San Antonio Breast Cancer Symposium, December 6-10, 2016

Targeted and Selective Degradation of ERα by PROTACs

John J. Flanagan, Yimin Qian, Ann Marie K. Rossi, Monica Andreoli, Ryan Willard, Deborah Gordon, John Harling, Ian Churcher, Ian Smith, Nico Zinn, Marcus Bantscheff, Craig M. Crews, Ian Taylor, Andrew Crew, Kevin Coleman, James Winkler

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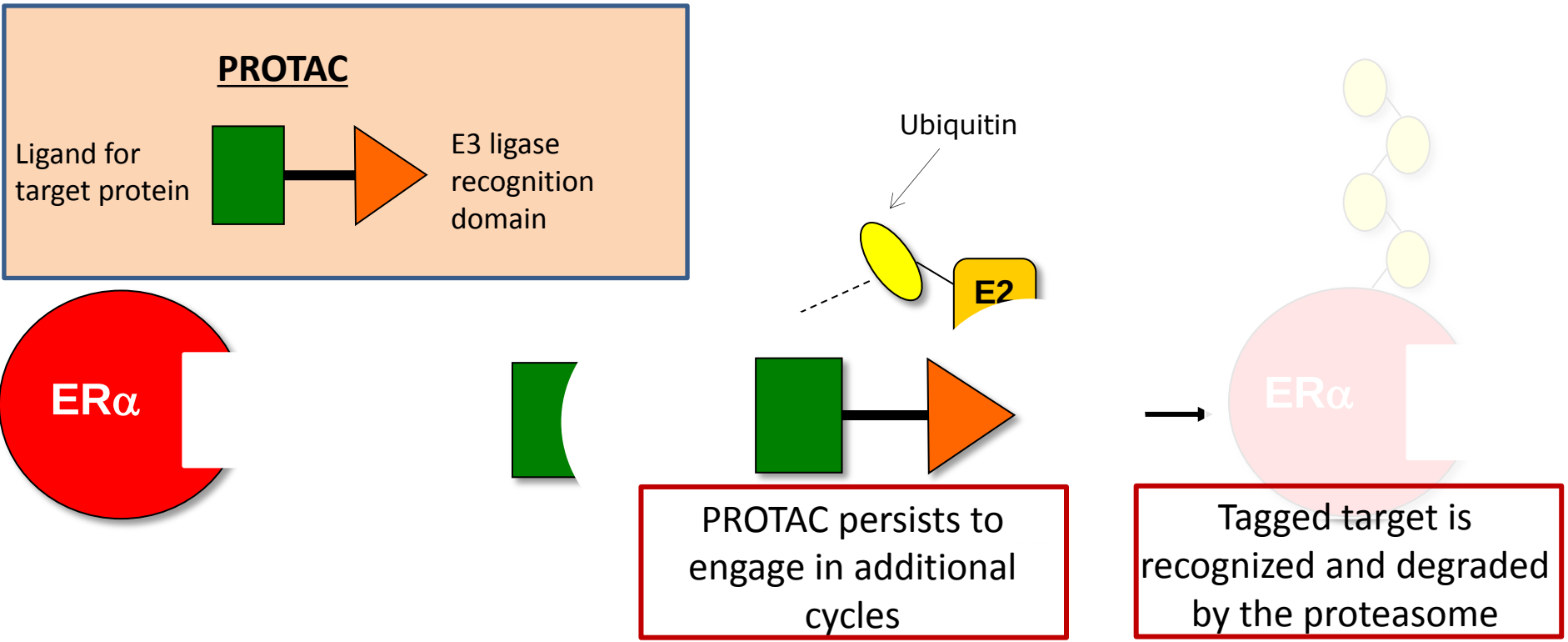
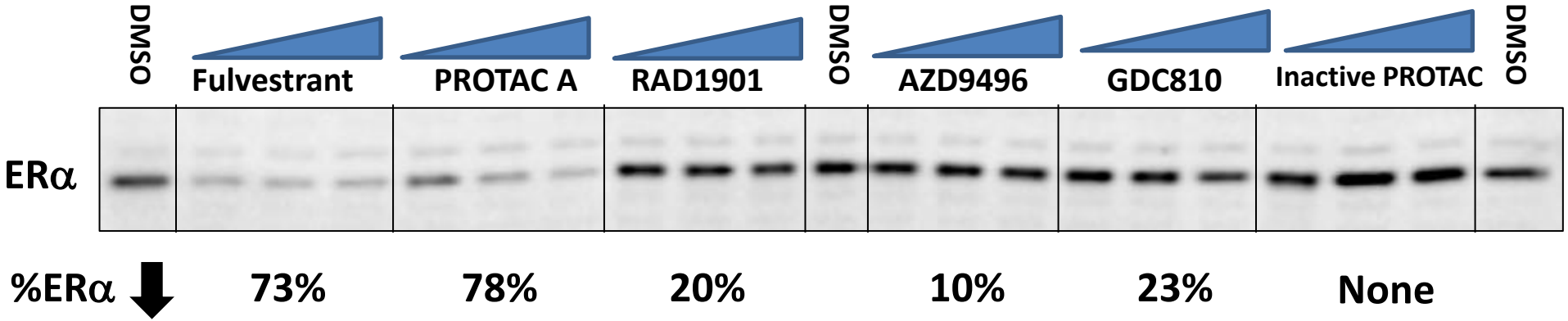
PROTAC: PROteolysis TArgeting Chimera

- Chimeric, small molecule PROTACs recruit E3 ligase to target proteins to promote polyubiquitination and induce their degradation via the proteasome



PROTAC potently reduces ERα levels in T47D cells



- Robust degradation of ERα with PROTACs and fulvestrant in other ER+ cell lines (BT474, HCC1428, MDA-MB-361, MCF7, MDA-MB-134-VI)
- Inactive PROTAC binds to ERα but not to any E3 ligase
- Concentrations tested were 6, 25, and 100 nM

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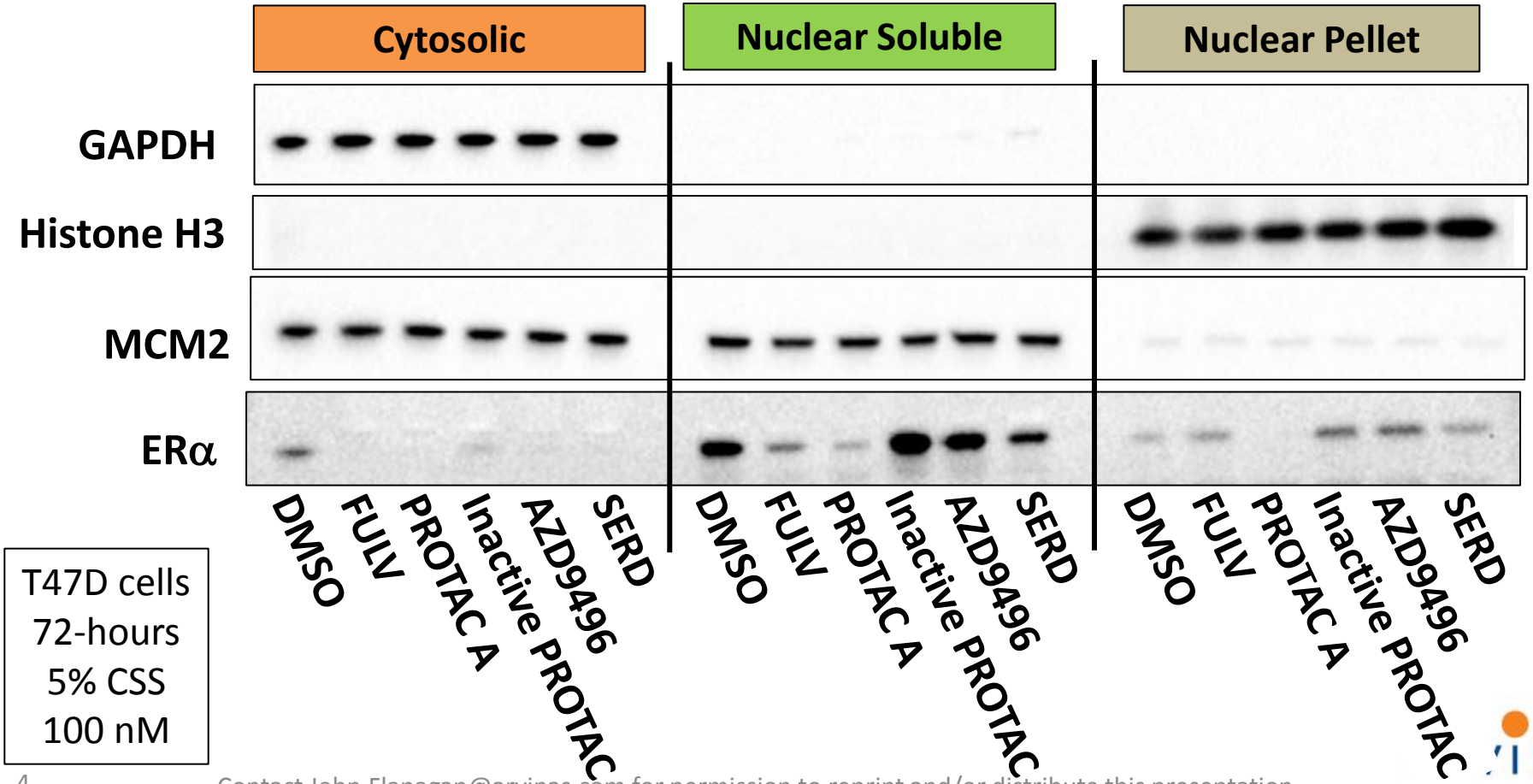
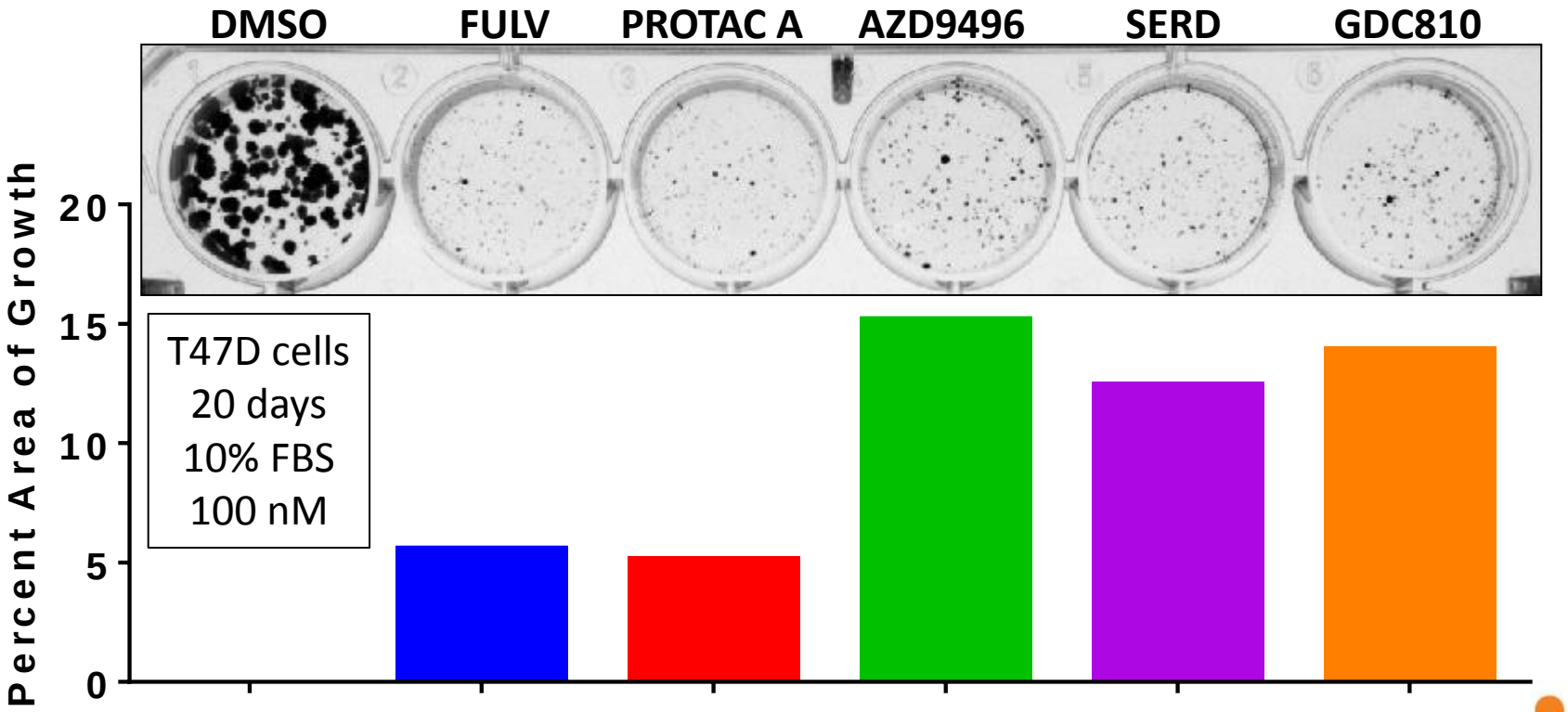
PROTAC reduces ERα levels in nuclear fractions

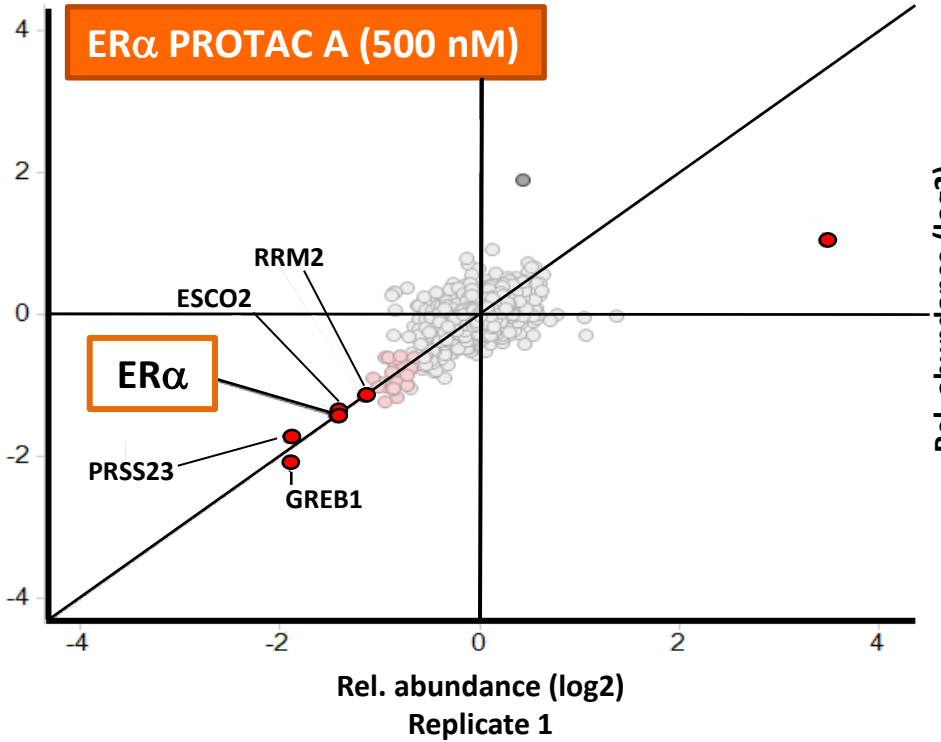


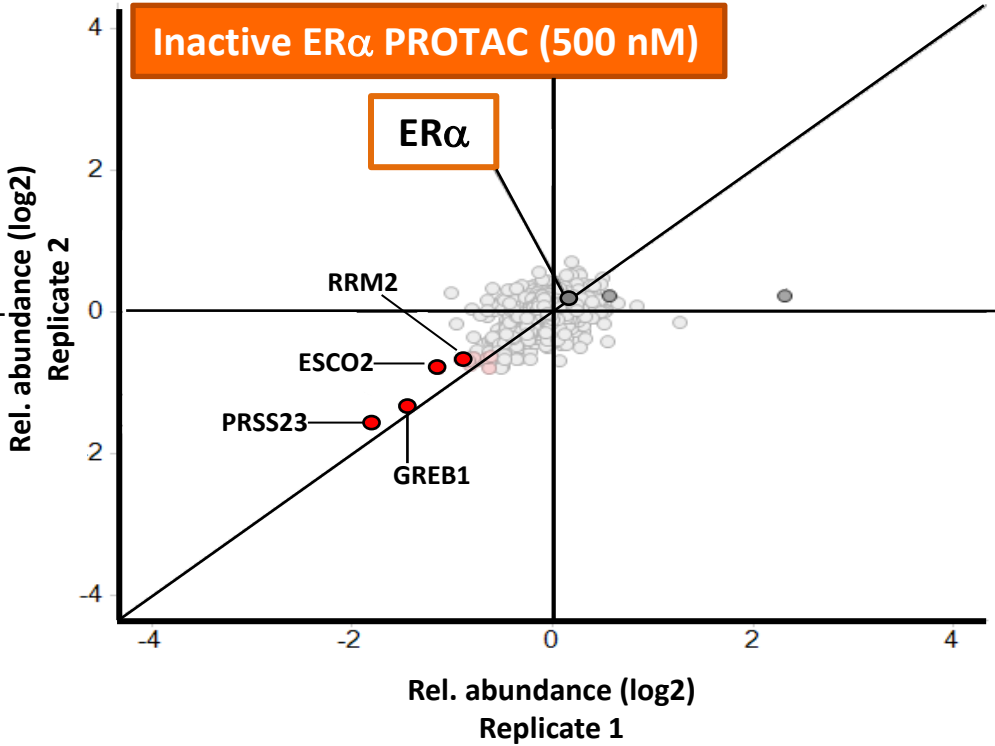
T47D cells
72-hours
5% CSS
100 nM

Greater anti-proliferative effects with ERα degraders



Selective degradation of ERα by PROTACs





LC/MS quantitation of >7600 proteins after overnight incubation of MCF7 cells with PROTACs

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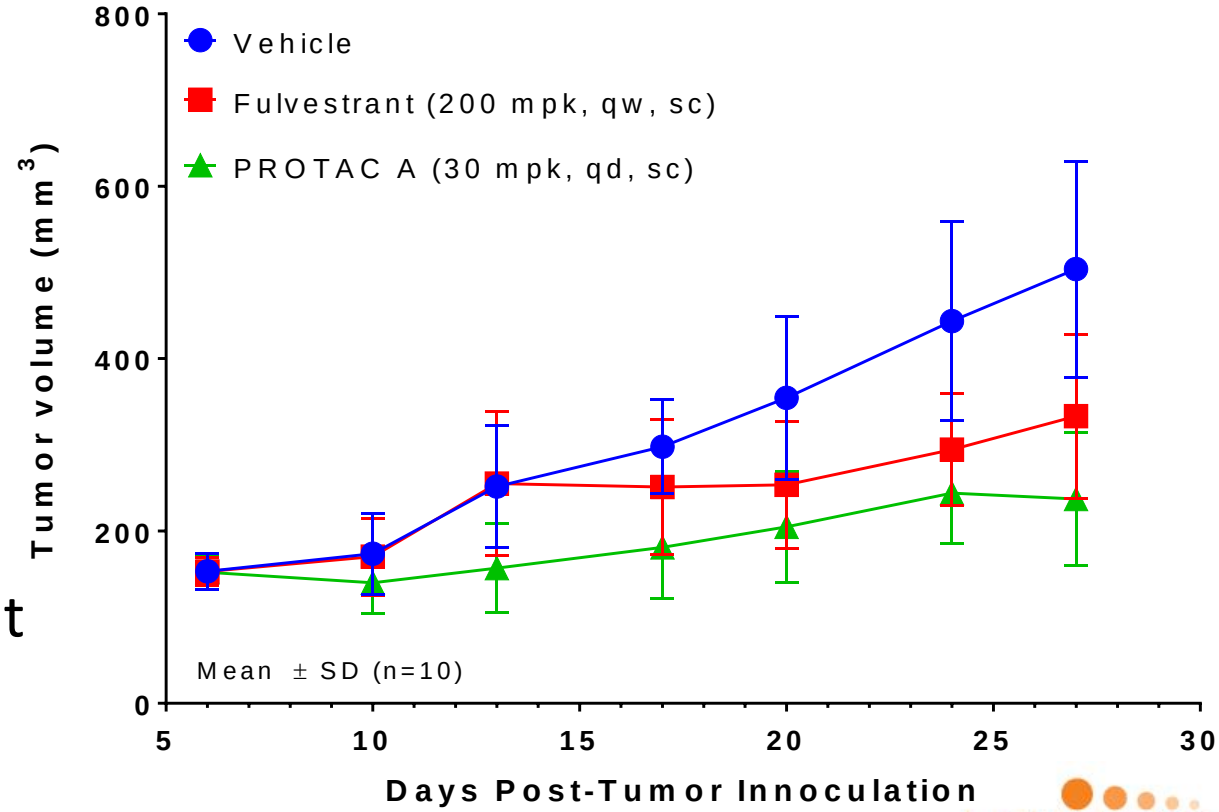
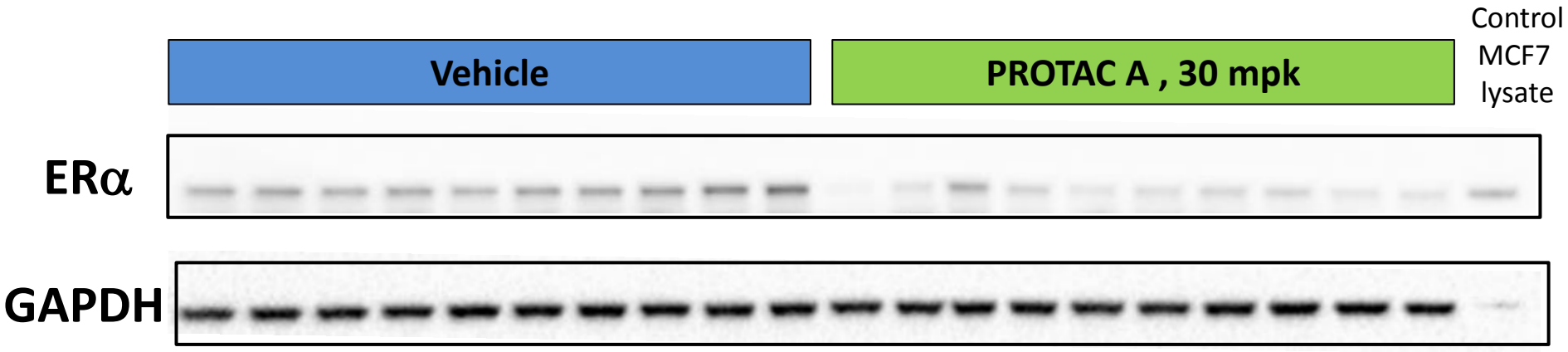
ERα PROTAC inhibits growth of MCF7 xenografts

- 21-day growth study
- 68% TGI achieved with daily 30 mpk PROTAC (subcutaneous)
- Estradiol required for model to grow so PROTAC anti-endocrine activity is likely better at post-menopausal E2 levels

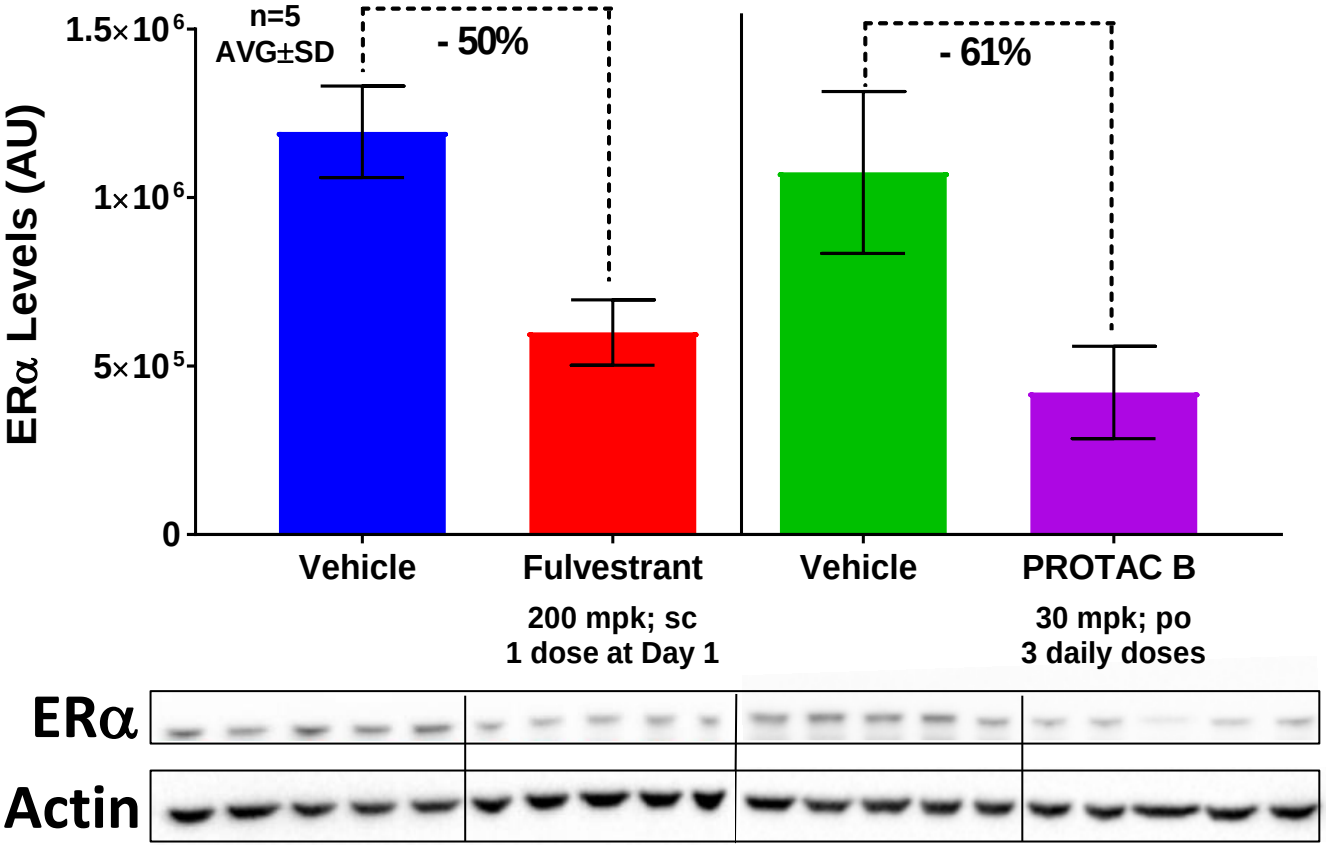


PROTAC decreases ERα levels in MCF7 xenografts



- ~60% reduction in ERα levels with PROTAC A (30 mpk, s.c.)
- Tumors were harvested four hours post-dose

ERα degradation after oral administration of PROTAC



- MCF7-estradiol deprived cells implanted in adult female mice
- Similar reduction of ERα also seen in immature rat uteri

Summary

- PROTAC-mediated degradation provides a distinct mechanism for reducing ERα when compared to fulvestrant and current clinical SERDs
- PROTACs reduce ERα levels in all ER+ cell lines tested
- Oral administration of PROTACs reduced ERα levels in ER+ xenografts and in rat uteri
- Currently evaluating oral PROTACs in a variety of clinically-relevant ER+ BC models

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