Aurora Kinase A (AURKA) a new druggable target in ER+ Inflammatory breast cancer

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Background

- ER+ inflammatory breast cancer (IBC) is under-appreciated and under-investigated as an aggressive subset of ER+ breast cancer, despite having rates of metastasis comparable to triple negative (TN) IBC.
- First line treatments for ER+ metastatic IBC are identical to high-risk non-IBC breast cancer. However, we found that ER+ metastatic IBC patients have far shorter progression-free survival than non-IBC metastatic patients on CDK inhibitors (accepted, BCR).
- Improving treatment options for ER+ metastatic IBC is a critical unmet need.
- AURKA synthetic lethal gene ARID1A is mutated in 63% of cases.

Hypothesis

Aurora Kinase A (AURKA) is a viable therapeutic target in ER+ metastatic IBC.

Objectives

- Characterize AURKA expression and role in ER+ and ER- IBC pre-clinical models and IBC patient tissues
- Characterize ER+ IBC models
- Demonstrate inhibition of AURKA inhibits IBC proliferation in vitro
- Test dependence on purported synthetic lethal mutations
- Test AURKA inhibitors with standard of care therapies in IBC PDX models to inform clinical trial design

Results

1. AURKA in IBC World Consortium Data

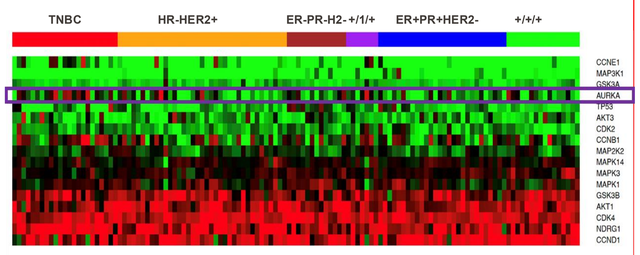


Figure 1. Heatmap of selected cell cycle genes by receptor subtypes demonstrating AURKA is expressed in ER+ and ER- IBC world consortium patient data.

2. AURKA is Increased in MDACC IBC patients with Boston Gene Genomic Testing Results

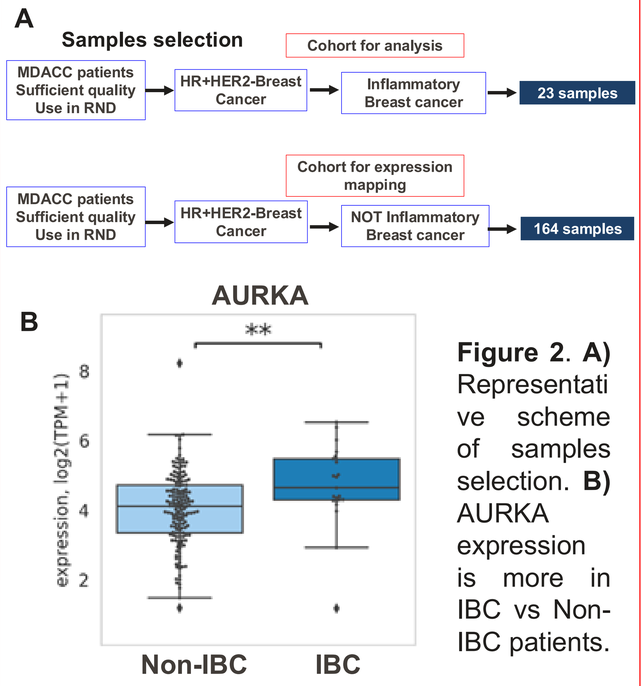


Figure 2. A) Representative scheme of samples selection. **B)** AURKA expression is more in IBC vs Non-IBC patients.

3. Potential AURKA synthetic lethal mutations common in MDACC ER+ IBC and ER- IBC patients

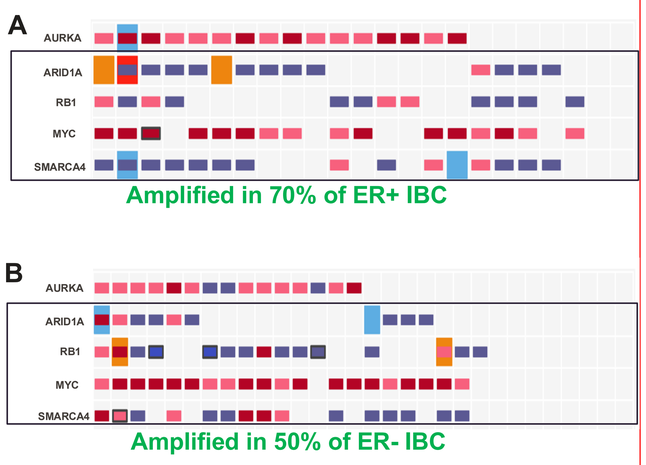


Figure 3. A and B) AURKA expression is associated with mutation in synthetic lethal partners in ER+HER2-IBC and ER-HER2-IBC patients of MDACC.

4. AURKA in IBC cells and ER+/- IBC PDX models

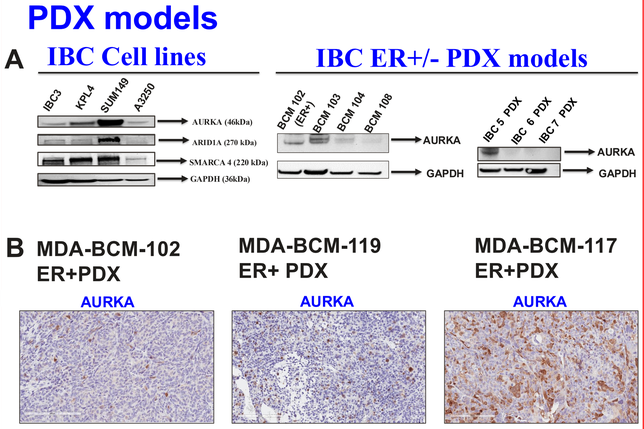


Figure 4. A) Immunobloting demonstrates AURKA expression in different TNIBC cells and ER+/- PDXs. **B)** IHC staining of ER+/- IBC PDX models for AURKA.

5. Alisertib reduces viability of TNIBC

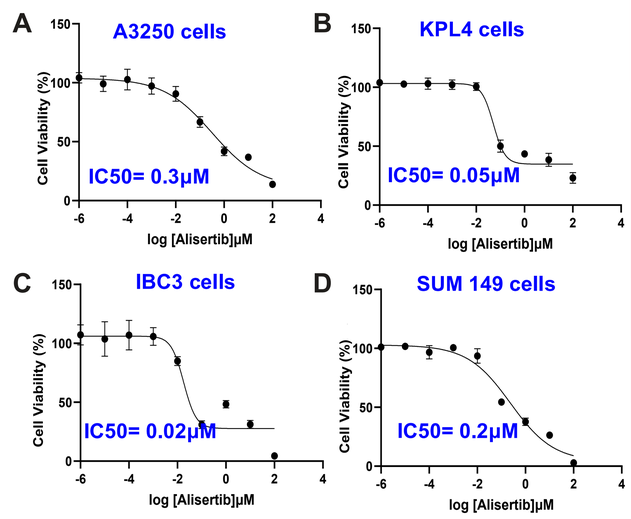


Figure 5. Dose response curve of TNIBC cells treated with Alisertib for 72 hr. **A)** A3250 cells. **B)** KPL4 cells. **C)** IBC cells. **D)** SUM149 cells.

6. Alisertib Inhibits Colony Formation Efficiency in A3250 cells

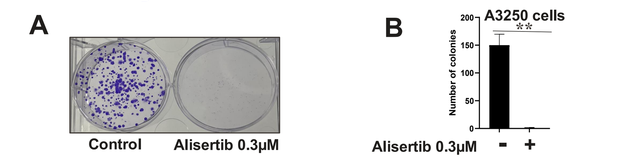


Figure 6. A) Alisertib inhibits colony formation efficiency of A3250 cells. **B)** Bar graph showing number of colonies formed after treatment. **p<0.005

7. Alisertib induces senescence in A3250 cells

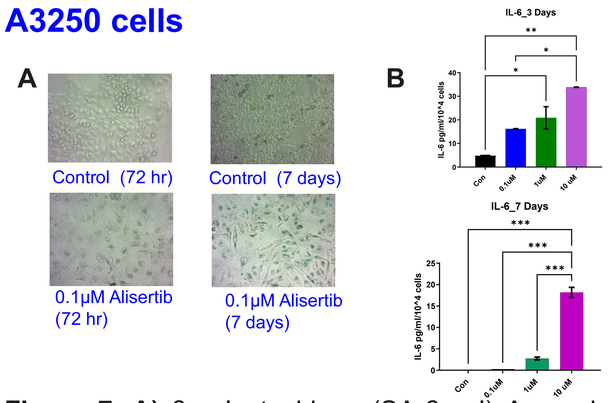


Figure 7. A) β-galactosidase (SA-β-gal) Assay in A3250 cells treated with alisertib. **B)** ELISA for IL-6 in A3250 cells treated with alisertib for 3 days and 7 days. ***p<0.0005, **p<0.005, *p<0.05

8. Navitoclax in Combination with Alisertib Inhibits Senescence

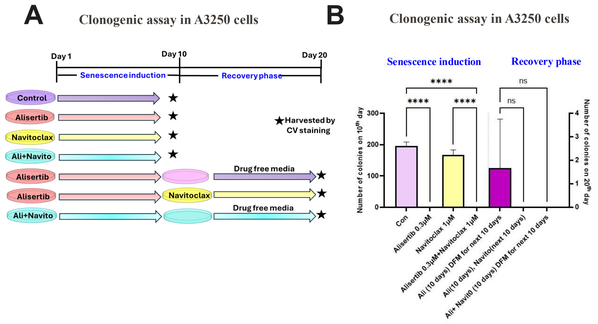


Figure 8. A) Treatment scheme for senescence induction. **B)** Bar graph showing number of colonies formed after treatment. ****p<0.0001, ns (non-significant)

9. Establishment of ER+ IBC PDX model

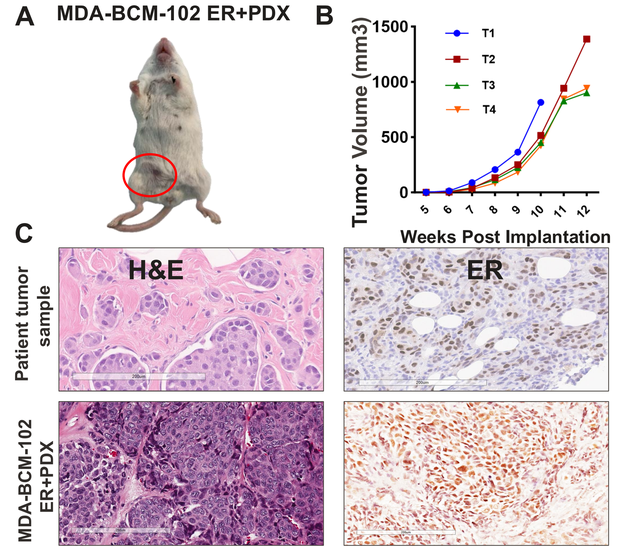


Figure 9. Novel PDX models are being developed from fresh patient biopsies after informed consent. A) MDA-BCM-102 ER+PDX skin invasion. **B)** The tumor growth curves of ER+ 102. **C)** H&E and ER staining of patient tumor sample and MDA-BCM-102 ER+ PDX.

10. *In vivo* efficacy of Alisertib, Fulvestrant, and their combination in ER+ MBI-102 PDX Model

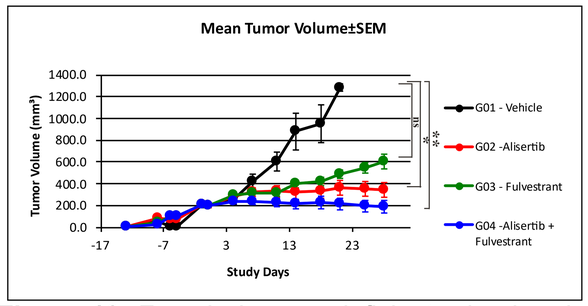


Figure 10. Female immunodeficient mice bearing ER+ patient-derived xenograft (PDX) tumors were randomized into four treatment groups: Vehicle control, Alisertib, Fulvestrant and Alisertib + Fulvestrant combination. Treatments were administered as Alisertib, OG (30 mg/kg; five times per week), Fulvestrant, SC (200 mg/kg; two times per week), for four weeks. **p<0.005, *p<0.05, ns (non-significant)

Conclusion

- AURKA is amplified and over-expressed in ER+ and ER- IBC patient tissues and cell lines.
- Alisertib prompts cell death in IBC cell lines (HER2 > TNIBC) and reversible senescence inhibited by navitoclax in A3250.
- The ER+ IBC model MBI-102 is sensitive to fulvestrant.
- Alisertib and fulvestrant combined demonstrate significant efficacy in MBI-102

Acknowledgement

- Patients who contributed data and tissues to the registry
- The State of Texas Grant for Rare and Aggressive Breast Cancers
- MDA IBC Bootwalk Funding
- CPRIT core #RP220646
- Alisertib kindly provided by Puma.