

Ce Riptac Platform: Linking Targetengagement To Selective Cancer Cell Killing

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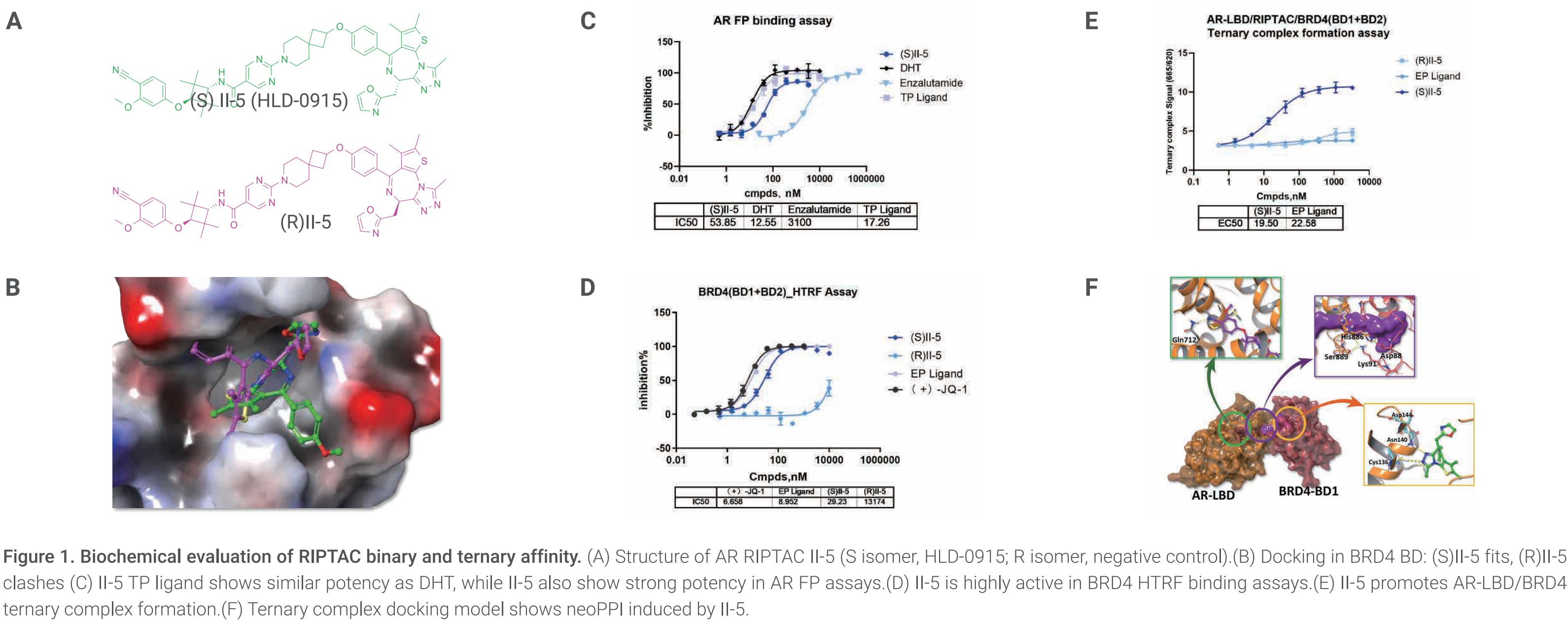
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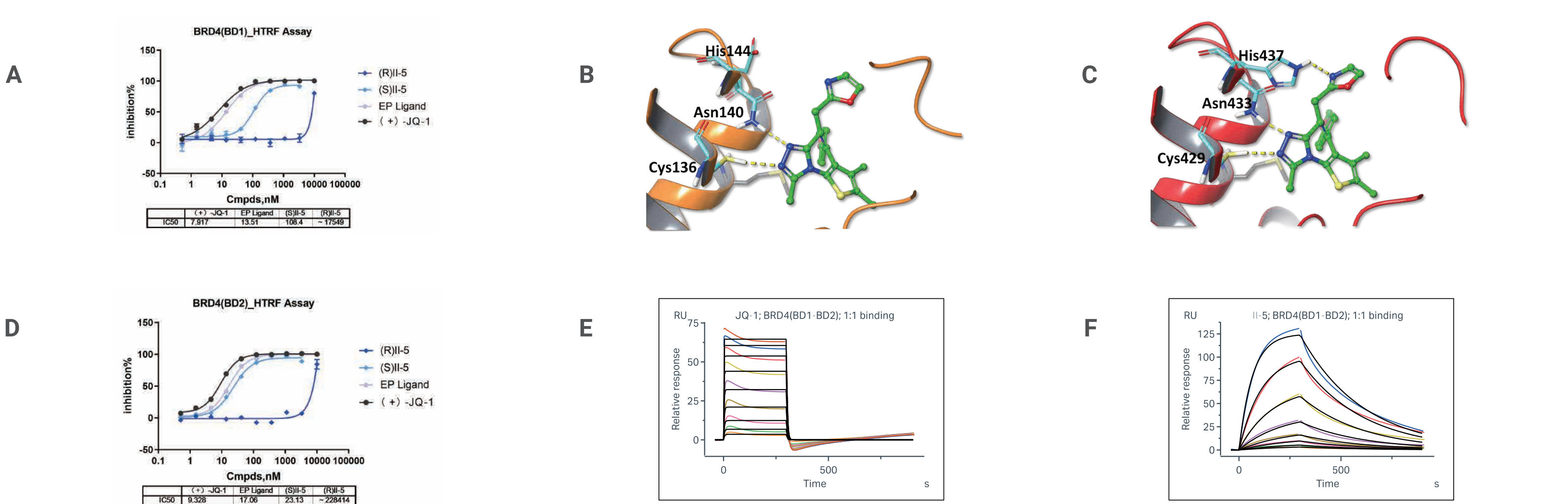
Abstract

RIPTAC (Regulated Induced Proximity Targeting Chimeras) introduces a novel strategy that leverages induced proximity to achieve selective cancer cell killing. Using AR–BRD4 RIPTAC II-5 as a tool compound, we integrated biochemical screening, computational docking, and multi-level cellular and in vivo assays to establish a direct link between target engagement and therapeutic efficacy. Biochemical evaluation confirmed binary and ternary affinity, supported by computational simulations that predicted novel AR–BRD4 ternary protein–protein interactions (neoPPIs) consistent with cooperativity observed experimentally. II-5's distinct slow on/off binding kinetics stabilize ternary complexes, translating into superior activity in ternary formation and downstream signaling modulation. Cellular assays demonstrated that II-5 induces ternary complexes in HEK293T AR OE, VCaP, and LNCaP cells, correlating with strong inhibition of BRD4-driven signaling (c-Myc) while only moderately inhibit AR signaling (reporter and PSA). In vivo CDX models further validated ternary complex formation, PSA reduction, and pharmacodynamic biomarker responses, showing that ternary assembly is preserved across biochemical, cellular, and tumor tissue contexts. II-5 was highly potent in AR-high prostate cancer models, with efficacy scaling across AR mutants and expression levels, highlighting a mechanistic correlation between AR expression and therapeutic effect. This enables RIPTAC to address resistance mechanisms such as AR amplification, point mutations, etc. Safety profiling raised concerns, but tissue distribution suggested a favorable therapeutic window. Beyond AR–BRD4, RIPTAC expands the induced proximity landscape, aligning with TCIP paradigms and demonstrating broader applicability across oncogenic drivers. Together, computational and experimental evidence converge to highlight ternary complex stability and AR expression dependence as the mechanistic drivers of RIPTAC's therapeutic window. Importantly, our induced proximity platform, built on extensive expertise in targeted protein degradation (TPD), can be rapidly migrated to other target pairs, enabling first-in-class drug discovery programs and supporting both domestic and international partners.

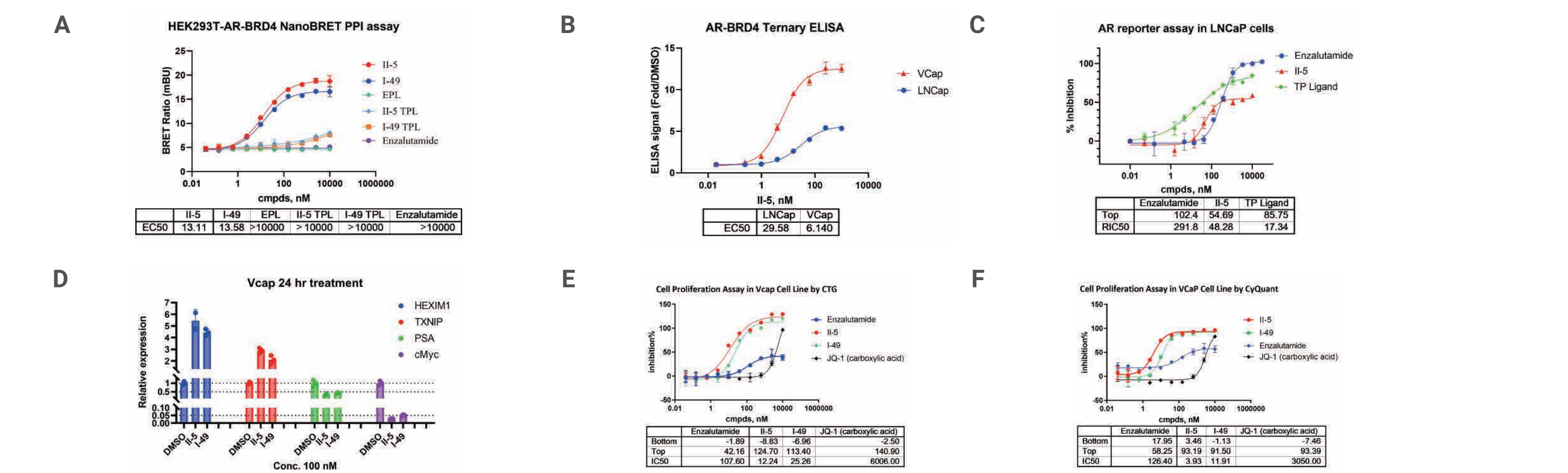
Binary and Ternary Binding of RIPTAC II-5: Cooperative and High Affinity



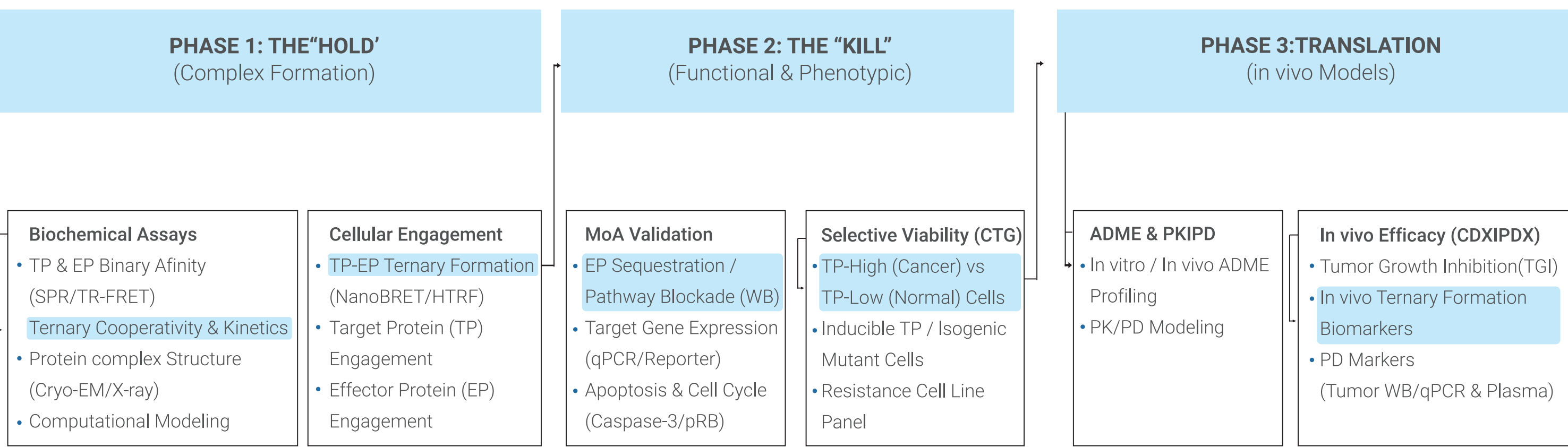
II-5 Engages BD1 and BD2 with Slow Binding Dynamics



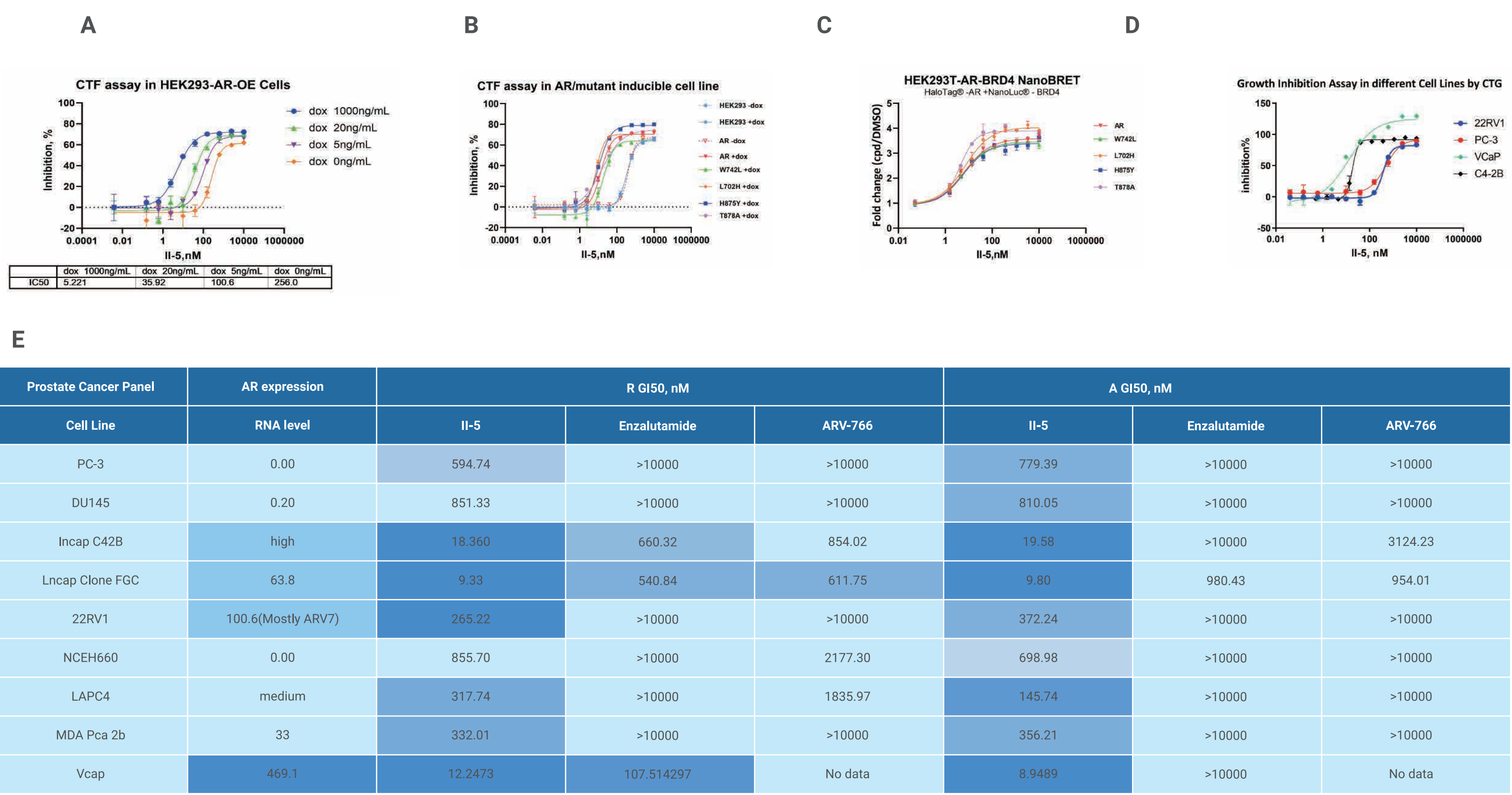
II-5 Ternary Complex Formation Drives Cellular Response (Hold to Kill)



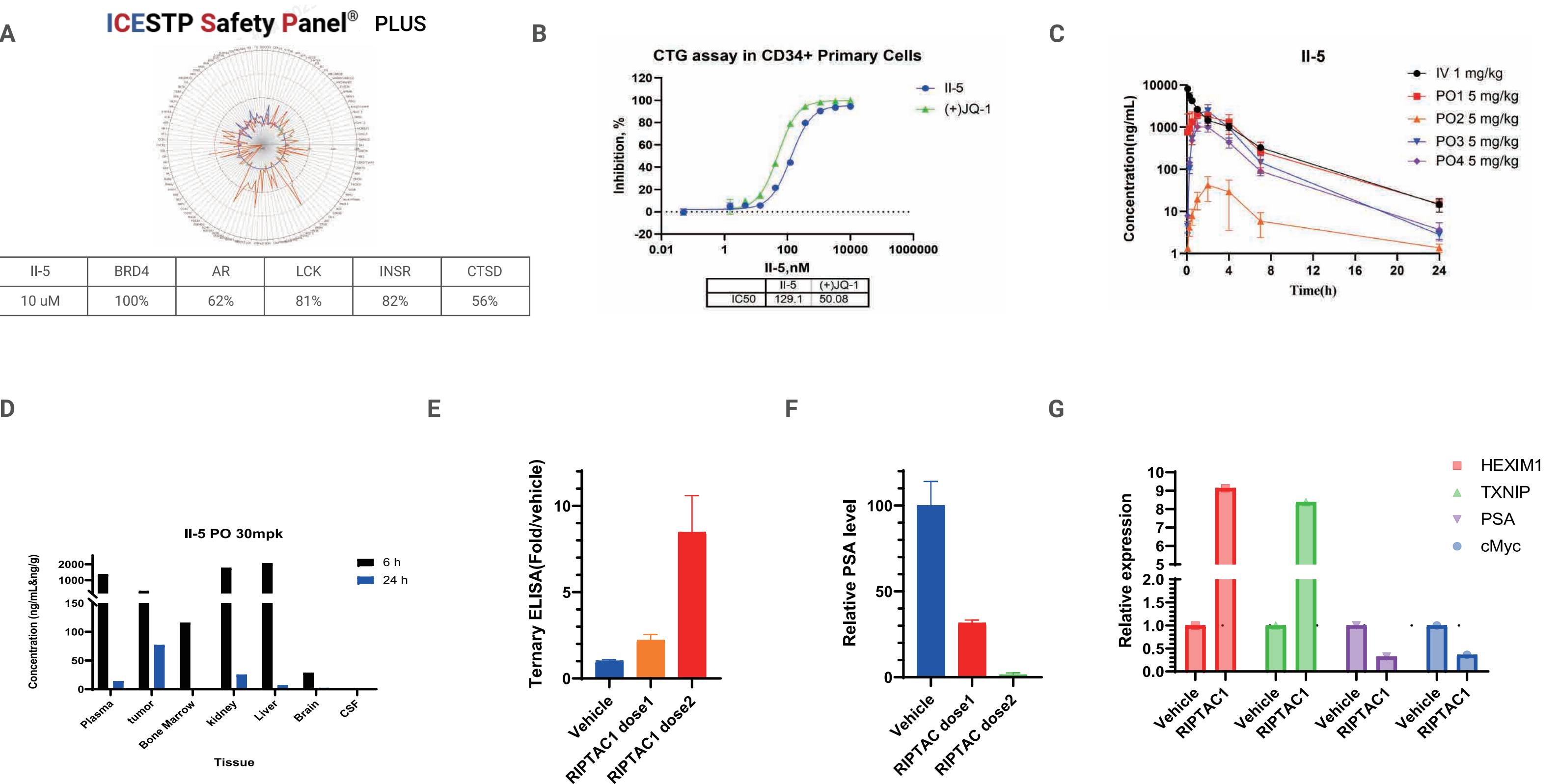
ICEbio RIPTAC platform



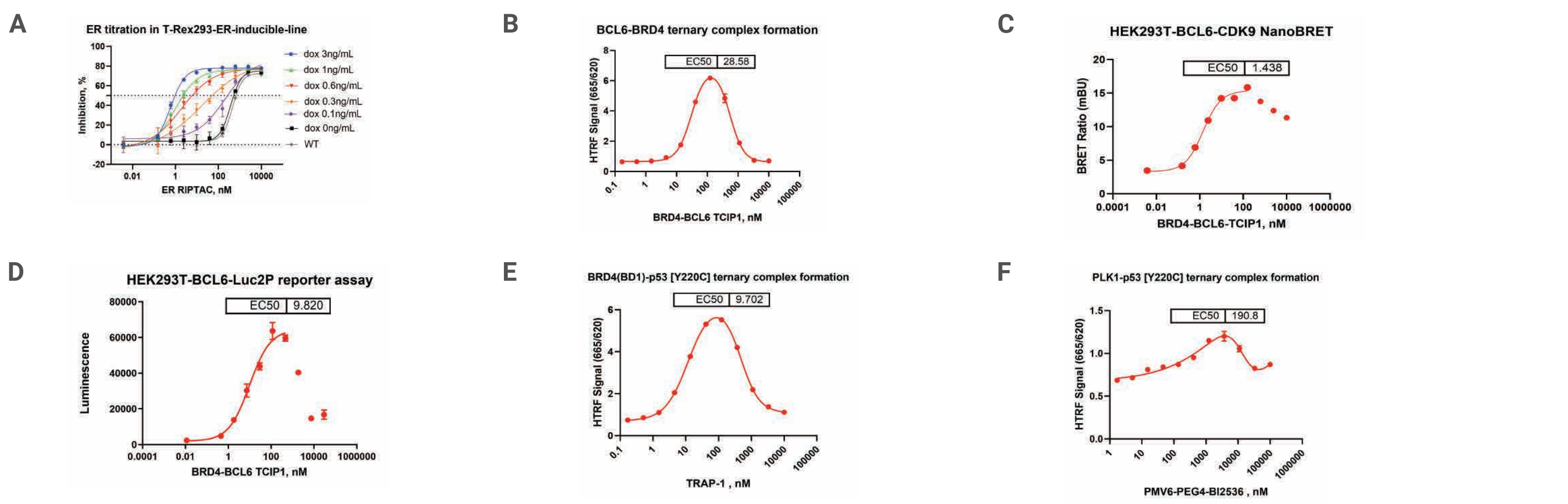
II-5 Activity Linked to AR Expression with Favorable Treatment Window



II-5: Safe Profile with In Vivo PD Modulation Through Ternary Complex



Broadening Induced Proximity: New RIPTAC Pairs and TCIPs



Summary

ICE Bioscience's RIPTAC platform integrates biochemical screening, computational docking, and multi-level cellular and in vivo assays to connect target engagement with therapeutic efficacy. By combining ternary complex prediction, kinetic modeling, and validation across biochemical, cellular, and tumor tissue contexts, the platform establishes mechanistic links between AR expression and selective cancer cell inhibition. Supported by our extensive expertise in targeted protein degradation (TPD), the modular design enables rapid migration to new target pairs. This flexibility, together with translational profiling and safety evaluation, empowers domestic and international partners to accelerate first-in-class drug discovery programs and expand the induced proximity landscape with clinically meaningful insights.

Reference

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