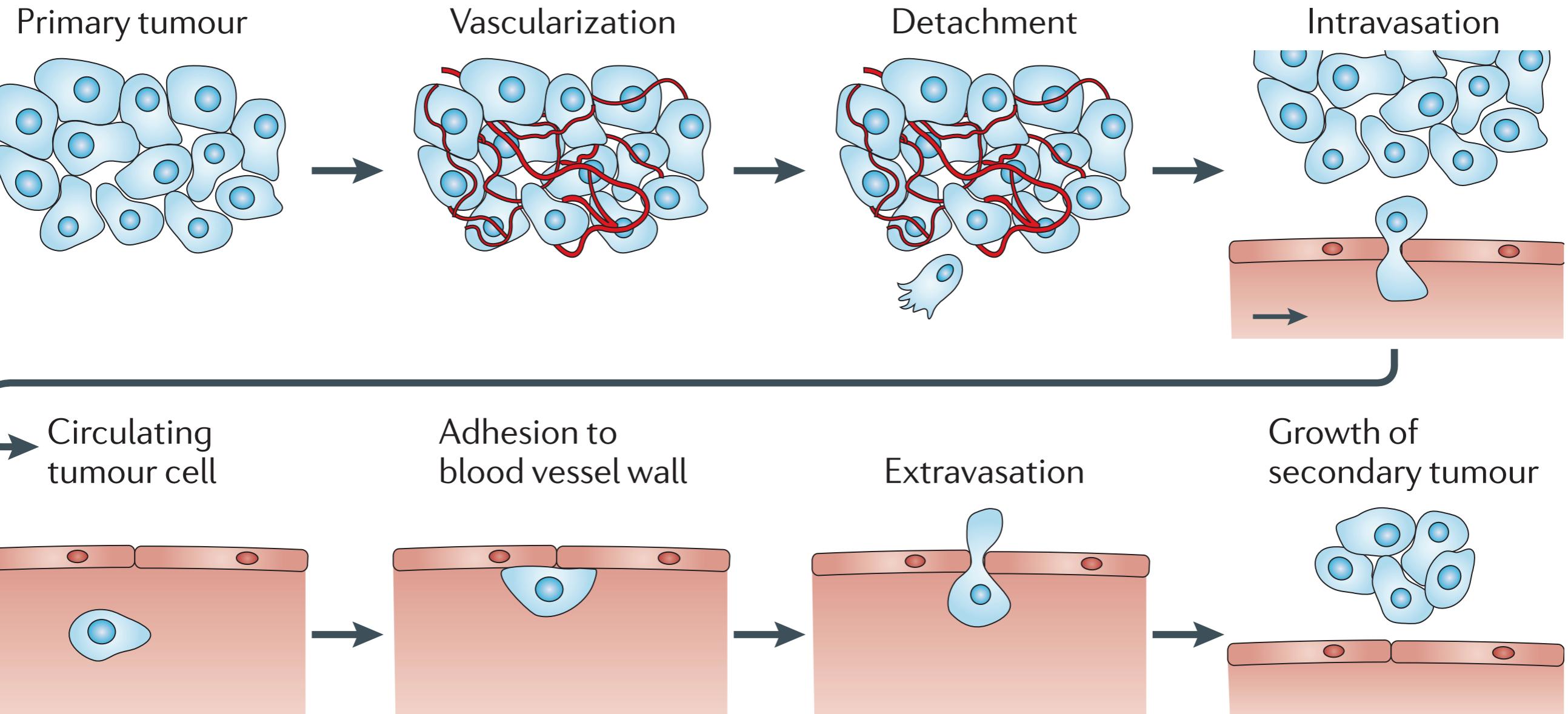


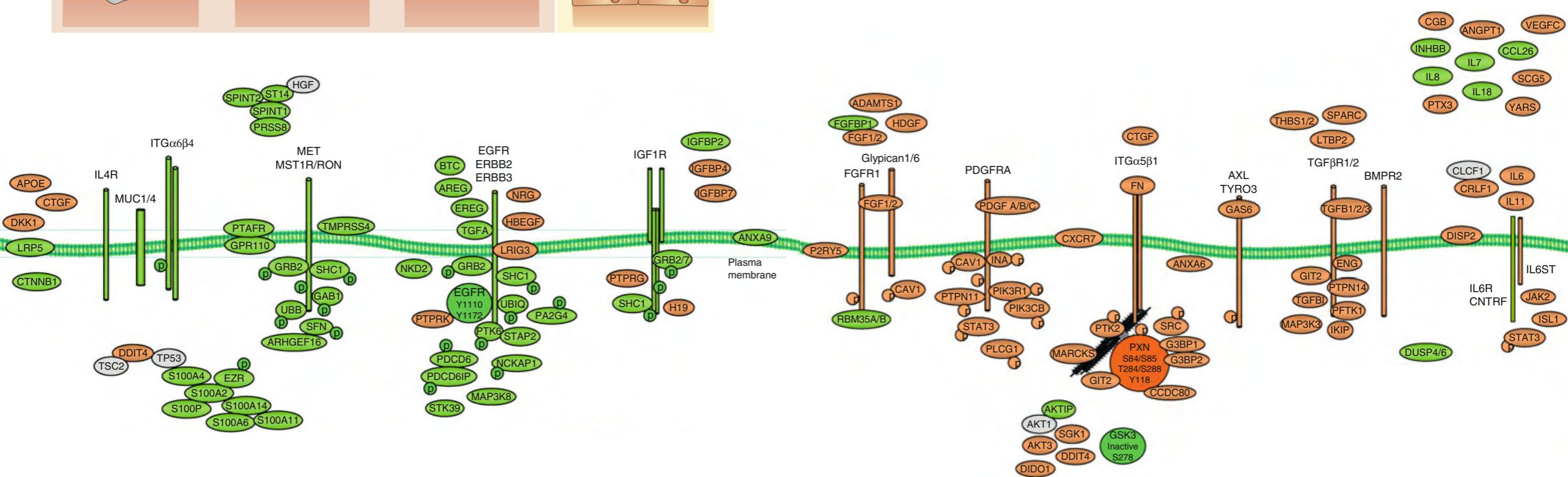
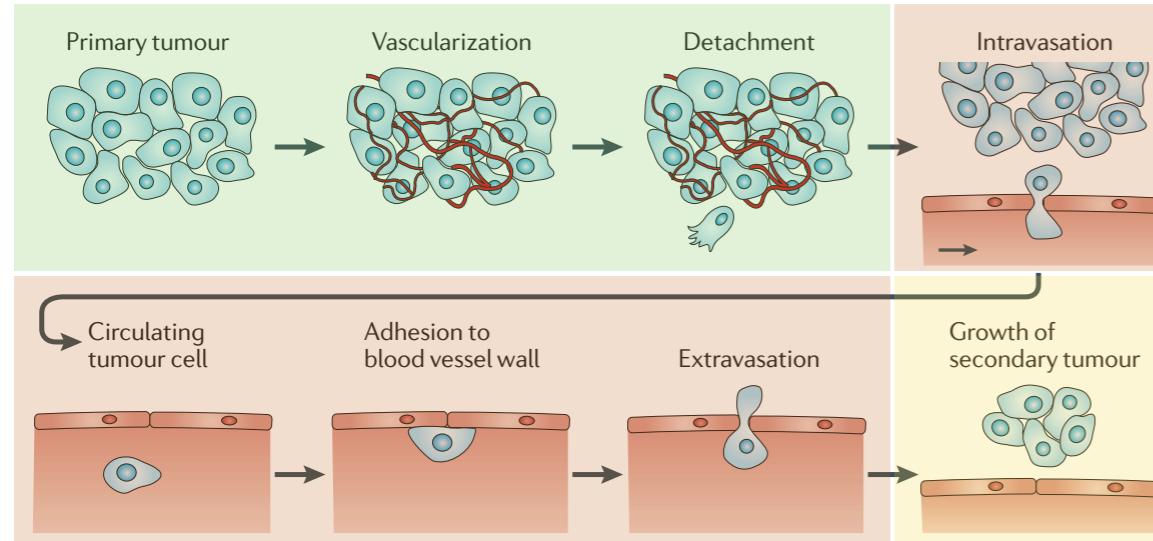
Quantitative approaches to understanding signaling regulation of 3D cell migration

April 8, 2014

Metastasis is a multistep process

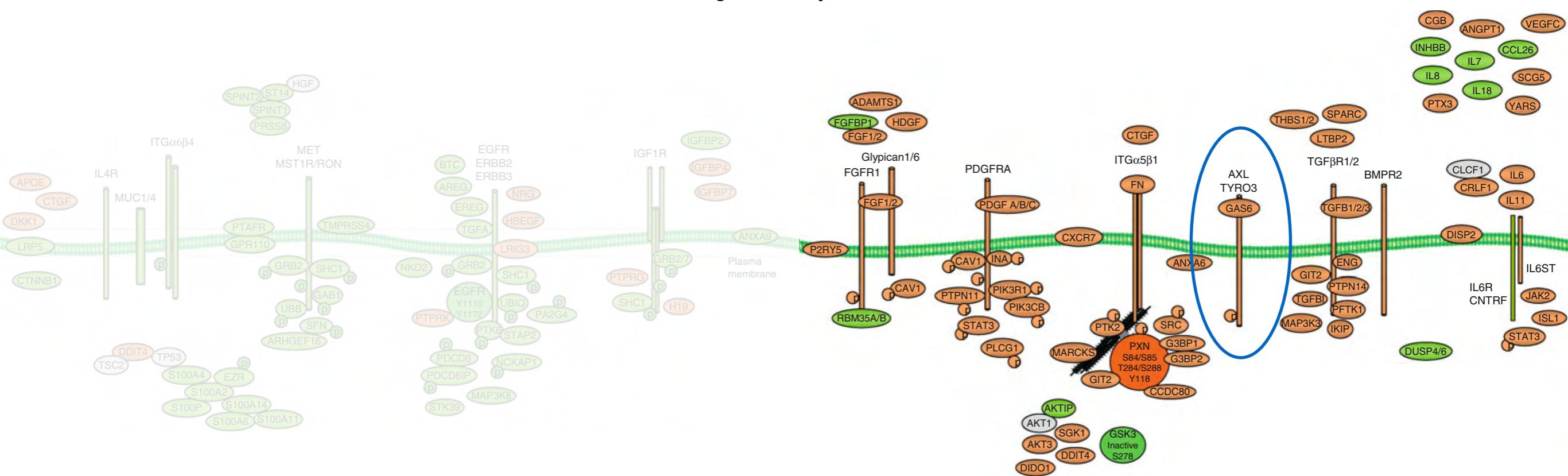


Invasive programs globally rewire cell signaling

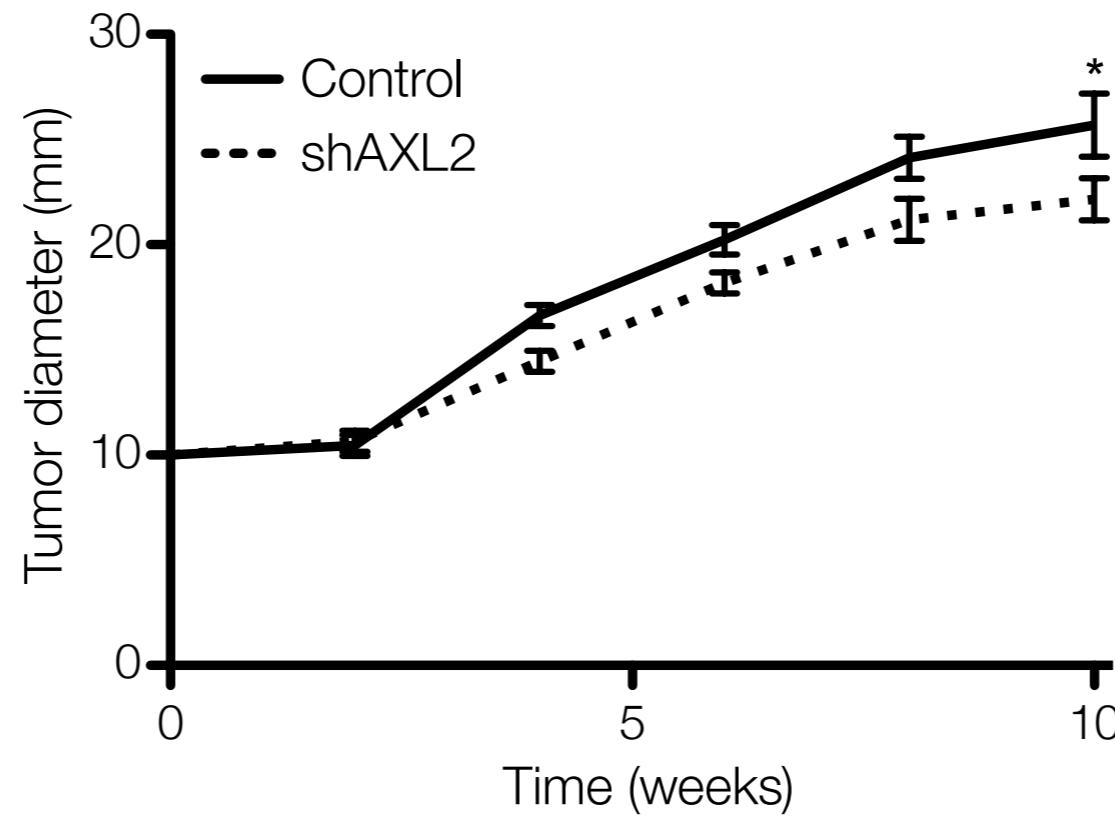


Invasive programs globally rewire cell signaling

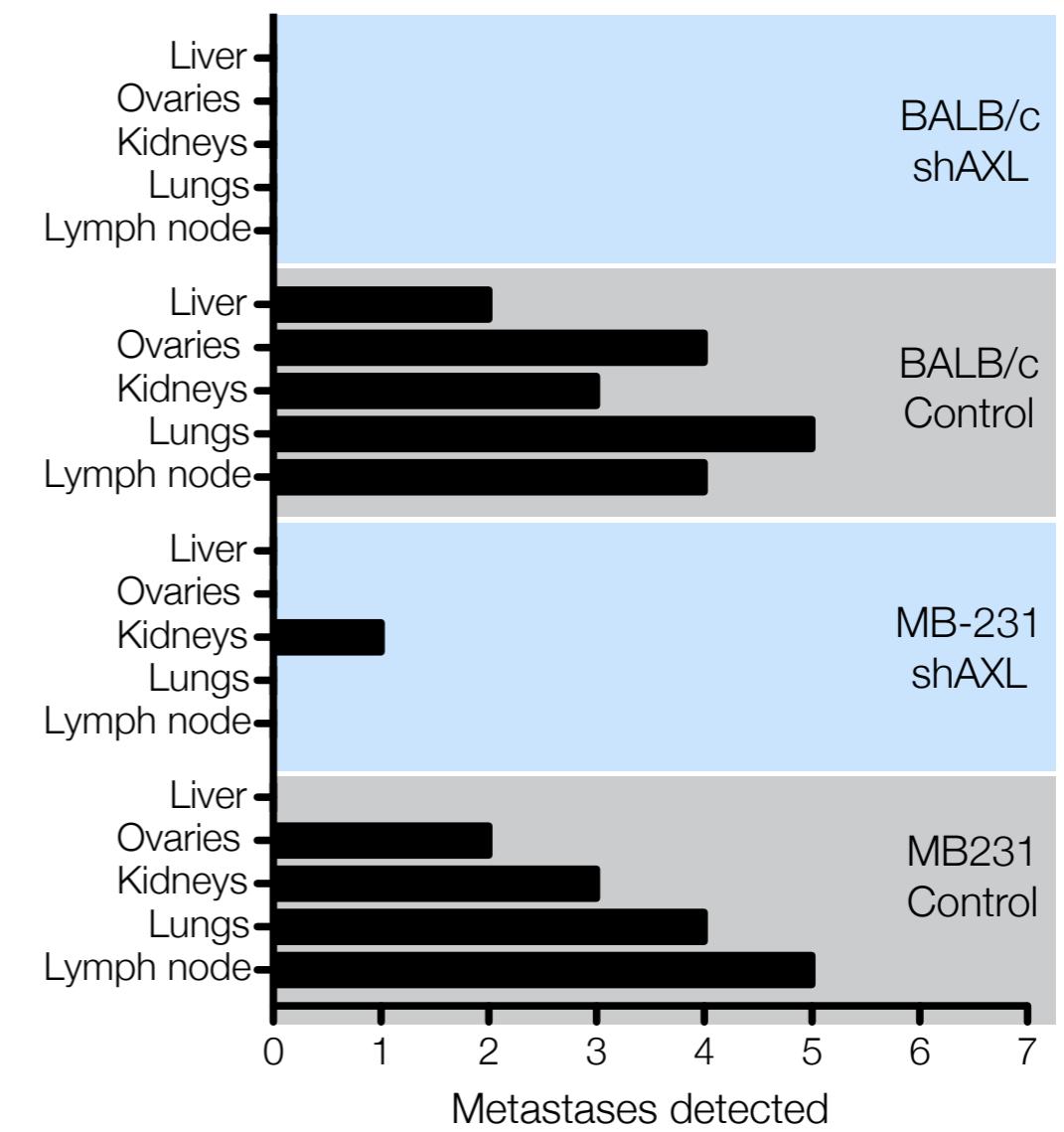
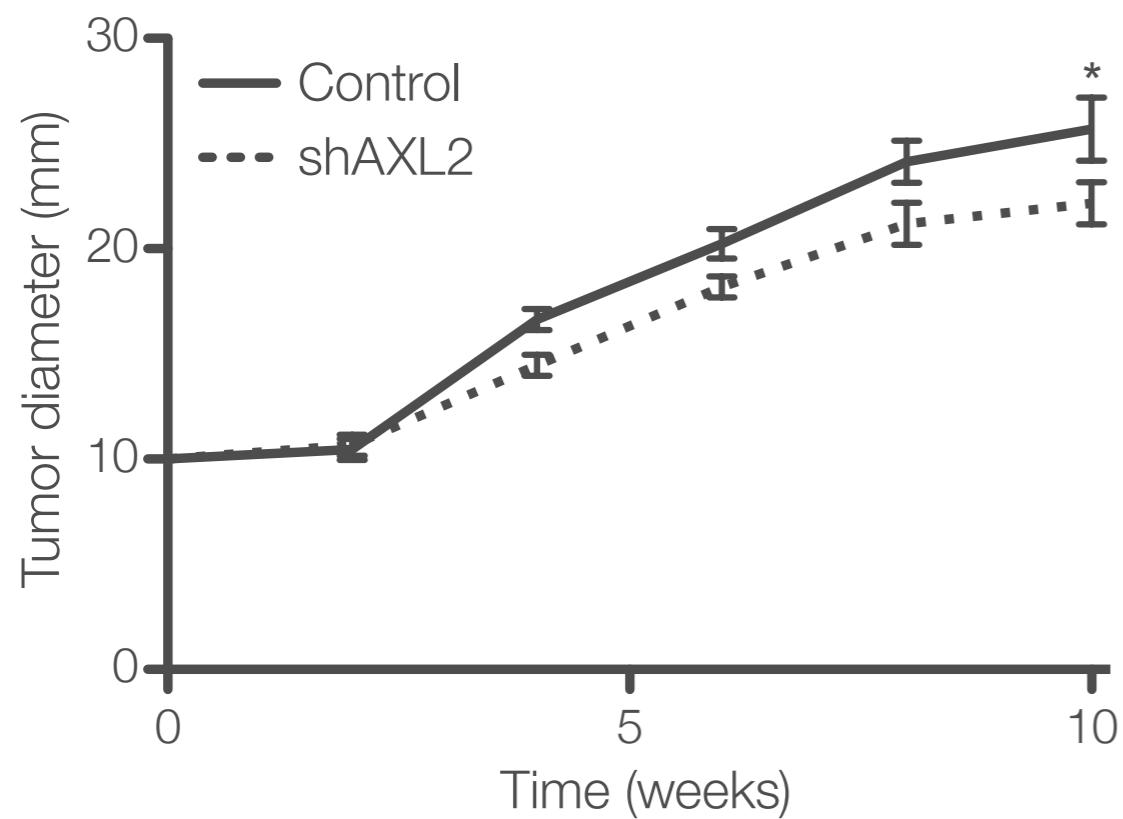
Targeting invasion-specific signaling may considerably improve survival



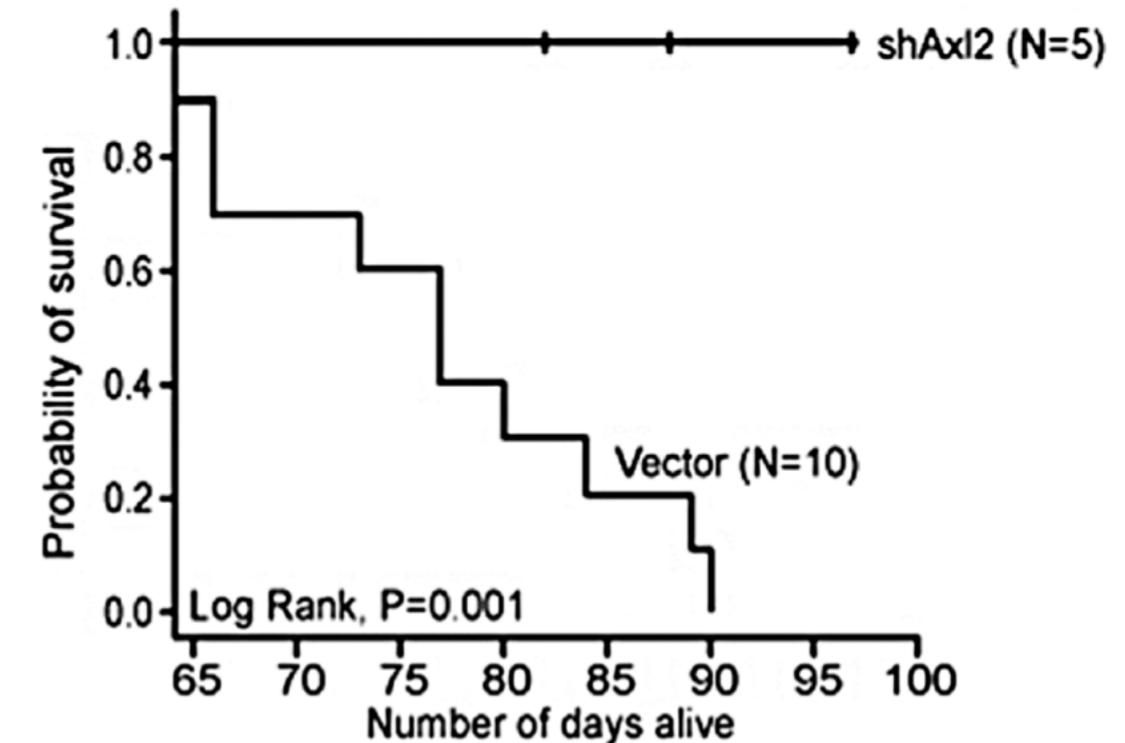
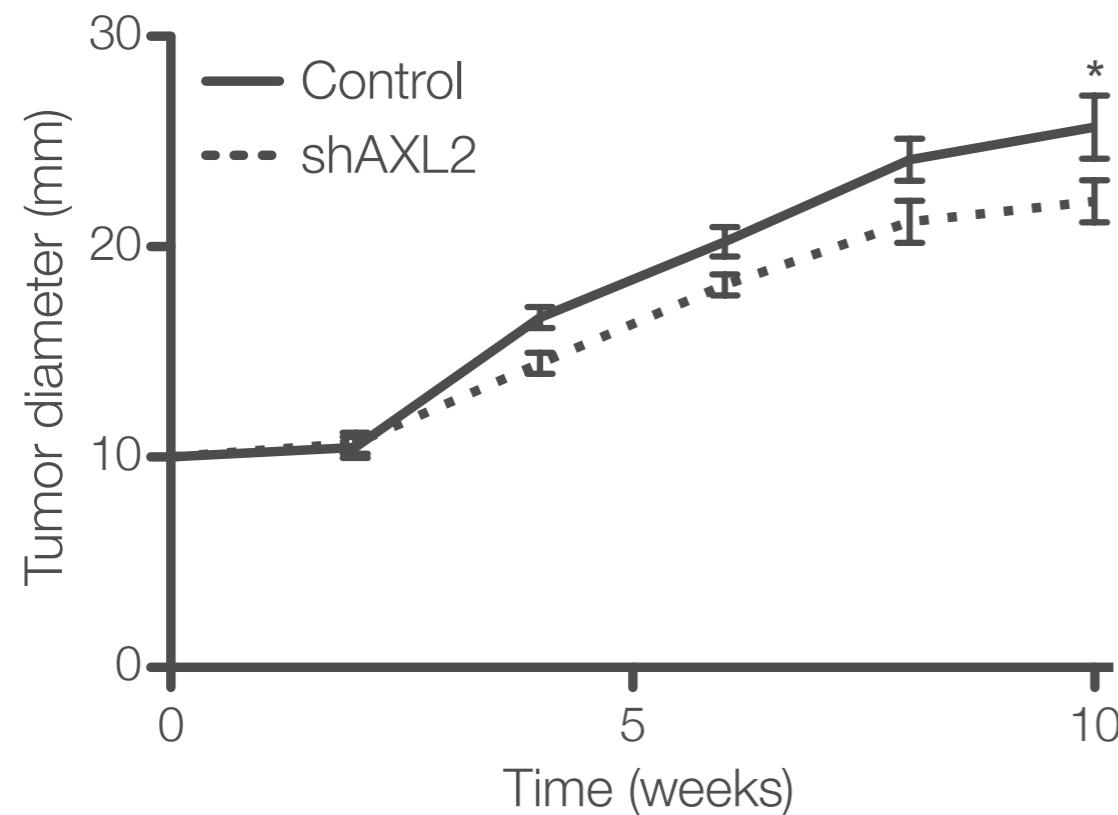
Targeting AXL has minor effects on the primary tumor



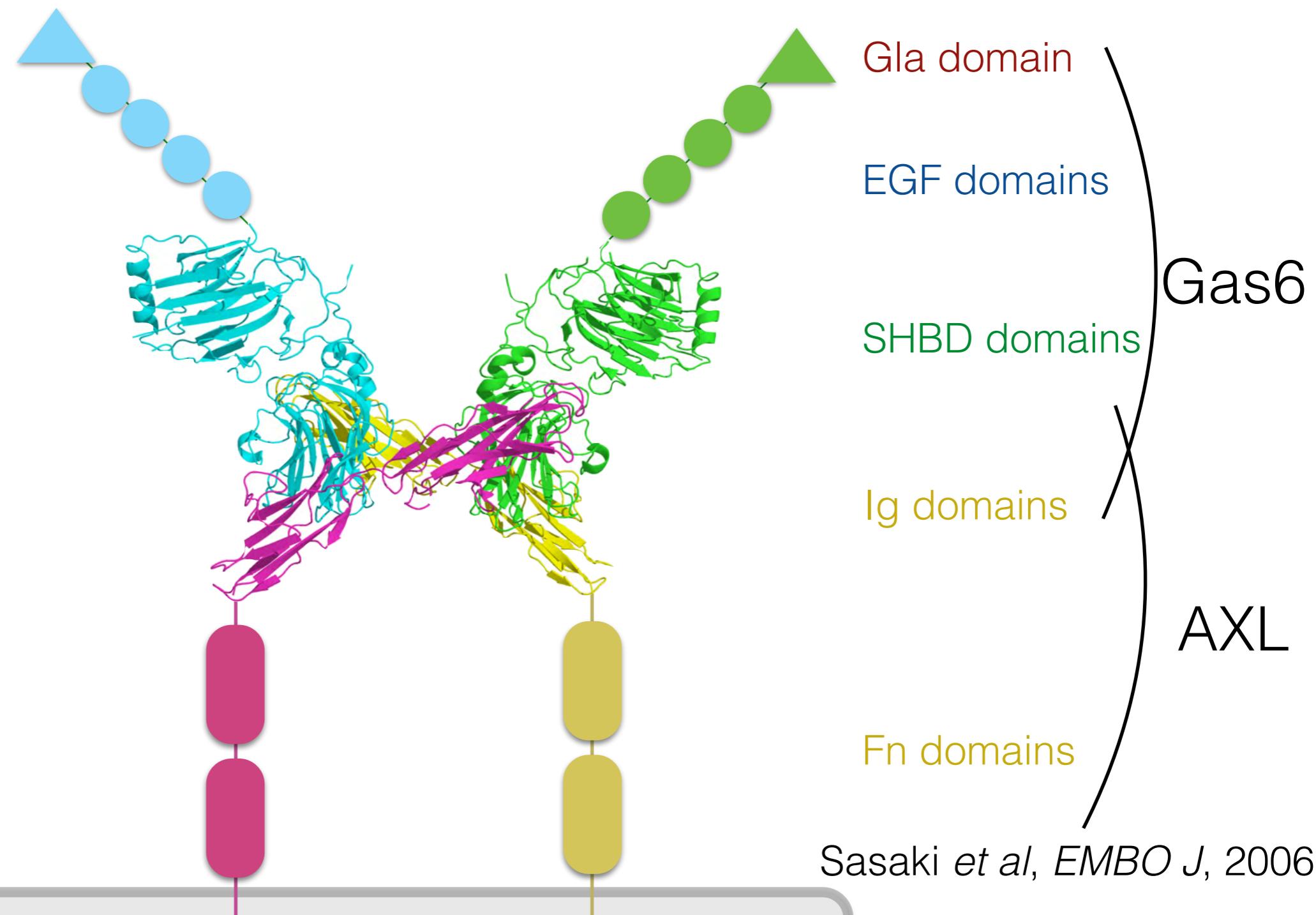
Targeting AXL potently blocks metastasis



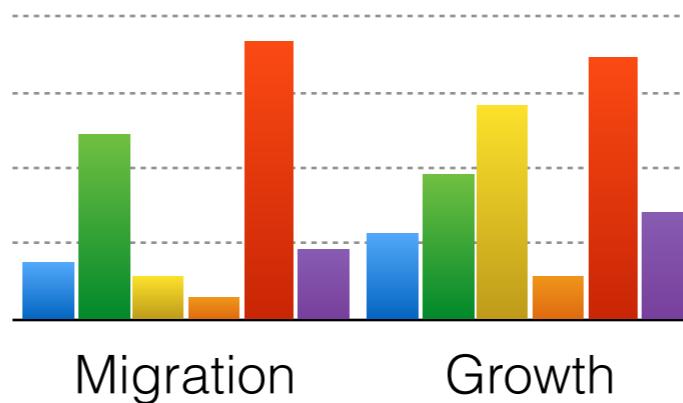
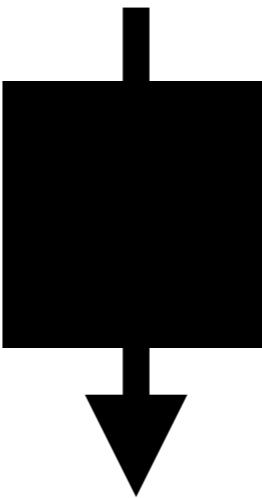
Blocking metastasis is sufficient for improving survival



Structure of AXL/Gas6 complex



The systems approach to studying cell phenotype

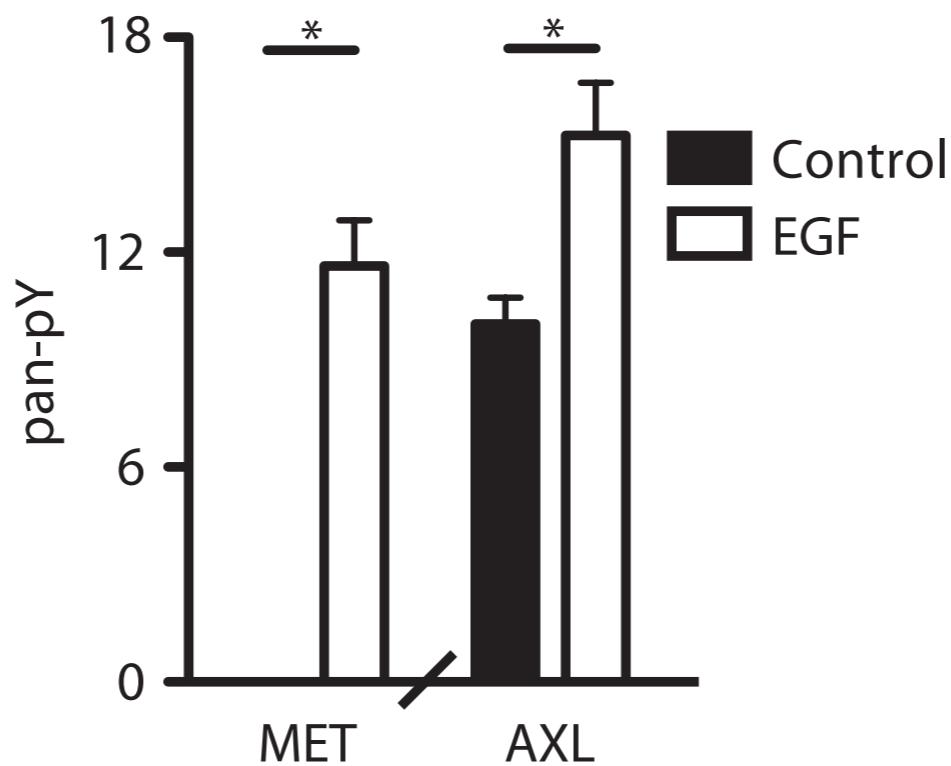


Quantitatively understanding 3D cell migration regulation

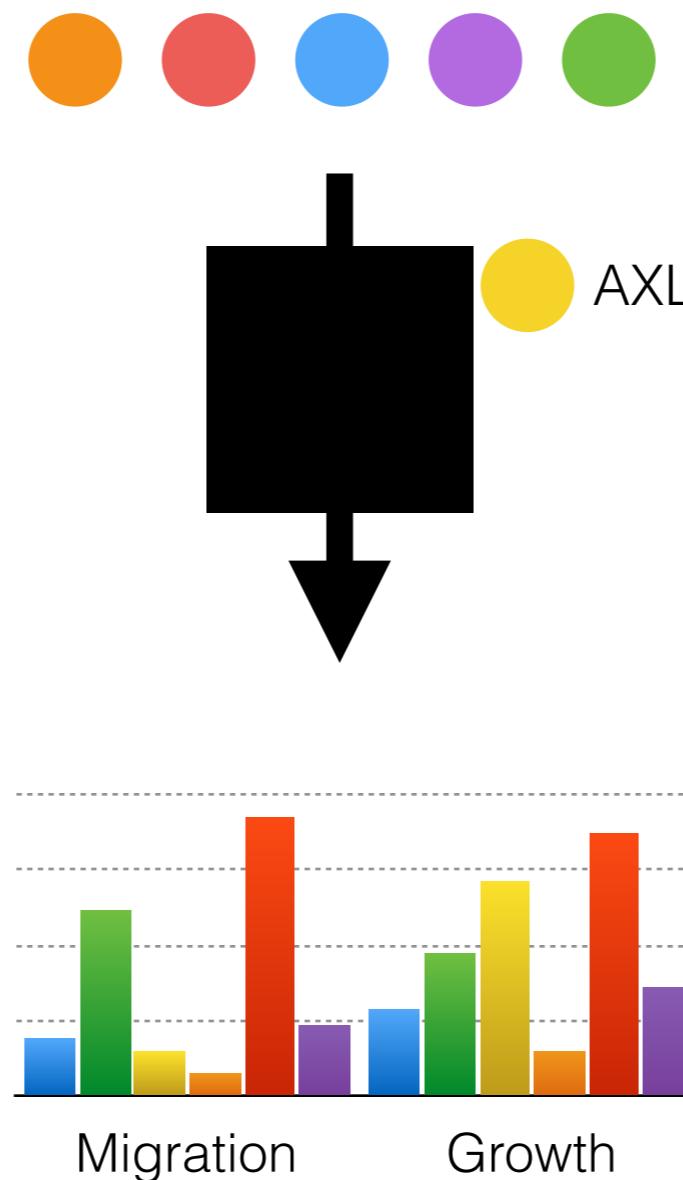


How does signal processing
modulate a migration response?

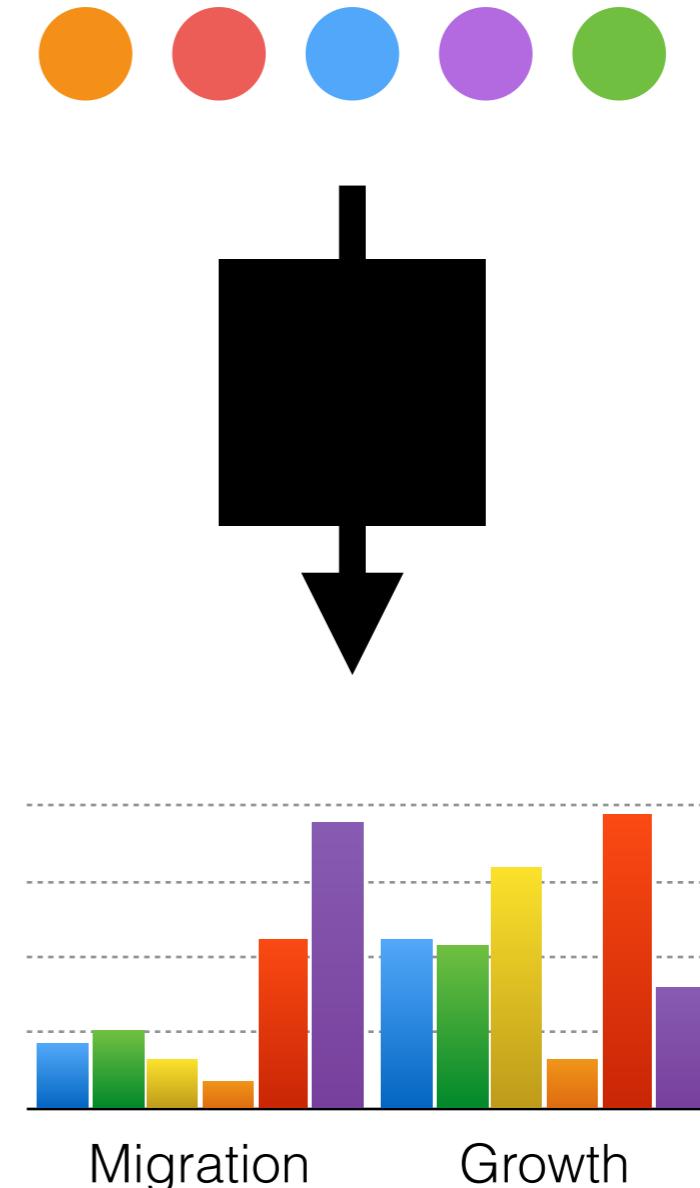
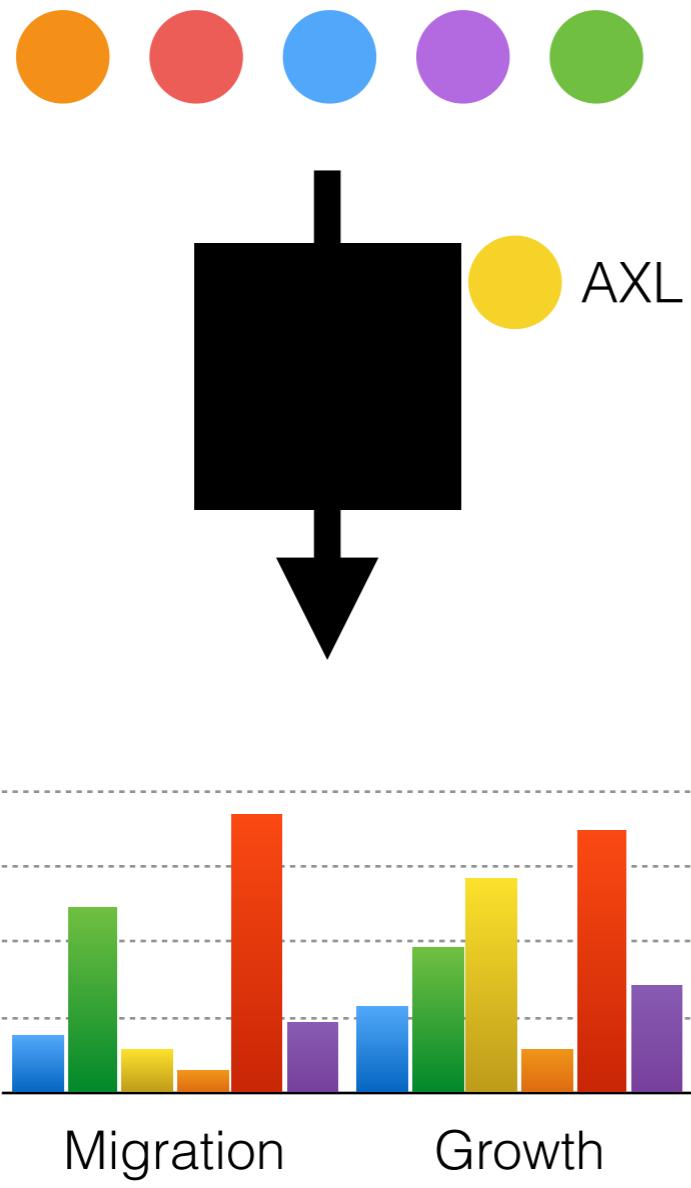
EGFR activation leads to AXL crosstalk



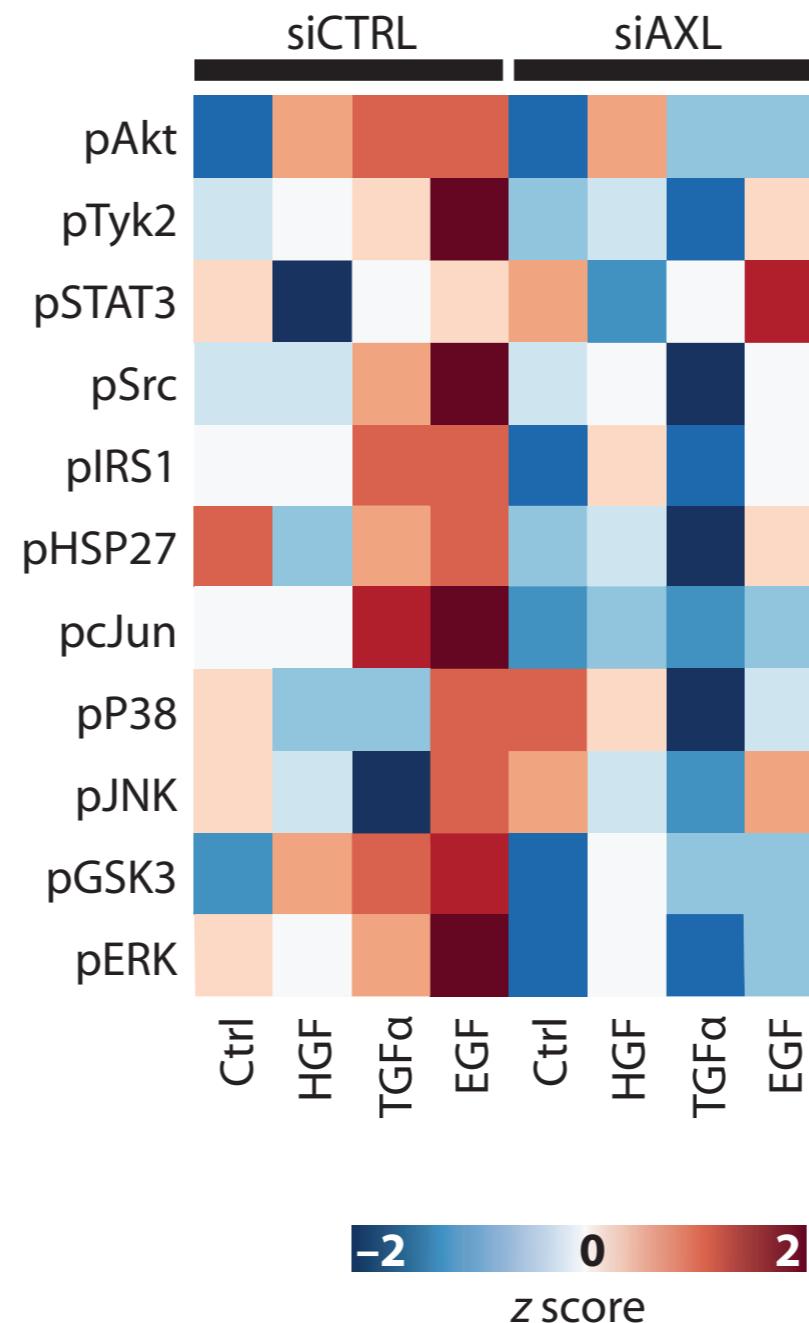
The systems approach to studying cell phenotype



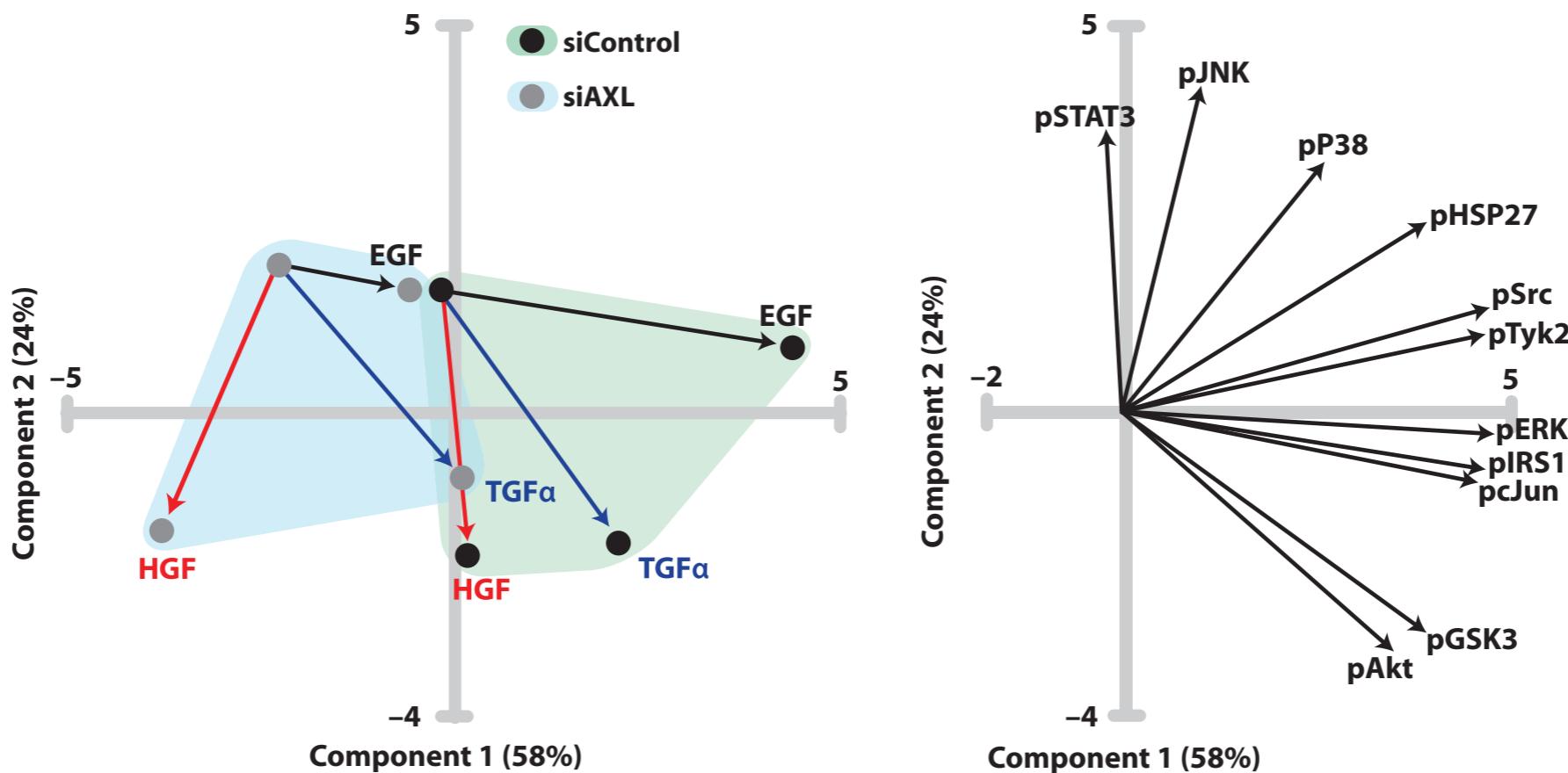
The systems approach to studying cell phenotype



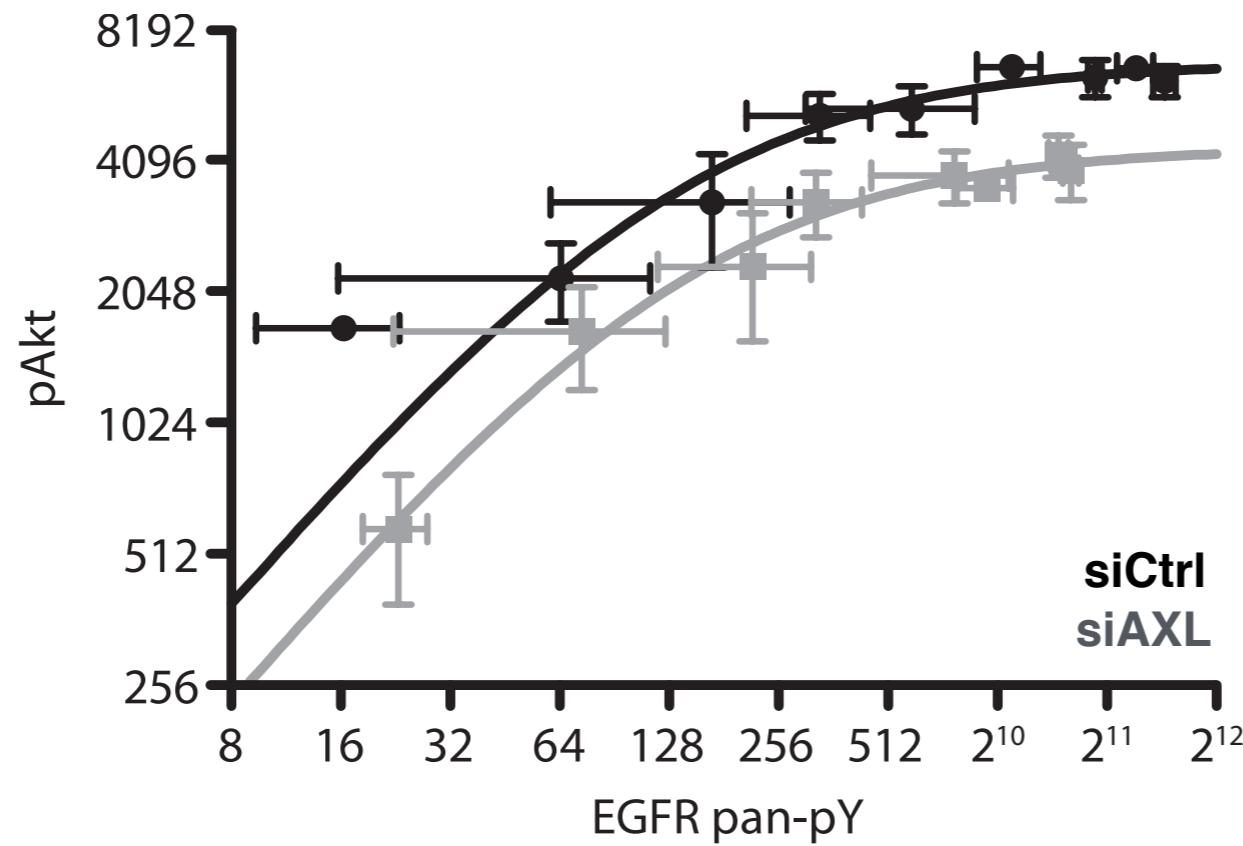
AXL knockdown broadly influences cell signaling



PCA deconvolves transactivation effect

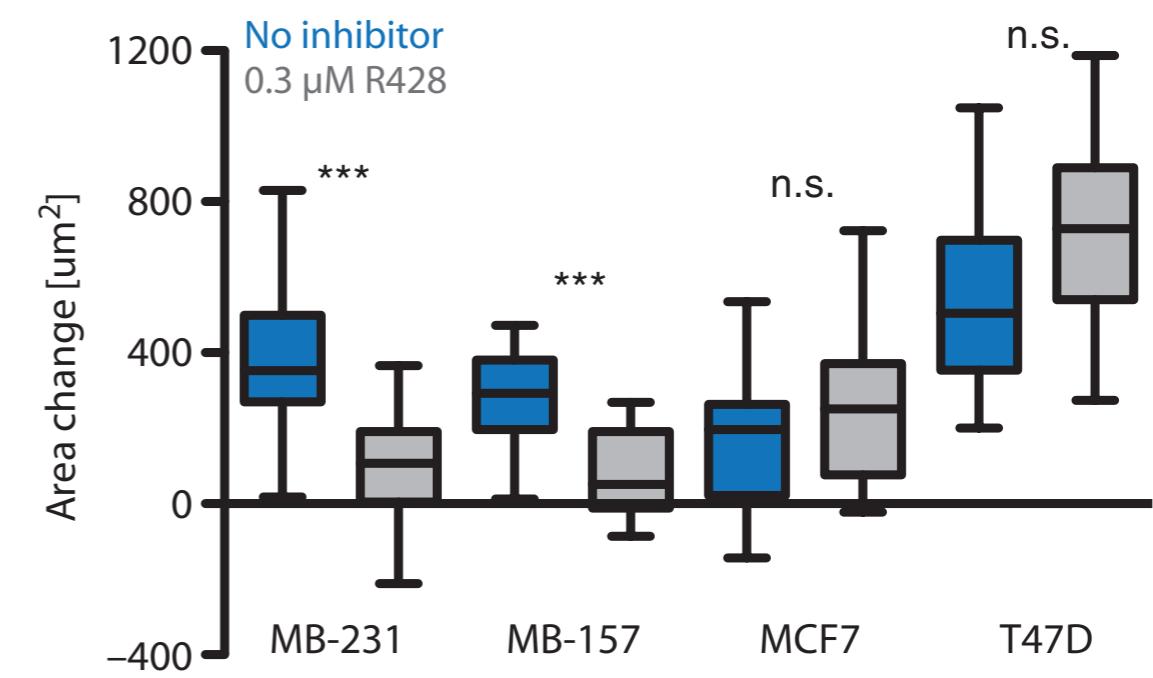
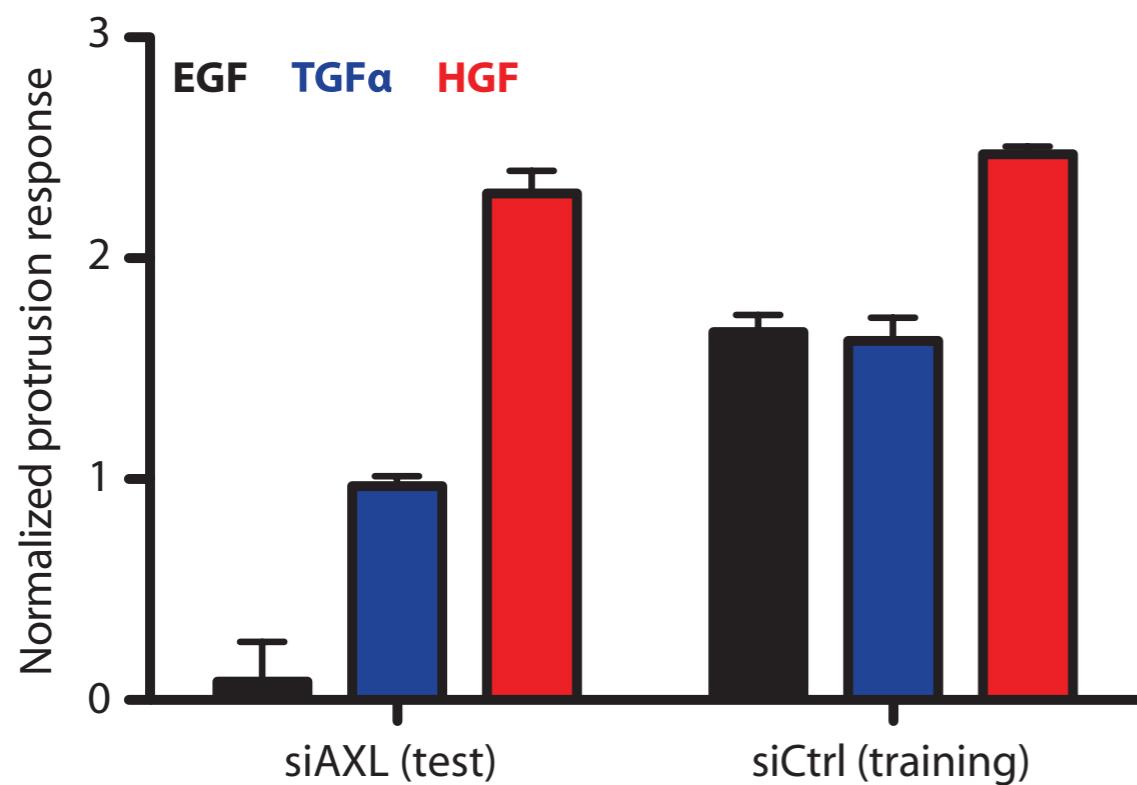


Crosstalk quantitatively amplifies a qualitatively distinct set of pathways



$$[pAkt] = \frac{B_{max,1} [pEGFR]}{K_{D,1} + [pEGFR]} + \frac{\xi B_{max,2} ([pEGFR] + \beta)}{K_{D,2} + ([pEGFR] + \beta)}$$

AXL is required for EGF-elicited protrusion

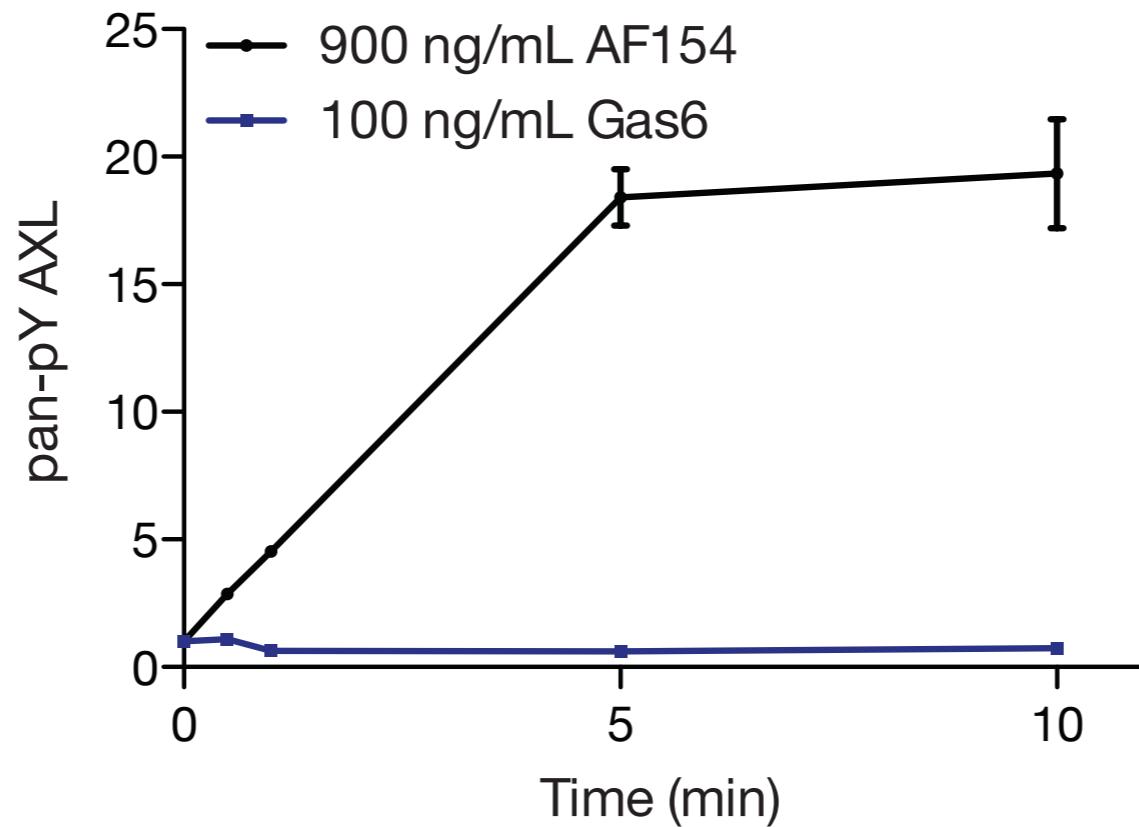


Quantitatively understanding 3D cell migration regulation



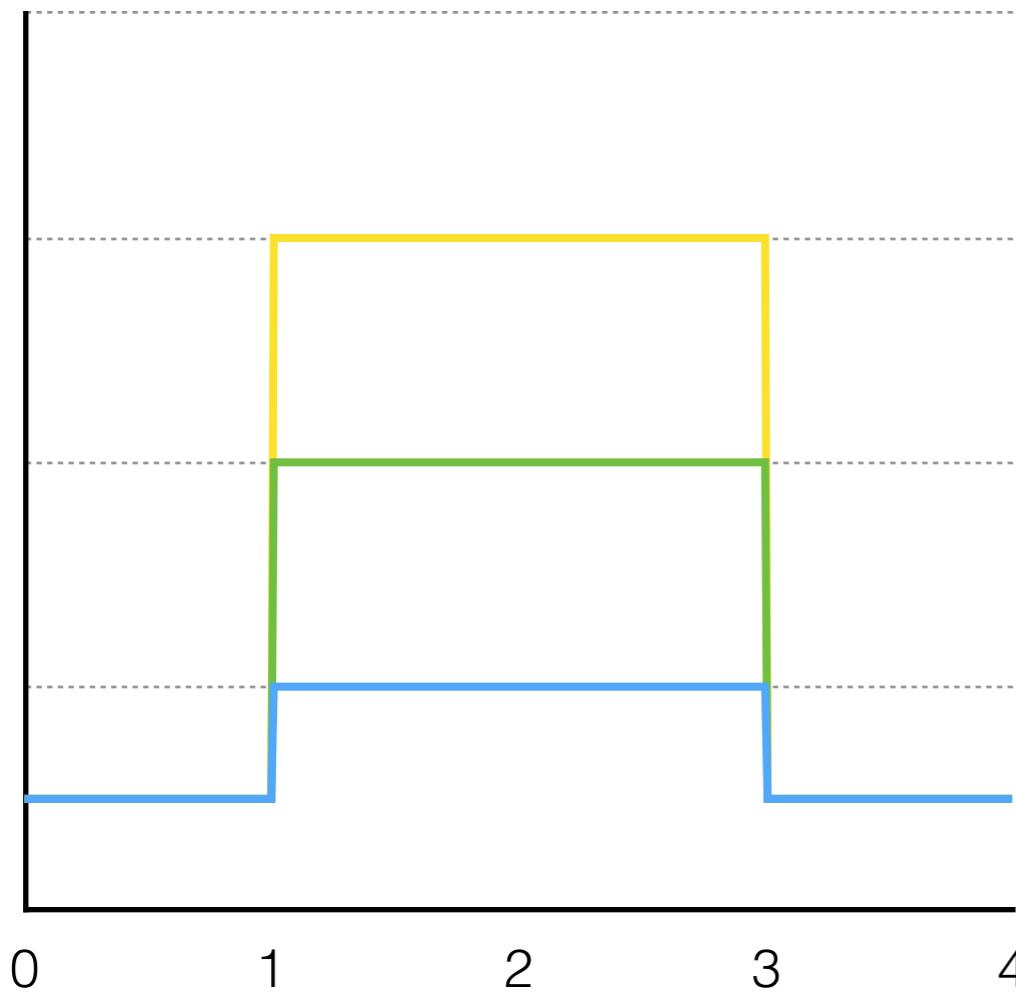
How do TAM receptors process extracellular cues?

Conundrum: AXL does not robustly respond to ligand stimulation

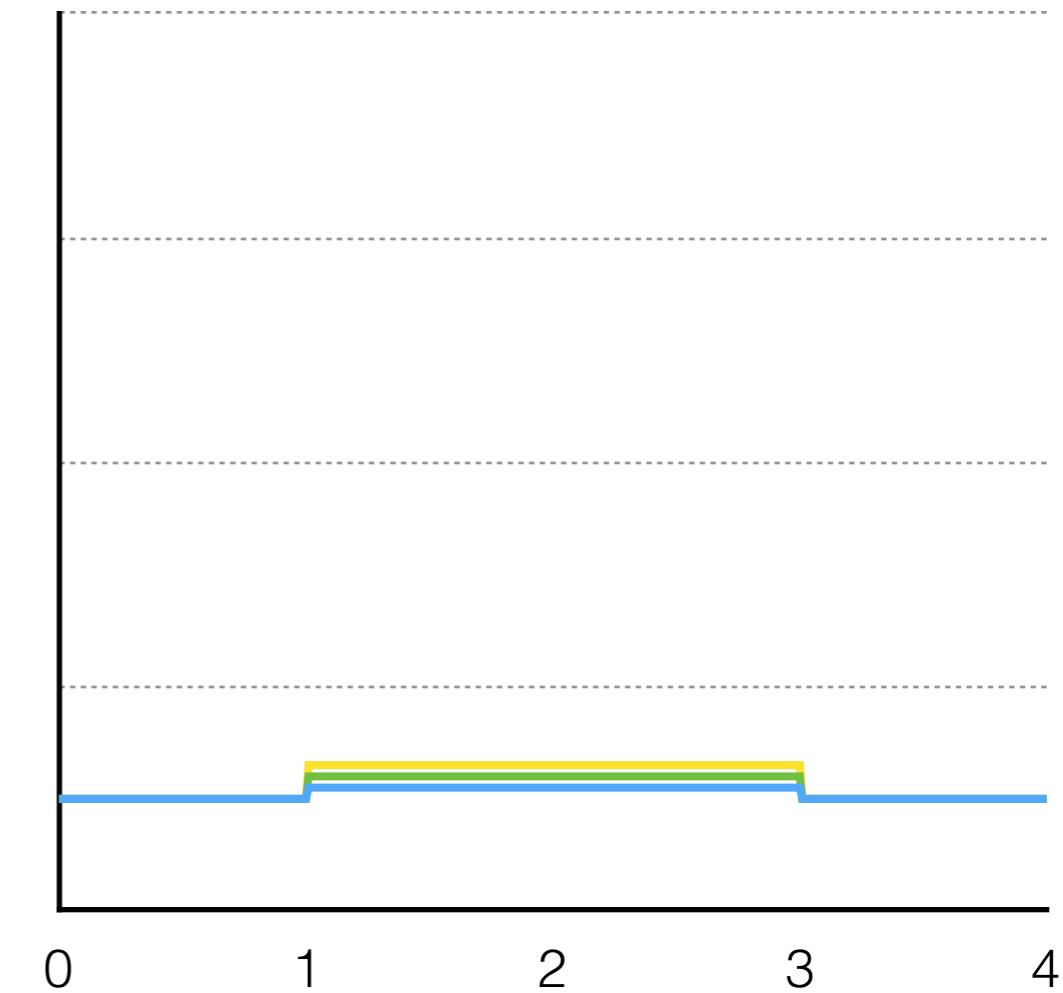


Attributes of a good sensor

Large dynamic range



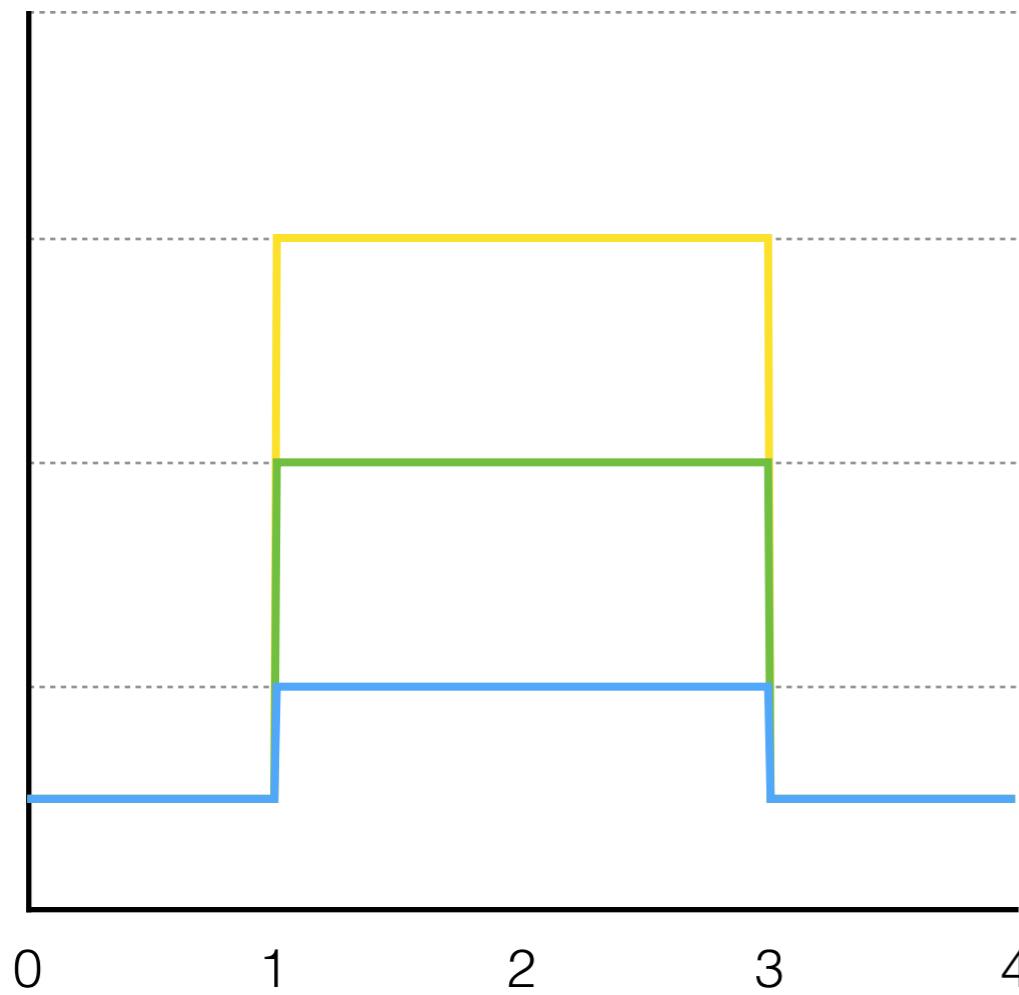
Input



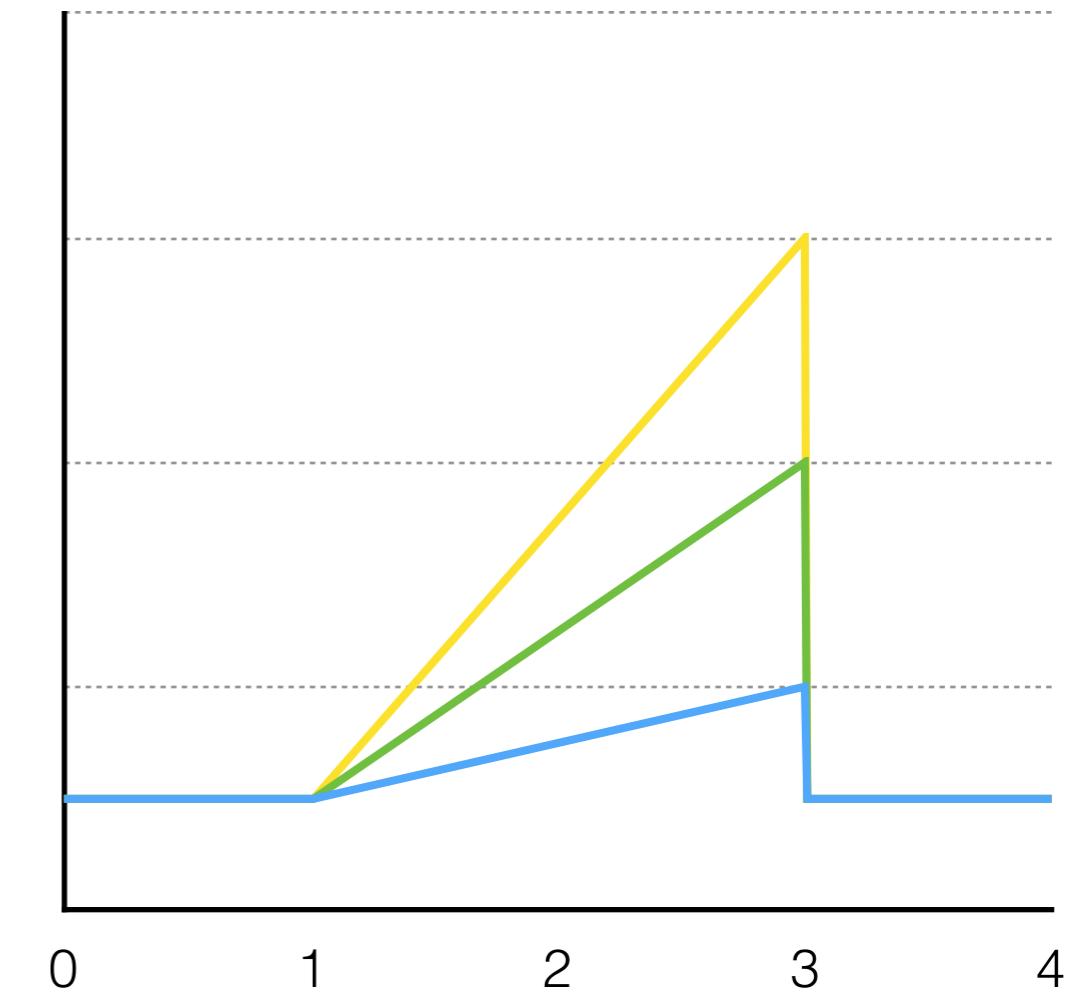
Output

Attributes of a good sensor

Rapid response

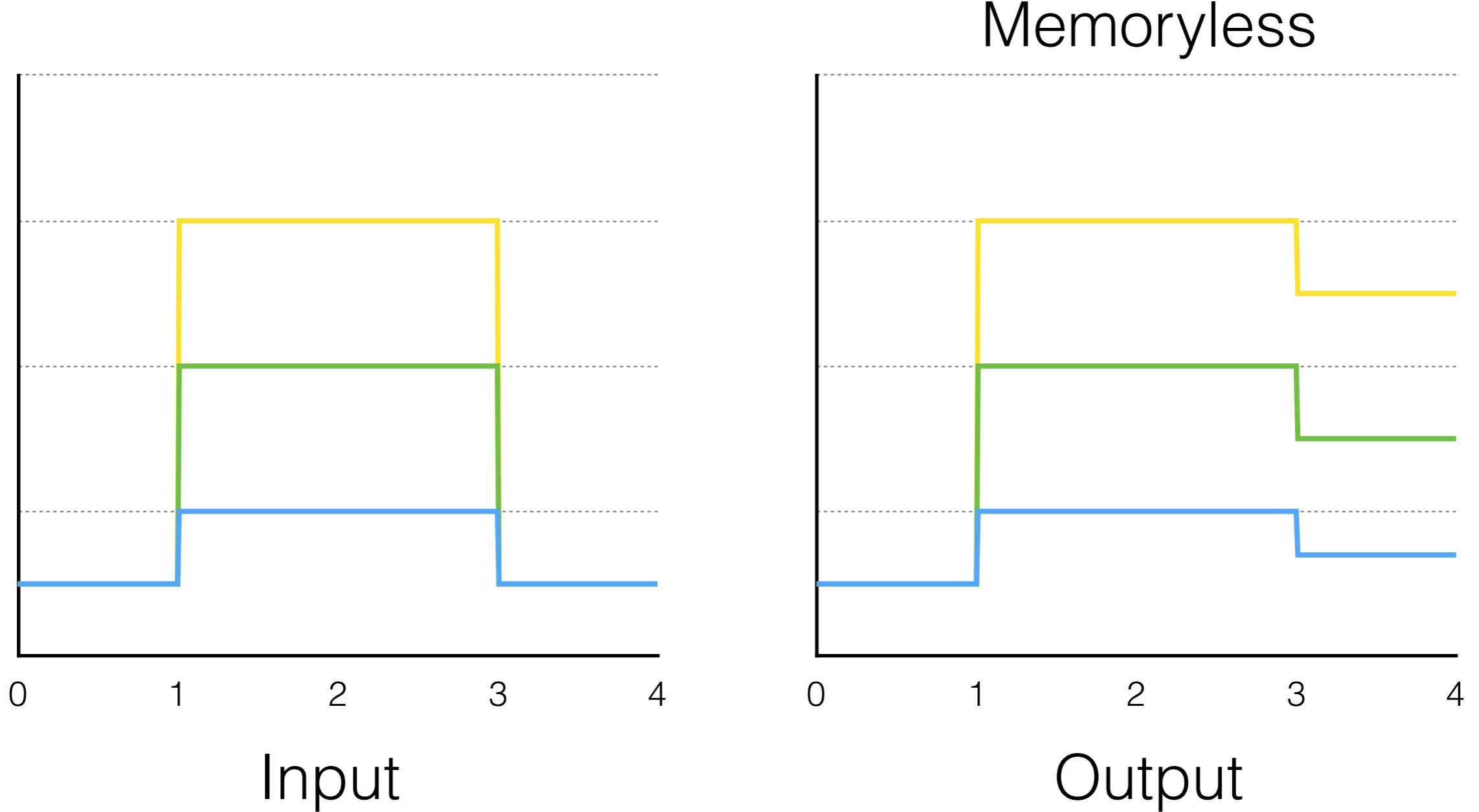


Input

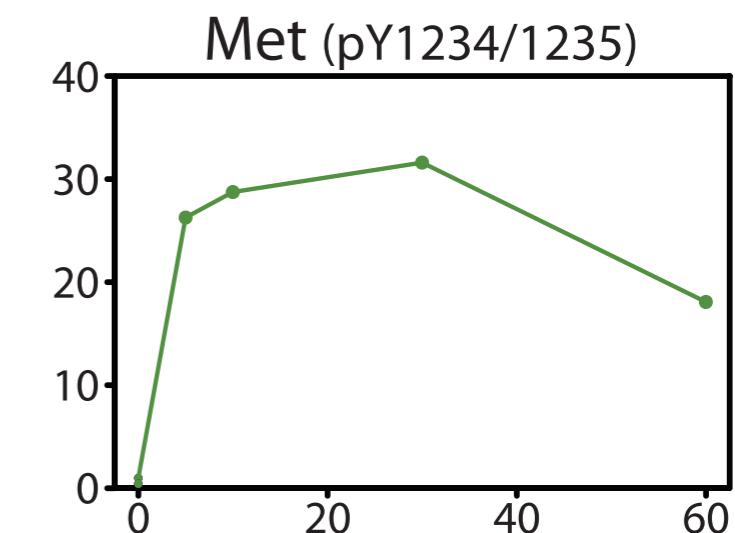
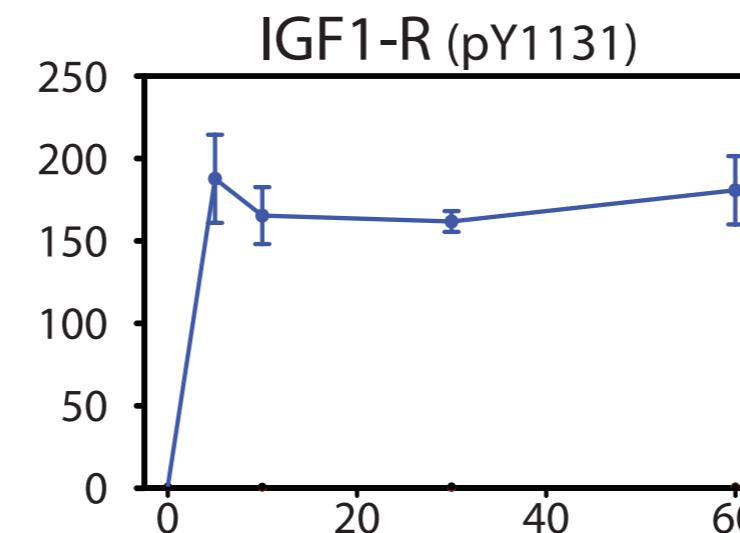
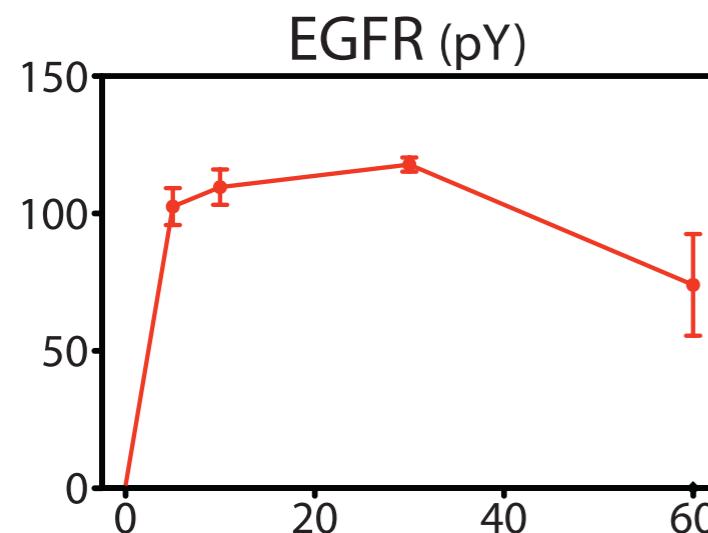


Output

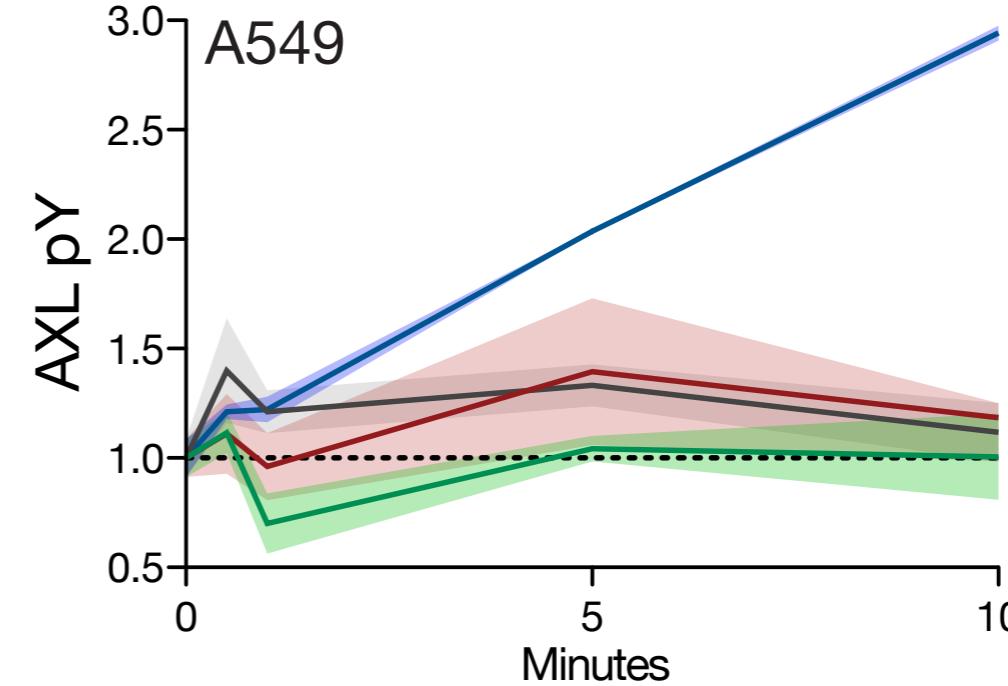
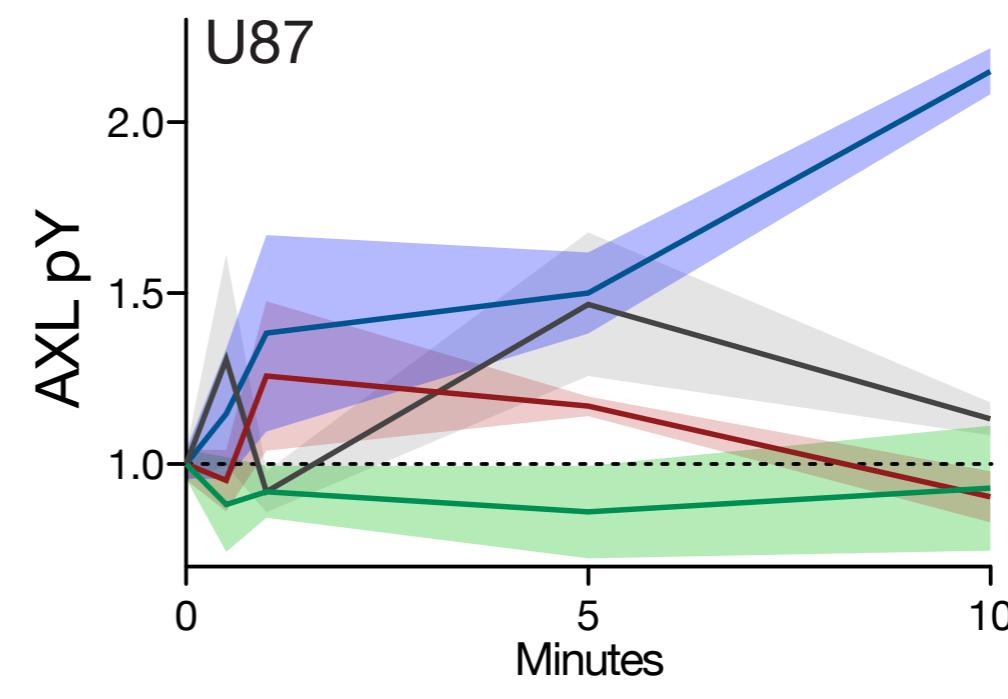
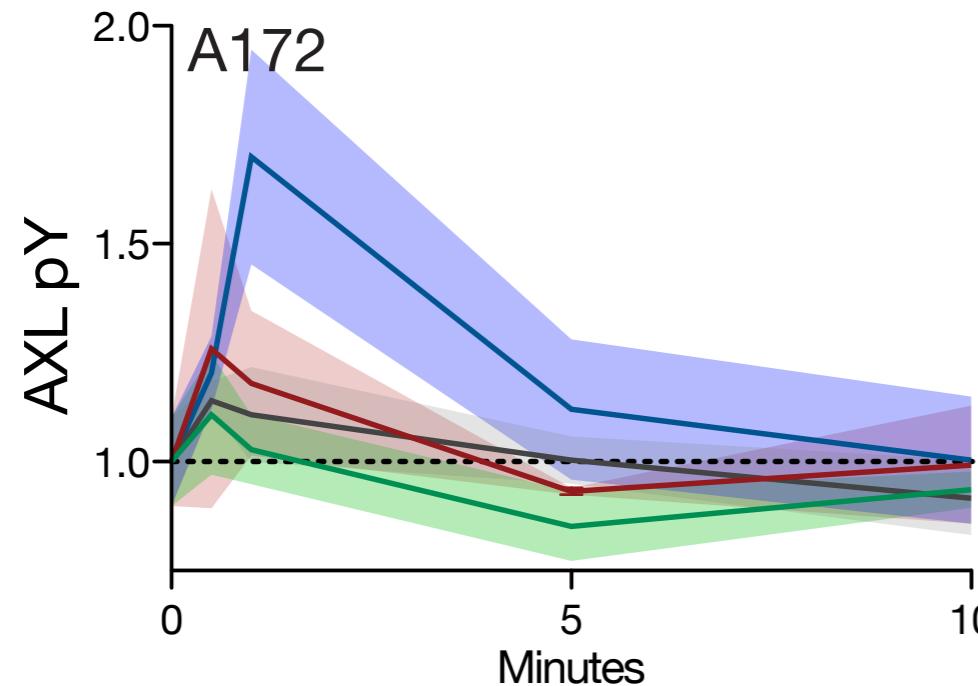
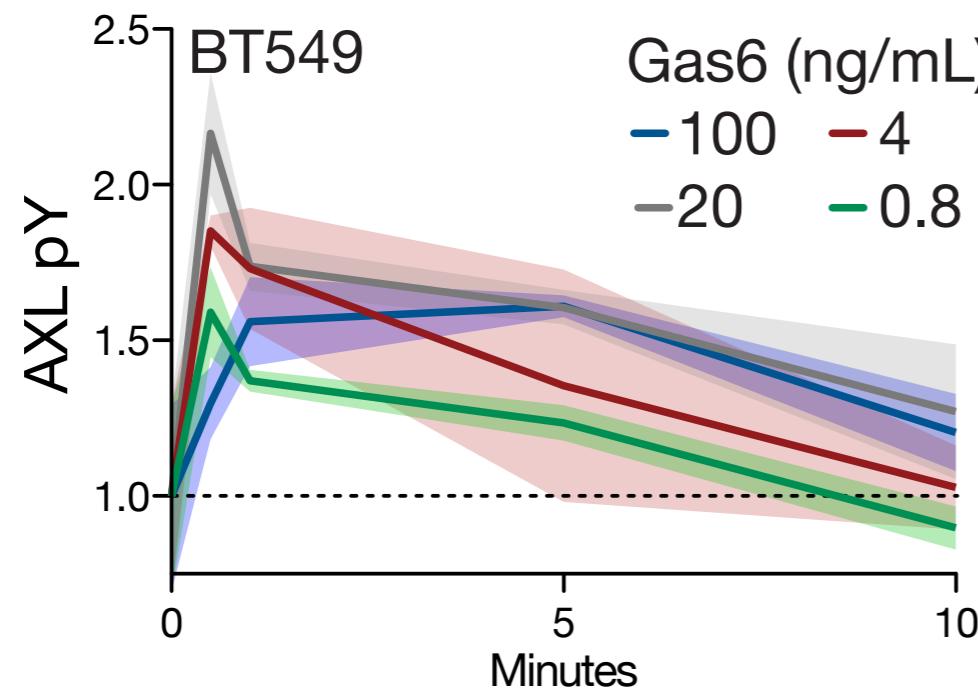
Attributes of a good sensor



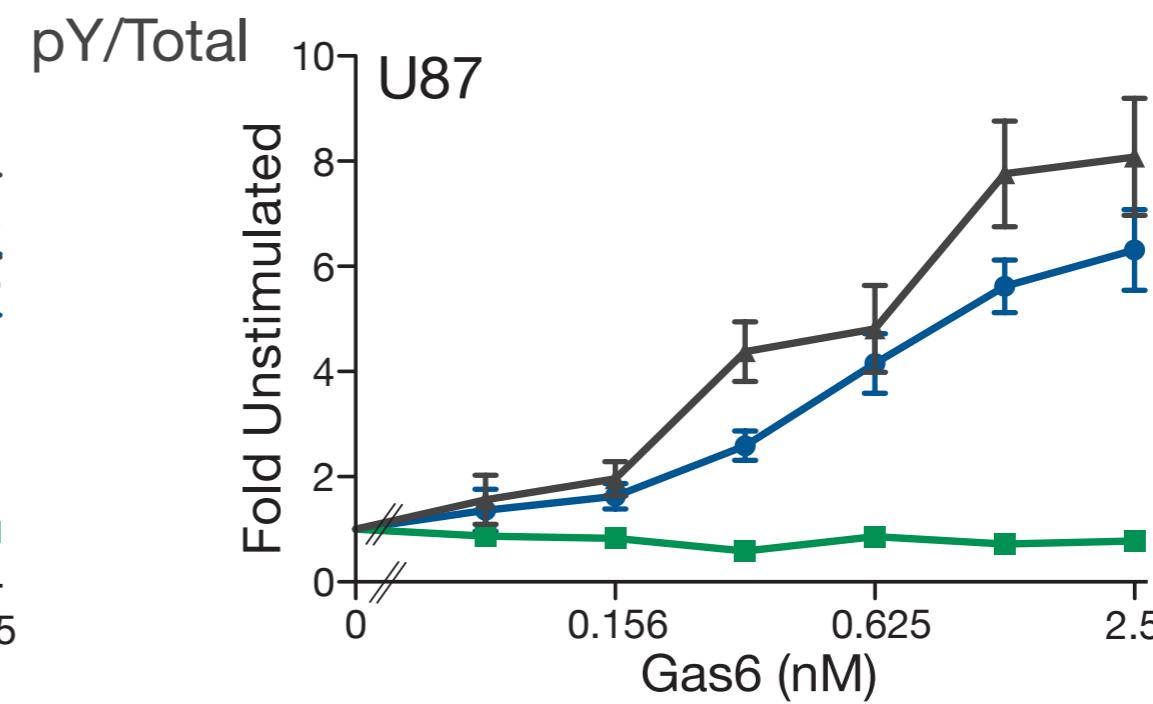
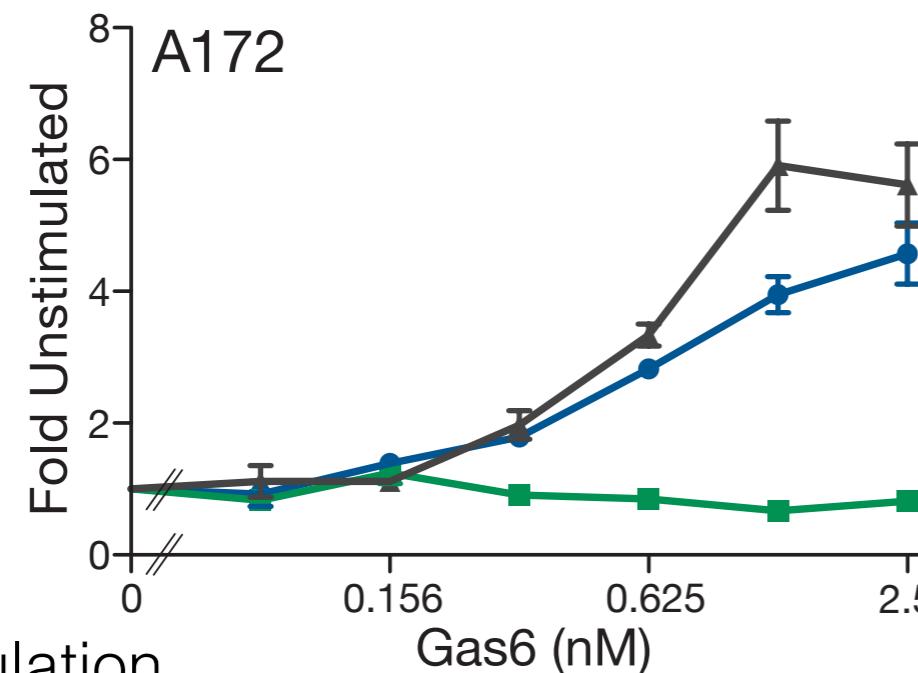
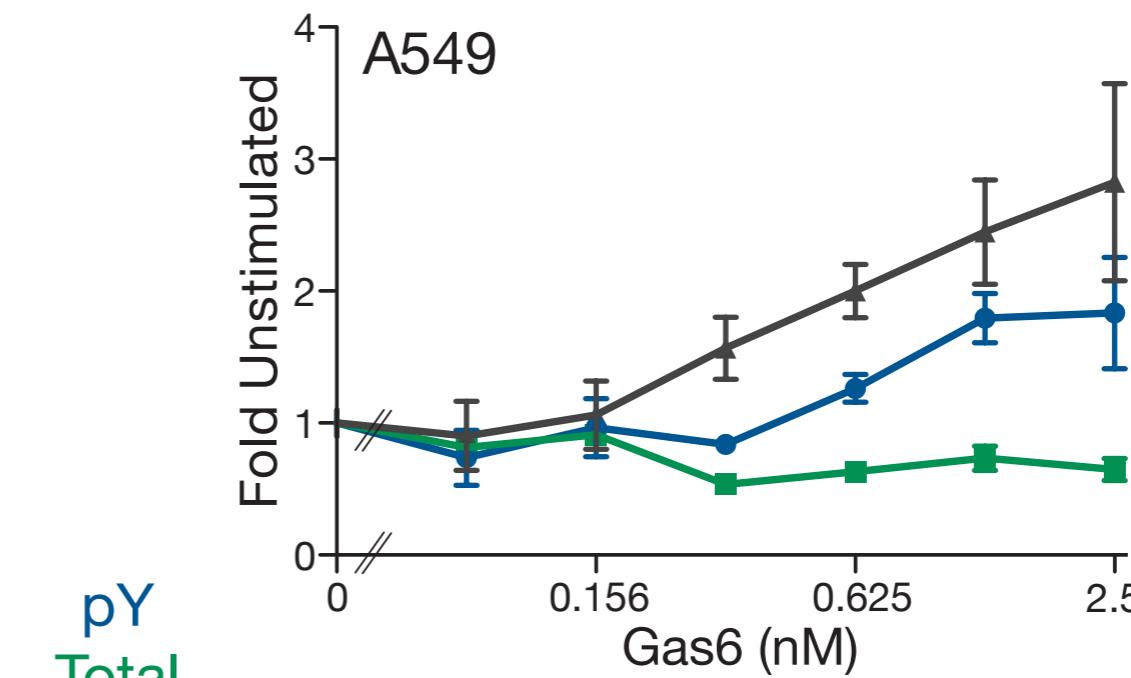
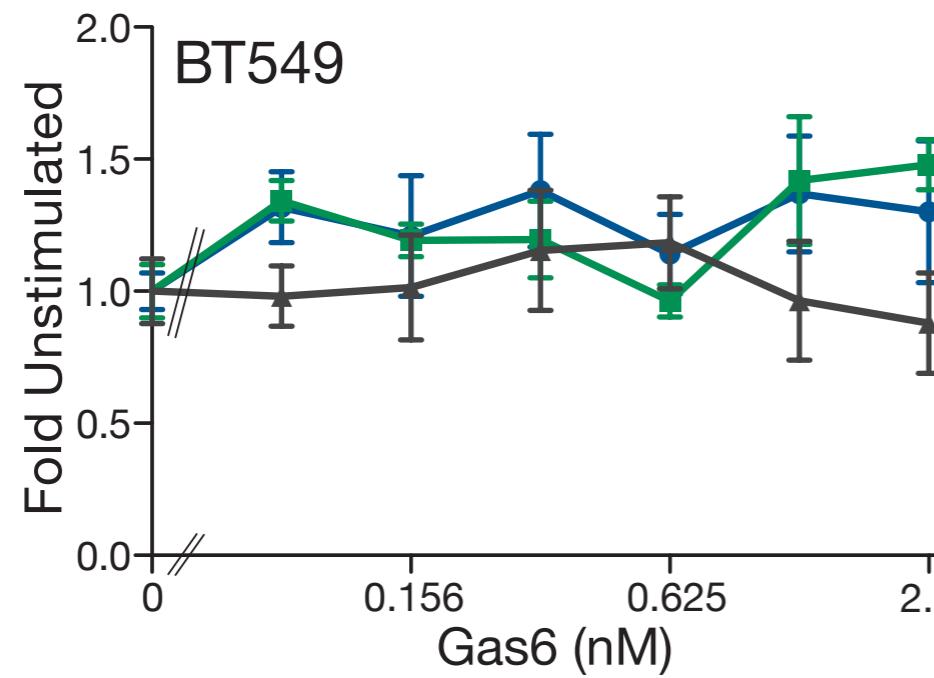
Many RTKs can be considered as
“ligand concentration sensors”



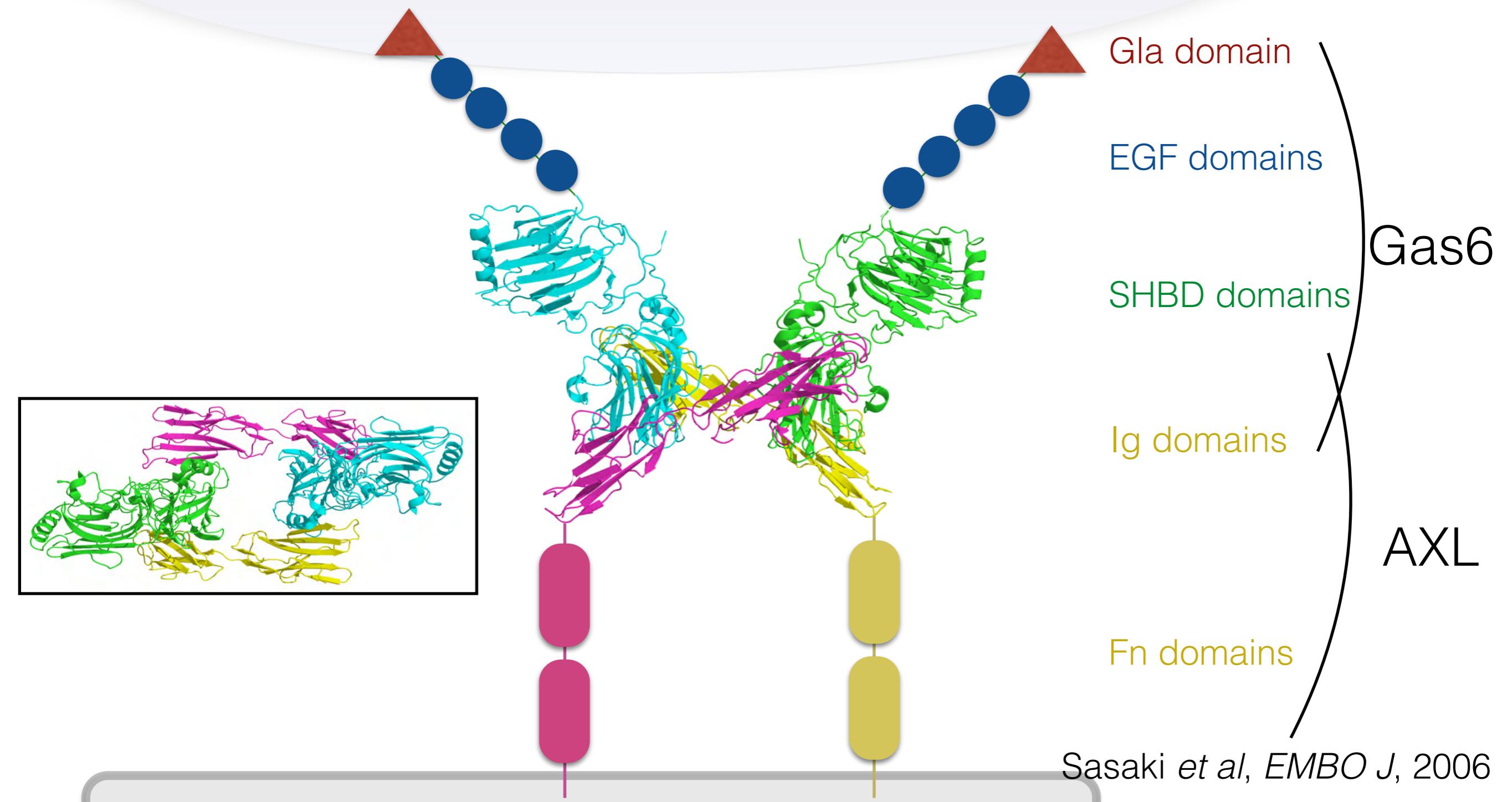
Gas6 stimulation reveals complex response patterns



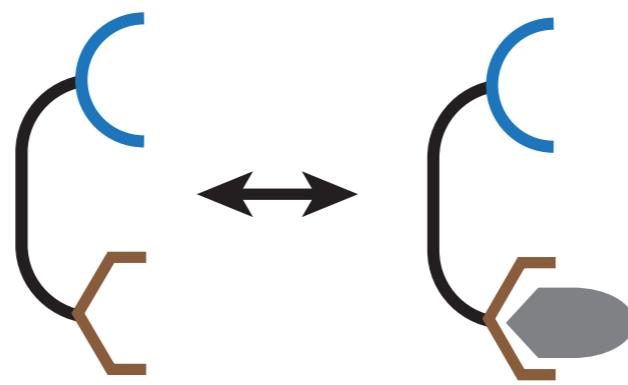
AXL still poorly responsive to Gas6 at longer times



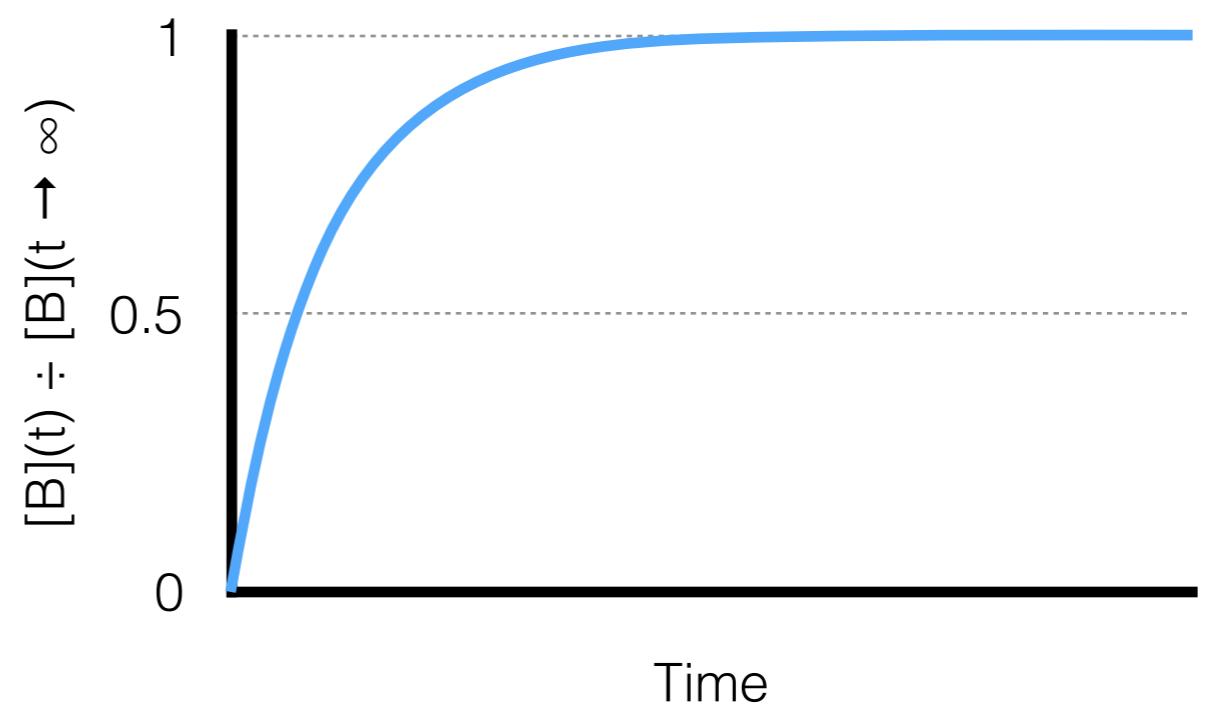
Structure of AXL/Gas6 complex



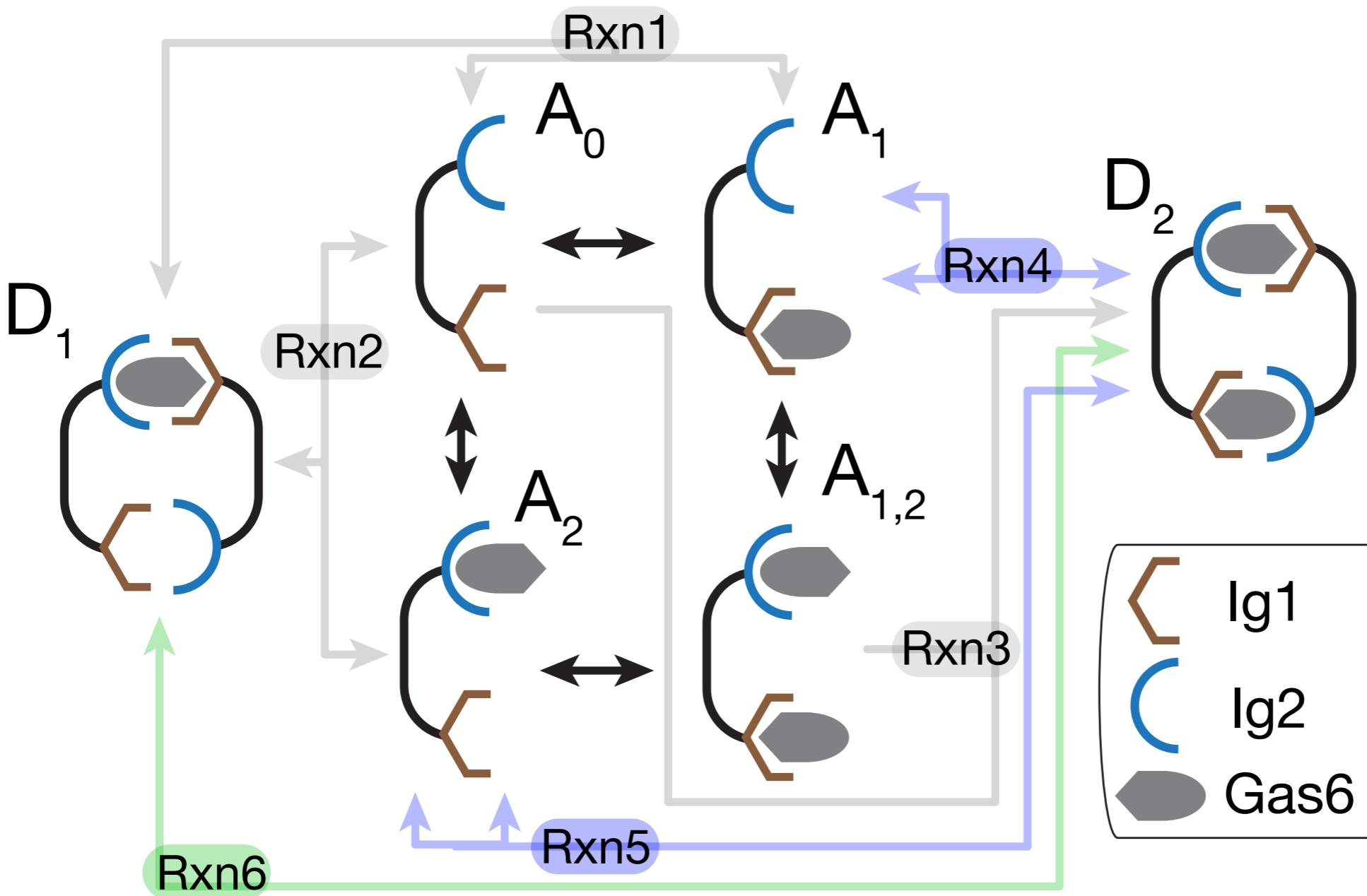
A differential equation model of receptor activation



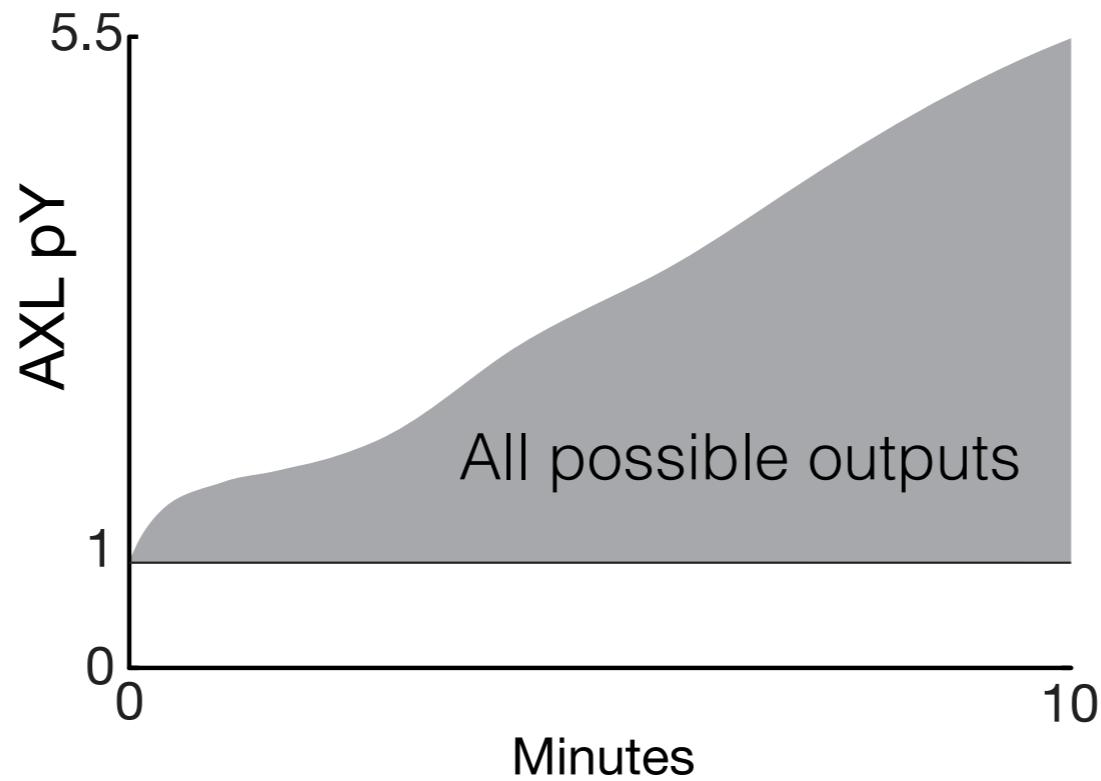
$$\frac{\delta[B]}{\delta t} = k_f[R][G] - k_r[B]$$



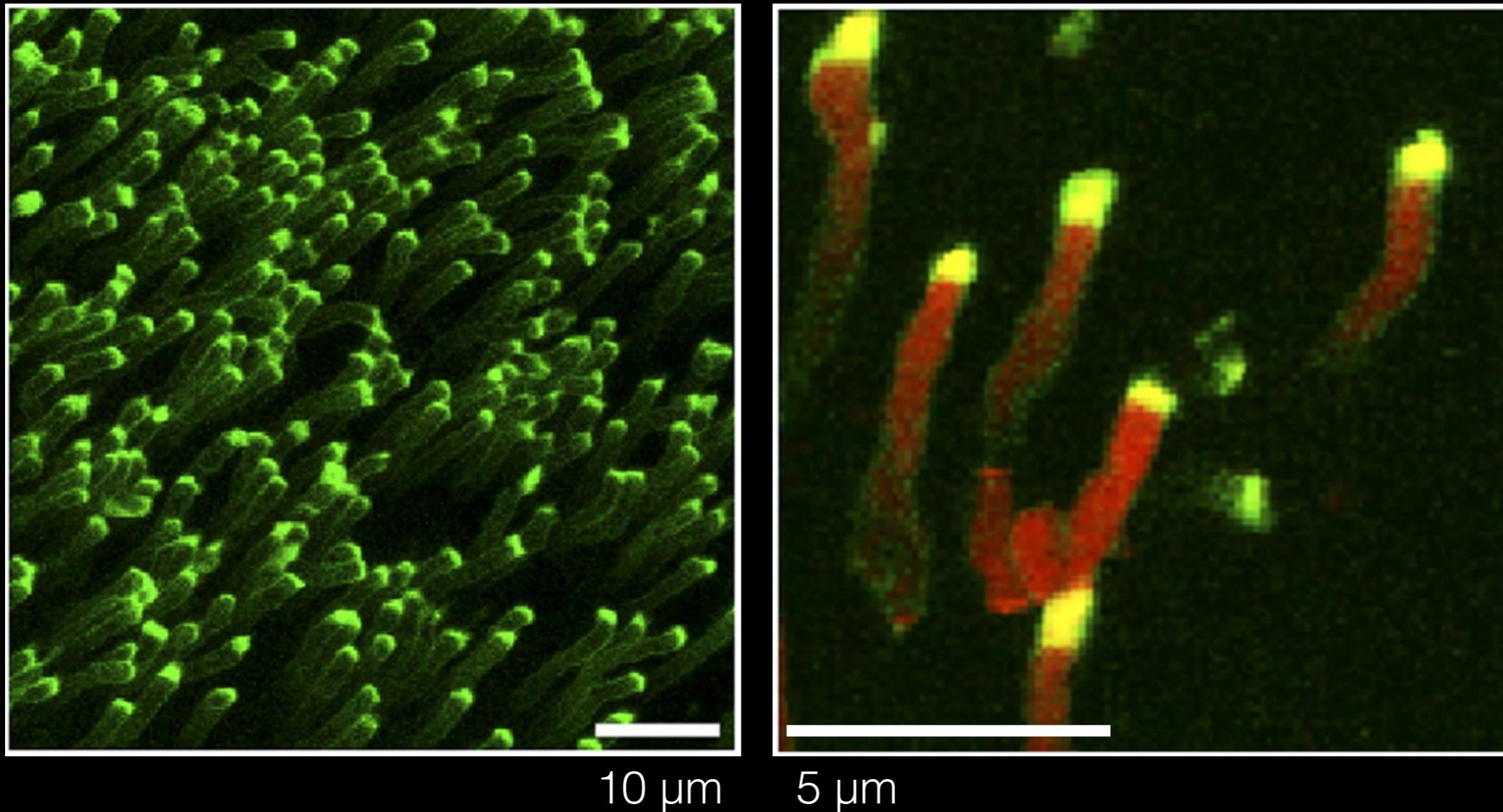
TAM kinetic model allows mechanistic interpretation



AXL has a limited rapid response to stimulation

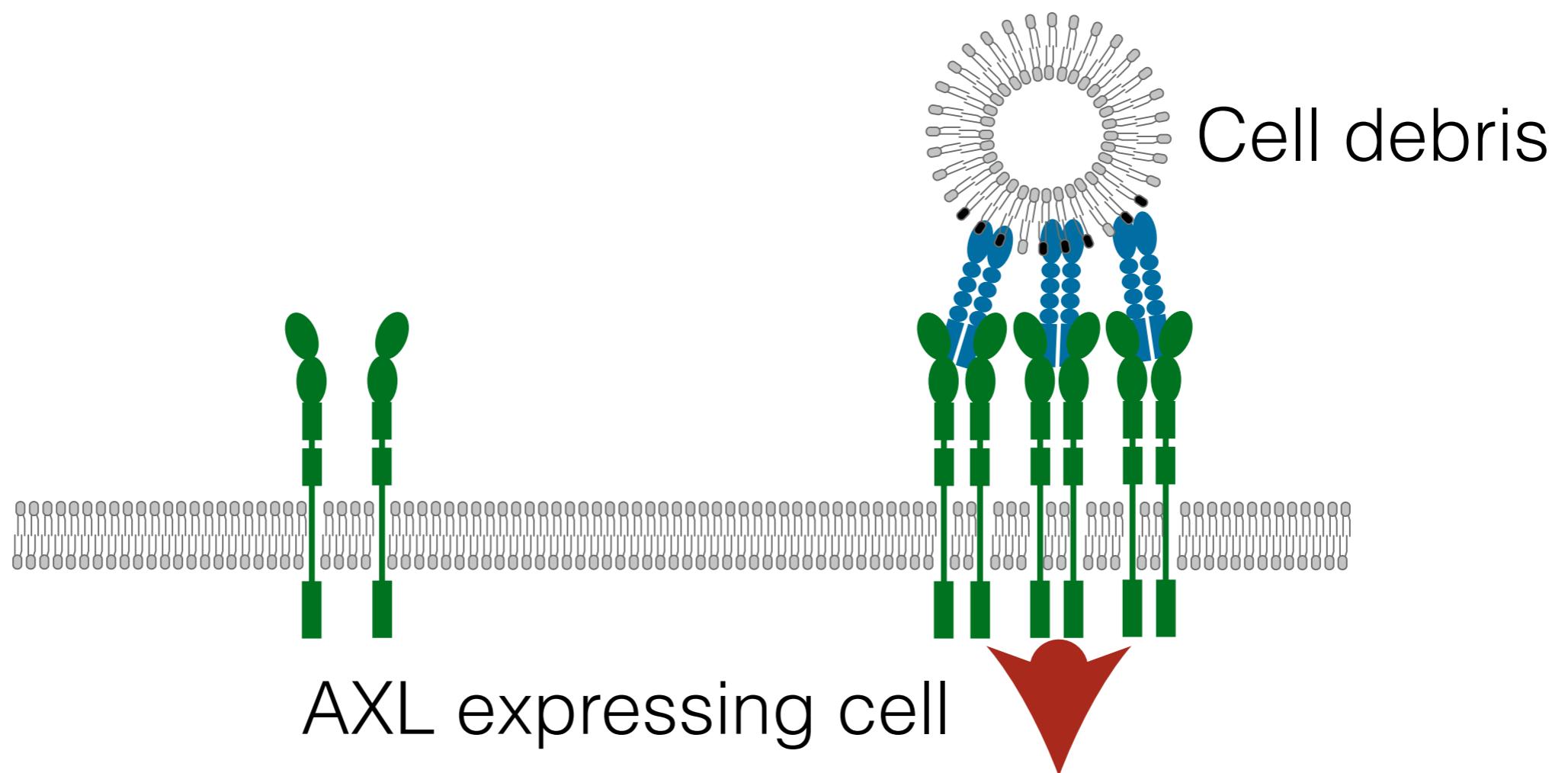


Ptds Exposure is a Spatially Localized Process

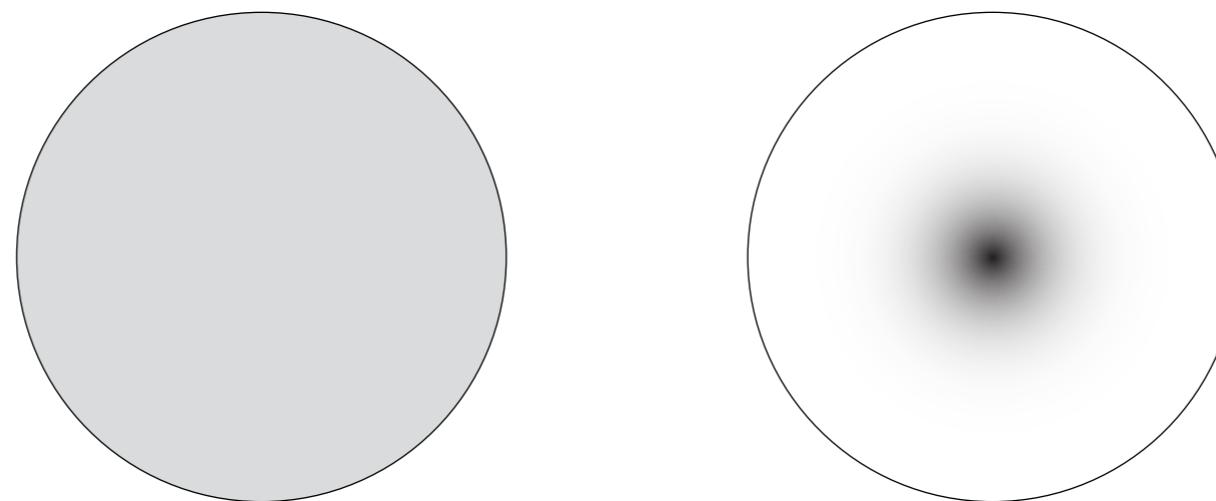
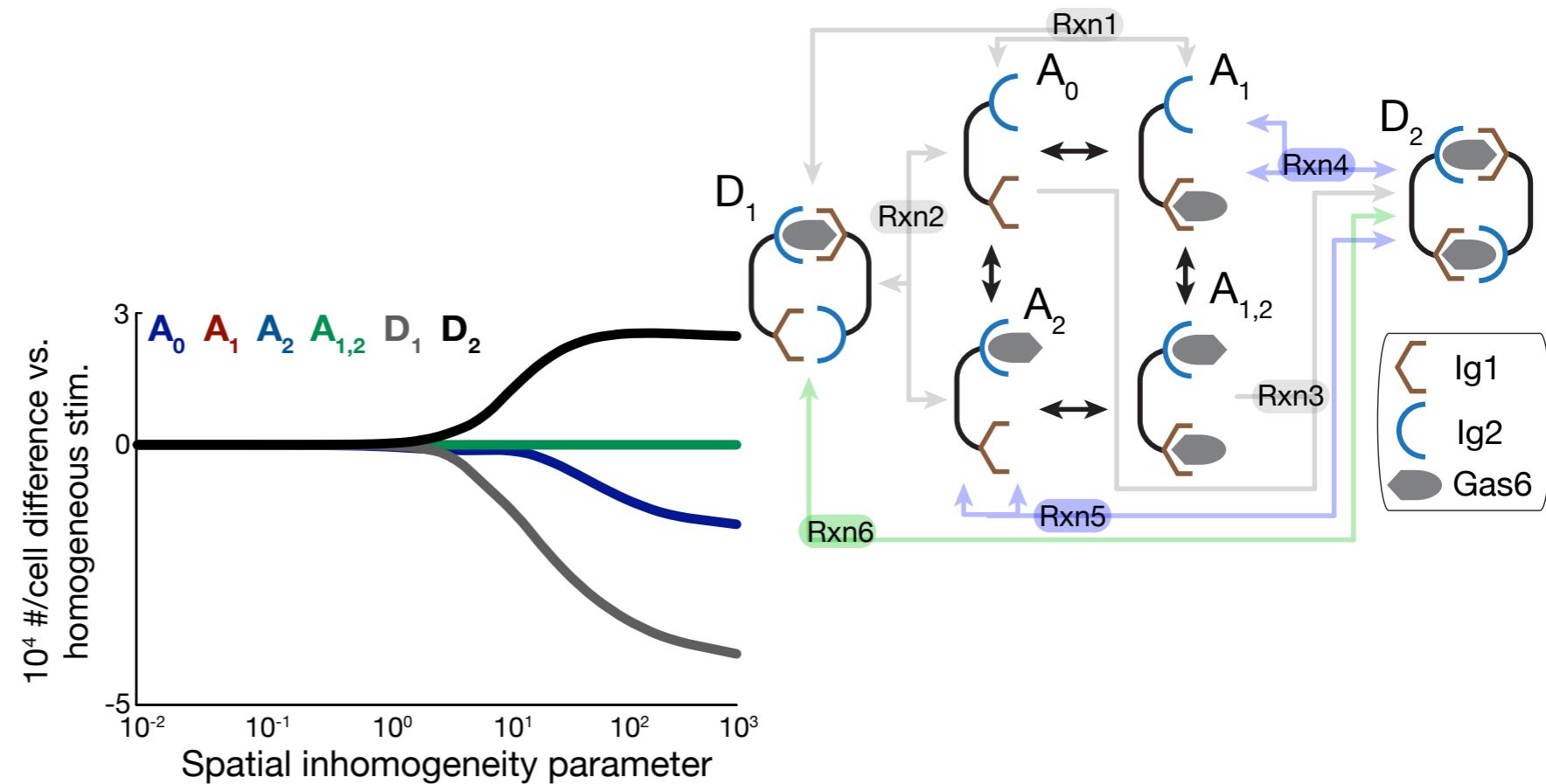


Exposed Ptds
Membrane

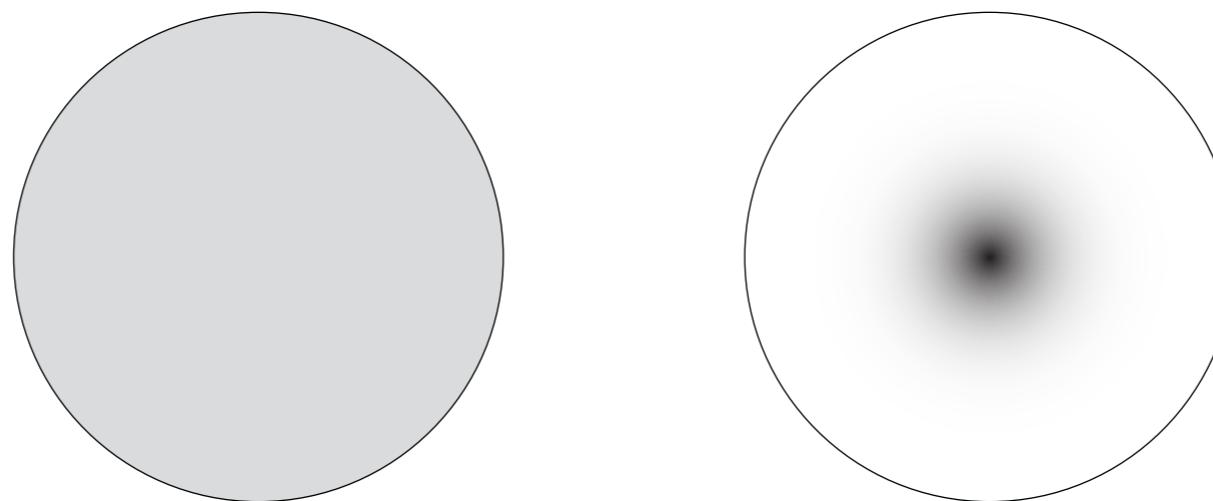
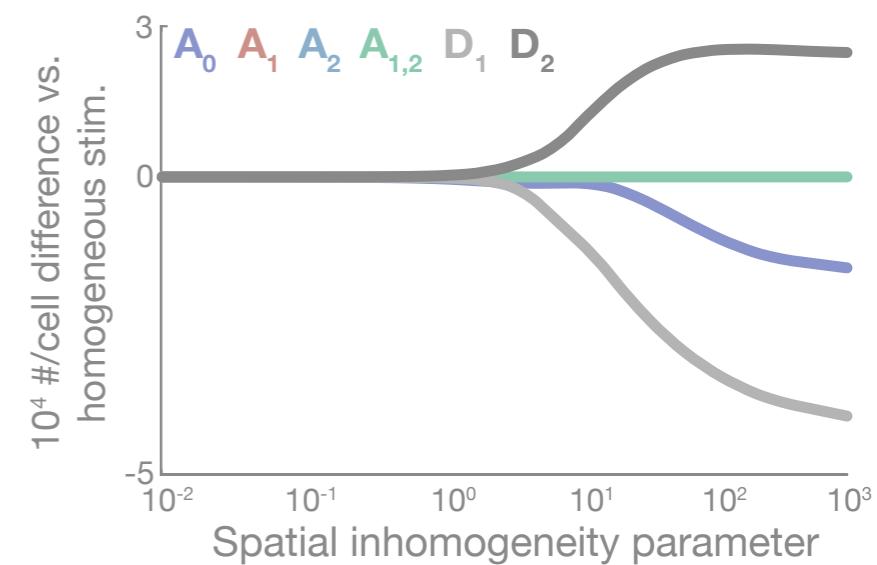
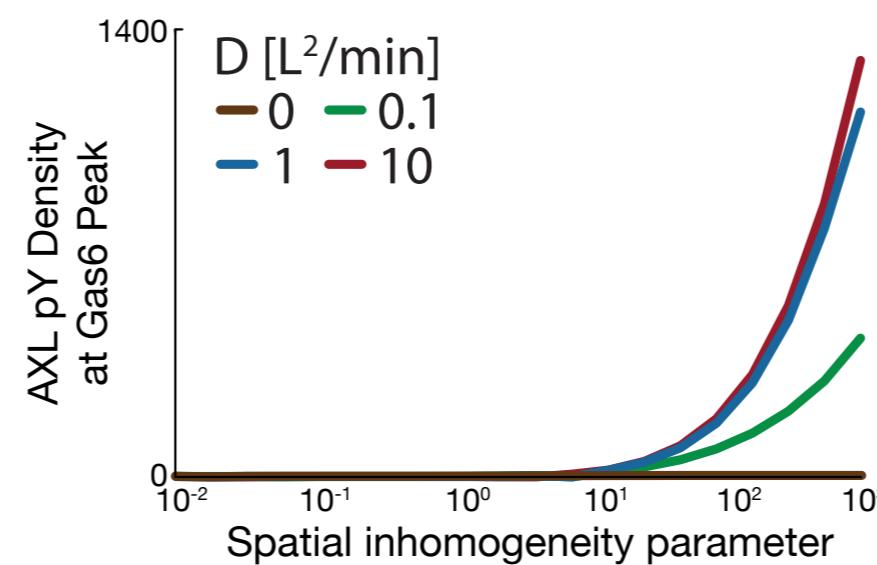
Perhaps robust receptor activation only occurs in response to local stimulation?



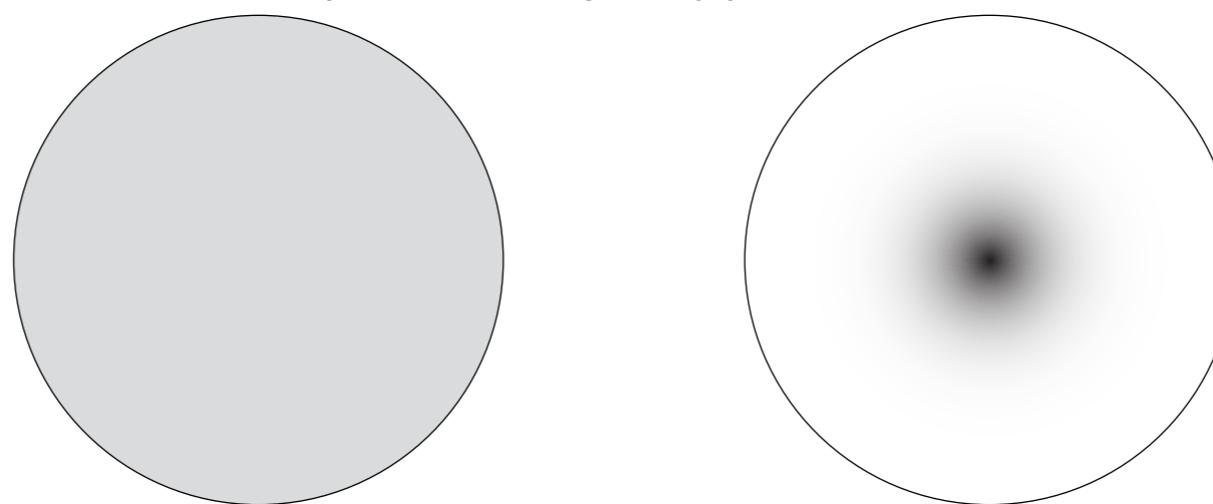
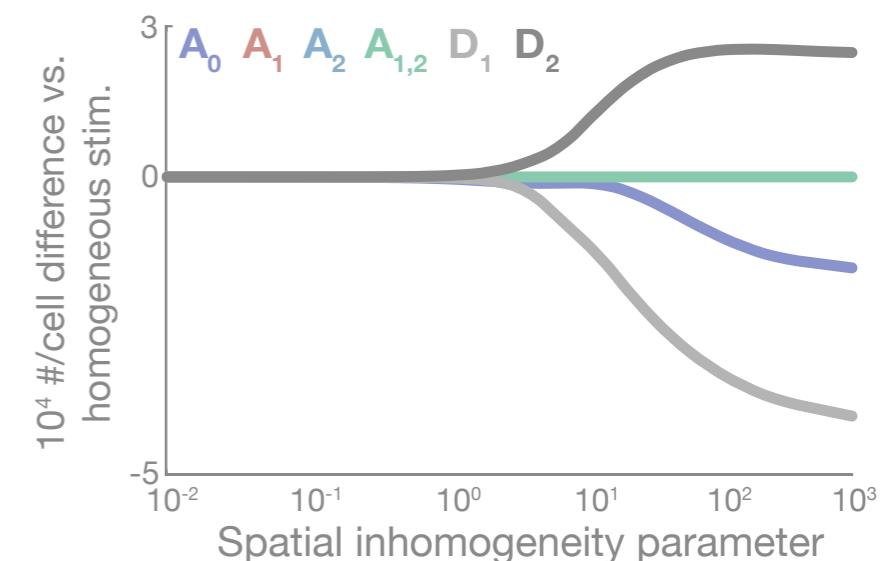
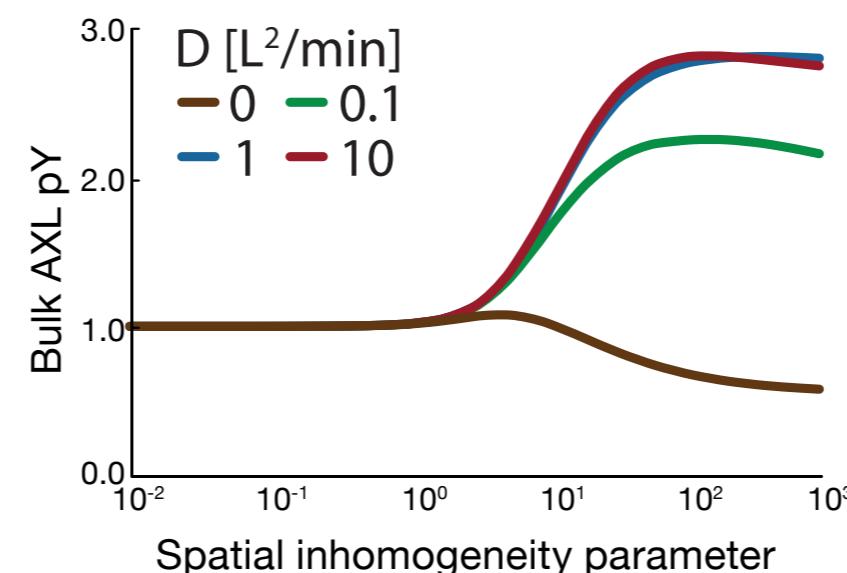
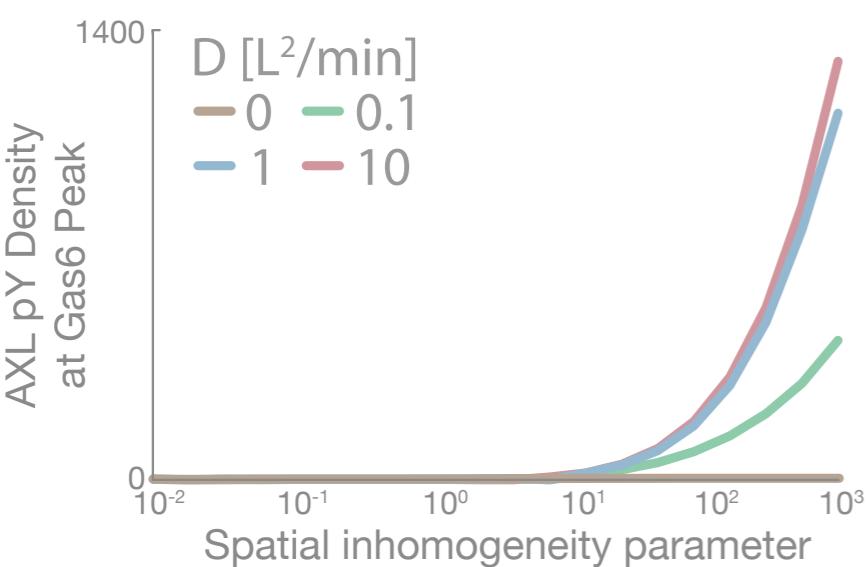
Local stimulation shifts species abundance



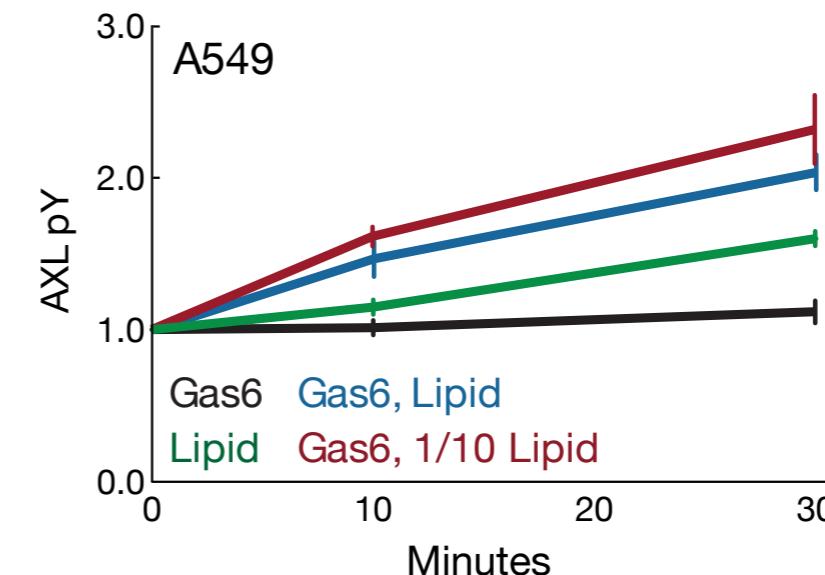
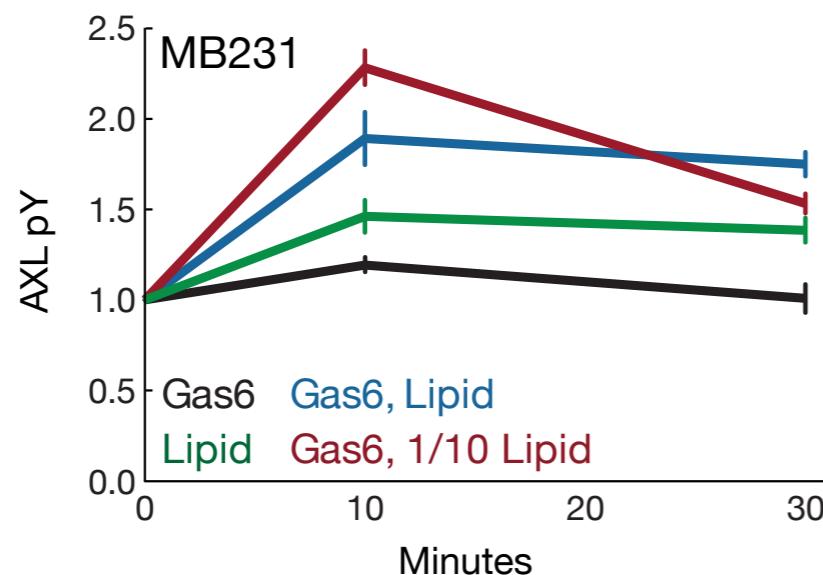
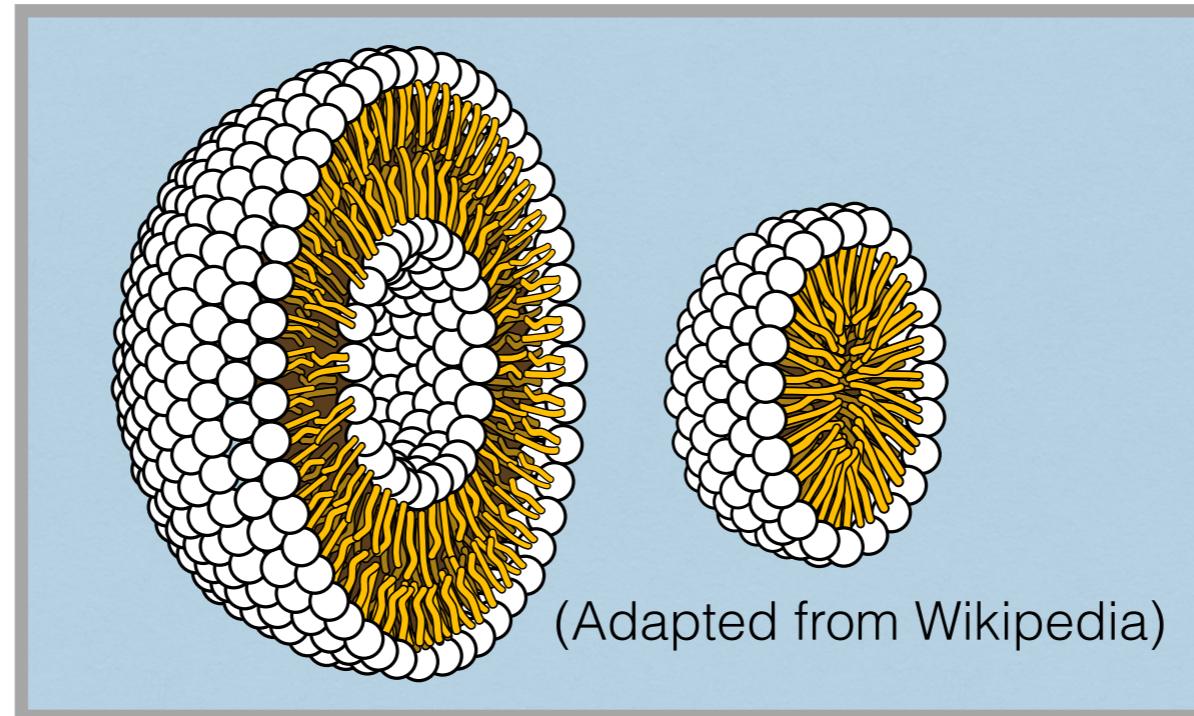
Local stimulation strongly promotes local AXL signaling



Local stimulation results in greater overall AXL signaling

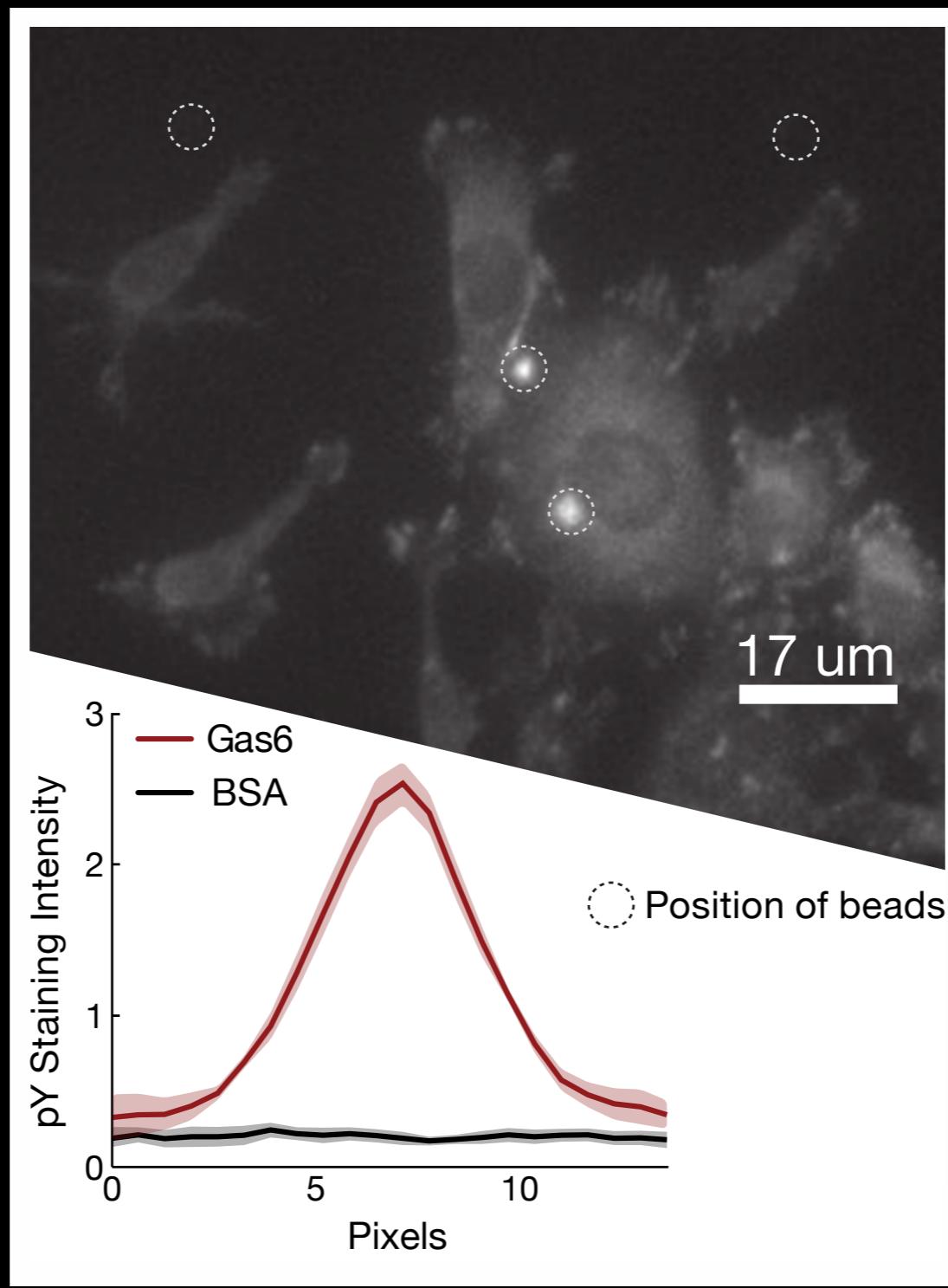


Local stimulation results in greater overall AXL signaling



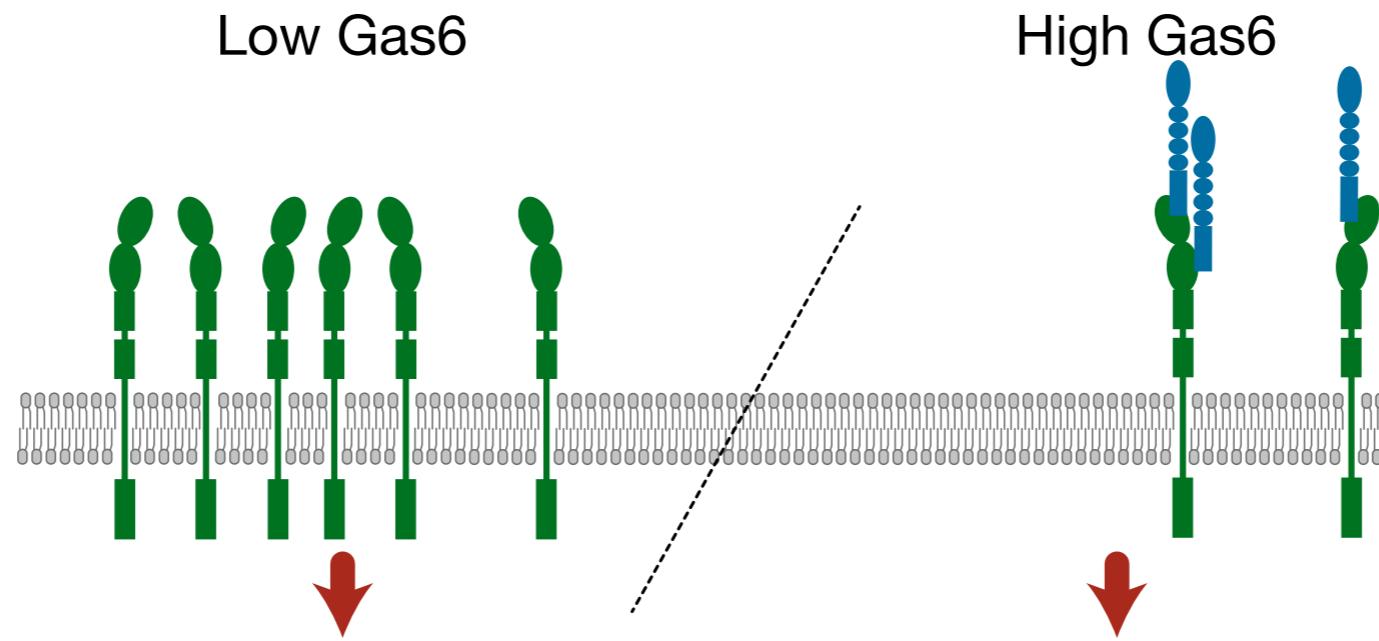
20 ng/mL Gas6; 1X lipid: 100 µg/mL 5:3:2 w/w PE:PS:PC

Synergistic activation is specifically due to local stimulation



Gas6-coated
polystyrene beads

AXL is a sensor of ligand spatial heterogeneity



Conclusion

- AXL transactivation leads to selective pathway amplification
- AXL-expressing cells rely on the receptor for robust migration response
- TAM receptors most robustly sense local ligand stimulation
- A quantitative model of AXL activation can be used to predict the consequence of novel interventions

Future directions

- Use the TAM signaling model to understand transactivation
- Model expansion to the full TAM family
- Rational design of improved TAM-targeted therapies
- Evaluation of TAM-mediated immune targeting

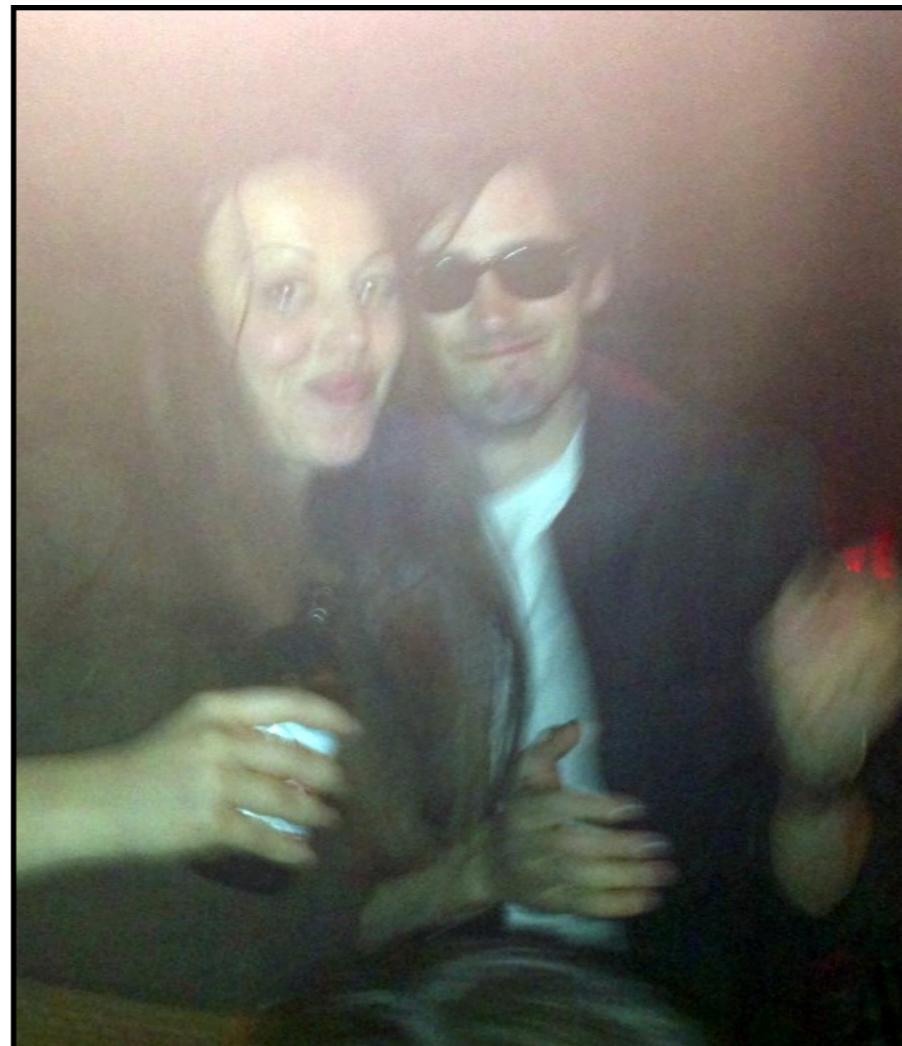
Thanks

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Collaborators

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Committee Members

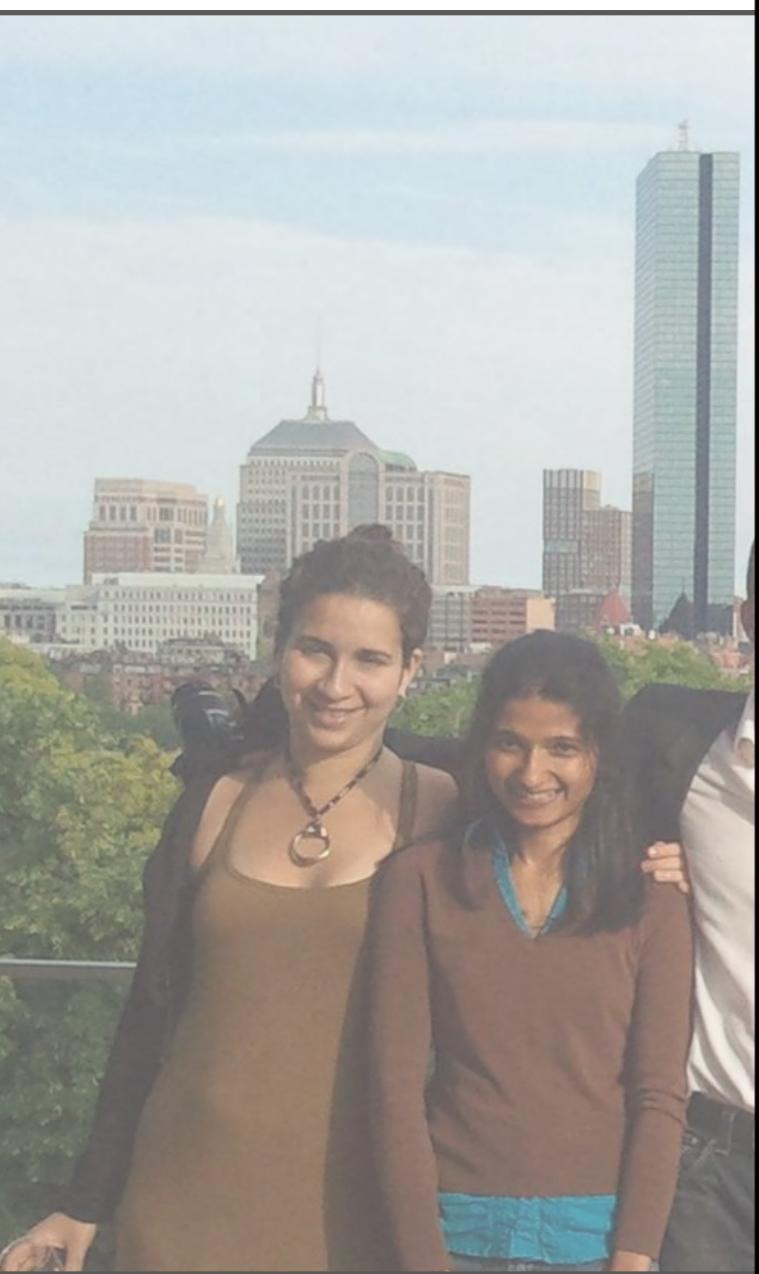
Forest White
Alan Wells

Facilities

Eliza Vasile



Thanks

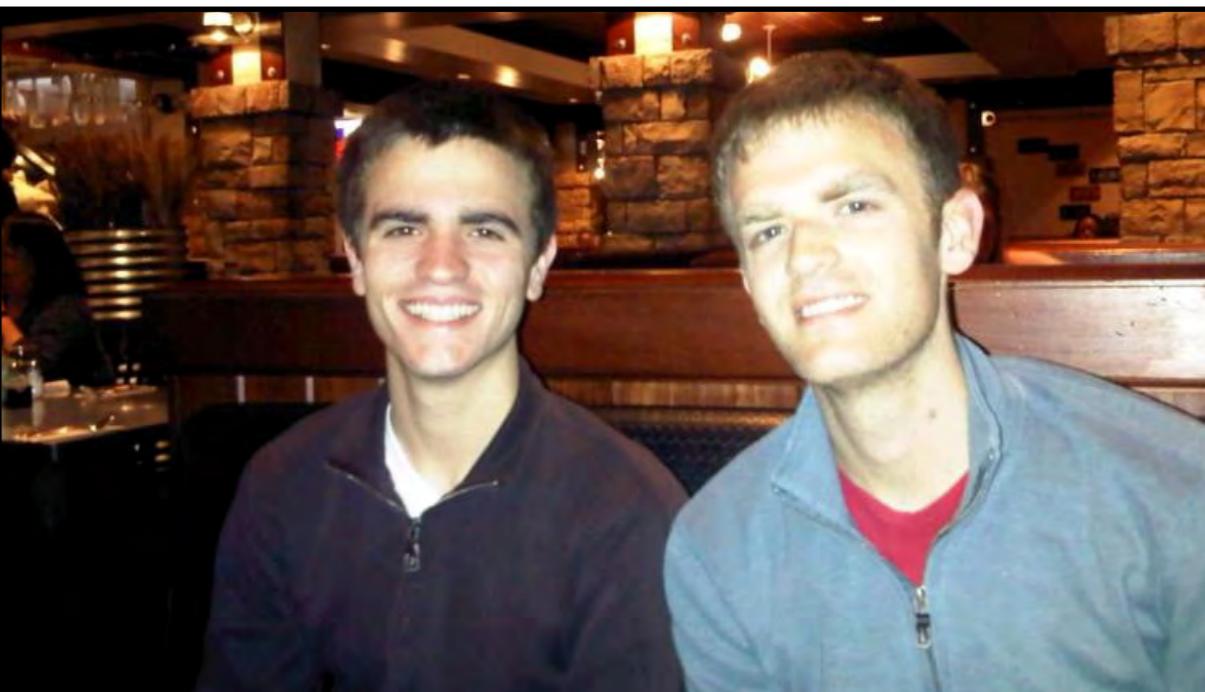


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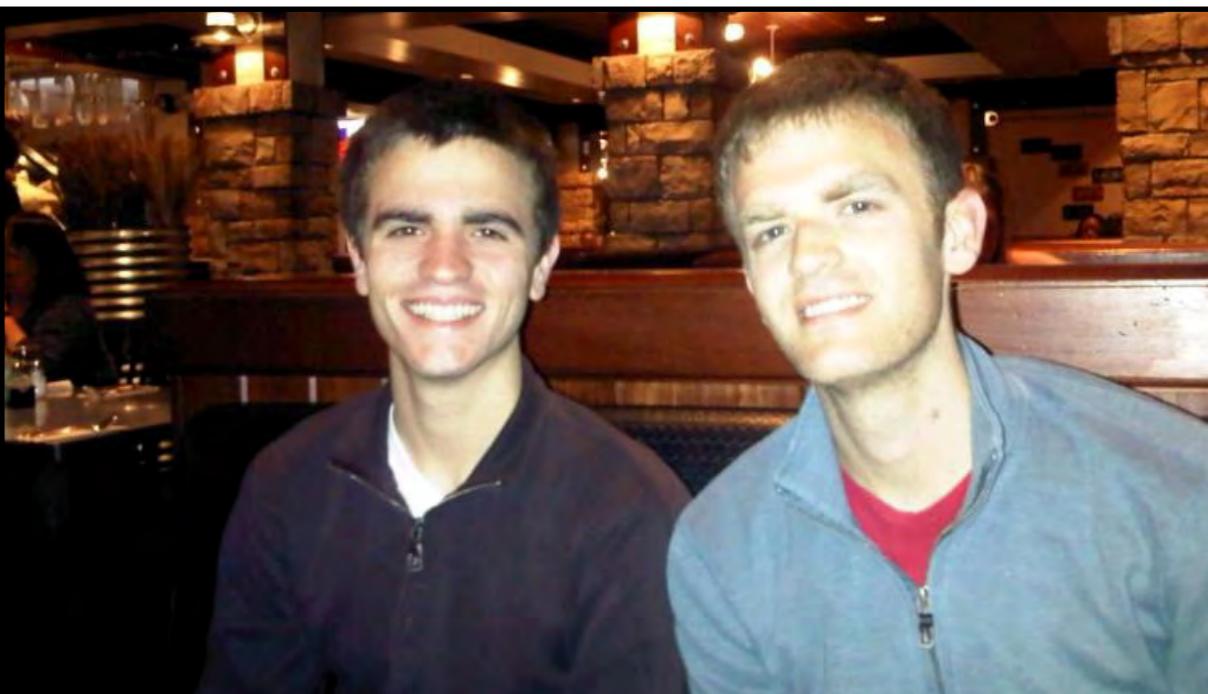
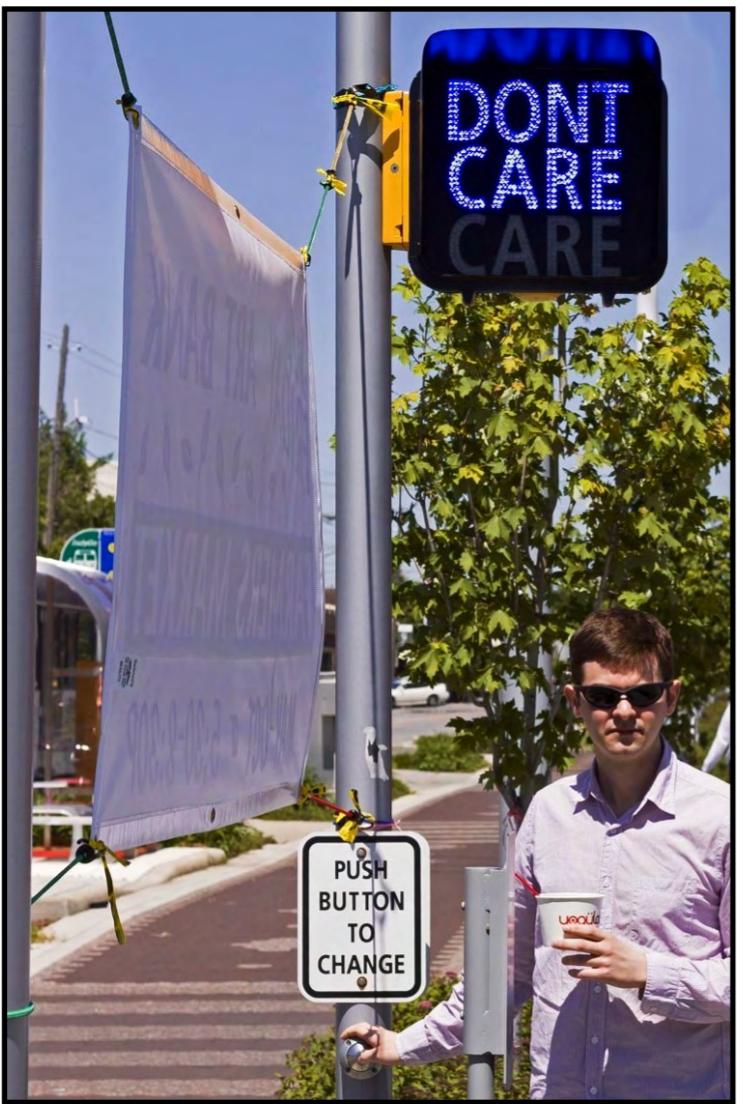




Thanks



Thanks



Questions?

