Universität Rostock Traditio et Innovatio

# Exploring the spatio-temporal dynamics of lipid raft dependent WNT/beta-catenin signaling *in vitro* and *in silico*

*Fiete Haack*

*10.10.2015*
*Sino-German Workshop, Beijing*

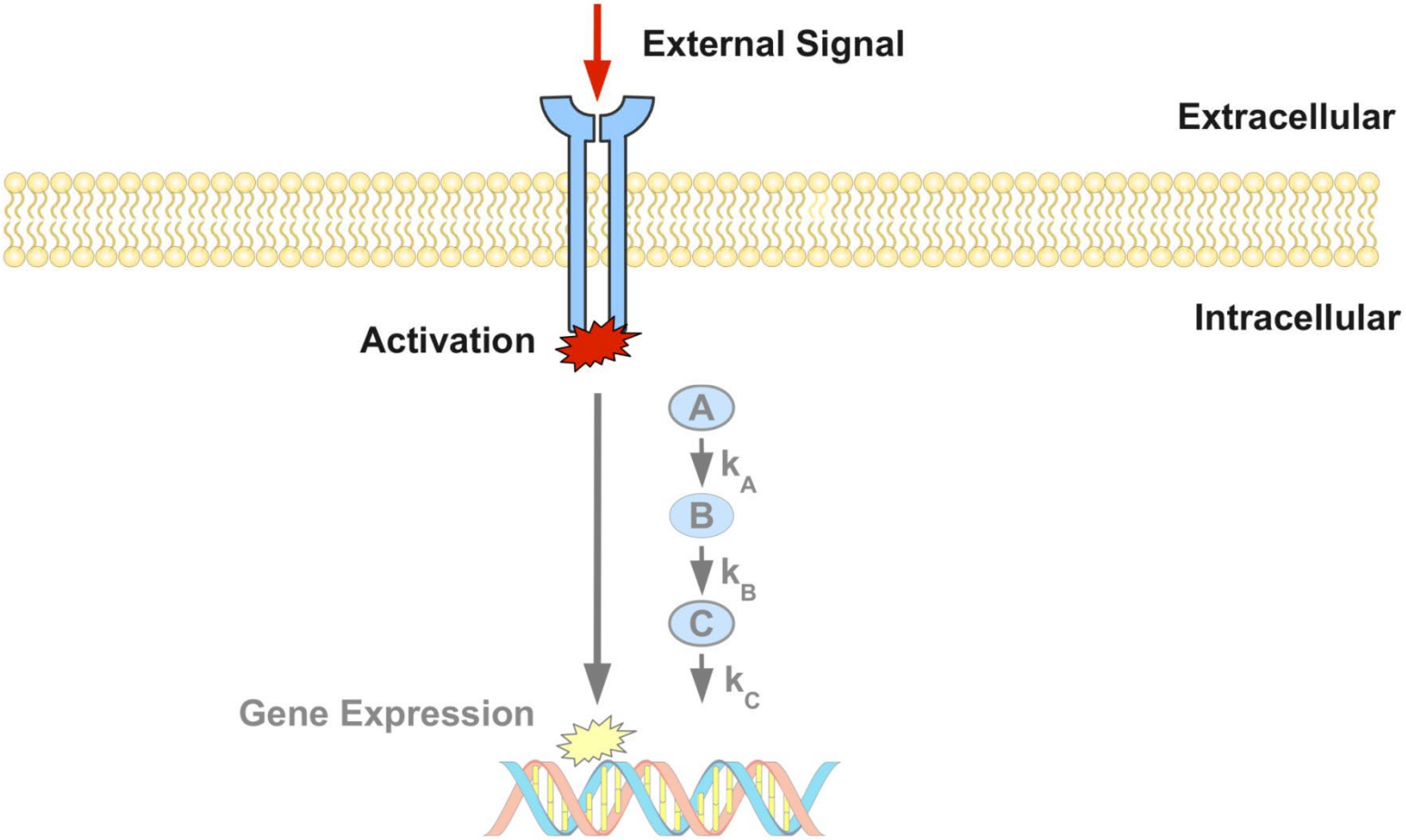
Universität Rostock Traditio et Innovatio

# Exploring the spatio-temporal dynamics of lipid raft dependent WNT/beta-catenin signaling *in vitro* and *in silico*

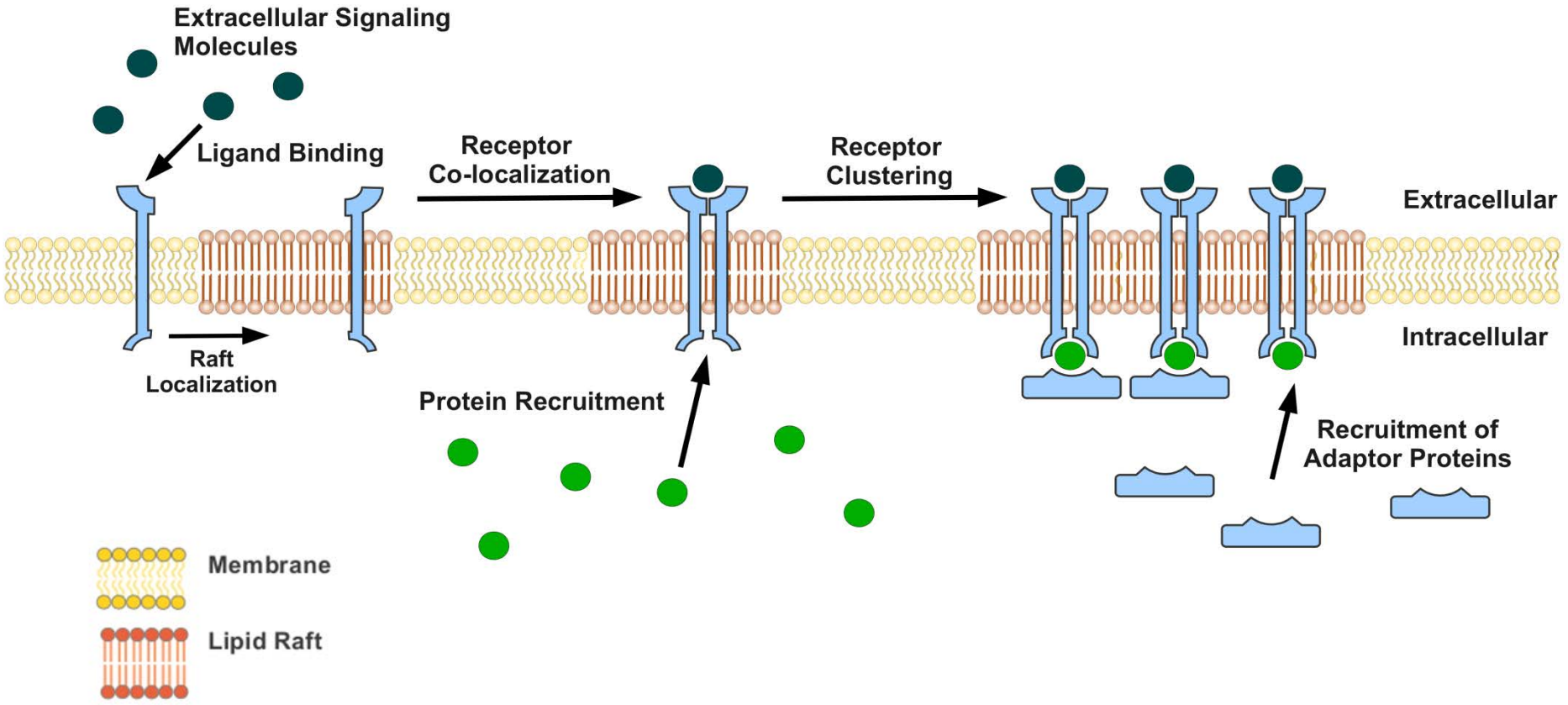
*Fiete Haack*

*10.10.2015*
*Sino-German Workshop, Beijing*

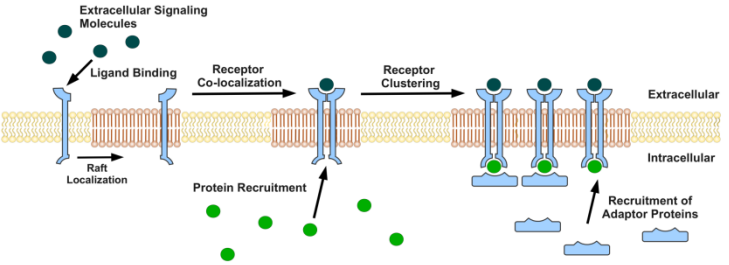
# „Simplified“ view on signal transduction



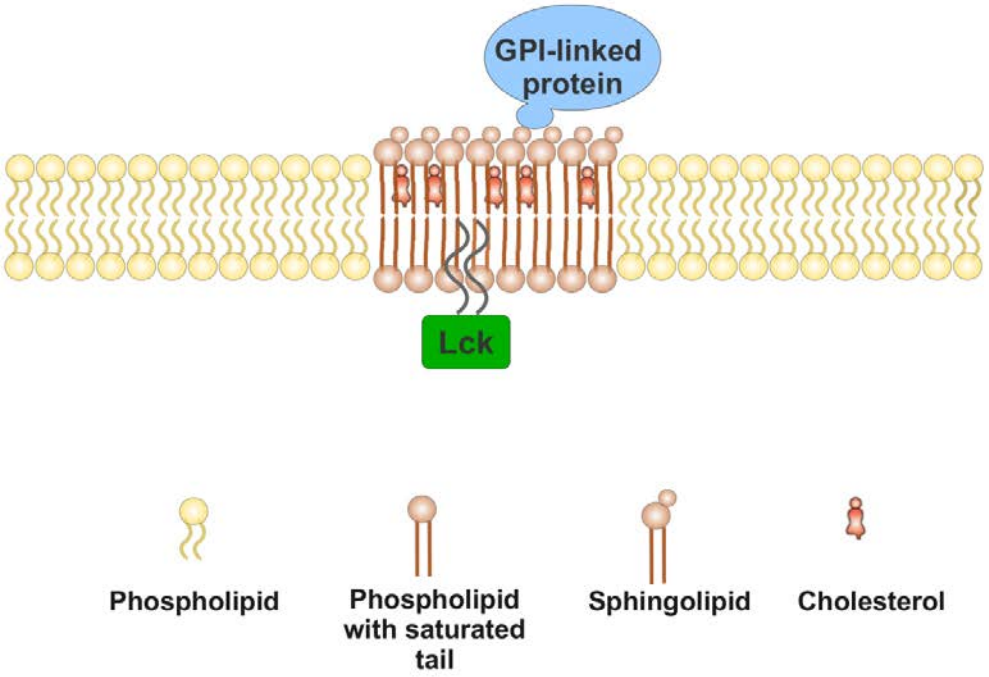
# A more „realistic“ view on signal transduction



# Structure and functions of lipid rafts

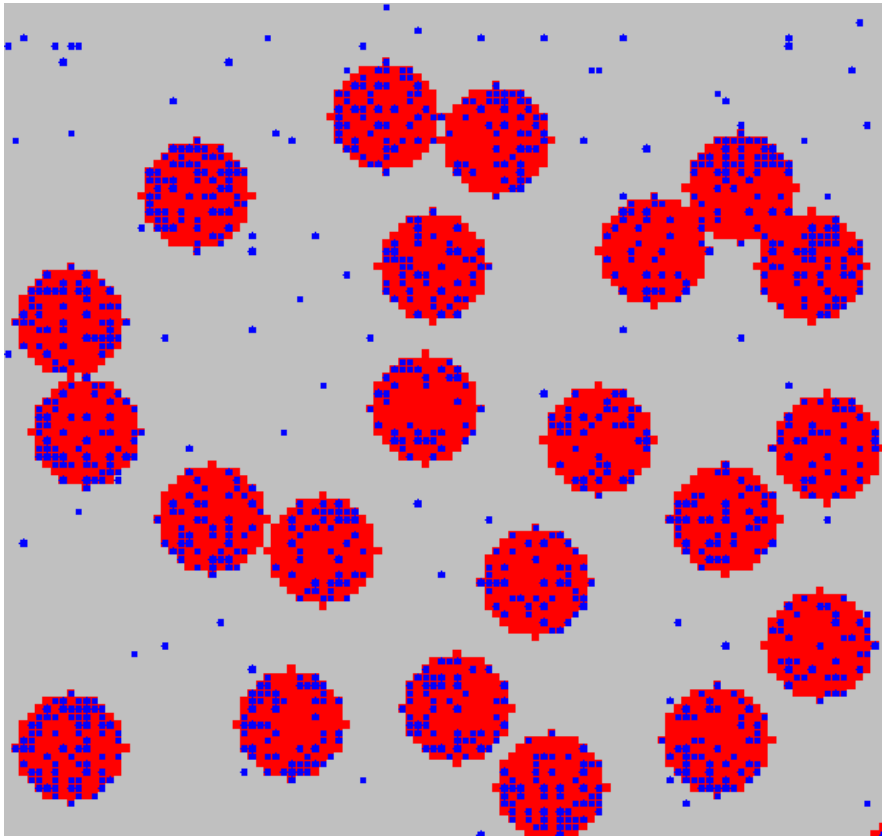



Local assemblies of highly concentrated sphingolipids and cholesterol in the cell membrane:




- Slow down protein diffusion due to tight packing (higher viscosity)
- Specifically include and exclude proteins
- Increase local protein concentration

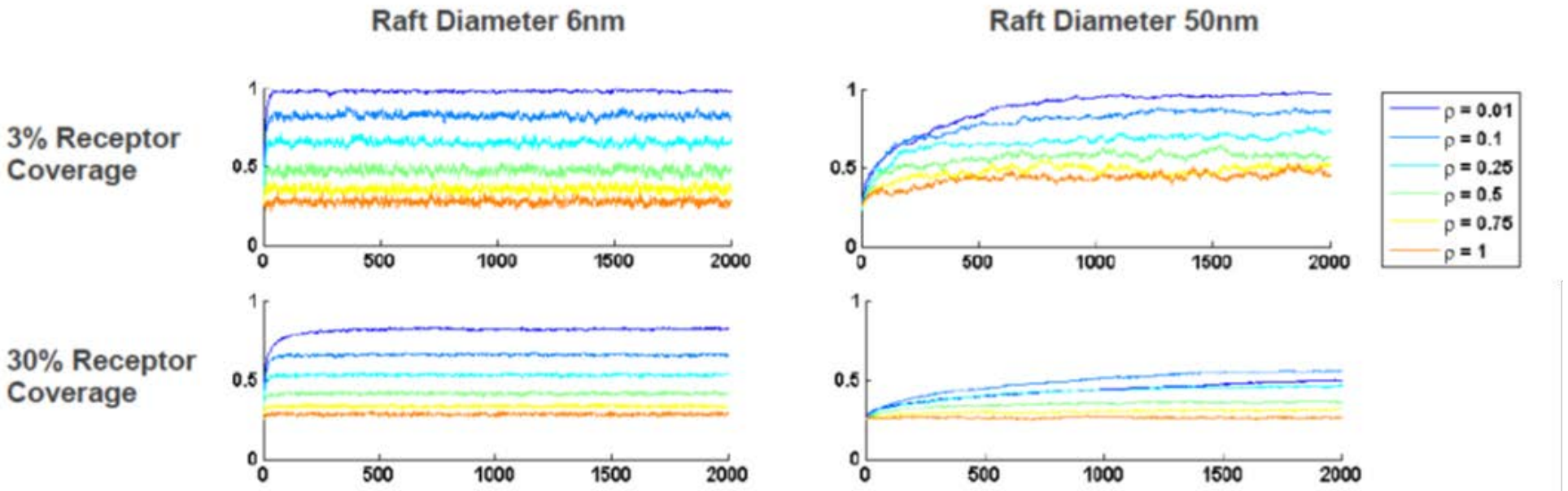
# Grid-based model of spatial lipid rafts / receptor dynamics



Cellular Automata implementation:

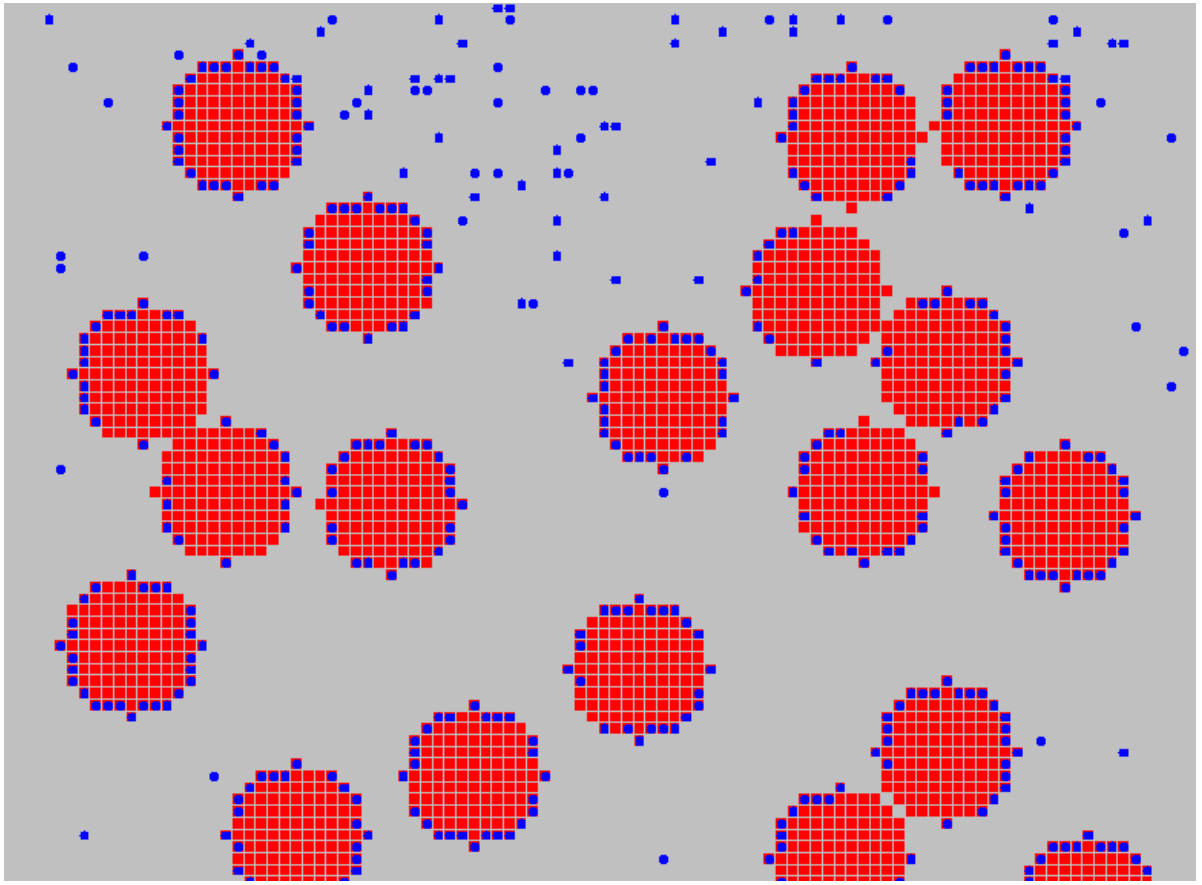
- Implemented in JAMES II
- Diffusion handling adapted from Lattice Gas Cellular Automata (LGCA)
- Volume exclusion for membrane-integral particles
- Coordinated group behaviour (movement) for rafts
- Receptor movement coupled to movement of rafts (sweeping effect)

# Impact of raft characeristics on receptor/raft accumulation




Haack et al, IEEE/ACM Trans Comput Biol Bioinform 2013

# „Shell“ effect of raft/receptor interaction

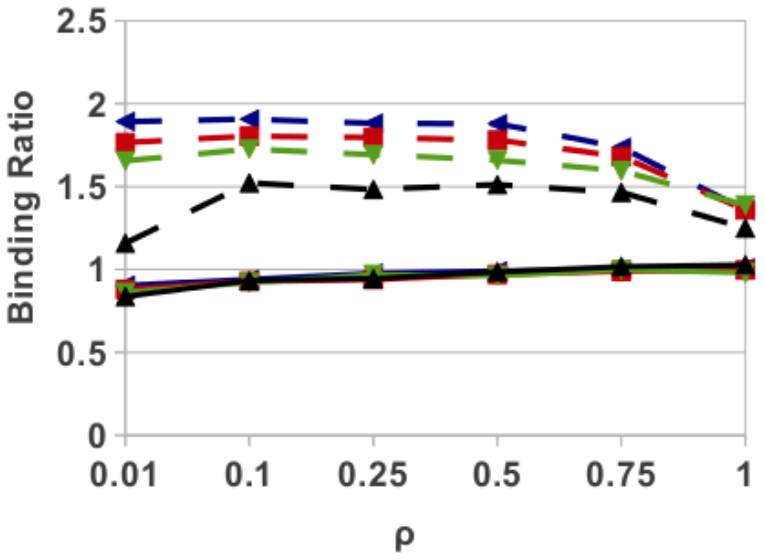


$\rho < 0.1$

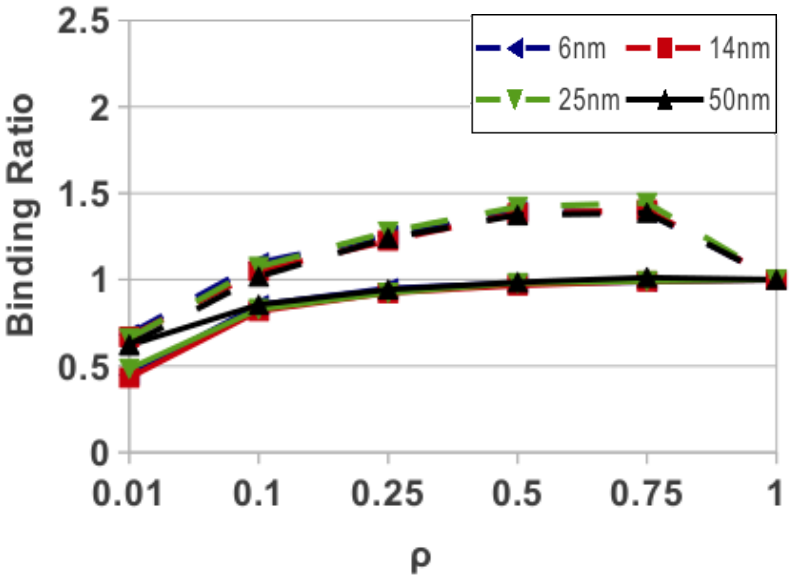
# Raft dependent binding kinetics

25% Raft Coverage

Mobile Rafts




Immobile Rafts

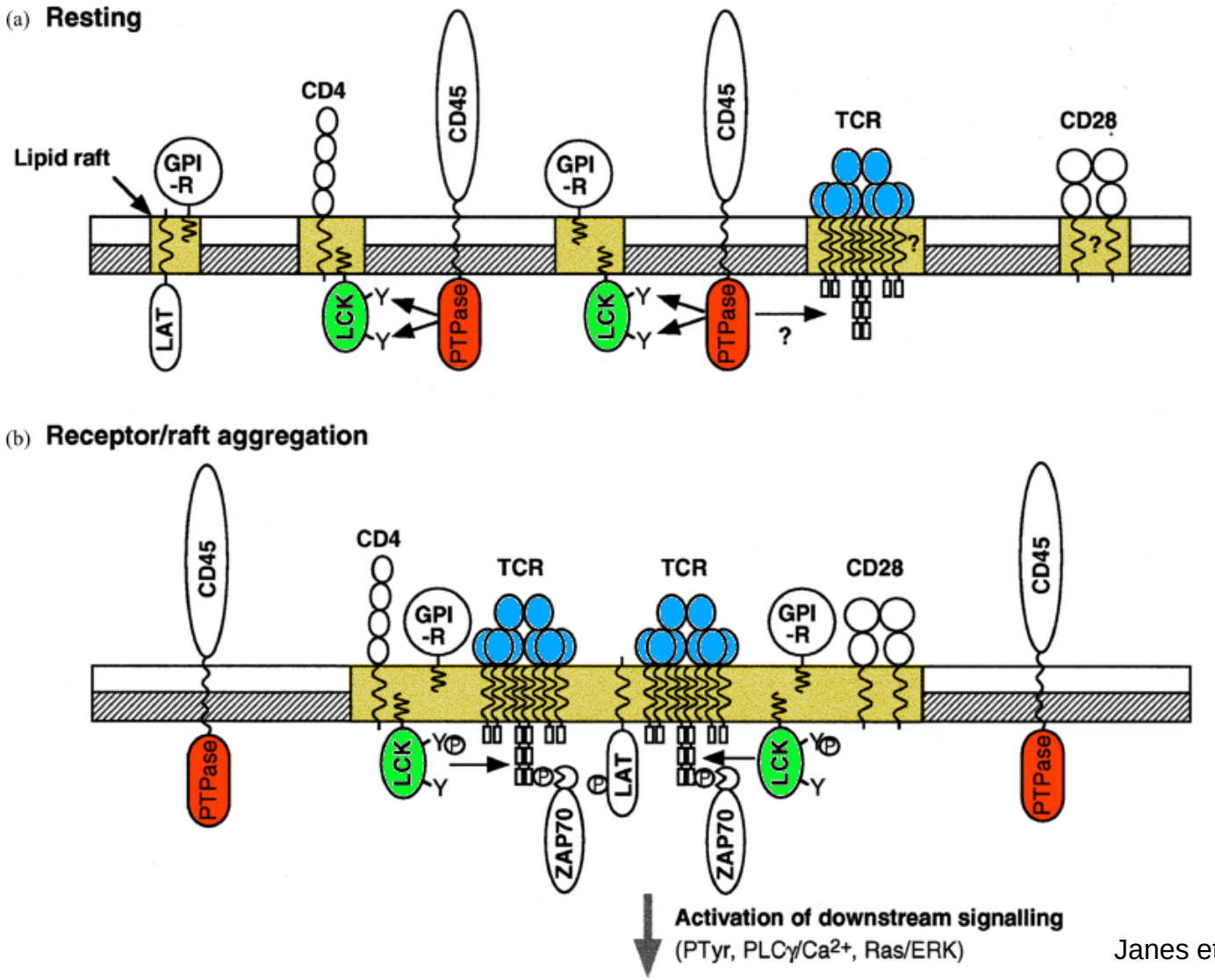



Haack et al, IEEE/ACM Trans Comput Biol Bioinform 2013

# Impact of lipid rafts on signal transduction

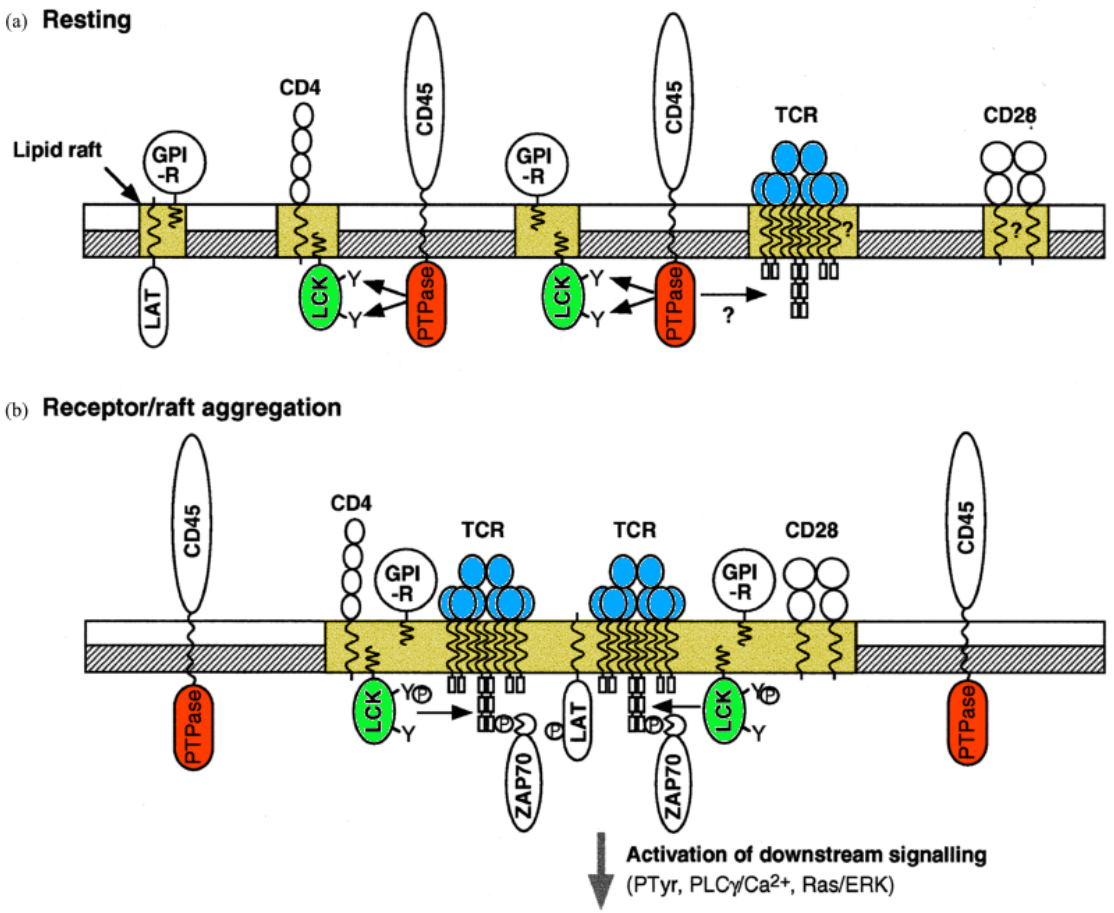
- Receptor diffusion -> clustering/Aggregation
- Protein/Receptor binding kinetics
- Signal amplification/Inhibition
- Ambiguous/non-linear impact of lipid raft characteristics

# Lipid Rafts in T-Cell Signaling




Janes et al, Sem Immunol. 2000

# Lipid Rafts in T-Cell Signaling




- Clustering and fusion of lipid rafts to build immunological synapse
- Increased Recruitment of kinases
- Segregation of phosphorylated substrates (LCK) from phosphatases (PTPase)

Janes et al, Sem Immunol. 2000

# Age-associated alterations in T-Cells

- Lipid raft assembly on stimulation is largely impaired in T-Cells from elderly humans and aged mice

- Increase of cholesterol concentration in membrane
  - Altered mobility & fluidity of lipid rafts
    - → Reduced merging & clustering

- Change of lipid raft composition
    - → Hampered recruitment of kinases and coupling factor
    - → No exclusion of phosphatases

Fulop et al, Drugs Aging 2005
*Lillemeier, Nat. Immunol. 2010*

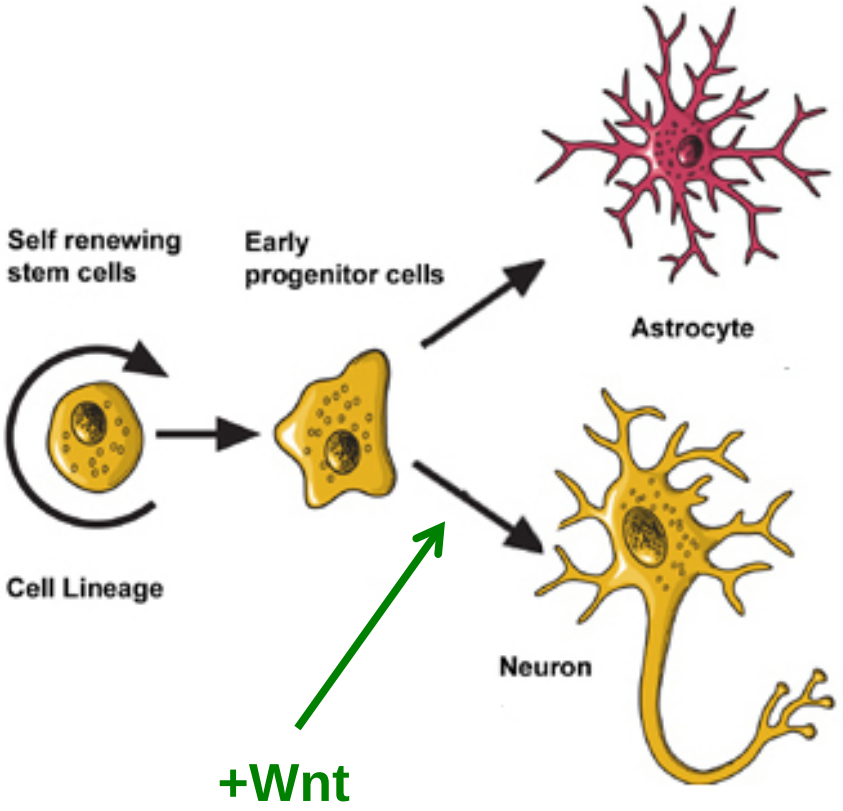
# Diseases for which rafts and raft proteins are targets

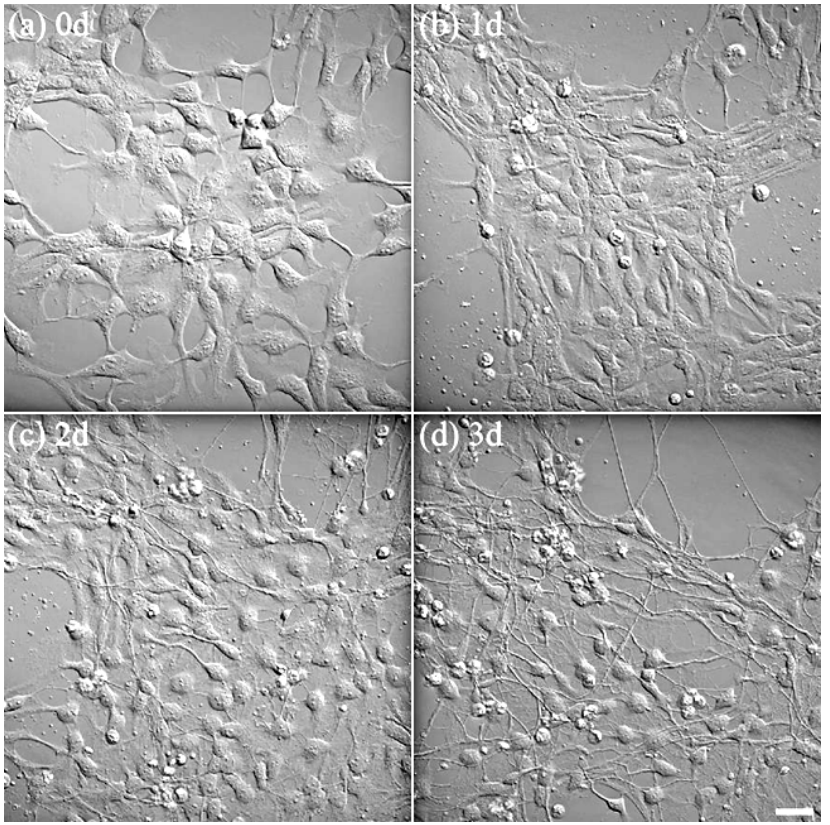
**Table 1**
Diseases for which rafts and raft proteins are targets

| |
|---|
| Alzheimer disease |
| Parkinson disease |
| Muscular dystrophy |
| Polyneuropathies, demyelinating diseases |
| Autoimmune disease, chronic inflammation, vaccine response |
| B cell response |
| T cell response |
| Asthma and allergic response |
| Neoplasia |
| Atherosclerosis |
| Hypertension, hemodynamic regulation |
| Diabetes |
| Hyperparathyroidism |
| Osteoarthritis |
| Gastrointestinal ulceration |
| Paroxysmal nocturnal hemoglobinuria |
| Lysosomal storage disease |
| Niemann-Pick disease |
| Tay-Sachs disease, morbus Fabry, metachromatic leukodystrophy |
| Pilzaeus-Merzbacher disease |
| Postsqualene cholesterol biosynthesis disorders |
| Pore-forming toxins (gas gangrene) |
| Sepsis, septic shock |
| Bacterial infections |
| *Escherichia coli* |
| *Mycobacteria tuberculosis* and *bovis* |
| *Campylobacter jejuni* |
| *Vibrio cholerae* |
| *Clostridium difficile* (pseudomembranous colitis) |
| *Clostridium tetani* |
| *Salmonella, Shigella* |
| Viral infections |
| Influenza virus |
| HIV-1 |
| Measles virus |
| Respiratory syncytial cell virus |
| Filoviridae (Ebolavirus, Marburgvirus) |
| Papillomaviridae and polyomaviridae |
| Epstein-Barr virus |
| Echovirus 1 |
| Other pathogens |
| *Plasmodium* (malaria) |
| *Trypanosoma* (sleeping sickness) |
| *Leishmania* |
| Prions (Creutzfeldt-Jakob disease, Kuru, Gerstmann-Sträussler-Scheinker syndrome) |
| *Toxoplasma gondii* |

Simons et al, Nat. rev. 2002

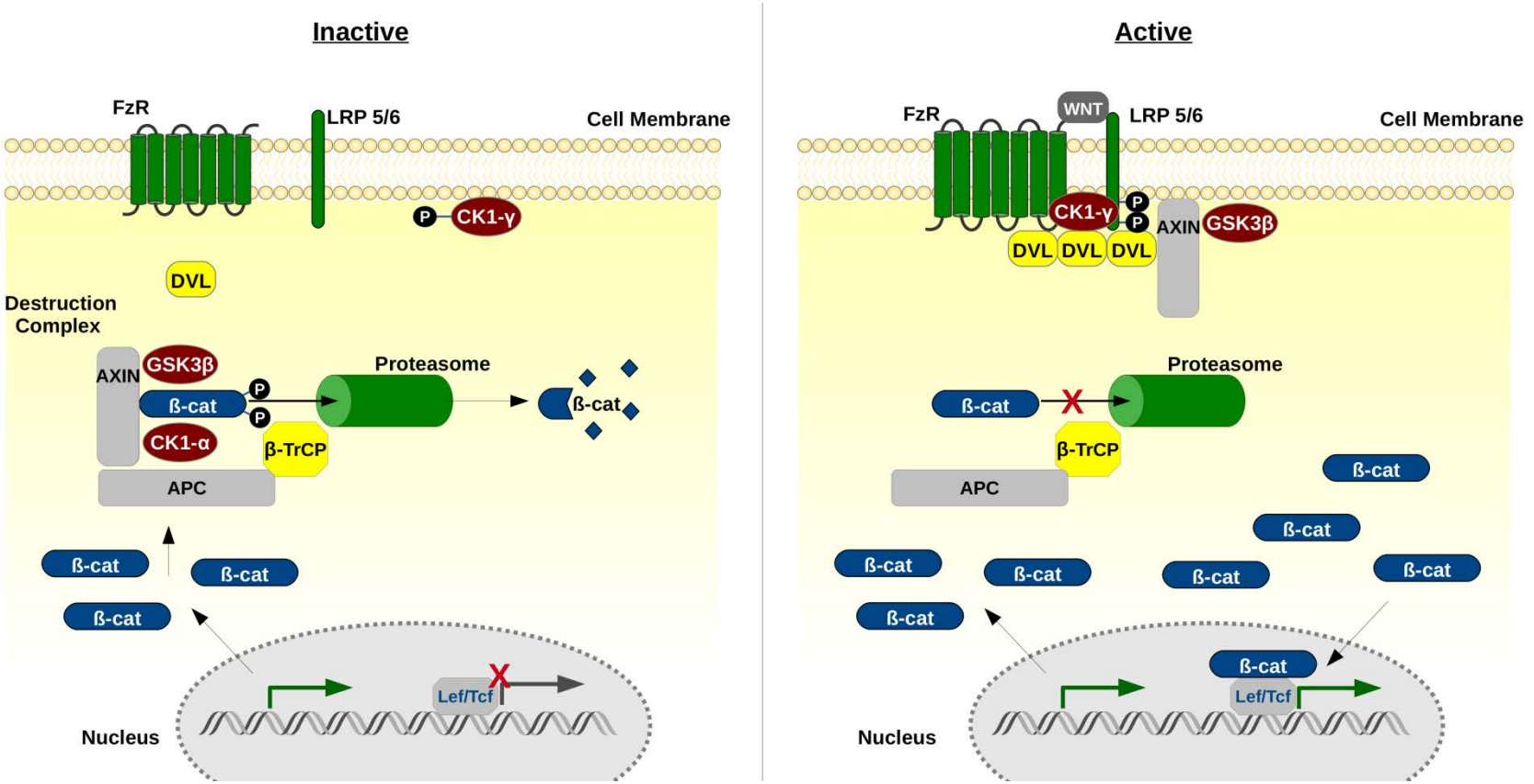
# Impact of lipid rafts on canonical Wnt signaling in neural progenitor cells



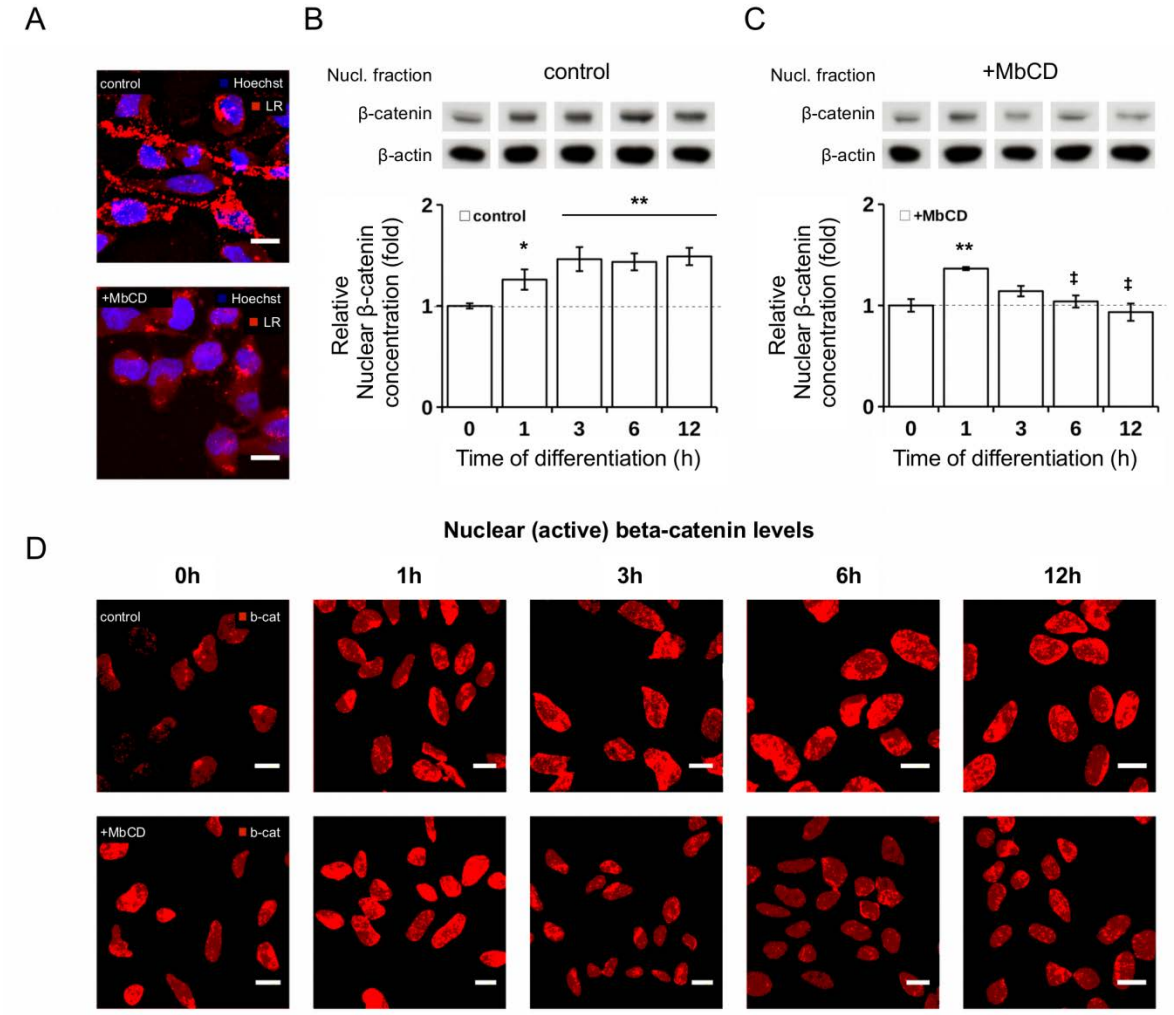




Lemcke et al Cell Sign 2013

# Canonical Wnt signaling

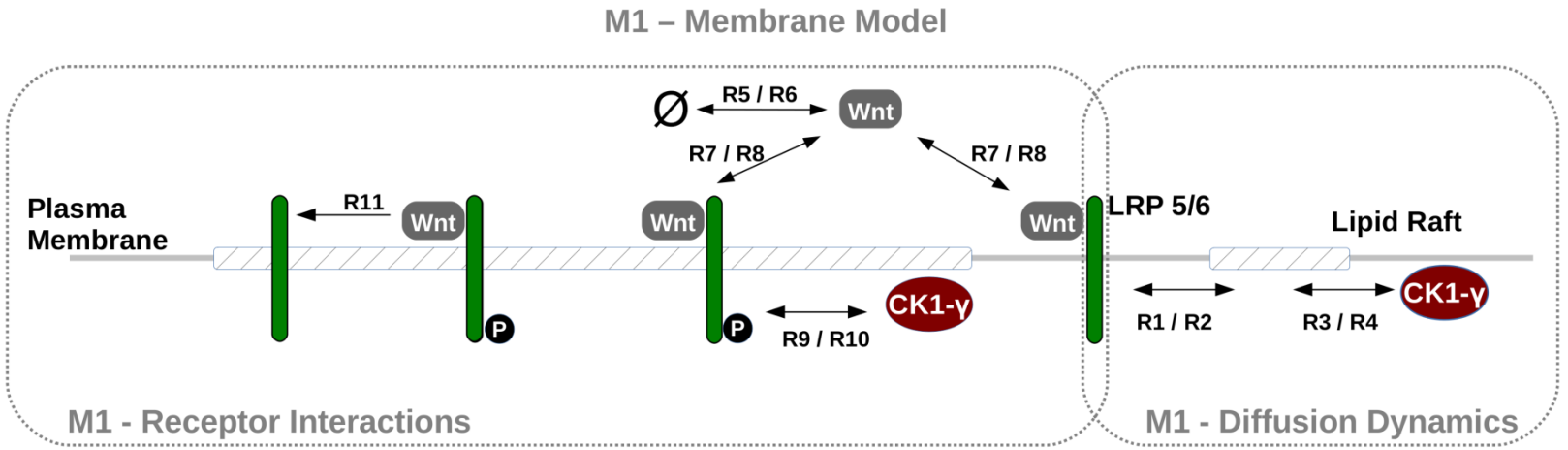


# Involvement of Lipid Rafts on canonical Wnt signaling?




Haack et al,
PLOS Comp. Biol. 2015

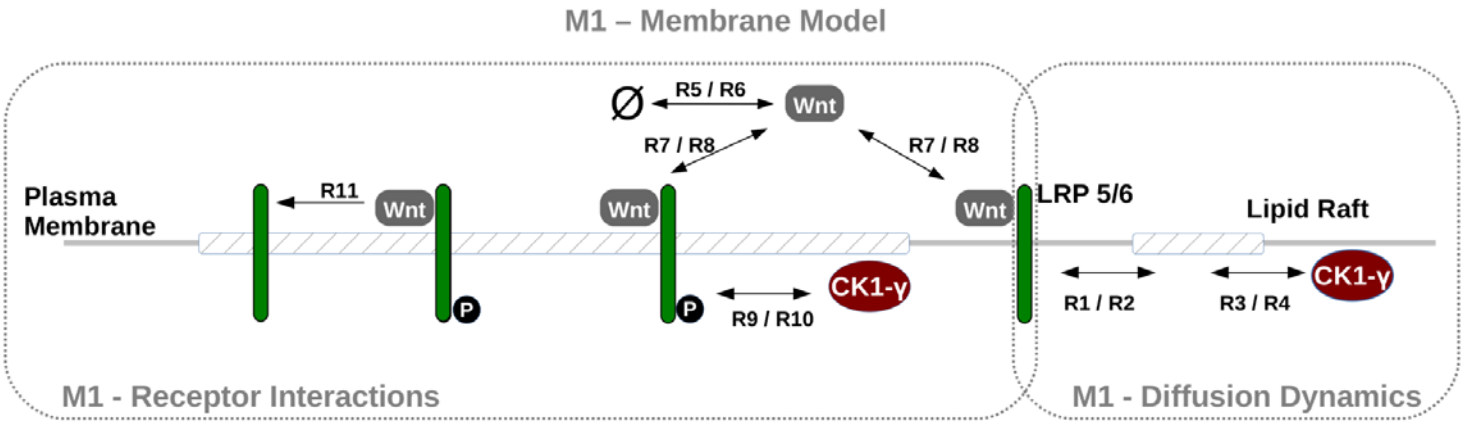
# Developing a hierarchical, rule-based model of raft-dependent Wnt signaling




ML-Rules specification of LRP6/Raft shuttling (simplified)

```
// LRP6 diffusion into Lipid Rafts
Cell[Membrane[LR[] + Lrp6]] -> Cell[Membrane[LR[Lrp6]]]

// LRP6 diffusion out of lipid rafts
Cell[Membrane[LR[Lrp6]]] -> Cell[Membrane[LR[] + Lrp6]]
```

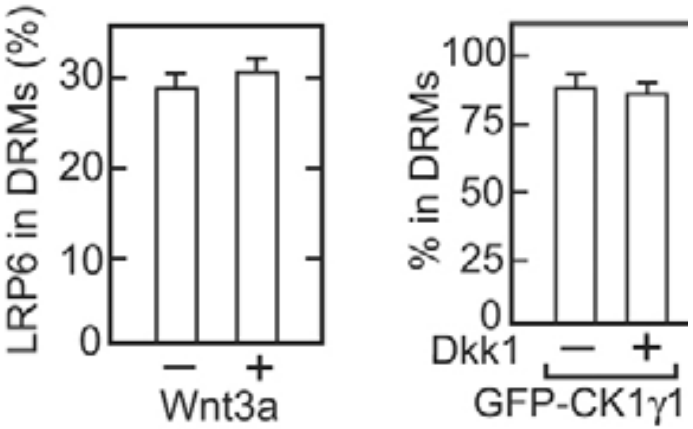
# Developing a hierarchical, rule-based model of raft-dependent Wnt signaling




ML-Rules specification of LRP6/Raft shuttling

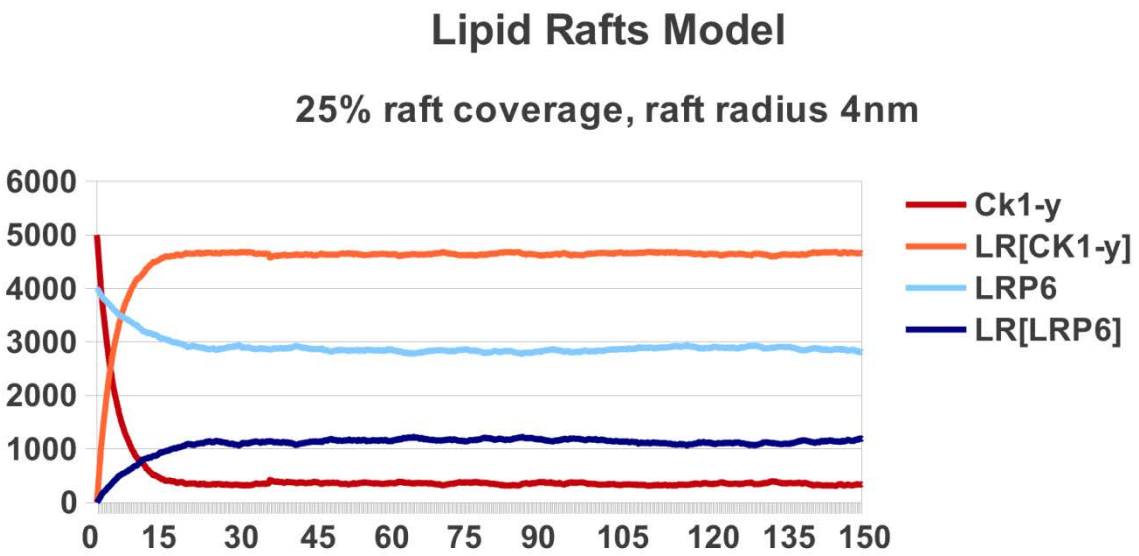
```
// (R1) LRP6 diffusion into Lipid Rafts
 Membrane(A)[LR(radius, p)[s?]:l + Lrp6(d, ra, phos, bind):r ] ->
 Membrane(A)[LR(radius, p)[Lrp6(d*p, ra, phos, bind) ]] @ k_1*#l*#r*ra

// (R2) LRP6 diffusion out of lipid rafts
Membrane(A)[LR(radius, p)[Lrp6(d, ra, phos, bind) + s?]:r ] ->
Membrane(A)[LR(radius, p)[s?] + Lrp6(d/p, ra, phos, bind) ] @ k_2*#l*#r
```

# Fitting raft/receptor aggregation to experimental data



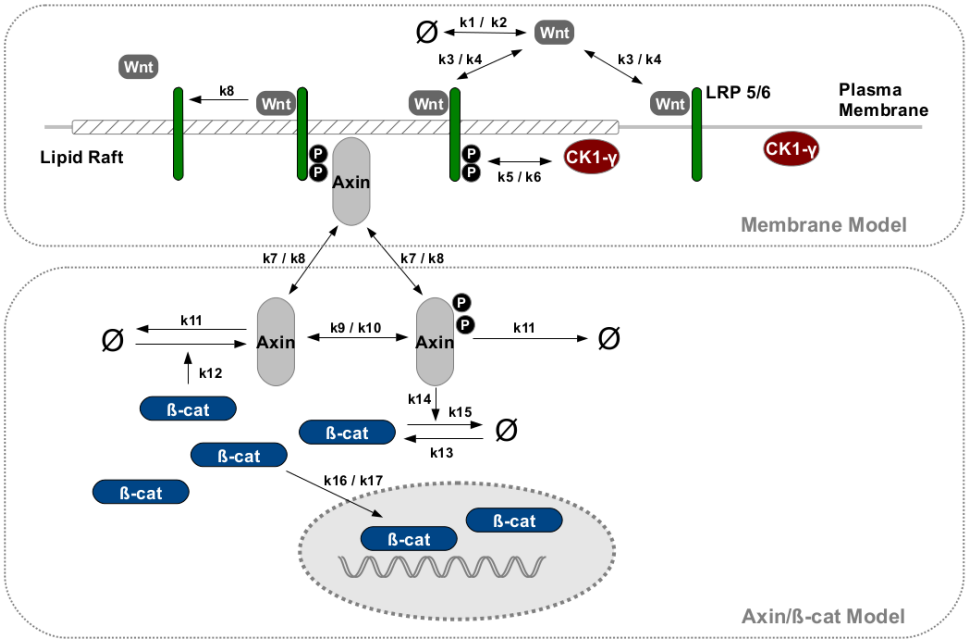


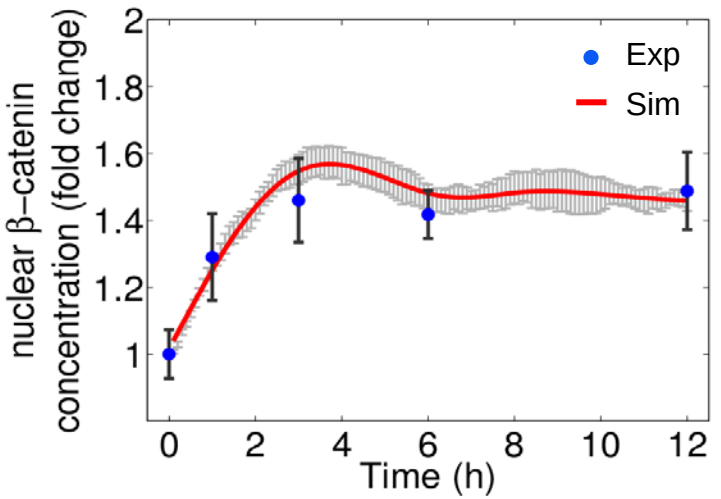





Sakane et al J Cell Sci 2010

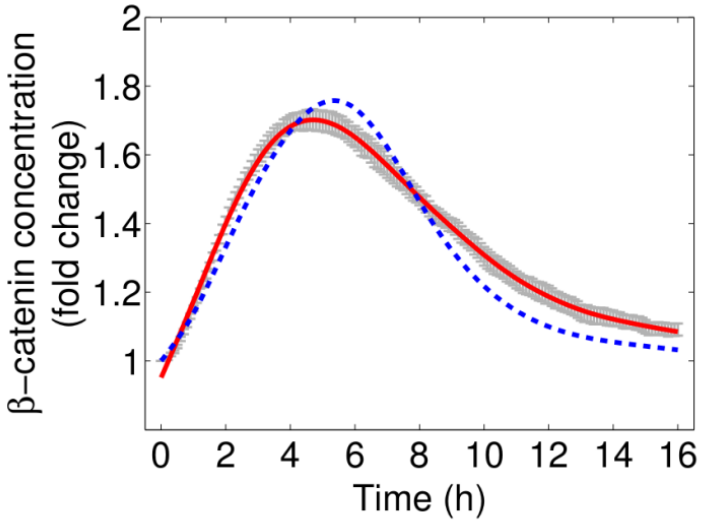
# Wnt Model (intracellular + membrane)



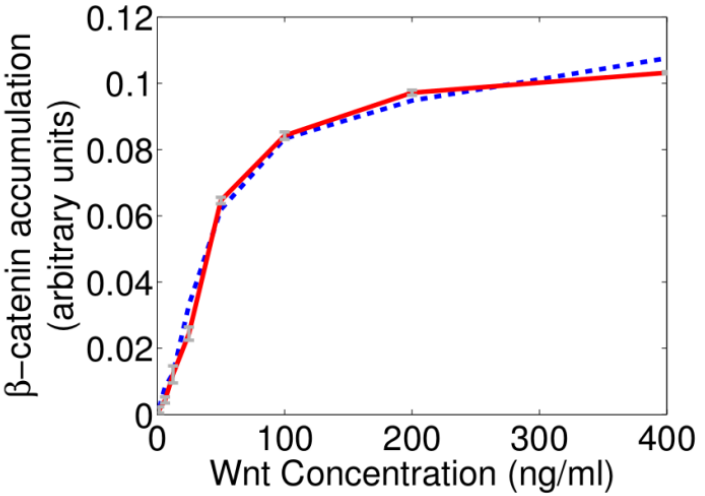




Haack et al, PLOS Comp. Biol. 2015

# Validation of Wnt Model (in silico)

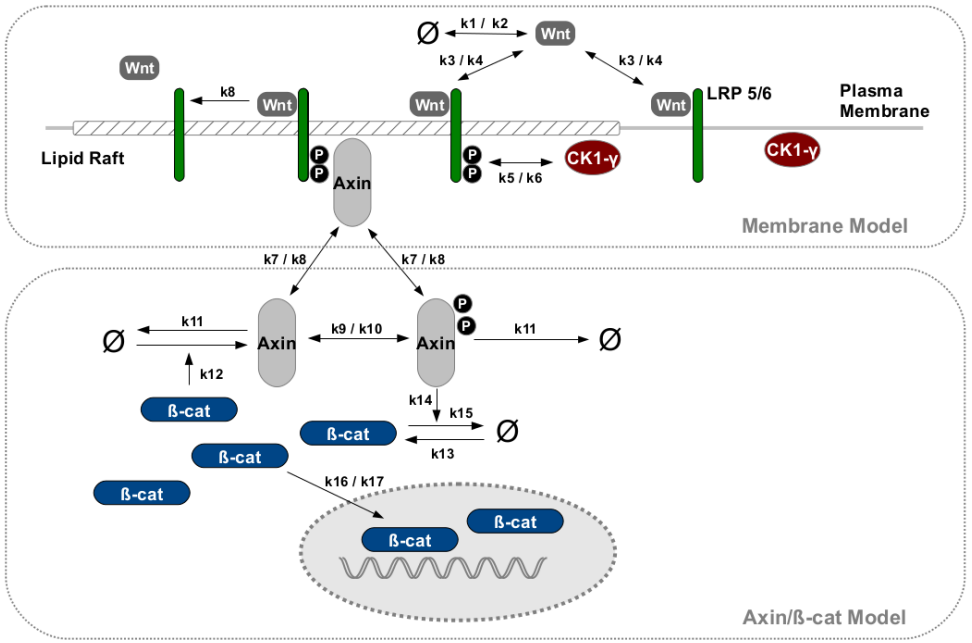


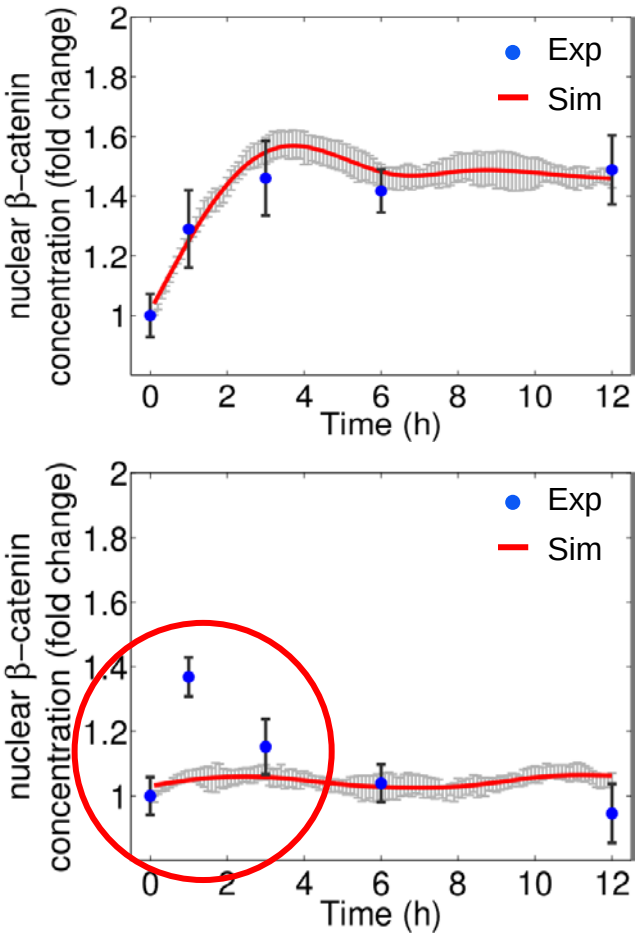

Lee et al, PLOS Biol 2003




Hannoush, PLOS One 2008

# Wnt Model (intracellular + membrane)

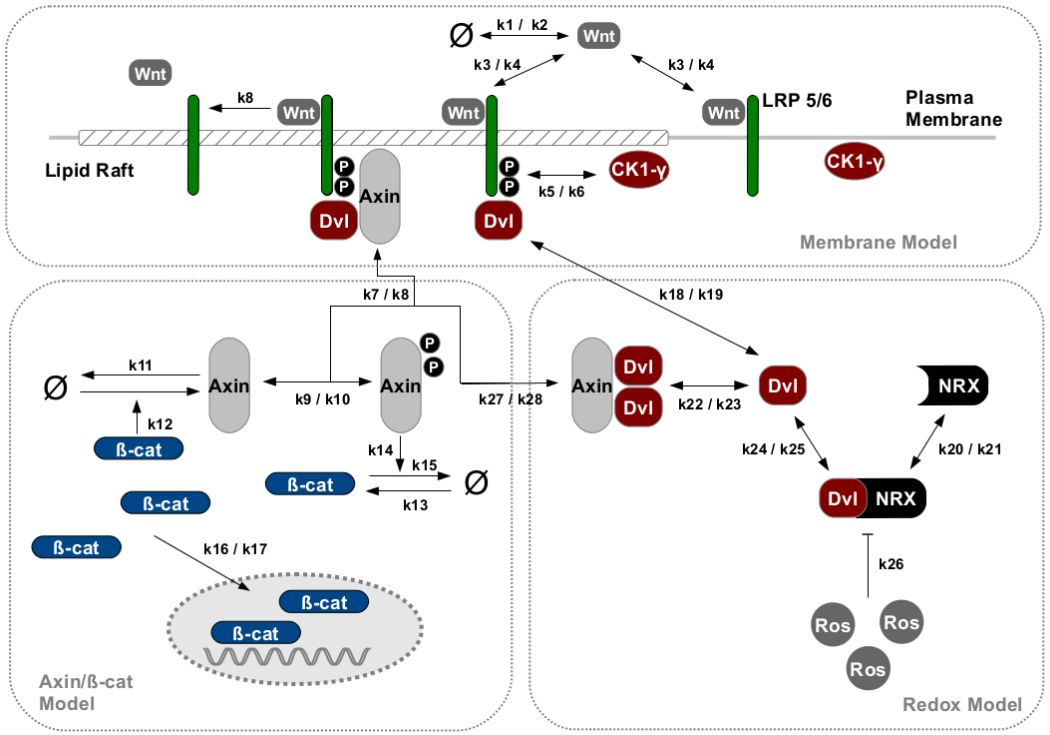


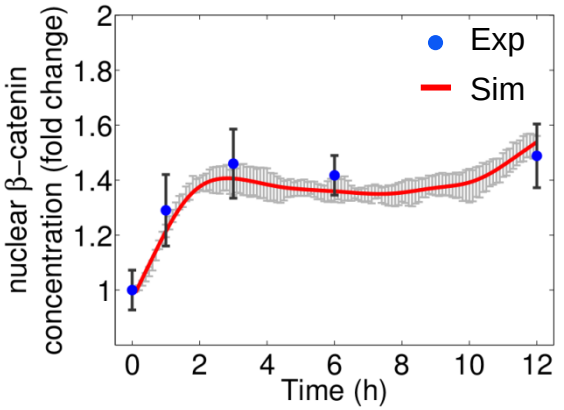



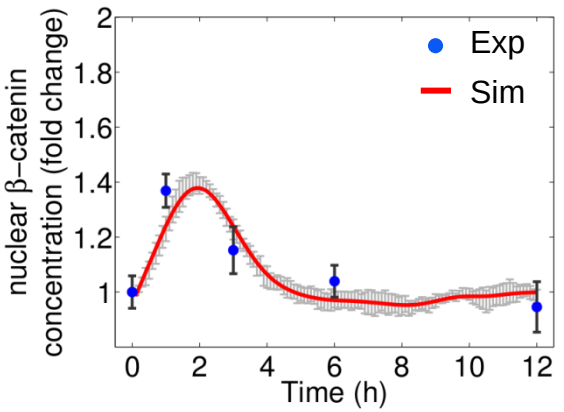

Haack et al, PLOS Comp. Biol. 2015

# Wnt Signal Transduction

## ROS/Wnt Model (extended intracellular + membrane)

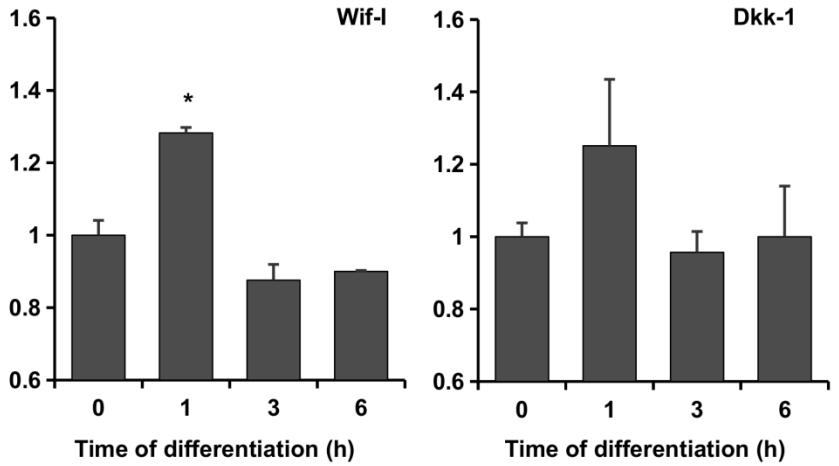


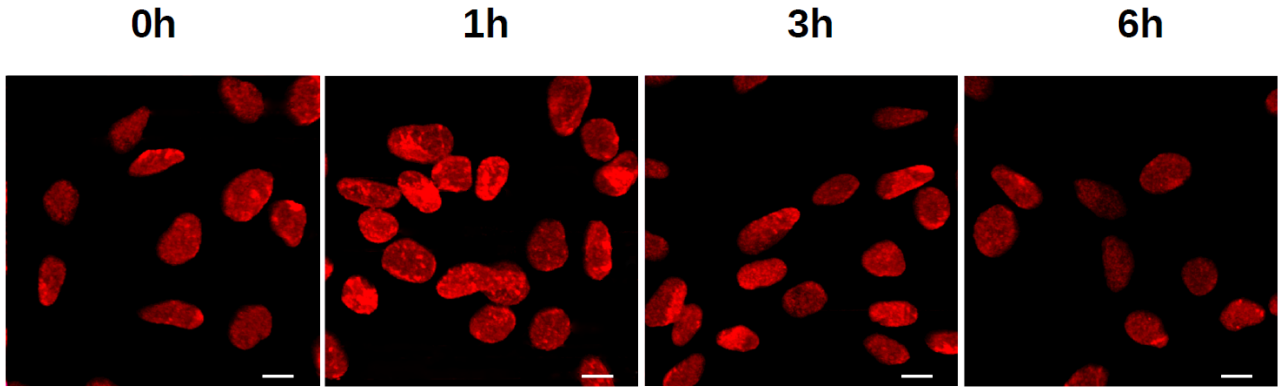




Haack et al, PLOS Comp. Biol. 2015

# Validation of ROS/Wnt model (in vitro)

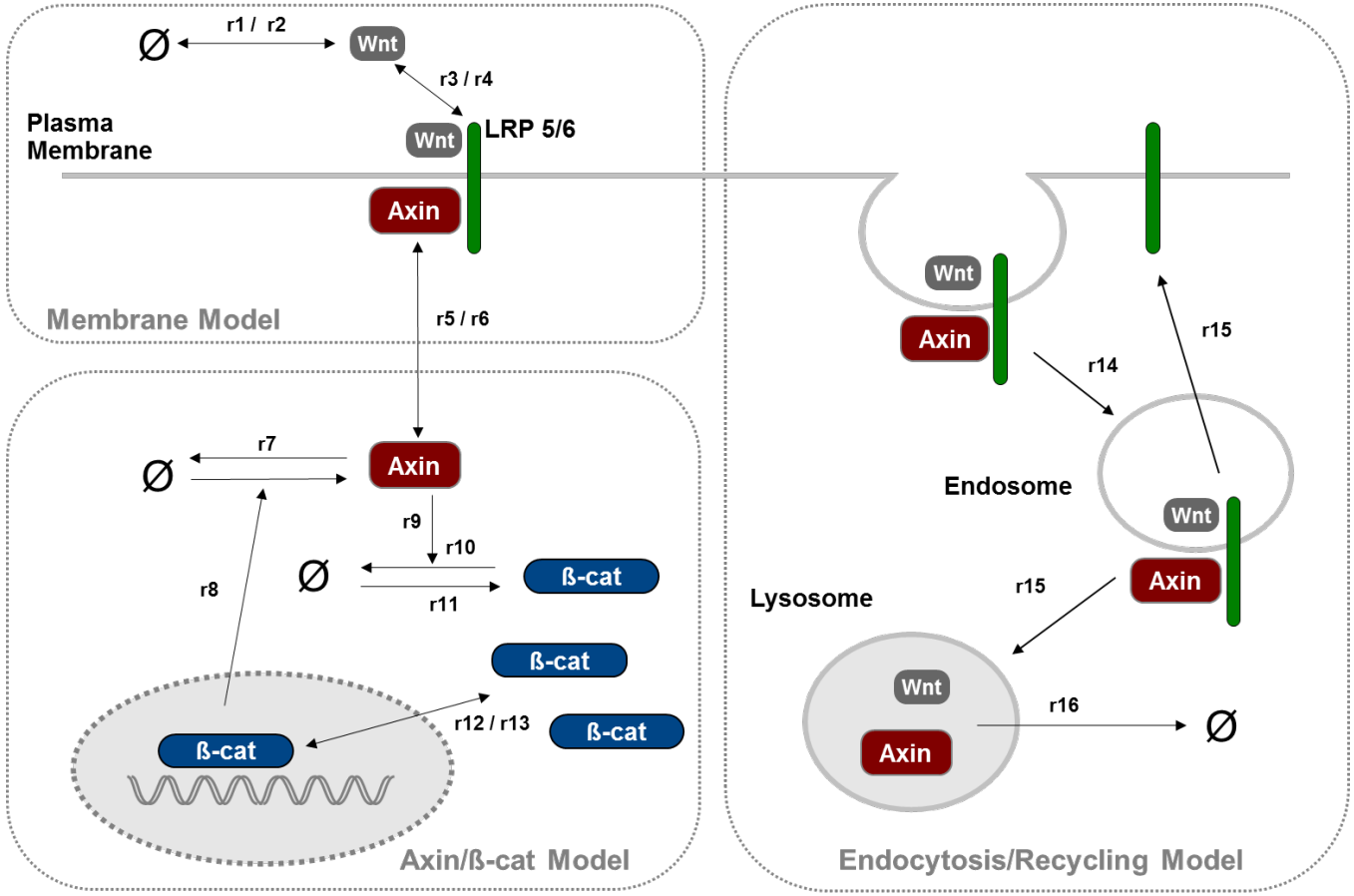



**+ Dkk-1 50ng/ml**




**Nucl. B-Cat**

# Future Directions

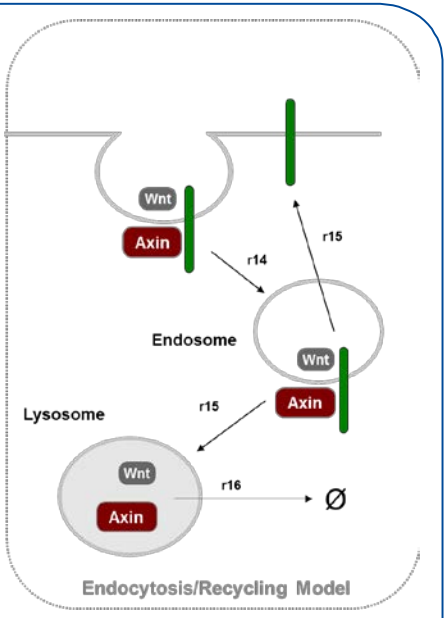


# Future Directions

- Endocytosis and recycling of receptor complex
  - Simulation of longer time scales

- Lipid rafts dynamics
  - Growth, fusion, fission

- Smale scale simulation?! More experiments?




```
Cell[Membrane[LR[LRP6(diff, ra, 'P', 'B', bind):rec + AXIN(phos, bind)]]] ->
Cell[Membrane[LR[s_l?] + s_m?] + Endosome[LRP6(diff, ra, 'P', 'B', bind) +
AXIN(phos, bind)] + s_c?]  @ if bind == 'free' then 0 else kEndo*#rec;

Cell[Endosome[LRP6(diff, ra, 'P', 'B', bind):e + AXIN(phos, bind)] + Membrane]->
Cell[Membrane[LRP6(1, 0.15, 'uP', 'uB') + s_m?] + s_c?]
@ if bind == 'free' then 0 else kRecycling*#e;
```

Universität Rostock Traditio et Innovatio

# Thank you!

## Acknowledgements

MoSi Group, University of Rostock

Heiko Lemcke, RTC, University Medical Center Rostock

Tareck Rharass, Max-Delbrück-Centrum für Molekulare Medizin, Berlin Buch

Kevin Burrage, University of Oxford, UK, Queensland University, of Technology, Austalia