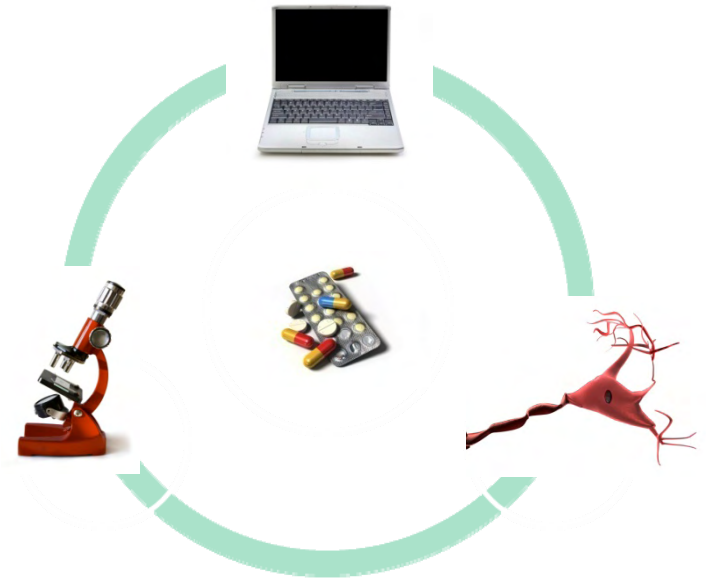


# Building a Computational Modeling Foundation for Emerging Information in Inflammatory Bowel Disease



Liam O'Mahony<sup>1,2</sup> and Tandy Herren<sup>3</sup>, John Bienenstock<sup>4</sup>,  
Fergus Shanahan<sup>1</sup>

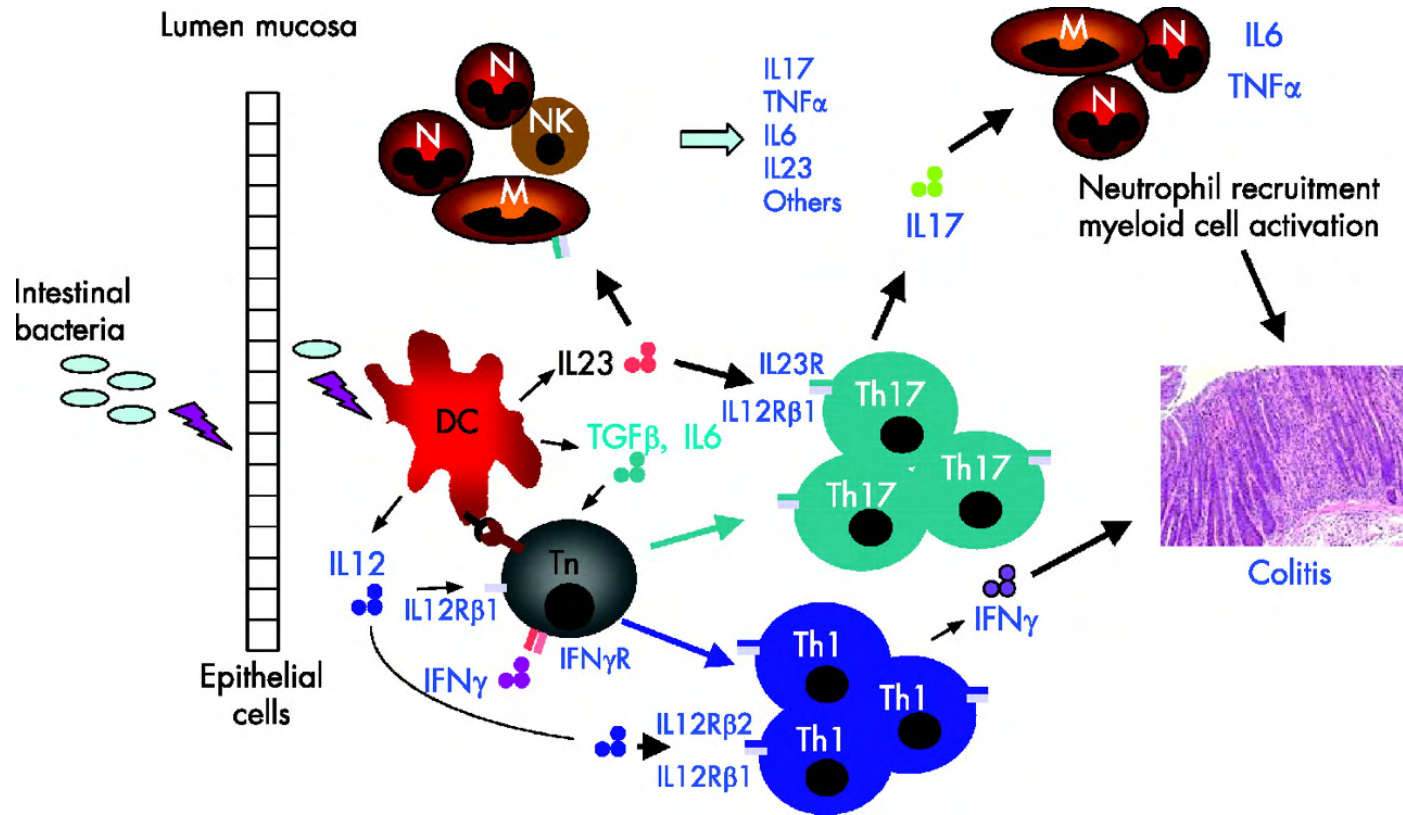
<sup>1</sup>Alimentary Pharmabiotic Centre, University College Cork, Ireland

<sup>2</sup>Swiss Institute of Allergy and Asthma research (SIAF), Davos, Switzerland

<sup>3</sup>DNA Print Pharmaceuticals, Harrisburg, USA

<sup>4</sup>McMaster University, Hamilton, Canada

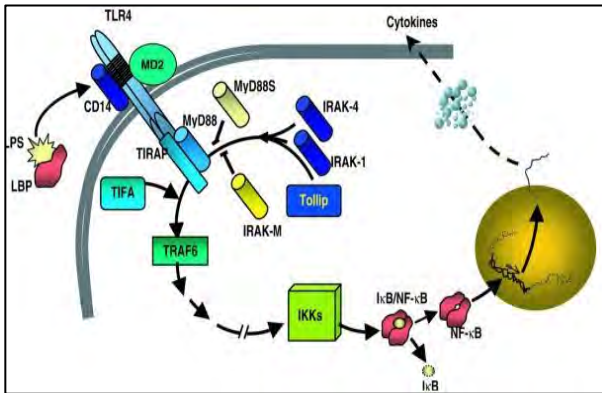
# Cellular Mechanisms in IBD



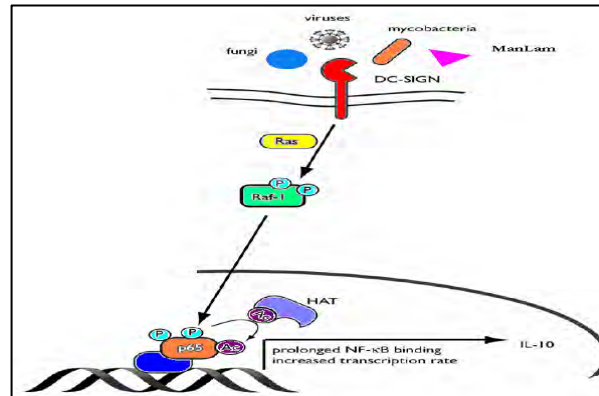
- Dendritic cells integrate environmental signals into a co-ordinated immune response which may result in inflammation – link innate and adaptive immune responses
- Dendritic cell activation is substantially influenced by Pattern Recognition Receptor (PRRs) activation



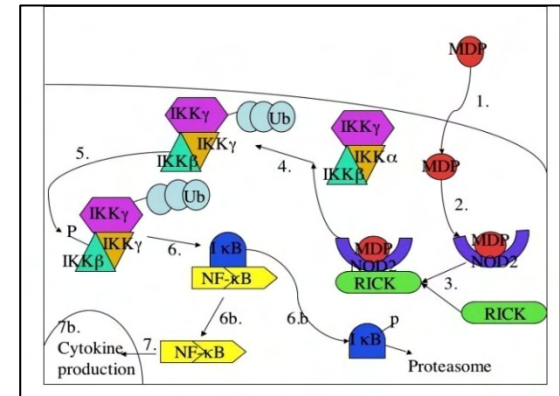
# Can We Model Dendritic Cell Signalling Pathways?



TLR-4



DC-SIGN

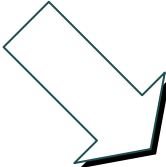


NOD-2

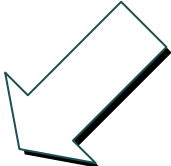
Use the model to predict NF- $\kappa$ B activity in response to simulated exposure to LPS, MDP, and ManLAM as a function of time and starting concentrations.

# COMPUTATIONAL MODEL

Ligand Exposure and Concentration

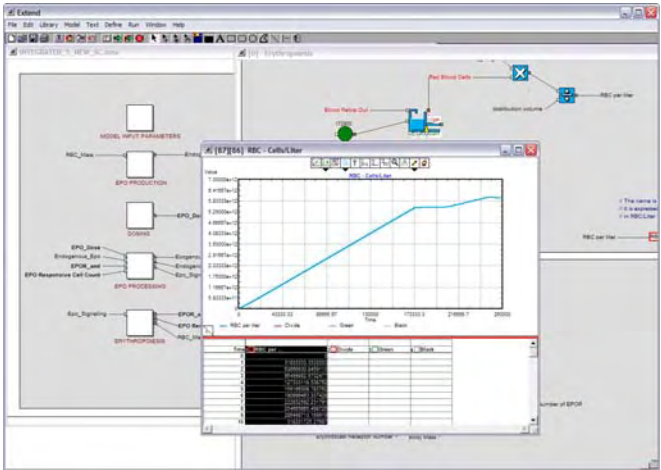


Receptor Kinetics (TLR4, DC-SIGN, and NOD2)



DC-SIGN Signaling Pathway

NOD2 Signaling Pathway



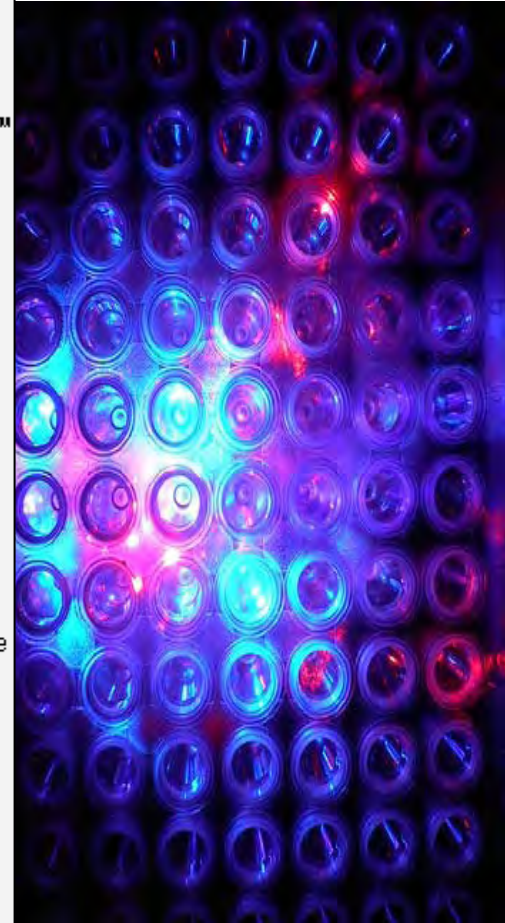
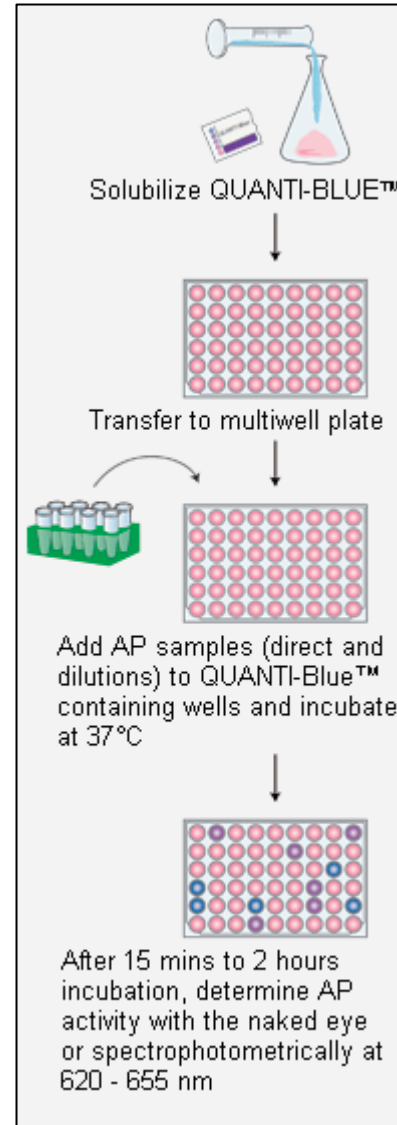
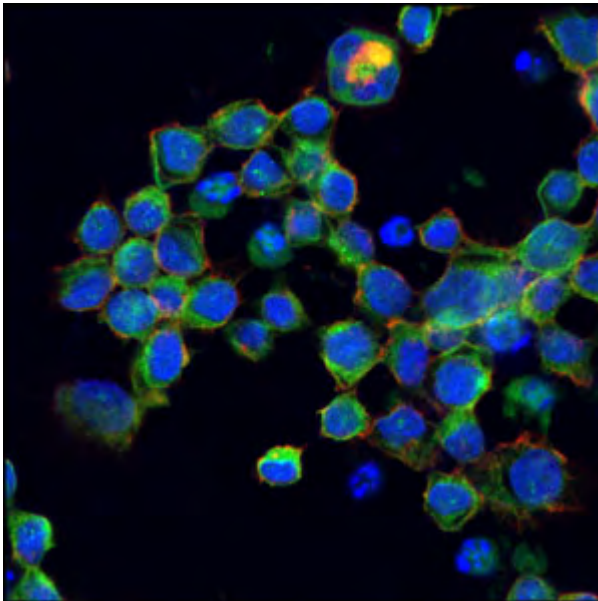
TLR4 Signaling Pathways (MyD88 dependent and independent)

# Model Basics

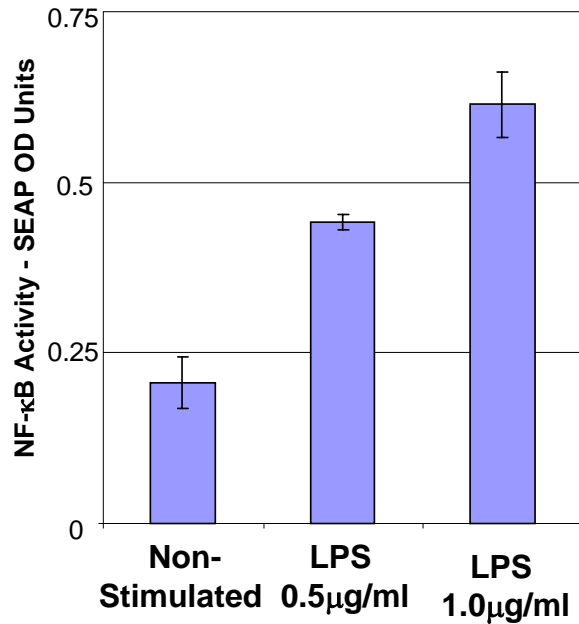
- The model starting point involved using published simulations of parts of the proposed pathways (Lipniacki et al 2004; Selvarjoo 2006)
- The model is represented by a series of ordinary differential equations describing the kinetics of interactions within the pathways
- Receptor kinetics are modeled using four parameters:  $K_{on}$ ,  $K_{off}$ ,  $K_{in}$ , and recycling rate.
- Some parameter values were obtained from published studies; others by fitting the model to data

# Laboratory Model

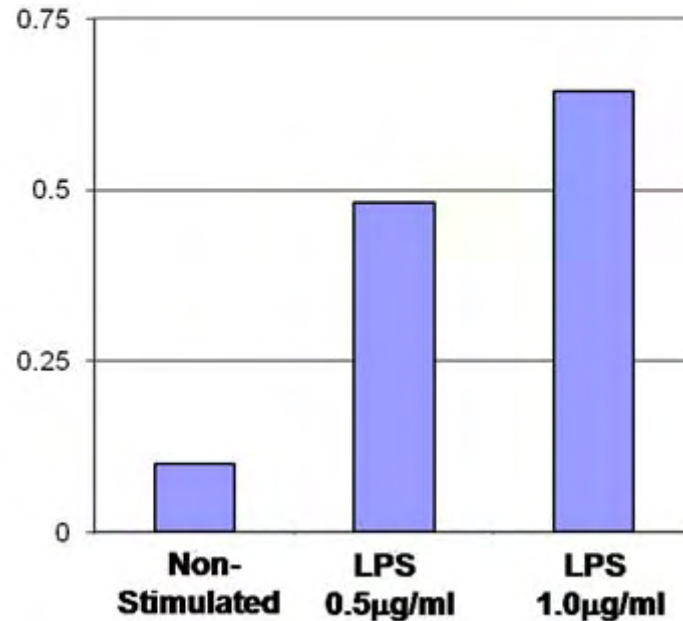
THP-1 cells are human peripheral blood monocytic cells which express a wide range of PRRs including TLR-4, DC-SIGN and NOD-2.



# LPS Stimulated NF-κB Activation

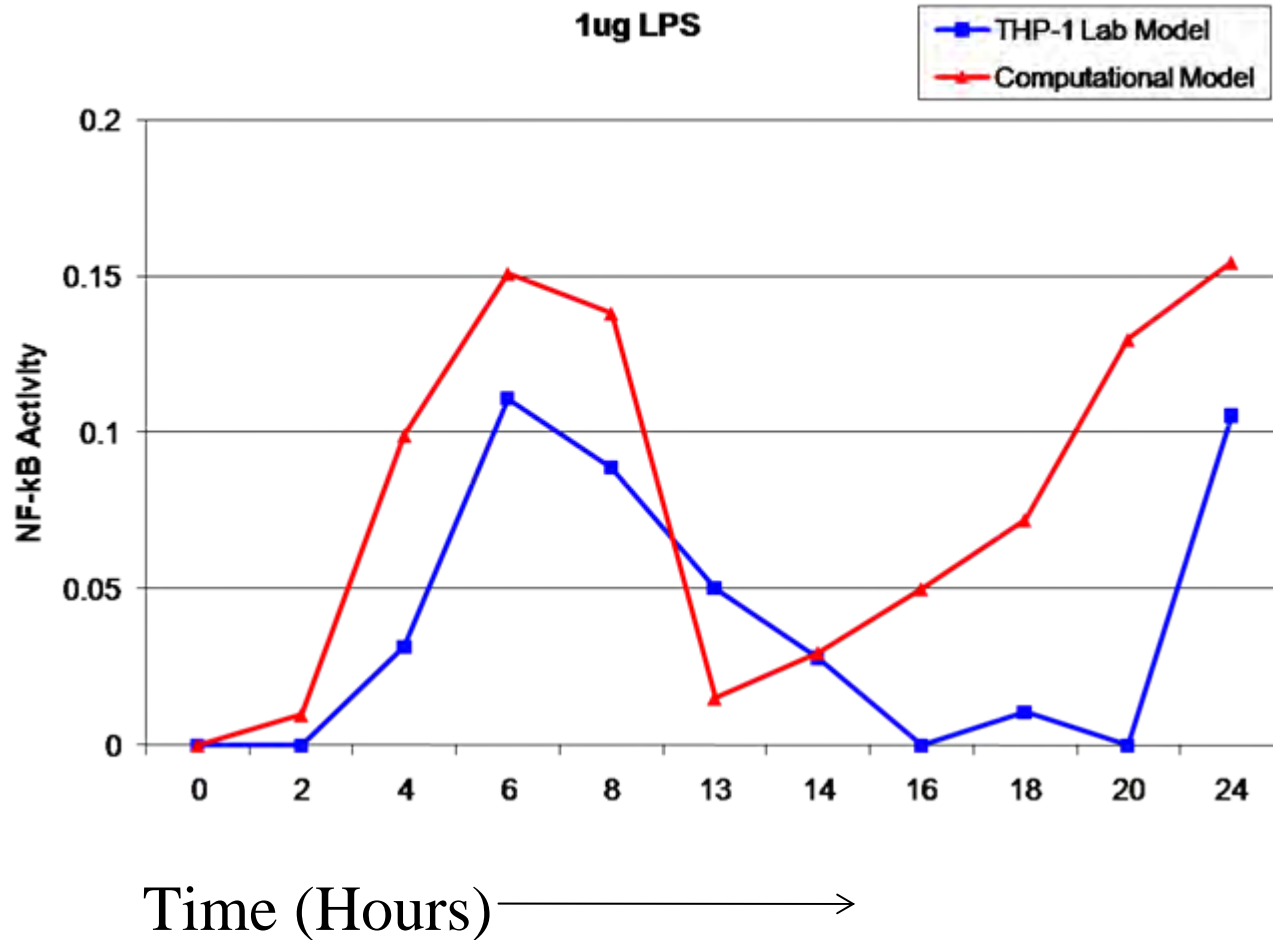


THP-1 Lab Model

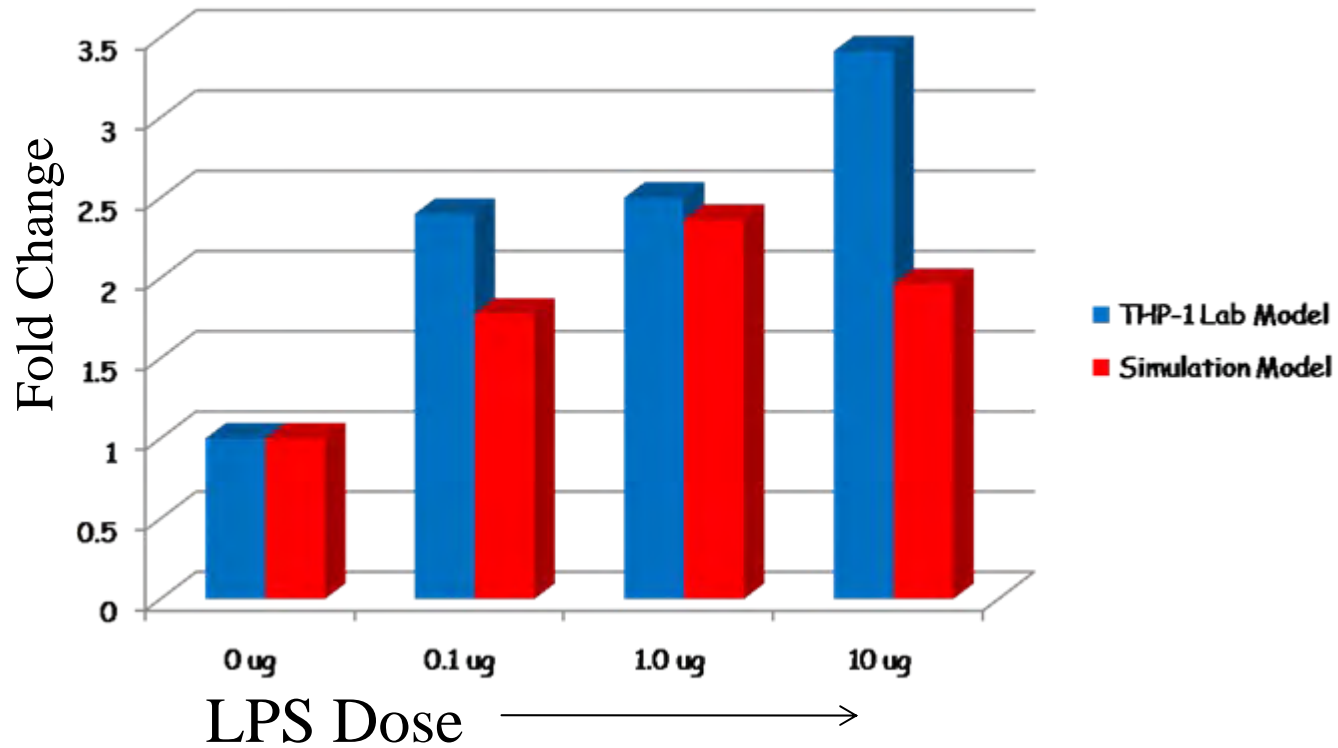


Computational Model

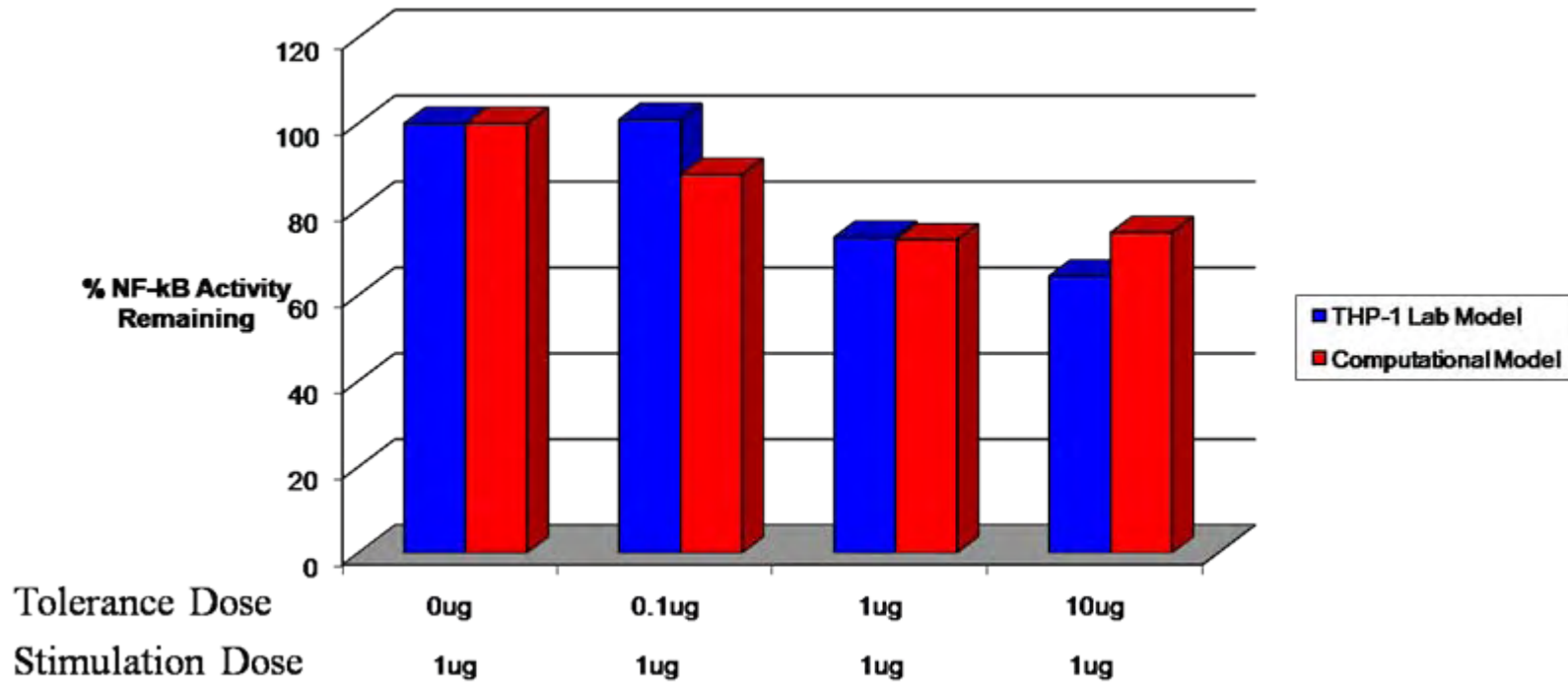
# Biphasic NF- $\kappa$ B Activation



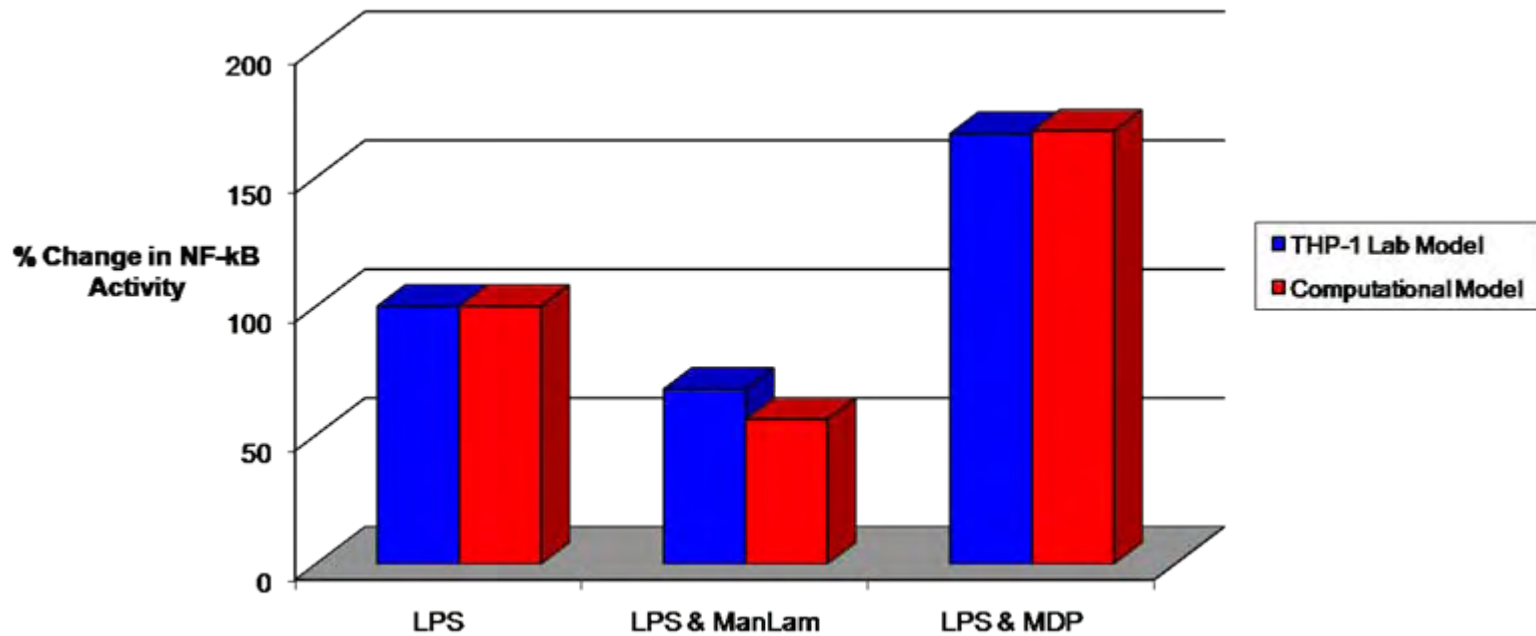
# TLR -4 Cell Surface Receptor Expression



# LPS Tolerance

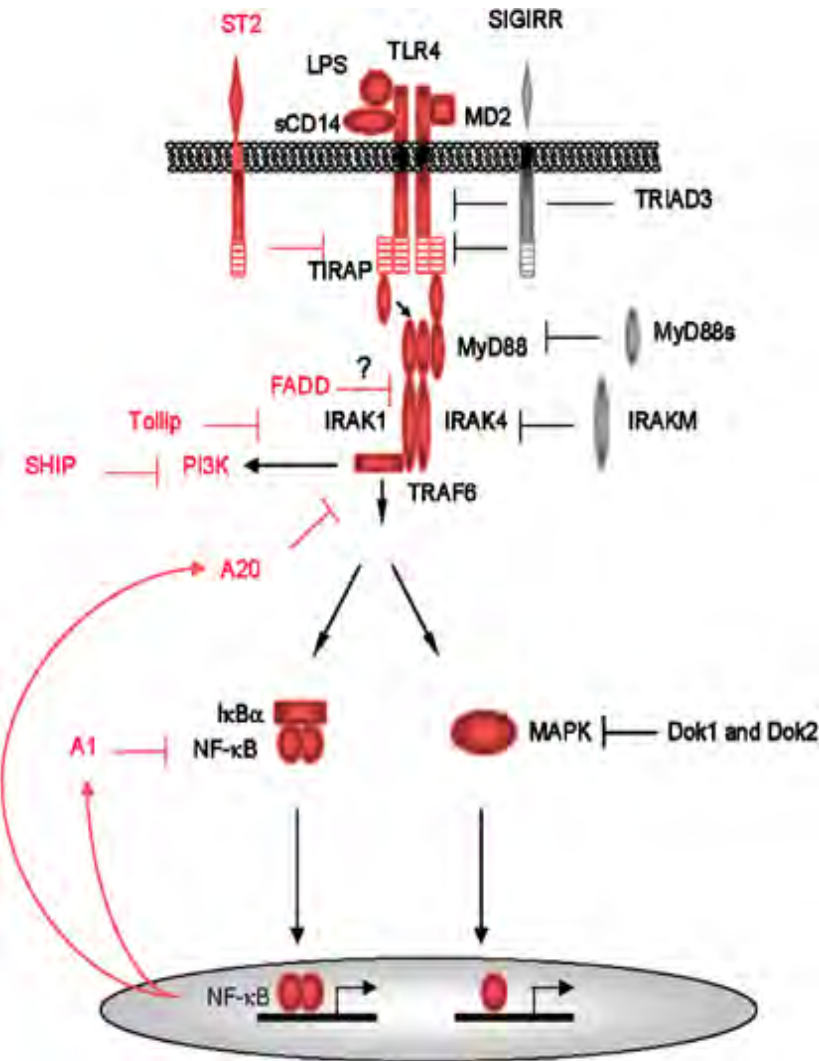


# PRR Co-Activation



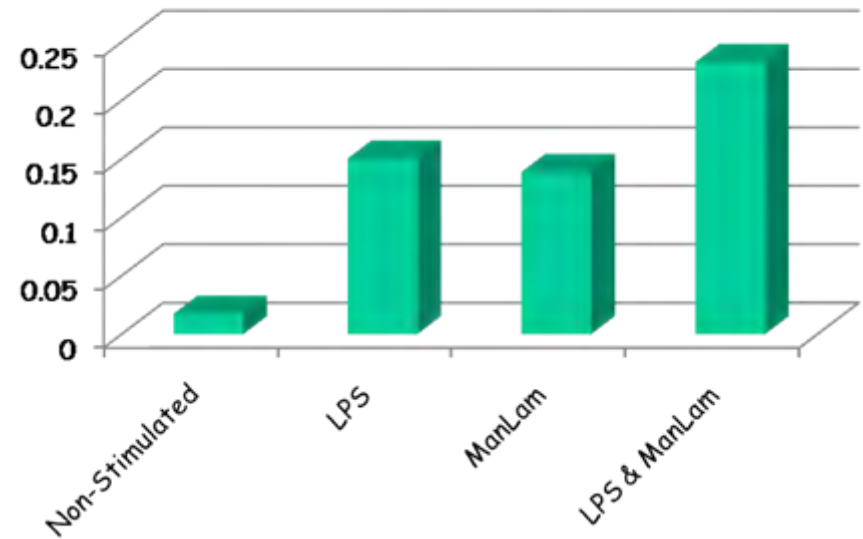
LPS stimulation dose was 1.0  $\mu\text{g}$

# Why is DC-SIGN Activation Modulating TLR-4 Induced NF- $\kappa$ B Activity?

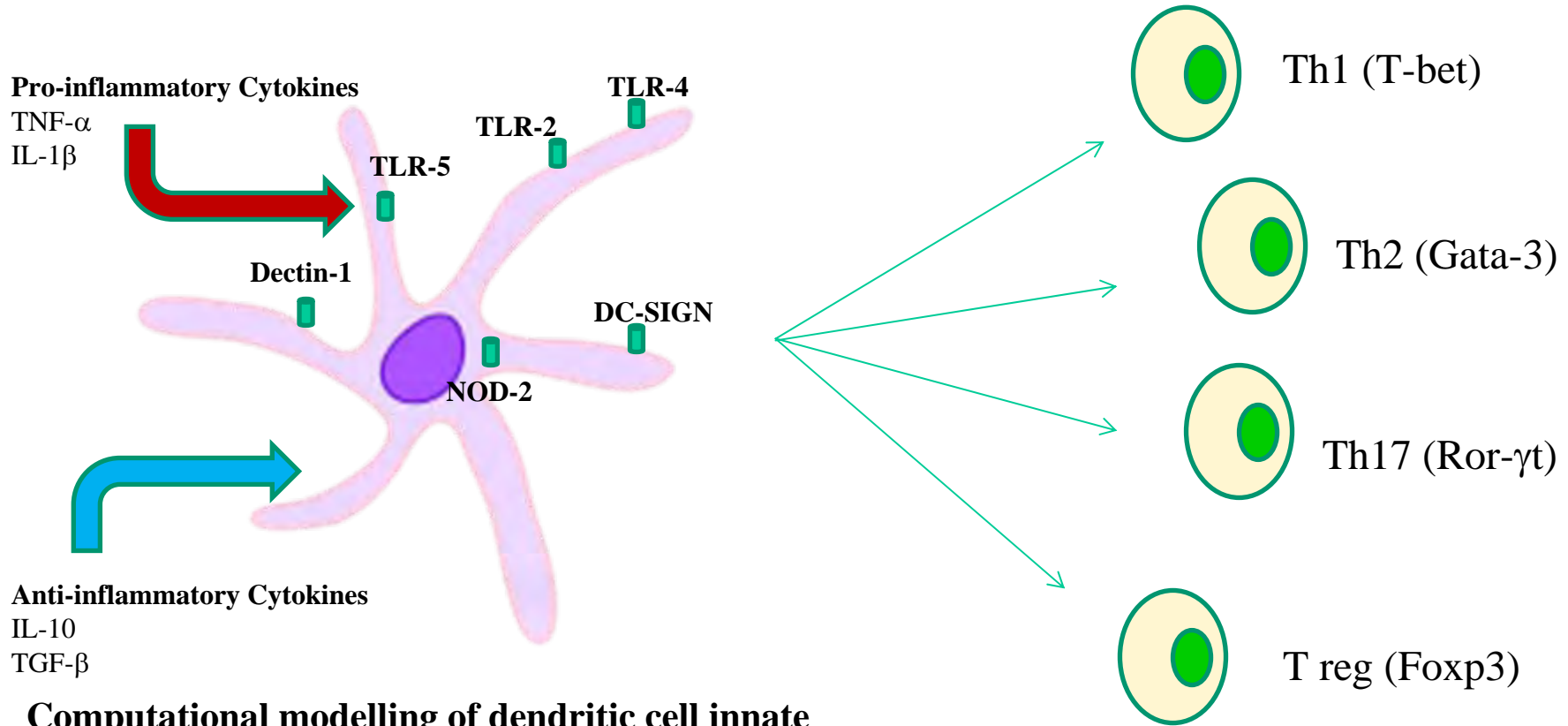


Pathak et al., Journal of Biological Chemistry 2005

IRAK-M Simulation by Computational Model



# Conclusions & Next Steps



**Computational modelling of dendritic cell innate responses recapitulates the laboratory findings**

**Incorporate additional PRRs into the simulation**

**Incorporate cytokine stimulation**

**Ultimate Goal:**

**Model Innate Signals that Direct T cell Differentiation in IBD Patients**