Talk: Thurs, Oct 6 at 2:00
Room 200A

Molecular systems engineering at the tumor/immune interface

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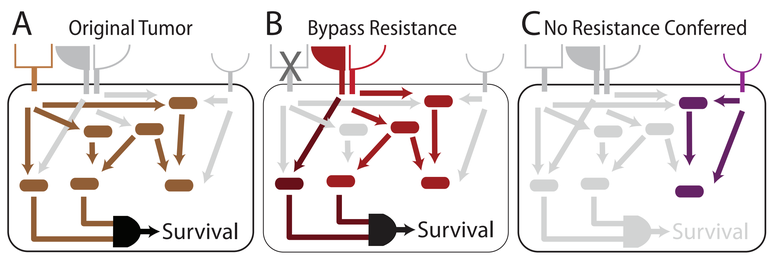
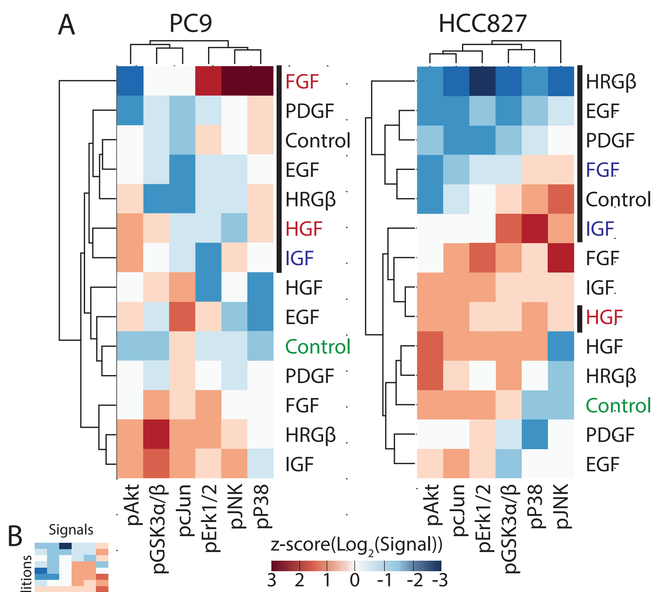
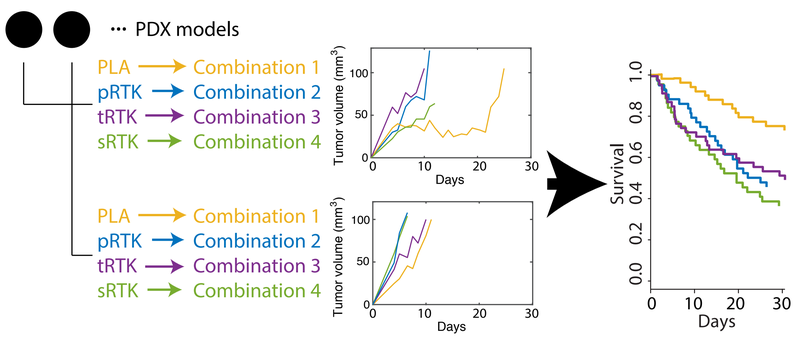
Aim 1: Identifying Shared Features Among Resistance Mechanisms to Help Predict Effective Combination Therapies for Individual Patients



(A) In RTK-driven tumors, signals are transduced from the receptor to various kinases. (B) Upon blocking the original cancer driver, resistance can be conferred by an untargeted receptor. (C) Some receptors, however, do not provide essential resistance signals. By identifying similarities and differences of signaling from each receptor, we will be able to identify measurements pinpointing the relevant receptor causing resistance.





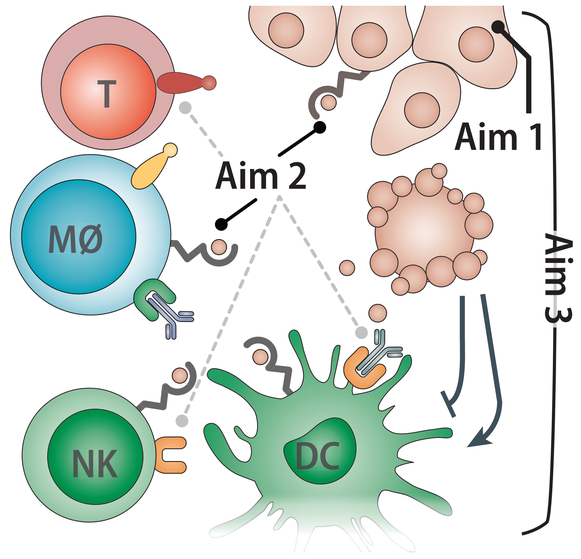
• Manole, S., E.J. Richards, **A.S. Meyer**. ``JNK pathway activation modulates acquired resistance to EGFR/HER2 targeted therapies." *Cancer Research*. 2016.

• **Meyer, A.S.**, M.A. Miller, F.B. Gertler, D.A. Lauffenburger. "The receptor AXL diversifies EGFR signaling and limits the response to EGFR-targeted inhibitors in triple-negative breast cancer cells." *Science Signaling*. 2013 Aug 6; 6(287):ra66.

• Miller, M.A., **A.S. Meyer** (co-first), M. Beste, Z. Lasisi, S. Reddy, K. Jeng, C.-H. Chen, J. Han, K. Isaacson, L.G. Griffith, D.A. Lauffenburger. "ADAM-10 and -17 regulate endometriotic cell migration via concerted ligand and receptor shedding feedback on kinase signaling." *Proc. Natl. Acad. Sci. U.S.A.* 2013 May 28; 110(22):E2074-83.

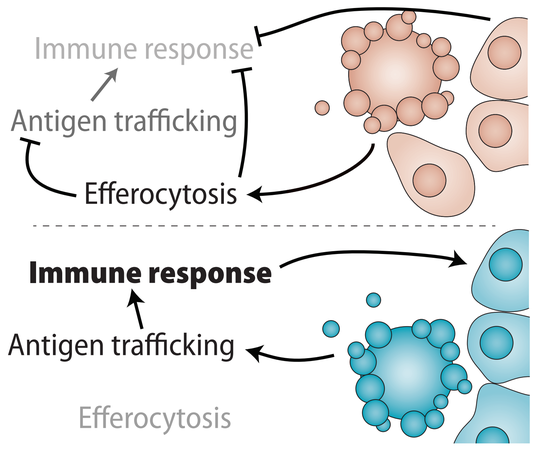
• Miller, M.A., M.J. Oudin, R.J. Sullivan, D.T. Frederick, **A.S. Meyer**, S. Wang, H. Im, J. Tadros, L.G. Griffith, H. Lee, R. Weissleder, K.T. Flaherty, F.B. Gertler, D.A. Lauffenburger. "Reduced proteolytic shedding of receptor tyrosine kinases is a post-translational mechanism of kinase inhibitor resistance." *Cancer Discovery*. 2016 Apr; 6:331-333.

Overview



Overview of our approach. We will first focus on tumor cell-intrinsic targeted therapy resistance, studying how activation of non-targeted RTKs (bypass activation) leads to resistance (Aim 1). In Aim 2, we will apply data-driven analytical methods to elucidate TAM RTK function and apply these approaches to rationally design innate immune-targeted agents. We will pioneer approaches for measuring and manipulating immune-tumor cell communication in Aim 3 to identify more effective therapeutic combinations targeting both. Each of these areas will take advantage of thorough modeling and experimental integration.

Aim 3: Measuring and Integrating Tumor & Immune Response to Optimally Target Both



In cancer, multiple factors including efferocytosis and direct signaling lead to an immunosuppressive environment. In contrast, diseases with autoimmune components often involve aberrant cell death and/or cellular clearance, leading to positive feedback disrupting self-tolerance. Through this similarity, studying the signaling and trafficking effects of cellular debris has important implications for both cancer and these diseases.

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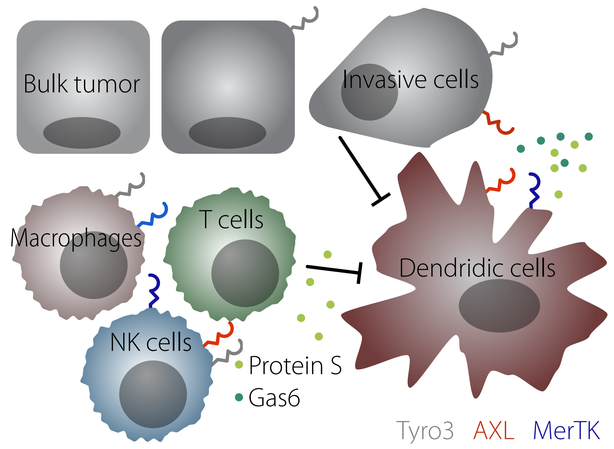
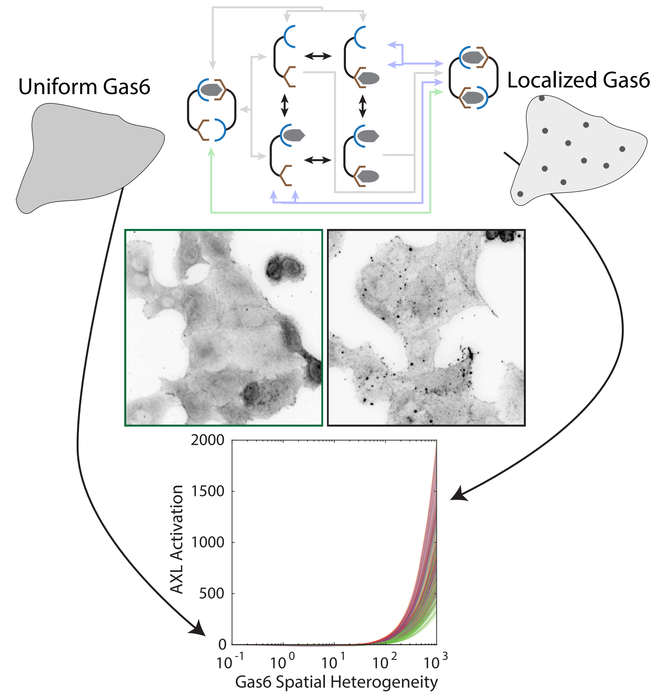
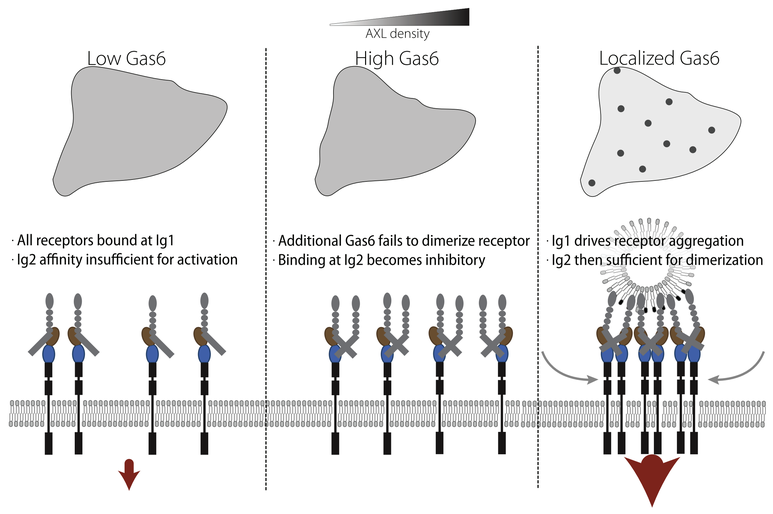
Aim 2: Systems Approaches for Rationally Designing Innate Immune Therapies



In many cancers, a subset of tumor cells overexpress AXL, making them invasive and resistant to therapy. TAM receptor activation within dendritic cells potently inhibits the innate immune response. T cell release of ProS further dampens the immune response. Activation of TAMs inhibits NK cell-mediated lysis. Each of these cell populations express distinct and dynamic combinations of TAM receptor, likely modulating functional changes in microenvironmental response.





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• Richards, E.J., S. Manole, A.S. Meyer. "Engineering more precise and potent TAM-targeted therapies." *In preparation*.

• Miller, M.A., M. Moss, G. Powell, R. Petrovich, L. Edwards, **A.S. Meyer**, L.G. Griffith, D.A. Lauffenburger. "Targeting autocrine HB-EGF signaling with specific ADAM12 inhibition using recombinant ADAM12 prodomain." *Scientific Reports*. 2015 Oct 19; 5:15150.