

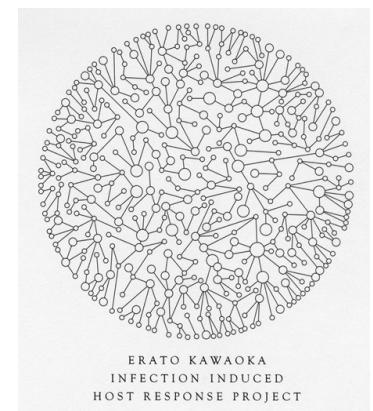
Challenges in Modeling and Curation of an Influenza Viral Life Cycle

@COMBINE 2011

Yukiko Matsuoka

JST ERATO Kawaoka infection-induced host response network project

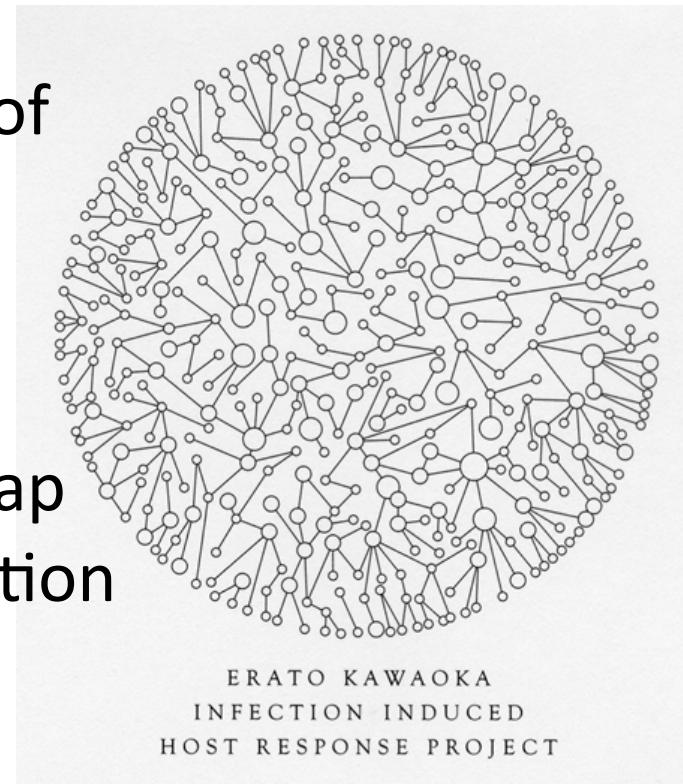
The Systems Biology Institute, Japan





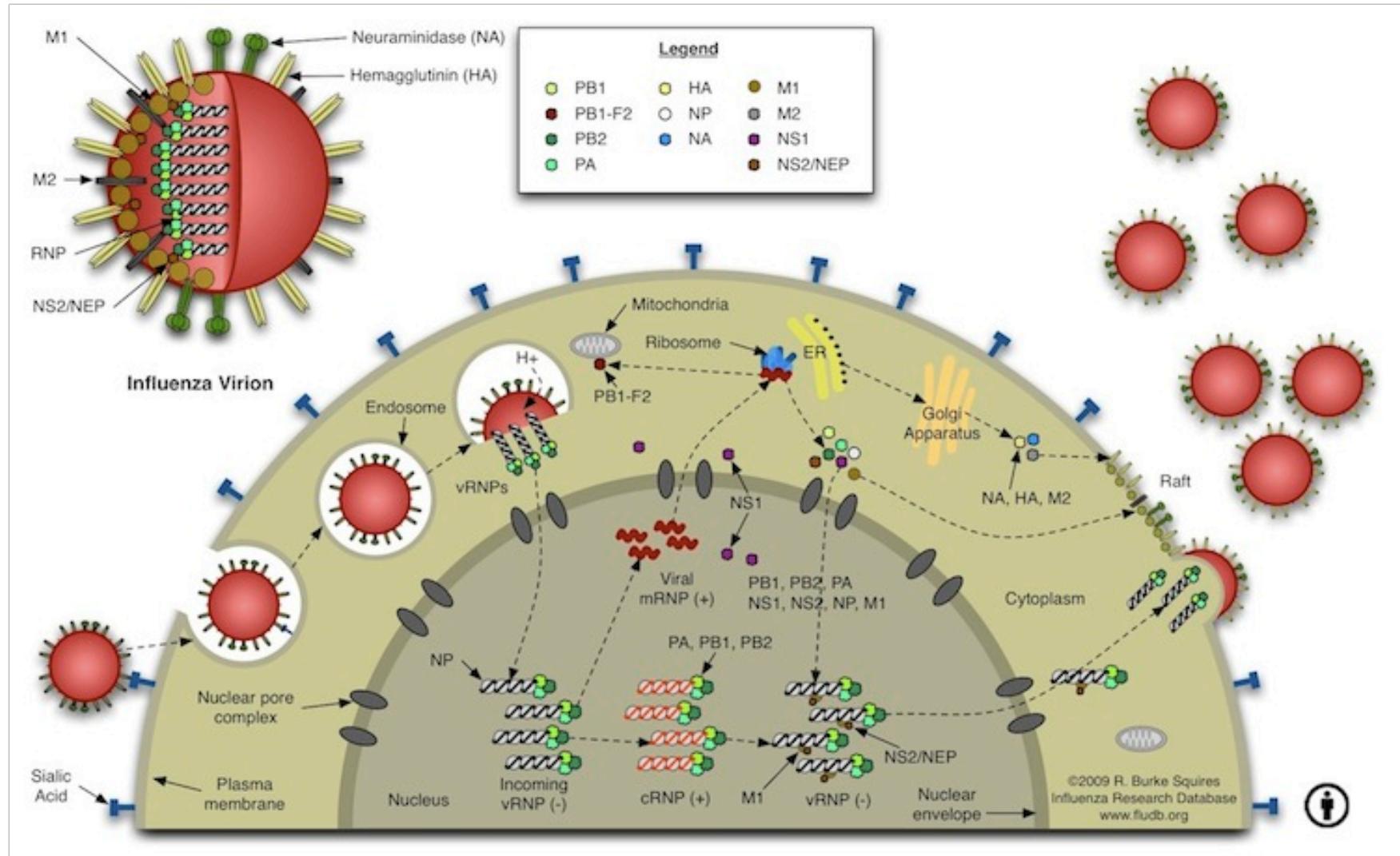
Modeling and Curation of an Influenza Viral Life Cycle

To understand the mechanisms of influenza viral replication and the host responses, construct a comprehensive influenza virus-host response map by literature-based manual curation approach.





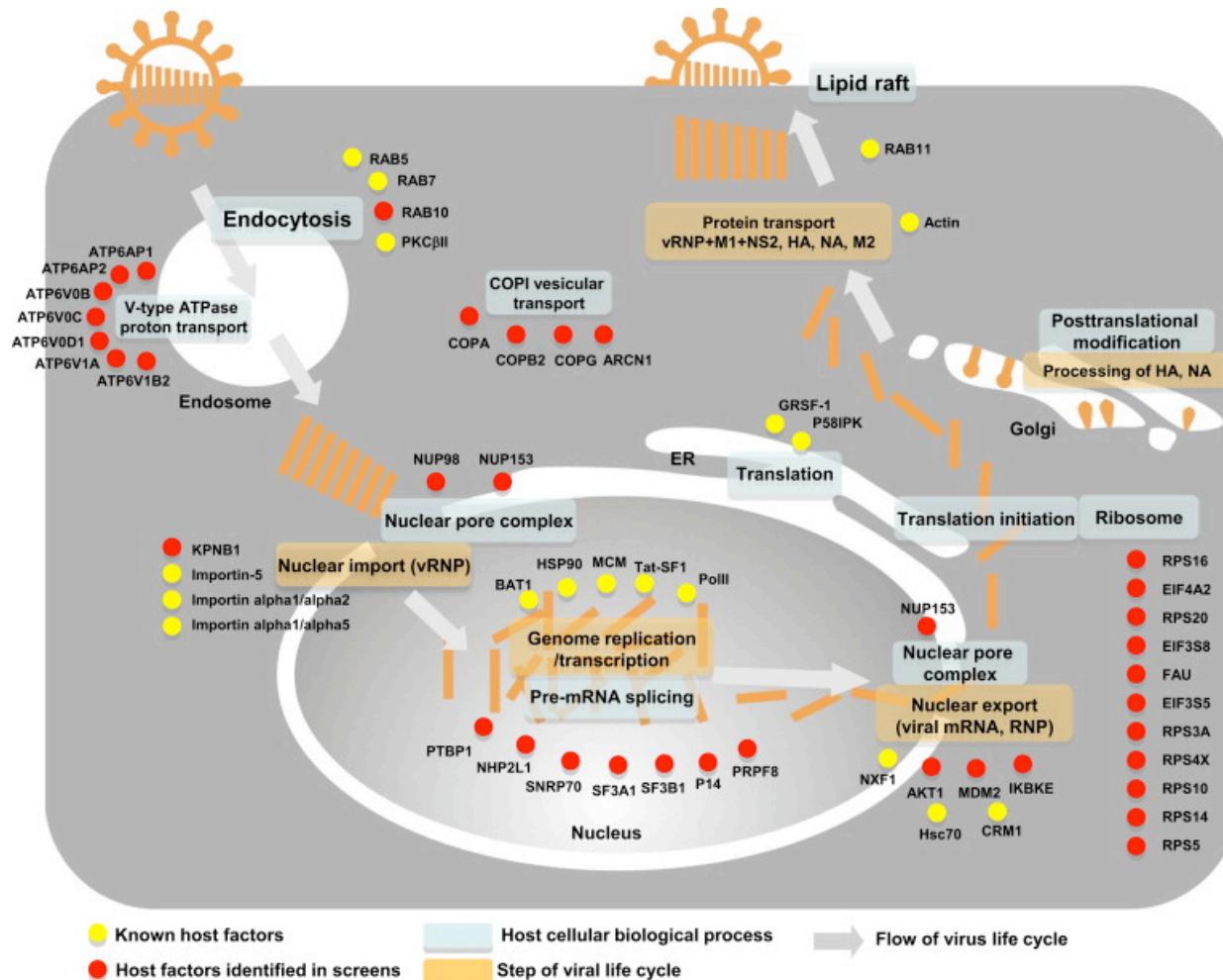
Influenza Viral Life



Based on Virology(5th edition) 2006

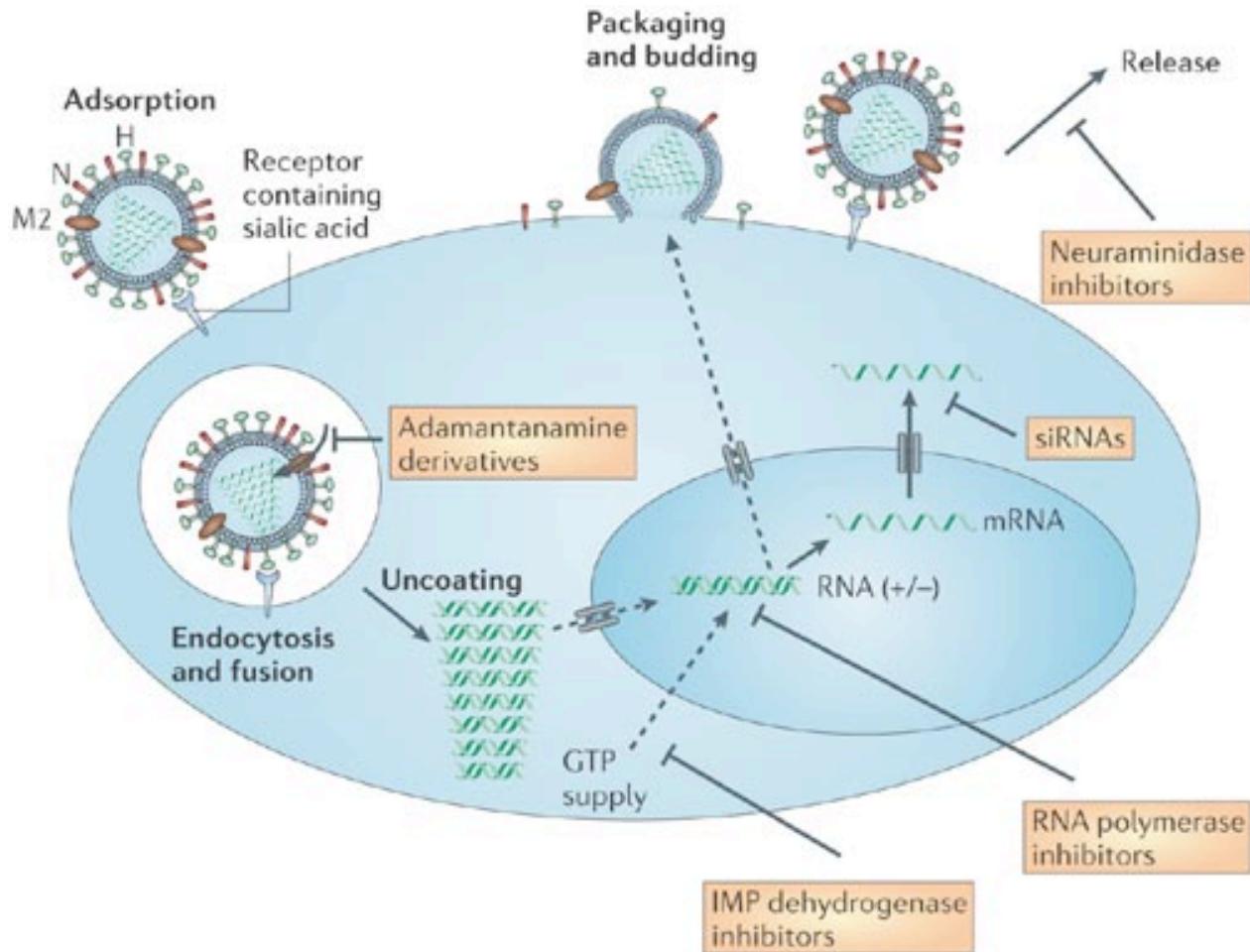


Host response



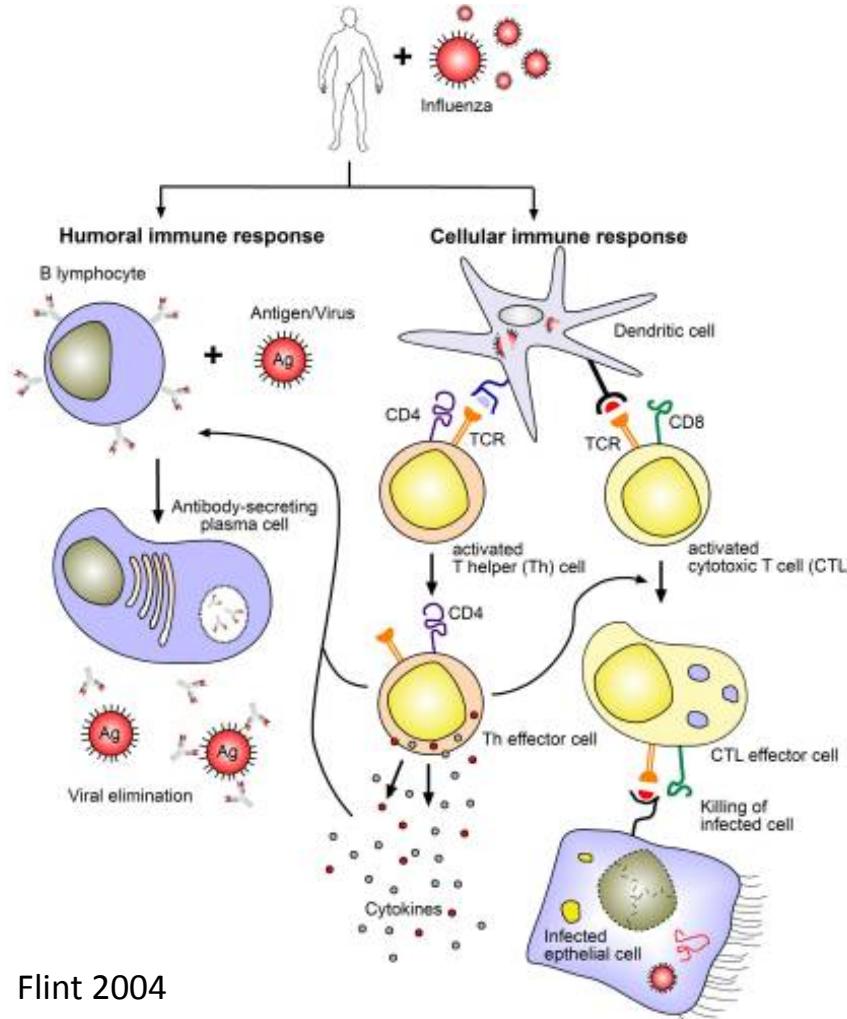
Watanabe et al. Cell Host Microbe (2010)

Antiviral Drugs





Infectious Immune Responses



Flint 2004

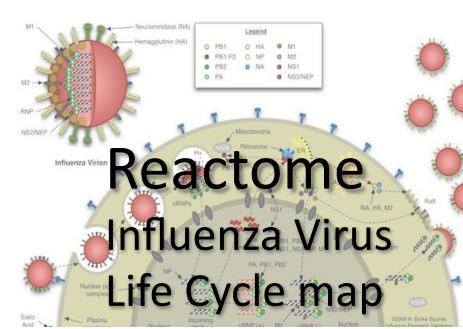
<http://www.influenzareport.com/ir/pathogen.htm>



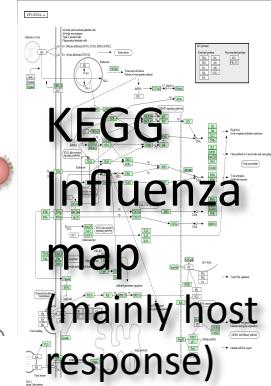
How we build a map?

- Take Pathways from **Reactome** and **KEGG** databases
- reconstruct with the process diagram pathway editor **CellDesigner** and
- store in **SBML** format
- enrich with **literature**-based information as well as the **experts inputs**.
- Annotation (Literature references and curation comments are stored in the model file in notes, **MIRIAM** format)
- Curate with CellDesigner interface or via a web-based SBML model community curation platform **Payao**.

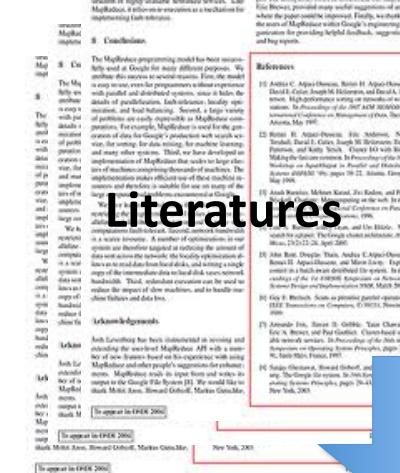
Existing Knowledge into a Map



Reactome
Influenza Virus
Life Cycle map



KEGG
Influenza
map
(mainly host
response)

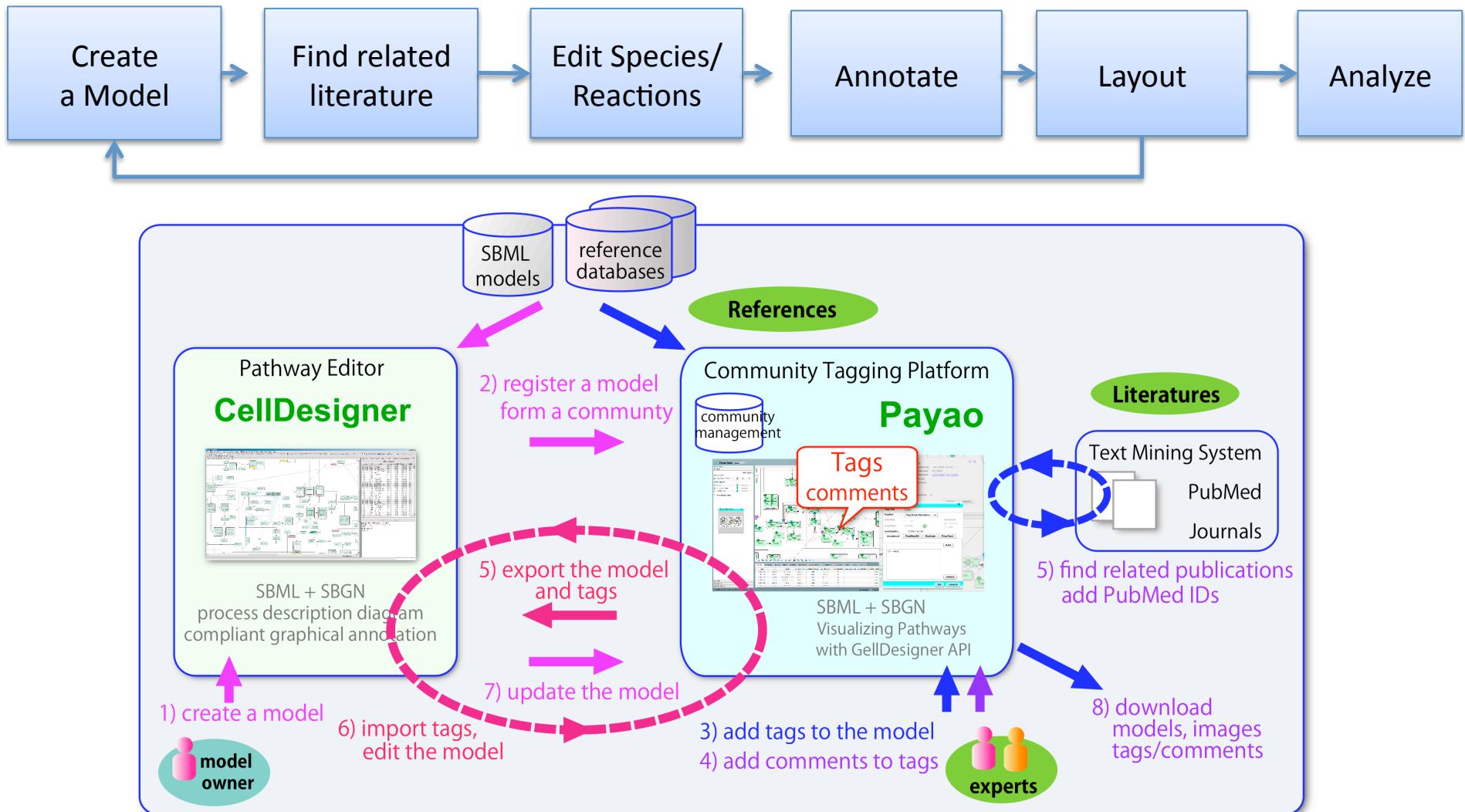


Literatures



a comprehensive “MAP”

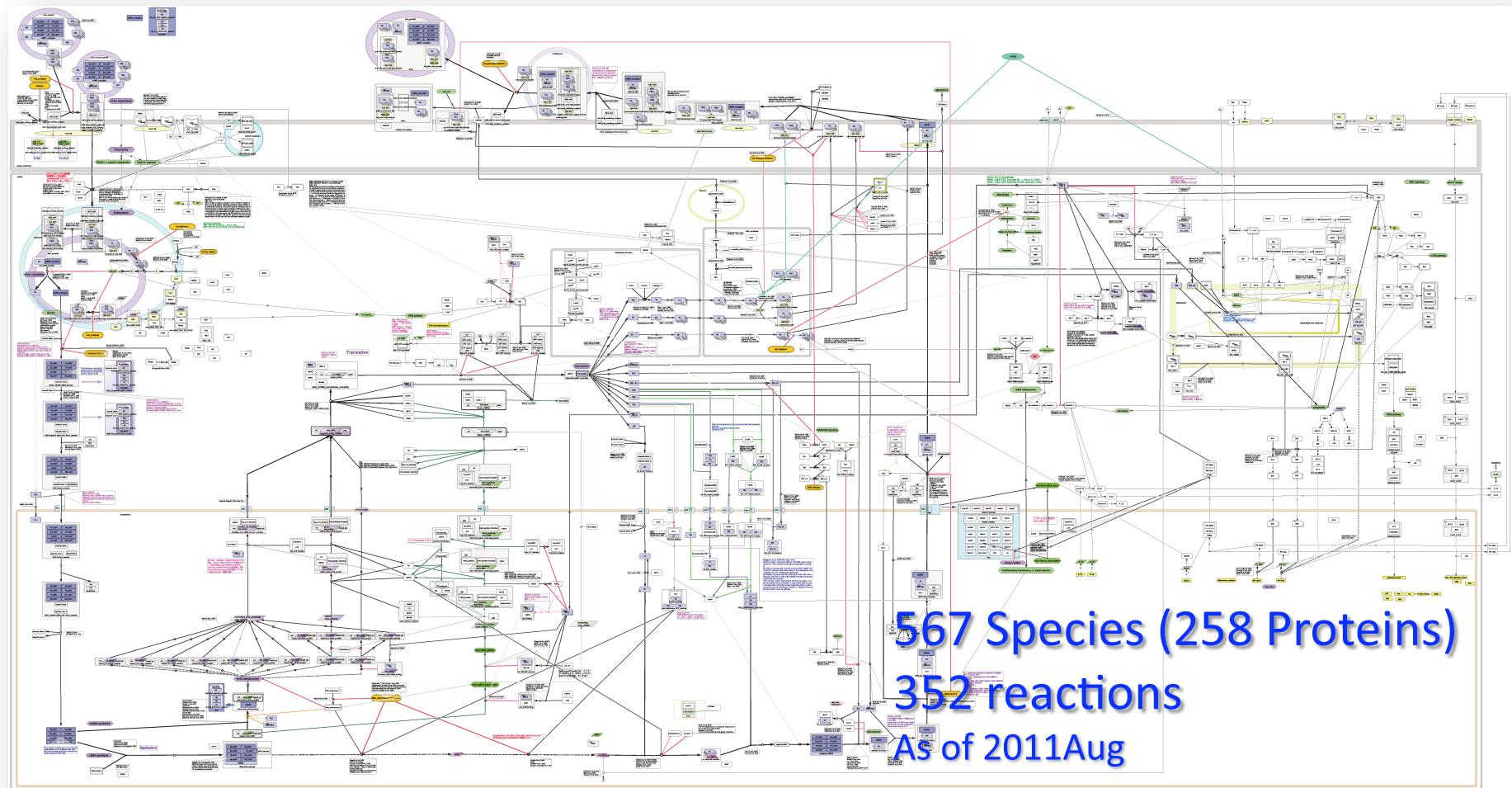
Modeling Pipeline





Influenza Viral Life Cycle Map

as of 20011 Aug





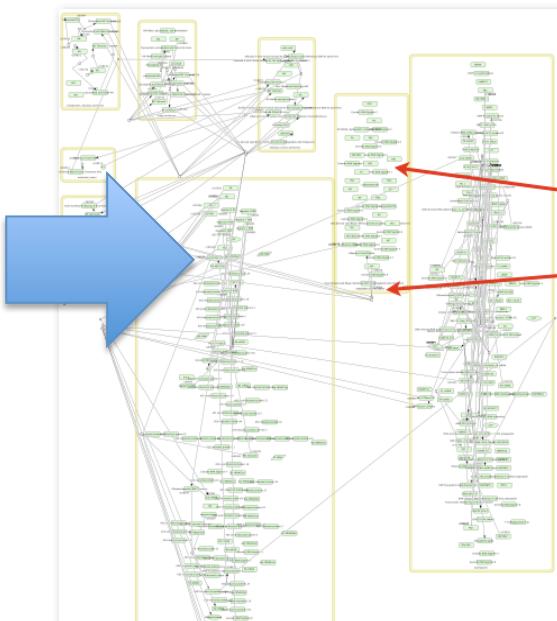
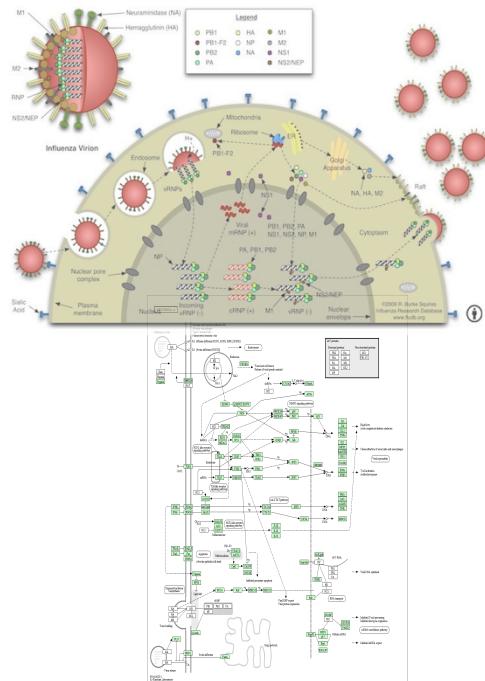
Challenges

1. Converting Pathways from Pathway databases
2. Merging Pathways
3. Layout
4. Work with Biologists: Graphical Notation
5. Interpretation of the literatures
6. Representations
7. Curation / Review Process
8. Annotation
9. Beyond a single cell





1: Converting Pathways



2010 Spring

Export **SBML** file from repositories and import it to CellDesigner

No reaction specified

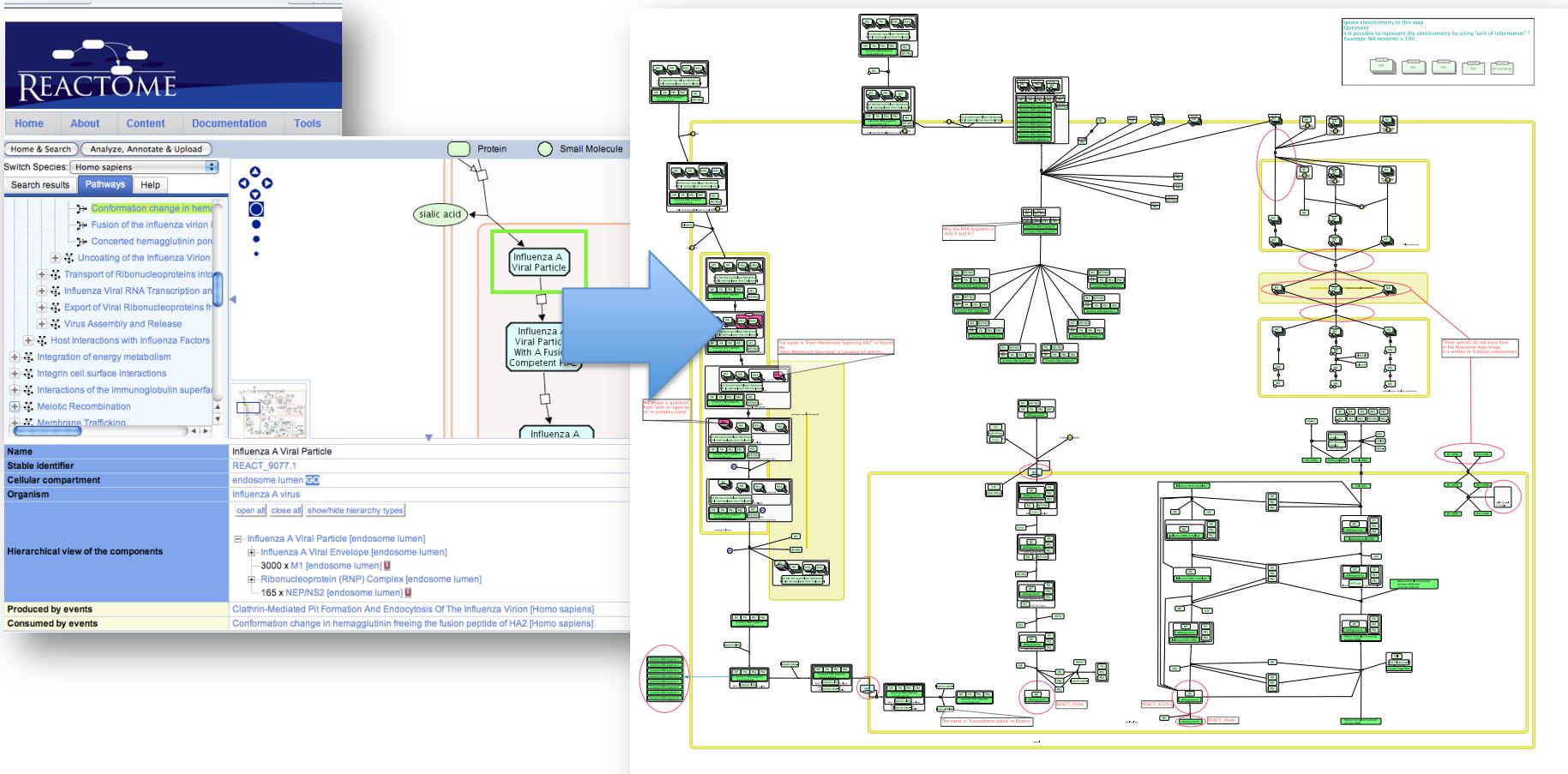
Localization unknown

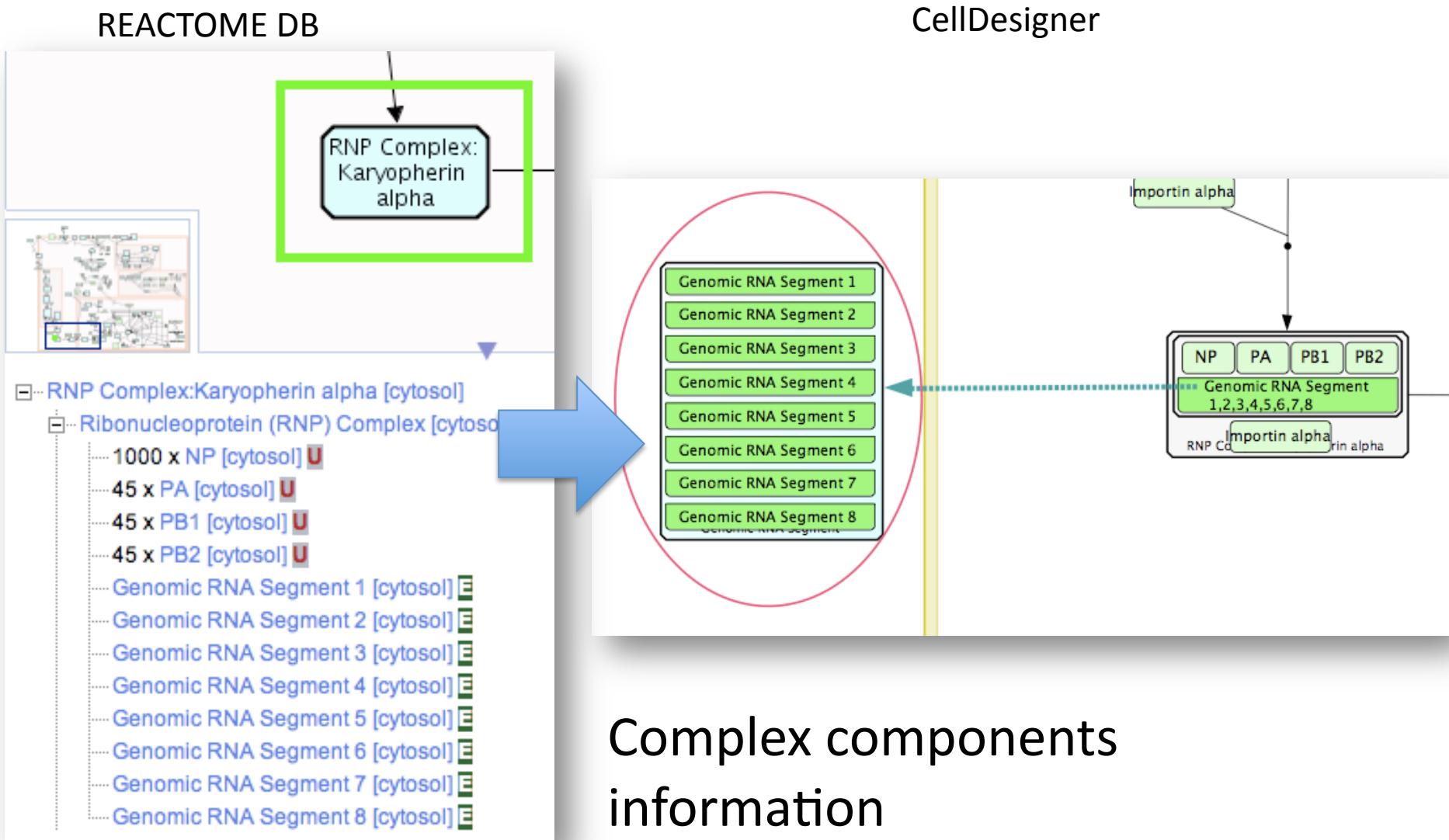
Detail Mechanisms not captured?

literature annotation missing

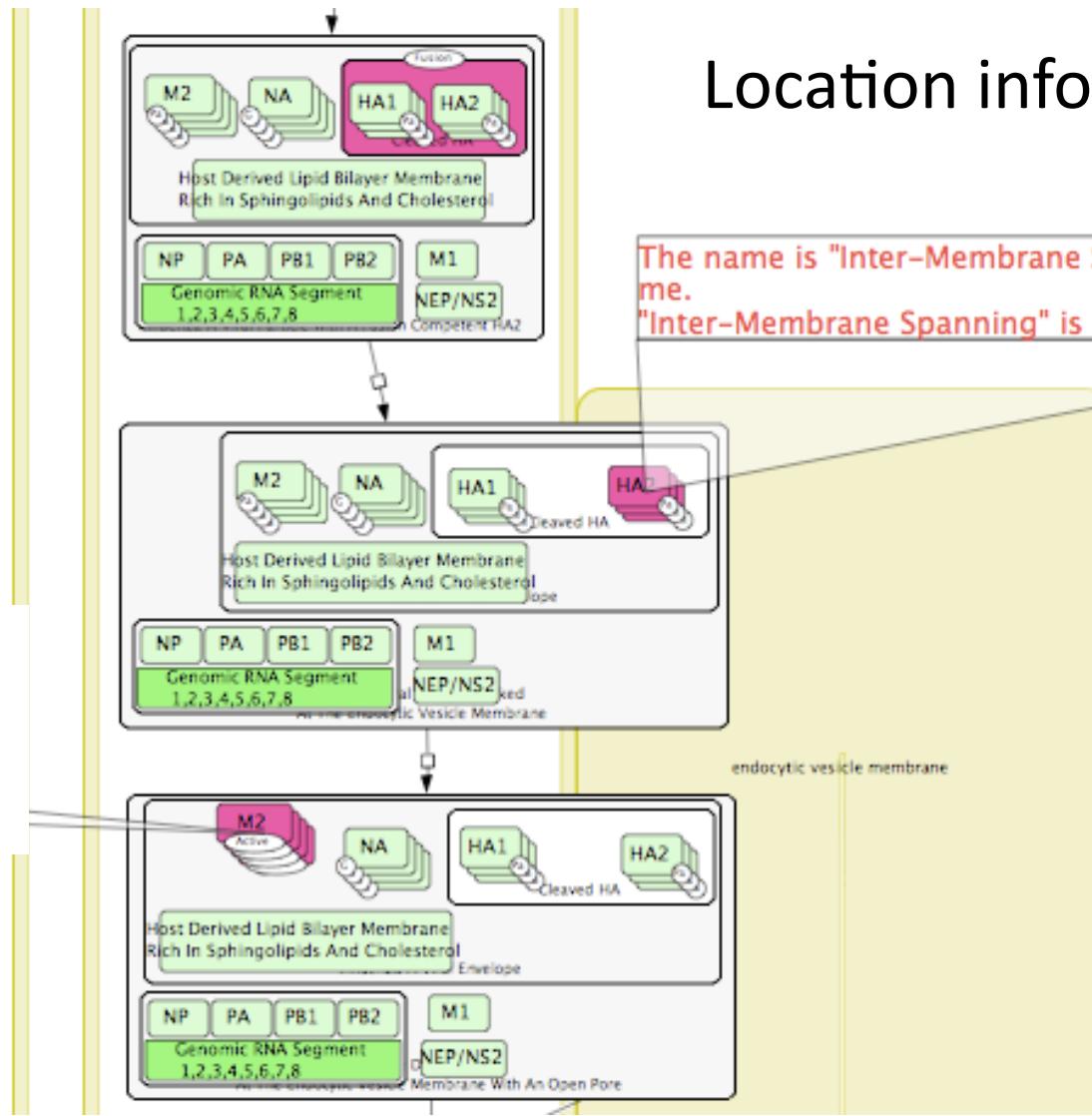
Reactome to CellDesigner

2011 Summer

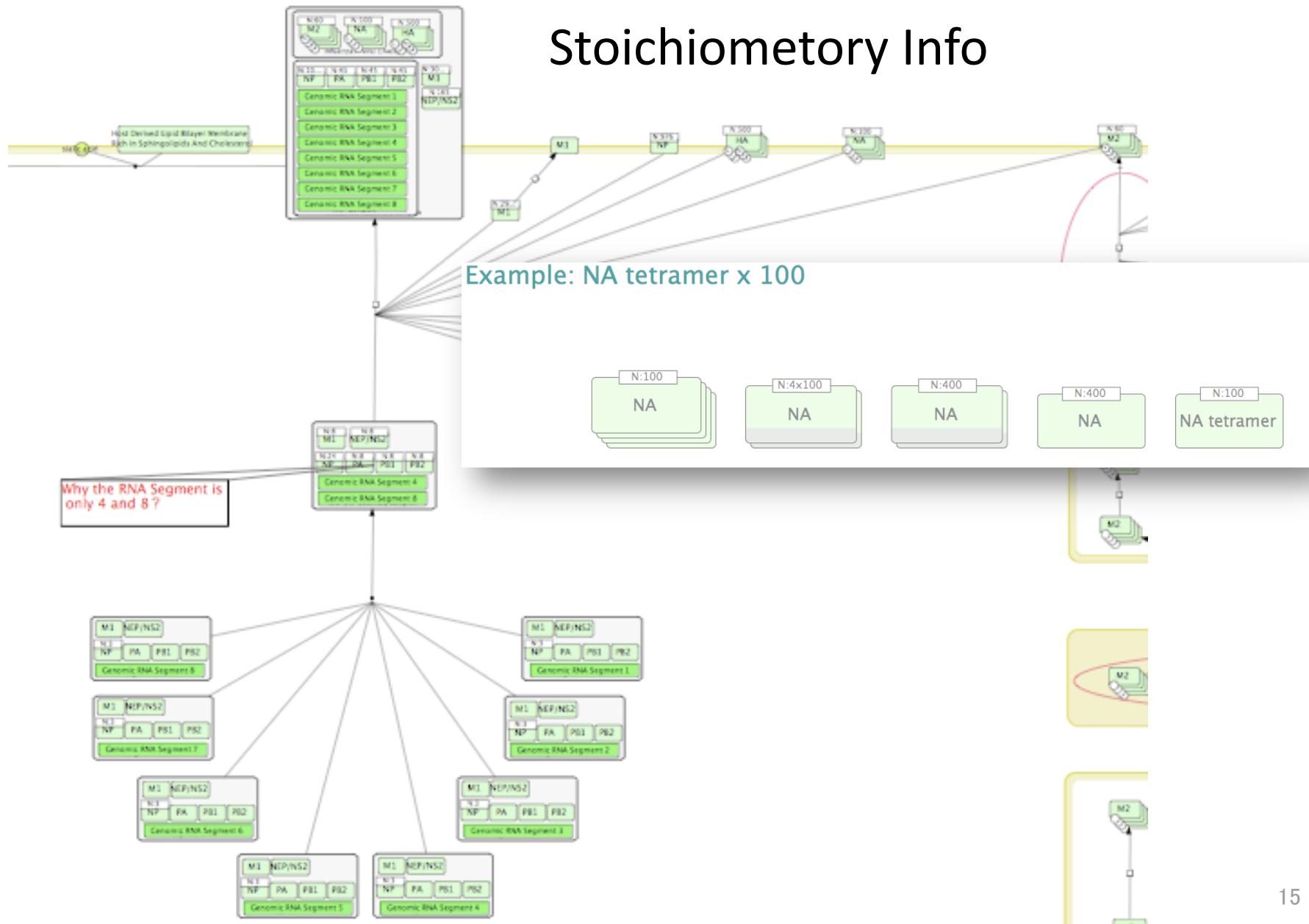




Location information



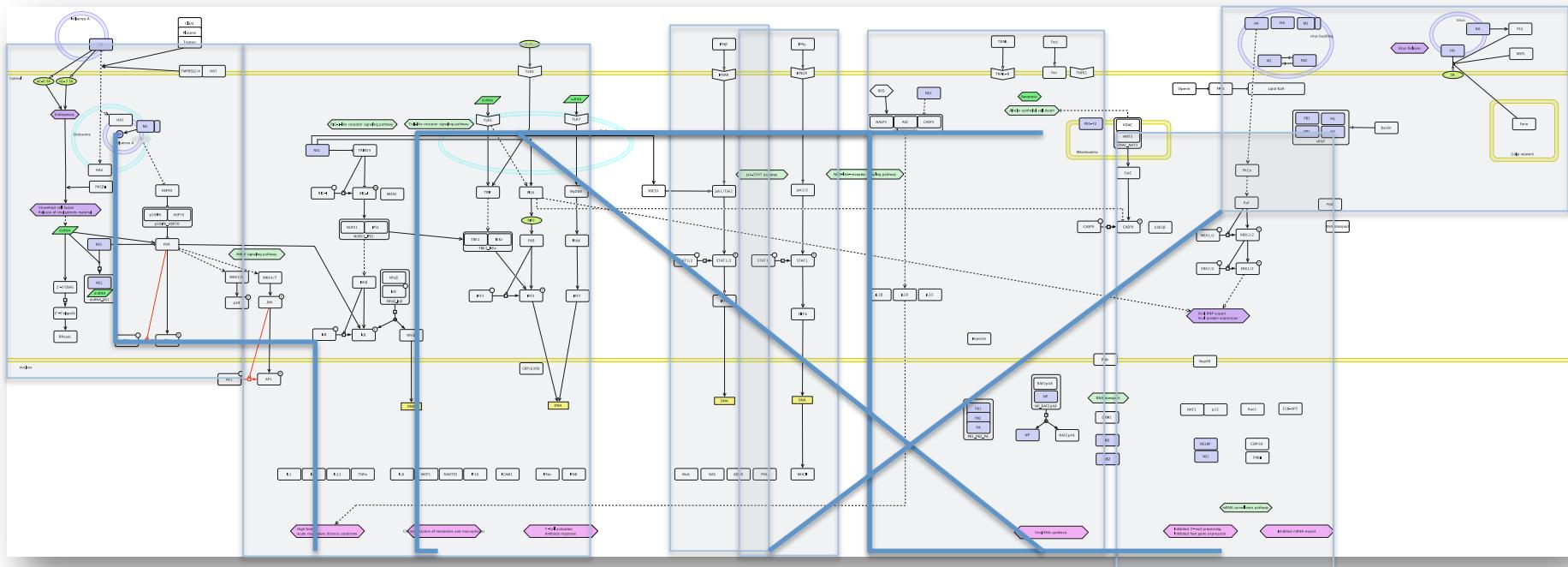
Stoichiometry Info





2: Combine Pathways

RIG-I, NFkB, JAK-STAT, TLR3/7



CellDesigner Merge Plugin

Merge Model

Layout: Manual, Species Merge, Reactions Merge
Grid: 1 x 2 Advanced Options

[01] JAK_STAT_signaling
[02] Inflammation_medium
[03] Insulin_IGF_pathway
[04] Insulin_IGF_pathway
[05] Interleukin_signaling
[06] Insulin_IGF_pathway

050
[03] Insulin_IGF_pathway_MAP_kinase_cascade [04] Insulin_IGF_pathway-protein_kinase_B_signaling

Hide Duplication Preview Merge Close Info

Duplication List - [06] Insulin_IGF_pathway_MAP_kinase_cascade_Clone1284432369257

File Edit View Search Window Highlight Reset Color Persist Color

Species	Reactions	
Name	Compartment	Id
ADP	c1	s9
ATP	c1	s8
Complex_br (insulin_br_IGF/INSR_br_IGF minus ...	c1	s5
INSR_br_IGF_minus_R_br_IGF	c1	s1
IRS space 1 minus 4	c1	s22
IRS space 1 minus 4	c1	s7
insulin_br_IGF	default	s2

CellDesigner

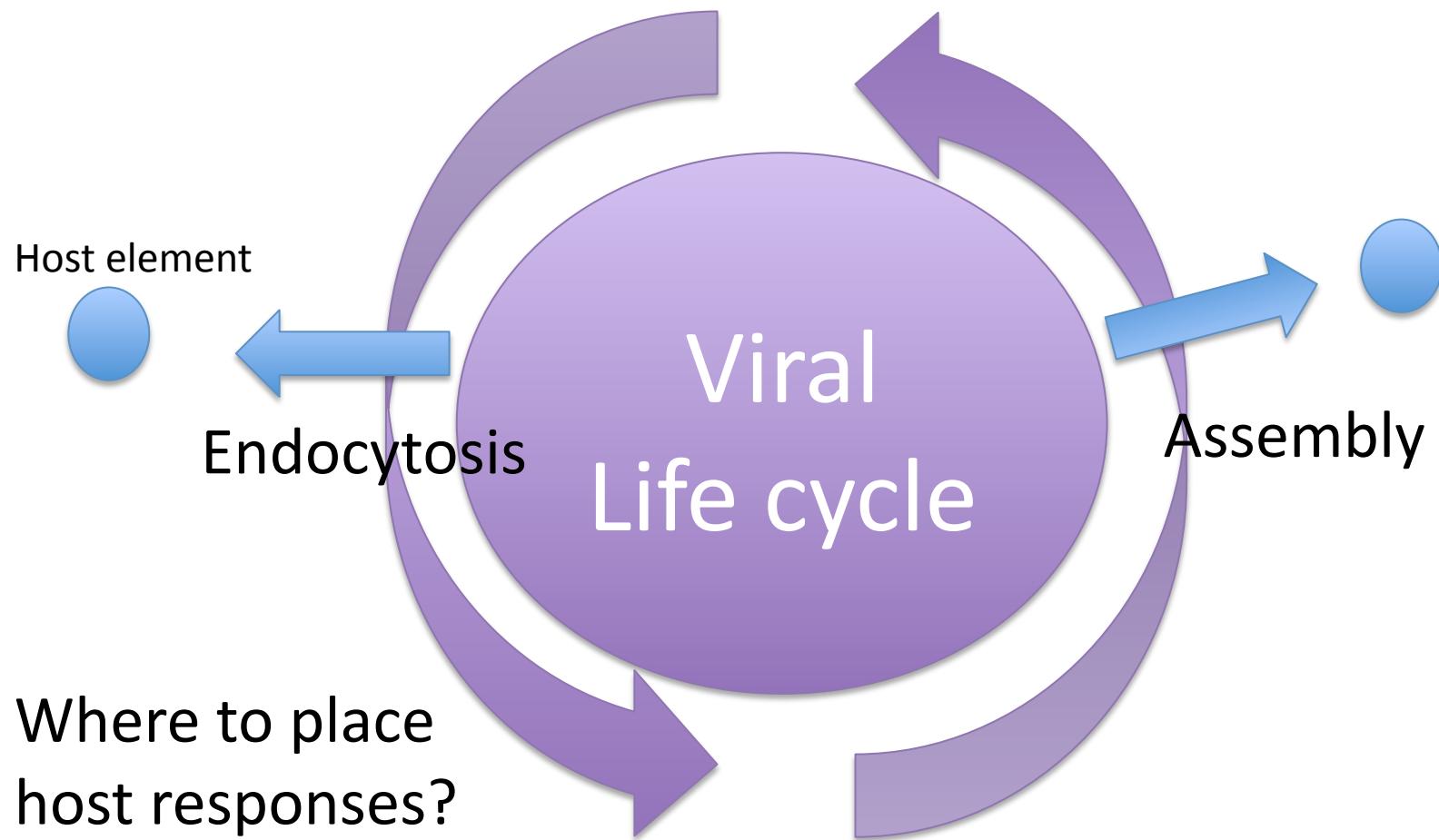
Interleukin_signaling_pathway.xml Insulin_IGF_pathway_MAP_kinase_cascade_Clone1284432369257.xml *

Cytosol Nucleus

PI3 pathway, Cell cycle synthesis, Cell division, Cell survival maintenance, Cell growth, Gene expression response

Grid Snap OFF

3. Layout





4: Modeling with Biologists

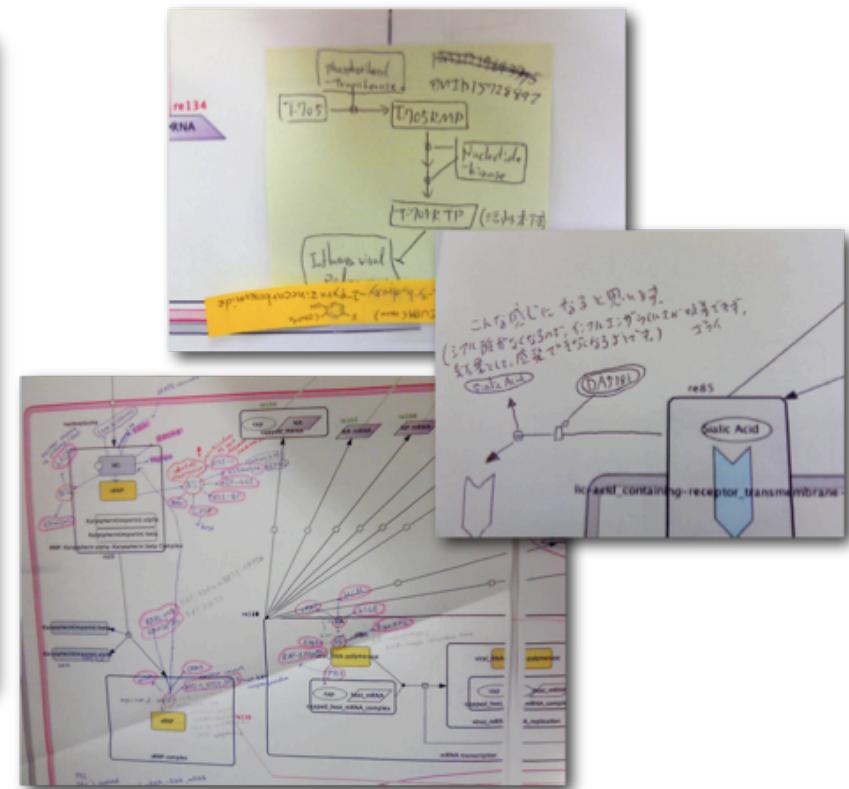


“Mapathon”

= Mapping Marathon

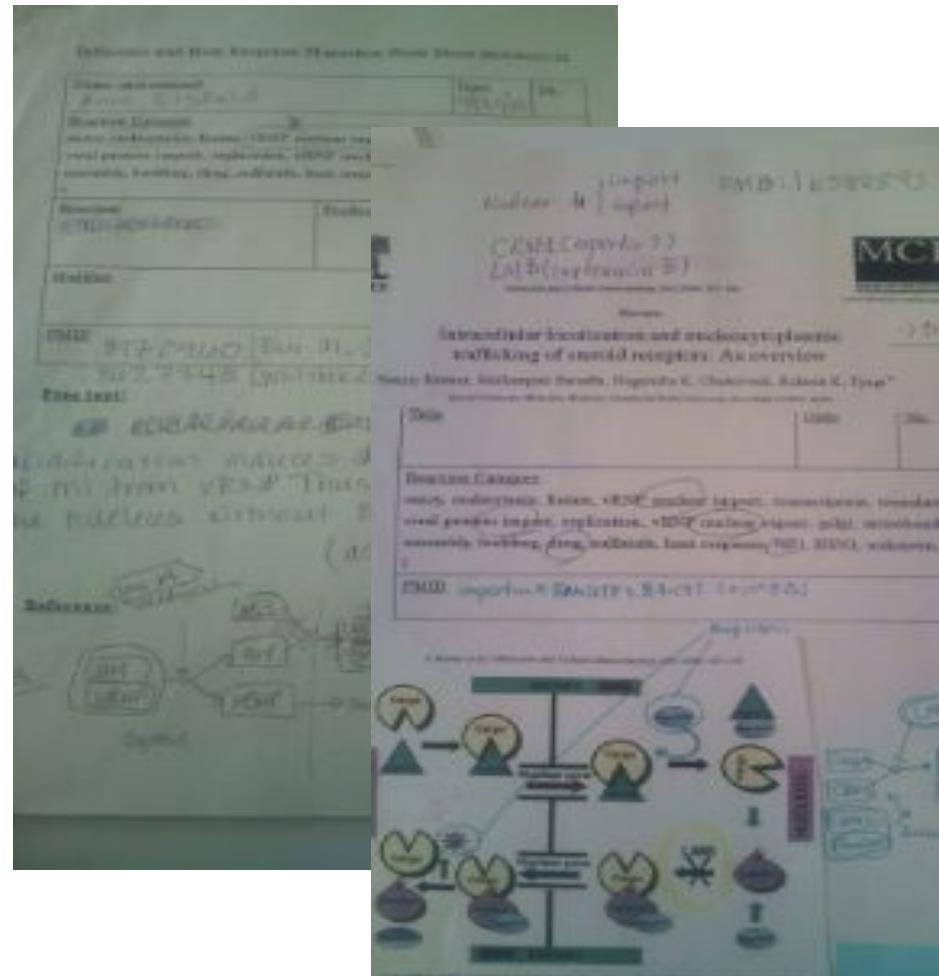


Approx. 20 students / researchers on
virology / immunology



CURATION SHEET

- PubMed ID
- Reaction Category
- Reactant
- Product
- Modifier
- Text
- Diagram





5: Interpretation



Virus infection rapidly activates the P58^{IPK} pathway, delaying peak kinase activation to enhance viral replication

Alan G. Goodman ^{a,*†}, Bertrand C.W. Tanner ^{b,†}, Stewart T. Chang ^c, Mariano Esteban ^a, Michael G. Katze ^{c,d}

^a Department of Cellular and Molecular Biology, Centro Nacional de Biotecnología, CSIC, Madrid, Spain

^b Department of Molecular Physiology and Biophysics, University of Vermont, Burlington, VT 05405, USA

^c Department of Microbiology, University of Washington, USA

^d Washington National Primate Research Center, Seattle, WA 98195, USA

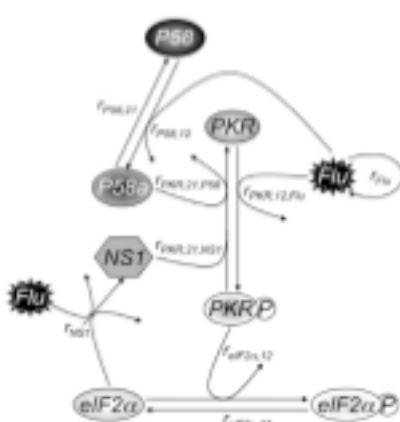
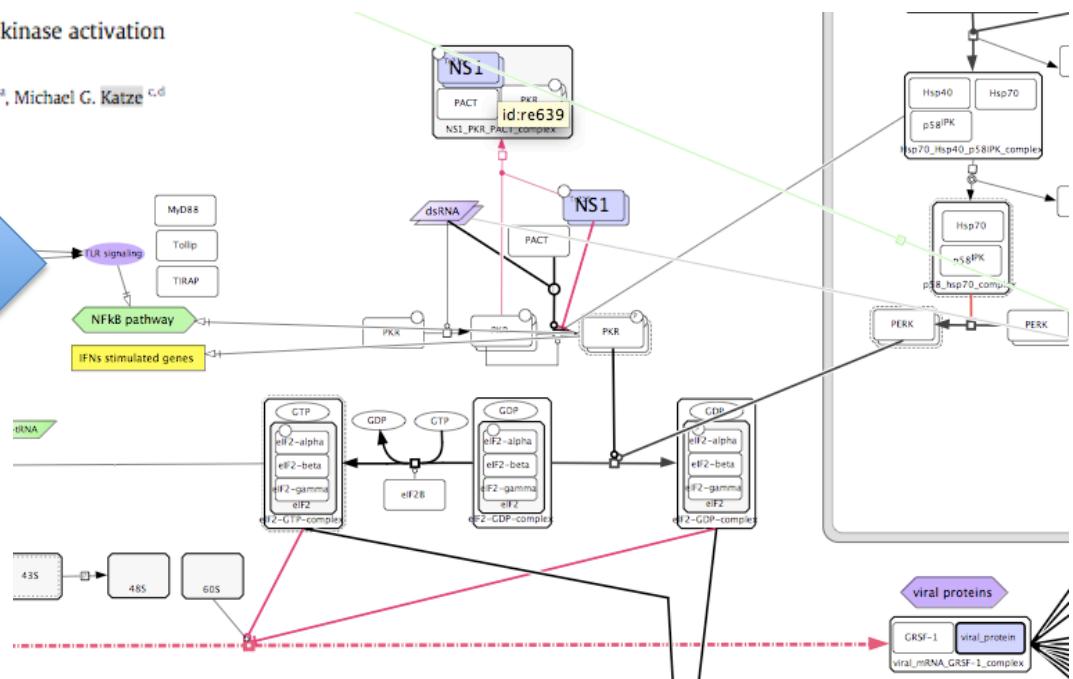
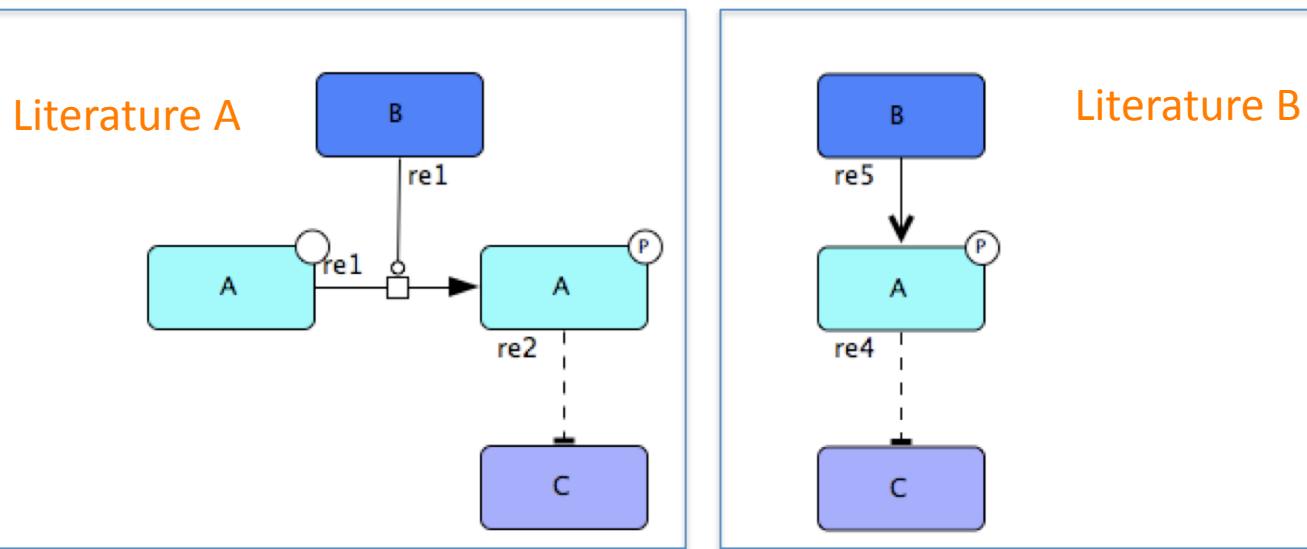


Fig. 1. Schematic of model. Flu, which grows logarithmically as described in Eq. (4), infects a cell and activates PKR at a rate of $r_{PKR,12,Flu}$ and activates P58 at a rate of $r_{P58,12,Flu}$. Active P58 (P58^a) inhibits active PKR (PKR^a) at a rate of $r_{P58,12,PKR}$, while NS1, which is synthesized in the presence of Flu and unphosphorylated elF2 α at a rate of $r_{NS1,12}$, inhibits PKR^a at a rate of $r_{NS1,12,PKR}$. P58^a is deactivated at an intrinsic rate of $r_{P58a,12}$. PKR^a phosphorylates elF2 α at a rate of $r_{elF2\alpha,12}$, while dephosphorylation of elF2 α ^P occurs at a rate of $r_{elF2\alpha,12,1}$. Equations and more detail are given in the text.



What is known? detail mechanism or just relations?



Process Diagram

Activity Flow?



Mixed Hybrid Notations

Multiple Hypothesis in a single map?

Use Colors
to distinguish
Hypothesis

Also Use Colors
to show
different
viral strains
effects
(e.g. Avian Flu)

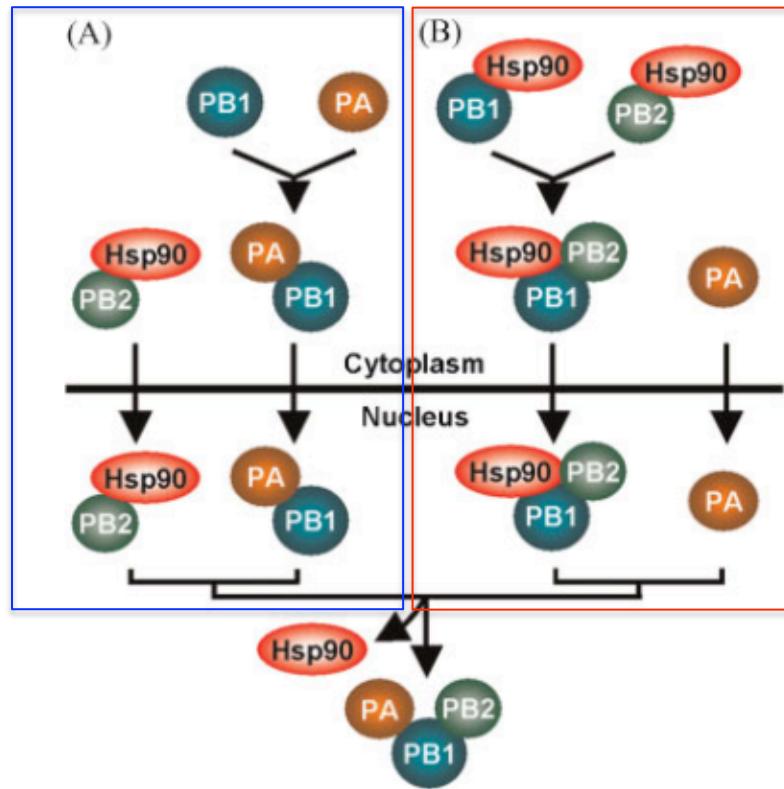


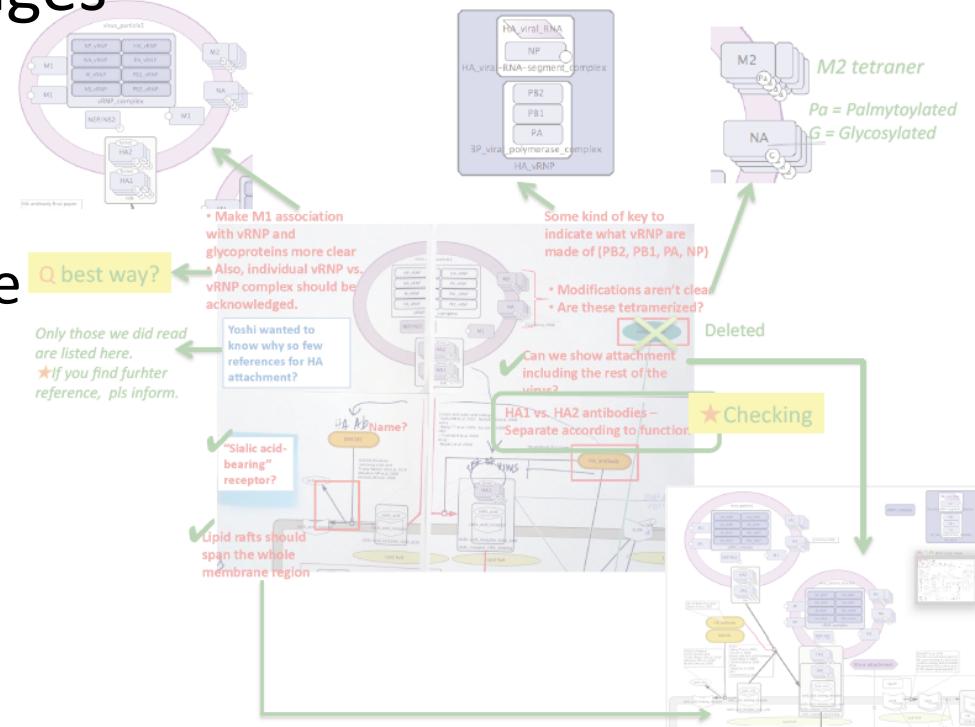
Figure 4. Nuclear import and assembly of viral RNA polymerase subunits. Two possible alternative pathways are shown. (A) PB2 is transported into the nucleus with Hsp90. PB1 and PA interact with each other in the cytoplasm and migrate into the nucleus as a complex. (B) Hsp90 interacts with PB1, PB2 and a PB1-PB2 subcomplex, and then a PB1-PB2-Hsp90 complex is transported into the nucleus. The nuclear import mechanism of PA is not clear. The ternary polymerase complex is assembled with nuclear transported viral polymerase subunits and/or subcomplexes, and concomitantly Hsp90 is released from subunits and/or subcomplexes

Nagata K. 2008



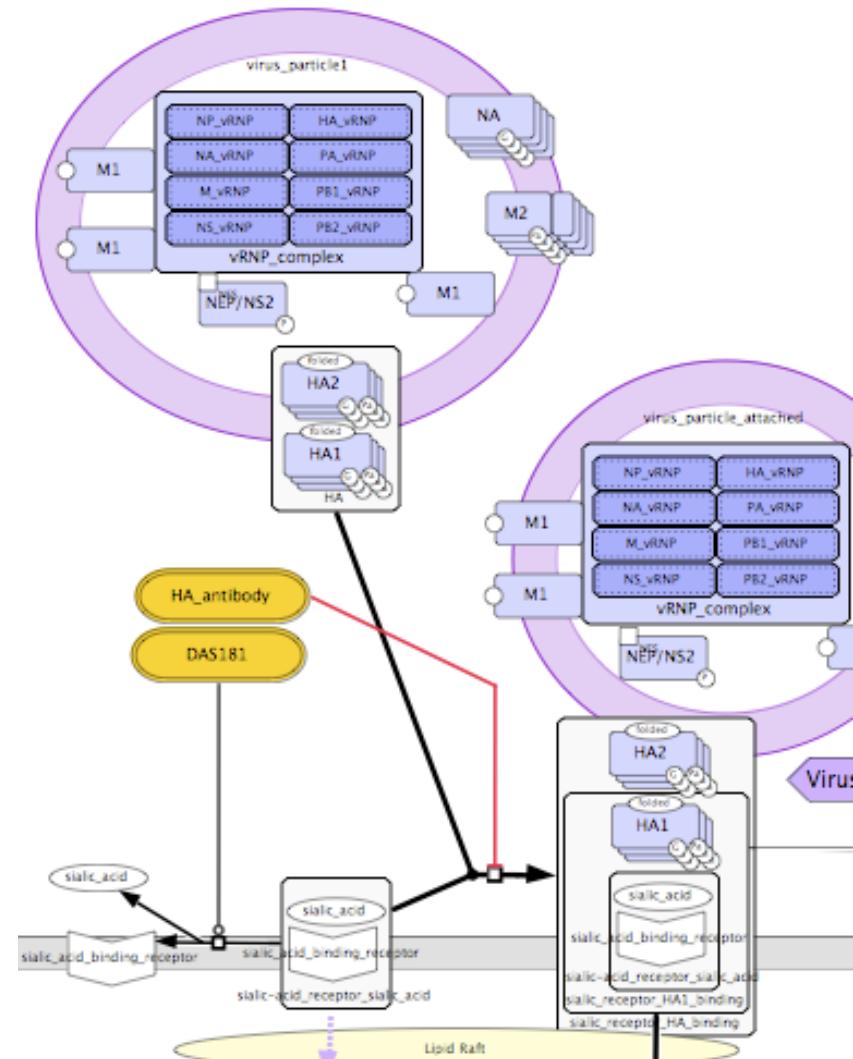
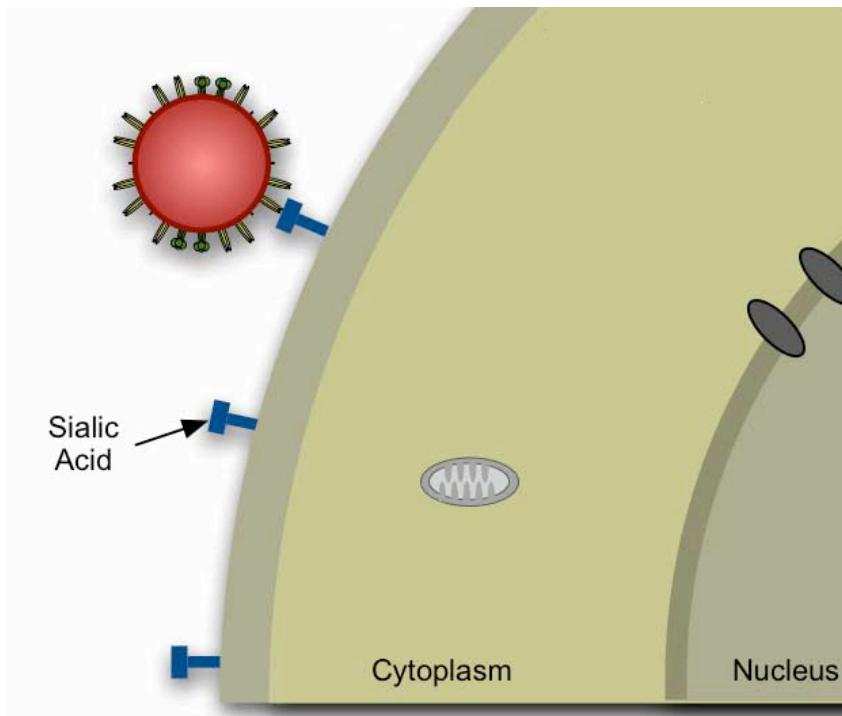
6: Representations

- Virus as a Compartment ? Complex ?
 - Virus attachment
- Conformational changes
 - Endocytosis, fusion...
- Phase shifts
 - Early / late endosome
 - autophagy

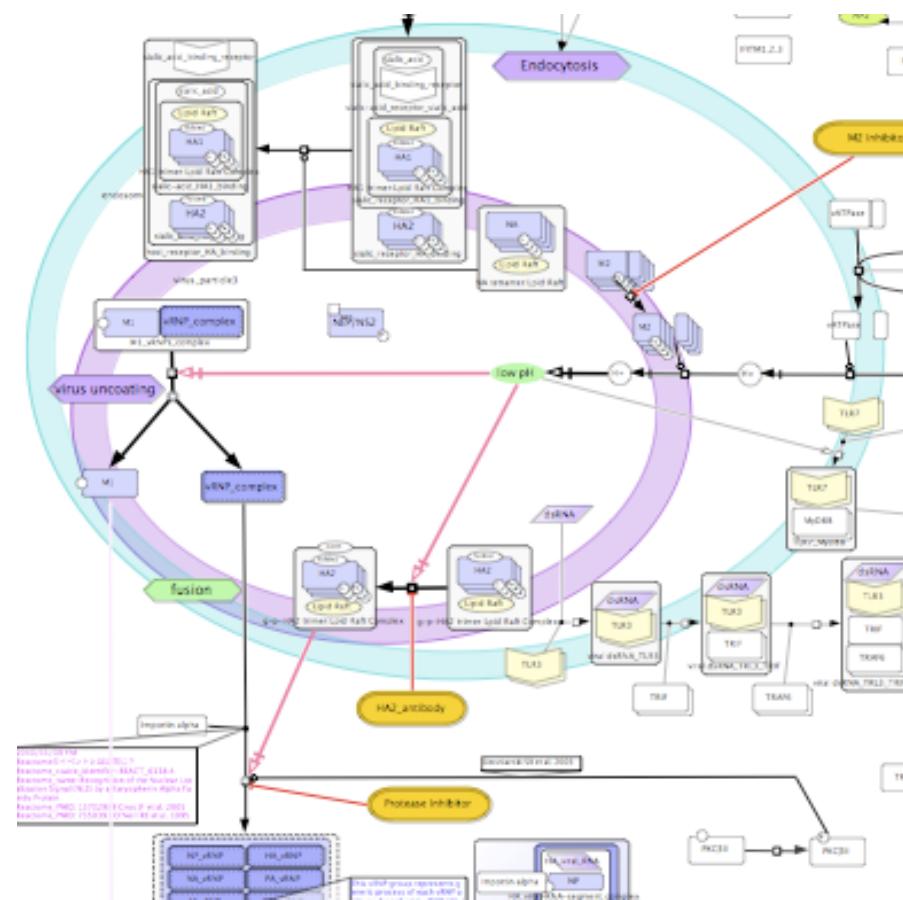
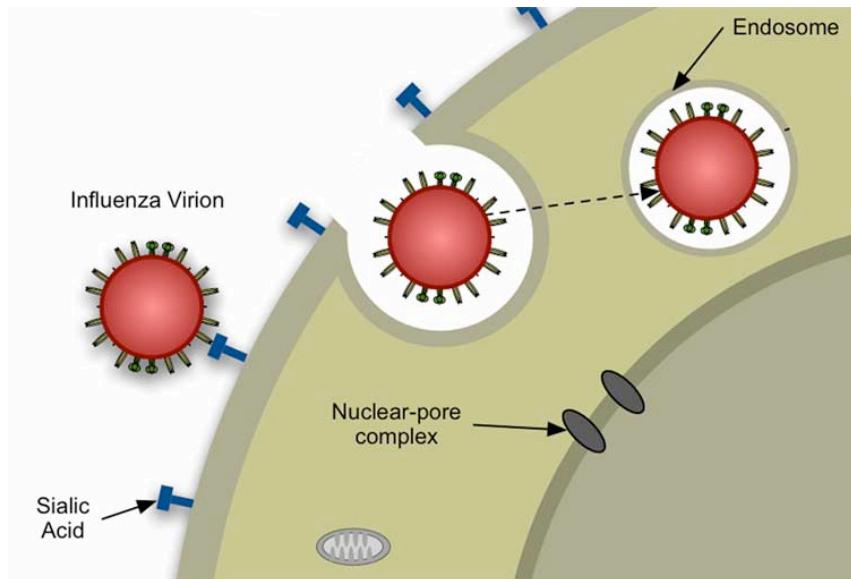


Virus Attachment

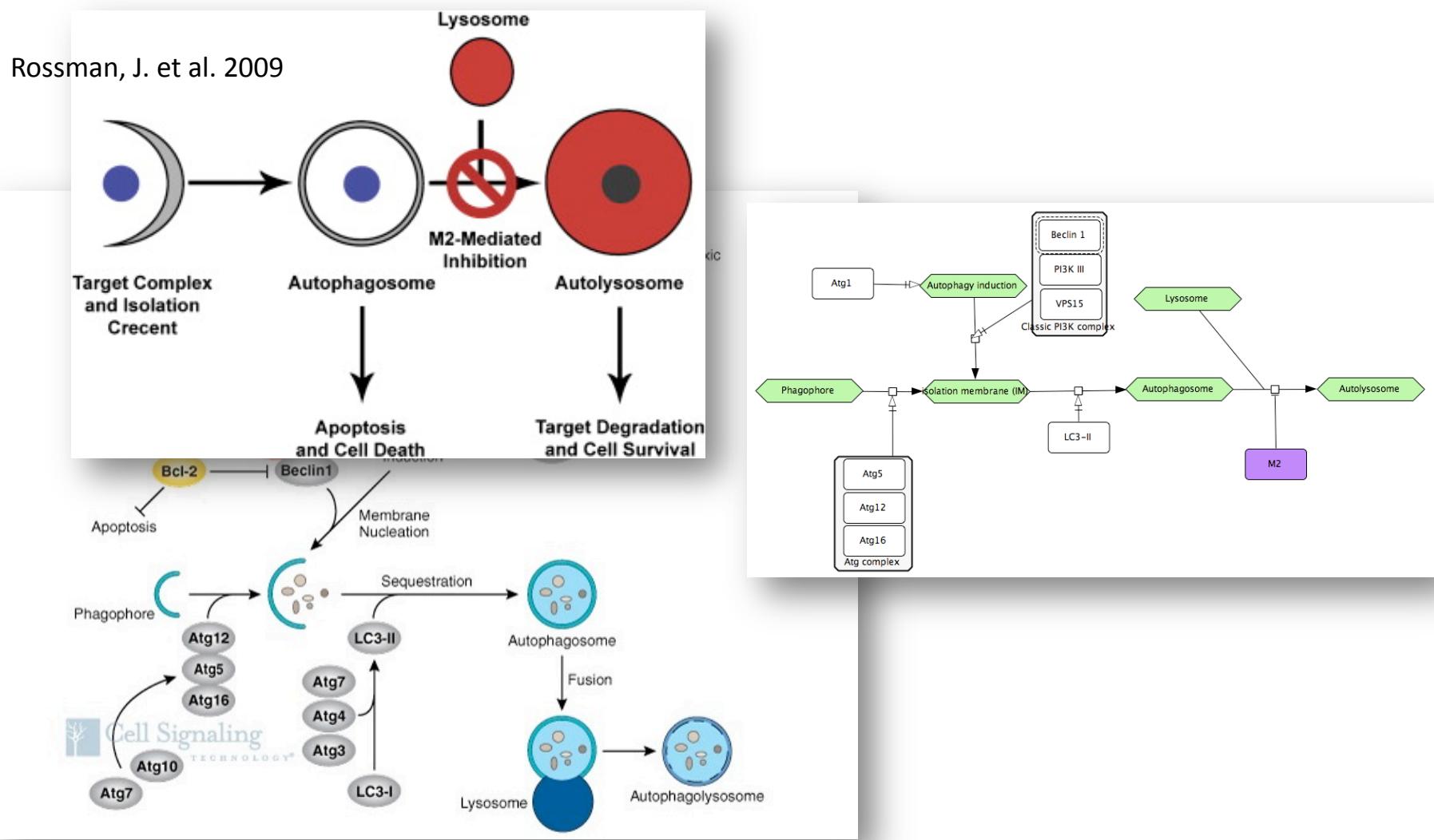
Viral protein HA (hemagultinin) attaches to Sialic Acid...



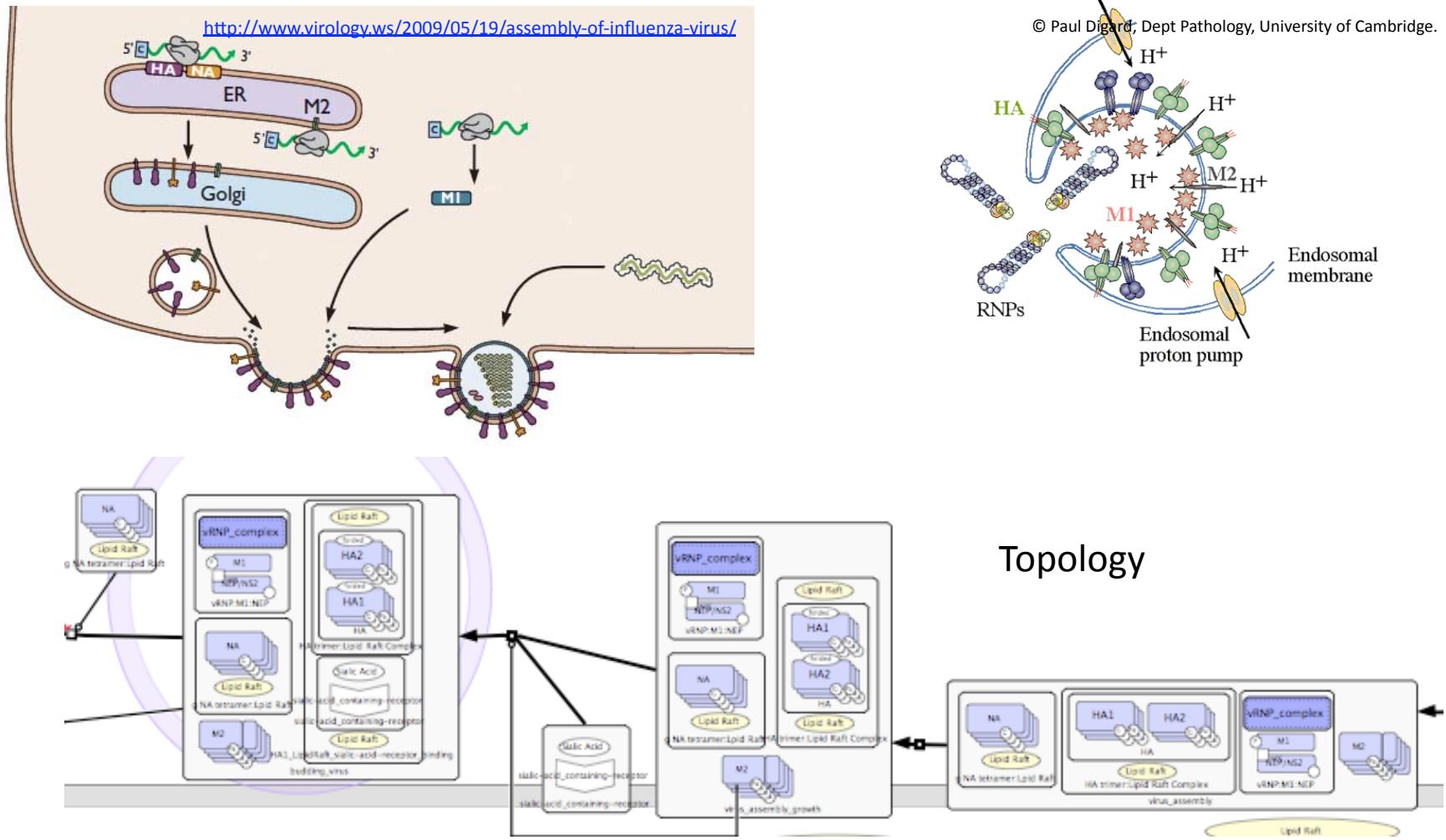
Endocytosis



Autophagy



Virus Budding





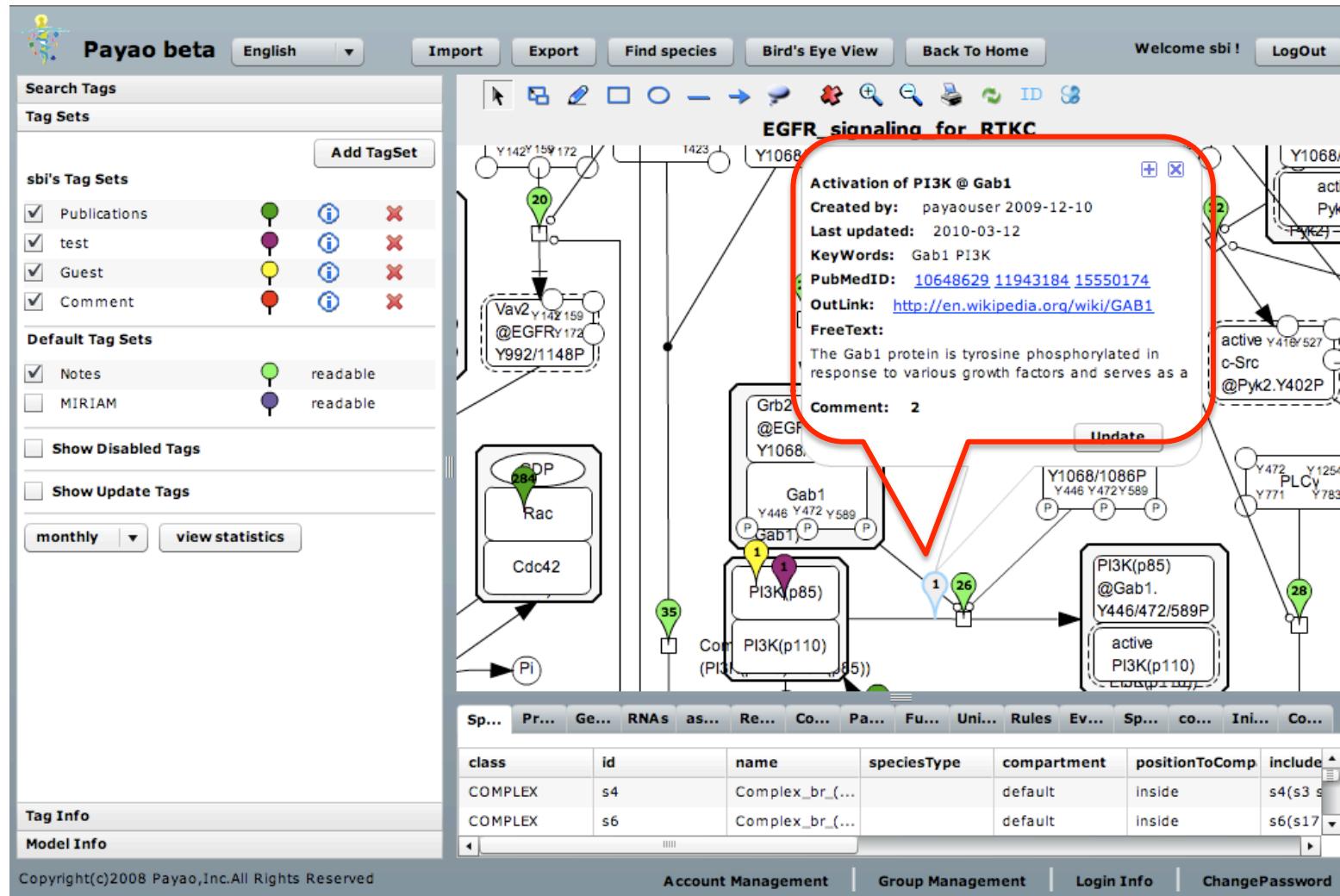
7: Curation/Review process



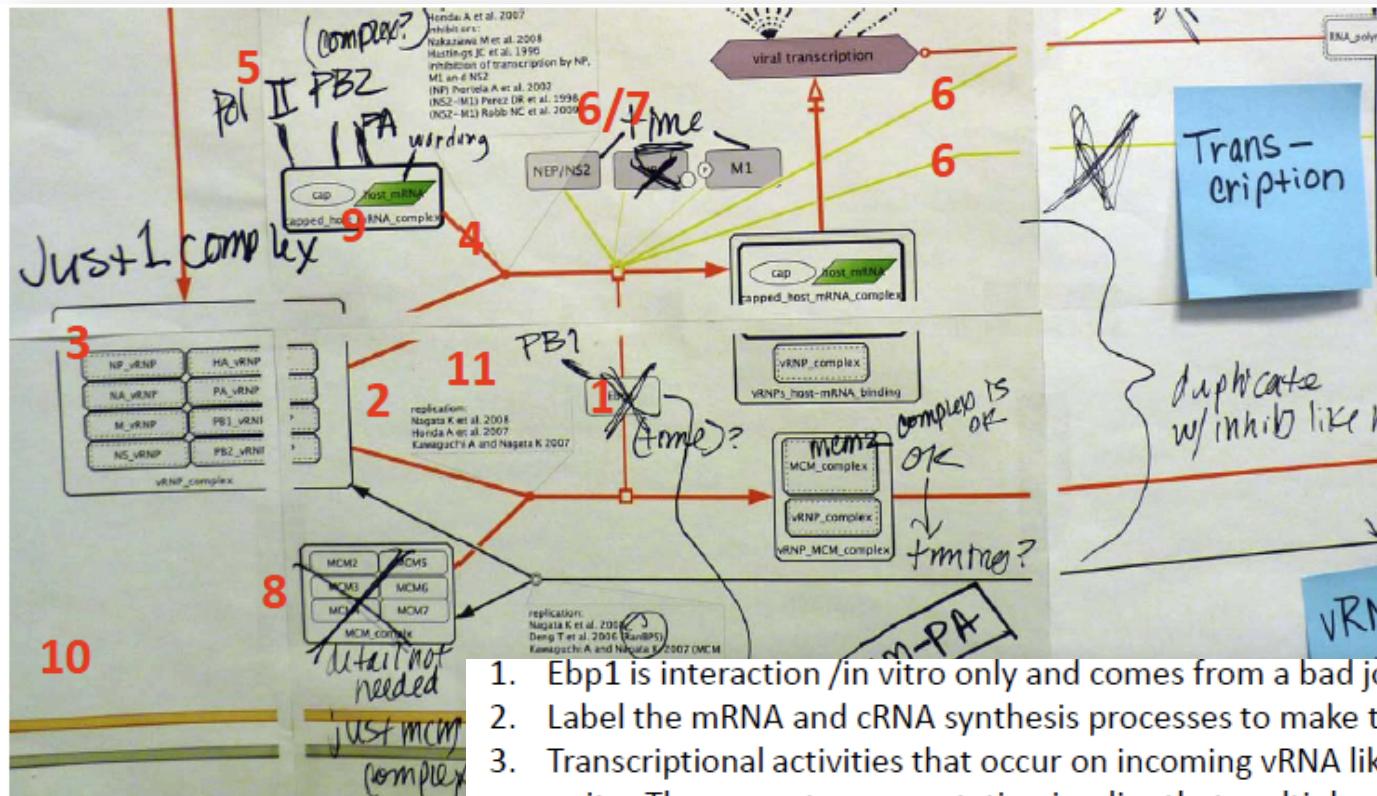
Map Builders vs. Reviewers (Curators)



Payao : Curation Platform



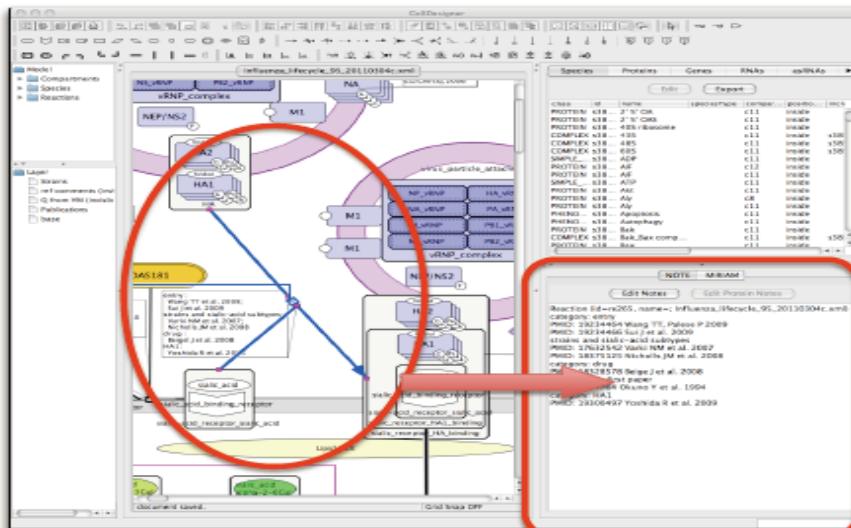
Feedbacks received from Reviewers...



1. Ebp1 is interaction /in vitro only and comes from a bad journal
2. Label the mRNA and cRNA synthesis processes to make this more clear
3. Transcriptional activities that occur on incoming vRNA likely occur on individual units. The current representation implies that multiple complexes are transcribing together.
4. Can we somehow indicate the different components of the polymerase complex? now vRNP complex might be a little vague. Also there are specific interactions



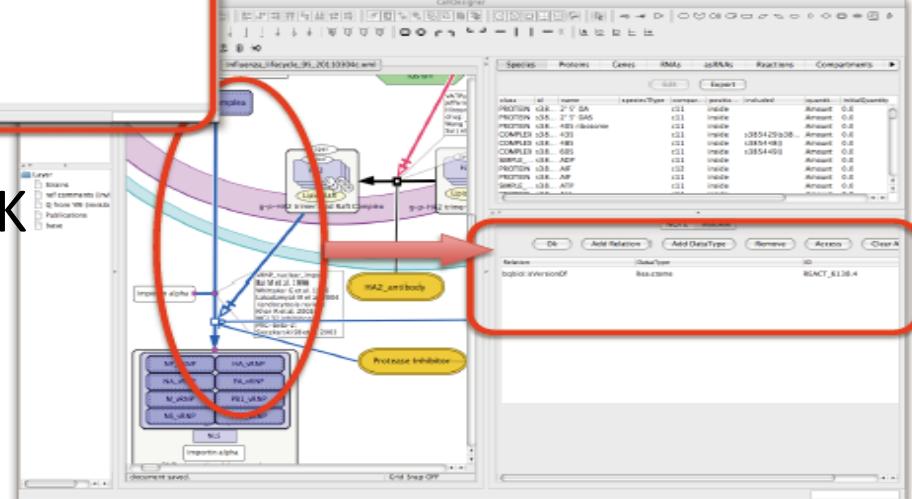
8: Annotation



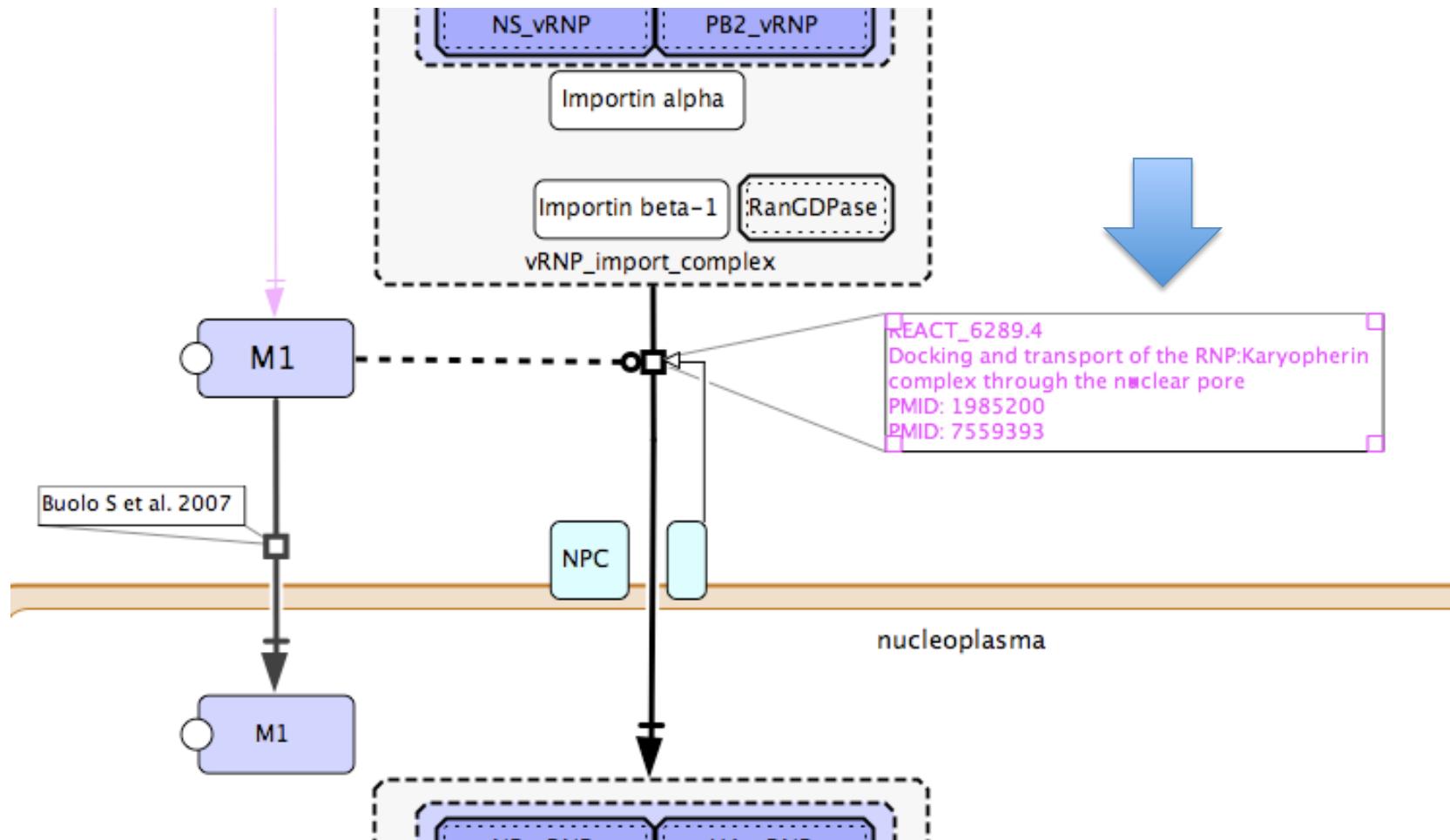
Time consuming!

MIRIAM Format

PubMedID, UniProtID : OK
MIRIAM relation: ??
IsPartOf....
IsVersionOf....



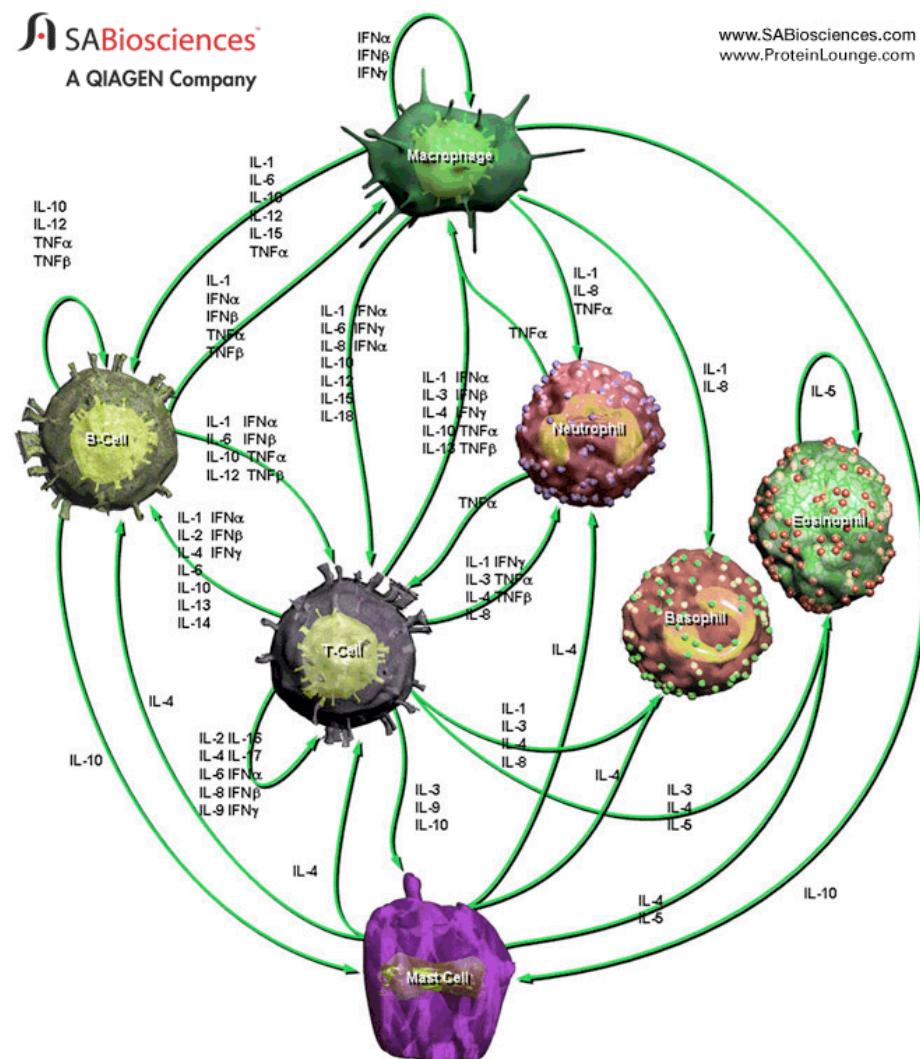
Annotations Visible on the Map



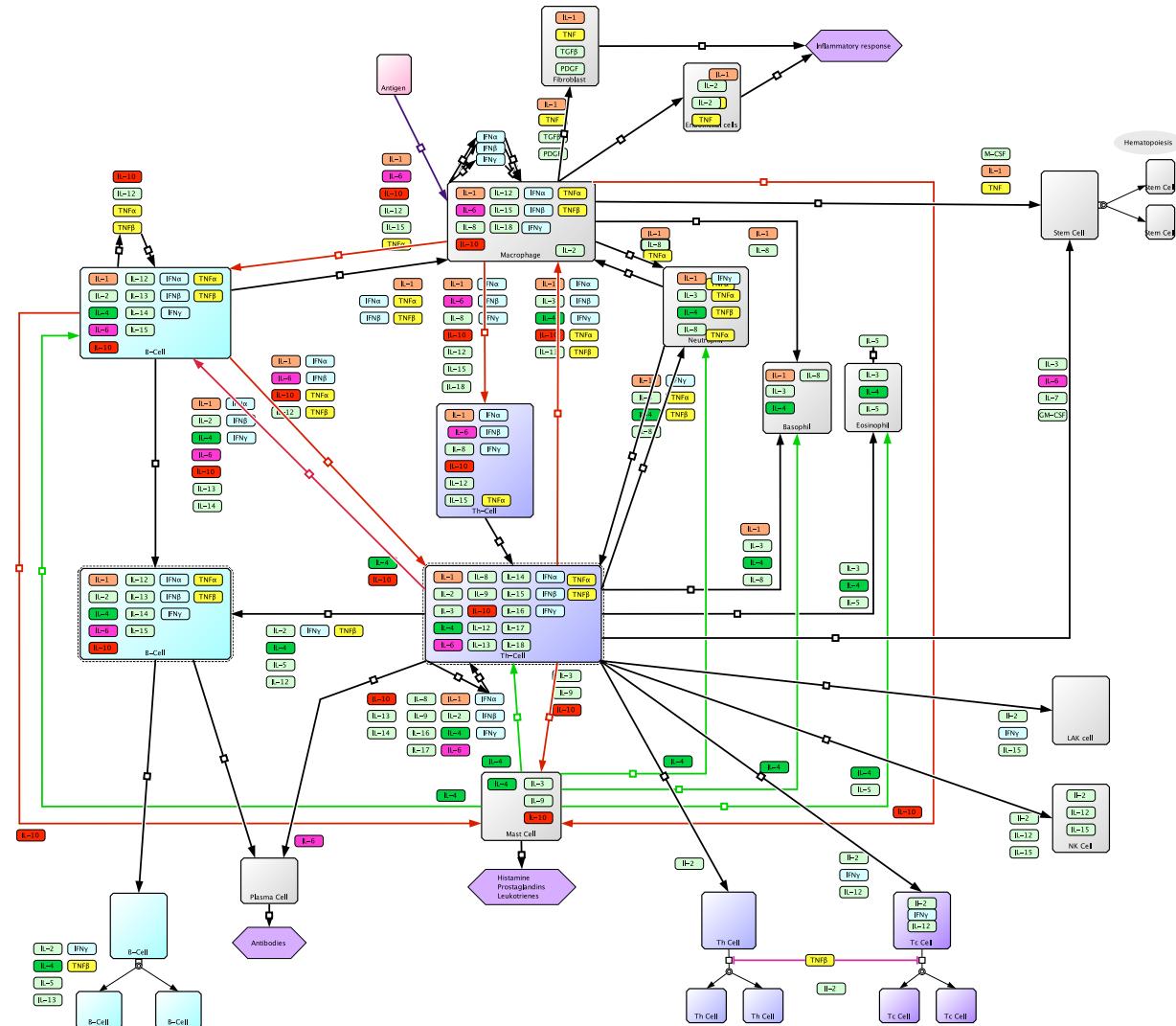


9: Beyond a single cell

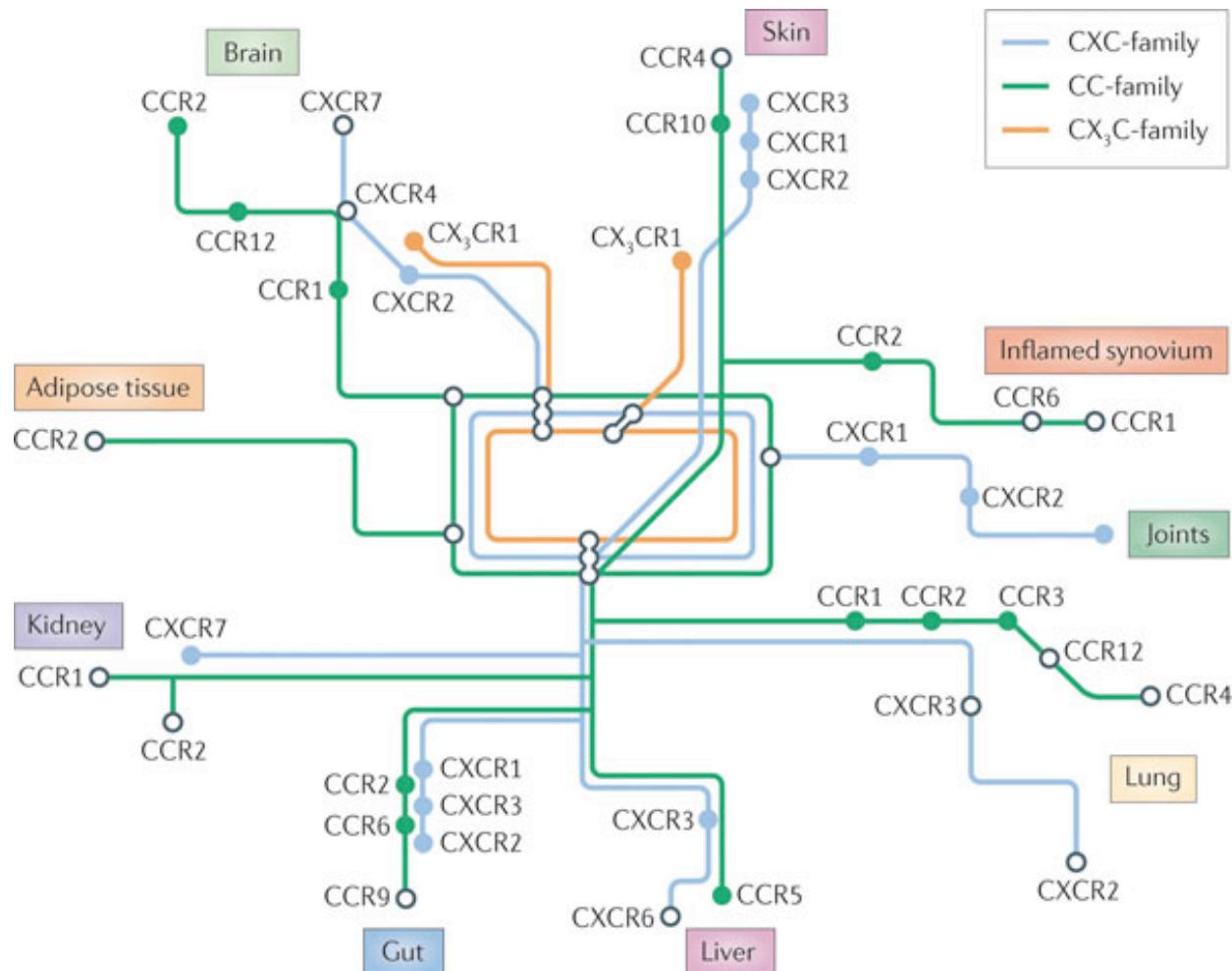
- Cytokine network



How to represent?



Chemokine system map example



Thomas J. Schall & Amanda E. I. Proudfoot
Nature Reviews Immunology 11, 355-363 (May 2011)

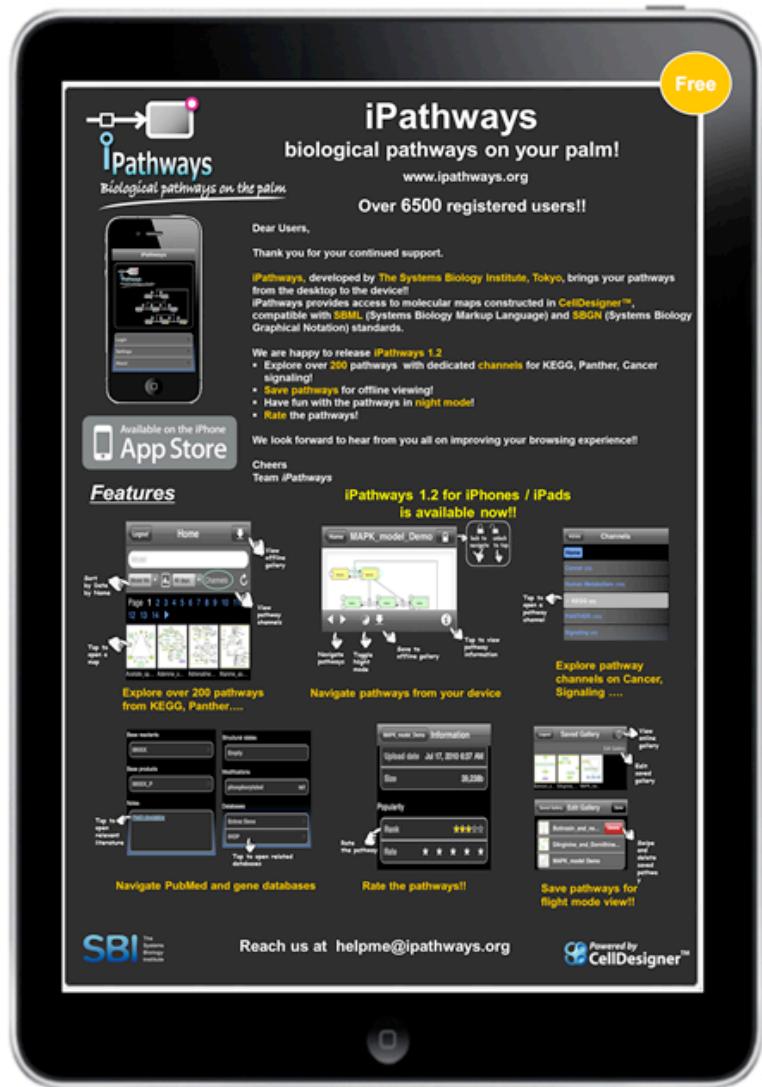
Nature Reviews | Immunology

Challenge 10. COMBINE!



helps the modelers life easier!

Please



Knowledge accessible from everywhere



Summary

- Describe the detail process to construct and curate a comprehensive map of Influenza viral life cycle and host responses.
- elucidate issues and challenges we face during the map-building process.
- Challenges continue
“How to build the map as knowledgebase?”

Acknowledgements



Influenza Map Building Project

- Manami Katoh
- Hiromi Matsumae
- Tadasuke Iijumi
- Amie Eisfeld and other curators @ Univ of Wisconsin
- And all the members at
ERATO Kawaoka Infection-Induced Host Response Project

CellDesigner Development Team

- Akira Funahashi (Univ of Keio)
- Samik Ghosh (SBI)
- Norihiko Kikuchi (MKI)

PAYAO Development Team

- Samik Ghosh (SBI)
- Asai (OIST)
- Norihiko Kikuchi (MKI)
- Hiroaki Kitano (SBI,OIST)

Yukiko Matsuoka myukiko@sbi.jp

