



# A Novel Class of Living Medicines

Synthetic Biotic™ medicines to perform and deliver  
critical therapeutic functions to treat diseases  
throughout the body

**Genetically Engineered E. coli Nissle attenuates hyperammonemia in  
a mouse model of hepatic encephalopathy by metabolizing gut  
ammonia and increasing urea production**

Yossi Dagon

6.3.2018

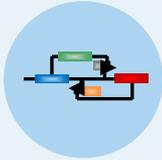
Digestive Disease Week

# Disclosures

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- Yossi Dagon is an employee of Synlogic Inc.

# Synthetic Biotic Medicines: A Novel Class of Living Medicines



## Synthetic

- Engineered bacteria
- With **designed genetic circuits**
- To **degrade metabolites** that induce disease or **synthesize substances** to treat disease



## Biotic: *E. coli* Nissle as chassis:

- Widely-used **oral probiotic**
- **Leverage the safety** of probiotic
- Found within natural human **microbiome**
- **Amenable to genetic manipulation**

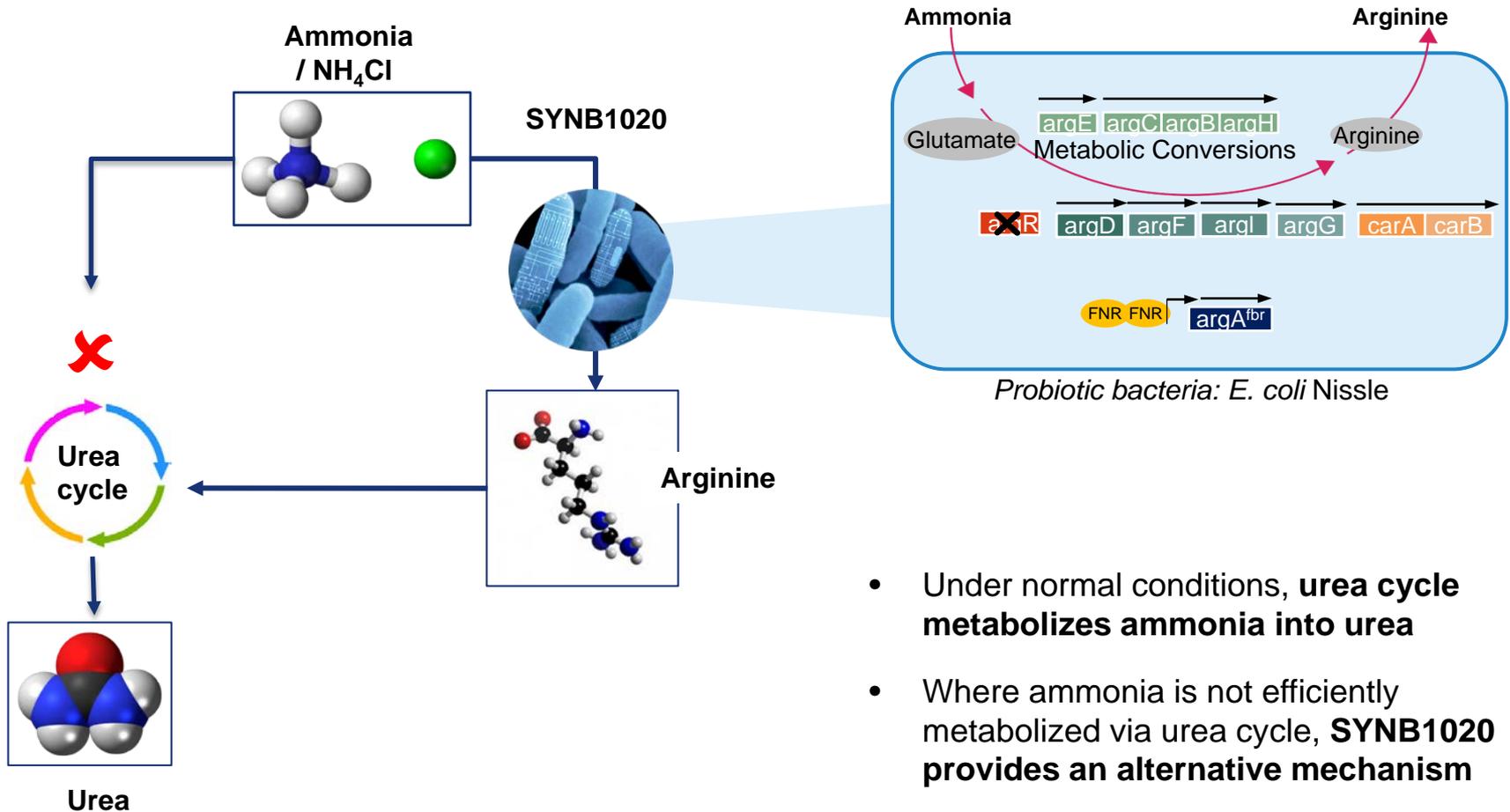
**Synthetic Biology + Bacteria =  
Synthetic Biotic Medicine**

**Therapeutic** delivered locally  
to treat systemic diseases



# A genetically engineered E. coli Nissle SYNB1020 converts Ammonia into Arginine

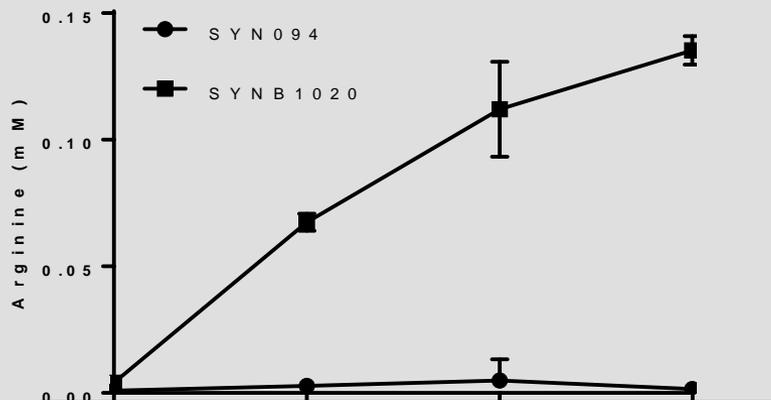
## Mechanism of Action:



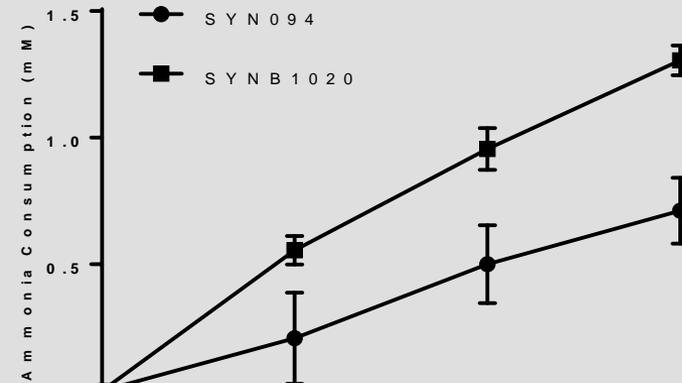
- Under normal conditions, **urea cycle metabolizes ammonia into urea**
- Where ammonia is not efficiently metabolized via urea cycle, **SYNB1020 provides an alternative mechanism**

# SYNB1020 Produces Arginine and Consumes Ammonia

## Arginine Production by SYNB1020

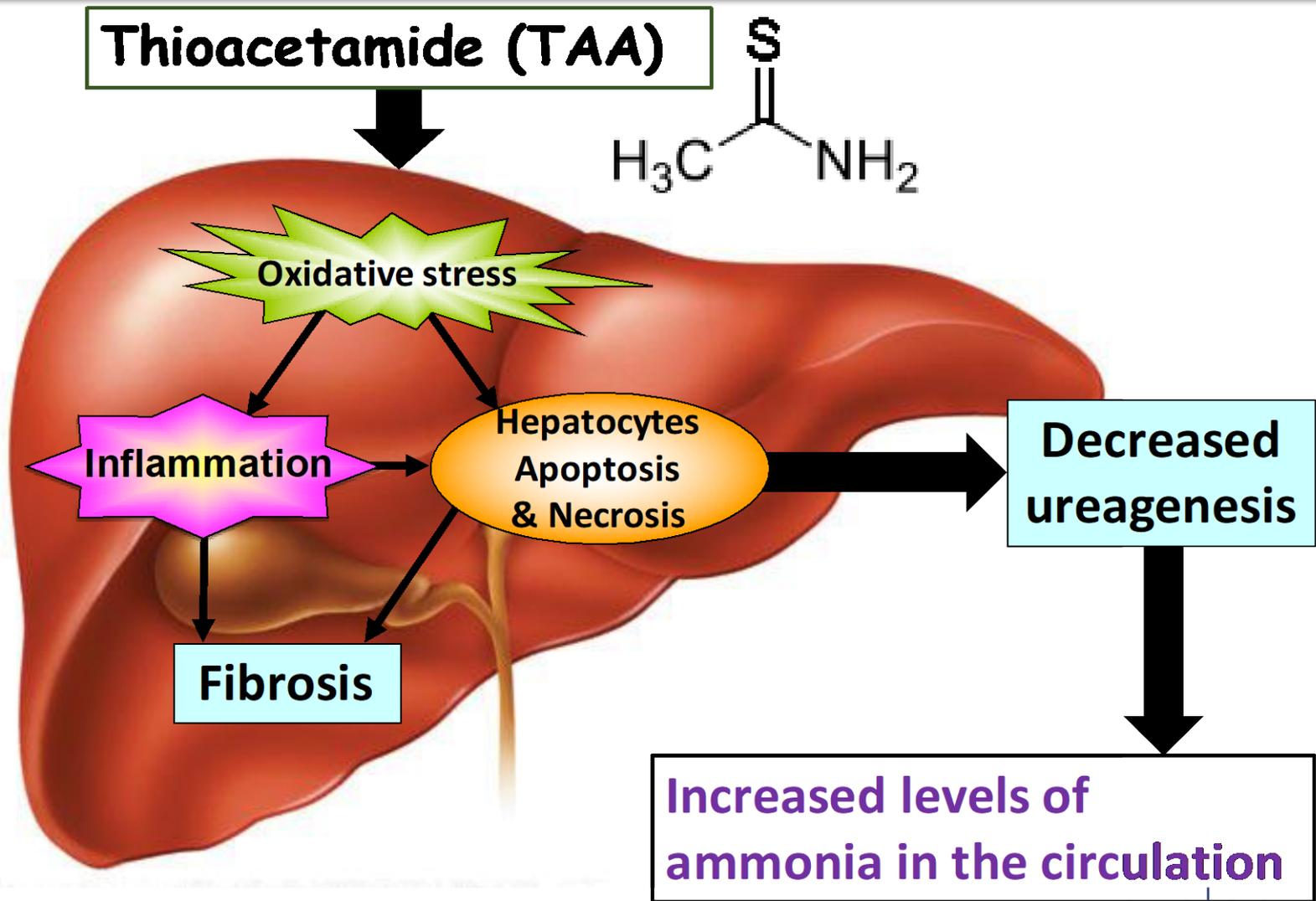


## Ammonia Consumption by SYNB1020

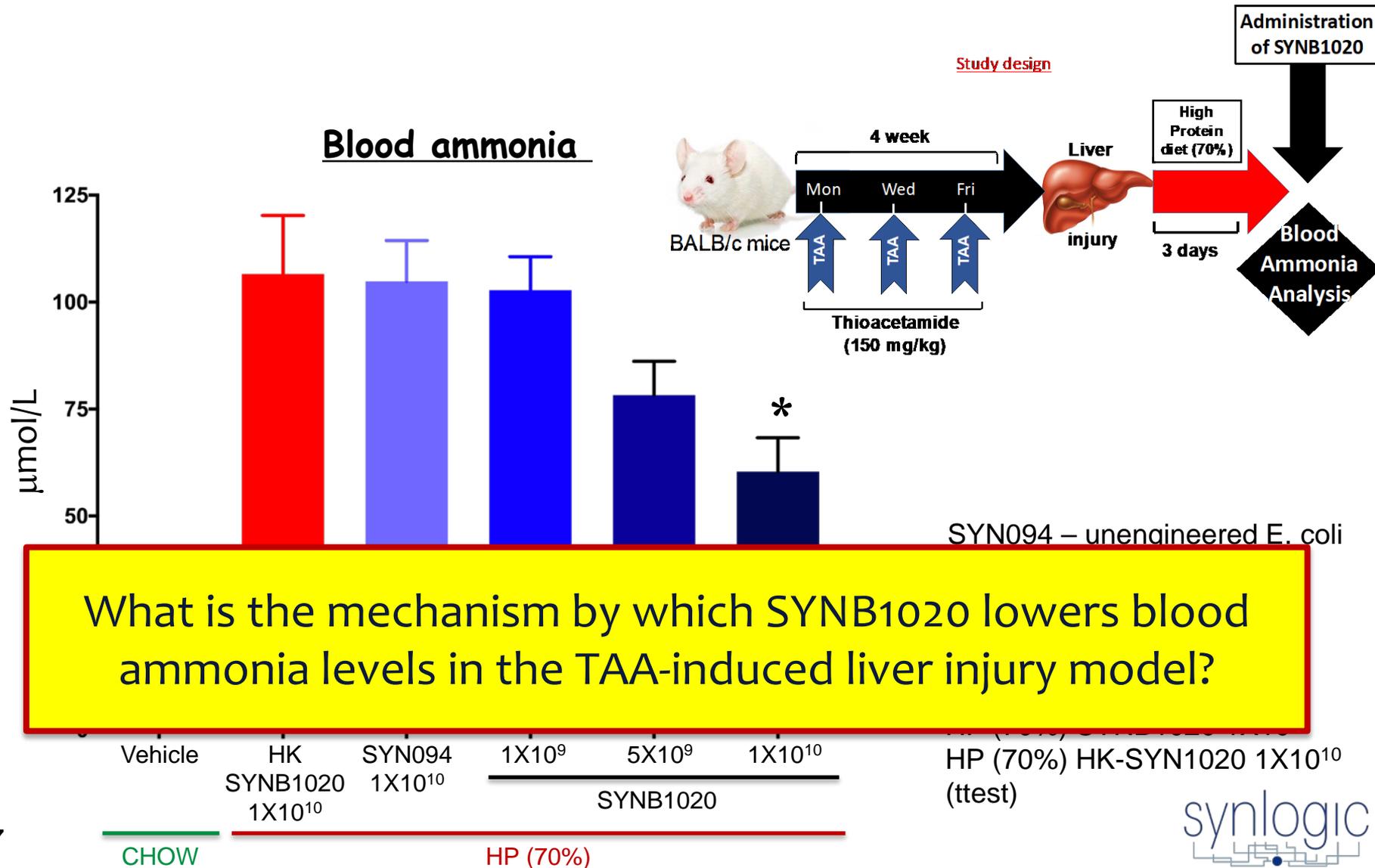


Can orally administered SYNB1020 lower systemic hyperammonemia in an animal model of hepatic encephalopathy?

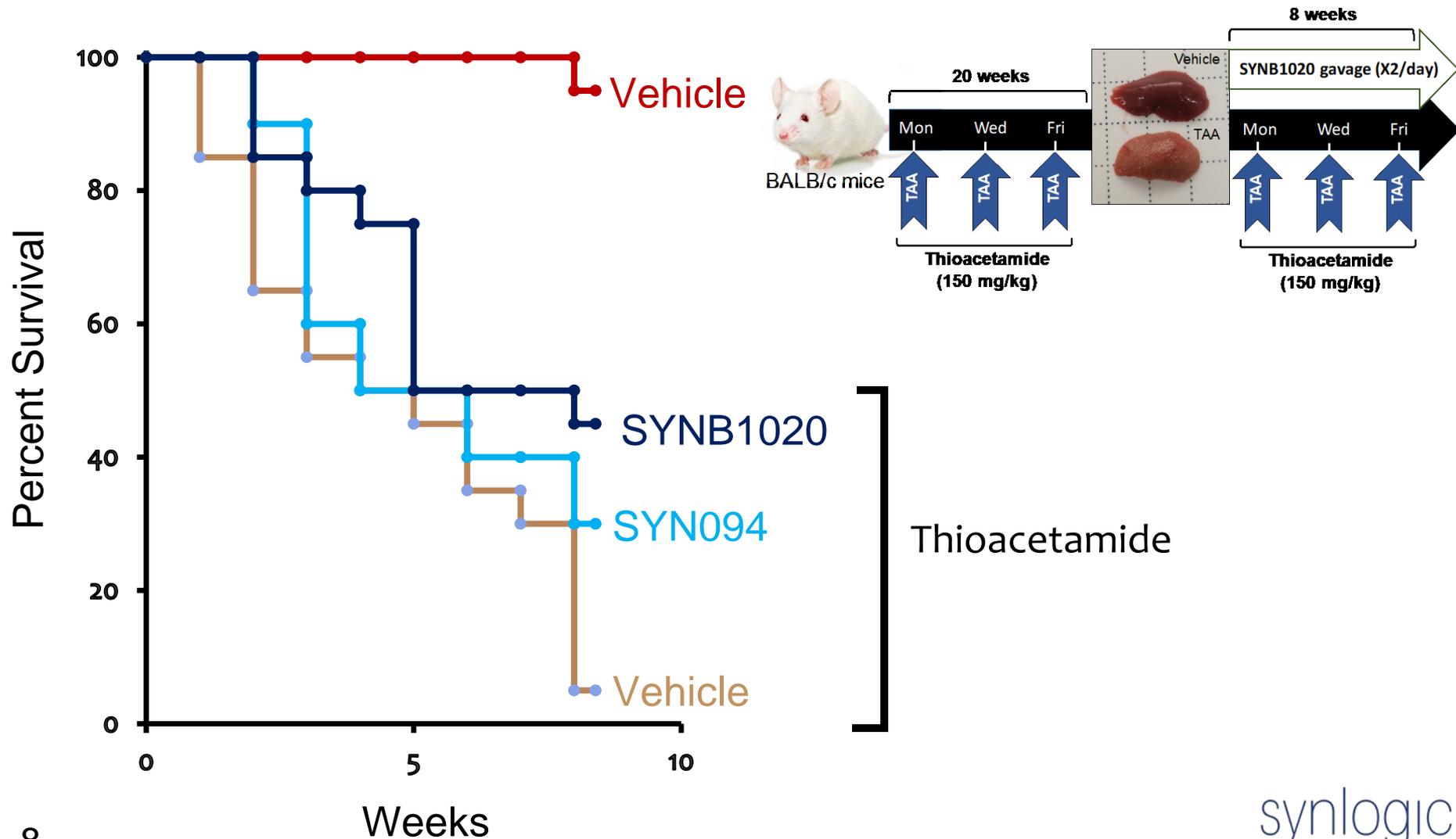
# A thioacetamide-induced hepatic encephalopathy model in BALB/c mice



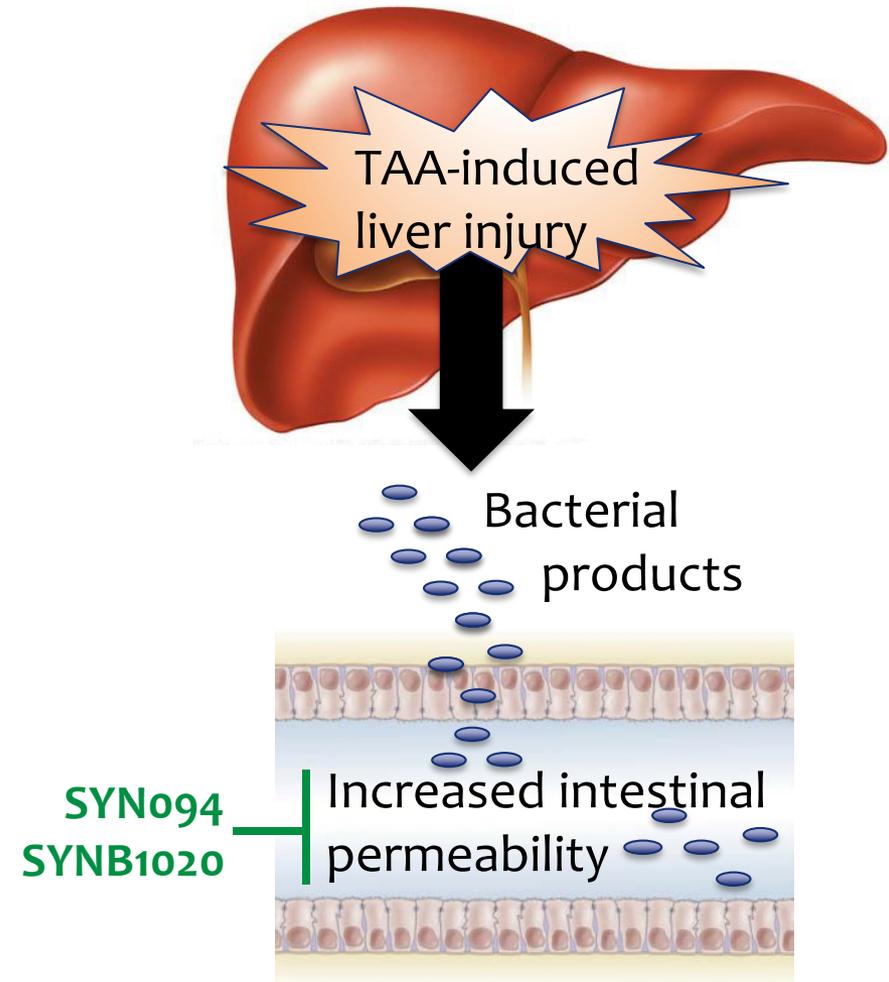
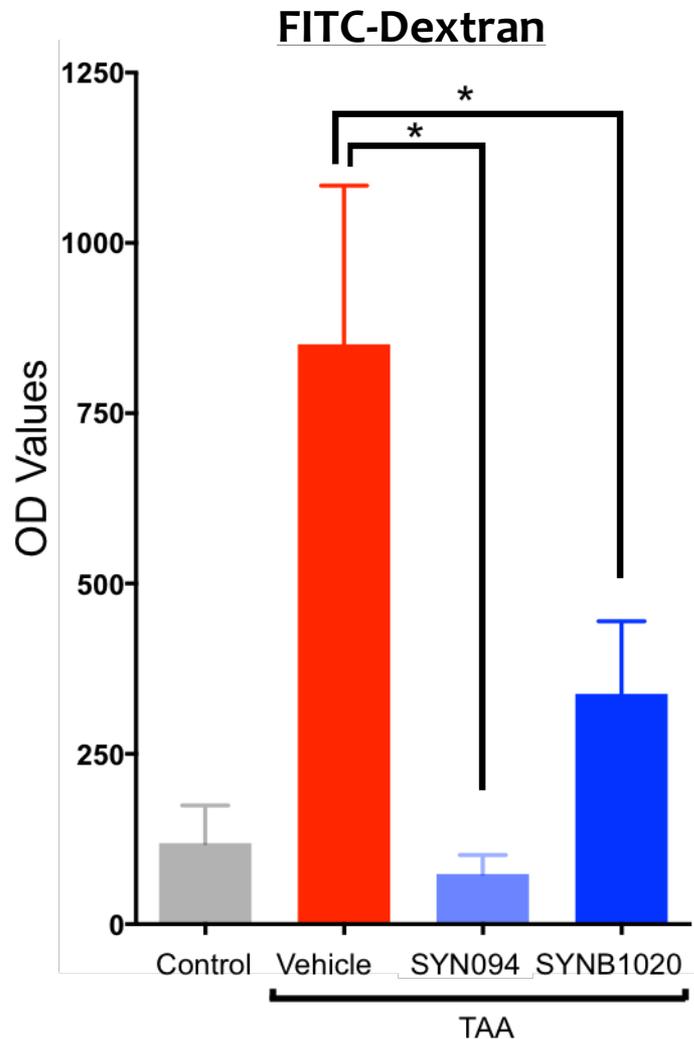
# SYNB1020 lowers blood ammonia levels in TAA-induced liver injury BALB/c mice fed 70% high protein diet



# SYNB1020 and SYN094 improve survival in BALB/c mice following chronic (20 weeks) treatment with TAA



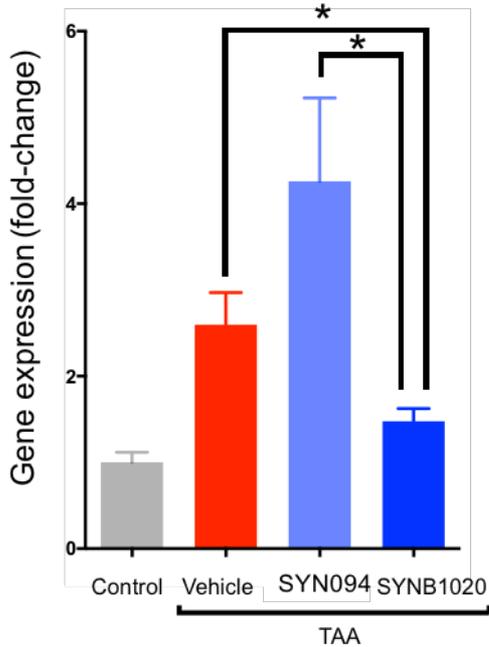
# SYNB1020 and SYN094 improve intestinal permeability in BALB/c mice Following chronic treatment with TAA



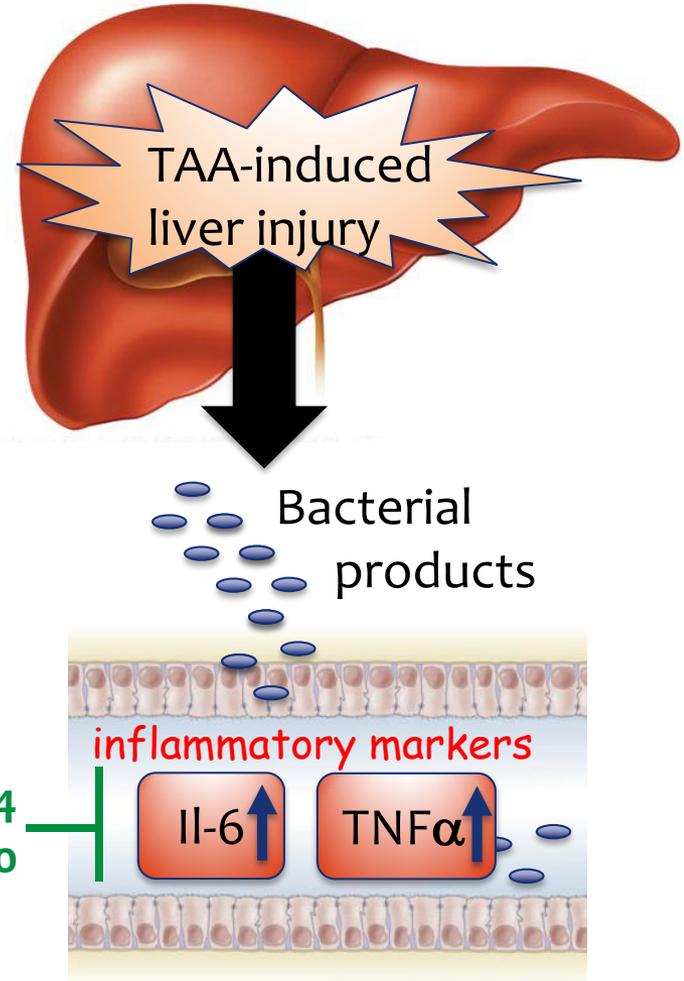
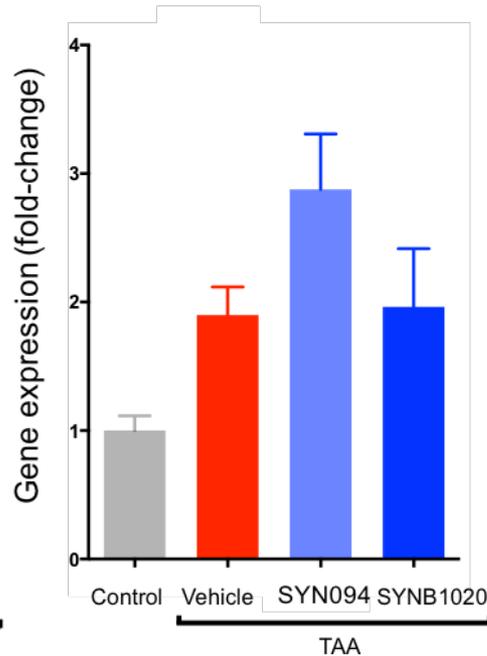
# SYNB1020 attenuates colon inflammatory cytokines in BALB/c mice Following chronic treatment with TAA

## qPCR analysis of colon mRNA expression:

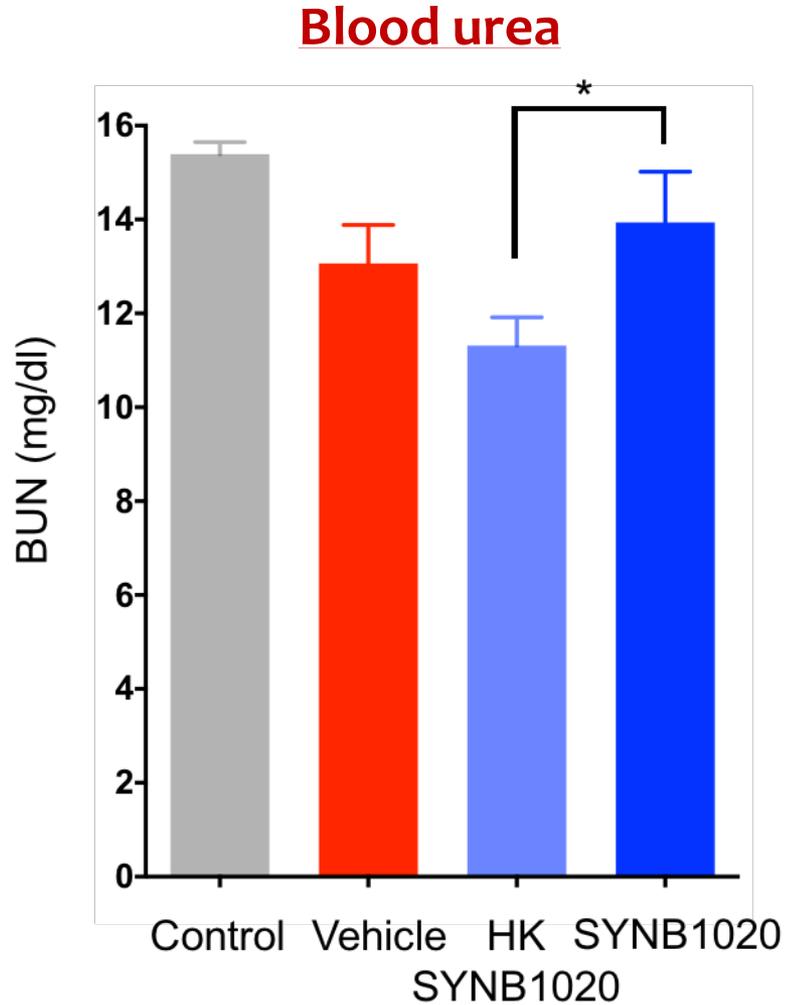
### Colon Il-6



### Colon TNF $\alpha$

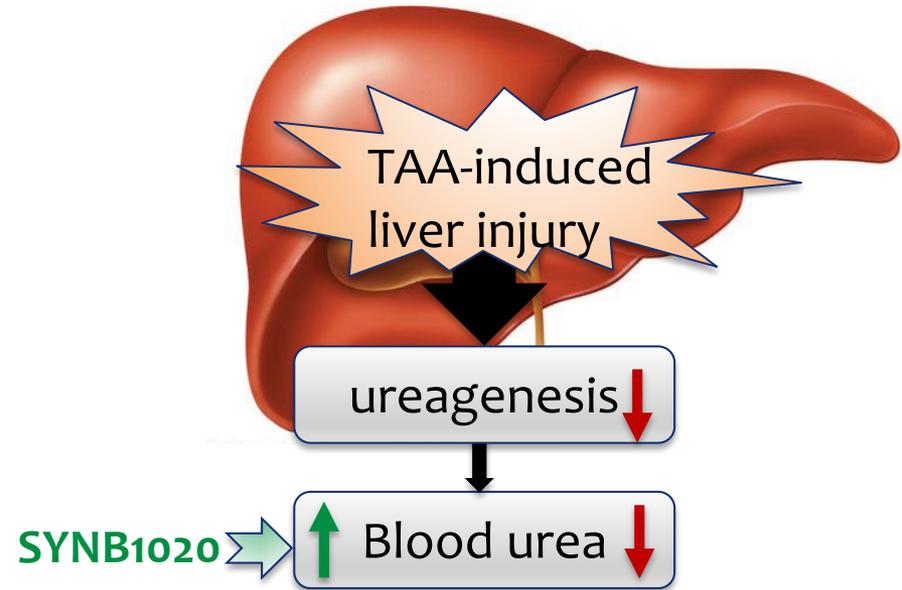


# The effect of SYN1020 on urea blood levels in BALB/c mice Following chronic treatment with TAA



\* $P < 0.05$

TAA

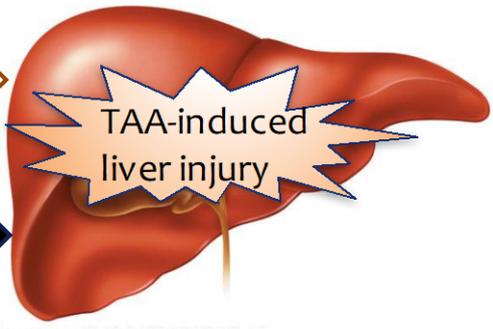
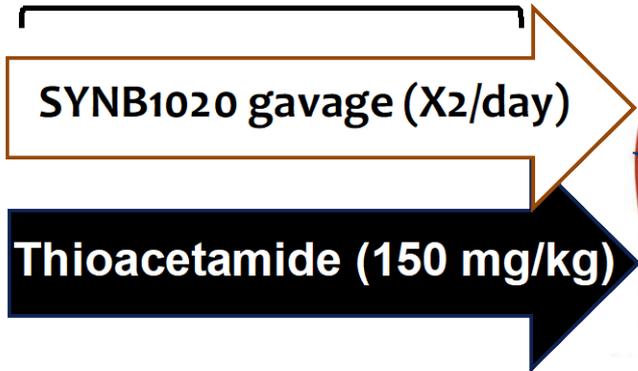


# Does oral administration of SYNB1020 affect the development of TAA-induced liver disease?

BALB/c mice were co-treated with SYNB1020 and TAA for 4 weeks

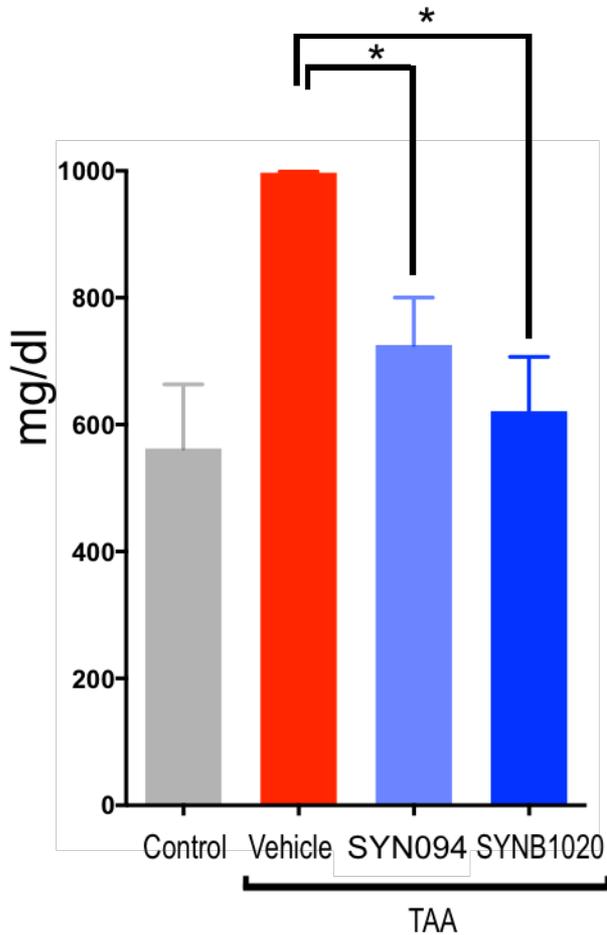


4 week

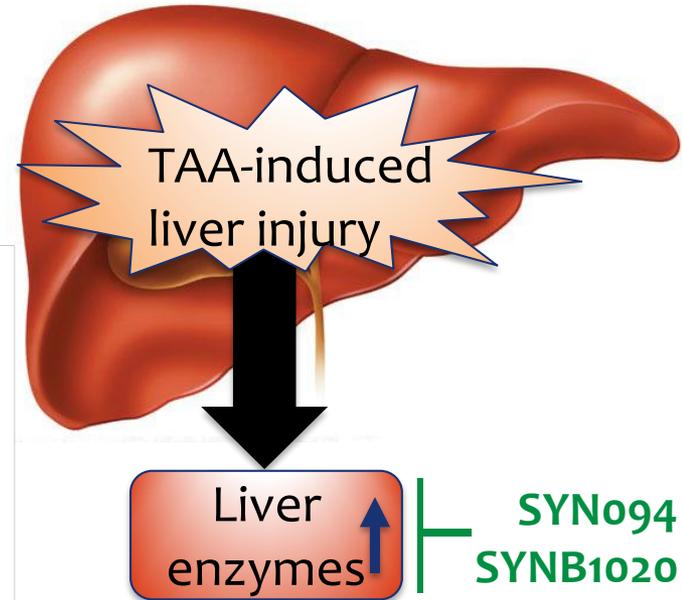
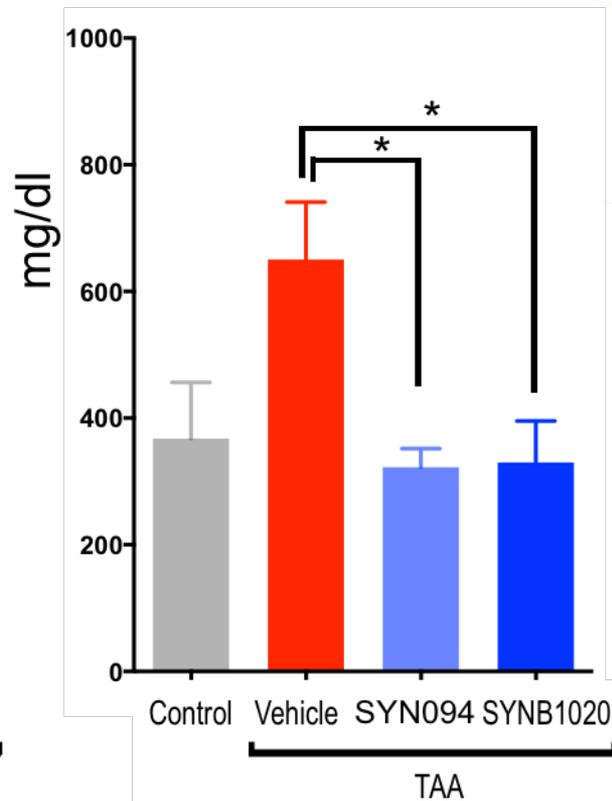


# SYNB1020 and SYN094 **improve** liver enzymes in a TAA-induced liver injury in BALB/c mice

**Liver enzyme: AST**

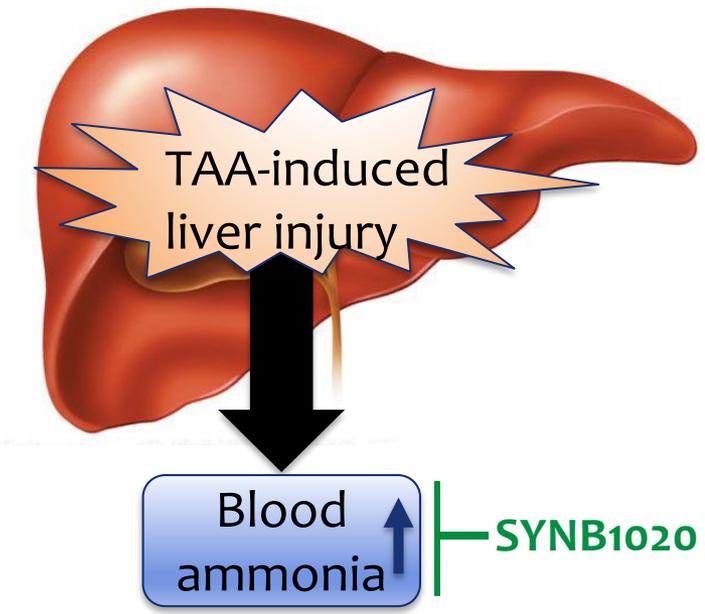
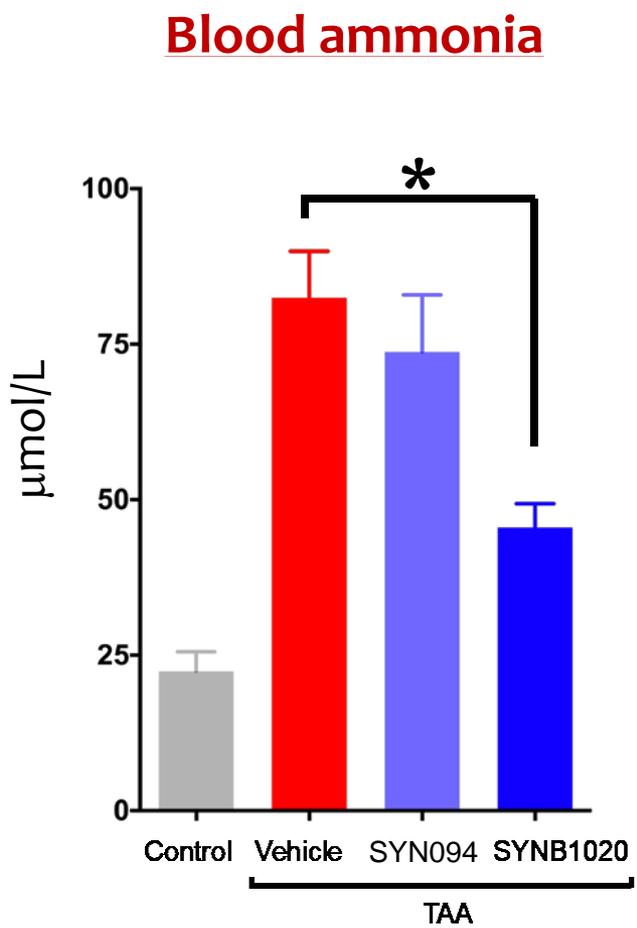


**Liver enzyme: ALT**



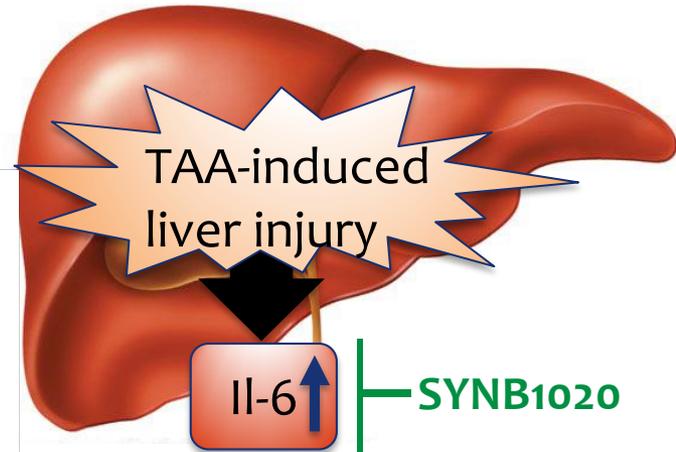
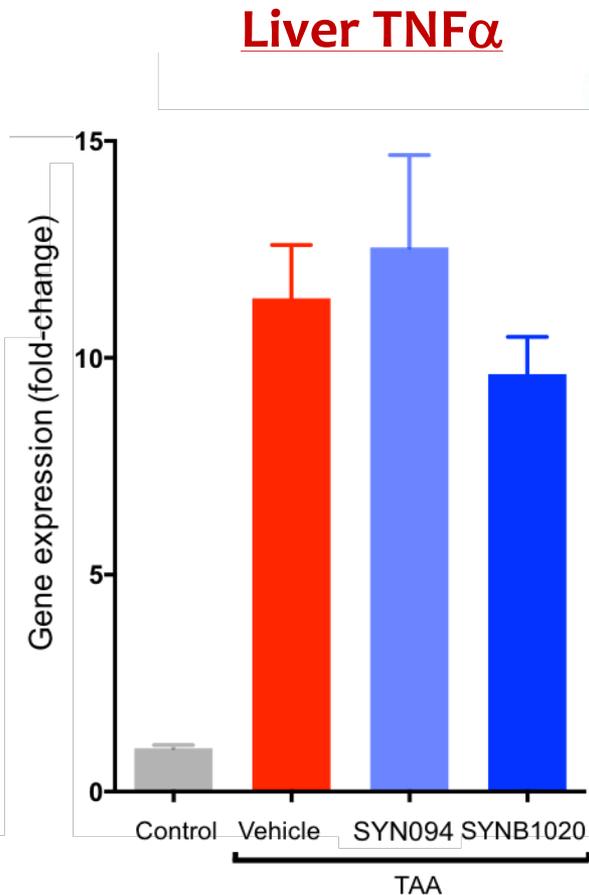
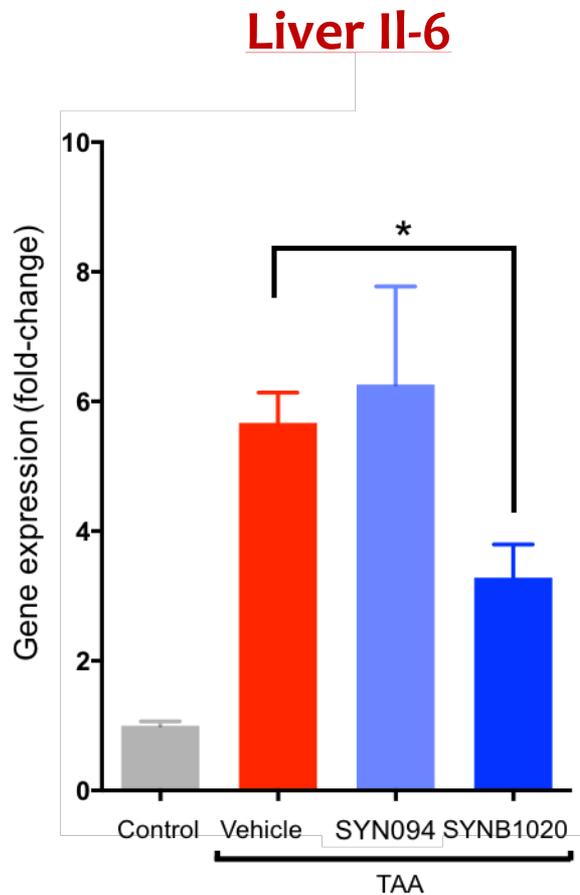
13 \*  $p < 0.05$  (ttest)

# SYNB1020 lowers blood ammonia in a TAA-induced liver injury in BALB/c mice



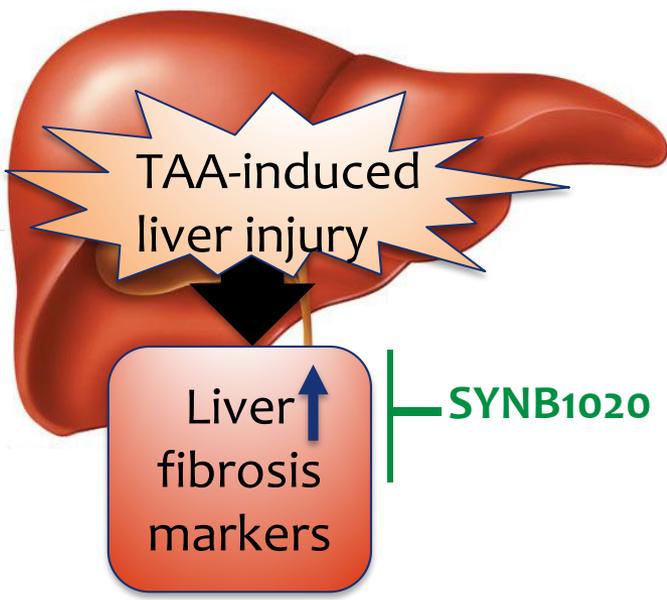
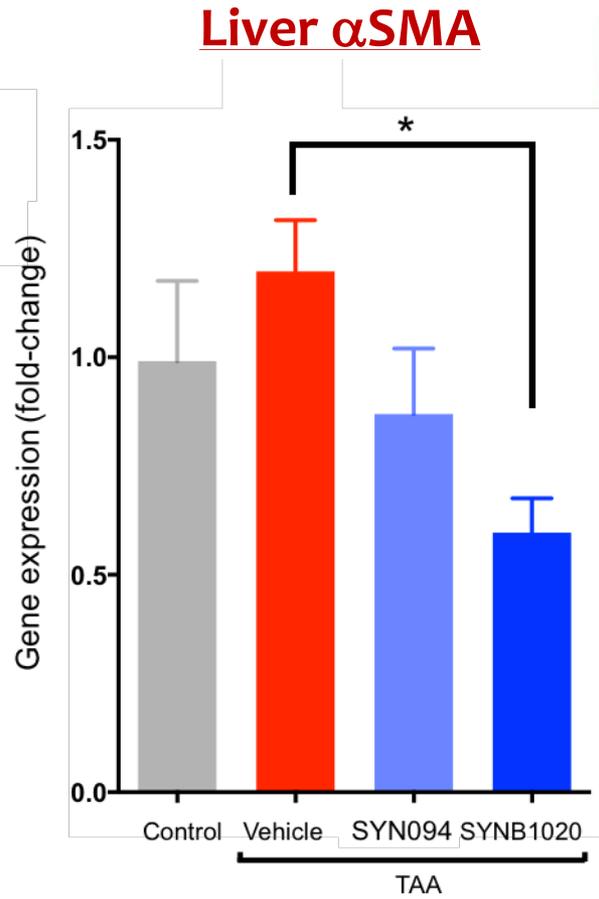
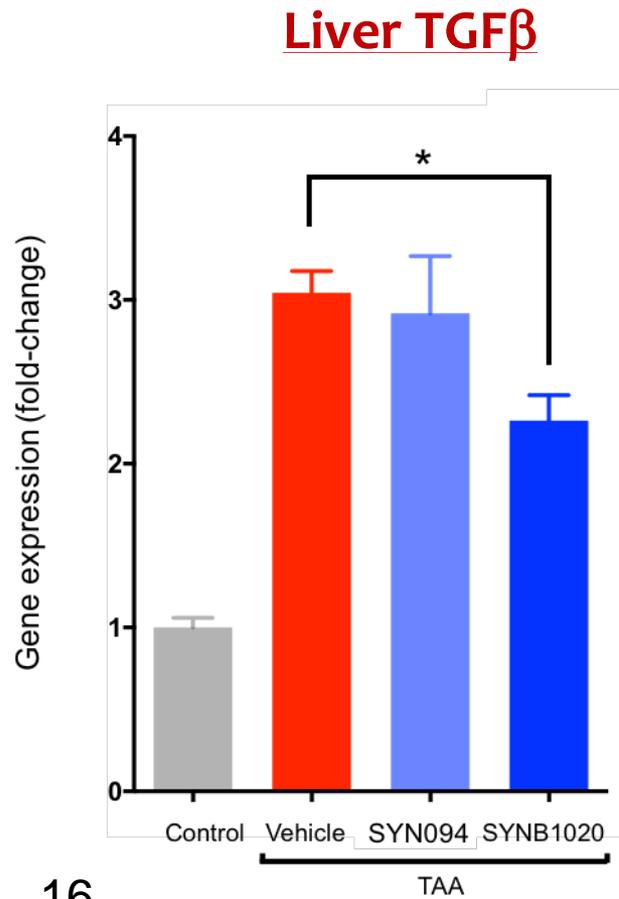
14 \* p < 0.05 (ttest)

# SYNB1020 lowers hepatic inflammatory cytokines expression in TAA-induced liver injury in BALB/c mice



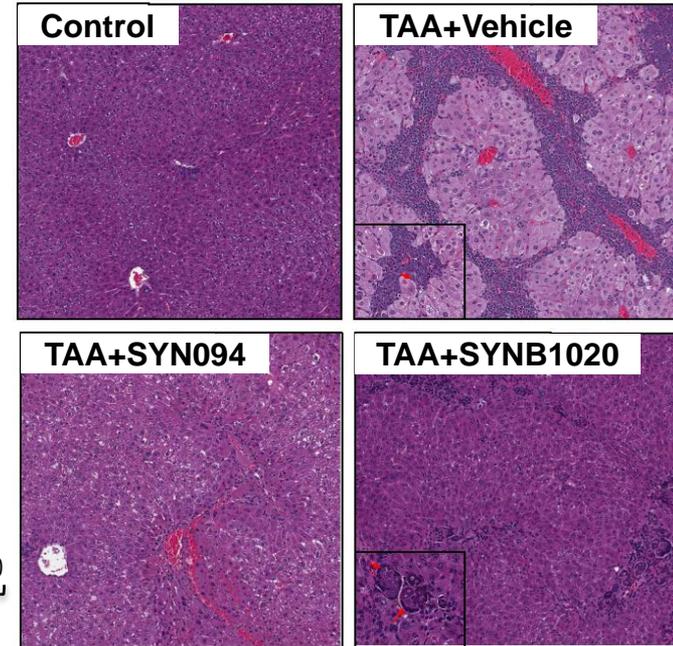
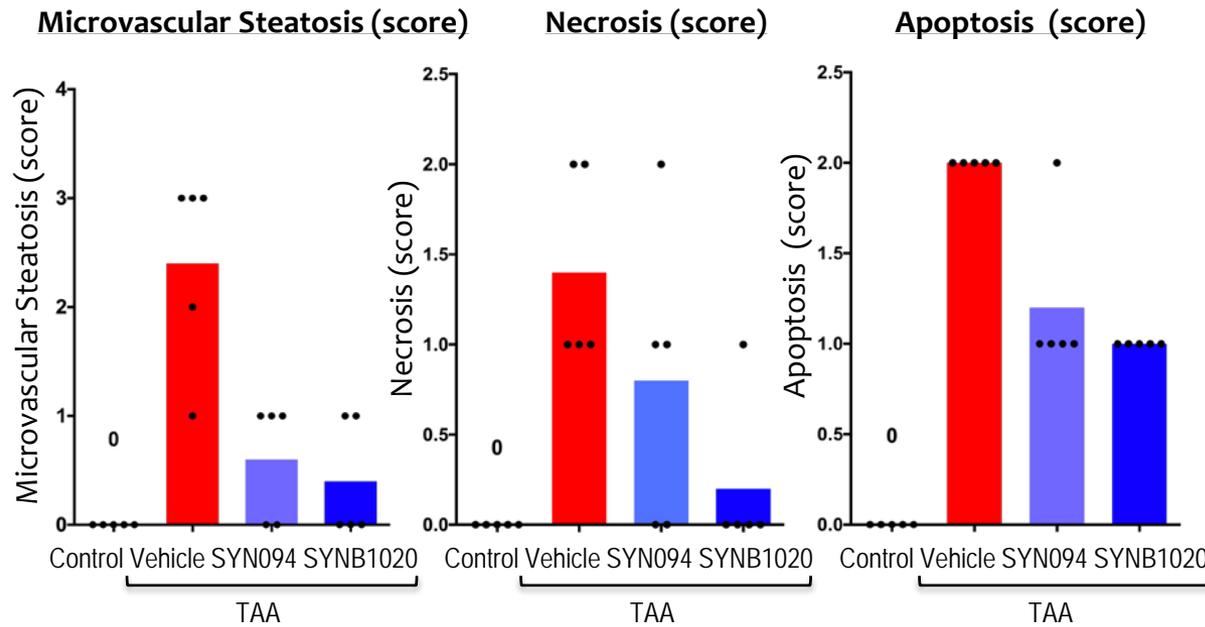
15 \*  $p < 0.05$  (ttest)

# SYNB1020 lowers liver fibrosis markers in TAA-induced liver injury in BALB/c mice



# SYNB1020 lowers liver fibrosis markers in TAA-induced liver injury in BALB/c mice

## H&E staining and scoring



H&E-stained sections were assessed by a pathologist blinded to the treatment groups at the time of scoring

# Summary and Conclusions

- SYN1020 is a modified *E. coli* Nissle that consumes ammonia and produces arginine
- Oral administration of SYN1020 lowers systemic hyperammonemia in a dose dependent manner and elevates blood urea levels in a TAA mouse model of hepatic encephalopathy.
- SYN1020 and the unengineered strain, SYN094, improve survival in a chronic TAA mouse model and reduce gut permeability and gut-inflammation.
- SYN1020 partially ameliorates TAA-induced liver injury as demonstrated by lowering elevated liver enzymes, inflammatory cytokines and markers of fibrosis.
- SYN1020 is currently being evaluated in a phase 1b/2a trial for treatment of hyperammonemia in patients with cirrhosis.

# Acknowledgements

## Thank you!

**Hyperammonemia Team:** Junning Wang, Lauren Renaud, Mylene Perreault,,  
Binh Ha, Denise Wong, Charlie Fox, Eugene Antipov, Vincent Isabella, John  
Thomas, Mike James, Mary Castillo, Caroline Kurtz

