

The Role of Metalloestrogens in Hormone-Independent Activation of ER α

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Outline

- June 10 – July 24
- Martin Lab located in the Lombardi Cancer Center in the Georgetown University Medical Center
- Lab's goal: understand the effect of metalloestrogens on the activation of estrogen receptor alpha on breast cancer treatment

Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER





Background



- Breast cancer is the most common cancer in women in the United States
- In the United States, 1 in 8 women will develop breast cancer in their lifetime
- 70% of these tumors are ER-positive at time of diagnosis but 1/3 of these tumors fail to respond to hormone therapy

Estimated New Cancer Cases and Deaths in 2019

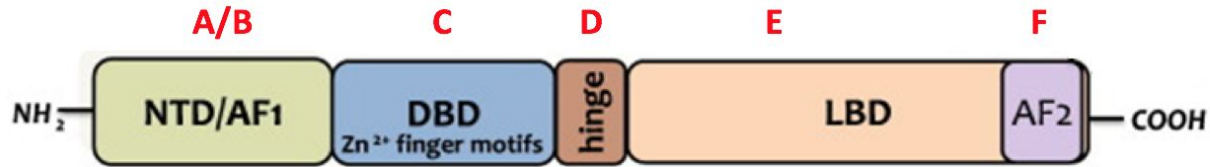
Estimated New Cases

			Males	Females			
Prostate	174,650	20%			Breast	268,600	30%
Lung & bronchus	116,440	13%			Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%			Colon & rectum	67,100	8%
Urinary bladder	61,700	7%			Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%			Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%			Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%			Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%			Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%			Pancreas	26,830	3%
Pancreas	29,940	3%			Leukemia	25,860	3%
All Sites	870,970	100%			All Sites	891,480	100%

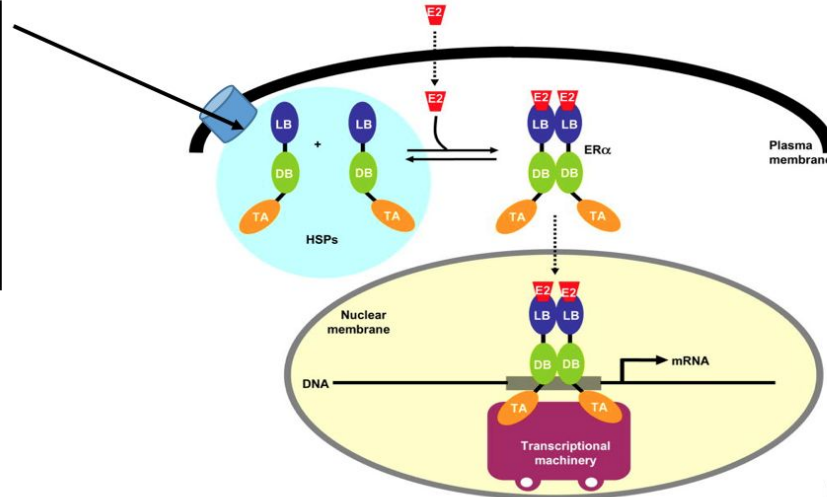
Estimated Deaths

			Males	Females			
Lung & bronchus	76,650	24%			Lung & bronchus	66,020	23%
Prostate	31,620	10%			Breast	41,760	15%
Colon & rectum	27,640	9%			Colon & rectum	23,380	8%
Pancreas	23,800	7%			Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%			Ovary	13,980	5%
Leukemia	13,150	4%			Uterine corpus	12,160	4%
Esophagus	13,020	4%			Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%			Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%			Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%			Brain & other nervous system	7,850	3%
All Sites	321,670	100%			All Sites	285,210	100%

ER α Structure and Function

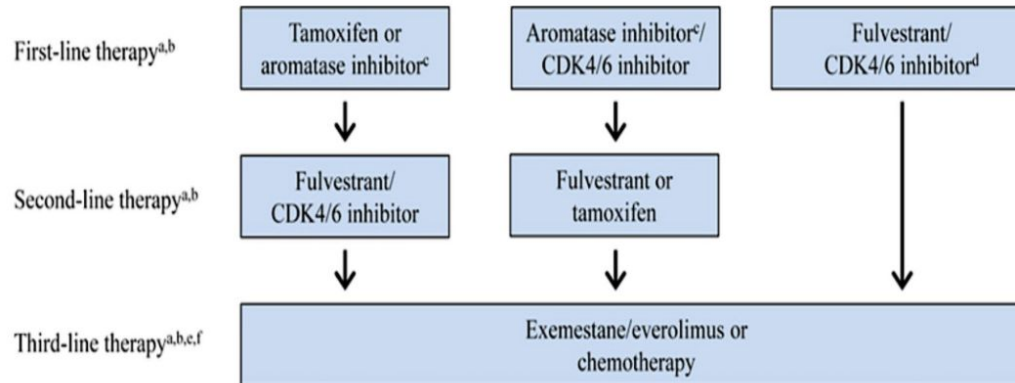


Ca²⁺, Cd²⁺,
Cu²⁺, Co²⁺,
Ni²⁺, Hg²⁺,
Pb²⁺, AsO₂⁻,
SeO₃⁻, VO₄⁻



Current Treatment For Advanced ER+ Tumors

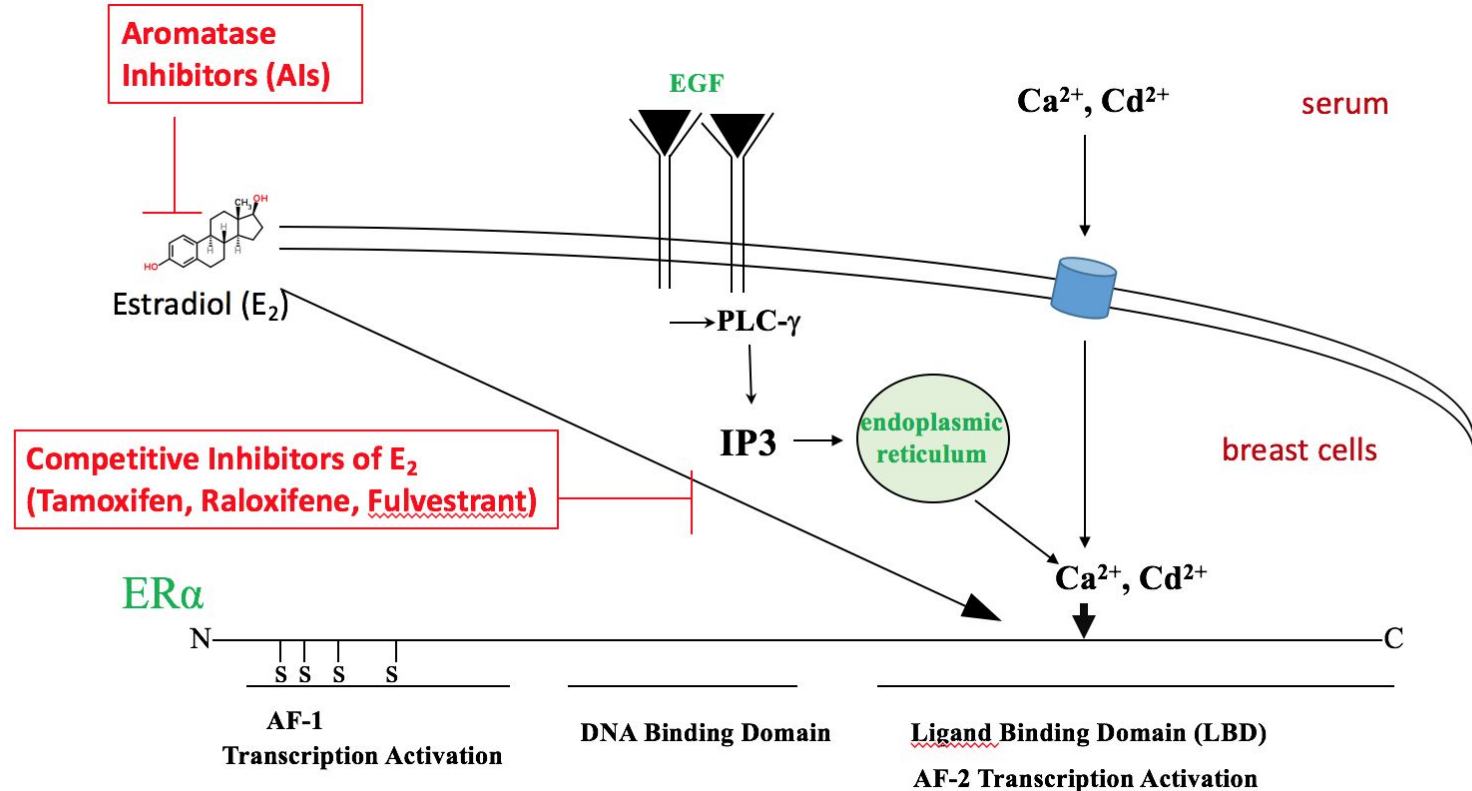
Most patients receive a sequence of endocrine therapies until they form an endocrine resistance and need chemotherapy instead



ER-positive Breast Cancer Treatment Strategies

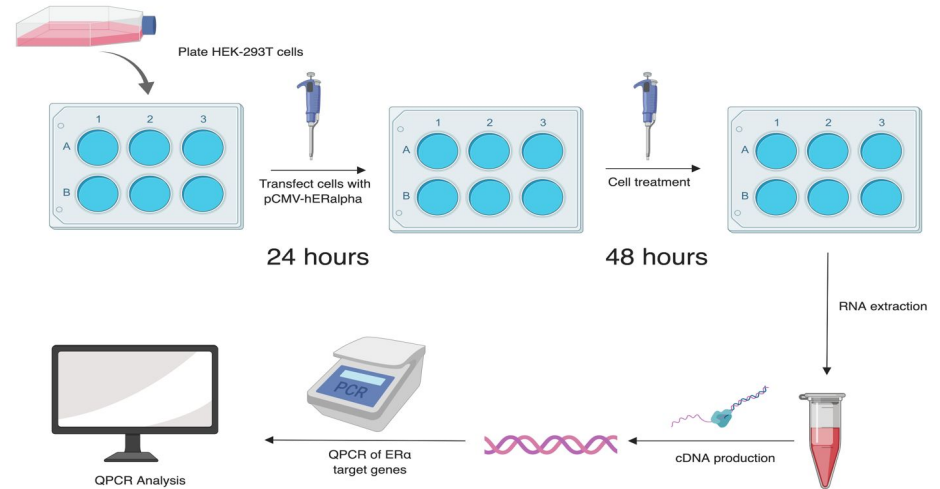
- SERMs (Tamoxifen)
 - Inhibits the growth of breast tumors by competitively binding to ER α to block estrogen from activating the receptor (Smith et al., 2003)
- Aromatase Inhibitors (AIs)
 - Inactivates aromatase, which is the enzyme that synthesizes estrogen from androgenic substrates, so that the estrogen cannot bind to the receptor (Smith et al., 2003)
- SERDs (Fulvestrant)
 - Binds to the estrogen receptor and downregulates the ER protein levels in the tumor (Howell et al., 2002)
- CDK4-6 Inhibitors
 - Prevents the cell from going from G1 to S and cause the cell to undergo senescence (2002 O'Leary et al., 2016)

ER α Activation by Estradiol or Metalloestrogen Signaling Pathways in Breast Cells

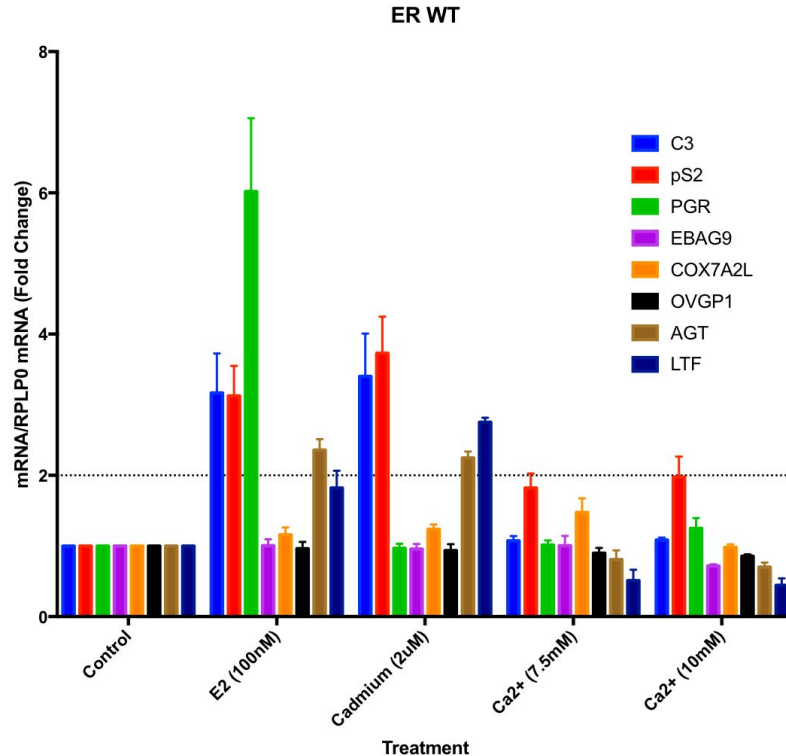


The Experiment

- Tested the ability of calcium and cadmium metalloestrogens to activate the ER α with anti-estrogens being either present or absent



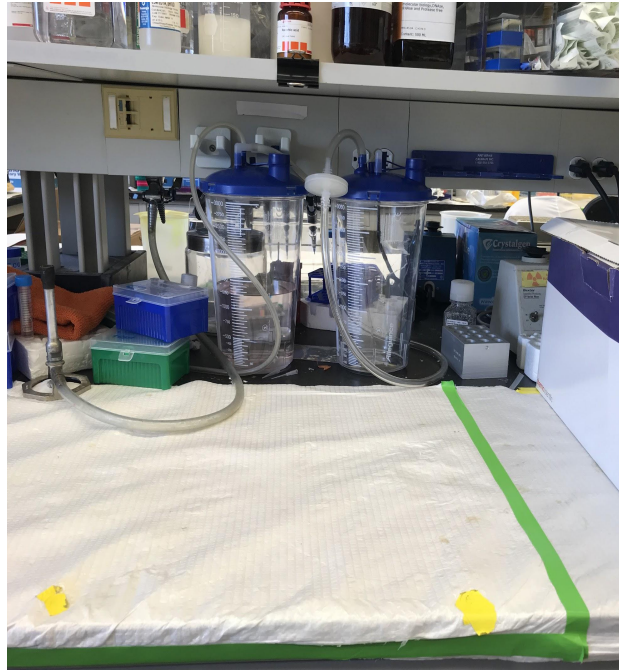
Results



- HEK-293T cells transiently transfected with ER α :
 - Estradiol (E2) increased expression of endogenous ER α genes PGR, C3, pS2, AGT and LTF
 - Cadmium increased expression of endogenous ER α genes C3, pS2, AGT and LTF
 - Calcium increased expression of endogenous ER α gene pS2
- Conclusion: Cadmium and calcium demonstrate estrogen-independent activation of ER α

What I Learned

- Many new techniques
- Always have patience
- Ask for help when you need it
- Always wear a lab coat and gloves



Acknowledgements

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- Dr. Mary Beth Martin
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