2016
ECLip Annual Meeting

March 8-9th 2016
School of Medicine
Santiago de Compostela

ABSTRACTS BOOK

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March 31st, World Lipodystrophy Day

CONTENTS

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AELiP
ASOCIACIÓN DE FAMILIARES Y AFECTADOS DE LIPODISTROFIAS
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Some words...,

Lipodystrophies are a very heterogeneous group of diseases, with a common feature: the lack or lost of adipose tissue. However, its diversity in terms of etiology, involved pathogenic mechanisms, clinical pictures, prognosis, and treatment response is enormous. Since year 2000, when the first gene related to lipodystrophy was discovered, more than 15 new loci have been found, and mechanisms as autophagy, transdifferentiation, impaired lipid droplets formation, autoimmunity or inflammation among others, have been proposed as possible pathogenetic process. Also amazing advances in therapeutical approaches have been reached with the use, for example, of recombinant human leptin, mainly in patients with generalised lipodystrophies. But also promising genetic therapies are being developed, mainly focused on progeroid syndromes.

Five years ago, a group of european researchers, devoted on clinical and basic investigation in lipodystrophies, decided that the time to work together had come, and that this could be a good way to advance, faster and more effectively, and so the European Consortium of Lipodystrophies began its path. In 2014, a group of people met in Bologna, invited by Giovanna Lattanzi, giving the first organising steps of ECLip, signing the Founding Act, and electing its Executive Board. A year later, in 2015 at Paris, organised by Jacqueline Capeau and Corinne Vigouroux, the Consortium taken its following decisions: to explore the possibilities to launch a european lipodystrophy patients registry and a virtual biobank; to look for funding and resources; and the commitment that next ECLip meetings should be devoted to the discussion about scientific topics. This last decision was a permanent demand from ECLip members, as the reason of being of this Consortium is the scientific discussion, the search for solutions to the problems which every day arise at the hospital office or at the lab bench.

During this last ECLip meeting in Santiago de Compostela, we have talked about, discussed, and shared our knowledge and skills; we have showed our last findings in this complex field, from new genes for known syndromes to interesting new pathogenic mechanisms or newfangled treatments. Moreover, for the first time, we have had the opportunity of hearing to the most important actors of this project, patients. Represented by Naca Perez de Tudela, President of the Spanish Lipodystrophy Advocacy Group (AELIP), and Juan Carrión, President of the Rare Diseases Spanish Federation (FEDER), they were the voice of those who are waiting for solutions. Finally, we agreed, representing to the most relevant Europeans teams in lipodystrophy research, with launching a patients registry and a virtual biobank during this year, which will be housed at Ulm University in Germany, with the invaluable support of Prof. Martin Wabitsch.

I would like to thank to all of the speakers and attendants, all of them with extremely busy agendas, their generosity and availability for coming to Santiago.

Lastly, ensuring ECLip continuity, Prof. Giuseppe Novelli has generously offered to host the 2017 ECLip meeting in Rome.

Ci vediamo a la Città Eterna!

David Araújo-Vilar, MD PhD
Professor of Medicine
Member, ECLip Executive Board

ECLip Executive Board

Prof. David Araújo-Vilar, Universidade de Santiago de Compostela, Spain
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Prof. Martin Wabitsch, University Medical Center Ulm, Germany

2016 ECLip Annual Meeting
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Program

March 8th

08:50 Welcome
Prof. David Araújo-Vilar, University of Santiago de Compostela, Spain

09:00 Opening Lecture: *Adipose tissue, foe or friend?*
Prof. Felipe F. Casanueva, University of Santiago de Compostela, Spain

09:30 Characteristic and atypical mutations in lipodystrophy patients
Prof. Katrin Hoffman, Martin Luther University Halle-Wittenberg, Germany

10:00 Central obesity, diabetes mellitus and hypertriglyceridemia: Understanding the Köbberling syndrome
Dr. Cristina Guillín-Amarelle, University of Santiago de Compostela, Spain

10:30 Fontaine-Petty syndrome, a rare cause of lipodystrophy, demonstrates a new pathogenesis for lipodystrophies
Prof. Raoul CM Hennekam, Academic Medical Center, University of Amsterdam, Netherlands

11:00 Coffee break

11:30 Progressive lipodystrophy associated with mutation in the *POLD1* gene
Prof Giuseppe Novelli, Universita Tor Vergata, Roma, Italy

12:00 Clinical reports of fat loss associated with disorders of the immune system: an opportunity for a further understanding of the pathogenesis of lipodystrophy
Prof. Ferruccio Santini/Dr Yaroslav Berger, University Hospital of Pisa, Italy

12:30 Decrease of osteocalcinemia linked with insulin resistance more than body fat mass in lipodystrophic syndromes, compared to obese and normal weight patients
Prof. Marie-Christine Vantyghem, Lille University Hospital, Lille, France

13:00 Celia's Encephalopathy (PELD): seipin, adipose tissue and beyond
Dr. Sofía Sánchez-Iglesias, University of Santiago de Compostela, Spain

13:30 Lunch

15:00 Young Researchers Session

15:00 Clinical, hormonal and molecular-genetic characteristics of inherited lipodystrophies in Russia
Dr Ekaterina Sorkina, Endocrinology Research Center, Moscow, Russia

15:20 Human induced pluripotent stem cells as a cellular tool for modelling laminopathies
Dr. Anne-Claire Guénantin, Centre de Recherche Saint-Antoine, Paris, France

15:40 Morpho-functional study of subcutaneous adipose tissue in patients affected by Familial Partial Lipodystrophy type 2-FPLD2
Dr Alessandra Gambineri, S. Orsola-Malpighi Hospital, Bologna, Italy

16:00 Coffee break

16:30 ECLip Databases (*for ECLip members only*)
Prof. Giovanna Lattanzi and Prof David Araújo-Vilar

March 9th

09:00 Lessons from *LMNA*-lipodystrophy in vitro models based on human mesenchymal stem cells that accumulate prelamin A
Dr Clara Isabel Rodríguez-López, BioCruces Health Research Institute, Spain

09:30 Modulation of brown adipose tissue differentiation in FPLD2
Prof. Giovanna Lattanzi, CNR, Unit of Bologna, Italy

10:00 Human SGBS cells as in vitro model for studying cellular phenotype of defects in lipodystrophy genes
Prof. Martin Wabitsch, University Medical Center Ulm, Germany

10:30 Maladaptative autophagy contributes to insulin resistance and altered adipocyte differentiation in Congenital Generalized Lipodystrophy due to PTRF/cavin-1 mutations.
Dr. Corinne Vigouroux, Centre de Recherche Saint-Antoine, Paris, France

11:00 Application of proteomics in lipodystrophy research
Prof. Juan Ramón Peinado-Mena, University of Castilla-La Mancha, Spain

11:30 Coffee break

12:00 Outcome of intensive dietary intervention in patients with lipodystrophy
Dr. Anne Stears, University of Cambridge, UK

12:30 Effects of metreleptin therapy on adipose tissue, liver and and systemic inflammation markers in lipodystrophic patients
Dr. Camille Vatier, Centre de Recherche Saint-Antoine, Paris, France

13:00 Antisense strategy in familial partial lipodystrophy
Prof. Harmut Schmidt, Universitätsklinikum Münster, Germany

13:30 MG132 enhances progerin clearance and reverses cellular phenotypes in Hutchinson-Gilford progeria cells.
Dr. Karim Harhouri, Faculty of Medicine La Timone, Marseille, France

14:00 Lunch

15:30 How advocacy groups can support research: the Spanish experience
Mr. Juan Carrión, President of the Spanish Federation of Rare Diseases

15:50 AELIP: an example of advocacy group supporting lipodystrophy patients and relatives
Ms. Naca Pérez de Tudela, President of AELIP

16:10 Coffee break

16:45 Closing lecture: Inflammation in progeroid laminopathies
Prof. José M. P. Freije, Universidad de Oviedo, Spain

Venue:

Aula Castelao (2nd floor)
Facultade de Medicina
Rua de San Francisco s/n
15782 Santiago de Compostela, Spain
Free registry

Contact mail: lipodistrofias@gmail.com

SPEAKER BIOSKETCHES

Dr. Yaroslav Berger

Yaroslav Berger, Ph.D., works as a postdoctoral fellow in the Department of Metabolism and Endocrinology in the University of Pisa after he DTI-IMPORT International Postdoctoral Program of the Dulbecco Telethon Institute. He obtained his PhD in 2012 at the Faculty of Medicine in the Technion - Israel institute of Technology in Haifa. His thesis was to establish the role of Endothelial Progenitor Cells in Cardiovascular Disease and Sleep Apnea. After the graduation, he continued working as a postdoc fellow at the same faculty until October 2014, when he joined the Dr. Maffei group in Pisa to find a link between the mutations in DNA polymerase delta and loss of adipose tissue in MDPL syndrome. In addition, during the last year, he joined a novel project in the lab to investigate the potential changes in regulation of the immune system in lipodystrophy.

Mr. Juan Carrión

Juan Carrión is the father of his little princess Celia. He is social worker, and coordinator of Social Work Department of Penitentiary Murcia I (Interior Ministry). He is member of the Advisory Committee of Rare Diseases in the Spanish Ministry of Health, President of the association of rare diseases D'GENES, President of the Spanish Federation of Rare Diseases (FEDER), President of the Foundation for Research on Rare Diseases (FEDER FOUNDATION), President of the Latin American Alliance for Rare Diseases (ALIBER), board member and technical coordinator of the association of families and affected of lipodystrophy (AELIP), and technical coordinator of the Multidisciplinary Center for Comprehensive Care to individuals and families with rare diseases Celia Carrión Pérez de Tudela Canovas.

Prof. Felipe F. Casanueva

Professor Felipe F Casanueva is currently Full Professor of Medicine and Head of the Endocrine Division at the Department of Medicine, University Hospital (CHUS), Santiago de Compostela University.
He is currently the President of the Spanish Society for Obesity (SEEDO) and Scientific Director of the Center for Biomedical Research on Obesity and Nutrition (CIBERobn), period 2006-2015.
Holds three Honorary Doctorates, of the University of Lodz, Poland; from the University of Caiseri, Turkey; and also from the University of Belgrade, Serbia. Is European Hormone Medal of European Society for Endocrinology's and full member of the Real Academia de Medicina y Cirugia de Galicia (RAMYCGA), and in the past was President of the Spanish Endocrine Society (SEEN); the European Federation of Endocrine Societies (Currently SEE), the International Society for Endocrinology (ISE) and The Pituitary Society.
Dr Casanueva has published more of 600 papers in peer review international journals with a cumulative Impact Factor of 1708,72. Has written 48 chapters on international books and textbooks and delivered 137 lectures by invitation at International Congresses. His current H-index is 75.
He has received several awards and acknowledgements, among them, the Xunta de Galicia Award for research (two times), The Spanish Society of Endocrinology highest award, The Rey Jaime I award, Danone, and the International Geoffrey Harris Award in Neuroendocrinology.

Member of several International Boards of learned journal and Continental Editor of Clinical Endocrinology until 2015.

Prof. José M.P. Freije

José M.P. Freije is an Associate Professor of Biochemistry and Molecular Biology at the University of Oviedo, Spain. After his predoctoral research, his work was aimed at studying the molecular mechanisms of cancer invasion and metastasis. This work led to the description of several new matrix metalloproteases, the biochemical characterization of metastasis suppressor proteins and the exploration of their utility to identify anti-cancer compounds preferentially active against the most aggressive tumor cells. The research work carried out by José M.P. Freije over the last years has approached different aspects of cancer and aging, using animal models as an essential tool to investigate the molecular mechanisms underlying these processes and to explore therapeutic strategies against the pathologic alterations that they involve.

Dr. Alessandra Gambineri

Alessandra Gambineri received her specialty trainings in Endocrinology at Bologna University in 2002 and reached her PhD in Clinical and Experimental Medical Science at the University of Verona in 2009. Since 2010 she has a position as Assistant Professor at the University of Bologna. She has conducted several clinical trials as Principal Investigator related to diabetes mellitus and lipodystrophies. She is interested in female hyperandrogenic disorders, female hypogonadism and severe insulin resistance states, steroids and metabolism, and she has published more than 75 full papers.

Dr. Anne-Claire Guénantin

Anne-Claire Guénantin, PhD, works as a post-doctoral researcher in cellular and molecular biology at Saint-Antoine Research Center (INSERM UMR_S938) and Medical University Pierre and Marie Curie (Paris 6), France, in the field of the pathophysiology of stem cells and laminopathies. After a PhD regarding cardiomyocyte differentiation of pluripotent stem cells, she joined the team of Corinne Vigouroux in 2012 to develop her expertise in endothelial and adipocyte differentiation of induced pluripotent stem cells (iPSC).

Dr. Cristina Guillín-Amarelle

Cristina Guillín-Amarelle studied Medicine at the University of Santiago de Compostela, and between the years 2009 and 2013 specialized in Endocrinology and Nutrition. At the present time, Dra Guillín works as an Endocrinologist at the Hospital of Santiago de Compostela, and is performing her predoctoral studies on the lipodystrophies topic, under the supervision of Prof. Araújo Vilar.

Dr. Karim Harhouri

Karim Harhouri is a postdoctoral fellow at Nicolas Levy's laboratory in the School of Medicine of Aix-Marseille University. His principal research interest is the molecular basis of Hutchinson-Gilford progeria, particularly he is trying to unveil the putative clearance pathways of progerin as well as potential new therapies for children with this syndrome.

Prof. Raoul Hennekam

Raoul Hennekam received his specialty trainings in Paediatrics and in Clinical Genetics at Utrecht University. He was appointed as professor of Paediatrics and Clinical Genetics in 2002 at the AMC of University of Amsterdam. During 2005-2010 he worked in London at Institute of Child Health and Great Ormond Street Hospital as professor of Clinical Genetics and Dysmorphology. He is presently working as Professor of Paediatrics and Translational Genetics in Amsterdam.

Main scientific interests include intellectual disabilities, autism, connective tissue disorders, and (molecular) dysmorphology. He is member of the Dutch Health Council, EUCERD, European Research Council, Editor of American Journal of Medical Genetics and of the European Journal of Medical Genetics, author of >450 papers in peer-reviewed journals (H-index 64) and 23 chapters in international texts, co-chair of the international Morphology Nomenclature Committee, and senior editor of 'Gorlin's Syndromes of the Head and Neck'.

Prof. Katrin Hoffmann

Prof. Hoffmann is Director of the Institute of Human Genetics, Martin Luther University of Halle-Wittenberg, Member of the Clinical Ethics Committee of the University Hospital Halle, and Member of the Commission guidelines of the Society of Human Genetics.

Prof. Giovanna Lattanzi

Dr. Giovanna Lattanzi is a Researcher at the National Research Council (CNR) Institute for Molecular Genetics (IGM), Bologna, Italy. She is director of the Bologna Unit of IGM. Dr. Lattanzi and her research team are elucidating the cell biology of lamins, emerin and lamin-linked proteins under normal or pathological conditions. Her first study on lipodystrophy has demonstrated the involvement of prelamin A in disease pathogenesis. Further studies have deepened prelamin A interplay with nuclear partners and chromatin and shown prelamin A involvement in genome maintenance during normal ageing. More recent papers from Dr. Lattanzi lab have reported on the efficacy of drug treatments based on the use of rapamycin alone or in combination with retinoic acid for the recovery of Mandibuloacral dysplasia and progeria cellular phenotype. Dr. Lattanzi has been partner of the Euro-laminopathies project. She is the coordinator of the Italian Network for Laminopathies aimed at connecting scientists, clinicians and families to improve quality of research and patient care.

Prof. Giuseppe Novelli

Giuseppe Novelli Is Head of the Human Genetics Research Unit at The Tor Vergata University of Rome (Italy). He served Tor Vergata University as Dean of the School of Medicine during the period 2008-2011. Professor Novelli is at present Rector of the University of Rome Tor Vergata (2013-2019). He is member of the Pharmacogenetics Working Party of the Committee for Human Medicinal Products (CHMP) at the EMA (European Medicines Agency) in London. He was Board Member of the Italian National Agency for Evaluation of Universities and Research Institutes (ANVUR) (2010-2013). He published over 400 original scientific publications including invited reviews for leader Journals in Human Genetics. The H-index is 53. Primary focus of G. Novelli was the mapping, identification and characterization of human-disease genes (e.g. Laron dwarfism, DiGeorge syndrome, Mandibuloacral dysplasia, Friedrich ataxia vitamin-E-deficiency, spinal muscular atrophy, hypoplastic glomerulocystic kidney disease, myotonic dystrophy). Recently he is actively involved in the field of complex diseases and pharmacogenetics.

Prof. Juan Ramón Peinado-Mena

Dr. Juan R. Peinado is Associate Professor of Cell Biology and Histology in the Faculty of Medicine of Ciudad Real, Spain. After his predoctoral research he made stays in several international laboratories, such as the Animal Physiology Department at the University of Nijmejen, Netherlands; the Department of Neuroendocrinology at INSERM, Rouen, France. He worked two years as Postdoc in the Department Of Biochemistry of the Louisiana Health Science Center (LSUHSC). He has also developed his research in Spanish centers of excellence such as proteolysis Laboratory located in the Scientific Park of Barcelona, belonging to CSIC; the Dept. of Biochemistry and Molecular Biology, University of Oviedo and the Department of Cell Biology, Physiology and Immunology at the University of Cordoba. His recent research focus on proteomic studies to face diseases that directly affect adipose tissue (obesity and / or lipodystrophy). He is also involved in proteomic studies on neurodegenerative disorders (Alzheimer), and brain tumor (glioblastoma).

Ms. Naca Pérez de Tudela

Naca Pérez de Tudela is the mom of Celia Carrión Pérez de Tudela Canovas. She is Thermomix commercial agent. She was founder and president of the association of rare diseases D'GENES (2008-2012). She is President of the association of families and affected of lipodystrophy (AELIP), and responsible for maintaining the Multidisciplinary Center for comprehensive care to individuals and families with rare diseases Celia Carrión Pérez de Tudela Canovas.

Dr. Clara I. Rodriguez-López

Clara I. Rodriguez obtained her Ph.D. in 1999 at the Universidad Autonoma de Madrid and the Centro de Biologia Molecular Severo Ochoa under the supervision of Prof. Manuel Fresno Escudero, working on parasite activation of the immune system. She next did a short one year postdoc in the same center in Dr. Maria Luisa Salas' Lab specializing on viral signaling. In 2000 she moved to the National Cancer Institute at Frederick (NIH; USA) for postdoctoral training in genetic manipulation in mammals. It was during those five years at the NCI where she was introduced and gained experience working on pluripotent stem cells. Dr. Rodriguez returned to Spain as researcher at the Valencia Stem Cell Bank (Centro de Investigacion Principe Felipe). In 2006 she moved to the Hospital de Cruces (Bilbao) where she was awarded an investigator contract under the Miguel Servet program to start a new research group focused on stem cell based therapy. Currently, she is Group Leader of the Stem Cells and Cell therapy Laboratory at the BioCruces Health Research Institute, interested in the potential of human

stem cells for the study of human disease and the design of new therapies. She is the Principal Investigator of a national multicenter clinical trial of cell therapy applied to pediatric patients suffering from Osteogenesis Imperfecta.

Dr. Sofía Sánchez-Iglesias

Sofía Sánchez-Iglesias is a gardener from the heart and researcher by choice. She was born in Geneva (Switzerland) where she earned her Bachelor's degree in Biochemistry. In 2010, she received her Ph.D. at the University of Santiago de Compostela (Spain). Her predoctoral research was focused on the understanding of the molecular mechanisms involved in the pathogenesis of Parkinson's disease and the development of new pharmacological strategies for treatment and prevention. The incorporation in 2011 within the group of Prof. David Araújo-Vilar was a major turnaround that allow her to gain expertise in a broad variety of experimental techniques. The new lines of research were based on the molecular basis and clinical characterisation of familial lipodystrophies, and the recently described neurodegenerative disease associated with the c.985C>T mutation in seipin. Fruits of her research were 16 publications in internationally recognised journals. During her career she received various grants and also participated in several research projects.

Prof. Ferruccio Santini

Ferruccio Santini is Associate Professor of Endocrinology at the University of Pisa and Head of the Obesity Center at the Endocrinology Unit, University Hospital of Pisa. He obtained his Medical Degree at the University of Pisa in 1985 and his PhD in Endocrinological and Metabolic Sciences in 1996. Main scientific interest include the pathogenesis and physiopathology of obesity, lipodystrophies and related diseases, thyroid physiology and thyroid diseases. His research has been published in more than 110 articles quoted in Pubmed. He is member of the Endocrine Society, European Society of Endocrinology, Italian Society of Endocrinology, Italian Society of Obesity, Italian Society of Obesity Surgery, Italian Thyroid Association.

Prof. Harmut Schmidt

Prof. Hartmut Schmidt has completed his MD at the age of 25 years from Medical University of Hannover in Germany. He received postdoctoral training in gastroenterology at Medical University of Hannover, NIH (Bethesda), Charité (Berlin), and the University Hospital Münster. Since 2010 he serves as director of Department of Transplantation Medicine at University Hospital Münster. He has published more than 125 original articles.

Dr Ekaterina Sorkina

Ekaterina Sorkina is an endocrinologist and research assistant at the Clamp-technologies laboratory, Institution of Diabetes, Endocrinology Research Center in Moscow, Russia
She is also PhD fellow in Endocrinology, I.M. Sechenov First Moscow State Medical University, and scientific research in inherited lipodystrophies, being her scientific advisor Anatoly Tiulpakov, MD, PhD, paediatrician-endocrinologist, Chief of the Department and Laboratory of Inherited Endocrine Diseases in Endocrinology Research Center. She is a member of Moscow State Association of Endocrinologists, Russian Association of Endocrinologists, ESE, ENEA, ENDO, DGE, ADA, and the ambassador of EYES (European Young Endocrine Scientists) in Russia. Her scientific interest covers endocrinology and genetics, anti-age medicine, different hormonal and metabolic disorders, lipodystrophies (inherited and acquired), laminopathies, inherited forms of diabetes mellitus and insulin resistance. She is an author of 20 publications, 3 of them quoted on Pubmed.

Dr Anna Stears

Anna Stears is a Consultant in Diabetes and Endocrinology at Addenbrooke's Hospital, Cambridge, UK. She has responsibility for the day to day running and development of the National Severe Insulin Resistance Service, a national multidisciplinary service for adults and children with Severe Insulin Resistance and/or lipodystrophy. This highly specialised service is funded directly by NHS England. It is the only UK centre currently permitted to treat patients with lipodystrophy with leptin therapy. Anna is supported by colleagues in the Institute of Metabolic Science who have had a long standing clinical and research interest in the pathophysiology and treatment of syndromes of Severe Insulin Resistance and by a multidisciplinary team including Consultants in Paediatric Diabetes and Endocrinology, specialist nurses, dieticians and administrators

Dr. Camille Vatier

Camille Vatier is a consultant physician in Endocrinology and Nutrition at Assistance-Publique Hôpitaux de Paris, Saint-Antoine hospital, France. Her clinical activity focus comprises diabetes, and abnormal fat tissue distribution.

She joined the team of Corinne Vigouroux at Saint-Antoine Research Center (INSERM UMRS_938) in 2008 to develop her clinical expertise and experimental research in lipodystrophic syndromes and she is PhD fellow at University Pierre and Marie Curie (Paris 6) .

Since 2015, she has a teaching position in cellular biology at medical University Pierre and Marie Curie (Paris 6).

Prof. Marie Christine Vantyghem

Marie-Christine Vantyghem, MD, PhD, received her specialty trainings in Endocrinology, Diabetology and Metabolism at the University of Lille, France. She has been involved in the islet transplantation program at the University Hospital of Edmonton, Alberta, Canada on the clinical side with Prof Ryan and at the Pacific Northwest Research Institute at Seattle, USA with Prof Robertson. She was appointed professor of Endocrinology in 2011 and is head of the Endocrinology Department of Lille University Hospital, which cares for a population of more than 4 millions people. In 2009, she has obtained an interface contract with the INSERM Unit U1190, devoted to «Translational Research in Diabetes", directed by Prof F Pattou, and belonging to EGID (European Genomic Institute for Diabetes)

Her main research areas are islet transplantation and lipodystrophies with a large cohort of more than a hundred patients investigated. A biobank (plasmatheque, DNAtheque and adipose tissue bank) has been organised under the name project PHRC IL7 lipodystrophies. (ClinicalTrial.gov identifiers: NCT 14144660- NCT00446264 - NCT01148680).

She is member of the executive board of the French Endocrine Society, member of the European Society of Endocrinology, of the Endocrine Society, of the French and European Societies of Transplantation and has been or is involved in two FP7 programs and in the CITR registry. She works as an Associate editor for the Annals of Endocrinology.

Prof. Corinne Vigouroux

Corinne Vigouroux, MD, PhD, develops her medical and research activities in the field of the pathophysiology of insulin resistance and lipodystrophic syndromes.

She works at Assistance-Publique Hôpitaux de Paris, Saint-Antoine hospital, France, as an hospital endocrinologist and molecular biologist.

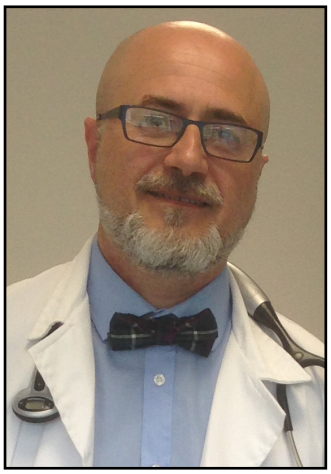
She has a teaching and research senior position in cellular and molecular biology at Saint-Antoine Research Center (INSERM UMR_S938) and Medical University Pierre and Marie Curie (Paris 6).

Prof. Martin Wabitsch

Martin Wabitsch MD, PhD is Professor of Pediatrics at the University of Ulm, Germany and is the Head of the Division of Pediatric Endocrinology and Diabetes at the Department of Pediatrics and Adolescents Medicine in Ulm's University Hospital (www.ped-u.de). His clinical research focus comprises childhood obesity, the physiology of body weight regulation in children, leptin deficiency in humans, and rare lipodystrophy syndromes. His experimental research focus is the biology of the human adipocyte. He and his group have established in vitro models for studying the biology of the human white and brown adipocyte including the human SGBS cell strain.
Dr. Wabitsch has had his clinical and experimental training at the Universities in Berlin (FU), Ulm, Baltimore (Johns Hopkins) and Nice (Sophia Antipolis). Within an ESPE research fellowship he performed

studies on the growth hormone receptor at the Hagedorn Research Institute. He has won several research prices of scientific societies, among them the Young Investigator Award of the (ESPE). Dr. Wabitsch has been the President of the German Society for Pediatric Endocrinology and Diabetes from 2008-2012. Dr. Wabitsch has published more than 200 peer reviewed articles.

Prof. David Araújo-Vilar



David Araújo-Vilar is a consultant physician in Endocrinology and Nutrition at the University Clinical Hospital of Santiago de Compostela and Associated Professor of Medical Genetics and Endocrinology at the School of Medicine of Santiago. Clinical and research postgraduate training was in Oxford University and in Santiago de Compostela General Hospital, including a PhD under the supervision of Prof. Cabezas-Cerrato investigating the mathematical modelling of glucose metabolism in diabetes mellitus and obesity. Over the past 10 years his clinical and research interests have centred on the genetic basis of rare lipodystrophic syndromes and severe insulin resistance syndromes. Lastly his research has particularly focused in Celia's encephalopathy and in the role of seipin in adipogenesis and neurodegeneration. He is the president of the Spanish Lipodystrophy Society and member of the Executive Board of the European Consortium of Lipodystrophies.

Adipose tissue, friend or foe?

Felipe F. Casanueva

Division of Endocrinology and Nutrition. University Clinical Hospital of Santiago de Compostela, Spain.
CIBER Fisiopatología de la Obesidad y la Nutrición (CIBERobn), Madrid, Spain

In a single individual, the adipose tissue is the only one that can duplicate its volume in a relatively short period of time. In fact, one person with 25 Kg of fat in total at 25 years old may show a total of 50 Kg 20 years later. As such, the secretion of any signal, either negative or positive for the health, may suffer an increase of astronomical perspectives. In this regard, no other tissue has experienced such a relevant transformation in the role accepted by the scientific community. Circa twenty years ago, the common view of the adipose tissue was of a dull gathering of cells, whose main function were to provide energy storing, cushioning and cold insulation to the individual. Nowadays, after the identification of more than 600 signals, either secreted or produced by or capable of acting on adipocytes, the common view is not of a tissue but of an organ and better, an endocrine organ.

The reason for such a conceptual change occurred 21 years ago with the discovery of Leptin and the subsequent revolution in physiology and medicine.

When present in excess, i.e., obesity, the adipose tissue is clearly detrimental for the health of the individuals. Obesity is, beyond any doubt, responsible by several disturbances, such as type 2 diabetes mellitus, dyslipidemia, high blood pressure, increase in cardiovascular morbidity and mortality and reduction in the life expectancy of the subjects affected. Moreover, the epidemiological data shows that obesity per se is one of the leading causes of generation of several types of cancer, among them, breast, uterine, colorectal, prostate cancers and so on. The mechanisms of how excess adipose tissue increases the risk of that long list of pathologies are, at present, unknown.

But adipose tissue, in correct quantities, may also be positive for the physiological function of the individuals. Some adipocytokines are of clear beneficial action, such as leptin, adipsin and more recently Irisin has been proposed as a signal produced by muscles after exertion to regulate metabolism. Our group has described that the adipose tissue is also able to secrete Irisin and that it's plasmatic levels parallel the amount of adipose mass.

One fascinating property of adipose tissue is its ability for physiological transdifferentiation. In fact the adipose organ is normally constituted by large amounts of white cells (WAT) for energy storage and by brown cells (BAT) for energy production and with net anti-obesity action. When an individual is exposed to a very low ambient temperature, some WAT can transdifferentiate in BAT and that process is reverted upon restitution of normal temperature. In the mammary gland, during the lactation period, WAT transdifferentiate into epithelial cells able to produce and secrete milk and that process is reversible after weaning. Such capability is presently being studied in order to develop new strategies for tissue reparation in other areas of the body.

Finally the most relevant function of the adipose tissue is to provide energy to the brain, the organ with higher calorie use of the body. In fact, during evolution, human beings developed a large brain, while maintaining stable the rest metabolic rate, and that was possible by the reduction of the gut, another organ with high energy expenditure. That gut reduction was only possible by the use of easy to digest aliments and with high energetic content. But in times of food shortage or famine, very common in the evolution process, the adipose tissue has been the only way to maintain the brain in perfect function without reduction in the

individual motility.
In summary, the adipose organ must be viewed as an endocrine organ, crucial for the normal physiological activity of individuals, with many surprising molecules and actions present, and probably with more surprises to come in the future.

Characteristic and atypical mutations in Lipodystrophies

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Inherited lipodystrophies are divided into congenital generalized lipodystrophies (e.g. CGL Type 1, CGL Type 2, CGL Type 3, CGL Type 4, MADB), familial partial lipodystrophies (e.g. FPLD Type 1, FPLD Type 2, FPLD Type 3, FPLD Type 4, MADA) and further lipodystrophies associated with syndromes such as e.g. SHORT Syndrome, MDP Syndrome, Hutchinson Gilford Progeria, Neonatal Progeroid Syndrome, Atypical Progeroid Syndrome, or Werner Syndrome.
Mutations in the genes encoding CAV1, AGPAT2, BSCL2 and PTRF are causative for subtypes of Congenital Generalized Lipodystrophies. Mutations in LMNA, CIDEC, PLIN1, PPARG, PPIR3A, and LIPE have been found in patients with Familial Partial Lipodystrophies. Affected pathways include e.g. the structure and formation of lipid droplets (CIDEC, perilipin 1 and Seipin), the formation of caveloae (Caveolin 1, caveolin 3 and PTRF), TG biosynthesis (AGPATs) and nuclear proteins such as Lamin A/C, (Lamin B2), Zinc metalloproteinase (ZMPSTE24) and POLD1.
We analyzed 57 lipodystrophy patients with an indication for diagnostic genetic analyses. We identified 12 heterozygous mutations in LMNA (among them 7 affecting R482 characteristic for FPLD type 2 Dunnigan), 2 heterozygous mutatons in PPRG consistent with FPLD3 (1x R425C described before, 1x novel mutation K347T) and a special de novo frameshift mutation in *FBN1*. Such FBN1 mutations at the 3‘ terminus predicted to escape nonsense mediated decay seem to predispose to inborn lipodystrophy with progeroid features, whereas symptoms of Marfan syndrome may develop later in childhood or adolescence.
Subsequent analyses of family members confirmed segregation of all mutations with lipodystrophy. However, despite (minor) signs and symptoms the diagnosis „lipodystrophy“ was sometimes missed, especially in early stages and in males.
Summary: Characteristic signs and symptoms may point to specific syndromes or LD subtypes, enabling a specific genetic testing. However, for the majority of LD patients a stepwise diagnostic scheme is suggested: 1) analysing the most frequent LD locus LMNA R482; 2) sequencing all coding parts of LMNA; 3) panel~ or exome analyses for identifying other LD relevant mutations.

Central obesity, diabetes mellitus and hypertriglyceridemia: Understanding the Köbberling syndrome

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Familial partial lipodystrophies (FPLD) are Mendelian disorders involving abnormal body fat distribution and insulin resistance. The current classification includes the Köbberling Syndrome (FPLD1), characterized by fat loss in the lower limbs and abnormal fat accumulation in other areas. FPLD1 appears to be heritable, but little is known about it, including putative contributing mutations. We aimed to characterize this syndrome better by evaluating a group of women with phenotypic features of FPLD1. SUBJECTS AND METHODS: This is a case-controlled study in which 98 women with FPLD1 that lacked classical mutations known to cause FPLD were compared to 60 women without lipodystrophy and 25 patients with type 2 FPLD (Dunnigan disease). Clinical course, body composition by DEXA, HbA1c, lipid profile, insulin, leptin and family history were evaluated in all of participants. Analyses of receiver-operating characteristic (ROC) curve were performed for FPLD1 diagnosis, comparing different truncal:limbs ratios. RESULTS: Among patients with FPLD1, 68% developed recognizable lipodystrophy before adolescence, and most displayed an autosomal dominant pattern (86%). Women with FPLD1 had less lower-limb adipose tissue than women without lipodystrophy, but significantly more than patients with Dunnigan disease. Moreover, metabolic disturbances occurred more frequently in the FPLD1 group (81%) than in a non-lipodystrophic group (30%, $p<0.05$). The severity of metabolic disturbances was inversely proportional to the percentage of fat in the lower extremities and directly proportional to the amount of visceral adipose tissue. Metabolic profiles were worse in FPLD1 than in Dunnigan disease. According to the ROC curve analysis, the best ratio was Subscapular/Calf skinfolds (KöB index), with a cut-off value of 3.477 (sensitivity: 89 %; specificity: 84%). CONCLUSIONS: FPLD1 was an early onset, autosomal dominant lipodystrophy characterized by fat loss in the lower limbs and abnormal fat accumulation in the abdominal visceral region, associated to insulin resistance and metabolic disorders. A KöB index higher than 3.477 is highly suggestive of this syndrome. (*Type 1 Familial Partial Lipodystrophy: Understanding the Köbberling Syndrome*, Endocrine 2016, DOI: 10.1007/s12020-016-1002-x).

Fontaine-Petty syndrome: A rare cause of lipodystrophy demonstrates another pathogenesis for lipodystrophies

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A series of sporadic patients have been reported sharing decreased subcutaneous fat tissue, bone dysplasia evident in fingers and skull, an unusual face, and prenatal and postnatal growth retardation which we named Fontaine-Petty syndrome. Through whole exome sequencing of four unrelated affected individuals we identified in all four a *de novo* missense variant at the same amino-acid residue in a mitochondrial membrane-embedded carrier. The protein coded by this gene allows an electroneutral and reversible exchange of ATP-Mg between the cytosol and mitochondria, needed for maintaining of optimal adenine nucleotide level in the mitochondrial matrix for metabolism, proliferation and permeability transition. Molecular dynamic simulation studies demonstrated that both mutations abolish the substrate cavity of the protein and disrupt transported dynamics. Fibroblasts showed that the protein encoded by the gene is located only in the mitochondria, and disrupts mitochondrial functioning evident in upregulated oxygen consumption rate when grown in a galactose rich environment.This disturbance in mitochondrial functioning was absent in fibroblasts of a patient with a deletion involving the gene; indeed this patient showed a completely different phenotype.
We conclude that Fontaine-Petty syndrome a sporadically occurring entity caused by *de novo* mutations in a gene that causes a disturbed mitochondrial functioning.

Progressive lipodystrophy associated with mutation in the *POLD1* gene

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Mandibular hypoplasia, Deafness and Progeroid features with concomitant progressive Lipodystrophy and insuline resistance, define a multisystem disorder named MDPL syndrome. Other early clinical features included generalized and severe muscular wasting with joint contractures and spine rigidity, hypogonadism in males, facial dismorfisms including narrow nose, micrognathia, and mild ptosis.

MDPL syndrome has been associated to heterozygous mutations in POLD1 gene which encodes the DNA polymerase δ and possesses both polymerase and 3' to 5' exonuclease activities. It is responsible for DNA synthesis of the lagging strand during DNA replication physically and functionally interacting with the Werner helicase which has already been implicated in human aging. A recurrent in-frame single amino-acid deletion (c.1812_1814delCTC, p.Ser605del) and a missense mutation (c.1519C>T, p.Arg507Cys) at the polymerase-active site of POLD1 were shown to cause MDPL syndrome.

These findings prompted us to analyze the POLD1 gene in patients for whom had been previously excluded mutations in LMNA, ZMPSTE24, WRN and BANF1, all genes that were reported to be also involved in human segmental progeroid disorders. We report other two MDPL patients sharing the common POLD1 deletion. In one family, we confirmed its de novo origin, as it was not identified in the patient's parents. In the other family, we showed the vertical transmission of the POLD1 germline mutation from mother to her daughter.

Finally, MDPL patient's fibroblasts present severe nuclear anomalies and a defect in DNA damage response after cysplatin exposure, supporting a crucial role of DNA polymerase δ in nuclear envelope integrity and in the regulation of DNA repair process.

Clinical reports of the association between fat loss and complex disorders of the hemopoietic system

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While several genetic mutations responsible for the inherited forms are now known, the pathogenic mechanisms of acquired lipodystrophies are less understood. We herein describe two cases of acquired lipodystrophies in patients with complex dysregulation of the hematopoietic system.

First, we describe the case of a 20 years old Caucasian girl who developed a myeloid acute leukemia during childhood. Complete remission of the neoplasia was obtained by allogeneic transplantation, following total body irradiation and conditioning chemotherapy. This treatment was complicated by chronic graft versus host disease. Approximately two years later the patient developed a lipoatrophy in the extremities, buttocks and the simultaneous accumulation of fat in the face, neck and intra-abdominal areas. The lipodystrophy was complicated by diabetes mellitus and severe hypertriglyceridemia.

The second case is related to a five years old girl affected by acquired generalized lipodystrophy complicated by diabetes mellitus, severe hypertriglyceridemia and steatohepatitis with massive hepatomegaly and fibrosis. At 6 months she developed panniculitis with progressive fat loss associated with autoimmune neutropenia. Later on she was diagnosed with an autoimmune lymphoproliferative syndrome (ALPS). Remission of diabetes and notable amelioration of the hepatic disease was achieved by metreleptin administration.

We believe that these cases, principally characterized by a dysregulation of the immune system which may favor autoimmunity, could be an opportunity for further understanding the pathogenesis of some acquired forms of lipodystrophy likely mediated by a cellular or humoral reaction directed against the adipocytes or their precursors.

Modifications of the immune system in lipodystrophy

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RATIONAL/AIM Emerging evidence links some forms of lipodystrophy (LD) to auto-immune disorders. Aim of the present study is to characterize critical players in the regulation of immunity in lipodystrophic patients with the long term goal of searching for possible causative links between alterations of the immune response and loss of adipose tissue. EXPERIMENTAL DESIGN - population: upon informed consent we collected blood samples from 8 matched healthy controls , 8 LD (with heterogeneous etiology) and 8 obese patients (BMI>30 Kg/m^2). The latter were included in the study to evaluate how an altered metabolic profile similar to that of LD, impacted the parameters under analysis.- methods: we used flow cytometry to assess the number of circulating regulatory T cells (Tregs) and natural killer T (NKT) cells that regulate T cell tolerance and reactivity and can prevent autoimmune diseases by suppressing self-reactive T cells. We performed the morphological characterization of monocyte-derived macrophages and monitored by Oil-Red-O (ORO) staining their lipid accumulation. We used conditioned medium from macrophages (Mac CM) to cultivate a human preadipocyte cell line (SGBS). RESULTS: LD patients have reduced levels of Tregs, as compared with lean and obese subjects. Both obese and LD patients have depletion of iNKT cells as compared to the

lean controls. LD patients have significantly higher numbers of ORO positive round Mac and depletion of ORO negative spindle-like cells with respect to controls while obese display an intermediate condition. Consistently, regression analysis revealed an inverse relationship between Tregs and ORO positive round Mac. Mac CM obtained from LD patients induced significantly higher lipid accumulation in a human cell line of undifferentiated preadipocytes as compared to controls and obese. Consistently, regression analysis revealed a positive relationship between accumulated lipids and ORO positive Macs. CONCLUSIONS: our preliminary data indicate that in LD the regulatory system that keeps the immune response under control is dysregulated, this being associated with an alteration of macrophages features including their morphology, triglyceride accumulation and capacity to trigger lipid deposition in other cell types such as predipocytes.

Decrease of osteocalcinemia linked with insulin resistance more than with body fat mass in lipodystrophic syndromes, compared to obese and normal-weighed patients.

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Bone is involved in both phosphate-calcium and energetic metabolisms. Osteocalcin is secreted by the osteoblasts, stimulates insulin secretion and sensitivity, and is supposed to decrease body fat mass. FGF-23 is secreted by the osteoclasts, increases phosphate urine excretion and is a marker of insulin resistance. Relationships between insulin resistance, leptin, body fat mass and bone are contradictory.

The objective of this study was to evaluate osteocalcin and FGF-23 in pathologies, differing in body fat mass and insulin resistance, particularly focusing on lipodystrophies, a model of extreme insulin resistance with hypoleptinemia without obesity.

The population from the PHRC-Clin.gov2009-AO-1169-48 was divided in five groups: LMNA-mutated lipodystrophies (LDM, n=11), non-mutated lipodystrophies (LDNM, n=21), diabetic obese patients (OB, n=13), non-diabetic obese patients (OND, n=13), normal-weighed controls (T, n=19).

Phosphate, calcium, metabolic and body composition parameters (DEXA) were compared between these five groups. Osteocalcin, crosslaps, leptin, BMI, body fat mass, mean body mass/height^2, fasting blood glucose, C peptide, HbA1c and HOMA-IR levels were significantly different between the five groups, with a trend for T-score, blood calcium and 25OHVitD. Serum phosphate, PTH, FGF-23 levels and urine calcium excretion were similar. By the two groups-comparison, osteocalcin was lower in the LDNM group (median (IQR):12(11-14) ng/mL) compared to OND (17(13-21)), and in the LDNM and LDM groups (14(12-19)) compared to controls (24(23-29)). Osteocalcin and HOMA-IR were negatively correlated (LDNM: 4(0.6-11); LDM: 3(2-5); OD: 4(3- 6); OND: 1.6(1-3); T: 1.1(0.8-1.4)). No correlation was found between osteocalcin and body fat mass (LDNM: 23(18-28); LDM: 15(11-18); OD: 41(37-43); OND:50(48-62); T: 17(12-22)kg) nor leptin (LDNM: 15(8-22);LDM: 6(4-12); OD: 27(24-41);OND: 49(32-67); T: 5(4-12)ng/mL).

Conclusion: osteocalcin is negatively correlated with insulin resistance, with no influence of body fat mass or leptin, without any difference of FGF-23 or T-score. The decrease of osteocalcin when insulin resistance is severe could result of a primitive or secondary osteoblast dysfunction.

Celia's Encephalopathy (PELD): seipin, adipose tissue and beyond

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In 2013, we described a new fatal and early onset neurodegenerative disease, mainly affecting cortical areas and basal ganglia: the Progressive Encephalopathy with or without Lipodystrophy. We dubbed the disease Celia's encephalopathy in memory of the index case. This disease is associated to the c.985C>T mutation in BSCL2, the gene which encodes seipin. Celia´s mutation generates an alternative splicing site leading to skipping of exon 7, a change in the reading frame, and C-terminal truncation. The resulting seipin variant of 351 amino acids long, called Celia seipin, thus exhibits an aberrant C-terminus. The same mutation c. 985C>T was identified in 6 children from 4 unrelated families from Murcia in southeastern Spain with autosomal recessive PELD. The phenotype was severe, resulting in the death of 5 children between ages 6 and 8 years. In four of them, the mutation was found in compound heterozygosity with another pathogenic truncating BSCL2 mutation. They present a mixed phenotype of lipodystrophy and encephalopathy, whereas the homozygote index case had a lipoatrophic appearance in the first months of life, phenotype that regressed subsequently, while she developed a progressive and severe encephalopathy.

The precise pathogenic mechanism of Celia seipin was unknown, but the increased expression of BSCL2 transcripts without exon 7 in tissues of the index case suggested that this transcript plays a key role in the pathogenesis of PELD. Furthermore, the increase of Bip expression (a reticulum stress marker) in primary preadipocytes overexpressing Celia seipin, the reactive intranuclear inclusions ubiquitin positive detected in the parietal cortex of the index case and the large endoplasmic reticulum dilatation in preadipocytes from the index case made PELD reminiscent of other neurodegenerative disorders.

In 2015 we proposed a model for the pathogenic mechanism of Celia seipin in homozygotes and the phenotype rescue in heterozygous carriers. We demonstrated that Celia seipin accumulates around the nucleus and in the cytoplasm and forms bigger macro-aggregates that would be responsible of the neuronal apoptosis, suggesting a toxic gain of function. Moreover, we also established the protective role of wt seipin as it recruits the Celia seipin at a 10 to 1 ratio and avoids its toxic action by impeding the aggregation into larger oligomers, fact that explains the absence of phenotype in heterozygotes BSCL2 c.985C>T carriers.

By the date, our current studies about PELD are aiming to quantify the BSCL2 expression of the different transcripts in peripheral tissue but mainly in the distinct brain areas of young and old individuals, comparing both cerebral hemispheres. Preliminary results of the regions analyzed (frontal and occipital lobes, thalamus, subcutaneous abdominal fat and skeletal calf muscle) indicated that there is a differential expression of BSCL2 transcripts, the most striking difference being the long isoform BSCL2-03 that is predominant in the central nervous system. It should be noted that this results are preliminary and we still have to analyze many other samples.

Clinical, hormonal and molecular-genetic characteristics of inherited lipodystrophies in Russia

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Background: In Russia lipodystrophy was first diagnosed only in 1972 as “hypermuscular lipodystrophy” or “generalized lipodystrophy”. In 1970s – 1990s 70 female lipodystrophic patients were studied, half of them had hereditary forms, but none underwent genetic study. Since then the track of these families was lost.
Study purpose: To diagnose different forms of lipodystrophies in Russian population and study their clinical and molecular-genetic characteristics. **Materials and methods:** 52 patients (40 adults and 12 children) from 46 families with different lipodystrophic fat loss pattern were included in this study. 14 congenital lipodystrophies candidate genes were sequenced using a Custom Ion Ampliseq panel and PGM semiconductor sequencer (Ion Torrent). **Results:** In our group, the majority of patients with partial lipodystrophy were female, and only 16% were male, what corresponds with the previously published data of women being more affected. Insulin resistance signs were revealed in most patients: mean basal insulin levels – 30.9 mc/ml [0.9; 68.9], mean HOMA-IR 8.9 [0.3; 44.8]. Mutations were found in the following genes: 5 in *WRN*, 1 in *AGPAT2*, 1 in *POLD1*, 1 in *LMNB2*, 1 in *LMNA*, 2 in *LMNA*, 1 in *PPARG*, 1 in *AKT2*, 2 in *PP1R3A*, 1 in *PTRF*, 2 in *BSCL2.* The most common mutation was a heterozygous R482W mutation in the 8 exon (hot-spot) of the *LMNA* gene found in 3 families (7 patients) with PL.
Conclusion: Lipodystrophies, especially partial types, often remain underdiagnosed in endocrinological practice in Russia.
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Efficient Differentiation of Human Induced Pluripotent Stem Cells Into Functional Beige Adipocytes

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Adipose tissue has a major role in the regulation of the whole body energy metabolism, which has been recently revisited with the discovery of brown fat in human adults (Cypess et al., 2009). Indeed, while white adipocytes are responsible for triglycerides storage, brown adipocytes perform efficient thermogenesis through mitochondrial uncoupling. A third type of adipocytes, named "brite" or "beige", which are also able to dissipate energy upon induction by thermogenic stimuli (Sharp et al., 2012, Cereijo et al., 2014), could compose the majority of energy-dissipating cells in human adults (Jespersen et al., 2013). Activation of thermogenic adipocytes could be an important therapeutic target in metabolic diseases such as obesity and diabetes. We report here a rapid and efficient protocol to differentiate human induced pluripotent stem cells (hiPSCs) into beige adipocytes, without adipogenic gene transfer or exogenous PPARγ agonists. HiPSCs-derived cells display a beige adipocyte phenotype *in vitro* as assessed by specific markers and by cyclic-AMP stimulation, which increased mitochondrial content and the expression of genes involved in thermogenesis. *In vivo* engraftment of hiPSCs-derived adipocyte precursors into immunodeficient mice resulted in the neoformation of a fat pad showing a dual white and beige phenotype. Thus our original method of hiPSCs adipocyte differentiation, which allows physiological studies, could also constitute an unlimited source of adipocytes for disease modeling, drug screening and potential cell therapy strategies.

Morpho-functional study of subcutaneous adipose tissue in patients affected by Familial Partial Lipodystrophy type 2-FPLD2

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Type-2 Familial Partial Lipodystrophy (FPLD2) is a genetic disorder associated with *LMNA* mutations and characterized by accumulation of prelamin A. It is usually associated with important metabolic abnormalities such us severe insulin resistance, diabetes mellitus not respondent to the common therapies, hepatic steatosis and cardiovascular diseases. Anomalous fat distribution is the main clinical feature of the disease. Patients gradually lose subcutaneous fat from the limbs, while they accumulate adipose tissue on the face and neck. No data are actually available on the mechanisms leading to the abnormality in fat distribution of FPLD2 patients.

We identified a deregulation of autophagy in both FPLD2 pre-adipocytes and experimental models obtained by drug-induced accumulation of prelamin A. In addition, adipose tissue from FPLD2 patient neck, an area of brown adipogenesis, showed an intermediate brown/white phenotype. Moreover, in vivo morfo-functional evaluation of the fat depots of the neck area of three FPLD2 patients by PET/CT analysis with cold stimulation showed the absence of BAT activity. These findings highlight a new pathogenetic mechanism leading to improper fat distribution in lamin A-linked lipodystrophies and suggest that failure of adipose tissue browning contributes to disease.

Lessons from LMNA-lipodystrophy in vitro model based on human mesenchymal stem cells that accumulate prelamin A

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The laminopathies comprise a variety of syndromes such as lipodystrophies, neuropathies, skeletal and/or cardiac myopathies and premature aging disease which in some cases show overlapping phenotypes. The LMNA-lipodystrophies, characterized by generalized or partial fat atrophy and metabolic complications in addition to age associated manifestations, exhibit a pathological accumulation of the lamin A precursor, prelamin A. These lipodystrophy disorders which can be either genetic (due to mutations in the LMNA gene or genes involved in the processing of lamin A protein) or acquired (as a consequence of antiretroviral therapy utilising HIV inhibitor proteases), are caused by primary alterations disturbing adipose tissue homeostasis and function with the consequent negative impact metabolism and health. Lamin A protein, encoded by the LMNA gene, is implicated in crucial functions such as gene transcription, chromatin organisation and DNA replication and repair. In fact, lamin A is one of the major components of the nuclear lamina meshwork underlying the inner nuclear membrane. In spite of the high relevance for the human health, the molecular mechanisms underlying lipodystrophies etiopathologies are not completely understood. Since the affected tissues, by pathological prelamin A accumulation, are mainly of mesenchymal origin we have generated human in vitro models of laminopathies through a pharmacological approach based on

human mesenchymal stem cells (hMSCs) differentiated, and no differentiated, to adipocytes which accumulate the lamin A precursor.

These human laminopathy models, founded on prelamin A accumulated hMSCs and stem cell derived adipocytes recapitulate the phenotypes observed in lipodystrophy patient samples and animal models, and are crucial for providing new information regarding the metabolic and aging features of these diseases. Furthermore, these human experimental models have been instrumental in revealing new insights into the molecular mechanisms governing these disorders, in which accumulated prelamin A alters the filamentous network of the nuclear lamina, thus establishing a “trap” for proteins, such as transcription factors, altering its function.

Modulation of brown adipose tissue differentiation in FPLD2

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Among the mechanisms that regulate pre-adipocyte commitment towards the brown or white adipose tissue lineage is the differential activation of autophagic processes. We identified deregulation of autophagy in both Type-2 Familial Partial Lipodystrophy (FPLD2) pre-adipocytes and experimental models obtained by drug-induced accumulation of prelamin A in adipocyte precursors. FPLD2 is a genetic disorder associated with *LMNA* mutations and characterized, at the molecular level, by prelamin A accumulation. Anomalous fat distribution is the main clinical feature of the disease. Patients gradually lose subcutaneous fat from the limbs, while they accumulate adipose tissue in the face and neck. Early activation of autophagy and subsequent block were observed in laminopathic brown and white adipocyte precursors. Precocious activation of autophagy at the onset of white adipogenesis impaired formation of large lipid droplets and was associated with PPARγ 2 downregulation and upregulation of the brown adipose tissue marker UCP-1. Conversely, activation of autophagy before the onset of brown adipogenesis, shifted the differentiation process towards the white pathway, causing downregulation of PPARγ 1 ultimately eliciting brite adipocytes. In agreement with these in vitro results, adipose tissue from FPLD2 patient neck, an area of brown adipogenesis, showed a white phenotype reminiscent of its brown origin. These findings highlight a new pathogenetic mechanism leading to improper fat distribution in lamin A-linked lipodystrophies and suggest that modulation of autophagic signaling may represent a tool to counteract pathogenetic processes.

Human SGBS cells as in vitro model for studying cellular phenotype of defects in lipodystrophy genes

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Objectives:
Studies on human adipocytes have been challenging due to technical difficulties, limited supply of cells and to some extent the variability in quality of human adipose tissue specimens. We have established a human preadipocytes cell strain (SGBS) which provides a unique and useful tool for studies of human adipocyte biology.
Methods:
Cells were initially derived from the stromal cells fraction of subcutaneous adipose tissue of a diseased infant with Simpson-Golabi-Behmel syndrome (SGBS) and characterized intensively.
Results:
SGBS cells are neither transformed nor immortalised and have been tested in a panel of different assays. The cells are efficiently differentiated in the presence of PPAR[illegible] agonists and in the absence of serum and albumin (1,2).

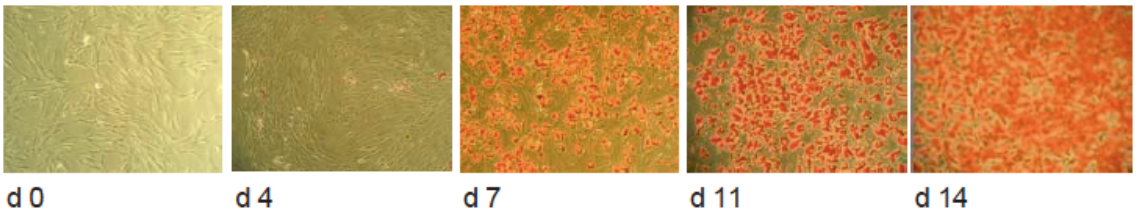

Fig.: Adipogenic differentiation of human SGBS cells 14d in a chemically-defined, serum-free, adipogenic medium (1,2)

During the differentiation process SGBS cells develop a gene expression pattern similar to that found in differentiating human preadipocytes. In mature SGBS adipocytes insulin stimulation induces glucose uptake (5-10 fold; EC_{50}~100pM) and a strong antilipolytic effect (IC_{50}~15pM). Mature SGBS adipocytes secrete leptin, adiponectin, IGF-1, and all other adipokines.
Studies using adipogenic differentiation, glucose uptake, de novo lipogenesis, lipolysis, apoptosis, transient and stable transfections have been performed. The biology of adipocyte expressed lipodystrophy genes can be studied by gene silencing or overexpression studies as well as by various functional studies (3-5).
Conclusion:
The human SGBS preadipocyte cell strain offers an excellent new tool for studies of human adipocyte biology. SGBS cells provide a suitable model system to study the biological function of lipodystrophy genes. CRISPR/Cas-9 system for genomic editing is currently being established.

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Maladaptative autophagy contributes to insulin resistance and altered adipocyte differentiation in Congenital Generalized Lipodystrophy due to *PTRF*/cavin-1 mutations

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Mutations in cavin-1/*PTRF* cause congenital generalized lipodystrophy (CGL4) with lipoatrophy, insulin resistance and muscular dystrophy. Cavin-1, and its partners caveolins are mandatory for the formation of plasma membrane caveolae domains, involved in lipid transport and signal transduction. Cavin-1 also associated with lipid droplets in adipocytes. Macroautophagy (referred to as 'autophagy') is a lysosomal degradative process of intracellular components which contributes to protein quality control. Adaptative autophagy also plays a critical role in adipogenesis and lipid metabolism.

We identified new homozygous mutations in cavin-1/*PTRF* in four patients from two unrelated families with typical CGL and associated metabolic abnormalities, increased creatine kinase levels with or without muscle weakness, and mild mental retardation in two unrelated patients.

In patients' fibroblasts, the expression of cavin-1, caveolin-1 and caveolin-2 and the number of membrane caveolae was reduced. Autophagy was activated, as shown by the presence of numerous autophagosomes and by decreased LC3-I-to-LC3-II ratio and p62 amount. Insulin signaling was blunted. These results were reproduced by siRNA-mediated *PTRF* knockdown in control fibroblasts and 3T3-F442A preadipocytes. Moreover, cavin-1 knockdown impaired *in vitro* 3T3-F442A adipocyte differentiation.

To study the role of increased autophagy in cellular alterations associated with cavin-1 deficiency, we inhibited the autophagic flux using siRNA directed against *ATG5*, encoding a key protein for the formation of autophagosomes. Suppression of autophagy improved insulin sensitivity in patients' fibroblasts and reversed *PTRF* knockdown-induced insulin resistance and altered adipocyte differentiation in 3T3-F442A cells.

In conclusion, this study shows that cavin-1 mutations responsible for CGL4 and/or cavin-1 deficiency resulted in maladaptative autophagy which contributed to insulin resistance and altered adipocyte differentiation. Autophagy could play an important role in the pathophysiology of CGL4 and modulation of this process could offer new therapeutic perspectives.

Application of proteomics in lipodystrophy research

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Adipose tissue has emerged as one of the most important organs regulating body homeostasis as it serves not only for the storage of energy in the form of triglycerides but it is also a source of paracrine and endocrine signals (i.e. adipokines) that influence systemic metabolism. Dysfunction of adipose tissue, as occurs in conditions of excess (obesity) or reduced (lipodystrophy) body fat, results in an abnormal management of triglycerides and alteration of adipokine secretion, leading to several metabolic disturbances such as insulin resistance, dyslipidemia, hepatic steatosis and type 2 diabetes. Accordingly, much effort has been directed at elucidate the molecular mechanisms underlying adipose tissue dysfunction and its role in the development of metabolic diseases, including the utilization of proteomic approaches (reviewed in Peinado et al., 2012). Although we gathered some information from proteomic studies, research of adipose tissue on lipodistrophic patients remain a complicated task. Herein we explore different possibilities to aim proteomic studies in lipodystrophy in humans and in animal models. This research cover liquid based proteomic and classical proteomics, and target fibroblasts, stem cells, cell lines, adipose tissue from different depots and from different point of views. These studies may be useful to draw an integrated proteomic map of the adipose tissue that will help to unveil the mechanisms underlying adipose tissue dysfunction in lipodystrophic syndromes.

Outcomes of Dietary Intervention in Patients with Lipodystrophy

AJ Stears on behalf of the National Severe Insulin Resistance Team

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Lipodystrophy is a group of rare conditions characterized by partial or complete loss of subcutaneous adipose tissue. The underlying cause may be genetic or acquired. Patients with lipodystrophy often have reduced capacity to store excess dietary fat in the peripheral limb/gluteal subcutaneous adipose tissue stores and store excess dietary fat ectopically in liver and muscle. This exacerbates insulin resistance and can lead to local tissue abnormalities including non-alcoholic fatty liver disease. Elevated circulating triglycerides can cause pancreatitis. Lipodystrophy is frequently complicated by insulin resistant diabetes which is difficult to control and which may require high insulin doses. Avoidance of excess dietary energy intake, despite the often lean appearance of the patient, is the current mainstay of treatment of lipodystrophy, aiming to avoid short- and long-term complications, while allowing normal growth in children. Effective interventions to reduce excess dietary energy intake include the use of diet diaries with feedback and support from an experienced dietitian, orlistat, GLP-1 agonists, leptin therapy, intensive weight management programmes using low calorie liquid diets, and in selected cases bariatric surgery. An individual approach is recommended for each patient determined by their age, metabolic status, lipodystrophy type, co-morbidities and current medication. Early involvement of a specialized multidisciplinary team in the diagnosis and management of patients with lipodystrophy is recommended.

Metreleptin therapy Improves insulin secretion and adipose tissue, liver and systemic inflammation markers in lipodystrophic patients

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Recombinant methionyl human leptin (metreleptin) therapy was shown to improve hyperglycemia, dyslipidemia and insulin sensitivity in patients with lipodystrophic syndromes, but its effects on insulin secretion and on adipose tissue remodeling and systemic inflammation were not studied.

First, we used dynamic intravenous clamp procedures to measure insulin secretion, adjusted to insulin sensitivity, at baseline and after one-year metreleptin therapy, in 16 consecutive lipodystrophic patients with diabetes and leptin deficiency. Second, we compared histologic, immunohistologic and protein expression features of abdominal subcutaneous adipose tissue samples as well as serum adipokines and inflammation markers at baseline and after one year metreleptin therapy.

Patients presented familial partial lipodystrophies or congenital generalized lipodystrophy. Their BMI (23.9 ± 0.7 kg/m2), HbA1c (8.5 ± 0.4%) and serum triglycerides (4.6 ± 0.9 mmol/l) significantly decreased within metreleptin therapy. Insulin sensitivity (from hyperglycaemic or euglycemic hyperinsulinemic clamps), insulin secretion during graded glucose infusion (n=12), and acute insulin response to intravenous glucose adjusted to insulin sensitivity (disposition index, n=12), significantly increased after one-year metreleptin therapy. Increase in disposition index was related to decrease in percent total and trunk body fat.

Ten patients had surgical biopsies of lipoatrophic fat showing, as compared to control samples, dystrophic features with extensive fibrosis, disorganized fat lobules and decreased expression of PPARG and SREBP1c adipose transcription factors, that were not significantly modified by metreleptin treatment. Lipoatrophic fat showed an increased macrophage infiltration, evaluated by CD68 and CD163 immunostaining, which was significantly decreased after metreleptin therapy. Although metreleptin did not improve patients' adiponectin low levels, it significantly decreased hsCRP, orosomucoid and ferritin serum concentrations. The steatotest and fibrotest scores, which are noninvasive measures of liver steatosis and fibrosis, also improved.

Metreleptin therapy improves not only insulin sensitivity, but also insulin secretion in patients with diabetes due to genetic lipodystrophies. It also improves adipose tissue, liver and and systemic inflammation markers in those patients, which could contribute to its overall beneficial metabolic effects.

Antisense strategy in familial partial lipodystrophy

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MG132 enhances progerin clearance and reverses cellular phenotypes in Hutchinson-Gilford progeria cells

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Hutchinson-Gilford progeria syndrome (HGPS) is a lethal premature and accelerated aging disease caused by a *de novo* point mutation in *LMNA* encoding A-type lamins. Progerin, a truncated and toxic form of prelamin A, accumulates in HGPS cells' nuclei and is a hallmark of the disease. Small amounts of progerin are also produced during normal aging. We show that progerin is sequestered into abnormally shaped Promyelocytic-Nuclear Bodies (PML-NB), identified as novel biomarkers in Progeria. MG132 induces progerin degradation through macroautophagy and strongly reduces progerin production through downregulation of SRSF-1 controlling prelamin A mRNA splicing. Treatment with MG132 reduces cellular senescence and enhances viability and proliferation in HGPS fibroblasts. *In vivo*, MG132 injection in skeletal muscle locally reduces progerin expression in *Lmna*$^{G609G/G609G}$ mice. Altogether, we demonstrate progerin reduction based on MG132 dual action and shed light on a promising class of molecules towards an encouraging therapy for Progeria and related diseases.

How advocacy groups can support research: the Spanish experience

Juan Carrión

President of the Spanish Federation of Rare Diseases

The Spanish Organization for Rare Diseases (FEDER) is a national organization founded with the aim of promoting and defending the rights of people with rare diseases.
Our mission is to improve the quality of life for people with rare diseases and their families. The vision of a just society; more egalitarian and more inclusive for people with ER society and their families.
It consists of 300 organizations, representing more than 800 diseases and is the voice of more than 3 million people with ER
ERDF was founded in 1999 and has since been working to give visibility to the common needs of people with rare diseases and propose solutions to increase life expectancy and improve their quality of life. FEDER represents 300 organizations rare disease patients in Spain. ERDF's Foundation was founded in 2004 to support research into rare diseases. Currently, both ERDF and its Foundation work together to promote research.
Both the ERDF and its Foundation work to support research into rare diseases through these key actions:
- Promote awareness of research on RD compilation of current resources in research to connect research activities and initiatives of current support.
- Promote partnerships and synergies with entities working in research and between them.
- Encourage research opportunities to carry out research projects with a call annual aid for research, who works as a liaison between the converging interests and approve research projects on rare diseases

Main difficulties in research on ER is the lack of commercial appeal, training of scientists and experts, public provision and coordination between resources; coupled with short duration of projects.

AELIP: an example of advocacy group supporting lipodystrophy patients and relatives

Naca Pérez de Tudela

President of AELIP

ORIGIN: AELIP was born when Celia part to eternity, we realize what she had gotten from us, our abilities, life and above all to begin a research project to give hope and future to those who suffer from this disease in the world.

The effort and suffering from people struggling with such complex and different disease, such as Lipodystrophy, makes us realize that we can not just disappear. That is why we need to continue those investigations that allow cure lipodystrophy. we continue fighting for others to come and demonstrate that it is possible a better future if it is investigated.

The Association of Relatives and Affected by Lipodystrophies, AELIP, is an entity created in April 2012 with a very clear line of main job: to promote research in the field of lipodystrophy in order to provide a path to hope.

The importance of associations for this entity lies in the reflection and the need for those affected to know and be known, promoting the claim of reference units to be addressed. The importance of having a record and specialization, all this in a coordinated way in order to improve the quality of life of patients and their families.

INTERNAL FIELD OF ACTION AND ALLIANCES.

Statewide: Spanish Federation for Rare Diseases (FEDER)

At European level: European Organization for Rare Diseases (EURORDIS)

Internationally: Latin American Alliance for Rare Diseases (ALIBER)

State level: we collaborate with the Spanish Society of Lipodystrophy (SEL)

European level: we collaborate with the European Consortium Lipodystrophies.

Globally: we collaborate with Lipodsitrophes United Connect

Goals and objetives:

The implementation of actions of awareness / sensitization that allow visualize the Lipodystrophy is necessary.

AELIP find essential to support research, support the Global Patient Registry, train professionals to get a thorough understanding of diseases so that patients can be cared for.

Main Objetives:

Create opportunities for exchange and coexistence between relatives and parents of children with lipodystrophy.

Bringing together people interested in the various scientific, clinical and social medical-related lipodystrophy aspects, promoting welfare-oriented activities, teaching and research.

Establish actions of coordination with agencies and public and private entities working in the field of lipodystrophy.

Inflammation in progeroid laminopathies

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Alterations in cell communication have been identified as a critical hallmark of aging, which results from a complex interplay of cell autonomous and systemic factors. However, the precise nature of the molecular signals that integrate cell-based and systemic alterations in aging and progeria remained incompletely defined. Based on the molecular characterization of two different animal models of accelerated aging (*Zmpste24*$^{-/-}$ and *Lmna*$^{G609G/G609G}$ mice), we have demonstrated the role of NF-κB signaling as a critical mediator of the aged phenotype. Thus, we have found that the accumulation of prelamin A isoforms at the nuclear envelope triggers ATM- and NEMO-dependent signaling, leading to NF-kB activation and secretion of proinflammatory cytokines. Remarkably, both genetic and pharmacological inhibition of NF-kB signaling prevented age-associated alterations in these animal models and extended significantly their lifespan, demonstrating the causal involvement of inflammation in the progeroid phenotype.

Next, we have explored the barriers that hamper somatic cell reprogramming in normal aging and in progeroid laminopathies. For this purpose, we have derived induced pluripotent stem cells (iPSCs) from individuals with physiological or premature ageing. We found that NF-κB activation constitutes a severe obstacle for the generation of iPSCs in aging, while NF-κB repression is observed during cell reprogramming towards a pluripotent state. The impairment of iPSC generation by NF-κB hyperactivation operates by stimulating DOT1L, a histone methyltransferase that represses reprogramming by reinforcing senescence signals and downregulating pluripotency genes. Accordingly, inhibition of either NF-κB or DOT1L increases dramatically the reprogramming efficiency of fibroblasts from Néstor–Guillermo progeria syndrome and Hutchinson–Gilford progeria syndrome patients, as well as from normal aged donors. Finally, we have demonstrated that the administration of DOT1L inhibitors extends lifespan and ameliorates the accelerated ageing phenotype of progeroid mice, supporting the interest of exploring this pathway as a target of rejuvenation strategies.

Authors' list