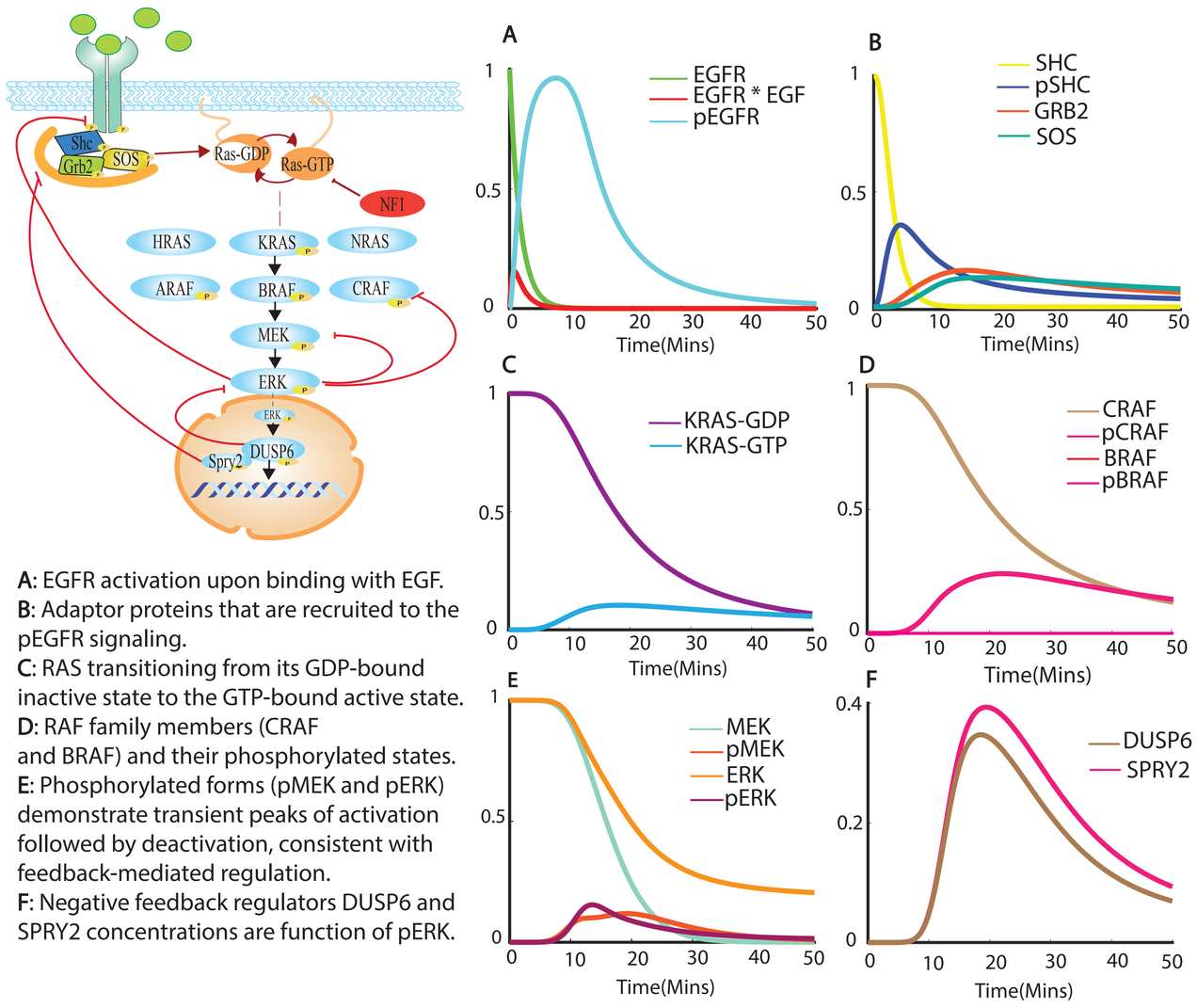
A Complete Mathematical Model of the MAPK Pathway Predicts Mechanisms of Resistance to BRAF Inhibition in BRAF V600E Driven Tumors.

Satya Bharadwaja Nandivada[1], Radha Mukherjee[2], Neal Rosen[2], Kiran Vanaja[*,1]*

[1]Roux Institute, Northeastern University, Portland, ME, USA [2]Memorial Sloan Kettering Cancer Center, NYC,USA

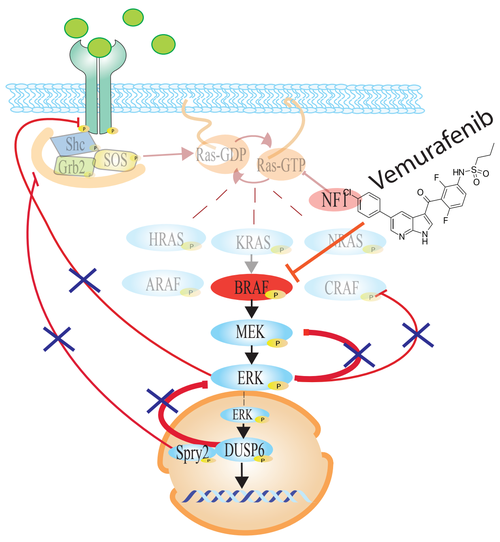
Abstract - The BRAF V600E mutation is most commonly found in melanoma. The V600E mutation imparts continuous activation to the MAPK cascade causing dysregulated growth. Recent advances in pharmaceutical research have produced small molecule drugs that inhibit the V600E BRAF signaling dimers like Vemurafenib. While Vemurafenib has been shown to be clinically relevant and efficacious, resistance to the drug is unfortunately a common occurrence. Understanding the mechanism of emergence of resistance is critical for optimizing treatment strategies and developing effective therapies. To this end, we built a complete mathematical model of the MAPK signaling network with multiple negative feedback loops. The model was implemented as a series of ODE equations describing the activation of EGFR followed by the recruitment and assembly of the Shc-Grb2-Sos complex. Ras GTP activation drives the MAPK cascade of Raf, Mek and Erk activation. Erk negatively feeds back to the levels of EGFR, SOS, Raf and Mek. Erk activation causes transcriptional activation of the dual Erk phosphatase DUSP6 and Sprouty which causes the disassembly of the Shc-Grb2-SOS complex. BRAFV600E mutation is modeled as a continuously active kinase and the model is `constrained using previously published literature and recent experimental data. We show that in the case of Vemurafenib based inhibition, the initial abrogation of MAPK activity drives all the negative feedback in the system to zero. This high-gain system then allows for the signal to propagate through the system to activate MAPK through c-Raf. The model predicts that combination therapies like Vemurafenib plus MEK inhibition would be successful.

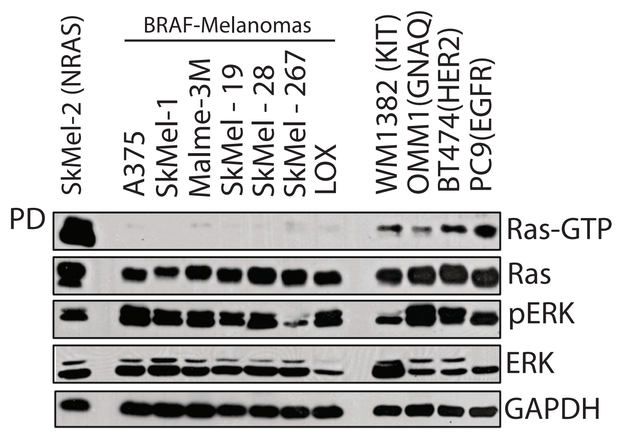
1.MAPK Pathway With Multiple Negative Feedback loops

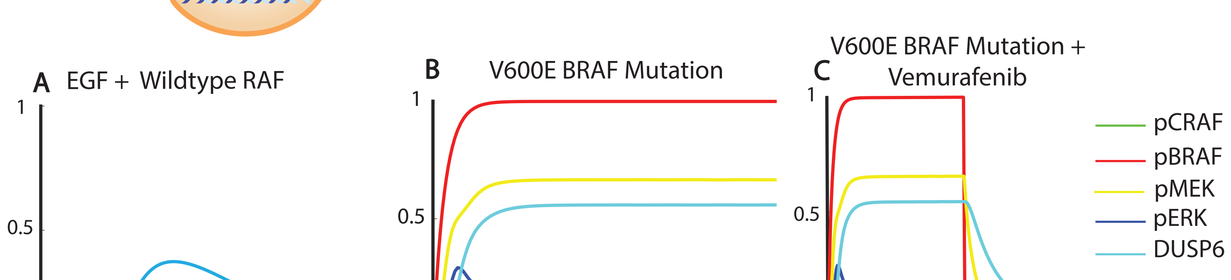


A: EGFR activation upon binding with EGF.
B: Adaptor proteins that are recruited to the pEGFR signaling.
C: RAS transitioning from its GDP-bound inactive state to the GTP-bound active state.
D: RAF family members (CRAF and BRAF) and their phosphorylated states.
E: Phosphorylated forms (pMEK and pERK) demonstrate transient peaks of activation followed by deactivation, consistent with feedback-mediated regulation.
F: Negative feedback regulators DUSP6 and SPRY2 concentrations are function of pERK.

2.V600E BRAF Mutation in Melanoma and Vemurafenib Effects





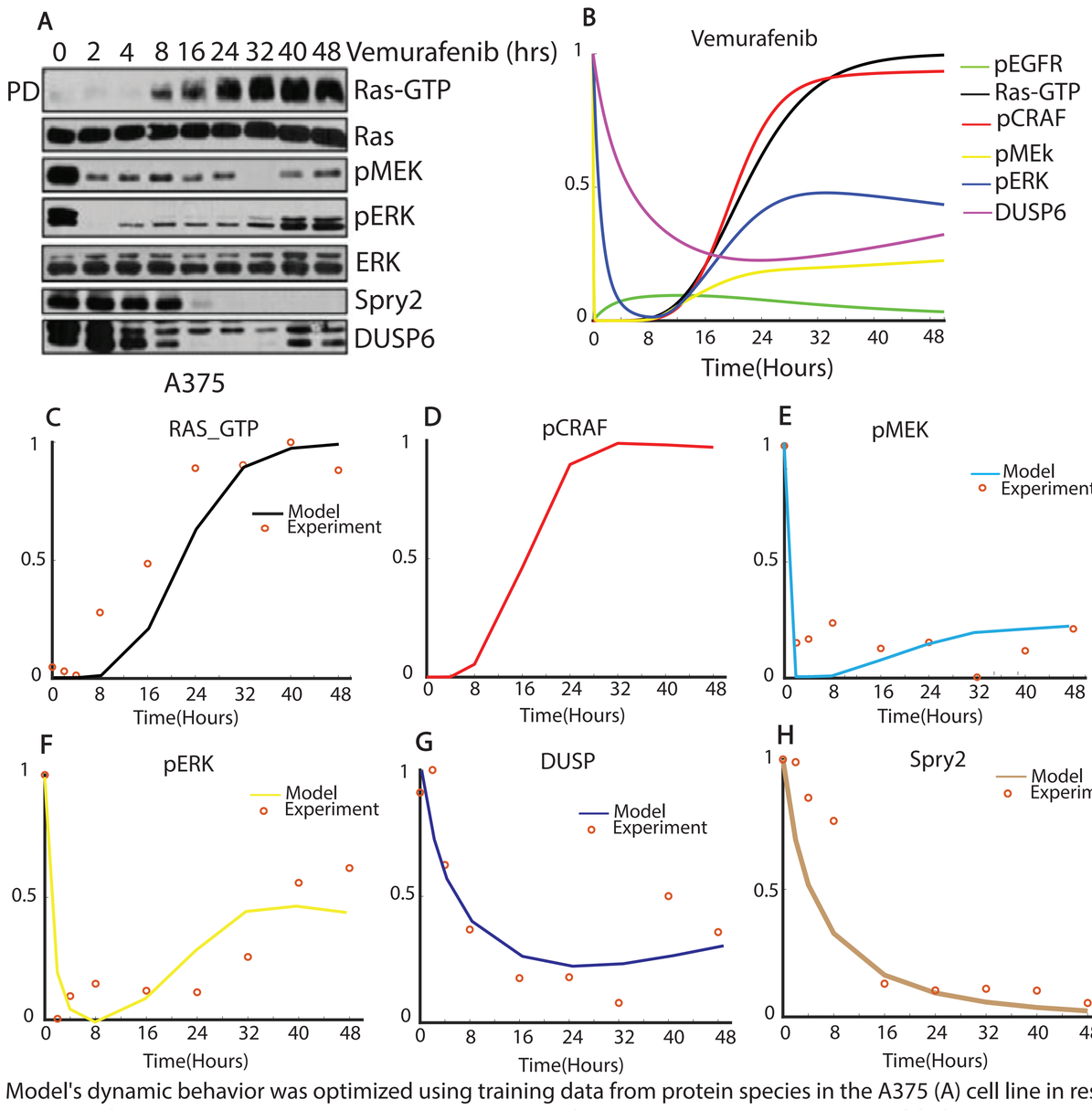


A and B show the modeling for wildtype RAF and V600E BRAF mutation, respectively, with the latter showing enhanced, sustained signaling. Panel C demonstrates the signaling response to the drug vemurafenib

Find Us Here

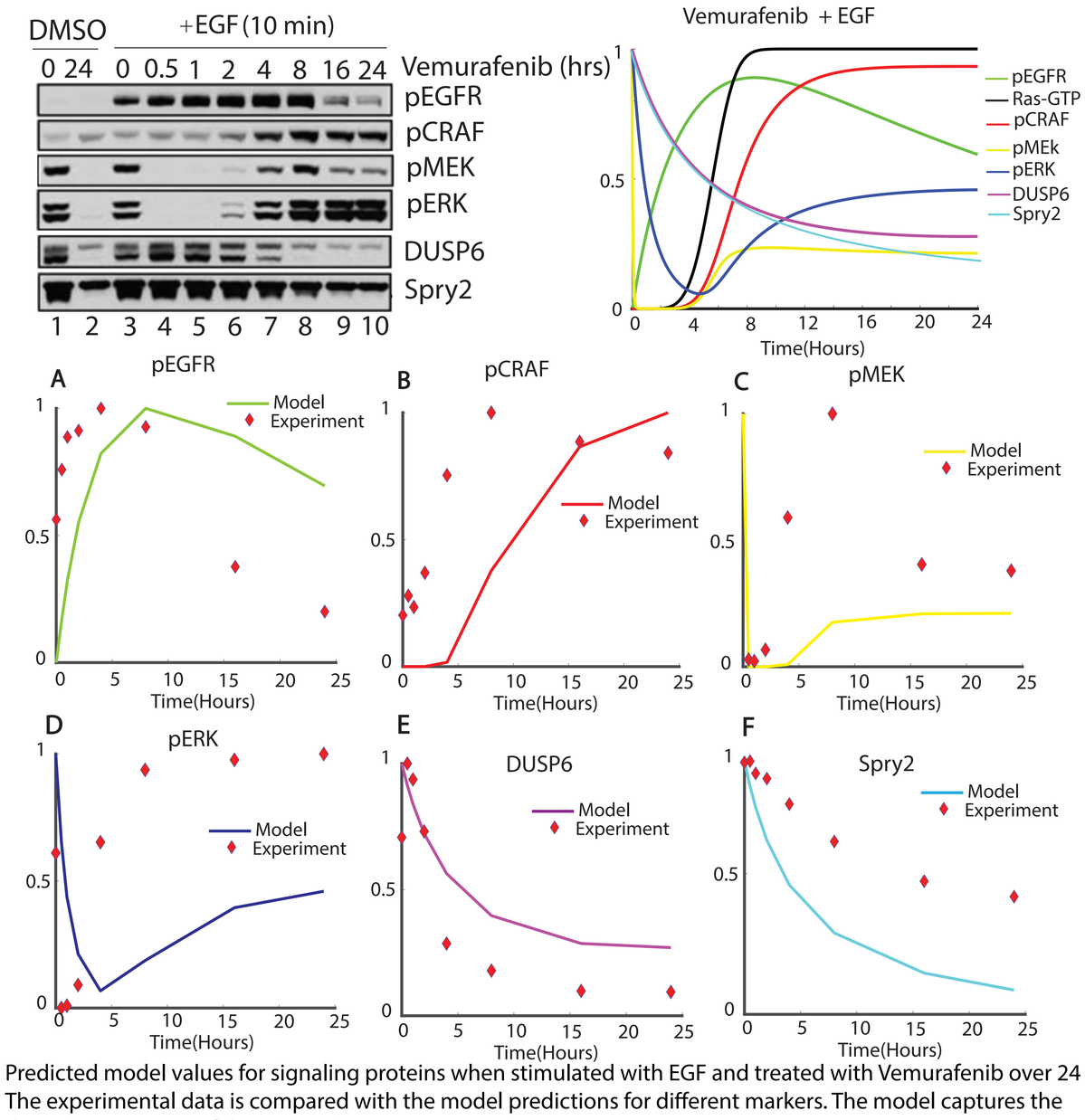
References - Lito, P., Pratilas, C. A., Joseph, E. W., et al. (2012). Relief of feedback inhibition by RAF inhibitors in BRAF V600E melanomas. Cancer Cell. PMCID: PMC3713778..

3.Modeling Dynamic Response to Vemurafenib Inhibition



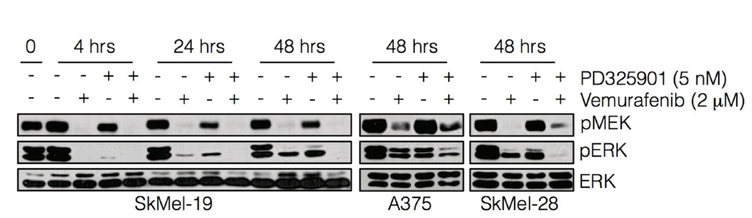
Model's dynamic behavior was optimized using training data from protein species in the A375 (A) cell line in response to vemurafenib inhibition over 48 hours. The experimental data is compared with the model fit for various signaling proteins, demonstrating how the model aligns with observed outcomes.

4.EGF-Driven Signaling Dynamics Under Vemurafenib

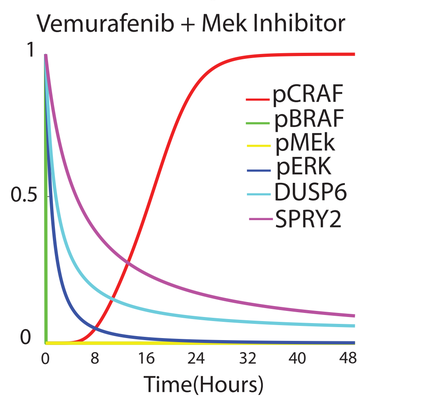


Predicted model values for signaling proteins when stimulated with EGF and treated with Vemurafenib over 24 hours. The experimental data is compared with the model predictions for different markers. The model captures the dynamic responses of these proteins

5. Combination Therapy Suppresses MAPK Pathway Activation



Vemurafenib and MEK inhibitor effectively block MAPK signaling, as shown by reduced pMEK and pERK levels in melanoma cells and validated through modeling



Conclusion - Cancers with MAPK pathway mutations, including melanoma, often face challenges of treatment resistance. This study developed a robust mathematical model integrating data to capture MAPK signaling dynamics and the effects of Vemurafenib. With new RAS-targeting drugs nearing FDA approval, understanding resistance mechanisms is crucial for improving patient outcomes and designing effective combination therapies across MAPK-driven cancers.