Precision Medicine for Fatty Liver Disease

Jason K. Kim, Ph.D.

Professor of Molecular Medicine

Director, Metabolic Disease Research Center

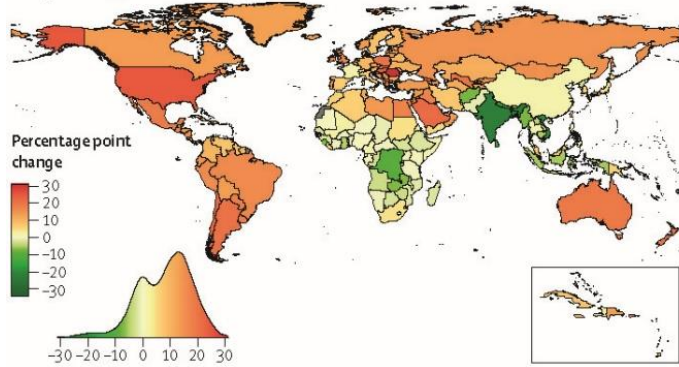**University of Massachusetts Chan Medical School**

Promoting Knowledge Exchange & Collaboration Between
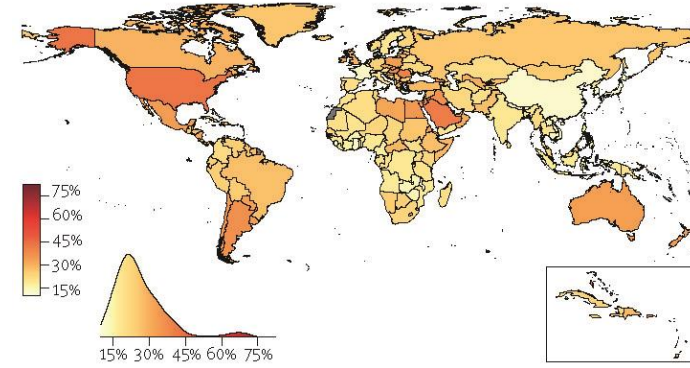
Kuwait and the United States

February 2, 2025

Reaching 1 Billion People with Obesity in the World!

Change from 1990 to 2022

Percentage point change

Obesity

Prevalence in 2022

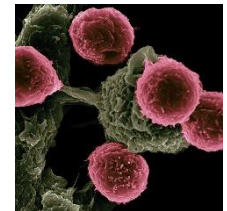NCD Risk Factor Collaboration. *Lancet* 403:1027-50 (2024)

Fatty Liver Disease

Type 2 Diabetes

Heart Disease
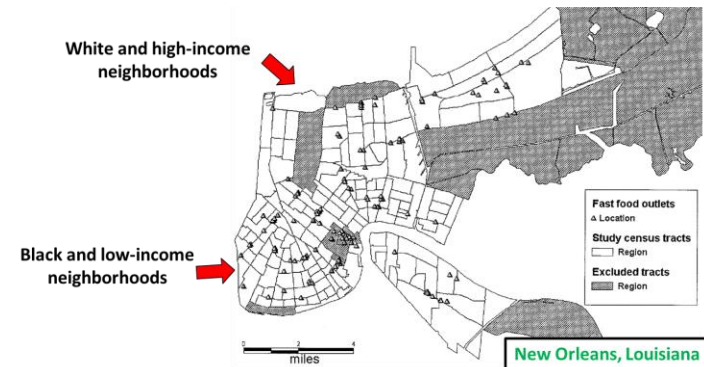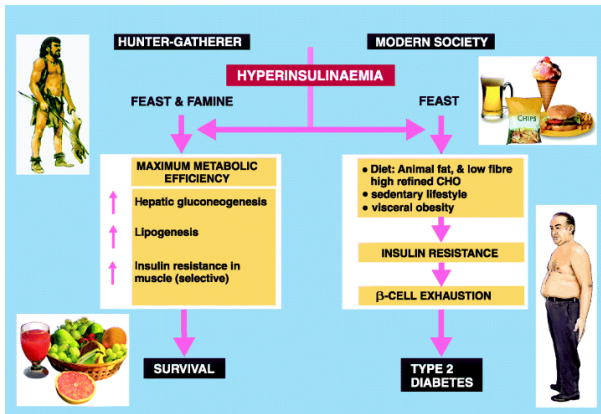
Dementia

Cancer

Obesity Is a Multi-Factorial Condition

Environmental

Obesity

Genetic

Socioeconomic

Block, J.P. et al. *Am. J. Prev. Med.* 27:211 (2004)
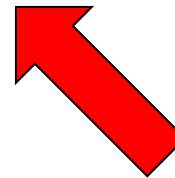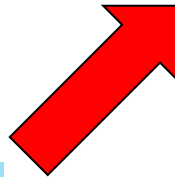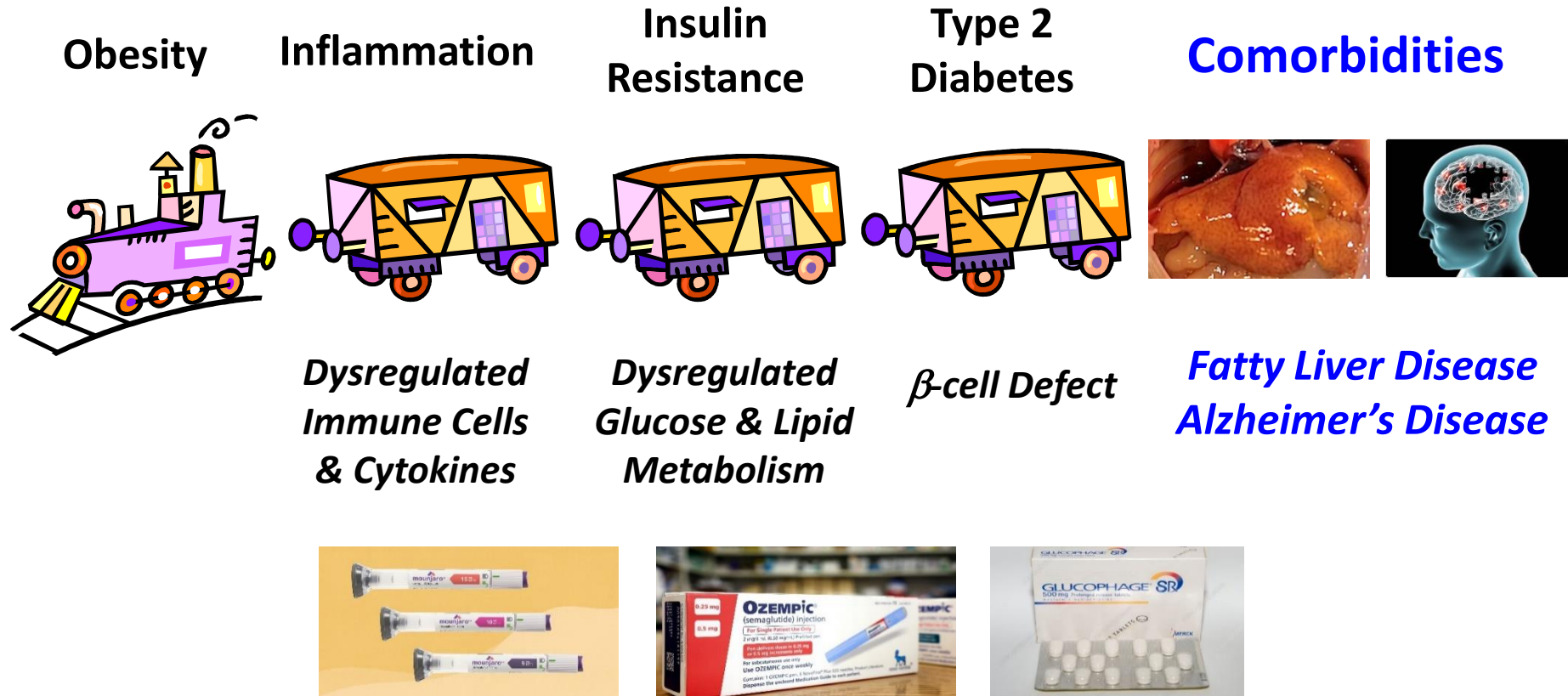
Type 2 Diabetes Is a **Chronic Inflammatory and Progressive Metabolic Disease** Led by Obesity and Insulin Resistance

Obesity | Inflammation | Insulin Resistance | Type 2 Diabetes | **Comorbidities**

Dysregulated Immune Cells & Cytokines | *Dysregulated Glucose & Lipid Metabolism* | *β-cell Defect* | *Fatty Liver Disease Alzheimer's Disease*

While there are drugs to manage type 2 diabetes, there is no effective treatment for its comorbidities.

Kim J.K. *Cell Metabolism* 4:417 (2006); *Circulation* 125:1081 (2012)

Metabolic Dysfunction-Associated Steatotic Liver Disease

Fatty Liver

Inflammation

Fibrosis

Insulin Resistance

MASH

MASH with Fibrosis
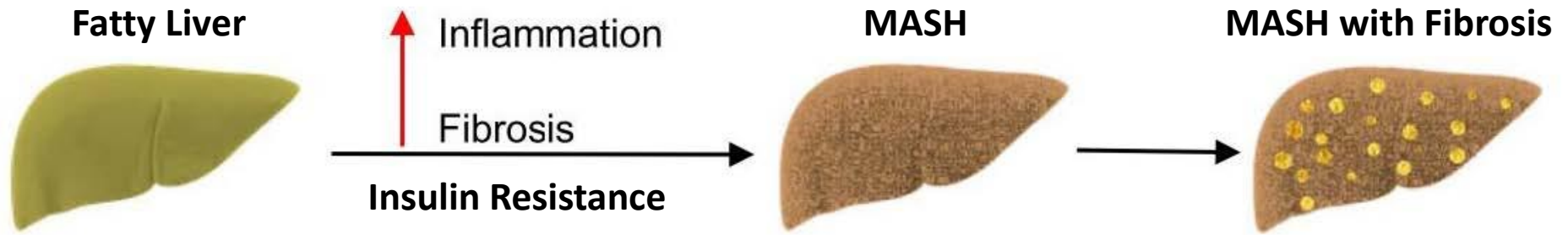
3 out of 4 obese subjects

20% of fatty liver develops MASH

Europe
68.0% (62.1 to 73.0)

United States
51.8% (31.3 to 71.6)

East Asia
52.0% (45.4 to 58.6)

South Asia
57.9% (52.9 to 62.7)

Latin America
56.8% (34.1 to 77.0)

West Asia
67.3% (60.4 to 73.6)

Africa
30.4% (11.6 to 67.1)

Younossi, Z.M. et al. *J. Hepatology* 71:793 (2019); Tomah, S. et al. *Clin. Diab. & Endo.* 6:9 (2020)
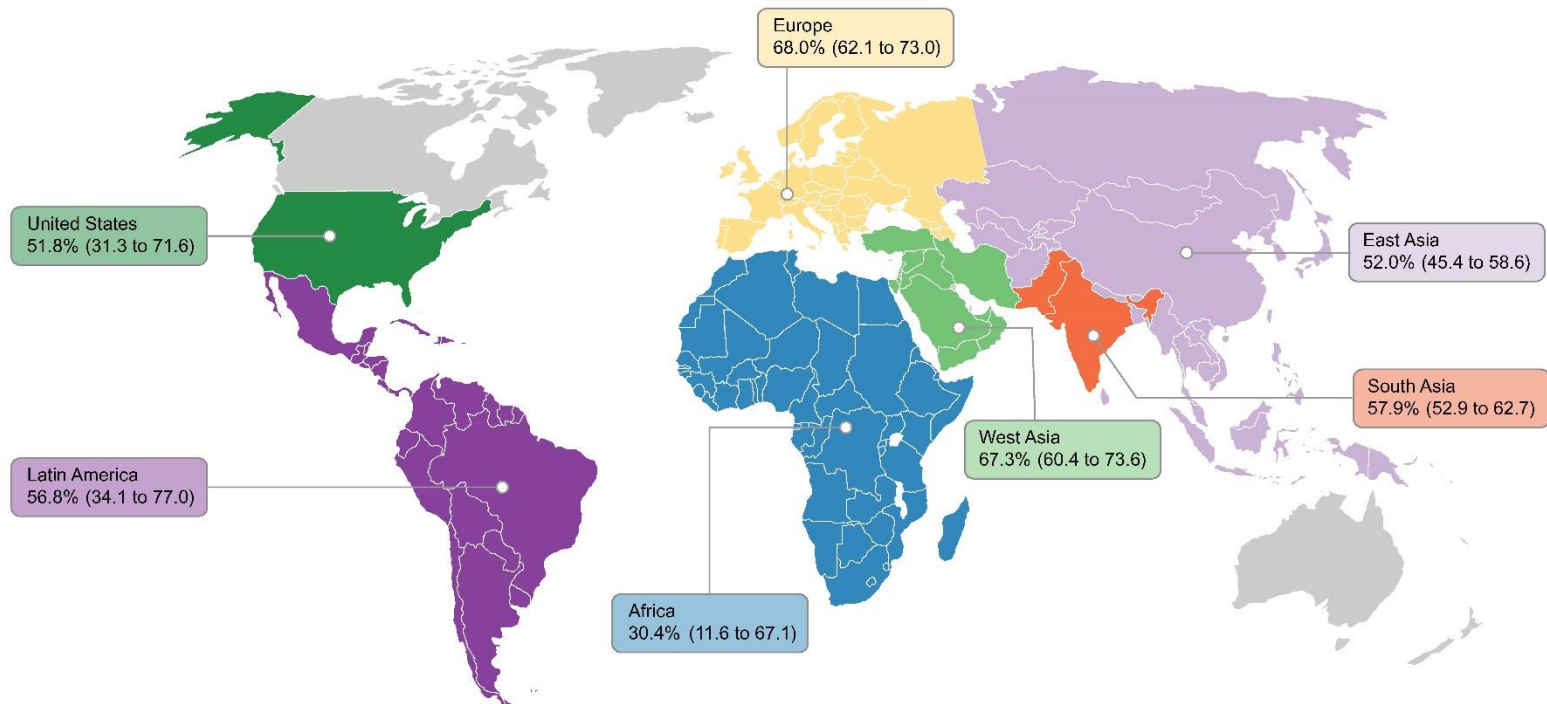
Liver Is a Heterogeneous Organ Consisting of Immunologic Cells
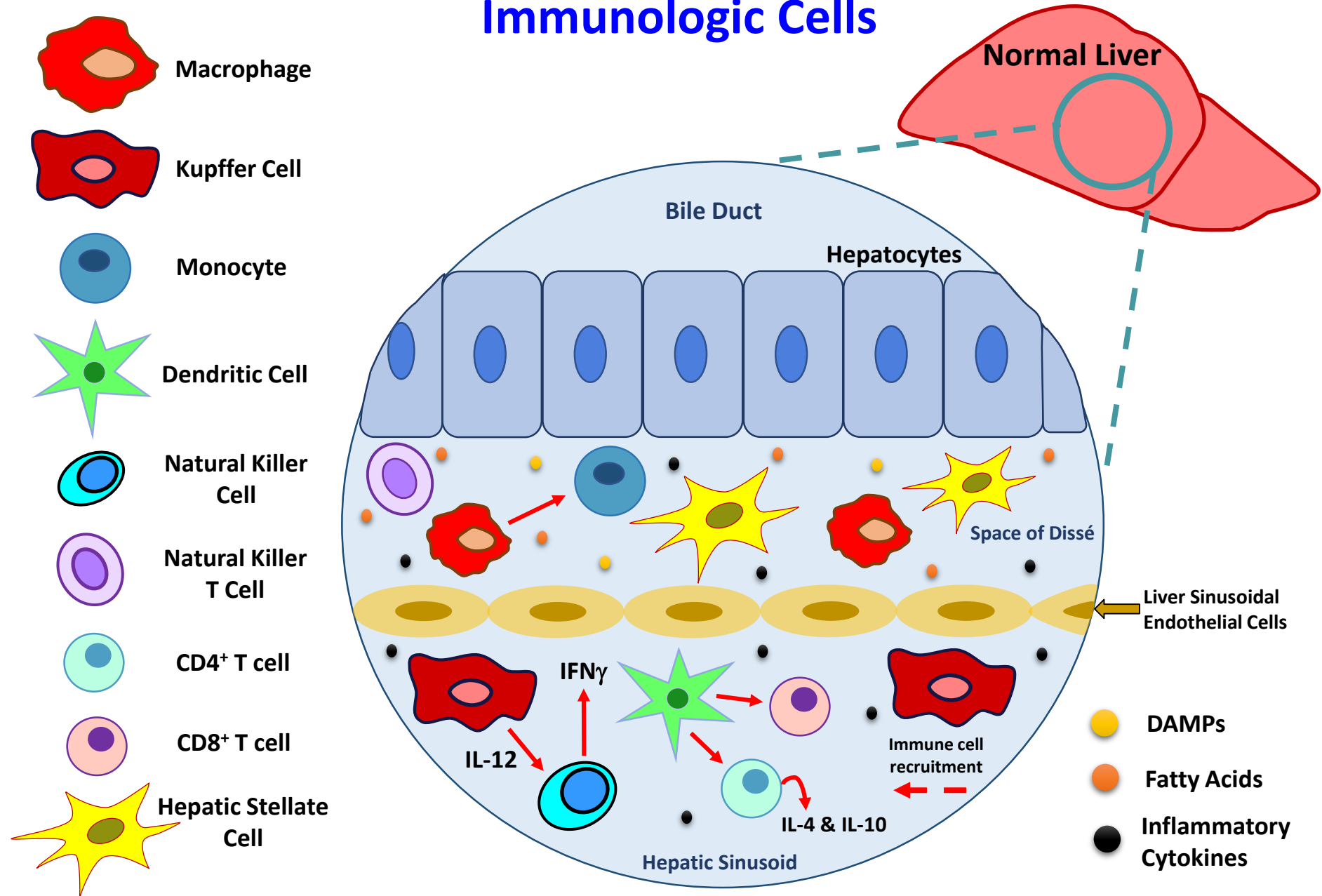
High-Fat Intake Alters Macrophage Genes
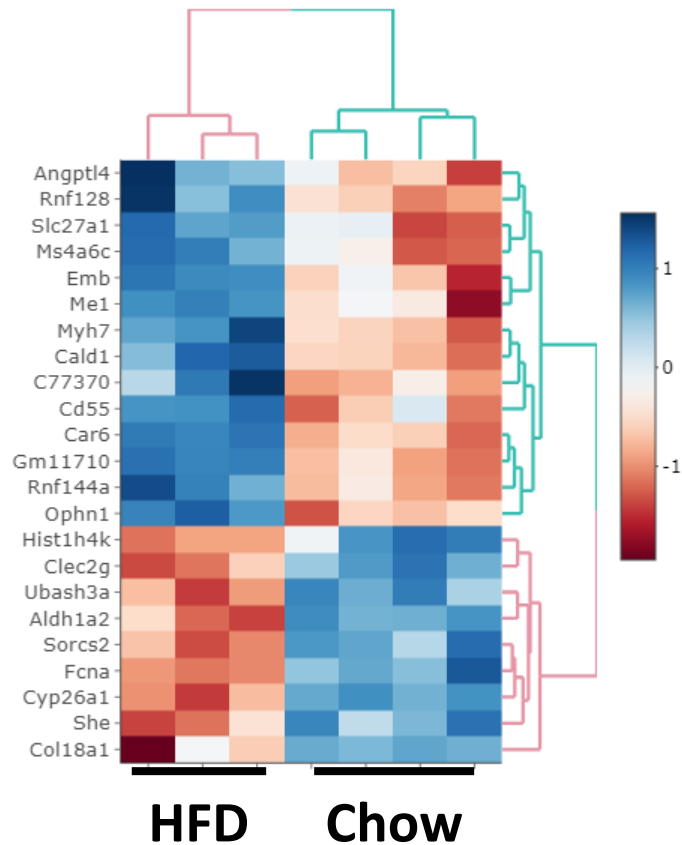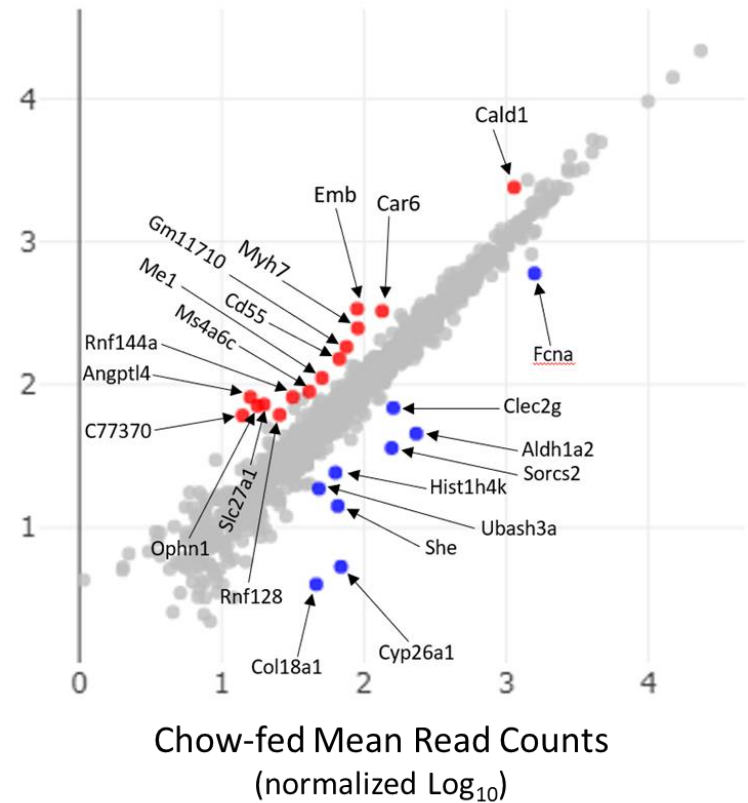
Gene	Fold Change
Angptl4	5.33
Slc27a1	3.73
Me1	2.20
Cald1	2.12

Gene	Fold Change
Clec2g	0.43
Fcna	0.38
Ubash3a	0.38
Aldh1a2	0.19

Increased M1-Macrophages and IFNγ Levels in Obesity

Lean State
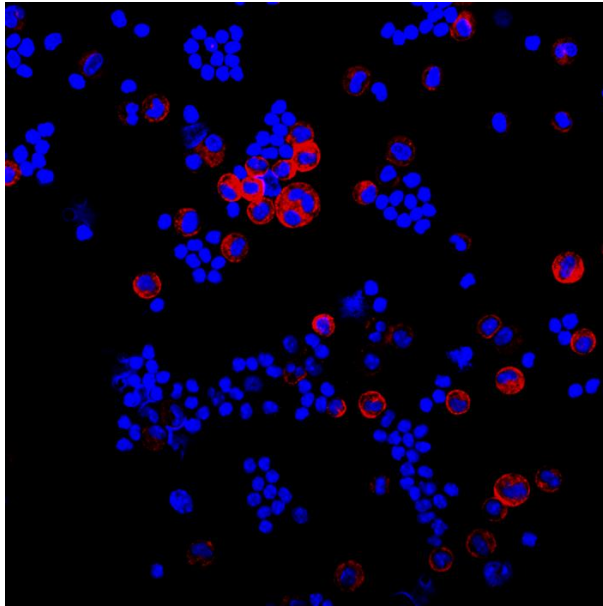
Obese State

Blue – DAPI
Red – CD11b+ Macrophages
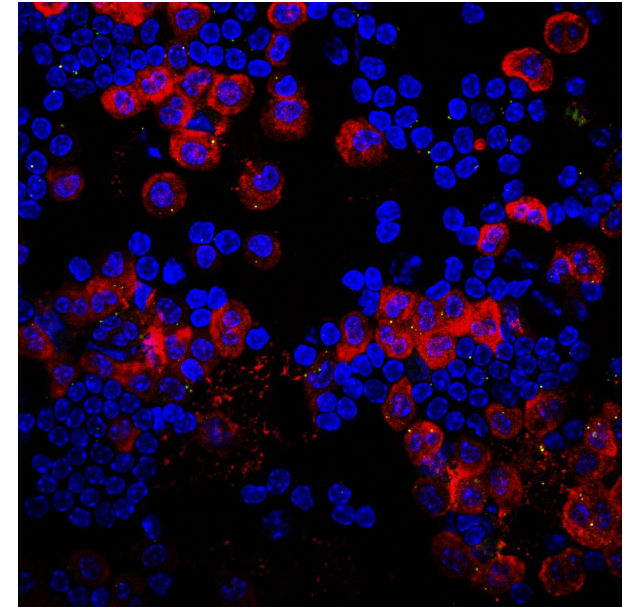
IFNγ Levels

*p<0.05 vs. Chow

Pleiotropic Effects of IFNγ on Immune and Non-Immune Cells

Immune Cells
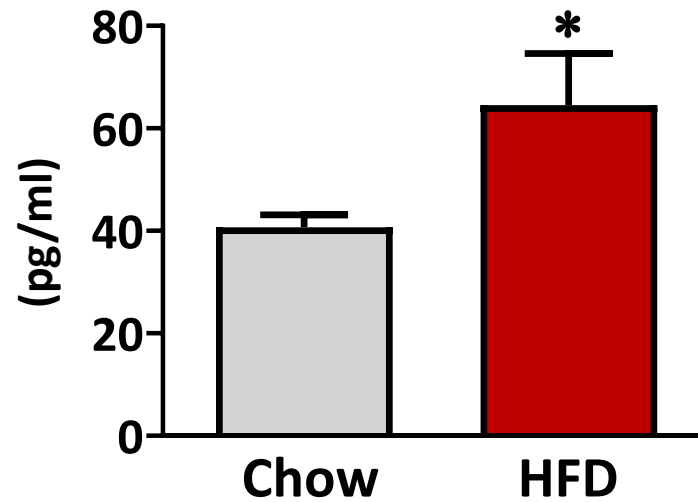
IFNγ

ILCs
↑ ILC1 function
↓ ILC2 function

Macrophages
↑ Pro-inflammatory function

T cells
↑ T_H1 cell function
↑ T_{FH} cell response
↓ T_H2 cell response
↓ T_H17 cell response
Dual effects on T_{reg} cells

B cells
↑ ABC production
↑ Class-switching
↑ Autoantibody production

Tissue Cells

IFNγ

Endothelial cell
↓ Angiogenesis

Stromal cell
• Tissue remodelling
• Metabolic regulation

Adipocyte
↑ Insulin resistance

Neural cell
Survival regulation
↑ Connectivity
↑ Tonic inhibition

Ivashkiv, L.B. *Nat. Rev. Immunol.* 18:545-558 (2018)

Mice with Conditional Loss of IFNγ Signaling in Macrophages

Randall Friedline, Ph.D.
Assistant Professor

IFNγ-IL12 axis regulates intercellular crosstalk in metabolic dysfunction-associated steatotic liver disease
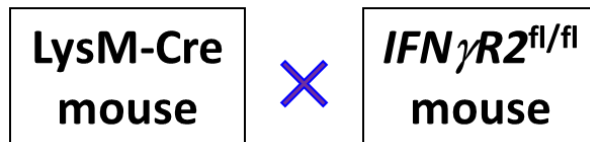
Randall H. Friedline [1], Hye Lim Noh[1], Sujin Suk[1,2], Mahaa Albusharif[1], Sezin Dagdeviren [1], Suchaorn Saengnipanthkul [1,3], Bukyung Kim[1,4], Allison M. Kim[1], Lauren H. Kim[1], Lauren A. Tauer [1], Natalie M. Baez Torres[1], Stephanie Choi[1], Bo-Yeon Kim[1,5], Suryateja D. Rao[1], Kaushal Kasina[1], Cheng Sun[6], Benjamin J. Toles[6], Chan Zhou [7], Zixiu Li[7], Vivian M. Benoit[1], Payal R. Patel[1], Doris X. T. Zheng[1], Kunikazu Inashima[1], Annika Beaverson[1], Xiaodi Hu[1], Duy A. Tran[1], Werner Muller [8], Dale L. Greiner[1,9], Alan C. Mullen [6], Ki Won Lee[2,10] & Jason K. Kim [1,2,9,11] ✉

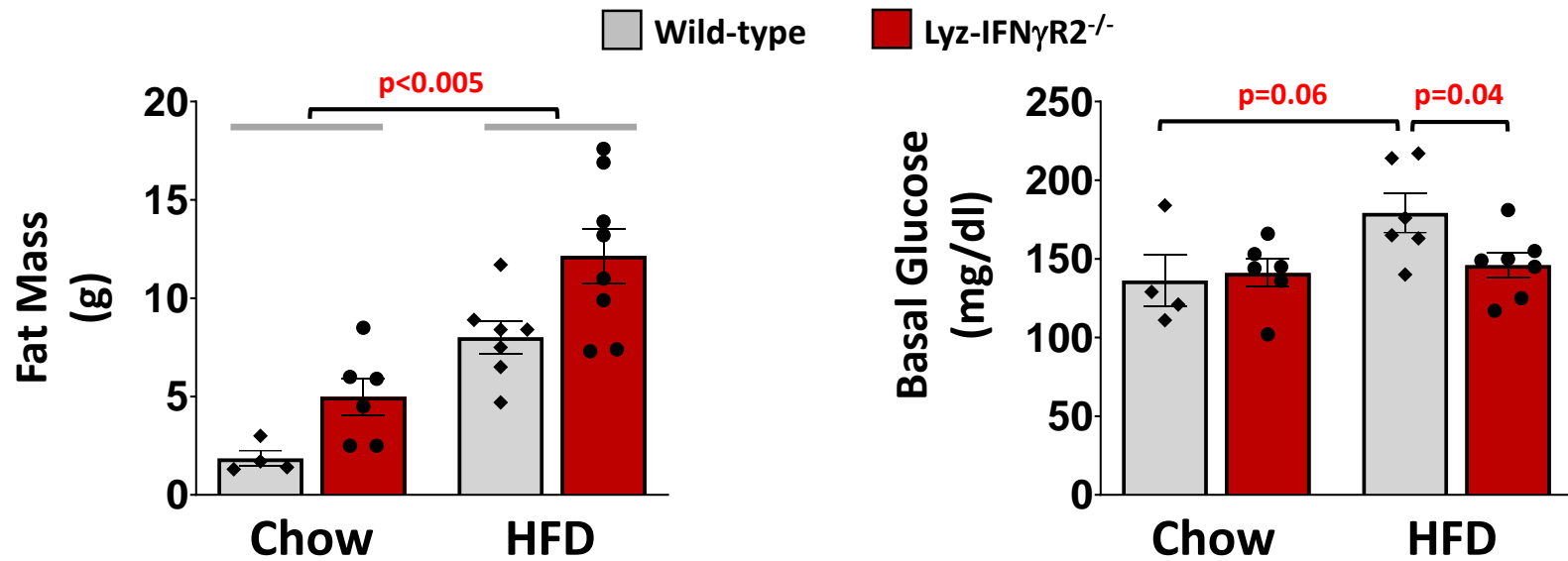C57BL/6J background

Myeloid-Cell Specific IFNγR2^{-/-} mice

LysM-Cre mouse ✕ IFNγR2^{fl/fl} mouse →

Wild-Type   Lyz-IFNγR2^{-/-}
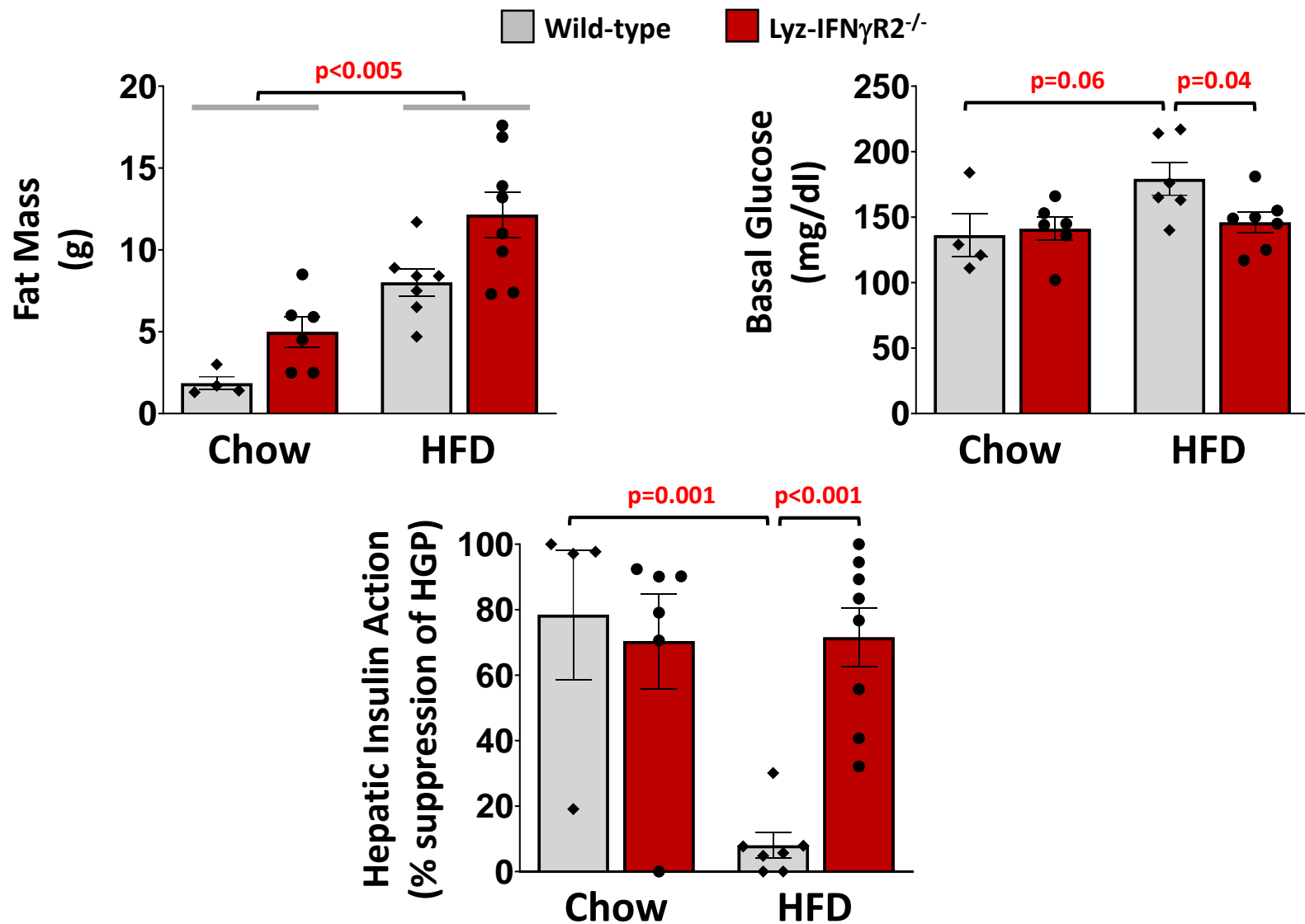
Friedline, R.H. et al. *Nature Communications*, 15, 5506 (2024)

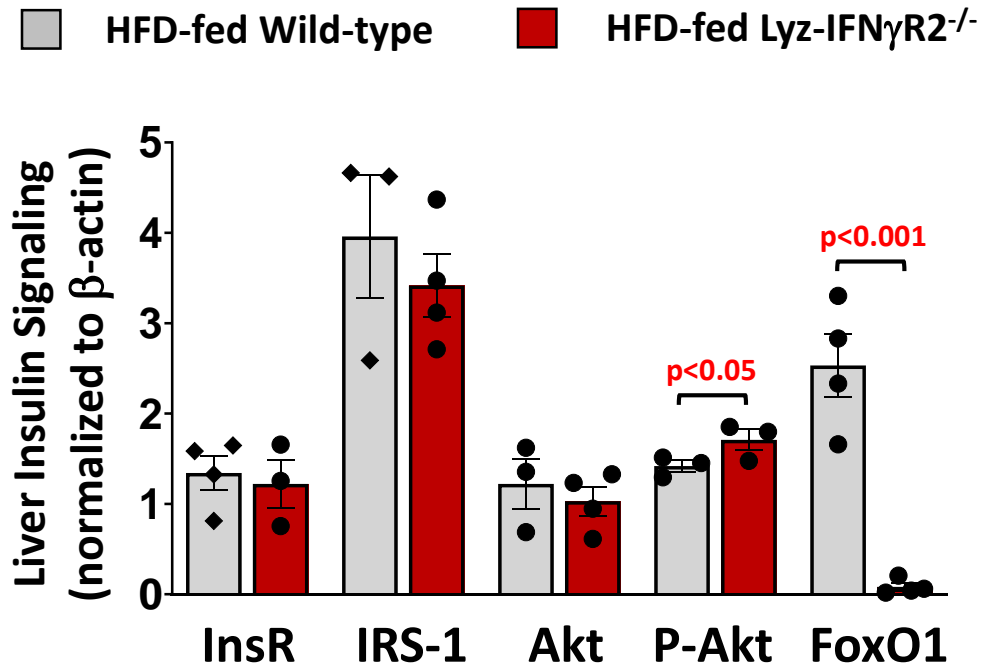# Lyz-IFNγR2$^{-/-}$ Mice Are Obese After 10 Weeks of High-Fat Diet But Do Not Develop Type 2 Diabetes Phenotypes

Lyz-IFNγR2⁻ᐟ⁻ Mice Are Protected from Diet-Induced Insulin Resistance in the Liver

Friedline, R.H. et al. *Nature Communications*, 15, 5506 (2024)

Liver Insulin Signaling Associated with Akt and FoxO1 Is Improved in HFD-fed Lyz-IFNγR2$^{-/-}$ Mice

Improved Insulin Signaling in the Liver Despite Diet-Induced Fatty Liver in Lyz-IFNγR2$^{-/-}$ Mice
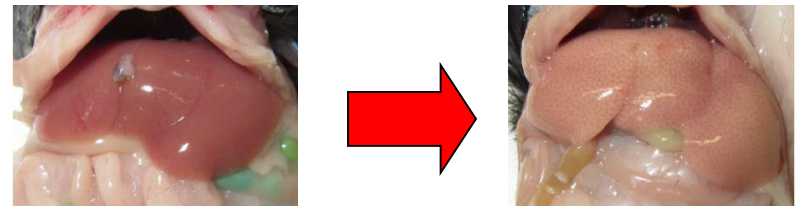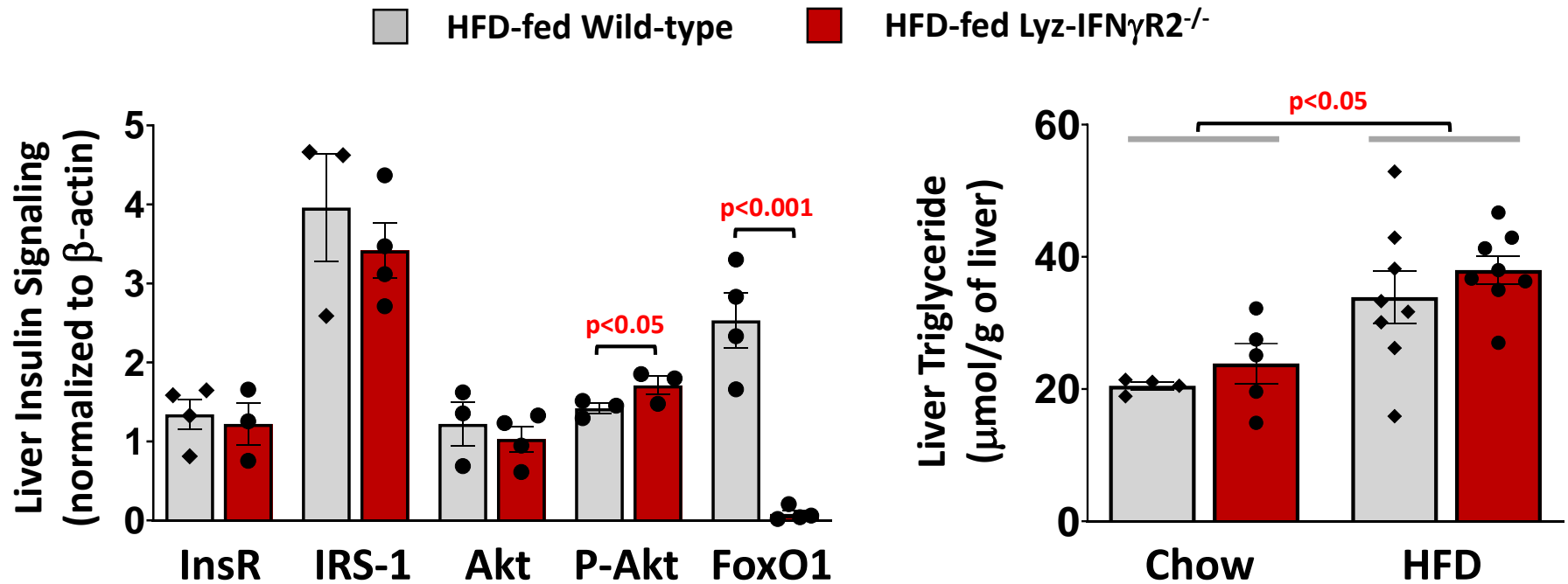
Obesity-mediated Inflammation in the Liver Is Attenuated in HFD-fed Lyz-IFNγR2$^{-/-}$ Mice
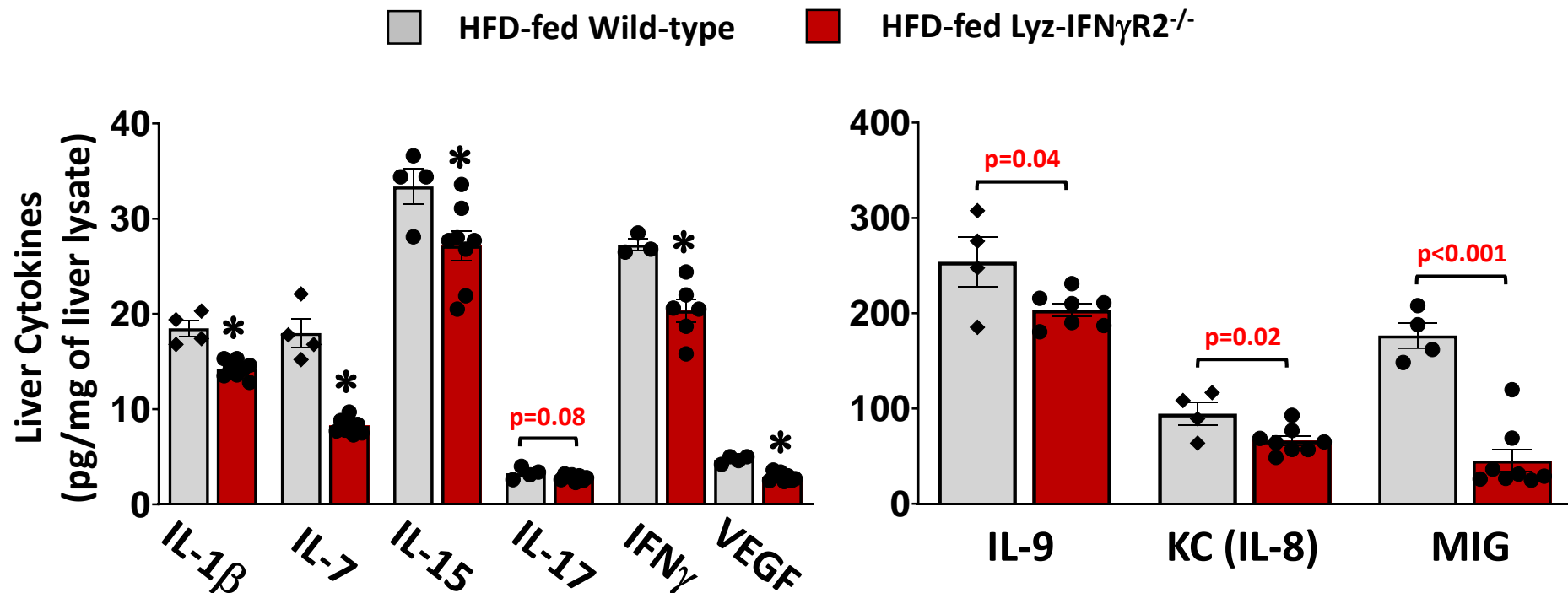
These results suggest that inflammation, not fatty liver, affects insulin resistance in the liver!

*$p < 0.05$ vs. HFD-WT

Intrahepatic IL-12 Levels Are Dramatically Decreased in Lyz-IFNγR2$^{-/-}$ Mice Following a High-Fat Diet
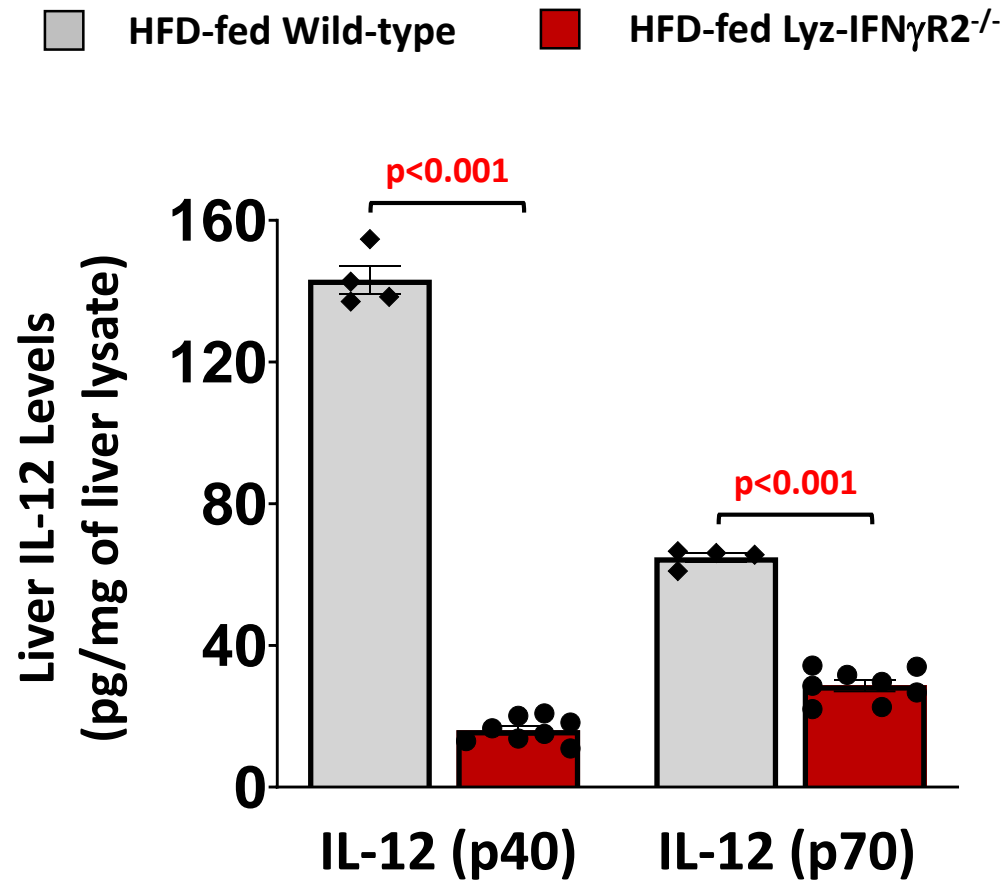
Pro-Inflammatory Cytokine IL-12 Plays a Major Role in Bridging Innate and Acquired Immunity
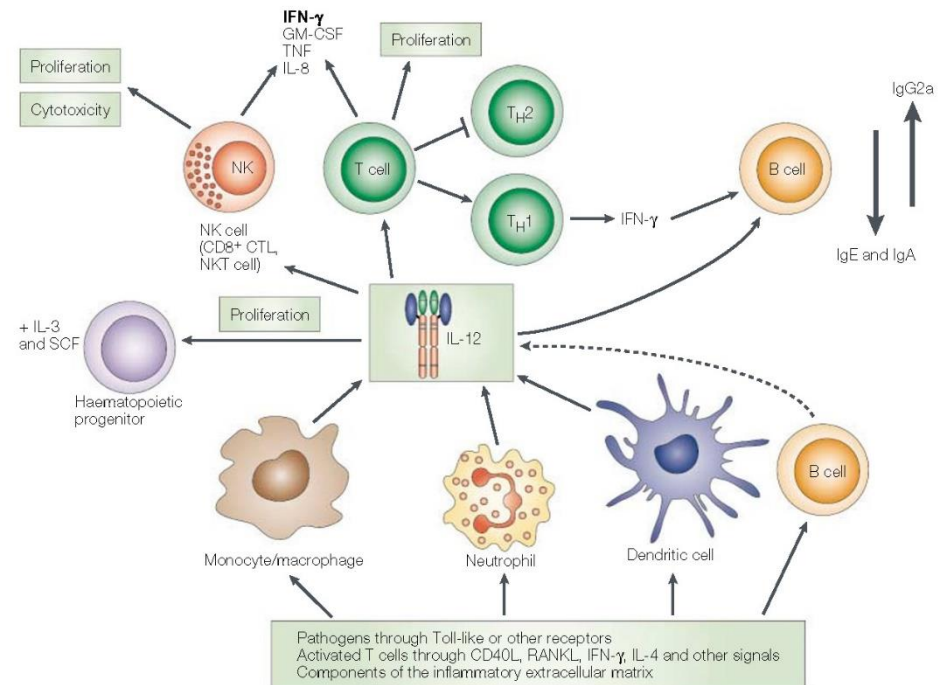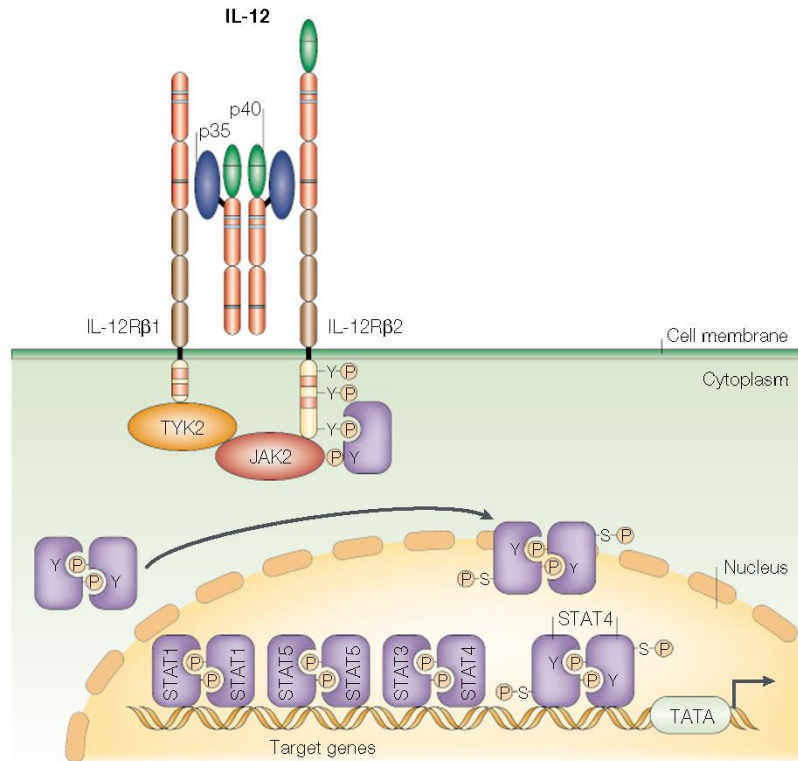
IL-12 is primarily secreted by macrophages and stimulates the proliferation of Th1 cells and NK cells.

Serum IL-12 Levels Are Elevated in Obese Adults and Children and Strongly Associated with Severity of Fatty Liver Disease

Suarez-Alvarez, K. *Mediators Inflamm.* 967067 (2013)
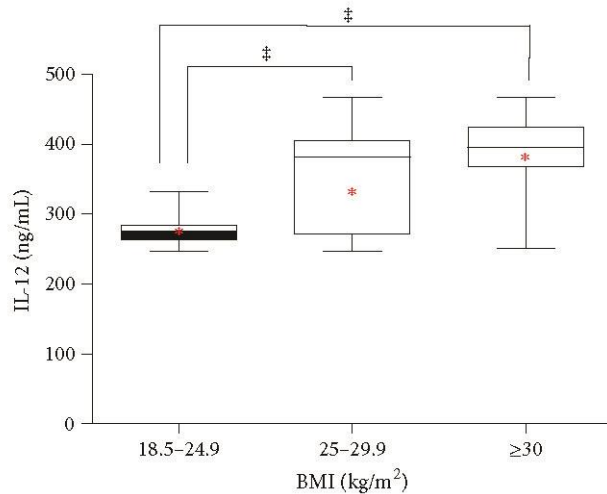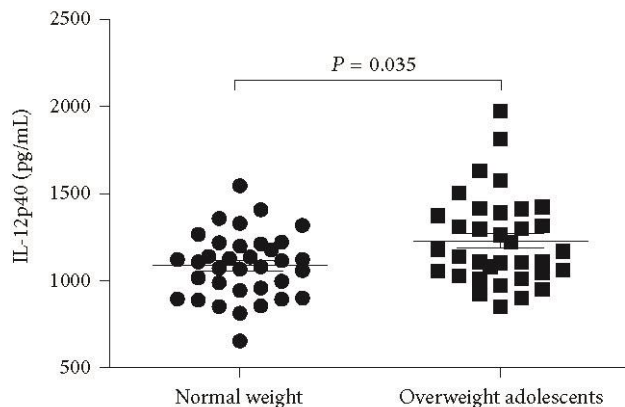

Lichtenauer, M. et al. *Biomed. Res. Int.* 940910 (2015)

Demographic, clinical, and laboratory characteristics of subjects with NAFLD

Characteristics	Degree of NAFLD			p
	Mild (n = 42)	Moderate (n = 33)	Marked (n = 25)	
Age, year	52.96±8.54	55.35±9.1	58.23±8.64	0.216
Gender, n (%)				
Male	30 (47.62%)	21 (33.33%)	12 (19.05%)	0.117
Female	13 (35.14%)	13 (35.14%)	11 (29.73%)	
Comorbidities, n (%)				
Type 2 diabetes				
Yes	22 (42.31%)	21 (40.38%)	9 (17.31%)	0.481
No	20 (41.67%)	14 (29.17%)	14 (29.17%)	
Dyslipidemia				
Yes	10 (30.3%)	12 (36.36%)	11 (33.33%)	0.532
No	31 (46.27%)	21 (31.34%)	15 (22.39%)	
Hypertension				
Yes	5 (38.46%)	5 (38.46%)	3 (23.08%)	0.958
No	37 (42.53%)	28 (32.18%)	22 (25.29%)	
Body mass index, kg/m^2	21.25 ± 2.4	23.56 ± 2.02	25.17 ± 3.43	<0.001
AST, U/L	24.68 ± 5.65	22.8 ± 4.2	22.73 ± 4.93	0.357
ALT, U/L	32.28 ± 6.54	49.15 ± 4.96	72.93 ± 5.47	<0.001
Platelet, x 10^3/mm^3	260.45 ± 43.27	274.2 ± 50.36	279.6 ± 44.78	0.256
Albumin, mg/dL	4.1 ± 0.6	4.2 ± 0.3	4 ± 0.2	0.600
IL-12, pg/mL	41.52± 12.45	49.6 ± 17.5	68.4 ± 21.74	<0.001

Darmadi, D. et al. *Rom. J. Intern. Med.* 59:66-72 (2021)

Acute IL-12 Infusion Causes Insulin Resistance in the Liver
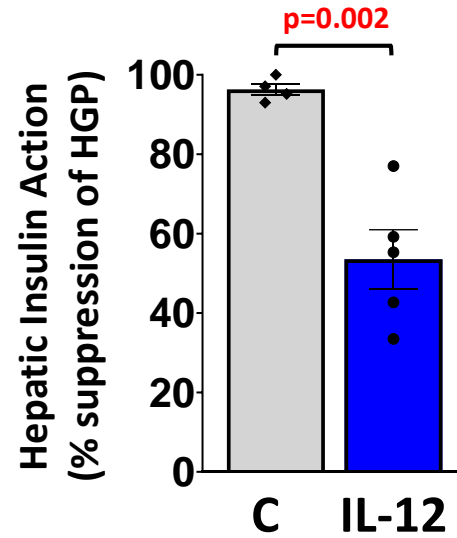
IL-12 Activates STAT4 and p38-MAPK and Downregulates Insulin Signaling in the Liver
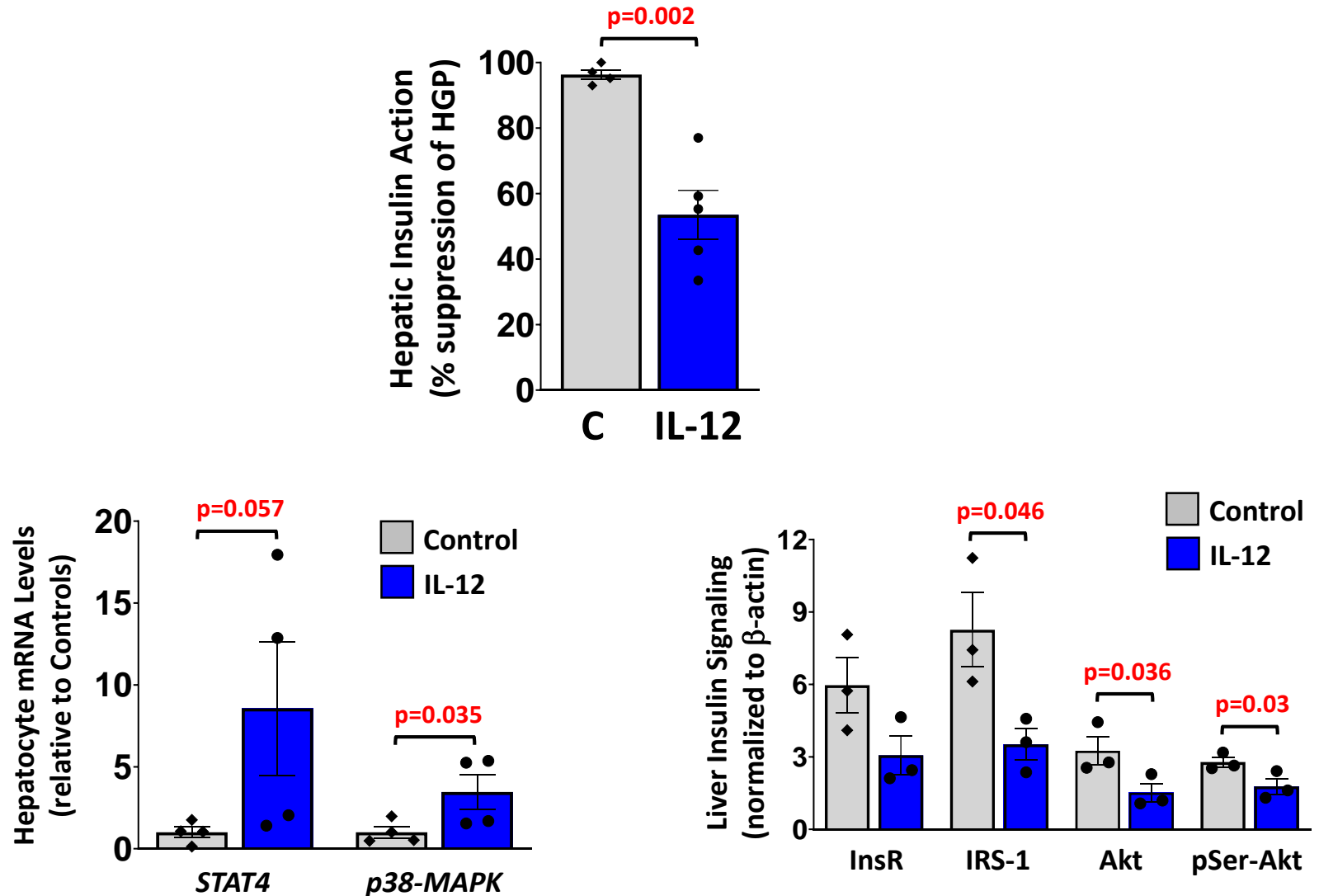
IL-12 Is a Novel Cytokine Modulating Insulin Resistance in the Liver
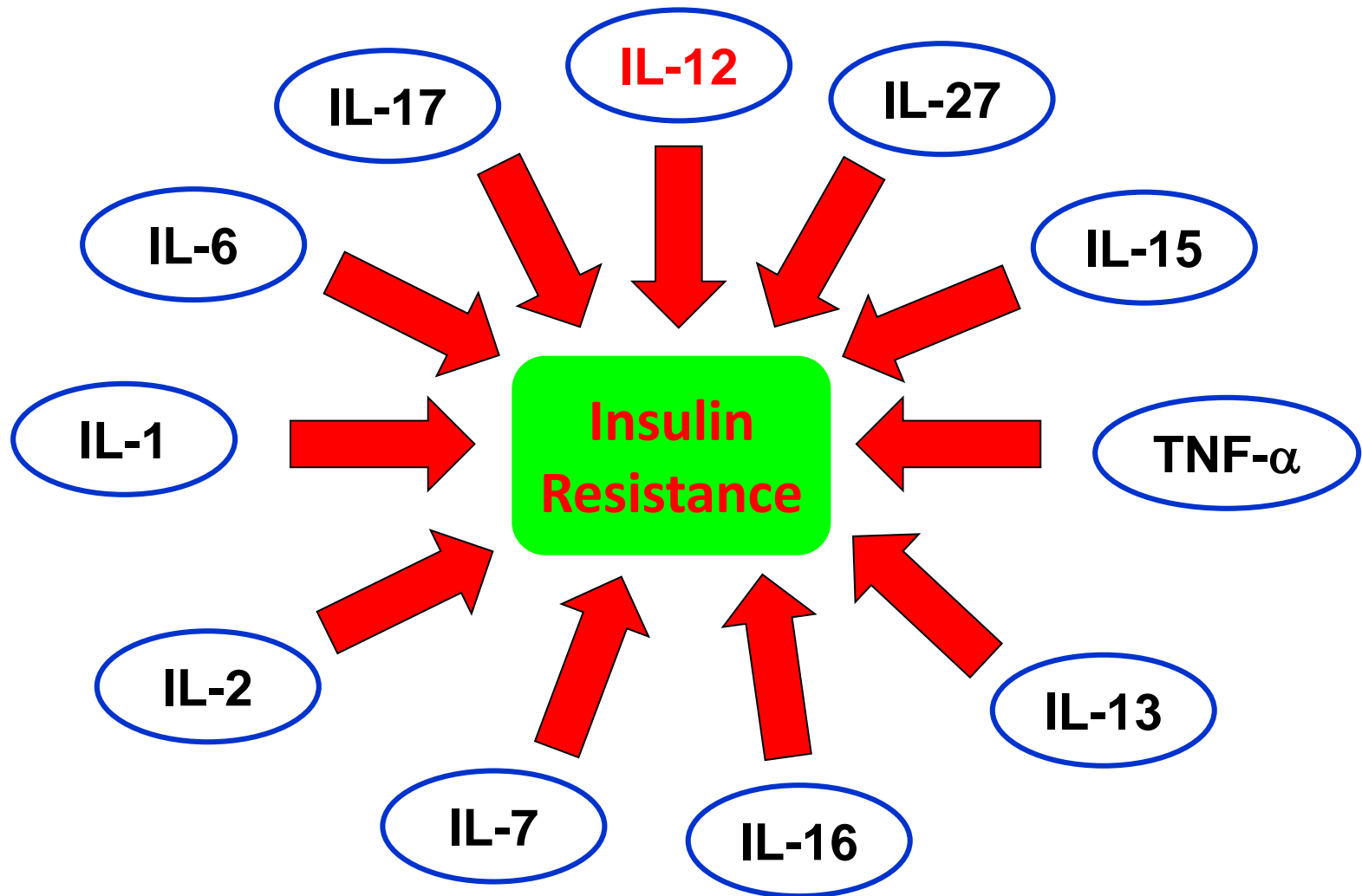
Since Inflammation Develops During Fatty Liver Progression to MASH, Are There Any Implications for Liver Fibrosis?

Fatty Liver → Inflammation / Fibrosis / **Insulin Resistance** → **MASH** → **MASH with Fibrosis**
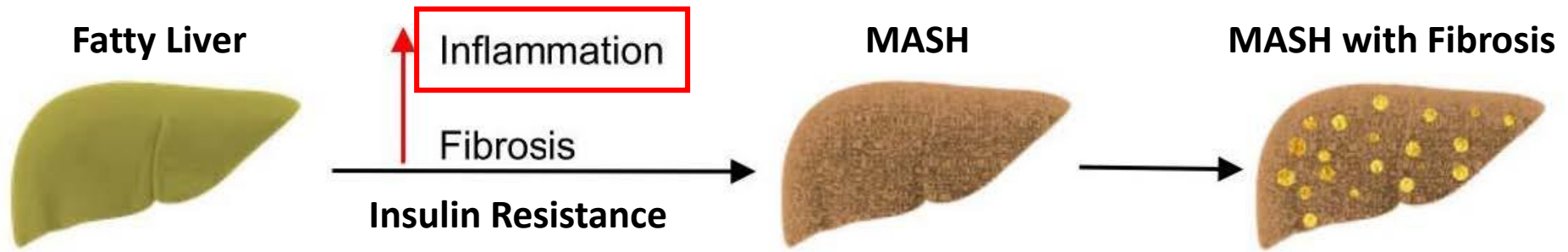
Noninvasive Assessment of Liver Steatosis and Fibrosis Using 3D-Ultrasound in Mice

Wild-type   Lyz-IFNγR2$^{-/-}$

Methionine-Choline Deficient (MCD) Diet, CDAHFD, and Gubra Amylin NASH (GAN) Diet
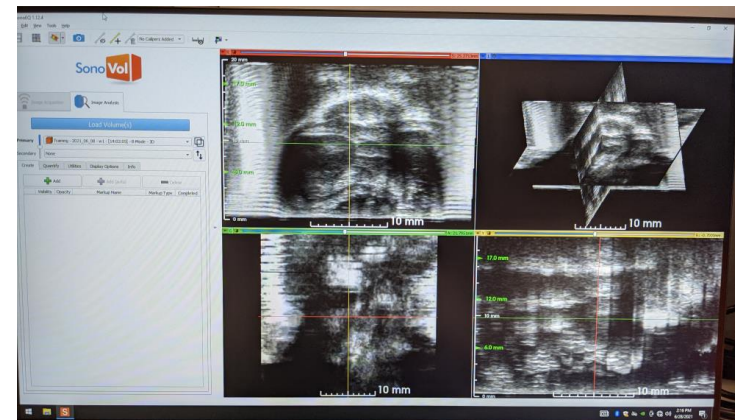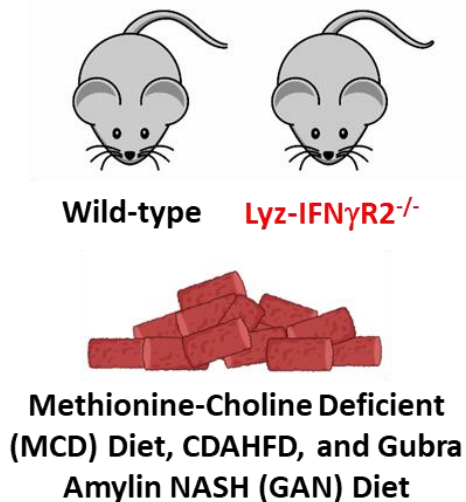
Mice with Conditional Loss of IFNγ Signaling in Macrophages Are Protected from Liver Fibrosis After 4 Weeks of MCD Diet

Wild-type

Lyz-IFNγR2^{-/-}

Shear Wave Elasticity
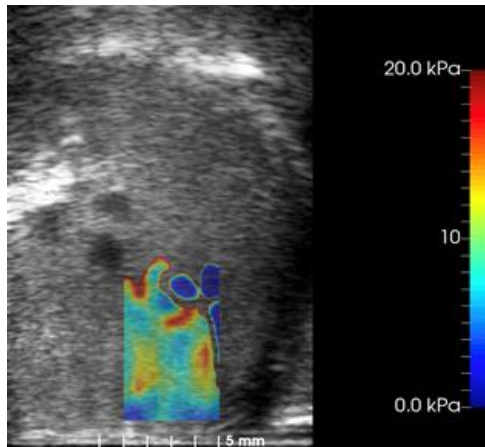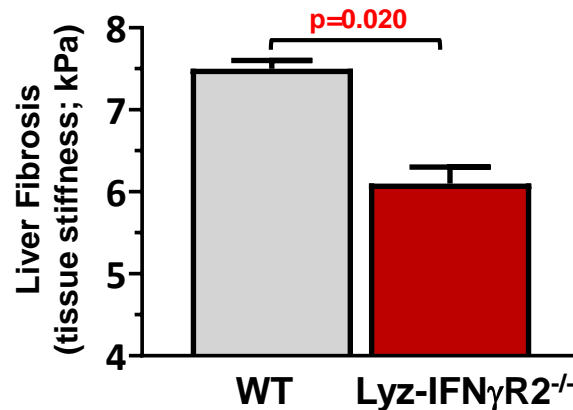
Liver Fibrosis

Shear Wave Elasticity
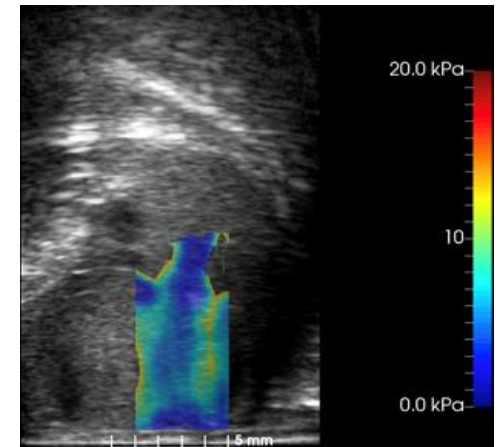
Liver Fibrosis But Not Steatosis Is Attenuated in Lyz-IFNγR2$^{-/-}$ Mice After Choline-Deficient L-Amino Acid HFD (CDAHFD) or GAN Diet

CDAHFD-fed Wild-type   CDAHFD-fed Lyz-IFNγR2$^{-/-}$
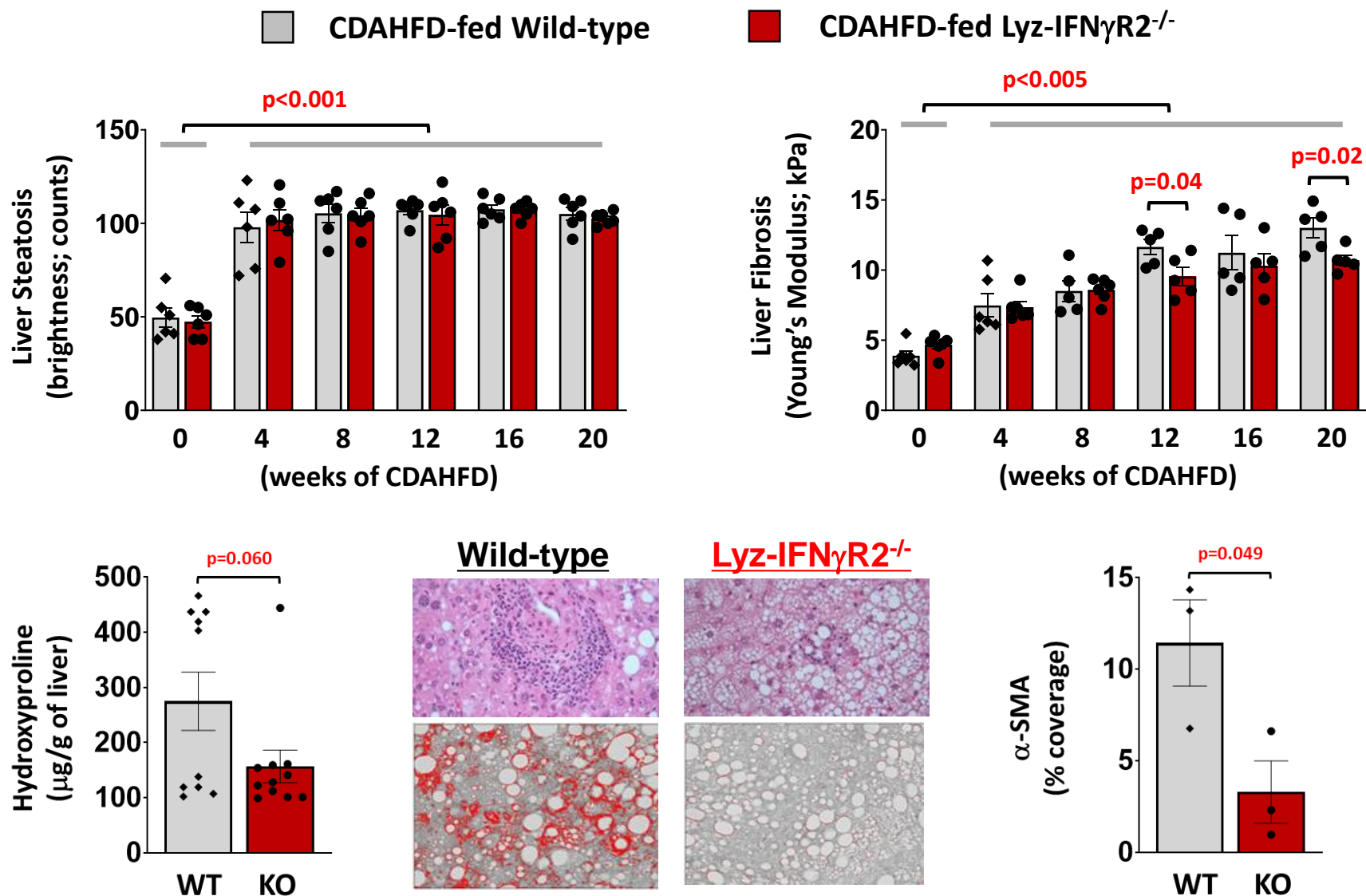
Increased Expression of IFNγR1/R2, IL-12, and FGF21 in Human MASH Livers with Advancing Fibrosis Stages
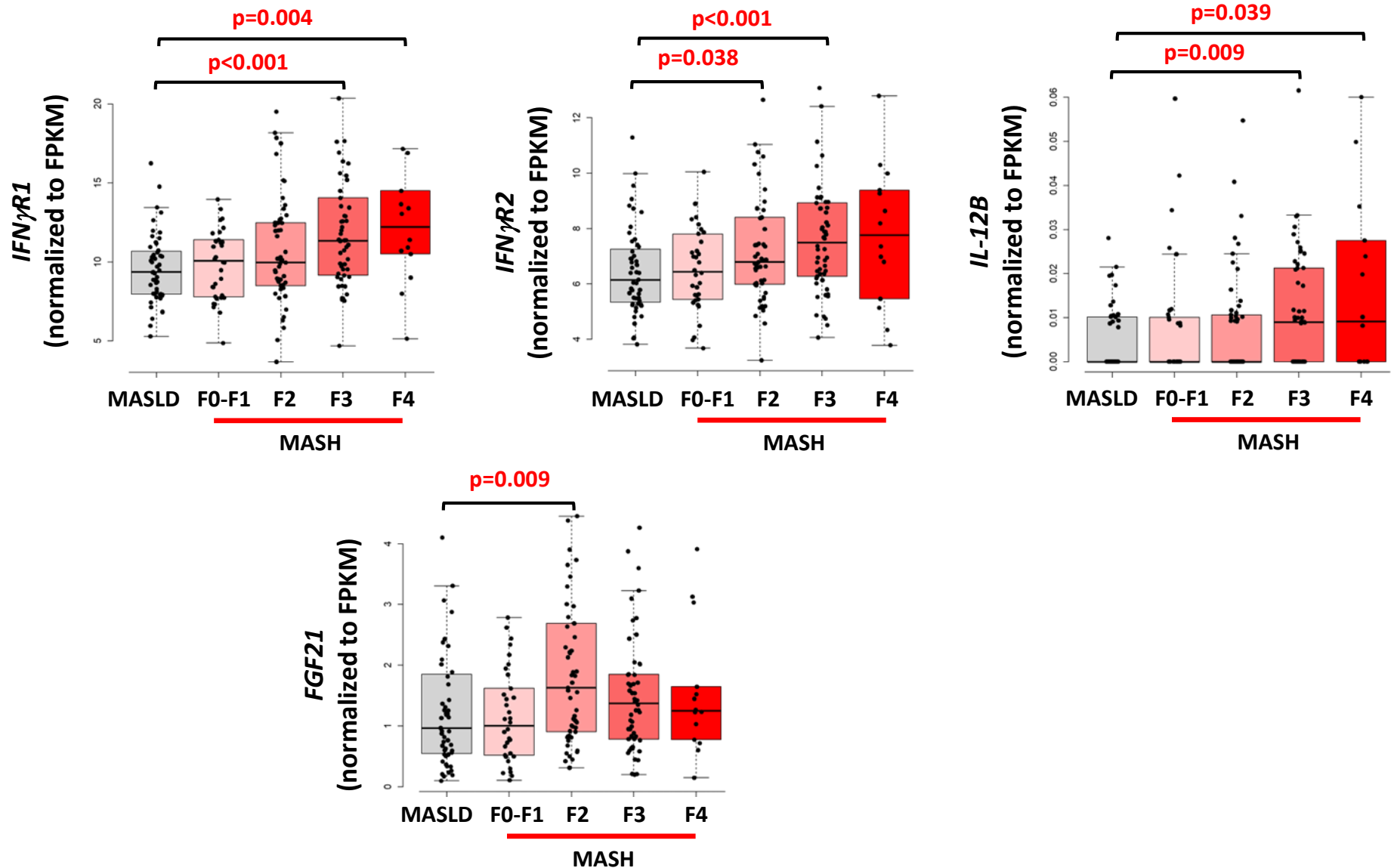
Macrophage IFNγ Signaling Orchestrates Immunological Events During Fatty Liver Transition to Insulin Resistance and MASH in Obesity
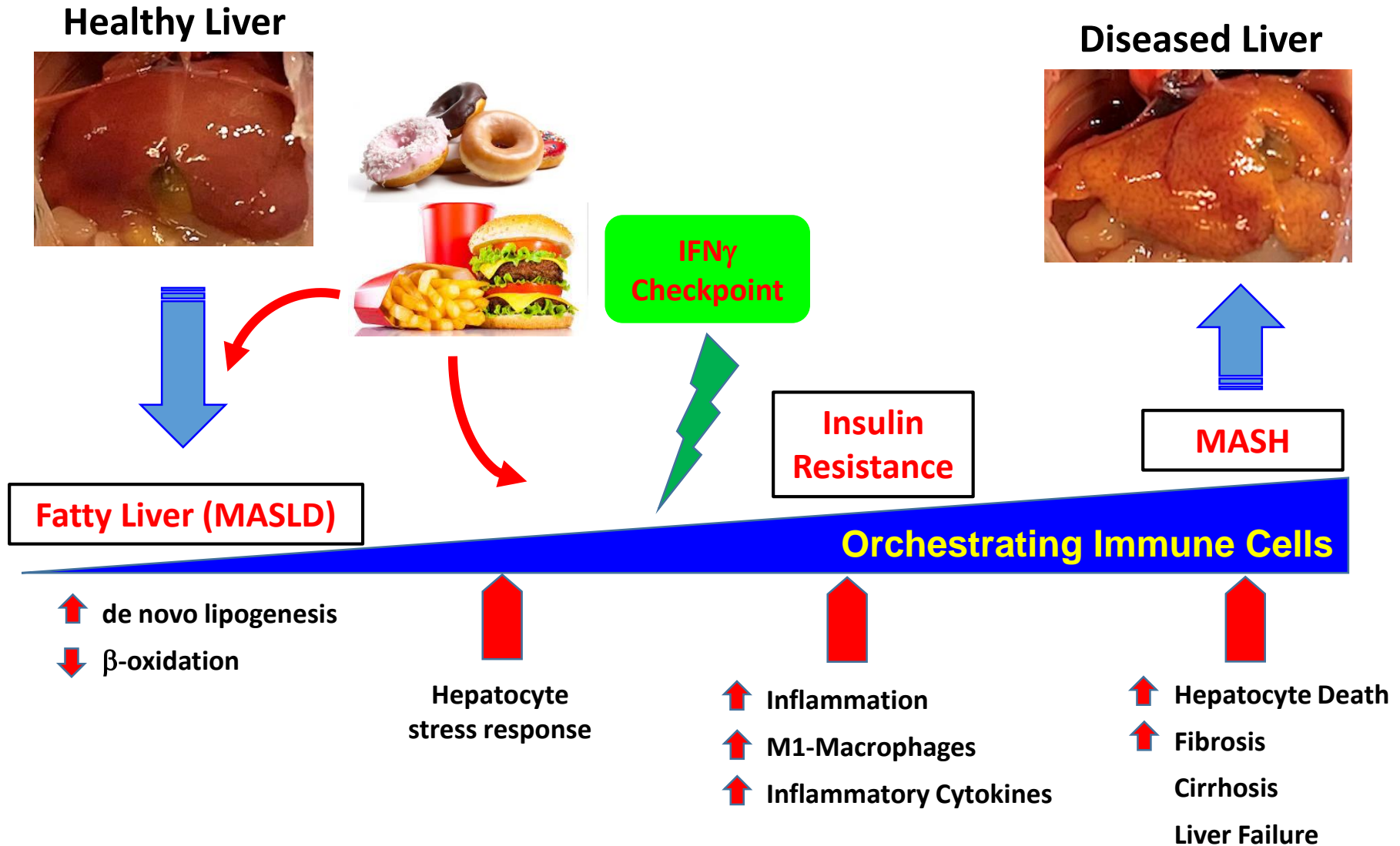
UMass Chan
MEDICAL SCHOOL

Jason Kim Lab
Program in Molecular Medicine, Diabetes Center of Excellence

Our Research is Funded by ....

NIH National Institute of Diabetes and Digestive and Kidney Diseases

NIH National Institute on Aging

Diabetes Virtual Camp

https://www.diabetesvirtualcamp.org

Lauren Kim

Allison Kim

Diabetes Virtual Camp

for future scientists and physicians

Home   Our Team   Our Experts   Our Community   Summer 2024   Past Camps   News   Contact Us

Educating Diabetes and Inspiring the Next Generation of Physicians & Scientists

Postdoc Opportunity

Post Doc - Open Rank

Job Number: 2024-46850
Category: Post Doc
Location: Worcester, MA
Shift: Day
Exempt/Non-Exempt: Exempt
Business Unit: UMass Chan Medical School
Department: School - Molecular Medicine - W400900
Job Type: Full-Time
Salary Grade: 86
Union Code: Non Union Position-W63-Residents/Post Docs
Num. Openings: 1
Post Date: Aug. 24, 2024

Job Description

Postdoctoral Associate in Type 2 Diabetes and Alzheimers Disease Research at UMass Chan Medical School

A postdoctoral associate position is available in the laboratory of Prof. Jason Kim, Program in Molecular Medicine, for a highly motivated candidate with a Ph.D. and/or M.D. to conduct new NIH-funded research investigating the important connection between type 2 diabetes and Alzheimers disease (AD) using physiologic, molecular, and cell-based approaches in transgenic mice.

The ideal candidate should have a strong background in molecular and cell biology, immunology, and neuroscience, as the newly funded project involves the use of primary macrophages, hepatocytes, natural killer cells, glial cells, and neurons from transgenic mouse models and various *in vitro* systems using AAV and siRNA.

The ideal candidate should demonstrate solid writing skills capable of drafting a manuscript and a grant application, analytical skills with statistics and a basic understanding of bioinformatics, communication skills to work effectively with other lab members, mentoring skills to oversee PhD students and student interns, a positive personality to engage in team research, and strong integrity and ethics.

Building on prior expertise in molecular and cell biology, immunology, and neuroscience, the candidate will be trained in elegant *in vivo* metabolic procedures and physiologic approaches, behavioral phenotyping tests for learning and memory, and spatial transcriptomic analysis to lead exciting and complex research projects aimed at determining the molecular link between type 2 diabetes and Alzheimers disease.

The candidate will also be trained in grant writing with the expectation to apply for postdoctoral grants during the 1st year and will be engaged in multiple collaborative projects with other leading diabetes and AD investigators, establishing professional networks.

Notably, the candidate must be fully committed to learning the investigative process, developing a strong hypothesis, comprehensively designing experiments with anticipated outcomes and pitfalls, carefully performing experiments with reproducibility, and analyzing the scientific data with utmost rigor for high-impact presentations and publications.

Strong publication history during graduate training, prior submission of predoctoral grant applications, and most enthusiastic letters from current and past mentors (minimum of 3 references) are highly encouraged.

Qualifications: Education, experience, and skills required for consideration:

- Ph.D. in molecular biology, cell biology, immunology, neuroscience, or related disciplines
- M.D. and prior research experiences in molecular biology, cell biology, immunology, or neuroscience
- Strong work ethic and motivation to apply skills toward solving biological problems of human diseases
- Meticulous and careful technical skills
- Excellent analytical skills with statistics and independent judgment
- Highly collegial and works well as a team member
- Solid written and verbal communication skills
- Desire to be trained in high-quality scientific research with the goal of becoming an independent investigator

To Apply:

Applicants should submit the following materials via email to Prof. Jason Kim at jason.kim@umassmed.edu: a cover letter describing the applicants research expertise, past and current projects, and training goals; a CV (including a complete list of publications), and contact information for three references, one of which should be a Ph.D. advisor or equivalent.

$3.6M to Study the Connection Between Type 2 Diabetes & Alzheimer's Disease

Jason Kim, PhD, was awarded a $3.6M grant (NIH-R01) from the National Institute on Aging to study an important relationship between type 2 diabetes and Alzheimer's disease.

"According to the Alzheimer's Association, there's a strong correlation between Alzheimer's disease and type 2 diabetes, and individuals with type 2 diabetes show accelerated cognitive decline," said Dr. Kim, Professor of Molecular Medicine and Professor of Medicine in the Division of Endocrinology, Diabetes and Metabolism. "But, the underlying connection between these two common human diseases remains unknown."

Dr. Kim is a leading expert in metabolism and type 2 diabetes, and he will be collaborating on the five-year project Dorothy Schafer, PhD, Associate Professor of Neurobiology and a leading expert in neurodegenerative diseases. They will investigate the impact of age-associated changes in peripheral metabolism, mainly focusing on insulin resistance and inflammation in the liver, on neurodegeneration.

This is a timely award to a $2M grant (NIH-R01) Dr. Kim received last year from the National Institute of Diabetes and Digestive and Kidney Diseases to study metabolic dysfunction-associated steatotic liver disease. One goal of **the Kim laboratory** is to identify new therapeutic targets to treat metabolic liver disease and Alzheimer's disease.
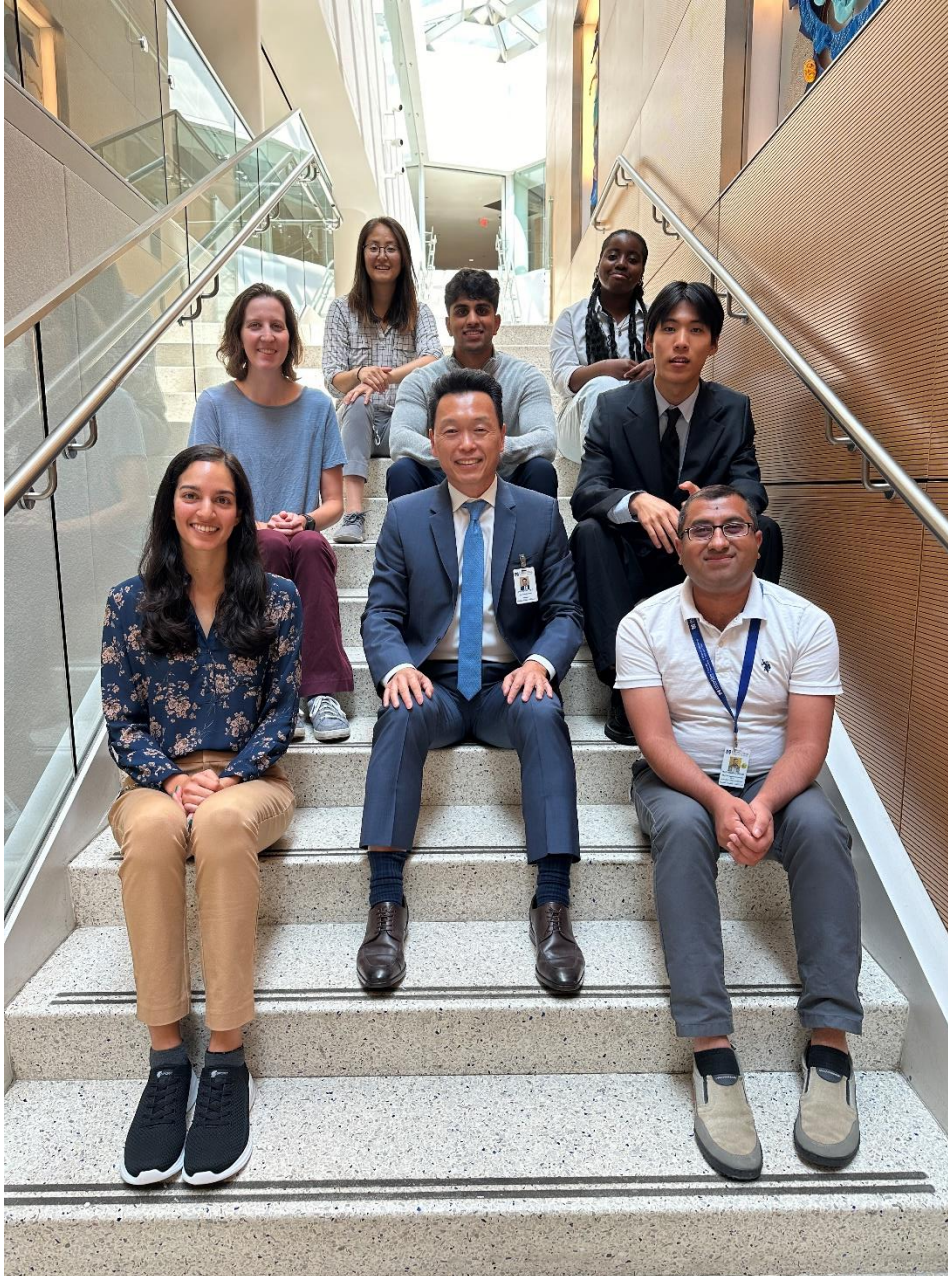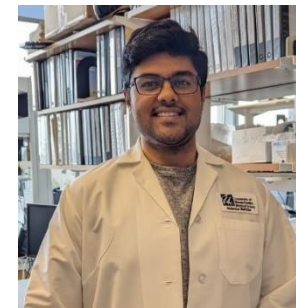
Randall Friedline, Ph.D.
Assistant Professor

Mahaa Albusharif, M.S.
Graduate Student

Allison Kim, B.S.
Research Intern

Sezin Dagdeviren, PhD
Postdoc Fellow

Suryateja Rao, M.S.
Medical Student IV

Lauren Kim, B.S.
Research Intern

Working to Cure Diabetes