SCIENTIFIC RESEARCH REPORT

BANC DE SANG I TEIXITS I 2013

Generalitat de Catalunya
Departament de Salut

Banc de Sang i Teixits

INDEX

PRESENTATION OF MANAGING DIRECTOR

We present the report of the research activity of the Blood and Tissue Bank for the year 2013. This has been a year marked by a change in the scientific management of the organization, as Dr. Jordi Sierra has embarked on a new professional challenge. The relay in front of the research area of Blood and Tissue Bank has been assumed by Dr. Sílvia Sauleda, professional of the Blood and Tissue Bank, transfusion safety expert and a recognized authority on the side of innovation.

We follow the path set by the Strategic Research Plan, and it is worth noting the efforts of professionals to maintain more than 50 active projects, half in collaboration with other entities.

The main research activity focuses on the diagnosis, transfusion medicine and hemostasis, in line with the mission of the Blood and Tissue Bank. But we also do research in hematopoietic transplantation, immunotherapy and regenerative medicine. In this section, note that the division of Advanced Therapies of the Blood and Tissue Bank, has completed a clinical trial phase I-II to treat osteonecrosis of the knee.

In 2013, our researchers have published an article in the New England Journal of Medicine which has involved a change in the paradigm of transfusion practice in patients with upper gastrointestinal bleeding worldwide.

We believe that professionals of the Blood and Tissue Bank can continue to provide year after year results of this research activity to society.

Enric Argelagués Vidal

INTRODUCTION BY THE SCIENTIFIC DIRECTOR

We present the Scientific Report of the Blood and Tissue Bank corresponding to the year 2013. This report reflects the efforts of many professionals who have contributed with their experience in research, development and innovation of the BST. Together, we have managed to maintain the quality and impact factor of scientific publications and bring up more than 50 research projects.

2013 began with the deployment of the new Strategic Plan for R+D+i designed by the former Scientific Director, Dr. Jordi Sierra. In this new plan, research in the BST is organized in 9 programs that will find detailed in this report.

Early in the year the BST grew, merging with the Tissue Bank of the Hospital Clínic (TSF: Transplant Service Foundation) and this has meant a significant enrichment in our R+D +i.

It is well known that these are difficult times for research in our country. Public funding for projects has decreased dramatically and this situation is not expected to reverse in the coming years. Therefore, the projects have to be competitive, we must look for synergies with groups of excellence, take into account the European calls, especially the Horizon 2020 program and generate opportunities for collaboration with industry.

We cannot underestimate the enthusiasm and tenacity of our investigators. The BST depends on them to remain leader in its activity.

Sílvia Sauleda Oliveras

1. BANC DE SANG I TEIXITS

The Banc de Sang i Teixits (Blood and Tissue Bank - BST) is the public company of the Catalan Ministry of Health whose mission is to guarantee the supply of blood of sufficient quality, for all the citizens of Catalonia. The BST manages and administers the donation, transfusion and analysis of blood and blood plasma. It also acts as a centre for obtaining and processing tissues and cord blood units and develops other lines of activity as a centre specialized in immunobiology, molecular analysis, cell therapy and regenerative medicine.

- BST is the backbone of the hemotherapy system in Catalonia
- Its activity extends to all public and private centres in Catalonia as well as others in Spain, providing a proximity service to donors and customers
- BST aims to be a first level centre in management, innovation research on hemotherapy and tissues

The BST participates in its own research projects or in collaboration with all the centres of the Catalan Health Institute, a large part of the Public Hospital Network and Catalan Universities and also promotes strategic alliances with research centres and industry.

1.1 GOVERNING BODIES

The Governing Bodies of the Banc de Sang i Teixits are the Board of Directors, his Commissions and the Strategic Committee of Tissues.

1.1.1 Board of Directors

President: Manel Peiró Posadas
Vice-president: Carles Constante Beitia
Secretary: Josep Ramon Arisa Clusella
Members: Francesc Brosa Llinares, Josep Brugada Terradellas, Enric Contreras Barbeta, Francesc Gòdia Casablancas, José J. Navas, Miquel Rutllant Bañeras, Santiago Suso Vergara, Jordi Teruel Boladeras, Roser Vallès Navarro and Maria Antònia Viedma Martí.

1.1.2 Commissions of the Board of Directors

Economics and audits: Francesc Brosa Llinares, Jordi Teruel Boladeras, Carles Constante Beitia i Carlos Soria Sendra
Quality and Security: Maria Antònia Viedma Martí and José J.Navas Palacios
R+D+i: Francesc Gòdia Casablancas
Communication: Miquel Rutllant Bañeras
Human Resources and Professional Development: Enric Contreras Barbeta and Manel Peiró Posadas

1.1.3 Strategic Committe of Tissues

President: Josep Brugada Terradellas
Santiago Suso Vergara
Maria Antònia Viedma Martí
Francesc Gòdia Casablancas
Guests: Enric Argelagués Vidal, Isabel López Asión, Esteve Trias Adroher, Dolors Heras Ribot and David Font Ferrer

1.2 DIRECTION AND MANAGEMENT BODIES

1.2.1 Direction Committee

Managing Director: Enric Argelagués Vidal
Assistant to Managing Director: Isabel López Asión
Director of People and Values: Esther Solà Saplana
Marketing Director: Aurora Masip Treig
General Services Director: Joan Ovejo Cortes
Director of the Blood Division: Lluís Puig Rovira
Coordinator of the Territorial Centres: Enric Contreras Barbeta

1.2.2 Territorial Centres Committee

Managing Director: Enric Argelagués Vidal
Assistant to Managing Director: Isabel López Asión
Director of the Blood Division: Lluís Puig Rovira
Director of the Immunohematology Division: Eduardo Muñiz Díaz
Barcelona. Vall d'Hebron and Clínic: Dolors Castellà Cahíz
Barcelona. Sant Pau: Alba Bosch Llobet
Badalona. Germans Trias i Pujol: Joan Ramon Grífols Ronda
L'Hospitalet. Bellvitge: Lluís Massuet Bosch
Manresa. Fundació Althaia/Terrassa. Mútua de Terrassa: Ramon Salinas Argente
Girona. Dr. Josep Trueta: Joan Profitós Tuset
Lleida. Arnau de Vilanova: Juan Manuel Sánchez Villegas
Tarragona. Joan XXIII/Tortosa. Verge de la Cinta/Reus. Sant Joan: Enric Contreras Barbeta

1.3 ADVISORY BODIES

1.3.1 Research and Innovation Committee

The Research and Innovation i Committee is the advisory body in charge of watch over the realization of those tasks linked with the promotion and development of the R+D+I in the organization.

Between the tasks that this committee has to perform we highlight:

- Reviews the R+D+i policy and assures its diffusion and knowledge
- Coordinates the development of the Strategic Plan for R+D+I and evaluates its degree of attainment
- Ensures the achievement of the annual objectives for R+D+I
- Leads the activities associated with the Technology Watch (vigilance, prospective, analysis…)
- Periodically reviews the scientific production, the economic aspects and the personnel of the Research Area
- Takes part, as responsible unit of the programs, of the research activities and evaluates the improvement of the projects (foreseeing deviations and problems)
- Review the methodology of the process for continuous improvement

Composition:

- BST Scientific Director

- Coordinators of the R+D+i programmes: Lluís Puig Rovira, Sílvia Sauleda Oliveras, Enric Contreras Barbeta, Eduard Muñiz Díaz, Francisco Vidal Pérez, José Luis Caro Oleas, Sergi Querol Giner, Joan Garcia López i Arnau Pla Calvet
- Members of the Area of Innovation and Projects
- Manager of the Information and Communication Technologies, General Services, Marketing and communication Divisions (when appropriate)

1.3.2 External Assessors Committee

The new Strategic Research Plan for R+D+i has restored the External Assessors Committee.

Between the tasks that this committee would have to perform we highlight:

- Evaluates annually the activity of R+D+I developed in the BST
- Gives opinion and suggestions on the adequacy and the monitoring of the Strategic Research Plan for R+D+i
- Makes recommendations on the lines of research and programs (foster, auditing, redirect...)
- Provides guidance on how to increase the external resources for research and on possible partnerships to establish
- Performs functions of external technology watch

Composition:

- Prof. Alejandro Madrigal, London (President)
- Prof. Miguel López Botet, IMIM UPF
- Prof. Juan Ignacio Esteban, HVH UAB
- Prof. Herman Einsele, Univ. Würzburg
- Prof. Ellen van der Schoot, Sanquin
- Dr. Jose Antonio Pérez Simón, IBIS, Sevilla
- Dr. Juan Antonio Bueren, CIEMAT
- Jordi Martí Pi-Figueras, Celgene

1.4 LOCATION

The corporate headquarters of the Banc de Sang i Teixits are located on the corner of Passeig Taulat and Lope De Vega, in the 22@ technological district of Barcelona. The building centralises the various lines of activity and a large part of the 600 professionals of the organisation. The BST has also headquarters in major hospitals of Catalonia.

Banc de Sang i Teixits
Dr. Frederic Duran i Jordà
Passeig Taulat, 106-116
08005 Barcelona
Phone: 93 557 35 00

1.5 SUMMARY OF RESEARCH ACTIVITY

1.5.1 Research and technical staff

	Number	FDA
Principal investigators	17	5.24
Senior physicians	5	5.00
Junior physicians	9	6.55
Technical staff	14	11.69
TOTAL	45	28.48

1.5.2 Economic data

Breakdown of BST research income for 2012	Euros
Projects funded by public agencies	276.296
Agreements with industry	423.198
Own funds	2.938.212
TOTAL	3.637.706

1.5.3 Organisation of the BST research

The R+D+i Strategic Plan 2013-2015 defines the following 9 Research Programs:

Diagnosis, transfusional medicine & hemostasis	Hematopoietic transplantation & immunotherapy	Reparative & immunomodulatory therapy
PR1 Blood process	PR6 Molecular biology of transplantation	PR8 Substitutive & reparative therapy
PR2 Transfusional safety	PR7 Transplantation of donors & alternative sources	PR9 Large-scale production of cells & tissues
PR3 Therapeutic apheresis		
PR4 Immunohematology		
PR5 Coagulopathies		

1.5.4 Research projects

The ongoing research projects funded by public organisations and private bodies are shown below. A total of 9 projects received grants in 2013. There were 51 ongoing research projects during 2013.

ONGONING PROJECTS IN 2013		
	PRINCIPAL INVESTIGATOR BST	COLLABORATION
PUBLIC AGENCIES		
Carlos III Health Institute	2	7
Spanish Ministry Economy & Competitivity	3	
ACC10		1
INSERM, FAPES		1
European Commission	1	1
AGAUR		1
Spanish Ministry Health Social Service & Equality		8
Marató TV3	1	1
NON-PROFIT PRIVATE AGENCIES		
BST+Anthony Nolan Trust+Nottingham Trent	1	
Mundo sano Foundation		1
FIPSE		1
AGREEMENTS WITH INDUSTRY		
Novartis	1	
Argos		1
B Braun Surgical, S.A.		1
Ablynx		1
Therakos		1
StemCyte		1
Pfizer	3	
StemCellsOpCo	1	
BSRI	1	
Grífols, S.A.	1	1
OWN FUNDS		
BST	8	
TOTAL	23	28

2013 projects by research areas:

Diagnosis, transfusional medicine & hemostasis	21
Hematopoietic transplantation & immunotherapy	11
Reparative & immunomodulatory therapy	19

1.5.5 Doctoral theses

Three doctoral theses were read or directed by BST investigators in 2013.

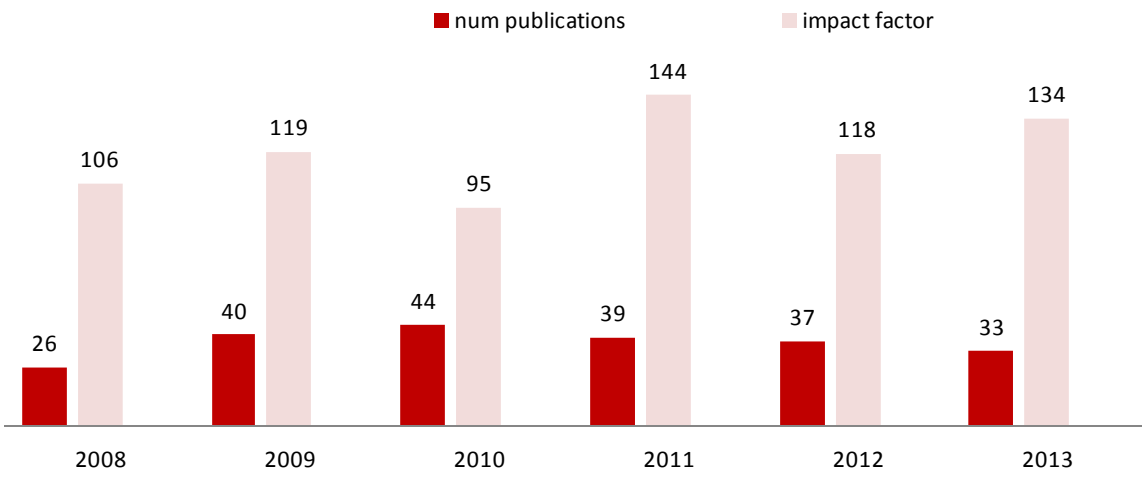
PhD student	Thesis title	Directors	Department	Grade
Ernest Milián González	Study about the effect of bhrf1 in inhibition of apoptosis & the control of the cell cycle in hybridoma cells	Francesc Gòdia Casablancas, Jordi Joan Cairó Badillo, Joaquim Vives i Armengol	Chemistry Engineering	Excellent cum laude
Alba Casamayor Genescà	Advanced cell therapy based in the expansion of hematopoietic stem cells from umbilical cord blood	Francesc Gòdia Casablancas, Arnau Pla Calvet i Joan Garcia Lopez	Chemistry Engineering	Excellent cum laude
Laia Freixa Puig	Development of new strategies of molecular diagnosis for the prevention of foetal/neonatal alloimmune thrombocytopenia	Núria Nogués Gálvez	Cellular Biology, Physiology & Immunology,	Excellent

1.5.6 Publications

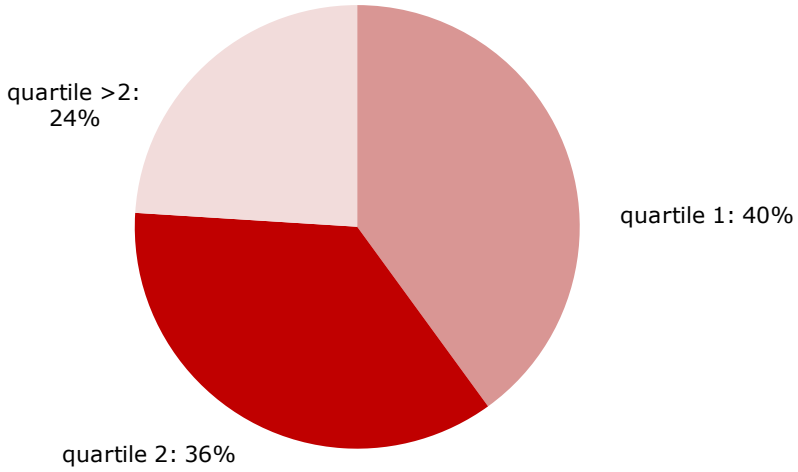
A total of 33 articles were published in scientific magazines by BST investigators in 2013 with an impact factor of 134.06.

The combined impact factor for 2013 was calculated using Journal Citation Reports (JCR) for 2011. The calculation included original articles, revisions and editorials. Presentations to congresses were excluded.

Evolution of the scientific production of the BST over the last 6 years:



Publications BST 2013:



2013 publications by research areas:

Diagnosis, transfusional medicine & hemostasis	17
Hematopoietic transplantation & immunotherapy	11
Reparative & immunomodulatory therapy	5

1.5.7 Patents

The BST currently has 8 patents in different stages of processing. Seven of them are granted in Spain and 5 are in process abroad.

1.6 TEACHING IN RESEARCH

The central element of teaching at the BST is the master of Transfusion Medicine and Cell Therapy, organised through the Autonomous University of Barcelona (UAB) with the support of the Doctor Robert Foundation. Even though this master is not research oriented, some students become interested in pursuing their doctoral studies. The master degree, begun in 2003, has improved in format and internationalisation. Its purpose is specialised training in all processes that take place in a blood bank (donation, processing, transfusion, immunohematology, management and certification) and a tissue bank with a far-reaching cell therapy program. The master for nurses in blood transfusion and cellular and tissue therapy has started in 2012.

The BST participates in directing professionals who are writing dissertations and doctoral theses. Also collaborates in the training of different degrees (Nursing, Medicine, Biology, Pedagogy, Economy and Pharmacy) with agreements with UB, UAB, UPF, UPC, UIC and URV.

The BST organizes stays of training for diverse professional through collaboration agreements with most Latin American countries (Argentina, Uruguay, Colombia, Mexico…) and other European countries like the United Kingdom, Portugal, Sweden, Italy, etc.

Since October 2012, BST has the accreditation as Teaching Unit (BOE law 495/2010 30th of April), with the responsibility of teaching the residents of haematology and hemotherapy of Catalonia.

Other related projects

Chair of Transfusion Medicine and Cell and Tissue Therapy

The Autonomous University of Barcelona, the Blood and Tissue Bank and the Doctor Robert Foundation, created in 2008, the Chair of Transfusion Medicine and Cell and Tissue Therapy (CMT3).

The Mission of the Chair is to promote, assist and strengthen the training, research and consultancy in the field of Transfusion Medicine and Cell and Tissue Therapy, promoting collaboration between researchers and teachers of biomedical, health and welfare.

Since its inception, the CMT3 has led a project included in the sub-European Erasmus Education, Audiovisual & Culture Executive Agency. It has also participated in the project Eurocord-ED, within the subprogram Leonardo da Vinci.

On the other hand, in terms of postgraduate training, the fourth edition of "Master in transfusion medicine and cellular and tissue therapy" is ongoing. The first edition of the EMTACT (European Master in Transfusion Medicine and Advanced Cell Therapies) has successfully started. The first edition of "Master for nurses in blood transfusion and cellular and tissue therapy" has finished and a second one is on preparation.

1.7 THE BANC DE SANG I TEIXITS WEB SITE

The Blood and Tissue Bank has two web sites: www.bancsang.net and www.donarsang.gencat.cat. Both have versions in Catalan, Spanish and English.

www.bancsang.net has information throughout the organization. The contents are divided into six contents blocks (corporate information, donors, receivers, professionals, R+D+i and teaching).

The page is regularly updated with news and has an application for managing online orders. It includes documentation in PDF and video.

www.donarsang.gencat.cat is a website aimed for donors and potential donors and aims to disclose the donation as an act of solidarity, civic engagement and citizen participation.

It offers all the information on the need to donate blood, its uses and the state of the reserves. Also allows searching by town or zip code of upcoming mobile donation campaigns. It also features a news section about donating blood.

In the private area of this site, the donor can modify his own contact details; view his history of donations and blood type.

2. RESEARCH ACTIVITY OF THE BANC DE SANG I TEIXITS

2.1 DIAGNOSIS, TRANSFUSIONAL MEDICINE & HEMOSTASIS

2.1.1 Program 1: Blood and breast milk process

This program includes projects whose purpose is to improve blood donation, the production of blood components, and their use in transfusions and other applications.

PERSON IN CHARGE
Lluís Puig Rovira

INVESTIGATORS
Joan Ramon Grífols Ronda
Gemma Valeta Juan

ONGOING RESEARCH PROJECTS
Principal investigator: Joan Ramon Grífols Ronda
Phase II clinical trial, single-blind, randomized, placebo controlled, to study the efficacy and security of Nanobody Anti-Factor Von Willebrand administered with adjuvant treatment in patients with Acquired Thrombotic Thrombocytopenic Purpura
Funding organisation: Ablynx
File N°: ALX-0681-2.1/10
Duration: 2012 to 2014

Principal investigator: Gemma Valeta Juan
Toxicological screening of abuse drugs in breast milk from a donor in a breast milk bank
Funding organisation: BST

Duration: 2011 to 2014

Principal investigator: Carmen Rosa Pallás Alonso (Hospital 12 Octubre), Gemma Valeta Juan (BST)
Comparative study of HTST with Holder pasteurization in a human milk bank: microbiological, nutritional, biochemical and immunological parameters
Funding organisation: Carlos III Health Institute
Duration: 2013 to 2015

PUBLICATIONS

Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argente C, Santaló M, Muñiz E, Guarner C. Transfusion strategies for acute upper gastrointestinal bleeding. Jan 3;368(1):11-21, N ENGL J MED 2013. QUARTILE 1, DECILE 1, IMPACT FACTOR 53.298

BACKGROUND: The hemoglobin threshold for transfusion of red cells in patients with acute gastrointestinal bleeding is controversial. We compared the efficacy and safety of a restrictive transfusion strategy with those of a liberal transfusion strategy. METHODS: We enrolled 921 patients with severe acute upper gastrointestinal bleeding and randomly assigned 461 of them to a restrictive strategy (transfusion when the hemoglobin level fell below 7 g per deciliter) and 460 to a liberal strategy (transfusion when the hemoglobin fell below 9 g per deciliter). Randomization was stratified according to the presence or absence of liver cirrhosis. RESULTS: A total of 225 patients assigned to the restrictive strategy (51%), as compared with 65 assigned to the liberal strategy (15%), did not receive transfusions (P<0.001). The probability of survival at 6 weeks was higher in the restrictive-strategy group than in the liberal-strategy group (95% vs. 91%; hazard ratio for death with restrictive strategy, 0.55; 95% confidence interval [CI], 0.33 to 0.92; P=0.02). Further bleeding occurred in 10% of the patients in the restrictive-strategy group as compared with 16% of the patients in the liberal-strategy group (P=0.01), and adverse events occurred in 40% as compared with 48% (P=0.02). The probability of survival was slightly higher with the restrictive strategy than with the liberal strategy in the subgroup of patients who had bleeding associated with a peptic ulcer (hazard ratio, 0.70; 95% CI, 0.26 to 1.25) and was significantly higher in the subgroup of patients with cirrhosis and Child-Pugh class A or B disease (hazard ratio, 0.30; 95% CI, 0.11 to 0.85), but not in those with cirrhosis and Child-Pugh class C disease (hazard ratio, 1.04; 95% CI, 0.45 to 2.37). Within the first 5 days, the portal-pressure gradient increased significantly in patients assigned to the liberal strategy (P=0.03) but not in those assigned to the restrictive strategy. CONCLUSIONS: As compared with a liberal transfusion strategy, a restrictive strategy significantly improved outcomes in patients with acute upper gastrointestinal bleeding. (Funded by Fundació Investigació Sant Pau; ClinicalTrials.gov number, NCT00414713).

Motlló C, Sancho JM, Grífols JR, Juncà J, Morgades M, Ester A, Rodríguez I, Vives S, Batlle M, Guardia R, Ferrà C, Gallardo D, Millá F, Feliu E, Ribera JM. Mobilization and engraftment of peripheral blood stem cells in healthy related donors >55 years old. CYTOTHERAPY 2013 Oct 28. QUARTILE 1, DECILE 3, IMPACT FACTOR 3,627

The increasing scarcity of young related donors has led to the use of older donors for related allogeneic hematopoietic stem cell transplantation (HSCT). This study analyzed the influence of age on the results of mobilization of peripheral blood stem cells (PBSCs) in healthy donors as well as on the engraftment and outcome of HSCT. METHODS: A retrospective analysis from a single center was performed comparing the results of PBSC mobilization from related healthy donors according to their age. RESULTS: The study included 133 consecutive related donors. The median age was 50 years (range, 4-77 years); 70 (53%) donors were males, and 44 (33%) were >55 years old. All donors were mobilized with granulocyte colony-stimulating factor for 5 days. The peak CD34+ cell count in peripheral blood was higher in younger than in older donors (median, 90.5

CD34+ cells/μL [range, 18-240 CD34+ cells/μL] versus 72 CD34+ cells/μL [range, 20-172.5 CD34+ cells/μL], P = 0.008). The volume processed was lower in younger than in older donors (16,131 mL [range, 4424-36,906 mL] versus 18,653 mL [range, 10,003-26,261 mL], P = 0.002) with similar CD34+ cells collected (579.3 × 106 cells [range, 135.14 × 106-1557.24 × 106 cells] versus 513.69 × 106 cells [range, 149.81 × 106-1290 × 106 cells], P = 0.844). There were no differences in time to recovery of neutrophils and platelets or in the incidences of acute and chronic graft-versus-host disease, overall survival, non-relapse mortality and relapse incidence. CONCLUSIONS: Donors >55 years old mobilized fewer CD34+ cells and required a greater volume to collect a similar number of CD34+ cells. The outcome of HSCT was not influenced by donor age. Donor age should not be a limitation for related allogeneic HSCT.

Aguilera X, Martinez-Zapata MJ, Bosch A, Urrútia G, González JC, Jordan M, Gich I, Maymó RM, Martínez N, Monllau JC, Celaya F, Fernández JA. Efficacy and Safety of Fibrin Glue and Tranexamic Acid to Prevent Postoperative Blood Loss in Total Knee Arthroplasty. A Randomized Controlled Clinical Trial. J BONE JOINT SURG AM 95:2001-7, 2013. QUARTILE 1, DECILE 1, IMPACT FACTOR 3,272

Cid J, Magnano L, Molina P, Diaz-Ricart M, Martínez N, Maymó RM, Puig L, Lozano M, Escolar G, Galán AM. Automated preparation of whole blood-derived platelets suspended in two different platelet additive solutions and stored for 7 days. TRANSFUSION 2013 May 30. QUARTILE 2, DECILE 4, IMPACT FACTOR 3,217

BACKGROUND: The Atreus system (Terumo BCT) automates the preparation of blood components from whole blood donations. Intermediate platelet (PLT) products can be pooled manually or with the OrbiSac (Terumo BCT) and suspended in different PLT additive solutions (PASs) to obtain PLT concentrates (PCs). The aim of our study was to compare the in vitro PLT quality of PCs obtained with either the Atreus 2C+ and the OrbiSac or the Atreus 3C and suspended in PAS-II or PAS-IIIM during storage for up to 7 days. STUDY DESIGN AND METHODS: We prepared eight PCs from buffy coats obtained with Atreus 2C+, pooled with the OrbiSac, and suspended in PAS-II and eight PCs from interim PLT units obtained with the Atreus 3C and suspended either in PAS-II or in PAS-IIIM. We measured volume, PLT content, and mean PLT component and performed metabolic assays (pH, glucose, lactate, pO2, and pCO2) and flow cytometry analyses (GPIb, GPIIbIIIa, GPIV, CD62P, CD63, von Willebrand factor [vWF], fibrinogen, Factor V, and annexin V). RESULTS: PCs prepared with the Atreus 3C showed lower volume and higher PLT concentration when compared with PCs prepared with the Atreus 2C+ and the OrbiSac ($p < 0.05$). Glucose consumption rate and the expression of CD62P, CD63, and vWF were lower in PCs suspended in PAS-IIIM when compared with PCs suspended in PAS-II ($p < 0.05$). CONCLUSION: PCs prepared with the Atreus 3C and suspended in PAS-IIIM preserve satisfactorily the in vitro PLT quality during 7-day storage. PLT activation during a 7-day storage period was lower when the storage solution was PAS-IIIM in comparison with PAS-II.

Villanueva C, Colomo A, Bosch A. Transfusion for acute upper gastrointestinal bleeding N ENGL J MED Apr 4;368(14); 1362-3, 2013.

2.1.2 Program 2: Transfusional safety

The Transfusion Safety Laboratory (LST) is comprised of the Healthcare Unit for Validation of Blood and other Components, and the R&D&I Unit for transmissible agents. The R&D&I activity of the LST can be classified in the following main lines:

A. Viral hepatitis (HAV, HBV, HCV and HEV) and co-infection with HIV.

B. Epidemiological research and development of new tools for the detection of emerging infectious agents (Chagas disease, HTLV-I/II, Chikungunya virus, malaria, XMRV).

The final end-point of these lines is to improve physiopathological and epidemiological knowledge and the detection of infectious agents relevant to the safety of blood products, cord blood and tissues.

It is also important to highlight the activity undertaken to improve knowledge of the presence of pathogens coming from other countries among the BST Catalan reference population. The objectives of studies performed along these lines is to plan and establish strategies to guarantee the safety of blood products based on the correct selection of blood donors and the application of diagnostic tests. It must be born in mind that the BST is the only centre that distributes blood products in Catalonia and is directly responsible for maintaining and promoting research along these lines.

PERSON IN CHARGE
Sílvia Sauleda Oliveras

INVESTIGATORS
Marta Bes Maijo
Natàlia Casamitjana Ponces
Maria Piron

TECHNICAL STAFF
Angeles Rico Blázquez

ONGOING RESEARCH PROJECTS

Principal investigator: Sílvia Sauleda Oliveras

Prevalence of Hepatitis E markers (anti-IgG/IgM and HEV RNA) in Catalonian blood donors
Funding organisation: Novartis
Duration: 2013 to 2014

Principal investigator: Maria Piron

Development of real time protocols for PCRs (Dengue, Chikungunya, HTLV-I, HTLV-II, etc) as screening tools or supplementary analyses of emerging infectious pathogens and a field study of emerging pathogens in high-risk travellers and immigrant donors
Funding organisation: BST
Duration: 2009 to 2014

Principal investigator: Maria Piron

Prevalence of antibodies anti-HBc in blood donors from areas of high risk of Hepatitis B virus infection
Funding organisation: BST
Duration: 2013

Principal investigator: Marta Bes Maijo

Association between the haplotypes of the rs12979860 polymorphism of the IL-28B gene and the occult hepatitis B infection
Funding organisation: BST
Duration: 2013 to 2014

Principal investigator: Juan Ignacio Esteban Mur (Institut de Recerca Vall d'Hebron), Sílvia Sauleda Oliveras (BST)

CD4 NS3 specific autologous cells functional restoration/expansion to prevent the recurrence of HCV after liver transplantation: optimization of the process for a clinical use
Funding organisation: Carlos III Health Institute
File N°: PI10/01505
Duration: 2011 to 2014

Principal investigator: Esteban Ribera Pascuet (Institut de Recerca Vall d'Hebron), Sílvia Sauleda Oliveras (BST)

XMRV prevalence in patients with a HIV-1 infection
Funding organisation: FIPSE
File N°: 241046/10
Duration: 2012 to 2013

Principal investigator: Michael Busch (BSRI), Sílvia Sauleda Oliveras (BST)

External Quality Assurance Program Oversight Laboratory. Global Surveillance of HIV Diversity and Evaluation of Test Performance Using Viral Panels Derived from Recently Infected Blood Donors
Funding organisation: Blood Systems Research Institute
Duration: 2012 to 2013

Principal investigator: Joaquim Gascón (Hospital Clínic), Maria Piron (BST)

Population pharmacokinetic study of benznidazole in adult patients with Chagas disease. Relation between the benznidazole pharmacokinetics and adverse events
Funding organisation: Fundación Mundo Sano
Duration: 2013 to 2015

PUBLICATIONS

Cubero M, Gregori J, Esteban JI, García-Cehic D, Bes M, Perales C, Domingo E, Rodríguez-Frías F, Sauleda S, Casillas R, Sanchez A, Ortega I, Esteban R, Guardia J, Quer

J. Identification of host and viral factors involved in a dissimilar resolution of a hepatitis C virus infection. LIVER INT 2013 Oct 17. QUARTILE 1, DECILE 3, IMPACT FACTOR 3.824.

BACKGROUND: Hepatitis C virus (HCV) transmission from a chronic patient to a susceptible individual is a good opportunity to study viral and host factors that may influence the natural course of hepatitis C infection towards either spontaneous recovery or chronicity. AIMS: To compare a documented case of a bottleneck event in the sexual transmission of HCV from a chronically infected patient to a recipient host that cleared infection. METHODS: Host genetic components such as Class I and II HLA and IL28B polymorphism (rs12979860 SNPs) were identified by direct sequencing and LightMix analysis, respectively. Deep nucleotide sequence analysis of quasispecies complexity was performed using massive pyrosequencing platform (454 GS-FLX), and the CD4 specific immune response was characterized by ELISPOT. RESULTS AND CONCLUSIONS: Sequencing analysis and CD4 response highlighted several NS3-helicase domains in which an interplay between amino acid variability and CD4 immune response might have contributed either to chronicity in the donor patient or to viral clearance in the receptor (newly infected) patient.

Bruhn R, Lelie N, Custer B, Busch M, Kleinman S; International NAT Study Group. Prevalence of human immunodeficiency virus RNA and antibody in first-time, lapsed, and repeat blood donations across five international regions and relative efficacy of alternative screening scenarios. TRANSFUSION Oct-53; 2013. QUARTILE 2, DECILE 4, IMPACT FACTOR 3.21

BACKGROUND: Twenty-one blood organizations from five geographical regions provided HIV individual donation (ID)-NAT and serology data on 11,787,610 donations. Infections were classified as anti-HIV-/RNA+ window period (WP), anti-HIV+/RNA+ concordant positive (CP) or anti-HIV+/RNA- elite controller (EC). Residual risk and efficacy of several screening scenarios were estimated for first time, lapsed and repeat donations. METHODS: WP residual risk estimates assumed a 50% infectious dose of 3.16 virions and a 50% detection limit of 2.7 HIV RNA copies/mL for ID-NAT and 10,000 copies/mL for p24Ag. Infectivity for CP (100%) and EC (2.2%) donations was estimated based on viral load distributions and 100-fold reduced infectivity by antibody neutralization as reported elsewhere. Efficacy was calculated as proportion of transmission risk removed from baseline (i.e. in absence of any screening). RESULTS: There was no significant difference in transmission risk between lapsed and repeat donations in any region. Risk was 3.8-fold higher in first time than combined lapsed/repeat donations in South Africa but not in other regions. Screening strategies were most efficacious at interdicting infectious transfusions in first time (98.7-99.8%) followed by lapsed (97.6-99.7%) and repeat (86.8-97.7%) donations in all regions combined. In each donor category the efficacy of ID-NAT alone (97.7-99.8%) was superior to that of minipool (MP)-NAT/anti-HIV (95.0-99.6%) and p24 Ag/anti-HIV (89.8-99.1%). CONCLUSIONS: Efficacy patterns were similar by donor/donation status in each region despite large differences in HIV prevalence and transmission risk. As similar data become available for HBV and HCV, this modeling may be useful in cost effectiveness analyses of alternative testing scenarios.

Piron M, Alegre J, Ribera E, Sauleda S. Absence of xenotropic murine leukaemia virus-related virus sequences in healthy blood donors and chronic fatigue syndrome patients in Catalonia, Spain. ENFERM INFECC MICROBIOL CLIN, Aug-Sep;31(7):491-2, 2013. QUARTILE 3, DECILE 7, IMPACT FACTOR 1.491

2.1.3 Program 3: Therapeutic apheresis

Therapeutic apheresis are procedures consisting of the external processing of the blood using a cell separator in order to remove a blood component that is causing a disease, with the return of the remaining components to the body.

The removed component can be blood cell (cytapheresis) or plasma (plasma exchange or selective plasmapheresis).

Although there are some conditions in which therapeutic apheresis are the first-line treatment, since they represent the best option for patients, generally they constitute second-line options or are contributing to other therapies. But the overall weight of this treatment is increasing in recent years, especially from the very studies that increase the scientific evidence that supports this type of procedure.

Currently the therapeutic apheresis program has three active studies:

- Photopheresis in patients with graft versus host disease
- Plasma exchange in patients with Alzheimer
- Immunotherapy with autologous dendritic cells in renal carcinoma

It is planned to incorporate more lines of therapy, as the treatment of age related macular degeneration and treatment of amyotrophic lateral sclerosis.

PERSON IN CHARGE
Enric Contreras Barbeta

INVESTIGATORS
Alba Bosch Llobet
Pilar Ortiz Murillo
Joan Ramon Grífols Ronda
Dolors Castellà Cahiz

ONGOING RESEARCH PROJECTS

Principal investigator: Alba Bosch Llobet, Joan Ramon Grífols Ronda & Dolors Castellà Cahiz

An International Phase 3 Randomized Trial of Autologous Dendritic Cell Immunotherapy (AGS 003) Plus Standard Treatment of Advanced Renal Cell Carcinoma
Funding organisation: Argos Therapeutics
File N°: 2012-000871-17
Duration: 2013 to 2014

Principal investigator: Mercè Boada Rovira (Fundació ACE), Pilar Ortiz Murillo (BST)

A multicenter, randomized, controlled study to evaluate the efficacy and safety of short-term plasma exchange followed by long-term plasmapheresis with infusion of human albumin combined with intravenous immunoglobulin in patients with mild-moderate Alzheimer's disease
Funding organisation: Grífols
File N°: IG1002
Duration: 2012 to 2014

Principal investigator: Jordi Sierra Gil (Hospital Sant Pau), Alba Bosch Llobet & Dolors Castellà Cahiz (BST)

A Randomized Controlled Study of Extracorporeal Photoapheresis (ECP) Therapy with UVADEXTM for the Treatment of Patients with Moderate to Severe Chronic Graft-versus-Host Disease (cGvHD)
Funding organisation: Therakos Inc
File N°: 10-005, 2010-022780-35
Duration: 2012 to 2014

PUBLICATIONS

Leal-Noval SR, Muñoz M, Asuero M, Contreras E, García-Erce JA, Llau JV, Moral V, Páramo JA, Quintana M. Spanish Consensus Statement on alternatives to allogeneic blood transfusion: the 2013 update of the "Seville Document". BLOOD TRANSFUS October; 11(4): 585–610, 2013. QUARTILE 3, DECILE 7, IMPACT FACTOR 2.099

Leal-Noval SR, Muñoz M, Asuero M, Contreras E, García-Erce JA, Llau JV, Moral V, Páramo JA, Quintana M, Basora M, Bautista-Paloma FJ, Bisbe E, Bóveda JL, Castillo-Muñoz A, Colomina MJ, Fernández C, Fernández-Mondéjar E, Ferrándiz C, García de Lorenzo A, Gomar C, Gómez-Luque A, M. Izuel, Jiménez-Yuste V, López-Briz E, López-Fernández ML, Martín-Conde JA, Montoro-Ronsano B, Paniagua C, Romero-Garrido JA, Ruiz JC, Salinas-Argente R, Sánchez C, Torrabadella P, Arellano V, Candela A, Fernández JA, Fernández-Hinojosa E, Puppo A. 2013. Documento Sevilla de Consenso sobre Alternativas a la Transfusión de Sangre Alogénica. Actualización del Documento Sevilla. MED INTENSIVA May;37(4):259-283, 2013. QUARTILE 4, DECILE 10, IMPACT FACTOR 1,072

Leal-Noval SR, Muñoz M, Asuero M, Contreras E, García-Erce JA, Llau JV, Moral V, Páramo JA, Quintana M, Basora M, Bautista-Paloma FJ, Bisbe E, Bóveda JL, Castillo-Muñoz A, Colomina MJ, Fernández C, Fernández-Mondéjar E, Ferrándiz C, García de Lorenzo A, Gomar C, Gómez-Luque A, M. Izuel, Jiménez-Yuste V, López-Briz E, López-Fernández ML, Martín-Conde JA, Montoro-Ronsano B, Paniagua C, Romero-Garrido JA, Ruiz JC, Salinas-Argente R, Sánchez C, Torrabadella P, Arellano V, Candela A, Fernández JA, Fernández-Hinojosa E, Puppo A. 2013. Documento Sevilla de Consenso sobre Alternativas a la Transfusión de Sangre Alogénica. Actualización del Documento Sevilla. REV ESP ANESTESIOL REANIM May;60(5):263.e1-263.e25 2013

2.1.4 Program 4: Immunohematology

The Immunohematology laboratory is a national and international reference in the diagnosis of immune cytopenia and the typing and characterisation of blood groups.

The project "Development of an alternative to the use of RBC panels for the detection of erythrocyte antibodies" forms part of the objective of seeking new techniques and strategies for typing blood groups and research into anti-erythrocyte antibodies that improve the sensitivity, and especially the specificity, of the techniques now being used. These techniques are based on the use of reactive red blood cells obtained from donors extensively typed for different erythrocyte antigens. Our proposal considers an alternative consisting of having a combination of cells each of which expresses a single erythrocyte antigen through transfection of cell lines that express an antigen variant of a particular erythrocyte protein. This system enables simplifying and clarifying the results obtained. Furthermore, in a second phase, a suitable support must be found for these cells so that they can be used as a routine test in all transfusion and immunohematology laboratories.

PERSON IN CHARGE
Eduardo Muñiz Diaz

INVESTIGATORS
Núria Nogués Galvez
Cecilia González Santesteban

ONGOING RESEARCH PROJECTS
Principal investigator: Núria Nogués Gálvez
Expression of the recombinant Miltemberger III or GP Mur antigen

Funding organisation: Diagnòstic Grífols
Duration: 2013 to 2014

PUBLICATIONS

Nogués N, Muñiz-Díaz E, Bertrand G. A new mutation in the platelet GPIbα gene interfering with HPA-2 genotyping approaches: A case report. TRANSFUSION Jun;53(6):1375-7, 2013. QUARTILE 2, DECILE 4, IMPACT FACTOR 3.217

Storry JR, Castilho L, Daniels G, Flegel WA, Garratty G, de Haas M, Hyland C, Lomas-Francis C, Moulds JM, Nogues N, Olsson ML, Poole J, Reid ME, Rouger P, van der Schoot E, Scott M, Tani Y, Yu LC, Wendel S, Westhoff C, Yahalom V, Zelinski T. International Society of Blood Transfusion Working Party on red cell immunogenetics and blood group terminology: Cancun report (2012). VOX SANG 2013 Dec 27. QUARTILE 2, DECILE 5, IMPACT FACTOR 2.856

The International Society of Blood Transfusion Working Party on red cell immunogenetics and blood group terminology convened during the International congress in Cancun, July 2012. This report details the newly identified antigens in existing blood group systems and presents three new blood group systems.

Baía F, Muñiz-Diaz E, Boto N, Salgado M, Montero R, Ventura T, Sousa H, Alves B, Nogués N, Koch C. A simple approach to confirm the presence of anti-D in sera with presumed anti-D+C specificity. BLOOD TRANSFUS 2013 Jan 23:1-4. QUARTILE 3, DECILE 7, IMPACT FACTOR 2.099

Flesch BK, Just B, Deitenbeck R, Reil A, Bux J, Nogués N, Muñiz-Diaz E. The AQP1 mutation c.601delG causes the Co-negative phenotype in four patients belonging to the Romani (Gypsy) ethnic group. BLOOD TRANSFUS 2013 Oct 18:1-5. QUARTILE 3, DECILE 7, IMPACT FACTOR 2.099

BACKGROUND: The Colton blood group antigens Coa, Cob and Co3 are encoded by the AQP1 gene which produces a water channel forming integral protein. The extremely rare Co-deficiency enables immunisation against the Co3 isoantigen. MATERIALS AND METHODS: Four patients from different regions of Europe who belong to the ethnic minority of Romani (Gypsy) presented with irregular antibodies against a high frequency red blood cell antigen. Positive cross-matches with all red blood cells tested were reported. An Anti-Co3 antibody was identified as the cause of incompatibility in the four cases. The genetic background was determined by polymerase chain reaction typing with sequence-specific primers and by DNA sequencing. RESULTS: The Co(a b) phenotype was confirmed in the four patients despite the fact that genotyping revealed the CO*01 allele of the AQP1 gene. A homozygous AQP1 c.601delG mutation, leading to a frame shift and producing a premature stop in the next codon, was responsible for the Co-negative phenotype in all four cases. While one patient was successfully transfused with blood from his sibling with the identical mutation, another case, a baby affected by haemolytic disease of the newborn, recovered without transfusion. DISCUSSION: Despite the difficulties in undertaking a population study to determine the prevalence of this AQP1 c.601delG allele in the ethnic minority of Romani, the observations described in this report clearly suggest an accumulation of this mutation, which causes the Co(a b) phenotype, in Romani (Gypsy) patients. Further studies are necessary to prove such an accumulation.

2.1.5 Program 5: Coagulopathies

The program of research into congenital coagulopathies of the Banc de Sang i Teixits has had a dual character since its foundation in 1998: support for the diagnosis of congenital coagulation disorders and other hereditary diseases; and the investigation and development of new perspectives in the diagnosis and therapeutic field. A large part of the current objectives is innovation of technological tools and their transfer into laboratory routine.

The main lines are centred on the study of hereditary diseases or blood defects of enormous clinical, economic and social relevance such as haemophilia or von Willebrand's disease, as well as other aspects derived from these, and other, coagulopathies. In detail, the research objectives of the unit can be described as:

A. Identification of the mutations responsible for haemophilia A and B in the Spanish population.

B. Applications to therapeutic orientation, genetic advice, prenatal and pre-implantation diagnosis.

C. Molecular diagnosis of von Willebrand's disease: study of genotype-phenotype relationship and their application to clinical diagnosis.

D. Establishment of protocols and the genetic study of rare monogenic bleeding disorders: FXI deficit, FXIII deficit, combined FV and FVIII deficit, FVII deficit, Glanzmann's thrombasthenia, etc…

E. Collection and use of stem cells with patient-specific induced pluripotency to improve diagnosis and treatment of hemophilia.

F. In-depth studies of the molecular events found in some affected individuals and the genotype-phenotype relationship constituting the most basic area of the team's objectives.

G. Clinical epidemiological studies aimed at the exhaustive identification of the clinical characteristics of patients with congenital coagulopathies and their response to different therapeutic options. These studies often entail the creation of different types of registers.

It is important to emphasise that epidemiological studies are reflected on the Hemobase web site (http://www.hemobase.com), dedicated to haemophilia and von Willebrand's disease. It includes the first register of characterised mutations of haemophilia patients in the Spanish population. It is a dynamic register with permanent updates. It includes general information on haemophilia, its classification, clinical characteristics and diagnosis difficulties, as well as the biochemical and molecular characteristics of the genes. Hemobase is recognised by the NCBI and Orphanet as a specific database of mutations of the FVIII, FIX and VWF loci.

The research activity is associated with the commitment of the Haemophilia Unit of Vall d'Hebron Hospital (reference centre for congenital coagulopathies in Catalonia) to the development of molecular protocols, applicable genetic advice and prenatal diagnosis. The Haemophilia Unit offers specialised healthcare to patients with hemorrhagic congenital coagulopathies such as haemophilia, von Willebrand's disease, thrombopathies and other coagulation factor deficits. Congenital coagulopathies, and especially haemophilia, are rare complex diseases. Achieving effective treatment requires a program of integral therapy. The Haemophilia Unit has an experienced multidisciplinary team that develops integral patient care, carries out daily healthcare control through clinical sessions, and has become a reference centre for congenital coagulopathies on a national and international level. Equally outstanding is the participation of the unit in numerous international multicentre studies (ITI, RODIN, HIGS and EUHASS).

PERSON IN CHARGE
Francisco Vidal Pérez

INVESTIGATORS
Rafael Parra López
Irene Corrales Insa
Lluis Martorell Cedrés

TECHNICAL STAFF
Lorena Ramírez Orihuela

ONGOING RESEARCH PROJECTS

Principal investigator: Rafael Parra López
Post-authorisation safety surveillance study of patients who have changed from ReFacto or other factor VIII products to ReFacto AF in the context of normal medical care.
Funding organisation: Pfizer
Duration: 2009 to 2013

Principal investigator: Francisco Vidal Pérez
Use of patient-specific induced pluripotent stem cells to improve diagnosis and treatment of hemophilia A
Funding organisation: European Commission
File Nº: PI11/03029
Duration: 2012 to 2014

Principal investigator: Francisco Vidal Pérez
Application of the new next generation sequencing technologies to the molecular diagnosis of congenital coagulopathies
Funding organisation: Carlos III Institute of Health
File N°: PI12/01494
Duration: 2013 to 2015

Principal investigator: Francisco Vidal Pérez
Design and development of a protocol for HLA very high resolution typing by new generation sequencing technology
Funding organisation: BST
Duration: 2012 to 2015

Principal investigator: Rafael Parra López
Non invasive prenatal diagnosis of hemophilia by massive sequencing
Funding organisation: Pfizer
File N°: WS2109762
Duration: 2012 to 2015

Principal investigator: Rafael Parra López
Development of an efficient high-throughput platform for hemophilia A. Drug screening and gene correction using patient specific induced pluripotent stem cells (iPSCs).
Funding organisation: Pfizer
Duration: 2013 to 2015

PUBLICATIONS

Lane J, McLaren PJ, Dorrell L, Shianna KV, Stemke A, Pelak K, Moore S, Oldenburg J, Alvarez-Roman MT, Angelillo-Scherrer A, Boehlen F, Bolton-Maggs PH, Brand B, Brown D, Chiang E, Cid-Haro AR, Clotet B, Collins P, Colombo S, Dalmau J, Fogarty P, Giangrande P, Gringeri A, Iyer R, Katsarou O, Kempton C, Kuriakose P, Lin J, Makris M, Manco-Johnson M, Tsakiris DA, Martinez-Picado J, Mauser-Bunschoten E, Neff A, Oka S, Oyesiku L, Parra R, Peter-Salonen K, Powell J, Recht M, Shapiro A, Stine K, Talks K, Telenti A, Wilde J, Yee TT, Wolinsky SM, Martinson J, Hussain SK, Bream JH, Jacobson LP, Carrington M, Goedert JJ, Haynes BF, McMichael AJ, Goldstein DB, Fellay J; for the NIAID Center for HIV/AIDS Vaccine Immunology (CHAVI). A genome-wide association study of resistance to HIV infection in highly exposed uninfected individuals with hemophilia A. HUM MOL GENET May 1;22(9):1903-10, 2013. QUARTILE 1, DECILE 1, IMPACT FACTOR 7,636

Human genetic variation contributes to differences in susceptibility to HIV-1 infection. To search for novel host resistance factors, we performed a genome-wide association study (GWAS) in hemophilia patients highly exposed to potentially contaminated factor VIII infusions. Individuals with hemophilia A and a documented history of factor VIII infusions before the introduction of viral inactivation procedures (1979-1984) were recruited from 36 hemophilia treatment centers (HTCs), and their genome-wide genetic variants were compared with those from matched HIV-infected individuals. Homozygous carriers of known CCR5 resistance mutations were excluded. Single nucleotide polymorphisms (SNPs) and inferred copy number variants (CNVs) were tested using logistic regression. In addition, we performed a pathway enrichment analysis, a heritability analysis, and a search for epistatic interactions with CCR5 Δ32 heterozygosity. A total of 560 HIV-uninfected cases were recruited: 36 (6.4%) were homozygous for CCR5 Δ32 or m303. After quality control and SNP imputation, we tested 1 081 435 SNPs and 3686 CNVs for association with HIV-1 serostatus in 431 cases and 765 HIV-infected controls. No SNP or CNV reached genome-wide significance. The additional analyses did not reveal any strong genetic effect.Highly exposed, yet uninfected hemophiliacs form an ideal study group to investigate host resistance factors. Using a genome-wide approach, we did not

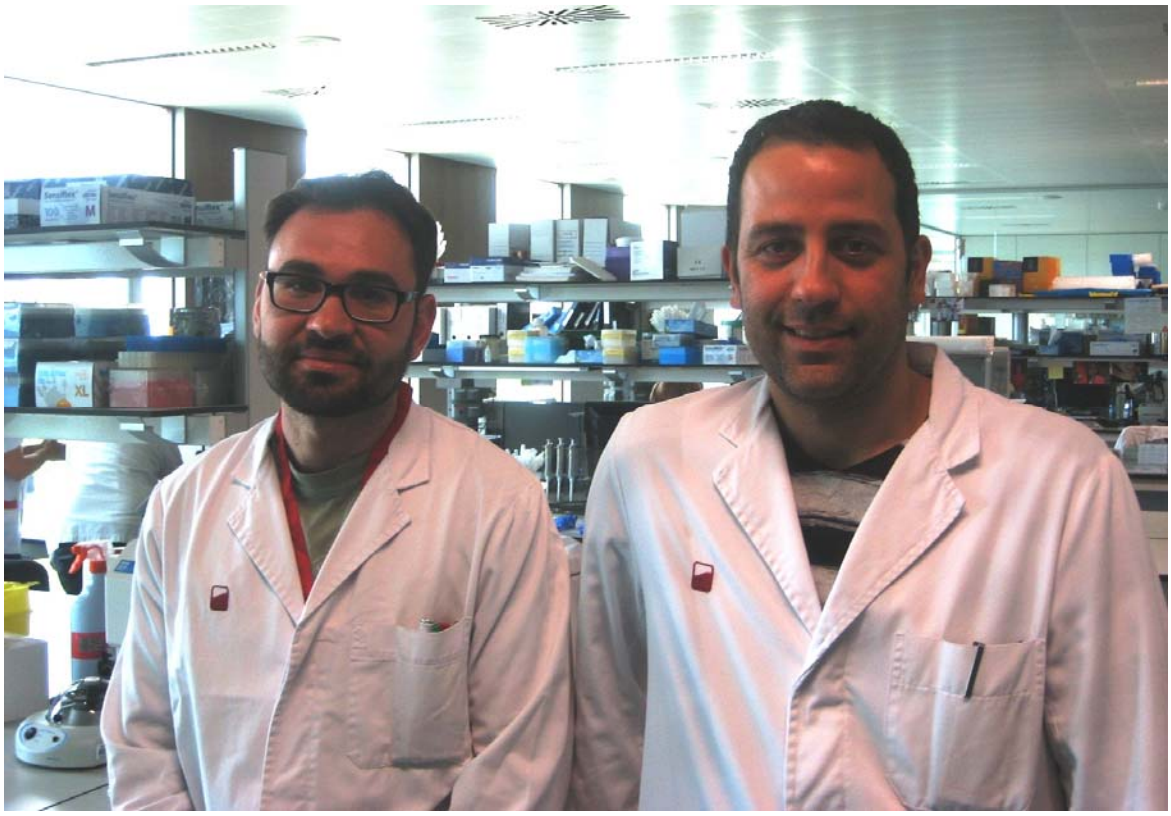
detect any significant associations between SNPs and HIV-1 susceptibility, indicating that common genetic variants of major effect are unlikely to explain the observed resistance phenotype in this population.

Feliciano A, Castellvi J, Artero-Castro A, Leal JA, Romagosa C, Hernández-Losa J, Peg V, Fabra A, Vidal F, Kondoh H, Ramón Y Cajal S, Lleonart ME. miR-125b Acts as a Tumor Suppressor in Breast Tumorigenesis via Its Novel Direct Targets ENPEP, CK2-α, CCNJ, and MEGF9. PLOS ONE 2013 Oct 3;8(10):e76247. QUARTILE 1, DECILE 2, IMPACT FACTOR 4,092

MicroRNAs (miRNAs) play important roles in diverse biological processes and are emerging as key regulators of tumorigenesis and tumor progression. To explore the dysregulation of miRNAs in breast cancer, a genome-wide expression profiling of 939 miRNAs was performed in 50 breast cancer patients. A total of 35 miRNAs were aberrantly expressed between breast cancer tissue and adjacent normal breast tissue and several novel miRNAs were identified as potential oncogenes or tumor suppressor miRNAs in breast tumorigenesis. miR-125b exhibited the largest decrease in expression. Enforced miR-125b expression in mammary cells decreased cell proliferation by inducing G2/M cell cycle arrest and reduced anchorage-independent cell growth of cells of mammary origin. miR-125b was found to perform its tumor suppressor function via the direct targeting of the 3'-UTRs of ENPEP, CK2-α, CCNJ, and MEGF9 mRNAs. Silencing these miR-125b targets mimicked the biological effects of miR-125b overexpression, confirming that they are modulated by miR-125b. Analysis of ENPEP, CK2-α, CCNJ, and MEGF9 protein expression in breast cancer patients revealed that they were overexpressed in 56%, 40-56%, 20%, and 32% of the tumors, respectively. The expression of ENPEP and CK2-α was inversely correlated with miR-125b expression in breast tumors, indicating the relevance of these potential oncogenic proteins in breast cancer patients. Our results support a prognostic role for CK2-α, whose expression may help clinicians predict breast tumor aggressiveness. In particular, our results show that restoration of miR-125b expression or knockdown of ENPEP, CK2-α, CCNJ, or MEGF9 may provide novel approaches for the treatment of breast cancer.

2.2 HEMATOPOIETIC TRANSPLANTATION & IMMUNOTHERAPY

2.2.1 Program 6: Molecular biology of transplantation



The main lines of research are:

A. Clinical Immunology
B. Technological Development

Our professionals have teaching, healthcare, and research obligations in the area of Immunology and Immunogenetics.

Our laboratory is actively involved in various research projects with clinical groups of the hospitals that we give support to, as well as the cord blood bank of the BST. All these studies are grouped in the section of Clinical Immunology.

We highlight the development of own protocols for HLA typing, especially in applications for diagnosis of diseases of autoimmune origin, which have been conducted in recent years. Some of these protocols have already reached the stage of commercialization in collaboration with an external company. Currently the development has been directed towards the use of new technologies, such as next-generation sequencing, in the HLA high-resolution typing. These examples demonstrate our ability to go all the way from the study of basic mechanisms and knowledge generation, until the application of the results in the laboratory and its extension to a commercial application.

PERSON IN CHARGE
María José Herrero Mata

INVESTIGATORS

José Luis Caro Oleas
Francesc Rudilla Salvador

ONGOING RESEARCH PROJECTS

Principal investigator: Eva Martínez Cáceres, (H Germans Trias i Pujol, María José Herrero Mata (BST)

Identification of biomarkers of tolerogenicity and cell -therapy response in autoimmune diseases (Multiple Sclerosis)
Funding organisation: Carlos III Health Institute
File N°: PI11/02416
Duration: 2012 to 2014

Principal investigator: Ricardo Pujol Borrell (H Vall d'Hebron), María José Herrero Mata (BST)

Consolidated immunology research group
Funding organisation: AGAUR
File N°: 2009 SGR 1442
Duration: 2009 to 2013

Principal investigator: Monica Martínez Gallo (H Vall d'Hebron), María José Herrero Matas (BST)

Cell mediated immunity in the diagnosis of combined immunodeficiency.
Funding organisation: Carlos III Health Institute
File N°: PI11/01086
Duration: 2012 to 2014

PUBLICATIONS

Vives-Pi M, Takasawa S, Pujol-Autonell I, Planas R, Cabre E, Ojanguren I, Montraveta M, Santos AL, Ruiz-Ortiz E. Biomarkers for Diagnosis and Monitoring of Celiac Disease J CLIN GASTROENTEROL, Apr;47(4):308-13, 2013 QUARTILE 2, DECILE 3, IMPACT FACTOR 3.16

Celiac disease (CD) is an autoimmune disorder, which damages the small intestine and is caused by ingestion of gluten in genetically susceptible individuals. The only known effective treatment is a lifelong gluten-free diet. Genetic risk factors have been identified and nearly all patients are HLA-DQ2 and/or HLA-DQ8 positive. Specific autoantibodies, IgA antitissue transglutaminase-2, antiendomysium, and antideaminated forms of gliadin peptide antibodies, are widely used as diagnostic aids in celiac patients. However, the discovery of new biomarkers may help in the diagnosis and follow-up of the disease. Recently, the molecule REG Iα, involved in tissue regeneration, has been proposed as a new biomarker of CD. REG Iα expression is increased in the target tissue and in the sera of celiac patients during damage and inflammation, decreasing after gluten-free diet. In this article we review the main biomarkers for diagnosis and monitoring of CD, focusing on the immune response-related mechanisms.

Ruíz-Ortiz E, Santos AL, Pujol-Autonell I, Planas R, Montraveta M, Pintos G, Doladé M, Cabré E, Vives-Pi M. Urinary levels of regenerating protein Iα do not differentiate celiac patients and healthy subjects. BIOMARKERS Mar;18(2):178-80, 2013. QUARTILE 2, DECILE 5, IMPACT FACTOR 2.215

Celiac disease is an autoimmune disorder induced by gluten in genetically predisposed people. The discovery of new biomarkers may help in the diagnosis and follow-up of celiac patients. Regenerating islet-derived 1 alpha (REGIα) - a biomarker related to tissue regeneration - is increased in serum at the onset of the disease, decreasing after gluten-free diet (GFD). As REGIα is a 18 kDa soluble glycoprotein, it may be detected in urine samples, increasing in celiac patients. We have determined REGIα levels by ELISA.

No differences were found among patients (onset or after GFD) and controls and no correlation exists among REGIα in sera and urine.

Pujol-Autonell I, Ampudia RM, Monge P, Lucas AM, Carrascal J, Verdaguer J, Vives-Pi M. Immunotherapy with Tolerogenic Dendritic Cells Alone or in Combination with Rapamycin Does Not Reverse Diabetes in NOD Mice. ISRN ENDOCRINOL. 2013:346987

Type 1 diabetes is a metabolic disease caused by autoimmunity towards β -cells. Different strategies have been developed to restore β -cell function and to reestablish immune tolerance to prevent and cure the disease. Currently, there is no effective treatment strategy to restore endogenous insulin secretion in patients with type 1 diabetes. This study aims to restore insulin secretion in diabetic mice with experimental antigen-specific immunotherapy alone or in combination with rapamycin, a compound well known for its immunomodulatory effect. Nonobese diabetic (NOD) mice develop spontaneous type 1 diabetes after 12 weeks of age. Autologous tolerogenic dendritic cells-consisting in dendritic cells pulsed with islet apoptotic cells-were administered to diabetic NOD mice alone or in combination with rapamycin. The ability of this therapy to revert type 1 diabetes was determined by assessing the insulitis score and by measuring both blood glucose levels and C-peptide concentration. Our findings indicate that tolerogenic dendritic cells alone or in combination with rapamycin do not ameliorate diabetes in NOD mice. These results suggest that alternative strategies may be considered for the cure of type 1 diabetes.

2.2.2 Program 7: Transplantation of donors & alternative sources

Hematopoietic stem cells are used in clinical situations to reconstitute bone marrow function. These cells can be obtained from bone marrow or mobilised peripheral blood of an adult, but also from the umbilical cord blood after giving birth. The administration of these cells to a patient regenerates haemapoietic and immune functions, contributing to the saving of many lives of patients suffering from cancer or acquired or genetic medullar insufficiency. The mission of the cell processing area of the Banc de Sang i Teixits is to transform the haemapoietic products collected in order to produce a therapeutic product with the expected qualities: safe and functional. The availability of high quality haemapoietic tissue is an essential factor for transplant and therefore investigating its improvement could contribute to therapeutic success.

All this is performed in BST laboratories using techniques for volume reduction, cell selection, cryopreservation and storage, and assays of product quality based on cell cultures and cytometric analysis. In addition, collaboration agreements have been established with centres of excellence that complement our own tools, including the Hospital del Mar Medical Research Institute, the Anthony Nolan Research Institute in the United Kingdom, as well as transplant centres of Catalonia to evaluate application of the products at a clinical level.

A. Collection and processing of high quality hemopoietic progenitor cells to enhance their graft

B. Selecting the best allogeneic donor

C. Mobilization and apheresis

D. Non-hematologic use of cord blood

PERSON IN CHARGE
Sergi Querol Giner

INVESTIGATORS
Carmen Azqueta Molluna
Marta Torrabadella Reynoso

ONGOING RESEARCH PROJECTS

Principal investigator: Sergi Querol Giner
Biomarkers of Stem Cell Circulating in Plasma of Cord Blood
Funding organisation: BST, Anthony Nolan Trust and Nottingham Trent University
Duration: 2009 to 2014

Principal investigator: Sergi Querol Giner, Nerea Castillo Flores (H Vall d'Hebron)
Clinical evaluation of the defrost method of umbilical cord blood previous to the infusion of stem cells and impact on clinical results
Funding organisation: BST
Duration: 2012 to 2014

Principal investigator: Carmen Azqueta Molluna
Implementation, validation and clinical evaluation of a functional cytometry method to predict the clonogenic potency of hematopoietic stem cells based on the determination of apoptopic cells with annexin
Funding organisation: BST
Duration: 2012 to 2014

Principal investigator: Marta Torrabadella de Reynoso
Evaluation of the utility of the umbilical cord plasma eye-drops for the treatment of Corneal tropic wounds
Funding organisation: BST
Duration: 2012 to 2014

Principal investigator: Renato Cunha (Faculty of Medicine of Ribeirâo Preto of Sâo Paulo University, Sergi Querol Giner (BST)
Prognostic association of genetic polymorphisms of drug metabolism and innate immune response on Umbilical Cord Blood Transplantation (UCBT) outcomes
Funding organisation: Institut National de la Santé et la Recherche Médicale, Sâo Paulo State Research Foundation, Brazil
Duration: 2012 to 2014

Principal investigator: Lawrence D. Petz (Stemcyte, International Blood Center), Sergi Querol Giner (BST)
Developing the special inventory of homozygous CCR5 delta32 cord blood units.
Unrelated Cord blood transplantation for patients with advanced AIDS using Δ32CCR5 / Δ32CCR5 single unit or Δ32CCR5 / Δ32CCR5 and CCR5Δ32/CCR5 double cord units.
Funding organisation: Stemcyte, International Blood Center
Duration: 2012 to 2014

Principal investigator: José Antonio Pérez Simón (H Virgen del Rocío), Sergi Querol Giner (BST)
Phase I/II clinical trial to treat refractory to first line treatment GVHD by sequential infusion of allogenic mesenchymal cells expanded in vitro
Funding organisation: Spanish Ministry Health Social Service & Equality
File N°: CSM/EICH2010 TRA-175
Duration: 2011 to 2011

Principal investigator: Cristina Diaz Heredia (H Vall d'Hebron), Sergi Querol Giner & Dolors Castellà Cahiz (BST)

Phase I/II clinical trial to evaluate the safety and effectiveness of the mobilization and collection of CD34+ cells after treatment with mozobil and filgrastim in Fanconi anemia patients for subsequent use in gene therapy trials

Funding organisation: Spanish Ministry Health Social Service & Equality

File N°: EC11-559

Duration: 2012 to 2014

PUBLICATIONS

Díaz-Beyá M, Brunet S, Nomdedéu J, Tejero R, Díaz T, Pratcorona M, Tormo M, Ribera JM, Escoda L, Duarte R, Gallardo D, Heras I, Queipo de Llano MP, Bargay J, Monzo M, Sierra J, Navarro A, Esteve J. MicroRNA expression at diagnosis adds relevant prognostic information to molecular categorization in patients with intermediate-risk cytogenetic acute myeloid leukemia. LEUKEMIA Sep 27 2013. QUARTILE 1, DECILE 1, IMPACT FACTOR 9.56

Acute myeloid leukemia (AML) is a heterogeneous disease, and optimal treatment varies according to cytogenetic risk factors and molecular markers. Several studies have demonstrated the prognostic importance of microRNAs (miRNAs) in AML. Here we report a potential association between miRNA expression and clinical outcome in 238 intermediate-risk cytogenetic AML (IR-AML) patients from 16 institutions in the CETLAM cooperative group. We first profiled 670 miRNAs in a subset of 85 IR-AML patients from a single institution and identified 10 outcome-related miRNAs. We then validated these 10 miRNAs by individual assays in the total cohort and confirmed the prognostic impact of 4 miRNAs. High levels of miR-196b and miR-644 were independently associated with shorter overall survival, and low levels of miR-135a and miR-409-3p with a higher risk of relapse. Interestingly, miR-135a and miR-409-3p maintained their independent prognostic value within the unfavorable molecular subcategory (wild-type NPM1 and CEBPA and/or FLT3-ITD), and miR-644 retained its value within the favorable molecular subcategory. miR-409-3p, miR-135a, miR-196b and mir-644 arose as prognostic markers for IR-AML, both overall and within specific molecular subgroups.

Brunet S, Martino R, Sierra J. Hematopoietic transplantation for acute myeloid leukemia with internal tandem duplication of FLT3 gene (FLT3/ITD). CURR OPIN ONCOL. 2013 Mar;25(2):195-204. QUARTILE 1, DECILE 3, IMPACT FACTOR 4.101

PURPOSE OF REVIEW: Patients with acute myeloid leukemia (AML) traditionally classified as having an intermediate cytogenetic risk [mostly cytogenetically normal AML (CN-AML)] really include a significant proportion of cases with a poor outcome. This is based on the molecular findings at diagnosis, mainly the presence of internal tandem duplication in the FMS-like tyrosine kinase 3 gene(s) (FLT3/ITD). Optimal postremission therapy for these high-risk molecular cases is not well established; as the prognosis is adverse hematopoietic cell transplantation (HCT), mainly allogeneic HCT (allo-HCT), is the most widely accepted strategy. RECENT FINDINGS: As a rule, patients with FLT3/ITD have a poor outcome with conventional chemotherapy alone. Only patients with an associated nucleophosmin 1 (NPM1) mutation and those with a low mutated-to-wild-type allelic ratio of FLT3/ITD have less unfavorable outcome. Most studies show an advantage of allo-HCT in first complete remission (CR1), with higher 3-5 year disease-free survival and lower relapse risk than with chemotherapy or autologous transplantation (auto-HCT). Regarding allo-HCT proceeding early after reaching CR1 seems to improve survival, rather than after several courses of consolidation chemotherapy. SUMMARY: Patients with intermediate-risk cytogenetics AML and FLT3/ITD, especially NPM1-wild cases and

those NPM1 mutated with a high allelic ratio, should proceed to allo-HCT if possible early after achieving CR1.

Alvarez-Gonzalez C, Duggleby R, Vagaska B, Querol S, Gomez S, Ferretti P, Madrigal A. Cord blood Lin-CD45- embryonic-like stem cells are a heterogeneous population that lack self-renewal capacity. PLOS ONE 2013 Jun, 8, 6: e67968. QUARTILE 1, DECILE 2, IMPACT FACTOR 4.092

Barba P, Martino R, Pérez-Simón JA, Fernández-Avilés F, Castillo N, Piñana JL, López-Anglada L, Rovira M, Bosch F, Carreras E, Corral LL, Sierra J, Valcárcel D. Combination of the Hematopoietic Cell Transplantation Comorbidity Index and the European Group for Blood and Marrow Transplantation Score Allows a Better Stratification of High-Risk Patients Undergoing Reduced-Toxicity Allogeneic Hematopoietic Cell Transplantation. BIOL BLOOD MARROW TRANSPLANT, 20, 66-72 2013. QUARTILE 2, DECILE 3, IMPACT FACTOR 3.87

This study was conducted to determine whether the integration of the hematopoietic cell transplantation (HCT) Comorbidity Index (HCT-CI) and the European Group for Blood and Marrow Transplantation (EBMT) score would improve their individual capacity for stratification of high risk HCT candidates. A total of 442 consecutive patients receiving an allogeneic HCT after reduced toxicity conditioning were included. Final HCT-CI and EBMT scores were calculated and validated. Then, patients were grouped into a 6-category new combination model according to the HCT-CI (0, 1-2, ≥3) and EBMT scores (0-3, 4-7) and its predictive capacity was also evaluated. Median HCT-CI and EBMT scores were 3 and 4, respectively. Increased HCT-CI was associated with higher 4y-NRM and lower 4y-OS while a high EBMT score was associated with higher 4y-NRM. The HCT-CI showed a trend for a better predictive capacity than the EBMT score (c-statistic 0.6 vs 0.54, p=0.1). According to the new model, patients within HCT-CI= 0 and HCT-CI= 1-2 groups had similar risk of NRM independently of their EBMT score. Within the HCT-CI≥ 3 group, patients with low EBMT score showed lower NRM (25% vs 40%, p=0.04) and a trend to higher OS (52% vs 36%, p=0.06) than patients with high EBMT score. Moreover, these patients with HCT-CI ≥3 and EBMT score 0-3 had similar outcomes than those with HCT-CI= 1-2. In conclusion, the combination of HCT-CI and the EBMT score is feasible and might contribute to a better identification of high risk patients, improving selection of best allo-HCT candidates.

Sánchez-Ortega I, Arnan M, Patiño B, Herrero MJ, Querol S, Duarte RF. Early engraftment and full-donor chimerism after single-cord blood plus third-party donor dual transplantation in patients with high-risk acute leukemia. BONE MARROW TRANSPLANT. 2013 Aug 12. QUARTILE 1, DECILE 3, IMPACT FACTOR 3.746

Hoyos M, Nomdedeu JF, Esteve J, Duarte R, Ribera JM, Llorente A, Escoda L, Bueno J, Tormo M, Gallardo D, de Llano MP, Martí JM, Aventín A, Mangues R, Brunet S, Sierra J. Core binding factor acute myeloid leukemia: The impact of age, leukocyte count, molecular findings, and minimal residual disease. EUR J HAEMATOL Sep;91(3):209-18; 2013. QUARTILE 2, DECILE 5, IMPACT FACTOR 2.614

PURPOSE: Most patients with acute myeloid leukemia (AML) and genetic rearrangements involving the core binding factor (CBF) have favorable prognosis. In contrast, a minority of them still have a high-risk of leukemia recurrence. This study investigated the adverse features of CBF-AML that could justify investigational therapeutic approaches. PATIENTS AND METHODS: One hundred and fifty patients (median age 42 years, range 16-69) with CBF-AML (RUNX1-RUNX1T1 n=74; CBFB-MYH11 n=76) were prospectively enrolled into two consecutive CETLAM protocols at 19 Spanish institutions. Main clinic and biologic parameters were analyzed in the whole series. In non-selected cases with available DNA samples, the impact of molecular characterization and minimal residual disease (MRD) was also studied. RESULTS: Overall, complete remission (CR) rate was 89% (94% in

<50 years-old and 72% in >50 years, P=.002). At 5 years, cumulative incidence of relapse (CIR) was 26±1%, disease-free survival (DFS) 62±6%, and overall survival (OS) 66±4%. In multivariate analyses, leukocyte count above 20x109 /l, BAALC over-expression and high copy numbers of RUNX1-RUNXT1 or CBFB-MYH11 after induction chemotherapy (CT) led to increased relapse rate. Regarding OS, age >50 years, leukocyte count above 20x109 /l and increased MN1 expression were adverse features. CONCLUSION: Age, leukocyte counts, BAALC and MN1 gene expressions as well as high and copy numbers of RUNX1-RUNXT1 or CBFB-MYH11 after induction chemotherapy are useful tools to predict the outcome and should be considered for risk-adapted therapy.

Radke TF, Barbosa D, Duggleby RC, Saccardi R, Querol S, Kögler G. The Assessment of Parameters Affecting the Quality of Cord Blood by the Appliance of the Annexin V Staining Method and Correlation with CFU Assays. STEM CELLS INTERNATIONAL Mar 7, 2013

The assessment of nonviable haematopoietic cells by Annexin V staining method in flow cytometry has recently been published by Duggleby et al. Resulting in a better correlation with the observed colony formation in methylcellulose assays than the standard ISHAGE protocol, it presents a promising method to predict cord blood potency. Herein, we applied this method for examining the parameters during processing which potentially could affect cord blood viability. We could verify that the current standards regarding time and temperature are sufficient, since no significant difference was observed within 48 hours or in storage at 4°C up to 26°C. However, the addition of DMSO for cryopreservation alone leads to an inevitable increase in nonviable haematopoietic stem cells from initially 14.8% ± 4.3% to at least 30.6% ± 5.5%. Furthermore, CFU-assays with varied seeding density were performed in order to evaluate the applicability as a quantitative method. The results revealed that only in a narrow range reproducible clonogenic efficiency (ClonE) could be assessed, giving at least a semiquantitative estimation. We conclude that both Annexin V staining method and CFU-assays with defined seeding density are reliable means leading to a better prediction of the final potency. Especially Annexin V, due to its fast readout, is a practical tool for examining and optimising specific steps in processing, while CFU-assays add a functional confirmation.

Sierra J. Els trasplantaments de progenitors hematopoètics a Catalunya: lideratge i inovació. ANNALS DE MEDICINA 96; 2-4, 2013

2.3 REPARATIVE & IMMUNOMODULATORY THERAPY

2.3.1 Program 8: Substitutive & reparative therapy & Program 9: Large-scale production of cells & tissues

Based on the conviction that cell therapies will be one of the main exponents of medicine in the future, the Banc de Sang i Teixits has promoted its Advanced Cell Therapy Division under the name of Xcelia. The purpose of this division is to develop personalised, safe cell medicines and tissue engineering to improve people's health. In accordance with this purpose and taking into account that the products of advanced cell therapy are considered drugs, Xcelia research is centred on four basic lines:

A. The development of candidates for cell drugs.

B. The development of bioprocesses under GMP standards.

C. The performance of non-clinical studies under GLP regulations.

D. The performance of clinical studies under GCP regulations.

The "MEDCEL" and "FACTOCEL" projects have been the driving forces behind this research activity. The first has enabled developing a pipeline composed of four products called Xcel-m-condro-alpha (mesenchymal cells for the treatment of arthrosis), Xcel-p-hemato-alpha (expanded hematopoietic stem cells for the treatment of myeloid aplasia), Xcel-mt-osteo-alpha (product of tissue engineering for the treatment of bone injuries) and Xcel-t-immuno-alpha (CMV-specific T-cells for the treatment of post transplant infections). At present these products are in different stages of development ranging from non-clinical studies to clinical phases I/II.

On the other hand, the "FACTOCEL" project has enabled the development of the specialised infrastructures and teams to work in compliance with the requirements of

GMP. As a result of this project new production facilities, with a capacity to manufacture up to 600 batches/year, are now completed.

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ONGOING RESEARCH PROJECTS

Principal investigator: Joan Garcia Lopez

FACTOCEL – Enlargement of the production facilities of a factory for producing cell drugs for regenerative medicine.
Funding organisation: Spanish Ministry of Economy and Competitivity
File N°: PLE2009-0092
Duration: 2009 to 2013

Principal investigator: Joan Garcia Lopez

REDONTAP-Continuous Proliferation & Simultaneous Maturation of Haematopoietic Stem Cells into Blood Cell Lineages
Funding organisation: European Commission
File N°: 229328
Duration: 2012 to 2014

Principal investigator: Joan Garcia Lopez

MEDAVAN – Advanced cell therapies: cellular products and tissue engineering
Funding organisation: Spanish Ministry of Economy and Competitivity
File N°: IPT-300000-2010-17
Duration: 2010 to 2013

Principal investigator: Joan Garcia Lopez

Injectable bone matching last generation hydrogels and bioactive allogenic products for fractures treatment
Funding organisation: Spanish Ministry of Economy and Competitivity
File N°: IPT-2012-0745-300000
Duration: 2013 to 2015

Principal investigator: Joan Garcia Lopez
Incorporation to the TERCEL network (Cell Therapy) of the RETICS
Funding organisation: Carlos III Health Institute
File N°: RD12/0019/0015
Duration: 2013 to 2016

Principal investigator: Joan Garcia Lopez
Production of 100 doses of human cardiac stem cells all derived from a single human cardiac stem cells clone, or derived from a reduced number of clones, all from the same master cell stock
Funding organisation: StemCellsOpCo
Duration: 2012 to 2014

Principal investigator: Enric Cáceres Palou (H Vall d'Hebron), Joan Garcia Lopez (BST)
Prospective randomized clinical trial comparing the spinal fusion in patients with degenerative pathology of lumbar spine, using autologous mesenchymal stem cells immobilized in human bone particles versus autologous iliac crest bone graft of the own patient
Funding organisation: Spanish Ministry of Health Social Service & Equality
File N°: EC10-209
Duration: 2012 to 2014

Principal investigator: Santiago Suso Vergara (H Clínic), Joan Garcia Lopez (BST)
Allogenic cell therapy pilot clinical trial of ex-vivo expanded adult stem cells conjugated with allogenic bone scaffold for the hip fracture treatment in elderly.
Funding organisation: Spanish Ministry of Health Social Service & Equality
File N°: EC11-158
Duration: 2012 to 2014

Principal investigator: Xavier Montalbán Gairin (H Vall d'Hebron), Joan Garcia Lopez (BST)
Transplantation of autologous mesenchymal stem cells from bone marrow as a potential therapeutic strategy for the treatment of multiple sclerosis
Funding organisation: Spanish Ministry of Health Social Service & Equality
File N°: EC10-266
Duration: 2012 to 2014

Principal investigator: Marius Aguirre Canyadell (H Vall d'Hebron), Joan Garcia Lopez (BST)
Autologous mesenchymal stem cell therapy applied to the osteonecrosis of the femoral head
Funding organisation: Spanish Ministry of Health Social Service & Equality
File N°: EC10-208
Duration: 2012 to 2014

Principal investigator: Joan Carles Monllau Garcia (ICATME), Joan Garcia López (BST)
A safety and efficacy phase i/iia pilot clinical trial for the meniscus lesion healing by means of autologous mesenchymal stem cells infiltration
Funding organisation: Spanish Ministry of Health Social Service & Equality
File N°: EC11-436
Duration: 2012 to 2014

Principal investigator: César García Fontecha (Bioengineering, orthopaedics and paediatric surgery, H Vall d'Hebron), Margarita Codinach Creus (BST)
Single-port fetoscopic repair of myelomeningocele using amniotic stem cells in sheep
Funding organisation: Carlos III Health Institute
File N°: PI10/02466
Duration: 2011 to 2013

Principal investigator: Joan Francesc Julián Ibañez (IGTP), Joan Ramon Grífols Ronda (BST)
Evaluation of volumetric reconstruction using platelet gel from healthy donors in the conservative treatment of breast cancer.
Funding organisation: ACC10
File N°: VALTEC09-2-0098
Duration: 2009 to 2014

Principal investigator: Joan Francesc Julián Ibañez (IGTP), Joan Ramon Grífols Ronda (BST)
Contribution of platelet rich plasma in the differentiation of mesenchymal stem cells
Funding organisation: B. Braun Surgical, S.A.
Duration: 2012 to 2014

Principal investigator: Marius Aguirre Canyadell (H Vall d'Hebron), Joaquim Vives Armengol i Marta Caminal Bobet (BST)
Experimental cell therapy study for the treatment of critical size defect with "ex vivo" expanded adult mesenchymal stem cells
Funding organisation: Carlos III Health Institute
File N°: PI11/02231
Duration: 2012 to 2014

Principal investigator: Joan Vidal Samsó (Institut Guttmann), Joan Garcia Lopez (BST)
A prospective, open-label, Intrathecal injection single-dose, phase I/IIa pilot study to assess the safety and to obtain preliminary efficacy results of allogenic stem cells from umbilical cord transplantation in patients with complete chronic traumatic spinal cord injury
Funding organisation: Fundació la Marató de TV3
File N°: 122831
Duration: 2013 to 2015

Principal investigator: Lluís Orozco Delclos (Teknon), Alba Bosch Llobet (BST)
Randomised, multicentre, controlled, parallel, double blind clinical trial to assess the efficiency of autologous platelet-rich plasma in the treatment of "tennis leg" muscle sprains.
Funding organisation: Carlos III Health Institute
File N°: P08/0724
Duration: 2009 to 2013

Principal investigator: María José Martínez Zapata (Hospital Santa Creu i Sant Pau), Alba Bosch Llobet (BST)
Prevention of postoperative bleeding: A multicenter, randomized, parallel, controlled clinical trial, evaluating the efficacy of fibrin glue and tranexamic acid in patients undergoing interventions for sub-capital femoral fracture.
Funding organisation: Spanish Ministry of Health Social Service & Equality
File N°: EC11-341
Duration: 2012 to 2013

PUBLICATIONS

Callejo J, Salvador C, González-Nuñez S, Almeida L, Rodriguez L, Marqués L, Valls A, Lailla JM. Live birth in a woman without ovaries after autograft of frozen-thawed ovarian tissue combined with growth factors. J OVARIAN RES. 2013 May 7;6(1):33. QUARTILE 2, DECILE 5, IMPACT FACTOR 2.57

Currently, cryopreservation of oocytes, embryos and ovarian tissue is considered the basis of fertility preservation programs for women with cancer and other diseases who are rendered sterile by gonadotoxic drugs or radiation.Numerous studies have confirmed that autograft of frozen-thawed ovarian tissue can restore ovarian function and fertility. A total of twenty-two live births have been reported but we still have to consider this technique as experimental. The main problem is that the implant undergoes ischemia until neoangiogenesis is restored, resulting in significant follicular loss.At the moment, there are numerous publications in different medical fields that publish successful experiences with plasma rich in platelets (PRP) in different clinical situations promoting angiogenesis. Thus, we considered the possibility of using it in the field of ovarian autologous transplantation in order to improve the vascularization of the implant and its quality. For this, both thawed ovarian tissue as practiced pockets on the rear side of the broad ligament which have been placed, have been impregnated with PRP. We can say that the implant treated in this way has had a rapid and successful response.We report a special interesting case because this is the first time that this technique is performed successfully in a woman without ovaries combined with growth factors to promote neoangiogenesis. Obviously, the results of the hormonal response come exclusively from the implanted tissue in these special conditions.

Fonseca C, Caminal M, Peris D, Barrachina J, Fàbregas PJ, Garcia F, Cairò JJ, Gòdia F, Pla A, Vives J. An arthroscopic approach for the treatment of osteochondral focal defects with cell-free and cell-loaded PLGA scaffolds in sheep. CYTOTECHNOLOGY 15 May, 2013. QUARTILE 3, DECILE 8, IMPACT FACTOR 1.207

Osteochondral injuries are common in humans and are relatively difficult to manage with current treatment options. The combination of novel biomaterials and expanded progenitor or stem cells provides a source of therapeutic and immunologically compatible medicines that can be used in regenerative medicine. However, such new medicinal products need to be tested in translational animal models using the intended route of administration in humans and the intended delivery device. In this study, we evaluated the feasibility of an arthroscopic approach for the implantation of biocompatible copolymeric poly-d,l-lactide-co-glycolide (PLGA) scaffolds in an ovine preclinical model of knee osteochondral defects. Moreover this procedure was further tested using ex vivo expanded autologous chondrocytes derived from cartilaginous tissue, which were loaded in PLGA scaffolds and their potential to generate hyaline cartilage was evaluated. All scaffolds were successfully implanted arthroscopically and the clinical evolution of the animals was followed by non invasive MRI techniques, similar to the standard in human clinical practice. No clinical complications occurred after the transplantation procedures in any of the animals. Interestingly, the macroscopic evaluation demonstrated significant improvement after treatment with scaffolds loaded with cells compared to untreated controls.

Garcia J, Navarro A, Genís X. Les cèl.lules mare, el pròxim pas en el trasplantament de teixits ANNALS DE MEDICINA 96; 5-8, 2013

Garcia J, Oliver I, Vives J, Lopez JR, Coll R. Capítulo 69: Terapia celular avanzada y su aplicación clínica. APLICACIONES Y PRÁCTICA DE LA MEDICINA TRANSFUSIONAL. TOMO II. GCIAMT 2013

Quintana S, Navarro A, Navas E, Genís X, Ferrer R. Consent to donate some but not all organs or tissues. ORGANS, TISSUES & CELLS, (16), 37-39, 2013

The 1979 Spanish Law on Organ Transplantation permits the use of organs unless a specific objection has been stated by the donor during his/her life. Despite the resulting high rate of organ donation in Spain, about 15-20% of the population refuse to give permission. The reasons for donation refusal have been widely studied in detail. However partial refusal, defined as the approval to donate some organs or tissues and the refusal to donate others, is less studied. Partial donation is not uncommon and could be agreed by family, close friends or the court. The aim of this study is to quantify this phenomenon that negatively influences the success of organ donation. Information on partial refusal of organ and tissue donation was retrospectively collected in the Universitari Mútua de Terrassa Hospital (Barcelona, Spain).
From 2005 to May 2012, 55 organ donors were recruited in our centre. Ten potential donors had a contraindication to donate an organ or tissue, age being the most frequent reason. Of the remaining 45 cases, eight (18%) reported a refusal to donate tissues: five refused to donate tissues in general and in the remaining three cases, there was a refusal to donate bone tissue (N=3) and skin (N=2). Eighteen per cent of donors failed to donate some organs or tissues. Bone tissue donation is the one that generates most rejection, probably because relatives are worried about body integrity. There is a lack of knowledge on the vital importance of skin donation, and that its removal produces a very superficial scar. Additionally, the donation coordinators are usually less strident in their efforts when demanding tissues and accept partial refusal as a minor setback. Informing people adequately on the importance and usefulness of some tissues may help to minimize partial refusal.

Some of the projects performed in the BST during 2013 have been funded by the Ministry of Economy and Competitiveness and co-financed by the European Regional Development Fund (ERDF), within the National Plan for Scientific Research, Development and Innovation 2008-2011.