Halt-RONIN

Funded by the European Union

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 June – September 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 provide our latest news and aim 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 34 months 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/

From **September 2–5** we came together for our **3rd Annual Meeting**, proudly hosted by the **Izmir Biomedicine and Genome Center (IBG)**. It was an inspiring week filled with outstanding science, and fresh ideas as we push forward in our mission to discover novel biomarkers for the MASLD-to-MASH transition. We also took important in preparing our second periodic report — a true team effort! https://halt-ronin.com/3rd-annual-meeting/

The first collaborative session within the **Stay Healthy project cluster** took place on March 26, marking an important step toward strengthening synergies among health-focused research initiatives. Organized by the IMMEDIATE consortium, the session brought together cluster projects focusing on four projects that presented their current status - INITIALISE, miGut-Health, GlycanTrigger, and IMMEDIATE. With a wide range of projects in the cluster, this initial meeting was a starting point for deeper collaboration. The **second session** will take place on **September 24** and will feature additional projects to ensure inclusive participation.

The presentations led to a lively discussion focused on identifying concrete opportunities for collaboration. A **third in-person session** is being organized for **December 1–2 in Berlin**.

An overview of all projects within the Stay Healthy cluster can be found here.

Over the summer, the **International Seminar Series on Liver Toxicity and Steatotic Liver Disease** took a short break — but we're excited to announce they'll be back in the coming months! Stay tuned for the new sessions.

You can rewatch past seminars here

Javier Cubero
Coordinator of Halt-RONIN
Complutense University, Madrid

Funded by the European Union

Interesting publications for the consortium:

Metabolic Dysfunction-Associated Steatotic Liver Disease

Abstract:

Metabolic dysfunction–associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), is now the most prevalent chronic liver disease worldwide, affecting up to 38% of adults and disproportionately impacting patients with obesity and type 2 diabetes. MASLD encompasses a spectrum of liver pathology, from simple steatosis to inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma, and is increasingly recognized as a multisystem disorder with extrahepatic complications, including cardiovascular disease, chronic kidney disease, type 2 diabetes, and certain cancers. Disease progression is driven by adiposity, insulin resistance, coexisting metabolic abnormalities, and genetic predisposition, with clinically significant fibrosis (≥F2) strongly predicting liver-related complications and mortality. Early identification of at-risk patients is facilitated by noninvasive biomarkers and imaging tools, including the Fibrosis-4 index and transient elastography. Lifestyle interventions, including weight loss and dietary modification, remain foundational, while emerging metabolism-targeted pharmacotherapies—such as resmetirom, GLP-1 receptor agonists, dual/triple incretin agonists, PPAR agonists, FGF21 analogues, and SGLT2 inhibitors—have shown efficacy in resolving steatohepatitis and reducing fibrosis, with potential benefits on systemic cardiometabolic outcomes. Ongoing studies of combination therapies, long-term safety, and precision medicine approaches, including genetic risk profiling, are needed to optimize treatment strategies. Addressing the global burden of MASLD will require integrated, multidisciplinary approaches that target both liver-specific and systemic complications of this complex metabolic liver disease.

Results:

MASLD is the most common chronic liver disease worldwide, affecting up to 38% of adults and 65% of patients with type 2 diabetes. Although progression to cirrhosis or hepatocellular carcinoma occurs in a minority, clinically significant fibrosis (≥F2) strongly predicts liver-related complications and mortality. MASLD is a multisystem disease, increasing the risk of cardiovascular disease, chronic kidney disease, type 2 diabetes, atrial fibrillation, heart failure, and certain cancers, with risks rising alongside fibrosis severity.

Noninvasive tools, including the Fibrosis-4 index, transient elastography, and the Enhanced Liver Fibrosis test, allow early identification of patients with at-risk MASH. Lifestyle modification, particularly sustained weight loss, remains foundational, but emerging pharmacotherapies show promise. Resmetirom improves MASH resolution and fibrosis, GLP-1 receptor agonists and dual/triple incretin agonists reduce liver fat and improve cardiometabolic outcomes, while PPAR agonists, FGF21 analogues, and SGLT2 inhibitors further benefit fibrosis and systemic metabolic health. Gastrointestinal events are the most common adverse effects across these therapies.

Combination strategies addressing both hepatic pathology and systemic metabolic dysfunction, alongside genetic risk profiling, may enhance patient outcomes. Early detection and targeted intervention are essential to prevent disease progression and mitigate multisystem complications, though long-term studies are needed to confirm sustained efficacy and safety.

Conclusion:

MASLD is a growing global public-health challenge, characterized by progressive liver disease and multisystem complications affecting the cardiovascular, renal, and metabolic systems. Lifestyle interventions, including sustained weight loss and dietary modification, remain the cornerstone of management. Resmetirom is the first FDA-approved drug for noncirrhotic MASH with moderate-to-advanced fibrosis, and metabolism-targeted therapies—including GLP-1 receptor agonists, dual/triple incretin agonists, PPAR agonists, FGF21 analogues, and SGLT2 inhibitors—show promise in resolving steatohepatitis, reducing fibrosis, and improving systemic outcomes.

Despite these advances, challenges remain. Long-term safety and efficacy data are limited, and cost-effectiveness, accessibility, and patient selection require further study. Predictive tools, including polygenic risk scores and biomarker panels, may help identify patients at greatest risk for adverse liver-related events and guide individualized therapy. Combination treatment strategies targeting both liver-specific pathology and systemic metabolic dysfunction are likely necessary to fully address the multisystem nature of MASLD.

In summary, integrated, multidisciplinary approaches that combine lifestyle modification with emerging pharmacotherapies and precision medicine strategies offer the best opportunity to reduce liver-related and extrahepatic complications. Continued research is essential to optimize treatment, ensure long-term safety, and define the most effective strategies for this complex metabolic liver disease.

IMPACT AND IMPLICATIONS:

MASLD represents a major global health challenge due to its high prevalence, progressive nature, and multisystem consequences. Affecting up to 38% of adults worldwide and even higher proportions among patients with type 2 diabetes, MASLD contributes not only to liver-related morbidity, including fibrosis, cirrhosis, and hepatocellular carcinoma, but also to significant extrahepatic complications such as cardiovascular disease, chronic kidney disease, metabolic dysfunction, and certain cancers. The systemic nature of MASLD underscores the need for a comprehensive, multidisciplinary approach that integrates lifestyle interventions, early risk stratification, and emerging pharmacotherapies targeting both hepatic and metabolic dysfunction. Advances in noninvasive diagnostics and metabolism-based treatments—including resmetirom, incretin-based therapies, PPAR agonists, FGF21 analogues, and SGLT2 inhibitors—have the potential to improve liver outcomes while mitigating cardiometabolic complications. Addressing MASLD effectively could reduce healthcare burdens, prevent disease progression, and improve long-term patient survival, highlighting the importance of early identification, individualized therapy, and ongoing research to optimize clinical management strategies.

Access to the original article:

Giovanni Targher, Luca Valenti and Christopher D Byrne. **Metabolic Dysfunction-Associated Steatotic Liver Disease.** N England J Med (2025), doi: 10.1056/NEJMra2412865

Scientific Impact:

According to the WoS, the Impact Factor (IF) of this journal was 78.5 (2024) and it shows a Journal Citation Indicator of 23.30. The Rank (by Journal Citation Indicator) situates this journal in the position 2/332 and the percentile 99.5, that is D1.

Degree of Originality and Innovation: This work demonstrates high originality and innovation by redefining MASLD as a multisystem disease and integrating emerging metabolism-targeted therapies into clinical management. It highlights novel diagnostic approaches, including noninvasive biomarkers and risk stratification tools, and introduces promising pharmacologic strategies—such as resmetirom, incretin-based agonists, PPAR and FGF21 analogues, and SGLT2 inhibitors—that simultaneously address liver pathology and systemic metabolic dysfunction. The focus on combination therapies, precision medicine, and long-term outcome assessment provides a forward-looking framework for personalized treatment and the development of innovative clinical strategies in metabolic liver disease.
Thematic Priority or Challenge Addressed and Contribution to the Scientific Debate:

Funded by the European Union

This work addresses the critical challenge of the growing global burden of MASLD, a complex metabolic liver disease with multisystem complications. By highlighting its pathophysiology, natural history, and emerging metabolism-targeted therapies, the study contributes to the scientific debate on early identification, risk stratification, and integrated management. It emphasizes the need for multidisciplinary approaches, precision medicine, and combination treatments, advancing understanding of both hepatic and systemic outcomes and informing strategies to reduce morbidity, mortality, and healthcare impact.

Methodological Contribution: This study provides a methodological contribution by integrating comprehensive analyses of MASLD's natural history, pathophysiology, and multisystem outcomes with evaluation of emerging pharmacotherapies. It highlights the use of noninvasive biomarkers, imaging techniques, and risk stratification tools, such as the Fibrosis-4 index and transient elastography, to identify patients with at-risk MASH. By combining clinical, metabolic, and genetic data, the approach enables a systematic framework for patient assessment, individualized therapy, and evaluation of treatment efficacy, offering a robust methodological foundation for future research and clinical trials in metabolic liver disease.

Interesting publications of the consortium:

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

Background and aims:

Cholestatic liver diseases are often accompanied by hepatocellular injury, fibrosis, and cirrhosis due to the intracellular accumulation of solutes that cannot be excreted into bile, including bile acids (BAs). These are synthesized in hepatocytes from cholesterol mainly via the classic pathway and in a lower proportion through the mitochondrial acidic pathway. The latter requires STARD1-dependent cholesterol transport to the mitochondrial inner membrane for metabolism, whose contribution to BA-induced hepatotoxicity and cholestatic liver disease is unknown.

Approach and results:

Here we show that patients with primary biliary cholangitis exhibit increased expression of STARD1 compared to control subjects. Mice with hepatocyte-specific Stard1 deletion (Stard1Δhep) were more resistant to experimental models of complete (bile duct ligation) and chemical obstructive cholestasis-induced liver injury, inflammation, and fibrosis than Stard1f/f mice. Stard1Δhep mice exhibited reduced hepatic BAs and mitochondrial cholesterol accumulation but increased mitochondrial glutathione levels following bile duct ligation compared to Stard1f/f mice. Pharmacological mGSH depletion sensitized primary mouse hepatocytes to a mix of BAs mimicking the profile seen in Stard1f/f mice after bile duct ligation leading to increased inflammatory response and cytotoxicity.

Conclusions:

These findings highlight a role for STARD1 in cholestatic liver injury and suggest that its targeting may be of relevance for cholestatic liver disease.

IMPACT AND IMPLICATIONS:

This study provides significant insights into the pathogenesis of cholestatic liver diseases by highlighting the pivotal role of STARD1 in mediating hepatocellular injury and disease progression. The research underscores the importance of STARD1 as a potential therapeutic target, offering new avenues for intervention in cholestatic liver conditions. By elucidating the mechanisms through which STARD1 sensitizes hepatocytes to bile acid-induced toxicity, the findings pave the way for developing targeted therapies aimed at mitigating liver damage and improving patient outcomes in cholestatic liver diseases.

Access to the original article:

Laura Conde de la Rosa, Laura Fàbrega, Sandra Torres, Susana Nuñez, Vicent Ribas, Paula Segalés, Ricardo Espinosa-Escudero, Estel Solsona, María Jesús Monte, Alvaro Diaz-Gonzalez , José J G Marin, Carmen García-Ruiz, Jose C Fernandez-Checa. **Stard1 promotes cholestatic liver injury and disease progression by sensitizing to bile acid hepatotoxicity.** Hepatology (2025), doi: 10.1097/HEP.0000000000001184

Scientific Impact:

According to the WoS, the Impact Factor (IF) of this journal was 15.8 (2024) and it shows a Journal Citation Indicator of 3.18. The Rank (by Journal Citation Indicator) situates this journal in the position 7/147 and the percentile 95.6, that is D1.

Degree of Originality and Innovation: This study demonstrates a high degree of originality by identifying STARD1 not merely as a cholesterol transport protein but as a critical mediator of hepatocyte sensitivity to bile acid-induced toxicity. The innovative aspect lies in linking STARD1 expression directly to the progression of cholestatic liver injury, a connection that had not been clearly established before. By uncovering this novel mechanistic pathway, the research challenges existing paradigms in cholestatic liver disease and opens new possibilities for targeted therapeutic strategies, representing a significant advancement in the field.

Thematic Priority or Challenge Addressed and Contribution to the Scientific Debate: This study directly addresses the critical challenge of understanding the mechanisms underlying cholestatic liver diseases, which remain a major clinical and research priority due to their prevalence and limited treatment options. By demonstrating the central role of STARD1 in sensitizing hepatocytes to bile acid toxicity, the research contributes significantly to the ongoing scientific debate on the molecular drivers of liver injury. It provides new mechanistic insights that refine current models of cholestatic pathology, stimulating discussion on potential intervention points and guiding future studies aimed at developing effective therapies.

Methodological contribution: This study makes a notable methodological contribution by employing a combination of advanced molecular, cellular, and in vivo approaches to dissect the role of STARD1 in cholestatic liver injury. The integration of genetic manipulation models with precise biochemical assays allowed the authors to establish a causal link between STARD1 expression and hepatocyte sensitivity to bile acid toxicity. This comprehensive methodological framework sets a benchmark for future research in liver disease, providing a robust and reproducible approach for investigating molecular mediators of liver pathology and for evaluating potential therapeutic targets.

Other publications of the Consortium.

Publications			
Title	**Authors**	**Title of the journal or equivalent**	**DOI**
Intestinal permeability and immune-inflammatory markers in patients with idiosyncratic drug-induced liver injury, drug-induced steatosis and metabolic dysfunction–associated steatotic liver disease (MASLD)	Daniel E. Di Zeo-Sánchez, Irene Díaz-Alberola, José María Pinazo-Bandera et al.	British Pharmacological Society	10.1111/bph.70123
GDF15 is associated with hepatocellular senescence and correlates with mortality in patients with alcohol-associated hepatitis	Teresa Rubio-Tomás, David Martí-Aguado, Delia Blaya, et al.	JHEP Reports	https://doi.org/10.1016/j.jhepr.2025.101478
Patient-derived liver organoids recapitulate liver epithelial heterogeneity and enable precision modeling of alcohol-related liver disease	Silvia Ariño, Raquel Ferrer-Lorente, Guillermo Serrano et al.	Journal of Hepatology	https://doi.org/10.1016/j.jhep.2025.07.014
Trajectory analysis of hepatic stellate cell differentiation reveals metabolic regulation of cell commitment and fibrosis.	Martínez García de la Torre, R. A., Vallverdú, J., Xu, Z.et al.	Nature Communications	https://doi.org/10.1038/s41467-025-56024-4
The gut–liver axis in progressive steatotic liver disease: A focus on bile acid dysregulation	Panayiotis Louca , Juan M. Pericàs, Yu Lin, et al	The Journal of Nutrition, health and aging	https://doi.org/10.1016/j.jnha.2025.100671
LSECtin attenuates hepatic Th17 expansion in a murine model of cirrhosis and signals through the LAG-3 receptor	Sebastián Martínez-López, Oriol Juanola, Isabel Gómez-Hurtado et al	JHEP Report	10.1016/j.jhepr.2025.101482

Role of CNNM4 in the progression of cholangiocarcinoma: implications for ferroptosis and therapeutic potential	Maria Mercado-Gómez Naroa Goikoetxea-Usandizaga, Alvaro Eguileor Giné, et al	GI cancer	https://doi.org/10.1136/gutjnl-2024-333255
Differential Protective Roles of c-Jun N-terminal Kinase-2 in Nonparenchymal Liver Cells and Hepatocytes During Cholestasis	Mohamed Ramadan Mohamed, Gang Zhao, Ines Volkert, et al	Cellular an molecular gastroenterology and Hepatology	10.1016/j.jcmgh.2025.101588

Communication and Dissemination activities:

Communication Activity Type	Description	Outcome
Oral Communication	Reunión de Hepatología Traslacional. Asociación Española para el Estudio del Hígado (AEEH). September 27th, Barcelona, Spain. **Increasing the cellular complexity of patient-derived liver organoids to model chronic liver disease.** Zhenqing Xu.	https://aeeh.es/congresos/6-reunion-de-hepatologia-traslacional/
Poster	ASSLD the Liver Meeting. **Identifying health-to-disease transitional cell states in 2D and 3D human organotypic models of MASLD-MASH**. Anabel Martínez Lyons.	Poster communication.
Poster	EASL Congress 2025, Amsterdam, Netherlands, 7-10 May. **Identifying health-to-disease transitional cell states in 2D and 3D human organotypic models of MASLD-MASH**. Anabel Martínez Lyons.	Poster communication.
Poster	ASSLD the Liver Meeting. **Dinamic Liver-on-chip model for health-to-disease transition in MASLD-MASH.** Debbie Neill	Poster communication.

Funded by the
European Union