Prospective optimization of ER degradation yields ligands with variable capacities for ER transcriptional suppression

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Genentech
SABCS, Thursday December 6th 2018:
General Session 3

Disclosure Information: SABCS 2018 – Ciara Metcalfe

I have the following financial relationships to disclose:

Employee of Genentech

and

I will not discuss off label use and/or investigational use in my presentation.

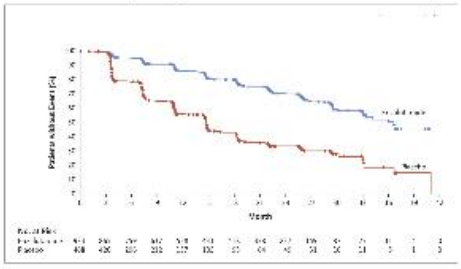
Direct Hormone Receptor targeting is superior to hormone deprivation

- *Lessons from AR & Prostate cancer*

The NEW ENGLAND JOURNAL of MEDICINE

Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer

Metastasis Free Survival:
Placebo + ADT (14.7) versus Enzalutamide + ADT (36.6)

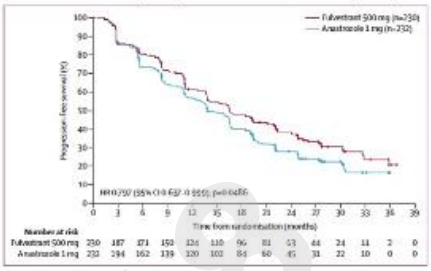


ADT = Androgen Deprivation Therapy
Enzalutamide & Apalutamide = AR antagonist

THE LANCET

Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial

Progression Free Survival:
Anastrazole (13.8) versus Fulvestrant (16.6)



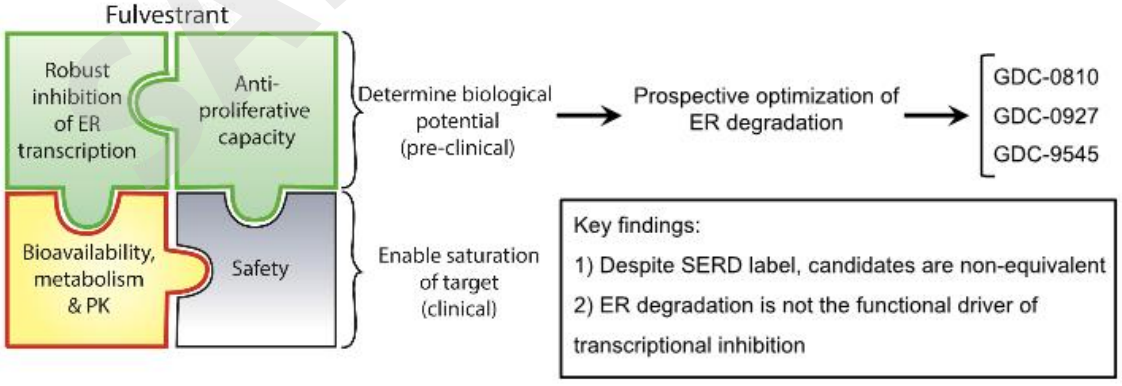
Anastrazole = Estrogen Deprivation
Fulvestrant = ER antagonist/"SERD"

Revealing the untapped clinical potential of direct ER targeting

- *Key properties required for hypothesis-testing*

Hypothesis

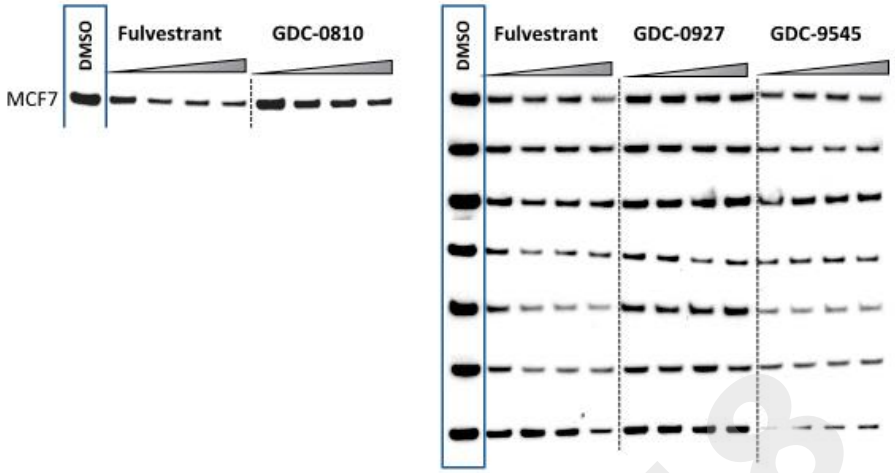
Direct, full & saturating ER inhibition will meaningfully improve clinical outcomes



Key findings:

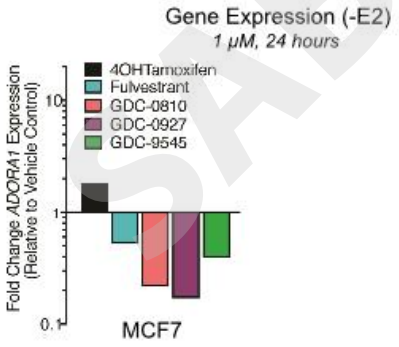
1) Despite SERD label, candidates are non-equivalent
2) ER degradation is not the functional driver of transcriptional inhibition

ER degradation capacity across “SERDs” is not equivalent



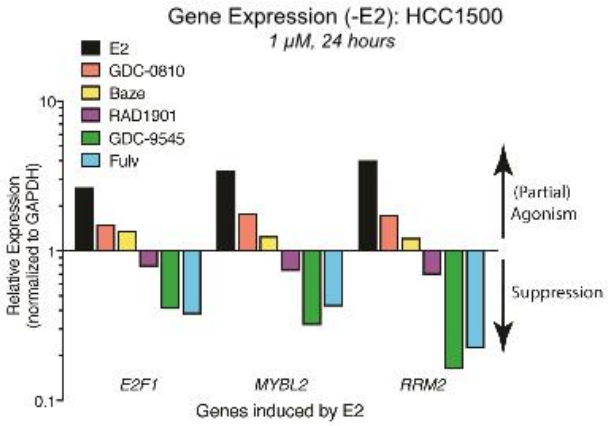
24 hour ligand treatment of hormone deprived cells; 1 nM, 10 nM, 100nM, 1000 nM; actin blots available & confirm equal loading

“SERDs” have distinct transcriptional and anti-proliferative profiles



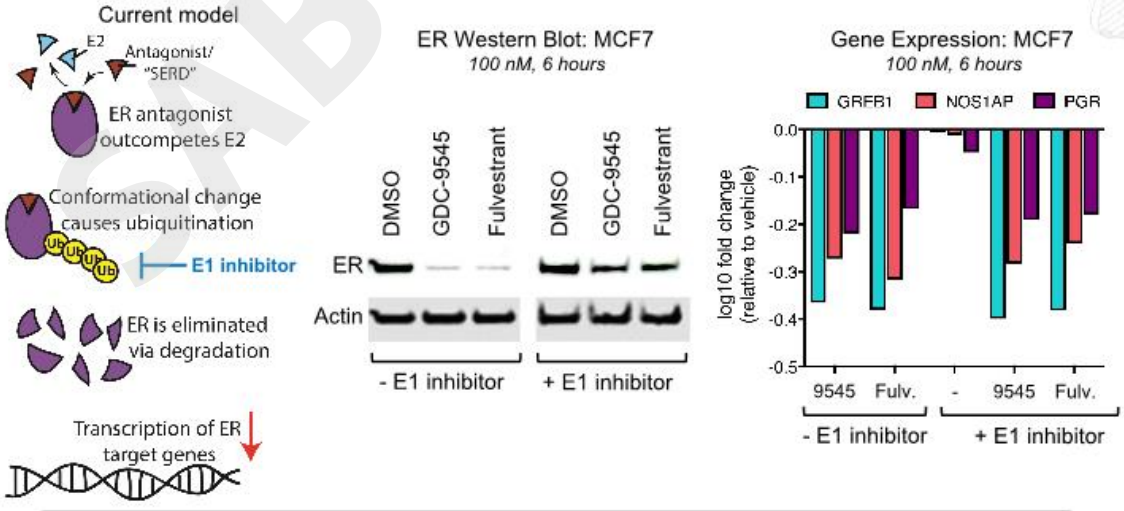
GDC-0810 displays partial ER agonism and sub-optimal anti-proliferative activity, despite prospective optimization of ER degradation

"SERDs" have distinct transcriptional and anti-proliferative profiles

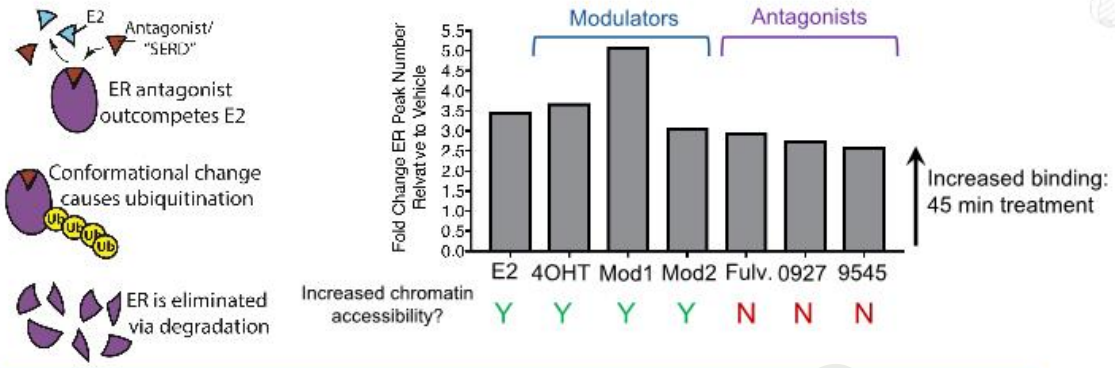


Bazedoxifene & RAD1901 display distinct anti-proliferative and/or transcriptional profiles versus fulvestrant, despite retrospective classification as "SERDs"

Transcriptional inhibition is maintained when ER degradation is attenuated



"SERDs" trigger the association of ER with chromatin



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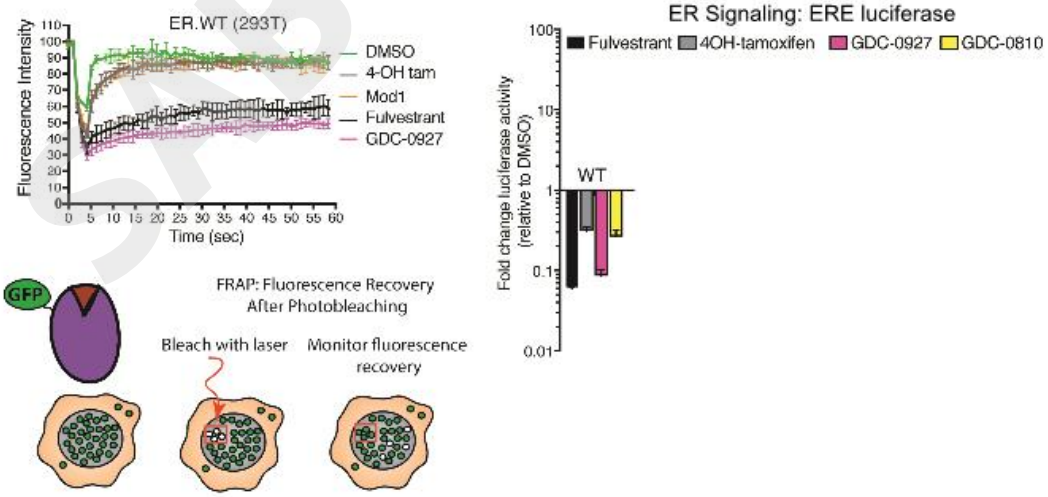
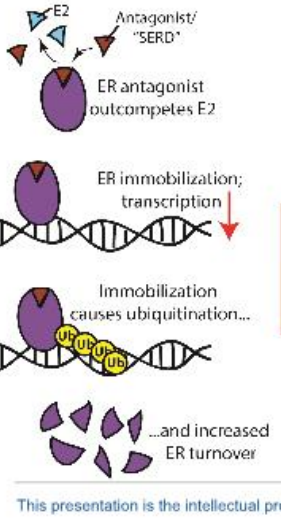
Cell fractionation and ER western blot analysis
&
ER chromatin immunoprecipitation and DNA seq. (ChIPseq)

"SERDs" profoundly reduce ER mobility, necessary for full antagonism



ER destabilization follows, rather than drives, ER inhibition

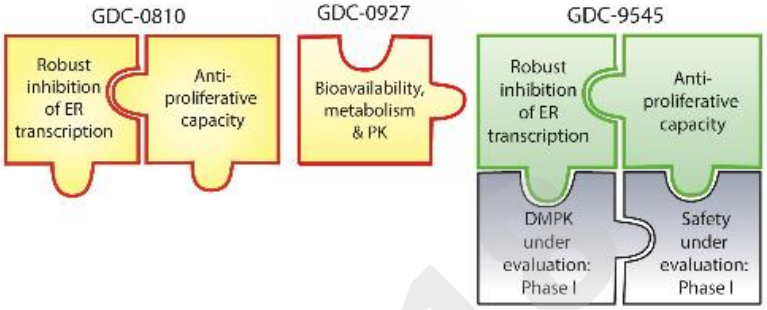
Revised model



- Emphasis → ER transcription
- "SERD" → misnomer

GDC-9545 pre-clinical poster:
Friday @ 5pm, P5-04-07

GDC-0927 Phase 1 biomarker poster:
Friday @ 5pm, P5-11-01



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