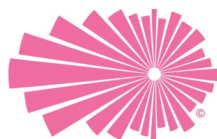


Persistent effects of pregnancy and xenoestrogen exposures in the mammary gland

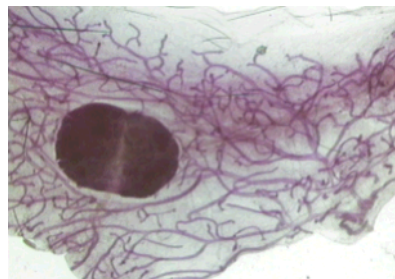
D. Joseph Jerry, University of Massachusetts-Amherst

***BCERP Annual Meeting
November 16th, 2017***



Rays of Hope
Center for Breast Cancer Research

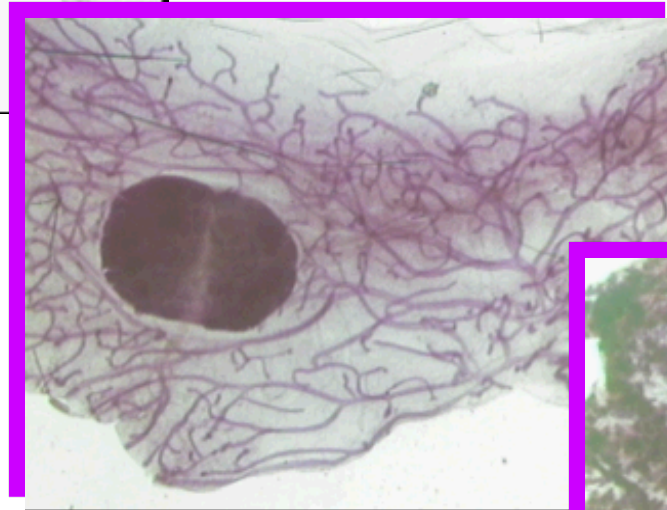
Baystate Regional Cancer Program and the Pioneer Valley Life Sciences Institute



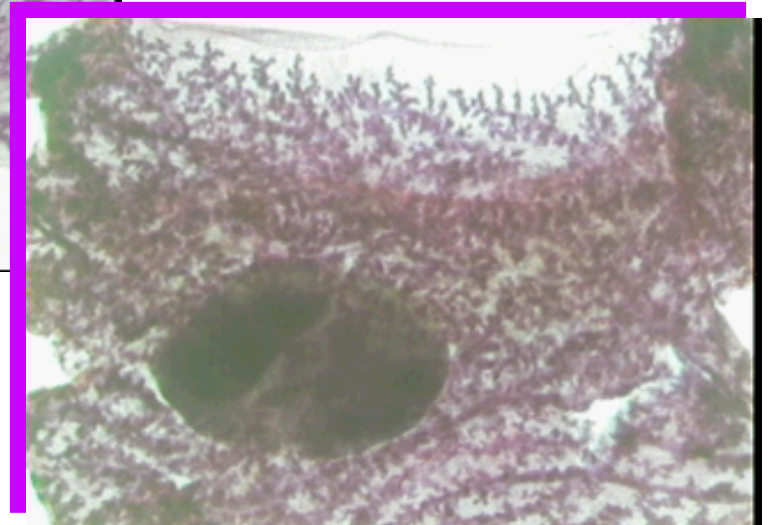
Mouse Mammary Development



Mature



Parous

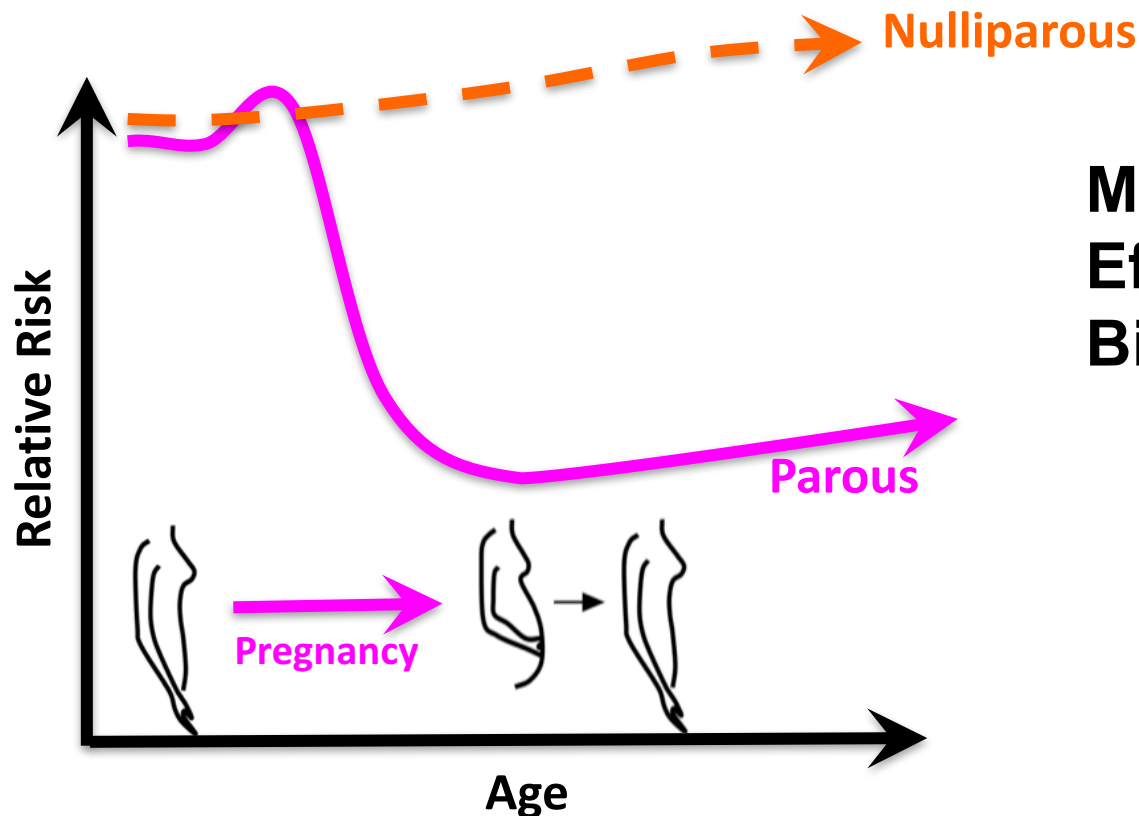


Lactating



Is pregnancy a window of susceptibility?

- Full-term pregnancy reduces risk of breast tumors.

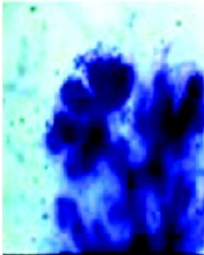
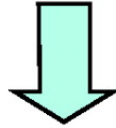


**Mechanisms?
Effects of exposures?
Biomarkers?**

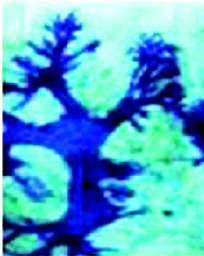
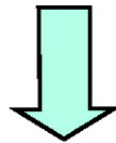
Differentiation



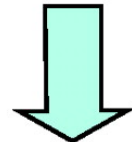
Terminal duct



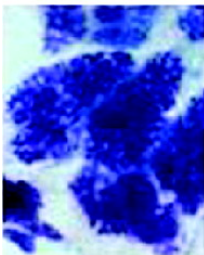
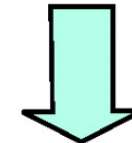
Alveolar duct



**Lobule type 1
(site of origin ductal carcinoma)**



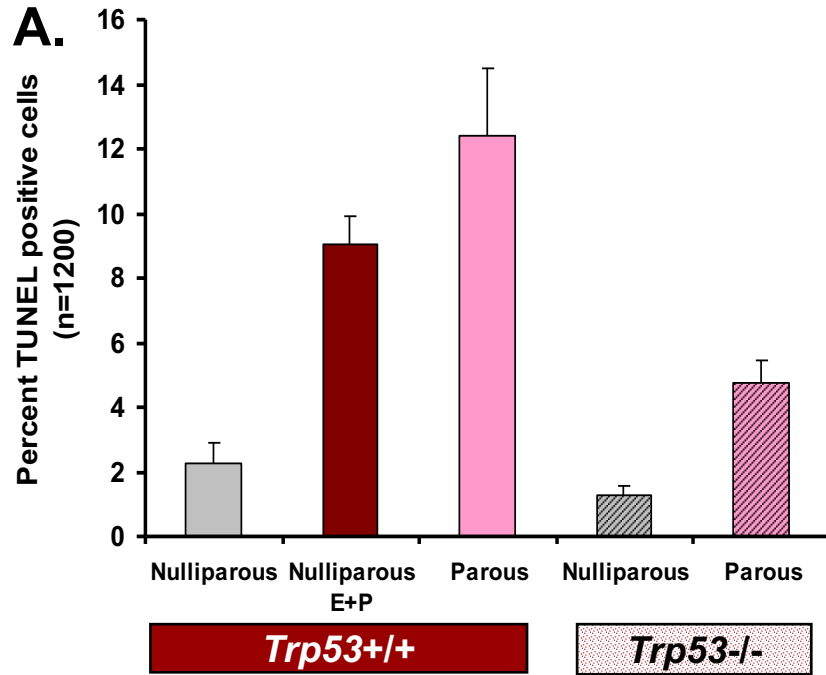
**Lobule type 2
(site of origin lobular carcinoma)**



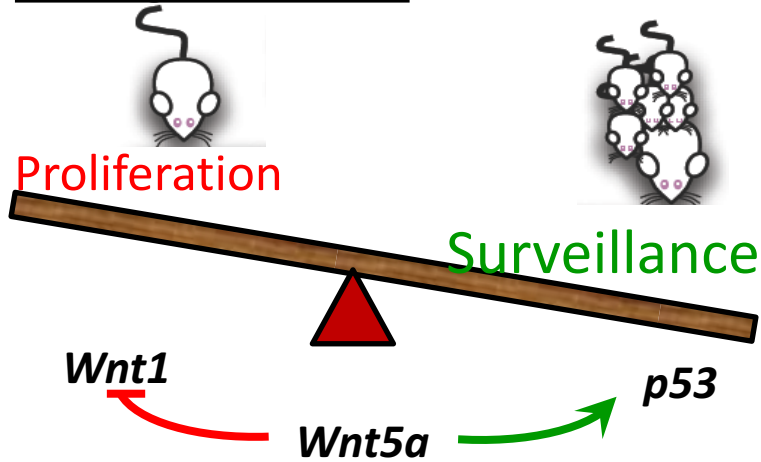
Lobule type 3

- **Morphologic differentiation is induced by prolactin, but did not confer protection.**
- **There must be a more subtle change in the patterns of genes expressed.**

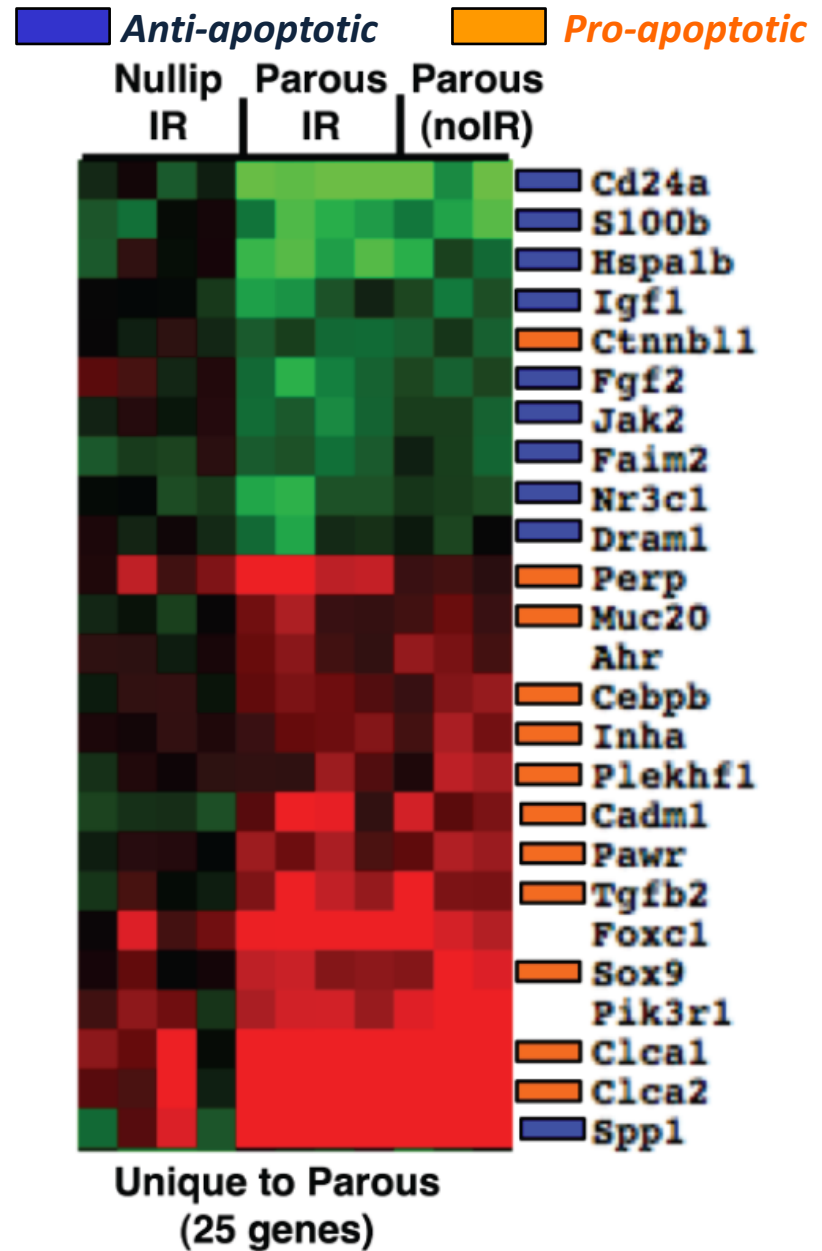
Genomic Surveillance

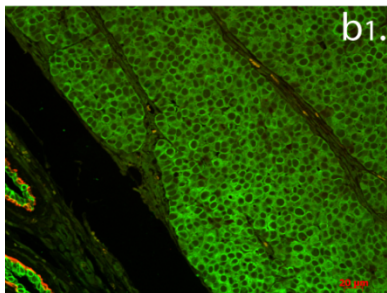
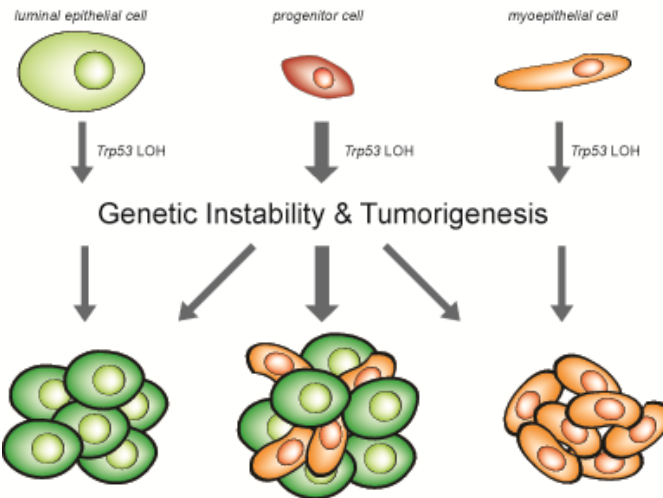
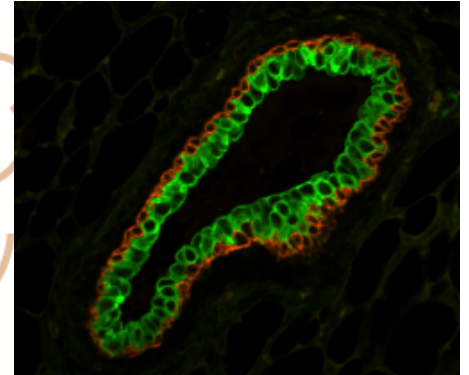
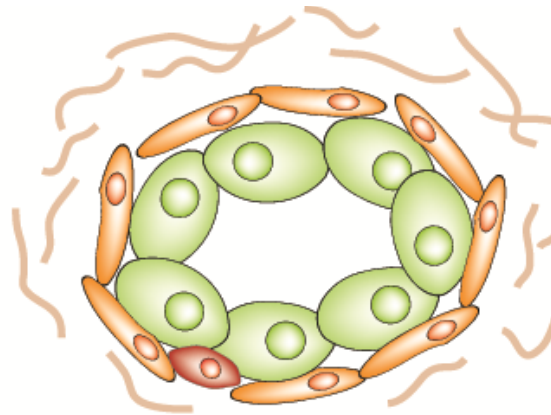


C. Shifting the balance

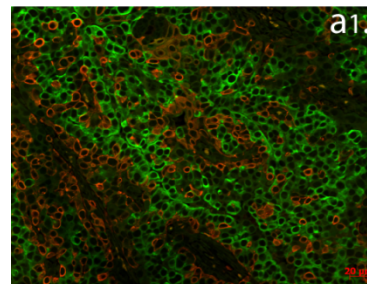


B. Increased apoptosis signature

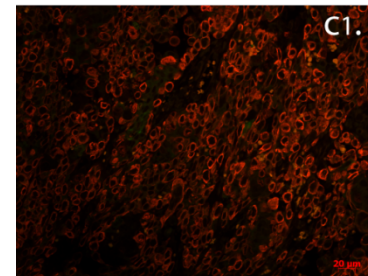




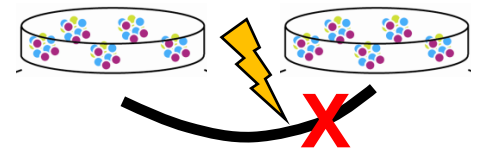
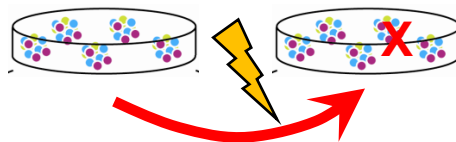
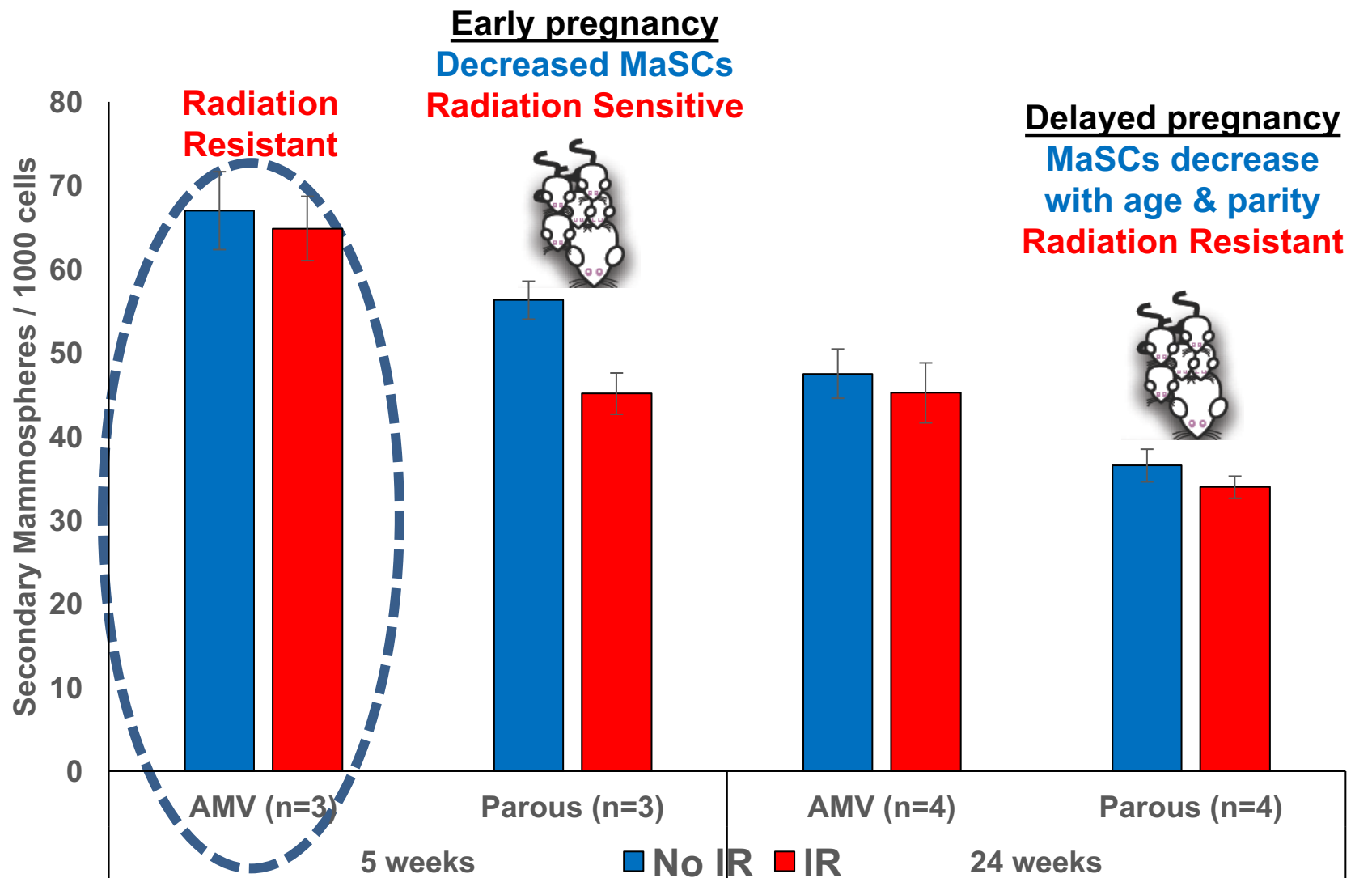
Luminal (26%)

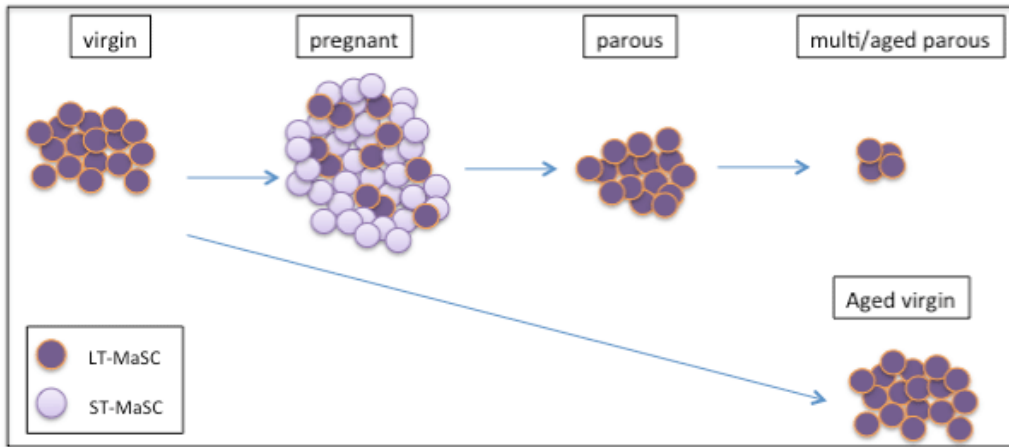


Mixed (63%)



Basal (11%)





Dall G, Anderson R, Britt K (2014) The Role of Stem Cells in Parity Induced Protection against Breast Cancer. J Cancer Biol Res 2(2): 1049.

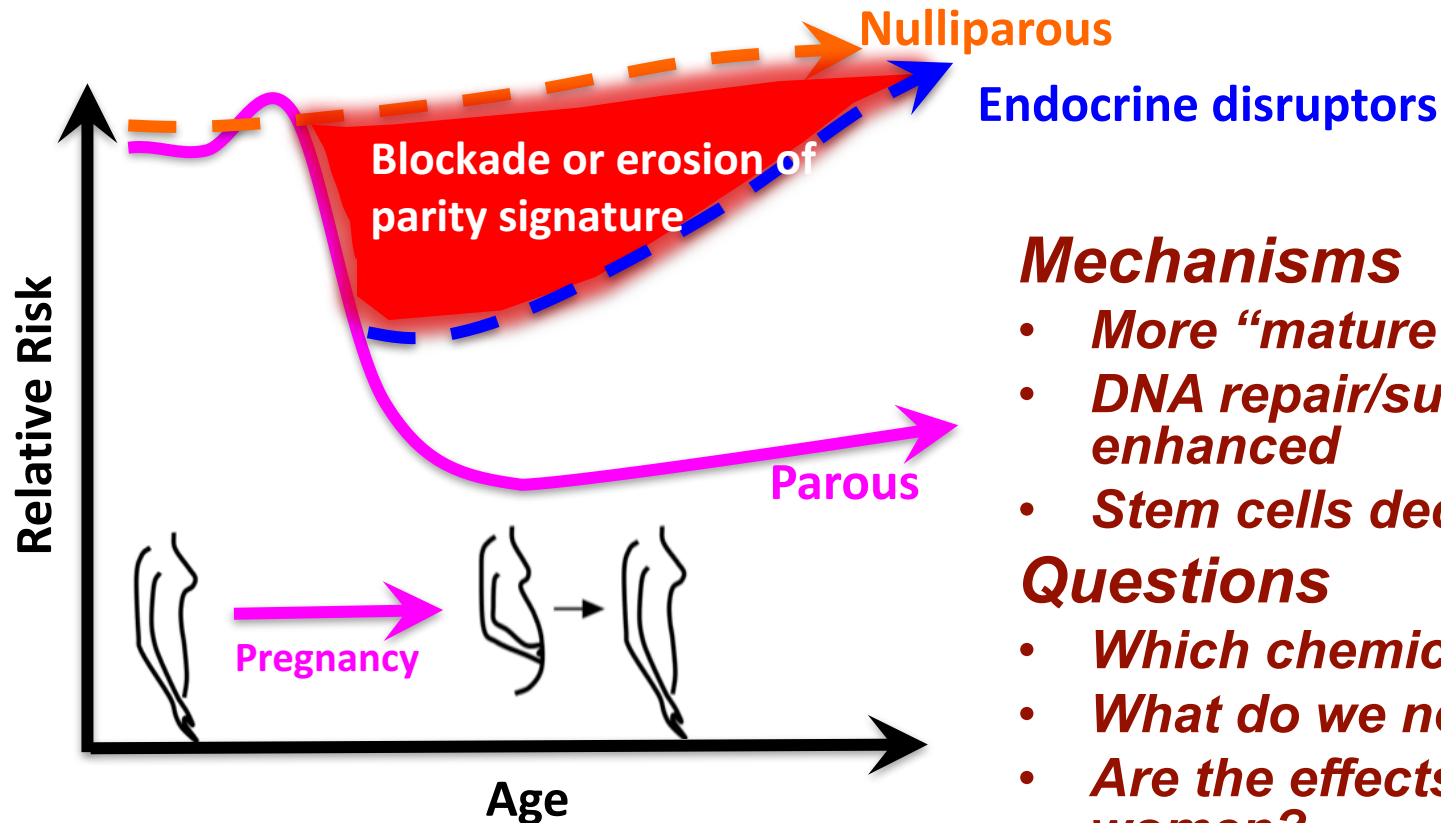
Early pregnancy

- Long-term stem cells (LT-MaSC) differentiate into "short-term stem cells" (ST-MaSC) during pregnancy
 - Expands the pool of MaSCs
 - ST-MaSCs are sensitive to cellular stress (DNA damage) and die.

Delayed pregnancy

- Aging decreases the LT-MaSCs.
- Pregnancy further dilutes the MaSC pool.
- But the LT-MaSCs remaining are resistant to radiation.

Is pregnancy a window of susceptibility?




Mechanisms

- *More “mature” structures*
- *DNA repair/surveillance enhanced*
- *Stem cells decreased*

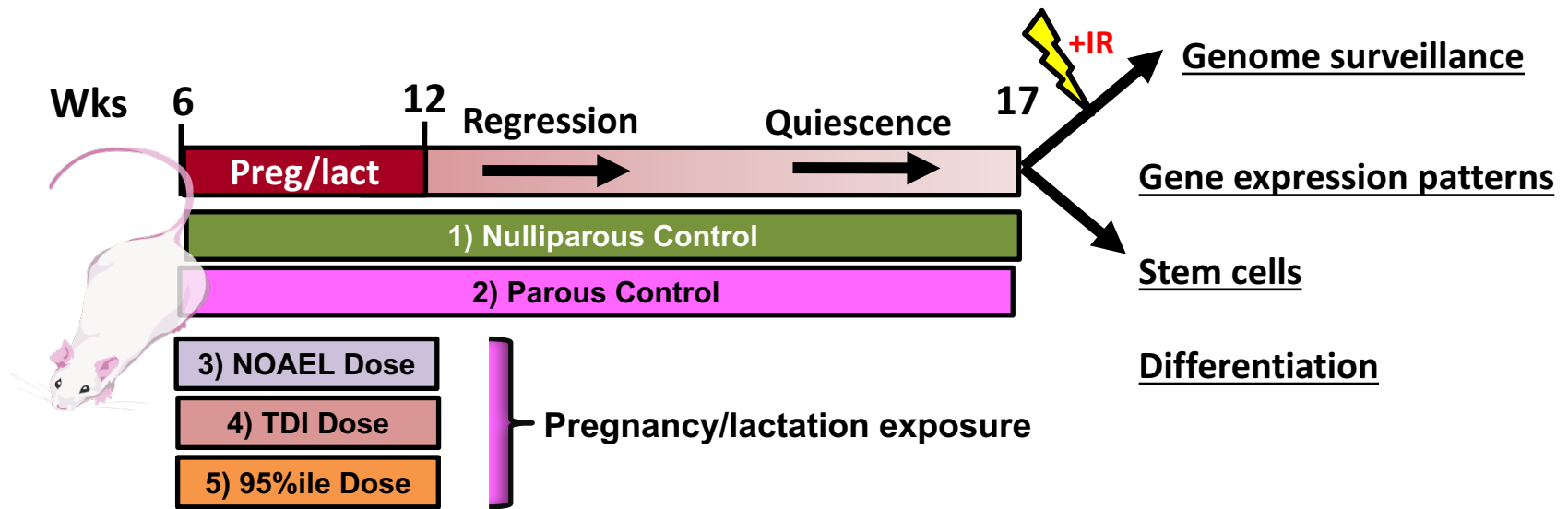
Questions

- *Which chemicals?*
- *What do we need to measure?*
- *Are the effects the same for all women?*
- *Can we identify biomarkers that are accessible in populations?*

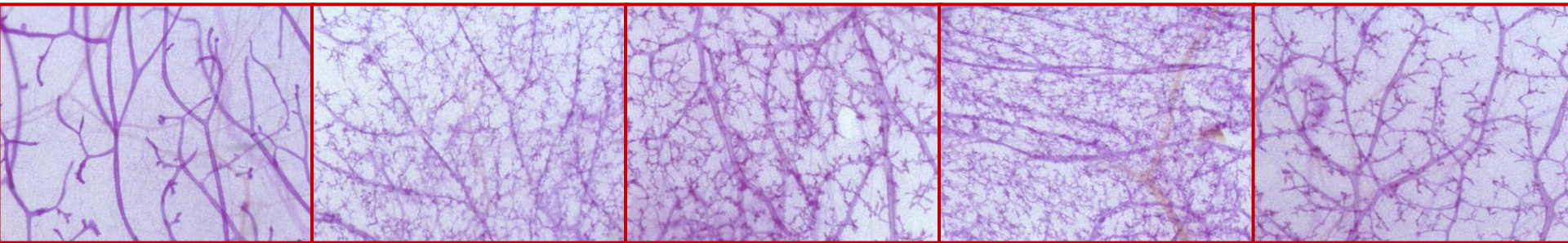
What chemicals?

Chemical	Exposures in pregnant women			Transactivation vs E2	
	Prevalence ¹	Mean	95%ile	ER α	ER β
Pregnancy (blood)	%	ug/L	ug/L	uM	uM
Pregnancy Estrone (E1)	100%	12.4 ug/L	---	0.00066	0.0016
Pregnancy 17 β -estradiol (E2)	100%	22.8 ug/L	---	0.00025	0.00048
Pregnancy Estriol (E3)	100%	8.3 ug/L	---	0.00016	0.00041
Phenols (urine)	%	ug/L	ug/L	EC50	EC50
Bisphenol A (BPA)	96%	2.53 ug/L	15 ug/L	0.51 uM	0.42 uM
Benzophenone-3 (BP-3)	98%	59-77 ug/L	6740 ug/L	89.8 uM	106.3 uM
Phthalates (urine)	%			REC20	REC20
Butylbenzyl phthalate (BBP)				0.0001 uM	3.8-1.9 uM
Monobenzyl phthalate (MBzP)	100%			<LOD	<LOD
Di-n-butyl phthalate (DBP)				<LOD	<LOD
Monoisobutyl phthalate (MiBP)	99%			---	---
Mono-n-butyl phthalate (MBP)	99%			<LOD	<LOD
Parabens (urine)	%	ug/L	ug/L	EC50	EC50
Butylparaben (BP)	70%	1.9 ug/L	56.3 ug/L	0.95 uM	0.63 uM
Propylparaben (PP)	100%	19.1-45.6 ug/L	531 ug/L	25.9 uM	7.0 uM

Effects of BP-3 during pregnancy



BP-3 alters mammary gland morphology after involution



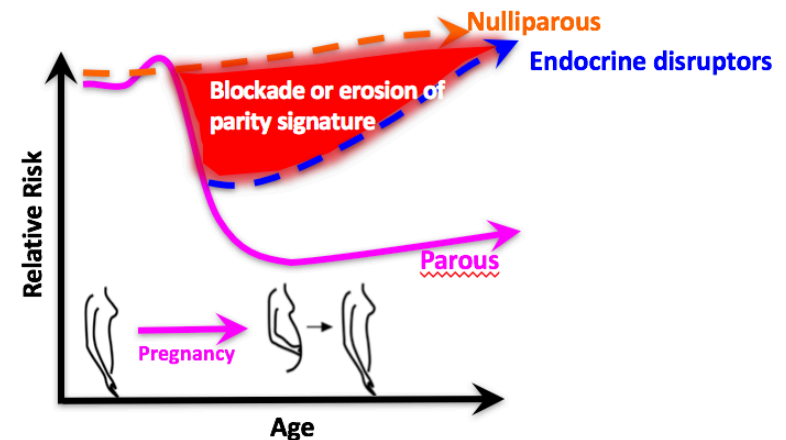
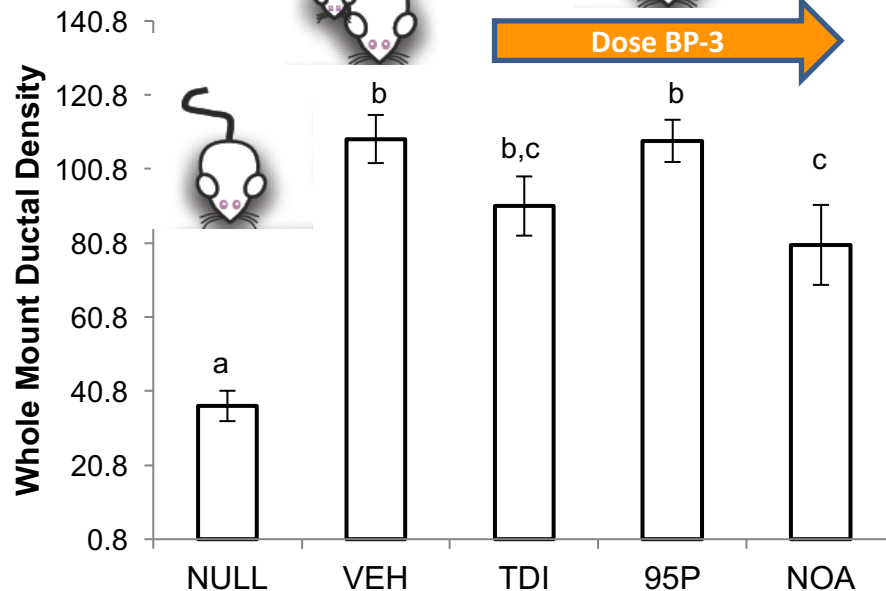
NULL

VEH

TDI

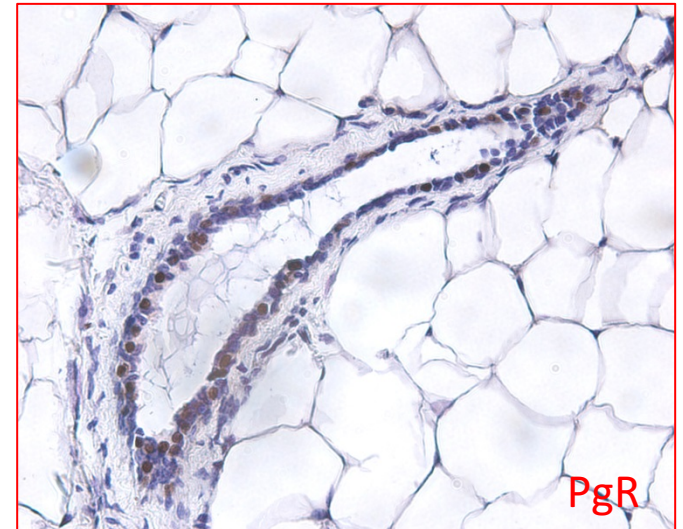
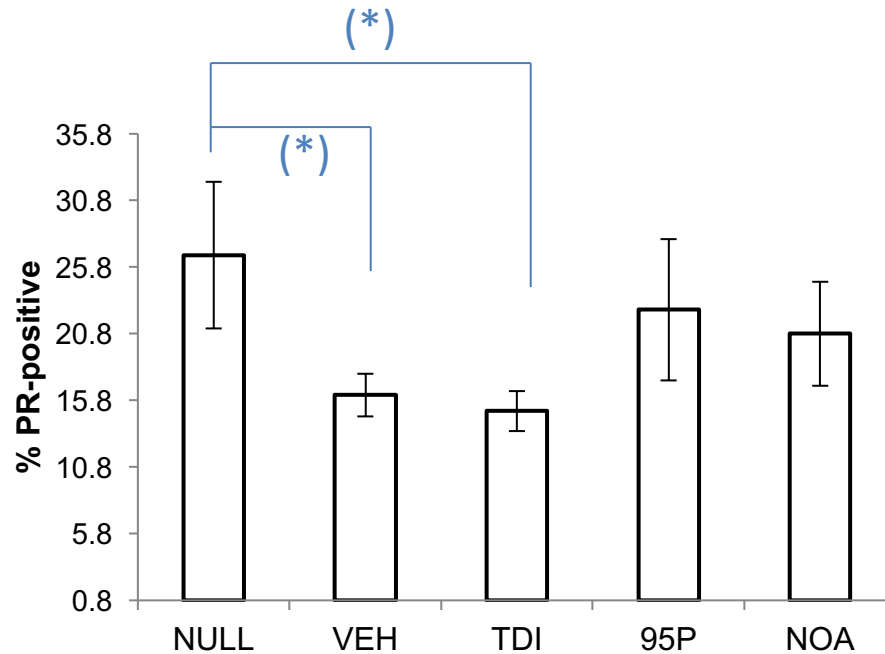
95P

NOA



ANOVA $p < 0.001$

BP-3 blocks parity-induced expression of Progesterone Receptor



For details see Poster 32:

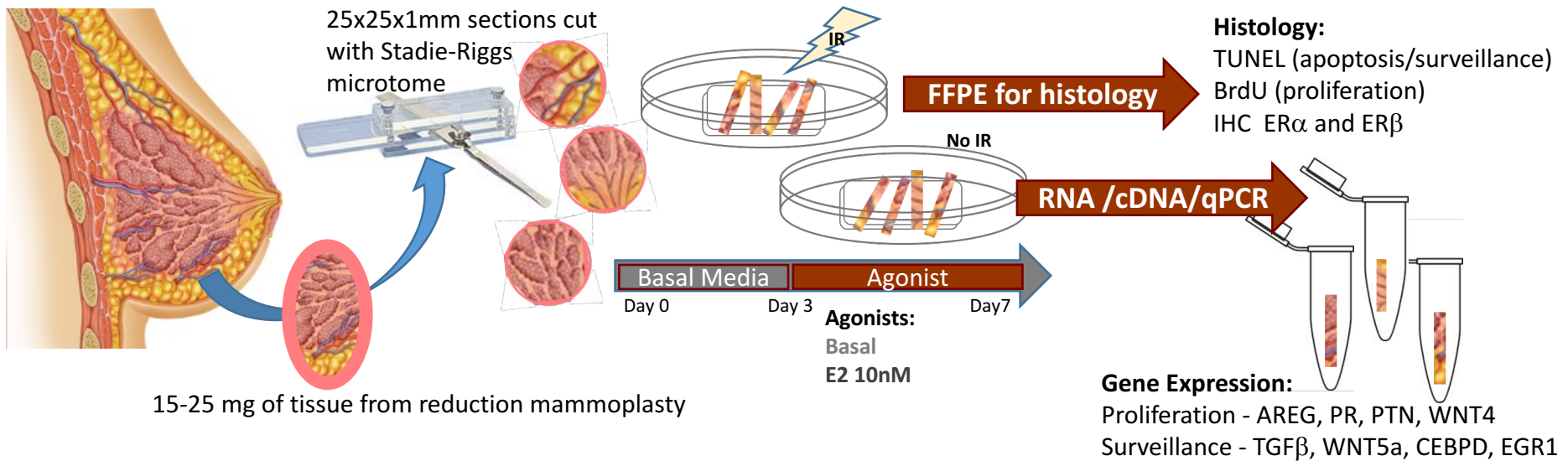
Charlotte D. LaPlante, Laura Vandenberg

Breast Cancer and the Environment Research Program

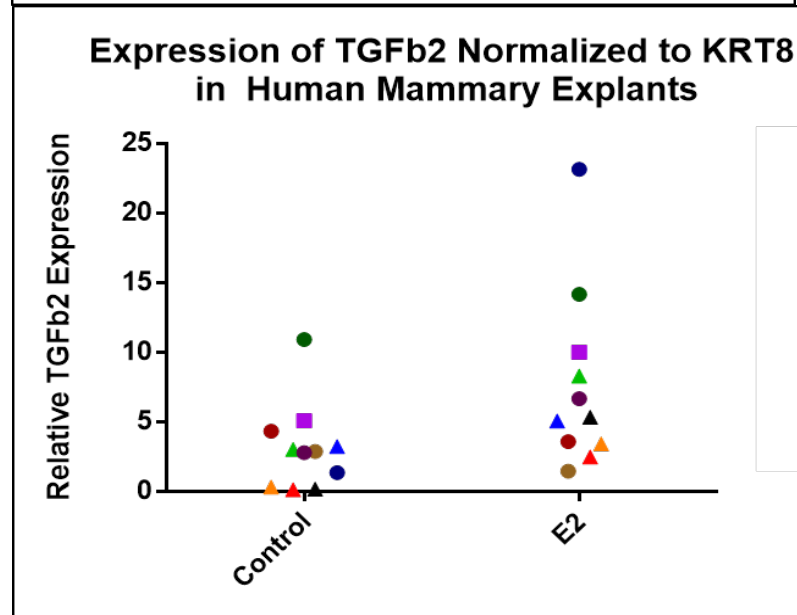
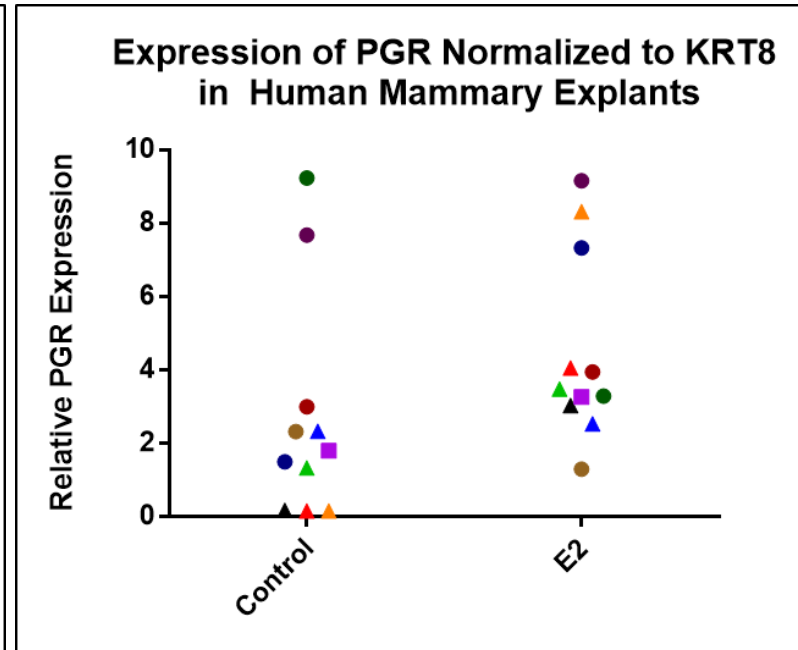
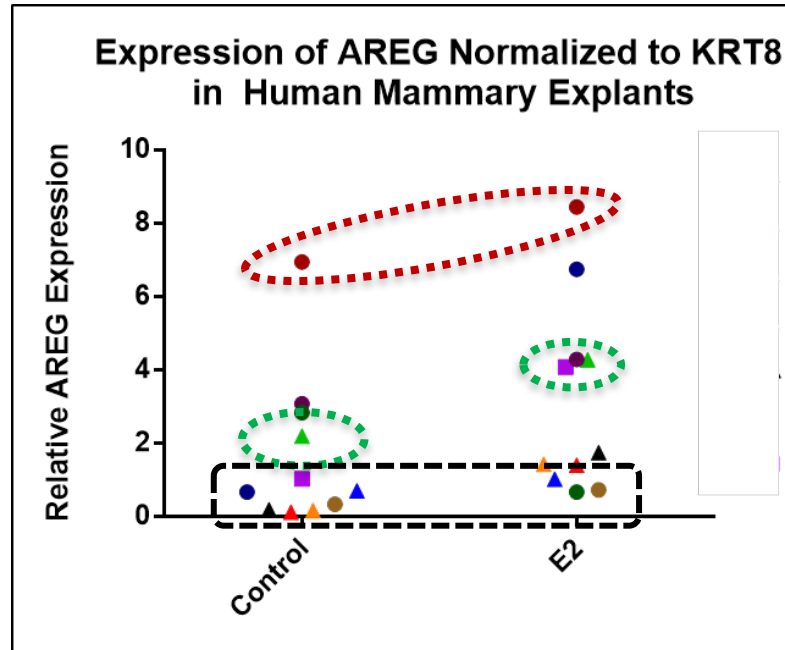


**SENSITIVITY TO ESTROGENS
AND ENDOCRINE DISRUPTORS IN
NORMAL HUMAN BREAST?**

The Human Breast Explant Model



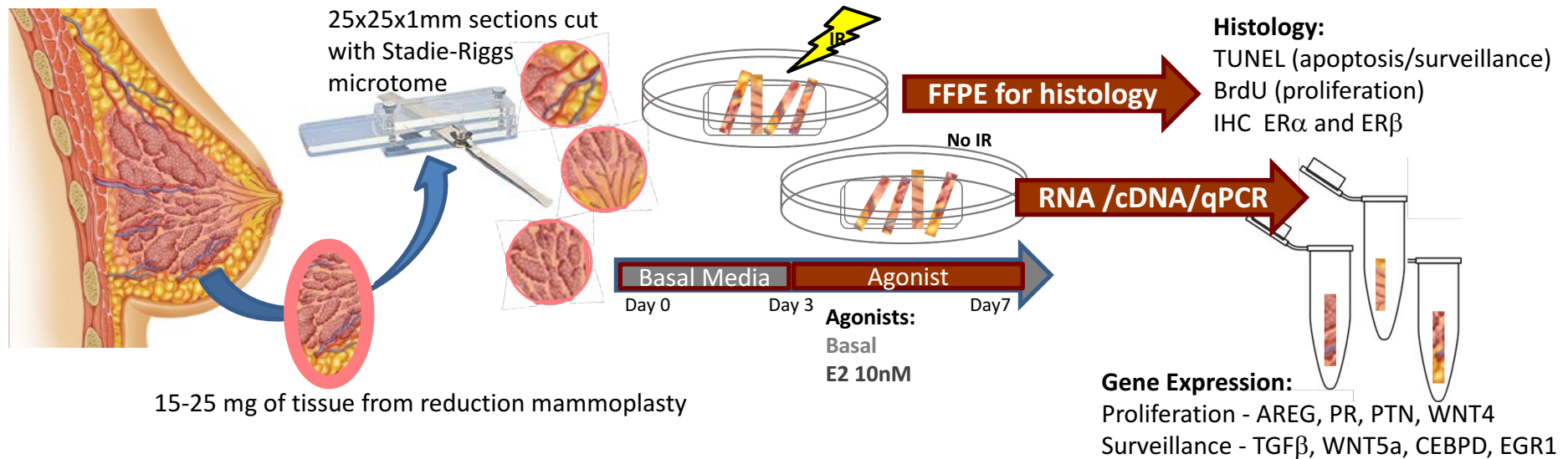
Responses to estrogen and parity



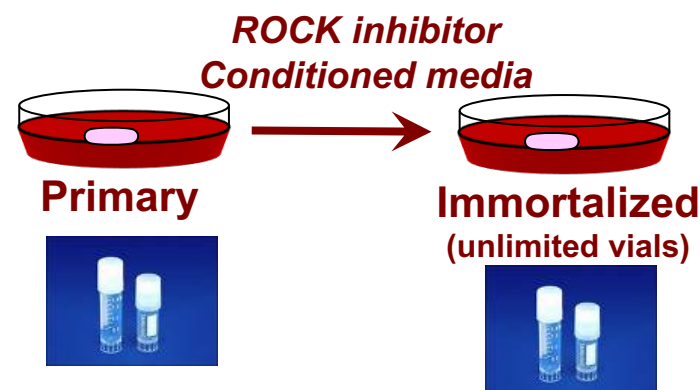
- Variation in basal expression and response to estrogen.
- Differs among target genes.
- Effect of parity.
 - E2 increased AREG, PGR, and TGFb2 expression in nulliparous ($p < 0.05$).
 - But not in parous.

The Human Breast Models

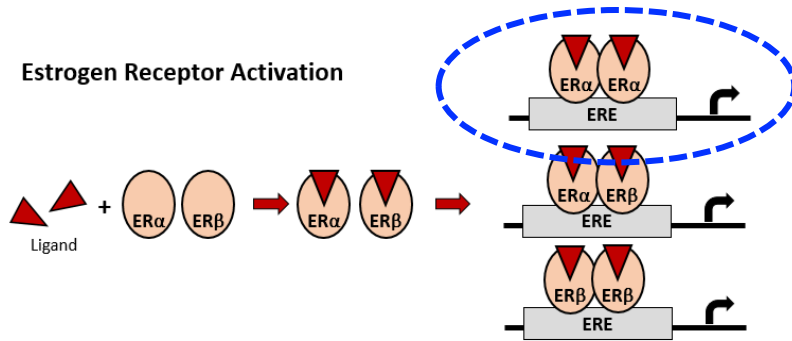
A. Explant cultures



B. Conditionally reprogrammed

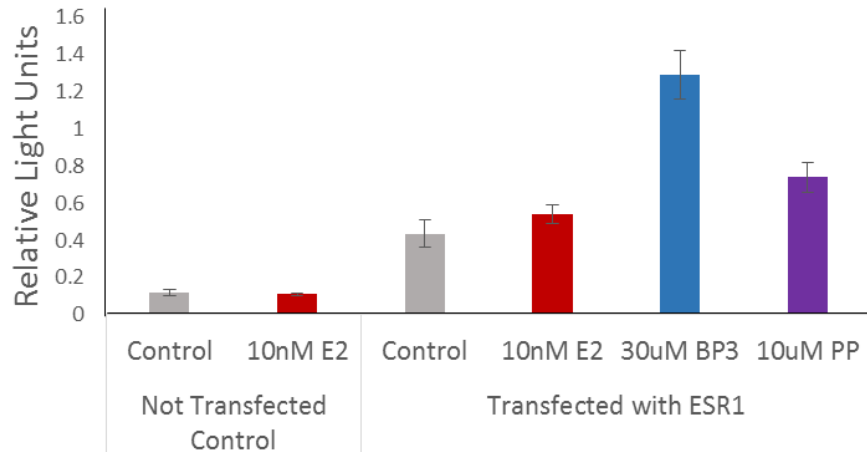


Effects of estrogen receptors

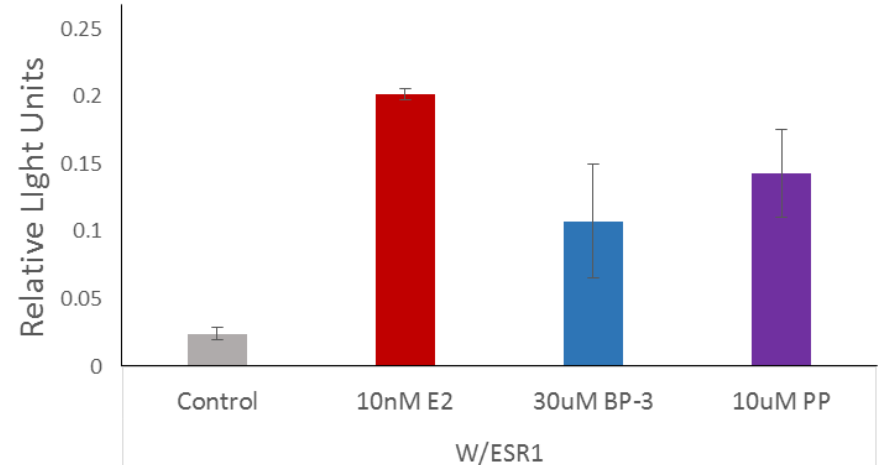


- Individuals vary in responsiveness to estrogens.
- Sensitivity to chemicals can differ from estrogen.

Ratio of Luciferase to Renilla - ciHMEC 847

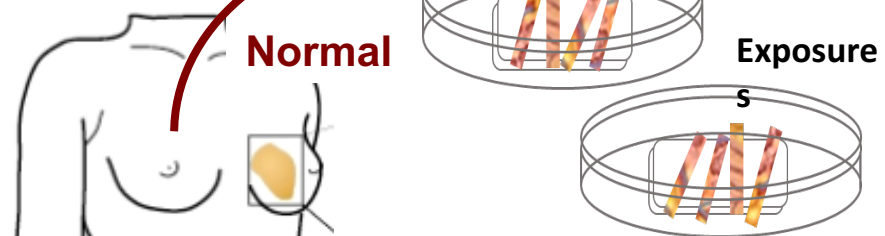


Ratio of Luciferase to Renilla - ciHMEC 910

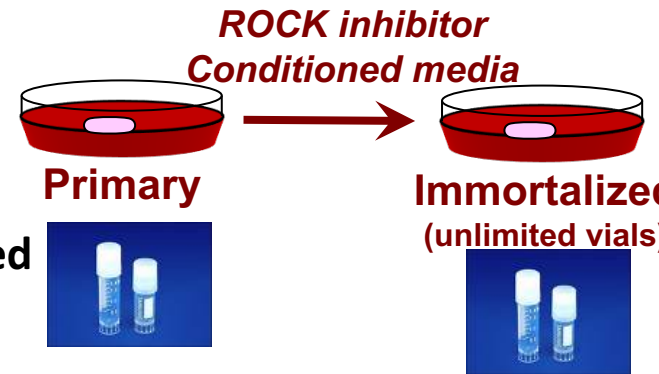


Poster 6: Stephanie Morin, Sallie Schneider
Poster 11: Amye Black, Joseph Jerry

A. Explant cultures



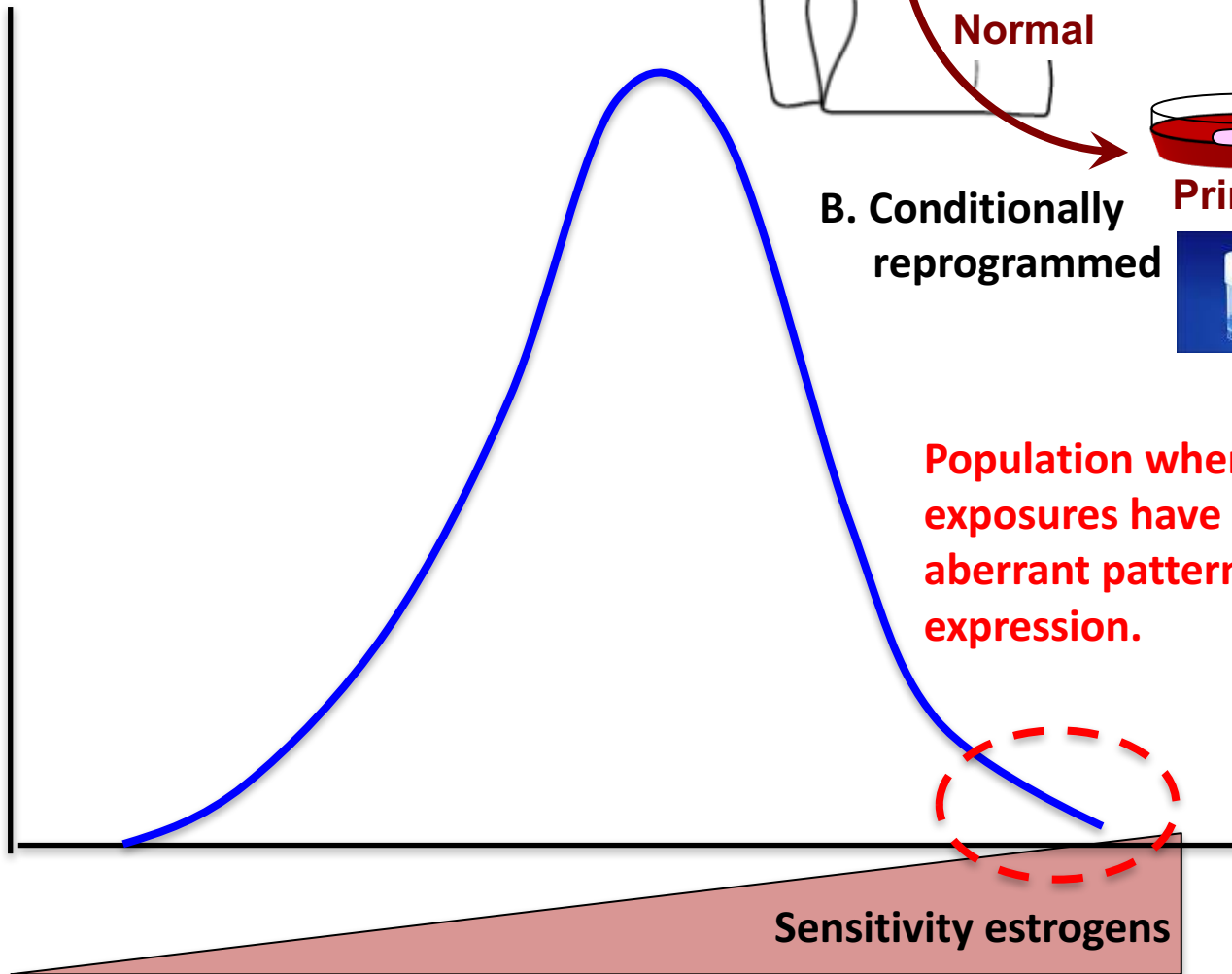
B. Conditionally reprogrammed



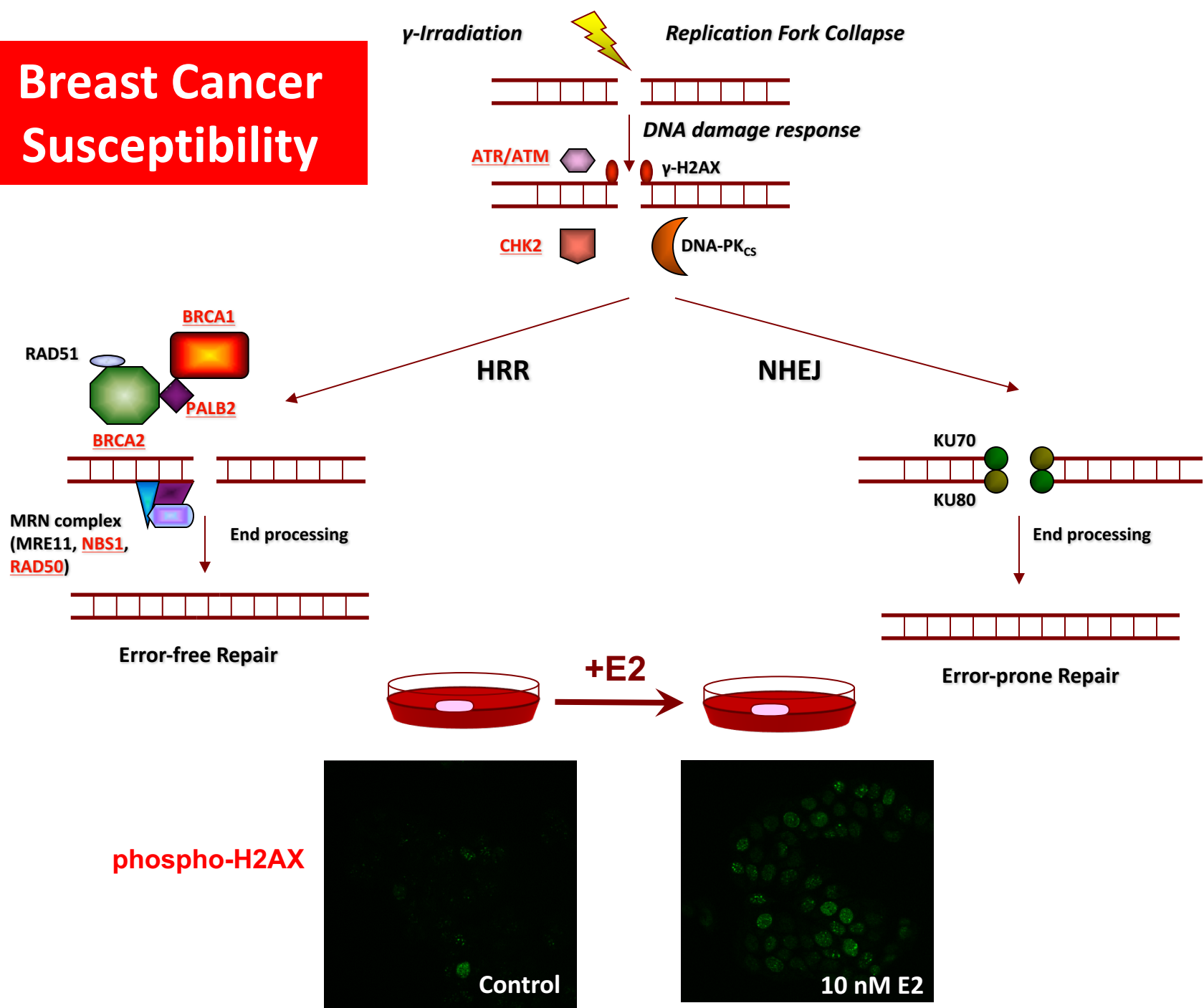
Population where estrogen exposures have increased risk or aberrant pattern of gene expression.

Sensitivity estrogens

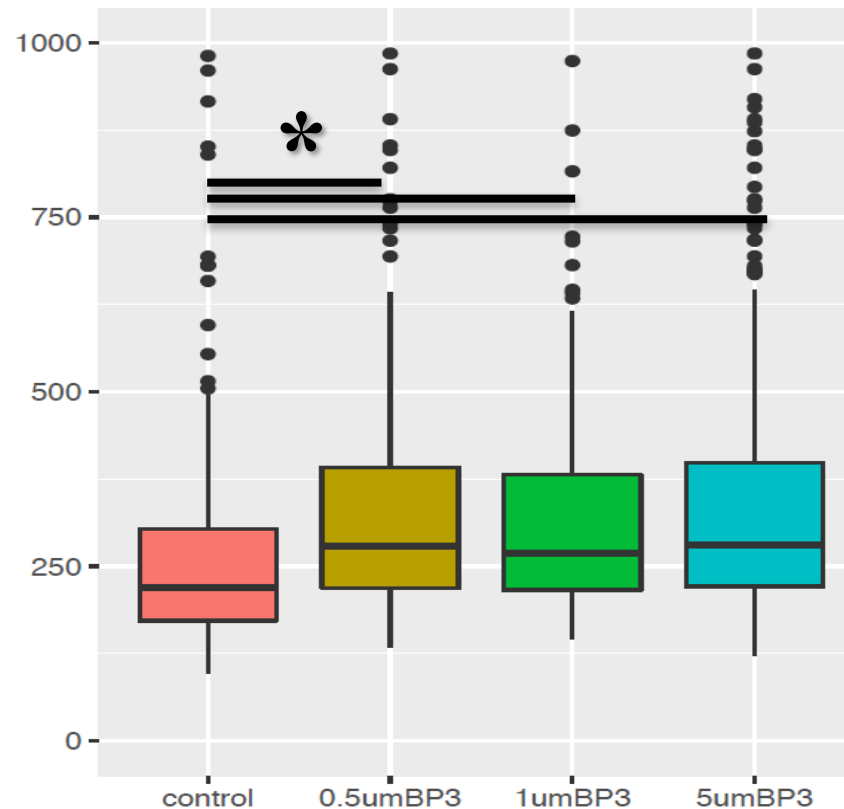
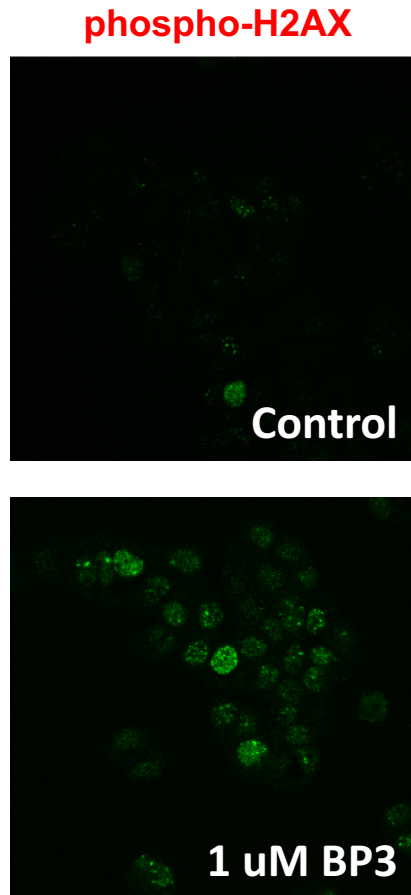
Proportion of women



Breast Cancer Susceptibility

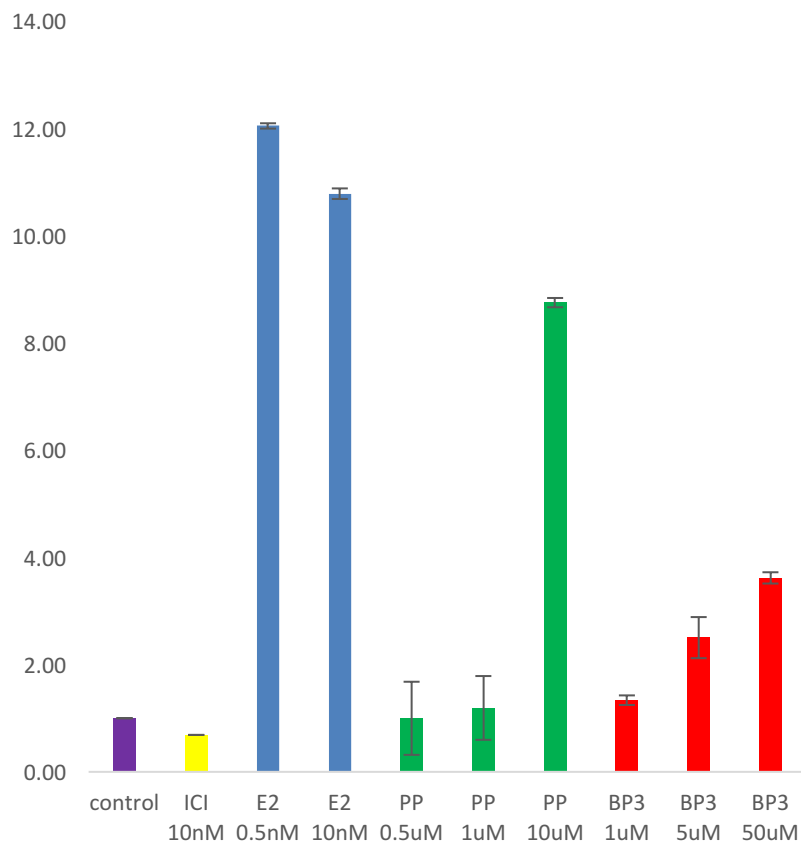


BP3 induces DNA damage at low doses

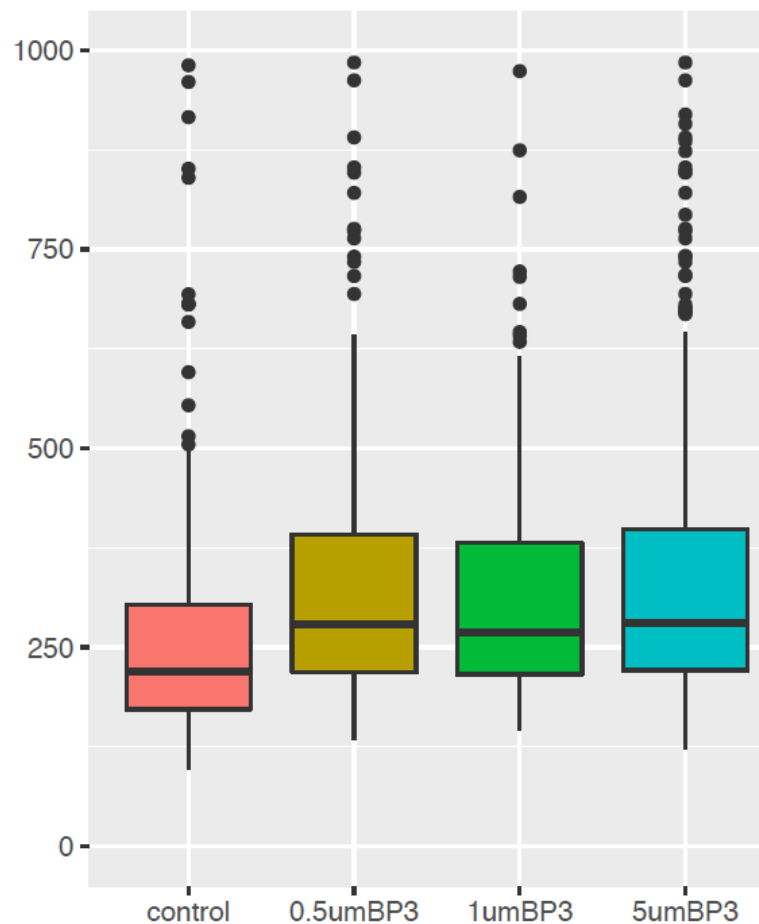


Should we be examining DNA damage?

T47D PgR (24hr XE treatments)



↔
↔
DNA damage



↔
DNA damage

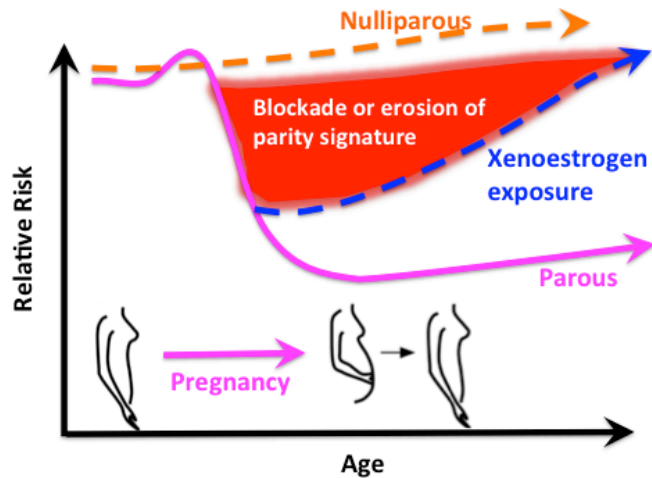


What does it mean for me?

Can you help me rank the risks?

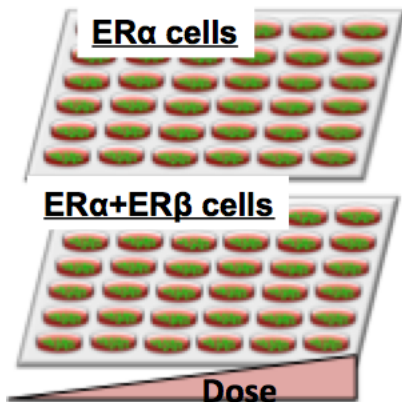
Hypothesis:

Tumor suppressors induced during pregnancy reduce the risk of tumors
but can be impaired or reversed by xenoestrogens.



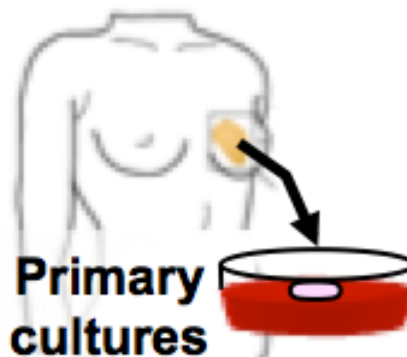
Aims 1 and 2

Breast cancer cell lines

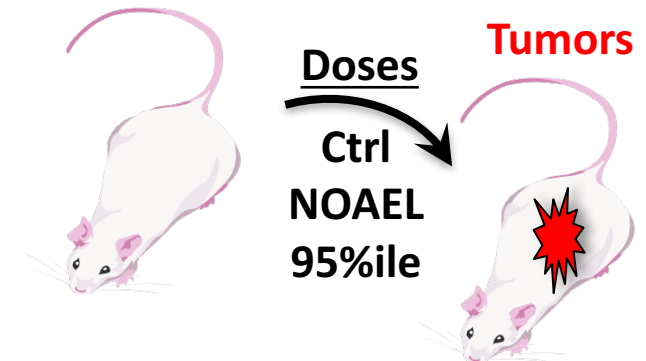


Aims 2 and 3

Breast cells and explants



In vivo effects



Research Team

- **D. Joseph Jerry** (PI), University of Massachusetts-Amherst, Dept of Veterinary & Animal Sciences and Pioneer Valley Life Sciences Institute
- **Sallie S. Schneider** (PI), Baystate Medical Center and Pioneer Valley Life Sciences Institute
- **Karen A. Dunphy**, Dept. of Veterinary & Animal Sciences
- **Laura N. Vandenberg**, University of Massachusetts-Amherst, Dept of Environmental Health Science
- **Clinical Collaborators:**
 - **Grace Makari-Judson** (Oncologist), **Giovanna Crisi** (Pathologist), **Richard Arenas** (Surgeon)
- **Anna G. Symington**, Community Outreach Coordinator
 - **Rays of Hope**
 - **Girls Inc**

