Amplification of the epidermal growth factor receptor (EGFR) is observed in \( \approx \) 50% of glioblastoma tumors. Half of EGFR-amplified tumors in-turn harbor the EGFRvIII mutant, a tumor-associated allele of EGFR which signals constitutively in the absence of ligand. We have previously shown that EGFR and EGFRvIII are co-expressed in rare cells in co-amplified glioblastoma, and that co-expression drives progression through activated STAT signaling. Others have shown that EGFRvIII-expressing cells signal though NF-\( \kappa \)B to activate adjacent EGFR-expressing cells, and that GBM without amplified EGFR activates NF-\( \kappa \)B through monoallelic inactivation of I\( \kappa \)B\( \alpha \), a negative regulator. Thus, NF-\( \kappa \)B is likely critical for gliomagenesis. We and others have shown that STAT3 is important for glioma, and that STAT3 and NF-\( \kappa \)B can cooperate to promote progression. We propose that the axis linking EGFR, NF-\( \kappa \)B, and STAT is a critical driver of stemness and aggression in glioblastoma, and that targeting this axis using available and emerging clinical agents will improve survival. We demonstrate that co-expression of EGFR and EGFRvIII activates NF-\( \kappa \)B in addition to STAT signaling. Blockade of STAT3 activates both EGFR and NF-\( \kappa \)B. Inhibition of NF-\( \kappa \)B blocks STAT3 but activates EGFR, and cooperates with EGFR inhibitors to shut down EGFR-NF-\( \kappa \)B-STAT signaling. Thus, the EGFR-STAT3-NF-\( \kappa \)B axis represents a critical axis for GBM, with complex feedback regulation thwarting attempts to block any single node. We hypothesize that targeting this axis using combinatorial, translatable approaches will suppress EGFR-STAT-NF-\( \kappa \)B signaling, leading to improved outcome in patients. We will present data testing combination therapies, prioritizing existing and emerging clinical agents, to determine effects on signaling and on malignant progression, in tumors expressing EGFR or co-expressing EGFR with EGFRvIII.