MIEP

# Modeling Immunity to Enteric Pathogens

VIRGINIA BIOINFORMATICS INSTITUTE
AT VIRGINIA TECH

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Nutritional Immunology & Molecular Medicine Lab
Center for Modeling Immunity to Enteric Pathogens
MMI Symposium in Computational Immunology
Virginia Tech, Blacksburg, VA

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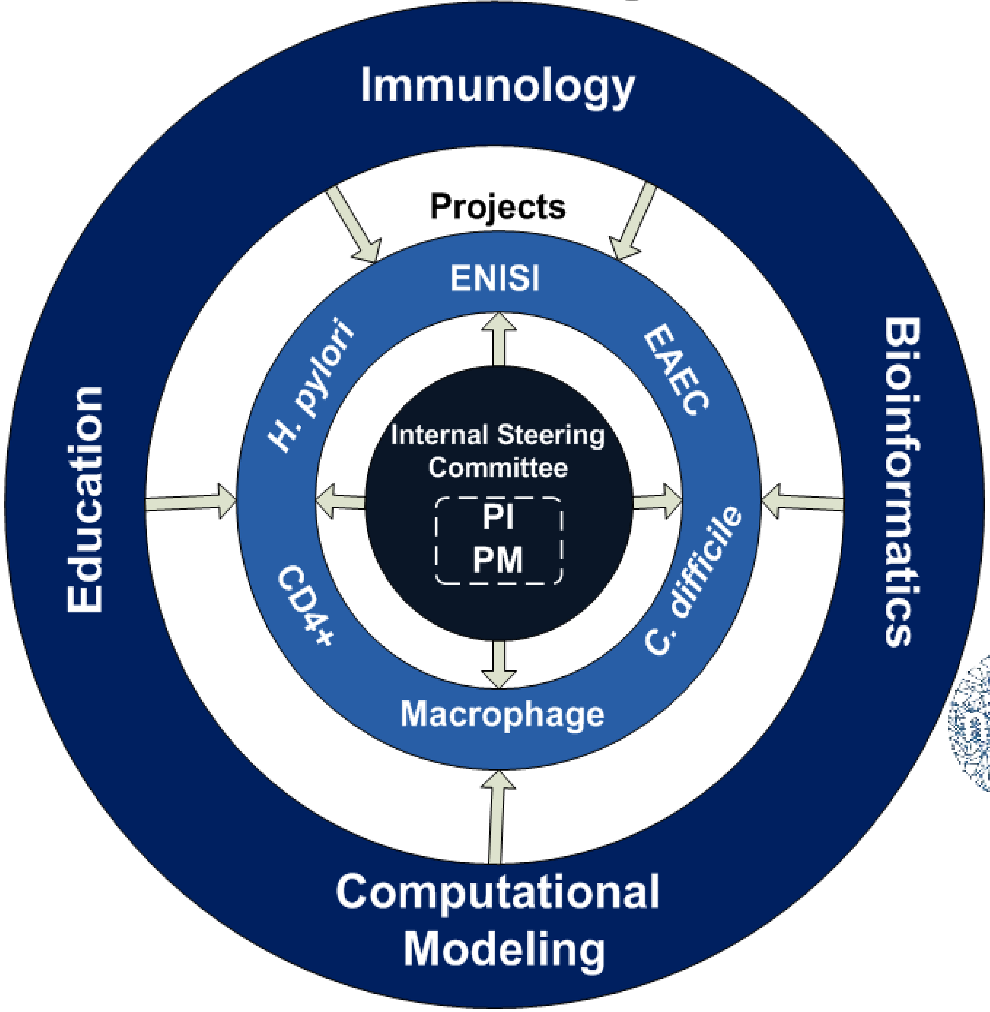
www.modelingimmunity.org

# Center for Modeling Immunity to Enteric Pathogens



Immunology

Projects

ENISI

*H. pylori*

EAEC

Internal Steering Committee

PI

PM

*C. difficile*

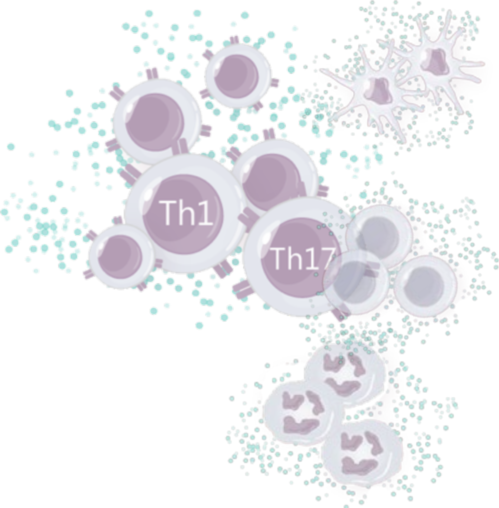
CD4+

Macrophage

Education

Bioinformatics

Computational Modeling



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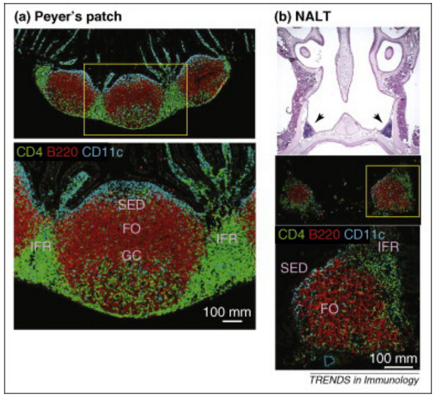
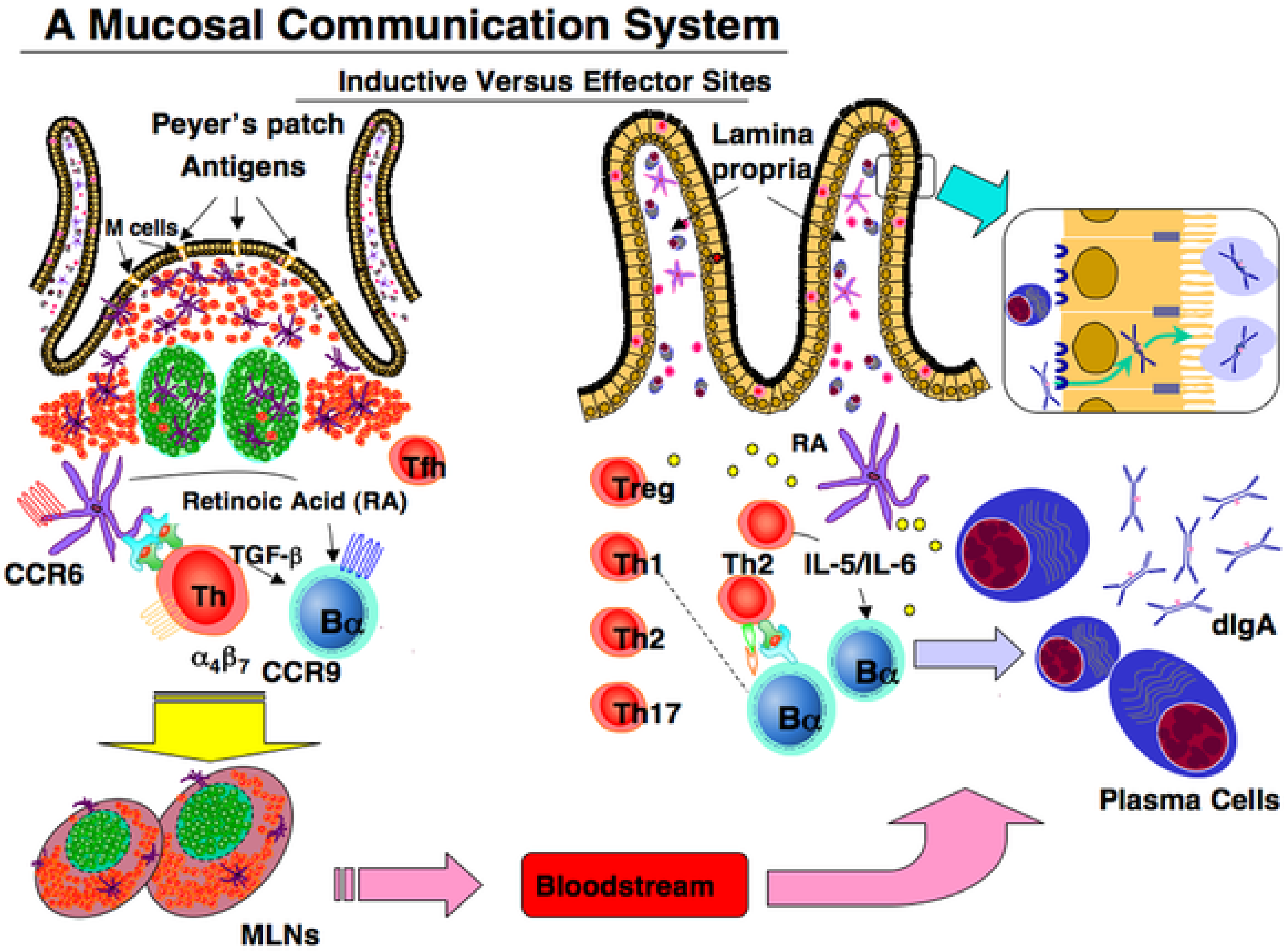
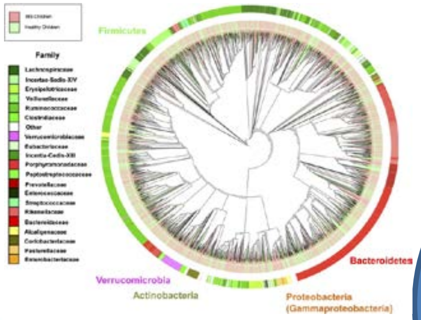
www.ndssl.vbi.vt.edu

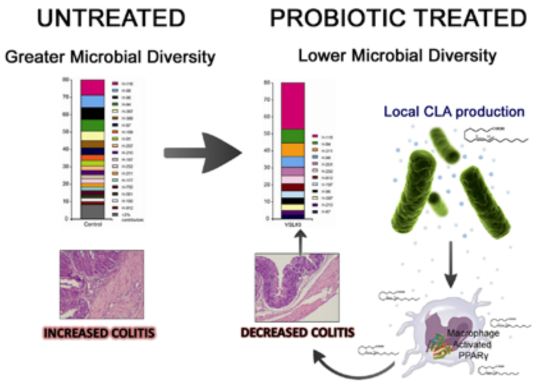
# Mucosal Immune System

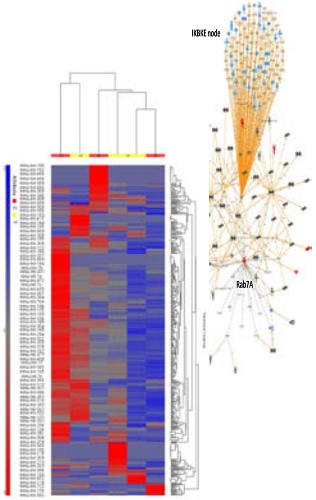




McGhee JR, Fujihashi K (2012) Inside the Mucosal Immune System. PLoS Biol 10(9): e1001397. doi:10.1371/journal.pbio.1001397







Microbiome

Genes

RNA

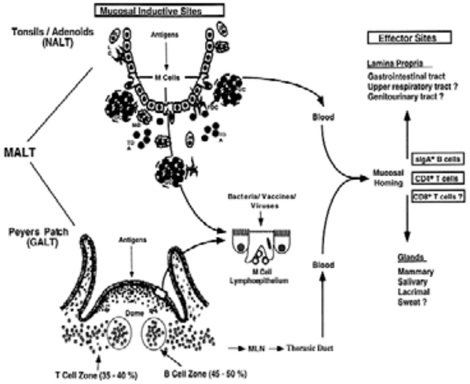
Proteins

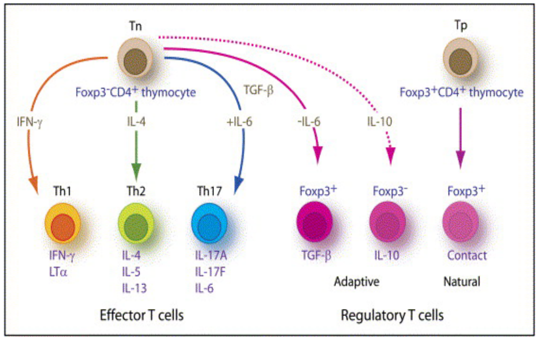
***Health vs. Disease***

Diet

Inflammation

& Immunity





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MODELING IMMUNITY
TO ENTERIC PATHOGENS

## Modeling immune responses to *Helicobacter pylori*

# *H. pylori*

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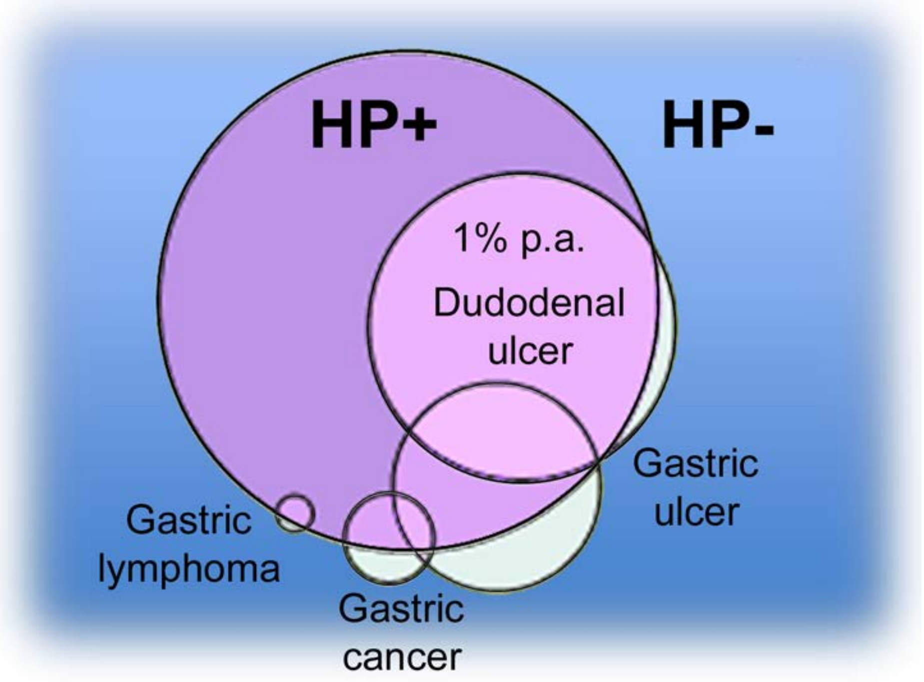
# Background

- High prevalence (> 50 % world's population)
- Extreme differences in geographic distribution (socioeconomic factors)

# Background

Most common cause of gastritis, with associated complications: peptic, duodenal ulcer, gastric adenocarcinoma, MALT lymphoma.



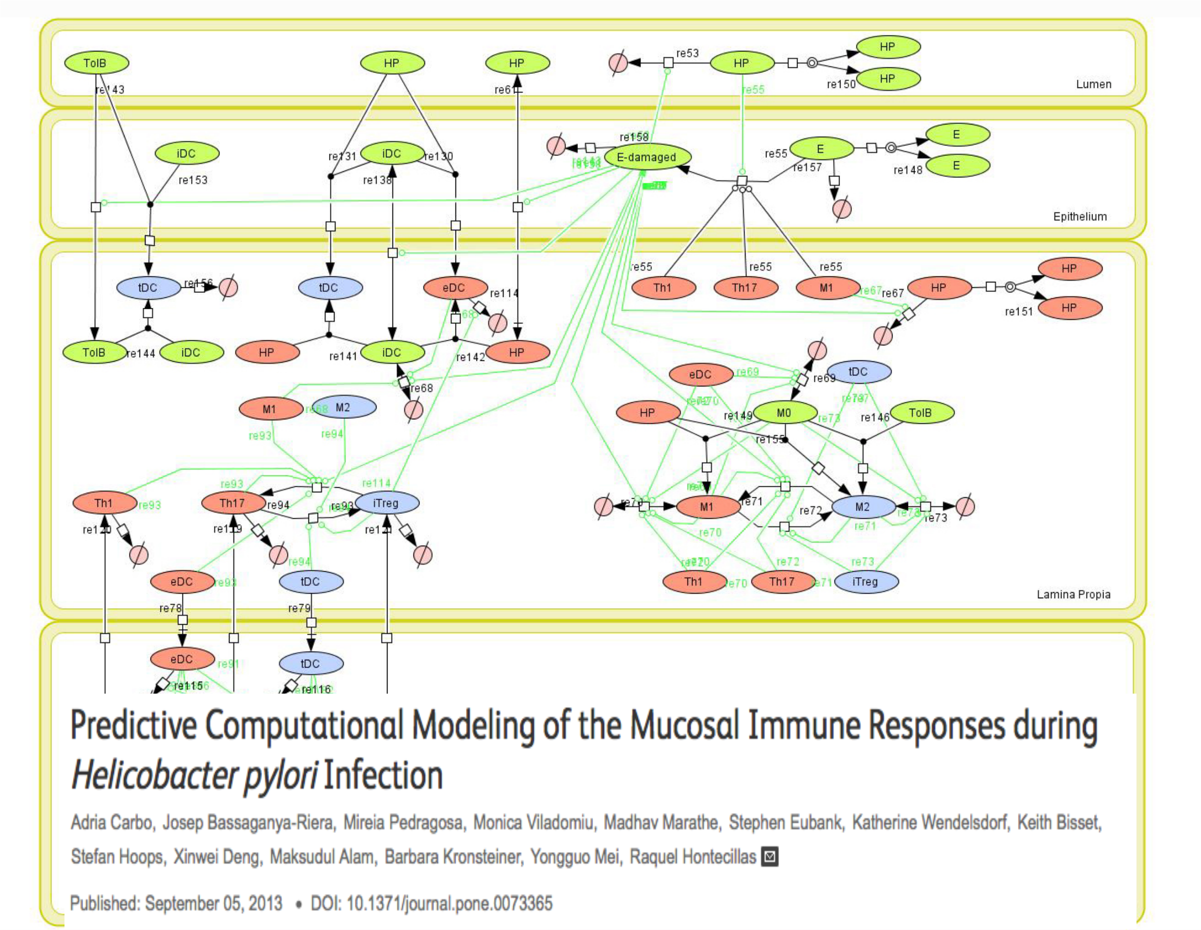
# *Helicobacter pylori*

- *H. pylori* was classified as a type I carcinogen by the WHO... Should it be eradicated?
- *H. pylori* should be included in the list of most endangered species (M. Blaser)...and preserved as a beneficial commensal
- Inverse correlation between H. pylori prevalence and rate of overweight/obesity (Lender, 2014)

**_Helicobacter pylori_ Colonization Ameliorates Glucose Homeostasis in Mice through a PPAR γ-Dependent Mechanism**

Josep Bassaganya-Riera[1,4]*, Maria Gloria Dominguez-Bello[2], Barbara Kronsteiner[1], Adria Carbo[1], Pinyi Lu[1], Monica Viladomiu[1], Mireia Pedragosa[1], Xiaoying Zhang[1], Bruno W. Sobral[1¤], Shrinivasrao P. Mane[1], Saroj K. Mohapatra[1], William T. Horne[1], Amir J. Guri[1], Michael Groeschl[3], Gabriela Lopez-Velasco[1], Raquel Hontecillas[1]

# Model of *H. pylori* infection



## Predictive Computational Modeling of the Mucosal Immune Responses during *Helicobacter pylori* Infection

Adria Carbo, Josep Bassaganya-Riera, Mireia Pedragosa, Monica Viladomiu, Madhav Marathe, Stephen Eubank, Katherine Wendelsdorf, Keith Bisset, Stefan Hoops, Xinwei Deng, Maksudul Alam, Barbara Kronsteiner, Yongguo Mei, Raquel Hontecillas

Published: September 05, 2013 • DOI: 10.1371/journal.pone.0073365

http://www.modelingimmunity.org/models/copasi-helicobacter-pylori-computational-model-archive/

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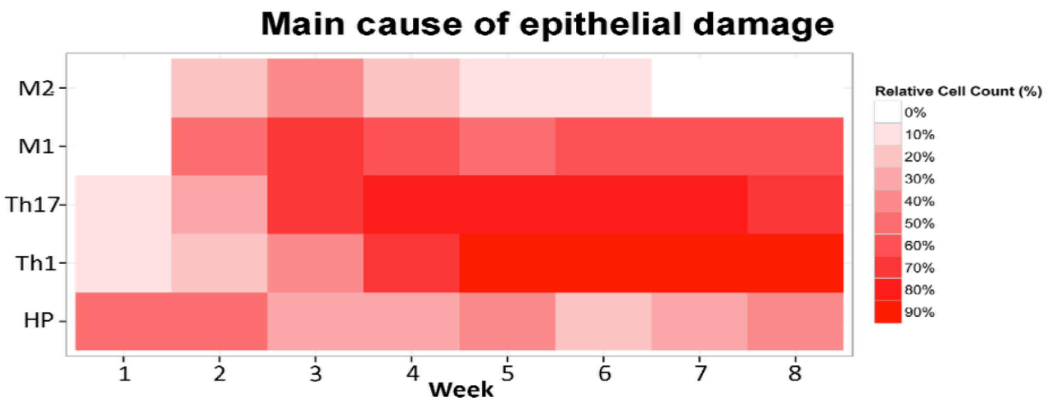
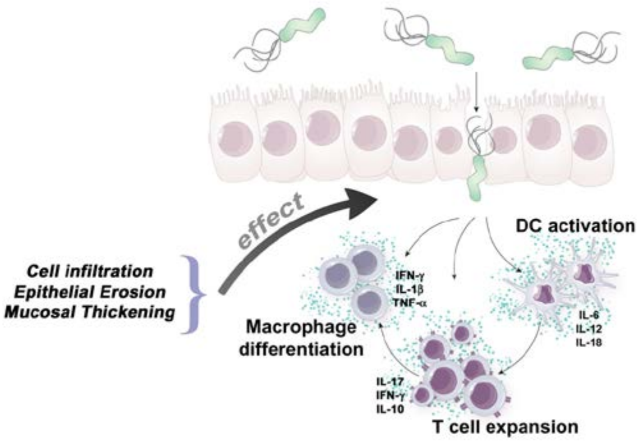
# Model predictions

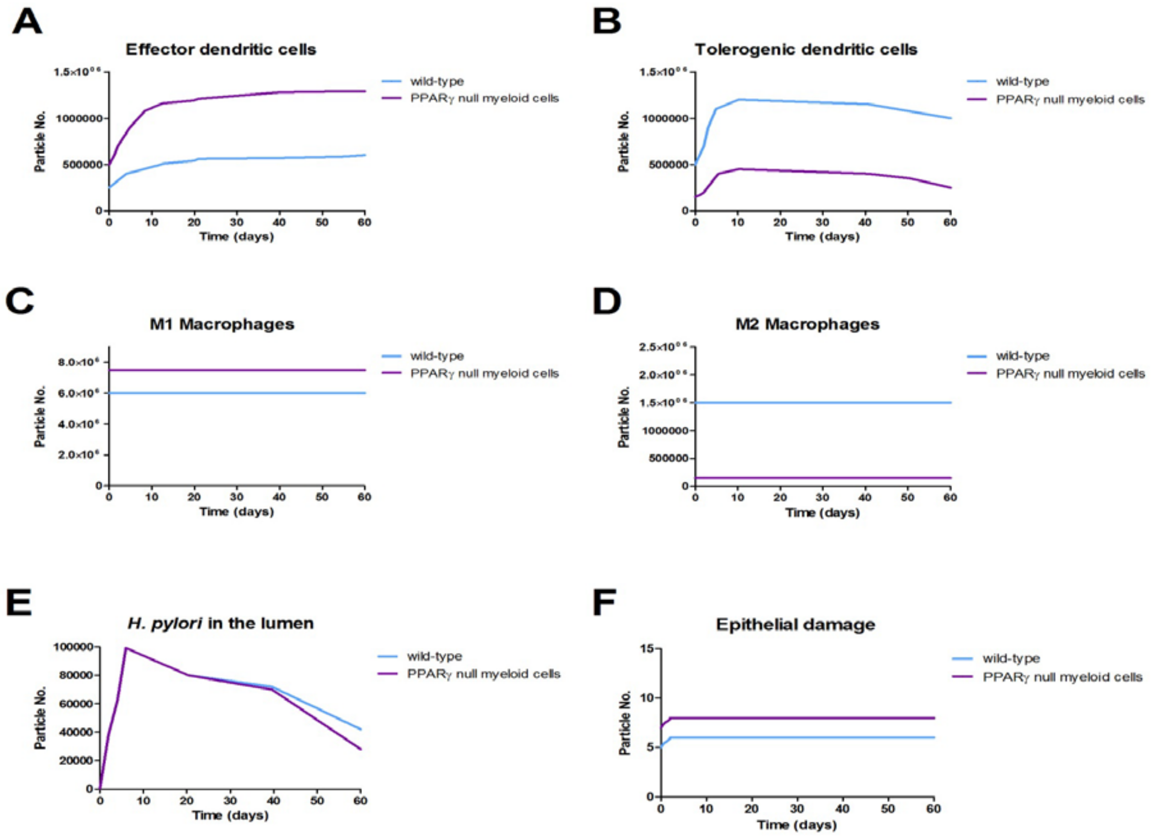


Th1 and Th17 effector responses contribute to gastritis in the chronic phase of infection.

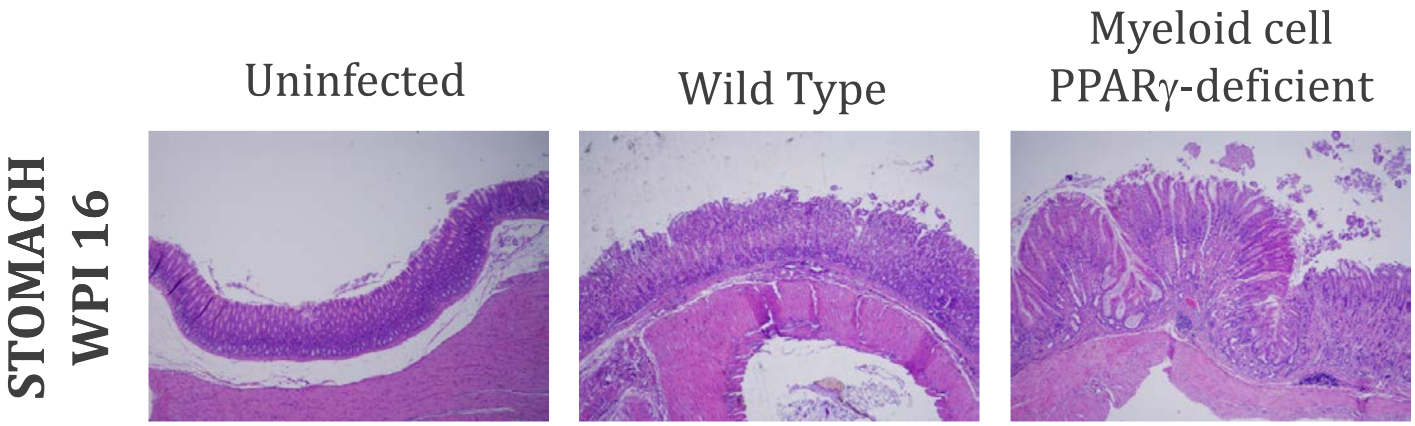


| Target | Correlation |
|---|---|
| M0 | -5.80E+04 |
| E | -1.73E+02 |
| HP{Lumen} | 0.253797 |
| HP{LP} | 0.570211 |
| nT | 29802.3 |
| eDC{GLN} | 5.38E+05 |
| tDC{GLN} | 5.38E+05 |
| tDC{LP} | 7.35E+05 |
| Th17{GLN} | 1.46E+06 |
| Th1{GLN} | 3.37E+06 |
| iTreg{GLN} | 4.80E+06 |
| M2 | 8.11E+06 |
| M1 | 3.22E+07 |
| Th17{LP} | 4.92E+07 |
| iTreg{LP} | 7.12E+07 |
| Th1{LP} | 8.71E+07 |

# Simulation of PPAR γ deletion



# *H. pylori* Loads and Lesions

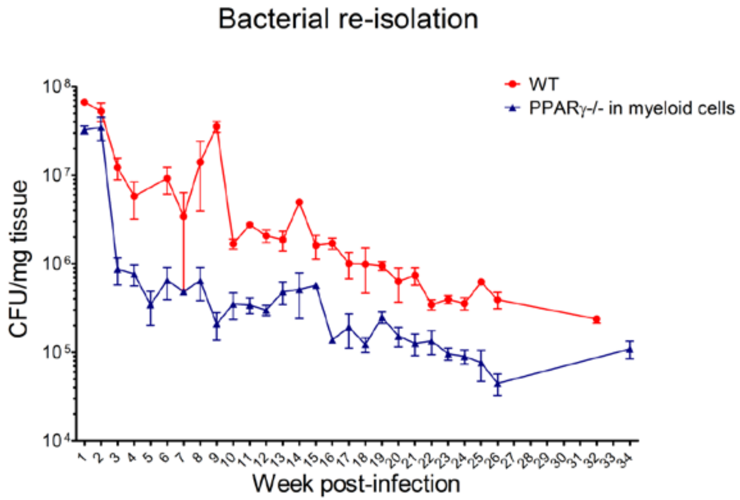


Uninfected

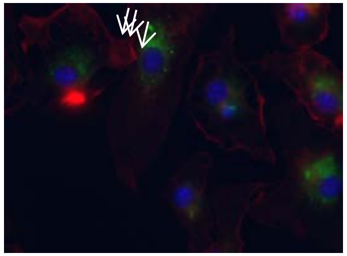
Wild Type

Myeloid cell PPARγ-deficient

STOMACH WPI 16

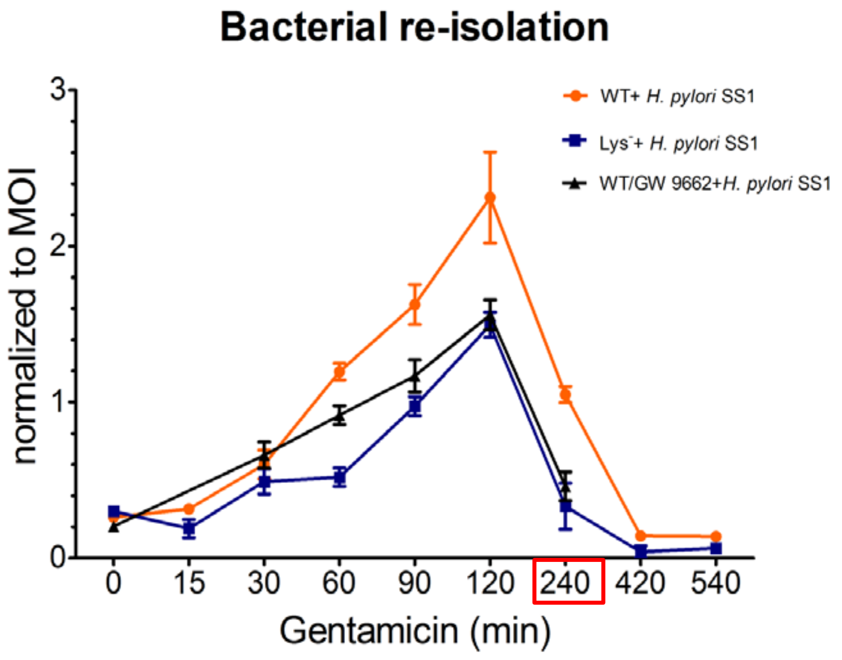


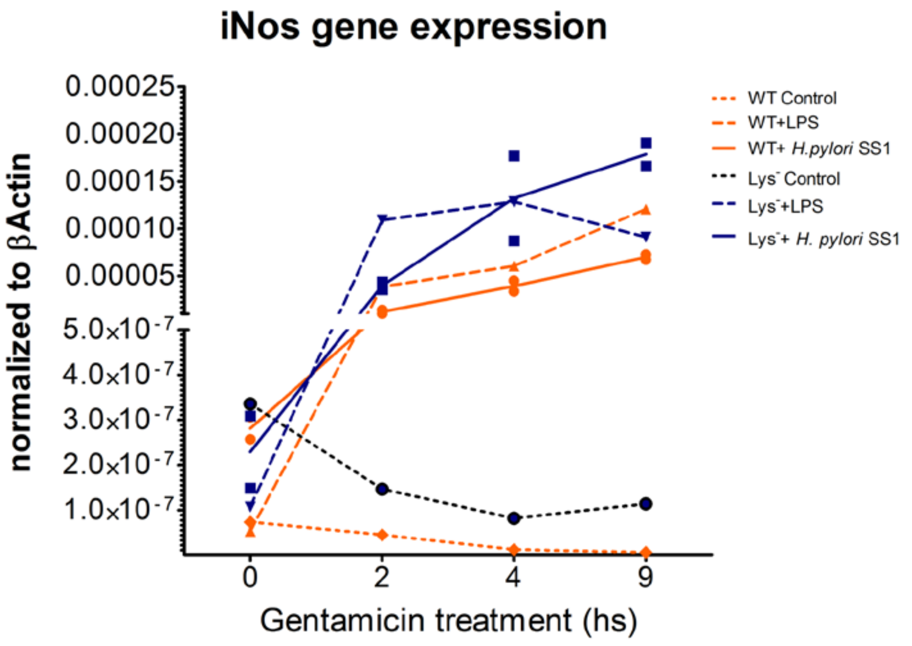
Bacterial re-isolation

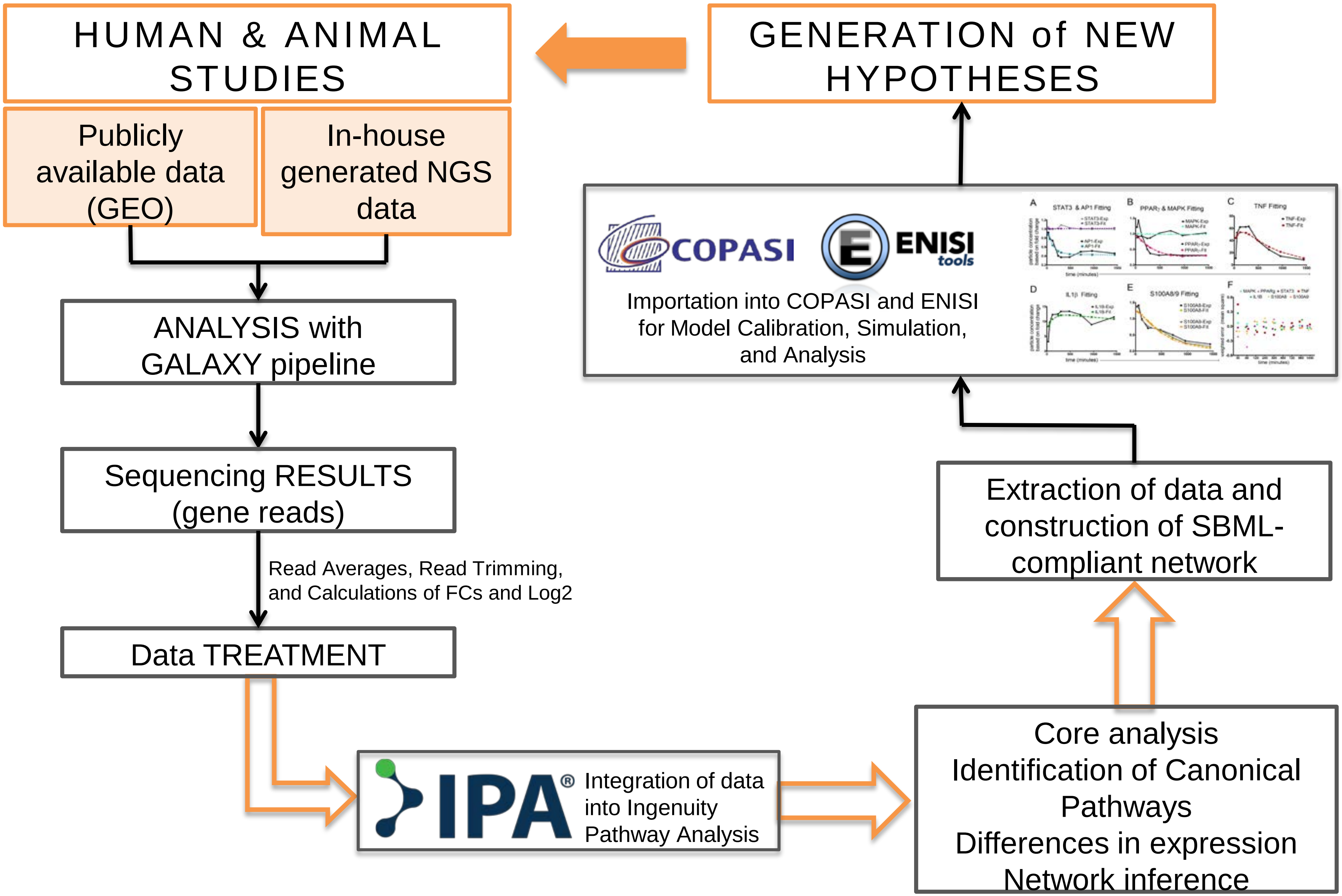


# Macrophage-Hp co-cultures

## 15min *H. pylori* co-culture


Bacterial re-isolation


iNos gene expression



HUMAN & ANIMAL STUDIES

Publicly available data (GEO)

In-house generated NGS data

ANALYSIS with GALAXY pipeline

Sequencing RESULTS (gene reads)

Read Averages, Read Trimming, and Calculations of FCs and Log2

Data TREATMENT

IPA® Integration of data into Ingenuity Pathway Analysis

Core analysis
Identification of Canonical Pathways
Differences in expression
Network inference

Extraction of data and construction of SBML-compliant network

COPASI ENISI tools

Importation into COPASI and ENISI for Model Calibration, Simulation, and Analysis

GENERATION of NEW HYPOTHESES

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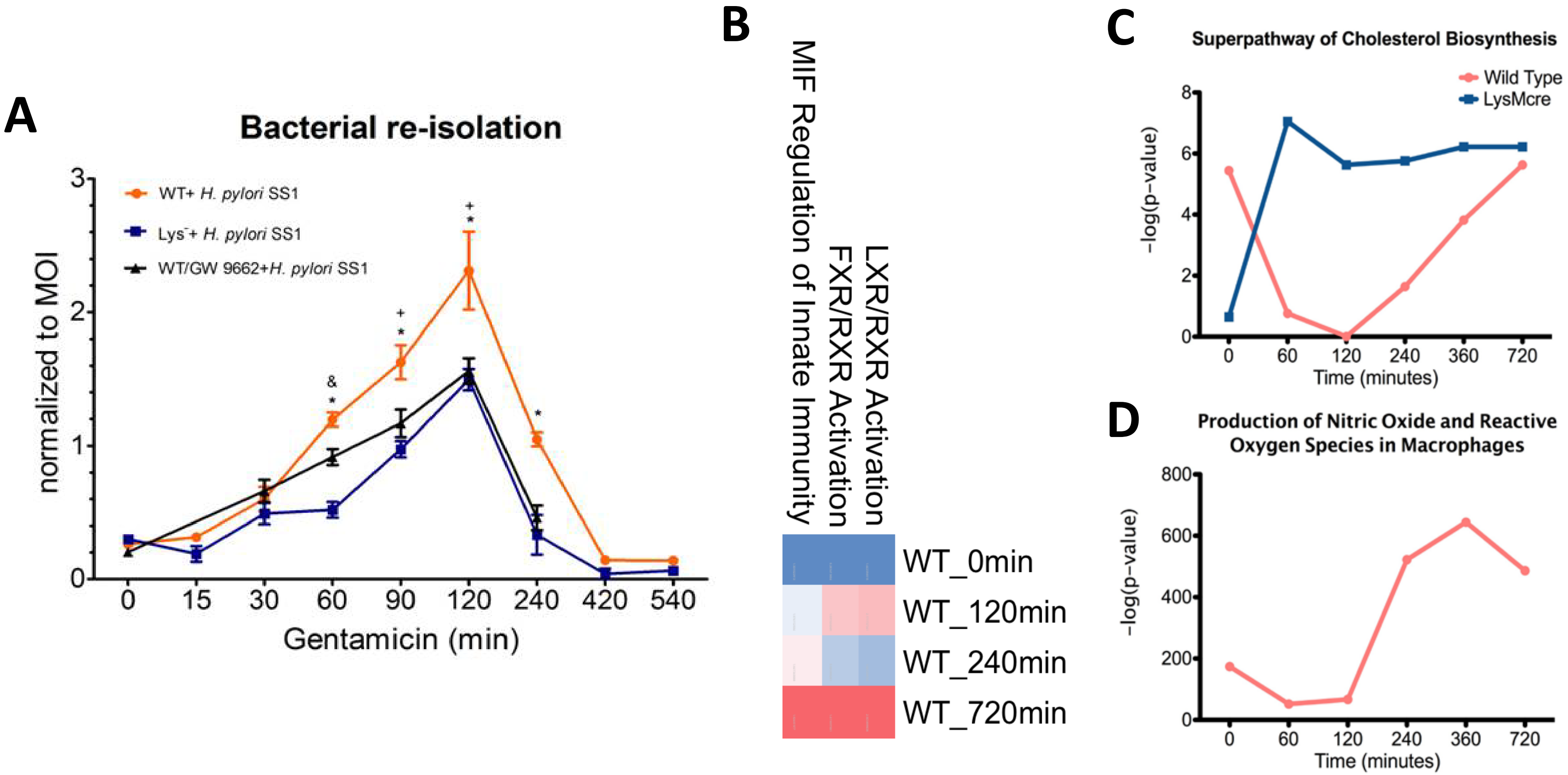
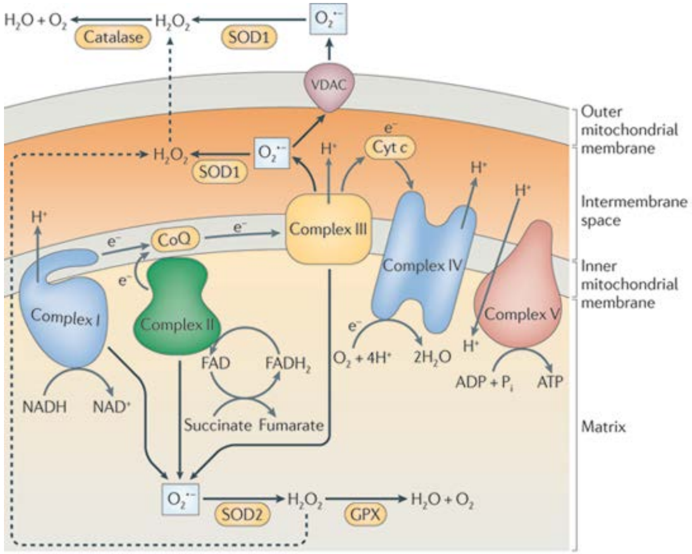
# Cholesterol Biosynthesis

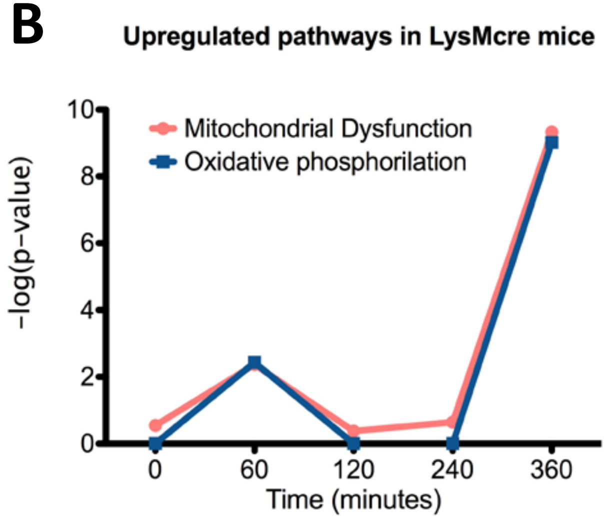


# Metabolic Response

**A**

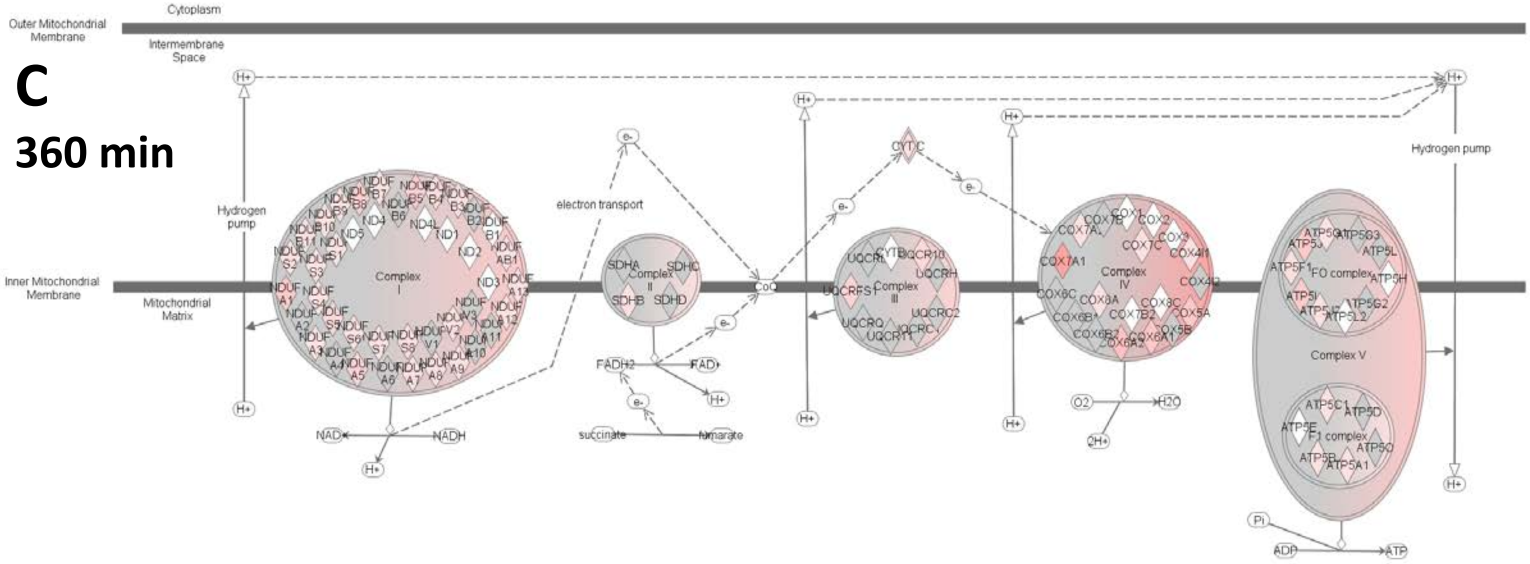


**B**



**C**

**360 min**



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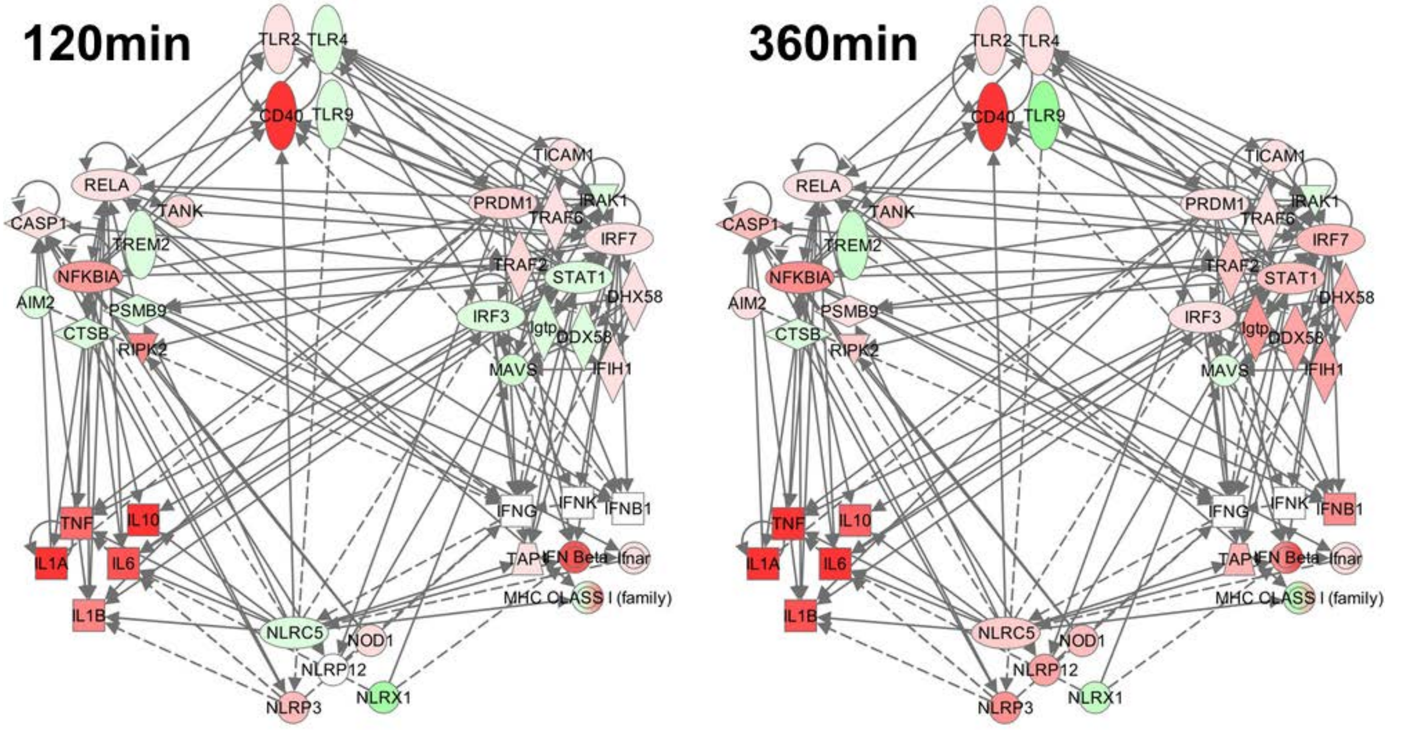
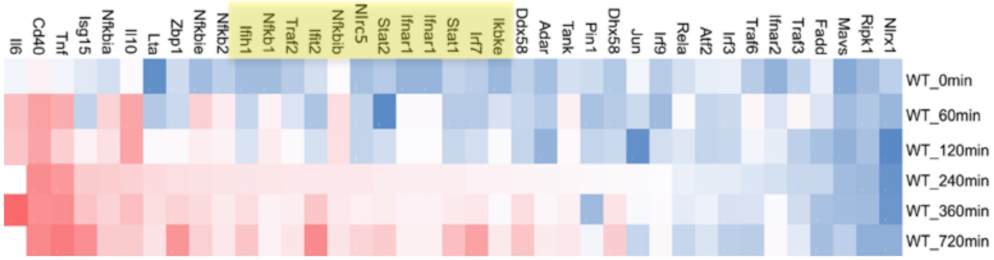
# Innate Responses to *H. pylori*





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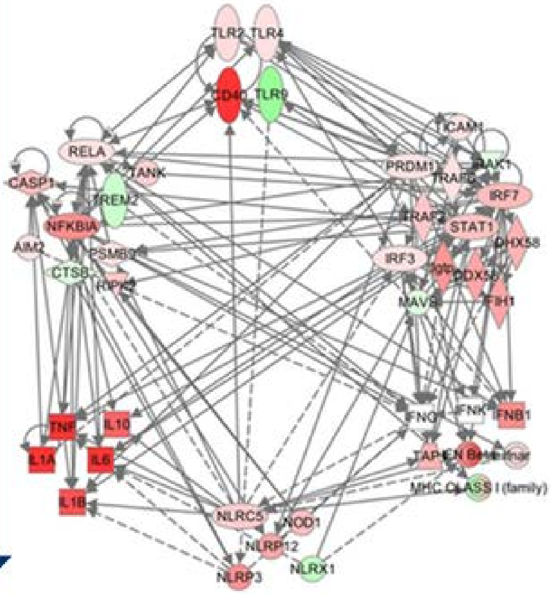
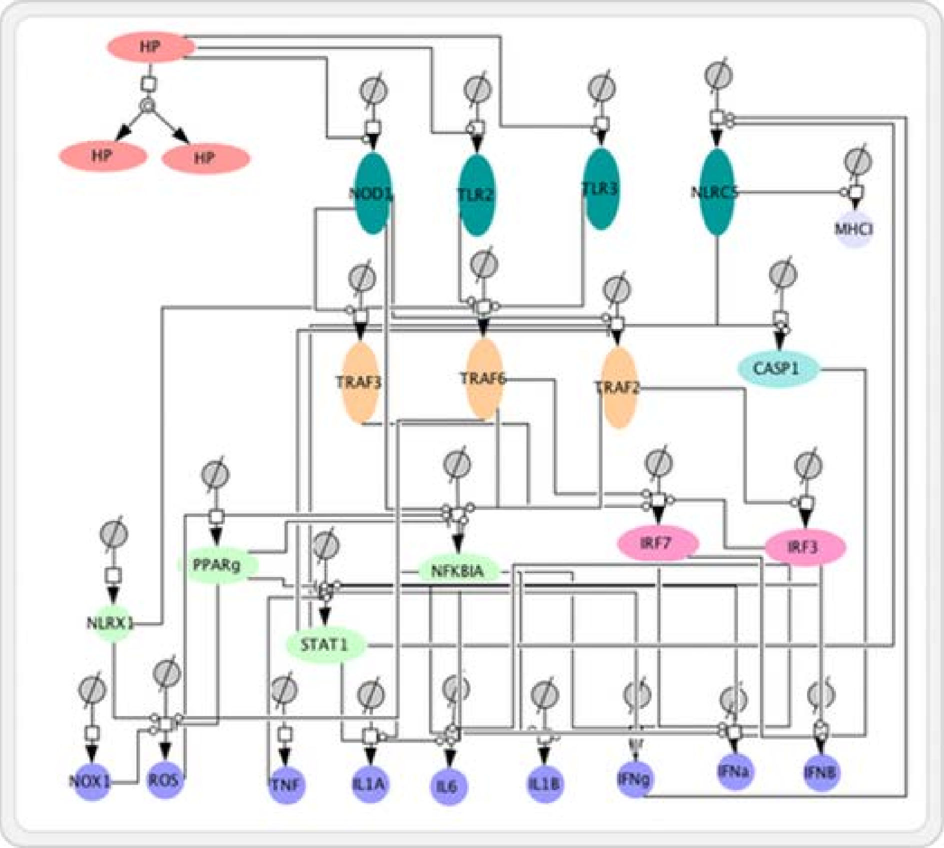
# Modeling Innate Responses to *H. pylori*

IPA®



CellDesigner Plugin



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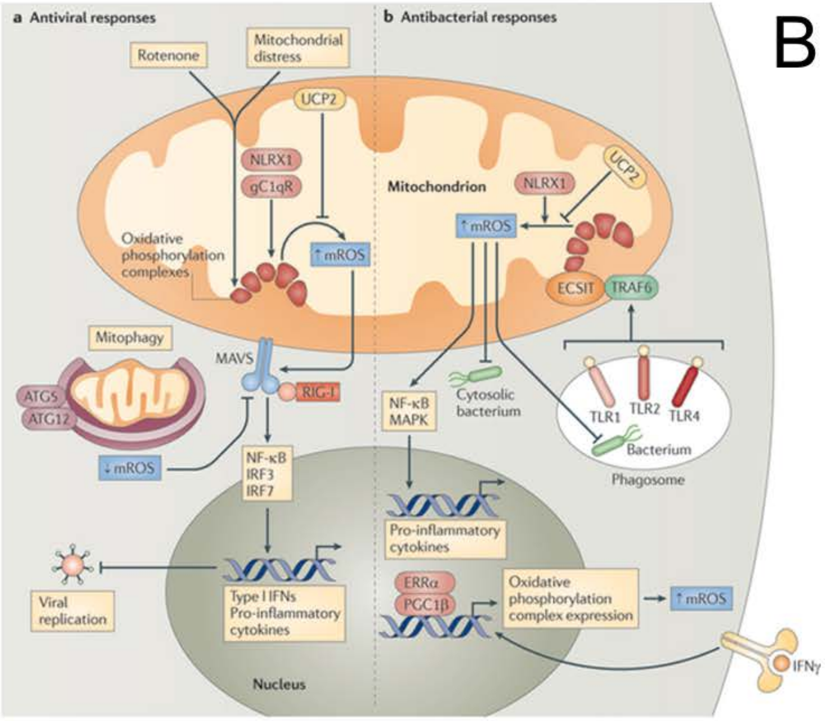
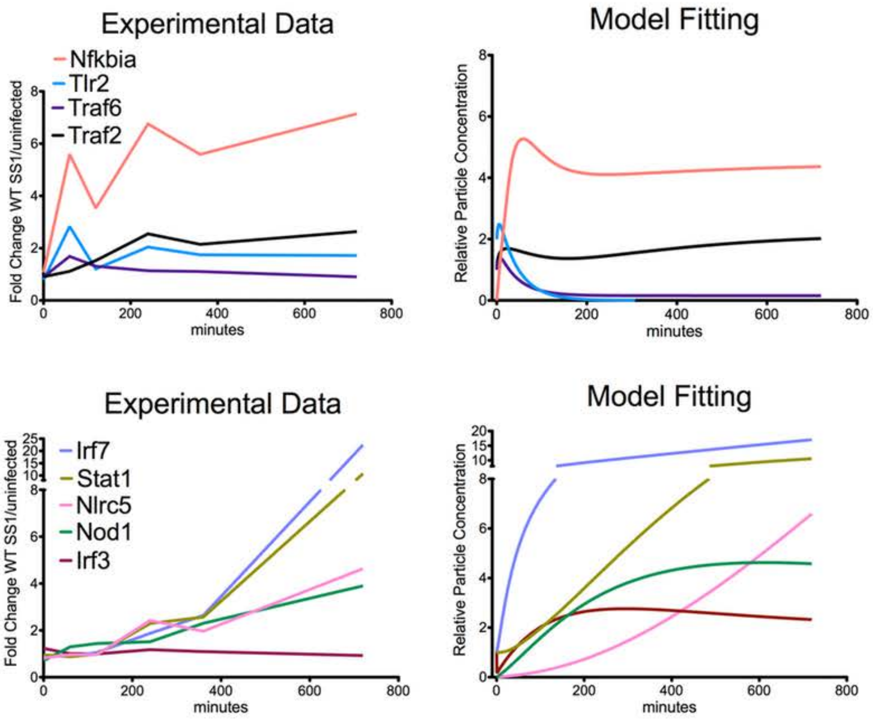
# Modeling Innate Responses to *H. pylori*

A



Nature Reviews | Immunology

B

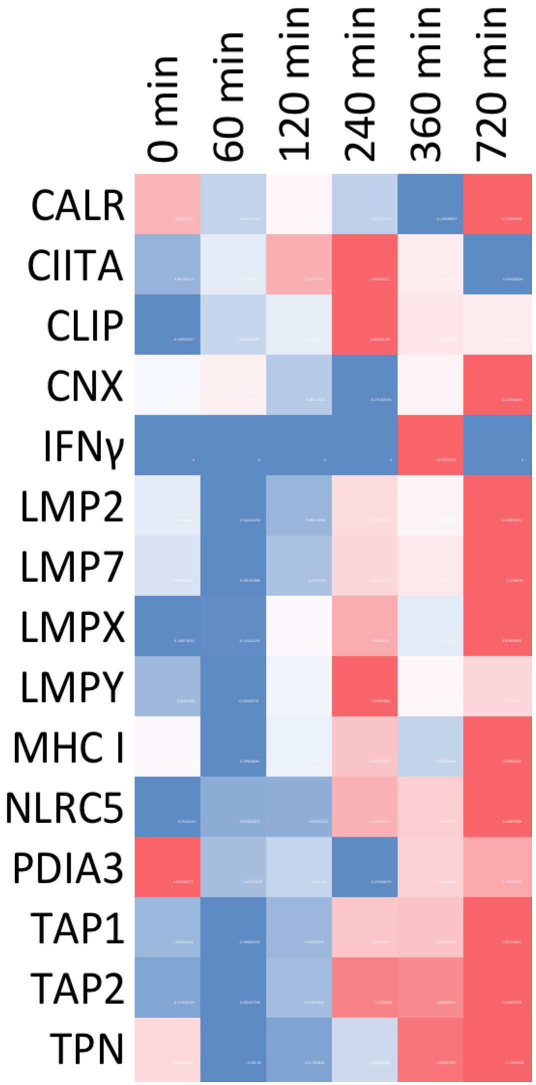


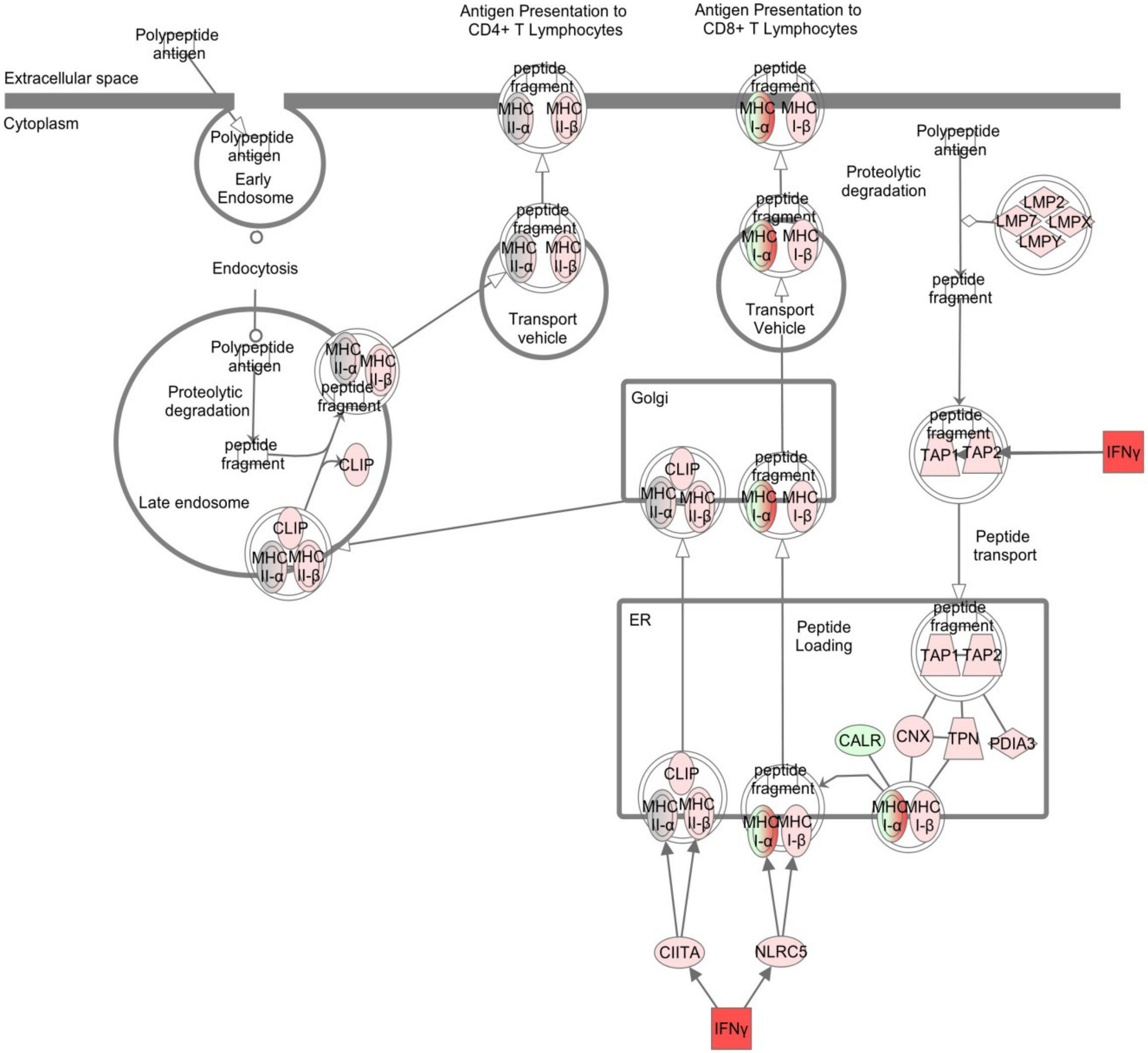
# NLRX1 Sensitivity Analysis

| | |
|---|---|
| TRAF6 | 3.96E+16 |
| IRF7 | 5.84E+16 |
| PPARg | 8.55E+16 |
| HP | 1.11E+17 |
| NOD1 | 1.16E+17 |
| TLR2 | 1.44E+17 |
| IRF7 | 2.02E+17 |
| STAT1 | 2.02E+17 |
| TNF | 3.20E+17 |
| IRF3 | 3.51E+17 |
| TRAF2 | 4.29E+17 |
| MHCI | 7.14E+18 |
| IFNb | 3.52E+21 |

- Local sensitivity analysis portrays relationship between NLRX1 and viral signaling cascades during intracellular *H. pylori* infection
- Intimate link between NLRX1 and IFN signaling
- Sensitivities suggest there may be a role for NLRX1 in MHC class I signaling as well

# MHC Class I Presentation





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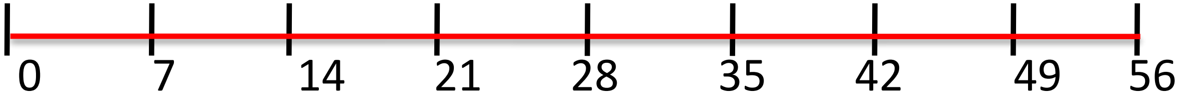
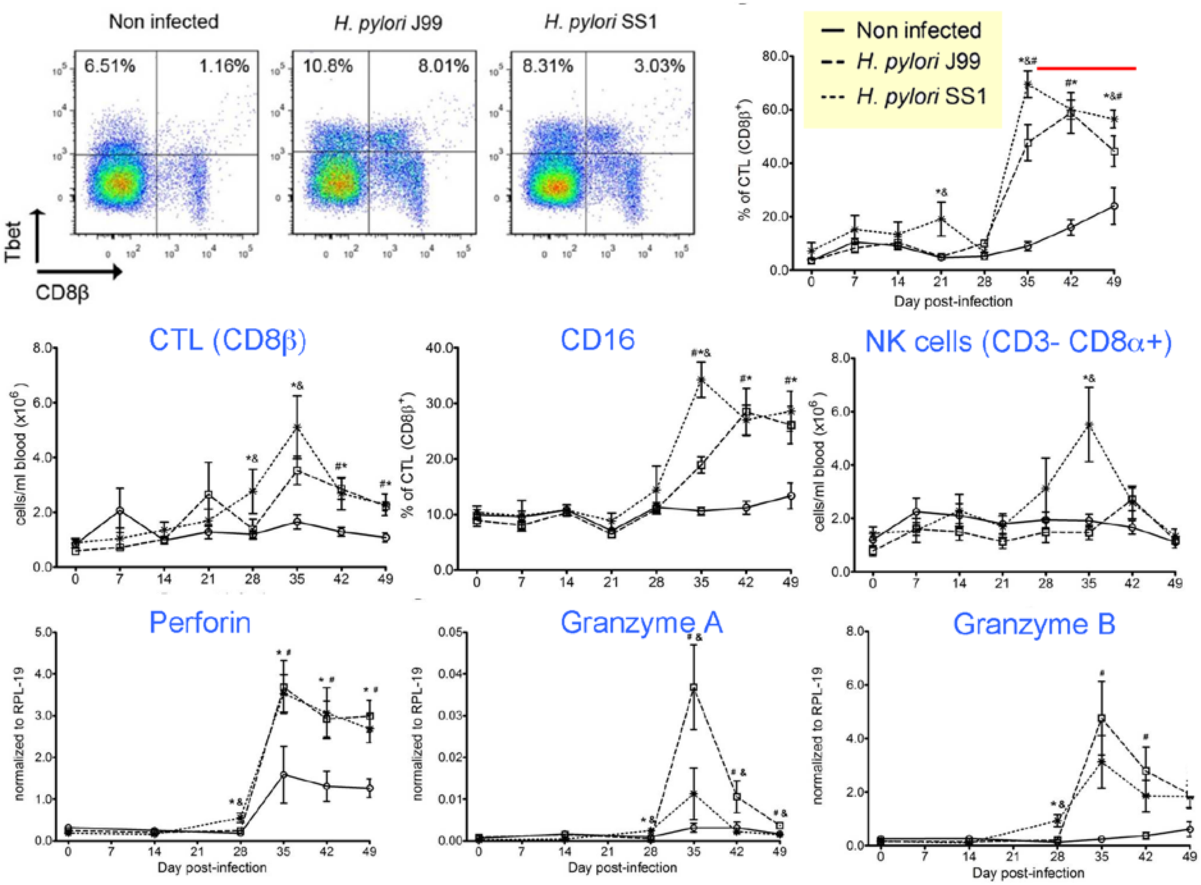
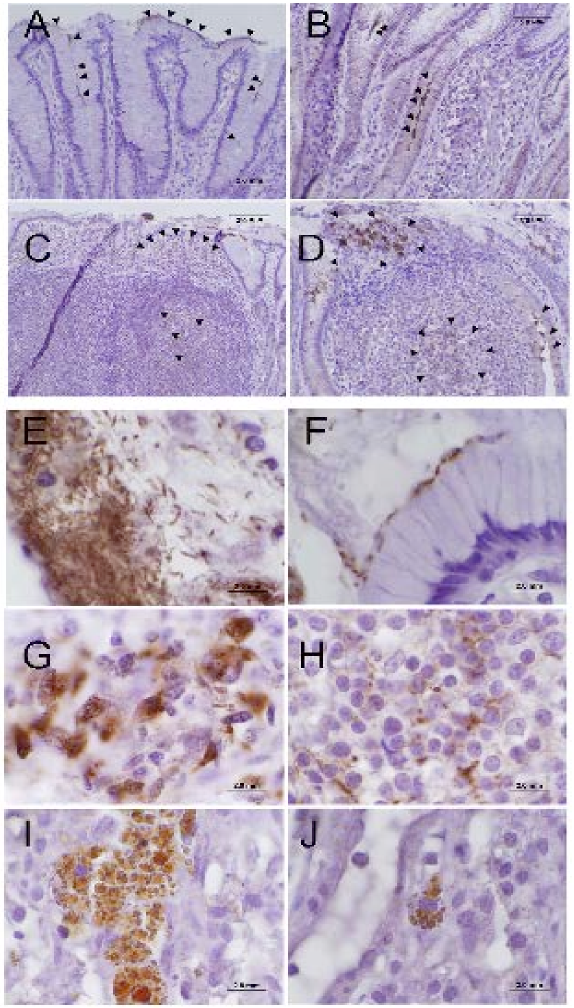
# CD8+ T cell responses



Control/ *H. pylori* J99/SS1





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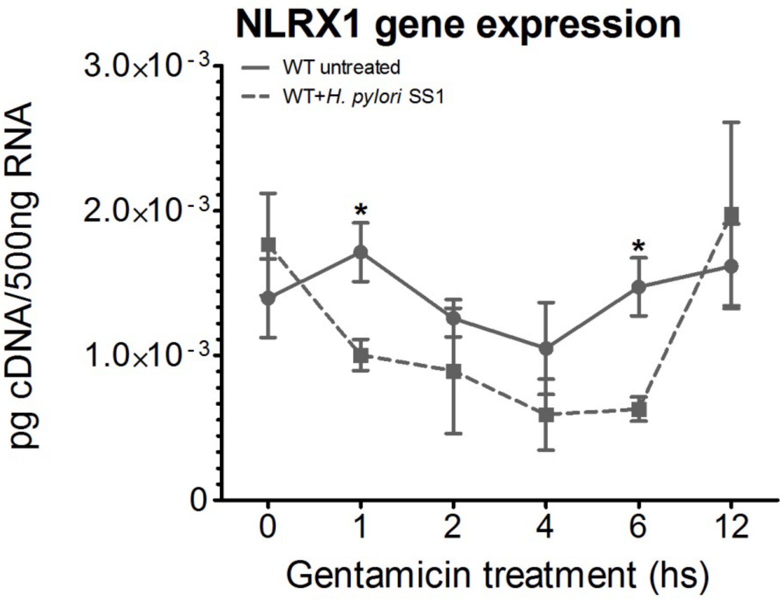
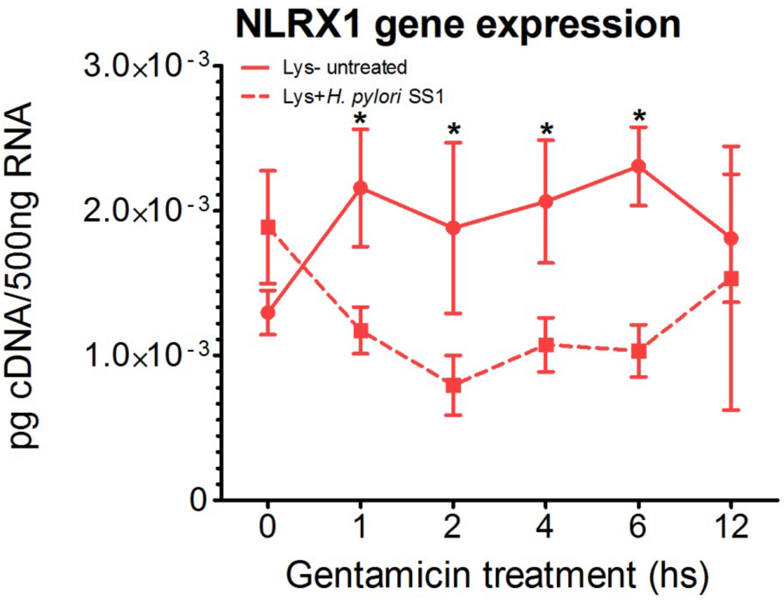
# NLRX1 Expression Validation in Macrophages

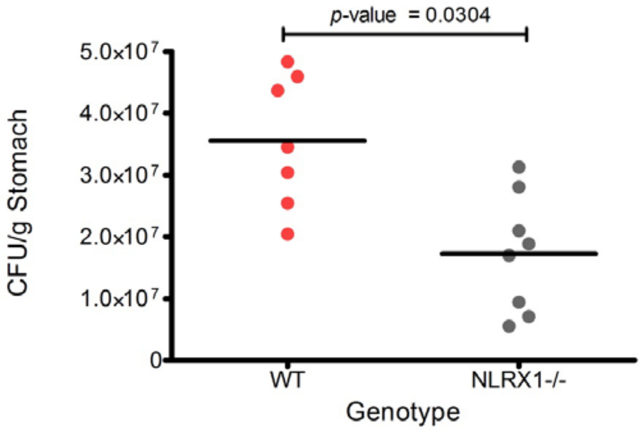
Wild type

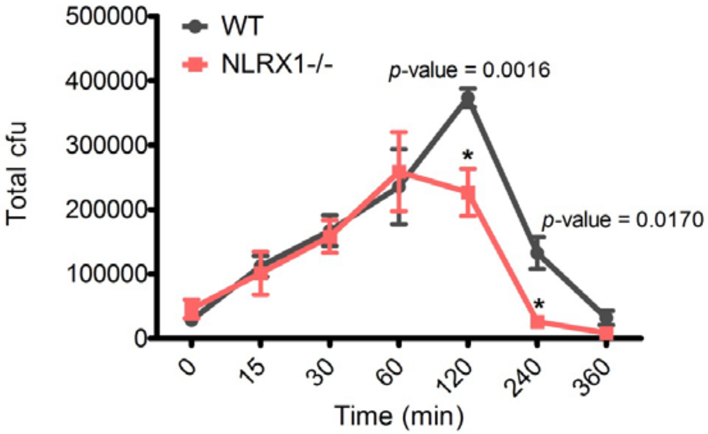


PPARγ-deficient



# Validation in NLRX1 ko


Reisolation 3 weeks post-infection


BMDM

# Summary

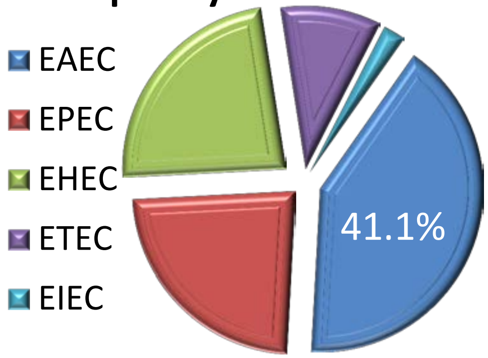
- *H. pylori* infection modulates two phases of innate immune pathways that intersect with metabolism
- NLRX1 regulates host responses to *H. pylori* infection in macrophages
- We identified an inverse relationship between expression of PPAR $\gamma$ and NLRX1 in macrophages
- Modeling was used to assess the sensitivities of our network to NLRs and their immunoregulatory mechanisms during *H. pylori* infection

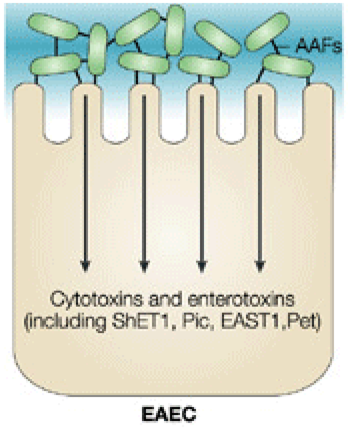
# EAEC *a leading cause of enteritis & persistent diarrhea worldwide*

## High risk populations:

- Travelers
- HIV infected
- Malnourished children

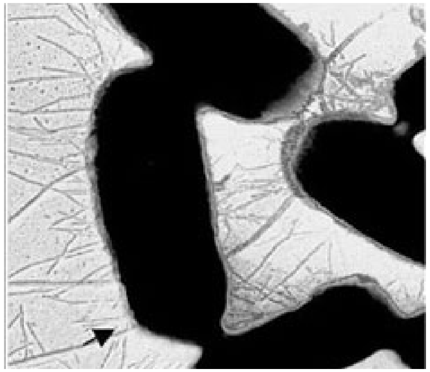
**Diarrheagenic Isolate Frequency Distribution**





## AAF fimbria:

primary virulence factor attributed to mucosal adherence



## Fli-C flagellin:

responsible for IL-8 secretion

## Dispersin:

Allows dissociation from biofilm and spread of colonization

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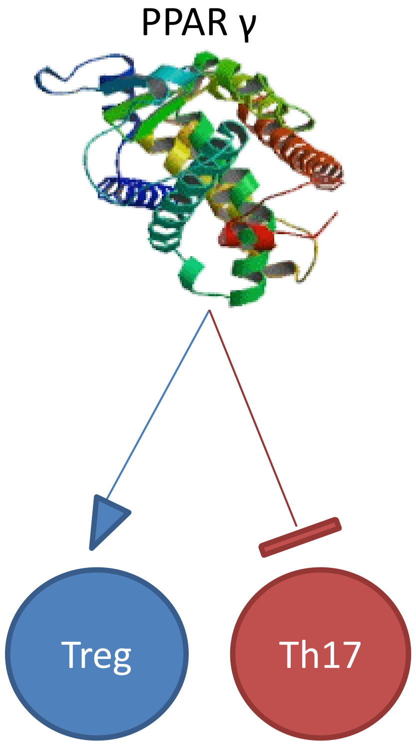
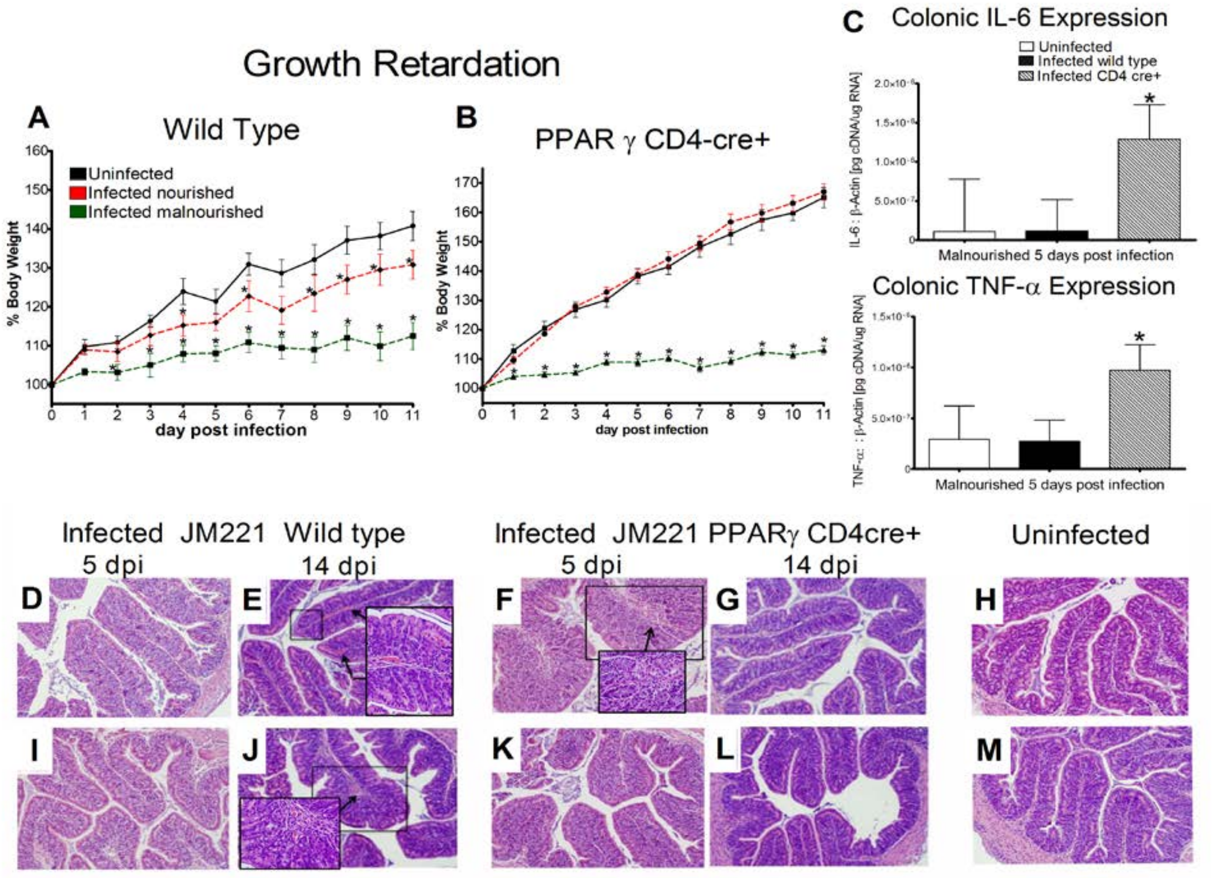
# EAEC

- Our *in vivo* murine model data suggested a beneficial role for Th17 cells and IL17A
- We used computational modeling to predict the effects of enhancing effector T cell populations during EAEC infection

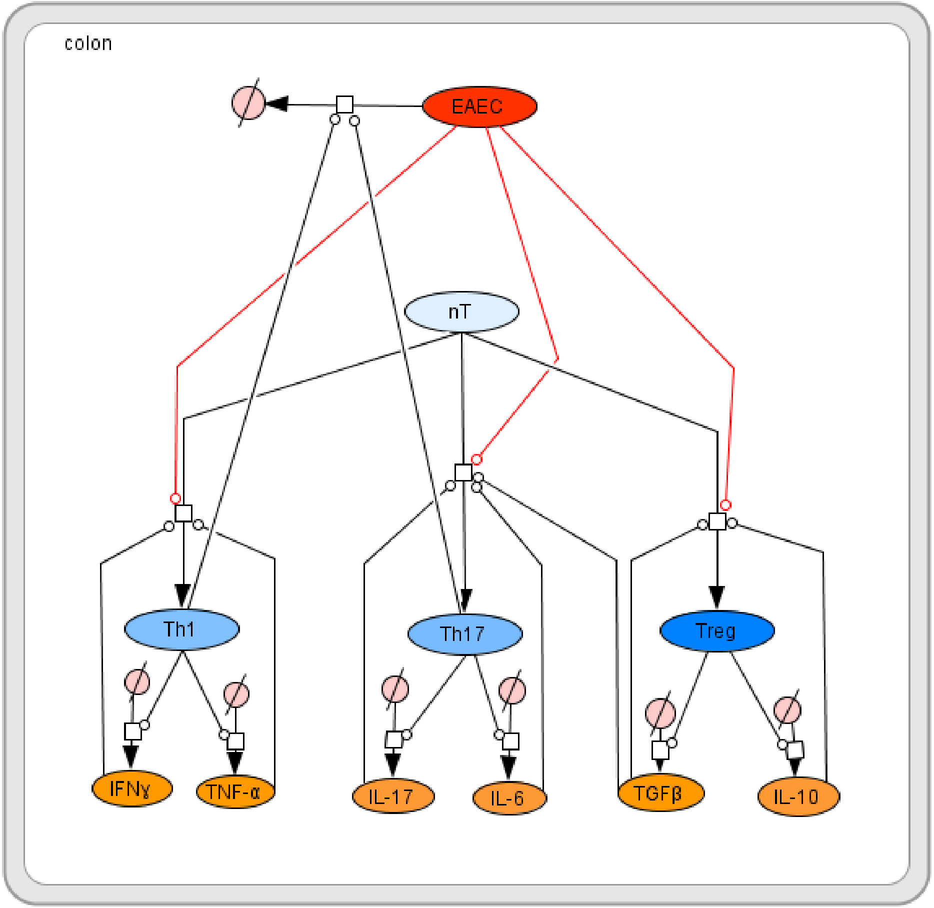
# Targeting PPARγ as an inflammatory mediator





- <u>Gene expression</u>: Upregulation of proinflammatory markers in CD4Cre+
- <u>Histopathology</u>: High leukocytic infiltration early during infection in CD4Cre+ followed by amelioration of colonic inflammation by day 14

# EAEC T cell Model



COPASI
Complex Pathway Simulator

Ordinary differential equations from EAEC T cell differentiation model

$$\frac{d([Treg])}{dt} = -V_{colon} \cdot (K1_{(re17)} \cdot [Treg]) + ([emT] \cdot (K1_{(re21)} \cdot [TGF\beta] + K2_{(re21)} \cdot [\mathrm{IL10}])) + V_{colon} \cdot ([nt] \cdot (K1_{(re7)}) \cdot [EAEC]$$

$$\frac{d([Th17])}{dt} = -V_{colon} \cdot (K1_{(re16)} \cdot [Th17]) + ([emT] \cdot (K1_{(re9)} \cdot [IL6] + K2_{(re9)} \cdot [TGF\beta] + K3_{(re9)} \cdot [IL17]) + V_{colon} \cdot ([nt] \cdot K1_{(re7)}) \cdot [EAEC]$$

$$\frac{d([Th1])}{dt} = -V_{colon} \cdot (K1_{(re16)} \cdot [Th1]) + ([emT] \cdot (K1_{(re20)} \cdot [IFN\gamma] + K2_{(re20)} \cdot [\mathrm{TNF}\alpha]) + V_{colon} \cdot ([nt] \cdot K1_{(re8)}) \cdot [EAEC]$$

$$\frac{d([EAEC])}{dt} = -V_{colon} \cdot ([EAEC] \cdot K1_{(re22)} \cdot [Th1] + K2_{(re22)} \cdot [Th17])$$

## *Parameter estimation → Calibration*

| Bacterial Load in Feces | | T cell populations using Flow Cytometry | | | |
|---|---|---|---|---|---|
| time | EAEC quantification | time | IL17 producing Th17 | IFNg producing Th1 | Regulatory T cells |
| 3 | 7123.13 | 14 | 90888.75 | 145422 | 327199.5 |
| 3 | 8110.87 | 14 | 92340 | 295488 | 203148 |
| 3 | 7029.98 | 14 | 65667.6 | 98816.64 | 86464.56 |
| 3 | 9648.13 | 14 | 38165.85 | 45002.25 | 64881.945 |
| 3 | 6342.8 | 14 | 103774.65 | 42936.39 | 45900 |
| 3 | 7262.77 | 14 | 65667.6 | 34765.2 | 38628 |
| 3 | 5831.49 | 14 | 56359.8 | 61065.36 | 31311 |
| 3 | 8028.2 | 14 | 73266.32143 | 103356.5486 | 113933.2864 |

0 | 1 | 3 | 5 | 7 | 10 | 14

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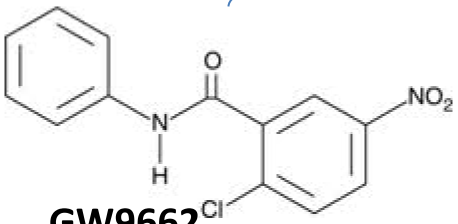
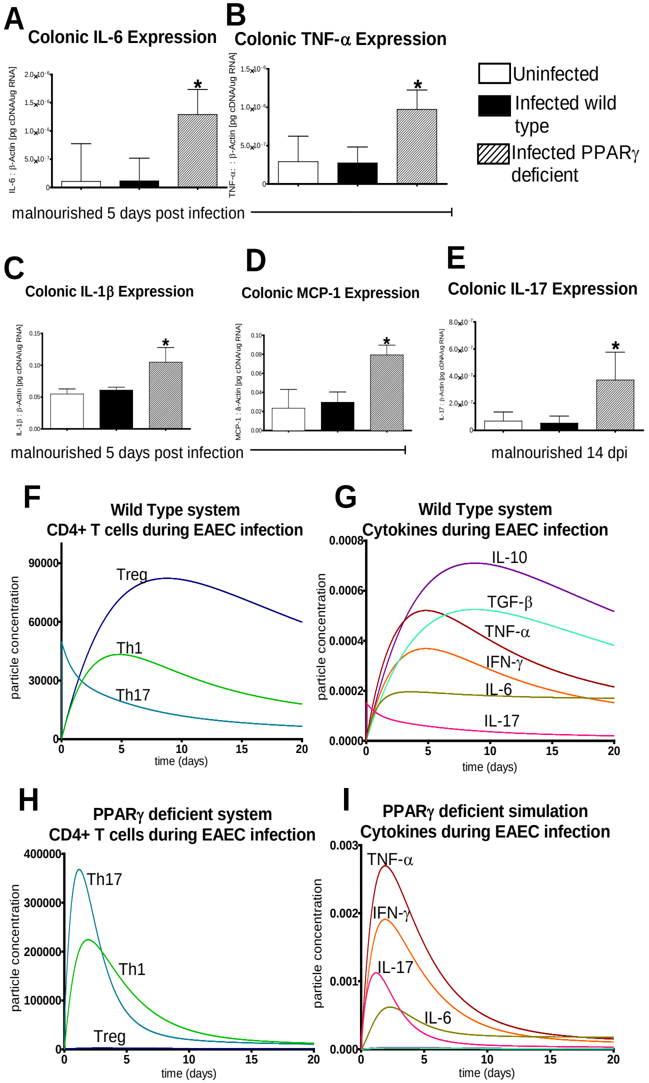
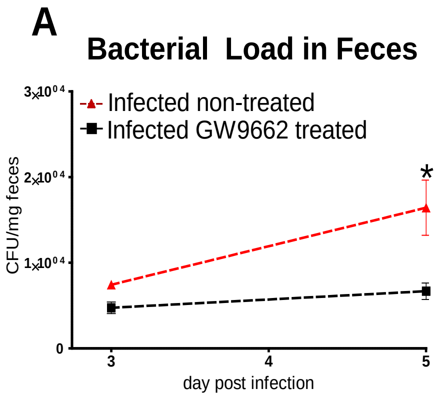
# Pharmacological blockade

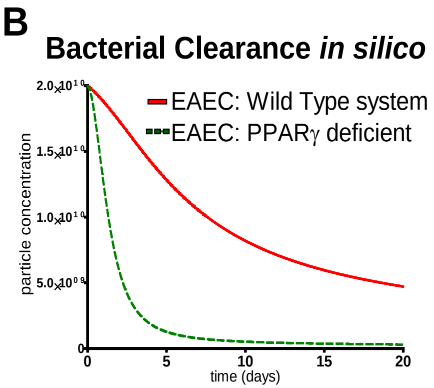


**GW9662**
a potent PPARγ
antagonist

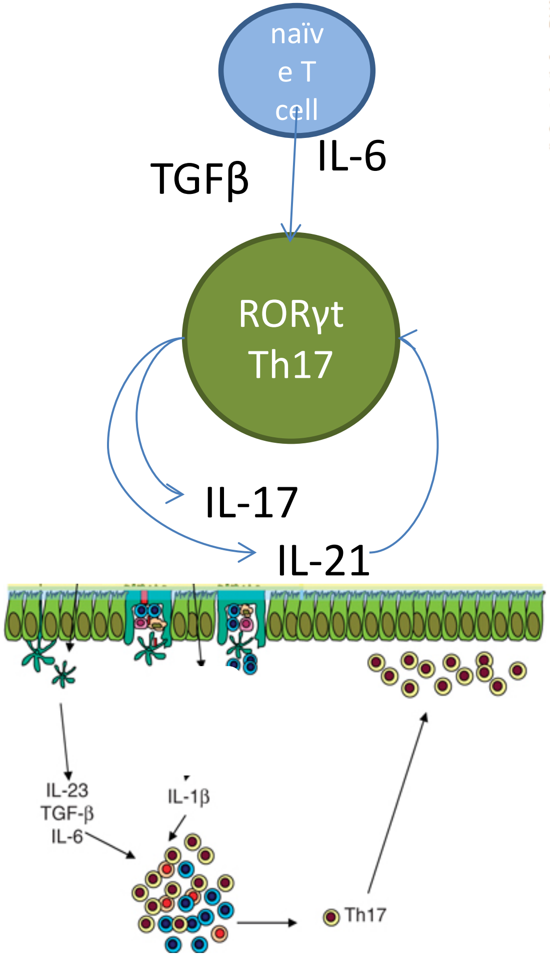
Administration of GW9662 promoted the upregulation of proinflammatory cytokines that correlated to significantly *lower levels of EAEC in feces* early during infection

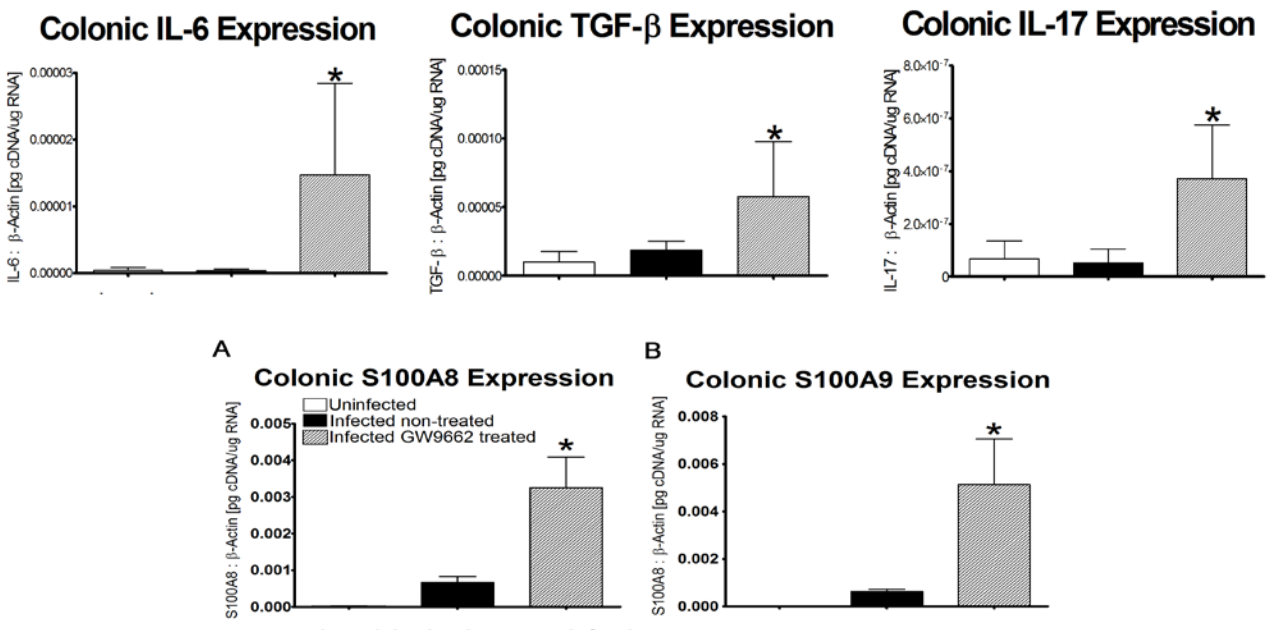






# Antimicrobial Peptides

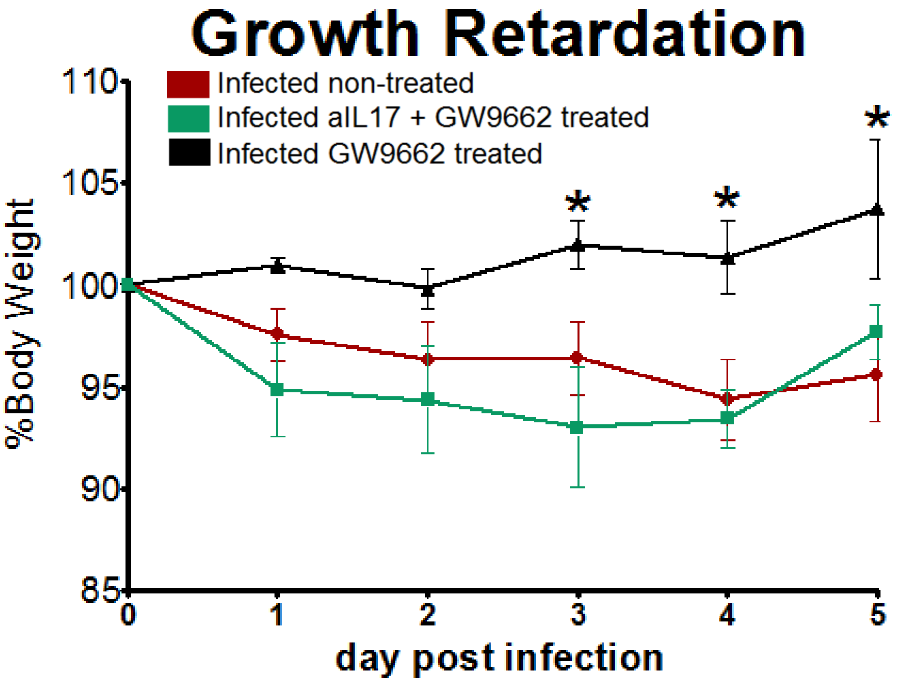


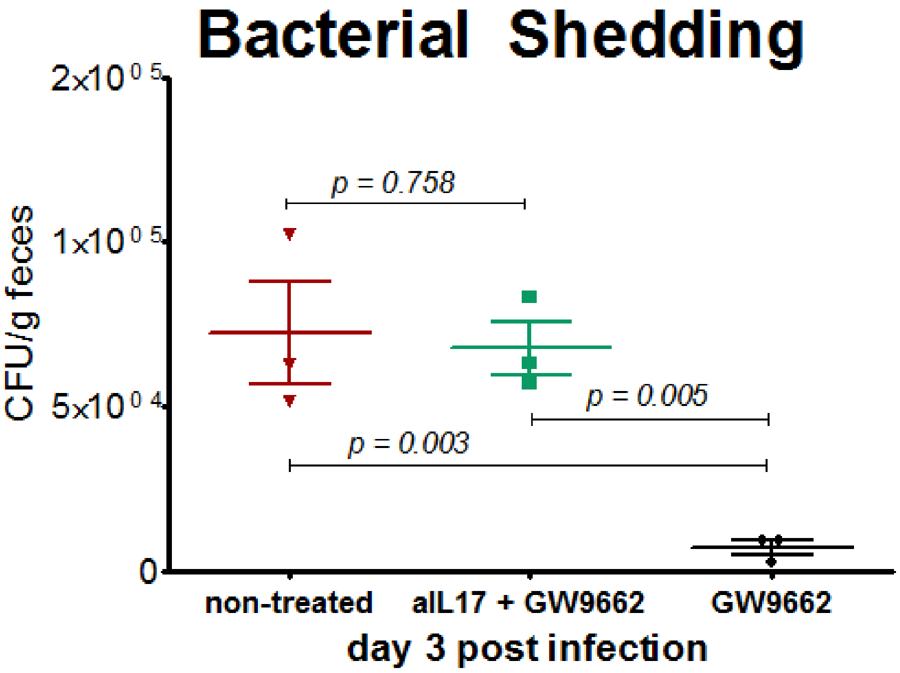


## Pharmacological blockade of PPARγ beneficial

Late during infection GW9662 treated mice expressed cytokines responsible for potentiating Th17 differentiation in addition to significantly higher levels of anti-microbial peptides.

# IL-17A Neutralization abrogates benefits of PPARγ Blockade


**Growth Retardation**


**Bacterial Shedding**

*Anti-IL-17A neutralizing antibody abrogates the beneficial effects of GW9662 in ameliorating disease based on weight loss and bacterial shedding*

---

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MIEP

MODELING IMMUNITY TO ENTERIC PATHOGENS

### COPASI & ENISI Tools and Models

# Computational Modeling

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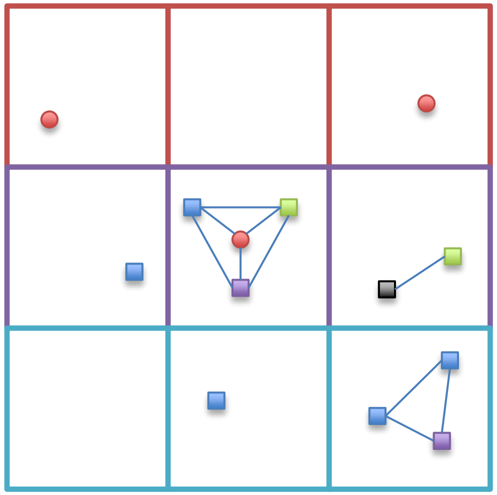
# ENISI Modeling Environment

- Host cells and bacteria are agents ($10^8$ agents)
- Agents move around gut mucosa and lymph nodes
- Agents in a same location are considered to be in contact
- Co-evolving Graphical Discrete Dynamical System (CGDDS): Linking mathematical theory and HPC
- Contacting agents can interact:
  - Agent-Agent interaction
  - Group-Agent interaction
  - Timed interaction
- Each agent represented as an automaton



## modeling approach

ODE models

cellular automata

potts models

agent-based (single cell) models

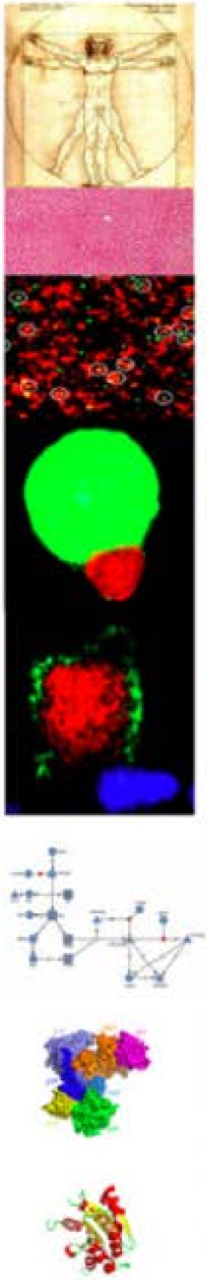
spatial PDE

ODE models

agent -based (single molecule)

molecular dynamics

## biological scale



$10^{0}$ m

organism

$10^{-2}$ m

organ systems single organ

cell populations

cell-cell communication

$10^{-5}$ m

single cells

sub-cellular compartmentalization intracellular distribution of molecules

$10^{-6}$ m

signaling / metabolic networks

protein interactions

$10^{-10}$ m

single molecules

biophysics ↔ molecular biology ↔ biochemistry ↔ cell biology ↔ histology ↔ physiology, anatomy

## experimental approach

radiological imaging

clinical chemistry

microscopy:

immunohisto-chemistry

flow cytometry

2-photon in vivo imaging

3-D confocal

proteomics

quantitative single-cell microscopy

protein biochemistry

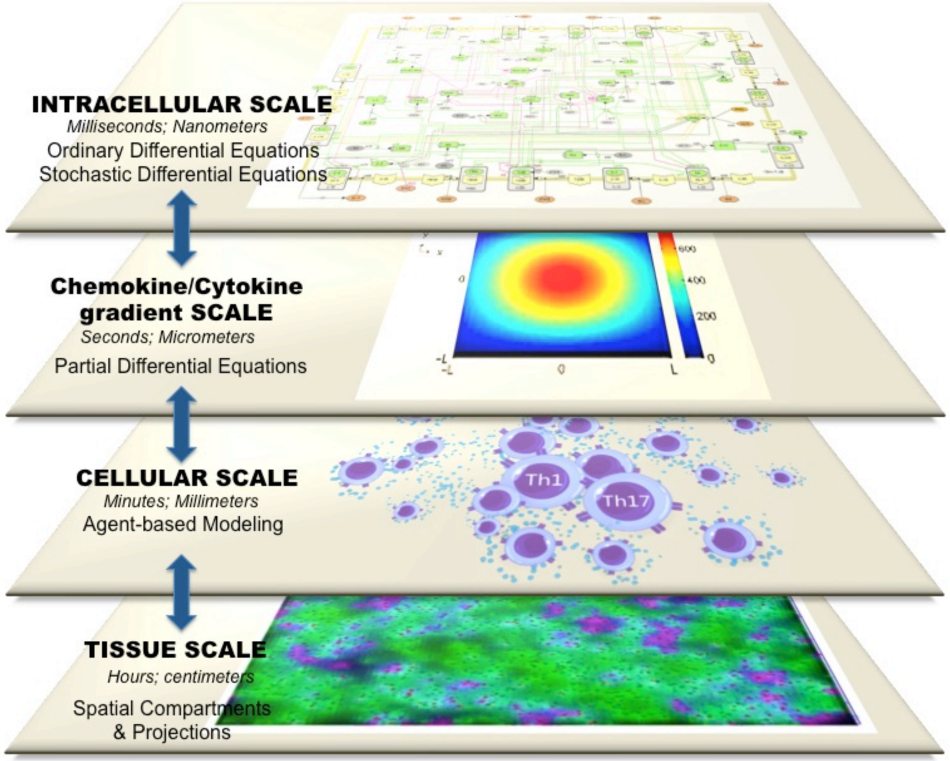
IP, SPR, Y2H

structural molecular biology

[Meier-Schellersheim'09]

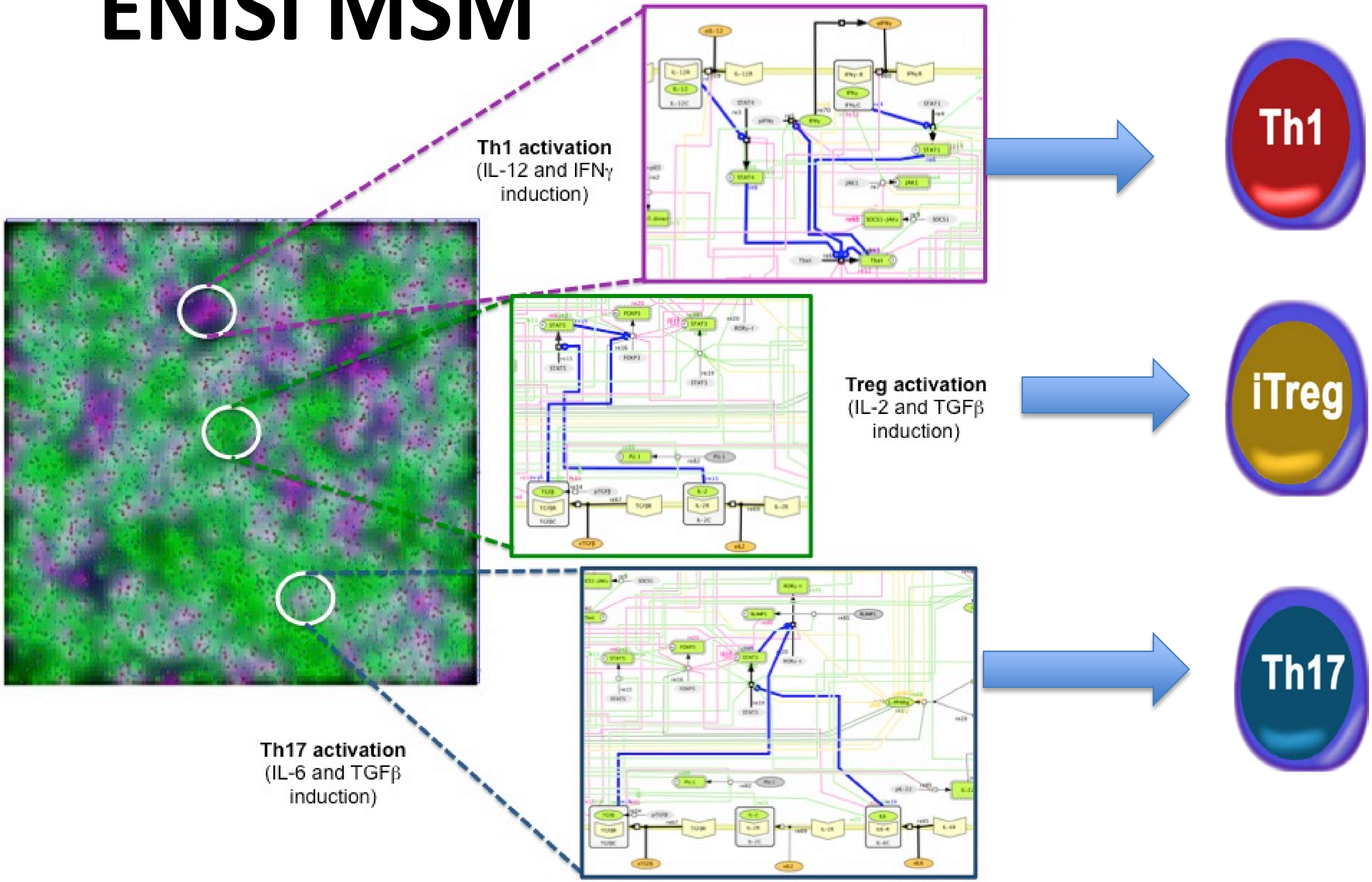
# ENISI MSM

- Tissue Scale
- Cellular Scale
- Chemokine Scale
- Intracellular Scale



| Scales | Time | Space | Mathematical Model | Software Environment |
|---|---|---|---|---|
| **Tissue** | Hours-Weeks | Centimeters | Spatial compartments | ENISI |
| **Cellular** | Minutes-Days | Millimeters | ABM | ENISI ABM |
| **Cytokines** | Seconds | Millimeters | PDE | ENISI |
| **Intracellular** | Millisecond | Nanometers | ODE/SDE | COPASI/ENISI SDE |

# ENISI MSM



**Th1 activation**
(IL-12 and IFNγ
induction)

**Treg activation**
(IL-2 and TGFβ
induction)

**Th17 activation**
(IL-6 and TGFβ
induction)

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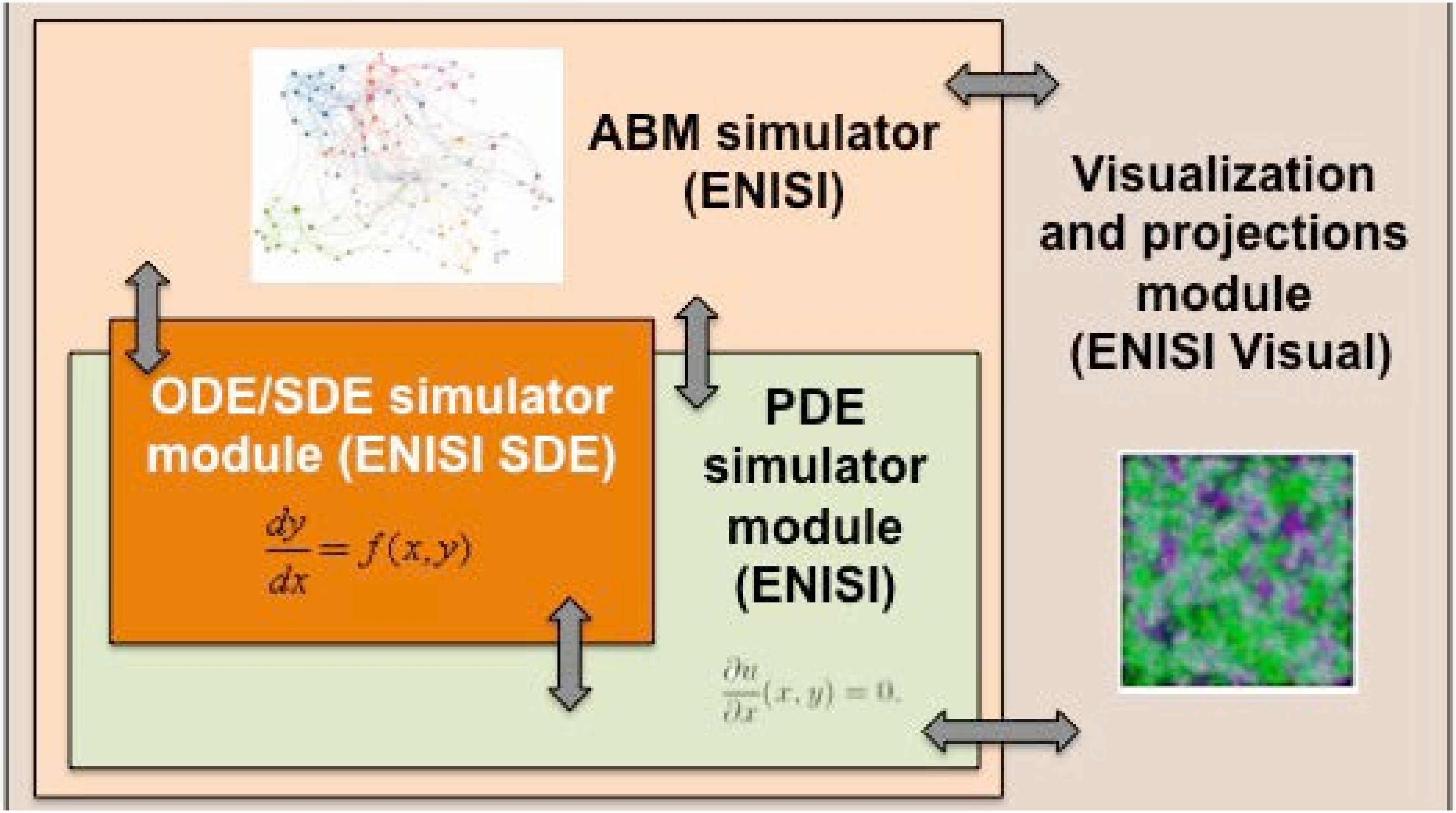
# ENISI MSM System Architecture



**ABM simulator (ENISI)**

**ODE/SDE simulator module (ENISI SDE)**

$$\frac{dy}{dx} = f(x,y)$$

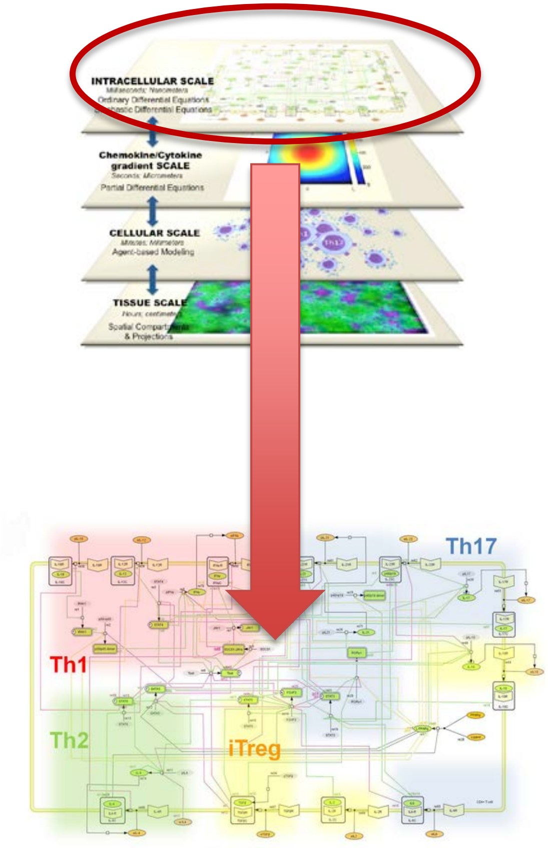
**PDE simulator module (ENISI)**

$$\frac{\partial u}{\partial x}(x,y) = 0.$$

**Visualization and projections module (ENISI Visual)**

# Intracellular Model: CD4+ T cells

- Comprehensive T cell differentiation model
  - 94 species
  - 46 reactions
  - 60 ODEs
- A deterministic model for *in silico* experiments with T cell differentiation: Th1, Th2, Th17, and Treg
- However, this model cannot represent the stochastic nature of T cell differentiation
  - Transcription
  - Translation rate



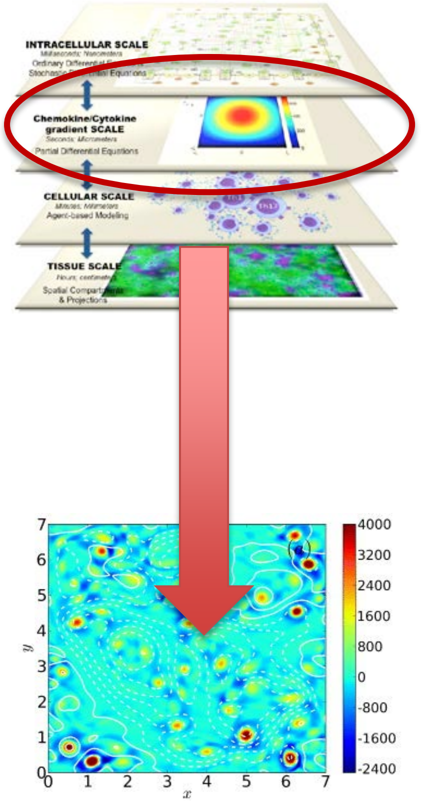
ODE intracellular model

# Chemokine/Cytokine Fluid Scale

- Consists of **concentration** of cytokines and chemokines
- Each cytokine or chemokine has **diffusion** process of the form:

$$\frac{\partial L}{\partial t} = D\left(\frac{\partial^2 L}{\partial x^2}+\frac{\partial^2 L}{\partial y^2}+\frac{\partial^2 L}{\partial z^2}\right) - \gamma L+\sigma$$

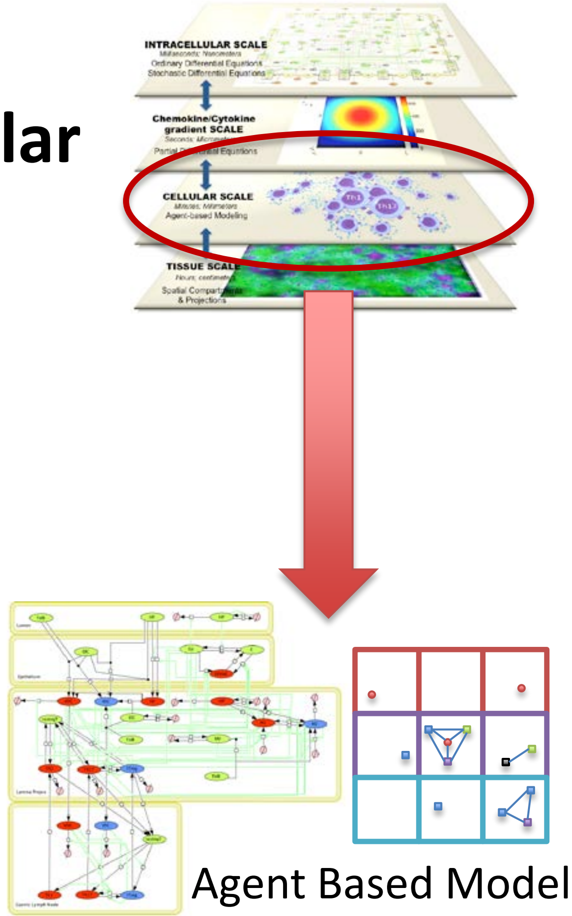
  - L(x,y,z)=concentration of cytokine/chemokine
  - D=diffusion rate
  - $\gamma$=degradation rate
- Realized with partial differential equations (PDE)



Cytokine/Chemokine Diffusion

# Cellular Scale: Agent Based Model

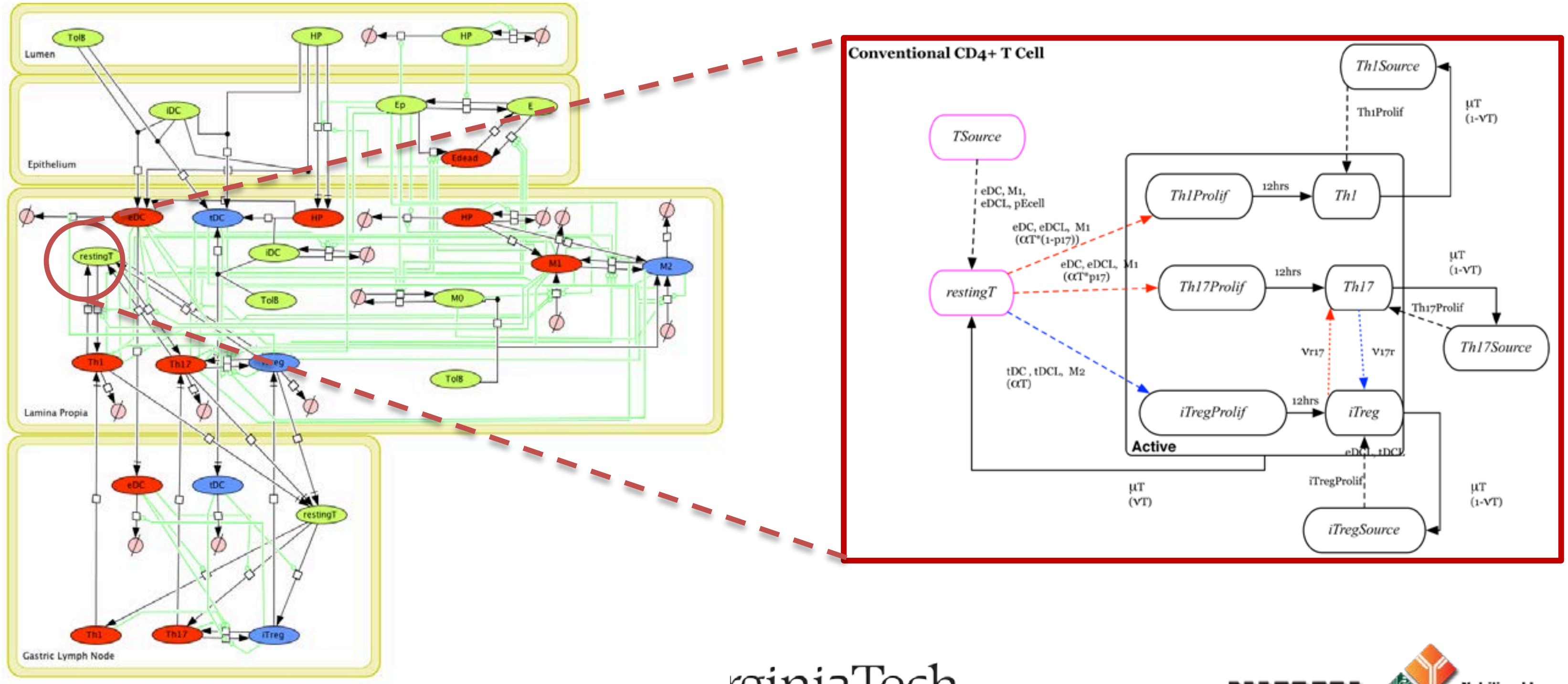
- Host cells and bacteria are agents
- Each agent has an associated **intracellular model**
- Agents move around gut mucosa and lymph nodes
- Nearby agents are "in contact"
- Agents in contact can interact:
  - Agent-Agent interaction
  - Group-Agent interaction
  - Timed interaction



Agent Based Model

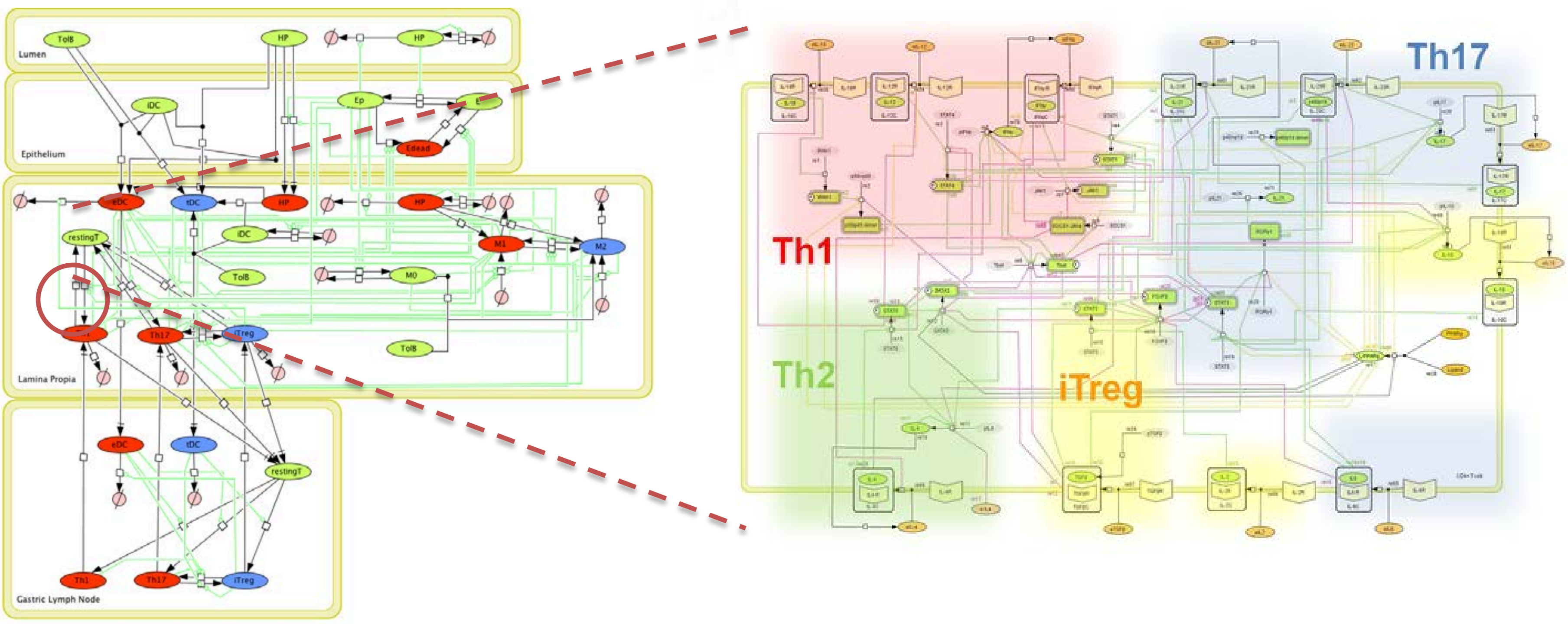
# ENISI V1

- In an early version of ENISI states of an agent were represented by rule-based automaton



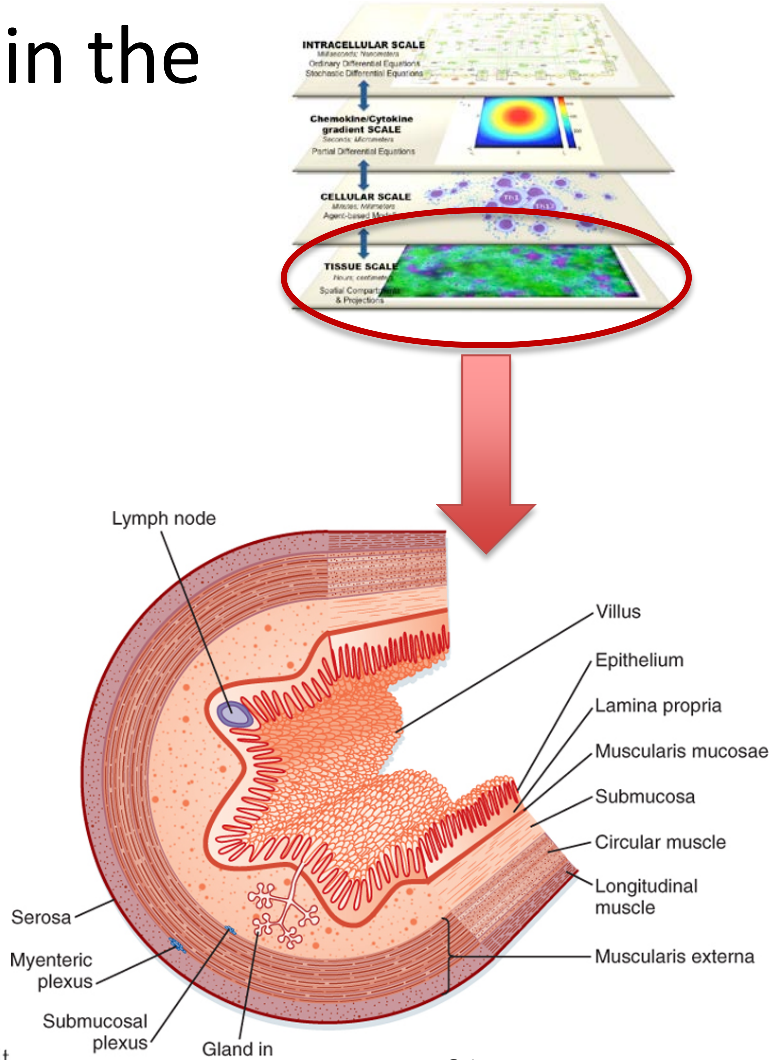
# ENISI MSM

- In current version of ENISI an agent has ODE based intracellular model



# Tissue Scale: ABM

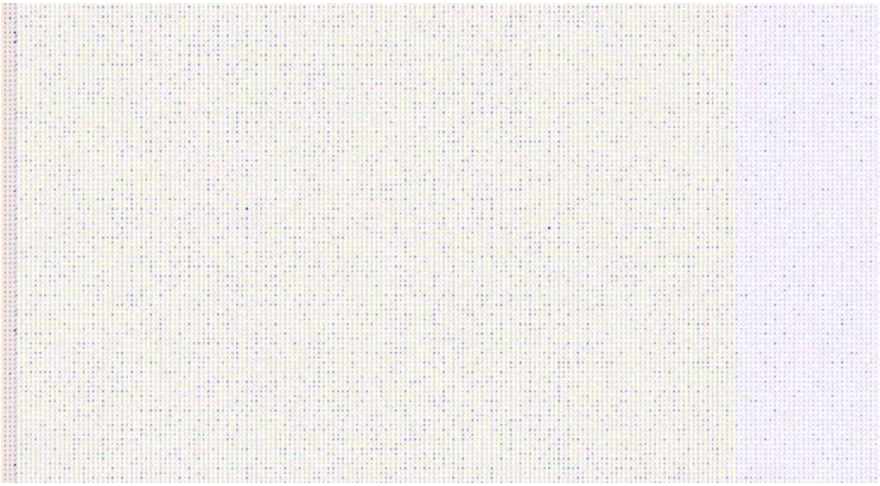
- Participating cells are located in the GI tract.
- Cells move in the tissue sites.
- Tissue Sites:
  - Lumen
  - Epithelial Cells
  - Lamina Propria
  - Gastric Lymph Node



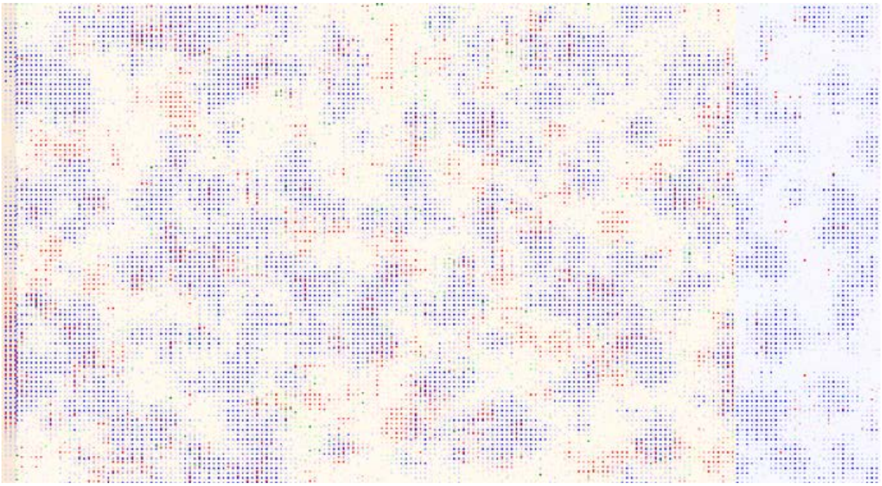
GI tract

# *In silico* Gut Lesion Formation

- Developing visualizations of cellular movements
- Lesion formation is observed in chemotaxis-based movement models

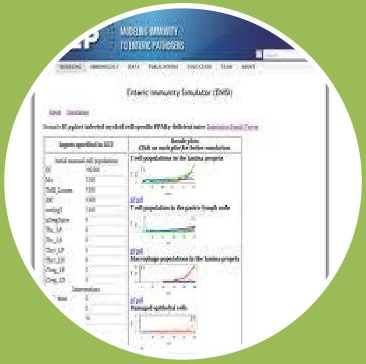


Without Chemotaxis
(Uniform Mix)



With Chemotaxis
(Formation of Lesion)

# VisIt Workflow

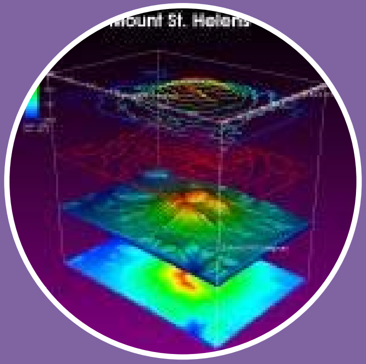


## Simulation Engine (ENISI)

- Generates output files

## Post-Processing and *.silo creation

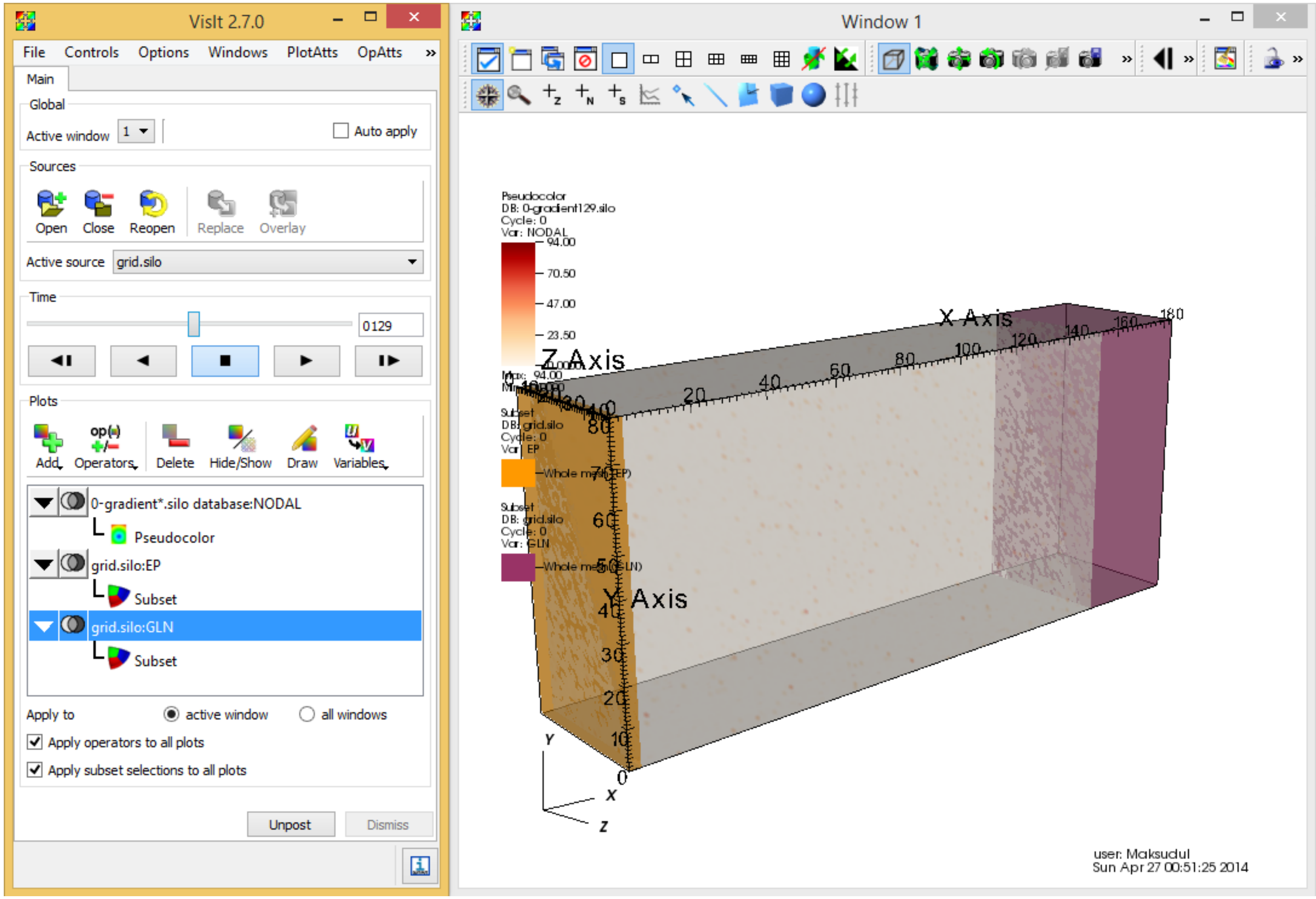
- Generates silo files from ENISI output



## Visualize with **VisIt** GUI

- Make plots with various options

# ENISI 3-D Visualizations



VisIt 2.7.0

Active window: 1

☐ Auto apply

Active source: grid.silo

Time: 0129

Plots:
- 0-gradient*.silo database:NODAL
  - Pseudocolor
- grid.silo:EP
  - Subset
- grid.silo:GLN
  - Subset

Apply to: ● active window ○ all windows

☑ Apply operators to all plots

☑ Apply subset selections to all plots

Window 1

Pseudocolor
DB: 0-gradient129.silo
Cycle: 0
Var: NODAL

Max: 94.00
Min: 0.000

Subset
DB: grid.silo
Cycle: 0
Var: EP

Subset
DB: grid.silo
Cycle: 0
Var: GLN

user: Maksudul
Sun Apr 27 00:51:25 2014

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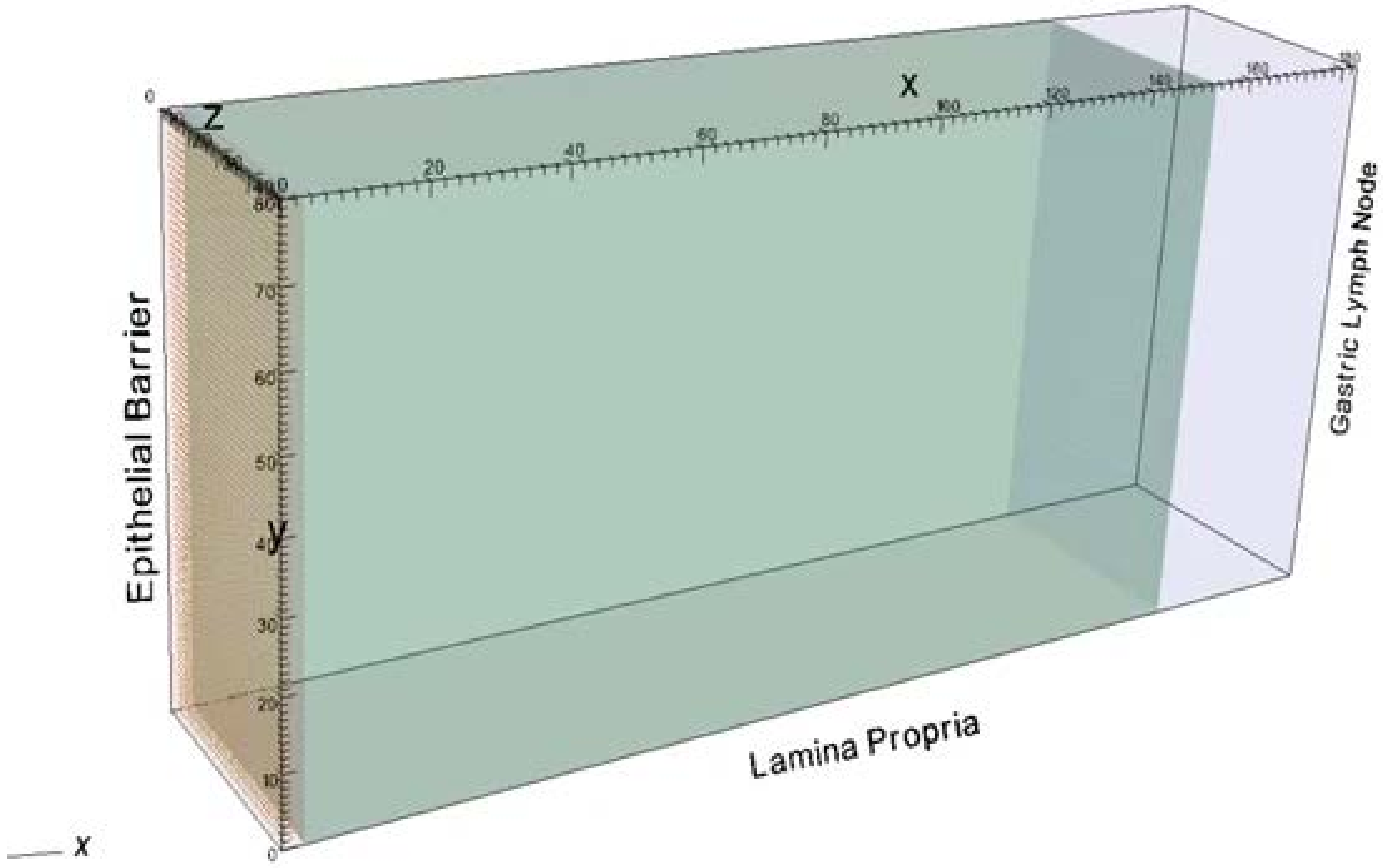
# ENISI 3-D Visualizations



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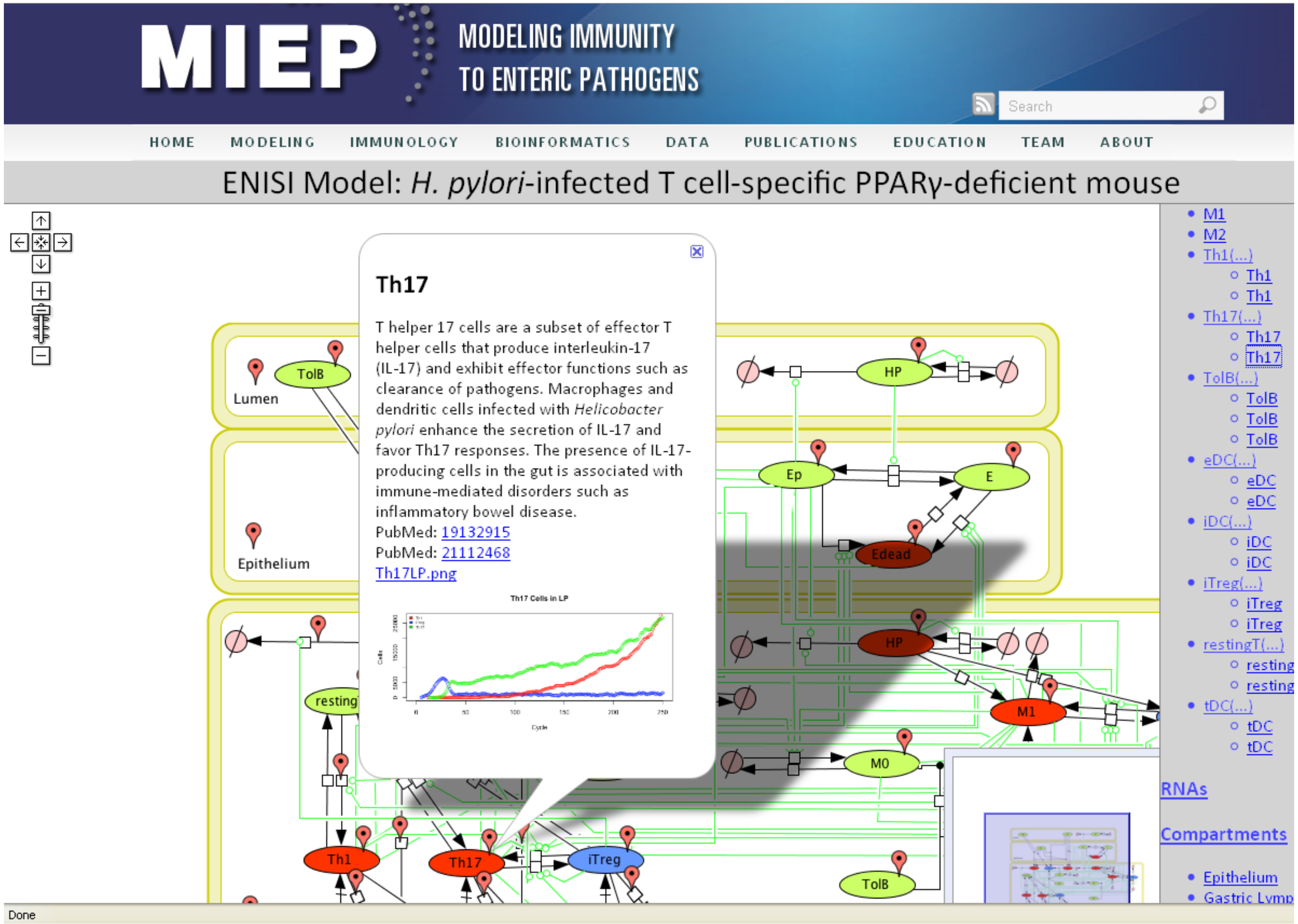
# Sharing: ENISI Pathway Navigator

- Network available at the MIEP web portal
- Interactive Modeling Tool
  - The user has the ability to modify parameters and experimental setup for the *H. pylori* model and simulate it on MIEP high performance cluster
- Statistical Results
  - We provide statistical results based on replicates of ENISI simulations displaying mean and standard deviation

# Results in ENISI Pathway Navigator



ENISI Model: *H. pylori*-infected T cell-specific PPARγ-deficient mouse

**Th17**

T helper 17 cells are a subset of effector T helper cells that produce interleukin-17 (IL-17) and exhibit effector functions such as clearance of pathogens. Macrophages and dendritic cells infected with *Helicobacter pylori* enhance the secretion of IL-17 and favor Th17 responses. The presence of IL-17-producing cells in the gut is associated with immune-mediated disorders such as inflammatory bowel disease.

PubMed: 19132915

PubMed: 21112468

Th17LP.png

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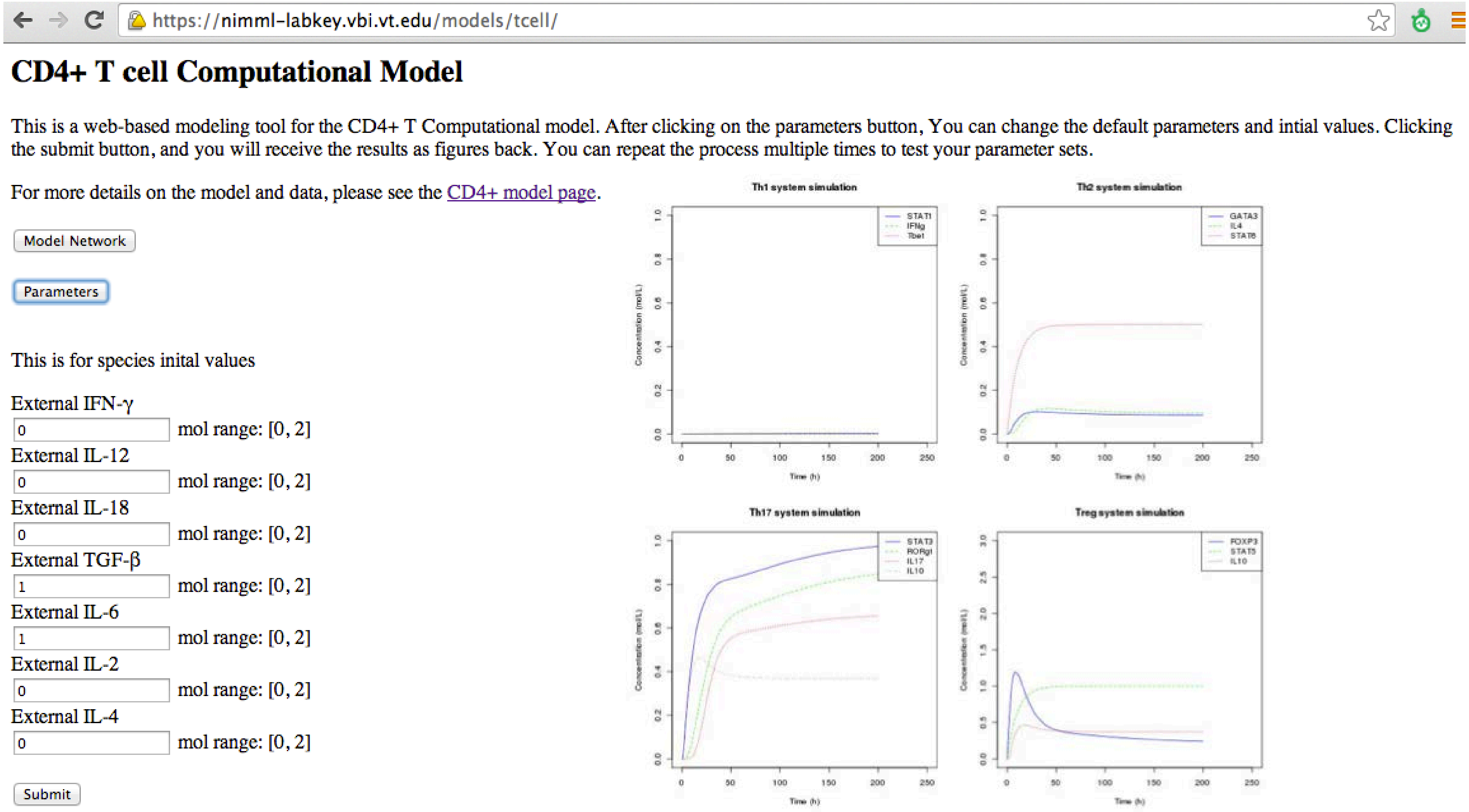
# ENISI ISE Web Interface



https://nimml-labkey.vbi.vt.edu/models/tcell/

## CD4+ T cell Computational Model

This is a web-based modeling tool for the CD4+ T Computational model. After clicking on the parameters button, You can change the default parameters and intial values. Clicking the submit button, and you will receive the results as figures back. You can repeat the process multiple times to test your parameter sets.

For more details on the model and data, please see the CD4+ model page.

This is for species inital values

External IFN-γ
0 mol range: [0, 2]
External IL-12
0 mol range: [0, 2]
External IL-18
0 mol range: [0, 2]
External TGF-β
1 mol range: [0, 2]
External IL-6
1 mol range: [0, 2]
External IL-2
0 mol range: [0, 2]
External IL-4
0 mol range: [0, 2]

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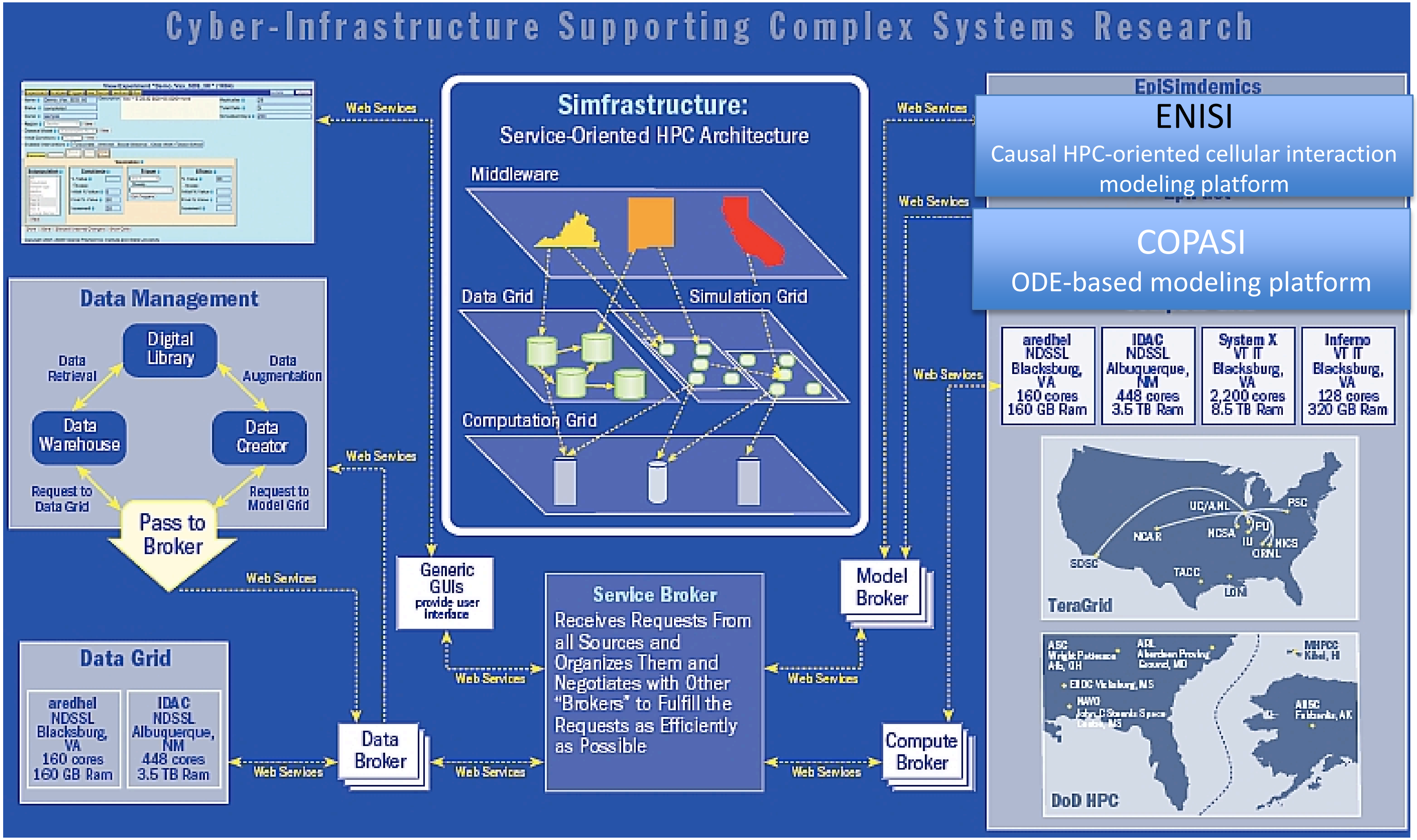
# Modeling Environment



## ENISI

Causal HPC-oriented cellular interaction modeling platform

## COPASI

ODE-based modeling platform

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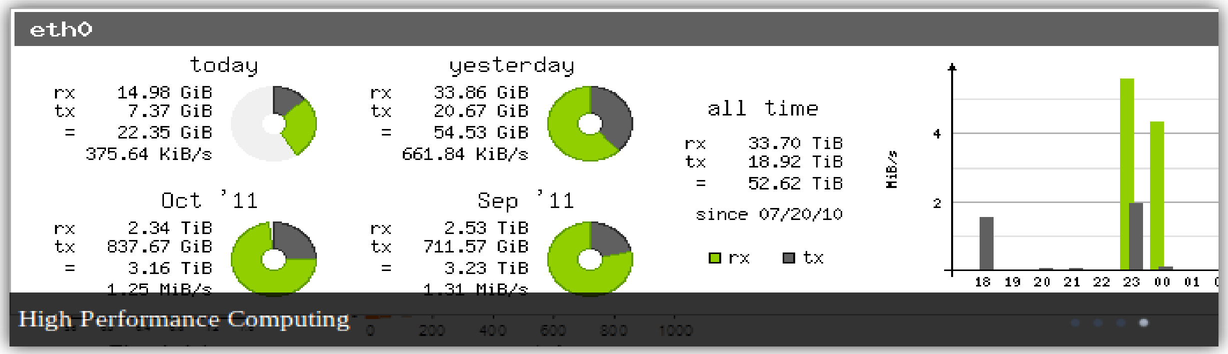

High Performance Computing

## NEWS AND ANNOUNCEMENTS

### Center for Modeling Immunity to Enteric Pathogens Releases a Revolutionary Modeling and Simulation Software: ENteric Immunity SImulator

**BLACKSBURG, Va., Oct. 5th, 2011** – Researchers from the Center for Modeling Immunity to Enteric Pathogens (MIEP) at the Virginia Bioinformatics Institute have released an upgrade to the revolutionary ENteric Immunity SImulator (ENISI) software. The ENISI models immune responses to beneficial and harmful bacteria that enter the gastrointestinal tract (GI) of mice, pigs and humans. ENISI allows users to create enteric systems such as the gut-associated mucosal immune system *in silico*, providing a better glimpse of how the immune system responds to pathogens that invade the bacteria-rich environment of the gut. [More ...]

### Healthy Volunteers Needed to Study Immune Responses to Intestinal Pathogens

**BLACKSBURG, Va., September 28, 2011** – You may be interested in a clinical study the Center for Modeling Immunity to Enteric Pathogens (MIEP) is conducting. We Are Looking for Healthy Volunteers to Study Immune Responses to Intestinal Pathogens. Compensation is available if you qualify and are enrolled in the study. Please Contact (434) 924-9922 if you live near Charlottesville or (540) 231-7276 if you live near Blacksburg for more information. [More ...]

## PRESS RELEASES

- Center for Modeling Immunity to Enteric Pathogens Releases a Revolutionary Modeling and Simulation Software: ENteric Immunity SImulator
- Center for Modeling Immunity to Enteric Pathogens Contributes Code to The Open Source Community
- Center for Modeling Immunity to Enteric Pathogens to Release New

## SELECTED PUBLICATIONS

- ENteric Immunity SImulator: A tool for *in silico* study of gut immunopathologies
- Modeling the Mechanisms of Action Underlying the Plasticity of the CD4+ T cell Differentiation Process
- Abscisic acid Regulates Inflammation via Ligand-Binding Domain-Independent Activation of PPAR gamma

## MIEP MISSION

The Center for Modeling Immunity to Enteric Pathogens (MIEP) is a NIAID funded program with the mission of understanding the mechanisms of action underlying immune responses to enteric pathogens.

## UPCOMING EVENTS

MIEP team to present ENteric Immunity SImulator (ENISI) at IEEE International Conference on Bioinformatics and Biomedicine.

MIEP team to attend Annual Meeting of the Modeling Immunity for Biodefense Program, Bethesda, MD Nov 1-2.

## RESEARCH HIGHLIGHTS

**PPARγ Modulates the Plasticity between Th17 and iTreg**

The MIEP team has created a network model of CD4+ T cell differentiation that reveals how the transcription factor peroxisome proliferator-activated receptor γ (PPARγ) modulates differentiation from Th17 to iTreg. [more ...]

# MIEP Team

## Virginia Bioinformatics Institute

**Josep Bassaganya-Riera -** Principal Investigator and Center Director

**Jim Walke** – Project Manager

**Raquel Hontecillas -** Immunology Lead
- **Barbara Kronsteiner-Dobramysl –** Immunology Researcher
- **Xiaoying Zhang –** Immunology
- **Pinyi Lu -** Bioinformatics and Modeling
- **Adria Carbo -** Immunology and Modeling
- **Kristin Eden-** Immunology and Modeling
- **Monica Viladomiu –** Immunology
- **Irving C. Allen** - Immunology
- **Ken Oestreich** - Immunology
- **Casandra Philipson –** Immunology and Modeling
- **Eric Schiff, Patrick Heizer, Nathan Palmer, Mark Langowski, Chase Hetzel, Emily Fung** – Interns

**David Bevan**- Education Lead

## Virginia Bioinformatics Institute (continued)

**Madhav Marathe -** Modeling Lead
- **Keith Bisset -** Modeling Expert
- **Stephen Eubank -** Modeling Expert
- **Tricity Andrew-** Modeling GRA
- **Maksudul Alam -** Modeling GRA

**Stefan Hoops/Yongguo Mei -** Bioinformatics Leads
- **Pinyi Lu** – Bioinformatics GRA
- **Pawel Michalak** – Genomics Tools
- **Nathan Liles** - Bioinformatician
- **Xinwei Deng** – Statistical Analysis

## University of Virginia

**Richard Guerrant -** Infectious Disease Expert
- **Cirle A. Warren -** Infectious Disease Expert
- **David Bolick -** Sr. Laboratory and Research Specialist

NIAID

**Funding:** Supported by NIAID Contract No. HHSN272201000056C

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# MMI Acknowledgements

- Adria Carbo
- Kimberly Borkowski
- David Bevan
- Jim Walke
- Kathy O’hara
- Noah Philipson
- Rachel Robinson
- Traci Roberts
- Tiffany Trent
- Kristopher Monger
- Ivan Morozov
- Josh Dunbar

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# MIEP

MODELING IMMUNITY
TO ENTERIC PATHOGENS

Modeling Mucosal Immunity
Summer School & Symposium

## We thank our sponsors:

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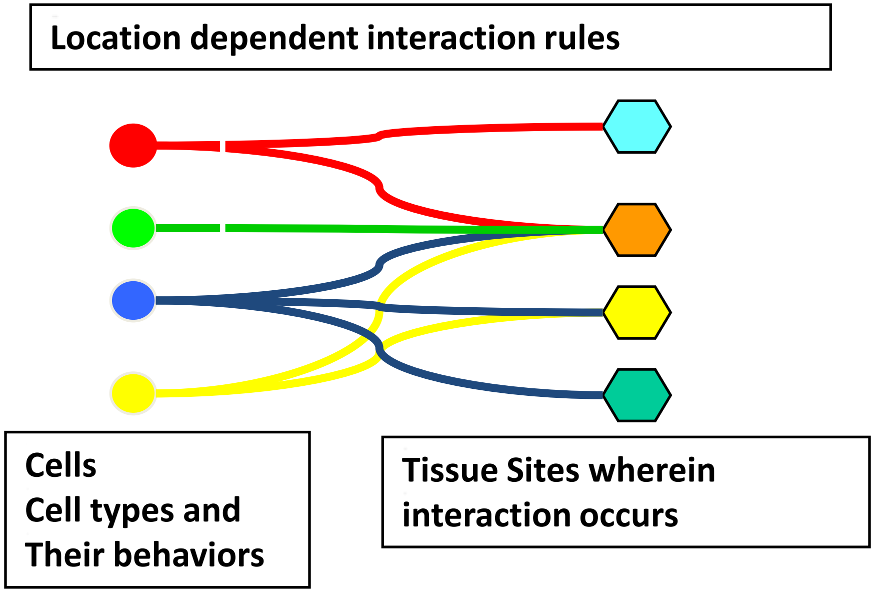
# Mathematical Model

- Each individual occupies a state (cell-type, immunological-state, location)
- Location changes based on cell-type/immunological state creating a contact network
- State changes upon contact according to specific rules
- Uses ENISI environment

**Can incorporate:**

- Spatial heterogeneity
- Stochasticity
- Phenotype emergence through individual evolution
- Moving from $10^4$ to $10^8$ agents within the model



**Location dependent interaction rules**

**Cells**
**Cell types and**
**Their behaviors**

**Tissue Sites wherein**
**interaction occurs**