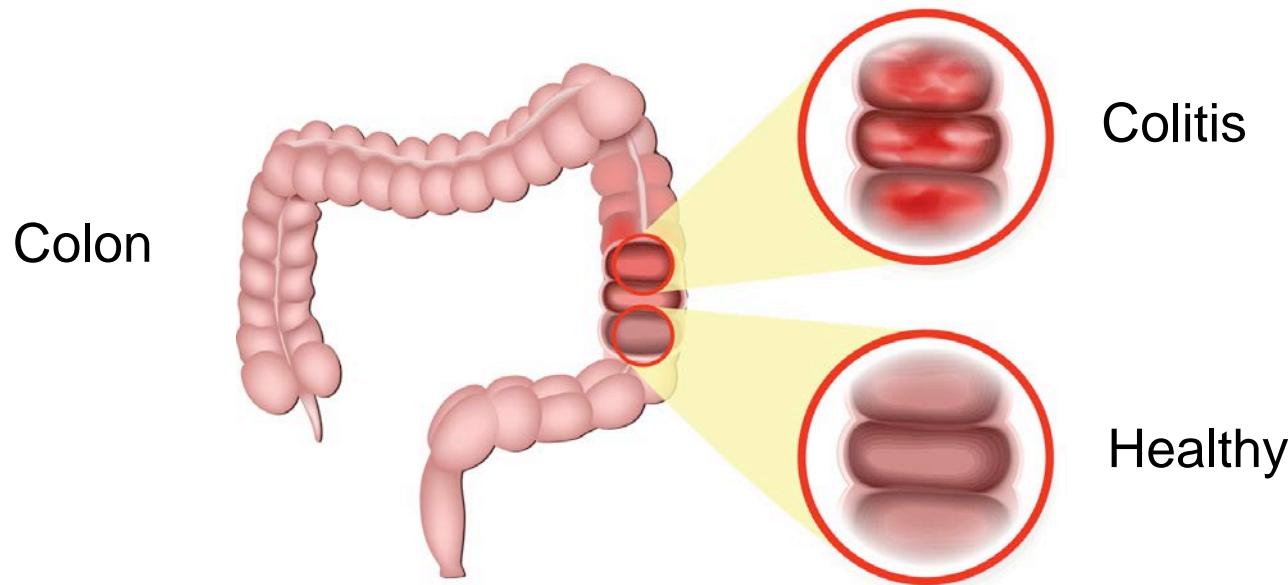


STAR Talks 2016

Mechanism of intestinal inflammation caused by antibiotics



Eric Velazquez
Laboratory of Andreas Bäumler

Factors Driving Gut Inflammation

Introduction

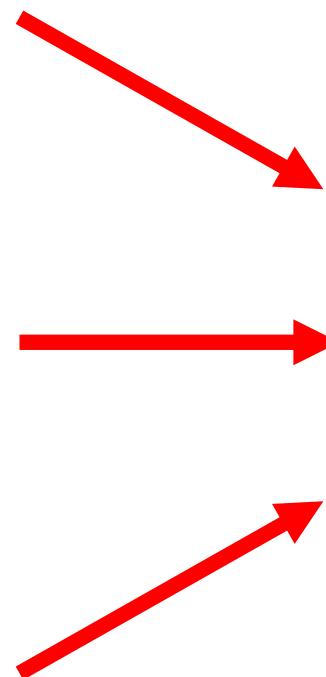
Hypothesis

Material & Methods

Results

Discussion

- Genetic Susceptibility
- Immune System
- Stress
- Surgery
- Food Sensitivity
- Enteric Bacteria



Experimental Colitis in Mice

Introduction

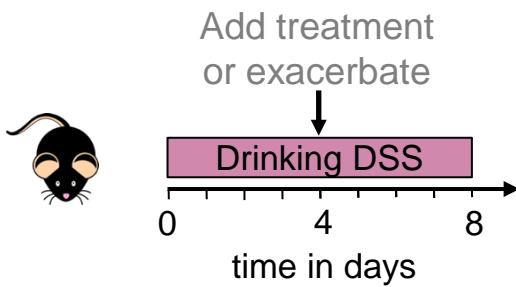
Hypothesis

Material & Methods

Results

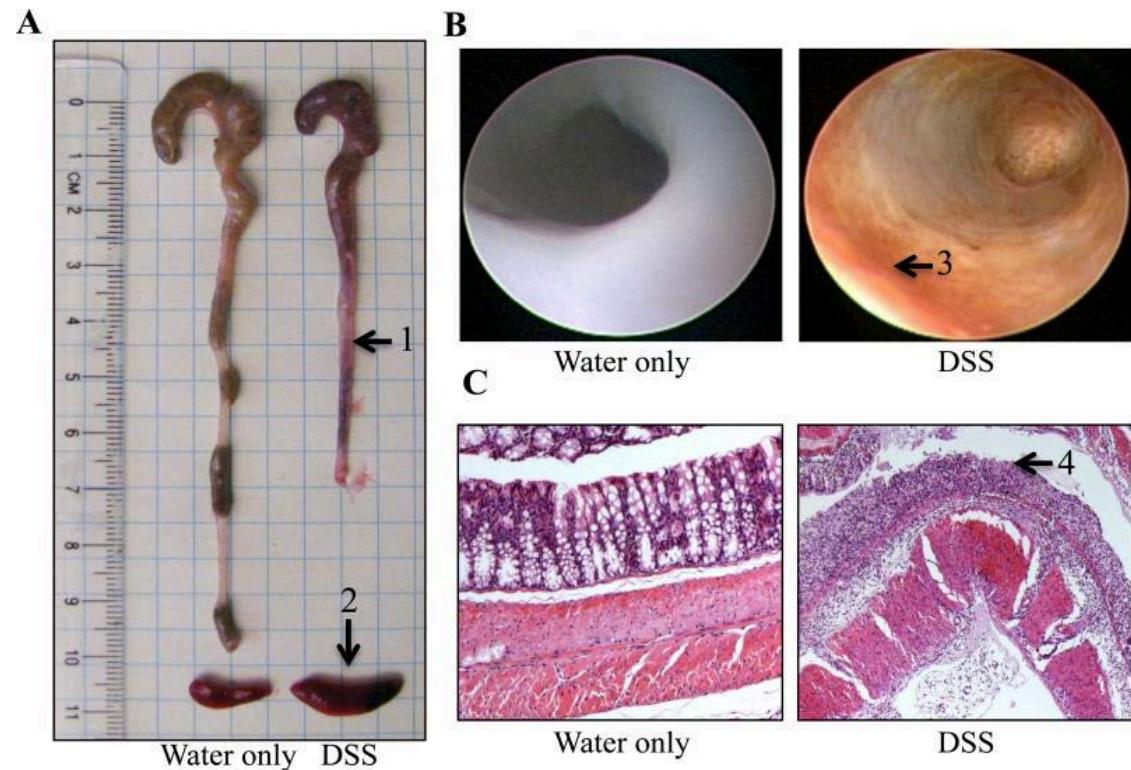
Discussion

Chemically-induced using Dextran Sodium Sulfate (DSS)



Pathophysiology:

- Localized to distal colon
- Direct mucosal damage
- Activation of inflammatory signaling pathways
- Infiltration of immune cells
- Erosion of epithelial layer
- Dissemination of bacteria



Preliminary Findings

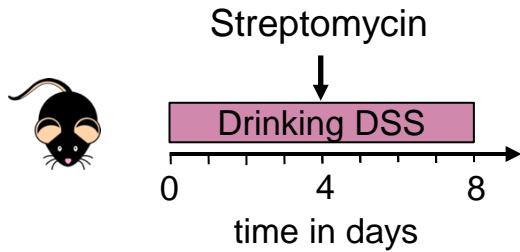
Introduction

Hypothesis

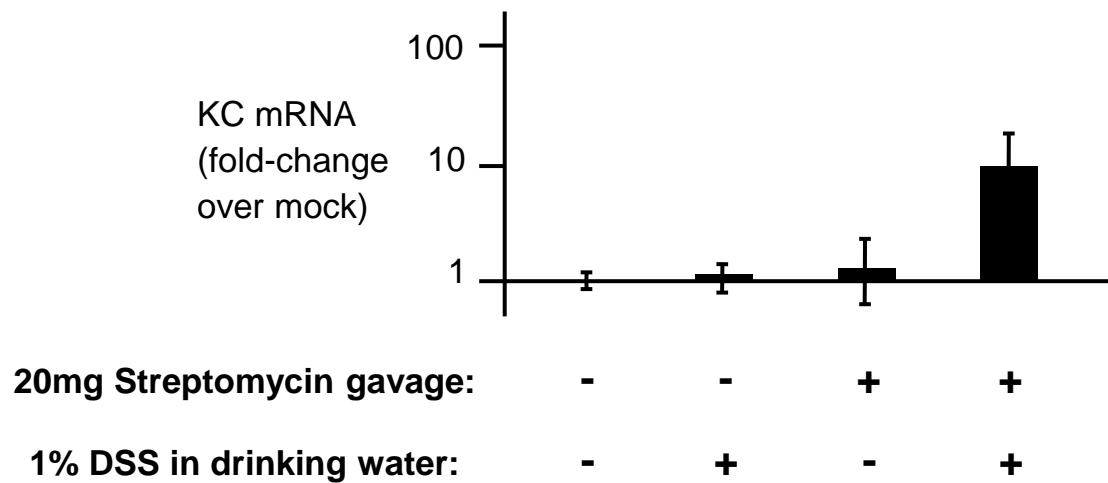
Material & Methods

Results

Discussion



Antibiotics exacerbate
sub-pathological colitis



Possible Mechanisms

Introduction

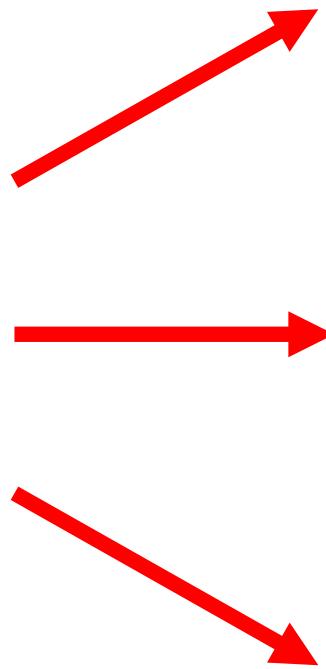
Hypothesis

Material & Methods

Results

Discussion

- How streptomycin worsens DSS?



- Direct toxicity to epithelial cells.
- Bacteria normally degrade DSS.
- Expansion of pro-inflammatory microbes.
- Loss of anti-inflammatory microbes.

Proposed Mechanism

Introduction

Hypothesis

Material & Methods

Results

Discussion

Antibiotics make the bowel more irritable by depleting anti-inflammatory signals from bacteria that help maintain immune homeostasis.

Experimental Model

Introduction

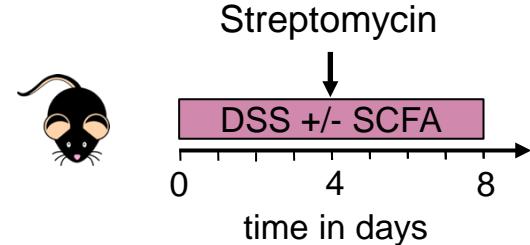
Hypothesis

Material & Methods

Results

Discussion

- DSS mouse model
 - 1% is sub-pathological
 - 20mg streptomycin worsens
- Short-chain fatty acid (SCFA) supplementation
 - 150mM in drinking water



SCFA Supplementation

Introduction

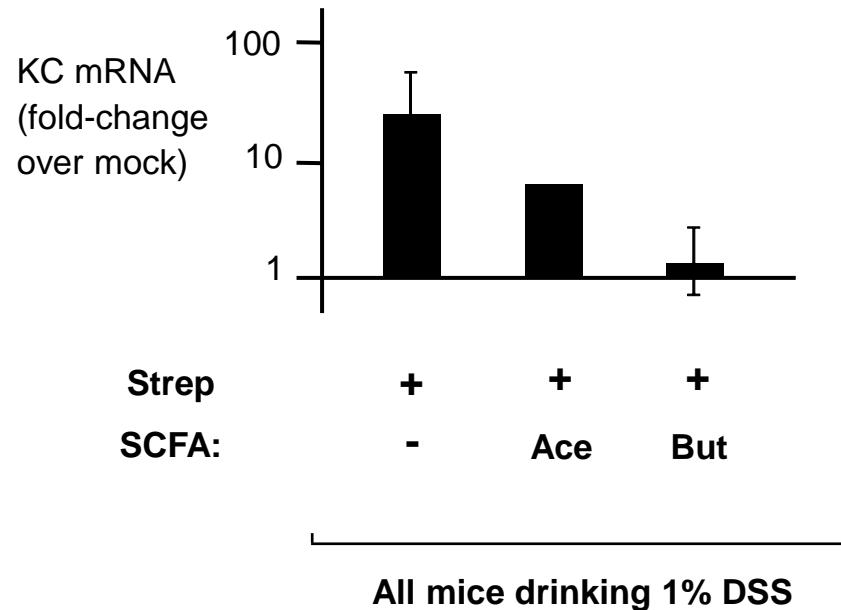
Hypothesis

Material & Methods

Results

Discussion

Microbial metabolites lower
pro-inflammatory activity



Multiple Targets of SCFAs

Introduction

Hypothesis

Material & Methods

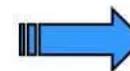
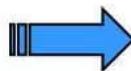
Results

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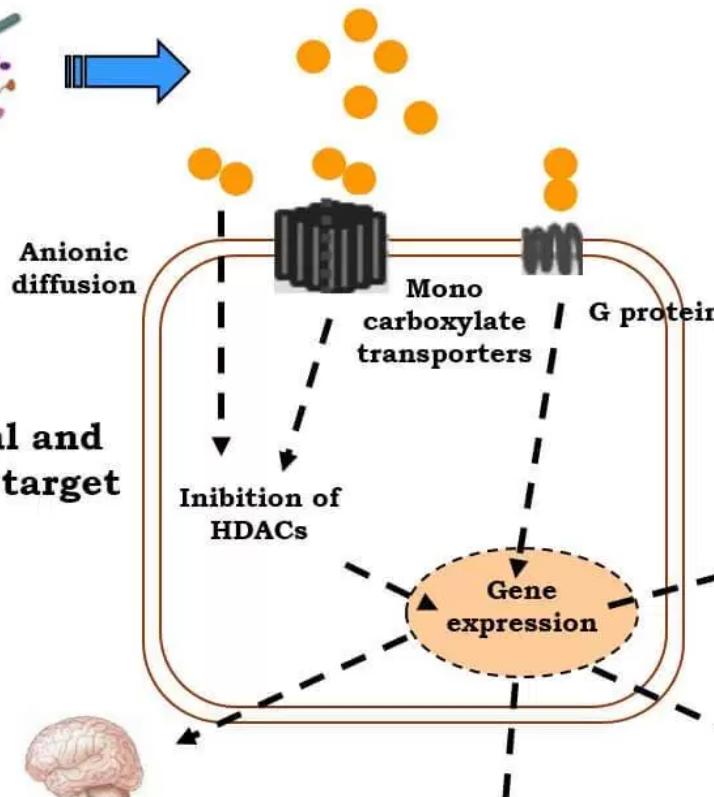
Dietary fibers

Microbiota

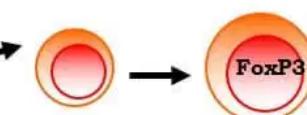
SCFAs



Epithelial and immune target cells



Promotion of Treg cells, tolerance



Regulation of enteric nervous system and behaviour through gut-brain axis

Stimulation of mucous production

Stimulation of cell growth and differentiation

Chemokines

Cytokines

Anti-inflammatory effects/Inhibition of NF- κ B

Antimicrobial peptides

Treg depletion

Introduction

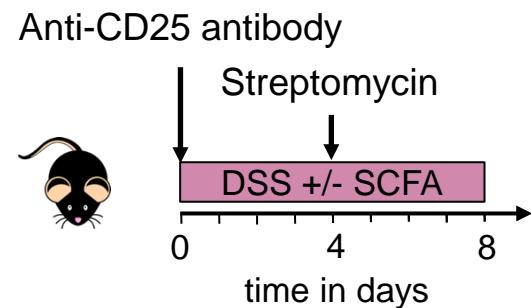
Hypothesis

Material & Methods

Results

Discussion

- DSS mouse model
 - 1% is sub-pathological
 - 20mg streptomycin worsens
- Short-chain fatty acid (SCFA) supplementation
- Regulatory T-cell depletion
 - Anti-CD25 antibody



SCFA Supplementation

Introduction

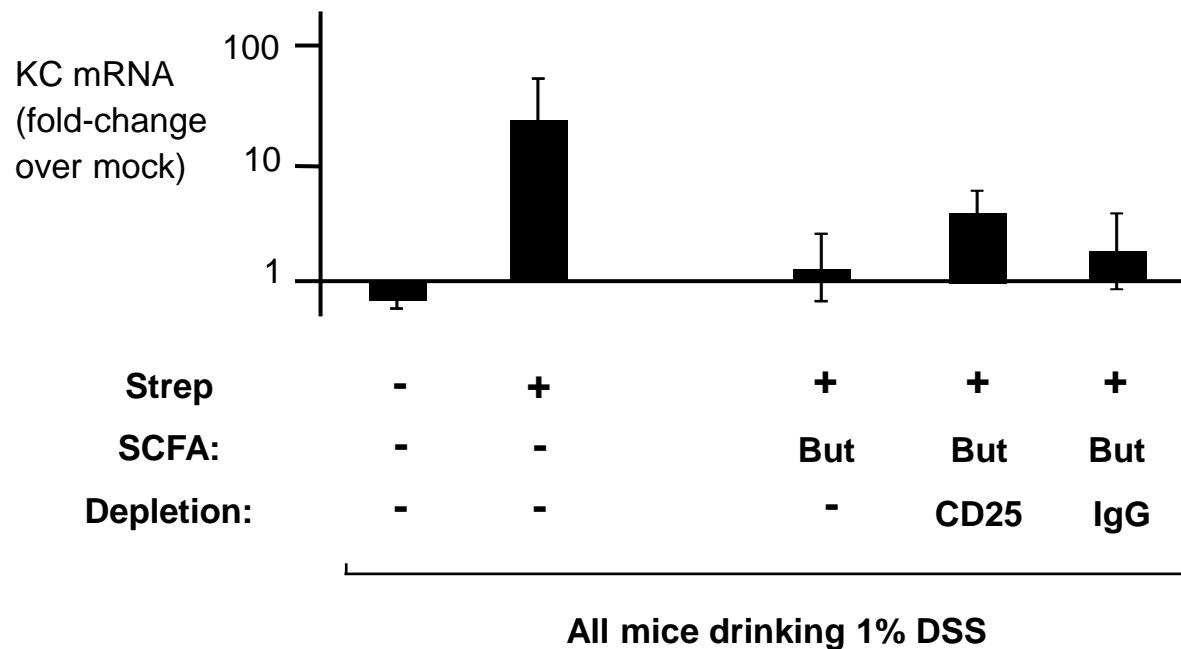
Hypothesis

Material & Methods

Results

Discussion

Butyrate may exert some protective effect via T-reg



Multiple-Hits Model

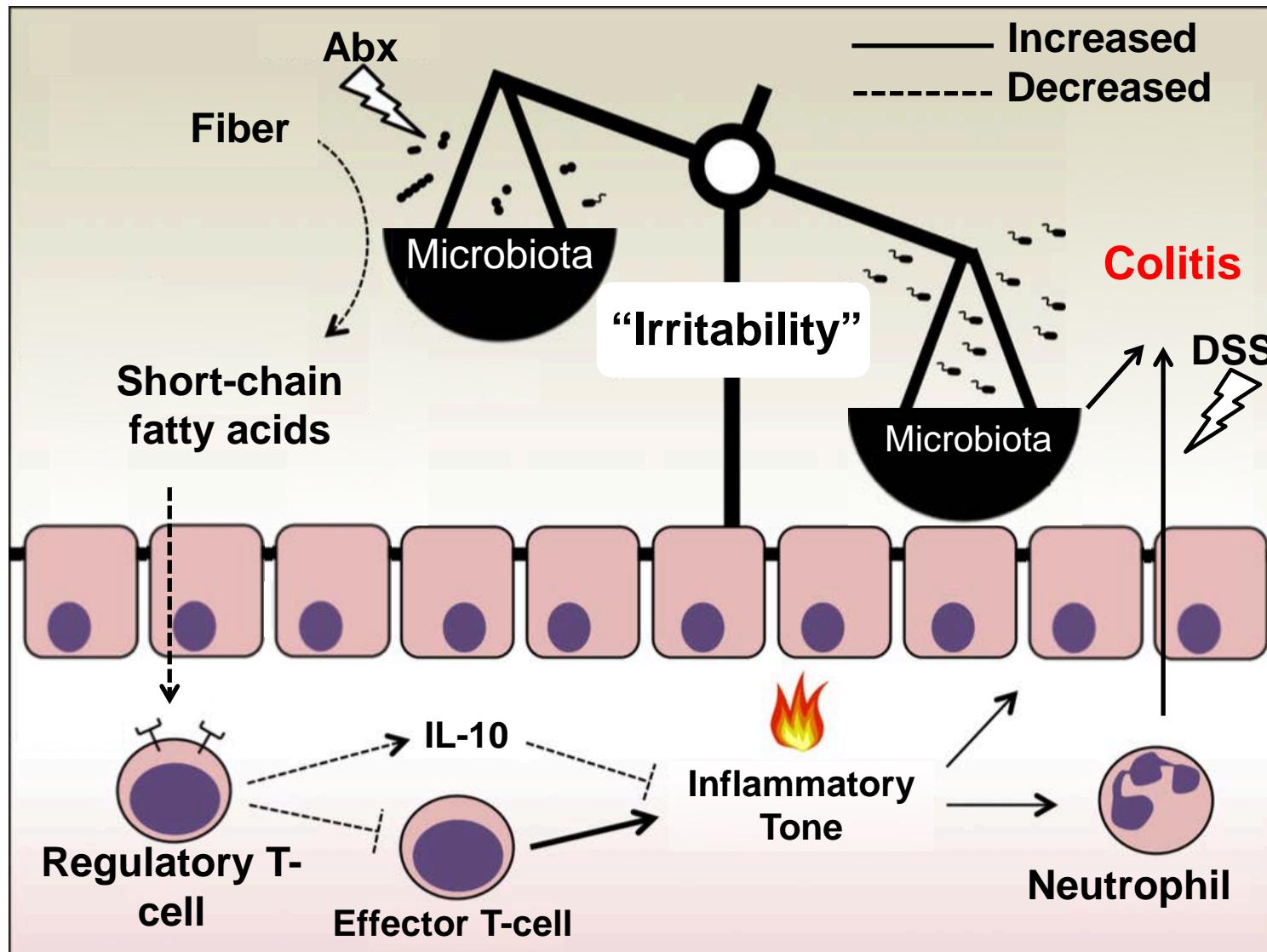
Introduction

Hypothesis

Material & Methods

Results

Discussion



Acknowledgements

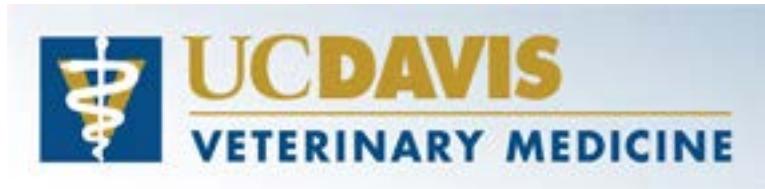
Introduction

Hypothesis

Material & Methods

Results

Discussion



- STAR 2016 Funding
- Baumler & Tsolis Labs
- Everyone in this room!