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Halt-RONIN

Discovering chronic inflammation biomarkers that define key stages in the Healthy-to-NASH (non-alcoholic steatohepatitis) transition to inform early prevention and treatments strategies.

Grant Agreement No. 101095679

Halt-RONIN Newsletter October 2024 – February 2025

Our project aims to **discover chronic inflammation biomarkers that define critical stages in the Healthy-to-MASLD/MASH transition to inform early prevention and treatment strategies**.

Our newsletters provides our latest news and aims to become a forum for analyzing relevant topics in the field of liver diseases and commenting on some of the most relevant articles published during these four months of the project. Halt-RONIN has reached its -26 month of life. This period has been filled with numerous exciting activities, all of which can be explored in our website: https://halt- ronin.com/news/

The meeting in Málaga "Bringing OMICS into the Clinics and vice versa" was a complete success, with lots of results and advances HaltRONIN project. It was celebrated on February 15-17, 2025, in Melià Costa del Sol Hotel, Torremolinos, Málaga. It was organized by **the UCM group, Universidad Complutense de Madrid**. Speakers presented their advances and results in the different omics research lines of each group participating in the meeting. The information about the meeting can be visited at Málaga Meeting

On November 2024, The **Cost Action PRO-EURO-DILI-NET** has been recognized as 1 of the 3 most innovative by COST programme. In interviews with Prof Raul Andrade from University of Malaga, Chair of the Action, and Francisco Javier Cubero from University of Madrid, STSM Coordinator and Principal Investigator of Horizon Europe Grant Halt RONIN discussed the innovative approach in the Action structure and its impacts for clinicians, regulators, and the pharmaceutical industry. The information can be consulted at Cost Action innovative

During these months, we have also organized the **International Seminar Series on Liver Toxicity and Steatotic Liver Disease**. These are taking place every third Wednesday of the month. We have celebrated four seminars:

Date	Speaker	Title
16 October	Águeda González Rodríguez	Inhibition of ALK3-mediated signalling pathway protects against acetaminophen-induced liver injury
04 December	José Carlos Fernández-Checa	Hepatic mitochondrial-derived oxysterols link MASH to cardiovascular disease
11 December	Naga Chalasani	MASLD: a potential link between metabolic risk factors and susceptibility to DILI
15 January	Bernard Fromenty	Drug-induced steatosis and steatohepatitis: role of mitochondrial dysfunction and other alterations of lipid homeostasis

You can watch the Seminars again here

Javier Cubero
Coordinator of Halt-RONIN
Complutense University, Madrid

Interesting publications of the consortium:

1. *Drug-induced Liver Injury in Latin America: 10-year Experience of the Latin American DILI (LATINDILI) Network*

The study analyzes drug-induced liver injury (DILI) cases in Latin America over a decade through the LATINDILI Network. Demographic data, clinical presentation, histological findings, and outcomes of 468 DILI cases were assessed using the RUCAM scale to determine causality.
Most patients were women (62%) with a mean age of 49 years. Hepatocellular injury was predominant (62%), with jaundice present in 60% of cases and hospitalization in 42%. A fatal outcome occurred in 4.1% of cases, and 12% developed chronic DILI.
The most commonly implicated drug classes were systemic anti-infectives (31%), musculoskeletal agents (12%), antineoplastic and immunomodulating agents (11%), and herbal and dietary supplements (9%). Notably, cases related to antibacterials and immunosuppressants had no fatal outcomes.
Hy's law showed drug-specific predictive value. The worst outcomes were linked to anti-tuberculosis drugs, nimesulide, and herbal/dietary supplements, whereas amoxicillin-clavulanate, nitrofurantoin, and diclofenac, despite meeting Hy's law criteria, had no fatal cases.
In conclusion, DILI characteristics in Latin America are comparable to other prospective registries, though the pattern of causative drugs differs. An increasing incidence of herbal and dietary supplements, with high mortality rates, as well as nimesulide and nitrofurantoin-related cases, was noted. Public health policies should raise awareness of the potential adverse effects of these compounds.

Access to the original article:

Fernando Bessone, Nelia Hernández, Inmaculada Medina-Cáliz, Miren García-Cortés, María I Schinoni, Manuel Mendizabal, Daniela Chiodi, Vinicius Nunes, Ezequiel Ridruejo, Ximena Pazos, Genario Santos, Eduardo Fassio, Raymundo Parana, Virginia Reggiardo, Hugo Tanno, Adriana Sanchez, Federico Tanno, Pedro Montes, Martín Tagle, Marcos Arrese, Javier Brahm, Marcos Girala, M Isabel Lizarzabal, Enrique Carrera, Alina Zerega, Carla Bianchi, Laura Reyes, Daina Arnedillo, Antonella Cordone, Gisela Gualano, Fernanda Jaureguizahar, Gabriel Rifrani, Mercedes Robledo-Díaz, Aida Ortega-Alonso, José M Pinazo-Bandero, Camilla Stephens, Judith Sanabria-Cabrera, Elvira Bonilla-Toyos, Hao Niu, Ismael Álvarez-Álvarez, M Isabel Lucena, Raúl J Andrade. **Drug-induced Liver Injury in Latin America: 10-year Experience of the Latin American DILI (LATINDILI) Network.** (2025), doi: 10.1016/j.cgh.2024.06.030

Scientific Impact:

According to the WoS, the Impact Factor (IF) of this journal was 11.6 (2023) and it shows a Journal Citation Indicator of 2.78. The Rank (by Journal Citation Indicator) situates this journal in the position 9/143 and the percentile 94.1, that is D1.

Degree of Originality and Innovation: This study provides a novel and comprehensive analysis of idiosyncratic drug-induced liver injury (DILI) in Latin America, a region previously underrepresented in global research. By leveraging data from the LATINDILI Network over a decade, it offers unique insights into the clinical patterns, implicated drug classes, and patient outcomes, distinguishing regional differences from other international registries. Notably, the study highlights the rising incidence and severe impact of herbal and dietary supplements, emphasizing the need for public health interventions. The drug-specific predictive value of Hy's law further underscores its innovative contribution to understanding DILI risk factors in this population.
Thematic Priority or Challenge Addressed and Contribution to the Scientific Debate: This study addresses the critical challenge of understanding drug-induced liver injury (DILI) in Latin America, a region with diverse healthcare systems and drug usage patterns. By identifying the most frequently implicated drug classes and highlighting the increasing incidence of herbal and dietary supplements with high mortality rates, it underscores the urgent need for pharmacovigilance and

regulatory measures. Additionally, it contributes to the scientific debate by revealing key differences in DILI patterns compared to other regions, challenging existing assumptions about Hy's law, as some drugs fulfilling its criteria did not result in fatal outcomes. The study also raises awareness of the growing role of herbal and dietary supplements in liver injury, fueling discussions on their regulation and safety. By leveraging data from the LATINDILI Network over a decade, it offers unique insights that enrich global DILI research and call for a more region-specific approach to drug safety policies.
Methodological Contribution: This study makes a significant methodological contribution by utilizing a large, prospectively recruited cohort from the LATINDILI Network, ensuring robust and region-specific data on drug-induced liver injury (DILI) in Latin America. The application of the Roussel Uclaf Causality Assessment Method (RUCAM) provides a standardized and reproducible approach to assessing drug causality, enhancing the reliability of the findings. Additionally, the study's classification of culprit drugs using the Anatomical Therapeutic Chemical system allows for a systematic comparison with global registries. By evaluating the predictive value of Hy's law in different drug classes, the research offers a nuanced perspective on its applicability, demonstrating its limitations and reinforcing the need for tailored risk assessment models. These methodological strengths position the study as a valuable reference for future DILI research, particularly in underrepresented populations.

2. Stard1 promotes cholestatic liver injury and disease progression by sensitizing to bile acid hepatotoxicity

This study explores the role of STARD1 in cholestatic liver diseases, which are characterized by hepatocellular injury, fibrosis, and cirrhosis due to bile acid (BA) accumulation. BAs are primarily synthesized via the classic pathway, but a secondary mitochondrial acidic pathway requires STARD1 for cholesterol transport. The study reveals that patients with primary biliary cholangitis exhibit increased STARD1 expression.
Using a mouse model, researchers found that hepatocyte-specific STARD1 deletion (Stard1Δhep) provided resistance to cholestatic liver injury, inflammation, and fibrosis compared to control mice. These mice showed lower hepatic BA and mitochondrial cholesterol levels but increased mitochondrial glutathione (mGSH) levels. Furthermore, mGSH depletion in primary mouse hepatocytes increased sensitivity to BA-induced inflammation and cytotoxicity.
These findings suggest that STARD1 plays a crucial role in cholestatic liver injury and that targeting it could be a potential therapeutic strategy for cholestatic liver diseases.

Access to the original article:

Laura Conde de la Rosa, Laura Fàbrega, Sandra Torres, Susana Núñez, Vicent Ribas, Paula Segalés, Ricardo Espinosa-Escudero, Estel Solsona, María Jesús Monte, Álvaro Díaz-González, José J Marin, Carmen García-Ruíz, José C Fernández-Checa. **Stard1 promotes cholestatic liver injury and disease progression by sensitizing to bile acid hepatotoxicity** (2024), doi: 10.1097/HEP.0000000000001184

Scientific Impact:

According web of science the Impact Factor (IF) of this journal was 13 (2023) and it shows a Journal Citation Indicator of 3.18. The Rank (by Journal Citation Indicator) situates this journal in the position 7/143 and the percentile 94.1, poisoning this in the Q1.

Degree of Originality and Innovation: This study presents a novel perspective on cholestatic liver disease by identifying STARD1 as a key player in bile acid-induced hepatotoxicity. Unlike previous research that focused primarily on bile acid metabolism and transport, this study innovatively links STARD1-dependent mitochondrial cholesterol transport to liver injury, inflammation, and fibrosis. Using both human and mouse models, it provides the first evidence that STARD1 deletion confers resistance to cholestatic damage by reducing mitochondrial cholesterol accumulation and increasing protective glutathione levels. These findings open new therapeutic avenues, suggesting that targeting STARD1 could be a groundbreaking approach for cholestatic liver disease treatment.
Thematic Priority or Challenge Addressed and Contribution to the Scientific Debate: This study addresses the critical challenge of understanding the molecular mechanisms underlying cholestatic liver disease, a condition characterized by bile acid accumulation, hepatotoxicity, and

fibrosis. By identifying STARD1 as a key regulator of mitochondrial cholesterol transport and its role in bile acid-induced liver damage, the study provides new insights into the pathophysiology of cholestasis. Furthermore, it contributes to the scientific debate by challenging the traditional focus on bile acid synthesis and transport, highlighting mitochondrial cholesterol accumulation as a previously overlooked factor in disease progression. These findings open new discussions on therapeutic strategies, suggesting that targeting STARD1 could be a novel approach to mitigating cholestatic liver injury and improving patient outcomes.

Methodological Contribution: This study makes a significant methodological contribution by integrating human patient data with innovative genetic and pharmacological mouse models to investigate the role of STARD1 in cholestatic liver disease. The use of hepatocyte-specific STARD1 knockout mice (Stard1Δhep) provides a precise and targeted approach to understanding mitochondrial cholesterol transport and its impact on bile acid-induced liver injury. Additionally, the study employs pharmacological depletion of mitochondrial glutathione (mGSH) to demonstrate its protective role, offering a novel experimental framework for evaluating hepatocellular resilience to cholestatic stress. These methodological advancements enhance the study's translational relevance and establish a foundation for future therapeutic research targeting STARD1 in liver disease.

3. *Other publications:*

Publications			
Title	**Authors**	**Title of the journal or equivalent**	**DOI**
Fatty acid-mediated induction of CYP2E1 activity in HepaRG cells is not systematically associated with exacerbated acetaminophen cytotoxicity	Clémence Penhoat, Julie Massart, Gregory Pinon, et al.	bioRxiv	https://doi.org/10.1101/2024.11.01.621521
Fecal Microbiota Transplantation from Young-Trained Donors Improves Cognitive Function in Old Mice Through Modulation of the Gut-Brain Axis	Camila Cerna, Nicole Vidal-Herrera, Francisco Silva-Olivares, et al.	Aging and disease	10.14336/AD.2024.1089
Loss of Cdkn1a protects against MASLD alone or with alcohol intake by preserving lipid homeostasis	Arantza Lamas-Paz, Alejandro Hionides-Gutiérrez, Feifei Guo, et al.	JHEP Rep.	10.1016/j.jhepr.2024.101230
Novel Emerging Mechanisms in Acetaminophen (APAP) Hepatotoxicity	Alejandro Hionides Gutiérrez, Naroa Goikoetxea-Usandizaga, Carlos Sanz-García, et al.	Liver Int.	10.1111/liv.16167
ECM1: a novel matricellular protein with promising antifibrotic potential	Isabel Fabregat and Francisco Javier Cubero	Gut	10.1136/gutjnl-2024-333455
Identification of PRMT5 as a therapeutic target in cholangiocarcinoma	Jasmin Elurbide, Leticia Colyn, María U Latasa, et al.	Gut	10.1136/gutjnl-2024-332998
Proceedings of the 5th Meeting of Translational Hepatology, organized by the Spanish Association for the Study of the Liver (AEEH)	Edilmar Alvarado-Tapias, Douglas Maya-Miles, Agustin Albillos et al.	Gastroenterol Hepatol.	10.1016/j.gastrohep.2024.502207

Communication and Dissemination activities:

Communication Activity Type	Description	Outcome
Poster	Annual Congress of the European Association for Cancer Research, Rotterdam, the Netherlands, 10-13 June. **Liver-specific metastasis is recapitulated in a zebrafish larval xenograft model that mimics the tumor microenvironment.** Ms. Basol, Merve	Oral communication/ Journal of Hepatology 2024 vol. 80(S1) | S1–S77
Meeting	Kickoff Meeting of the MPS_NOVA Twinning - European Hub of Excellence in Microphysiological Systems, ITQB NOVA Oeiras, Portugal, November 8. **Presentation of the Halt -RONIN project and UNL's Activities**. Dr. Michel Kranendonk	Oral communication
Poster	16th Workshop on Biomedical Engineering, Universidade de Lisboa, PORTUGAL, October 19. **Development of specialized multicellular 3D-organotypic models for the interrogation of pathogenic mechanisms in MASLD.** Catarina Baptista**.**	Poster
Poster	28 th Annual Meeting of the Sociedade Portuguesa de Genética Huaman, Porto, PORTUGAL, December 5. **Evaluation of POR Gene Variants in the HepaRG Model: Implications for Drug Metabolism.** Daniel Crispim.	Poster
Poster	PhDay UCM. Madrid, Spain, October 4. I**solation and characterization of extracellular vesicles in fecal matter: implications for future biomarker discovery.** Héctor Leal	Poster
Poster	AASLD, The Liver Meeting, San Diego, CA, November 15-19. **Nuclear factor erythroid 2-related factor 2 (NRF2) activation aggravates liver injury by causing mitochondrial dysfunction.** Alejandro Hionides	Poster