



PARIS MASH MEETING

10th edition

**Organized by
Arun Sanyal & Lawrence Serfaty**



**September 5 & 6 2024
Institut Pasteur, Paris**



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MASH
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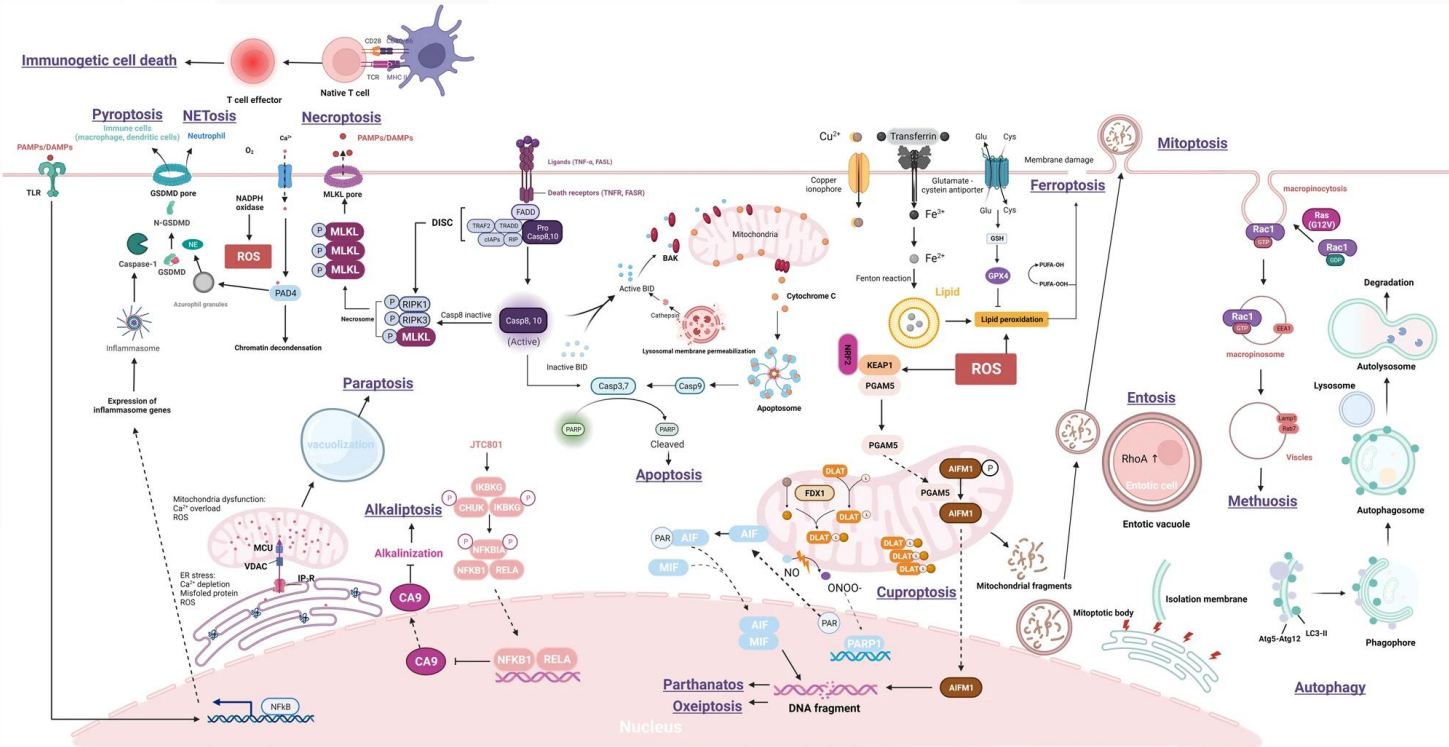
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Biologic relevance of different paths to cell death in MASLD

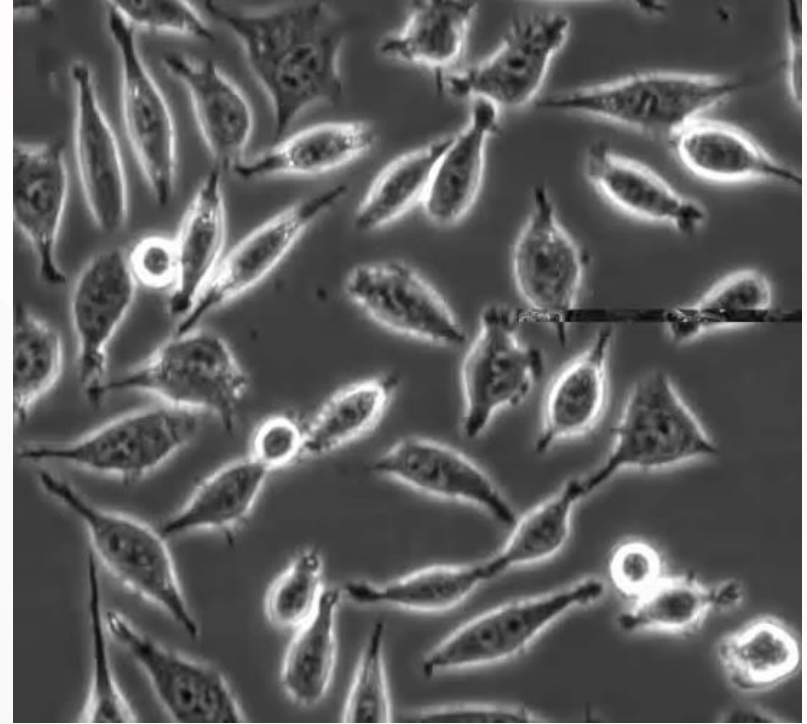
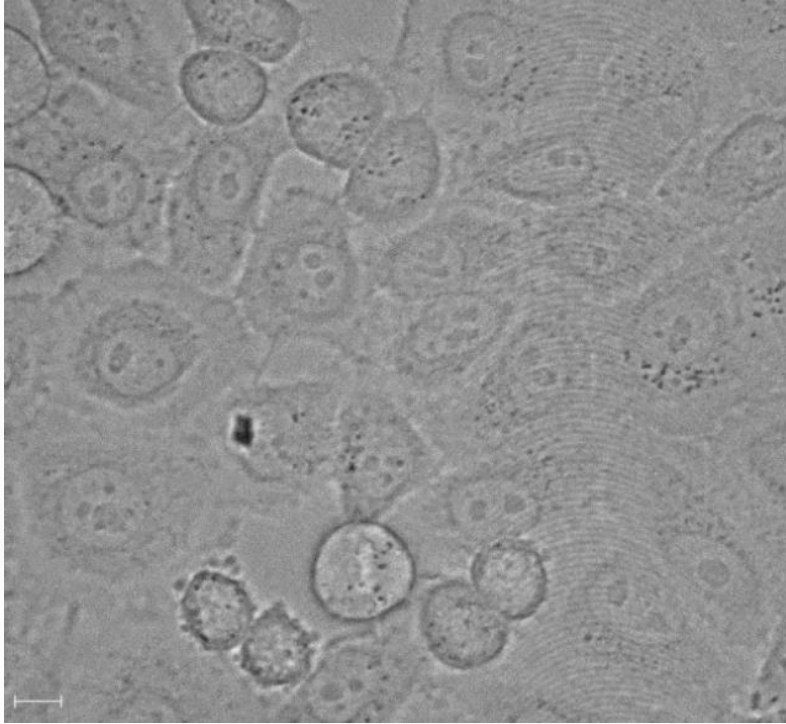
- I have no conflict of interests.

Diversity and complexity of cell death.



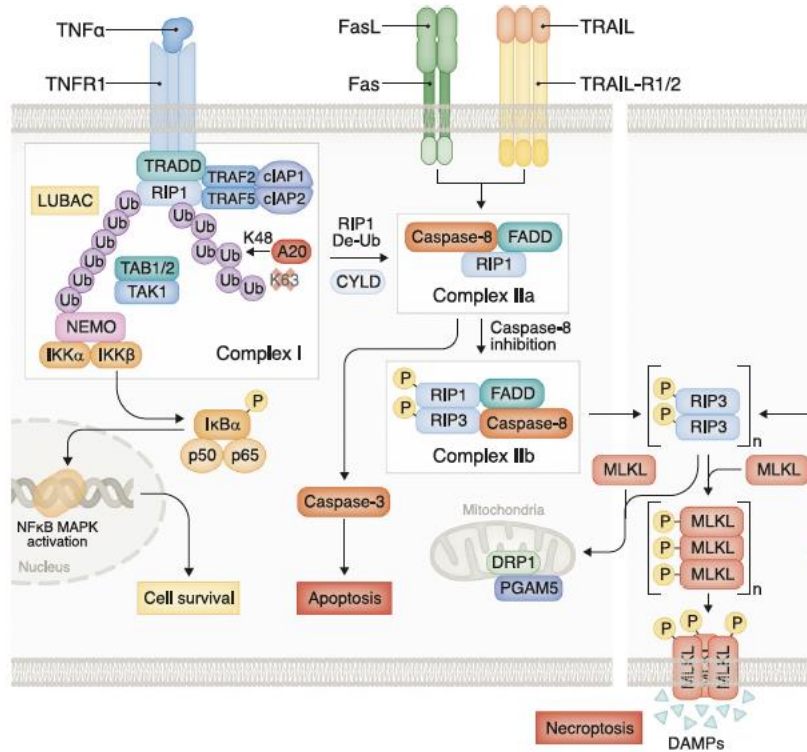
Park et al, 2023 Exp & Mol Medicine

Apoptosis vs Necrosis

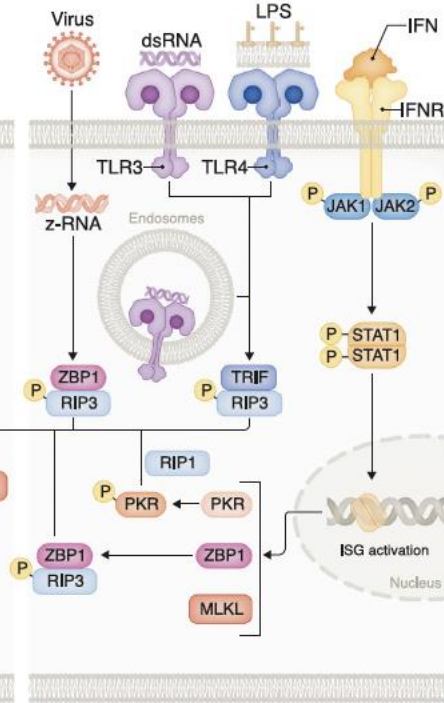


Apoptosis vs Necrosis

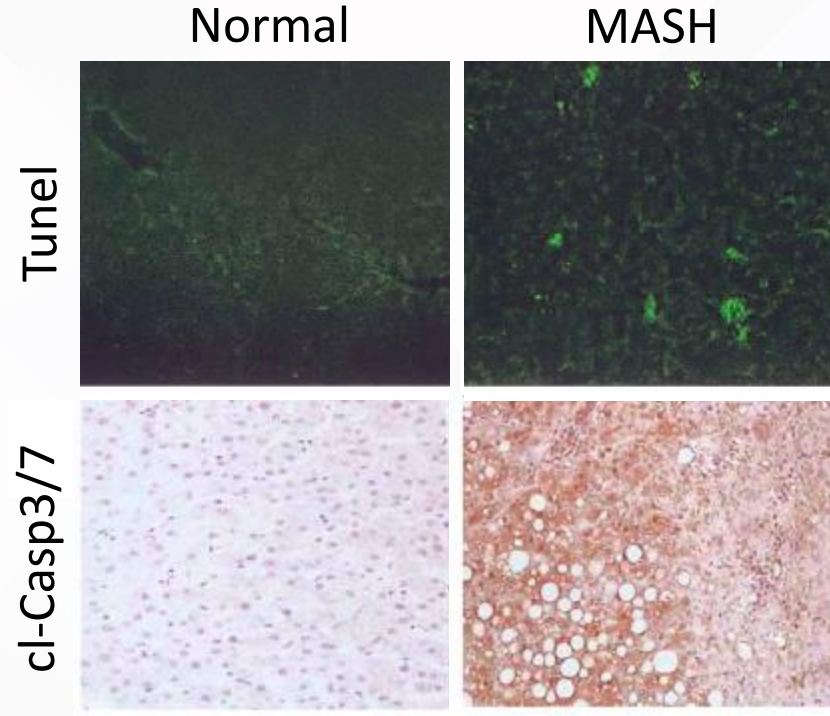
A. Classical necroptotic pathways



B. Non-classical necroptotic pathways



MASH and Apoptosis



Feldstein et al, 2003 Gastroenterology

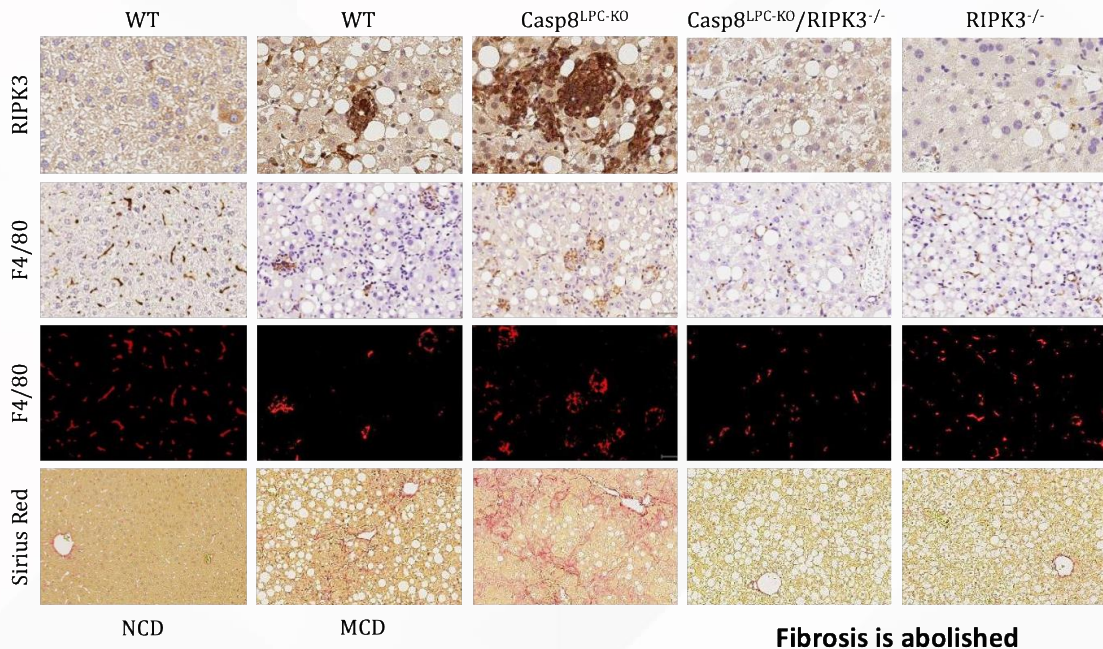
MASH and Apoptosis

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of GS-9450 in Subjects With Nonalcoholic Steatohepatitis

Vlad Ratziu,¹ Muhammad Y. Sheikh,² Arun J. Sanyal,³ Joseph K. Lim,⁴ Hari Conjeevaram,⁵ Naga Chalasani,⁶
Manal Abdelmalek,⁷ Anezi Bakken,⁸ Christophe Renou,⁹ Melissa Palmer,¹⁰ Robert A. Levine,¹¹
B. Raj Bhandari,¹² Melanie Cornpropst,¹³ Wei Liang,¹³ Benjamin King,¹³ Elsa Mondou,¹³
Franck S. Rousseau,¹³ John McHutchison,¹³ and Mario Chojkier¹⁴

Ratziau et al, 2011 Hepatology

RIPK3-dependent necroptosis promotes NASH-induced liver fibrosis and inflammation.



Gautheron et al, 2014 EMBO Mol Med; Afonso et al, 2015 Clin Sci

Pan-caspase inhibition may have shifted cell death to programmed necrosis

Research Article

NAFLD and Alcohol-Related Liver Diseases

JOURNAL
OF HEPATOLOGY

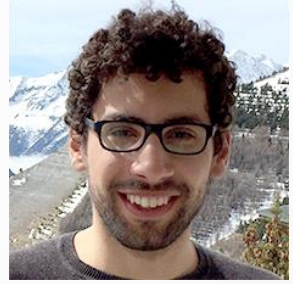
A randomized, placebo-controlled trial of emricasan in patients with NASH and F1-F3 fibrosis

Highlights

- Pan-caspase inhibition with emricasan did not improve liver histology in NASH and may have worsened fibrosis and ballooning.
- Caspase inhibition lowered average serum ALT values in the overall population but did not consistently normalize values in individual patients.
- Emricasan was generally well-tolerated over 72 weeks of treatment.
- While speculative, pan-caspase inhibition may have shifted cells from apoptotic to more inflammatory forms of cell death.

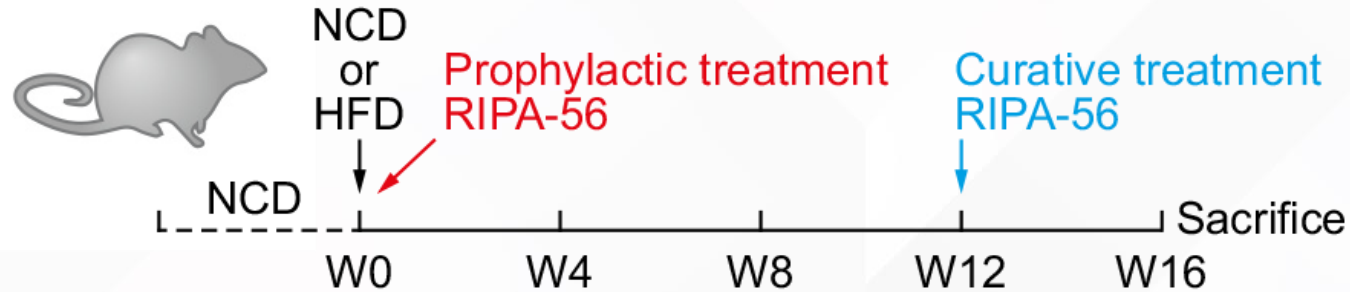
Harrison et al, 2020 Journal of Hepatology

Mouse model



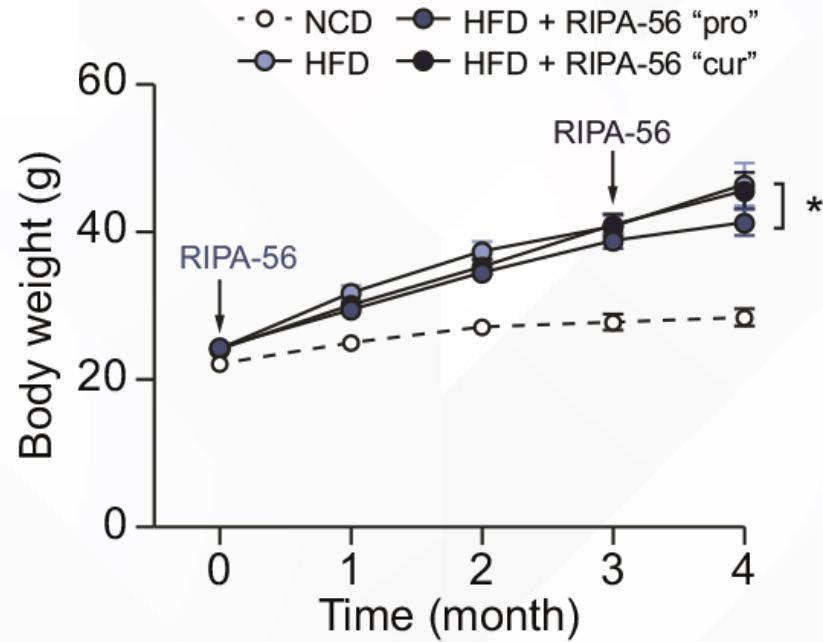
Amine Majdi

RIPK1 inhibition

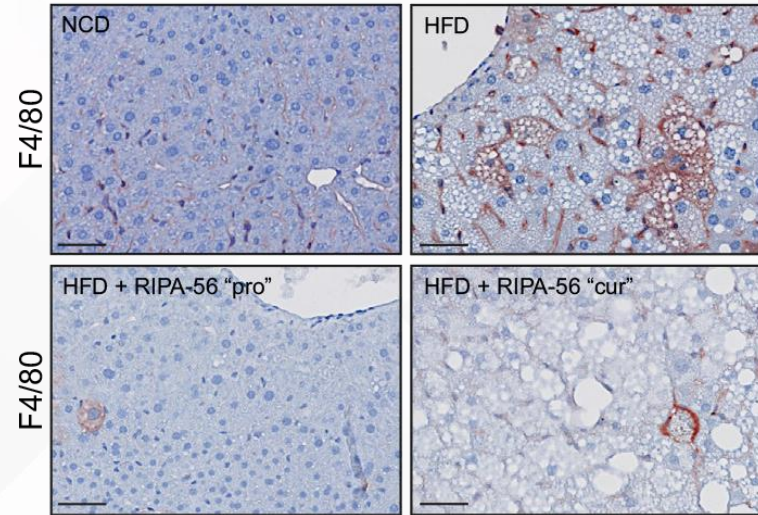
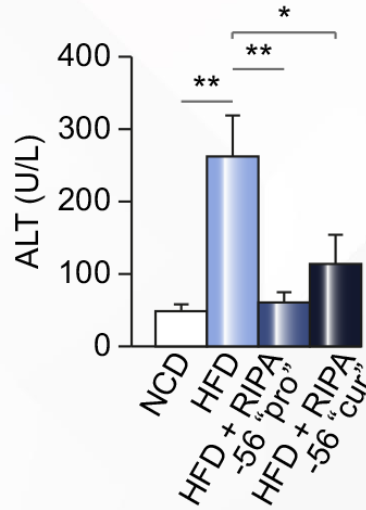
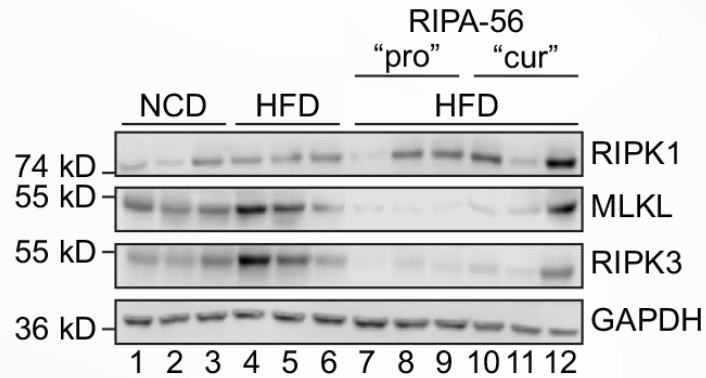


Majdi et al, 2020 Journal of Hepatology

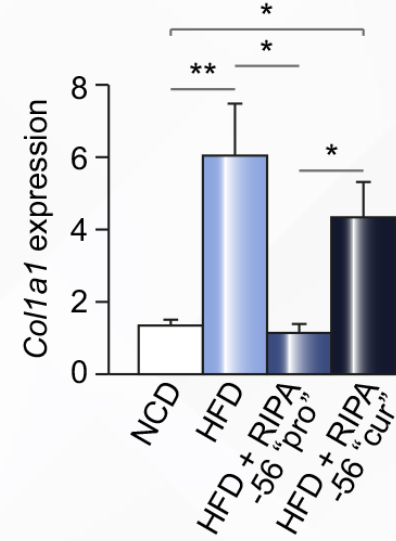
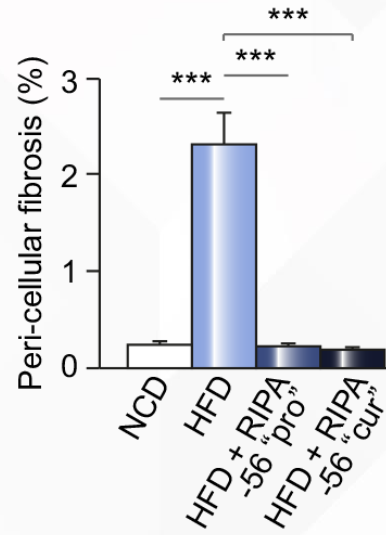
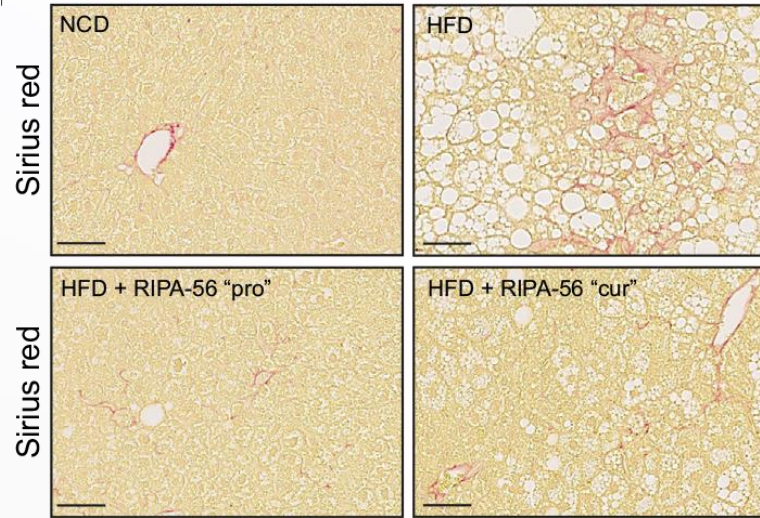
Weight gain



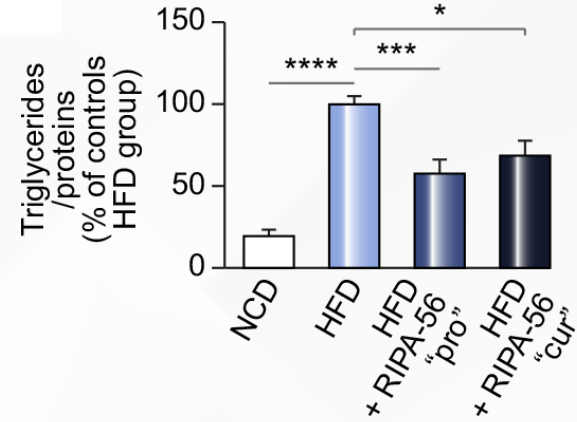
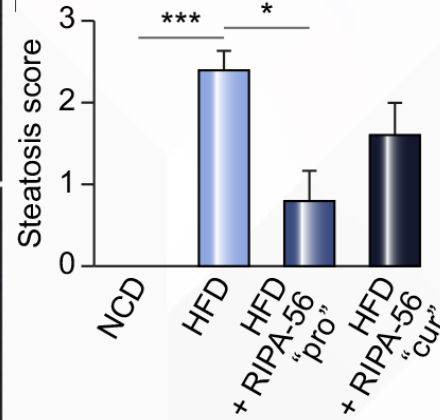
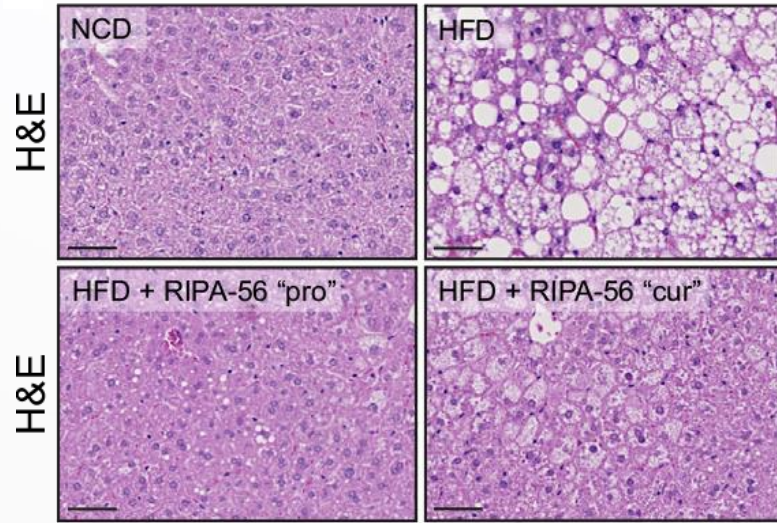
RIPA-56 treatment improves liver injury and inflammation in HFD-fed mice



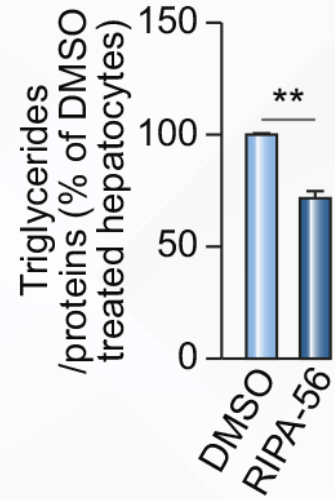
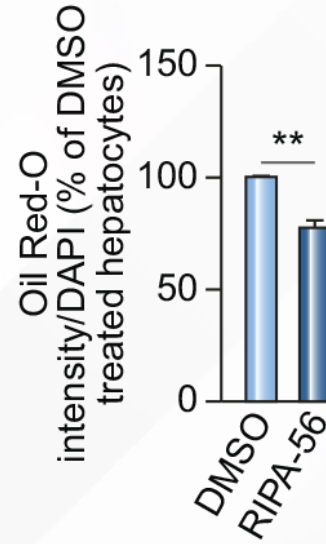
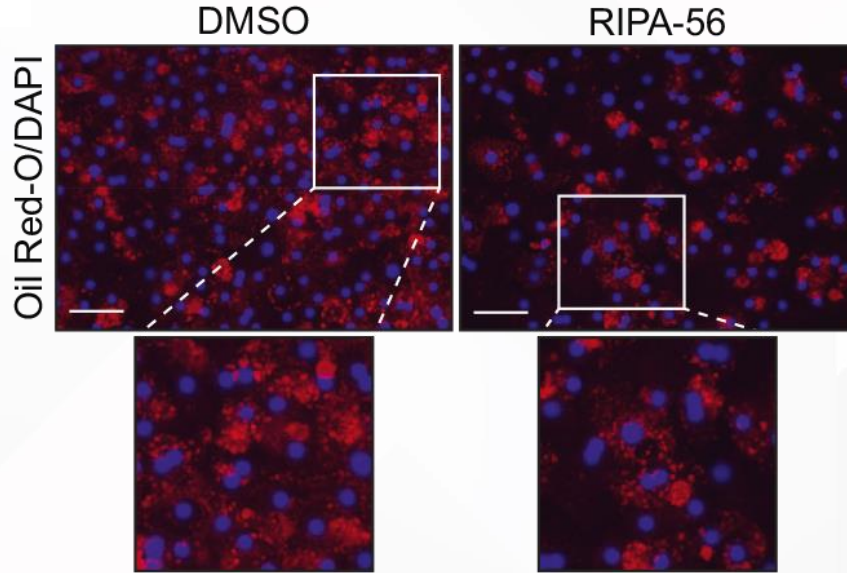
RIPA-56 treatment improves fibrosis in HFD-fed mice



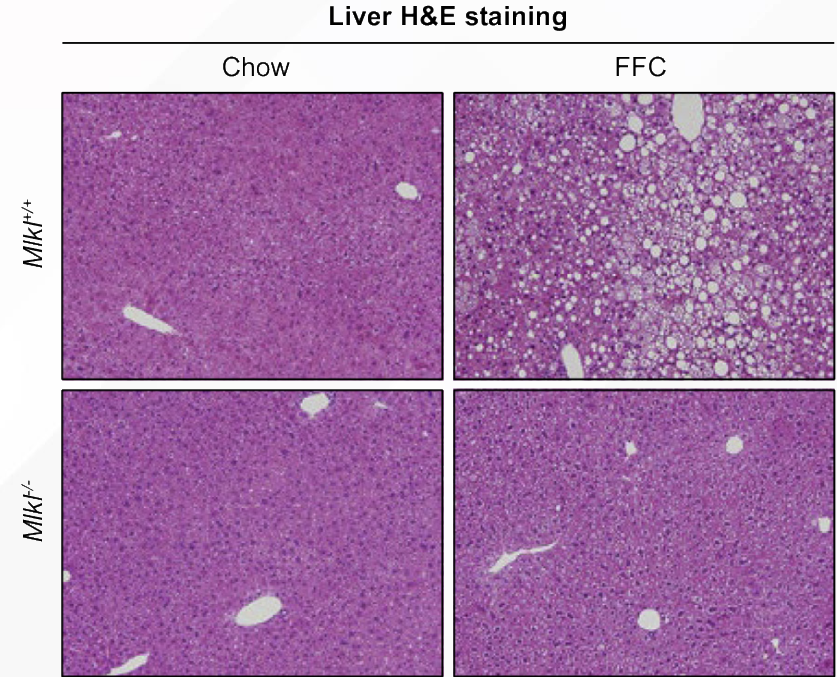
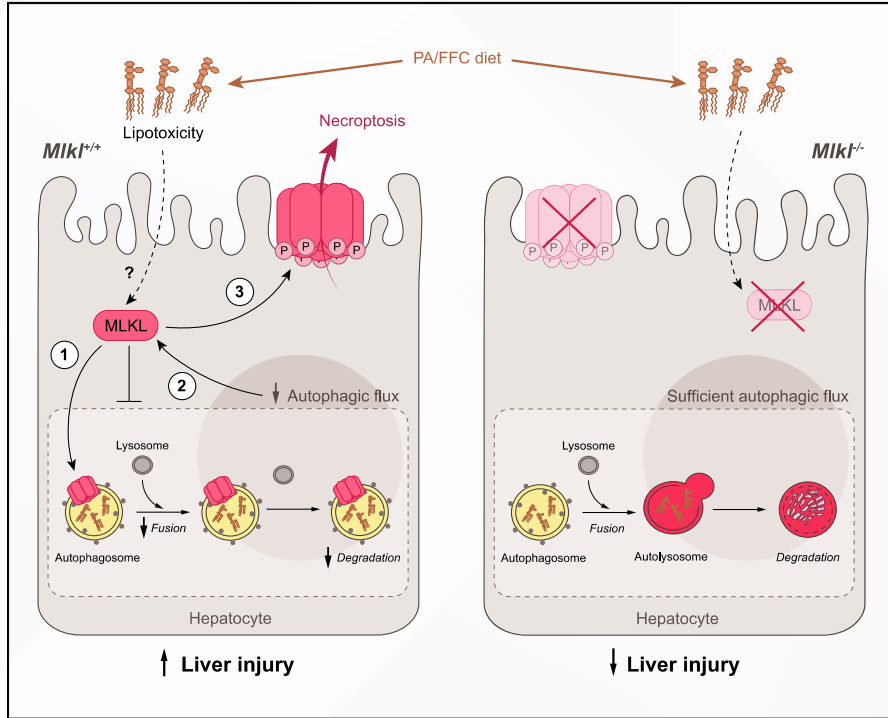
RIPA-56 treatment improves HFD-induced steatosis



RIPA-56 treatment induces fat depletion in primary human hepatocytes

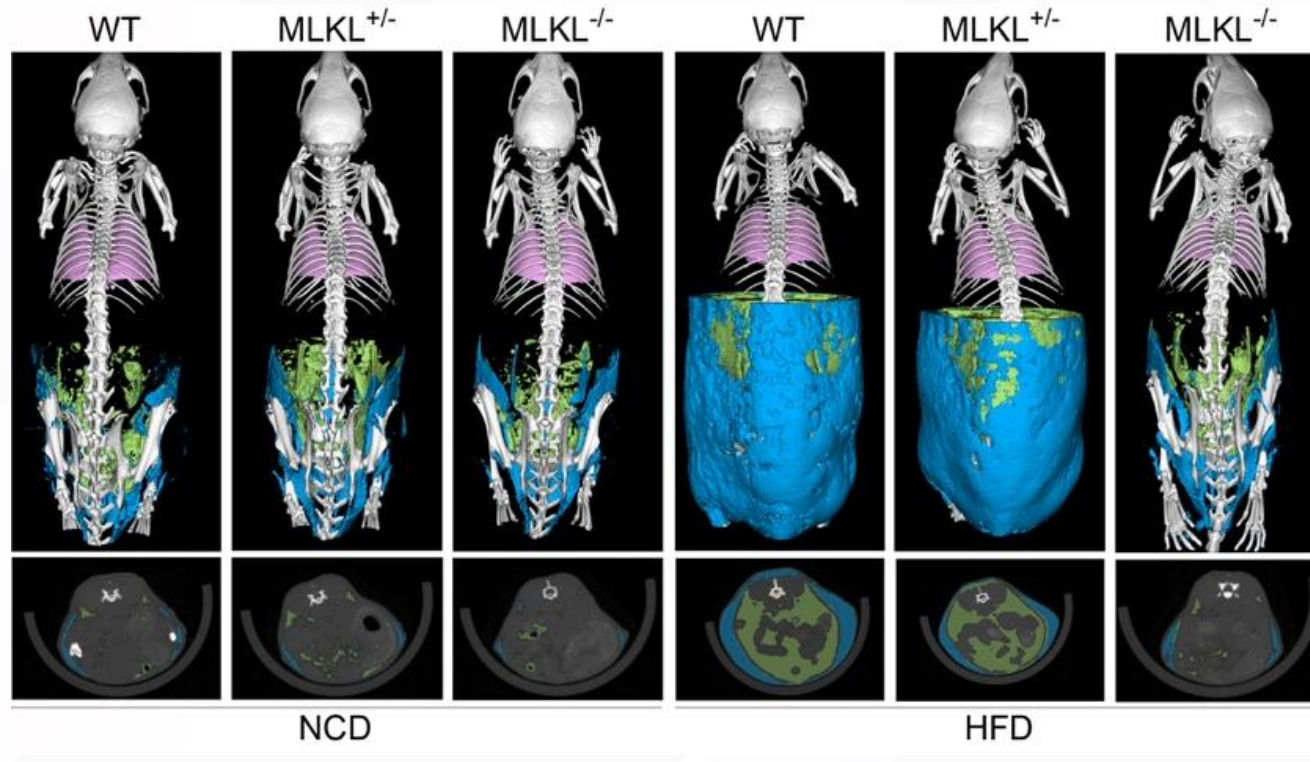


MLKL also regulates autophagy flux



Wu et al, 2020 Journal of Hepatology

MLKL deficiency protects mice against HFD-induced obesity

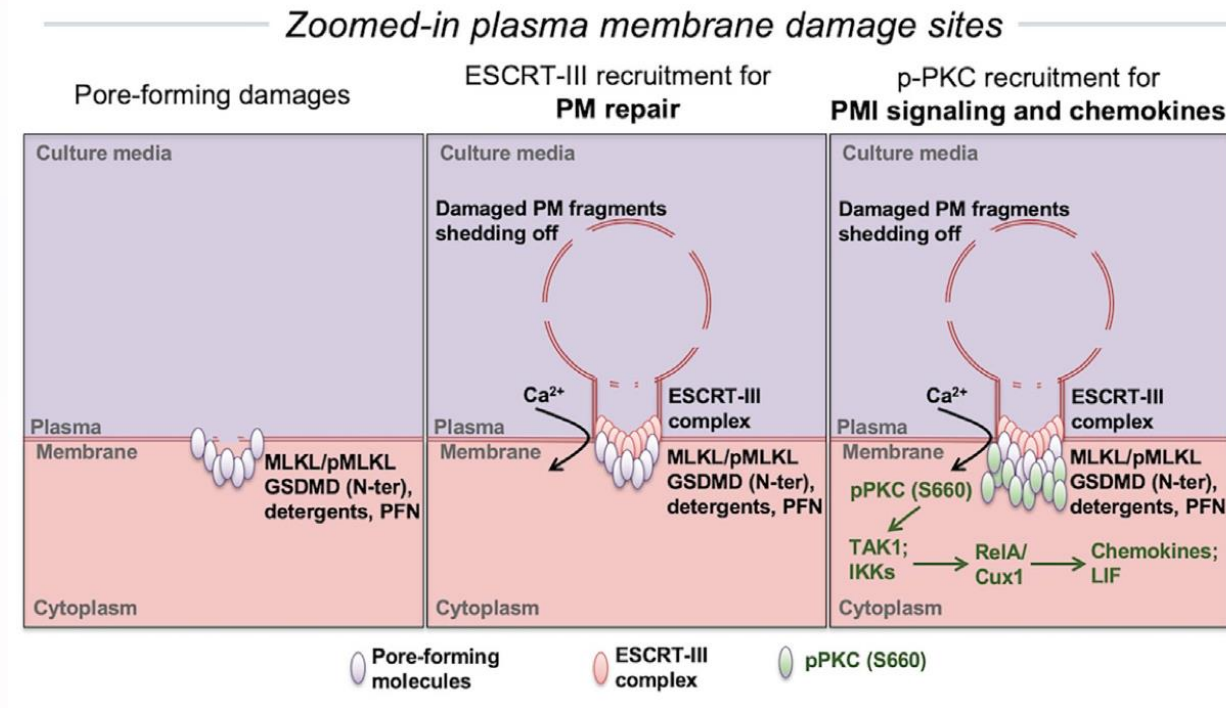


Why necroptosis inhibition may work in MASH patients !

- it has pleiotropic effects : it not only reduces liver injury and inflammation but also steatosis in murine models of NASH.
- it also inhibits NF-kappaB and apoptosis.
- RIPK1 inhibitor shows beneficial effects not only on prophylactic setting but also on curative setting (few other drugs have been tested in that context).
- RIPK1 and MLKL inhibitors work on primary human steatotic hepatocytes (derived from liver grafts of NASH patients).

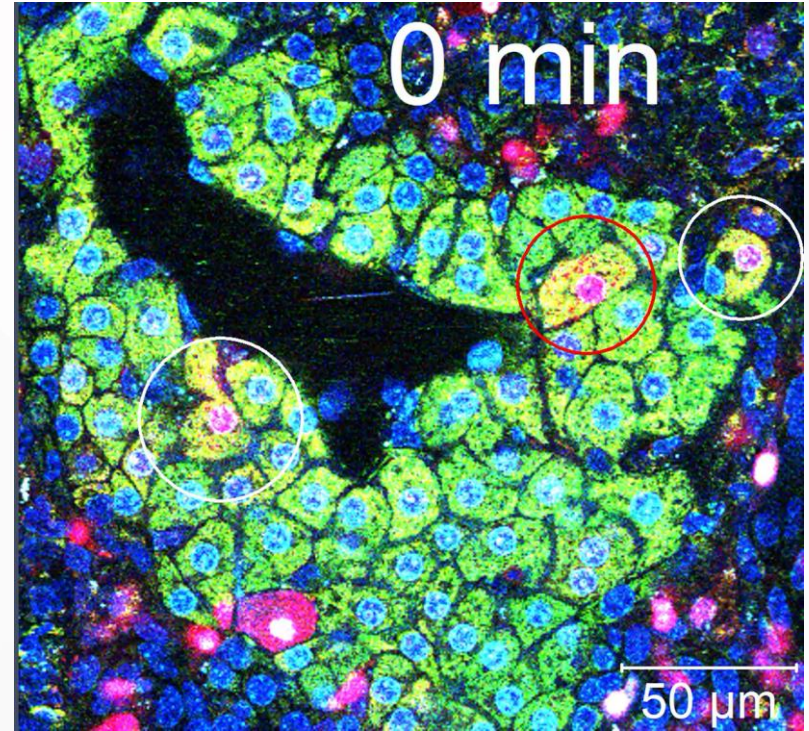
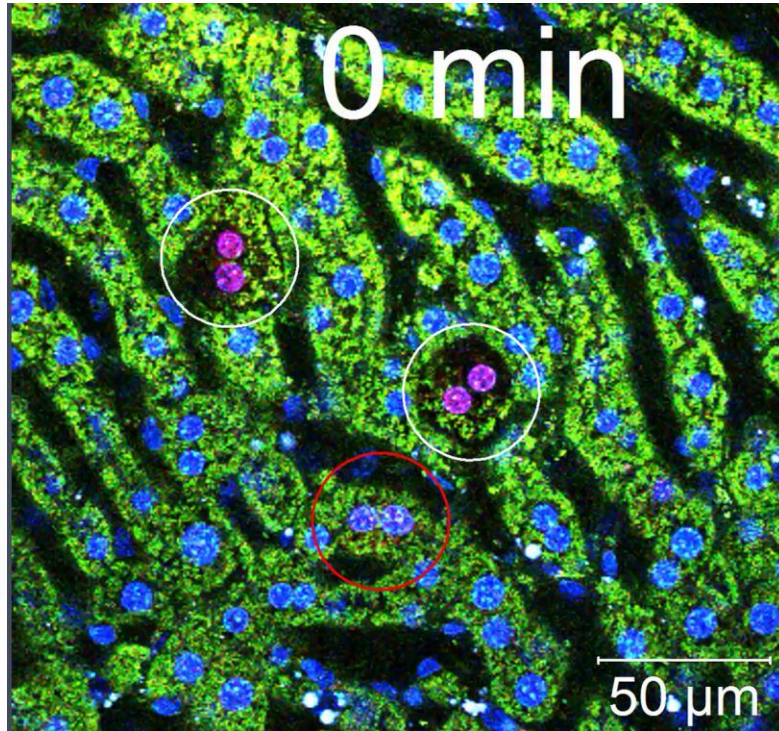
Can hepatocytes die without dying ?

Cells can tolerate a limited level of plasma membrane damage



Gong et al, 2017 Cell; Wang et al, 2022 Developmental Cell

Sublethal necroptosis in hepatocytes exists



Vucur et al, 2023 Immunity

Team, Collaborators, Funding

Team

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