in terms of predicting viral control for therapeutic vaccine strategies. Especially interesting is the identification of genetic fingerprints linked to control that have important implications for the neurofunction. Since HIV is associated with accelerated ageing and greater neural dysfunction, our aim is to continue research into these issues. For these studies, our group works with two local cohorts of HIV-infected individuals and also uses samples of blood and spinal fluid obtained from San Francisco.

Research into liver transplant patients has enhanced knowledge of viral evolution in HCV-infected individuals and of the impact of host genetic factors on survival or organ rejection. Our studies have been extended to identify factors associated with liver fibrosis and dysfunction and to investigate these markers in transplanted individuals with chronic HCV infection, irrespective of whether they are co-infected or not with HIV. Extension was possible because of a collaboration agreement with a Cape Town (South Africa) centre where HIV-infected people receive kidneys from donors who also have HIV. This first worldwide cohort of HIV-positive to HIV-positive transplant patients offers a unique opportunity to study virological and immunological parameters in this context. Our data indicate that HLA coincidence or discrepancy can be used to predict organ rejection, with the presence of single-nucleotide polymorphisms associated with higher levels of rejection in the HIV/HCV co-infected cohort. This conclusion may have high translational value in that it may aid decisions as to the best organ to transplant, thereby reducing rejection and improving liver transplantation outcomes.

HIV Pathogenesis

Networks
- Thematic AIDS Research Network (ISCIII RETIC RIS RD12/0017/0002)
- Recognized Group SSGR2014/121
- HIV pathogenesis

Awards and recognition
- Presidency of the International Society for Antiviral Research (2016-2018) **(JE)**
- FI-Gencat Grant 2016-2018 **(EG)**

Projects
The HIV Persistent Cell Encyclopaedia.
Funding body(ies): Spanish Ministry of the Economy and Competitiveness. 2016-2018
PIs: **Eva Riveira** and **José Esté**

Papillofactor.
Funding body(ies): Carlos III Health Institute (ISCIII) 2016–2018
Research supervisor(s): **José Esté** and Guillem Sirera

Innate immunity to HIV.
Funding body(ies): Carlos III Health Institute (ISCIII) 2017–2019
Research supervisor(s): **José Esté** and **Bonaventura Clotet**

Granted patents
Title: Human helicase ddx3 inhibitors as therapeutic agents.
Inventor(s): Meyerhans A, Martínez Delasma, Brai A, Fazi R, Tintori C, Botta M, **Esté J**, **Martínez MA**
Patent number: WO2016128541A1
Date granted: 18 Aug 2016
Institution(s): Azienda Ospedaliera Univesitaria Senese

Master's theses
Title: *ADAR1 regulates innate immune activation and HIV—1 replication in primary macrophages*
Author: **Maria Pujantell**
Master's in AIDS Pathogenesis and Treatment, UAB
Submitted: May 2016
Grade: Excellent

Principal investigator

José Esté
jaeste@irsicaixa.es

Our laboratory focuses on the study of cofactors associated with HIV-1 infection and the relationship with AIDS pathogenesis. **Dr. Esté**, with a degree in Medical Sciences from the Katholieke Universiteit Leuven, has directed 13 doctoral theses in the last ten years, has filed four patents in the last five years and has participated in the publication of over 160 papers. His research group has received external funding since 1999, including under national and European projects and contracts with pharmaceutical companies.

He is Chairperson of the International Society for Antiviral Research and participates in the organization of various international meetings. He is the editor of *Antiviral Research* and a member of the editorial boards of *Antimicrobial Agents and Chemotherapy* and the *Journal of Biological Chemistry*, among others. He acts as an expert consultant to the Research Executive Agency of the European Commission and participates in various international project evaluation panels.

Team

Associate researcher(s)
Ester Ballana

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

Pre-doc researcher(s)
Edurne García
Maria Pujantell

Presentation
The HIV Pathogenesis laboratory focuses on main lines of research as follows:

1. Identification of new cellular cofactors of 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, including the identification and validation of new targets, the monitoring of drugs approved for treatment and technology transfers through reports to pharmaceutical companies or patent registration.

2. Study of viral entry and between-cell transfer mechanism
HIV needs cell activation and inter- and intracellular signalling mechanisms to ensure productive replication and the establishment of chronic infection. Chemokines and other cytokines induce maturation, survival and proliferation of lymphocytes that serve as a target for HIV and, at the same time, regulate the expression of the chemokine receptors, CXCR4 or CCR5, which act as the main co-receptors of HIV entry and intracellular signalling that leads to cell death induced by the virus. In the entry process, and particularly in cell-to-cell transmission, different receptors play a key role. Chemokines and cytokines modulate expression in the cell surface and the cell activation necessary for viral replication. The aim of our group is to deepen understanding of the mechanisms of interaction between HIV and the target cells admitting HIV entry, as well as the subsequent process of viral replication.

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 viral infection cellular 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) are 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. We propose to study the expression of HIV infection cofactors modulated by early infection events or reactivation of HPV in infected cell models and in patients coinfected to varying degrees. Our project results will provide the foundations for new treatment strategies, prophylaxis and the prevention of sexually transmitted viral infections.

2016 milestones
A significant effort has been invested in applying for and obtaining competitive funding to improve the quantity and quality of the scientific output of our group and to acquire more staff. The group has received ongoing funding from the Secretariat of State for Research, Development and Innovation of the Spanish Ministry of the Economy and Competitiveness over the last 20 years. In 2016, two further research projects were approved (Spanish Ministry of the Economy and Competitiveness and Carlos III Health Institute (ISCIII)) to add to the two existing projects with external funding. All our researchers are funded or are principal investigators of a project.

This past year was also one of encouragement and recognition for our group in other ways. **Dr. Esté** continues to be an expert advisor to the Research Executive Agency of the European Commission and Chairperson of the International Society for Antiviral Research.

Perspectives for the future
Basic research is and will continue to be a cornerstone in generating the necessary knowledge to uncover 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 the mechanisms of action and their possible role in the formation of viral reservoirs in patients. Preliminary results enable possible therapeutic targets to be established that will limit or reduce the viral reservoir and induce immunity to HIV and which, furthermore, may even assist in the eradication of HIV. Based on these preliminary results, the group is confident that it will be able to contribute important findings in terms of understanding HIV/AIDS immunopathogenesis and establishing new therapy and immune reconstitution alternatives.

Retrovirology and Clinical Studies (GREC)

Xarxes

- Recognized Group SGR2014/211
- Clinical and Basic AIDS Research Group
- Thematic AIDS Research Network (ISCIII RETIC RIS RD12/0017/0002)
- Member of the American Society for Microbiology (JMP)
- Member of the International AIDS Society and the Scientific Working Group on HIV Cure at IAS **(JMP)**
- Member of the Forum HIV Cure Project **(JMP)**
- Member of the US Consortium for Functional Glycomics (CFG) **(JMP)**
- Member of the Catalan Biology Society (Virology Group) **(JMP)**
- Member of the Spanish Virology Society **(JMP)**

Projects

New genetic engineering tools for the treatment of AIDS "STOP-AIDS".
Funding body(ies): Spanish Ministry of the Economy and Competitiveness,
Secretariat of State for Research, Development and Innovation,
Retos-Colaboración programme
Apr 2016 - Dec 2019
Research supervisor(s): **Javier Martínez-Picado**

Low viral reservoir in treated subjects (LoViReT). Predictors of extremely low HIV-1 DNA reservoir in subjects initiating cART during chronic infection.
Funding body(ies): MSD
Sept 2016 - Aug 2017
Research supervisor(s): **Javier Martínez-Picado**

Crossroads programme for clinical research applied to AIDS.
Funding body(ies): Gilead
Jan 2016 - Dec 2016
Research supervisor(s): **Javier Martínez-Picado**

Principal investigator

Javier Martínez-Picado
jmpicado@irsicaixa.es

Dr. Javier Martinez-Picado is a Catalan Institute for Research and Advanced Studies (ICREA) researcher at IrsiCaixa and associate lecturer at the University of Vic-Central University of Catalonia (UVic-UCC) and —until August 2016— at the Autonomous University of Barcelona (UAB). He obtained his PhD on Bacterial Genomics from the University of Barcelona (UB) in 1996 and was subsequently contracted by Massachusetts General Hospital in Boston as a researcher at Harvard Medical School, where he engaged in research into AIDS. In 2000 he obtained a position as a Spanish Ministry of Health biomedical researcher assigned to the Germans Trias i Pujol University Hospital, where he focused on translational aspects of HIV-1 infection. **Dr. Martinez-Picado** is a member of several scientific, industrial and academic committees, has published some 150 papers in international journals (H-index 45), has presented findings at numerous conferences (some 150 papers and 125 keynote speeches) and has directed eight doctoral theses (with three more currently underway).

Team

Associate researcher(s)
Nuria Izquierdo-Useros

Post-doc researcher(s)
Maria Salgado

Pre-doc researcher(s)
Maria Pino
Sara Morón-López
Susana Benet
Daniel Pérez-Zsolt
Maria Francesca Cortese
Cristina Gálvez

Laboratory technician(s)
Mª Carmen Puertas
Itziar Erkizia

Cohorts and project management
Judith Dalmau

Biostatistician(s)
Víctor Urrea

Presentation

Our group, through a combination of basic and applied research, focuses on translational studies of HIV-1 and the search for new therapeutic strategies against HIV/AIDS.

The group works closely with the Germans Trias i Pujol University Hospital, attending some 2,000 people infected with HIV. Our research programmes focus on four priority areas.

— HIV cure. We evaluate replication persistence in the presence of an effective antiretroviral treatment, study the location and impact of viral reservoirs and conduct clinical studies focused on developing therapeutic interventions aimed at reducing viral reservoirs and eradicating HIV. Our group is leader of the first consortium for allogeneic stem cell transplantation in patients with HIV (IciStem).

— HIV pathogenesis via dendritic cells. Our studies are based on discovery of the axis of recognition between viral gangliosides and the Siglec-1 receptor and its role in transinfection and in the design of therapeutic strategies taking advantage of this mechanism.

— Extreme HIV infection phenotypes. We evaluate the immunological and virological characteristics of these patient profiles, so as to enhance knowledge of infection pathogenesis that can be applied to new personalized therapeutic, diagnostic and follow-up strategies for patients.

— New therapeutic strategies. We focus especially on antiretroviral treatment and immunotherapies, mechanisms of emerging resistance to treatments and the impact on viral fitness.

2016 milestones and perspectives for the future

Our main achievements during 2016 were as follows:

1. HIV-1 cure

— Consolidation of an international cohort of HIV-infected patients who have received allogeneic stem cell transplantation as a treatment for severe haematological disease (IciStem). So far, this is the only therapeutic intervention —virologically and immunologically unique— capable of significantly reducing the viral reservoir.

— Studies of the impact of immunotherapy with IFNα on HIV-1 infection in HIV-positive patients on antiretroviral treatment.

— Demonstration of good penetration in the male reproductive tract of a new inhibitor of viral integration called dolutegravir, which inhibits viral replication with a dynamic similar to that of blood plasma, thereby facilitating HIV elimination from this anatomical compartment considered a potential viral reservoir.

— Demonstration by highly sensitive sequencing techniques that residual viraemia in HIV-positive patients on antiretroviral therapy does not come mainly CD4 lymphocytes circulating in peripheral blood.

— Demonstration of the involvement of P-glycoprotein in the extrusion of antiretroviral drugs in HIV-positive patients and, thus, in the generation of cellular resistance.

— Description of the impact of genetic polymorphisms in lamivudine transportation by the hOCT1 protein.

2. Siglec-1 role in viral pathogenesis

— Identification of HIV-positive individuals who do not express the Siglec-1 receptor, reinforcing our search for a specific inhibitor for this molecule.

3. Extreme HIV infection phenotypes

— Studies of the relationship between spontaneous control of HIV infection, a low viral reservoir and inefficient viral reactivation.

— Identification of factors underlying the clinical phenotype of the non-progressor viraemic who, as the natural host, maintains a healthy immune system despite having high blood viraemia levels.

— Advancement in the study of functional resistance to infection in haemophiliacs exposed to HIV-1 but resistant to infection.

Perspectives for the future are mainly centred on consolidation of the innovative advances arising from our research, studies of the potential direct impact on the health of patients

Novel therapeutic agents to block interactions between enveloped viruses and myeloid cells: combating the settlement of infections.
Funding body(ies): Spanish Ministry of the Economy and Competitiveness
Jan 2017 - Dec 2019
Research supervisor(s): **Javier Martínez-Picado** and **Nuria Izquierdo-Useros**

Targeting engineered nanoparticles for therapeutic purge of HIV-1 reservoirs.
Funding body(ies): amfAR Foundation for AIDS Research
Apr 2016 - Apr 2017
Research supervisor(s): **Nuria Izquierdo-Useros**

Non-invasive viral reservoir characterization in lymph nodes through fine-needle biopsies in patients with different HIV progression profiles.
Funding body(ies): Gilead
Jan 2017- Dec 2018
Research supervisor(s): **Javier Martínez-Picado**

Phase II exploratory study of MEDI4736 monotherapy in HIV-1 patients with advanced solid tumours.
Funding body(ies): AstraZeneca
Jan 2017- Dec 2019
Research supervisor(s): **Javier Martínez-Picado**

An open-label study of safety, pharmacokinetics and pharmacodynamics of ABX464 in HIV-1 seronegative and seropositive adults.
Funding body(ies): ABIVAX
Jan 2017 - Dec 2018
Research supervisor(s) (reservoirs): **Javier Martínez-Picado**

Awards and recognition

Scientific committees:
- Institute of Biotechnology and Biomedicine (UAB)

- Plasmia Biotech
- Innovex Therapeutics SL
- AlbaJuna Therapeutics SL

Advisory committees:
- 7th and 8th International Workshop on HIV Persistence during Therapy
- 15th and 16th European AIDS Conference/EACS
- 8th Spanish AIDS Conference (GeSIDA)

Doctoral theses

Title: *Evaluation of clinical strategies to cure HIV-1 infection in patients receiving antiretroviral therapy.*
Author: **Sara Morón-López**
Autonomous University of Barcelona (UAB)
Director(s): J**avier Martínez-Picado**
Defended: 20 Sept 2016
Grade: *Cum Laude*

Title: *HIV-1 immune activation induces Siglec-1 expression and enhances viral dissemination in myeloid cells.*
Author: **Maria Pino**
Autonomous University of Barcelona (UAB)
Director(s): **Javier Martínez-Picado** and **Nuria Izquierdo-Useros**
Defended: 7 July 2016
Grade: *Cum Laude*

Master's theses

Title: *Determination of HIV-1 coreceptor tropism using proviral DNA (pvDNA) in patients on effective suppression treatment and correlation with proviral load.*
Author: **María González Cao**
Autonomous University of Barcelona (UAB)
Tutor*:* **Javier Martínez-Picado**
Grade: 10/10

and a continued search for new methodologies. More specifically, our programmes will lead to the development of new strategies for treatment and cure of HIV/AIDS.
Regarding the entire set of programmes, our group aims to do the following:

1. To quantify the size of the viral reservoir and analyse its role 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 interaction between the virus and Siglec-1.
4. To build nanoliposomes that specifically target Siglec-1 as expressed in dendritic cells as a mechanism to release drugs, latency reactivation agents or viral immunogens.
5. To continue exploring the role of virus-host interactions in extreme HIV-1 infection phenotypes.
6. To explore therapeutic applications of factors underlying the non-progressor viraemic phenotype, whose profile is similar to that of the natural host in having an immune system that is not affected by high levels of viraemia.
7. To understand cellular protection against HIV-1 infection in individuals who remain uninfected despite exposure to the virus.
8. To study —via optical super-resolution imaging and the monitoring of single molecules— Siglec-1 spatial organization in the membrane of myeloid cells and Siglec-1 internalization routes in the presence of the virus.

HIV and HCV Genetic and Phenotypic Variability

Networks
- Thematic AIDS Research Network (ISCIII RETIC RIS RD12/0017/0002)
- Recognized Group SGR2014/92
- HIV and HCV Genetic Variability

Projects
Recoding viral genomes through synonymous mutations as a way to alter the biological efficacy of the virus.
Funding body(ies):
Spanish Ministry of the Economy and Competitiveness
Jan 2017- Dec 2019
Research supervisor(s): **MA Martínez**

Innate immunity to HIV as a means to cure the infection.
Funding body(ies):
Spanish Ministry of the Economy and Competitiveness
Carlos III Health Institute (ISCIII)
Jan 2017- Dec 2019
Research supervisor(s): **MA Martínez, J. Esté**

Granted patents
Title: Human helicase ddx3 inhibitors as therapeutic agents.
Inventor(s): Meyerhans A, Martínez Delasma, Brai A, Fazi R, Tintori C, Botta M, Esté J, **Martínez MA**
Patent number: WO2016128541A1
Date granted: 18 Aug 2016
Institution(s): Azienda Ospedaliera Univesitaria Senese

Master's theses
Author: **ME. Sáez Moya**
University Master's in AIDS Pathogenesis and Treatment (UAB)
End date: June 2016
Grade: Excellent

Author: **Leire Díaz Tercero**
Master in Advanced Immunology
University of Barcelona (UB) and Autonomous University of Barcelona (UAB)
End date: June 2016
Grade: Excellent

Principal investigator

Miguel Ángel Martínez
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Author of 106 research papers published in journals indexed in PubMed (mostly in the HIV field) and three worldwide patents. Director of nine doctoral theses. Editor of *Antimicrobial Agents and Chemotherapy* (American Society for Microbiology, ASM) and member of the editorial board of *Antiviral Research* (International Society for Antiviral Research, ISAR). Author of ten book chapters and guest editor of the book *RNA Interference and Viruses: Current Innovations and Future Trends* (Caister, Norfolk (UK), 2010). For 10 years, Chairperson of the Virology section of the Catalan Biology Society (attached to the Institute of Catalan Studies, IEC). Recipient in 2006 of the International AIDS Society (IAS) award for the most cited basic research author in the journal *AIDS*.

Team

Post-doc researcher(s)
Sandra Franco
Maria Nevot

Pre-doc researcher(s)
Ana Jordán

Presentation
The main goal of our group is to understand the molecular bases for HIV and HCV variation and evolution. A better understanding of the evolutionary dynamics of these viruses would enable a definition of the factors that contribute to immune evasion, immune persistence and the emergence of variants resistant to new antivirals. The study of viral variation can potentially contribute to the design of new antiviral strategies, bearing in mind the high mutation rates in HIV and HCV.

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 attenuating virulence. SAVE has been successfully used to develop attenuating poliovirus and influenza virus vaccines.

Deoptimization of different moieties of the HIV-1 gag and pol genes has enabled the development of variants of HIV-1 with attenuated phenotypes in MT-4 cells and PBMCs obtained from healthy donors (Martrus et al. *Retrovirology* 2013; Nevot et al. 2015).

Great potential for the development of a new class of live attenuated vaccines is offered by large-scale and low-cost production of the desired DNA sequences and recoding the viral genome — all the while adding to our biological knowledge of the virus. Currently underway is preclinical development of live attenuated vaccines for seasonal and pandemic influenza, respiratory syncytial virus and dengue virus. Gene therapy and vaccine vectors can also benefit from synonymous recoding, since the deoptimized sequence of the vector may be safer for the host. Furthermore, the use of optimized sequences for an antigen or protein would enhance expression levels. Although synonymous genome recoding has been used primarily with RNA viruses, it can also be used for other organisms and biological systems.

The study of viruses is a pioneering endeavour in the new research field of synonymous genome recoding and, together with synthetic biology, is giving rise to novel therapies and basic biology applications. Despite great progress in research into viral genome recoding and attenuation, several questions as yet remain unanswered. A key priority would be to decipher the mechanism through which synonymous mutations affect the virus phenotype.

2016 milestones and perspectives for the future
Our group is currently studying the stability of attenuated viruses, as well as the possibility of obtaining a new attenuated 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 translation of the corresponding messenger — and on the other hand, on base pair content (e.g., the presence of CpG and/or TPA).

An important issue is to develop a protocol for HIV-1 infection tissue culture production (MT-4 cells) from transfection of synthetic DNA fragments (produced by chemical synthesis or PCR) in the absence of infectious virus clones. We have produced infectious virus from one or more DNA fragments (up to six fragments have been tested) covering the complete HIV-1 genome. Preliminary results indicate that the stability of the different viral variants is associated with the loss of replicative capacity and, more importantly, with the number of mutations introduced, thereby determining the phenotypic stability of viruses whose biological effectiveness is reduced. The sequencing of individual clones (viral quasispecies) by massive sequencing has yielded information on the sequence spaces explored by different viral variants.

An unexplored aspect of HIV-1 genetic architecture is how choice regarding use of synonymous codons influences the diversity and evolutionary capacity of the virus. To be clarified is whether the HIV-1 genome sequences are optimized not only in their 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 able to develop genotypic and phenotypic resistance to viral protease inhibitors in a similar way to wild-type viruses. Our results have shown 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 2017, in press). These results confirm that viruses recoded in their use of codon pairs occupy sequence spaces that are different from those of the wild virus. Note that although the recoded viruses show different patterns of resistance, their phenotypic resistance is similar to that of the wild virus, suggesting that the recoded virus is mutationally just as robust as the wild virus. These results were reported in the first published study of the evolutionary capacity of an enzyme recoded in its use of synonymous codons.

For the future, we plan to continue using and deepening our knowledge of the SAVE technology. We also plan to study the possible effect of bias in the use of codon pairs in HIV-1 and HCV translation and evolutionary capacity, as well as the stability of recoded viral variants. These variants will also be used to identify functional redundant RNA elements in the coded sequence for HIV-1 and HCV. Because synonymous recoding is directed to a basic function like translation, our hypothesis is that the 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.

Cell Virology and Immunology (VIC)

Networks

— Recognized Group SGR2014/211
— Clinical and Basic AIDS Research Group
— Thematic AIDS Research Network (ISCIII RETIC RIS RD12/0017/0002). **Dr. Blanco** coordinates WP3 (immune impairment) of the immunopathogeny programme (role of the viral envelope and apoptosis) and participates in WP4 (vaccines).
— HIVphagy. The group participates in the PICS consortium, which studies the role of autophagy in HIV infection.

Projects

DTS15/00185.
Funding body(ies):
Carlos III Health Institute (ISCIII)
Jan 2016 - Dec 2017
Research supervisor(s): **Julià Blanco**

Awards and recognition

European Myalgic Encephalomyelitis Research Group (EMERG). **Dr. Blanco** is a member of the Scientific Committee as an advisor regarding immunological aspects

Doctoral theses

Title: *Targeting a major HIV-1 vulnerability region: the gp41 Membrane Proximal External Region.*
Author: **Luis M. Molinos**
Defended: 15 July 2016
Department of Immunology, Autonomous University of Barcelona (UAB)
Director(s): **Julià Blanco** and **Jorge Carrillo**
Grade: *Cum Laude*

Filed patents

Title: Virus-like particles with high-density coating for the production of neutralizing antibodies.

Principal investigator

Julià Blanco
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Dr. Blanco has studied the HIV envelope protein and its role in viral transmission and CD4 cell death in depth and has developed various tools for analysing, both in vitro and in vivo, the destructive capacity of this protein. The knowledge generated from a virological perspective has resulted in this IrsiCaixa group leading a study of this protein nationwide (Spanish AIDS Research Network), while the analysis of immunological disorders has resulted in **Dr. Blanco**'s participation in different international study groups. The interface between the immune system and the envelope protein, the analyses of antibodies and the design of vaccines reflect more recent —yet priority— work. **Dr. Blanco**, along with **Dr. Carrillo** and **Dr. Clotet**, constitute the scientific management of the spin-off AlbaJuna Therapeutics, SL, whose creation was the main achievement of the group in 2016.

Team

Associate researcher(s)
Jorge Carrillo

Pre-doc researcher(s)
Lucía Pastor
Luis M. Molinos
Ferran Tarrés
Montserrat Jiménez

Laboratory technician(s)
Silvia Marfil

Other
Víctor Urrea
Mª Luisa Rodríguez

AlbaJuna Therapeutics, SL

Post-doc researcher(s)
Francesc Cunyat
Cristina Lorca
Ester Aparicio

Presentation

Our group focuses on studies of the HIV envelope protein, the only viral protein exposed to the outside of the HIV particle. It is, therefore:
— the viral factor that determines virus spread and the target protein for neutralizing humoral response
— the main determinant of CD4 cell destruction and the resulting chronic inflammation in patients with HIV

These two aspects of the viral envelope have shaped our activity in recent years. We have invested significant efforts in the study of the humoral response to the viral envelope, developing new tests to identify protective and non-protective responses and optimizing technologies to isolate natural human antibodies and design and produce synthetic antibodies to apply them in therapy. We have also developed two platforms for VLPs and proteoliposomes to produce anti-HIV vaccines that generate protective antibodies.

CD4 cell destruction, chronic inflammation and immune system ageing (known as inflammageing) have been addressed through the analysis of different cohorts of HIV-infected patients, for whom we have extensively characterized the viral envelope function and cell production and destruction mechanisms (thymic production, activation, immunosenescence and cell death mechanisms such as apoptosis and autophagy). Our group has also developed new tools for analysing these data (OurFlow software).

The ultimate goal of both research lines is to develop vaccines that protect against HIV infection and to develop therapeutic strategies (based on antibodies or inflammageing modulators) for HIV-infected individuals that contribute to functional cure or eradication of HIV.

2016 milestones and perspectives for the future

Vaccine development

In 2016 we patented the invention of new VLPs for the development of vaccines (patent EP1638234.4). These VLPs, based on the fusion of immunogens with the gag viral protein, provide an excellent platform for the development of new vaccines against HIV and other pathogens. This project has involved the inclusion of doctoral student **Ferran Tarrés**.

Article *Proteoliposomal formulations of an HIV-1 gp41-based miniprotein elicit a lipid-dependent immunodominant response overlapping the 2F5 binding motif*. During 2016 we completed our study of proteoliposome immunogenicity, with excellent results. However, a redesign of the immunogen is already underway to improve the protective capacity of this vaccine.

Antibody characterization

The task of identifying new antibodies isolated from HIV-positive individuals is in its final stage. With all technical requirements resolved, we selected 25 candidates and the first results are expected by 2017.

Recombinant antibodies

The in vitro design of antibodies was the exceptional basis for the creation of the spin-off AlbaJuna Therapeutics, SL. The activity of the spin-off has become an important focus for the group, which has recruited three post-doctoral researchers with extensive experience.

Immune impairment in persons with HIV

Analysis of immune impairment induced by HIV has given rise to various publications. Different situations were analysed, from acute infection in the GAMA study (Pastor et al, 2016) to patients who fail to regain a satisfactory level of CD4 cells (Perez-Santiago et al, 2016). This research line has been reinforced by the inclusion of **Montserrat Jiménez** in our group.

New immunological analysis tools

During 2016 we developed the software OurFlow (project DTS15/00185) as a key tool for rapidly analysing complex immunological data (multicolour flow cytometry). This will enable us to launch new projects and to respond to key questions regarding the relationship between the immune system, the gut microbiota and the earliest immunological events in HIV infection.

Inventor(s): **Jorge Carrillo**, **Luis M. Molinos**, **Julià Blanco**
Application number: EP1638234.4
Applicant(s): Esteve and **IrsiCaixa**

Title: HIV antibody derivatives with dual antiviral and immunomodulatory activity.
Inventor(s): **J. Carrillo**, **B. Clotet**, **J. Blanco**
Application number: PAT08-00003190-2016 (Spanish patent complementing the US patent filed in 2015)
Applicant(s): **IrsiCaixa**

Spin-off(s)

Name: AlbaJuna Therapeutics, SL
Date established: Jan 2016
Description: AlbaJuna Therapeutics, SL develops new treatment strategies based on monoclonal antibodies with great potential to neutralize HIV and activate the natural killer cells responsible for destroying infected cells. Three candidates exist that, in vitro, are 100 times more potent than any similar molecule. Grifols has initially invested 3.75 billion euros, although the total investment will increase as project goals are met.

Tissue Virology (VITI)

Networks
- Thematic AIDS Research Network (ISCIII RETIC RIS RD12/0017/0002)
- Recognized Group SGR2014/211
- Clinical and Basic AIDS Research Group

Principal investigator

Cecilia Cabrera
ccabrera@irsicaixa.es

Cecilia Cabrera graduated in Biological Sciences from the University of Barcelona (UB) in 1994. She pursued her doctoral studies in **IrsiCaixa**, obtaining a PhD in Biological Sciences from the Autonomous University of Barcelona (UAB) in 2001. After a period of postdoctoral studies at **IrsiCaixa** in 2005, she obtained a Miguel Servet researcher contract, eventually confirmed as stable from 2010, and since 2013 she has headed the Tissue Virology group. She has published 47 scientific papers, has benefited from ongoing public and private funding for her research and collaborates with several national and international groups. In terms of teaching, she has directed one and co-directed a second doctoral thesis.

Team

Pre-doc researcher(s)
Elisabet Gómez
Sònia Pedreño
Roberto Martínez

Laboratory technician(s)
Elisabet García

Presentation

HIV infection can be viewed as a disease associated with the mucosa, 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 the 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 a high level of immunological activation and massive production of pro-inflammatory cytokines.

The mechanisms of destruction of CD4 T-cells and the reasons for GALT incomplete immune recovery, despite antiretroviral treatment (unlike what is observed in peripheral blood), is a current topic of debate. This difference between blood and tissue has highlighted the importance of assessing both the effect of the virus and of antiretroviral therapy on lymphoid tissue, as this is where latent viral infection (viral reservoir) is established. Therefore, studies in this area are needed to achieve total eradication of the virus. Our group evaluates the viral pathogenic effect (HIV and SIV) and the impact of antiretroviral drugs on the tissue of HIV-positive individuals with different levels of viral and/or immune control and in ex vivo models of healthy donor tissue.

The group has also launched a new line of research into bladder cancer.

2016 milestones

In 2016, the results obtained in our different lines of work were as follows:

1. HIV pathogenesis. Our group is beginning to produce results in characterizing the pathogenic effect of HIV in lymphoid tissues. It has been determined that virus replication in lymphoid tissues leads to massive CD4 T-cell death through inflammation (pyroptosis) and there is also cell loss through apoptosis. This characterization of the type of cell death improves understanding of the inflammatory process underlying viral infection and will help us design possible therapeutic strategies aimed at prevention. These results were presented at the 2016 Conference on Retroviruses and Opportunistic Infections in Boston (USA).

2. CMV co-infection in HIV-positive patients. Our results show that reactivation of CMV is increased in patients with poor immune recovery and that the greater humoral response may be related to the greater mortality observed in these patients. These results have been submitted for publication (Gómez-Mora et al, JID 2016). Following this line of work, in collaboration with **Dr. Blanco**'s Cell Virology and Immunology group (IrsiCaixa) and Dr. Biard Piechaczyk (CNRS in Montpellier), we also evaluated the role of death by autophagy in patients with poor immune recovery. This research was recently published in *JAIDS*.

3. Immune response and bladder cancer progression. We have begun to obtain results in characterizing the immune response involved in the progression of bladder cancer. Preliminary results were presented at the conference of the American Society of Urology (AUA 2016) held in San Diego (USA). We are currently preparing the documentation necessary to perform a clinical trial to evaluate local and systemic immune response after standard bladder treatment.

Research Management

Scientific and Technical Services

Sample Conservation and Processing Service

The **IrsiCaixa** Retrovirology Laboratory began operations in 1993, processing and preserving biological samples from HIV-infected patients.

Over the years, the laboratory has amassed and maintained a large collection of different types of samples — used in numerous scientific studies and clinical trials — that have contributed to breakthroughs in research to improve the immune system and the quality of life of HIV patients.

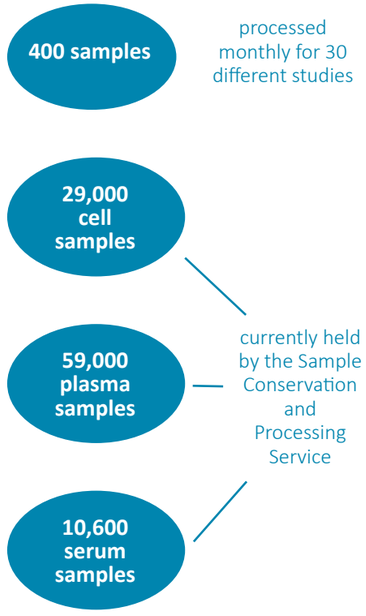
Sequencing Service

Since its launch **IrsiCaixa** has used the HIV genotyping technique to determine resistance to antiretrovirals, initially on an experimental basis for patients included in clinical trials. Since this technique was soon found to be very useful in optimizing antiretroviral treatments, the need arose to create the Sequencing Service to ensure that all patients would have access to this technique.

In 1999 the Sequencing Service commenced operations as a healthcare service receiving samples from the Germans Trias i Pujol University Hospital and other public and private centres. Since 2002 the HIV genotyping test has been funded by the Catalan Health Service (CatSalud), which has designated IrsiCaixa as the reference laboratory for Girona, Barcelona and Maresme North and Central (regions 4, 6 and 7, respectively).

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. The Sequencing Service determines resistance to antiretrovirals (RT-PROT and integrase) and genotypic tropism of HIV from plasma. Resistance is usually determined from plasma, but can also be determined from PBMCs or low-viral-load plasma (ultracentrifugation) for patients with a low viral load or with non-assessable results.

To ensure the quality of its results, the Sequencing Service is subject to regular external quality control inspections (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

Research and Innovation Management Office

During 2016, the Research and Innovation Management Office (RIMO) focused on consolidating and improving tools and mechanisms aimed at managing and providing support to research groups during the lifecycle of their projects.

RIMO's task is to mainstream its procedures and tools to ensure that they are adapted to the specific needs of each research group. RIMO also works closely with **IrsiCaixa** management and Living Lab for Health to provide support as needed, identify emerging needs, optimize mechanisms and tools and maximize synergies.

In 2016 RIMO consolidated alliances with scientific, legal and patent experts so as to acquire the necessary knowledge regarding results transfer, product development and market access. New partnerships were also established aimed at intensifying efforts to attract international competitive funding from 2017.

Head
Mireia Manent

Team
Judith Dalmau
Chiara Mancuso

Patents

Granted
Title: Human helicase ddx3 inhibitors as therapeutic agents
Inventors: A. Meyerhans, D. Martínez, A Brai, R Fazi, C Tintori, M Botta, **J. Esté**, **M. Martínez**
Patent number: WO2016128541A1
Data granted: 18/08/2016
Institution(s): Azienda Ospedaliera Univesitaria Senese

Filed
Title: HIV antibody derivatives with dual antiviral and immunomodulatory activity
Inventors: **J. Carrillo, B. Clotet, J. Blanco**
Application number: PAT08-00003190-2016 (Spanish patent complementing USA patent 2015)
Applicant(s): **IrsiCaixa**

Title: Virus-Like particles with high density coating for the production of neutralizing antibodies
Inventors: **J. Carrillo, Luis M. Molinos, J. Blanco**
Application number: EP1638234.4
Applicant(s): Esteve | **IrsiCaixa**

Spin-off

AlbaJuna Therapeutics SL, established on 13 January 2016, by agreement between IrsiCaixa, the multinational Grifols and researchers **Bonaventura Clotet**, **Jorge Carrillo** and **Julià Blanco**, with the aim of synthesizing new antibodies against HIV.

Living Lab for Health

In 2016 the Biomedical Research Outreach Unit was renamed Living Lab for Health. Living Lab for Health operates along two specific lines: (1) it coordinates institutional communications, communicates science knowledge and publicizes research results; and (2) it implements health promotion projects co-developed with a range of stakeholders, including the scientific community, politicians, the business and educational communities and civil society organizations. These latter projects are inspired by Responsible Research and Innovation (RRI), which aims to develop innovative methodologies that make research more open and inclusive.

RRI projects fall into one of two categories:

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

— Participatory processes with and for the community that promote community involvement in research and governance.

Finally, Living Lab for Health also participates in European RRI projects and offers training, outreach and counselling in RRI mainly to the scientific community.

Head
Rosina Malagrida

Education
Josep Carreras

Institutional communication
Júlia Bestard

Communication

One of the responsibilities of Living Lab for Health is to communicate **IrsiCaixa** research results and institutional activities to the media. This area is also responsible for communicating events organized or participated in by **IrsiCaixa** researchers.

During 2016, 24 news stories were reported, 12 leading to press conferences that had a major impact in local and national media.

Communications, managed by Living Lab for Health, are published through the website and via Twitter and the media. In 2016, a major activity was the complete overhaul of the institutional website at www.irsicaixa.es (see page 36). **IrsiCaixa** has also started to revamp its newsletter.

HEALTH PROMOTION AND EDUCATIONAL PROJECTS

Secondary school health promotion programmes

In collaboration with Obra Social "la Caixa", **IrsiCaixa** coordinates outreach and educational programmes —based on innovative teaching methodologies— regarding different biomedical research areas, supplying multimedia resources aimed at encouraging innovation in the classroom and reducing the gap between education and research.

Part of the RRI project, these programmes also aim to encourage students to participate in the science and innovation system and to train them as responsible and active citizens of the knowledge society.

— **IrsiCaixa** leads the EU Xplore Health educational programme in collaboration with Obra Social "la Caixa" and Amgen. The Xplore Health website includes videos, online games, virtual experiments and reports of interviews with experts on ethical, legal and social aspects (ELSA). It also provides resources for educators, such as worksheets and playing cards, to encourage debates on ELSA and experimental protocols. Xplore Health also runs courses for teachers and experimental workshops. Its network of pilot centres encourages innovative teaching and student participation in research. These activities are operated from different museums around Spain. A breakthrough in 2016 was the creation of a new cluster at the National Museum of Natural History in Madrid.

— **IrsiCaixa** runs the **IrsiCaixa** Outreach educational programme on HIV/AIDS, consisting of participatory sessions for young people and educational resources made available online. The objective of this programme, now in its sixth year, is to promote disease prevention by providing basic HIV/AIDS information and research updates to secondary school students.

Participatory programmes

— Creation of a mental health promotion community 2015-2016. Some 1,000 young people from Catalonia participated in defining an agenda of health promotion needs, identifying mental health and HIV/AIDS as areas that need to be prioritized.

— Participatory research to promote mental health in schools. This project was carried out in collaboration with researchers from four research centres and universities, master's degree students, teachers and 450 secondary students. As the outcome, students prepared a decalogue with recommendations to different stakeholders.

— Community Advisory Committee (CAC). Living Lab for Health participates in the CAC for the HIVACAT programme for AIDS vaccine research. The CAC is an external body that facilitates communication and dialogue between the scientific community, HIV experts, HIV-affected groups and individuals at risk. The mission of the CAC is to provide HIVACAT researchers with a broader and complementary perspective on the impact, consequences and feasibility of their research. In 2016, the CAC met twice monthly.

RRI involvement

— RRI education, outreach and counselling. **IrsiCaixa** provides training and advice on RRI to politicians, research centres, science communicators, universities and the educational community, offering customized training and doctoral, master and undergraduate RRI sessions. **IrsiCaixa** also participates in national and international conferences, seminars and workshops on RRI and develops resources, like the RRI Toolkit, as its contribution to the RRI Tools project.

— Participation in EU-funded RRI projects.
Under the leadership of Obra Social "la Caixa" **IrsiCaixa** participates in the RRI Tools coordination team aimed at raising awareness, publicizing and implementing RRI and providing RRI training. IrsiCaixa also coordinates the Spanish RRI Hub. The goal of the RRI initiative, driven by a consortium of 26 institutions from 29 countries, is to have a significant impact on the future governance of R+D+i.

EnRRICH (Enhancing Responsible Research and Innovation through Curricula in Higher Education). This project aims to promote RRI in higher education and to foster transdisciplinary and participative research that responds to the needs and expectations of society. As its contribution to EnRRICH, **IrsiCaixa** implements participatory training and research within the framework of Xplore Health.

450 — Sana Ment project participants

228 — press, radio and TV mentions

2,796 — Twitter followers

3,173 — RRI Tools project participants (2014-2016)

8,955 — IrsiCaixa Outreach website visits

+25,000 — Xplore Health workshop participants
* 2015-2016 academic year

1,219 — HIV/AIDS open day attendees
*2015-2016 academic year

25,210 — IrsiCaixa website visits

4 — research centres participating in Sana Ment

+25 — meetings with ed/sci policy makers

1,398 — participants in RRI conferences and courses

129,616 — Xplore Health website visits

New institutional website

One of the activities implemented during 2016 by **IrsiCaixa**'s Living Lab for Health was a full overhaul of the institutional website (www.irsicaixa.es). The aim was to offer a more user-friendly experience to visitors, adapt the website to new browsing modes and fully harness the potential of the digital environment.

The website was renewed on the basis of an exhaustive review of website design, content and functionalities. Rethought to optimize browsing and facilitate access by each user type to the content of most interest to them, the new architecture —usable and intuitive— ensures easy, clear and efficient browsing and rapid location of, and access to, content.

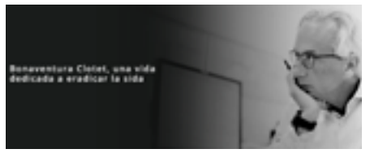
In terms of design, a new online identity was created for **IrsiCaixa** that is attractive, innovative and compelling. The new website design is also more responsive and suitable for any type of device.

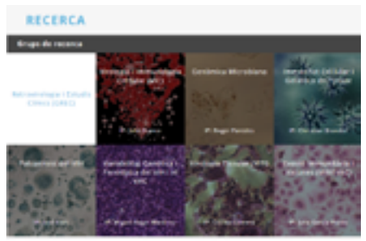
Content has been reviewed and updated to showcase graphic and audiovisual material: more videos, larger images, an improved typeface and smaller quantities of text.

Research is the backbone of **IrsiCaixa** and, for this reason, the corresponding website section clearly describes what each of the eight **IrsiCaixa** research groups does, with all research activities encompassed under **IrsiCaixa**'s five strategic lines.

The News section includes not just the latest scientific and institutional news from **IrsiCaixa** but also Blog 365, where researchers and research group members describe personal perspectives on their everyday research experiences. Three new menus in the revamped website are Innovation and Transfer, Learning and Collaborate.

All in all, the new **IrsiCaixa** AIDS Research Institute website reflects the quality and rigour of a world-leading biomedical research centre.





Collaboration with the Glòria Soler Foundation

The **Glòria Soler Foundation** is a private, nonprofit organization created in 2015 by Josep Suñol i Soler, son of Josep Suñol i Garriga and Glòria Soler i Elías. Its mission is to promote solidary and innovative programmes with a high social impact in the scientific, social and humanistic fields by providing material and human resources to prestigious institutions with proven track records.

The work of the **Glòria Soler Foundation** is based on making a commitment to collaboration by establishing lines of action based on ongoing dialogue, while looking to the future in building pioneering experiences in healthcare, scientific research and humanities.

The **Glòria Soler Foundation** recently signed two agreements with **IrsiCaixa** to develop the following research projects:

BCN02-Romi eradication clinical trial

Following on from a 2015 collaboration project —when the **Glòria Soler Foundation** made a major contribution to the development of a therapeutic vaccine against HIV/AIDS by **IrsiCaixa** in the framework of HIVACAT— a new two-year cooperation agreement was signed in 2016 to develop and analyse the results of the BCN02-Romi eradication clinical trial. This pioneering clinical trial aims to evaluate the efficacy of a new drug called romidepsin administered in combination with vaccines tested in the BCN01 clinical trial. The results are expected to clarify our understanding of which mechanisms, in addition to therapeutic vaccines, can potentially eradicate or functionally cure HIV.

Microbiome and HIV research programme

The contribution of the **Glòria Soler Foundation** will be crucial to achieving the objectives established for microbiome and HIV infection research in the next two years, including:

— to improve our understanding of the bacteria and corresponding metabolic functions associated with immune impairment and chronic inflammation in people with HIV infection.
— to better understand how the microbiome affects response to therapeutic vaccines and treatments aimed at eradicating HIV infection and vice versa.
— to develop diagnostic markers.
— to identify candidate bacteria for developing new probiotics that would counteract the effects of HIV infection in cases of chronic inflammation.

Research into the microbiome undoubtedly has enormous health, social and economic potential, not to mention great industrial biotechnological promise.

Fundació Glòria Soler

Clinical trials

1. CONTROLLERS

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

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 viraemic controllers). The aim is to study the virological and immunological mechanisms involved in spontaneously controlling the HIV virus in order to develop new therapeutic vaccines. There is no clinical intervention other than the extraction of additional biological samples.
Study type: Observational
Design: Cohort, prospective
Start – end: 3/6/2009 - /
Sponsor: IrsiCaixa AIDS Research Institute
Principal investigator(s): Dr. Beatriz Mothe
Participating centre(s): Germans Trias i Pujol University Hospital (Fight AIDS Foundation), Hospital Vall d'Hebron and 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
Start – end: 24/07/2014- /
Sponsor: IrsiCaixa AIDS Research Institute
Principal investigator(s): Dr. Beatriz Mothe
Participating centre(s): Germans Trias i Pujol University Hospital (Fight AIDS Foundation)
CEIC Code: PI-14-072

3. Seronegatius_tipats

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
Start – end: 30/10/2009 -
Sponsor: IrsiCaixa AIDS Research Institute
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 a study to evaluate the effectiveness of a kick-and-kill eradication 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 (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: Intervention
Design: Open-label, multicentre
Phase: I
Start – end: 02/2015 – 10/2017
Sponsor: IrsiCaixa AIDS Research Institute
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 and BCN Checkpoint
CT Code: NCT02616874
Eudra Code: 2015-002300-84

5. iHIVARNA-01

Phase I open-label dose-escalation study to evaluate the safety of the iHIVARNA therapeutic vaccine in individuals with chronic HIV-1 infection on a stable antiretroviral treatment regime.

Summary and objectives: Phase I open-label dose-escalation study to evaluate the safety of the therapeutic vaccine candidate iHIVARNA. Included are 21 individuals with chronic fully suppressed HIV-1 infection consecutively receiving increasing doses of the iHIVARNA vaccine containing the HTI immunogen and the adjuvant TriMix. The HTI immunogen was developed in IrsiCaixa as a therapeutic vaccine to re-educate the immune system of patients and to induce a specific immune response to HIV similar to that of controllers. Vaccine administration at weeks 0, 2 and 4 is intranodal (direct to the groin lymph nodes). The objectives include studying vaccine administration safety, the immune response and the effect on viral reactivation.
Study type: Intervention
Design: Open-label, single-centre, dose escalation
Phase: I
Start – end: 01/06/2015 - /
Sponsor: Clinic Foundation for Biomedical Research
Principal investigator(s): Dr. Felipe García
Participating centre(s): Hospital Clínic de Barcelona
Codi NCT: NCT02413645

6. CUTHIVAC-003

Phase I clinical trial with intramuscular or transcutaneous MVA-B administration to volunteers uninfected by HIV and with a low infection risk in Lima (Peru).

Summary and objectives: CUTHIVAC-03 is a comparative study to evaluate CD4- and CD8 T-cell mediated immune response to the vaccine insert and the MVA vector, as well as to assess the ability of vaccine-induced, HIV-specific CD8 T-cells to inhibit viral replication in vitro. Also included is an analysis of signatures of the innate immune response following vaccination and an analysis of the microbiome in faeces and at the superficial skin.
Study type: Intervention
Design: Single-centre
Phase: I
Start – end: 01/01/2015 - 31/12/2015 (extended to the end of 2016)
Sponsor: IMPACTA (Lima, Peru)
Principal investigator(s): Dr. Javier Lama, Dr. Christian Brander
Participating centre(s): IMPACTA

7. DAA

Determining the causes of clinical failure of direct-action antiretroviral (DAAs) treatment of patients with HCV co-infected with HIV-1.

Summary and objectives: No effective treatment options have been defined for patients who fail to respond to current DAA regimens. The aim is to dissect the different possible causes of treatment failure by monitoring HCV viral load and mass-sequencing samples before and after treatment.
Study type: Observational
Design: Single-centre
Start – end: 01/04/2015 - /
Sponsor: Fight AIDS Foundation
Principal investigator(s): Dr. Cristina Tural, Dr. Miguel Àngel Martínez
Participating centre(s): Germans Trias i Pujol University Hospital (Fight AIDS Foundation)

8. 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
Start – end: 2015 - /
Sponsor: IrsiCaixa AIDS Research Institute
Principal investigator(s): Dr. Cecilia Cabrera
Participating centre(s): Germans Trias i Pujol University Hospital (Fight AIDS Foundation)

9. 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 Martinez-Picado, Dr. Annemarie Wensing

10. RIPIM

Clinical trial to evaluate the impact of intensification with raltegravir in HIV-positive patients with full viral suppression and in monotherapy with protease inhibitors.

Summary and objectives: Pilot phase III proof-of-concept open-label clinical trial, with the aim of evaluating the impact of intensification with raltegravir on the level of both the persistent viral reservoir and immune activation in patients receiving treatment with protease inhibitors as monotherapy. Included were 41 patients who, after 8 weeks of baseline monitoring, were treated and followed up for 24 weeks.
Study type: Clinical trial
Design: Pilot, proof of concept, open-label
Phase: III
Start – end: 28/10/2011- /
Sponsor: IrsiCaixa AIDS Research Institute
Principal investigator(s): Dr. Javier Martinez-Picado

11. INDOOR

Clinical trial to evaluate HIV reservoir dynamics after switching patients receiving treatment based on protease inhibitors to dolutegravir.

Summary and objectives: Phase IV open-label randomized clinical trial that aims to comprehensively evaluate the viral reservoir in CD4+ T-cells in peripheral blood and lymphoid tissue obtained from biopsies of the ileum and to prospectively analyse changes in immune activation and inflammation after switching to dolutegravir.
Study type: Clinical trial
Design: Randomized, open-label
Phase: IV
Start – end: 01/06/2015 - /
Sponsor: IrsiCaixa AIDS Research Institute
Principal investigator(s): Dr. Javier Martinez-Picado, Dr. Manel Crespo, Dr. Linos Vandekerckhove

12. DTG in semen

Clinical observational study to evaluate viraemia control and dolutegravir concentrations in the seminal fluid of patients initiating antiretroviral treatment.

Summary and objectives: Clinical observational study in collaboration with the Hospital de Bellvitge based on obtaining semen samples from patients initiating an antiretroviral treatment regimen that includes dolutegravir. The samples will be used to study viraemia control and dolutegravir

concentrations in seminal fluids in the context of treatments aimed at curing HIV infection.
Study type: Clinical observational
Design: Collaborative
Start – end: 01/01/2015 - /
Principal investigator(s): **Dr. Javier Martinez-Picado**

13. 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 pro-viral 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 Martinez-Picado**

14. Siglec-1

Clinical observational study to evaluate the effect of SIGLEC-1 mutations in HIV pathogenesis in vivo.
Summary and objectives: Clinical observational study involving genetic screening of some 2,000 patients to select patients with mutations in the gene encoding SIGLEC-1 in order to evaluate clinical effect and impact on HIV pathogenesis.
Study type: Clinical observational
Start – end: 01/01/2015 - /
Principal investigator(s): **Dr. Javier Martinez-Picado**

15. Immune checkpoint inhibitors

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.
Study type: Clinical trial
Phase: II
Start – end: 01/01/2015 - /
Principal investigator(s): **Dr. Javier Martinez-Picado**

Talks and conferences

Talks held in Barcelona in 2016, organized by **IrsiCaixa**:

Innovation management & entrepreneurship
Antoni Rosselló. Lawyer specializing in spin-offs and start-ups, Rousaud Costas Duran.
18 April 2016

Innovation management
Joan Bigorra. Director of Strategy and Innovation at ISGlobal.
19 April 2016

Innovation management & entrepreneurship
Lluís Pareras. Department of Innovation and Technology of the Official College of Physicians of Barcelona (COMB) and Director of Healthequity.
20 April 2016

Knowledge management & protection
Anna Bosch. Founder of Bosch Rovira Patents SL, offering patent-related and pharmaceutical services.
21 April 2016

Advanced microscopy studies of HIV-1 dynamic structure and virus-cell interactions
Dr. Jakub Chojnacki. Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, University of Oxford.
26 September 2016

Innate lymphoid cells - do they play a role in HIV infection?
Henrik Kloverpris. K-RITH, KwaZulu-Natal Research Institute for Tuberculosis and HIV (Durban, South Africa).
17 June 2016

B.DEBATE

For the second consecutive year, between 30 June and 1 July CosmoCaixa hosted the Barcelona Debate on the Human Microbiome. From Microbes to Medicines. This Biocat–Obra Social "la Caixa" initiative was organized by **IrsiCaixa** in collaboration with the Vall d'Hebron Research Institute, the University of VIC-Central University of Catalonia and the National Centre for Cancer Research (CNIO).

The conference brought together internationally recognized experts representing a wide range of disciplines who have focused their research efforts on the microbiome in all life stages (including from before birth) and in endemic diseases such as cancer, HIV/AIDS and other infectious conditions, metabolism disorders and obesity. Also unveiled were the latest innovations in probiotics and faecal transplants and new information on the impact of drugs and diet as determinants of microbiome health.

The Scientific Committee is currently working on the 2017 edition.

CROSSROADS PROGRAMME FOR CLINICAL RESEARCH APPLIED TO AIDS

The **IrsiCaixa** Retrovirology and Clinical Studies group organized this year's Crossroads programme for clinical research applied to AIDS, a pioneering national forum for the exchange of experiences in applied research in HIV and other biomedical specialties.

The aim is to encourage links between clinical practice and research in the field of HIV and to seek out new applications for existing skills and knowledge from other specialties.

Aimed at healthcare staff, biomedical researchers, pharmaceutical companies and scientific management, the programme consisted of six sessions based on debates between two accredited researchers, an HIV specialist and a researcher representing the specific theme of the day: paediatrics research, haematology transplants, hepatitis B, Ebola, Responsible Research and Innovation (RRI) or cancer.

WHAT WILL IT TAKE TO END HIV IN AFRICA?

On 29 November 2016, **Drs. Roger Paredes** and **Bonaventura Clotet** co-organized a seminar in Barcelona on the emerging epidemic of resistance to HIV treatments —a major challenge to overcome if we are to achieve the World Health Organization 90-90-90 target. This encounter brought together international researchers and clinical specialists in HIV/AIDS.

As well as the presentation by **Dr. Paredes** —a member of the WHO advisory committee on HIV treatment resistance— there were presentations by **Bonaventura Clotet** (**IrsiCaixa** Director), **Silvia Bertagnolio** (Head of the WHO HIV Drug Resistance Programme), **Edy Nacarapa** (Clinical Director of the Carmelo Hospital of Chokwé, Mozambique), **Denise Naniche** (Head of the HIV/TB Programme at ISGlobal) and **Seth Inzaule** (doctoral student at the Amsterdam Institute for Global Health and Development).

Training

UNIVERSITY MASTER'S IN AIDS PATHOGENESIS AND TREATMENT (UAB)

In 2010, **IrsiCaixa** and the Autonomous University of Barcelona (UAB) reached an agreement to create a postgraduate programme focused on research into HIV and related fields.

The outcome was the Master's in AIDS Pathogenesis and Treatment, a UAB qualification that covers virology, immunology and clinical research.

The successful first edition of the Master's commenced in September 2011 and an application for formal recognition was lodged during 2012-2013. An agreement was also reached with the Gimbernat University School of Nursing and Physiotherapy (attached to the UAB) to take over academic management of the programme. The programme name was also changed to University Master's in AIDS Pathogenesis and Treatment. Noteworthy was the key role played by Obra Social "la Caixa" in implementing the programme by granting scholarships during the first four courses, thereby enabling 36 students to take this high-level biomedical research training programme.

	Year	Participants	Profile	Satisfaction survey (max 5)
In-house qualification	2011-2012	10	Intensive medicine, Biology	4.50
	2012-2013	9	Intensive medicine, Biology, Biotechnology, Pharmacy	4.48
University qualification	2013-2014	8	Intensive medicine, Biology, Biotechnology, Pharmacy Biochemistry	4.59
	2014-2015	9	Intensive medicine, Biology, Biotechnology, Microbiology	4.25
	2015-2016	7	Intensive medicine, Biotechnology, Biochemistry	-

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. Headed by **Dr. Bonaventura Clotet**, the Chair was created to enhance collaboration between the three institutions in the interest of fostering biomedical research at the UVic-UCC and promoting the teaching and training of new researchers and healthcare professionals.

Although HIV and AIDS are considered to be the core elements in this initiative, the Chair also covers research into related conditions such as ageing, hepatitis, cancer and chronic fatigue. Activities under the auspices of the Chair in 2016 were as follows:

Science communication: *On maths and microscopic beings,* 11 March 2016. Website: U-Divulga (UVic-UCC research and innovation blog). **Javier Rivera**.

Roundtable: *Careers for biotechnologists,* 4 May 2016. Location: UVic-UCC. **Julià Blanco**.

Continuous professional development: *Update on AIDS and related diseases and their treatment,* 17 May 2016. Location: Conference Hall, Vic General Hospital (Vic Hospital Consortium). Talks:
— *Antiretroviral drugs and their development since 1987*, **Bonaventura Clotet**.
— *Early treatment*, **Beatriz Mothe**.
— *Rapid progression*, **J. Martínez-Picado**.
— *Immune recovery with cART: what to do when it fails?*, **Julià Blanco**.
— *Ageing and comorbidities*, **E. Negredo**.
— *Resistance to antiretrovirals*, **Roger Paredes**.
— *Therapeutic vaccine*, **C. Brander**.
— *Summary of current hepatitis C treatment*, **Cristina Tural**.

International Workshop on Higher Education at the University of Vic-Central University of Catalonia (UVic-UCC), 13-17 June 2016. Talks:
— *Integrated -omics analyses to identify correlates of HIV control*, **C. Brander.** Workshop in translational bioinformatics.
— *Responsible Research and Innovation (RRI)*, **Rosina Malagrida**.

Conference/seminar: *Obtaining Vaccines,* 23 November 2016, Faculty of Science and Technology, UVic-UCC, **Beatriz Mothe**.

Conference/seminar: *Ageing with HIV: an Accelerated and Accentuated Process,* 14 December 2016, Masia Torre dels Frares, UVic-UCC, **Eugènia Negredo**.

Publications and presentations

Publications

Original publications

1. Álvarez H, Mariño A, García-Rodríguez JF, Vilas-Sueiro A, Valcarce N, Llibre JM. **Immune reconstitution inflammatory syndrome in an HIV-infected patient using subcutaneous silicone fillers**. *AIDS*. 2016 Oct 23;30(16):2561-2563. IF: 4.378

2. Arimany-Nardi C, Minuesa G, Keller T, Erkizia I, Koepsell H, Martinez-Picado J, Pastor-Anglada M. **Role of Human Organic Cation Transporter 1 (hOCT1) Polymorphisms in Lamivudine (3TC) Uptake and Drug-Drug Interactions**. *Front Pharmacol*. 2016 Jun 24;7:175. IF: 4.418

3. Badia R, Pujantell M, Riveira-Muñoz E, Puig T, Torres-Torronteras J, Martí R, Clotet B, Ampudia RM, Vives-Pi M, Esté JA, Ballana E. 2016. **The G1/S specific cyclin D2 is a regulator of HIV-1 restriction in non-proliferating cells**. *Plos Pathogens*. 2016; 12:e1005829. doi:1005810.1001371/journal.ppat.1005829. IF: 7.003

4. Badia R, Angulo G, Riveira-Muñoz E, Pujantell M, Puig T, Ramirez C, Torres-Torronteras J, Martí R, Pauls E, Clotet B, Ballana E, Esté JA. 2016. **Inhibition of herpes simplex virus type 1 by the CDK6 inhibitor PD-0332991 (palbociclib) through the control of SAMHD1**. *Journal of Antimicrobial Chemotherapy* 71:387-394. IF: 4.919

5. Baptista MJ, Hernandez-Rodriguez A, Martinez-Caceres E, Morgades M, Martinez-Picado J, Sirera G, Sancho JM, Feliu E, Ribera JM, Navarro JT. **Epstein-Barr viral loads and serum free light chains levels are potential follow-up markers of HIV-related lymphomas**. *Leuk Lymphoma*. 2016 Apr 28:1-3. IF: 3.093

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8. Bonjoch A, Puig J, Pérez-Alvarez N, Juega J, Echeverría P, Clotet B, Romero R, Bonet J, Negredo E. **Impact of protease inhibitors on the evolution of urinary markers: Subanalyses from an observational cross-sectional study.** *Medicine* (Baltimore). 2016 Aug;95(32):e4507. IF: 2.133

9. Bonjoch A, Echeverría P, Perez-Alvarez N, Puig J, Estany C, Bonaventura Clotet, Negredo E. **Prospective study to assess progression of renal markers after interruption of tenofovir due to nephrotoxicity**. *Biomedical Research international.* 2016; 2016:4380845. doi: 10.1155/2016/4380845. IF: 2.134

10. Blanco-Heredia J, Lecanda A, Valenzuela-Ponce H, Brander C, Ávila-Ríos S, Reyes-Terán G. **Identification of Immunogenic Cytotoxic T Lymphocyte Epitopes Containing Drug Resistance Mutations in Antiretroviral Treatment-Naïve HIV-Infected Individuals**. *PLoS One*. 2016 Jan 25;11(1):e0147571. IF: 3.057

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20. Brander C. **Immune studies in HIV+ to HIV+ organ transplantation**. Oral presentation.University of Capetown. 21/05/2016. Stellenbosch, South Africa.

21. Brander C. **Influence of genetic, virologic and immunologic factors on outcomes of HCV/HIV OLT.** Oral presentation. 28/09/2016. FIPSE.

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