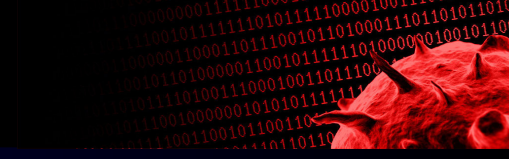


# Cell Collective tutorial

Tomas Helikar

[www.cellcollective.org](http://www.cellcollective.org) || [www.helikarlab.org](http://www.helikarlab.org) || [@helikarlab](https://twitter.com/helikarlab) ||  
[thelikar2@unl.edu](mailto:thelikar2@unl.edu)

Department of Biochemistry  
University of Nebraska at Lincoln

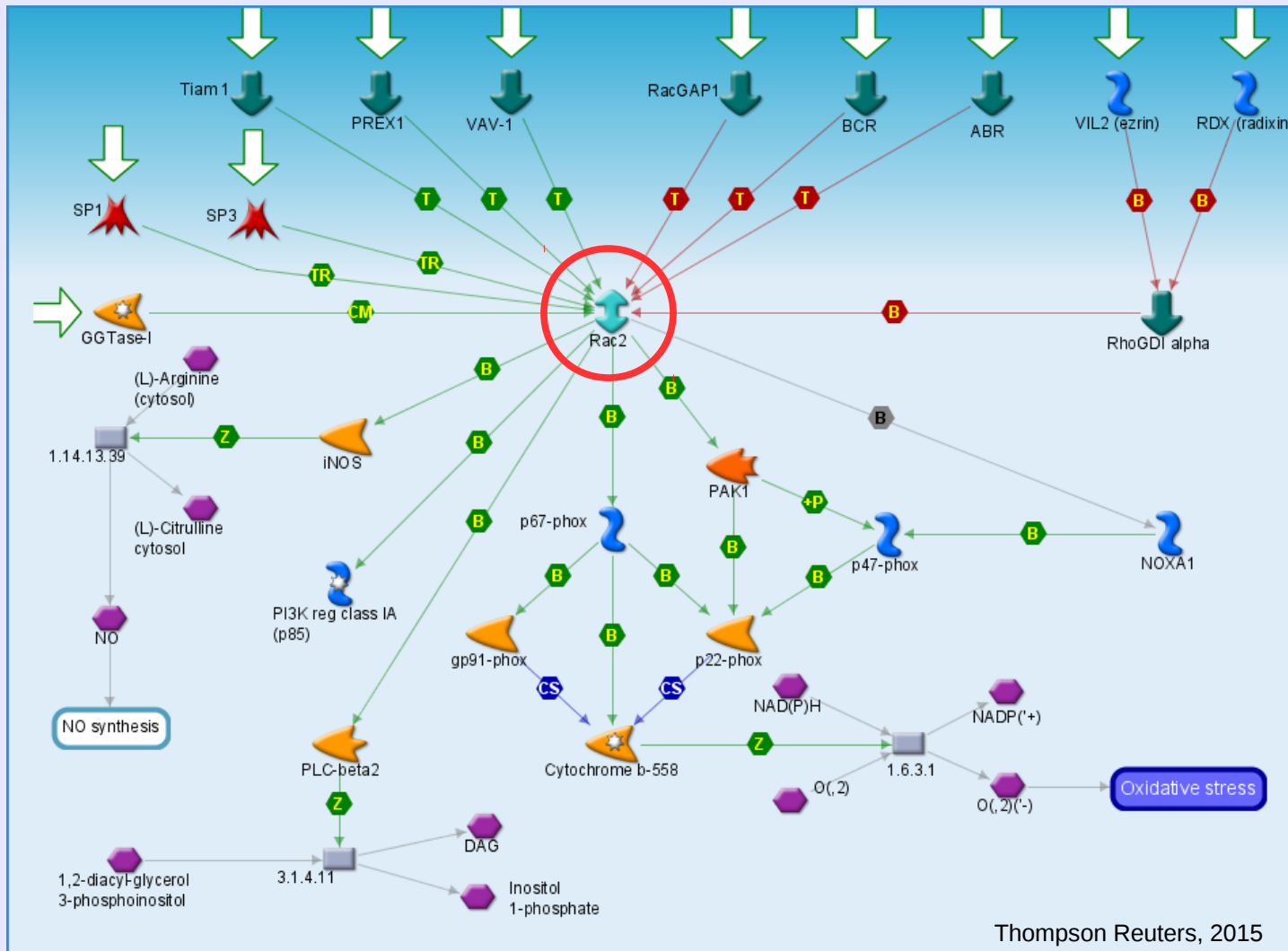


# Computational Modeling Challenges

- Combinatorial explosion of the number of states with the number of components ( $2^n$  states for  $n$  network components)
- Scalability of creating large-scale and accurate models
- Model transparency (can I believe the model?)
- Model (re-)usability and sharing



# Challenge: Complexity





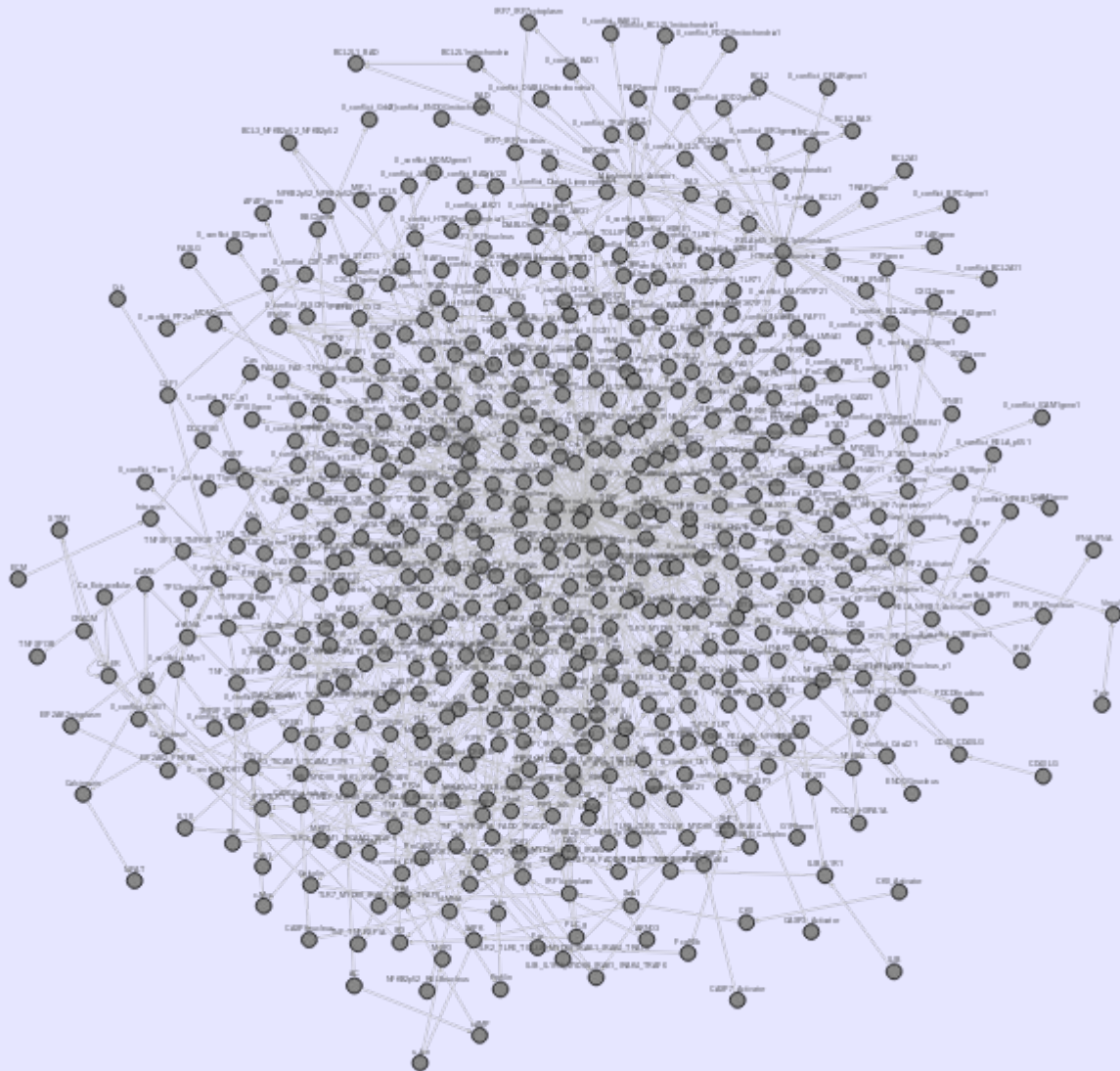
# Mathematical description of the regulatory mechanism of Rac

$$\begin{aligned} & (RasGRF \wedge \neg(RhoGDI \wedge \neg PAK) \wedge \neg(p190RhoGAP \wedge Rac) \wedge \neg(RalBP1 \wedge Rac) \\ & \wedge ECM \wedge Integrins) \vee (Tiam \wedge \neg(RhoGDI \wedge \neg PAK) \wedge \neg(p190RhoGAP \wedge Rac) \\ & \wedge \neg(RalBP1 \wedge Rac) \wedge (ECM \wedge Integrins)) \vee (Pix_{Cool} \wedge \neg(RhoGDI \wedge \neg PAK) \\ & \wedge ((PAK \wedge G\beta\gamma \wedge ((\neg Cdc42 \wedge \neg Rac) \wedge (Integrins \wedge ECM)))) \vee (\neg G\beta\gamma \wedge (Cdc42 \\ & \wedge (Integrins \wedge ECM) \wedge \neg Rac)) \vee (\neg PAK \wedge (\neg RhoGDI \wedge (\neg DOCK180 \wedge \neg(RhoGDI \wedge \neg PAK) \\ & \wedge \neg(p190RhoGAP \wedge Rac) \wedge \neg(RalBP1 \wedge Rac) \wedge \neg RasGRF \wedge \neg(RhoGDI \wedge \neg PAK) \\ & \wedge \neg(p190RhoGAP \wedge Rac) \wedge \neg(RalBP1 \wedge Rac) \wedge \neg Tiam \wedge \neg(RhoGDI \wedge \neg PAK) \\ & \wedge \neg(p190RhoGAP \wedge Rac) \wedge \neg(RalBP1 \wedge Rac)) \wedge (Integrins \wedge ECM) \wedge Cdc42 \wedge \neg Rac)))) \\ & \vee (DOCK180 \wedge \neg(RhoGDI \wedge \neg PAK) \wedge \neg(p190RhoGAP \wedge Rac) \wedge \neg(RalBP1 \wedge Rac) \\ & \wedge (ECM \wedge Integrins)) \end{aligned} \tag{1}$$



# Challenge: Size

## Macrophage Signaling and Gene Regulation



- 1,600+ components (proteins/protein complexes, genes, etc.)
- HIV replication cycle
- CCR5 (gp120, MIP-1)
- CSF1
- Integrin
- IFNGR
- FcγR (FcγRIIb)
- Toll-like Receptor
- Interferon (alpha, beta, gamma)
- NF-κB
- Apoptosis (FAS, TNF)



# Cell Collective Overview

Cell Collective: <https://www.cellcollective.org>

## Accessibility

... to non-modelers

## Collaboration

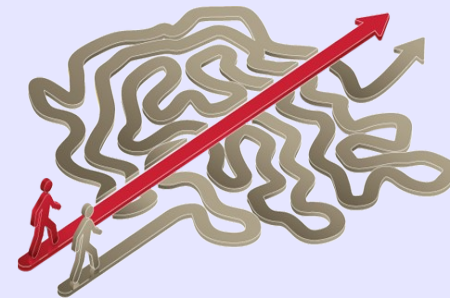
## Scalability

... bigger and more accurate models

## Transparency

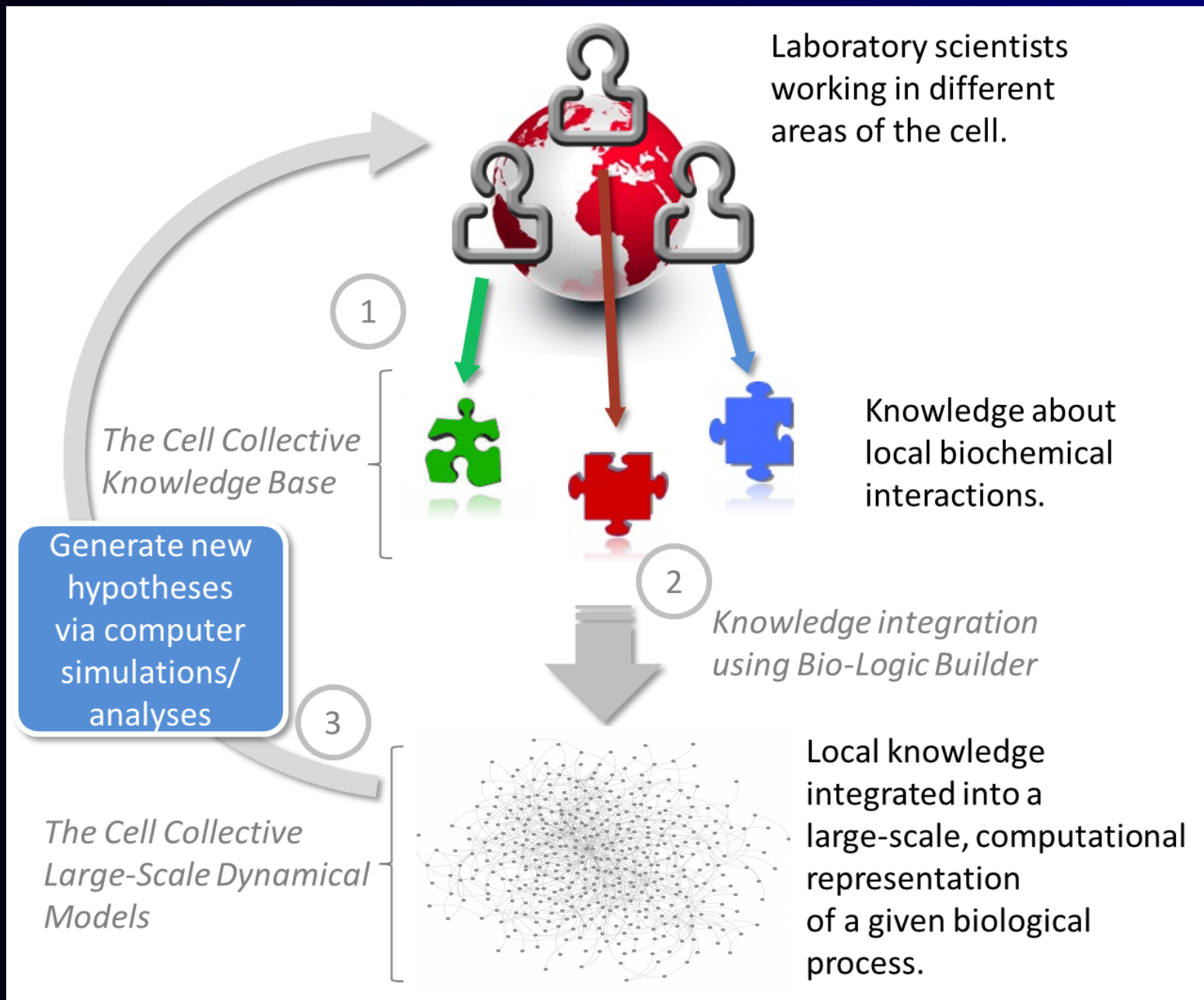
... can I believe the models??

## Re-usability & Reproducibility



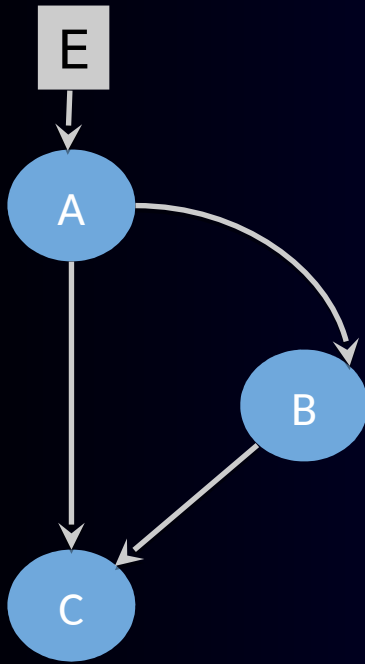


# Cell Collective Overview

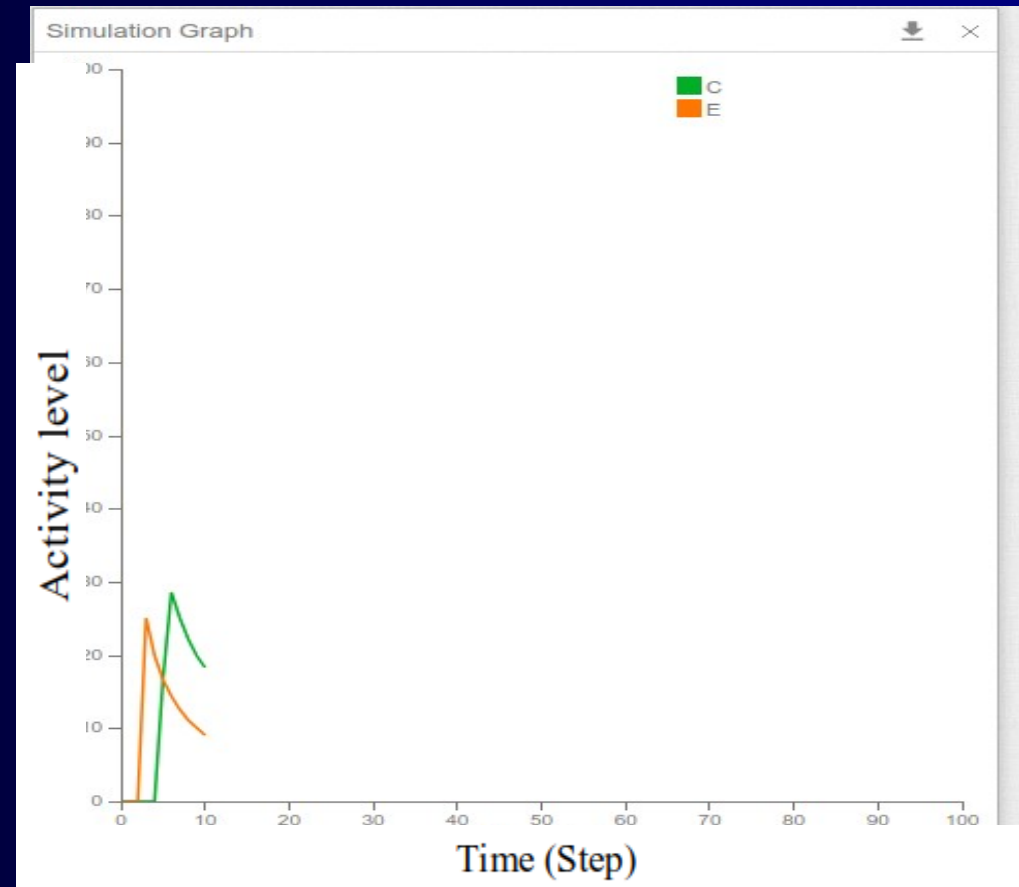




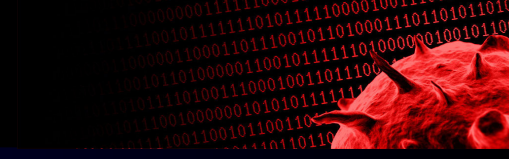
# Logical Model



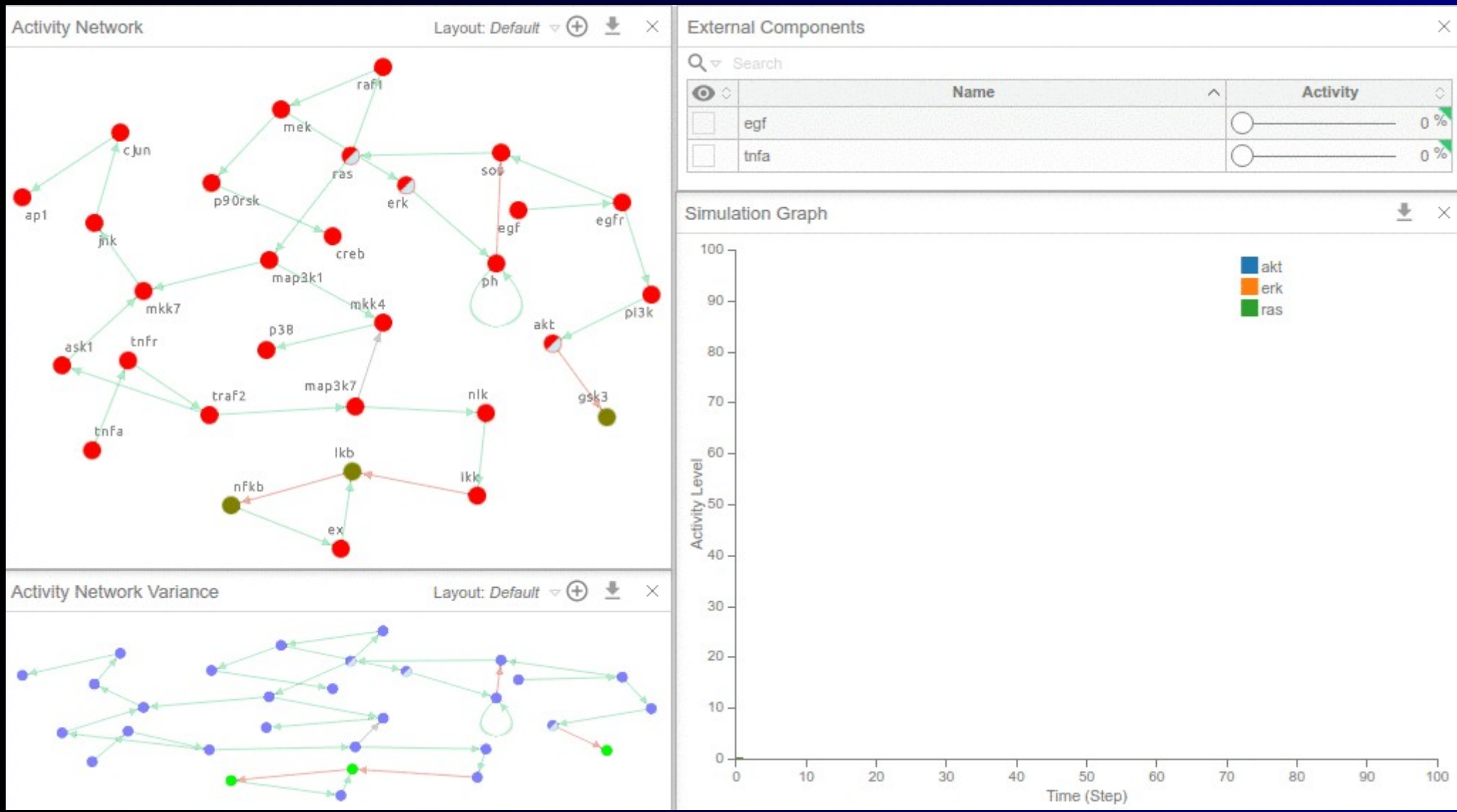
- Mechanistic
- Qualitative logic, i.e., “Proteins A or B activate protein C” ( $A \vee B \rightarrow C$ )
- (Kinetic) parameter independent
- Efficient simulations





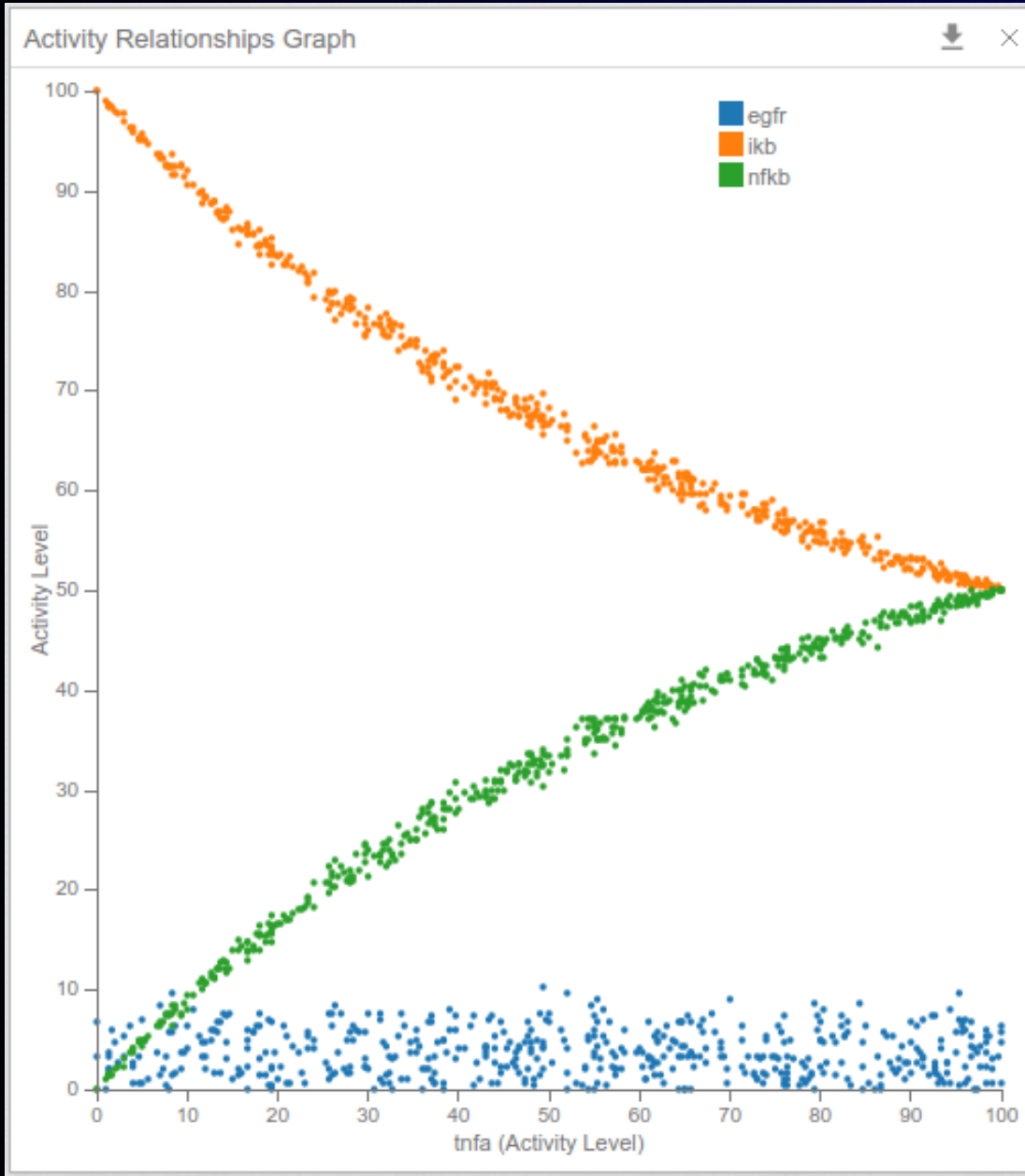


# Cell Collective Real-Time Simulations





# Input-Output Analysis (titration curves)



### External Components

Search

Name	Activity Range
egf	0 % <input type="range"/> 7 %
tnfa	0 % <input type="range"/> 100 %

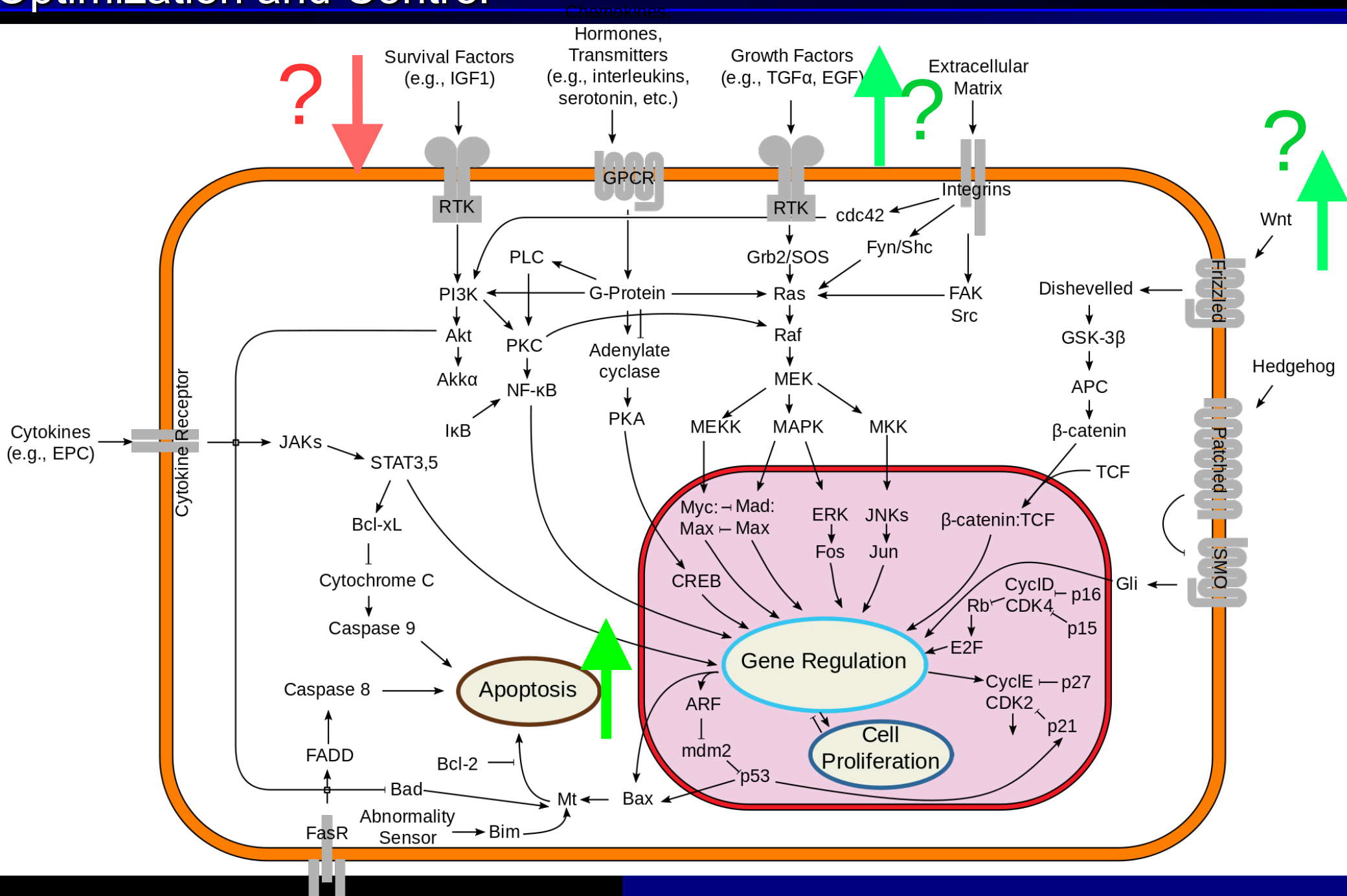
### Graph Components

Search

Name	X	Y
akt	<input type="checkbox"/>	<input type="checkbox"/>
ap1	<input type="checkbox"/>	<input type="checkbox"/>
ask1	<input type="checkbox"/>	<input type="checkbox"/>
cjun	<input type="checkbox"/>	<input type="checkbox"/>
creb	<input type="checkbox"/>	<input type="checkbox"/>
egf	<input type="checkbox"/>	<input type="checkbox"/>
egfr	<input type="checkbox"/>	<input checked="" type="checkbox"/>
erk	<input type="checkbox"/>	<input type="checkbox"/>
ex	<input type="checkbox"/>	<input type="checkbox"/>
gsk3	<input type="checkbox"/>	<input type="checkbox"/>
ikb	<input type="checkbox"/>	<input checked="" type="checkbox"/>
ikk	<input type="checkbox"/>	<input type="checkbox"/>
jnk	<input type="checkbox"/>	<input type="checkbox"/>
map3k1	<input type="checkbox"/>	<input type="checkbox"/>
map3k7	<input type="checkbox"/>	<input type="checkbox"/>



# Optimization and Control





# Cell Collective: Models annotation and transparency



Tomas Helikar

IGVH mutations in chronic lymphocytic leukemia.

Knowledge Base Simulation Analysis Model Description

Components

Knowledge Base ADM

Reference Graph Layout: Default

Name
ADM
AEBP1
AFF1
AICDA
AKAP12
AKT3
ALOX5
ANXA2
APLP2
APOBEC3G
APP
BLNK
BMI1
CASP3
CAV1
CCL5
CCND2
CD27
CD63
CD69
CD70

### Description

- Adrenomedullin
- Gene ID: 133
- ADM and PAMP act as hypotensive and vasodilator agents. Both mediate the loss of plasma volume in the brain and pituitary gland and inhibit aldosterone secretion. (Álvarez-Silva MC, 2015)
- Gene: ADM
- UniProt ID: P35318

### Regulatory Mechanism Summary

HSP90AA1 or TNF in conjunction with HSP0AA1 activates ADM. (Hofbauer KH, 2002) (Masoud GN, 2015)

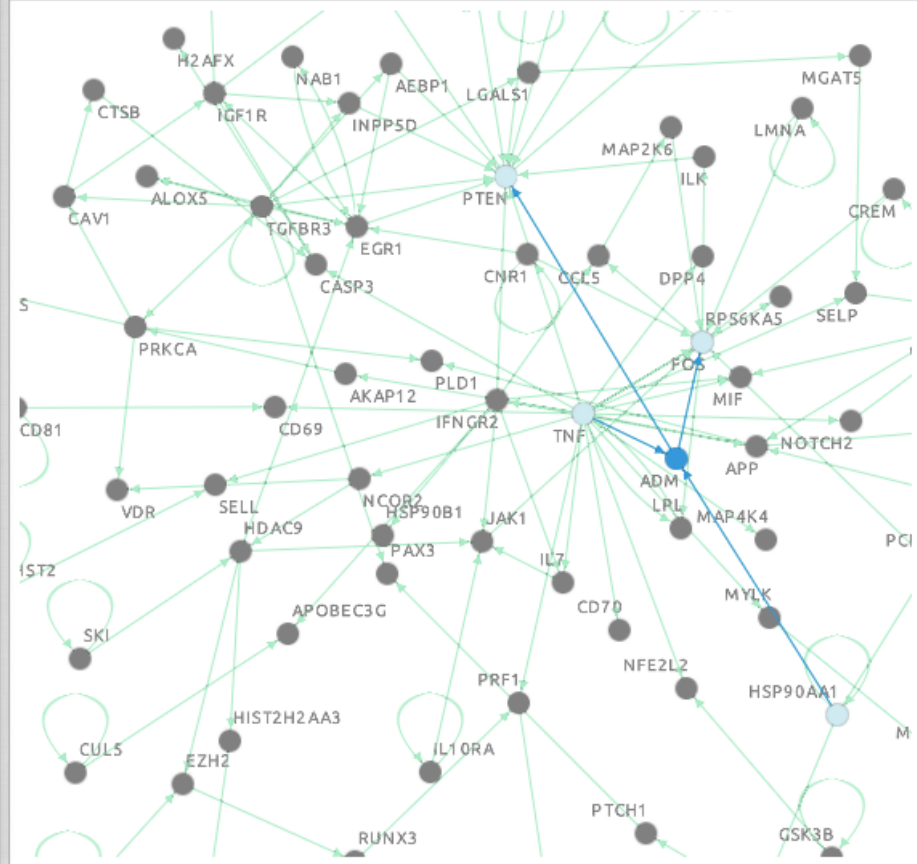
### Upstream Regulators

**HSP90AA1**  
HSP90AA1 indirectly upregulates ADM expression. (Masoud GN, 2015)

**TNF**  
Cells treated with TNF showed upregulation of ADM mRNA. (Hofbauer KH, 2002)

### References

- Hofbauer KH, Schoof E, Kurtz A, and Sandner P. *Inflammatory cytokines stimulate adrenomedullin expression through nitric oxide-dependent and -independent pathways.* Hypertension 2002 Jan39; (1) 161-7. PMID:11799096
- Masoud GN and Li W. *HIF-1α pathway: role, regulation and intervention for cancer therapy.* Acta Pharm Sin B 2015 Sep5; (5) 378-89. PMID:26579469
- Álvarez-Silva MC, Yenes S, Torres MM, and Barrios AF. *Proteins interaction network and modeling*





# Cell Collective: Collaboration and Model Repository

SBML Qual Paper Final Model demo    Knowledge Base    Simulation    Analysis    Model    Description

### Share with Collaborators

Search

Email
audrey.crowther@huskers.unl.edu

### Publish your Model

By publishing this model, it will become visible to all Cell Collective users who will be able to simulate the model and create their own copy to help expand on it in a collaborative fashion (only the original model creator and the users with whom the creator shared the model can continue to directly edit the published model).

**PUBLISH** Model cannot be published.

#### Publishing requirements

- ✗ *Model has to have been included in at least one peer-reviewed publication.*  
There are no publications associated with this model (You can add publications under the Description page).
- ✗ *Each model component should be annotated in the knowledge base in an effort to make models more reproducible, transparent and accessible to the community.*  
Components without knowledge base information:  

akt ap1 ask1 cjun creb egf egfr erk ex gsk3 ikb ikk jnk map3k1 map3k7 mek mkk4 mkk7 nfb nik p38 p90rsk ph pi3k raf1 ras sos tnfa tnfr traf2
- ✓ *User profile of the model owner has to be filled.*

### Experiments Publishing

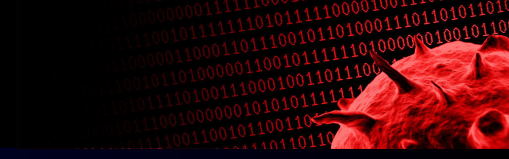
Search

Name
TNFalpha titration

### Shareable Links

Search

Link
https://cellcollective.org/#a2b73520-ffc4



# Cell Collective: Collaboration and Model Repository

Published Models (76) My Models (45) Shared with Me (133)



## RECENTLY PUBLISHED

**Mammalian Cell Cycle**  
version 1.0  
Components: 20 Interactions: 51

Author: O Sahin et. al.  
Score: 51.1 Cited: 124  
Created: 10/19/2011 Updated: 6/7/2018

**T-LGL Survival Network 2011**  
version 1.0  
Components: 60 Interactions: 195

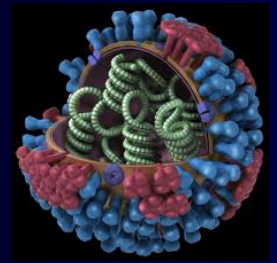
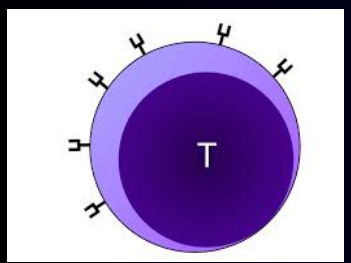
Author: A Saddatpour et. al.  
Score: 30.0 Cited: 56  
Created: 6/2/2014 Updated: 6/5/2018

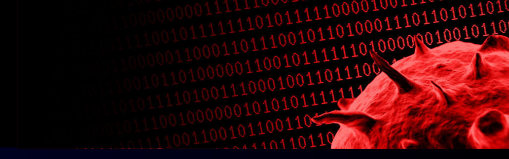
**Aurora Kinase A in Neuroblastoma**  
version 1.0  
Components: 23 Interactions: 43

Author: M Dahlhaus et. al.  
Score: 25.0 Cited: 0  
Created: 4/20/2017 Updated: 4/23/2018

**Yeast Apoptosis**  
version 1.0  
Components: 73 Interactions: 114

Author: L Kazemzadeh et. al.  
Score: 48.0 Cited: 10  
Created: 6/4/2013 Updated: 4/18/2018





## Example Case Studies



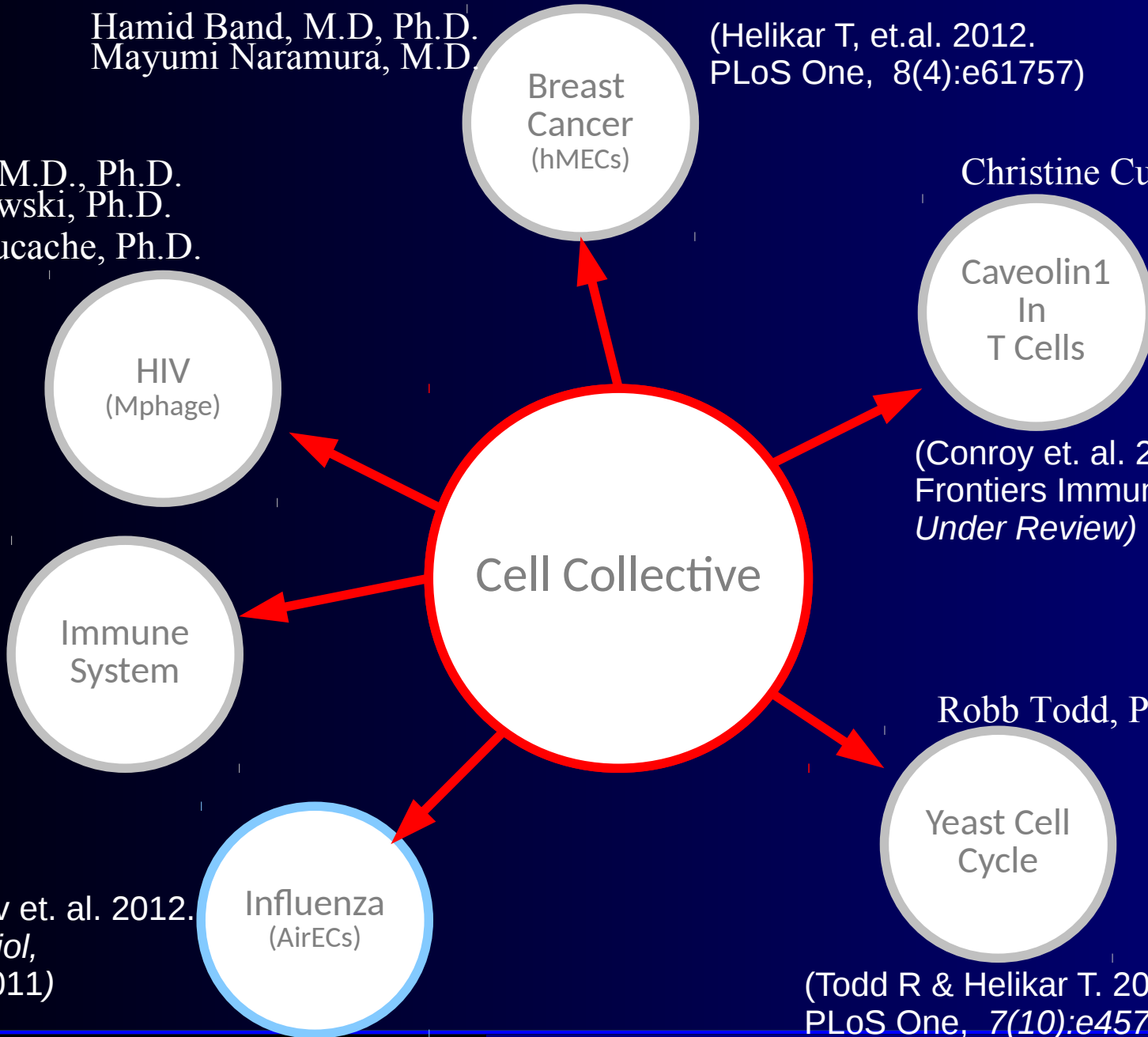
# Applications and Case Studies

Hamid Band, M.D, Ph.D.  
Mayumi Naramura, M.D.

(Helikar T, et.al. 2012.  
PLoS One, 8(4):e61757)

Howard Fox, M.D., Ph.D.  
Pawel Ciborowski, Ph.D.  
Christine Cutucache, Ph.D.

Christine Cutucache, Ph.D



(Madrahimov et. al. 2012.  
*Bull Math Biol*,  
75(6):988-1011)

(Todd R & Helikar T. 2012.  
PLoS One, 7(10):e45780)

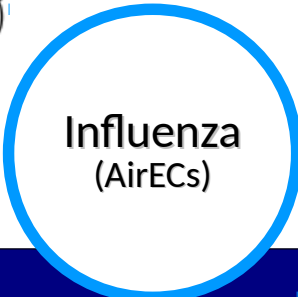
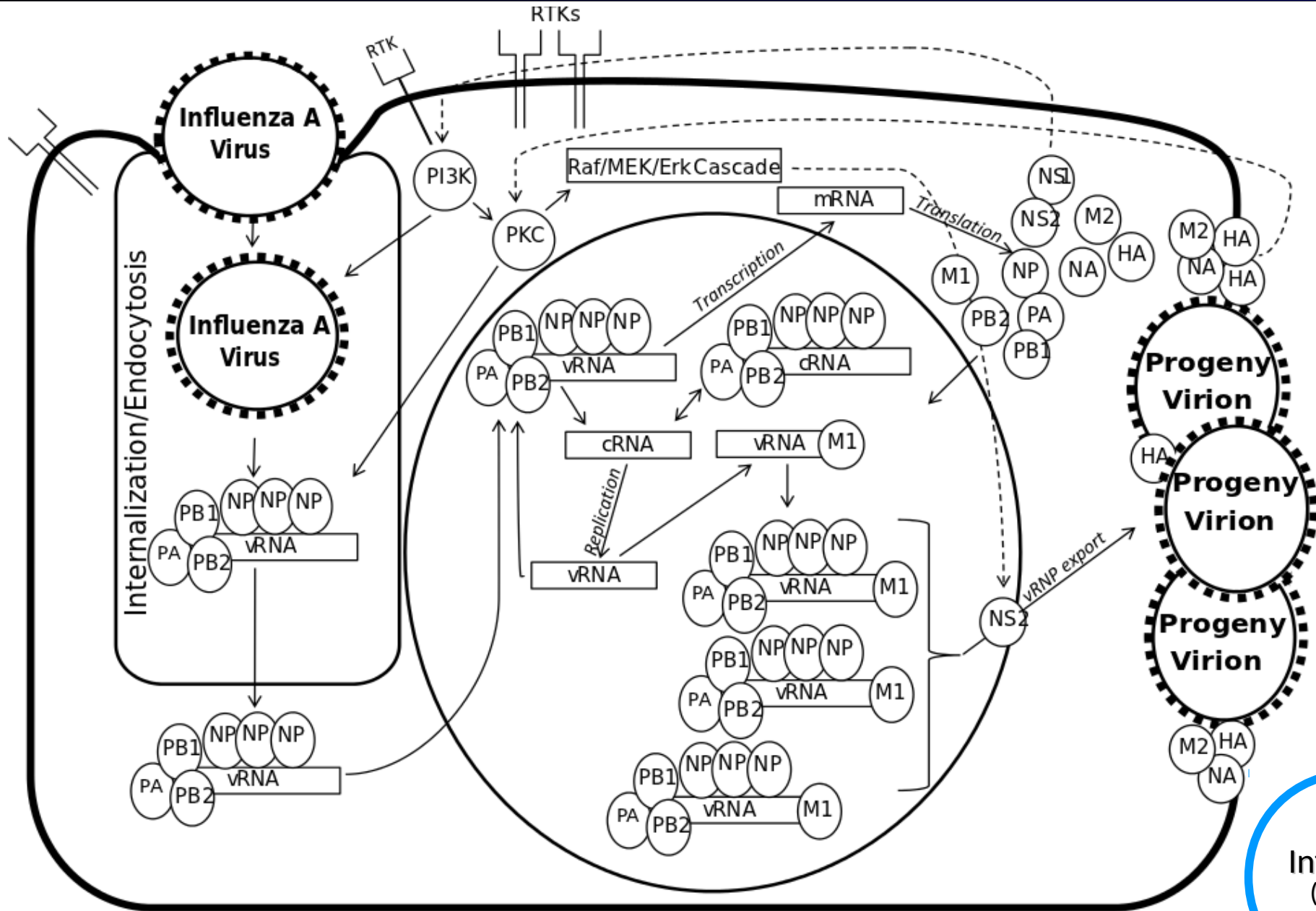
(Conroy et. al. 2014.  
*Frontiers Immunology*,  
*Under Review*)

Robb Todd, Ph.D



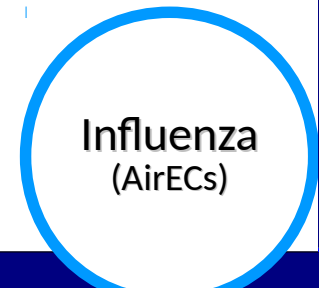
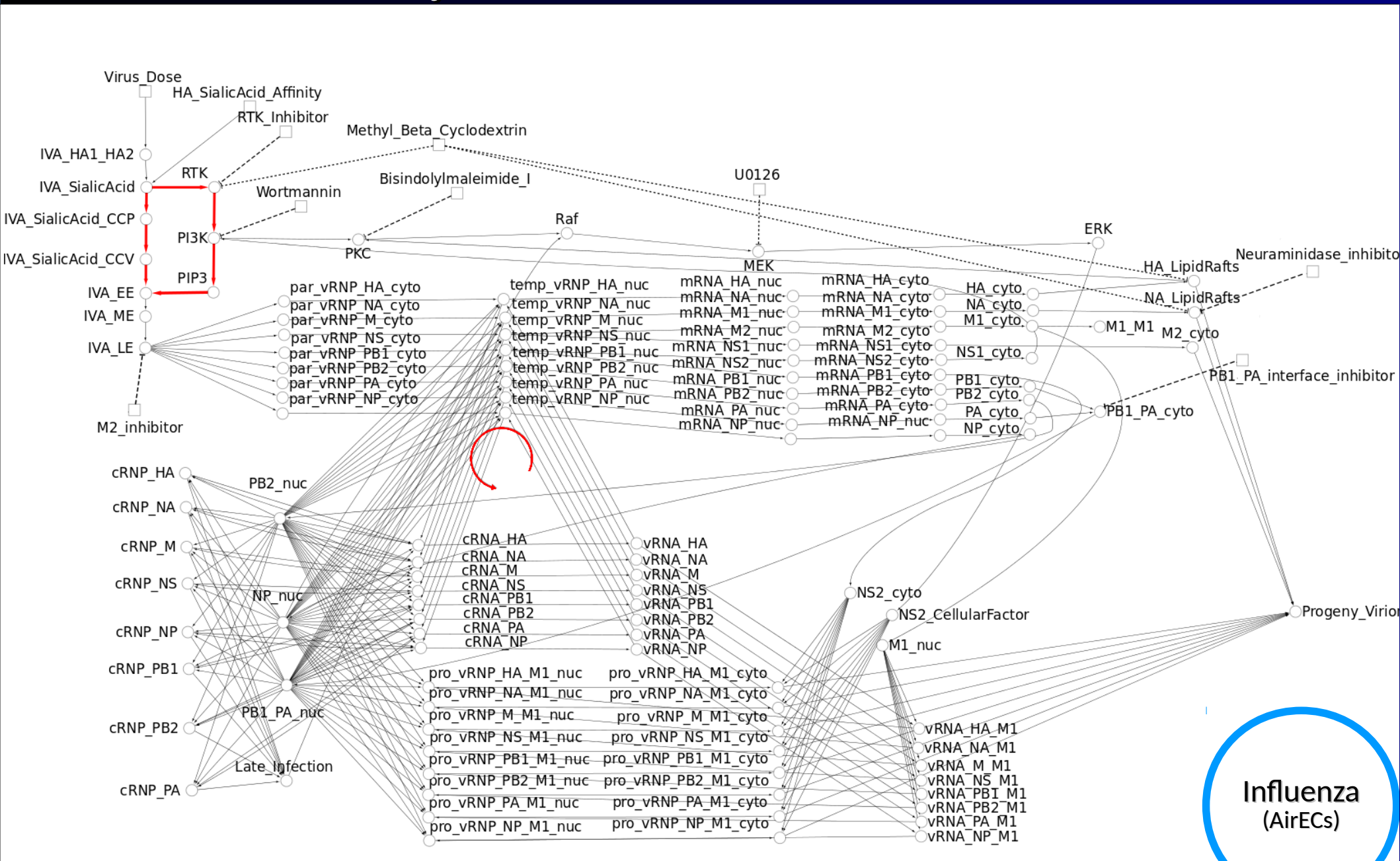


# Influenza Infection Dynamics



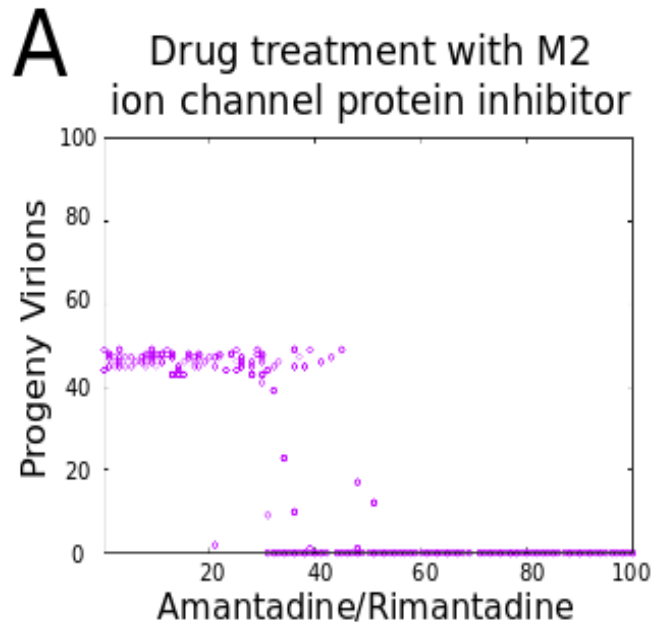


# Influenza Infection Dynamics

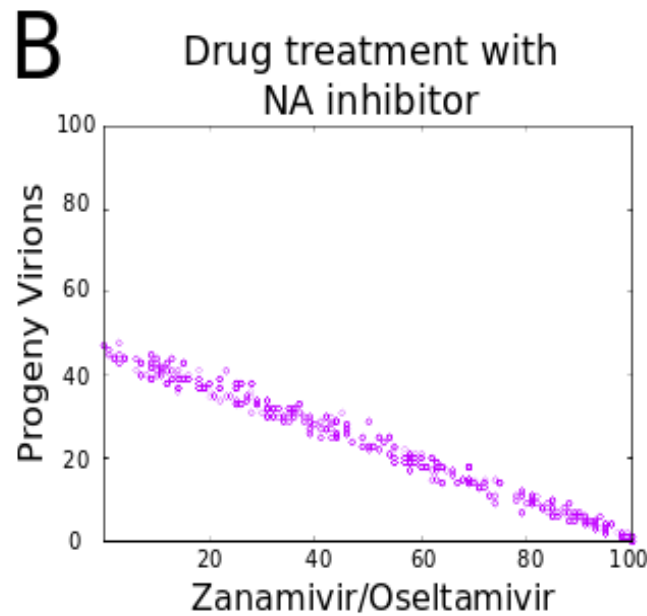




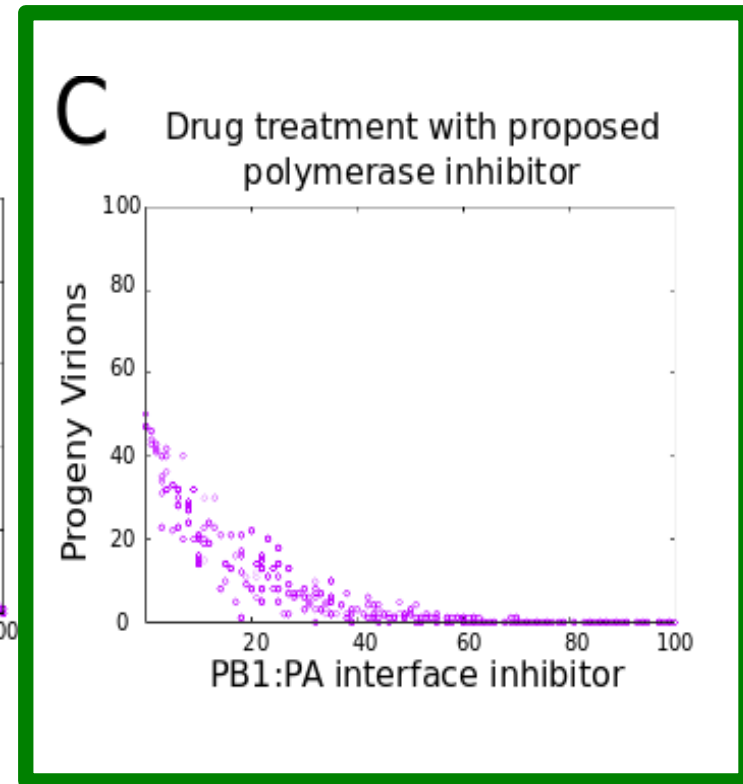
# Influenza Infection Dynamics



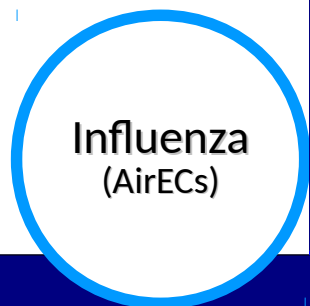
Progeny virion exit



Virus entry



Viral replication





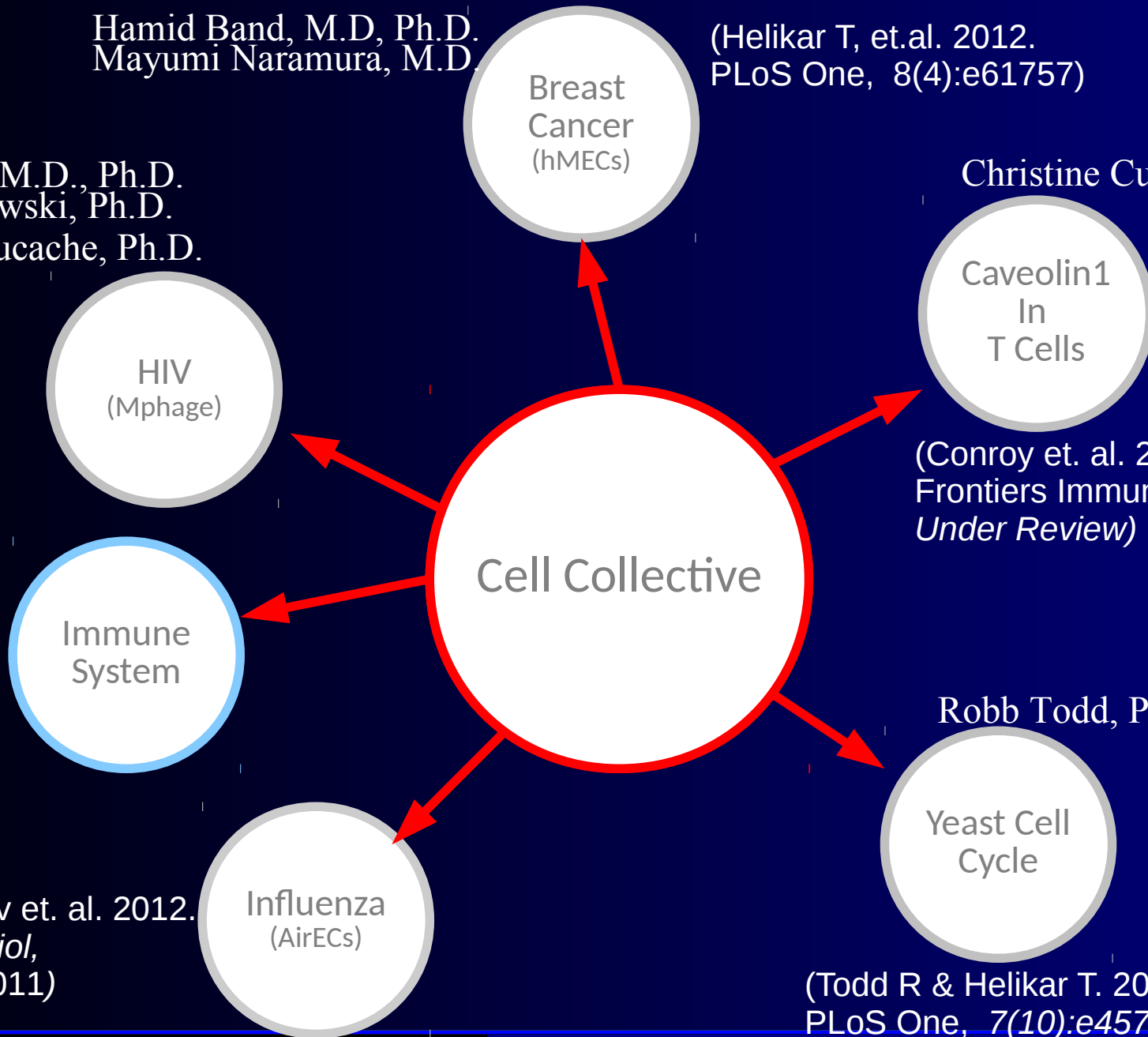
# Applications and Case Studies

Hamid Band, M.D, Ph.D.  
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(Helikar T, et.al. 2012.  
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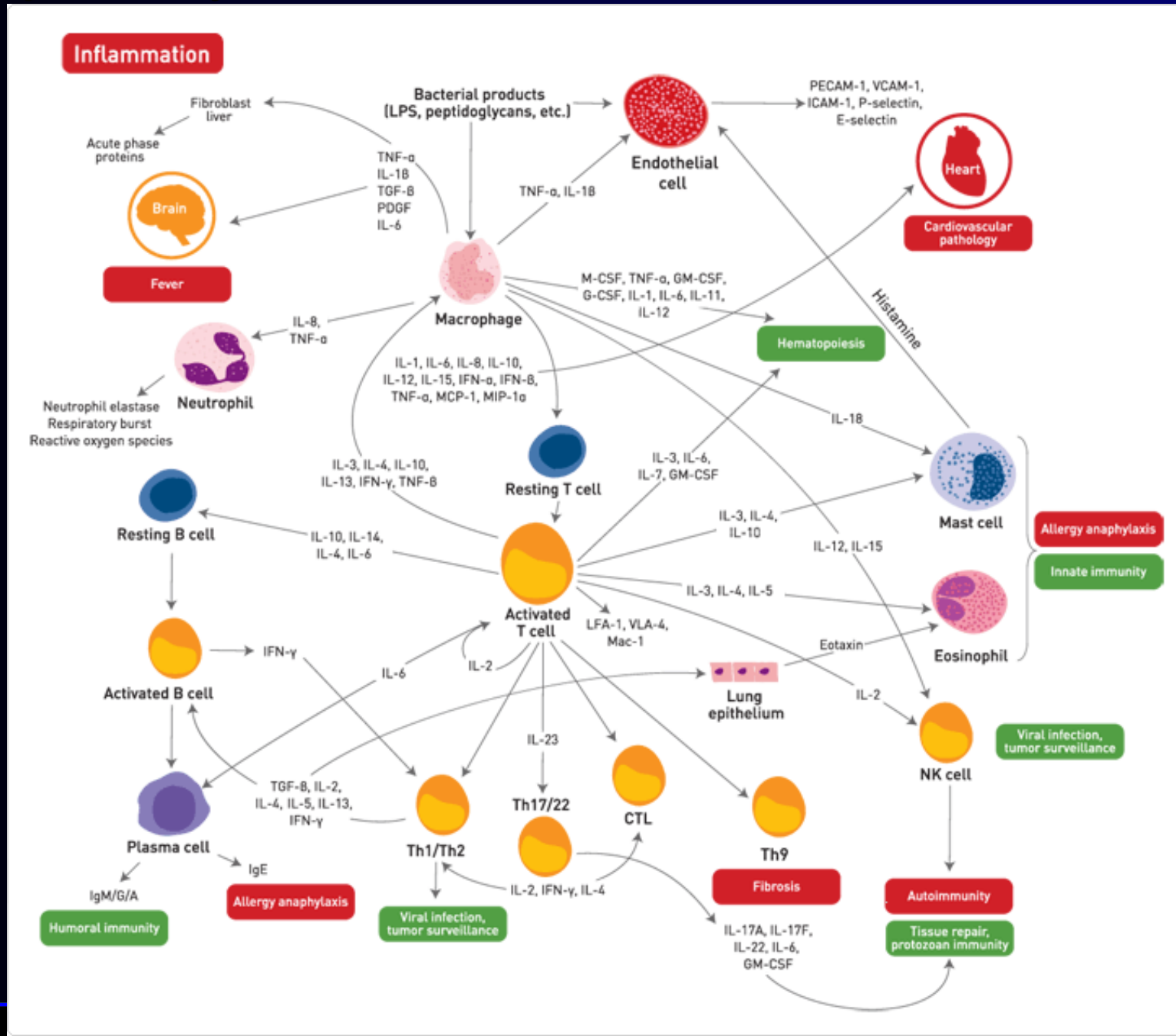
Christine Cutucache, Ph.D



(Madrahimov et. al. 2012.  
*Bull Math Biol*,  
75(6):988-1011)

(Todd R & Helikar T. 2012.  
PLoS One, 7(10):e45780)

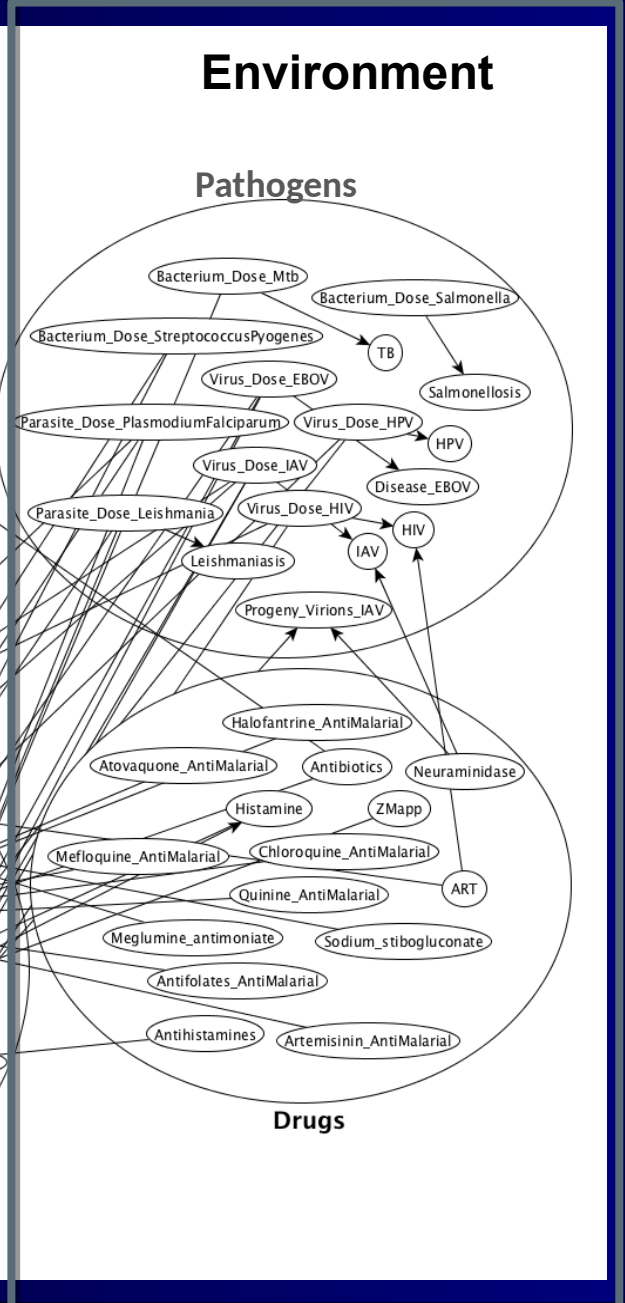
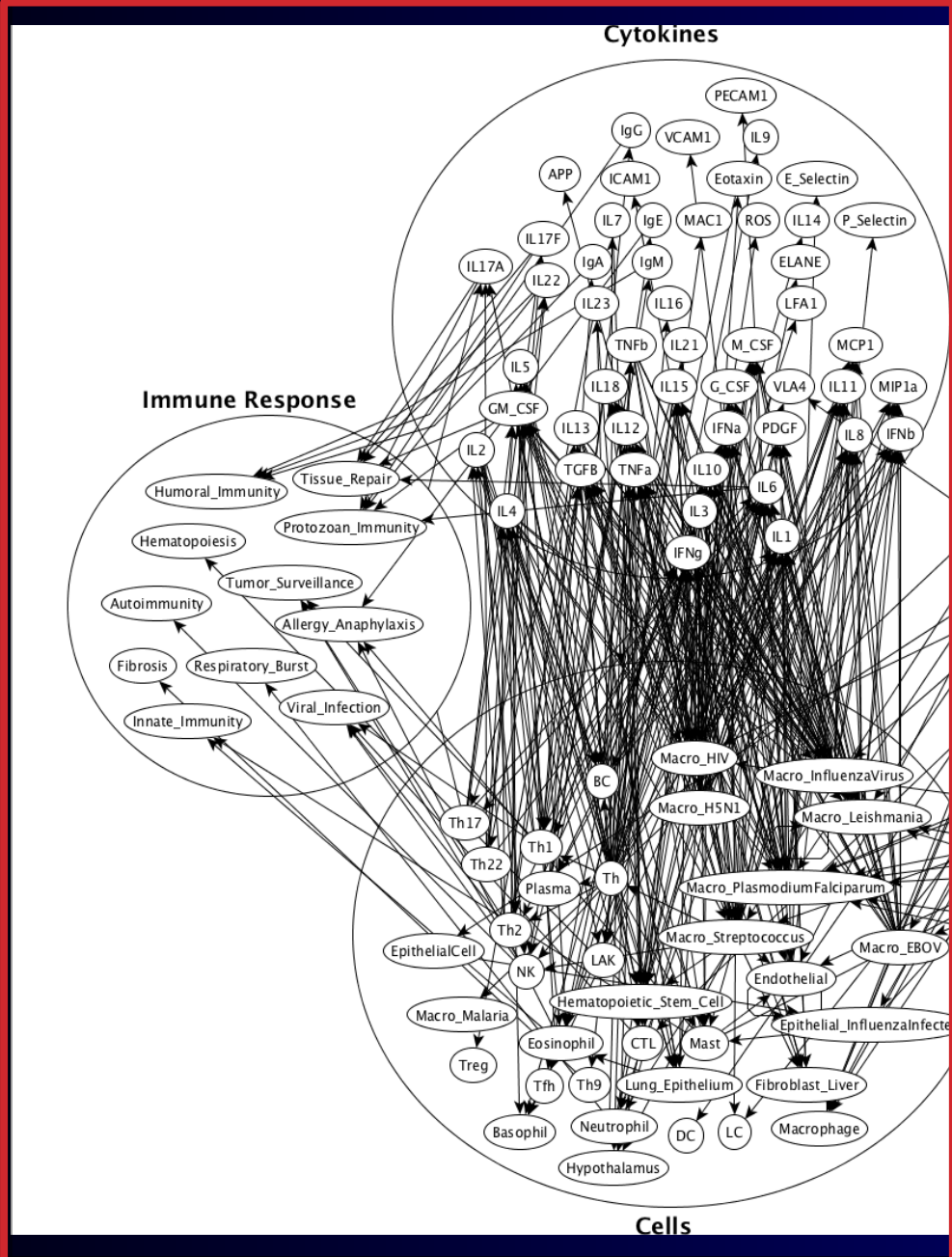
(Conroy et. al. 2014.  
*Frontiers Immunology*,  
*Under Review*)

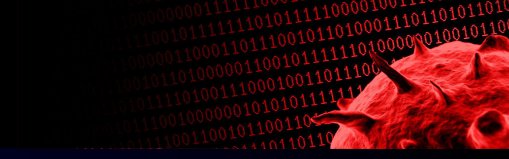




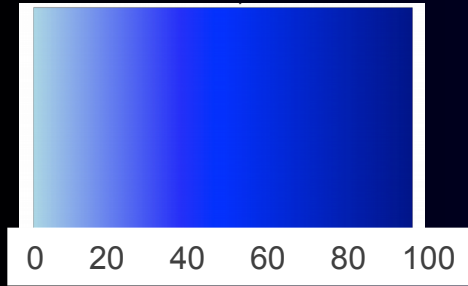
# Comprehensive Computational Model of the Immune System

- \* 164 Components
- \* 9 Pathogens:
  - Mtb*
  - Helminth*
  - Influenza*
  - Ebola*
  - HIV*
  - HPV*
  - Leishmania*
  - Candida Albicans*
  - Plasmodium Falc*
- \* 35 Cytokines
- \* 26 Cell types
- \* 506 interactions
- \* 224 papers



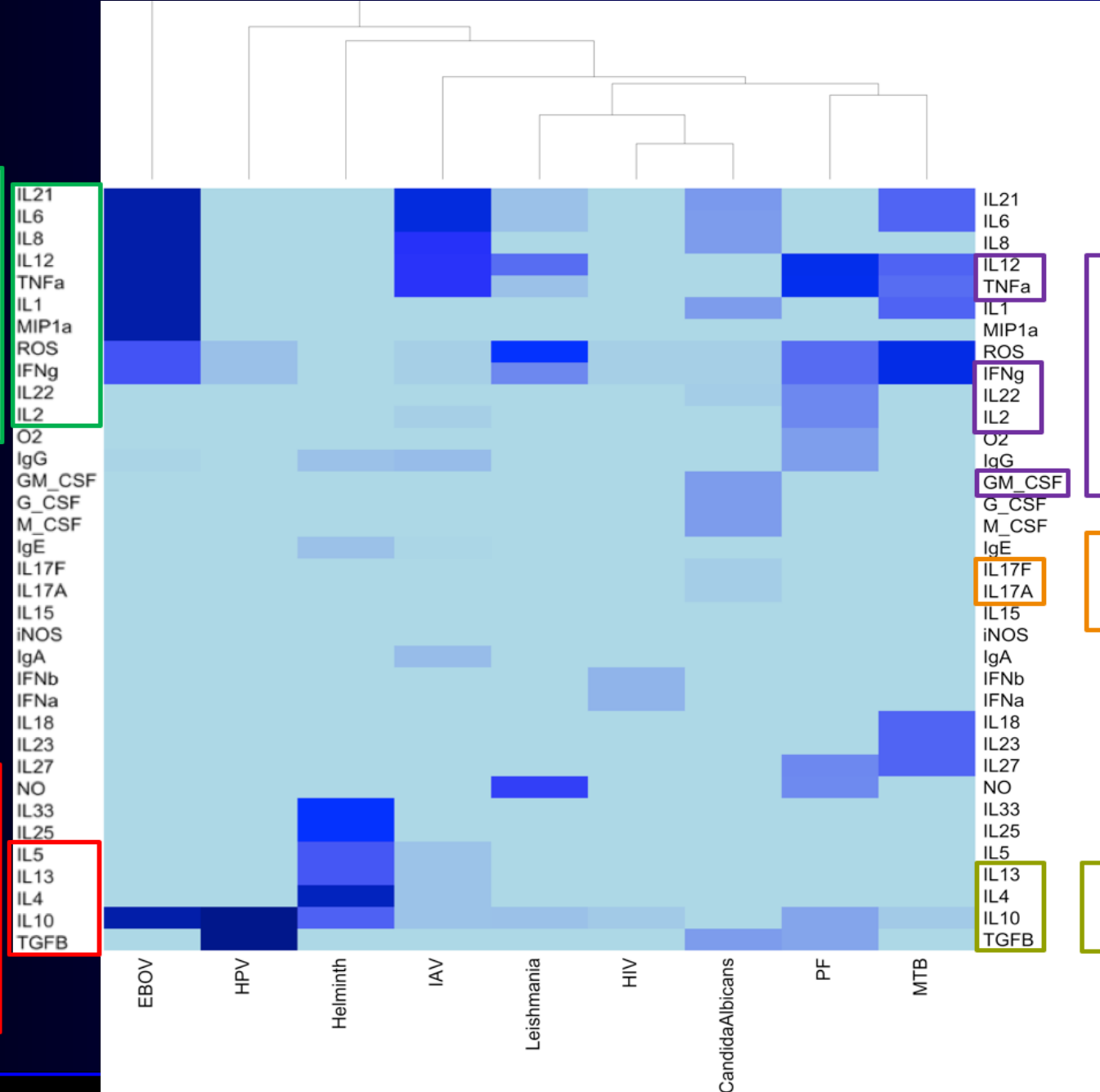


# Model Simulations



Pro-inflammatory

Anti-inflammatory



Th1

Th17

Th2



# Comprehensive Computational Model of the Immune System - validation

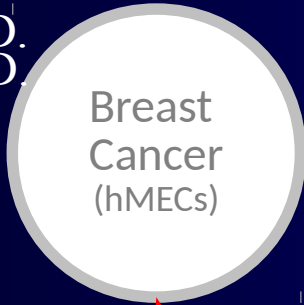
Infectious Agent	Cell Target	Immune Response	Reference
<i>HIV</i>	DCs, Macrophages, CD4 T	Th1, Th2, CD8+	<i>Banks et al. 2008</i>
<i>HPV</i>	Keratinocytes	Th1, CD8+	<i>Scott et al. 2001</i>
<i>Ebola</i>	Dendritic Cells, Macrophages, Monocytes	Th1, Th2, CD8+, IgG	<i>Le Roy et al. 2001</i>
<i>Influenza A virus</i>	Epithelial, Dendritic	Th1, Th2, CD8+, IgA, IgG, IgM	<i>Ada et al. 1986</i>
<i>Mycobacterium tuberculosis</i>	Macrophages, Neutrophils	Th1, CD8+	<i>O'Garra et al. 2013</i>
<i>Helminth</i>	Endothelial, Epithelial, Macrophages, NKT	Th2, IgE, IgG	<i>Gause et al. 2003</i>
<i>Plasmodium</i>	Erythrocytes	Th1, IgE, IgG	<i>Malaguarnera et al. 2002</i>
<i>Leishmania</i>	DCs, Mac, Monocytes, Neutrophil, NK	Th1, IgE	<i>Awasthi et al. 2004</i>





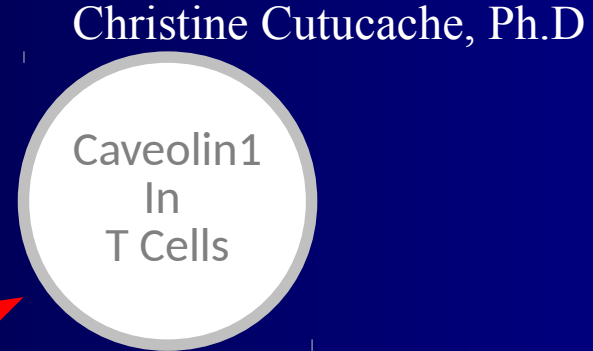
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(Helikar T, et.al. 2012.  
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Pawel Ciborowski, Ph.D.  
Christine Cutucache, Ph.D.



(Conroy et. al. 2014.  
Frontiers Immunology,

[Front Physiol.](#) 2018; 9: 878.

Published online 2018 Aug 2. doi: [10.3389/fphys.2018.00878](https://doi.org/10.3389/fphys.2018.00878)

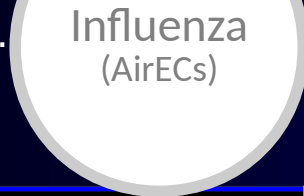
PMCID: [PMC6083813](https://pubmed.ncbi.nlm.nih.gov/PMC6083813/)

PMID: [30116195](https://pubmed.ncbi.nlm.nih.gov/30116195/)

## A Mechanistic Computational Model Reveals That Plasticity of CD4<sup>+</sup> T Cell Differentiation Is a Function of Cytokine Composition and Dosage

[Bhanwar Lal Puniya](#),<sup>1</sup> [Robert G. Todd](#),<sup>2,\*</sup> [Akram Mohammed](#),<sup>1</sup> [Deborah M. Brown](#),<sup>3,4</sup> [Matteo Barberis](#),<sup>5,6,\*</sup> and [Tomáš Helikar](#)<sup>1,\*</sup>

(Madrahimov et. al. 2012.  
*Bull Math Biol*,  
75(6):988-1011)

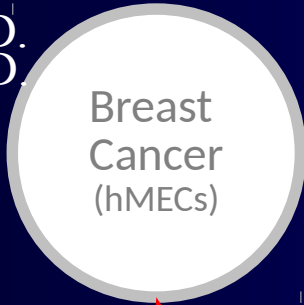


(Todd R & Helikar T. 2012.  
PLoS One, 7(10):e45780)



# Applications and Case Studies

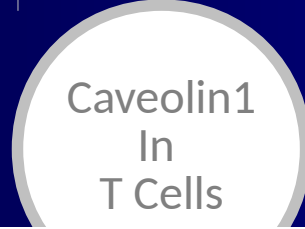
Hamid Band, M.D, Ph.D.  
Mayumi Naramura, M.D.



(Helikar T, et.al. 2012.  
PLoS One, 8(4):e61757)

Howard Fox, M.D., Ph.D.  
Pawel Ciborowski, Ph.D.  
Christine Cutucache, Ph.D.

Christine Cutucache, Ph.D



**ORIGINAL RESEARCH ARTICLE**

Front. Bioeng. Biotechnol., 11 February 2016 | <http://dx.doi.org/10.3389/fbioe.2016.00010>



## Systems Perturbation Analysis of a Large-Scale Signal Transduction Model Reveals Potentially Influential Candidates for Cancer Therapeutics

4.  
ogy,



(Madrahimov et. al. 2012.  
*Bull Math Biol*,  
75(6):988-1011)



(Todd R & Helikar T. 2012.  
PLoS One, 7(10):e45780)



# Applications and Case Studies

Hamid Band, M.D, Ph.D.  
Mayumi Naramura, M.D.

Breast  
Cancer  
(hMECs)

(Helikar T, et.al. 2012.  
PLoS One, 8(4):e61757)

Howard Fox, M.D., Ph.D.  
Pawel Ciborowski, Ph.D.  
Christine Cutucache, Ph.D.

Christine Cutucache, Ph.D

Caveolin1  
In  
T Cells

## ORIGINAL RESEARCH ARTICLE

Front. Immunol., 05 December 2014 | <http://dx.doi.org/10.3389/fimmu.2014.00599>

# Design, assessment, and *in vivo* evaluation of a computational model illustrating the role of CAV1 in CD4<sup>+</sup> T-lymphocytes

Brittany D. Conroy<sup>1†</sup>, Tyler A. Herek<sup>1†</sup>, Timothy D. Shew<sup>1†</sup>, Matthew Latner<sup>1</sup>,  
 Joshua J. Larson<sup>1</sup>, Laura Allen<sup>1</sup>, Paul H. Davis<sup>1</sup>, Tomáš Helikar<sup>2</sup> and Christine E. Cutucache<sup>1\*</sup>

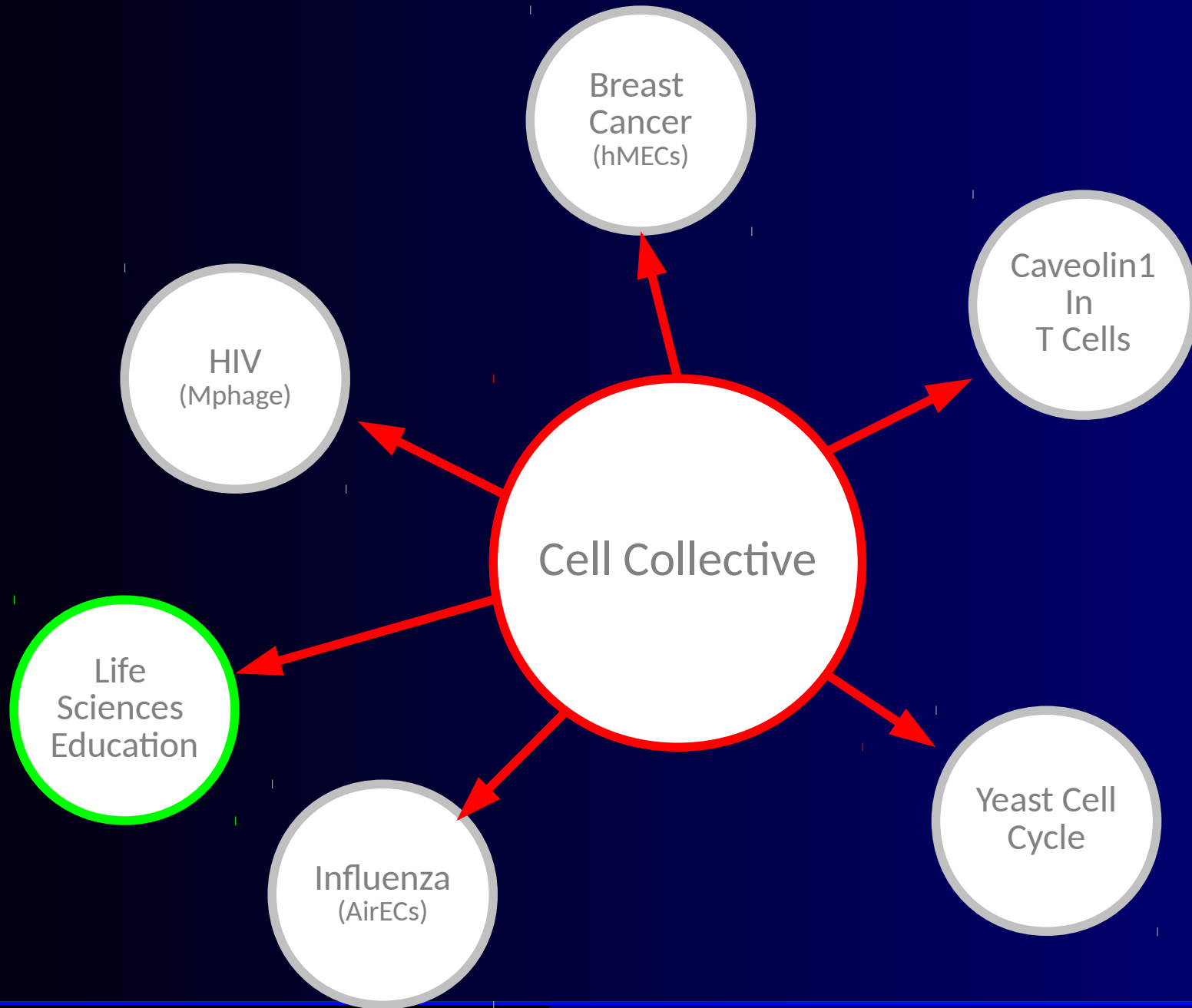
(Madrahimov et. al. 2012.  
*Bull Math Biol*,  
75(6):988-1011)

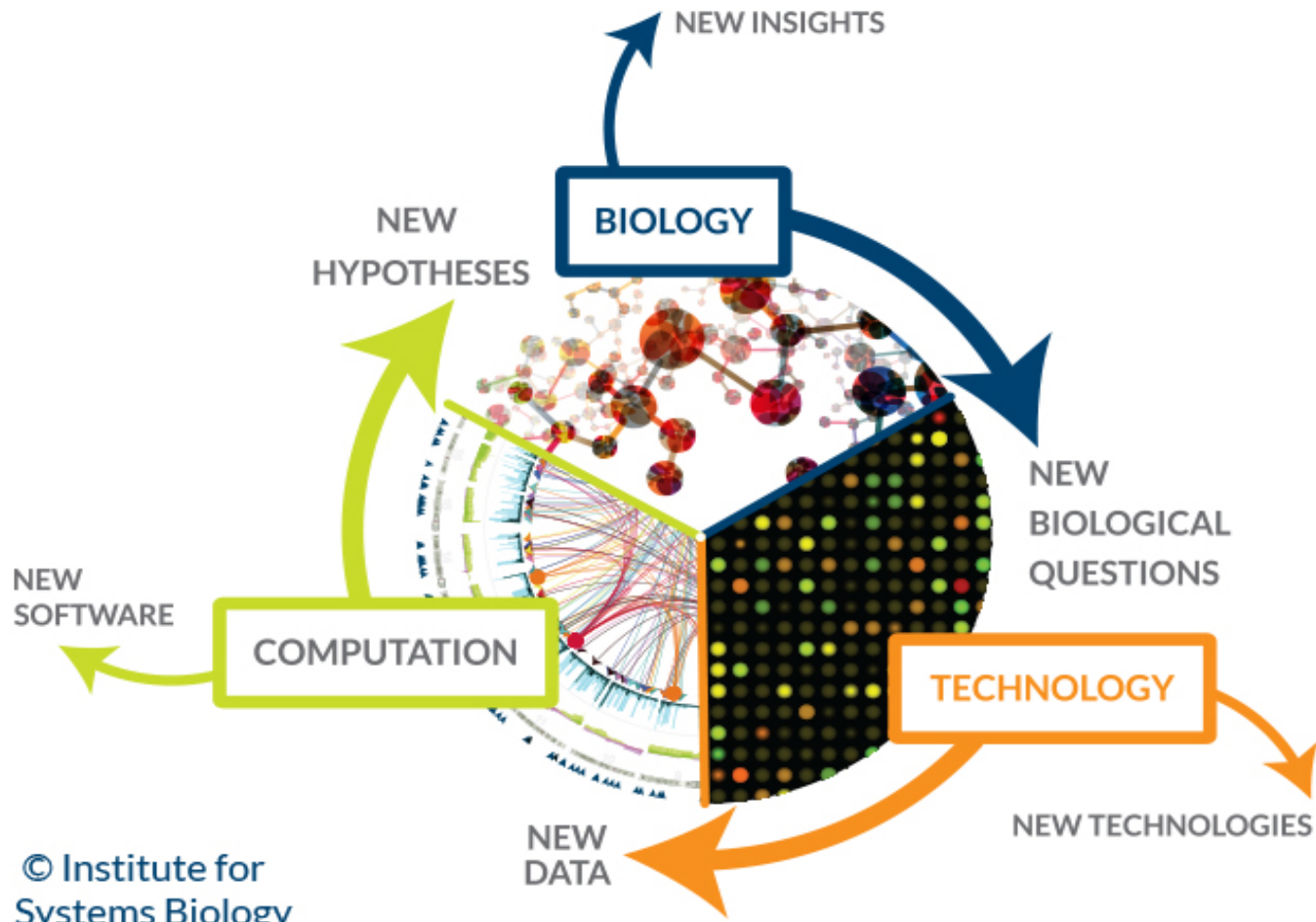
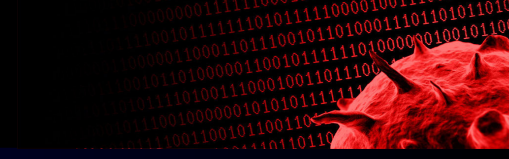
Influenza  
(AirECs)

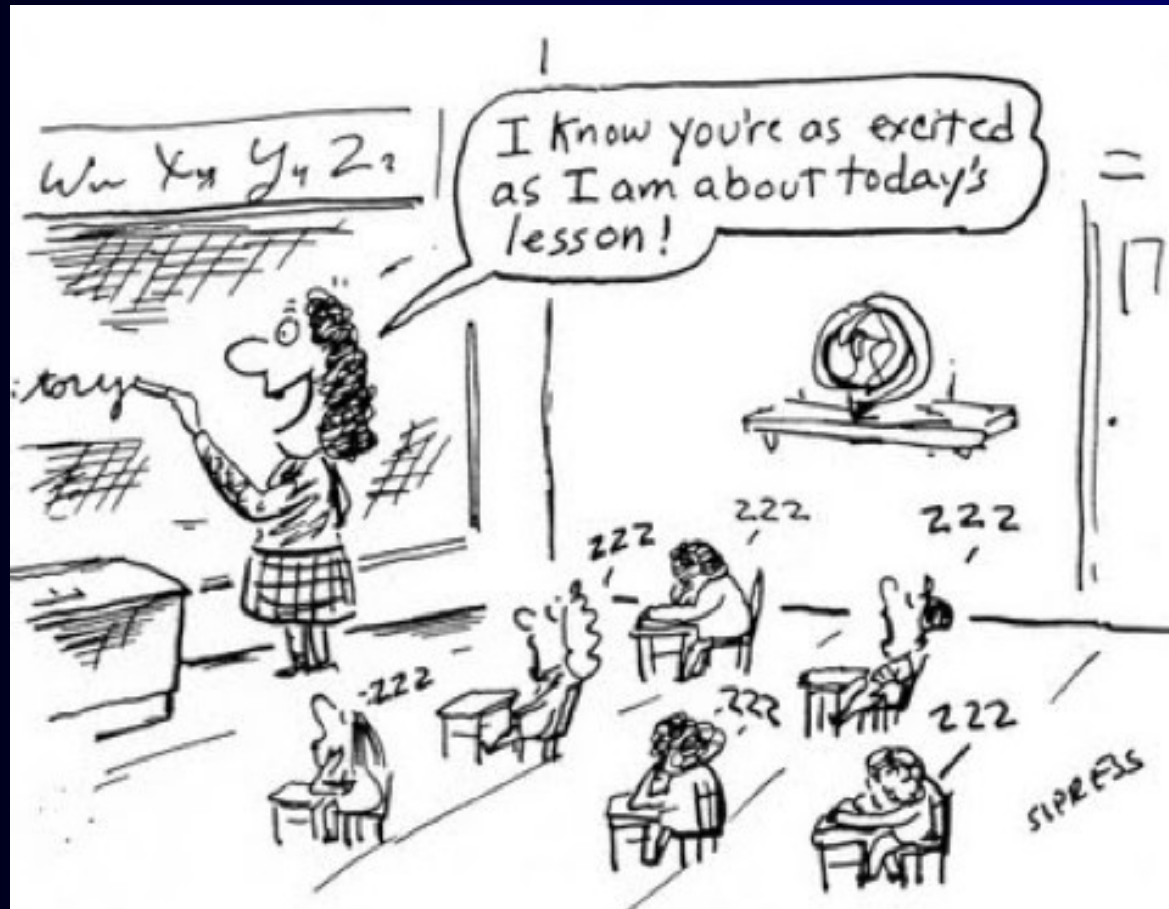
(Todd R & Helikar T. 2012.  
PLoS One, 7(10):e45780)

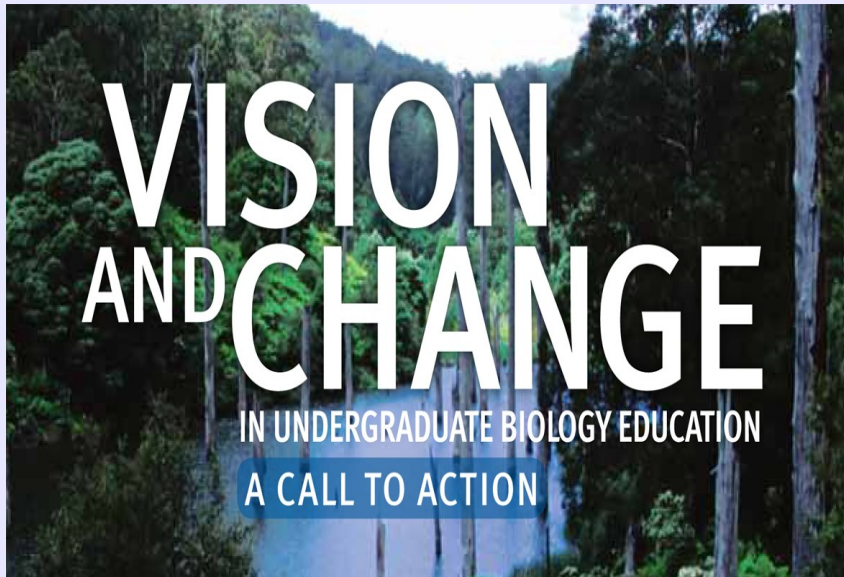


# Computational biology in complex networks









### Core Concepts

- **Systems**
- Structure and function
- Information flow, exchange, storage
- Evolution
- Pathways and transformation of energy and matter



### Core Competencies

- **Modeling, simulations, computational, and systems-level approaches to discovery and analysis**
- Process of science
- Quantitative reasoning
- Interdisciplinary communication and collaboration
- Science and Society



# Broad application

## Activity Types

- Concept Maps
- Simulation and investigation of pre-constructed models
- Model Construction and Simulation

## Key Design Features

- Self-contained
- Simple, turn-key implementation
- Predict/observe/explain scenarios
- Assessible
- Modular implementation
  - Laboratory activity
  - Homework
  - In-class activity

Published Models (11) My Learning (1) My Models (293) Shared with Me (47)

### Lac Operon Construction

Components: 0 Interactions: 0

Author: Nicholas Galt  
Audience: Freshmen Time: ~ 60 minutes  
Created: 6/20/2016 Updated: 6/20/2016

### Glucose Homeostasis

Components: 0 Interactions: 0

Author: Nicholas Galt  
Audience: Freshmen Time: ~ 60 minutes  
Created: 6/19/2016 Updated: 6/19/2016

### Regulation of Cellular Respiration

Components: 26 Interactions: 59

Author: Nicholas Galt  
Audience: Freshmen Time: ~ 90 hours  
Created: 5/20/2016 Updated: 6/19/2016

### G2 Checkpoint Regulation and the FAJ/E

Components: 31 Interactions: 127

Author: Audrey Crowther  
Audience: Sophomore Time:  
Created: 6/15/2016 Updated: 6/16/2016

### Cell Cycle Regulation: The G1/S Transition

Components: 21 Interactions: 54

Author: Audrey Crowther  
Audience: Sophomore Time:  
Created: 6/13/2016 Updated: 6/13/2016

### Cell-to-Cell Communication Networks In

Components: 29 Interactions: 60

Author: Audrey Crowther  
Audience: Senior Time:  
Created: 6/3/2016 Updated: 6/10/2016

### Regulation of CD4+ T Cell Differentiation

Components: 16 Interactions: 30

Author: Audrey Crowther  
Audience: Senior Time:  
Created: 6/3/2016 Updated: 6/9/2016

### Cell Cycle Regulation and Tumorigenesis

Components: 34 Interactions: 165

Author: Audrey Crowther  
Audience: Freshmen Time:  
Created: 6/3/2016 Updated: 6/7/2016

### Positive and Negative Feedback Loops

Components: 13 Interactions: 14

Author: Audrey Crowther  
Audience: Freshmen Time:  
Created: 6/3/2016 Updated: 6/7/2016





# Broad application

## Topics

- Cell respiration
- Glucose homeostasis
- Cell cycle
- Photosynthesis
- Gene regulation
- Food web dynamics

## Courses

- Biochemistry
- Intro biology courses
- Immunology
- Cancer Biology
- Many others

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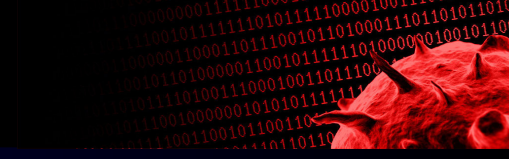
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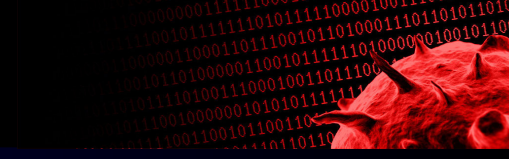
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**Questions?**



<https://www.cellcollective.org>