

1. Computational Discovery 3. Immunomodulatory Characterization 0 3 A. Metabolism module TFCR Target gene ŧ, ~11,000 TCGA patients ~1 400 CCLF cell lines single cell RNA-seq and ATAC-seq Effect on tumor ~23,000 PRECOG patients ~18 CRISPR screens C. Model Integration ~380 ICB patients Relationship with Relationship with cell extrinsic factors, immune cell-intrisic immune factors microenviroment at single-cell resolution infiltration and cytokines 2. In-vitro Testing 4. Mice Model Validation Vehicle Extract TF-regulated gene signature -1355 TF inhibitor TF inhibitor 4T1 mice and B16 mice

Fig. S17. Overall design.

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(A) Effect of ESRRAi in tumor microenvironments. ESRRAi induces antigen presentation in cancer cells that in turn mobilizes CD8⁺ T cells. ESRRAi also induces M1-polarizing cytokines in cancer cells, which polarizes macrophages toward M1. (B) Overall schematic of the target discovery and validation platform of the study involving: computationally discover immune-metabolic regulators (BipotentR), determine effects of targeting an immune-metabolic regulator, and test those effects *in vitro* and *in vivo*.