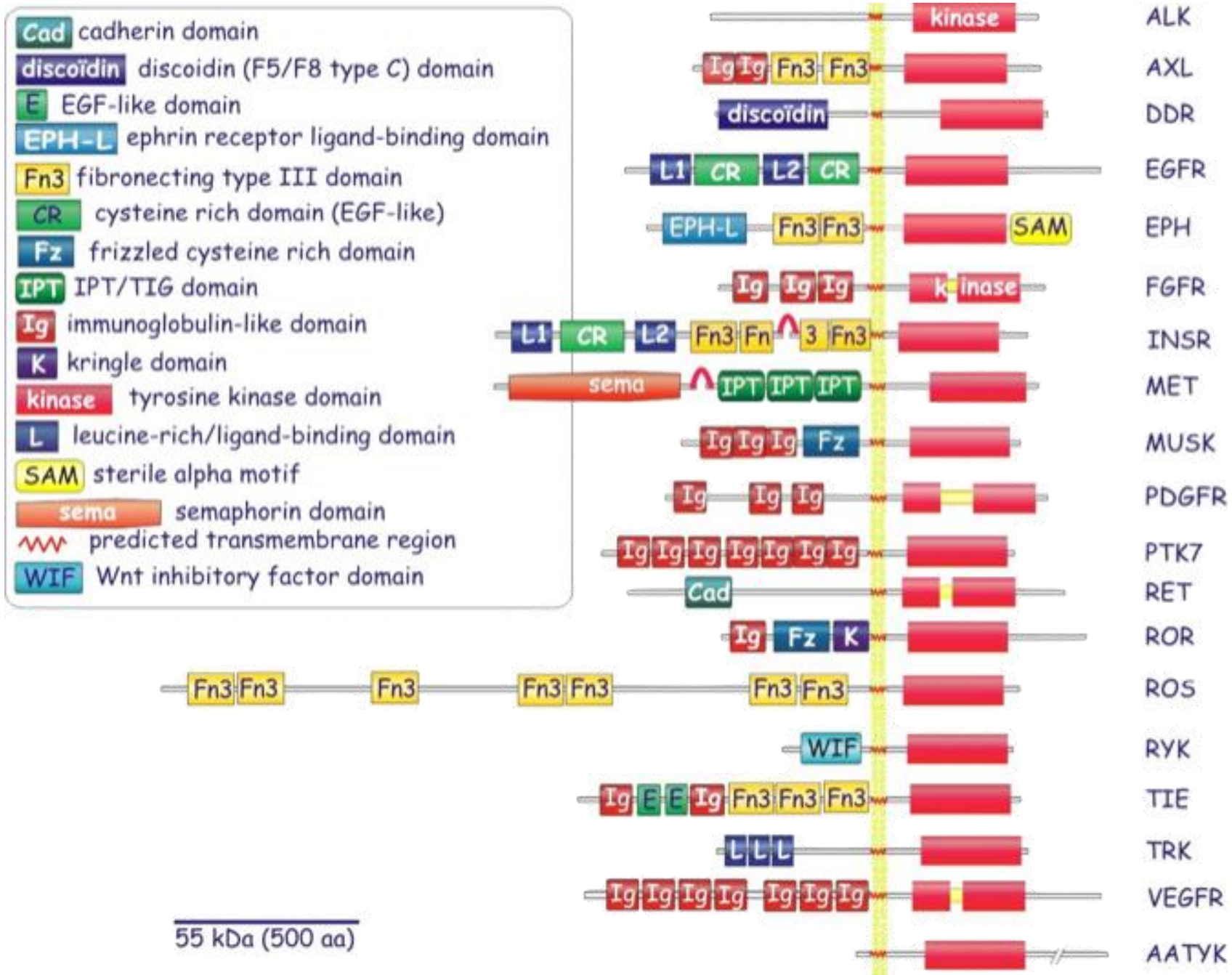
The AXL Receptor is a Sensor of Ligand Spatial Heterogeneity

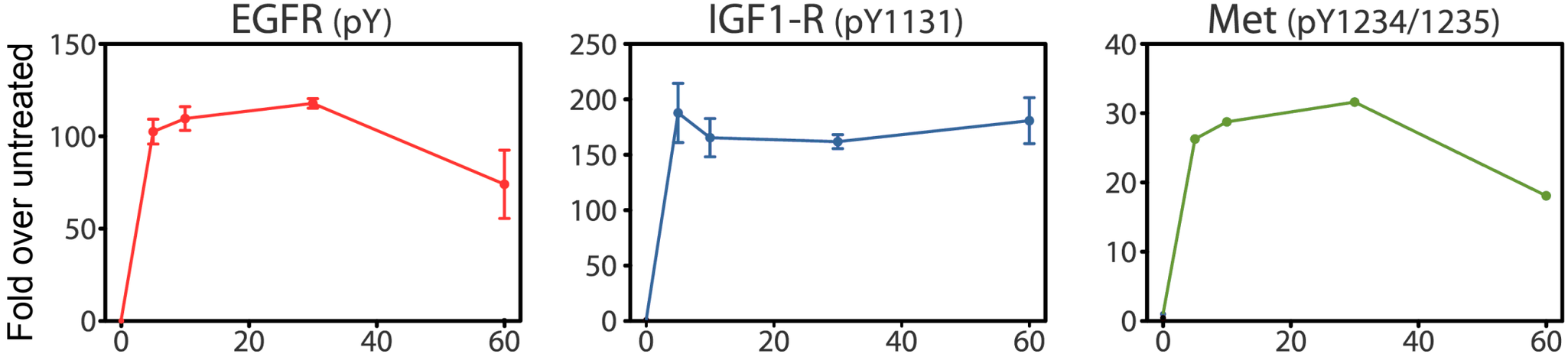
KOCH INSTITUTE for Integrative Cancer Research at MIT

Aaron Meyer 10.24.2014

RTKs are extremely diverse



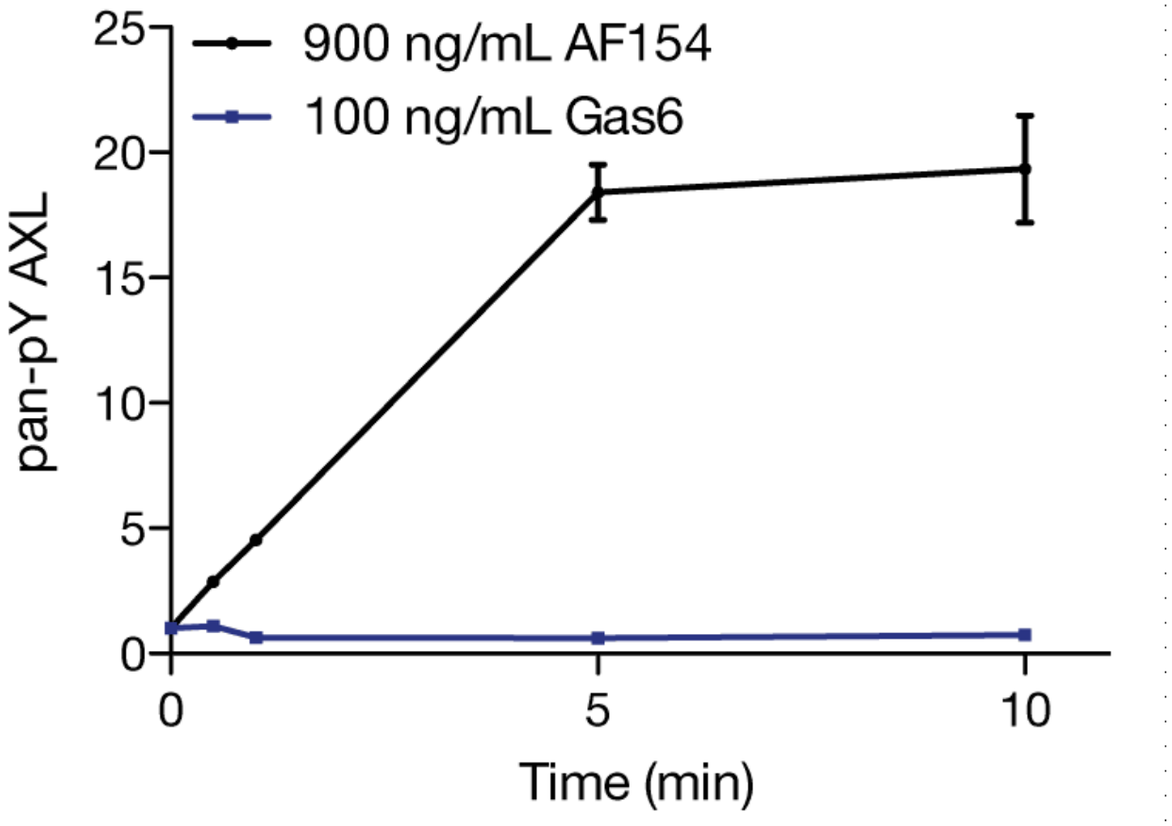
Many RTKs are effectively ligand concentration sensors



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

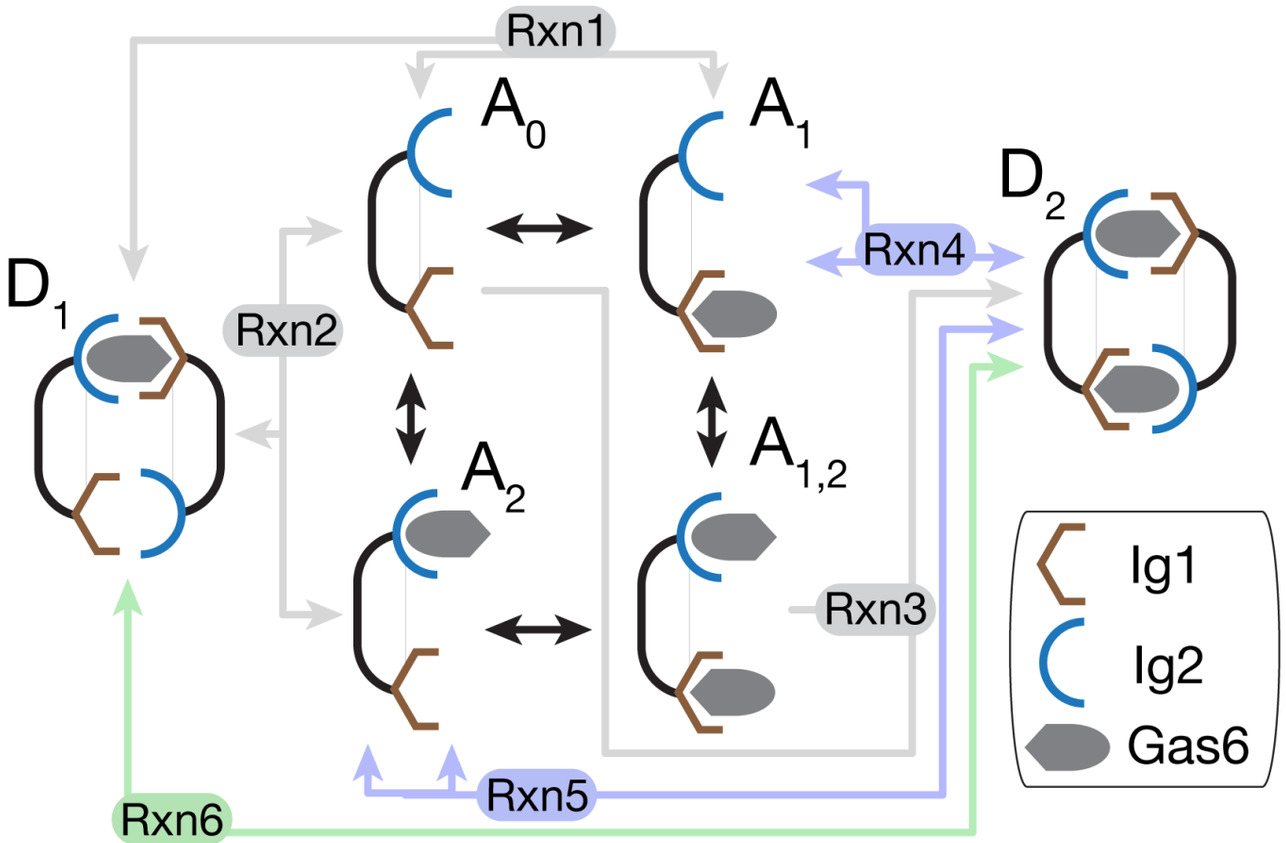
Kim *et al*, *Mol Cell Proteomics*, 2011

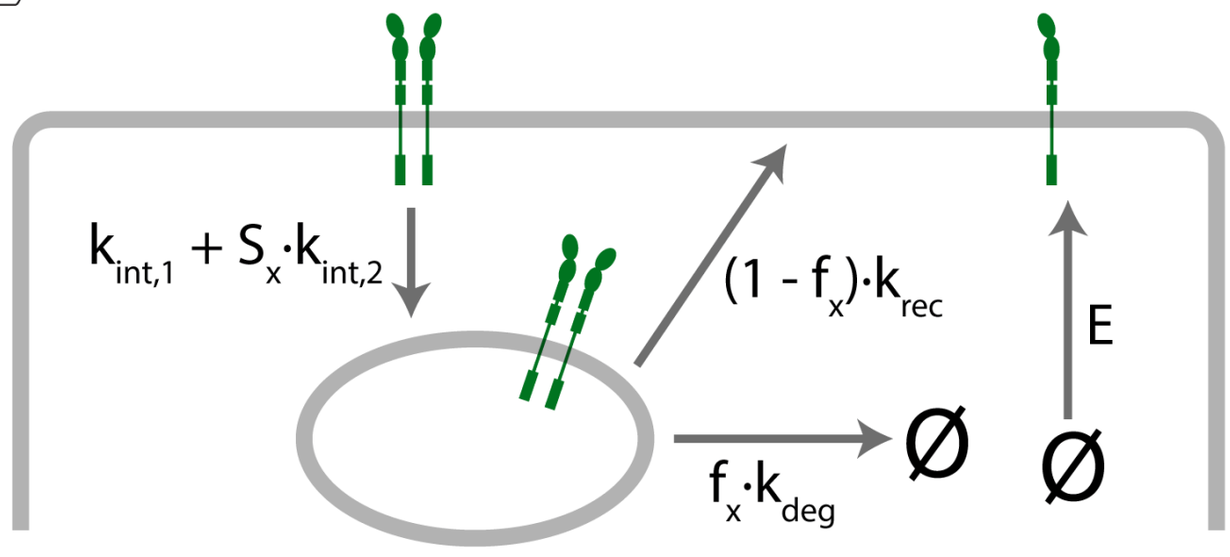
Conundrum: AXL does not robustly respond to ligand stimulation



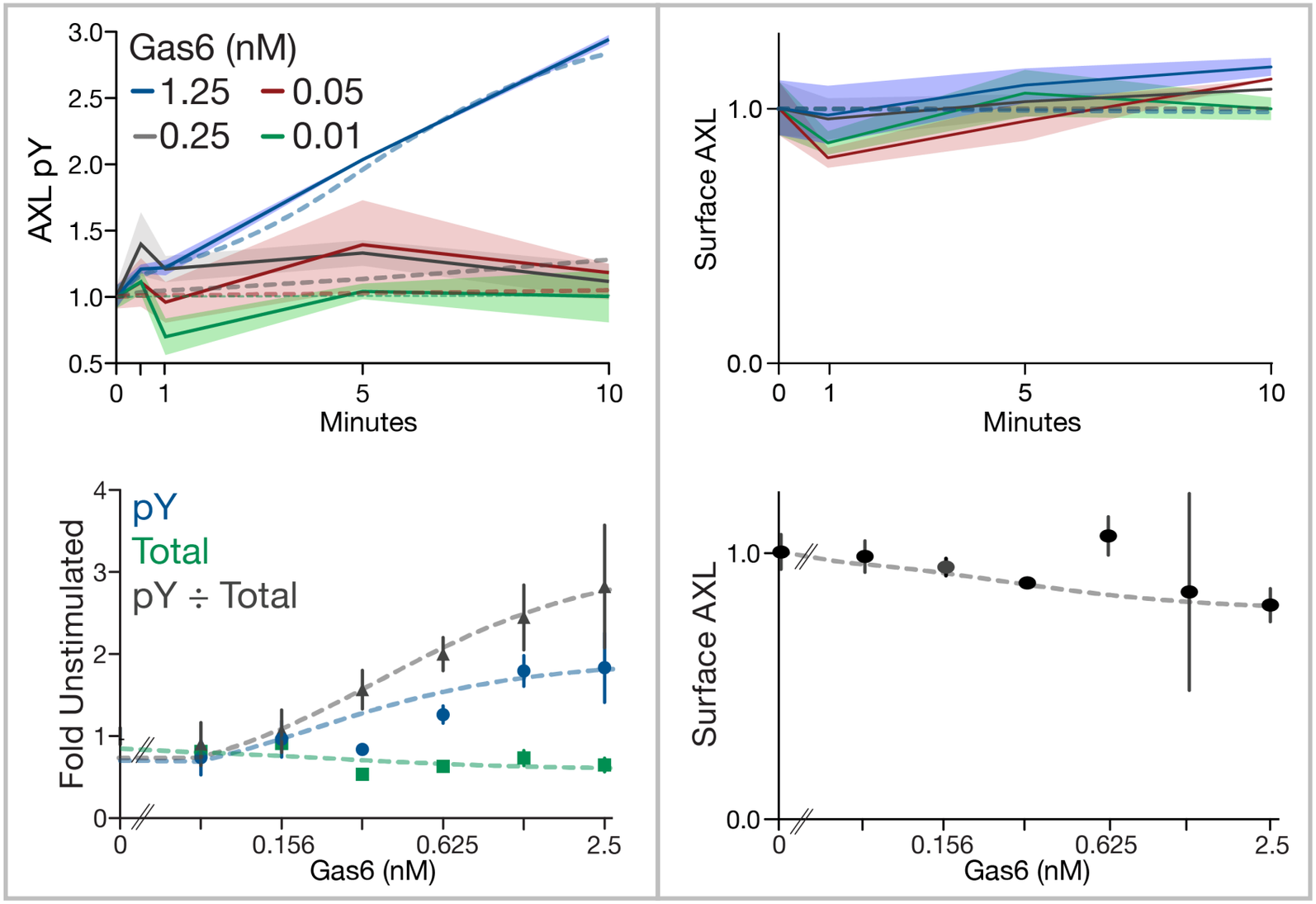
MDA-MB-231

TAM kinetic model allows mechanistic interpretation





TAM model can capture activation kinetics

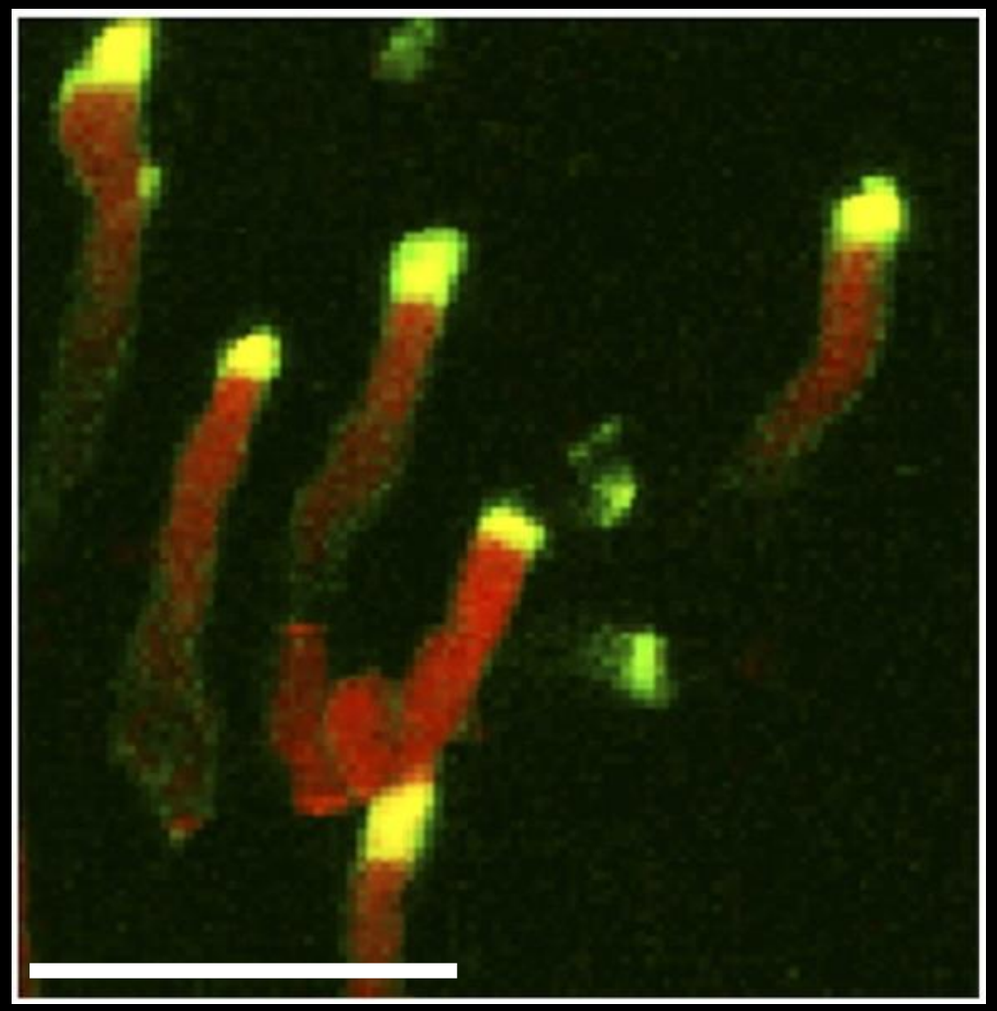


Total/pY

Surface

A549

Ptds Exposure is a Spatially Localized Process

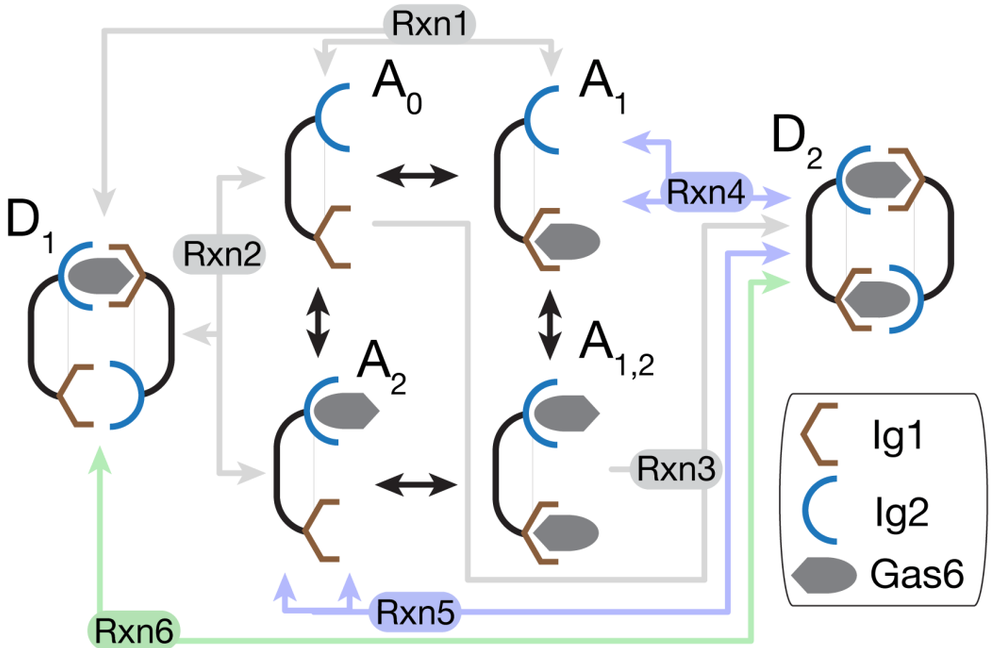


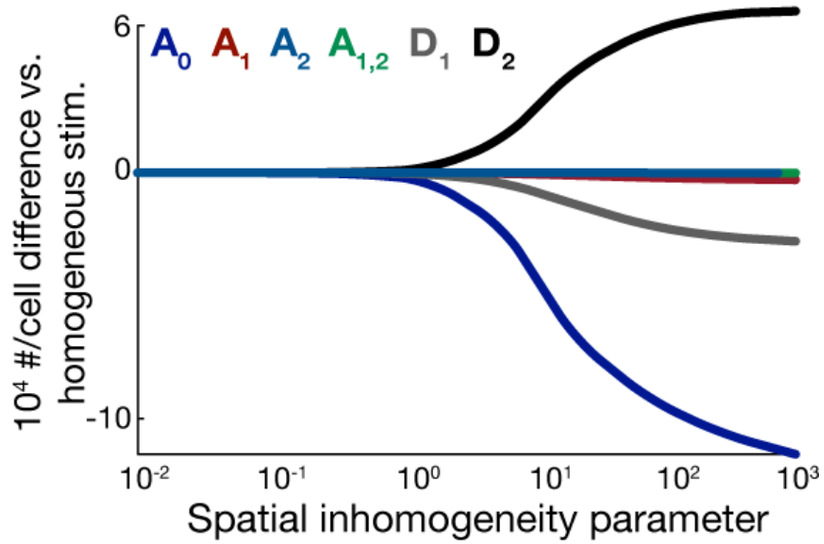
5 µm

Exposed Ptds
Membrane

Ruggiero *et al*, *PNAS*, 2012

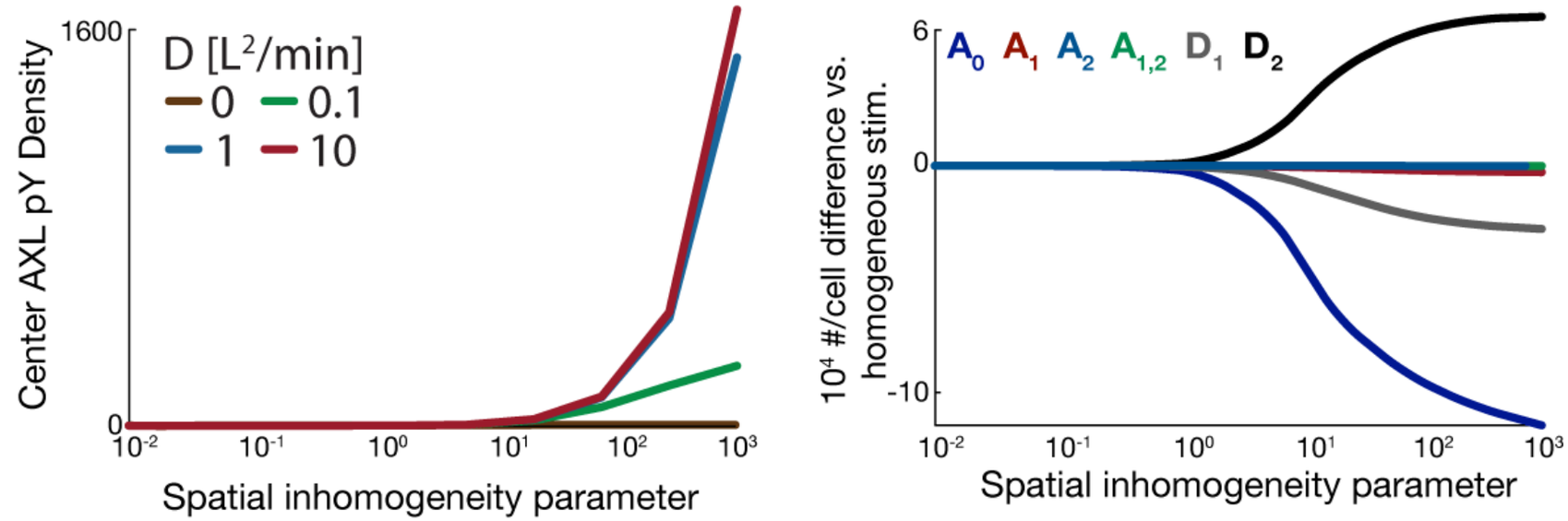
Local stimulation shifts species abundance





A549

Local stimulation strongly promotes local AXL signaling



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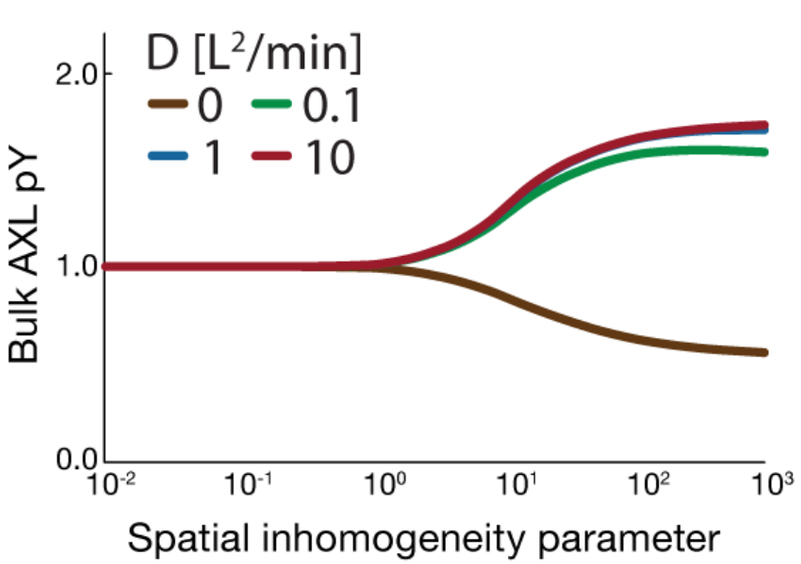
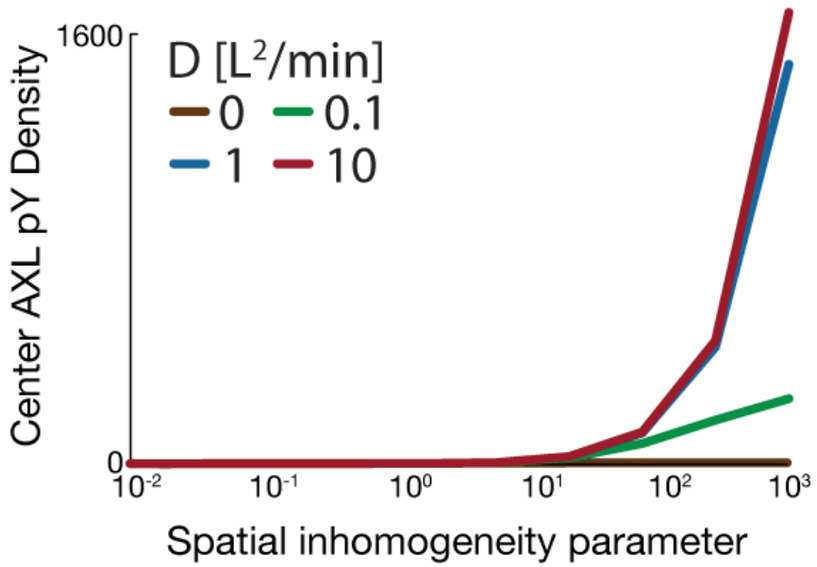
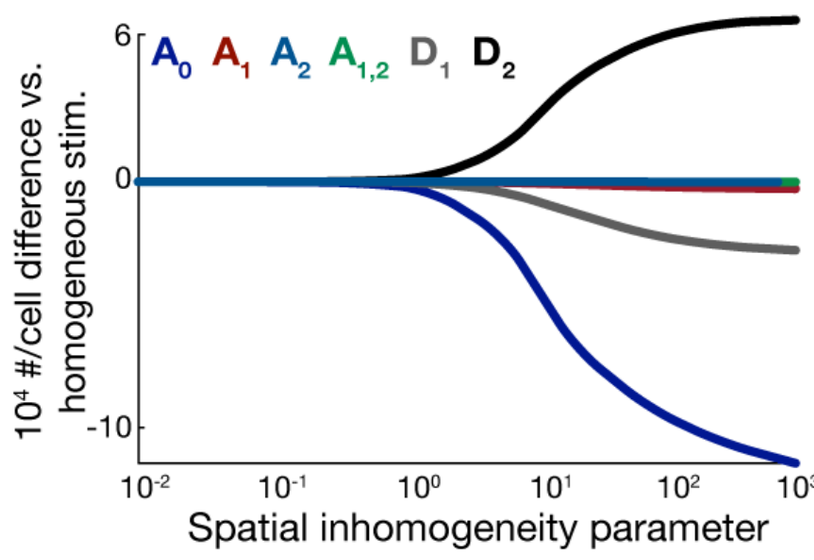
Local stimulation results in greater overall AXL signaling







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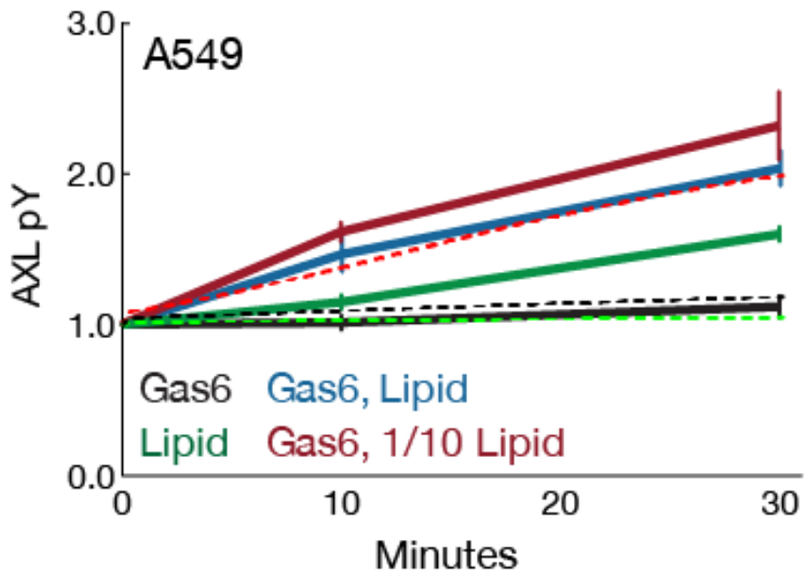

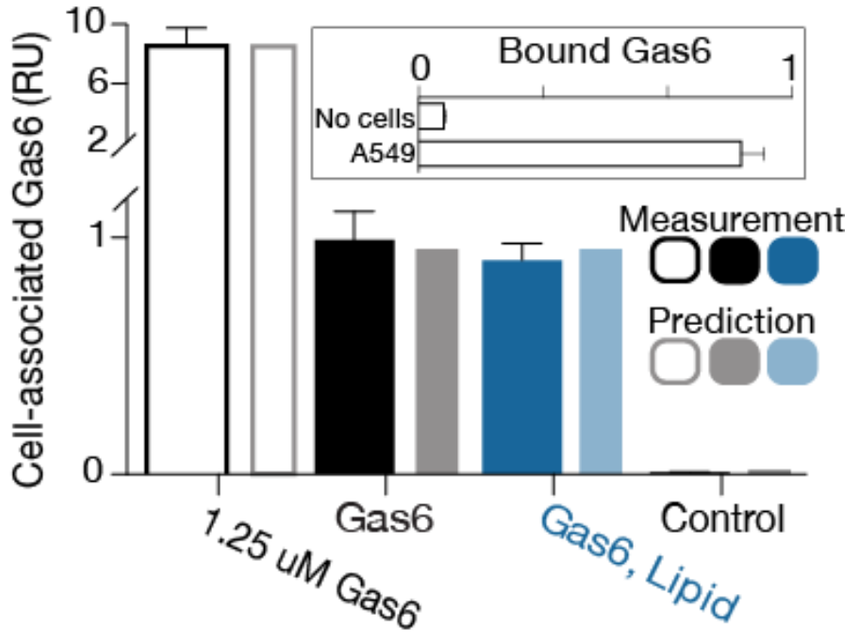

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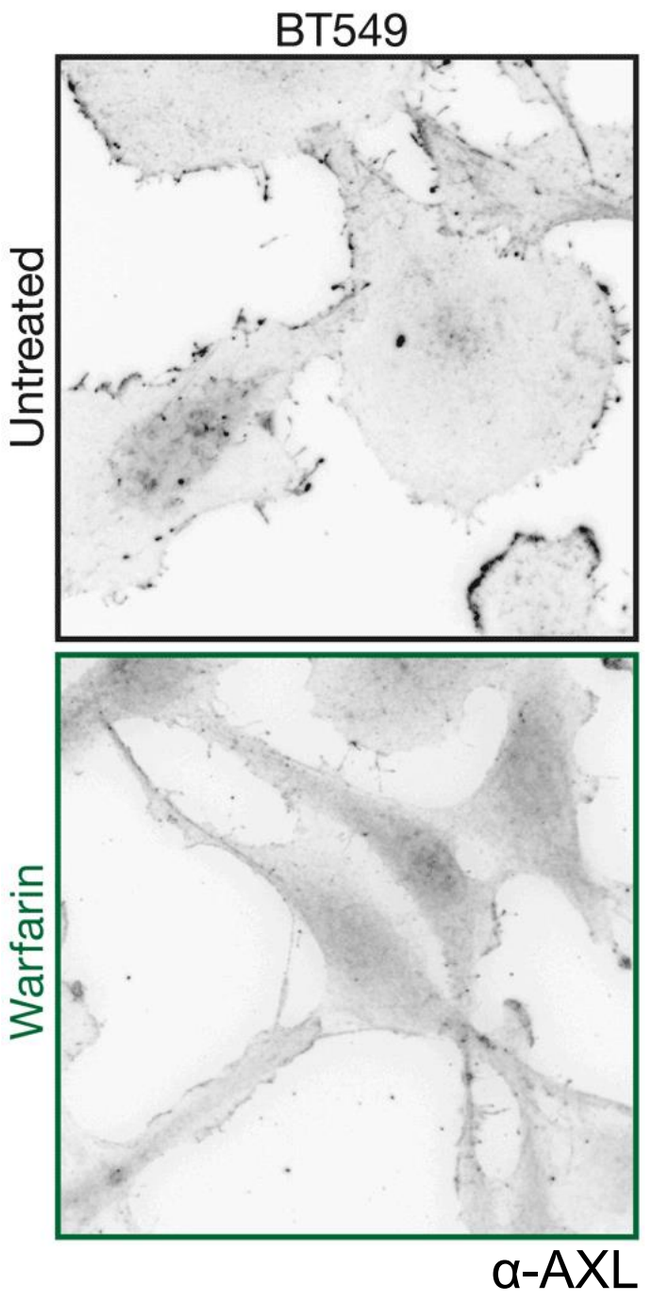
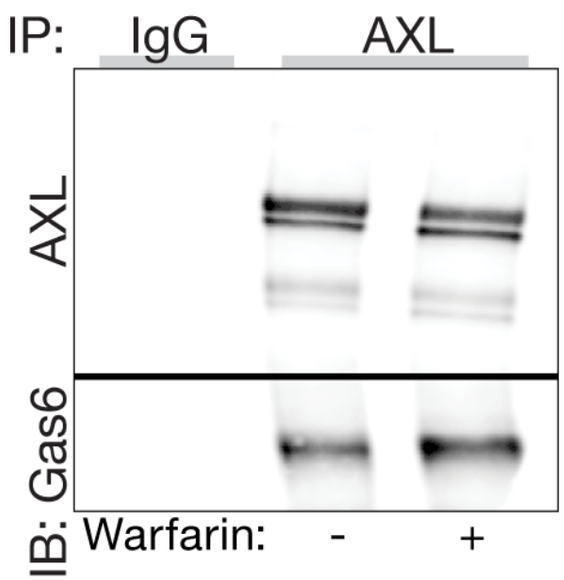
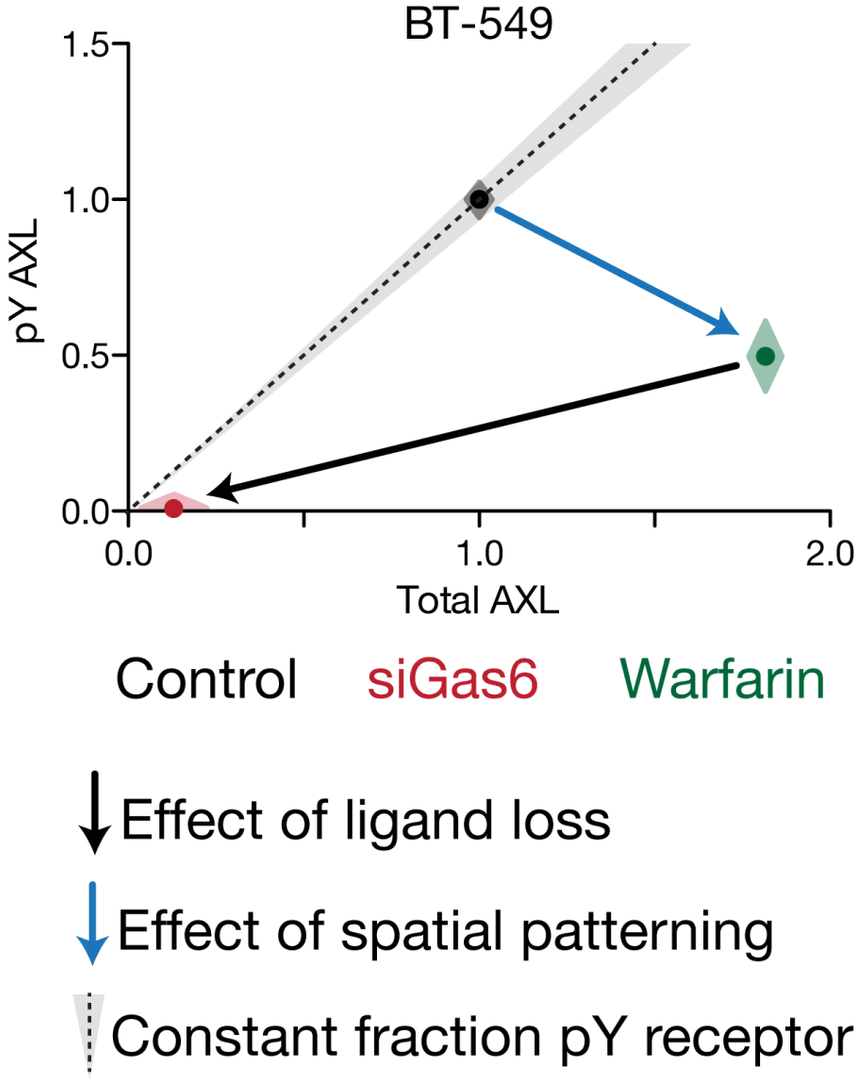
20 ng/mL Gas6; 1X lipid: 100 µg/mL 5:3:2 w/w PE:PS:PC

Relocalization of AXL promotes autocrine activation







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Conclusion

- TAM receptors most robustly sense local ligand stimulation
- Localization of ligand is utilized by cancer cells to promote autocrine AXL activation
- A quantitative model of AXL activation can be used to predict the consequence of novel interventions

Acknowledgements

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Interested in postdoctoral fellow applicants with strong background in quantitative molecular biology—contact aameyer@mit.edu or visit asmlab.org

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