Engineering more precise and potent TAM-targeted therapies

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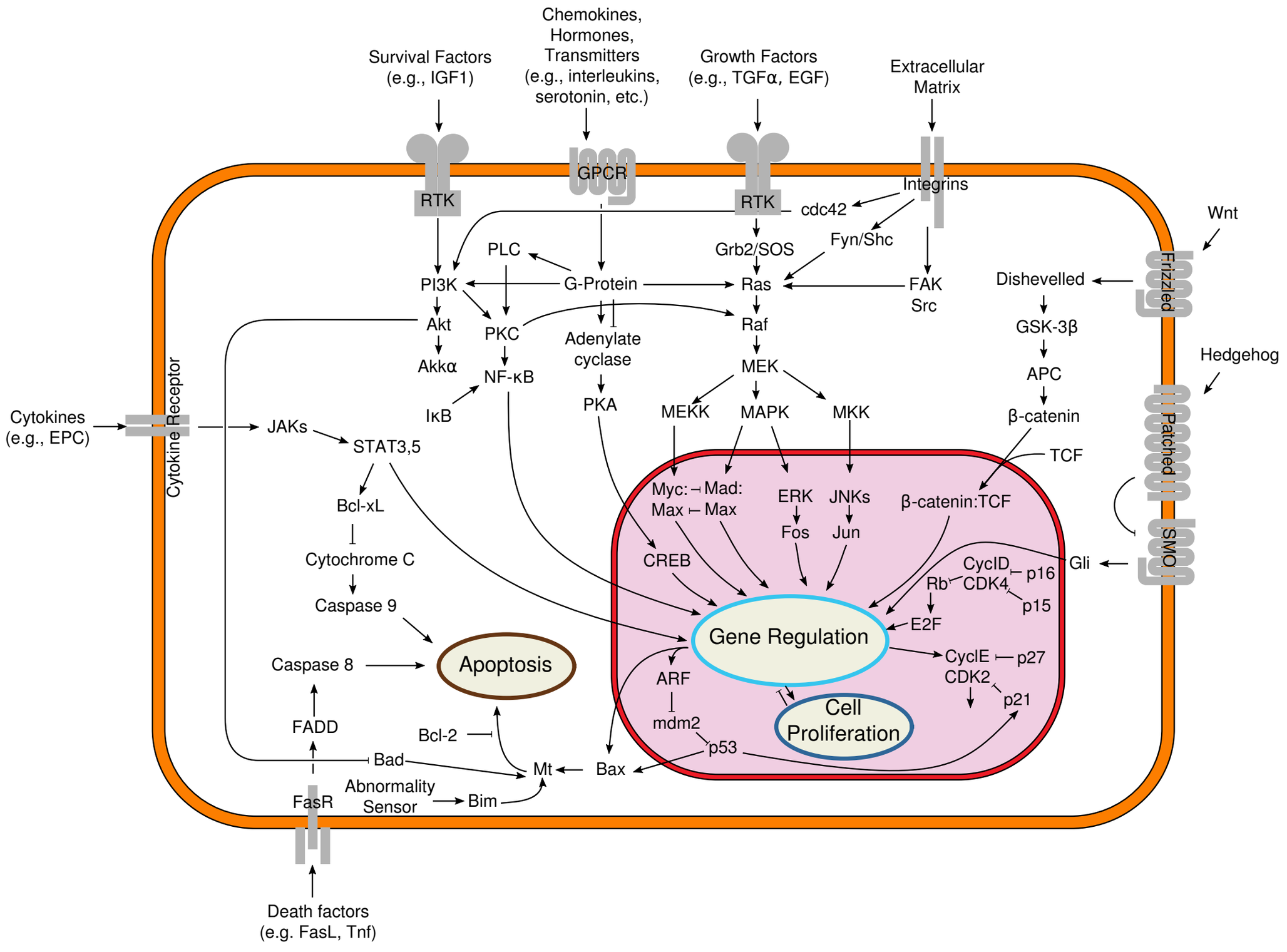
March 20, 2017

KOCH INSTITUTE
for Integrative Cancer Research at MIT

Massachusetts
Institute of
Technology

Cell signaling is complex, and challenging to apply toward a desired goal



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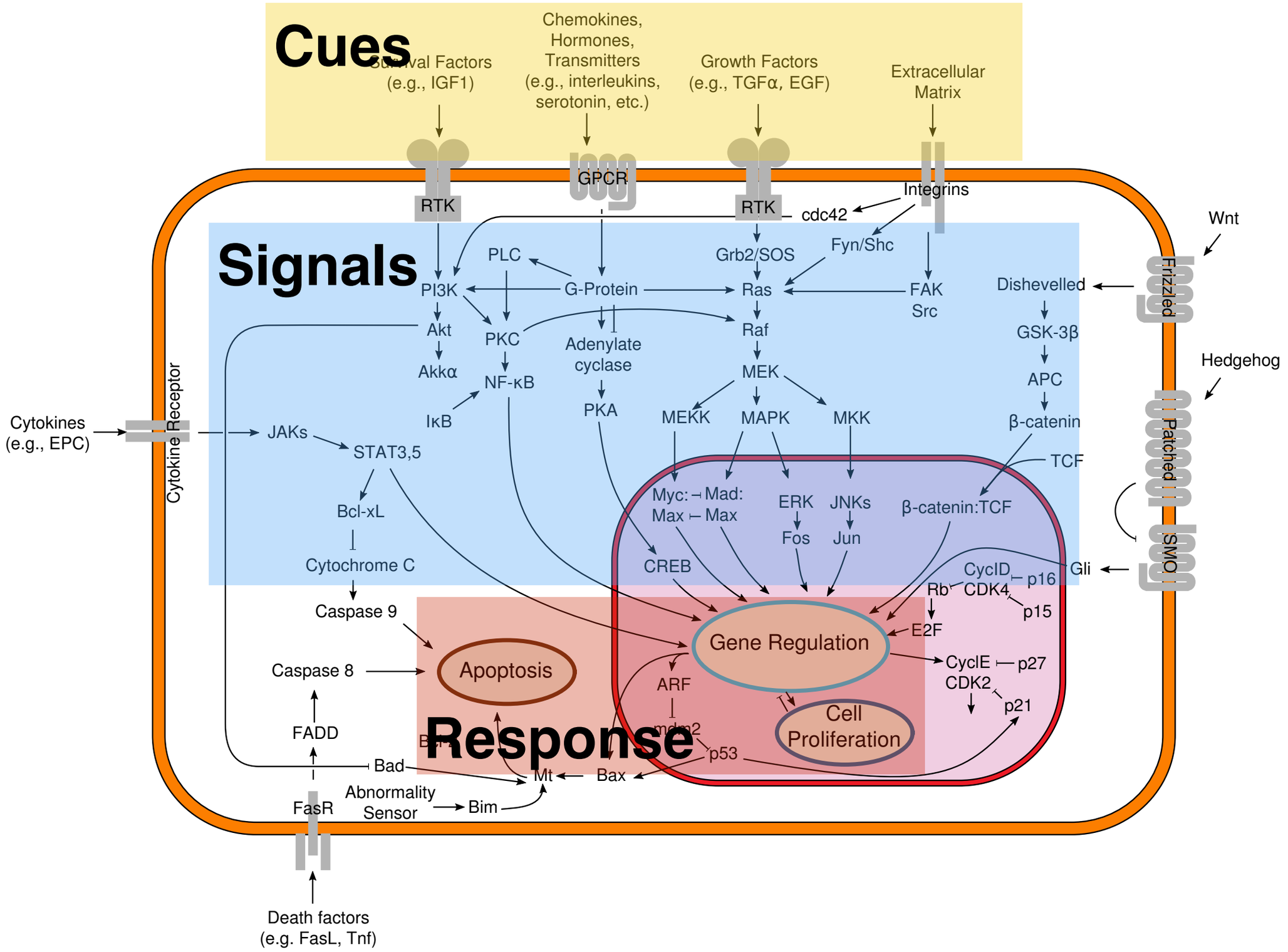


Receptors enable information transmission across the plasma membrane

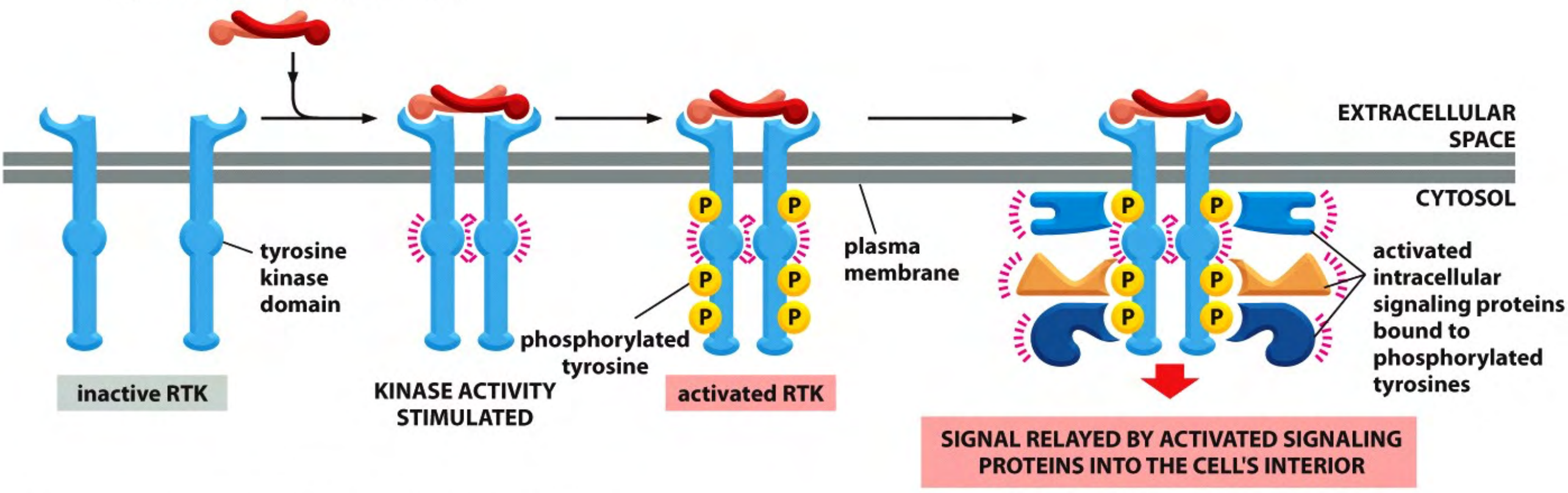
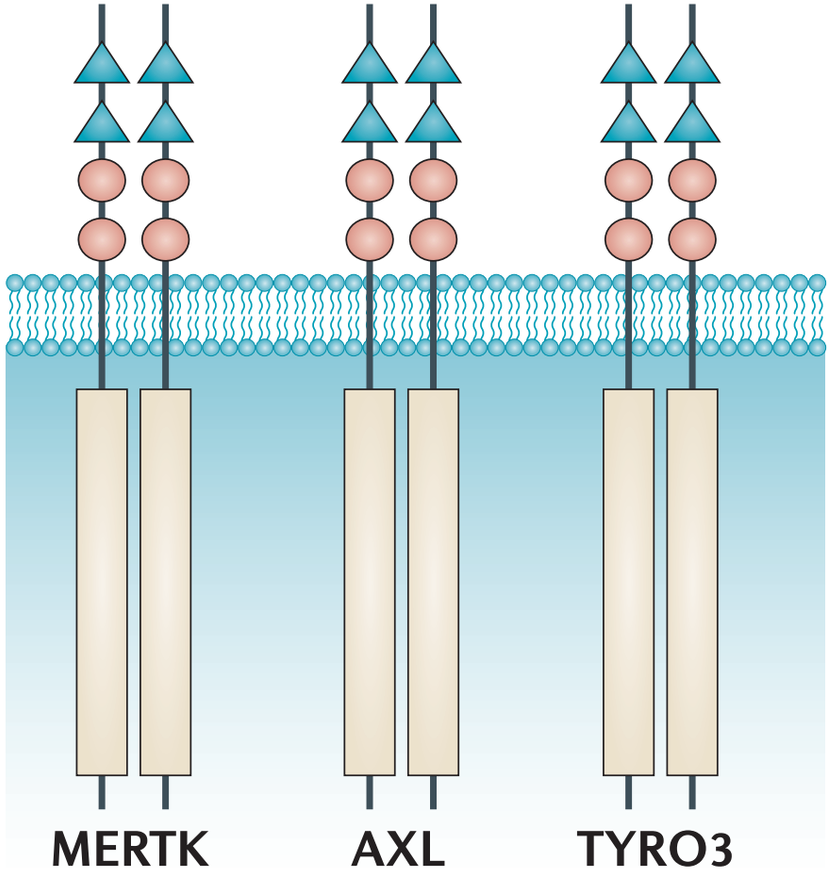


Figure 16-30 Essential Cell Biology 3/e (© Garland Science 2010)

TAM receptors: important yet poorly characterized



Graham *et al, Nat Rev Canc*, 2014

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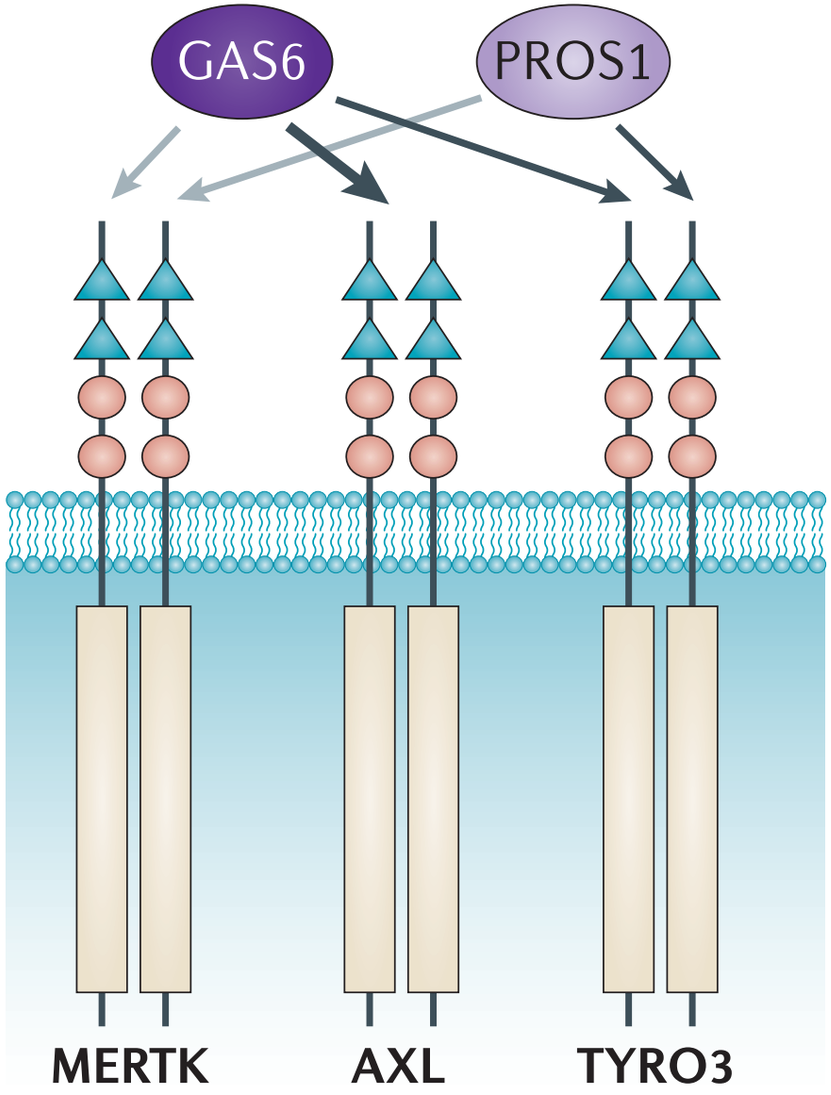

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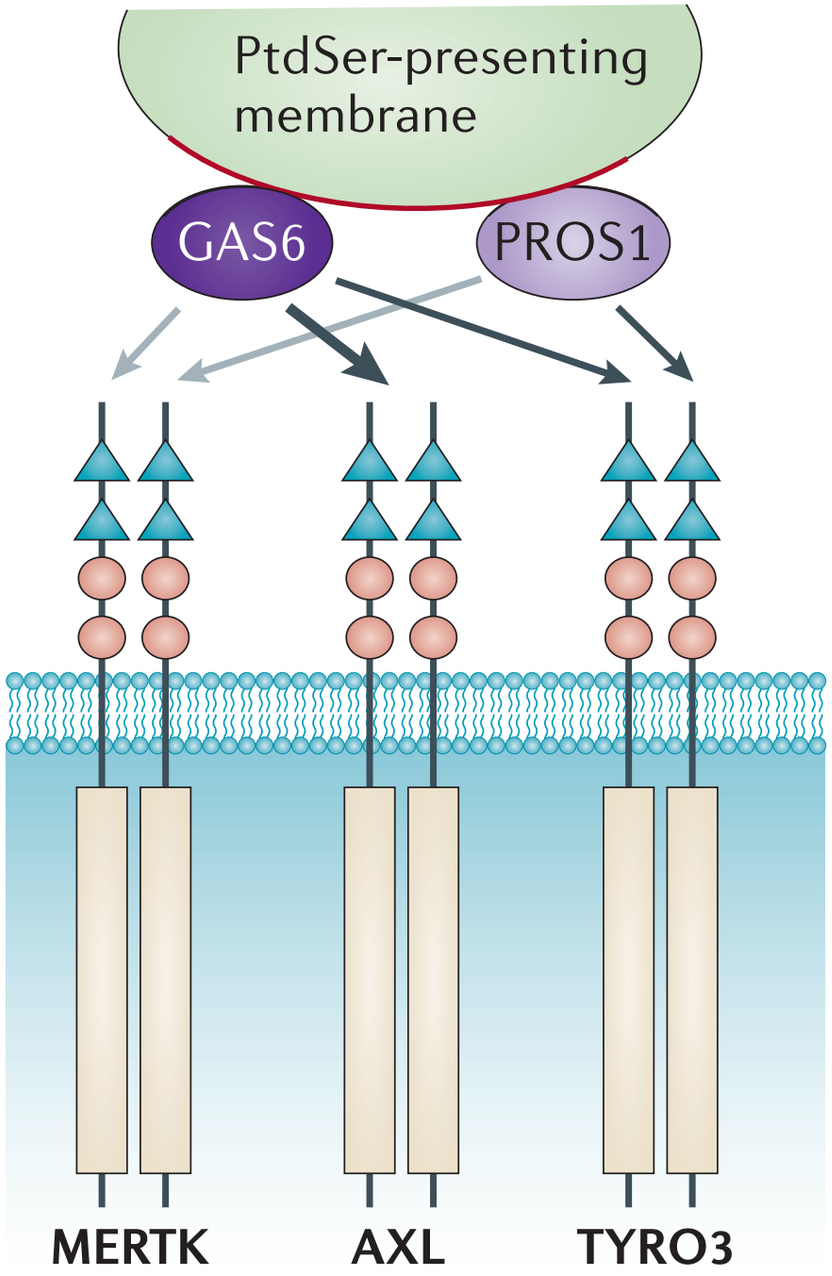

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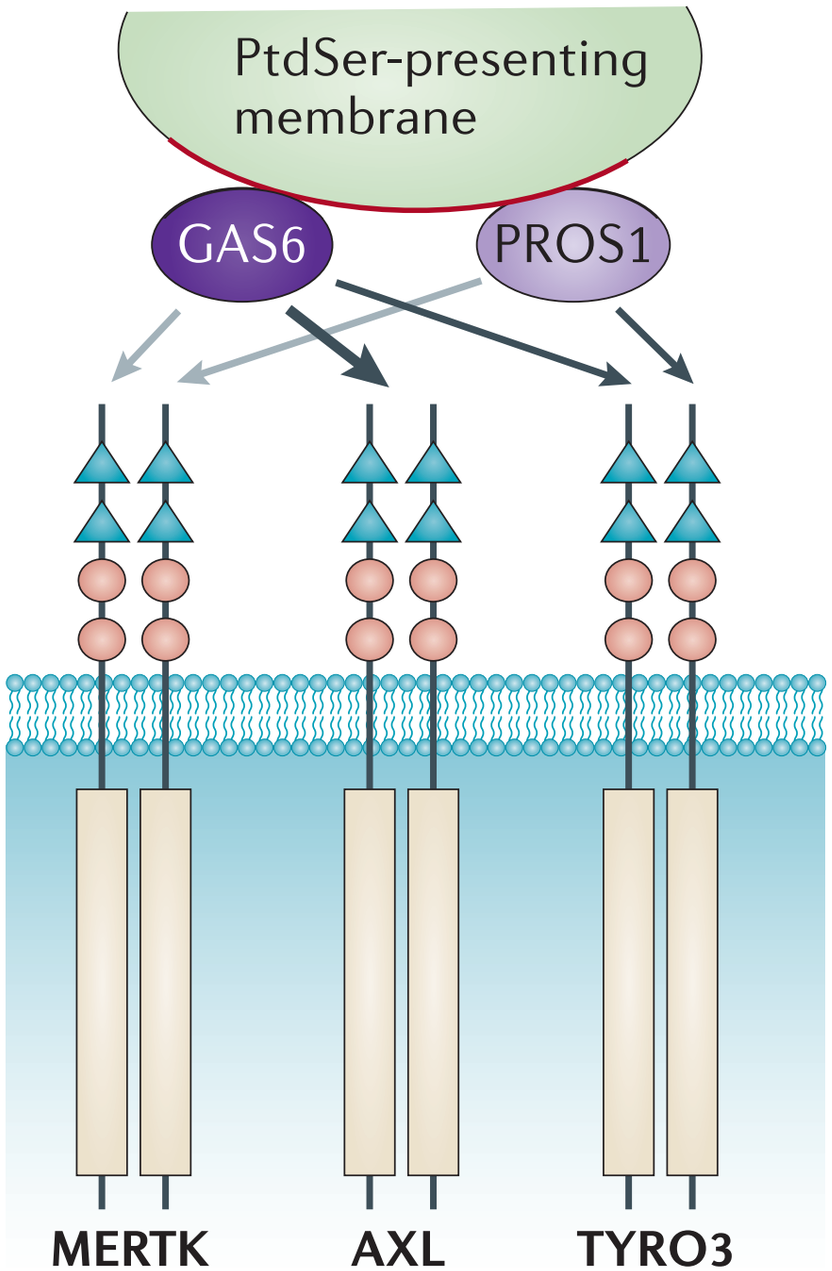
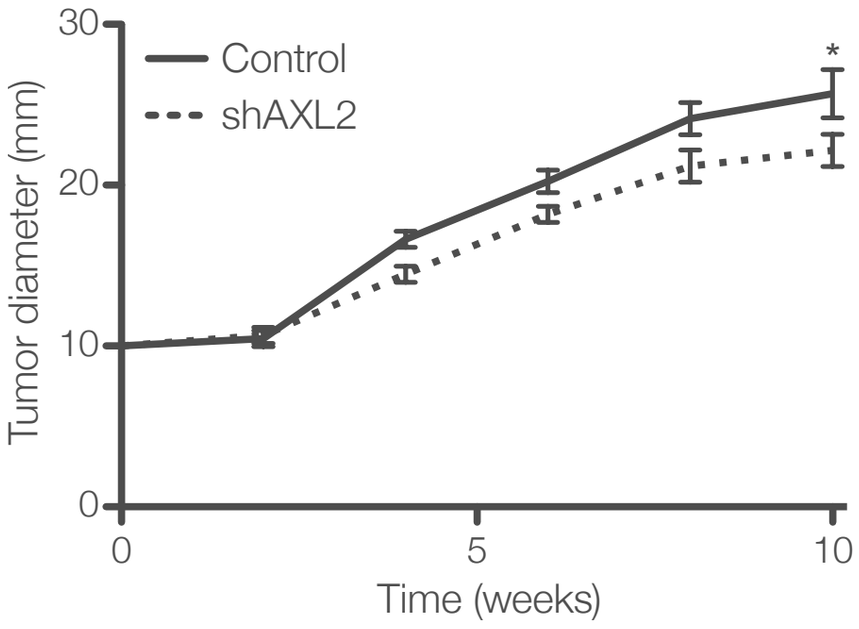


Important effects on:

- Metastasis
- Resistance
- Immunosuppression

Graham *et al, Nat Rev Canc*, 2014

Targeting AXL potently blocks metastasis



7 mice/group, MDA-MB-231

Gjerdrum *et al*, *PNAS*, 2010

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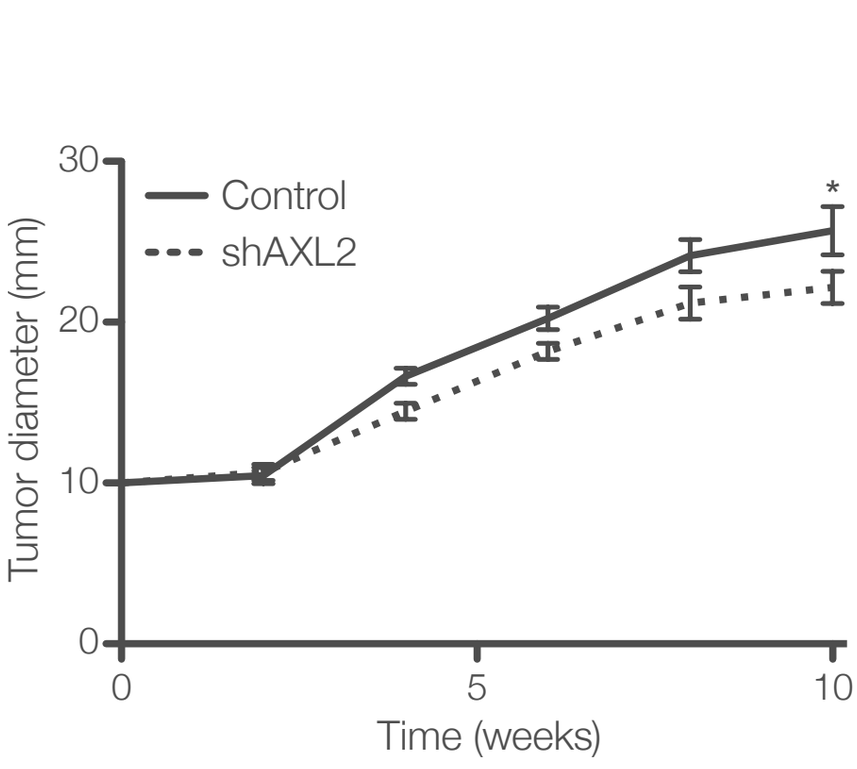

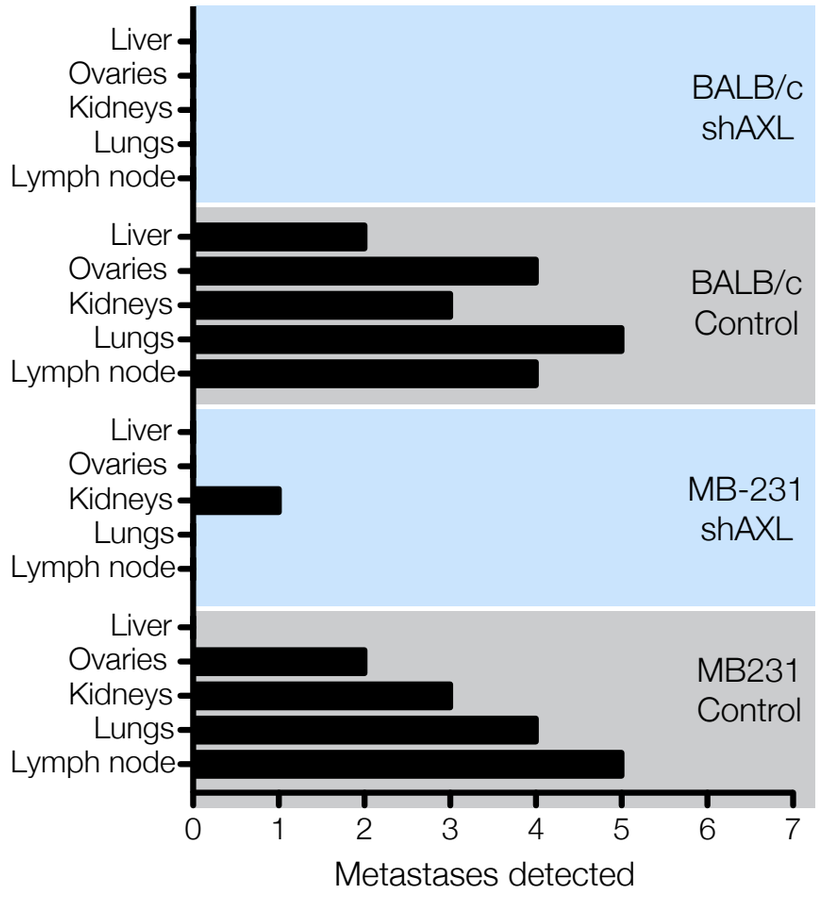

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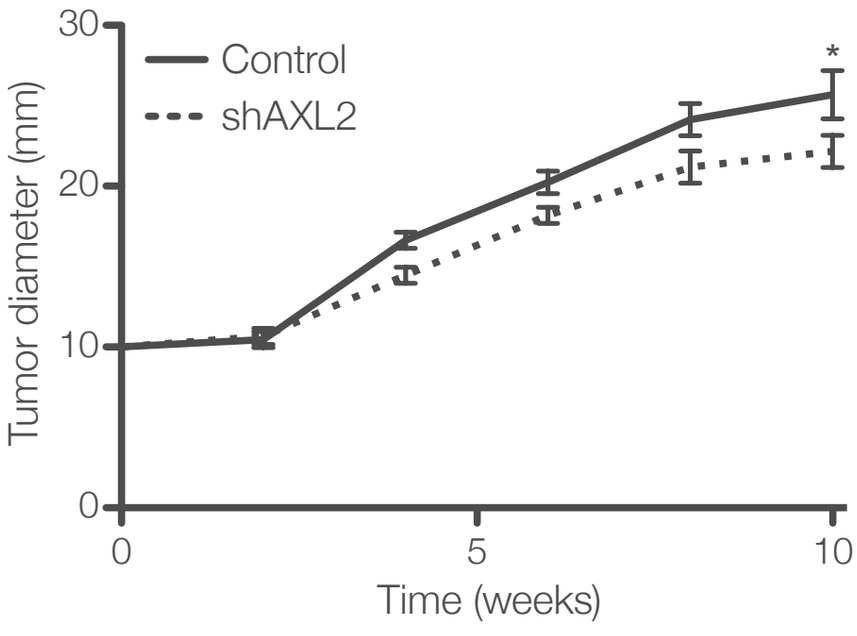

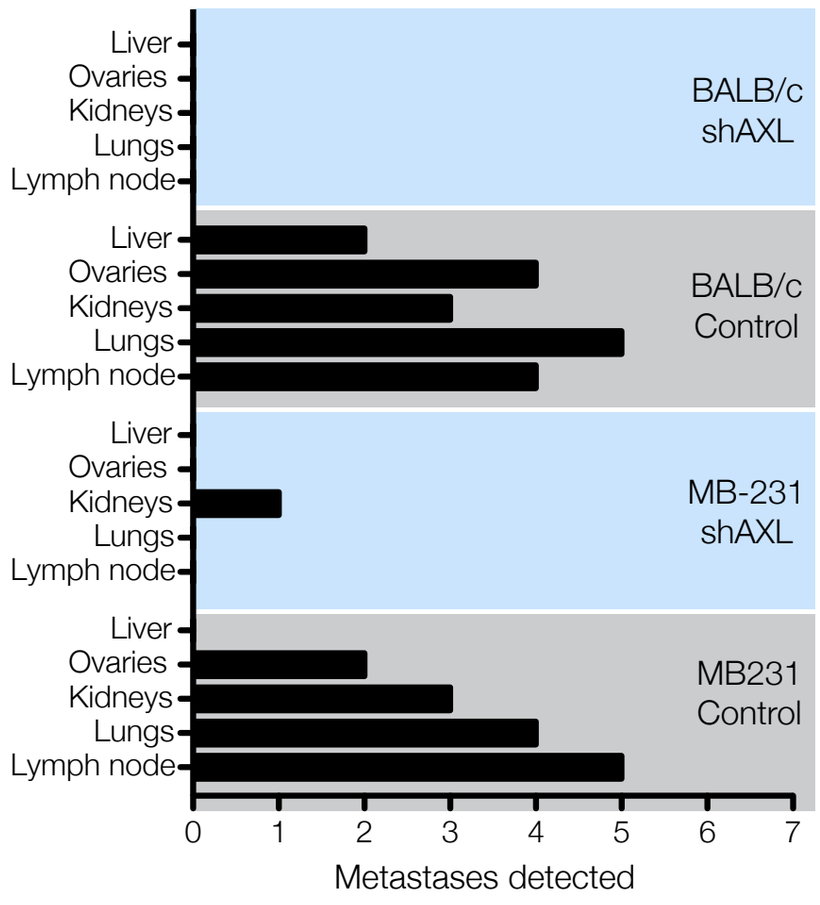

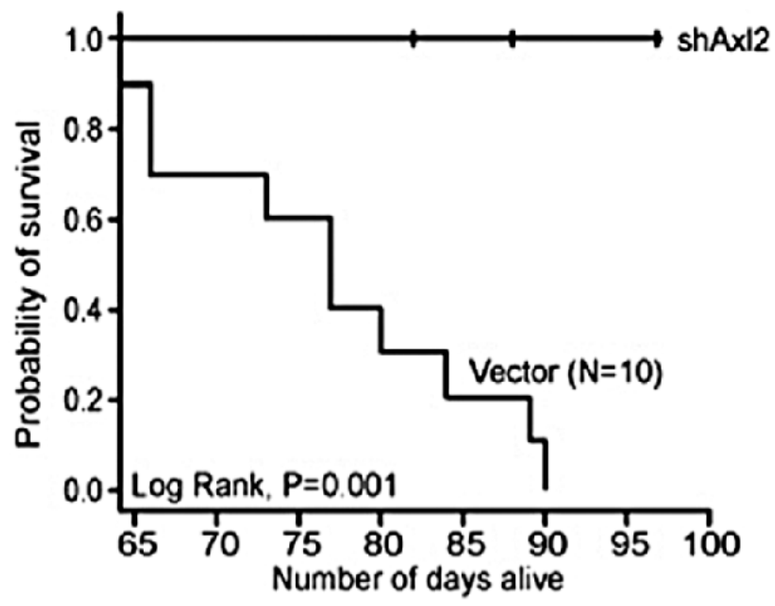

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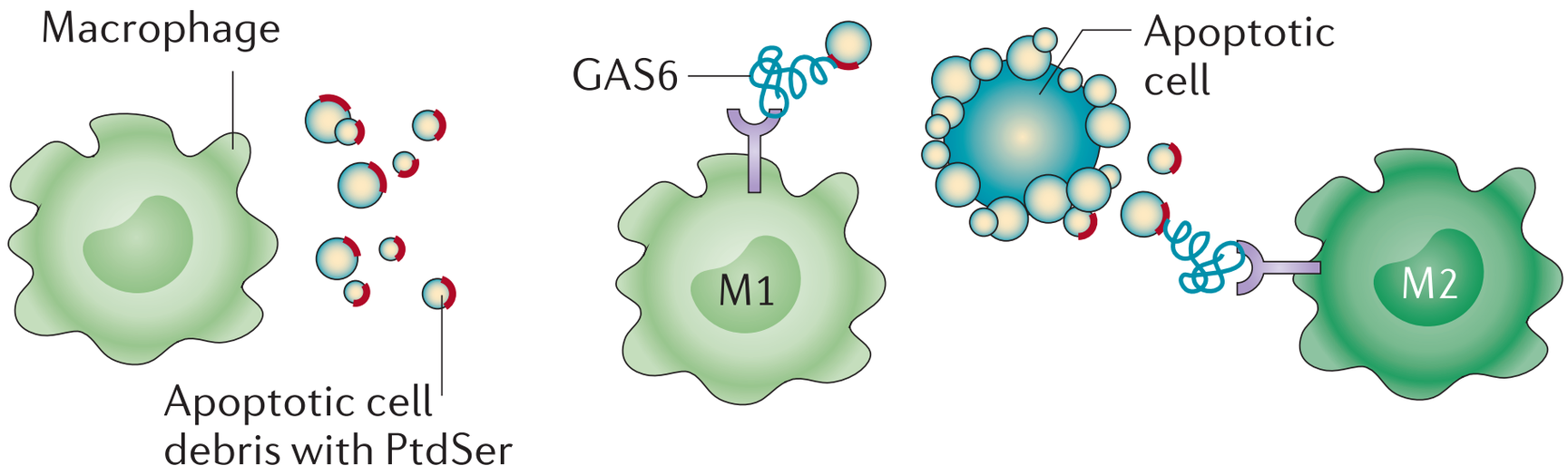
Gjerdrum *et al*, *PNAS*, 2010

TAM receptors have widespread roles in immune regulation



Graham *et al, Nat Rev Canc*, 2014

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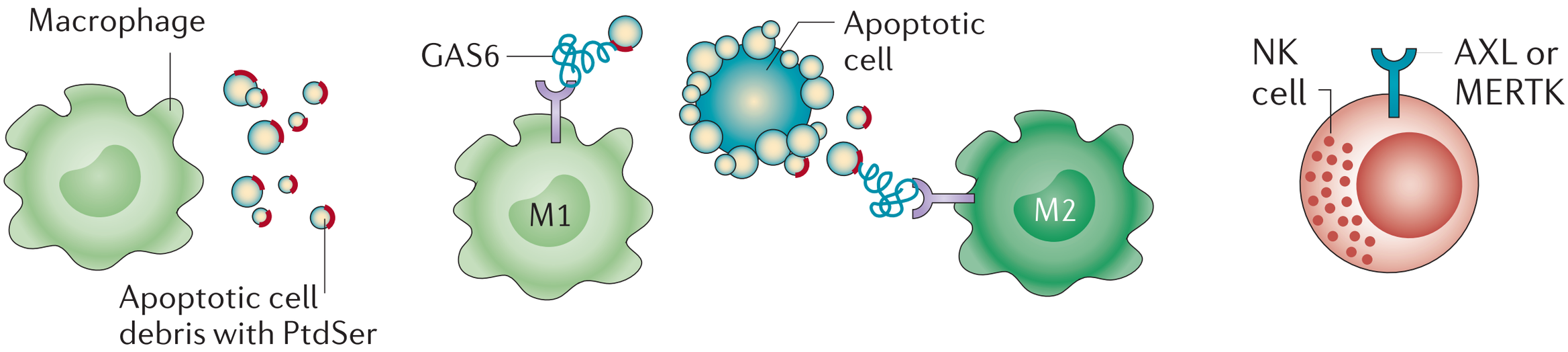

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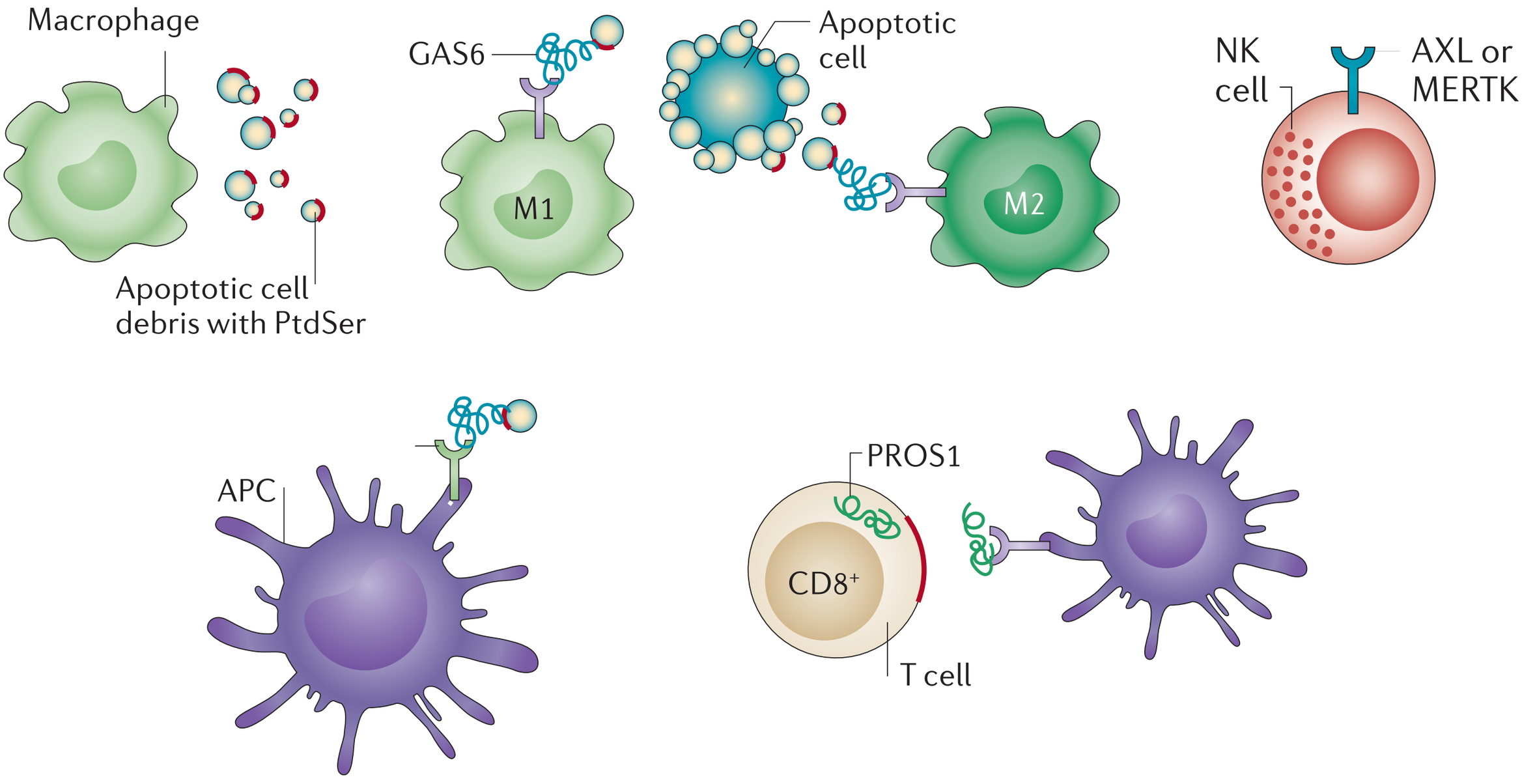
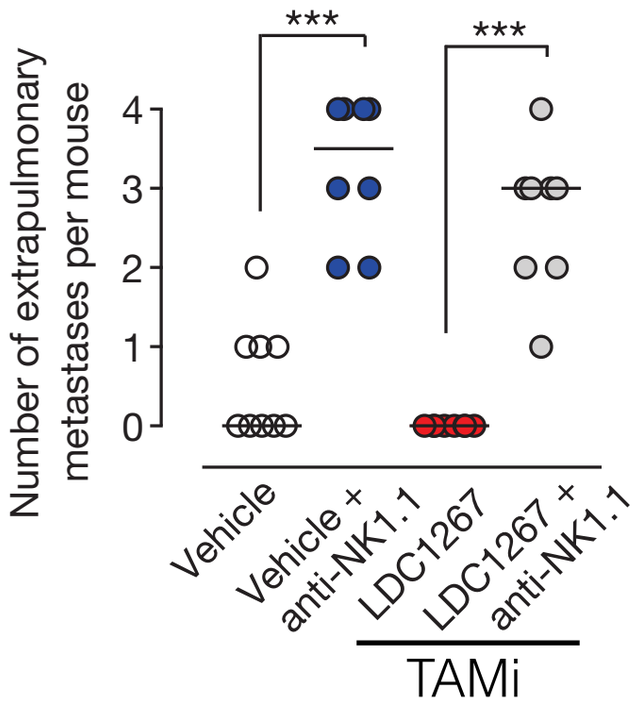
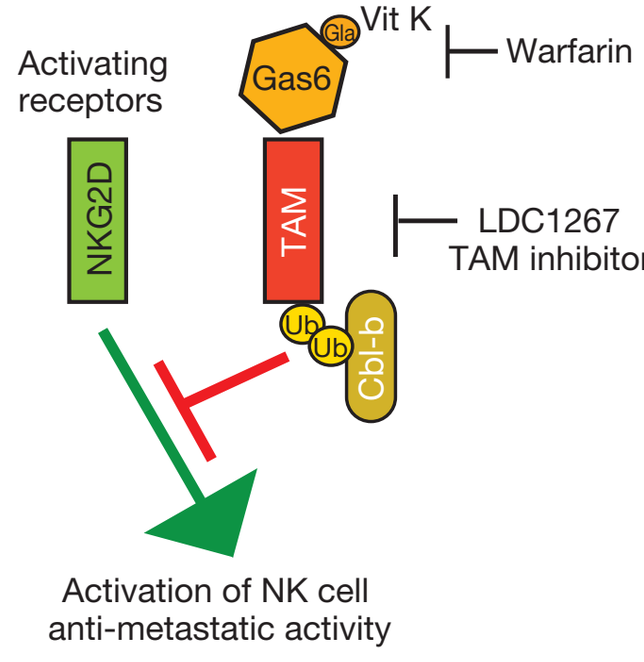


Graham *et al, Nat Rev Canc*, 2014

TAM receptors inhibit NK cell clearance

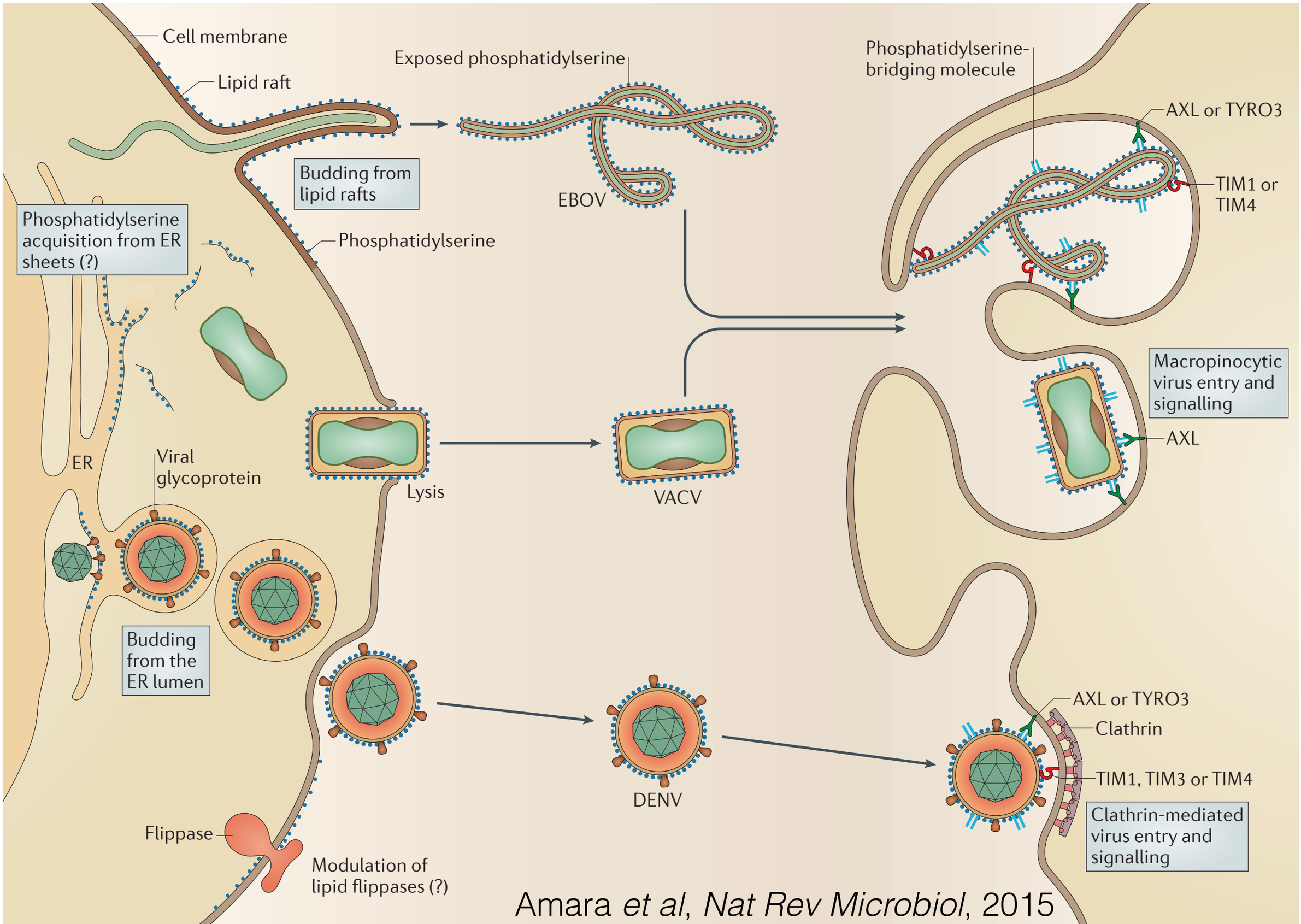




Subcutaneous B16F10 shown. TC-1, 4T1, NeuT+ also tested.

Paolino *et al*, *Nature*, 2014

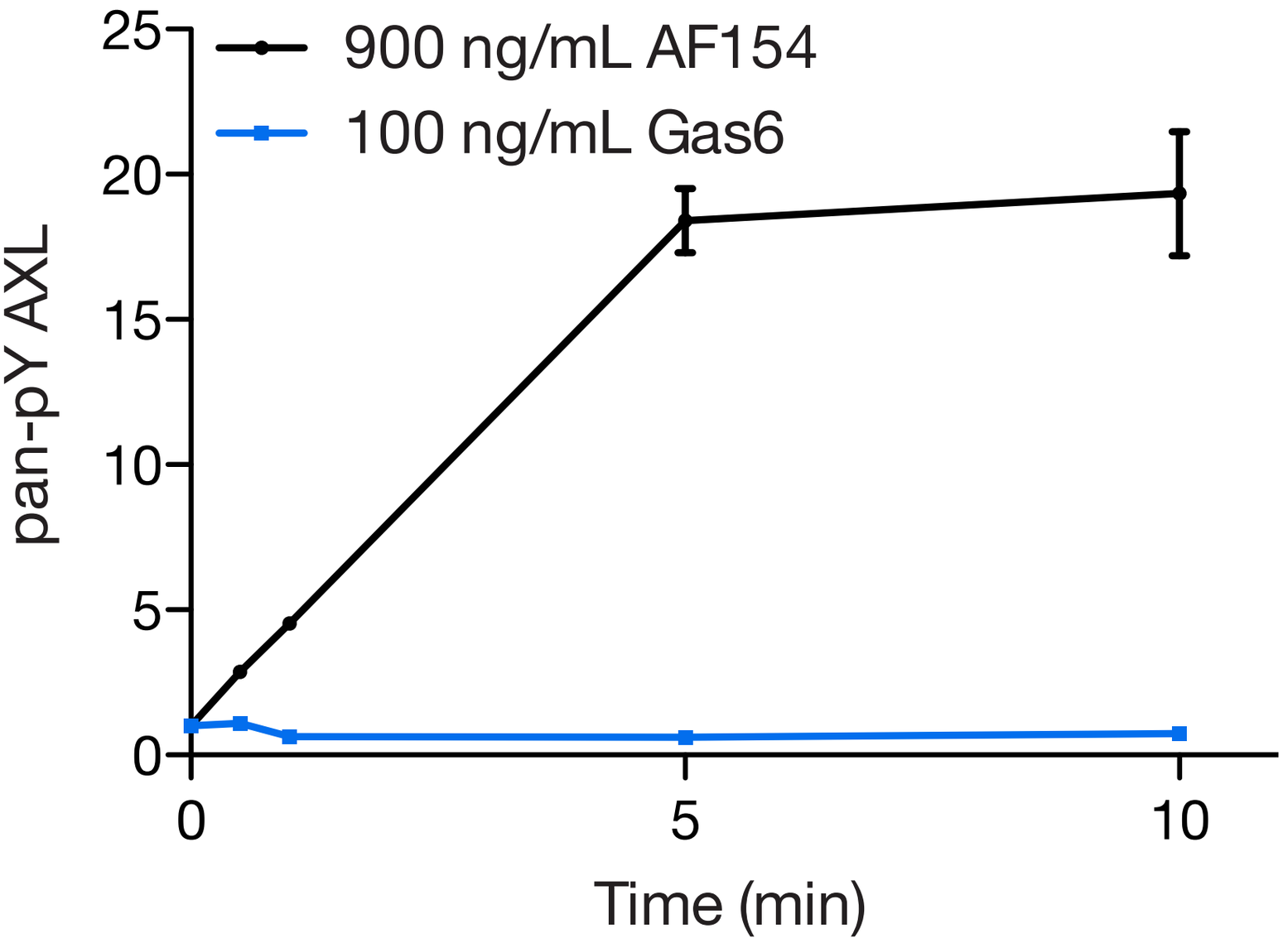
Many viruses “play dead” for cell entry and immune suppression



Amara *et al*, *Nat Rev Microbiol*, 2015

How do TAMs function?

Conundrum: AXL does not robustly respond to ligand stimulation



MDA-MB-231

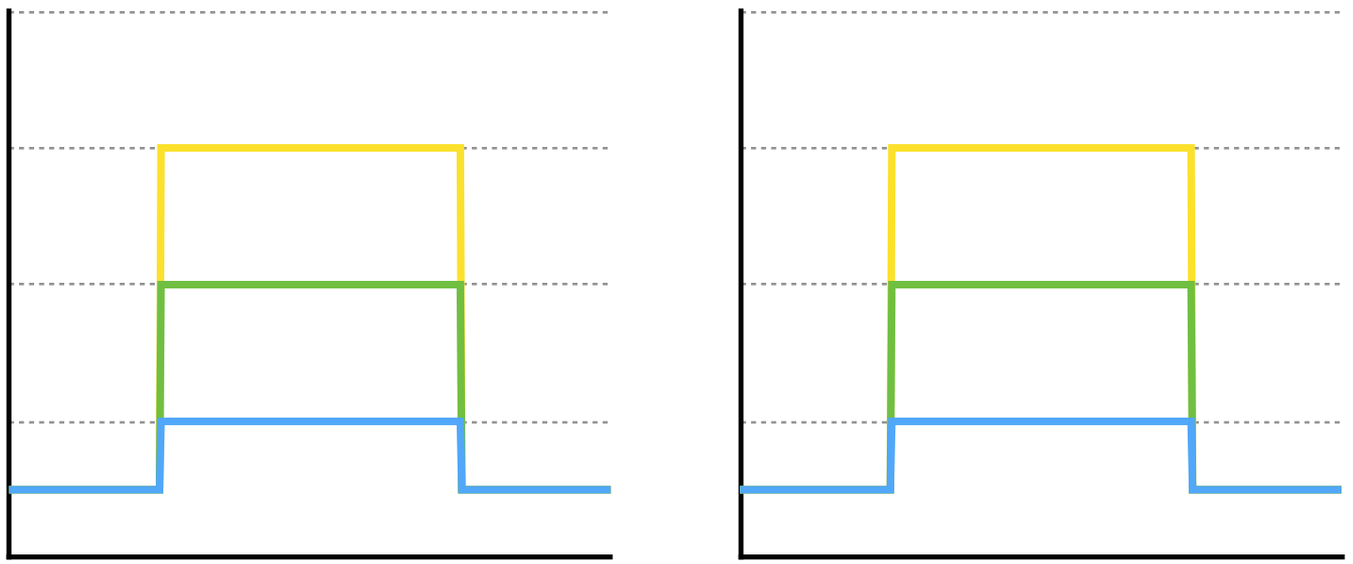
Meyer *et al, Cell Sys*, 2015

Attributes of a good sensor

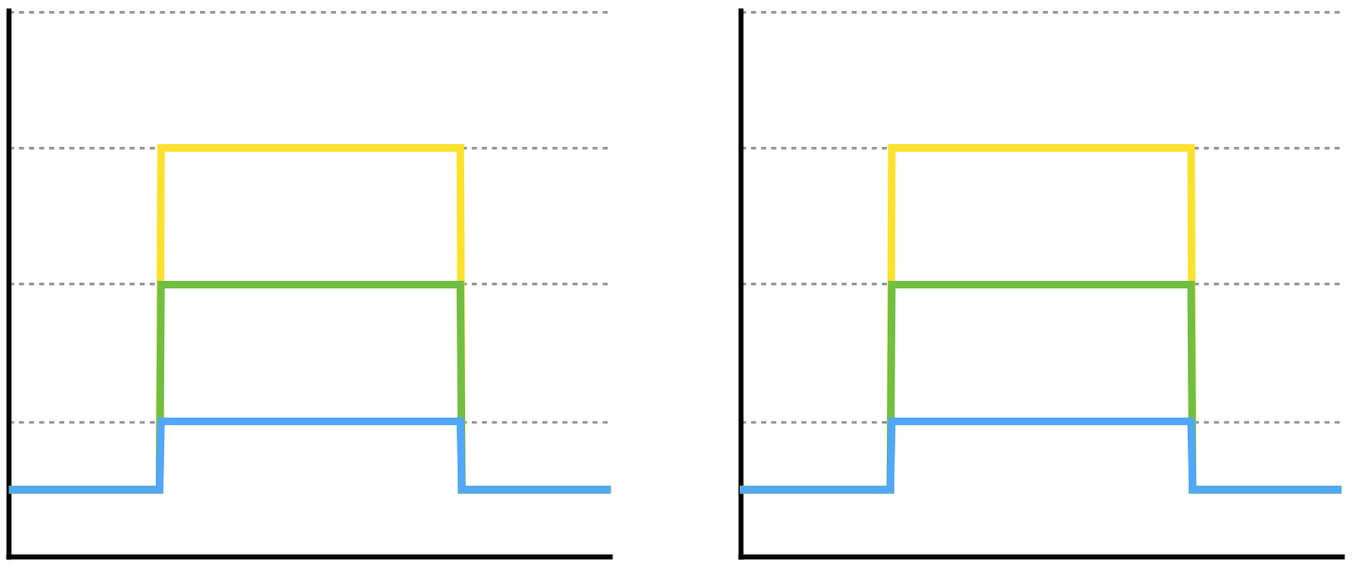
Input

Output

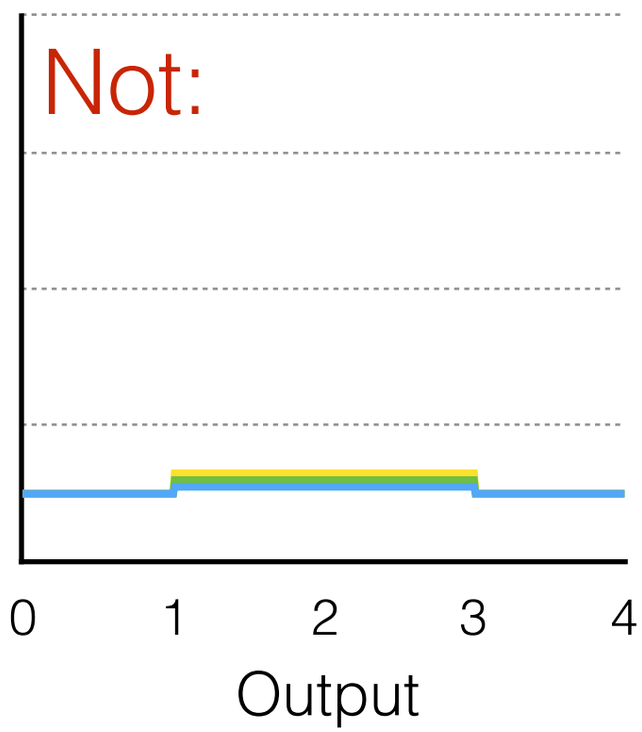
Attributes of a good sensor



Attributes of a good sensor



Large dynamic range



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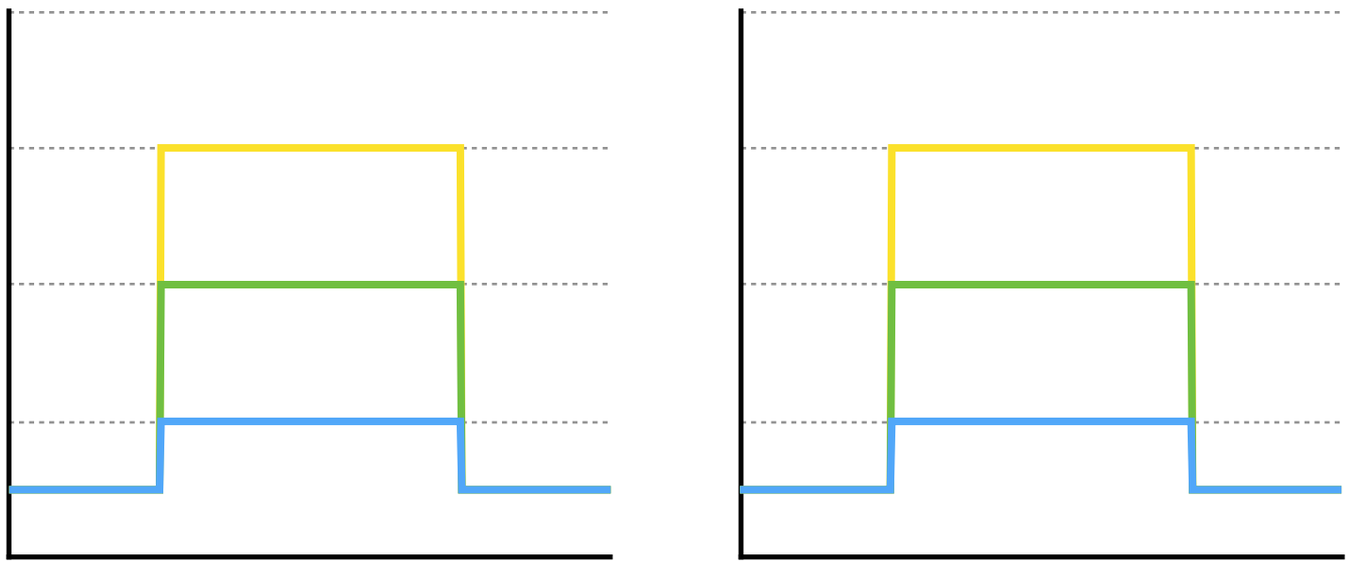
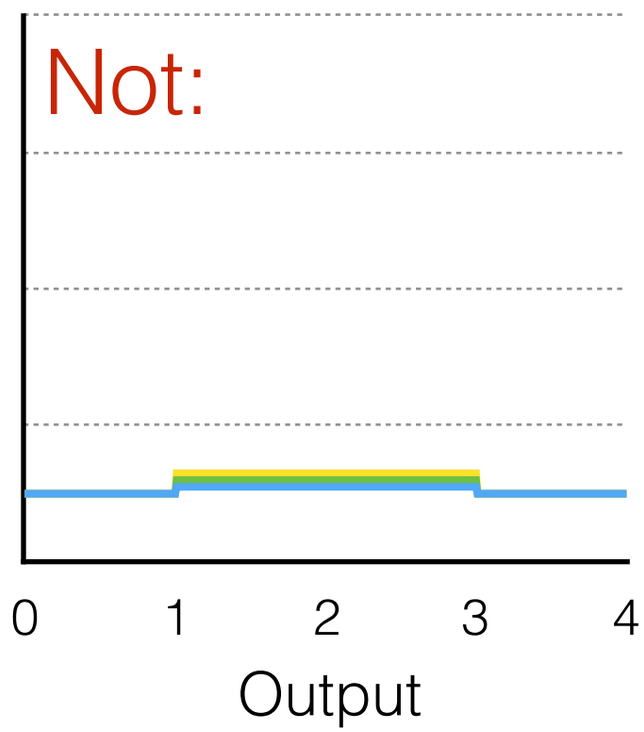
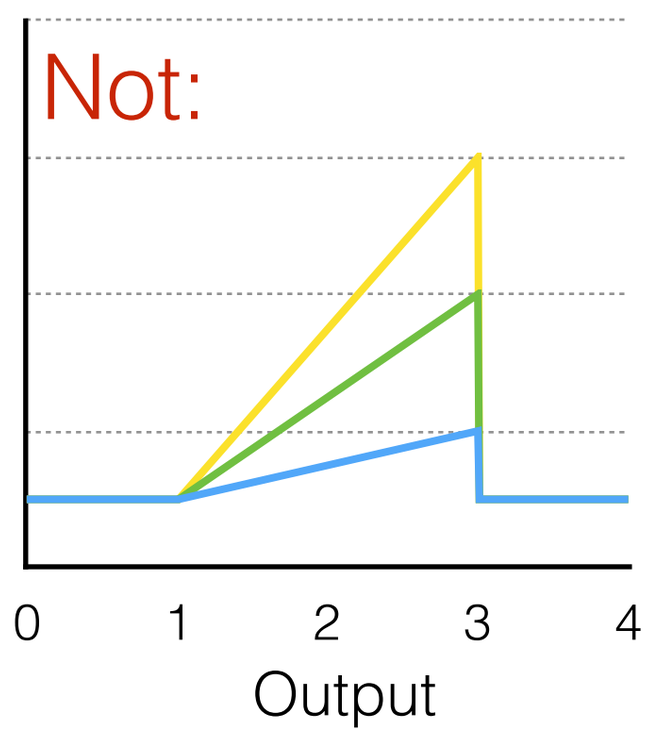


Large dynamic range

Rapid response





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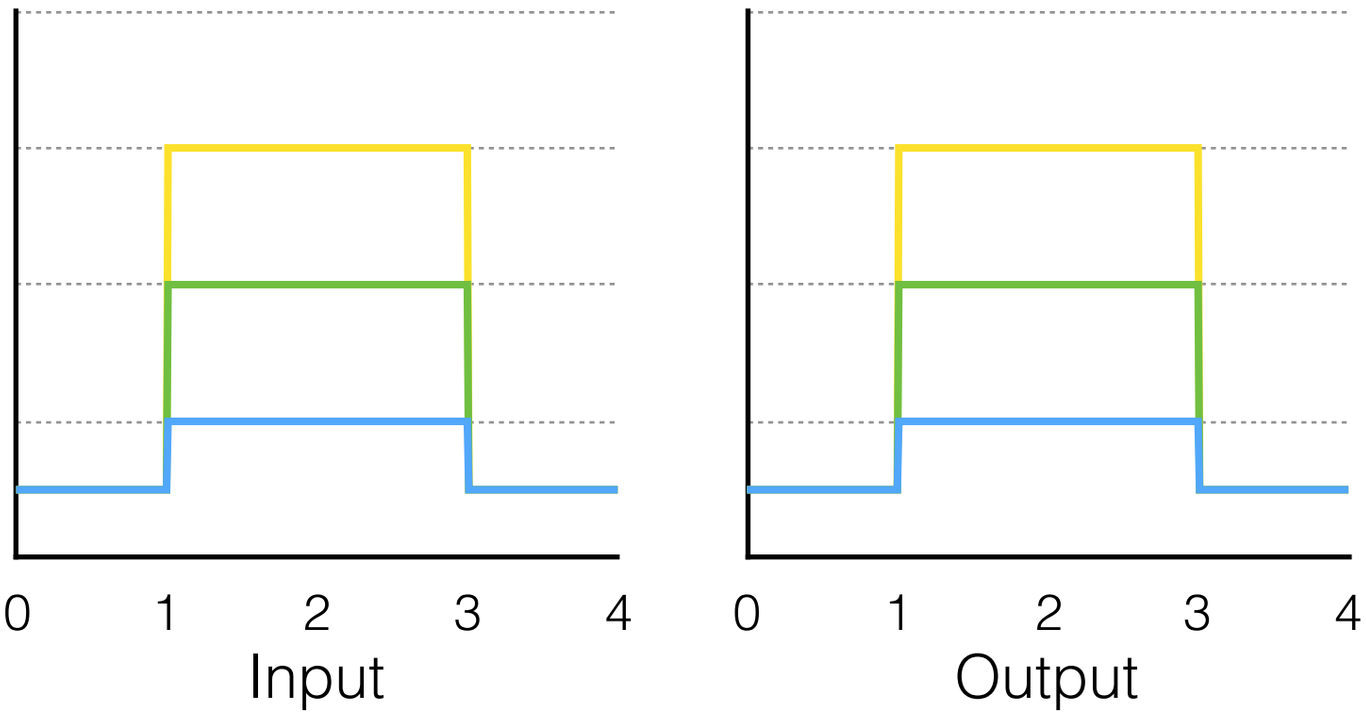
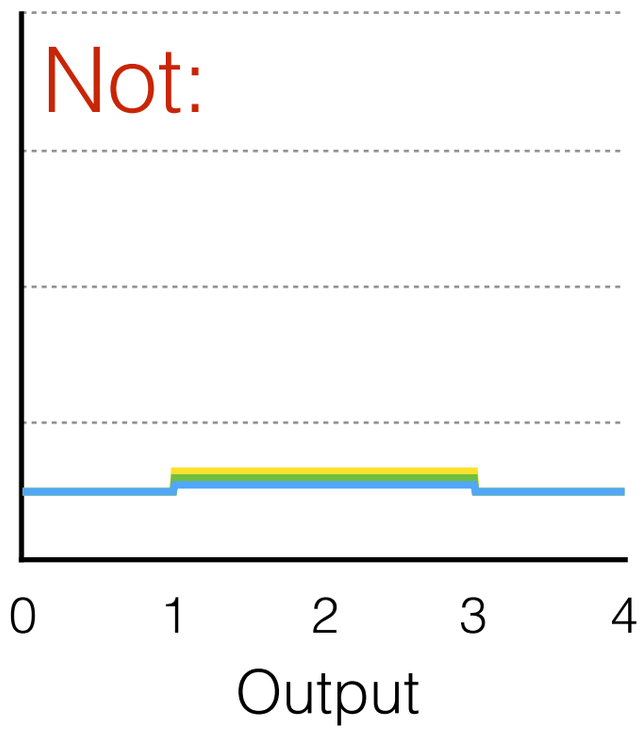
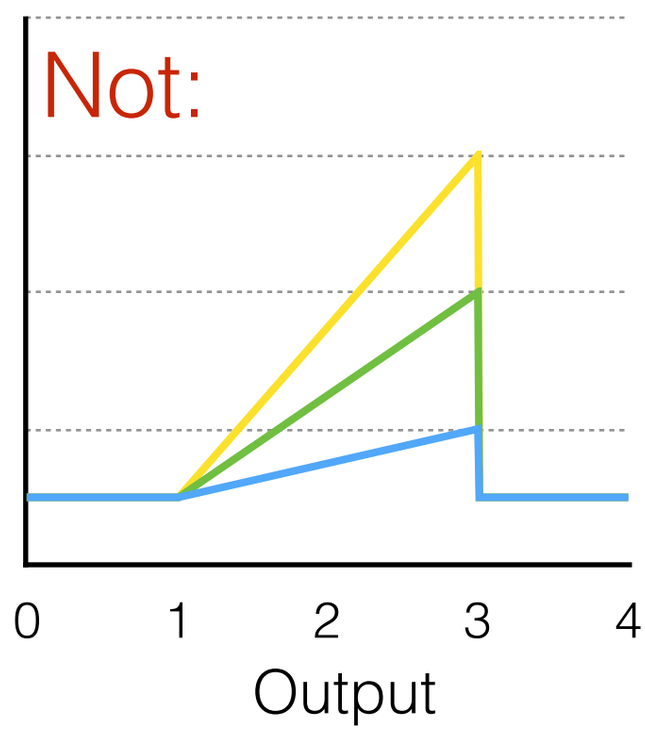


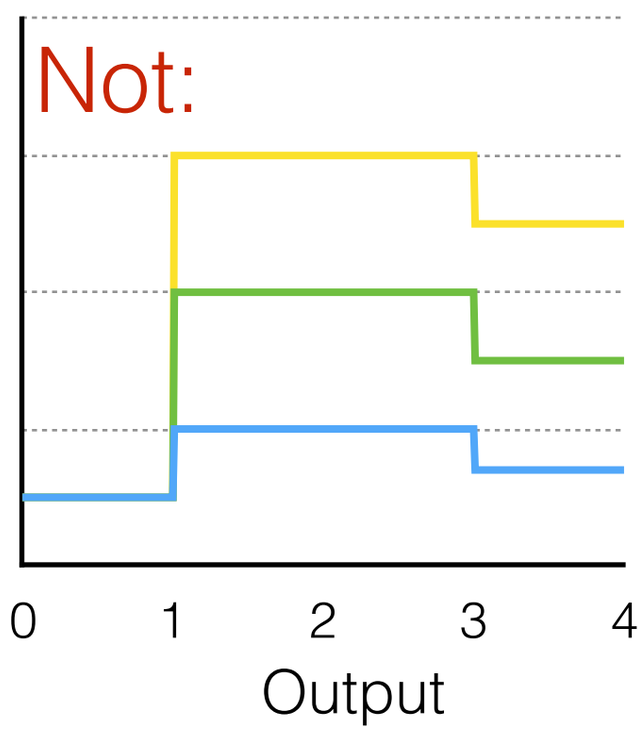
Large dynamic range

Rapid response

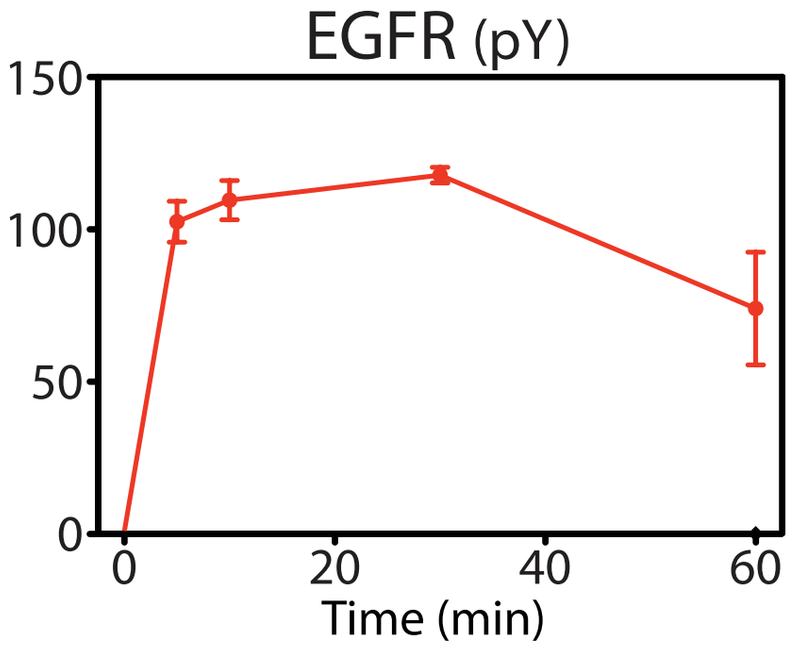
Memoryless

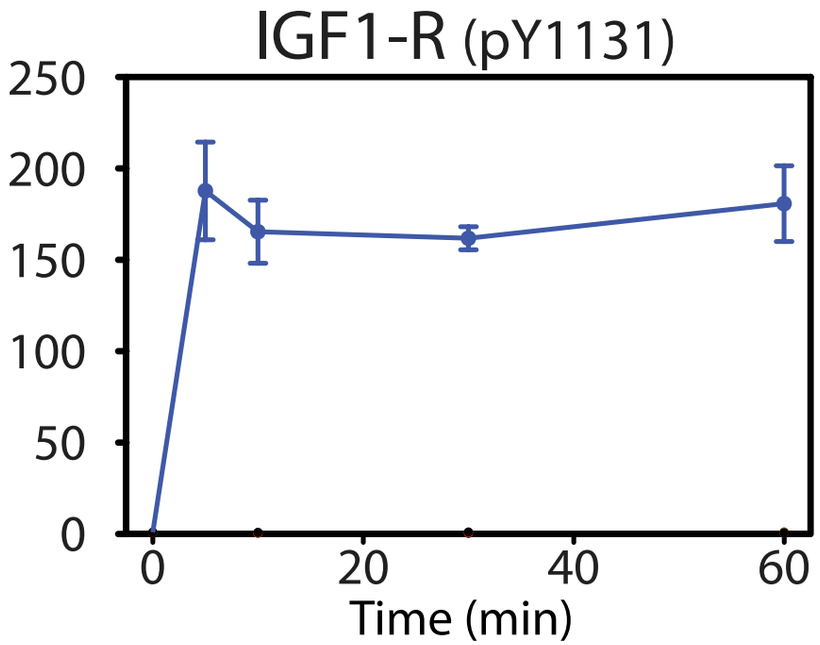


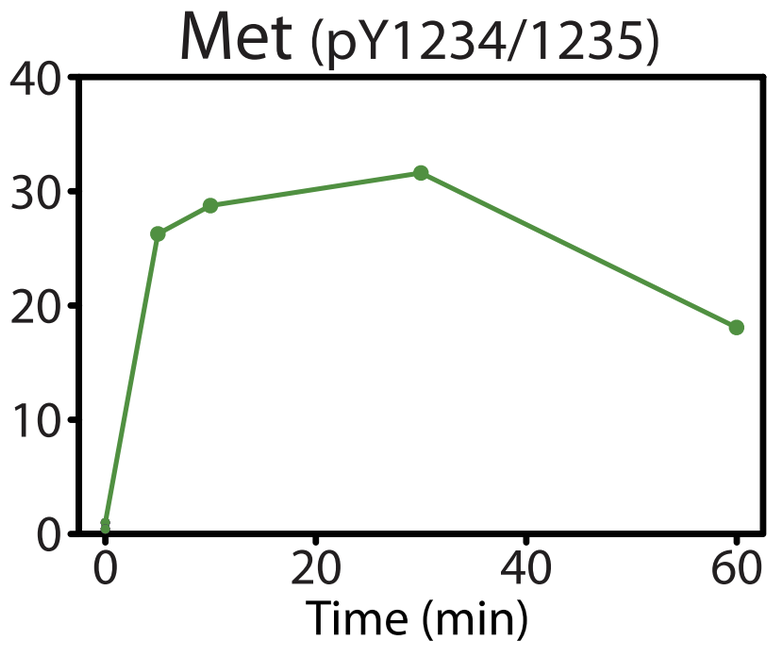




Many RTKs can be considered as "ligand concentration sensors"



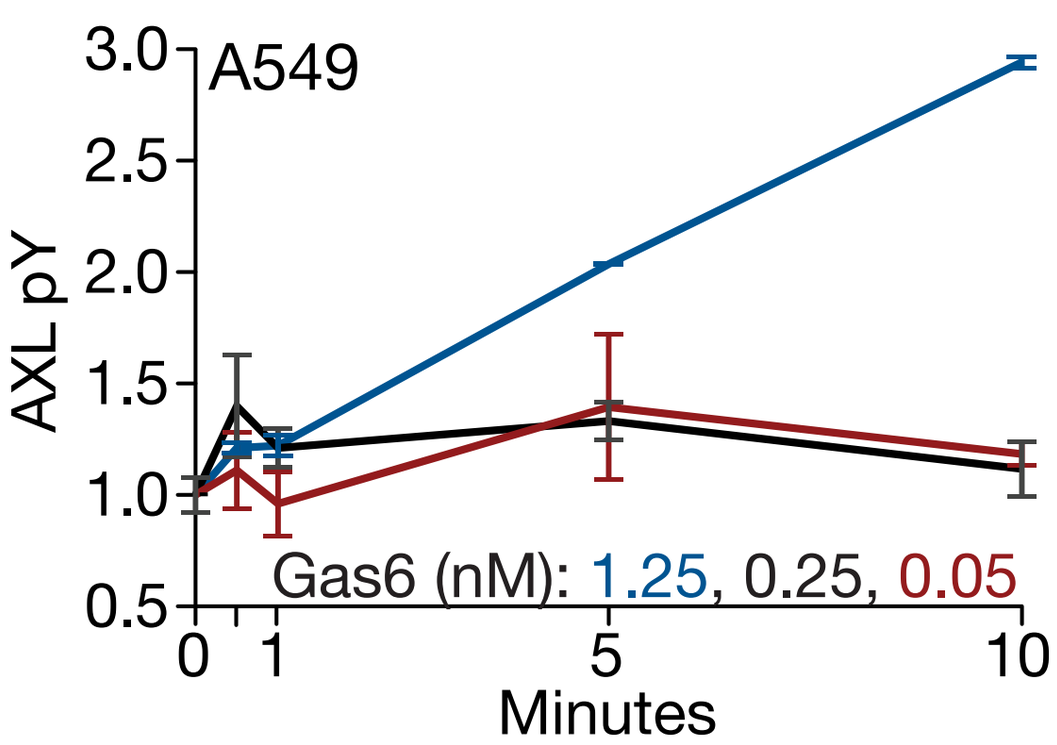


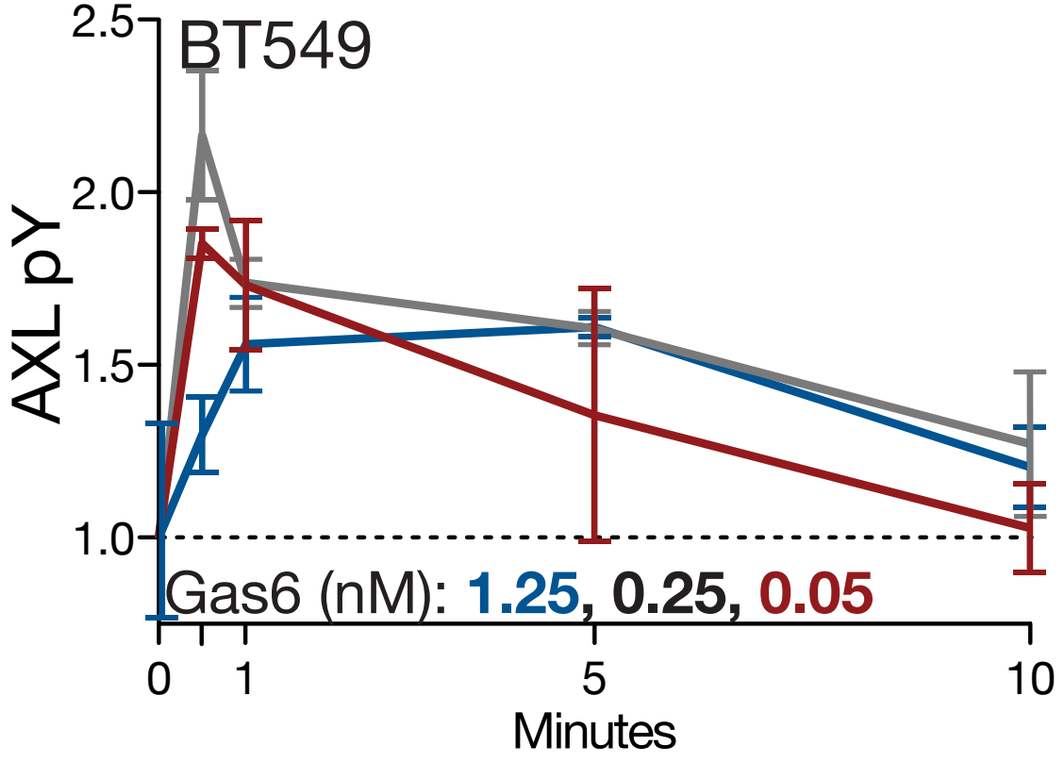


100 ng/mL EGF/IGF1, 50 ng/mL HGF, hMLE-Twist1

Kim, Meyer, *et al*, *Mol Cell Proteomics*, 2011

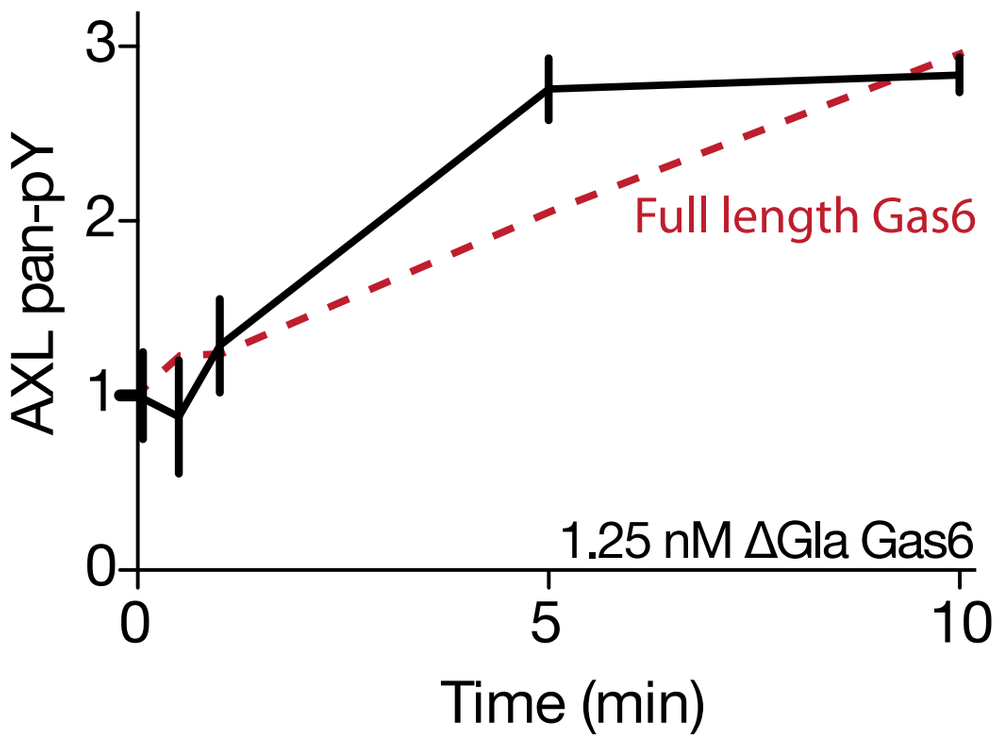
AXL responses to Gas6 stimulation are complex and dynamic

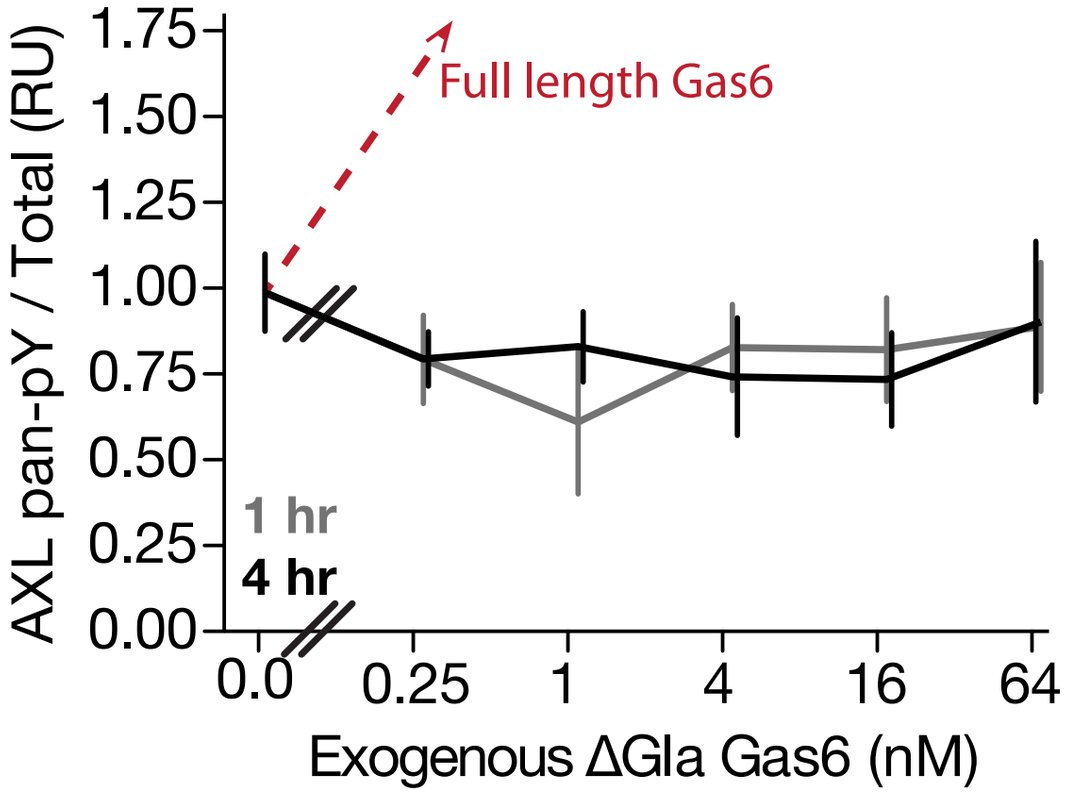




Meyer *et al, Cell Sys*, 2015

PtdSer interaction is required for sustained AXL activation

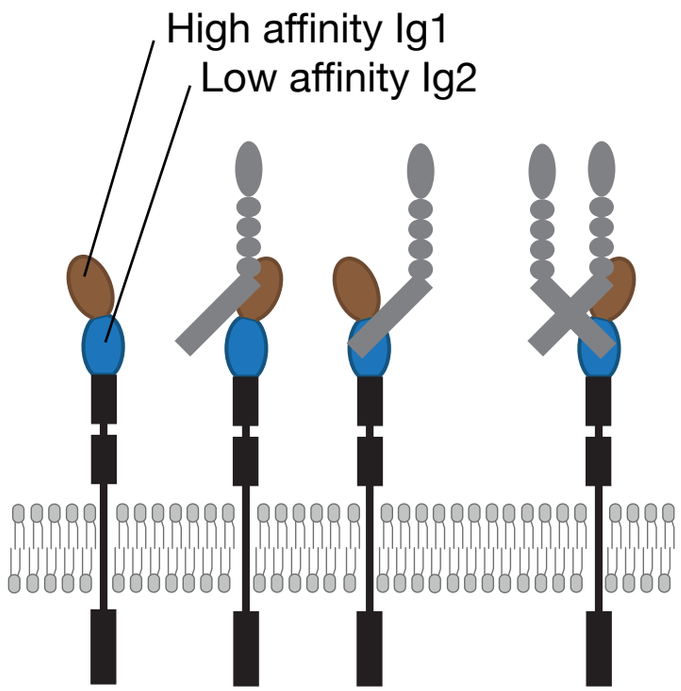




A549

Meyer *et al, Cell Sys*, 2015

TAM ligands act as a receptor-PtdSer bridge



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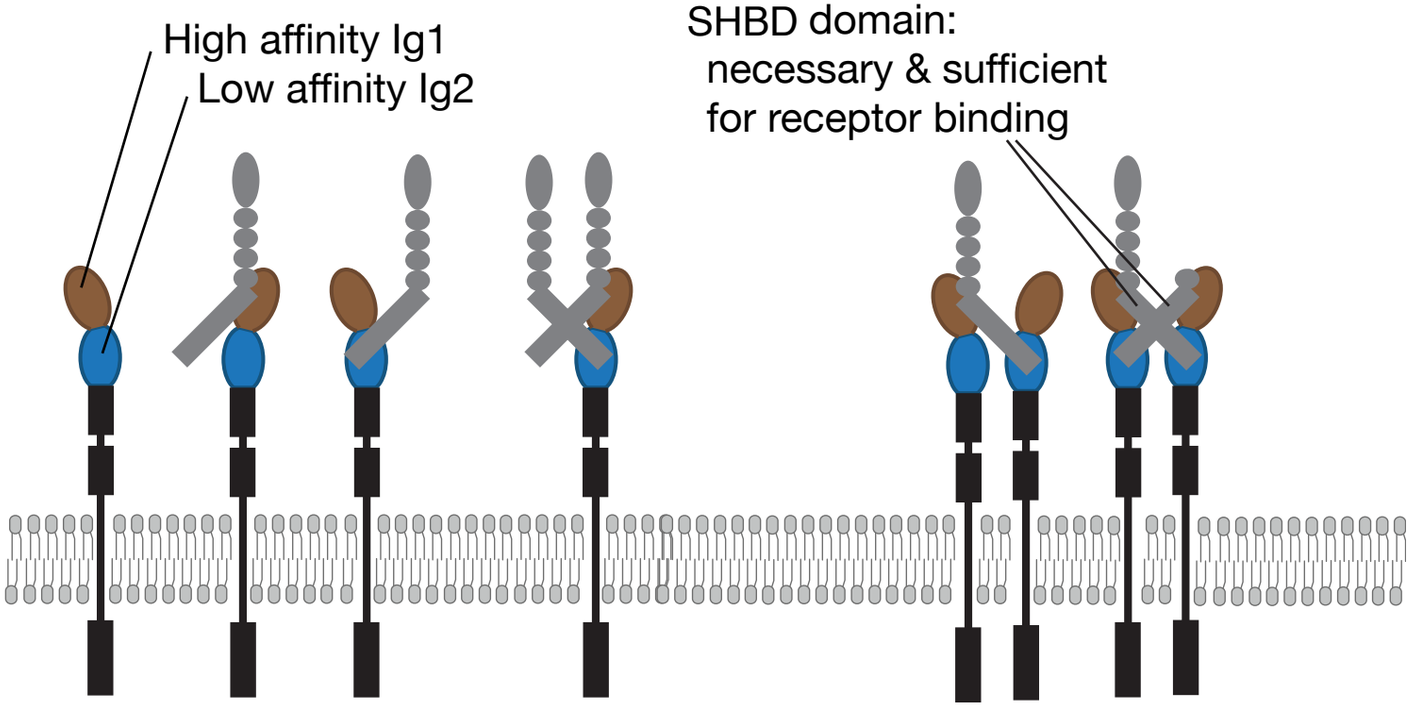

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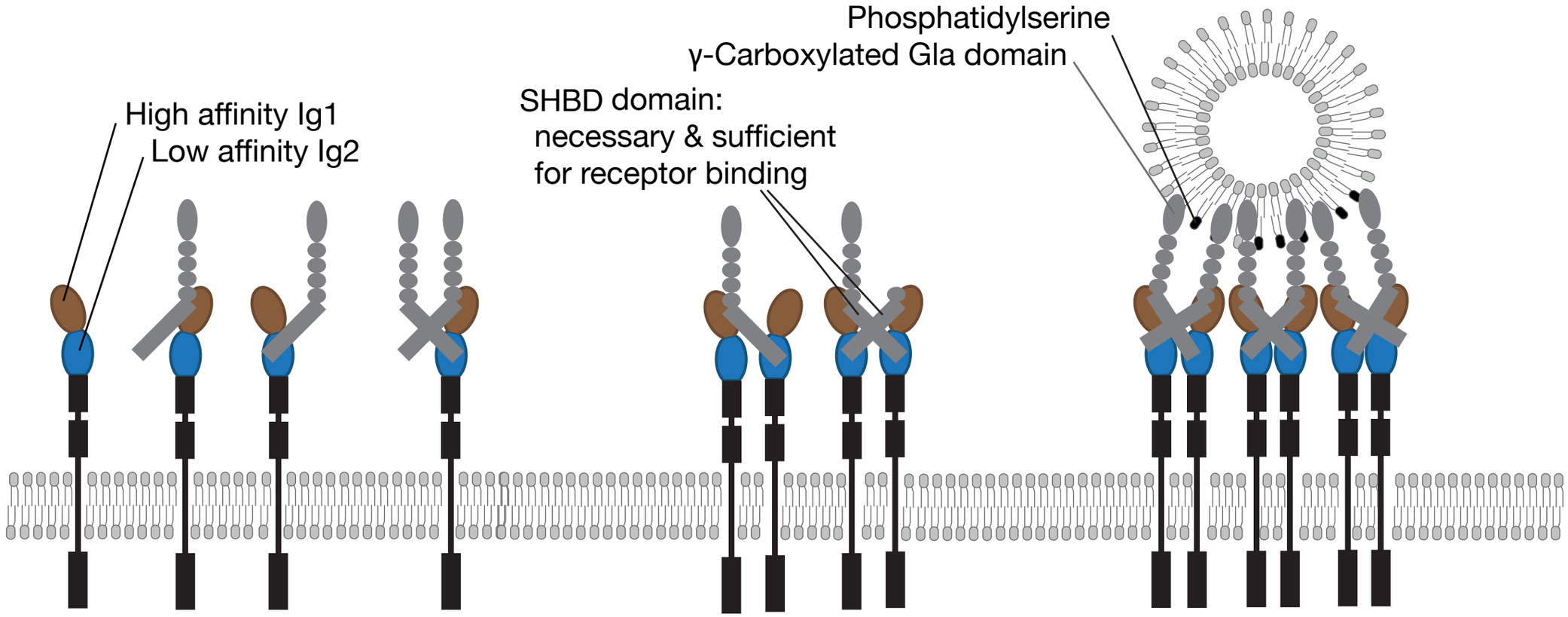
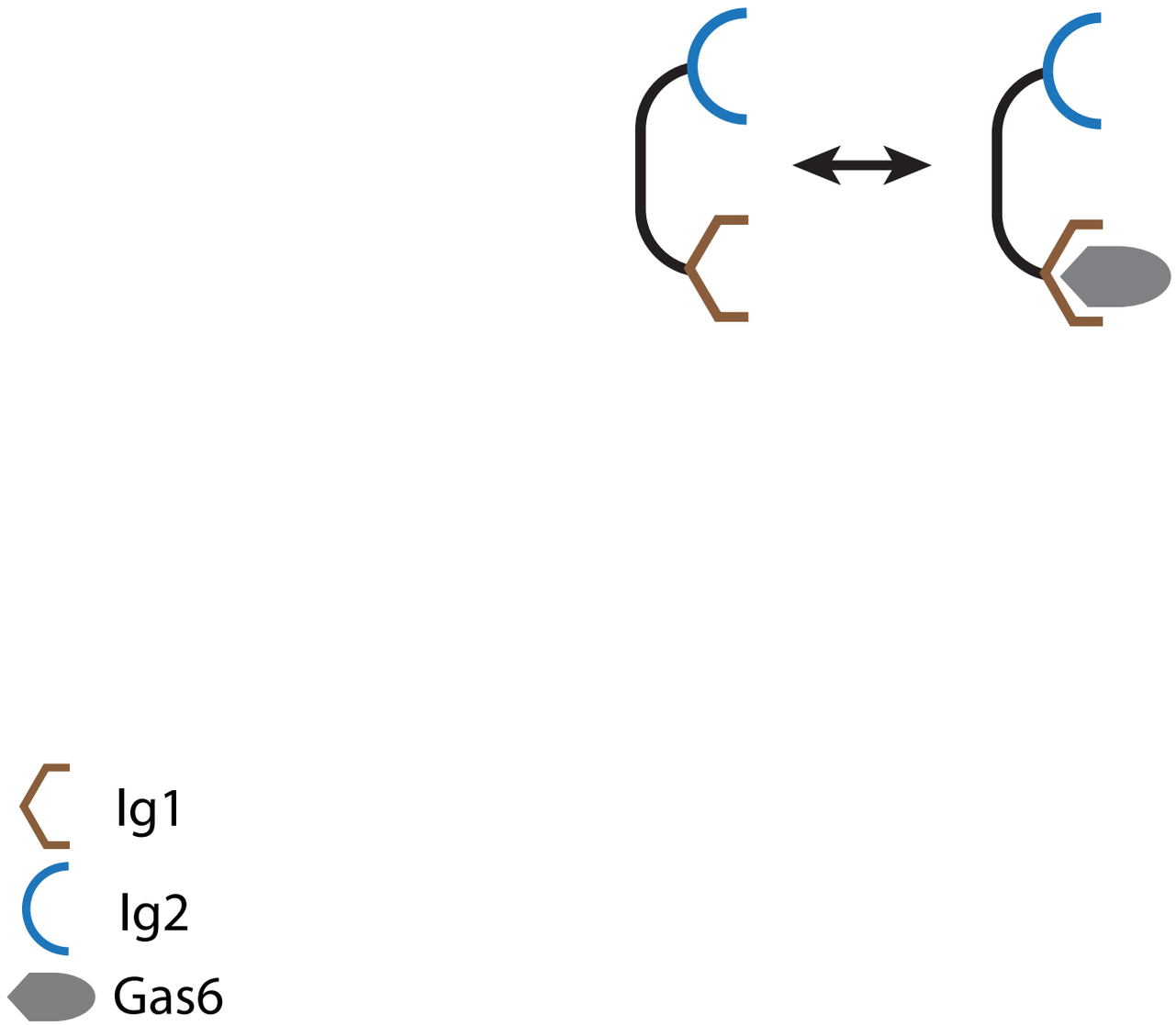


Meyer *et al, Cell Sys*, 2015

Differential equations allow us to map our knowledge to kinetics



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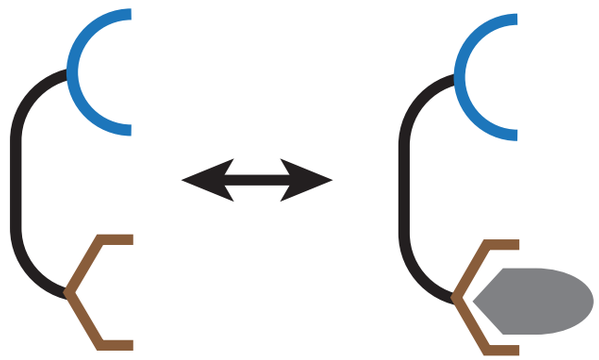
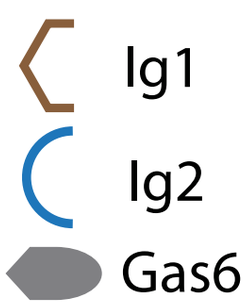
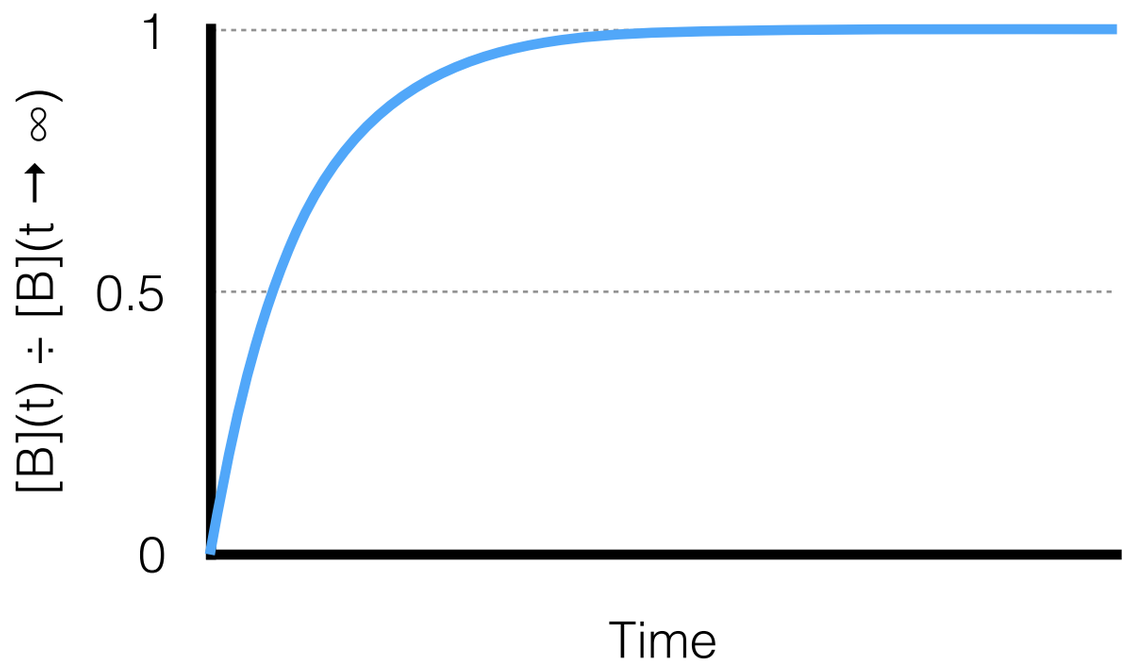
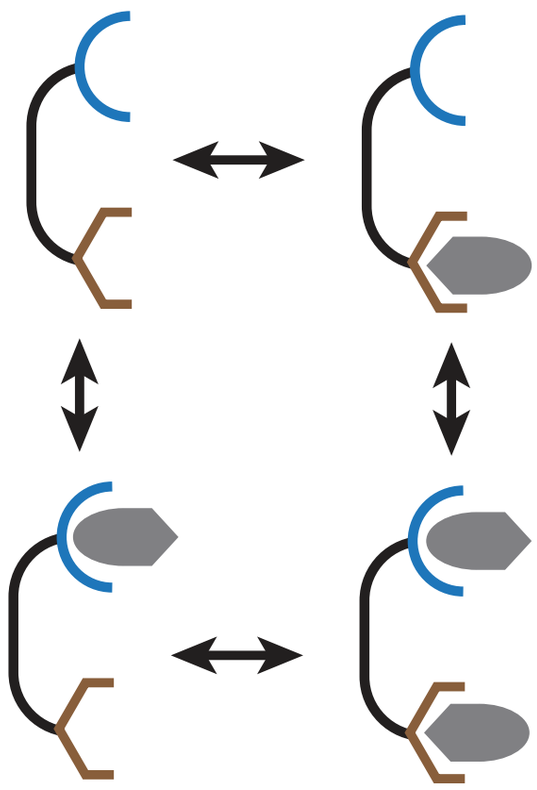


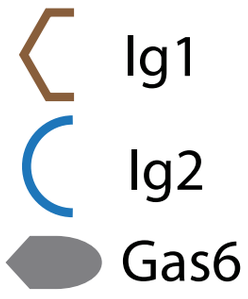
$$\frac{\delta[B]}{\delta t} = k_f[R][G] - k_r[B]$$





TAM kinetic model enables mechanistic interpretation of kinetic response measurements





Fit
Measured/defined
Detailed balance

Meyer *et al, Cell Sys*, 2015

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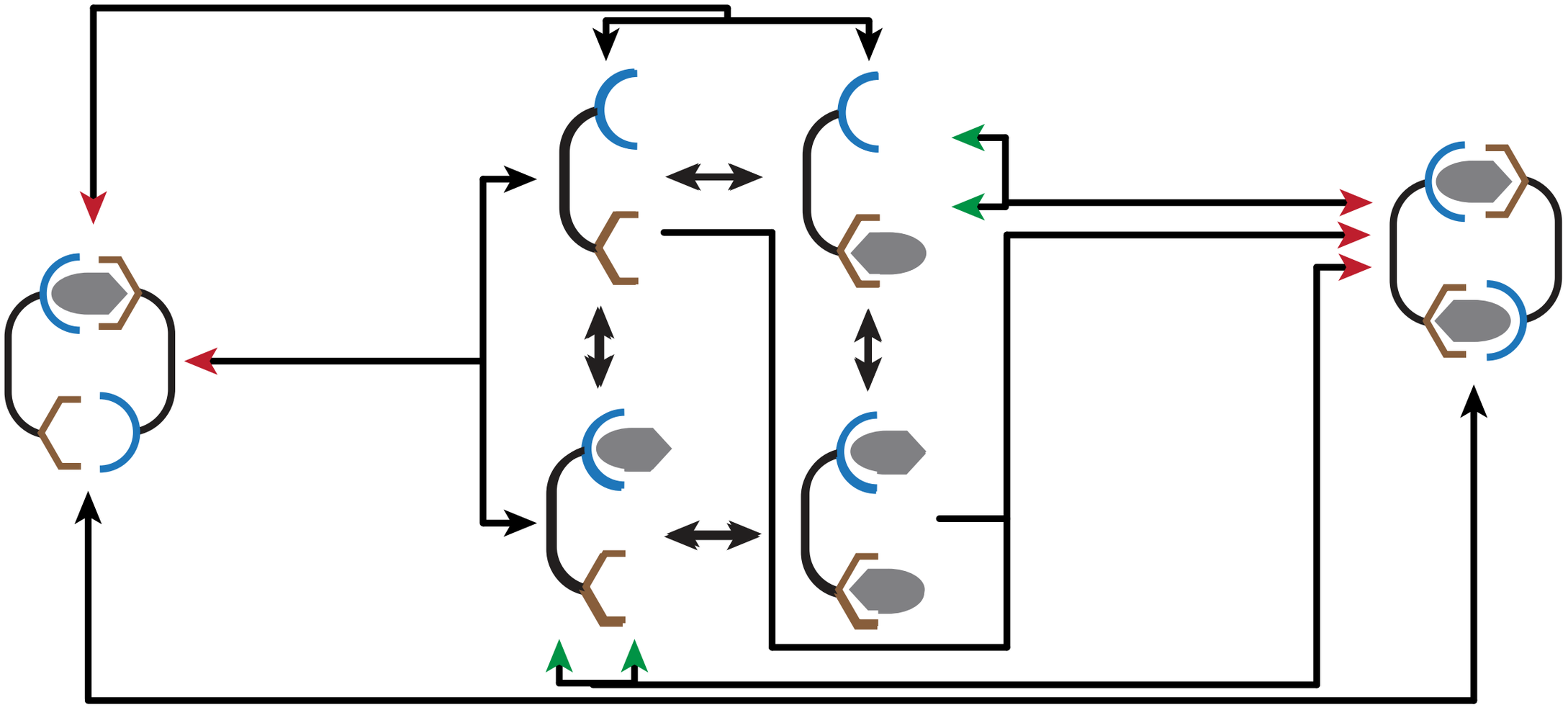

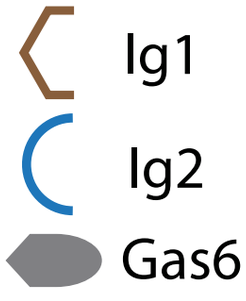

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Meyer *et al, Cell Sys*, 2015

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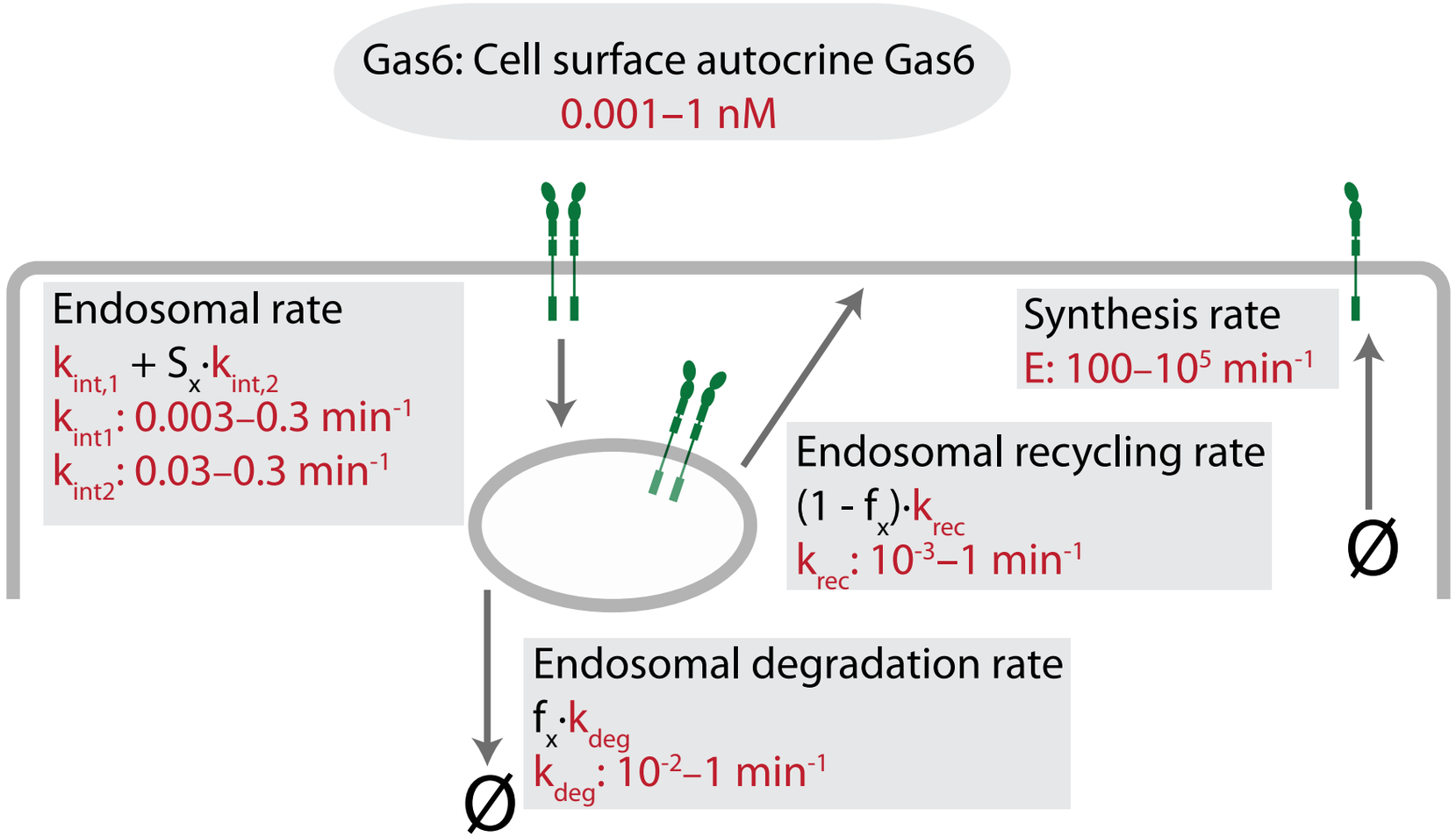
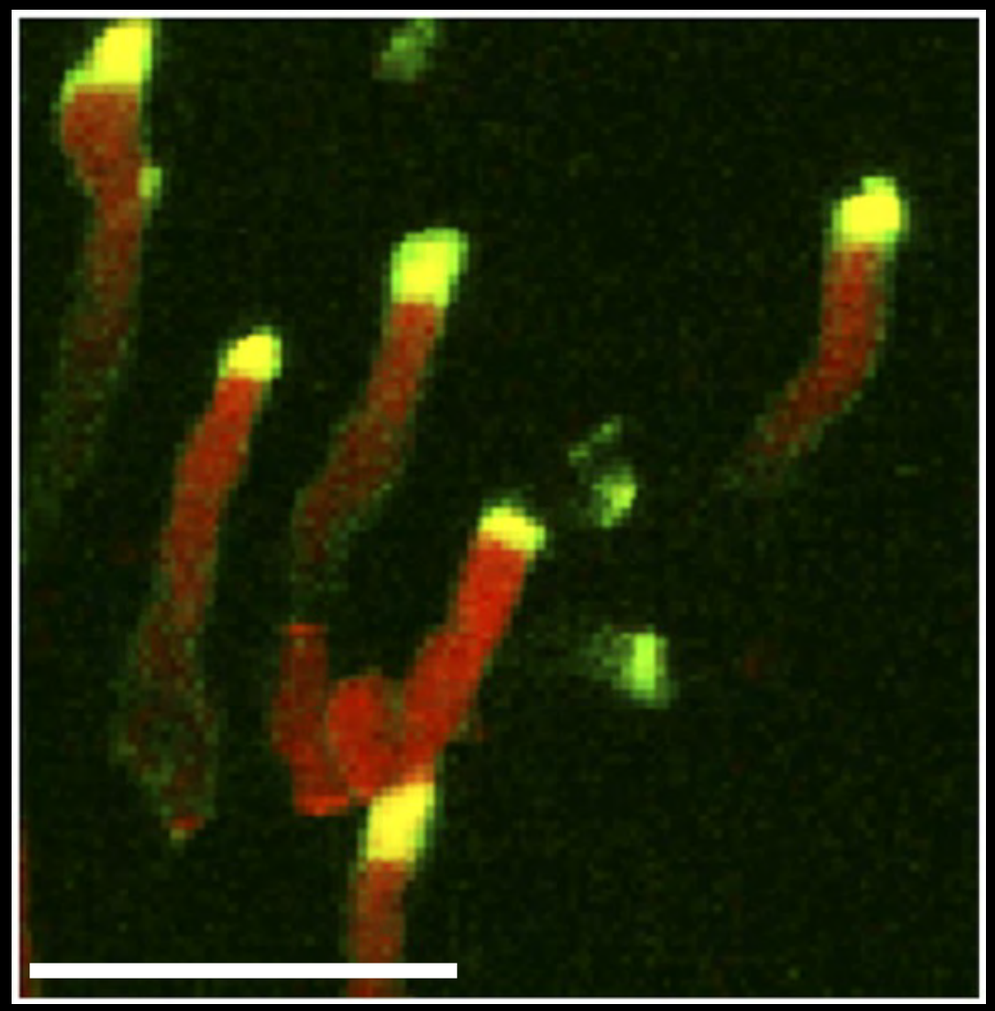


Fit
Assumed/defined
Detailed balance

Meyer *et al, Cell Sys*, 2015

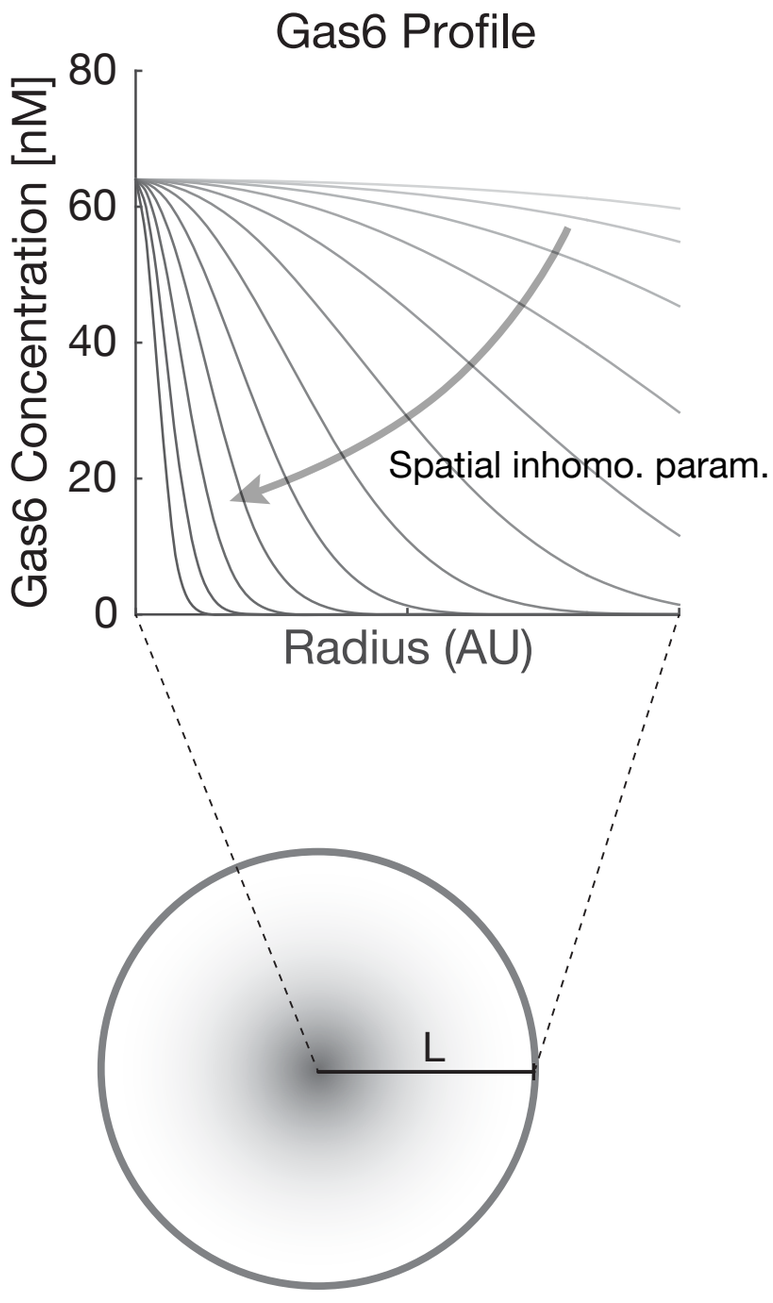
PtdSer exposure is a spatially localized process



Exposed PtdSer
Membrane

Ruggiero *et al*, 2012

A spatial model can test effect of ligand presentation



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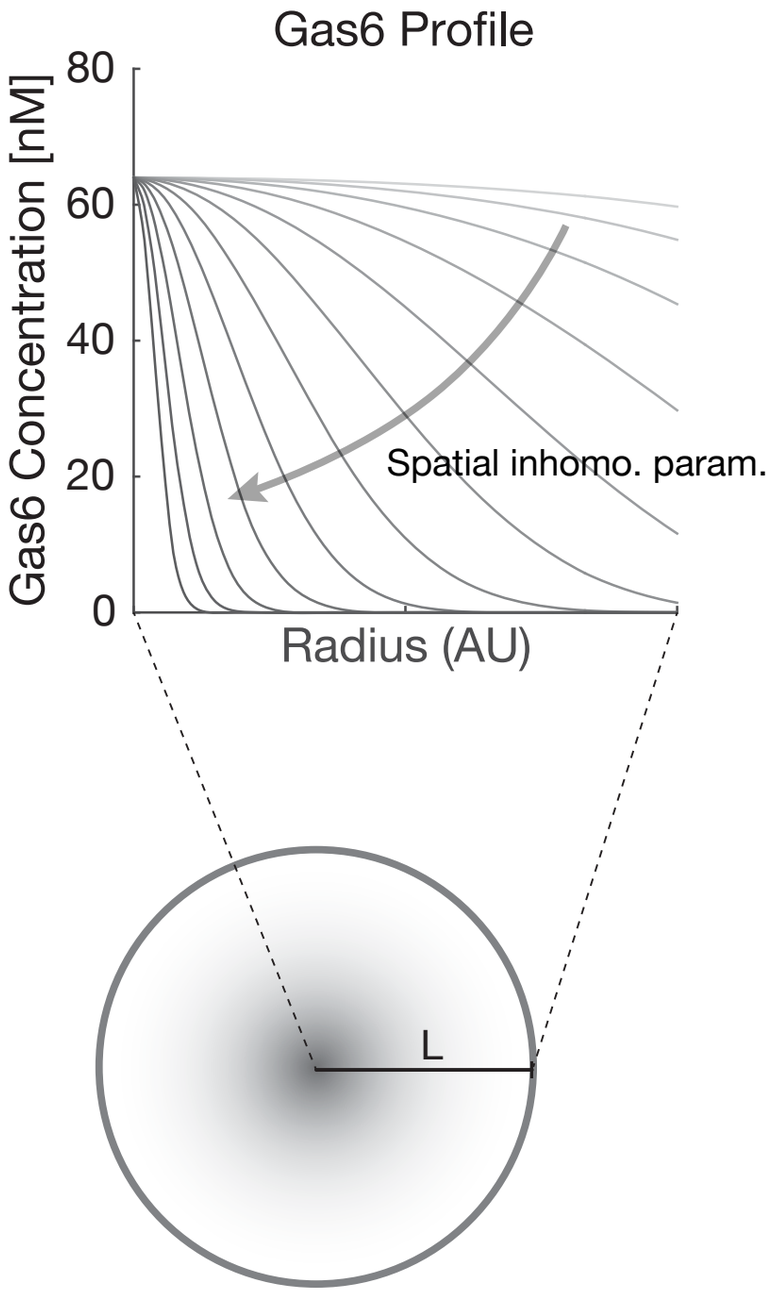
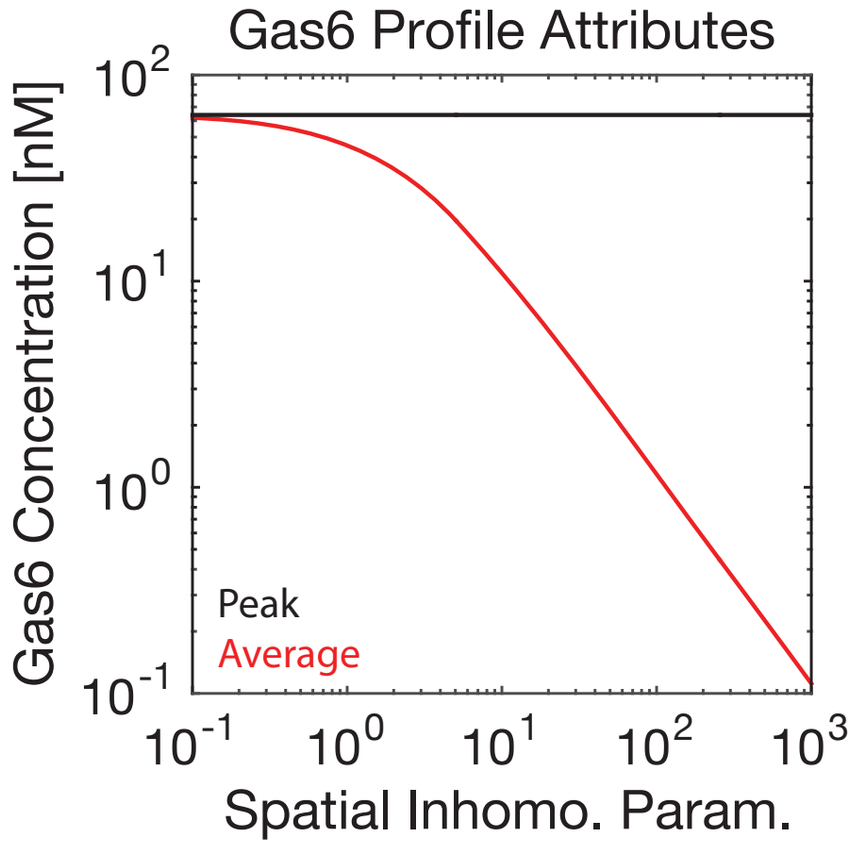
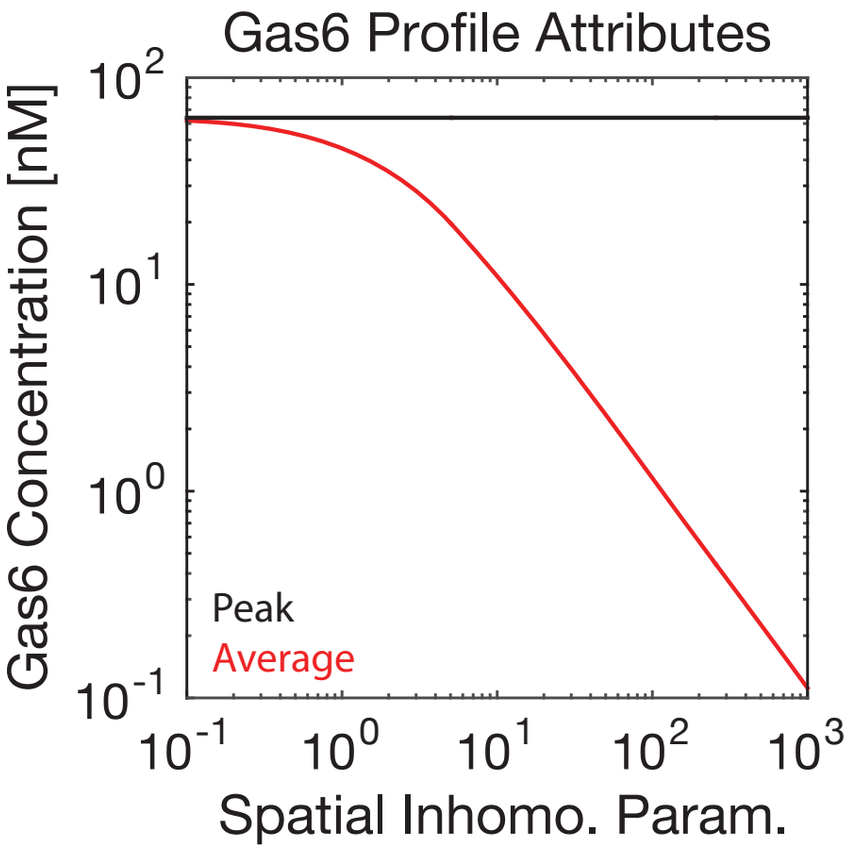




Meyer *et al, Cell Sys*, 2015

Local stimulation results in greater overall AXL signaling



Uniform Gas6

PS-clustered Gas6

Meyer *et al, Cell Sys*, 2015

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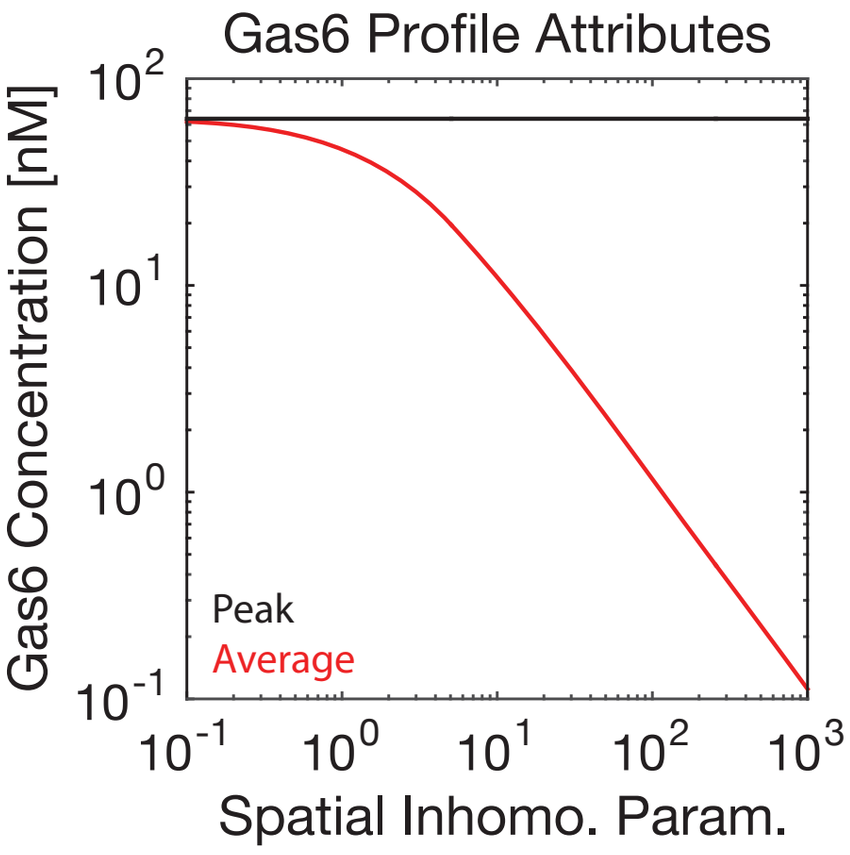

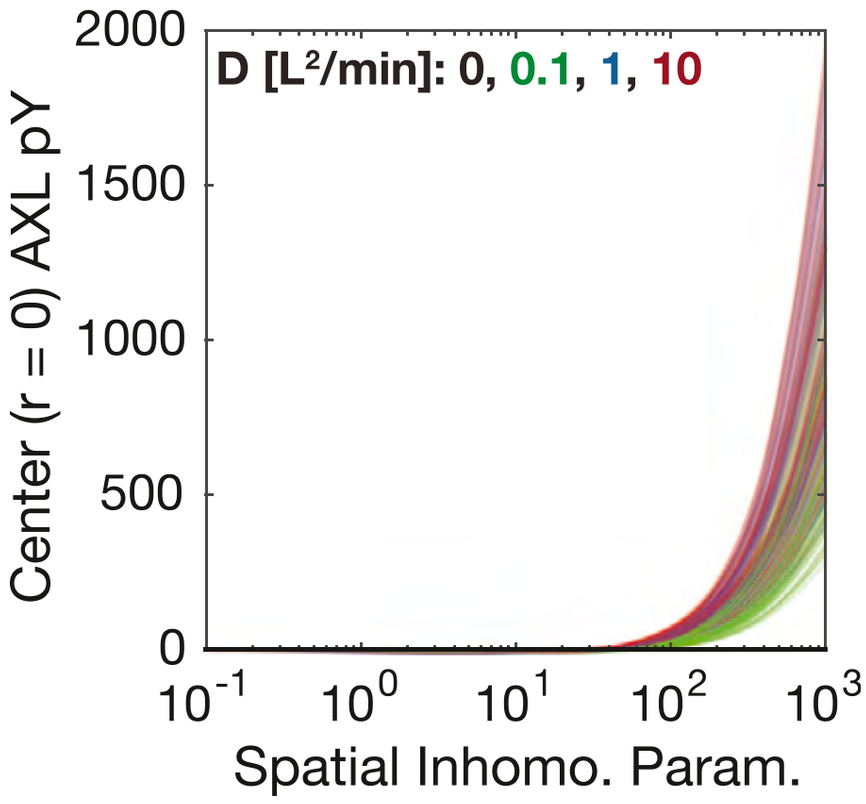

Uniform Gas6

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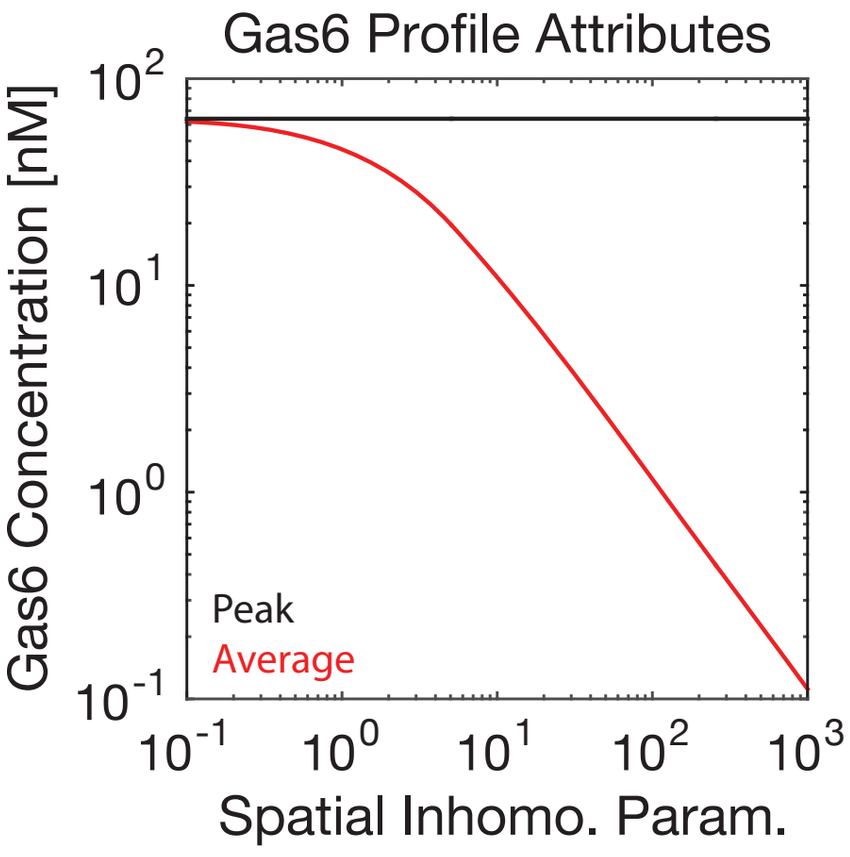
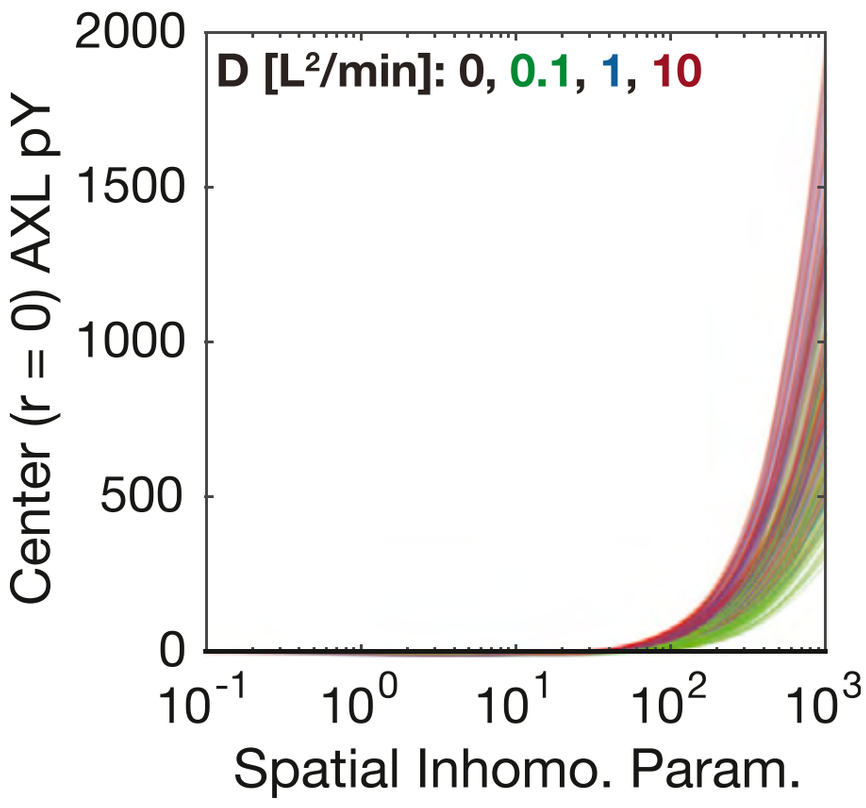
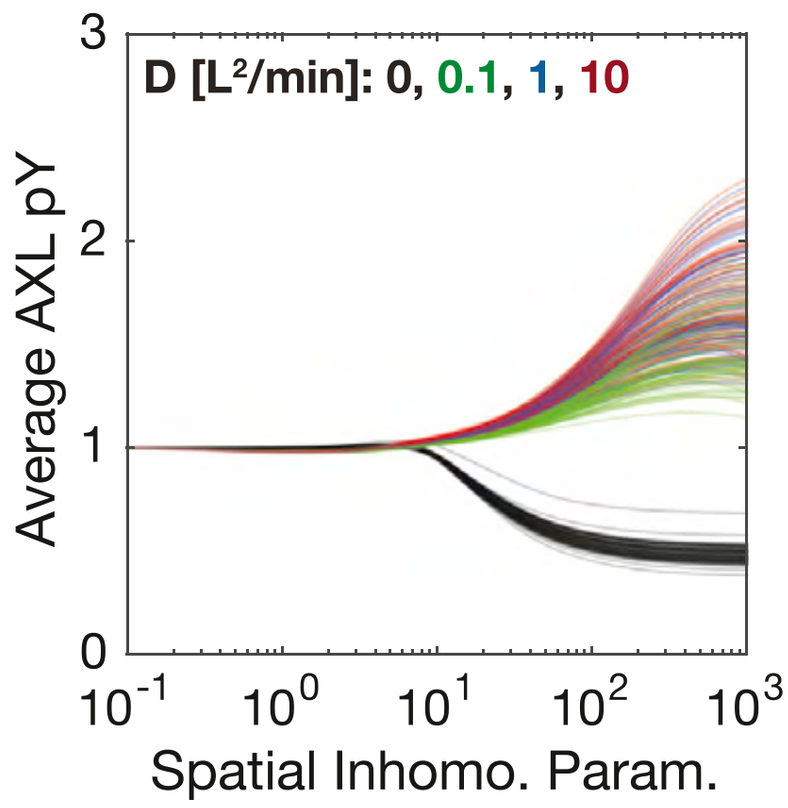


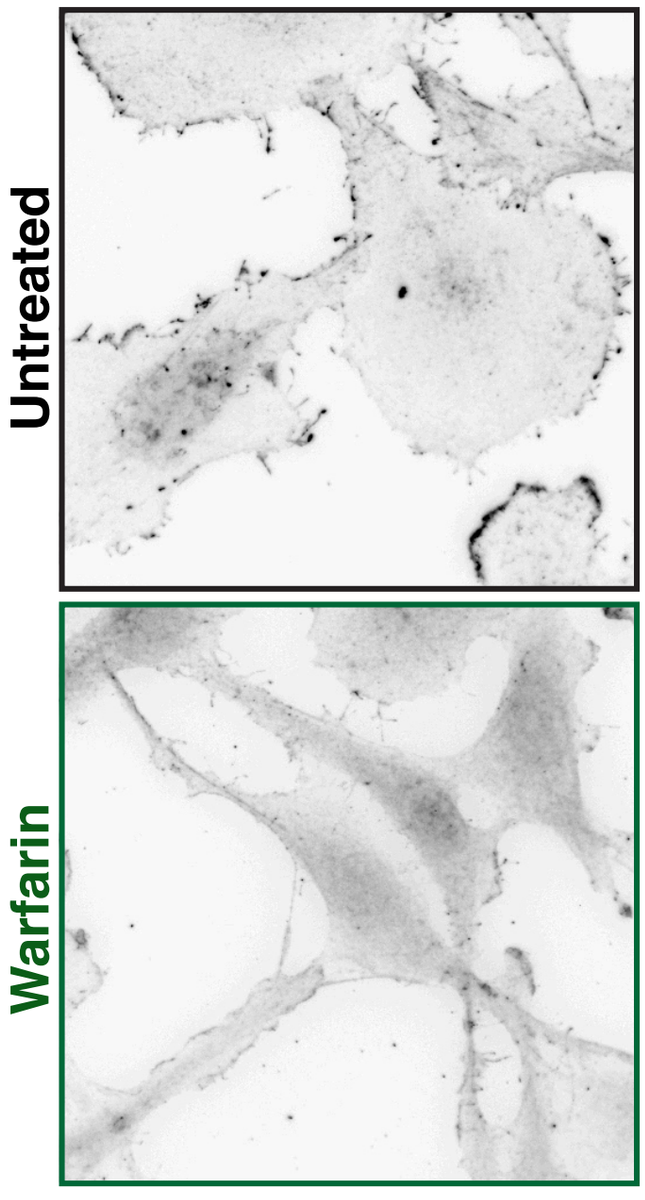




Uniform Gas6 ← → PS-clustered Gas6

Meyer *et al, Cell Sys*, 2015

Relocalization of AXL promotes autocrine activation



BT-549

Meyer *et al, Cell Sys*, 2015

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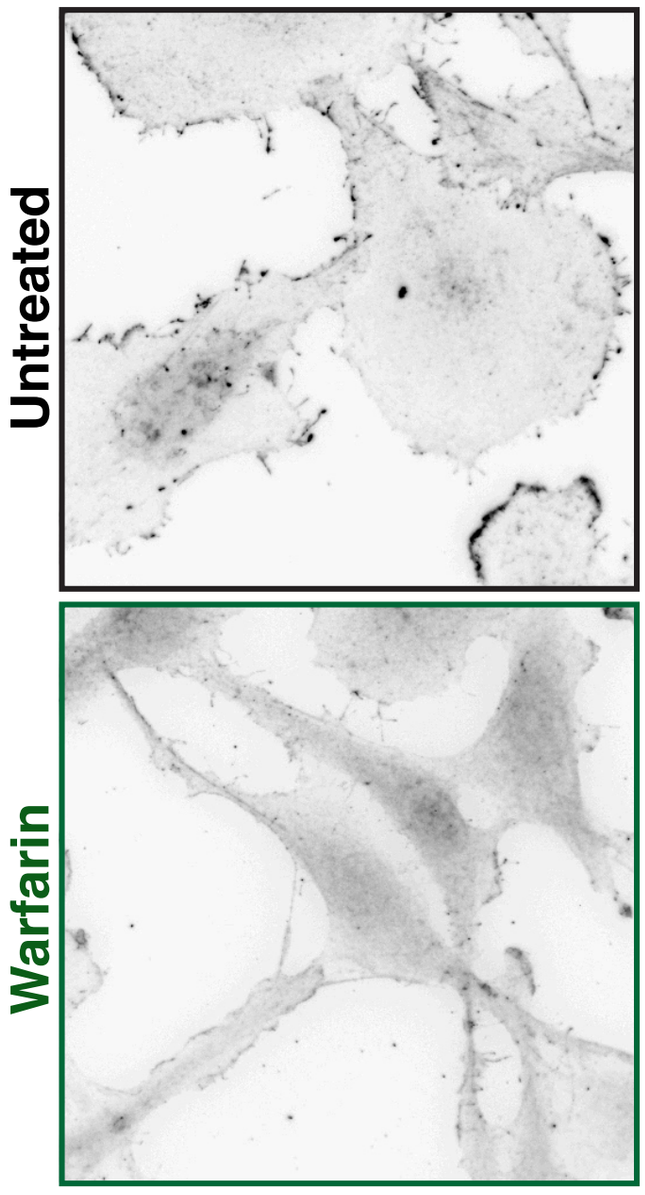

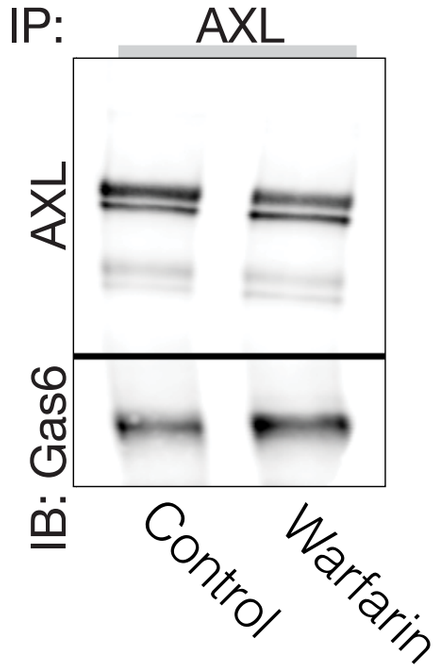

BT-549

Meyer *et al, Cell Sys*, 2015

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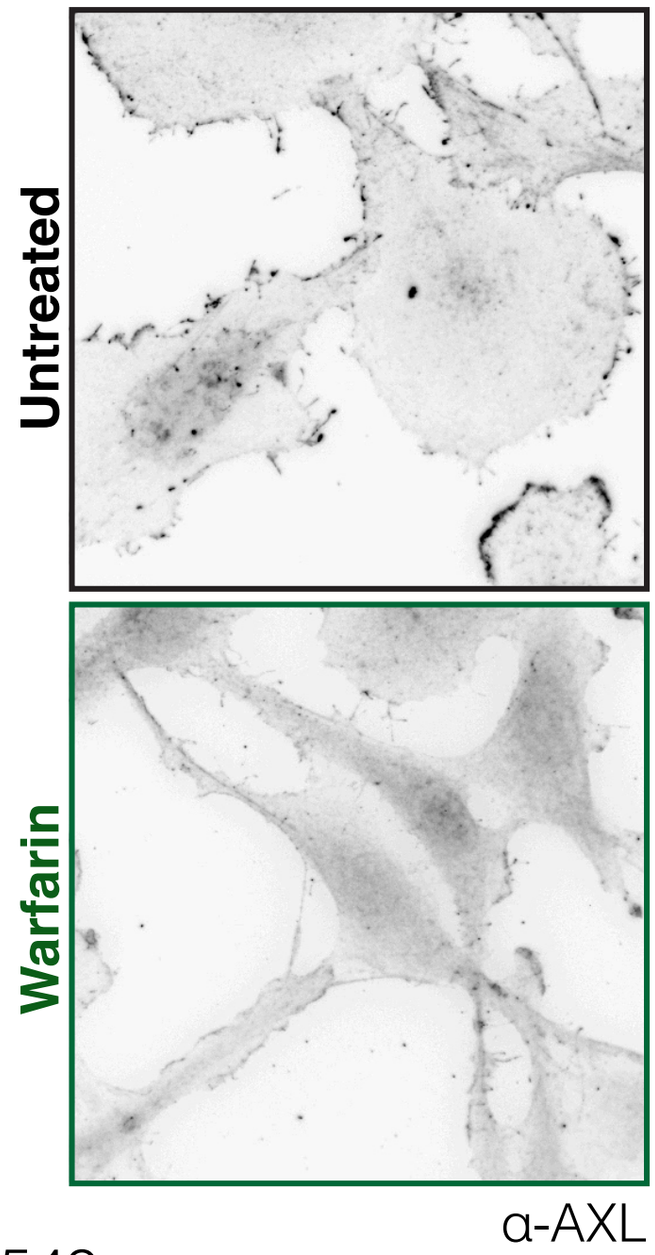

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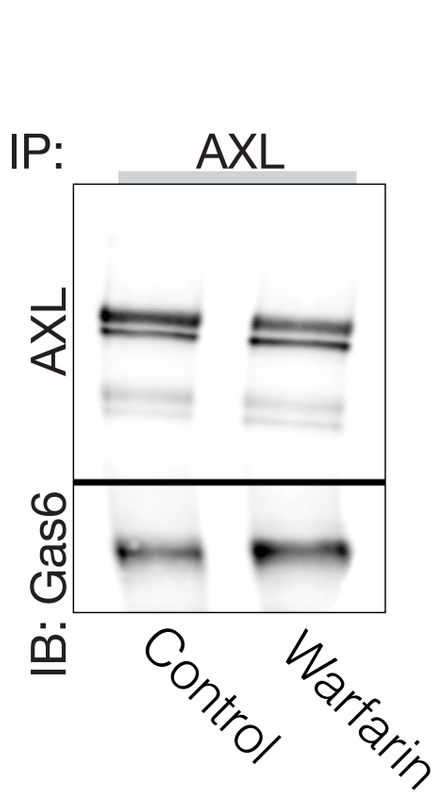
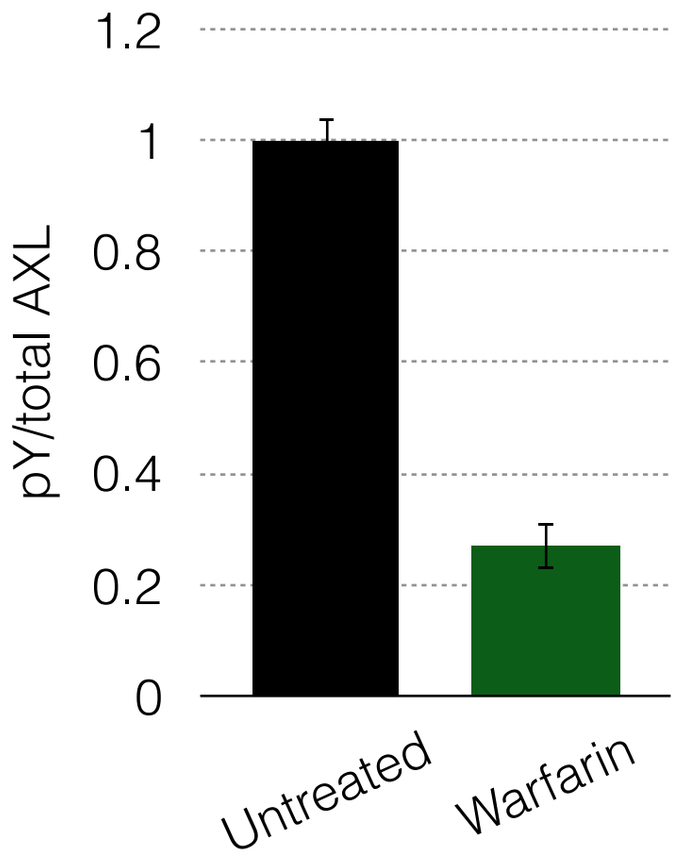
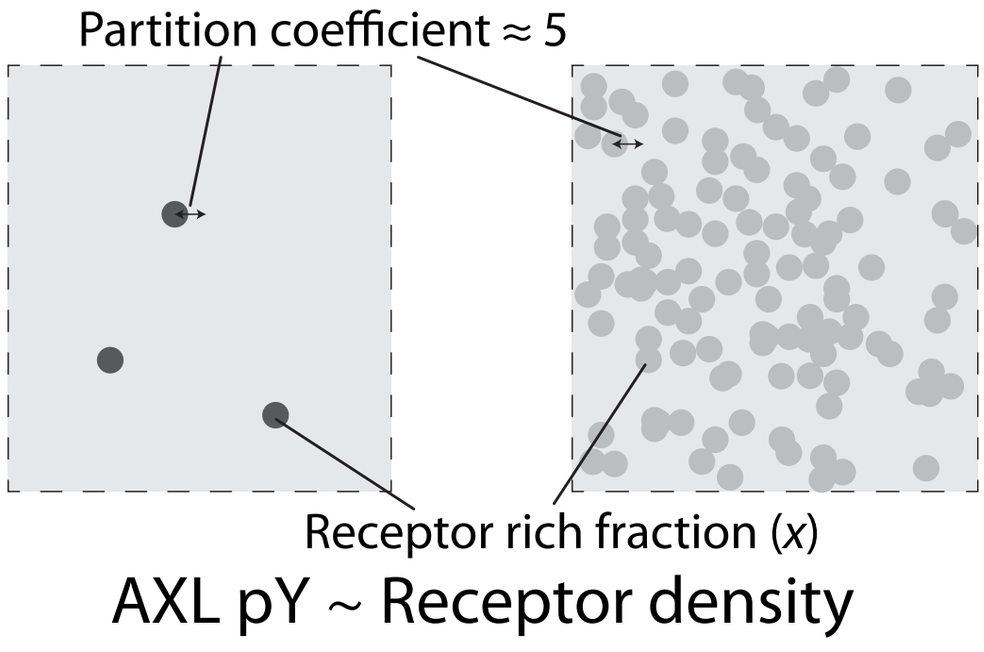




Meyer *et al, Cell Sys*, 2015

Biphasic response to PtdSer emphasizes the importance of localization



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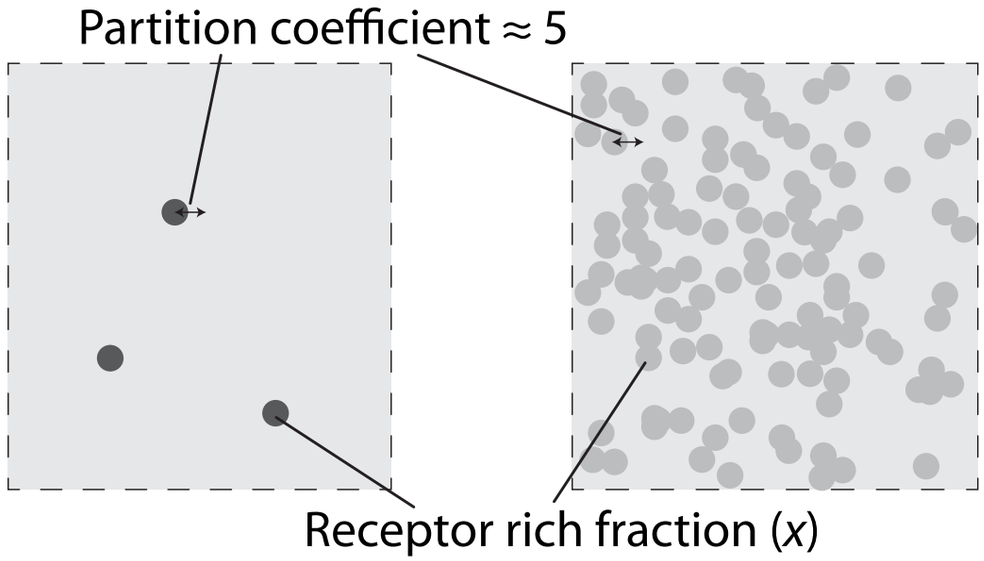
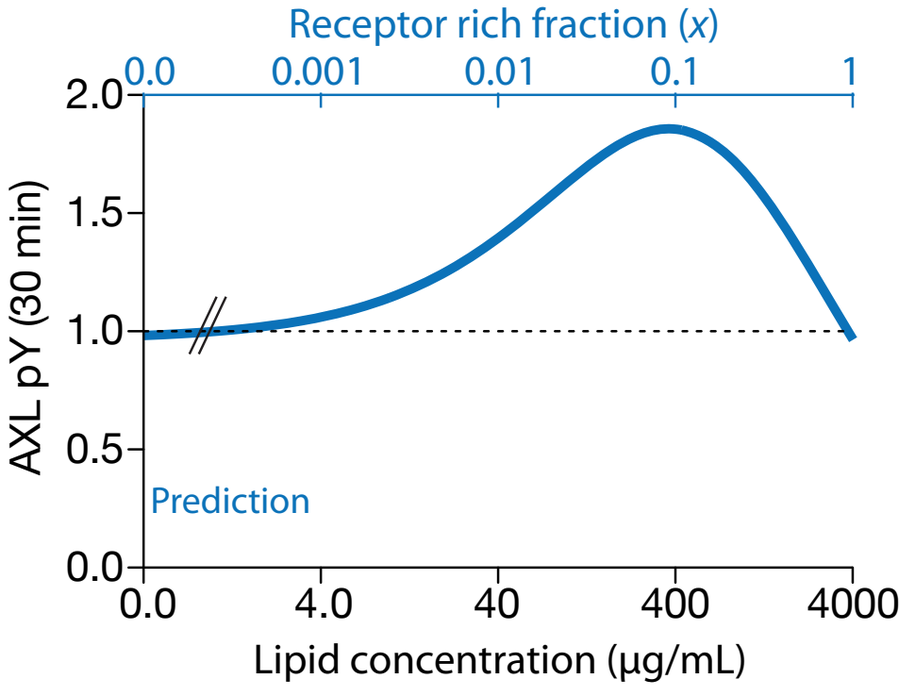


AXL pY ~ Receptor density



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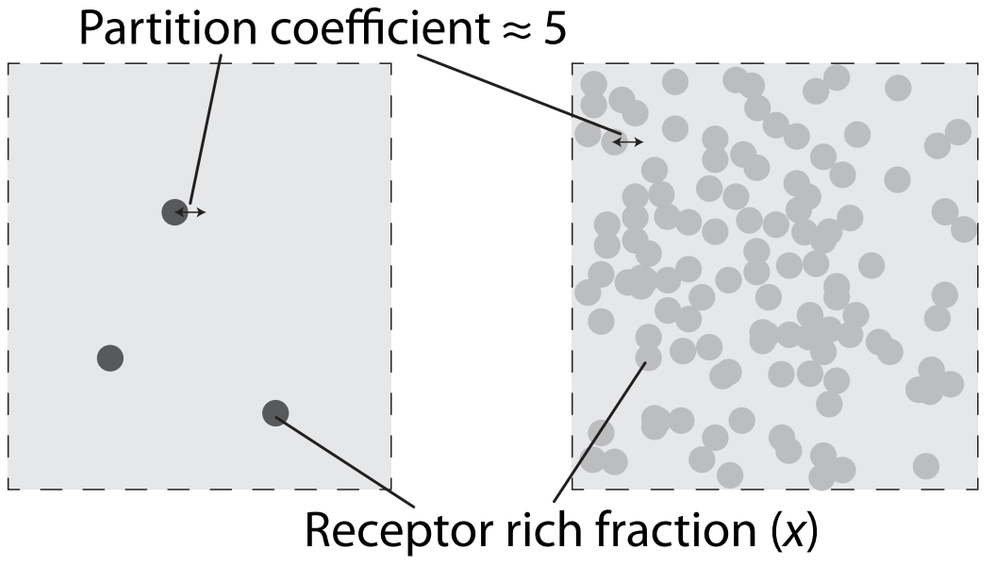

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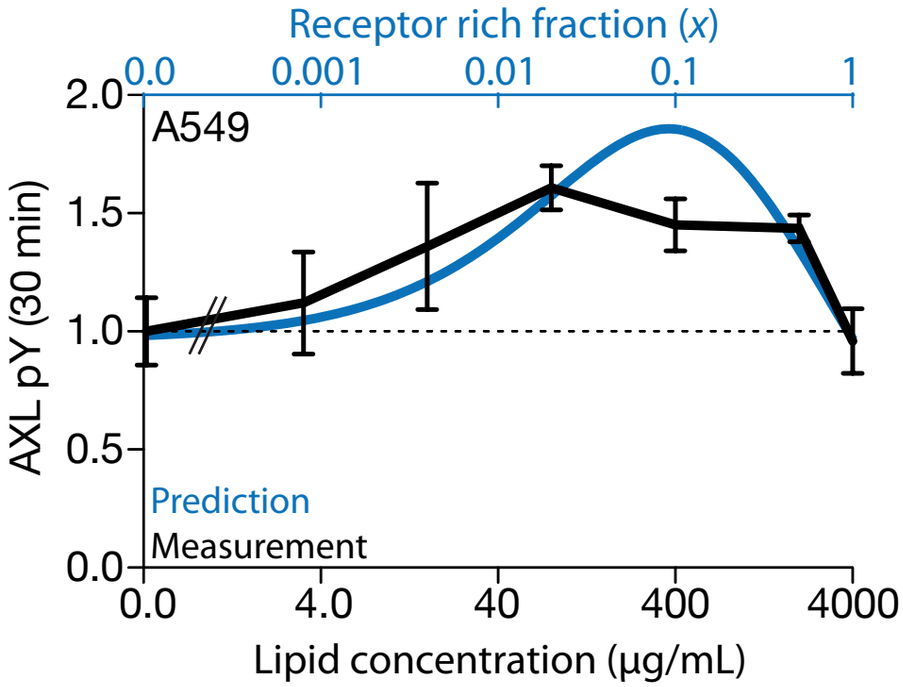

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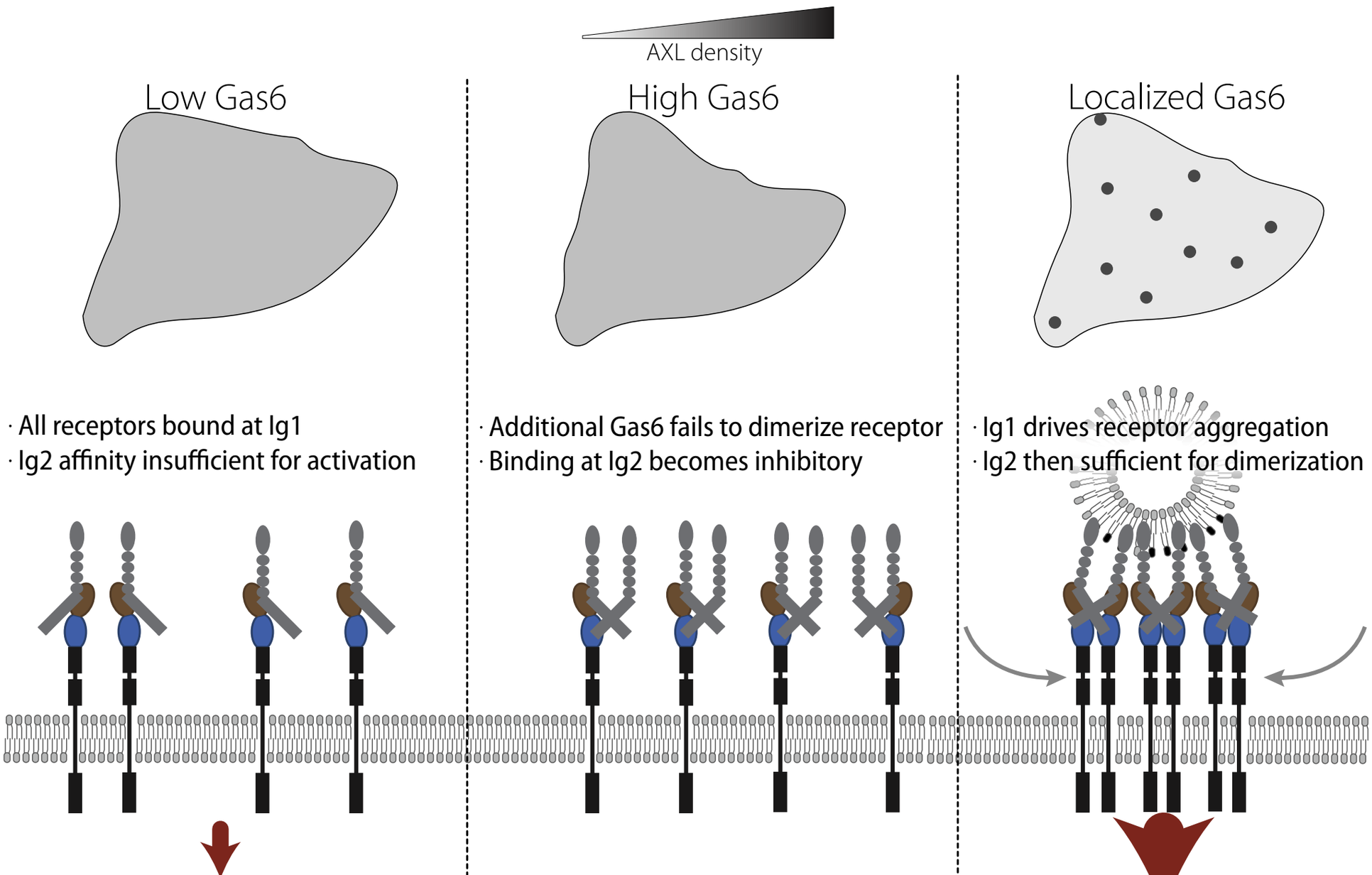
Meyer *et al, Cell Sys*, 2015

TAM receptor spatial sensing arises from ligand binding asymmetry



Meyer *et al, Cell Sys*, 2015

Expanding to all three TAMRs: combinatorial complexity makes modeling essential

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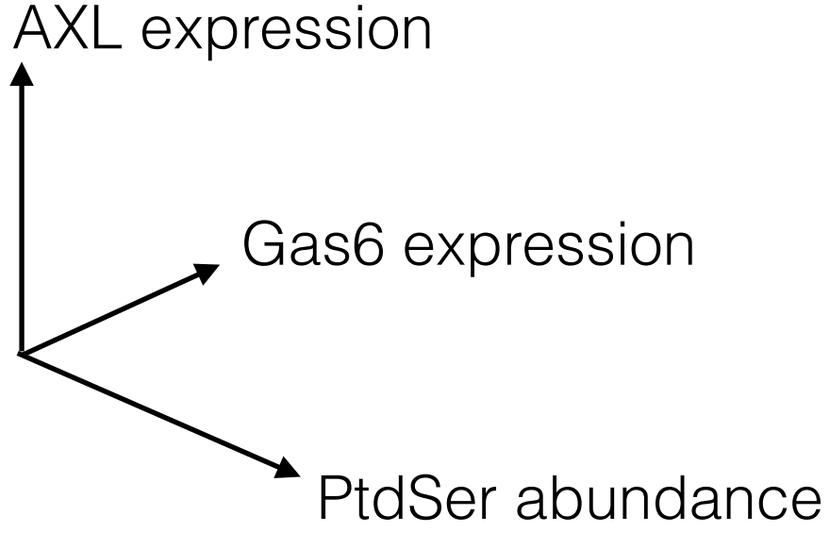
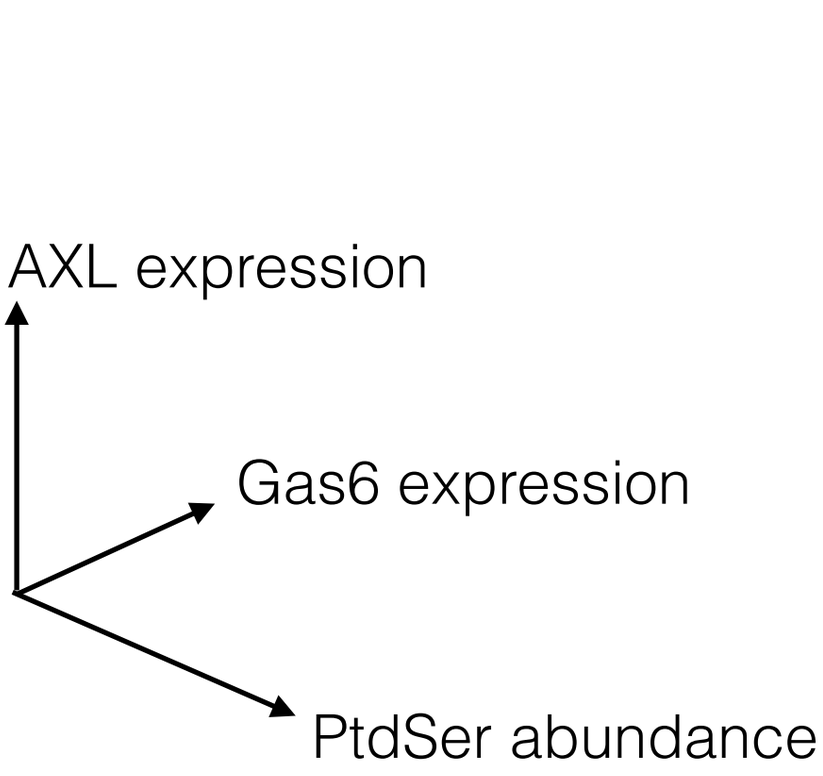


64 responses

Assuming 4 levels of each quantity

Expanding to all three TAMRs: combinatorial complexity makes modeling essential



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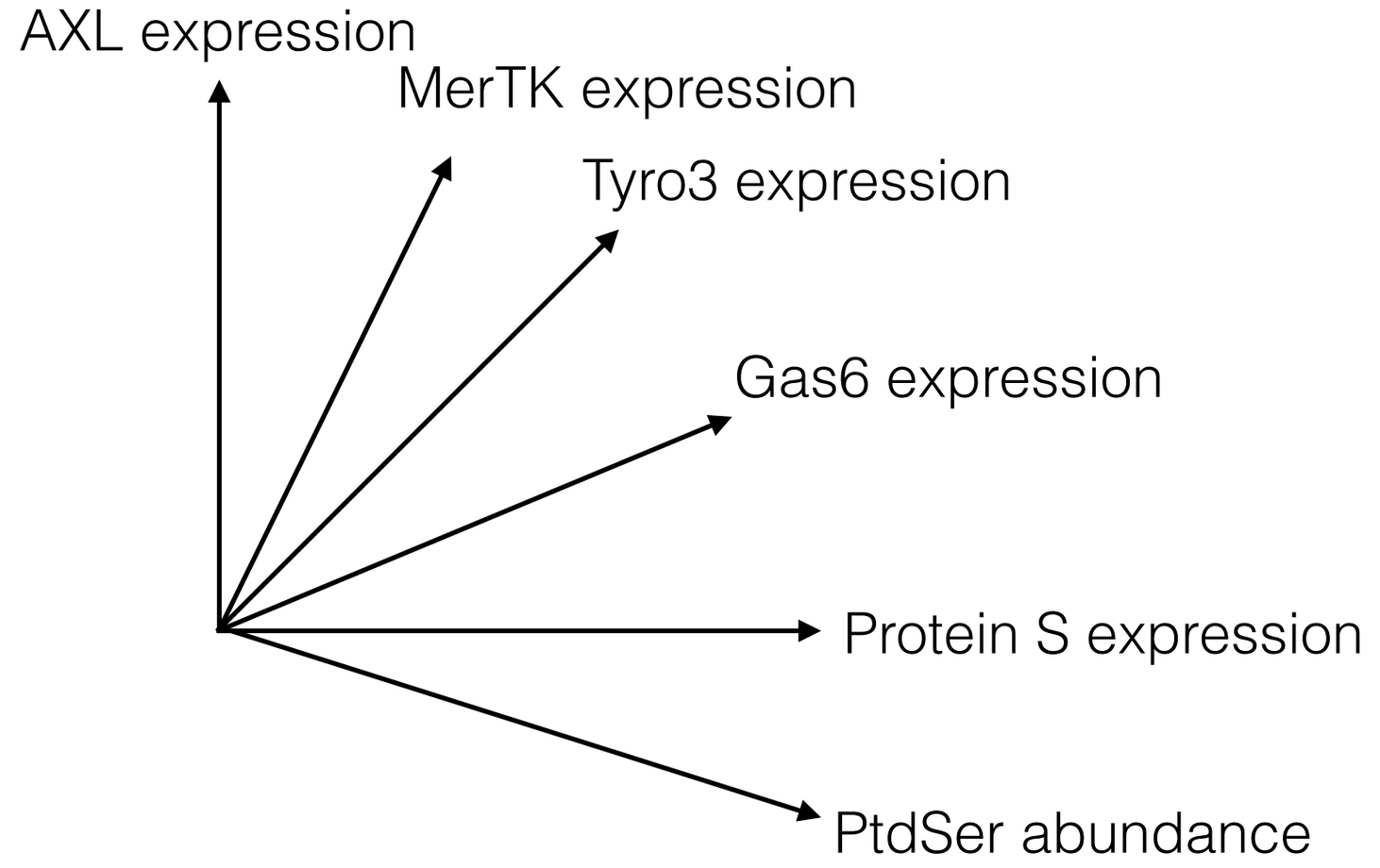
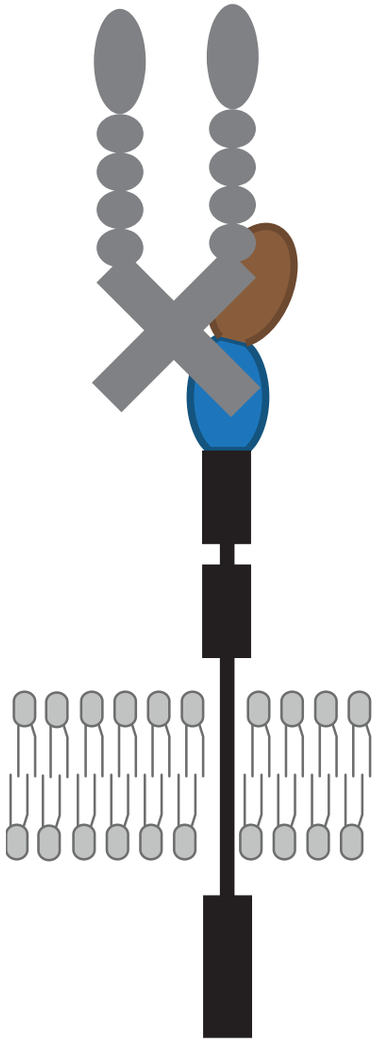


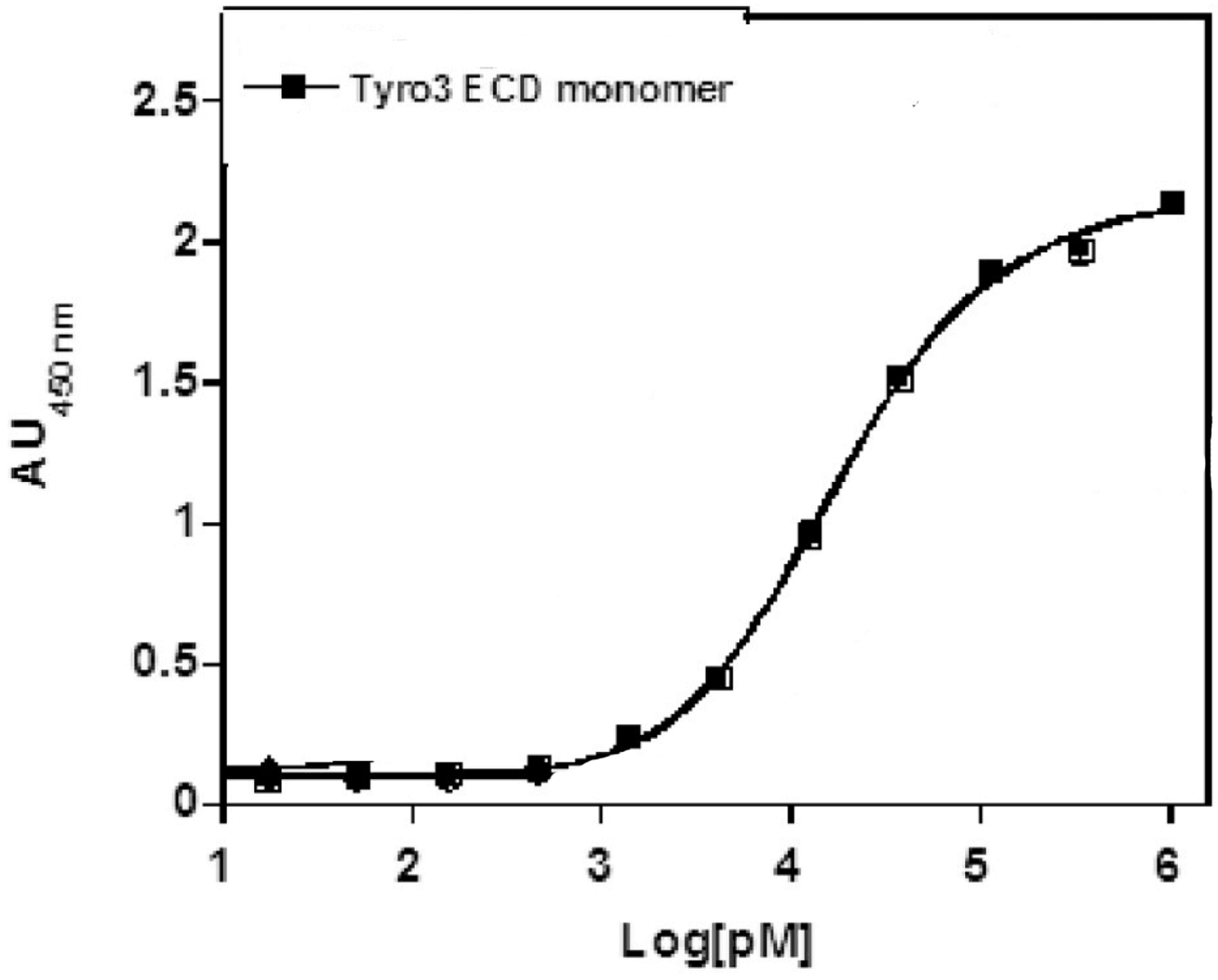
4,096 responses

Assuming 4 levels of each quantity

Measuring TAM binding kinetics

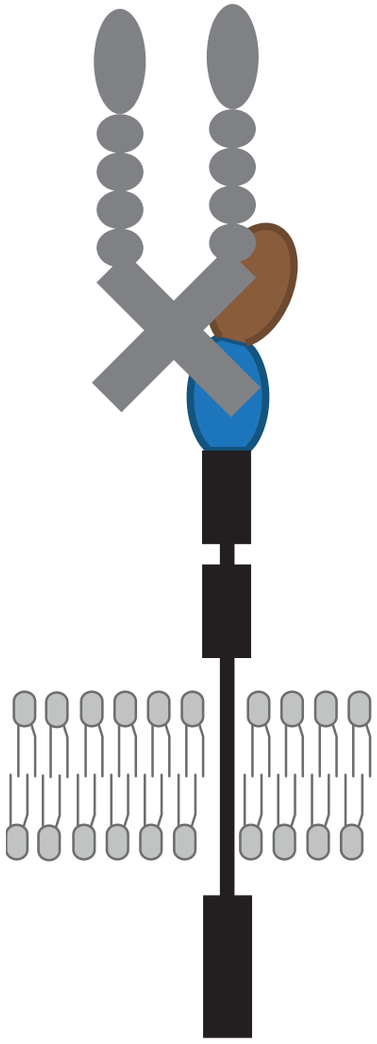
TAM receptor-ligand affinities have been measured before

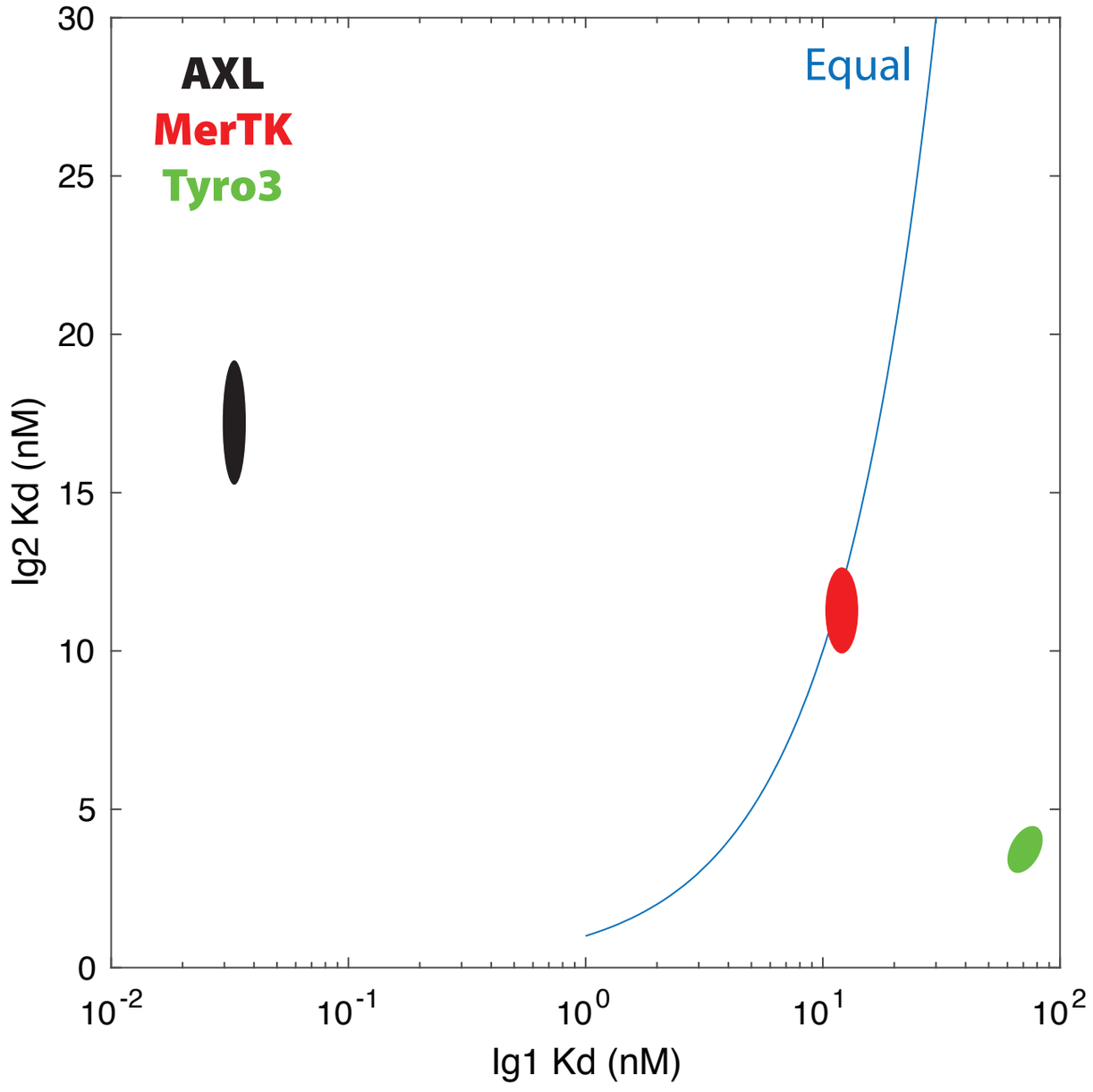




Demarest et al., 2013

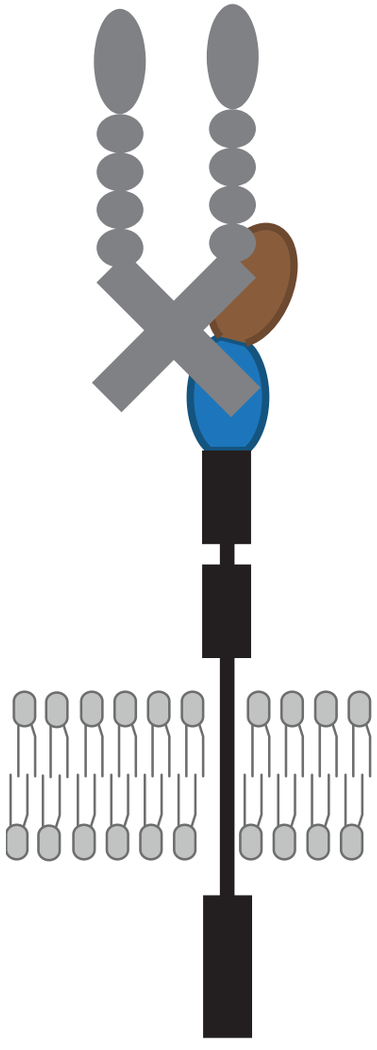
Separating the TAM Ig affinities reveals diverse binding models

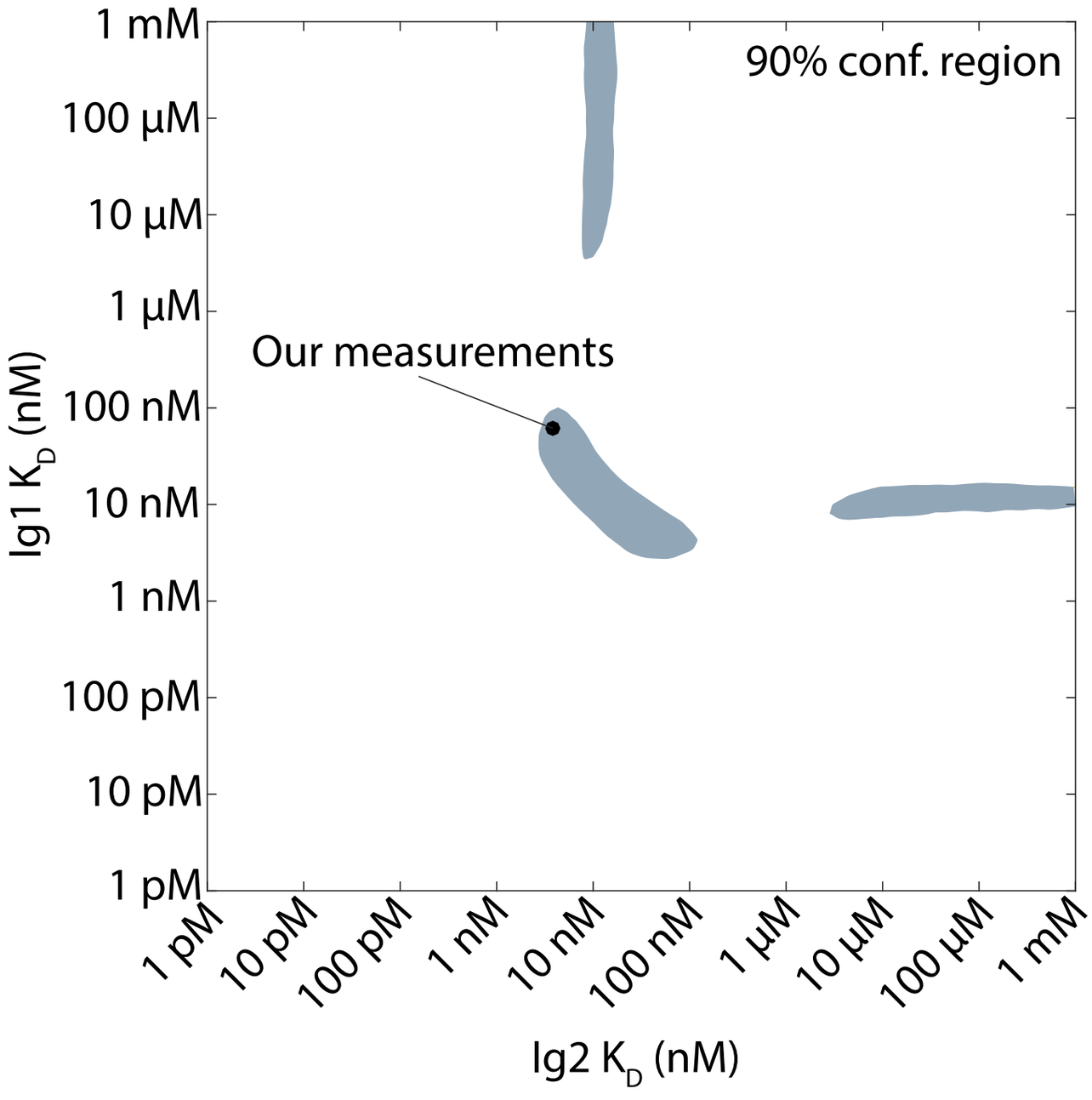




Richards & Meyer, *In prep.*

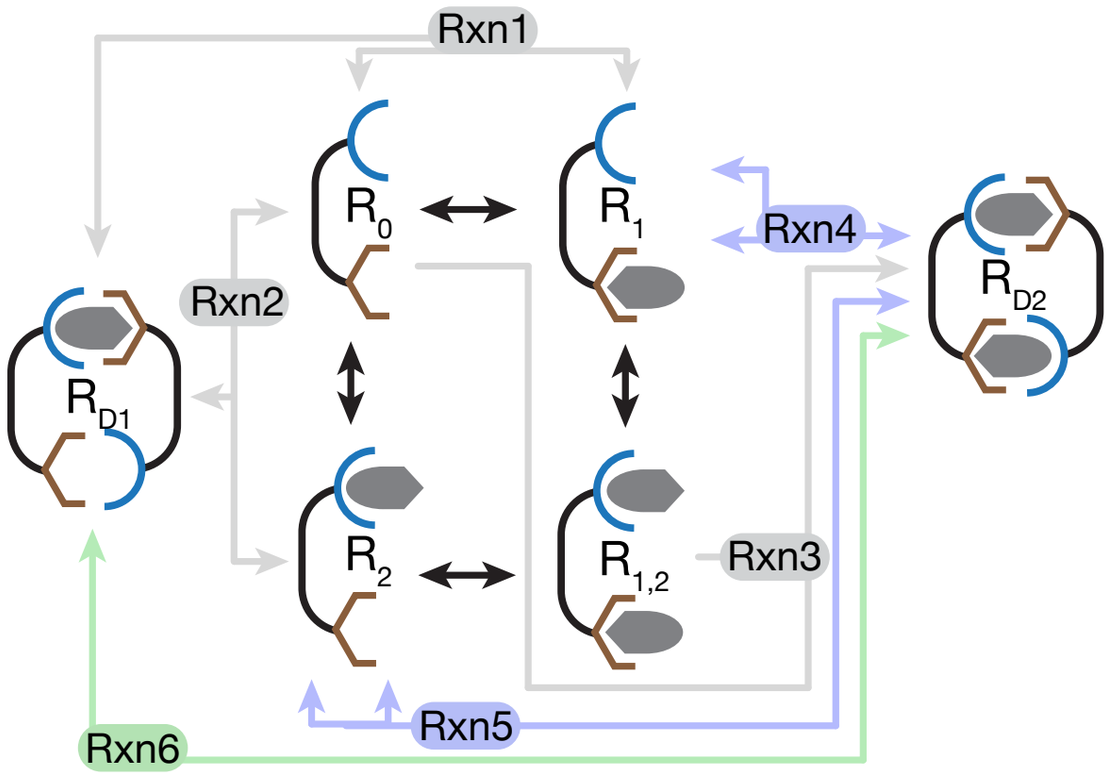
Individual Tyro3 affinities are consistent with overall receptor binding





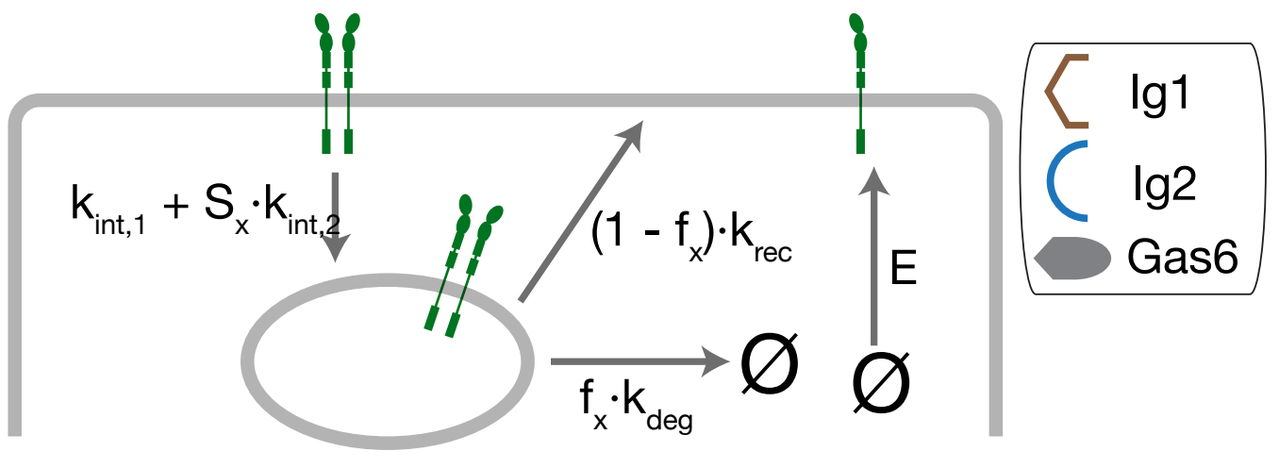
Richards & Meyer, *In prep.*

Model for all three receptors and one ligand



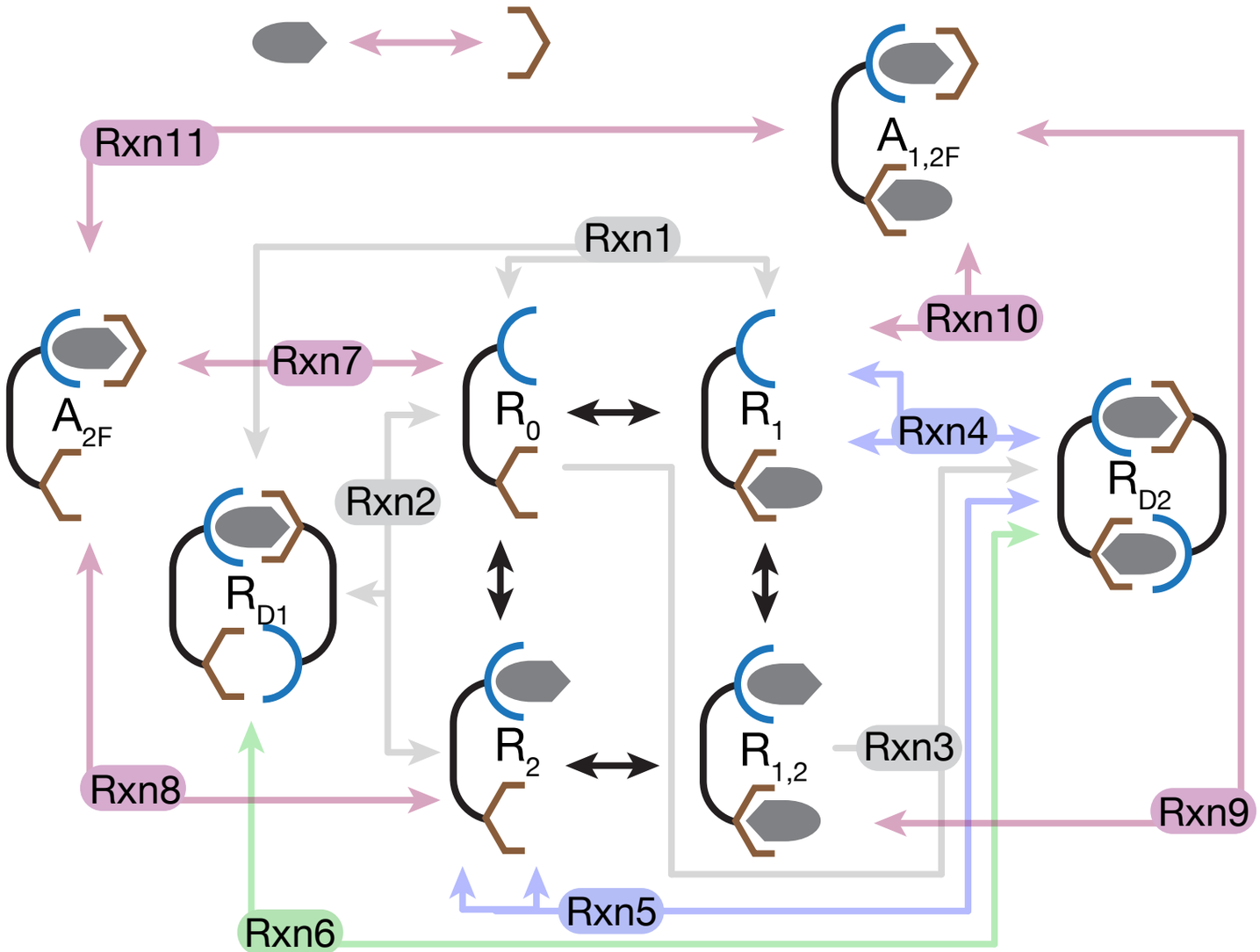
Every pairwise heterodimerization partner included

No additional parametric uncertainty due to detailed balance



Richards & Meyer, *In prep.*

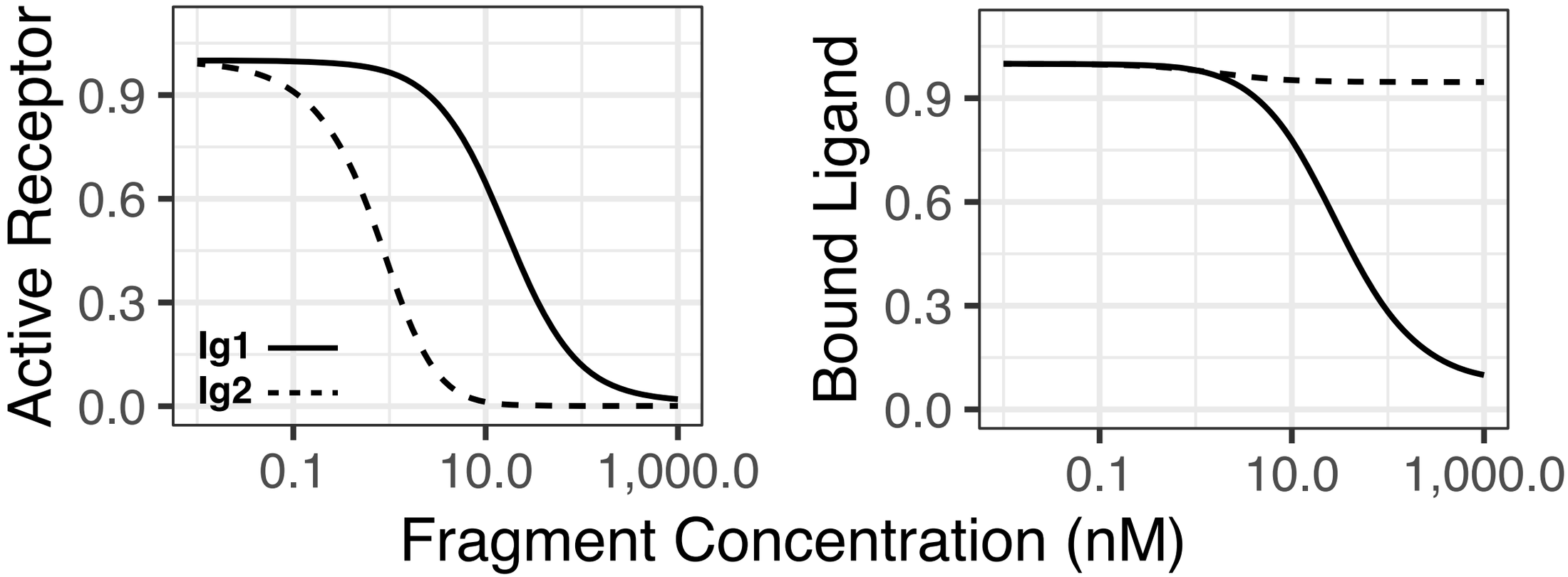
Model for receptor decoy fragments provides specific predictions for inhibition specificity



Assume ligand in solution becomes bound with receptor fragment to equilibrium

Richards & Meyer, *In prep.*

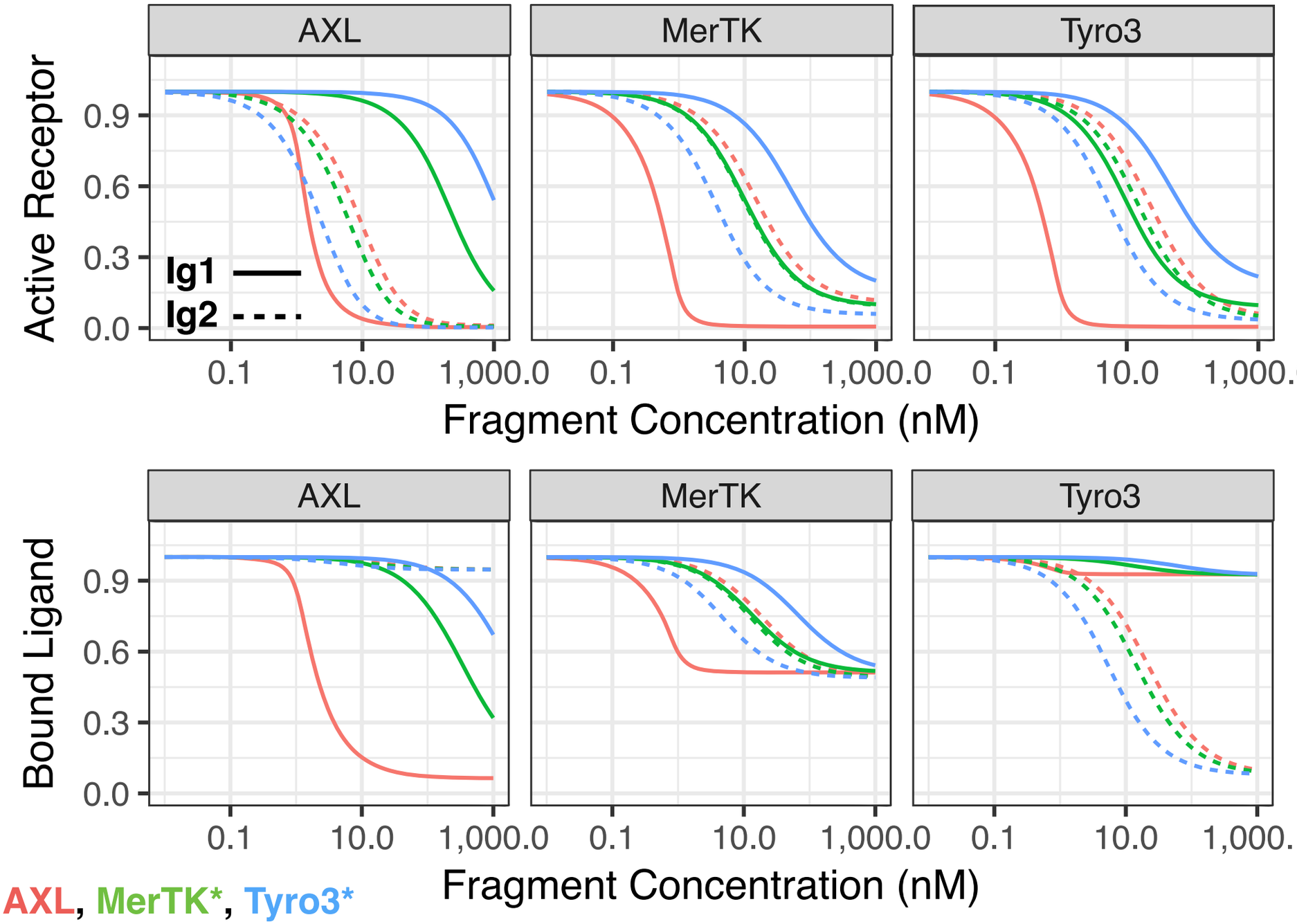
Target binding site influences the effect of competitive ligand inhibitors



1 nM Gas6, high AXL expression

Richards & Meyer, *In prep.*

TAM Ig fragments can be used as a tool for probing the *in vivo* environment

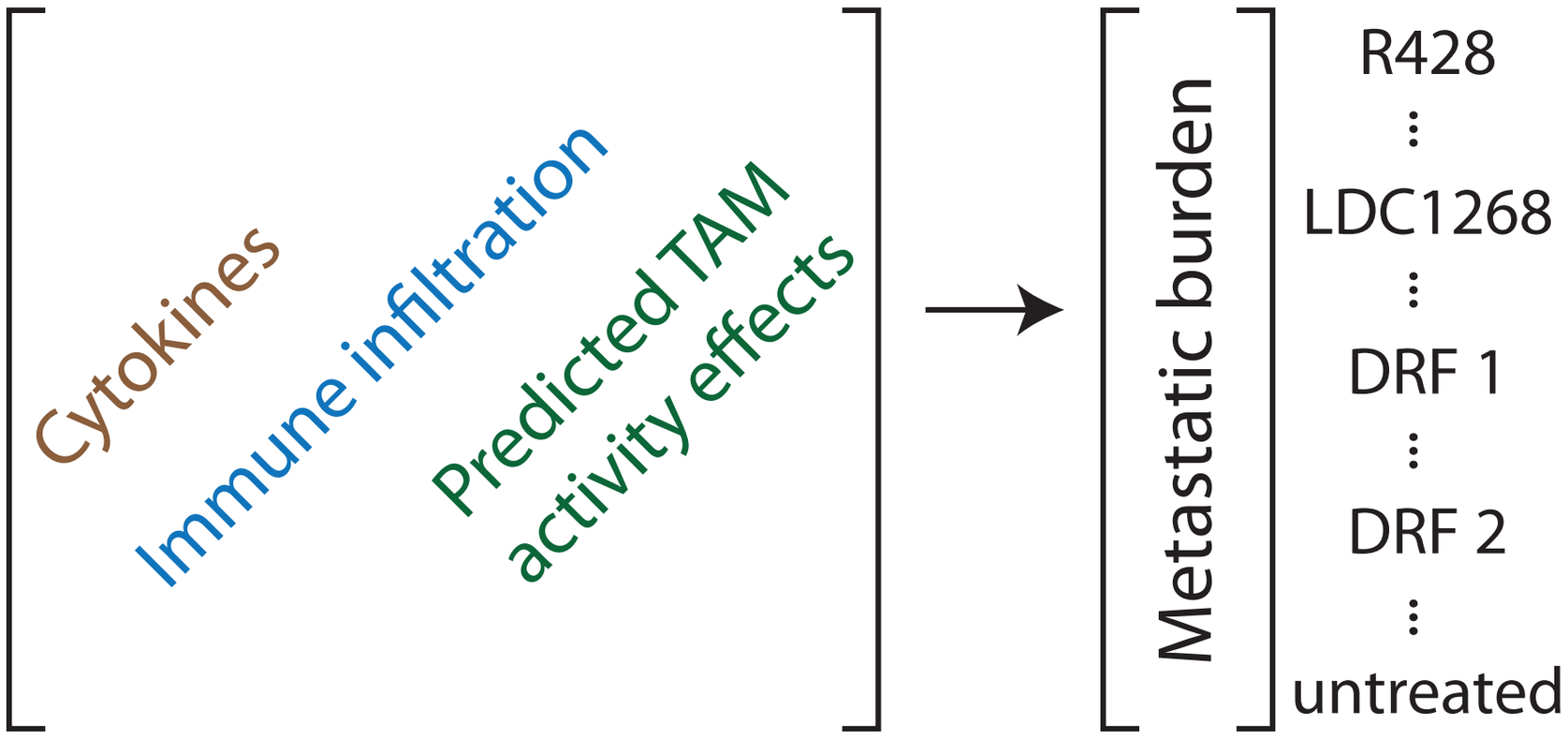


Fragments: **AXL**, **MerTK***, **Tyro3***

*Should also have activity against ProS

Richards & Meyer, *In prep.*

Future plan: Use combinations of targeted TAM therapies to deconvolve their *in vivo* role



Richards & Meyer, *In prep.*

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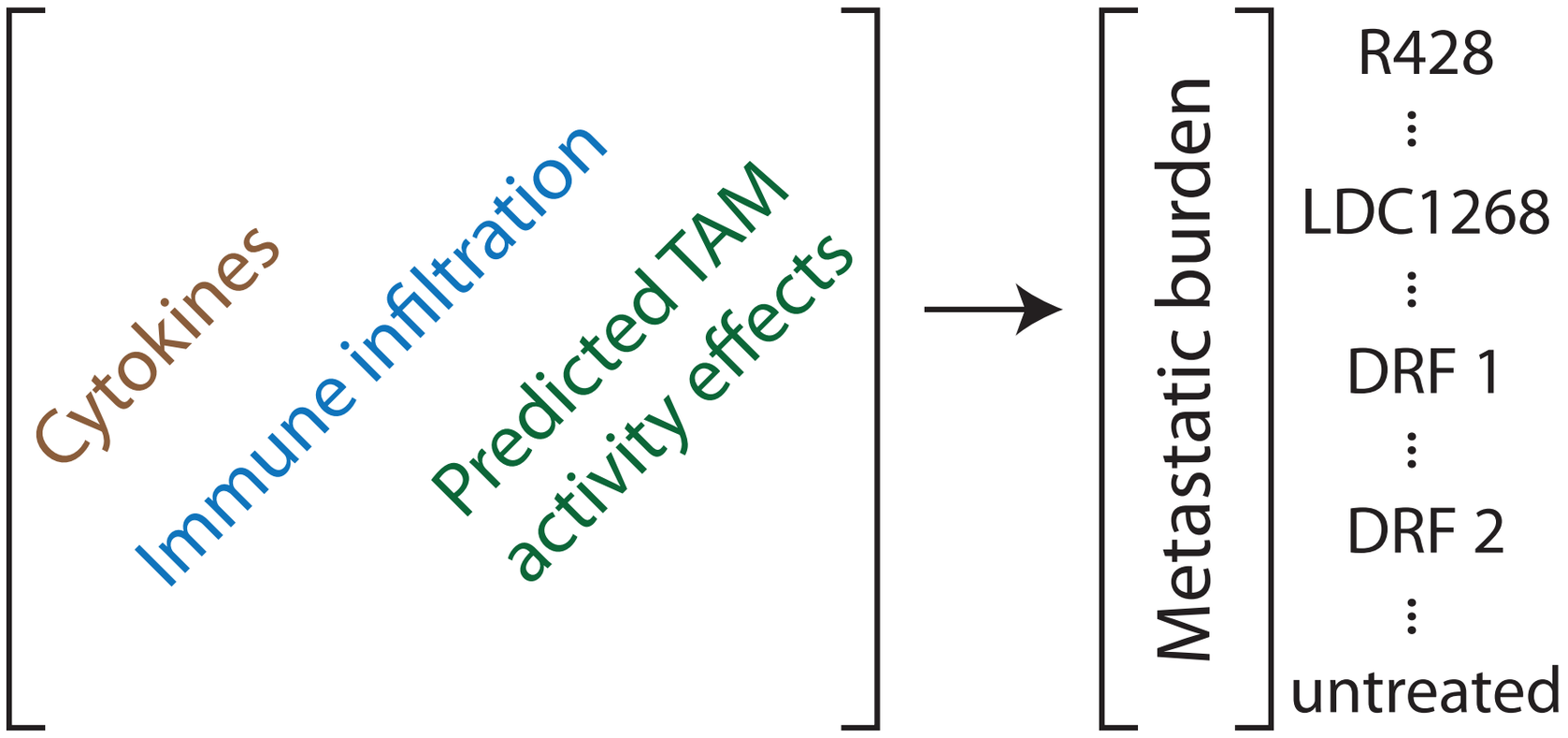


Ted Richards

Terri Brodeur Breast Cancer Foundation

Richards & Meyer, *In prep.*

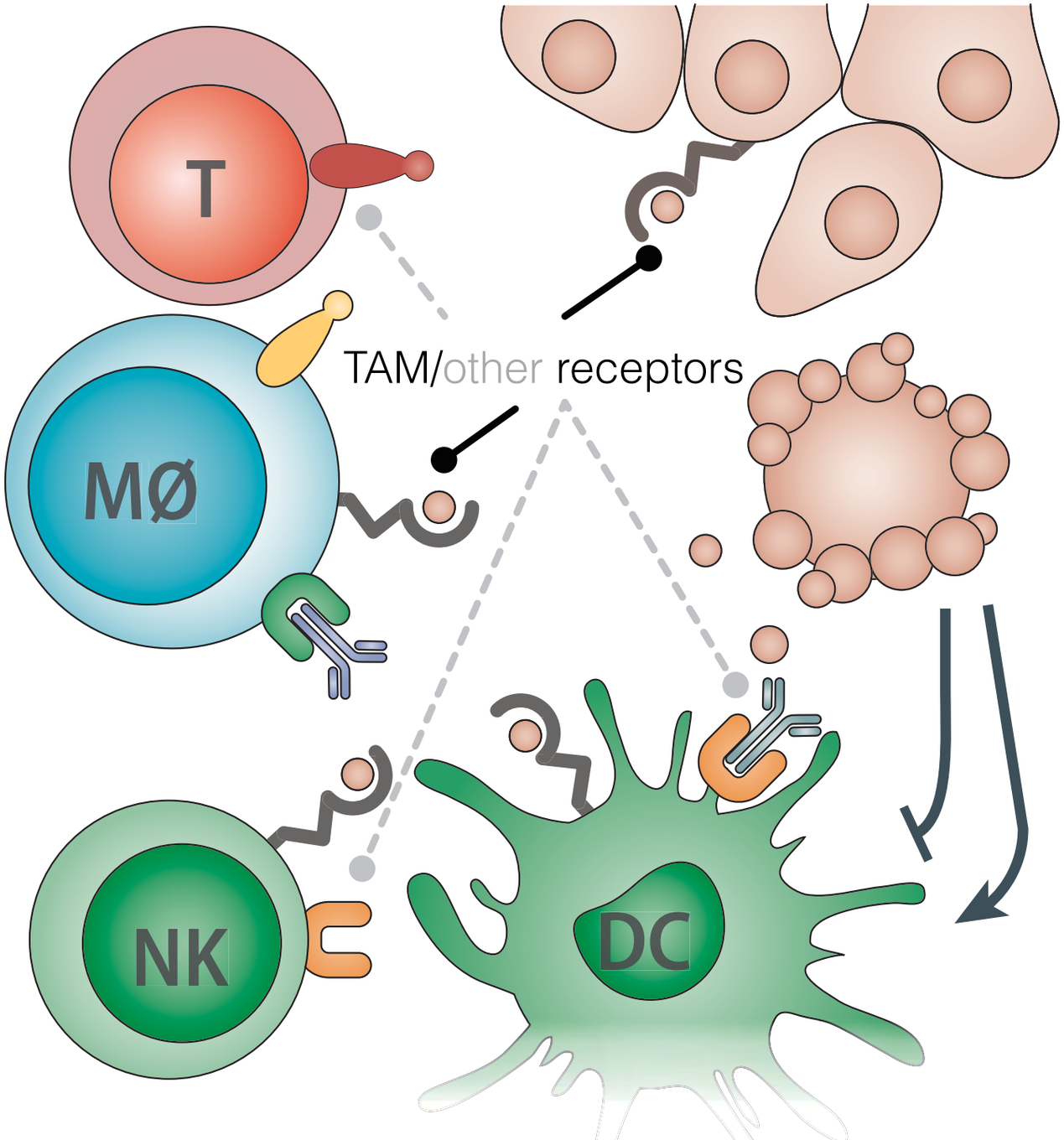
Conclusions

- Each TAM shows striking diversity in its Ig domain affinities

- Ig-specific targeting can decouple ligand binding and activation

- Enormous complexity can underlie activation of even just a single, small receptor-ligand family

Systems approaches for rationally designing innate immune therapies



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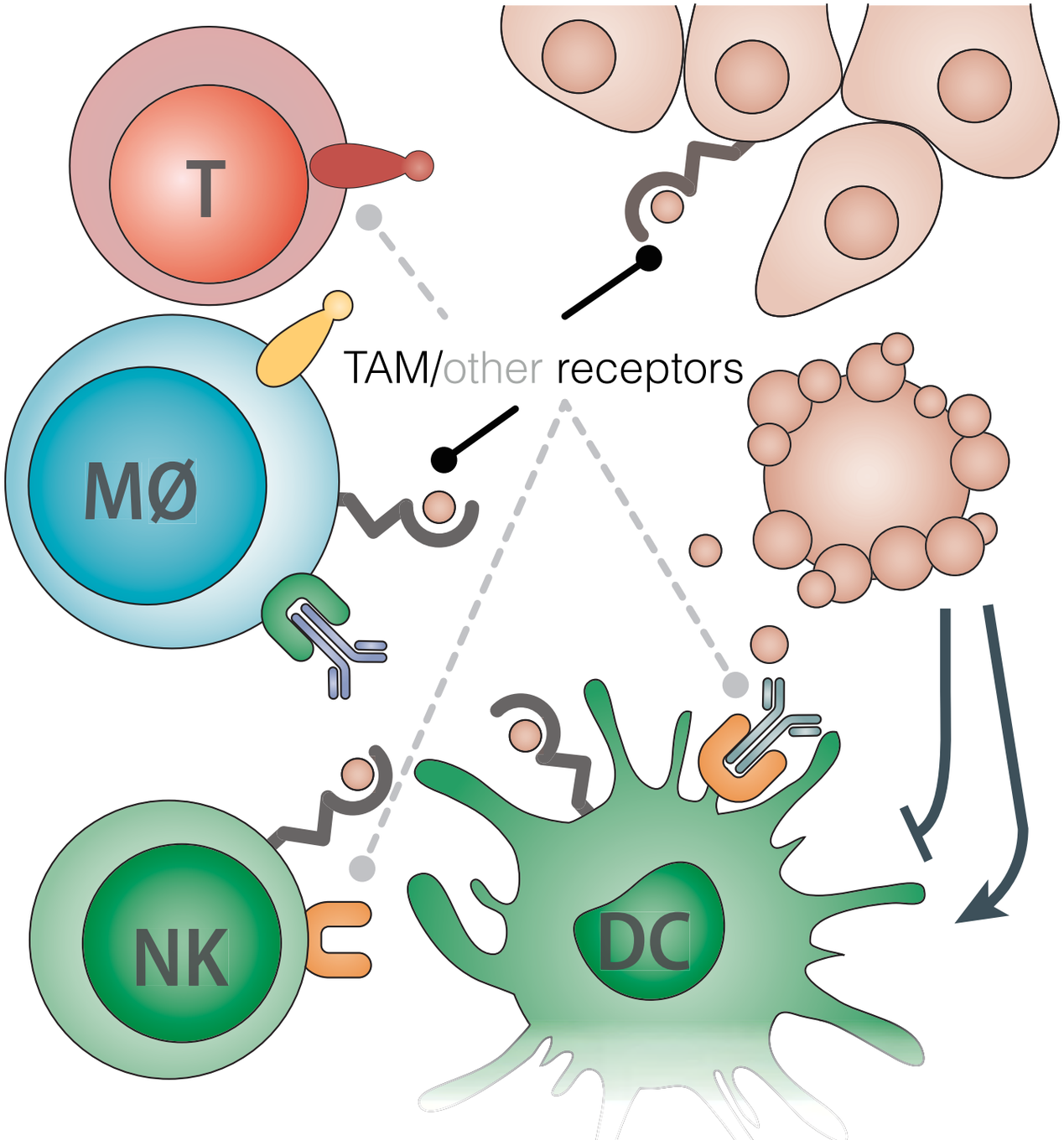
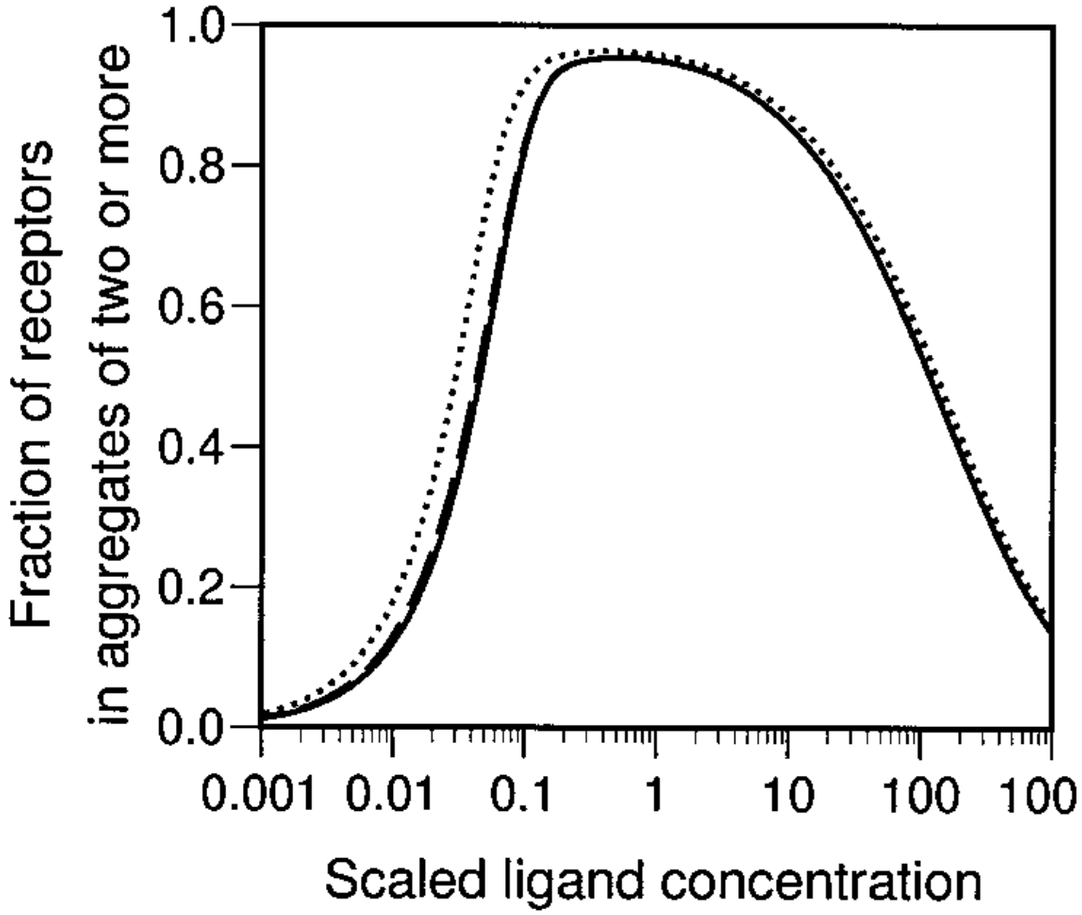
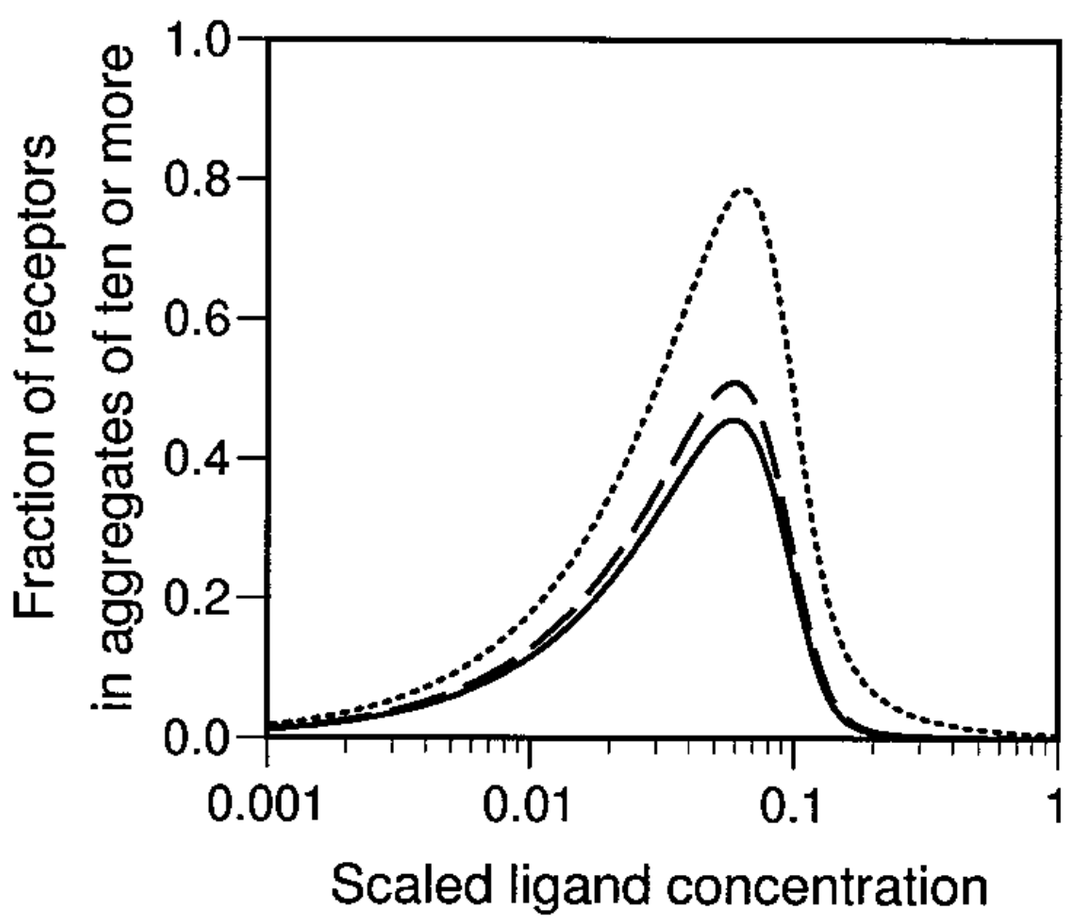


Innate immune receptors share molecular features

- Signaling effects poorly understood
- Simultaneous signaling & trafficking
- Activated through clustering rather than strictly ligand interaction

Time to link theory with data-driven analysis

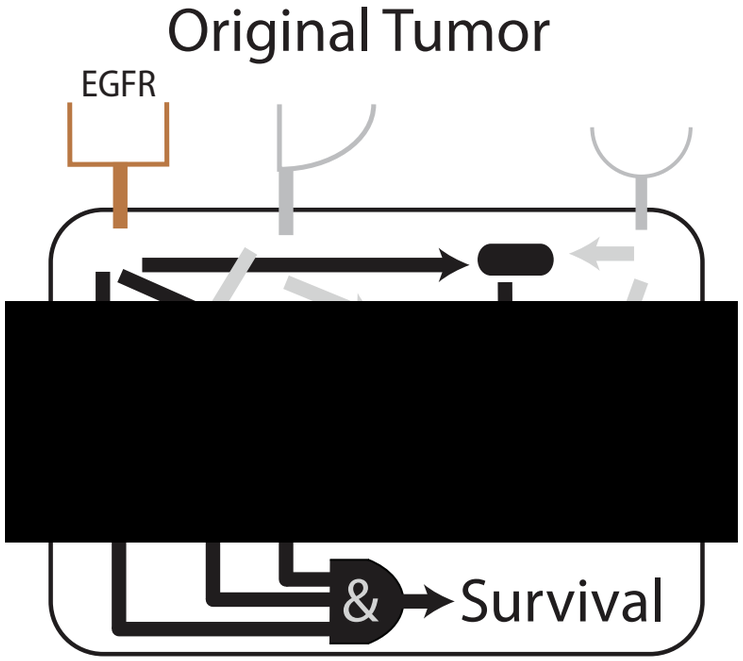




Hlavacek, Posner, Perelson, *Biophys J*, 1999

What does AXL do in cancer cells?

Sets of resistance mechanisms can uncover conserved molecular regulation



Manole, Richards, Meyer, *Canc Res*, 2016

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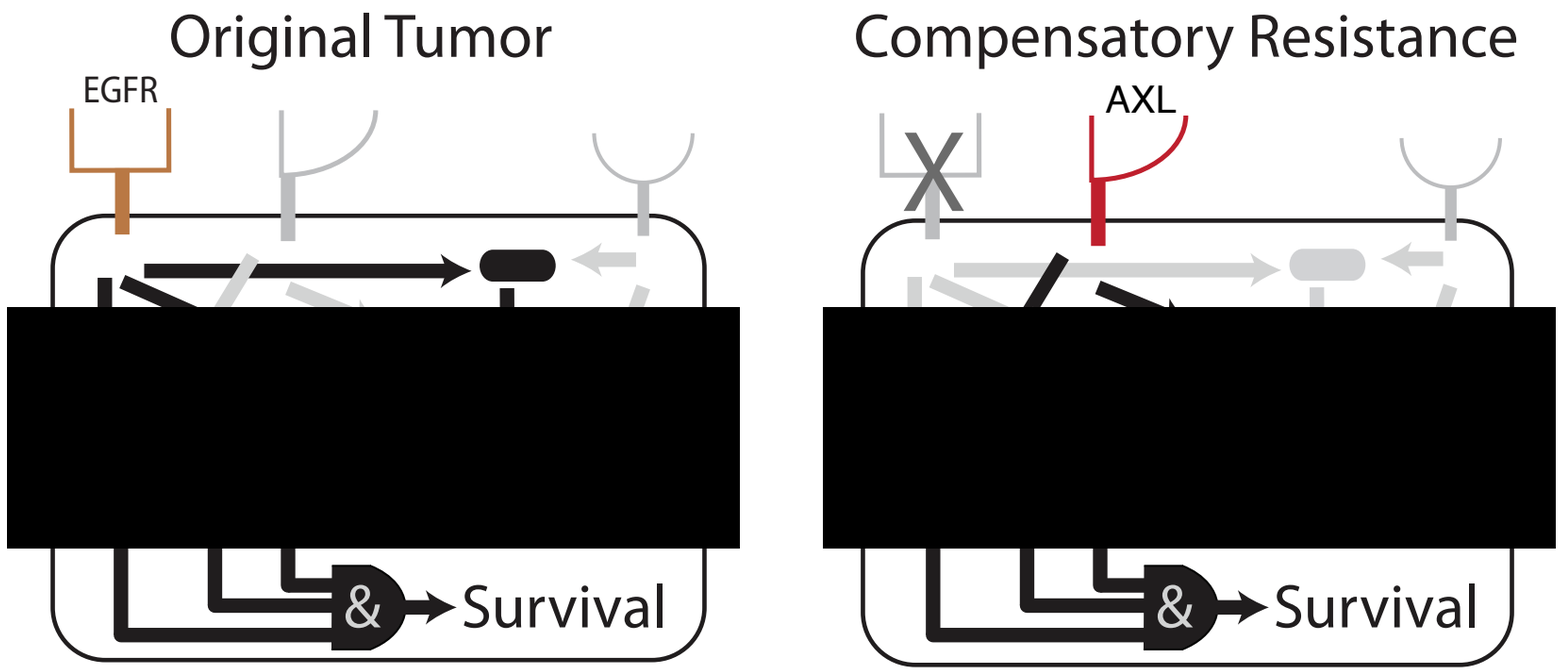

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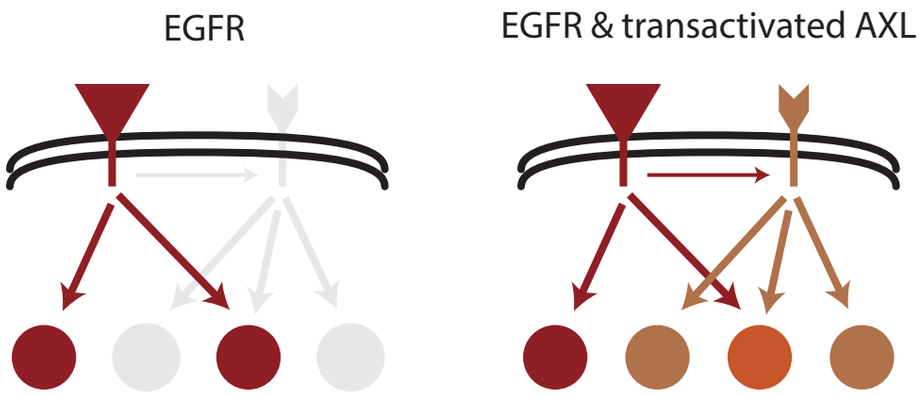

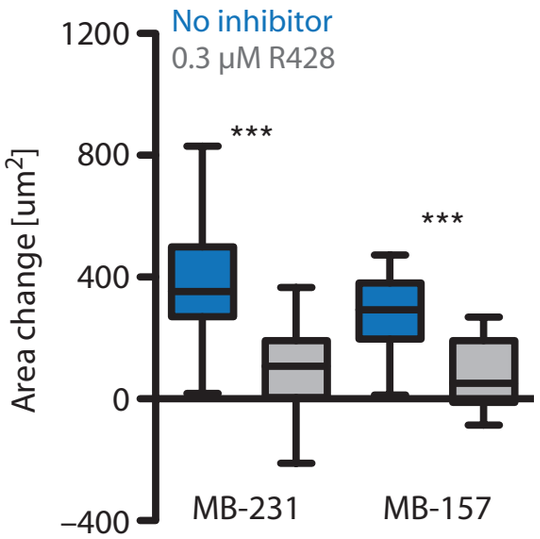

Meyer *et al*, *Sci Sig*, 2013

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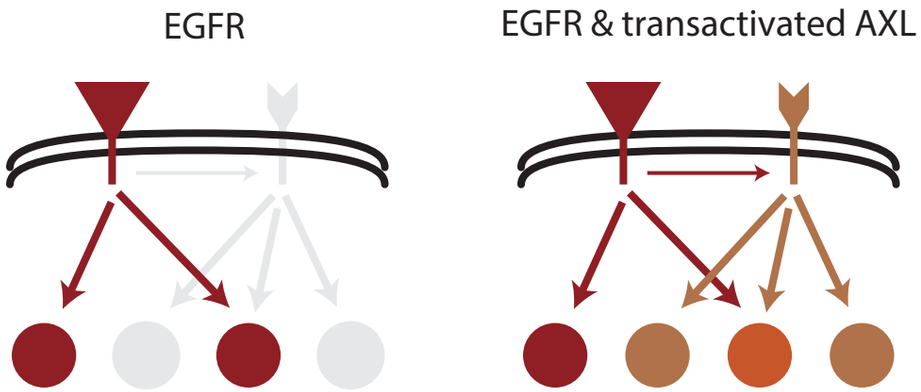
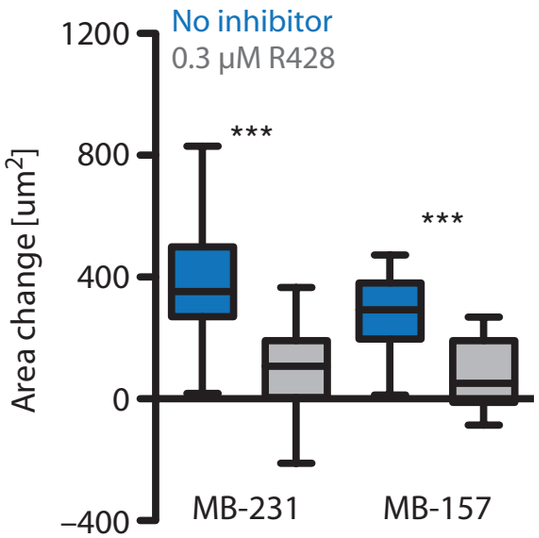
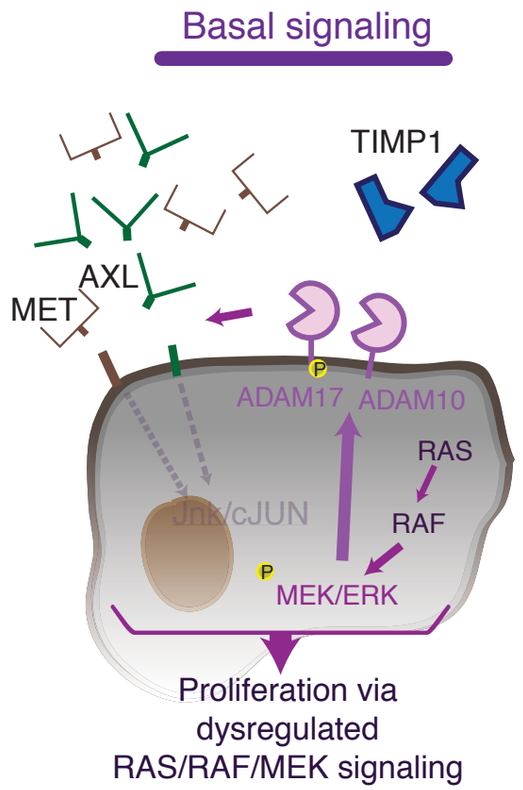




Meyer *et al*, *Sci Sig*, 2013



Miller & Meyer et al, *PNAS*, 2013
Miller… Meyer… Lauffenburger, *Canc Discov*, 2015

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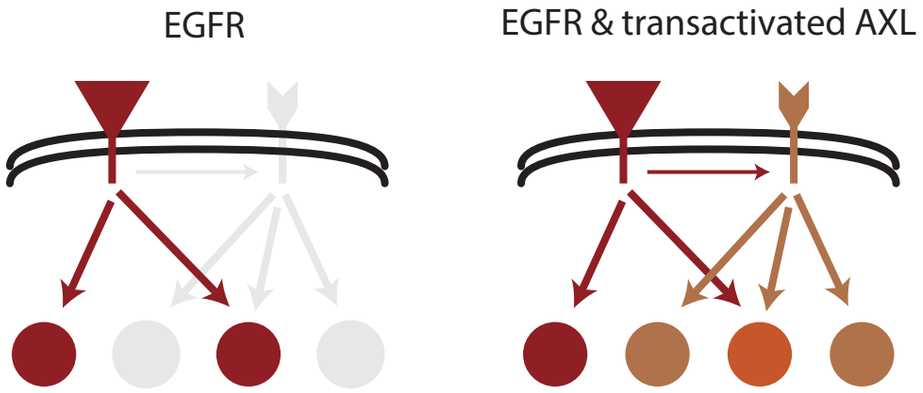
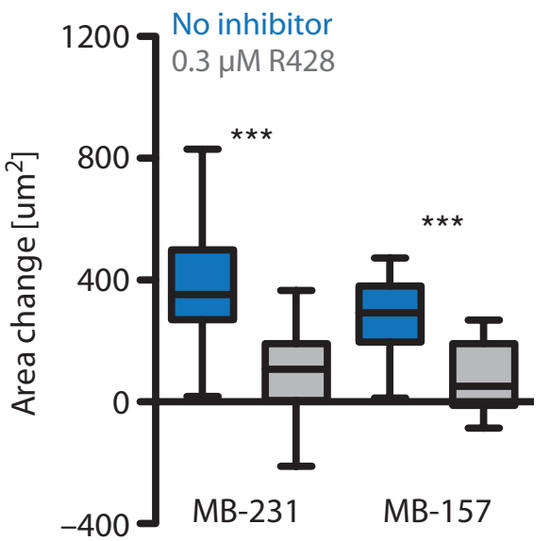
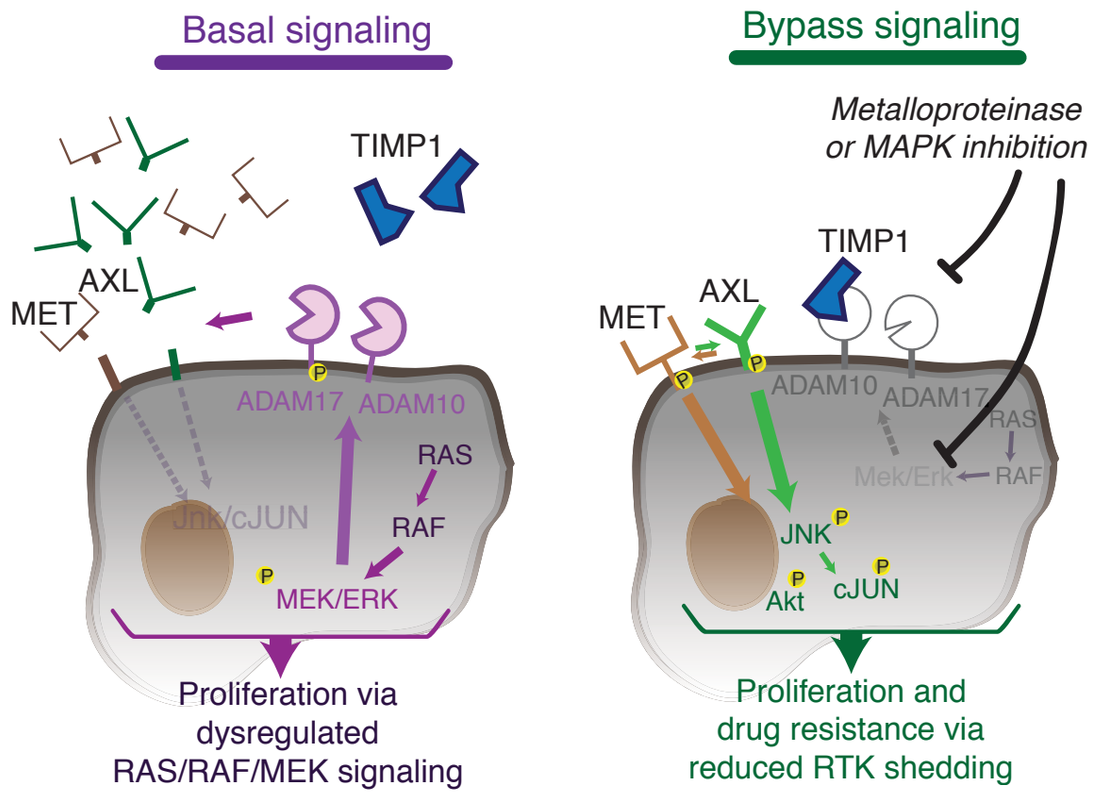




Meyer *et al*, *Sci Sig*, 2013



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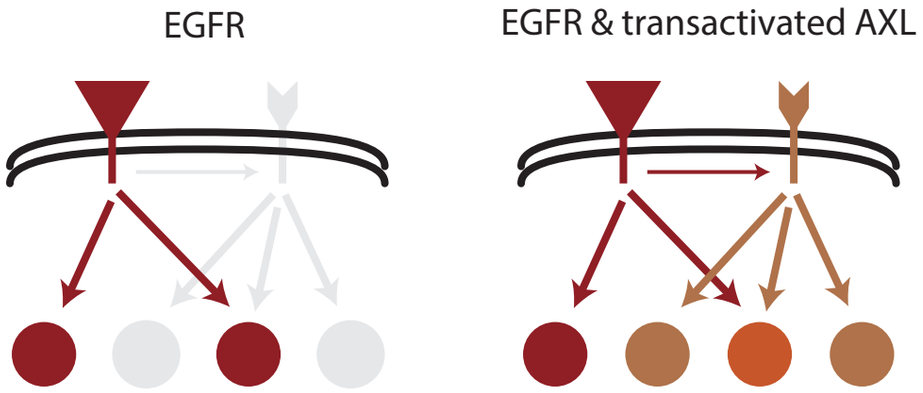
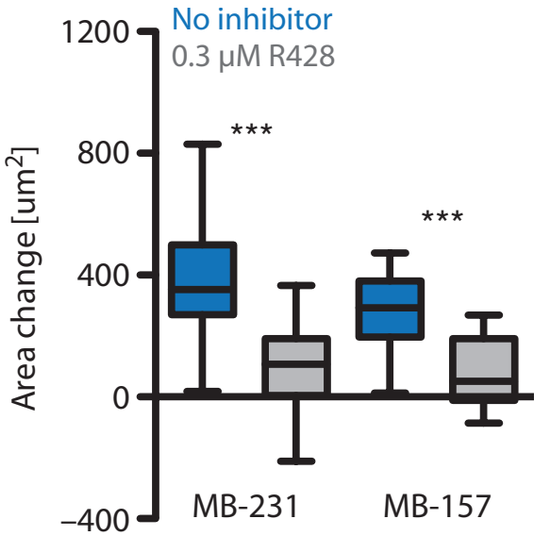
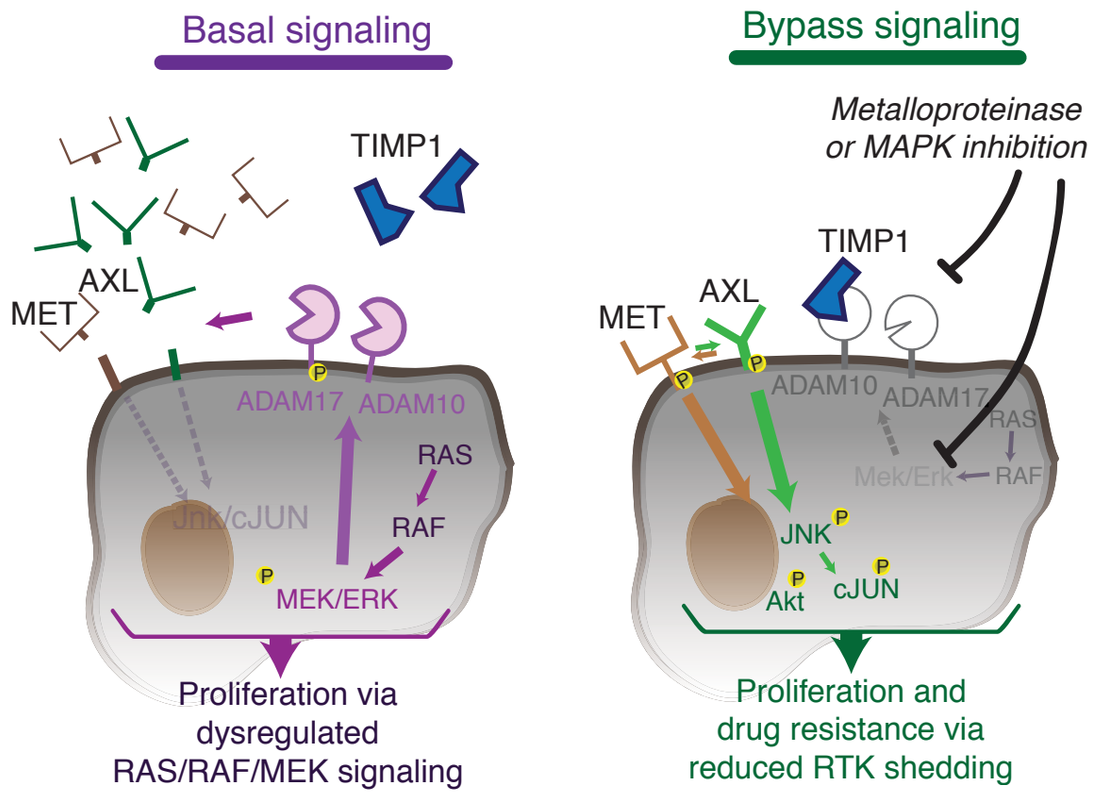




Meyer *et al*, *Sci Sig*, 2013



Miller & Meyer et al, *PNAS*, 2013
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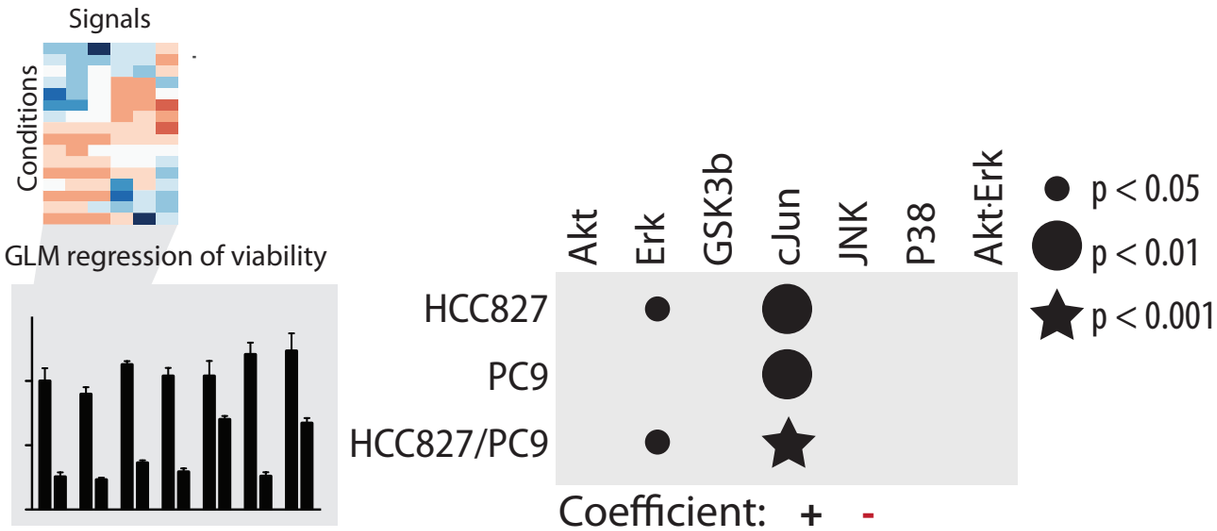
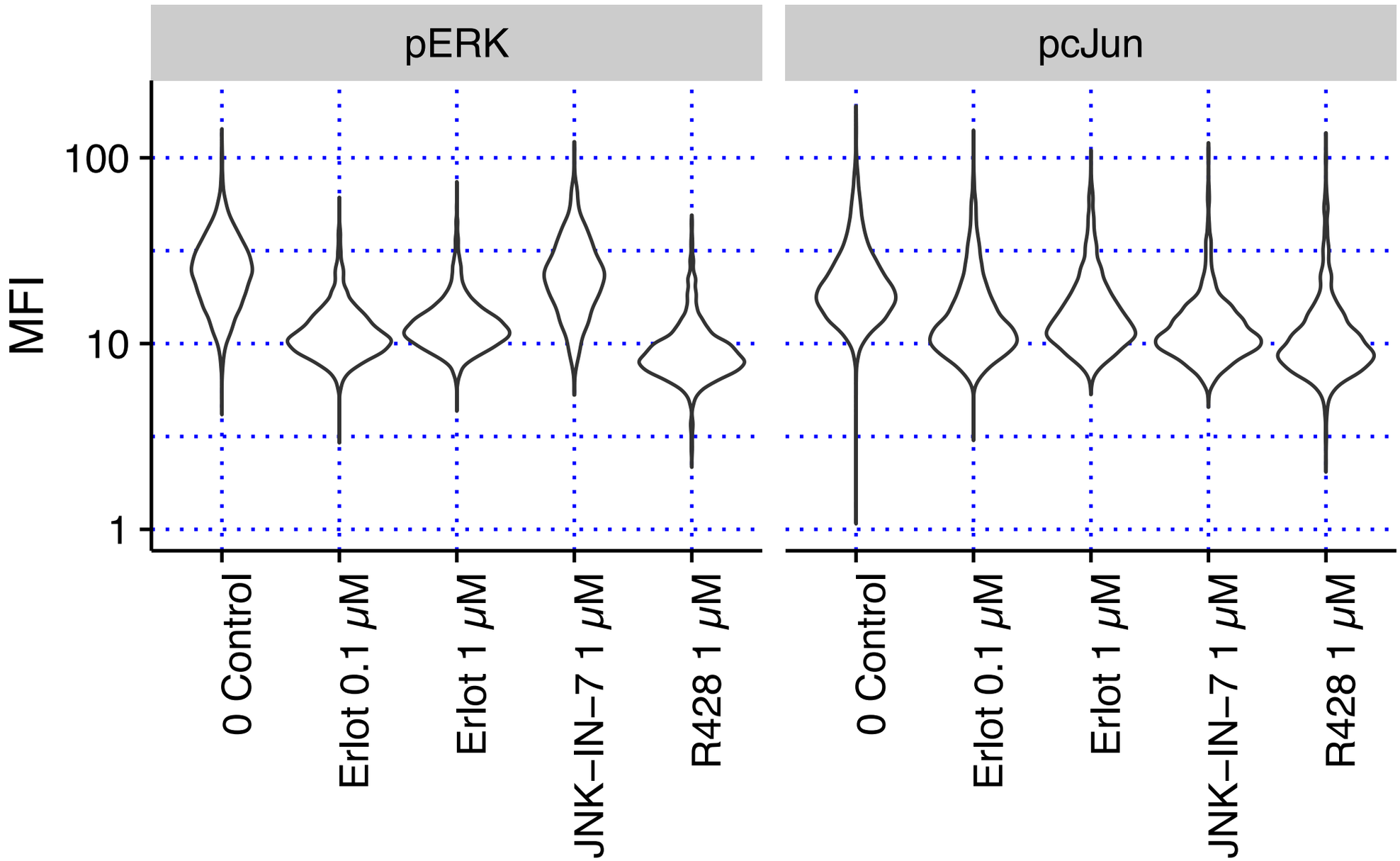


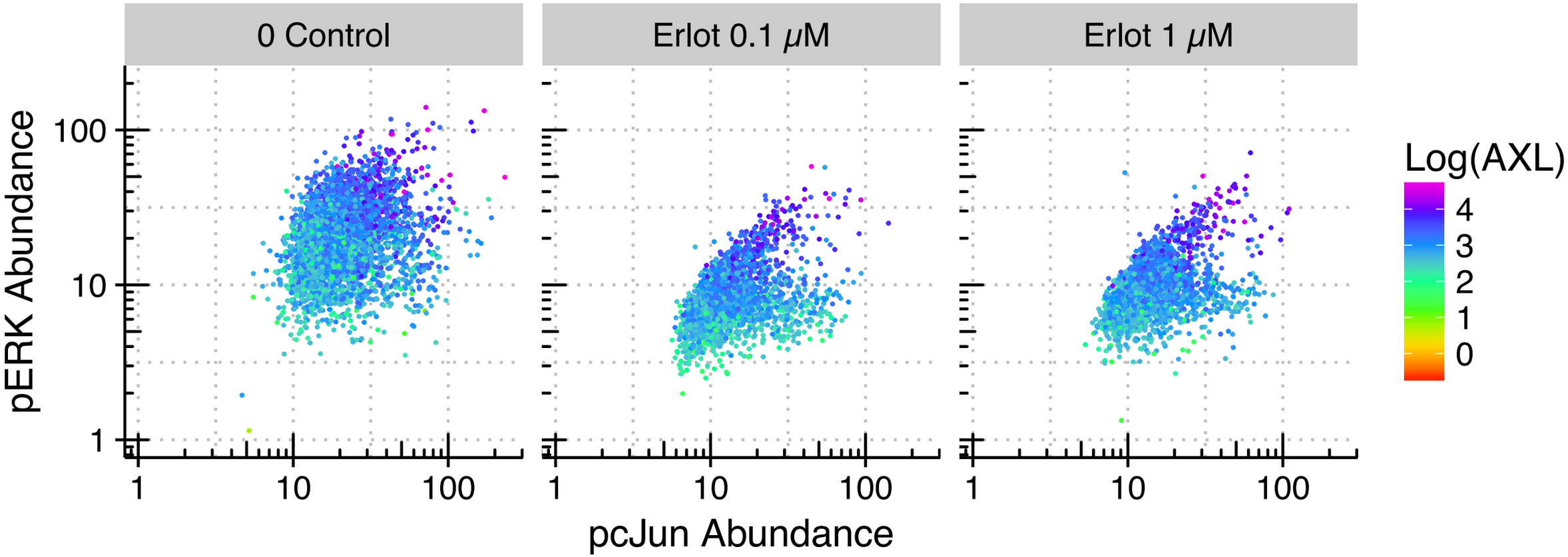
Manole, Richards, Meyer, *Canc Res*, 2016

Population average measurements do not capture cell-cell variation in response



PC9

A subpopulation of AXL+ cells maintain bypass Erk/JNK activation



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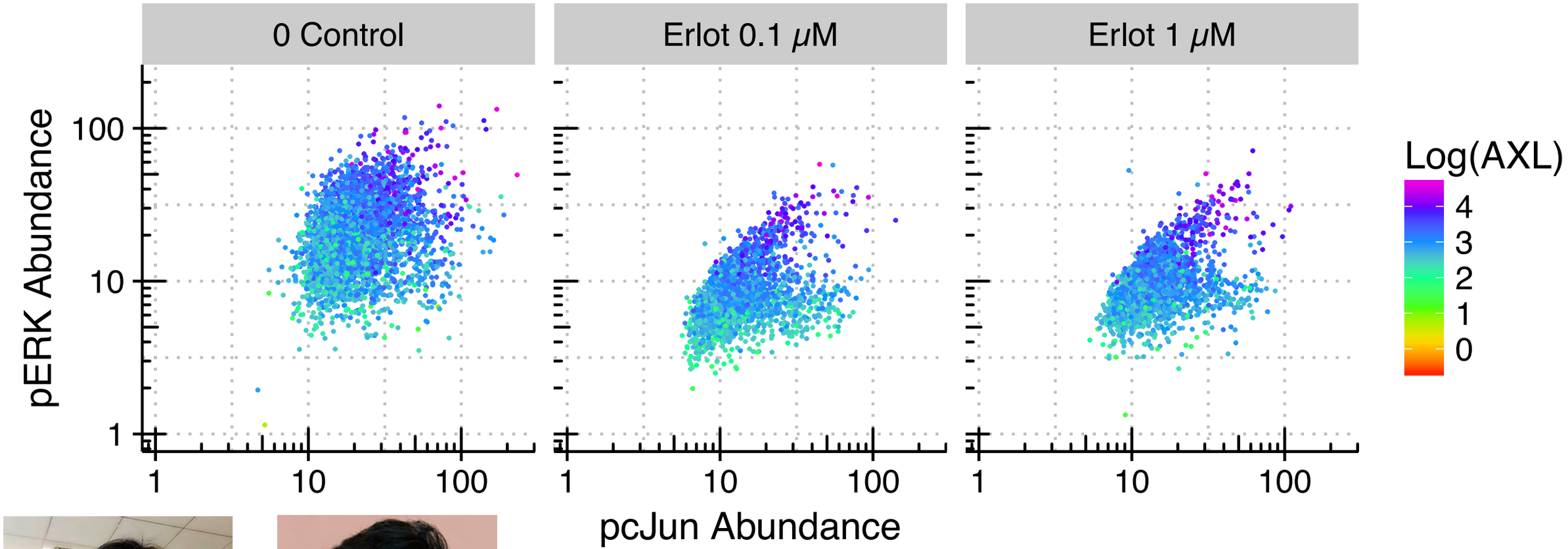

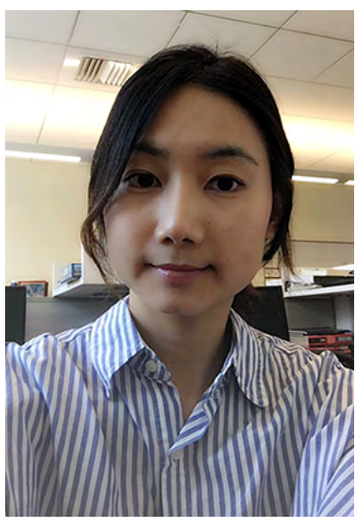

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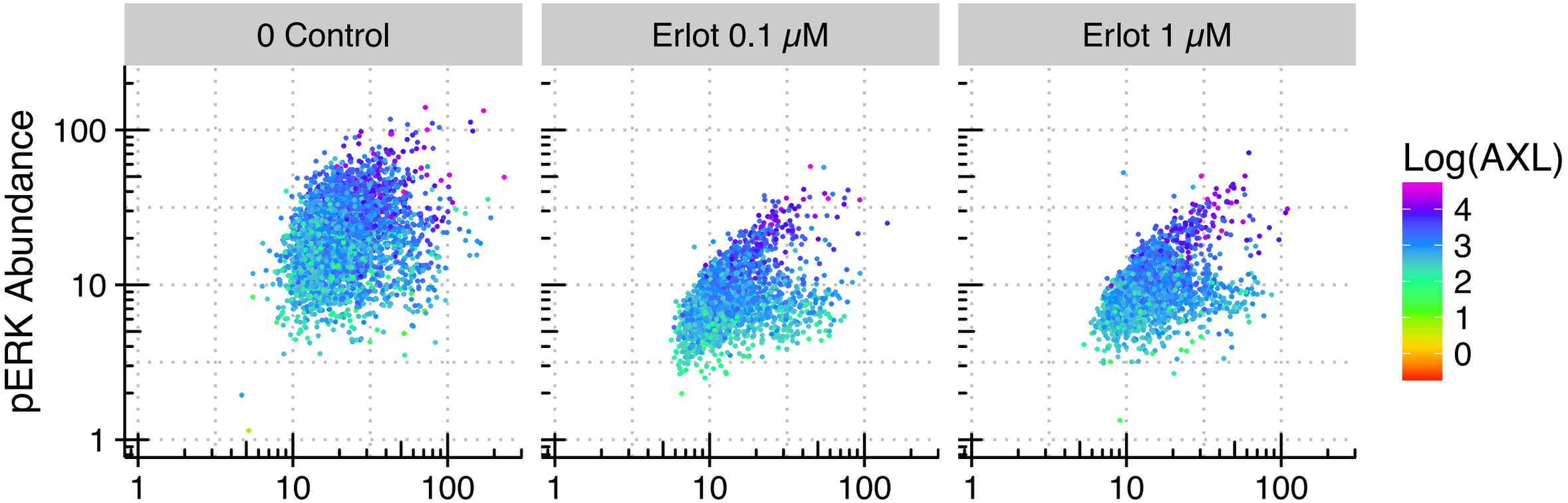
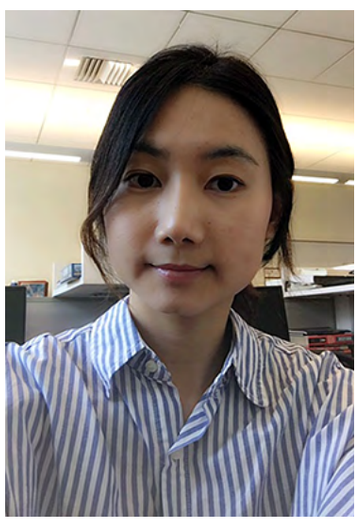
A subpopulation of AXL+ cells maintain bypass Erk/JNK activation





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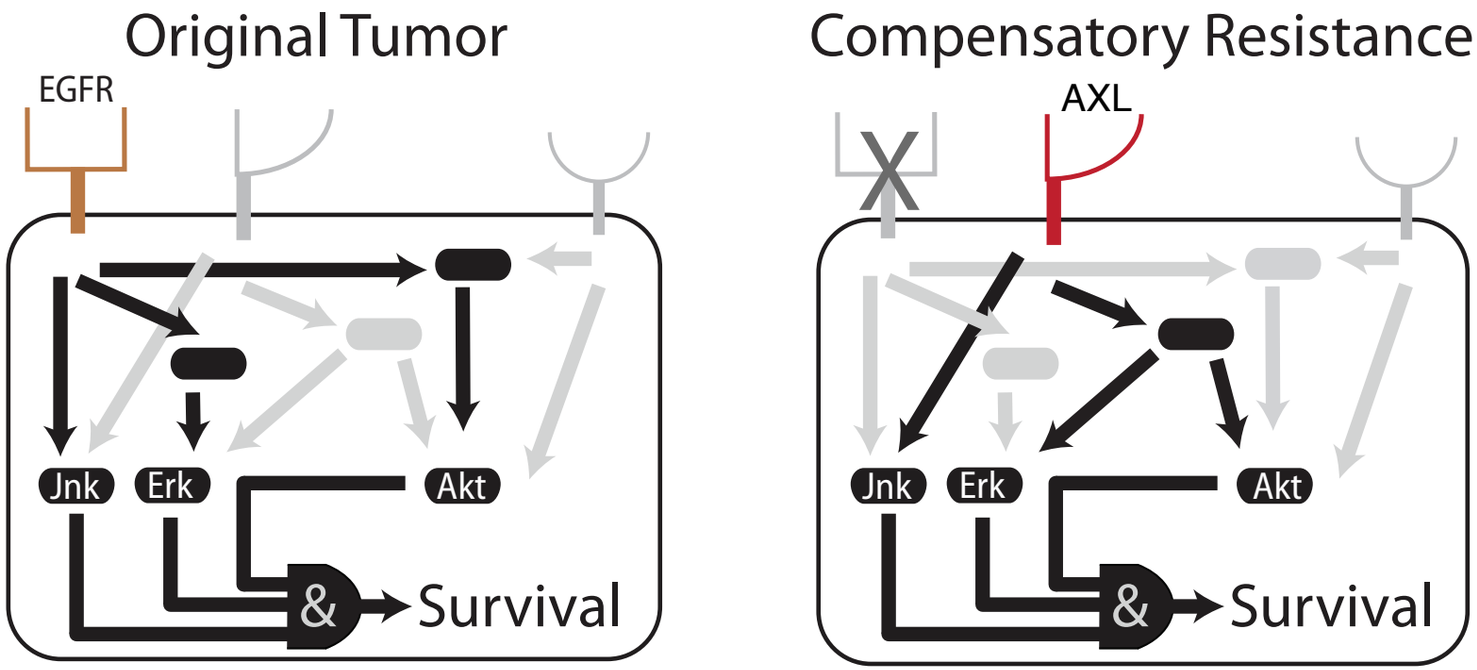
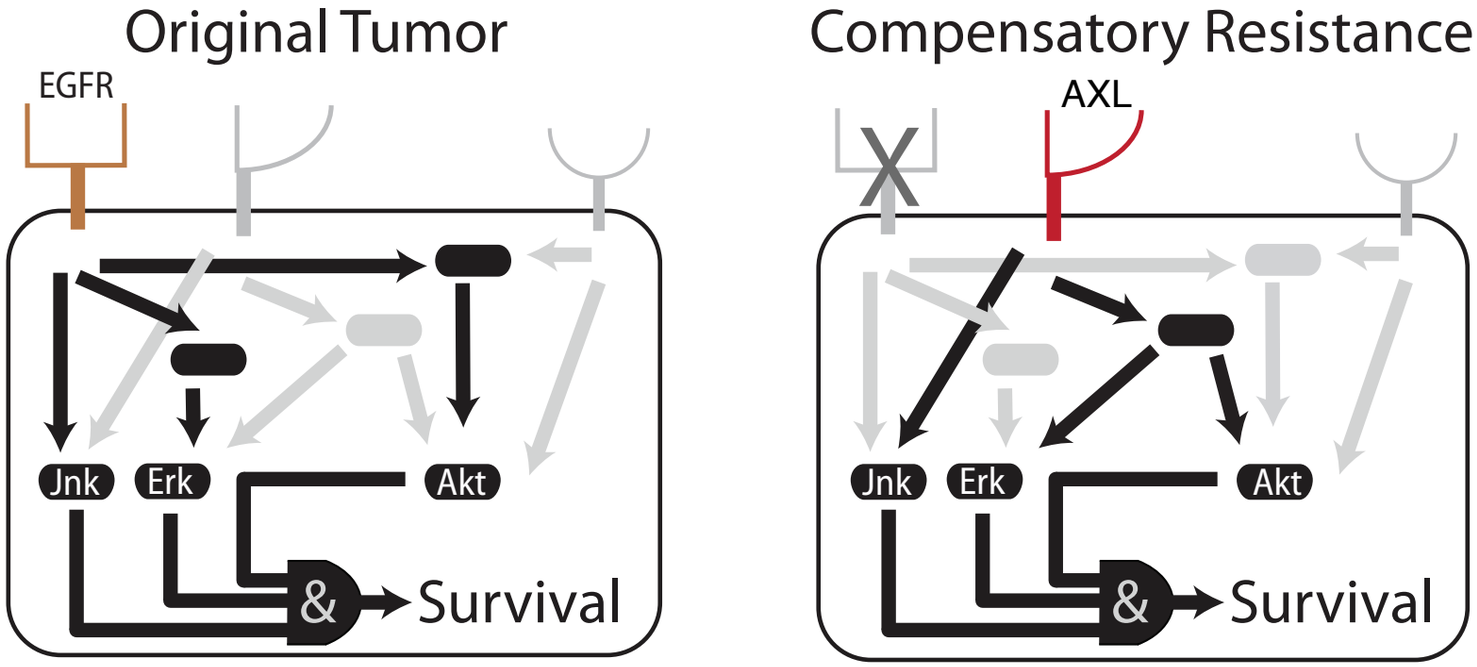
Sets of resistance mechanisms can uncover conserved molecular regulation



- Bypass resistance involves a conserved set of molecular changes
- Recognizing this allows us to reason about cell-cell heterogeneity, response to inhibitors, and RTK transactivation

Sets of resistance mechanisms can uncover conserved molecular regulation



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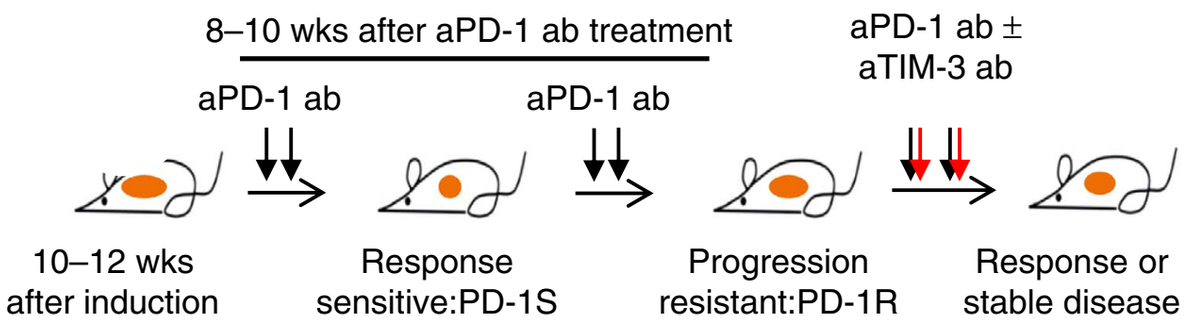
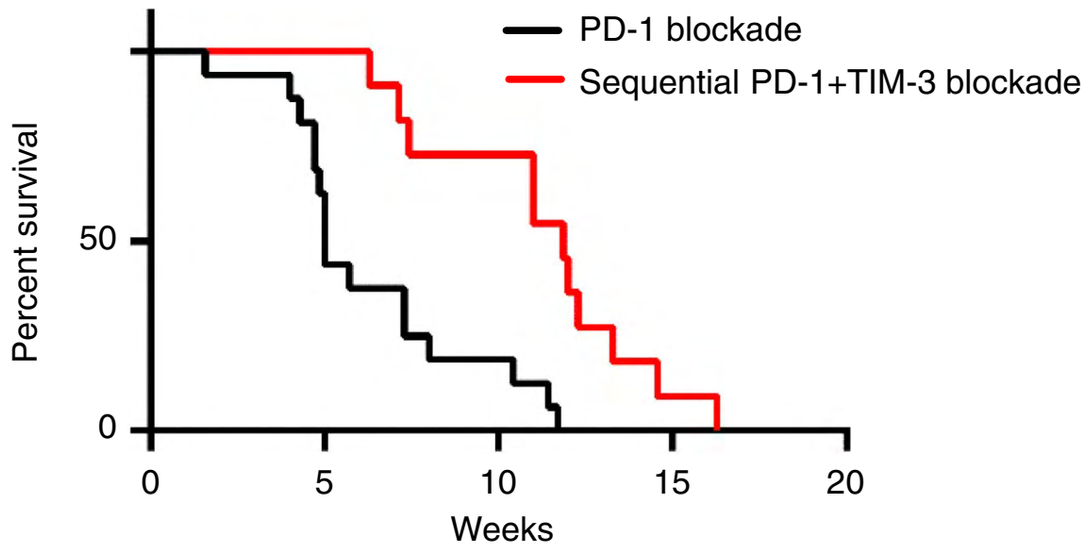
Moffitt

Forest White
MIT

- Bypass resistance involves a conserved set of molecular changes
- Recognizing this allows us to reason about cell-cell heterogeneity, response to inhibitors, and RTK transactivation

Far-future direction: A “bypass” receptor view of cancer immune evasion





Toyama *et al*, *Nat Comm*, 2015

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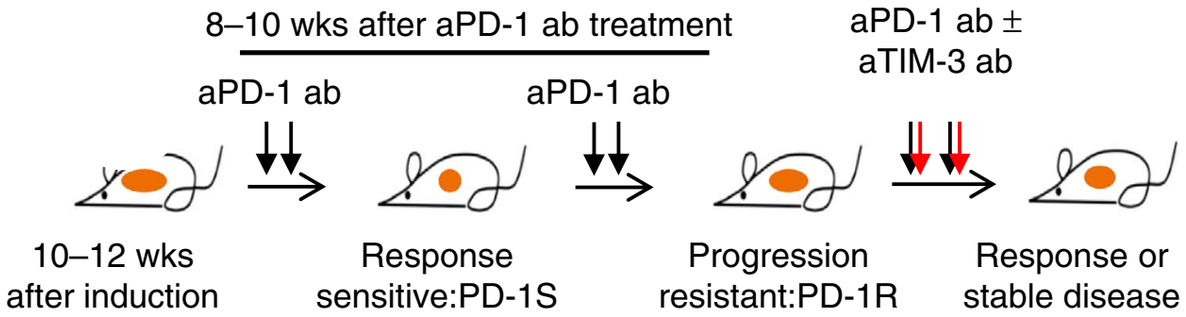
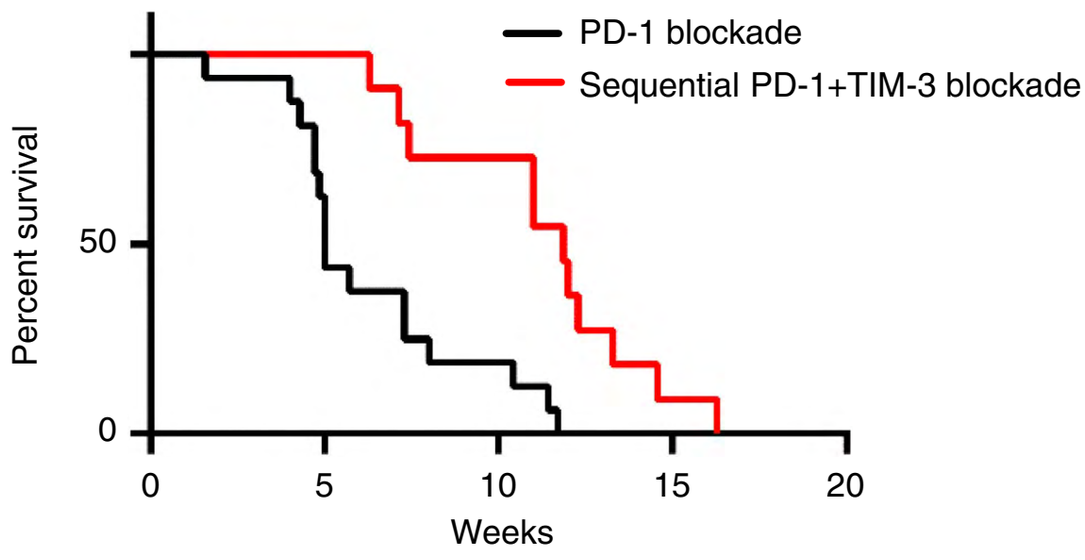
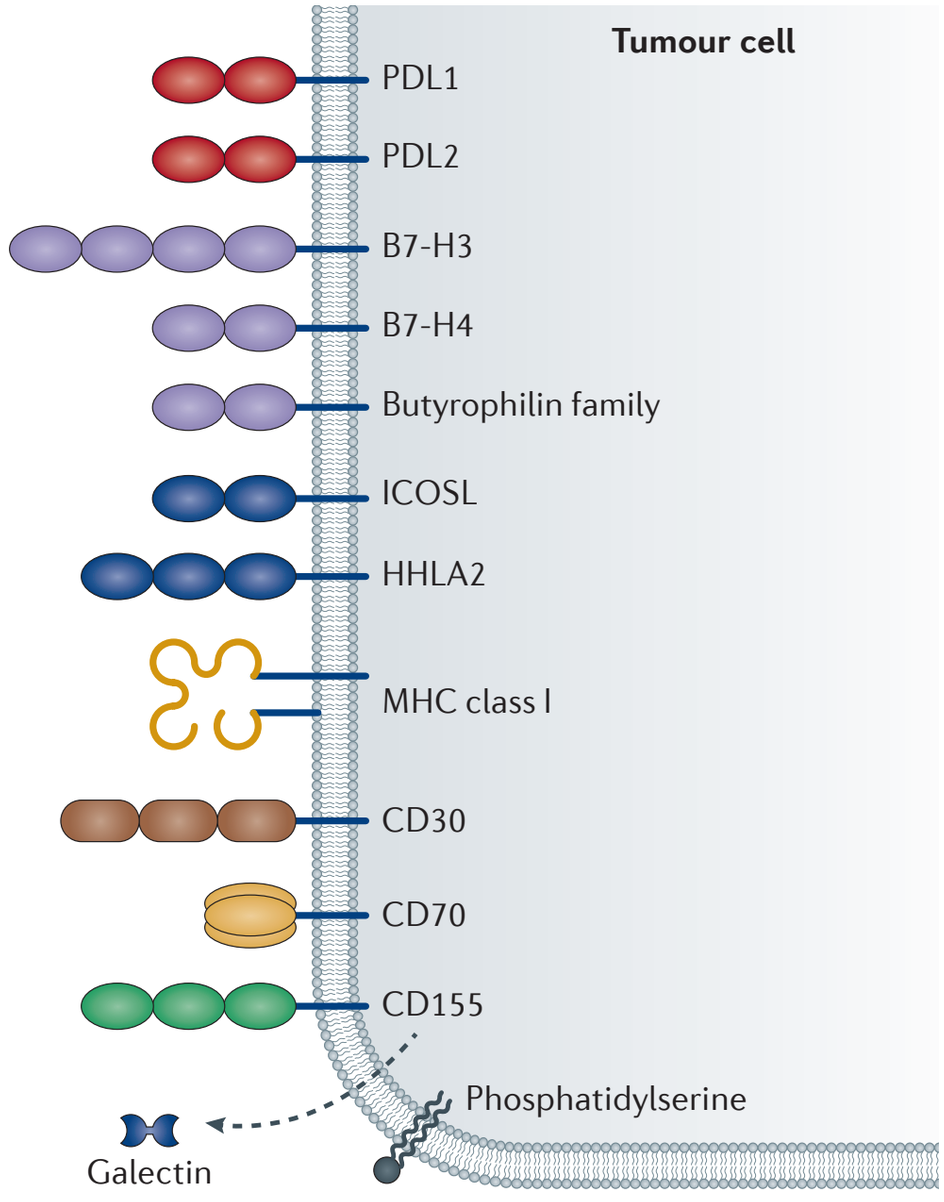




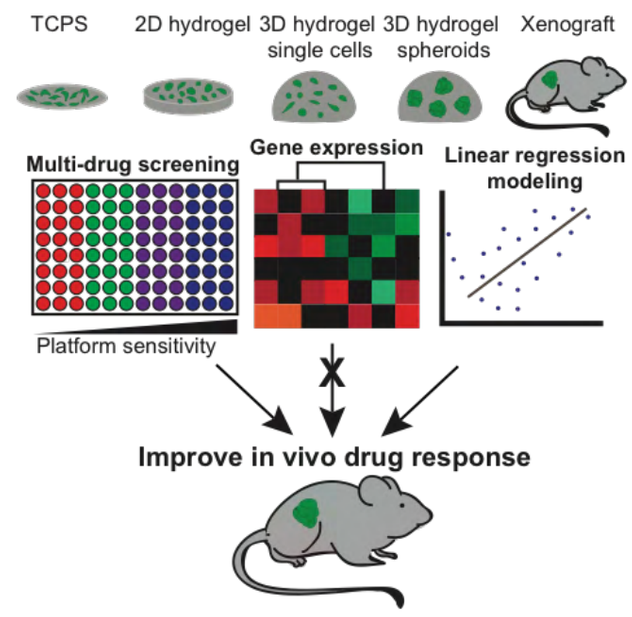
Toyama *et al*, *Nat Comm*, 2015



Mahoney *et al*, *Nat Rev Drug Discov*, 2015

Systems level measurement, modeling, and manipulation are an essential part of bioengineering

Systems biology in/of physiological extracellular environments

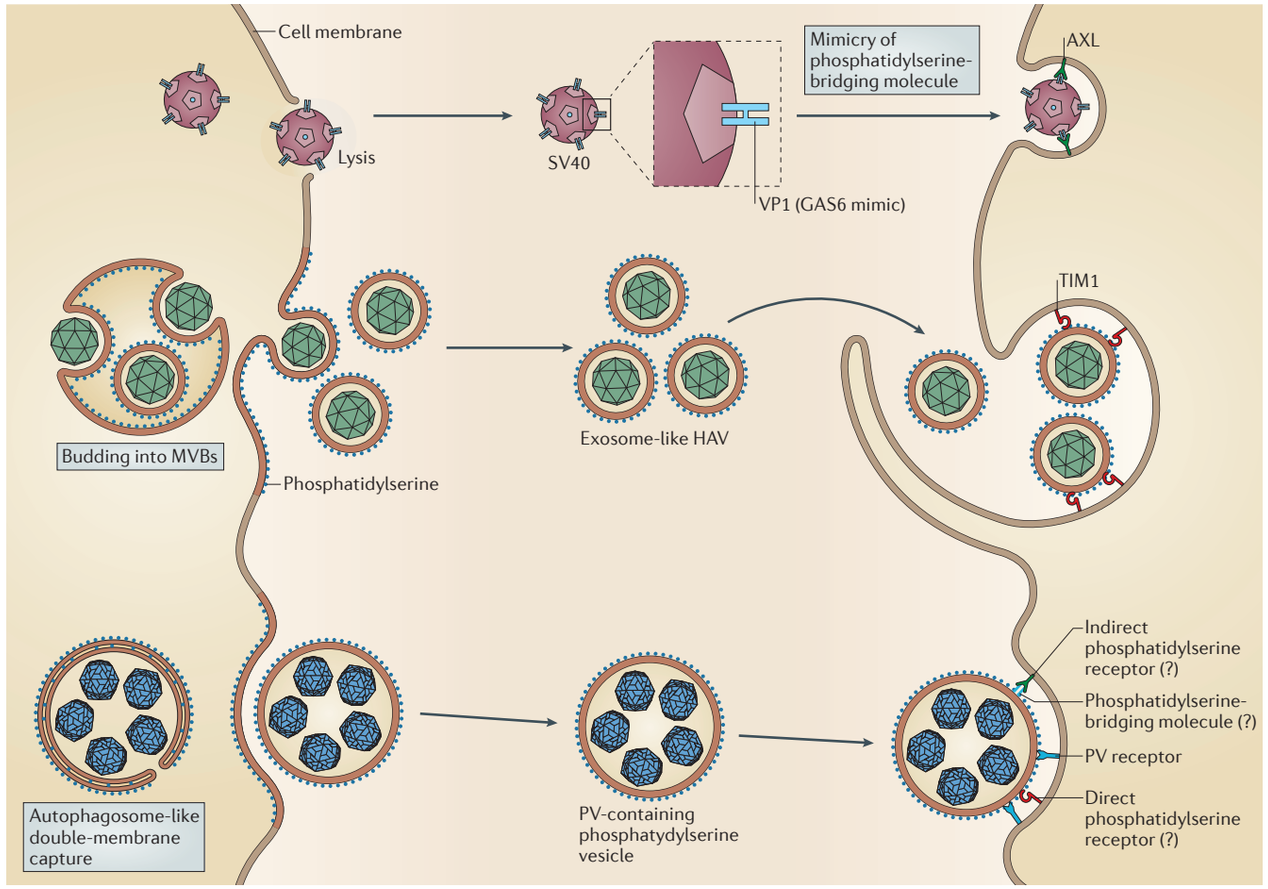


Incorporating data-driven modeling in design

Barney… Meyer, Peyton, *Submitted*

Systems level measurement, modeling, and manipulation are an essential part of bioengineering

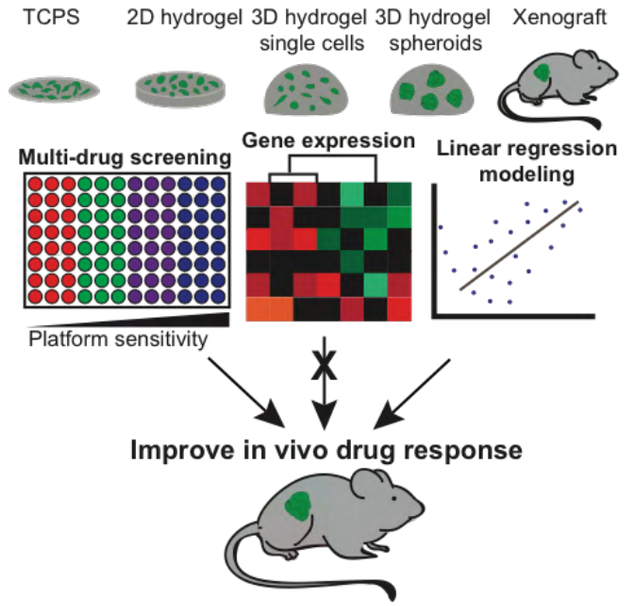
PS-based materials development



Detecting and manipulating PS and its interactions

Amara *et al*, *Nat Rev Microbiol*, 2015

Systems biology in/of physiological extracellular environments



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Acknowledgements


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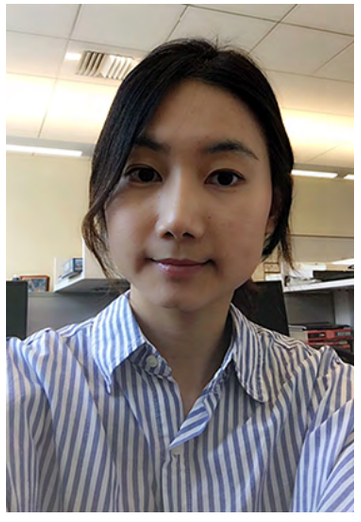
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- Forest White
- Angela Koehler
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