

# UhpC is the Chlamydial Environmental Senses of Glucose Availability

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# C. Trachomatis Disease Burden

The **STATE**  
of **STDs**  
in the United States



in 2017



**1.7 million**  
**CASES OF CHLAMYDIA**

22% increase since 2013



**62,876**  
**IN NORTH CAROLINA**

#7 by infections per 100,000 people

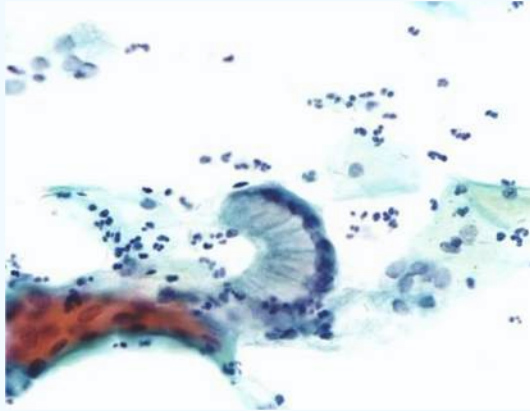
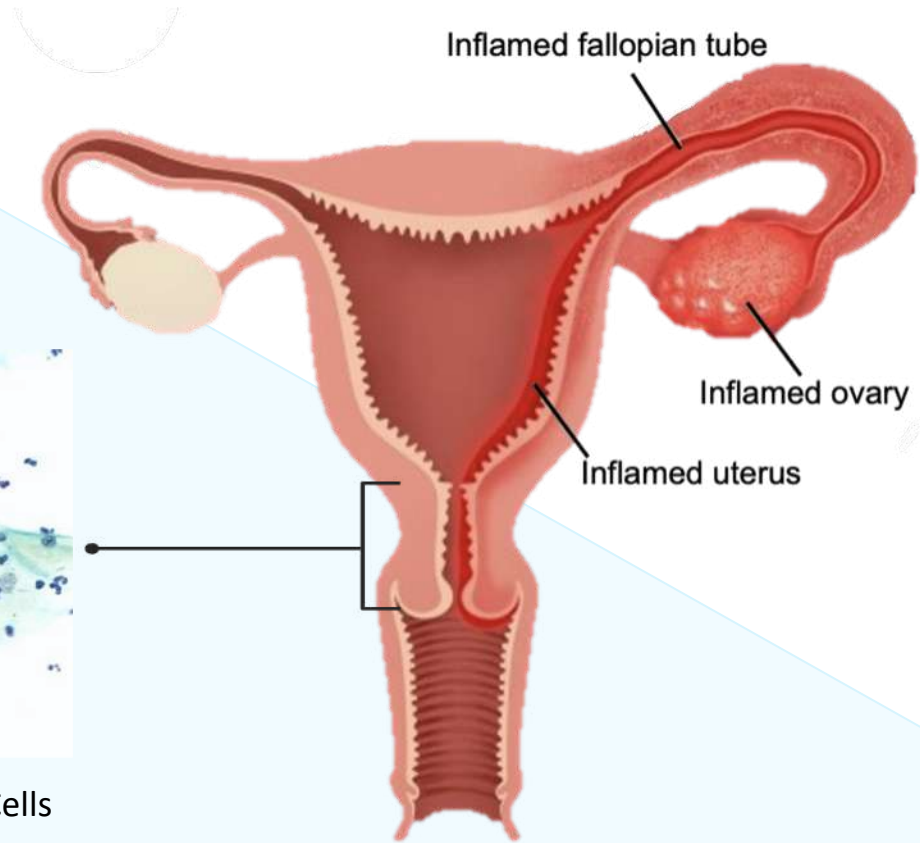


**About 2/3**  
**OCCUR IN WOMEN**

Most prevalent in women ages 15-29

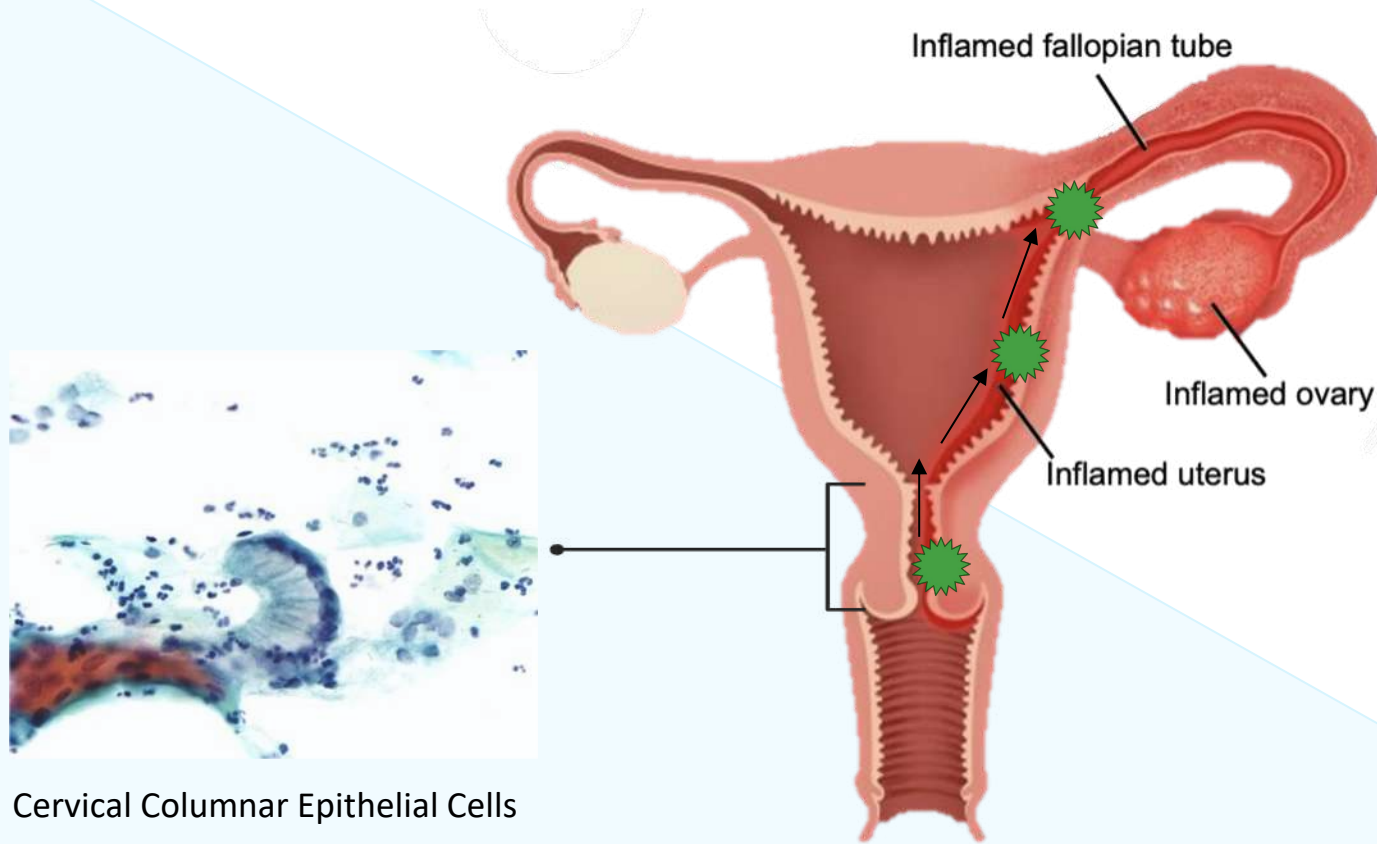
LEARN MORE AT: [www.cdc.gov/std/](http://www.cdc.gov/std/)

# Long-term Sequelae in Women

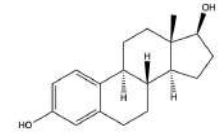
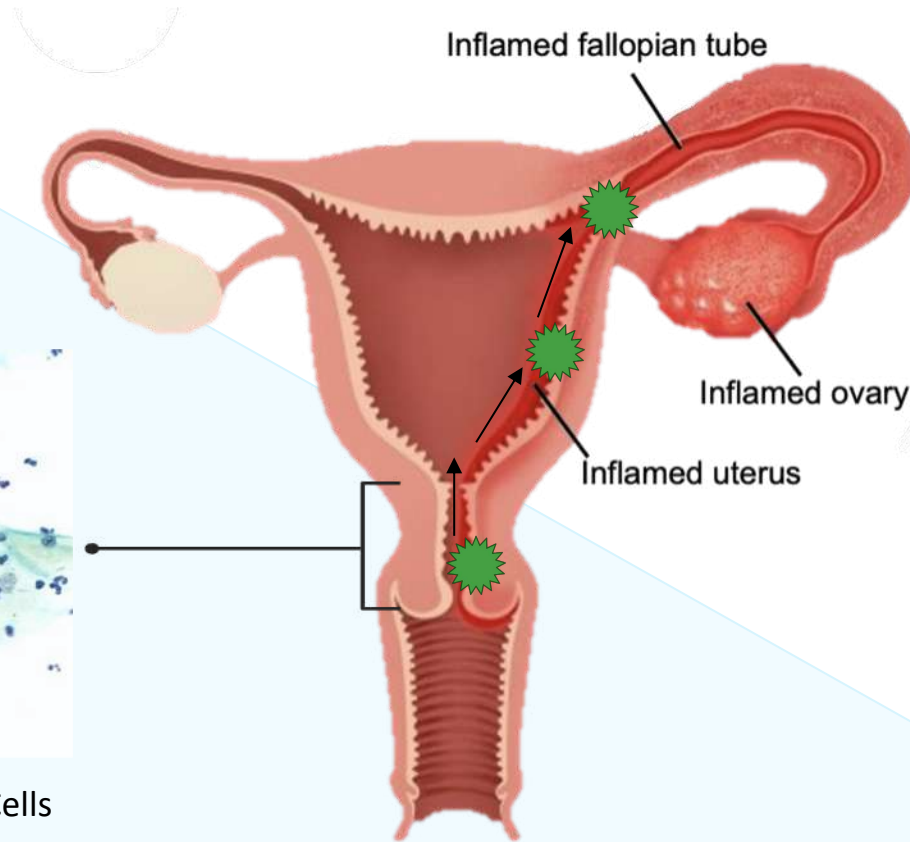


Cervical Columnar Epithelial Cells

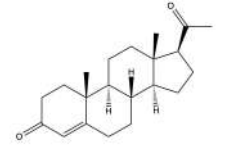
# Long-term Sequelae in Women



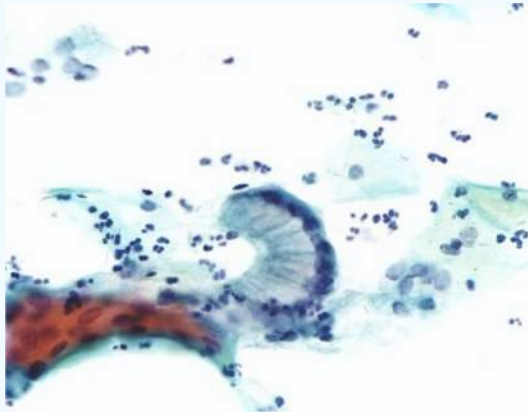
# Long-term Sequelae in Women



Estrogen

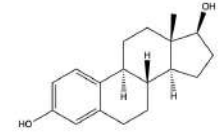
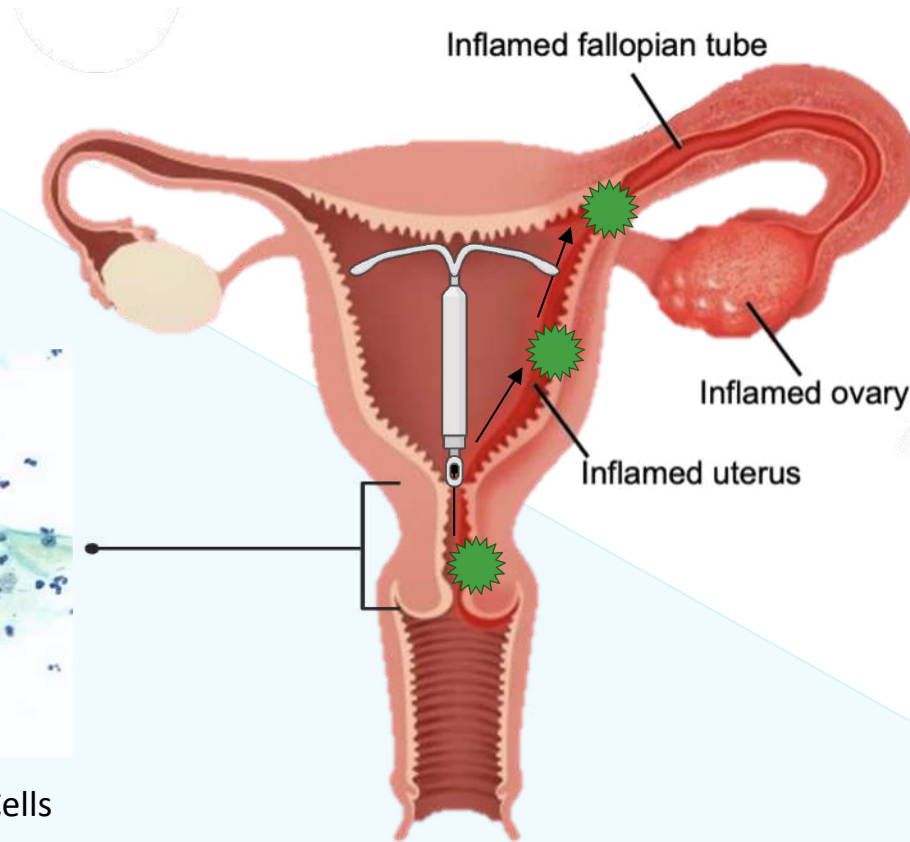


Progesterone

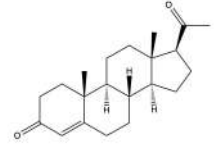


Cervical Columnar Epithelial Cells

# Long-term Sequelae in Women



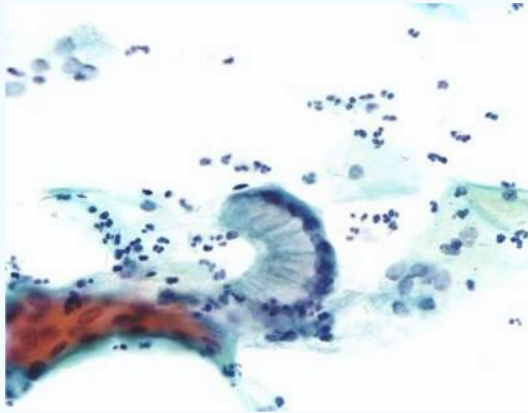
Estrogen



Progesterone



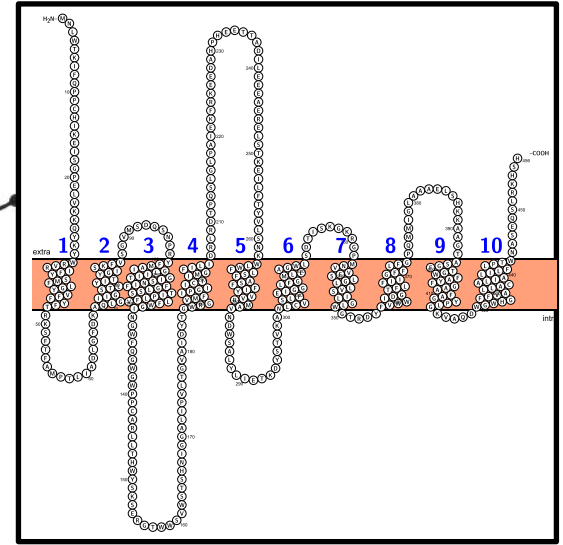
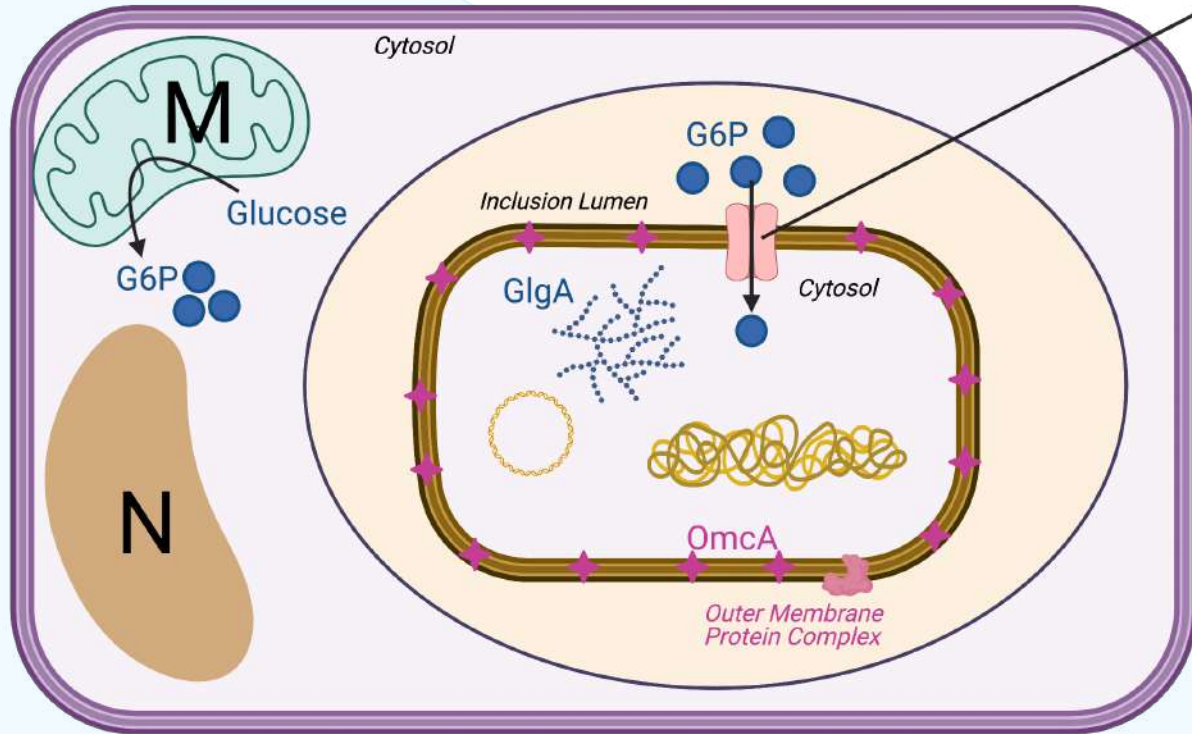
Oral Contraceptives



Cervical Columnar Epithelial Cells

# Glycogen Metabolism in *C. trachomatis*

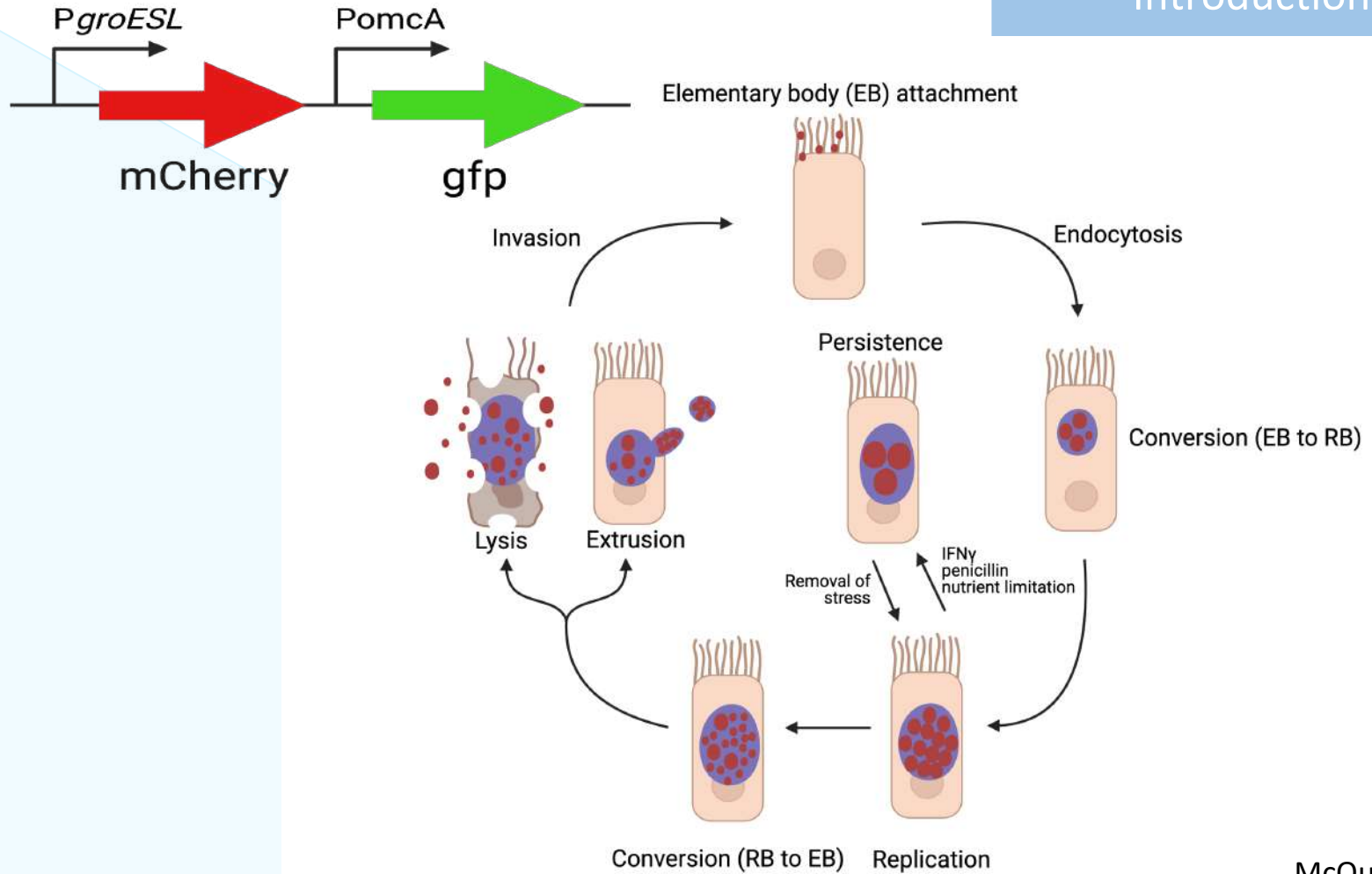
## Introduction

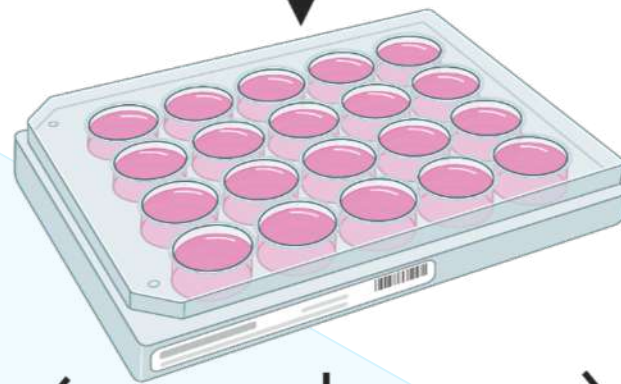
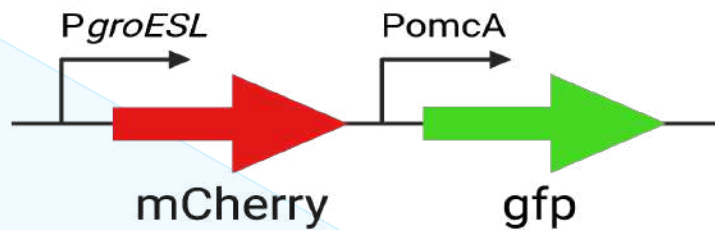


UhpC

Hypothesis: *C. trachomatis*  
responds to glucose-limitation by  
down-regulating transcription of  
virulence genes.





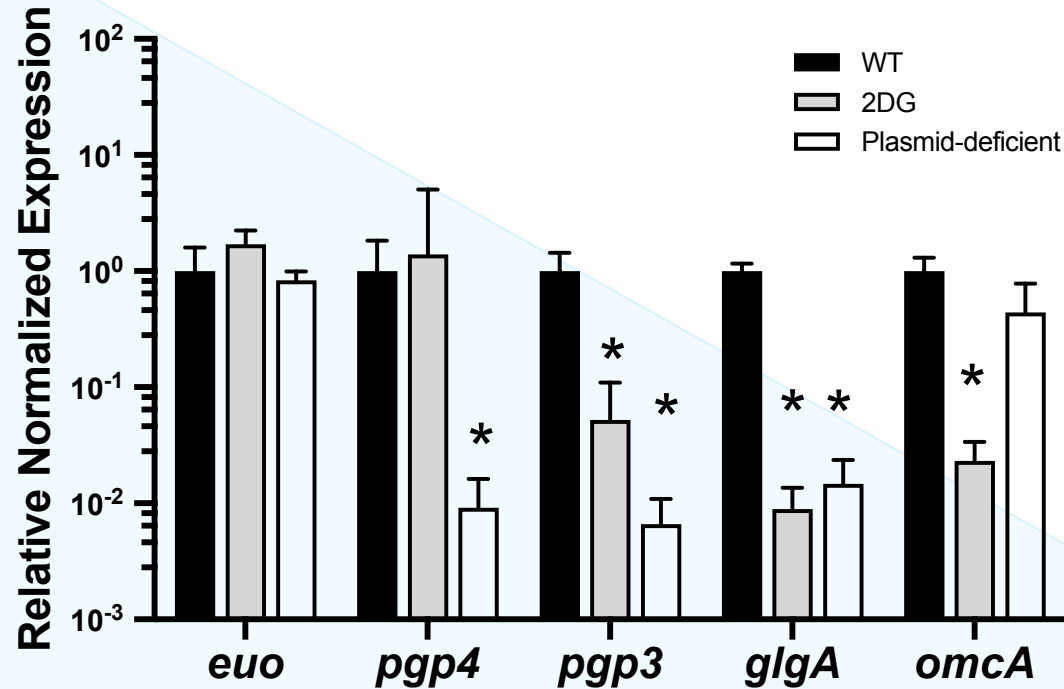


Glycogen Staining

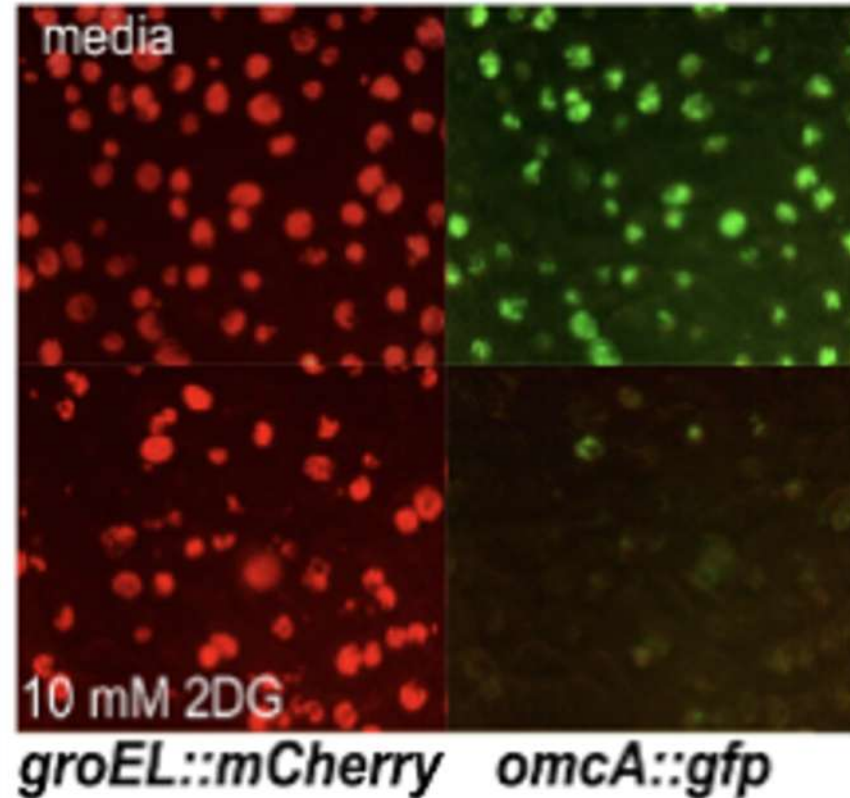
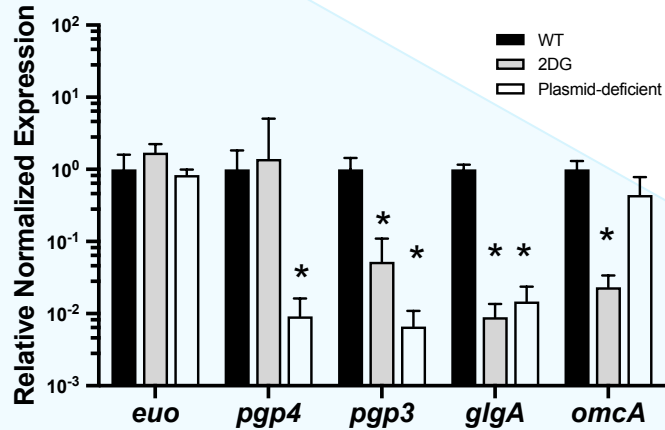
RNA/DNA  
Extraction and  
qPCR

Infection  
Forming  
Units Assay

# *omcA* is down-regulated by 2DG inhibition of cellular G6P synthesis

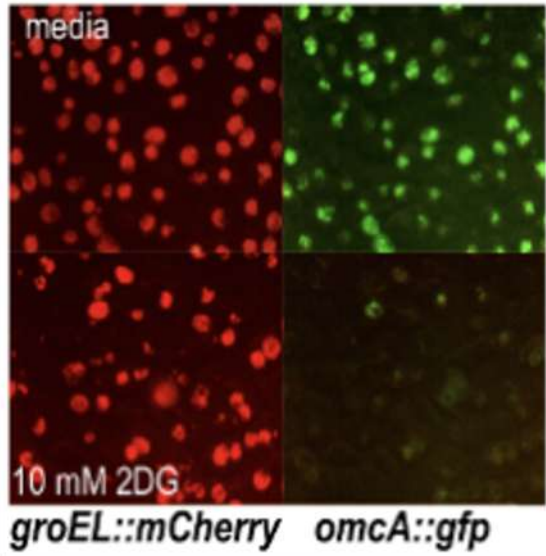


# *omcA* is down-regulated by 2DG inhibition of cellular G6P synthesis

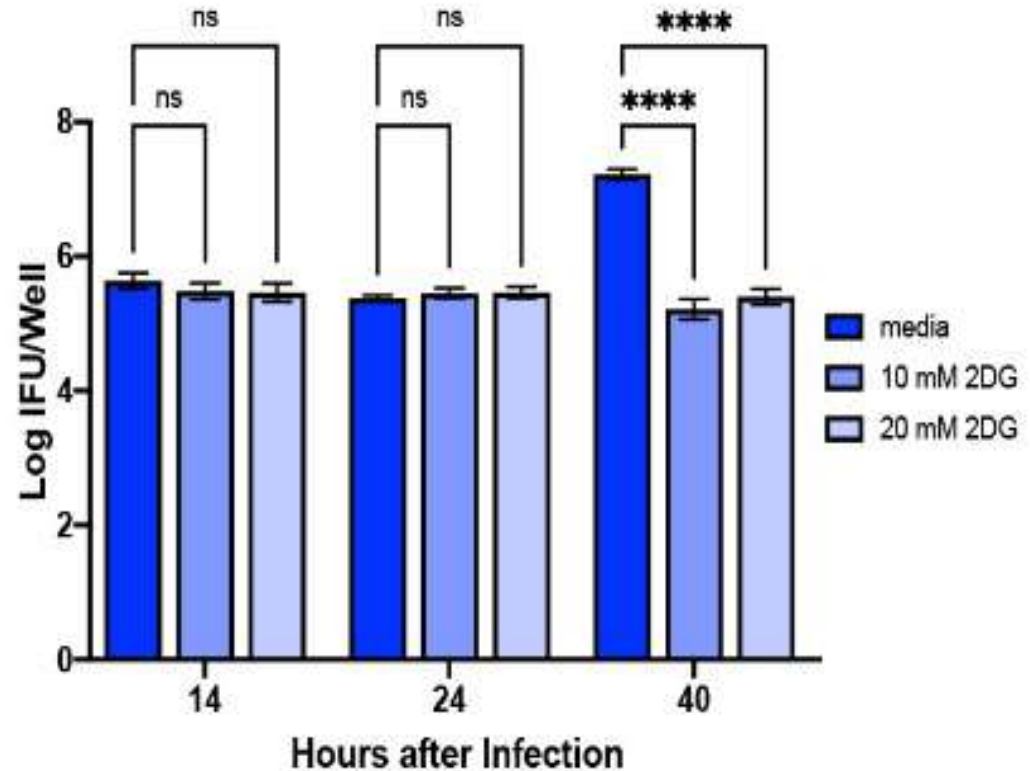


*C. trachomatis*

When *omcA* is down-regulated by 2DG  
inhibition of cellular G6P synthesis- fewer  
infectious progeny



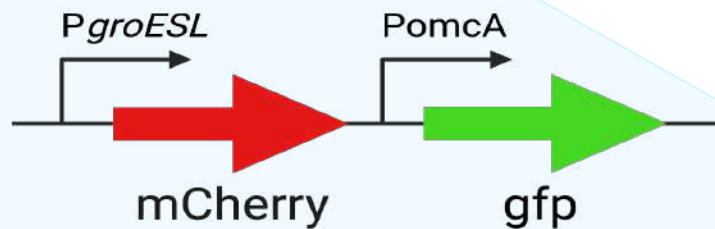
*C. trachomatis*



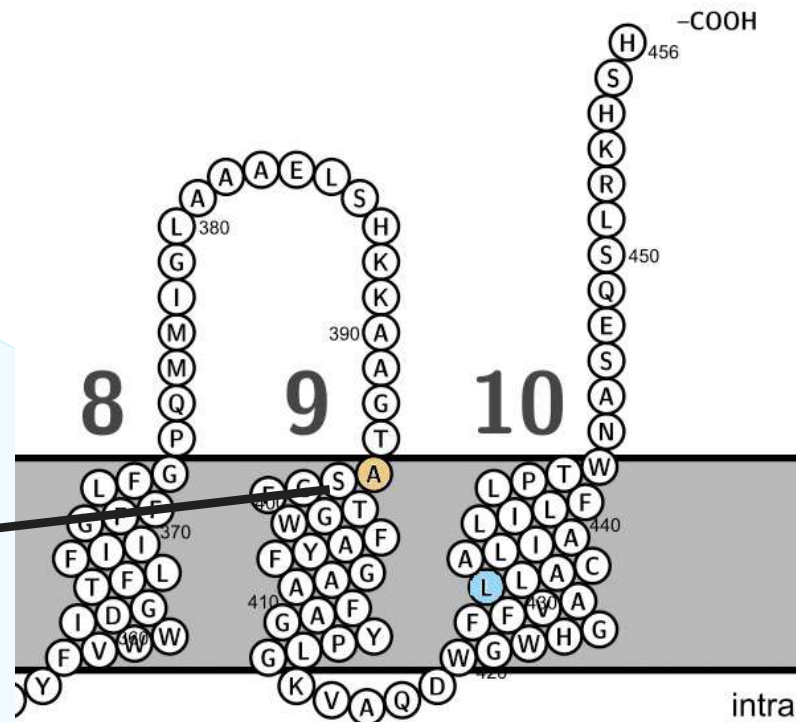
How do chlamydiae “know” when  
G6P levels have dropped?

Could the UhpC transporter also serve as the chlamydial sensor of glucose availability?

# *C. trachomatis* M2-C6 has a point mutation in *uhpC*

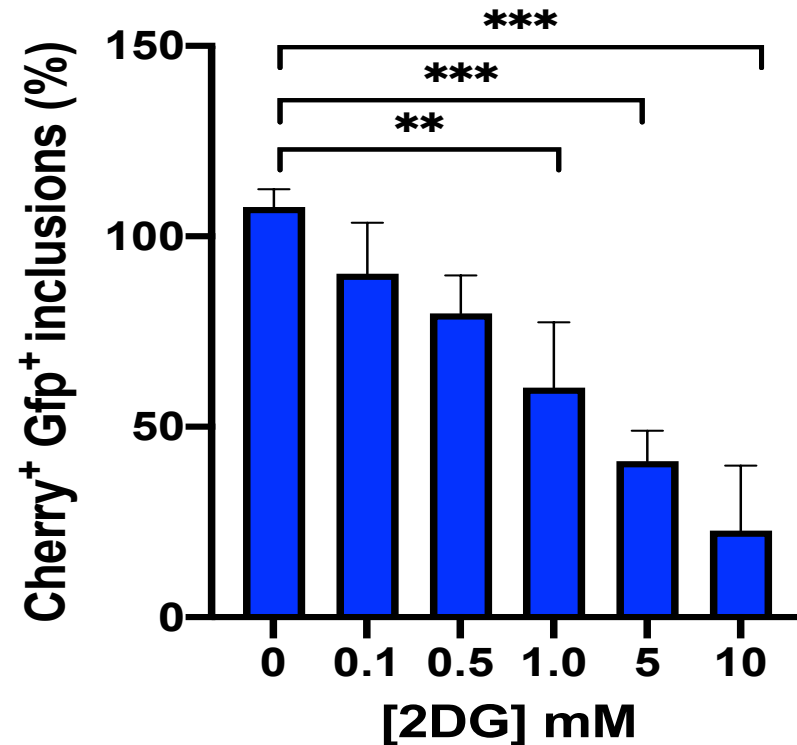
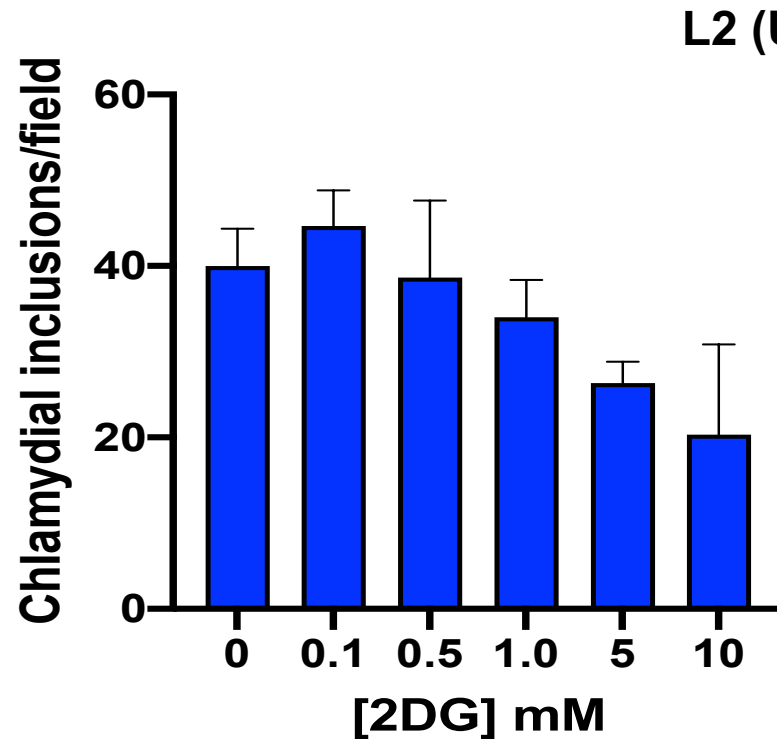


*C. trachomatis*  
M2-C6 (A394T)



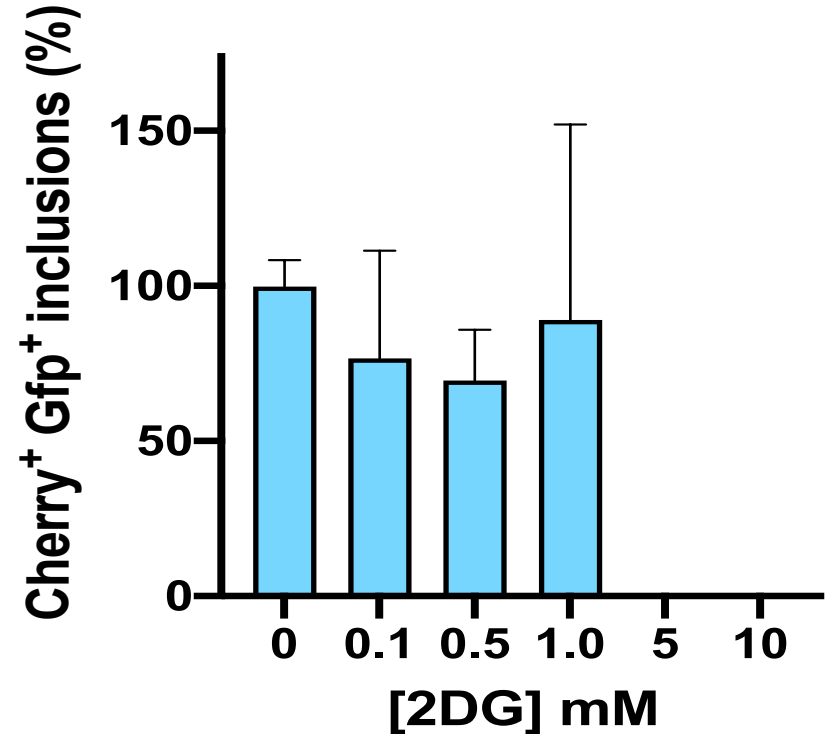
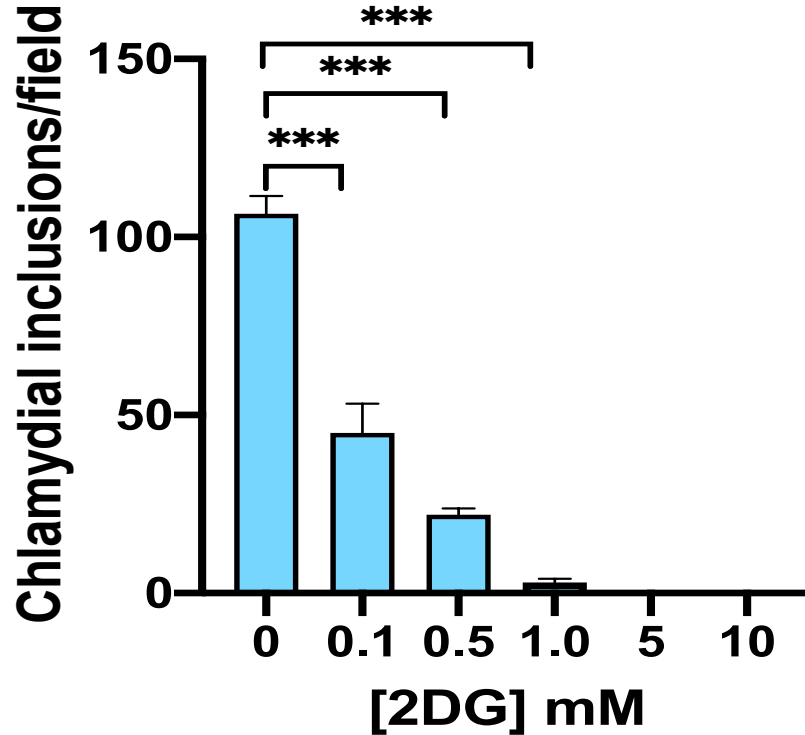


# M2C6 *pomcA::gfp* is Sensitive to Sub-Inhibitory 2DG Concentrations

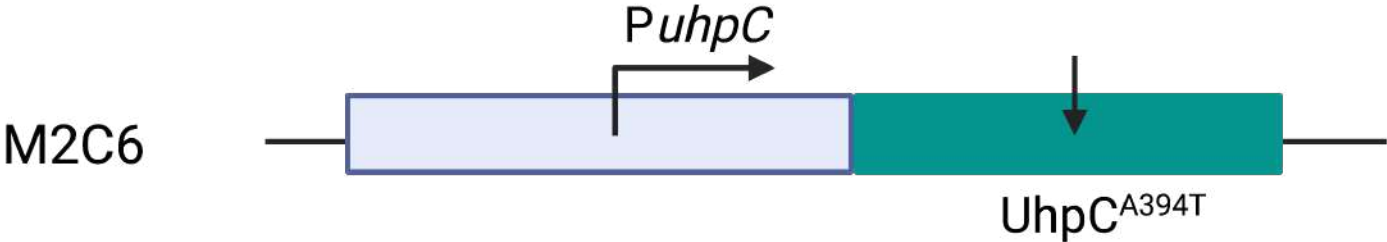


# M2C6 *pompA::gfp* is Sensitive to Sub-Inhibitory 2DG Concentrations

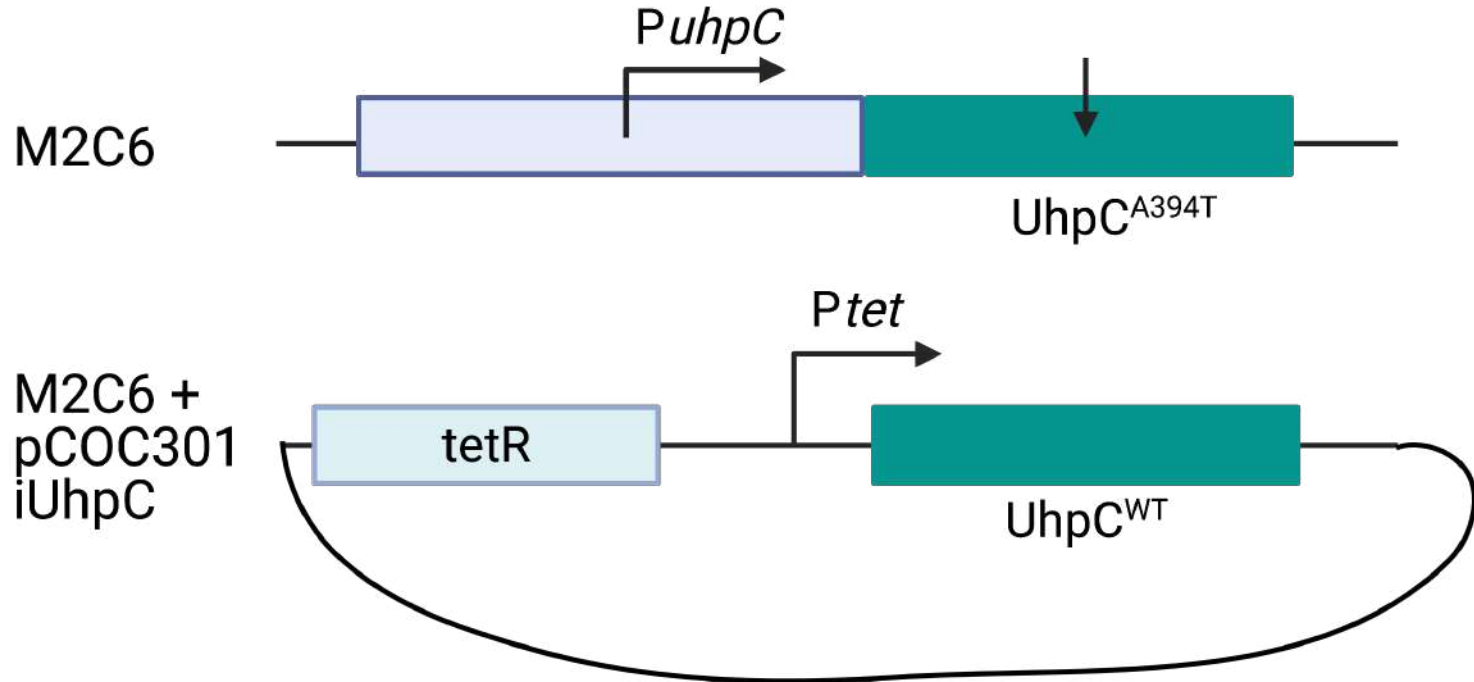
M2-C6 (UhpC<sup>A394T</sup>)



# Complementation Experiment:

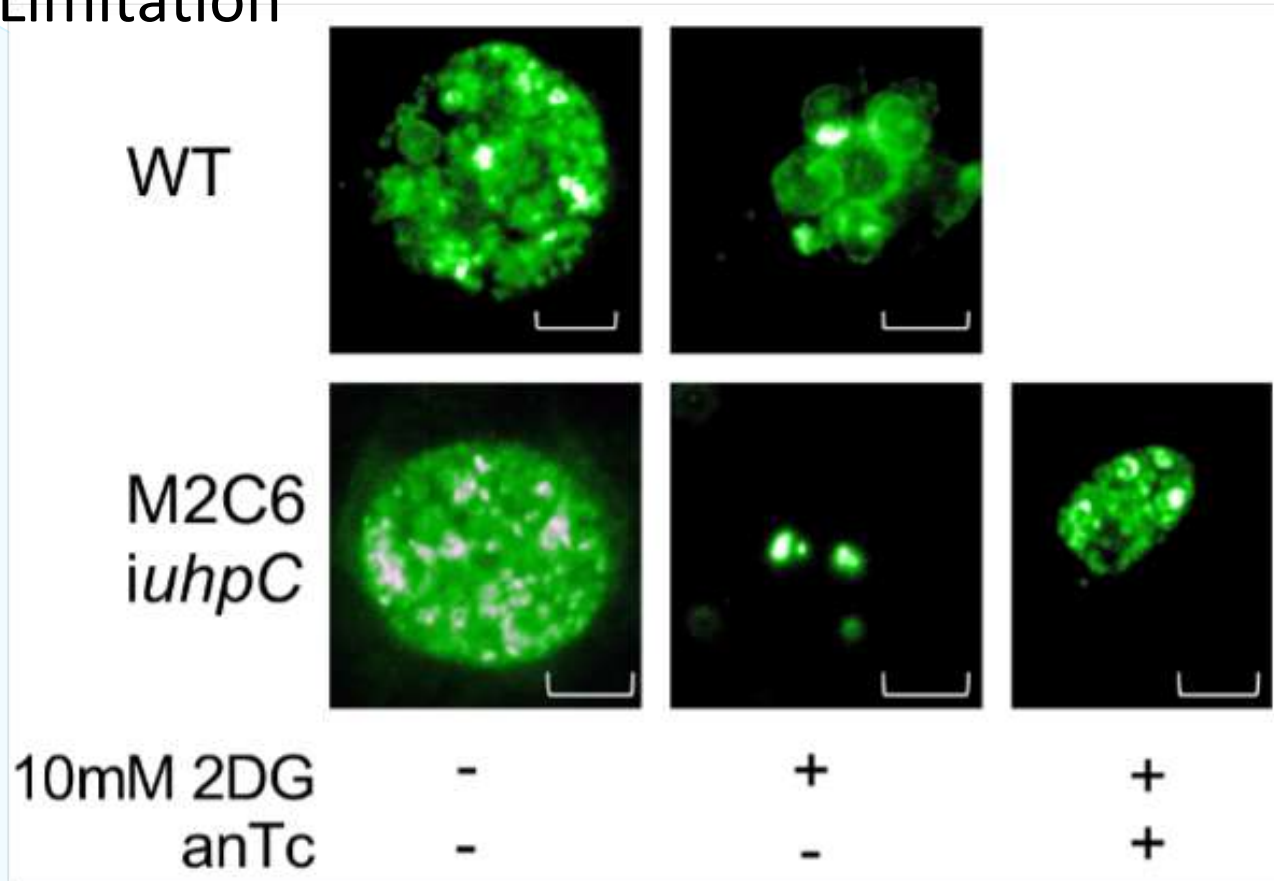


# Complementation Experiment:



Inducible TetR Promoter System

# Complementation Restores Sensitivity to Glucose Limitation

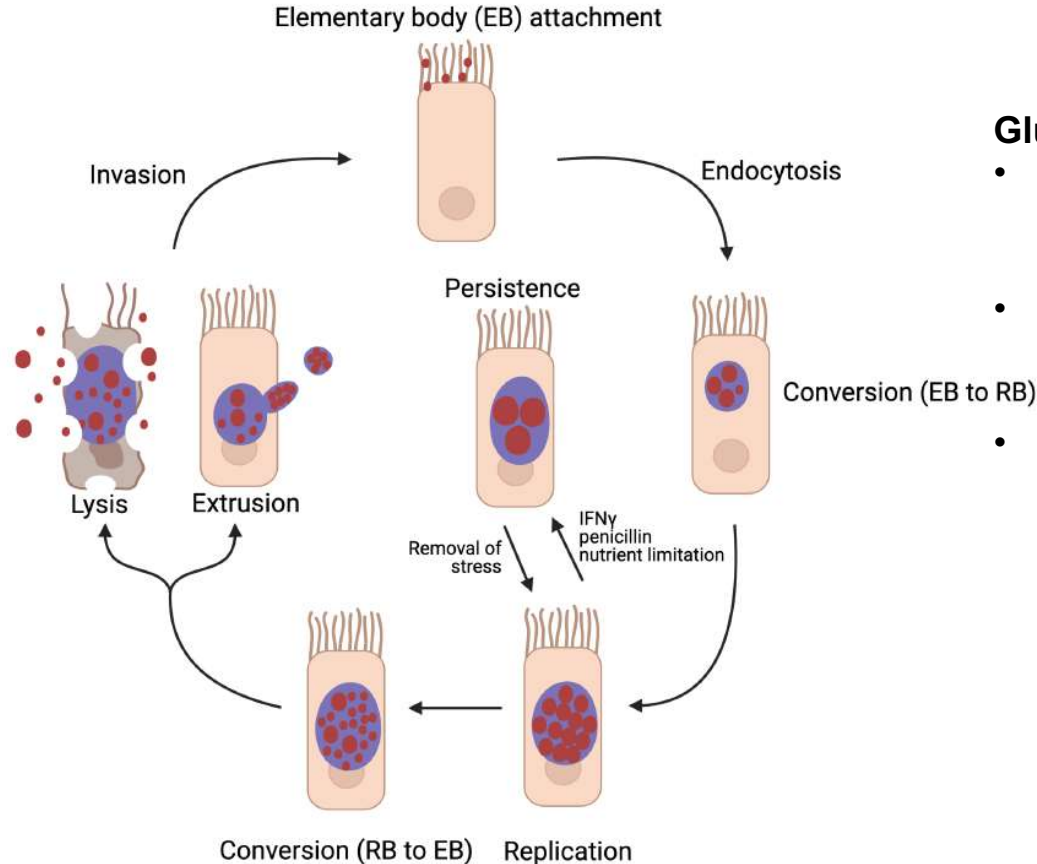


- The UhpC mutant M2C6 is sensitive to 2DG at concentrations that do not inhibit wild type chlamydiae
- Sub-inhibitory concentrations of 2DG induce down-regulation of *omcA::gfp* in the WT, but expression is unaltered in M2C6
- Complementation with inducible UhpC<sup>WT</sup> restores a “persistent” inclusion morphology. Assessment of *omcA* transcription by RT-PCR is ongoing.

# Model:

## Glucose abundant:

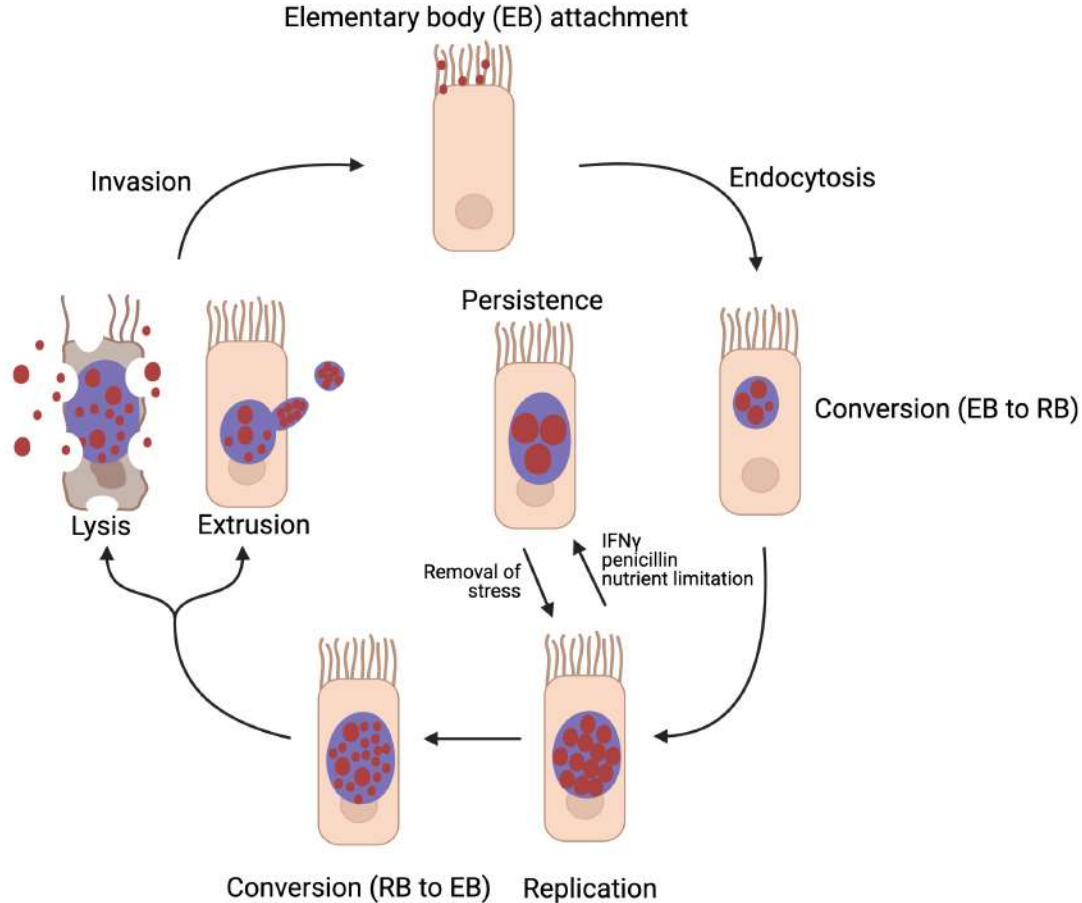
- Developmental cycle proceeds
- Full expression of virulence genes and maximum inflammation
- Normal yield of infectious EB promotes **spread to upper genital tract**
- **Increased risk of PID or sequelae**



## Glucose “blind”:

- EB entry and conversion to RB
- No further division of RB forms
- Reduced or absent production of infectious progeny

# Model:



## Glucose “sensing”:

- Developmental cycle stalls
- RBs alter transcription profile with reduced pro-inflammatory virulence gene expression
- RBs become “persistent” forms, with reduced EB production
- Low-level ‘chronic’ infection maintained



## Darville Lab

- Dr. Catherine O'Connell
- Samuel Omesi
- Bryan McQueen
- Christine Dequito
- Michael McNally

## UNC Biology Department

- Dr. Amy Gladfelter

## University of Virginia

- The lab of Dr. Isabelle Derré for the generous gift of the `omcA::gfp` reporter fusion

## Duke University

- The lab of Dr. Robert Bastidas for the generous gift of the P9-C22 and M2-C6 CT UhpC mutants

