



The Role of Toll-like Receptors in of Diabetic Cardiomyopathy

Joel Schilling MD, PhD

Jean Schaffer, MD

Washington University School of Medicine

The Link Between Diabetes and Heart Failure

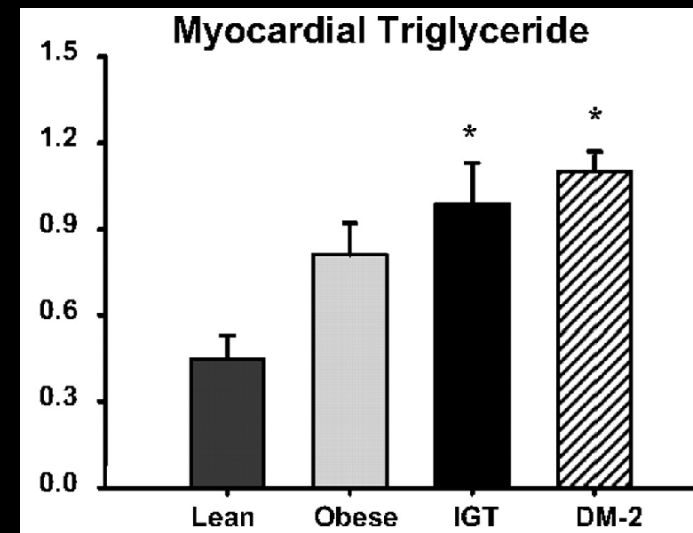
- **Diabetes is over-represented in HF patients**
~30% of those with HF have DM
- **Individuals with diabetes are more likely to develop HF**
~ 2-5 higher risk compared to non-diabetics
- **Diabetes is associated with a worse prognosis in HF patients**
~2 fold increased risk of death

Diabetic Cardiomyopathy

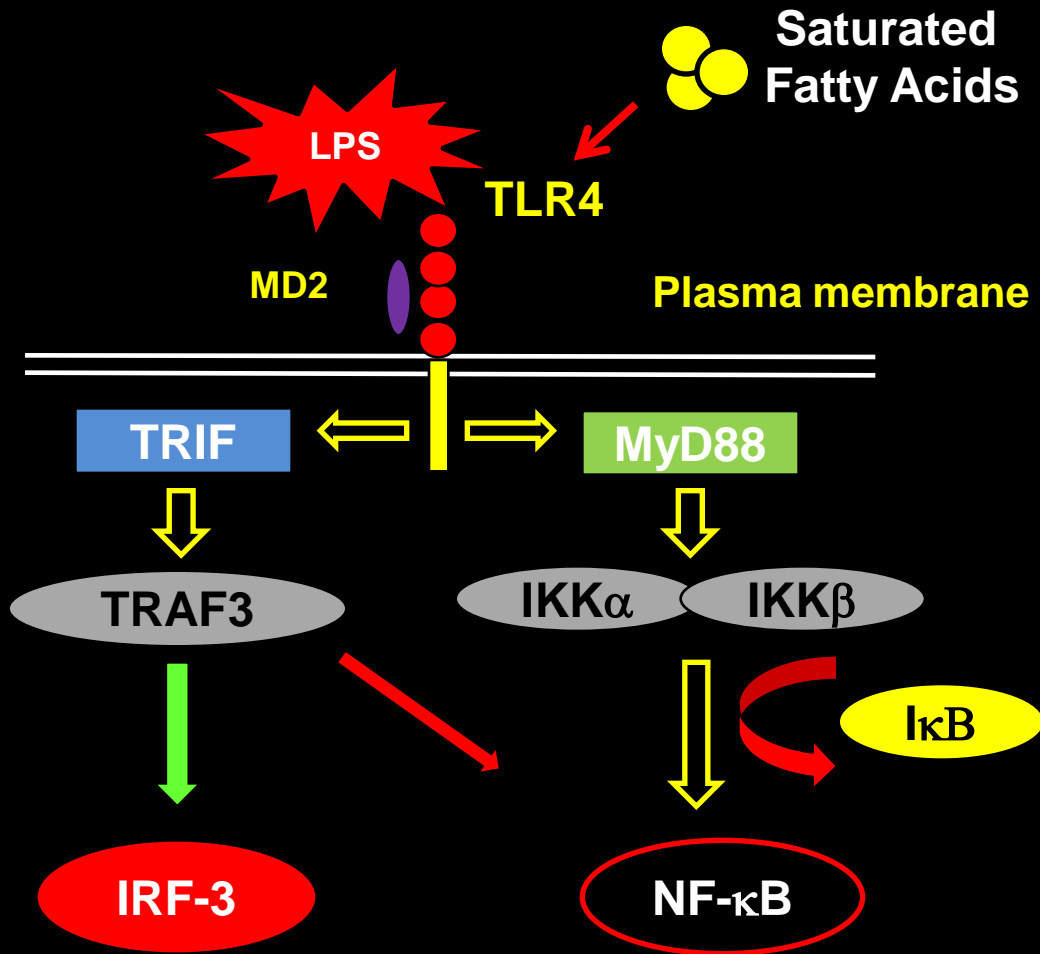
Definition:

Diabetes with diastolic +/- systolic LV dysfunction in the absence of significant HTN, CAD, or valvular dz

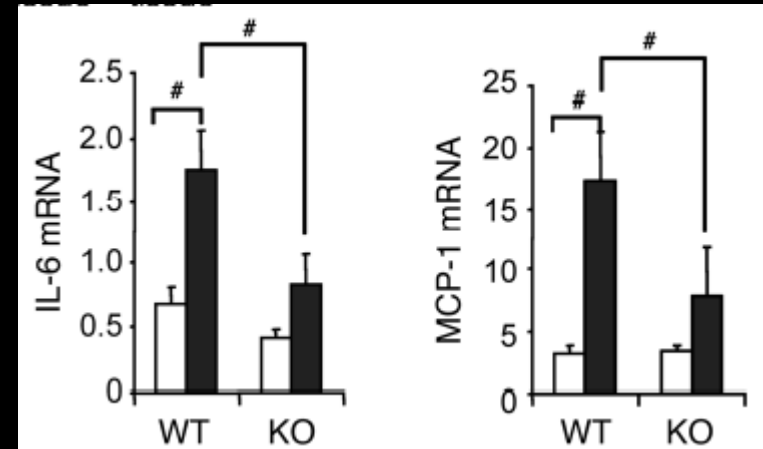
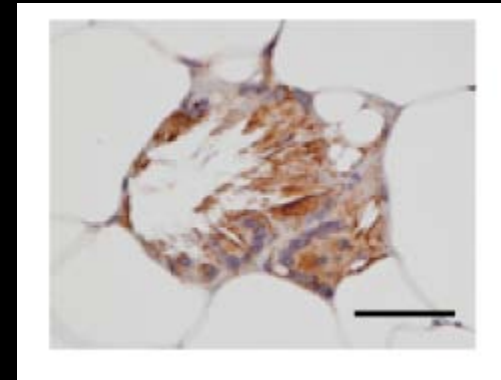
- Mitochondrial Dysfunction
- Dysregulated Substrate Utilization
- Myocyte apoptosis / fibrosis
- Myocardial lipid accumulation



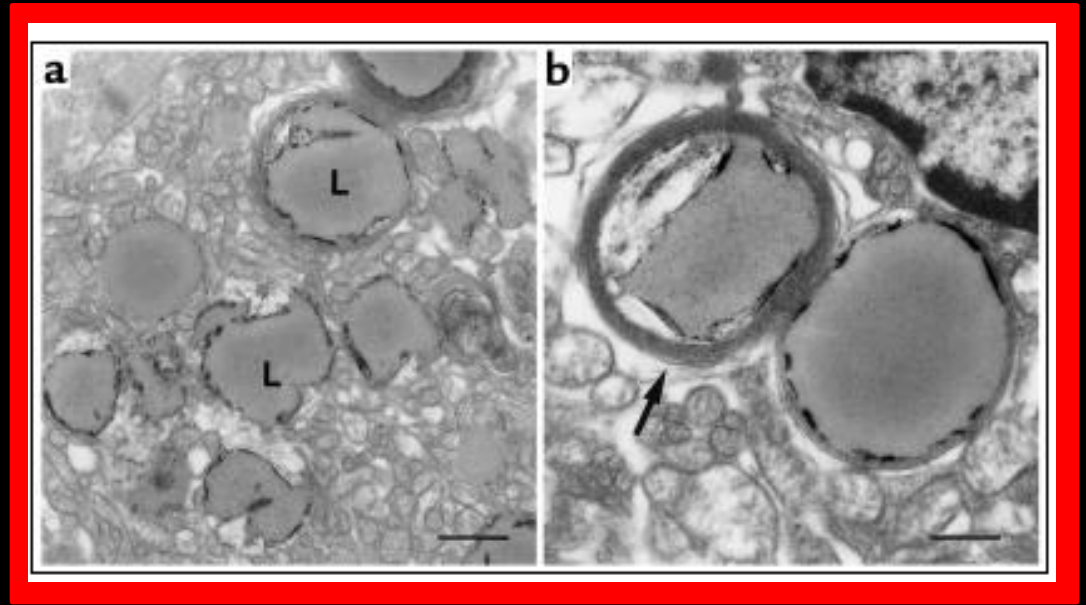
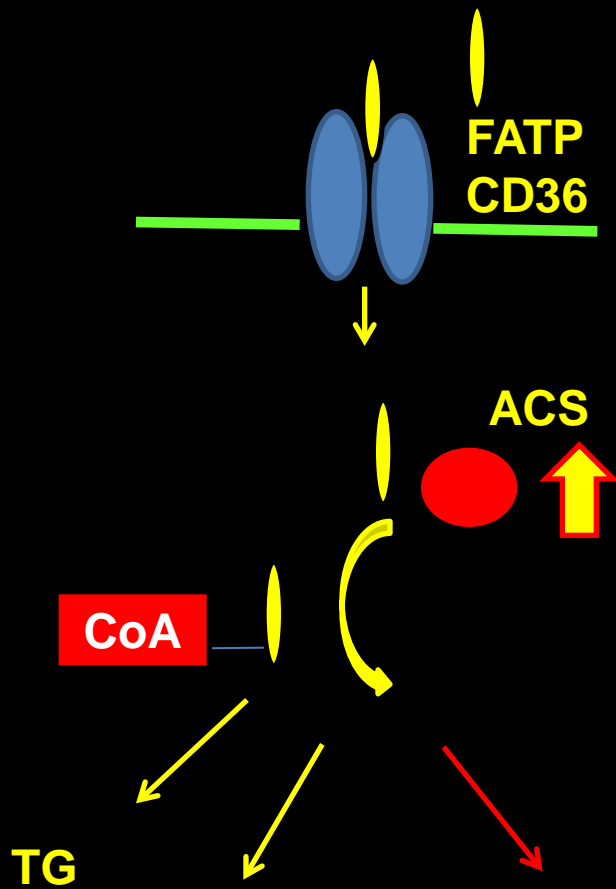
TLRs and Diabetic Inflammation



MAC-3



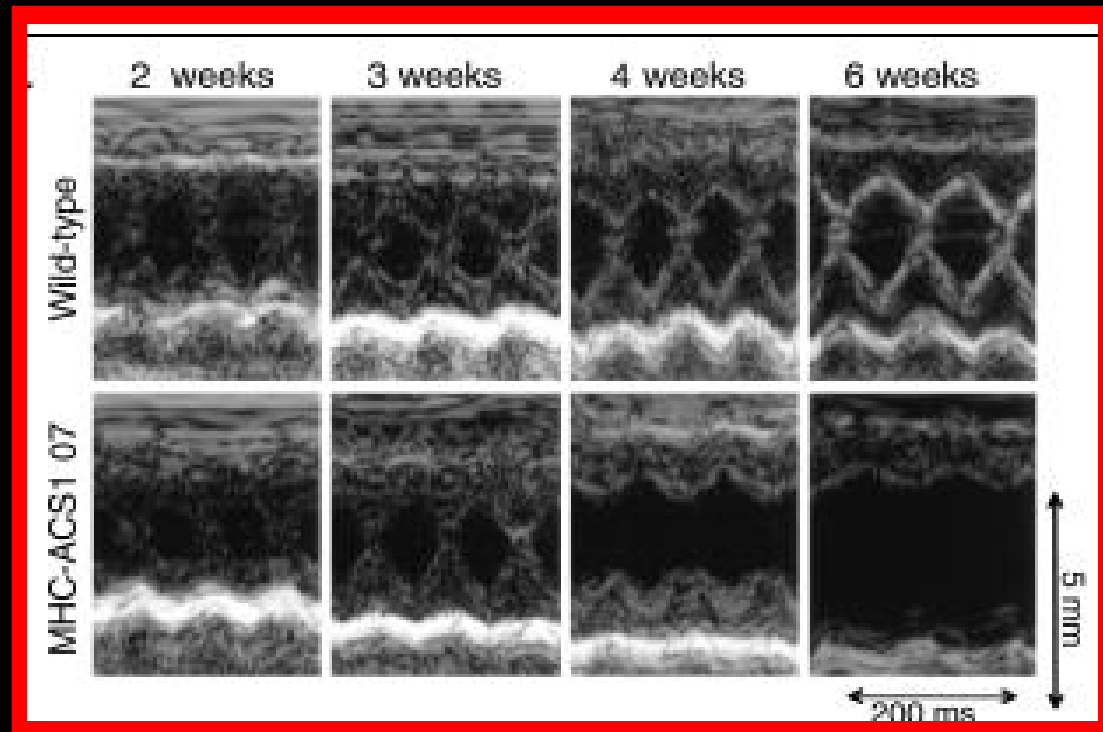
MHC-ACS Model of Cardiac Lipotoxicity



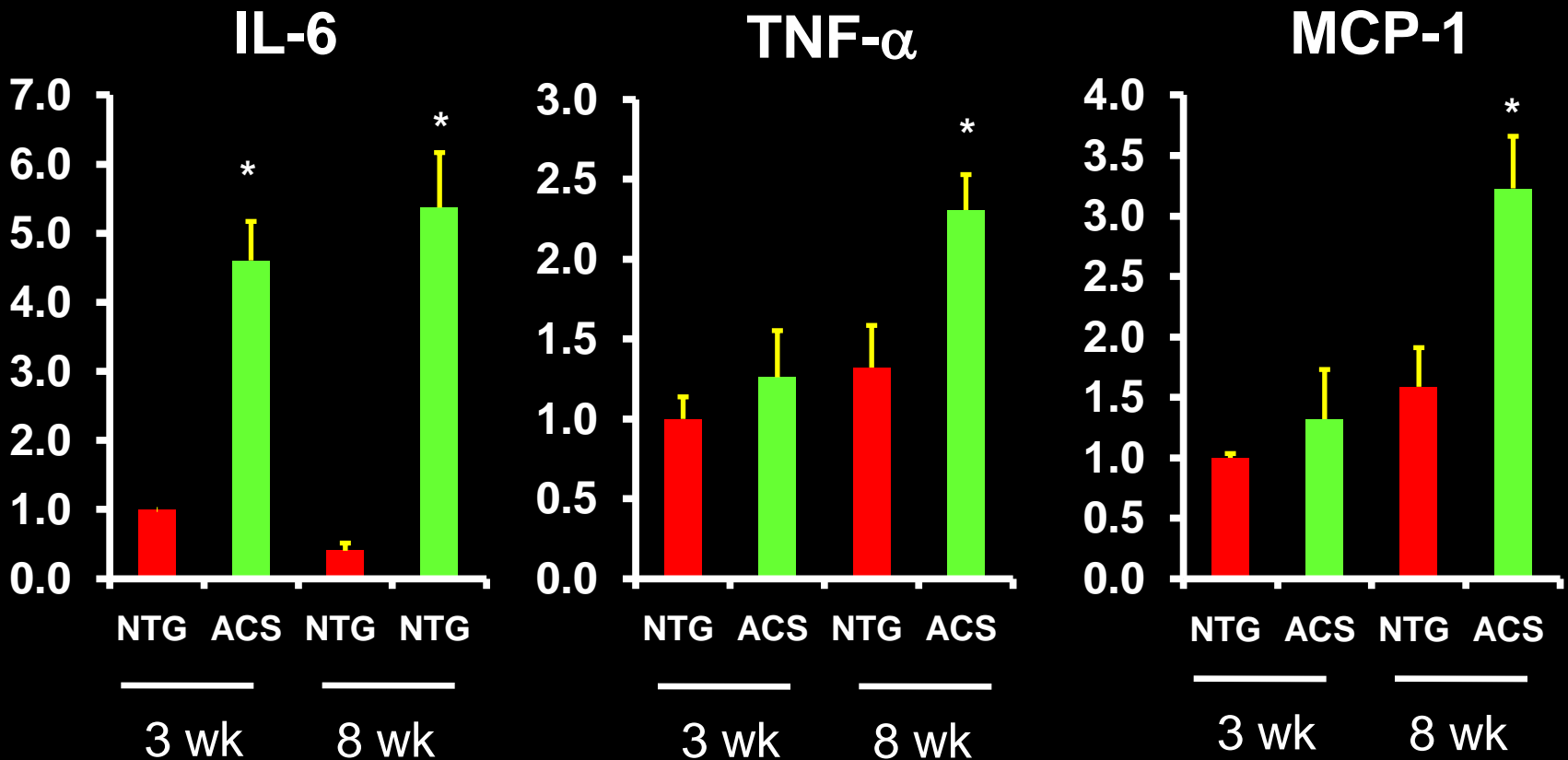
Beta Oxidation **Toxic Lipid Species** **→ Cellular Dysfunction**

MHC-ACS Model of Cardiac Lipotoxicity

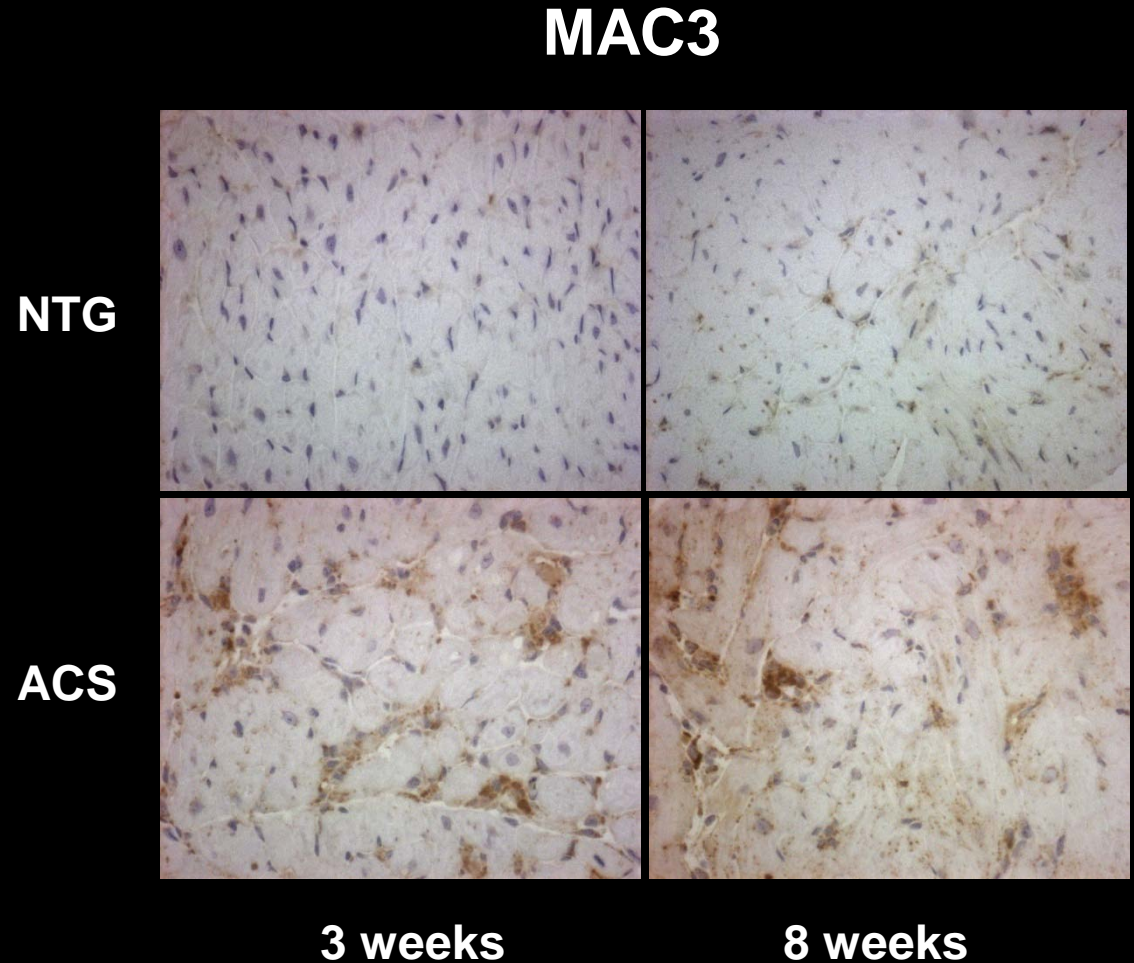
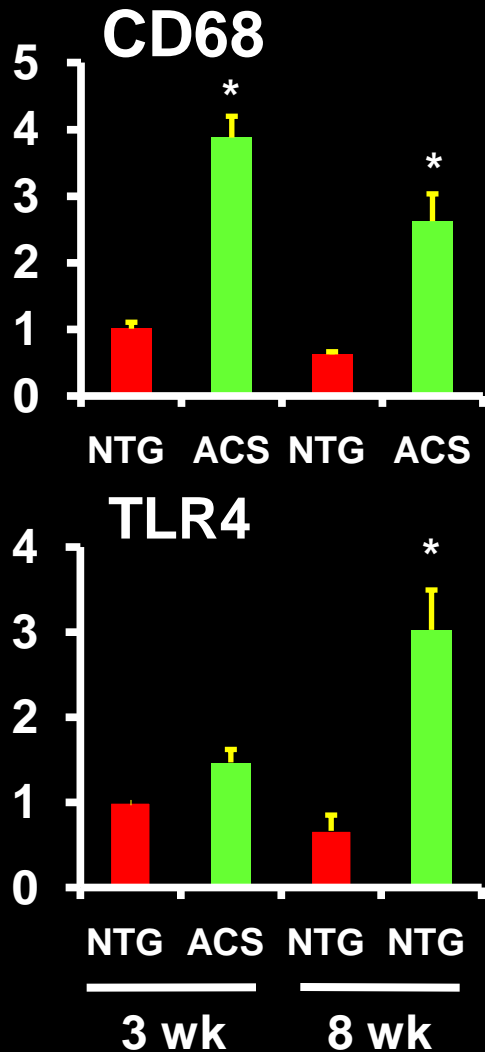
- Myocyte Lipid Accumulation
- Cardiac Dysfunction
- Myocyte Cell Loss
- Reduced Survival



MHC-ACS Mice have Evidence of Myocardial Inflammation



Myocardial Macrophage Infiltration in MHC-ACS Mice



Proposed Experiments

MHC-ACS

TLR4KO
TLR4/2 KO



Assess Phenotypes at 3 wk and 8 wk

Myocardial Function – 2D ECHO

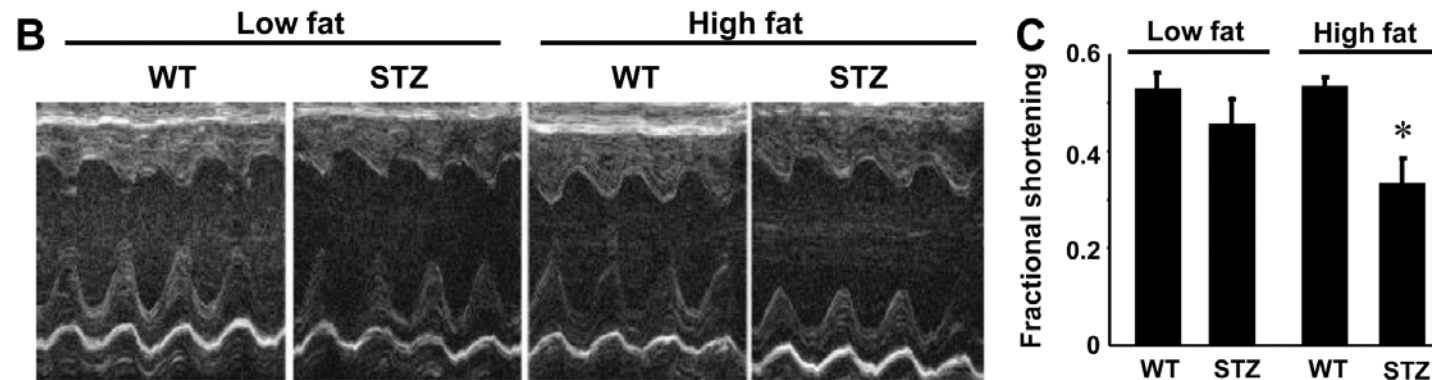
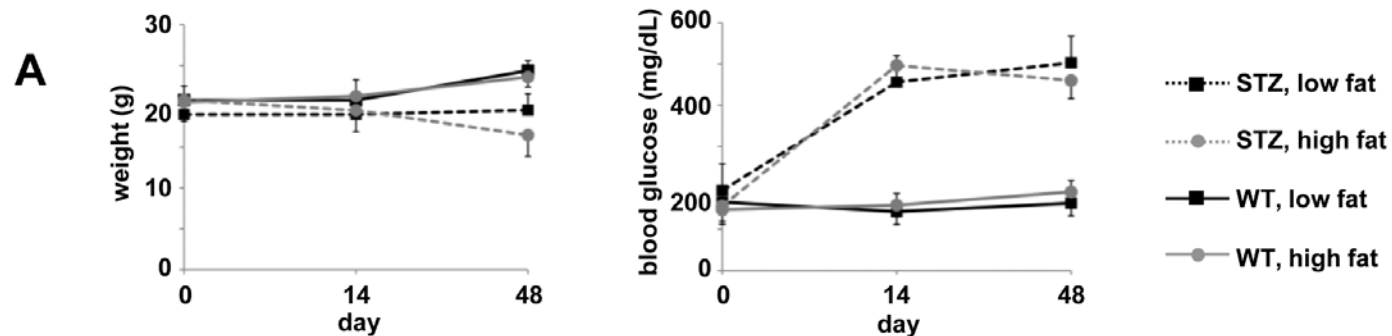
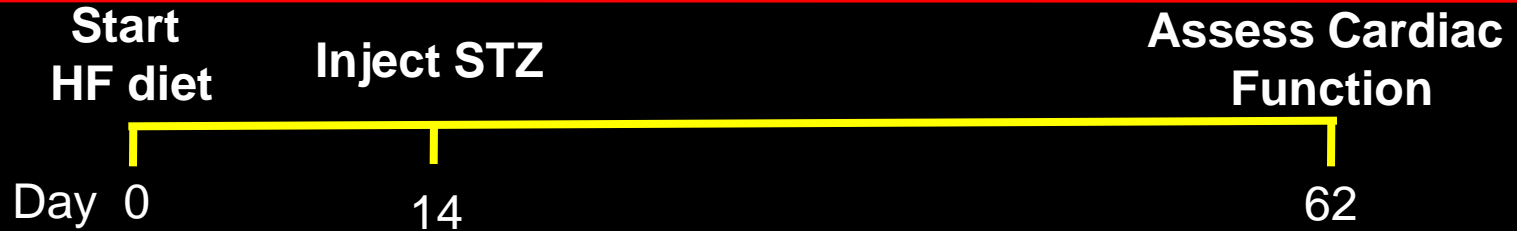
Macrophage Infiltration – IHC and qRTPCR

Inflammatory Cytokine Production –
qRTPCR

Myocyte Apoptosis

Survival

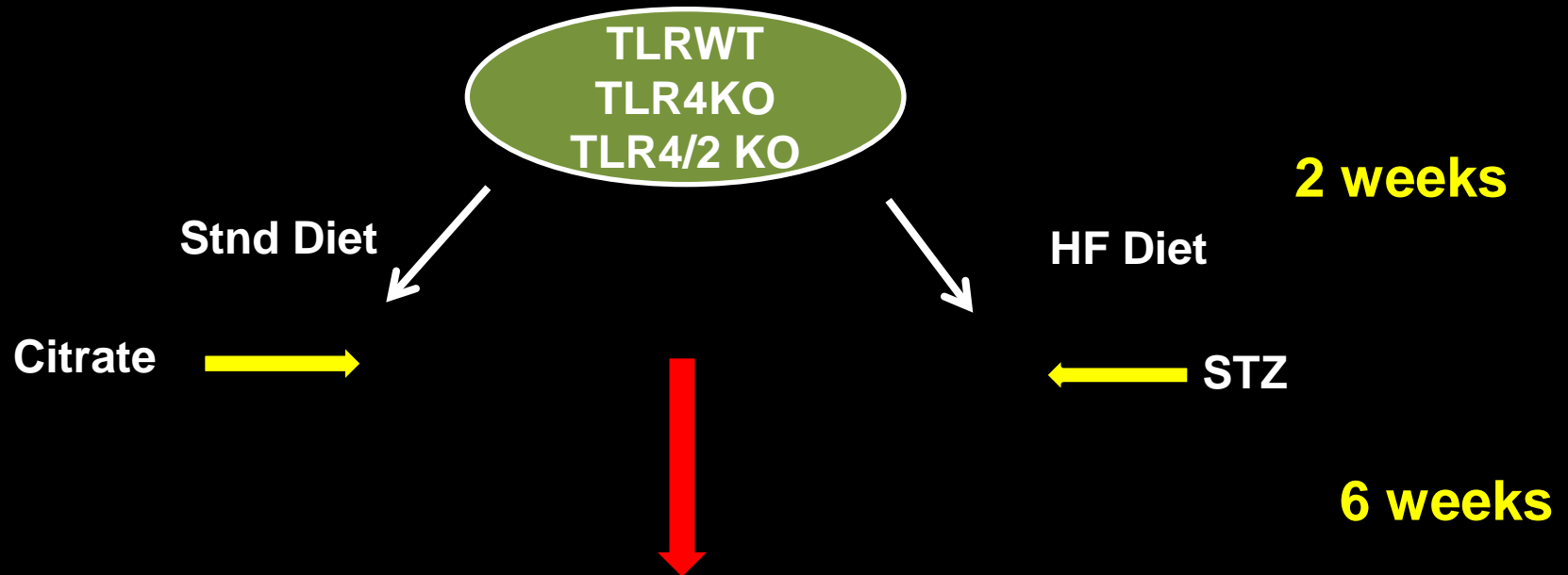
Diabetic Cardiomyopathy Model



STZ-Induced Diabetes Induces Myocardial Inflammation

	SD	STZ
Collagen type 1 (% AF)	0.5 ± 0.06	2.2 ± 0.2*
Collagen type 3 (% AF)	1.3 ± 0.02	7.5 ± 0.4*
ICAM-1 (% AF)	0.4 ± 0.02	2.8 ± 0.4*
VCAM-1 (% AF)	0.03 ± 0.005	0.18 ± 0.02*
TNF- α (infiltrates/mm ²)	0.6 ± 0.02	6.9 ± 0.5*
IL1- β (infiltrates/mm ²)	0.7 ± 0.05	3.1 ± 0.5*
CD 11a (cells/mm ²)	3.9 ± 0.2	38.9 ± 3.6*
CD 11b (cells/mm ²)	16.4 ± 1.2	65.9 ± 6.7*
CD 18 (cells/mm ²)	10.7 ± 0.8	76.9 ± 4.3*
CD 68 (cells/mm ²)	0.3 ± 0.04	4.8 ± 0.3*

TLRs in Diabetic Cardiomyopathy: Experimental Design

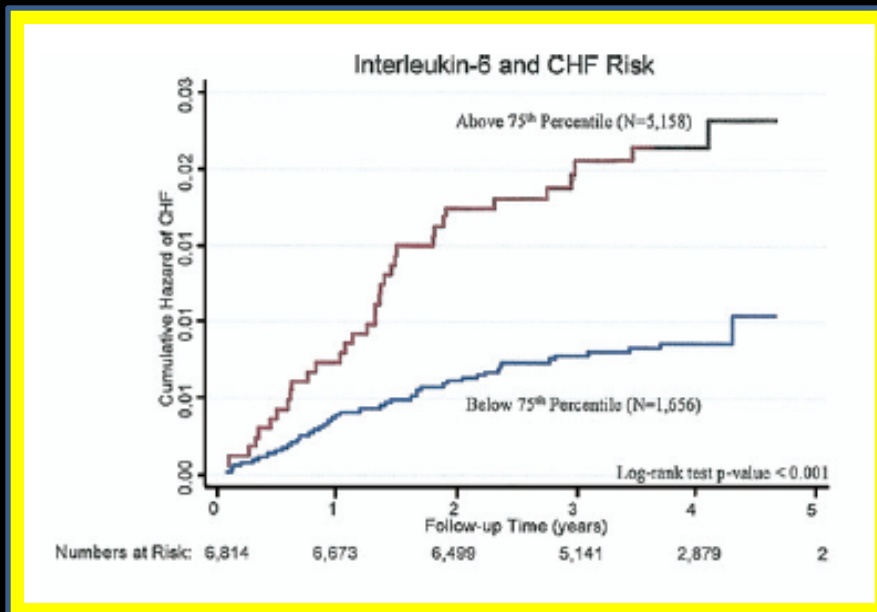


Myocardial Function – 2D ECHO
Macrophage Infiltration – IHC and qRTPCR
Inflammatory Cytokine Production – qRTPCR
Myocyte Apoptosis

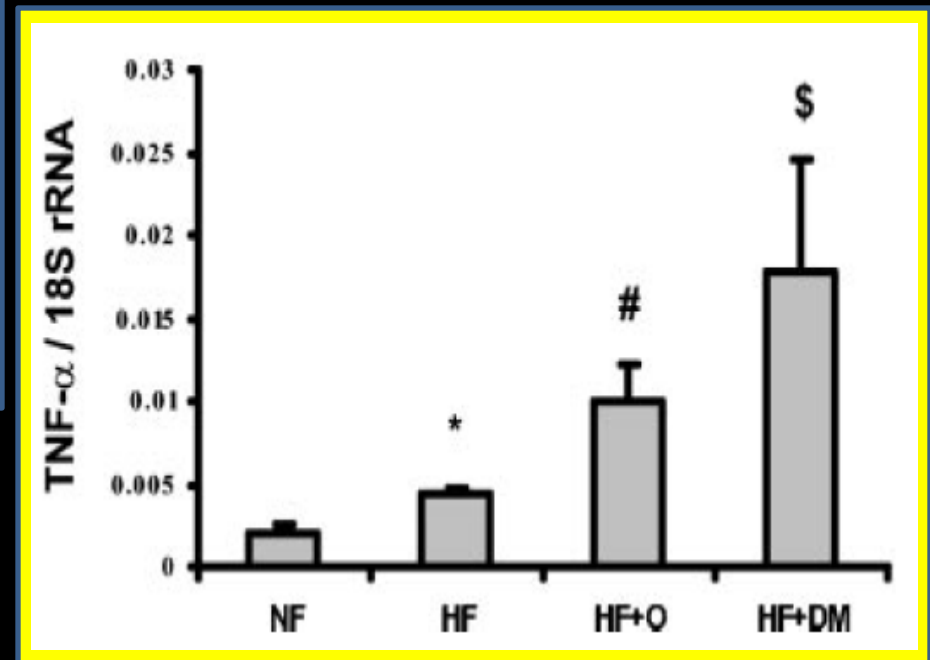
Summary

- Diabetes is associated with ectopic lipid accumulation and inflammation
- TLR4 is activated in settings of nutrient stress and may contribute to end-organ dysfunction in DM
- TLR loss of function models will provide insight into the role of inflammation in diabetic cardiomyopathy

Inflammation is Associated with Obesity, Diabetes, and Heart Failure



Hossein Bahrami, et al. JACC. 2008.



Saumya Sharma et al. FASEB. 2004