

Biologics Delivery

Virender Kumar, PhD

CRS 2022 Annual Meeting & Expo

July 11 – 15, 2022 | Montreal Congress Center, Montreal Canada

Advanced Delivery Science





University of Nebraska
Medical Center™

BREAKTHROUGHS FOR LIFE.®

Anti-miR-96 and Hedgehog Pathway Inhibitor MDB5 Synergistically Ameliorates Alcoholic Liver Injury in Mice

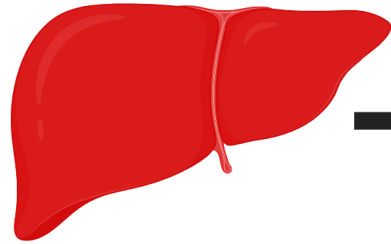
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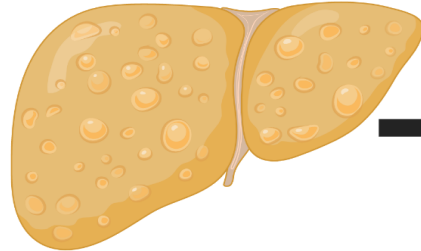
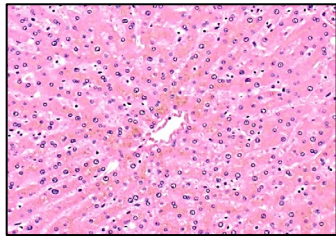
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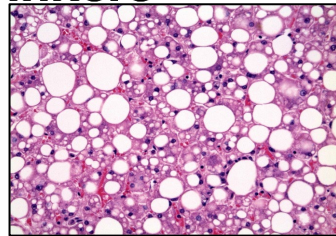
Alcoholic Liver Disease



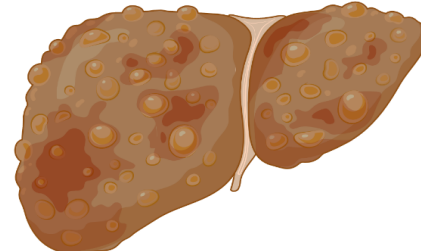
Healthy Tissue



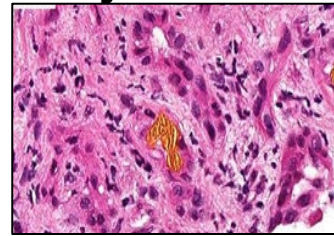
Alcoholic Fatty liver
(in >90% of heavy drinkers)



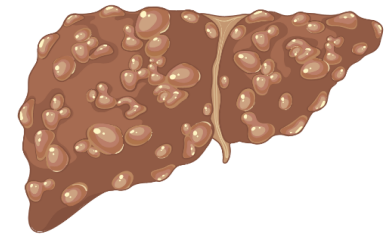
- Fat accumulation
- Enlarged liver
- Asymptomatic
- Reversible



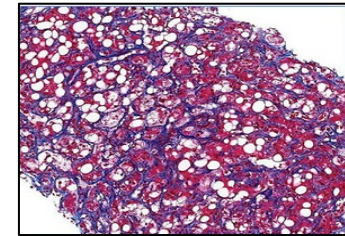
Alcoholic hepatitis
(in 10-30% of heavy drinkers)



- Inflammation
- Fever, fatigue
- Jaundice
- Enlarged liver



Cirrhosis
(in 10-20% of heavy drinkers)

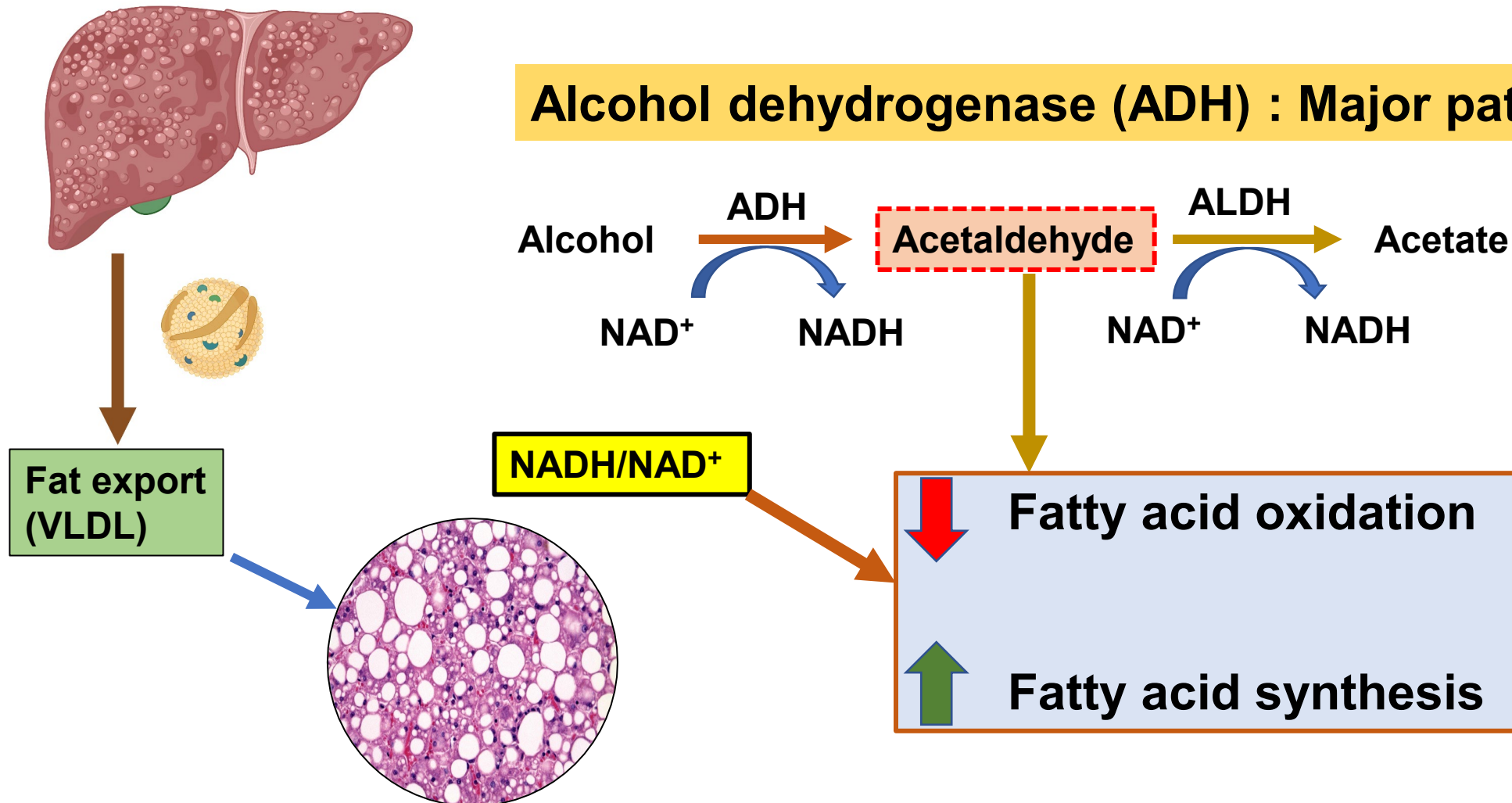


- Scar tissue (fibrosis)
- End stage hepatitis
- Liver shrinks
- Irreversible



Pathophysiology

Alcohol dehydrogenase (ADH) : Major pathway



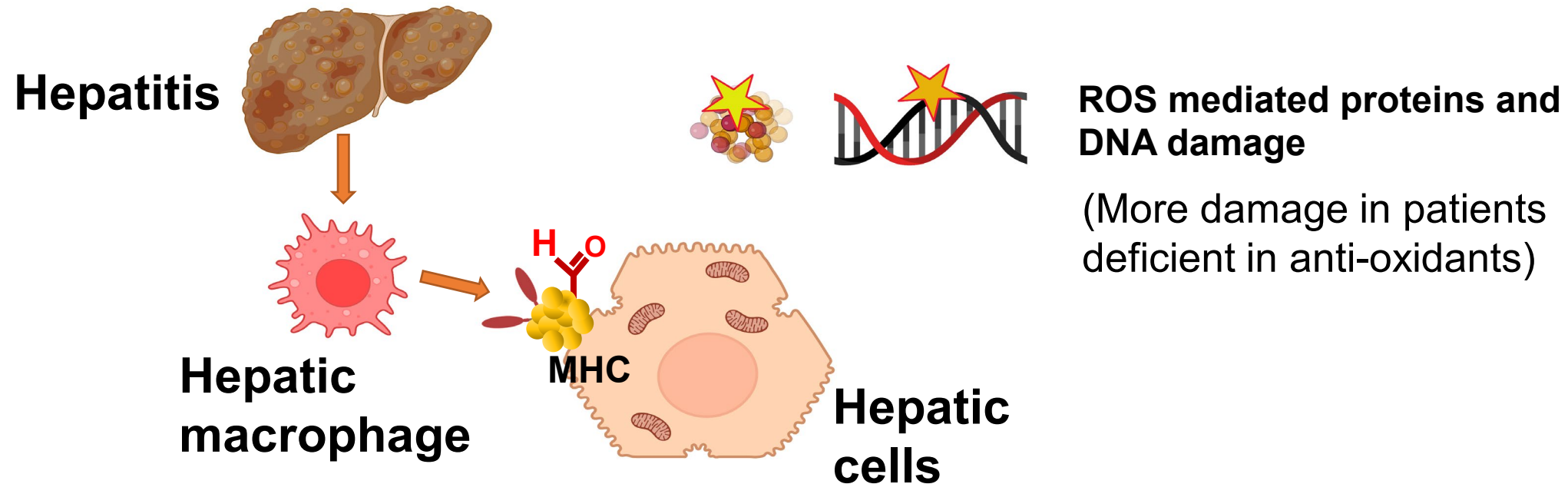
Pathophysiology

Cytochrome P450 2E1 (CYP 2E1) : Minor pathway



Reactive oxygen species (ROS)

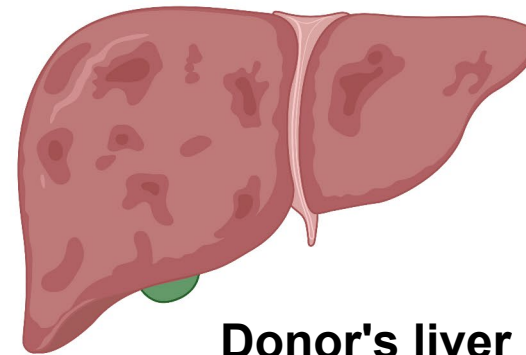
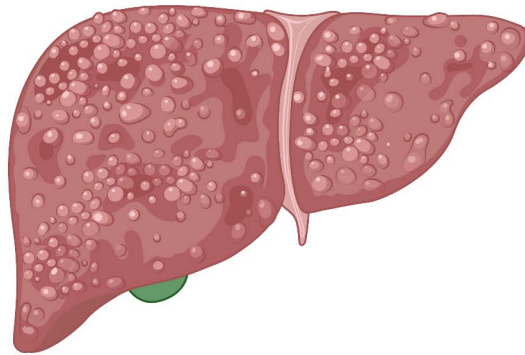
(Superoxide – O_2^- oxygen species (ROS); Hydroxyl radicals $\text{OH}^\cdot$)



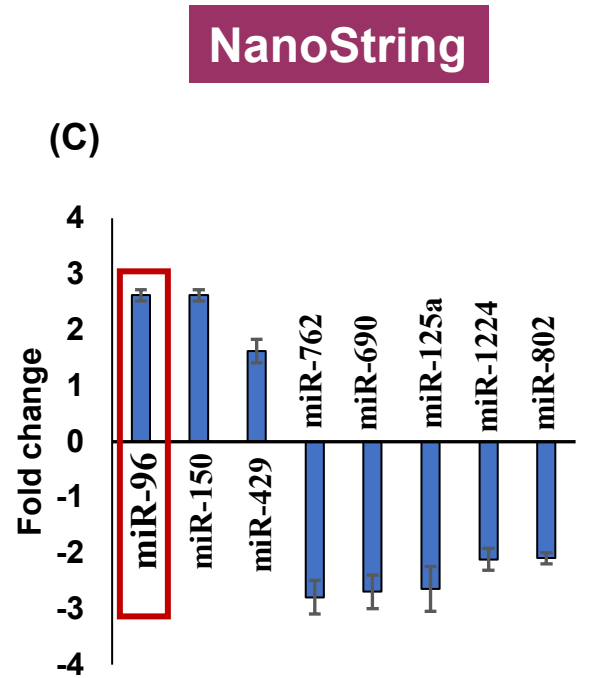
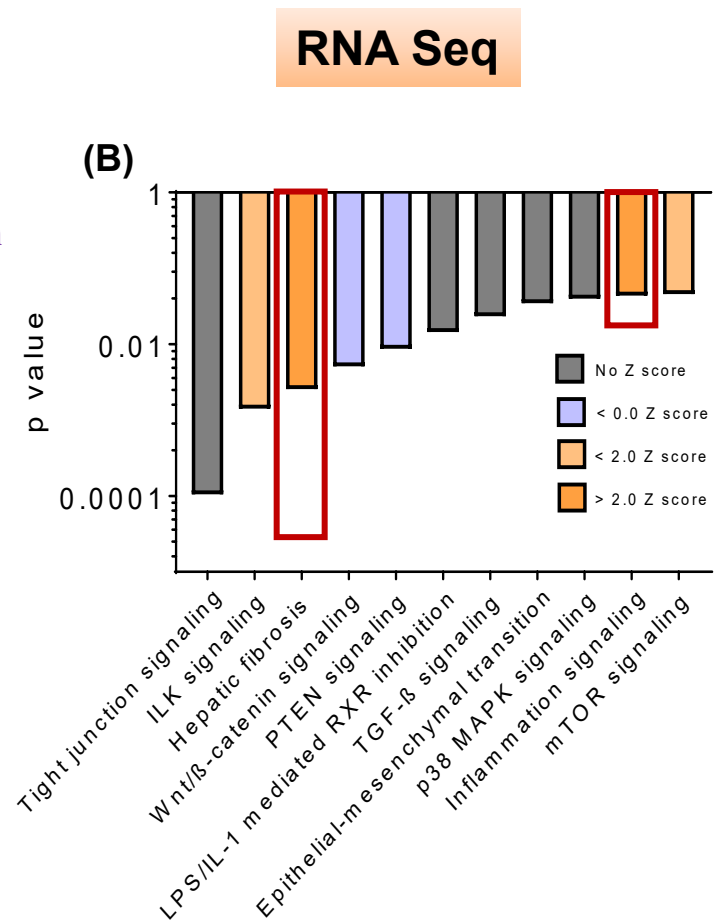
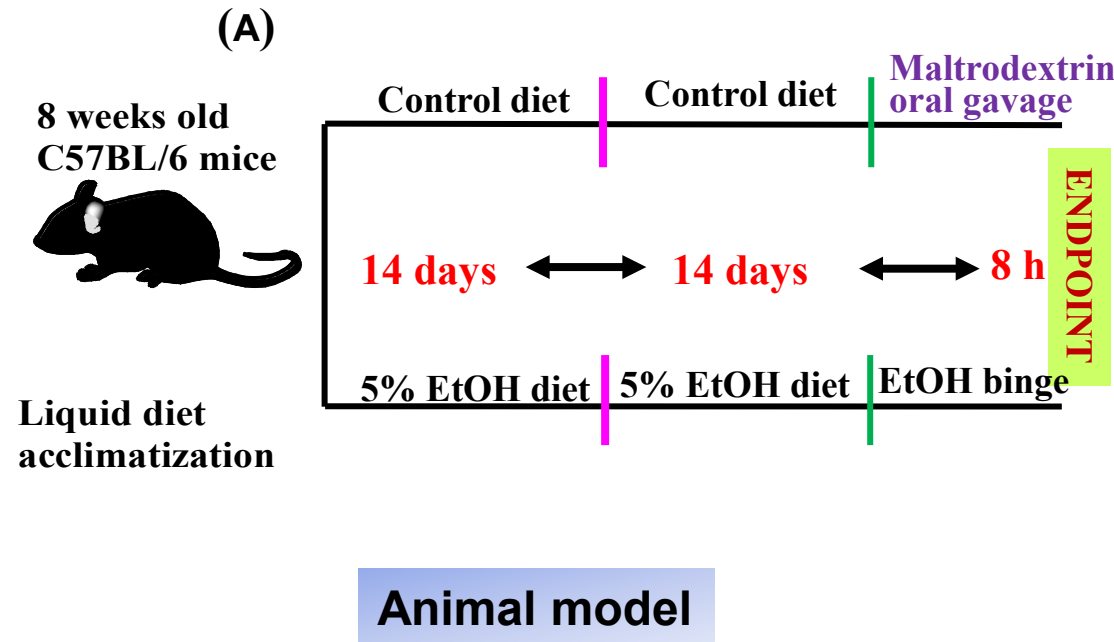
Treatment



- Abstinence
- Corticosteroids to reduce inflammation
- Liver transplantation



Research findings



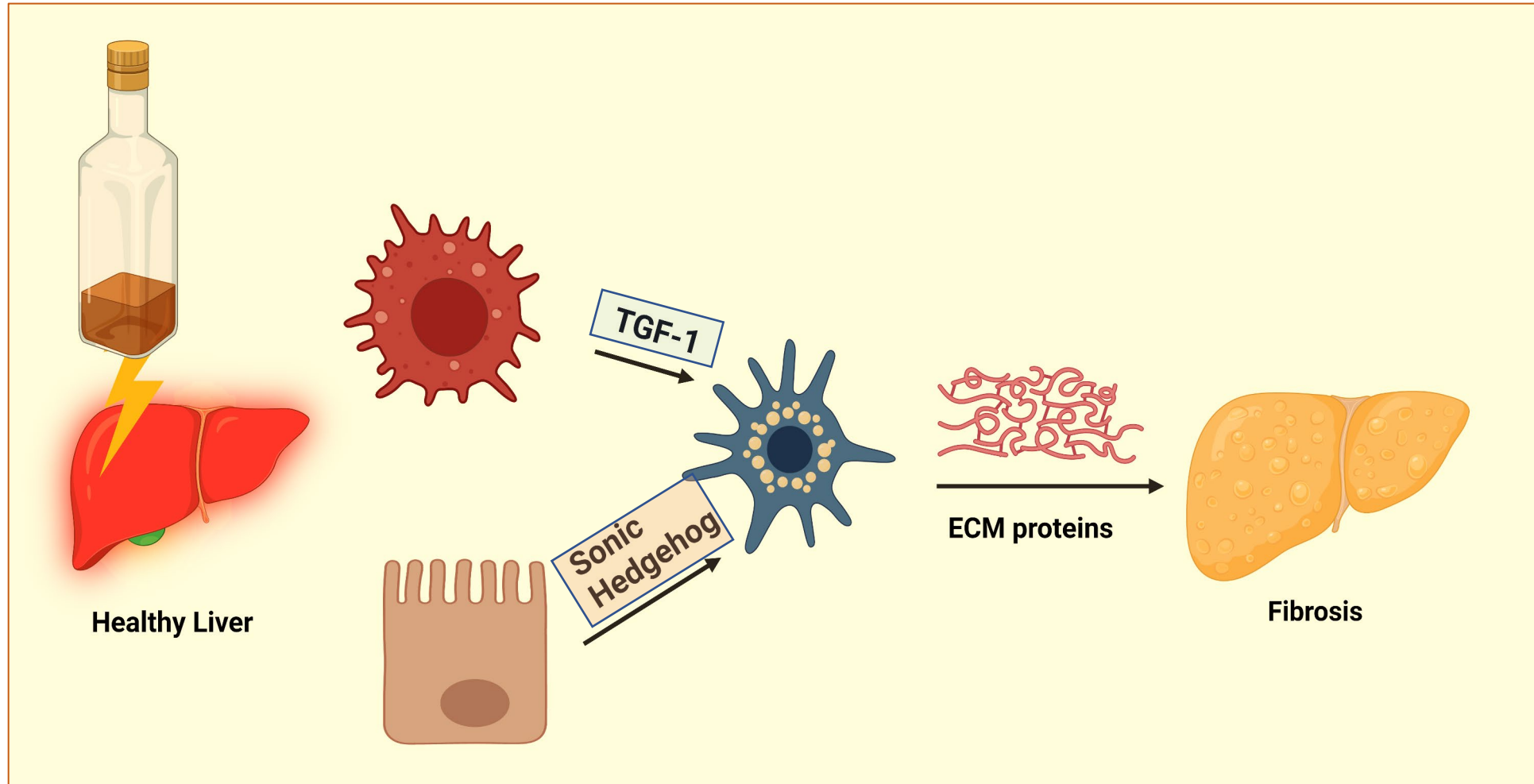
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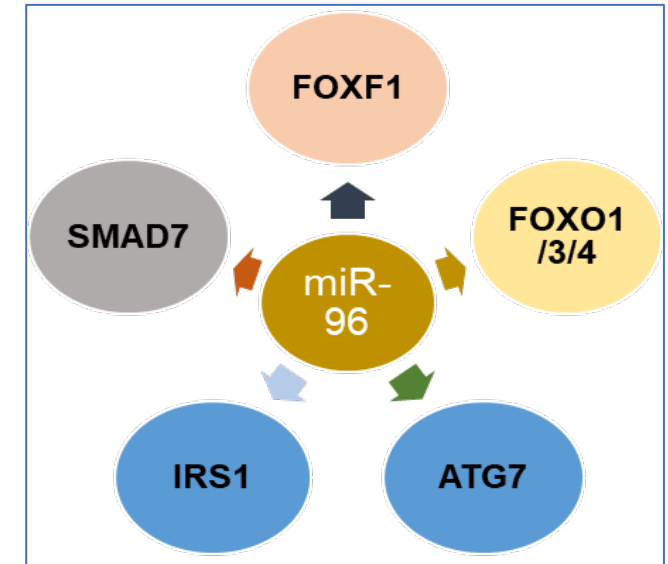
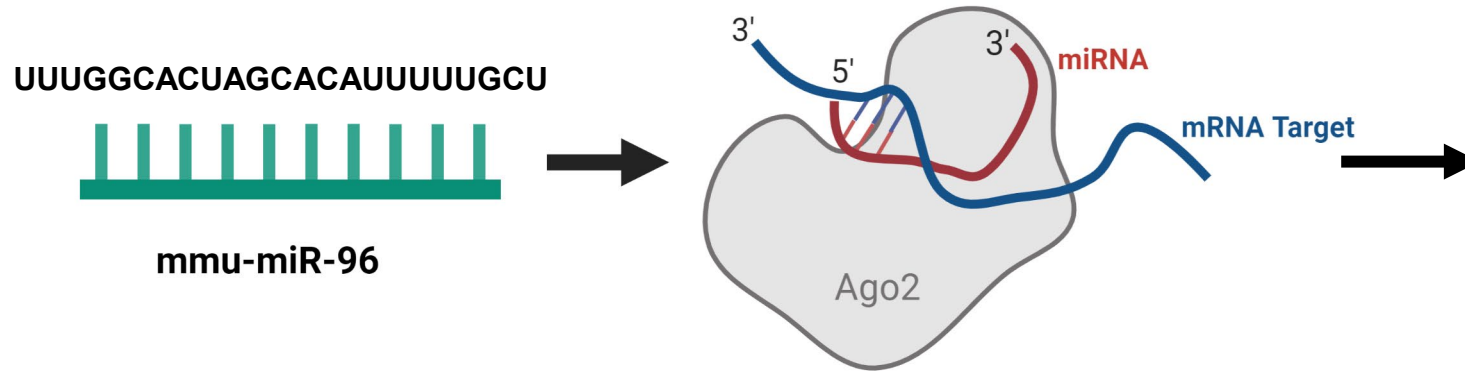
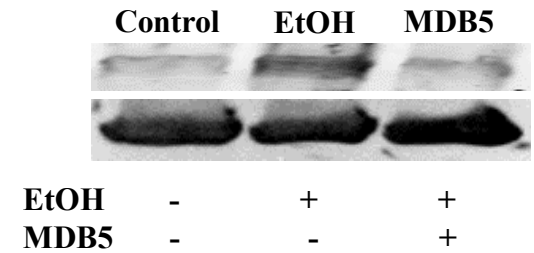
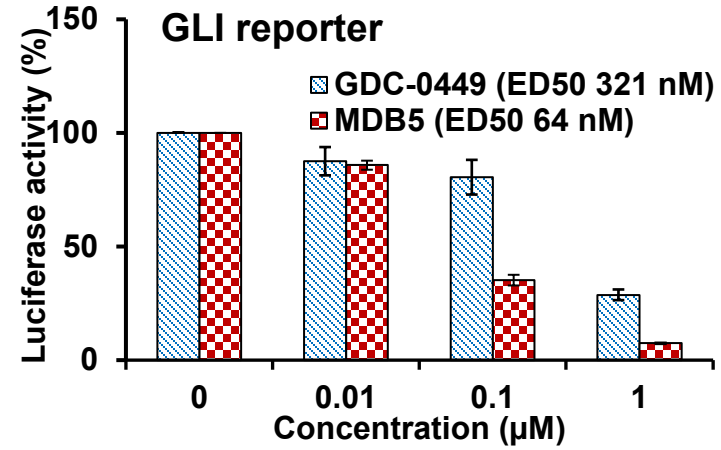
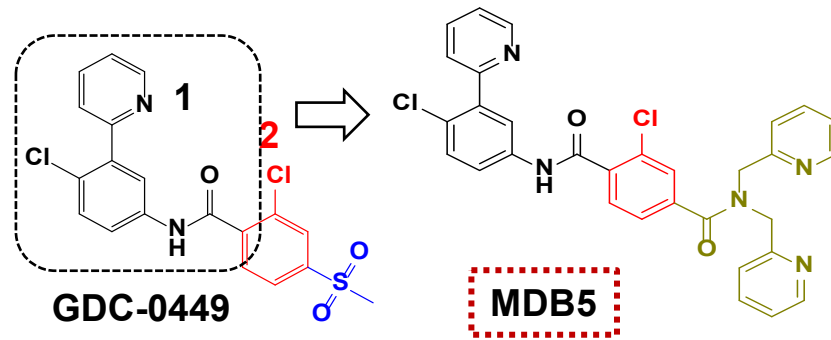
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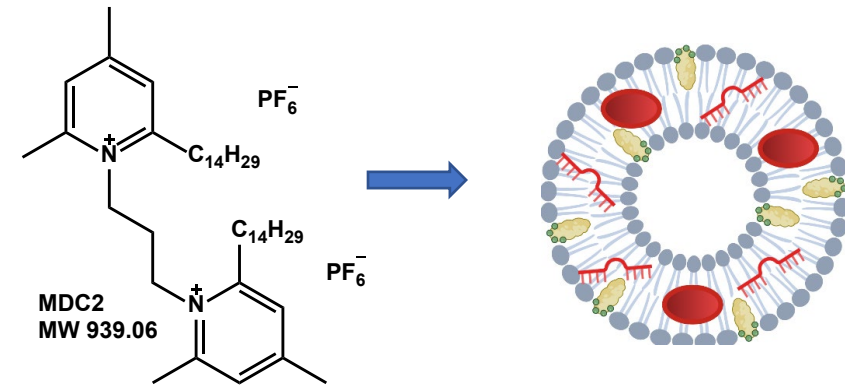
Major pathways



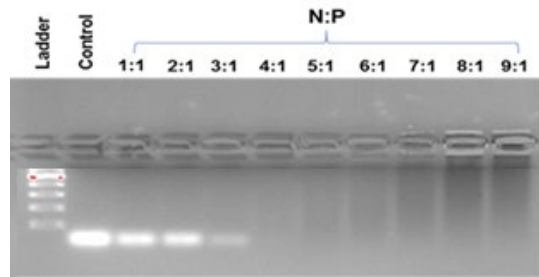
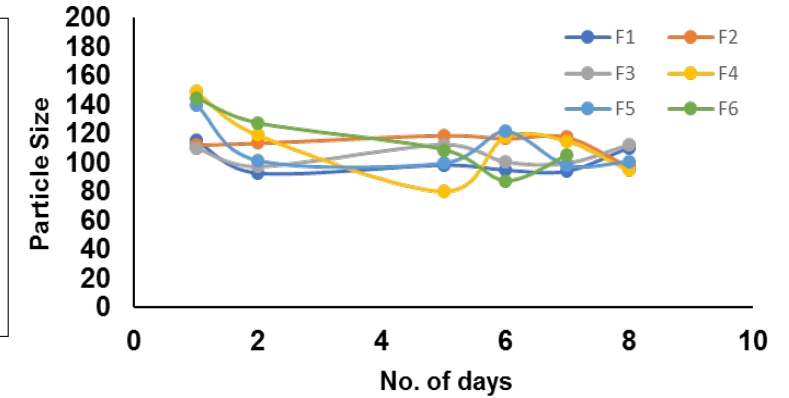
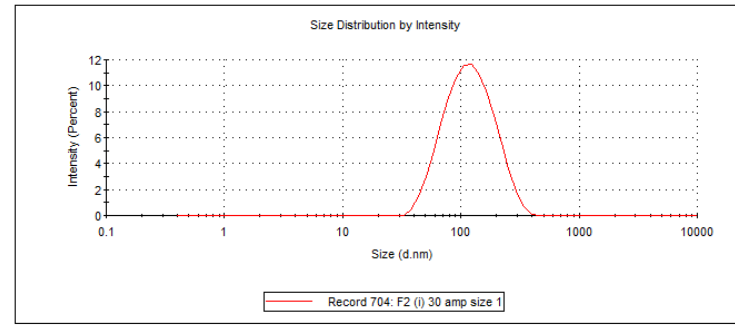
(Novel hedgehog pathway inhibitor)



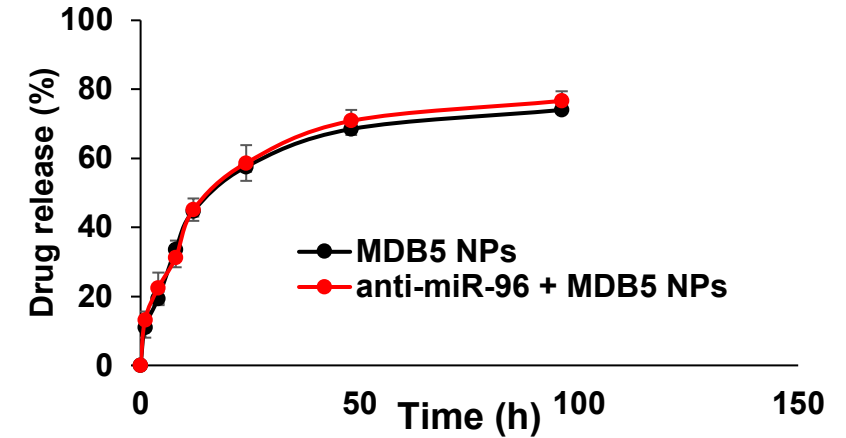
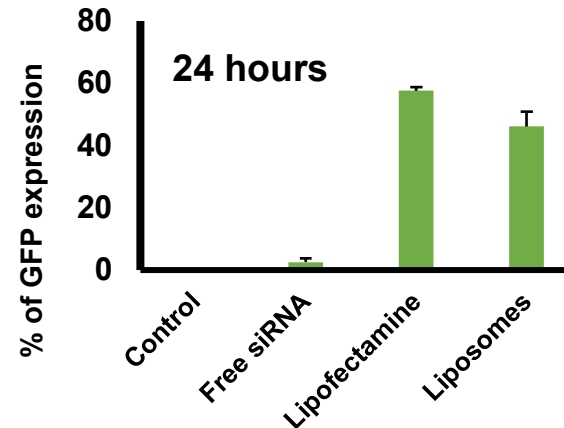
Liposomes formulation



Size (d.nm): % Intensity: St Dev (d.nm):
 Z-Average (d.nm): 101.4
 Peak 1: 129.3 100.0 60.53
 Peak 2: 0.000 0.0 0.000
 Peak 3: 0.000 0.0 0.000
 Intercept: 0.971
 Result quality: Good



F3
 Composition- MDC2: Chol: DOPC
 1 : 0.5 : 1

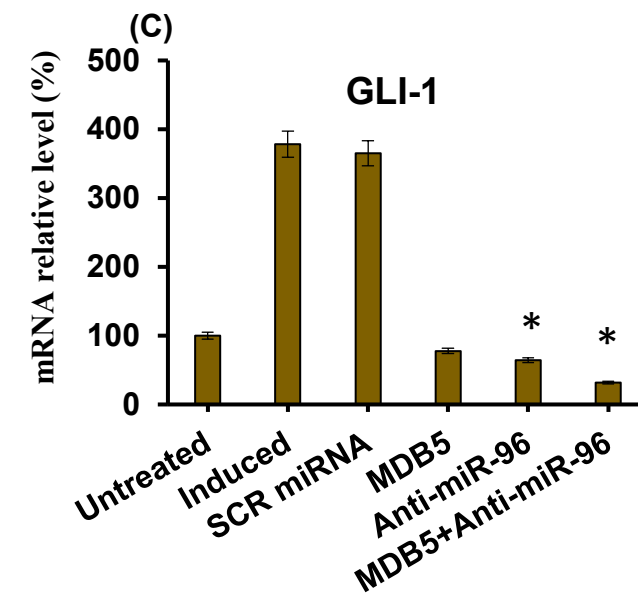
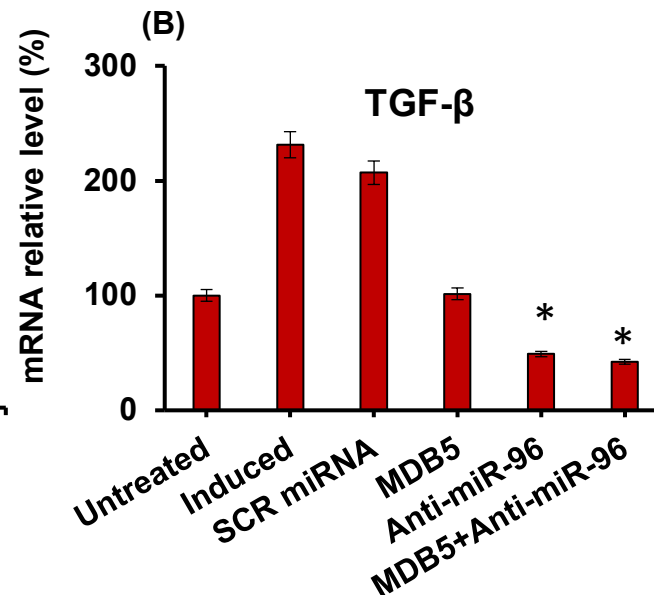
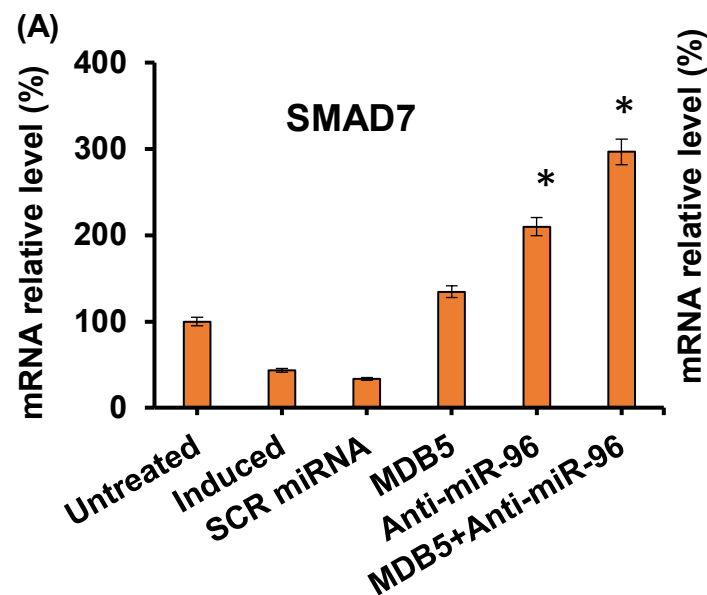


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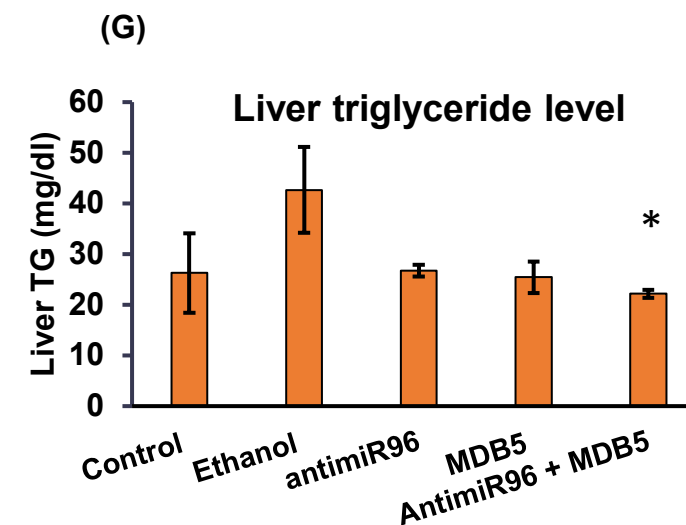
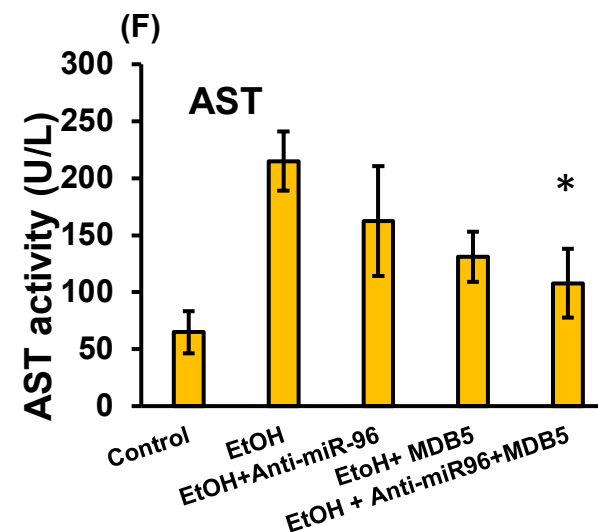
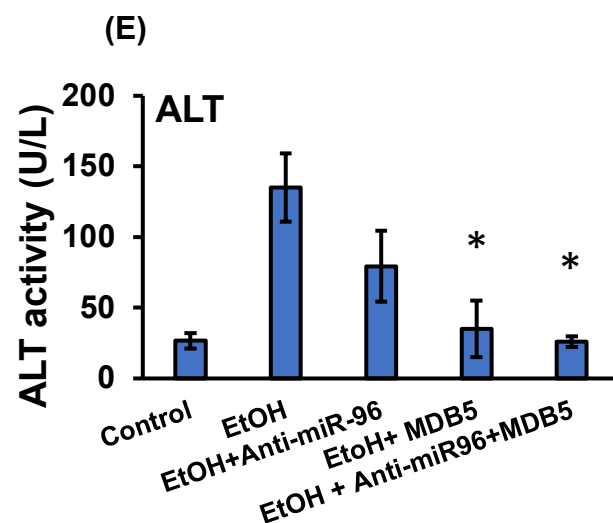
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In-vitro



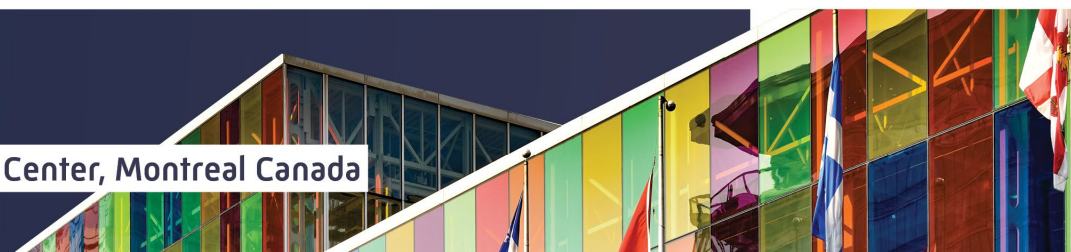
In-vivo

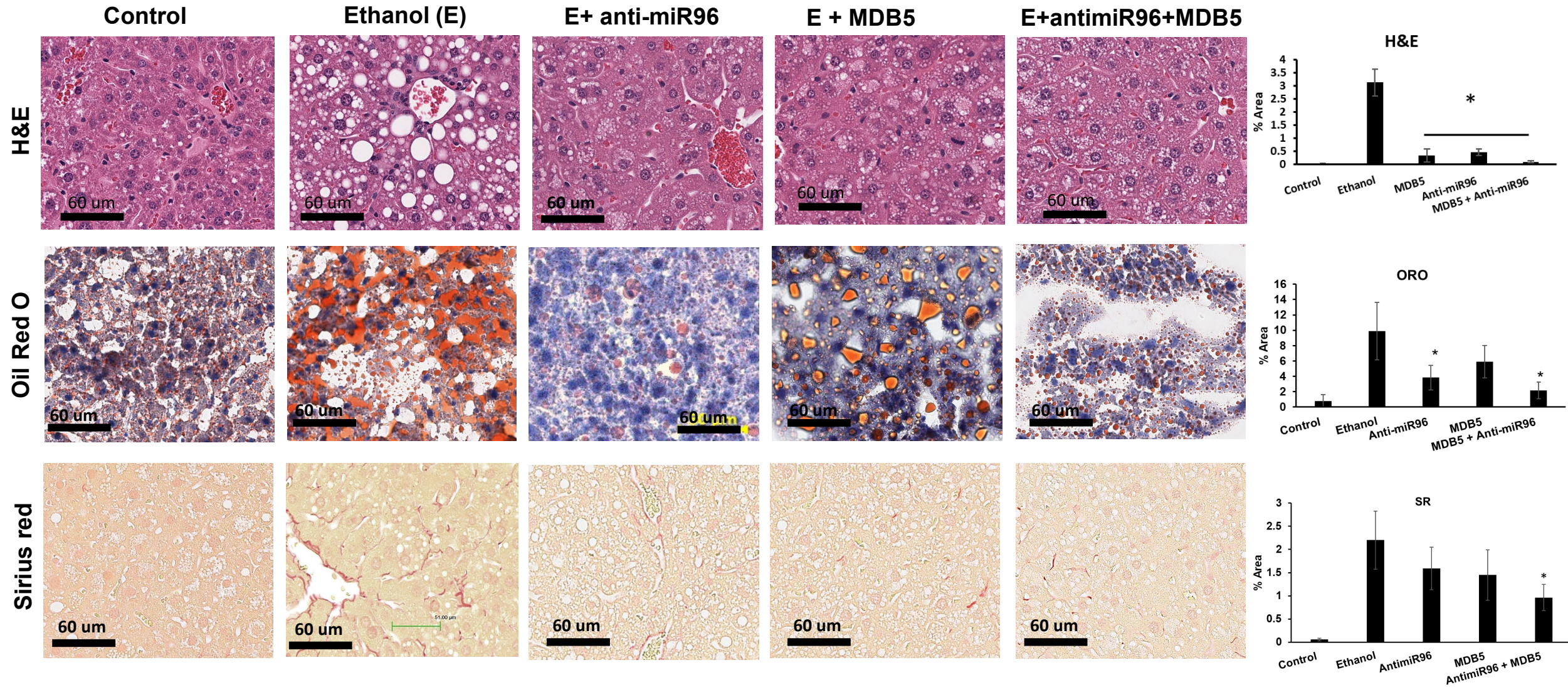


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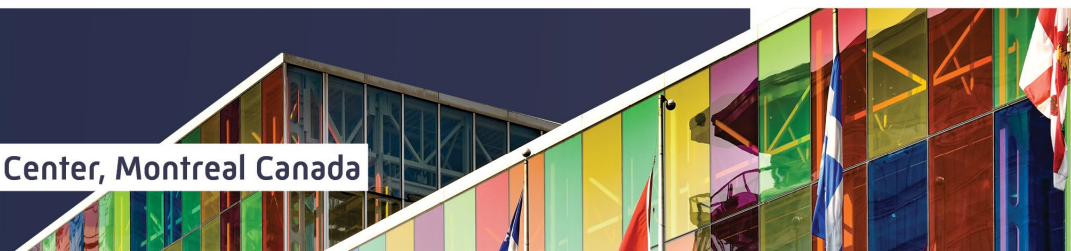




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Summary

- Hh pathway and miR-96 was found upregulated in ALD mice
- Lipid formulation containing Hh inhibitor MDB5 and anti-miR-96 were prepared
- Combination treatment with MDB5 and miR-96 loaded LNPs decrease ALD severity

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